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Atrial Fibrillation

Atrial fibrillation: comorbidities, lifestyle, and patient factors

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Summary
Modern anticoagulation therapy has dramatically reduced the risk of stroke and systemic thromboembolism in people with atrial fibrillation (AF). However, AF still impairs quality of life, increases the risk of stroke and heart failure, and is linked to cognitive impairment. There is also a recognition of the residual risk of thromboembolic complications despite anticoagulation. Hence, AF management is evolving towards a more comprehensive understanding of risk factors predisposing to the development of this arrhythmia, its' complications and interventions to mitigate the risk. This review summarises the recent advances in understanding of risk factors for incident AF and managing these risk factors. It includes a discussion of lifestyle, somatic, psychological, and socioeconomic risk factors. The available data call for a practice shift towards a more individualised approach considering an increasingly broader range of health and patient factors contributing to AF-related health burden. The review highlights the needs of people living with co-morbidities (especially with multimorbidity), polypharmacy and the role of the changing population demographics affecting the European region and globally.

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Introduction
Management of atrial fibrillation (AF) has been revolutionised by advances in anticoagulation for stroke prevention leading to the widespread use of non-vitamin K antagonist oral anticoagulants (NOACs, sometimes referred to as direct oral anticoagulants, DOACs). There have also been major advances in the field of treating AF with catheter ablation. Despite widespread anticoagulation for stroke prevention, there remains a residual risk of thromboembolic complications despite anticoagulation. Hence, there is the evolution of AF management towards a more holistic or integrated care approach. This review provides an update on the recent advances in understanding and managing risk factors for AF development and its complications, including a discussion of lifestyle, somatic, psychological and socioeconomic risk factors.

Lifestyle factors
Cardiovascular risk factors and concomitant diseases detection and management were emphasized in recent AF guidelines.[1] An unhealthy lifestyle and risk factors could contribute to an increase in the risk of AF, which is typically influenced by the interaction of multiple factors. Recent studies have reported that lifestyle modification, including weight loss, physical activity, and risk factor modification reduce AF burden and symptom severity.

Physical activity
Regular physical activity (PA) improves cardiovascular health and is associated with lower incidence, recurrence, and burden of AF and better cardiac function, and quality of life (Table 1, Fig. 1) in AF patients.[2,3] Conversely, a sedentary lifestyle is a risk factor for the development of AF.[4,5] A study of accelerometer-measured PA concluded that patients who adhered to the PA guidelines (performing moderate-to-vigorous

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Key messages

- A sedentary lifestyle is a risk factor for the development of AF, and high-intensity interval training improves functional capacity and quality of life in AF.
- Obesity increases the risk of AF, whilst weight loss reduces AF recurrence and symptoms.
- There is a linear dose–response relationship between alcohol use and AF risk.
- Hypertension is associated with a 1.7–2.5-fold increased risk of AF, which can be reduced by antihypertensive therapy.
- Diabetes mellitus is associated with a 1.28-fold increased relative risk of incident AF.
- A history of myocardial infarction increases the risk of AF by 60–77%.
- Chronic obstructive pulmonary disease doubles AF risk.
- Men are usually reported to have a 30–70% higher prevalence of AF than women, but the lifelong risk of AF is similar.
- White people more often develop AF than people of South Asian and Black origin.

physical activity ≥150 min/week) had an 18% lower AF incidence.[6] Meanwhile, concerns exist regarding extreme or endurance exercise increasing AF risk. Several studies reported a higher risk of AF in high-endurance athletes whose exercise levels far exceed standard PA recommendations.[7,8] Nonetheless, high-intensity interval training has recently received attention due to its time efficiency, and reduction of AF burden.[9] High-intensity interval training improves functional capacity and quality of life in AF, similar to moderate-to-vigorous continuous training.[10]

Relatively little is known about the benefit of PA in the context of cardiovascular outcomes such as stroke, heart failure (HF), or mortality in patients with AF. Population-level cohort studies have demonstrated that increasing regular PA is inversely related to all-cause and cardiovascular mortality, sudden cardiac death, dementia, and HF (Table 2).[42–46] The benefit of PA for stroke prevention in AF is inconclusive.[11,42,44,47] A mixture of positive and insignificant results with a lack of statistical power might originate from the small number of stroke events in each study, requiring long-term follow-up (Table 3). The less secure benefit of PA on a lower risk of stroke might be explained by the apparent culprit pathology of stroke in AF—left atrial remodelling and reduced function of the left atrial appendage[48]—which is primarily modified by the use of anticoagulants.

A recent systematic review of exercise interventions in AF patients (12 studies, 670 participants) demonstrated improvements in exercise capacity and quality of life, and a decrease in AF burden with exercise.[113] However, the interventions were limited and heterogenous and future research to co-develop interventions to address the needs of the varied AF population, are warranted. A Cochrane review update examining exercise-based cardiac rehabilitation for AF patients to non-exercise comparators (19 trials, 1948 participants) reported a significant reduction in AF symptom severity and burden, and AF episode frequency and duration, and improvement in quality of life with exercise-based cardiac rehabilitation but no difference in overall quality of life, major adverse CV events or death.[114] The quality of the evidence was low and therefore future high-quality RCTs to examine the efficacy of exercise-based interventions for AF patients are needed.

Patients with AF engage in much less PA than patients without AF.[115] The lower participation in PA could be attributed to advanced age and the multimorbid status.[116] Understanding the reasons for this, and the best strategies for PA promotion needs further exploration.

Obesity

Obesity is a global epidemic and a risk factor for AF development, recurrence, complications after catheter ablation, ischaemic stroke, and death in pre-existing AF.[14,49,50] There are multiple pathophysiological links between obesity and AF (Fig. 2). Conversely, weight loss reduces AF recurrence, burden, and symptoms.[82–84] Although a recent RCT in people with obesity found no benefit from a structured weight reduction program for AF recurrence after catheter ablation, a healthy weight should be promoted in all AF patients.[84]

Several studies have evaluated the impact of weight loss interventions, either focusing on weight loss alone or as a part of multiple risk factor management.[81–83,117] Weight reduction is demonstrated to be associated with lower AF recurrence, burden, duration, and less symptoms.[82–84] Intense weight reduction may improve the profiles of collateral cardiovascular risk factors, thereby contributing to better outcomes in AF. Meanwhile, a recent randomized clinical trial of AF ablation in obese patients demonstrated no difference in AF burden between those with or without a structured weight reduction program.[84] However, a positive effect of BMI reduction on recurrence-free survival in persistent AF was observed, suggesting the importance of weight management as an adjunct to other AF treatment strategies.

Smoking

Smoking is a major modifiable risk factor for cardiovascular diseases. Epidemiological studies and meta-analyses have reported that smoking, especially current smoking, increases the risk of AF.[16] There is a strong dose–response relationship between current smoking and AF risk, with a weaker dose-dependent risk for previous smoking.[16] Childhood second-hand smoke exposure increases risk of adulthood AF, demonstrating the chronic deleterious effects on AF risk after the first exposure.[118] Smoking increases the risk of all-cause death and cardiovascular death in AF.[52] Promotion of smoking cessation is essential as this lowers the risk of ischaemic stroke, dementia, and reduces mortality in AF.[88,89]

Study	Country	Predictor	Number of participants	Results risk estimate (95% CI)
Physical activity (sedentary)				
Faselis, 2016[2]	*United States* Veterans Affairs Medical Center, Washington, DC	Physical fitness on exercise tolerance test vs least fit	5962	Moderately fit: HR 0.80 (0.67–0.97) Fit: HR 0.55 (0.45–0.68) Highly fit: HR 0.37 (0.29–0.47)
Mozaffarian, 2008[4]	*United States* Cardiovascular Health Study	Leisure-time activity vs 1st quintile of activity	5446	3rd quintile: aHR 0.75 (0.61–0.90) 4th quintile: aHR 0.78 (0.65–0.95) 5th quintile: aHR 0.64 (0.52–0.79)
Garnvik, 2018[5]	*Norway* Third Nord-Trøndelag Health study (HUNT 3)	Active vs inactive (in people with obesity)	43,602	HR 0.78 (0.55–1.09)
Andersen, 2013[7]	*Sweden* Vasaloppet skiers (national registries)	Highest number of completed skiing races vs lower number of skiing races (in endurance skiers)	52,755	aHR 1.29 (1.04–1.61)
Svedberg, 2019[11]	*Sweden* Vasaloppet skiers (national registries)	Skiers vs non-skiers	736,102	Women: HR 0.55 (0.48–0.64) Men: HR 0.98 (0.93–1.03)
Jin, 2019[13]	Korea Korean National Health Insurance Service database	WHO recommended physical activity (500–1000 MET min/week) vs inactive	501,690	aHR 0.88 (0.80–0.97)
Obesity				
Wong, 2015[14]	Meta-analysis	Effect of 5 kg/m^2 BMI increase	626,603 [51][a]	Cohort studies: OR 1.29 (1.23–1.36) Case-control studies: OR 1.19 (1.13–1.26)
Obstructive sleep apnoea				
Cadby, 2015[15]	*Australia* Sleep clinic registry	Presence vs absence of apnea/hypopnea index (AHI) > 5/h	6841	aHR 1.55 (1.21–2.00)
Smoking				
Aune, 2018[16]	Meta-analysis	Smoking vs no smoking	Current smokers 388,030 [11][a] Former smokers 372,229 [9][a]	Current smokers: RR 1.32 (1.12–1.56) Former smokers: RR 1.09 (1.00–1.18)
Alcohol				
Larsson, 2014[17]	Meta-analysis	Drinks/week (12 g alcohol/drink) vs < 1 drink/week	79,019	1–6 drinks: aRR 1.01 (0.94–1.09) 7–14 drinks: aRR 1.07 (0.98–1.17) 15–21 drinks: aRR 1.14 (1.01–1.28) >21 drinks: aRR 1.39 (1.22–1.58)
Caffeine				
Shen, 2011[18]	United States The Framingham Heart Study	Caffeine consumption vs lowest quartile	4526	Quartile 2: HR 0.84 (0.62–1.15) Quartile 3: HR 0.87 (0.64–1.20) Quartile 4: HR 0.98 (0.70–1.39)
Conen, 2010[19]	*United States* Women's Health Study	Caffeine consumption vs lowest quintile	33,638	Quintile 2: aHR 0.88 (0.72–1.06) Quintile 3: aHR 0.78 (0.64–0.95) Quintile 4: aHR 0.96 (0.79–1.16) Quintile 5: aHR 0.89 (0.73–1.09)
Cheng, 2014[20]	Meta-analysis	Caffeine consumption vs no consumption	228,465	Any consumption: RR 0.90 (0.81–1.01) Low consumption: RR 0.89 (0.80–0.99) High consumption: RR 0.84 (0.75–0.94)
Bazal, 2021[21]	*Spain* 'Seguimiento Universidad de Navarra' (SUN) and 'Prevención con Dieta Mediterránea' (PREDIMED) cohorts	Moderate coffee intake (1–7 cups/week) vs no intake	25,462	HR 0.60 (0.44–0.82)
Bodar, 2019[22]	*United States* Physicians' Health Study	coffee consumption (cup/week) vs rarely/never	18,960	≤1 cup: aHR 0.85 (0.71–1.02) 1 cup: aHR 0.85 (0.74–0.98) 2–4 cups: aHR 1.07 (0.88–1.30) 5–6 cups: aHR 0.93 (0.74–1.17)
Hypertension				
Rattani, 2019[23]	Atherosclerosis Risk in Communities (ARIC)	Hypertension vs no hypertension	14,915	aHR 1.44 (1.32–1.56)
Lee, 2021[24]	*Korea* Korean National Health Insurance Service database	Hypertension burden category (incremental burden) vs no hypertension	3,726,172	Category 1: aHR 1.13 (1.07–1.19) Category 2: aHR 1.29 (1.23–1.36) Category 3: aHR 1.41 (1.35–1.49) Category 4: aHR 1.46 (1.39–1.53)

