

Repatriation Medical Authority

Investigation into **Atrial fibrillation and atrial flutter**

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For the **Repatriation Medical Authority**
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Glossary/abbreviations

ACE	angiotensin converting enzyme
ACM	atrial cardiomyopathy
ACS	acute coronary syndrome
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AF	Atrial fibrillation
AFL	Atrial flutter
AF/f	fibrillation and flutter
AID	Autoimmune disease
APE	Acute pulmonary embolism
ARIC	Atherosclerosis Risk in Communities
AS	Ankylosing spondylitis
ATTR-CA	Transthyretin cardiac amyloidosis
AV	atrioventricular
aVB	atrioventricular block

BCI	Blunt chest/cardiac injury
BD	Behçet's disease
BF	Body fat
BMI	Body mass index
BoP	balance of probabilities
BP	Bisphosphonates
BTK	Bruton tyrosine kinase
CA	Cardiac amyloidosis
CABG	coronary artery bypass surgery
cAMP	cyclic adenosine monophosphate
CC	Commotion cordis
CD	Coeliac disease
CHD	coronary heart disease
CHF	Congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CAE	cardiovascular adverse events
CKD	Chronic kidney disease
COX	cyclooxygenase
CPAP	Continuous positive airway pressure
CPB	cardiopulmonary bypass
CRF	cardiorespiratory fitness
CRF	Chronic renal failure
CRP	C-reactive protein
CRT	cardiac resynchronisation therapy
CS	Cardiac sarcoidosis
CS	corticosteroid
CT	computerised tomography
CTI	cavo-tricuspid isthmus
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	Diabetes mellitus
ECG	electrocardiogram
ED	emergency department
eGFR	Estimated glomerular filtration rate
EMR	electronic medical records
ETS	Environmental tobacco smoke
GC	glucocorticoid
GCA	Giant cell arteritis
GD	Graves' disease
GORD	Gastro-oesophageal reflux disease
GWAS	genome-wide association studies
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFrEF	HF with reduced ejection fraction
HH	Hiatus hernia

HH	Hereditary haemochromatosis
HT	hypertension
IBD	inflammatory bowel disease
ICD	implantable cardioverter-defibrillators
ICI	Immune checkpoint inhibitors
ICS	Inhaled corticosteroid
ICU	intensive care unit
IRR	incidence risk ratio
LA	left atrium
LOS	length of stay
LV	left ventricle
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MESA	Multi-Ethnic Study of Atherosclerosis
METs	metabolic equivalent of task
MI	Myocardial infarction
MR	Mitral regurgitation
MR	mendelian randomisation
MS	Mitral stenosis
MS	multiple sclerosis
MV	mechanical ventilation
NAFLD	non-alcoholic fatty liver disease
NHIRD	National Health Insurance Research Database
NOAF	new-onset atrial fibrillation
NSAIDs	non-steroid anti-inflammatory drugs
NSR	normal sinus rhythm
NVAF	non-valvular atrial fibrillation
OA	oral anticoagulation
OR	odds ratio
OSA	Obstructive sleep apnoea
PA	Physical activity
PAC	Premature atrial complex
PAF	paroxysmal atrial fibrillation
PCI	percutaneous coronary intervention
P(T)E	pulmonary (thrombo)embolus
PM	particulate matter
POAF	post-operative AF
PsA	psoriatic arthritis
PV	pulmonary veins
PWD	P wave dispersion
RA	Rheumatoid arthritis
RAAS	renin-angiotensin-aldosterone system
RCT	Randomised controlled trial
RH	reasonable hypothesis
RHD	Rheumatic heart disease
RMA	Repatriation Medical Authority

RR	relative risk
RT	radiotherapy
S(A)N	Sino-atrial node
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAVR	surgical aortic valve replacement
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCI	Spinal cord injury
SD	standard drink
SD	Standard deviation
SHS	Secondhand smoke
SMSE	sound medical-scientific evidence
SND	Sinus node dysfunction
SoP	Statement of Principles
SSS	Sick sinus syndrome
TAVI/R	Transcatheter aortic valve replacement
TIA	transient ischaemic attack
TNF	tumor necrosis factor
TSH	Thyroid stimulating hormone
TCM	Takotsubo cardiomyopathy
UFP	ultrafine particles
uSpA	undifferentiated spondyloarthritis
VEA	Veterans' Entitlements Act 1986
VF	Ventricular fibrillation
VTE	venous thromboembolism
VEA	<i>Veterans' Entitlements Act 1986</i>
WC	<i>Waist circumference</i>
WHR	waist to hip ratio

Current Statements of Principles

The current SoPs are 49 and 50/2014. They have factors for

- valvular heart disease
- ischaemic heart disease
- myocarditis
- cardiomyopathy
- familial hypertrophic cardiomyopathy
- cardiac failure
- hypertension
- pericarditis
- hyperthyroidism, thyrotoxicosis, Graves' disease or thyrotoxic goitre
- subclinical hyperthyroidism
- alcohol
- cardiac or thoracic surgery

surgery
 chronic obstructive pulmonary disease
 high level, endurance physical activity
 sick sinus syndrome
 neoplasm
 non-neoplastic mass lesion
 diabetes mellitus
 penetrating trauma
 non-penetrating blow to the chest
 spinal cord injury
 injury or illness requiring admission to an intensive care unit or mechanical ventilation
 autoimmune or inflammatory disease
 obesity
 binge drinking
 obstructive sleep apnoea
 smoking
 gastro-oesophageal reflux disease
 chronic renal disease

TABLE 1 DIFFERENCES BETWEEN RH AND BoP SoPs

<p>The following factors are in the RH SoP only</p> <p> autoimmune or inflammatory disease binge drinking obstructive sleep apnoea smoking gastro-oesophageal reflux disease chronic renal disease </p>
<p>The following factors have lower dosage/time factors in the RH SoP [BoP]</p> <p> consuming an average of at least 140 grams [BoP 175 grams] of alcohol per week undertaking strenuous, high level, endurance physical activity greater than six METs, for an average of at least 20 hours per week for a continuous period of at least five years before the clinical onset of atrial fibrillation or atrial flutter, and where strenuous physical activity has ceased, the clinical onset of atrial fibrillation or atrial flutter has occurred within 20 years [BoP 10 years] of cessation; having an injury or illness requiring admission to an intensive care unit or mechanical ventilation within the one month [BoP 14 days] before the clinical onset of atrial fibrillation or atrial flutter; </p>

Background

This investigation was notified in order to comply with the sunset provisions of the *Legislation Act 2003*.

The Repatriation Medical Authority (the Authority) gave notice under section 196G of the Veterans' Entitlements Act 1986 (the VEA) that it intends to carry out investigations under subsection 196B (7) of the VEA to review the contents of Statements of Principles concerning atrial fibrillation and atrial flutter (Instrument Nos. 49 & 50 of 2014).

Under the VEA, the Authority is required to find out whether there is new information available about how the above listed conditions may be suffered or contracted, or death from the above listed conditions may occur; and the extent to which the above listed conditions or death from the above listed conditions may be war-caused, defence-caused, a service injury, a service disease or a service death.

An investigation notice was placed in the Government Notices Gazette on 22 October 2021.

Submissions/correspondence

An Investigation Request in relation to atrial fibrillation and atrial flutter was received from a person eligible under the VEA (ALA) on 30 December 2021. The request was to carry out an investigation to make a SOP in relation to atrial fibrillation and atrial flutter. As this SoP was already under review, the request for investigation was treated as a submission to the investigation.

The submission notes that “[e]xtensive use of steroid medication for the treatment of asthma and a variety of skin conditions are not currently accepted under the SOP. This is despite asthmatics and those suffering skin conditions requiring, as an integral part of their on-going treatment, sometimes extensive and for many years, steroid medication with prednisolone being one such medication.” There has been little by way of medical research to establish a higher incidence of atrial fibrillation in patients with a prior history of asthma and/or skin conditions where oral steroids have been part of the treatment for these medical conditions. What literature that has been published is overwhelming evidence the use of steroids in its treatment are associated with an increased risk of atrial fibrillation, especially when higher doses are taken.”

The request was that the SoPs be updated to include medical conditions that require oral steroids use, e.g. asthma and skin conditions, as factors for later developing AF.

The submission cites studies by **Huerta et al (2005)**,¹ **van der Hooft et al. (2006)**² and **Chan et al (2014)**³ as evidence of the link between taking oral steroids for asthma and skin conditions leading to a diagnosis of AF.

¹ Huerta, C., Lanes, S. F., & García Rodríguez, L. A. (2005). Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology (Cambridge, Mass.)*, 16(3), 360–6.

² van der Hooft, C. S., Heeringa, J., Brusselle, G. G., et al. (2006). Corticosteroids and the risk of atrial fibrillation. *Archives of internal medicine*, 166(9), 1016–20.

³ Chan, W. L., Yang, K. P., Chao, T. F., et al (2014). The association of asthma and atrial fibrillation--a nationwide population-based nested case-control study. *International journal of cardiology*, 176(2), 464–9.

Van der Hooff et al. (2006) tested the hypothesis that high-dose corticosteroid exposure increases the risk of new-onset atrial fibrillation, in a nested case-control study within the Rotterdam Study, a population-based cohort study among 7983 older adults. Cases were defined as persons with incident atrial fibrillation between 1991 and 2000. The date of diagnosis was defined as the index date. All non-cases in the Rotterdam Study who were alive and eligible on the index date were used as controls. The authors compared the proportion of cases and controls that received a corticosteroid prescription within 1 month before the index date. Corticosteroid exposure was categorised into high-dose exposure (oral or parenteral steroid at a daily dose \geq 7.5 mg of prednisone equivalents) and low-intermediate-dose exposure ($<$ 7.5 mg of prednisone equivalents or inhaled corticosteroids).

There were 385 eligible cases of new-onset atrial fibrillation during the study period. The risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the index date than for those without (OR 3.75; 95CI 2.38-5.87). However, only high-dose corticosteroid use was associated with an increased risk (OR 6.07; 95CI 3.90-9.42), whereas low-intermediate-dose use was not (OR 1.42; 95CI 0.72-2.82). The association of atrial fibrillation with high-dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset atrial fibrillation was not only increased in patients with asthma or chronic obstructive pulmonary disease (OR 4.02; 95CI 2.07-7.81) but also in patients with rheumatic, allergic, or malignant hematologic diseases (OR, 7.90; 95CI 4.47-13.98).

These findings strongly suggested that patients receiving high-dose corticosteroid therapy are at increased risk of developing atrial fibrillation.

Huerta et al (2005)⁴ noted that several medications used to treat respiratory diseases, including beta-adrenoceptors, antimuscarinics, inhaled and oral corticosteroids, and theophyllines, have been associated indirectly with cardiac rhythm disorders, but that epidemiological evidence was limited.

Huerta et al evaluated the association between respiratory drugs and the occurrence of rhythm disorders among patients with asthma and those with chronic obstructive pulmonary disease, the authors conducted a case-control study nested in a population-based cohort of people aged 10-79 years and registered in the U.K. General Practice Research Database after January 1994. The analysis included 710 confirmed cases and 5000 controls frequency-matched to cases by age and sex.

No increased risk of arrhythmias overall was found in users of inhaled steroids (RR 1.0; 95CI 0.8-1.3). Short-term use of theophylline was weakly associated with arrhythmia (RR 1.8; 95CI 1.0-3.3). An increased risk of arrhythmias was found in users of oral steroids, and the relative risk was greater at the beginning of therapy (RR 2.6; 95CI 2.0-3.5). The risk of atrial fibrillation was increased, especially for short-term use of oral steroids (RR 2.7; 95CI 1.9-3.8), and a weak association with theophyllines, especially short-term use (RR 1.8; 95CI 0.9-3.7).

⁴ Huerta, C., Lanes, S. F., & García Rodríguez, L. A. (2005). Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology (Cambridge, Mass.)*, 16(3), 360–6.

Supraventricular tachycardia was associated with long-term use of oral steroids (RR 2.1; 95CI 0.8-5.7), long-term use of antimuscarinics (RR 1.7; 0.7-4.1), and short-term use of theophylline (4.0; 95CI 0.9-18.1).

It was suggested that oral steroids and theophylline are associated with risk of developing atrial fibrillation, especially with new courses of therapy.

This material is incorporated into the section of this briefing paper concerning corticosteroids (below).

Literature Search

A PubMed search was conducted on 8 February 2022 using the search terms atrial fibrillation, with Filters applied: in the last 10 years, English and human studies, with a preliminary focus on review studies. Articles were selected based on relevance, study quality, reliability and journal authority. The above search was supplemented by specific searches for atrial fibrillation and various factors of interest, internet searches, manual searches of reference lists, review of citations and consideration of relevant sections of textbooks.

A PubMed search was conducted on 8 February 2022 using the search terms corticosteroids AND atrial fibrillation, with Filters applied: in the last 10 years, English. A total of 185 results was obtained.

Definition

Current definition

Atrial fibrillation and atrial flutter means atrial fibrillation or atrial flutter, either alone or in combination.

"atrial fibrillation" means a paroxysmal, persistent or permanent cardiac arrhythmia, in which normal and regular electrical impulses generated by the sinoatrial node are overwhelmed by disorganised, rapid, and irregular atrial activation, leading to irregular conduction of impulses to the ventricles, and an irregular ventricular rate and rhythm; and

"atrial flutter" means a macroreentrant arrhythmia arising from a rapid electrical circuit in the atrial myocardium, with a regular atrial rate typically exceeding 240 beats per minute, and with a characteristic electrocardiographic appearance with a uniform and regular continuous sawtooth wave-form.

ICD codes

Atrial fibrillation and atrial flutter attracts ICD-10-AM code I48.

Introduction

Atrial flutter is an abnormal cardiac rhythm characterised by rapid, regular atrial depolarisations at a characteristic rate of approximately 300 beats/min and a regular ventricular rate of about 150 beats/min in patients not taking atrioventricular (AV) nodal blockers.^{5 6} It can lead to symptoms of palpitations, shortness of breath, fatigue, or lightheadedness, as well as an increased risk of atrial thrombus formation that may cause cerebral and/or systemic embolisation.

Atrial flutter occurs in many of the same situations as atrial fibrillation, which is much more common. Atrial flutter may be a stable rhythm or a bridge arrhythmia between sinus rhythm and atrial fibrillation, or an organised rhythm in atrial fibrillation patients treated with antiarrhythmic drugs. It may also be associated with a variety of other supraventricular arrhythmias

Epidemiology

Atrial fibrillation (AF) is a global health care problem with evidence suggesting an increasing prevalence and incidence worldwide.⁷ Atrial fibrillation is the most common sustained arrhythmia in clinical practice, with a preference for older age groups. The prevalence of AF increases with age, and it is estimated to affect over 4% of the population above age 60 years.

The prevalence of AF depends upon population characteristics, with differences apparent due to age, sex, race, geography, and time period. Most data has been derived from studies in which an electrocardiogram was obtained during an office visit rather than ambulatory monitoring. The prevalence of paroxysmal AF, which is more likely to be detected with ambulatory monitoring, is much higher.

AF is uncommon in infants and children, and when present, almost always occurs in association with structural heart disease. Healthy young adults are also at low risk. The prevalence of AF increases with age. In the ATRIA study, a cross-sectional study of almost 1.9 million subjects in a health maintenance organisation in the US [Go et al 2001], the overall prevalence of AF was 1%; 70% were at least 65 years old and 45% were ≥75 years old. The prevalence of AF ranged from 0.1% among adults less than 55 years of age to 9% in those aged ≥80 years. The prevalence was higher in men than women (1.1 versus 0.8%), and seen in every age group. The prevalence of AF in the population is increasing.

The incidence of AF, similar to the prevalence, increases with advancing age. In a longitudinal study in which 3983 male Air Force recruits were followed for 44 years, 7.5% developed AF [Krahn et al 1985]. The risk increased with advancing age (from 0.5 per 1000 person-years before age 50 to 9.7 per 1000 person years after age 70).

⁵ https://www.uptodate.com/contents/overview-of-atrial-flutter?search=atrial%20flutter&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

⁶ Perry M, Kemmis Betty S, Downes N, et al (2021). Atrial fibrillation: diagnosis and management-summary of NICE guidance. *BMJ*.;373:n1150.

⁷ https://www.uptodate.com/contents/overview-of-atrial-fibrillation?search=Atrial%20fibrillation&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Atrial fibrillation may occur after an acute precipitant and subsequently resolve. Management guidelines for AF in these settings are unclear as the risk of recurrent AF and related morbidity is poorly understood. **Wang et al (2020)** examined the relations between acute precipitants of AF and long-term recurrence of AF in a clinical setting.⁸ From a multi-institutional longitudinal electronic medical record database, they identified patients with newly diagnosed AF between 2000 and 2014. Wang et al developed algorithms to identify acute AF precipitants (surgery, sepsis, pneumonia, pneumothorax, respiratory failure, myocardial infarction, thyrotoxicosis, alcohol, pericarditis, pulmonary embolism, and myocarditis). The risks of AF recurrence were assessed in individuals with and without a precipitant and the relations between AF recurrence and heart failure, stroke, and mortality.

Among 10 723 patients with newly diagnosed AF (67.9±9.9 years, 41% women), 19% had an acute AF precipitant, the most common of which were cardiac surgery (22%), pneumonia (20%), and non-cardiothoracic surgery (15%). The cumulative incidence of AF recurrence at 5 years was 41% in individuals with a precipitant compared with 52% in those without a precipitant (adjusted HR 0.75, 95CI, 0.69-0.81; P<0.001). The lowest risk of recurrence among those with precipitants occurred with postoperative AF (5-year incidence 32% in cardiac surgery and 39% in non-cardiothoracic surgery). Regardless of the presence of an initial precipitant, recurrent AF was associated with increased adjusted risks of heart failure (HR 2.74, 95CI 2.39-3.15; P<0.001), stroke (HR 1.57, 95CI 1.30-1.90; P<0.001), and mortality (HR 2.96, 95CI 2.70-3.24; P<0.001).

AF after an acute precipitant frequently recurs, although the risk of recurrence is lower than among individuals without an acute precipitant. Recurrence is associated with substantial long-term morbidity and mortality.

In the general population, the development of new onset atrial flutter is uncommon and occurs with significantly less frequency than atrial fibrillation.⁹

In a population-based study, lone atrial flutter with neither identifiable recent predisposing events nor chronic pre-existing comorbidities occurred in 3 of 181 patients (1.7%) [Granada et al 2000]. 16% of cases were attributable to heart failure and 12% to COPD. The incidence increased markedly with age, ranging from 5 per 100,000 person years under age 50 to 587 per 100,000 person years over age 80. The rate of lone atrial flutter was 8% in another series of 380 children and young adults [Garson et al 1985].

Much of the information about atrial flutter is derived from patients referred to tertiary care centres; and the incidence of atrial flutter in the general population has been uncertain. This issue was addressed in a large database of 58,820 residents who obtained their care from one major medical centre. The overall incidence of new cases of atrial flutter during a four-

⁸ Wang, E. Y., Hulme, O. L., Khurshid, S., et al. (2020). Initial Precipitants and Recurrence of Atrial Fibrillation. *Circulation. Arrhythmia and electrophysiology*, 13(3), e007716.

⁹ https://www.uptodate.com/contents/overview-of-atrial-flutter?search=atrial%20flutter&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

year period was 88 per 100,000 person-years, ranging from 5 per 100,000 in those less than 50 and 587 per 100,000 in those more than 80 years of age. Atrial flutter was 2.5 times more common in men.

The incidence of AFL, as with atrial fibrillation, is greatest when underlying heart disease is associated with left atrial enlargement, or left ventricular or biventricular failure

Despite the many comorbidities associated with atrial fibrillation, the relative risk has been varying and not well-documented. **Rivington & Twohig (2020)** quantified the risk of diseases associated with AF using a population-based retrospective analysis in IBM Explorix (1999-2019), an electronic database with over 63 million patients in the US.¹⁰ Odds ratios were calculated between AF and other diseases. AF patients were also stratified by age, gender, and race to assess trends of AF in different demographic groups.

1,812,620 patients had AF in the database. Congestive heart failure had the highest association with AF (OR 42.95). Cardiomyopathy, coronary artery disease, hypertension, and myocardial infarction all had odds greater than 15. Anaemia of chronic disease and chronic kidney disease had odds greater than 18, the highest for chronic inflammatory conditions. Other conditions commonly associated with AF had odds less than 8, including hyperthyroidism, alcohol use, and sleep apnoea. Helicobacter pylori infection had the lowest odds at 1.98.

Morseth et al (2021) examined age-specific risk factor associations with incident atrial fibrillation and their attributable fraction in a large European cohort.¹¹

The investigators used individual-level data (n=66 951, 49.1% men, age range 40-98 years at baseline) from five European cohorts of the MONica Risk, Genetics, Archiving and Monograph Consortium. The participants were followed for incident AF for up to 10 years and the association with modifiable risk factors from the baseline examinations (BMI, hypertension, diabetes, daily smoking, alcohol consumption and history of stroke and myocardial infarction (MI)) was examined. Participants were followed up for incident stroke and all-cause mortality after new-onset AF.

AF incidence increased from 0.9 per 1000 person-years at baseline age 40-49 years, to 17.7 at baseline age ≥ 70 years. Multivariable-adjusted Cox models showed that higher BMI, hypertension, high alcohol consumption and a history of stroke or MI were associated with increased risk of AF across age groups ($p < 0.05$). Between 30% and 40% of the AF risk was attributed to BMI, hypertension and a history of stroke or MI. New-onset AF was associated with a twofold increase in risk of stroke and death at ages ≥ 70 years ($p \leq 0.001$).

¹⁰ Rivington, J., & Twohig, P. (2020). Quantifying Risk Factors for Atrial Fibrillation: Retrospective Review of a Large Electronic Patient Database. *Journal of atrial fibrillation*, 13(3), 2365

¹¹ Morseth, B., Geelhoed, B., Linneberg, A., et al (2021). Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open heart*, 8(2), e001624. <https://doi.org/10.1136/openhrt-2021-001624>

Pathophysiology

Atrial flutter is an abnormal cardiac rhythm characterised by rapid, regular atrial depolarisations at a characteristic rate of approximately 300 beats/min and a regular ventricular rate of about 150 beats/min.¹²

Atrial flutter is unusual in patients without heart disease. It frequently coexists with atrial fibrillation and may be associated with valvular heart disease, cardiomyopathy, and post-cardiac surgery, pericardial disease including pericardiectomy, prior heart surgery, and acute or chronic pulmonary diseases.

Atrial flutter was previously classified as type I or type II. That terminology is no longer used.

Distinguishing typical from atypical atrial flutter has useful treatment implications, particularly the high success rate of catheter ablation in typical atrial flutter

The designation of "typical" atrial flutter involves a macroreentrant circuit traversing the cavo-tricuspid isthmus (CTI). This isthmus is the region of right atrial tissue between the orifice of the inferior vena cava and the tricuspid valve annulus. If this isthmus is involved, it is called "typical" atrial flutter or CTI-dependent atrial flutter. The circuit is usually a counter clockwise rotation around the tricuspid valve, exhibiting a classic sawtooth appearance in the inferior ECG leads (II, III, aVF). If the circuit is clockwise, it is called "reverse" or "clockwise" typical flutter, exhibiting positive flutter waves in the inferior ECG leads. The clockwise circuit occurs far less frequently than the counter clockwise circuit; rare patients exhibit both circuits at different times. The ECG hallmark of typical atrial flutter is discordance in flutter wave "direction" between the inferior leads and lead V1. In counter clockwise circuits, flutter waves are directly negative in the inferior leads but are positive in lead V1. In clockwise circuits, the opposite is true. These ECG rules are generally less reliable after atrial ablation or surgery.

The CTI is not involved in the underlying mechanism, and it is called "atypical" atrial flutter. This can involve any region of the right or left atria, around areas of scar tissue due to intrinsic heart disease or surgical/ablated scar tissue. Atrial flutter is uncommon in the structurally normal heart.

A variety of underlying conditions can predispose to atrial flutter. Atrial flutter may occur after initiation of an antiarrhythmic drug for the suppression of atrial fibrillation. It may occur in up to 15% of patients treated with flecainide or propafenone, and is also seen in patients treated with dronedarone or amiodarone. Any disorder that can cause atrial fibrillation, including thyrotoxicosis, obesity, obstructive sleep apnoea, sinus node dysfunction, pericarditis, pulmonary disease, and pulmonary embolism. Atrial flutter is a relatively uncommon complication of an acute myocardial infarction and is rarely, if ever, a manifestation of digitalis toxicity

¹² https://www.uptodate.com/contents/overview-of-atrial-flutter?search=atrial%20flutter&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
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Atrial flutter can occur after cardiac surgery, both as a postoperative complication and as a late arrhythmia. The atrial flutter in these patients is re-entrant and may be typical or involve atypical isthmuses between natural barriers, atrial incisions, and scar.

Some patients develop atypical left atrial flutter after atrial fibrillation ablation. These arrhythmias may be due to circuits created by scar from left atrial (LA) ablations, but are often amenable to ablation themselves.

Atrial fibrillation may present as a *paroxysmal* (self-terminating AF within seven days), a *persistent* (lasts greater than seven days), or a *long-standing persistent* AF (continuous AF for 12 months or greater).¹³ The term “permanent AF” is adopted when the patient and doctor agrees to not pursue strategies to restore or maintain sinus rhythm.

The precise mechanisms by which age and other risk factors such as hypertension, coronary artery or valvular heart disease, or heart failure increase the propensity for development of AF are poorly understood. These conditions may affect the triggers of or the substrate for the maintenance of AF.

These mechanisms are complex and involve a dynamic interplay between the triggers and substrate abnormalities. It is likely that short-lived episodes are due to specific triggers, including autonomic perturbations, focal discharges, specific reentry circuits in the pulmonary veins (PVs), and effects of stretch, whereas inflammation, dilatation, fibrosis, repolarisation abnormalities, and conduction disturbances allow for perpetuation of episodes of AF.

AF is initiated by rapid firing (or triggers) from the pulmonary veins. Early in the course of AF the atrium is relatively healthy and as a result sinus rhythm is spontaneously restored. As the substrate remodels further over time, AF no longer terminates spontaneously and becomes persistent. With more extensive remodelling of the atrium, it becomes increasingly difficult to maintain sinus rhythm and the patient and doctor may agree no longer to attempt to maintain sinus rhythm, with the AF thereby being considered permanent.

It has been known for many years that a single focus firing rapidly in the atria can be a trigger for fibrillatory conduction throughout the atria. The most common site of the rapid atrial firing that triggers AF is the pulmonary veins. Catheter ablation of AF depends on the electrical isolation of the PVs from the remainder of the atrium. Electrophysiological evaluation of the PVs has identified myocardial tissue that can lead to repetitive firing or even the presence of episodic reentrant activation in the veins.

Stretch also can increase the propensity for rapid firing from the PVs as a result of stretch sensitive ion channels. The mechanism of atrial stretch may explain the association between AF and mitral regurgitation and various types of heart failure.

¹³ https://www.uptodate.com/contents/mechanisms-of-atrial-fibrillation?search=Atrial%20fibrillation&topicRef=1004&source=see_link
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Atrial tachycardia, atrial flutter, and other supraventricular tachycardias can initiate AF in predisposed patients. The interaction between these arrhythmias and AF is not well understood, but atrial flutter and AF commonly coexist.

In some instances, elimination of atrial flutter will diminish or eliminate episodes of AF. Elimination of the right atrial reentry circuit responsible for typical flutter frequently does not eliminate the predisposition to AF that is predominately a left-atrial problem in a large number of patients. Many studies have demonstrated that patients who undergo catheter ablation of typical atrial flutter have a very high probability of developing AF during the following five years, regardless of whether AF had been observed before development of typical atrial flutter.

In patients with persistent AF, once triggered, the arrhythmia is sustained by one or more abnormalities in the atrial tissue. The trigger(s) may have been treated but not the abnormalities that sustain AF once triggered (initiated).

Paroxysmal AF commonly precedes chronic AF. Even after only a few minutes, AF induces transient changes in atrial electrophysiology that promote its perpetuation. This might occur through a tachycardiomyopathy or by "electrical remodelling" of the atria by AF, leading to a progressive decrease in atrial refractoriness. Electrical remodelling results from the high rate of electrical activation, which stimulates the AF-induced changes in refractoriness.

Atrial remodeling involves structural changes, such as fibrosis, or electrical changes, such as refractory-period dispersion or conduction delay, in the atria that can predispose to the development and maintenance of AF. In some instances, structural and electrical changes occur simultaneously. These processes can facilitate or create electrical reentrant circuits or triggers that can lead to AF. The presence of AF results in remodeling of the atrium over time, which underlies the well-established concept that AF begets AF. The longer a patient has been in continuous AF, the less likely it is to terminate spontaneously, and harder it is to restore and maintain sinus rhythm

The mechanism for electrical remodelling and shortening of the atrial refractory period is not fully known. One possible explanation is ion-channel remodeling, with a decrease in the protein content of the L-type calcium channel

Changes in the anatomy and electrophysiology of the atrial myocardium are important in the pathophysiology of AF.¹⁴ Atrial fibrillation is usually associated with some underlying heart disease. Atrial enlargement, an elevation in atrial pressure, or infiltration or inflammation of the atria are often seen.

Premature atrial complex (PAC; also known as premature- atrial beat/ supraventricular complex or beat) is most important as a trigger in patients with paroxysmal AF who have

¹⁴ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H2
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normal or near-normal hearts. The importance of PAC or other triggers versus an abnormal substrate is less clear in patients with significant structural heart disease.

Hypertensive heart disease and coronary heart disease are the most common underlying disorders in patients with AF in developed countries. Rheumatic heart disease is strongly associated with AF.

Medical conditions associated with an increased risk of the development of atrial fibrillation, are chronic. Historically, it was assumed that the risk of AF decreases after a non-chronic (secondary) condition has been corrected. However, evidence suggests that the risk persists. In the Framingham Heart Study, 1409 individuals with new onset AF were evaluated for their risk of subsequent occurrences based on whether they had a secondary precipitant or not [62]. A precipitant was found in 439 (31%) and included cardiothoracic surgery (30%), infection (23%), non-cardiothoracic surgery (20%) and acute myocardial infarction (18%). Other secondary precipitants included acute alcohol consumption, thyrotoxicosis, acute pericardial disease, acute pulmonary embolism, and other acute pulmonary pathology. While the 15-year cumulative incidence of recurrent AF was significantly lower among those with secondary causes (62 versus 71%), the finding that AF recurred in the majority with secondary causes was unexpected.

The presence of AF in a first-degree relative, particularly a parent, has long been associated with an increase in risk, independent of standard risk factors such as age, sex, hypertension, diabetes, or clinically overt heart disease.

Several haemodynamic changes occur with atrial flutter, many of which follow from the rapid atrial and ventricular rates. These changes include an increase in the mean right and left atrial pressures, a reduction in right and left ventricular end-diastolic pressures, a decrease in systolic blood pressure, and an increase in diastolic pressure. The cardiac index is generally unaltered. The reduction in left ventricular pressure is a result of the rapid heart rate, while the increase in atrial pressure is due to contraction against closed atrioventricular valves.

In recent decades, systemic inflammation as a clinical phenomenon, has been the focus of much research, particularly regarding to its potential association with cardiovascular diseases.¹⁵ There is a potential link between systemic inflammation and cardiac arrhythmogenesis. Systemic inflammation response as measured with inflammation markers (cytokines, etc.) has been investigated in the setting of well-known cardiac arrhythmias including atrial fibrillation and ventricular tachycardia. Based on current literature, clinical utility of these markers might potentially yield important prognostic implications in the setting of certain arrhythmogenic conditions. There is limited data regarding therapeutic implications including clinical benefit of primary anti-inflammatory agents (corticosteroids, colchicine, etc.) in the setting of arrhythmia management. The present review primarily aims to discuss potential triggers and fundamental mechanisms of inflammation-related arrhythmias along with a particular emphasis on clinical implications of systemic inflammation in the setting of cardiac arrhythmogenesis.

¹⁵ Yalta, T., & Yalta, K. (2018). Systemic Inflammation and Arrhythmogenesis: A Review of Mechanistic and Clinical Perspectives. *Angiology*, 69(4), 288–96
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Clinical presentation

The clinical manifestations of AF result from symptoms related to the irregular, often rapid but sometimes slow ventricular rates that result; the haemodynamic consequences of altered cardiac function; the consequences of cardioembolic phenomena; and the impact of AF on cardiovascular function over time. AF is diagnosed by electrocardiogram (ECG), either 12-lead standard ECG or limited lead ambulatory monitor ECG, with findings of lack of organised atrial activity (no P wave), with an irregular ventricular response. The role of screening populations for AF is evolving with the use of wearable monitors and home ECG capabilities.

With irregular, rapid ventricular rates, there is variable cardiac displacement and contraction, resulting in the sensation of palpitations and awareness of the heartbeat, many patients are, for the most part, unaware of the irregular ventricular beating for unknown reasons.

During AF, there is loss of the contribution of atrial systole to overall cardiac output and, with irregular ventricular rates, variable ventricular filling. As a consequence, there is variable stroke volume. The impact on overall cardiac output may result in exercise intolerance, fatigue, weakness, presyncope, or dyspnoea. In patients with underlying cardiac disease, the additional haemodynamic compromise resulting from AF may exacerbate the disease or symptoms. Patients with hypertrophic cardiomyopathy, coronary artery disease, heart failure with depressed or preserved ejection fraction, or amyloidosis are particularly susceptible. In patients with concomitant AV nodal conduction disease, bradycardia during AF may result in presyncope or syncope. Pauses at the time of spontaneous conversion from AF to sinus rhythm, a manifestation of sinus node dysfunction that commonly occurs in patients with AF, may result in presyncope or syncope as well.

With the loss of atrial mechanical contraction, blood stasis may promote thrombosis, which, when embolised, may result in a range of clinical consequences, including ischaemic stroke. Thrombus formation occurs primarily in the left atrial appendage. Recurrent thromboembolism to the brain, even if asymptomatic, may result in debilitating neurological sequelae. This may eventually result in an increased risk of dementia in patients with AF.

In patients with prolonged periods of rapid ventricular rates resulting from AF, there is a risk of developing a tachycardia-induced cardiomyopathy, with associated depressed left ventricular function. Tachycardia-induced myopathy is generally reversible once ventricular rates are controlled. In patients with long-standing persistent AF, the atria, especially the left atrium, tend to be more dilated and contain fibrotic, noncontractile atrial tissue. The haemodynamic consequences of a noncompliant, fibrotic left atrium, including elevated left atrial filling pressures, volume overload, and congestive heart failure, have been described as “stiff left atrial syndrome.”

The clinical manifestations of atrial flutter are similar to atrial fibrillation.¹⁶ Typical complaints with atrial flutter include palpitations, fatigue, lightheadedness, and/or mild shortness of

¹⁶ https://www.uptodate.com/contents/overview-of-atrial-flutter?search=atrial%20flutter&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
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breath. Less common problems include significant dyspnoea, angina, hypotension, anxiety, presyncope, or infrequently, syncope. These symptoms are largely attributable the rapid heart rate

The physical examination may reveal tachycardia, hypotension, diaphoresis, and evidence of congestive heart failure. The diagnosis can usually be made from a 12 lead ECG.

For patients in atrial flutter at the time of the ECG, it generally shows an atrial rate of about 300 beats per minute (range 240 to 340). Typical P waves are absent, and the atrial activity is seen as a saw tooth pattern (F waves) in leads II, III, and aVF. The ECG hallmark of typical atrial flutter is discordance in flutter wave "direction" between the inferior leads and lead V1. In counterclockwise circuits, flutter waves are directly negative in the inferior leads but are positive in lead V1. In clockwise circuits, the opposite is true. These ECG rules are less reliable after atrial ablation or surgery.

There is typically 2:1 conduction across the AV node, particularly in counterclockwise typical atrial flutter; as a result, the ventricular rate is usually one-half the flutter rate in the absence of AV node dysfunction.

The diagnosis of atrial flutter is almost always established by a characteristic ECG pattern which includes the presence of continuous, regular atrial electrical activity. Sawtooth negative flutter waves in leads II, III, and aVF are typical of atrial flutter, especially at a characteristic atrial rate of 300 beats/min with a regular ventricular rate of 150 beats/min in patients not taking atrioventricular nodal blockers.

Serious complications of atrial flutter include myocardial ischaemia, dizziness or syncope, heart failure, stroke, or systemic embolism. Control of the ventricular rate or reversion to normal sinus rhythm will improve or prevent the first three; anticoagulation is frequently used to decrease the risk of embolization

Atrial flutter with a rapid ventricular response is an important cause of tachycardia induced cardiomyopathy. Control of the ventricular rate or reversion to normal sinus rhythm will improve many symptoms in these patients.

Management

four major issues must be considered in the management of atrial flutter and fibrillation:

- Control of the ventricular rate
- Reversion to normal sinus rhythm (NSR)
- Maintenance of normal sinus rhythm.
- Prevention of systemic embolisation

Rate control usually involves the administration of a non-dihydropyridine calcium channel blocker or a beta blocker.

Due to the high rate of recurrence of atrial flutter in patients without a correctable cause, and because of its high success rate with low rate of complications, definitive treatment with radiofrequency catheter ablation is the preferred treatment for most patients. It is less preferable for most patients to consider antiarrhythmic drugs because of potential for side effects. Class IA and IC drugs risk causing rapidly conducted atrial flutter

The rate of recurrence of atrial flutter is difficult to determine because most published data combine atrial flutter with atrial fibrillation. However, the recurrence rate is substantial.

Antiarrhythmic drug mechanisms, for atrial flutter and atrial fibrillation, may suppress triggering premature atrial complex, which may require the use of class IA and IC drugs, beta blockers, and amiodarone, or to prolong the atrial refractory period with class III drugs.

Because of the high rate of recurrence in patients without a correctable cause, and because of its high success rate, radiofrequency catheter ablation is generally preferable to long-term pharmacological therapy in patients with typical atrial flutter. The isthmus between the inferior vena cava and the tricuspid annulus (cavotricuspid isthmus) is an obligatory route for typical flutter, and, as such, is the preferred anatomic target for ablation

Sustained atrial flutter, while much less common than atrial fibrillation, carries an elevated thromboembolic risk. The approach to anticoagulation in patients with atrial flutter is identical to that for atrial fibrillation. It is appropriate to use anticoagulation in atrial flutter as similar to atrial fibrillation.

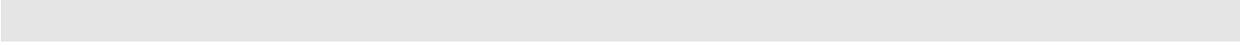
A preventive approach to AF is needed because virtually all treatments such as cardioversion, antiarrhythmic drugs, ablation, and anticoagulation are associated with high cost and carry significant risk.¹⁷

The control of hypertension, ideally with a renin-angiotensin-aldosterone system inhibitor, is effective for preventing primary AF and recurrence. Obstructive sleep apnoea is a common cause of AF, and treating it effectively reduces AF episodes. Alcohol increases the risk of AF in a dose-dependent manner, and abstinence reduces risk of recurrence. Sedentary behaviour and chronic high-intensity endurance exercise are both risk factors for AF; however, moderate physical activity is associated with lower risk of AF. Recently, sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists have been associated with reduced risk of AF. Among overweight/obese patients, weight loss of $\geq 10\%$ is associated with reduced AF risk. Lifestyle changes and risk factor modification are highly effective for preventing AF.

There has been sustained focus on the secondary prevention of coronary heart disease and heart failure; but other than stroke prevention, the evidence base for secondary prevention of

¹⁷ O'Keefe, E. L., Sturgess, J. E., O'Keefe, J. H., Gupta, S., & Lavie, C. J. (2021). Prevention and Treatment of Atrial Fibrillation via Risk Factor Modification. *The American journal of cardiology*, 160, 46–52

atrial fibrillation recurrence, AF, and complications is modest.¹⁸ Although there are multiple observational studies, there are few large, robust, randomised trials providing definitive effective approaches for the secondary prevention of AF. Once AF has been detected, lifestyle changes and novel models of care delivery may contribute to the prevention of AF recurrence, AF progression, and AF-related complications. Although impressive benefits have been documented in small subgroups, cohort studies, and selected randomised trials, the widespread effectiveness of AF secondary prevention strategies remains unknown.



¹⁸ Benjamin, E. J., Al-Khatib, S. M., Desvigne-Nickens, P., et al. (2021). Research Priorities in the Secondary Prevention of Atrial Fibrillation: A National Heart, Lung, and Blood Institute Virtual Workshop Report. *Journal of the American Heart Association*, 10(16), e021566.
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Findings

Valvular heart disease

Current factor

RH and BoP - onset and worsening

having valvular heart disease at the time of the clinical onset of atrial fibrillation or atrial flutter;

"valvular heart disease" means haemodynamically significant stenosis or incompetence of one or more cardiac valves. This definition includes rheumatic heart disease, aortic stenosis or mitral valve prolapse, but excludes isolated valvular calcification.

Summary of important issues

Almost any valvular lesion that causes significant stenosis or regurgitation is associated with the development of AF. Heart valve disease is universally recognised as risk factor for AF in standard clinical literature; and is incorporated into management algorithms of AF in clinical practice. A few case series related to rheumatic heart disease continue to be published.

Summary of previous investigation

Valvular disease is a well-known risk factor for nonsurgical AF. Heart valve disease is universally recognised as risk factor for AF in standard clinical literature; and is incorporated into management algorithms of AF in clinical practice. In the past, atrial fibrillation was frequently a consequence of rheumatic heart disease.

There is relatively little new data describing the condition, although a few case series continue to be published. For example, Ozaydin et al (2010) described AF in patients with rheumatic mitral stenosis, and Turker et al (2009) described AF in patients with mitral valve prolapse.

It is unlikely that all valve diseases equally affect the risk of developing AF. Arrhythmias are described most commonly in symptomatic patients with mitral valve prolapse.

Pathophysiological mechanisms of atrial arrhythmias in relation to valvular heart disease are not established, but it is likely that left atrial enlargement likely contributes to the risk of AF in patients with mitral stenosis. Rheumatic disease affects valves, also chronic inflammation in atria, fibrosis; electrical remodelling of left atrium, creating a propensity to develop atrial fibrillation.

It is likely that atrial fibrillation is related to valvular disease associated with functional heart dysfunction, such as congestive cardiac failure and atrial stretching; although there is some evidence that valvular disease in the absence of cardiac decompensation is associated with AF. There is little data relating atrial fibrillation to valve calcification in the absence of concomitant valve incompetence or stenosis, but Tsagalidis et al (2011) noted the presence of valvular calcifications on cardiac echo was independently associated with presence of AF.

Valvular heart disease is routinely listed among the cardiovascular diseases associated with AF, but there is minimal published data concerning AFL specifically. Some general review studies (e.g. Lee et al 2005), cite valvular heart disease (i.e., rheumatic, mitral, tricuspid) as a recognised cause of atrial flutter, without providing additional data.

In many cases of AF associated with valve disease there may be shared risk factors, rather than valvular disorder being an independent cause. AF often coexists with heart failure, and both AF and CHF share common risk factors, such as valvular heart disease

Several cross-sectional clinical studies describe AF in patients with mitral valve disease, in those who have developed left atrial enlargement or heart failure. The causal relationship of valvular disease with AF likely relates mainly to valvular disease associated with heart failure and atrial stretching. Heart failure or atrial enlargement predict onset of AF in patients with valvular heart disease. There is a moderate amount of evidence that valvular disease in the absence of cardiac decompensation is associated with AF.

Valvular heart disease has been recognised to be a risk factor for AF in population cohorts, such as the Framingham Heart Study (Benjamin et al 1994). Abnormal mitral or aortic valve function was a risk factor for AF in the Cardiovascular Health Study (Furberg et al 1994). Hodgkinson et al noted that an association between valvular disease and AF has also been reported in studies from Spain (Cea-Calvo et al 2007), US (Krahn et al. 1995; Anderson et al. 2004), and the UK (Wanahita et al. 2008). However, there is minimal data concerning the risk of AFL specifically in relation to valvular disease. Some general review studies (e.g. Lee et al 2005), cite valvular heart disease (i.e., rheumatic, mitral, tricuspid) as recognised cause of atrial flutter.

In the past, atrial fibrillation was frequently recognised to be a consequence of rheumatic heart disease. In addition to the valves, rheumatic disease also causes chronic inflammation in the atria, leading to fibrosis. Electrical remodeling of the left atrium has been described, with a propensity to develop atrial fibrillation.

Reviews

Rheumatic heart disease, although now uncommon in developed countries, is associated with a much higher incidence of AF. Paroxysmal AF (PAF) is associated with the same disorders as chronic (permanent) AF.¹⁹

Almost any valvular lesion that causes significant stenosis or regurgitation is associated with the development of AF.²⁰

¹⁹ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

²⁰ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

In a review of 89 patients with mitral valve prolapse (and grade 3 or 4 MR) and 360 with flail leaflets, the rate of development of AF was about 5% per year with both types of lesions [Grigioni et al 2002]. The major independent risk factors were age ≥ 65 years and baseline left atrial dimension ≥ 50 mm.

Rheumatic heart disease is uncommon in developed countries. It is associated with a high prevalence of AF. Rheumatic mitral stenosis (MS) constitutes an important Cause of AF. There is a complex interplay of structural remodelling and electrophysiological abnormalities that promote the onset and perpetuation of AF. It has been hypothesised that initiation and sustenance of AF are due to a combination of both focal firing and reentry, facilitated by LA fibrosis.²¹

Pawar et al (2021) notes that there is a complex interplay of structural remodelling and electrophysiological abnormalities that promote the onset and perpetuation of AF. It has been hypothesised that initiation and sustenance of AF are due to a combination of both focal firing and reentry, facilitated by LA fibrosis.²² Vaziri et al (1994) in the Framingham heart study observed that incidence of AF rises from 3% when the LA diameter is < 40 mm to 54% if the LA diameter is > 40 mm. Kim et al (2015) reported that in patients with rheumatic MS in sinus rhythm, the annual rate of development of AF was 3.5% per year and increased according to LA size and MS severity.

The role of LA fibrosis as a causative agent for atrial fibrillation is not clear. Studies have implicated leucocyte infiltration, effect of decreased LA local conduction velocity and myocytolysis seen on histopathology.²³ Whether LA fibrosis is a cause or an effect of AF is up for debate. It is hypothesised that AF and continuous electrical remodelling in atrial myocytes ultimately can cause cell apoptosis -fibrotic tissue could then replace the dead atrial myocytes, thus explaining the fibrosis. AF alters atrial electrophysiological properties and can promote induction and maintenance ("AF begets AF"). Atrial fibrillation induces electrical remodelling primarily due to a very rapid atrial rate and consequent tachycardia-induced atrial remodelling.

Zhu et al (2015) found that DGE showed moderate agreement with LA pathology in patients with rheumatic persistent AF.²⁴ Lee et al performed MRI in 195 patients with chronic AF and found fibrosis in persistent than in paroxysmal AF patients.²⁵ However, several studies findings are contrary to the above. Bois et al in their study of 149 consecutive patients with AF, found that DGE within LA walls was uncommon and when present, did not correlate with AF type or risk of AF recurrence. Shenthar et al conducted histological studies of left and right atria in rheumatic MS. They found that sinus rhythm was associated with myocyte hypertrophy

²¹ Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

²² Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

²³ Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

²⁴ Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

²⁵ Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

whereas AF was associated with myocytolysis. Interstitial fibrosis was seen in >90% of patients but was independent of the rhythm. In patients without manifest scar, AF could be due to chronically elevated LA pressures and volumes, and hence, following relief of MS by surgery or BMV, can maintain sinus rhythm in the long term.

Cohort studies

Pawar et al (2021) prospectively studied whether left atrial (LA) fibrosis is a determinant of AF in mitral stenosis in patients who underwent balloon mitral valvotomy.²⁶ There were 2 groups: Group A (n = 16), with AF and Group B (n = 27), without AF. Fibrosis was assessed by MRI. Patients underwent cardioversion before MRI. There were 27 females and 16 males, aged 29 ± 6 years. The LA areas in Groups A and B were $54.3 \pm 4.4 \text{ mm}^2$ and $39.4 \pm 2.3 \text{ mm}^2$ ($p < 0.05$) and the LA volume index was $46.2 \pm 2.9 \text{ ml/m}^2$ vs $33 \pm 3 \text{ ml/m}^2$ respectively ($p < 0.0001$). The presence of LA scarring was not statistically different in the two groups.

LA diameter and volume were higher in Group A, as were the mean transmitral gradient and pulmonary artery systolic pressure. However that there was no difference in patients of AF and sinus rhythm, as far as presence of LA fibrosis was concerned. Nonetheless, the amount of LA scarring was significantly higher in Group A.

Mitral valve disease is associated with enlarged LA, elevated atrial pressures, myocardial stretch resulting in slow conduction velocities, increased dispersion of refractoriness and increased automaticity, all of which serve to initiate and perpetuate AF.

Pawar et al (2021) did not find any statistical differences in the presence or absence of atrial scarring and occurrence of AF in RHD. However, the amount of scarring was greater in patients with AF.

International records indicate that only 2.6% of patients with heart transplants have valvular heart disease. **Rose et al (2015)** evaluated the epidemiological and clinical profile of patients with valvular heart disease undergoing heart transplantation.²⁷

Between 1985 and 2013, 569 heart transplants was performed at the authors' institution. 20 patients (13 men, seven women; mean age 39.5 ± 15.2 years) underwent heart transplant due to structural (primary) valvular disease. Analyses were made of the patients' clinical profile, laboratory data, echocardiographic and histopathological data, and mortality and rejection.

Rheumatic fever was the main valve disease aetiology. 18 patients (90%) had a rheumatic aetiology, with 85% having undergone previous valve surgery (45% had one or more operations), and 95% with a normal functioning valve prosthesis at the time of transplantation. **Atrial fibrillation was present in seven patients (35%),** while nine (45%) were in NYHA functional class IV and eight (40%) in class III. The indication for cardiac transplantation was

²⁶ Pawar, P., Mumtaz, Z., Phadke, M., et al. (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis?. *Indian heart journal*, 73(4), 503–55.

²⁷ Rosa, V. E., Lopes, A. S., Accorsi, T. A., et al (2015). Heart Transplant in Patients with Predominantly Rheumatic Valvular Heart Disease. *The Journal of heart valve disease*, 24(5), 629–34. August meeting 2022

refractory heart failure in seven patients (35%) and persistent NYHA class III/IV in ten (50%). The mean left ventricular ejection fraction (LVEF) was 26.6 +/- 7.9%. The one-year mortality was 20%. Histological examination of the recipients' hearts showed five (27.7%) to have reactivated rheumatic myocarditis without prior diagnosis at the time of transplantation. Univariate analysis showed that age, sex, LVEF, rheumatic activity and rejection were not associated with mortality at one year.

rheumatic heart disease was the leading cause of heart transplantation in the cohort, and a significant proportion of these patients had reactivated myocarditis diagnosed in histological analyses.

Cross-sectional studies.

Dhungana & Ghimire (2020) conducted a descriptive cross-sectional study in 260 patients admitted to a tertiary care hospital with a diagnosis of atrial fibrillation from 2019 to 2020.²⁸ Convenient sampling was used. Predisposing conditions for atrial fibrillation, risk factors for stroke, and the use of antithrombotics were obtained based on the pre-structured questionnaires.

The prevalence of valvular atrial fibrillation was 48.0% (n=125), and non-valvular AF 51.9% (n=135). There were 120 cases of mitral stenosis.

Among patients with a non-valvular variant, 102 (75.5%) had a CHA₂DS₂-VASc-score of ≥ 2 who were eligible for oral anticoagulants, 13 (9.6 %) patients received it with a majority having sub-therapeutic international normalized ratio. Among patients with valvular type, only 47 (37.6%) patients were receiving oral anticoagulants and 20 (42.5%) patients achieved therapeutic international normalized ratio. 243 (93.4%) patients had a dilated left atrium (≥ 40 mm), 119 (45.9%) had hypertension, and 27 (10.3%) had diabetes mellitus. It was considered that antithrombotics were underused in AF patients.

Uno et al (2021) investigated geometric differences in mitral valve apparatus between atrial functional mitral regurgitation (A-FMR) and functional mitral regurgitation (FMR) with left ventricular (LV) dysfunction in patients with atrial fibrillation using 3D trans oesophageal echocardiography (TOE).²⁹

135 moderate or greater FMR patients with persistent AF or atrial flutter underwent 3D TOE. Fifty-six patients had A-FMR, defined as preserved LV ejection fraction (LVEF) of $\geq 50\%$ and normal LV wall motion. 79 patients had ventricular FMR (V-FMR), defined as LV dysfunction (LVEF of $< 50\%$) or LV wall motion abnormality. To evaluate mitral leaflet coaptation, the

²⁸ Dhungana, S. P., & Ghimire, R. (2020). Prevalence of Valvular and Non-valvular Atrial Fibrillation and the Application of Antithrombotic Treatment in a Tertiary Care Hospital. *JNMA; journal of the Nepal Medical Association*, 58(231), 851–5

²⁹ Uno, G., Omori, T., Shimada, S., et al. (2021). Differences in mitral valve geometry between atrial and ventricular functional mitral regurgitation in patients with atrial fibrillation: a 3D transoesophageal echocardiography study. *European heart journal. Cardiovascular Imaging*, 22(10), 1106–16.

coapted area was calculated as follows: total leaflet area (TLA) in end-diastole - closed leaflet area in mid-systole.

Although annular area (AA) did not significantly differ between the two groups, TLA was significantly smaller in A-FMR than in V-FMR ($P = 0.005$). TLA/AA, indicating the degree of the leaflet remodelling, was significantly smaller in A-FMR than in V-FMR ($P < 0.001$). A-FMR had significantly smaller posterior mitral leaflet tethering height and angle measured at three anteroposterior planes (lateral, central, and medial) than V-FMR (all $P < 0.001$). However, vena contracta width (VCW) measured on long-axis view on TOE and coapted area, which correlated with VCW ($r = -0.464$, $P < 0.001$), were similar between the two groups.

Mitral leaflet remodelling may be less in A-FMR compared with V-FMR. However, leaflet tethering was smaller in A-FMR than in V-FMR, and may result in a similar degree of mitral leaflet coaptation and mitral regurgitation severity

Kim et al (2015) evaluated the predictors of atrial fibrillation and adverse clinical events in patients with rheumatic mitral stenosis (RMS) in sinus rhythm.³⁰ The patients who diagnosed with RMS in sinus rhythm were evaluated retrospectively between March 2003 and June 2013. The primary outcome was the development of new-onset AF with annual event rates and the secondary outcome was the incidence of clinical events including development of new-onset AF, systemic embolism and all-cause death during follow-up. Among 293 patients,

AF developed in 60 (20.5 %) patients with average annual event rate of 3.5 %/year during mean follow-up period of 68.2 ± 36.6 months (median 72 months). All cause death or systemic embolism occurred in 7.2 % (21 patients; all cause death 9, embolism 12) with an average annual event rate of 2.1 %. In the multivariate analysis, large left atrium (LA) dimension (HR 1.06, 95CI 1.02–1.10; $P = 0.001$) and severe mitral stenosis ($\leq 1.5 \text{ cm}^2$) were independent predictors of AF development (HR 1.97, 95CI 1.06–4.14; $P = 0.032$) after adjustment for confounding factors. Patients with enlarged LA ($\geq 47 \text{ mm}$) had an average annual AF development rate of 6.0 %/year. In patients with RMS in sinus rhythm, annual AF development rate was 3.5 %/year and increased according to LA size and mitral stenosis (MS) severity. Because of very high risk embolism, RMS with enlarged LA dimension need focused follow up for early detection of AF development and clinical events

Summary and conclusions

Rheumatic heart disease, although now uncommon in developed countries, is associated with a much elevated incidence of AF.

Almost any valvular lesion that causes significant stenosis or regurgitation is associated with the development of AF. Heart valve disease is universally recognised as risk factor for AF in standard clinical literature; and is incorporated into management algorithms of AF in clinical practice. In the past, atrial fibrillation was frequently a consequence of rheumatic heart disease. Rheumatic mitral stenosis (MS) constitutes an important Cause of AF (Pawar et al

³⁰ Kim H, Cho G, Kim Y, et al. (2015) Development of atrial fibrillation in patients with rheumatic mitral valve disease in sinus rhythm. *Int J Cardiovasc Imag*; 31(4): 735-42

2021). There is a complex interplay of structural remodelling and electrophysiological abnormalities that promote the onset and perpetuation of AF. It has been hypothesised that initiation and sustenance of AF are due to a combination of both focal firing and reentry, facilitated by LA fibrosis.

Not all valve diseases equally affect the risk of AF/AFL Arrhythmias are described most commonly in symptomatic patients with mitral valve prolapse.

Pathophysiological mechanisms of atrial arrhythmias in relation to valvular heart disease are not established, but it is likely that left atrial enlargement likely contributes to the risk of AF in patients with mitral stenosis.

There is minimal data concerning atrial flutter specifically; some general review studies cite valvular disease (i.e., rheumatic, mitral, tricuspid) as cause of atrial flutter.

Pawar et al (2021) observes that mitral valve disease is associated with enlarged LA, elevated atrial pressures, myocardial stretch resulting in slow conduction velocities, increased dispersion of refractoriness and increased automaticity, all of which serve to initiate and perpetuate AF. Pawar et al (2021) did not find any statistical differences in the presence or absence of atrial scarring and occurrence of AF in RHD. However, the amount of scarring was greater in patients with AF.

There is limited new data describing the condition, although a few case series continue to be published. Rose et al (2015) identified AF in seven of 18 patients (35%) receiving a heart transplant for rheumatic fever,

Dhungana & Ghimire (2020) conducted a descriptive cross-sectional study in 260 patients admitted to a tertiary care hospital with a diagnosis of atrial fibrillation from 2019 to 2020. The prevalence of valvular atrial fibrillation was 48.0% (n=125), and non-valvular AF 51.9% (n=135). There were 120 cases of mitral stenosis.

Kim et al (2015) evaluated the predictors of atrial fibrillation and adverse clinical events in patients with rheumatic mitral stenosis in sinus rhythm. AF developed in 60 (20.5 %) patients with average annual event rate of 3.5%/year during a median follow-up period of 72 months). Large left atrium (LA) dimension (HR 1.06, 95CI 1.02–1.10) and severe mitral stenosis (≤ 1.5 cm²) were independent predictors of AF development (HR 1.97, 95CI 1.06–4.14) after adjustment for confounding factors.

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between valvular heart disease and atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between valvular heart disease and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

A factor for valvular heart disease should be retained in the RH and BoP SoPs.

Rheumatic heart disease should be listed as an example of a cause of valvular heart disease in a note, but it is unnecessary to list the anatomical lesions (eg mitral stenosis), or valve calcification.

Ischaemic heart disease

Current factor

RH and BoP - onset and worsening

having ischaemic heart disease at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

AF is not commonly associated with coronary heart disease (CHD) unless it is complicated by acute myocardial infarction (MI) or heart failure (HF). AF occurs transiently in 6 to 10% of patients with an acute MI, The incidence of new-onset AF after MI is 2.3-37 %, and it is an important predictor of a patient's morbidity, mortality, and prolonged hospitalisation (Wang et al 2015). Various risk factors for new-onset AF after acute coronary syndrome have been identified, including: old age, hypertension, and enlarged left atrium. Experimental and clinical investigations show that new-onset AF is multifactorial, involving atrial ischaemia and atrial stretch, inflammation, autonomic nervous system activity, and hormone activation.

Summary of previous investigation

Myocardial infarction is an important risk factor for atrial fibrillation, but the role of subclinical atherosclerosis is less well studied. There is a well recognised increased risk of AF after coronary artery bypass grafting surgery, but this risk; may relate more to the underlying surgical procedure than to concomitant myocardial ischaemia. There is very little data concerning the risk of AFL specifically, but several analytical studies on post-MI arrhythmias have pooled cases of AF and AFL. Ischaemic heart disease is recognised in the medical literature to be a biological substrate for the development of AFL.

Transient AF is also a well-recognised complication after myocardial infarction (MI). Recent studies indicated that new onset atrial fibrillation following hospitalization for heart failure or myocardial infarction is associated with a greater risk of death and stroke than permanent/persistent AF. Atrial fibrillation often coexists with myocardial infarction; but it is not known whether AF that occurs after an MI is purely a consequence of the infarction process, or whether patients who develop AF have an underlying predisposition to the arrhythmia

Recent cohort studies show that the risk of new-onset AF is highest during the first 2 months after an acute MI (16% event rate) and decreases until month 12 post-MI, after which the risk for new-onset AF/AFL is stable (Jons et al 2011).

No analytical population studies specifically report on AFL as a specific outcome after MI; but much data affirms high incidence of new-onset combined AF+/AFL in patients with a recent MI. For example, a population-based cohort study from Olmstead County, Minnesota indicates that, in the community, AF+/AFL and MI often coexist (Jabre et al 2011). About 1 in 10 subjects who present with MI have a documented history of AF/AFL and 1 out of 4 subjects

without prior AF/AFL will develop AF+/AFL at or after the incident MI and one-half of first-ever documented AF+/AFL cases post MI developed in the first month after MI onset.; the estimated incidence of AF+/AFL after MI of 42 per 1000 person-years is substantially greater than the age- and sex-adjusted incidence of 3.7 per 1000 person-years previously described in the Olmstead County population.

In contrast to the abundant epidemiological data concerning AF after myocardial infarction, there is less data concerning the association between conduction disturbances and atherosclerotic coronary heart disease, which has been investigated in only a few small studies in the early 1970s. De Bono et al (2010) found significantly greater incidence of occult coronary atheroma in asymptomatic patients undergoing ablation for AFL than for AF, suggesting that mechanism underlying atherosclerosis may also contribute substrate that allows AFL to develop. This study demonstrated an increased incidence of occult coronary artery atheroma in unselected, asymptomatic patients with typical right AFL compared with other arrhythmia mechanisms. In contrast, despite the association of AF with acute coronary ischaemia, there was no increased incidence of occult coronary artery disease in patients presenting for ablation of AF compared with patients with supraventricular tachycardia. This suggests that patients with AFL have a particular right atrial substrate that specifically allows the initiation and maintenance of AFL

Myocardial infarction is an important risk factor for atrial fibrillation, but the role of subclinical atherosclerosis is less well studied. There is a well recognised increased risk of AF after coronary artery bypass grafting surgery, but this risk; may relate more to the underlying surgical procedure than to concomitant myocardial ischaemia. There is very little data concerning the risk of AFL specifically, but several analytical studies on post-MI arrhythmias have pooled cases of AF and AFL. Ischaemic heart disease is recognised in the medical literature to be a biological substrate for the development of AFL.

Transient AF is also a well recognised complication after myocardial infarction (MI). Recent studies indicated that new onset atrial fibrillation following hospitalization for heart failure or myocardial infarction is associated with a greater risk of death and stroke than permanent/persistent AF. Atrial fibrillation often coexists with myocardial infarction; but it is not known whether AF that occurs after an MI is purely a consequence of the infarction process, or whether patients who develop AF have an underlying predisposition to the arrhythmia

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than the age- and sex-adjusted incidence of 3.7 per 1000 person-years previously described in the Olmstead County population.

Reviews

Hypertensive heart disease and coronary heart disease (CHD) are the most common underlying chronic disorders in patients with atrial fibrillation in developed countries.³¹ AF is not commonly associated with coronary heart disease unless it is complicated by acute myocardial infarction (MI) or heart failure (HF). AF occurs transiently in 6 to 10% of patients with an acute MI, due to atrial ischaemia or atrial stretching secondary to heart failure. These patients have a worse prognosis that is mostly due to comorbidities such as older age and HF

The incidence of AF is much lower in patients with chronic stable coronary heart disease. In the Coronary Artery Surgical Study (CASS), which included over 18,000 patients with angiographically documented coronary artery disease, AF was present in only 0.6% . These patients probably had chronic AF; the prevalence of PAF may be higher. AF was associated with age over 60 years, male sex, mitral regurgitation, and HF; there was no association between AF and the number of coronary arteries involved.

Atrial fibrillation is one of the most common arrhythmia complications of acute coronary syndrome (ACS).³² The incidence of new-onset AF is 2.3-37 %, and it is an important predictor of a patient's morbidity, mortality, and prolonged hospitalisation. Risk factors for the development of new-onset AF after ACS include: old age, higher Killip class, hypertension and enlarged left atrium. Insights into the pathophysiological mechanisms of new-onset AF have been provided by experimental and clinical investigations and show that new-onset AF is multifactorial, involving atrial ischaemia and atrial stretch, inflammation, autonomic nervous system activity, and hormone activation.

Cohort studies

The incidence of atrial fibrillation in patients with ST segment elevation myocardial infarction (STEMI) varies between 7% and 21%, and most studies were in the thrombolytic era. The frequency of new-onset AF during the primary percutaneous coronary intervention (PCI) period remains unclear. **Arslan et al (2021)** investigated the frequency of new-onset AF and its effects on long-term clinical events in patients undergoing primary PCI.³³

³¹ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

³² Wang, J., Yang, Y. M., & Zhu, J. (2015). Mechanisms of new-onset atrial fibrillation complicating acute coronary syndrome. *Herz*, 40 Suppl 1, 18–26.

³³ Arslan, Ş., Batit, S., Kılıçarslan, O., et al (2021). Incidence of atrial fibrillation and its effects on long-term follow-up outcomes in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Anatolian journal of cardiology*, 25(9), 609–16.

A total of 1,603 patients who were diagnosed with STEMI and underwent primary PCI were included in the study. All patients were monitored for at least 48 hours after the procedure. The primary endpoint of the study was defined as new-onset AF during hospitalization.

The median follow-up period was 44 months. New-onset AF developed in 85 (6.1%) patients. CHADs-VASc > 2, KILLIP > 2, and left atrial diameter were independent predictors for the development of new-onset AF. In the AF (+) group, the all-cause and in-hospital mortality rates were significantly higher. New-onset AF development in patients with STEMI was detected as an independent predictor of in-hospital mortality.

In the era of primary percutaneous transluminal coronary angioplasty, new-onset AF rates were lower than previously published data. new-onset AF was found to be a predictor of in-hospital mortality, and deaths occurred mostly in the early period.

Summary and conclusions

Underlying chronic disorders in patients with atrial fibrillation in developed countries. AF is not commonly associated with CHD unless it is complicated by acute myocardial infarction (MI) or heart failure (HF). AF occurs transiently in 6 to 10% of patients with an acute MI, presumably due to atrial ischaemia or atrial stretching secondary to HF. These patients have a worse prognosis that is mostly due to comorbidities such as older age and HF.

Myocardial infarction is an important risk factor for atrial fibrillation, but the role of subclinical atherosclerosis is less well studied. The incidence of AF is much lower in patients with chronic stable coronary heart disease.

Patients with AF are also at increased risk for coronary artery disease owing to shared aetiologies and risk factors (Al-Makhamreh et al 2021).

Atrial fibrillation is one of the most common arrhythmia complications of acute coronary syndrome (Wang et al 2015). The incidence of new-onset AF is 2.3-37%, and it is an important predictor of a patient's morbidity, mortality, and prolonged hospitalisation. Experimental and clinical investigations show that new-onset AF is multifactorial, involving atrial ischaemia and atrial stretch, inflammation, autonomic nervous system activity, and hormone activation. Various risk factors for the development of new-onset AF after acute coronary syndrome have been identified, including: old age, higher Killip class, relevant history (e.g. hypertension), and enlarged left atrium.

The incidence of atrial fibrillation in patients with ST segment elevation myocardial infarction (STEMI) varies between 7% and 21%, and most studies were in the thrombolytic era (Arslan et al 2021). In the era of primary percutaneous transluminal coronary angioplasty, new-onset AF rates were lower than previously published data.

There is a well recognised increased risk of AF after coronary artery bypass grafting surgery, but this risk may relate more to the underlying surgical procedure than to concomitant myocardial ischaemia.

There is very little data concerning the risk of AFL specifically, but several analytical studies on post-MI arrhythmias have pooled cases of AF and AFL. An abundance of clinical data affirms a high incidence of new-onset AF+/AFL in patients with a recent MI.

It is therefore concluded that in relation to ischaemic heart disease, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between ischaemic heart disease, particularly acute myocardial infarction, and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A factor for ischaemic heart disease should be retained in RH and BoP SoPs.

Myocarditis and pericarditis

Current factor

RH and BoP - onset and worsening

having myocarditis within the one month before the clinical onset of atrial fibrillation or atrial flutter;

having pericarditis within the one month before the clinical onset/ worsening of atrial fibrillation or atrial flutter;

Summary of important issues

Atrial inflammation of the myocardium (acute and chronic) is known to cause conduction disturbances. Cardiac conduction system defects and arrhythmias are recognised to be one form of presentation of myocarditis (Block 2021). Experimental and clinical studies show how atrial inflammation enhances AF and AFL susceptibility.

Cardiac inflammation may stimulate myocardial infarction, symptomatic arrhythmias, heart failure, cardiogenic shock or sudden cardiac death. Myocarditis can be idiopathic, or related to infectious and immunological causes.

Cardiac arrhythmias have been reported to occur during the acute phase of pericarditis. Although data relevant to their nature and incidence are sparse, AF appears to be the most common sustained arrhythmia in patients with acute pericarditis (Imazio et al 2012). In published series, the incidence of AF in acute pericarditis ranges between 6% and 25%.

Summary of previous investigation

Atrial inflammation of the myocardium (acute and chronic) is known to cause conduction disturbances. Several experimental and clinical studies document how cardiac inflammation enhances the AF and AFL susceptibility of atrial tissue.

Chronic inflammation in patients can cause atrial structural remodelling, and promote fibrillatory mechanisms (Maesen et al 2012). AF is identified in cases of chronic pericarditis. For example, AF is common in patients with tuberculous pericarditis (Syed et al 2012); with spontaneous resolution of AF amongst survivors by the after completion of TB treatment suggesting that this is an inflammatory model of AF which resolves on specific treatment of the underlying inflammatory disease. AF has also been described in patients with giant cell myocarditis (GCM), in which the arrhythmia accompanies histological changes in the atria such as giant cell and lymphocytic infiltrates, lymphocytic myocarditis-like foci, cardiomyocyte necrosis, and cardiomyocyte hypertrophy.

There are inconsistent findings in the medical literature concerning the association between pre-operative inflammatory markers and the risk of post-operative AF (POAF). It has been hypothesised that induction of inflammation during surgery, such as local inflammation caused by a surgical incision, contributes to the occurrence of POAF, and likely contributes more to the development of arrhythmia than a pre-existing inflammation process. A transient sterile pericarditis, part of the healing process, might contribute to occurrence of post-operative AF (Maesen et al 2012). Anti-inflammatory drugs have been shown to be effective in lowering AF incidence after CABG and/or valve surgery.

Myocarditis is not currently defined in the SoP for atrial fibrillation. It likely overlaps to some degree with the broadly defined cardiomyopathy factor, which includes such entities as infection-related myocarditis.

It is recognised in review studies that AF may be related to acute or chronic pericarditis, but there is little medical literature specifically relating to this. AF is uncommon in acute pericarditis, or in the absence of concomitant structural heart disease, but some clinical descriptions of AF in acute pericarditis have been reported.

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Reviews

Myocarditis and pericarditis are non-ischaemic inflammatory diseases of the myocardium and pericardium.³⁴ The clinical presentation of these conditions is variable and may be preceded by coryzal symptoms or non-specific features of general malaise, fatigue or diarrhoea. Cardiac inflammation may stimulate myocardial infarction, symptomatic arrhythmias, heart failure, cardiogenic shock or sudden cardiac death. Although the aetiology of myocarditis and pericarditis is heterogeneous, infection is the most common cause,¹ with viral pathogens the most commonly implicated in the developed world.

The exact mechanism of arrhythmias in acute myocarditis is unknown. However, myocardial cell death with resulting fibrosis, autoimmune-mediated cell damage, proarrhythmic effects of cytokines, and unmasking of pre-existing cardiomyopathy have been postulated as possible mechanisms. abnormal cardiac rhythm have long been implicated in the pathogenesis of sudden cardiac death in varieties of structural heart diseases (Adegbala et al 2019).³⁵

Myocarditis is a cardiac disease which is heterogeneous in aetiology and pathophysiology. Most commonly myocarditis is caused by viral infection, resulting in a distinct lymphocytic infiltration of the myocardium (lymphocytic myocarditis).³⁶ A non-infectious form of myocarditis is catecholamine-induced myocarditis, which is found in 62% of patients diagnosed with stress-induced cardiomyopathy. Although the mechanisms underlying catecholamine-induced myocarditis are poorly understood, an increased infiltration of different inflammatory cells was described in human ventricular heart tissue. both the diagnosis and research into myocarditis are focused on the ventricles of the heart (ventricular myocarditis), whereas very little is known about how myocarditis affects the atria.

³⁴ Buckley, B., Harrison, S. L., Fazio-Eynullayeva, E., et al. (2021). Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *European journal of clinical investigation*, 51(11), e13679.

³⁵ Adegbala, O., Olagoke, O., Akintoye, E., et al. (2019). Predictors, Burden, and the Impact of Arrhythmia on Patients Admitted for Acute Myocarditis. *The American journal of cardiology*, 123(1), 139–44.

³⁶ Begieneman, M. P., Emmens, R. W., Rijvers, L., et al (2016). Ventricular myocarditis coincides with atrial myocarditis in patients. *Cardiovascular Pathology*, 25(2), 141–8.

Myocarditis is a known precursor of atrial fibrillation and AF is found in 14% of patients with suspected myocarditis.³⁷ There is strong evidence linking both systemic and local inflammation to the initiation and perpetuation of AF in general. Increased infiltration of macrophages and lymphocytes has been described in the left and right atria of patients with symptomatic AF, compared to control patients. These studies suggest that (cardiac) inflammation may predispose patients into developing AF. However, it is not known whether ventricular myocarditis coincides with infiltration of inflammatory cells in the atria (referred to as atrial myocarditis) in myocarditis patients. The presence of atrial myocarditis in myocarditis patients may predispose these patients to the development of AF.

Acute myocarditis represents a challenging diagnosis as there is no pathognomonic clinical presentation. In patients with myocarditis, electrocardiogram can display a variety of non-specific abnormalities and is widely used as an initial screening tool for myocarditis.

Butta et al (2020) reviewed all ECG alterations during acute myocarditis evaluating prevalence, physiopathology, correlation with clinical presentation patterns, role in differential diagnosis, and prognostic yield.³⁸

Both supraventricular and ventricular arrhythmias can occur in patients with inflammatory heart disease (Kindermann et al. 2012). The most common ECG abnormality in myocarditis is sinus tachycardia associated with nonspecific ST/T-wave changes (Punja et al. 2010). Sinus tachycardia mainly reflects the degree of systemic inflammation and/or of haemodynamic impairment and is common in FM.

Beyond sinus tachycardia, other supraventricular tachycardias are described in acute myocarditis, including atrial fibrillation and atrial flutter. These arrhythmias are usually found in patients with more severe clinical courses or with underlying cardiac disease and/or in specific conditions such as Chagas disease (Rojas et al. 2018). They typically develop in patients with underlying structural cardiac disease and/or haemodynamic impairment. AF is an almost universal finding in giant cell myocarditis with isolated atrial involvement due to massive atrial dilatation, atrial wall thickening, and oedema (Larsen et al. 2013).

Cardiac complications such as chest pain, arrhythmias, pulmonary oedema and refractory shock have been reported in patients with severe leptospirosis.³⁹ However, the frequency and extent of cardiac involvement in leptospirosis, are under-reported and poorly understood. Multiple factors may contribute to clinical manifestations that suggest cardiac involvement, causing diagnostic confusion.

A variety of ECG changes occur in leptospirosis, with atrial fibrillation, atrioventricular conduction blocks and non-specific ventricular repolarisation abnormalities being the most

³⁷ Begieneman, M. P., Emmens, R. W., Rijvers, L., et al (2016). Ventricular myocarditis coincides with atrial myocarditis in patients. *Cardiovascular Pathology*, 25(2), 141–8.

³⁸ Buttà, C., Zappia, L., Lattera, G., et al. (2020). Diagnostic and prognostic role of electrocardiogram in acute myocarditis: A comprehensive review. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc.*, 25(3), e12726.

³⁹ Navinan, M. R., & Rajapakse, S. (2012). Cardiac involvement in leptospirosis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 106(9), 515–20.

common. Electrolyte abnormalities are likely to contribute to electrocardiographic changes; direct effects on Na(+)-K(+)-Cl(-) transporters in the renal tubules have been postulated. Echocardiographic evidence of myocardial dysfunction has not been adequately demonstrated. The diagnostic value of cardiac biomarkers is unknown. Histopathological changes in the myocardium have been clearly shown, with myocardial inflammation and vasculitis present in post-mortem studies. However the pathophysiology of cardiac involvement in leptospirosis is poorly understood. Cardiac involvement, demonstrated electrocardiographically or clinically, tends to predict poor outcome.

AF related to myocarditis has also been recently described in patients with Covid-19. Severe COVID-19 has been implicated in multi-organ involvement, with several observational case series showing a significant proportion of cardiac involvement among hospitalised patients.⁴⁰ Cardiac injury seems to be significantly correlated with increased in-hospital mortality in COVID-19 patients. COVID-19 has a wide spectrum of cardiovascular sequelae, including acute-onset heart failure, arrhythmias, acute coronary syndrome, myocarditis and cardiac arrest. A growing body of evidence has described cardiac involvement in COVID-19, including myocarditis, pericarditis, or more generally, increased biomarkers of cardiac injury, all of which may associate with poor prognosis.

The cardiac conduction system is more frequently involved in Lyme carditis; however, the myocardium and pericardium can also be involved. Cardiac involvement (Lyme carditis) occurs in 1% of untreated patients in the early disseminated phase of infection.⁴¹ Although the exact mechanism of cardiac tissue injury is not established in Lyme carditis, in addition to direct myocardial invasion by *Borrelia burgdorferi*, Typically, patients experience palpitations, chest pain, dyspnoea and syncope. A small number of cases in young males have been described with atrial fibrillation, all of which had a favourable outcome after completion of antibiotic treatment.

90% of Lyme carditis presents as high-degree atrioventricular block (AVB), and 10% with myocarditis, pancarditis or other types of arrhythmias and conduction disorders. Typically, cardiac involvement leads to varying severities of first-degree AVB. Varying degrees of AVB minutes to hours apart are also unusual such as in the patient who presented with atrial fibrillation, second-degree Mobitz I heart block and profound first-degree heart block.

Some studies emphasise the influence of immunological and autoimmunological processes. Cardiac manifestations can occur after a median of 21 days from the onset of exposure.

As outlined by **Imazio et al (2015)**, cardiac arrhythmias have been reported to occur during the acute phase of pericarditis.⁴² The in-hospital mortality rate of acute pericarditis is estimated at 1.1% and prognosis is determined by the underlying cause. Although arrhythmias

⁴⁰ Buckley, B., Harrison, S. L., Fazio-Eynullayeva, E., et al. (2021). Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *European journal of clinical investigation*, 51(11), e13679.

⁴¹ Zainal, A., Hanafi, A., Nadkarni, N., et al. (2019). Lyme carditis presenting as atrial fibrillation. *BMJ case reports*, 12(4), e228975.

⁴² Imazio, M., Lazaros, G., Picardi, E., et al. (2015). Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Heart (British Cardiac Society)*, 101(18), 1463–7.

are not rare in the setting of acute pericarditis, limited data is available on their incidence and prognostic impact both, in the short and long-term. atrial fibrillation is the most frequently reported rhythm disturbance in the context of acute pericarditis.

Syed et al (2012) reported data on the prevalence, correlates and natural history of AF in patients with tuberculous pericarditis were reported from five hospitals in Cape Town (South Africa). AF was common (25% of cases at presentation) with most cases resolving in the first 2 weeks and no additional cases after 6 months of follow-up. LV dysfunction was associated with an increased risk of AF.

A potential link between AF/f and acute pericarditis may be due to the vicinity of sinus node to the atrial surface. sinus node involvement in the inflammatory process of pericarditis may account for AF/f onset, and epicardial inflammation may extend to the sinus node. This was supported by a necropsy study on 38 patients with pericarditis, where sinus node involvement has been confirmed in all cases. (James 1962). Available data in this setting are not unanimous since sinus node was not clearly affected in another post-mortem investigation and the relationship between sinus node involvement and AF/f is not well established.

Mayosi (2015) observes that there are few prospective clinical studies of the frequency and outcome of atrial fibrillation in the context of pericarditis.⁴³ Early reports in the literature showed that atrial fibrillation was uncommon in acute pericarditis ($\leq 7\%$ of cases) and was associated with underlying structural heart disease of the myocardium, valves or coronary arteries. It is known that PQ-segment depression. A marker of atrial pericarditis, is associated with the occurrence of atrial fibrillation in acute Q-wave myocardial infarction. A small prospective study of subacute pericarditis shows that atrial fibrillation may be common in tuberculous pericardial effusion ($\sim 25\%$ of cases) associated with left ventricular dysfunction and high N-terminal pro-brain natriuretic peptide levels (Syed et al 2012). Pericarditis-associated atrial fibrillation is a transient condition that remits spontaneously within 6 weeks of treatment with ant tuberculosis medication in patients tuberculous pericardial effusion.

In contrast, chronic constrictive tuberculous pericarditis is associated with persistent atrial fibrillation in 8% of cases, and usually occurs with a calcified pericardium. **Tubeeckx et al (2021)** presented a model of sterile pericarditis-induced atrial myopathy in Aachener minipigs.⁴⁴ Sterile pericarditis was induced by spraying sterile talcum and leaving a layer of sterile gauze over the atrial epicardial surface. This led to inflammation and fibrosis, two crucial components of the pathophysiology of atrial myopathy, making the atria susceptible to the induction of AF. Two pacemaker electrodes were positioned epicardially on each atrium and connected to two pacemakers from different manufacturers. This strategy allowed for repeated non-invasive atrial programmed stimulation to determine the inducibility of AF at specified time points after surgery. Different protocols to test AF inducibility were used. The advantages of this model are its clinical relevance, with AF inducibility and the rapid induction of inflammation and fibrosis-both present in atrial myopathy-and its reproducibility. The model will be useful in the development of novel therapies targeting atrial myopathy and AF.

⁴³ Mayosi BM. (2015), Pericarditis-associated atrial fibrillation Heart.;101(18):1439-40

⁴⁴ Tubeeckx, M., Laga, S., Jacobs, C., et al (2021). Sterile Pericarditis in Aachener Minipigs As a Model for Atrial Myopathy and Atrial Fibrillation. Journal of visualized experiments : JoVE, (175), August meeting 2022

Cohort studies

Immune checkpoint inhibitors (ICIs) can cause life-threatening cardiovascular adverse events (CVAEs) that may not be attributed to therapy. The outcomes of clinical trials may underestimate treatment-related adverse events due to restrictive eligibility, limited sample size, and failure to anticipate selected toxicities. **Jain et al (2021)** evaluated the incidence and clinical determinants of CVAEs in real-world population on ICI therapy.⁴⁵

Among 2 687 301 patients diagnosed with cancer from 2011 to 2018, 16 574 received ICIs for any cancer. Patients in ICI and non-ICI cohorts were matched in a 1 : 1 ratio according to age, sex, National Cancer Institute comorbidity score, and primary cancer. The non-ICI cohort was stratified into patients who received chemotherapy (N = 2875) or targeted agents (N = 4611). All CVAEs, non-cardiac immune-related adverse events occurring after treatment initiation, baseline comorbidities, and treatment details were identified and analysed using diagnosis and billing codes.

Median age was 61 and 65 years in the ICI and non-ICI cohorts, respectively (P < 0.001). ICI patients were predominantly male (P < 0.001). Lung cancer (43.1%), melanoma (30.4%), and renal cell carcinoma (9.9%) were the most common cancer types. CVAE diagnoses in the dataset by incidence proportion (ICI cohort) were stroke (4.6%), heart failure (3.5%), **atrial fibrillation (2.1%)**, conduction disorders (1.5%), myocardial infarction (0.9%), myocarditis (0.05%), vasculitis (0.05%), and pericarditis (0.2%).

Buckley et al (2021) investigated the prevalence of new-onset myocarditis/pericarditis and associated adverse cardiovascular events in patients with COVID-19.⁴⁶

A retrospective cohort study was conducted using electronic medical records from a global federated health research network. Patients were included based on a diagnosis of COVID-19 and new-onset myocarditis or pericarditis. Patients with COVID-19 and myocarditis/pericarditis were 1:1 propensity score matched for age, sex, race and comorbidities to patients with COVID-19 but without myocarditis/pericarditis. The outcomes of interest were 6-month all-cause mortality, hospitalisation, cardiac arrest, incident heart failure, incident atrial fibrillation and acute myocardial infarction, comparing patients with and without myocarditis/pericarditis.

Of 718,365 patients with COVID-19, 35,820 (5.0%) developed new-onset myocarditis and 10,706 (1.5%) developed new-onset pericarditis. Six-month all-cause mortality was 3.9% (n = 702) in patients with myocarditis and 2.9% (n = 523) in matched controls (p < .0001), odds ratio 1.36 (95% confidence interval (CI): 1.21-1.53). Six-month all-cause mortality was 15.5% (n = 816) for pericarditis and 6.7% (n = 356) in matched controls (p < .0001), odds ratio 2.55 (95% CI: 2.24-2.91).

⁴⁵ Jain, P., Gutierrez Bugarin, J., Guha, A., et al. (2021). Cardiovascular adverse events are associated with usage of immune checkpoint inhibitors in real-world clinical data across the United States. *ESMO open*, 6(5), 100252

⁴⁶ Buckley, B., Harrison, S. L., Fazio-Eynullayeva, E., et al. (2021). Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *European journal of clinical investigation*, 51(11), e13679.

Following PSM, six-month all-cause mortality was 3.9% ($n = 702$) in patients with COVID-19 who presented with myocarditis and 2.9% ($n = 523$) in matched controls without myocarditis (OR 1.36, 95CI 1.21–1.53). Associated odds of rehospitalisation (OR 1.90, 95CI 1.80–2.01) and acute myocardial infarction (OR 1.37, 95CI 1.17–1.61) were higher in the myocarditis cohort than controls. Associated odds of cardiac arrest, incident heart failure and incident AF (OR 0.95, 95CI 0.74- 1.21) were not significantly different between the myocarditis cohort and controls.

TABLE 2 SIX-MONTH ODDS RATIOS (95CI) FOR ADVERSE EVENTS AND CARDIOVASCULAR SEQUALAE IN PATIENTS WITH COVID-19– ASSOCIATED MYOCARDITIS, FOLLOWING PROPENSITY SCORE MATCHING

Cohort	Sample size	Atrial fibrillation
Total	35,820	0.95 (0.74, 1.21)
Female	20,194	0.83 (0.56, 1.22)
Male	15,592	0.91 (0.66, 1.24)
Age <45	20,774	0.77 (0.37, 1.58)
Age 45–70	14,444	0.85 (0.59, 1.20)
Age >70	5,556	1.02 (0.70, 1.48)
Not hospitalised following COVID–19 diagnosis	27,438	0.57 (0.40, 0.80)
Hospital inpatient following COVID–19 diagnosis	6,452	1.48 (0.94, 2.34)
Received critical care following COVID–19 diagnosis	1,898	1.42 (0.62, 2.53)

Buckley et al (2021), Table 1

6-month all-cause mortality was 15.5% ($n = 816$) in patients with COVID-19 who presented with new-onset pericarditis and 6.7% ($n = 356$) in the matched controls without pericarditis (OR 2.55, 95CI 2.24–2.91). Associated odds of rehospitalisation, cardiac arrest, incident heart failure, incident AF (OR 2.50, 95CI 1.90-3.20) and acute myocardial infarction were also significantly higher in the pericarditis cohort compared with controls. Mortality was higher among all subgroups.

TABLE 3 SIX-MONTH ODDS RATIOS (95CI) FOR ADVERSE EVENTS AND CARDIOVASCULAR SEQUALAE IN PATIENTS WITH COVID-19– ASSOCIATED PERICARDITIS, FOLLOWING PROPENSITY SCORE MATCHING

Cohort	Sample size	Atrial fibrillation
Total	10,706	2.50 (1.90, 3.20)
Female	5,282	2.17, (1.50, 3.17)
Male	5,268	2.02 (1.45, 2.82)
Age <45	2,210	1.57 (0.70, 5.00)
Age 45–70	5,432	2.78 (1.93, 3.99)
Age >70	3,420	1.95 (1.33, 2.86)
Not hospitalised following COVID–19 diagnosis	5,986	2.31 (1.58, 3.38)
Hospital inpatient following COVID–19 diagnosis	4,180	2.07 (1.42, 3.01)
Received critical care following COVID–19 diagnosis	1,746	2.16 (1.23, 3.79)

Receiving critical care was associated with significantly higher odds of mortality for patients with myocarditis and pericarditis. Patients with pericarditis seemed to associate with more new-onset cardiovascular sequelae than those with myocarditis. This finding was consistent when looking at pre-COVID-19 data with pneumonia patients.

Although new-onset myocarditis was more prevalent (5.0%) than pericarditis (1.5%) in patients with COVID-19, the latter seems to be associated with more substantial adverse events and cardiovascular sequelae.

A significant proportion of patients with acute myocarditis experience sudden cardiac death presumably due to cardiac arrhythmia. **Adegbala et al (2019)** explored the burden, the predictors of arrhythmia in acute myocarditis and the association between arrhythmias and adverse in-hospital outcomes.⁴⁷ After evaluating the frequency of various tachyarrhythmias and bradyarrhythmia in myocarditis population, a logistic model was used to determine the independent predictors of arrhythmias in myocarditis and a 1:1 propensity-matched analysis to examine the impact of arrhythmias.

Overall, cardiac arrhythmias were identified in 33.71% of hospitalised myocarditis cases. The most common form of arrhythmias was atrial fibrillation (26.90%) followed by ventricular tachycardia (22.34%). This is similar to the result of previous case series where arrhythmias was reported in up to 40% of patients with myocarditis, some of which may manifest as sudden cardiac death.

⁴⁷ Adegbala, O., Olagoke, O., Akintoye, E., et al. (2019). Predictors, Burden, and the Impact of Arrhythmia on Patients Admitted for Acute Myocarditis. *The American journal of cardiology*, 123(1), 139–44.

There were increased odds of in-hospital mortality, cardiogenic shock, use of mechanical circulatory support, pacemaker implantation, and nonroutine hospital discharges in the arrhythmia cohorts. Length of stay and cost of hospitalization were also significantly higher. A significant proportion of patients with myocarditis have cardiac arrhythmias.

Data on the incidence of new onset atrial fibrillation and flutter (AF/f) in patients with acute pericarditis are limited. **Imazio et al. (2015)** determined the incidence and prognostic significance of AF/f in this setting.⁴⁸

The authors prospectively evaluated the incidence and prognostic role of AF/flutter (AF/f) in the specific context of acute pericarditis in European countries with a low prevalence of tuberculosis, with particular emphasis on the appearance of AF/f recurrences and embolic events during follow-up. Between January 2006 and June 2014, consecutive new cases of acute pericarditis were included in two urban referral centres for pericardial diseases. All new cases of AF/f defined as episodes lasting ≥ 30 s were recorded. Events considered during follow-up consisted of AF/f and pericarditis recurrence, cardiac tamponade, pericardial constriction and death.

822 consecutive new cases of acute pericarditis (mean age 53 ± 15 years, 444 men) were analysed. 32 patients had AF (91.4%) and three patients had atrial flutter (8.6%). All patients were symptomatic.

Patients with AF/f were significantly older ($p=0.017$) and presented more frequently with pericardial effusion ($p<0.001$). Arrhythmias developed within 24 h of pericarditis onset in 91.4% of cases, lasted >24 h in 25.7% and spontaneously converted in 74.3% of patients. Underlying structural heart disease was present in 17% of AF/f cases. In a 30-month follow-up, patients with history of AF/f at the initial episode had a higher rate of arrhythmia occurrence (34.3% vs 0.9%, $p<0.001$), mostly (75%) within 3 months. No other differences were detected in additional clinical events including haemorrhagic complications in patients receiving oral anticoagulation.

The occurrence of AF/f in acute pericarditis identifies a predisposed population to AF/f with a high recurrence risk (about 35%). In these patients, pericarditis may act as an arrhythmic trigger and oral anticoagulation should be seriously considered according to guidelines.

In this prospective cohort study, the incidence of AF/f in patients with a first episode of acute pericarditis and the long-term outcome was assessed. The incidence to AF/f during a first episode of acute pericarditis was 4.3%, with AF being the most common arrhythmia. Patients with AF/f were older, and more commonly had a presentation with pericardial effusion. There was a trend for higher temperature at presentation in such patients. AF/f was recorded within 24 h from symptoms onset in the great majority ($>90\%$); it was transient in all cases and converted spontaneously to sinus rhythm within 24 h in $\sim 75\%$ of cases. No differences in outcomes (first or additional recurrences of AF/f) were recorded between those with

⁴⁸ Imazio, M., Lazaros, G., Picardi, E., et al. (2015). Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Heart (British Cardiac Society)*, 101(18), 1463–7.
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spontaneous or pharmacological/electrical conversion. Structural heart disease was present in ~17% of cases and a history of relevant arrhythmic events in the past was uncommon.

Atrial fibrillation resolved within 24 h in 74.3% of cases, but recurred in one-third of patients in association with recurrent pericarditis over a 30-month follow-up period (75% within 3 months). The independent predictors of atrial fibrillation were older age and the presence of pericardial effusion. Underlying structural heart disease was present in only 17% of cases with pericarditis-associated atrial fibrillation. Spontaneous conversion to sinus rhythm was observed in 26 patients (74.3%), whereas pharmacological conversion was performed in 8 patients (22.8%) and electrical in 1 (2.8%). There was a significantly greater frequency of recurrent atrial fibrillation in patients with pericarditis-associated atrial fibrillation or flutter than those without after a mean follow-up period of 30 months (34.3% vs 8.9%, $p < 0.001$). There were no cases of TIA, stroke, peripheral embolism or death during follow-up.

Although data relevant to their nature and incidence are sparse, AF is the most common sustained rhythm disturbance in patients with acute pericarditis (Imazio et al 2012). In published series, the incidence of AF in acute pericarditis ranges between 6% and 25%. In Imazio et al's study, the incidence of AF/f was lower than previously reported, possibly due to different definitions of AF.

As noted in a commentary by **Mayosi (2015)**, this study dispels the long-held teaching that 'pericarditis is not a cause of arrhythmias' which suggested that pericarditis-associated atrial fibrillation was almost always associated with structural heart disease.⁴⁹ Over 80% of patients in this study had no evidence of structural heart disease. Studies of animal models support the direct causal link between pericarditis and atrial fibrillation. In a canine sterile pericarditis model, vulnerability to the development of atrial fibrillation is substantially increased through the production of proinflammatory cytokines. Imazio et al showed that pericarditis-associated atrial fibrillation may recur in up to one-third of cases, concomitantly with recurrent pericarditis. The temporal relationship of atrial fibrillation with recurrent pericarditis in a cohort that was largely free of structural heart disease underlines the role of inflammation as a trigger of atrial fibrillation. The correlation between pericarditis-associated atrial fibrillation with factors that are generally associated with rising incidence of atrial fibrillation such as increasing age, hypertension and an enlarged left atrium suggests that acute inflammation may serve as a cofactor in the initiation of atrial fibrillation in people who are at high risk for cardiovascular disease.

Cross-sectional studies

In many cases, atrial fibrillation is associated with a history of cardiac inflammation. One of the potential pathogens responsible for atrial inflammation might be *Borrelia burgdorferi* - the pathogen involved in Lyme carditis. Exposure to *Borrelia* spp. infection is associated with an increased risk of AF. Whether the early treatment of Lyme disease lowers the risk of AF development remains uncertain

⁴⁹ Mayosi BM. (2015), Pericarditis-associated atrial fibrillation *Heart*.;101(18):1439-40
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Szymanska et al. (2020) assessed whether the serological history of *Borrelia burgdorferi* infection was associated with the risk of AF.⁵⁰ The study included 113 AF patients and 109 patients in sinus rhythm. All patients underwent a clinical evaluation, echocardiography and had their blood taken for the assessment of anti-Borrelia IgG antibodies.

Patients with AF compared with the non-AF group had more often serological signs of Borrelia infection (34.5% vs 6.4%; $p < 0.0001$). The multivariate analysis showed that positive results for anti-*Borrelia* IgG antibodies were a strong independent predictor of AF (OR 8.21; 95CI 3.08-21.88; $p < 0.0001$).

Clinical series

Atrial inflammation has been suggested to play an important role in the pathophysiology of AF. However, little is known about the occurrence of atrial inflammation in myocarditis patients. **Begieneman et al (2016)** analysed inflammatory cell numbers in the atria of myocarditis patients without symptomatic AF.⁵¹

Cardiac tissue was obtained post-mortem from lymphocytic myocarditis patients (n=6), catecholamine-induced myocarditis patients (n=5), and control patients without pathological evidence of heart disease (n=5). Tissue sections of left and right ventricle and left and right atrium were stained for myeloperoxidase (neutrophilic granulocytes), CD45 (lymphocytes), and CD68 (macrophages). These cells were subsequently quantified in atrial and ventricular myocardium and atrial adipose tissue.

In lymphocytic myocarditis patients, a significant increase was observed for lymphocytes in the left atrial adipose tissue. In catecholamine-induced myocarditis patients, significant increases were found in the atria for all three inflammatory cell types. Infiltrating inflammatory cell numbers in the atrial myocardium correlated positively with those in the ventricles, especially in catecholamine-induced myocarditis patients.

The study aimed to quantify the infiltration of inflammatory cells in the atria of patients diagnosed with myocarditis based on the ventricles. In lymphocytic myocarditis patients, a significant increase of lymphocytes in the left atrial adipose tissue only was observed. Next to these patients, the atrial myocarditis in catecholamine-induced myocarditis patients appeared more extensively. In the myocardium and adipose tissue of the right atrium, a significant increase was observed for neutrophilic granulocytes, for lymphocytes in the left atrial adipose tissue, and for macrophages in the myocardium of both atria. The numbers of infiltrating inflammatory cells in the atrial myocardium correlated with those in the ventricles, especially in catecholamine-induced myocarditis patients.

To a varying extent, atrial myocarditis occurs concurrently with ventricular myocarditis in patients diagnosed with myocarditis of different aetiology. This provides a substrate that

⁵⁰ Szymanska, A., Platek, A. E., Dluzniewski, M., et al. (2020). History of Lyme Disease as a Predictor of Atrial Fibrillation. *The American journal of cardiology*, 125(11), 1651–4

⁵¹ Begieneman, M. P., Emmens, R. W., Rijvers, L., et al (2016). Ventricular myocarditis coincides with atrial myocarditis in patients. *Cardiovascular Pathology*, 25(2), 141–8.

potentially predisposes myocarditis patients to the development of AF and subsequent complications such as sudden cardiac death and heart failure.

Myocarditis is commonly diagnosed via (immuno) histological analysis of endomyocardial biopsies obtained from the ventricles. Atrial myocarditis has been observed before in atrial tissue obtained post-mortem from young patients after sudden death and in atrial tissue obtained from living patients with idiopathic enlargement of bilateral atria, with transient sinoatrial disease and with atrial giant cell myocarditis. In all these cases, atrial myocarditis occurred in the absence of ventricular myocarditis. Begieneman et al demonstrated for the first time that atrial myocarditis also occurs in patients diagnosed with ventricular myocarditis.

Atrial myocarditis coincided with ventricular myocarditis of different aetiology (lymphocytic myocarditis), which is mostly caused by viral infection and resulting autoimmunity and catecholamine-induced myocarditis. In the study, atrial myocarditis was most pronounced in catecholamine-induced myocarditis patients, although the extent of the inflammatory infiltrate did not differ significantly between both myocarditis patient groups. Local catecholamine overload is an important cause of ventricular catecholamine-induced myocarditis

Elevated blood pressure is expected, as high levels of catecholamines can result in hypertension. This could result in pressure overload and stretching of cardiomyocytes in the heart, including the atria. Stretching of atrial cardiomyocytes has been shown to promote inflammation. Alternatively, viral infection of the atria could directly cause atrial myocarditis in lymphocytic myocarditis patients. In a mouse model of coxsackievirus B3- induced myocarditis, atrial myocarditis was induced and coincided with high virus titres in the atria. However, viral infection of the atria coinciding with viral infection of the ventricles in humans has not been reported

The clinical relevance of the atrial myocarditis remains to be established. Myocarditis is a cardiac precursor for AF and AF is found in 14% of patients with suspected myocarditis. Both local and systemic inflammation have been implicated in the pathophysiology of AF, ranging from increased local and systemic production of pro-inflammatory cytokines to increased inflammatory cell infiltration in the atria in patients with lone AF. Although the myocarditis patients included in the study did not have symptomatic AF, the increase in atrial inflammatory cell infiltration may indicate a predisposition toward the development of AF.

Inflammation can induce the formation of atrial fibrosis, which increases the risk of AF development. In Begieneman et al's analysis, atrial myocarditis did not coincide with an increase in atrial fibrosis, so it remains uncertain if the observed atrial myocarditis precedes AF. However, the amount of collagen differed between left and right atria of the same patient group. This difference in intramyocardial collagen deposition indicates that the left and right atrium may respond differently to myocarditis.

Case series

Severe leptospirosis is known to cause multiorgan dysfunction including cardiac involvement. In the clinical setting with limited resources, high degree of suspicion is needed to diagnose cardiac involvement including myocarditis. Although myocarditis is not a common complication due to lack of diagnostic facilities, there are evidence to support myocarditis is more prevalent

in post mortem studies of patients died due to leptospirosis. **Jayathilaka et al (2019)** presented a case series of severe leptospirosis with cardiac involvement observed during a period of one month at a teaching hospital in Sri Lanka.

The authors reported five patients with severe leptospirosis complicated with cardiac involvement, admitted to a single medical ward. Of six suspected leptospirosis patients admitted during this period, five developed severe leptospirosis with cardiac involvement. Diagnosis was confirmed serologically in four patients or with quantitative PCR and one patient had possible leptospirosis. All patients developed shock during their course of illness.

Two patients developed rapid atrial fibrillation. All five patients had elevated cardiac troponin I titre and it was normalized with the recovery. Four patients needed inotropic/vasopressor support to maintain mean arterial pressure and one patient recovered from shock with fluid resuscitation. All patients were recovered from their illness and repeat 2D echocardiograms after recovery did not show residual complications.

Datta and Mitra (2019) reported a clinical study on cardiac manifestations of Dengue fever.⁵² Two patients had pericardial effusion which resolved within two weeks. Transient 2:1 AV block and atrial fibrillation were observed in two cases. Cardiac manifestations of Dengue were present in 11.4 % of patients.

Case reports

Zainal et al (2019) described a rare case of Lyme carditis presenting with atrial fibrillation as well as varying degrees of heart block.⁵³ A 46-year-old man presented with chest pressure, dyspnoea, palpitations and syncope. He presented initially with atrial fibrillation with rapid ventricular response, a rare manifestation of Lyme carditis. In another hospital presentation, he had varying degrees of atrioventricular block including Mobitz I second-degree heart block. After appropriate antibiotic treatment, he made a full recovery and ECG normalised.

Shabbir et al. (2019) presented a case of a 23-year-old man coming with palpitations, found to be in atrial fibrillation.⁵⁴ He was initially managed with metoprolol for rate-controlled therapy-reverted to normal sinus rhythm and discharged home. He returned a few days later-this time in varying degrees of atrioventricular block including transient complete heart block. He was empirically started on intravenous ceftriaxone for suspected Lyme carditis, which subsequently led to the resolution of high-degree heart block. Lyme immunoglobulin G (IgG) and IgM returned positive. Follow-up ECG after the course of antibiotic exhibited normal sinus rhythm. AF is a rare presentation of Lyme disease.

⁵² Datta G, Mitra P. (2019). A Study on Cardiac Manifestations of Dengue Fever. J Assoc Physicians India.; 67(7): 14-6.

⁵³ Zainal, A., Hanafi, A., Nadkarni, N., et al. (2019). Lyme carditis presenting as atrial fibrillation. BMJ case reports, 12(4), e228975.

⁵⁴ Shabbir, M. A., Saad Shaukat, M. H., Arshad, M. H., et al. (2019). Lyme carditis presenting as atrial fibrillation in a healthy young male. BMJ case reports, 12(6), e229261

Gaine et al (2021) described a patient with COVID-19-associated myocarditis presenting as new-onset heart failure and atrial fibrillation.⁵⁵ A 58-year-old man presented to the emergency department with recent-onset palpitations and progressive exertional dyspnoea. ECG demonstrated new-onset atrial fibrillation. Transthoracic echocardiogram showed global impairment in left ventricular systolic function.

Giant cell arteritis (temporal arteritis; GCA) is a systemic vasculitis of medium and large arteries, affecting predominantly the aortic branches to the head and neck.⁵⁶ Temporal arteritis classically presents with a combination of polymyalgia rheumatica, headache, and manifestations of systemic illness (fever, anaemia, anorexia, malaise, and weight loss). GCA usually occurs in the elderly with a mean age at diagnosis of 72 years. Patients with GCA seem to be at increased risk for cardiovascular events, with heightened rate of acute myocardial infarction, cerebral vascular attack, and peripheral vascular disease. Myocarditis and myopericarditis are not commonly documented in patients with GCA. There have been at least 6 reports of giant cell arteritis causing myocarditis.

Kushnir et al (2016) presented a biopsy-proven GCA presenting with diplopia and new diagnosis of atrial fibrillation and myocarditis with left ventricular systolic dysfunction. The patient promptly responded to corticosteroid therapy, confirming the diagnosis of GCA. The coincidence of paroxysmal AF and diplopia suggests that flares of systemic inflammation precipitated both symptoms.

The AF in this patient likely responded to solumedrol and not to amiodarone because arrhythmia activity correlated with C-reactive protein levels. Many inflammatory conditions have been associated with myocarditis including necrotising vasculitis, scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. This report highlights the contribution of systemic inflammation to myocardial pump dysfunction and atrial arrhythmias.

Kashif et al. (2017) reported a rare case of purulent pericarditis caused by *Streptococcus agalactiae*.⁵⁷

A 65-year-old diabetic woman presented with generalized weakness, high-grade fever, and altered mental status. There were no signs or symptoms suggestive of cardiac tamponade on presentation. A computerised tomography (CT) scan of the chest showed a small pericardial effusion. She was managed for diabetic ketoacidosis and sepsis. An electrocardiogram was significant for new-onset AF. Her clinical status deteriorated rapidly as she developed acute hypoxic respiratory failure and shock. A bedside echocardiogram showed large pericardial effusion around the right ventricle and right ventricular diastolic collapse. She developed cardiac arrest, and during resuscitation bedside pericardiocentesis was done with drainage of 15cc of serosanguineous fluid. The patient could not be revived.

⁵⁵ Gaine S, Devitt P, Coughlan JJ, et al (2021). COVID-19-associated myocarditis presenting as new-onset heart failure and atrial fibrillation. *BMJ Case Rep.*; 14(7):e244027.

⁵⁶ Kushnir, A., Restaino, S. W., & Yuzefpolskaya, M. (2016). Giant Cell Arteritis as a Cause of Myocarditis and Atrial Fibrillation. *Circulation. Heart failure*, 9(2), e002778.

⁵⁷ Kashif, M., Raiyani, H., Niazi, M., et al. (2017). Purulent Pericarditis: An Uncommon Presentation of a Common Organism. *The American journal of case reports*, 18, 355–60.

Blood cultures grew *Streptococcus agalactiae* a day after she died. At autopsy, there were findings of infective endocarditis and purulent pericarditis.

Summary and conclusions

Myocarditis and pericarditis are non-ischaemic inflammatory diseases of the myocardium and pericardium. Atrial inflammation of the myocardium (acute and chronic) is known to cause conduction disturbances. Cardiac conduction system defects and arrhythmias are recognised to be one form of presentation of myocarditis (Block 2021). Experimental and clinical studies show how atrial inflammation enhances AF and AFL susceptibility.

Cardiac inflammation may stimulate myocardial infarction, symptomatic arrhythmias, heart failure, cardiogenic shock or sudden cardiac death. Although the aetiology of myocarditis and pericarditis is heterogeneous, infection is the most common cause, with viral pathogens the most commonly implicated in the developed world (Buckley et al 2021).

Other than sinus tachycardia, supraventricular tachycardias are described in acute myocarditis, including atrial fibrillation and atrial flutter (Butta et al 2020). These arrhythmias are usually found in patients with more severe clinical courses or with underlying cardiac disease and/ or in specific conditions such as Chagas disease (Rojas et al. 2018).

In a recent cohort using a nationally representative sample, Adegala et al (2019) identified cardiac arrhythmias in 33.71% of hospitalised acute myocarditis cases. The most common form of arrhythmias was atrial fibrillation (26.90%) followed by ventricular tachycardia (22.34%). This is similar to the result of previous case series where arrhythmias was reported in up to 40% of patients with myocarditis, some of which may manifest as sudden cardiac death.

The exact mechanism of arrhythmias in acute myocarditis is unknown. However, myocardial cell death with resulting fibrosis, autoimmune-mediated cell damage, proarrhythmic effects of cytokines, and unmasking of preexisting cardiomyopathy have been postulated as possible mechanisms. abnormal cardiac rhythm have long been implicated in the pathogenesis of SCD in varieties of structural heart diseases (Adegala et al 2019).

Myocarditis is a known precursor of atrial fibrillation and AF is found in 14% of patients with suspected myocarditis (Begieneman et al 2016). There is strong evidence linking both systemic and local inflammation to the initiation and perpetuation of AF in general. Increased infiltration of macrophages and lymphocytes has been described in the left and right atria of patients with symptomatic AF, compared to control patients. These studies suggest that (cardiac) inflammation may predispose patients into developing AF. However, it is not known whether ventricular myocarditis coincides with infiltration of inflammatory cells in the atria (referred to as atrial myocarditis) in myocarditis patients.

AF is an almost universal finding in giant cell myocarditis with isolated atrial involvement due to massive atrial dilatation, atrial wall thickening, and oedema (Larsen et al. 2013).

Myocarditis can be idiopathic, or related to infectious and immunological causes. Several experimental and clinical studies document how cardiac inflammation enhances the AF and AFL susceptibility of atrial tissue.

Atrial myocarditis has been observed before in atrial tissue obtained post-mortem from young patients after sudden death and atrial tissue obtained from living patients with idiopathic enlargement of bilateral atria, with transient sinoatrial disease and with atrial giant cell myocarditis. In all these cases, atrial myocarditis occurred in the absence of ventricular myocarditis. Begieneman et al (2015) demonstrated for the first time that atrial myocarditis also occurs in patients diagnosed with ventricular myocarditis.

Among infectious forms of myocarditis, various ECG changes occur in leptospirosis, including AF. Histopathological changes in the myocardium have been clearly shown, with myocardial inflammation and vasculitis in post-mortem studies. However the pathophysiology of cardiac involvement in leptospirosis is poorly understood.

Cardiac involvement (Lyme carditis) occurs in 1% of untreated patients in the early disseminated phase of infection. The mechanism of cardiac tissue injury is not established, in addition to direct myocardial invasion by *Borrelia burgdorferi*, some studies emphasise the influence of immunological and autoimmunological processes. Cardiac manifestations occur a median of 21 days after exposure. AF is less common than heart block in Lyme carditis. Zainal et al (2019) describe a rare case of Lyme carditis presenting with atrial fibrillation and varying degrees of heart block.

COVID-19 has a spectrum of cardiovascular sequelae, including myocarditis, pericarditis, or increased biomarkers of cardiac injury, all of which may associate with poor prognosis. Several observational case series showing a significant proportion of cardiac involvement in hospitalised patients (Buckley et al 2021). Cardiac injury seems to be significantly correlated with increased in-hospital mortality in COVID-19 patients. Patients with COVID-19 who present with myocarditis/ pericarditis associate with increased odds of major adverse events and new-onset cardiovascular sequelae.

In a cohort of COVID patients, Buckley et al 2021 did not find that the odds of incident AF (OR 0.95, 95CI 0.74- 1.21) was higher in COVID patients with myocarditis cf COVID patients without myocarditis, but the odds of incident AF were higher in COVID patients with pericarditis than controls (OR 2.50, 95CI 1.90-3.20). Although new-onset myocarditis was more prevalent (5.0%) than pericarditis (1.5%) in patients with COVID-19, the latter seems to be associated with more substantial adverse events and cardiovascular sequelae.

Myocarditis can be immunologically driven. Cardiovascular adverse events are associated with usage of immune checkpoint inhibitors, including AF (Jain et al 2021), and which may be related to various cardiac pathologies including myocarditis and heart failure. Cardiac arrhythmias have been reported to occur during the acute phase of pericarditis. Although data relevant to their nature and incidence are sparse, AF appears as the most common sustained rhythm disturbance in patients with acute pericarditis (Imazio et al 2012). In published series, the incidence of AF in acute pericarditis ranges between 6% and 25%.

Much literature describes acute pericarditis occurring as a complication of AF ablation procedures, rather than being a cause of AF; but the occurrence of AF/f in acute pericarditis identifies a predisposed population to AF/f with a high recurrence risk (about 35%): in these patients, pericarditis may act as an arrhythmic trigger and oral anticoagulation should be seriously considered according to guidelines (Imazio et al 2015).

There are few prospective clinical studies of the frequency and outcome of atrial fibrillation in the context of pericarditis (Mayosi 2015). Early reports in the literature showed that AF was uncommon in acute pericarditis ($\leq 7\%$ of cases) and was associated with underlying structural heart disease of the myocardium, valves or coronary arteries. It is known that PQ-segment depression, a marker of atrial pericarditis, is associated with the occurrence of AF in acute Q-wave myocardial infarction.

Animal models support a direct causal link between pericarditis and atrial fibrillation (Mayosi et al 2015). A small prospective study of subacute pericarditis shows that AF may be common in tuberculous pericardial effusion ($\sim 25\%$ of cases) associated with left ventricular dysfunction (Syed et al 2012). Pericarditis-associated atrial fibrillation is a transient condition that remits spontaneously within 6 weeks of treatment with antituberculosis medication in patients with tuberculous pericardial effusion. In contrast, chronic constrictive tuberculous pericarditis is associated with persistent atrial fibrillation in 8% of cases, and usually occurs with a calcified pericardium.

In a prospective cohort study, the incidence of AF/f in patients with a first episode of acute pericarditis and the long-term outcome was assessed (Imazio et al 2015). The incidence of AF/f during a first episode of acute pericarditis was 4.3%, with AF being the most common arrhythmia. Patients with AF/f were older, and more commonly had a presentation with pericardial effusion. There was a trend for higher temperature at presentation in such patients. AF/f was recorded within 24 h from symptoms onset in the great majority ($>90\%$); it was transient in all cases and converted spontaneously to sinus rhythm within 24 h in $\sim 75\%$ of cases.

The temporal relationship of atrial fibrillation with recurrent pericarditis in a cohort that was largely free of structural heart disease underlines the role of inflammation as a trigger of AF. The correlation between pericarditis-associated AF with factors that are generally associated with rising incidence of atrial fibrillation such as increasing age, hypertension and an enlarged left atrium suggests that acute inflammation may serve as a cofactor in the initiation of atrial fibrillation in people who are at high risk for cardiovascular disease.

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between myocarditis and atrial fibrillation and atrial flutter (Grade one). A consistent association has been observed between myocarditis and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

A factor for myocarditis should be retained in the RH and BoP SoPs.

There is an uncertain distinction between the current factor for myocarditis, and SoP factors for autoimmune disease, myocardial infection (below), infiltrative disease (e.g. cardiac

sarcoidosis), and cardiomyopathy. Consideration should be given as to whether this factor be confined to non-infectious myocardial inflammation, or whether it should cover viral myocarditis in addition to non-infectious causes of cardiac inflammation.

The current myocarditis factor is under-specified. Along the lines of other arrhythmia SoPs, it is proposed that a separate factor be created for viral myocarditis, and a second factor for non-infectious myocarditis. Non-viral myocardial infection should continue to be covered by a separate factor. Myocarditis should be specified in a note to cover acute and chronic myocarditis. Most cases of atrial fibrillation appear to be related to acute myocarditis.

The causes of myocarditis are not specified in the current factor. Examples of causes could be included in a note. Examples of viral causes of myocarditis include HIV, coronavirus disease 2019 (COVID-19), and dengue fever. Examples of non-viral causes of myocarditis can be specified, including autoimmune and immunological causes.

The myocarditis factor should also be modified to refer to myocarditis occurring "at the time of" the clinical onset or worsening of atrial fibrillation and atrial flutter.

Besides viruses, multiple infectious agents have been associated with myocarditis with atrial fibrillation, including protozoa, rickettsia, and bacteria (Barra et al 2012).

Myocarditis may occur in 10–25% of patients with respiratory diphtheria and has been reported to cause high mortality. Samdani et al. (2018) studied cardiac complications in diphtheria patients in a single centre prospective analysis of 60 patients diagnosed with diphtheria. ECG changes included right bundle branch block (5%),

Dengue fever affecting the heart can lead to cardiac arrhythmias and left ventricular dysfunction.

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between myocardial infection with bacteria, protozoa and other non-viral organisms and atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between non-viral myocarditis related to infection and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

Viral myocarditis is already effectively covered by the existing SoP factor for myocarditis (above), although this is not specified in the current factor.

Consideration could be given to having a single factor for bacterial and protozoal myocardial infection, with notes specifying infectious agents, along the lines of other arrhythmia SoPs.

It is concluded that there is evidence strong enough to support a judgement of a suggestive causal relationship (Grade 2) between atrial fibrillation and atrial flutter and pericarditis. A consistent association has been observed between atrial fibrillation and atrial flutter and pericarditis, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for pericarditis should be retained in the RH and BoP SoPs.

The pericarditis factor should be modified to refer to pericarditis occurring "at the time of" the clinical onset or worsening of atrial fibrillation and atrial flutter.

The SoPs should be reordered such that the factor for pericarditis should be placed immediately after the factor for myocarditis.

Cardiomyopathy

Current factor

RH and BoP - onset and worsening

having cardiomyopathy at the time of the clinical onset of atrial fibrillation or atrial flutter; or

having familial hypertrophic cardiomyopathy at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Cardiomyopathy is a structural heart disease that is routinely cited as being associated with the development of AF. Most AF patients have an established form of an atrial cardiomyopathy.

Cardiac infiltrative diseases (sarcoidosis, amyloidosis), which are common causes of cardiomyopathy related to AF, are considered separately in a subsequent section of this comparison paper (autoimmune and inflammatory disease).

Summary of previous investigation

Cardiomyopathy is among the structural heart diseases that are routinely cited in the medical literature as being associated with the development of atrial fibrillation. For example, the American Heart Association/American College of Cardiology guidelines for the evaluation of patients with AF require an echocardiography to assess left heart dimensions and function and to exclude occult valvular or pericardial disease and hypertrophic cardiomyopathy (Fuster et al 2006).⁵⁸

Cardiomyopathy is included as a factor in the current SoPs for atrial fibrillation. the RMA SoPs for cardiomyopathy cover a very broad range of conditions that affect the myocardium, and include autoimmune, infectious, heritable, infiltrative and endocrine causes. Forms of cardiomyopathy that are currently covered by this factor include alcohol, haemochromatosis and infection-related myocarditis. Several of these particular causes are covered by specific factors in the atrial fibrillation SoPs. For example, studies of the association between alcohol

⁵⁸ Cohen JE, Kogan J, Oren S, Mazza M. (2011) Primary cardiac lymphoma presenting with atrial fibrillation. *Isr Med Assoc J.*;13(10):635-37.
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intake and the risk of AF posit that alcohol-related cardiomyopathy could account for some AF episodes; as it is recognised that heavy drinkers are prone to cardiomyopathy, which might lead to heart failure and a consequently increased risk of AF.

While there is very little recent literature examining the association of atrial fibrillation and cardiomyopathy conceptualised as a generic category, it is acknowledged in the medical literature that structural diseases affecting the atrium are closely related to the development of atrial arrhythmias. It is submitted that a generic cardiomyopathy factor should be retained in the SoPs, as such a factor would cover a very broad range of conditions that may induce structural abnormalities in the heart that would otherwise have to be specified in other SoP factors.

Atrial fibrillation is recognised in the medical literature to occur in relation to various forms of congenital heart diseases, and also as a consequence of related paediatric cardiac surgery. However, the relevance of these instances to the SoP regime is negligible. The SoP regime includes instrument for familial hypertrophic cardiomyopathy, but no other congenital heart diseases.

Reviews.

Cardiac infiltrative diseases are considered separately in a subsequent section of this briefing paper (below).

A newly clinical and histopathological entity of atrial cardiomyopathy (ACM) has been described.⁵⁹ As ventricular structural adverse remodelling and dysfunction has been universally recognised to be a risk factor for adverse cardiovascular outcomes, ACM is increasingly recognised as a clinically important pathophysiological process. The investigation of atrial cardiomyopathies is becoming increasingly more prominent.

ACM refers to the electromechanical changes-appreciated subclinically and/or clinically-that underlie atrial dysfunction and create an environment ripe for the development of clinically apparent AF.⁶⁰ There are several subtypes of ACM, distinguished by histological features. Recent progress in cardiovascular imaging, including echocardiography with speckle-tracking (e.g., strain analysis), cardiovascular magnetic resonance imaging (CMR), and atrial 4-D flow CMR, has enabled increased recognition of ACM. Identification of ACM and its features carry clinical implications, including elevating a patient's risk for development of AF, as well as associations with outcomes related to catheter-based and surgical AF ablation.

Most AF patients have an established form of an atrial cardiomyopathy. The concept of atrial cardiomyopathy was introduced in 2016.⁶¹ Therapy of underlying diseases and atrial tissue changes appear as a cornerstone of AF therapy. Therapy or prevention of atrial endocardial

⁵⁹ Baman, J. R., Cox, J. L., McCarthy, P. M., et al (2021). Atrial fibrillation and atrial cardiomyopathies. *Journal of cardiovascular electrophysiology*, 32(10), 2845–53

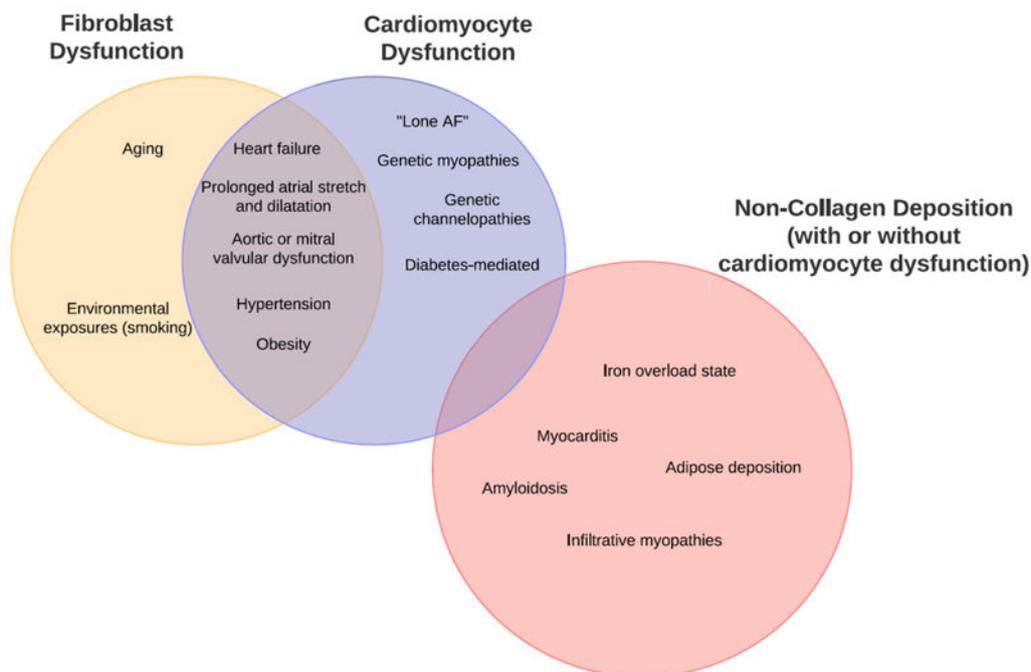
⁶⁰ Baman, J. R., Cox, J. L., McCarthy, P. M., et al (2021). Atrial fibrillation and atrial cardiomyopathies. *Journal of cardiovascular electrophysiology*, 32(10), 2845–53

⁶¹ Goette, A., & Lendeckel, U. (2021). Atrial Cardiomyopathy: Pathophysiology and Clinical Consequences. *Cells*, 10(10), 2605.

changes has the potential to reduce atrial thrombogenesis and thereby cerebral stroke. summarize the underlying pathophysiology and remodeling processes observed in the development of an atrial cardiomyopathy, thrombogenesis, and atrial fibrillation. In particular, the impact of oxidative stress, inflammation, diabetes, and obesity will be addressed.

Invasive electrophysiological studies and advanced multimodality imaging demonstrate that the subclinical electrical signalling and flow dynamics within the atria are disrupted in those with ACM, in contrast to normal atria.⁶² a striking feature of this association is its reproducibility when assessed during periods of sinus rhythm in those with nonpermanent AF. There is a complex interplay between ACM and AF. While AF is a clinically recognized entity, this may only be the tip of the iceberg. Before the onset of AF, the atria may undergo periods of electrical, structural and cellular remodeling that create the environment for arrhythmia development. Underlying genetic and gene-environment interactions also influence this process.

FIGURE 1 PRIMARY HISTOPATHOLOGICAL PROCESSES THAT CONTRIBUTE TO ACM AND MAJOR ASSOCIATED CLINICAL CONDITIONS. **ACM**, ATRIAL CARDIOMYOPATHY

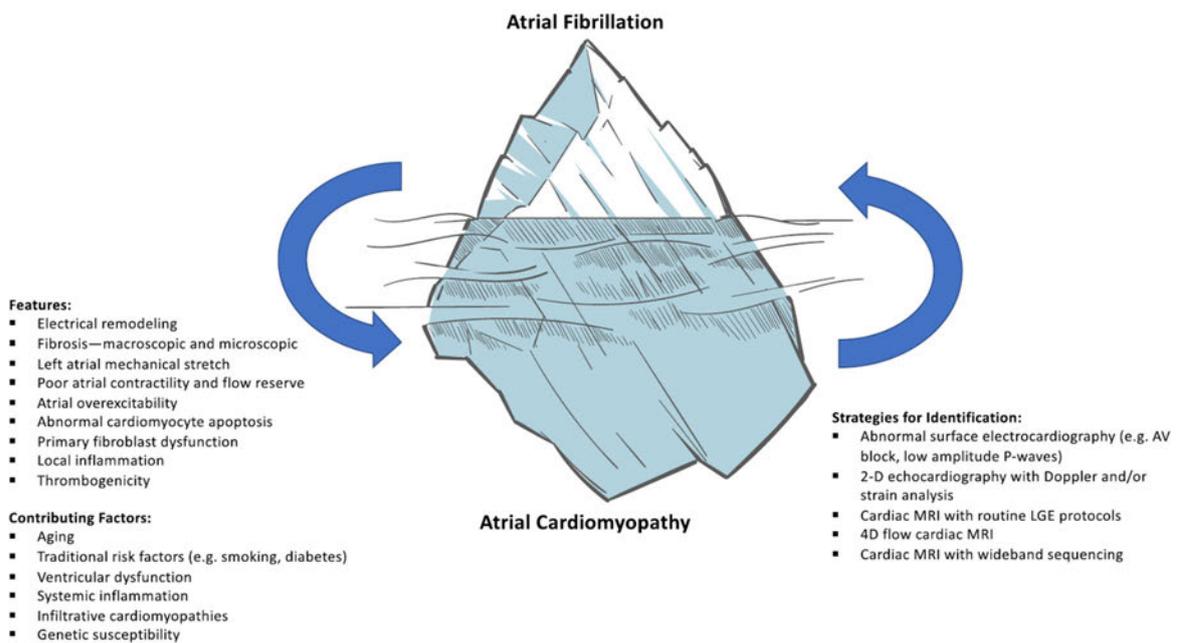


Bamen et al (2021), Fig 1

Bamen et al (2021) have reviewed the definition and classifications of ACM, its complex relationship with clinical AF, imaging modalities, and clinical implications.

⁶² Baman, J. R., Cox, J. L., McCarthy, P. M., et al (2021). Atrial fibrillation and atrial cardiomyopathies. *Journal of cardiovascular electrophysiology*, 32(10), 2845–53
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FIGURE 2 INTERPLAY BETWEEN AF AND ACM,



Bamen et al (2021), Fig 2

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder with a spectrum of clinical manifestations.⁶³ Patients with HCM are predisposed to developing atrial fibrillation due primarily to advanced diastolic dysfunction and left atrial (LA) dilatation and remodelling. Atrial fibrillation causes a progressive symptomatic and functional decline, as well as increased thromboembolic risk and mortality, particularly in the setting of rapid ventricular rates and left ventricular outflow tract (LVOT) obstruction. The mainstay of management of AF in HCM is a combination of non-pharmacological lifestyle and risk factor modification, long-term anticoagulation, and rhythm control with antiarrhythmic medications. There is a growing body of evidence indicating that an early and aggressive rhythm control strategy may result in more favourable outcomes.

Takotsubo cardiomyopathy (TCM) is rarely associated with life-threatening arrhythmic complications. ECG findings of Takotsubo cardiomyopathy usually show ST-segment elevation or depression, T-wave inversion, left bundle branch block or high-grade atrioventricular block. AF is also described in patients with stress-induced cardiomyopathy.⁶⁴

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⁶³ Vaidya, K., Semsarian, C., & Chan, K. H. (2017). Atrial Fibrillation in Hypertrophic Cardiomyopathy. *Heart, lung & circulation*, 26(9), 975–82.

⁶⁴ Bandyopadhyay D, Jain V, Herzog E, et al (2019). Atrial Fibrillation and Morbidity and Mortality in Stress-Induced Cardiomyopathy. *Mayo Clin Proc.*; 94(10): 2146-8.

⁶⁵ Morin DP, Bernard ML, Madias C, et al (2019). In reply-Atrial Fibrillation and Morbidity and Mortality in Stress-Induced Cardiomyopathy. *Mayo Clin Proc.*;94(10): 2148-9
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Cohort studies

Atrial fibrillation is the most common arrhythmia in patients with dilated cardiomyopathy (DCM). The epidemiology as well as clinical and prognostic significance of AF in DCM are poorly defined. **Dziewięcka et al.(2020)** assessed the impact and prognostic value of AF in dilated cardiomyopathy (DCM) and investigated the concept of AF-induced DCM.⁶⁶

Hospital records of 285 patients with DCM from 2012 to 2018 with follow-up were analysed. Atrial fibrillation was present in 89 patients (31%). They were older, more frequently male, had higher body mass index, New York Heart Association class, heart rate (HR), creatinine levels, and larger atria (all $P < 0.05$) than patients without AF. During follow-up (mean [SD], 35 [24] months), death occurred in 20 of the 82 available patients with AF and 22 of the 188 patients without AF (24% and 12%, respectively; $P = 0.007$). Atrial fibrillation was independently associated with a worse outcome (hazard ratio, 2.4; 95% CI, 1.3-4.3) and was found to be the major cause of DCM in 21 patients (24%). The diagnostic accuracy of the most optimal predictive model for AF-induced DCM was 0.935 (95% CI, 0.903-0.967). Despite numerical differences, survival was similar in DCM patients with and without AF ($P = 0.15$).

Almost one-third of patients with DCM had AF. Most of the parameters analysed differed between patients with and without AF, and AF was found to be an independent prognostic factor of DCM. One-fourth of patients with DCM and AF met the diagnostic criteria for AF-induced DCM.

Summary and conclusions

Cardiomyopathy is among the structural heart diseases that are routinely cited in the medical literature as being associated with the development of AF. AF is recognised to be a complication of various types of cardiomyopathy. This include cardiomyopathy related to hypertension, infiltrative cardiomyopathies such as that related to cardiac sarcoidosis or amyloidosis, as well as Takotsubo or stress' cardiomyopathy (Bandyopadhyay et al 2019; Morin et al 2019).

Cardiac infiltrative diseases (sarcoidosis, amyloidosis), which are common causes of cardiomyopathy related to AF, are considered separately in a subsequent section of this comparison paper

Atrial fibrillation is the most common arrhythmia in patients with dilated cardiomyopathy (DCM). However, the epidemiology as well as clinical and prognostic significance of AF in DCM are poorly defined. (Dziewięcka et al 2020). Causes of dilated cardiomyopathy, such as alcohol consumption, are covered by separate factors in these SoPs.

Most AF patients have an established form of an atrial cardiomyopathy. A newly clinical and histopathological entity of atrial cardiomyopathy (ACM) has been described (Bamen et al 2021). As ventricular structural adverse remodelling and dysfunction has been universally

⁶⁶ Dziewięcka, E., Gliniak, M., Winiarczyk, M., et al. (2020). The burden of atrial fibrillation and its prognostic value in patients with dilated cardiomyopathy. *Kardiologia polska*, 78(1), 37–44
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recognised to be a risk factor for adverse cardiovascular outcomes, ACM is increasingly recognised as a clinically important pathophysiological process. Many diseases can cause alterations in the atria, which can be evident as primarily cardiomyocyte changes, primarily fibrotic changes, a combination of both, or noncollagen infiltration. Fibrotic ACM and muscular dystrophies are relevant factors from the spectrum of atrial cardiomyopathies.

There is a complex interplay between ACM and AF. Invasive electrophysiological studies and advanced multimodality imaging demonstrate that the subclinical electrical signalling and flow dynamics within the atria are disrupted in those with ACM, in contrast to normal atria.

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder with a spectrum of clinical manifestations (Vaidya et al 2017). Patients with HCM are predisposed to developing atrial fibrillation due primarily to advanced diastolic dysfunction and left atrial (LA) dilatation and remodelling. HCM is presently specified in a separate factor in these SoPs, but this should be incorporated into a single factor for cardiomyopathy.

