REVIEW ARTICLE

RECENT DEVELOPMENTS IN HFpEF AND ATRIAL FIBRILLATION

Somida Kuka, Eneida Hoxha, Margarita (Gjata) Resuli

Department of Internal Medicine, UHC :Mother Teresa“ Tirana, Albania.

Corresponding E-mail: somida.kuka@gmail.com

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) often coexist and exacerbate each other through left atrial remodeling, increased filling pressures, inflammation, obesity, renal dysfunction, endothelial dysfunction, and impaired exercise tolerance. Recent data have shifted treatment from symptomatic therapy alone to phenotype-targeted therapy. Significant developments include the use of first-line sodium-glucose cotransporter-2 (SGLT2) inhibitors, recent validation of non-steroidal mineralocorticoid receptor antagonists, the utility of GLP-1/GIP-targeted weight-loss therapy for obesity-associated HFpEF, and increased proactive approaches to rhythm control in AF.

The effect of HFpEF on AF is bidirectional and clinically important. HFpEF leads to atrial fibrosis and raised filling pressures, while AF aggravates diastolic dysfunction via atrial contraction loss and irregular ventricular filling. Modern management thus depends on an integrated approach targeting congestion, metabolic failure, atrial disease, obesity, hypertension, diabetes mellitus, renal dysfunction and thromboembolic hazard.

This review provides an overview of recent pathophysiologic advances, diagnostic and treatment considerations, alongside recent and ongoing therapeutic developments for HFpEF followed by AF, including updates on the ESC guideline and large clinical trials.

Keywords: Heart failure; atrial fibrillation; preserved ejection fraction (HFpEF).

ZHVILLIMET E FUNDIT NË HFpEF DHE FIBRILACIONIN ATRIAL

ABSTRAKT

Hyrje. HFpEF dhe fibrilacioni atrial (FA) bashkëshoqërohen shpesh dhe përkeqësojnë njëri-tjetrin përmes rimodelimit atrial, inflamacionit dhe çrregullimeve metabolike. Zhvillimet e fundit përfshijnë përdorimin e inhibitorëve SGLT2, finerenonit, terapive GLP-1/GIP dhe strategjive më aktive të kontrollit të ritmit.HFpEF përfaqëson një nga format më të zakonshme të insuficiencës kardiake. FA është një komorbiditet shumë i shpeshtë dhe lidhet me simptoma më të rënda, hospitalizime të shpeshta dhe rrezik më të lartë tromboembolik. HFpEF shkakton dilatacion dhe fibrozë atriale, ndërsa FA përkeqëson funksionin diastolik dhe mbushjen ventrikulare.

Metoda. Ky review u realizua mbi bazën e literaturës së fundit shkencore dhe guideline-ve ESC. U analizuan studime të rëndësishme si EMPEROR-Preserved, DELIVER, FINEARTS-HF, STEP-HFpEF dhe EAST-AFNET 4. Fokus kryesor ishte diagnostika, terapia moderne dhe strategjitë e kontrollit të ritmit në pacientët me HFpEF dhe FA.
Resultate. Inhibitorët SGLT2 kanë treguar reduktim të hospitalizimeve dhe përmirësim të cilësisë së jetës në HFpEF. Finerenoni demonstroi reduktim të eventeve kardiovaskulare në pacientët me EF të ruajtur ose lehtësisht të reduktuar. Terapitë metabolike si semaglutide dhe tirzepatide përmirësuan simptomat dhe tolerancën fizike te pacientët obezë me HFpEF. Strategjitë e hershme të kontrollit të ritmit dhe ablacioni kateterik mund të përmirësojnë simptomat dhe kapacitetin funksional në pacientë të përzgjedhur.

Menaxhimi modern i HFpEF dhe FA po kalon drejt një qasjeje të personalizuar dhe multidisiplinare. Kontrolli i faktorëve të riskut si obeziteti, hipertensioni, diabeti dhe apnea e gjumit, mbetet esencial për suksesin afatgjatë terapeutik.

Përfundime. HFpEF dhe FA janë sindroma të ndërlidhura ngushtë. Terapitë moderne, veçanërisht SGLT2 inhibitorët dhe trajtimet metabolike, kanë ndryshuar ndjeshëm menaxhimin klinik. E ardhmja pritet të fokusohet në terapi të individualizuara sipas fenotipit të pacientit.