(Table 1 continues on next page)

Study	Country	Predictor	Number of participants	Results risk estimate (95% CI)
(Continued from previous page)				
Lipids				
Mora, 2014[25]	*United States*	LDL cholesterol highest versus lowest quintile	23,738	aHR 0.72 (0.56–0.92)
Watanabe, 2011[29]	*Japan*	Low vs normal HDL cholesterol	28,449	Women: aHR 2.86 (1.49–5.50) Men: aHR 1.35 (0.77–2.38)
Ding, 2022[26]	*Sweden* Swedish Apolipoprotein-Related Mortality Risk (AMORIS) cohort	Total cholesterol >5.17 mmol/L LDL cholesterol >3.34 mmol/L	65,136	aHR 0.64 (0.45–0.92) aHR 0.61 (0.41–0.99)
Diabetes mellitus				
Aune, 2018[27]	Meta-analysis	Diabetes vs no diabetes	464,229 [32][a]	RR 1.30 (1.03–1.66)
Benjamin, 1994[141]	*United States* Framingham Heart Study	Diabetes vs no diabetes	4731	OR 2.1 (1.5–2.8)
Lee, 2017[28]	*Korea* Korean National Health Insurance Service database	Combined risk factors (IFG + prehypertension) vs no risk	366,507	HR 1.27 (1.05–1.54)
COPD				
Grymonprez, 2019[30]	*The Netherlands* Rotterdam Study population-based cohort	COPD vs no-COPD COPD with frequent exacerbations vs no COPD	10,943	aHR 1.28 (1.04–1.57) aHR 1.99 (1.42–2.79)
CKD				
Nelson, 2012[31]	*United States* Medicare database	CKD vs no CKD (end-stage CKD excluded)	55,962	Stage 1–2: aHR 1.02 (0.94–1.11) Stage 3–5: aHR 1.13 (1.09–1.18)
Baber, 2011[37]	*United States* Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	CKD vs no CKD	26,917	Stage 1–2: aOR 2.67 (2.04–3.48) Stage 3: aOR 1.68 (1.26–2.24) Stage 4–5: aOR 3.52 (1.73–7.15)
Ethnicity				
Almulhem, 2021[33]	*United Kingdom* Health Improvement Network (THIN) database	South Asian vs White ethnicity	284,610	aHR 0.53 (0.48–0.59)
Aurelius, 2023[285]	*United Kingdom* UK arm of a prospective repository of people with ischaemic stroke	South Asian vs. White ethnicity	3515	OR 0.40 (0.33–0.49)
Mental health				
Ahn, 2022[36]	*Korea* Korean National Health Insurance Database	Mental disorder (depression, insomnia, anxiety, bipolar disorder or schizophrenia) vs no mental disorder	6,576,582	aHR 1.53 (1.44–1.62)
Bae, 2022[218]	*Korea* Korean National Health Insurance Database	Mental disorder (depression, insomnia, anxiety, bipolar disorder or schizophrenia) vs no mental disorder	2,512,690	aHR 1.19 (1.17–1.21)
Chou, 2017[221]	*Taiwan* National Health Insurance Database	Exposure to antipsychotic drugs vs no exposure	68,972	aOR 1.17 (1.10–1.26)
Du, 2022[39]	Systematic review	Anxiety vs no anxiety	549 [5][a]	aRR 2.36 (1.71–3.26)
Feng, 2020[220]	*Norway* Third Nord-Trøndelag Health study (HUNT 3)	Anxiety or depression vs no anxiety or depression	37,402	Mild-moderate anxiety: aHR 1.1 (0.9–1.5) Severe anxiety: aHR 1.0 (0.8–1.4) Mild-moderate depression: aHR 1.5 (1.2–1.8) Severe depression: aHR 0.9 (0.6–1.3)
Fransson, 2018[60]	*Sweden* Swedish Longitudinal Occupational Survey of Health (SLOSH)	Job strain vs no job strain	13,477	aHR 1.48 (1.00–2.18)
Graff, 2017[41]	*Denmark* Danish National Health Survey	Highest vs lowest quintile of perceived stress	114,337	HR 1.01 (0.88–1.16)
Wu, 2022[219]	Meta-analysis	Anxiety Anger Depression Work stress	21,791 [3][a] 21,791 [3][a] 5,160,247 [6][a] 51,664 [4][a]	HR 1.10 (1.02–1.19) HR 1.15 (1.04–1.26) HR 1.25 (1.12–1.39) HR 1.18 (1.05–1.32)

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HDL: high density lipoproteins; HR, hazard ratio; LDL: low density lipoproteins; MMSE, mini mental state examination; OAC, oral anticoagulation; OR, odds ratio; RD, risk difference; RR, relative risk; SEE, systemic embolic events; UD, use difference. [a]Number of studies in a meta-analysis.

Table 1: **Risk factors for the development of atrial fibrillation.**

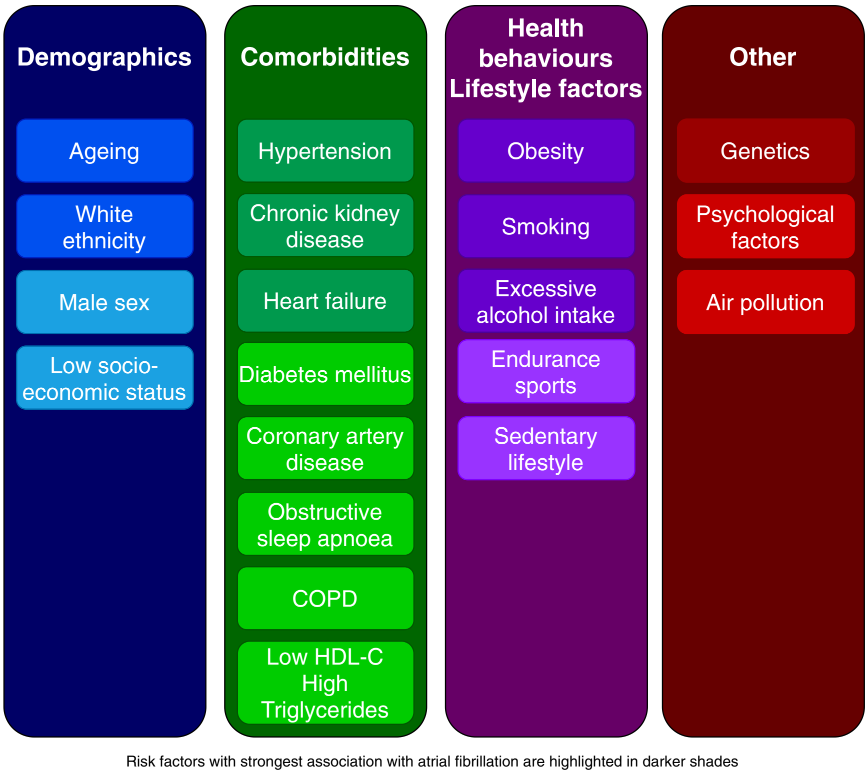

Fig. 1: Factors associated with incident atrial fibrillation.

Alcohol

Alcohol consumption is a well-established risk factor for AF. Although the exact mechanism by which alcohol causes AF is not fully understood, alcohol has a direct effect on the atrium (myocyte injury, inflammation, and fibrosis) and autonomic modulation (sympathetic activation and vagal inhibition), which shorten the atrial action potential and atrial effective refractory period and in turn promote initiation and maintenance of AF.[119] While moderate-high alcohol consumption clearly increases AF risk, effects of low alcohol intake is controversial.[17] A linear rather than a J-shaped dose–response relationship was reported by a meta-analysis.[17] Regarding particular alcoholic beverages, drinking wine and liquor but not beer was related to higher AF risk.[17] In addition to direct cardiac effects (e.g., cardiomyopathy), alcohol could worsen AF risk factor profile, including obesity, hypertension, and OSA.

