American Heart Journal Plus: Cardiology Research and Practice 33 (2023) 100309

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Review article

A review of the impact, pathophysiology, and management of atrial fibrillation in patients with heart failure with preserved ejection fraction

Cicely Dye [a], Mark Dela Cruz [b], Timothy Larsen [a], Gatha Nair [c], Karolina Marinescu [a], Tisha Suboc [a], Erica Engelstein [a], Jennifer Marsidi [a], Priya Patel [a], Parikshit Sharma [a], Annabelle Santos Volgman [a,*]

[a] Division of Cardiology, Rush University Medical Center, Chicago, IL 60612, USA
[b] Advocate Heart Institute, Advocate Christ Medical Center, Chicago, IL 60453, USA
[c] Division of Cardiology, University of Washington, Seattle, WA 98105, USA

ARTICLE INFO

Keywords:
Heart failure
Preserved ejection fraction
Atrial fibrillation
Rhythm control
Anticoagulation

ABSTRACT

Patients with heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) have increased mortality and increased risk of stroke. Due to the heterogeneous nature of both disease processes, it is difficult to ascertain whether the diagnosis and progression of AF is the cause of deterioration or if it is a symptom of worsening heart failure. This presents physicians with a clinical conundrum of whether optimizing their heart failure will decrease the overall AF burden or if restoration of sinus rhythm is necessary to optimize patients with HFpEF. In this paper, we will review the impact of AF in patients with HFpEF, the pathophysiology and heterogeneity of HFpEF and AF, and the management of these patients. As HFpEF and AF become more prevalent, managing these disease processes needs standardization to improve outcomes. Further research is needed to understand the complex interplay between AF and HFpEF to help determine the best management strategy.

1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous disease process diagnosed in patients with "signs and symptoms of HF with elevated natriuretic peptides and evidence of structural heart disease with a left ventricular ejection fraction greater than 50%" [1]. It is often associated with hypertension, older age, female sex, and atrial fibrillation (AF). Fig. 1 shows the hazard ratios of specific risk factors for the incidence of HFpEF and AF. Advanced age, increasing BMI, hypertension, diabetes and obstructive sleep apnea all increase the risk of both HFpEF and AF. Alcohol and cigarette smoking have different effects on HFpEF and AF. AF can be seen in as many as 41.9 % of patients with HFpEF compared to 37.6 % in patients with HF with reduced ejection fraction (HFrEF). Although the presence of AF increased mortality in both types of HF, a multivariate regression analysis showed AF to be associated with in-hospital mortality only in HFpEF but not in HFrEF [2]. This is noteworthy because in patients with HFpEF, AF is associated with increased mortality and stroke [3].

Patients with HFpEF and AF are typically complex patients with multiple comorbidities. It can be challenging to ascertain whether the diagnosis and progression of AF cause deterioration or if it is a symptom of worsening HF. This presents physicians with a clinical conundrum of

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BB, Beta-blocker; BMI, body mass index; CAD, coronary artery disease; CD, cluster of differentiation; CHA_2DS_2-VASc score, congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category; CRP, C-reactive protein; DOAC, Direct oral anticoagulants; EAT, epicardial adipose tissue; ECM, extra-cellular matrix; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with moderately reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; CI, confidence interval; ICA, isolated cardiac amyloidosis; ICAM, immunoglobulin-like cell adhesion molecule; IDA, iron deficiency anemia; IL, interleukin; LA, left atrium; LAAO, left atrial appendage occlusion; LV, left ventricle; MACE, major adverse cardiovascular events; NLRP3, NOD-like receptor family, pyrin domain-containing protein 3; RAAS, renin-angiotensin-aldosterone; AFL, atrial flutter; RCTs, randomized controlled trials; SE, systemic embolism; SERCA2, sarco/endoplasmic reticulum calcium ATPase-2; SGLT2i, Sodium-glucose linked transporter-2 inhibitors; T2DM, Type 2 diabetes mellitus; TGFb, transforming growth factor b; TNFa, tumor necrosis factor-alpha; VCAM, vascular cellular adhesion molecule; VKA, Vitamin K antagonists.

* Corresponding author at: RUSH University Medical Center, 1725 W Harrison St, Suite 1159, Chicago, IL 60612, USA.
E-mail address: Annabelle_Volgman@rush.edu (A.S. Volgman).

https://doi.org/10.1016/j.ahjo.2023.100309
Received 8 July 2023; Accepted 11 July 2023
Available online 18 July 2023

whether optimizing their HF will decrease the overall AF burden or if restoration of sinus rhythm is necessary to optimize patients with HFpEF, even in patients with adequate rate control. There has been a growing body of evidence that in patients with both AF and HFpEF, there is an increase in their overall mortality despite adequate rate control [4]. Despite this information, the role of rhythm control in this population is still under debate.

In this paper, we will review the impact of AF in patients with HFpEF regarding its growing incidence and morbidity in our aging population. We will discuss the pathophysiology and heterogeneity of HFpEF and how AF interplays with each sub-group to include its predominance in women. Finally, we will review the recent literature on managing patients with HFpEF and AF regarding stroke prevention, heart failure optimization, and rhythm control.

1.1. Methods

An outline of topics pertaining to AF and HFpEF was created to guide the group of authors to review the literature on their assigned topics. A heart failure specialist and a cardiac electrophysiologist were paired for each topic to search and review the literature and summarize their findings. All AF types were included, and if specific types were studied, this was noted in the review. Studies included in the review were randomized clinical trials, systematic reviews, meta-analyses, and cohort studies. The first and last authors reviewed all the sections, created the tables and Fig. 1, and created the manuscript for this narrative review.

2. Impact of AF on Patients with HFpEF

2.1. Prevalence

AF and HF are two frequently encountered cardiovascular disease diagnoses, often called epidemics of modern medicine. Nearly 6.5 million individuals in the United States (US) carry the diagnosis of HF [5], with preserved systolic function and reduced systolic function (HFrEF) represented in a similar proportion [6]. Conversely, the burden of AF is significant. In 2010, the prevalence of AF in the US was estimated at 5.1 million [7]. HFpEF and AF often coexist, with the concomitant prevalence estimated to be 40–60 %. In the Framingham Heart Study with new-onset AF or HF, AF occurred in more than half of individuals with AF, and HF occurred in more than one-third of individuals with AF.

The prevalence of AF was more strongly associated with HFpEF with a multivariable-adjusted hazard ratio of 2.34 [8]. Since both conditions are challenging to diagnose, both are likely being underdiagnosed, and the incidence of the two comorbidities is likely higher. AF appears to be more common in those with preserved EF and diastolic dysfunction. In the Korean acute HF registry, the prevalence of AF significantly

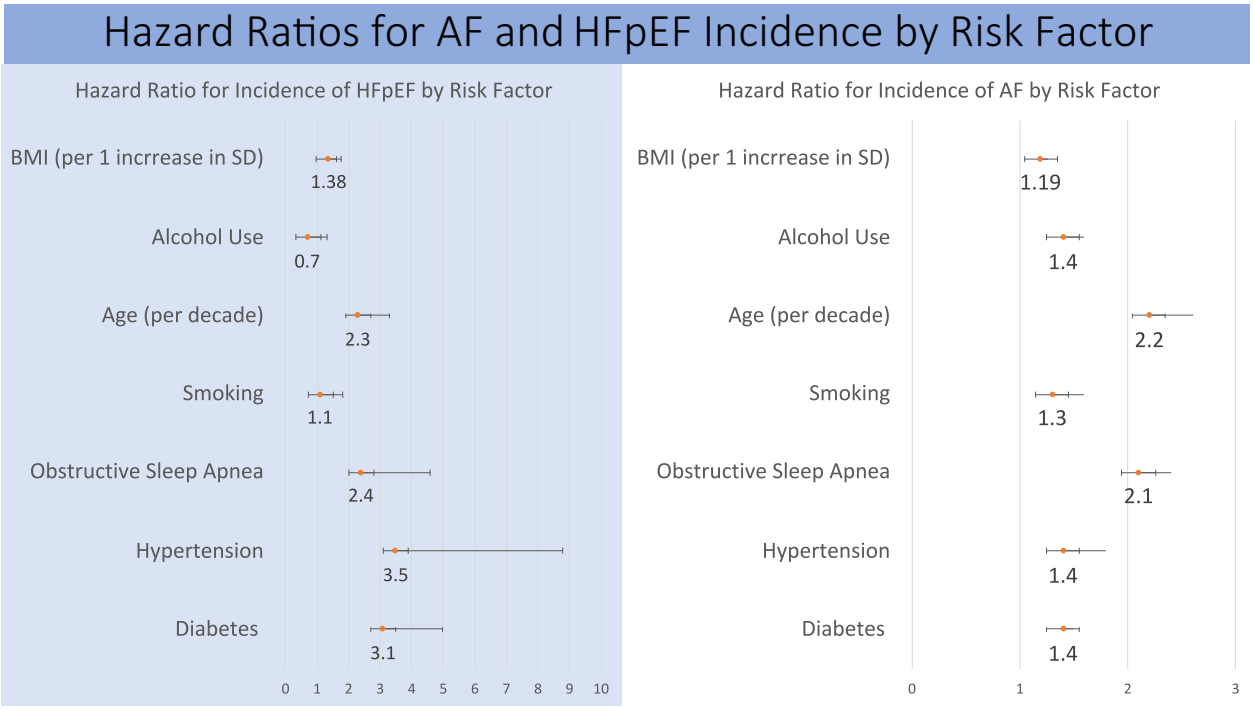

Fig. 1. Hazard Ratios for AF and HFpEF Incidence by Risk Factor.
Abbreviations: AF – atrial fibrillation, HFpEF – heart failure with preserved ejection fraction, BMI – body mass index, SD – standard deviation.
References:

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.
Benjamin EJ. Independent risk factors for atrial fibrillation in a population-based cohort. JAMA. 1994;271:840.
Pandey A, LaMonte M, Klein L, et al. Relationship between physical activity, body mass index and risk of heart failure. JACC. 2017;69:1129-1142
Wong CX, Sullivan T, Sun MT et al. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation. JACC EP. 2015;1:139-152.
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.
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
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.
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.
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.

increased with increasing EF (HFrEF 28.9 %, HF with moderately reduced EF (HFmrEF) 39.8 %, HFpEF 45.2 %; p for trend <0.001) [9]. In the Swedish HF registry, the prevalence of AF was 53 %, 60 %, and 65 % in HFrEF, HFmrEF, and HFpEF, respectively [10]. The presence of AF in patients with dyspnea makes HFpEF a more likely diagnosis than other non-cardiac causes of dyspnea since AF is weighted as 3 out of 9 points [11].

2.2. Impact on mortality, heart failure, and stroke

Prior history of AF not only significantly increases the likelihood of new-onset HFpEF [12] but is also associated with worse outcomes. Patients with HFpEF and AF have been shown to have increased mortality and hospital admissions [13]. A meta-analysis of trials of AF and HFpEF showed that AF was associated with an 11 % increased risk of all-cause mortality in patients with HFpEF (HR 1.11, 95 % CI 1.09–1.12). AF was an independent predictor of hospitalization for HF (HR 1.32, 95 % CI 1.15–1.52), cardiovascular death (HR 1.38, 95 % CI 1.01–1.89), and stroke (HR 1.87, 95 % CI 1.54–2.27) [14].

