Heart failure with preserved ejection fraction: An alternative paradigm to explain the clinical implications of atrial fibrillation

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Atrial fibrillation (AF) is associated with exercise intolerance, stroke, and all-cause mortality. However, whether this can be solely attributable to the arrhythmia itself or alternative mechanisms remains controversial. Heart failure with preserved ejection (HFpEF) commonly coexists with AF and may contribute to the poor outcomes associated with AF. Indeed, several invasive hemodynamic studies have confirmed that patients with AF are at increased risk of underlying HFpEF and that the presence of HFpEF may have important prognostic implications in these patients.

Mechanistically, AF and HFpEF are closely linked. Both conditions are driven by the presence of common cardiovascular risk factors and are associated with left atrial (LA) myopathy, characterized by mechanical and electrical dysfunction. Progressive worsening of this left atrial (LA) myopathy is associated with both increased AF burden and worsening HFpEF. In addition, there is growing evidence to suggest that worsening LA myopathy is associated with poorer outcomes in both conditions and that reversal of the LA myopathy could improve outcomes. In this review article, we will present the epidemiologic and mechanistic evidence underlying the common coexistence of AF and HFpEF, discuss the importance of a progressive LA myopathy in the pathogenesis of both conditions, and review the evidence from important invasive hemodynamic studies. Finally, we will review the prognostic implications of HFpEF in patients with AF and discuss the relative merits of AF burden reduction vs HFpEF reduction in improving outcomes of patients with AF and HFpEF.

KEYWORDS Atrial fibrillation; Atrial myopathy; Cardiovascular risk factors; Heart failure with preserved ejection fraction; Left atrial hemodynamics

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Introduction

Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) are 2 highly prevalent chronic cardiovascular conditions that commonly coexist (AF-HFpEF). AF is the most common cardiac arrhythmia, while HFpEF is a myocardial functional disorder associated with abnormal intracardiac hemodynamics. Mechanistically, however, both conditions are associated with a progressive left atrial (LA) myopathy driven by the presence of common cardiovascular risk factors.[1] Historically, HFpEF has been difficult to diagnose in patients with AF, but several recently published invasive hemodynamic studies of patients with AF have demonstrated a high prevalence of occult HFpEF.[2–4] HFpEF commonly afflicts patients with AF, raising important questions that challenge current thinking; are the clinical implications associated with AF due to the rhythm disturbance of AF or underlying HFpEF? Do evidence-based AF treatments work through reduction of AF burden or treatment of underlying HFpEF?

In this article we will review the epidemiologic evidence for the close association between AF and HFpEF as well as describe the mechanisms that drive the development of both HFpEF and AF, focusing on the importance of underlying cardiovascular risk factors. Specifically, we will highlight the role of LA myopathy in both conditions and discuss the contribution of invasive hemodynamic studies that have progressed our understanding of the symbiotic relationship between AF and HFpEF. We will then discuss the growing controversy regarding the relative contributions of cardiac rhythm disturbance and HFpEF in predicting the poor outcomes associated with AF. Finally, we will review established treatment strategies for AF, discussing their mechanisms of efficacy in the context of cardiac rhythm control vs HFpEF reduction and discuss how further development of our understanding of HFpEF in AF may allow for improved treatments and outcomes.

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KEY FINDINGS

- Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) commonly coexist. Large-scale epidemiological studies estimate a high prevalence of AF in patients with HFpEF and vice versa. Invasive hemodynamic studies suggest the coexistence of AF and HFpEF may be even more common than epidemiological studies suggest and is likely underappreciated in clinical practice.
- AF and HFpEF are both underpinned by several common cardiovascular risk factors, including obesity, hypertension, diabetes, obstructive sleep apnea, alcohol consumption, and smoking. The mechanisms by which these risk factors lead to AF and HFpEF include systemic inflammation, hemodynamic alterations, coronary microvascular dysfunction, and atrial fibrosis.
- AF and HFpEF are both associated with a progressive and comprehensive left atrial (LA) myopathy, encompassing structural, mechanical, and electrical dysfunction.
- Progressive worsening of the LA myopathy is associated with poorer outcomes in AF and HFpEF, including increased risk of all-cause mortality and systemic thromboembolism.
- Several evidence-based treatments for AF focus on reducing AF burden. However, outcomes may be further improved by reversing LA myopathy and reducing HFpEF. Renewed focus on reversing LA myopathy and reducing HFpEF may provide prognostic benefit in patients with AF.

Epidemiology

AF and HFpEF

AF and HFpEF represent growing worldwide epidemics. Current estimates suggest that 37.5 million people (0.51% of the worldwide population) suffer with AF globally, with ever-rising prevalence and incidence.[5] An even larger proportion of people suffer with heart failure, with an estimated 64.3 million people (0.9% of worldwide population) affected.[6] HFpEF is thought to account for at least half of these cases,[7,8] meaning the overall prevalence of HFpEF is likely to be very similar to that of AF. Future projections suggest that the global burden of both AF and HFpEF will continue to rise in the coming years, with significant implications for healthcare such as an exponential rise in hospitalizations and healthcare costs.[5,9]

AF-HFpEF

In addition to being highly prevalent conditions, epidemiologic studies also show that AF and HFpEF frequently coexist. Figure 1 shows the epidemiologic relationship between both conditions. In large heart failure registries recruiting both inpatients and outpatients, the overall prevalence of AF is estimated to be around 51%.[10–15] Similarly, in AF cohorts, the average prevalence of HFpEF is around 21%.[11,16–18] Both values are likely to represent underestimates; the diagnosis of AF in patients with HFpEF is often limited by its paroxysmal nature and the absence of continuous rhythm monitoring, while the diagnosis of HFpEF in patients with AF is challenged by the overlapping symptomatology and clinical presentation. As a result, the nature of the close relationship between the 2 conditions may be significantly underappreciated epidemiologically.

Community cohort studies examining the temporal relationship between AF and HFpEF provide unique insight into the bidirectional relationship between the 2 conditions. The Framingham Heart Study, which followed individuals with new-onset AF or heart failure for up to 7.5 years, showed that patients with AF had more than double the risk of developing HFpEF compared to those without AF.[11] Similarly, patients with HFpEF were more than 3 times more likely to develop AF. The PREVEND study, which invited the entire population of the city of Groningen, the Netherlands, to participate showed that AF increased the risk of HFpEF development by almost 7 times compared to those without AF over the course of a longer follow-up period (almost 10 years).[13] These studies highlight the symbiotic nature of the relationship between AF and HFpEF and the impact that each condition has on the development of the other.

Risk factors

Epidemiologic studies have also been important in highlighting the common risk factors underlying both conditions (Table 1). Age, hypertension, body mass index, diabetes, and obstructive sleep apnea have all been identified as frequent comorbidities associated with both conditions. Furthermore, the coexistence of AF and HFpEF also appears to be underpinned by the presence of the same risk factors.[14,19]

Mechanisms

The shared risk factors described above lead to the development of both AF and HFpEF via a variety of mechanisms, all of which appear to be inextricably linked (Figure 2). Systemic inflammation, hemodynamic alterations, microvascular dysfunction, epicardial adiposity, and myocardial fibrosis are all important consequences of cardiovascular risk factors and play key roles in the development of the atrial and ventricular myopathies underlying both AF and HFpEF. However, these mechanisms are not independent of each other but rather represent a complex network of interacting processes. In addition to these mechanisms, development of AF and HFpEF potentiate the development and progression of each other, resulting in the creation of a vicious cycle that, left untreated, results in the rapid, unabated progression of both AF and HFpEF. The final common pathway of all these mechanisms appears to be the development and