Moderate-heavy alcohol consumption is associated with an increased risk of progression from paroxysmal AF to persistent AF.[53] After catheter ablation, daily alcohol consumption is associated with unfavourable atrial remodelling and AF recurrence.[54,55] Heavy alcohol consumption (>27 standard drinks/week) increases the risk of thromboembolism and mortality in AF, but moderate consumption may lower risk of ischaemic stroke.[56] However, a recent observational study reported an increased risk of ischaemic stroke in patients with newly diagnosed AF irrespective of the amount of alcohol they consumed.[58]

Alcohol abstinence reduces risk of new AF[90] and its recurrence after catheter ablation.[55] A recent RCT found that alcohol abstinence for 6 months reduced AF recurrence and burden, and improved AF-related quality of life in patients with AF who previously drank ≥10 drinks/week.[92] Furthermore, abstinence from alcohol following a diagnosis of AF may lower the risk of composite outcome and an ischaemic stroke.[57,58]

Caffeine

Coffee is widely consumed worldwide, and a rich source of caffeine. Sympathetic activation could promote AF.[120] However, the antiarrhythmic properties of caffeine include the non-selective inhibition of adenosine receptors and antioxidant properties.[121,122] The net effects of caffeine consumption on AF risk have been debated. Large-scale observational studies, such as the Framingham Heart Study and the Women's Health Study, have found no relationship between chronic caffeine consumption and AF.[18,19] Several meta-analyses reported that caffeine exposure did not increase the risk of AF, or even reduced it.[20] Two recent prospective cohort studies showed that moderate coffee consumption (1–7 cups/week) lowered AF risk.[21,22] Also, even high caffeine

Study	Country	Predictor	Outcomes	Number of patients	Results risk estimate (95% CI)
Exercise					
Garnvik, 2020[42]	*Norway* Third Nord-Trøndelag Health study (HUNT 3)	Active (adherence to physical activity guidelines) vs inactive (self-reported)	Death CV death CV disease Stroke	1117	HR 0.55 (0.41–0.75) HR 0.54 (0.34–0.86) HR 0.78 (0.58–1.04) HR 0.70 (0.42–1.15)
Proietti, 2017[43]	*European region* EURObservational Research Programme on AF (EORP-AF) General Registry	Regular or intense physical activity vs inactive (self-reported)	Stroke or TIA Bleeding CV death or TE or bleeding	2442	*Regular activity:* OR 0.35 (0.07–1.62) OR 0.75 (0.47–1.19) OR 0.40 (0.26–0.63) *Intense activity:* OR 0.83 (0.10–6.65) OR 0.49 (0.17–1.37) OR 0.29 (0.10–0.80)
Ahn, 2021[44]	*Korea* Korea National Health Insurance Service database	New exercisers and exercise maintainers vs non-exercisers	Ischaemic stroke HF Death	66,692	*New exercisers:* HR 0.90 (0.79–1.03) HR 0.95 (0.90–0.99) HR 0.82 (0.73–0.91) *Exercise maintainers:* HR 0.86 (0.77–0.96) HR 0.92 (0.88–0.96) HR 0.61 (0.55–0.67)
Dai, 2022[47]	*United States* Systemic Assessment of Geriatric Elements in AF (SAGE-AF) study	Active (adherence to physical activity guidelines) vs inactive (self-reported)	Death Stroke Major bleeding	1244	aHR 0.60 (0.38–0.95) aHR 1.44 (0.50–4.09) aHR 0.86 (0.56–1.32)
Obesity					
Wong, 2015[14]	Meta-analysis	Effect of 5 kg/m2 BMI increase	Post-operative and post-ablation AF	626,603 [51][a]	*Cohort studies:* OR 1.10 (1.04–1.17) *Case-control studies* OR 1.13 (1.06–1.22)
Tonnesen, 2022[49]	*Denmark* Danish nationwide registers	Increased vs normal weight	Recurrent AF post catheter ablation	9188	*Overweight:* HR 1.15 (1.07–1.23) *Obese:* HR 1.18 (1.09–1.28) *Morbidly obese:* HR 1.26 (1.13–1.41)
Overvad, 2013[50]	*Denmark* Danish Diet, Cancer and Health study	Increased vs normal weight	Ischaemic stroke or TE or death	57,053	*Overweight:* HR 1.31 (1.09–1.56) *Obese:* HR 1.55 (1.27–1.90)
Obstructive sleep apnoea					
Holmqvist, 2015[51]	United States Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)	OSA vs no OSA	Hospitalisation Death CV death or MI or stroke or TIA Major bleeding	10,132	HR 1.12 (1.03–1.22) HR 0.94 (0.77–1.15) HR 1.07 (0.85–1.34) HR 1.18 (0.96–1.46)
Smoking					
Zhu, 2016[52]	Meta-analysis	Smoking vs no smoking	Death CV death Stroke or TE Major bleeding	87,373 [8][a]	RR 1.82 (1.33–2.49) RR 1.54 (1.31–1.81) RR 1.19 (0.97–1.46) RR 1.93 (1.08–3.47)
Alcohol					
Ruigomez, 2005[53]	*United Kingdom* General Practice Research Database (GPRD)	Moderate-high alcohol consumption vs lower or no consumption	Progression to permanent AF	525	OR 3.0 (1.1–8.0)
Qiao, 2015[54]	*China*	Alcohol consumption vs no consumption	AF recurrence after catheter ablation	122	aHR 1.58 (1.09–2.30)
Takigawa, 2016[55]	*Japan*	Risk per 1 day/week increase in alcohol consumption	AF recurrence after catheter ablation	1361	HR 1.07 (1.00–1.15, p = 0.04)

(Table 2 continues on next page)

Study	Country	Predictor	Outcomes	Number of patients	Results risk estimate (95% CI)
(Continued from previous page)					
Overvad, 2013[56]	Denmark The Danish Diet, Cancer and Health study	≥14 drinks/week vs < 14 drinks/week	TE Death	57,053	14–20 drinks/week aHR 0.72 (0.39–1.33) aHR 1.08 (0.79–1.49) 21–27 drinks/week: aHR 1.08 (0.65–1.80) aHR 1.10 (0.80–1.52) >27 drinks/week aHR 1.02 (0.68–1.54) aHR 1.51 (1.20–1.89)
Lim, 2021[57]	*Korea*	Heavy alcohol consumption vs abstainers	Composite adverse outcomes	9411	aHR 1.32 (1.06–1.66)
Lee, 2021[58]	*Korea* Korean nationwide claims and health examination database	Non-drinkers vs current drinkers (per 1000 person-years)	Ischaemic stroke	97,869	Adjusted incidence rate differences −2.98 (−3.81 to −2.15)
Hypertension					
Vemulapalli, 2016[59]	*International* ROCKET-AF trial	Effect of 10 mm Hg increase in screening SBP Hypertension vs no hypertension	Stroke or TE	14,256	Effect of 10 mm Hg increase HR 1.07 (1.02–1.13) Controlled hypertension HR 1.22 (0.89–1.66) Uncontrolled hypertension HR 1.42 (1.03–1.95)
Rao, 2015[136]	*International* ARISTOTLE trial	Hypertension vs no hypertension	Stroke or TE Haemorrhagic stroke Ischaemic stroke Major bleeding	18,201	HR 1.53 (1.25–1.86) HR 1.85 (1.26–2.72) HR 1.50 (1.18–1.90) HR 0.80 (0.66–0.98)
Kim, 2018[61]	*Korea* Korean nationwide claims and health examination database	Hypertension vs no hypertension	Major cardiovascular events, ischaemic stroke, intracranial haemorrhage	298,374	MACE HR 1.12 (1.09–1.14) Stroke HR 1.16 (1.12–1.20) ICH HR 1.27 (1.17–1.39)
Kim, 2019[62]	*Korea* Korean nationwide claims and health examination database	Increase of hypertension duration vs no hypertension	Ischaemic stroke	245,459	0–3 years HR 1.32 (1.23–1.41) 3–5 years HR 1.50 (1.38–1.63) ≥5 years HR 1.51 (1.39–1.65)
Kim, 2020[63]	*Korea* Korean nationwide claims and health examination database	Optimal BP (120–129/80–84 mmHg) vs non-optimal BP (≥140/90 mmHg)	Overall dementia Vascular dementia	171,228	Overall dementia HR 1.07 (1.01–1.13) Vascular dementia HR 1.23 (1.08–1.39)
Diabetes mellitus					
Anselmino, 2015[64]	Meta-analysis	Raised basal glycated haemoglobin	AF recurrence after catheter ablation	1464 [15][a]	Regression coefficient 0.5 (0.1–0.9, p = 0.001)
Proietti, 2016[67]	*Nine European Countries* EURObservational Research Programme Pilot Survey on Atrial Fibrillation Registry (EORP-AF survey)	Diabetes vs no diabetes	CV death TE	3086	aOR 2.30 (1.40–3.80) NS (values not provided)
Coronary artery disease					
Proietti, 2016[67]	*Nine European Countries* EURObservational Research Programme Pilot Survey on Atrial Fibrillation Registry (EORP-AF survey)	CAD vs no CAD	TE CV death	3086	aOR 3.54 (2.24–5.59) NS (values not provided)

(Table 2 continues on next page)

Study	Country	Predictor	Outcomes	Number of patients	Results risk estimate (95% CI)
(Continued from previous page)					
Heart failure					
Uhm, 2021[66]	*Korea* Multicentre, prospective, registry—CODE-AF (COmparison study of Drugs for symptom control and complication prEvention of AF)	- HF with preserved EF - HF with mid-range EF - HF with reduced EF vs no HF	Stroke or TE Major bleeding	10,780	*HF with preserved EF:* aHR 3.19 (1.04–9.81) aHR 4.12 (0.46–36.95) *HF with mid-range EF:* aHR 0.81 (0.18–3.62) No data *HF with reduced EF:* aHR 1.26 (0.34–4.72) aHR 1.22 (0.08–19.62)
Proietti, 2016[67]	*Nine European Countries* EURObservational Research Programme Pilot Survey on Atrial Fibrillation Registry (EORP-AF survey)	HF vs no HF	CV death TE	3086	aOR 9.90 (4.48–21.88) NS (values not provided)
Chronic obstructive pulmonary disease					
Rodriguez-Manero, 2019[192]	*Spain* Data warehouse of the Galician Healthcare Service	COPD vs no COPD	Death TE Bleeding	7990	aHR 1.92 (1.54–2.40) NS (no values not provided) aHR 1.72 (1.16–2.54)
Hirayama, 2018[68]	*United States*	Acute exacerbation of chronic obstructive pulmonary disease vs no acute exacerbation	AF-related emergency department visits or hospitalisations	944	RR 1.93 (1.63–2.29)
Proietti, 2016[67]	*Nine European Countries* EURObservational Research Programme Pilot Survey on Atrial Fibrillation Registry (EORP-AF survey)	COPD vs no COPD	CV death TE	3086	aOR 2.03 (1.15–3.58) NS (values not provided)
Chronic kidney disease					
Ocak, 2022[69]	*Netherlands* The Utrecht Cardiovascular Cohort Second Manifestation of Arterial disease (UCC-SMART) cohort	Combination of CKD with AF, vs CKD or AF alone	Bleeding Ischaemic stroke Death	12,394	RERI 0.62 (−0.75–1.99) RERI 1.88 (0.31–3.46) RERI 0.34 (−0.12–0.81)
Nelson, 2012[31]	*United States* Medicare database	CKD (excluding end-stage CKD) vs no CKD	Death	55,962	*Stage 1–2:* aHR 1.14 (1.00–1.30) *Stage 3–5:* aHR 1.27 (1.20–1.35)
Guo, 2013[76]	China	eGFR $\leq$60 vs eGFR >60	Death Ischaemic stroke Major bleeding	617	aHR 1.78 (1.01–3.11) aHR 1.45 (0.69–3.02) aHR 0.95 (0.35–2.56)
Cognitive decline or dementia					
Nagata, 2023[231]	*Japan* All Nippon AF In the Elderly (ANAFIE) Registry	Cognitive decline (>2 MMSE points)	Death Stroke or TE Major bleeding	2963	HR 1.96 (1.11–3.47) HR 0.97 (0.57–1.65) HR 1.61 (0.79–3.26)
Frailty					
Proietti, 2022[75]	Meta-analysis	Frailty vs no frailty	Death Ischaemic stroke Bleeding	1,187,651 [33][a]	OR (3.46–8.94) OR (1.00–2.52) OR. (1.11–2.41)
He, 2022[251]	Meta-analysis	Frailty vs no frailty	Death Major bleeding	97,413 [10][a]	RR 2.77 (1.68–4.57) RR 1.83 (1.24–2.71)
Wilkinson, 2021[255]	*England* 384 general practices	Severe frailty vs no frailty	All-cause death Gastrointestinal bleeding Falls Stroke	536,955	aHR 4.09 (3.43–4.89) aHR 2.17 (1.45–3.25) aHR 8.03 (4.60–14.0) aHR 1.67 (1.48–1.88)
Wilkinson, 2020[257]	*Multiple countries* Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial	Frailty (for each 0.1 increase in the frailty index)	Stroke or TE Major bleeding	20,867	aHR 1.37 (1.19–1.58) aHR 1.42 (1.27–1.59)
Wilkinson, 2019[253]	Meta-analysis	Frailty vs no frailty	Stroke or death	1321 [3][a]	aOR 0.45 (0.22–0.93)