In a multicenter prospective registry of patients with AF and HF, the cumulative incidence of AF/systemic embolism (SE) was significantly the highest in the HFpEF group at 22.8 ± 10.0 months ($P = 0.020$). The stroke/SE risk was higher in the HFpEF group than in the HFmrEF and HFrEF groups (hazard ratio, 3.192; 95 % confidence interval, 1.039–9.810; $P = 0.043$). E/e' value was an independent risk factor for stroke/SE. There were no significant differences in the incidence of major bleeding across the groups [15].

Since AF and HFpEF often coexist, developing a correlative versus causative relationship is complex. The three most common hypotheses regarding the relationship between HFpEF and AF are: AF may be the sole cause or one of the main causal agents for HF; AF is the result of the atrial hemodynamics caused by progressive myocardial dysfunction in HF; and AF and HF are both associated with a third factor that affects the underlying atrial and ventricular myocardium such as ischemia, inflammation or infiltration [16]. Likely, all the scenarios play a role in HFpEF and AF, but which approach a clinician takes can significantly impact management and outcomes [8].

Clinicians are more often aware of the presence of AF once a patient is diagnosed with HF. This may be because AF is not tolerated as well in patients with diastolic dysfunction and therefore triggers earlier clinical recognition [17]. Clinicians also tend to be more aggressive in pursuing rhythm control in patients once they are diagnosed with HFpEF, given that the most significant benefit of rhythm control is typically seen in patients already diagnosed with HF [16,18,19]. In contrast, the development of AF in patients with preexisting HF, whether HFrEF or HFpEF, is usually associated with a worse prognosis [14,20]. Even when these patients have improved clinical outcomes, they remain at risk for recurrent HF, especially if significant cardiac remodeling occurs before rhythm control is achieved [21]. However, those with left atrial reverse remodeling (about 60 %) have a better prognosis [22].

2.3. AF and HFpEF in specific conditions

2.3.1. Mitral regurgitation

Functional mitral regurgitation is frequently seen in patients with AF and HFpEF and is postulated to be related to the left atrial dimension [23]. In the ARIC (Atherosclerosis Risk in Communities) study, AF was more likely in those with higher mitral regurgitation severity regardless of HF subtype; however, when stratified by HF type, the association between AF and 1-year mortality was noted in patients with HFpEF (OR, 1.28, 95 % CI 1.04–1.56) but not HFrEF (OR 0.96, 95 % CI 0.79–1.16) (interaction by EF subtype, $P = 0.02$) [24].

2.3.2. Coronary artery disease

The impact of coronary artery disease (CAD) on AF and HFpEF was studied in 408 hospitalized HFpEF patients enrolled in the Japanese Heart Failure Syndrome with Preserved Ejection Fraction Nationwide Multicenter Registry. Patients were divided into 4 groups according to the presence of AF and CAD. The primary outcome was the composite of all-cause death and HF rehospitalization. The incidence of adverse events was higher in the AF/non-CAD than non-AF/non-CAD group ($P = 0.004$). In contrast, the risk was comparable between the AF/CAD and non-AF/CAD groups (adjusted HR, 1.24; 95 % CI: 0.64–2.47). In other words, in patients with HFpEF but without CAD, AF was independently related to adverse events; in patients with CAD and HFpEF, AF had no prognostic impact [25].

2.3.3. Amyloidosis

Cardiac amyloidosis may be an underappreciated cause of both AF and HFpEF. In an autopsy study of 1083 patients without known amyloidosis, 3 % were found to have isolated cardiac amyloidosis [ICA]. Among those with ICA, half had a history of persistent AF. In patients without ICA, a history of AF was noted in 16 %, half persistent and half paroxysmal. Patients with ICA were older and had higher odds of AF independent of age and CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category). Among patients with AF, those with ICA were more likely to have persistent forms of AF and had a lower sinus rhythm P-wave amplitude [26]. Amyloidosis is a known cause of HFpEF. While the exact prevalence of cardiac amyloidosis is unknown, studies estimate the presence of 13–14 % in HFpEF patients [27,28].

3. Pathophysiology and Heterogeneity of HFpEF and AF

The complex pathophysiology of AF in HFpEF has been the subject of intense investigation. AF is typically initiated by ectopic electrical excitation emanating from the pulmonary veins [29]. In order for AF to propagate and persist, an arrhythmogenic atrial substrate is essential. The concurrence of HFpEF and AF would indicate that the many risk factors and underlying mechanisms driving the progression of HFpEF are also necessary for the formation of arrhythmogenic atrial substrate [30–32]. These processes likely culminate in atrial fibrosis and left atrial (LA) myopathy, key abnormalities that distinguish AF in HFpEF.

Fig. 2 shows the possible mechanisms of left atrial myopathy in HFpEF-AF [33]. The physiologic hallmarks of HFpEF are impaired ventricular relaxation and decreased ventricular compliance, leading to increased atrial filling pressures. These findings are reflected in the reversal of the E:A ratio on echocardiography. Reduced passive blood flow from the LA to the LV (i.e. reduced E wave) results in increased atrial preload, requiring increased atrial ejection fraction during active filling (the A wave) in order to maintain cardiac output. Increased atrial ejection fraction increases energy demands on atrial myocytes and may play a role in subsequent atrial hypertrophy, dilation, and remodeling. As diastolic dysfunction progresses, increased LA pressure results in increased early diastolic filling accompanied by reduction of the A wave (due to impaired ventricular compliance and increased LV end-diastolic pressure) resulting in the "pseudo-normalization" pattern. This is followed by a restrictive filling pattern where nearly all LV filling occurs in the beginning of diastole. This results in a large E wave, short deceleration time, and small A wave, findings associated with very high filling pressures.

Increased atrial volume and filling pressures likely contribute to LA dilatation, which commonly occurs in patients with HFpEF [34]. Atrial volume index is a strong predictor of incident AF [35]. Increased atrial wall stress due to increased volume and pressure promotes fibrosis and ion channel remodeling, resulting in shortened refractory periods. LA enlargement allows for multi-wavelet reentry phenomenon which promotes the maintenance of persistent AF.

On the cellular level, a primary factor that leads to AF in HFpEF may be systemic inflammation [36]. The various risk factors for AF and HFpEF, including aging, hypertension, obesity, and sleep apnea, have

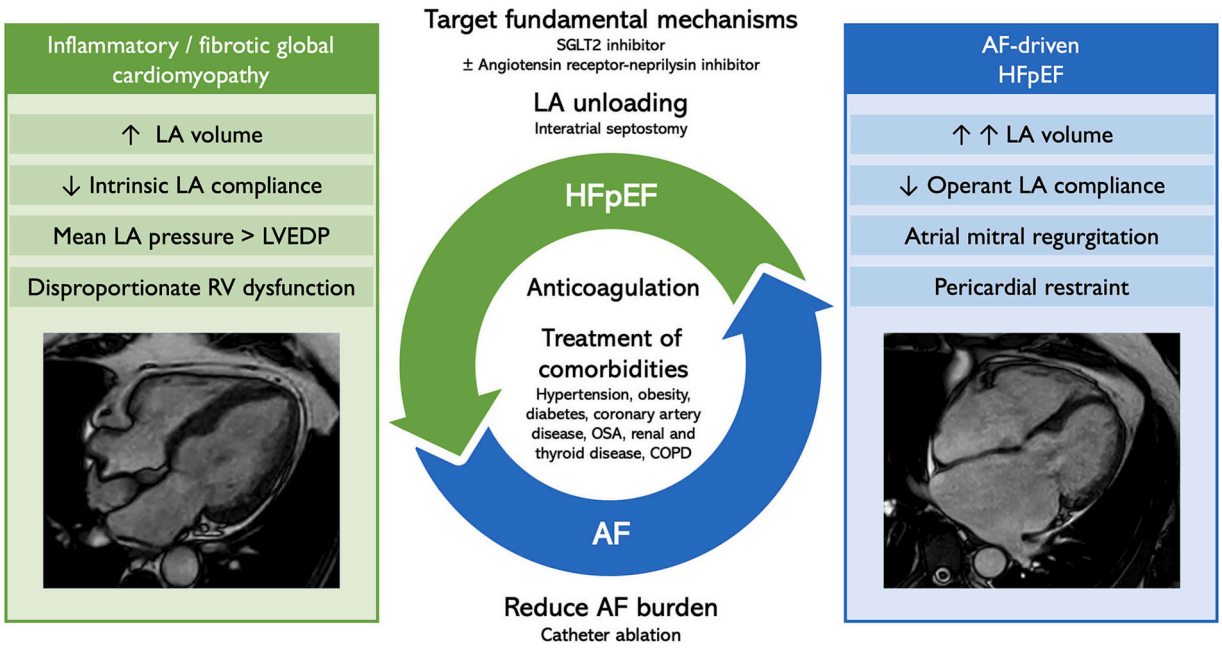

Fig. 2. Proposed mechanisms of left atrial myopathy in atrial fibrillation–heart failure with preserved ejection fraction and current treatment options.
HFpEF is characterized by a global inflammatory/fibrotic cardiomyopathy concurrently involving the left atrium (LA). AF promotes atrial remodeling that can lead to marked LA dilatation, incurring a mechanism of LA pressure elevation related to pericardial restraint and heightened ventricular interaction (described by Reddy et al14). COPD indicates chronic obstructive pulmonary disease; LVEDP, left ventricular end-diastolic pressure; OSA, obstructive sleep apnea; RV, right ventricle; and SGLT2, sodium-glucose cotransporter 2 inhibitors. Copied with permission from Zakeri, R [33].

long been associated with high circulating levels of proinflammatory cytokines [37,38]. These comorbidity-associated systemic inflammatory states are observed to be predictive of incident HFpEF but not of HFrEF [39]. Both acute (e.g. sepsis) and chronic inflammatory states (e.g. rheumatoid arthritis, psoriasis, inflammatory bowel disease) have also been linked to higher rates of AF [40–44]. Similarly, patients with autoimmune diseases more commonly develop HFpEF than HFrEF [45].

Longitudinal cohort studies that utilize inflammatory markers to predict either HFpEF or AF bear striking similarities. Elevated plasma levels of tumor-necrosis factor alpha (TNFa), *E*-selectin, ICAM-1, and VCAM were found to increase the risk of incident HFpEF [39,46,47]. Similarly, various inflammatory markers, including TNFa, CRP, IL-6, and white blood cell count, have been associated with an increased risk of incident AF and are markedly higher in patients experiencing recurrent AF after ablation [48–50].

It is important to note that the exact causative mechanisms linking inflammatory markers and AF in HFpEF remain unclear. These inflammatory processes must promote alterations to the electrophysiological properties of atrial tissue resulting in decreased conduction velocity, shorter refractory periods, and shortened action potential duration [36]. An important step in this process, inflammatory cell infiltration, especially of CD68 positive macrophages, has been observed in atrial tissue among patients with AF meeting HFpEF criteria [51,52]. Macrophages in atrial tissue of patients with AF have been found to have elevated IL-6 and transforming growth factor b (TGFb) production [53]. Furthermore, atrial tissue of patients with AF demonstrate increased IL-6, IL-8, IL-10, and TNF levels [54].