While there is little recent literature examining the association of atrial fibrillation and cardiomyopathy conceptualised as a generic category, it is acknowledged in the medical literature that structural diseases affecting the atrium are closely related to the development of atrial arrhythmias.

Cardiomyopathy is included as a factor in the current SoPs for atrial fibrillation/flutter. The RMA SoPs for cardiomyopathy cover a broad range of conditions that affect the myocardium, and include autoimmune, infectious, heritable, infiltrative and endocrine causes. Forms of cardiomyopathy that are currently covered by this factor include alcohol, haemochromatosis and infection-related myocarditis. Several of these particular causes are covered by specific factors in the Af/AFI SoPs. For example, studies of the association between alcohol intake and the risk of AF posit that alcohol-related cardiomyopathy could account for some AF episodes; as it is recognised that heavy drinkers are prone to cardiomyopathy, which might lead to heart failure and a consequently increased risk of AF.

Atrial fibrillation is recognised in the medical literature to occur in relation to various forms of congenital heart diseases, and also as a consequence of related paediatric cardiac surgery. However, the relevance of these instances to the SoP regime is negligible.

Atrial fibrillation and atrial flutter can be seen in patients with infiltrative processes such as amyloidosis and sarcoidosis. These are specifically covered in the section of this briefing paper concerning infiltrative and autoimmune diseases (below)

It is concluded that there is evidence strong enough to support a judgement of a suggestive causal relationship (Grade 2) between atrial fibrillation and atrial flutter and cardiomyopathy (unspecified). A consistent association has been observed between atrial fibrillation and atrial flutter and cardiomyopathy, but chance, bias or confounding cannot be ruled out with reasonable confidence.

The current factor for cardiomyopathy is not well defined. This factor may overlap with existing factor concerning cardiac infiltrative, inflammatory and autoimmune disease (below);

cardiomyopathy (amyloidosis, haemochromatosis, and sarcoidosis) and myocardial infection (e.g. Chagas cardiomyopathy).

A standalone factor for cardiomyopathy (generic) should be retained in RH and BoP SoPs without substantial modification. Familial hypertrophic cardiomyopathy is covered by a separate factor in these SoPs, but this should be incorporated into the single factor for cardiomyopathy. It is recognised that HCM would not be relevant to the clinical worsening of atrial fibrillation or atrial flutter, but it is unlikely to be necessary to specify this in the factor.

There is an overlap of the cardiomyopathy factor with some types of autoimmune and inflammatory diseases involving the heart, listed in another factor in this SoP, which covers amyloidosis and sarcoidosis. These, along with haemochromatosis, are usually considered to be forms of infiltrative cardiomyopathy. These could be covered within the cardiomyopathy factor, or a separate factor for cardiac infiltration could be cleaved off from the existing factor for inflammatory and autoimmune diseases of the heart (below). There is also an overlap with the factor for heart failure.

The current factor for *cardiomyopathy* should cover infiltrative cardiomyopathy, hypertensive hypertrophic cardiomyopathy, dilated and other types of cardiomyopathy).

The existing combined factor for autoimmune, inflammatory and infiltrative heart disease (below) should be separated into two factors for cardiac infiltration and autoimmune diseases, along the lines of the heart block SoPs (detailed below).

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Cardiac failure

Current factor

RH and BoP - onset and worsening

having cardiac failure at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Heart failure and AF are among the commonest causes of cardiovascular disease. While the coexistence of both diseases is quite common as the presence of HF increases the likelihood of AF and vice versa. The prevalence of AF in HF patients ranges from 10 to 50%, depending on the severity of HF; the more severe the HF, the more likely is the AF to appear. The new onset or permanent AF is related with worse prognosis in patients with established HF.

Summary of previous investigation

Congestive heart failure is a well-known risk factor for non-surgical AF.

Atrial fibrillation is the most common arrhythmia complicating heart failure. Both conditions are common, associated with significant morbidity and mortality. Heart failure and AF frequently coexist and share many risk factors. Either condition may predispose to the other through

several potential mechanisms. Rather than being independent disease processes, it has been suggested that they may be different endpoints along a disease continuum. The complex epidemiology of HF and AF coexistence involves bilateral self-perpetuating pathomechanisms. Many cases of AF and HF result from the cumulative exposure of the atria and ventricles to a common set of systemic cardiovascular risk factors.

Congestive heart failure is known to cause left atrial dilatation due to increased atrial filling pressures secondary to decreased ventricular function, increased atrial fibrosis, and regional conduction abnormalities. HF may predispose to AF through atrial stretch, increased interstitial fibrosis, neurohormonal activation, which promotes structural remodeling and atrial fibrosis, and dysregulation of intracellular calcium. A role of CHF in the induction of atrial interstitial fibrosis which leads to AF has been documented in multiple animal studies.

The prevalence of AF in patients with HF is generally high both in clinical studies and in the outpatient setting (Rewiuk et al 2011) and the prevalence of AF increases with severity of HF.

New onset AF continues to be described in cohort studies of CHF. For example, Schmiegelow et al (2011) reported in the DIAMOND-heart failure study that 1 in 10 patients with new or worsening heart failure developed new onset AF during 42 months of follow-up. Heart failure was the strongest predictor of new-onset AF (HR 3.14, 95CI 1.78-5.52) in the combined analysis.

A strong association between incident AF and a history heart failure (RR 2.91, 95CI 2.59-3.27) was reported in the UK GPRD case control study (Hodgkinson et al 2011). The risk of AF associated with heart failure or did not reduce over time in this study population

Reviews

There have been many recent review studies concerning atrial fibrillation and heart failure.⁶⁷
⁶⁸ ⁶⁹ ⁷⁰ Summary data from a handful of these reviews is presented here.

As outlined by **Tsigkas et al (2021)** heart failure (HF) and atrial fibrillation are among the commonest causes of cardiovascular disease.⁷¹ While the coexistence both of these diseases is quite common as the presence of HF increases the likelihood of AF and vice versa. The prevalence of AF in HF patients ranges from 10 to 50%, depending on the severity

⁶⁷ Kim I. C. (2021). Atrial Fibrillation and Heart Failure with Preserved Ejection Fraction: Two Chronic Troublemakers. *Heart failure clinics*, 17(3), 377–86.

⁶⁸ Kotecha, D., & Piccini, J. P. (2015). Atrial fibrillation in heart failure: what should we do?. *European heart journal*, 36(46), 3250–7

⁶⁹ Vinter N, Frost L, Benjamin EJ. (2021) Heart failure and atrial fibrillation - does heart failure subtype matter? *Int J Cardiol.*; 341: 46-47

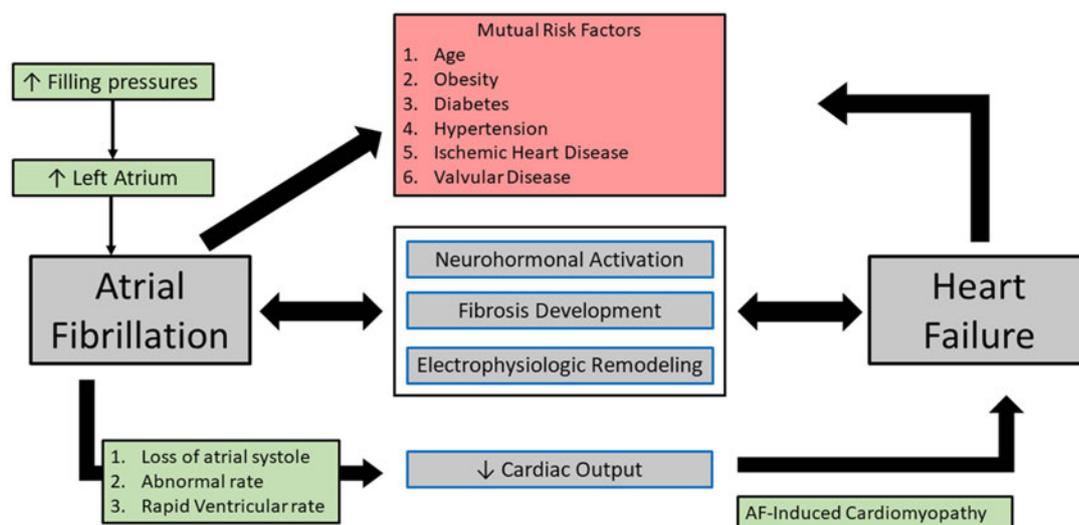
⁷⁰ Verhaert, D., Brunner-La Rocca, H. P., van Veldhuisen, D. J., et al. (2021). The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases. *Europace*., 23(23 Suppl 2), ii40–ii45.

⁷¹ Tsigkas, G., Apostolos, A., Despotopoulos, S., et al (2021). Heart failure and atrial fibrillation: new concepts in pathophysiology, management, and future directions. *Heart failure reviews*, 10.1007/s10741-021-10133-6.

of HF; the more severe the HF, the more likely is the AF to appear. the new onset or permanent AF is related with worse prognosis in patients with established HF

A bidirectional pathophysiological link connects heart failure and atrial fibrillation, creating a frequent and challenging comorbidity, which includes neurohormonal hyperactivation, fibrosis development, and electrophysiological remodeling, while they share mutual risk factors. Many mechanisms contribute to AF developing in HF

FIGURE 3 BIDIRECTIONAL, PATHOPHYSIOLOGICAL RELATIONSHIP BETWEEN HEART FAILURE AND ATRIAL FIBRILLATION



Source: Tsigkas et al (2021), Fig. 1.

HF is characterized by increased filling pressures in both atria and ventricles. Increased afterload and filling pressure leads to left atrial dilation, scarring, and fibrosis, which then result in the shortening of atrial refractory effective period, creating the ideal environment for AF establishment and perpetuation. Neuro-hormonal changes in HF include the elevation of angiotensin and catecholamine serum levels. These hormones are also trigger factors that cause AF. HF usually occurs with other comorbidities, like coronary artery disease, obesity, diabetes mellitus, and hypertension. The accompanying chronic inflammation results in structural and electrical remodelling that contributes to AF.

The irregularly irregular rhythm, rapid ventricular rate, and atrioventricular valve regurgitation, which are common findings in AF patients, can lead to cardiac output reduction and pump failure. tachycardia-induced cardiomyopathy, is provoked from persistent AF or newly diagnosed AF of unknown onset. Tachycardia-induced cardiomyopathy is associated with significant, reversible left ventricle (LV) dysfunction. Both diseases share mutual comorbidities.

Bavishi & Patel (2020) observe that up to 62% of individuals with HF may have AF at some point during their life course.⁷² AF and HF share several common, underlying risk factors. There appears to be a bidirectional relationship between these disease states, in which each

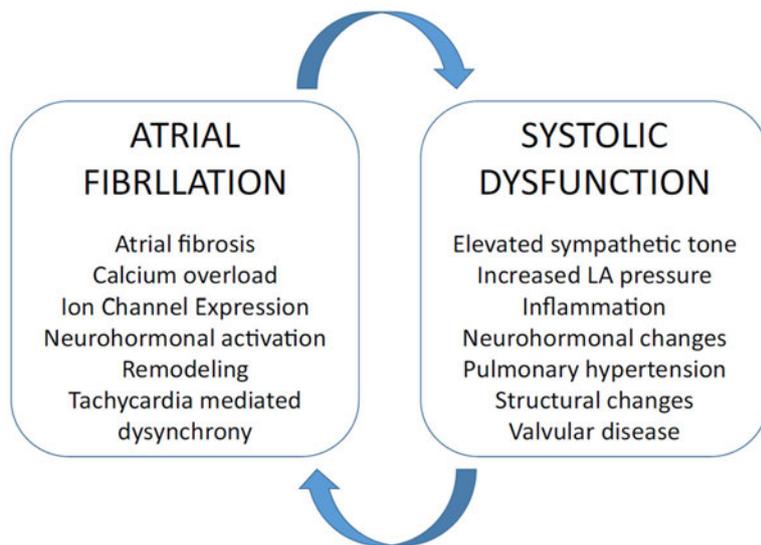
⁷² Bavishi, A., & Patel, R. B. (2020). Addressing Comorbidities in Heart Failure: Hypertension, Atrial Fibrillation, and Diabetes. *Heart failure clinics*, 16(4), 441–56
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disease induces inflammatory, neurohormonal, and structural changes that predisposes to the other syndrome.³⁸ Additionally, numerous studies have demonstrated that patients with both AF and HF have worse short term and long term outcomes than either condition alone.^{8,39–}

Due to current gaps in evidence, there is no widely-accepted treatment pathway for the management of AF in HF. The approach to management of AF in HF patients depends on several factors including the acuity of each condition, degree of HF decompensation, left ventricular function, and presence of other structural heart abnormalities.

AF and HF frequently co-exist, often synergistically increasing cardiovascular disease (CVD) risk.⁷³ HF can increase the risk of development of AF by activating neurohormones, elevating inflammatory markers, driving up sympathetic tone and increasing left atrial (LA) pressure. AF can beget HF by uncoupling atrio-ventricular contractions, disturbing calcium homestasis, altering ion channel expression, generating LA fibrosis, increasing neurohormonal activation and causing tachycardia-mediated cardiomyopathy. Conversely, maintaining normal rhythm can reverse HF and can result in favourable remodelling for patients with arrhythmia induced cardiomyopathy.

FIGURE 4 INTERACTION OF ATRIAL FIBRILLATION AND HEART FAILURE



Source: Bernard et al (2021), Fig 1

Cohort studies

To determine the prevalence and incidence of AF among HF subtypes in a biracial community-based cohort, **Nji et al. (2021)** studied 6496 participants in the Atherosclerosis Risk in Community study (mean age 75.8 ± 5.3 , 59% women, 23% black) who attended the 2011-2013 visit.⁷⁴ HF was identified from physician adjudicated diagnosis, hospital discharges, and self-report. HF subtypes were based on echocardiography. A left ventricular

⁷³ Bernard, M. L., Benn, F., Williams, C. M., et al (2021). The role of atrial fibrillation catheter ablation in patients with heart failure. *Progress in cardiovascular diseases*, 66, 80–5.

⁷⁴ Nji, M., Solomon, S. D., Chen, L. Y., et al. (2021). Association of heart failure subtypes and atrial fibrillation: Data from the Atherosclerosis Risk in Communities (ARIC) study. *International journal of cardiology*, 339, 47–53

ejection fraction <40% represents HF with reduced ejection fraction (HFrEF), 40%-49% for HF with midrange ejection fraction (HFmEF), and ≥ 50% for HF with preserved ejection fraction (HFpEF). AF was ascertained to 2017 from study ECGs, hospital discharges, and death certificates. Confounder-adjusted logistic regression and Cox models were used to estimate associations of HF subtype with prevalent and incident AF.

Among eligible participants, 393 had HF (HFpEF = 232, HFmEF = 41, HFrEF = 35 and unclassified HF = 85) and 735 had AF. Compared to those without HF, all HF subtypes were more likely to have prevalent AF (OR 7.4, 95CI 5.6-9.9) for HFpEF, OR 8., 95CI 4.3-15.3 for HFmEF, OR 10.0, 95CI 5.0-20.2 for HFrEF, and OR 8.8, 95CI 5.6-14.0 for unclassified HF.. Among participants without AF at baseline (n = 5761), 610 of them developed AF. Prevalent HF was associated with increased risk of AF (HR 2.3, 95CI 1.6-3.2) for HFpEF, 5.0 (95CI 2.7-9.3) for HFmEF, 3.5 (95CI 1.7-7.6) for HFrEF, 1.9 (95CI 0.9-3.7) for unclassified HF.

TABLE 4 HAZARD RATIOS (95CI) OF AF BY HEART FAILURE SUBTYPES, ARIC, 2011-17

	No HF	HFpEF	HFmEF	HFrEF	Unclassified HF
AF cases	550	36	9	6	9
Person-years	28220.6	536.5	74	56.6	135.3
AF incidence *	19.5	67.1	121.6	106.0	66.5
Model 1 †	1 (ref)	3.4 (2.4-4.7)	5.7 (3.1-10.3)	5.0 (2.3-10.5)	3.0 (1.5-5.7)
Model 2 ‡	1 (ref)	2.3 (1.6-3.3)	4.6 (2.4-8.6)	3.8 (1.8-8.2)	2.3 (0.9-5.6)

Table 3; † Model 1: Cox proportional hazard model adjusted for age, sex and race

‡ Model 2: Model 1 additionally adjusted for study site, BMI, systolic and diastolic blood pressure, smoking history, use of antihypertensive medication, diabetes mellitus, coronary heart disease and estimated glomerular filtration rate

The study showed that AF and HF frequently co-occur, with small differences by HF subtype..

Heart failure is a complex clinical syndrome with 3 subtypes based on LVEF- HFpEF, HFmEF, and HFrEF, all posing an increased independent risk of AF. The analysis of the ARIC cohort showed that the prevalence and incidence of AF was high among HF patients of all subtypes, particularly among those with HFrEF. These findings highlight the co-occurrence of AF and HF. Heart failure, particularly HFrEF was associated with a 6 to 7 times increased odds of prevalent AF. Similarly, the risk of incident AF was 2-5 times higher in participants with HF

The high prevalence and incidence of AF among participants with HF of any subtype, also previously demonstrated in large community-based Framingham and Olmsted cohorts, partly reflects the shared predisposing factors such as age, race, diabetes, hypertension and other cardiovascular diseases in both conditions. Furthermore, the pathophysiological processes underlying HF and AF are closely related. As a result of sustained increase in atrial pressure in persons with left ventricular dysfunction and overt HF, a process of atrial remodeling ensues

which leads to atrial wall fibrosis, heterogeneity in conduction and impaired contraction of this atria. This eventually can lead to AF onset among patients with HF.

This study was the first to evaluate the association of AF in HF in an epidemiologically representative population-based cohort using the modified 2016 ESC classification which makes a further distinction in HF categories by defining an HFmEF subtype. The ARIC cohort is a large community-based, racially and geographically diverse population consisting of whites and blacks from four communities in the US. This

AF was ascertained using study ECGs and hospital discharge records. This could lead to under ascertainment of AF cases diagnosed on outpatient basis as well as asymptomatic and paroxysmal AF cases, although the validity of using these methods for AF ascertainment is satisfactory. 22% of HF cases were unclassified due to the absence of LVEF measurements which may have led to misclassification bias. Despite the large sample, the number of AF events in each HF category was limited, reducing the precision of estimates of association.

According to previous studies, the prevalence of AF among those with HFrEF is high, ranging from 15% to 40% and is higher among participants with HFpEF reflecting older age. In a large community-based cohort study in Olmsted county, the incidence of AF among HFpEF was 31.6%, similar to Nji et al's incidence of 27.5%. However, in an analysis of a cohort of ambulatory patients with HF, the AF incidence only 15%. This contrast could be due to differences between the studied populations, such as mean age, race and distribution of risk factors of AF.

Reinhardt et al (2021) examined current trends in AF among hospitalisations for HF with preserved (HFpEF) ejection fraction or HF with reduced ejection fraction (HFrEF) in the US.⁷⁵ Methods and Results Using the National Inpatient Sample, they identified 10 392 189 hospitalizations for HF between 2008 and 2017, including 4 250 698 with comorbid AF (40.9%). HF hospitalisations with AF involved patients who were older (average age, 76.9 versus 68.8 years) and more likely White individuals (77.8% versus 59.1%; $P < 0.001$ for both). HF with preserved ejection fraction hospitalisations had more comorbid AF than HF with reduced ejection fraction (44.9% versus 40.8%). Over time, the proportion of comorbid AF increased from 35.4% in 2008 to 45.4% in 2017, and patients were younger, more commonly men, and Black or Hispanic individuals.

Comorbid hypertension, diabetes mellitus, and vascular disease all increased over time. HF hospitalizations with AF had higher in-hospital mortality than those without AF (3.6% versus 2.6%); mortality decreased over time for all HF (from 3.6% to 3.4%) but increased for HF with reduced ejection fraction (from 3.0% to 3.7%; $P < 0.001$ for all). Median hospital charges were higher for HF admissions with AF and increased 40% over time (from \$22 204 to \$31 145; $P < 0.001$). Conclusions AF is increasingly common among hospitalizations for HF and is associated with higher costs and in-hospital mortality. Over time, patients with HF and AF

⁷⁵ Reinhardt, S. W., Chouairi, F., Miller, P. E., et al . (2021). National Trends in the Burden of Atrial Fibrillation During Hospital Admissions for Heart Failure. *Journal of the American Heart Association*, 10(11), e019412.
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were younger, less likely to be White individuals, and had more comorbidities; in-hospital mortality decreased.

Understanding the temporal association by left ventricular ejection fraction (LVEF) group may be relevant to optimize and personalize care for HF patients to target preventive efforts and reduce risk of AF. However, the sample size of the FHS was too small to stratify by HF subtypes and follow-up for incident AF.

Pellicori et al (2019) determined the prevalence and incidence of AF in ambulatory patients with HF.⁷⁶ HF was defined by the presence of symptoms or signs supported by objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) $\leq 45\%$ (HF and a reduced ejection fraction, HFrEF), or LVEF $>45\%$ and a raised plasma concentration of amino-terminal pro-B type natriuretic peptide (NT-proBNP >220 ng/L; HFpEF). Of 3,570 patients with HF, 1,164 were in AF at baseline (33%), with a higher prevalence among patients with HFpEF compared with HFrEF (40% vs 26%, respectively, $p < 0.001$).

Compared with patients with HF in sinus rhythm, those in AF were older, had more severe symptoms and higher NT-proBNP, worse renal function, and were more likely to receive loop diuretics, despite having a higher LVEF. Of those in sinus rhythm, 1,372 patients had HFrEF and 1,034 had HFpEF. The incidence of AF at 1 year (3.0%) was similar for each phenotype ($p = 0.73$). Increasing age, male gender, history of paroxysmal AF, and higher plasma concentrations of NT-proBNP were independent predictors of incident AF during a median follow-up of 1,574 (interquartile range: 749 to 2,821) days; the predictors were similar for each phenotype. In conclusion, the prevalence of AF is high, especially in patients with HFpEF, but its incidence is modest. This may be because their onset is near simultaneous with the development of AF precipitating the onset of HF.

Summary and conclusions

Congestive heart failure is a well-known risk factor for non-surgical AF.

Atrial fibrillation and heart failure are both highly prevalent diseases and are accompanied by a significant disease burden and increased mortality (Verhaert et al 2021). There is a complex inter-relationship between heart failure and atrial fibrillation and either condition may predispose to the other through several potential mechanisms. Although the conditions may exist independently, they often go hand in hand as each is able to provoke, sustain, and aggravate the other. In addition, the diseases share a risk profile with several coinciding cardiovascular risk factors, promoting the odds of developing both AF and HF separately from each other. When the diseases coexist, this provides additional challenges but also opportunities for the optimal treatment. Bavishi & Patel (2020) observe that up to 62% of individuals with HF may have AF at some point during their life course.

As outlined by Tsigkas et al (2021) heart failure and atrial fibrillation are among the commonest causes of cardiovascular disease. While the coexistence both of these diseases

⁷⁶ Pellicori, P., Urbinati, A., Kaur, K., et al (2019). Prevalence and Incidence of Atrial Fibrillation in Ambulatory Patients With Heart Failure. *The American journal of cardiology*, 124(10), 1554–60. August meeting 2022

is quite common as the presence of HF increases the likelihood of AF and vice versa. The prevalence of AF in HF patients ranges from 10 to 50%, depending on the severity of HF; the more severe the HF, the more likely is the AF to appear. The new onset or permanent AF is related with worse prognosis in patients with established HF.

Atrial fibrillation is the most common arrhythmia complicating heart failure. Heart failure and AF frequently coexist and share many risk factors. Either condition may predispose to the other through several potential mechanisms. Rather than being independent disease processes, it has been suggested that they may be different endpoints along a disease continuum. The complex epidemiology of HF and AF coexistence involves bilateral self-perpetuating pathomechanisms. Many cases of AF and HF result from the cumulative exposure of the atria and ventricles to a common set of systemic cardiovascular risk factors.

A bidirectional pathophysiological link connects heart failure and atrial fibrillation, creating a frequent and challenging comorbidity, which includes neurohormonal hyperactivation, fibrosis development, and electrophysiological remodelling, while they share mutual risk factors. Management for these devastating comorbidities includes most of the established treatment measures for heart failure as well as rhythm or rate control and anticoagulation mostly for atrial fibrillation, which can be achieved with either pharmaceutical or non-pharmaceutical approaches (Tsigas et al 2021).

The association of heart failure with incident AF continues to be demonstrated in recent analytical studies such as Nij et al (2021). The analysis of the ARIC cohort showed that the prevalence and incidence of AF was high among HF patients of all subtypes, particularly among those with HF with reduced ejection fraction. Prevalent HF was associated with increased risk of AF (HR 2.3, 95CI 1.6-3.2) for HF with preserved ejection fraction, 5.0 (95CI 2.7-9.3) for HF with midrange ejection fraction, 3.5 (95CI 1.7-7.6) for HF with reduced ejection fraction, 1.9 (95CI 0.9-3.7) for unclassified HF.

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between heart failure and atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between heart failure and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

A factor for heart failure should be retained in the RH and BoP SoPs, with wording changed from 'cardiac failure' to 'heart failure'.

Hypertension

Current factor

RH and BoP - onset and worsening

having hypertension at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Arterial hypertension plays a significant role in the pathogenesis of AF and its complications (Dzheka et al 2017). Hypertension is a well recognised causal factor for AF; and was documented in several large cohort studies in the 1990s. Hypertension has is the most prevalent, independent, and potentially modifiable risk for atrial fibrillation, although the relative risk of developing atrial fibrillation in patients with hypertension is modest (RR 1.4 to 2.1).

Summary of previous investigation

Atrial fibrillation and hypertension often coexist. Hypertension is considered to be an established risk factor for AF; and was documented in several large cohort studies in the 1990s. Hypertension has been described as the most prevalent, independent, and potentially modifiable risk for atrial fibrillation (Healey and Connolly 2003), although the relative risk of developing atrial fibrillation in patients with hypertension is modest (RR 1.4 to 2.1).

The treatment of hypertension is recognised in the medical literature to postpone or prevent development of atrial fibrillation. It is known that elevated blood pressure causes left ventricular hypertrophy, left atrial dilatation, and modifications of atrial mechanical function, which promote AF.

The absence of a history of hypertension was documented as a risk factor for AF in the UK GRPD study (Hodgkinson et al 2010). Previously, the Framingham Heart Study found that hypertension significantly associated with risk AF (Benjamin et al 1994); Cardiovascular Health Study identified, echocardiographic evidence of enlarged left atrium, treated systemic hypertension, as independently associated with AF (Furberg et al 1994). The findings of an increased risk of AF in relation to hypertension have been replicated in studies from several countries.

There is, however, no clear epidemiological data describing the temporal relationship between hypertension and the onset of AF. The Framingham Heart Study shows no clear risk gradient between baseline blood pressure and lifetime risk of AF. It is possible that AF risk may be more strongly related to proximate hypertension.

In the Framingham cohort (Lloyd-Jones et al 2004) lifetime risk AF/AFL was similar across blood pressure strata in younger participants, with better discrimination of lifetime risk at older index ages. The lifetime risk for AF did not increase markedly with increasing level of baseline blood pressure, particularly for younger index ages. The failure to identify a positive association of AF with baseline blood pressure is attributed to the presence of competing risk for death in lifetime risk analysis, and the weak gradient of lifetime risk for AF across blood pressure strata in younger participants may be due to the long interval between baseline blood pressure assessment and incidence of AF.

Reviews

There have been many comprehensive narrative review studies of the association between hypertension and atrial fibrillation.^{77 78 79 80}

As outlined in one of these qualitative review studies of risk factors for AF by **Staerk et al (2017)**, hypertension is a well recognised causal factor for this arrhythmia.⁸¹

Due to close relation between the both diseases and their frequent coexistence, hypertension and AF become major health issues.⁸² The multidirectional link between raised blood pressure and AF is based on complex associations including structural, haemodynamic, neuroendocrine, and autonomic mechanisms. Hypertension provokes excessive fibroblasts proliferation and increased collagen accumulation. It stimulates cardiomyocytes apoptosis and inflammation, leading to diffused fibrosis and left ventricular hypertrophy development. This is mainly driven by renin-angiotensin-aldosterone system (RAAS) activation, and autonomic dysregulation. Exposure on long-term stretch due to hypertension causes arterial stiffness with subsequent systolic and diastolic function loss resulting in further heart muscle remodelling.

The CHARGE-AF consortium observed that both systolic and diastolic blood pressure were predictive of AF risk. (Alonso et al 2013) systolic blood pressure that approaches the upper limit of normal is associated with increased AF risk in healthy, middle aged men and women. The Women's Health Study showed that when an individual's blood pressure remained elevated at follow-up visits, the risk of AF was higher compared to those whose subsequent blood pressure recordings were lower suggesting a role for secondary prevention (Conon et al 2009). The 50-year analysis of the Framingham Health Study showed that while the rate of treated hypertension increased and severe hypertension became less prevalent, the population-attributed risk of AF was unaffected suggesting that anti-hypertensive therapy does not completely eliminate the elevated AF risk associated with hypertension (Schnabel et al 2015).

Increased left atrial size is a well-established independent predictor of AF, but other pathological features of chronic hypertension including left ventricular hypertrophy and impaired diastolic dysfunction, are also associated with AF. Common to all is an elevated left ventricular end-diastolic pressure, which increases left atrial pressure and volume. Atrial

⁷⁷ Kallistratos, M. S., Poulimenos, L. E., & Manolis, A. J. (2018). Atrial fibrillation and arterial hypertension. *Pharmacological research*, 128, 322–326.

⁷⁸ Andreadis, E. A., & Geladari, C. V. (2018). Hypertension and atrial fibrillation: a bench to bedside perspective. *Frontiers in bioscience (Scholar edition)*, 10(2), 276–284.

⁷⁹ Gumprecht, J., Domek, M., Lip, G., et al. (2019). Invited review: hypertension and atrial fibrillation: epidemiology, pathophysiology, and implications for management. *Journal of human hypertension*, 33(12), 824–36.

⁸⁰ Dzeshka, M. S., Shahid, F., Shantsila, A., et al. (2017). Hypertension and Atrial Fibrillation: An Intimate Association of Epidemiology, Pathophysiology, and Outcomes. *American journal of hypertension*, 30(8), 733–55.

⁸¹ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17.

⁸² Gumprecht, J., Domek, M., Lip, G., et al. (2019). Invited review: hypertension and atrial fibrillation: epidemiology, pathophysiology, and implications for management. *Journal of human hypertension*, 33(12), 824–36.

remodelling is associated with slower and more heterogeneous atrial conduction and increased pulmonary vein firing. Increased left atrial mass supports multiple reentry circuits.

Studies of animal models of hypertension have reported that early left atrial remodeling is characterized by atrial dilation with hypertrophy, reduced atrial ejection fraction, increased refractoriness, and prominent inflammatory infiltrates. Chronically, interstitial fibrosis and conduction slowing and heterogeneity are observed, as is increased atrial apoptosis. Electrophysiology studies in patients with chronically treated hypertension without AF, have shown global conduction slowing, regionally delayed conduction in the crista terminalis and increased AF inducibility.

Animal studies have suggested that the renin-angiotensin-aldosterone system, which stimulates myocyte hypertrophy and intracellular fibrosis, may contribute to atrial remodeling. While upstream RAAS blockage was effective in animal models for reducing AF remodeling, two separate meta-analyses have reported that the benefit of RAAS blockade was limited to patients with HF or left ventricular hypertrophy.

Individual BP variability may represent an individual's inability to maintain homeostasis and is an important marker of cardiovascular outcomes.⁸³ BP variability over time may be an important factor in determining atrial arrhythmia risk. Atrial arrhythmias are often asymptomatic. Focusing on clinically detected arrhythmias identified from periodic ECGs, diagnosis codes, and death certificates will underestimate the population burden of atrial arrhythmias.

Cohort studies

Krittayaphong et al (2021) investigated the associations between average systolic blood pressure (SBP) and outcomes in a nationwide cohort of Asian patients with non-valvular atrial fibrillation (NVAf).⁸⁴

Patients and methods: A multicentre nationwide registry of patients with NVAf in Thailand was conducted during 2014-2017. Clinical data, including blood pressure, were recorded at baseline and then every 6 months. Average SBP was calculated from the average of SBP from every visit. Cox regression models were used to calculate the rate of clinical outcomes of interest, i.e. ischemic stroke or transient ischaemic attack (TIA), intracerebral haemorrhage (ICH), and all-cause death. Average SBP was categorized into three groups: <120, 120-140, and ≥140 mmHg.

A total of 3402 patients were included, and the mean age was 67.4±11.3 years. The mean (±SD) baseline and average SBPs were 128.5±18.5 and 128.0±13.4 mmHg, respectively. The mean follow-up duration was 25.7±10.6 months. The median rate of ischemic stroke/TIA, ICH,

⁸³ Harding, B. N., Norby, F. L., Heckbert, S. R., et al. (2021). Longitudinal Measures of Blood Pressure and Subclinical Atrial Arrhythmias: The MESA and the ARIC Study. *Journal of the American Heart Association*, 10(11), e020260.

⁸⁴ Krittayaphong, R., Pumprueg, S., Ratanasumawong, K., et al (2021). Average Systolic Blood Pressure and Clinical Outcomes in Patients with Atrial Fibrillation: Prospective Data from COOL-AF Registry. *Clinical interventions in aging*, 16, 1835–46.

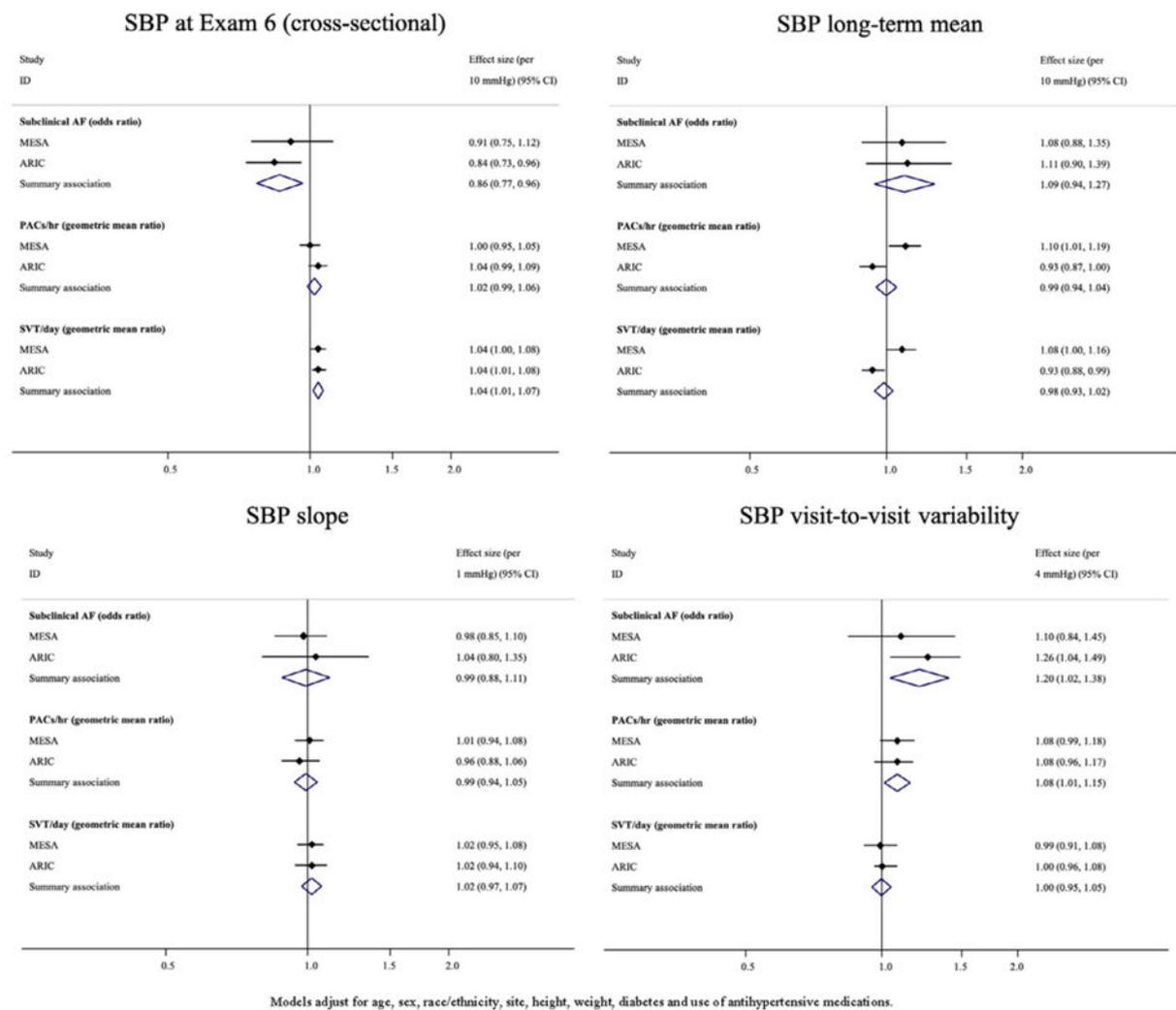
and all-cause death was 1.43 (1.17-1.74), 0.70 (0.52-0.92), and 3.77 (3.33-4.24) per 100 person-years, respectively. The rate of ischaemic stroke/TIA and ICH was lowest in patients with average SBP <120 mmHg, and highest among those with average SBP ≥140 mmHg. The death rates were consistent with a J-curve effect, being lowest in patients with an average SBP 120-140 mmHg. Sustained SBP control is more important than the SBP from a single visit.

Sustained control of SBP was significantly associated with a reduction in adverse clinical outcomes in patients with NVAf.

Although high blood pressure is a well-known risk factor for atrial fibrillation, a single BP measurement may provide limited information about AF risk in older adults. **Harding et al (2021)** studied longitudinal measures of blood pressure and subclinical atrial arrhythmias. This cohort study included 1256 MESA (Multi-Ethnic Study of Atherosclerosis) and 1948 ARIC (Atherosclerosis Risk in Communities) study participants who underwent extended ambulatory electrocardiographic monitoring and who were free of clinically detected cardiovascular disease, including AF. The MESA (Multi-Ethnic Study of Atherosclerosis) and the ARIC (Atherosclerosis Risk in Communities) study recently conducted extended ambulatory cardiac monitoring on study participants. This extended ECG monitoring provides an unbiased, high-quality assessment of atrial fibrillation (AF) as well as supraventricular

Using BP measurements from 6 examinations (2000-2018 in MESA and 1987-2017 in ARIC study), Harding et al calculated individual long-term mean, trend, and determined visit-to-visit variability in systolic BP and pulse pressure for each participant. Outcomes, assessed at examination 6, included subclinical AF and supraventricular ectopy. Results from each study were combined with inverse variance-weighted meta-analysis. At examination 6, the mean age was 73 years in MESA and 79 years in ARIC study, and 4% had subclinical AF. Higher visit-to-visit detrended variability in systolic BP was associated with a greater prevalence of subclinical AF (OR 1.20; 95CI 1.02-1.38) and with more premature atrial contractions/hour (geometric mean ratio, 1.08; 95CI 1.01-1.15). For pulse pressure as well, higher visit-to-visit detrended variability was associated with a greater prevalence of AF (OR 1.18; 95CI 1.00-1.37). Higher long-term mean pulse pressure was associated with a greater prevalence of subclinical AF (OR 1.36; 95CI 1.08-1.70).

FIGURE 5 META-ANALYSIS FOR ASSOCIATIONS BETWEEN SYSTOLIC BLOOD PRESSURE (SBP) EXPOSURE VARIABLES AND ATRIAL ARRHYTHMIAS.



Harding et al (2021), Fig 3

It was concluded that antecedent visit-to-visit variability in systolic BP and pulse pressure, but not current BP, was associated with a higher prevalence of subclinical atrial arrhythmias. Prior longitudinal BP assessment, rather than current BP, may be more helpful in identifying older adults who are at higher risk of atrial arrhythmias

In contrast to prior studies, which found that elevated cross-sectional SBP is associated with a greater prevalence of clinical AF, Harding et al found that higher cross-sectional SBP was associated with less subclinical AF. This difference may be explained in part by the older age of MESA and ARIC study participants, or by differences in the underlying demographics of the MESA and ARIC study populations. One possible explanation is selection bias; healthy participants in MESA and ARIC are more likely to return for follow-up examinations.

The association between the cumulative hypertension burden and the development of atrial fibrillation is unclear. **Lee et al (2021)** investigated the relationship between hypertension

burden and the development of incident AF.⁸⁵ Using the Korean National Health Insurance Service database, 3 726 172 subjects were identified who underwent 4 consecutive annual health check-ups between 2009 and 2013, with no history of AF. During the median follow-up of 5.2 years, AF was newly diagnosed in 22 012 patients (0.59% of the total study population; 1.168 per 1000 person-years).

Using blood pressure values at each health check-up, the authors determined the burden of hypertension (systolic BP \geq 130 mm Hg or diastolic BP \geq 80 mm Hg), stratified as 0 to 4 per the hypertension criteria. Subjects were grouped according to hypertension burden scale 1 to 4: 20% (n=742 806), 19% (n=704 623), 19% (n=713 258), 21% (n=766 204), and 21% (n=799 281).

Compared with normotensive people, those with hypertension burdens of 1, 2, 3, and 4 were associated with an 8%, 18%, 26%, and 27% increased risk of incident AF, respectively. In semi quantitative analyses with stratification of stage 1 (systolic BP of 130-139 mm Hg or diastolic BP of 80-89 mm Hg) and stage 2 (systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg) hypertension, the risk of AF increased with hypertension burden by up to 71%. In this study, both a sustained exposure and the degree of increased BP were associated with an increased risk of incident AF.

Summary and conclusions

Hypertension is strongly associated with incident atrial fibrillation and AF-related complications. On a population basis, high blood pressure is considered to be the major independent risk factor for atrial fibrillation. The incidence of both diseases has increased significantly in the recent decades

Atrial fibrillation and arterial hypertension often coexist, because arterial hypertension increases the incidence of new onset of atrial fibrillation, and also because both conditions share common risk factors that increase the incidence of each disorder.

Hypertension is an established risk factor for AF; and was documented in several large cohort studies in the 1990s. Hypertension is associated with a 1.8-fold increase in the risk of developing new-onset AF and a 1.5-fold increase in the risk of progression to permanent AF (Ogonsua et al 2015). Hypertension predisposes to cardiac structural changes that influence the development of AF such as atrial remodelling. Hypertension has been described as the most prevalent, independent, and potentially modifiable risk for atrial fibrillation, although the relative risk of developing atrial fibrillation in patients with hypertension is modest (RR 1.4 to 2.1).

The treatment of hypertension is recognised in the medical literature to postpone or prevent development of atrial fibrillation. It is known that elevated blood pressure causes left

⁸⁵ Lee, S. R., Park, C. S., Choi, E. K., et al . (2021). Hypertension Burden and the Risk of New-Onset Atrial Fibrillation: A Nationwide Population-Based Study. *Hypertension* (Dallas, Tex. : 1979), 77(3), 919–28

ventricular hypertrophy, left atrial dilatation, and modifications of atrial mechanical function, which promote AF.

Antecedent visit-to-visit variability in systolic BP and pulse pressure, but not current BP, is associated with a higher prevalence of subclinical atrial arrhythmias. Prior longitudinal BP assessment, rather than current BP, may be more helpful in identifying older adults who are at higher risk of atrial arrhythmias (Harding et al 2021).

Arterial hypertension plays a significant role in the pathogenesis of AF and its complications (Dzheka et al 2017). Structural changes in left and right cardiac chambers that occur in arterial hypertension may lead to an increased risk of atrial fibrillation (Cameli et al 2018). Despite the large amount of data in the existing medical literature, the pathophysiology of AF in patients with hypertensive heart disease is poorly understood, and the underlying signalling pathways linking hypertension to AF remain to be fully elucidated. The multidirectional association between raised blood pressure and AF is based on complex associations including structural, hemodynamic, neuroendocrine, and autonomic mechanisms. Hypertension provokes excessive fibroblasts proliferation and increased collagen accumulation. It also stimulates cardiomyocytes apoptosis and inflammation, leading to diffused fibrosis and left ventricular hypertrophy development.

Left ventricular hypertrophy and left atrial remodelling during hypertension favour the development of atrial fibrillation. AF during hypertension increases the risk of thromboembolic complications and heart failure. In patients with hypertension, pharmacological treatment may control the cardiac structural changes and retard or prevent the occurrence of atrial fibrillation.

Fibroblast proliferation, apoptosis of cardiomyocytes, gap junction remodeling, accumulation of collagen both in atrial and ventricular myocardium all accompany ageing-related structural remodeling with impact on electrical activity. The presence of hypertension also stimulates oxidative stress, systemic inflammation, rennin-angiotensin-aldosterone and sympathetic activation, which further drives the remodelling process in AF

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between hypertension and atrial fibrillation and atrial flutter (Grade one). A consistent association has been observed between hypertension and atrial fibrillation and atrial flutter and chance, bias and confounding can be ruled out with reasonable confidence.

A factor for hypertension should be retained in the RH and BoP SoPs, but the temporal parameters should be changed to hypertension *before* the clinical onset of atrial fibrillation and flutter, as per other arrhythmia SoPs

Pulmonary embolism

No factor

Summary of important issues

Pulmonary thromboembolism, particularly pulmonary embolism (PE) is routinely listed in the clinical literature as an acute precipitant of atrial fibrillation, but the amount and quality of evidence is limited. There is growing evidence of atrial fibrillation involvement in PE.

Review studies

Venous thromboembolic disease, which includes deep vein thrombosis and pulmonary embolism, is associated with an increased risk of AF. The mechanism is not known but has been speculated to be related to the increase in pulmonary vascular resistance and cardiac afterload, which may lead to right atrial strain.⁸⁶

Pulmonary embolism (PE) is a common, potentially fatal thrombotic disease. Atrial fibrillation, the most common arrhythmia, may also lead to thromboembolic complications. Although initially appearing as distinct entities, PE and AF may coexist. The direction and extent of this association has not been well characterised.

Bikdeli et al (2017) performed a search of PubMed, Scopus, and the Cochrane Database of Systematic Reviews for publications that reported coexisting AF in patients with PE, or vice versa, to provide a systematic overview of pathophysiological and epidemiological aspects of this association to October 2016.⁸⁷

The authors screened 650 articles following the PubMed search, and 697 through Scopus. PE and AF share many common risk factors, including old age, obesity, heart failure, and inflammatory states. PE may lead to AF through right-sided pressure overload or inflammatory cytokines. AF, in turn, might lead to right atrial appendage clot formation and thereby PE. AF can be a presenting sign during the early phase, or later in the course of recovery from PE. Patients with AF are also at increased risk of developing PE, a risk that correlates with the CHA2DS2-VASc score. .

Ptaszynska-Kopczynska et al (2019) observed in a review study of this topic that pulmonary embolism is one of the most common causes of cardiovascular death. The most common PE aetiology is a deep vein thrombosis (DVT) of the lower extremities, but embolic material can arise in pelvic or upper extremity veins as well as in right heart chambers. There is growing evidence of atrial fibrillation involvement in PE. The presence of AF in patients with PE may be both the cause and the consequence of PE.⁸⁸

⁸⁶ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

⁸⁷ Bikdeli, B., Abou Ziki, M. D., & Lip, G. (2017). Pulmonary Embolism and Atrial Fibrillation: Two Sides of the Same Coin? A Systematic Review. *Seminars in thrombosis and hemostasis*, 43(8), 849–63

⁸⁸ Ptaszynska-Kopczynska, K., Kiluk, I., & Sobkowicz, B. (2019). Atrial Fibrillation in Patients with Acute Pulmonary Embolism: Clinical Significance and Impact on Prognosis. *BioMed research international*, 2019, 7846291

AF may arise as a consequence of an abrupt increase in pulmonary vascular resistance due to the occlusion of the pulmonary vessels. Large-scale population-based studies have provided a considerable body of evidence on the involvement of PE in the onset of subsequent AF. Although the pathophysiological basis of this bidirectional relationship exists, many questions are still unresolved. The significance of paroxysmal AF accompanying an acute PE episode, the usefulness of PE risk scales in patients with concomitant AF, and the effect of anticoagulant treatment on PE and AF occurrence remains uncertain.

Cohort study.

Pulmonary embolism may trigger atrial fibrillation through increased right atrial pressure and subsequent atrial strain, but the quantity of analytical evidence describing this well-recognised association is limited. **Hald et al (2014)** investigated the impact of incident venous thromboembolism (VTE) on future risk of atrial fibrillation in a prospective population-based study.⁸⁹

The study included 29 974 subjects recruited from the Tromsø study (1994-1995, 2001-2002, 2007-2008). Incident VTE and atrial fibrillation events were registered from date of enrolment to end of follow-up, December 31, 2010. Cox proportional hazard regression models using age as time-scale and VTE as a time-dependent variable were used to estimate crude and multivariable hazard ratios (HRs) for atrial fibrillation with 95% confidence intervals (CIs).

During 16 years of follow up, 540 (1.8%) subjects had an incident VTE event, and 1662 (5.54%) were diagnosed with atrial fibrillation. Among those with VTE, 50 (9.3%) developed subsequent atrial fibrillation. Patients with VTE had 63% higher risk of AF compared to subjects without VTE (multivariable-adjusted HR: 1.63, 95CI 1.22-2.17). The risk of atrial fibrillation was particularly high during the first 6 months after the VTE event (HR 4.00, 95CI 2.21 - 7.25) and among those with PE (HR 1.78, 95CI 1.13 - 2.80).

In this cohort study, incident VTE was associated with future risk of atrial fibrillation. These findings support the hypothesis that PE may lead to cardiac dysfunctions that, in turn, could trigger atrial fibrillation.

The incidence of AF in patients with acute or chronic venous thromboembolic disease has not been well studied. It has been reported to be in the 10 to 14% percent range in patients with documented pulmonary embolism (Goldhaber et al 1999)

Cross-sectional studies

Acute pulmonary embolism (APE) is a serious clinical situation and atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The Pulmonary Embolism Severity Index (PESI) is an accepted risk stratification tool used to predict short term mortality in APE. **Sahan et al**

⁸⁹ Hald EM, Enga KF, Løchen ML, et al (2014) Venous thromboembolism increases the risk of atrial fibrillation: the Tromsø study. *J Am Heart Assoc.*;3(1):e000483. Epub 2014 Jan 2
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(2019) conducted a study to evaluate the relationship between the PESI score and new-onset AF in patients with APE.⁹⁰

The records of 869 APE patients admitted between May 2012 and December 2015 were evaluated retrospectively. The PESI score was calculated for every patient. Clinical variables associated with new-onset AF in APE were assessed after the exclusion of patients with hypertension, coronary or hemodynamically significant valvular heart disease, hepatic or renal dysfunction, chronic obstructive pulmonary disease, thyroid dysfunction, diabetes mellitus, sleep apnea, any history of inflammatory or infectious disease, or recent trauma. New-onset AF was detected in 42 (4.8%) patients.

Age, sex, systolic and diastolic blood pressure, heart rate, fasting glucose level, serum creatinine, left ventricle ejection fraction, tricuspid annular plane systolic excursion value, and pulmonary artery systolic pressure measures were not significantly different between patients with and without AF. New-AF patients demonstrated larger LVEDD and LAD dimensions ($p < 0.001$ for both). The PESI score was higher in the new-onset AF group (93 ± 23 vs. 75 ± 17 ; $p < 0.001$). LVEDD, LAD, levels of uric acid, bilirubin, albumin, and troponin, and PESI score were univariate predictors of new-onset AF.

In patients with APE, the PESI score was positively correlated with new-onset AF. It was suggested that a PESI score > 82.50 may be useful to predict new-onset AF in these patients.

Summary and conclusions

Pulmonary thromboembolism, particularly pulmonary embolism (PE) is routinely listed in the clinical literature as an acute precipitant of atrial fibrillation but the amount and quality of evidence is limited.

PE is a common, potentially fatal thrombotic disease (Bikdeli et al 2017). Atrial fibrillation, the most common arrhythmia, may also lead to thromboembolic complications. Although initially appearing as distinct entities, PE and AF may coexist. The direction and extent of this association has not been well characterised.

Pulmonary embolism may trigger atrial fibrillation through increased right atrial pressure and subsequent atrial strain. The incidence of AF in patients with acute or chronic venous thromboembolic disease has not been well studied. It has been reported to be in the 10 to 14% range in patients with documented pulmonary embolism (Goldhaber et al 1999)

PE and AF share many common risk factors, including old age, obesity, heart failure, and inflammatory states. PE may lead to AF through right-sided pressure overload or inflammatory cytokines. AF, in turn, might lead to right atrial appendage clot formation and thereby PE (Bikdeli et al 2017). AF can be a presenting sign during the early phase, or later in the course of recovery from PE. Patients with AF are also at increased risk of developing PE.

⁹⁰ Şahan, E., Şahan, S., Karamanlıoğlu, M., et al (2019). Prediction of new onset atrial fibrillation in patients with acute pulmonary embolism: The role of sPESI Score. Akut pulmoner emboli hastalarında yeni gelişen atriyal fibrilasyon öngörücülüğü: sPESI Skoru'nun rolü. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir, 47(3), 191–7. Abstract only
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There is growing amount of evidence of atrial fibrillation involvement in PE. The presence of AF in patients with PE may be both the cause and the consequence of PE (Ptaszynska-Kopczynska et al 2019). Although the pathophysiological basis of this bidirectional relationship exists, many questions are still unresolved

AF may arise as a consequence of an abrupt increase in pulmonary vascular resistance due to the occlusion of the pulmonary vessels. Large-scale population-based studies have provided evidence on the involvement of PE in the onset of subsequent AF. The significance of paroxysmal AF accompanying an acute PE episode, the usefulness of PE risk scales in patients with concomitant AF, and the effect of anticoagulant treatment on PE and AF occurrence remains uncertain.

In the Tromso study, a prospective population-based study of nearly 30,000 individuals of whom 1.8% had an incident venous thromboembolism (VTE) event and 5.4% were diagnosed with AF during 16-year follow-up [Hald et al 2014]. The risk of AF was higher in those with VTE than in those without after multivariable adjustment (HR 1.63, 95CI 1.22-2.17). This risk was particularly high in the first six months after the VTE event. The risk of atrial fibrillation was particularly high during the first 6 months after the VTE event (HR 4.00, 95CI 2.21 - 7.25) and among those with PE (HR 1.78, 95CI 1.13 - 2.80).

In relation to pulmonary thromboembolism, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between pulmonary embolus and the triggering of atrial fibrillation and flutter, but the evidence is limited in quality or quantity. Case reports provide evidence of temporal link and a biomechanical or pathophysiological mechanism.

A new factor for pulmonary thromboembolism should be added for pulmonary thromboembolism (RH and BoP).

Thyroid disease

Current factor

RH and BoP - onset and worsening

having hyperthyroidism, thyrotoxicosis, Graves' disease or thyrotoxic goitre at the time of the clinical onset of atrial fibrillation or atrial flutter; or

having subclinical hyperthyroidism at the time of the clinical onset of atrial fibrillation or atrial flutter;

"subclinical hyperthyroidism" means having normal free thyroxine (FT4) and total triiodothyronine (T3) levels in conjunction with a thyrotropin (TSH) level persistently below the normal range in the absence of factors known to suppress TSH;

Summary of important issues

It is well recognised that overt hyperthyroidism is associated with AF. In general, the frequency and severity of symptoms correlates with the biochemical severity of thyrotoxicosis,

and antithyroid treatment reverses the acute risk of AF in hyperthyroidism. Observational studies also report an association between subclinical hyperthyroidism and incident atrial fibrillation. There is little data about the relationship between hypothyroidism and AF, although previous studies suggested that hypothyroidism might be associated with AF.

Summary of previous investigation

It is well recognised in the medical literature that overt hyperthyroidism is associated with atrial fibrillation. AF was evident in 6% of a consecutive case-control series of hyperthyroid patients (Osman et al 2007). A population-based study showed that 8.3% of hyperthyroid participants had a new diagnosis of atrial fibrillation within 30 days of diagnosis of hyperthyroidism (Frost and Vestergaard 2004). In general, the frequency and severity of symptoms correlates with the biochemical severity of thyrotoxicosis, and antithyroid treatment reverses the acute risk of atrial fibrillation in hyperthyroidism. Observational studies have also increasingly reported an association between subclinical hyperthyroidism and incident atrial fibrillation.

Selmer et al (2012) demonstrated a linear relation (“dose-response”) between levels of thyroid dysfunction (TSH levels) and atrial fibrillation risk in a nationwide cohort study from Denmark, with a low risk in overt hypothyroidism, high risk in hyperthyroidism, and a dose-response relation between TSH level and atrial fibrillation across the spectrum of subclinical hyperthyroid disease; data suggests a long term effect on the heart caused by the subclinical thyroid dysfunction.

A meta-analysis by Collet et al (2012), based on 10 prospective cohorts and a total of 52 674 pooled participants, found increased risk of atrial fibrillation in subclinical hyperthyroid patients (HR 1.68; 95CI 1.16-2.43) and 150% increased risk in those with TSH levels <0.1 mIU/L; with attributable risk of 41.5% for AF in individuals with subclinical hyperthyroidism. Pooled data suggested that the risk of AF in individuals with endogenous subclinical hyperthyroidism is higher with lower thyrotropin levels and is mostly pronounced in those with thyrotropin levels < 0.10 mIU/L. No clinical trials have assessed whether treating subclinical hyperthyroidism results in improved cardiovascular outcomes.

Reviews

Atrial fibrillation is recognised as the most common supraventricular arrhythmia in patients with thyrotoxicosis.⁹¹ In patients with hyperthyroidism, the prevalence of AF ranges between 2 and 20%, and their risk of AF is approximately six-fold higher than that of healthy people (Klein and Danzi 2007). The primary consideration for the management of AF is to control heart rate. B-blockers are one of the widely used drugs in the treatment of AF in cases of hyperthyroidism. These drugs can bring down the ventricular rate and stabilize the rapid symptoms, but they have little effect on converting AF to sinus rhythm or on hyperthyroidism. Therefore, treatment of hyperthyroidism is optimal for long-term AF management. This normally employs radioiodine treatment or antithyroid drugs (ATDs), which can restore sinus rhythms within a few months in the majority of hyperthyroidism patients (Nakazawa et al.

⁹¹ Yamakawa, H., Kato, T. S., Noh, J. Y., et al. (2021). Thyroid Hormone Plays an Important Role in Cardiac Function: From Bench to Bedside. *Frontiers in physiology*, 12, 606931
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2000). One prospective study in middle-aged and elderly people in Rotterdam (Rotterdam Study) reported that the risk of AF, sudden cardiac death, and decreased life expectancy is associated with elevated free T4 levels, even if thyroid function is within normal limits (Bano et al. 2017; Razvi et al. 2018).⁹²

There have been many review studies decreasing the association of AF and thyroid diseases.

93 94 95

The comprehensive review study by **Higa et al (2021)** summarised the current state of knowledge about the AF risk factors diabetes mellitus and thyroid disease, and discusses the impact of the modification of these risk factors on primary and secondary prevention of AF.⁹⁶

Hyperthyroidism has been reported to have a three- to six-fold risk of AF s compared with euthyroid. AF is reported in 10% to 15% of those with hyperthyroidism and the prevalence increases with age. 25% of elderly patients with hyperthyroidism (>60 years old) had AF as compared with 5% in younger patients (<60 years).

Currently, there are little data about the relationship between hypothyroidism and AF. Although a few previous studies suggested that hypothyroidism might be associated with AF, a population cohort from Denmark demonstrated that there is a low risk of AF in overt hypothyroidism (Selmer et al. 2013).

Both genomic and nongenomic actions of thyroid hormones on ionic currents and their mRNA expression, myosin heavy chain (alfa isoforms) expression, sarcoplasmic reticulum calcium activated ATPase, β_1 -adrenergic receptors, and phospholamban all contribute to AF genesis. Thyroid hormone increased the automaticity and enhanced triggered activity of PV cardiomyocytes. These findings were followed by a clinical study showing increased ectopic activity in hyperthyroidism. genome-wide association studies have highlighted PITX2 as a major player causing AF. Lozano-Valasco et al reported that hyperthyroidism impairs PITX2 expression leading to Wnt-microRNA-ion channel remodeling.

There are few studies regarding the association between hypothyroidism and AF. An increased AF susceptibility in hypothyroidism has been reported. Chen et al reported that hypothyroidism accelerates myocardial fibrosis. Therefore, increased myocardial fibrosis may lead to prolongation of the effective refractory period and slow conduction with anisotropy promoting reentry formation causing AF arrhythmogenesis.

⁹² Yamakawa, H., Kato, T. S., Noh, J. Y., et al. (2021). Thyroid Hormone Plays an Important Role in Cardiac Function: From Bench to Bedside. *Frontiers in physiology*, 12, 606931

⁹³ Gawalko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

⁹⁴ Yamakawa, H., Kato, T. S., Noh, J. Y., et al. (2021). Thyroid Hormone Plays an Important Role in Cardiac Function: From Bench to Bedside. *Frontiers in physiology*, 12, 606931

⁹⁵ Baumgartner, C., da Costa, B. R., Collet, T. H., et al (2017). Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. *Circulation*, 136(22), 2100–16.

⁹⁶ Higa, S., Maesato, A., Ishigaki, S., et al. (2021). Diabetes and Endocrine Disorders (Hyperthyroidism/Hypothyroidism) as Risk Factors for Atrial Fibrillation. *Cardiac electrophysiology clinics*, 13(1), 63–75

Because hyperthyroid and hypothyroid animals show different anatomical and electrophysiological remodelling, different mechanisms may be involved in AF genesis in hyperthyroidism and hypothyroidism.

AF spontaneously converts to sinus rhythm in 62% of patients once a euthyroid state is achieved, but a higher age and longer AF duration can predict persistent AF. In amiodarone-induced hypothyroidism, Huang et al reported that thyroxine monotherapy without amiodarone enhanced AF recurrences and might be an unfavourable treatment. Ablation outcomes in patients with a previous history of hyperthyroidism have been reported.

Machino et al reported that hyperthyroidism was not associated with a higher risk of AF recurrence. Sousa et al showed that the F-T3 level influenced ablation outcomes. Although PV isolation alone has a lower efficacy for hyperthyroidism, the final overall outcomes after repeat procedures are similar to control subjects. A higher prevalence of non-PV ectopy is demonstrated in hyperthyroidism. Ablation strategies to eliminate all AF-initiating ectopic foci are essential to achieve favourable outcome

TABLE 5 STUDIES OF CATHETER ABLATION OUTCOMES RELATED TO THYROID DISEASE

Publication Year (Ref.)	Study Design	Population n (%)	Age y/o (SD)	History of Hyperthyroidism (+) n (%)	History of Hyperthyroidism (-) n (%)	Mean Follow-Up (mo)	Risk of AF/AT Recurrence
Ma et al, ⁶⁹ 2007	Retrospective/observational	16, paroxysmal/persistent (62%/38%)	60 (11)	16 (100%)	—	16	9 (56%) were AF free (off drug) 7 (44%) recurred, and 4 (25%) responded to AADs
Machino et al, ⁷⁰ 2012	Retrospective/observational	337, paroxysmal/persistent (57%/43%)	61 (9)	16 (4.7%)	321 (95.3%)	48	No significant difference between the 2 groups (HR, 0.87; 95% CI, 0.40–1.88; P = .73)
Mikhaylov et al, ⁷¹ 2013 ^a	Retrospective/observational/case-control	704, paroxysmal (100%)	58 (5)	AIH (+) 20 (33%)	AIH (-) 40 (67%)	12	AIH (+) was an independent predictor of a recurrence
Sousa et al, ⁷² 2015 ^b	Retrospective/observational	1095, paroxysmal/persistent/LAAT (59.7%/32.3%/8%)	60 (10)	FT4 (ng/L): 10.6–14.6, ≥14.6 824 (75%)	FT4 (ng/L): <10.6 271 (25%)	13	FT4 level could predict recurrence with a 15% increase per quartile (interquartile range, 10.6–14.6; HR, 1.15; 95% CI, 1.03–1.29; P = .014)
Wongcharoen et al, ⁷³ 2015 ^c	Retrospective/observational	717, paroxysmal/persistent (75%/25%)	55 (10)	84 (12%)	633 (88%)	32	History of hyperthyroidism could be an independent predictor of a recurrence after a single procedure (HR, 2.07; 95% CI, 1.27–3.38; P = .014)
Wang et al, ⁷⁴ 2016	Retrospective/observational/case-control	146, paroxysmal (100%)	61 (9)	20 AIH (+)	30 AIH (-)	<3, 3–12	AIH (+) exhibited a significantly higher early recurrence within the blanking period but not beyond 3–12 mo

Source: Higa et al (2021), Table 2

Subclinical hyperthyroidism is a common clinical entity, defined by serum TSH below the reference range, with normal FT4 and FT3 levels in an asymptomatic patient. Whether subclinical hyperthyroidism should be treated remains uncertain.⁹⁷ Cross-sectional and longitudinal population-based studies demonstrate association of subclinical hyperthyroidism with risk of atrial fibrillation and osteoporosis, and with cardiovascular and all-cause mortality. However, there are no randomized clinical trials addressing whether long-term health outcomes are improved by treating subclinical hyperthyroidism; in the absence of evidence one way or the other, it seems appropriate to use decision trees taking account of TSH concentration and presence of risk factors (age>65 years or post-menopause, osteoporosis and cardiac disease

⁹⁷ Bel Lassen, P., Kyriilli, A., Lytrivi, M., et al. (2019). Graves' disease, multinodular goiter and subclinical hyperthyroidism. *Annales d'endocrinologie*, 80(4), 240–9.

Although overt thyroid dysfunction has been associated with adverse clinical outcomes, uncertainty remains about the implications of subclinical thyroid disease. Available data suggest that subclinical hypothyroidism may be associated with increased risk of cardiovascular disease and death.⁹⁸ However, treatment with thyroid hormone has not been consistently demonstrated to reduce cardiovascular risk. Subclinical hyperthyroidism has been associated with increased risk of atrial fibrillation and osteoporosis, but the association with cardiovascular disease and death is uncertain. The decision to treat depends on the degree of thyroid-stimulating hormone suppression and underlying comorbidities.

The risk of AF is increased in subclinical hyperthyroidism, but it is uncertain whether variations in thyroid function within the normal range or subclinical hypothyroidism are also associated with AF.

Cohort studies

Subclinical thyroid dysfunction, defined as thyroid-stimulating hormone levels outside the reference range with normal free thyroxine levels in asymptomatic patients, is associated with alterations in cardiac hemodynamic. **Larsson et al (2019)** used Mendelian randomisation to assess the role of thyroid dysfunction for cardiovascular disease (CVD).⁹⁹

Single-nucleotide polymorphisms associated with thyroid function were identified from a genome-wide association meta-analysis in up to 72 167 individuals. Data for genetic associations with CVD were obtained from meta-analyses of genome-wide association studies of AF (n=537 409 individuals), coronary artery disease (n=184 305 individuals), and ischaemic stroke (n=438 847) as well as from the UK Biobank (n=367 703 individuals).

Genetically predicted thyroid-stimulating hormone levels and hyperthyroidism were statistically significantly associated with atrial fibrillation but no other CVDs at the Bonferroni-corrected level of significance ($P < 7.8 \times 10^{-4}$). The odds ratios of atrial fibrillation were 1.15 (95CI 1.11-1.19) per genetically predicted 1 SD decrease in thyroid-stimulating hormone levels and 1.05 (95CI 1.03-1.08) for genetic predisposition to hyperthyroidism. Genetically predicted free thyroxine levels were not statistically significantly associated with any CVD.

This Mendelian randomisation study supports evidence for a causal association of decreased thyroid-stimulating hormone levels in the direction of a mild form of hyperthyroidism with an increased risk of atrial fibrillation but no other CVDs

Increased free thyroxine (FT4) and decreased thyrotropin are associated with increased risk of atrial fibrillation in observational studies, but direct involvement is unclear. **Ellervik et al. (2019)** assessed the relationship between genetic determinants of thyroid function and AF in a Mendelian randomisation study, to evaluate the potential direct involvement of thyroid traits on

⁹⁸ Evron, J. M., & Papaleontiou, M. (2021). Decision Making in Subclinical Thyroid Disease. *The Medical clinics of North America*, 105(6), 1033–45.

⁹⁹ Larsson, S. C., Allara, E., Mason, A. M., et al. (2019). Thyroid Function and Dysfunction in Relation to 16 Cardiovascular Diseases. *Circulation. Genomic and precision medicine*, 12(3), August meeting 2022

AF.¹⁰⁰ The Study-level Mendelian randomisation (MR) included 11 studies, and summary-level MR included 55 114 AF cases and 482 295 referents, all of European ancestry.

Genome wide significant variants were used as instruments for standardised FT4 and thyrotropin levels within the reference range, standardized triiodothyronine (FT3):FT4 ratio, hypothyroidism, standardized thyroid peroxidase antibody levels, and hyperthyroidism. Mendelian randomization used genetic risk scores in study-level analysis or individual single-nucleotide polymorphisms in 2-sample MR for the summary-level data.

The study-level analysis included 7679 individuals with AF and 49 233 referents (mean age [62 years; 15 859 men [29.7%]). In study-level random-effects meta-analysis, the pooled hazard ratio of FT4 levels (nanograms per decilitre) for incident AF was 1.55 (95CI 1.09-2.20; P = .02; I² = 76%) and the pooled OR for prevalent AF was 2.80 (95CI, 1.41-5.54; P = .003; I² = 64%) in multivariable-adjusted analyses. The FT4 genetic risk score was associated with an increase in FT4 by 0.082 SD (standard error, 0.007; P < .001) but not with incident AF (RR 0.84; 95CI 0.62-1.14; P = .27) or prevalent AF (OR 1.32; 95CI 0.64-2.73; P = .46). Similarly, in summary-level inverse-variance weighted random-effects MR, gene-based FT4 within the reference range was not associated with AF (OR 1.01; 95C, 0.89-1.14; P = .88). However, gene-based increased FT3:FT4 ratio, increased thyrotropin within the reference range, and hypothyroidism were associated with AF with inverse-variance weighted random-effects OR of 1.33 (95CI 1.08-1.63; P = .006), 0.88 (95CI 0.84-0.92; P < .001), and 0.94 (95CI 0.90-0.99; P = .009), respectively, and robust to tests of horizontal pleiotropy. However, the subset of hypothyroidism single-nucleotide polymorphisms involved in autoimmunity and thyroid peroxidase antibodies levels were not associated with AF. Gene-based hyperthyroidism was associated with AF with MR-Egger OR of 1.31 (95CI 1.05-1.63; P = .02).

It was concluded that genetically increased FT3:FT4 ratio and hyperthyroidism, but not FT4 within the reference range, were associated with increased AF, and increased thyrotropin within the reference range and hypothyroidism were associated with decreased AF, supporting a pathway involving the pituitary-thyroid-cardiac axis.

Cross-sectional studies

Sonawale & Chichkhede (2018) evaluated the incidence of cardiovascular abnormalities in newly identified hyperthyroid patients and their outcome with anti-thyroid therapy.¹⁰¹ 96 patients newly diagnosed with hyperthyroid disease were screened. 40 patients presenting with cardiovascular symptoms and signs and were included (30 females, 10 males). Hyperthyroid patients were re-evaluated after antithyroid therapy. Findings in patients were compared at presentation, and after 3 month of treatment. All underwent a structured

¹⁰⁰ Ellervik, C., Roselli, C., Christophersen, I. E., et al. (2019). Assessment of the Relationship Between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study. *JAMA cardiology*, 4(2), 144–52.

¹⁰¹ Sonawale, A., & Chichkhede, A. (2018). Cardiovascular Manifestations in Newly Diagnosed Hyperthyroid Patients and their Outcome with Anti-Thyroid Treatment. *The Journal of the Association of Physicians of India*, 66(6), 22–26
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cardiovascular history and examination, including measurements of blood pressure (BP) and pulse rate. All had resting 12-lead electrocardiogram and 2D ECHO.

Cardiovascular symptoms and signs, as well as abnormal hemodynamic and dysrhythmias, especially supraventricular, were frequent among patients with hyperthyroidism. Palpitation and atrial fibrillation were more recurrent in overt hyperthyroid subjects than those with subclinical hyperthyroidism and remained more prevalent after 3 months of antithyroid treatment in the subject with persistently high serum T3 and T4.

Whether patients with atrial fibrillation and thyroid disease are clinically distinct from those with AF and no thyroid disease is unknown. **Goldstein et al. (2019)** described the characteristics and outcomes of AF in patients with thyroid disease (from the ARISTOTLE Trial).¹⁰² Patients enrolled in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, which compared apixaban with warfarin in patients with AF (n = 18,201), were categorized by thyroid disease history at randomization (hypothyroidism, hyperthyroidism, and no thyroid disease). Adjusted hazard ratios derived from Cox models were used to compare outcomes by thyroid disease history.

Associations between randomized treatment and outcomes by thyroid disease history were examined using Cox models with interaction terms. A total of 18,021/18,201 (99%) patients had available thyroid disease history at randomization: 1,656 (9%) had hypothyroidism, 321 (2%) had hyperthyroidism, and 16,044 (89%) had no thyroid disease. When compared with those without a history of thyroid disease, patients with hypo- or hyperthyroidism were more likely to be female (60.4% vs 32.1%; 52.0% vs 32.1%; both p <0.0001). Patients with hypothyroidism were older (73 vs 70 years, p <0.0001) and more likely to have had previous falls (8.7% vs 4.3%, p <0.0001).

There was no difference in clinical outcomes by thyroid disease history. The benefit of apixaban compared with warfarin was similar regardless of thyroid disease history (interaction p >0.10). In conclusion, despite differences in baseline characteristics of patients with and without thyroid disease, their clinical outcomes were similar. The benefit of apixaban compared with warfarin was preserved regardless of thyroid disease history

Summary and conclusions

It is well recognised in the medical literature that overt hyperthyroidism is associated with atrial fibrillation. In general, the frequency and severity of symptoms correlates with the biochemical severity of thyrotoxicosis, and antithyroid treatment reverses the acute risk of atrial fibrillation in hyperthyroidism. Observational studies have also increasingly reported an association between subclinical hyperthyroidism and incident atrial fibrillation.

¹⁰² Goldstein, S. A., Green, J., Huber, K., et al. (2019). Characteristics and Outcomes of Atrial Fibrillation in Patients With Thyroid Disease (from the ARISTOTLE Trial). *The American journal of cardiology*, 124(9), 1406–12.
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Hyperthyroidism is a strong independent risk factor for AF and worsens outcomes of rhythm control strategies. (Higa et al 2021 Atrial fibrillation is recognised as the most common supraventricular arrhythmia in patients with thyrotoxicosis (Yamakawa et al 2021). In patients with hyperthyroidism, the prevalence of AF ranges between 2 and 20%, and their risk of AF is approximately six-fold higher than that of healthy people.

The most common cardiac rhythm disorder in Graves' disease patients is AF (Gawalko et al 2020). Sawin et al reported a 2.8-fold increased risk of AF in individuals with subclinical hyperthyroid aged >60 years. AF in hyperthyroid patients is explained by a decreased atrial refractory period, increased sympathetic tone with decreased HRV, and automaticity in the pulmonary vein. AF spontaneously converts to sinus rhythm in 62% of patients once a euthyroid state is achieved, but a higher age and longer AF duration can predict persistent AF.

Berker et al reported that improvements in atrial conduction were associated with euthyroidism regardless of the chosen therapy. Patients with GD and AF who become hypothyroid are more likely to revert to sinus rhythm than those who are rendered euthyroid during this period.

Subclinical hyperthyroidism is a common clinical entity, defined by serum TSH below the reference range, with normal FT4 and FT3 levels in an asymptomatic patient. Whether or not subclinical hyperthyroidism should be treated remains a matter of debate. Cross-sectional and longitudinal population-based studies demonstrate association of subclinical hyperthyroidism with risk of atrial fibrillation (Bel Lassen et al. 2019).

There are little data about the relationship between hypothyroidism and AF, although a few previous studies suggested that hypothyroidism might be associated with AF. A population cohort from Denmark demonstrated that there is a low risk of AF in overt hypothyroidism (Selmer et al. 2013.). Chen et al reported that hypothyroidism accelerates myocardial fibrosis. increased myocardial fibrosis may lead to prolongation of the effective refractory period and slow conduction with anisotropy promoting reentry formation causing AF arrhythmogenesis.

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between hyperthyroidism and atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between hyperthyroidism, in coding Grave's disease and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

In relation to hypothyroidism, evidence the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality and quantity. Case reports provide evidence of temporal link and a biomechanical or pathophysiological mechanism.

A factor for hyperthyroidism, including subclinical hyperthyroidism, should be retained in the RH and BoP SoPs. This factor should accommodate the existing RMA SoPs covering thyroid disorders, which include Graves' disease; and hyperthyroidism and thyrotoxicosis.

Hypothyroidism should be added to the RH SoPs. This should be included as a subfactor in the list of thyroid disorders.

Alcohol, including binge drinking

Current factors

RH and BoP - onset and worsening

consuming an average of at least 140 grams [BoP 175 grams] of alcohol per week for a continuous period of at least the five years before the clinical onset of atrial fibrillation or atrial flutter; or

"**alcohol**" is measured by the alcohol consumption calculations utilising the Australian Standard of ten grams of alcohol per standard alcoholic drink;

onset only - RH only

binge drinking within the seven days before the clinical onset of atrial fibrillation or atrial flutter; or

"**binge drinking**" means drinking an excessive amount of alcohol in a short amount of time, resulting in a blood alcohol concentration exceeding 0.08. This typically involves the consumption of four or more standard alcoholic drinks for a woman or five or more standard alcoholic drinks for a man within a two hour time period;

Summary of important issues

Alcohol is an increasingly recognised risk factor for both new onset AF and a trigger of discrete AF episodes. AF occurs in up to 60% of binge drinkers with or without an underlying alcoholic cardiomyopathy. Most cases occur during and following weekends or holidays when alcohol intake is increased, termed "the holiday heart syndrome". Even modest amounts of alcohol (one to two drinks) can trigger AF in some patients.

Binge drinking is an important risk factor in paroxysmal AF, especially in younger people, but is not a risk factor for persistent or permanent AF. Habitual alcohol consumption is associated with atrial remodelling, higher risk of incident AF, and AF recurrence. Randomised data suggest that reduction in excessive alcohol consumption may reduce the risk of recurrent AF episodes and AF burden.

Summary of previous investigation

Alcohol is the dietary factor most frequently assessed in relation to AF.

Alcohol has been traditionally linked to AF through the "holiday heart" syndrome, in which AF episodes after periods of intense "binge-" drinking on weekends or holidays. Binge drinking is considered to be main risk factor in paroxysmal AF, the most common form of AF in younger

people, but is not considered to be a risk factor for persistent or permanent AF. Up to 34% of patients with paroxysmal AF report that alcohol consumption precedes episodes, but previous studies are descriptive and lack comparator group, precluding quantitative evaluation of whether alcohol as trigger for AF more often than expected by chance alone.

Mandayanm et al (2012) conducted a clinical experimental study; patients with paroxysmal AF had a 4.42 greater odds (95CI 1.35-14.44) of reporting alcohol consumption and a 2.02 greater odds (95CI 1.02-4.00) of reporting vagal activity as an arrhythmia trigger compared to patients with other SVT. Biological mechanisms underlying the association between alcohol consumption and PAF episodes remain unclear. Given the relatively acute timing between alcohol consumption or vagal activation and arrhythmia episodes, it is presumed that these triggers act by some dynamic mechanism that leads to functional, rather than structural, changes. Vagal activation and acute alcohol exposure appear to have electrophysiological effects that can promote

Recently, it has been hypothesised that not only episodic but also habitual heavy alcohol consumption is associated with the risk of AF. However, epidemiological studies of this hypothesis have been inconsistent; Acute alcohol intake and binge drinking have been related to AF. Epidemiological data of the long-term relation of alcohol intake have been inconsistent.

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However the data is not wholly consistent. A recent update of the Framingham Heart study- (Shen et al 2011) found only a marginal association between moderate-to-heavy drinking and increased risk of AF, possibly because of a small group of moderate-to-heavy drinkers in this population. in the Danish Diet, Cancer, and Health Study (Frost and Vestergaard 2004). the consumption of alcohol was associated with an increased risk of atrial fibrillation or flutter in men. In women, moderate consumption of alcohol did was not associated with risk of atrial fibrillation or flutter. There was a stronger association between alcohol and atrial flutter than with atrial fibrillation in case control study (Marcus et al 2008)

Reviews

Alcohol is both a chronic risk factor for the development of new AF and also an acute trigger for AF episodes.¹⁰³ AF occurs in up to 60 percent of binge drinkers with or without an underlying alcoholic cardiomyopathy. Most cases occur during and following weekends or holidays when alcohol intake is increased, a phenomenon that has been termed "the holiday heart syndrome." However, even modest amounts of alcohol (one to two drinks) can trigger AF in some patients [Marcus et al 2021].¹⁰⁴

The evidence is mixed for long-term alcohol consumption being a risk factor for developing new AF. Moderate, long-term alcohol consumption was not shown to be a risk factor for AF in relatively small studies. A positive association was found in a study of 79,019 men and women

¹⁰³ Uptodate

¹⁰⁴ Marcus GM, Vittinghoff E, Whitman IR, et al. Acute Consumption of Alcohol and Discrete Atrial Fibrillation Events. *Ann Intern Med* 2021; 174:1503.

free from AF at baseline [Larsson et al 2014]. Compared with current drinkers of <1 drink per week, the multivariable risk ratios of AF were 1.01 (95CI 0.94-1.09) for one to six drinks per week, 1.07 (95CI 0.98-1.17) for 7 to 14 drinks per week, 1.14 (95CI 1.01-1.28) for 15 to 21 drinks per week, and 1.39 (95CI 1.22-1.58) for >21 drinks per week.

Heavy alcohol consumption is associated with a greater increase in incidence of AF. Two large cohort studies found an increased incidence among men with heavy alcohol consumption (HR 1.45 in both) [Frost et al 2004; Mukamal et al 2005]. Neither study found a correlation between heavy alcohol use and AF in women, but the ability to detect such a correlation was limited by the small numbers of women with alcohol consumption in this range. Another study of 1055 cases of AF occurring during long-term follow-up found an increased risk (relative risk 1.34, 95CI 1.01-1.78) with consumption of > 36 grams per day (approximately >3 drinks/day) [Djousse et al 2005].

There have been many recent comprehensive review studies on alcohol and AF.^{105 106 107 108 109 110 111} Selected findings from one or two of these reviews are reported herein.

Atrial fibrillation following an alcohol binge or the "holiday heart syndrome" is well characterised.¹¹² However, more modest levels of alcohol intake on a regular basis may also increase the risk of AF. The pathophysiological mechanisms responsible for the relationship between alcohol and AF may include direct toxicity and alcohol's contribution to obesity, sleep-disordered breathing, and hypertension.

Voskoboinik & Marcus (2020) evaluated the impact of acute and habitual alcohol consumption on atrial fibrillation and atrial remodelling and the role of alcohol reduction and/or abstinence in the primary and secondary prevention of AF.¹¹³

Alcohol is an increasingly recognised risk factor for both new onset AF and discrete AF episodes. Acute alcohol consumption appears to be a common AF trigger, with animal and human studies demonstrating changes in electrophysiological parameters, autonomic tone, and cellular properties expected to promote AF. Habitual consumption is associated with adverse atrial remodelling, higher risk of incident AF, and AF recurrence. Randomised data

¹⁰⁵ Voskoboinik, A., Prabhu, S., Ling, L. H., et al. (2016). Alcohol and Atrial Fibrillation: A Sobering Review. *Journal of the American College of Cardiology*, 68(23), 2567–76.

¹⁰⁶ O'Sullivan J. W. (2021). Alcohol and atrial fibrillation: to or not to drink?. *BMJ evidence-based medicine*, 26(6), e14

¹⁰⁷ Day, E., & Rudd, J. (2019). Alcohol use disorders and the heart. *Addiction (Abingdon, England)*, 114(9), 1670–8

¹⁰⁸ Gallagher C, Hendriks JML, Lau DH, et al (2018). Alcohol and atrial fibrillation. *Int J Cardiol.*; 251:6.

¹⁰⁹ Roerecke M. (2021). Alcohol's Impact on the Cardiovascular System. *Nutrients*, 13(10), 3419

¹¹⁰ Sidhu, K., & Tang, A. (2017). Modifiable Risk Factors in Atrial Fibrillation: The Role of Alcohol, Obesity, and Sleep Apnea. *The Canadian journal of cardiology*, 33(7), 947–949

¹¹¹ Mittal, R., Su, L., Ramgobin, D., et al. (2022). A narrative review of chronic alcohol-induced atrial fibrillation. *Future cardiology*, 18(1), 27–34.

¹¹² Voskoboinik, A., & Marcus, G. M. (2020). The Impact of Alcohol Intake on Atrial Fibrillation. *Current cardiology reports*, 22(10), 111.

¹¹³ Voskoboinik, A., & Marcus, G. M. (2020). The Impact of Alcohol Intake on Atrial Fibrillation. *Current cardiology reports*, 22(10), 111.

suggest that reduction in excessive alcohol consumption may reduce the risk of recurrent AF episodes and AF burden.

The acute onset of arrhythmias following binge drinking was first described in the 1970s and termed “holiday heart syndrome” due to the observed higher incidence of AF episodes after weekends and public holidays. Since then, numerous studies have studied the relationship between alcohol and AF..

Many observational studies have established a temporal association between acute alcohol consumption and onset of an AF episode in vulnerable individuals. This was first reported by Ettinger et al. who observed a higher incidence of alcohol-related atrial arrhythmias in binge drinkers following the weekend and in December and January. This was termed the “Holiday heart syndrome,” and while episodes usually terminated within 24 h, 26% of patients had recurrences over the next 12 months with subsequent binges.

In a case control of 100 individuals presenting with acute AF, alcohol intake within 2 days prior to presentation was significantly higher than in matched controls [Koskinen et al 1987]. In patients with paroxysmal AF, alcohol is the most commonly reported trigger—“sometimes” triggering AF in 31% and “always” triggering AF in 4% [Groh et al 2019].¹¹⁴ This study confirmed that alcohol was the most commonly reported AF trigger by patients.

However, the absolute incidence of arrhythmias following binge drinking in those without prior AF remains low. In 3028 young adults who undertook smartphone-based ECG monitoring after binge drinking during Oktoberfest, 26% had sinus tachycardia, 1.3% had premature atrial complexes, and 0.8% developed AF (Brunner et al 2017). There are likely undetermined mechanistic interactions between acute alcohol consumption and some underlying propensities, potentially genetic or environmental, that renders some individuals more versus less prone to alcohol induced AF.

Chronic alcohol intake is also related to risk of AF. Large-scale meta-analyses based on many population-based cohorts suggest that habitual alcohol consumption increases the risk of incident AF. The threshold for harm remains the uncertain, and not every study has demonstrated a clear association.

A meta-analysis of 7 prospective studies with 12,554 new cases of AF found a linear dose-response relationship starting at 1 standard drink per day (RR 1.08; 95CI 1.06-1.10), increasing by ~ 8% for each additional daily standard drink (1 standard drink ~ 12 g alcohol). Results were significant even after exclusion of binge drinkers, and wine and spirits appeared to have a stronger association than beer [Larsson et al 2014]. Therefore, no clear threshold regarding the amount of alcohol consumed in relation to AF risk has been established, but it appears that the risk simply increases as the amount of alcohol consumed increases.

A more recent meta-analysis suggested that “moderate” habitual consumption (1–2 drinks per day) was only associated with a heightened risk of AF in males (HR 1.26, 95CI 1.04–1.54) but

¹¹⁴ Groh CA, Faulkner M, Getabecha S, et al (2019). Patient-reported triggers of paroxysmal atrial fibrillation. *Heart Rhythm*, 16(7): 996-1002.

not females (HR 1.03, 95CI 0.86–1.25) while > 2 drinks/day remained significant for both sexes [Gallagher et al 2017].

A large Korean population-based study found that drinking frequency, rather than the amount consumed, carried the greatest risk of new AF. Patients who drank on a daily basis had the highest risk (HR 1.412, 95CI 1.373–1.453), while a larger amount of alcohol per drinking session did not increase the risk [Kim et al 2020]. The potential benefits of mild alcohol consumption on risk of cardiovascular disease, represented by a “U shaped” curve [21], need to be counterbalanced against the higher risk of AF, and individual-level predispositions that influence those relative harms and benefits. Interestingly, in a study comparing “wet” (no alcohol restrictions) and “dry” (alcohol prohibited) counties in Texas, wet counties had a higher prevalence and incidence of AF, but a lower incidence and prevalence of myocardial infarction. Conversion of a county from “dry” to “wet” was associated with a higher AF incidence [Dukes et al 2016].

There is consistent evidence of harmful effects on all cardiovascular outcomes when alcohol is consumed in excess. In a large Californian longitudinal healthcare database, those who “abused” alcohol had a higher risk of AF (HR 2.14, 95CI 2.08–2.19) [Whitman et al 2017],

In those with a history of AF, habitual alcohol consumption increases the risk of AF progression. In a UK registry of 418 paroxysmal AF patients followed for 2.7 years, moderate to- high alcohol consumption (> 21 drinks/week) was associated with progression to persistent AF (OR 3.0, 95CI 1.1–8.0) [Ruigomez et al 2005].

Higher recurrence rates in regular drinkers following catheter ablation of AF have also been observed. In a study of 1361 consecutive paroxysmal AF patients undergoing ablation, alcohol consumption (88 ± 137 g/week, 46% of patients) was associated with a higher AF recurrence rate after initial ablation (41.9% vs 34.1%; $p = 0.003$) [25]. Consumption frequency (HR 1.07, 95CI 1.00–1.15 per 1 day/week increase) most strongly predicted recurrence risk [Takigawa et al 2016]. In a smaller study of 122 consecutive patients with paroxysmal AF undergoing ablation, abstainers had the highest success rates (81.3%), followed by moderate (1–7 drinks/week in women, 1–14 drinks per week in men) drinkers (69.2%), and then heavy drinkers (35.1%; log-rank $p < 0.001$), with alcohol being a multivariate predictor of recurrence (HR 1.58; 95CI 1.09–2.30) [Qiao et al 2015]. In 40 patients with persistent AF undergoing ablation, consumption > 30 g/week was associated with a higher risk of arrhythmia recurrence [Hussein et al 2018].

TABLE 6 KEY STUDIES OF HABITUAL ALCOHOL INTAKE AND RISK OF INCIDENT AF

Study	AF cases/ participants	Follow-up	Study design	Summary of key findings
Krahn et al. [8] 1995	299/ 3983	44 years	Prospective cohort	“Alcoholism” was associated with higher risk of new AF (RR 2.07; 95% CI 1.38–3.10)
Wilhelmsen et al. [9] 2001	754/ 7495	25.2 years	Population-based cohort	“Alcohol abuse” associated with higher risk of AF hospitalization (OR 1.21; 95% CI 1.02–1.42)
Frost et al. [10] 2004	556/ 47,949	5.7 years	Prospective cohort	Increased risk of AF in men with increasing consumption, with adjusted HRs in quintiles 2, 3, 4, and 5 of 1.04, 1.44, 1.25, and 1.46, respectively (<i>p</i> for trend = 0.04). Trend not statistically significant for women
Mukamal et al. [11] 2005	1071/ 16,415	16.3 years	Prospective cohort	Heavier consumption in men (35+ SDs/week) increased the risk of incident AF (HR 1.45; 95% CI 1.02–2.04)
Conen et al. [12] 2008	653/ 34,715	12.4 years	Prospective cohort	Alcohol consumption \geq 14 SDs/week in women increased incident AF risk (HR 1.49; 95% CI 1.05–2.11)
Larsson et al. [13] 2014	6019/ 68,848	12 years	Prospective cohort	Dose-dependent increase in AF risk (RR 1.12, 1.18, 1.43 for 7–14 SDs/week, 15–21 SDs/week, >21 SDs/week, respectively, compared with < 1 SD/week). Wine and spirits increased AF risk, but not beer
McManus et al. [14] 2016	1088/5220	6.0 years	Prospective cohort	Each 10 g/day of alcohol associated with a 5% higher risk of new AF (HR 1.05; 95% CI, 1.01–1.09) and 24% (95% CI, 8–75) of this association explained by left atrial dilatation
Gemes et al. [15] 2017	1697/47002	8 years	Population-based cohort	Overall higher risk of AF in those drinking > 7 SDs/week compared with abstainers (HR 1.38; 95% CI 1.06–1.80), although “non-risky” drinking (< 1 SD/day in women, < 2 SD/day in men) did not demonstrate an association with AF
Dixit et al. [16] 2017	1631/15222	19.7 years	Prospective cohort	Each decade abstinent associated with a 20% (95% CI 11–28%) lower risk of new AF; every additional decade of previous consumption associated with a 13% (95% CI 3–25%) increase in AF risk
Bazal et al. [17] 2019	241/6527	4.4 years	Prospective observational study	Mediterranean drinking pattern (10–30 g/d in men & 5–15 g/day in women, red wine preferred) did not increase AF risk compared with non-drinkers (HR: 0.96; 95% CI: 0.67–1.37)
Johansson et al. [18] 2020	5320/ 109,230	1,484,547 person-years	Population-based cohort	Alcohol consumption was associated with higher risk of AF in men (HR 1.21; 95% CI 1.09–1.34 for > 5 SDs/week compared with < 1 SD/week; <i>p</i> = 0.001 for trend), but not women (<i>p</i> = 0.09 for trend)
Kim et al. [19] 2020	195,829/ 9,776,956	79,960,860 person-years	Population-based cohort	Daily drinkers had the highest risk of incident AF (HR 1.41; 95% CI 1.37–1.45) compared with those drinking twice/week; however, amount of intake per drinking session did not increase risk of incident AF

Voskoboinik & Marcus (2020), Table 1

Meta-analyses

Whilst high levels of alcohol consumption are known to be associated with atrial fibrillation (AF), it is unclear if any level of alcohol consumption can be recommended to prevent the onset of the condition. **Gallagher et al (2017)** conducted a systematic review and meta-analysis to characterise the association between chronic alcohol intake and incident AF.¹¹⁵

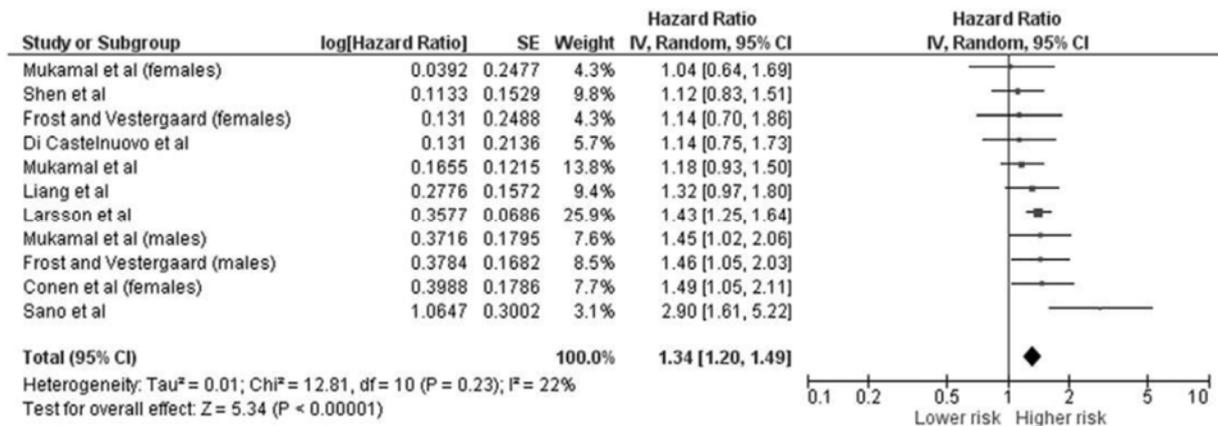
Electronic literature searches were undertaken using PubMed and Embase databases up to 1 February 2016 to identify studies examining the impact of alcohol on the risk of incident AF. Prospective studies reporting on at least three levels of alcohol intake and published in English were eligible for inclusion. Studies of a retrospective or case control design were excluded. The primary study outcome was development of incident AF.

Consistent with previous studies, high levels of alcohol intake (i.e the highest alcohol category in each study compared to the reference group) were associated with a significantly

¹¹⁵ Gallagher, C., Hendriks, J., Elliott, A. D., et al (2017). Alcohol and incident atrial fibrillation - A systematic review and meta-analysis. *International journal of cardiology*, 246, 46–52
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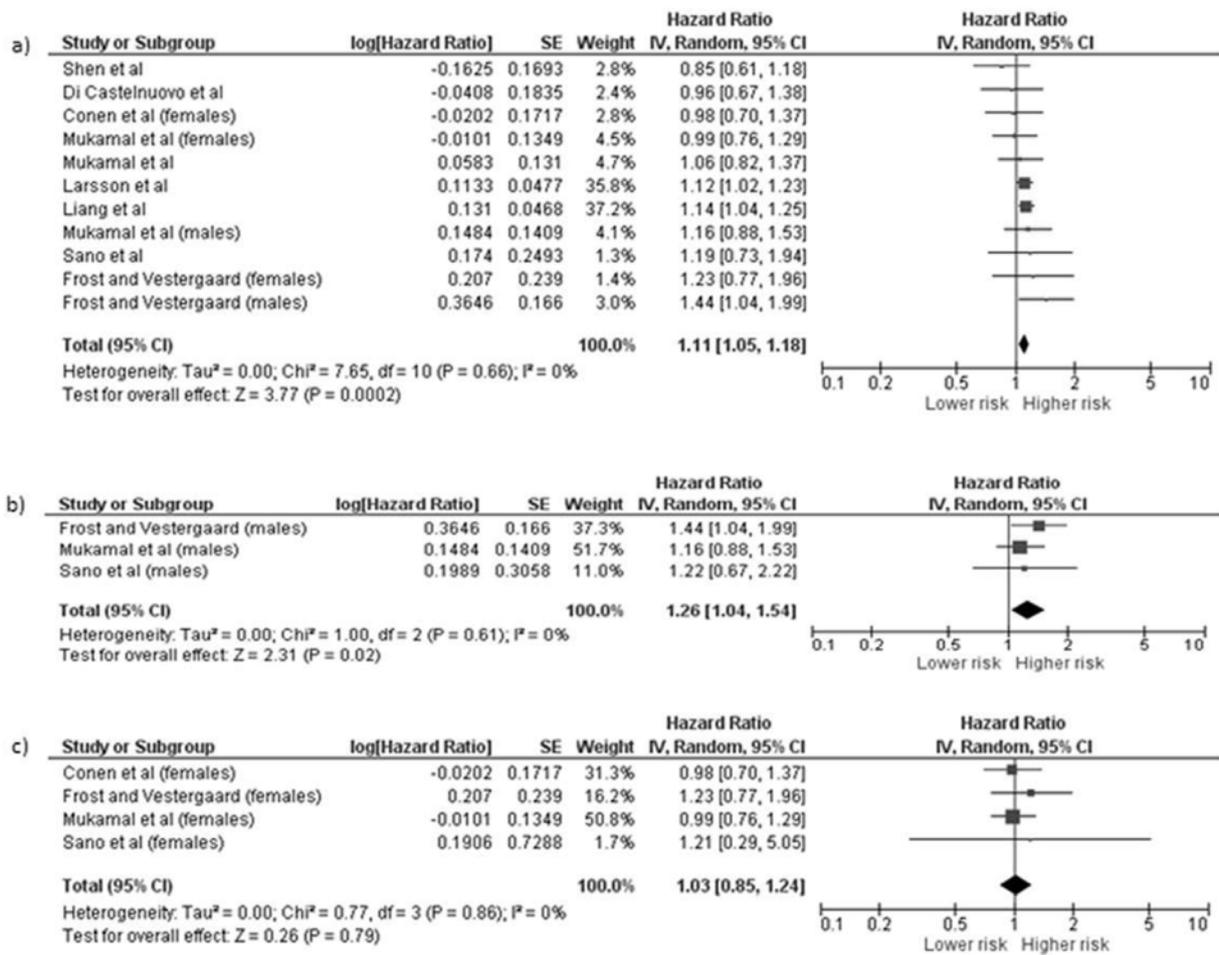
increased incident AF risk (HR 1.34, 95CI 1.20-1.49, $p < 0.001$), without evidence of significant heterogeneity between studies. High alcohol intake was associated with AF in both males and females. Chronic moderate levels of alcohol intake were associated with a small heightened AF risk in males (HR 1.26, 95CI 1.04-1.54) but not females (HR 1.03, 95CI 0.86-1.25). Chronic low alcohol consumption of up to 1 standard drink (SD) per day, was not associated with AF development (HR 0.95, 95CI 0.85-1.06, $p = 0.37$). there was no evidence that consumption of up to 6-7 standard drinks per week is associated with increased risk of AF.

FIGURE 6 RISK OF INCIDENT AF WITH HIGH ALCOHOL INTAKE COMPARED TO LOW OR NO INTAKE



Gallagher et al (2017), Fig 1, p 49

FIGURE 7 RISK OF INCIDENT AF WITH MODERATE ALCOHOL INTAKE OVERALL, IN MALES AND IN FEMALES



Gallagher et al (2017), Fig 1, p 49

Low levels of alcohol intake are not associated with the development of AF. Sex differences exist in the association between moderate alcohol intake and AF with males demonstrating greater increases in risk, whilst high alcohol intake is associated with a heightened AF risk across both genders.

Cohort studies

Cha et al (2020) investigated the effect of alcohol consumption on new-onset AF development in asymptomatic healthy individuals.¹¹⁶

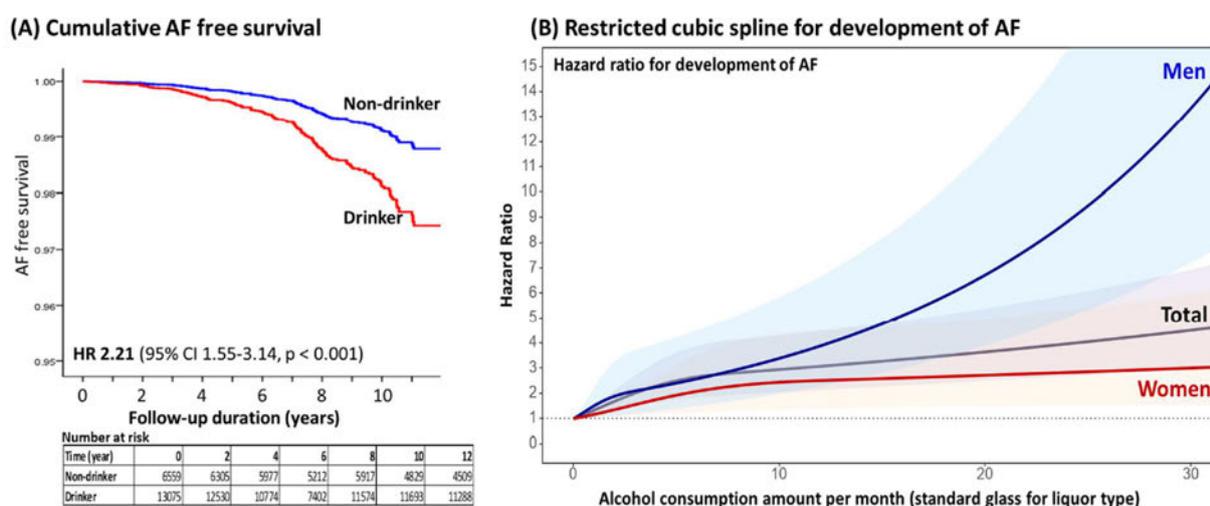
Asymptomatic healthy adults (age <75 years; body mass index <30 kg/m²) undergoing routine health examinations from 2007 to 2015 were screened. Those with sinus rhythm and without any previously diagnosed medical or surgical illness were recruited for analysis. The primary outcome was new-onset AF. Secondary outcomes were a composite of non-AF cardiac events, including clinically significant tachy- or bradyarrhythmias, acute myocardial infarction, heart failure, or cardiac death.

¹¹⁶ Cha, M. J., Oh, G. C., Lee, H., et al. (2020). Alcohol consumption and risk of atrial fibrillation in asymptomatic healthy adults. *Heart rhythm*, 17(12), 2086–92.
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Among 19,634 individuals (50% male; age 19-74 years), during a follow-up of 7.0 ± 2.8 years, 160 (0.8%) new-onset AF events were recorded (1.0% in 18 men and 0.7% in women).

The annual incidence of new-onset AF was higher in drinkers than non-drinkers (13 versus 8 per 10,000 person-year), regardless of sex. The incidence of new-onset AF was higher in drinkers (HR 2.21; 95CI 1.55-3.14; $P < .001$), whereas composite non-AF cardiac events were not correlated to alcohol. There was a dose-dependent increase in the risk of AF according to amount of alcohol consumed, and the risk increased more abruptly in men than in women. The risk of AF was highest in frequent binge drinkers (HR 3.15; 95CI 1.98-4.99; $P < .001$), compared to infrequent light drinkers.

FIGURE 8 RISK OF AF DEVELOPMENT IN DRINKERS



Cha et al (2020), Fig 2

The risk of alcohol consumption on AF development was consistent across various subgroups, except in the old age group (≥ 60 years) and the low body weight group (BMI < 20).

24% of drinkers consumed more than 5 standard drinks, and were defined as 'binge drinkers,' and 23% consumed alcohol more than once a week, and were defined as 'frequent drinkers.' The risk of AF in frequent, binge drinkers was 3.2 times higher than in infrequent, light drinkers (HR 3.15, 95CI 1.98-4.99, $p < 0.001$). Infrequent binge drinkers had a higher rate of AF development than frequent light drinkers (HR 1.54, 95CI 0.80-2.98, $p = 0.207$). The risk of AF with frequent, light drinking was not different from infrequent light drinking. Other than drinking frequency, binge drinking had a higher risk compared with light drinking (HR 2.31, 95CI 1.59-3.34, $p < 0.001$). After correcting for competing risks for AF development, frequent binge drinkers still had higher AF risks than infrequent light drinkers (SHR= 1.20, 95CI 1.13-1.27, $p < 0.001$)

In the asymptomatic healthy population, drinking increases the risk of new-onset AF in a dose-dependent manner, regardless of sex. Frequent binge drinking should be avoided

Excessive alcohol consumption is associated with incident atrial fibrillation and adverse atrial remodeling; however, the effect of abstinence from alcohol on secondary prevention of atrial fibrillation is unclear.

Voskoboinik et al (2020) conducted a multicentre, prospective, open-label, randomized, controlled trial at six hospitals in Australia.¹¹⁷ Adults who consumed 10 or more standard drinks (1 standard drink containing 12 g of pure alcohol) per week and who had paroxysmal or persistent atrial fibrillation in sinus rhythm at baseline were randomly assigned in a 1:1 ratio to either abstain from alcohol or continue their usual alcohol consumption. The two primary end points were freedom from recurrence of atrial fibrillation (after a 2-week "blinking period") and total AF burden (proportion of time in AF) during 6 months of follow-up.

Of 140 patients who underwent randomisation (85% men; mean [\pm SD] age, 62 \pm 9 years), 70 were assigned to the abstinence group and 70 to the control group. Patients in the abstinence group reduced their alcohol intake from 16.8 \pm 7.7 to 2.1 \pm 3.7 standard drinks per week (a reduction of 87.5%), and patients in the control group reduced their alcohol intake from 16.4 \pm 6.9 to 13.2 \pm 6.5 drinks per week (a reduction of 19.5%). After a 2-week blinking period, atrial fibrillation recurred in 37 of 70 patients (53%) in the abstinence group and in 51 of 70 patients (73%) in the control group. The abstinence group had a longer period before recurrence of atrial fibrillation than the control group (HR 0.55; 95CI 0.36-0.84; P = 0.005). The atrial fibrillation burden over 6 months of follow-up was significantly lower in the abstinence group than in the control group (median percentage of time in atrial fibrillation, 0.5% [interquartile range, 0.0 to 3.0] vs. 1.2% [interquartile range, 0.0 to 10.3]; P = 0.01).

It was concluded that arrhythmia recurrences in regular drinkers with atrial fibrillation were reduced after abstinence from alcohol.

There is inconsistent evidence on the relation of alcohol intake with incident atrial fibrillation in particular at lower doses. **Csengeri et al (2021)** assessed the association between alcohol consumption, biomarkers, and incident AF across the spectrum of alcohol intake in European cohorts.¹¹⁸

In a community-based pooled cohort, 107 845 individuals were followed for the association between alcohol consumption, including types of alcohol and drinking patterns, and incident AF. Information was collected on classical cardiovascular risk factors and incident heart failure (HF) and measured the biomarkers N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I. The median age was 47.8 years, 48.3% were men. The median alcohol consumption was 3 g/day.

¹¹⁷ Voskoboinik, A., Kalman, J. M., De Silva, A., et al. (2020). Alcohol Abstinence in Drinkers with Atrial Fibrillation. *The New England journal of medicine*, 382(1), 20–8.

¹¹⁸ Csengeri, D., Sprünker, N. A., Di Castelnuovo, A., et al. (2021). Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *European heart journal*, 42(12), 1170–7 August meeting 2022

5854 individuals developed AF (median follow-up time: 13.9 years). In a sex- and cohort-stratified Cox regression analysis alcohol consumption was non-linearly and positively associated with incident AF. The hazard ratio for one drink (12 g) per day was 1.16, 95CI 1.11-1.22, $P < 0.001$. Associations were similar across types of alcohol. In contrast, alcohol consumption at lower doses was associated with reduced risk of incident HF. The association between alcohol consumption and incident AF was neither fully explained by cardiac biomarker concentrations nor by the occurrence of HF.

In contrast to other cardiovascular diseases such as HF, even modest habitual alcohol intake of 1.2 drinks/day was associated with an increased risk of AF.

Marcus et al (2021) objectively assessed whether alcohol consumption heightens risk for an AF episode in a prospective, case-crossover analysis of ambulatory patients with paroxysmal AF.¹¹⁹ The study used wearable health devices to document drinking events in real time and established a causal relationship between acute alcohol consumption and the occurrence of AF in patients with paroxysmal AF.

Participants were fitted with a continuous ECG monitor and an ankle-worn transdermal ethanol sensor for 4 weeks. Real-time documentation of each alcoholic drink consumed was self-recorded using a button on the ECG recording device. Fingertick blood tests for phosphatidylethanol (PEth) were used to corroborate ascertainties of drinking events.

Of 100 participants (mean age 64 years [SD 15]; 79% male; 85% white), 56 had at least 1 episode of AF. Results of PEth testing correlated with the number of real-time recorded drinks and with events detected by the transdermal alcohol sensor. An AF episode was associated with 2-fold higher odds of 1 alcoholic drink (OR 2.02, 95CI 1.38-3.17) and > 3-fold higher odds of at least 2 drinks (OR 3.58, 95 CI 1.63-7.89) in the preceding 4 hours.

Even consuming 1 drink within the preceding 4 hours was associated with higher odds of AF (OR 2.02, 95CI 1.38-3.17). Although the median number of real-time recorded drinks was similar between those who had an AF episode (20 drinks) and those who did not (18 drinks), “any transdermal alcohol event” was higher in the AF group (38 events) than the non-AF group (21 events). Analysis of blood alcohol concentration measured using the transdermal alcohol sensor during the 12 hours preceding the AF episode showed 38% greater odds of AF per 0.1% increase in peak blood alcohol concentration measured phosphatidylethanol (PEth), which is formed in the presence of alcohol, has a half-life of 4 to 10 days, and is a biomarker of regular moderate to heavy alcohol use). There were a similar number of PEth-positive values (≥ 8 ng/mL) between groups (AF, 68.9%; no AF, 67.9%).

Episodes of AF were also associated with higher odds of peak blood alcohol concentration (OR 1.38, 95CI 1.04-1.83] per 0.1% increase in blood alcohol concentration) and the total area under the curve of alcohol exposure (OR 1.14, 95CI 1.06-1.22] per 4.7% increase in alcohol exposure) inferred from the transdermal ethanol sensor in the preceding 12 hours. These PEth positive levels suggest that more than half of all participants were regular drinkers. In this

¹¹⁹ Marcus, G. M., Vittinghoff, E., Whitman, I. R., et al. (2021). Acute Consumption of Alcohol and Discrete Atrial Fibrillation Events. *Annals of internal medicine*, 174(11), 1503–9.

study, PEth levels were positively correlated with real-time recorded drinking events and blood alcohol concentration detected by the alcohol sensor.

Actual blood alcohol concentrations were not reported, and the definition of “any transdermal alcohol event”, as well as the clinical meaning of area under the blood alcohol concentration curve derived from the transdermal alcohol sensor, was unclear.

Collectively, these findings suggest that alcohol consumption may increase the risk for an AF episode in the short term. Confounding by other time-varying exposures that may accompany alcohol consumption cannot be excluded, and the findings from the current study of patients with AF consuming alcohol may not apply to the general population.

Individual AF episodes were associated with higher odds of recent alcohol consumption..

Summary and conclusions

Alcohol is both a chronic risk factor for the development of new AF and also an acute trigger for AF episodes (Uptodate). AF occurs in up to 60% of binge drinkers with or without an underlying alcoholic cardiomyopathy. Most cases occur during and following weekends or holidays following an alcohol binge, termed “the holiday heart syndrome.” Acute alcohol consumption is a common AF trigger, with animal and human studies demonstrating changes in electrophysiological parameters, autonomic tone, and cellular properties expected to promote AF (Voskoboinik & Marcus 2020).

However, more modest levels of alcohol intake on a regular basis may also increase the risk of AF. The pathophysiological mechanisms responsible for the relationship between alcohol and AF may include direct toxicity and alcohol’s contribution to obesity, sleep-disordered breathing, and hypertension

Binge drinking is considered to be main risk factor in paroxysmal AF, the most common form of AF in younger people, but is not considered to be a risk factor for persistent or permanent AF. Up to 34% of patients with paroxysmal AF report that alcohol consumption precedes episodes, but previous studies are descriptive and lack comparator group, precluding quantitative evaluation of whether alcohol as trigger for AF more often than expected by chance alone.

Habitual alcohol consumption is associated with adverse atrial remodelling, higher risk of incident AF, and AF recurrence. Randomised data suggest that reduction in excessive alcohol consumption may reduce the risk of recurrent AF episodes and AF burden. Alcohol is an increasingly recognised risk factor for both new onset AF and discrete AF episodes.

The evidence is mixed but growing for long-term alcohol consumption being a risk factor for developing new AF. Moderate, long-term alcohol consumption was not shown to be a risk factor for AF in relatively small studies. However, a positive association was found in a study of 79,019 men and women free from AF at baseline [Larsson et al 2014]. Compared with current drinkers of <1 drink per week, the multivariable risk ratios of AF were 1.01 (95CI 0.94-1.09) for one to six drinks per week, 1.07 (95CI 0.98-1.17) for 7 to 14 drinks per week, 1.14

(95CI 1.01-1.28) for 15 to 21 drinks per week, and 1.39 (95CI 1.22-1.58) for >21 drinks per week.

Heavy alcohol consumption is strongly associated with a greater increase in incidence of AF.

Recently, it has been hypothesised that not only episodic but also habitual heavy alcohol consumption is associated with increased AF risk. However, epidemiological data of the long-term relation of alcohol intake have been inconsistent, in contrast to acute effects.

A randomised controlled trial showed that recurrences of AF were significantly decreased after a 2-week alcohol reduction intervention (from 17 to 2 drinks per week) in patients with paroxysmal or persistent AF (Voskoboinik et al 2020).

In a meta-analysis of pooled studies that included adults with AF and paroxysmal AF, the association between AF risks and the highest versus lowest alcohol consumption became stronger when the dominant type of AF was paroxysmal AF (OR 1.92, 95CI 1.44-2.56) or AF recurrence (OR 2.37, 95CI 1.44-3.90), suggesting higher risk in patients with a history of AF (Kodama et al 2011). Others have reported that 13 to 14 drinks or more per week was associated with a 3-fold increase in the progression of paroxysmal AF to persistent AF. A randomized controlled trial showed that recurrences of AF were significantly decreased after a 2-week alcohol reduction intervention (from 17 to 2 drinks per week) in patients with paroxysmal or persistent AF (Voskoboinik et al 2020).

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between both acute alcohol consumption (binge drinking), and chronic alcohol consumption and the development and worsening of atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between acute and chronic alcohol consumption and atrial fibrillation and atrial flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

The existing factor for binge drinking should be added to the BoP SoP, and clinical worsening should be added to the factor. A separate factor for chronic alcohol consumption should be retained in the RH and BoP SoPs. The standard definition for binge drinking should be incorporated into the factor.

It is suggested that there is sufficient sound medical and scientific evidence to lower the dose of alcohol in the chronic alcohol consumption factor. There is no clear threshold regarding the amount of alcohol consumed in relation to AF risk has been established, but it appears that the risk simply increases as the amount of alcohol consumed increases (Voskoboinik & Marcus 2020)..

AF is the most common arrhythmia associated with chronic high-volume alcohol intake, and above 14 g alcohol/day the relative risk increases 10% for every extra standard drink (14 g ethanol). (Day and Rudd 2019)

A meta-analysis of 7 prospective studies with 12,554 new cases of AF found a linear dose-response relationship starting at 1 standard drink per day (RR 1.08; 95CI 1.06-1.10), increasing by ~ 8% for each additional daily standard drink (1 standard drink ~ 12 g alcohol). Results were significant even after exclusion of binge drinkers, and wine and spirits appeared to have a stronger association than beer [Larsson et al 2014]. A more recent meta-analysis suggested that “moderate” habitual consumption (1–2 drinks per day) was only associated with a heightened risk of AF in males (HR 1.26, 95CI 1.04–1.54) but not females (HR 1.03, 95CI 0.86–1.25) while > 2 drinks/day remained significant for both sexes [Gallagher et al 2017].

Recent analytical studies also support a fairly low threshold. For example, Csengeri et al (2021) identified an elevated risk of AF at low doses. The hazard ratio for one drink (12 g) per day was 1.16, 95CI 1.11-1.22).

Consideration should be given to reducing the dose of alcohol in RH SoP to 100 g/ week; and in the BoP SoP to 150 g/ week.

Cardiac or thoracic surgery

Current factor

onset and worsening - RH and BoP

having cardiac or thoracic surgery within the three months before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Atrial arrhythmias, and AF in particular, are well-known complications after cardiac surgery. The majority of studies report poAF rates between 20-40% following coronary artery bypass grafting (CABG), 40-50% after valvular surgery, up to 60% following combined valvular and CABG surgery, and up to 80% after multiple valve surgery. In comparison the incidence of poAF is 10-20% following pulmonary resection and 0.14-26% for non-cardiothoracic surgery.

Summary of previous investigation

Atrial arrhythmias, and atrial fibrillation in particular, are well-known complications after cardiac surgery with a reported incidence between 10 and 60%. Post-operative atrial fibrillation (POAF) is common during the recovery phase of major vascular, abdominal, thoracic surgery, it is a frequent complication of cardiac surgery and an important predictor of patient morbidity as well as of prolonged hospitalisation.

The incidence is higher in patients undergoing valve surgery than in patients undergoing coronary artery bypass surgery (CABG). Post-operative atrial arrhythmias also occur after non-cardiac surgery, especially after oesophagectomy, lung surgery, and major abdominal surgery. In non-cardiac forms of surgery, the incidence of POAF is higher after thoracic surgery than after non-thoracic surgical procedures. After thoracic surgery POAF is more

frequent, with reported incidences of 9–29%. In non-cardiac, non-thoracic surgery, POAF occurs relatively infrequently (0.37% for ophthalmic surgery up to 13% for large colorectal surgery).

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There is a typical time course for the condition. Up to 70% of POAF occurs within the first 4 post-operative days, with a peak incidence on the 2nd post-operation day. A recurrence of POAF peaks on the 3rd post-operation day, suggesting pro-arrhythmic mechanisms require time to become apparent. The transient nature of the arrhythmia suggests a predominantly reversible mechanism, caused by factors which develop soon after surgery, which subside in the long run, although persistent arrhythmia can also develop.

Post-operative atrial fibrillation (POAF) is a frequent complication of cardiac surgery reported incidence 10 to 60%. Acute AF is particularly common during the acute or early recovery phase of major vascular, abdominal, and thoracic surgery, in which case autonomic fluxes and/or direct mechanical irritation potentiate the arrhythmia.

Most studies do not differentiate postoperative AF from AFL. The incidence of atrial arrhythmia varies with type of surgery; AFL after coronary artery bypass surgery (CABG) is not well documented; AFL after heart, lung transplantation. AFL after cardiothoracic surgery has been described, but its incidence unclear because most studies report on the incidence of AF and AFL combined.

The time course of the onset of POAF after cardiac surgery is stereotyped, with 70% of patients developing POAF in the first 4 post-operative days and only 6% developing AF after the 6th day. After CABG, postoperative atrial flutter occurred average at post-operative day 6.9 (Mori et al 2003); after lung transplant, AFL documented a mean 11.7 days after transplantation (range 1 to 51). *Azdani et al* (2011) notes that in most cases, AFL is a self-limited arrhythmia that resolves spontaneously with no need for ablation. The transient nature of the arrhythmia suggests a reversible mechanism, caused by factors which come into play shortly after surgery, but seem to subside on the long run.

Reviews

There have been many comprehensive review studies of post-operative atrial fibrillation (POAF). The major findings from one of these reviews are reported herein.^{120 121}

As outlined by **Boons et al (2021)**, advances in anaesthetic and surgical techniques have reduced the risk of complications in patients undergoing cardiac surgery. However, AF remains the most common postoperative complication, with an incidence reported to vary from

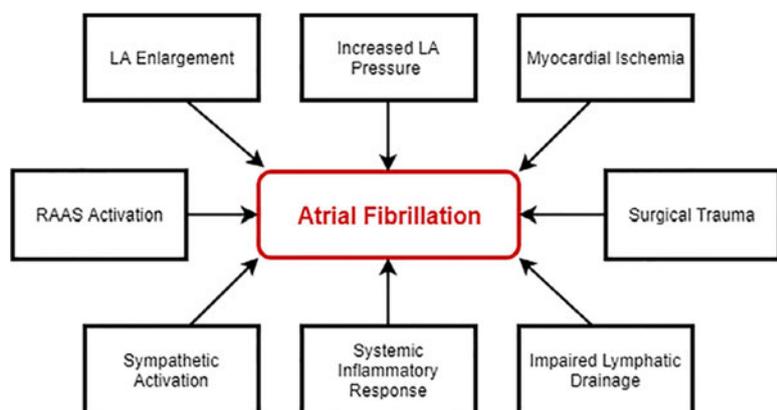
¹²⁰ Qureshi, M., Ahmed, A., Massie, V., et al. (2021). Determinants of atrial fibrillation after cardiac surgery. *Reviews in cardiovascular medicine*, 22(2), 329–41.

¹²¹ Baeza-Herrera, L. A., Rojas-Velasco, G., Márquez-Murillo, M. F., et al. (2019). Atrial fibrillation in cardiac surgery. *Fibrilación auricular en cirugía cardíaca. Archivos de cardiología de Mexico*, 89(4), 348–59

10% to 50%.¹²² After coronary artery bypass graft (CABG) surgery, AF occurs in 15% to 40% of cases. Patients may have AF in 37% to 50% of cases after valve surgery alone, and up to 60% in patients undergoing combined procedures (valve surgery with CABG). The peak time of onset of AF occurs typically on the second or third postoperative day, with an average of 2.4 days after surgery.

The electrophysiological mechanism of postoperative AF is believed to be a reentry phenomenon resulting from the dispersion of refractory atrial areas. When adjacent refractory atrial areas are dissimilar or nonuniform, the depolarizing wave front is fragmented as it encounters both refractory and excitable myocardium. This allows the wave front to return and stimulate the previously refractory but now repolarized myocardium, leading to constant propagation of the wave front or reentry. Maesen et al. stressed the importance of temporary surgery-induced factors, such as inflammation, sympathetic stimulation, and oxidative stress, as triggers for AF after cardiac surgery. However, these are not the only predisposing factors, because many patients in whom one or even several of these factors are noticeably present do not develop arrhythmias. This illustrates the complex multifactorial pathogenesis of AF after cardiac surgery.

FIGURE 9 SUMMARY OF MECHANISMS LEADING TO POSTOPERATIVE AF



Source: Boons et al (2021), Fig 2

¹²² Boons, J., Van Biesen, S., Fizez, T., et al . (2021). Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery: A Narrative Review. *Journal of cardiothoracic and vascular anesthesia*, 35(11), 3394–403
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TABLE 7 **RISK FACTORS FOR NEW-ONSET ATRIAL FIBRILLATION AFTER CARDIAC SURGERY**

Preoperative	Increasing age Male sex Mitral valve disease Lack or discontinuation of beta blockade Obesity COPD EF < 40%/history of heart failure White race Left main coronary disease Arterial hypertension Impaired kidney function
Intraoperative	Valve surgery CPB duration
Postoperative	Withdrawal of beta blockade Withdrawal of ACE inhibitor

Source: Boons et al (2021), Table 1, p 3396

Age is the most reported risk factor of AF after cardiac surgery.¹²³ Elderly patients often have many comorbidities and structural alterations in the atrial myocardium, such as distention and fibrosis Mathew et al. revealed that every ten-year increase in age was associated with a 75% increase in the odds of developing AF, and everyone aged over 70 years is considered to be at high risk for AF. The same alterations also may be why a previous history of AF plays an essential role in its postoperative reoccurrence. However, most studies excluded patients with a previous history of AF.

Male sex is an important predisposing factor for AF. This is attributable to sex-associated differences in ion channels and the effect of hormone levels on the autonomous tonus

Mitral valve disease is another risk factor. It tends to increase left atrium dimensions, causing structural adaptations, with a detrimental effect on electrical conduction. A left atrium diameter of more than 40 mm increases the risk of developing AF.

A retrospective study by Zacharias et al. provided the first data linking an elevated body mass index to an increased risk of developing new-onset AF after cardiac surgery, equivalent to a 1% increase in AF incidence per 1 kg/m² increase in BMI (p = 0.046). The authors believed this to originate in secondary left atrial enlargement. The study also identified chronic obstructive pulmonary disease, vascular disease, and heart failure as additional risk factors.¹³

Wong et al. explored the association between obstructive sleep apnoea (OSA) and postoperative complications in cardiac surgery in a retrospective cohort study. Patients with OSA had an increased risk of AF. this was confirmed in a systematic review and meta-analysis by Nagappa et al (2017). The odds of AF after cardiac surgery was

¹²³ Boons, J., Van Biesen, S., Fizez, T., de Velde, M. V., et al . (2021). Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery: A Narrative Review. *Journal of cardiothoracic and vascular anesthesia*, 35(11), 3394–403.

18,1% higher in OSA than non-OSA (OSA v non- OSA: 31% v 21%; OR 1.94; 95CI 1.13-3.33; p = 0.02). .

Intraoperative Risk Factors for post-operative AF include type of surgery.¹²⁴ Patients undergoing coronary artery bypass graft (CABG) surgery have a 15%-to-40% risk of developing AF. Rates of AF increase to 37% to 50% after isolated valve surgery and up to 60% in combined procedures (valve surgery with CABG. Mitral valve intervention is a major risk factor for the development of AF. Isolated mitral valve surgery is associated with an incidence of AF at least 50%.

A prospective multicentre trial by Mathew et al.¹² demonstrated that concurrent valve surgery was the only intraoperative variable correlating with increased risk of AF compared to coronary revascularisation alone (incidence of AF 154/286 [53.9%]; OR 1.74; 95% CI, 1.31-2.32; p <.001). This was attributed to structural and haemodynamic abnormalities and surgical trauma of valve surgery.

A prospective randomised study in 200 patients by Ascione et al.² was the first to investigate the role of cardiopulmonary bypass (CPB) on postoperative AF in patients undergoing CABG. The risk of AF was seven times higher in the on-pump than the off-pump group. This may be related to the duration of myocardial ischaemia, the required atrial cannulation, inflammatory responses after CPB, adverse effects of cardioplegia, or sympathetic activation.

The administration of nonsteroidal anti-inflammatory drugs was associated with a reduction in the odds of developing AF, suggesting an inflammatory contribution to the pathogenesis of postoperative AF (Tayyareci et al 2010).¹²⁵

Meta-analyses

Eikelboom et al (2021) conducted a systematic literature review to investigate the impact of postoperative atrial fibrillation (POAF) on long-term death and stroke in adult patients who undergo cardiac operations.¹²⁶

Electronic databases (Cochrane, Embase, Ovid MEDLINE, and PubMed) were queried from inception to October 2018. Included studies compared long-term outcomes after cardiac operations in patients with and without POAF. Adjusted and unadjusted meta-analyses examined death, stroke, and major adverse cardiac and cerebrovascular events. Risk of bias was evaluated with the Newcastle-Ottawa Scale.

32 studies met inclusion criteria, describing 155,575 patients who had undergone cardiac operations. POAF occurred in 36,988 patients (23.7%). Meta-analysis of 10 studies (44,367

¹²⁴ Boons, J., Van Biesen, S., Fivez, T., de Velde, M. V., et al . (2021). Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery: A Narrative Review. *Journal of cardiothoracic and vascular anesthesia*, 35(11), 3394–403

¹²⁵ Boons, J., Van Biesen, S., Fivez, T., de Velde, M. V., et al . (2021). Mechanisms, Prevention, and Treatment of Atrial Fibrillation After Cardiac Surgery: A Narrative Review. *Journal of cardiothoracic and vascular anesthesia*, 35(11), 3394–403.

¹²⁶ Eikelboom, R., Sanjanwala, R., Le, M. L., et al (2021). Postoperative Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Meta-Analysis. *The Annals of thoracic surgery*, 111(2), 544–54.

patients) demonstrated increased 1-year death in patients with POAF (OR 2.60; 95CI 2-3.38; $P < .01$). Aggregate adjusted hazard of death (16 studies, $n = 84,295$) was also increased in patients with POAF (HR 1.25; 95CI 1.2-1.3).

This systematic review and meta-analysis identified an association between POAF and long-term death after cardiac surgery. More comprehensive POAF prevention and management, including more stringent follow-up for POAF recurrence after hospital discharge, may be indicated. The included studies used inconsistent definitions of POAF and variable exclusion criteria; however, estimates of heterogeneity are low. Differences in preoperative comorbidities, such as age, ejection fraction, and obesity, may not be fully accounted for in adjusted analyses. Future work is required to delineate mechanisms linking POAF and death in this population

Transcatheter aortic valve replacement (TAVR) as an effective and convenient intervention has been adopted extensively for patients with severe aortic disease. However, after surgical aortic valve replacement (SAVR) and TAVR, the incidence of new-onset atrial fibrillation (NOAF) is prevalently found. **Ding et al (2021)** conducted a meta-analysis to compare the incidence of NOAF at different times after TAVR and SAVR for patients with severe aortic disease.¹²⁷

A systematic search of PubMed, Embase, Cochrane Library, and Web of Science up to October 2020 was conducted for relevant studies that comparing TAVR and SAVR in the treatment of severe aortic disease. The primary outcomes were the incidence of NOAF with early, midterm and long term follow-up. The secondary outcomes included permanent pacemaker (PM) implantation, myocardial infarction (MI), cardiogenic shock, as well as mortality and other complications. Two reviewers assessed trial quality and extracted the data independently. All statistical analyses were performed using the standard statistical procedures provided in Review Manager 5.2.

A total of 16 studies including 13,310 patients were identified. The pooled results indicated that, compared with SAVR, TAVR experienced a significantly lower incidence of 30-day /in-hospital NOAF, (pooled risk ratio 0.31, 95CI 0.23-0.41; $n= 5725$), 1-year NOAF, (RR 0.30 (95CI 0.24-0.39; $n= 6321$), 2 year NOAF (RR 0.48, 95CI 0.38-0.61; $n= 3441$), and 5 year NOAF (RR 0.45, 95CI 0.37-0.55; $n=2268$).

The analysis showed that TAVR was superior to SAVR in decreasing both short and long term post procedural NOAF. TAVR was equal to SAVR in early, midterm and long term mortality. In addition, TAVR showed lower incidence of 30-day/in-hospital MI and cardiogenic shock after procedure. However, pooled results showed that TAVR was inferior to SAVR in reducing permanent pacemaker implantation, neurological events, TIA, major vascular complications, and re-intervention.

¹²⁷ Ding, Y., Wan, M., Zhang, H., et al (2021). Comparison of postprocedural new-onset atrial fibrillation between transcatheter and surgical aortic valve replacement: A systematic review and meta-analysis based on 16 randomized controlled trials. *Medicine*, 100(28), e26613

Cohort studies

Shahim et al (2021) assessed the incidence and prognostic impact of early and late postoperative atrial fibrillation or flutter in patients with severe aortic stenosis (AS) treated with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).¹²⁸

There is an ongoing controversy regarding the incidence, recurrence rate, and prognostic impact of early (in-hospital) POAF and late (post discharge) POAF in patients with AS undergoing TAVR or SAVR.

In the PARTNER (Placement of Aortic Transcatheter Valve) 3 trial, patients with severe AS at low surgical risk were randomised to TAVR or SAVR. Analyses were performed in the as-treated population excluding patients with pre-existent atrial fibrillation or flutter.

Among 781 patients included in the analysis, early POAF occurred in 152 (19.5%) (18 of 415 [4.3%] and 134 of 366 [36.6%] following TAVR and SAVR, respectively). Following discharge, 58 new or recurrent late POAF events occurred within 1 year following the index procedure in 55 of 781 patients (7.0%). Early POAF was not an independent predictor of late POAF following discharge (OR 1.04; 95CI 0.52-2.08; P = 0.90). Following adjustment, early POAF was not an independent predictor of the composite outcome of death, stroke, or rehospitalisation (HR 1.10; 95CI: 0.64-1.92; P = 0.72), whereas late POAF was associated with an increased adjusted risk for the composite outcome (HR 8.90; 95CI 5.02-15.74; P < 0.0001), regardless of treatment modality.