(Table 2 continues on next page)

Study	Country	Predictor	Outcomes	Number of patients	Results risk estimate (95% CI)
(Continued from previous page)					
Perera, 2009[80]	Australia	Frailty vs no frailty	Death Embolic stroke Major haemorrhage	207 (acute admission)	RR 2.8 (1.2–6.5) RR 3.5 (1.0–12.0) RR 1.5 (0.7–3.0)
Madhavan, 2019[71]	*United States* Outcomes Registry for Better Informed Care in AF (ORBIT AF)	Frailty vs no frailty	Death	9749	HR 1.29 (1.08–1.55)
Mental health disorders					
Farran, 2022[224]	Meta-analysis	Serious mental disorders vs no serious disorders	Stroke Major bleeding	220,014 [3][a] 120,757 [3][a]	HR 1.09 (0.85–1.40) HR 1.11 (0.95–1.28)
Sogaard, 2017[226]	*Denmark* Nationwide Danish Health Registry	Schizophrenia Severe depression Bipolar disease vs none of the above	Ischaemic stroke	534 400 569 matched 1:5 to people without mental disorders	HR 1.37 (0.88–2.14) HR 1.36 (0.89–2.08) HR 1.04 (0.69–1.56)

AF, atrial fibrillation; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HR, hazard ratio; MMSE, mini mental state examination; OAC, oral anticoagulation; OR, odds ratio; OSA, obstructive sleep apnoea; RD, risk difference; RERI: relative excess risk due to interaction; RR, relative risk; SBP, systolic blood pressure; TE, thromboembolic events; TIA, transient ischaemic attack. [a]Number of studies in a meta-analysis.

Table 2: **Effect of risk factors on outcomes in atrial fibrillation.**

intake (>320 mg/day) was associated with a lower AF risk.[123] Overall, current data do not describe moderate coffee consumption as a risk for AF.

Comorbidities

The risk of AF and its complications can be amplified by comorbidities that interfere with the pathogenesis of the arrhythmia. The contributing mechanisms vary and depend on the nature of the comorbidities, including effects on intracardiac haemodynamics, inflammation, hypoxia and metabolic changes.

Obstructive sleep apnoea

OSA, the most common form of sleep-disordered breathing, is common in AF (prevalence 21–74%).[124,125] Intermittent nocturnal hypoxemia or hypercapnia, oscillations in intrathoracic pressure, sympathovagal imbalance, oxidative stress, and systemic inflammation driven by OSA results in the development of a prothrombotic state, atrial fibrosis, and electrical remodeling.[126] OSA increases the risk of AF, and a Mendelian randomization study has confirmed the causal effect.[127] OSA is also associated with the recurrence of AF after electrical cardioversion or catheter ablation, and there is a dose–response relationship between OSA severity and AF incidence and burden.[15] In contrast, continuous positive airway pressure may reduce the incidence, progression, recurrence, and symptoms of AF.[51,86,128] Considering OSA's causal and prognostic effect on AF, screening for OSA in patients with AF should be considered as part of lifestyle modification and treatment strategies.[82,129]

Hypertension

Hypertension is a well-known risk factor for AF and is associated with a 1.7–2.5-fold increased risk of developing AF.[130] The risk of developing AF is particularly high in poorly controlled hypertension.[131] Multivariate analyses from the Atherosclerosis Risk in Communities (ARIC) study reported the risk of development of AF was 1.44-fold higher in people with hypertension, particularly in women who had 1.55-fold higher risk vs. men.[23] There is increasing focus on the dynamic nature of the risk associated with hypertension burden over time and high visit-to-visit variability in BP (a measure of BP control over follow up) which have been associated with AF risk.[24,132,133]

Among people with known AF, hypertension is the most prevalent risk factor, with 1 in 6 cases of AF attributable to hypertension.[134] Identifying new or uncontrolled BP in patients with AF and optimising pharmacological and lifestyle measures to control BP is a key component of the 'C' (cardiovascular and comorbidity) part of the ABC pathway for AF.[135] Left untreated, hypertension results in renal impairment and left ventricular hypertrophy which further increases the risk of AF and its complications.[1] Uncontrolled BP increases both the risk of stroke (ischaemic and haemorrhagic) and the risk of major bleeding associated with oral anticoagulation, as demonstrated in the sub-group analyses of the NOAC trials in AF.[59,62,63,136,137] The Blood Pressure Lowering Treatment Trialists' Collaboration individual patient data meta-analysis demonstrated a significantly lower risk of major adverse cardiovascular events (MACE) and stroke associated with blood pressure lowering drugs in patients with AF at baseline but no difference in cardiovascular or all-cause mortality, over a median 4.5 year follow-up period (Table 3).[93] Therefore, detection of hypertension and control of BP are paramount to prevent development of AF and in those with AF, to optimise management and reduce adverse events.

Study	Country	Treatment	Outcomes	Number of patients	Results risk estimate (95% CI)	Level of evidence
Physical activity						
Mozaffarian, 2008[4]	US	Low- vs. moderate vs. high-intensity exercise	Incident AF	5446	Moderate-intensity exercise: HR 0.72 (0.58–0.89) High-intensity exercise: HR 0.87 (0.64–1.19)	Prospective, Observational cohort study
Azarbal, 2014[85]	US	Total weekly physical activity (MET-h/week)	Incident AF	93,676	Exercise >9 vs. 0 MET-h/week: HR 0.90 (0.85–0.96)	Prospective, Observational cohort study
Garnvik, 2018[5]	Norway	High level of physical activity in obese patients	Incident AF	43,602	HR 1.53 (1.03–2.28) in active HR 1.96 (1.44–2.67) in inactive	Prospective, Observational cohort study
Obesity						
Abed, 2013[81]	Australia	Physician-led multiple risk factor (weight loss, OSA, hypertension, tobacco, alcohol, and glycemic control) modification clinic	AF symptom burden and severity	150	Greater reduction in AF symptom burden scores (11.8 and 2.6 points, P < 0.001), symptom severity scores (8.4 and 1.7 points, P < 0.001) in the intervention group compared with the control group	RCT
Pathak, 2014[82]	Australia	Weight loss target BMI <27 kg/m^2 or >10% weight loss	Recurrent AF after AF ablation	149	HR 4.8 (2.04–11.4)	Prospective, Observational cohort study
Pathak, 2015[83]	Australia	Goal-directed weight loss: - 3–9% weight loss - <3% weight loss compared to weight loss ≥10%	AF burden as determined by symptom burden and AF freedom	355	weight loss 3–9%: HR 2.0 (1.4–2.9) weight loss <3%: HR 3.0 (2.0–4.3)	Prospective, Observational cohort study
Gessler, 2021[84]	Germany	weight-reduction	AF burden between 3 and 12 months after AF ablation	133	OR 1.14 (0.37–3.61)	RCT (SORT-AF)
Obstructive sleep apnoea						
Patel, 2010[87]	US	Continuous positive airway pressure	AF recurrence after AF ablation	640	HR 0.17 (0.08–0.36)	Retrospective, observational
Qureshi, 2015[86]	Multiple countries	Continuous positive airway pressure	incident AF	[8][a]	Pooled RR 0.58 (0.47–0.70)	Meta-analysis
Hunt, 2022[91]	Norway	Continuous positive airway pressure	AF recurrence after AF ablation	83	OR 1.0 (0.4–2.4)	RCT
Smoking						
Lee, 2021[88]	Korea	Smoking cessation	Incident ischaemic stroke and all-cause death in AF patients	97,637	ischaemic stroke: HR 0.70 (0.60–0.83) all-cause death: HR 0.84 (0.75–0.95)	Observational study
Lee, 2022[89]	Korea	Smoking cessation	Incident dementia in AF patient	126,252	HR 0.83 (0.72–0.95)	Observational study
Alcohol						
Dixit, 2017[90]	US	Alcohol cessation	Incident AF	15,222	HR per decade 0.80 (0.72–0.89)	Prospective, Observational cohort study
Takahashi, 2021[94]	Japan	Alcohol cessation	AF recurrence after AF ablation	3474	Alcohol reduction ≥1%: HR 0.63 (0.52–0.77)	Prospective, Observational cohort study
Voskoboinik, 2020[92]	Australia	Alcohol abstinence	freedom from recurrence of AF	140	HR 0.55 (0.36–0.84)	RCT
Lee, 2021[58]	Korea	Alcohol abstinence	incident ischaemic stroke in AF patient	97,869	HR 0.86 (0.77–0.96)	Observational study
Hypertension						
Pinho-Gomes, 2021[93]	Multiple countries Blood Pressure Lowering Treatment Trialists' Collaboration	BP-lowering drugs versus placebo in patients with AF recorded at baseline	Composite endpoint: stroke, IHD, or HF Stroke CV death All-cause mortality	188,570 [22][a] 13,266 (7%) had AF at baseline	5-mm Hg SBP reduction: Composite: HR 0.91 (0.83–1.00) Stroke: HR 0.83 (0.71–0.96) CV death: HR 0.92 (0.80–1.03) ACM: HR 1.01 (0.91–1.10)	Individual patient data meta-analysis
Emdin, 2015[98]	Multiple countries	BP-lowering drugs vs no BP-lowering treatment	Incident AF	214,763 [27][a]	RR 0.90 (0.86–0.94)	Meta-analysis of RCTs

(Table 3 continues on next page)