These cytokines may have a direct impact on the electrophysiological properties and arrhythmogenicity of atrial tissue. In vitro and murine models demonstrate how IL-6 may regulate the expression of gap junction channels on cardiomyocytes and may enhance L-type calcium channel and decrease sarco/endoplasmic reticulum calcium ATPase-2 (SERCA2) expression [55–58]. TNF may directly impact murine cardiomyocytes resulting in abnormal calcium handling [59–61]. In a rabbit model, direct TNF treatment of isolated pulmonic vein cardiomyocytes resulted in decreased SERCA2 expression, abnormal calcium handling, and thus increased susceptibility to delayed after depolarizations [62]. Experimental models have also demonstrated electrical remodeling that promote AF in response to other cytokines such as nuclear factor-kappaB and NLRP3 [36].

Moreover, inflammation may result in atrial tissue with heterogeneous electrical properties that can propagate AF. A key driver of this heterogeneity, atrial fibrosis plays a central role by decreasing atrial conduction velocity [36]. It has been postulated that common inflammatory precursors result in differing disease manifestations depending on the site of fibrosis i.e. AF in the atria and HFpEF in the ventricle.

Much like in the ventricular myocardium in HFpEF [63–66], inflammation and oxidative stress can precipitate atrial fibrosis [67]. Pro-inflammatory cytokines and other signals, including mechanical stress, activate various pro-fibrotic cell membrane receptors i.e. connective tissue growth factor, angiotensin-II, platelet-derived growth factor, and TGFb [68,69]. Downstream, these activate systems that result in phosphorylation of mitogen-activated protein kinases that then increase the production of certain ECM proteins, enzymes that process collagen, and signaling molecules that further potentiate the fibrotic process in a positive feedback loop [67]. TGFb and angiotensin II type 1 activation result in the production of reactive oxygen species that affect further fibrosis and atrial structural remodeling [70].

Interactions between fibroblasts and cardiomyocytes also introduce an arrhythmogenic substrate. In vitro models have demonstrated the formation of low-resistance electric junctions that are capable of mutually modulating electrical activity [71,72]. Interactions between these cell types may enhance delayed after depolarization and promote ectopic impulse generation, slow conduction, and arrhythmia generation [72,73]. Mathematical models suggest that fibroblast remodeling may significantly alter the persistence of AF [74]. Beyond fibroblast-cardiomyocyte electrical coupling, collagen formation may also result in physical separation of cardiomyocytes [75]. The degree to which electrical coupling or physical separation influence AF propagation remains unclear.

Another factor further linking co-morbidity associated inflammation to AF risk in HFpEF is epicardial adipose tissue (EAT). EAT expansion

has been observed particularly among HFpEF patients with obesity and Type 2 diabetes mellitus (T2DM) and found to be strongly predictive of AF [76–78]. Since it shares a common vascular supply and exists without fascial barriers, EAT may be poised to exert paracrine action on atrial myocardium [79]. In support of this, rat models have shown EAT release of pro-fibrotic cytokine activin A, a TGFb subtype, to neighboring atrial tissue [80]. EAT may also infiltrate atrial subepicardium introducing areas of low voltage, conduction slowing, greater fractionation, and worsening atrial electrical heterogeneity [81].

Despite the common inflammatory precursors, atrial fibrosis and resultant LA myopathy may occur independently of LV myopathy [82]. LA myopathy is associated with distinct alterations in plasma proteins associated with cardiomyocyte stretch, ECM remodeling, and immune dysregulation [83]. Beyond electrophysiological alterations, LA fibrosis results in abnormal LA mechanics, which progressively worsen with increasing AF burden in HFpEF [84]. AF-HFpEF patients also demonstrate inappropriate activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems that result in heterogeneous shortening of refractory periods within atrial tissue, creating a prime arrhythmogenic substrate [85]. RAAS activation further increases angiotensin II production which in turn stimulates fibroblasts and further fibrosis [86,87]. Additionally, AF-HFpEF patients experience relatively high LA pressures as a result of LV diastolic dysfunction, elevated filling pressures, intrinsic LA stiffness, or mitral regurgitation. The heterogenous degrees of LA wall stress introduced by these factors may further create niduses for fibrosis and AF [88].

4. Management of patients with HFpEF and AF

Medical management of HFpEF with concomitant AF is still a challenge due to the heterogeneity of the HFpEF population. Currently, the 2022 heart failure guidelines has a class 2b recommendation to treat AF in patients with HFpEF to improve symptoms [89]. Treatment targets for AF in HFpEF can be divided into three categories: lifestyle modifications, pharmacologic interventions, and catheter ablations.

4.1. Stroke prevention in HFpEF-AF

There is increased stroke risk in patients with HF and AF (HF-AF) compared to those with AF and no heart failure [90]. Stroke risk in HFrEF and HFpEF are similar, and the presence of HF, regardless of ejection fraction, remains a risk factor [91]. Stroke prevention is also challenging in patients with HFpEF-AF due to the heterogeneity and diverse phenotypes of the population [92]. As the 2023 American College of Cardiology Expert Consensus Decision Pathway on Management of HFpEF stated, most patients with HFpEF would benefit from anticoagulation by CHA_2DS_2-VASc (congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category) score since the prevalence of older age and hypertension [93]. Current guidelines recommend chronic anticoagulation for patients diagnosed with AF and thromboembolic risk factors. In HF patients, embolic risk at baseline is higher, which limits the discriminatory value of when to initiate anticoagulation with the CHA_2DS_2-VASc score.

Nonvitamin K direct oral anticoagulants (DOAC) are the first-line treatment for stroke prevention in AF. Rivaroxaban and apixaban (factor Xa inhibitors) are efficacious and safe compared to warfarin along with dabigatran (direct thrombin inhibitor) [94]. Currently, no trial has randomized HFpEF-AF only patients to anticoagulation. Meta-analysis of randomized controlled trials (RCTs) studied patients with HF and AF, concluding high-dose and single-dose DOACs had better safety profiles and efficacy compared to warfarin for reducing stroke and systemic embolism rates and lower rates of major bleeding, specifically, intracranial bleeding [95]. There was no difference in lower doses between those with and without HF [95].

Vitamin K antagonists (VKA) were the gold standard until the arrival of DOACs. VKAs are superior to the single agent (aspirin) and dual antiplatelet therapy for preventing vascular events [96]. For HF-AF patients with mechanical valves, moderate mitral valve stenosis, and antiphospholipid syndrome, VKAs remain first line [97]. Specific challenges to using VKAs in patients with HF are commonly attributable to polypharmacy and episodes of decompensated HF leading to hepatic congestion and the effect on the metabolism of VKAs. Additionally, from the patient's perspective, using VKAs can be burdensome with a narrow therapeutic window, frequent monitoring, and dietary impacts [98].

The left atrial appendage is the most common site of thrombus formation and left atrial appendage occlusion (LAAO) device is another method for stroke prevention in HFpEF and AF [99,100]. A review of four-year data from the National Inpatient Sample from 2015 to 2019 evaluated post-procedure and in-hospital outcomes and found no difference between patients with HFrEF-AF and HFpEF-AF compared to patients without HF [100]. However, HF was associated with more extended hospital stays and increased cost [100]. In Germany, a study found that patients with congestive heart failure (CHF) had no increased major adverse cardiovascular events (MACE) compared to non-HF after LAAO, similar across all types of HF (preserved, mid-range, and reduced EF) [101]. LAAO devices were non-inferior in the efficacy of stroke prevention but did show increased implantation failure for patients with HF [102]. Further research is necessary to determine whether there are differences in long-term outcomes in patient with HFpEF and LAAO due to their underlying progressive atrial myopathy and fibrosis.

4.2. HFpEF-AF medical therapy

Sodium-glucose linked transporter-2 inhibitors (SGLT2i) are associated with reduction and possibly protective effects against the development of AF [103]. In PRESERVED-HF and EMPEROR-Preserved, SGLT2i efficacy in HFpEF decreased HF hospitalizations and improved quality of life with no AF interaction [104–106]. In DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events), a population with risk factors for HFpEF, dapagliflozin reduced the first-time overall incidence of AF/atrial flutter (AFL) episodes independent of whether or not the patient had diabetes [107]. There are several suggested ways that SGLT2i play a role in reducing AF/AFL burden. They have been shown to lower blood pressure, oxidative stress, inflammation, and sympathetic overdrive, all contributing to AF burden [107]. Through natriuresis and diuresis, SGLT2i may reduce LA dilatation. Epicardial fat has also been linked with worse AF burden, and SGLT2i are associated with decreased epicardial fat volume [108]. Increased glycemic variation is also proposed to worsen AF in animal studies and the low risk of hypoglycemia with SGLT2i may contribute to their favorable association with reduced AF [109]. Based on the results of the EMPEROR-Preserved trial, the 2022 ACC/AHA/HFSA guidelines for the management of HF give SGLT2i a class 2a recommendation as potentially beneficial for reducing HF hospitalizations and CV mortality [89].

Aside from the treatment of hypertension, diuretics remain the only class I recommended therapy for HFpEF with congestive symptoms in HF guidelines. AF has been associated with elevated filling pressures during right catheterization [84]. However, when HF type was further stratified, AF did not significantly impact response to diuretic therapy in hospitalized HFpEF patients, and treating AF remains a 2a recommendation for treatment in the current HF guidelines [89,110]. Few studies have sufficient HFpEF patients with AF. IMPRESS-AF trial studied HFpEF-AF randomized to spironolactone or placebo and showed no benefit with quality of life or exercise capacity [111]. The RATE-HF trial showed that in patients with predominant HFpEF, BB had no benefits in permanent AF compared to digoxin for rate control [112]. Excessive rate control in HFpEF may exacerbate chronotropic incompetence and worsen activity tolerance [113]. Withdrawal of BB showed improved symptoms and functional class in stable HFpEF with 38.5 % having a

prior history of AF. The optimal rate control agent for AF in HFpEF remains unclear [114].

4.3. HFpEF-AF lifestyle intervention and risk factor modification

HFpEF and AF are diseases of aging and a manifestation of patient comorbidities [7,91,115]. HFpEF-AF patients' morbidity and mortality are commonly from noncardiac causes, highlighting the necessity of targeting non-cardiovascular comorbidities that can impact HFpEF-AF patients [116]. The treatment of pro-inflammatory conditions such as HTN, iron deficiency, obesity, and sleep disordered-breathing are helpful in slowing the progression of HFpEF-AF [65].

Lifestyle modifications should be recommended in patients with HFpEF-AF for optimal treatment. RACE 3 was a randomized controlled AF trial that showed targeted therapy of underlying conditions (hypertension, hyperlipidemia, obesity, heart failure) improves sinus rhythm maintenance in patients with persistent AF [117]. Hypertension is also a known risk factor for development of AF and HFpEF [118]. In fact, the prevalence of hypertension in patients with HFpEF was 67 % in the European Society of Cardiology HF registry [119].

In the Women's Health Initiative cohort of 93,676 females, for every 1 kg/m2 increase in BMI, AF relative risk increased by 12 % [120]. The LEGACY trial showed a 6-fold reduction of probability of AF recurrence with a 10 % reduction in weight [121]. Due to the link between obesity and HFpEF a Body Mass Index >30 is factored with 2 points in the H2FPEF score [12]. In a randomized control trial, weight loss decreased AF recurrence and the maladaptive left atrial remodeling [122]. Another randomized control trial showed that weight loss led to improvement in exercise capacity and quality of life [123]. Although, substantial weight loss can reduce epicardial fat, which is thought to release proinflammatory and profibrotic mediators leading to myocardial injury, myocardial remodeling, and ultimately worse hemodynamics and exercise tolerance [124].