In the PARTNER 3 trial, early POAF was more frequent following SAVR compared with TAVR. Late POAF, but not early POAF, was significantly associated with worse outcomes at 2 years, irrespective of treatment modality.

The impact of new-onset atrial fibrillation after aortic valve (AV) surgery on mid- and long-term outcomes is under debate. **Xiang et al (2021)** followed up heart rhythm outcomes after AV surgery, to evaluate the mid-term prognosis and effectiveness of treatment for patients with new-onset AF.¹²⁹

This single-centre cohort study included 978 consecutive patients (median age, 59 years; male, 68.5%) who underwent surgical AV procedures between 2017 and 2018. All patients with postoperative new-onset AF were treated with Class III antiarrhythmic drugs with or without electrical cardioversion (rhythm control). Status of survival, stroke, and rhythm outcomes were collected and compared between patients with and without new-onset AF.

New-onset AF was detected in 256 (26.2%) patients. postoperative survival was comparable with those without new-onset AF (1-year: 96.1% vs. 99.3%; adjusted P = .30), but rate of

¹²⁸ Shahim, B., Malaisrie, S. C., George, I., et al. (2021). Postoperative Atrial Fibrillation or Flutter Following Transcatheter or Surgical Aortic Valve Replacement: PARTNER 3 Trial. *JACC. Cardiovascular interventions*, 14(14), 1565–74.

¹²⁹ Xiang, B., Ma, W., Yan, S., et al. (2021). Rhythm outcomes after aortic valve surgery: Treatment and evolution of new-onset atrial fibrillation. *Clinical cardiology*, 44(10), 1432–9

stroke was significantly higher (1-year: 4.0% vs. 2.2%; adjusted P = .020). With rhythm control management, the 3-month and 1-year rates of paroxysmal or persistent AF between patients with and without new-onset AF were 5.1% versus 1.3% and 7.5% versus 2.1%, respectively (both P < .001). Multivariate models showed that advanced age, impaired ejection fraction, new-onset AF and discontinuation of beta-blockers were predictors of AF at 1 year.

In most cases, new-onset AF after AV surgery could be effectively converted and suppressed by rhythm control therapy. Nevertheless, new-onset AF predisposed patients to higher risks of stroke and AF within 1 year, for whom prophylactic procedures and continuous beta-blockers could be beneficial.

Akintoye et al. (2018) evaluated the impact of various surgical characteristics and practices on the risk of postoperative atrial fibrillation and other adverse outcomes after cardiac surgery.¹³⁰

By using the prospectively collected data of patients who underwent cardiac surgery in 28 centres across the United States, Italy, and Argentina, the details of surgery characteristics were collected for each patient and the outcomes, including postoperative atrial fibrillation, major adverse cardiovascular events, and mortality. These were evaluated via multivariable-adjusted models.

In 1462 patients, 460 cases of postoperative atrial fibrillation, 33 major adverse cardiovascular events, 23 cases of 30-day mortality, and 46 cases of 1-year mortality occurred. type of surgery and cardiopulmonary bypass use predicted the occurrence of postoperative atrial fibrillation. Compared with coronary artery bypass grafting alone, there was a higher risk of postoperative atrial fibrillation with valvular surgery alone (OR 1.4; 95CI 1.1-1.9), and the risk was higher with concomitant valvular and coronary artery bypass grafting surgery (OR 1.8; 95CI 1.2-2.7). Compared with no bypass, use of cardiopulmonary bypass was associated with higher risk of postoperative atrial fibrillation (OR 2.4; 95CI 1.7-3.5), but there were significant age and sex differences of the impact of bypass use among patients undergoing coronary artery bypass grafting (P interaction = .04). In addition, compared with spontaneous return of rhythm, ventricular pacing was associated with a higher risk of major adverse cardiovascular events (OR 5.0; 95CI 1.4-18), whereas concomitant coronary artery bypass grafting and valvular surgery was associated with a higher risk of 30-day mortality (HR 4.3; 95CI 1.2-14) compared with coronary artery bypass grafting alone. Occurrence of postoperative atrial fibrillation was associated with greater length of stay and 1-year mortality (HR 2.2; 95CI 1.2-3.9).

In this multicentre trial, Akintoye et al. (2018) identified specific adverse outcomes that are associated with concomitant valvular and coronary artery bypass graft surgery, cardiopulmonary bypass, ventricular pacing, and occurrence of postoperative atrial fibrillation

¹³⁰ Akintoye, E., Sellke, F., Marchioli, R., et al. (2018). Factors associated with postoperative atrial fibrillation and other adverse events after cardiac surgery. *The Journal of thoracic and cardiovascular surgery*, 155(1), 242–51.
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Hung et al (2021) developed a risk index to predict atrial fibrillation after cardiac surgery.¹³¹

A prospective cohort study of 405 patients who had undergone adult cardiac surgery from 2015 to 2016 at a cardiac surgical unit were obtained. In order to predict POAF, a logistic regression model was developed, and a risk score was derived and validated by bootstrap.

In the study, 98 patients developed POAF (24.2%). The risk score included three significant risk factors (age ≥ 60 , left atrial diameter > 41 mm, CABG with concomitant mitral valve replacement or repair) that were consistent with other reports. Each of these risk factors was assigned one point. The total risk score ranged from 0 to 3 (AUC = 0.69, 95CI: 0.63-0.75) with the best cutoff point at 1. According to this scoring system, the incidences of POAF in patients associated with each score of 0, 1, 2, and 3 were 8.6%, 30.1%, 40.8%, and 58.3% respectively. Bootstrapping with 5000 samples confirmed the final model was consistent with predictions.

Summary and conclusions

Post-operative atrial fibrillation (poAF) is common during the recovery phase of major surgery,

According to the definition of the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, poAF is a new onset of atrial fibrillation or atrial flutter requiring treatment.⁷ A more specific definition is new-onset AF/flutter detected on a rhythm monitor/ telemetry and/or ECG, with duration of ≥ 5 minutes and initiation of treatment for AF/flutter. The strict definition of poAF as an event requiring treatment likely leads to a significant underestimation of the true incidence and wider definitions have been suggested

Atrial arrhythmias, and atrial fibrillation in particular, are well-known complications after cardiac surgery. Despite advances in anaesthetic and cardiac surgical techniques which have reduced the risk of complications in patients undergoing cardiac surgery, and despite recommendations for the prevention of poAF, for example, by perioperative use of oral beta-blockers or corticosteroids, the incidence of poAF has remained unchanged over the years (Boons et al(2021)). AF remains the most common postoperative complication, with an incidence reported to vary from 10% to 50%. The arrhythmia usually occurs within the first five postoperative days with a peak incidence on the second or third postoperative day, with an average of 2.4 days after surgery. Nearly 80% of patients convert to sinus rhythm (SR) within 24 hours, and 6 weeks after initial diagnosis, 98% of patients have converted to SR, most often related to spontaneous or pharmacologic conversion.

Although believed to be transient and self-limiting, new-onset perioperative/postoperative atrial fibrillation) might be a risk factor for stroke and mortality (Lin et al 2019)

There are many pre/intra/post operative risk factors for AF after cardiac surgery (Boons et al 2021). Age is the most reported risk factor of AF after cardiac surgery. Additional preoperative risk factors include male sex, valve disease, obesity and obstructive sleep apnoea.

¹³¹ Hung, L. T., Alshareef, A., Al-Ahdal, T., et al (2021). Predicting atrial fibrillation after cardiac surgery using a simplified risk index. *Journal of electrocardiology*, 67, 45–9.

Intraoperative risk factors include . Mitral valve intervention is considered a major risk factor for the development of AF

The administration of nonsteroidal anti-inflammatory drugs has been associated with a reduction in the odds of developing AF, suggesting an inflammatory contribution to the pathogenesis of postoperative AF

There is an ongoing controversy regarding the incidence, recurrence rate, and prognostic impact of early (in-hospital) POAF and late (post-discharge) POAF in patients with aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). Shahim et al (2021) In the PARTNER 3 trial, early POAF was more frequent following SAVR compared with TAVR. Late POAF, but not early POAF, was significantly associated with worse outcomes at 2 years, irrespective of treatment modality. Following discharge, 58 new or recurrent late POAF events occurred within 1 year following the index procedure in 55 of 781 patients (7.0%).

Ding et al (2021) conducted a meta-analysis to compare the incidence of NOAF at different times after TAVR and SAVR for patients with severe aortic disease. Studies including 13,310 patients were identified. The pooled results indicated that, compared with SAVR, TAVR experienced a significantly lower incidence of 30-day /in-hospital NOAF, (pooled risk ratio 0.31, 95CI 0.23-0.41;n= 5725), 1-year NOAF, (RR 0.30 (95CI 0.24-0.39;n= 6321), 2 year NOAF (RR 0.48, 95CI 0.38-0.61; n= 3441), and 5 year NOAF (RR 0.45, 95CI 0.37-0.55; n=2268).

Xiang et al (2021) detected new-onset AF in 256 (26.2%) patients after aortic valve surgery. Multivariate models showed that advanced age, impaired ejection fraction, new-onset AF and discontinuation of beta-blockers were predictors of AF at 1 year.

Ishibashi et al (2020) reported that the incidence of postoperative AF after pulmonary lobectomy ranges from 6.4 to 12.6%. POAF patients include more males, patients with poor performance status, and history of paroxysmal atrial fibrillation

In a multicentre trial, Akintoye et al. (2018) identified specific adverse outcomes that are associated with concomitant valvular and coronary artery bypass graft surgery, cardiopulmonary bypass, ventricular pacing, and occurrence of postoperative atrial fibrillation. type of surgery and cardiopulmonary bypass use predicted the occurrence of postoperative atrial fibrillation. Compared with coronary artery bypass grafting alone, there was a higher risk of postoperative atrial fibrillation with valvular surgery alone (OR 1.4; 95CI 1.1-1.9), and the risk was higher with concomitant valvular and coronary artery bypass grafting surgery (OR 1.8; 95CI 1.2-2.7). Compared with no bypass, use of cardiopulmonary bypass was associated with higher risk of postoperative atrial fibrillation (OR 2.4; 95CI 1.7-3.5),

It is concluded that there is evidence strong enough to support a judgement of a convincing causal relationship between cardiothoracic surgery and atrial fibrillation and atrial flutter (Grade 1). A consistent association has been observed between cardiothoracic surgery,

including a range of invasive therapeutic cardiac procedures, and atrial fibrillation and flutter, and chance, bias and confounding can be ruled out with reasonable confidence.

Factors for thoracic and cardiac surgery should be retained in the RH and BoP SoPs, with adjustment of the factor to correspond to comparable factors in the heart block SoPs. A note should be added with examples of relevant surgical procedures that may involve the heart. Examples of an invasive cardiac procedure relevant to AF should also be listed, including:

- a) coronary artery bypass grafting;
- b) heart transplant;
- c) open heart surgery; and
- d) transcatheter aortic valve implantation.

A latency period of at one year should be retained for the RH and BoP SoPs.

Surgery (non-cardiothoracic)

Current factor

onset and worsening - RH and BoP

having a surgical procedure involving general or regional anaesthesia, other than cardiac or thoracic surgery, and which requires hospitalisation, within the one month before the clinical onset of atrial fibrillation or atrial flutter; or

Summary of important issues

New onset AF is less common after non-cardiac than cardiac surgery. The reported incidence ranges from 0.37 to 11.6% (Bjerrum et al 2020). This range is due to variability in patient and surgical characteristics.

Post-operative atrial fibrillation following non cardiac surgery is associated with a greater risk of stroke and mortality over the long-term. AF has been reported to occur most frequently following emergency orthopaedic, vascular and neurosurgery. Emergency surgery and age were independent risk factors for developing atrial fibrillation.

Summary of previous investigation

Post-operative atrial arrhythmias also occur after non-cardiac surgery. Their incidence is higher after thoracic surgery than after non-thoracic surgical procedures; especially after oesophagectomy, lung surgery, and major abdominal surgery. Post-surgical AFL is reported far less commonly than AF, but is the second most common arrhythmia reported in published series after non-cardiac surgery (Walsh et al 2007):

Reviews

Postoperative atrial fibrillation (POAF) occurs frequently following cardiothoracic surgery and is associated with a higher mortality and a longer hospital stay. The condition is less studied following noncardiothoracic surgery as well as emergency surgery.

Reported incidence of POAF following non-cardiothoracic surgery vary from 0.37 to 11.6% due to large differences between surgical specialties, techniques, underlying pathologies and patient populations.¹³² POAF is associated with higher mortality as well as a longer hospital stay.

The mechanisms of POAF following non-cardiothoracic surgery are believed to include an increased neuroendocrine and inflammatory stress response in an individual already susceptible of developing POAF. The surgical stress response is enhanced in patients undergoing emergency surgery. Patients undergoing emergency general surgery have higher mortality and risk of complications compared with patients undergoing elective procedures.

There have been recent reviews of POAF after non-cardiac surgery.¹³³ This section of the briefing paper will outline the evidence reported in one comprehensive review study. **Bjerrum et al (2020)** conducted a systematic review to investigate the occurrence of atrial fibrillation following emergency non-cardiothoracic surgery and associated risk factors and mortality.¹³⁴

A systematic literature search of PubMed, EMBASE and Scopus was carried out in August 2019. Observational studies and randomised controlled trials were assessed for risk of bias. Studies were included if data on POAF occurring after an emergency, noncardiothoracic, surgical intervention on adult patients could be extracted.

15 studies eligible for inclusion covering orthopaedic-, abdominal-, vascular-, neuro- and miscellaneous noncardiothoracic surgery. 13 were observational studies and two were RCT. The surgical interventions were orthopaedic (n=6), abdominal (n=4), vascular (n=2), neurosurgery (n=1) and miscellaneous (n=2). The sizes of the emergency surgical populations were: orthopaedic (n=1553), abdominal (n=49 126), vascular (n=204), neurosurgery (n=480) and miscellaneous noncardiothoracic (n=1368) with a total population of 52 741 patients

The occurrence of POAF after emergency non-cardiothoracic surgery ranged from 1.5 to 12.2% depending on type of surgery and intensity of cardiac monitoring.

¹³² Bjerrum, E., Wahlstroem, K. L., Gögenur, et al. (2020). Postoperative atrial fibrillation following emergency noncardiothoracic surgery: A systematic review. *European journal of anaesthesiology*, 37(8), 671–9

¹³³ Albini, A., Malavasi, V. L., Vitolo, M., et al. (2021). Long-term outcomes of postoperative atrial fibrillation following non cardiac surgery: A systematic review and metanalysis. *European journal of internal medicine*, 85, 27–33.

¹³⁴ Bjerrum, E., Wahlstroem, K. L., Gögenur, et al. (2020). Postoperative atrial fibrillation following emergency noncardiothoracic surgery: A systematic review. *European journal of anaesthesiology*, 37(8), 671–9

Higher occurrences of POAF were found in every surgical specialty, except abdominal surgery, when compared with studies investigating a mix of emergency and elective noncardiothoracic surgery. The overall range was 1.5 to 12.2%.

The occurrence of POAF in emergency orthopaedic, vascular and neurosurgery was generally higher than with studies investigating mixed populations of emergency and elective patients that have reported occurrences of 1.7, 2.7 and 3.9% respectively. The study that reported the lowest occurrence might have had a degree of selection bias, as patients with an expected low survival were not included. The risks of POAF after emergency abdominal surgery, 2.1 to 12.2%, were comparable with rates following elective colorectal surgery. Studies that investigated emergency noncardiothoracic surgical procedures reported a risk of 1.5 and 12%, respectively. The low risk of 1.5% was possibly due to heterogeneity in the surgical population as well as underreporting, as the diagnosis was retrieved retrospectively from medical records. The reason for the high risk of 12% might be that the majority of surgical interventions were abdominal and that ECG measurements were standard practice.

Of the 15 studies, seven reported POAF as a secondary outcome with no consensus in terms of diagnosing the condition or period of follow-up. Only three studies conducted systematic ECG monitoring. The highest occurrences of POAF were reported in studies where ECGs were assessed routinely rather than obtaining the diagnosis from medical records. This suggests that the condition is likely underreported in the clinic when systematic monitoring is not conducted, as POAF is often asymptomatic.

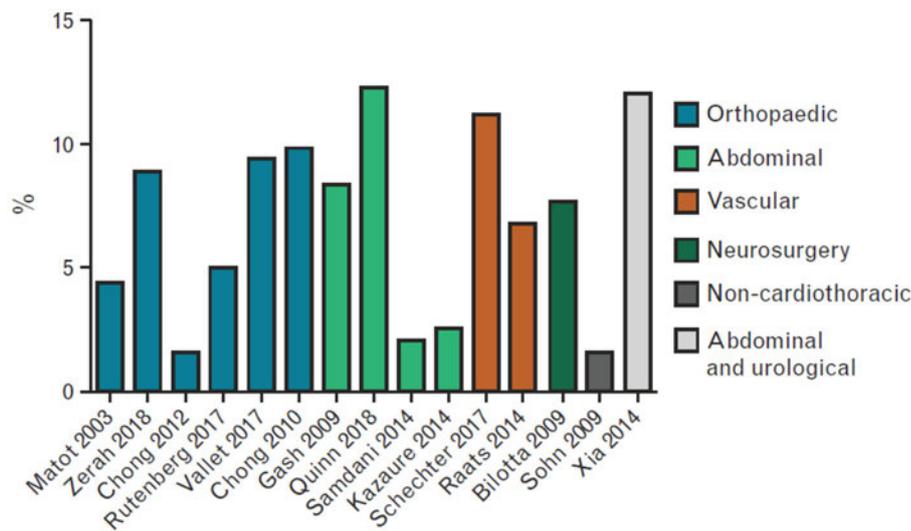
The occurrence of POAF after orthopaedic surgery varied from 1.6 to 9.8%. Two studies included routine ECG measurements during the initial 3 postoperative days and reported rates of 4.4 and 9.3%. The remaining studies obtained the diagnosis from medical records or by confirming a clinical suspicion and reported rates between 1.6 and 9.8%.

Studies that investigated abdominal surgery reported rates between 2.1 and 12.2%. No study included routine ECGs, though the study that retrospectively reviewed ECGs reported the highest occurrence of POAF. Significantly more patients developed POAF after emergency surgery compared with elective surgery, as emergency surgery comprised two-thirds of the POAF cases compared with patients without POAF (66.7 vs. 34.1%, $P = 0.0001$). POAF most often occurred in the initial postoperative week.

Neither of the two studies relating to vascular surgery described how a POAF diagnosis was obtained. Both studies investigated open and endovascular repair of ruptured abdominal aortic aneurysms and reported POAF among adverse events occurring during the initial 30 days after surgery. The reported occurrences were 6.7 and 11.1%.

The study examining neurosurgical interventions conducted partially systematic surveillance of POAF reported an occurrence of 7.7% during the hospital stay. A statistically significant difference in the incidence of POAF was reported when comparing emergency with elective surgery; 2.1% developed POAF following elective surgery, and 7.7% following emergency surgery, $P < 0.0001$.

FIGURE 10 OCCURRENCE OF POSTOPERATIVE ATRIAL FIBRILLATION IN INCLUDED STUDIES



Bjerrum et al (2020), Fig 2

No studies investigated risk factors specifically in the emergency cohort. However, four studies investigated risk factors and POAF-associated morbidity and mortality in general.. All studies found increasing age to be associated with the development of POAF, and POAF to be associated with higher mortality and a longer in-hospital stay.

The studies that investigated risk factors of POAF all found increasing age to be associated with the development of POAF, consistent with existing literature. Age is associated with degenerative changes, structural remodelling and conduction abnormalities of the atria, making the atrial substrate more vulnerable. Development of atrial fibrillation is believed to require a susceptible substrate as well as the presence of a trigger, such as the stress response induced by surgery. Several studies reported a significant association between emergency surgery and the development of POAF. The pathophysiological mechanisms of POAF after non-cardiothoracic surgery include surgical stressors including increased inflammation and endocrine dysfunction as well as a modulation of the autonomous nervous system anaesthetic factors, patient comorbidity and peri-operative circumstances are likely to play a role. These pathophysiological processes might be further enhanced in an emergency setting.

TABLE 8 FACTORS ASSOCIATED WITH POSTOPERATIVE ATRIAL FIBRILLATION

Author	Type of surgery	Pre and intra-operative factors associated with POAF	POAF-associated morbidity and mortality
Quinn (2018)	Abdominal	Increasing age, ASA score ≥ 3 , smoking, ischaemic heart disease, use of beta-blockers and ACE-I, emergency procedure, higher blood loss, malignancy	Pneumonia, wound dehiscence/infection, abdominal collection, acute kidney injury, sepsis, ICU-admission, reoperation, longer hospital-stay Increased in-hospital-mortality and 1-year-mortality
Kazaure (2014)	Abdominal	Age >65 years, male sex, white race, hypokalaemia, fluid overload, congestive heart failure, MI, cerebrovascular disease, chronic obstructive pulmonary disease, malignancy	Surgical site infection, sepsis, deep venous thrombosis/pulmonary emboli, stroke, MI, pneumonia, renal insufficiency, reoperation, acute mesenteric ischaemia, cardioversion, electrolyte imbalance, longer hospital stay. Increased in-hospital-mortality
Bilotta (2009)	Neurosurgery	Age >60 years, emergency procedure	Increased 180-day mortality ^a
Sohn (2009)	Noncardiothoracic	Increasing age, emergency procedure	Longer in-hospital-stay Increased in-hospital mortality

Studies that investigated risk factors and associated mortality found emergency surgery and increasing age is associated with risk of POAF. POAF was generally associated with an increase in long-term and short-term mortality

Koren et al (2020) examined the incidence of POAF in noncardiothoracic surgeries performed under general anaesthesia and its effects on the length of hospitalization stay, short-term and long-term morbidity, and mortality.¹³⁵ This was a retrospective observational descriptive study. The study population consists of patients hospitalized in surgical wards from January 2014 to December 2017. Surgery was defined as noncardiac or thoracic procedure conducted under general anaesthesia.

A total of 24,125 general anaesthesia operations were performed at 7 surgical wards. About two-fifth of the operations (40%) were operated electively, and the rest underwent emergency surgery. The mean age was 63.78 ± 11.50 , and more than half (56.9%) of the participants were female. The prevalence of POAF was 2.69 per 1000 adult patients and vary significantly among wards. The highest prevalence was observed after hip fixation and laparotomy surgeries (54.9 and 26.7 per 1000 patients, respectively). The median length of hospitalisation was significantly higher in POAF patients (21.0 vs. 4.8 days, $p < 0.001$).

Patients who developed POAF had significantly higher mortality rates, both in hospital (200 vs. 7.56 deaths per 1000, $p=0.001$) and 1 year (261.5 vs. 33.3 per 1000, $p=0.001$, respectively). There was no significant association between outcome and treatment modalities such as rate or rhythm control and anticoagulant use.

New-onset AF following noncardiac surgery is rare, yet poses significant clinical implications, both immediate and long-term. POAF is associated with a longer length of hospitalization and a significantly higher mortality rate, both in short- and long-term.

Case reports

Postoperative atrial fibrillation following noncardiac surgery increases mortality, length of hospital stay, and medical expenses; moreover, compared to nonvalvular atrial fibrillation, it poses a similar risk of thromboembolic complications.

Cho & Lee (2021) described the decision-making process for diagnosis and treatment in case with unexpected postoperative new-onset atrial fibrillation causing acute mesenteric ischaemia.¹³⁶

A 78-year-old man received varicose vein stripping and ligation in his right leg. The patient was previously healthy with no known comorbidities. The day after surgery, he complained of sudden epigastric pain unresponsive to conservative treatment, and new-onset atrial fibrillation was observed on electrocardiography.

¹³⁵ Cross-sectional studies

¹³⁶ Cho, J., & Lee, D. (2021). Postoperative new-onset atrial fibrillation causing acute embolic occlusion of the superior mesenteric artery: A case report. *Medicine*, 100(17), e25700.

Abdominal CT scan revealed acute embolic occlusion of the superior mesenteric artery. Emergent surgical embolectomy was performed, 6 hours after recognition of abdominal pain was 6 h. Surgical critical care was performed for life-threatening ischaemic reperfusion injury. The patient was discharged from on the 40th postoperative day.

Summary and conclusions

Perioperative/postoperative atrial fibrillation (POAF) is less studied following noncardiothoracic surgery as well as emergency surgery than after cardiothoracic surgery (Bjerrum et al 2020). AF is less common after noncardiac than after cardiac surgery. The reported incidence of new onset AF in patients undergoing noncardiac surgery ranges from 0.37 to 11.6% Bjerrum et al (2020) This range is likely due to variability in patient and surgical characteristics (Uptodate)

POAF following non cardiac surgery is associated with a greater risk of stroke and mortality over the long-term. Studies focusing on AF recurrence have corrected the perception of POAF as a benign transient entity (Albani et al 2020).

Reported incidence rates of POAF following non-cardiothoracic surgery vary from 0.37 to 11.6% due to large differences between surgical specialties, techniques, underlying pathologies and patient populations. POAF is associated with higher mortality and a longer hospital stay.

The mechanisms of POAF following non-cardiothoracic surgery are believed to include an increased neuroendocrine and inflammatory stress response in an individual already susceptible of developing POAF The surgical stress response is enhanced in patients undergoing emergency surgery. patients undergoing emergency general surgery have higher mortality and risk of complications compared with patients undergoing elective procedures.

AF may also occur spontaneously during general and local anaesthesia administration (Kounis et al 2020).

A systematic review investigating the occurrence of AF following emergency noncardiothoracic surgery identified 15 eligible studies covering orthopaedic-, abdominal-, vascular-, neuro- and miscellaneous noncardiothoracic surgery (Bjerrum et al 2020). The occurrence of POAF after emergency noncardiothoracic surgery ranged from 1.5 to 12.2% depending on type of surgery and intensity of cardiac monitoring. AF occurred frequently, especially following emergency orthopaedic, vascular and neurosurgery. Emergency surgery and age were independent risk factors for developing atrial fibrillation.

In relation to non-cardiothoracic surgery, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between undergoing a non-cardiothoracic surgical procedure and atrial fibrillation and flutter, but the evidence is limited in quality or quantity. Case reports provide evidence of temporal link and a biomechanical or pathophysiological mechanism.

A factor should be retained in the SoPs (RH and BoP). The requirement for hospitalisation should be removed. A note with relevant examples should be added. Examples of non-cardiothoracic surgical procedures should include emergency or elective orthopedic and abdominal surgery and neurosurgery.

Chronic obstructive pulmonary disease

Current factor

onset and worsening - RH and BoP

having chronic obstructive pulmonary disease at the time of the clinical onset of atrial fibrillation or atrial flutter; or

Summary of important issues

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide. Among extra-pulmonary manifestations of COPD, atrial fibrillation is commonly observed in clinical practice. The coexistence of COPD and AF significantly affects the risk of cardiovascular morbidity and mortality. The mechanisms explaining the increased risk of vascular events and death associated to the presence of COPD in AF are complex and not completely understood.

Summary of previous investigation

The association between chronic obstructive pulmonary disease (COPD) and new onset AF is still under discussion.

Very little published data confirms the association between chronic airways disease, particularly acute decompensation of chronic airways disease, although it is a clinical commonplace that acute respiratory failure is associated with supraventricular arrhythmias.

There is little recent scientific data documenting this relationship, as it is regarded as sufficiently sound in practice, is widely accepted in the medical textbook, and is considered biologically plausible.

COPD has been identified as an independent predictor of AF progression. The occurrence of post-operative AF, COPD is often identified as a risk factor. However, the pathogenesis of AF in patients with COPD is unclear. Mechanisms involved in a relationship between AF and reduced pulmonary function are suggested to involve hypoxia, elevation of pulmonary pressure, and chronic inflammation. Hypoxia reportedly induces sympathetic drive, resulting in the incidence of AF. It is postulated that COPD may predispose patients to cardiac arrhythmia either by the direct effects on the right heart through pulmonary hypertension, right ventricular strain, and stretching of the right atrium or as a result of therapeutic modalities used to treat COPD.

Chronic pulmonary disorders, such as COPD and fibrosing lung diseases, and atrial fibrillation, are prevalent in elderly people. Few epidemiological studies on the relationship between the incidence of AF and pulmonary function Shibata et al 2011- reviewed published data, and concluded that there was a relationship between AF and the impairment of pulmonary function, but this relationship was not conclusive.

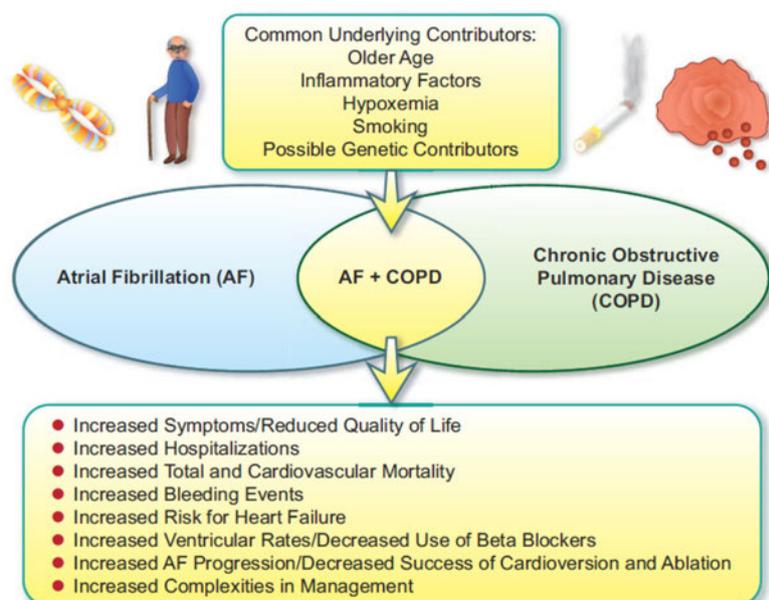
Recent epidemiological data relating chronic lung disease to AF is not consistent. In the GPRD case control study, Hodgkinson et al (2011) identified no association between AF and history of chronic obstructive pulmonary disease.

Reviews

As outlined by **Goudis (2017)**, chronic obstructive pulmonary disease (COPD) is independently associated with atrial fibrillation. COPD is often accompanied by extra-pulmonary manifestations such as thrombo-embolic and haemorrhagic events. Decreased oxygenation, hypercapnia, pulmonary hypertension, diastolic dysfunction, oxidative stress, inflammation, changes in atrial size by altered respiratory physiology, increased arrhythmogenicity from nonpulmonary vein foci commonly located in the right atrium, and respiratory drugs have been implicated in the pathogenesis of AF in COPD.¹³⁷

The understanding of the relationship between COPD and AF is of particular importance, as the presence of the arrhythmia has significant impact on mortality, especially in COPD exacerbations. COPD in AF is associated with AF progression, success of cardioversion, recurrence of AF after catheter ablation, and increased cardiovascular and all-cause mortality.

FIGURE 11 COMMON UNDERLYING CONTRIBUTORS TO BOTH ATRIAL FIBRILLATION AND COPD, AND ADVERSE OUTCOMES ASSOCIATED WITH COMBINATION OF AF AND COPD.



Reiffel (2021), Fig, p 3335

¹³⁷ Goudis C. A. (2017). Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship. *Journal of cardiology*, 69(5), 699–705.
August meeting 2022

Treatment of the underlying pulmonary disease and correction of hypoxia and acid-base imbalance represents first-line therapy for COPD patients who develop AF.¹³⁸ Cardioselective β -blockers are safe and can be routinely used in COPD. AF ablation is efficient and safe, and improves quality of life.

There have been many recent comprehensive review studies concerning COPD and AF.¹³⁹
140 141 142 143 Only the essential points of the association are highlighted in this section of the briefing paper, based on the systematic review of COPD and AF by **Romiti et al (2021)**.

The prevalence of COPD in AF patients is unclear, and its association with adverse outcomes is often overlooked.¹⁴⁴ The authors estimated the prevalence of COPD, its impact on clinical management and outcomes in patients with AF, and the impact of beta-blockers (BBs) on outcomes in patients with COPD.

A systematic review and meta-analysis was conducted. All studies reporting the prevalence of COPD in AF patients were included. Data on comorbidities, BBs and oral anticoagulant prescription, and outcomes (all-cause death, cardiovascular (CV) death, ischaemic stroke, major bleeding) were compared according to COPD and BB status.

Among 46 studies, pooled prevalence of COPD was 13% [95CI 10-16%, 95% prediction interval 2-47%]. COPD was associated with higher prevalence of comorbidities, higher CHA2DS2-VASc score and lower BB prescription (OR 0.77, 95CI 0.61-0.98). COPD was associated with higher risk of all-cause death (OR 2.22, 95CI 1.93-2.55), CV death (OR 1.84, 95CI 1.39-2.43), and major bleeding (OR 1.45, 95CI 1.17-1.80); no significant differences in outcomes were observed according to BB use in AF patients with COPD.

It was concluded that COPD is common in AF, being found in 13% of patients, and is associated with increased burden of comorbidities, differential management, and worse outcomes, with more than a two-fold higher risk of all-cause death and increased risk of CV death and major bleeding. Therapy with BBs does not increase the risk of adverse outcomes in patients with AF and COPD.

¹³⁸ Goudis C. A. (2017). Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship. *Journal of cardiology*, 69(5), 699–705.

¹³⁹ Simons, S. O., Elliott, A., Sastry, M., et al. (2021). Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective. *European heart journal*, 42(5), 532–40.

¹⁴⁰ Goudis C. A. (2017). Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship. *Journal of cardiology*, 69(5), 699–705

¹⁴¹ Matarese, A., Sardu, C., Shu, J., et al. (2019). Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms. *International journal of cardiology*, 276, 149–51.

¹⁴² Shin SY, Manuel ARG, Lip GYH. (2019). Atrial Fibrillation and End-Stage COPD: A Close Association Revisited. *Chest.*; 155(5): 888-9.

¹⁴³ Leong, P., Macdonald, M. I., Ko, B. S., et al. (2019). Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge. *The Medical journal of Australia*, 210(9), 417–23

¹⁴⁴ Romiti, G. F., Corica, B., Pipitone, E., et al (2021). Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients. *European heart journal*, 42(35), 3541–54.

The higher prevalence of comorbidities and lower use of BBs in the AF patients with COPD vs. those without COPD must confound the outcome results reported by Romiti et al. as does the use of large administrative databases rather than detailed individual patient information, despite attempts to correct for these imbalances.¹⁴⁵ Smoking is a major factor in causing COPD, and is also a risk factor for vascular disease, ischaemic heart disease, heart failure, total mortality, and cardiovascular death.

While statistical approaches accounting for the effects of confounding variables may help identify the independent role of each variable, they cannot determine many relevant clinical factors, such as number and type of cigarettes smoked, the anatomical location and degree of atherosclerotic lesions, specific treatments used for comorbidities and their consequences. This is a major limitation of all studies that review prior literature, as well as studies using propensity matching scores in an attempt to correct for imbalances among groups not being studied prospectively in large, randomized, blinded clinical trials.

In an earlier review, Roversi et al. (2016) observed that co-existing cardiac diseases and COPD have been 'repeatedly identified as negative prognostic factors for each other and that the coexistence of COPD with AF, ischaemic heart disease, and/or heart failure has been correlated with higher rates of hospitalisation, greater mortality, and lower quality of life as compared with either COPD or heart disease alone.¹⁴⁶ They reported that AF in patients with COPD has an estimated risk ratio for hospitalization of 2–2.3 and for all-cause mortality of 1.2–3. The reported prevalence of AF in patients with stable COPD ranges from 4.7% to 15%, with rates as high as 20–30% with very severe COPD. Similar findings have been reported by Goudis and by Leong et al.

COPD in patients with AF has been associated with AF progression, reduced success of cardioversion, lower likelihood of maintaining sinus rhythm following cardioversion, and increases in cardiovascular and total mortality. The large Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF; Durheim et al 2018) reported that among 9749 patients with AF, 1605 (16.5%) had COPD, and that relative to patients without COPD, those with COPD were older, and were more likely to have been smokers (73% vs. 44%), and to have heart failure (54% vs. 29%) and coronary artery disease (49% vs. 34%). Symptom burden was higher and AF-specific quality of life scores were lower in those with COPD plus AF vs. AF without COPD. AF patients with COPD had a higher risk of all-cause mortality (adjusted HR 1.52), a higher risk of cardiovascular hospitalization (adjusted HR 1.16), and a higher risk of major bleeding events (adjusted HR 1.27).

Acute exacerbation of COPD transiently increases AF risk due to hypoxia-mediated mechanisms, inflammation, increased use of beta-2 agonists, and autonomic changes.¹⁴⁷

¹⁴⁵ Reiffel JA. (2021). When two is not better than one: the amalgamation of atrial fibrillation and chronic obstructive pulmonary disease. *Eur Heart J.*; 42(35): 3555-7

¹⁴⁶ Reiffel JA. (2021). When two is not better than one: the amalgamation of atrial fibrillation and chronic obstructive pulmonary disease. *Eur Heart J.*; 42(35): 3555-7

¹⁴⁷ Simons, S. O., Elliott, A., Sastry, M., et al. (2021). Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective. *European heart journal*, 42(5), 532–40.

Observational data suggest that COPD promotes AF progression, increases AF recurrence after cardioversion, and reduces the efficacy of catheter-based antiarrhythmic therapy. However, it remains unclear whether treatment of COPD improves AF outcomes and which metric should be used to determine COPD severity and guide treatment in AF patients. Data from non-randomised studies suggest that COPD is associated with increased AF recurrence after electrical cardioversion and catheter ablation. Future prospective cohort studies in AF patients are needed to confirm the relationship between COPD and AF, the benefits of treatment of either COPD or AF in this population, and to clarify the need and cost-effectiveness of routine COPD screening.

Meta-analyses

Ye et al (2021) assessed the impact of chronic obstructive pulmonary disease on outcomes of atrial fibrillation in a systematic literature review and meta-analysis.¹⁴⁸

PubMed, Scopus, Embase, and Web of Science databases were searched for studies comparing overall mortality, cardiovascular death, and other outcomes for AF patients with and without COPD. The data retrieved were subjected to both qualitative and quantitative analyses. The hazard ratios (HR) obtained for mortality in presence of COPD were pooled to meta-analysis using generic inverse variance function of RevMan 5.3 software. The association of various risk factors and HRs were pooled with 95% confidence interval (CI). The quality of the included studies was assessed using Newcastle Ottawa scale (NOS).

The hazard ratios (HR) were calculated with 95% confidence intervals (CIs). A total of seven studies were included. The pooled HR for the impact of COPD on overall mortality and cardiovascular mortality in AF patients was 1.70 (95CI 1.47-1.97; $p < 0.0001$) and 1.80 (95CI 1.29-2.52; $p = 0.0005$), respectively. Haemorrhagic events were significantly higher in AF patients with COPD (OR 1.84; 95CI 1.58, 2.14; $p < 0.00001$).

It was concluded that COPD has a deleterious impact on AF progression in terms of overall mortality, cardiovascular death, stroke and haemorrhagic complications.

Cohort studies

Grymonprez et al. (2019) analysed the development of atrial fibrillation in patients with COPD in the Rotterdam Study, a large, population-based cohort study with long-term follow-up.¹⁴⁹ Time dependent Cox proportional hazard models were constructed to study the effect of COPD on incident AF, adjusted for age, sex and pack years of cigarette smoking, and additionally stratified according to exacerbation frequency, left atrial size and baseline systemic inflammatory levels.

1369 of 10,943 subjects had COPD, of whom 804 developed AF. The AF incidence rate was 14 per 1000 person years in COPD and 8 per 1000 person years in subjects without COPD.

¹⁴⁸ Ye, J., Yao, P., Shi, X., et al. (2021). A systematic literature review and meta-analysis on the impact of COPD on atrial fibrillation patient outcome. *Heart & lung : the journal of critical care*, 51, 67–74

¹⁴⁹ Grymonprez, M., Vakaet, V., Kavousi, M., et al. (2019). Chronic obstructive pulmonary disease and the development of atrial fibrillation. *International journal of cardiology*, 276, 118–24.

The adjusted hazard ratio (HR) for COPD subjects to develop AF as compared to subjects without COPD was 1.28 (95CI 1.04-1.57). COPD subjects with frequent exacerbations had a twofold increased AF risk (HR 1.99, 95CI 1.42-2.79) and COPD subjects with a left atrial size ≥ 40 mm also had an elevated AF risk (HR 1.77, 95CI 1.07-2.94). COPD subjects with baseline systemic inflammatory levels above the median had significantly increased AF risks (hsCRP ≥ 1.83 mg/L: HR 1.51, 95CI 1.13-2.03 and IL6 ≥ 1.91 ng/L: HR 2.49, 95CI 1.18- 5.28), whereas COPD subjects below the median had in both analyses no significantly increased AF risk.

COPD subjects had a 28% increased AF risk, which further increased with frequent exacerbations and an enlarged left atrium. The risk was driven by COPD subjects having elevated systemic inflammatory levels.

Little is known about whether acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of repeated AF-related healthcare utilisation. **Hirayama et al. (2018)** evaluated whether acute exacerbation of COPD influence the subsequent risk of emergency department visits and hospitalisations for atrial fibrillation.¹⁵⁰

This was a self-controlled case series study using the population-based emergency department (ED) and inpatient databases of 5 US states from 2007 through 2012. Among patients with existing AF, patients with an AECOPD hospitalisation and at least 1 ED visit or hospitalisation for AF during the observation period identified. The authors constructed conditional Poisson regression models to compare the rate of AF-related ED visits or hospitalizations during sequential 90-day periods after the AECOPD hospitalization, with pre-AECOPD days 1 to 90 as the reference.

The study analysed 944 patients who were hospitalized for AECOPD and had an ED visit or hospitalisation for AF during a 450-day period. The median age was 77 years, and 41% were men. Compared with the reference period, the rate of AF-related ED visits or hospitalizations significantly increased in the post-AECOPD days 1 to 90 (7.3 versus 14.1 per 100 person-months; rate ratio, 1.93; 95CI 1.63-2.29; $P < 0.001$). The rate decreased to the reference level in the post-AECOPD days 91 to 180 (7.5 per 100 person-months; RR 1.03; 95CI 0.85-1.25; $P = 0.77$) and remained at the reference level during post-AECOPD days 181 to 270 (RR 0.84; 95CI 0.68-1.03; $P = 0.09$) and days 271 to 360 (RR 0.90; 95CI 0.73-1.10; $P = 0.29$). These temporal associations persisted with stratification by age, sex, and season.

Among patients with existing AF, acute exacerbating of COPD was associated with a higher risk of AF-related ED visit or hospitalization in the first 90-day post-AECOPD period.

Dong et al (2021) assessed the incidence, causes and predictors of hospitalization in AF patients.¹⁵¹

¹⁵⁰ Hirayama, A., Goto, T., Shimada, Y. J., et al. (2018). Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Subsequent Risk of Emergency Department Visits and Hospitalizations for Atrial Fibrillation. *Circulation. Arrhythmia and electrophysiology*, 11(9), e006322.

¹⁵¹ Dong, Z., Du, X., Lu, S., et al. (2021). Incidence and predictors of hospitalization in patients with atrial fibrillation: results from the Chinese atrial fibrillation registry study. *BMC cardiovascular disorders*, 21(1), 146.

From August 2011 to December 2017, 20,172 AF patients from the Chinese Atrial Fibrillation Registry (China-AF) Study were prospectively selected for study. The Fine-Gray competing risk model was employed to identify predictors of first all-cause and first cause-specific hospitalization.

After a mean follow-up of 37.3 ± 20.4 months, 7,512 (37.2%) AF patients experienced one or more hospitalizations. The overall incidence of all-cause hospitalisation was 24.0 per 100 patient-years. Patients aged < 65 years were predominantly hospitalised for AF (42.1% of the total hospitalizations); while patients aged 65-74 and ≥ 75 years were mainly hospitalized for non-cardiovascular diseases (43.6% and 49.3%, respectively).

More than one-third of AF patients included in this study were hospitalised at least once during over 3-year follow-up. Patients complicated with COPD (HR 1.28, 95CI 1.02-1.62), among other disorders, had higher risks of hospitalisation.

The main cause for hospitalisation among elderly patients (≥ 65 years) in this cohort was non-cardiovascular diseases rather than AF. Multidisciplinary management of comorbidities should be advocated to reduce hospitalization in AF patients older than 65 years old.

Rodríguez-Mañero et al (2019) described the prevalence of COPD in a sizeable cohort of real-world AF patients belonging to the same healthcare area and to examine the relationship between comorbid COPD and AF prognosis.¹⁵²

Prospective analysis performed in a specific healthcare area. Data were obtained from several sources within the "data warehouse of the Galician Healthcare Service" using multiple analytical tools. Statistical analyses were completed using SPSS 19 and STATA 14.0.

A total of 7,990 (2.08%) patients with AF were registered throughout 2013 in a healthcare area (n=348,985). Mean age was 76.83 ± 10.51 years and 937 (11.7%) presented with COPD. COPD patients had a higher mean CHA2DS2-VASc (4.21 vs 3.46; $P=0.02$) and received less beta-blocker and more digoxin therapy than those without COPD. During a mean follow-up of 707 ± 103 days, 1,361 patients (17%) died. All-cause mortality was close to doubled in the COPD group (28.3% vs 15.5%; $P<0.001$). Independent predictive factors for all-cause mortality were age, heart failure, diabetes, previous thromboembolic event, dementia, COPD, and oral anticoagulation (OA). There were nonsignificant differences in thromboembolic events (1.7% vs 1.5%; $P=0.7$), but the rate of haemorrhagic events was significantly higher in the COPD group (3.3% vs 1.9%; $P=0.004$). Age, valvular AF, OA, and COPD were independent predictive factors for haemorrhagic events. In COPD patients, age, heart failure, vasculopathy, lack of OA, and lack of beta-blocker use were independent predictive factors for all-cause mortality.

¹⁵² Rodríguez-Mañero, M., López-Pardo, E., Cordero, A., et al. (2019). A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population. *International journal of chronic obstructive pulmonary disease*, 14, 371–80
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AF patients with COPD have a higher incidence of adverse events with significantly increased rates of all-cause mortality and haemorrhagic events than AF patients without COPD. However, comorbid COPD was not associated with differences in cardiovascular death or stroke rate. OA and beta-blocker treatment presented a risk reduction in mortality while digoxin use exerted a neutral effect.

Case-control study

Angeli et al (2019) analysed data from an Italian network database to identify markers and mediators of increased vascular risk among subjects with AF and COPD.¹⁵³ This was a cross-sectional analysis of the Umbria Atrial Fibrillation (Umbria-FA) Registry, a multicentre, observational, prospective on-going registry of patients with non-valvular AF. Of the 2205 patients actually recruited, 2159 had complete clinical data and were included in the analysis. Results: the proportion of patients with COPD was 15.6%. COPD patients had a larger proportion of permanent AF when compared to the control group (49.1% vs. 34.6%, $p < 0.0001$) and were more likely to be obese and current smokers. Other cardiovascular risk factors including chronic kidney disease (CKD), peripheral artery disease and subclinical atherosclerosis were more prevalent in COPD patients (all $p < 0.0001$). COPD was also significantly associated with higher prevalence of previous vascular events and a history of anaemia (all $p < 0.0001$).

The thromboembolic and bleeding risk, as reflected by the CHA₂DS₂VASc and HAS-BLED scores, were higher in patients with COPD. Patients with COPD were also more likely to have left ventricular (LV) hypertrophy at standard ECG than individuals forming the cohort without COPD ($p = 0.018$). Conclusions: AF patients with COPD have a higher risk of vascular complications than AF patients without this lung disease. The analysis identified markers and mediators of increased risk that can be easily measured in clinical practice, including LV hypertrophy, CKD, anaemia, and atherosclerosis of large arteries.

Summary and conclusions

Chronic obstructive pulmonary disease (COPD) is often accompanied by extra-pulmonary manifestations such as thrombo-embolic and haemorrhagic events (Goudis 2017).

Among extra-pulmonary manifestations of COPD, AF is commonly observed in clinical practice (Angeli et al 2019). COPD is independently associated with the risk of atrial fibrillation. The coexistence of COPD and AF significantly affects the risk of cardiovascular morbidity and mortality. The reported prevalence of AF in patients with stable COPD ranges from 4.7% to 15%, with rates as high as 20–30% with very severe COPD.

Roversi et al. (2016) observed that co-existing cardiac diseases and COPD have been repeatedly identified as negative prognostic factors for each other and that the coexistence of

¹⁵³ Angeli, F., Reboldi, G., Trapasso, M., et al. (2019). Detrimental Impact of Chronic Obstructive Pulmonary Disease in Atrial Fibrillation: New Insights from Umbria Atrial Fibrillation Registry. *Medicina* (Kaunas, Lithuania), 55(7), 358.

COPD with AF, ischaemic heart disease, and/or heart failure has been correlated with higher rates of hospitalisation, greater mortality, and lower quality of life.

COPD is prevalent among patients with atrial fibrillation, shares common risk factors, and adds to the overall morbidity and mortality in this population (Simons et al 2021). It may promote AF and impair treatment efficacy. the presence of this arrhythmia has significant impact on mortality, especially in COPD exacerbations.

Acute exacerbation of COPD is reported to transiently increase AF risk due to hypoxia-mediated mechanisms, inflammation, increased use of beta-2 agonists, and autonomic changes (Simons et al 2021). Observational data suggest that COPD promotes AF progression, increases AF recurrence after cardioversion, and reduces the efficacy of catheter-based antiarrhythmic therapy. However, it remains unclear whether treatment of COPD improves AF outcomes. Only limited published data confirms the association between chronic airways disease, particularly acute decompensation of chronic airways disease, although it is a clinical commonplace that acute respiratory failure is associated with supraventricular arrhythmias.

Using a pooled database of 46 studies involving >4 million subjects, Romiti et al (2021) reported that COPD is common in AF patients, with an average prevalence of 13%. COPD in AF populations is associated with an increased burden of comorbidities, differential management, and worse outcomes, including a more than two-fold higher risk of all cause death and increased risk of cardiovascular death and major bleeding.

The association of COPD and AF appear to be increasingly recognised in the medical literature. Many new studies confirm that COPD is independently associated with AF risk. Decreased oxygenation, hypercapnia, pulmonary hypertension, diastolic dysfunction, oxidative stress, inflammation, changes in atrial size by altered respiratory physiology, increased arrhythmogenicity from nonpulmonary vein foci commonly located in the right atrium, and respiratory drugs have been implicated in the pathogenesis of AF in COPD (Goudis et al 2017).

Grymonprez et al. (2019) analysed the development of atrial fibrillation in patients with COPD in the Rotterdam Study. COPD subjects had a 28% increased AF risk, which further increased with frequent exacerbations and an enlarged left atrium. The adjusted HR for incident AF in COPD patients compared to those without COPD was 1.28 (95CI 1.04-1.57). COPD patients with frequent exacerbations had a doubled AF risk (HR 1.99, 95CI 1.42-2.79) and COPD patients with a left atrial size ≥ 40 mm also had an elevated AF risk (HR 1.77, 95CI 1.07-2.94) The risk was driven by COPD subjects having elevated systemic inflammatory levels.

Hirayama et al. (2018) found that among patients with existing AF, acute exacerbation of COPD was associated with a higher risk of AF-related emergency visit or hospitalisation in the first 90-days after acute COPD exacerbation. Compared with the reference period, the rate of AF-related ED visits or hospitalizations significantly increased in the post-AECOPD days 1 to 90 (rate ratio, 1.93; 95CI, 1.63-2.29;). The rate decreased to the reference level in the post-AECOPD days 91 to 180 and remained at the reference level during days 181 to 270.

In the Chinese atrial fibrillation registry study (Dong et al (2021), AF hospitalisation risk was elevated in patients with COPD (HR 1.28, 95CI 1.02-1.62).

In relation to having chronic obstructive pulmonary disease, evidence strong enough to support a judgement of a suggestive causal relationship with the onset or worsening of atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between having COPD, including COPD exacerbation, and atrial fibrillation and flutter, but the evidence is limited in quality or quantity. Case reports provide evidence of temporal link and a biomechanical or pathophysiological mechanism.

A factor for COPD should be retained in the RH and BoP SoPs.

Asthma

No factor

Summary of important issues

Asthma and AF are prevalent conditions with distinct phenotypes that share inflammatory pathophysiological pathways (Tattersall et al 2020). Recognition that asthma is a heterogeneous and inflammatory disorder has altered therapeutic targets for its management. Epidemiological studies have demonstrated an independent association of elevated markers of systemic inflammation with incident of AF. Markers of coagulation, such as D-dimer and fibrin degradation products, are elevated in both AF and asthma and independently predict AF and cardiovascular disease mortality.

Potential AF triggers in asthma may include specific asthma treatments, such as oral glucocorticoids and β -agonists and methylxanthines. Because asthma treatment is based on asthma severity and the severity of asthma is associated with higher levels of systemic inflammation, the role of controller medications is difficult to discern

The association of asthma, and immunosuppressive medications (specifically corticosteroids) was the topic of a submission for the current Investigation.

A PubMed search was conducted on 8 February 2020 using the search terms asthma AND atrial fibrillation. The search identified 178 results

Review

There is only limited population level data exploring associations of asthma and AF,¹⁵⁴ Until the publication of Tattersall et al (2020), only 3 studies had investigated a potential link between asthma and AF, but had inconsistent results and were in populations with restricted

¹⁵⁴ Tattersall, M. C., Dasiewicz, A. S., McClelland, R. Let al. (2020). Persistent Asthma Is Associated With Increased Risk for Incident Atrial Fibrillation in the MESA. *Circulation. Arrhythmia and electrophysiology*, 13(2), e007685.
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race/ethnic diversity and asthma phenotypes. A nested case-control study using administrative claims data from Taiwan (Chan et al 2014) found an association between asthma and AF with an OR of 1.2, 95CI 1.1–1.3). In the Norwegian population based Nord-Trøndelag Health Study (Capelis et al 2018) , uncontrolled asthmatics also had an elevated risk of incident AF (HR 1.7, 95CI, 1.3–2.4). However, administrative data from National Health Services hospitals in England (Carter et al 2019) found no association of asthma with AF (OR 1.02, 95CI 0.97–1.07).

Corlateanu et al (2021) recently published a narrative review of asthma and stroke, which includes relevant information linking asthma and atrial fibrillation.¹⁵⁵ The review notes that heart diseases, such as acute myocardial infarction, atrial fibrillation and other can induce stroke. These abnormalities are frequent comorbidities in asthma patients.

Among relevant studies, the results from the Nord-Trøndelag health study (HUNT) study showed that asthma and lack of asthma control were associated with moderately increased risks of atrial fibrillation [Capelis et al 2018].¹⁵⁶

A nationwide population-based nested case-control study in Taiwan documented that inhaled bronchodilators were independently associated with an increased risk of AF. New users of bronchodilator had the highest risk of atrial fibrillation during first 6 months. 2-agonists have been described as a direct or indirect potential mechanism of death in asthmatics; they can induce increased risk of myocardial infarction, congestive heart failure, cardiac arrhythmia/arrest and sudden cardiac death with particularly high-risk of cardiac event in patients with long-QT syndrome . However, an Australian cohort study reported significant associations of incident cardiovascular disease and stroke events in both male and female subjects with traditional risk factors, including use of a bronchodilator. These events were positively associated with as needed beta-agonist use (OR, 2.66) but not at least once-daily use (OR 0.81), and there was an inverse and non-significant

Asthma has been shown by several studies to be associated with arrhythmias. Warnier et al (2012) showed high prevalence of tachycardia and premature ventricular tachycardia in asthmatics while Cepelis et al (2018) and Tattersall et al (2020) showed high prevalence of AF. Taha et al (2020) is the only study to examine the frequency of other types of arrhythmias, including atrial flutter.¹⁵⁷ The frequency of AF was about 8.95% in Taha et al, which was higher than the frequency observed in Warnier et al (0.6%) Cepelis et al (4.5%–6%), and Tattersall et al (1.3%). The main reason is that these studies followed up asthma patients in clinic who generally had mild disease compared to the hospitalized patients and arrhythmias have been found to be associated with disease severity in Taha et al (2020). However, Carter's study cohort compared to Taha et al's cohort. Taha et al may have overestimated the prevalence of AFib by not recognising patients with recurrent admissions.

¹⁵⁵ Corlateanu, A., Stratan, I., Covantev, S., et al (2021). Asthma and stroke: a narrative review. *Asthma research and practice*, 7(1), 3.

¹⁵⁶ Cepelis A, Brumpton BM, Malmö V, et al. (2018) Associations of asthma and asthma control with atrial fibrillation risk: results from the Nord-Trøndelag health study (HUNT). *JAMA Cardiol.*;3(8): 721–8.

¹⁵⁷ Taha M, Mishra T, Shokr M, et al (2020). Burden and impact of arrhythmias in asthma-related hospitalizations: Insight from the national inpatient sample. *J Arrhythmia*.37(1), 113–20

The association between asthma and AF is not fully understood, but might be explained by several mechanisms. Respiratory failure associated with asthma exacerbation. There was a higher risk of arrhythmia and mortality among asthma patients with respiratory failure requiring invasive or noninvasive ventilation. This finding is similar to previous studies on patients with asthma as well as patients with COPD. Hypoxaemia, hypercapnia and both respiratory and metabolic alkalosis developed in respiratory failure might contribute to the higher risk of arrhythmia among these patients.

Chronic airway inflammation is the pathogenesis of asthma disease. Inflammatory cells accumulate in the airway, activate cytokines, and enhance airway remodeling. Previous studies demonstrated that asthma is not just a local inflammatory disease but rather a systemic inflammatory disease with high serum levels of inflammatory markers. This systemic inflammation can increase the risk of arrhythmias directly or indirectly by enhancing the formation and rupture of coronary atherosclerotic plaques. Tattersall et al (2020) demonstrated that IL-6, D-dimer, and TNF- α were independent risk factors for AF among asthmatics.

Several studies reported evidence that asthma therapy, including bronchodilators and corticosteroids, increases the risk of arrhythmias (Adimadhyam et al 2014; Sears 2002) and this might confound the association between asthma and arrhythmia. Chan et al (2014) demonstrated that asthma patients were at higher risk of new onset AFib independent of corticosteroid and bronchodilators use.

Asthma and atrial fibrillation are prevalent conditions with distinct phenotypes that share inflammatory pathophysiological pathways (Tattersall et al 2020).¹⁵⁸ Recognition that asthma is a heterogeneous and inflammatory disorder has markedly altered therapeutic targets for its management. Previous epidemiological studies demonstrated an independent association of elevated markers of systemic inflammation with incident of AF. Markers of coagulation, such as D-dimer and fibrin degradation products, are elevated in both AF and asthma and independently predict AF and cardiovascular disease mortality.

Asthmatics may have many potential AF triggers that could, in part, explain the observed increased AF risk. Chronic systemic inflammation in asthma may lead to electrical and structural remodeling of the atria promoting a substrate favourable for AF. In asthma, inflammation is mediated by numerous pathways. In the eicosanoid pathway, arachidonic acid is catalysed by 5 lipo-oxygenase into leukotrienes, which are potent inflammatory paracrine substances formed primarily in leukocytes.

Other potential AF triggers in asthma may include specific asthma treatments, such as oral glucocorticoids and β -agonists and methylxanthines. Because asthma treatment is based on asthma severity and the severity of asthma is associated with higher levels of systemic inflammation, the role of controller medications is difficult to discern

¹⁵⁸ Tattersall, M. C., Dasiewicz, A. S., McClelland, R. et al. (2020). Persistent Asthma Is Associated With Increased Risk for Incident Atrial Fibrillation in the MESA. *Circulation. Arrhythmia and electrophysiology*, 13(2), e007685.
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Cohort studies

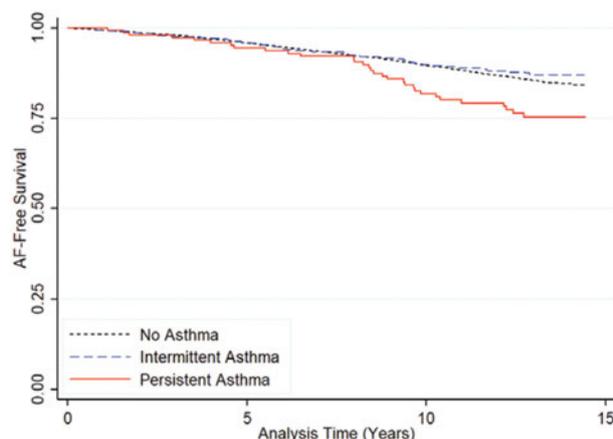
Asthma is a heterogeneous syndrome with differing pathophysiology impacted by genetic and environmental exposures, Asthma and atrial fibrillation may share an underlying inflammatory pathophysiology. **Tattersall et al (2020)** hypothesised that persistent asthmatics are at higher risk for developing AF and that this association would be attenuated by adjustment for baseline markers of systemic inflammation.¹⁵⁹

The MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective longitudinal study of adults free of cardiovascular disease at baseline. Presence of asthma was determined at exam 1. Persistent asthma was defined as asthma requiring use of controller medications. Intermittent asthma was defined as asthma without use of controller medications. Participants were followed for a median of 12.9 (interquartile range 10-13.6) years for incident AF. Multivariable Cox regression models were used to assess associations of asthma subtype and AF.

The 6615 participants were a mean (SD) 62.0 (10.2) years old (47% male, 27% black, 12% Chinese, and 22% Hispanic).

During the observation period, there were 875 incident AF events (787 in the nonasthmatic group, 57 in the intermittent asthmatic group, and 31 in persistent asthmatic group). The 10-year AF incidence rates were 0.11 events per 10 person-years (95% CI, 0.01–0.12) for nonasthmatics, 0.11 events per 10 person-years (95% CI, 0.08–0.14) for intermittent asthmatics, and 0.19 events per 10 person-years (95% CI, 0.12–0.49) for persistent asthmatics, (log-rank $P=0.008$).

FIGURE 12 KAPLAN-MEIER ATRIAL FIBRILLATION-FREE SURVIVAL ESTIMATES FOR PARTICIPANTS BASED ON ASTHMA SUBTYPE.



Tattersall et al (2020), Fig, p 126

In models adjusted for age, race, and sex, compared with non-asthmatics, those with persistent asthma had a higher risk of incident AF (HR 1.66, 95CI 1.16–2.38], $P\leq 0.01$). In fully

¹⁵⁹ Tattersall, M. C., Dasiewicz, A. S., McClelland, R. Let al. (2020). Persistent Asthma Is Associated With Increased Risk for Incident Atrial Fibrillation in the MESA. *Circulation. Arrhythmia and electrophysiology*, 13(2), e007685.
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adjusted models, persistent asthma remained associated with a higher risk of incident AF (HR 1.49, 95CI 1.03– 2.14).

TABLE 9 ASSOCIATION OF ASTHMA SUBTYPE WITH INCIDENT ATRIAL FIBRILLATION (N=6615)

Model	Intermittent Asthma*		Persistent Asthma*	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Model 1	0.87 (0.67–1.14)	0.32	1.69 (1.18–2.42)	<0.01
Model 2	1.13 (0.87–1.48)	0.36	1.66 (1.16–2.38)	<0.01
Model 3	1.09 (0.83–1.42)	0.55	1.50 (1.05–2.15)	0.03
Model 4	1.10 (0.82–1.41)	0.59	1.49 (1.03–2.14)	0.03

Tattersall et al (2020), Table 2, p 125; Model 1: unadjusted. Model 2: adjusted for age, race, and sex. Model 3: model 2 + systolic blood pressure, smoking, antihypertensive medication use at baseline, body mass index, diabetes mellitus, and alcohol consumption. Model 4: model 3 + education.

Participants with persistent asthma had the highest systemic inflammatory marker levels. Persistent asthmatics, compared with intermittent asthmatics and nonasthmatics, respectively, had higher levels of CRP and fibrinogen ($P<0.01$). IL-6 levels were higher in persistent asthmatics compared with nonasthmatics ($P<0.01$). D-dimer and sTNF- α R1 levels did not significantly vary by asthma group ($P>0.1$).

Incident AF was predicted by baseline levels of IL (Interleukin)-6 (HR 1.26, 95CI 1.13-1.42), TNF (tumor necrosis factor)- α receptor 1 (HR 1.09, 95CI 1.08-1.11) and D-dimer (HR 1.10, 95CI, 1.02-1.20), but the relationship between asthma and incident AF was not attenuated by adjustment for any inflammation marker (IL-6, CRP [C-reactive protein], TNF- α R1, D-dimer, and fibrinogen).

In this large multiethnic US cohort study with nearly 13 years of follow-up, persistent asthma was associated with a 1.5-fold increase in risk of incident AF in models fully adjusted for potential confounders. There was no evidence of attenuation of the association between asthma subtype and AF by serum levels of inflammatory/ coagulation markers, short-term autonomic tone measures, or obstructive sleep apnoea. Persistent asthma may be associated with a greater relative risk of AF in women than men.

Some cases of AF may have not been detected by the study’s ascertainment methods. The severity of AF was not assessed in MESA, which limits the ability to investigate a dose-dependent relationship. Consistent with prior studies, asthma was diagnosed as self-reported physician-diagnosed asthma, which may be prone to misclassification bias. There was a gradient of inflammatory and coagulation markers between nonasthmatics, intermittent asthmatics, and persistent asthmatics supportive of the classification of asthma subtype. Because asthma treatment is based on asthma severity, it was not possible to assess a potential medication effect on AF incidence. The analysis adjusted for available known and measured confounders, but residual confounding by unmeasured or unknown confounders may exist.

Carter et al (2019) investigated the relationship between chronic obstructive pulmonary disease (COPD), asthma and interstitial lung disease (ILD), and individual cardiovascular diseases, and evaluate the impact of individual cardiovascular diseases on all-cause mortality in respiratory conditions.¹⁶⁰

The authors conducted a cohort study of all patients admitted to 7 National Health Service hospitals across the North West of England, between 2000 and 2013, with relevant respiratory diagnoses, with age-matched and sex-matched control groups.

A total of 31,646 COPD, 60,424 asthma, and 1,662 ILD patients were included. Control groups comprised 158,230, 302,120, and 8,310 patients, respectively (total follow-up 2,968,182 patient-years).

COPD was independently associated with ischaemic heart disease (IHD), heart failure (HF), atrial fibrillation, and peripheral vascular disease, all of which were associated with all-cause mortality (e.g., odds ratio for the association of COPD with HF: 2.18, 95CI 2.08 -2.2; HR for the contribution of HF to mortality in COPD: 1.65, 95CI 1.61-1.68).

Asthma was independently associated with IHD, and multiple cardiovascular diseases contributed to mortality, but in this database, asthma was not associated independently with the risk of AF.

Taha et al (2020) analysed the burden and impact of cardiac arrhythmias in adult patients hospitalised with asthma exacerbation using the nationwide inpatient database.¹⁶¹

The authors used the National Inpatient Sample (NIS) database (2010-2014) to identify arrhythmias in asthma-related hospitalisation and its impact on inpatient mortality, hospital length of stay (LOS), and hospitalisation charges. multivariable analysis was used to identify predictors of in-hospital arrhythmia and mortality.

The authors identified 12,988,129 patients hospitalised with primary diagnosis of asthma; among them, 2,014,459 (16%) patients had cardiac arrhythmia. The most frequent arrhythmia identified was atrial fibrillation (AF) (8.95%) and the incidence of atrial flutter was 0.93%.

Asthma patients with AFib were predominantly older {mean age ~72 (AF) vs 52 (non-AFib) and 46 years (no arrhythmia)}, white {75.8% (AF) vs 59.9% (non-AF) and 58.8% (no arrhythmia)}, and Medicare beneficiaries {76.8% (AF) vs 42.5% (non-AF) and 34.0% (no arrhythmia)} as compared to those with non-AFib arrhythmia and those without arrhythmia ($P < .005$). Percentage of female patients were higher in all study groups (63.6% for AFib, 65.4% for non-AF, and 68.1% for non-arrhythmia groups, $P < .005$). The authors analysed the prevalence of comorbidities among hospitalized asthmatics with and without arrhythmia.

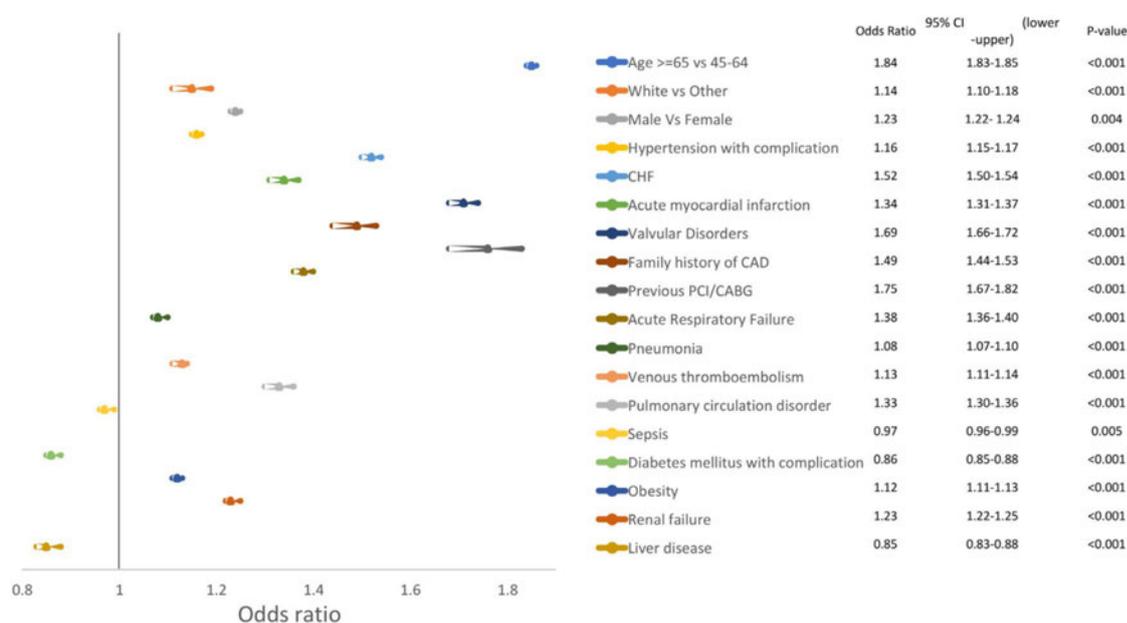
¹⁶⁰ Carter, P., Lagan, J., Fortune, C., et al (2019). Association of Cardiovascular Disease With Respiratory Disease. *Journal of the American College of Cardiology*, 73(17), 2166–77.

¹⁶¹ Taha, M., Mishra, T., Shokr, M., et al L. (2020). Burden and impact of arrhythmias in asthma-related hospitalizations: Insight from the national inpatient sample. *Journal of arrhythmia*, 37(1), 113–20.

The AF and non-AF arrhythmia groups were more likely to have cardiac comorbidities such as CHF {27.1% (AF), 9.90% and 6.25% (no arrhythmia)}, hypertension {73.6% (AF), 53.4% (non-AF), and 44.2% (no arrhythmia)}, and valvular heart diseases {10.9% (AF), 4.49% (non-AF), and 2.38% (no arrhythmia)} as compared to non-arrhythmia group (P < .005).

The AFib and non-AFib arrhythmia group had higher mortality (3.40% & 2.22% vs 0.74%), mean length of stay (LOS) (5.9 & 5.4 vs 4.2 days), and hospital charges, compared to the non-arrhythmia group (P < .005). Predictors of arrhythmia in asthma-related hospitalisation were history of PCI or CABG, valvular heart disease, congestive heart failure, and acute respiratory failure. Predictors of higher mortality in arrhythmia group were acute respiratory failure, sepsis, and acute myocardial infarction.

FIGURE 13 MULTIVARIABLE PREDICTORS OF ARRHYTHMIA AMONG ASTHMA HOSPITALIZATION



Taha et al (2020), Fig 3

Around 16% of adult patients hospitalised with asthma exacerbation experience arrhythmia (mostly AFib 8.95%). The presence of arrhythmias was associated with higher in-hospital mortality, LOS, and hospital charges in hospitalized asthmatics.

Cepelis et al (2018) assessed the association between asthma, levels of asthma control, and AF.¹⁶² This prospective population cohort analysed data on adults from a second and third iteration of the survey-based Nord-Trøndelag Health Study (HUNT) in Norway. All included participants were free from AF at baseline. Atrial fibrillation was ascertained by linking HUNT data with hospital records from the 2 hospitals in Nord-Trøndelag County. Data analysis was completed from May to November 2017.

Self-reported asthma was categorised into 3 groups: those who had ever had asthma, those who self-report being diagnosed with asthma, and those who had active asthma. Asthma

¹⁶² Cepelis, A., Brumpton, B. M., Malmo, V., et al (2018). Associations of Asthma and Asthma Control With Atrial Fibrillation Risk: Results From the Nord-Trøndelag Health Study (HUNT). *JAMA cardiology*, 3(8), 721–8.

control was defined according to Global Initiative for Asthma guidelines and was categorized into controlled, partly controlled, and uncontrolled cases.

A total of 54 567 adults were included, of whom 28 821 [52.8%] were women). Of these, 5961 participants (10.9%) reported ever having asthma, 3934 participants (7.2%) reported being diagnosed with asthma, and 2485 participants (4.6%) reported having active asthma. During a mean (SD) follow-up of 15.4 (5.8) years, 2071 participants (3.8%) developed AF. Participants with physician-diagnosed asthma had an estimated 38% higher risk of developing AF (adjusted HR 1.38, 95CI 1.18-1.61) compared to participants without asthma. There was a dose-response association between levels of asthma control and risk of AF with the highest risk for AF in participants with uncontrolled asthma (adjusted HR 1.74, 95CI, 1.26-2.42;).

Asthma and lack of asthma control were associated with moderately increased risks of AF in a dose-response manner.

Case-control studies

To examine the association between asthma and AF risk, **Chan et al (2014)** conducted a population-based nested case-control study including a total of 7439 newly-diagnosed adult patients with AF and 10,075 age-, sex-, comorbidity-, and cohort entry date-matched subjects without AF from the Taiwan National Health Insurance database.¹⁶³ Exposure to asthma as well as medications including bronchodilators and corticosteroid before the index date was evaluated to investigate the association between AF and asthma as well as concurrent medications.

AF patients were 1.2 times (adjusted OR 1.2, 95CI 1.109-1.298) more likely to be associated with a future occurrence of asthma independent of comorbidities and treatment with corticosteroids and bronchodilator. In addition, the risks of new-onset AF were significantly higher among current users of inhaled corticosteroid, oral corticosteroids, and bronchodilators. Newly users (within 6 months) have the highest risk (inhaled corticosteroid: OR 2.13; 95CI 1.226-3.701, P=0.007; oral corticosteroid: OR 1.932; 95CI 1.66-2.25;; non-steroid bronchodilator: OR 2.849; 95CI 2.48-3.273). A graded association with AF risk was also observed among subjects treated with corticosteroid (inhaled and systemic administration) and bronchodilators.

New users (within 6 months) of these medications had the highest risk of AF (ICS: OR 2.13; 95CI 1.226-3.701, P=0.007; oral corticosteroid: OR, 1.932; 95CI 1.66-2.25, P<0.001; non-steroid bronchodilator: OR 2.849; 95CI 2.48-3.273, P<0.001). A graded association with AF risk was also observed among subjects treated with ICS or bronchodilator.

Asthma was associated with an increased risk of developing future AF.

¹⁶³ Chan, W. L., Yang, K. P., Chao, T. F., et al (2014). The association of asthma and atrial fibrillation-- a nationwide population-based nested case-control study. *International journal of cardiology*, 176(2), 464–9.

Cross-sectional study

Although the relationship between obesity-asthma, obesity-atrial fibrillation (AF) and obesity-sudden cardiac death is clearly known, the risk of AF and ventricular arrhythmia has not been clearly determined in asthmatic patients.

Bozkurt Yilmaz et al (2018) investigated whether AF, ventricular arrhythmia, and sudden cardiac death risk were increased in asthmatic patients using P wave dispersion (PWD) and corrected QT interval dispersion (CQTD).¹⁶⁴

The cross-sectional study included 164 participants (88 patients with asthma and 76 healthy volunteers). PWD and CQTD were measured and recorded in both groups. The statistical difference between the two groups was examined.

P wave dispersal was higher in asthmatic patients than in controls (31.53 ± 3.18 vs. 30.33 ± 3.53 , $p = 0.023$). However, there was no statistically difference between the groups in terms of corrected QT interval dispersion measurement (43.9 ± 1.84 vs. 43.63 ± 2.06 , $p = 0.385$). In comparison between control group and asthma subgroups (mild, moderate and severe), there was a statistically significant difference among these four groups in terms of PWD ($p = 0.017$). Subgroup analyses showed that this difference was mainly due to patients with severe asthma.

P wave dispersion value was elevated in asthmatics. The corrected QT interval dispersion measurement was not statistically significant between the groups. These results indicate that the risk of developing AF in asthmatic patients might be higher than in the normal population. Ventricular arrhythmia and sudden cardiac death risk may not be high in asthmatic patients.

Case report

Funakoshi et al. (2021) reported a case where β 2-AR agonist inhalation possibly induced tachycardia and paroxysmal atrial fibrillation (PAF) in a 78-year-old Japanese woman.¹⁶⁵ The inter-individual variability in bronchial absorption is not well investigated; but, the variability in the drug volume reaching the bronchus in patients owing to inadequate inhalation is known.

Summary and conclusions

Asthma, a chronic inflammatory airway disease, and atrial fibrillation share several common pathophysiological mechanisms.

Asthma is one topic of the investigation request, specifically in relation to chronic steroid use for asthma. There are no factors in the current SoPs concerning asthma or steroid use.

¹⁶⁴ Bozkurt Yilmaz, H. E., Yilmaz, M., Şen, N., et al (2018). Assessment of atrial fibrillation and ventricular arrhythmia risk in patients with asthma by P wave/corrected QT interval dispersion. *European review for medical and pharmacological sciences*, 22(3), 756–62.

¹⁶⁵ Funakoshi, H., Momo, K., Okazaki, K., et al. (2021). β 2 -adrenoceptor agonist inhalation induced paroxysmal atrial fibrillation and tachycardia in a patient with severe bronchial asthma. *British journal of clinical pharmacology*, 87(8), 3375–7

Asthma and AF are prevalent conditions with distinct phenotypes that share underlying inflammatory pathophysiological pathways (Tattersall et al 2020). Recognition that asthma is a heterogeneous and inflammatory disorder has altered therapeutic targets for its management. Previous epidemiological studies demonstrated an independent association of elevated markers of systemic inflammation with incident AF. Markers of coagulation, such as D-dimer and fibrin degradation products, are elevated in both AF and asthma, and independently predict AF and cardiovascular disease mortality

It has been hypothesised that persistent asthmatics are at higher risk for developing AF and that this association would be attenuated by adjustment for baseline markers of systemic inflammation (Cepelis et al 2018).

There is limited population level data exploring associations of asthma and AF. Until Tattersall et al (2020), only 3 studies had investigated a potential link between asthma and AF, but they had inconsistent results.

A nested case-control study using administrative claims data from Taiwan (Chan et al 2014) found an association between asthma and AF (OR 1.2, 95CI 1.1–1.3). In the population based Nord-Trøndelag Health Study (Capelis et al 2018), of 54 567 adults in Norway, participants with doctor-diagnosed asthma had a higher risk of developing AF (adjusted HR 1.38, 95CI 1.18-1.61) compared with those without asthma. There was a dose-response association between levels of asthma control and risk of AF with the highest risk for AF in those with uncontrolled asthma (adjusted HR 1.74, 95CI 1.26-2.42; P trend < .001).

In a large multiethnic cohort with 13 years follow-up (MESA cohort), persistent asthma was associated with increased risk for incident AF (Tattersall et al 2020). This association was not attenuated by adjustment for baseline inflammatory biomarkers.

Taha et al (2020) evaluated the burden of arrhythmias in adult patients hospitalised with asthma exacerbation using the nationwide inpatient database National Inpatient Sample database (2010-2014). Around 16% of adult patients hospitalised with asthma exacerbation experienced arrhythmia (mostly AF 8.95%).

Bozkurt Yilmaz et al (2018) investigated whether AF, ventricular arrhythmia, and sudden cardiac death risk were increased in asthmatic patients using P wave dispersion and corrected QT interval dispersion. P wave dispersion value was elevated in asthmatics. The corrected QT interval dispersion measurement was not statistically significant between the groups. These results indicated that the risk of developing AF in asthmatic patients was higher than in the normal population.

Not all recent studies are supportive. Administrative data from National Health Services hospitals in England found no association of asthma with AF (OR 1.02, 95CI 0.97–1.07). (Carter et al 2019).

Other potential AF triggers in asthma may include specific asthma treatments, such as oral glucocorticoids and β -agonists and methylxanthines. Because asthma treatment is based on

asthma severity and the severity of asthma is associated with higher levels of systemic inflammation, the role of controller medications is difficult to discern

It is therefore concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with asthma (Grade 2). A consistent association has been observed between asthma, including asthma exacerbations and atrial fibrillation and flutter, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A new factor for asthma is proposed for the RH and BoP SoPs (onset and worsening).

Physical activity

Current factor

onset only - RH and BoP

undertaking strenuous, high level, endurance physical activity greater than six METs, for an average of at least 20 hours per week for a continuous period of at least five years before the clinical onset of atrial fibrillation or atrial flutter, and where strenuous physical activity has ceased, the clinical onset of atrial fibrillation or atrial flutter has occurred within 20 years [BoP 10 years] of cessation; or

"MET" means a unit of measurement of the level of physical exertion. 1 MET = 3.5 ml of oxygen/kg of body weight per minute, or 1.0 kcal/kg of body weight per hour, or resting metabolic rate;

Summary of important issues

The association between physical activity (PA) and AF remains controversial. Activity has been associated with both higher and lower AF risk (Albrecht et al 2018). Both sedentary behaviour and chronic high-intensity endurance exercise are risk factors for AF; and moderate physical activity is protective (O'Keefe et al 2021). Emerging evidence that very low/low levels of physical activity are associated with higher risk of AF, with moderate to high levels of activity being protective, and higher risks of AF in the physically inactive.

Summary of previous investigation

There is growing evidence that long-term endurance exercise may increase the risk of developing AF and atrial flutter in middle-aged populations. Although the benefits of regular exercise in controlling cardiovascular risk factors have been extensively proven, little is known about the long-term cardiovascular effects of regular and extreme endurance sport practice, such as jogging, cycling, rowing, swimming. Recent observational and review studies have shown that the prevalence of AF is higher in individuals who are involved in intense short-term training and long-term sports participation compared to general population of the same age, although clear evidence about the causal relation between these conditions is lacking. Human

data suggest an association between regular, long-term endurance sport practice and atrial fibrillation and flutter. Atrial fibrillation is the most common arrhythmia in athletic subjects and is more frequently observed in middle-aged than in young athletes. Atrial flutter can co-exist in the athlete with atrial fibrillation or present in isolation.

Several observational studies have reported that the prevalence of AF increases in younger athletes after many years of training. This has been documented in case–control studies comparing athletes with not athlete controls from the general population. Most series have recruited only male patients, or more than 70% males, who had been involved in intense training for many years. Endurance sport practice increases between 2 and 10 times the probability of suffering AF, after adjusting for other risk factors.

A review study by Calvo et al (2010) affirmed that previous studies support an association between long-term endurance sports practice and the occurrence of arrhythmias such as AF or AFL in the middle-aged male population. These observations suggest that sustained, intensive overtraining could produce a chronic inflammatory response in athletes that increases their risk for AF, but no studies in the literature confirm the association between AF, inflammation and exercise.

....

The underlying mechanism explaining this association is unclear, although structural atrial changes (dilatation and fibrosis) are probably present. Anatomical adaptation, chronic systemic inflammation, and alterations in the autonomic system are all possible explanations for the increased prevalence of AF in athletes. Some published studies found that atrial size was larger in athletes than in controls, and this was a predictor for AF. It has been shown that the left atrium may be enlarged in as many as 20% of competitive athletes. Athletes' vulnerability to AF has been explained by the increased vagal tone with consequent bradycardia that may lead to dispersion of atrial repolarisation, which in turn may increase the susceptibility to AF. Other studies have attributed the frequent occurrence of AF in athletes to remodelling

AF in athletes is initially paroxysmal, and most episodes have a vagal origin. becoming more frequent and prolonged, and may progress to persistent AF. Treatment of AF in this population can be challenging because of a lack of randomized trials and clear guidelines. Antiarrhythmic agents are usually the preferred choice of drugs. Several reports of catheter ablation have demonstrated encouraging results. Pulmonary vein isolation can be curative in the athlete with symptomatic lone atrial fibrillation.

In contrast to the findings in relation to athletes with a long history of vigorous physical training, there is evidence that modest degrees of activity may protect against AF. In prospective analysis of healthy women, regular physical activity was associated with a

Reviews

There have been several recent comprehensive review studies describing the association between physical activity and the risk of atrial fibrillation.^{166 167 168 169 170}

Flannery et al. (2017) observes that despite recognised health benefits, many studies have shown that endurance athletes are more likely to develop atrial fibrillation than non-athletes.¹⁷¹ The type, intensity and amount of sport appears to influence the risk of developing AF. Several endurance sport activities have been shown to increase the risk of developing AF but an excess in AF has not been shown in non-endurance sports. Lifetime hours of participation appear to increase the risk of developing AF. Women appear relatively protected and an association between endurance sport and AF has not been clearly demonstrated amongst female endurance athletes. The mechanisms by which endurance sport promotes the development of AF are unclear. There are, however, a number of pathophysiological mechanisms which are known to increase the risk of AF in non-athletes which have correlates in athletes. These include structural remodelling of the left atrium, elevated left atrial pressure, inflammation, myocardial fibrosis, vagal tone, sinus bradycardia and genetic predisposition.

A detailed review by **Franklin et al (2020)** notes that epidemiological and biological plausibility studies support a cause-and-effect relationship between increased levels of physical activity or cardiorespiratory fitness and reduced coronary heart disease events.¹⁷² These data, plus the well-documented anti-ageing effects of exercise, have likely contributed to the escalating numbers of adults who have embraced the notion that "more exercise is better." As a result, worldwide participation in endurance training, competitive long distance endurance events, and high-intensity interval training has increased markedly since the previous American Heart Association statement on exercise risk. Vigorous physical activity, particularly when performed by unfit individuals, can acutely increase the risk of sudden cardiac death and acute myocardial infarction in susceptible people. Recent studies have also shown that large exercise volumes and vigorous intensities are both associated with potential cardiac maladaptations, including accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, and atrial fibrillation. The relationship between these

¹⁶⁶ Elliott, A. D., Linz, D., Verdicchio, C. V., & Sanders, P. (2018). Exercise and Atrial Fibrillation: Prevention or Causation?. *Heart, lung & circulation*, 27(9), 1078–85.

¹⁶⁷ Flannery, M. D., Kalman, J. M., Sanders, P., et al. (2017). State of the Art Review: Atrial Fibrillation in Athletes. *Heart, lung & circulation*, 26(9), 983–9.

¹⁶⁸ Nattel S. (2020). Physical activity and atrial fibrillation risk: it's complicated; and sex is critical. *European heart journal*, 41(15), 1487–9.

¹⁶⁹ Morseth, B., Løchen, M. L., Ariansen, I., et al (2018). The ambiguity of physical activity, exercise and atrial fibrillation. *European journal of preventive cardiology*, 25(6), 624–36

¹⁷⁰ Franklin, B. A., Rusia, A., Haskin-Popp, C., et al. (2021). Chronic Stress, Exercise and Cardiovascular Disease: Placing the Benefits and Risks of Physical Activity into Perspective. *International journal of environmental research and public health*, 18(18), 9922.

¹⁷¹ Flannery, M. D., Kalman, J. M., Sanders, P., et al. (2017). State of the Art Review: Atrial Fibrillation in Athletes. *Heart, lung & circulation*, 26(9), 983–9.

¹⁷² Franklin, B. A., Thompson, P. D., Al-Zaiti, S. S., et al (2020). Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. *Circulation*, 141(13), e705–e36.

maladaptive responses and physical activity often forms a U- or reverse J-shaped dose-response curve.

The relation between exercise and incident AF is complicated. Low levels of CRFe (<6 METs) are associated with a higher risk for AF, and individuals with higher levels of CRFe (7.9 ± 1.0 and 9.3 ± 1.2 METs) have a dose-dependent decrease in AF risk. Fit AF patients have a lower risk for AF recurrences during follow-up than their unfit counterparts (Pathak et al 2015). AF burden and symptom severity decreased significantly in patients with AF who increased their fitness during an exercise training program versus those who failed to improve and among patients with AF randomized to aerobic interval training in a small clinical trial. Although these observations suggest that fitter individuals have the lowest AF risk, there is substantial evidence that the risk for AF is higher in athletes than in control subjects.

High-intensity exercise training (Mozaffarian et al 2008) and faster finishing times (Andersen et al 2013) were associated with an increase of AF in physically active older adults and long-distance cross-country skiers, respectively.¹⁷³

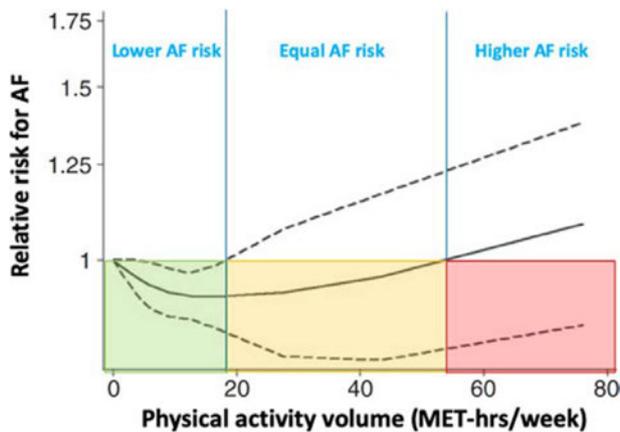
In the US Physician's Health Study, men who jogged 5 to 7 times per week had a 50% higher risk of AF than men who did not exercise vigorously, even after adjustment for multiple cardiovascular risk factors (Aizer et al 2009).

Three meta-analyses cited by Franklin et al found that AF risk was 2- to 10-fold higher in endurance athletes than in control participants (Sorokin et al 2011; Abdulla et al 2009; Mont et al 2009).

Long-term volume of vigorous endurance exercise (≥ 2000 hours of training or ≥ 20 years of training) was strongly associated with an increased risk for lone AF. These data suggest that both low and very high volumes of exercise training are associated with an increased risk for AF, whereas moderate exercise volumes appear to reduce risk. In a nonlinear meta-regression analysis including data from 19 studies and 29 855 AF cases found a J-shaped association between PA volumes and risk for AF. Individuals performing 5 to 20 MET-hours of PA per week had a significantly lower risk for AF, whereas physically inactive or highly active individuals (20–55 MET-h/wk) had similar relative risks for AF (Ricci et al 2018). A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk, equalling >9.5 hours of vigorous exercise training per week.

¹⁷³ Franklin, B. A., Thompson, P. D., Al-Zaiti, S. S., et al (2020). Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. *Circulation*, 141(13), e705–e36.
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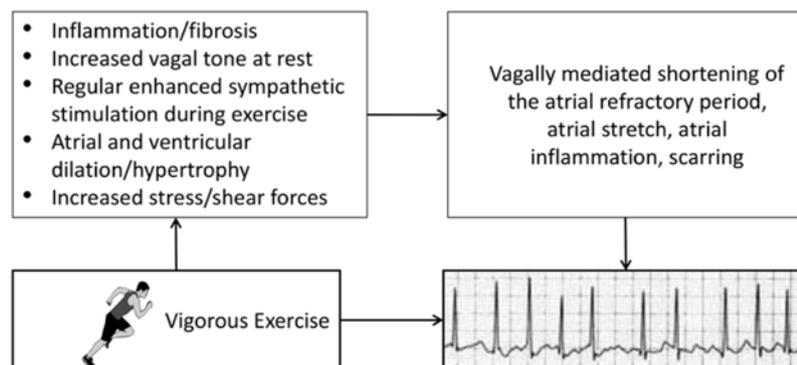
FIGURE 14 DOSE–RESPONSE ASSOCIATION BETWEEN PHYSICAL ACTIVITY VOLUME AND AF RISK.



Franklin et al (2020), Fig 8

The underlying mechanisms responsible for the increased prevalence of AF among athletes are unknown,¹⁷⁴ but several pathways have been proposed. A prolonged (2 year) training study incorporating high intensity training sessions showed that although left ventricular remodelling appears to plateau when training load plateaus, left atrial remodelling continues, even when the training dose is stable. This suggests that the atria are especially prone to dilation and remodelling in individuals who have trained at a high level for many years. Interindividual genetic variability could also put some athletes at a higher risk of pathological remodelling leading to lone AF. increased parasympathetic tone in combination with left atrial enlargement is likely to contribute to the increased AF risk, but exercise-induced sympathetic stimulation, sustained hemodynamic stress, and inflammation and oxidative stress could contribute to the development of AF in the most active exercisers.

FIGURE 15 POTENTIAL MECHANISMS AND ASSOCIATED SEQUELAE FOR ATRIAL FIBRILLATION INDUCED BY STRENUOUS ENDURANCE EXERCISE.



Franklin et al (2020), Fig 7; adapted from Eijssvogels et al

The combination of autonomic, structural, and hemodynamic effects of high-volume, high-intensity aerobic exercise, repeated over time, likely impart some of the increased

¹⁷⁴ Franklin, B. A., Thompson, P. D., Al-Zaiti, S. S., et al (2020). Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. *Circulation*, 141(13), e705–e36. August meeting 2022

risk for atrial fibrillation.¹⁷⁵ Differences in study methodology have led to varying estimates regarding the magnitude of risk, ranging from an ≈20% increase to a >10-fold risk of incident AF. .

Staerk et al (2017) also examined the association of AF and exercise.¹⁷⁶ The relationship between level of physical activity and risk of AF has been described as nonlinear. Sedentary lifestyle is associated with higher risk of AF, but paradoxically extreme levels of physical activity also are associated with increased AF risk.

A large retrospective cohort study of 64,561 patients showed a graded and inverse relationship between cardiorespiratory fitness (CRF) as objectively assessed with treadmill testing. The incidence rate of AF in patients with lowest CRF was 18.8% as compared to 3.7% in those with highest CRF. Every 1-MET increase in CRF was associated with a dose-dependent 7% reduction in AF risk (Qureshi et al 2015).

A meta-analysis of pooled data from seven studies showed that sedentary lifestyle was associated with increased risk of AF (OR 2.47; 95CI 1.25–3.7) compared to moderate or intense physical activity (Mohanty et al 2016).¹⁷⁷

Male endurance athletes are at increased AF risk. In a prospective case-control study, individuals who performed <2000 hours of lifetime-accumulated high-intensity exercise had an attenuated risk of lone AF (OR 0.38; 95CI 0.12–0.98) compared with sedentary individuals. But the AF risk in those with ≥2000 hours of high-intensity exercise was increased (OR 3.88; 95CI 1.55–9.73). Calvo et al (2016) The type of exercise modulates AF risk with endurance sports, such as marathon running or long distance cross-country skiing, conferring the highest AF risk.

Sex-differences in the association of physical activity with AF have been identified. In men a U-shaped association of AF risk and physical activity was observed where moderate physical activity was found to confer lowest risk (OR 0.81; 95CI 0.26–1.00) and intense activity conferred the highest risk (OR 3.30; 95CI 1.97–4.63). In women, however, the association was inverse and linear. Increasing physical activity was associated with progressive and decreasing AF risk with ORs of 0.91 (95CI 0.77–0.97) and 0.72 (95CI 0.57–0.88) for moderate and intense activity, respectively (Mohanty et al 2016).

Sedentary lifestyle is known to increase risk of AF risk factors including hypertension, obesity, and diabetes. Obstructive sleep apnoea (OSA) is common in obese individuals and has been associated with sedentary lifestyle. These conditions have been shown to independently

¹⁷⁵ Franklin, B. A., Thompson, P. D., Al-Zaiti, S. S., et al (2020). Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective-An Update: A Scientific Statement From the American Heart Association. *Circulation*, 141(13), e705–e36.

¹⁷⁶ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17

¹⁷⁷ Mohanty S, Mohanty P, Tamaki M, et al (2016). Differential Association of Exercise Intensity With Risk of Atrial Fibrillation in Men and Women: Evidence from a Meta-Analysis. *Journal of cardiovascular electrophysiology*. 2016; 27:1021–9.

induce structural and electrical remodelling of the atrium. Physical inactivity also increases systemic inflammation, which may induce atrial remodelling and has been associated with AF. Sedentary lifestyle is associated with autonomic dysfunction and elevated sympathetic tone, which enhances afterdepolarization triggering and AF susceptibility.

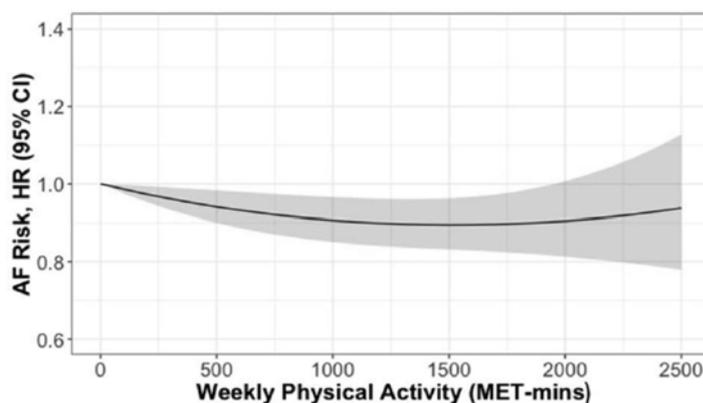
In endurance athletes, the pathogenesis of AF has been attributed to two primary mechanisms. Increased vagal tone in these individuals may shorten and increase the dispersion of atrial ERP promoting PV firing and localized reentry. Also, long-term endurance training causes progressive cardiac remodeling including left atrial enlargement, which may promote AF. Atrial fibrosis and increased AF susceptibility has been observed in a rat model of prolonged, intensive exercise.

Meta-analyses

Mishima et al (2021) systematically summarised the evidence pertaining to the relationship of physical activity (PA) and risk of AF, based on prospective cohort studies reporting the risk of AF associated with a specific PA volume to March 2020.¹⁷⁸ The authors extracted the risk associated with a given PA level, in comparison with insufficiently active ("inactive") individuals. The reported risk was normalized to metabolic equivalent of task (MET)-minutes per week. A random-effects meta-analysis was used to compare AF risk between those who met and those who did not meet PA recommendations (450 MET-minutes per week), and a dose-response analysis between the level of PA and the risk of AF was performed.

Fifteen studies reporting data from 1,464,539 individuals (median age 55.3 years; 51.7% female) were included. Individuals achieving guideline-recommended level of PA had a significantly lower risk of AF (HR 0.94; 95CI 0.90-0.97). Dose-response analysis showed that PA levels up to 1900 MET-minutes per week were associated with a lower risk of AF, with less certainty beyond that level.

FIGURE 16 PA AND AF RISK, DOSE RESPONSE



Mishima et al (2021), Fig 5

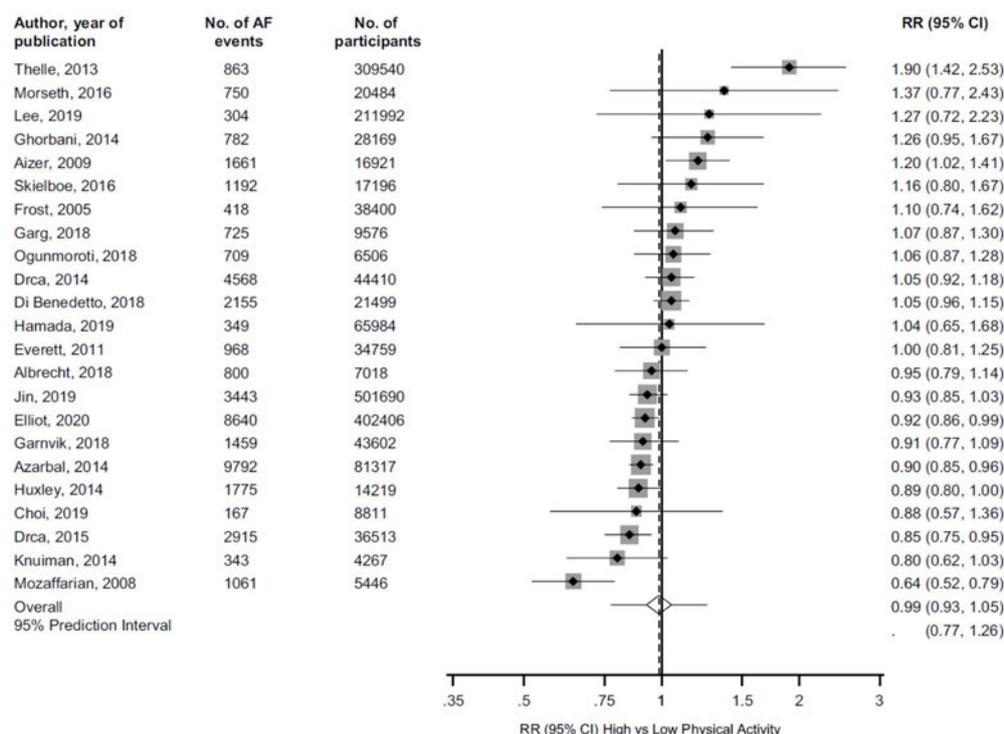
¹⁷⁸ Mishima, R. S., Verdicchio, C. V., Noubiap, J. J., et al. (2021). Self-reported physical activity and atrial fibrillation risk: A systematic review and meta-analysis. *Heart rhythm*, 18(4), 520–8.
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Physical activity at guideline-recommended levels and above are associated with a significantly lower AF risk. At 2000 MET-minutes per week and beyond, the benefit was less clear.

Using a systematic review and meta-analysis of published observational cohort studies in general populations with at least one-year of follow-up, **Kunutsor et al (2021)** evaluate the association between regular physical activity and the risk of AF¹⁷⁹. Relevant studies were sought from inception until October 2020 in. Extracted relative risks for the maximum versus the minimal amount of physical activity groups were pooled using random-effects meta-analysis. Quality of evidence was assessed by GRADE.

A total of 23 unique observational cohort studies comprising of 1,930,725 participants and 45,839 AF cases were eligible. The pooled multivariable-adjusted RR for AF comparing the most physically active versus the least physically active groups was 0.99 95CI (0.93-1.05). This association was modified by sex: an increased risk was observed in men: 1.20 (95CI 1.02-1.42), with a decreased risk in women: 0.91 (95CI 0.84-0.99). The quality of evidence ranged from low to moderate.

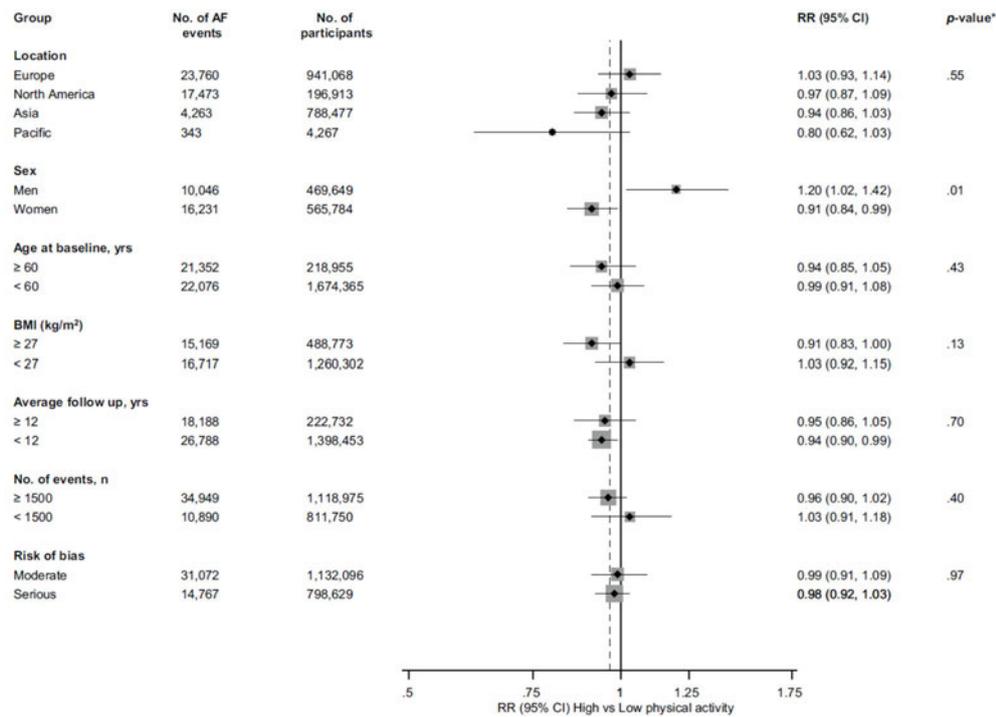
FIGURE 17 OBSERVATIONAL COHORT STUDIES OF PHYSICAL ACTIVITY AND RISK OF ATRIAL FIBRILLATION INCLUDED IN META-ANALYSIS. RANDOM EFFECTS MODELS



Kunutsor et al (2021), Fig 2

¹⁷⁹ Kunutsor, S. K., Seidu, S., Mäkikallio, T. H., et al. (2021). Physical activity and risk of atrial fibrillation in the general population: meta-analysis of 23 cohort studies involving about 2 million participants. *European journal of Epidemiology*, 36(3), 259–74. August meeting 2022

FIGURE 18 RELATIVE RISKS FOR ATRIAL FIBRILLATION COMPARING MAXIMAL VERSUS MINIMAL AMOUNT OF PHYSICAL ACTIVITY, GROUPED ACCORDING TO STUDY-LEVEL CHARACTERISTICS.



Kunutsor et al (2021), Fig 3

Given the controversial relationship between physical activity and the risk of AF and the inclusion of case–control designs and a mix of general population participants and athletes in previous pooled analyses, the authors evaluated the relationship by conducting a meta-analysis of only population-based observational cohort studies limited to general populations. In a pooled analysis of 23 unique cohort studies with 2 million participants, there was no strong evidence suggesting regular physical activity was associated with the risk of AF in the overall population. However, subgroup analysis by sex demonstrated that regular physical activity was associated with increased risk of AF in men and a decreased risk in women.

There have been several previous efforts to aggregate the existing data on the relationship between physical activity and AF and the findings have been divergent. The overall null findings of Kunutsor et al are consistent with previous reviews. In a pooled analysis of four prospective cohort studies based on general populations, Ofman et al (2013) did not support a significant association between regular physical activity and increased or decreased risk of AF. In an analysis of 10 general population studies, Kwok et al (2014) demonstrated no evidence of an association between intensive or leisure-time activity and the risk of AF. Ricci et al in a pooled random-effects meta-analysis of 18 studies showed no significant association between physical activity and risk of AF, although a dose–response analysis suggested a J-shaped relationship. A significant limitation of their dose–response analysis was that it was only based on a subset of studies because of limited data on studies reporting physical activity exposure in terms of metabolic equivalents. As described by Orsini et al. [2006] a dose–response analysis requires that the number of cases, person-years of follow-up or non-cases, and the RRs with the variance estimates for at least three quantitative categories of exposure levels are known for each study.

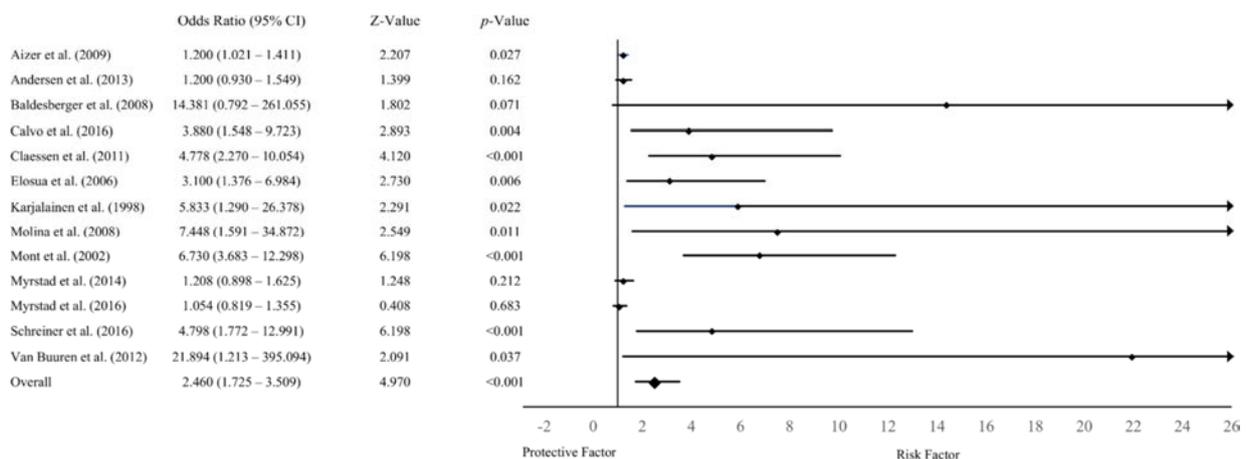
Several reviews have also noted sex-specific associations of physical activity with AF. Mohanty et al (2016) reported that moderate amounts of physical activity reduced the risk of AF in both men and women, but observed that intense exercise had a sex-specific association with AF risk. Zhu et al (2016), in their evaluation of sex differences in the association, showed total physical activity to be associated with an increased AF risk in men and a reduced risk in women.

Pooled observational cohort studies suggest that the absence of associations reported between regular physical activity and AF risk in previous general population studies and their aggregate analyses could be driven by a sex-specific difference in the associations - an increased risk in men and a decreased risk in women.

Newman et al. (2021) conducted a systematic review, meta-analysis and meta-regression on selected studies to investigate the incidence of atrial fibrillation among athletes compared with non-athlete controls.¹⁸⁰ The mode of exercise (endurance and mixed sports) and age were the a priori determined covariates.

The risk of developing AF was significantly higher in athletes than in non-athlete controls (OR: 2.46; 95CI 1.73 t-.51; p<0.001, Z=4.97). Mode of exercise and risk of AF were moderately correlated (B=0.1259, p=0.0193), with mixed sport conferring a greater risk of AF than endurance sport (B=-0.5476, p=0.0204). Younger athletes (<55 years) were significantly more likely to develop AF compared with older athletes (B=-0.02293, p<0.001).

FIGURE 19 RANDOM EFFECTS META-ANALYSIS OF AF RISK IN ATHLETE’S VS CONTROLS. AF, ATRIAL FIBRILLATION

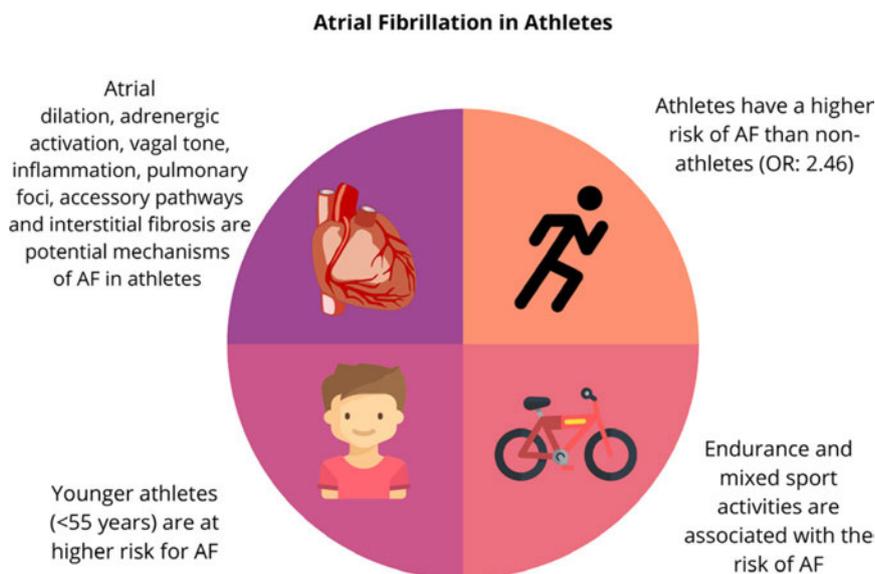


Newman et al. (2021), Fig 2

Athletes have a significantly greater likelihood of developing AF compared with non-athlete controls, with those participating in mixed sport and younger athletes at the greatest risk.

¹⁸⁰ Newman, W., Parry-Williams, G., Wiles, J., et al. (2021). Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *British journal of sports medicine*, 55(21), 1233–8 August meeting 2022

FIGURE 20 MAIN STUDY OUTCOMES. ATRIAL FIBRILLATION.



Newman et al. (2021), Fig 4

Despite the increased risk observed among different study sizes, sport types, ages and exercise modalities, there remains a lack of high-quality studies with consistent methodologies to quantify the maximum safest regular ‘dose’ of exercise before AF risk becomes significant.

The observation that endurance sports correlate with AF is generally accepted. Mechanistically, biatrial remodelling, dilation and fibrosis as crucial substrates to developing this pathology. However, it has been suggested that mechanical and electrical remodelling of the atria seen with chronic endurance sport is functional and does not predispose individuals to a higher risk of AF.¹⁸¹ Despite this, current evidence does indicate a potential increase in AF risk with endurance exercise specifically. Separately, the association of ‘mixed sports’ with an increase in AF risk is difficult to interpret due to the broad range of sports analysed, complicating the process of elucidating true effects from specific training modalities. However, training volume may be an important risk factor for the development of AF and merits future research.

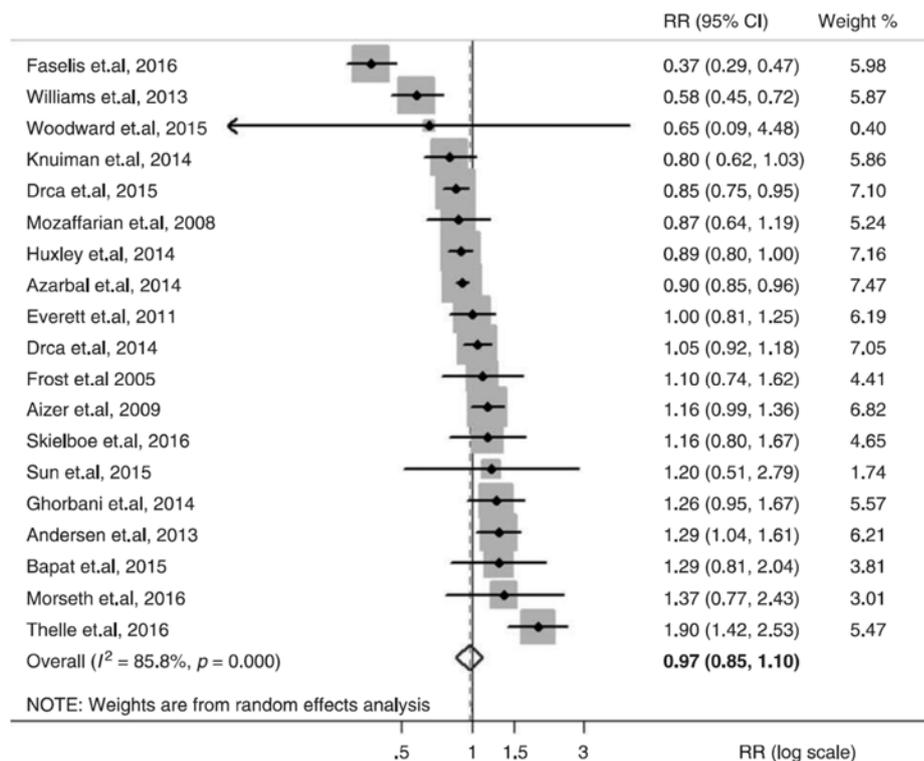
Light physical activity is known to reduce atrial fibrillation risk, whereas moderate to vigorous physical activity may result in an increased risk. However, the question of what volume of physical activity can be considered beneficial remains poorly understood. **Ricci et al (2018)** examined the relation between physical activity volume and atrial fibrillation risk.¹⁸² A comprehensive systematic review was performed following the PRISMA guidelines. A non-linear meta-regression considering the amount of energy spent in physical activity was carried out. The first derivative of the non-linear relation between physical activity and atrial fibrillation risk was evaluated to determine the volume of physical activity that carried the minimum atrial fibrillation risk.

¹⁸¹ Newman, W., Parry-Williams, G., Wiles, J., et al. (2021). Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *British journal of sports medicine*, 55(21), 1233–8.

¹⁸² Ricci, C., Gervasi, F., Gaeta, M., et al (2018). Physical activity volume in relation to risk of atrial fibrillation. A non-linear meta-regression analysis. *European journal of preventive cardiology*, 25(8), 857–66.

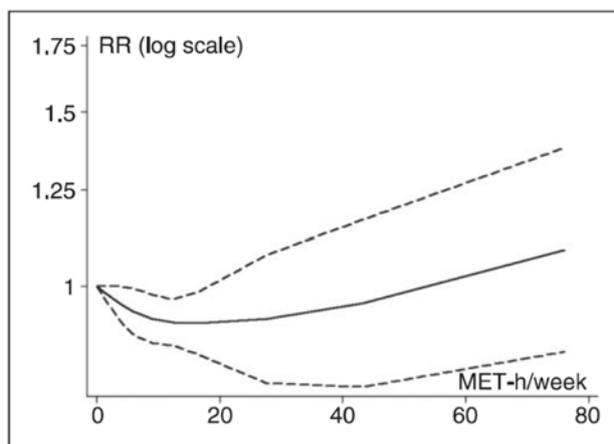
The dose-response analysis showed that physical activity at volumes of 5-20 metabolic equivalents per week (MET-h/week) was associated with significant reduction in atrial fibrillation risk (relative risk for 19 MET-h/week = 0.92, 95CI 0.87- 0.98). In comparison, physical activity volumes exceeding 20 MET-h/week were unrelated to AF risk (RR for 21 MET-h/week = 0.95, 95CI 0.88- 1.02).

FIGURE 21 RANDOM EFFECTS META-ANALYSIS OF RISK OF AF FOR HIGH VS LOW PHYSICAL ACTIVITY



Ricci et al (2018), Fig 2

FIGURE 22 DOSE RESPONSE ANALYSIS OF PHYSICAL ACTIVITY AND RISK OF AF



Ricci et al (2018), Fig 3

In a non-linear dose response analysis, a statistically significant decreasing risk of AF was observed for increasing levels of PA volume between 5 and 20 MET-h/week. Above that range

of MET values, an inflection of the dose-response was observed, the 95CI started to widen, and the association became statistically non-significant. This reflects uncertainty of the nature of the relationship at higher volumes of PA. In the high vs low PA analysis, a null association was found for AF risk.

The dose response between PA and AF risk follows a J-shaped curve. The meta-analysis showed that PA at 5-20 METS-h/week may result in reduced risk of AF. PA exceeding 20 MET-h/week showed no association with risk. The data requires cautious interpretation because PA exposure in terms of MET-h/week was not reported uniformly in studies.

These data show a J-shaped relation between physical activity volume and atrial fibrillation risk. Physical activity at volumes of up to 20 MET-h/week is associated with reduced atrial fibrillation risk, whereas volumes exceeding 20 MET-h/week show no relation with risk.

Cohort studies

Bonnesen et al (2021) investigated the association between within-individual changes in physical activity and onset of atrial fibrillation.¹⁸³

1410 participants from the general population (46.2% women, mean age 74.7 ± 4.1 years) with risk factors but with no prior AF diagnosis underwent continuous monitoring for AF episodes along with daily accelerometric assessment of physical activity using an implantable loop recorder during 3.5 years. The combined duration of monitoring was ≈ 1.6 million days, where 10 851 AF episodes lasting ≥ 60 min were detected in 361 participants (25.6%) with a median of 5 episodes (2, 25) each. The median daily physical activity was 112 (66, 168) min/day. A dynamic parameter describing within-individual changes in daily physical activity, i.e. average daily activity in the last week compared to the previous 100 days, was computed and used to model the onset of AF.

A 1-h decrease in average daily physical activity was associated with AF onset the next day [OR 1.24, 95CI 1.18-1.31]. This effect was modified by overall level of activity ($P < 0.001$ for interaction), and the signal was strongest in the tertile of participants with lowest activity overall [low: 1.62, 95CI 1.41-1.86), mid: 1.27 (95CI 1.16-1.39), and high: 1.10 (95CI 1.01-1.19)].

Within-individual changes in physical activity were associated with the onset of AF episodes as detected by continuous monitoring in a high-risk population. For each person, a 1-h decrease in daily physical activity during the last week increased the odds of AF onset the next day by $\approx 25\%$. The strongest association was in the group with the lowest activity overall.

Khurshid et al (2021) analysed 93 669 participants of the UK Biobank prospective cohort study without prevalent AF who wore a wrist-based accelerometer for 1 week.¹⁸⁴ The authors categorised whether measured activity met the standard recommendations of the European

¹⁸³ Bonnesen, M. P., Frodi, D. M., Haugan, K. J., et al (2021). Day-to-day measurement of physical activity and risk of atrial fibrillation. *European heart journal*, 42(38), 3979–88.

¹⁸⁴ Khurshid, S., Weng, L. C., Al-Alusi, M. A., et al. (2021). Accelerometer-derived physical activity and risk of atrial fibrillation. *European heart journal*, 42(25), 2472–83.

Society of Cardiology, American Heart Association, and World Health Organization [moderate-to-vigorous physical activity (MVPA) ≥ 150 min/week]. tested associations between guideline-adherent activity and incident AF (primary) and stroke (secondary) using Cox proportional hazards models adjusted for age, sex, and each component of the Cohorts for Heart and Aging Research in Genomic Epidemiology AF (CHARGE-AF) risk score. assessed correlation between accelerometer-derived and self-reported activity.

The mean age was 62 ± 8 years and 57% were women. Over a median of 5.2 years, 2338 incident AF events occurred. Greater accelerometer-derived physical activity was associated with lower risks of AF and stroke. In multivariable adjusted models, guideline-adherent activity was associated with lower risks of AF (HR 0.82, 95CI 0.75-0.89; incidence 3.5/1000 person-years, 95CI 3.3-3.8 vs. 6.5/1000 person-years, 95CI 6.1-6.8]. Correlation between accelerometer-derived and self-reported MVPA was weak (Spearman $r = 0.16$, 95CI 0.16-0.17). Self-reported activity was not associated with incident AF.

O'Neal et al (2020) examined the association between moderate and vigorous physical activity (MVPA) with incident AF in 5,147 participants who completed accelerometer assessment for 4 to 7 consecutive days in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.¹⁸⁵ MVPA was defined as $>1,065$ counts/minute, and daily mean time spent in MVPA was computed. Incident AF was identified during follow-up by a study-scheduled electrocardiogram and also from self-reported medical history of a physician diagnosis. Logistic regression was used to assess the relation between daily time in MVPA and incident AF.

A total of 429 (8.3%) incident AF cases were detected after a median follow-up of 3.5 years following accelerometer assessment. In this study, higher levels of objectively measured daily MVPA were protective against the development of AF. Participants with higher daily time spent in MVPA were less likely to develop AF than those with lower MVPA achievement (Quartile 1 = 12.4%; Quartile 2 = 8.3%; Quartile 3 = 7.1%; Quartile 4 = 5.4%; p-trend <0.001). In a multivariable model adjusted for AF risk factors, the risk of AF decreased with higher levels of daily MVPA (Quartile 1: Ref; Quartile 2: HR 0.77, 95CI 0.58 - 1.01; Quartile 3: HR 0.72, 95CI 0.53 to 0.98; Quartile 4: HR 0.62, 95CI 0.44 to 0.87; p-trend = 0.0056).

Albrecht et al (2018) investigated the association of total and types of physical activity, including walking, cycling, domestic work, gardening and sports, with atrial fibrillation in the Rotterdam Study, a prospective population-based cohort. included 7018 participants aged 55 years and older with information on physical activity between 1997-2001.¹⁸⁶ Cox proportional hazards models were used to examine the association of physical activity with atrial fibrillation risk. Models were adjusted for biological and behavioural risk factors and the remaining physical activity types. Physical activity was categorised in tertiles and the low group was used as reference.

¹⁸⁵ O'Neal, W. T., Bennett, A., Singleton, M. J., et al (2020). Objectively Measured Physical Activity and the Risk of Atrial Fibrillation (from the REGARDS Study). *The American journal of cardiology*, 128, 107–12.

¹⁸⁶ Albrecht, M., Koolhaas, C. M., Schoufour, J. D., et al. (2018). Physical activity types and atrial fibrillation risk in the middle-aged and elderly: The Rotterdam Study. *European journal of preventive cardiology*, 25(12), 1316–23.

During 16.8 years of follow-up (median: 12.3 years, interquartile range: 8.7-15.9 years), 800 atrial fibrillation events occurred (11.4% of the study population). observed no association between total physical activity and atrial fibrillation risk in any model. After adjustment for confounders, the hazard ratio and 95% confidence interval for the high physical activity category compared to the low physical activity category was: 0.71 (0.80-1.14) for total physical activity. did not observe a significant association between any of the physical activity types with atrial fibrillation risk.

The results suggest that physical activity is not associated with higher or lower risk of atrial fibrillation in older adults. Neither total physical activity nor any of the included physical activity types was associated with atrial fibrillation risk.

Summary and conclusions

The association between physical activity and atrial fibrillation remains controversial. Physical activity has been associated with both a higher and lower atrial fibrillation risk (Albrecht et al 2018). Some, but not all studies have suggested that regular physical activity is associated with a risk of AF in the general population.

Atrial fibrillation has been linked to extensive and long-term exercise, as prolonged endurance exercise has shown to increase prevalence and risk of atrial fibrillation. In contrast, more modest physical activity is associated with a decreased risk of atrial fibrillation, and current research indicates a J-shaped association between atrial fibrillation and the broad range of physical activity and exercise. This has led to the hypothesis that the mechanisms underlying an increased risk of atrial fibrillation with intensive exercise are different from those underlying a reduced risk with moderate physical activity, possibly linked to distinctive characteristics of the population under study (Morseth et al 2018). High volumes of exercise over many years performed by lean, healthy endurance trained athletes may lead to cardiac pathophysiological alterations involving the autonomic nervous system and remodelling of the heart. The mechanisms underlying a reduced risk of atrial fibrillation with light and moderate physical activity may involve a distinctive pathway, as physical activity can potentially reduce the risk of atrial fibrillation through favourable effects on cardiovascular risk factors.

Sedentary behaviour and chronic high-intensity endurance exercise are both risk factors for AF; however moderate physical activity is associated with lower risk of AF (O'Keefe et al 2021)

Studies have shown that regular physical activity and high cardiorespiratory fitness both contribute to a reduction in incident atrial fibrillation (Elliot et al 2018). However, the risk of AF appears to be paradoxically increased by participation in endurance exercise. There is a substantial body evidence that long-term endurance exercise may increase the risk of developing AF and atrial flutter in middle-aged men, and that endurance male athletes are more likely to develop atrial fibrillation than non-athletes Flannery et al. (2017).

The type, intensity and amount of sport appears to influence the risk of developing AF. Several endurance sport activities have been shown to increase the risk of developing AF but

an excess in AF has not been shown in non-endurance sports. Lifetime hours of participation appear to increase the risk of developing AF. Women appear to be protected, and an association between endurance sport and AF has not been demonstrated in female endurance athletes.

The observation that endurance sports correlate with AF is generally accepted (Newman et al 2021). Despite the increased risk observed among different study sizes, sport types, ages and exercise modalities, there remains a lack of high-quality studies with consistent methodologies to quantify the maximum safest regular 'dose' of exercise before AF risk becomes significant.

Although the mechanisms responsible for an increased prevalence of AF in endurance athletes are not well understood, several pathways have been proposed. Mechanistically, biatrial remodelling, dilation and fibrosis are substrates for this pathology. Exercise-induced changes in autonomic tone and the development of an arrhythmogenic atrial substrate, contribute to excess AF in athletes, despite an overall reduction in cardiovascular disease incidence. The atria are especially prone to dilation and remodelling in individuals who have trained at a high level for many years (Franklin et al 2020). However, Brugger *et al* suggested that mechanical and electrical remodelling of the atria seen with chronic endurance sport is functional and does not predispose individuals to a higher risk of AF. Despite this, current evidence indicates a potential increase in AF risk with endurance exercise.

At low to moderate volumes, the beneficial effect of PA could be due to its ability to counteract the main determinants of AF i.e PA reduces excess body fat, chronic inflammation and adverse effects of smoking and alcohol intake.

Inter-individual genetic variability could put some athletes at a higher risk of pathological remodelling leading to lone AF. Increased parasympathetic tone in combination with left atrial enlargement likely contributes to increased AF risk, along with exercise-induced sympathetic stimulation, sustained haemodynamic stress, and inflammation and oxidative stress.

Despite the link between high level, sustained endurance activity and AF, in general, apart from males who have a long history of participating in high level endurance activity, it appears that moderate to vigorous physical activity is largely protective against AF, and that risk of AF is higher in those with low levels of activity.

Individuals performing physical activity for 5 to 20 MET-h/wk demonstrate a significant risk reduction for AF, whereas higher exercise volumes do not appear to attenuate AF risk (Franklin et al 2020, citing Ricci et al). A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk.

Mohanty et al (2016) reported that moderate amounts of physical activity reduced the risk of AF in men and women, but that intense exercise had an association with AF risk in men. The risk of developing AF was significantly higher in athletes than in non-athlete controls (OR: 2.46; 95CI 1.73-3.51). Mode of exercise and risk of AF were moderately correlated ($p=0.0193$), with mixed sport conferring a greater risk of AF than endurance sport ($p=0.0204$). Younger (<55 years) athletes were significantly more likely to develop AF than older athletes.

Zhu et al (2016), in their evaluation of sex differences, showed total physical activity to be associated with an increased AF risk in men and a reduced risk in women.

Several recent meta-analyses provide limited evidence of an increased risk of AF in males with the highest activity levels, while moderate to high activity levels are overall protective against AF, especially in women. Efforts to aggregate the existing data on the relationship between physical activity and AF and have provided divergent findings. Pooled observational cohort studies suggest that the absence of associations between regular physical activity and AF risk in previous general population studies and their aggregate analyses could be driven by a sex-specific difference in the associations - an increased risk in men and a decreased risk in women.

Kunutsor et al (2021) analysed 23 observational cohort studies with 1,930,725 participants and 45,839 AF cases. The pooled multivariable-adjusted RR for AF in the most physically active versus least active groups was 0.99, 95CI 0.93-1.05. This association was modified by sex: an increased risk was observed in men: 1.20 (95CI 1.02-1.42), with a decreased risk in women: 0.91 (95CI 0.84-0.99). The quality of the evidence ranged from low to moderate. There was inadequate information to evaluate the dose-response.

In a pooled random-effects meta-analysis of 18 studies, Ricci et al (2018) reported no significant association between physical activity and risk of AF, although a dose-response analysis based on a subset of studies suggested a non-linear J-shaped relationship. Physical activity at 5-20 metabolic equivalents per week (MET-h/week) was associated with significant reduction in AF risk (RR for 19 MET-h/week = 0.92, 95CI 0.87- 0.98). Above that range, the dose-response was inflected. Physical activity > 20 MET-h/week was unrelated to AF risk (RR for 21 MET-h/week = 0.95, 95CI 0.88- 1.02). This reflected uncertainty of the nature of the relationship at higher volumes of PA in the high vs low PA analysis, a null association was found for AF risk.

Newman et al. (2021) conducted a meta-analysis to investigate the incidence of AF in athletes and non-athlete controls. The risk of developing AF was significantly higher in athletes than in those not exercising or performing regular, non-competitive physical activity (OR 2.46; 95CI 1.73 t-.51; p). The association of 'mixed sports' with an increase in AF risk is difficult to interpret due to the broad range of sports analysed, complicating the process of elucidating true effects from specific training modalities.

Recent analytical studies have typically identified no association of very high level PA and AF risk; or a reduced AF risk with moderate- high levels of PA compared with those with the lowest levels of activity.

Albrecht et al (2018) investigated the association of total and types of physical activity, including walking, cycling, domestic work, gardening and sports, with atrial fibrillation in the prospective Rotterdam (cohort) Study. After adjustment for confounders, the hazard ratio for the high total physical activity category of low activity was 0.71, 95CI 0.80-1.14. There was no significant association between any specific activity type and AF risk.

Khurshid et al (2021) analysed 93 669 participants of the UK Biobank prospective cohort study without prevalent AF who wore a wrist-based accelerometer for 1 week. In multivariable adjusted models, guideline-adherent activity was associated with lower risks of AF (HR 0.82, 95CI 0.75-0.89).

O'Neal et al (2020) examined the association between moderate and vigorous physical activity (MVPA) with incident AF in 5,147 participants who completed accelerometer assessment for 4 to 7 consecutive days in the REGARDS study. Participants with higher daily time spent in MVPA were less likely to develop AF than those with lower MVPA. In a multivariable model, the risk of AF decreased with higher levels of daily MVPA compared to the risks in those in the lowest activity quartile (Quartile 2: HR 0.77; Quartile 3: HR 0.72; Quartile 4: HR 0.62; p-trend = 0.0056).

The existing factor for high level physical activity should be retained in the RH and BoP SoPs, with no substantive change to the factors, other than the addition of a factor for clinical worsening. It is recognised that the association has only been documented in men, but the factor should be retained without restriction of sex.

It has proved difficult to establish precise cutoff levels of activity associated with increased risk of AF. The relation between different intensities of physical activity and AF risk remains uncertain. The data requires cautious interpretation because activity exposure in terms of MET-h/week is not reported uniformly in studies.

In a pooled random-effects meta-analysis of 18 studies, Ricci et al (2018) reported no significant association between physical activity and risk of AF, although a dose-response analysis suggested a J-shaped relationship. The meta-analysis showed that low-moderate activity levels (5-20 METS-h/week) may result in reduced risk of AF. High activity levels (PA > 20 MET-h/week) showed no association with AF risk. The dose-response analysis was only based on a subset of studies because of limited data reporting physical activity exposure in terms of metabolic equivalents.