Study	Country	Treatment	Outcomes	Number of patients	Results risk estimate (95% CI)	Level of evidence
(Continued from previous page)						
Diabetes mellitus						
Dublin 2010[95]	USA	Pharmacological treatment of DM	Incident AF (treated DM vs. no-DM) Effect of DM treatment on incident AF (per additional 1 year of duration) Duration of DM on incident AF (DM vs. no DM) ≤5 years >5 but ≤10 years >10 years	1410 with AF 2203 controls without AF	aOR 1.40 (1.15–1.71) aOR 1.03 (1.01–1.06) aOR 1.07 (0.75–1.51) aOR 1.51 (1.05–2.16) aOR 1.64 (1.22–2.20)	Population based case–control
Larsson, 2018[96]	Sweden	Pharmacological DM treatment	Incident AF Incident AF (only for ≥20 years DM duration)	71,483	HR 1.01 (0.91–1.12) HR 1.44 (1.02–2.04)	Two population based prospective cohorts
Huxley, 2012 ARIC study[97]	USA	Pharmacological DM treatment	Incident AF	13,025	aHR 1.35 (1.14–1.60)	Prospective cohort study
Chang, 2014[144]	Taiwan	Metformin vs. no DM drugs	Incident AF	645,710	aHR 0.81 (0.76–0.86)	National Health Insurance Research Database
Chao, 2012[100]	Taiwan	Thiazolidinediones vs. no thiazolidinediones	Incident AF	12,065	aHR 0.69 (0.49–0.61)	National Health Insurance Research Database
Zhang, 2017[99]	Multiple countries	Thiazolidinediones vs. no thiazolidinediones	Incident AF	130,854 [7, 3 RCTs, 4 cohorts][a]	OR 0.73 (0.62–0.87)	Meta-analysis
Coronary artery disease						
Hiraya, 2019[101]	Japan	CAD vs. no CAD as modifiers of catheter ablation outcomes	Recurrence of AF after AF ablation	681	HR 1.45 (1.05–1.97)	Observational study
Kornej, 2015[103]	Germany	CAD vs. no CAD as modifiers of catheter ablation outcomes	Recurrence of AF after AF ablation	1310	OR 0.87 (0.6–1.25)	Observational study
Heart failure						
Marrouche, 2018[102]	Multiple countries	AF ablation vs.pharmacological therapy in patients with HF	Composite: death, unplanned hospitalisation for HF	363	HR 0.62 (0.43–0.87)	RCT (CASTLE-AF)
Packer, 2021[106]	Multiple countries	AF ablation vs. pharmacological therapy in patients with HF	Composite: death, disabling stroke, serious bleeding, or cardiac arrest Death	778	HR 0.64 (0.41–0.99) HR 0.57 (0.33–0.96)	Subanalysis of RCT (CABANA)
Rillig, 2021[104]	Multiple countries	Rhythm vs rate control in patients with HF	Composite: cardiovascular death, stroke, hospitalisation for worsening of HF or acute coronary syndrome	798	HR 0.74 (0.56–0.97)	Subanalysis of RCT (EAST-AFNET 4)
Yang, 2021[105]	Korea	AF ablation vs.pharmacological therapy in patients with HF	Death Cardiovascular death hospitalisation for HF Stroke/systemic embolism	3173	HR 0.42 (0.27–0.65) HR 0.38 (0.32–0.62) HR 0.39 (0.33–0.46) HR 0.44 (0.37–0.53)	Observational study
Asad, 2019[107]	Multiple countries	AF ablation vs.pharmacological therapy in patients with HF	Death Cardiovascular admission Atrial arrhythmia	4464 [18][a]	RR 0.52 (0.35–0.76) HR 0.56 (0.39–0.81) RR 0.42 (0.33–0.53)	Meta-analysis
Wang, 2022[108]	Multiple countries	SGLT2 inhibitors vs. placebo	Incidence of AF or atrial flatter	52,951 [20][a]	OR 0.82 (0.73–0.93)	Meta-analysis
Abraham, 2021[109]	11 countries EMPERIAL-Reduced RCT	Empagliflozin vs. placebo	Incidence of AF or atrial flatter	312	OR 0.33 (0.01–8.19)	RCT
Abraham, 2021[109]	11 countries EMPERIAL-Preserved RCT	Empagliflozin vs. placebo	Incidence of AF or atrial flatter	315	OR 0.66 (0.11–3.99)	RCT

(Table 3 continues on next page)

Study	Country	Treatment	Outcomes	Number of patients	Results risk estimate (95% CI)	Level of evidence
(Continued from previous page)						
McMurray, 2019[300]	20 countries DAPA-HF RCT	Dapagliflozin vs. placebo	Incidence of AF or atrial flatter	4744	OR 0.98 (0.74–1.30)	RCT
Chronic obstructive pulmonary disease						
Noubiap, 2023[194]	UK	Pharmacological treatment with achieved FEV1/FVC ratio <0.70 vs ≥ 0.70	AF incidence	348,219	HR 1.23 (1.19–1.28)	Prospective registry (UK biobank)
Chronic kidney disease						
Naruse, 2011[216]	Japan	CKD vs. no CKD as modifiers of catheter ablation outcomes	AF recurrence	221	HR 2.10 (1.29–3.38)	observational study
Mental health disorders						
Cao, 2022[112]	Multiple countries	Antidepressants vs no antidepressants	AF incidence	2,626,746 [6][a]	RR 1.37 (1.16–1.61)	Systematic review
Chou, 2017[221]	Taiwan	Antipsychotics vs no antipsychotics	AF incidence	68,972	aOR: 1.17 (1.10–1.26)	Nationwide observational study

aHR, adjusted hazards ratio; aOR, adjusted odds ratio; AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; FEV, forced expiratory volume; FVC, forced vital capacity; HF, heart failure; HR, hazards ratio; MET, Metabolic equivalent of task; OR, odds ratio; OSA, obstructive sleep apnoea; RCT, randomised controlled trial; SGLT2, Sodium-glucose co-transporter-2. [a]Number of studies in a meta-analysis. No studies assessed the effect of approved treatments for dementia on AF or its outcomes, including donepezil, rivastigmine, galantamine and memantine.

Table 3: **Effect of treatment of modifiable risk factors on incidence of atrial fibrillation.**

Lipids

Although the association between hypercholesterolaemia and development of atherosclerosis and coronary artery disease (CAD) is well-established,[138] and the presence of CAD increases the risk of AF, the relationship between lipids and incident AF remains unclear. A systematic review,[130] examining the relationship between total cholesterol and incident AF found no significant association. However, several studies reported a reduction in risk of incident AF with elevated total cholesterol (relative risk 0.76–0.94).[25,130,139] Multiple prospective and retrospective cohort studies have shown that high levels of low-density lipoprotein cholesterol (LDL-C), and total cholesterol are associated with lower risk of AF, the so-called 'cholesterol paradox'.[25,140] A recent retrospective analysis of >65,000 people aged 45–60 years free of cardiovascular disease from the Swedish national registries, found a lower risk of incident AF associated with higher levels of LDL-C and total cholesterol (HR 0.64, 95% CI 0.45–0.92; and HR 0.61, 95% CI 0.41–0.99) within the first 5 years of follow-up.[26] In contrast, a higher risk of AF was associated with lower levels of HDL-C, and higher triglycerides.[26]

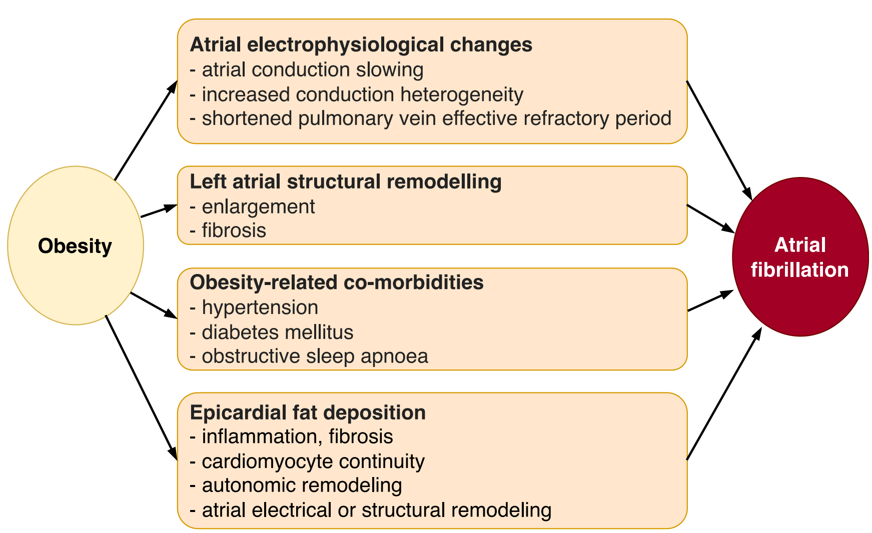

Fig. 2: Mechanisms linking obesity and risk of atrial fibrillation.

The effect of lipoproteins on haemostasis increases the risk of thromboembolism but the evidence in patients with AF has not yet been well-elucidated, with several studies reporting increased risk of ischaemic stroke with high LDL-C levels[140] with less robust findings for the stroke risk associated with lipoprotein (a), A1 and B1.[140] Lipid management in patients with AF reduces overall cardiovascular risk and its associated complications, and is one of the cardiovascular risk factors in the 'C' component of the ABC pathway.[135]

Diabetes mellitus

Diabetes mellitus is a recognised risk factor for incident AF.[130] The Framingham Heart Study identified diabetes mellitus as a risk factor for AF and it has been included as component in multiple stroke risk scores.[141] A recent meta-analysis confirmed an 1.28-fold increased relative risk of incident AF associated with diabetes mellitus.[27] In addition, those with pre-diabetes (defined as HbA1c level 5.7%–6.4%) were at 1.2-fold greater relative risk of AF in a meta-analysis of observational studies.[27]

There is some evidence that duration of diabetes and quality of glycaemic control impacts the risk of developing AF. In a population-based case–control study, among patients treated for diabetes, there was a 3% greater risk of incident AF for every extra year of diabetes duration (adjusted odds ratio per year 1.03) and with worsening glycaemic control with adjusted odds approximately 1.5 for HbA1c ranging 7–9, and adjusted odds of about 2 for HbA1c over 9.[95] In a Swedish population-based study, risk of incident AF was only increased in those with 20-years of insulin treatment, or where concomitant cardiovascular disease was present.[96] In other studies,[97] after adjustment for other risk factors/confounders, the risk of incident AF associated with diabetes was not significant. In a healthy Asian population-based study without comorbidities, prehypertension and IFG were important risk factors of AF.[28] There are several common underlying pathophysiological mechanisms underpinning diabetes mellitus and AF, atrial structural remodelling (atrial fibrosis and dilatation), plus electromechanical, and autonomic remodelling, and oxidative stress, inflammation, and glycaemic fluctuations.[142]