Meta-analysis of six RCTs, showed that exercise training in HFpEF is associated with improved cardiorespiratory fitness and quality of life [125]. In a trial of obese patients with HFpEF, a low-calorie diet with an exercise regimen showed improvement in peak VO2 [123]. Physical activity is closely related to both AF and HFpEF. In the TOPCAT trial, every ten-fold increase of physical activity was associated with a 42.8 % risk reduction of AF occurrence, suggesting that a higher physical activity level is associated with a lower risk of AF in HFpEF patients [126].

There is a high incidence of sleep apnea in patients with AF and HFpEF. In a prospective study of 188 consecutive AF patients referred for catheter ablation, home sleep apnea testing was positive in 82 % of patients, moderate or severe in more than half [127]. Similarly, the prevalence of sleep disordered breathing was found to be around 70 % in patients with HFpEF [128].

Multiple large population-based studies have shown associations between DM and AF. The Framingham Heart Study showed that in 4731 individuals, DM was significantly associated with development of AF after adjustment for confounders (odds ratio, 1.4 for men, 1.6 for women) [129]. Among patients with HFpEF older than 50 years, 50 % of patients in the PARAGON-HF trial and conferred an increased risk of cardiovascular death and HF hospitalizations [130].

It is established that iron deficiency anemia (IDA) is a significant contributor to worse outcomes in HFrEF. Additionally, there is evidence that IDA is an independent risk factor for heart failure, major bleeding, and death in patients with AF [131]. One study found a higher recurrence of AF after catheter ablation in patients with IDA [132]. DAMOCLES was a prospective cohort study looking at IDA in HFpEF and found IDA associated with decreased quality of life and worse exercise capacity [133]. IDA effect on HFpEF with concomitant AF needs further investigation.

4.4. HFpEF-AF Rhythm control strategies

Rhythm control for AF in patients with HFpEF can be achieved by anti-arrhythmic drugs or catheter-based ablation strategies. Anti-arrhythmic medications used for rhythm control in atrial fibrillation are Vaughn Williams class I or class III. Most of these medications can be used in patients with HFpEF, however, class I anti-arrhythmic drugs should be avoided in patients that do not have structurally normal hearts but with preserved ejection fraction such as those with amyloid, sarcoidosis, hypertrophic cardiomyopathy, coronary artery disease with infarct.

Catheter ablation for AF has been shown to decrease HF hospitalization, mortality and decrease AF burden in HFrEF patients [134]. In contrast, there are no RCTs comparing rhythm to rate control in HFpEF-AF. However, some data suggest favorable outcomes of rhythm control over rate control. An observational study showed patients with rhythm control had lower rates of all-cause mortality, all-cause readmissions, HF readmissions, and ischemic stroke readmissions compared to those receiving rate control [135]. In addition, a meta-analysis of 5 observational studies showed that rhythm control (ablation and/or antiarrhythmic medications) was associated with lower all-cause mortality (odds ratio 0.735, 95 % confidence interval 0.665–0.813; $P < 0.001$) compared to rate control [136]. Regarding specific options for rhythm control, RCTs showed no benefit in using antiarrhythmics versus rate-controlling strategies in patients with HF. However, these studies did not specifically look at HFpEF patients.

Similarly, although there are no RCTs comparing catheter ablation to medical management of HFpEF-AF, a post hoc subgroup analysis of the CABANA trial showed a significant reduction in all-cause mortality in the ablation group [137]. A single center study on HFpEF-AF compared catheter ablation with medical therapy also showed improvement in HF symptoms, diastolic function and heart failure hospitalization with catheter ablation [138]. Currently available data favors catheter ablation in reducing HFpEF severity, hospital admission rates, and all-cause mortality, however, dedicated prospective RCTs are warranted to support evidenced-based guidelines, specifically for HFpEF with AF. Table 1 is a summary of clinical trials that are currently investigating patients with HF including those with HFpEF and how to manage AF. These studies will be crucial in how we effectively manage these complex patients.

5. Conclusion

In conclusion, HFpEF and AF are becoming more prevalent as the population ages with increased longevity and more comorbidities. This narrative review of the current literature provided an update on the impact, pathophysiology, and management of patients with concomitant HFpEF and AF. Studies from Korea and Sweden have found that the prevalence of AF significantly increased with increasing EF. HFpEF and AF share many comorbidities, and it is especially important to consider cardiac amyloidosis as a cause of HFpEF since it can be found in 13–14 % of patients with HFpEF. A registry found that HFpEF is associated with a higher risk of stroke or systemic embolism than in patients with HFmrEF and HFrEF. In addition, studies have shown that AF increases mortality and hospital admission in patients with HFpEF but not with HFrEF. It has also been found that SGLT2i are associated with reduction and possibly protective effects against the development of AF. These important findings of this review are listed in Table 2. Further research is needed to understand the complex interplay between AF and HFpEF to help determine the best management strategy.

Currently, there is limited data for this growing population. Adequately powered prospective clinical trials would be useful in determining which strategy has the best efficacy and safety profile. There are some promising trials (Table 1) evaluating interventions that target left atrial substrate and risk factors for AF and HFpEF with the goal that perhaps the best intervention may be prevention. Currently,

Table 1
Clinical trials investigating rate and/pr rhythm management of patients with AF that includes HFpEF patients.

Study	Inclusion Criteria	# of patients	Mean Age	Women	Management Comparison	Endpoint	Treatment (PVI/meds/ both)	Duration of follow-up (years)	Outcome
RACE-AF	NHYA II/III	261	69	35 %	Rate versus rhythm	Mortality and hospitalization	Meds	2.3	Non-inferiority
CABANA-HF (post hoc)	NHYA II-IV	778	68	44 %	PVI versus medications	Mortality, Stroke, Bleeding, Cardiac Arrest	Both (PVI 49 %)	4.0	PVI superior
RACE 3	HFpEF = NYHA I-III and LVEF >45 % (HFrEF = NYHA I-III and LVEF <45 %)	245	64	21 %	Rhythm control for AF and treatment for HF versus treatment of comorbidities	Maintenance of sinus rhythm for a week on ambulatory cardiac monitoring	Meds	1.0	HF and AF treatment is superior
EAST-AFNET4	Stable HF (56 % with HFpEF)	2789	70	46 %	Early rhythm control versus usual care	CV Death, stroke, HF or ACS hospital stay	Both (PVI 13 %)	5.1	Early rhythm control is superior

Abbreviations: ACS – acute coronary syndrome, AF- atrial fibrillation, CABANA-HF - Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation in heart failure patients, CVD – cardiovascular, EAST-AFNET4 - Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, HF- heart failure, HFpEF – heart failure with preserved ejection fraction, LVEF – left ventricular ejection fraction, NYHA – New York Heart Association, PVI – pulmonary vein isolation, RACE-AF – RAte Control versus Electrical cardioversion for persistent atrial fibrillation.

Table 2
Summary of important findings.

Epidemiology
- The prevalence of AF is significantly increased with increasing EF in studies from Korea and Sweden.

Associated co-morbidities and risk factors
- HFpEF and AF share the following comorbidities and risk factors: hypertension, older age, increased body mass index, obstructive sleep apnea, and diabetes.
- 13–14 % of patients with HFpEF may be due to cardiac amyloidosis

Stroke risk
- A registry showed that the risk of stroke or systemic embolism was higher in the HFpEF group than in the HFmrEF and HFrEF groups.

Mortality risk
- Studies have shown that AF increases mortality in patients with HFpEF but not with HFrEF.
- Patients with HFpEF and AF have been shown to have increased mortality and hospital admissions.

Pathophysiology and treatment
- In patients with HFpEF, increased inflammatory markers are associated with recurrent AF after ablation.
- Patients with AF and HFpEF demonstrate inappropriate activation of the renin-angiotensin-aldosterone system and sympathetic nervous systems resulting in heterogeneous shortening of atrial refractory periods, creating a prime arrhythmogenic substrate.
- Sodium-glucose linked transporter-2 inhibitors are associated with reduction and possibly protective effects against the development of AF.

Abbreviations: AF – atrial fibrillation, HFpEF – heart failure with preserved ejection fraction, HFmrEF- heart failure with moderately reduced ejection fraction.

there are no guidelines for lifesaving devices such as implantable cardioverter-defibrillator devices for patients with HFpEF. As more data shows the higher risk of mortality in patients with HFpEF-AF compared to HFrEF-AF, studies will need to evaluate whether treatment of AF alone can decrease the risk of mortality or if these patients can benefit from implantable cardioverter-defibrillator devices.

5.1. Practical implications of this review

This review offers a summary of the current literature on the intersection of two important diseases that afflict many patients, AF and HFpEF. As the population ages, these two diseases are becoming more common. Since AF increases mortality and hospital admission in patients with HFpEF but not with HFrEF, careful attention to ensure that patients with HFpEF are treated with guideline-directed medical therapy are needed. American guidelines for the treatment of heart failure have only been recently published and may not be as widely implemented as the treatment for HFrEF.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Volgman – Consulting - Sanofi, Pfizer, Merck, Janssen, Clinical Trials -Janssen, Novartis and NIH, Stock - Apple Inc.

Larsen - Speaker's bureau - Medtronic, Consulting - Abbott, and Biosense Webster

Sharma: Consulting - Medtronic, Abbott, Biotronik, Honorarium – Medtronic

References

[1] B. Bozkurt, R.E. Hershberger, J. Butler, K.L. Grady, P.A. Heidenreich, M.L. Isler, J. K. Kirklin, W.S. Weintraub, 2021 ACC/AHA key data elements and definitions for heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop clinical data standards for heart failure), Circ. Cardiovasc. Qual. Outcomes 14 (2021), e000102, https://doi.org/10.1161/HCQ.0000000000000102.

[2] P. Goyal, Z.I. Almarzooq, J. Cheung, H. Kamel, U. Krishnan, D.N. Feldman, E. M. Horn, L.K. Kim, Atrial fibrillation and heart failure with preserved ejection fraction: insights on a unique clinical phenotype from a nationally-representative United States cohort, Int. J. Cardiol. 266 (2018) 112–118, https://doi.org/10.1016/j.ijcard.2018.02.007.

[3] M. Packer, C.S.P. Lam, L.H. Lund, M.M. Redfield, Interdependence of atrial fibrillation and heart failure with a preserved ejection fraction reflects a common underlying atrial and ventricular myopathy, Circulation. 141 (2020) 4–6, https://doi.org/10.1161/CIRCULATIONAHA.119.042996.

[4] N. Prasitlumkum, R. Chokesuwattanaskul, W. Cheungpasitporn, J. Kewcharoen, C. Thongprayoon, T. Bathini, S. Vallabhajosyula, K. Jongnarangsin, Rhythm control in patients with heart failure with preserved ejection fraction: a meta-analysis, J. Clin. Med. (2021) 10, https://doi.org/10.3390/jcm10184038.