The dose in the current factor related to high level activity greater than 6 METs, for an average of at least 20 hours per week for a continuous period of 5 years is a generous interpretation of the literature, but should be retained in the SoPs.

Bonnesen et al (2021) investigated the association between within-individual changes in physical activity and onset of AF. A 1-h decrease in average daily physical activity was associated with AF onset the next day [OR 1.24, 95CI 1.18-1.31]. The signal was strongest in the tertile of participants with lowest activity overall [low: 1.62, 95CI 1.41-1.86), mid: 1.27 (95CI 1.16-1.39), and high: 1.10 (95CI 1.01-1)].

O'Neal et al (2020) examined the association between moderate and vigorous physical activity (MVPA) with incident AF in 5,147 participants who completed accelerometer assessment for 4 to 7 consecutive days in the REGARDS study. Participants with higher daily time spent in MVPA were less likely to develop AF than those with lower moderate and vigorous physical

activity. Higher levels of objectively measured daily moderate and vigorous physical activity were protective against the development of AF.

It is therefore concluded that there is evidence strong enough to support a judgement of a suggestive causal relationship of high level, sustained physical activity and the risk of developing atrial fibrillation and atrial flutter, at least in men (Grade 2). A consistent association has been observed between sustained activity and AF risk, but chance, bias or confounding cannot be ruled out with reasonable confidence. The association is only documented in men, and the strength of the association appears to have weakened considerably in recently published studies. The reasons for the weakened evidence is not certain.

A factor for high level, sustained physical activity should be retained in the RH and BoP SoPs.

It is concluded that there is evidence strong enough to support a judgement of a suggestive causal relationship of inability to undertake low level physical activity and the risk of developing atrial fibrillation and atrial flutter, at least in men (Grade 2). A consistent association has been observed between undertaking low levels of physical activity and elevated AF risk, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A new factor for low levels of physical activity, expressed as inability to undertake such activity; comparable to the levels in the corresponding factor in the hypertension SoPs, should be added to the RH and BoP SoPs. This refers to an inability to undertake any physical activity greater than 3 METs for at least the 1 year before the clinical onset of the disease.

Sick sinus syndrome

Current factor

onset and worsening - RH and BoP

having sick sinus syndrome at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

AF and AFL develop in the natural history of sick sinus syndrome (SSS). AF is the most common arrhythmia in patients with sick sinus syndrome; paroxysmal or intermittent AF arises in 20-30% of patients with sick sinus syndrome; may eventually develop chronic AF. Atrial remodelling in chronic AF can also contribute to sinus node dysfunction.

Summary of previous investigation

AF develops in the natural history of sick sinus syndrome (sinus node dysfunction). AF is the most common arrhythmia in patients with sick sinus syndrome; paroxysmal or intermittent AF arises in 20-30% of patients with sick sinus syndrome; may eventually develop chronic AF

Atrial remodelling in chronic AF can also contribute to sinus node dysfunction. There is little information about clinical determinants of AF in patients with SSS.

AFL develops in the natural history of sick sinus syndrome (sinus node dysfunction), although AF is the most common arrhythmia in patients with sick sinus syndrome. Clinical studies have shown that sick sinus syndrome is frequently associated with AF and atrial flutter, the “bradycardia-tachycardia syndrome.” Paroxysmal or intermittent AF arises in 20-30% of patients with sick sinus syndrome. atrial remodelling in chronic AF can also contribute to sinus node dysfunction. There is little information about clinical determinants of AF and AFL in patients with SSS.

Reviews

Atrial fibrillation is commonly associated with sinus node dysfunction (SND), which complicates the management of both conditions.

Sick sinus syndrome is responsible for the implantation of the majority of electronic pacemakers worldwide.¹⁸⁷ It is a more complex disease than it was believed when first described. It involves the innate leading pacemaker region of the heart, the sinoatrial node, and also the atrial myocardium, predisposing to atrial tachydysrhythmias. It remains controversial as to whether the dysfunction of the sinoatrial node directly causes the dysfunction of the atrial myocardium, or vice versa, or whether these two aspects of the condition arise through some related underlying pathological mechanism, such as extracellular matrix remodeling, i.e., fibrosis.

Jackson et al. (2017) reviewed the epidemiology, pathophysiology, and clinical trial data investigating therapeutic approaches for treatment of patients with both SND and AF.¹⁸⁸

SND affects up to one in five patients with AF. AF can lead to anatomical and electrophysiological remodelling in both atria, including the region of sinoatrial node. Changes including atrial fibrosis, altered calcium channel metabolism, and transformed gene expression have been demonstrated in patients with AF and SND. Nonrandomized clinical trial data have failed to demonstrate whether any pacing strategy can reduce the risk of AF. Pulmonary vein isolation appears to decrease episodes of tachybrady syndrome and sinus pauses.

The pathophysiological derangements in gene expression, ion channel metabolism, and alterations in myocardial architecture associated with AF may lead to anatomic and electrical changes in the region of the sinoatrial node. Ablation may improve symptoms associated with SND in patients with AF.

SN dysfunction is common in patients with AF. In a canine model with pacing-induced AF, persistent rapid atrial pacing for more than two weeks resulted in SN dysfunction

¹⁸⁷ Monfredi, O., & Boyett, M. R. (2015). Sick sinus syndrome and atrial fibrillation in older persons - A view from the sinoatrial nodal myocyte. *Journal of molecular and cellular cardiology*, 83, 88–100.

¹⁸⁸ Jackson, L. R., Rathakrishnan, B., Campbell, K., et al. (2017). Sinus Node Dysfunction and Atrial Fibrillation: A Reversible Phenomenon?. *Pacing and clinical electrophysiology*, 40(4), 442–50.

characterised by a slow intrinsic heart rate and prolonged SN recovery time, which gradually recovered after termination of rapid atrial pacing.¹⁸⁹ In human volunteers, rapid atrial pacing for only 10 to 15 minutes was reported to impair SAN function, which suggests that short durations of atrial pacing or paroxysmal episodes of AF are associated with SN remodeling and SN dysfunction in humans. Accordingly, AF can result in SN dysfunction. Electrical, structural, and autonomic remodelling contribute to SN dysfunction in patients with AF.

In a canine model, atrial tachypacing has been shown to downregulate the mRNA expression of HCN4 and reduce SN I_f , suggesting that AF results in electrical remodelling of SN. AF induced by rapid atrial pacing is associated with atrial structural change characterised by marked bi-atrial dilation, an increase in mitochondrial size and number, and disruption of the SR. The atrial dilation combined with rapid atrial rate may predispose atrial ischaemia and SN dysfunction. Loss of muscle fibres in the SN was found in AF patients in an autopsy study [73]. The structural remodelling of SN from repeated episodes of AF or prolonged persistence of AF can result in atrial cardiomyocyte apoptosis with progressive atrial fibrosis and dilation. Structural remodeling of SN can contribute to SN dysfunction in patients with AF.

Although sinus node dysfunction and atrial arrhythmias frequently coexist and interact, the putative mechanism linking the two remain unclear.¹⁹⁰ Although SND is accompanied by atrial myocardial structural changes in the right atrium, atrial fibrillation is a disease of variable interactions between left atrial triggers and substrate most commonly of left atrial origin. Significant advances have been made in understanding of the genetic and pathophysiological mechanism underlying the development and progression of SND and AF. Although some patients manifest SND as a result of electric remodelling induced by periods of AF, others develop progressive atrial structural remodelling that gives rise to both conditions together. The treatment strategy will thus vary according to the predominant disease phenotype. Although catheter ablation will benefit patients with predominantly AF and secondary SND, cardiac pacing may be the mainstay of therapy for patients with predominant fibrotic atrial cardiomyopathy.

In patients with normal heart and no previous history of atrial fibrillation,¹⁹¹ electroanatomical mapping of the right and left atrium showed an inverse correlation between age and left atrial wavelength, which may explain the age-related modifications of the atrial substrate and the increase in the prevalence of AF. Therefore, the association between SND and atrial tachyarrhythmias observed during ageing favours the hypothesis that these entities share pathophysiological aspects and interstitial atrial fibrosis is a possible link.

Atrial structural alterations leading to SND predispose also to the development of atrial arrhythmias. However, AF *per se* could also cause SND. In dogs, pacing-induced chronic AF causes SND and a reversible electrical remodelling with atrial conduction time prolongation

¹⁸⁹ Chan, C. S., Lin, Y. K., Chen, Y. C., et al. (2019). Heart Failure Differentially Modulates Natural (Sinoatrial Node) and Ectopic (Pulmonary Veins) Pacemakers: Mechanism and Therapeutic Implication for Atrial Fibrillation. *International journal of molecular sciences*, 20(13), 3224.

¹⁹⁰ John, R. M., & Kumar, S. (2016). Sinus Node and Atrial Arrhythmias. *Circulation*, 133(19), 1892–1900.

¹⁹¹ De Ponti, R., Marazzato, J., Bagliani, G., et al. (2018). Sick Sinus Syndrome. *Cardiac electrophysiology clinics*, 10(2): 183–95

and shortening of atrial refractoriness, which favours perpetuation of AF.¹⁹² In patients undergoing electrical cardioversion of long-standing persistent AF, a depressed SN function is observed, which is independent of the autonomic tone and recovers after sinus rhythm restoration, suggesting that AF remodels the SN. A canine model has demonstrated that atrial tachyarrhythmias downregulate ion channel expression in the SN, particularly the pacemaker subunit I(f), which may contribute to worsening SND when AF is concomitantly present. These data highlight the pathophysiological bi-univocal relationship between SND and atrial arrhythmias.

Zhao et al (2014) reviewed advances in the relationship between sinus node dysfunction and atrial fibrillation.¹⁹³ Clinical and animal experiments have proven that structural and electrophysiological remodelling of sinoatrial node and atrium underlie a relationship between SND and AF. Atrial remodelling is often related to RAS activation. Funny current (If) and Ca(2+) clock mainly contributing to the SAN automaticity may be another link between SND and AF. Gap junctions such as Cx40, Cx43 and Cx45 were proven to participate in both automaticity and conductivity of electrical impulses in SAN and atrial tissue, which was accepted as another link between SND and AF. Common genetic mutations such as the emerging gene, SCN5A gene and HCN4 gene mutation were also the mechanism for the correlation between SND and AF.

Cohort studies

Bukari et al (2018) determined the incidence, prevalence, and predictors of atrial arrhythmias (AAs) in patients with symptomatic sinus node dysfunction (SND) who required permanent pacemaker implantation. evaluated the impact of atrial pacing (AP) on AAs.¹⁹⁴

consecutive patients who underwent pacemaker implantation from 2005 to 2011 were included. Atrial fibrillation, atrial flutter (AFL), atrial tachycardia (AT), and AV nodal reentrant tachycardia (AVNRT) were detected via pacemaker interrogation and clinical documentation.

The study group included 322 patients (44% male) with mean age 68.8 ± 15 years and followed for an average of 5.6 ± 2.2 years (median 5.7 years). Overall, 61.8% were found to have any AA at follow-up. Individual prevalence of AAs was high: AF 43.5%, AFL 6.5%, AT 25%, and AVNRT 6.8%. AF was documented in 23% of patients (n = 74) prior to pacemaker; among those, 15% (n = 11) had no recurrence of AF with average AP of 74%. The incidence of new-onset AF after pacemaker was 15.8%. In subgroup analysis, prevalence of AF was increased by 16% with high rate of AP (81-100%) and 17% with lower rate of AP (0-20%). Incidence of new-onset AF was not affected by AP. Diabetes, hypertension, and left atrial enlargement were predictors of AAs. White men and women had higher prevalence of AF.

¹⁹² De Ponti, R., Marazzato, J., Bagliani, G., et al. (2018). Sick Sinus Syndrome. *Cardiac electrophysiology clinics*, 10(2): 183–95.

¹⁹³ Zhao, J., Liu, T., & Li, G. (2014). Relationship between two arrhythmias: sinus node dysfunction and atrial fibrillation. *Archives of medical research*, 45(4), 351–5.

¹⁹⁴ Bukari, A., Wali, E., Deshmukh, A., et al (2018). Prevalence and predictors of atrial arrhythmias in patients with sinus node dysfunction and atrial pacing. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*, 53(3), 365–371.

AAs are highly prevalent in SND, particularly in white patients. Paroxysmal AF is suppressed with AP in minority, but there is no impact of AP on new-onset AF. Patients with diabetes, hypertension, and dilated atria must be monitored closely for early detection of AAs

Summary and conclusions

The pathophysiological derangements in gene expression, ion channel metabolism, and alterations in myocardial architecture associated with AF may lead to anatomical and electrical changes in the region of the sinoatrial (SA) node.

The SA node may undergo electrophysiological changes in response to atrial arrhythmias; these changes result in SA node dysfunction and are referred to as SA nodal remodelling.

Sinus node dysfunction (SND) affects up to one in five patients with AF (Jackson et al 2017). AF can lead to anatomical and electrophysiological remodelling in both atria, including the region of sinoatrial node. Changes including atrial fibrosis, altered calcium channel metabolism, and transformed gene expression have been demonstrated in patients with AF and SND.

In patients undergoing electrical cardioversion of long-standing persistent AF, a depressed SN function is observed, which is independent from the autonomic tone and recovers after sinus rhythm restoration, suggesting that AF remodels the SN.

Scientific data highlight the pathophysiological bi-univocal relationship between SND and atrial arrhythmias. Animal experimental data documents that atrial structural alterations leading to SND predispose also to the development of atrial arrhythmias. However, AF *per se* can also cause SND. In dogs, pacing-induced chronic AF causes SND and a reversible electrical remodeling with atrial conduction time prolongation and shortening of atrial refractoriness, which favours perpetuation of AF. A canine model has demonstrated that atrial tachyarrhythmias downregulate ion channel expression in the SN, which may contribute to worsening SND when AF is concomitantly present.

Significant biatrial fibrosis has been described in association with clinically significant sinus node dysfunction in patients with AF.

It is therefore concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with sick sinus syndrome (Grade 2). A consistent association has been observed between atrial tachyarrhythmias and sick sinus syndrome, but chance, bias or confounding cannot be ruled out with reasonable confidence.

Specific mention of atrial fibrillation was removed from the examples of clinical manifestations included in the definition of sick sinus syndrome. However, a factor should be retained on the grounds of administrative efficiency in handling claims where AF develops during the course of SSS. It would be prudent to retain a factor for SSS in these SoPs on the grounds that new

onset of AF developing in patients with SSS may be regarded as a new disease, rather than a manifestation of underlying SSS, but the distinction is subtle..

Neoplasm (cardiac)

Current factor

onset and worsening - RH and BoP

having a benign or malignant neoplasm involving the cardiac atrium at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Cardiac tumours are recognised to be a rare cause of AF, but there is fairly limited evidence for localised neoplastic effects.

Summary of previous investigation

Cardiac tumours are recognised to be a rare cause of AF. Most cardiac tumours are metastatic lesions. Primary cardiac tumours are rare (prevalence of 0.001–0.028%), with most being benign myxomas. Although rarely reported, cases of atrial myxoma and lymphoma causing AF have been documented in recent medical literature.

Atrial flutter can be caused by various structural atrial changes; lesions described in patients presenting with AFL in recent literature include primary cardiac lymphoma, myocardial infiltration by lung cancer, left atrial aneurysm. Cardiac tumours are recognised to be a rare cause of AFL. Although rarely reported, cases of atrial myxoma and lymphoma causing AFL have been documented in recent literature.

Reviews

Prior literature suggests that while primary cardiac lymphoma accounts for about 1% of primary cardiac tumours, secondary cardiac involvement by lymphoma can occur in up to 20% of lymphoma cases.¹⁹⁵ Preference of right-sided involvement is common and infiltration of the conducting system can produce many types of arrhythmias including atrial fibrillation..

The clinical presentations of cardiac involvement of lymphoma depend on tumour location, size, growth speed, degree of invasion, and friability. These presentations might include arrhythmias, pericardial effusion or tamponade, tumour embolisation and obstruction of blood flow, and valvular dysfunction. Arrhythmias caused by cardiac involvement of lymphoma

¹⁹⁵ Haq, M., Patel, A., & Guglin, M. (2014). Cardiac lymphoma: sinus pauses disappear after chemotherapy. *Annals of Hematology*, 93(5), 891–2.

include atrial flutter, atrial fibrillation, atrioventricular conduction disturbances, and sick sinus syndrome.¹⁹⁶

Cardiac involvement of lymphoma should be suspected in patients presenting with sick sinus syndrome with unknown causes. Cardiac involvement of lymphoma is often subclinical, therefore cardiac involvement as an initial presentation of malignant lymphoma is rare.

Secondary cardiac involvement of lymphoma is relatively common, reported in 8.7-25% of documented clinical cases of lymphoma. Nevertheless, manifestations of cardiac involvement of lymphoma are often subclinical, and cardiac involvement as an initial presentation of malignant lymphoma is rare.

Mechanical stress, such as extra cardiac masses of bronchial or small lung cell carcinoma compressing the left atrium, or local invasion of metastatic tumours into the left atrium, may facilitate the onset of AF.

Case reports

Kondo et al. (2021) described an 85-year-old man with recent history of syncope and palpitations. with atrial fibrillation and sick sinus syndrome as the main symptoms.¹⁹⁷ Computed tomography showed a mass in the right atrium extending into the superior vena cava (SVC). The patient was implanted with a leadless pacemaker. Transvenous biopsy revealed a diffuse large B-cell lymphoma. The patient was treated successfully with chemotherapy including rituximab.

Haq et al (2014) described a patient in whom right atrial invasion of T lymphoblastic lymphoma resulted in atrial fibrillation and multiple symptomatic episodes of sinus arrest lasting up to 6 seconds.¹⁹⁸ Reduction in size of the cardiac mass and resolution of sinus pauses were noted after only 7 days of treatment with systemic chemotherapy.

Vishwanathan et al. (2016) reported a rare case of atrial fibrillation caused by a thymic mass.¹⁹⁹ A 62-year-old man admitted to the emergency room with chest pain and exertional dyspnoea. He was found to be in rapid atrial fibrillation with pulmonary oedema. A transoesophageal echocardiogram performed prior to cardioversion showed a depressed left ventricular function (ejection fraction 30%) and an extracardiac heterogeneous echodensity compressing the right atrium and the superior vena cava. CT of the chest confirmed an anterior mediastinal mass measuring 13.5×6.6×10.1 cm, exerting a mass effect on the right

¹⁹⁶ Kondo, S., Osanai, H., Sakamoto, Y., et al. (2021). Secondary Cardiac Lymphoma Presenting as Sick Sinus Syndrome and Atrial Fibrillation Which Required Leadless Pacemaker Implantation. *Internal medicine (Tokyo, Japan)*, 60(3), 431–4.

¹⁹⁷ Kondo, S., Osanai, H., Sakamoto, Y., et al. (2021). Secondary Cardiac Lymphoma Presenting as Sick Sinus Syndrome and Atrial Fibrillation Which Required Leadless Pacemaker Implantation. *Internal medicine (Tokyo, Japan)*, 60(3), 431–4.

¹⁹⁸ Haq, M., Patel, A., & Guglin, M. (2014). Cardiac lymphoma: sinus pauses disappear after chemotherapy. *Annals of Hematology*, 93(5), 891–2.

¹⁹⁹ Vishwanathan, S., Tayshetye, P., Bilimoria, F., et al. (2016). Rare cause of atrial fibrillation: a thymic mass. *BMJ case reports*, , bcr2016216710.

atrium with mediastinal and right hilar adenopathy. CT-guided biopsy of the mediastinal mass revealed thymic carcinoma (squamous cell subtype). The metastatic workup was negative. The mass was deemed surgically unresectable due to its proximity to the heart.

Chemotherapy was initiated with carboplatin/paclitaxel every 3 weeks with plans for intensity modulated radiotherapy after one to two cycles of chemotherapy. The patient recently had a repeat CT scan of the chest showing regression of the tumour.

Summary and conclusions

Cardiac tumours are recognised to be a rare cause of atrial fibrillation. Arrhythmias caused by cardiac involvement of lymphoma include atrial flutter, atrial fibrillation. There is fairly limited medical and scientific evidence for localised neoplastic effects.

Mechanical stress, such as extra cardiac masses of bronchial or small lung cell carcinoma compressing the left atrium, or local invasion of metastatic tumours into the left atrium, may facilitate the onset of AF. Localised inflammation, such as that due to cancer involvement

Several case reports have been published since the last review of this condition. Haq et al (2014) described a patient in whom right atrial invasion of T lymphoblastic lymphoma resulted in atrial fibrillation and multiple symptomatic episodes of sinus arrest lasting up to 6 seconds. Kondo et al. (2021) described a patient with secondary cardiac lymphoma presenting as Sick sinus syndrome and atrial fibrillation, and which required leadless pacemaker implantation. Ng et al. (2019) presented a case of primary cardiac lymphoma in an HIV patient presenting with both symptomatic tachy- and bradyarrhythmias.

Based on this limited body of descriptive clinical evidence, it is concluded that in relation to cardiac neoplasms, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between benign or malignant cardiac neoplasms and atrial fibrillation and atrial flutter, but chance, bias or confounding cannot be ruled out with reasonable confidence.

The existing SoP factor for benign and malignant neoplasm should be retained. A note specifying that cardiac lymphomas are included in this factor should be added.

Malignant neoplasm

No factor

Summary of important issues

A spectrum of rhythm disorders may complicate the clinical course of cancer patients, Cancer patients have a higher risk of atrial fibrillation than general population. The prevalence of AF varies depending on type of neoplasm, chemotherapy treatment instituted, and surgical procedure (Hajjar et al 2021). Cancer patients have consistently been documented to have a higher risk of AF than the general population. Studies have shown a 20% prevalence of AF in

patients with cancer, regardless of type (Menichelli et al 2021). The highest risk is in the first three months after the diagnosis of cancer, and progressively decreases after 6 months. The risk is higher in patients > 65 years.

Review studies

Cancer patients have a higher risk of atrial fibrillation than general population.²⁰⁰ The pathophysiology mechanisms involves the pro-inflammatory status of immune system in these patients and the exacerbated inflammatory response to cancer treatment and surgery. There is a challenge in AF related to cancer to predict thromboembolic and bleeding risk in these patients.

Atrial fibrillation in cancer patients is associated with multiple predisposing factors, and there are several mechanisms for its occurrence.²⁰¹

Epidemiological evidence is limited. However, cancer patients have consistently been documented to have a higher risk of AF than the general population. Atrial fibrillation in the general population occurs around 1.5–2%. Several studies have shown a 20% prevalence of AF in patients with cancer, regardless of type.²⁰² The highest risk of new AF was found in the first three months after the diagnosis of cancer, with the risk progressively decreasing after 6 months. This early detection of AF may be due to a tighter clinical monitoring of these patients after cancer diagnosis. The prevalence of AF varies depending on type of neoplasm, chemotherapy treatment instituted, and surgical procedure.

The risk of AF is higher in patients older than 65 years and may occur in 2 of 3 patients with cancer and those with pre-existing cardiovascular diseases. AF in cancer patients encompasses several risk factors, such as traditional risk factors present in the general population as hypertension, diabetes mellitus, hypercholesterolemia, smoking status, alcohol consumption, heart failure, myocardial ischaemia, chronic pulmonary disease, thyroid dysfunction, chronic kidney disease, and advanced age, and inherent factors related to cancer, as hydro electrolyte abnormalities, hypoxia, and metabolic disorders.²⁰³ There are other risk factors related to cancer, such as autonomic nervous system (ANS) imbalance with an increase of sympathetic stimulus caused by pain and others forms of physical or emotional stress. Cancer surgical treatments, chemo- and radiation therapies, and even the malignancies and their progression cause extreme inflammatory stress and facilitate the occurrence of AF.

²⁰⁰ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768.

²⁰¹ Chu, G., Versteeg, H. H., Verschoor, A. J., et al. (2019). Atrial fibrillation and cancer - An unexplored field in cardiovascular oncology. *Blood reviews*, 35, 59–67

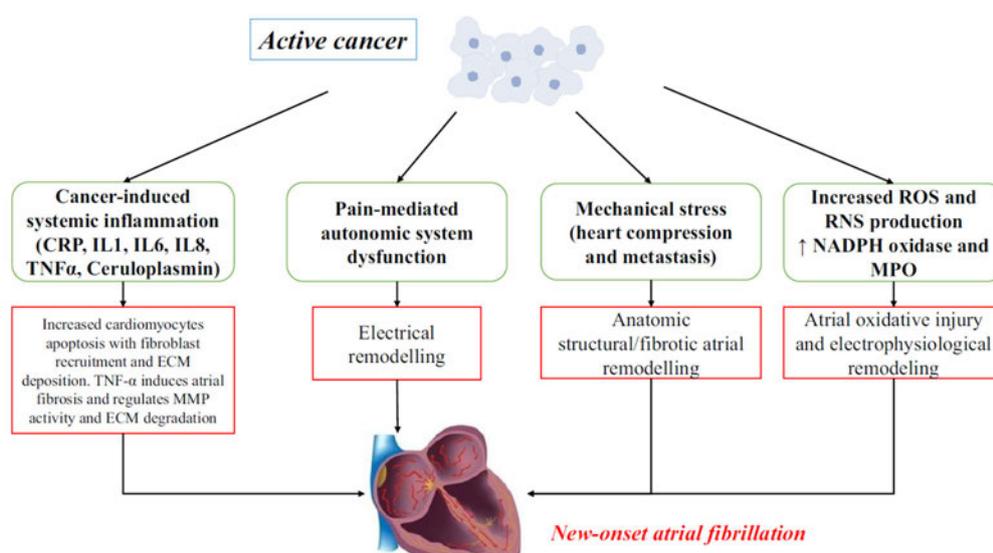
²⁰² Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36

²⁰³ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768

The pathophysiological mechanisms are related to the pro-inflammatory status of the immune system and also related to treatment, the inflammatory response to cancer surgery, and the cardiotoxic effects of anti-cancer drugs and radiotherapy. The mechanisms by which certain cancer treatments trigger arrhythmia are unclear, but risks vary depending on treatment, clinical circumstances, and tumour-induced metabolic and inflammatory changes. Chemotherapy related AF is considered separately in the current briefing paper.

There are several mechanisms potentially linking AF and cancer, including systemic inflammation which seems to represent a common milieu for both conditions.²⁰⁴ Increased production of chemokines and cytokines, such as interleukins 1 and 6, and systemic acute phase proteins such as C-reactive protein (CRP), has been described in patients with cancer.²⁰⁵ Inflammation markers, such as high white blood cells, CRP and ceruloplasmin have been associated with an increased risk of developing preclinical⁵¹ and overt AF (Adamsson et al 2011), possibly by inducing structural and electrical atrial remodelling.

FIGURE 23 POTENTIAL MECHANISMS ACCOUNTING FOR AN INCREASED RISK OF ATRIAL FIBRILLATION IN CANCER PATIENTS.



Menichelli et al (2021), Fig 3

In a study with 5806 subjects (Aviles et al 2003), elevated CRP was associated with prevalent AF and also predicted incident cases of this arrhythmia (aHR 1.31, 95CI 1.08–1.58). Other interleukins involved in development of AF are tumor necrosis factor- α , interleukin-2, interleukin-6, and interleukin-8,¹⁸ which are also increased in patients with cancer.

Oxidative stress is an important factor for cancer development and response to chemotherapies.²⁰⁶ An increased level of reactive oxygen species (ROS) and reactive nitrogen

²⁰⁴ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36.

²⁰⁵ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36.

²⁰⁶ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36.

species (RNS) has been described in several types of cancers, showing that ROS and RNS could induce DNA damage and could activate pro-oncogenic pathways and contribute to cancer development. oxidative stress may cause new onset AF and its complications.

Another factor potentially involved in the association between AF and cancer is autonomic system activation due to pain-mediated sympathetic activation that may influence heart rhythm and then AF onset.

Postoperative AF is the most frequent form of cancer-related AF. Its prevalence ranges from 16 to 46% for cardiothoracic surgery and 0.4–12% in non-cardiothoracic surgery. AF occurs in about 5.6–28% of cases of lung resection in lung cancer, according to a systematic review.²⁰⁷

In relation to anticancer drugs, the incidence of AF secondary to treatment is between 2.2 and 16.7%. Most cytotoxic agents including alkylating agents (Cisplatin, Cyclophosphamide, Ifosfamide, Melphalan), anthracyclines, tyrosine kinase inhibitors (Ibrutinib, Sorafenib, Sunitinib), antimetabolites, taxanes, and topoisomerase II inhibitors have been found to largely induce AF cardiotoxicity. Haemorrhagic and thromboembolic events occur twice as often in cancer patients.

Cardiotoxicity is one of the most significant adverse effects in cancer treatment, causing a considerable increase in morbidity and mortality. The inflammatory stress caused by cancer and its treatment increases risk to unstable previous cardiovascular disease. Several modalities of cancer treatment, such as chemotherapy, radiotherapy, and target therapies are related to cardiotoxicity, and its association enhance risk of AF.

It is believed that the higher prevalence of AF in cancer patients is due to malignancy resulting in systemic inflammation that facilitates the occurrence of AF due to atrial re-structuring. supporting this idea is the increased levels of C-Reactive Protein (CRP), such as Tumour Necrosis Factor a (TNF a) and Interleukins 2, 6, and 8, inflammatory markers, that are found in cancer patients and are associated with risk of this arrhythmia.²⁰⁸ The involvement of the immune system has also been hypothesized as autoimmune paraneoplastic syndrome sustained by antibodies direct against tumor antigens and may lead to immune reaction against atrial structures that may trigger atrial fibrillation.

Menichelli et al. (2021) outlined evidence linking radiotherapy to the development of AF.²⁰⁹ Ionising radiation is routinely used in the treatment of patients with a wide range of cancer manifestations, including localised neoplasms, metastases, and lymphoma. Exposure to ionising radiation increases the risk of developing inflammatory processes at the vascular level, including the coronary circulation, and favours the development of fibrosis in the atrial tissue, resulting in an increased risk of cardiovascular complications including AF.

²⁰⁷ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768.

²⁰⁸ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768.

²⁰⁹ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36.

The risk of AF is highest in patients who undergo a treatment that may induce myocardial fibrosis, including left breast RT. Myocardial injury is strongly related to the total cumulative dose of radiation, the body area irradiated, and patient's age at the time of exposure.

A phase III randomised clinical trial including 451 patients with locally advanced squamous cell carcinoma of the oesophagus (Yang et al 2018) showed an increased risk of arrhythmia in patients treated with neoadjuvant RT and CT compared with surgery alone (13% and 4.0%, respectively, $p = 0.001$). RT had a synergic effect with CT on cardiotoxicity and heart injury (e.g. ischaemic disease, valvular heart disease, arrhythmia).

Summary and conclusions

A spectrum of rhythm disorders may complicate the clinical course of cancer patients, Cancer patients have a higher risk of atrial fibrillation than general population. The prevalence of AF varies depending on type of neoplasm, chemotherapy treatment instituted, and surgical procedure (Hajjar et al 2021).

Epidemiological evidence is fairly limited. However, cancer patients have consistently been documented to have a higher risk of AF than the general population. Several studies have shown a 20% prevalence of AF in patients with cancer, regardless of type (Menichelli et al 2021). The highest risk of new AF is in the first three months after the diagnosis of cancer, with the risk progressively decreasing after 6 months. This early detection. The risk of AF is higher in patients older than 65 years and may occur in 2 of 3 patients with cancer and those with pre-existing cardiovascular diseases.

Atrial fibrillation in cancer patients is closely correlated to multiple predisposing factors. There are several mechanisms for its occurrence.

The pathophysiological mechanisms are related to the pro-inflammatory status of the immune system and also related to treatment, the inflammatory response to cancer surgery, and the cardiotoxic effects of anti-cancer drugs and radiotherapy. Systemic inflammation in cancer facilitates the occurrence of AF due to atrial re-structuring. The mechanisms by which certain cancer treatments trigger arrhythmia are unclear, but risks vary depending on treatment, clinical circumstances, and tumour-induced metabolic and inflammatory changes. AF in cancer patients also encompasses traditional risk factors present in the general population.

Chemotherapy related AF is considered separately in the current briefing paper (below, see drugs).

Therapeutic radiation is considered immediately below. Ionising radiation is routinely used in the treatment of patients with a wide range of cancer manifestations, including localised neoplasms, metastases, and lymphoma (Menichelli et al 2021). Exposure to ionising radiation increases the risk of developing inflammatory processes at the vascular level, including the coronary circulation, and favours the development of fibrosis in the atrial tissue, resulting in an increased risk of cardiovascular complications including AF.

The risk of AF is highest in patients who undergo a treatment that may induce myocardial fibrosis, including left breast RT. Myocardial injury is strongly related to the total cumulative dose of radiation, the body area irradiated, and patient's age at the time of exposure.

It is concluded that in relation to having a malignant neoplasm, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between having a malignant neoplasm, and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A new factor for having malignant neoplasm, other than non-melanotic malignant neoplasm of the skin, should be added to the RH and BoP SoPs.

It is concluded that in relation to having received ionising radiation for cancer, the evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between having received ionising radiation for cancer to the region of the heart, and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A new factor for having received ionising radiation for cancer to the region of the heart should be added to the RH and BoP SoPs.

Non-neoplastic cardiac lesion

Current factor

onset and worsening - RH and BoP

having a non-neoplastic mass lesion involving the cardiac atrium at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

There is little formal data in humans concerning non-neoplastic mass lesion involving the cardiac atrium as a cause of atrial fibrillation and atrial flutter. However, the mechanism is uncontroversial.

Case reports

Hiatal hernia (HH) is the protrusion of an intraabdominal organ in the thorax cavity through an oesophageal hiatus of the diaphragm. Sliding HH is usually associated with non-specific symptoms, including heartburn, regurgitation or epigastric pain. True paraesophageal hernia may lead to cardiac compression. Knowledge of cardiac manifestations of HH is limited.

Krawiec et al. (2021) present a rare case of a patient with gastrothorax due to hiatal hernia which caused cardiac arrest, and conducted a literature-based review of the cardiac aspects of hiatal hernia.²¹⁰

A 51-year-old, obese (BMI 30.86kg/m²) agricultural worker was admitted to the Emergency Department due to severe epigastric pain and vomiting, following the lifting of heavy fertilizer bags. At admission the patient was tachycardiac (150/min) with tachypnoea (30/min). Blood pressure was normal 110/60 mmHg although the pulse was hypokinetic and jugular vein distention was present. Chest examination revealed a dull percussion note and absence of respiratory sounds in the left haemothorax. The abdomen was distended, with tenderness in the epigastric area. ECG displayed sinus tachycardia, intermediate heart axis, low voltage of QRS complexes, incomplete right bundle branch block, q in leads II, III and aVF.

Although the exact mechanism of changes in electrocardiogram related to the hiatal hernia is not well understood, some hypotheses have attempted to explain these findings. Schilling et al. suggested that persistent compression of the left atrium by the hiatal hernia may result in an area of relative ischemia and conduction block, causing reentry. Another explanation of changes in electrocardiogram may be the stimulation of the vagal nerve by pressure from the hiatal hernia

Patients with paraesophageal hernia may experience arrhythmia, including sinus tachycardia, atrial flutter, atrial fibrillation,. In echocardiograph, HH may appear as an extracardiac posterior mass encroaching on the left atrial cavity, mimicking the left atrial mass. Rarely, HH may be manifested as tension gastrothorax leading cardiac arrest.

TABLE 10 CASE REPORTS OF PATIENTS WITH HIATAL HERNIA AND ATRIAL FIBRILLATION/FLUTTER

Case	Gender	Age	Symptoms	ECG	ECHO	X-ray	CT	Surgical method
Gürgün C. et al. 2002 [28]	F	76	Dyspnea	Atrial fibrillation	Normal	Cardiomegaly, a dome shaped air level overlapping cardiac silhouette	No information	Laparoscopy
Duygu H. et al. 2008 [29]	F	79	Chest pain	Atrial fibrillation	TR, MR, high PAP	No information	HH	Non-operative treatment
Cristian D.A. et al. 2015 [30]	F	77	Dyspnea	Atrial fibrillation	Mass compressing LA, MR	Widening of the mediastinum, large shadow overlapping the heart	No information	Nissen fundoplication
Schilling R.J. et al. 1998 [31]	M	72	Heath palpitations	Atrial flutter with 2:1 AV block	Normal	Large mediastinal mass	No information	Not described
Patel A. et al 2014 [32]	F	80	Failure to thrive and weakness	Atrial flutter	High PAP	Cardiomegaly, a large lucency involving the mid and lower hemi-thoraces	Large HH	Gastropexy
Tursi A. et al. 2001 [33]	F	75	Weakness, dysphagia, heartburn	Supraventricular extrasystole, atypical right bundle branch block pattern, and inferior axis	No information	Giant gastric HH compressing LA	No information	Nissen-Rossetti fundoplication

Source: Krawiec et al. (2021), Table 1, p 23

²¹⁰ Krawiec, K., Szczasny, M., Kadej, A., et al. (2021). Hiatal hernia as a rare cause of cardiac complications - case based review of the literature. *Annals of agricultural and environmental medicine: AAEM*, 28(1): 20–6 August meeting 2022

Extrinsic compression of the left atrium (LA) due to oesophageal achalasia is rare. Patients might present with dysphagia, dyspnoea, and haemodynamic compromise. **Chen et al (2021)** presented a patient with LA compression by oesophageal achalasia and performed a literature review to gather information as regards the clinical manifestation, diagnosis, and treatment strategy of this rare disease.²¹¹

A 59-year-old man with intermittent palpitation, heartburn sensation, and difficulty swallowing came to an emergency department due to acute onset of chest compression and breathlessness after a large meal. As per his chest X-ray, dilated mediastinum and small gastric bubble were noted. ECG implied left atrial enlargement, and the Holter monitor reported one episode of paroxysmal atrial fibrillation attack during his meal. Transthoracic echocardiogram showed a round-shaped, well-bordered, hyperechogenic, and heterogeneous mass compressing the LA irrespective of the systolic or diastolic phase. A chest contrast-enhanced computed tomography scan was then performed, showing diffuse oesophageal dilatation with a smoothly thickening wall compressing the LA. Barium swallow esophagogram revealed contrast pooling at the oesophagogastric junction. Extrinsic compression of LA by oesophageal achalasia was diagnosed.

Summary and conclusions

Patients with para-oesophageal hernia may experience arrhythmia, including sinus tachycardia, atrial flutter, atrial fibrillation.

Krawiec et al. (2021) presented a rare case of a patient with gastrothorax due to hiatal hernia which caused cardiac arrest, and conducted a literature-based review of the cardiac aspects of hiatal hernia.

Extrinsic compression of the left atrium due to oesophageal achalasia has been considered a rare occurrence and a rare cause of atrial fibrillation (Chen et al 2020)

Vishwanathan et al. (2016) reported that thymic mass is a rare cause of atrial fibrillation.

Based on this limited body of descriptive clinical evidence, it is concluded that in relation to non-neoplastic cardiac lesions, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between benign or malignant cardiac neoplasms and atrial fibrillation and atrial flutter, but chance, bias or confounding cannot be ruled out with reasonable confidence.

The existing SoP factor for benign non- neoplastic mass lesion should be retained, with some adjustments. Specific mention of 'mass' should be removed from the factor and replaced with a lesion 'involving' the atrium, to cover non-compressive effects, as per other arrhythmia SoPs. There may be potential overlap with cardiac infiltration factor (below)

²¹¹ Chen, S. Y., Toh, H. S., Chang, W. T., et al. (2021). A Rare Cause of Left Atrium Compression. *International heart journal*, 62(4), 944–8.
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A note with clinical examples of relevant cardiac lesions should be added. A note specifying that cardiac lymphomas are included in this factor should be added.

Diabetes mellitus

Current factor

onset and worsening - RH and BoP

having diabetes mellitus for a continuous period of at least the five years before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Patients with coexisting diabetes have an elevated risk of atrial fibrillation development (Gumprecht & Kalarus 2022). Because of the high prevalence of AF and DM in the general population, the frequent coexistence of these conditions is unsurprising (Şerban & Scridon 2018). However, a large amount of epidemiological, clinical and experimental data indicates that DM as an independent risk factor for AF (Wang et al 2019)

Up to 20% of patients with AF have DM, and the presence of DM is associated with a 3-fold greater risk of AF (Şerban & Scridon 2018).

Summary of previous investigation

There is little data concerning the risk of AFL specifically in relation to diabetes mellitus, but some cross-sectional data suggests a positive association. Movahed et al (2005) reported that DM correlated significantly with atrial flutter in uni- and multivariate analysis (OR 2.20, 95CI 2.15-2.26). Mareedu et al (2010) found that patients with history of DM have the same risk of developing AF as AFL.

Instead, most published studies deal with AF as an endpoint, or AF combined with AFL

Some, but not all epidemiological studies, have identified diabetes, especially type 2 DM, as an independent risk factor for AF.

A recent meta-analysis by Huxley et al (2011) indicated that patients with DM had an~ 40% greater risk of AF than those without type 2 DM (summary RR 1.39, 95CI 1.10-1.75). The authors suggested that the true risk between DM and subsequent risk of AF may be closer to 25% than 40%, due to problems with residual confounding, and publication bias that may have inflated the risk estimate. There was no evidence that the positive relationship between patients with treated DM varied according to AF subtype, but there is little data available concerning that topic.

Aside from a small number of case-reports, there is no evidence to indicate that type-1 diabetes is associated with an increase in the risk of AF; suggesting that it is not the chronic

hyperglycaemia associated with DM but rather insulin resistance which might be the mechanism responsible for the observed increased risk of AF among those with DM.

The pathophysiological mechanisms that may underpin the relationship between DM and AF remain speculative. It has been suggested that insulin resistance might be involved in the pathogenesis of this arrhythmia. However, in Fontes et al (2012) large, prospective, middle-age to elderly community-based cohort, there was no association between insulin resistance and incident AF.

Recent data is not wholly consistent. In the UK GPRD case control study, Hodgkinson et al (2010) found no association between AF and history of diabetes (adj RR 0.86, 95CI 0.77-0.96). However, in a large VA database from the US (Movahed et al 2005), DM was independently associated with the risk of atrial fibrillation (OR 2.13, 95CI 2.10-2.16) and atrial flutter (OR 2.20, 95CI 2.15-2.26) in hospitalised patients.

In the ARIC cohort study (Huxley et al 2012), type 2 diabetes was associated with a significant increase in the risk of AF (HR 1.35, 95CI 1.14 to 1.60). there was an independent linear relationship between duration of self-reported diabetes with incident AF individuals with diabetes, and a significant linear association between fasting serum glucose and risk of AF: HR 1.03 (95CI 1.01–1.05 per 10 mg/dl increase in FSG). However, there was no association of AF with pre- diabetes. A strong positive association between HbA1c level with risk of AF in people with diabetes supports the hypothesis that poor glycaemic control is an independent risk factor for AF; suggestive evidence that relationship between diabetes and AF may be a function of the severity of diabetes and apparent only after long-term cumulative exposure to hyperglycaemia.

A population-based case-control study (Dublin et al 2010) found that people receiving pharmacological treatment for diabetes had 40% higher risk of developing atrial fibrillation than people without diabetes. Risk was higher with longer duration of treated diabetes, and there was a suggestion of higher risk with worse glycaemic control ; people with diabetes were at increased risk for all subtypes of atrial fibrillation, regardless of its duration or persistence.

Reviews

There are many recent comprehensive review studies that have outlined the association between diabetes mellitus and the risk of AF.^{212 213 214 215 216 217}

In one review, **Higa et al (2021)** confirms that DM entails a higher risk of AF.²¹⁸ A longer duration with poor glycaemic control has been independently associated with an increased incidence of AF. The NAVIGATOR Trial reported that fasting plasma glucose level could be a predictor of AF (Latini et al 2013). DM independently increased the overall risk of AF onset more in females (Nichols et al 2009). The younger DM population has a significantly higher relative risk of AF than the elderly DM population (Pallisgaard et al 2016).

TABLE 11 ASSOCIATION BETWEEN DM AND RISK OF THE ONSET OF AF

Publication Year (Ref.)	Study Design	Study Period (y)	Characteristics of Sample Population (n)	AF Patients (n)	Mean Follow-Up (mo)	Risk of New Onset of AF
Nichols et al, ⁴ 2009	Observational cohort	1999–2008	50% DM (+)/50% DM (–) (total 34,744)	3.6% in DM (+) 2.5% in DM (–)	86	AF was significantly greater among DM patients (9.1 per 1000 person/year in DM [+] and 6.6 per 1000 person/year in DM [-]; $P < .0001$). DM was associated with a 26% increased risk of AF among females (HR, 1.26; 95% CI, 1.08–1.46; $P = .003$) but was not statistically significant factor among males (HR, 1.09; 95% CI, 0.96–1.24; $P = .17$) after a full adjustment of the other risk factors.
Dublin et al, ⁵ 2010	Population-based case control	2001–2004	Newly diagnosed AF/control (total 3613)	1410	NA	Among patients treated for DM, the risk of developing AF was 3% higher for each additional year of the DM duration (95% CI, 1%–6%). AF risk was higher with poor glycemic control (HR, 1.06; 95% CI, 0.74–1.51, in $HbA_{1c} < 7$), (HR, 1.48; 95% CI, 1.09–2.01, in HbA_{1c} , 7–8), (HR, 1.46; 95% CI, 1.02–2.08, in HbA_{1c} , 8–9), (HR, 1.96; 95% CI, 1.22–3.14, in $HbA_{1c} > 9$) per an additional 1 v.

²¹² Gawalko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

²¹³ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17.

²¹⁴ Gumprecht, J. J., & Kalarus, Z. (2022). Atrial Fibrillation in patients with concomitant diabetes mellitus – What do we already know and what do we need to discover? *Wiadomosci lekarskie (Warsaw, Poland : 1960)*, 75(1), 123–7

²¹⁵ Bell, D., & Goncalves, E. (2019). Atrial fibrillation and type 2 diabetes: Prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes, obesity & metabolism*, 21(2), 210–7

²¹⁶ Wang, A., Green, J. B., Halperin, J. L., et al (2019). Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, 74(8), 1107–15.

²¹⁷ Şerban, R. C., & Scridon, A. (2018). Data Linking Diabetes Mellitus and Atrial Fibrillation-How Strong Is the Evidence? From Epidemiology and Pathophysiology to Therapeutic Implications. *The Canadian journal of cardiology*, 34(11), 1492–1502.

²¹⁸ Higa, S., Maesato, A., Ishigaki, S., et al. (2021). Diabetes and Endocrine Disorders (Hyperthyroidism/Hypothyroidism) as Risk Factors for Atrial Fibrillation. *Cardiac electrophysiology clinics*, 13(1), 63–75

Huxley et al, ⁶ 2012	Prospective cohort ^a	1990–2007	Pre-DM (51.4%)/DM (14.9%)/non-DM (33.7%) (total 13,025)	1311	174	Type II DM was associated with a significant increase in the risk of AF (HR, 1.35; 95% CI, 1.14–1.60) after an adjustment for cofounders (HR, 1.13; 95% CI, 1.07–1.20) in DM (+) and (HR, 1.05; 95% CI, 0.96–1.15) in DM (–) patients per a 1% increment increase in the HbA _{1c} .
Schoen et al, ⁷ 2012	Randomized ^b	1993–2011	Females without CVD (total 34,720)	1079	197	A significant relationship between baseline DM and the onset of AF (HR, 1.95; 95% CI, 1.49–2.56; <i>P</i> <.0001 [age adjusted]), (HR, 1.37; 95% CI, 1.03–1.83; <i>P</i> = .03 [multivariate adjusted]), (HR, 1.14; 95% CI, 0.93–1.40; <i>P</i> = .02 [time updated model adjusted]) for changes in the risk factors and cardiovascular events.
Latini et al, ⁸ 2013	Double-blinded randomized ^c	NA	IGT (total 8943)	613	78	IGT could predicted the risk of AF (HR, 1.33; 95% CI, 1.11–1.59; <i>P</i> = .018) (per 1 mmol/L increment increase in fasting plasma glucose).
Pallisgaard et al, ⁹ 2016	Danish nationwide cohort	1996–2012	DM (5%)/non-DM (95%) (total 5,081,087)	^d	216	DM is an independent predictor of AF, particularly in young DM patients.

Source: Higa et al (2021) Table 1

Electrical, structural, and electromechanical remodelling, and cardiac autonomic neuropathy contribute to the pathophysiology of AF in DM. Several important concepts regarding the pathophysiological association between AF and DM have been reported. Basic studies have demonstrated that DM is associated with proarrhythmic conditions including a decrease in sodium currents and increase in L-type calcium currents, prolonged interatrial conduction time and action potential duration, and increased expression of connexin-43 and suppressed expression of connexin. A hyperglycaemic state enhances oxidative stress and inflammation, and causes excessive production of advanced glycation end products and reactive oxygen species, and activation of the renin angiotensin aldosterone system can cause fibrosis. Animals with DM have impaired atrial electromechanical function, associated with fibrotic changes and conduction slowing.

In clinical studies, DM had a higher interatrial electromechanical delay, which is an independent predictor of the onset and recurrence of AF.²¹⁹ A clinical study also showed a significantly longer atrial activation time and lower bipolar voltage with DM suggesting advanced electrical remodelling. Cardiac autonomic neuropathy in DM encompasses parasympathetic denervation and subsequent sympathetic denervation.

Glucose fluctuations, rather than hyperglycaemia alone, may have greater importance of in AF genesis. High blood glucose levels with larger fluctuations may have a significant impact on the risk of cardiovascular complications. A correlation between larger blood glucose fluctuations and the onset of AF has been reported (Gu et al 2017). In basic studies, glucose fluctuations are associated with enhanced oxidative stress, fibrosis, and AF inducibility. Glucose fluctuations are harmful because of increased oxidative stress and abnormal sympathetic nerve stimulation rather than a hyperglycaemic state.

²¹⁹ Higa, S., Maesato, A., Ishigaki, S., et al. (2021). Diabetes and Endocrine Disorders (Hyperthyroidism/Hypothyroidism) as Risk Factors for Atrial Fibrillation. *Cardiac electrophysiology clinics*, 13(1), 63–75
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In relation to secondary prevention, DM could be a risk factor of a poor cardioversion efficacy in patients with or without AF ablation. Because of the poor efficacy and adverse events of antiarrhythmic drugs, there may be less benefit of antiarrhythmic drugs for DM. Although a meta-analysis showed the association between haemoglobin A1c level and risk of late AF recurrences with DM (Anselmino et al 2015) there have been controversial results concerning the impact of DM on catheter ablation outcomes. According to those reports, preoperative pioglitazone use and better glycaemic control may improve ablation outcomes.

The pathophysiology of arrhythmias in T1D includes inflammation and oxidative stress.²²⁰ Cytokines (interleukin [IL]-6, IL-2, tumour necrosis factor [TNF]- α , transforming growth factor [TGF]- β , connective TGF) promote collagen deposition, myocyte apoptosis, and fibrosis. Increased levels of systemic oxidative stress coupled with production of reactive oxygen species via the mitochondrial pathway induce the nuclear factor (NF)- κ B pathway, leading to atrial remodelling. T1D-related oxidative stress attenuates potassium, L-type calcium, and sodium-potassium and sodium-calcium exchanger currents, resulting in a small depolarisation in the resting membrane potential that prolongs the action potential duration.

Advanced glycation end-products and their receptors, the Rho associated protein kinase pathway, and decreased expression of peroxisome proliferator activated receptor γ and the paired-like homeodomain transcription factor 2 (Pitx2) gene can play a role in the development of atrial fibrosis in diabetic hearts.

Left ventricular dysfunction and hypertrophy, the first proarrhythmic changes in patients with impaired glucose tolerance, increase LA afterload pressure, leading to atrial dilation and AF. In many animal models, increased expression of connexin-43 and cathepsin A (the expression of which is associated with impaired LA emptying function, increased LA fibrosis, and regions of slow conduction) has been noted as a potential proarrhythmic mechanism. T1D-related enhanced sympathetic and decreased parasympathetic activity are also crucial contributors to increased AF in diabetics.

Sympathetic activation in response to hypoglycaemia contributes to the occurrence of AF and ventricular arrhythmias in certain cases. It has been suggested that stringent glycaemic control could reduce the incidence of AF in T2D. However, the Action to Control Cardiovascular Risk in Diabetes trial failed to show a benefit of intensive vs. standard glycaemic control on the occurrence of new-onset AF in T2D.⁶⁷ Various antidiabetic agents have been shown to reduce AF risk since metformin, rosiglitazone, pioglitazone, and thiazolidinediones were reported to attenuate oxidative stress, inflammation, fibrosis, and associated atrial remodelling.

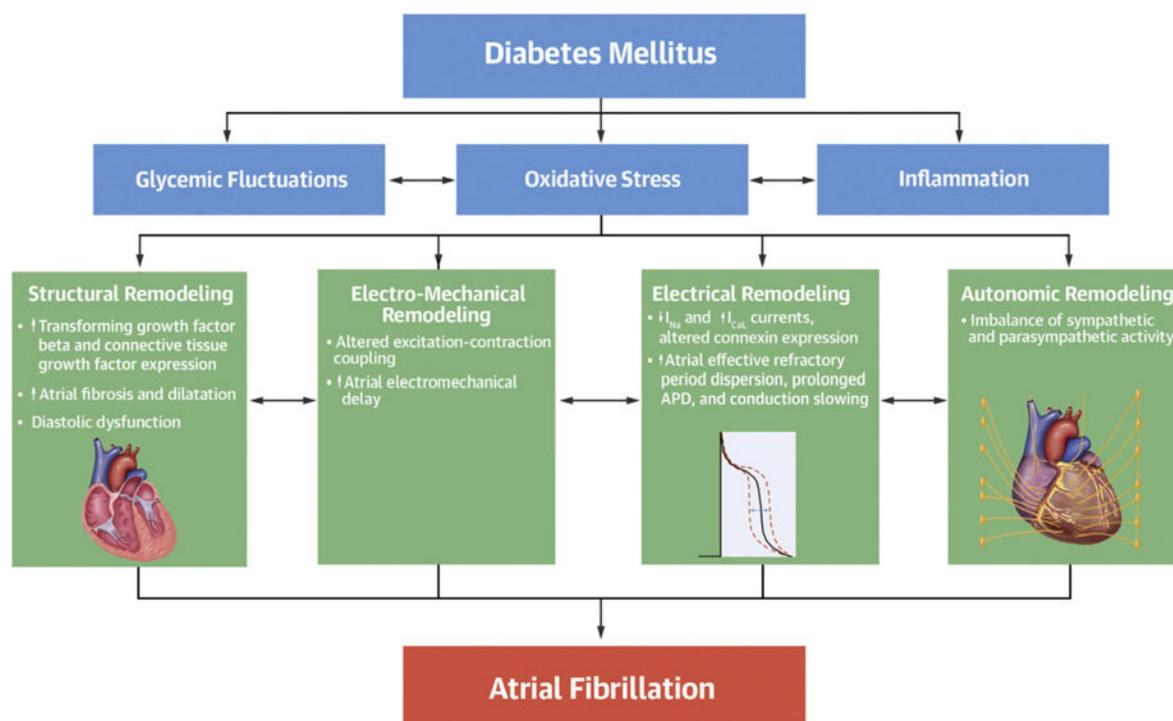
Compared with antiarrhythmic drug therapy, catheter ablation of AF was associated with improved quality of life, reduced AF hospitalisations (8.6% vs. 34.3%; $P=0.01$) and a

²²⁰ Gawałko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.
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decreased likelihood of AF recurrence (20% vs. 57.1%; $P=0.001$).²²¹ However, in the study of Tang et al, pulmonary vein isolation was similarly effective in patients with and without T2D, but T2D patients were more prone to develop post-procedural complications. In patients undergoing catheter ablation for AF, maintenance of sinus rhythm was higher and the need for a second ablation was lower in the group of patients treated with pioglitazone. In patients with T1D/T2D (no information regarding diabetes type in the article), low voltage areas were more frequently observed than in the control group.

The complex underlying pathophysiology linking diabetes and AF is related to structural, electrical, electromechanical, and autonomic remodelling.²²²

FIGURE 24 PATHOPHYSIOLOGY OF DIABETES AND ATRIAL FIBRILLATION



Wang et al (2019), Figure

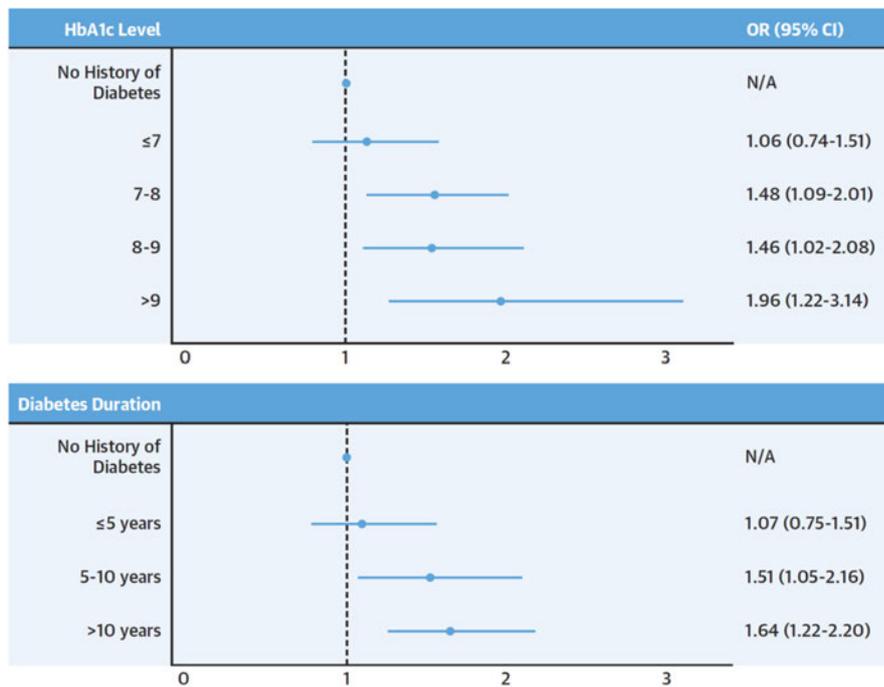
Cumulative exposure to DM also affects the risk of AF.²²³ In a population-based case-control study of 311 patients with treated diabetes, the risk of developing AF increased by 3% for each additional year of treatment (Dubin et al 2010). In the same study, higher glycaemic levels were also associated with increased risk of AF, with an adjusted OR of 1.14 per 1% increase in HbA1c. In a recent meta-analysis, higher serum glycated haemoglobin levels were significantly associated with incident AF in prospective cohort studies, but not in retrospective case-control studies (Qi et al 2017). Therefore, the overall evidence seems to support the link between diabetes and AF.

²²¹ Gawałko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

²²² Wang, A., Green, J. B., Halperin, J. L., et al (2019). Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, 74(8), 1107–15.

²²³ Wang, A., Green, J. B., Halperin, J. L., et al (2019). Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *Journal of the American College of Cardiology*, 74(8), 1107–15.

FIGURE 25 EFFECT OF GLYCAEMIC CONTROL AND DURATION OF DIABETES ON RISK OF AF



Wang et al (2019), Fig 1, p 1109; after Dubin et al (2010)

The presence of comorbid diabetes and AF may confer worse prognosis than either condition alone. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation) study, T2DM patients with AF had increased risks of major coronary events, stroke, heart failure, cardiovascular death, and all-cause mortality compared with T2DM patients without AF (Du et al 2009). In ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), AF patients with diabetes had significantly higher hospitalization rates, cardiovascular mortality, and overall mortality, as well as worse symptoms and lower quality of life compared with AF patients without diabetes (Echouffo-Tcheugui et al 2017). The greater burden of persistent and permanent AF, and higher prevalence of comorbidities, such as heart failure, chronic kidney disease, and coronary artery disease, among patients with diabetes may explain this overall pattern.

Meta-analyses

Non-paroxysmal AF is associated with an increased risk of complications. Diabetes contributes to AF initiation, yet its role in AF maintenance is unclear. **Alijla et al (2021)** conducted a systematic review and meta-analysis to summarise the evidence regarding the association of diabetes with AF types.²²⁴

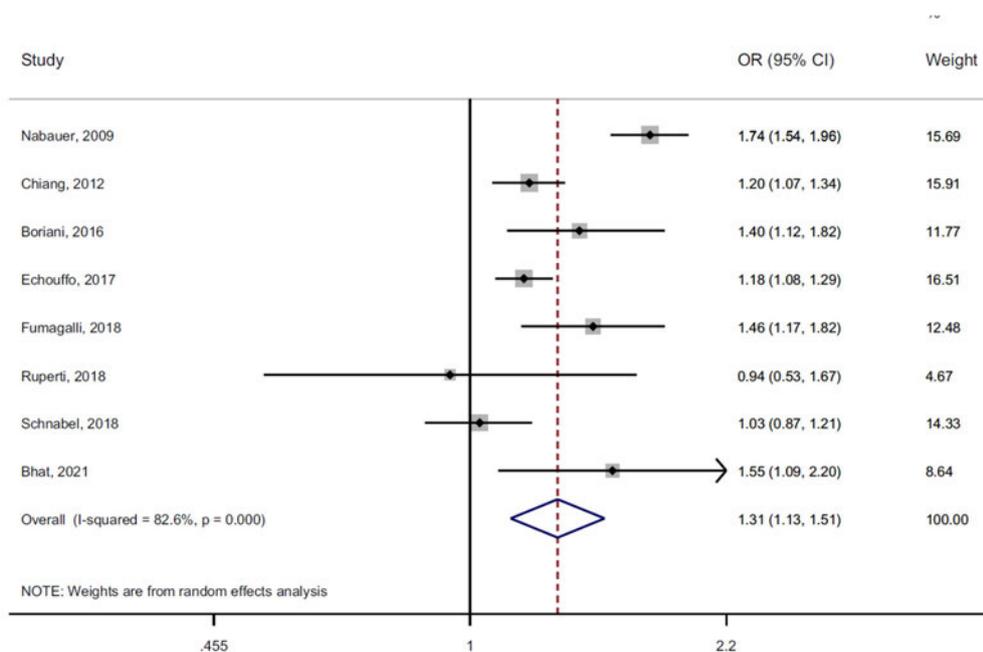
The authors searched 5 databases for observational studies investigating the association of diabetes with the likelihood of an AF type (vs another type) in humans. Study quality was evaluated using the Newcastle-Ottawa Scale. Studies classifying AF types as paroxysmal (reference) and non-paroxysmal were pooled in a meta-analysis using random effects models.

²²⁴ Alijla, F., Buttia, C., Reichlin, T., et al (2021). Association of diabetes with atrial fibrillation types: a systematic review and meta-analysis. *Cardiovascular diabetology*, 20(1), 230.

Of 1997 articles, 20 were included in the systematic review. The population sample size ranged from 64 to 9816 participants with mean age ranging from 40 to 75 years and percentage of women from 24.8 to 100%. The quality of studies varied from poor (60%) to fair (5%) to good (35%).

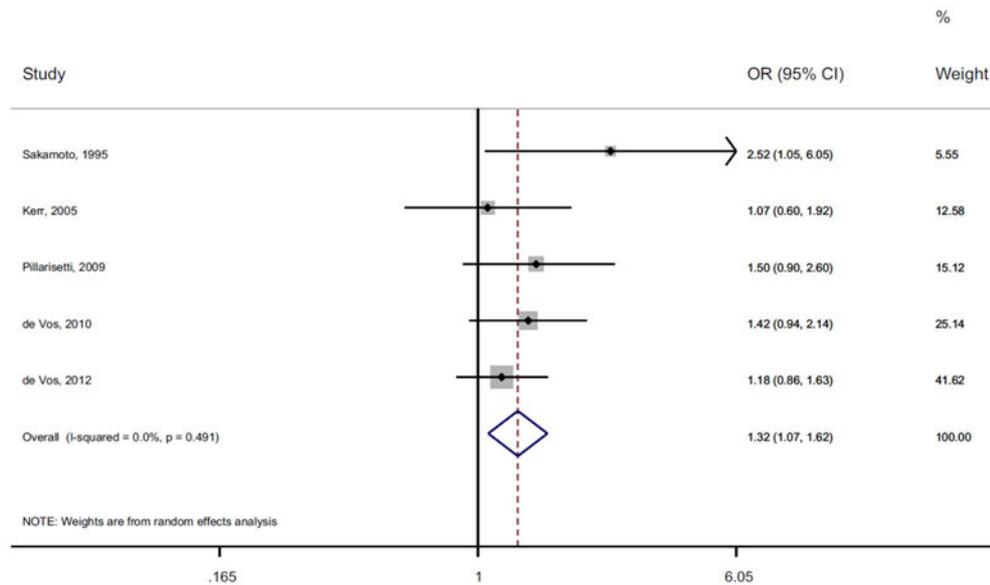
8 studies among patients with AF investigated the cross-sectional association of diabetes with non-paroxysmal AF (vs paroxysmal) of which 6 showed a positive association and 2 showed no association. Fourteen studies investigated the longitudinal association of diabetes with "more sustained" AF types (vs "less sustained") of which 2 showed a positive association and 12 showed no association. In the meta-analysis of cross-sectional studies, patients with AF and diabetes were 1.31-times more likely to have non-paroxysmal AF than those without diabetes [8 studies; pooled OR 1.31, 95CI 1.13-1.51, I2 = 82.6%. The meta-analysis of longitudinal studies showed that for patients with paroxysmal AF, diabetes is associated with 1.32-times increased likelihood of progression to non-paroxysmal AF [five studies; pooled OR 1.32, 95CI 1.07-1.62; I2 = 0%.

FIGURE 26 CROSS- SECTIONAL ASSOCIATION OF DIABETES WITH NON-PAROXYSMAL AF (VS PAROXYSMAL AF)



Alijla et al (2021), Fig 1

FIGURE 27 LONGITUDINAL ASSOCIATION OF DIABETES WITH NON-PAROXYSMAL AF (VS PAROXYSMAL AF).



Alijla et al (2021), Fig 2

The findings suggest that diabetes is associated with an increased likelihood of non-paroxysmal AF rather than paroxysmal AF. However, further high quality studies are needed to replicate these findings, adjust for potential confounders, elucidate mechanisms linking diabetes to non-paroxysmal AF, and assess the impact of antidiabetic medications on AF types. These strategies could eventually help decrease the risk of non-paroxysmal AF among patients with diabetes

The meta-analysis included studies with relatively large sample sizes with a range of ages from different parts of the world. The quality of studies spanned poor (60%), fair (5%), and good (35%). Additional sensitivity analyses provided similar findings. No evidence of publication bias was observed in included studies. The meta-analysis of cross-sectional studies indicated a high heterogeneity. However, the heterogeneity was reduced ($I^2 = 44%$) in the “leave one out analysis” when removing the study from Nabauer et al. [13]. The study from Nabauer et al. was conducted in 2004–2006, and was the earliest cross-sectional investigation of diabetes with AF types. No heterogeneity was observed in the meta-analysis of longitudinal studies.

Longitudinal studies in the review focused on several transitions of AF types. AF is a dynamic disease. Over time, patients without AF can progress to paroxysmal or non-paroxysmal AF; and patients with paroxysmal AF can progress to non-paroxysmal AF. Evaluation requires repeated long-term rhythm monitoring, and assessment of AF types and progression can be challenging.

The limited number and small frequency of AF evaluations may impede the detection of paroxysmal AF. This may further hamper the comparison between AF types. Long-term follow-up studies do not comprehensively account for the progressive nature of AF and evaluate the role of diabetes in these dynamic processes. All studies in the systematic review

that investigated the longitudinal association of diabetes with AF progression only evaluated diabetes status at baseline.

Although the results of the cross-sectional and longitudinal analyses were consistent, the possibility of residual or unmeasured confounding cannot be excluded due to the observational character of the study. risk of bias in the review and meta-analysis mainly related to definitions of AF types and adjustments for potential confounders.

Aune et al (2018) conducted a systematic review and meta-analysis to clarify the association between diabetes mellitus, blood glucose and the risk of atrial fibrillation, based on cohort studies.²²⁵

The authors searched the PubMed and Embase databases for studies of diabetes and blood glucose and atrial fibrillation to July 2017. Cohort studies were included if they reported relative risk (RR) estimates and 95% confidence intervals (CIs) of atrial fibrillation associated with a diabetes diagnosis, prediabetes or blood glucose. Summary RRs were estimated using a random effects model.

Thirty four studies were included in the meta-analysis of diabetes, pre-diabetes or blood glucose and atrial fibrillation. Thirty two cohort studies (464,229 cases, >10,244,043 participants) were included in the analysis of diabetes mellitus and atrial fibrillation. The summary RR for AF in patients with diabetes mellitus versus patients without diabetes was 1.30m 95CI 1.03-1.66. There was extreme heterogeneity, I² = 99.9%) and evidence of publication bias with Begg's test, p < 0.0001. After excluding a large outlying study, the summary RR was 1.28 (95CI 1.22-1.35, I² = 90%, n = 31, 249,772 cases, 10,244,043 participants). The heterogeneity was mainly due to differences in the size of the association between studies and the results persisted in a number of subgroup and sensitivity analyses.

The summary RR was 1.20 (95CI 1.03-1.39, I² = 30%, n = 4, 2392 cases, 58,547 participants) for the association between prediabetes and atrial fibrillation. The summary RR was 1.11 (95CI 1.04-1.18, I² = 61%, n = 4) per 20 mg/dl increase of blood glucose in relation to atrial fibrillation (3385 cases, 247,447 participants) and there was no evidence of nonlinearity, pnonlinearity = 0.34.

This meta-analysis suggest that prediabetes and diabetes increase the risk of atrial fibrillation by 20% and 28%, respectively, and there was a dose-response relationship between increasing blood glucose and AF risk. Any further studies should clarify whether the association between diabetes and blood glucose and atrial fibrillation is independent of adiposity

Cohort studies

Hypoglycaemia is associated with an increased risk of cardiovascular disease including cardiac arrhythmias. **Andersen et al (2021)** investigated the effect of hypoglycaemia in the

²²⁵ Aune, D., Feng, T., Schlesinger, S., et al. (2018). Diabetes mellitus, blood glucose and the risk of atrial fibrillation: A systematic review and meta-analysis of cohort studies. *Journal of diabetes and its complications*, 32(5), 501–11
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setting of acute glycaemic fluctuations on cardiac rhythm and cardiac repolarization in insulin-treated patients with type 2 diabetes compared with matched controls without diabetes.²²⁶

This was a non-randomised, mechanistic intervention study. Insulin-treated patients with type 2 diabetes (n = 21, age (mean ± s.d.): 62.8 ± 6.5 years, BMI: 29.0 ± 4.2 kg/m², HbA1c: 6.8 ± 0.5% (51.0 ± 5.4 mmol/mol)) and matched controls (n = 21, age: 62.2 ± 8.3 years, BMI 29.2 ± 3.5 kg/m², HbA1c: 5.3 ± 0.3% (34.3 ± 3.3 mmol/mol)) underwent a sequential hyperglycaemic and hypoglycaemic clamp with three steady-states of plasma glucose: (i) fasting plasma glucose, (ii) hyperglycaemia (fasting plasma glucose +10 mmol/L) and (iii) hyperinsulinaemic hypoglycaemia (plasma glucose < 3.0 mmol/L). Participants underwent continuous ECG monitoring and blood samples for counter regulatory hormones and plasma potassium were obtained.

Both groups experienced progressively increasing heart rate corrected QT (Fridericia's formula) interval prolongations during hypoglycaemia (mean 31 ms, 95CI 16-45) and 39 ms (24-53) in the group of patients with type 2 diabetes and controls, respectively) with similar increases from baseline at the end of the hypoglycaemic phase (P = 0.43). The incidence of ventricular premature beats increased significantly in both groups during hypoglycaemia (P = 0.033 and P < 0.0001, respectively). One patient with type 2 diabetes developed atrial fibrillation during recovery from hypoglycaemia.

In insulin-treated patients with type 2 diabetes and controls without diabetes, hypoglycaemia caused clinically significant and similar increases in cardiac repolarisation that might increase vulnerability for serious cardiac arrhythmias and sudden cardiac death

Seyed Ahmadi et al (2020) examined the incidence of atrial fibrillation in individuals with type 2 diabetes compared with age- and sex-matched controls from the general population and its variation in relation to glycaemic control and renal function.²²⁷

A total of 421,855 patients with type 2 diabetes from the Swedish National Diabetes Registry and 2,131,223 controls from the Swedish Population Registry, matched for age, sex and county, were included and followed from 2001 to 2013.

Overall, 8.9% of individuals with type 2 diabetes and 7.0% of controls were diagnosed with atrial fibrillation during follow-up, unadjusted incidence risk ratio (IRR) 1.35 (95CI 1.33-1.36). Women < 55 years old with type 2 diabetes had an IRR of 2.36 (95CI 2.10-2.66), in relation to controls, whereas the corresponding value for men < 55 years old with type 2 diabetes was IRR 1.78, 95CI 1.67-1.90). In the fully adjusted Cox regression, the risk of type 2 diabetes on incident atrial fibrillation was 28% greater vs controls, (HR 1.28, 95CI 1.26-1.30). The excess risk of atrial fibrillation in individuals with type 2 diabetes increased with worsening glycaemic control and renal complications. For individuals with HbA1c ≤ 6.9% (≤ 52 mmol/mol) and

²²⁶ Andersen, A., Bagger, J. I., Baldassarre, M., et al (2021). Acute hypoglycemia and risk of cardiac arrhythmias in insulin-treated type 2 diabetes and controls. *European journal of endocrinology*, 185(2), 343–53.

²²⁷ Seyed Ahmadi, S., Svensson, A. M., Pivodic, A., et al. (2020). Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovascular diabetology*, 19(1), 9.

normoalbuminuria the excess risk vs controls was still increased, adjusted HR 1.16 (95CI 1.14-1.19); $p < 0.0001$.

Individuals with type 2 diabetes had an overall 35% higher risk of atrial fibrillation than age- and sex-matched controls from the general population. The excess risk for atrial fibrillation increased with renal complications or poor glycaemic control. Individuals with type 2 diabetes with good glycaemic control and normoalbuminuria had slightly increased risk.

Groenewegen et al. (2021) evaluated the incidence of atrial fibrillation, ischaemic heart disease and heart failure in patients with diabetes in a dynamic longitudinal cohort study.²²⁸ The study was performed using primary care databases of the Julius General Practitioners' Network. Diabetes status was determined at baseline in 2014 and participants were followed-up for atrial fibrillation, ischaemic heart disease and heart failure until 2019. Age and sex-specific incidence and incidence rate ratios were calculated.

Mean follow-up was 4.2 years, 12,168 patients were included in the diabetes group, and 130,143 individuals in the background group. There was a clear association between diabetes and incidence of the major chronic progressive heart diseases, including AF. Incidence rate ratios for atrial fibrillation, adjusted for age and sex, in diabetic patients was 1.17 (95CI 1.06-1.30).

Hsu et al (2021) conducted a cohort study evaluating BMI and risk of AF in diabetics using a database from a tertiary medical centre in Taiwan.²²⁹ Between 2014 and 2019, 64,339 adult patients with T2DM were enrolled for analysis. BMI was measured and categorized as underweight (BMI < 18.5), normal ($18.5 \leq \text{BMI} < 24$), overweight ($24 \leq \text{BMI} < 27$), obesity class 1 ($27 \leq \text{BMI} < 30$), obesity class 2 ($30 \leq \text{BMI} < 35$), or obesity class 3 (BMI ≥ 35). Multivariate Cox regression and spline regression models were employed to estimate the relationship between BMI and the risk of AF in patients with T2DM.

The incidence of AF was 1.97 per 1000 person-years (median follow-up, 70.7 months). In multivariate Cox regression, using normal BMI as the reference group, underweight was associated with a significantly higher risk of AF (HR 1.52, 95CI 1.25-1.87, $p < 0.001$), while overweight was associated with significantly reduced risk of AF (HR 0.82, 95CI 0.73-0.89, $p < 0.001$). Kaplan-Meier analysis showed AF risk was highest in the underweight group, followed by obesity class 3, while the overweight group had the lowest incidence of AF (log-rank test, $p < 0.001$). The cubic restrictive spline model revealed a "J-shaped" or "L-shaped" relationship between BMI and AF risk. Underweight status conferred the highest AF risk in Asian patients with T2DM.

The excess risk of AF in relation to the presence of proteinuria in diabetics has not been elucidated. **Kim et al (2021)** determined the association between the incidence of AF and

²²⁸ Groenewegen, A., Zwartkuis, V. W., Cekic, B., et al. (2021). Incidence of atrial fibrillation, ischaemic heart disease and heart failure in patients with diabetes. *Cardiovascular diabetology*, 20(1), 123.

²²⁹ Hsu, J. C., Yang, Y. Y., Chuang, S. L., et al. (2021). Underweight is a major risk factor for atrial fibrillation in Asian people with type 2 diabetes mellitus. *Cardiovascular diabetology*, 20(1), 226

proteinuria in diabetic population.²³⁰ A total of 240,499 individuals aged ≥ 60 years from the Korea National Health Insurance Service-Senior cohort from 2004 to 2014 were included. 4.2% of individuals with DM and 3.7% of controls were diagnosed with AF during a median follow-up period of 7.2 years. Amongst controls (participants without proteinuria and DM), DM only, proteinuria only, and DM with proteinuria groups, the crude incidences of AF were 0.58, 0.70, 0.96, 1.24 per 100 person-years respectively.

Degree of proteinuria in diabetic patients was associated with a significantly higher rate of incident AF in dose dependent manner. Compared with controls, the weighted risk of AF was increased by 11% in DM only (HR 1.11, 95CI 1.02-1.20), 48% with proteinuria only (HR 1.48, 95CI 1.30-1.69), and 66% (HR 1.66, 95CI 1.26-2.18) in those with DM and proteinuria (P trend $< .001$).

Cross-sectional studies

Metabolic abnormalities may exacerbate the risk of adverse outcomes in patients with type 2 diabetes mellitus. **Lee et al (2021)** assessed the predictive value of HbA1c and lipid variability on the risks of sudden cardiac death (SCD) and incident atrial fibrillation.²³¹

The retrospective observational study consists of type 2 diabetic patients prescribed with insulin, who went to publicly funded clinics and hospitals in Hong Kong between January and December 2009. Variability in total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride, and HbA1c were assessed through their SD and coefficient of variation. The primary outcomes were incident ventricular tachycardia/ventricular fibrillation, SCD and AF.

A total of 23 329 patients (mean \pm SD age: 64 ± 14 years old; 51% male; mean HbA1c $8.6 \pm 1.3\%$) were included. On multivariable analysis, HbA1c, total cholesterol, LDL-C and triglyceride variability were found to be predictors of SCD ($p < 0.05$). HbA1c and lipid variability were predictive of SCD. Therefore, poor glucose control and variability in lipid parameters in diabetic patients are associated with aborted or actual SCD.

Summary and conclusions

Patients with coexisting diabetes have an elevated risk of developing atrial fibrillation (Gumprecht & Kalarus 2022). This association have not yet been comprehensively elucidated.

Because of the high prevalence of AF and DM in the general population, the frequent coexistence of these conditions is unsurprising (Şerban & Scrido 2018). However, a large amount of epidemiological, clinical and experimental data indicates that DM is an independent risk factor for AF.

²³⁰ Kim, J., Yang, P. S., Park, B. E., et al. (2021). Association of proteinuria and incident atrial fibrillation in patients with diabetes mellitus: a population-based senior cohort study. *Scientific reports*, 11(1), 17013.

²³¹ Lee, S., Jeevaratnam, K., Liu, T., et al (2021). Risk stratification of cardiac arrhythmias and sudden cardiac death in type 2 diabetes mellitus patients receiving insulin therapy: A population-based cohort study. *Clinical cardiology*, 44(11), 1602–12.

A longer duration of diabetes with poor glycaemic control has been independently associated with an increased incidence of AF (Higa et al 2021). Up to 20% of patients with AF have DM, and the presence of DM was associated with a 3-fold greater risk of AF (Şerban & Scridon 2018). Many epidemiological studies have established diabetes as an independent risk factor for the development of AF (Wang et al 2019). The risk of AF in men and women with type 1 DM is 9–13% and 26–50% higher, respectively, than that in the general population. QT interval prolongation has been reported in Type 2 D. (Gawalko et al 2020).

The NAVIGATOR Trial reported that the fasting plasma glucose level could be a predictor of AF (Latini et al 2013). DM independently increased the overall risk of AF onset more in females (Nichols et al 2009). The younger DM population has a significantly higher relative risk of AF than the elderly DM population (Pallisgaard et al 2016).

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, new-onset DM was associated with a 49% increase in the relative risk of new-onset AF (Aksnes et al 2018), whereas in the Atherosclerosis Risk in Communities study, the incidence of AF in diabetics was twice that in nondiabetic patients (Huxley et al 2012).

A causal link between DM and AF is supported by the association between the cumulative exposure to DM and poor glycaemic control and the risk of prevalent AF. In a population-based case-control study, the risk of prevalent AF was more than 50% higher in patients taking DM-specific medication for more than 10 years than in those using such medication for less than 5 years (Dubin et al 2011). In the same study, there was a significant association between HbA1c levels and the risk of prevalent AF. In the ARIC cohort, each 1% increase in HbA1c levels in diabetics was associated with 13% higher risk of AF (Huxley et al 2012).

Several recent meta-analyses have firmly established the elevated risk of AF in diabetic patients.

In a meta-analysis, higher serum glycated haemoglobin levels were significantly associated with incident AF in prospective cohort studies, but not in retrospective case-control studies (Qi et al 2017).

More recently, Alijla et al (2021) conducted a meta-analysis to summarise the evidence regarding the association of diabetes with AF types. Based on cross-sectional studies, patients with AF and diabetes were 1.31-times more likely to have non-paroxysmal AF than those without diabetes [8 studies; pooled OR 1.31, 95CI 1.13-1.51, I2 = 82.6%]. The meta-analysis of longitudinal studies showed that diabetes was associated with 1.32-times increased likelihood of progression of paroxysmal to non-paroxysmal AF [five studies; pooled OR 1.32, 95CI 1.07-1.62; I2 = 0%].

Aune et al (2018) also conducted a systematic review and meta-analysis to clarify the association between diabetes mellitus, blood glucose and the risk of atrial fibrillation, based on 32 cohort studies (464,229 cases, >10,244,043 participants). The summary RR for AF in diabetic patients versus patients without diabetes was 1.30, 95CI 1.03-1.66. There was extreme heterogeneity, I2 = 99.9%) and evidence of publication bias with Begg's test, $p <$

0.0001. After excluding a large outlying study, the summary RR was 1.28 (95CI 1.22-1.35, I² = 90%, n = 31, 249,772 cases, 10,244,043 participants). The results persisted in a number of subgroup and sensitivity analyses. There was a dose-response relationship between increasing blood glucose and AF risk. The summary RR was 1.11 (95CI 1.04-1.18, I² = 61%, n = 4) per 20 mg/dl increase of blood glucose in relation to atrial fibrillation (3385 cases, 247,447 participants) and there was no evidence of nonlinearity, p_{nonlinearity} = 0.34.

A significant association of DM with risk of AF continues to be reported in more recent cohort studies, including Groenewegen et al. (2021); Seyed Ahmadi et al (2020); Kim et al (2021). Various parameters have been found to further increase the risk of AF in diabetic patients in these cohorts, including degree of proteinuria (Kim et al), underweight (Hsu et al 2021), poor glycaemic control (Seyed Ahmadi et al 2020).

Despite the body of evidence linking DM to AF, the DM-AF relationship is far from reaching consensus (Serban and Sendon). The complex underlying pathophysiology is related to structural, electrical, electromechanical, and autonomic remodelling (Wang et al 2019; Bell and Goncalves 2019). The common clinical profile of the diabetic patient creates the perfect environment for AF to occur. The diabetic patient typically has multiple coexisting medical conditions, ranging from sleep apnoea, to obesity, dyslipidaemia, hypertension, and coronary artery disease (Serban and Sendon). Electrical, structural, and electromechanical remodelling, and cardiac autonomic neuropathy contribute to the pathophysiology of AF in DM, but the final mechanisms remain unknown (Higa et al 2021). DM is associated with proarrhythmic conditions including a decrease in sodium currents, prolonged interatrial conduction time and action potential duration, and suppressed expression of connexin. A hyperglycaemic state enhances oxidative stress and inflammation, and causes excessive production of advanced glycation end products and reactive oxygen species, and activation of the renin angiotensin aldosterone system can cause fibrosis. Glucose fluctuations, rather than hyperglycaemia alone, may have greater importance of in AF genesis (Gu et al 2017).

It is therefore concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with diabetes mellitus (Grade 2). A consistent association has been observed between atrial tachyarrhythmias and diabetes, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for diabetes mellitus should be retained in the RH and BoP SoPs.

Penetrating trauma

Current factor

onset and worsening - RH and BoP

experiencing penetrating trauma to the heart, excluding surgical trauma, within the two years before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Penetrating trauma is recognised to cause various arrhythmias, but there is little empirical data specifically documenting post-traumatic SSS. The concept is recognised in some review studies.

The factor is theoretically reasonable and should be retained in the SoPs.

Summary of previous investigation

Supraventricular arrhythmias (SVA), including atrial fibrillation and flutter, are reported to be common in surgical and nonsurgical intensive care unit (ICU) patients, including both new onset and recurrence of arrhythmia.

Atrial fibrillation and atrial flutter have been reported in case series to be complications of blunt cardiac and thoracic trauma.

Several mechanisms are hypothesised to explain cardiac arrhythmias resulting from trauma, including abnormal perfusion patterns, vagal sympathetic reflex, and aberrant conduction by damaged myocardial cells (Ismailov et al 2007).

Atrial fibrillation has been found to be the most common form of arrhythmia after chest injury. A study by Seguin et al. (2004) found that blunt thoracic trauma was associated with a 17-fold increased risk for atrial fibrillation, independent of confounding factors.

Relatively mild mechanical impacts to the chest may result in serious cardiac dysrhythmia even without significant blunt cardiac injury. Traumatic cardiac dysrhythmias usually develop within the first several hours or within 24 to 48 hours after injury; but some patients with trauma experienced life-threatening dysrhythmias several days after an episode of injury

There are few longitudinal studies that establish the association between trauma and cardiac dysrhythmias, and most data is derived from case reports and case series.

Cardiac dysfunctions are also reported to be common complications following spinal cord injury. Atrial flutter and atrial fibrillation have been documented to occur in both acute and chronic stages (Grigorean et al 2009).

Reviews

Penetrating cardiac trauma carries a high prehospital mortality. These injuries can result from stab wounds or from projectile injuries (e.g. firearms, nail, or wood guns) and are most commonly seen in young adult males.²³² The mortality rate exponentially increases with projectile injuries, such as gunshot wounds, with an approximate 81% to 90% as compared to stab wounds which is 16% to 67%. Thoracic penetrating injuries involving precordium “cardiac box” and epigastrium.

²³² Qamar SR, Wu Y, Nicolau S et al (2020). State of the Art Imaging Review of Blunt and Penetrating Cardiac Trauma Canadian Association of Radiologists' Journal, 71(3): 301-12
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Iatrogenic cardiac injuries have increasingly been seen due to availability of advanced interventional catheter-based diagnostic and therapeutic procedures. An array of cardiac injuries are seen in thoracic procedures including cardiovascular, mediastinal, pulmonary or chest wall surgeries, diagnostic and therapeutic coronary angiogram, insertion of central lines, pacemaker lead or drains, and manual or device-assisted chest compressions.

Summary and conclusions

Very little additional information but well recognised in the clinical literature concerning penetrating injury (non-surgical) and atrial fibrillation and atrial flutter.

There are few longitudinal studies that establish the association between trauma to the heart and cardiac dysrhythmias, and most data is derived from case reports and case series.

Several mechanisms are hypothesised to explain cardiac arrhythmias resulting from trauma, including abnormal perfusion patterns, vagal sympathetic reflex, and aberrant conduction by damaged myocardial cells

Little data specifically concerns penetrating cardiac injury and AF, but atrial fibrillation and atrial flutter have been reported in case series to be complications of cardiac and thoracic trauma. Penetrating cardiac trauma carries a high prehospital mortality. These injuries can result from stab wounds or from projectile injuries (e.g. firearms, nail, or wood guns) and are most commonly seen in young adult males

It is therefore concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with penetrating injury to the heart (Grade 2). A consistent association has been observed between atrial tachyarrhythmias and penetrating trauma, particularly that requiring surgery, or admission to an intensive care unit, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for penetrating injury should be retained in the SoPs. The trauma factor should be repositioned to follow directly after the surgery factor (above).

The exclusion of surgical trauma from the factor should be removed. The time frame should be changed to one year for consistency with other arrhythmia SoPs.

Non-penetrating blow to the chest

Current factor

onset and worsening - RH and BoP

experiencing a powerful, non-penetrating blow to the chest, resulting in injury warranting medical attention, within the one month before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

New-onset atrial fibrillation (NOAF) is common in patients admitted with trauma or burn injuries (Morsy et al 2016). In surgical ICU patients, the predictors of NOAF were older age, blunt trauma chest, shock, previous treatment with calcium channel blocker, and use of pulmonary artery catheter. Dilated LA and LVH are independent predictors of new-onset AF in patients with blunt trauma or burn. Such severe trauma is covered by SoP factor for critical illness (below)

Recent reviews of blunt cardiac injuries (e.g. Fadel et al 2019).do not specifically report AF as a complication, although other arrhythmias are reported, including AV block and ventricular fibrillation.

Outside the context of ICU admission, blunt chest injury has almost never been related to AF, with only two case reports.

Reviews

Cardiac injuries are classified as blunt and penetrating injuries. In both sorts of injury, the major issue is missed diagnosis and high mortality. Blunt cardiac injuries (BCI) are much more common than penetrating injuries.

Review studies of blunt cardiac injuries report the development of various arrhythmias after the trauma, but atrial fibrillation is not usually listed among these.

El-Menyar et al (2012) reviewed the causes, diagnosis, and management of BCI.²³³ Traumatic cardiac injury is a major challenge in critical trauma care, but guidelines are lacking. A high index of suspicion, application of current diagnostic protocols, and prompt and appropriate management is mandatory.

Blunt cardiac injury is a challenging clinical entity to understand, due to a lack of clear diagnostic criteria and is complicated by a lack of a uniform grading system. Blunt cardiac trauma can present a diagnostic challenge in subtle cardiac injuries.

Blunt cardiac trauma, one of the commonest types of cardiac injuries, can result from direct blows to the precordium, compression of the heart between the sternum and the posterior spine, laceration from surrounding sternal or rib fractures, or indirect forces transmitted from injuries to the lower extremities.²³⁴ The right ventricle is the most commonly injured chamber in pericardial and myocardial contusions due to its anterior position, while the mitral and aortic valves are mostly injured valves given the higher intramural pressures in the left cardiac chambers.

²³³ El-Menyar, A., Al Thani, H., Zarour, A., et al. (2012). Understanding traumatic blunt cardiac injury. *Annals of Cardiac anaesthesia*, 15(4): 287–95.

²³⁴ Qamar SR, Wu Y, Nicolau S et al (2020). State of the Art Imaging Review of Blunt and Penetrating Cardiac Trauma *Canadian Association of Radiologists' Journal*, 71(3): 301-12

Blunt cardiac injury is defined as injuries sustained due to blunt trauma to the heart. The spectrum of BCI ranges from a minor “bruise” to specific postcontusion cardiac conditions such as free-wall rupture.²³⁵

Blunt cardiac injury is more common than penetrating injuries. Misdiagnosis and high mortality are major concerns in these injuries. The true incidence rate of BCIs varies greatly in the literature.

The incidence of cardiac injury following blunt chest trauma varies between 8% and 86%. The main reported cause was high-speed vehicle collision, followed by falls from height or crushing incidents. Damage to the myocardium falls within a wide range from asymptomatic to death based on the severity and mechanism of injury. Cardiac manifestations include arrhythmias, wall motion abnormalities, myocardial wall rupture, and valve damage. However, the most prevalent pathology is myocardial contusion.

The common causes of BCI include motor vehicle accidents with impact at a speed >30 mph with deceleration sheering forces or direct blow to the chest wall by airbag deployment, sports (e.g. contact sports), fall from heights, acts of violence, crush injuries, and blast trauma.

Commotio cordis is sudden cardiac death triggered by a relatively innocent blow to the precordium over the left chest wall. Collapse typically follows instantaneously or within a few seconds due to arrhythmias (typically ventricular fibrillation), making it one of the most common causes of sudden cardiac death in recreational and competitive sports. Left ventricular pressure increases with the impact, leading the myocardial cell membrane to stretch and activating stretch-sensitive ion channels.

Commotio cordis is difficult to diagnose, because of the absence of a reliable objective pathological change on the postmortem examination. In addition to sports and motor vehicle-related injuries, assaults leading to blunt injuries on chest contribute to a male preponderance.

The term “cardiac contusion” has been used to describe an injury to the heart after blunt chest trauma.²³⁶ Histologically, it is characterised by a contused myocardium with haemorrhagic infiltrate, localized necrosis, and oedema. Findings are best confirmed during surgery or at autopsy. Clinically, blunt cardiac injury is the preferred diagnosis term, as blunt chest trauma can result in a broad range of cardiac injury. BCIs can be further described by specific injuries or observed dysfunction. Significant BCI usually occurs from high-impact trauma from motor vehicle accidents (50%), pedestrians struck by motor vehicles (35%), motorcycle crashes (9%), and falls from significant heights (6%). Diagnosing BCI can be challenging as there is no accepted gold standard diagnostic test. The reported incidence of cardiac injury following blunt chest trauma ranges from 8% to 76%, in large part due to a lack of standardized diagnostic criteria.

²³⁵ Fadel, R., El-Menyar, A., ElKafrawy, S., et al (2019). Traumatic blunt cardiac injuries: An updated narrative review. *International journal of critical illness and injury science*, 9(3), 113–9.

²³⁶ Singh, S., Heard, M., Pester, J. M., et al. (2021). Blunt Cardiac Injury. In *StatPearls*. StatPearls Publishing.

Most patients who survive BCI have less severe injuries that range from structural injuries to electrical and conduction disturbances. An intramural haematoma is a structural injury that typically has a benign clinical course that resolves in 4 to 12 weeks, but which can cause premature ventricular contraction and transient bundle branch block.

In the absence of severe arrhythmia and haemodynamic instability, the significance of BCI is sometimes questioned. In the setting of blunt trauma, a high clinical suspicion for BCI is required, and there are no pathognomonic clinical signs or symptoms that correlate with the risk of cardiac complications.

Overall, complications from blunt cardiac trauma are rare. Acute complications from severe cardiac injuries usually necessitate immediate management, and survivors may have long-term complications related to their injury. Most BCI patients do not have long-term sequelae, but a few, late complications have been reported including delayed cardiac rupture, complete atrioventricular block, heart failure, pericardial effusion, and constrictive pericarditis. Good clinical practice entails reevaluating these patients in 3 to 6 months.

Low-energy blunt chest trauma can cause commotio cordis and ventricular fibrillation (VF) in otherwise healthy young individuals. If the chest wall impact occurs during a narrow vulnerable window of ventricular repolarization, the generated premature ventricular impulse can lead to VF and sudden death. The association of commotio cordis and VF in young athletes is well documented, but atrial fibrillation in association with a blunt chest trauma has rarely been reported in a child or adolescent.²³⁷

Ota & Bratincsak (2015) propose that mechanical forces similar to those that induce VF may trigger AF in an otherwise healthy individual. Mechanical forces applied to cardiac tissue are known to affect its electrical properties. The activation of mechano-sensitive ion channels can generate premature ventricular depolarisation. If the timing of the premature depolarisation occurs during a vulnerable period of ventricular repolarisation, it may trigger VF. Similarly, an increase in atrial pressure and atrial wall stretch can activate mechano-sensitive ion channels and induce AF.

In commotion cordis, the timing and the location of the chest wall impact determine the development of VF.²³⁸ The relatively low-energy impact has to occur during a critical 20-millisecond window of the cardiac repolarisation and the impact has to be directly over the cardiac silhouette to induce VF. It is plausible that if a low-energy chest wall impact occurs during the vulnerable window of atrial repolarization, the impact induced elevated atrial pressure will trigger a premature atrial depolarization and the initiation of AF. As a result of the impact, the atrial tissue may exhibit a dispersion of refractoriness inducing a so-called heterogeneity of atrial repolarization, which can perpetuate and sustain AF.

²³⁷ Ota, K., & Bratincsak, A. (2015). Atrial fibrillation induced by commotio cordis secondary to a blunt chest trauma in a teenage boy. *Pediatrics*, 135(1), e199–e201.

²³⁸ Ota, K., & Bratincsak, A. (2015). Atrial fibrillation induced by commotio cordis secondary to a blunt chest trauma in a teenage boy. *Pediatrics*, 135(1), e199–e201.

Although AF was not studied or induced in animal models of low energy chest wall impact, and AF was not documented in young athletes related to chest trauma, there is a case report in an adult that proposes the association of a fall injury with AF. Ghose 1988 It is possible that due to the relatively benign nature of chest trauma–induced AF (no syncope, no dizziness, no hemodynamic compromise) the occurrence of “atrial commotion cordis” is underreported. It is plausible that “lone AF” reported in otherwise healthy athletes could be triggered by a previous blunt chest trauma; therefore, a careful history should be taken when evaluating young athletes with a history of palpitation or evidence of AF.

The authors hypothesise that similar to developing VF in commotio cordis, a blunt mechanical trauma to the heart may trigger AF in an otherwise healthy individual. Because AF may lead to rapid ventricular rate and even VF in certain underlying conditions such as Wolff-Parkinson-White syndrome, the recognition of AF due to commotio cordis may have implications for potentially life-threatening arrhythmias in young athletes.

Cross-sectional studies

New-onset atrial fibrillation (NOAF) is common in patients admitted with trauma or burn injuries.²³⁹ Previous studies have noted that the incidence of NOAF was about 5.5% in trauma patients and 5%–8% in ICU patients. Acute trauma or burns result in an acute sympathetic surge, electrolyte shifts, fluid shifts, and infections that potentially predispose patients to the development of NOAF. The vast majority of trauma patients do not develop AF, and it is plausible that the presence of underlying structural or functional cardiac abnormalities such as left ventricular systolic or diastolic dysfunction, left ventricular hypertrophy (LVH), or left atrial (LA) enlargement may predisposes these patients to the development of AF when exposed to increased sympathetic surge, electrolyte/ fluid shifts, or infections.

Several studies have identified clinical risk factors for NOAF in critically ill and trauma patients.²⁴⁰ In surgical ICU patients, the predictors of NOAF were older age, blunt trauma chest, shock, previous treatment with calcium channel blocker, and use of pulmonary artery catheter. Patients who developed NOAF were sicker, had greater systemic inflammatory response syndrome, shock, renal failure, or severity of the injury, or had coronary artery bypass surgery, or were on mechanical ventilation. Other than these clinical predictors, there is a paucity of data on structural and functional cardiac abnormalities as a risk factor for NOAF in patients with blunt trauma or burn injury.

Moray et al (2018) investigated risk factors for new-onset AF in patients admitted with blunt trauma or burn injuries at a Level 1 academic trauma centre, and to determine its effects on the short-term clinical outcomes.²⁴¹ This case-control study compared patients with new-onset

²³⁹ Morsy, M., Slomka, T., Shukla, A., et al. (2018). Clinical and echocardiographic predictors of new-onset atrial fibrillation in patients admitted with blunt trauma. *Echocardiography (Mount Kisco, N.Y.)*, 35(10), 1519–24.

²⁴⁰ Morsy, M., Slomka, T., Shukla, A., et al. (2018). Clinical and echocardiographic predictors of new-onset atrial fibrillation in patients admitted with blunt trauma. *Echocardiography (Mount Kisco, N.Y.)*, 35(10), 1519–24.

²⁴¹ Morsy, M., Slomka, T., Shukla, A., et al. (2018). Clinical and echocardiographic predictors of new-onset atrial fibrillation in patients admitted with blunt trauma. *Echocardiography (Mount Kisco, N.Y.)*, 35(10), 1519–24.

AF with a cohort of patients without AF during the hospital stay after trauma or burn injury. Patients with prior AF or lack of transthoracic echocardiogram were excluded. Demographic, clinical factors including injury severity score and echocardiographic parameters were compared in both cohorts. Risks of short-term clinical outcomes, namely persistent AF, new stroke, myocardial infarction, or death, were compared.

Older age, sepsis, CHADS2-VASC score >1, larger left atrium (LA) size, left ventricular hypertrophy (LVH), and left ventricular diastolic dysfunction imposed a significant risk for new-onset AF on univariate analysis. In multivariate analysis, independent predictors of new-onset AF were LA dilation and LVH. LA enlargement increased odds of new-onset AF by 23-fold (OR 23; CI: 5.7-92, P < 0.0001) and the presence of LVH increased the odds of new-onset AF more than 20-fold (OR 20.8; CI: 5-87, P < 0.0001).

Dilated LA and LVH are independent predictors of new-onset AF in patients with blunt trauma or burn. New-onset AF did not confer increased risk for in-hospital mortality.

Case reports

Alkhamisi et al. (2021) reported a rare patient in whom AF was induced from commotio cordis (CC).²⁴²

A 20-year-old male collegiate basketball player was evaluated for sudden chest pain, shortness of breath, dizziness, and blurry vision, following an elbow to the anterior chest by another player. His symptoms improved over 10 minutes of observation, but rhythm strip performed onsite showed atrial fibrillation, and the athlete was transmitted to the emergency department for further evaluation. Electrocardiogram confirmed atrial fibrillation with a rate of 85 bpm. Electrocardioversion was being arranged when he spontaneously converted to normal sinus rhythm, 2.5 hours from the traumatic event.

The association of commotion cordis and ventricular fibrillation is well documented and is a significant cause of morbidity and mortality in young athletes. AF induced by CC is less recognised, and has only been reported in two case reports. One case involved a 16 year old boy who developed CC after blunt chest trauma during football practice, with AF spontaneously resolving at 72 hours (Ohta and Bratinsak 2015). Alkhamisi et al (2021) described a second case that took longer to resolve.

Although rarely described and less life threatening as ventricular fibrillation, AF in relation to commotion cordis may be among cardiac conditions caused by blunt chest trauma. There is little data concerning its management or risk factors.

The mechanism of AF induction after chest trauma is not defined, but could be related to chest wall impact during a vulnerable window of atrial repolarisation, causing an elevated atrial pressure that could trigger premature atrial depolarisation and the induction of AF.

²⁴² Alkhamisi, A., Carek, S. M., Dillon, M. C., et al. (2021). Atrial Fibrillation Induced From Commotio Cordis. *Clinical journal of sport medicine*, 31(4), e213–5.
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Ota & Bratincsak (2015) described a healthy 16-year-old boy who suffered blunt chest trauma during football practice. He was found to have AF, which resolved in 3 days without any therapy. He did not have any identifiable structural or electrical cardiac abnormality and had no previous history of arrhythmia.²⁴³

The authors hypothesised that AF, similar to commotio cordis-induced VF, may occur as a result of a blunt chest trauma in healthy young individuals. Animal studies evaluating arrhythmias related to chest wall impact may elucidate the timing and mechanism of AF induced by commotio cordis

The absence of structural heart defect in this teenage boy, the lack of electrical abnormalities on his follow-up ECG, and the fact that the arrhythmia resolved spontaneously within 72 hours suggest that the high-speed chest trauma was the cause of the AF.

This case illustrates an unusual example of atrial fibrillation induced by commotio cordis (AFCC). Although less acutely life threatening and much less frequently described than ventricular fibrillation induced by commotio cordis, CC should be considered in the differential after blunt chest wall trauma.

Summary and conclusions

Atrial fibrillation is an extremely rare complication of rare with isolated blunt cardiac/chest injury (BCI). Clinically, BCI is the preferred diagnostic term, as blunt chest trauma can result in a broad range of cardiac injury.

The term “cardiac contusion” has been used to describe an injury to the heart after blunt chest trauma. Blunt cardiac injuries are much more common than penetrating injuries. Blunt cardiac trauma can present a diagnostic challenge in subtle cardiac injuries. The spectrum of BCI ranges from a minor “bruise” to specific postcontusion cardiac conditions such as free-wall rupture. The true incidence rate of BCIs varies greatly in the literature.

New-onset atrial fibrillation (NOAF) is common in patients admitted with trauma or burn injuries. Previous studies have noted that the incidence of NOAF was about 5.5% in trauma patients (Morsy et al 2016). Significant BCI usually occurs from high-impact trauma from motor vehicle accidents (50%), pedestrians struck by motor vehicles (35%), motorcycle crashes (9%), and falls from significant heights (6%). The reported incidence of cardiac injury following blunt chest trauma ranges from 8% to 76%, in large part due to a lack of standardised diagnostic criteria.

In the absence of severe arrhythmia and hemodynamic instability, the significance of BCI is sometimes questioned. Most patients who survive BCI have less severe injuries that range from structural injuries to electrical and conduction disturbances. *Commotio cordis* is a rare type of blunt cardiac injury in which low impact chest trauma causes sudden cardiac arrest, usually occurs from being struck by a projectile during sports. The most common arrhythmia

²⁴³ Ota, K., & Bratincsak, A. (2015). Atrial fibrillation induced by commotio cordis secondary to a blunt chest trauma in a teenage boy. *Pediatrics*, 135(1), e199–e201
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during commotio cordis is ventricular fibrillation, and complete heart block has been reported, although there is an almost complete silence in the medical literature concerning AF developing after BCI, outside the context of multi-trauma admission to intensive care units.

Recent reviews of traumatic blunt cardiac injuries (e.g. Fadel et al 2019) do not specifically report AF as a complication, although other arrhythmias have been reported, including AV block and ventricular fibrillation.

Several studies have identified clinical risk factors for NOAF in critically ill trauma patients. In surgical ICU patients, the predictors of NOAF were older age, blunt trauma chest, shock, previous treatment with calcium channel blocker, and use of pulmonary artery catheter (Morsy et al). Dilated LA and LVH are independent predictors of new-onset AF in patients with blunt trauma or burn. There is a separate factor in the SoPs for critical illness requiring admission to an intensive care unit, so patients with injury of this severity would be covered by that specific factor.

Most patients who survive BCI have less severe injuries that range from structural injuries to electrical and conduction disturbances. The association of commotio cordis and ventricular fibrillation is well documented and is a significant cause of morbidity and mortality in young athletes. AF induced by commotio cordis is less recognised, and has only been reported in only two case reports. One case involved a 16 year old boy who developed commotio cordis after blunt chest trauma during football practice, with AF spontaneously resolving at 72 hours (Ohta and Bratinsak 2015). Alkhamisi et al (2021) more recently described a second case that took longer to resolve.

Although rarely described and less life threatening as ventricular fibrillation, it has been speculated that AF in relation to commotio cordis may be among the cardiac conditions caused by blunt chest trauma. There is little data concerning its management or risk factors.

The mechanism of possible AF induction after chest trauma is not defined, but could be related to chest wall impact during a vulnerable window of atrial repolarisation, causing an elevated atrial pressure that could trigger premature atrial depolarisation and the induction of AF. Ota & Bratinsak (2015) propose that mechanical forces similar to those that induce ventricular fibrillation may trigger AF in an otherwise healthy individual. Similar to VF, an increase in atrial pressure and atrial wall stretch can activate mechano-sensitive ion channels and induce AF.

Although AF was not studied or induced in animal models of low energy chest wall impact, and AF has not been documented in young athletes related to chest trauma, there is one case report in an adult that proposed the association of a fall injury with AF (Ghose 1988). It is plausible that “lone AF” reported in otherwise healthy athletes could be triggered by a previous blunt chest trauma.

In relation to having a blunt cardiac injury, independent of critical illness sufficient to warrant admission to an intensive care unit, it is concluded that the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is very

limited in quality or quantity, being confined to two case reports. It is suggested that a factor for blunt cardiac injury, independent of critical illness requiring ICU admission, should be retained in the RH SoP, but the evidence is insufficient to retain a factor in the BoP SoP.

The existing factor for blunt chest injury should be retained in the RH SoP only, but with some revisions. Instead of experiencing a powerful, non-penetrating blow to the chest, resulting in injury warranting medical attention, the factor should be rephrased as experiencing a blunt chest injury, within the 60 days before the clinical onset/ worsening of heart block. Blunt chest injury should be defined in broad terms as meaning a non-penetrating blow to the chest. and examples of causes included in a note. Examples of causes of blunt chest injury include motor vehicle accidents, a direct blow to the chest wall by airbag deployment, impact in contact sports, a fall from heights, crush injuries, and being struck by a projectile while playing sport.

Spinal cord injury

Current factor

onset and worsening - RH and BoP

having a spinal cord injury with quadriplegia and symptoms of autonomic dysreflexia within the two years before the clinical onset of atrial fibrillation or atrial flutter;

"spinal cord injury" means an injury to the long tracts of the spinal cord resulting in permanent motor or sensory deficits below the level of the lesion;

Summary of important issues

Arrhythmia is often observed in patients with traumatic spinal cord injury (SCI) but is an under-recognised cause (Teo et al 2020). SCI can result in substantial sensorimotor and autonomic dysfunctions and an adverse prognosis. Cardiovascular disease is the leading cause of death in patients with chronic SCI (Wang et al 2016).

Despite the clinical significance of AF, no systemic analysis of a large cohort has been conducted to investigate the association between SCI and the incidence of AF.

Summary of previous investigation

Cardiac dysfunctions are also reported to be common complications following spinal cord injury. Atrial flutter and atrial fibrillation have been documented to occur in both acute and chronic stages (Grigorean et al 2009).

Reviews

As noted in a review by **Wang et al (2016)**, spinal cord injury (SCI) can result in substantial sensorimotor and autonomic dysfunctions and an adverse prognosis. Cardiovascular disease is the leading cause of death in patients with chronic SCI.²⁴⁴

Cardiac arrhythmia is frequently observed in patients with SCI and is generally considered to be caused by autonomic dysfunction. Because the spinal sympathetic pathways that control the heart and maintain vascular tone exit at the first thoracic vertebra to fourth thoracic vertebra (Th1-Th4) levels, an unopposed parasympathetic tone may be present at the cervical or high thoracic (above Th5) level in patients with SCI. Life-threatening bradyarrhythmia or sinus arrest requiring the implantation of a pacemaker has also been reported

Despite the clinical significance of AF, no systemic analysis of a large cohort has been conducted to investigate the association between SCI and the incidence of AF.

Proposed mechanisms of cardiac arrhythmia in patients with SCI have been postulated. The autonomic nervous system plays an important role in cardiovascular control. After SCI, disruption of the communication between the brainstem and the autonomic nervous system can occur. Sympathetic preganglionic fibres exit at the T1-4 level to form synapses in the thoracic ganglia with postganglionic fibres, which may innervate the heart and be responsible for increasing heart rate and cardiac output. Parasympathetic fibres exit the CNS at the brainstem level through the vagal nerve to innervate the heart and antagonize the effect of the sympathetic nervous system. Patients with SCI at the cervical or high thoracic level (above T 6) could have impaired sympathetic impulses and unopposed parasympathetic activity, thereby leading to autonomic dysfunction.

Traumatic spinal cord injury is an under-recognised cause of atrial fibrillation.²⁴⁵ Studies commonly discuss bradyarrhythmias in patients with SCI. With regard to AF, a population-based cohort study in Taiwan showed the long-term risk of AF was higher in patients with SCI (Wang et al 2016). The pathogenesis of AF in SCI is complex and involves dynamic interplay between triggers and substrate abnormalities.

Studies have found patients with SCI had higher P-wave dispersion (PWD) values (Ravensbergen et al 2012), which is a novel predictor in evaluating risk of AF. PWD is affected by autonomic dysfunction in SCI as loss of normal heart sympathetic modulation results in prolonged intra-atrial conduction time and higher PWD values. This non-homogenous propagation of sinus impulses in the atria confers a higher risk of AF.

Some authorities believe that AF represents early manifestation of autonomic dysreflexia. Some hypothesise the loss of central control and reflexes of the heart causes spontaneous sympathetic activity, which is reinforced by denervation hypersensitivity and triggers AF. Secondary myocardium remodelling changes following SCI may result in AF. AF may be triggered by pain from trauma. Patients may develop AF independent of SCI.

²⁴⁴ Wang, C. C., Chang, C. T., Lin, C. L., et al. (2016). Spinal cord injury is associated with an increased risk of atrial fibrillation: A population-based cohort study. *Heart rhythm*, 13(2), 416–23.

²⁴⁵ Teo, T. W., Tan, B. Y., & Sia, C. H. (2020). 32-year-old with Paroxysmal Atrial Fibrillation after Traumatic Spinal Cord Injury. *Journal of atrial fibrillation*, 13(2), 2324.

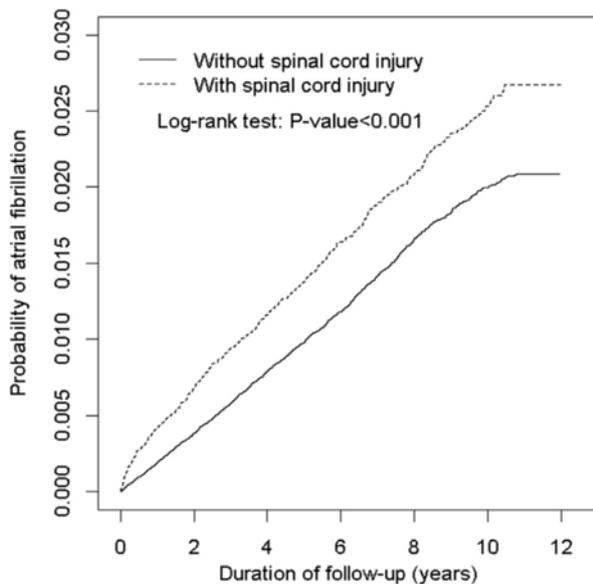
Cross-sectional studies

Wang et al (2016) conducted a retrospective cohort study to investigate the association between atrial fibrillation and SCI.²⁴⁶

Using the National Health Insurance Research Database, the authors identified 41,691 patients without a history of AF who were newly hospitalised for SCI between 2000 and 2011. The comparison group included 166,724 patients without AF or SCI who were matched to the SCI group according to age, sex, and index year at a ratio of 4:1. Both cohorts were followed up to the end of 2011, and the cumulative incidence of AF was calculated. Univariate and multivariate Cox proportional hazards regression models and Kaplan-Meier curve analysis were used to compare differences in the cumulative incidence of AF between the 2 groups.

During the mean follow-up periods of 5.69 years for the SCI group and 6.17 years for the non-SCI group, the overall incidence rates were 2.70 and 1.99 cases per 1000 person-years, respectively (crude HR 1.36; 95CI 1.24-1.48). After adjusting for age, sex, and comorbidities, the risk of AF remained significantly higher in the SCI group than in the non-SCI group (adjusted HR 1.28; 95CI 1.17-1.40).

FIGURE 28 PROBABILITY OF ATRIAL FIBRILLATION IN PATIENTS WITH AND WITHOUT SPINAL CORD INJURY USING THE KAPLAN-MEIER METHOD



Source: Wang et al (2016), Fig 2

²⁴⁶ Wang, C. C., Chang, C. T., Lin, C. L., et al. (2016). Spinal cord injury is associated with an increased risk of atrial fibrillation: A population-based cohort study. *Heart rhythm*, 13(2), 416–23. August meeting 2022

TABLE 12 COMPARISONS OF RISKS OF ATRIAL FIBRILLATION STRATIFIED BY SEX AND AGE BETWEEN THOSE WITH AND WITHOUT SPINAL CORD INJURY

Variable	Spinal cord injury						Crude HR (95% CI)	Adjusted HR (95% CI)
	No			Yes				
	Event	PY	Rate	Event	PY	Rate		
All	2045	1,028,783	1.99	642	237,418	2.70	1.36 (1.24–1.48) [*]	1.28 (1.17–1.40) [*]
Sex								
Female	967	382,864	2.53	304	89,719	3.39	1.34 (1.18–1.52) [*]	1.16 (1.01–1.32) [†]
Male	1078	645,919	1.67	338	147,699	2.29	1.37 (1.21–1.55) [*]	1.40 (1.23–1.58) [*]
Stratify by age (y)								
≤49	64	522,616	0.12	29	128,163	0.23	1.85 (1.19–2.86) [†]	1.37 (0.87–2.17)
50–65	262	250,677	1.05	102	57,238	1.78	1.72 (1.37–2.17) [*]	1.41 (1.11–1.78) [†]
>65	1719	255,490	6.73	511	52,017	9.82	1.46 (1.32–1.61) [*]	1.21 (1.09–1.34) [*]
Comorbidity [§]								
No	1176	905,409	1.30	202	176,692	1.14	0.88 (0.76–1.02)	1.33 (1.14–1.54) [*]
Yes	869	123,374	7.04	440	60,726	7.25	1.03 (0.92–1.15)	1.25 (1.11–1.40) [*]

Source: Wang et al (2016), Table 2; Adjusted HR multivariate-adjusted hazard ratio for age, sex, and comorbidities of diabetes, hypertension, hyperlipidaemia, COPD, heart failure, CAD, stroke, hyperthyroidism, cancer, and chemotherapy

TABLE 13 COX MODEL WITH HRs AND 95CIs OF AF ASSOCIATED WITH SPINAL CORD INJURY AND COVARIATES

Variable	Crude		Adjusted	
	HR	95% CI	HR	95% CI
Sex: women vs men	1.51	1.40–1.63 [*]	1.12	1.04–1.21 [†]
Age	1.10	1.10–1.11 [*]	1.10	1.09–1.10 [*]
Baseline comorbidities: no vs yes				
Spinal cord injury	1.36	1.24–1.48 [*]	1.28	1.17–1.40 [*]
C-spinal injury	1.23	1.07–1.43 [†]	1.12	0.97–1.30
T-spinal injury	1.57	1.31–1.88 [*]	1.31	1.09–1.57 [†]
L-S-Co-spinal injury	1.58	1.38–1.80 [*]	1.31	1.14–1.50 [*]
Multilevel spinal injury	2.13	1.68–2.68 [*]	1.83	1.45–2.31 [*]
Diabetes	3.41	3.06–3.80 [*]	1.16	1.03–1.30 [†]
Hypertension	5.14	4.73–5.58 [*]	1.23	1.12–1.36 [*]
Hyperlipidemia	2.51	2.12–2.98 [*]	0.86	0.82–1.03
COPD	6.61	5.85–7.47 [*]	1.25	1.10–1.43 [†]
Heart failure	11.2	9.79–12.9 [*]	2.02	1.74–2.36 [*]
CAD	6.29	5.70–6.94 [*]	1.54	1.37–1.73 [*]
Stroke	4.54	4.01–5.08 [*]	1.12	0.99–1.26
Hyperthyroidism	1.93	1.07–3.50 [†]	1.41	0.78–2.56
Cancer	1.98	1.59–2.45 [*]	0.86	0.68–1.09
Chemotherapy	1.37	0.83–2.28	1.03	0.59–1.79

Source: Wang et al (2016), Table 3

The risk of AF after long-term follow-up was higher in the SCI group than in the non-SCI group, particularly in patients with T-spinal injury, L-S- Co-spinal injury, and multilevel spinal injury. Cardiovascular dysfunction is a common cause of death in patients with chronic SCI. Among these dysfunctions, cardiac failure, ventricular tachycardia, AF, CAD and cerebrovascular disease are the most common causes of death.

Despite the clinical importance of AF in patients with chronic SCI, epidemiological evidence linking the incidence of AF to SCI is scant. Two case reports (Pine et al 1991; Forrest 1991) demonstrated that AF occurs during episodes of autonomic dysreflexia. Prakash et al (2002) compared ECG findings from patients with chronic SCI with those from able-bodied controls and found that the prevalence of AF was similar in both groups. However, in Wang et al's study, the risk of AF was higher in the chronic SCI group. The differences between results may be due to the different baseline demographic characteristics of control groups. In Wang et al August meeting 2022

al's study, the SCI group had significantly higher proportions of hypertension, CHF, CAD, and COPD than did the non-SCI group. However, Prakash et al reported significantly higher proportions of hypertension, CHF, CAD, and COPD in their able-bodied control group than in the SCI group.

To clarify whether SCI is an independent risk factor for predicting the risk of AF after controlling for these potential confounding factors, Wang et al performed additional subgroup analyses. The subgroup without any comorbidities, patients with SCI still had a significantly higher risk of AF in the long-term follow-up period.

Wang et al notes that previous studies reported that most cardiac arrhythmias (e.g., sinus bradycardia and sinus arrest) that occur in patients with SCI mainly do so because of autonomic dysfunction that the risk is usually attenuated after the acute stage.²⁴⁷ In Wang et al's study, the cumulative incidence of AF increased steadily with time, implying that the pathogenesis of AF in patients with SCI cannot be explained by autonomic dysfunction. In the chronic stage, cardiac arrhythmia such as AF may occur secondary to autonomic dysreflexia, a syndrome of reflex sympathetic discharge from the preganglionic neurons in the thoracolumbar spinal cord in response to viscerosensitive stimuli originating below the level of injury in patients with SCI above T6.

Wang observed an increased risk of AF in patients with T-spinal injury, L-S-Co-spinal injury, and multilevel SCI, while patients with C-spinal injury showed only a non-significant trend toward an increased risk of AF. There are several possible explanations. Some patients with C-spinal injury may have multilevel injury and were therefore assigned to the multilevel SCI subgroup; hence, the association between C-spinal injury and AF may be underestimated in. Compared with patients with C-spinal injury, patients with T-spinal injury, L-S-Co spinal injury, and multilevel SCI were significantly older and had higher proportions of cancer, hypertension, diabetes, chronic kidney disease, COPD, hyperthyroidism, heart failure, CAD, and stroke, all of which may contribute to an increased risk of AF. Wang et al proposed that the pathogenesis of AF in patients with chronic SCI involves both autonomic dysfunction and other coexisting cardiovascular risk factors

Cross-sectional study

Rabadi et al (2013) conducted a retrospective study to determine the predictors of mortality in veterans with traumatic spinal cord injury (tSCI).²⁴⁸ 147 patients with tSCI who were enrolled in a Spinal Cord Injury program from 2000 to 2011 were retrospectively studied. The study sample was divided into two groups, based on the survival status by the end of 2011.

In this sample, survival at the end of the 12-year study period was 60%. There were three major causes of death: infection-related, such as pneumonia (21%), urinary infection (14%), and infection of the pressure ulcers (11%); cardiovascular-related, such as congestive heart failure (16%), coronary arterial disease (13%), and atrial fibrillation (2%); and cancer-related

²⁴⁷ Wang, C. C., Chang, C. T., Lin, C. L., et al. (2016). Spinal cord injury is associated with an increased risk of atrial fibrillation: A population-based cohort study. *Heart rhythm*, 13(2), 416–23.

²⁴⁸ Rabadi, M. H., Mayanna, S. K., & Vincent, A. S. (2013). Predictors of mortality in veterans with traumatic spinal cord injury. *Spinal cord*, 51(10), 784–

(16%). In veterans with complete SCI, deaths were mainly infection-related and occurred in the hospital (51%), while deaths in veterans with incomplete SCI were primarily cardiovascular and cancer-related and occurred in the community. A Cox regression analysis showed the age at the time of injury to be the main predictor of SCI-related mortality.

This study suggested that older age at the time of injury is a significant predictor of mortality following tSCI with patients more likely to die from cardiovascular deaths than the general population. These findings support the need for preventative strategies, including a focus on cardiovascular risk factor management, in order to decrease long-term mortality.

Case reports

Teo et al (2020) described a young man with a structurally normal heart and no secondary risk factors with cervical SCI, cord compression and resultant paroxysmal AF, demonstrating the “heart-brain axis” in the pathogenesis of AF.²⁴⁹

A healthy 32-year-old man presented with sudden loss of consciousness after passing urine with resultant trauma to the back of his neck. There were no palpitations prior. Examination revealed flaccid paralysis of all 4 limbs with priapism. ECG demonstrated atrial fibrillation with rapid ventricular response. Laboratory showed normal potassium, magnesium, calcium, thyroid stimulating hormone and troponin I levels. MRI of the cervical spine demonstrated left C4 facet dislocation with grade 1 spondylolisthesis of C4 over C5, with moderate to severe narrowing of the spinal canal with cord compression and oedema. Transthoracic echocardiogram demonstrated an ejection fraction of 60% and no valvular abnormalities. Left atrium size was normal. The atrial fibrillation subsequently spontaneously reverted to sinus rhythm without treatment.

This case highlights the intricate pathophysiological interplay between the cardiovascular and autonomic nervous system in the pathogenesis of AF. High cervical SCI is characterized by disruption of descending spinal sympathetic pathways with preservation of parasympathetic output, causing disordered cardiovascular control like blood pressure derangements and arrhythmias.

Summary and conclusions

Cardiac arrhythmia is frequently observed in patients with traumatic spinal cord injury (SCI) but it is an under-recognised cause of atrial fibrillation (Teo et al 2020). SCI can result in substantial sensorimotor and autonomic dysfunctions and an adverse prognosis. Cardiovascular disease is the leading cause of death in patients with chronic SCI (Wang et al 2016).

Despite the clinical significance of AF, no systemic analysis of a large cohort has been conducted to investigate the association between SCI and the incidence of AF.

²⁴⁹ Teo, T. W., Tan, B. Y., & Sia, C. H. (2020). 32-year-old with Paroxysmal Atrial Fibrillation after Traumatic Spinal Cord Injury. *Journal of atrial fibrillation*, 13(2), 2324.

Studies commonly discuss bradyarrhythmias in patients with SCI. With regard to AF, a population-based cohort study in Taiwan showed the long-term risk of AF was higher in patients with SCI (Wang et al 2016). The mechanism behind pathogenesis of AF in SCI is complex and involves dynamic interplay between triggers and substrate abnormalities some hypothesise the loss of central control and reflexes of the heart causes spontaneous sympathetic activity, which is reinforced by denervation hypersensitivity and triggers AF.

Because the spinal sympathetic pathways that control the heart and maintain vascular tone exit at the first thoracic vertebra to fourth thoracic vertebra (Th1-Th4) levels, an unopposed parasympathetic tone may be present at the cervical or high thoracic (above Th5) level in patients with SCI (Wang et al 2016). Life-threatening bradyarrhythmia or sinus arrest requiring the implantation of a pacemaker has also been reported. AF can occur in the context of traumatic spinal cord injury due to disruption of the autonomic pathways in the cervical spine.

A population-based cohort study in Taiwan showed the long-term risk of AF was higher in patients with SCI (Wang et al 2016). After adjusting for age, sex, and comorbidities, the risk of AF remained significantly higher in the SCI group than in the non-SCI group (adjusted HR 1.28; 95CI 1.17-1.40). The risk of AF after long-term follow-up was higher in the SCI group than in the non-SCI group, particularly in patients with T-spinal injury, L-S- Co-spinal injury, and multilevel spinal injury. patients with SCI without any comorbidities still had a significantly higher risk of AF in the long-term follow-up period.

Rabadi et al (2013) conducted a retrospective study to determine the predictors of mortality in veterans with traumatic SCI; 2% of SCI deaths were attributed to AF.

The exact mechanisms behind AF and SCI remains unclear. secondary myocardium remodelling changes following SCI may result in AF. AF may be triggered by pain from trauma. Patients may develop AF independent of SCI.

Despite the clinical importance of AF in patients with chronic SCI, epidemiological evidence linking the incidence of AF to SCI is lacking.

Some authorities believe AF represents early manifestation of autonomic dysreflexia. Two case reports (Pine et al 1991; Forrest 1991) demonstrated that AF occurs during episodes of autonomic dysreflexia.as this remains a hypothesis, it should not be required in the SoPs

It is therefore concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with a spinal cord injury (Grade 2). A consistent association has been observed between atrial fibrillation and spinal cord trauma, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for spinal cord injury should be retained in the RH and BoP SoPs.

There is some uncertainty about the temporal relationship between SCI and AF. Wang et al (2016) noted that SCI is associated with an increased risk of AF in a long-term follow-up period, demonstrated to be at least 10 years. In Wang et al's study, the cumulative incidence

of AF increased steadily with time, implying that the pathogenesis of AF in patients with SCI cannot be explained by autonomic dysfunction. In the chronic stage, cardiac arrhythmia such as AF may occur secondary to autonomic dysreflexia, a syndrome of reflex sympathetic discharge from the preganglionic neurons in the thoracolumbar spinal cord in response to viscerosensitive stimuli originating below the level of injury in patients with SCI above T6.

An increase latency is suggested, with removal of a defined period suggested as a reasonable option.

Critical illness

Current factor

onset and worsening - RH and BoP

having an injury or illness requiring admission to an intensive care unit or mechanical ventilation within the one month [BoP 14 days] before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

AF frequently complicates the course of critically ill patients, with an incidence ranging from 4 to 25% in non-cardio-surgical intensive care unit (ICU) patients to 32 to 50% in patients after cardiac surgery, and AF is the most frequent arrhythmia in patients with sepsis (Aibar & Schulman 2021). The mean incidence of new-onset AF in patients with sepsis is 20.6%. The prevalence of new-onset AF ranges from 4.1% to 46% in an analysis of new-onset atrial fibrillation in critically ill patients (Wu et al 2020).

Summary of previous investigation

Supraventricular arrhythmias, including AF and AFL, are reported to common in surgical and nonsurgical intensive care unit patients. These are more likely to occur in older patients and those with severe sepsis or septic shock. Previous studies have demonstrated that 6% to 20% of patients with severe sepsis develop new onset AF. Goodman et al (2007) observed that sepsis/systemic inflammatory response syndrome greatly increased the odds of developing SVAs, consistent with published reports that sepsis is closely associated with SVA development, especially in postoperative patients, and for which inflammatory response has been implicated as part of the triggering mechanism. Small, single-centre studies suggest that new-onset AF is associated with higher mortality and prolonged hospitalisation during severe sepsis.

Walkey et al (2011) reported in an analysis of the California State Inpatient Database that many acute factors were associated with increased risk of first diagnosed AF during severe sepsis. Whether these acute factors serve as markers of illness severity or represent other potential mechanisms for AF is unclear. Increasing number of organ failures, respiratory failure, haematological failure, renal failure, use of right heart catheter, pulmonary or abdominal source of infection, and gram-positive or fungal organisms associated with increased risk of new-onset AF during severe sepsis. Sepsis is closely associated with SVA

development, especially in postoperative patients, inflammatory response implicated as triggering mechanism

Reviews

There have been many recent clinical review studies of incident AF in the context of sepsis or critical illness.^{250 251 252 253}

In one recent review, **Aibar & Schulman (2021)** observe that AF frequently complicates the course of critically ill patients, with an incidence ranging from 4 to 25% in non-cardio-surgical intensive care unit (ICU) patients to 32 to 50% in patients after cardiac surgery, and is the most frequent arrhythmia in patients with sepsis.²⁵⁴ In ICU patients, AF may be responsible for new heart failure and thromboembolism and is an independent risk factor for ischaemic stroke and systemic embolism, with five-fold higher risk than patients in sinus rhythm (SR). Possible triggers for new-onset AF in this setting may include systemic inflammation, higher levels of hormones implicated in the neuroendocrine stress system, autonomic dysfunction, fluid and electrolyte imbalance, adrenergic overstimulation, and ischaemia.

The sepsis-3 task force defined sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” As part of the resulting multiorgan dysfunction, the cardiovascular system can be impaired

New-onset AF that occurs in the setting of sepsis could be associated with increased length of stay in ICU, long-term stroke risk, and mortality risk. The risk of ischaemic stroke among patients with new-onset AF during sepsis seems to be higher than in the general population with AF and higher than in patients with sepsis who do not have new-onset AF. However, there is no evidence to support anticoagulant treatment for stroke prevention in patients with new-onset AF during sepsis.

17 studies were included in the narrative review.²⁵⁵ The mean incidence of new-onset AF in patients with sepsis was 20.6% (14.7% in retrospective studies and 31.6% in prospective). Risk factors for new-onset AF include advanced age, white race, male sex, obesity, history of cardiopulmonary disease, heart or respiratory failure, and higher disease severity score. In-hospital mortality was higher in patients with than in those without new-onset AF in 10 studies. In four studies the overall intensive care unit and hospital mortality rates were comparable between patients with and without new-onset AF, while three other studies did not provide

²⁵⁰ Aibar, J., & Schulman, S. (2021). New-Onset Atrial Fibrillation in Sepsis: A Narrative Review. *Seminars in thrombosis and hemostasis*, 47(1), 18–25.

²⁵¹ Bosch, N. A., Cimini, J., & Walkey, A. J. (2018). Atrial Fibrillation in the ICU. *Chest*, 154(6), 1424–34.

²⁵² Wetterslev, M., Haase, N., Hassager, C., et al (2019). New-onset atrial fibrillation in adult critically ill patients: a scoping review. *Intensive care medicine*, 45(7), 928–38.

²⁵³ Kanjanahattakij, N., Rattanawong, P., Krishnamoorthy, P., et al. (2019). New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta cardiologica*, 74(2), 162–9.

²⁵⁴ Aibar, J., & Schulman, S. (2021). New-Onset Atrial Fibrillation in Sepsis: A Narrative Review. *Seminars in thrombosis and hemostasis*, 47(1), 18–25.

²⁵⁵ Aibar, J., & Schulman, S. (2021). New-Onset Atrial Fibrillation in Sepsis: A Narrative Review. *Seminars in thrombosis and hemostasis*, 47(1), 18–25.

mortality data. One study reported on the in-hospital incidence of stroke, which was 2.6 versus 0.69% in patients with or without new-onset AF, respectively. Seven studies provided follow-up data after discharge. In three studies, new-onset AF was associated with excess mortality at 28 days, 1 year, and 5 years after discharge of , and 3% patients, respectively. In two studies, the mortality rate was comparable in patients with and without new-onset AF. Post-discharge stroke was reported in five studies, two studies had no events after 30 and 90 days, one study showed a non-significant increase in stroke, and two studies demonstrated a significant increase in risk of stroke after new-onset AF. The absolute risk increase was 0.6 to 1.6%.