Diabetes mellitus is prevalent in 20–25% of people with AF[143] and optimising the management of diabetes is also a key element in the 'C' part of the ABC pathway.[135] Treatment should focus on glycaemic control and management of other risk factors associated with diabetes (obesity, physical inactivity, poor diet, and alcohol consumption). Good glycaemic control reduces the risk of AF by preventing/slowing atrial remodelling, although the evidence is limited and varies by pharmacological agent, with metformin[144] and thiazolidinediones[99] demonstrating a lower risk of incident AF (Table 3). There is no evidence of a reduction in incident AF associated with sulfonylureas or insulin.[142] Further studies are required on the newer glycaemic agents, DDP-4 inhibitors, GLP-1 receptor agonists, and SLGT2 inhibitors which have demonstrated significant reductions in cardiovascular events and death but not on AF incidence to date.[145]

In those with AF, good glycaemic control may reduce AF burden although supporting evidence is limited. A meta-analysis showed greater risk of AF recurrence among patients with higher HbA1c levels following catheter ablation.[64] Diabetes mellitus also increases the risk of thromboembolism in AF and sub-group analyses from the NOAC trials demonstrate a reduction in stroke and systemic embolism, intracranial haemorrhage and cardiovascular death with NOAC compared to warfarin among patients with diabetes.[146]

Coronary artery disease

The risk of incident AF rises by 60–77% post-myocardial infarction (MI), and AF itself may increase the risk of acute coronary events.[147,148] New-onset AF typically occurs during the first 4 days after acute MI, and is associated with more than doubling of the risk of death, congestive HF, and stroke.[149] Patients with AF and acute coronary syndromes are less likely to receive appropriate antithrombotic therapy and more likely to experience adverse outcomes than patients without AF.[1] Overall, 10–15% of AF patients undergo percutaneous coronary interventions (PCI) for CAD and combined antithrombotic treatment-related benefits and bleeding need to be carefully balanced.[150] Dual antithrombotic therapy including oral anticoagulation (preferably NOAC) and a P_2Y_{12} inhibitor (preferably clopidogrel) is associated with less major bleeding and intracranial haemorrhage than triple therapy. Dual therapy is recommended for the first 12 months after PCI for acute coronary syndromes, or 6 months after PCI for stable CAD.[151] Thereafter, oral anticoagulant monotherapy is continued, similar to patients with stable CAD.[152]

Heart failure

AF and HF share common risk factors and frequently coexist.[153] About half of patients with HF develop AF, but AF prevalence varies depending on clinical settings (acute versus chronic), left ventricular function, functional class, and HF therapies.[154] AF may exacerbate HF through decreased cardiac output secondary to loss of atrial systole, increased myocardial oxygen consumption and diminished coronary perfusion during rapid ventricular responses, neurohormonal activation and tachycardia-induced cardiomyopathy.[155]

AF increases mortality and thromboembolism in HF.[156] Higher stroke risks are observed in the HF with preserved ejection fraction (HFpEF) than other types of HF.[66] Unless contraindicated, long-term oral anticoagulation is recommended in all patients with HF with AF. NOAC is preferred for the prevention of thromboembolic events in patients with AF.[157] The efficacy and safety of NOACs is comparable in AF irrespective of HF.[158]

All patients with HF and AF should receive guideline-adherent HF therapy.[159] The optimal heart rate target in AF with HF remains unclear, although a heart rate under 100–110 bpm (lenient rate control) is usually recommended.[159] Higher heart rates are associated with worse outcomes in observational studies.[160,161] The benefit of beta-blocker therapy in reducing mortality in AF patients with HF with reduced ejection fraction (HFrEF) has been questioned by some meta-analyses.[162]

Recent controlled trials and observational analyses demonstrated that early rhythm control therapy is beneficial for AF patients.[155,163–167] Combined with the effectiveness of early rhythm control,[163] these findings suggest a wider use of rhythm control therapy to improve symptoms and quality of life, and provide an additional avenue to prevent outcomes such as stroke and cardiovascular death.[104,163,168] Benefit of early rhythm control was demonstrated in asymptomatic patients,[168] those with heart failure,[104] and high stroke risk.[169] In real-world data, the benefit of early rhythm control was also observed in those with low stroke risk.[170]

In patients with HF and reduced LVEF, two RCTs have shown a reduction in all-cause mortality and hospitalisations with AF catheter ablation.[102,171] The generalizability of the trial has recently been evaluated in a large HF patient population.[105,172] The smaller AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) RCT, which included patients with more advanced HFrEF, did not show benefits gained by AF catheter ablation at 1-year follow-up,[173] whereas a recent CABANA subgroup analysis supported the benefits of AF catheter ablation in patients with HFrEF.[165] Overall, AF catheter ablation in patients with HFrEF results in higher rates of preserved sinus rhythm and greater improvement in LVEF, exercise performance, and QoL compared with AAD and rate control.[102,171,174–181] A recent single-centre, open-label trial was terminated early given the clear benefits of catheter ablation for symptomatic AF compared to medical therapy in end-stage HF, but improving the composite primary outcome of death from any cause, implantation of a left ventricular assist device or urgent heart transplantation (HR 024, 95% CI 0.11–0.52) and all-cause mortality (HR 0.29, 95% CI 0.12–0.72).[182] Accordingly, AF ablation in patient with HFrEF patients is a class I indication regardless of their symptom status according to the current ESC AF guidelines.[1]

Cardiomyopathies

AF is common in patients with inherited cardiomyopathies, and maybe the presenting feature.[183] Inherited cardiomyopathies, due to mutations in genes encoding specific structural proteins, are associated with atrial remodelling, histological changes, and modifications in atrial action predisposing to AF.[184] AF may occur as a consequence of disease-specific defects and/or non-specific cardiac chamber changes secondary to the primary illness.[185] AF occurs in 20–30% of patients with hypertrophic cardiomyopathy (HCM) with an annual incidence of 2%.[186,187] AF in HCM is associated with a high risk of strokes, systemic embolism and death.[186–190] Oral anticoagulation is recommended the HCM with AF (considered part of 'C' criterion of CHA_2DS_2-VASc score).[191] AF is also common in arrhythmogenic right ventricular dysplasia/cardiomyopathy (11–30%), familial dilated cardiomyopathy (33%), and left ventricular non-compaction cardiomyopathies (1–29%), and associated with worsened prognosis.[185] The risk of stroke is not well-defined in cardiomyopathies except HCM, but there is stronger consensus for oral anticoagulation in left ventricular non-compaction cardiomyopathies with AF/atrial flutter.[65] Maintenance of sinus rhythm has been achieved in up to two-thirds of HCM patients, although repeat procedures or continuation of antiarrhythmic medications are often necessary.[185] The role of ablation procedures in other cardiomyopathies is unclear.

Respiratory disease

Chronic obstructive pulmonary disease (COPD) is present in up to 23% of AF patients[67] and COPD is associated with a 2-fold increase in AF risk.[192,193] A recent study reported that among 46 studies, the pooled prevalence of COPD was 13% in AF patients. COPD was associated with higher prevalence of comorbidities, higher CHA_2DS_2-VASc score and lower beta-blocker prescription. COPD was also associated with higher risk of all-cause death (OR 2.22, 95% CI 1.93–2.55), CV death (OR 1.84, 95% CI 1.39–2.43), and major bleeding (OR 1.45, 95% CI 1.17–1.80); no significant differences in outcomes were observed according to beta-blocker use in AF patients with COPD.[110] Reduced ventilatory function is associated with increased risk of AF independently from age, sex, smoking, and other known AF risk factors.[194] COPD and AF share common risk factors, but COPD might also directly contribute to the onset of AF through right ventricular strain-triggered changes in cardiac geometry and haemodynamics.[193] Both corticosteroids and theophylline used in COPD may increase the risk of AF.[193]

COPD should be suspected and spirometry considered in AF patient with chronic dyspnoea or reduced exercise tolerance, especially as it may co-exist with HF. Acute exacerbation of COPD transiently increases AF risk due to hypoxia-mediated mechanisms, inflammation, increased use of beta-2 agonists, and autonomic changes. COPD in patients with AF is associated with the reduced success of rhythm control strategies using cardioversion or catheter ablation.[195–197] It remains unclear whether treatment of COPD improves AF outcomes.[193] Whilst both the inhaled beta2-agonists and anticholinergics have been associated with tachyarrhythmias,[198] the risk for cardiac arrhythmias in patients treated by anticholinergics is much lower. Inhaled corticosteroids do not seem to increase AF risk. Studies showed a reduction in mortality and a reduction in exacerbation rate in AF patients with COPD treated by selective beta-1 blockers.[199,200]

Air pollution

One in five CVD deaths are attributable to air pollution and the effect varies according to age, sex, socioeconomic status, comorbidities, and geographical location.[201,202] Older people, those with concomitant cardiovascular disease, higher BMI, and people from LMICs and Asia (due to the higher levels of air pollution) are at greater risk of AF.[203] Four meta-analyses have demonstrated that increased short-term exposure to air pollution is associated with higher risk of AF but the data regarding long-term exposure was inconsistent.[204–207]

Renal disease

AF and chronic kidney disease (CKD) also share common risk factors, such as hypertension.[208] They often coexist: 20% of patients with CKD have AF, and 50% of patients with AF have some degree of renal impairment.[209] The risks and benefits of oral anticoagulation in AF may be altered by renal dysfunction.[210] In mild-to-moderate CKD (CrCl 30–49 mL/min), NOACs can be safely used.[211–213] In patients with CrCl 15–29 mL/min, robust RCT-derived data on NOAC use are lacking, even more so for end-stage kidney disease. Observational data questions the benefit of oral anticoagulation in end-stage kidney disease but suggests possible lower bleeding risk of NOACs vs. warfarin.[214,215]

Reduced renal function predisposes to adverse drug effects.[209] Patients with AF and CKD have more periprocedural complications with PCI or catheter ablation,[209] yet, catheter ablation has lower rates of symptomatic AF recurrence compared with drug treatment.[111,165] In patients under haemodialysis, catheter ablation is increasingly performed for rhythm control since the use of antiarrhythmic agents is restricted.[216]