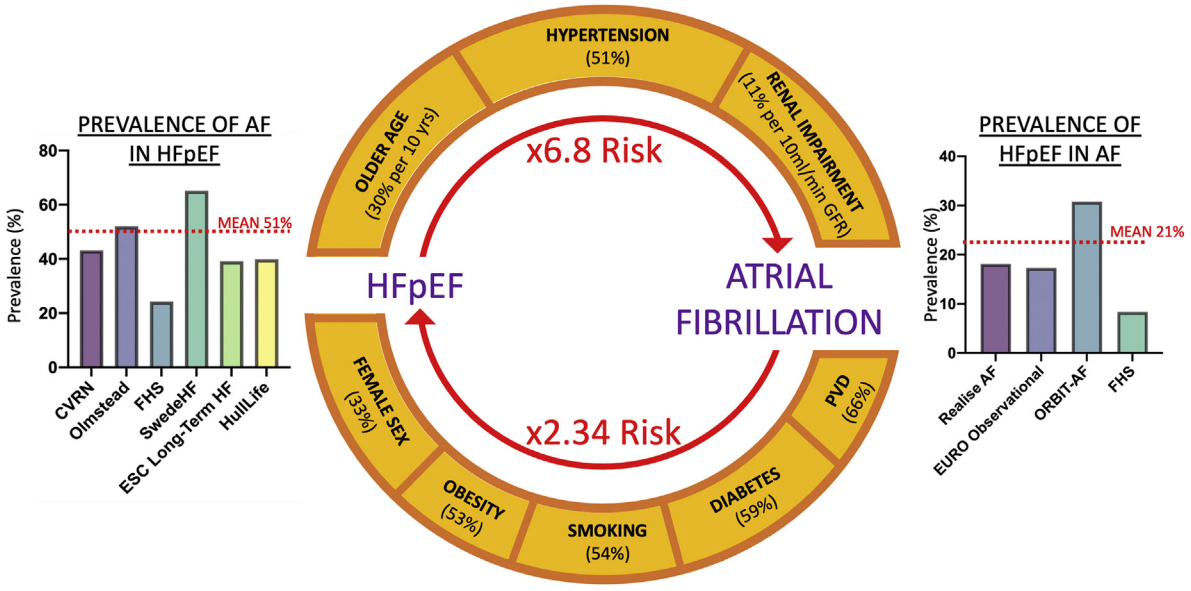

Figure 1 Epidemiology of coexisting atrial fibrillation and heart failure with preserved ejection fraction (AF-HFpEF); HFpEF is associated with increased prevalence of AF and vice versa. The presence of HFpEF increases the risk of incident AF by 6.8 times.[13] Similarly, the presence of AF increases the risk of HFpEF by 2.34 times.[11] These increased risks are driven by several underlying risk factors.[13,14] AF = atrial fibrillation; CVRN = Cardiovascular Research Network; ESC = European Society of Cardiology; FHS = Framingham Heart Study; HFpEF = heart failure with preserved ejection fraction; HullLife = Hull LifeLab; ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; SwedeHF = Swedish Heart Failure Registry.

progression of LA disease, which is increasingly recognized as the most important linking factor between AF and HFpEF.

Systemic inflammation

Systemic inflammation plays a central role in the pathophysiology of both AF and HFpEF. The risk factors associated with AF and HFpEF are associated with high circulating levels of proinflammatory mediators.[20–22] For example, the activation of the renin-angiotensin-aldosterone system (RAAS) in hypertension has been shown to mediate the production of a vast number of proinflammatory cytokines and activation of immune cells.[23] Similarly, diabetes, obesity, the metabolic syndrome, renal disease, and smoking have all been shown to drive systemic inflammation.[20,24]

The importance of systemic inflammation in both AF and HFpEF is highlighted by longitudinal observational studies in which systemic inflammatory mediators at baseline were used to predict the onset of the 2 conditions. In large population-based cohorts, elevated plasma levels of proinflammatory TNFa, E-selectin, ICAM-1, and VCAM were all found to be associated with increased risk of incident HFpEF during long-term follow-up.[25–27] Similarly, elevated levels of numerous inflammatory biomarkers, including TNFa, CRP, and IL-6, as well as increased white blood cell count, have been shown to be associated with increased risk of incident AF.[28,29] In addition, they were shown to be associated with increased AF recurrence after ablation or electrical cardioversion.[28] Furthermore, patients with systemic inflammatory disorders such as rheumatoid arthritis and systemic sclerosis have been shown to be at significantly increased risk of both incident AF and HFpEF.[30,31] These studies highlight the significance of systemic inflammatory processes in patients with AF and HFpEF.

The mechanisms by which systemic inflammation leads to AF and HFpEF remain incompletely understood. However, cardiac fibrosis, coronary microvascular dysfunction (CMD), cardiomyocyte hypertrophy, decreased cardiomyocyte distensibility owing to titin alterations, and increased myocardial accumulation of degraded proteins have all been implicated.[21] Interestingly, statins have been shown to reduce the incidence of AF in patients with HFpEF, possibly via anti-inflammatory effects.[14,22] While strong data

Table 1 Hazard ratios for incident atrial fibrillation and heart failure with preserved ejection fraction associated with the presence of individual cardiovascular risk factors, taken from observational studies or meta-analyses

Cardiovascular risk factor	Risk of incident HFpEF, HR (95% CI)[130]	Risk of incident AF, HR (95% CI)
Aging	2.3 (1.6–3.3) per decade	2.1 (1.8–2.5) in males, 2.2 (1.9–2.6) in females per decade[131]
BMI	1.38 (1.18–1.61) per 1 SD increase[132]	1.19 (1.13–1.26) per 5 U increase[133]
Hypertension	3.5 (1.4–8.8)	1.4 (1.2–1.8)[134]
Diabetes	3.1 (1.9–5.0)	1.4 (1.3–1.5)[135]
Obstructive sleep apnea	2.4 (1.3–4.6)	2.1 (1.8–2.4)[136]
Smoking	1.1 (0.7–1.8)	1.3 (1.1–1.6)[137]
Alcohol consumption	0.7 (0.4–1.3)	1.4 (1.2–1.6)[138]

AF = atrial fibrillation; BMI – body mass index; CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio.

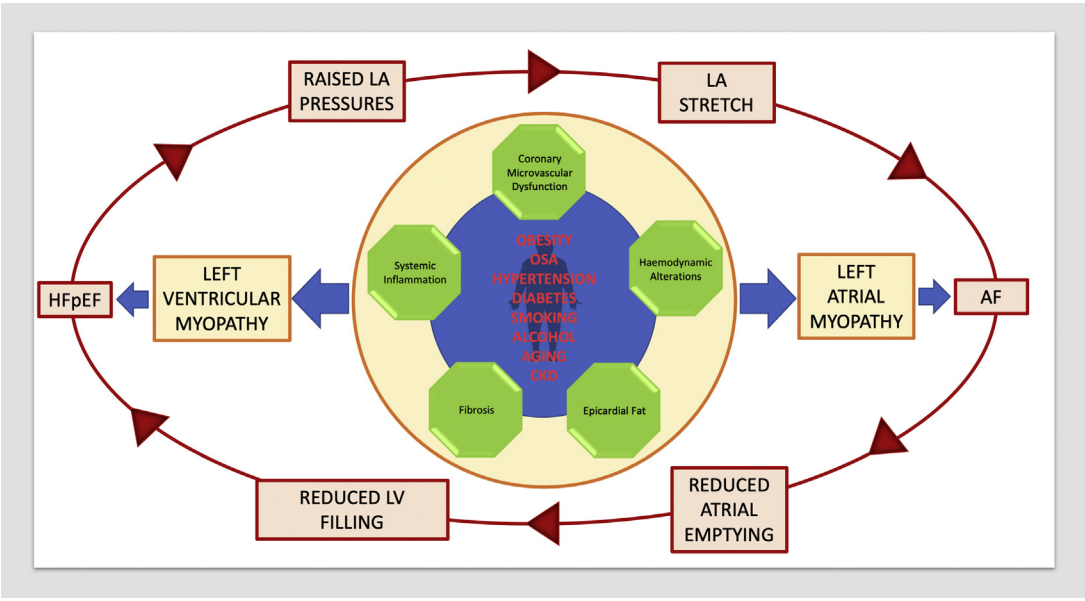

Figure 2 Mechanisms underlying coexisting atrial fibrillation and heart failure with preserved ejection fraction (AF-HFpEF); both AF and HFpEF are underpinned by the presence of multiple cardiovascular risk factors. These risk factors drive several processes leading to atrial and ventricular myopathies and resultant AF and HFpEF. AF and HFpEF interact with each other in a vicious cycle through reduced left atrial function. AF = atrial fibrillation; CKD = chronic kidney disease; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; OSA = obstructive sleep apnea.