Sepsis could be responsible for biventricular dilatation with both diastolic and systolic dysfunction. Underlying cause of these dysfunctions can be related to circulating cytokines and cardio-depressant factors as tumor necrosis factor- α and interleukin-1b. These changes can occur even in the absence of coronary artery disease. The ventricular dilatation associated with use of high volumes of fluids for resuscitation recommended in the patient with sepsis can lead to an increase in the diastolic pressure of the left ventricle, causing in turn a dilatation of the left atrium, providing ideal anatomical conditions for the appearance of AF. Ventricular remodelling secondary to sepsis can decrease ventricular compliance with associated changes in left atrial and pulmonary haemodynamics. Aoki et al suggested that systemic inflammation in sepsis may induce an electrophysiological substrate for AF, responsible for the high incidence of new-onset AF in septic patients. However, these proposed pathophysiological mechanisms have not been verified.

Clinical risk factors associated with new-onset AF during sepsis include demographics (age, sex, and race), comorbidities (heart disease, obesity, diabetes, and hypertension), factors related to acute disease (cardiac and respiratory failure, renal failure, severity of illness), and echocardiographic findings. Risk factors that have been consistently reported to increase the risk of new-onset AF include advanced age, white race, male sex, respiratory and cardiovascular diseases, cardiac and respiratory failure, and those with increased severity of illness. In 14 of 17 studies analysed, older age was an independent risk factor for new-onset AF in septic patients.

Regarding other classical risk factors for AF like diabetes, hypertension, obesity, and cardiovascular disease, 11 studies showed that some were associated with new-onset AF in sepsis. However in five studies these classical risk factors were unrelated to new-onset AF, New-onset AF in patients with septic syndromes may rather be initiated by elevated levels of pro-inflammatory cytokines by activation of the catecholaminergic system, electrolyte alterations, and alteration in volume status during sepsis.

Regarding echocardiographic findings, Ferrera et al and Liu et al reported that left atrial dimension was larger in patients with new-onset AF than in those who remained in SR. Conversely, Guenancia et al described no differences in left atrial dimension among patients with new-onset AF and those with SR, although new-onset AF patients had a lower left ventricular ejection fraction than patients in SR.

In another review study, **Bosch et al (2018)** observes that although critical illness-induced AF likely follows the development of a susceptible atrial substrate combined with a triggering

event, the specific factors that contribute to the arrhythmogenic substrate and the specific triggers may differ from community-acquired AF.²⁵⁶ Risk factors associated with AF in the community setting (structural and valvular heart disease) have not been consistently linked to new onset AF during critical illness. Emerging evidence suggests that acute events during critical illness accelerate cardiac remodelling and fibrosis to rapidly produce a susceptible atrial substrate, providing fertile ground for the development of sustained AF in response to the many arrhythmogenic triggers of critical illness.

Accelerated cardiac structural and electrical remodelling can occur due to infection and inflammation that are common during critical illness. Murine and primate models of pneumonia show that bacteria deposit within the myocardium and result in development of atrial fibrosis and an arrhythmogenic substrate, despite treatment with antibiotics. Bacteria can also alter calcium ion channel gene expression through toxin release, resulting in a shortened atrial-effective refractory period which produces electrical remodelling that further predisposes to AF during sepsis.

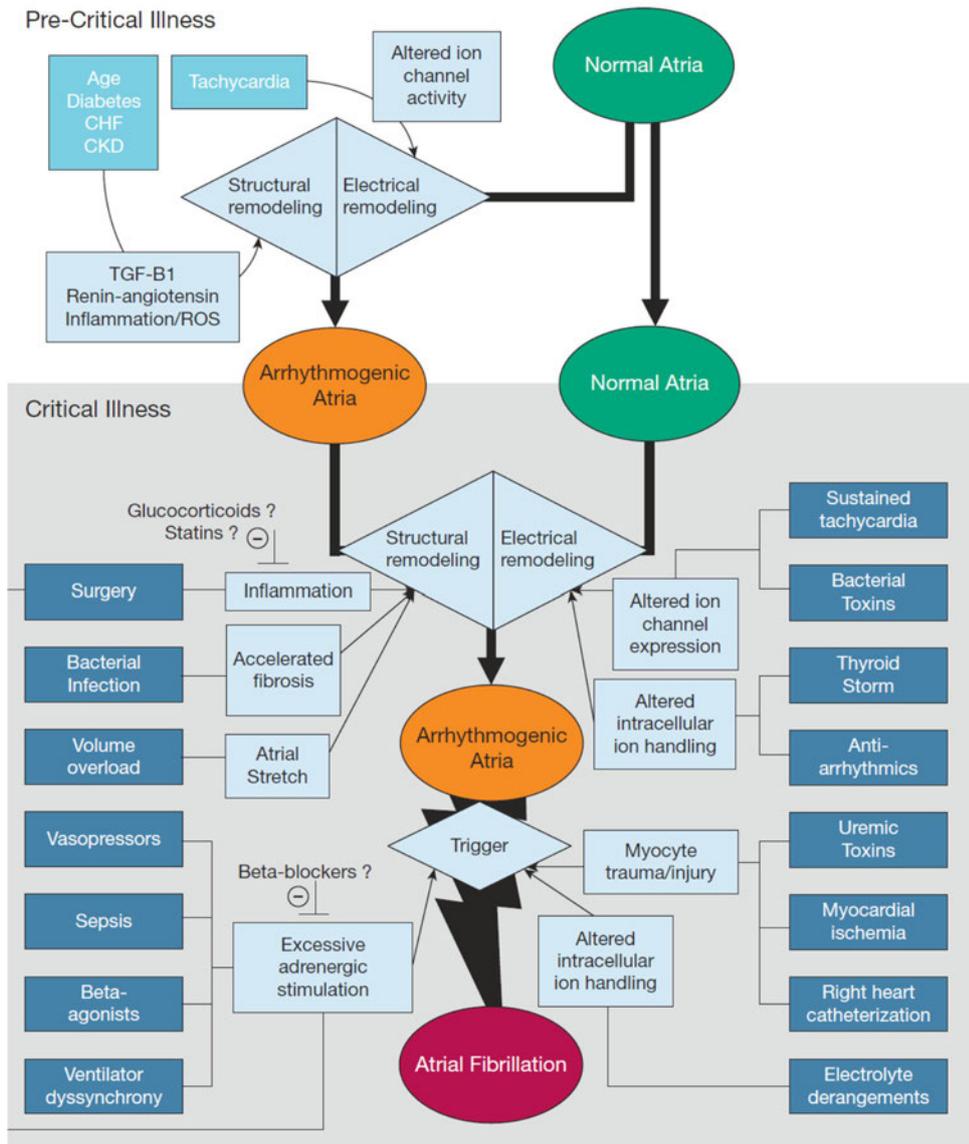
Inflammation, regardless of the presence of infection, may also play a role in the development of AF.²⁵⁷ Elevated inflammatory markers in patients with sepsis and postoperative patients are associated with an increased risk of developing AF. Inflammation may predispose to arrhythmia development as a result of direct inflammatory cell infiltration and oxidative damage to atrial myocytes. Inflammation and oxidative damage may also help explain associations between obesity and new-onset AF, in the community and during critical illness.

In the ICU, AF is more frequent among patients receiving vasopressor agents, in patients with electrolyte derangements, and in patients with greater disease severity. For example, hypokalaemia and changes in the balance of autonomic activity as a result of vasopressors may alter ion channel activity and cell automaticity that predispose to AF. Dopamine and epinephrine in particular have chronotropic effects that can lead to increased atrial ectopic discharges triggering new AF. Greater illness severity is also associated with the risk of new AF development, which may be a consequence of increased release of catecholamines and progressive autonomic dysfunction. Atrial size on echocardiography is associated with new-onset AF in the ICU, suggesting that iatrogenic atrial pressure/ volume overload may also be important in the development of AF in the critically ill.

²⁵⁶ Bosch, N. A., Cimini, J., & Walkey, A. J. (2018). Atrial Fibrillation in the ICU. *Chest*, 154(6), 1424–34.

²⁵⁷ Bosch, N. A., Cimini, J., & Walkey, A. J. (2018). Atrial Fibrillation in the ICU. *Chest*, 154(6), 1424–34.

FIGURE 29 PROPOSED MECHANISMS FOR AF DEVELOPMENT IN PATIENTS WHO ARE CRITICALLY ILL.



Bosch et al (2018), Fig 1, p 1426

Meta-analyses

Wu et al (2020) systematically evaluated the prevalence, outcomes, and risk factors of new-onset atrial fibrillation (AF) in critically ill patients.²⁵⁸ Medline, Embase, Science Citation Index, Wanfang, CNKI, and Wiley Online Library were thoroughly searched to identify relevant studies. Studies were assessed for methodological quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence interval (CI) were used to assess the strength of the association. Heterogeneity, subgroup, sensitivity analyses, and publication bias were conducted.

²⁵⁸ Wu, Z., Fang, J., Wang, Y., et al. (2020). Prevalence, Outcomes, and Risk Factors of New-Onset Atrial Fibrillation in Critically Ill Patients. *International heart journal*, 61(3), 476–85
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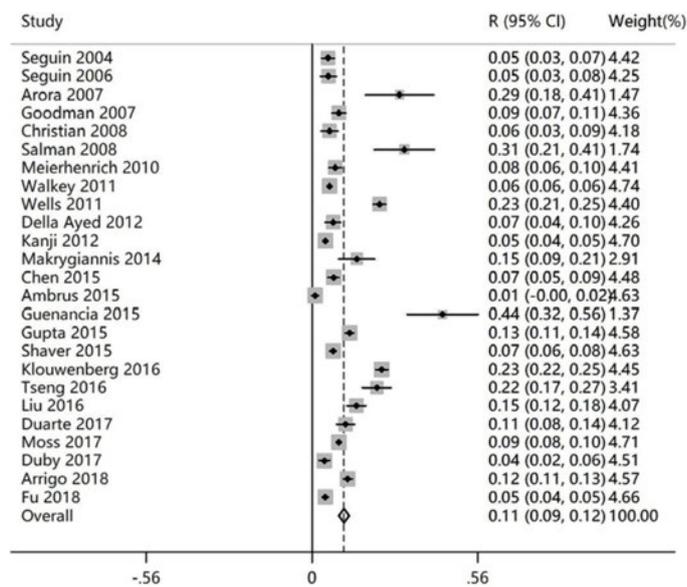
A total of 25 studies were included. The prevalence of new-onset AF ranged from 4.1% to 46%. The random-effects pooled prevalence was 10.7%. The pooled result jumped up to 35.8% in patients with septic shock.

TABLE 14 PREVALENCE OF NEW-ONSET AF AND SEVERITY SCORES IN CRITICALLY ILL PATIENTS

Name	Year	Case	Incidence of AF (no.)	Severity index	Severity score
Seguin	2004	453	5.3% (24)	SAPS II	45 ± 20/31 ± 17
Seguin	2006	293	5.5% (16)	SAPS II	47 ± 12/31 ± 16
Arora	2007	61	29.5% (18)	APACHE II	25.4 ± 6.4/20 ± 6.4
Goodman	2007	611	9% (52)	APACHE II	23 ± 8/16 ± 8
Christian	2008	272	5.9% (16)	APACHE II	NR
Salman	2008	81	31% (25)	APACHE III	106 ± 31.9/85 ± 33
Meierhenrich	2010	628	All patients 7.8% (49/628)	NR	NR
			Septic shock 46.0% (23/50)	SAPS II	31 (15-63)/30 (12-65)
Walkey	2011	49082	5.9% (2896)	NR	NR
Wells	2011	1466	22.7% (328)	NR	NR
Della Ayed	2012	377	7% (26)	APACHE II	19 ± 7/15.1 ± 9
Kanji	2012	3081	4.5% (139)	APACHE II	22.6 ± 9.0/N
Makrygiannis	2014	133	15% (20)	APACHE II	17.9 ± 5.1/15.7 ± 6.8
Chen	2015	741	7.2% (53)	APACHE II	27 ± 7.2/21 ± 9.2
Ambrus	2015	282	10% (28)	APACHE III	91 ± 28/97 ± 32
Guenancia	2015	66	44% (29)	SAPS II	56 (45-71)/50 (39-57)
Gupta	2015	2018	12.6% (254)	APACHE II	19 (15-23)/16 (11-19)
Shaver	2015	1770	7% (123)	APACHE II	27 (21-33)/25 (20-31)
Klouwenberg	2016	1782	23.5% (418)	APACHE IV	89 (72-108)/74 (58-94)
Tseng	2016	285	21.8% (62)	APACHE II	18.6 ± 4.2/18.0 ± 5.1
Liu	2016	503	All 47.7% (240)	APACHE II	NR
			NeOAF to SR (31.1%)	APACHE II	22.8 ± 5.8/21.6 ± 5.5
			NeOAF to AF (14.9%)	APACHE II	24.6 ± 6.1/21.6 ± 5.5
Duarte	2017	430	11.2% (48)	APACHE II	19.2 ± 9.3/17.0 ± 8.2
Moss	2017	8356	9% (749)	OASIS	NR
			New subclinical AF	OASIS	30 (24-36)/26 (21-32)
			New clinical AF	OASIS	32 (28-38)/26 (21-32)
Duby	2017	506	4.1% (106)	ISS	20.5 ± 14.2/15.8 ± 10.9
Arrigo	2018	1841	12% (212)	SAPS II	NR
Fu	2018	1673	4.5% (75)	APACHE II	27.7 ± 8.3/23.4 ± 7.1

Wu et al (2020), Table 2, p 479

FIGURE 30 POOLED PREVALENCE OF NEW-ONSET AF



Wu et al (2020), Fig 2, p 480

Pooled analysis showed significant associations between new-onset AF with intensive care unit (ICU) mortality (OR 3.11; 95CI 2.45-3.96) and in-hospital mortality (OR 1.63; 95CI 1.27-2.08) compared to patients without AF. Both ICU and hospital length of stay were longer in patients with new-onset AF than those without AF (WMD = 1.87; 95CI 0.89-2.84 and WMD = 2.73; 95CI 0.77-4.69). Independent risk factors included increasing age, shock, sepsis, use of a pulmonary artery catheter and mechanical ventilation, fluid loading, and organ failure.

Bosch et al (2019) conducted a systematic review and meta-analysis to identify risk factors for new-onset atrial fibrillation during sepsis.²⁵⁹

The authors extracted the adjusted odds ratio for each risk factor associated with new-onset atrial fibrillation during sepsis. For risk factors present in more than one study, pooled odds ratios (meta-analysis) were calculated, risk factors were classified according to type and effect sizes were quantified. Before comparing sepsis-associated AF risk factors with risk factors for community-associated atrial fibrillation.

Forty-four factors were examined as possible risk factors for new-onset atrial fibrillation in sepsis, 18 of which were included in meta-analyses. Risk factors for new-onset atrial fibrillation included demographic factors, comorbid conditions, and most strongly, sepsis-related factors. Sepsis-related factors with a greater than 50% change in odds of new-onset atrial fibrillation included corticosteroid use, right heart catheterisation, fungal infection, vasopressor use, and a mean arterial pressure target of 80-85 mm Hg. Several cardiovascular conditions that are known risk factors for community-associated atrial fibrillation were not identified as risk factors for new-onset AF in sepsis.

²⁵⁹ Bosch, N. A., Cohen, D. M., & Walkey, A. J. (2019). Risk Factors for New-Onset Atrial Fibrillation in Patients With Sepsis: A Systematic Review and Meta-Analysis. *Critical care medicine*, 47(2), 280–7. August meeting 2022

The analysis shows that risk factors for new-onset atrial fibrillation during sepsis are mainly factors that are associated with the acute sepsis event and are not synonymous with risk factors for community-associated atrial fibrillation.

New-onset AF was associated with worse outcome in critically ill patients in another meta-analysis of critically ill patients in ICU.

Cohort studies

Sepsis is defined by life-threatening organ dysfunction during infection and is the leading cause of death in hospitals. During sepsis, there is a high risk that new onset of atrial fibrillation can occur, which is associated with significant morbidity and mortality.

Bashar et al (2021) presented a novel automated AF prediction algorithm for critically ill sepsis patients using ECG signals.²⁶⁰ From the heart rate signal collected from 5-min ECG, feature extraction is performed using the traditional time, frequency, and nonlinear domain methods. variable frequency complex demodulation and tunable Q-factor wavelet-transform-based time-frequency methods are applied to extract novel features from the heart rate signal.

Using a selected feature subset, several machine learning classifiers, including support vector machine (SVM) and random forest (RF), were trained using only the 2001 Computers in Cardiology data set. For testing the proposed method, 50 critically ill ICU subjects from the Medical Information Mart for Intensive Care (MIMIC) III database were used in this study. Using distinct and independent testing data from MIMIC III, the SVM achieved 80% sensitivity, 100% specificity, 90% accuracy, 100% positive predictive value, and 83.33% negative predictive value for predicting AF immediately prior to the onset of AF, while the RF achieved 88% AF prediction accuracy. When the authors analysed how far in advance it was possible predict AF events in critically ill sepsis patients, the algorithm achieved 80% accuracy for predicting AF events 10 min early. The algorithm outperformed a state-of-the-art method for predicting AF in ICU.

Brunetti et al (2021) examined the incidence, associated risk factors, and associated outcomes of new-onset atrial fibrillation (NOAF) in patients in the medical intensive care unit (MICU).²⁶¹

This single-centre retrospective observational cohort study included 2234 patients with MICU stays in 2018. An automated extraction process using ICD-10 codes, validated by a 196-patient manual chart review, was used for data collection. Demographics, medications, and risk factors were collected. Multiple risk scores were calculated for each patient, and AF recurrence was also manually extracted. Length of stay, mortality, and new stroke were primary recorded outcomes.

²⁶⁰ Bashar, S. K., Ding, E. Y., Walkey, A. J., et al. (2021). Atrial Fibrillation Prediction from Critically Ill Sepsis Patients. *Biosensors*, 11(8), 269.

²⁶¹ Brunetti, R., Zitely, E., Newman, N., et al. (2021). New-onset atrial fibrillation incidence and associated outcomes in the medical intensive care unit. *Pacing and clinical electrophysiology : PACE*, 44(8), 1380–6

241 patients of the 2234 patient cohort (11.4%) developed NOAF during their MICU stay. NOAF was associated with greater length of stay in the MICU (5.84 vs. 3.52 days, $p < .001$) and in the hospital (15.7 vs. 10.9 days, $p < .001$). Patients with NOAF had greater odds of hospital mortality (odds ratio (OR)1.92, 95CI 1.34-2.71) and 1-year mortality (OR 1.37, 95CI 1.02-1.82). CHARGE-AF scores performed best in predicting NOAF (area under the curve (AUC) 0.691, $p < .001$).

The incidence of NOAF in this MICU cohort was 11.4%, and NOAF was associated with a significant increase in hospital LOS and mortality, and the CHARGE-AF score performed best in predicting NOAF.

Lin et al (2021) evaluated temporal trends of atrial fibrillation prevalence in critically ill patients who received prolonged mechanical ventilation (MV) in the US.²⁶²

The authors used the 2008 to 2014 National Inpatient Sample to compute the weighted prevalence of AF among hospitalised adult patients on prolonged MV. Multivariable-adjusted models evaluated the association of AF with clinical factors, in-hospital mortality, hospitalization cost, and length of stay (LOS).

A total of 2,578,165 patients who received prolonged MV (21.27% of AF patients) were identified. The prevalence of AF increased from 14.63% in 2008 to 24.43% in 2014 (p trend < 0.0001). Among phenotypes of critically ill patients, the prevalence of AF increased in patients with severe sepsis, asthma exacerbation, congestive heart failure exacerbation, acute stroke, and cardiac arrest. Older age, male sex, white race, medicare access, higher income, urban teaching hospital setting, and Western region were associated with a higher prevalence of AF. AF in critical illness was a risk factor for in-hospital death (OR 1.13; 95CI 1.11-1.15), but in-hospital mortality in critically ill patients with AF decreased from 11.6% to 8.3%. AF was linked to prolonged LOS (2%, $p < 0.0001$) and high hospitalization cost (4%, $p < 0.0001$). LOS (-1%, $p < 0.0001$) and hospitalisation cost (-4%, $p < 0.0001$) decreased yearly.

The prevalence of comorbid AF is increasing, particularly in older patients. AF may lead to poorer prognosis, and high-quality intensive care is imperative for this population

Summary and conclusions

AF frequently complicates the course of critically ill patients, with an incidence ranging from 4 to 25% in non-cardio-surgical intensive care unit (ICU) patients to 32 to 50% in patients after cardiac surgery, and AF is the most frequent arrhythmia in patients with sepsis (Aibar & Schulman 2021). The mean incidence of new-onset AF in patients with sepsis is 20.6% (14.7% in retrospective studies and 31.6% in prospective). The prevalence of new-onset AF ranged from 4.1% to 46% in an analysis of new-onset atrial fibrillation in critically ill patients, based on 56 studies (Wu et al 2020).

²⁶² Lin, Z., Han, H., Guo, W., et al. (2021). Atrial fibrillation in critically ill patients who received prolonged mechanical ventilation: a nationwide inpatient report. *The Korean journal of internal medicine*, 36(6), 1389–1401.

Atrial fibrillation is the most common arrhythmia encountered in the ICU (Bosch et al 2018). Preexisting AF is prevalent among older patients with chronic conditions who are at risk for critical illness, whereas new-onset AF can be triggered by accelerated atrial remodelling and arrhythmogenic triggers encountered during critical illness. The acute loss of atrial systole and onset of rapid ventricular rates that characterise new-onset AF often lead to decreased cardiac output and hemodynamic compromise. Thus, new-onset AF is both a marker of disease severity as well as a likely contributor to poor outcomes.

Among survivors of critical illness, new-onset AF frequently resolves prior to discharge, and “secondary AF” has long been thought of as a self-limited event in patients in whom the AF trigger is transient (Bosch et al). However, emerging evidence suggests that AF following critical illness often recurs after resolution of the critical illness and that long-term outcomes following critical illness may be associated with arrhythmia persistence or reoccurrence. Risk factors for new-onset atrial fibrillation during sepsis are mainly factors that are associated with the acute sepsis event and are not synonymous with risk factors for community-associated atrial fibrillation. Risk factors for new-onset AF include advanced age, white race, male sex, obesity, history of cardiopulmonary disease, heart or respiratory failure, and higher disease severity score.

Sepsis is defined by life-threatening organ dysfunction during infection and is the leading cause of death in hospitals. During sepsis, there is a high risk that new onset of atrial fibrillation can occur, which is associated with significant morbidity and mortality. Bashar et al 2021 New-onset AF that occurs in the setting of sepsis could be associated with increased length of stay in ICU, long-term stroke risk, and mortality risk. The risk of ischaemic stroke among patients with new-onset AF during sepsis seems to be higher than in the general population with AF and higher than in patients with sepsis who do not have new-onset AF

Lin et al (2021) evaluated temporal trends of atrial fibrillation prevalence in critically ill patients who received prolonged mechanical ventilation (MV) in the US. A total of 2,578,165 patients who received prolonged MV (21.27% of AF patients) were identified. The prevalence of AF increased from 14.63% in 2008 to 24.43% in 2014 (p trend < 0.0001). Among phenotypes of critically ill patients, the prevalence of AF increased in patients with severe sepsis, asthma exacerbation, congestive heart failure exacerbation, acute stroke, and cardiac arrest.

Aoki et al suggested that systemic inflammation in sepsis may induce an electrophysiological substrate for AF, responsible for the high incidence of new-onset AF in septic patients. Most patients have classic AF risk factors, but new-onset AF in patients with septic syndromes may also be initiated by elevated levels of pro-inflammatory cytokines by activation of the catecholaminergic system, electrolyte alterations, and alteration in volume status during sepsis.

AF develops through a two-step process: creation of an arrhythmogenic substrate followed by a triggering event. During critical illness, both acute and chronic risk factors have roles in the development of AF. Prior to critical illness, chronic risk factors for AF may alter the normal atrial myocardium into an arrhythmogenic substrate predisposing to AF during critical illness. During critical illness, patients with both normal and arrhythmogenic atria can develop new-

onset AF in the setting of acute risk factors. Risk factors potentially lead to accelerated structural and electrical remodelling and may trigger AF through multiple mechanisms, including adrenergic stimulation.

Although critical illness-induced AF likely follows the development of a susceptible atrial substrate combined with a triggering event, the specific factors that contribute to the arrhythmogenic substrate and the specific triggers may differ from community-acquired AF. Emerging evidence suggests that acute events during critical illness accelerate cardiac remodelling and fibrosis to rapidly produce a susceptible atrial substrate, providing fertile ground for the development of sustained AF in response to the many arrhythmogenic triggers of critical illness.

It is concluded that in relation to atrial fibrillation and atrial flutter, there is evidence strong enough to support a judgement of a suggestive causal relationship with sepsis, or having a critical illness requiring admission to an intensive care unit (Grade 2). A consistent association has been observed between atrial tachyarrhythmias and sepsis or critical illness, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for critical illness should be retained in the RH and BoP SoPs. Specific mention of sepsis should be added to the factor, with a new definition being proposed. A cessation period of 30 days should be retained in both RH and BoP SoPs.

Autoimmune or inflammatory disease

Current factor

onset and worsening - RH only

having a specified autoimmune or inflammatory disease involving the atria of the heart at the time of the clinical onset of atrial fibrillation or atrial flutter;

"a specified autoimmune or inflammatory disease" means:

- (a) amyloidosis;
- (b) rheumatoid arthritis;
- (c) sarcoidosis;
- (d) scleroderma;
- (e) systemic lupus erythematosus; or
- (f) systemic sclerosis;

Summary of important issues

Autoimmune diseases (AIDs) are frequently systemic disorders, so cardiac involvement is common.

The topic of a submission request for this investigation was steroid administration for asthma and skin diseases. Some autoimmune cutaneous diseases associated with AF are considered in this section.

Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodelling. Chronic inflammation is the pathophysiological basis linking AD to autonomic dysfunction, including sympathetic overactivation and a decline in parasympathetic function. Autoantibody-mediated inhibitory effects of cellular events can lead to cardiac arrhythmia. Drug-induced arrhythmias, caused, by corticosteroids are also observed among autoimmune disease patients.

The most common AID linked to AF is rheumatoid arthritis. Other autoimmune diseases may be related to AF. Pujades-Rodriguez et al. (2020) investigated dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases in a population-based cohort study. Increased AF risk seen in patients with giant cell arteritis, polymyalgia rheumatica, inflammatory bowel disease and vasculitis, as well as rheumatoid arthritis and SLE.

Summary of previous investigation

Cardiac arrhythmias have been described to occur in the presence of several immunological and connective diseases. However, the aetiological role of autoimmune diseases in AF aetiology is unknown; and any identified association may operate through intermediary mechanisms such as underlying cardiomyopathy.

AF, among other arrhythmias, has been documented in clinical studies of patients with SLE, cardiac sarcoidosis, atrial amyloidosis and systemic sclerosis.

The overall incidence of atrial fibrillation has been documented to be about 40% higher in rheumatoid arthritis patients than general population in Danish cohort (Lindhardsen et al 2012). However, only a very limited number of small clinical studies have examined the occurrence of arrhythmias in these patients.

Coeliac disease was risk factor for later AF (HR 1.34; 95CI 1.24–1.44) in a cohort study (Emilsson et al 2011). The association was seen both before and after diagnosis and strongest around the time of diagnosis. If this is a causal relationship, then this suggests that immune-mediated disorders (such as coeliac disease) might increase the risk of AF, through an unknown mechanism.

Reviews

Because autoimmune diseases (ADs) are frequently systemic disorders, cardiac involvement is common. There have been several recent comprehensive review studies concerning autoimmune and inflammatory diseases and atrial fibrillation.²⁶³

²⁶³ Gawałko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.
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Gawałko et al. (2020) reviewed typical arrhythmias and their pathogenesis, arrhythmia-associated mortality, and possible treatment options among selected autoimmune diseases (ADs) (sarcoidosis, systemic lupus erythematosus, scleroderma, type 1 diabetes, Graves' disease, rheumatoid arthritis, ankylosing spondylitis [AS], psoriasis, celiac disease [CD], and inflammatory bowel disease [IBD]).²⁶⁴

Rhythm disorders have different underlying pathophysiologies; myocardial inflammation and fibrosis seem to be the most important factors. Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodelling. Chronic inflammation is the pathophysiological basis linking AD to autonomic dysfunction, including sympathetic overactivation and a decline in parasympathetic function. Autoantibody-mediated inhibitory effects of cellular events (i.e., potassium or L-type calcium currents, M2muscarinic cholinergic or β 1-adrenergic receptor signalling) can lead to cardiac arrhythmia. Drug-induced arrhythmias, caused, by corticosteroids, methotrexate, and chloroquine, are also observed among AD patients.

The most common arrhythmia in most autoimmune disease presentations is atrial arrhythmia (primarily atrial fibrillation), except for sarcoidosis and scleroderma, which are characterized by a higher burden of ventricular arrhythmia. Arrhythmia-associated mortality is highest among patients with sarcoidosis and lowest among those with AS; there are scant data related to mortality in patients with psoriasis, CD, and IBD

Ventricular tachycardia (VT) is the most rhythm disorder in sarcoidosis, encountered up to 23% of patients. Atrial arrhythmias are less common, occurring in 15–17% of patients, although small studies have reported a 32% risk of supraventricular arrhythmia. The most common observed supraventricular arrhythmia is atrial fibrillation (18%), followed by atrial tachycardias (7%), atrial flutter (5%), and atrioventricular nodal re-entry tachycardia (2%).

Postulated proarrhythmic mechanisms include active inflammation and enhanced automaticity. The re-entrant pathway can result from active granulomatous inflammation, but can also be found in association with the healing of cardiac granulomas in the inactive phase of the disease.

Atrial dilatation or pulmonary involvement contributes to the development of atrial arrhythmias. The role of corticosteroids remains inconsistent, because they can improve cardiac function and reduce a patient's arrhythmic burden, but they also promote fibrosis of active granulomas and subsequent re-entrant pathways, leading to recurrent ventricular tachycardia.

Sinus tachycardia (15–50%), AF, and atrial ectopic beats are the most frequent cardiac rhythm disorders in SLE patients. Teixeira et al, who studied 317 patients with SLE, observed frequent Holter-monitoring abnormalities in 85% of SLE patients, including supraventricular ectopy (63.4%), ventricular ectopy (45.8%), bradycardia (31.7%), atrial tachycardia (15.5%), and AF (2.8%).

²⁶⁴ Gawałko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.
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The pathophysiology of arrhythmias in SLE includes initial inflammatory cell infiltration and, as the disease advances, myocardial necrosis and fibrotic replacement. Consequently, multiple small areas of fibrosis can affect atrial and ventricular repolarization and conduction, leading to cardiac rhythm disorders

Catheter ablation seems to be safe in drug-resistant AF. However, dal Piaz et al reported frequent recurrences of AF that could be explained by the presence of thickening of the left atrial (LA) wall associated with extensive atrial fibrosis. Electro anatomical mapping frequently reveals large areas of low bipolar voltage in the anterior wall, septum, posterior wall, and roof (~52% of the LA surface).

Gawalko et al notes that the most frequent arrhythmia in RA patients is AF, especially in young (<50 years) females with sedimentation rates >60 mm/h or anti-TNF- α antibodies.²⁶⁵ In a Danish cohort study of 4,182,335 participants, including 18,247 with RA, the overall incidence of AF was 40% higher than in the general population (Lindhardsen et al 2012). However, in a subsequent meta-analysis of 3 retrospective cohort studies, the pooled risk ratio of developing AF in patients with RA vs. controls was only 1.29, because in 2 studies no increased risk of incident AF was observed after adjusting for comorbidity and medication (Ungprasert et al 2017).

The basis for rhythm disorder in RA is diffuse cardiac involvement (rheumatoid nodules or inflammatory lesions), as well as coronary vasculitis and coronary atherosclerotic disease, which lead to perfusion defects of the myocardium with proarrhythmic effects. Antibodies against the cardiac conduction system, found in 35% of patients with RA, which increase P-wave dispersion (PWD) and LA diameter, may play important an role in conduction abnormalities in RA patients.

Early therapy with disease-modifying anti-rheumatic drugs has been demonstrated to have beneficial effects on the lipid profile and to reduce atherosclerotic processes and endothelial dysfunction by decreasing inflammation. The success rate of catheter ablation for AF in patients with RA is comparable to that in patients without RA. However, RA patients tend to develop early atrial tachyarrhythmia recurrence after AF ablation.

Coeliac disease (CD), a life-long gluten-sensitive AD primarily involving the small intestine, has potential effects in other organ systems, genetically affecting susceptible individuals.²⁶⁶ The most common cardiac arrhythmia in CD is AF, with a reported incidence 30% higher than in the general population (Emilsson et al 2011). This increased risk of AF has been attributed to inflammation and fibrosis, the coexistence of other autoimmune conditions (T1D, RA, and thyroid disease), and hyperhomocysteinaemia, resulting from vitamin B deficiency, which affects sodium and potassium channels in the atria.

²⁶⁵ Gawalko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

²⁶⁶ Gawalko, M., Balsam, P., Lodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

Inflammatory bowel disease (IBD) is a chronic, inflammatory disease of the gastrointestinal tract and includes ulcerative colitis and Crohn's disease. AF represents the most common sustained cardiac arrhythmia among patients with IBD, and its incidence increases more than 2-fold during active flare-ups of IBD.²⁶⁷

The powerful inflammatory cytokines implicated in AF development are C-reactive protein (CRP) and IL-6. Studies suggest that IL-6 is significantly correlated with increased LA size by stimulating matrix metalloproteinase-2, whereas increased circulating CRP may localise in atrial tissue, inducing myocarditis and electrical changes in the atrium. PWD and electromechanical delay, well-described predictors of AF, are high in IBD patients.¹³⁸ These results confirm the significant decrease in parasympathetic function in patients with IBD as an important factor triggering arrhythmia.

Among other autoimmune diseases related to AF, psoriasis is a common chronic immune-mediated dermatological disease that increases the risk of cardiovascular disease. Psoriasis is a chronic inflammatory condition characterised by excessive growth of the epidermal layer of the skin and associated patches of abnormal, thickened skin. Patients with psoriasis are more susceptible to AF than the general population (Ungprasert et al 2016; Upala et al 2017) with a severity-adjusted risk of 1.50–2.98 in patients aged <50 years and 1.16–1.29 in those aged ≥50 years (Ahlehoff et al 2012).²⁶⁸

Chronic inflammation mediated by systemic inflammatory cytokines, such as TNF- α , IL-6, and IL-17, is the most important contributor linking psoriasis to increased AF incidence. Another structural remodelling factor with increased bioactivity in psoriasis is platelet-derived growth factor α (PDGF α), which promotes cell proliferation and collagen expression in cardiac fibroblasts.

Sympathetic nervous system dysregulation, inflammation-related structural mitral valve changes, and depression may contribute to the high incidence of AF among those with psoriasis. Statins, with anti-inflammatory and antioxidative effects, also reduce the incidence of both AF and psoriasis.

Upala et al (2017) conducted a systematic review and meta-analysis to evaluate the association between psoriasis and AF from prospective observational studies.²⁶⁹

A comprehensive search of the databases of the MEDLINE and EMBASE was performed from inception through November 2015. The inclusion criterion was the prospective observational study that assessed the risk of new-onset atrial fibrillation in adults with psoriasis. Outcome was the adjusted hazard ratio (HR) of atrial fibrillation comparison between patients with psoriasis and controls. Pooled HR were calculated using a random-effects model.

²⁶⁷ Gawałko, M., Balsam, P., Łodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

²⁶⁸ Gawałko, M., Balsam, P., Łodziński, P., et al. (2020). Cardiac Arrhythmias in Autoimmune Diseases. *Circulation journal*, 84(5), 685–94.

²⁶⁹ Upala, S., Shahnawaz, A., & Sanguankeo, A. (2017). Psoriasis increases risk of new-onset atrial fibrillation: a systematic review and meta-analysis of prospective observational studies. *The Journal of dermatological treatment*, 28(5), 406–10.

Fifteen articles underwent full-length review and data were extracted from 4 observational studies. Incidence of atrial fibrillation was ascertained by cardiologist-reviewed ECGs. There was a significant increased risk of new-onset atrial fibrillation in patients with psoriasis compared to controls with a pooled HR 1.42 (95CI 1.22-1.65).

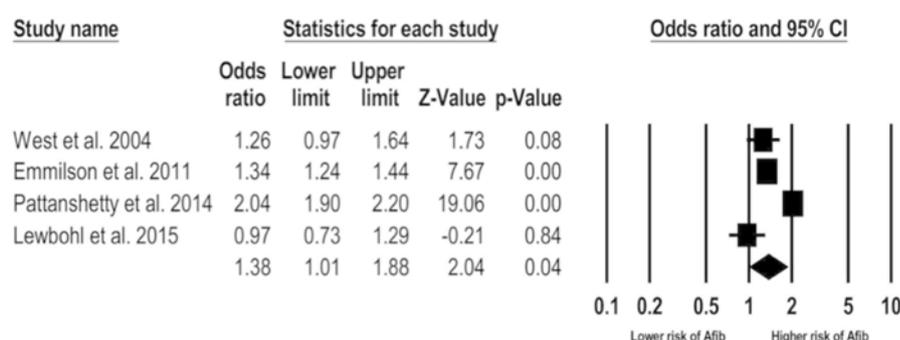
Meta-analyses

Coeliac disease is an autoimmune condition. This inflammatory state predisposes patients to develop AF. Several studies have found coeliac disease may be associated with a variety of cardiac manifestations. Atrial fibrillation is one of the most common arrhythmias that can cause significant morbidity. However, the risk of atrial fibrillation in patients with coeliac disease according to epidemiological studies remains unclear. **Hidalgo et al (2020)** conducted a meta-analysis to assess the risk of atrial fibrillation in patients diagnosed with celiac disease compared to controls.²⁷⁰

A systematic literature review was conducted in MEDLINE, EMBASE, Cochrane databases from inception to 2017 to identify studies that evaluated the risk of atrial fibrillation in patients with celiac disease. included randomized controlled trial, cross sectional and cohort studies that reported the odds ratio, relative risk, hazard ratio, and standardized incidence ratio comparing the risk of developing atrial fibrillation among patients with celiac disease, versus patients without celiac disease as control. The Newcastle-Ottawa scale was used to determine the quality of the studies. Effect estimates from individual studies were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird.

After a review of the literature, four observational studies with 64,397 participants were enrolled. The association between coeliac disease and increased risk of atrial fibrillation was significant, with a pooled OR of 1.38 (95CI 1.01-1.88). No publication bias as assessed by the funnel plots and Egger's regression asymmetry test with $p = 0.54$. However, the heterogeneity of the included studies was high ($I^2 = 96$).

FIGURE 31 OR FOR AF IN PATIENTS WITH COELIAC DISEASE



Hidalgo et al (2020), Fig 3

²⁷⁰ Hidalgo, D. F., Boonpheng, B., Nasr, L., et al. (2020). Celiac Disease and Risk of Atrial Fibrillation: A Meta-analysis and Systematic Review. *Cureus*, 12(2), e6997. August meeting 2022

A significant association between coeliac disease and risk of atrial fibrillation was reported in this study. There is a 38% increased risk of atrial fibrillation. Additional studies are needed to clarify the mechanistic link between atrial fibrillation and celiac disease. Some limitations of this study are that all were observational studies, some were medical registry-based and there was high heterogeneity between studies.

Many studies have supported the role of the immune system in the pathophysiology of AF in patients with CD. Inflammation and oxidative stress have been found to be responsible of many molecular mechanisms of CD including activation of immune cells such as macrophages, T and B cells, neutrophils and inflammatory cytokines (IL-6, TNF- α). These cytokines and activated immune cells could affect the contractility and electrical myocytes stability inducing fibroblast activation and cellular fibrosis. These atrial changes provide re-entrant arrhythmias confirmed clinically and through ECG.

Ma et al (2021) assessed the risk of AF in inflammatory arthritis patients.²⁷¹ The authors systematically searched cohort studies regarding the risk of AF in patients with rheumatoid arthritis, or spondyloarthritis through PubMed, Web of Science, Cochrane Library, Clinical Trials Registry, and China National Knowledge from inception to August 1, 2019. Meta-analysis was performed using fixed effect model, estimating both crude and adjusted hazard ratios (HRs). Subgroup analysis and meta-regression based on geographic characteristics, comorbidities, and medication use were conducted to explore the source of heterogeneity.

The literature search identified 388 potentially relevant studies, and five studies containing seven cohorts of rheumatoid arthritis or spondyloarthritis were included in the meta-analysis. The AF risk of inflammatory arthritis patients was significantly increased compared with health controls (HR 1.42, 95CI 1.36-1.49), and the pooled HR of studies adjusted factor, like demographic characteristics, medications use, and comorbidities, was 1.37 (95CI 1.29 -1.46).

It was concluded that patients with inflammatory arthritis have increased risk of AF, probably due to the underlying chronic inflammation. Although various confounders have been adjusted like medications use and comorbidities, the risk of AF is still significantly increased in inflammatory arthritis patients.

Zuin et al (2020) investigated the prevalence of AF in inflammatory bowel disease (IBD) patients and to estimate the risk of AF in these patients in a systematic literature review and meta-analysis.²⁷² A literature search based on Cochrane Library, Embase, PubMed and Google scholar were performed to locate articles regarding the occurrence of AF in IBD patients published through November 2019. English language articles were included if they reported data regarding patients with confirmed diagnosis of IBD and AF and reported data regarding the prevalence of AF. Quality of the included studies was assessed using the Newcastle–Ottawa quality assessment scale (NOS).

²⁷¹ Ma, Y., Pan, Z., Fan, D., et al (2021). The increased risk of atrial fibrillation in inflammatory arthritis: a systematic review and meta-analysis of cohort studies. *Immunological investigations*, 1–13

²⁷² Zuin M, Zuliani G, Rigatelli G, et al (2020). Atrial fibrillation in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Eur J Intern Med.*; 76:120–2.

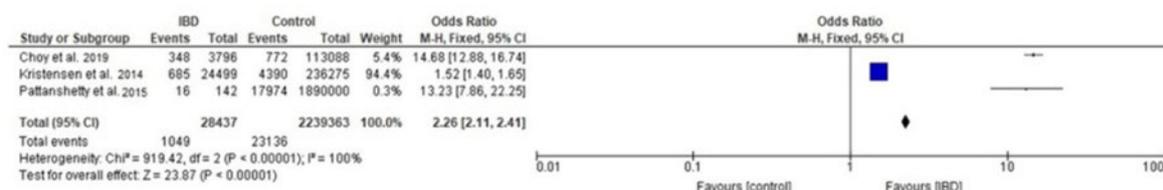
Continuous variables were expressed as mean ± standard deviation (SD) while categorical variables, were presented as proportions. Data were pooled using the Mantel–Haenszel random effects models. Statistical heterogeneity between groups was measured using the Higgins I2 statistic.

A total of 67 articles were retrieved after excluding duplicates. After evaluation of the full-text articles, 36 articles including editorial/letter, reviews, case reports, and investigations not in English language were excluded. ultimately 3 articles were included into the analysis. Two of were classified as high quality and one was moderate quality.

The final population included 429.624 patients (62.287 IBD and 367.337 controls patients) enrolled between 2001 and 2014. No evidence of publication bias using the Begg rank correlation method were observed. Among IBD patients, 1049 (1.6%) had AF. the prevalence of AF resulted significantly higher in all IBD cohorts reviewed compared to controls groups ($p < 0.001$ for all). IBD patients had a significant higher risk of AF compared to controls (OR 2.26; 95CI 2.11–2.41] with a high degree of heterogeneity between the studies ($I^2 = 100\%$). both CD (OR 1.34; 95CI 1.16–1.53) and UC patients (OR 1.51; 95CI 1.40–1.63) were at higher risk of AF.

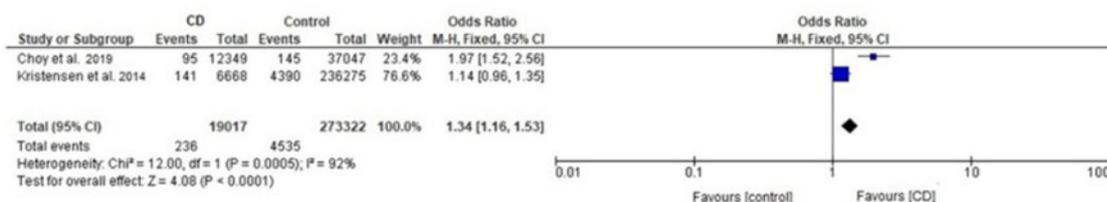
The results suggest that IBD patients had a 2.2-fold increased risk of AF compared to controls.

FIGURE 32 RISK OF ATRIAL FIBRILLATION (AF) IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) COMPARED TO CONTROLS



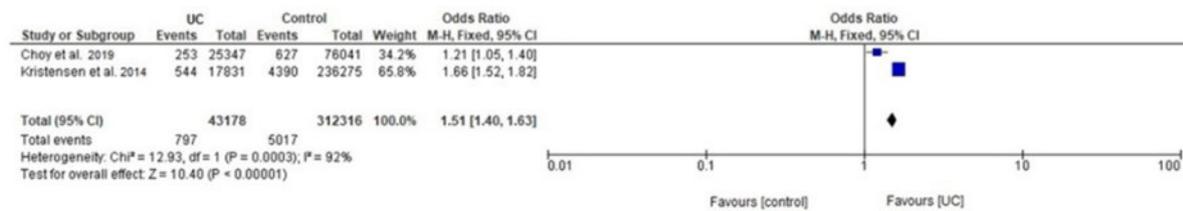
Zuin et al (2020), Fig 1B

FIGURE 33 RISK OF AF IN PATIENTS WITH CROHN'S DISEASE COMPARED DO CONTROLS



Zuin et al (2020), Fig 1C

FIGURE 34 RISK OF AF IN PATIENTS WITH CROHN'S DISEASE COMPARED DO CONTROLS



Zuin et al (2020), Fig 1D

The pathophysiological mechanisms linking AF and IBD patients have not been completely clarified, this association likely involves the CD40/CD40L co-stimulatory pathway which is activated in IBD tissue while its levels are significantly higher in non-valvular atrial fibrillation.

The meta-analysis had several limitations related to the observational nature of the studied reviewed with all inherited biases. Few investigations have analysed the link between AF and IBD, limiting the number of the studies included into the meta-analysis. The degree of increased risk of AF was largely due to a study having >90% of weight. high heterogeneity observed, due largely to inclusion criteria and study design, may have resulted in relatively weak conclusions

Patients with rheumatoid arthritis (RA) might be at an increased risk of developing atrial fibrillation as a result of deleterious effects of inflammatory cytokines on cardiomyocytes. This study aimed to comprehensively review all available evidence to further characterize this possible association.

Unprasert et al (2017) conducted a systematic review and meta-analysis of cohort studies that reported relative risk, hazard ratio, incidence ratio or standardized incidence ratio with 95% confidence intervals comparing the risk of incidence of AF in patients with RA versus non-RA participants.²⁷³ Pooled risk ratio were calculated using random-effect, generic inverse-variance methods of DerSimonian and Laird.

Three retrospective cohort studies with 39 912 cases of RA and 4 269 161 non-RA controls were included in the data analysis. Two of the three studies revealed an increased risk of AF among patients with RA, while the other study revealed no difference between the two groups.

²⁷³ Unprasert P, Srivali N, Kittanamongkolchai W. (2017). Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Int J Rheum Dis*; 20: 434–41.

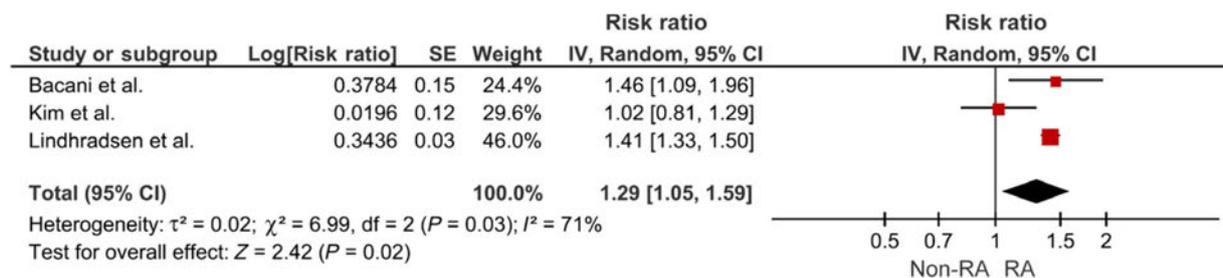
TABLE 15 MAIN CHARACTERISTICS OF INCLUDED STUDIES IN THE META-ANALYSIS

	Lindhardsen <i>et al.</i> ¹¹	Kim <i>et al.</i> ¹²	Bacani <i>et al.</i> ¹³
Country	Denmark	USA	USA
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort
Year	2012	2014	2015
Case	All patients who were first diagnosed with RA from 1997 to 2009. Cases were identified from the Danish national patient register which covered the entire Danish population. Cases with diagnosis of AF before the diagnosis of RA were excluded from the study	All patients who were diagnosed with RA from January 1, 2001 to June 30, 2008. Cases were identified from the HealthCore Integrated Research Database, a commercial health plan which covered 28 million fully-insured subscribers across the USA. Cases with diagnosis of any arrhythmia and cases with prescriptions for anticoagulants or anti-arrhythmic drugs in the 12-month period prior to the diagnosis of RA were excluded from the study	All residents of Olmsted county, Minnesota, USA who were first diagnosed with RA from January 1, 1980 to December 31, 2007. Cases were identified from the database of Rochester Epidemiology Project. Cases with diagnosis of AF before the diagnosis of RA were excluded from the study
Diagnosis of RA	Diagnostic code from the database plus at least one prescription for DMARDs within 1 year prior or after the diagnosis of RA	Diagnostic code from the database plus at least one prescription for DMARDs. Cases must have at least two visits coded for RA	Cases were identified by diagnostic codes from the database. The diagnosis was then verified by chart review to ensure that cases fulfilled at least four of the seven ACR 1987 classification criteria for RA
Control group	The rest of the Danish population who did not have AF at the start of the study (January 1, 1997)	Sex, age and index date matched, randomly selected from the same database. Controls must never have a diagnosis of any arrhythmia and did not have prescriptions for anticoagulants or anti-arrhythmic drugs in the 12-month period prior to the index date	Sex and age matched, randomly selected from the same database. Controls must never have a diagnosis of AF prior to the index date
Diagnosis of AF	Inpatient diagnostic code from the database	Inpatient or outpatient diagnostic code from the database plus at least one dispense of anticoagulants within 30 days of the diagnosis	The medical records of each cohort were electronically cross-matched with a database of ECG. The diagnosis of AF was made base on cardiologist interpretation of ECG
Follow-up	Until occurrence of the study endpoint, death, emigration out of the system or December 31, 2009	Until occurrence of the study endpoint, death, loss of health plan coverage or June 30, 2008	Until death, emigration out of the system or December 31, 2008
Number of cases	18 247	20 852	813
Number of controls	4 164 088	104 260	813
Mean age for cases/controls, years	52.4/45.6	51.9/51.9	55.9/55.9
Percentage of females for cases/controls	69.7/50.9	74.0/74.0	68.0/68.0

Ungrasert et al (2017), Table 1, p 438

The pooled analysis demonstrated a statistically significantly increased risk of subsequent development of AF in patients with RA compared to non-RA participants with the pooled RR of 1.29 (95CI 1.05–1.59). The individual RRs from each study were adjusted for age, sex, medications and co-morbidities. The result of the study by Bacani et al. was also adjusted for smoking. The statistical heterogeneity was moderate with an I2 of 71%.

FIGURE 35 FOREST PLOT OF META-ANALYSIS



Ungprasert et al (2017), Fig 2

The meta-analysis demonstrated a statistically significant increased risk of subsequent development of AF among patients with RA. The association might be non-causal and result from confounding by, for example by smoking is an established risk factor for both RA and AF. CAD and congestive heart failure (CHF), both strong risk factors for AF, are more prevalent among patients with RA than the general population. Inflammation from RA could play a direct role in the initiation and perpetuation of AF. The meta-analysis could not conclude that RA itself or other potential confounders, such as smoking and use of non-steroidal anti-inflammatory medications are responsible for the increased incidence of AF. There was a risk of detection bias, as RA patients might undergo more medical investigations, including ECGs, leading to a higher likelihood of AF detection.

Ankylosing spondylitis (AS) is a rheumatological disorder characterised by inflammatory involvement of the sacroiliac and spinal joints and a marked association with human leukocyte antigen (HLA)-B27. One study reported is a 25% increased risk of cardiovascular disease (CVD) in valvular heart disease, ischaemic heart disease, congestive heart failure and other cardiovascular diseases in AS patients [3]. Recent research has confirmed the effects of systemic inflammation in AS on different parts of the heart such as cardiac valves, conduction system, myocardium and vessels that can result in cardiovascular disturbances. Some studies have suggested an increased risk of cardiac conduction abnormalities in AS patients; but the magnitude of the risk contributed by AS is unclear.

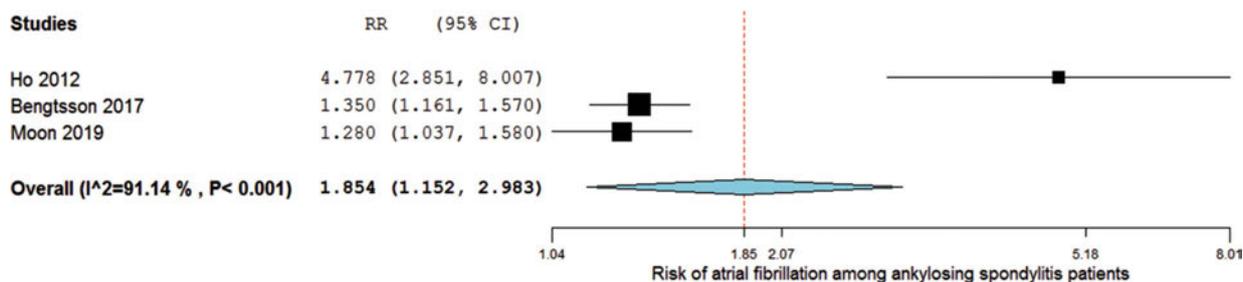
Morovatdar et al. (2021) assessed the association between ankylosing spondylitis (AS) and risk of heart conduction disorders and arrhythmia in a meta-analysis.²⁷⁴

PubMed, Embase, and Web of Science databases were systematically searched for observational studies that investigated the association between AS and risk of heart conduction disorders and arrhythmia with no language or date restrictions until September 16, 2019. The authors used random and fixed-effects models to pool the results of the studies. Publication bias was assessed by Egger's test. Subgroup analysis was carried out based on the study design. A p-value < 0.05 was considered significant. Comprehensive Meta-Analysis (CMA) software was used to perform meta-analysis.

²⁷⁴ Morovatdar, N., Watts, G. F., Bondarsahebi, Y., et al. (2021). Ankylosing Spondylitis and Risk of Cardiac Arrhythmia and Conduction Disorders: A Systematic Review and Meta-analysis. *Current cardiology reviews*, 17(5), e150521193326.

The authors reviewed 135 articles. included seven articles in the meta-analysis, of which four studies reported AV block and any conductive abnormality and three focused on atrial fibrillation and any arrhythmia. Based on random-effect model, an increased risk of atrial fibrillation (RR: 1.85, 95CI 1.15-2.98) was found in AS subjects compared to the general population. Egger’s test found no publication bias (p=0.2).

FIGURE 36 FOREST PLOT SHOWING THE ASSOCIATION BETWEEN ANKYLOSING SPONDYLITIS AND RISK OF ATRIAL FIBRILLATION



Morovatdar et al. (2021), Fig 3

Based on fixed-effect model meta-analysis, no association was observed between the risk of conductive disorders and AS (OR 0.64, 95CI 0.38-1.06). No publication bias was found by Egger’s test (p=0.6).

The systematic review and meta-analysis showed an increased risk of AF in AS patients. This was the first study that systematically investigated associations between AS and the arrhythmia, AF, AV block or conduction disorders.

Ankylosing spondylitis, as a chronic inflammatory rheumatic disease, is associated with a number of cardiovascular conditions. Inflammation is a major contributor to arrhythmia occurrence. Several inflammatory factors, such as interleukin (IL)-2, IL-6, IL-8, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF- α), have been reported to be associated with the pathogenesis of AF.

In a prospective cohort study conducted in Korea, AS patients receiving TNF inhibitor (TNFi) had a higher risk of AF development than with those not receiving TNFi [Moon et al 2019]. This finding could be related to a higher severity in these patients for whom non-steroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modifying anti-rheumatic drugs could not control the disease symptoms. These results support an association between inflammation and AF.

Cohort studies

Behçet’s disease (BD) is a chronic and multi-systemic vascular inflammatory disorder affecting mucocutaneous, genital, ocular, and vascular organ systems along with others. Although BD has been linked to various inflammation-related disorders, its association with AF has not

been established.. **Lee et al (2019)** conducted population-based study to determine the risk of AF in patients with BD.²⁷⁵

A total of 6636 newly diagnosed BD patients without a history of AF were included from the Korean National Health Insurance Service database between 2010 and 2014. Newly diagnosed non-valvular AF was identified using the claims data. An age- and sex-matched non-BD subjects were extracted at a ratio of 1:5 (n = 31,040). The incidence and risk of AF were compared between groups.

During a mean follow-up of 3.6 ± 1.5 years, AF was newly diagnosed in 173 patients (51 in the BD group, 122 in the control group). The incidence was 2.3 and 1.1 per 1000 person-years, respectively. After adjustment, the BD group showed a 1.8-fold higher risk of AF compared to the control group.

The effect of BD on AF risk was more prominent in young men (≤ 40 years) than older men (≥ 65 years). Ageing did not exert additional risk or synergistic effect on AF incidence in BD patients. This suggests a non-aging related cause could be the direct link between BD and AF pathology Men with BD had a 2.5-fold increased risk of AF, whereas women with BD did not. Severe BD had a higher risk for AF compared to non-severe BD and controls.

BD was associated with an increased risk of AF, particularly in men and young patients. This study corroborates other reports by the same group which established a higher incidence of AF with inflammatory bowel disease and ankylosing spondylitis using the Korean National Health Insurance Service database.

Several potentially useful biochemical data were not available at the time of analysis. Levels of the sensitive inflammatory biomarkers such as C-reactive protein (CRP), IL-6, etc. in BD patients were not measured; therefore, the correlation between AF incidence and the inflammatory status and severity of BD cannot be directly established.

The study provided limited insights into the causative mechanisms underlying AF development as a consequence of BD. A previous study showed that the left atrial volume (a predictor of AF) was increased in BD patients, suggesting the structural remodelling caused by BD could provide a re-entry substrate for AF development.²⁷⁶

Atopic dermatitis is characterised by chronic inflammation, which is a risk factor for atrial fibrillation. **Schmidt et al (2020)** examined the association between hospital-diagnosed atopic dermatitis and atrial fibrillation.²⁷⁷

²⁷⁵ Lee, E., Choi, E. K., Jung, J. H., et al (2019). Increased risk of atrial fibrillation in patients with Behçet's disease: A nationwide population-based study. *International journal of cardiology*, 292, 106–11.

²⁷⁶ Suryavanshi, S. V., & Li, N. (2019). Behçet's disease: A (silk) route to atrial fibrillation?. *International journal of cardiology*, 293, 117–8.

²⁷⁷ Schmidt, S., Olsen, M., Schmidt, M., et al (2020). Atopic dermatitis and risk of atrial fibrillation or flutter: A 35-year follow-up study. *Journal of the American Academy of Dermatology*, 83(6), 1616–24
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Using linked population-based Danish registries, people with an inpatient or outpatient hospital diagnosis of atopic dermatitis during 1977-2013 were identified and a comparison cohort individually matched to the atopic dermatitis cohort. The cohorts were followed until death, emigration, atrial fibrillation diagnosis, or end of study (January 2013). The authors compared 35-year risk of atrial fibrillation and estimated hazard ratios with 95% confidence intervals using Cox regression, adjusting for birth year and sex. The authors validated 100 atopic dermatitis diagnoses from a dermatological department through record review.

The study included 13,126 persons with atopic dermatitis and 124,211 comparators and followed them for a median of 19.3 years. The 35-year risk of atrial fibrillation was 0.81% and 0.67%, respectively. The positive predictive value of atopic dermatitis diagnoses was 99%. The hazard ratio was 1.2 (95CI 1.0-1.6) and remained increased after adjusting for various atrial fibrillation risk factors.

Analyses were limited to persons with moderate-to-severe atopic dermatitis, and there was no lifestyle data.

Several recent studies have suggested a positive association between IBD and AF [Pattanshetty et al 2015), and that patients with IBD have a higher risk of developing AF, especially during the active stage of IBD (Kristensen et al 2014).²⁷⁸ Using a population-based cohort study, Choi et al (2019) identified 1,120 AF cases. Multivariable Cox regression indicated that patients with IBD had a 36% higher risk of AF than controls. A systematic review and meta-analysis suggested that compared to controls, IBD patients were at a 2.2-fold increased risk of developing AF [Zuin et al 2020].²⁷⁹

This increased risk of AF in IBD, although not entirely understood, has been proposed to have different underlying pathophysiologies. Myocardial inflammation and fibrosis seem to be the pivotal factor. Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodelling. Other than idiopathic electrophysiological abnormalities, left atrial volume and mechanical function degeneration were detected using echocardiography in patients with UC, indicating that structural changes also could lead to the development of AF. Various pathological processes such as oxidative stress, fibrosis, and apoptosis, are involved in the systemic inflammation of IBD and lead to structural and electrical remodeling of the atria, which may contribute to the development of AF.

Despite growing evidence indicating that patients with inflammatory bowel disease have an increased risk of atrial fibrillation, owing to the potential biases of confounding effects and reverse causation, the specific relationship between IBD and AF remains controversial.

Chen et al (2021) conducted a two-sample Mendelian randomisation (MR) study to determine whether there is a causal effect of IBD on AF.²⁸⁰

²⁷⁸ Chen, L., Fu, G., & Jiang, C. (2021). Mendelian randomization as an approach to assess causal effects of inflammatory bowel disease on atrial fibrillation. *Aging*, 13(8), 12016–30.

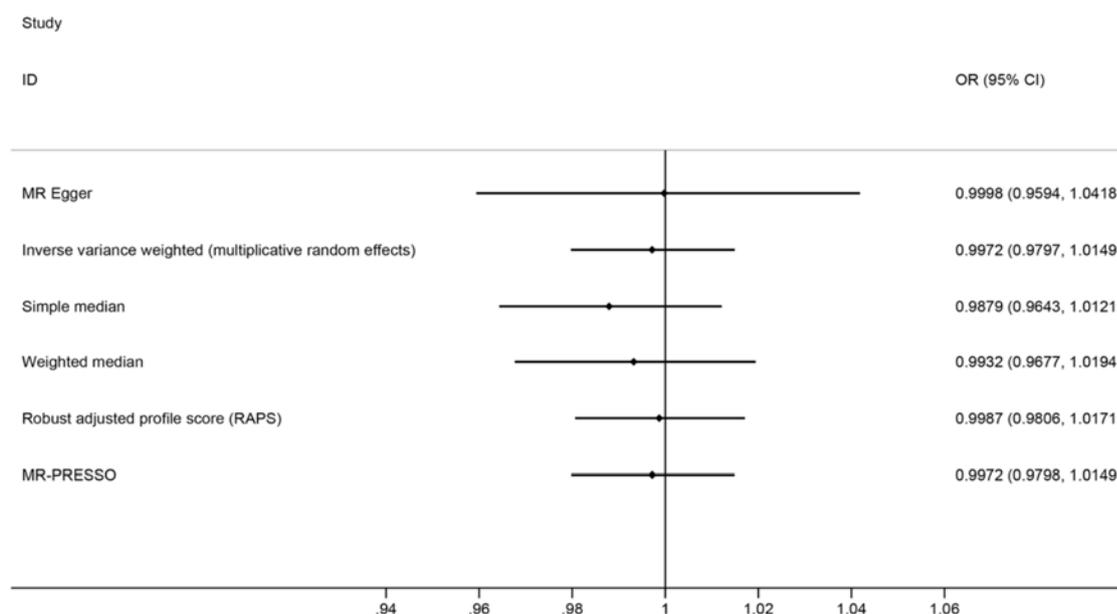
²⁷⁹ Zuin M, Zuliani G, Rigatelli G, et al (2020). Atrial fibrillation in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Eur J Intern Med.*; 76:120–22.

²⁸⁰ Chen, L., Fu, G., & Jiang, C. (2021). Mendelian randomization as an approach to assess causal effects of inflammatory bowel disease on atrial fibrillation. *Aging*, 13(8), 12016–30.

Statistical summaries for the associations between single nucleotide polymorphisms (SNPs) and traits of interest were obtained from independent consortia with European populations. The dataset of IBD was acquired from genome-wide association studies (GWAS), including more than 75,000 cases and controls. A GWAS with 60,620 AF cases and 970,216 controls was used to identify genetic variation underlying AF. The causal effect was estimated using the multiplicative random effects inverse-variance weighted method (IVW), followed by sensitivity analysis.

There is a lack of evidence to suggest an association between genetic predisposition to IBD and AF. As the primary estimator, the multiplicative random effect IVW model showed that genetic predisposition to IBD was not associated with the risk of AF (OR 0.9972, 95CI 0.9797-1.0149, $p = 0.75$). A null association was also observed using the MR-Egger (OR 0.9998, 95CI 0.9594-1.0418,), simple median (OR 0.9879, 95CI 0.9643 -1.0121) weighted median (OR 0.9932, 95CI 0.9677-1.0194), RAPS (OR 0.9987, 95CI 0.9806 -1.0171) and MR-PRESSO methods (OR 0.9972, 95CI: 0.9798 1.0149,).

FIGURE 37 MENDELIAN RANDOMISATION ESTIMATES OF THE CAUSAL EFFECT OF INFLAMMATORY BOWEL DISEASE ON ATRIAL FIBRILLATION



Chen et al (2021), Fig 1

There was no evidence of substantial heterogeneity in the IVW analysis and the MR-PRESSO global test of heterogeneity also demonstrated the same result. MR-Egger regression showed no evidence of directional pleiotropy for the association between the included SNP and the risk of AF. The funnel plot showed no evidence of heterogeneity across estimates. The results of leave-one-out sensitivity analysis showed that the null association between genetic predisposition to IBD and AF was not strongly affected by any individual SNP.

Using 81 SNPs, there was no evidence of an association between genetically predicted IBD and risk of AF with multiplicative random-effects IVW MR analysis (OR 1.0000, 95CI 0.9994 1.0005, $p = 0.88$).

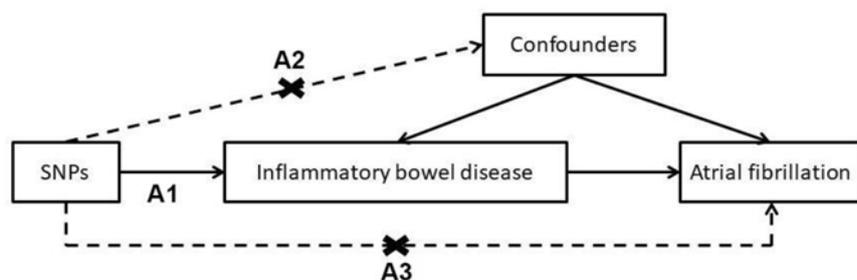
In contrast to most recent evaluations, no substantial evidence was found to support a causal role of genetically mediated IBD in the development of AF.²⁸¹

In this study, MR analysis was performed to control potential confounders and avoid reverse causation. MR analysis did not provide sufficient evidence to support a causal effect of IBD on the risk of AF. The lack of a genetic causal effect of IBD with the risk of AF suggested that the positive linkage between the presence of IBD and the risk of developing AF demonstrated in previous observational studies may have been the residual confounding due to common risk factors.

There were reported that several patients with IBD had incidences of AF after taking azathioprine, indicating that medication may be a potential confounder for the association between IBD and AF.

The null association could be explained by several interpretations, there may be insufficient power to support a significant association between IBD and AF. The MR analysis had 80% power to detect small effect sizes for the development of AF. However, a very small effect of IBD on AF could not be excluded. IBD susceptibility variants tended to be associated with both higher and lower risk of AF, which may cancel the causal effect, resulting in a null association. However, leave-one-out sensitivity analysis showed that the null association was not remarkably affected by any individual SNP. Some individuals in the datasets for IBD may have been taking medication, which may distort the relationship between IBD and AF.

FIGURE 38 CONCEPTUAL FRAMEWORK FOR MENDELIAN RANDOMISATION ANALYSIS OF INFLAMMATORY BOWEL DISEASE AND RISK OF ATRIAL FIBRILLATION.



Chen et al (2021), Fig 5

Sparse data are available regarding the trends of cardiovascular diseases and complications in rheumatoid arthritis (RA). **Bandyopadhyay et al. (2021)** conducted a National Inpatient Sample database analysis to demonstrate the trends of cardiac complications in patients with RA.²⁸²

The authors used National Inpatient Sample data from 2005 to 2014 to identify admissions with the diagnosis of RA and identified who had associated cardiovascular complications. The International Classification of Diseases-9th Revision-Clinical Modification codes were used for

²⁸¹ Chen, L., Fu, G., & Jiang, C. (2021). Mendelian randomization as an approach to assess causal effects of inflammatory bowel disease on atrial fibrillation. *Aging*, 13(8), 12016–30.

²⁸² Bandyopadhyay, D., Banerjee, U., Hajra, A., et al. (2021). Trends of Cardiac Complications in Patients With Rheumatoid Arthritis: Analysis of the United States National Inpatient Sample; 2005-2014. *Current problems in cardiology*, 46(3), 100455

the diagnoses of RA; congestive heart failure (CHF), acute myocardial infarction (AMI), and atrial fibrillation (AF).

A total of 774,808 (unweighted) RA hospitalizations were identified in the NIS database between 2005 and 2014. During this period, the trends of CVD complications, such as AMI, CHF, and AF were found to be statistically significant ($P < 0.05$)

A statistically significant increasing trend of AMI, CHF, and AF was found. In multivariate analysis, independent predictors of mortality in patients of RA with concomitant AF were age (OR 1.02, 95CI 1.015-1.025;), race (non-white vs white) (OR 1.16, 95CI 1.02-1.31), HTN (OR 0.62, 95CI 0.57-0.68), DM (OR 0.90, 95CI 0.82-1.0;), COPD (OR 1.56, 95CI 1.42-1.71), PAD (OR 1.34, CI 1.16-1.53), cerebrovascular disease (OR 2.27, 95CI 2.0-2.58), renal disease (OR 1.60, 95CI 1.44-1.79), and smoking (OR 0.80, 95CI 0.66-0.98).

Overall, the number of AF complications in RA patients significantly increased over the 10 years ($P < 0.001$).

A population-based study by Bacani et al in Minnesota showed an increased risk for AF in RA patients. Chronic inflammation in RA has been implicated in the development of AF. Patients with RA are known to have an increased prevalence of diastolic dysfunction, and this can be associated with the occurrence of AF. Other potential risk factors for the development of AF in RA patients include severe extra-articular RA, use of cox-2 inhibitors, and increased atherosclerosis. A meta-analysis involving 39,912 patients of RA supports the increased risk of AF in RA individuals. Bandyopadhyay found 14.6% of patients with the diagnosis of AF. In patients of RA with AF, independent predictors of mortality were advancing age, HTN, DM, COPD, PAD, cerebrovascular disease, renal disease, and smoking.

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, associated with a number of cardiovascular diseases. **Moon et al (2019)** investigated whether AS increases the risk of atrial fibrillation in a nationwide population-based study.²⁸³ A total of 14,129 patients newly diagnosed with AS (mean age 41.8 ± 15.3 years, 72% male) were recruited from the Korean National Health Insurance Service database between 2010 and 2014 and followed up for new onset AF. Age- and sex-matched non-AS subjects (1:5, $n = 70,645$) were selected and compared with the AS patients.

During a mean follow-up of 3.5 years, AF was newly diagnosed in 486 patients (114 patients of the AS group). The AS patients developed AF more frequently than the non-AS subjects (2.32 vs. 1.51 per 1000 person-years). In multivariate Cox regression analysis, AS was an independent risk factor for AF (HR 1.28, 95CI 1.03–1.58). The AS with tumour necrosis factor inhibitor (TNFi) therapy group showed higher risk for AF (HR 1.60, 95CI 1.02–2.39). In younger AS patients of (<40 years), the risk for AF was three times higher than patients at same age in the non-AS group. AS was an independent risk factor for AF in men (HR 1.53, 95CI 1.18–1.95), but not in women (HR 1.42, 95CI 0.94–2.08).

²⁸³ Moon I, Choi EK, Jung JH, et al.(2019). Ankylosing spondylitis: A novel risk factor for atrial fibrillation - A nationwide population-based study. *Int J Cardiol*; 275: 77-82
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Bengtsson et al. (2018) described the incidence of atrial fibrillation and other arrhythmias in patients with ankylosing spondylitis (AS), undifferentiated spondyloarthritis (uSpA) and psoriatic arthritis (PsA) compared with the general population (GP) and with each other.²⁸⁴

A prospective nationwide study with cohorts of patients with AS (n=6448), PsA (n=16 063) and uSpA (n=5190) and a GP (n=2 66 435) cohort, identified in 2001–2009 in the Swedish National Patient and Population registers. Follow-up began in January 2006 and ended at event, death, emigration or end of 2012. Age-standardised and sex-standardised incidence rates and hazard ratios (HRs) were calculated.

The highest incidence rates were observed for AF (5.5–7.4 events per 1000 person-years). HRs for AF were significantly increased in AS (2.3), uSpA (2.9) and PsA (1.5,) compared with the GP cohort.

Patients with SpA are at increased risk of aortic regurgitation, cardiac rhythm disturbances and, as a probable consequence, also PM. Particularly for AF, the most common arrhythmia, increased caution is warranted, whereas AV block should be looked for especially in men with AS or uSpA.

Cardiovascular involvement in systemic sclerosis (SSc) comprises a range of manifestations with prevalence and incidence that remain uncertain. **Butt et al (2019)** investigated cardiovascular manifestations of Systemic Sclerosis in a Danish Nationwide Cohort Study.²⁸⁵ In the Danish administrative registries between 1995 and 2015, all patients aged ≥ 18 years with a first diagnosis of SSc were matched by age and sex with controls (1:5) from the general population. Prevalence of cardiovascular diseases at the time of the SSc diagnosis and incidence during follow-up were assessed by in- and outpatient discharge diagnoses. Conditional logistic and Cox proportional hazards regression models were used respectively to calculate odds ratios for prevalent cardiovascular diseases and hazard ratios (HRs) for incident diseases associated with SSc.

Patients with SSc (n=2778; 76% women; mean \pm SD age: 55 \pm 15 years) had more established cardiovascular risk factors than controls at baseline, including greater prevalence of hypertension (31.2% versus 21.0%, $P < 0.0001$) and treated dyslipidaemia (9.8% versus 8.5%, $P = 0.02$). SSc was associated with an increased relative risk of developing most cardiovascular diseases, including atrial fibrillation (HR: 1.75; 95CI 1.51-2.04). Additional adjustment for medications and comorbidities yielded results similar to the main analyses. In this nationwide study, SSc was associated with greater risks of distinct cardiovascular diseases for patients than for matched controls, suggesting a significant disease-related adverse impact across the vascular bed and specific cardiac structures.

²⁸⁴ Bengtsson K, Forsblad-d'Elia H, Lie E, et al. (2018). Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Ann Rheum Dis* ; 77(4): 541-8.

²⁸⁵ Butt, S. A., Jeppesen, J. L., Torp-Pedersen, C., et al (2019). Cardiovascular Manifestations of Systemic Sclerosis: A Danish Nationwide Cohort Study. *Journal of the American Heart Association*, 8(17), e013405

Cross-sectional studies

Proinflammatory markers such as interleukin (IL)-6 have been closely associated with atrial fibrillation. These markers are characteristically elevated in chronic inflammatory bowel disease (IBD) and positively correlate with disease activity. Although IBD and AF have similar pathogenesis, there have been very limited studies looking at their association.

Pattanshetty et al (2015) determined the prevalence of AF in patients with IBD.²⁸⁶ Patients and Methods: Medical records of patients with biopsy proven IBD (n = 203, both in and outpatient) were retrospectively reviewed. 141 IBD patients with documentary evidence of ECGs were included. The “Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)” study, a large cross-sectional study (n = 1.89 million) to evaluate the prevalence of AF among the US population, was the control population. All ECGs available to December 2010 for each IBD patient were reviewed for evidence of AF. The prevalence of AF in the IBD population was compared to the control (ATRIA) population.

The prevalence of AF was significantly higher in IBD patients than in ATRIA patients (11.3% vs 0.9%, $P < 0.0001$). The IBD patient population were much younger than controls (64.4 ± 10.7 vs 71.2 ± 12.2 , $P = 0.02$).

Summary and conclusions

Autoimmune diseases (AIDs) are frequently systemic disorders, so cardiac involvement is common.

The topic of a submission request for this investigation was steroid administration for asthma and skin diseases. Some autoimmune cutaneous diseases associated with AF are considered in this section.

Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodelling (Gawalko et al 2020). Chronic inflammation is the pathophysiological basis linking AD to autonomic dysfunction, including sympathetic overactivation and a decline in parasympathetic function. Autoantibody-mediated inhibitory effects of cellular events (potassium or L-type calcium currents, M2 muscarinic cholinergic or β 1-adrenergic receptor signalling) can lead to cardiac arrhythmia. Drug-induced arrhythmias, caused, by corticosteroids are also observed among autoimmune disease patients.

The most common AID linked to AF is rheumatoid arthritis (RA). Other autoimmune diseases may be related to AF. Pujades-Rodriguez et al. (2020) investigated dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases in a population-based cohort study. Increased AF risk seen in patients with giant cell arteritis, polymyalgia rheumatica, inflammatory bowel disease and vasculitis, as well as rheumatoid arthritis and SLE.

²⁸⁶ Pattanshetty DJ, Anna K, Gajulapalli RD, et al (2015) Inflammatory bowel “Cardiac” disease: point prevalence of atrial fibrillation in inflammatory bowel disease population. Saudi J Gastroenterol.; 21:325–9

The most frequent arrhythmia in RA patients is AF, especially in young (<50 years) females with sedimentation rates >60 mm/h or anti-TNF- α antibodies (Gawalko et al). In a Danish cohort study of 4,182,335 participants, including 18,247 with RA, the overall incidence of AF was 40% higher than in the general population. (Lindhardsen et al 2012).

In a meta-analysis of 3 retrospective cohort studies, the pooled risk ratio of developing AF in patients with RA vs. controls was 1.29, 95CI 1.05–1.59 (Ungprasert et al 2017). The analysis demonstrated a statistically significant increased risk of subsequent development of AF among patients with RA. Other recent meta-analyses support an increased risk of AF in patients with rheumatoid and other inflammatory arthritides. Ma et al (2021) assessed the risk of AF in inflammatory arthritis, based on 5 studies containing seven cohorts of RA or spondyloarthritis. The AF risk in inflammatory arthritis patients was significantly increased compared with healthy controls (HR 1.42, 95CI 1.36-1.49), and the adjusted pooled HR was 1.37 (95CI 1.29 -1.46).

The pathophysiological basis for rhythm disorder in RA is diffuse cardiac involvement (rheumatoid nodules or inflammatory lesions), as well as coronary vasculitis and coronary atherosclerotic disease, which lead to perfusion defects of the myocardium with proarrhythmic effects. Antibodies against the cardiac conduction system are found in 35% of patients with RA, which increase P-wave dispersion and LA diameter, may play important an role in conduction abnormalities in RA patients.

RA has been associated with cardiac damage due to inflammation at all levels, including arrhythmia (Alcaida et al 2018). Magnetic resonance studies have shown frequent myocardial abnormalities even in asymptomatic RA patients, associated with arthritis activity.

Sinus tachycardia (15–50%), AF, and atrial ectopic beats are the most frequent cardiac rhythm disorders among systemic lupus erythematosus (SLE) patients. The pathophysiology of arrhythmias in SLE includes initial inflammatory cell infiltration and, as the disease advances, myocardial necrosis and fibrotic replacement. Consequently, multiple small areas of fibrosis can affect atrial and ventricular repolarisation and conduction, leading to cardiac rhythm disorders Gawalko et al

Psoriasis is a chronic inflammatory condition characterised by excessive growth of the epidermal layer of the skin and associated patches of abnormal, thickened skin. Patients with psoriasis are more susceptible to AF than the general population (Ungprasert et al 2016; Upala et al 2017) with a severity-adjusted risk of 1.50–2.98 in patients aged <50 years and 1.16–1.29 in those aged \geq 50 years. Ahlehoff et al 2012)

Chronic inflammation mediated by systemic inflammatory cytokines, such as TNF- α , IL-6, and IL-17, is the most important contributor linking psoriasis to increased AF incidence. Another structural remodelling factor with increased bioactivity in psoriasis is platelet-derived growth factor α (PDGF α), which promotes cell proliferation and collagen expression in cardiac fibroblasts.

Recent research has confirmed the effects of systemic inflammation in ankylosing spondylitis (AS) on different parts of the heart such as cardiac valves, conduction system, myocardium and vessels that can result in cardiovascular disturbances. Some studies have suggested an increased risk of cardiac conduction abnormalities in AS patients; but the magnitude of the risk contributed by AS is unclear.

Morovatdar et al. (2021) assessed the association between ankylosing spondylitis and risk of heart conduction disorders and arrhythmia in a meta-analysis. Of seven articles in the meta-analysis, three focused on atrial fibrillation and any arrhythmia. An increased risk of atrial fibrillation (RR: 1.85, 95CI 1.15-2.98) was found in AS subjects compared to the general population in a random effects model.

Engtsson et al. (2018) described the incidence of AF and other arrhythmias in patients with ankylosing spondylitis, undifferentiated spondyloarthritis (uSpA) and psoriatic arthritis (PsA) compared with the general population in a prospective US cohort. The highest incidence rates were noted for AF (5.5–7.4 events per 1000 person-years). HRs for AF were significantly increased in AS (2.3), uSpA (2.9) and PsA (1.5,) compared with the GP cohort.

The most common cardiac arrhythmia in coeliac disease is AF, with a reported incidence 30% higher than in the general population (Emilsson et al 2011). This increased risk of AF has been attributed to inflammation and fibrosis (Gawalko et al 2020),

Several studies have found coeliac disease may be associated with a variety of cardiac manifestations. Atrial fibrillation is one of the most common arrhythmias that can cause significant morbidity. However, the risk of atrial fibrillation in patients with coeliac disease according to epidemiological studies remains unclear

Hidalgo et al (2020) conducted a meta-analysis to assess the risk of atrial fibrillation in patients diagnosed with coeliac disease compared to controls. Four observational studies with 64,397 participants were enrolled. The association between coeliac disease and increased risk of AF was significant, with a pooled OR of 1.38 (95CI 1.01-1.88).

Despite growing evidence indicating that patients with inflammatory bowel disease have an increased risk of atrial fibrillation, owing to the potential biases of confounding effects and reverse causation, the specific relationship between IBD and AF remains controversial (Chen et al 2021)

Gawalko et al (2020) maintains that AF represents the most common sustained cardiac arrhythmia among patients with IBD, and its incidence increases more than 2-fold during active flare-ups of IBD. The powerful inflammatory cytokines implicated in AF development are C-reactive protein (CRP) and IL-6.

Several recent studies suggest a positive association between IBD and AF [Pattanshetty et al 2015] especially during IBD flares (Kristensen et al 2014). Using a population-based cohort study, Choi et al (2019) identified 1,120 AF cases. Multivariable Cox regression indicated that patients with IBD had a 36% higher risk of AF than controls (Choi et al 2019). A systematic

review and meta-analysis suggested that compared to controls, IBD patients were at a 2.2-fold increased risk of developing AF [Zuin et al 2020].

Another meta-analysis by Zuin et al (2020) investigated the prevalence of AF in IBD patients. ultimately The final population included 429,624 patients (62,287 IBD and 367,337 controls) from 3 studies, enrolled between 2001 and 2014. IBD patients had a significant higher risk of AF than controls (OR 2.26; 95CI 2.11–2.41) with a high degree of heterogeneity between the studies ($I^2 = 100\%$). both CD (OR 1.34; 95CI 1.16–1.53) and UC patients (OR 1.51; 95CI 1.40–1.63) were at higher risk of AF.

This increased risk of AF in IBD, although not entirely understood, has been proposed to have different underlying pathophysiologies. Myocardial inflammation and fibrosis seem to be the pivotal factor. Inflammatory processes and oxidative stress lead to cardiomyocyte necrosis, with subsequent electrical and structural remodelling (Chen et al 2021)

Chen et al (2021) conducted a two-sample Mendelian randomisation (MR) study to determine whether there is a causal effect of IBD on AF. The dataset of IBD was acquired from genome-wide association studies (GWAS), including more than 75,000 cases and controls. There was no evidence of an association between genetic predisposition to IBD and AF

The lack of a genetic causal effect of IBD with the risk of AF suggested that the positive linkage between the presence of IBD and the risk of developing AF demonstrated in previous observational studies may be residual confounding due to common risk factors.

Atopic dermatitis (AD) is characterised by chronic inflammation, which is a risk factor for atrial fibrillation. Pandher et al (2020) reviewed cardiovascular and haematological comorbidities of AD, the population attributable risks of AD for atrial fibrillation among other cardiovascular diseases are low, but real. The pathophysiology underlying these potential associations is not entirely clear. Corticosteroids, cyclosporine, and antimetabolites, used to treat AD, may also be associated with many comorbidities.

Schmidt et al (2020) examined the association between hospital-diagnosed atopic dermatitis (moderate to severe) and atrial fibrillation using linked population-based Danish registries. The authors compared 35-year risk of AF in 13,126 persons with atopic dermatitis and 124,211 comparators. The hazard ratio was 1.2 (95CI 1.0-1.6) and remained increased after adjusting for various atrial fibrillation risk factors.

There is a paucity of information about whether Behçet's disease is associated with an increased risk of AF. Lee et al (2020) conducted a population-based study to determine the risk of AF in patients with BD. Using data from the Korean National Health Insurance Service database between 2010 and 2014. After adjustment, the BD group showed a 1.8-fold higher risk of AF compared to the control group. Men with BD had a 2.5-fold increased risk of AF, whereas women with BD did not have an elevated risk. AF risk was higher in patients with severe BD than those with non-severe BD and controls.

Myocarditis and myopericarditis are not commonly documented in patients with giant cell arteritis (GCA) (Kushnir et al (2016)). However, there have been at least 6 reports of giant cell arteritis (GCA) causing myocarditis. The coincidence of paroxysmal AF and diplopia suggests that flares of systemic inflammation precipitated both symptoms. Kushnir et al (2016) present a biopsy-proven GCA presenting with diplopia and new diagnosis of atrial fibrillation and myocarditis with left ventricular systolic dysfunction. The patient promptly responded to corticosteroid therapy, confirming the diagnosis of GCA.

It is concluded that in relation to the autoimmune diseases ankylosing spondylitis or another autoimmune inflammatory spondyloarthritis; coeliac disease; giant cell arteritis; inflammatory bowel disease; psoriasis; rheumatoid arthritis; systemic lupus erythematosus; and systemic sclerosis (scleroderma), there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between atrial tachyarrhythmias and sepsis or critical illness, but chance, bias or confounding cannot be ruled out with reasonable confidence.

In relation to the autoimmune diseases, atopic dermatitis; Behçet's disease and polymyalgia rheumatica it is concluded that the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is very limited in quality or quantity, being confined to two case reports. It is suggested that a factor for blunt cardiac injury, independent of critical illness requiring ICU admission should be retained in the RH SoP, but the evidence is insufficient to retain a factor in the BoP SoP.

The existing factor and corresponding definition for specified autoimmune or inflammatory disease should be replaced with a standalone factor containing a specified list of autoimmune diseases. New autoimmune diseases ankylosing spondylitis; coeliac disease; inflammatory bowel disease; giant cell arteritis, psoriasis; Behcet disease, atopic dermatitis, polymyalgia rheumatic should be added to the list, and rheumatoid arthritis, systemic sclerosis (scleroderma) and systemic lupus erythematosus should be retained.

Cardiac infiltrative disease

Summary of important issues

The existing factor covers autoimmune (inflammatory) and infiltrative diseases. Cardiac infiltration due to amyloidosis and sarcoidosis are typically considered to be a natural category, causing restrictive cardiomyopathy. These conditions, along with haemochromatosis, should be considered separately from autoimmune (inflammatory) diseases.

Cardiac involvement in amyloidosis and sarcoidosis is poorly understood, and is associated with high morbidity and mortality (Ashraf et al 2020). Cardiac amyloidosis (CA) and sarcoidosis are typically known as infiltrative cardiomyopathies. Both diseases may involve cardiac tissue either as a part of the systemic condition or in isolation. Heart failure,

conduction abnormalities, and arrhythmias are the most common signs of cardiac involvement.

Atrial and ventricular arrhythmias, along with conduction defects, are frequent in cardiac amyloidosis and sarcoidosis. Atrial dysfunction in cardiac amyloidosis may result in atrial fibrillation and increases the risk of stroke, making anticoagulation significant and challenging.

The association of cardiac arrhythmia with hereditary haemochromatosis (HH) has been well documented in the clinical literature, but atrial fibrillation is rarely reported (Sudmantaitė et al 2020). Previous reports of cardiac arrhythmias in HH are for advanced stages of disease, often with concomitant heart failure symptoms

Review studies

Among cardiac infiltrative diseases, cardiac involvement in amyloidosis and sarcoidosis is associated with high morbidity and mortality. Atrial and ventricular arrhythmias, along with conduction defects, are frequent in cardiac amyloidosis and sarcoidosis.

Transthyretin cardiac amyloidosis (ATTR-CA) is a systemic disorder resulting from the extracellular deposition of amyloid fibrils of misfolded transthyretin protein in the heart.²⁸⁷ ATTR-CA is a life-threatening disease, which can be caused by progressive deposition of wild type transthyretin (wtATTR) or by aggregation of an inherited mutated variant of transthyretin (mATTR). mATTR is a rare condition transmitted in an autosomal dominant manner with incomplete penetrance, causing heterogeneous phenotypes which can range from predominant neuropathic involvement, predominant cardiomyopathy, or mixed.

Atrial fibrillation and flutter frequently complicate transthyretin cardiac amyloidosis (ATTR-CM). Dale et al (2021) reported outcomes of AF/AFL in ATTR-CM in a single centre observational study of patients seen at an amyloidosis centre with wild-type or hereditary ATTR-CM diagnosed between 2005-2019, including 84 patients (average age 74 ± 10 years, 94% male) with 27.6 ± 22.8 months follow-up. AF/AFL occurred in 61 patients (73%). Rapid ventricular response was common as was attempted rate control.²⁸⁸ However, discontinuation of rate control drugs was frequent (80%), often for adverse effects.

Rhythm control was attempted in 64%, usually with cardioversion (DCCV) or ablation. Post-DCCV recurrence was common (91%) and time to recurrence was similar with or without anti-arrhythmic drugs (5.8 months (IQR 1.9-12.5) vs 6.2 months (IQR 1.9-12.5) $p = 0.83$). Ablation was performed in 23% with AFL (all for typical AFL) with 14% recurrence after mean of 60.9 months. Ablation for AF was performed in 12% with 86% recurrence after median of 6.2 months (IQR 5.6-12.3).

²⁸⁷ Lioncino, M., Monda, E., Palmiero, G., et al (2022). Cardiovascular Involvement in Transthyretin Cardiac Amyloidosis. *Heart failure clinics*, 18(1), 73–87.

²⁸⁸ Dale, Z., Chandrashekar, P., Al-Rashdan, L., et al (2021). Management Strategies for Atrial Fibrillation and Flutter in Patients with Transthyretin Cardiac Amyloidosis. *The American journal of cardiology*, 157, 107–114.

Most patients (62%) with rhythm control had subjective improvement (≥ 1 NYHA class or resolved palpitations).

AF/AFL was common in the cohort. Rate control was poorly tolerated and often abandoned. Rhythm control led to symptomatic improvement in a majority of cases, but durable success was limited. DCCV was modestly successful and not significantly improved with anti-arrhythmics. Ablation was successful with typical AFL but had limited success in AF.

Cardiac involvement in amyloidosis and sarcoidosis is poorly understood, and is associated with high morbidity and mortality.²⁸⁹ Atrial and ventricular arrhythmias, along with conduction defects, are frequent in cardiac amyloidosis and sarcoidosis. Atrial dysfunction in cardiac amyloidosis may result in atrial fibrillation and increases the risk of stroke, making anticoagulation significant and challenging. Ventricular arrhythmia and conduction defects are more common in AL amyloidosis and cardiac sarcoidosis. Premature ventricular contractions (PVCs) from Purkinje fibres trigger ventricular arrhythmias in cardiac amyloidosis, while the inflammation and scarring leading to the reentrant process is the cause in cardiac sarcoidosis.

The typical treatment modalities include Class II and III antiarrhythmic drugs and ablation techniques, while corticosteroids and immunosuppressants are indicated in cardiac sarcoidosis to reduce the burden of the disease and arrhythmias. Sudden cardiac death can be a manifestation of both disorders that can be prevented by the Implantable cardioverter-defibrillator (ICD), although the predictive risk factors for primary prevention remain uncertain.

Cardiac amyloidosis (CA) and sarcoidosis are typically known as *infiltrative cardiomyopathies*. Amyloidosis is characterized by the deposition of insoluble amyloid fibrils in extracellular tissues involving multiple body systems, including cardiac tissue. Several forms of precursor protein significantly affect the heart: light-chain (LC) immunoglobulin, mutant hereditary transthyretin (TTR), wild-type TTR, mutant apolipoprotein AI, amyloid atrial natriuretic peptide localised to the atrium, fibrinogen alpha type and serum amyloid A protein. Sarcoidosis is a granulomatous multisystem disease in which CD4+ T-lymphocytes aggregate to induce a Th-1 type immune response.

Both diseases may involve cardiac tissue either as a part of the systemic condition or in isolation. Heart failure, conduction abnormalities, and arrhythmias are the most common signs of cardiac involvement.

Arrhythmias in cardiac amyloidosis vary by amyloidosis type, as conduction defects and supraventricular arrhythmias are more prevalent in transthyretin amyloidosis. Atrioventricular (AV) block is the most common type of arrhythmia in cardiac sarcoidosis, followed by ventricular tachycardia and supraventricular arrhythmia.

Atrial fibrillation and atrial tachycardia (AT) are the most common arrhythmias in cardiac amyloidosis. The combination of intramyocardial amyloid accumulation, leading to restricted ventricular relaxation and elevated filling pressures, which eventually causes left atrial

²⁸⁹ Ashraf, I., Peck, M. M., Maram, R., et al (2020). Association of Arrhythmias in Cardiac Amyloidosis and Cardiac Sarcoidosis. *Cureus*, 12(8), e9842
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enlargement, and the intrinsic left atrial dysfunction due to direct amyloid deposition, are the causes of atrial dysfunction in CA. Atrial fibrillation is more frequent in wild-type transthyretin amyloidosis (ATTRwt).

Barbhaiya et al. performed an atrial arrhythmia substrate analysis, which showed supraventricular tachycardia in all 18 patients with CA. Amyloid accumulation in atria isolates atrial myocyte bundles. AF in CA appears to have longer cycle lengths because the mechanism induces a pronounced delay in intra-atrial conduction

The prevalence of atrial arrhythmias in cardiac sarcoidosis is unclear. Atrial arrhythmias like AF/AT, are less frequent than ventricular arrhythmias in CS. Viles-Gonzalez et al. (2013) documented supraventricular arrhythmia in 32% of CS cases (atrial fibrillation 18%, atrial tachycardias 7%, atrial flutter 5%, and other types of supraventricular tachycardias 2%). In contrast, Cain et al. (2014) evaluated 192 patients with extracardiac sarcoidosis (confirmed with a biopsy and CMR imaging) and found that atrial arrhythmias (36%) were more common than ventricular arrhythmias (27%). CS induces inflammation and scarring of the atrial tissue and atrial enlargement due to ventricular dysfunction that leads to atrial arrhythmias. Autopsy of patients with cardiac sarcoidosis showed sarcoidosis lesions in the left ventricular free wall (96%), the ventricular septum (73%), the right ventricular wall (46%), the right atrium (11%), and the left atrium (7%) [Roberts et al 1977]. Multivariate analysis showed that left atrial enlargement was the only independent factor consistent with atrial arrhythmias in CS patients (Viles-Gonzalez et al. 2013).

Cross-sectional studies

The occurrence of stroke in patients with cardiac sarcoidosis (CS) is an under-recognized entity. **Subramanian et al (2020)** evaluated the clinical presentation, risk factors, aetiology, temporal relationship and management of stroke in patients with CS.²⁹⁰

The data of 111 patients with cardiac sarcoidosis from the Granulomatous Myocarditis Registry was analysed. Clinical data regarding the clinical presentation, risk factors for vascular disease, electrocardiogram, echocardiogram and 18 Fluorodeoxyglucose (FDG) PET-CT were extracted from the registry database.

Among the 111 patients with CS, 8 patients (7.2%) had a history of ischemic stroke. Six of the eight patients with ischemic stroke were young (<50 years) without conventional risk factors for vascular disease. In five patients, stroke occurred prior to the diagnosis of CS. In all except one patient the ischemic stroke occurred in the anterior cerebral circulation. LV dysfunction was noted in all patients at the time of stroke, with the presence of an LV apical clot in four of the eight patients. Atrial fibrillation was documented in 2 patients. Two patients received thrombolysis and mechanical thrombectomy, while the others were treated with standard antiplatelets and statins. There was a significant improvement in the LV Ejection fraction (33.6 ± 15.2 to $49.1 \pm 13.8\%$, $p = 0.043$) following immunosuppression. Two patients developed

²⁹⁰ Subramanian, M., Yalagudri, S., Saggu, D., et al. (2020). Stroke in cardiac sarcoidosis: Need to worry?. Indian heart journal, 72(5), 442–4.
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refractory HF and respiratory sepsis, respectively, and succumbed following prolonged ICU admissions.

Case reports.

Primary iron overload cardiomyopathy is a potentially preventable cause of heart failure, usually manifesting in the 4-5th decade of life. Patients may be asymptomatic early in the disease with hidden progression of cardiac dysfunction.

The association of cardiac arrhythmia with hereditary hemochromatosis (HH) has been well documented in the clinical literature, but atrial fibrillation is rarely reported. They are assumed to be directly associated with myocardial accumulation of iron. Previous literature has often not defined whether the mechanism is related to iron overload accumulation *per se* (i.e. direct effects of the physical presence of iron on or in cardiomyocytes), a cardiomyopathic mechanism induced by heart failure secondary to iron overload, elevated oxidative stress secondary to increased either systemic or myocardial iron overload, or a combination of these.

A study by Shizukada et al's (2012) indicates that the arrhythmogenic effect of iron overload by HH in asymptomatic stage is marginal. This observation questions a highly publicized view of the arrhythmogenicity of systemic iron overload. Previous reports of cardiac arrhythmias in HH are for advanced stages of disease, often with concomitant heart failure symptoms

Sudmantaitė et al (2020) described 48-year-old man who was referred to a clinic due to the episode of atrial fibrillation.²⁹¹ The specific features of bronze skin and yellow eyes together with a combination of syndromes (cardiomyopathy, cirrhosis, ascites and portal hypertension, diabetes mellitus, and chronic kidney disease) stimulated the testing of iron metabolism markers, which were far above the normal range. Echocardiography and cardiac magnetic resonance (CMR) showed the dilatation of all cardiac cavities and biventricular systolic dysfunction. CMR T2* mapping was consistent with the diagnosis of myocardial and hepatic siderosis. Hereditary Type I haemochromatosis was confirmed by a genetic test. After 6 months of standard HF treatment, chelation therapy with deferoxamine and regular phlebotomies imaging tests showed a reduction of ventricular and atrial volumes, an improvement in the cardiac systolic function and a decrease of iron accumulation.

In this case, complicating syndromes were detected earlier than underlying disease of primary haemochromatosis.

Summary and conclusions

Cardiac involvement in amyloidosis and sarcoidosis is poorly understood, and is associated with high morbidity and mortality (Ashraf et al 2020). Cardiac amyloidosis (CA) and sarcoidosis are typically known as infiltrative cardiomyopathies. Both diseases may involve cardiac tissue either as a part of the systemic condition or in isolation. Heart failure, conduction abnormalities, and arrhythmias are the most common signs of cardiac

²⁹¹ Sudmantaitė, V., Čelutkienė, J., Glaveckaitė, S., et al. (2020). Difficult diagnosis of cardiac haemochromatosis: a case report. *European heart journal. Case reports*, 4(1), 1–6
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involvement. Atrial and ventricular arrhythmias, along with conduction defects, are frequent in cardiac amyloidosis and sarcoidosis. Atrial dysfunction in cardiac amyloidosis may result in atrial fibrillation and increases the risk of stroke, making anticoagulation significant and challenging.

Sarcoidosis is a multisystem granulomatous disease predominantly affecting the lungs, with increased risk of cardiovascular disease, pulmonary hypertension and cardiac sarcoidosis (CS), the latter due to direct granuloma infiltration (Ho et al 2019). The most serious consequence of cardiac sarcoidosis is sudden cardiac death due to ventricular tachyarrhythmias or complete atrioventricular block.

Cardiac sarcoidosis usually occurs in the context of systemic disease; however, isolated cardiac involvement can occur in up to 25% of cases and tends to be clinically silent (Chamorro-Pareja et al 2019). Restrictive cardiomyopathy is the main finding in cardiac amyloidosis, resulting from the replacement of normal myocardial contractile elements by infiltration and interstitial deposits of amyloid (Barra et al 2012). This process may also involve the cardiac conduction system and cause different types of heart block and arrhythmias. Fibrosis of the sinoatrial and atrioventricular nodes has been correlated with the severity of amyloid deposition elsewhere in the heart and may require pacemaker placement.

Atrial arrhythmias are less common in sarcoidosis than ventricular tachycardia, but occur in 15–17% of patients (Gawalko et al 2020). Viles-Gonzalez et al. (2013) documented supraventricular arrhythmia in 32% of CS cases (atrial fibrillation 18%, atrial tachycardias 7%, atrial flutter 5%, and other types of supraventricular tachycardias 2%). In contrast, Cain et al. (2014) evaluated 192 patients with extracardiac sarcoidosis (confirmed with a biopsy and CMR imaging) and found that atrial arrhythmias (36%) were more common than ventricular arrhythmias (27%).

Postulated proarrhythmic mechanisms include active inflammation and enhanced automaticity. The re-entrant pathway can result from active granulomatous inflammation, but can also be found in association with the healing of cardiac granulomas in the inactive phase of the disease. Case reports and descriptions of AF continue to be reported in patients with sarcoidosis. Although fibrosis of the cardiac conduction system is common, direct amyloid infiltration of the specialised conduction tissue of the heart does not appear to account for the majority of these disturbances

Atrial fibrillation and flutter frequently complicate transthyretin cardiac amyloidosis (ATTR-CM). (Dale et al 2020). Several case reports demonstrate the occurrence of severe cardiac abnormalities (including AF) as a consequence of cardiac amyloidosis, even in the absence of prior symptoms of heart disease.

The combination of intramyocardial amyloid accumulation, leading to restricted ventricular relaxation and elevated filling pressures, which eventually causes left atrial enlargement, and the intrinsic left atrial dysfunction due to direct amyloid deposition, are the causes of atrial dysfunction in CA.

documented in the clinical literature. They are assumed to be directly associated with myocardial accumulation of iron. Previous literature has often not defined whether the mechanism is related to iron overload accumulation *per se* (i.e. direct effects of the physical presence of iron on or in cardiomyocytes), a cardiomyopathic mechanism induced by heart failure secondary to iron overload, elevated oxidative stress secondary to increased either systemic or myocardial iron overload, or a combination of these.

A study by Shizukada et al's (2012) indicates that the arrhythmogenic effect of iron overload by HH in asymptomatic stages is marginal. This observation questions a highly publicized view of the arrhythmogenicity of systemic iron overload. Previous reports of cardiac arrhythmias in HH are for advanced stages of disease, often with concomitant heart failure symptoms

It is concluded that in relation to the cardiac infiltrative diseases amyloidosis and sarcoidosis, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between cardiac amyloidosis and sarcoidosis and atrial fibrillation and, but chance, bias or confounding cannot be ruled out with reasonable confidence. Sarcoidosis and amyloidosis should be retained in the RH and BoP SoPs

In relation to the haemochromatosis, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is very limited in quality or quantity, being confined to a handful of case reports. A new factor for haemochromatosis should be added to the RH SoP only.

The existing factor and definition of specified autoimmune or inflammatory disease should be replaced with a specified list of cardiac infiltrative diseases, which includes amyloidosis, sarcoidosis and haemochromatosis (RH only).

Obesity

Current factor

onset and worsening - RH and BoP

being obese for a continuous period of at least three years within the ten years before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Obesity is an established risk factor for cardiovascular diseases, including atrial fibrillation. Obese individuals have a 50% increased risk of developing AF (Zia et al 2021).

Measures of *overall* obesity (body mass index, body fat percentage (*BF %*) and weight) and *abdominal* obesity (WC, waist to hip ratio (*WHR*) and WHtR) have both been shown to correlate with the risk of developing AF.

Obesity has adverse effects on cardiovascular haemodynamics and cardiac structure and function, and increases the prevalence of AF, partly related to electroanatomic remodelling in obese patients (Lavie et al 2017). However, many studies have demonstrated an obesity paradox, where overweight and obese patients with cardiac disorders have a better prognosis than leaner patients with the same degree of severity of cardiovascular disease/AF.

Summary of previous investigation

Obesity is a risk factor for the development of new onset atrial fibrillation. Multiple studies have documented a strong and independent association between body mass index (BMI) and the incidence of AF. The association between obesity, left atrial size, and AF is well established. Obesity is identified as the most important determinant of left atrial enlargement

Several prospective studies have reported significant associations between obesity and incident AF. Guglin et al notes that obesity was first reported as an important, potentially modifiable risk factor for new-onset AF by the Framingham investigators (Wang et al 2004). A 4% increase in AF risk per 1 kg/m² increase in BMI was observed, with adjusted hazard ratios for AF associated with obesity of 1.52 (95CI 1.09-2.13) in men and 1.46 (95CI 1.03-2.07) for women, compared to subjects with normal BMIs. In the Framingham Heart Study, obese participants had a 45% to 50% increased risk for incident AF compared to participants with normal BMI, independent of other cardiovascular risk factors (Wang et al 2004). In a Danish cohort study, overweight subjects were at increased risk for incident AF (Frost et al 2005).

A meta-analysis of population-based cohort studies (Wanahita et al 2008) found that obese individuals had a 49% increased risk of developing AF compared to nonobese individuals (RR 1.49, 95CI 1.36-1.64). There was a graded relationship between increased BMI and increased risk of AF in the general population. In post-cardiac surgery studies, obese individuals did not have an increased risk of developing AF compared to nonobese individuals (RR 1.02, 95CI 0.99-1.06). A graded relationship of BMI and AF risk was not present in the post-cardiac surgery cohorts.

It has been shown that the association of obesity with sustained AF is stronger than for transitory or intermittent AF. On average, AF risk is 3% higher per unit increase in BMI. The risk is higher by 7% per BMI unit increase for sustained AF, by 4% for intermittent AF, and by 1% for transitory AF. The obesity-AF association appears to be partially mediated by diabetes mellitus but minimally through other cardiovascular risk factors.³ In the longitudinal cohort study from Olmsted County, BMI independently predicted progression to permanent AF. Compared to normal BMI, obesity (BMI 30 to 34.9) and severe obesity (BMI ≥35) were associated with increased risk for progression to permanent AF. This relation was not weakened by left atrial volume, which was independent of and incremental to BMI for the prediction of progression to permanent AF (Tsang et al 2008). Similarly, in the Swedish Primary Prevention Study (Rosengren et al 2009), body surface area at age 20 years was strongly related to subsequent AF ($p < 0.0001$), as were midlife BMI and weight gain from age 20 years to midlife ($p < 0.0001$).

Reviews

There have been many review studies documenting the increased incidence of AF in obese individuals.^{292 293 294 295}

Obese individuals (BMI >30 kg/m²) are significantly more likely to develop AF than those with a normal BMI (<25 kg/m²). In the Framingham Heart Study, every unit increase in BMI was associated with a 5% increase in risk [Wang et al 2004].²⁹⁶

A primary mechanism for the role of obesity may be increase in the size of the left atrium. Increased left atrial pressure and volume, often associated with diastolic dysfunction, as well as a shortened effective refractory period in the left atrium and in the proximal and distal pulmonary veins have been identified as potential factors facilitating and perpetuating AF in obese patients [Munger et al 2012]. Inflammation and pericardial fat may also play a role.

There is evidence to suggest that long-term weight loss is associated with a reduction of AF burden [Mahajan et al 2015; Munger et al 2012].

As outlined by **Zia et al (2021)** in a study of anthropometric measures and the risk of developing atrial fibrillation, obesity is an established risk factor for several cardiovascular diseases (CVDs), including increased incidence of atrial fibrillation.²⁹⁷ Obese individuals have a 50% increased risk of developing AF.

Obesity increases total blood volume, which causes structural changes to the heart, such as left and right ventricular hypertrophy. It leads to increased epi- and pericardial adipose tissue, which is associated with higher AF recurrence rate after ablation and higher burden of symptoms in patients with AF. These structural changes alter cardiac electrical circuits, which could increase the risk of AF

Measures of *overall* obesity (i.e. body mass index (*BMI*), body fat percentage (*BF %*) and weight) and *abdominal* obesity (i.e. WC, waist to hip ratio (*WHR*) and WHtR) have both been shown to correlate positively with the risk of developing AF. Obesity has been associated with higher risk of developing AF, and high BMI, height, weight, WC and BF % have all been associated with an increased risk of AF.

²⁹² Lavie, C. J., Pandey, A., Lau, D. H., et al. (2017). Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *Journal of the American College of Cardiology*, 70(16), 2022–25

²⁹³ Chokesuwattanaskul, R., Thongprayoon, C., Bathini, T., et al. (2020). Incident atrial fibrillation in patients undergoing bariatric surgery: a systematic review and meta-analysis. *Internal medicine journal*, 50(7), 810–87.

²⁹⁴ Sidhu, K., & Tang, A. (2017). Modifiable Risk Factors in Atrial Fibrillation: The Role of Alcohol, Obesity, and Sleep Apnea. *The Canadian journal of cardiology*, 33(7), 947–9.

²⁹⁵ Nalliah CJ, Sanders P, Kottkamp H, et al. (2016) The role of obesity in atrial fibrillation. *Eur Heart J* ;37:1565-72.

²⁹⁶ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

²⁹⁷ Zia, I., Johnson, L., Memarian, E., et al. (2021). Anthropometric measures and the risk of developing atrial fibrillation: a Swedish Cohort Study. *BMC cardiovascular disorders*, 21(1), 602.

Although the underlying biological mechanism is uncertain, it has been shown that obesity is associated with increased heart volume—especially left atrial volume— which has been proved a precursor for AF. tall non-obese individuals have bigger hearts and increased risk of AF and some studies show that height itself could be a risk factor for AF. It is thought that increased left atrial volume is correlated with increased number of cardiomyocytes in the pulmonary sleeves, triggering AF. obesity is also associated with increased pericardial tissue, which is a risk for structural changes within the heart that alter the cardiac electrical circuits, causing AF. Obesity-related hypertension as well as various obesity-related hormones, such as leptin, adiponectin and tumor necrosis factor α could be common links between obesity, cardiac remodelling and increased risk of AF.

Obesity and AF are common conditions that may be related. Emerging evidence is linking obesity and coexistent obstructive sleep apnoea with an increased incidence of AF. **Sidhu & Tang (2017)** reviewed recent evidence looking at these modifiable risk factors for AF, including obesity and coexistent obstructive sleep apnoea.²⁹⁸

In the Atherosclerosis Risk in Communities (ARIC) study, which prospectively followed patients in 4 US communities for cardiovascular risk factors, 40% of patients were overweight and 27% were obese, and 34% of men and 40% of women had poor levels of physical activity (Nalliah et al 2016). During follow-up, 1775 cases of AF were documented (7 events per 1000 patient-years). There was a linear relationship between increasing BMI and waist circumference and the development of AF. Compared with individuals with normal weight, being obese nearly doubled the risk of AF after adjusting for other confounders. In obese men only, there was an attenuation of this risk with increasing levels of physical activity after adjusting for confounders.

The relationship between obesity and AF was substantiated in a meta-analysis that included 16 studies and 123,429 patients (Wanahita et al 2008).²⁹⁹ Obese individuals had a nearly 50% increased risk of AF developing compared with nonobese counterparts. There was a graded relationship between BMI and risk of AF, with the overweight cohort having a 39% increase and a staggering 87% increase in the obese cohort. This effect was amplified in obese women compared with obese men.

There are controversial data regarding the relationship between bariatric surgery and atrial fibrillation.³⁰⁰ **Chokesuwattanaskul et al (2020)** conducted a meta-analysis to evaluate the incidence and the risk of AF in patients following bariatric surgery.³⁰¹

²⁹⁸ Sidhu, K., & Tang, A. (2017). Modifiable Risk Factors in Atrial Fibrillation: The Role of Alcohol, Obesity, and Sleep Apnea. *The Canadian journal of cardiology*, 33(7), 947–9.

²⁹⁹ Nalliah CJ, Sanders P, Kottkamp H, et al. (2016) The role of obesity in atrial fibrillation. *Eur Heart J* ;37:1565-72.

³⁰⁰ Krakowiak, A., Rajzer, M., Gaczoł, M., et al. (2021). OBESITY AND ATRIAL FIBRILLATION - BARIATRIC SURGERY AS A METHOD OF AF RISK DECREASE. *Wiadomosci lekarskie (Warsaw, Poland : 1960)*, 74(9 cz 1), 2218–21.

³⁰¹ Chokesuwattanaskul, R., Thongprayoon, C., Bathini, T., et al. (2020). Incident atrial fibrillation in patients undergoing bariatric surgery: a systematic review and meta-analysis. *Internal medicine journal*, 50(7), 810–87.

A literature search was conducted utilising MEDLINE, EMBASE and Cochrane Database from inception to March 2019. included studies that evaluated the (i) incidence and (ii) risk of AF in patients after bariatric surgery. Pooled incidence and odds ratios (OR) with 95% confidence interval (CI) were calculated using random effects meta-analysis.

Seven cohort studies consisting of 7681 patients undergoing bariatric surgery were enrolled in this systematic review. The prevalence of AF in patients undergoing bariatric surgery ranged between 0% and 4.6%. Overall, the pooled estimated incidence of AF following bariatric surgery was 5.3% (95CI: 1.9-13.8) at a median follow-up time of 7.9 years (interquartile range (IQR) 4.1-15.0 years). Compared to controls, the pooled OR of AF among patients who underwent bariatric surgery was 0.42 (95CI: 0.22-0.83) after a median of 7.9 years follow-up (IQR 7.2-19.0 years). Egger regression test demonstrated no significant publication bias in the meta-analysis of AF incidence following bariatric surgery.

The overall estimated incidence of AF following bariatric surgery was 5.3%. The meta-analysis study demonstrates a significant beneficial association between bariatric surgery and AF, with a 0.42-fold decreased risk of AF.

Weight reduction may reduce AF burden, as demonstrated in a study of 150 patients with AF and BMI>27 who were randomised to physician-directed weight loss or general lifestyle measures. Both groups underwent management of other risk factors such as hypertension, dyslipidaemia, diabetes, OSA, smoking, and alcohol consumption. BMI decreased by 3.5 points in the intervention group. There was a significant reduction in AF symptom burden and symptom severity between 6 and 15 months in the intervention arm. The number of AF episodes determined by Holter monitoring reduced from 3.3 episodes at baseline to 1 episode at 1 year. The duration of AF was also significantly decreased from 1176 minutes to 491 minutes. There was also a greater decrease in alcohol consumption in the intervention arm, which may have impacted the results.

Mechanisms for the development of AF in the obese population may be linked to other risk factors such as diabetes and hypertension, but the ARIC study accounted for these and still noted an increased risk. Other mechanisms include systemic inflammation associated with obesity as well as activation of the neurohormonal cascade. Obesity is also postulated to increase pericardial fat and fatty infiltration into the left atrium. OSA may also be the missing link between obesity and AF.

Many studies have demonstrated an obesity paradox, where overweight and obese patients with these disorders have a better prognosis than do leaner patients with the same degree of severity of cardiovascular disease/AF.³⁰² there are benefits of weight loss, physical activity/exercise training, and increases in cardiorespiratory fitness on the prognosis of obese patients with AF.

³⁰² Lavie, C. J., Pandey, A., Lau, D. H., et al . (2017). Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *Journal of the American College of Cardiology*, 70(16), 2022–25.

Meta-analyses

Kim et al (2021) investigated the causal relationship and evidence of an association between increased adiposity and the risk of incident cardiovascular disease (CVD) events or mortality.³⁰³

Observational (informing association) and Mendelian randomisation (MR) (informing causality) studies were assessed to gather mutually complementary insights and elucidate perplexing epidemiological relationships. Systematic reviews and meta-analyses of observational and MR studies that were published until January 2021 and evaluated the association between obesity-related indices and CVD risk were searched. Twelve systematic reviews with 53 meta-analyses results (including 501 cohort studies) and 12 MR studies were included in the analysis.

A body mass index increase was associated with higher risks of coronary heart disease, heart failure, atrial fibrillation, all-cause stroke, haemorrhagic stroke, ischaemic stroke, hypertension, aortic valve stenosis, pulmonary embolism, and venous thrombo-embolism. The MR study results demonstrated a causal effect of obesity on all indices but stroke.

Main outcomes	Equivalent body fat ^a		Central adiposity ^a		Concordance (between observational and MR studies) ^b	Summary of evidence ^a	Interpretations and proposals for future study
	BMI category	BMI continuous (per unit increase)	WC	WHR			
Atrial fibrillation	Moderate for obese	High	High	Not significant (low)	Yes	Generally high, with causality supported by MR study	Collective evidence suggested that adiposity is a causal risk factor for developing atrial fibrillation. Of note, two central adiposity indices (WC and WHR) provided contradictory results, which should be addressed in future studies. This discrepancy may be partially attributable to the small number of studies; thus, an updated meta-analysis is necessary.

The collective evidence suggested that adiposity is a causal risk factor for developing atrial fibrillation. two central adiposity indices (WC and WHR) provided contradictory results. This discrepancy may be partially attributable to the small number of studies; thus, an updated metaanalysis is necessary.

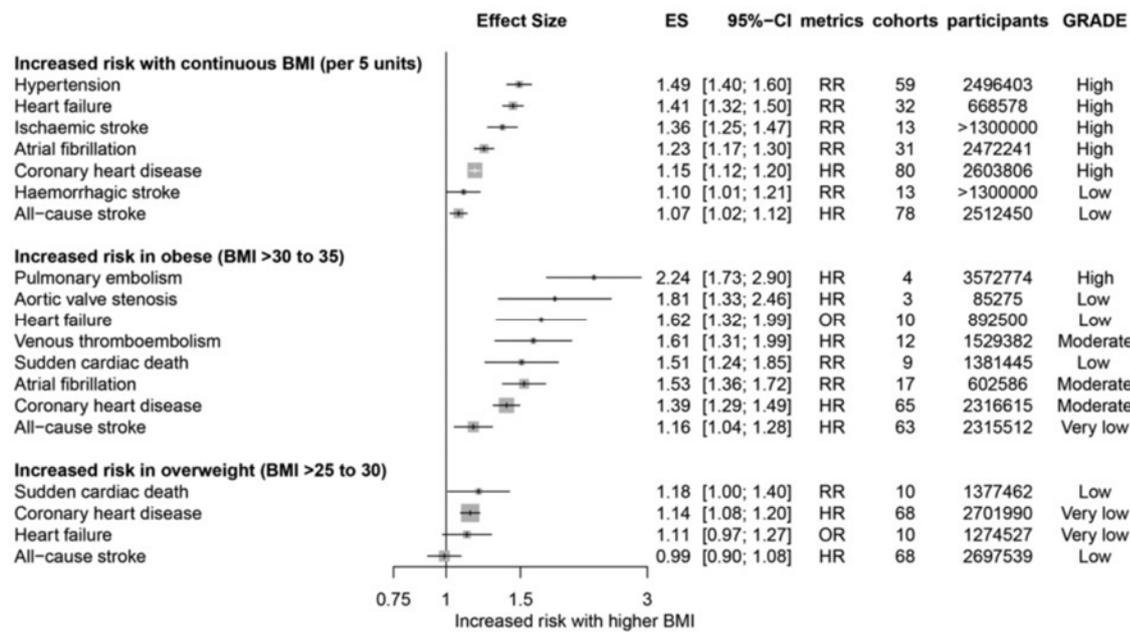
All but 6 of the 53 associations were statistically significant according to the random-effect model results. The increase in the risk of developing AF for every 5 kg/ m² increase in BMI was 23% (RR 1.23; 95CI 1.17–1.30; certainty of evidence, high).

The risk of AF was increased in the overweight population (BMI > 25–30 kg/m²) vs. the reference group with normal BMI values (HR 1.14; 95CI 1.08–1.20; certainty of evidence high).

The risk of developing AF was increased in the obese population (BMI > 30–35 kg/m²) compared with the normal group (HR 1.53; 95CI 1.36–1.72; certainty of evidence high).

³⁰³ Kim, M. S., Kim, W. J., Khera, A. V., et al. (2021). Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *European heart journal*, 42(34), 3388–403.

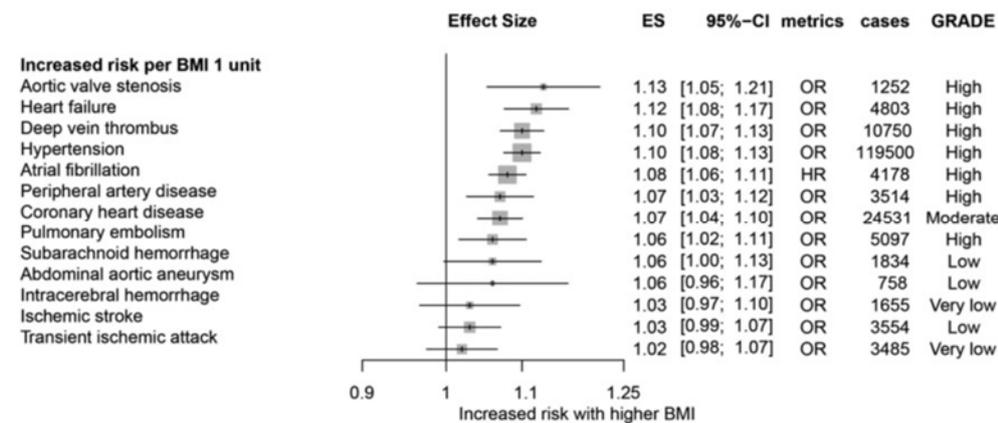
TABLE 16 RISK OF CARDIOVASCULAR EVENTS. OBSERVATIONAL STUDIES.



Source: Kim et al. (2021), Fig 2a

In an analysis of Mendelian randomization studies, 12 MR analyses (25 cohorts) were identified and classified into 22 outcomes. The proportion of variance (R²) explained by GI was 1.6–1.82%. Thirteen of the 22 outcomes were supported by a statistical power greater than 80%. All but transient ischaemic attacks (TIAs) and CHD (per 1kg/m²) met the MR assumptions. In the analysis, every 1 kg/m² increment in BMI was associated with an 8% increased risk of atrial fibrillation.

Table 17 RISK OF CARDIOVASCULAR EVENTS. PER 1KG/M2 MENDELIAN RANDOMISATION STUDIES

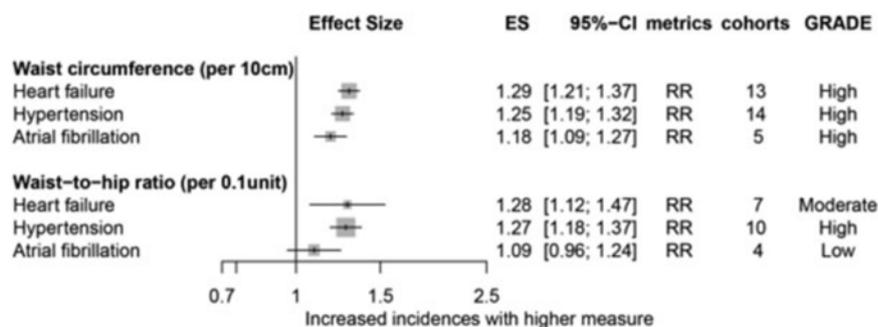


Source: Kim et al. (2021), Fig 2a

Subgroup analyses was conducted to evaluate the risk of cardiovascular diseases for central adiposity (A), All results were based on random-effects models. The risk of AF increased with

increasing waist circumference (ES 1.18, 95CI 1.09-1.27) per 10 cm. The risk of AF increased with increasing waist to hip ratio (ES 1.09, 95CI 0.96-1.25) per 0.1 unit, but the association was not statistically significant.

FIGURE 39 RISK OF CARDIOVASCULAR DISEASES FOR CENTRAL ADIPOSITY



High adiposity was associated with increased AF risk, supported by high-level evidence. The associations were consistent between sexes and across regions.

Cohort studies

Zia et al (2021) investigated how different anthropometric measures correlate to the risk of developing clinical AF in the Malmö Diet and Cancer cohort (MDC-cohort).³⁰⁴

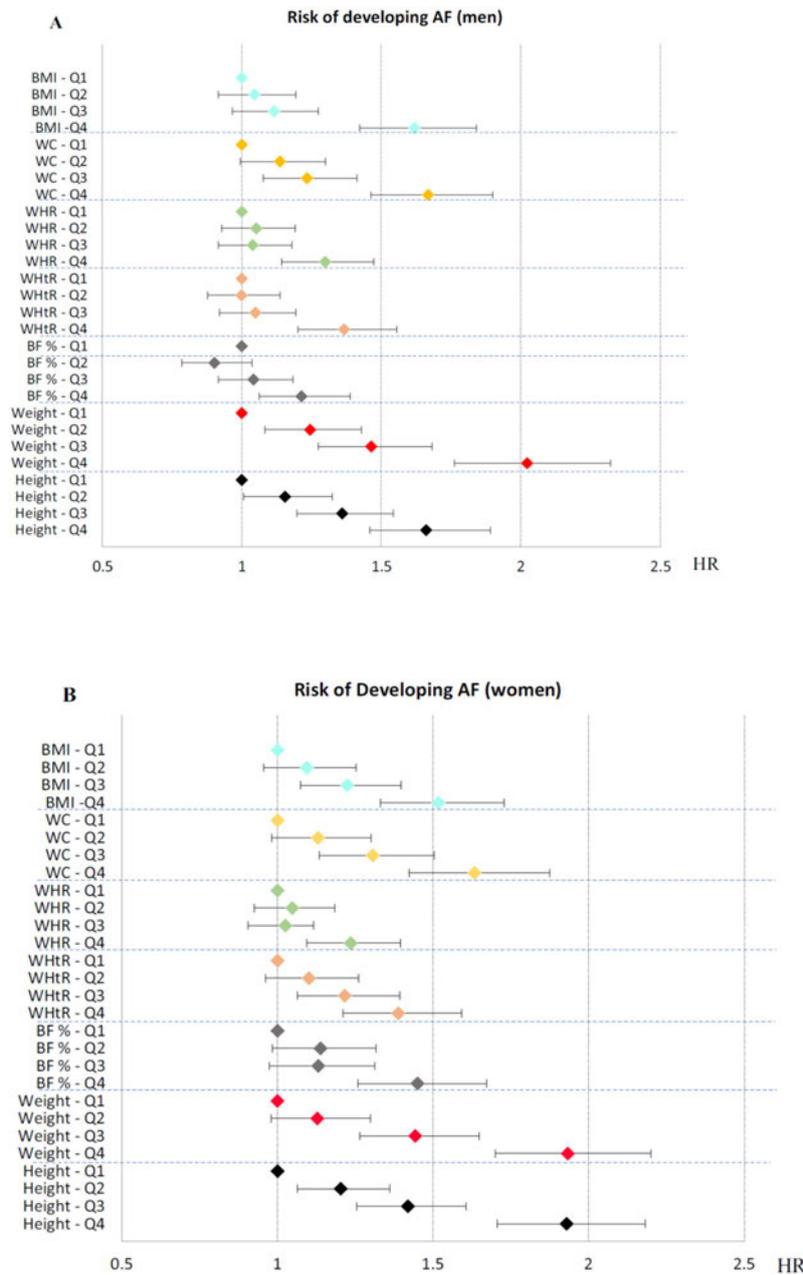
The MDC-cohort (n = 25,961) was examined in 1991-1996. The endpoint was clinical AF diagnosed in a hospital setting, and retrieved via linkage with national registers. Hazard Ratios for incident AF was calculated in relation to quartiles of body mass index, waist circumference, waist hip ratio, waist height ratio, body fat percentage, weight and height, using Cox regression with adjustment for age, biological (e.g. blood pressure, diabetes, blood lipid levels), and socioeconomic risk factors.

High values of BMI, WC, WHR, WHtR, BF %, weight or height were all associated with an increased risk for developing AF in both sexes, in three models.

After adjustment for multiple risk factors, the risk of AF was significantly increased in the 4th versus 1st quartile of weight (HR for men/women = 2.02/1.93), BMI (HR = 1.62/1.52), waist circumference (HR = 1.67/1.63), waist to hip ratio (HR = 1.30/1.24), waist to height ratio (1.37/1.39) and body fat percentage (HR = 1.21/1.45) in men/women. Measures of overall weight (BMI, weight) were slightly more predictive than measures of abdominal obesity (waist hip ratio and waist height ratio) both in men and women. All HRs were significant, with *p*-values (first vs. fourth quartile) ≤ 0.001. *P*-values for trends across quartiles were also statistically significant (*p* ≤ 0.002).

³⁰⁴ Zia, I., Johnson, L., Memarian, E., et al. (2021). Anthropometric measures and the risk of developing atrial fibrillation: a Swedish Cohort Study. *BMC cardiovascular disorders*, 21(1), 602. August meeting 2022

FIGURE 40 RISK OF DEVELOPING AF AND MEASURES OF OBESITY IN MEN AND WOMEN



All measures of obesity were associated with increased risk of developing AF. Both overall obesity and abdominal obesity were related to incidence of AF in this population-based study, although the relationship for overall obesity was stronger.

TABLE 18 COMPARISON OF HRs FOR DIFFERENT ANTHROPOMETRIC MEASURES

Men	HR	Δ C-statistics	p-value	Women	HR	Δ C-statistics	p-value
BMI	1.18 (1.13–1.23)			BMI	1.15 (1.11–1.2)		
Weight	1.26 (1.21–1.32)	0.005 (0.002–0.008)	<0.01	Weight	1.26 (1.21–1.31)	0.005 (0.004–0.007)	<0.01
BF %	1.08 (1.04–1.13)	−0.004 (−0.006 to −0.001)	0.01	BF %	1.13 (1.08–1.18)	−0.003 (−0.004 to −0.001)	0.01
WHR	1.08 (1.04–1.13)	−0.004 (−0.007 to −0.002)	<0.01	WHR	1.07 (1.02–1.11)	−0.003 (−0.004 to −0.001)	0.01
WC	1.18 (1.14–1.23)	0.001 (−0.001 to 0.003)	0.55	WC	1.18 (1.13–1.23)	0.001 (−0.001 to 0.002)	0.34
WHtR	1.11 (1.06–1.16)	−0.003 (−0.005 to −0.001)	<0.01	WHtR	1.12 (1.07–1.17)	−0.002 (−0.003 to −0.001)	<0.01
Height	1.19 (1.14–1.24)	0.001 (−0.004 to 0.005)	0.76	Height	1.24 (1.19–1.29)	0.004 (0.001–0.008)	0.02

Zia et al (2021) Table 3

This study confirmed the association between obesity and the risk of developing AF, BMI, height, weight, WC, WHR, WHtR and BF % were all risk factors for AF. However, HRs comparing the 4th versus 1st quartiles of anthropometric measures indicated that overall weight (e.g. BMI and weight) was more predictive than measures of abdominal obesity (e.g. WHR and WHtR).

Obesity is also a well-documented risk factor for hypertension and diabetes. Although Zia et al adjusted for hypertension and diabetes at the baseline examination, it was not possible to adjust for these risk factors during the follow-up period. It is therefore still possible that incidence of hypertension and diabetes could contribute to the increased risk of AF in obese individuals. Obesity is also a risk factor for other conditions associated with AF, such as obstructive sleep apnoea, heart failure and myocardial infarction, all of which are risk factors for AF.

Although several baseline characteristics were adjusted for there are still potential confounders, such as thyroid disease or pulmonary diseases, that have not been adjusted for. This is a limitation to this study.

The results indicate that an increase in weight, height, BMI, WC, WHR, WHtR and BF % all increase the risk of AF in both sexes, confirming previous results from similar studies. In contrast to several other cardiometabolic diseases, where abdominal obesity is associated with a higher risk, weight and general obesity seems to be more important than abdominal obesity as a risk factor for developing AF.

Summary and conclusions

Obesity is an established risk factor for several cardiovascular diseases, including increased incidence of atrial fibrillation. Obese individuals (body mass index >30 kg/m²) are significantly more likely to develop AF than those with a normal BMI (<25 kg/m²), with up to a 50% increased risk of developing AF (Zia et al 2021). In the Framingham Heart Study, every unit increase in BMI was associated with an approximate 5 % increase in risk [Wang et al 2004].

Measures of overall obesity (body mass index, body fat percentage (BF %) and weight) and abdominal obesity (WC, waist to hip ratio (WHR) and WHtR) have both been shown to correlate with the risk of developing AF.