Mental health disorders

In addition to somatic risk factors, stress, psychological factors, and the state of an individual's mental health may influence the occurrence, symptoms, treatments, and outcomes of AF.[217] The presence of mental health disorders increases the risk of AF perhaps through predisposition to risk factors for AF (e.g., alcohol, illicit substance misuse), inadequate management of risk factors (poor adherence to antihypertensive drugs, lifestyle modifications), or side effects of medications (antipsychotic drugs, lithium).[35,218] The psychological morbidity associated with AF requires close attention given the impact on AF course and quality of life.[40]

Stress is associated with a higher risk of hypertension, and MI, contributed to by adrenergic and endocrine stimulation (especially acute stress) and unhealthy lifestyle behaviours (chronic stress). The Danish National Health Survey showed a higher AF incidence in people with greater perceived stress, but this was non-significant after adjustment for comorbidities, socioeconomic and lifestyle factors.[41] The Swedish Longitudinal Occupational Survey of Health (SLOSH) showed that job strain was independently associated with an almost 50% increase in AF risk, consistent with a recent meta-analysis.[219] However, such analyses do not allow mechanistic insights into the associations. For example, a stressful job may impair adherence to antihypertensive treatments. In contrast, relaxation techniques, such as yoga, may help to mitigate the risk.[38]

Anxiety disorders generally do not increase AF risk,[220] although anxiety is highly prevalent in people with AF. Analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) data found no significant association for anger, anxiety, or chronic stress with the development of AF.[217] However, depression has been consistently related to higher AF incidence. MESA data showed that the presence of depression and the use of antidepressants was associated with a 34% and 36% higher risk of AF, respectively.[217] Also, people with depression tend to have more AF symptoms, which improve with better depression control.[34] Most studies show a higher risk of AF in people with schizophrenia, partially attributed to antipsychotic medications.[36] Antipsychotic drug use poses a dose-dependent AF risk, especially for antipsychotics with higher binding affinity to muscarinic M2 receptors.[221]

In the Danish health registries, only 33.7% of people with schizophrenia received oral anticoagulation within the first year after AF diagnosis, compared with 54.4% of patients without schizophrenia.[222] Bipolar disorder and schizophrenia were associated with a lower frequency of initiation of oral anticoagulation within 90 days after incident AF and lower oral anticoagulant use in patients with prevalent AF.[223] In the Finnish Anti-Coagulation in Atrial Fibrillation (FinACAF) registry, a lower proportion of patients with any mental health disorder were initiated on oral anticoagulation (64.9% vs 73.3% with a similar pattern for all considered mental disorders).[78] Non-persistence to NOACs was also reported in people with mental health disorders (HR 1.32 for depression, HR 1.44 for bipolar disorder, and HR 1.30 for schizophrenia). When receiving warfarin, people with bipolar disorder experienced poorer anticoagulation control (time in INR therapeutic range).[224] However, patients with anxiety without other mental health disorders were not at increased risk of non-persistence with oral anticoagulation.[225] These high-quality observational studies are consistent with the results of a systematic review showing that people with

AF and mental health disorders were less likely to receive oral anticoagulation.[79]

It remains unclear if severe mental health disorders increase the risk of AF-related stroke. In the Danish nationwide registry with over 5-years follow up of patients with AF, those diagnosed with schizophrenia, depression or bipolar disorder were not at higher risk of stroke or major bleeding.[226] A systematic review did not find an association between serious mental health illnesses and stroke or major bleeding after adjustment for risk factors for stroke and bleeding.[224] It is likely any excess of AF-related strokes and bleeding in people with mental health disorders is due to poorly controlled risk factors. Although treatment adherence may be challenging for people with mental health disorders, limited data exist on how this influences rhythm and rate control strategies in AF. People with mental health disorders tend to be underrepresented in clinical trials, making the results less generalisable to this population.

Cognitive impairment

Cognitive impairment does not have established links with the risk of developing AF. There are cautions about prescribing cholinesterase inhibitors used to treat Alzheimer's disease, although these have not been associated with increased risk of AF.[227] In contrast, people with AF are at higher risk of cognitive decline and dementia, including vascular dementia and, to a lesser degree, Alzheimer's disease.[228,229] The risk relates to survivors of AF-related stroke and those without stroke history.[228] AF may increase the dementia risk in those younger than 65.[230] However, the strength of such evidence is inconsistent, and some data only showed a significant and steep increase in dementia risk after the age of 65.[70] Of note, dementia reciprocally puts people with AF at higher risk of cardiovascular and all-cause death.[231]

Proving the causative relationship between AF and dementia is challenging due to the shared risk factors, such as advanced age, hypertension, diabetes, and dyslipidemia. However, the association between AF and cognitive impairment remains after adjusting for these risk factors.[232,233] Repeated ischaemic brain injuries led to stepwise cognitive decline, and stroke survivors had a 2.4-fold risk of dementia in a meta-analysis of observational studies.[229] Silent cerebral infarcts also increased risk of cognitive decline.[234] AF also contributes to cognitive impairment through the chronic decrease in cerebral perfusion due to reduction of the stroke volume (loss of atrial systole), variability of stroke volume (irregular rhythm), atrial-ventricular desynchrony and cerebral vascular dysfuncion.[235,236] Nearly all participants of the SWISS-AF study had brain matter lesions, and about 20% had small infarcts, large infarcts, or microbleeds.[237]

A 27–50%-reduction in dementia rates in people with sinus rhythm restored by catheter ablation supports the mechanistic link between AF and dementia.[238–240] Catheter ablation reduced risk of both vascular dementia and Alzheimer's disease.[238] The prospective European Strat-AF study demonstrated that the risk of cognitive impairment in AF paralleled the risk of stroke quantified using the CHA_2DS_2-VASc score.[241] Accordingly, population-level data from Sweden indicated a 56% reduction in dementia risk if people received anticoagulation, especially if the treatment was within the first year of AF diagnosis.[242] Oral anticoagulation was associated with a 60% reduction in dementia risk in AF.[243–246] Adequate OAC is essential in mitigating the risk of AF-related cognitive impairment. Population-level observational studies showed lower incidence of dementia in people managed by rhythm control vs rate control strategy (sub-distribution HR 0.86, 95% CI 0.80–0.93) and in patients treated by ablation vs medical therapy (HR 0.73, 95% CI 0.58–0.93).[238,247] Initial promising data indicate benefits of SGLT2 inhibitors for dementia reduction in AF, but further evidence is needed.[248] Lifestyle improvement reduces the risk of dementia in AF, especially regular exercise (adjusted HR 0.66; 95% CI 0.61–0.72) and smoking cessation (HR 0.83, 95% CI 0.72–0.95).[89,249] While AF increases the risk of dementia, integrated care mitigates the risk. Adherence to the ABC pathway reduced the risk of dementia by 20%.[250]

Frailty

Frailty is a clinical state characterised by a decrease in homeostatic reserves, vulnerability to endogenous and exogenous stressors, and increased risk of adverse health-related outcomes.[72] People with frailty often have multimorbidity and polypharmacy and need special consideration regarding optimal AF management. Studies vary on frailty assessment methods and thresholds that must be considered when interpreting study results. The prevalence of frailty in patients with AF ranged between 5.9% and 89.5%, influenced by assessment method, age, history of stroke, and geographical location.[251] The overall prevalence of frailty in AF patients in the community is estimated at 17%, which is higher than previous estimates (12% prevalence) in general community cohorts, irrespective of frailty tools used for assessment.[252] Analyses of the ESC-EHRA EORP-AF General Long-Term Registry of 10,177 AF patients predominantly recruited from secondary care identified 21.3% as frail.[75] A pooled analysis of 33 studies (1,187,651 patients) showed a frailty prevalence of 39.7% (95 %CI 29.9 %–50.5%).[253] The variability likely reflects different approaches studies used to define frailty and the frailty spectrum of patients.

In people with AF, frailty was associated with increased stroke incidence, all-cause mortality, and major bleeding.[251] Frailty is a stronger predictor of mortality in patients with AF than in the general population.[77] Frail patients were less likely to receive oral anticoagulation (OR 0.70, 95% CI 0.55–0.89) and were at higher risk of death (HR 3.54, 95% CI 2.56–4.89), MACE (HR 3.41, 95% CI 2.44–4.77) and major bleeding (HR 2.87, 95% CI 1.55–5.29).[75] The frailty assessment method influences the effect sizes, with the pooled relative risk for mortality at 4.93 for the frailty index and 1.63 for the frailty scale.[251] The impact of severity of comorbidities is higher in older populations, and frailty is thus more predictive of mortality in relatively younger populations.[251] In an adjusted analysis of the ORBIT-AF registry, frailty was independently associated with all-cause death but was no longer associated with thromboembolic or bleeding risk.[71]

Data on the impact of OAC prescribing on people with frailty are inconsistent.[253] OAC prescription is influenced by age, baseline thromboembolic risk, and study setting.[254] Analysis of the Systematic Assessment of Geriatric Elements in Atrial Fibrillation (SAGE-AF) database found no relationship between frailty status and OAC prescribing.[73] In the nationwide English primary care cohort, a progressively higher burden of frailty was associated with a higher prescription of OAC.[255] An Irish community-based study showed higher rates of OAC prescribing in people with frailty.[256] In contrast, among nursing residents, only 25% of eligible patients were prescribed OAC.[74] OAC prescribing in people with frailty is influenced by competing indications and risks in this vulnerable population.

There is a limited evidence base to guide OAC prescribing in people with frailty to account for individual risks of bleeding complications accurately. However, in an ENGAGE AF-TIMI 48 trial analysis, participants with mild-to-moderate frailty showed a lower risk for all the composite clinical endpoints and death risk for edoxaban vs warfarin.[257] Similarly, in favourable outcome profile for NOACs vs warfarin was reported in the ARISTOPHANES registry population of frail patients,[258] and the nationwide AF cohort of Korea.[259] Also, rhythm-control vs rate-controlled strategy did not significantly reduce a combined cardiovascular outcome in AF patients with moderate-severe frailty.[260] A holistic approach is therefore needed, as promoted by the ABC pathway.[135] Adherence to the ABC pathway reduced the risk of all-cause death by 26%.[261] Chronological age per se should not be used as a metric of frailty. Frailty assessment should be considered for optimal pharmacological management of multimorbidity but should not restrict the use of oral anticoagulation.