regarding anti-inflammatory agents for the treatment of AF or HFpEF remain lacking, there is some evidence to suggest that steroids may reduce postablation and postsurgical AF[32,33] and studies investigating the use of anti-inflammatory agents in HFpEF are underway.[21]

Hemodynamic alterations

Several cardiovascular risk factors are associated with significant intracardiac hemodynamic changes that promote the development of both AF and HFpEF. Chronic hypertension is associated with increased afterload and left ventricular (LV) hypertrophy, impaired LV filling, and the raised LV diastolic pressures diagnostic of HFpEF.[34,35] Moreover, these mechanisms further lead to increased LA stretch, dilatation, and increased risk of AF.[36] In spontaneously hypertensive rats, similar LV and LA structural changes were identified and these were associated with lower atrial effective refractory period, increased atrial interstitial fibrosis, and increased inducibility of AF.[37] In addition to the direct effects of pressure changes on cardiac structure, these hemodynamic alterations are also associated with neurohormonal activation of the RAAS, which has been shown in animal models to cause atrial and ventricular myocardial remodeling.[23]

Similarly, obesity is also associated with significant hemodynamic alterations leading to AF and HFpEF.[38] Chronically obese sheep exhibited raised LA pressures and significant electroanatomical mapping abnormalities, consisting of reduced conduction velocities and increased conduction heterogeneity, resulting in more frequent and prolonged episodes of AF.[39] Furthermore, obese patients with AF have been shown to exhibit raised LA pressures and shorter effective refractory periods compared to nonobese patients with AF.[38] These studies highlight the important influence of obesity on LA hemodynamics and the development in AF. Obesity is also closely associated with diastolic function and HFpEF; obesity has been shown to be associated with concentric LV remodeling, reduced LV diastolic function, and raised LV end-diastolic pressures.[40–42] Furthermore, recent data suggest that hemodynamic effects of obesity represent a specific phenotype of HFpEF patients within the heterogeneous HFpEF clinical syndrome.[43] Patients with obesity-related HFpEF exhibited markedly different hemodynamics compared with nonobese HFpEF, including greater plasma volume expansion, worse right ventricular dysfunction, higher intracardiac pressures at rest and during exercise, and increased exertion-induced pericardial restraint.[43] These findings highlight the marked effects of obesity on intracardiac hemodynamics, which contribute to the development of both AF and HFpEF.

Coronary microvascular dysfunction

Myocardial ischemia in the absence of macrovascular epicardial coronary artery disease is defined as CMD.[44] CMD has been shown to be highly prevalent in patients with both HFpEF and AF and has been shown to be associated with systemic and local inflammatory processes resulting from the presence of cardiovascular risk factors.[45] CMD causes abnormalities in LV systolic function despite the presence of normal ejection fraction. These abnormalities in systolic function are subtle and include reduced LV longitudinal strain,[46] midwall fractional shortening,[47] and mitral annular

systolic excursion.[48] In addition, CMD likely accounts for the exercise-induced myocardial ischemia and subendocardial systolic dysfunction often seen with HFpEF.[49] These subtle deficits result in the impaired systolic reserve characteristic of patients with HFpEF and AF.

CMD has been shown to be closely associated with elevated LV filling pressures at rest and during exercise and reduced cardiorespiratory fitness.[50] The most extensive clinical investigation of CMD in HFpEF, showed that up to 75% of patients with HFpEF had underlying CMD.[51] Of note, 58% of these patients had coexisting AF while the prevalence of AF in those without CMD was only 25%. Furthermore, atrial microvascular dysfunction has been identified in patients with AF but without HFpEF.[52] These findings suggest that CMD may play a significant role in the pathogenesis of both AF and HFpEF and could also be potential targets for treatment.

Of note, occult but clinically significant macrovascular coronary artery disease has been identified in half of patients with confirmed HFpEF undergoing coronary angiography, further emphasizing the relevance of myocardial ischemia in the pathogenesis of HFpEF. These patients with obstructive coronary artery disease had higher rates of adverse clinical outcomes, suggesting a possible role for revascularization in selected HFpEF patients.[53]

Epicardial adiposity

Adipose tissue has important proinflammatory, neurohormonal, and hemodynamic effects on the cardiovascular system, all of which increase the risk of both AF and HFpEF (as discussed in previous sections). However, deposition of adipose tissue around the heart (epicardial adipose tissue [EAT]) is particularly relevant to both. When compared with overall body mass index, EAT confers a 2-fold increased risk of AF,[54] while patients with HFpEF have almost 40% more epicardial fat compared to non-HFpEF patients with matched body mass index.[55]

EAT has several characteristics that render it detrimental to cardiac structure and function and increasing the risk of both AF and HFpEF. Anatomically, there is no fascial plane separating the adipose tissue from the myocardium, meaning adipocytes can communicate directly with cardiac myocytes. As a result, EAT can directly infiltrate the myocardium, causing reduced voltages and conduction heterogeneity and thereby creating the electrophysiological milieu for the development of AF.[56,57] Additionally, EAT and the myocardium share the same microcirculation, leaving the myocardium vulnerable to paracrine effects from the adipose tissue. EAT is a particularly active secretory tissue (more than visceral adipose tissue), expressing high levels of proinflammatory cytokines and atherogenic molecules, which lead to local inflammation, tissue fibrosis, and cardiomyocyte dysfunction.[58,59] Finally, the presence of EAT can directly affect cardiac mechanics, its encasing of the myocardium causing pericardial restraint and increased left-sided pressures at rest and during exercise.[60]

Fibrosis

Cardiac fibrosis is the histologic hallmark of the structural remodeling associated with both AF and HFpEF and is closely linked with the presence of cardiovascular risk factors. Fibrotic change is driven by neurohormonal and inflammatory mediators released in response to cardiovascular risk factors.[61] Animal models of hypertension, diabetes, obesity, and sleep apnea have all demonstrated increased levels of atrial fibrosis on histology.[62] Furthermore, clinical electroanatomical mapping studies show increased low-voltage areas and complex fractionated atrial electrograms associated with chronic hypertension,[63] obesity,[64] and obstructive sleep apnea,[65] suggestive of increased atrial fibrosis. These changes in the cardiac architecture lead to aniostropic conduction, facilitating the stabilization of electrical reentry and the development of AF.[66]

Patients with AF exhibit both atrial and ventricular myocardial fibrosis, suggesting a ubiquitous rather than localized phenomenon, possibly in response to systemic disease. HFpEF is also characterized by global myocardial fibrosis. An autopsy study comparing ventricular histology between HFpEF patients and age-matched controls demonstrated significantly increased ventricular fibrosis in HFpEF.[67] Ventricular fibrosis has been linked with LV stiffening,[68] which is a characteristic feature of the HFpEF syndrome.[47] Moreover, both clinical studies and experimental models of HFpEF have identified significant atrial fibrosis,[69–71] which likely contributes to the increased LA stiffness seen in patients with HFpEF. Global myocardial fibrosis is therefore a common pathophysiological mechanism in both AF and HFpEF, causing both mechanical and electrical dysfunction and likely contributing to the epidemiologic overlap between the 2 conditions. Fibrosis likely represents the final common pathway of all the pathophysiological mechanisms described above, but noninvasive methods for quantifying fibrotic change within the atria remain rudimentary. Given the association between increasing fibrosis and poorer outcomes, novel methods to quantify atrial fibrosis have the potential to provide new possibilities for the investigation and management of both AF and HFpEF.

Vicious cycle

While shared risk factors and common pathophysiological mechanisms contribute significantly to the frequent coexistence of AF and HFpEF, additional and important contributory factors are the direct influences that each condition has on the other.[72] The 2 conditions interact with each other in a vicious cycle, each potentiating the risk of the other.

The unifying hemodynamic abnormality in HFpEF is raised LV end-diastolic pressure (LVEDP) and this inevitably increases LA pressures. Increased LA pressures lead to LA stretch, dilatation, and structural remodeling. LA stretch activates stretch-sensitive ion channels and promotes ion channel dysregulation within the LA, altering ionic currents and resulting in reduced LA voltages, slowed conduction, and increased susceptibility to AF.[73,74] In addition,

HFpEF results in neurohormonal activation of the RAAS owing to renal underperfusion. RAAS activation is associated with fibrotic change within the LA,[75] partly mediated through inflammatory cytokines.[76] Hemodynamic, neurohormonal, and proinflammatory mechanisms therefore all contribute to the development and potentiation of AF in patients with HFpEF.