[5] Collaborators GDaIIaP, 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. 392 (2018) 1789–1858, https://doi.org/10.1016/S0140-6736(18)32279-7.

[6] S.M. Dunlay, V.L. Roger, M.M. Redfield, Epidemiology of heart failure with preserved ejection fraction, Nat. Rev. Cardiol. 14 (2017) 591–602, https://doi.org/10.1038/nrcardio.2017.65.

[7] S. Colilla, A. Crow, W. Petkun, D.E. Singer, T. Simon, X. Liu, Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population, Am. J. Cardiol. 112 (2013) 1142–1147, https://doi.org/10.1016/j.amjcard.2013.05.063.

[8] R. Santhanakrishnan, N. Wang, M.G. Larson, J.W. Magnani, D.D. McManus, S. A. Lubitz, P.T. Ellinor, S. Cheng, R.S. Vasan, D.S. Lee, et al., Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction, Circulation. 133 (2016) 484–492, https://doi.org/10.1161/CIRCULATIONAHA.115.018614.

[9] M.K. Son, J.J. Park, N.K. Lim, W.H. Kim, D.J. Choi, Impact of atrial fibrillation in patients with heart failure and reduced, mid-range or preserved ejection fraction, Heart. 106 (2020) 1160–1168, https://doi.org/10.1136/heartjnl-2019-316219.

[10] U. Sartipy, U. Dahlstrom, M. Fu, L.H. Lund, Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction, JACC Heart Fail. 5 (2017) 565–574, https://doi.org/10.1016/j.jchf.2017.05.001.

[11] Y.N.V. Reddy, R.E. Carter, M. Obokata, M.M. Redfield, B.A. Borlaug, A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction, Circulation. 138 (2018) 861–870, https://doi.org/10.1161/circulationaha.118.034646.
[12] F.P. Brouwers, R.A. de Boer, P. van der Harst, A.A. Voors, R.T. Gansevoort, S. J. Bakker, H.L. Hillege, D.J. van Veldhuisen, W.H. van Gilst, Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND, Eur. Heart J. 34 (2013) 1424–1431, https://doi.org/10.1093/eurheartj/eht066.
[13] P. Khazanie, L. Liang, L.G. Qualls, L.H. Curtis, G.C. Fonarow, B.G. Hammill, S. C. Hammill, P.A. Heidenreich, F.A. Masoudi, A.F. Hernandez, et al., Outcomes of medicare beneficiaries with heart failure and atrial fibrillation, JACC Heart Fail. 2 (2014) 41–48, https://doi.org/10.1016/j.jchf.2013.11.002.
[14] G. Liu, M. Long, X. Hu, C.H. Hu, Z.M. Du, Meta-analysis of atrial fibrillation and outcomes in patients with heart failure and preserved ejection fraction, Heart Lung Circ. 30 (2021) 698–706, https://doi.org/10.1016/j.hlc.2020.10.010.
[15] J.S. Uhm, J. Kim, H.T. Yu, T.H. Kim, S.R. Lee, M.J. Cha, E.K. Choi, J.M. Lee, J. B. Kim, J. Park, et al., Stroke and systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type, ESC Heart Fail. 8 (2021) 1582–1589, https://doi.org/10.1002/ehf2.13264.
[16] M. Grogan, H.C. Smith, B.J. Gersh, D.L. Wood, Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy, Am. J. Cardiol. 69 (1992) 1570–1573, https://doi.org/10.1016/0002-9149(92)90705-4.
[17] R. Zakeri, B.A. Borlaug, S.E. McNulty, S.F. Mohammed, G.D. Lewis, M. J. Semigran, A. Deswal, M. LeWinter, A.F. Hernandez, E. Braunwald, et al., Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study, Circ. Heart Fail. 7 (2014) 123–130, https://doi.org/10.1161/CIRCHEARTFAILURE.113.000568.
[18] L.F. Hsu, P. Jaïs, P. Sanders, S. Garrigue, M. Hocini, F. Sacher, Y. Takahashi, M. Rotter, J.L. Pasquié, C. Scavée, et al., Catheter ablation for atrial fibrillation in congestive heart failure, N. Engl. J. Med. 351 (2004) 2373–2383, https://doi.org/10.1056/NEJMoa041018.
[19] P.J. Gentlesk, W.H. Sauer, E.P. Gerstenfeld, D. Lin, S. Dixit, E. Zado, D. Callans, F. E. Marchlinski, Reversal of left ventricular dysfunction following ablation of atrial fibrillation, J. Cardiovasc. Electrophysiol. 18 (2007) 9–14, https://doi.org/10.1111/j.1540-8167.2006.00653.x.
[20] M. Cikes, I. Planinc, B. Claggett, J. Cunningham, D. Milicic, N. Sweitzer, M. Senni, M. Gori, G. Linssen, S.J. Shah, et al., Atrial fibrillation in heart failure with preserved ejection fraction: the PARAGON-HF trial, JACC Heart Fail. 10 (2022) 336–346, https://doi.org/10.1016/j.jchf.2022.01.018.
[21] J.E. Wilcox, J.C. Fang, K.B. Margulies, D.L. Mann, Heart failure with recovered left ventricular ejection fraction: JACC scientific expert panel, J. Am. Coll. Cardiol. 76 (2020) 719–734, https://doi.org/10.1016/j.jacc.2020.05.075.
[22] Y. Sun, X. Chen, Y. Zhang, Y. Yu, X. Zhang, J. Si, Z. Ding, Y. Xia, G. Tse, Y. Liu, Reverse atrial remodeling in heart failure with recovered ejection fraction, J. Am. Heart Assoc. 12 (2023), e026891, https://doi.org/10.1161/JAHA.122.026891.
[23] K. Akamatsu, Y. Abe, Y. Matsumura, K. Shimeno, T. Naruko, Y. Takahashi, T. Shibata, M. Yoshiyama, Etiology of atrial functional mitral regurgitation: insights from transthoracic echocardiography in 159 consecutive patients with atrial fibrillation and preserved left ventricular ejection fraction, Cardiology. 145 (2020) 511–521, https://doi.org/10.1159/000508279.
[24] S. Arora, Z.D. Brown, K. Sivaraj, M.J. Hendrickson, A.J. Mazzella, P.P. Chang, M. Vaduganathan, A. Qamar, A.K. Gehi, A. Pandey, et al., The relationship between atrial fibrillation, mitral regurgitation, and heart failure subtype: the ARIC study, J. Card. Fail. 28 (2022) 883–892, https://doi.org/10.1016/j.cardfail.2021.10.015.
[25] T. Temma, T. Nagai, M. Watanabe, R. Kamada, Y. Takahashi, H. Hagiwara, T. Koya, M. Nakao, K. Omote, K. Kamiya, et al., Differential prognostic impact of atrial fibrillation in hospitalized heart failure patients with preserved ejection fraction according to coronary artery disease status - report from the Japanese Nationwide Multicenter Registry, Circ. J. 84 (2020) 397–403, https://doi.org/10.1253/circj.CJ-19-0963.
[26] D. Krishnappa, R. Dykoski, I. Can, M. Mbai, I.S. Anand, V. Florea, Y. S. Chandrashekar, J.M. Li, V.N. Tholakanahalli, Atrial fibrillation in the elderly: the role of sub-clinical isolated cardiac amyloidosis, Sci. Rep. 9 (2019) 16584, https://doi.org/10.1038/s41598-019-53119-z.
[27] V.S. Hahn, L.R. Yanek, J. Vaishnav, W. Ying, D. Vaidya, Y.Z.J. Lee, S.J. Riley, V. Subramanya, E.E. Brown, C.D. Hopkins, et al., Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis, JACC Heart Fail. 8 (2020) 712–724, https://doi.org/10.1016/j.jchf.2020.04.007.
[28] M.I.F.J. Oerlemans, K.H.G. Rutten, M.C. Minnema, R.A.P. Raymakers, F. W. Asselbergs, N. de Jonge, Cardiac amyloidosis: the need for early diagnosis, Neth. Hear. J. 27 (2019) 525–536, https://doi.org/10.1007/s12471-019-1299-1.
[29] M. Haïssaguerre, P. Jaïs, D.C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Métayer, J. Clémenty, Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins, N. Engl. J. Med. 339 (1998) 659–666, https://doi.org/10.1056/nejm199809033391003.
[30] T. Tokushima, C.L. Reid, J.M. Gardin, Left ventricular diastolic function in the elderly, Am. J. Geriatr. Cardiol. 10 (2001) 20–29, https://doi.org/10.1111/j.1076-7460.2001.90851.x.
[31] D.S. Lee, P. Gona, R.S. Vasan, M.G. Larson, E.J. Benjamin, T.J. Wang, J.V. Tu, D. Levy, Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung, and blood institute, Circulation. 119 (2009) 3070–3077, https://doi.org/10.1161/circulationaha.108.815944.
[32] U.B. Tedrow, D. Conen, P.M. Ridker, N.R. Cook, B.A. Koplan, J.E. Manson, J. E. Buring, C.M. Albert, The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study), J. Am. Coll. Cardiol. 55 (2010) 2319–2327, https://doi.org/10.1016/j.jacc.2010.02.029.
[33] R. Zakeri, Is there a role for catheter ablation of atrial fibrillation in the treatment of patients with heart failure and preserved ejection fraction? Circ. Heart Fail. 15 (2022), e009835 https://doi.org/10.1161/CIRCHEARTFAILURE.122.009835.
[34] P.S. Douglas, The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk, in: J Am Coll Cardiol. United States, 2003, pp. 1206–1207.
[35] T.S. Tsang, M.E. Barnes, B.J. Gersh, K.R. Bailey, J.B. Seward, Risks for atrial fibrillation and congestive heart failure in patients >/=65 years of age with abnormal left ventricular diastolic relaxation, Am. J. Cardiol. 93 (2004) 54–58, https://doi.org/10.1016/j.amjcard.2003.09.012.
[36] K. Ihara, T. Sasano, Role of inflammation in the pathogenesis of atrial fibrillation, Front. Physiol. 13 (2022), 862164, https://doi.org/10.3389/fphys.2022.862164.
[37] W.B. Kannel, P.A. Wolf, E.J. Benjamin, D. Levy, Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates, Am. J. Cardiol. 82 (1998) 2n–9n, https://doi.org/10.1016/s0002-9149(98)00583-9.
[38] T.J. Wang, H. Parise, D. Levy, R.B. D'Agostino Sr., P.A. Wolf, R.S. Vasan, E. J. Benjamin, Obesity and the risk of new-onset atrial fibrillation, Jama. 292 (2004) 2471–2477, https://doi.org/10.1001/jama.292.20.2471.
[39] A. Kalogeropoulos, V. Georgiopoulou, B.M. Psaty, N. Rodondi, A.L. Smith, D. G. Harrison, Y. Liu, U. Hoffmann, D.C. Bauer, A.B. Newman, et al., Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study, J. Am. Coll. Cardiol. 55 (2010) 2129–2137, https://doi.org/10.1016/j.jacc.2009.12.045.
[40] P.E. Lazzerini, P.L. Capecchi, F. Laghi-Pasini, Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis, Eur. Heart J. 38 (2017) 1717–1727, https://doi.org/10.1093/eurheartj/ehw208.
[41] P. Ungprasert, N. Srivali, W. Kittanamongkolchai, Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis, Int. J. Rheum. Dis. 20 (2017) 434–441, https://doi.org/10.1111/1756-185x.12820.
[42] A.K. Bacani, C.S. Crowson, V.L. Roger, S.E. Gabriel, E.L. Matteson, Increased incidence of atrial fibrillation in patients with rheumatoid arthritis, Biomed. Res. Int. 2015 (2015), 809514, https://doi.org/10.1155/2015/809514.
[43] O. Ahlehoff, G.H. Gislason, C.H. Jørgensen, J. Lindhardsen, M. Charlot, J. B. Olesen, S.Z. Abildstrøm, L. Skov, C. Torp-Pedersen, P.R. Hansen, Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study, Eur. Heart J. 33 (2012) 2054–2064, https://doi.org/10.1093/eurheartj/ehr285.
[44] Y.J. Choi, E.K. Choi, K.D. Han, J. Park, I. Moon, E. Lee, W.S. Choe, S.R. Lee, M. J. Cha, W.H. Lim, et al., Increased risk of atrial fibrillation in patients with inflammatory bowel disease: a nationwide population-based study, World J. Gastroenterol. 25 (2019) 2788–2798, https://doi.org/10.3748/wjg.v25.i22.2788.
[45] S. Prasada, A. Rivera, A. Nishtala, A.E. Pawlowski, A. Sinha, J.D. Bundy, S. A. Chadha, F.S. Ahmad, S.S. Khan, C. Achenbach, et al., Differential associations of chronic inflammatory diseases with incident heart failure, JACC Heart Fail. 8 (2020) 489–498, https://doi.org/10.1016/j.jchf.2019.11.013.
[46] R.B. Patel, L.A. Colangelo, S.J. Bielinski, N.B. Larson, J. Ding, N.B. Allen, E. D. Michos, S.J. Shah, D.M. Lloyd-Jones, Circulating vascular cell adhesion Molecule-1 and incident heart failure: the Multi-Ethnic Study of Atherosclerosis (MESA), J. Am. Heart Assoc. 9 (2020), e019390, https://doi.org/10.1161/jaha.120.019390.
[47] R.B. Patel, L.A. Colangelo, A.P. Reiner, M.D. Gross, D.R. Jacobs Jr., L.J. Launer, J. A.C. Lima, D.M. Lloyd-Jones, S.J. Shah, Cellular adhesion molecules in young adulthood and cardiac function in later life, J. Am. Coll. Cardiol. 75 (2020) 2156–2165, https://doi.org/10.1016/j.jacc.2020.02.060.
[48] N. Wu, B. Xu, Y. Xiang, L. Wu, Y. Zhang, X. Ma, S. Tong, M. Shu, Z. Song, Y. Li, et al., Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis, Int. J. Cardiol. 169 (2013) 62–72, https://doi.org/10.1016/j.ijcard.2013.08.078.
[49] R.J. Aviles, D.O. Martin, C. Apperson-Hansen, P.L. Houghtaling, P. Rautaharju, R. A. Kronmal, R.P. Tracy, D.R. Van Wagoner, B.M. Psaty, M.S. Lauer, et al., Inflammation as a risk factor for atrial fibrillation, Circulation 108 (2003) 3006–3010, https://doi.org/10.1161/01.cir.0000103131.70301.4f.
[50] M. Rienstra, J.X. Sun, J.W. Magnani, M.F. Sinner, S.A. Lubitz, L.M. Sullivan, P. T. Ellinor, E.J. Benjamin, White blood cell count and risk of incident atrial fibrillation (from the Framingham Heart Study), Am. J. Cardiol. 109 (2012) 533–537, https://doi.org/10.1016/j.amjcard.2011.09.049.
[51] M.C. Chen, J.P. Chang, W.H. Liu, C.H. Yang, Y.L. Chen, T.H. Tsai, Y.H. Wang, K. L. Pan, Increased inflammatory cell infiltration in the atrial myocardium of patients with atrial fibrillation, Am. J. Cardiol. 102 (2008) 861–865, https://doi.org/10.1016/j.amjcard.2008.05.038.
[52] N. Smorodinova, M. Bláha, V. Melenovský, K. Rozsívalová, J. Přidal, M. Ďurišová, J. Pirk, J. Kautzner, T. Kučera, Analysis of immune cell populations in atrial myocardium of patients with atrial fibrillation or sinus rhythm, PLoS One 12 (2017), e0172691, https://doi.org/10.1371/journal.pone.0172691.
[53] T. Yamashita, A. Sekiguchi, Y.K. Iwasaki, T. Date, K. Sagara, H. Tanabe, H. Suma, H. Sawada, T. Aizawa, Recruitment of immune cells across atrial endocardium in