Multimorbidity and polypharmacy

People with AF often experience multimorbidity (70–80%) and polypharmacy (40–95%).[262] Ageing and accumulation of co-existing conditions increase risk of AF and its complications, such as stroke.[263] Multimorbidity is associated with high mortality, reduced functional status, and increased healthcare expenditure in observational studies and in the multimorbidity subgroup of the mAFA-II RCT.[116,262,264]

Polypharmacy, the intake of ≥5 drugs, is a well-established prognosticator of poor health outcomes due to drug–drug interactions overlaying comorbidities.[265–267] Treatment with warfarin requires particularly careful consideration in view of multiple food- and drug–drug interactions.[268] However, polypharmacy negatively influences prognosis in AF irrespective of use of oral anticoagulation.[269] Polypharmacy was associated with higher stroke or systemic embolism in analysis of Belgian nationwide data (adjusted HR 1.08, 95% CI 1.02–1.15), mortality (adjusted HR 1.45, 95% 1.40–1.50), and major bleeding risks (adjusted HR 1.29, 95% CI 1.23–1.35).[270] Despite fewer interactions, NOACs still increase potential drug interactions in polypharmacy. In ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials, patients with polypharmacy had similar relative benefits from NOACs, despite higher absolute event rates (particularly bleeding and deaths) compared to people without polypharmacy.[266,267,271] In a meta-analysis of RCTs and observational studies (12 studies, 767,544 patients) NOACs compared with VKAs reduced risk of stroke or systemic embolism in AF patients with moderate polypharmacy (HR 0.77, 95% CI 0.69–0.86) and severe polypharmacy (HR 0.76, 95% CI 0.69–0.82), without affecting the risk of bleeding.[272] In contrast, warfarin use posed excess risk of adverse events in polypharmacy. These data indicate that polypharmacy itself should not be a barrier for NOAC use but requires careful and holistic approach for prescribing (ABC pathway).[273,274]

Patient factors

Gender

The impact of gender and sex in AF-related risk is complex, with significant gaps in knowledge. Available studies focus on sex and lack data on the role of gender identity. Despite men traditionally reported to have a 30–70% higher incidence and prevalence of AF than women, due to the greater longevity in women, the lifelong risk of AF is similar.[275,276] Women with AF tend have a higher risk of mortality and stroke.[277,278] The reasons why women are at higher risk of complications may be related to biological factors (e.g., sex hormones) but are also related to socio-economic and psychological factors and reduced healthcare access.

Women are usually older at the time of AF diagnosis and have higher CHA_2DS_2-VASc scores.[279] However, higher CHA_2DS_2-VASc scores are partly due to the female gender contributing to the score (1 point); sex is increasingly considered as a risk modifier rather than a risk factor per se.[279] UK data show that while women were less likely to receive oral anticoagulation and have a higher risk of stroke, the stroke risk was similar in anticoagulated men and women.[280] Several European registries have shown that women with AF are more symptomatic than men, with atypical symptoms such as dyspnea, chest pain, and fatigue, which may mask initial presentation.[281] Sex-related psychological factors, including the stress response, may also contribute to AF risk. Toxic psychosocial stress was linked to AF risk in women (but not men) in the Malmö Diet Cancer Study in Europe and the Women's Health Study.[282,283] The PaTH AF cohort study showed a correlation between severe AF symptoms and symptoms of anxiety and depression in women. However, it remains unclear whether this modifies healthcare-seeking behaviour and outcomes.[284]

Ethnic minority groups, migrants

The risk of AF varies between ethnic groups (Fig. 3). Although few European countries collect data on ethnicity, the UK CPRD data show a higher standardised AF incidence (per 1000) in White people (8.1, 95% CI 8.1–8.2) than in Asians (5.4, 95% CI 4.6–6.3) and Black origin individuals (4.6, 95% CI 4.0–5.3).[32] The South Asian diaspora is one of the largest ethnic minority groups in Europe and worldwide. A retrospective UK cohort population-based study using The Health Improvement Network (THIN) data showed that people of South Asian origin, compared to White ethnicity, were at an increased risk of type 2 diabetes, hypertension, coronary artery disease and HF but had a 2-fold lower risk of AF.[33] Similarly, among UK stroke survivors, AF was present in 13% of South Asians vs 22.7% of white British participants. The ethnicity-related risk of South Asians having AF was lower despite the higher rates of traditional risk factors (odds ratio for AF 0.40 after adjustment for risk factors). Both ethnic groups have similar rates of oral anticoagulation prescribing on admission and discharge.[285] People of South Asian ethnicity eligible for the NHS Health Check, attend it more often than any other ethnic group, especially South Asian women.[286] This is likely to help mitigate the higher overall cardiovascular risk in the South Asian population. Similar to South Asian ethnicity, people of African origin have a lower lifetime risk of AF compared to White ethnicity.[287] The Multi-Ethnic Study of Atherosclerosis (MESA) in the USA also reported the highest risk of AF in White subjects, with lower rates in Hispanic individuals, followed by those of Black and Chinese ethnicity.[288] White people of Latin background have a lower adjusted risk of AF than white people of other origin (HR 0.76, 95% CI 0.75–0.77).[289]

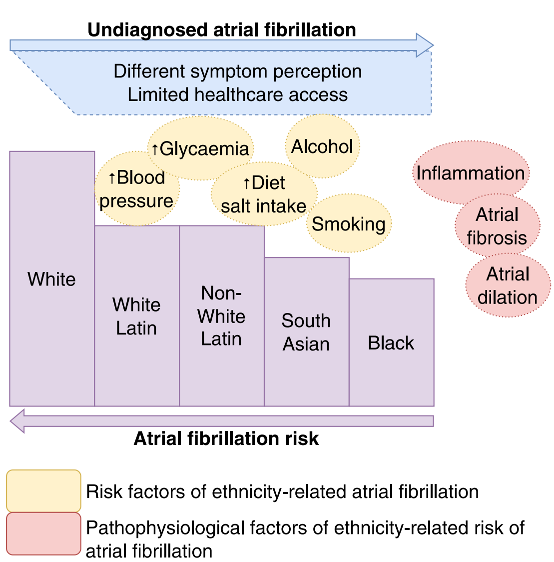

Fig. 3: Ethnicity and risk of atrial fibrillation.

Despite the lower risk of AF, people of non-White ethnicity are at higher risk of complications when AF occurs. In the ARIC study, Black people had a 1.5–2.0-fold higher rate difference for stroke, heart failure and CHD vs. White people.[290] A systematic review suggests a possibly lower overall likelihood of receiving anticoagulant prescriptions among Black patients than among White patients.[79] However, high-quality data in European regions are lacking. Overall, belonging to ethnic minority groups is unlikely to contribute to AF-related risk significantly and is not part of established tools for stroke risk prediction.

Globally, the highest rates of AF were estimated in North America and the lowest in the Asia–Pacific and Sub-Saharan regions.[275,291] There are regional differences in the effects of individual risk factors with hypertension having a higher impact in Southern Sub-Saharan Africa and Central Asia and excessive weight in Eastern and Central Europe.[292] The gradual decline in AF incidence and prevalence in countries with the high socio-demographic index contrasts with the growing AF rates in countries with middle and low socio-demographic indexes.[292] New data also showed a 2-fold rise in AF prevalence in China.[293]

Socio-economic factors/deprivation, care access

Data on the association of socioeconomic status (SES) and AF risk are inconsistent, with only some studies demonstrating lower incidence of AF in higher SES groups.[294] This likely reflects SES definitions and healthcare service access and population risk factor profile.[295] In those with AF, SES was associated with poorer outcomes, including increased risk of mortality and morbidity in a systematic review of 39 studies.[295] A Swedish primary care cohort of 12,283 patients with AF aged ≥45 years found 1.49-fold higher mortality among men from low vs. middle SES neighbourhoods.[296] Further, in a Danish nationwide registry cohort, lower SES was associated with a higher risk of HF or stroke, less likelihood of cardioversion or catheter ablation, and a higher mortality.[297]

There are significant differences in AF treatment by SES and access (geographical) to care. A Norwegian

Search strategy and selection criteria

We searched PubMed for original articles and reviews published in English up to 14th February 2023, using the search terms: "atrial fibrillation", "risk factors", "patient factors" or individual risk factors, listed as section headings in the review. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant, including publications and other data sources that we considered important contributions to the topic. We prioritised publications reporting findings from the European regions and complemented them with global data where appropriate.

national population-based cohort found that those from higher SES groups (higher level of education and high income) and who lived closer to the referring hospital were more likely to receive catheter ablation.[298] A Finnish cohort study found that patients who were better educated or had higher incomes were more adherent initially but there was no difference in long-term adherence by SES.[299] The SES differences in outcomes may be associated with access to care particularly in countries where healthcare is not free at the point of need, with poorer health literacy and ability for self-advocacy for appropriate treatments, and ability to adhere to medication and lifestyle modifications to self-manage AF. There is a need for greater allocation of resources in primary care in more deprived areas.

Tackling the social determinants of health (SDoH), early childhood development, economic circumstance, neighbourhood and built environment, social and community context, and health and healthcare (health literacy), could contribute to decreased CVD burden. A recent umbrella review of SDoH demonstrated a greater risk of CVD morbidity and mortality for those with lower or worse SDoH in all domains except health; there were no reviews on health literacy and CVD risk.[12] There is less data for the impact of SDoH on AF and existing data is inconsistent. This umbrella review suggests that addressing childhood development (ensuring education access and quality and preventing adverse childhood events) and the economic environment (stable employment/occupation, food and housing security, and income) within a multifactorial risk factor-based approach, could substantially impact CVD risk and burden.

Summary and future directions

The multitude of factors contributing to AF pathogenesis calls for a holistic, comprehensive approach to their identification and management, essential for AF prevention and reducing the burden of its complications. Risk factors often co-exist, influencing and amplifying their overall effect. Also, the magnitude of the impact of individual risk factors varies by patient factors, including gender and ethnicity, access to healthcare resources, and resources for an optimal lifestyle. It is currently unclear how to account for all these factors for individual risk prediction beyond the existing scoring systems. This requires new predictive models based on advanced statistical methods and machine learning techniques to account for longer-term trajectories in risk factors. Risk prediction would need to be supplemented by developing tailored therapeutic approaches. Successful mitigation of AF-related health requires an individualised approach considering all somatic, psychological, demographic, and social factors. This can be challenging, particularly with the increasing multimorbidity, polypharmacy and changing population demographics, across the European region. At present, attention should be paid to meticulous following of the ABC pathway approach. It is crucial to engage the patient as partners in the discussions of the lifestyle modifications and treatment options, with access to education, clinical feedback, and access for advice. Particular support is needed for people who may have cognitive impairment, physical disabilities, disabilities, or belonging to hard-to-reach groups. A multidisciplinary approach is vital for future research and practice to achieve optimal management of risk factors for AF.[300]

Contributors

ES: conceptualisation, writing—original draft, writing—review & editing, project administration. EKC: conceptualisation, writing—original draft, writing—review & editing. DAL: conceptualisation, writing—original draft, writing—review & editing. BJ: conceptualisation, writing—original draft, writing—review & editing. GYHL: conceptualisation, writing—review & editing.

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