Fjalët kyce: insuficiencë kardiake, fibrilacion atrial, funksion i ruajtur.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) represents one of the fastest-growing cardiovascular syndromes in the world and accounts for over half of all heart failure cases globally. HFpEF does not consist of the same pathophysiologic mechanism as heart failure with reduced ejection fraction (HFrEF), and is due to impaired ventricular relaxation, increased ventricular stiffness, endothelial dysfunction, systemic inflammation, obesity, and multiple comorbidities. Atrial fibrillation (AF) is one of the most common and clinically significant comorbidities of HFpEF, and is highly prevalent in patients. Depending on the studied population, fibrillation in the HFpEF population accounts for about 40–60% of patients with AF. When HF happens simultaneously with both conditions, it is associated with increased mortality, recurrent heart-failure hospitalization, poor exercise capacity, decreased exercise ability, and increased thromboembolic risk (2). The relationship between AF and HFpEF is multifaceted and bidirectional. In HFpEF, elevated LV filling pressures cause left atrial enlargement, atrial fibrosis, and electrical remodeling and drive AF. In contrast, AF causes worsening diastolic filling due to loss of atrial contraction and shortened diastolic filling time, tachycardia-induced myocardial dysfunction, and increased neurohormonal activation (1,2). The therapeutic landscape of HFpEF has radically changed in the last few years. Treatments used to be mostly symptomatic and to control comorbidities. However, SGLT2 inhibitors are shown to lead to beneficial

effects in randomized clinical trials and may show further favorable effects with finerenone and obesity-targeted classes, including semaglutide and tirzepatide. At the same time, AF treatment has been moving toward integrated care strategies and earlier rhythm-control methodologies. The acknowledgment that AF might directly participate in the progression of HFpEF has sparked interest in catheter ablation and aggressive management of a subset of patients with increased risk factors (2). This review's objective is to review recent progress in the pathogenesis, diagnosis, management and treatment of HFpEF and AF along with the corresponding clinical significance.

MATERIAL AND METHODS

This review was performed as a narrative literature review with an emphasis on recent developments of heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF). A systematic search of the medical literature was conducted using PubMed, ESC guideline publications, and major peer-reviewed cardiovascular journals. The search encompassed studies published between 2020 and 2026, with a focus on randomized clinical trials, meta-analyses, and international guideline recommendations. The search terms used separately and together are as follows: “HFpEF,” “atrial fibrillation,” “SGLT2 inhibitors,” “empagliflozin,” “dapagliflozin,” “finerenone,” “GLP-1 agonists,” “tirzepatide,” “semaglutide,” “catheter ablation,” “rhythm control,” and “ESC Guidelines.” Priority was given to landmark studies and official guideline documents from the European Society of Cardiology (ESC). The major trials included EMPEROR-Preserved, DELIVER, FINEARTS-HF, STEP-HFpEF, SUMMIT, EAST-AFNET 4, and CABANA. Articles were selected based on their clinical applicability, methodological merits, and relevance to the management of current HFpEF and AF. Pathophysiology, diagnosis, pharmacotherapy, drug treatment, rhythm-control measures, obesity-associated HFpEF, and cardiovascular outcomes were targeted by data extraction.

The review was presented in themes that dealt with:

- Association of HFpEF and AF for disease progression;
- Novel pharmaceutical developments and developments in pharmaceutical therapy;
- Rhythm-control strategies;
- Diagnostic considerations;
- Phenotype-oriented management methods/protocols;
- Implications for practice.

As this is a narrative review of previously published studies, it did not require ethical committee approval or the consent of the patient.

RESULTS

Pathophysiological Interaction between HFpEF and AF

Recent reports found that HFpEF and AF are closely related disease processes, rather than separate clinical entities (3,4). High left ventricular filling pressures in HFpEF contribute to degenerative left atrial remodeling with dilation, fibrosis, endothelial dysfunction, and impaired reservoir function. Restructuring provides a proarrhythmogenic substrate that supports the genesis of AF.

The AF itself contributes to deteriorating HFpEF physiology due to:

- Atrial contractions collapse and ventricular filling impairment;
- Enhanced heart rate fluctuations;
- Cardiac output decreases during exertion;
- Myocardial damage due to tachycardia-driven heart failure;
- Neurohormonal activation;
- Increased pulmonary venous pressure.