human atrial fibrillation, Circ. J. 74 (2010) 262–270, https://doi.org/10.1253/circj.cj-09-0644.
[54] Y.C. Qu, Y.M. Du, S.L. Wu, Q.X. Chen, H.L. Wu, S.F. Zhou, Activated nuclear factor-kappaB and increased tumor necrosis factor-alpha in atrial tissue of atrial fibrillation, Scand. Cardiovasc. J. 43 (2009) 292–297, https://doi.org/10.1080/14017430802651803.
[55] P.E. Lazzerini, F. Laghi-Pasini, M. Acampa, U. Srivastava, I. Bertolozzi, B. Giabbani, F. Finizola, F. Vanni, A. Dokollari, M. Natale, et al., Systemic inflammation rapidly induces reversible atrial electrical remodeling: the role of Interleukin-6-mediated changes in Connexin expression, J. Am. Heart Assoc. 8 (2019), e011006, https://doi.org/10.1161/jaha.118.011006.
[56] S. Villegas, F.J. Villarreal, W.H. Dillmann, Leukemia Inhibitory Factor and Interleukin-6 downregulate sarcoplasmic reticulum Ca2+ ATPase (SERCA2) in cardiac myocytes, Basic Res. Cardiol. 95 (2000) 47–54, https://doi.org/10.1007/s003950050007.
[57] T. Tanaka, T. Kanda, T. Takahashi, S. Saegusa, J. Moriya, M. Kurabayashi, Interleukin-6-induced reciprocal expression of SERCA and natriuretic peptides mRNA in cultured rat ventricular myocytes, J. Int. Med. Res. 32 (2004) 57–61, https://doi.org/10.1177/147323000403200109.
[58] Y. Hagiwara, S. Miyoshi, K. Fukuda, N. Nishiyama, Y. Ikegami, K. Tanimoto, M. Murata, E. Takahashi, K. Shimoda, T. Hirano, et al., SHP2-mediated signaling cascade through gp130 is essential for LIF-dependent I CaL, [Ca2+]i transient, and APD increase in cardiomyocytes, J. Mol. Cell. Cardiol. 43 (2007) 710–716, https://doi.org/10.1016/j.yjmcc.2007.09.004.
[59] S. Saba, A.M. Janczewski, L.C. Baker, V. Shusterman, E.C. Gursoy, A.M. Feldman, G. Salama, C.F. McTiernan, B. London, Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-{alpha}, Am. J. Physiol. Heart Circ. Physiol. 289 (2005) H1456–H1467, https://doi.org/10.1152/ajpheart.00733.2004.
[60] Y.H. Kao, Y.C. Chen, C.C. Cheng, T.I. Lee, Y.J. Chen, S.A. Chen, Tumor necrosis factor-alpha decreases sarcoplasmic reticulum Ca2+-ATPase expressions via the promoter methylation in cardiomyocytes, Crit. Care Med. 38 (2010) 217–222, https://doi.org/10.1097/CCM.0b013e3181b4a854.
[61] S. Zuo, L.L. Li, Y.F. Ruan, L. Jiang, X. Li, S.N. Li, S.N. Wen, R. Bai, N. Liu, X. Du, et al., Acute administration of tumour necrosis factor-α induces spontaneous calcium release via the reactive oxygen species pathway in atrial myocytes, Europace 20 (2018) 1367–1374, https://doi.org/10.1093/europace/eux271.
[62] S.H. Lee, Y.C. Chen, Y.J. Chen, S.L. Chang, C.T. Tai, W. Wongcharoen, H.I. Yeh, C. I. Lin, S.A. Chen, Tumor necrosis factor-alpha alters calcium handling and increases arrhythmogenesis of pulmonary vein cardiomyocytes, Life Sci. 80 (2007) 1806–1815, https://doi.org/10.1016/j.lfs.2007.02.029.
[63] D. Westermann, D. Lindner, M. Kasner, C. Zietsch, K. Savvatis, F. Escher, J. von Schlippenbach, C. Skurk, P. Steendijk, A. Riad, et al., Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction, Circ. Heart Fail. 4 (2011) 44–52, https://doi.org/10.1161/circheartfailure.109.931451.
[64] L. van Heerebeek, N. Hamdani, I. Falcão-Pires, A.F. Leite-Moreira, M. P. Begieneman, J.G. Bronzwaer, J. van der Velden, G.J. Stienen, G.J. Laarman, A. Somsen, et al., Low myocardial protein kinase G activity in heart failure with preserved ejection fraction, Circulation. 126 (2012) 830–839, https://doi.org/10.1161/circulationaha.111.076075.
[65] W.J. Paulus, C. Tschöpe, A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation, J. Am. Coll. Cardiol. 62 (2013) 263–271, https://doi.org/10.1016/j.jacc.2013.02.092.
[66] L. Zuo, C.C. Chuang, B.T. Hemmelgarn, T.M. Best, Heart failure with preserved ejection fraction: defining the function of ROS and NO, J. Appl. Physiol. 2015 (119) (1985) 944–951, https://doi.org/10.1152/japplphysiol.01149.2014.
[67] S. Nattel, Molecular and cellular mechanisms of atrial fibrosis in atrial fibrillation, JACC Clin. Electrophysiol. 3 (2017) 425–435, https://doi.org/10.1016/j.jacep.2017.03.002.
[68] W. Carver, E.C. Goldsmith, Regulation of tissue fibrosis by the biomechanical environment, Biomed. Res. Int. 2013 (2013), 101979, https://doi.org/10.1155/2013/101979.
[69] C.Y. Li, J.R. Zhang, W.N. Hu, S.N. Li, Atrial fibrosis underlying atrial fibrillation (review), Int. J. Mol. Med. (2021) 47, https://doi.org/10.3892/ijmm.2020.4842.
[70] J.Y. Youn, J. Zhang, Y. Zhang, H. Chen, D. Liu, P. Ping, J.N. Weiss, H. Cai, Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase, J. Mol. Cell. Cardiol. 62 (2013) 72–79, https://doi.org/10.1016/j.yjmcc.2013.04.019.
[71] M. Miragoli, G. Gaudesius, S. Rohr, Electrotonic modulation of cardiac impulse conduction by myofibroblasts, Circ. Res. 98 (2006) 801–810, https://doi.org/10.1161/01.RES.0000214537.44195.a3.
[72] S. Zlochiver, V. Muñoz, K.L. Vikstrom, S.M. Taffet, O. Berenfeld, J. Jalife, Electrotonic myofibroblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers, Biophys. J. 95 (2008) 4469–4480, https://doi.org/10.1529/biophysj.108.136473.
[73] L. Yue, J. Xie, S. Nattel, Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation, Cardiovasc. Res. 89 (2011) 744–753, https://doi.org/10.1093/cvr/cvq329.
[74] T. Ashihara, R. Haraguchi, K. Nakazawa, T. Namba, T. Ikeda, Y. Nakazawa, T. Ozawa, M. Ito, M. Horie, N.A. Trayanova, The role of fibroblasts in complex fractionated electrograms during persistent/permanent atrial fibrillation: implications for electrogram-based catheter ablation, Circ. Res. 110 (2012) 275–284, https://doi.org/10.1161/circresaha.111.255026.
[75] B. Burstein, P. Comtois, G. Michael, K. Nishida, L. Villeneuve, Y.H. Yeh, S. Nattel, Changes in connexin expression and the atrial fibrillation substrate in congestive heart failure, Circ. Res. 105 (2009) 1213–1222, https://doi.org/10.1161/circresaha.108.183400.
[76] A. Elsanhoury, V. Nelki, S. Kelle, S. Van Linthout, C. Tschöpe, Epicardial fat expansion in diabetic and obese patients with heart failure and preserved ejection fraction-a specific HFpEF phenotype, Front. Cardiovasc. Med. 8 (2021), 720690, https://doi.org/10.3389/fcvm.2021.720690.
[77] G. van Woerden, T.M. Gorter, B.D. Westenbrink, T.P. Willems, D.J. van Veldhuisen, M. Rienstra, Epicardial fat in heart failure patients with mid-range and preserved ejection fraction, Eur. J. Heart Fail. 20 (2018) 1559–1566, https://doi.org/10.1002/ejhf.1283.
[78] Q. Fan, Y. Zhan, M. Zheng, F. Ma, L. Ji, L. Zhang, G. Liu, The predictive value of epicardial fat tissue volume in the occurrence and development of atrial fibrillation: a systematic review and meta-analysis, Cardiol. Res. Pract. 2022 (2022) 2090309, https://doi.org/10.1155/2022/2090309.
[79] G. Iacobellis, Epicardial adipose tissue in contemporary cardiology, Nat. Rev. Cardiol. 19 (2022) 593–606, https://doi.org/10.1038/s41569-022-00679-9.
[80] N. Venteclef, V. Guglielmi, E. Balse, B. Gaborit, A. Cotillard, F. Atassi, J. Amour, P. Leprince, A. Dutour, K. Clément, et al., Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines, Eur. Heart J. 36 (2015) 795–805a, https://doi.org/10.1093/eurheartj/eht099.
[81] R. Mahajan, A. Nelson, R.K. Pathak, M.E. Middeldorp, C.X. Wong, D.J. Twomey, A. Carbone, K. Teo, T. Agbaedeng, D. Linz, et al., Electroanatomical remodeling of the atria in obesity: impact of adjacent epicardial fat, JACC Clin. Electrophysiol. 4 (2018) 1529–1540, https://doi.org/10.1016/j.jacep.2018.08.014.
[82] R.B. Patel, C.S.P. Lam, S. Svedlund, A. Saraste, C. Hage, R.S. Tan, L. Beussink-Nelson, J. Tromp, C. Sanchez, J. Njoroge, et al., Disproportionate left atrial myopathy in heart failure with preserved ejection fraction among participants of the PROMIS-HFpEF study, Sci. Rep. 11 (2021) 4885, https://doi.org/10.1038/s41598-021-84133-9.
[83] G. Peigh, S.J. Shah, R.B. Patel, Left atrial myopathy in atrial fibrillation and heart failure: clinical implications, mechanisms, and therapeutic targets, Curr. Heart Fail. Rep. 18 (2021) 85–98, https://doi.org/10.1007/s11897-021-00510-5.
[84] Y.N.V. Reddy, M. Obokata, F.H. Verbrugge, G. Lin, B.A. Borlaug, Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation, J. Am. Coll. Cardiol. 76 (2020) 1051–1064, https://doi.org/10.1016/j.jacc.2020.07.009.
[85] R. Arora, Recent insights into the role of the autonomic nervous system in the creation of substrate for atrial fibrillation: implications for therapies targeting the atrial autonomic nervous system, Circ. Arrhythm. Electrophysiol. 5 (2012) 850–859, https://doi.org/10.1161/circep.112.972273.
[86] B. Burstein, S. Nattel, Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation, J. Am. Coll. Cardiol. 51 (2008) 802–809, https://doi.org/10.1016/j.jacc.2007.09.064.
[87] H.D. Xiao, S. Fuchs, D.J. Campbell, W. Lewis, S.C. Dudley Jr., V.S. Kasi, B.D. Hoit, G. Keshelava, H. Zhao, M.R. Capecchi, et al., Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death, Am. J. Pathol. 165 (2004) 1019–1032, https://doi.org/10.1016/s0002-9440(10)63363-9.
[88] R.B. Patel, M. Vaduganathan, S.J. Shah, J. Butler, Atrial fibrillation in heart failure with preserved ejection fraction: insights into mechanisms and therapeutics, Pharmacol. Ther. 176 (2017) 32–39, https://doi.org/10.1016/j.pharmthera.2016.10.019.
[89] P.A. Heidenreich, B. Bozkurt, D. Aguilar, L.A. Allen, J.J. Byun, M.M. Colvin, A. Deswal, M.H. Drazner, S.M. Dunlay, L.R. Evers, et al., 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines, J. Am. Coll. Cardiol. 79 (2022) 1757–1780, https://doi.org/10.1016/j.jacc.2021.12.011.
[90] S. Chung, T.H. Kim, J.S. Uhm, M.J. Cha, J.M. Lee, J. Park, J.K. Park, K.W. Kang, J. Kim, H.W. Park, et al., Stroke and systemic embolism and other adverse outcomes of heart failure with preserved and reduced ejection fraction in patients with atrial fibrillation (from the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation [CODE-AF]), Am. J. Cardiol. 125 (2020) 68–75, https://doi.org/10.1016/j.amjcard.2019.09.035.
[91] D. Kotecha, R. Chudasama, D.A. Lane, P. Kirchhof, G.Y. Lip, Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes, Int. J. Cardiol. 203 (2016) 660–666, https://doi.org/10.1016/j.ijcard.2015.10.220.
[92] G. Tsigkas, A. Apostolos, S. Despotopoulos, G. Vasilagkos, A. Papageorgiou, E. Kallergis, G. Leventopoulos, V. Mplani, I. Koniari, D. Velissaris, et al., Anticoagulation for atrial fibrillation in heart failure patients: balancing between Scylla and Charybdis, J. Geriatr. Cardiol. 18 (2021) 352–361, https://doi.org/10.11909/j.issn.1671-5411.2021.05.006.
[93] M.M. Kittleson, G.S. Panjrath, K. Amancherla, L.L. Davis, A. Deswal, D.L. Dixon, J. L. Januzzi Jr., C.W. Yancy, 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution set oversight committee, J. Am. Coll. Cardiol. 81 (2023) 1835–1878, https://doi.org/10.1016/j.jacc.2023.03.393.
[94] J. Ferreira, M.D. Ezekowitz, S.J. Connolly, M. Brueckmann, M. Fraessdorf, P. A. Reilly, S. Yusuf, L. Wallentin, Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial, Eur. J. Heart Fail. 15 (2013) 1053–1061, https://doi.org/10.1093/eurjhf/hft111.