Obesity increases total blood volume, causes structural changes to the heart, such as left and right ventricular hypertrophy. increased epi- and pericardial adipose tissue is associated with higher AF recurrence rate after ablation and higher burden of symptoms in patients with AF. These structural changes alter cardiac electrical circuits, which increase the risk of AF

Obesity has adverse effects on cardiovascular haemodynamics and cardiac structure and function, and increases the prevalence of AF, partly related to electroanatomic remodelling in obese patients (Lavie et al 2017). However, numerous studies, including in AF, have demonstrated an obesity paradox, where overweight and obese patients with these disorders

have a better prognosis than leaner patients with the same degree of severity of cardiovascular disease/AF.

Kim et al. (2021).conducted a review and meta-analysis of observational and Mendelian randomisation studies of adiposity and incident cardiovascular disease events. High adiposity was associated with increased AF risk in men and women, supported by high-level evidence.

From observational studies, BMI increase was associated with higher risks of AF. The risk of developing AF for every 5 kg/m² increase in BMI (RR 1.23; 95CI 1.17–1.30). The risk of AF was increased in overweight (BMI > 25–30) HR 1.14; 95CI 1.08–1.20; certainty of evidence high), and obese (BMI > 30–35): HR 1.53; 95CI 1.36–1.72; certainty of evidence high. The risk of AF also increased with increasing waist circumference (ES 1.18, 95CI 1.09-1.27) per 10 cm, and increasing waist to hip ratio (ES 1.09, 95CI 0.96-1.25) per 0.1 unit (not statistically significant, Mendelian randomisation studies indicated that each 1 kg/m² increment in BMI was associated with 8% increased risk of AF,

In the Atherosclerosis Risk in Communities (ARIC) study, 40% of patients were overweight and 27% were obese (Nalliah et al 2016). During follow-up, 1775 cases of AF were documented (7 events per 1000 patient-years). There was a linear relationship between increasing BMI and waist circumference and development of AF. Compared with individuals with normal weight, being obese nearly doubled the risk of AF.

Zia et al (2021) investigated how different anthropometric measures correlate to the risk of developing clinical AF in the Malmö Diet and Cancer cohort. All measures of obesity (BMI, WC, WHR, WHtR, BF %, weight or height) were associated with increased risk of developing AF in both sexes. All HRs were significant, with p-values (first vs. fourth quartile) ≤ 0.001. P-values for trends across quartiles were also statistically significant (p ≤ 0.002). Both overall obesity and abdominal obesity were related to incidence of AF in this population-based study, although the relationship for overall obesity was stronger. Measures of overall weight (BMI, weight) were slightly more predictive than measures of abdominal obesity (waist hip ratio and waist height ratio) both in men and women.

After adjustment for multiple risk factors, the risk of AF was significantly increased in the 4th versus 1st quartile of weight (HR for men/women = 2.02/1.93), BMI (HR = 1.62/1.52), waist circumference (HR = 1.67/1.63), waist to hip ratio (HR = 1.30/1.24), waist to height ratio (1.37/1.39) and body fat percentage (HR = 1.21/1.45) in men/women.

There is some evidence to suggest that long-term weight loss is associated with a reduction of AF burden [Mahajan et al 2015; Munger et al 2012]. Emerging data highlights the importance of weight loss and cardiovascular exercise in prevention and management of AF (Miller et al 2015). A meta-analysis including 7 cohort studies and 7681 patients evaluated the incidence and risk of AF following bariatric surgery (Chokesuwattanaskul et al 2020). Compared to controls, the pooled OR of AF in patients who underwent bariatric surgery was 0.42 (95CI: 0.22-0.83) after a median 7.9 years follow-up.

It is therefore concluded that in relation to obesity and being overweight, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation

and atrial flutter (Grade 2). A consistent association has been observed between obesity or overweight and atrial fibrillation and atrial flutter, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor should be retained in the RH and BoP SoPs.

The current definition of obesity should be adopted, including measures of waist circumference. Overweight should be added to the factor and definition.

Obstructive sleep apnoea

Current factor

onset and worsening - RH only

having obstructive sleep apnoea within the five years before the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

A growing body of evidence, detailed in recent review studies, supports a clear association between OSA and elevated likelihood of AF. There is evidence that OSA may contribute to the development of cardiac rhythm disorders. AF is the arrhythmia most commonly described in patients with OSA (Wu et al 2016). Although causality of the association is not established, there is growing evidence of a true biological link.

Summary of previous investigation

Many studies have reported a correlation between obstructive sleep apnoea (OSA) and atrial fibrillation. The nature of the relationship between these diseases is controversial; OSA has been found to be increased in patients with AF, and studies have proposed that OSA may increase the risk of AF/AFL.

Recent studies have shown that cardiac arrhythmias are common in patients with SA, with a reported prevalence of atrial fibrillation of 32–49%. There is uncertainty about the temporal relationship between sleep apnoea and AF. Most available data is derived from cross-sectional studies. An increased prevalence of OSA has been documented in patients with AF, and studies have proposed that OSA may increase the risk of AF. Gami et al (2007) reported that OSA was strong predictor of incident AF in Olmstead county cohort; especially in subjects aged under 65 years. This study showed for the first time that OSA strongly predicts the incidence of AF within about 5 years of its diagnosis, and the degree of nocturnal oxygen desaturation independently correlates with the risk of incident AF. The study identified an interaction of degree of OSA and obesity on risk of AF.

OSA is associated with multiple pathophysiological mechanisms that may be directly implicated in the pathogenesis of AF either by triggering its initiation or by affecting the

myocardial substrate to promote or maintain the arrhythmia; evidence supporting the biological plausibility of an association between sleep apnoea and AF, although mechanism is not completely understood. The postulated mechanisms of this association include increased sympathetic tone and systemic and pulmonary hypertension, intermittent hypoxia, and inflammation, which all facilitate electrical atrial remodeling.

Some authorities maintain that the association between obstructive sleep apnoea and atrial fibrillation is strong and is well established (e.g. Ng et al 2011). A recent review study by Loomba and Arora (2012) concluded that that available data concerning a causal relationship between AF and sleep apnoea is "quite convincing", but other investigators are more guarded in their assessment of whether sleep apnoea increase the incidence of AF (e.g. Gami et al 2007). Loomba and Arora (2012) maintain that OSA seems to lend itself to the development, progression, and post-ablation recurrence of AF.

Many studies have noted a correlation between obstructive sleep apnoea and atrial fibrillation, but studies on the role of OSA on AF recurrence after catheter ablation have yielded conflicting results, although OSA has been shown to be a predictor of AF recurrence following pulmonary vein isolation in some studies. There is some clinical evidence that treatment of OSA before ablation of AF lowers AF recurrence rate after cardioversion (Kanagala et al 2003). A meta-analysis on the role of OSA on AF recurrence after catheter-based pulmonary vein isolation by Ng et al (2011) found that OSA patients had a 25% greater risk of AF recurrence after catheter ablation than those without OSA (risk ratio 1.25, 95CI 1.08-1.45), based on 6 studies, with heterogeneous results....

Reviews

A growing body of evidence, detailed in recent review studies, supports a clear association between OSA and an elevated likelihood of atrial fibrillation.^{305 306}

AF is associated with pulmonary disease and obstructive sleep apnoea in particular.³⁰⁷ In a study of 188 consecutive patients with AF and no prior diagnosis of sleep apnoea who were scheduled to undergo AF ablation (Shapira-Daniels et al 2020), home sleep apnoea testing was positive in 155 (82.4%), of whom 82% had a predominant obstructive component. Among the 155 patients, sleep apnoea was considered severe in 23.2%, moderate in 32.9%, and mild in 43.8%. Continuous positive airway pressure (CPAP) therapy was prescribed in 85.9% of patients with moderate or severe sleep apnoea.

In a series of 39 patients diagnosed with both PAF and OSA, patients receiving treatment with continuous positive pressure ventilation had a lower incidence of AF recurrence at 12 months (42 versus 82% for patients who were not treated) [Kanagala et al 2003]. In another observational study, the incidence of OSA was compared between 151 patients referred for

³⁰⁵ Patel, N., Donahue, C., Shenoy, A., Patel, A., & El-Sherif, N. (2017). Obstructive sleep apnea and arrhythmia: A systemic review. *International journal of cardiology*, 228, 967–70.

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³⁰⁷ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

cardioversion for AF and 312 controls without AF referred for general cardiology evaluation [Garni et al 2004]. OSA was significantly more common in the patients with AF than in the control group (49 versus 32%). preoperative sleep studies were performed in a series of 121 patients referred for coronary artery bypass surgery [Moore et al 1996]. Postoperative AF was significantly more common among the 49 patients with an abnormal sleep study (39 versus 18% in patients with normal sleep studies).

As outlined in a review of AF by **Staerk et al (2017)**, OSA is highly prevalent and has been associated with other AF risk factors including hypertension, diabetes, coronary heart disease, myocardial infarction, and HF.³⁰⁸

The Sleep Heart Health Study found a 4-fold increase in the prevalence of AF with OSA and one third of participants had arrhythmia during sleep (Mehra et al 2006). The Olmsted County Study similarly found that OSA and its severity strongly predicted 5-year incidence of AF (HR 2.18; 95CI 1.34–3.54). In older individuals only the magnitude of nocturnal oxygen desaturation was predictive of AF (Gami et al 2004).

A meta-analysis of five prospective studies reported that OSA was associated with about a two-fold increased odds of post-operative AF (Qaddoura et al 2014).³⁰⁹

Patients with OSA have a higher recurrence of AF after cardioversion and catheter ablation (RR 1.25; 95CI 1.08–1.45) (Ng et al 2011).

The impact of OSA on AF outcomes was studied in the ORBIT-AF registry (Holmqvist et al 2015). Patients with OSA had more severe symptoms were at higher risk of hospitalization (HR 1.12; 95CI 1.03–1.22) than those without OSA, but had similar mortality, risk of stroke, or myocardial infarction. Patients with OSA who were treated with CPAP were less likely to progress to permanent AF subtype than those who were untreated (HR 0.66; 95CI 0.46–0.94).

Electroanatomical mapping in patients undergoing AF ablation has been used to characterize the AF substrate associated with OSA. Observed structural changes included increased atrial size and expansive areas of low voltage or electrical silence, which indicate fibrosis, loss of atrial myocardium, or electrical uncoupling. Prolonged and regional disparities in atrial conduction also were seen. AF associated with OSA tends to be refractory to cardioversion and catheter ablation particularly in patients with untreated OSA, highlighting the expansive atrial remodeling associated with OSA. In a rat model of AF, OSA was associated with atrial conduction slowing attributed to connexin-43 down-regulation and increased atrial fibrosis. Such atrial remodeling promoted the persistence of AF.

³⁰⁸ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17.

³⁰⁹ Qaddoura A, Kabali C, Drew D, et al (2014) . Obstructive sleep apnea as a predictor of atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *Can J Cardiol.*; 30:1516–22

Several mechanisms may account for the development of AF and the AF substrate in patients with OSA.³¹⁰ Surges of sympathetic activity induced by hypoxia and the chemoreflex near the end of an apnoeic episode result in transient blood pressure rises. Vigorous inspiratory efforts during apnoea accentuate the fluctuation of intrathoracic pressure increasing left atrial volume (stretch) and pressure. An increase in oxidative stress signalling and systemic inflammatory mediators may promote atrial remodelling. Hypercapnia acutely prolongs ERP and slows conduction velocity, but with return of eucapnia delayed recovery of conduction has been associated with increased AF vulnerability. Negative tracheal pressure shortens atrial ERP and atrial monophasic action potential via vagal stimulation, which enhances AF inducibility.

Some reviewers emphasise the importance of obesity as a comorbidity of OSA and a confounder in the association between OSA and cardiovascular disease.³¹¹ Although adults with OSA have almost 2 to 4 times increased risk of developing AF, and those with AF have a high prevalence of OSA reported in some trials up to 39%, OSA may not be the cause of AF in all of these individuals.³¹² Their coexistence may in part be due to common risk factors, including advanced age, obesity, diabetes, hypertension, and structural heart disease. The relationship between AF and OSA is multifactorial; however, there may be a direct causal relationship that is mutually perpetuating.

As outlined by **Goudis and Kelikoglou (2017)**, several pathophysiological mechanisms, including apnoea-induced hypoxia, intrathoracic pressure shifts, sympathovagal imbalance, atrial remodelling, oxidative stress, inflammation and neurohumoral activation have been implicated in the occurrence of AF in OSA patients.³¹³ OSA has been shown to reduce success rates of antiarrhythmic drugs, electrical cardioversion and catheter ablation in AF. Effective prevention of obstructive respiratory events by continuous positive airway pressure ventilation (CPAP) reduces sympathovagal activation and recurrence of AF.

During an apnoeic episode, when there is collapse of the pharyngeal airway leading to interruption of ventilation, vagal efferent output is enhanced, which leads to transient bradycardia as well as a shortened atrial effective refractory period.³¹⁴ Episodic hypoxaemia during sleep apnoea in animal models results in surges of the sympathetic nervous system, thus reducing the induction threshold for AF. However, the pathophysiology involves more than neurohormonal activation. Sympathetic ganglion blockade provides only incomplete protection against AF associated with apnoea. There is also electrical and structural remodelling of atrial tissue due to stretch mediated shortening of atrial refractoriness with resultant susceptibility to excitatory stimuli. Collagen deposition and changes in gap junction

³¹⁰ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17.

³¹¹ Bauters, F., Rietzschel, E. R., Hertegonne, K. B., et al. (2016). The Link Between Obstructive Sleep Apnea and Cardiovascular Disease. *Current atherosclerosis reports*, 18(1), 1

³¹² Diamond, J. A., & Ismail, H. (2021). Obstructive Sleep Apnea and Cardiovascular Disease. *Clinics in geriatric medicine*, 37(3), 445–46.

³¹³ Goudis, C. A., & Ketikoglou, D. G. (2017). Obstructive sleep and atrial fibrillation: Pathophysiological mechanisms and therapeutic implications. *International journal of cardiology*, 230: 293–300.

³¹⁴ Diamond, J. A., & Ismail, H. (2021). Obstructive Sleep Apnea and Cardiovascular Disease. *Clinics in geriatric medicine*, 37(3), 445–46.

function have been described in individuals with OSA. Repetitive apnoeic episodes resulting in exaggerated changes in intrathoracic pressure lead to left atrial dilatation and fibrosis.

Electrophysiology studies of atria in patients with OSA show areas of slow conduction, reduced atrial ECG amplitude, and complex fractionated atrial ECGs, correlating with the electrical remodeling, Atrial electrical remodelling, structural remodelling, and neuro-hormonal activation during apnoeic episodes provide the milieu for the induction of AF.

Treatment of AF is more difficult in patients with OSA. In the ORBIT-AF trial, patients with OSA had significantly worse symptoms and were more likely to be on rhythm control therapy. Holmqvist et al 2016 Individuals with OSA had more episodes of recurrent AF, even after catheter ablation.

Treatment of OSA is necessary for proper management of AF and maintenance of sinus rhythm.³¹⁵ The cohort of patients treated with CPAP in the ORBIT-AF trial were less likely to progress to persistent AF than those not treated with CPAP (Fava et al 2014) Other trials have shown less AF after catheter ablation in those patients with OSA treated with CPAP compared with a 57% risk of recurrence of AF in those not treated with CPAP (Li et al 2014).

Summary and conclusions

A growing body of evidence, detailed in recent review studies, supports a clear association between OSA and an elevated likelihood of atrial fibrillation There is evidence that OSA may contribute to the development of cardiac rhythm disorders. AF is the arrhythmia most commonly described in patients with OSA (Wu et al 2016). There is a possible causal relationship between obstructive sleep apnoea and AF, but the causality of the association is not established.

AF is associated with pulmonary disease and obstructive sleep apnoea in particular. In a study of 188 consecutive patients with AF and no prior diagnosis of sleep apnoea who were scheduled to undergo AF ablation, home sleep apnoea testing was positive in 155 (82.4%), of whom 82% had a predominant obstructive component (Shapira-Daniels et al 2020)

It is not clear if OSA causes cardiovascular disease or is only associated with cardiac disease, because both conditions share independent risk factors, such as age and obesity (Diamond & Ismail 2021).

OSA is highly prevalent and has been associated with other AF risk factors including hypertension, diabetes, coronary heart disease, myocardial infarction, and HF (Staerk et al 2017)

Obstructive sleep apnoea is recognised to be an independent risk factor for AF. Goudis & Ketikoglou 2017). Several pathophysiological mechanisms, including apnoea-induced

³¹⁵ Diamond, J. A., & Ismail, H. (2021). Obstructive Sleep Apnea and Cardiovascular Disease. *Clinics in geriatric medicine*, 37(3), 445–46.
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hypoxia, intrathoracic pressure shifts, sympathovagal imbalance, atrial remodelling, oxidative stress, inflammation and neurohumoral activation have been implicated in the pathogenesis of AF in OSA patients. OSA has been shown to reduce success rates of antiarrhythmic drugs, electrical cardioversion and catheter ablation in AF. Some reviewers emphasise the importance of obesity as a comorbidity of OSA and a confounder in the association between OSA and cardiovascular disease

A meta-analysis of five prospective studies reported that OSA was associated with about a two-fold increased odds of post-operative AF (Qaddoura et al 2014).

The impact of OSA on AF outcomes was studied in the ORBIT-AF registry (Holmqvist et al 2015). Patients with OSA had more severe symptoms were at higher risk of hospitalisation (HR 1.12; 95CI 1.03–1.22) than those without OSA, but had similar mortality, risk of stroke, or myocardial infarction. Patients with OSA who were treated with CPAP were less likely to progress to permanent AF subtype than those who were untreated (HR 0.66; 95CI 0.46–0.94).

Several mechanisms may account for the development of AF and the AF substrate in patients with OSA (Staerk et al 2017) Surges of sympathetic activity induced by hypoxia and the chemoreflex near the end of an apnoeic episode result in transient blood pressure rises. Vigorous inspiratory efforts during apnoea accentuate the fluctuation of intrathoracic pressure increasing left atrial volume (stretch) and pressure. An increase in oxidative stress signalling and systemic inflammatory mediators may promote atrial remodelling. Hypercapnia acutely prolongs ERP and slows conduction velocity, but with return of eucapnia delayed recovery of conduction has been associated with increased AF vulnerability negative tracheal pressure shortens atrial ERP and atrial monophasic action potential via vagal stimulation, which enhances AF inducibility.

It is not clear if OSA causes cardiovascular disease or is only associated with cardiac disease, because both conditions share independent risk factors (Diamond & Ismail 2021). Although adults with OSA have almost 2 to 4 times increased risk of developing AF, and those with AF have a high prevalence of OSA reported in some trials up to 39%, OSA may not be the cause of AF in all of these individuals. Their coexistence may in part be due to common risk factors, including old age, obesity, diabetes, hypertension, structural heart disease. The relationship between AF and OSA is multifactorial; and a direct causal relationship that is mutually perpetuating is possible.

Treatment of OSA is necessary for proper management of AF and maintenance of sinus rhythm. Patients with OSA have a higher recurrence of AF after cardioversion and catheter ablation (RR 1.25; 95CI 1.08–1.45) (Ng et al 2011).

It is therefore concluded that in relation to obstructive sleep apnoea, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between obstructive sleep apnoea and atrial tachyarrhythmias, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for obstructive sleep apnoea should be added to the BoP SoP.

Smoking

Current factor

onset and worsening - RH only

smoking at least three pack-years of cigarettes, or the equivalent thereof in other tobacco products, before the clinical onset of atrial fibrillation or atrial flutter, and where smoking has ceased, the clinical onset of atrial fibrillation or atrial flutter has occurred within one year of cessation;

Summary of important issues

Smoking is associated with incident AF (Staerk et al 2017) and smoking is a RF for AF across various races and ethnicities. Smoking is a risk factor for AF and also for conditions that can predispose to heart failure and subsequent development of AF. Based on published literature, smoking is associated with a modest increased risk of incident AF. Smoking cessation seems to reduce, but not entirely eliminate, excess risk of AF.

Summary of previous investigation

It has been suggested that the acute effects of smoking may be involved in the initiation of AF. However, whether smoking increases the risk of atrial fibrillation is uncertain. Some modest positive associations between smoking and AF risk have been reported in cohort studies from the US, but Scandinavian studies have documented null associations.

In the ARIC cohort study (Chamberlain et al 2011) smoking was associated with an increased incidence of AF, with more than a two-fold increased risk of AF/AFL attributed to current smoking. The associations were similar for AF and AFL. The risk of incident AF/AFL increased with increasing cigarette-years of smoking, and appeared to be greater among current smokers than former smokers with similar cigarette-years of smoking. There was a stronger association of AF/AFL risk with current smoking than that previously reported in similar cohort studies.

In the Framingham Heart Study, cigarette smoking conferred a 40% increased odds of developing AF/AFL among women, but there was no association among men (Benjamin et al 1994). Current smoking was not a significant predictor for AF in the Framingham risk score for AF (Schnabel et al 2009). Compared with never smokers, the Rotterdam study reported a 51% and 49% increased risk of incident AF among current and former smokers, respectively, which did not differ by sex (Heeringa et al 2008). A 37% increased risk of AF among ever smokers was reported in the Manitoba Follow-Up Study (Krahn et al 1995). No association was found between smoking and AF in the Danish Diet, Cancer, and Health Study (Frost et al 2005) or the Multifactor Primary Prevention Study (Wilhelmsen et al 2001)

Reviews

Sever recent narrative review studies note that smoking is associated with incident AF.^{316 317}
318

Among relevant analytical studies, the Framingham Heart Study showed that within the last 50 years, the frequency of smoking among participants with new-onset AF has decreased. Between 1998–2007, only 12.7% of AF-affected participants were smokers as compared to 15.6% in the prior decade (Schnabel et al 2015).³¹⁹

The Rotterdam Study found that both former and current smoking were equally associated with increased AF risk (Heeringa et al 2018). In the Atherosclerosis Risk in Communities Study (ARIC) study, the multivariable-adjusted incidence of AF was 1.58 times higher in ever smokers (former and current) and two-fold higher (HR 2.05) in current smokers as compared with non-smokers. A dose-response association was observed with increasing cigarette-years (Chamberlain et al 2011). In the CHARGE-AF consortium, incident AF was 1.44 times higher in current smokers as compared with nonsmokers (Alonso et al 2013).

Second-hand tobacco exposure during very early life also has been associated with risk of AF (O’Neal et al 2014).³²⁰ Exposure during gestational development or early childhood is associated with approximately 40% increased risk of AF (Dixit et al 2016).

Smoking is thought to increase AF susceptibility through indirect and direct mechanisms.³²¹ Smoking may increase myocardial ischemia by increasing systemic catecholamine and myocardial work, reducing oxygen carrying capacity, and promoting coronary vasoconstriction. In addition, smoking accelerates atherosclerosis through effects on lipids, endothelial function, oxidative stress, inflammation, and thrombosis. These effects may indirectly increase AF susceptibility by predisposing to atrial ischaemia, myocardial infarction, and HF. Reduced lung function and chronic obstructive pulmonary disease also increase vulnerability to AF.

Smoking and nicotine directly contribute to the AF substrate.³²² In a case-control study of patients undergoing coronary artery bypass, the volume of atrial fibrosis in smokers was shown to be dose-dependent, and in non-smokers nicotine was shown to induce a pattern of collagen type III expression in atrial tissue culture that was similar to that observed in smokers. In a dog model, nicotine induced interstitial fibrosis and increased AF susceptibility.

³¹⁶ Seccia TM, Calò LA. (2018). Smoking causes atrial fibrillation? Further evidence on a debated issue. *Eur J Prev Cardiol.*; 25(13): 1434-6

³¹⁷ Panchal, G., Mahmood, M., & Lip, G. (2019). Revisiting the risks of incident atrial fibrillation: a narrative review. Part 1. *Kardiologia polska*, 77(4), 430–6

³¹⁸ Watanabe I. (2018). Smoking and risk of atrial fibrillation. *Journal of cardiology*, 71(2), 111–112

³¹⁹ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17.

³²⁰ O’Neal WT, Qureshi WT, Judd SE, et al (2015). Environmental Tobacco Smoke and Atrial Fibrillation: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Journal of occupational and environmental medicine*. 2015; 57:1154–8.

³²¹ Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17

³²² Staerk, L., Sherer, J. A., Ko, D., et al (2017). Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circulation research*, 120(9), 1501–17

Prolongation in the APD may increase arrhythmia susceptibility, but the pro-arrhythmic effect of nicotine has not been confirmed.

Ahmed et al. showed that atrial fibrillation was identified in 9.5% in smokers vs 7.8% in non-smokers ($p < 0.001$) and smoking was associated with a 15% increased risk of AF during 10 years follow up in 11,047 participants.³²³ However, heterogeneities in the association were observed among subgroups; the association was stronger in young compared to older participants and in those with prior cardiovascular disease compared to without cardiovascular disease, also the association was significant in blacks but not in whites.

As noted in a narrative review by Panchal et al (2019), several studies have explored the relationship between smoking and development of AF, in particular, the influence of duration and quantity of tobacco on AF risk.³²⁴ An analysis of 15 221 patients diagnosed with AF from the Shinken database revealed that smokers were more likely to develop AF, with an incidence rate of 9.0 and 5.0 per 1000 patient-years for smokers and nonsmokers, respectively (Suzuki et al 2011/2015).

There was no difference in the risk of AF between men and women ($P = 0.195$). The Manitoba follow-up study (Krahn et al 1995) also demonstrated an increased risk of AF in smokers (RR 1.37; 95CI 1.00–1.87). The ARIC study (Chamberlain et al 2011) showed that both current (HR 2.05; 95CI, 1.71–2.47) and former smokers (HR 1.32; 95CI 1.10– 1.57) had an increased risk of AF, compared with never smokers. Those with the longest smoking history (>675 cigarette-years) had the highest risk of AF (RR 2.10; 95CI 1.74–2.53) compared with non-smokers. Those who quit smoking had a marginally lower risk of AF (HR 0.88; 95CI 0.65–1.17), compared with current smokers, although the difference was nonsignificant ($P = 0.38$). Chamberlain et al 2011

The Rotterdam study also noted that current (RR 1.51; 95CI 1.07–2.12) and former (RR 1.49; 95CI 1.14–1.97) smokers had an increased risk of incident AF (Heeringa et al 2008).

Smoking leads to an increased risk of AF by inducing oxidative stress, inflammation, and atrial fibrosis. It is not known which pathophysiological changes are reversible to return AF risk to baseline.

Meta-analyses

Although smoking is known to be associated with cardiovascular diseases, the number of large-scale cohort studies on the association between smoking and atrial fibrillation is limited and the results obtained are also inconsistent. **Wang et al (2018)** conducted a meta-analysis of prospective cohort studies of smoking as a risk factor for incident AF in men and women.³²⁵ Using AF- and smoking-related keywords, a comprehensive literature search on PubMed, Embase and Web of Science to December 2016. The pooled relative risk (RR) of the included

³²³ Watanabe I. (2018). Smoking and risk of atrial fibrillation. *Journal of cardiology*, 71(2), 111–112

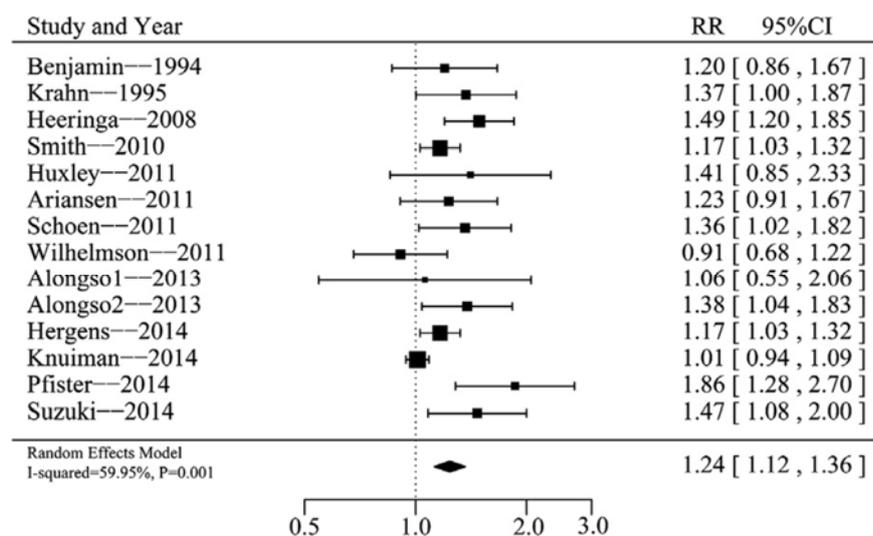
³²⁴ Panchal, G., Mahmood, M., & Lip, G. (2019). Revisiting the risks of incident atrial fibrillation: a narrative review. Part 1. *Kardiologia polska*, 77(4), 430–6

³²⁵ OSA is highly prevalent and has been associated with other AF risk factors including hypertension, diabetes, coronary heart disease, myocardial infarction, and HF

studies was estimated by using the random-effects model. Subgroup, heterogeneity and sensitivity analyses were also conducted.

A total of 14 prospective studies and 222,159 individuals were included in the meta-analysis, and the pooled RR of the 14 studies for the occurrence of AF in smoking populations was 1.24 (95CI 1.12-1.36; $p < 0.0001$).

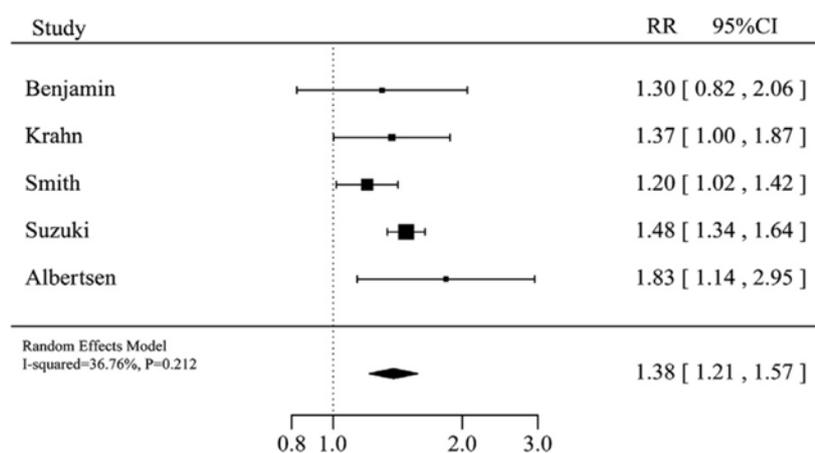
FIGURE 41 THE RR AND 95% CI FOR AF BY SMOKING. RR AND 95% CI OF AF FOR SMOKING VERSUS NON-SMOKING GROUPS.



Wang et al (2018), Fig 2, p 62

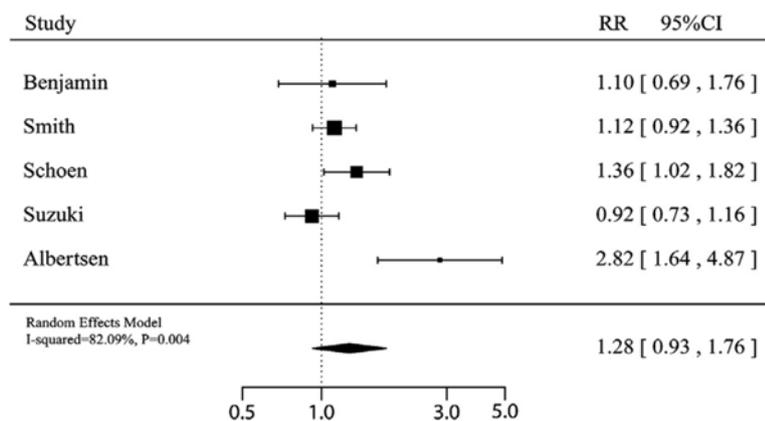
The pooled RR in men was 1.38 (95CI 1.21-1.57 $p < 0.0001$) versus 1.28 in women (95CI, 0.93-1.76; $p = 0.1356$).

FIGURE 42 RR FOR AF, SMOKING COMPARED WITH NON-SMOKING FOR MALES



Wang et al (2018), Fig 3 p 62

FIGURE 43 RR FOR AF, SMOKING COMPARED WITH NON-SMOKING FOR FEMALES



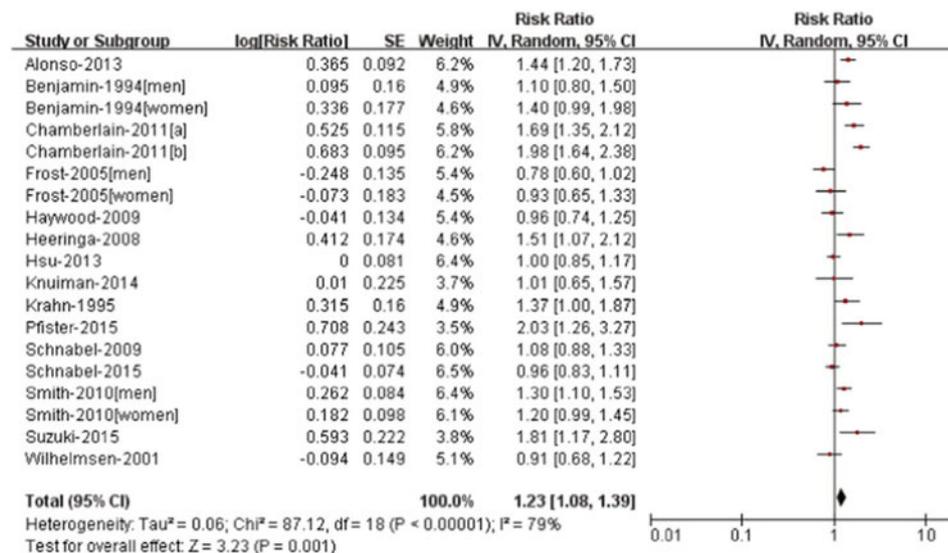
Wang et al (2018), Fig 4, p 63

The male-to-female ratio of relative risk (RRR) was 1.17 (95CI 0.84-1.63; p=0.3418) of smoking versus non-smoking individuals.

Zhu et al (2016) conducted a meta-analysis to identify the quantitative association between smoking and AF risk.³²⁶ systematically retrieved relevant studies reporting on the association between smoking and AF using the Cochrane Library, PubMed, and Embase databases. a random effects model was used to pool the effect estimates.

Sixteen prospective studies with 286,217 participants and 11,878 AF cases met inclusion criteria. A higher prevalence of AF was confirmed among smokers (RR 1.23, 95CI 1.08-1.39; P=0.001).

FIGURE 44 SMOKING AND RISK OF AF



Zhu et al (2016), Fig 3

The results were stable in sensitivity analysis. The pooled RRs showed consistent positive associations in most subgroups. Specifically, 8 articles compared both current smokers (RR

³²⁶ Zhu, W., Yuan, P., Shen, Y., et al. (2016). Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies. International journal of cardiology, 218, 259–66. August meeting 2022

1.39, 95CI 1.11-1.75) and former smokers (RR 1.16, 95CI 1.00-1.36) with never smokers. Four articles compared ever smokers (pooled RR 1.21, 95CI 0.93-1.57) with never smokers, and 7 articles compared current smokers (pooled RR 1.21, 95CI 1.03-1.42) with non-current smokers

TABLE 19 SUBGROUP ANALYSES OF SMOKING STATUS AND RISK OF INCIDENT AF

	Numbers of reports	RR	95% CI	I ² values(%)	P values for heterogen
Overall results	19	1.23	1.08-1.39	79	<0.00001
Comparisons by smoking status					
Former vs. never smoking	7	1.16	1.00-1.36	60	0.02
Current vs. never smoking	9	1.39	1.11-1.75	82	<0.00001
Ever vs. never smoking	4	1.21	0.93-1.57	84	0.0003
Current vs. non-current smoking	9	1.21	1.03-1.42	80	<0.00001
Smoking exposure					
As a main exposure	3	1.85	1.59-2.16	0	0.39
As a confounder	16	1.15	1.03-1.28	71	<0.00001
Sex					
Men	3	1.05	0.76-1.44	81	0.006
Women	3	1.18	1.01-1.37	25	0.27
Mixed	13	1.29	1.09-1.52	83	<0.00001
Geographic region					
Europe or Oceania	8	1.13	0.95-1.36	69	0.02
North America	10	1.26	1.06-1.50	85	<0.00001
Asia	1	1.81	1.17-2.79	NA	NA
Selection of population					
Population-based	16	1.24	1.08-1.42	80	<0.00001
Hospital-based	3	1.13	0.85-1.50	71	0.03
Study quality					
High (8-9 scores)	17	1.24	1.09-1.41	81	<0.00001
Low (≤7 scores)	2	1.11	0.74-1.66	71	0.06
Follow-up years					
<10 years	6	1.17	0.92-1.48	80	0.2
≥10 years	12	1.36	1.16-1.58	84	<0.00001
Publication year					
≤2000	3	1.28	1.06-1.54	0	0.51
2001-2009	6	1.00	0.85-1.17	51	0.07
≥2010	10	1.36	1.14-1.63	85	<0.00001
Maximum adjusted covariates					
Only adjusted for age/sex/race	5	1.13	0.95-1.36	69	0.002
Adjusted for more covariates	14	1.25	1.08-1.45	79	<0.00001

Zhu et al (2016), Table 2

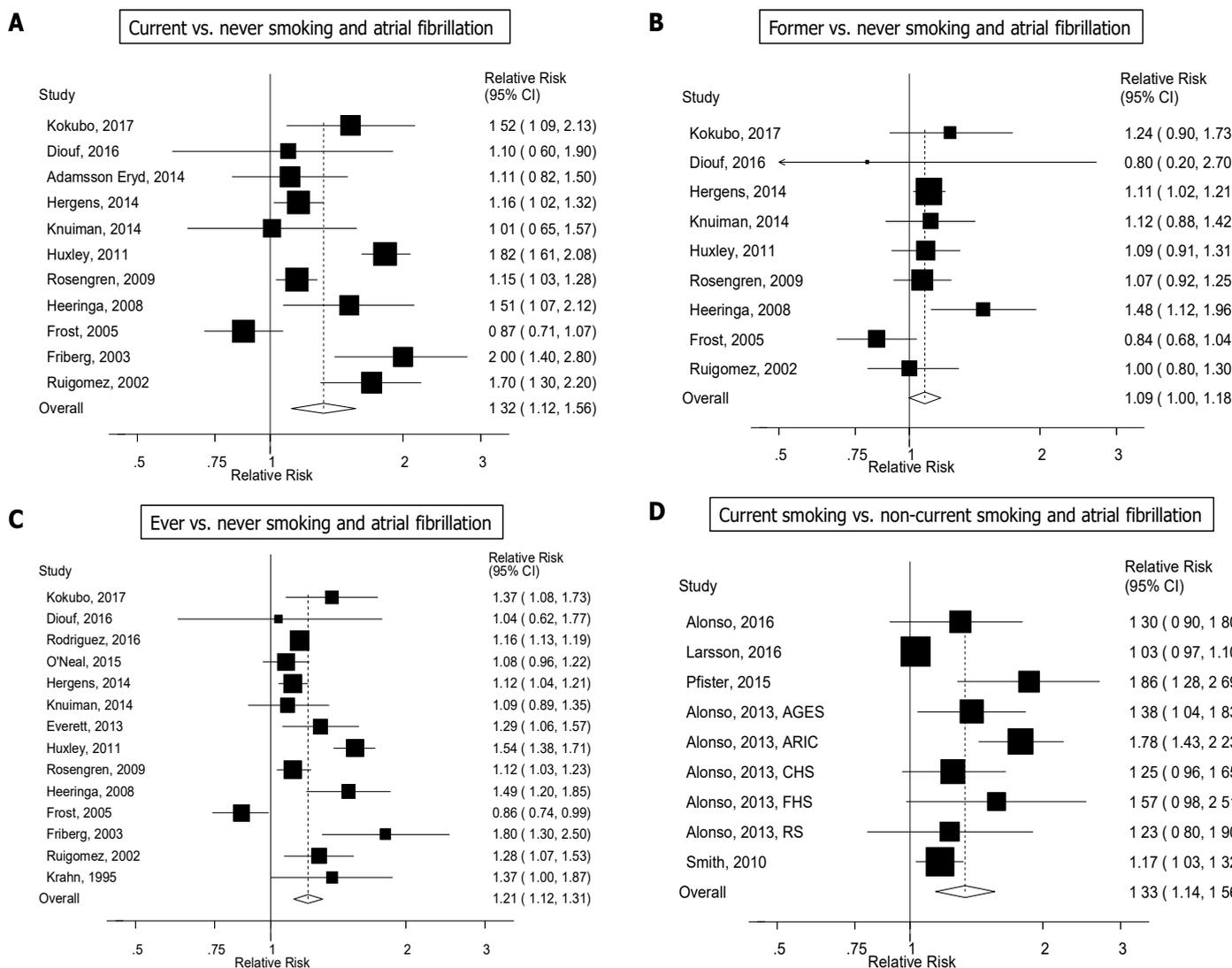
Based on the published literature, Zhu et al concluded that smoking is associated with a modest increased risk of incident AF. It was estimated that 6.7% of the total risk of AF in men and 1.4% of the risk in women were attributable to smoking worldwide. Smoking cessation seemed to reduce, but not entirely eliminate the excess risk of AF

Aune et al (2018) conducted a systematic review and meta-analysis to clarify the association of Tobacco smoking and the risk of atrial fibrillation: searched the PubMed and Embase databases for studies of smoking and atrial fibrillation to July 2017.³²⁷ Prospective studies and nested case-control studies within cohort studies reporting adjusted relative risk estimates and 95% confidence intervals (CIs) of atrial fibrillation associated with smoking were included. Summary relative risks (95% CIs) were estimated using a random effects model.

Twenty nine prospective studies (22 publications) were included. The summary relative risk was 1.32 (95CI 1.12-1.56, I² = 84%, n = 11 studies) for current smokers, 1.09 (95CI 1.00-1.18, I² = 33%, n = 9) for former smokers and 1.21 (95CI 1.12-1.31, I² = 80%, n = 14) for ever smokers compared to never smokers. the summary relative risk for AF in current versus non-current smokers was 1.33 (95CI 1.14-1.56, I² = 78%, n = 10).

³²⁷ Aune, D., Schlesinger, S., Norat, T., et al. (2018). Tobacco smoking and the risk of atrial fibrillation: A systematic review and meta-analysis of prospective studies. *European journal of preventive cardiology*, 25(13), 1437-51
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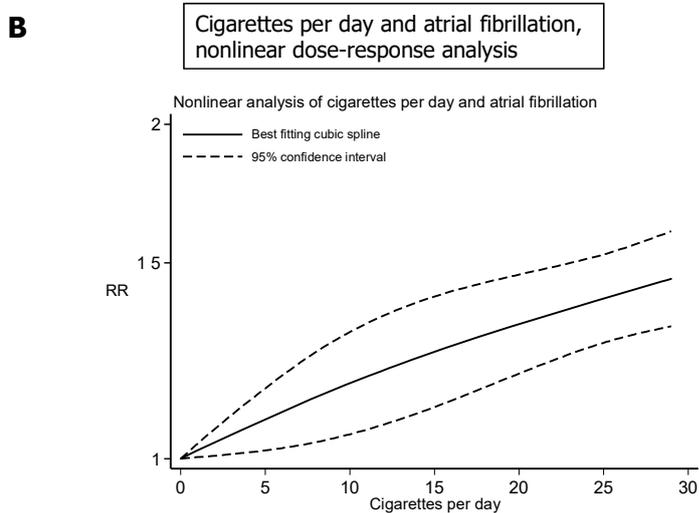
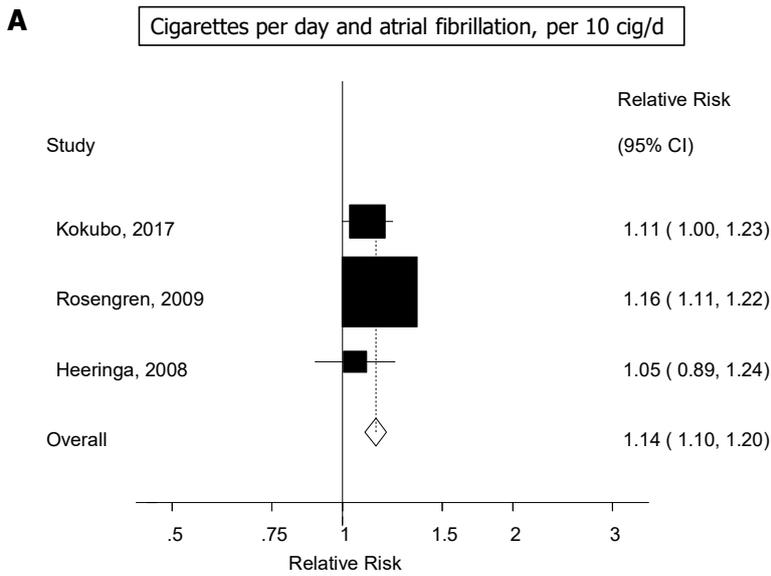
FIGURE 45 SMOKING STATUS AND AF



Aune et al (2018), Fig 2

The summary relative risk was 1.14 (95CI 1.10-1.20, I2 = 0%, n = 3) per 10 cigarettes per day and 1.16 (95CI 1.09-1.25, I2 = 49%, n = 2) per 10 pack-years, there was no evidence of a non-linear association for cigarettes per day, P non-linearity = 0.17. The summary RRs were 1.09 (95CI 1.02-1.16) for 5 cigarettes per day, 1.17 (95CI 1.05-1.30) for 10 cigarettes per day, 1.25 (95CI 1.11-1.40) for 15 cigarettes per day, 1.32 (95CI 1.19-1.46) for 20 cigarettes per day, 1.39 (95CI 1.27-1.53) for 25 cigarettes per day, and 1.45 (95CI 1.32-1.60) for 29 cigarettes per day compared to zero.

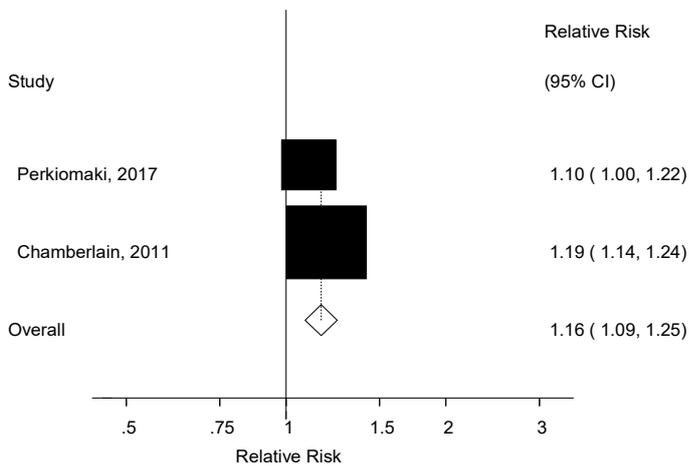
FIGURE 46 DOSE RESPONSE OF DAILY SMOKING DOSE AND AF



Aune et al (2018), Fig 3, p 32

The summary RR was 1.16 (95CI 1.09-1.25, $I^2=49\%$, $p_{\text{heterogeneity}}=0.16$, $n=2$) per 10 pack-years

FIGURE 47 PACK-YEARS AND ATRIAL FIBRILLATION, DOSE-RESPONSE PER 10 PACK-YEARS



This meta-analysis of prospective studies suggests that smoking is associated with an increased risk of atrial fibrillation in a dose-dependent manner, that current, former and ever smoking is associated with a 32%, 9%, and 21% increased risk of developing atrial fibrillation compared to never smokers. current vs. non-current smoking was associated with a 33% increase in the risk and in dose-response analyses smoking 10 cigarettes per day and 10 pack-years was associated with 14% and 16% increases in the relative risk of atrial fibrillation, respectively. There was a clear dose-response relationship between increasing number of cigarettes per day and risk of atrial fibrillation and no evidence that the association was nonlinear. The strength of the association by smoking status is consistent with a dose-response relationship as the association was strongest for current smokers, intermediate for ever smokers (current and former smokers combined) and lowest for former smokers.

The impact of smoking on postoperative atrial fibrillation in patients undergoing cardiac surgery remains controversial. **Wan et al (2021)** performed a meta-analysis to explore the association of smoking with postoperative atrial fibrillation in patients with cardiac surgery.³²⁸

The authors systematically searched 2 computer-based databases (PubMed and EMBASE) to July 2019 for relevant studies. A random-effects model was selected to pool the odds ratios (ORs) and 95% confidence intervals (CIs). In this meta-analysis, the protocol and reporting of the results were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

A total of 36 studies were included in the meta-analysis. Overall, smoking was not associated with an increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery (OR 0.89; 95CI 0.79-1.02). The corresponding results were stable in the subgroup analyses. smoking was not associated with an increased risk of postoperative atrial fibrillation regardless of the type of cardiac surgery: coronary artery bypass grafting (OR 0.91; 95CI 0.77-1.07), valve surgery (OR 0.15; 95CI 0.01-1.56), and coronary artery bypass grafting+valve surgery (OR 0.91; 95CI 0.70-1.18).

Based on currently published studies, smoking is not associated with an increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery.

Cohort studies

Zuo et al (2018) examined the associations of smoking status and plasma cotinine levels, a marker of nicotine exposure, with risk of incident AF in the Hordaland Health Study.³²⁹ this was a prospective analysis of 6682 adults aged 46-74 years without known AF at baseline. Participants were followed via linkage to the Cardiovascular Disease in Norway (CVDNOR) project and the Cause of Death Registry. Smoking status was assessed by both questionnaire and plasma cotinine levels.

³²⁸ Wan, Q., Li, S., & Hu, J. (2021). Association of smoking with postoperative atrial fibrillation in patients with cardiac surgery: A PRISMA-compliant article. *Medicine*, 100(23), e26179.

³²⁹ Zuo, H., Nygård, O., Vollset, S. E., et al (2018). Smoking, plasma cotinine and risk of atrial fibrillation: the Hordaland Health Study. *Journal of internal medicine*, 283(1), 73–82

A total of 538 participants developed AF over a median follow-up period of 11 years. Using questionnaire data, current smoking (HR: 1.41, 95CI 1.09-1.83), but not former smoking (HR 1.03, 95CI 0.83-1.28), was associated with an increased risk of AF after adjustment for sex, age, body mass index, hypertension, physical activity and education. Using plasma cotinine only, the adjusted HR was 1.40 (95CI 1.12-1.75) for participants with cotinine \geq 85 nmol L⁻¹ compared to those with cotinine <85 nmol L⁻¹. However, the risk increased with elevated plasma cotinine levels until 1199 nmol L⁻¹ (HR: 1.55, 95CI 1.16-2.05 at the third group vs. the reference group) and plateaued at higher levels.

Current, but not former smokers, had a higher risk of developing AF. Use of plasma cotinine measurement corroborated this finding.

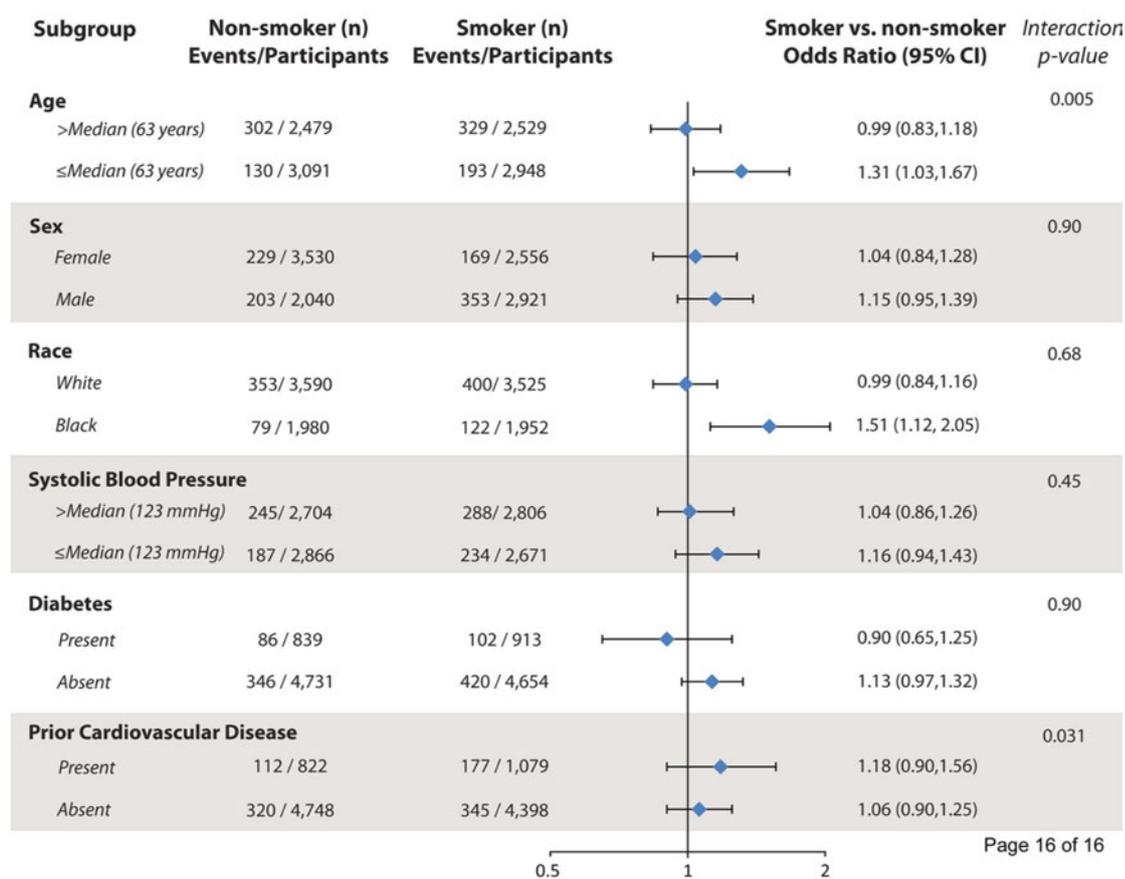
Imtiaz Ahmad et al (2018) examined the association between smoking and incident AF in 11,047 participants from the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, one of the largest biracial, population-based cohort studies in the US.³³⁰ Baseline (2003-2007) cigarette smoking status and amount (pack-years) were self-reported. Incident AF was determined by electrocardiography and history of a prior physician diagnosis at a follow-up examination conducted after a median of 10.6 years.

Over a mean follow up of 10.6 years, 954 incident AF cases were identified (9.5% in smokers vs. 7.8% in non-smokers; $p < 0.001$). In a socio-demographic model, smoking (ever vs. never) was associated with a 15% increased risk of AF (OR 1.15, 95CI 1.00-1.31; p -value = 0.018). However, after further adjustment for cardiovascular risk factors, the association was not significant [OR 1.12, 95CI 0.97–1.29]. Similar results was observed for current, former, and never smokers.

Heterogeneities in the association were observed among subgroups; the association was stronger in young vs. old participants [OR 1.31, 95CI 1.03-1.67] vs. 0.99 95CI (0.83-1.18) respectively; interaction p -value=0.005] and in those with vs. without prior cardiovascular disease [OR 1.18, 95CI 0.90-1.56] vs. 1.06 (95CI 0.90-1.25) respectively. The association was significant in blacks [OR 1.51, 95CI 1.12-2.05] but not in whites (0.99, 95CI 0.84-1.16; interaction p -value=0.65).

³³⁰ Imtiaz Ahmad, M., Mosley, C. D., O'Neal, W. T., et al (2018). Smoking and risk of atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Journal of cardiology*, 71(2), 113–7
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FIGURE 48 SMOKING AND RISK OF ATRIAL FIBRILLATION IN SUBGROUPS



Imtiaz Ahmad et al (2018), Fig 1

Current smokers were more likely to smoke more (30 pack-years on average) than former smokers (19 pack-years years on average) (p<0.001). Among smokers, increasing pack-years of smoking was associated with increased risk of AF in the sociodemographic models, but was no longer significant after adjusting for cardiovascular risk factors.

TABLE 20 ASSOCIATION BETWEEN PACK-YEARS SMOKED AND INCIDENT ATRIAL FIBRILLATION IN SMOKERS

Smoking Status	Participants (n)	AF(n)	Odds Ratio (95% Confidence Interval) per 10 pack-year increase	
			Model 1*	Model 2††
Current	1193	91	1.02 (0.93–1.12)	0.99 (0.90–1.08)
Former	4284	431	1.06 (1.02–1.11)	1.03 (0.99–1.08)
All Smokers	5477	522	1.05 (1.01–1.09)	1.03 (0.99–1.07)

Imtiaz Ahmad et al (2018); Table 2 *Model 1 adjusted for age, sex, race, education, income, geographic region.†Model 2 adjusted for covariates in Model 1 plus systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, body mass index, diabetes, antihypertensive medications, left ventricular hypertrophy, prior cardiovascular disease, and statin use.

The association between smoking and AF is possibly mediated by a higher prevalence of cardiovascular risk factors in smokers, but there is marked heterogeneity in the strength of this association among subgroups which may explain the conflicting results in prior studies.

Summary and conclusions

Smoking is associated with the risk of incident AF (Staerk et al 2017) and smoking is a risk factor for AF across various races and ethnicities. Smoking is a risk factor for AF and also for conditions that can predispose to heart failure and subsequent development of AF. Based on the published literature, summarised in several recent meta-analyses, smoking is associated with a modest increased risk of incident AF. Smoking cessation seems to reduce, but not entirely eliminate the excess risk of AF.

Nonetheless, epidemiological studies on smoking and atrial fibrillation are inconsistent, with some studies showing a positive association while others have found no association. It is unclear whether there is a dose-response relationship between the number of cigarettes smoked or pack-years and atrial fibrillation risk (Aune et al 2018). At least three recent meta-analysis have confirmed that smoking is a risk factor for the occurrence of AF. Wang et al (2018) conducted a meta-analysis of prospective cohort studies of smoking as a risk factor for incident AF in men and women. 14 prospective studies and 222,159 individuals were included, and the pooled RR for incident AF in smoking populations was 1.24 (95CI 1.12-1.36; $p < 0.0001$). The pooled RR in men was 1.38 (95CI 1.21-1.57) and 1.28 (95CI 0.93-1.76) in women. .

Zhu et al. (2016) previously conducted a meta-analysis of prospective studies of smoking and incident atrial fibrillation. Sixteen prospective studies with 286,217 participants and 11,878 AF cases were included. A higher prevalence of AF was confirmed in smokers (RR 1.23, 95CI 1.08-1.39). AF risk was elevated in both current (RR 1.39, 95CI 1.11-1.75) and former smokers (RR 1.16, 95CI 1.00-1.36) vs never smokers. It was estimated that 6.7% of the total risk of AF in men and 1.4% of the risk in women were attributable to smoking worldwide.

Aune et al (2018) conducted a meta-analysis of 29 prospective studies to clarify the association of smoking and the risk of atrial fibrillation: Smoking was associated with an increased risk of atrial fibrillation in a dose-dependent matter, and the association was weaker in former than current smokers. The summary relative risk was 1.32 (95CI 1.12-1.56) for current smokers, 1.09 (95CI 1.00-1.18) for former smokers and 1.21 (95CI 1.12-1.31) for ever smokers compared to never smokers. Comparing current versus non-current smokers the summary relative risk was 1.33 (95CI 1.14-1.56). The summary relative risk was 1.14 (95CI 1.10-1.20) per 10 cigarettes per day and 1.16 (95CI 1.09-1.25) per 10 pack-years. There was no evidence of a non-linear association for cigarettes per day. The strength of the association by smoking status is consistent with a dose-response relationship as the association was strongest for current smokers, intermediate for ever smokers (current and former smokers combined) and lowest for former smokers.

Among relevant cohort studies, the Framingham Heart Study showed that the frequency of smoking among participants with new-onset AF has decreased over the last 50 years.

Between 1998–2007, only 12.7% of AF-affected participants were smokers, compared to 15.6% in the prior decade (Schnabel et al 2015).

Zuo et al (2018) examined the associations of smoking status and plasma cotinine levels, a marker of nicotine exposure, with risk of incident AF in the Hordaland Health Study. 538 participants developed AF over a median follow-up period of 11 years. Current smoking (HR 1.41, 95CI 1.09-1.83), but not former smoking (HR 1.03, 95CI 0.83-1.28), was associated with increased risk of AF. Use of plasma cotinine measurement corroborated this finding.

Imtiaz Ahmad et al (2018) examined the association between smoking and incident AF in 11,047 participants from the REGARDS Study, smoking was not associated with significantly increased risk of AF after adjustment for cardiovascular risk factors (OR 1.12, 95CI 0.97–1.29). Similar results were observed for current, former, and never smokers. Heterogeneities in the association were observed among subgroups. Among smokers, increasing pack-years of smoking was associated with increased risk of AF in the sociodemographic models, but was no longer significant after adjusting for cardiovascular risk factors.

The Rotterdam Study found that both former and current smoking were equally associated with increased AF risk (Heeringa et al 2018). In the ARIC study, the multivariable-adjusted incidence of AF was 1.58 times higher in ever smokers and two-fold higher (HR 2.05) in current smokers compared to non-smokers. A dose-response association was observed with increasing cigarette-years (Chamberlain et al 2011). In the CHARGE-AF consortium, incident AF was 1.44 times higher in current smokers than nonsmokers (Alonso et al 2013).

Smoking is thought to increase AF susceptibility through indirect and direct mechanisms (Gawalka et al). Smoking leads to an increased risk of AF by inducing oxidative stress, inflammation, and atrial fibrosis. Smoking may increase myocardial ischaemia by increasing systemic catecholamine and myocardial work, reducing oxygen carrying capacity, and promoting coronary vasoconstriction. Smoking accelerates atherosclerosis through effects on lipids, endothelial function, oxidative stress, inflammation, and thrombosis. Smoking and nicotine also directly contribute to the AF substrate. It is not known which pathophysiological changes are reversible to return AF risk to baseline (Panchal et al 2019)

Published studies do not show that smoking is associated with an increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery. Wan et al (2021) evaluated the association of smoking with postoperative AF in patients with cardiac surgery. 36 studies were included in this meta-analysis. Overall, smoking was not associated with increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery (OR 0.89; 95CI 0.79-1.02). Smoking was not associated with an increased risk of postoperative AF regardless of the type of cardiac surgery: coronary artery bypass grafting (OR 0.91; 95CI 0.77-1.07), valve surgery (OR 0.15; 95CI 0.01-1.56), and coronary artery bypass grafting+valve surgery (OR 0.91; 95CI 0.70-1.18).

It is therefore concluded that in relation to active cigarette smoking, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between active smoking

and atrial tachyarrhythmias, but chance, bias or confounding cannot be ruled out with reasonable confidence.

A factor for smoking should be added to the BoP SoP.

The current smoking factor format should be adopted.

The dose of smoking should be adjusted in the SoPs. The meta-analysis of prospective studies by Aune et al (2018) observed that current vs. non-current smoking was associated with a 33% increase in AF risk. There was a clear dose-response relationship and no evidence that the association was nonlinear. Smoking 10 cigarettes per day was associated with 14% increase in risk of atrial fibrillation (RR 1.14, 95CI 1.10-1.20), and 10 pack-years smoking increased the risk of AF by 16% (HR 1.16, 95CI 1.09-1.25).

Based on this data, it is suggested that the total dose of smoking should be changed to 5/10 pack years for active smoking in the RH and BoP SoPs.

Second hand smoke

No factor

The role of cigarette smoking on cardiac arrhythmia is less clearly defined and secondhand smoke (SHS) impact on the risk of atrial fibrillation remains unknown. Epidemiological studies have shown an association between SHS exposure and cardiac autonomic dysfunction as measured by reduced heart rate variability, which is associated with increased susceptibility to development of arrhythmias. These findings provide biological plausibility for a potential association between SHS and sustained arrhythmias, such as AF.

Case-control studies

Regev-Avraham et al (2020) evaluated the relationship between SHS and AF risk in Israeli women.³³¹ This was a population-based case-control study consisting of never-smoking women aged 30-80 years from Israel: 102 cases (diagnosed) of AF and 109 population-based controls. All participants were interviewed using a socio-demographic questionnaire that also related to past and current exposure to SHS.

SHS was associated with AF risk with adjusted OR of 3.81 (95CI 2.02-7.18). Higher exposure to SHS was associated with higher risk of AF compared to never-exposed women. Those exposed to SHS during one, two, or three life-periods (childhood, adolescence or adulthood) had an OR of 1.71 (95CI 0.76-3.86), 2.87 (95CI 1.25-6.56), and 9.14 (95CI 4.09-20.44), respectively. Exposure to one pack/day increased the risk of AF by 2.89 times compared to 'never exposed' (95CI 2.05-4.09).

³³¹ Regev-Avraham, Z., Rosenfeld, I., Sharabi-Nov, A., et al. (2020). Is second hand smoking associated with atrial fibrillation risk among women in Israel? A case-control study. *International journal of cardiology*, 304, 56–60.
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TABLE 21 MULTIVARIABLE LOGISTIC REGRESSION MODELS FOR CORRELATION BETWEEN DIFFERENT TYPES OF SECOND HAND SMOKING AND RISK OF ATRIAL FIBRILLATION

Exposure variable	Type of variable	Category	Model 1			Model 2			Model 3		
			OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Age (years)	Continuous		1.01	0.98–1.04	0.687	1.02	0.99–1.06	0.250	1.03	0.97–1.07	0.211
Family history of atrial fibrillation	Binary	No vs. Yes	1.86	0.91–3.78	0.088	1.87	0.88–3.96	0.103	2.51	1.12–5.63	0.025
Chronic hypertension	Binary	No vs. Yes	3.84	1.88–7.86	>0.001	3.84	1.77–8.31	0.001	2.98	1.27–6.97	0.012
Hyperlipidemia	Binary	No vs. Yes	2.08	1.01–4.28	0.046	2.18	1.01–4.70	0.046	2.30	1.00–5.29	0.050
SHS	Binary	Never vs. Ever	6.29	2.76–14.33	<0.001						
Number of any life Periods exposure to SHS	Ordinal	0				1.00	Ref.	Ref.			
		1				2.07	0.75–5.71	0.161			
		2				6.32	2.18–18.28	0.001			
		3				17.74	6.28–50.16	<0.001			
		P for trend									
Current exposure to SHS (packs/day)	Continuous							3.40	2.24–5.18	<0.001	

SHS, second hand smoking; OR, odds ratio; CI, confidence interval; Ref., reference

Regev-Avraham et al (2020) Table 3

This population-based case-control study measured the association between SHS exposure and AF in never-smoking Israeli women. SHS exposure in childhood, adolescence, and adulthood (in each period separately and as a cumulative exposure across different life periods) was significantly associated with increased AF risk with adjustment for age, family history of AF, chronic hypertension and hyperlipidaemia.

The results are accord with several previous studies that suggested an increased risk in AF among people exposed to SHS (Dixit et al 2016; O'Neill et al 2015), The authors maintain that the accumulated epidemiological, observational, and experimental evidence to demonstrates the detrimental cardiovascular consequences of SHS exposure in children. However, it is not possible to attribute a causal relationship between exposure to SHS in adolescence or adulthood and development of AF from this data.

Cross-sectional studies

O'Neal et al. (2015) examined the cross-sectional association between SHS exposure and atrial fibrillation risk³³² The study analysed the cross-sectional association between ETS exposure and AF in 12,021 participants (mean age: 65 ± 9.9 years; 60% women; 40% blacks) from the REasons for Geographic And Racial Differences in Stroke study (REGARDS) who self-identified as never smokers between 2003 and 2007.

A total of 12,021 study participants (mean age: 65 ± 9.9 years; 60% women; 40% blacks) were included in the primary analysis. Participants who reported more than 1 hour per week of passive smoke exposure were defined as the ETS group. There were 2,503 (21%) participants who reported ETS exposure. The prevalence of AF was higher for those with ETS exposure (8.5%) compared with those without (7.6%).

In a multivariate logistic regression model adjusted for sociodemographics, cardiovascular risk factors and potential confounders, ETS exposure was significantly associated with AF (OR 1.27, 95CI 1.08-1.50). In subgroup analysis by race, a stronger association was observed

³³² O'Neal, W. T., Qureshi, W. T., Judd, S. E., et al (2015). Environmental Tobacco Smoke and Atrial Fibrillation: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. Journal of occupational and environmental medicine, 57(11), 1154–8
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between ETS exposure and AF for black (OR 1.63, 95CI 1.27- 2.08) compared with white (OR 1.03, 95CI 0.82, 1.30) participants (p-interaction=0.0007)

These findings suggest that the harmful effects of ETS exposure extend to sustained arrhythmias such as AF. This was the first study to suggest that the harmful effects of ETS exposure extend to arrhythmias.

Exposure to ETS was self-reported and subject to recall bias and misclassification bias. Non-permanent AF cases possibly were missed due to the time-dependent nature of various AF events. The intensity of ETS exposure was not quantified, and the relationship between ETS and AF potentially varies by exposure duration. It was not possible to establish the temporal relationship between ETS exposure and AF due to the cross-sectional design of the study.

Epidemiological studies have shown an association between ETS exposure and cardiac autonomic dysfunction as measured by reduced heart rate variability. The reduction of heart rate variability is associated with an increased susceptibility to the development of arrhythmias. These findings provide biological plausibility for a potential association between ETS and sustained arrhythmias, such as atrial fibrillation.

In China, there is a high active smoking rate among men (52.9% in 2010) and a low active smoking rate among women (2.4% in 2010)..

Groh et al. (2019) analysed longitudinal data from the Framingham Heart and Offspring studies, providing evidence that secondhand smoke exposure in childhood is a risk factor for The development of AF later in life.³³³

Dixit et al (2016) evaluated if secondhand smoke (SHS) exposure is associated with an increased risk of AF, in a cross-sectional analysis of data from participants enrolled in the Health eHeart Study, an internet-based, longitudinal cardiovascular cohort study, who completed baseline SHS exposure and medical conditions questionnaires.³³⁴ SHS was assessed through a validated 22-question survey, and prevalent AF was assessed by self-report, with validation of a subset (n = 42) by review of electronic medical records. Elements of the survey were qualitative, assessing the presence of any regular exposure to SHS, while other aspects were quantitative, assessing years and hours per day of exposure in various settings, as well as number of smokers in home environment.

Of 4976 participants, 593 (11.9%) reported having AF. In unadjusted analyses, patients with AF were more likely to have been exposed to SHS in utero, as a child, as an adult, at home, and at work. However, those without AF were more likely to have visited social environments with significant SHS. After multivariable adjustment for potential confounders, having had a smoking parent during gestational development (OR 1.37, 95CI 1.08-1.73) and residing with a smoker during childhood (OR 1.40, 95CI 1.10-1.79,) were each significantly associated with

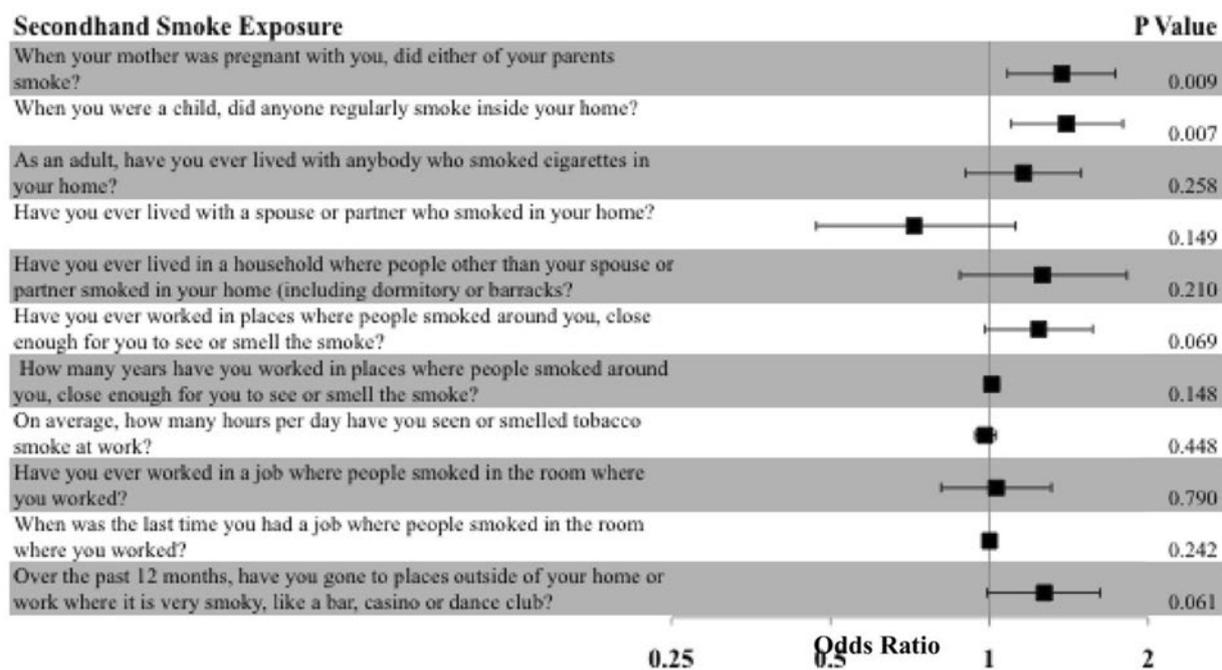
³³³ Groh CA, Vittinghoff E, Benjamin EJ, et al (2019). Childhood tobacco smoke exposure and risk of atrial fibrillation in adulthood. *J Am Coll Cardiol*; 74: 1658–64.

³³⁴ Dixit, S., Pletcher, M. J., Vittinghoff, E., et al. (2016). Secondhand smoke and atrial fibrillation: Data from the Health eHeart Study. *Heart rhythm*, 13(1), 3–9.

AF. Both positive associations were more pronounced among patients without risk factors for AF (P values for interaction <0.05). When examining persistent AF and paroxysmal AF as separate outcomes, in utero exposure and childhood exposure were each significantly associated with persistent AF before and after adjustment (adjusted OR 1.43, 95CI 1.01–2.01, p=0.042 and adjusted OR 1.46, 95CI 1.02–2.07, p=0.036 respectively).

There did not appear to be a statistically significant association between SHS in adulthood, or recent STS exposure, and the risk of AF.

FIGURE 49 ODDS RATIOS FOR ATRIAL FIBRILLATION BY SECONDHAND SMOKE EXPOSURE



Dixit et al (2016), Fig 2

The study suggests that SHS, particularly when present during development and early childhood, was statistically significantly associated with the presence of AF. This relationship was particularly strong in the absence of known AF risk factors, suggesting a direct connection between SHS in early life and AF pathophysiology.

Due to the cross-sectional nature of the study design, it was possible to investigate prevalent but not incident AF, and it is not possible to attribute causality to SHS exposure. However, as early life SHS exposure likely preceded the development of any AF, there is temporality inherent to the relationship. Residual confounding remains a concern, although the analysis adjusted for potential confounders, certain possible confounding variables, such as obesity, were unavailable. Residual confounding due to cigarette smoking is possible.

Though current research into the mechanism of the effect of SHS on AF is lacking, theories abound as to how SHS may predispose individuals to arrhythmias. Nicotine itself has been linked to cardiac arrhythmias, including AF and several canine and human studies have demonstrated that nicotine leads to atrial fibrosis and atrial structural remodeling, processes known to promote AF. SHS may lead to autonomic dysfunction, potentially predisposing to

cardiac arrhythmias. Exactly how early exposure to SHS may influence the propensity to develop AF later in life remains unknown. The survey is that it did not assess quantitative, only qualitative, exposure in utero and in childhood and does not further characterize the time frame or duration of the exposure.

Summary and conclusions

As outlined previously, cigarette smoking is a risk factor for atrial fibrillation, but the role of second-hand smoke (SHS) on cardiac arrhythmia is less clearly defined and its impact on the risk of atrial fibrillation remains unknown. Epidemiological studies have shown some evidence of association between SHS exposure and cardiac autonomic dysfunction as measured by reduced heart rate variability, which is associated with increased susceptibility to development of arrhythmias. These findings provide biological plausibility for a potential association between SHS and sustained arrhythmias, such as AF.

Several studies that suggested an increased risk in AF among people exposed to SHS (Dixit et al 2016; O'Neill et al 2015). The overwhelming focus of these studies was exposure in utero or during childhood. The accumulated epidemiological, observational, and experimental evidence demonstrates detrimental cardiovascular consequences of SHS exposure in children. However, it is not possible to attribute a causal relationship between exposure to SHS in adolescence or adulthood and development of AF from this data.

O'Neal et al. (2015) examined the cross-sectional association between SHS exposure and atrial fibrillation risk in 12,021 participants from the REasons for Geographic And Racial Differences in Stroke study who self-identified as never smokers between 2003 and 2007.³³⁵ In a multivariate logistic regression model adjusted for sociodemographics and potential confounders, ETS exposure was significantly associated with AF (OR 1.27, 95CI 1.08-1.50). The findings suggest that the harmful effects of ETS exposure extend to sustained arrhythmias such as AF.

Dixit et al. [2016] determined that SHS exposure is associated with an increased risk of AF. In a cross-sectional analysis of data from participants enrolled in the Health eHeart Study, an internet-based, longitudinal cardiovascular cohort study. Patients with AF were more likely to have been exposed to SHS in utero, as children, as adults, at home, and at work. After multivariable adjustment for potential confounders, having had a smoking parent during gestational development (OR 1.37) and residing with a smoker during childhood (OR 1.40) were significantly associated with AF. The researchers' conclusions were that SHS exposure during gestational development and during childhood was associated with having AF later in life and the association was stronger in the absence of established risk factors for AF.

Epidemiological studies have shown an association between ETS exposure and cardiac autonomic dysfunction as measured by reduced heart rate variability. The reduction of heart rate variability is associated with an increased susceptibility to the development of

³³⁵ O'Neal, W. T., Qureshi, W. T., Judd, S. E., et al (2015). Environmental Tobacco Smoke and Atrial Fibrillation: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Journal of occupational and environmental medicine*, 57(11), 1154–8
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arrhythmias. These findings provide biological plausibility for a potential association between ETS and sustained arrhythmias, such as atrial fibrillation.

Regev-Avraham et al (2020) evaluated the relationship between SHS and AF risk. This population-based case-control study measured the association between SHS exposure and AF in never-smoking Israeli women. SHS exposure in childhood, adolescence, and adulthood (in each period separately and as a cumulative exposure across different life periods) was significantly associated with increased AF risk with adjustment for age, family history of AF, chronic hypertension and hyperlipidaemia.

SHS was associated with AF risk with adjusted OR of 3.81 (95CI 2.02-7.18). Higher exposure to SHS was associated with higher risk of AF compared to never-exposed women. Those exposed to SHS during one, two, or three life-periods (childhood, adolescence or adulthood) had an OR of 1.71 (95CI 0.76-3.86), 2.87 (95CI 1.25-6.56), and 9.14 (95CI 4.09-20.44), respectively. Exposure to one pack/day increased the risk of AF by 2.89 times compared to 'never exposed' (95CI 2.05-4.09).

It is concluded that the evidence is too limited to permit a judgement of a possible causal relationship between exposure to secondhand smoke in adulthood or adolescence and the development of atrial fibrillation or atrial flutter (Grade 4). An association is demonstrated in some studies, but the evidence is inconsistent and studies are limited in quality or quantity. Chance, bias or confounding are likely to account for observed associations. Although there appears to be evidence of a link between exposure to smoke in utero or during early childhood and subsequent development of AF, the evidence of an association with adulthood exposure, independent of earlier exposures, remains extremely limited.

No factor for the SoPs is suggested.

Gastro-oesophageal reflux disease

Current factor

onset and worsening - RH only

having gastro-oesophageal reflux disease at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

Associations between gastro-oesophageal reflux disease (GORD) and atrial fibrillation are inconclusive. Some studies found that AF was a risk factor for GORD whereas other studies showed opposite results.

Both AF and GORD are common disorders that share common predisposing factors, and there is a link between them. The precise mechanism of reflux disease as a possible cause of atrial fibrillation remains uncertain (Mohamed et al 2020)

Summary of previous investigation

During the past decade, there have been many case reports and large retrospective cross-sectional studies that have suggested an association between AF and gastro-oesophageal reflux disease (GORD), manifest as hiatus hernia and oesophagitis. It has also been suggested that AF may be a cause of reflux disease.

Several possible mechanisms have been proposed to account for an association between these diseases, such as inflammation, autoimmune, and autonomic stimulation. Hiatal hernia has been associated with an increased incidence of AF, possibly attributed to a direct mechanical effect. Possible explanations for the association between GORD and AF include locally released cytokines from esophageal injury, can provide an environment that is conducive to AF. Oesophageal inflammation or acid in the oesophagus may affects receptors, which overstimulate the parasympathetic system. It remains uncertain whether there is true causal mechanism between these two common diagnoses; the response of AF-related symptoms to PPI therapy and the potential for PPI therapy to reduce the development of AF has not been established.

Two recent qualitative review studies (Armaganijan et al 2012; Velagapudi et al 2012) provide cautious support for hypothesis of a causal association between GORD and AF, while acknowledging that methodological problems with available data precludes certainty the nature of the association. These studies did not document AFL as a specific outcome. Available human studies are retrospective or too small to show a definitive association between GORD and AF or AF and hiatus hernia. It is possible that the findings are due to multivariate statistical noise, and there are no large prospective cohort studies of the association.

The association between GORD and AF is debated because the two diseases share many risk factors. Many factors that predispose a patient to AF are similar to those that are seen in patients with GORD. Increasing age, sleep apnoea, obesity and diabetes are all shared risk factors, and it is challenging to distinguish whether GORD predisposes a patient to AF or whether it can be attributed to shared confounding factors

Reviews

Atrial fibrillation is a common arrhythmia, and gastroesophageal reflux disease (GORD) is a common gastroenterology disease; both are commonly encountered in clinical practice³³⁶. Both AF and GORD share common predisposing factors, and there is a link between them. The mechanism of reflux disease as a possible cause of atrial fibrillation remains uncertain. However, some possibilities can be postulated, such as the inflammation process, and sympathovagal imbalance represents the main factors for how GORD can initiate AF.

³³⁶ Mohamed, A., Ochoa Crespo, D., Kaur, G., et al. (2020). Gastroesophageal Reflux and Its Association With Atrial Fibrillation: A Traditional Review. *Cureus*, 12(9), e10387.
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Vigorous aerobic exercise in healthy people can induce acidic oesophageal reflux, which is a common risk factor for AF. Various inflammatory markers such as C-reaction protein (CRP) and interleukins have been a central role in initiating AF. A large hiatal hernia (HH) can cause direct compression on the left atrium that may predispose to atrial arrhythmogenesis. It has been sporadically reported that using a proton pump inhibitor to treat GORD in patients with coexisting AF has a noticeable effect on decreasing symptoms of AF and recurrence with less cost and side effects.

Maruyama et al (2018) maintains that increasing evidence indicates that GORD induces the initiation and the perpetuation of AF. This is caused by the autonomic nerve influence, mechanical compression, and propagation of local inflammation due to proximity of left atrium (LA) and lower oesophagus. AF also develops GORD by mechanical and inflammatory actions of LA characterized by remodeling and inflammation.

The robust association of AF with GORD is not limited to their natural interaction, i.e., pharmacological or nonpharmacological treatment of AF is reported to aggravate GORD. Many cardiac drugs (anticoagulants, calcium antagonists, and nitrates) induce oesophageal mucosal damage and lower oesophageal sphincter relaxation promoting acid reflux. These drugs are frequently prescribed in patients with AF for stroke prevention, rate control, and for coexisting coronary heart disease. Catheter ablation causes both GORD and oesophageal thermal injury, which is a precursor lesion of atrioesophageal fistula.

The notion that AF and GORD are mutually interdependent is empirically recognised, but the mechanistic link of the two common diseases and objective evaluation of PPI as an adjunctive AF treatment warrant future large-scale prospective trials.

Meta-analyses

Xu et al (2019) systematically evaluated whether GORD and AF have a bidirectional association using a meta-analysis.³³⁷ a review was conducted of longitudinal, case-control, and cross-sectional studies on the association between GORD and AF, in English and included in Cochrane CENTRAL, PubMed and EMBASE until February 2017.

Among 548 studies, seven fulfilled the inclusion criteria (two longitudinal studies, two case-control studies, and three cross-sectional studies). four studies, including one cohort study, two case-control studies and one cross-sectional study for a total of 29,671 healthy participants and 82,882 GORD cases showed no statistically significant association between GORD and risk of AF. The summary RR was 1.06 (95C, 0.86-1.31) and heterogeneity was high ($p = 0.004$; $I^2 = 77.6$).

³³⁷ Xu, L., Zhang, Y., Xie, J., et al. (2019). Association between gastroesophageal reflux disease and atrial fibrillation: a systematic review and meta-analysis. *Revista espanola de enfermedades digestivas*, 111(11), 874–9.

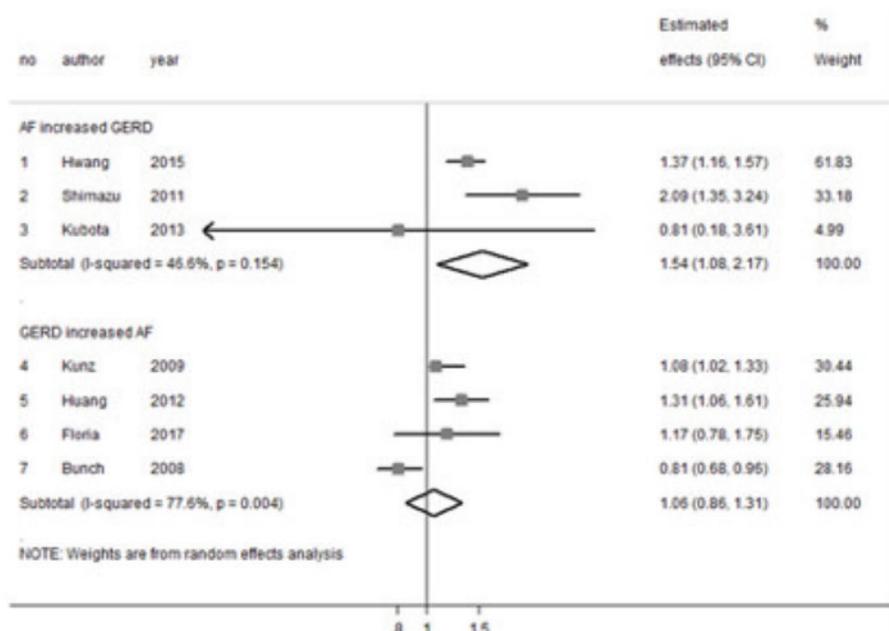
TABLE 22 GORD ASSOCIATED WITH THE RISK OF ATRIAL FIBRILLATION

Author, year	Study design	Country	Sample size	Mean age (years)	GERD diagnosis	AF diagnosis	Estimated effects (95% CI)	NOS	Conclusion
Bunch, 2008	Cohort study	USA	n = 5,288	53 ± 17	A self-report instrument	ECG	RR, 0.81 (0.68-0.96)	7	There was no relationship between AF and GERD. Patients with esophagitis were more likely to develop AF
Huang, 2012	Cohort study	Taiwan	GERD (n = 29,688), comparison cohort (n = 29,597)	50.99 ± 16.61, 50.85 ± 16.8	Endoscopy or 24-hour pH-metry inspection	Electrocardiography and Holter monitors	RR, 1.31 (1.06-1.61)	8	GERD was independently associated with an increased risk of future AF in a nationwide population-based cohort
Kunz, 2009	Cohort study	USA	n = 163,627	51.8	ICD-9	ICD-9	RR, 1.08 (1.02-1.33)	7	GERD is associated with increased risk of diagnosis of atrial fibrillation
Floria, 2017	Case-control study	Romania	GERD (n = 64)	GERD: 61.5 ± 9 Non-GERD: 58 ± 9	According to the Montreal Consensus	ECG	OR, 1.17 (0.78-1.75)	5	Sympathovagal balance seems to be disrupted in patients with GERD, with dominance of the parasympathetic system and increased risk for arrhythmias

Xu et al (2018), Table 2

The summary adjusted relative risks for GORD-induced AF was 1.06 (95CI 0.86-1.31).

FIGURE 50 GORD-INDUCED AF



Xu et al (2018), Fig 2

The subgroup analysis showed that the associations were not significantly modified by sample size, study design, age, or geographic area.

Summary and conclusions

Associations between gastro-oesophageal reflux disease (GORD) and atrial fibrillation are inconclusive. Some studies found that AF was a risk factor for GORD whereas other studies showed opposite results.

Both AF and GORD are common disorders that share common predisposing factors, and there is a link between them. The precise mechanism of reflux disease as a possible cause of atrial fibrillation remains uncertain (Mohamed et al 2020). It remains uncertain whether treatment of GORD reduces the risk of AF.

Increasing evidence suggests that GORD can initiate and perpetuate AF (Maruyama et al 2018). This is caused by the autonomic nerve influence, mechanical compression, and propagation of local inflammation due to proximity of left atrium and lower oesophagus.

Xu et al (2019) systematically evaluated whether GORD and AF have a bidirectional association using a meta-analysis with 7 studies. The summary adjusted RRs for GORD-induced AF 1.06 (95CI 0.86-1.31).

In relation to the gastro-oesophageal reflux disease, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality or quantity.

The existing factor for gastro-oesophageal reflux disease should be retained in the RH SoPs only, without amendment.

Chronic renal disease

Current factor

onset and worsening - RH only

having chronic renal disease requiring renal transplantation or dialysis at the time of the clinical onset of atrial fibrillation or atrial flutter;

Summary of important issues

There is a bidirectional relationship between atrial fibrillation and chronic kidney disease (CKD), with multiple shared risk factors (Kotalczyk et al 2021). The incidence of AF is increased in the presence of CKD and patients with AF suffer from greater deterioration in renal function over time (Ding et al 2021). Although the relationship between AF and CKD has long been recognised, there remain many unanswered questions.

The two comorbidities frequently coexist. Previous observational studies suggested that the two diseases are risk factors for each other, suggesting a bidirectional relationship. (Park et al. 2021). Due to overlap is present in risk factors, and common presence of CKD and AF in the elderly with complex comorbidities, identifying causality between CKD and AF is difficult.

Summary of previous investigation

Atrial fibrillation is common among patients with end-stage renal disease. Chronic kidney disease may increase the risk of atrial fibrillation, but existing studies have reported inconsistent results.

Previous research has shown that individuals with end-stage renal disease have a higher risk of developing atrial fibrillation, and some cross-sectional studies have found a higher prevalence of atrial fibrillation among those with decreased kidney function. Evidence from prospective studies in the general population is limited, and inconsistent.

A meta-analysis (Zimmerman et al 2012) concluded that the incidence and prevalence of AF/AFL in ESRD patients are higher than in the general population and are associated with an increased risk of stroke and mortality. Reduced kidney function, as measured by both higher cystatin C levels or reduced eGFR_{creat}, was not associated with AF risk in the Cardiovascular Health Study, a population-based study of elderly individuals in the US (Deo et al 2010) nor in subset of Framingham Heart Study (Schnabel et al 2010), but impaired kidney function strongly associated with AF +/AFL risk in ARIC study (Alonso et al 2011).

In an analysis of 10,328 men and women participating in the Atherosclerosis Risk in Communities Study, Alonso et al (2011) observed that impaired kidney function, measured by lower cystatin-based or creatinine-based estimated glomerular filtration rate, was strongly associated with a higher risk of AF/AFL. Individuals with increased levels of urinary albumin-creatinine ratio, a marker of kidney damage, had higher risk of developing atrial arrhythmia.

In contrast to limited data from prospective cohort studies, cross-sectional analyses have consistently shown a higher prevalence of AF among individuals with chronic kidney disease.

Few data are available on the prevalence of AF among adults with chronic kidney disease of milder severity than end stage disease. In a large population-based sample of U.S. adults, Baber et al (2011) found that regardless of severity, CKD was associated with an increased prevalence of AF. CKD was associated with an increased prevalence of AF. This association was present among individuals with stage 1 or 2 CKD, stage 3 CKD and stage 4 or 5 CKD, and remained consistent across several subgroups and persisted after adjustment for multiple potential confounders.

Reviews

There exists a bidirectional relationship between AF and chronic kidney disease (CKD) such that the incidence of AF is increased in the presence of CKD and patients with AF suffer from greater deterioration in renal function over time. Chronic kidney disease increases the risk of developing AF. Several recent review studies have comprehensively documented the association of these disorders.^{338 339}

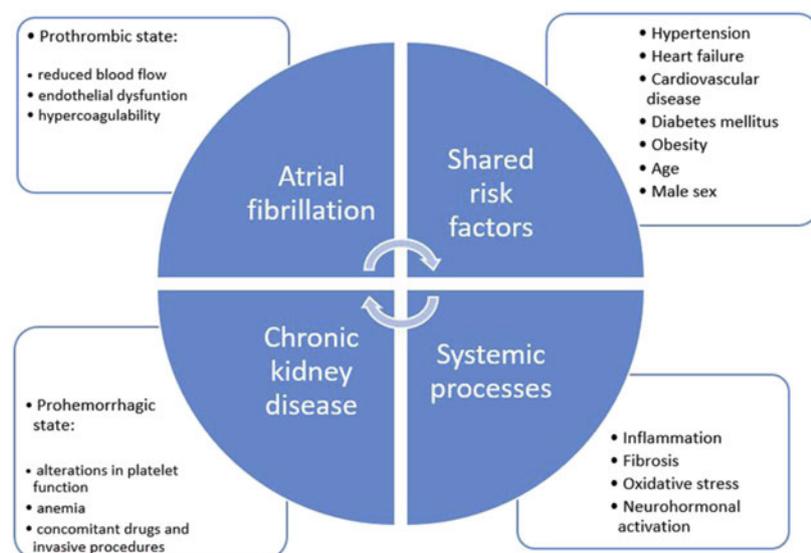
³³⁸ Benn M. (2021). Atrial Fibrillation and Chronic Kidney Disease. *Eur Heart J.*;42(29):2824-2826

³³⁹ Park, S., Lee, S., Kim, Y., et al. (2021). Atrial fibrillation and kidney function: a bidirectional Mendelian randomization study. *European heart journal*, 42(29), 2816–23

The association has been demonstrated in several prospective, cohort studies. In a study of 235,818 individuals, the hazard ratio for the development of AF was 1.32 for patients with estimated glomerular filtration rates (eGFRs) of 30 to 59 mL/min/1.73m² compared with those with normal renal function [Watanabe et al 2009].³⁴⁰ The relationship between CKD and AF was evaluated in a report of 10,328 individuals free of AF participating in the Atherosclerosis Risk in Communities (ARIC) study who had a baseline cystatin C-based estimated glomerular filtration rate (eGFR_{cys}) [Alonso et al 2011]. Compared with individuals with eGFR_{cys} ≥90 mL/min/m², the multivariable hazard ratios for the development of AF were significantly increased at 1.3, 1.6, and 3.2 in those with eGFR_{cys} of 60 to 89, 30 to 59, and 15 to 29 mL/min/m², respectively, during a median follow-up of 10.1 years. In addition, macroalbuminuria and microalbuminuria were significantly associated with higher AF risk.

As outlined in a review study by **Kotalczyk et al (2021)**, there is a bidirectional relationship between atrial fibrillation and chronic kidney disease, with multiple shared risk factors.³⁴¹ There is an increasing risk of both ischaemic stroke and bleeding with progressive deterioration of renal function, complicating the decision of optimal stroke prevention strategies among patients with AF and CKD. The optimal stroke prevention strategy in patients with AF and severe CKD remains uncertain.

FIGURE 51 BIDIRECTIONAL RELATIONSHIP BETWEEN AF AND CKD.



Kotalczyk et al 2021, Fig 1

Another review study by **Franczyk et al. (2016)** demonstrates that atrial fibrillation is common in CKD patients.³⁴² Factors contributing to the occurrence of AF in patients undergoing dialysis include age, presence of coronary heart disease, echocardiographic abnormalities (low ejection fraction, atrial enlargement, valvular calcification, left ventricular hypertrophy),

³⁴⁰ https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation?sectionName=EPIDEMIOLOGY&search=Atrial%20fibrillation&topicRef=1022&anchor=H2&source=see_link#H13

³⁴¹ Kotalczyk, A., Ding, W. Y., Wong, C. F., (2021). Atrial Fibrillation in Patients with Chronic Kidney Disease. *Cardiology clinics*, 39(3), 435–46.

³⁴² Franczyk, B., Gluba-Brzózka, A., Ciałkowska-Rysz, A., et al. (2016). The Problem of Atrial Fibrillation in Patients with Chronic Kidney Disease. *Current vascular pharmacology*, 14(3), 260–5 ?? August meeting 2022

heart failure, chronic obstructive pulmonary disease, hypertension, stroke, malnutrition (low levels of albumin, total cholesterol and high-density lipoprotein (HDL), secondary hyperparathyroidism, low predialysis systolic blood pressure, duration of renal replacement therapy as well as the method of renal replacement therapy (more frequent in haemodialysis patients).

The optimal management of thromboprophylaxis in patients with CKD and AF is complex due to the fact that in patients with CKD many physiologic mechanisms are altered which lead to substantial changes in haemostasis and thus this group of patients is characterized by an increased risk of thrombotic and haemorrhagic complications.

Recommendations concerning the treatment of patients with AF do not include guidelines on how to manage patients with advanced CKD, due to the lack of large randomized trials assessing the efficacy and benefits of drugs in these patients. Patients with CKD and permanent, persistent, and paroxysmal AF ought to be treated as a group with high risk of bleeding and ischaemic stroke. In case of patients with no or only one moderate risk factors, it seems that anticoagulation with antiplatelet drugs can be considered as efficient therapy, while in patients with ≥ 2 risk factors an oral anticoagulation therapy may be used. During long-term treatment, the international normalized ratio (INR) must be controlled at least every 14 days and adjusted within a target range of 2.0-2.5. Moreover, renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and re-evaluated when clinically indicated and at least annually.

As CKD and AF are prevalent in elderly individuals and share metabolic risk factors in common, the two comorbidities frequently coexist.³⁴³ Previous observational studies suggested that the two diseases are risk factors for each other, with a bidirectional relationship. CKD and AF are considered to synergistically aggravate the risk of stroke, adverse cardiac outcomes, and mortality.

Due to large overlap is present in risk factors and that CKD and AF commonly occurs in elderly individuals with complex comorbidities, identifying causality between CKD and AF is difficult. Evidence independent from reverse causation or confounding which is inevitable in observational studies is warranted to investigate causal effects between CKD and AF.

a close association between CKD and AF has been reported by observational studies. studies have evaluated the bidirectional relationship between CKD and AF, and the diseases were suspected to increase the risk of each other. However, assessment of direct causality between CKD and AF is difficult, as undiagnosed AF or CKD is possible, the disorders share many risk factors raising the concerns of confounding, and issue of reverse causality cannot be disregarded in observational studies.

Meta-analyses

Some new trials have reported the effectiveness of chronic kidney disease on recurrence of atrial fibrillation following catheter ablation. Limited by small numbers of studies and

³⁴³ Park, S., Lee, S., Kim, Y., et al. (2021). Atrial fibrillation and kidney function: a bidirectional Mendelian randomization study. *European heart journal*, 42(29), 2816–23
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insufficient outcomes, previous meta-analyses failed to draw a consistent conclusion on this topic.

Lee et al (2021) performed a meta-analysis of seven observational studies with 23,468 patients who underwent AF ablation using radiofrequency or cryoballoon ablation.³⁴⁴ A comprehensive search strategy was employed using several key databases to identify studies published between 2010 and 2020. The authors reported that the prevalence of CKD was 8.0% in this cohort. The mean estimated glomerular filtration rate was 48.7 mL/min/1.73 m² in the CKD group compared to 82.8 mL/min/1.73 m² in the non-CKD group.

Patients with CKD were older (64.2 vs 58.7 years) and had greater prevalence of comorbidities including diabetes mellitus (38.4% vs 18.7%), hypertension (79.8% vs 59.1%) and heart failure (52.7% vs 29.5%). These patients were more likely to have non-paroxysmal AF (39.7% vs 25.0%) and had larger left atrial diameter (38.6 vs 37.5 mm). CKD was associated with a higher risk of AF recurrence (OR 3.71, 95CI 1.35-10.19), regardless of whether radiofrequency or cryoballoon ablation was performed.

The conclusion of this study should also be interpreted with caution given the relatively few included studies. The results are supported by previous studies and meta-analyses. It is consistent with understanding of CKD as a pro-inflammatory condition and the links between inflammation and AF recurrence post-ablation. However, there was a high degree of heterogeneity with evidence of significant publication bias among the studies included in this analysis, despite all but one study reporting excess AF recurrence following ablation. The definition of CKD varied between studies.

The similar results found in subgroups of patients with paroxysmal AF and by ablation method support the theory that it is CKD and its comorbidities that are essential factors contributing to excess AF recurrence post-ablation. CKD is rarely a standalone condition and frequently occurs in conjunction with other cardiovascular-related diseases. Therefore, it is unclear if the greater AF recurrence observed in CKD patients were due to this condition itself or the presence of other factors which contribute to poor outcomes (e.g. greater left atrial size, increased age).

As the mechanism, ablation techniques and outcomes between patients with paroxysmal and persistent AF are different, additional analysis is needed to determine the effects of CKD in both these subsets of patients. Whether or not the severity of CKD influences the risk of recurrence, as reported in previous studies, warrants investigation as it could not be determined from this meta-analysis.

Cohort studies

³⁴⁴ Lee W-C, Wu P-J, Fang C-Y, et al (2021) Impact of chronic kidney disease on atrial fibrillation recurrence following radiofrequency and cryoballoon ablation: a meta-analysis. *Int J Clin Pract*. :e14173

Park et al (2021) investigated the causal effects between atrial fibrillation and kidney function.³⁴⁵ This was a bidirectional summary-level Mendelian randomisation (MR) analysis implementing the results from a large-scale genome-wide association study for estimated glomerular filtration rate (eGFR) by the CKDGen (N = 765 348) and AF (N = 588 190) to identify genetic instruments. The inverse variance weighted method was the main MR method used. For replication, an allele score-based MR was performed by individual-level data within a UK Biobank cohort of white British ancestry individuals (N = 337 138). A genetic predisposition to AF was significantly associated with decreased eGFR [for log-eGFR, beta - 0.003 (standard error, 0.0005), P < 0.001] and increased risk of chronic kidney disease [beta 0.059 (0.0126), P < 0.001]. The significance remained in MR sensitivity analyses and the causal estimates were consistent when analysis was limited to individuals of European ancestry.

Genetically predicted eGFR did not show a significant association with the risk of AF [beta - 0.366 (0.275), P = 0.183]. The results were similar in allele score-based MR, as allele score for AF was significantly associated with reduced eGFR [for continuous eGFR, beta -0.079 (0.021), P < 0.001], but allele score for eGFR did not show a significant association with risk of AF [beta -0.005 (0.008), P = 0.530].

The study supports AF as a causal factor for kidney function impairment, but an effect of kidney function on AF was not identified.

The authors assessed the bidirectional causal effect between CKD and AF using MR analysis. MR tests the effect from genetic predisposition to an exposure, which precedes any confounders or outcome occurrence, MR can demonstrate causal effects but requires to meet three assumptions. The relevance assumption, which means the genetic instrument should be strongly associated with the exposure of interest, which was fulfilled by the previous GWAS meta-analysis which robustly provided the genetic variants with strong association with the exposures.

The authors performed multiple pleiotropy-robust MR methods and disregarded variants that might have horizontal pleiotropic effect on the results. Extensive MR analysis suggests that AF causally increases the risk of kidney function impairment, but the causal effects from kidney function on AF were insignificant.

That kidney function did not show significant causal effects for AF should be interpreted in caution. The study suggests that effects from AF to CKD may be stronger than the effects of the reverse direction. However, as genetic instrument explains a portion of a phenotype, a possibility remains that a modest degree of effect may be present from kidney function on AF. The authors tested the effects mostly from mild-to-moderate CKD, the cardiovascular effects from severe kidney failure or acute kidney injury may be different as CKD and AF share risk factors, certain CKD events would still precede AF.

³⁴⁵ Park, S., Lee, S., Kim, Y., et al. (2021). Atrial fibrillation and kidney function: a bidirectional Mendelian randomization study. *European heart journal*, 42(29), 2816–23.

Yang et al (2021) explore the frequency and impact of AF on clinical outcomes in CKD patients with acute coronary syndrome (ACS).³⁴⁶

CKD inpatients with ACS between 2014 and 2018 were included based on the improving care for cardiovascular disease in China-ACS (CCC-ACS) project. Patients were divided into an AF group and a non-AF group according to the discharge diagnosis. Multivariable logistic regression was used to adjust for potential confounders.

16,533 CKD patients with ACS were included. A total of 1418 (8.6%) patients had clinically recognised AF during hospitalisation, 654 of whom had an eGFR of 45 to < 60 ml/min/1.73 m², and 764 had an estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m². Compared with the non-AF group, the AF group had a higher risk of in-hospital mortality [OR 1.250; 95CI 1.001-1.560], $P = 0.049$ and major adverse cardiovascular events (MACEs) [OR 1.361; 95CI 1.197-1.547], $P < 0.001$. Compared to patients with eGFR 45 to < 60 ml/min/1.73 m², patients with eGFR < 45 ml/min/1.73 m² had a 1.512-fold increased risk of mortality and a 1.435-fold increased risk of MACEs.

AF was a risk factor affecting the short-term prognosis of ACS patients in the CKD population. The lower the eGFR, the higher the risk of in-hospital mortality and MACEs in CKD patients with ACS.

Guo et al (2019) compared the clinical epidemiological features of atrial fibrillation in chronic kidney disease (CKD) and non-CKD populations.³⁴⁷ 88,312 adults aged ≥ 45 years old were enrolled from the KAILUAN study. This included 21,578 CKD individuals (eGFR < 60 mL/min/1.73 m² and/or proteinuria) and 66,725 non-CKD individuals (eGFR > 60 mL/min/1.73 m² without proteinuria). AF was ascertained with 12-lead ECG.

The prevalence of AF among CKD and non-CKD individuals was 1.00% and 0.26%, respectively.

There were 390 (0.44%) cases of ECG-detected AF among the 88,312 qualified participants; of these, 174 (0.26%) cases of AF were identified in adults without CKD and 216 (1.00%) cases in adults with CKD. In sub-groups stratified by age, sex, diabetes, hypertension, and waist circumference, the prevalence of AF in participants with CKD was significantly higher than in those without CKD.

There were 106, 105, and 5 cases of ECG-detected AF among CKD adults with eGFR ≥ 60 , 30 to < 60, and < 30 mL/min/1.73 m², respectively. The prevalence of AF increased significantly with worsening eGFR. The prevalence of AF was 0.26% among adults with non-CKD, and 1.08%, 0.91%, and 3.21% among adults with eGFR ≥ 60 , 30 to < 60, and < 30 mL/min/1.73 m², respectively. Compared with non-CKD participants, the unadjusted ORs for AF were 4.16

³⁴⁶ Yang, L., Ye, N., Wang, G., et al (2021). The association between atrial fibrillation and in-hospital outcomes in chronic kidney disease patients with acute coronary syndrome: findings from the improving care for cardiovascular disease in China-acute coronary syndrome (CCC-ACS) project. *BMC cardiovascular disorders*, 21(1), 345.

³⁴⁷ Guo Y, Gao J, Ye P, et al. (2019) Comparison of atrial fibrillation in CKD and non-CKD populations: a cross-sectional analysis from the Kailuan study. *Int J Cardiol*; 277: 125–9.

(95CI 3.27–5.30) for those with CKD (eGFR \geq 60 mL/min/1.73 m²), 3.49 (95CI 2.74–4.46) for those with CKD (eGFR 30 to <60 mL/min/1.73 m²), and 12.66 (95CI 5.13–31.25) for those with CKD (eGFR <30 mL/min/1.73 m²).

After adjustment for age and sex; for age, sex, and clinical history of smoking, alcohol intake, hypertension, diabetes, myocardial infarction, congestive heart failure and peripheral artery disease; and after further multivariable adjustment, these associations were attenuated but remained statistically significant. The multivariable-adjusted ORs of participants for prevalent AF associated with CKD versus non-CKD within subgroups stratified by age, diabetes, hypertension and waist circumference sex, in all subgroups were >1.0.

Regardless of CKD status, older age, smoking, and larger waist circumference were associated with an increased OR for AF. Among those without CKD, a clinical history of hypertension, diabetes and reduced eGFR were significantly associated with ORs for AF. Alternatively, among those with CKD, baseline elevated serum CRP, reduced eGFR, and urine protein positive were significantly associated with an increased OR for AF.

Multivariable-adjusted analysis showed that older age, smoking, hypertension, diabetes, and larger waist circumference were significantly associated with AF in the non-CKD group.

In the CKD group, older age, smoking, larger waist circumference, reduced eGFR, proteinuria and raised serum C-reactive protein were significantly associated with AF.

Summary and conclusions

The relationship between atrial fibrillation and chronic kidney disease (CKD) has long been recognised, although there remain many unanswered questions. Atrial fibrillation is a common finding in patients with chronic kidney disease. There exist a bidirectional relationship between AF and CKD with multiple shared risk factors (Kotalczyk et al 2021). Such that the incidence of AF is increased in the presence of CKD and patients with AF suffer from greater deterioration in renal function over time (Ding et al 2021).

Chronic renal disease and atrial fibrillation are common clinical comorbid conditions with a complex relationship. In addition to common risk factors such as advanced age, diabetes, and hypertension, the presence of chronic kidney disease independently increases the risk of atrial fibrillation (Liu et al 2021). Patients with both conditions also have an increased risk of stroke and anticoagulation-related haemorrhage. In addition, atrial fibrillation may accelerate the deterioration of renal function, which can be maintained or improved by maintaining sinus rhythm.

Deteriorating renal function significantly increases the risk of incident AF (Kwon et al 2019). The Kailuan cohort study revealed that the prevalence of AF was 4-fold higher among adults with CKD than in non-CKD populations. Lower estimated glomerular filtration rate (eGFR) (OR 0.97; 95CI 0.95–0.99) and proteinuria (OR 2.01, 95CI 1.09–3.74) were significantly related to AF among patients with CKD (Guo et al 2019).

Previous observational studies suggested that the two diseases are risk factors for each other, suggesting a bidirectional relationship. CKD and AF are considered to synergistically aggravate the risk of stroke, adverse cardiac outcomes, and mortality (Psrk et al 2021).

Due to large overlap is present in risk factors and that CKD and AF commonly occurs in elderly individuals with complex comorbidities, so that identifying causality between CKD and AF is difficult. Evidence independent from reverse causation or confounding which is inevitable in observational studies is warranted to investigate causal effects between CKD and AF. Assessment of direct causality between CKD and AF was difficult, as undiagnosed AF or CKD is possible, the disorders share many risk factors raising the concerns of confounding, and issue of reverse causality cannot be disregarded in observational studies.

Factors contributing to the occurrence of AF in patients undergoing dialysis include age, presence of coronary heart disease, echocardiographic abnormalities (low ejection fraction, atrial enlargement, valvular calcification, left ventricular hypertrophy), heart failure, chronic obstructive pulmonary disease, hypertension, stroke, malnutrition (low levels of albumin, total cholesterol and high-density lipoprotein (HDL), secondary hyperparathyroidism, low predialysis systolic blood pressure, duration of renal replacement therapy as well as the method of renal replacement therapy (Franczyk et al 2016).

In a meta-analysis of seven observational studies with 23,468 patients who underwent AF ablation, the prevalence of CKD was 8.0% (Lee et al 2021). Patients with CKD were older (64.2 vs 58.7 years) and had greater prevalence of comorbidities including diabetes mellitus, hypertension and heart failure. These patients were more likely to have non-paroxysmal AF and larger left atrial diameter. CKD was associated with a higher risk of AF recurrence (OR 3.71, 95CI 1.35-10.19), regardless of whether radiofrequency or cryoballoon ablation was performed. The authors hypothesised that chronic kidney disease is associated with increased atrial fibrosis and a higher risk of arrhythmia.

Guo et al. (2019) compared atrial fibrillation in CKD and non-CKD populations in a large cross-sectional analysis from the Kailuan study. The prevalence of AF in CKD and non-CKD individuals was 1.00% and 0.26%, respectively. In sub-groups stratified by age, sex, diabetes, hypertension, and waist circumference, the prevalence of AF in participants with CKD was significantly higher than in those without CKD. The prevalence of AF increased significantly with worsening eGFR the unadjusted ORs for AF were 4.16 (95CI 3.27–5.30) for those with CKD (eGFR \geq 60 mL/min/1.73 m²), 3.49 (95CI 2.74–4.46) for those with CKD (eGFR 30 to <60 mL/min/1.73 m²), and 12.66 (95CI 5.13–31.25) for those with CKD (eGFR <30 mL/min/1.73 m²).

Not all studies are supportive of a causal effect of kidney dysfunction on AF risk. Park et al (2021) conducted a bidirectional summary-level Mendelian randomisation (MR) analysis to evaluate the association of genetically determined renal disease and risk of AF, using the results from a large-scale genome-wide association study for estimated glomerular filtration rate to identify genetic instruments. Genetically predicted eGFR did not show a significant association with the risk of AF [P = 0.183]. The study supports AF as a causal factor for kidney function impairment, but an effect of kidney function on AF was not identified.

The authors performed multiple pleiotropy-robust MR methods and disregarded variants that might have horizontal pleiotropic effect on the results. Extensive MR analysis suggests that AF causally increases the risk of kidney function impairment, but the causal effects from kidney function on AF were insignificant. However, the finding that kidney function did not show significant causal effects for AF should be interpreted cautiously.

It is therefore concluded that in relation to chronic kidney disease, there is evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A consistent association has been observed between chronic kidney disease and the development or worsening of atrial fibrillation and atrial flutter, but chance, bias or confounding cannot be ruled out with reasonable confidence, particularly in relation to underlying cardiovascular disease.

It is suggested that a factor for chronic kidney disease should be added to the BoP SoPs. The factor should be rephrased using the current standard SoP definition of chronic kidney disease.

Infection

HIV

No factor

Summary of important issues

HIV is associated with cardiovascular disease, although it is not evident that HIV is associated with AF.

Review

Cardiovascular events, such as myocardial infarction, heart failure, sudden cardiac death, and stroke are more common in HIV+ than HIV– individuals.

The relationship between HIV infection and atrial fibrillation is unclear.³⁴⁸ A study from the Veterans Affairs (VA) HIV Clinical Case Registry found that low CD4+ T cell count and elevated HIV ribonucleic acid viral load were associated with incident AF. A more recent matched case-control study in the HIV Electronic Comprehensive Cohort of CVD Complications found an elevated unadjusted odds of AF among HIV+ compared with HIV– individuals, which was not significant after adjustment for demographics (Sanders et al 2018). Data from the Healthcare Cost and Utilization project in California found that HIV was associated with incident AF (Sardana et al 2019).³⁴⁹

³⁴⁸ Osuji, N., Haberlen, S. A., Ashikaga, H., et al. (2021). Association between human immunodeficiency virus serostatus and the prevalence of atrial fibrillation. *Medicine*, 100(29), e26663.

³⁴⁹ Sardana M, Hsue PY, Tseng ZH, et al. (2019) Human immunodeficiency virus infection and incident atrial fibrillation. *J Am Coll Cardiol*; 74: 1512–4.

Cross-sectional study

Osuji et al (2021) evaluated the association between HIV serostatus and the prevalence of AF in the Multicenter AIDS Cohort Study.³⁵⁰

A cross sectional study was conducted among 1674 HIV-infected (HIV+) and uninfected (HIV-) men who completed resting 12-lead electrocardiograms, and/or ambulatory electrocardiogram monitoring. Multivariable logistic regression was used to evaluate the association between AF, defined as the presence of either AF or atrial flutter, and HIV+ serostatus. Associations were adjusted for demographic variables, and then also for CVD risk factors. HIV+ men were younger than HIV- men (median 55.5 vs 61.7 years, $P < .001$) and were more frequently African-American (30.5% vs 17.8%, $P < .001$). Most HIV+ men (81%) had undetectable viral load. The age and race adjusted prevalence of AF was 3.0% in HIV+ and 3.3% in HIV- men.

There was only 1 case of AF among African-American men. There were no associations between AF and HIV serostatus after adjusting for demographic factors (OR 0.76; 95CI 0.37 to -1.58) or after further adjustment for CVD risk factors (OR 0.84; 95CI 0.39 to -1.81).

TABLE 23 ASSOCIATIONS BETWEEN HIV SEROSTATUS AND ATRIAL FIBRILLATION.

	Model 1 unadjusted odds ratio (95% CI), P -value $n=1674$	Model 2 adjusted odds ratio (95% CI), P -value $n=1674$	Model 3 adjusted odds ratio (95% CI), P -value $n=1587$
HIV-infected (vs HIV-uninfected)	0.39 (0.20–0.79) $P=.008$	0.77 (0.37–1.58) $P=.47$	0.84 (0.39–1.81) $P=.66$
Age per year	1.10 (1.06–1.14) $P < .001$	1.08 (1.03–1.12) $P < .001$	1.08 (1.02–1.13) $P=.002$
Race category			
Caucasian	Reference	Reference	Reference
Non-Caucasian	0.04 (0.01–0.31) $P=.002$	0.08 (0.01–0.66) $P=.02$	0.06 (0.01–0.53) $P=.01$
Body mass index (per 1 kg/m ²)			1.02 (0.96–1.09) $P=.46$
Alcohol use >13 drinks per week (vs ≤13)			0.73 (0.24–2.40) $P=.55$
Cumulative pack-years of smoking			0.99 (0.98–1.01) $P=.23$
Systolic blood pressure (per 1 mm Hg)			1.00 (0.98–1.02) $P=.94$
Fasting glucose (per 1 mg/dL)			1.01 (1.00–1.02) $P=.01$
On hypertension medications (vs none)			2.61 (1.18–5.76) $P=.02$
On diabetes medications (vs none)			0.63 (0.21–1.90) $P=.41$

HIV=human immunodeficiency virus.

Osuji et al. (2021) Table 2

Osuji et al. found no association between HIV and AF in the cohort in which viral replication among the HIV+ men is generally suppressed. The overall prevalence of AF was low and was rare in African-American men

There were no difference in the frequency of AF between HIV+ and HIV- men, after adjusting for demographics or additionally adjusting for cardiovascular risk factors. As expected, AF was strongly associated with aging. There was generally a low prevalence of AF in the cohort and a remarkably low prevalence of AF in non-Caucasian men. Among HIV+ participants, there was no association between AF and CD4+ T cell counts.

³⁵⁰ Osuji, N., Haberen, S. A., Ashikaga, H., et al. (2021). Association between human immunodeficiency virus serostatus and the prevalence of atrial fibrillation. *Medicine*, 100(29), e26663. August meeting 2022

Sanders et al (2018) was the first study comparing atrial fibrillation and atrial flutter prevalence and associated characteristics for HIV+ persons and matched uninfected controls.³⁵¹

Persons with diagnoses of HIV receiving care at a large urban academic medical centre were frequency-matched 1:2 on age, sex, race, zip code, and clinic location with uninfected persons. Possible AF/AFL was screened for using administrative codes and diagnoses of AF/AFL were subsequently adjudicated using electrocardiography and physician notes; adjudication was performed given the inconsistent validity of administrative code-derived AF diagnoses found in previous studies.

There were 101 confirmed AF/AFL cases (2.00%) among 5,052 HIV+ patients and 159 confirmed AF/AFL cases (1.57%) among 10,121 uninfected controls (OR 1.27, 95CI 0.99-1.64; p = 0.056]. The association between HIV serostatus and AF/AFL was attenuated after adjustment for demographics and CVD risk factors. Among HIV+ persons, nadir CD4+ T cell count <200 cells/mm³ was associated with approximately twofold elevated odds of AF/AFL even after adjustment for demographics and CVD risk factors (Multivariable-adjusted OR 1.98, 95% CI 1.21-3.25).

There was no significant association between log₁₀ of peak HIV viral load and AF/AFL (-adjusted OR 1.03, 95CI 0.86-1.24). Older age, diabetes, hypertension, and chronic obstructive pulmonary disease were associated with similarly elevated odds of AF/AFL for HIV+ persons and uninfected controls.

HIV-related immunosuppression (nadir CD4 T cell count <200 cells/mm³) and traditional CVD risk factors are associated with significantly elevated odds of AF/AFL among HIV+ persons. Although atrial fibrillation and flutter was more common among HIV+ versus uninfected persons in this cohort, this difference was attenuated by adjustment for demographics and CVD risk factors.

Little is known about the differences in arrhythmias seen in patients with HIV following acute myocardial infarction (AMI). **Ramphul et al (2021)** used the 2017 National Inpatient Sample (NIS) to study the outcomes of HIV patients admitted in the US.³⁵²

The authors identified 662,055 hospitalised cases of AMI among adults in the United States in 2017, and 2,860 had a diagnosis of HIV (0.4%). The incidences of long QT syndrome, atrial flutter, paroxysmal atrial fibrillation, supraventricular tachycardia, and ventricular fibrillation in patients with HIV were 105 cases/10,000 patients with HIV, 297 cases/10,000 patients with HIV, 350 cases/10,000 patients with HIV, 192 cases/10,000 patients with HIV, and 280 cases/10,000 patients with HIV, respectively, while they were 48 cases/10,000 patients

³⁵¹ Sanders, J. M., Stevenson, A. B., Pawlowski, A. E., et al (2018). Atrial arrhythmia prevalence and characteristics for human immunodeficiency virus-infected persons and matched uninfected controls. *PloS one*, 13(3), e0194754

³⁵² Ramphul, K., Kumar, N., Verma, R., et al (2021). Higher risk of long QT syndrome and atrial flutter in adults with HIV admitted for acute myocardial infarction. *Anatolian journal of cardiology*, 25(9), 673–4
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without HIV, 230 cases/10,000 patients without HIV, 899 cases/10,000 patients without HIV, 233 cases/10,000 patients without HIV, and 304 cases/10,000 patients without HIV.

The results were statistically significant for atrial flutter 1.300 (95CI 1.047-1.614, $p=0.017$) times more likely in patients with HIV. findings among cases of supraventricular tachycardia ($p=0.15$) and ventricular fibrillation ($p=0.45$) were not statistically significant. A lower OR of 0.367 (95CI 0.300-0.448, $p<0.001$) was found for paroxysmal atrial fibrillation in patients with HIV.

Hsu et al. (2013) found that the risk of atrial flutter in patients with HIV could be associated with their viral load. It was, however, not possible for us to further investigate this aspect owing to some of the limitations of the HCUP database.³⁵³

Summary and conclusions

Human immunodeficiency virus (HIV) is associated with cardiovascular disease (CVD), although it is unclear if HIV is associated with the risk of developing AF.

The relationship between HIV infection and atrial fibrillation is unclear. A study from the Veterans Affairs (VA) HIV Clinical Case Registry found that low CD4+ T cell count and elevated HIV ribonucleic acid viral load were associated with incident AF (Osuji et al 2021]. A more recent matched case-control study in the HIV Electronic Comprehensive Cohort of CVD Complications found an elevated unadjusted odds of AF among HIV+ compared with HIV- individuals, which was not significant after adjustment for demographics (Sanders et al 2018). Data from the Healthcare Cost and Utilization project in California found that HIV was associated with incident AF (Sardana et al 2019).]

Ramphul et al (2021) used the 2017 National Inpatient Sample (NIS) to study the outcomes of HIV patients admitted in the United States. Of 662,055 hospitalized cases of AMI among adults in the United States in 2017, and 2,860 had a diagnosis of HIV (0.4%). The results were statistically significant for atrial flutter 1.300 (95CI 1.047-1.614) times more likely in patients with HIV. findings among cases of supraventricular tachycardia ($p=0.15$) and ventricular fibrillation ($p=0.45$) were not statistically significant. A lower OR of 0.367 (95CI 0.300-0.448) was found for paroxysmal atrial fibrillation in patients with HIV.

Sanders et al (2018) was the first study to compare atrial fibrillation and atrial flutter (AFL) prevalence and associated characteristics for HIV+ persons and matched uninfected controls. There were 101 confirmed AF/AFL cases (2.00%) among 5,052 HIV+ patients and 159 confirmed AF/AFL cases (1.57%) among 10,121 uninfected controls (OR 1.27, 95CI 0.99-1.64). The association between HIV serostatus and AF/AFL was attenuated after adjustment for demographics and CVD risk factors. Among HIV+ persons, nadir CD4+ T cell count <200 cells/mm³ was associated with twofold elevated odds of AF/AFL even after adjustment for demographics and CVD risk factors (OR 1.98, 95CI 1.21-3.25). There was no significant

³⁵³ Hsu JC, Li Y, Marcus GM, Hsue PY, , et al. (2013) Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity. J Am Coll Cardiol 2013; 61: 2288-95
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association between log₁₀ of peak HIV viral load and AF/AFL (-adjusted OR 1.03, 95CI 0.86-1.24).

Osuji et al. (2021) evaluated the association between HIV serostatus and the prevalence of AF in the Multicenter AIDS Cohort Study. A cross sectional study was conducted among 1674 HIV-infected (HIV+) and uninfected (HIV-) men. There was only 1 case of AF among African-American men. There were no associations between AF and HIV serostatus after adjusting for demographic factors (OR 0.76; 95CI 0.37 to -1.58) or after further adjustment for CVD risk factors (OR 0.84; 95CI 0.39 to -1.81). No difference in the frequency of AF between HIV+ and HIV- men, after adjusting for demographics or additionally adjusting for cardiovascular risk factors.

It is concluded that the evidence is too limited to permit a judgement of a possible causal relationship between HIV infection and the development of atrial fibrillation or atrial flutter (Grade 4). An association is demonstrated in some studies, but the evidence is inconsistent and studies are limited in quality or quantity. Chance, bias or confounding are likely to account for observed associations.

No factor for the SoPs is suggested.

Influenza virus infection

No factor

Cardiac injury is a known potential complication of influenza infection.

Case-control study

Influenza infection could activate systemic inflammatory responses and increase the sympathetic tone that plays an important role in the pathogenesis of atrial fibrillation. **Chang et al (2016)** investigated whether influenza infection was a risk factor for AF.³⁵⁴

From 2000 to 2010, a total of 11,374 patients with newly diagnosed AF were identified from the Taiwan National Health Insurance Research Database. On the same date of enrolment, 4 control patients (without AF) with matched age and sex were selected to be the control group for each study patient. The relationship between AF and influenza infection or vaccination 1 year before the enrolment was analysed.

Compared with patients without influenza infection or vaccination (reference group; n = 38,353), patients with influenza infection without vaccination (n = 1369) were associated with a significantly higher risk of AF with an OR of 1.182 (P = .032) after adjustment for baseline differences. The risk of AF was lower in patients receiving influenza vaccination without influenza infection (n = 16,452) with an OR of 0.881 (P<.001). In patients who received

³⁵⁴ Chang TY, Chao TF, Liu CJ, et al (2016). The association between influenza infection, vaccination, and atrial fibrillation: A nationwide case-control study. *Heart Rhythm.*; 13(6):1189-94
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influenza vaccination and experienced influenza infection (n = 696), the risk of AF was similar to that in the reference group (OR 1.136; P = 0.214). The lower risk of AF with vaccination was consistently observed in subgroup analyses.

Influenza infection was significantly associated with the development of AF, with an 18% increase in risk.

Cross-sectional study

Because U.S. veterans cared for at the U.S. Department of Veterans Affairs are older and have more cardiovascular disease (CVD) risk factors than the general U.S. population, veterans are at risk for cardiac complications of influenza infection. **Ludwig et al (2015)** investigated biomarkers of cardiac injury characteristics and associated cardiac events among veterans who received cardiac biomarker testing ≤ 30 days after laboratory-confirmed influenza virus infection.³⁵⁵

Laboratory-confirmed influenza cases among veterans cared for at U.S. Department of Veterans Affairs' facilities from October 2010 to December 2012 were identified using electronic medical records (EMRs). Influenza confirmation was based on respiratory specimen viral culture or antigen or nucleic acid detection. Acute cardiac injury (ACI) was defined as an elevated cardiac biomarker (troponin I or creatinine kinase isoenzyme MB) > 99 % of the upper reference limit occurring ≤ 30 days after influenza specimen collection. EMRs were reviewed for demographics, CVD history and risk factors, and ACI-associated cardiac events.

Among 38,197 patients with influenza testing results, 4,469 (12 %) had a positive result; 600 patients had cardiac biomarker testing performed ≤ 30 days after influenza testing, and 143 (24%) had one or more elevated cardiac biomarkers. All patients had one or more CVD risk factors, and 98 (69%) had a history of CVD. 86% of ACI-associated events occurred within 3 days of influenza specimen collection date. Seventy patients (49%) had documented or probable acute myocardial infarction, 8 (6%) acute congestive heart failure, 6 (4%) myocarditis, **and 4 (3%) atrial fibrillation**. Eleven (8%) had non-cardiac explanations for elevated cardiac biomarkers, and 44 (31 %) had no documented explanation. Sixty-eight (48%) patients had received influenza vaccination during the related influenza season.

Among veterans with laboratory-confirmed influenza infection and cardiac biomarker testing ≤ 30 days after influenza testing, 25 % had evidence of acute cardiac injury, the majority within 3 days. The findings emphasise the importance of considering acute cardiac injury associated with influenza infection among patients at high risk, including older populations with prevalent CVD risk factors.

³⁵⁵ Ludwig, A., Lucero-Obusan, C., Schirmer, P., et al. (2015). Acute cardiac injury events ≤ 30 days after laboratory-confirmed influenza virus infection among U.S. veterans, 2010-2012. BMC cardiovascular disorders, 15, 109.

Covid-19

No factor

Summary of important issues

COVID-19 has a spectrum of cardiovascular manifestations including myocarditis, pericarditis, or increased biomarkers of cardiac injury, all of which may associate with poor prognosis. Several case series showing a significant proportion of cardiac involvement in hospitalised patients (Buckley et al 2021). Patients with COVID-19 who present with myocarditis/pericarditis associate with increased odds of major adverse events and new-onset cardiovascular sequelae including AF.

Reviews

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. SARS-CoV-2 caused COVID-19 has reached a pandemic level.³⁵⁶ COVID-19 can significantly affect patients' cardiovascular systems. patients with COVID-19 and preexisting cardiovascular disease have an increased risk of severe disease and death. Mortality from COVID-19 is strongly associated with cardiovascular disease, diabetes, and hypertension. Therapies under investigation for COVID-19 may have cardiovascular side effects of arrhythmia.

COVID-19 is associated with multiple direct and indirect cardiovascular complications. A high inflammatory burden related to cytokine release, COVID-19 can induce vascular inflammation, acute myocardial injury, myocarditis, arrhythmias, venous thromboembolism, metabolic syndrome and Kawasaki disease. patients with cardiac arrhythmias are emerging due to the effects of COVID-19 on the respiratory and cardiovascular (CV) systems and the systemic inflammation that it incurs, and also as a result of the proarrhythmic effects of COVID-19 pharmacotherapies and other drug interactions and the associated autonomic imbalance that enhance arrhythmogenicity.³⁵⁷

A high incidence of AF/AFL has been reported with COVID-19. However, as available studies have been limited in scope and specificity, the true incidence of AF/AFL in this population is unknown.³⁵⁸

Despite a large number of asymptomatic cases, the course of coronavirus disease (COVID-19) can be serious. Myocardial injury in coronavirus disease (COVID-19) is caused by multiple

³⁵⁶ Chang, W. T., Toh, H. S., Liao, C. T., et al. (2021). Cardiac Involvement of COVID-19: A Comprehensive Review. *The American journal of the medical sciences*, 361(1), 14–22.

³⁵⁷ Manolis, A. S., Manolis, A. A., Manolis, T. A., et al (2020). COVID-19 infection and cardiac arrhythmias. *Trends in cardiovascular medicine*, 30(8), 451–60.

³⁵⁸ Musikantow, D. R., Turagam, M. K., Sartori, S., et al. (2021). Atrial Fibrillation in Patients Hospitalized With COVID-19: Incidence, Predictors, Outcomes, and Comparison to Influenza. *JACC. Clinical electrophysiology*, 7(9), 1120–30.

triggers. The occurrence of cardiac arrhythmias in COVID-19 patients with myocardial involvement and a critical course is common.³⁵⁹

Myocardial involvement in patients infected by COVID-19 is associated with critical or fatal course. One study revealed mortality rates up to 51% in this patient population compared with 4.5% of patients without elevated troponin levels. Admission to intensive care unit is much more common, if myocardial involvement is present. The mechanisms of acute cardiac injury are multicausal, including myocarditis, acute myocardial infarction, deep vein thrombosis and consecutive pulmonary embolism, aggravation of preexisting CVDs and oxygen demand–supply mismatch due to ARDS combined with shock.

There have been several comprehensive reviews of the literature on COVID-19 regarding cardiovascular virus involvement.^{360 361 362 363 364} These review studies provide evidence that COVID-19 is related to increased risk of AF through several mechanisms, many of which converge through the causation of myocarditis.

Duckheim & Schreieck (2021) reviewed published literature concerning COVID-19 and arrhythmias.³⁶⁵ The occurrence of cardiac arrhythmias in patients with cardiac injury and severe course of COVID-19 is common. Common arrhythmias in COVID-19 patients include sinus tachycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, atrioventricular block, sinusoidal block or QTc prolongation.

AF was the most common heart rhythm disorder. About 10% of COVID-19 patients develop new-onset AF and 23 to 33% showed recurrence of AF in patients with known AF. Both AF and VT are associated with worse outcome. The diversity of arrhythmias suggests various potential mechanisms for arrhythmogenesis. Both extracardiac and intracardiac processes can lead to cardiac arrhythmias in COVID-19 patients: Direct viral toxicity of both lung and myocardial tissue triggering myocarditis, myocardial dysfunction and ARDS can account for hypoxia of the myocardium which in turn result in cardiac arrhythmias. An abnormal host immune response, commonly seen in COVID-19 patients, myocardial stress caused by pulmonary hypertension, electrolyte or volume imbalances and myocardial ischemia might also be common triggers in COVID-19 patients.