The coexistence of HFpEF and AF correlates with reduced exercise tolerance; elevated levels of natriuretic peptide, increased hospitalization, and increased mortality. A growing number of studies have now suggested atrial cardiomyopathy as a main risk factor of HFpEF pathophysiology. Left atrial dysfunction may precede overt ventricular dysfunction, leading to symptomatology and disease progression (3,5).

SGLT2 Inhibitors

One of the most important changes in the management of HFpEF has been the implementation of SGLT2 inhibitors (6,7). The EMPEROR-Preserved trial showed that empagliflozin markedly reduced the combined endpoint of cardiovascular death and hospitalization due to heart failure in patients with HFpEF. Likewise, the DELIVER trial demonstrated good results with dapagliflozin in patients with mildly diminished or preserved ejection fraction. Notably, the most recent ESC guidelines recommend SGLT2 inhibitors across all categories of heart failure regardless of left ventricular ejection fraction. In patients with concomitant AF, SGLT2 inhibitors may also promote reduced atrial remodeling, inflammation, oxidative stress, and volume overload. Initial indications of potential antiarrhythmic action have been reported, but there is no randomized data specifically aimed at AF burden.

Clinical benefits of SGLT2 inhibitors include:

- Decreased heart-failure hospitalization;
- Symptom and quality of life benefits;
- Beneficial renal protection;
- Decrease of cardiovascular mortality;
- Common to HF phenotypes.

Finerenone and Mineralocorticoid Receptor Antagonism

Activation of mineralocorticoid receptors is associated with myocardial fibrosis, inflammation, vascular dysfunction, and renal dysfunction. Finerenone has been

shown to decrease worsening heart-failure events and cardiovascular death in patients with mildly reduced or preserved ejection fraction in the FINEARTS-HF trial. Finerenone may have a more selective receptor profile and lower rates of hyperkalemia and endocrine adverse events as compared with classical steroidal mineralocorticoid receptor antagonists (8). These findings provide support for a widening role of non-steroidal mineralocorticoid receptor antagonism for HFpEF patients, especially in patients with concomitant renal dysfunction and diabetes mellitus and with an increased inflammatory-metabolic load. However, continued surveillance of potassium concentration and renal function is key.

Obesity-Related HFpEF and Metabolic Therapy

Obesity-related HFpEF has become among the most clinically relevant HFpEF phenotypes (9,10). Obesity is associated with systemic inflammation, decreased ventricular compliance, and pulmonary hypertension, as well as endothelial dysfunction and epicardial adipose tissue build-up. AF is highly common in patients with obesity-related HFpEF. The STEP-HFpEF trial proved that semaglutide significantly improved symptoms, exercise capacity, quality of life, and body weight in obese HFpEF patients. Likewise, in the SUMMIT trial of tirzepatide, quality-of-life scores improved, and worsening heart-failure events declined. These results support the idea that targeted metabolic treatment can alter HFpEF progression significantly for certain phenotypes. Reducing weight also reduces blood pressure, decreases insulin resistance, severity of sleep apnea, alleviates inflammatory burden, and alters atrial remodeling, all of which can impact AF burden positively.

Rhythm-Control Strategies

Recent standards for AF emphasize holistic and individualized rhythm-control treatment. Sinus rhythm may be especially relevant in HFpEF patients, given that atrial contraction plays a crucial role in ventricular filling and exercise tolerance. The EAST-AFNET 4 trial was beneficial to patients with AF for early rhythm-control therapy in terms of cardiovascular status. Results are not limited to HFpEF, however, the implications are unambiguous for early intervention alternatives. For many selected symptomatic HFpEF patients with AF, catheter ablation has become an increasingly pertinent therapeutic option. Some possible benefits might include:

Improved symptoms and exercise capacity;

Reduction of AF burden;

Better quality of life;

Possible reduction in heart-failure hospitalization.

However, in HFpEF patients, advanced remodeling of the atria, obesity, sleep apnea, renal dysfunction and hypertension can often limit their chance of success. So aggressive risk-factor modification is considered necessary before and after rhythm-control measures.

Diagnostic Considerations

Diagnosing HFpEF in AF patients continues to be difficult. An elevated level of natriuretic peptide due to AF may also contribute to a poor clinical discriminative index, with its clinical significance related to AF. Beat-to-beat variability and abnormal filling dynamics also complicate the interpretation of echocardiography.

Key diagnostic parameters include:

Left atrial volume index (LAVI);

E/e' ratio;

Tricuspid regurgitation velocity;

Pulmonary artery pressure estimation;

Left ventricular mass index;

Global longitudinal strain (GLS);

Diastolic stress testing.