[95] Q. Xiong, Y.C. Lau, K. Senoo, D.A. Lane, K. Hong, G.Y.H. Lip, Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials, Eur. J. Heart Fail. 17 (2015) 1192–1200, https://doi.org/10.1002/ejhf.343.

[96] S. Connolly, J. Pogue, R. Hart, M. Pfeffer, S. Hohnloser, S. Chrolavicius, M. Pfeffer, S. Hohnloser, S. Yusuf, Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial, Lancet. 367 (2006) 1903–1912, https://doi.org/10.1016/s0140-6736(06)68845-4.

[97] R. De Caterina, S. Husted, L. Wallentin, F. Andreotti, H. Arnesen, F. Bachmann, C. Baigent, K. Huber, J. Jespersen, S.D. Kristensen, et al., General mechanisms of coagulation and targets of anticoagulants (section I). Position paper of the ESC working group on thrombosis–task force on anticoagulants in heart disease, Thromb. Haemost. 109 (2013) 569–579, https://doi.org/10.1160/th12-10-0772.

[98] M.V. Holmes, B.J. Hunt, M.J. Shearer, The role of dietary vitamin K in the management of oral vitamin K antagonists, Blood Rev. 26 (2012) 1–14, https://doi.org/10.1016/j.blre.2011.07.002.

[99] S. Yaghi, C. Song, W.A. Gray, K.L. Furie, M.S.V. Elkind, H. Kamel, Left atrial appendage function and stroke risk, Stroke. 46 (2015) 3554–3559, https://doi.org/10.1161/STROKEAHA.115.011273.

[100] M.B. Munir, M.Z. Khan, D. Darden, Z.U. Abideen Asad, M. Osman, G.D. Singh, U. N. Srivatsa, F.T. Han, R. Reeves, J.C. Hsu, Association of heart failure with procedural complications and in-hospital outcomes from left atrial appendage occlusion device implantation in patients with atrial fibrillation: insights from the national inpatient sample of 62 980 procedures, Europace. 24 (2022) 1451–1459, https://doi.org/10.1093/europace/euac043.

[101] M. Saad, M. Osman, H. Hasan-Ali, M. Abdel Ghany, A.A. M, O. Risha, M. Sano, T. Fink, C.H. Heeger, J. Vogler, et al., Atrial appendage closure in patients with heart failure and atrial fibrillation: industry-independent single-centre study, ESC Heart Fail. 9 (2022) 648–655, https://doi.org/10.1002/ehf2.13698.

[102] M.B. Munir, J.C. Hsu, Left atrial appendage occlusion should be offered only to select atrial fibrillation patients, Heart Rhythm. O2 (3) (2022) 448–454, https://doi.org/10.1016/j.hroo.2022.07.001.

[103] B.M. Bonora, E. Raschi, A. Avogaro, G.P. Fadini, SGLT-2 inhibitors and atrial fibrillation in the Food and Drug Administration adverse event reporting system, Cardiovasc. Diabetol. 20 (2021) 39, https://doi.org/10.1186/s12933-021-01243-4.

[104] S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner-La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, et al., Empagliflozin in heart failure with a preserved ejection fraction, N. Engl. J. Med. 385 (2021) 1451–1461, https://doi.org/10.1056/NEJMoa2107038.

[105] M.E. Nassif, S.L. Windsor, B.A. Borlaug, D.W. Kitzman, S.J. Shah, F. Tang, Y. Khariton, A.O. Malik, T. Khumri, G. Umpierrez, et al., The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial, Nat. Med. 27 (2021) 1954–1960, https://doi.org/10.1038/s41591-021-01536-x.

[106] P.L. Myhre, M. Vaduganathan, B.L. Claggett, Z.M. Miao, P.S. Jhund, R.A. de Boer, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, et al., Influence of NT-proBNP on efficacy of Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction, JACC Heart Fail. 10 (2022) 902–913, https://doi.org/10.1016/j.jchf.2022.08.007.

[107] T.A. Zelniker, M.P. Bonaca, R.H.M. Furtado, O. Mosenzon, J.F. Kuder, S. A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, et al., Effect of Dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus, Circulation. 141 (2020) 1227–1234, https://doi.org/10.1161/CIRCULATIONAHA.119.044183.