Similarly, AF can promote the development of HFpEF. The loss of atrial systole associated with AF results in a 20% reduction in cardiac output owing to reduced ventricular filling.[77] This reduced LV filling results in impaired cardiac output at normal diastolic filling pressures, leading to HFpEF.[78] Furthermore, AF has been shown to be associated with increased LV fibrotic change, which is known to cause LV stiffening and therefore elevated LVEDP.[79] Finally, the fast ventricular rate and irregularity associated with AF can result in abnormal hemodynamics, structural remodeling, and neurohormonal activation, all of which can increase the risk of HFpEF in patients with AF.[80]

Left atrial myopathy

LA disease is characterized by structural, mechanical, electrical, and thrombogenic dysfunction. While AF is primarily considered an electrical disease of the left atrium and HFpEF is increasingly associated with mechanical LA dysfunction, these abnormalities likely do not occur in isolation, but rather occur in conjunction with each other. Indeed, AF is associated with LA dilatation, mechanical dysfunction, and increased risk of thrombus formation, highlighting a comprehensive failure of the left atrium.[81] Similarly, HFpEF has been shown to be associated with LA dilatation[82] and increased risk of AF,[1] suggesting a similar comprehensive LA myopathy may occur.

Importantly, the LA myopathy underlying both AF and HFpEF is a progressive condition, and this is reflected in the disease processes of both AF and HFpEF. AF is characterized by the gradual progression from short, intermittent episodes (paroxysmal AF) to longer-lasting episodes (persistent AF) and finally to permanent AF. This clinical progression is associated not only with worsening electrical disease (lower LA voltages, conduction heterogeneity, increasing fractionation)[83] but also with LA dilatation,[84] impaired mechanical function,[85] and increased risk of LA thrombus.[86] Similarly, progressive worsening of LV diastolic dysfunction, which is characteristic of HFpEF, is associated with LA enlargement and reducing LA function, as determined by echocardiographic measures of LA strain.[87,88] While clear evidence of electrical dysfunction and increased thrombus susceptibility in HFpEF remains lacking, there is still significant evidence to suggest that a progressive and comprehensive LA myopathy is associated with both AF and HFpEF progression.

Diagnostic challenges

Despite its clinical importance, the diagnosis of HFpEF in patients with AF remains a complex clinical challenge. Symptoms of AF and HFpEF overlap significantly; in patients with known AF, symptoms such as shortness of breath or exercise intolerance will often be attributed to the AF rather than coexisting HFpEF. Furthermore, routine diagnostic tests normally used for the diagnosis of HFpEF are often affected by the presence of AF, meaning their values are less clinically useful in the context of AF.[89] In the real world, diagnosis of HFpEF relies on noninvasive echocardiographic parameters. However, echocardiographic parameters used for the diagnosis of HFpEF, including mitral valve early inflow velocities, mitral annular tissue Doppler velocities, and LA volumes, are all significantly altered by the presence of AF.[89] Similarly, serum N-terminal pro-B-type natriuretic peptide is significantly elevated in patients with AF compared to those with sinus rhythm.[89] These changes associated with AF make the noninvasive diagnosis of HFpEF in patients with AF particularly challenging. As a result, the gold-standard criterion for diagnosis of HFpEF remains invasive hemodynamic estimation or measurement of LVEDP at rest (>15 mm Hg) and during exercise (>25 mm Hg). However, this testing is largely restricted to specialist, high-volume centers and is therefore unavailable to the majority of the population. Historically, therefore, the coexistence of HFpEF in patients with AF has been difficult to identify.

Recently, 2 novel scoring systems utilizing integrated diagnostic approaches have been developed to assist in the diagnosis of HFpEF.[90,91] The first scoring system, the HFA-PEFF algorithm, was developed as part of an expert-directed consensus guideline for the diagnosis of HFpEF. This scoring system involves pretest probability assessment followed by diagnostic work-up involving resting echocardiography and serum natriuretic peptide assessment. Importantly, this scoring system accounts for alterations caused by AF by incorporating different cut-off levels for B-type natriuretic peptide and LA volume according to the presence or absence of AF. A high score reflects a definitive diagnosis of HFpEF while a low score represents low likelihood of HFpEF. However, an intermediate score necessitates further investigation involving exercise testing with either stress echocardiography or invasive hemodynamic cardiopulmonary exercise testing. Whereas invasive hemodynamic cardiopulmonary exercise testing is a proven diagnostic tool in HFpEF, stress echocardiography currently lacks the convincing evidence to support its use for this purpose.[78]

The second diagnostic algorithm for HFpEF is the H_2FPEF scoring system derived by Reddy and colleagues.[90] This algorithm was developed using clinical data from a cohort of 414 consecutive patients with unexplained dyspnea undergoing invasive hemodynamic assessment. A total of 267 of these patients were found to have HFpEF on the basis of their intracardiac hemodynamics, while the remaining 147 were diagnosed with noncardiac dyspnea. All clinical variables were then reviewed and multivariate logistic regression performed to identify those variables that reliably discriminated between HFpEF and noncardiac dyspnea. Interestingly, the variables that discriminated best were largely cardiovascular risk factors, including obesity,

hypertension, and advancing age. Important components of the HFA-PEFF scoring system such as LA volume and natriuretic peptides were found to be poorly discriminative and not included in this algorithm. The most important multivariate predictor of HFpEF was found to be AF, providing further evidence for the close association between AF and HFpEF. Indeed, the presence of AF scores 3 points in the H2FPEF system, conferring a minimum intermediate probability of HFpEF in all patients with AF. As with the HFA-PEFF algorithm, intermediate scores necessitate further evaluation with invasive exercise hemodynamics.

A recent retrospective analysis of patients with suspected HFpEF showed that both scoring systems for HFpEF accurately identified those at highest risk for heart failure hospitalizations and all-cause mortality.[92] Importantly, a significant proportion of these patients had coexistent AF, raising hopes that the diagnosis of AF-HFpEF has been made simpler with the use of these 2 scoring systems. However, a large proportion of the AF cohort had intermediate HFpEF scores according to these models. A definitive diagnosis of HFpEF would therefore require invasive hemodynamic testing in many AF patients.

Invasive hemodynamic studies

Several recent investigations have utilized invasive hemodynamic studies to identify the true proportion of AF patients with underlying HFpEF. Table 2 provides an overview of these studies. Two of the studies investigated patients going for AF ablation and assessed mean LA pressures following transseptal puncture.[3,93] In the remaining 2 studies, patients with AF underwent invasive right heart catheter for assessment of mean pulmonary capillary wedge catheter (PCWP).[2,4] The response of intracardiac pressures to exercise was also assessed in all studies; studies involving right heart catheter utilized supine bicycle ergometer, whereas those involving AF ablation utilized arm exercises done in the supine position following transseptal puncture.

In all 4 studies, a high proportion of AF patients exhibited the raised intracardiac pressures diagnostic of HFpEF. The highest proportion of AF patients meeting HFpEF criteria was seen in the study by Reddy and colleagues,[2] who demonstrated elevated pressures in 94.1% of AF patients. However, it is unlikely that this study was representative of the general AF population; the patients included in this study had significant dyspnea of uncertain cause and had been investigated extensively prior to referral for invasive hemodynamic studies. Sugumar and colleagues[4] included a smaller number (54) of patients awaiting first-time AF ablation and found that 64% met the criteria for HFpEF diagnosis. However, again this study was limited by a highly selected population of AF patients (only 20% of patients referred for AF ablation were ultimately included in the study). Of note, the majority of those meeting HFpEF criteria in this study were identified only on exercise, suggesting that these patients had early rather than established HFpEF, representing perhaps early LA remodeling. Importantly, all studies showed that AF

Table 2 Invasive hemodynamic studies involving patients with atrial fibrillation

Study	Population	Numbers included	Age	Sex (% male)	Persistent AF (%)	PCWP/LA pressures	Exercise	Proportion meeting HFpEF criteria at rest (%)	Proportion meeting HFpEF criteria during exercise (%)	Total proportion HFpEF (%)
Sramko et al 2017[3]	• AF Ablation • LVEF >40%	240	60 ± 10	67	38	LA	3-minute isometric handgrip	15	19	34
Meluzin et al 2017[93]	• AF ablation • SR at time of evaluation • LVEF >50%	100	58.9 ± 9.6	69	0	LA	Supine arm exercise	14	25	39
Reddy et al 2018[2]	• Unexplained exertional dyspnea referred for further investigation • LVEF >50%	101	-	-	47.5	PCWP	Supine bicycle exercise	-	-	94.1
Sugumar et al 2021[4]	• Index AF ablation • LVEF >50%	54	60.5 ± 11.8	59	46.3	PCWP	Supine bicycle exercise	16.7	48.1	64.8

AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; SR = sinus rhythm.

cohorts exhibited a broad spectrum of LA pressures, highlighting the fact that despite the diagnosis of HFpEF being reliant on meeting strict LA pressure cutoffs, the reality is that the LA myopathy progresses on a more continuous spectrum.