More advanced imaging methods are used to characterize the phenotype. Speckle tracking echocardiography may detect subtle atrial and ventricular failure well before more typical parameters become abnormal. Cardiac magnetic resonance imaging may supply valuable information on fibrosis, infiltration, and characterization of myocardial structures. The concept of functional atrial mitral regurgitation has also come into discussion among HFpEF and AF patients, caused by progressive atrial remodeling and annular dilatation.

DISCUSSION

The coexistence of HFpEF and AF is a major clinical issue due to mutual support for one another through hemodynamic, structural, inflammatory, and neurohormonal mechanisms. HFpEF treatment has historically targeted symptom control and management of comorbidities, which complicate the management of symptoms. The lack of effective disease-modifying therapies helped fuel the poor long-term outcomes. However, recent clinical trials have dramatically changed this therapeutic picture. Of all recent therapies, SGLT2 inhibitors have emerged as the best evidence-based treatment for HFpEF. These beneficial effects seem to be independent of diabetes status and involve hemodynamic, renal, anti-inflammatory, and metabolic pathways. Finerenone further expands the paradigm of targeted neurohormonal modulation in HFpEF. Its favourable cardiovascular effects point out that fibrosis and inflammation are important points in the pathophysiology of HFpEF. Another major development is the emergence of obesity-related HFpEF as a discrete and medicalizable phenotype. Semaglutide and tirzepatide showed significant improvement in symptoms, exercise output, and general life quality. These data highlight the central role of metabolic disturbance in HFpEF progression (9,10). The new paradigms for managing AF in HFpEF are moving towards earlier and more aggressive rhythm-control strategies for managing AF. Compared to prior evidence that favored a predominantly rate-directed approach to rate control, sinus rhythm maintenance may confer potential hemodynamic advantage in selected patients with

HFpEF (e.g., heart failure). (11,12) However, rhythm control interventions alone are usually inadequate if the underlying comorbidities are not treated. Obesity, hypertension, sleep apnea, diabetes mellitus, and renal insufficiency are highly implicated in atrial remodeling and AF regrowth. Integrated therapeutic management has been of growing significance.

Many evidence limitations remain. HFpEF is very heterogeneous, and in numerous clinical trials, there are large-scale patient populations with a wide phenotypic variability. Prospective work will presumably investigate further the more detailed phenotyping based on imaging, biomarkers, hemodynamic evaluation, and artificial intelligence-based methods. Furthermore, advanced imaging and analysis of atrial strain are becoming more important, along with invasive hemodynamic assessment. Currently, strong evidence supports a phenotype-oriented and individualized treatment strategy, rather than a uniform therapeutic approach.

CONCLUSIONS

FpEF and AF commonly coexist and are closely interconnected cardiovascular syndromes with severe morbidity and mortality. The management of HFpEF has greatly improved over recent years through therapeutic innovations in SGLT2 inhibition, with early support for finerenone and obesity-targeted agents (e.g., semaglutide, tirzepatide). Meanwhile, AF therapy continues to focus on early rhythm-control mechanisms and aggressive therapy of cardiovascular risk factors.An effective contemporary approach should include phenotype-guided HFpEF treatment, optimal management of comorbidities, appropriate anticoagulation based on thromboembolic risk, weight reduction in obese patients, and individualized rhythm-control strategies. Long-term multidisciplinary care is essential. Future progress will improve the identification of HFpEF phenotypes, enhance the understanding of atrial remodeling, and facilitate more personalized multimodal treatment strategies.

Conflict of interest: Nothing to declare.

Author contribution. All authors contributed to the preparation of the manuscript and approved the final version.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2023 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023.
2. Hindricks G, Potpara T, Dagres N, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2024.
3. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018;138:861–870.

4. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm. Eur Heart J. 2019;40:3297–3317.
5. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2020;17:559–573.
6. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with preserved ejection fraction. N Engl J Med. 2021;385:1451–1461.
7. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387:1089–1098.
8. Pitt B, Filippatos G, Agarwal R, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2024.
9. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. Semaglutide in patients with obesity-related HFpEF. N Engl J Med. 2023;389:1069–1084.
10. Tirzepatide in patients with obesity-related heart failure with preserved ejection fraction. N Engl J Med. 2024.
11. 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.
12. Packer DL, Mark DB, Robb RA, et al. Catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation. JAMA. 2019;321:1261–1274.