[108] T. Sato, Y. Aizawa, S. Yuasa, S. Kishi, K. Fuse, S. Fujita, Y. Ikeda, H. Kitazawa, M. Takahashi, M. Sato, et al., The effect of dapagliflozin treatment on epicardial adipose tissue volume, Cardiovasc. Diabetol. 17 (2018) 6, https://doi.org/10.1186/s12933-017-0658-8.

[109] S. Saito, Y. Teshima, A. Fukui, H. Kondo, S. Nishio, M. Nakagawa, T. Saikawa, N. Takahashi, Glucose fluctuations increase the incidence of atrial fibrillation in diabetic rats, Cardiovasc. Res. 104 (2014) 5–14, https://doi.org/10.1093/cvr/cvu176.

[110] E. Yang, J. Vaishnav, E. Song, J. Lee, S. Schulman, H. Calkins, R. Berger, S. D. Russell, K. Sharma, Atrial fibrillation is an independent risk factor for heart failure hospitalization in heart failure with preserved ejection fraction, ESC Heart Fail. 9 (2022) 2918–2927, https://doi.org/10.1002/ehf2.13836.

[111] E. Shantsila, F. Shahid, Y. Sun, J. Deeks, M. Calvert, J.P. Fisher, P. Kirchhof, P. S. Gill, G.Y.H. Lip, Spironolactone in atrial fibrillation with preserved cardiac fraction: the IMPRESS-AF trial, J. Am. Heart Assoc. 9 (2020), e016239, https://doi.org/10.1161/jaha.119.016239.

[112] D. Kotecha, K.V. Bunting, S.K. Gill, S. Mehta, M. Stanbury, J.C. Jones, S. Haynes, M.J. Calvert, J.J. Deeks, R.P. Steeds, et al., Effect of digoxin vs Bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial, JAMA. 324 (2020) 2497–2508, https://doi.org/10.1001/jama.2020.23138.

[113] P. Palau, J. Seller, E. Domínguez, I. Gómez, J.M. Ramón, C. Sastre, R. de la Espriella, E. Santas, G. Miñana, F.J. Chorro, et al., Beta-blockers withdrawal in patients with heart failure with preserved ejection fraction and chronotropic incompetence: effect on functional capacity rationale and study design of a prospective, randomized, controlled trial (The Preserve-HR trial), Clin. Cardiol. 43 (2020) 423–429, https://doi.org/10.1002/clc.23345.

[114] P. Palau, J. Seller, E. Domínguez, C. Sastre, J.M. Ramón, R. de La Espriella, E. Santas, G. Miñana, V. Bodí, J. Sanchis, et al., Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction, J. Am. Coll. Cardiol. 78 (2021) 2042–2056, https://doi.org/10.1016/j.jacc.2021.08.073.

[115] J. Kornej, C.S. Börschel, E.J. Benjamin, R.B. Schnabel, Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights, Circ. Res. 127 (2020) 4–20, https://doi.org/10.1161/circresaha.120.316340.

[116] O. Țica, O. Țica, K.V. Bunting, J. deBono, G.V. Gkoutos, M.I. Popescu, D. Kotecha, Post-mortem examination of high mortality in patients with heart failure and atrial fibrillation, BMC Med. 20 (2022) 331, https://doi.org/10.1186/s12916-022-02533-8.

[117] M. Rienstra, A.H. Hobbelt, M. Alings, J.G.P. Tijssen, M.D. Smit, J. Brügemann, B. Geelhoed, R.G. Tieleman, H.L. Hillege, R. Tukkie, et al., Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial, Eur. Heart J. 39 (2018) 2987–2996, https://doi.org/10.1093/eurheartj/ehx739.

[118] D.H. Lau, S. Nattel, J.M. Kalman, P. Sanders, Modifiable risk factors and atrial fibrillation, Circulation. 136 (2017) 583–596, https://doi.org/10.1161/CIRCULATIONAHA.116.023163.

[119] O. Chioncel, M. Lainscak, P.M. Seferovic, S.D. Anker, M.G. Crespo-Leiro, V. P. Harjola, J. Parissis, C. Laroche, M.F. Piepoli, C. Fonseca, et al., Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry, Eur. J. Heart Fail. 19 (2017) 1574–1585, https://doi.org/10.1002/ejhf.813.

[120] M.V. Perez, P.J. Wang, J.C. Larson, E.Z. Soliman, M. Limacher, B. Rodriguez, L. Klein, J.E. Manson, L.W. Martin, R. Prineas, et al., Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study, Heart. 99 (2013) 1173–1178, https://doi.org/10.1136/heartjnl-2013-303798.

[121] R.K. Pathak, M.E. Middeldorp, M. Meredith, A.B. Mehta, R. Mahajan, C.X. Wong, D. Twomey, A.D. Elliott, J.M. Kalman, W.P. Abhayaratna, et al., Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a Long-Term Follow-Up Study (LEGACY), J. Am. Coll. Cardiol. 65 (2015) 2159–2169, https://doi.org/10.1016/j.jacc.2015.03.002.

[122] H.S. Abed, G.A. Wittert, D.P. Leong, M.G. Shirazi, B. Bahrami, M.E. Middeldorp, M.F. Lorimer, D.H. Lau, N.A. Antic, A.G. Brooks, et al., Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial, Jama. 310 (2013) 2050–2060, https://doi.org/10.1001/jama.2013.280521.

[123] D.W. Kitzman, P. Brubaker, T. Morgan, M. Haykowsky, G. Hundley, W.E. Kraus, J. Eggebeen, B.J. Nicklas, 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: a randomized clinical trial, Jama. 315 (2016) 36–46, https://doi.org/10.1001/jama.2015.17346.

[124] C.X. Wong, M.T. Sun, A. Odutayo, C.A. Emdin, R. Mahajan, D.H. Lau, R.K. Pathak, D.T. Wong, J.B. Selvanayagam, P. Sanders, et al., Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation, Circ. Arrhythm. Electrophysiol. (2016) 9, https://doi.org/10.1161/circep.116.004378.

[125] A. Pandey, A. Parashar, D.J. Kumbhani, S. Agarwal, J. Garg, D. Kitzman, B. D. Levine, M. Drazner, J.D. Berry, Exercise training in patients with heart failure and preserved ejection fraction, Circulation 8 (2015) 33–40, https://doi.org/10.1161/CIRCHEARTFAILURE.114.001615.

[126] W. Zhu, W. Liang, Z. Ye, Y. Wu, X. He, R. Xue, Z. Wu, Y. Zhou, J. Zhao, Y. Dong, et al., Association of physical activity and risk of atrial fibrillation in heart failure with preserved ejection fraction, in: Nutrition, Metabolism, and Cardiovascular Diseases: NMCD 31, 2021, pp. 247–253, https://doi.org/10.1016/j.numecd.2020.08.022.

[127] A. Shapira-Daniels, S. Mohanty, F.M. Contreras-Valdes, H. Tieu, R.J. Thomas, A. Natale, E. Anter, Prevalence of undiagnosed sleep apnea in patients with atrial fibrillation and its impact on therapy, JACC Clin. Electrophysiol. 6 (2020) 1499–1506, https://doi.org/10.1016/j.jacep.2020.05.030.

[128] T. Bitter, L. Faber, D. Hering, C. Langer, D. Horstkotte, O. Oldenburg, Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction, Eur. J. Heart Fail. 11 (2009) 602–608, https://doi.org/10.1093/eurjhf/hfp057.

[129] E.J. Benjamin, D. Levy, S.M. Vaziri, R.B. D'Agostino, A.J. Belanger, P.A. Wolf, Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study, Jama 271 (1994) 840–844.

[130] A.M. Jackson, R. Rørth, J. Liu, S.L. Kristensen, I.S. Anand, B.L. Claggett, J.G. F. Cleland, V.K. Chopra, A.S. Desai, J. Ge, et al., Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction, Eur. J. Heart Fail. 24 (2022) 497–509, https://doi.org/10.1002/ejhf.2403.

[131] S.J. Tu, N. Hanna-Rivero, A.D. Elliott, N. Clarke, S. Huang, B.M. Pitman, C. Gallagher, D. Linz, R. Mahajan, D.H. Lau, et al., Associations of anemia with stroke, bleeding, and mortality in atrial fibrillation: a systematic review and meta-analysis, J. Cardiovasc. Electrophysiol. 32 (2021) 686–694, https://doi.org/10.1111/jce.14898.

[132] M. Kim, M. Hong, J.Y. Kim, I.S. Kim, H.T. Yu, T.H. Kim, J.S. Uhm, B. Joung, M. H. Lee, H.N. Pak, Clinical relationship between anemia and atrial fibrillation recurrence after catheter ablation without genetic background, Int. J. Cardiol. Heart Vasc. 27 (2020), 100507, https://doi.org/10.1016/j.ijcha.2020.100507.

[133] A. Alcaide-Aldeano, A. Garay, L. Alcoberro, S. Jiménez-Marrero, S. Yun, M. Tajes, E. García-Romero, C. Díez-López, J. González-Costello, G. Mateus-Porta, et al., Iron deficiency: impact on functional capacity and quality of life in heart failure

with preserved ejection fraction, J. Clin. Med. (2020) 9, https://doi.org/10.3390/jcm9041199.

[134] N.F. Marrouche, J. Brachmann, D. Andresen, J. Siebels, L. Boersma, L. Jordaens, B. Merkely, E. Pokushalov, P. Sanders, J. Proff, et al., Catheter ablation for atrial fibrillation with heart failure, N. Engl. J. Med. 378 (2018) 417–427, https://doi.org/10.1056/NEJMoa1707855.

[135] J.P. Kelly, A.D. DeVore, J. Wu, B.G. Hammill, A. Sharma, L.B. Cooper, G. M. Felker, J.P. Piccini, L.A. Allen, P.A. Heidenreich, et al., Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from get with the guidelines—heart failure, J. Am. Heart Assoc. 8 (2019), e011560, https://doi.org/10.1161/JAHA.118.011560.

[136] M. Al-Sadawi, S. Aleem, F. Aslam, R. Jacobs, G. Stevens, I. Almasry, A. Singh, R. Fan, E. Rashba, Rhythm versus rate control for atrial fibrillation in heart failure with preserved ejection fraction, Heart Rhythm. O2 (3) (2022) 520–525, https://doi.org/10.1016/j.hroo.2022.06.009.

[137] D.L. Packer, J.P. Piccini, K.H. Monahan, H.R. Al-Khalidi, A.P. Silverstein, P. A. Noseworthy, J.E. Poole, T.D. Bahnson, K.L. Lee, D.B. Mark, Ablation versus drug therapy for atrial fibrillation in heart failure, Circulation. 143 (2021) 1377–1390, https://doi.org/10.1161/CIRCULATIONAHA.120.050991.

[138] M. Rattka, A. Kühberger, A. Pott, T. Stephan, K. Weinmann, M. Baumhardt, D. Aktolga, Y. Teumer, C. Bothner, D. Scharnbeck, et al., Catheter ablation for atrial fibrillation in HFpEF patients-a propensity-score-matched analysis, J. Cardiovasc. Electrophysiol. 32 (2021) 2357–2367, https://doi.org/10.1111/jce.15200.