The studies measuring transseptal LA pressures rather than PCWP identified similar proportions of HFPEF patients at rest but lower proportions of patients meeting criteria with exercise. There are several possible reasons for these differences in prevalence: (1) the studies involving LA pressures involved larger and more representative AF populations; (2) the methods of exercise used in the transseptal studies (arm exercises) were less exhaustive than bicycle ergometry and therefore elevated intracardiac pressures to a lesser extent; (3) exercise studies undertaken immediately prior to AF ablation likely involved some level of sedation (although this was not explicitly stated in either study), which may have had some impact on exertional levels; and (4) the mean PCWP values were overestimates of LVEDP; an investigation into the relationship between mean PCWP and LVEDP showed that PCWP was consistently higher than LVEDP in patients in AF, likely owing to the poor operating compliance of a stiff LA and the uncoupling of LVEDP from PCWP.[94]

Aside from the prevalence of HFpEF in patients with AF, these invasive hemodynamic studies provide numerous additional insights into the association between AF and HFpEF. Sramko and colleagues[3] showed that elevated LA pressures were independently associated with an increased risk of AF recurrence following ablation. Sugumar and colleagues[4] further showed that patients without AF recurrence had reduced mean PCWP at follow-up, while symptomatic improvement following ablation was also associated with significantly reduced mean PCWP. In another invasive hemodynamic study investigating the impact of progressively increasing AF burden in patients with a known diagnosis of HFpEF, higher AF burden was associated with progressively increased intracardiac pressures, reduced LA function, and worse long-term survival.[95] Taken together, these findings not only highlight the close links between LA myopathy, AF, and HFpEF and the progressive nature of all 3 conditions, but also suggest that reversal of this progression is possible and may be related to a reduction in LA myopathy.

Prognostic implications

Prior data regarding the prognostic implications of AF-HFpEF have considered the 2 conditions as entirely separate entities. Numerous studies have shown that patients with HFpEF fare significantly worse when they have coexistent AF, and a recently published meta-analysis confirmed a significant increased risk of all-cause mortality, cardiovascular mortality, stroke, and heart failure hospitalizations.[96] Mortality is also increased in AF patients who develop incident HFpEF.[11] However, these data are based on the assumption that HFpEF is a discrete entity that patients with AF either have or do not have. Increasingly, with the aid of hemodynamic testing described above, we are understanding that both HFpEF and AF are progressive conditions; in AF cohorts, some patients have severe HFpEF, while others have mild HFpEF, which may only be present during exertion. Importantly, there is growing data to suggest that the level of HFpEF and LA myopathy progression within the cohort of patients with AF has direct consequences on cardiovascular outcomes (including mortality and systemic thromboembolism), symptoms, and quality of life (Figure 3).[97]

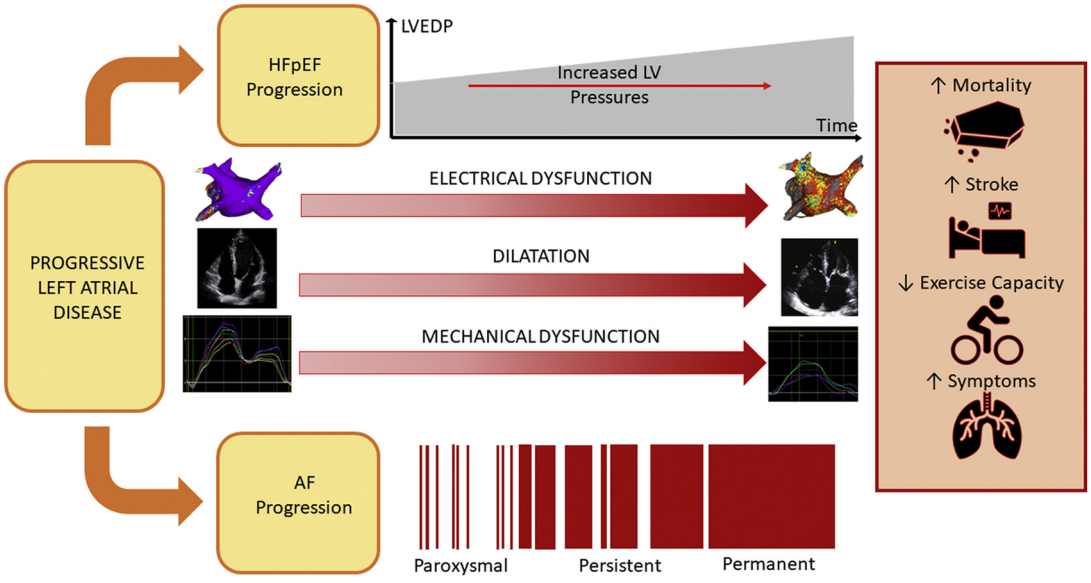

Figure 3 Progressive left atrial disease is central to the development and progression of both atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Deteriorating left atrial function (mechanical and electrical) is associated with poorer outcomes in both AF and HFpEF. LV = left ventricle; LVEDP = left ventricular end-diastolic pressure.

Mortality

Mortality in AF is linked to AF burden according to the classical classification scheme of paroxysmal, persistent, and permanent AF. Patients with persistent AF, who have been adequately anticoagulated, demonstrate increased all-cause mortality compared to those with paroxysmal AF, even after adjustment for other cardiovascular risk factors.[98] However, whether this increased risk of mortality is truly attributable to AF burden or, alternatively, to the severity of the underlying LA myopathy remains unclear. Patients with persistent AF demonstrate increased LA size, reduced LA function, and lower LA voltages when compared with patients with persistent and permanent AF, suggesting that LA myopathy is significantly worse in these patients.[99] This raises the possibility that LA myopathy rather than AF burden may underlie the increased risk of all-cause mortality in patients with increased burden of AF.

Systemic thomboembolism

As with mortality, systemic thromboembolic risk is associated with increased AF burden as well as worsening LA myopathy.[100,101] However, in this case the evidence for LA myopathy as the chief mitigator of systemic thromboembolism is strong. Advancing LA myopathy is associated with all 3 components of Virchow's triad: increased stasis of blood within the LA, increased blood coagulability, and endothelial injury.[102] Furthermore, increasing atrial fibrosis has been shown to be directly associated with LA appendage thrombus and prior history of strokes.[103,104] In addition, while rhythm control strategies and reduced AF burden have not been shown to have a significant effect on subsequent stroke risk in patients with AF,[97,105] mitral regurgitation and its associated increased blood flow within the LA have been shown to protect against thrombus formation despite increasing the risk of higher AF burden.[106] Finally, in patients with cryptogenic stroke and no evidence of AF on prolonged cardiac rhythm monitoring, stroke was associated with significantly reduced LA strain.[107]

Exercise intolerance

Exercise intolerance is a characteristic symptom of AF. More than 60% of symptomatic AF patients suffer with exertional dyspnea or exercise intolerance and these symptoms are associated with significantly impaired quality of life.[16] Exercise intolerance is closely linked with AF burden, and cardioversion of patients from AF to sinus rhythm significantly improves maximal exercise tolerance.[108] However, exercise intolerance is also a classical feature of HFpEF and has been shown to be closely associated with LA function in HFpEF patients without AF.[109,110] Furthermore, in a large cohort of patients with AF, cardiopulmonary exercise testing showed that diastolic function rather than cardiac rhythm predicted maximal VO_2.[111] These studies suggest that LA myopathy and HFpEF play critical roles in the development of exercise intolerance in patients with AF.