³⁵⁹ Duckheim, M., & Schreieck, J. (2021). COVID-19 and Cardiac Arrhythmias. *Hamostaseologie*, 41(5), 372–8.

³⁶⁰ Duckheim, M., & Schreieck, J. (2021). COVID-19 and Cardiac Arrhythmias. *Hamostaseologie*, 41(5), 372–8.

³⁶¹ Stone, E., Kiat, H., & McLachlan, C. S. (2020). Atrial fibrillation in COVID-19: A review of possible mechanisms. *FASEB journal*, 34(9), 11347–54.

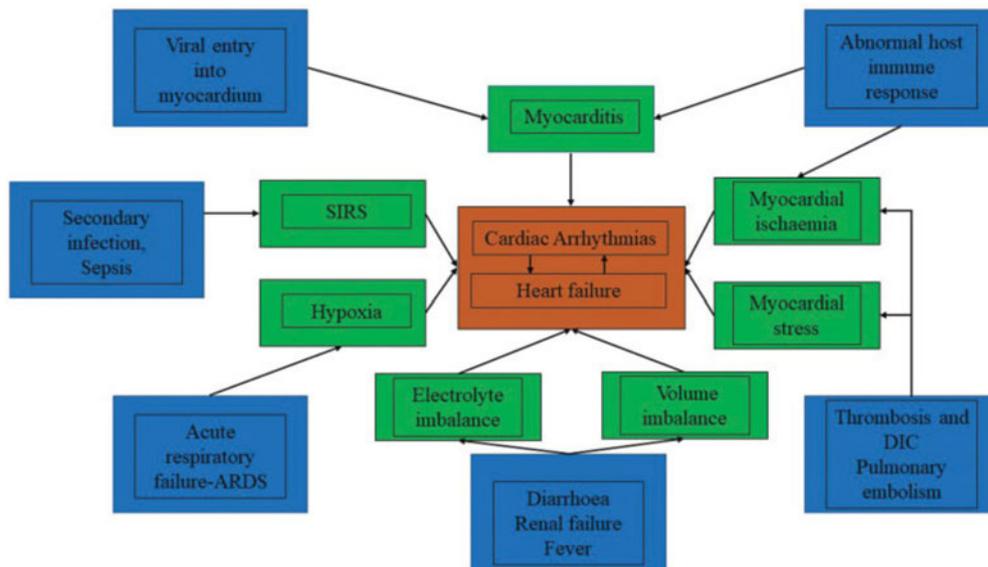
³⁶² Chang, W. T., Toh, H. S., Liao, C. T., et al. (2021). Cardiac Involvement of COVID-19: A Comprehensive Review. *The American journal of the medical sciences*, 361(1), 14–22.

³⁶³ Vadakken, M. E., Belley-Cote, E. P., & McIntyre, W. F. (2021). COVID-19 and AF: What About the Long Game?. *JACC. Clinical electrophysiology*, 7(9), 1196–7

³⁶⁴ Chinitz L. A. (2021). Atrial Arrhythmias and the Pandemic. *JACC. Clinical electrophysiology*, 7(9), 1131–3.

³⁶⁵ Duckheim, M., & Schreieck, J. (2021). COVID-19 and Cardiac Arrhythmias. *Hamostaseologie*, 41(5), 372–8.

FIGURE 52 POTENTIAL AETIOLOGIES OF CARDIAC ARRHYTHMIAS IN COVID-19 PATIENTS



Source: Duckheim & Schreieck (2021), Fig 1

Several mechanisms such as hypoxia, myocarditis, myocardial ischemia, or abnormal host immune response, which induce cardiac arrhythmias, have been described.

The occurrence of myocarditis in patients with COVID-19 has been described. This has been detailed in a previous section of the briefing paper. Hypotheses for the pathophysiology of myocarditis in COVID-19 patients include direct viral penetration of the myocardial cell by the viral spike protein, which binds to angiotensin converting enzyme 2 receptor (ACE-2 receptor) on the myocardial cell membrane, causing direct myocardial injury. Binding of the spike protein downregulates the ACE-2 receptor, which might trigger accumulation of angiotensin II and consecutively adverse remodelling of the myocardium. Both remodeling and viral penetration might disrupt electrical conduction and enhance arrhythmic risk.

Another possible mechanism of inducing myocarditis and consecutively cardiac arrhythmias in COVID-19 patients is cellular-based. CD8 β T-lymphocytes as part of the systemic inflammation trigger inflammation of the myocytes. This mechanism is enhanced by a massive cytokine release, which increases the activity of T-lymphocytes, which releases cytokines

The pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterised by overproduction of inflammatory cytokines (IL-6 and TNF- α) leading to systemic inflammation and multiple organ dysfunction syndrome, acutely affecting the cardiovascular system. Cardiac injury in patients infected with the novel coronavirus (COVID-19) seems to be associated with higher morbidity and mortality.

Azevedo et al (2021) reviewed the clinical evolution of COVID-19, emphasizing its impact and implications on the cardiovascular system.³⁶⁶ Hypertension (56.6%) and diabetes (33.8%) are the most prevalent comorbidities among individuals with COVID-19, who require

³⁶⁶ Azevedo, R. B., Botelho, B. G., Hollanda, J., et al (2021). Covid-19 and the cardiovascular system: a comprehensive review. *Journal of human hypertension*, 35(1), 4–11. August meeting 2022

hospitalisation. cardiac injury, defined as elevated us-troponin I, significantly relates to inflammation biomarkers (IL-6 and C-reactive protein (CRP), hyperferritinaemia, and leukocytosis), portraying an important correlation between myocardial injury and inflammatory hyperactivity triggered by viral infection. Increased risk for myocardial infarction, fulminant myocarditis rapidly evolving with depressed systolic left ventricle function, arrhythmias, venous thromboembolism, and cardiomyopathies mimicking STEMI presentations are the most prevalent cardiovascular complications described in patients with COVID-19. SARS-CoV-2 tropism and interaction with the RAAS system, through ACE2 receptor, possibly enhances inflammation response and cardiac aggression, leading to imperative concerns about the use of ACEi and ARBs in infected patients.

There are few reports in the literature regarding cardiac arrhythmias in COVID-19, with no clear pathophysiological correlation.³⁶⁷ The potential mechanism seems to be viral myocarditis caused by SARS-CoV-2. Fulminant myocarditis associated with cardiogenic shock may be associated with the development of both ventricular and atrial arrhythmias, as myocardial inflammation itself with severe necrosis may develop re-entry points in the electrical circuit, evolving with ventricular tachycardia and ventricular fibrillation

Current understanding of the impact of coronavirus disease-2019 (COVID-19) on arrhythmias continues to evolve as new data emerge.³⁶⁸ Cardiac arrhythmias are more common in critically ill COVID-19 patients. The potential mechanisms that could result in arrhythmogenesis among COVID-19 patients include hypoxia caused by direct viral tissue involvement of lungs, myocarditis, abnormal host immune response, myocardial ischaemia, myocardial strain, electrolyte derangements, intravascular volume imbalances, and drug side effects.

Cohort studies

Musikantow et al (2021) determined the incidence, predictors, and outcomes of atrial fibrillation or atrial flutter in patients hospitalised with coronavirus disease-2019 (COVID-19).³⁶⁹

This was a retrospective analysis of 3,970 patients admitted with polymerase chain reaction-positive COVID-19 between February and April 2020, with manual review performed of 1,110. The comparator arm included 1,420 patients with influenza hospitalised between January 1, 2017 and January 2020.

Among 3,970 inpatients with COVID-19, the incidence of AF/AFL was 10% (n = 375). Most patients with inpatient AF/AFL (61%) had a history of atrial arrhythmias, and of those with a

³⁶⁷ Azevedo, R. B., Botelho, B. G., Hollanda, J., et al (2021). Covid-19 and the cardiovascular system: a comprehensive review. *Journal of human hypertension*, 35(1), 4–11.

³⁶⁸ Dherange, P., Lang, J., Qian, P., et al . (2020). Arrhythmias and COVID-19: A Review. *JACC. Clinical electrophysiology*, 6(9), 1193–204.

³⁶⁹ Musikantow, D. R., Turagam, M. K., Sartori, S., et al. (2021). Atrial Fibrillation in Patients Hospitalized With COVID-19: Incidence, Predictors, Outcomes, and Comparison to Influenza. *JACC. Clinical electrophysiology*, 7(9), 1120–30.

history of atrial arrhythmias, 71% manifested AF/AFL during hospitalisation. In patients without a history of atrial arrhythmias, the incidence of new-onset AF/AFL was 4% (n = 146).

Patients with new-onset AF/AFL were older with increased inflammatory markers including interleukin 6 (93 vs. 68 pg/ml; p < 0.01), and more myocardial injury (troponin-I: 0.2 vs. 0.06 ng/ml; p < 0.01). AF and AFL were associated with increased mortality (46% vs. 26%; p < 0.01). Manual review captured a higher incidence of AF/AFL (13%, n = 140).

To understand the specificity of observed atrial arrhythmias in COVID-19, the authors studied a cohort of 1,420 influenza patients. Comorbidities occurred more frequently in patients hospitalised with influenza than COVID-19. The incidence of in-hospital AF/AFL was higher in the Influenza primary than the COVID-19 cohort (12% vs. 10%, p = 0.03), but the incidence of new-onset AF/AFL was similar (4% vs. 4%; p = 0.93). Despite more frequent comorbidities, the Influenza primary cohort had a substantially lower incidence of in-hospital mortality (9% vs. 29%, p < 0.01).

Compared to inpatients with COVID-19, patients with influenza (n = 1,420) had similar rates of AF/AFL (12%, n = 163) but lower mortality. The presence of AF/AFL correlated with similarly increased mortality in both COVID-19 (RR: 1.77) and influenza (RR: 1.78).

AF/AFL occurs in a subset of patients hospitalised with either COVID-19 or influenza and is associated with inflammation and disease severity in both infections. The incidence and associated increase in mortality in both cohorts suggests that AF/AFL is not specific to COVID-19, but is rather a generalised response to the systemic inflammation of severe viral illnesses. The similar rates of in-hospital all and new-onset AF/AFL in the influenza group collected from the same New York hospitals suggests that these atrial arrhythmias occurred as a nonspecific response to severe viral respiratory illness.

the incidence of AF/AFL in patients with COVID-19 is not exceedingly high, the occurrence of in-hospital AF/AFL appears impactful to a patient's clinical course, as indicated by the frequent use of antiarrhythmic therapy.

Mortality in critically ill patients with coronavirus disease 2019 (COVID-19) is high. **Ergun et al (2021)** determined the incidence, risk factors, and outcomes of NOAF in a cohort of critically ill patients with COVID-19.³⁷⁰

This was a retrospective study on patients admitted to the intensive care unit (ICU) with a diagnosis of COVID-19. NOAF was defined as atrial fibrillation that was detected after diagnosis of COVID-19 without a prior history. The primary outcome of the study was the effect of NOAF on mortality in critically ill COVID-19 patients.

NOAF incidence was 14.9% (n = 37), and 78% of patients (n = 29) were men in NOAF positive group. Median age of the NOAF group was 79.0 (interquartile range, 71.5-84.0). Hospital mortality was higher in the NOAF group (87% vs 67%, respectively, P = .019).

³⁷⁰ Ergün, B., Ergun, B., Sözmen, M. K., et al (2021). New-onset atrial fibrillation in critically ill patients with coronavirus disease 2019 (COVID-19). *Journal of arrhythmia*, 37(5), 1196–1204.

However, in multivariate analysis, NOAF was not an independent risk factor for hospital mortality (OR 1.42, 95% CI 0.40-5.09, P = .582).

The incidence of NOAF was 14.9% in critically ill COVID-19 patients. Hospital mortality was higher in the NOAF group. However, NOAF was not an independent risk factor for hospital mortality in patients with COVID-19.

Summary and conclusions

Cardiac injury is a known potential complication of influenza infection. Chang et al (2016) investigated whether influenza infection was a risk factor for AF using the Taiwan National Health Insurance Research Database. Compared to patients without influenza infection or vaccination (reference group; n = 38,353), patients with influenza infection without vaccination (n = 1369) were associated with a significantly higher risk of AF with an OR of 1.182

Ludwig et al (2015) investigated biomarkers of cardiac injury characteristics and associated cardiac events among veterans who received cardiac biomarker testing. Among 4,469 veterans with laboratory-confirmed influenza infection and cardiac biomarker testing ≤ 30 days after influenza testing, 25% (n=600) had evidence of acute cardiac injury, the majority within 3 days. 4 (3%) had documented atrial fibrillation. The study highlighted the risk of acute cardiac injury associated with influenza infection in older populations with prevalent CVD risk factors.

A high incidence of AF/AFL has been reported with COVID-19. However, as available studies have been limited in scope and specificity, the true incidence of AF/AFL in this population is unknown (Musikantow et al 2021). It is uncertain if the inflammatory milieu of COVID-19 is uniquely responsible for AF/AFL, or whether these arrhythmias reflect part of a nonspecific byproduct of severe viral respiratory illness

COVID-19 results in increased inflammatory markers previously associated with atrial arrhythmias; AF/AFL occurs in a subset of patients hospitalised with COVID-19 or influenza and is associated with inflammation and disease severity in both infections. The incidence and associated increase in mortality in both cohorts suggests that AF/AFL is not specific to COVID-19, but is rather a generalised response to the systemic inflammation of severe viral illnesses (Musikantow et al 2021).

Myocardial injury in coronavirus disease is caused by multiple triggers (Duckheim & Schreieck 2021). The occurrence of arrhythmias in COVID-19 patients with myocardial involvement and a critical course is common. Common arrhythmias in COVID-19 patients include AF. About 10% of COVID-19 patients develop new-onset AF and 23 to 33% showed recurrence of AF in patients with known AF. Both AF and VT are associated with worse outcome.

There are few studies regarding cardiac arrhythmias in COVID-19, with no clear pathophysiological correlation. The potential mechanism seems to be viral myocarditis caused by SARS-CoV-2. Fulminant myocarditis associated with cardiogenic shock may be associated with the development of both ventricular and atrial arrhythmias, as myocardial inflammation itself with severe necrosis may develop re-entry points in the electrical circuit, evolving with ventricular tachycardia and ventricular fibrillation (Azevedo et al 2021).

Musikantow et al (2021) determined the incidence, predictors, and outcomes of atrial fibrillation or atrial flutter in patients hospitalised with COVID-19. Among 3,970 inpatients with COVID-19, the incidence of AF/AFL was 10% (n = 375). Most patients with inpatient AF/AFL (61%) had a history of atrial arrhythmias, and of those with a history of atrial arrhythmias, 71% manifested AF/AFL during hospitalisation. In patients without a history of atrial arrhythmias, the incidence of new-onset AF/AFL was 4% (n = 146).

To understand the specificity of observed atrial arrhythmias in COVID-19, the authors studied a cohort of 1,420 influenza patients. Compared to inpatients with COVID-19, patients with influenza (n = 1,420) had similar rates of AF/AFL (12%, n = 163) but lower mortality. The presence of AF/AFL correlated with similarly increased mortality in both COVID-19 (RR: 1.77) and influenza (RR: 1.78).

AF/AFL occurs in a subset of patients hospitalised with either COVID-19 or influenza and is associated with inflammation and disease severity in both infections. The incidence and associated increase in mortality in both cohorts suggests that AF/AFL is not specific to COVID-19, but is rather a generalised response to the systemic inflammation of severe viral illnesses. Although the incidence of AF/AFL in patients with COVID-19 is not greatly elevated high, the occurrence of in-hospital AF/AFL appears impactful to a patient's clinical course, as indicated by the frequent use of antiarrhythmic therapy.

It is concluded that in relation to having a viral upper respiratory tract infection, particularly influenza virus infection and Covid-19 infection, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality or quantity. The data links influenza viral infection and Covid-19 infection with the development of atrial arrhythmias, independent of myocarditis.

A new factor for viral upper respiratory tract infection is proposed for the RH SoP only. As the relevant literature concerns patients hospitalised for respiratory infection, a factor should be confined to infection of sufficient severity to warrant hospitalisation.

A note with examples of relevant causes should be added. These examples should include influenza virus infection and Covid-19 infection.

Drugs

No factor

Review studies

Certain antiarrhythmic drugs may increase the risk of AF. A 2020 scientific statement from the American Heart Association details drugs associated with AF [Tisdale et al 2020]. While exhaustive, this statement includes many medications for which the association with AF is likely relatively weak.

Many widely used medications may cause or exacerbate arrhythmias. Mechanisms of arrhythmias are well known for some medications but, in other instances, remain poorly understood.³⁷¹ For some drug-induced arrhythmias, particularly torsades de pointes, risk factors are well defined. Modification of risk factors, when possible, is important for prevention and risk reduction. In patients with nonmodifiable risk factors who require a potentially arrhythmia-inducing drug, enhanced electrocardiographic and other monitoring strategies may be beneficial for early detection and treatment. Management of drug-induced arrhythmias includes discontinuation of the offending medication and following treatment guidelines for the specific arrhythmia. In overdose situations, targeted detoxification strategies may be needed.

Drugs that may cause or exacerbate AF/AFL include cardiovascular medications, alcohol, stimulants, anticancer agents, and immunomodulators.

³⁷¹ Tisdale, J. E., Chung, M. K., Campbell, K. B., et al (2020). Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*, 142(15), e214–e233.
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TABLE 24 DRUGS THAT MAY CAUSE/EXACERBATE AF OR AFL

Drug Class	Drug	Incidence, % or Odds/Hazard/Incidence Ratio or Relative Risk	Mechanism
Antiarrhythmic ¹	Adenosine	1–12	↑ Pulmonary vein ectopic activity ↓ Atrial effective refractory period/wavelength
	Amiodarone	...	Thyrotoxicosis
	Flecainide	...	Sodium channel blockade, slowing atrial conduction
	Propafenone	Up to 9.0†	Sodium channel blockade, slowing atrial conduction
Anticancer ⁸	Tyrosine kinase inhibitors (cetuximab, sunitinib, sorafenib, * ⁹ ibrutinib ¹⁰)	3.3–6.5	↓ nitric oxide signaling, ↑ endothelin-1, lipid accumulation, reactive oxygen species production, inhibition of AMPK, inhibition of K ⁺ channels, mitochondrial disorders, apoptosis, thyrotoxicosis (sunitinib, sorafenib), ↑ hypertension and ↓ cardioprotective effect through cardiac ↓ PI3K-Akt signaling pathway (ibrutinib)
	Anthracyclines (doxorubicin, aclacinomycin A, 7-con-O-methylnogaril, mitoxantrone)	1.4–13.8	Connexin channels, CaMKII, Ca ₂ ⁺ ATPase, reactive oxygen species, mitochondrial dysfunction, apoptosis
	Alkylating agents (cisplatin, melphalan, cyclophosphamide, * ¹¹ ifosfamide)	Up to–15.5	↓ DNA and RNA synthesis, mitochondrial, contractile, endothelial reticulum stress, apoptosis, reactive oxygen species, inflammation, ion channel effects, ATP, lysosome injury, cytotoxic effects
	HER2/Neu receptor blockers (etaracizumab, trastuzumab)	1.2–19.9	Oxidative stress/reactive oxygen species, ↑ inflammation causing ion channel dysfunction and remodeling, apoptosis, ErbB2-ErbB4 signaling
	Antimetabolites (5-fluorouracil, leucovorin)	2.6	Impaired DNA synthesis, coronary spasm, myocardial ischemia
	Microtubule agents (paclitaxel, docetaxel, gemcitabine, ¹² gemcitabine+vinorelbine)	1.0–9.4	Cell division, coronary flow, LV systolic pressure effects, possibly sinoatrial node dysfunction (gemcitabine)
	Histone deacetylase inhibitors (belinostat)	4.6	...
Antidepressant (SSRI)	Fluoxetine*
Antiemetic	Ondansetron*
Anti-inflammatory	Diclofenac ¹³	IR (95% CI): 1.2 (1.1–1.4) vs no NSAID, 1.4 (1.2–1.6) vs paracetamol, 1.1 (1.0–1.3) vs ibuprofen, 1.3 (1.0–1.7) vs naproxen	↓ Endogenous antiarrhythmic effect of prostacyclin through ↑ COX-2 inhibition
	COX-2 inhibitors (etoricoxib ¹⁴)	HR 1.16 (95% CI, 1.05–1.29) Etoricoxib HR 1.35 (95% CI, 1.19–1.54)	↓ Endogenous antiarrhythmic effect of prostacyclin through ↑ COX-2 inhibition
	Corticosteroids (methylprednisolone)	1.8	Inconsistent associations of AF in patients on corticosteroids; may be secondary to underlying conditions
Antiplatelet	Ticagrelor*	...	Speculated to increase adenosine
Antipsychotic ^{1,15}	Chlorpromazine	OR, 1.96 (95% CI, 1.44–2.67)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Clozapine	OR, 2.81 (95% CI, 1.24–6.39)	Serotonin receptor subunit 5-HT2A antagonist
			Alteration of autonomic tone ↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Prochlorperazine	OR, 1.22 (95% CI, 1.15–1.29)	Alteration of autonomic tone
			↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
	Olanzapine	OR, 1.81 (95% CI, 1.14–2.88)	Alteration of autonomic tone ↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Risperidone	OR, 1.25 (95% CI, 1.00–1.55)	Alteration of autonomic tone ↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Quetiapine	OR, 1.55 (95% CI, 1.25–1.92)	Alteration of autonomic tone ↑ Cardiac muscarinic blockade, leading to atrial conduction abnormalities
	Loxapine*	...	Dopamine antagonist, serotonin 5-HT ₂ blocker
Bisphosphonates	Alendronate	0.5	Equivocal or conflicting data
		OR, 1.86 (95% CI, 1.09–3.15)	↓ Atrial effective refractory period/wavelength
		OR, 1.97 (95% CI, 1.59–2.43)	↑ Release of inflammatory cytokines
		IR, 1.58 (95% CI, 1.07–2.33)	
Zoledronic acid	0.8–2.2	Equivocal or conflicting data ↓ Atrial effective refractory period/wavelength ↑ Release of inflammatory cytokines	
Bronchodilator	Albuterol	...	β ₂ -Adrenergic agonist
	Terbutaline*	...	β-Adrenergic agonist
	Metaproterenol	2.5	β ₂ -Adrenergic agonist
	Theophylline	...	Phosphodiesterase inhibition ↑ Atrial automaticity
	Aminophylline	...	Phosphodiesterase inhibition
	Ipratropium bromide	...	Anticholinergic
	Tiotropium	1.7/100 person-y	Anticholinergic
Cannabinoid	Cannabis, synthetic cannabinoids*	...	Adrenergic stimulation, altered atrial coronary or microvascular flow, coronary spasm, postulated ↑ pulmonary vein ectopy, increased sympathetic and parasympathetic activity
Catecholaminergic	Dobutamine	0–18	β-adrenergic agonist
	Dopamine	...	α- and β-adrenergic, dopamine receptor agonist
	Epinephrine	..	β-Adrenergic agonist
Central nervous system depressant	Alcohol	Pooled OR/RR, 1.51 (95% CI, 1.3–17.4)	↓ Atrial effective refractory period/wavelength ↑ Sympathetic nervous system activity ↑ Interatrial electromechanical delays
		HR, 1.14 (95% CI, 1.04–1.26)	↑ Vagal activity
		HR, 1.29 (95% CI, 1.02–1.62)	
		HR, 1.60 (95% CI, 1.02–2.51)	
Cognitive function enhancer	Physostigmine*	...	Acetylcholinesterase inhibitor
I _f current inhibitor	Ivabradine	1.3	...
		OR, 1.35 (95% CI, 1.19–1.53)	
		RR, 1.15 (95% CI, 1.07–1.24)	
		RR, 1.24 (95% CI, 1.08–1.42)	
Illicit	Cocaine* ¹⁶	...	Catecholamine excess; increased sympathetic tone; ischemia; hyperthermia; sodium and potassium channel blockade
	Amphetamine, methamphetamine, and derivatives, 3,4-methylenedioxymethylamphetamine* (MDMA, ecstasy)	...	Catecholamine excess from release of norepinephrine, dopamine, and serotonin from central and autonomic nerve terminals

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
Immune-modulating agents	Fingolimod	0.5	...
Immunotherapy	Interleukin-2	3.5–6.0	Proinflammatory cytokines, calcium and calcium channel effects, inflammation, activation of c-Src kinases
Inotropes/vasodilators	Levosimendan	0–9.1	↑ Calcium sensitivity
	Milrinone	2.9–5.0	Phosphodiesterase inhibitor
	Enoximone	8.3	Phosphodiesterase inhibitor
Opioid	Morphine	HR, 4.37 (95% CI, 3.56–5.36)	↑ intracellular calcium, activates protein kinase C, open mitochondrial KATP channels
Phosphodiesterase inhibitor	Sildenafil*	...	Selective inhibitor of cGMP-specific phosphodiesterase type 5
	Vardenafil*	...	Selective inhibitor of cGMP-specific phosphodiesterase type 5
Stimulant	Caffeine	...	Phosphodiesterase inhibitor
	1,3 Dimethylamylamine*	...	Indirect sympathomimetic agent
Sympathomimetic agent	Isoproterenol	...	β-Adrenergic agonist
Uterine stimulant	Ergometrine* ¹⁷	...	Ergot alkaloid, coronary spasm, vascular smooth muscle contraction, alteration of autonomic tone

Tisdale et al (2020), Table 2

Mechanisms of drug-induced AF vary by medication. Many stimulants act via catecholaminergic augmentation, resulting in β-receptor stimulation, shortened atrial effective refractory period, increased cAMP (cyclic adenosine monophosphate), cytosolic calcium, atrial automaticity, and pulmonary vein ectopic depolarisations. Adenosine shortens atrial effective refractory period and promotes pulmonary vein ectopy. Alcohol promotes sympathetic nervous system stimulation, shortens atrial effective refractory period, increases interatrial electromechanical delays, and acts via vagal pathways.

The mechanism of bisphosphonates-induced AF is unclear, but these drugs release inflammatory cytokines and shorten atrial action potential duration and effective refractory period. Mechanisms of atrial proarrhythmia for many other agents remain unknown, including ivabradine, as If inhibition has been theorised to exert antiarrhythmic effects. Certain antiarrhythmics can cause or exacerbate AFL, including the sodium channel–blocking drugs flecainide and propafenone, which slow atrial conduction, increase the flutter cycle length, and can result in 1:1 atrioventricular conduction with a wide QRS. Consequently, atrioventricular node– blocking drugs should be prescribed when flecainide or propafenone is used in patients with AFL. Amiodarone may result in AF related to its ability to induce thyrotoxicosis in some patients.

Newer mechanisms of drug induced AF/AFL have been proposed for some drugs such as trastuzumab, which increases inflammation, oxidative stress, and reactive oxygen species, causing ion channel dysfunction and remodeling.

Risk factors for drug-induced AF/AFL are drug specific: adenosine (premature atrial complexes), alcohol (dose >30 g/d, ≥1–3 drinks per day; withdrawal syndrome), and dobutamine (advanced age, prior AF, heart failure).

Strategies for prevention include administering the lowest effective dose of AF/AFL–inducing drugs, minimising or avoiding the use of stimulants, and avoiding excessive alcohol intake (e.g., <30 g/d, <7–14 drinks per week, or even abstinence)

Patients taking drugs with the potential to provoke AF/AFL should be aware of symptoms; monitor their pulse, heart rate, or rhythm daily, potentially with a wearable monitor if at high risk; and seek medical attention if they have persistent tachycardia, especially with symptoms. Management of drug-induced AF/AFL includes discontinuation of the offending agent.¹ Many hemodynamically stable patients convert to sinus rhythm spontaneously. Rate control can be achieved with atrioventricular node–blocking agents (β -blockers, CCBs, digoxin). If AF/ AFL duration is >48 hours or unknown, the presence/ absence of an atrial thrombus should be investigated via transesophageal echocardiography, or ≥ 3 weeks of therapeutic anticoagulation must be achieved before cardioversion.

Hemodynamically unstable patients may require urgent cardioversion, performed as per current guidelines. Longer-term management may include anticoagulation, other pharmacological therapies, or catheter ablation, as recommended. If AF is caused by theophylline or other oral drug overdose, activated charcoal can be considered.

While other arrhythmias such as torsades de pointes and sinus bradycardia are more typically thought of as drug induced,³⁷² AF may also be precipitated by drug therapy, although ascribing causality to drug-associated AF is more difficult than with other drug-induced arrhythmias. Drug-induced AF is more likely to occur in patients with risk factors and comorbidities that commonly co-exist with AF, such as advanced age, alcohol consumption, family history of AF, hypertension, thyroid dysfunction, sleep apnoea and heart disease.

Ascribing causality to drug-associated AF is difficult, due to the nature of reports of drug-induced AF, as well as due to the fact that there is no clear biomarker for drug-induced AF. For some drugs, there are multiple studies assessing a potential association between a specific drug and new-onset AF, but many studies show conflicting results.

Kaakeh et al (2012) used a literature-derived “Quality of Evidence” designation to indicate the quality of evidence associating specific drugs with the occurrence of AF.³⁷³

AF can result from a number of mechanisms that may be influenced by an underlying pathophysiological state and concurrent risk factors. Many of the drugs that have been linked to increasing the risk for AF modify these risk factors or underlying pathophysiological conditions.

New-onset AF has been associated with cardiovascular drugs such as adenosine, dobutamine and milrinone.

³⁷² Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.

³⁷³ Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.

Cardiac drugs

Summary of important issues

Certain antiarrhythmic drugs may increase the risk of AF. A 2020 scientific statement from the American Heart Association details drugs associated with AF [Tisdale et al 2020]. While exhaustive, this statement includes many medications for which the association with AF is likely relatively weak. That review listed adenosine, amiodarone, flecainide and propafenone as antiarrhythmics that can increase AF risk.

Review studies

Certain antiarrhythmics can cause or exacerbate AFL, including the sodium channel–blocking drugs flecainide and propafenone, which slow atrial conduction, increase the flutter cycle length, and can result in 1:1 atrioventricular conduction with a wide QRS. A 2020 scientific statement from the American Heart Association details drugs associated with AF [Tisdale et al 2020]. While exhaustive, this statement includes many medications for which the association with AF is likely relatively weak. That review listed adenosine, amiodarone, flecainide and propafenone as antiarrhythmics that can increase AF risk.

Amiodarone may result in AF related to its ability to induce thyrotoxicosis in some patients.

Risk factors for drug-induced AF/AFL are drug specific: adenosine (premature atrial complexes) and dobutamine (advanced age, prior AF, heart failure).

Ivabradine, a selective blocker of the If channel that slows the sinus rate, has been associated with a higher incidence of AF. A meta-analysis of 11 studies suggests a 15% excess of AF in patients treated with ivabradine [Martin et al 2014].

Although adenosine is effective at terminating supraventricular tachycardias with AV nodal involvement, it may induce AF with an incidence of 1–12%.³⁷⁴ Episodes of adenosine-induced AF have been reported to be short-lived and transient during stress testing, as a result of adenosine's short half-life (10 seconds). A case-series of eight patients with adenosine-induced AF reported the duration ranged between 15 seconds to eight hours and converted to sinus rhythm without intervention or complication. However, there can be significant clinical consequences in a subset of patients with an accessory pathway, such as those with Wolff-Parkinson-White syndrome.

Case studies have reported haemodynamic instability due to a rapid ventricular response from adenosine-induced AF in patients with accessory pathways.

Adenosine is largely effective at terminating supraventricular tachycardias due to its slowing of AV nodal conduction. However, in atrial tissue, adenosine enhances activity of the acetylcholine-activated inward rectifier potassium current (IK(ACh)). The resulting shortening of atrial repolarization and effective refractory periods may promote re-entry. In addition to its

³⁷⁴ Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.
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direct electrophysiological effects, adenosine may enhance adrenergic tone which may increase in the risk of AF.

Adenosine may enhance the substrate for AF by direct electrophysiological effects or by enhancing autonomic tone. Although adenosine-induced AF is often clinically inconsequential, it can be of significant clinical importance when an accessory pathway is present. The quality of evidence for an association with AF is considered to be high.

Dobutamine (Quality of evidence – High)³⁷⁵ —Dobutamine is an inotropic agent that acts directly through β -adrenergic receptor activation to increase automaticity and conduction velocity while shortening effective refractory periods. β -adrenergic receptor activation increases the risk of AF through enhancement of intracellular 3'-5'-cyclic adenosine monophosphate (cAMP). Increased cAMP activates protein kinase A, which enhances the activity of several target proteins such as the ryanodine receptor, phospholamban, and the L-type calcium channel, modulating intracellular calcium cycling. The resulting cytosolic calcium accumulation can trigger depolarisations in pulmonary veins and atrial tissue to trigger AF which can be perpetuated by reentry or rapid atrial depolarisations. Increased calcium loading triggers ectopic impulses and is one mechanism of adrenergically-mediated AF.

Ventricular dysfunction after cardiac surgery can necessitate the administration of vasopressors and/or inotropic agents to maintain hemodynamic stability. The use of an agent with a predominant adrenergic component is an independent predictor of postoperative AF. In a sample of 127 patients undergoing cardiac surgery and treated with an inotropic agent, 49 (39%) developed postoperative AF [$p < 0.01$ compared with 10 of 72 (14%) in the control group]. Dopamine and dobutamine were used in 44% and 41% of patients who developed postoperative AF, respectively.

The incidence of dobutamine induced AF is unclear in non-surgical patients with acute decompensated heart failure due to the lack of an appropriate comparator group.

Milrinone (Quality of evidence – Moderate)³⁷⁶ Milrinone is a phosphodiesterase inhibitor that increases intracellular cAMP while bypassing the β -adrenergic receptor pathway to exert a positive inotropic effect and vasodilation. Similar to dobutamine, milrinone likely results in cytosolic calcium accumulation which can trigger ectopic impulses in pulmonary veins or atrial tissue to promote AF. Milrinone increased the risk of atrial arrhythmias when used for short-term for management of heart failure exacerbations that did not require the use of inotropic agents (4.6% versus 1.5%; $p < 0.01$) in a randomised, placebo-controlled, clinical trial. These numbers of AF induction are relevant in this population because of the rare use of a placebo in the comparator group to assess the ability of a drug to induce AF. This is important given the high incidence of AF during heart failure which is likely due to increased sympathetic tone and intracellular calcium accumulation.

³⁷⁵ Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.

³⁷⁶ Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.

Ivabradine, a selective blocker of the If channel that slows the sinus rate, has been associated with a higher incidence of AF. A meta-analysis of 11 studies suggests a 15% excess of AF in patients treated with ivabradine [Martin et al 2014].

Summary and conclusions

Certain antiarrhythmic drugs may increase the risk of AF. A 2020 scientific statement from the American Heart Association details drugs associated with AF [Tisdale et al 2020]. While exhaustive, this statement includes many medications for which the association with AF is likely relatively weak. That review listed adenosine, amiodarone, flecainide and propafenone as antiarrhythmics that can increase AF risk.

Certain antiarrhythmics can cause or exacerbate AFL, including the sodium channel–blocking drugs flecainide and propafenone, which slow atrial conduction, increase the flutter cycle length, and can result in 1:1 atrioventricular conduction with a wide QRS. *Amiodarone may result in AF related to its ability to induce thyrotoxicosis in some patients.*

Risk factors for drug-induced AF/AFL are drug specific: adenosine (premature atrial complexes) and dobutamine (advanced age, prior AF, heart failure).

Adenosine may enhance the substrate for AF by direct electrophysiological effects or by enhancing autonomic tone (Kaakeh et al 2012). Although adenosine-induced AF is often clinically inconsequential, it can be of significant clinical importance when an accessory pathway is present. The quality of evidence for an association with AF is considered to be high.

Dobutamine is an inotropic agent that acts directly through β -adrenergic receptor activation to increase automaticity and conduction velocity while shortening effective refractory periods. The use of an agent with a predominant adrenergic component is an independent predictor of postoperative AF (Kaakeh et al 2012). The outcomes of drug-induced AF in this population have not been assessed but the development of AF following cardiac surgery prolongs duration of hospital stay and increases morbidity. The incidence of dobutamine induced AF is unclear in non-surgical patients with acute decompensated heart failure due to the lack of an appropriate comparator group.

Milrinone increased the risk of atrial arrhythmias when used for short-term for management of heart failure exacerbations that did not require the use of inotropic agents. The use of milrinone for heart failure increases the risk of AF.

Ivabradine, a selective blocker of the If channel that slows the sinus rate, has been associated with a higher incidence of AF. A meta-analysis of 11 studies suggests a 15% excess of AF in patients treated with ivabradine [Martin et al 2014].

In relation to taking the cardiac drugs adenosine; dobutamine; or milrinone, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between taking

these drugs and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A factor for taking cardiac drugs should be added to the RH and BoP SoPs.

Cancer chemotherapy

Summary of important issues

AF is the most common primary arrhythmia secondary to chemotherapy, and in the untreated cancer patient (Essa et al 2021). Cancer and chemotherapeutic agents create an arrhythmogenic substrate. Atrial fibrillation rates in cancer patients are more than twice that of controls, even after adjusting for confounding factors.

Reviews

Atrial fibrillation is the most common primary arrhythmia secondary to chemotherapy, and in the untreated cancer patient. Cancer and chemotherapeutic agents are known to create an arrhythmogenic substrate. atrial fibrillation rates in cancer patients are more than twice that of controls, even when adjusting for confounding factors.

The association of AF with anti-cancer chemotherapy is well recognised and has been detailed in several recent review studies.^{377 378 379 380 381}AF in patients with cancer are related to the use of antineoplastic agents, which can elicit this arrhythmia by various mechanisms.

Arrhythmias appear to be an underappreciated adverse effect of anticancer agents and the incidence, significance and underlying mechanisms remain uncertain. The causal relationship of a particular anticancer drug with cardiac arrhythmia occurrence remains challenging due in part to patient comorbidities and complex treatment regimens. any cancer patient may also be diagnosed with common diseases such as hypertension, diabetes or heart failure which increase an individual's arrhythmia susceptibility.³⁸² Anticancer drugs are usually used in combination, making establishing causation more difficult.

³⁷⁷ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768.

³⁷⁸ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

³⁷⁹ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36.

³⁸⁰ Burashnikov A. (2021). Atrial fibrillation induced by anticancer drugs and underlying mechanisms. *Journal of cardiovascular pharmacology*, 10.1097/FJC.0000000000001182.

³⁸¹ Alexandre, J., Moslehi, J. J., Bersell, K. R., et al (2018). Anticancer drug-induced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms. *Pharmacology & therapeutics*, 189, 89–103.

³⁸² Alexandre, J., Moslehi, J. J., Bersell, K. R., et al (2018). Anticancer drug-induced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms. *Pharmacology & therapeutics*, 189, 89–103.

As noted by **Hajjar et al (2021)**, the incidence of AF secondary to anticancer drug treatment is between 2.2 and 16.7%.³⁸³ Most cytotoxic agents including alkylating agents (Cisplatin, Cyclophosphamide, Ifosfamide, Melphalan), anthracyclines, tyrosine kinase inhibitors (Ibrutinib, Sorafenib, Sunitinib), antimetabolites, taxanes, and topoisomerase II inhibitors have been found to largely induce AF cardiotoxicity. Haemorrhagic and thromboembolic events occur twice as often in cancer patients, compared to the general population when associated with the use of anticancer drugs.

TABLE 25 ANTI-CANCER DRUGS RELATED TO ATRIAL FIBRILLATION.

Alkylating agents:

- Nitrogen mustards: Melphalan, Cyclophosphamide
- Platinum complexes: Cisplatin.

Antimetabolites: Capecitabine, 5-Fluorouracil, Gemcitabine.

Anthracycline agents: Doxorubicin.

Bruton tyrosine kinase: Ibrutinib

Taxanes: Docetaxel, Paclitaxel

HER2 inhibitors: Trastuzumab

Monoclonal antibodies: Alemtuzumab, Cetuximab, Ipilimumab, Obinutuzumab, Ofatumumab, Rituximab.

Small molecules: Sorafenib, Sunitinib.

Vascular endothelial growth factor inhibitors: Bevacizumab

Histone deacetylase inhibitors: Dacinostat, Belinostat, Romidepsin

Proteasome inhibitors: Carfilzomib, Bortezomib

Immunotherapy: Interleukin 2

Hormones:

- Gonadotropin-releasing hormone (GnRH) antagonist: Degarelix
- Androgen Synthesis Inhibitors: Abiraterone
- Aromatase inhibitors
- Glucocorticoids: high doses of Dexamethasone.

Source: Hajjar et al (2021), Table 1

Another review by **Essa et al (2021)** confirms that chemotherapy-induced arrhythmia is a potential complication of treatment that confers increased morbidity and mortality.³⁸⁴ The relationship between chemotherapeutic agents and arrhythmias is poorly established. Atrial fibrillation, ventricular ectopic beats, and prolonged QTc are the most common arrhythmias suffered by cancer patients undergoing chemotherapy. The treatment of atrial fibrillation in cancer is complicated by complex drug-drug interactions and a lack of evidence guiding practice. The normal risk assessment scores utilized in the decision-making for anticoagulation in the normal population are not validated in the cancer population.

³⁸³ Hajjar, L. A., Fonseca, S., & Machado, T. (2021). Atrial Fibrillation and Cancer. *Frontiers in cardiovascular medicine*, 8, 590768.

³⁸⁴ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31
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TABLE 26 CHEMOTHERAPEUTIC AGENTS AND THE INCIDENCE RATE OF ATRIAL FIBRILLATION

Drug Name, Reference #	Year	Source of Evidence	Number of Patients	Female/Male	Mean Age (Years)	Incidence of AF (%)	Duration of Follow-Up
Ibrutinib ²³	2017	Systematic review from 4 trials	1505	491/1014	Median 67	13.8%	3 y
Gemcitabin ¹⁷	2001	Prospective	49	7/42	Median 74	8.2%	8 mo
Doxorubicin ¹³	2007	Prospective	29	17/12	45.8	10.3%	Participants screened with a 24-h ambulatory monitor at first cycle and last cycle
5-Fluorouracil ¹²	1990	Prospective	80	15/65	63	6.3% (also includes atrial premature complex)	ECG on day 1/3/5
Melphalan ¹⁰	1998	Prospective	76	41/35	46.5	6.6%	Unclear
Paclitaxel ⁴⁰	2003	Retrospective	119	80/39	51	1%	8 y
Interleukin 2 ³⁴	1989	Retrospective	317	N/A	N/A	8%	Unclear
Trastuzumab ⁴¹	2018	Systematic review of 15 trials	8124	8122/2	48-71.6	1.2%	2-6 y
Amsacrine ⁴²	1986	Retrospective	5340	N/A	N/A	0.0005%	Unclear

Essa et al (2021), Table 1, p 1228

Alkylating and alkylating-like agents such as cyclophosphamide, chlorambucil, busulfan, and cisplatin are often used against lymphomas, Hodgkin's disease, breast cancer, and multiple myeloma. Cyclophosphamide has been implicated in a variety of cardiac arrhythmias, including atrial fibrillation.³⁸⁵ These occur rapidly after treatment initiation and affect around 10% of patients. Most occur in the context of myopericarditis and congestive cardiac failure. Melphalan is a well-recognised cause of atrial fibrillation, with up to 6.6% of patients suffering atrial fibrillation.

Cisplatin is an alkylating-like agent that is known to cause hypomagnesemia, which is possibly the cause of its associated arrhythmias, including atrial fibrillation. Arrhythmias are unrelated to the dose given and occur with an unpredictable time spectrum from immediately post-infusion to several months later. Intrapericardial and intrapleural administration has been recognised to be much more arrhythmogenic, with rates of atrial fibrillation as high as 32% reported.

Anthracyclines such as doxorubicin and daunorubicin are used in leukaemias, lymphomas, and breast, stomach, uterine, ovarian, and lung cancers. Atrial fibrillation is the most common primary arrhythmia and affects around 10% of patients. one study, a cardiac arrhythmia was detected in ≤65.5% of patients.³⁸⁶ The burden of arrhythmias secondary to cardiomyopathy is greater than that caused primarily by anthracyclines, and is comparable with patients with non-chemotherapy related cardiomyopathy.

³⁸⁵ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

³⁸⁶ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

Common examples of antimetabolites include methotrexate, 5-fluorouracil, fludarabine, and capecitabine. These are often featured in the treatment of leukaemia and breast, ovarian, and colonic cancer. Among antimetabolites, 5-fluorouracil (and capecitabine—a pro drug of 5-fluorouracil) have been implicated in atrial fibrillation and other arrhythmias.³⁸⁷ Myocardial ischaemia is likely the primary dominant driver of arrhythmia with 5-fluorouracil. Most arrhythmias are likely secondary to ischaemia rather than chemotherapeutic complications.

Gemcitabine has been associated with supraventricular tachycardias, in particular, atrial fibrillation, where rates of 8.2% have been reported in case series. A systematic review demonstrated that over 60% of cardiac arrhythmias reported with gemcitabine have been atrial fibrillation events.

Tyrosine kinase inhibitors have been widely implicated in multiple cardiac side effects. Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor that is estimated to cause atrial fibrillation in 6%-16% of patients. Atrial fibrillation occurs most commonly around 3-4 months after initiation, with over 75% of cases occurring in the first year. Atrial fibrillation can often be a therapy-limiting side effect.³⁸⁸ There is also an increased bleeding risk for patients on ibrutinib and various drug interactions with oral anticoagulants.

Vinca alkaloids have been associated with atrial fibrillation transiently, and insignificant QTc prolongation.

Proteasome inhibitors include bortezomib and carfilzomib. These are often used in the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib has been linked to significant bradycardia, with subsequent complete heart block and pacemaker insertion. It has been linked to episodes of supraventricular tachycardia and atrial fibrillation.

Thalidomide is an immunomodulatory drug often used in multiple myeloma.³⁸⁹ It has been implicated in causing bradyarrhythmia, including sinus bradycardia, in up to 53% of patients. Thalidomide has been associated with AF in around 4.7%, and more rarely, with ventricular tachycardia and sudden cardiac death.

Interferon- α has been linked to a variety of arrhythmias, including AF, in around 20% of patients. Interferons are often utilised in the treatment of renal cell cancer, malignant melanoma, and multiple myeloma. In the vast majority of patients, arrhythmias are reversible.

Interleukin-2 is associated with supraventricular tachycardias and atrial fibrillation, with an incidence rate up to 17%.³⁹⁰ Most events are recorded fairly rapidly following drug infusion, and reverse rapidly after discontinuation.

³⁸⁷ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

³⁸⁸ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

³⁸⁹ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

³⁹⁰ Essa, H., Wright, D. J., Dobson, R., & Lip, G. (2021). Chemotherapy-Induced Arrhythmia - Underrecognized and Undertreated. *The American journal of medicine*, 134(10), 1224–31

Gemcitabine, a purine analogue with known activity against many solid tumours, has been associated with new onset AF.³⁹¹ An increased incidence rate of AF (about 19%) has also been described in cancer patients treated with alkylating agents such as cisplatin. In addition, taxanes and melphalan have been shown to be associated with increased risk of AF.

The proteasome inhibitor bortezomib (also used for non-small-lung cancer) and carfilzomib (with a dose-dependent toxic effect) represent the agents used for haematological malignancies most commonly associated with AF. Proposed mechanisms for proteasome inhibitor associated cardiovascular events include oxidative stress in cardiomyocytes and endothelial dysfunction, with an increase in coronary vascular tone and reactivity.

The tyrosine kinase inhibitor ibrutinib, approved for treatment of chronic lymphocytic leukaemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia, has been associated with a 5-fold increased risk of developing atrial arrhythmia. Ibrutinib may induce AF by exerting an atrial-specific toxicity in human stem cell-derived cardiomyocytes and causing significant myocardial fibrosis in the left atrium and calcium handling disorders in atrial myocytes.

TABLE 27 ANTINEOPLASTIC DRUGS ASSOCIATED WITH CARDIAC DAMAGE AND AF ONSET

Drugs	Mechanisms of direct cardiotoxicity	Indirect mechanisms of heart injury
Alkylating agents	Cisplatin, Cyclophosphamide, Ifosfamide, Melphalan	Myocardial ischemia (typically high dose) by ROS, inflammation, lysosome injury.
Anthracyclines	Doxorubicin (Adriamycin), Idarubicin, Epirubicin, Mitoxantrone, Lyosomal anthracyclines	Fluid overload during infusion of drugs.
Antimetabolites	Capecitabine, 5-FU, Gemcitabine	QT prolongation.
Small molecule TKIs (anti-VEGF)	Ponatinib, Sorafenib, Sunitinib, Ibrutinib, Bevacizumab	Hypoxia due to depletion of the high-energy phosphate compounds in cardiomyocytes
Topoisomerase II inhibitors	Amsacrine, Etoposide	Coronary artery spasm and myocardial ischaemia
Taxanes	Docetaxel, Paclitaxel	Calcium dysregulation, direct toxicity on cardiomyocytes (Ibrutinib).
Vinca alkaloids	Vinblastine, Vincristine	Leads to replication fork arrest and double-strand break formation resulting in apoptosis
Immunomodulant	IL-2, Interferons	Promote polymerization of tubulin, leading to dysfunctional microtubules and disturbing cell division.
Monoclonal antibodies	Trastuzumab, Etaricizumab	-
Histone deacetylases	Romidepsin	Arrhythmia and atrioventricular blocks, increase anthracyclines activity.
		Inducing ischaemic events and artery spasm (Prinzmetal angina)
		-
		-
		QT prolongation.

Menichelli et al (2021), Table 1

Ibrutinib may increase the production of reactive oxygen species (ROS), inducing oxidative and inflammatory damage.

Summary and conclusions

Anticancer agents are recognised to be drugs that may cause or exacerbate AF/AFL (Tisdale et al 2020). AF and other supraventricular tachycardias are frequently observed in patients receiving chemotherapy. High rates of AF are seen with agents such as tyrosine kinase

³⁹¹ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36. August meeting 2022

inhibitors e.g... ibrutinib and the mechanism for this is poorly defined but likely related to off-target effects (Essa et al 2021).

AF is the most common primary arrhythmia secondary to chemotherapy, and in the untreated cancer patient (Essa et al 2021). Cancer and chemotherapeutic agents create an arrhythmogenic substrate. atrial fibrillation rates in cancer patients are more than twice that of controls, even after adjusting for confounding factors.

Arrhythmias appear to be an underappreciated adverse effect of anticancer agents and the incidence, significance and underlying mechanisms remain uncertain. the causal relationship of a particular anticancer drug with cardiac arrhythmia occurrence remains challenging due in part to patient comorbidities and complex treatment regimens. Alexandre et al 2018 any cancer patient may also be diagnosed with common diseases such as hypertension, diabetes or heart failure which increase an individual's arrhythmia susceptibility. anticancer drugs are generally usually used in combination, increasing the challenge around establishing causation.

Arrhythmias are a widespread complication of some antineoplastic drugs, with AF being the most often encountered drug-associated arrhythmia. Burashnikov et al 2021 Preexisting AF risk factors are commonly present in cancer patients who develop drug-associated AF, and active cancer itself may cause or promote AF. While anticancer drugs may induce AF in cancer patients without AF risk factors, it appears that most drug-associated AF develop when cancer drugs add or aggravate pre-cancer-existing and cancer-related pro-AF factors/alterations, additively or synergistically producing AF.

Among specific chemotherapeutic agents, the alkylating agent cyclophosphamide has been implicated in a variety of cardiac arrhythmias, including atrial fibrillation.

Interleukin-2 is associated with supraventricular tachycardias and atrial fibrillation, with an incidence rate up to 17%. Most events are recorded fairly rapidly following drug infusion, and reverse rapidly after discontinuation

Cisplatin is an alkylating-like agent that is known to cause hypomagnesemia, which is possibly the cause of its associated arrhythmias, including atrial fibrillation. Most occur in the context of myopericarditis and congestive cardiac failure.

Melphalan is a well-recognised cause of atrial fibrillation, with up to 6.6% of patients suffering atrial fibrillation.

Anthracyclines such as doxorubicin and daunorubicin are used in leukaemias, lymphomas, and breast, stomach, uterine, ovarian, and lung cancers. Atrial fibrillation is the most common primary arrhythmia and affects around 10% of patients.

Among antimetabolites, 5-fluorouracil is implicated in AF. Myocardial ischaemia is likely the primary dominant driver of arrhythmia with 5-fluorouracil, and most arrhythmias are likely secondary to ischaemia rather than chemotherapeutic complications.

Gemcitabine has been associated with supraventricular tachycardias, in particular, atrial fibrillation, where rates of 8.2% have been reported in case series. A systematic review demonstrated that over 60% of cardiac arrhythmias reported with gemcitabine have been atrial fibrillation events

Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor that is estimated to cause atrial fibrillation in around 6%-16% of patients. of atrial fibrillation occurs most commonly around 3-4 months after initiation, with over 75% of cases occurring in the first year. Atrial fibrillation can often be a therapy-limiting side effect.

Vinca alkaloids have been associated with atrial fibrillation transiently, and insignificant QTc prolongation.

The proteasome inhibitor bortezomib has been linked to episodes of AF.

Thalidomide has been associated with atrial fibrillation in around 4.7%.

Interferon-a has been linked to a variety of arrhythmias, including AF.

In relation to taking chemotherapy for cancer, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between chemotherapy for cancer, and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A factor for taking chemotherapy for cancer should be retained in RH and BoP.

Examples of chemotherapeutic agents that have been related to the development of AF include:

- abiraterone;
- alkylating agents including cisplatin, cyclophosphamide, ifosfamide and melphalan;
- anthracyclines including doxorubicin;
- antimetabolites including 6-fluorouracil and gemcitabine;
- aromatase inhibitors;
- HER2 inhibitors including trastuzumab;
- interleukin 2;
- monoclonal antibodies including rituximab and ipilimumab; proteasome inhibitors including carfilzomib;
- small molecules including sorafenib, and sunitinib;
- taxanes including docetaxel and paclitaxel;
- thalidomide;
- topoisomerase II inhibitors:
- tyrosine kinase inhibitors including ibrutinib,
- vascular endothelial growth factor inhibitors including bevacizumab;

A note with selected examples can be included with the factor. The selected agents include anthracyclines including doxorubicin, HER2 inhibitors including trastuzumab, and tyrosine kinase inhibitors including ibrutinib.

Corticosteroids

Summary of important issues

The association of corticosteroids and AF has been controversial, as glucocorticoids can alternatively be pro-arrhythmic or anti-arrhythmic (Granier et al 2013). It is now apparent that although corticosteroids can reduce the risks of developing post-operative AF after cardiac procedures, AF can be induced by high doses of oral corticosteroids, particularly after chronic use. Clinical and analytical studies have linked corticosteroids, primarily methylprednisolone, to new onset AF (Kaakeh et al 2012). AF has been attributed to the administration of high-dose methylprednisolone in pulse doses, and with lower dose intravenous or oral prednisolone. Some case reports and analytical studies have implicated inhalator corticosteroids as triggers of AF.

Review studies

Glucocorticoids can alternatively be pro-arrhythmic or anti-arrhythmic, depending on the type of arrhythmia and the underlying cause.³⁹²

Atrial fibrillation is a serious and common complication following heart surgery.³⁹³ Cardiac surgery triggers inflammation in the heart and makes it susceptible to the incidence of AF. Therefore, anti-inflammatory drugs may reduce the rate of AF incidence in the post-surgery conditions. Immunosuppressant agents, steroidal anti-inflammatory drugs (corticosteroids), non-aspirin non-steroid anti-inflammatory drugs (NSAIDs), colchicine and omega-3 unsaturated fatty acids (n-3 UFA) are drugs with well-known anti-inflammatory properties. The efficacy, safety and other aspects of using these drugs in the prevention of post-operative AF (POAF) have been reviewed.

There are some case reports of an association between AF occurrence or recurrence and some immunosuppressants such as azathioprine (Cassinotti et al. 2007; Dodd et al. 1985; Riccioni et al. 2011), certolizumab pegol (Talotta et al. 2016), fingolimod (Rolf et al. 2014), cyclophosphamide (Ifran et al. 2005) and cyclosporine (LoVecchio and Goltz 2000). The association of immunosuppressant therapy with AF occurrence may illustrate that severe underlying inflammatory diseases themselves trigger AF. No studies have evaluated the effect of these drugs on AF after cardiac surgery.

Corticosteroids can modulate AF substrates because of their electrophysiological and anti-inflammatory effects (Calo et al. 2011).³⁹⁴

Several randomised clinical trials (RCTs) have examined the effectiveness of steroids in the prevention of post-operative atrial fibrillation, and have been evaluated in several meta-

³⁹² Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93.

³⁹³ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

³⁹⁴ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29

analyses of RCTs concerning POAF.³⁹⁵ These studies have shown that the administration of glucocorticoids pre- or peri-operatively is successful in reducing the risk of POAF. However, there are also conflicting studies. Different corticosteroids have been studied including dexamethasone, methylprednisolone, hydrocortisone, triamcinolone and prednisolone. These individual corticosteroids have been tested with different dosages, routes of administration, initiation times and durations in different cardiac surgeries, with a consequent increase in heterogeneity among studies.

Despite the heterogeneity and negative results of some RCTs, recent meta-analyses have shown that corticosteroids are an effective option for POAF prevention.^{396 397 398} The optimal corticosteroid regimen for POAF prevention with the highest efficacy and the lowest safety considerations remains uncertain.

Apart from the specific situation of a protective effect against post-operative AF, corticosteroids might increase the risk of AF.³⁹⁹ Van der Hooft et al. (2004) initially reported an increased risk of AF in patients taking high doses of inhaled corticosteroids, based on several case reports. In a case control study, the same authors confirmed that high dose corticosteroids (>7.5 mg daily of prednisone equivalents) increased the risk of new onset AF in the month following the initiation of the treatment [Van der Hooft et al 2006]. The risk was independent of treatment indication, as AF was increased in patients with asthma or chronic pulmonary obstructive disease, and also in patients with rheumatic, allergic, or malignant haematological diseases. Intermediate-low dose (<7.5 mg prednisone equivalents daily), and inhaled corticosteroids did not increase the risk of new onset AF.

Evidence of a relationship between glucocorticoids and cardiovascular diseases comes primarily from studies of associations with current baseline medication use or dose, ignoring the doses previously administered and their changes over time, as well as the concomitant use of other common medications that can affect the risk of CVDs (e.g., nonsteroidal anti-inflammatory drugs). Many studies have failed to adjust for important cardiovascular risk factors.⁴⁰⁰ These studies have reported a dose-dependent risk of CVD with weaker associations for daily prednisolone-equivalent doses lower than 5 to 10 mg.

³⁹⁵ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29

³⁹⁶ Liu, L., Jing, F. Y., Wang, X. W., et al. (2021). Effects of corticosteroids on new-onset atrial fibrillation after cardiac surgery: A meta-analysis of randomized controlled trials. *Medicine*, 100(11), e25130.

³⁹⁷ Ng, K. T., Van Paassen, J., Langan, C., et al. (2020). The efficacy and safety of prophylactic corticosteroids for the prevention of adverse outcomes in patients undergoing heart surgery using cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials. *European journal of cardio-thoracic surgery*, 57(4), 620–7.

³⁹⁸ Patoulis D, Papadopoulos C, Toumpourleka M, et al (2021). Meta-Analysis Addressing the Effect of Mineralcorticoid Receptor Antagonists on the Risk for New-Onset Atrial Fibrillation. *Am J Cardiol.*;157: 150-2

³⁹⁹ Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93

⁴⁰⁰ Pujades-Rodriguez, M., Morgan, A. W., Cubbon, R. M., et al. (2020). Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS medicine*, 17(12), e1003432

The main hypothesis to explain this pro-arrhythmic effect of corticosteroids is the increase in potassium efflux. Caterina et al. (2010) reported that corticosteroids use was associated with an increased risk of chronic AF in a nested case-control study. Patients were pooled according to low (<5mg daily), intermediate (5-10 mg daily) or high (> 10 mg daily) dose of equivalent prednisolone. Patients with low or intermediate dose also exhibited an increased risk. Although corticosteroids use was not associated with an increased risk of paroxysmal AF.

TABLE 28 GLUCOCORTICOIDS AND AF RISK IN GENERAL POPULATION

Van der Hooft <i>et al.</i> [40]	2006	General population	Case control 7983 pts/385 control	Prednisone equivalent >7.5 mg daily	Increased risk of AF in the month following initiation of treatment	Pro-arrhythmic
Van der Hooft <i>et al.</i> [40]	2006	General population	Case control 7983 pts/385 control	Prednisone equivalent <7.5 mg daily or inhaled	Risk of AF not increased	No effect
De caterina <i>et al.</i> [42]	2010	General population	Case control Chronic AF 1035 pts Paroxysmal 525 pts	Prednisolone equivalent <5mg, 5-10 mg, or >10 mg /d	Increased risk of chronic AF No association with paroxysmal AF	Pro-arrhythmic

Granier et al (2013), Table 1

In summary, Granier et al (2013) determined that corticosteroids may have atrial antiarrhythmic effects in prophylaxis of post-operative AF after cardiac surgery, even if in clinical practice, this indication is not widely accepted because of other side effects, particularly hyperglycaemia and slowing healing. On the other hand, when corticosteroids are indicated in other clinical conditions, high doses may have a pro-arrhythmic effect on atrium, mostly due to potassium imbalance and/or other metabolic disturbance.

In the previously cited review study by **Kaakeh et al (2012)**, the quality of evidence linking corticosteroids to AF was considered to be low.⁴⁰¹ At that time, it was observed that several published reports have associated corticosteroids, primarily methylprednisolone, with development of AF. AF has been attributed to the administration of high-dose methylprednisolone in pulse doses, and also with lower dose intravenous or oral methylprednisolone therapy.

In a nested case-control study of individuals 55 years of age or older in Rotterdam, the Netherlands (van der Hooft et al 2006) the adjusted odds ratio for new-onset AF associated with corticosteroid therapy was 3.75 (95CI 2.38–5.87). The association was significant only in patients who received high doses (OR 6.07, 95CI 3.90–9.42) defined as ≥ 7.5 mg prednisone equivalents daily. In another nested case-control study of primary care patients between the ages of 40–89 years enrolled in the United Kingdom General Practice Research Database (De et al 2010), current corticosteroid use was associated with an increased risk of chronic AF (RR 2.49, 95CI 1.56–3.97). There was no significant association between corticosteroid use and development of paroxysmal AF.

⁴⁰¹ Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.
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Postulated mechanisms by which corticosteroids may contribute to causing nonsurgical AF include sodium and fluid retention, leading to elevated atrial pressures; modulation of myocardial potassium efflux; and promotion of the development of late potentials.⁴⁰²

Since that study was published, evidence has accumulated in relation to the pro- and anti-arrhythmic qualities of corticosteroids. It is now apparent that although corticosteroids can reduce the risks of developing post-operative atrial fibrillation after cardiac procedures, AF can be induced by high doses of oral corticosteroids, particularly after chronic use.

Corticosteroid-related AF is well documented, as outlined in detail in a review study by *Nomani et al* (2020).⁴⁰³ Within the context of primary prevention, a few case reports describe increased susceptibility to AF with steroids when administered for the first time with high doses in several inflammatory conditions (Dogukan et al. 2008; Hebb et al. 2014; Iqbal et al. 2008; Yamamura et al. 2011). Some observational case–control population-based studies show patients using glucocorticoids have an increased risk of AF (Christiansen et al. 2009). In a Danish cohort study, including 20,221 patients with AF or atrial flutter and 202,130 controls without AF, exposure to glucocorticoids almost doubled the odds of AF diagnosis (Christiansen et al. 2009). This finding did not depend on underlying pulmonary or cardiovascular disease.

In the previously described case–control study within the Rotterdam cohort study, administration of glucocorticoids within the 1-month period prior to AF diagnosis was associated with a 3.75-fold elevation of new-onset AF odds (van der Hooft et al. 2006). This association just was significant in patients receiving high-dose steroids, while intermediate-low-dose corticosteroids failed to show significant association with AF occurrence. A nested case–control analysis of 710 patients with chronic obstructive respiratory disease or asthma and 5000 controls demonstrated that recent oral steroid administration doubled the risk of AF after adjustment for the severity of pulmonary diseases (Huerta et al. 2005).

These studies might be subject to scrutiny bias, as patients receiving corticosteroids were more hospitalised which led to more clinical investigations and it is probable that asymptomatic AFs were diagnosed more frequently and accurately in these patients. However, they have documented a proarrhythmic potential, especially at high doses (Savelieva et al. 2011).⁴⁰⁴

Several cases of AF following high dose pulse corticosteroid treatment have been documented.⁴⁰⁵ Moretti et al. (2000) described a 59-year-old male diagnosed with primary progressive multiple sclerosis (MS) and treated with high doses of methylprednisolone. After the third dose of methylprednisolone (1 g intravenously over 2 h) the ECG showed AF. After

⁴⁰² Kaakeh, Y., Overholser, B. R., Lopshire, J. C et al . (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12), 1617–30.

⁴⁰³ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

⁴⁰⁴ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

⁴⁰⁵ Pavičić, T., Ruška, B., Adamec, I., et al. (2019). Recurrent atrial fibrillation after pulse corticosteroid treatment for a relapse of multiple sclerosis. *Multiple sclerosis and related disorders*, 32, 30–2.

being treated with digoxin and propafenone for two days, the AF resolved completely. He developed AF on two more occasions, despite prophylaxis with 80 mg of sotalol and 125 mg of intramuscular methylprednisolone for 10 days. The fourth time he received propafenone two days prior to methylprednisolone and he did not develop AF.

AF as a complication of high dose corticosteroids has been described in neurofibromatosis type 2, systemic lupus erythematosus and after an acute onset of hiccoughs (Hebb et al. 2014; Ueda et al. 1988; McLuckie and Savage 1993), as well as in multiple sclerosis. It is not dependent on the route of administration. While the patient described by Pavičić was administered methylprednisolone intravenously, other cases with intramuscular administration of methylprednisolone or oral dexamethasone (1 week course of up to 4 mg dexamethasone three times per day) have been described (Hebb et al. 2014; Moretti et al. 2000).

A clinical trial was designed for multiple sclerosis patients to investigate cardiac arrhythmias while receiving high-dose methylprednisolone (Vasheghani-Farahani et al. 2011).⁴⁰⁶ 52 MS patients with acute relapse underwent cardiac monitoring three times: 4 h before, during and 18 h after receiving high-dose (1000 mg) methylprednisolone (equivalent to 5000 mg hydrocortisone) intravenously. Various types of arrhythmias were recorded, including AF. All patients were asymptomatic and AF resolved after the pulse infusions were terminated. The study lacked a control group.

Nomani et al suggests that the association between corticosteroids and AF may be because high-dose corticosteroid alters the potassium and sodium urinary excretion, which leads to a decrease in the serum potassium levels.⁴⁰⁷ These changes may lead to altered stimulation threshold of myocardial cells due to changes in electrolyte shifts across cell membranes (Liu et al. 2014; Vasheghani-Farahani et al. 2011). The final effect is predisposition to cardiac rhythm changes such as AF.

The retention of sodium and intracellular fluids caused by the mineralocorticoid activity of high-dose corticosteroids can result in incidence of high blood pressure and congestive heart failure (Savelieva et al. 2011; Vasheghani-Farahani et al. 2011) or deterioration of these pre-existing conditions, which are well-known risk factors of AF occurrence. Corticosteroid therapy is associated with higher incidence of diabetes mellitus (Savelieva et al. 2011).

Overall, electrolyte changes mediated by high-dose corticosteroids and their association with well-known AF risk factors can offset any desirable anti-inflammatory properties of steroids on POAF prevention and may explain the corticosteroid-related AF reports (Savelieva et al. 2011).⁴⁰⁸

⁴⁰⁶ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

⁴⁰⁷ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

⁴⁰⁸ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

These possible AF-triggering mechanisms usually occur with high doses while such a high-dose steroid may not be necessary for effective POAF prevention.⁴⁰⁹ Clinical studies and reports on corticosteroid-related AF are not related to post-operative AF, and there is robust evidence in glucocorticoid efficacy in POAF prevention. Major side effects have not been reported in clinical trials evaluating glucocorticoid efficacy in POAF prevention.

In animal models, Shiroshita-takeshita et al. demonstrated that prednisone can prevent AF promoting factors in dogs submitted to prolonged rapid atrial pacing. In a canine model of sterile pericarditis,⁴¹⁰ Goldstein et al. showed that prednisone could prevent the occurrence of sustained AF or atrial flutter. This model emphasises inflammation as a trigger of AF. However, in clinical practice, AF occurs mostly without any pre-existing overt inflammatory condition, except in the specific field of post-operative AF.

Cohort studies

Pujades-Rodriguez et al. (2020) analysed data from a population-based cohort study to quantify glucocorticoid dose-dependent cardiovascular risk in people with 6 immune-mediated inflammatory diseases.⁴¹¹ Glucocorticoids are widely used to reduce disease activity and inflammation in patients with a range of immune-mediated inflammatory diseases. It is uncertain whether to moderate glucocorticoid dose increases cardiovascular risk.

This study analysed medical records from 389 primary care practices contributing data to the United Kingdom Clinical Practice Research Datalink (CPRD), linked to hospital admissions and deaths in 1998-2017. The authors estimated time-variant daily and cumulative glucocorticoid prednisolone-equivalent dose-related risks and hazard ratios (HRs) of first all-cause and type-specific cardiovascular diseases (CVDs). There were 87,794 patients with giant cell arteritis and/or polymyalgia rheumatica (n = 25,581), inflammatory bowel disease (n = 27,739), rheumatoid arthritis (n = 25,324), systemic lupus erythematosus (n = 3,951), and/or vasculitis (n = 5,199), and no prior CVD. Mean age was 56 years and 34.1% were men. The median follow-up time was 5.0 years,

For each prescription of oral glucocorticoids issued between 1 year before the start and end of follow-up, the authors derived the daily dose from recorded product name, which included information on product strength, directions given and quantity prescribed. The duration of each oral glucocorticoid prescription was estimated dividing the quantity of tablets prescribed by the daily dose. Owing to variation in relative anti-inflammatory effects of different types of glucocorticoids, the daily dosage for each prescription was converted into milligrams of prednisolone-equivalent dose.

⁴⁰⁹ Nomani, H., Mohammadpour, A. H., Moallem, S., et al. (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1), 111–29.

⁴¹⁰ Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93

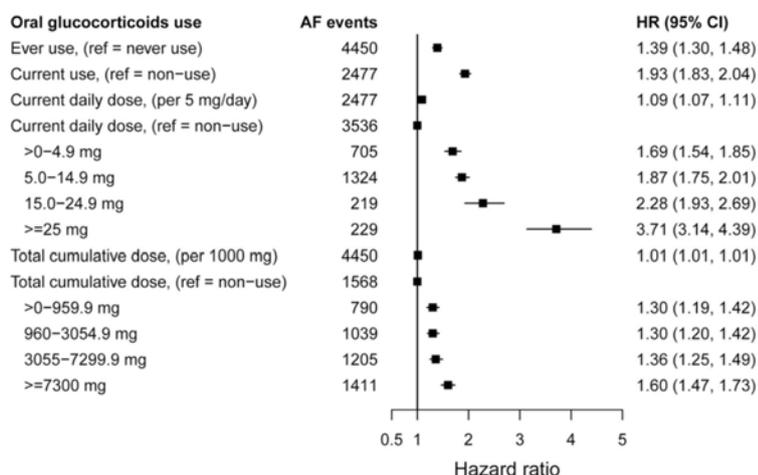
⁴¹¹ Pujades-Rodriguez, M., Morgan, A. W., Cubbon, R. M., et al. (2020). Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS medicine*, 17(12), e1003432

Several time-variant glucocorticoid variables were defined to quantify current and cumulative drug exposure. The first onset of AF was one of the secondary outcomes. Variables classified as a priori confounders were baseline age, sex, ethnicity, socioeconomic status, smoking status, BMI, biomarkers (lipoprotein-cholesterol, systolic blood pressure, c-protein reactive protein, and creatinine), underlying disease (e.g., rheumatoid arthritis), comorbidities recorded in primary or hospital care, prescribed non-oral glucocorticoid medication (inhaled, nasal, parenteral/intra-articular, topical, and rectal), and number of hospital visits one year before baseline.

The proportions of person-years spent at each level of glucocorticoid daily exposure were 80% for non-use, 6.0% for <5 mg, 11.2% for 5.0-14.9 mg, 1.6% for 15.0-24.9 mg, and 1.2% for ≥25.0 mg. Incident CVD occurred in 13,426 (15.3%) people, including 6,013 atrial fibrillation cases. One-year cumulative risks of all-cause CVD increased from 1.4% in periods of non-use to 8.9% for a daily prednisolone-equivalent dose of ≥25.0 mg. Five-year cumulative risks increased from 7.1% to 28.0%, respectively.

Increased dose-dependent risk ratios were found regardless of disease activity level and for all type-specific CVDs. HRs for atrial fibrillation and <5.0-mg daily dose use were **1.69 (95CI 1.54-1.85)**. The lack of hospital medication records and drug adherence data might have led to underestimation of the dose prescribed when specialists provided care and overestimation of the dose taken during periods of low disease activity. The resulting dose misclassification in some patients is likely to have reduced the size of dose-response estimates.

FIGURE 53 ASSOCIATIONS BETWEEN TIME-VARIANT ORAL GLUCOCORTICOID PREDNISOLONE-EQUIVALENT DOSE AND INCIDENT ATRIAL FIBRILLATION FOR PATIENTS WITH 6 IMMUNE-MEDIATED INFLAMMATORY DISEASES



HR for incident AF was elevated in patients with a current daily dose of prednisolone equivalent HR 1.09, 95CI 1.07-1.11 per 5 mg/day. Risks of AF increased roughly with current daily dose to a maximum of HR 3.71, 95CI 3.14-4.39) for daily doses of 25mg+.

Risk of AF was marginally elevated in relation to total cumulative dose: HR 1.01/ 1000mg, risk increased with cumulative dose from 1.30 for doses up to 3055 mg, HR 1.36 for doses 3055 to 7300 mg and 1.60 for 7300+.mg.

The duration of inflammatory disease averaged 9.768.7 years, thus suggesting a prolonged glucocorticoid use, possibly responsible for a higher risk of CVD.⁴¹² The baseline CVD risk profile of this cohort of 70% female patients appears to be low, considering their metabolic and hemodynamic parameters. Overall, 22% of patients had hypertension and 6% were diabetic, <10% of patients were on statin therapy, and <25% took blood pressure lowering medications. This indirectly confirms the low CVD risk profile or under-treatment of study population. 45% of the study population (range 18.5% for IBD to 70% for RA) was also prescribed NSAIDs in the year before follow-up.

Case control study

Chan et al (2014) examined the association between asthma and AF risk in a population-based nested case–control study including a total of 7439 newly diagnosed adult patients with AF and 10,075 age-, sex-, comorbidity-, and cohort entry date matched subjects without AF from the Taiwan National Health Insurance database.⁴¹³ Exposure to asthma as well as medications including bronchodilators and corticosteroid before the index date was evaluated to investigate the association between AF and asthma as well as concurrent medications.

AF patients were 1.2 times (adjusted OR 1.2, 95CI 1.109–1.298) more likely to be associated with a future occurrence of asthma independent of comorbidities and treatment with corticosteroids and bronchodilator. The risks of new-onset AF were significantly higher in current users of inhaled corticosteroid, oral corticosteroids, and bronchodilators. A graded association with AF risk was also observed among subjects treated with corticosteroid (inhaled and systemic administration) and bronchodilators. New users (within 6 months) of these medications had the highest risk of AF (ICS: OR 2.13; 95CI 1.226–3.701; oral corticosteroid: OR 1.932; 95CI 1.66–2.25).

The request for review is considered in detail in three sections of the current briefing paper, being those concerning asthma, autoimmune and inflammatory disease (including psoriasis) and drugs (including corticosteroids and anti-inflammatory drugs).

In a study that has been quoted above, **van der Hooff et al. (2006)** tested the hypothesis that high-dose corticosteroid exposure increases the risk of new-onset atrial fibrillation, in a nested case-control study within the Rotterdam Study, a population-based cohort study among 7983 older adults. This study was included in a submission for the current investigation. Cases were defined as persons with incident atrial fibrillation between 1991 and 2000. The date of diagnosis was defined as the index date. All non-cases in the Rotterdam Study who were alive and eligible on the index date were used as controls. The authors compared the proportion of cases and controls that received a corticosteroid prescription within 1 month before the index date. Corticosteroid exposure was categorised into high-dose exposure (oral or parenteral

⁴¹² Galiuto L, Volpe M. (2021). Glucocorticoids in patients with immune-mediated inflammatory diseases: a neglected cardiovascular risk factor. *Eur Heart J.*; 42(13): 1197-8.

⁴¹³ Chan, W. L., Yang, K. P., Chao, T. F., et al (2014). The association of asthma and atrial fibrillation-- a nationwide population-based nested case-control study. *International journal of cardiology*, 176(2), 464–9.

steroid at a daily dose \geq 7.5 mg of prednisone equivalents) and low-intermediate-dose exposure ($<$ 7.5 mg of prednisone equivalents or inhaled corticosteroids).

There were 385 eligible cases of new-onset atrial fibrillation during the study period. The risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the index date than for those without (OR 3.75; 95CI 2.38-5.87). However, only high-dose corticosteroid use was associated with an increased risk (OR 6.07; 95CI 3.90-9.42), whereas low-intermediate-dose use was not (OR 1.42; 95CI 0.72-2.82). The association of atrial fibrillation with high-dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset atrial fibrillation was not only increased in patients with asthma or COPD (OR 4.02; 95CI 2.07-7.81) but also in patients with rheumatic, allergic, or malignant haematological diseases (OR, 7.90; 95CI 4.47-13.98).

These findings strongly suggested that patients receiving high-dose corticosteroid therapy are at increased risk of developing atrial fibrillation.

Case reports

Shono et al (2019) described a patient with glucocorticoid-sensitive paroxysmal atrial fibrillation.⁴¹⁴ An 80-year-old woman with rheumatoid arthritis presented with chest pain. Clinical examination revealed new-onset paroxysmal atrial fibrillation with symptomatic sinus pauses and worsening mitral regurgitation, which were resistant to conventional therapies. Rheumatoid vasculitis was diagnosed. Subsequent glucocorticoid therapy suppressed systemic inflammation, resulting in structural, functional, and electrical reverse remodelling of the left atrium with complete remission of atrial arrhythmias and also an improvement of mitral regurgitation.

ECG changes that can lead to arrhythmia have been reported in people with multiple sclerosis (pwMS) (Razazian et al. 2014) and the risk for developing rhythm abnormalities differs for the type of arrhythmia and depends on the therapies being used.⁴¹⁵ The risk for atrial fibrillation is overall decreased in MS (Roshanisefat et al. 2014), while standard relapse therapy with corticosteroids increases the risk of AF immediately after therapy.

Cardiovascular adverse events have also been described in MS patients treated with high dose corticosteroids, ranging from palpitations to more severe adverse events including AF (1.8%) (Jongen et al. 2016; Vasheghani-Farahani et al. 2011). The underlying mechanism behind the development of AF and treatment of multiple sclerosis relapse with steroids is still unclear.

⁴¹⁴ Shono, A., Mori, S., Nakamura, K., et al (2019). Glucocorticoid-sensitive Paroxysmal Atrial Fibrillation, Sick Sinus Syndrome, and Mitral Regurgitation in a Patient with Malignant Rheumatoid Vasculitis. *Internal medicine (Tokyo, Japan)*, 58(21), 3093–8. [freet](#)

⁴¹⁵ Pavičić, T., Ruška, B., Adamec, I., et al. (2019). Recurrent atrial fibrillation after pulse corticosteroid treatment for a relapse of multiple sclerosis. *Multiple sclerosis and related disorders*, 32, 30–2. August meeting 2022

Pavičić et al. (2019) reported a patient with recurrent atrial fibrillation after pulse corticosteroid treatment for a relapse of multiple sclerosis.⁴¹⁶ A 27-year-old male with multiple sclerosis developed AF on two occasions following two consecutive treatments with high dose methylprednisolone for treatment of multiple sclerosis relapse.

A new high dose corticosteroid treatment, consisting of **1000 mg of methylprednisolone** in 250 ml of saline intravenously during one hour for 5 days, was administered. During the second day he developed dyspnoea with palpitations and arrhythmia. The ECG showed AF with 115 beats per minute. He was treated with propafenone after which the AF resolved completely.

Extensive work-up revealed mild sympathetic autonomic system dysfunction. Based on this case and previous studies, the authors propose that a disturbed function of the autonomic system increases the risk of atrial fibrillation and/or other arrhythmias in people with multiple sclerosis.

Summary and conclusions

The use of steroids as treatment for asthma and skin conditions is a topic of a submission/request for review of these SoPs.

The association of corticosteroids (CS) and AF has been controversial, as glucocorticoids can alternatively be pro-arrhythmic or anti-arrhythmic (Granier et al 2013) It is now apparent that although corticosteroids can reduce the risks of developing post-operative atrial fibrillation after cardiac procedures, AF can be induced by high doses of oral corticosteroids, particularly after chronic use.

All anti-inflammatory drugs have anti-arrhythmic properties against post-operative AF. The effectiveness of steroids in lowering the risk of new onset post-operative AF in patients undergoing heart surgery using cardiopulmonary bypass has been confirmed in several meta-analyses (e.g. Ng et al 2020; Liu et al 2021; Dvirnik et al 2018), or RCTs (e.g. Al-Shawabkeh et al 2017). However some recent reports from large RCTs found no protective effect of CSs against new-onset AF after cardiac surgery, and the results of a meta-analysis by Jaiswal et al (2018) are ambivalent.

Apart from this specific situation of a protective effect against post-operative AF following cardiac surgery, there is clear evidence that corticosteroids can increase the risk of AF, although an association of may only be apparent in certain limited situations (Granier et al 2013). Clinical and analytical studies have linked corticosteroids, primarily methylprednisolone, to new onset AF (Kaakeh et al 2012). AF has been attributed to the administration of high-dose methylprednisolone in pulse doses, and also with lower dose intravenous or oral methylprednisolone therapy.

⁴¹⁶ Pavičić, T., Ruška, B., Adamec, I., et al. (2019). Recurrent atrial fibrillation after pulse corticosteroid treatment for a relapse of multiple sclerosis. *Multiple sclerosis and related disorders*, 32, 30–2. August meeting 2022

It is not certain why corticosteroids are effective for prevention of post-CABG AF, but are associated with induction of AF in patients not undergoing surgery. Corticosteroids may have atrial antiarrhythmic effects in prophylaxis of post-operative AF after cardiac surgery, even if in clinical practice, this indication is not widely accepted because of other side effects. On the other hand, when corticosteroids are indicated in other clinical conditions, high doses may have a pro-arrhythmic effect on the atrium, mostly due to potassium imbalance and/or other metabolic disturbance.

Corticosteroids can modulate AF substrates because of their electrophysiological and anti-inflammatory effects. They may contribute to nonsurgical AF by inducing sodium and fluid retention, leading to elevated atrial pressures; modulation of myocardial potassium efflux; and promotion of the development of late potentials. The pathophysiological link between glucocorticoid therapy and cardiovascular diseases may be related to the development of metabolic disorders and the consequences of a variable mineralocorticoid effect. Hypertension, diabetes, and the consequent vascular diseases are major putative factors concurring to the increased overall CV risk (Galiuto and Volpe 2021).

Glucocorticoids are widely used to reduce disease activity and inflammation in patients with a range of immune-mediated inflammatory diseases. It is uncertain whether low to moderate glucocorticoid dose increases cardiovascular risk (Pujades-Rodriguez et al. 2020).

In the context of primary prevention, some case reports described increased susceptibility to AF with steroids when administered for the first time with high doses in severe inflammatory conditions (outlined by Nomani et al 2020). Several cases of AF following high dose pulse corticosteroid (intravenous, intramuscular) treatment have been documented. AF as a complication of high dose corticosteroids has been described in neurofibromatosis type 2, systemic lupus erythematosus and acute onset of hiccoughs and multiple sclerosis. It is not dependent on the route of administration. The risk for atrial fibrillation is overall decreased in MS (Roshanisefat et al. 2014), while standard relapse therapy with pulse corticosteroids increases the risk of AF immediately after the therapy (Pavicic et al 2019)

Some analytical studies showed increased risk of AF in patients using glucocorticoids.

Van der Hooft et al. initially reported an increased risk of AF in patients taking high doses of inhaled corticosteroids, based on several case reports. In a case control study,

In a case–control study nested in the Rotterdam cohort study (van der Hooft et al. 2006), administration of glucocorticoids within the 1-month before AF diagnosis was associated with elevated new-onset AF (OR 3.75, 95CI 2.38–5.87). High dose corticosteroids (>7.5 mg daily of prednisone equivalents) increased risk of new onset AF (OR 6.07, 95CI 3.90–9.42), independent of treatment indication (asthma or COPD, rheumatic, allergic, or malignant haematological diseases). Intermediate-low dose (<7.5 mg prednisone equivalents daily) and inhaled corticosteroids did not increase the risk of new onset AF (Granier et al 2013).

Exposure to glucocorticoids doubled the odds of AF diagnosis in a Danish cohort with 20,221 AF/Afl patients and 202,130 controls (Christiansen et al 2009). This did not depend on underlying pulmonary or cardiovascular disease.

Caterina et al. (2010) reported that corticosteroids use was associated with an increased risk of chronic AF in a nested case-control study. Patients with low (<5mg daily) or intermediate (5-10 mg daily) equivalent prednisolone dose exhibited increased risk.

Recent oral steroid administration doubled the risk of AF in a nested case-control analysis of 710 patients with COPD or asthma, after adjustment for the severity of pulmonary diseases (Huerta et al. 2005).

There might be scrutiny bias in these studies, but they clearly documented a proarrhythmic potential for steroids, especially at high doses (Savelieva et al. 2011).

Chan et al (2014) examined the association between asthma and AF risk in a population-based nested case-control study including a total of 7439 newly diagnosed adult patients with AF and 10,075 matched subjects from the Taiwan National Health Insurance database. The risks of new-onset AF were significantly higher in current users of inhaled corticosteroid, oral corticosteroids, and bronchodilators. New users (within 6 months) had the highest risk (inhaled corticosteroid: OR 2.13; 95CI 1.226–3.701; oral corticosteroid (OR 1.932; 95CI 1.66–2.25); non-steroid bronchodilator (OR, 2.849; 95CI 2.48– 3.273, P < 0.001). A graded association with AF risk was observed in subjects treated with corticosteroid (inhaled and systemic administration) and bronchodilators

There is limited evidence from a recent cohort study that steroid use in some autoimmune diseases may increase the risk of cardiovascular disease in patients with giant cell arteritis and/or polymyalgia rheumatica (n = 25,581), inflammatory bowel disease (n = 27,739), rheumatoid arthritis (n = 25,324), systemic lupus erythematosus (n = 3,951), and/or vasculitis (n = 5,199), and no prior cardiovascular disease (Pujades-Rodriguez et al 2020) median follow-up was 5.0 years. 6,013 incident AF cases were identified. Increased dose-dependent risk ratios were found regardless of disease activity level. HR for AF and <5.0-mg daily dose prednisolone use was 1.69 (95CI 1.54-1.85). the duration of inflammatory disease averaged 9.7+/-8.7 years, suggesting prolonged glucocorticoid use, possibly responsible for a higher risk of CVD. About half of the study population (45%) was prescribed NSAIDs in the year before follow-up.

In relation to taking corticosteroids, evidence strong enough to support a judgement of a suggestive causal relationship with atrial fibrillation and atrial flutter (Grade 2). A generally consistent association has been observed between taking corticosteroids, particularly acute myocardial infarction, and the onset or worsening of atrial fibrillation and atrial flutter, but the evidence is limited in quality or quantity.

A factor for corticosteroid use should be added to the RH and BoP SoPs.

The evidence to establish a dose in relation to AF risk is uncertain. Evidence of a relationship between glucocorticoids and cardiovascular diseases comes primarily from studies of associations with current baseline medication use or dose, ignoring the doses previously administered and their changes over time, as well as the concomitant use of other common medications that can affect the risk of CVDs. Many studies have failed to adjust for important

cardiovascular risk factors. These studies have reported a dose-dependent risk of CVD with weaker associations for daily prednisolone-equivalent doses lower than 5 to 10 mg.

In a nested case-control study by Caterina et al. (2010), patients with low (<5mg of equivalent prednisolone daily) or intermediate (5-10 mg daily) dose exhibited an increased risk of AF.

Pujades-Rodriguez et al (2020) found increased dose-dependent risk ratios regardless of disease activity level in patients with chronic inflammatory diseases. HRs for AF and <5.0-mg daily dose use was 1.69 (95CI 1.54-1.85), the duration of inflammatory disease averaged 9.7+/-8.7 years, suggesting a prolonged glucocorticoid use, HR for incident AF was elevated in patients with a current daily dose of prednisolone equivalent HR 1.09, 95CI 1.07-1.11 per 5 mg/day. Risks of AF increased roughly with current daily dose to a maximum of HR 3.71, 95CI 3.14-4.39) for daily doses of 25mg+. Risk of AF was marginally elevated in relation to total cumulative dose: HR 1.01/ 1000mg, risk increased with cumulative dose from 1.30 for doses up to 3055 mg, HR 1.36 for doses 3055 to 7300 mg and 1.60 for 7300+.mg.

A new SoP factor can cover both acute and chronic steroid use and could be based upon the existing standard glucocorticoid factor. Although there is evidence of an association of AF risk with doses as low as 5mg per day prednisone equivalent, which is lower than the 12.5mg cited in the standard factor, the dose in the standard factor is considered to be reasonable.

NSAIDs

No factor

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for many inflammatory disorders and pain-related illnesses. Despite their widespread use, the association between NSAIDs and the incidence of atrial fibrillation remains unclear.

Review studies

Evidence that a number of drugs can cause atrial fibrillation has been accumulating since the 2000s.⁴¹⁷ A case-control analysis of a UK general medicine database showed statistically significant increases in the risk of chronic atrial fibrillation in patients taking NSAIDs, after as little as one month of treatment. When NSAID treatment lasted more than 30 days, the incidence was 9.4%, versus 4.7% in the control group, corresponding to a relative risk of 1.57, 95CI 1.15-2.15). Similar results were found in patients with no history of heart failure. A Danish case-control study yielded similar results. In the UK case-control study, a statistically significant increase in the risk of chronic atrial fibrillation was found in patients taking corticosteroids (5% versus 1.4% in the control group, RR=2.5, 95CI 1.6-4). The risk increased with dose. Another Danish case-control study showed that hospitalisation for atrial fibrillation or flutter was twice as frequent among patients exposed to corticosteroids. In contrast, trials in which corticosteroids were given shortly after cardiac surgery, a highly specific setting, showed a decreased risk of atrial fibrillation. In practice, the risk of atrial fibrillation should be

taken into account before deciding whether or not to prescribe a corticosteroid or an NSAID, especially to a patient with known risk factors for atrial fibrillation. The heart rate of treated patients should be closely monitored.

It is difficult to examine long term risk associated with use of NSAIDs due to heterogeneity in the patients who use NSAIDs (e.g. age, co-morbidities) and duration of use and adherence.⁴¹⁸ Categorising participants at baseline based on their use of NSAIDs and then examining outcomes years later is problematic because in that time frame exposure to NSAIDs could have changed multiple times from exposed to not exposed and vice versa. AF can be difficult to detect and extended monitoring may enhance the detection of AF, heterogeneity in the measurements used to identify incident AF is present.

NSAIDs are often used for inflammatory conditions and as inflammation is important for the initiation of AF, this potential confounding needs to be considered when examining the association between NSAIDs and AF. Although NSAIDs are anti-inflammatory, Chokesuwattanaskul et al. propose underlying mechanisms such as inhibition of cyclooxygenase (COX) enzymes and hyperkalaemia caused by NSAIDs may explain the association between NSAIDs and higher risk of AF.

Inflammatory process is strongly associated with cardiac arrhythmia, either as a cause or a consequence. Anti-inflammatory drugs are widely prescribed, and some have been associated with an increased cardiovascular risk. Then, the eventual pro- or anti-arrhythmic effect of these drugs is of high interest for clinical practice. **Granier et al (2013)** reviewed pro- and anti-arrhythmic effects of anti-inflammatory drugs, based on the analysis of published clinical trials.⁴¹⁹ As outlined previously, all anti-inflammatory drugs have demonstrated anti-arrhythmic properties in post-operative AF. Apart from this specific condition, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids increase the risk of AF.

In two large case-control studies, use of NSAIDs was associated with an increased risk of AF.⁴²⁰ De Caterina et al. (2010) reported that the current use of NSAIDs was associated with a statistically significant 44% increase in the risk of chronic AF. However, indications of NSAID therapy were not reported. It is established that inflammation can promote AF by many ways. As such, authors emphasise the hypothesis that the use of anti-inflammatory drugs may have been a proxy for an underlying inflammatory substrate favouring AF.

Schmidt et al. (2011) reported an increased relative risk of 40-70% of AF or flutter in new users of NSAIDs as compared with non-users in a large case-control study from northern Denmark (32,602 patients). The study recorded confounding factors like history of cancer, ischemic heart disease, COPD or underlying inflammatory condition. None of these

⁴¹⁸ Harrison, S. L., O'Flaherty, M., & Lip, G. (2020). Revisiting the dynamic risks of incident atrial fibrillation: does the use of nonsteroidal anti-inflammatory drugs contribute to risk?. *QJM : monthly journal of the Association of Physicians*, 113(2), 77–78.

⁴¹⁹ Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93

⁴²⁰ Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93

confounding factors was strong enough to explain the increased risk of atrial arrhythmias. Of note in this study, COX2-Inhibitors users were more exposed to the risk of AF.

Bäck et al. (2012) evaluated a nationwide, population-based cohort of 7 million subjects in Sweden, regarding the risk of developing cardiovascular disease in patients using COX2-Inhibitors over a 3-year period. There was no significant association of COX2-Inhibitors use with the risk of myocardial infarction, ischaemic stroke, or heart failure, but there was a strong significant positive correlation with a first episode of AF. This study was conducted after the withdrawal of rofecoxib that has been previously involved in cardiac arrhythmias and renal failure.

TABLE 29 NSAIDs USE AND RISK OF AF IN CASE-CONTROL AND COHORT STUDIES.

Author	Year	Population	Method	Drug/dose	Main finding	Arrhythmia?
De Caterina et al. [42]	2010	Chronic AF 1035 pts Paroxysmal 525 pts	Nested case-control	NSAIDs (COX- inhibitors excluded)	Increased risk of chronic AF No increased risk of paroxysmal AF	Pro-arrhythmic
Schmidt et al. [57]	2011	First diagnosis of AF or AFL, 2925 cases	Population based case-control	NSAIDs non selective or COX 2-inhibitors	Current use associated with increased risk of AF or AFL	Pro-arrhythmic
Bäck et al. [58]	2011	National cohort of 7 millions subject, 139323 AF pts	Nation-wide cohort study	COX2-inhibitors, after withdrawal of Rofecoxib	COX2-inhibitors use associated with increased risk of first AF episode	Pro-arrhythmic

Granier et al (2013) Table 2

In summary, Grandier et al determined that (then) recent trials had demonstrate that the use of NSAID increases the risk of AF.⁴²¹

Menichelli et al. (2021) note in a review study of cancer and atrial fibrillation, that patients with cancer, especially in the advanced stages of the disease, often require drugs to treat cancer-associated pain, including nonsteroidal anti-inflammatory drugs (NSAIDs), which are associated with an increased risk of developing AF.⁴²²

Among relevant studies, Chuang et al. (2016) performed a case-control study of 28,529 AF patients and matched controls using the National Health Insurance Research Database in Taiwan. The control group had a lower prevalence of chronic kidney disease, sleep apnoea, myocardial infarction and coronary artery disease than the AF group. NSAID use was associated with new-onset AF (adjusted OR 1.18, 95CI 1.14–1.23), especially if the NSAID was not selective for cyclo-oxygenase isoenzyme type 2 (COX-2), such as naproxen, diclofenac, ketoprofen, ibuprofen (aOR 1.18, 95CI 1.13–1.23). These results are consistent with the risk of new-onset AF in NSAID users in the general population. The risk of new-onset AF in non-selective NSAIDs users may have different explanations; concomitant inhibition of

⁴²¹ Granier, M., Massin, F., & Pasquié, J. L. (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Anti-inflammatory & anti-allergy agents in medicinal chemistry*, 12(1), 83–93

⁴²² Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36
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cyclo-oxygenase isoenzyme type 1 (COX-1) and to a lesser extent of COX-2 enzymes, which produce some homeostatic prostaglandins at renal³⁹ and endothelial sites⁴⁰ regulating blood volume, vascular resistance and blood pressure may result in sodium retention, fluid overload and hypertension, which is a well-known risk factor for AF.

Lee et al., (2016) performed a retrospective study that analysed 73,917 women with breast cancer without an AF history, of whom 18,761 were morphine-users and 55,246 non-users. The morphine-users were older, with more comorbidities and tamoxifen, bisphosphonates and paclitaxel use than non-users. Cox proportional hazards regression showed an increased risk of AF in morphine-user patients (aHR 4.37, 95CI 3.56–5.36, $p < 0.001$), independently from comorbidities and chemotherapy.

As a potential mechanism, it is hypothesised that morphine treatment may reduce the number of opioid receptors, which physiologically exert cardio protective effects, in the atrial tissue thereby increasing the risk of AF in cancer patients⁴²³ However, the lack of data from National Health Insurance Research Database about malnutrition, lifestyle factors such as smoking or alcohol consumption, body mass index, socioeconomic status and family history, may represent some residual potential confounding risk factors for AF onset.

Menichelli et al. (2021) concluded that a causal link between the use of specific drugs and the risk of new-onset AF is difficult to deduce from observational studies with small samples.⁴²⁴ Important confounders in this association, such as concomitant underlying comorbidities, systemic inflammation, and cardiac involvement related to cancer, may account, at least in part, for the observed risk.

Meta-analysis .

Chokesuwattanaskul et al. (2020) conducted a systematic review and meta-analysis to investigate the association of nonsteroidal anti-inflammatory drugs and incidence of atrial fibrillation.⁴²⁵

A systematic review was conducted in MEDLINE, EMBASE and Cochrane databases from inception through August 2019 to identify studies that evaluated the risk of AF among patients using NSAIDs. Pooled risk ratios and 95CI were calculated using a random-effect, generic inverse variance method.

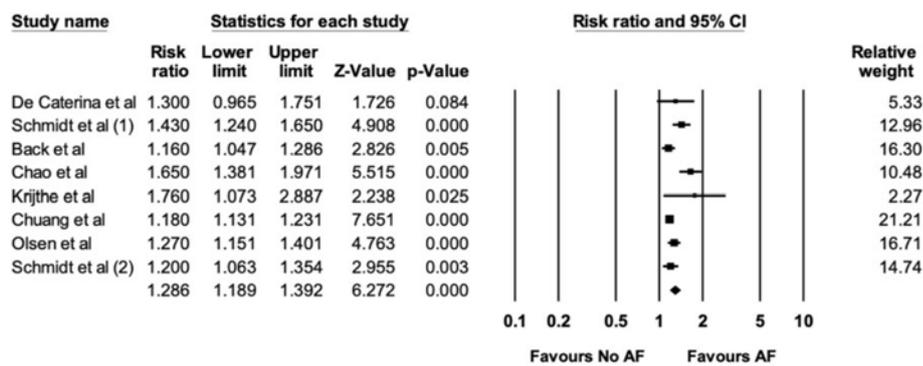
Eight observational studies (four case-control studies and four cohort studies) with 14 806 420 patients were enrolled. compared with non-NSAIDs users, the pooled RR of AF in patients with NSAIDs use was 1.29 (95CI 1.19-1.39).

⁴²³ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36

⁴²⁴ Menichelli, D., Vicario, T., Ameri, P., et al. (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Progress in cardiovascular diseases*, 66, 28–36

⁴²⁵ Chokesuwattanaskul, R., Chiengthong, K., Thongprayoon, C., et al. (2020). Nonsteroidal anti-inflammatory drugs and incidence of atrial fibrillation: a meta-analysis. *QJM : monthly journal of the Association of Physicians*, 113(2), 79–85

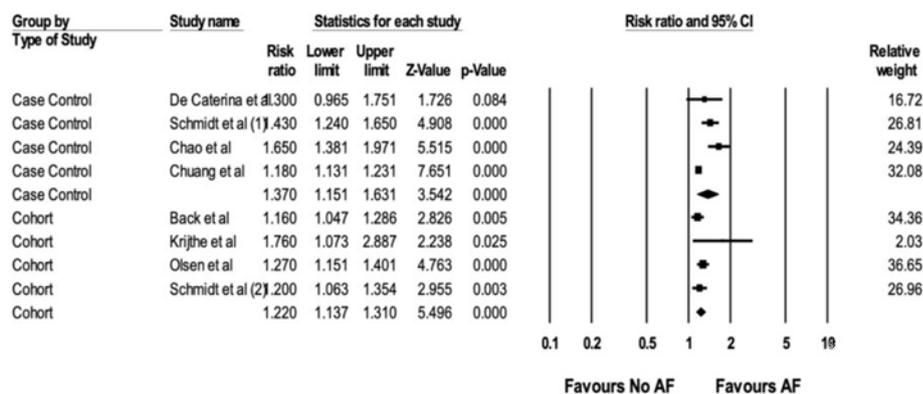
FIGURE 54 FOREST PLOT OF ALL STUDIES EVALUATING THE ASSOCIATION BETWEEN NSAIDs AND AF.



Source: Chokesuwattanaskul et al (2020), Fig 2

Subgroup analysis by study design revealed a significant association between the use of NSAIDs and AF in both case-control studies (pooled RR 1.37; 95CI 1.15-1.63) and cohort studies (pooled RR 1.22; 95CI 1.14-1.31).

FIGURE 55 FOREST PLOT OF SUBGROUP ANALYSIS BY STUDY DESIGN EVALUATING THE ASSOCIATION BETWEEN NSAIDs AND AF.



Source: Chokesuwattanaskul et al (2020), Fig 3

Sub-analyses based on specific NSAIDs showed pooled RRs of AF in patients using ibuprofen of 1.30 (95CI 1.22-1.39), naproxen of 1.44 (95CI 1.18-1.76) and diclofenac of 1.37 (95CI 1.10-1.71). Funnel plot and Egger's regression asymmetry tests were performed and showed no publication bias.

The study demonstrated an association between the use of NSAIDs and incident AF. The result was consistent among different NSAIDs (diclofenac, Ibuprofen and naproxen) with a trend towards less risk with ibuprofen. The result was significant whether examining case-control or cohort studies.

It is recognised that patients with serious inflammatory conditions are already at a high-risk of developing AF and this population commonly uses NSAIDs as part of their management. It is challenging to identify the agent actually responsible for the occurrence of AF in the presence of concomitant systemic inflammatory conditions and NSAIDs use. Despite systemic inflammation being well recognised as an aetiology of AF, NSAIDs, used for their anti-inflammatory properties, are associated with an increased incidence of AF.

Liu et al (2014) previously conducted a meta-analysis to quantify the association between use of NSAIDs and risk of AF incidence.⁴²⁶ MEDLINE and EMBASE were searched for studies that reported risk of AF associated with nonaspirin NSAID use. Combined relative risk (RR) estimates and 95CIs were calculated using the random-effects model. Stratified meta-analyses were used to discern which patients were at the highest risk of AF due to NSAID use.

Five studies were identified that met the inclusion criteria, 3 of which reported specifically on the association between selective NSAIDs and risk of AF. Overall, NSAID use was associated with a 12% increased risk for AF incidence (RR 1.12, 95CI 1.06-1.18). The association was apparent among new users (RR 1.53, 95CI 1.37-1.70).

The increased risk of AF might be explained by the occurrence of chronic heart failure and kidney disease. In addition, use of selective NSAIDs was related to an increased risk of AF (RR 1.24, 95CI 1.18-1.30). Sensitivity analyses found results to be robust.

Cohort studies

Chuang et al (2018) evaluated the association between NSAID use and the risk of AF in a nationwide population-based study of middle-aged individuals in Taiwan.⁴²⁷

A nested case-control study was conducted using the National Health Insurance Research Database (NHIRD) in Taiwan. Cases with a diagnosis of AF (ICD-9-CM codes: 427.31) and the matched controls from three independent Longitudinal Health Insurance Databases (LHIDs) derived from the NHIRD from data collected from 2001 to 2013. Conditional logistic regression models with covariate adjustment were performed to evaluate the association between NSAID use and the risk of AF.

A total of 57 058 participants (28 529 AF cases and 28 529 matched controls) were included. Participants with NSAID use had an elevated risk of AF compared to non-users [adjusted odds ratio (AOR) = 1.18, 95CI 1.14-1.23]. When further assessing the effects of different classes of NSAIDs on the risk of AF, the results showed that participants who used non-selective NSAIDs had a significantly elevated risk of AF (AOR 1.18, 95CI 1.13-1.23), as did participants with a combined use of selective and non-selective NSAIDs (AOR 1.30, 95CI 1.21-1.39).

NSAID use was associated with an increased risk of AF occurrence in the cohort.

⁴²⁶ Liu, G., Yan, Y. P., Zheng, X. X., et al (2014). Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of atrial fibrillation. *The American journal of cardiology*, 114(10), 1523–9.

⁴²⁷ Chuang, S. Y., Hsu, P. F., Lin, F. J., et al. (2018). Association between nonsteroidal anti-inflammatory drugs and atrial fibrillation among a middle-aged population: a nationwide population-based cohort. *British journal of clinical pharmacology*, 84(6), 1290–1300.

Using nationwide administrative registries in Denmark, **Schjerning Olsen et al. (2015)** examined whether NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction.⁴²⁸

They studied patients aged ≥ 30 years admitted with first-time MI and without prior AF in the period of 1997-2011. Risk of AF associated with NSAID use vs. no NSAID use was analysed by multivariable time-dependent Cox proportional hazard models. Of 86 496 patients [mean age 66 (SD 13) years; 64% men], 44.1% filled at least one NSAID prescription after discharge from MI. During a mean follow-up of 5.3 years, 7831 (8.9%) developed AF.

The incidence of AF per 100 person-years with NSAID treatment was 2.2 (95CI .0-2.4) compared with 1.7 (95CI 1.6-1.7) without NSAIDs. In the adjusted model, the risk of AF after NSAID treatment increased (HR 1.27, 95CI 1.14-1.40). An increased risk of AF was seen regardless of type of NSAID or with short-term (0-14 days) treatment [HR 1.45, 95CI 1.24-1.69]. When the risk of death in patients exposed [crude rate 23.3, 95CI 19.7-27.5) vs. not exposed [crude rate 17.4 (95CI 16.8-18.1) to NSAIDs at the time of AF was compared, NSAID use was associated with a poorer prognosis [HR 1.35, 95CI 1.14-1.60).

The study suggests that the use of NSAIDs might be associated with the increased risk of AF in post-MI patients.

Chao et al (2013) investigated whether exposure to NSAIDs was a risk factor for AF, and to discern which patients were at the highest risk for AF due to NSAID use.⁴²⁹

A total of 7280 patients with newly diagnosed AF from 2000 to 2009 were identified from the National Health Insurance Research Database. On the same date of enrolment, 10 patients without AF, who were matched for age, sex, and underlying disease for each study patient, were selected to be the control group. The relationship between NSAID exposure before enrolment and AF risk was analysed.

NSAID use was associated with an increased AF risk, especially for new users (OR 1.651). Among new users, subgroup analysis revealed that patients with heart failure were at the highest risk for AF (OR 1.920). For patients who were only exposed to selective cyclooxygenase 2 (COX2) inhibitors, no significant associations were found between AF and selective COX2 inhibitor use (OR 1.656), except for patients with chronic kidney or pulmonary disease (OR 1.707).

New NSAID use may predispose patients to AF, and the risk is almost doubled in heart failure patients. Use of selective COX2 inhibitors was not significantly related to AF occurrence, except in patients with chronic kidney or pulmonary disease.

⁴²⁸ Schjerning Olsen, A. M., Fosbøl, E. L., Pallisgaard, J., et al. (2015). NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction: a nationwide study. *European heart journal. Cardiovascular pharmacotherapy*, 1(2), 107–14.

⁴²⁹ Chao, T. F., Liu, C. J., Chen, S. J., et al (2013). The association between the use of non-steroidal anti-inflammatory drugs and atrial fibrillation: a nationwide case-control study. *International journal of cardiology*, 168(1), 312–6.

Summary and conclusions

The inflammatory pathway may be an important target for reducing risk of AF, but current evidence suggests the use of NSAIDs is associated with an increased risk of AF (Harrison et al 2020). Despite systemic inflammation being well recognised as an aetiology of AF, NSAIDs, used for their anti-inflammatory properties, are associated with an increased incidence of AF.

Case-control studies suggest a modest increased risk for the development of AF in patients taking NSAIDs [Chokesuwattanaskul et al 2020]. However, the absence of an accepted biological mechanism and the susceptibility of case-control studies to unmeasured confounders suggests cautious about the strength of this association (Uptodate).

It is recognised that patients with serious inflammatory conditions are already at a high-risk of developing AF, and this population also commonly uses NSAIDs. It is challenging to confidently identify the agent actually responsible for the occurrence of AF in the presence of concomitant systemic inflammatory conditions and NSAIDs use (Chokesuwattanaskul et al 2020). The use of NSAIDs is also associated with many adverse cardiovascular events (e.g. heart failure and myocardial infarction) which are well recognised as causes of AF.

All anti-inflammatory drugs have demonstrated anti-arrhythmic properties against post operative AF. Apart from this specific condition, NSAIDs and corticosteroids **can increase the risk of AF**. Observational studies and clinical trials demonstrate that the use of NSAID increases the risk of AF (Granier et al 2013).

Despite their widespread use, the association between NSAIDs and the incidence of AF remains unclear (Chokesuwattanaskul, et al. 2020). A systematic review and meta-analysis that investigated the association included 8 observational studies (4 case-control and 4 cohort studies) with 14 806 420 patients confirmed an association of NSAIDs use with incident AF. Compared with non-NSAIDs users, the pooled RR of AF in patients with NSAIDs use was 1.29 (95CI 1.19-1.39). The significant association was present in both case-control studies (pooled RR 1.37; 95CI 1.15-1.63) and cohort studies (pooled RR 1.22; 95CI 1.14-1.31).

Sub-analyses based on specific NSAIDs showed pooled RRs of AF in patients using ibuprofen of 1.30 (95CI 1.22-1.39), naproxen of 1.44 (95CI 1.18-1.76) and diclofenac of 1.37 (95CI 1.10-1.71).

Similar results were obtained in an earlier meta-analysis by Liu et al (2014) which included 5 studies. Overall, NSAID use was associated with a 12% increased risk for AF incidence (RR 1.12, 95CI 1.06-1.18). The association was apparent in new users (RR 1.53, 95CI 1.37-1.70). The increased risk of AF might have been explained by the occurrence of chronic heart failure and kidney disease. The use of selective NSAIDs was related to an increased risk of AF (RR 1.24, 95CI 1.18-1.30).

Although NSAIDs are anti-inflammatory, Chokesuwattanaskul et al. propose underlying mechanisms such as inhibition of cyclooxygenase (COX) enzymes and hyperkalaemia caused by NSAIDs may explain the association between NSAIDs and higher risk of AF.

Methodological difficulties of establishing a causal effect of NSAIDs in context of chronic

inflammation are recognised (Harrison et al 2020). It is difficult to examine long term risk associated with use of NSAIDs due to heterogeneity in patients who use NSAIDs, duration of use and adherence. Categorising participants at baseline based on their use of NSAIDs and then examining outcomes years later is problematic because in that time frame exposure to NSAIDs could have changed multiple times from exposed to not exposed and vice versa. Confounding by heart failure, other cardiovascular risk factors remains a fundamental issue in published studies.

An association of NSAIDs with AF risk is supported by some recent cohort studies Chuang et al (2018) studied the risk of AF in a nationwide population-based study of middle-aged individuals in Taiwan National Health Insurance Research Database (NHIRD). 28 529 AF cases and 28 529 matched controls were included. Participants with NSAID use had an elevated risk of AF compared to non-users [adjusted OR 1.18, 95CI 1.14-1.23]. the risk was increased in users of non-selective NSAIDs (OR 1.18, 95CI 1.13-1.23), and both selective and non-selective NSAIDs (OR 1.30, 95CI 1.21-1.39).

Schjerning Olsen et al. (2015) examined whether NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction. During a mean follow-up of 5.3 years, 7831 (8.9%) developed AF. In the adjusted model, the risk of AF after NSAID treatment increased (HR 1.27, 95CI 1.14-1.40). An increased risk of AF was seen regardless of type of NSAID or with short-term (0-14 days) treatment (HR 1.45, 95CI 1.24-1.69).

In relation to taking NSAIDs, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality or quantity, and confounding by other cardiovascular risk factors and underlying inflammatory disease remains an unresolved issue.

A new factor for taking NSAIDs should be added to the RH SoPs only.

There is little data concerning dose of NSAID related to AF risk. A time period of 15- 30 days use is suggested based on observations that AF risk may increase during the early stages of treatment.

Bisphosphonates

No factor

Summary of important issues

A link between bisphosphonates (BPs) and atrial fibrillation has been proposed, with early clinical trials reporting that BPs are associated with increased risk of AF Park & Ko (2022) a meta-analysis including 4 case-control and 8 cohort studies yielded an OR for AF in patients treated with bisphosphonates of 1.171 (95CI 1.011-1.356), with substantial heterogeneity. No publication bias was observed.

The results are consistent with a previous meta-analysis that included RCTs, which showed that AF increased with BP treatment, compared to the non-BP comparators (Sharma et al 2014). The studies showed a high degree of heterogeneity, including differences in the dose and duration of treatment, route of administration, and type of BP used to treat patients.

The mechanism of bisphosphonates-induced AF is unclear, but these drugs release inflammatory cytokines and shorten atrial action potential duration and effective refractory period

Review study

Bisphosphonates (BPs) are widely prescribed drugs used to treat osteoporosis, commonly arising in postmenopausal women and in chronic glucocorticoid use.⁴³⁰ Their mechanism of action is through inhibiting osteoclast-induced bone remodeling, and they also possess calcium sequestering properties. Common side effects involve the gastrointestinal system and rare but serious side effects, including osteonecrosis of the jaw.

A link between BPs and atrial fibrillation has been proposed, with early clinical trials, such as the Fracture Intervention Trial and the HORIZON Pivotal Fracture Trial, reporting that BPs are associated with increased risk of AF.⁴³¹ Subsequent studies have reported contrasting results, ranging from no effect of BPs to antiarrhythmic effects of BPs. Preclinical and electrophysiological studies on proarrhythmic effects of BPs are limited in scope and number, but suggest possible mechanisms that include antiangiogenesis-related myocardial remodeling, calcium handling abnormalities, and inflammatory changes. Some studies indicate that BPs are antiarrhythmic by inhibiting fibrotic myocardial remodelling.

Concerns were first raised about a possible association between bisphosphonate therapy and atrial fibrillation following the report of a significant increase in risk of serious AF in women treated with zoledronic acid in the HORIZON study. Subsequent studies have produced conflicting results but have not excluded the possibility of such an association.

There is no direct evidence that bisphosphonates exert acute or chronic effects on cardiac electrophysiology. However, altered intracellular electrolyte homeostasis and proinflammatory, profibrotic, and antiangiogenic effects provide potential mechanisms by which atrial conduction could be affected in patients treated with bisphosphonates. In studies in which an increase in risk of AF has been identified, there is no evidence that this translates into increased mortality or increased risk of stroke, and the risk-benefit balance of bisphosphonate therapy in patients with osteoporosis and other forms of metabolic bone disease remains strongly positive.

⁴³⁰ Fazmin, I. T., Huang, C. L., & Jeevaratnam, K. (2020). Bisphosphonates and atrial fibrillation: revisiting the controversy. *Annals of the New York Academy of Sciences*, 1474(1), 15–26.

⁴³¹ Fazmin, I. T., Huang, C. L., & Jeevaratnam, K. (2020). Bisphosphonates and atrial fibrillation: revisiting the controversy. *Annals of the New York Academy of Sciences*, 1474(1), 15–26.

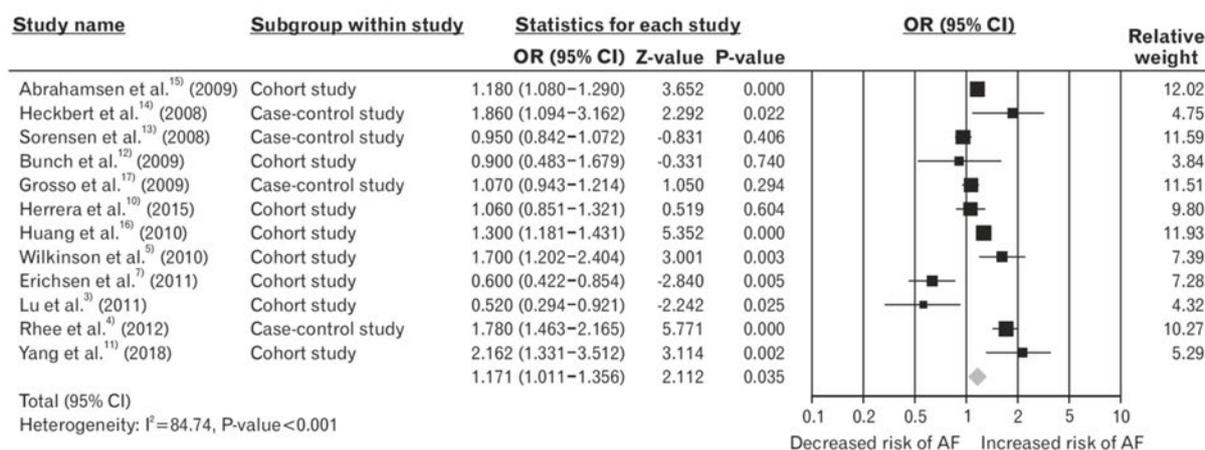
Meta-analysis

Studies evaluating the association between treatment with bisphosphonate and the risk of atrial fibrillation have reported conflicting results. **Park and Ko (2022)** conducted a meta-analysis of observational studies to assess this association.⁴³²

Databases were searched to find relevant observational studies, and the identified articles were selected according to the selection criteria. Sensitivity and subgroup analysis based on various confounding factors were performed. The pooled odds ratios (ORs) and 95CIs for the risk of atrial fibrillation were estimated using a random-effects model.

The authors selected 12 studies, including four case-control and eight cohort studies, for the meta-analysis. Assessment of the estimated effect size yielded an OR of 1.171 (95CI 1.011-1.356; P=0.035), with substantial heterogeneity (I² =84.74%, P<0.001).

FIGURE 56 ASSOCIATION BETWEEN TREATMENT WITH BISPHOSPHONATES AND RISK OF AF, RANDOM-EFFECTS MODEL



Park & Ko (2022), Fig 2, p 72

Subgroup analyses found that treatment with bisphosphonates was associated with the risk of atrial fibrillation in studies in Western countries (OR 1.263; 95CI 1.092-1.462) and lower-quality studies (OR 1.214; 95CI 1.035-1.423). No publication bias was observed.

⁴³² Park, J. H., & Ko, H. J. (2022). The Association between Treatment with Bisphosphonates and the Risk of Atrial Fibrillation: A Meta-Analysis of Observational Studies. Korean journal of family medicine, 43(1), 69–76.

TABLE 30 SUBGROUP ANALYSIS OF THE ASSOCIATION BETWEEN TREATMENT WITH BISPHOSPHONATES AND THE RISK OF ATRIAL FIBRILLATION

Subgroup	No. of studies	Effect size	
		OR (95% CI)	P-value
Study design			
Case-control	4 ^{13,14,16,17}	1.290 (0.960–1.725)	0.091
Cohort	8 ^{3-5,7,10-12,15}	1.116 (0.927–1.343)	0.247
Countries			
Asian	4 ^{3,4,11,16}	0.925 (0.549–1.558)	0.769
Western	8 ^{5,7,10,12-15,17}	1.263 (1.092–1.462)	0.002
Quality of study			
High (NOS >8)	8 ^{3,4,10-15}	1.125 (0.880–1.438)	0.347
Low (NOS ≤7)	4 ^{5,7,16,17}	1.214 (1.035–1.423)	0.017
Women only	7 ^{3,4,11,13,14,16,17}	1.025 (0.829–1.267)	0.820

Park & Ko (2022), Table 3, p 73

The meta-analysis showed that treatment with bisphosphonates was significantly associated with a 17% greater risk of developing AF. The results of this meta-analysis of observational studies are consistent with those of a previous meta-analysis that included RCTs, which showed that the risk of AF increased with BP treatment, compared to the non-BP comparators (Sharma et al 2014)

The studies in the analysis showed a high degree of heterogeneity, including differences in the dose and duration of treatment, route of administration, and type of BP used to treat patients. To overcome these limitations, a random-effects model was used to determine the average effect size of these heterogeneous populations and sensitivity and subgroup analyses were conducted. There was no assessment of the association between dose or duration of treatment with BPs and the risk of AF, because only four of the 12 studies analysed dose responses to BPs, and the duration of treatment with BPs was unclear in each study. The type of BP differed among the studies, with seven involving oral administration of BPs, two including intravenous administration, and three including both,

Summary and conclusions

Bisphosphonates, including alendronate, risedronate, and etidronate, are widely used in the treatment of osteoporosis, and concern has been raised that these drugs can cause AF. The weight of evidence suggests that the risk of AF from oral bisphosphonates is small, if it exists at all

Early clinical trials, such as the Fracture Intervention Trial and the HORIZON Pivotal Fracture Trial, reporting that BPs are associated with increased risk of AF (Fazmin et al 2020). Subsequent studies have reported contrasting results, ranging from no effect of BPs to antiarrhythmic effects of BPs. Preclinical and electrophysiological studies on any proarrhythmic effect of BPs are limited in scope and number, but suggest possible mechanisms that include antiangiogenesis-related myocardial remodeling, calcium handling

abnormalities, and inflammatory changes. Contrastingly, some studies indicate that BPs are antiarrhythmic by inhibiting fibrotic myocardial remodelling.

A recent meta-analysis of observational studies assessed this association between treatment with bisphosphonates and the risk of AF (Park & Ko 2022). The analysis included 12 studies (four case-control and eight cohort studies). The estimated effect size yielded an OR of 1.171 (95CI 1.011-1.356; P=0.035), with substantial heterogeneity (I² =84.74%, P<0.001).

Treatment with bisphosphonates was associated with increased risk of AF in studies in Western countries (OR 1.263; 95CI 1.092-1.462) and lower-quality studies (OR 1.214; 95CI 1.035-1.423). No publication bias was observed.

The results are consistent with those of a previous meta-analysis that included RCTs, which showed that the risk of AF increased with BP treatment, compared to the non-BP comparators (Sharma et al 2014)

The studies showed a high degree of heterogeneity, including differences in the dose and duration of treatment, route of administration, and type of BP used to treat patients. To overcome these limitations, a random-effects model was used to determine the average effect size of these heterogeneous populations and sensitivity and subgroup analyses were conducted.

The mechanism of bisphosphonates-induced AF is unclear, but these drugs release inflammatory cytokines and shorten atrial action potential duration and effective refractory period (Tisdale et al 2020).

In relation to taking bisphosphonates, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality or quantity, and confounding by other cardiovascular risk factors and underlying inflammatory disease remains an unresolved issue.

A new factor for taking bisphosphonates should be added to the RH SoPs only.

Diet

No factor

Summary of important issues

Reviews

As outlined by Linz et al. (2021), dietary intake has been shown to change the composition of gut microbiota and some changes in microbiota (dysbiosis) have been linked to diabetes,

hypertension, and obesity, which are established risk factors for atrial fibrillation.⁴³³ intestinal dysbiosis generates microbiota-derived bioactive metabolites that might exert proarrhythmic actions. Although emerging preclinical investigations and clinical observational cohort studies suggest a possible role of gut dysbiosis in AF promotion, the exact mechanisms through which dysbiosis contributes to AF remain unclear. This Viewpoint article briefly reviews evidence suggesting that abnormalities in the intestinal microbiota play an important and little-recognized role in the pathophysiology of AF and that an improved understanding of this role may open up new possibilities in the management of AF.

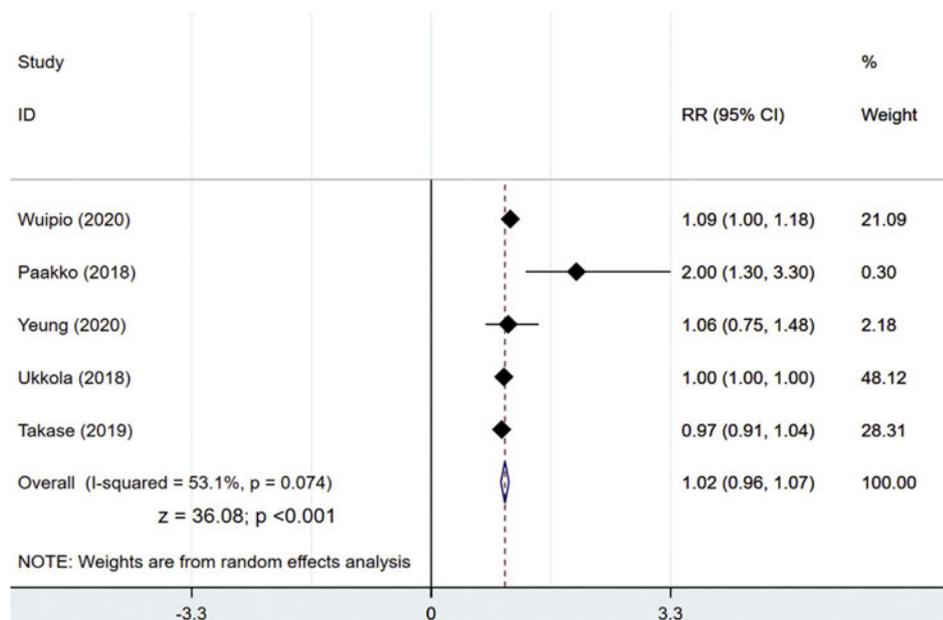
Meta-analyses

Bhagavathula and Rahmani (2021) conducted a systematic review and metaanalysis of observational studies to clarify the association between salt intake and risk of new-onset AF. Included population-based studies investigating the association between salt intake and AF incidence and providing related data as risk ratio.⁴³⁴

Five studies, including Yeung et al., met all inclusion criteria comprising 1,421,826 participants, and reported new-onset AF in 133,645 (4.7%) subjects. All studies reported new-onset AF with salt intake.

The meta-analysis showed no significant increased risk of new-onset AF with salt consumption (RR 1.02; 95CI 0.96-1.07, P < 0.001; I² = 53.1%; P heterogeneity 0.074).

FIGURE 57 SALT INTAKE AND ONSET OF AF



Bhagavathula AS, Rahmani J. (2021), Fig 1

⁴³³ Linz, D., Gawalko, M., Sanders, P., et al. (2021). Does gut microbiota affect atrial rhythm? Causalities and speculations. *European heart journal*, 42(35), 3521–5.

⁴³⁴ Bhagavathula AS, Rahmani J. (2021). Salt intake and new-onset of atrial fibrillation: A meta-analysis of over 1.4 million participants. *Clin Nutr.*;40(5):2600-2601 August meeting 2022

The meta-analysis, including cohort studies and a Mendelian randomization study presently available, demonstrated that salt intake was not associated with increased risk of new-onset AF. Due to the nature of the association, other factors rather than salt intake may have a more prominent impact on the new-onset AF

Yeung et al used urinary sodium as a proxy for salt intake. However, some studies included in the meta analyses used dietary salt intake as exposures.⁴³⁵ This would complicate result interpretation given different units of exposure across studies.

Observational studies, almost inevitably only recruit survivors, meaning they are open to selection bias from missing people who have already died, here possibly of cardiovascular disease because of their salt intake. As AF may occur relatively late in life, it is possible that the observed null associations of salt intake with AF is an artefact of competing risk instead of implying salt intake not related to AF risk.

Cohort studies

Hypertension predisposes to atrial fibrillation - a major risk factor for ischaemic stroke. Since a high dietary salt consumption is associated with hypertension, **Wuopio et al. (2021)** investigated the association between urinary sodium excretion as a marker for dietary sodium intake and risk of new-onset AF in community-dwelling adults.⁴³⁶

The UK Biobank includes 40- to 69-year-old British residents recruited 2006-2010. Participants were divided into sex-specific quintiles according to 24-hour sodium excretion estimated based on spot samples with the Kawasaki equation. The study excluded participants with AF at baseline. Cox regression adjusted for cardiovascular risk factors was used to assess associations with risk of AF, using the third quintile as reference.

A total of 257 545 women and 215 535 men were included. During up to 10 years' follow-up, 2221 women and 3751 men were diagnosed with AF. There was a tendency for an increased risk of AF in the lowest and highest quintiles of estimated daily salt intake in both women and men. In the fully adjusted model, significant associations were seen amongst men in the lowest and highest quintiles of sodium excretion (hazard ratio, HRQv1, 1.20; 95% CI, 1.08-1.32, $P < 0.001$, and HRQv5 1.15, 95% CI, 1.03-1.27, $P = 0.011$).

The study identified evidence for a U-shaped association between estimated daily salt intake and AF risk amongst men. A suggestive J-shaped association in women was not statistically confirmed, but analyses were likely underpowered. The results suggest that above a certain physiological minimum level progressively higher salt intake is associated with increasing risk of AF.

⁴³⁵ He, B., Au Yeung, S. L., & Schooling, C. M. (2021). Reply to letter to the editor: Salt intake and new-onset of atrial fibrillation: A meta-analysis of over 1.4 million participants. *Clinical nutrition (Edinburgh, Scotland)*, 40(7), 4615.

⁴³⁶ Wuopio, J., Orho-Melander, M., Ärnlov, J., et al. (2021). Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort. *Journal of internal medicine*, 289(5), 700–8. August meeting 2022

Au Yeung et al (2021) examined the causal role of urinary sodium in these CVDs and risk factors using Mendelian randomisation.⁴³⁷

The authors identified strong, independent single nucleotide polymorphisms (SNPs) of urinary sodium from the most up to date genome wide association studies (GWAS) (n = 446,237) and applied them to GWAS of stroke and its subtypes (40,585 cases and 406,111 non-cases), atrial fibrillation (60,620 cases and 970,216 non-cases) and heart failure (47,309 cases and 930,014 non-case). They assessed the impact of sodium on these diseases and associated risk factors using inverse variance weighting. Sensitivity analyses included weighted median, contamination mixture method, MR-PRESSO, and multivariable Mendelian randomisation.

Higher log transformed urinary sodium was not associated with risk of AF (OR 1.06, 95CI 0.75-1.48).

Higher risk of stroke (OR 1.45, 95CI 1.01-2.08), ischaemic stroke (OR 1.60 95CI 1.12 to 2.30), heart failure (OR 1.77 95CI 1.19 to 2.62), and type 2 diabetes (OR 4.17 95CI 1.53 to 11.35). Sensitivity analyses produced directionally similar estimates.

Higher sodium likely increases stroke, heart failure and type 2 diabetes risk.

Summary and conclusions

Although sodium increases the risk of coronary artery disease and hypertension, whether sodium also impacts other cardiovascular disease and its risk factors is less clear.

Some positive evidence has been derived from cohort studies such as a community-based cohort study by Wuopio et al. (2020), which reported increased risk of new-onset atrial fibrillation with salt intake in men and J-shaped association in women.

No association between salt intake and risk of AF was identified in a recent Mendelian randomization study (Au Yeung et al 2021).

Bhagavathula and Rahmani (2021) conducted a systematic review and meta-analysis of observational studies to clarify the association between salt intake and risk of new-onset AF. The meta-analysis included 4 previous cohort studies and the Mendelian randomisation study by Au Yeung et al. The meta-analysis showed no significant increased risk of new-onset AF with salt consumption (RR 1.02; 95CI: 0.96-1.07) and it was determined that salt intake was not associated with increased risk of new-onset AF;

It is therefore concluded that the evidence is too limited to permit a judgement of a possible causal relationship between salt consumption and the development of atrial fibrillation or atrial flutter (Grade 4). An association is demonstrated in some studies, but the evidence is

⁴³⁷ Ah Yeung SL, Schooling CM.(2021) Impact of urinary sodium on cardiovascular disease and risk factors: a 2 sample Mendelian randomization study. Clin Nutr; 40(4): 1990-6.
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inconsistent and studies are limited in quality or quantity. Chance, bias or confounding are likely to account for observed associations.

No factor for the SoPs is suggested.

Air pollution

No factor

Summary of important issues

Recent studies suggest that the exposure to air pollutants, particularly particulate matter, may increase the prevalence of AF.

Particulate matter (PM₁₀, PM_{2.5}, and ultrafine particles) and gaseous air pollutants can exert undesirable effects on cardiac rhythms (Shahrbaf et al (2021). Wang et al (2021) affirms that a growing body of epidemiological evidence shows that exposure to air pollution. Zhang et al (2021) suggests that AF is the most common arrhythmia induced by particulate matter exposure.

Controlled exposure studies in healthy volunteers and patients with coronary heart disease have not shown any pro-arrhythmic effect of air pollution, whereas positive associations have been found between PM_{2.5} exposure and hospitalisation for AF and paroxysmal AF episodes. Some studies on hospitalisation rates for AF found an association with PM, whereas other found no association.

Scientific evidence for the roles of gaseous pollutants in arrhythmias are limited and contradictory, with relatively little data specifically dealing with AF.

Reviews

Air pollution is the mixture of chemical and environmental agents including dust, fumes, gases, particulate matters, and biological materials which can be harmful for the environment and the human body.⁴³⁸ The potentially harmful effects of air pollution on health have been recognised and many epidemiological studies have suggested the strong association between air pollution exposure and increased morbidity and mortality.