Clinical management strategies

Management of AF has traditionally focused on stroke prevention and symptom control via rate or rhythm control. However, emerging data suggest that a progressive LA myopathy and HFpEF may underlie many if not all of the prognostic consequences of AF, suggesting that a re-evaluation of the treatment strategies for AF may be needed, with renewed focus on reversal of the progressive LA myopathy. However, evidence suggests that many of the established treatments for AF may already involve reversal of the LA myopathy and treatment of the occult underlying HFpEF. While these treatments have not yet shown any proven benefit in stroke risk reduction, meaning the need for anticoagulation continues, a number of proven treatments may exert their effects through reversal of the HFpEF process. These treatments include early rhythm control, catheter ablation, and risk factor management.

Early rhythm control

Rhythm control has long been established as an important treatment strategy in AF to improve symptoms and quality of life.[112] Recent data suggest that early rhythm control may also reduce major cardiovascular events, including cardiovascular mortality, stroke, and heart failure hospitalization.[113] The mechanisms for these improvements in outcomes are purported to be related to a reduction in AF burden but could also be attributable to reverse remodeling and treatment of the underlying LA myopathy. It is well known that duration of time in AF is directly correlated with structural, contractile, and electrical remodeling of the LA.[114] Indeed, it has been shown that longer time to treatment of AF is associated with increased risk of AF recurrence.[115] Early rhythm control of AF may therefore halt progression of adverse LA remodeling, resulting in reduced likelihood of developing HFpEF and improved outcomes.

Catheter ablation

Catheter ablation for rhythm control has also been consistently associated with improvements in symptoms and quality of life.[112] Historically, the efficacy of catheter ablation for the treatment of AF has been considered the result of a reduction in AF burden. The cornerstone of catheter ablation for the treatment of AF remains pulmonary vein isolation, a technique aimed at targeting commonly occurring AF triggers arising in the pulmonary veins. In addition, catheter ablation may also reduce AF burden through modulation of ganglionic plexi, which have also been implicated in the genesis of AF, or through atrial debulking, whereby extensive catheter ablation results in a reduction of electrically active atrial tissue capable of sustaining AF.

However, an alternative theory to explain the symptomatic benefit derived from catheter ablation is a reduction in HFpEF. The imaging substudy of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial showed that catheter ablation was associated with significantly reduced LA volumes compared with

antiarrhythmic drug therapy.[116] This suggests that catheter ablation may be associated with a significant reverse remodeling process, perhaps via an atrial debulking process, resulting in reduced LA myopathy and therefore improved outcomes. Evidence regarding LA mechanical function following ablation is less clear; early studies suggested that LA function decreased after ablation,[117] although a more recent study suggested that LA strain may improve at 6 months postablation.[118] Two meta-analyses investigating LA function postablation delivered conflicting results.[119,120] More data are required to determine the effect of catheter ablation on overall LA function.

Symptomatic benefits may therefore arise from reduced LA myopathy in addition to reduced AF burden. In their hemodynamic assessment of patients with AF pre- and postablation, albeit in a relatively small cohort, Sugumar and colleagues[4] showed that patients remaining arrhythmia-free postablation showed significant reductions in their mean PCWP with exercise, reflecting an improvement in their underlying HFpEF. The resultant improvement in their heart failure symptoms was therefore possibly related to reduced arrhythmia burden as well as improved LA myopathy. While there can be little doubt that catheter ablation is an effective strategy in the treatment of patients with AF, the precise mechanisms of its efficacy remain unclear.

Risk factor management

Numerous observational and randomized studies have demonstrated the significant benefits of aggressive risk factor management (RFM) in patients with AF.[121–124] The symptomatic and quality-of-life benefits seen with RFM have been consistently associated with reductions in AF burden. However, RFM has also been associated with reverse remodeling of the LA. The LEGACY study showed that substantial weight loss was associated with structural reverse remodeling of the LA; weight loss of more than 10% resulted in significant reductions in LA volumes and improvements in LV diastolic function.[121] In addition, animal studies of AF have demonstrated significant reversal of the LA myopathy with weight loss.[64] While the symptomatic and quality-of-life benefits associated with RFM may be due to the significant reduction in AF burden, there is evidence to suggest that LA myopathy reversal and, therefore, improved HFpEF management may also underlie the benefits of RFM. There is also evidence to support aggressive RFM in HFpEF cohorts; a 20-week supervised exercise program and/or hypocaloric diet regimes were associated with significant improvements in exercise tolerance as measured by cardiopulmonary exercise testing compared to a control group who did not make any lifestyle changes.[125] The majority of these patients did not have a history of AF. However, the improvements in exercise tolerance were not accompanied by significant changes in LA size. Additional research is therefore required to further delineate the precise mechanisms underlying the efficacy of RFM and to establish any long-term mortality or thromboembolic benefits.

Pharmacological therapy

A vast number of randomized clinical trials have been carried out to investigate the use of various medical therapies in patients with HFpEF.[78] However, the majority have reported neutral outcomes. The TOPCAT trial investigated the use of spironolactone in patients with a confirmed diagnosis of HFpEF.[126] The primary composite outcome of cardiovascular death, aborted sudden death, or heart failure hospitalization was not reduced in the treatment arm. However, when only patients from the Americas were included in the analysis, the composite primary outcome was significantly reduced and cardiovascular death and heart failure hospitalizations were also independently reduced.[127] For these reasons, mineralocorticoid receptor antagonists are now recommended for patients with HF and preserved ejection fraction (>45%) according to the ACC guidelines (class IIb indication). However, substudies of the TOPCAT trial showed that LA structure was not influenced by spironolactone and AF incidence and recurrences were not reduced by spironolactone, suggesting that reversal of the LA myopathy may not have been the mechanism of effect.[128] Given the lack of pharmacological options for patients with HFpEF, the results of the EMPEROR-Preserved trial, investigating the use of the SGLT2-inhibitor empagliflozin in patients with HFpEF, are highly anticipated.[129]

Future directions

Establishing the true extent of HFpEF in patients with AF is critical to improving outcomes. Invasive hemodynamic studies of large, unselected cohorts of patients with AF are urgently required to develop a greater understanding of the true prevalence of HFpEF in AF. In addition, alternative noninvasive methods to diagnose and quantify LA myopathy in patients with AF should be sought, with a focus on quantifying LA fibrosis and stiffness. Prospective longitudinal outcome studies of patients with AF and known LA myopathy are required to further understand the prognostic impact of occult HFpEF on both mortality and systemic thromboembolism. Finally, interventional studies evaluating the effect of AF treatments on the reversal of the underlying LA myopathy and HFpEF are required to determine whether improvements in mortality, stroke risk, symptoms, and quality of life can be achieved.

Conclusion

The true nature of the relationship between AF and HFpEF is likely underappreciated; invasive hemodynamic studies suggest a large number of AF patients have occult HFpEF, associated with a progressive LA myopathy. As LA myopathy worsens, both AF burden and diastolic dysfunction increase and evidence suggests this may result in increased risk of mortality, systemic thromboembolism, and exercise intolerance. While many evidence-based treatments for AF are centered around reduction in AF burden, there is growing evidence to suggest that these treatments are also associated with reduced LA myopathy and reduced HFpEF. Further

work is required to establish whether reversal of the LA myopathy and HFpEF can significantly reduce mortality and systemic thromboembolism in AF.

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References

1. Kotecha D, Lam CSP, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation. J Am Coll Cardiol 2016;68:2217–2228.
2. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. Circulation 2018;137:534–535.
3. Sramko M, Wichterle D, Melenovsky V, et al. Resting and exercise-induced left atrial hypertension in patients with atrial fibrillation. JACC Clin Electrophysiol 2017;3:461–469.
4. Sugumar H, Nanayakkara S, Vizi D, et al. A prospective STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF: STALL AF. Eur J Heart Fail 2021;23:785–796.
5. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke 2021; 16:217–221.
6. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–1858.
7. Gurwitz JH, Magid DJ, Smith DH, et al. Contemporary prevalence and correlates of incident heart failure with preserved ejection fraction. Am J Med 2013;126:393–400.
8. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
9. Gallagher C, Hendriks JM, Giles L, et al. Increasing trends in hospitalisations due to atrial fibrillation in Australia from 1993 to 2013. Heart 2019; 105:1358–1363.
10. Pellicori P, Urbinati A, Kaur K, et al. Prevalence and incidence of atrial fibrillation in ambulatory patients with heart failure. Am J Cardiol 2019; 124:1554–1560.
11. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa. Circulation 2016;133:484–492.
12. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail 2017; 5:565–574.
13. Vermond RA, Geelhoed B, Verweij N, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality. J Am Coll Cardiol 2015;66:1000–1007.
14. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction. Circulation 2013;128:1085–1093.
15. Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction. Circulation 2015; 131:1247–1259.
16. Freeman JV, Simon DN, Go AS, et al. Association between atrial fibrillation symptoms, quality of life, and patient outcomes. Circ Cardiovasc Qual Outcomes 2015;8:393–402.
17. Lip GYH, Laroche C, Popescu MI, et al. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation. Eur J Heart Fail 2015;17:570–582.
18. Silva-Cardoso J, Zharinov OJ, Ponikowski P, et al. Heart failure in patients with atrial fibrillation is associated with a high symptom and hospitalization burden: the RealiseAF Survey. Clin Cardiol 2013;36:766–774.
19. Chamberlain AM, Gersh BJ, Alonso A, et al. No decline in the risk of heart failure after incident atrial fibrillation: a community study assessing trends overall and by ejection fraction. Heart Rhythm 2017;14:791–798.
20. Korantzopoulos P, Letsas KP, Tse G, Fragakis N, Goudis CA, Liu T. Inflammation and atrial fibrillation: a comprehensive review. J Arrhythmia 2018; 34:394–401.
21. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis. Circ Res 2021;128:1451–1467.
22. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction. J Am Coll Cardiol 2013;62:263–271.
23. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens 2007;21:20–27.
24. Hu Y-F, Chen Y-J, Lin Y-J, Chen S-A. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015;12:230–243.
25. Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults. J Am Coll Cardiol 2010; 55:2129–2137.
26. Patel RB, Colangelo LA, Bielinski SJ, et al. Circulating vascular cell adhesion molecule-1 and incident heart failure: the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc 2020;9:e019390.
27. Patel RB, Colangelo LA, Reiner AP, et al. Cellular adhesion molecules in young adulthood and cardiac function in later life. J Am Coll Cardiol 2020; 75:2156–2165.
28. Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. Int J Cardiol 2013; 169:62–72.
29. Rienstra M, Sun JX, Magnani JW, et al. White blood cell count and risk of incident atrial fibrillation (from the Framingham Heart Study). Am J Cardiol 2012; 109:533–537.
30. Prasada S, Rivera A, Nishtala A, et al. Differential associations of chronic inflammatory diseases with incident heart failure. JACC Heart Fail 2020; 8:489–498.
31. Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. BMJ 2012; 344. e1257–e1257.

32. Kim YR, Nam G-B, Han S, et al. Effect of short-term steroid therapy on early recurrence during the blanking period after catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol 2015;8:1366–1372.
33. Van Osch D, Dieleman JM, Van Dijk D, et al. Dexamethasone for the prevention of postoperative atrial fibrillation. Int J Cardiol 2015;182:431–437.
34. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. Prog Cardiovasc Dis 2020;63:10–21.
35. Norton GR, Woodiwiss AJ, Gaasch WH, et al. Heart failure in pressure overload hypertrophy. J Am Coll Cardiol 2002;39:664–671.
36. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size. The Framingham Heart Study. Hypertension 1995; 25:1155–1160.
37. Lau DH, Shipp NJ, Kelly DJ, et al. Atrial arrhythmia in ageing spontaneously hypertensive rats: unraveling the substrate in hypertension and ageing. PLoS One 2013;8:e72416.
38. Munger TM, Dong YX, Masaki M, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. J Am Coll Cardiol 2012;60:851–860.
39. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol 2015;66:1–11.
40. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266–274.
41. Woodiwiss AJ, Libhaber CD, Majane OH, Libhaber E, Maseko M, Norton GR. Obesity promotes left ventricular concentric rather than eccentric geometric remodeling and hypertrophy independent of blood pressure. Am J Hypertens 2008;21:1144–1151.
42. Frank RC, Min J, Abdelghany M, et al. Obesity is associated with pulmonary hypertension and modifies outcomes. J Am Heart Assoc 2020;9:e014195.
43. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19.
44. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014;35:1101–1111.
45. Franssen C, Chen S, Unger A, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection Fraction. JACC Heart Fail 2016;4:312–324.
46. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation 2015;132:402–414.
47. Borlaug BA, Lam CSP, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease. J Am Coll Cardiol 2009;54:410–418.
48. Yip G. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121–125.
49. Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial injury and cardiac reserve in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2018;72:29–40.
50. Ahmad A, Corban MT, Toya T, et al. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:765–772.
51. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018;39:3439–3450.
52. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. J Am Coll Cardiol 2008;51:2053–2057.
53. Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. JAMA Cardiol 2021;6:1130–1143.
54. Wong CX, Sun MT, Odutayo A, et al. Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation. Circ Arrhythm Electrophysiol 2016;9:e004378.
55. Van Woerden G, Gorter TM, Westenbrink BD, Willems TP, Van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail 2018;20:1559–1566.
56. KankaanpäÄ M, Lehto H-R, PäRkkÄ JP, et al. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. J Clin Endocrinol Metab 2006;91:4689–4695.
57. Malavazos AE, Di Leo G, Secchi F, et al. Relation of echocardiographic epicardial fat thickness and myocardial fat. Am J Cardiol 2010;105:1831–1835.
58. Greulich S, Maxhera B, Vandenplas G, et al. Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction. Circulation 2012;126:2324–2334.
59. Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. Am J Physiol Endocrinol Metab 2012;303:E937–E949.
60. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. JACC Heart Fail 2020;8:657–666.
61. Harada M, Nattel S. Implications of inflammation and fibrosis in atrial fibrillation pathophysiology. Card Electrophysiol Clin 2021;13:25–35.
62. Lau DH, Linz D, Schotten U, Mahajan R, Sanders P, Kalman JM. Pathophysiology of paroxysmal and persistent atrial fibrillation: rotors, foci and fibrosis. Heart Lung Circ 2017;26:887–893.
63. Medi C, Kalman JM, Spence SJ, et al. Atrial electrical and structural changes associated with longstanding hypertension in humans: implications for the substrate for atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:1317–1324.
64. Mahajan R, Lau DH, Brooks AG, et al. Atrial fibrillation and obesity: reverse remodeling of atrial substrate with weight reduction. JACC Clin Electrophysiol 2021;7:630–641.
65. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm 2012;9:321–327.
66. Everett TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhythm 2007;4:S24–S27.
67. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 2015;131:550–559.
68. Yamamoto K. Myocardial stiffness is determined by ventricular fibrosis, but not by compensatory or excessive hypertrophy in hypertensive heart. Cardiovasc Res 2002;55:76–82.
69. Mesquita TRR, Zhang R, De Couto G, et al. Mechanisms of atrial fibrillation in aged rats with heart failure with preserved ejection fraction. Heart Rhythm 2020; 17:1025–1033.
70. Bode D, Lindner D, Schwarzl M, et al. The role of fibroblast – cardiomyocyte interaction for atrial dysfunction in HFpEF and hypertensive heart disease. J Mol Cell Cardiol 2019;131:53–65.
71. Duca F, Kammerlander AA, Zotter-Tufaro C, et al. Interstitial fibrosis, functional status, and outcomes in heart failure with preserved ejection fraction. Circ Cardiovasc Imaging 2016;9:e005277.
72. Ariyaratnam JP, Lau DH, Sanders P, Kalman JM. Atrial fibrillation and heart failure: epidemiology, pathophysiology, prognosis, and management. Card Electrophysiol Clin 2021;13:47–62.
73. Solti F, Vecsey T, Kékesi V, Juhász-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. Cardiovasc Res 1989;23:882–886.
74. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure. Circulation 2003;108:1461–1468.
75. Kitzman DW. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144.
76. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing–induced congestive heart failure. Circulation 2001; 104:2608–2614.
77. Mitchell JH, Gupta DN, Payne RM. Influence of atrial systole on effective ventricular stroke volume. Circ Res 1965;17:11–18.
78. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559–573.
79. Ling L-H, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation. J Am Coll Cardiol 2012;60:2402–2408.
80. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. Am J Cardiol 1996;78:1433–1436.
81. Bisbal F, Baranchuk A, Braunwald E, Bayés De Luna A, Bayés-Genís A. Atrial failure as a clinical entity. J Am Coll Cardiol 2020;75:222–232.
82. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction. Circ Heart Fail 2014; 7:1042–1049.
83. Teh AW, Kistler PM, Lee G, et al. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J Cardiovasc Electrophysiol 2012;23:232–238.
84. Takahashi N, Imataka K, Seki A, Fujii J. Left atrial enlargement in patients with paroxysmal atrial fibrillation. Jpn Heart J 1982;23:677–683.
85. Kuppahally SS, Akoum N, Burgon NS, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation. Circ Cardiovasc Imaging 2010;3:231–239.
86. Liu Y, Zhu D, Xiao Y, et al. Risk factors of left atrial appendage thrombus in patients with non-valvular atrial fibrillation. Open Med 2021;16:361–366.
87. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail 2019;21:891–900.

88. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail 2015;8:295–303.
89. Lam CSP, Rienstra M, Tay WT, et al. Atrial fibrillation in heart failure with preserved ejection fraction. JACC Heart Fail 2017;5:92–98.
90. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 2018;138:861–870.
91. Pieske B, Tschöpe C, De Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297–3317.
92. Verbrugge FH, Reddy YNV, Sorimachi H, Omote K, Carter RE, Borlaug BA. Diagnostic scores predict morbidity and mortality in patients hospitalized for heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:954–963.
93. Meluzin J, Starek Z, Kulik T, et al. Prevalence and predictors of early heart failure with preserved ejection fraction in patients with paroxysmal atrial fibrillation. J Card Fail 2017;23:558–562.
94. Dickinson MG, Lam CS, Rienstra M, et al. Atrial fibrillation modifies the association between pulmonary artery wedge pressure and left ventricular end-diastolic pressure. Eur J Heart Fail 2017;19:1483–1490.
95. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. J Am Coll Cardiol 2020;76:1051–1064.
96. Liu G, Long M, Hu X, Hu C-H, Du Z-M. Meta-analysis of atrial fibrillation and outcomes in patients with heart failure and preserved ejection fraction. Heart Lung Circ 2021;30:698–706.
97. Packer M. HFpEF is the substrate for stroke in obesity and diabetes independent of atrial fibrillation. JACC: Heart Fail 2020;8:35–42.
98. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Eur Heart J 2015;36:288–296.
99. Gupta DK, Shah AM, Giugliano RP, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. Eur Heart J 2014;35:1457–1465.
100. Go AS, Reynolds K, Yang J, et al. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation. JAMA Cardiol 2018;3:601.
101. Hamatani Y, Ogawa H, Takabayashi K, et al. Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Sci Rep 2016;6:31042.
102. Mulder BA, Veldhuisen DJ, Rienstra M. What should the C ('congestive heart failure') represent in the CHA 2 DS 2 -VASc score? Eur J Heart Fail 2020; 22:1294–1297.
103. Akoum N, Fernandez G, Wilson B, McGann C, Kholmovski E, Marrouche N. Association of atrial fibrosis quantified using lge-mri with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:1104–1109.
104. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011;57:831–838.
105. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. JAMA 2019;321:1261.
106. Movsowitz C, Movsowitz HD, Jacobs LE, Meyerowitz CB, Podolsky LA, Kotler MN. Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. J Am Soc Echocardiogr 1993;6:107–114.
107. Bhat A, Khanna S, Chen HH, et al. Impairment of left atrial function and cryptogenic stroke: potential insights in the pathophysiology of stroke in the young. Int J Cardiol Heart Vasc 2019;26. 100454–100454.
108. Atwood JE, Myers JN, Tang XC, Reda DJ, Singh SN, Singh BN. Exercise capacity in atrial fibrillation: a substudy of the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). Am Heart J 2007;153:566–572.
109. Von Roeder M, Rommel K-P, Kowallick JT, et al. Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. Circ Cardiovasc Imaging 2017;10:e005467.
110. Maffeis C, Morris DA, Belyavskiy E, et al. Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction. ESC Heart Fail 2021;8:116–128.
111. Elliott AD, Verdicchio CV, Gallagher C, et al. Factors contributing to exercise intolerance in patients with atrial fibrillation. Heart Lung Circ 2021;30:947–954.
112. Parameswaran R, Al-Kaisey AM, Kalman JM. Catheter ablation for atrial fibrillation: current indications and evolving technologies. Nat Rev Cardiol 2021; 18:210–225.
113. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 2020;383:1305–1316.
114. Allessie M. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230–246.
115. Bunch TJ, May HT, Bair TL, et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. Heart Rhythm 2013;10:1257–1262.
116. Rettmann ME, Holmes DR 3rd, Monahan KH, et al. Treatment-related changes in left atrial structure in atrial fibrillation: findings from the CABANA Imaging Substudy. Circ Arrhythm Electrophysiol 2021;14:e008540.
117. Wylie JV, Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. Heart Rhythm 2008;5:656–662.
118. Kuppahally SS, Akoum N, Badger TJ, et al. Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablation delayed enhancement of left atrium by magnetic resonance imaging. Am Heart J 2010;160:877–884.
119. Xiong B, Li D, Wang J, Gyawali L, Jing J, Su L. The effect of catheter ablation on left atrial size and function for patients with atrial fibrillation: an updated meta-analysis. PLoS One 2015;10:e0129274.
120. Jeevanantham V, Ntim W, Navaneethan SD, et al. Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. Am J Cardiol 2010;105:1317–1326.
121. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort. J Am Coll Cardiol 2015;65:2159–2169.
122. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation. J Am Coll Cardiol 2014;64:2222–2231.
123. Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace 2018;20:1929–1935.
124. Middeldorp ME, Ariyaratnam J, Lau D, Sanders P. Lifestyle modifications for treatment of atrial fibrillation. Heart 2020;106:325–332.
125. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction. JAMA 2016;315:36.
126. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–1392.
127. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.
128. Neefs J, Van Den Berg NWE, Krul SPJ, Boekholdt SM, De Groot JR. Effect of spironolactone on atrial fibrillation in patients with heart failure with preserved ejection fraction: post-hoc analysis of the randomized, placebo-controlled TOPCAT trial. Am J Cardiovasc Drugs 2020;20:73–80.
129. Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail 2019; 21:1279–1287.
130. Gong FF, Jelinek MV, Castro JM, et al. Risk factors for incident heart failure with preserved or reduced ejection fraction, and valvular heart failure, in a community-based cohort. Open Heart 2018;5:e000782.
131. Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort. JAMA 1994;271:840.
132. Pandey A, LaMonte M, Klein L, et al. Relationship between physical activity, body mass index, and risk of heart failure. J Am Coll Cardiol 2017; 69:1129–1142.
133. Wong CX, Sullivan T, Sun MT, et al. Obesity and the risk of incident, postoperative, and post-ablation atrial fibrillation. JACC Clin Electrophysiol 2015; 1:139–152.
134. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors. Circulation 2011; 123:1501–1508.
135. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. J Diabetes Complications 2018;32:501–511.
136. Youssef I, Kamran H, Yacoub M, et al. Obstructive sleep apnea as a risk factor for atrial fibrillation: a meta-analysis. J Sleep Disord Ther 2018;7:282.
137. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of atrial fibrillation: a systematic review and meta-analysis of prospective studies. Eur J Prev Cardiol 2018;25:1437–1451.
138. Gallagher C, Hendriks JML, Elliott AD, et al. Alcohol and incident atrial fibrillation - a systematic review and meta-analysis. Int J Cardiol 2017;246:46–52.