Air pollutants are classified into gaseous pollutants including carbon monoxide, nitrogen oxides, ozone and sulphur dioxide, and particulate matters (PMs). Many studies have demonstrated an effect of air pollutant on the occurrence of ST elevation myocardial infarction, sudden cardiac death, cardiac arrhythmias, and peripheral arterial disease.

⁴³⁸ Shahrbaf, M. A., Akbarzadeh, M. A., Tabary, M., et al (2021). Air Pollution and Cardiac Arrhythmias: A Comprehensive Review. *Current problems in cardiology*, 46(3), 100649
August meeting 2022

PM are mixtures of very small solid particles and liquid droplets, consisting of chemical agents, including acids, metals, soil, and dust.⁴³⁹ PMs are broadly categorised by aerodynamic diameter. Particles with an aerodynamic diameter 10 µm are called coarse particles, particles with an aerodynamic diameter 2.5 µm are fine particles, and particles with a diameter below 0.1 µm are categorised as ultra-fine particles. Gaseous pollutants, including CO, nitrogen oxides, SO₂, and O₃, are common air pollutants which are generated from fossil fuel combustion and transportation.

Air pollutants, especially particulate matter, are likely risk factors for cardiovascular events including arrhythmia. Epidemiological studies have assessed the association between particulate matter and arrhythmia through implantable cardioverter-defibrillator (ICD) discharge episodes, electrocardiography study, hospital admission, and mortality data.

There have been many recent narrative review studies concerning the association between exposure to air pollution and atrial fibrillation.^{440 441 442 443 444}

Several epidemiological studies have identified an association between acute exposure to fine particulate matter of less than 2.5 µm and 10 µm in aerodynamic diameter (PM_{2.5} and PM₁₀) and cardiovascular diseases.⁴⁴⁵ The effects of pollution on atrial fibrillation beyond the first several hours of exposure remain controversial.

Epidemiological studies evaluating the association between short-term exposure to air pollution and AF with two main approaches: analysing hospital admissions or enrolling subjects for whom continuous monitoring of the heart rhythm was possible (patients with implantable devices or subjects that underwent a Holter screening).⁴⁴⁶ Evidence of an association between AF onset and an increase in particulate matter < 2.5 µm in aerodynamic diameter (PM_{2.5}) concentration in the 2 h prior to AF has been demonstrated by Link et al (2013) and for the whole day by Liu et al. (2018) in a healthy community-dwelling sample of

⁴³⁹ Shahrbafe, M. A., Akbarzadeh, M. A., Tabary, M., et al (2021). Air Pollution and Cardiac Arrhythmias: A Comprehensive Review. *Current problems in cardiology*, 46(3), 100649

⁴⁴⁰ Gallo, E., Folino, F., Buja, G., et al. (2020). Daily Exposure to Air Pollution Particulate Matter Is Associated with Atrial Fibrillation in High-Risk Patients. *International journal of environmental research and public health*, 17(17), 6017.

⁴⁴¹ Zhang, S., Lu, W., Wei, Z., et al. (2021). Air Pollution and Cardiac Arrhythmias: From Epidemiological and Clinical Evidences to Cellular Electrophysiological Mechanisms. *Frontiers in cardiovascular medicine*, 8, 736151

⁴⁴² Wang, F., Ahat, X., Liang, Q., et al (2021). The relationship between exposure to PM_{2.5} and atrial fibrillation in older adults: A systematic review and meta-analysis. *The Science of the total environment*, 784, 147106.

⁴⁴³ Shahrbafe, M. A., Akbarzadeh, M. A., Tabary, M., et al (2021). Air Pollution and Cardiac Arrhythmias: A Comprehensive Review. *Current problems in cardiology*, 46(3), 100649

⁴⁴⁴ Chen, M., Zhao, J., Zhuo, C., et al. (2021). The Association Between Ambient Air Pollution and Atrial Fibrillation. *International heart journal*, 62(2), 290–7

⁴⁴⁵ Gallo, E., Folino, F., Buja, G., et al. (2020). Daily Exposure to Air Pollution Particulate Matter Is Associated with Atrial Fibrillation in High-Risk Patients. *International journal of environmental research and public health*, 17(17), 6017.

⁴⁴⁶ Gallo, E., Folino, F., Buja, G., et al. (2020). Daily Exposure to Air Pollution Particulate Matter Is Associated with Atrial Fibrillation in High-Risk Patients. *International journal of environmental research and public health*, 17(17), 6017.

nonsmokers, AF predictors were associated with increased levels of PM_{2.5} [Liao et al 2011], and lagged alterations in the ECG were found in association with PM_{2.5} in patients undergoing catheterisation [Zhang et al 2018].

Controlled exposure studies in both healthy volunteers and patients with coronary heart disease have not shown any pro-arrhythmic effect of air pollution, whereas a positive but not statistically significant association was found between PM_{2.5} exposure and hospitalisation for both AF and paroxysmal atrial fibrillation episodes. Some studies on hospitalisation rates for AF found an association with PM, whereas others highlighted a lack of association.

It is widely acknowledged that epidemiological studies have shown that exposure to air pollution could increase the risk of AF (Dahlquist et al.2020; Yang et al.,2020; Shin et al. 2019).⁴⁴⁷ A 2016 meta-analysis (Shao et al., 2016) including four articles (Rich et al., 2006; Link et al, 2013; Milojevic et al., 2014; Cakmak et al. 2014) found a positive correlation between PM 2.5 exposure and AF. One more recent meta-analysis (Pranata et al. 2020) including three articles (Kwon et al. 2019; Kim et al. 2019; Stockfelt et al. 2017) failed to confirm the association. the results were inconsistent in relation to whether exposure to PM_{2.5} can trigger AF (Link et al. 2013; Milojevic et al. 2014).

Although growing epidemiological evidence links air pollution and cardiac arrhythmias, suggesting a detrimental influence of air pollution on cardiac electrophysiological functionality., the proarrhythmic mechanisms underlying the air pollution-induced cardiac arrhythmias are not fully understood.⁴⁴⁸

Among several recent comprehensive review studies, **Zhang et al (2021)** outlined advances in air pollution-induced arrhythmias.⁴⁴⁹ Zhang et al determined that a significant association exists between PM exposure and the incidence of various arrhythmias. Atrial fibrillation is the most common arrhythmia induced by PM exposure. A nationwide cohort study concerning the proarrhythmic effects of long-term exposure to PM reported that 10 µg/m³ increments of PM_{2.5} were associated with a 17.9% increase of AF, and 10 µg/m³ increments of PM₁₀ was associated with a 3.4% increase (Kim et al 2019). A study from Canada demonstrated that long-term exposure to PM_{2.5} was associated with incident AF even at a very low concentrations (Shin et al 2019). A correlation was found between short-term PM exposure and increased risks of AF. An investigation based on patients with dual-chamber implantable cardioverter-defibrillators (ICDs) suggested significant effects of PM_{2.5} on triggering AF. The odds of AF increased by 26% for each 6 µg/m³ increase in PM_{2.5} in the 2 h prior to the onset of AF. For healthy individuals, Lee et al. (2019) demonstrated that short-term exposure to

⁴⁴⁷ Wang, F., Ahat, X., Liang, Q., et al (2021). The relationship between exposure to PM_{2.5} and atrial fibrillation in older adults: A systematic review and meta-analysis. *The Science of the total environment*, 784, 147106.

⁴⁴⁸ Zhang, S., Lu, W., Wei, Z., et al. (2021). Air Pollution and Cardiac Arrhythmias: From Epidemiological and Clinical Evidences to Cellular Electrophysiological Mechanisms. *Frontiers in cardiovascular medicine*, 8, 736151

⁴⁴⁹ Zhang, S., Lu, W., Wei, Z., et al. (2021). Air Pollution and Cardiac Arrhythmias: From Epidemiological and Clinical Evidences to Cellular Electrophysiological Mechanisms. *Frontiers in cardiovascular medicine*, 8, 736151

PM2.5 was associated with AF in the general population with no AF history. Similar findings were reported in other studies (Kwon et al 2019, Solimini et al 2017).

The interactive effects among pollutants have not been examined at the molecular and cellular levels, while epidemiological or exposure studies concerning individual air pollutant are needed.⁴⁵⁰ Existing studies have proved that some combinations of pollutants might enhance the toxicity of each other and lead to unexpected biological alterations; however, the corresponding cellular mechanisms remain unclear, with most basic medical research still focusing on a single factor, i.e., an individual pollutant or a specific component of PM. Epidemiological or exposure studies concerning a specific pollutant or PM component are relatively rare, which reinforces a mismatch of epidemiological evidence and mechanical findings at the cellular level.

In discussion, **Gallo et al (2020)** notes that It has been observed there is a significant association between AF and daily levels of both PM2.5 and PM10.⁴⁵¹ The first evidence of the role of air pollution in triggering AF was highlighted by Liao et al (2011). Acute exposure to PM2.5 was associated with predictors of AF with more complex P-wave morphology and PR duration in a sample of subjects without severe cardiac problems.

A recent study in China on patients who had cardiac implantable electronic devices showed an increased risk of AF onset in association with high levels of PM2.5 and PM10 [Liu et al 2018]. Two studies found an association between air pollution and cardiac arrhythmias' hospitalisations [Solimini et al 2017, Zheng et al 2018], and both recorded average air pollution concentrations exceeding WHO thresholds. Rich et al (2006), in a less polluted area, observed a positive (nonsignificant) increased risk between paroxysmal AF and PM2.5 in ICD implanted patients. Link et al (2013) found a significant association between AF and increased levels of PM2.5 in the 2 hours prior to the AF onset, only examining the highest quartile of PM values distribution, supporting the hypothesis that PM only increases the risk of arrhythmias at medium to high PM concentrations.

Some studies focused on AF hospitalisations did not find an association between increased PM concentration and risk of hospitalisation [Saifipour et al 2019, Kwon et al 2019, Bunch et al 2011]. In these studies, the outcome definition did not include people with asymptomatic AF, and the target population was the general population, not exclusively high-risk subjects. Indeed, patients implanted with ICDs, ICD-CRT, or pacemakers could be defined as high-risk, as they might be more susceptible to air pollution due to their underlying pathological condition.

⁴⁵⁰ Zhang, S., Lu, W., Wei, Z., et al. (2021). Air Pollution and Cardiac Arrhythmias: From Epidemiological and Clinical Evidences to Cellular Electrophysiological Mechanisms. *Frontiers in cardiovascular medicine*, 8, 736151

⁴⁵¹ Gallo, E., Folino, F., Buja, G., et al. (2020). Daily Exposure to Air Pollution Particulate Matter Is Associated with Atrial Fibrillation in High-Risk Patients. *International journal of environmental research and public health*, 17(17), 6017.

Shahrbaf et al (2021) also comprehensively reviewed recent evidence related to the association of air pollutant and arrhythmias.⁴⁵² The review determined that particulate matter (PM10, PM2.5, and ultrafine particles (UFP) and gaseous air pollutants exert adverse effects on cardiac rhythm. Short-term and long-term exposure to air pollutants can influence cardiac rhythm through oxidative stress, autonomic dysfunction, coagulation dysfunction and inflammation. Particulate matter, especially PM2.5, appears to have stronger association with arrhythmias than other air pollutants. However, evidence regarding the roles of gaseous pollutants on the development of cardiac arrhythmia are limited and contradictory.

The role of PM10 in the development of arrhythmia has been addressed in several studies.⁴⁵³ Link et al. (2013) suggested that PM10 were associated with increased risk of AF onset after a few hours following exposure in patients with ICDs. Liu et al. (2018) reported that a 10 mg/m³ increase in PM10 was associated with 2.7% increase in risk of AF. Wichmann et al. (1989) observed a 50% increase in hospital admission for cardiac arrhythmia after a 5 day exposure to air pollutants, especially particulate matter from smog.

Feng et al. (2019) also suggested that the risk of arrhythmias is associated with PM2.5 concentration. Pope et al. (2004) reported that long-term exposures to PM2.5 was strongly associated with cardiovascular mortality related to ischaemic heart disease, arrhythmia and cardiac arrest due to inflammation and autonomic dysfunction. Halonen et al. (2009) and Chen et al. (2015) observed high levels of PM2.5 were associated with arrhythmia admission at the same day. Ueda et al. (2009) found that high concentration of PM2.5 was associated with cardiac mortality resulting from acute myocardial infarction, and cardiac arrhythmia in younger patients. Berger et al. (2006) demonstrated that PM2.5 could increase the risk of supraventricular and ventricular arrhythmias in all age groups. Ebel et al. (2005) suggested that the risk of supraventricular arrhythmia was related to ambient and non-ambient PM2.5.

Riediker et al. (2014) concluded that PM2.5 may cause pathophysiological changes involving inflammation, coagulation, and cardiac rhythm. Chiu et al (2013) showed that the risk of cardiac arrhythmia emergency visits increased after short term exposure to PM2.5 on both warm and cool days. Liu et al. (2018) showed that a 10 mg/m³ increase in the concentration of PM2.5 was associated with 3.8% increase in risk of atrial fibrillation.

Some studies also document effects of ultrafine particles (UFP) on arrhythmia.⁴⁵⁴ Berger et al. (2006) found that 2-5 days exposure to UFP might be associated with the episodes of supraventricular arrhythmia. Folino et al. (2009) suggested that exposure to ultrafine particles was associated with arrhythmia resulting from autonomic dysfunction in patients with a history of myocardial infarction; and the risk of arrhythmia was related to particulate matter concentration.

⁴⁵² Shahrbaf MA, Akbarzadeh MA, Tabary M, et al (2021). Air pollution and cardiac arrhythmias: a comprehensive review. *Curr Probl Cardiol*, 46(3): 100649.

⁴⁵³ Shahrbaf MA, Akbarzadeh MA, Tabary M, et al (2021). Air pollution and cardiac arrhythmias: a comprehensive review. *Curr Probl Cardiol*, 46(3): 100649.

⁴⁵⁴ Shahrbaf MA, Akbarzadeh MA, Tabary M, et al (2021). Air pollution and cardiac arrhythmias: a comprehensive review. *Curr Probl Cardiol*, 46(3): 100649

Scientific evidence for the roles of gaseous pollutants in the development of arrhythmias are limited and contradictory, and there appears to be relatively little data specifically dealing with AF as an outcome.⁴⁵⁵ Tsai et al. (2009) demonstrated a strong association between the concentration of SO₂ in warm days (>23°C) and NO₂ and O₃ in both warm and cool days with emergency visits for arrhythmia in a case-crossover study from Taiwan. Santos et al (2008) showed a 1.5 ppm increase in CO and 49,5 mg/m³ increase in NO₂ was associated with 12.3% and 10.4% increase in arrhythmia emergency visit. Hoek et al.(2001) concluded that the risk of life-threatening arrhythmias increased after exposure to SO₂, CO, and NO₂. Liu et al. (2018) demonstrated no relation between NO₂, SO₂, CO, and O₃ exposure with the incidence of atrial fibrillation. Considering the conflicting results, Shahrbaaf et al (2021) concluded that additional studies are needed to confirm a role of gaseous pollutants in cardiac arrhythmia.

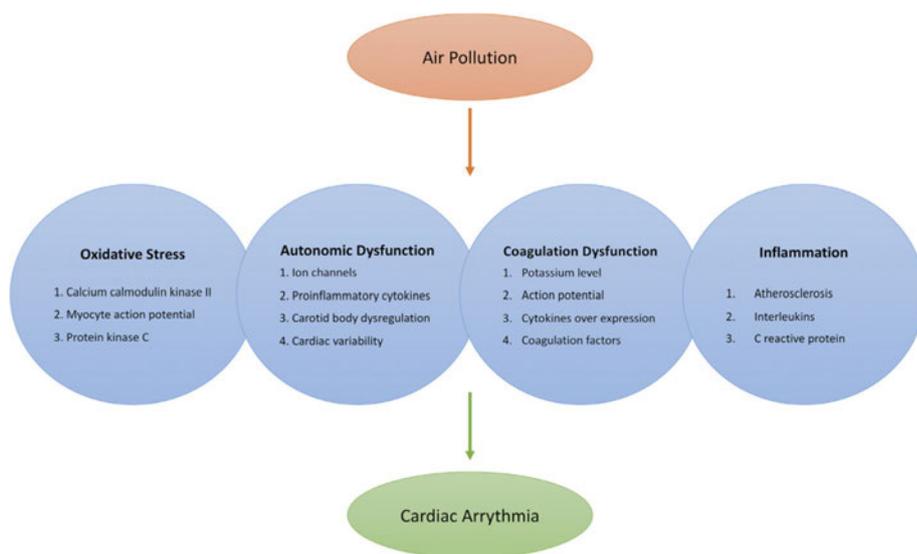
In another review study, **Chen et al. (2021)** note that although recent studies have shown that air pollution and air PM are associated with AF, the underlying mechanisms remain unknown.⁴⁵⁶ There are several possible reasons for this association. acute autonomic nervous system dysfunction has been demonstrated in air pollution study which could lead to decreased heart rate variability; AF may be triggered by autonomic imbalance. This mechanism was thought to be the most plausible reason for the short-term effect. exposure to air PM can elicit an acute-phase response and an increase right heart pressure. irritants can cross the pulmonary epithelium directly into circulation, which may affect blood coagulability.

Acute exacerbations of pulmonary diseases such as COPD during short-term exposure to air pollutants might potentiate arrhythmia risk. These pathophysiological changes provide a rationale for the hypothesis that short-term exposure to air pollutants can trigger AF in patients with AF history or those who are at high risk. An increasing body of evidence indicates that air pollutants involves several pathophysiology processes of AF such as inflammation, oxidative stress, and autonomic imbalance such that long-term exposures to air pollutants might increase the risk of AF.

⁴⁵⁵ Shahrbaaf MA, Akbarzadeh MA, Tabary M, et al (2021). Air pollution and cardiac arrhythmias: a comprehensive review. *Curr Probl Cardiol*, 46(3): 100649

⁴⁵⁶ Chen, M., Zhao, J., Zhuo, C., et al. (2021). The Association Between Ambient Air Pollution and Atrial Fibrillation. *International heart journal*, 62(2), 290–7

FIGURE 58 POTENTIAL MECHANISMS RELATED TO ARRHYTHMIA AFTER EXPOSURE TO AIR POLLUTION



Source: Shahrbaaf et al (2021)

Meta-analyses

Several recent meta-analyses have been published concerning air pollution and AF, with largely congruent results,^{457 458 459} although the findings of Pranata et al are somewhat divergent.⁴⁶⁰

Yue et al (2021) evaluated studies concerning the correlation between exposure to air pollution and AF in a systematic review of studies published to July 2020 to explore the association between air pollutants and AF in the general population.⁴⁶¹ According to study design, outcomes were classified into "short-term-exposure group" and "long-term-exposure group" for each pollutant. I2 statistics and Q-test were used to examine statistical heterogeneity, and sensitivity analysis to exclude the heterogeneous study. Fixed or random-effect models were used to combine the effects. The final result was presented as the OR and 95CI of AF prevalence for every 10 µg/m³ increase in concentration of PM2.5 and PM10; 10 ppb increase in the concentration of SO₂, NO₂, O₃; and 1 ppm increase in the CO concentration.

⁴⁵⁷ Yue, C., Yang, F., Li, F., & Chen, Y. (2021). Association between air pollutants and atrial fibrillation in general population: A systematic review and meta-analysis. *Ecotoxicology and environmental safety*, 208, 111508.

⁴⁵⁸ Chen, M., Zhao, J., Zhuo, C., et al. (2021). The Association Between Ambient Air Pollution and Atrial Fibrillation. *International heart journal*, 62(2), 290–7.

⁴⁵⁹ Wang, F., Ahat, X., Liang, Q., et al (2021). The relationship between exposure to PM2.5 and atrial fibrillation in older adults: A systematic review and meta-analysis. *The Science of the total environment*, 784, 147106.

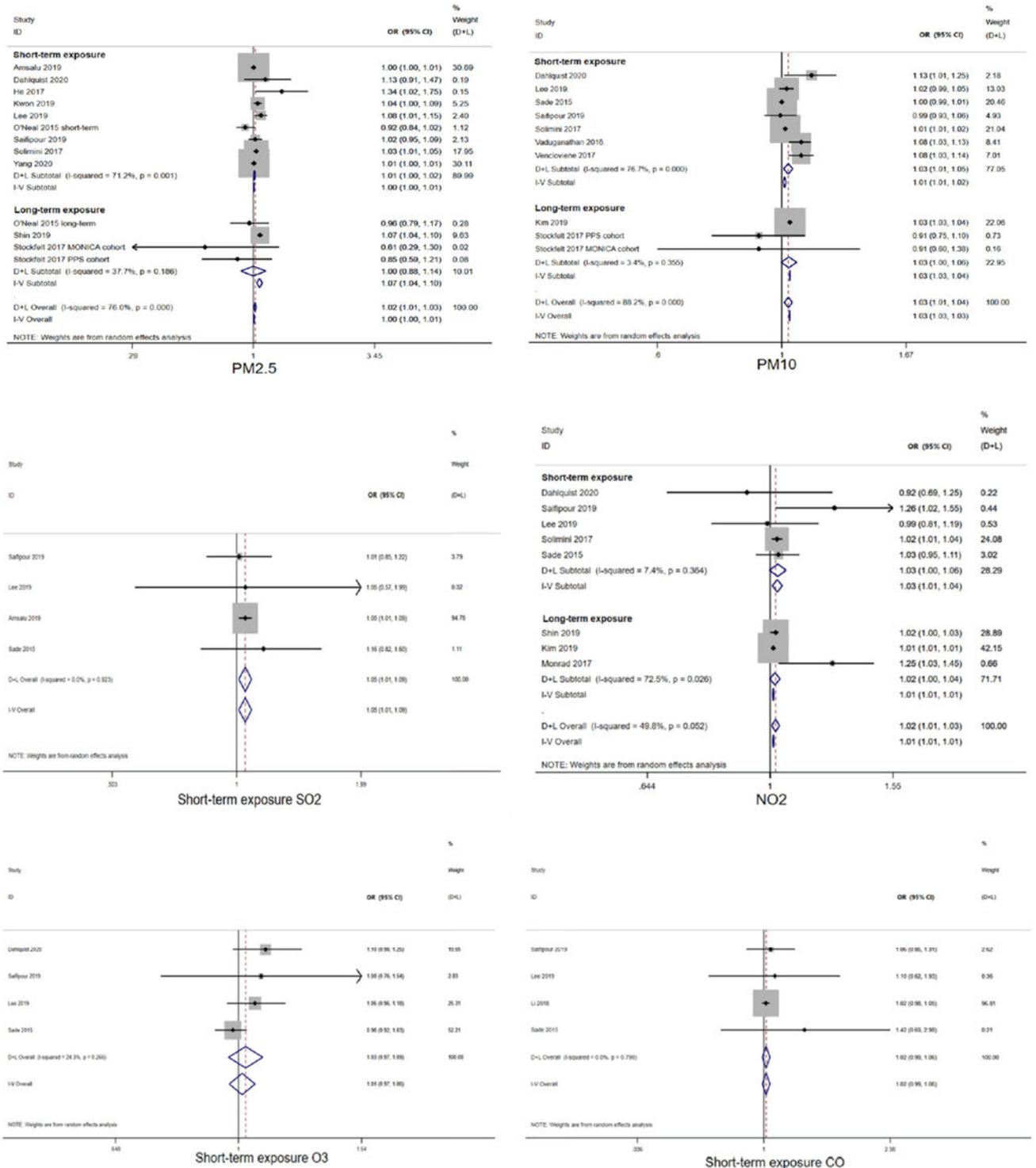
⁴⁶⁰ Pranata, R., Vania, R., Tondas, A.E., Setianto, B., Santoso, A., 2020. A time-to-event analysis on air pollutants with the risk of cardiovascular disease and mortality: a systematic review and meta-analysis of 84 cohort studies. *J. Evid. Based Med.* 13, 102–15.

⁴⁶¹ Yue, C., Yang, F., Li, F., & Chen, Y. (2021). Association between air pollutants and atrial fibrillation in general population: A systematic review and meta-analysis. *Ecotoxicology and environmental safety*, 208, 111508.

The meta-analysis included 18 studies from nine countries, involving 479,508 AF events. The combined OR of pollutants indicated that long-and short-term exposure had an adverse effect upon AF prevalence

In relation to *short-term* exposure effects, for each increment of 10 $\mu\text{g}/\text{m}^3$ in PM_{2.5} concentration, the combined OR of AF prevalence was 1.01 (95CI 1.00-1.02), for PM₁₀ was 1.03 (95CI 1.01-1.05). The OR for AF prevalence in relation to a 10 ppb increment in concentration of SO₂ was 1.05 (95CI 1.01-1.09), for a 10 ppb increment in NO₂ was 1.03 (95CI 1.01-1.04), a 10 ppb increment in NO₂ was 1.01 (95CI 0.97-1.06), and for a 1 ppm increase of CO concentration was 1.02 (95CI 0.99-1.06).

FIGURE 59 ASSOCIATION BETWEEN AIR POLLUTANTS AND AF PREVALENCE IN SHORT- OR LONG-TERM EXPOSURE OF PM10, PM2.5, SO2, NO2, O3 AND CO. OR FOR INCREASE OF 10 MG/M3 OF PM2.5 AND PM10, 10 PPB OF SO2, NO2, O3, AND 1 PPM OF CO.

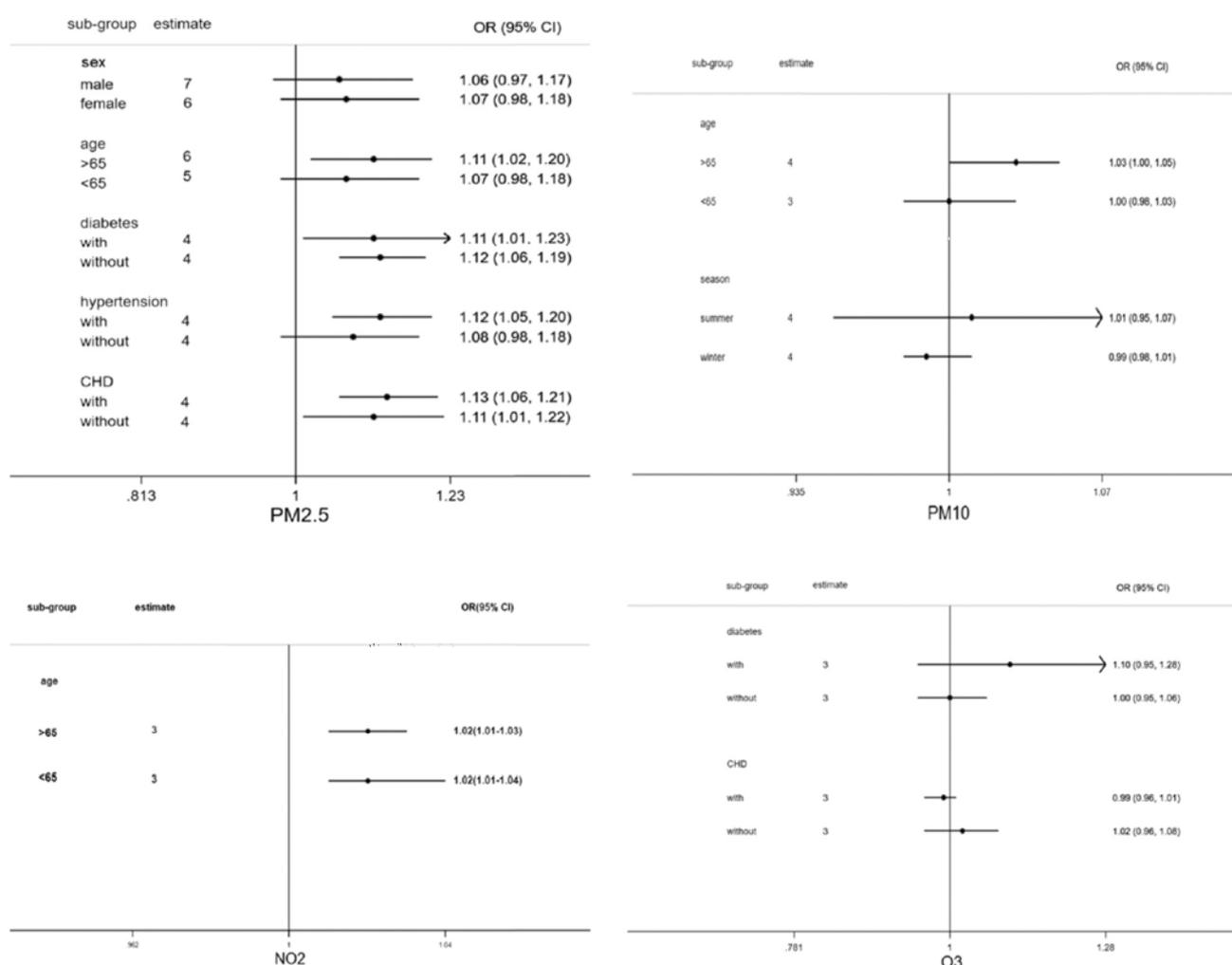


In relation to long-term-exposure effects for each increment of 10 $\mu\text{g}/\text{m}^3$ in PM2.5 concentration; the combined OR of AF prevalence was 1.07 (95CI 1.04-1.10) and that for PM10 was 1.03 (95CI 1.03-1.04). For a 10 ppb increment in NO2 concentration, the OR was 1.02 (95CI 1.00-1.04).

For PM2.5 exposure, subgroup analyses revealed that people aged >65 years (OR 1.11, 95CI 1.02–1.20) were more likely to develop AF than those aged <65 years (OR 1.07, 95CI 0.98–1.18). AF was more common in patients with hypertension (1.12, 95CI 1.05–1.20) than those without hypertension (OR 1.08, 95CI 0.98–1.18). There was little substantial difference in risk in relation to sex, DM and coronary heart disease.

For PM10 exposure, subgroup analyses revealed that people aged >65 years (OR 1.03, 95CI 1.00–1.05) were more likely to develop AF than those aged <65 years (OR 1.00, 95CI 0.98–1.03). Age > 65 years, 1.02 (95CI 1.01–1.03) vs <65 years (1.02, 95CI 1.01–1.04)) did not have significant effect on AF induced by NO2 exposure.

FIGURE 60 ASSOCIATION BETWEEN AIR POLLUTANTS AND AF PREVALENCE IN SUBGROUP ANALYSES OF PM10, PM2.5, NO2, AND O3; OR FOR INCREASE OF 10 MG/M3 OF PM2.5 AND PM10, 10 PPB OF NO2 AND O3



Yue et al (2021), Fig 3

The meta-analysis affirmed that all air pollutants exposure had an adverse effect on AF prevalence in the general population.

The meta-analysis showed positive associations between all pollutants and AF prevalence in the general population.⁴⁶² Although the effect of unit concentration increase was slight, when the pollutant concentration is very high, which in heavily polluted areas maybe a few times more than the unit concentration, the corresponding OR value is greatly increased. All pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, O₃, CO) were associated with AF after short-term or long-term exposure.

Chen et al (2021) also undertook a systematic review and meta-analysis to assess the short- and long-term effects of ambient air pollution on AF.⁴⁶³ The analysis included all studies up to October 2019 and used random-effects models to estimate the excess risk percentage (ER%) and confidence intervals for particulate matter with diameter ≤ 2.5 (PM_{2.5}) and ≤ 10 μm (PM₁₀), sulphur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), and carbon monoxide (CO). Results were analysed by subgroups according to location, age, outcome, and sex.

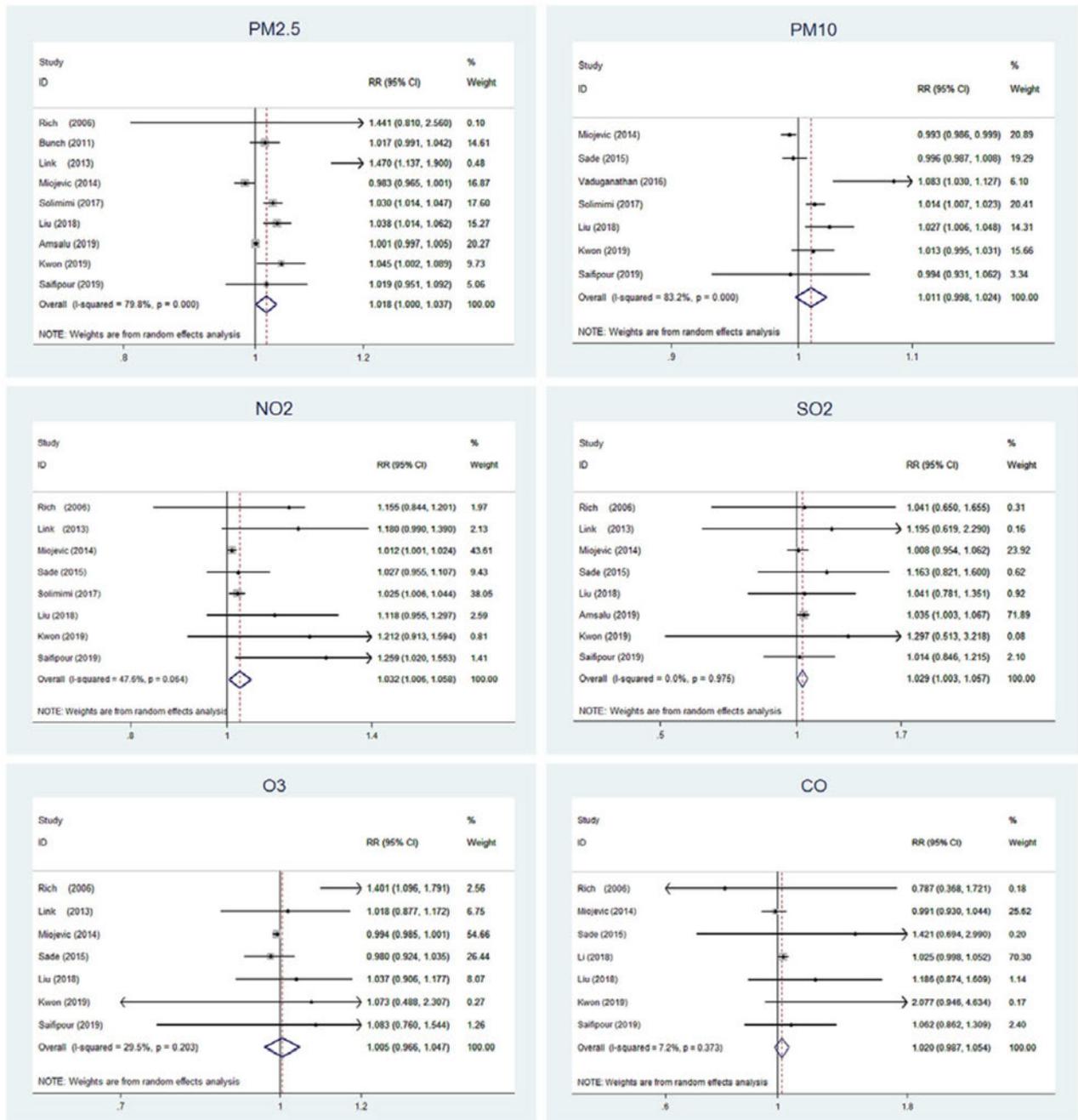
18 studies were included in the meta-analysis: 5 evaluated long-term effects, 12 evaluated short-term effects, and 1 both long- and short-term effects. Among studies examining the short-term impact of air pollutants on AF, nine used a case-crossover approach, and four used a time-series analysis. Daily mean pollution levels reported in short-term studies varied widely for PM_{2.5} (range 8.4-91.4 $\mu\text{g}/\text{m}^3$), PM₁₀ (20.0-121.0 $\mu\text{g}/\text{m}^3$), NO₂ (11.7-28.4 ppb), SO₂ (1.1-8.7 ppb), O₃ (20.7-72.2 ppb), and CO (160-1088 ppb).

A random-effects summary estimate of the short-term effect of air pollutant on AF. ER per 10 $\mu\text{g}/\text{m}^3$ increase of pollutants was 1.8% (0%-3.7%) for PM_{2.5} and 1.1% (-0.2%-2.4%) for PM₁₀. These studies were significantly heterogeneous; the degree of I² was large in pooled estimates for PM_{2.5} (79.8%) and PM₁₀ (83.2%). The excess risk of AF per 10 ppb increment of gaseous pollutions was 3.2% (0.6%-5.8%) for NO₂, 2.9% (0.3%-5.7%) for SO₂, 0.5% (-3.4%-4.7%) for O₃, and 2.0% (-1.3%-5.4%) for CO per 1000 ppb change. Subgroup analysis showed the short-term effect was significantly different by region, sex, and age.

⁴⁶² Yue, C., Yang, F., Li, F., & Chen, Y. (2021). Association between air pollutants and atrial fibrillation in general population: A systematic review and meta-analysis. *Ecotoxicology and environmental safety*, 208, 111508.

⁴⁶³ Chen, M., Zhao, J., Zhuo, C., et al. (2021). The Association Between Ambient Air Pollution and Atrial Fibrillation. *International heart journal*, 62(2), 290–7.

FIGURE 61 SHORT-TERM EFFECT OF AMBIENT AIR POLLUTION (PM2.5, PM10, SO2, O3, NO2, AND CO) ON AF. RRS ARE FOR INCREASE OF 10 MG/M3 OF PM2.5 AND PM10; 10 PPB OF SO2, NO2, AND O3; AND 1000 PPB OF CO.



Chen et al (2021), Fig

The evidence of long-term association between air pollutants and AF was limited; six studies were included in the meta-analysis. The range of daily mean pollution levels in long-term studies were 1.45-25 $\mu\text{g}/\text{m}^3$ for PM2.5, 13-49.1 $\mu\text{g}/\text{m}^3$ for PM10, 8.08-34 ppb for NO2, 5.2-5.5 ppb for SO2, 18.0- 45.8 ppb for O3, and 560-600 ppb for CO. For long-term effects, ER per 10 $\mu\text{g}/\text{m}^3$ increase of pollutants was 11.6% (3.1%-20.7%) for PM2.5 and 3.4% (3.2%-3.5%) for PM10; per 10 ppb increment of gaseous pollutions was 1.7% (0.1%-3.3%) for NO2, 0.5% (0.4%-0.7%) for SO2, 0.7% (-7.3%-9.4%) for O3, and 2.0% (1.3%-2.2%) for CO per 1000 ppb change. In the long term, except for O3, a statistically significant association was noted between AF incidence and all pollutants.

The meta-analysis suggests that short-term exposure to part of pollutants (PM2.5, SO2, and NO2) increases AF attack, and that long-term exposure to air pollution can significantly contribute to the incidence of AF in a healthy population.

Fine particle matter (PM2.5) is recognised as atrial fibrillation risk factor, especially for older adults. However, studies on the relationship between PM2.5 and AF are inconsistent. **Wang et al (2021)** conducted a systematic review and meta-analysis to explore the relationship between exposure to PM2.5 and incidence of AF in older adults.⁴⁶⁴

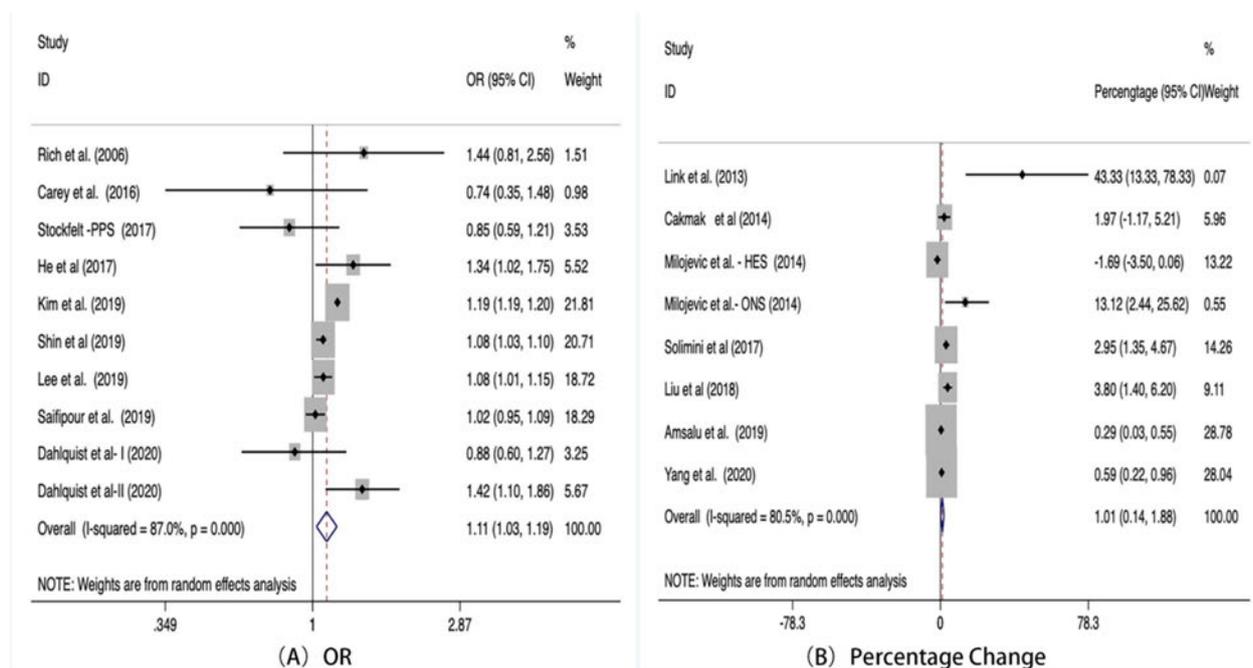
A total of 16 observational studies were included, involving 10,580,394 participants (average age > 50 years). The results confirmed that PM2.5 exposure was significantly related to increased incidence of AF in older adults. Both the pooled OR and %-change value were higher in areas with higher levels of PM2.5 ($\geq 25 \mu\text{g}/\text{m}^3$).

An association was found between exposure to PM2.5 (per $10 \mu\text{g}/\text{m}^3$ increase) and AF in older adults, with the corresponding pooled OR (1.11, 95CI 1.03-1.19; n=9 studies) and pooled %-change (1.01%, 95CI 0.14%-1.88%; n= 7 studies).

A stronger association between PM2.5 and AF was evident in Asia ($\geq 25 \mu\text{g}/\text{m}^3$). Higher study quality (score ≥ 7) showed a stronger correlation in older adults. The risk of AF for PM2.5 exposure $\geq 25 \mu\text{g}/\text{m}^3$ (OR 1.12, 95CI 1.02–1.24) was higher than in the group with exposure $< 25 \mu\text{g}/\text{m}^3$ (1.08, 95CI 0.91–1.27). The %-change value also indicated PM2.5 $\geq 25 \mu\text{g}/\text{m}^3$ were higher (0.64%, 95CI 0.01%–1.26%) than PM2.5 $< 25 \mu\text{g}/\text{m}^3$ (2.62%, 95CI –1.24%–6.47%).

⁴⁶⁴ Wang, F., Ahat, X., Liang, Q., et al (2021). The relationship between exposure to PM2.5 and atrial fibrillation in older adults: A systematic review and meta-analysis. *The Science of the total environment*, 784, 147106.

FIGURE 62 FOREST PLOT OF META-ANALYSIS: PER 10 MG/M3 INCREASE OF PM2.5 WAS ASSOCIATED WITH ATRIAL FIBRILLATION: (A) OR (B) PERCENTAGE CHANGE.



Wang et al (2021), Fig 2

Exposure to PM2.5 increased the risk of AF in older adults, which is consistent with most analytical studies (Lee et al. 2019; Shin et al. 2019).

Pranata et al (2020) performed a comprehensive analysis of the time-to-event for different types of air pollutants on cardiovascular disease (CVD) events based on cohort studies.⁴⁶⁵

There were 28 215 394 subjects from 84 cohorts. Increased PM10 was associated with heart failure [HR 1.25), all-cause mortality [HR 1.16), CVD mortality [HR 1.17), and IHD mortality [HR 1.03) but not with AF. Increased NO2 was associated with increased composite CVD [HR 1.15) and **atrial fibrillation [HR 1.01, 95CI 1.01-1.02]**, among other cardiovascular diseases.

Cohort studies

Halldorsdottir et al (2022) studied the association between traffic-related ambient air pollution in the Reykjavik capital area and emergency hospital visits for heart diseases and particularly atrial fibrillation and flutter.⁴⁶⁶

A multivariate time-stratified case-crossover design was used to study the association. Cases were those patients aged 18 years or older living in Reykjavik area during the study period, 2006-2017, who made emergency visits to a University Hospital for heart diseases. the

⁴⁶⁵ Pranata, R., Vania, R., Tondas, A.E., Setianto, B., Santoso, A., 2020. A time-to-event analysis on air pollutants with the risk of cardiovascular disease and mortality: a systematic review and meta-analysis of 84 cohort studies. *J. Evid. Based Med.* 13, 102–15.

⁴⁶⁶ Halldorsdottir, S., Finnbjornsdottir, R. G., Elvarsson, B. T., et al (2022). Ambient nitrogen dioxide is associated with emergency hospital visits for atrial fibrillation: a population-based case-crossover study in Reykjavik, Iceland. *Environmental health : a global access science source*, 21(1), 2.

primary discharge diagnoses were registered according to ICD-10). The pollutants studied were NO₂, PM₁₀, PM_{2.5}, and SO₂, with adjustment for H₂S, temperature, and relative humidity. The 24-h mean of pollutants was used with lag 0 to lag 4.

During the study period 9536 cases of AF were identified. 24-h mean NO₂ was 20.7 µg/m³. Each 10 µg/m³ increase in NO₂ was associated with an increased risk of AF on the same day, OR 1.030 (95CI 1.011-1.049). Females were at higher risk for AF, OR 1.051 (95CI 1.019-1.083) at lag 0, and OR 1.050 (95CI 1.019-1.083) at lag 1. Females aged < 71 years had a higher risk for AF, OR 1.077 (95CI 1.025-1.131) at lag 0. Significant associations were found for other pollutants and emergency hospital visits, but were weaker and did not show a discernible pattern.

In this study, short-term increase in NO₂ concentrations was associated with heart diseases, particularly AF. The associations were stronger in females, and among females at younger age.

Gallo et al. (2020) exemplified the association between daily exposure to air pollution particulate matter and risk of AF in high-risk patients.⁴⁶⁷ 145 patients with implantable cardioverter-defibrillators (ICDs), cardiac resynchronisation therapy defibrillators (ICD-CRT), or pacemakers were enrolled in this multicentre prospective study. Daily levels of PM_{2.5} and PM₁₀ were collected from monitoring stations within 20 km of the patient's residence.

A multivariable logistic model assessed the effects of the daily level of PM_{2.5} and PM₁₀ on the risk of AF. Models were adjusted for three groups of variables: environmental variables, i.e., the median daily levels of humidity, pressure, and temperature; clinical variables, i.e., beta-blocker therapy and antiarrhythmics drugs; demographical variables, (age and sex). The association between pollutants and AF was flexibly modelled with a restricted cubic spline function to allow for potential nonlinear relationships.

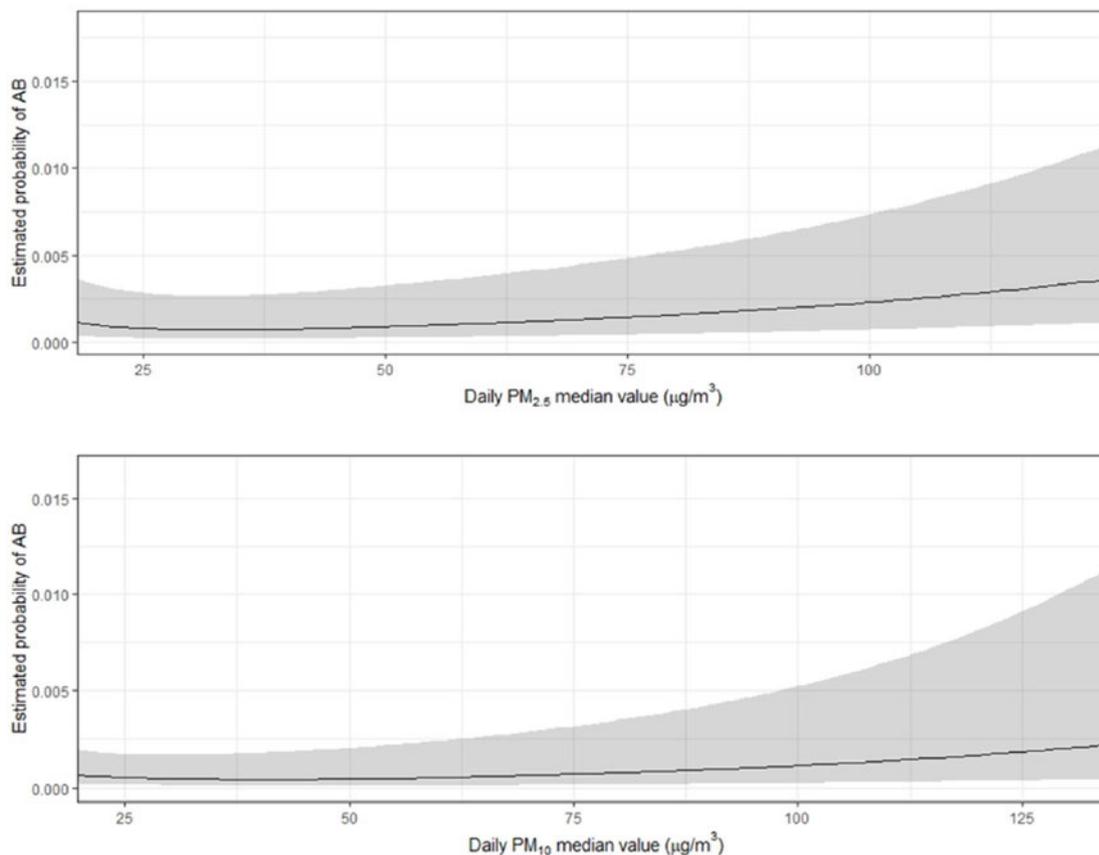
A total of 145 patients living in 137 municipalities of the Veneto region were included in the cohort. PM_{2.5} exceeded the WHO threshold of 25 g/m³ for 26% of days, whereas PM₁₀ was detected above the threshold of 50 g/m³ for 18% of days during follow-up. Overall, 26 episodes of AF were observed. The odds ratios of the models indicated a significant association between AF and daily levels of both PM_{2.5} and PM₁₀.

Univariate logistic model for pollutants modelled with a restricted cubic spline; logistic model with Firth's correction adjusted for antiarrhythmic and -blockers therapy, age, sex, median daily pressure, temperature and humidity. The risk of AF onset increased nonlinearly for concentrations above the WHO thresholds. PM_{2.5} and PM₁₀ seem to increase the AF risk, mostly at higher concentrations

⁴⁶⁷ Gallo, E., Folino, F., Buja, G., et al. (2020). Daily Exposure to Air Pollution Particulate Matter Is Associated with Atrial Fibrillation in High-Risk Patients. *International journal of environmental research and public health*, 17(17), 6017.
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An association was found between AF and daily levels of PM_{2.5} of 75 µg/m³ (OR 1.8, 95CI 1.34-2.40) and PM₁₀ of 100 µg/m³ (OR 2.48, 95CI 1.44-4.28), an increase of 50 µg/m³ above the WHO threshold.

FIGURE 63 ESTIMATED DAILY PROBABILITY OF ATRIAL BURDEN (AB) AT DIFFERENT CONCENTRATIONS OF PARTICULATE MATTERS OF LESS THAN 2.5 M (PM_{2.5}) AND LESS THAN 10 M (PM₁₀) IN AERODYNAMIC DIAMETER



Gallo et al (2020), Fig 1

A Firth Logistic Regression model was used to evaluate the association between AF and daily exposure to PM_{2.5} and PM₁₀. Exposure levels to PM_{2.5} and PM₁₀ were moderate, being above the WHO PM_{2.5} and PM₁₀ thresholds of 25 µg/m³ and 50 µg/m³, respectively, on 26% and 18% of follow-up days.

TABLE 31 FIRTH'S LOGISTIC REGRESSION WITH DELAYED EFFECTS IN TIME ANALYSED WITH A DISTRIBUTED LAG MODEL

Pollutant	Effect	OR (95% CI) Lag 0	OR (95% CI) Lag 1	OR (95% CI) Lag 2
PM _{2.5}	75 vs. 25	3.46 (1.36–8.74)	1.42 (0.56–3.59)	1.21 (0.70–2.10)
PM ₁₀	100 vs. 50	3.74 (2.52–5.55)	1.48 (0.90–2.42)	0.69 (0.44–1.06)

Gallo et al (2020), Table 4

Gallo et al showed that daily exposure to moderate PM2.5 and PM10 levels was associated with AF in patients who are not prone to AF. The results are in line with other epidemiological and observational investigations that found an association between PM exposure and AF.

Case-control studies

Liu et al (2018) explored the potential relationship between short-term air pollution exposure and occurrence of AF.⁴⁶⁸

A case-crossover design was used to investigate the effect of pollutants on AF occurrence among 100 patients from 2013 to 2014. The air pollutants included ambient particulate matter less than 2.5 µm in aerodynamic diameter (PM2.5), particulate matter less than 10 µm in aerodynamic diameter (PM10), nitrogen dioxide (NO2), sulphur dioxide (SO2), carbon monoxide (CO), and ozone (O3). Participants with cardiac implantable electronic devices implanted were followed-up to December 31, 2014.

A 10 µg/m³ increase of PM2.5 and PM10 was associated with 3.8% (95CI 1.4-6.2) increase in the risk of AF. A 10 µg/m³ increase of PM10 was associated with a 2.7% (95CI 0.6-4.8) increase in the risk of AF. No statistically significant association was noted with SO2, NO2, CO, and O3.

In this study, short-term exposure to particular matter, both PM2.5 and PM10 was associated with an increased risk of AF.

Summary and conclusions

Recent studies suggest that the exposure to air pollutants may increase the prevalence of AF.

Particulate matter (PM10, PM2.5, and ultrafine particles) and gaseous air pollutants can exert undesirable effects on cardiac rhythms (Shahrbaf et al (2021). Zhang et al (2021) suggests that AF is the most common arrhythmia induced by particulate matter exposure.

As reported by Gallo et al (2020), evidence of an association between AF onset and increases in PM2.5 concentration in 2 hours prior to AF has been demonstrated by Link et al (2013) and for the whole day by Liu et al. (2018) in a healthy community-dwelling sample of nonsmokers, AF predictors were associated with increased levels of PM2.5 [Liao et al 2011], and lagged alterations in ECG were found in association with PM2.5 in patients undergoing catheterisation [Zhang et al 2018].

Controlled exposure studies in healthy volunteers and patients with coronary heart disease have not shown any pro-arrhythmic effect of air pollution, whereas positive associations have been found between PM2.5 exposure and hospitalisation for AF and paroxysmal AF episodes. Some studies on hospitalisation rates for AF found an association with PM, whereas other found no association.

⁴⁶⁸ Liu X, Kong D, Liu Y, et al. (2018). Effects of the short-term exposure to ambient air pollution on atrial fibrillation. *Pacing Clin Electrophysiol*; 41: 1441–6.
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Although growing epidemiological evidence links air pollution and cardiac arrhythmias, suggesting a detrimental influence of air pollution on cardiac electrophysiological functionality, the proarrhythmic mechanisms underlying the air pollution-induced cardiac arrhythmias are not fully understood (Zhang et al 2021). Short- and long-term exposure to air pollutants can influence cardiac rhythm through oxidative stress, autonomic dysfunction, coagulation dysfunction, and inflammation. It seems that particulate matters, especially PM_{2.5} have stronger association with arrhythmias than other air pollutants.

Wang et al (2021) affirms that a growing body of epidemiological evidence shows that exposure to air pollution can increase the risk of AF. A meta-analysis (Shao et al 2016) including four articles found a positive correlation between PM_{2.5} exposure and AF. Another meta-analysis (Pranata et al. 2020) including three articles failed to confirm the association. Whether exposure to PM_{2.5} can trigger AF, the results were inconsistent.

Shahrbarf et al (2021) notes that particulate matter, especially PM_{2.5}, appears to have stronger association with arrhythmias than other air pollutants, but evidence regarding the roles of gaseous pollutants on the development of cardiac arrhythmia are limited and contradictory. Scientific evidence for the roles of gaseous pollutants in the development of arrhythmias are limited and contradictory, and there appears to be relatively little data specifically dealing with AF as an outcome.

A more recent review and meta-analysis (Yue et al 2021), with 18 studies from nine countries involving 479,508 AF events, indicated that all air pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, O₃, CO) were associated with AF prevalence after short-term or long-term exposure in the general population. There was a short-term exposure effect, for each increment of 10 µg/m³ in PM_{2.5} concentration, the combined OR of AF prevalence was 1.01 (95CI 1.00-1.02), for PM₁₀ was 1.03 (95CI 1.01-1.05). For a 10 ppb increment in the concentration of SO₂, NO₂, and O₃ was 1.05 (95CI 1.01-1.09), 1.03 (95CI 1.01-1.04), and 1.01 (95CI 0.97-1.06), respectively, for a 1 ppm increase of CO concentration was 1.02 (95CI 0.99-1.06).

There was also a long term exposure effect for each increment of 10 µg/m³ in the PM_{2.5} concentration; the combined OR of AF prevalence was 1.07 (95CI 1.04-1.10) and for PM₁₀ was 1.03 (95CI 1.03-1.04) For a 10 ppb increment in the NO₂ concentration was 1.02 (95CI 1.00-1.04).

Although the effect of unit concentration increase was slight, when the pollutant concentration is very high, which in heavily polluted areas maybe several times more than the unit concentration, the corresponding OR value was greatly increased.

Another meta-analysis by Chen et al (2021) indicated that short-term change in ambient air pollutions (PM_{2.5}, NO₂, and SO₂) is associated with AF attack within days in patients with AF history or those who are considered high risk. In the long term, all pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, and CO) were associated with AF incidence in healthy population, except for O₃. There was a trend that PM₁₀ increased the risk of AF, but was not statistically significant.

in another meta-analysis with 16 articles, Wang et al (2021) evaluated exposure to PM_{2.5} increased the risk of AF in older adults. Both the pooled OR and %-change value were higher in areas with higher levels of PM_{2.5} ($\geq 25 \mu\text{g}/\text{m}^3$). **an** association was found between exposure to PM_{2.5} (per $10 \mu\text{g}/\text{m}^3$ increase) and AF in older adults, with the corresponding pooled OR (1.11, 95CI 1.03-1.19; n=9 studies) and pooled %-change (1.01%, 95CI 0.14%-1.88%; n= 7 studies). The evidence of an effect of long-term association between air pollutants and AF was more limited

In another meta-analysis of cohort studies (Pranata et al 2020), the association of PM_{2.5} with AF became significant after removal of a study. Increased NO₂ was marginally associated with AF risk [HR 1.01, 95CI 1.01, 1.02].

Recent analytical studies tend to be supportive of an association between air pollution and risk of AF, but there is little consistency in risk estimates in relation to concentration or duration of exposure to specific pollutants.

Halldorsdottir et al (2022) showed that short-term increase in ambient nitrogen dioxide is associated with emergency hospital visits for AF in a population-based case-crossover study in Iceland. During the study period 9536 cases of AF were identified. Each $10 \mu\text{g}/\text{m}^3$ increase in NO₂ was associated with increased risk of AF on the same day, OR 1.030 (95CI 1.011-1.049).

A case-crossover study investigated short term effect of pollutants on AF in 100 patients (Liu et al 2018). A $10 \mu\text{g}/\text{m}^3$ increase of PM_{2.5} was associated with 3.8% (95CI 1.4-6.2) increase in AF risk. A $10 \mu\text{g}/\text{m}^3$ increase of PM₁₀ was associated with a 2.7% (95CI 0.6-4.8) increase in AF risk. No significant association was noted with SO₂, NO₂, CO, O₃.

Gallo et al. (2020) exemplified the association of daily exposure to PM and risk of AF in 145 high-risk patients with implantable cardioverter-defibrillators (ICDs), cardiac resynchronisation therapy defibrillators (ICD-CRT), or pacemakers. PM_{2.5} exceeded WHO threshold of $25 \mu\text{g}/\text{m}^3$ for 26% of days, PM₁₀ $> 50 \mu\text{g}/\text{m}^3$ WHO threshold for 18% of days during follow-up. 26 episodes of AF were observed. PM_{2.5} and PM₁₀ increased AF risk, mostly at higher concentrations. An association was found between AF and daily levels of PM_{2.5} of $75 \mu\text{g}/\text{m}^3$ (OR 1.8, 95CI 1.34-2.40) and PM₁₀ of $100 \mu\text{g}/\text{m}^3$ (OR 2.48, 95CI 1.44-4.28), an increase of $50 \mu\text{g}/\text{m}^3$ above WHO threshold.

A nationwide cohort study of proarrhythmic effects of long-term exposure to PM reported that $10 \mu\text{g}/\text{m}^3$ increments of PM_{2.5} were associated with a 17.9% increase of AF, and $10 \mu\text{g}/\text{m}^3$ increments of PM₁₀ was associated with a 3.4% increase (Kim et al 2019). A study from Canada demonstrated that long-term exposure to PM_{2.5} was associated with incident AF even at a very low concentrations (Shin et al 2019). An investigation based on patients with dual-chamber implantable cardioverter-defibrillators (ICDs) suggested significant effects of PM_{2.5} on triggering AF. The odds of AF increased by 26% for each $6 \mu\text{g}/\text{m}^3$ increase in PM_{2.5} in the 2 h prior to the onset of AF. For healthy individuals, Lee et al. (2019) demonstrated that short-term exposure to PM_{2.5} was associated with AF in the general population with no AF history. Similar findings were reported in other studies (Kwon et al 2019, Solimini et al 2017).

The interactive effects among pollutants have not been examined at the molecular and cellular levels. Existing studies suggest that some combinations of pollutants might enhance the toxicity of each other and lead to unexpected biological alterations; but corresponding cellular mechanisms remain unclear. Most basic medical research still focuses on individual pollutant or a specific component of PM, which is unlikely to reflect real world exposures (Zhang et al 2021).

In relation to air pollution, the evidence is too limited to permit a judgement of a suggestive or convincing causal relationship, but supports a judgement of a possible causal relationship with atrial fibrillation and flutter (Grade 3). The evidence is limited in quality or quantity, and confounding by other cardiovascular risk factors remains an unresolved issue.

A new factor for air pollution should be added to the RH SoPs only.

There is little consistency in the quantitative data linking specific pollutants to AF in terms of concentration and duration of exposure from recent meta-analyses. In general terms, there is stronger evidence of acute than chronic effects, of particulates than gaseous matter but the results are heterogeneous. No absolute threshold of concentration or duration of exposure is discernible from the data. It is suggested that a reasonable approach is to include a factor based on PM 2.5 levels only, as a marker of ambient polluted air.

Gallo et al (2020) studies support the hypothesis that PM only increases the risk of arrhythmias at medium to high PM concentrations. An association was found between AF and daily levels of PM_{2.5} of 75 µg/m³ (OR 1.8, 95CI 1.34-2.40) and PM₁₀ of 100 µg/m³ (OR 2.48, 95CI 1.44-4.28), an increase of 50 µg/m³ above the WHO threshold.

Chen et al (2021) meta-analysis suggests short-term exposure to part of pollutants (PM_{2.5}, SO₂, and NO₂) increases AF attack, and long-term exposure to air pollution significantly contributes to AF incidence in a healthy population. For short term effects, the ER for AF per 10 µg/m³ increase of pollutants was 1.8% (0%-3.7%) for PM_{2.5} and 1.1% (-0.2%-2.4%) for PM₁₀; per 10 ppb increment of gaseous pollutants was 3.2% (0.6%-5.8%) for NO₂, 2.9% (0.3%-5.7%) for SO₂, 0.5% (-3.4%-4.7%) for O₃, and 2.0% (-1.3%-5.4%) for CO per 1000 ppb change. These results are heterogeneous.

Wang et al 2021 PM_{2.5} exposure was significantly related to increased incidence of AF in older adults. Both pooled OR and %-change value were higher in areas with higher levels of PM_{2.5} (≥25 µg/m³).

Long term effects have more limited data (Chen et al 2021). In the long term, except for O₃, a statistically significant association was noted between AF incidence and all pollutants. There was a greater than 1% increase per unit for PM_{2.5}, PM 10, NO₂, CO. For long-term effects, ER per 10 µg/m³ increase of pollutants was 11.6% (3.1%-20.7%) for PM_{2.5} and 3.4% (3.2%-3.5%) for PM₁₀; per 10 ppb increment of gaseous pollutants was 1.7% (0.1%-3.3%) for NO₂, 0.5% (0.4%-0.7%) for SO₂, 0.7% (-7.3%-9.4%) for O₃, and 2.0% (1.3%-2.2%) for CO per 1000 ppb change.

Liver disease

No factor

Summary of important issues

The association between NAFLD and atrial fibrillation has been suggested by recent epidemiological studies although the results are inconsistent. A recent meta-analysis (Gonh et al 2021) found a significantly higher risk of cardiac arrhythmia in patients with NAFLD, but the observational design of the studies does not permit conclusions regarding causality.

Reviews

There are increasing data on the association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVD).⁴⁶⁹ The association between NAFLD and atrial fibrillation has been suggested by recent epidemiological studies although the results are inconsistent.

Polyzos et al (2021) summarised evidence on the association between NAFLD and CVD in the clinical setting.⁴⁷⁰ Evidence was primarily derived from meta-analyses. and, if data were insufficient, from clinical trials, and observational studies.

NAFLD has been linked to various cardiovascular diseases, including atrial fibrillation. Advanced liver fibrosis is a crucial prognostic factor for end-stage liver disease and for cardiovascular and overall mortality. Weight loss through lifestyle modifications (diet and exercise) remains the cornerstone of the management of both NAFLD and CVD, but is difficult to achieve and possibly more difficult to sustain long term. pharmacological management of NAFLD seems to be important, although no licenced medication currently exists. Pioglitazone, proposed for non-alcoholic steatohepatitis (NASH) by most guidelines, increases weight and should be avoided in congestive heart failure. Statins should not be avoided in NAFLD patients at risk for CVD. Glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, two classes of anti-diabetic drugs, have shown promising results in NAFLD and CVD, but more studies with hard end points are needed. Obeticholic acid, a promising medication for NASH under investigation, should be carefully considered, owing to its adverse effect on lipid profile.

⁴⁶⁹ Polyzos, S. A., Kechagias, S., & Tsochatzis, E. A. (2021). Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations. *Alimentary pharmacology & therapeutics*, 54(8), 1013–25.

⁴⁷⁰ Polyzos, S. A., Kechagias, S., & Tsochatzis, E. A. (2021). Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations. *Alimentary pharmacology & therapeutics*, 54(8), 1013–25.

Meta-analyses

Wijarnpreecha et al (2017) conducted a meta-analysis to summarise available data reporting the risk of AF among patients with NAFLD versus those without NAFLD.⁴⁷¹ Effect estimates from each study were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird.

Of 1009 studies, 5 studies (two cross-sectional studies and three cohort studies) with 238,129 participants met the eligibility criteria and were included in the meta-analysis. The risk of AF in patients with NAFLD was significantly higher than subjects without NAFLD with the pooled RR of 2.06 (95CI 1.10-3.85). The statistical heterogeneity was high with an I² of 78%, which was the major limitation of this meta-analysis.

A significantly increased risk of AF among patients with NAFLD was demonstrated in this study.

Gong et al (2021) performed a meta-analysis to create a quantitative estimate of the association between non-alcoholic fatty liver disease (NAFLD) and the risk of cardiac arrhythmia (including atrial fibrillation, prolonged QT interval, premature atrial/ventricular contraction [PAC/PVC] and heart block).⁴⁷²

A literature review was conducted using PubMed, Embase, Web of Science and the Cochrane Library database to identify observational studies of the link between NAFLD and cardiac arrhythmia. Effect sizes were expressed as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). The method of analysis of AF was also analysed separately, according to the effect estimate (OR or HR).

Nineteen studies of 7,012,960 individuals were included. NAFLD was independently associated with higher risks of AF (OR 1.71, 95CI 1.14-2.57; HR 1.12, 95CI 1.11-1.13), prolonged QT interval (OR 2.86, 95CI 1.64-4.99), PAC/PVC (OR 2.53, 95CI 1.70-3.78) and heart block (OR 2.65, 95CI 1.88-3.72). The heterogeneity of data with respect to AF and prolonged QT was moderate on sensitivity analysis.

Gong et al found a significantly higher risk of cardiac arrhythmia in patients with NAFLD, but the observational design of the studies does not permit conclusions regarding causality.

Summary and conclusions

There are increasing data on the association between non-alcoholic fatty liver disease (NAFLD) and cardiovascular diseases

⁴⁷¹ Wijarnpreecha, K., Boonpheng, B., Thongprayoon, C., et al (2017). The association between non-alcoholic fatty liver disease and atrial fibrillation: A meta-analysis. *Clinics and research in hepatology and gastroenterology*, 41(5), 525–32.

⁴⁷² Gong, H., Liu, X., & Cheng, F. (2021). Relationship between non-alcoholic fatty liver disease and cardiac arrhythmia: a systematic review and meta-analysis. *The Journal of international medical research*, 49(9), August meeting 2022

Wijarnpreecha et al (2017) conducted a meta-analysis to summarise available data reporting the risk of AF among patients with NAFLD versus those without NAFLD. 5 studies (two cross-sectional studies and three cohort studies) with 238,129 participants met the eligibility criteria and were included in the meta-analysis. The risk of AF in patients with NAFLD was significantly higher than subjects without NAFLD with the pooled RR of 2.06 (95CI 1.10-3.85).

Gonh et al (2021) conducted a meta-analysis; 19 studies of 7,012,960 individuals were included. NAFLD was independently associated with higher risks of AF (OR 1.71, 95CI 1.14-2.57; HR 1.12, 95CI 1.11-1.13), prolonged QT interval (OR 2.86, 95CI 1.64-4.99), PAC/PVC (OR 2.53, 95CI 1.70-3.78) and heart block (OR 2.65, 95CI 1.88-3.72). The heterogeneity of data with respect to AF and prolonged QT was moderate on sensitivity analysis.

The authors found a significantly higher risk of cardiac arrhythmia in patients with NAFLD, but the observational design of the studies does not permit conclusions regarding causality

It is concluded that the evidence is too limited to permit a judgement of a possible causal relationship between non--alcoholic fatty liver disease and the development of atrial fibrillation or atrial flutter (Grade 4). An association is demonstrated in some studies, but the evidence is inconsistent and studies are limited in quality or quantity. Chance, bias or confounding are likely to account for observed associations.

No factor for the SoPs is suggested.

Bibliography

Adegbala O, Olagoke O, Akintoye E, et al (2019). Predictors, burden, and the impact of arrhythmia on patients admitted for acute myocarditis. *Am J Cardiol*, 123(1): 139-44.

Au Yeung SL, Schooling CM (2021). Impact of urinary sodium on cardiovascular disease and risk factors: A 2 sample Mendelian randomization study. *Clin Nutr*, 40(4): 1990-6.

Aibar J, Schulman S (2021). New-onset atrial fibrillation in sepsis: a narrative review. *Semin Thromb Hemost*, 47(1): 18-25.

Akintoye E, Sellke F, Marchioli R, et al (2018). Factors associated with postoperative atrial fibrillation and other adverse events after cardiac surgery. *J Thorac Cardiovasc Surg*, 155(1): 242-51.e10.

Albini A, Malavasi VL, Vitolo M, et al (2021). Long-term outcomes of postoperative atrial fibrillation following non cardiac surgery: A systematic review and metanalysis. *Eur J Intern Med*, 85: 27-33.

Albrecht M, Koolhaas CM, Schoufour JD, et al (2018). Physical activity types and atrial fibrillation risk in the middle-aged and elderly: The Rotterdam Study. *Eur J Prev Cardiol*, 25(12): 1316-23.

Alexandre J, Moslehi JJ, Bersell KR, et al (2018). Anticancer drug-induced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms. *Pharmacol Ther*, 189: 89-103.

Alijla F, Buttia C, Reichlin T, et al (2021). Association of diabetes with atrial fibrillation types: a systematic review and meta-analysis. *Cardiovasc Diabetol*, 20(1): 230.

Alkhamisi A, Carek SM, Dillon MC, et al (2021). Atrial fibrillation induced from commotio cordis. *Clin J Sport Med*, 31(4): e213-5..

Andersen A, Bagger JI, Baldassarre MP, et al (2021). Acute hypoglycemia and risk of cardiac arrhythmias in insulin-treated type 2 diabetes and controls. *Eur J Endocrinol*, 185(2): 343-53.

Andreadis EA, Geladari CV (2018). Hypertension and atrial fibrillation: a bench to bedside perspective. *Front Biosci (Schol Ed)*, 10(2): 276-84.

Angeli F, Reboldi G, Trapasso M, et al (2019). Detrimental impact of chronic obstructive pulmonary disease in atrial fibrillation: New insights from Umbria atrial fibrillation registry. *Medicina (Kaunas)*, 55(7): 358.

Arslan S, Batit S, Kilicarslan O, et al (2021). Incidence of atrial fibrillation and its effects on long-term follow-up outcomes in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction.

Ashraf I, Peck MM, Maram R, et al (2020). Association of arrhythmias in cardiac amyloidosis and cardiac sarcoidosis. *Cureus*, 12(8): e9842.

Aune D, Feng T, Schlesinger S, et al (2018). Diabetes mellitus, blood glucose and the risk of atrial fibrillation: A systematic review and meta-analysis of cohort studies. *J Diabetes Complications*, 32(5): 501-11.

Azevedo RB, Botelho BG, Hollanda JV, et al (2021). Covid-19 and the cardiovascular system: a comprehensive review. *J Hum Hypertens*, 35(1): 4-11.

Baeza-Herrera LA, Rojas-Velasco G, Marquez-Murillo MF, et al (2019). Atrial fibrillation in cardiac surgery. *Arch Cardiol Mex*, 89(4): 348-59.

Baman JR, Cox JL, McCarthy PM, et al (2021). Atrial fibrillation and atrial cardiomyopathies. *J Cardiovasc Electrophysiol*, 32(10): 2845-53.

Bandyopadhyay D, Jain V, Herzog E, et al (2019). Atrial fibrillation and morbidity and mortality in stress-induced cardiomyopathy. *Mayo Clin Proc*, 94(10): 2146-8.

Bandyopadhyay D, Banerjee U, Hajra A, et al (2021). Trends of cardiac complications in patients with rheumatoid arthritis: analysis of the United States National Inpatient Sample; 2005-2014. *Curr Probl Cardiol*, 46(3): 100455. 104736

Bashar SK, Ding EY, Walkey AJ, et al (2021). Atrial fibrillation prediction from critically ill sepsis patients. *Biosensors (Basel)*, 11(8): 269. 107091

Baumgartner C, da Costa BR, Collet TH, et al (2017). Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation*, 136(22): 2100-16.

Bauters F, Rietzschel ER, Hertegonne KB, et al (2016). The link between obstructive sleep apnea and cardiovascular disease. *Curr Atheroscler Rep*, 18(1): 1.

Bavishi A, Patel RB (2020). Addressing comorbidities in heart failure: hypertension, atrial fibrillation, and diabetes. *Heart Fail Clin*, 16(4): 441-56.

Begieneman MP, Emmens RW, Rijvers L, et al (2016). Ventricular myocarditis coincides with atrial myocarditis in patients. *Cardiovasc Pathol*, 25(2): 141-8.

Bel Lassen P, Kyrilli A, Lytrivi M, et al (2019). Graves' disease, multinodular goiter and subclinical hyperthyroidism. *Ann Endocrinol (Paris)*, 80(4): 240-9.

Bell DS, Goncalves E (2019). Atrial fibrillation and type 2 diabetes: Prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab*, 21(2): 210-7

Bengtsson K, Forsblad-d'Elia H, Lie E, et al (2018). Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Ann Rheum Dis*, 7

Benjamin EJ, Al-Khatib SM, Desvigne-Nickens P, et al (2021). Research priorities in the secondary prevention of atrial fibrillation: A National Heart, Lung, and Blood Institute virtual workshop report. *J Am Heart Assoc*, 10(16): e021566.

Benn M (2021). Atrial fibrillation and chronic kidney disease. *Eur Heart J*, 42(29): 2824-6.

Bernard ML, Benn F, Williams CM, et al (2021). The role of atrial fibrillation catheter ablation in patients with heart failure. *Prog Cardiovasc Dis*, 66: 80-5.

Bhagavathula AS, Rahmani J (2021). Salt intake and new-onset of atrial fibrillation: A meta-analysis of over 1.4 million participants. *Clin Nutr*, 40(5): 2600-1.

Bikdeli B, Abou Ziki MD, Lip GY (2017). Pulmonary embolism and atrial fibrillation: two sides of the same coin? A systematic review. *Semin Thromb Hemost*, 43(8): 849-63.

Bjerrum E, Wahlstroem KL, Gogenur I, et al (2020). Postoperative atrial fibrillation following emergency noncardiothoracic surgery: A systematic review. *Eur J Anaesthesiol*, 37(8): 671-9.

Bonnesen MP, Frodi DM, Haugan KJ, et al (2021). Day-to-day measurement of physical activity and risk of atrial fibrillation. *Eur Heart J*, 42(38): 3979-88.

Boons J, Van Biesen S, Fivez T, et al (2021). Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery: a narrative review. *J Cardiothorac Vasc Anesth*, 35(11): 3394-403.

Bosch NA, Cimini J, Walkey AJ (2018). Atrial fibrillation in the ICU. *Chest*, 154(6): 1424-34. 107094

Bosch NA, Cohen DM, Walkey AJ (2019). Risk factors for new-onset atrial fibrillation in patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*, 47(2): 280-7.

Bozkurt Yilmaz HE, Yilmaz M, Sen N, et al (2018). Assessment of atrial fibrillation and ventricular arrhythmia risk in patients with asthma by P wave/corrected QT interval dispersion. *Eur Rev Med Pharmacol Sci*, 22(3): 756-62.

Brunetti R, Zitelny E, Newman N, et al (2021). New-onset atrial fibrillation incidence and associated outcomes in the medical intensive care unit. *Pacing Clin Electrophysiol*, 44(8): 1380-6.

Buckley BJ, Harrison SL, Fazio-Eynullayeva E, et al (2021). Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *Eur J Clin Invest*, 51(11): e13679.

Bukari A, Wali E, Deshmukh A, et al (2018). Prevalence and predictors of atrial arrhythmias in patients with sinus node dysfunction and atrial pacing. *J Interv Card Electrophysiol*, 53(3): 365-71.

Burashnikov A (2021). Atrial fibrillation induced by anticancer drugs and underlying mechanisms. *J Cardiovasc Pharmacol*: Epub ahead of print.

Butt SA, Jeppesen JL, Torp-Pedersen C, et al (2019). Cardiovascular manifestations of systemic sclerosis: A Danish nationwide cohort study. *J Am Heart Assoc*, 8(17): e013405.

Butta C, Zappia L, Laterra G, et al (2020). Diagnostic and prognostic role of electrocardiogram in acute myocarditis: A comprehensive review. *Ann Noninvasive Electrocardiol*, 25(3): e12726.

Carter P, Lagan J, Fortune C, et al (2019). Association of cardiovascular disease with respiratory disease. *J Am Coll Cardiol*, 73(17): 2166-77.

Cepelis A, Brumpton BM, Malmo V, et al (2018). Associations of asthma and asthma control with atrial fibrillation risk: Results from the Nord-Trondelag Health Study (HUNT). *JAMA Cardiol*, 3(8): 721-8. 107100

Cha MJ, Oh GC, Lee H, et al (2020). Alcohol consumption and risk of atrial fibrillation in asymptomatic healthy adults. *Heart Rhythm*, 17(12): 2086-92.

Chamberlain AM (2019). Secondhand smoke and atrial fibrillation: importance of managing modifiable risk factors. *J Am Coll Cardiol*, 74(13): 1665-6.

Chan CS, Lin YK, Chen YC, et al (2019). Heart failure differentially modulates natural (sinoatrial node) and ectopic (pulmonary veins) pacemakers: mechanism and therapeutic implication for atrial fibrillation. *Int J Mol Sci*, 20(13): 3224.

Chan WL, Yang KP, Chao TF, et al (2014). The association of asthma and atrial fibrillation--a nationwide population-based nested case-control study. *Int J Cardiol*, 176(2): 464-9.

Chang TY, Chao TF, Liu CJ, et al (2016). The association between influenza infection, vaccination, and atrial fibrillation: A nationwide case-control study. *Heart Rhythm*, 13(6): 1189-94

Chang WT, Toh HS, Liao CT, et al (2021). Cardiac involvement of COVID-19: A comprehensive review. *Am J Med Sci*, 361(1): 14-22.

Chao TF, Liu CJ, Chen SJ, et al (2013). The association between the use of non-steroidal anti-inflammatory drugs and atrial fibrillation: a nationwide case-control study. *Int J Cardiol*, 168(1): 312-6.

Chen L, Fu G, Jiang C (2021). Mendelian randomization as an approach to assess causal effects of inflammatory bowel disease on atrial fibrillation. *Aging (Albany NY)*, 13(8): 12016-30.

Chen M, Zhao J, Zhuo C, et al (2021). The association between ambient air pollution and atrial fibrillation. *Int Heart J*, 62(2): 290-7.

Chen SY, Toh HS, Chang WT, et al (2021). A rare cause of left atrium compression. *Int Heart J*, 62(4): 944-8.

Chen YC, Voskoboinik A, Gerche A, et al (2021). Prevention of pathological atrial remodeling and atrial fibrillation: JACC state-of-the-art review. *J Am Coll Cardiol*, 77(22): 2846-64.

Chhabra L, Bhattad VB, Sareen P, et al (2015). Atrial fibrillation in acute pericarditis: an overblown association. *Heart*, 101(18): 1518.

Chinitz LA (2021). Atrial arrhythmias and the pandemic. *JACC Clin Electrophysiol*, 7(9): 1131-3.

Cho J, Lee D (2021). Postoperative new-onset atrial fibrillation causing acute embolic occlusion of the superior mesenteric artery: A case report. *Medicine (Baltimore)*, 100(17): e25700.

Chokesuwattanaskul R, Thongprayoon C, Bathini T, et al (2020). Incident atrial fibrillation in patients undergoing bariatric surgery: a systematic review and meta-analysis. *Intern Med J*, 50(7): 810-7.

Chokesuwattanaskul R, Chiengthong K, Thongprayoon C, et al (2020). Nonsteroidal anti-inflammatory drugs and incidence of atrial fibrillation: a meta-analysis. *QJM*, 113(2): 79-85.

Chu G, Versteeg HH, Verschoor AJ, et al (2019). Atrial fibrillation and cancer - An unexplored field in cardiovascular oncology. *Blood Rev*, 35: 59-67.

Chuang SY, Hsu PF, Lin FJ, et al (2018). Association between nonsteroidal anti-inflammatory drugs and atrial fibrillation among a middle-aged population: a nationwide population-based cohort. *Br J Clin Pharmacol*, 84(6): 1290-300.

Cohen JE, Kogan J, Oren S, et al (2011). Primary cardiac lymphoma presenting with atrial fibrillation. *Isr Med Assoc J*, 13(10): 635-7.

Corlateanu A, Stratan I, Covantev S, et al (2021). Asthma and stroke: a narrative review. *Asthma Res Pract*, 7(1): 3.

Csengeri D, Sprunker NA, Di Castelnuovo A, et al (2021). Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *Eur Heart J*, 42(12): 1170-7.

Dale Z, Chandrashekar P, Al-Rashdan L, et al (2021). Management strategies for atrial fibrillation and flutter in patients with transthyretin cardiac amyloidosis. *Am J Cardiol*, 157: 107-14.

Datta G, Mitra P (2019). A study on cardiac manifestations of Dengue fever. *J Assoc Physicians India*, 67(7): 14-6.

Day E, Rudd JH (2019). Alcohol use disorders and the heart. *Addiction*, 114(9): 1670-8.

De Ponti R, Marazzato J, Bagliani G, et al (2018). Sick sinus syndrome. *Card Electrophysiol Clin*, 10(2): 183-195.

Dherange P, Lang J, Qian P, et al (2020). Arrhythmias and COVID-19: A review. *JACC Clin Electrophysiol*, 6(9): 1193-204.

Dhungana SP, Ghimire R (2020). Prevalence of valvular and non-valvular atrial fibrillation and the application of antithrombotic treatment in a tertiary care hospital. *JNMA J Nepal Med Assoc*, 58(231): 851-5.

Diamond JA, Ismail H (2021). Obstructive sleep apnea and cardiovascular disease. *Clin Geriatr Med*, 37(3): 445-56.

Di Dalmazi G, Vicennati V, Pizzi C, et al (2020). Prevalence and incidence of atrial fibrillation in a large cohort of adrenal incidentalomas: a long-term study. *J Clin Endocrinol Metab*, 105(8): dgaa270.

Ding WY, Gupta D, Wong CF, et al (2021). Atrial fibrillation in the presence of chronic kidney disease: To ablate or not to ablate. *Int J Clin Pract*, 75(11): e14723.

Ding, Y., Wan, M., Zhang, H., et al (2021). Comparison of postprocedural new-onset atrial fibrillation between transcatheter and surgical aortic valve replacement: A systematic review and meta-analysis based on 16 randomized controlled trials. *Medicine*, 100(28), e26613

Dixit S, Pletcher MJ, Vittinghoff E, et al (2016). Secondhand smoke and atrial fibrillation: Data from the Health eHeart Study. *Heart Rhythm*, 13(1): 3-9.

Dong Z, Du X, Lu S, et al (2021). Incidence and predictors of hospitalization in patients with atrial fibrillation: results from the Chinese atrial fibrillation registry study. *BMC Cardiovasc Disord*, 21(1): 146.

Duckheim M, Schrieck J (2021). COVID-19 and cardiac arrhythmias. *Hamostaseologie*, 41(5): 372-8.

Durheim MT, Holmes DN, Blanco RG, et al (2018). Characteristics and outcomes of adults with chronic obstructive pulmonary disease and atrial fibrillation. *Heart*, 104(22): 1850-8.

Dvirnik N, Belley-Cote EP, Hanif H, et al (2018). Steroids in cardiac surgery: a systematic review and meta-analysis. *Br J Anaesth*, 120(4): 657-67. 104651

Dzeshka MS, Shahid F, Shantsila A, et al (2017). Hypertension and atrial fibrillation: an intimate association of epidemiology, pathophysiology, and outcomes. *Am J Hypertens*, 30(8): 733-55.

Dziewiecka E, Gliniak M, Winiarczyk M, et al (2020). The burden of atrial fibrillation and its prognostic value in patients with dilated cardiomyopathy. *Kardiol Pol*, 78(1): 37-44.

Eikelboom R, Sanjanwala R, Le ML, et al (2021). Postoperative atrial fibrillation after cardiac surgery: a systematic review and meta-analysis. *Ann Thorac Surg*, 111(2): 544-54.

Ellervik C, Roselli C, Christophersen IE, et al (2019). Assessment of the relationship between genetic determinants of thyroid function and atrial fibrillation: A mendelian randomization study. *JAMA Cardiol*, 4(2): 144-52.

Elliott AD, Linz D, Verdicchio CV, et al (2018). Exercise and atrial fibrillation: prevention or causation? *Heart Lung Circ*, 27(9): 1078-85.

El-Menyar A, Al Thani H, Zarour A, et al (2012). Understanding traumatic blunt cardiac injury. *Ann Card Anaesth*, 15(4): 287-95.

El Helou G, Hellinger W (2019). *Cryptococcus neoformans* pericarditis in a lung transplant recipient: Case report, literature review and pearls. *Transpl Infect Dis*, 21(5): e13137.

Ergun B, Ergun B, Sozmen MK, et al (2021). New-onset atrial fibrillation in critically ill patients with coronavirus disease 2019 (COVID-19). *J Arrhythm*, 37(5): 1196-204.

Essa H, Dobson R, Lip GY (2021). Chemotherapy induced arrhythmias. *J Cardiovasc Pharmacol*: Epub ahead of print.

Essa H, Wright DJ, Dobson R, et al (2021). Chemotherapy-induced arrhythmia - underrecognized and undertreated. *Am J Med*, 134(10): 1224-31.e1.

Evron JM, Papaleontiou M (2021). Decision making in subclinical thyroid disease. *Med Clin North Am*, 105(6): 1033-45.

Fadel R, El-Menyar A, ElKafrawy S, et al (2019). Traumatic blunt cardiac injuries: An updated narrative review. *Int J Crit Illn Inj Sci*, 9(3): 113-9.

Fauchier G, Bisson A, Bodin A, et al (2021). Metabolically healthy obesity and cardiovascular events: A nationwide cohort study. *Diabetes Obes Metab*, 23(11): 2492-501.

Fazmin IT, Huang CL, Jeevaratnam K (2020). Bisphosphonates and atrial fibrillation: revisiting the controversy. *Ann N Y Acad Sci*, 1474(1): 15-26.

Flannery MD, Kalman JM, Sanders P, et al (2017). State of the art review: atrial fibrillation in athletes. *Heart Lung Circ*, 26(9): 983-9. 104752

Franczyk B, Gluba-Brzozka A, Cialkowska-Rysz A, et al (2016). The problem of atrial fibrillation in patients with chronic kidney disease. *Curr Vasc Pharmacol*, 14(3): 260-5.

Franklin BA, Rusia A, Haskin-Popp C, et al (2021). Chronic stress, exercise and cardiovascular disease: Placing the benefits and risks of physical activity into perspective. *Int J Environ Res Public Health*, 18(18): 9922.

Franklin BA, Thompson PD, Al-Zaiti SS, et al (2020). Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement

Funakoshi H, Momo K, Okazaki K, et al (2021). [Comment] Beta-2-adrenoceptor agonist inhalation induced paroxysmal atrial fibrillation and tachycardia in a patient with severe bronchial asthma. *Br J Clin Pharmacol*, 87(8): 3375-7.

Gaine S, Devitt P, Coughlan JJ, et al (2021). COVID-19-associated myocarditis presenting as new-onset heart failure and atrial fibrillation. *BMJ Case Rep*, 14(7): e244027.

Galiuto L, Volpe M (2021). Glucocorticoids in patients with immune-mediated inflammatory diseases: a neglected cardiovascular risk factor. *Eur Heart J*, 42(13): 1197-8.

Gallagher C, Hendriks JM, Lau DH, et al (2018). Alcohol and atrial fibrillation. *Int J Cardiol*, 251: 56.

Gallagher C, Hendriks JM, Elliott AD, et al (2017). Alcohol and incident atrial fibrillation - A systematic review and meta-analysis. *Int J Cardiol*, 246: 46-52.

Gallo E, Folino F, Buja G, et al (2020). Daily exposure to air pollution particulate matter is associated with atrial fibrillation in high-risk patients. *Int J Environ Res Public Health*, 17(17): 6017. 107113

Garratt CJ, O'Nunain S, Griffith MJ, et al (1994). Effects of intravenous adenosine in patients with preexcited junctional tachycardias: therapeutic efficacy and incidence of proarrhythmic events. *Am J Cardiol*, 74(4): 401-4.

Gawalko M, Balsam P, Lodzinski P, et al (2020). Cardiac arrhythmias in autoimmune diseases. *Circ J*, 84(5): 685-94.

Goette A, Lendeckel U (2021). Atrial cardiomyopathy: Pathophysiology and clinical consequences. *Cells*, 10(10): 2605.

Ghosh S, Chandra A, Sen S, et al (2021). Atrial fibrillation following low voltage electrical injury. *BMJ Case Rep*, 14(1): e239306.

Goldstein SA, Green J, Huber K, et al (2019). Characteristics and outcomes of atrial fibrillation in patients with thyroid disease (from the ARISTOTLE Trial). *Am J Cardiol*, 124(9): 1406-12.

Gong H, Liu X, Cheng F (2021). Relationship between non-alcoholic fatty liver disease and cardiac arrhythmia: a systematic review and meta-analysis. *J Int Med Res*, 49(9): 3000605211047074.

Goudis CA (2017). Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship. *J Cardiol*, 69(5): 699-705.

Goudis CA, Ketikoglou DG (2017). Obstructive sleep and atrial fibrillation: Pathophysiological mechanisms and therapeutic implications. *Int J Cardiol*, 230: 293-300.

Granier M, Massin F, Pasquie JL (2013). Pro- and anti-arrhythmic effects of anti-inflammatory drugs. *Antiinflamm Antiallergy Agents Med Chem*, 12(1): 83-93.

Groenewegen A, Zwartkruis VW, Cekic B, et al (2021). Incidence of atrial fibrillation, ischaemic heart disease and heart failure in patients with diabetes. *Cardiovasc Diabetol*, 20(1): 123.

Groh CA, Faulkner M, Getabecha S, et al (2019). Patient-reported triggers of paroxysmal atrial fibrillation. *Heart Rhythm*, 16(7): 996-1002.

Groh CA, Vittinghoff E, Benjamin EJ, et al (2019). Childhood tobacco smoke exposure and risk of atrial fibrillation in adulthood. *J Am Coll Cardiol*, 74(13): 1658-64.

Grymonprez M, Vakaet V, Kavousi M, et al (2019). Chronic obstructive pulmonary disease and the development of atrial fibrillation. *Int J Cardiol*, 276: 118-24.

Gudbjartsson T, Helgadóttir S, Sigurdsson MI, et al (2020). New-onset postoperative atrial fibrillation after heart surgery. *Acta Anaesthesiol Scand*, 64(2): 145-55.

Gumprecht J, Domek M, Lip GY, et al (2019). Invited review: hypertension and atrial fibrillation: epidemiology, pathophysiology, and implications for management. *J Hum Hypertens*, 33(12): 824-36.

Gumprecht JJ, Kalarus Z (2022). Atrial fibrillation in patients with concomitant diabetes mellitus - what do we already know and what do we need to discover? *Wiad Lek*, 75(1): 123-7.

Guo Y, Gao J, Ye P, et al (2019). Comparison of atrial fibrillation in CKD and non-CKD populations: A cross-sectional analysis from the Kailuan study. *Int J Cardiol*, 277: 125-9.

Hajjar LA, Fonseca SM, Machado TI (2021). Atrial fibrillation and cancer. *Front Cardiovasc Med*, 8: 590768.

Hald EM, Enga KF, Lochen ML, et al (2014). Venous thromboembolism increases the risk of atrial fibrillation: the Tromso study. *J Am Heart Assoc*, 3(1): e000483.

Halldorsdottir S, Finnbjornsdottir RG, Elvarsson BT, et al (2022). Ambient nitrogen dioxide is associated with emergency hospital visits for atrial fibrillation: a population-based case-crossover study in Reykjavik, Iceland. *Environ Health*, 21(1)

Haq, M., Patel, A., & Guglin, M. (2014). Cardiac lymphoma: sinus pauses disappear after chemotherapy. *Annals of Hematology*, 93(5), 891–2.

Harding BN, Norby FL, Heckbert SR, et al (2021). Longitudinal measures of blood pressure and subclinical atrial arrhythmias: The MESA and the ARIC Study. *J Am Heart Assoc*, 10(11): e020260.

Harrison SL, O'Flaherty M, Lip GY (2020). Revisiting the dynamic risks of incident atrial fibrillation: does the use of nonsteroidal anti-inflammatory drugs contribute to risk? *QJM*, 113(2): 77-8.

He B, Au Yeung SL, Schooling CM (2021). [Comment] Reply to letter to the editor: Salt intake and new-onset of atrial fibrillation: A meta-analysis of over 1.4 million participants. *Clin Nutr*, 40(7): 4615.

Hidalgo DF, Boonpheng B, Nasr L, et al (2020). Celiac disease and risk of atrial fibrillation: A meta-analysis and systematic review. *Cureus*, 12(2): e6997.

Higa S, Maesato A, Ishigaki S, et al (2021). Diabetes and endocrine disorders (hyperthyroidism/hypothyroidism) as risk factors for atrial fibrillation. *Card Electrophysiol Clin*, 13(1): 63-75.

Hirayama A, Goto T, Shimada YJ, et al (2018). Acute exacerbation of chronic obstructive pulmonary disease and subsequent risk of Emergency Department visits and hospitalizations for atrial fibrillation. *Circ Arrhythm Electrophysiol*, 11(9): e0063

Hsu JC, Yang YY, Chuang SL, et al (2021). Underweight is a major risk factor for atrial fibrillation in Asian people with type 2 diabetes mellitus. *Cardiovasc Diabetol*, 20(1): 226.

Hsu JC, Li Y, Marcus GM, et al (2013). Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity. *J Am Coll Cardiol*, 61(22): 2288-95.

Huerta C, Lanes SF, Garcia Rodriguez LA (2005). Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology*, 16(3): 360-6.

Hung LT, Alshareef A, Al-Ahdal TM, et al (2021). Predicting atrial fibrillation after cardiac surgery using a simplified risk index. *J Electrocardiol*, 67: 45-9.

Imazio M, Lazaros G, Picardi E, et al (2015). Incidence and prognostic significance of new onset atrial fibrillation/flutter in acute pericarditis. *Heart*, 101(18): 1463-7.

Imtiaz Ahmad M, Mosley CD, O'Neal WT, et al (2018). Smoking and risk of atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *J Cardiol*, 71(2): 113-7.

Itoh H, Kaneko H, Fujii K, et al (2021). Risk factors and lifestyles in the development of atrial fibrillation among individuals aged 20-39 years. *Am J Cardiol*, 155: 40-4.

Jackson LR 2nd, Rathakrishnan B, Campbell K, et al (2017). Sinus node dysfunction and atrial fibrillation: A reversible phenomenon? *Pacing Clin Electrophysiol*, 40(4): 442-50.

Jain P, Gutierrez Bugarin J, Guha A, et al (2021). Cardiovascular adverse events are associated with usage of immune checkpoint inhibitors in real-world clinical data across the United States. *ESMO Open*, 6(5): 100252.

Jamieson A (2019). [Comment] Drugs, the thyroid, and the heart: a lethal cocktail. *Am J Med*, 132(3): e514-6.

John RM, Kumar S (2016). Sinus node and atrial arrhythmias. *Circulation*, 133(19): 1892-900.

Kaakeh Y, Overholser BR, Lopshire JC, et al (2012). Drug-induced atrial fibrillation. *Drugs*, 72(12): 1617-30.

Kallistratos MS, Poulimenos LE, Manolis AJ (2018). Atrial fibrillation and arterial hypertension. *Pharmacol Res*, 128: 322-6.

Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, et al (2019). New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. *Acta Cardiol*, 74(2): 162-9.

Kashif M, Raiyani H, Niazi M, et al (2017). Purulent pericarditis: An uncommon presentation of a common organism. *Am J Case Rep*, 18: 355-60.

Khurshid S, Weng LC, Al-Alusi MA, et al (2021). Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J*, 42(25): 2472-83.

Kim HJ, Cho GY, Kim YJ, et al (2015). Development of atrial fibrillation in patients with rheumatic mitral valve disease in sinus rhythm. *Int J Cardiovasc Imaging*, 31(4): 735-42.

Kim IC (2021). Atrial fibrillation and heart failure with preserved ejection fraction: two chronic troublemakers. *Heart Fail Clin*, 17(3): 377-86.

Kim J, Yang PS, Park BE, et al (2021). Association of proteinuria and incident atrial fibrillation in patients with diabetes mellitus: a population-based senior cohort study. *Sci Rep*, 11(1): 17013.

Kim MS, Kim WJ, Khera AV, et al (2021). Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *Eur Heart J*, 42(34): 3388-403.

Kondo S, Osanai H, Sakamoto Y, et al (2021). Secondary cardiac lymphoma presenting as sick sinus syndrome and atrial fibrillation which required leadless pacemaker implantation. *Intern Med*, 60(3): 431-4.

Kotalczyk A, Ding WY, Wong CF, et al (2021). Atrial fibrillation in patients with chronic kidney disease. *Cardiol Clin*, 39(3): 435-46.

Kotecha D, Piccini JP (2015). Atrial fibrillation in heart failure: what should we do? *Eur Heart J*, 36(46): 3250-7.

Krakowiak A, Rajzer M, Gaczol M, et al (2021). Obesity and atrial fibrillation - bariatric surgery as a method of AF risk decrease. *Wiad Lek*, 74(9 cz 1): 2218-21.

Krawiec K, Szczasny M, Kadej A, et al (2021). Hiatal hernia as a rare cause of cardiac complications - case based review of the literature. *Ann Agric Environ Med*, 28(1): 20-6.

Krittayaphong R, Pumprueg S, Ratanasumawong K, et al (2021). Average systolic blood pressure and clinical outcomes in patients with atrial fibrillation: prospective data from COOL-AF registry. *Clin Interv Aging*, 16: 1835-46.

Kumar K (2022). Overview of atrial fibrillation. Retrieved 30 May 2022, from <https://www.uptodate.com/contents/overview-of-atrial-fibrillation>

Kunutsor SK, Seidu S, Makikallio TH, et al (2021). Physical activity and risk of atrial fibrillation in the general population: meta-analysis of 23 cohort studies involving about 2 million participants. *Eur J Epidemiol*, 36(3): 259-74.

Kushnir A, Restaino SW, Yuzefpolskaya M (2016). Giant cell arteritis as a cause of myocarditis and atrial fibrillation. *Circ Heart Fail*, 9(2): e002778.

Larsson SC, Allara E, Mason AM, et al (2019). Thyroid function and dysfunction in relation to 16 cardiovascular diseases. *Circ Genom Precis Med*, 12(3): e002468.

Latushko A, Ghazi LJ (2016). A case of thiopurine-induced acute myocarditis in a patient with ulcerative colitis. *Dig Dis Sci*, 61(12): 3633-4.

Lavie CJ, Pandey A, Lau DH, et al (2017). Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol*, 70(16): 2022-35.

Lee WC, Wu PJ, Fang CY, et al (2021). Impact of chronic kidney disease on atrial fibrillation recurrence following radiofrequency and cryoballoon ablation: A meta-analysis. *Int J Clin Pract*, 75(10): e14173.

Lee E, Choi EK, Jung JH, et al (2019). Increased risk of atrial fibrillation in patients with Behcet's disease: A nationwide population-based study. *Int J Cardiol*, 292: 106-11.

Lee SR, Park CS, Choi EK, et al (2021). Hypertension burden and the risk of new-onset atrial fibrillation: A nationwide population-based study. *Hypertension*, 77(3): 919-28.

Lee S, Jeevaratnam K, Liu T, et al (2021). Risk stratification of cardiac arrhythmias and sudden cardiac death in type 2 diabetes mellitus patients receiving insulin therapy: A population-based cohort study. *Clin Cardiol*, 44(11): 1602-12.

Leong P, Macdonald MI, Ko BS, et al (2019). Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge. *Med J Aust*, 210(9): 417-23.

Lin Z, Han H, Guo W, et al (2021). Atrial fibrillation in critically ill patients who received prolonged mechanical ventilation: a nationwide inpatient report. *Korean J Intern Med*, 36(6): 1389-401.

Lin MH, Kamel H, Singer DE, et al (2019). Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. *Stroke*, 50(6): 1364-71.

Linz D, Gawalko M, Sanders P, et al (2021). Does gut microbiota affect atrial rhythm? Causalities and speculations. *Eur Heart J*, 42(35): 3521-5.

Lioncino M, Monda E, Palmiero G, et al (2022). Cardiovascular involvement in transthyretin cardiac amyloidosis. *Heart Fail Clin*, 18(1): 73-87.

Liu X, Kong D, Liu Y, et al (2018). Effects of the short-term exposure to ambient air pollution on atrial fibrillation. *Pacing Clin Electrophysiol*, 41(11): 1441-6.

Liu G, Yan YP, Zheng XX, et al (2014). Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of atrial fibrillation. *Am J Cardiol*, 114(10): 1523-9.

Liu L, Jing FY, Wang XW, et al (2021). Effects of corticosteroids on new-onset atrial fibrillation after cardiac surgery: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*, 100(11):.

Ludwig A, Lucero-Obusan C, Schirmer P, et al (2015). Acute cardiac injury events ≤ 30 days after laboratory-confirmed influenza virus infection among U.S. veterans, 2010-2012. *BMC Cardiovasc Disord*, 15: 109.

Ma Y, Pan Z, Fan D, et al (2021). The increased risk of atrial fibrillation in inflammatory arthritis: a systematic review and meta-analysis of cohort studies. *Immunol Invest*: Epub ahead of print.

MacGregor RM, Khiabani AJ, Bakir NH, et al (2021). Impact of obesity on atrial fibrillation recurrence following stand-alone cox maze IV procedure. *Innovations (Phila)*, 16(5): 434-40.

Maharaj S, Perez-Downes J, Seegobin K, et al (2018). Consideration of atrial arrhythmias associated with cardiac tamponade and pericarditis. *Am J Emerg Med*, 36(2): 338.

Manolis AS, Manolis AA, Manolis TA, et al (2020). COVID-19 infection and cardiac arrhythmias. *Trends Cardiovasc Med*, 30(8): 451-60.

Marcus GM, Vittinghoff E, Whitman IR, et al (2021). Acute consumption of alcohol and discrete atrial fibrillation events. *Ann Intern Med*, 174(11): 1503-9.

Matarese A, Sardu C, Shu J, et al (2019). Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms. *Int J Cardiol*, 276: 149-51.

Mayosi BM (2015). Pericarditis-associated atrial fibrillation. *Heart*, 101(18): 1439-40.

Menichelli D, Vicario T, Ameri P, et al (2021). Cancer and atrial fibrillation: Epidemiology, mechanisms, and anticoagulation treatment. *Prog Cardiovasc Dis*, 66: 28-36.

Messerli FH, Dobner S (2021). Alcohol and atrial fibrillation: not all drinks are created equal. *Eur Heart J*, 42(25): 2506.

Mishima RS, Verdicchio CV, Noubiap JJ, et al (2021). Self-reported physical activity and atrial fibrillation risk: A systematic review and meta-analysis. *Heart Rhythm*, 18(4): 520-8.

Mittal R, Su L, Ramgobin D, et al (2022). A narrative review of chronic alcohol-induced atrial fibrillation. *Future Cardiol*, 18(1): 27-34.

Mohamed A, Ochoa Crespo D, Kaur G, et al (2020). Gastroesophageal reflux and its association with atrial fibrillation: a traditional review. *Cureus*, 12(9): e10387.

Mohanty S, Mohanty P, Tamaki M, et al (2016). Differential association of exercise intensity with risk of atrial fibrillation in men and women: evidence from a meta-analysis. *J Cardiovasc Electrophysiol*, 27(9): 1021-9.

Monfredi O, Boyett MR (2015). Sick sinus syndrome and atrial fibrillation in older persons - A view from the sinoatrial nodal myocyte. *J Mol Cell Cardiol*, 83: 88-100.

Moon I, Choi EK, Jung JH, et al (2019). Ankylosing spondylitis: A novel risk factor for atrial fibrillation - A nationwide population-based study. *Int J Cardiol*, 275: 77-82.

Morin DP, Bernard ML, Madias C, et al (2019). In reply-atrial fibrillation and morbidity and mortality in stress-induced cardiomyopathy. *Mayo Clin Proc*, 94(10): 2148-9.

Morovatdar N, Watts GF, Bondarsahebi Y, et al (2021). Ankylosing spondylitis and risk of cardiac arrhythmia and conduction disorders: a systematic review and meta-analysis. *Curr Cardiol Rev*, 17(5): e150521193326.

Morseth B, Lochen ML, Ariansen I, et al (2018). The ambiguity of physical activity, exercise and atrial fibrillation. *Eur J Prev Cardiol*, 25(6): 624-36.

Morseth B, Geelhoed B, Linneberg A, et al (2021). Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart*, 8(2): e001624.

Morsy M, Slomka T, Shukla A, et al (2018). Clinical and echocardiographic predictors of new-onset atrial fibrillation in patients admitted with blunt trauma. *Echocardiography*, 35(10): 1519-24.

Musikantow DR, Turagam MK, Sartori S, et al (2021). Atrial fibrillation in patients hospitalized with COVID-19: incidence, predictors, outcomes, and comparison to influenza. *JACC Clin Electrophysiol*, 7(9): 1120-30.

Nalliah CJ, Sanders P, Kottkamp H, et al (2016). The role of obesity in atrial fibrillation. *Eur Heart J*, 37(20): 1565-72.

Nattel S (2020). Physical activity and atrial fibrillation risk: it's complicated; and sex is critical. *Eur Heart J*, 41(15): 1487-9.

Navinan MR, Rajapakse S (2012). Cardiac involvement in leptospirosis. *Trans R Soc Trop Med Hyg*, 106(9): 515-20.

Newman W, Parry-Williams G, Wiles J, et al (2021). Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *Br J Sports Med*, 55(21): 1233-8.

Ng, K. T., Van Paassen, J., Langan, C., et al. (2020). The efficacy and safety of prophylactic corticosteroids for the prevention of adverse outcomes in patients undergoing heart surgery using cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials. *European journal of cardio-thoracic surgery*, 57(4):620–7.

Nji MA, Solomon SD, Chen LY, et al (2021). Association of heart failure subtypes and atrial fibrillation: Data from the Atherosclerosis Risk in Communities (ARIC) study. *Int J Cardiol*, 339: 47-53.

Nishikawa T, Tanaka Y, Tada H, et al (2021). Association between cardiovascular health and incident atrial fibrillation in the general Japanese population aged ≥ 40 years. *Nutrients*, 13(9): 3201.

Nomani H, Mohammadpour AH, Moallem SM, et al (2020). Anti-inflammatory drugs in the prevention of post-operative atrial fibrillation: a literature review. *Inflammopharmacology*, 28(1): 111-29.

O'Neal WT, Qureshi WT, Judd SE, et al (2015). Environmental tobacco smoke and atrial fibrillation: the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *J Occup Environ Med*, 57(11): 1154-8.

O'Keefe EL, Sturgess JE, O'Keefe JH, et al (2021). Prevention and treatment of atrial fibrillation via risk factor modification. *Am J Cardiol*, 160: 46-52.

Olshansky B, Arora R (2022). Mechanisms of atrial fibrillation. Retrieved 30 May 2022, from <https://www.uptodate.com/contents/mechanisms-of-atrial-fibrillation>

O'Neal WT, Bennett A, Singleton MJ, et al (2020). Objectively measured physical activity and the risk of atrial fibrillation (from the REGARDS Study). *Am J Cardiol*, 128: 107-12.

O'Neal WT, Qureshi WT, Judd SE, et al (2015). Environmental tobacco smoke and atrial fibrillation: the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *J Occup Environ Med*, 57(11): 1154-8.

Osuji N, Haberlen SA, Ashikaga H, et al (2021). Association between human immunodeficiency virus serostatus and the prevalence of atrial fibrillation. *Medicine (Baltimore)*, 100(29): e26663.

O'Sullivan JW (2021). Alcohol and atrial fibrillation: to or not to drink? *BMJ Evid Based Med*, 26(6): e14.

Ota K, Bratincsak A (2015). Atrial fibrillation induced by commotio cordis secondary to a blunt chest trauma in a teenage boy. *Pediatrics*, 135(1): e199-201.

Oud L (2019). Temporal patterns of atrial fibrillation in end-stage COPD. *Chest*, 156(6): 1269-70.

Panchal G, Mahmood M, Lip GY (2019). Revisiting the risks of incident atrial fibrillation: a narrative review. Part 1. *Kardiol Pol*, 77(4): 430-6.

Papathanasiou KA, Giotaki SG, Vrachatis DA, et al (2021). Molecular insights in atrial fibrillation pathogenesis and therapeutics: a narrative review. *Diagnostics (Basel)*, 11(9): 1584.

Park JH, Ko HJ (2022). The association between treatment with bisphosphonates and the risk of atrial fibrillation: a meta-analysis of observational studies. *Korean J Fam Med*, 43(1): 69-76.

Park S, Lee S, Kim Y, et al (2021). Atrial fibrillation and kidney function: a bidirectional Mendelian randomization study. *Eur Heart J*, 42(29): 2816-23.

Patel N, Donahue C, Shenoy A, et al (2017). Obstructive sleep apnea and arrhythmia: A systemic review. *Int J Cardiol*, 228: 967-70.

Patel RS, Gonzalez MD, Ajibawo T, et al (2021). Cannabis use disorder and increased risk of arrhythmia-related hospitalization in young adults. *Am J Addict*, 30(6): 578-84. 104783

Patoulias D, Papadopoulos C, Toumpourleka M, et al (2021). Meta-analysis addressing the effect of mineralcorticoid receptor antagonists on the risk for new-onset atrial fibrillation. *Am J Cardiol*, 157: 150-2.

Pattanshetty DJ, Anna K, Gajulapalli RD, et al (2015). Inflammatory bowel "Cardiac" disease: Point prevalence of atrial fibrillation in inflammatory bowel disease population. *Saudi J Gastroenterol*, 21(5): 325-9.

Pavicic T, Ruska B, Adamec I, et al (2019). Recurrent atrial fibrillation after pulse corticosteroid treatment for a relapse of multiple sclerosis. *Mult Scler Relat Disord*, 32: 30-2. 104784

Pawar P, Mumtaz Z, Phadke M, et al (2021). Is left atrial fibrosis an independent determinant of atrial fibrillation in mitral stenosis? *Indian Heart J*, 73(4): 503-5.

Pellicori P, Urbinati A, Kaur K, et al (2019). Prevalence and incidence of atrial fibrillation in ambulatory patients with heart failure. *Am J Cardiol*, 124(10): 1554-60.

Perry M, Kemmis Betty S, Downes N, et al (2021). Atrial fibrillation: diagnosis and management-summary of NICE guidance. *BMJ*, 373: n1150.

Peters S (2020). [Comment] Editorial: Atrial fibrillation in arrhythmogenic cardiomyopathy. *Int J Cardiol*, 298: 54.

Piano MR, Hwang CL (2021). Holiday heart confirmed: alcohol-associated atrial fibrillation. *Ann Intern Med*, 174(11): 1616-7.

Polyzos SA, Kechagias S, Tsochatzis EA (2021). Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations. *Aliment Pharmacol Ther*, 54(8): 1013-25.

Pranata R, Vania R, Tondas AE et al (2020). A time-to-event analysis on air pollutants with the risk of cardiovascular disease and mortality: A systematic review and meta-analysis of 84 cohort studies. *J Evid Based Med*, 13(2): 102-15.

Ptaszynska-Kopczynska K, Kiluk I, Sobkowicz B (2019). Atrial fibrillation in patients with acute pulmonary embolism: clinical significance and impact on prognosis. *Biomed Res Int*, 2019: 7846291.

Pujades-Rodriguez M, Morgan AW, Cubbon RM, et al (2020). Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS Med*, 17(12): e1003432.

Qaddoura A, Kabali C, Drew D, et al (2014). Obstructive sleep apnea as a predictor of atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *Can J Cardiol*, 30(12): 1516-22.

Qamar SR, Wu Y, Nicolaou S, et al (2020). State of the art imaging review of blunt and penetrating cardiac trauma. *Can Assoc Radiol J*, 71(3): 301-12.

Qureshi M, Ahmed A, Massie V, et al (2021). Determinants of atrial fibrillation after cardiac surgery. *Rev Cardiovasc Med*, 22(2): 329-41.

Rabadi MH, Mayanna SK, Vincent AS (2013). Predictors of mortality in veterans with traumatic spinal cord injury. *Spinal Cord*, 51(10): 784-8.

Ramalho SH, Shah AM (2021). Lung function and cardiovascular disease: A link. *Trends Cardiovasc Med*, 31(2): 93-8.

Ramphul K, Kumar N, Verma R, et al (2021). Higher risk of long QT syndrome and atrial flutter in adults with HIV admitted for acute myocardial infarction. *Anatol J Cardiol*, 25(9): 673-4.

Raphael CE, Liew AC, Mitchell F, et al (2020). Predictors and mechanisms of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol*, 136: 140-8.

Raubenheimer PJ, Cushman WC, Avezum A, et al (2022). Dulaglutide and incident atrial fibrillation or flutter in patients with type 2 diabetes: A post hoc analysis from the REWIND randomized trial. *Diabetes Obes Metab*: Epub ahead of print.

Regev-Avraham Z, Rosenfeld I, Sharabi-Nov A, et al (2020). Is second hand smoking associated with atrial fibrillation risk among women in Israel? A case-control study. *Int J Cardiol*, 304: 56-60.

Rehm J, Roerecke M (2017). Cardiovascular effects of alcohol consumption. *Trends Cardiovasc Med*, 27(8): 534-8.

Reiffel JA (2021). When two is not better than one: the amalgamation of atrial fibrillation and chronic obstructive pulmonary disease. *Eur Heart J*, 42(35): 3555-7.

Reinhardt SW, Chouairi F, Miller PE, et al (2021). National trends in the burden of atrial fibrillation during hospital admissions for heart failure. *J Am Heart Assoc*, 10(11): e019412. 107164

Ricci C, Gervasi F, Gaeta M, et al (2018). Physical activity volume in relation to risk of atrial fibrillation. A non-linear meta-regression analysis. *Eur J Prev Cardiol*, 25(8): 857-66.

Rivington J, Twohig P (2020). Quantifying risk factors for atrial fibrillation: retrospective review of a large electronic patient database. *J Atr Fibrillation*, 13(3): 2365.

Rodriguez-Manero M, Lopez-Pardo E, Cordero A, et al (2019). A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population. *Int J Chron Obstruct Pulmon Dis*, 14: 371-80.

Roerecke M (2021). Alcohol's impact on the cardiovascular system. *Nutrients*, 13(10): 3419.

Romiti GF, Corica B, Pipitone E, et al (2021). Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients. *Eur Heart J*, 42(35): 3541-54.

Rosa VE, Lopes AS, Accorsi TA, et al (2015). Heart transplant in patients with predominantly rheumatic valvular heart disease. *J Heart Valve Dis*, 24(5): 629-34.

Sahan E, Sahan S, Karamanlioglu M, et al (2019). Prediction of new onset atrial fibrillation in patients with acute pulmonary embolism: The role of sPESI Score. *Turk Kardiyol Dern Ars*, 47(3): 191-7.

Sanders JM, Steverson AB, Pawlowski AE, et al (2018). Atrial arrhythmia prevalence and characteristics for human immunodeficiency virus-infected persons and matched uninfected controls. *PLoS One*, 13(3): e0194754.

Sardana M, Hsue PY, Tseng ZH, et al (2019). Human immunodeficiency virus infection and incident atrial fibrillation. *J Am Coll Cardiol*, 74(11): 1512-4.

Schjerning Olsen AM, Fosbol EL, Pallisgaard J, et al (2015). NSAIDs are associated with increased risk of atrial fibrillation in patients with prior myocardial infarction: a nationwide study. *Eur Heart J Cardiovasc Pharmacother*, 1(2): 107-14.

Schmidt SA, Olsen M, Schmidt M, et al (2020). Atopic dermatitis and risk of atrial fibrillation or flutter: A 35-year follow-up study. *J Am Acad Dermatol*, 83(6): 1616-24.

Schnabel RB, Yin X, Gona P, et al (2015). 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*, 386(9989): 154-62.

Seccia TM, Calo LA (2018). Smoking causes atrial fibrillation? Further evidence on a debated issue. *Eur J Prev Cardiol*, 25(13): 1434-6.

Selmer C, Faber J (2017). Mild thyroid dysfunction: a potential target in prevention of atrial fibrillation? *Circulation*, 136(22): 2117-8.

Serban RC, Scridon A (2018). Data linking diabetes mellitus and atrial fibrillation-how strong is the evidence? From epidemiology and pathophysiology to therapeutic implications. *Can J Cardiol*, 34(11): 1492-502. 104933

Seyed Ahmadi S, Svensson AM, Pivodic A, et al (2020). Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol*, 19(1): 9.

Shabbir MA, Saad Shaukat MH, Arshad MH, et al (2019). Lyme carditis presenting as atrial fibrillation in a healthy young male. *BMJ Case Rep*, 12(6): e229261.

Shah SN, Varghese RG, Theodore S (2021). Histopathological changes in the right atrial appendages triggering atrial fibrillation: A tertiary care center study. *Indian J Pathol Microbiol*, 64(3): 464-8.

Shahim B, Malaisrie SC, George I, et al (2021). Postoperative atrial fibrillation or flutter following transcatheter or surgical aortic valve replacement: PARTNER 3 trial. *JACC Cardiovasc Interv*, 14(14): 1565-74.

Shahrbaf MA, Akbarzadeh MA, Tabary M, et al (2021). Air pollution and cardiac arrhythmias: a comprehensive review. *Curr Probl Cardiol*, 46(3): 100649.

Shin SY, Manuel AR, Lip GY (2019). Atrial fibrillation and end-stage COPD: a close association revisited. *Chest*, 155(5): 888-9.

Shono A, Mori S, Nakamura K, et al (2019). Glucocorticoid-sensitive paroxysmal atrial fibrillation, sick sinus syndrome, and mitral regurgitation in a patient with malignant rheumatoid vasculitis. *Intern Med*, 58(21): 3093-8.

Sidhu K, Tang A (2017). Modifiable risk factors in atrial fibrillation: the role of alcohol, obesity, and sleep apnea. *Can J Cardiol*, 33(7): 947-9.

Simons SO, Elliott A, Sastry M, et al (2021). Chronic obstructive pulmonary disease and atrial fibrillation: an interdisciplinary perspective. *Eur Heart J*, 42(5): 532-40.

Singh S, Heard M, Pester JM, et al (2021). Blunt cardiac injury. Retrieved 16 September 2021, from <https://www.ncbi.nlm.nih.gov/books/NBK532267/>

Sonawale A, Chichkhede A (2018). Cardiovascular manifestations in newly diagnosed hyperthyroid patients and their outcome with anti-thyroid treatment. *J Assoc Physicians India*, 66(6): 22-6.

Spragg D (2022). Epidemiology of and risk factors for atrial fibrillation. Retrieved 30 May 2022, from <https://www.uptodate.com/contents/epidemiology-of-and-risk-factors-for-atrial-fibrillation>

Staerk L, Sherer JA, Ko D, et al (2017). Atrial fibrillation: Epidemiology, pathophysiology, and clinical outcomes. *Circ Res*, 120(9): 1501-17.

Stone E, Kiat H, McLachlan CS (2020). Atrial fibrillation in COVID-19: A review of possible mechanisms. *FASEB J*, 34(9): 11347-54.

Subramanian M, Yalagudri S, Saggi D, et al (2020). Stroke in cardiac sarcoidosis: Need to worry? *Indian Heart J*, 72(5): 442-4.

Sudmantaitė V, Celutkienė J, Glaveckaitė S, et al (2020). Difficult diagnosis of cardiac heamochromatosis: a case report. *Eur Heart J Case Rep*, 4(1): 1-6.

Suryavanshi SV, Li N (2019). Behcet's disease: a (silk) route to atrial fibrillation? *Int J Cardiol*, 293: 117-8.

Szymanska A, Platek AE, Dluzniewski M, et al (2020). History of Lyme disease as a predictor of atrial fibrillation. *Am J Cardiol*, 125(11): 1651-4.

Taha M, Mishra T, Shokr M, et al (2020). Burden and impact of arrhythmias in asthma-related hospitalizations: Insight from the national inpatient sample. *J Arrhythm*, 37(1): 113-20.

Takahira H, Kajiyama T, Kondo Y, et al (2021). Pathophysiological background and prognosis of common atrial flutter in non-elderly patients: Comparison to atrial fibrillation. *J Cardiol*, 78(5): 362-7..

Tattersall MC, Dasiewicz AS, McClelland RL, et al (2020). Persistent asthma is associated with increased risk for incident atrial fibrillation in the MESA. *Circ Arrhythm Electrophysiol*, 13(2): e007685.

Teo TW, Tan BY, Sia CH (2020). 32-year-old with paroxysmal atrial fibrillation after traumatic spinal cord injury. *J Atr Fibrillation*, 13(2): 2324.

Tisdale JE, Chung MK, Campbell KB, et al (2020). Drug-induced arrhythmias: a scientific statement from the American Heart Association. *Circulation*, 142(15): e214-33.

Tsigkas G, Apostolos A, Despotopoulos S, et al (2021). Heart failure and atrial fibrillation: new concepts in pathophysiology, management, and future directions. *Heart Fail Rev*: Epub ahead of print.

Tsagkaris C, Zacharopoulou L (2020). Thyroid Disease (TD), Chronic Obstructive Pulmonary Disease (COPD) and Valvular Heart Disease (VHD) as modifiable risk factors of Atrial Fibrillation. *Rom J Intern Med*, 58(1): 3-4.

Tubeckx MR, Laga S, Jacobs C, et al (2021). Sterile pericarditis in Aachener minipigs as a model for atrial myopathy and atrial fibrillation. *J Vis Exp*, (175): doi: 10.3791/63094.

Ungprasert P, Srivali N, Kittanamongkolchai W (2017). Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Int J Rheum Dis*, 20(4): 434-41.

Uno G, Omori T, Shimada S, et al (2021). Differences in mitral valve geometry between atrial and ventricular functional mitral regurgitation in patients with atrial fibrillation: a 3D transoesophageal echocardiography study. *Eur Heart J*, 22(10):

Upala S, Shahnawaz A, Sanguankeo A (2017). Psoriasis increases risk of new-onset atrial fibrillation: a systematic review and meta-analysis of prospective observational studies. *J Dermatolog Treat*, 28(5): 406-10.

Vadakken ME, Belley-Cote EP, McIntyre WF (2021). New-onset atrial fibrillation in the medical intensive care unit: Catch me if you can. *Pacing Clin Electrophysiol*, 44(11): 1952.

Vaidya K, Semsarian C, Chan KH (2017). Atrial fibrillation in hypertrophic cardiomyopathy. *Heart Lung Circ*, 26(9): 975-82.

van der Hooft CS, Heeringa J, Brusselle GG, et al (2006). Corticosteroids and the risk of atrial fibrillation. *Arch Intern Med*, 166(9): 1016-20.

Ventejou S, Genet T, Leducq S, et al (2021). Multiple erythema migrans and carditis-related atrial fibrillation: exceptional manifestations of early disseminated Lyme disease. *Eur J Dermatol*, 31(1): 112-4.

Verhaert DV, Brunner-La Rocca HP, van Veldhuisen DJ, et al (2021). The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases. *Europace*, 23(Suppl 2): ii40-5.

Vinter N, Frost L, Benjamin EJ (2021). Heart failure and atrial fibrillation - does heart failure subtype matter? *Int J Cardiol*, 341: 46-7. 104942

Vishwanathan S, Tayshetye P, Bilimoria F, et al (2016). Rare cause of atrial fibrillation: a thymic mass. *BMJ Case Rep*, 2016: bcr2016216710.

Viviano A, Kanagasabay R, Zakkar M (2014). Is perioperative corticosteroid administration associated with a reduced incidence of postoperative atrial fibrillation in adult cardiac surgery? *Interact Cardiovasc Thorac Surg*, 18(2): 225-9.

Voskoboinik A, Prabhu S, Ling LH, et al (2016). Alcohol and atrial fibrillation: a sobering review. *J Am Coll Cardiol*, 68(23): 2567-76.

Voskoboinik, A., & Marcus, G. M. (2020). The Impact of Alcohol Intake on Atrial Fibrillation. *Current cardiology reports*, 22(10), 111.

Voskoboinik A, Kalman JM, De Silva A, et al (2020). Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med*, 382(1): 20-8.

Voskoboinik A, Marcus GM (2020). The impact of alcohol intake on atrial fibrillation. *Curr Cardiol Rep*, 22(10): 111.

Vrachatis DA, Papathanasiou KA, Kossyvakis C, et al (2021). Atrial fibrillation risk in patients suffering from type I diabetes mellitus. A review of clinical and experimental evidence. *Diabetes Res Clin Pract*, 174: 108724.

Wan Q, Li S, Hu J (2021). Association of smoking with postoperative atrial fibrillation in patients with cardiac surgery: A PRISMA-compliant article. *Medicine (Baltimore)*, 100(23): e26179.

Wang F, Ahat X, Liang Q, et al (2021). The relationship between exposure to PM2.5 and atrial fibrillation in older adults: A systematic review and meta-analysis. *Sci Total Environ*, 784: 147106.

Wang A, Green JB, Halperin JL, et al (2019). Atrial fibrillation and diabetes mellitus: JACC review topic of the week. *J Am Coll Cardiol*, 74(8): 1107-15.

Wang CC, Chang CT, Lin CL, et al (2016). Spinal cord injury is associated with an increased risk of atrial fibrillation: A population-based cohort study. *Heart Rhythm*, 13(2): 416-23.

Wang Q, Guo Y, Wu C, et al (2018). Smoking as a risk factor for the occurrence of atrial fibrillation in men versus women: a meta-analysis of prospective cohort studies. *Heart Lung Circ*, 27(1): 58-65.

Wang EY, Hulme OL, Khurshid S, et al (2020). Initial precipitants and recurrence of atrial fibrillation. *Circ Arrhythm Electrophysiol*, 13(3): e007716.

Wang X, Hou Y, Wang X, et al (2021). Relationship between serum uric acid levels and different types of atrial fibrillation: An updated meta-analysis. *Nutr Metab Cardiovasc Dis*, 31(10): 2756-65.

Wang N, Sun Y, Zhang H, et al (2021). Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease. *Eur Heart J*, 42(40): 4180-8.

Wang J, Yang YM, Zhu J (2015). Mechanisms of new-onset atrial fibrillation complicating acute coronary syndrome. *Herz*, 40(Suppl 1): 18-26.

Watanabe I (2018). Smoking and the risk of atrial fibrillation. *J Cardiol*, 71(2): 111-2.

Wetterslev M, Haase N, Hassager C, et al (2019). New-onset atrial fibrillation in adult critically ill patients: a scoping review. *Intensive Care Med*, 45(7): 928-38.

Wayne TF Jr, Morales GX, Darrat YH (2018). Clinical aspects of systemic inflammation and arrhythmogenesis, especially atrial fibrillation. *Angiology*, 69(4): 281-5.

Wijarnpreecha K, Boonpheng B, Thongprayoon C, et al (2017). The association between non-alcoholic fatty liver disease and atrial fibrillation: A meta-analysis. *Clin Res Hepatol Gastroenterol*, 41(5): 525-32.

Williams J, Mills MT, Warriner DR (2021). Implications of the 2021 National Institute for Health and Care Excellence atrial fibrillation guidelines. *Br J Hosp Med (Lond)*, 82(9): 1-4.

Wu Z, Fang J, Wang Y, et al (2020). Prevalence, outcomes, and risk factors of new-onset atrial fibrillation in critically ill patients. *Int Heart J*, 61(3): 476-85.

Wuopio J, Arnlov J, Nowak C (2021). [Comment] Response to letter about "Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort". *J Intern Med*, 289(4): 593-4.

Wuopio J, Orho-Melander M, Arnlov J, et al (2021). Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort. *J Intern Med*, 289(5): 700-8.

Xiang B, Ma W, Yan S, et al (2021). Rhythm outcomes after aortic valve surgery: Treatment and evolution of new-onset atrial fibrillation. *Clin Cardiol*, 44(10): 1432-9.

Xu L, Zhang Y, Xie J, et al (2019). Association between gastroesophageal reflux disease and atrial fibrillation: a systematic review and meta-analysis. *Rev Esp Enferm Dig*, 111(11): 874-9.

Yalta T, Yalta K (2018). Systemic inflammation and arrhythmogenesis: a review of mechanistic and clinical perspectives. *Angiology*, 69(4): 288-96.

Yamakawa H, Kato TS, Noh JY, et al (2021). Thyroid hormone plays an important role in cardiac function: from bench to bedside. *Front Physiol*, 12: 606931.

Yang, L., Ye, N., Wang, G., et al (2021). The association between atrial fibrillation and in-hospital outcomes in chronic kidney disease patients with acute coronary syndrome: findings from the improving care for cardiovascular disease in China-acute coronary syndrome (CCC-ACS) project. *BMC cardiovascular disorders*, 21(1), 345.

Ye J, Yao P, Shi X, et al (2021). A systematic literature review and meta-analysis on the impact of COPD on atrial fibrillation patient outcome. *Heart Lung*, 51: 67-74.

Yue C, Yang F, Li F, et al (2021). Association between air pollutants and atrial fibrillation in general population: A systematic review and meta-analysis. *Ecotoxicol Environ Saf*, 208: 111508.

Yun JP, Choi EK, Han KD, et al (2021). Risk of atrial fibrillation according to cancer type: a nationwide population-based study. *JACC CardioOncol*, 3(2): 221-32.

Zainal A, Hanafi A, Nadkarni N, et al (2019). Lyme carditis presenting as atrial fibrillation. *BMJ Case Rep*, 12(4): e228975.

Zanoni S, Siefert JA, Darracq MA (2013). Atrial fibrillation with rapid ventricular response resulting from low-voltage electrical injury. *J Emerg Med*, 45(5): e149-51.

Zhang S, Lu W, Wei Z, et al (2021). Air pollution and cardiac arrhythmias: from epidemiological and clinical evidences to cellular electrophysiological mechanisms. *Front Cardiovasc Med*, 8: 736151.

Zhao J, Liu T, Li G (2014). Relationship between two arrhythmias: sinus node dysfunction and atrial fibrillation. *Arch Med Res*, 45(4): 351-5.

Zhu W, Yuan P, Shen Y, et al (2016). Association of smoking with the risk of incident atrial fibrillation: A meta-analysis of prospective studies. *Int J Cardiol*, 218: 259-66.

Zia I, Johnson L, Memarian E, et al (2021). Anthropometric measures and the risk of developing atrial fibrillation: a Swedish Cohort Study. *BMC Cardiovasc Disord*, 21(1): 602.

Zolotarova TV, Brynza MS, Volkov DY, et al (2021). Predictors of atrial fibrillation recurrence after radiofrequency ablation in patients with chronic heart failure. *Wiad Lek*, 74(8): 1850-5.

Zuin M, Zuliani G, Rigatelli G, et al (2020). [Comment] Atrial fibrillation in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Eur J Intern Med*, 76: 120-2.

Zuo H, Nygard O, Vollset SE, et al (2018). Smoking, plasma cotinine and risk of atrial fibrillation: the Hordaland Health Study. *J Intern Med*, 283(1): 73-82.