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Review Article

Functional Mitral Regurgitation and Heart Failure With Preserved Ejection Fraction: Clinical Implications and Management

Mauro Riccardi, MD[1] Maja Cikes, MD[2] Marianna Adamo, MD[1] Matteo Pagnesi, MD[1] Carlo Mario Lombardi, MD[1] Scott David Solomon, MD[3] Marco Metra, MD[1] and Riccardo Maria Inciardi, MD, PhD[1]

Italy; Zagreb, Croatia; and Boston, Massachusetts

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is highly prevalent and associated with worse cardiovascular outcomes. The pathophysiology of HFpEF mostly relies on the development of elevated left ventricle filling pressure, diastolic dysfunction, and atrial dilatation and impairment. This dynamic process may eventually lead to the development of functional mitral regurgitation (MR), characterized by mitral annular dilatation and consequent leaflet remodeling, in the context of preserved left ventricular ejection fraction. These observations highlight the possible common pathophysiology of MR and HFpEF. However, less is known about the prevalence and the clinical value of MR in the context of HFpEF. This review aims to provide an overview of the association and interplay between functional MR and HFpEF, discuss the underlying mechanisms that are common to these diseases, and summarize potential targeted pharmacological treatments. (*J Cardiac Fail 2024;30:929–939*)

The prevalence of heart failure (HF) is approximately 1%–2% in adults, and the overall incidence is increasing, most notably in the context of an ageing population. The European Society of Cardiology (ESC)-HF Long-Term Registry,[1] reports that 16% of patients in the outpatient setting have HF with preserved ejection fraction (HFpEF) and this phenotype accounts for more than one-half of all HF hospital admissions.[2] The pathophysiology of HFpEF is complex and mostly relies on the development of elevated left ventricle (LV) filling pressure, diastolic dysfunction, atrial dilatation and impairment, and annular remodelling.[3] This dynamic process may eventually lead to the development of functional mitral regurgitation (FMR), frequently called atrial FMR (AFMR) and characterized by mitral annular dilatation and consequent adaptive leaflet growth and thickening, in the context of preserved LV EF.

In general, FMR is due to an imbalance between increased tethering forces and decreased closing forcing, in the presence of a structurally normal valve. This process occurs more in ischemic or nonischemic patients with structural heart disease and LV dysfunction. Although the impact of regional LV dysfunction is less characterized in the context of HFpEF, tethering related to annular dimension and reduced contraction, reduced closing forces owing to increased left atrial (LA) pressure characterized HFpEF as compared with HF with reduced EF. Additionally, the role of microvascular dysfunction on LV impairment may contribute to decreased closing forced favoring FMR.[4]

From the [1]Institute of Cardiology, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Italy; [2]Department of Cardiovascular Diseases, University of Zagreb School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia and [3]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

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Reprint requests: Riccardo Maria Inciardi, MD, PhD, Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy, Tel: +393281526343. E-mail: riccardo.inciardi@libero.it

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Common pathophysiological mechanisms are observed in HFpEF and AFMR, such as diastolic dysfunction, preserved EF, atrial dilatation and dysfunction and annular remodeling. However, less is known about the prevalence and the clinical value of MR in the context of HFpEF.

This review aims to provide an overview about the association and interplay between FMR and HFpEF, discuss the underlying mechanisms linking these 2 diseases, and summarize potential targeted pharmacological treatments (Central Illustration).

LV Diastolic Dysfunction and LA Myopathy: Common Thread for FMR and HFpEF

The left atrium plays a critical role in modulating LV filling by acting as a reservoir to store venous return during ventricular systole, avoiding untoward elevation in the LA pressure.[5] The LA reservoir function is governed by various mechanisms: atrial distensibility (stiffness), LA relaxation rate, LA systolic shortening, and systolic ventricular function. As a result, an alteration of one of these mechanisms is sufficient to compromise the overall reservoir function of the LA. In addition to the reservoir function, the LA also plays an important role as a priming pump to boost LV filling during active atrial systole, as a passive blood duct, and in maintaining mitral valve competence. LA myopathy, defined as any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations, is very common in HFpEF.[6] There is not a single gold standard test to diagnose LA myopathy, and different diagnostic methods may be used, such as echocardiography, cardiac magnetic resonance (CMR), invasive hemodynamic measurements, and electroanatomic mapping. Owing to its cost effectiveness and ability to detect subtle changes in myocardial dynamics, echocardiography (and specifically speckle tracking, which results in superior atrial volume evaluation) may have the broadest clinical applicability.[7] However, because there is no gold standard technique for evaluating LA myopathy, clinical studies often use different criteria for its evaluation making it difficult to make a head-to-head comparison between them.

The principal form of LA myopathy in HFpEF is secondary to diastolic dysfunction and an elevation of LV filling pressures. It mainly develops through the mechanism of afterload uncoupling (mismatch), where LA contractility is preserved but fails to overcome an extremely high afterload. Therefore, there is a direct correlation between the degree of LV diastolic dysfunction and the severity of impairment in the LA function (being a more reversible impairment). As a result, increased LV filling pressure and LA myopathy could determine the development of FMR in a dynamic process often exacerbated during physical exercise.[8] Physical exercise can indeed exacerbate the imbalance between tethering and closing valve forces, the annular dysfunction, and the reduced LA function. Reduction of myocardial flow owing to microvascular dysfunction can favor a decrease of closing forces owing to subclinical myocardial tethering, eventually increasing MR entity during effort. At the same time the limitation of LA conduit and contraction functions during exercise, limits the increase in cardiac output through combined forward and backward unfavorable hemodynamics.[9,10] In addition, LA remodeling and/or atrioventricular asynchrony favored by atrial fibrillation (AF) contribute to the development of MR, reported as up to 32% during exercise,[11] which aggravates biventricular filling damage and pulmonary vascular dysfunction.[9]

However, the increased LA afterload through LV diastolic dysfunction is not the sole cause for the development of LA dysfunction in HFpEF (Fig. 1). Common HFpEF comorbidities, namely, older age, arterial hypertension, obesity, diabetes mellitus, and chronic kidney disease, may also precipitate the development of LA dysfunction and contribute to LA fibrosis through inflammation.[12] An example is represented by the presence of AF, with a prevalence of 30%−60% in patients with HFpEF across different clinical trials or epidemiological registries.[13] In fact, AF adversely affects LA pressure, reduces LV filling, reduces LA compliance by increasing fibrosis, and is responsible for LA dilation and annular enlargement resulting in FMR. Also in this context, MR development may contribute maintaining AF by favoring atrial enlargement and electrophysiological remodeling,[14] creating a vicious circle that further increases the likelihood or severity of HFpEF. Last, there is an HFpEF subtype (ie, p0atients with amyloidosis) in which LA myopathy develops as a primary intrinsic intramyocardial pathology, in the absence of systemic disease and ventricular involvement (atrial amyloidosis). Is has been shown that the transthyretin amyloid cardiomyopathy promotes significant infiltration of the atrial walls, with progressive loss of atrial function and increased stiffness.[15] Mild or moderate MR in cardiac amyloidosis is a common finding.

It is important to highlight that not only the LA myopathy in HFpEF can predispose to the development of MR, but the opposite may also apply. Indeed, in patients with primary LA myopathy and preserved EF without history of HF, the presence of even mild or moderate MR may be associated with the development of higher LV pressures resulting in diastolic dysfunction and development of HFpEF.[14]

In summary, LA myopathy and elevated LV filling pressure in HFpEF have been associated with MR. In addition, patients with MR, regardless of severity, may be at high risk of developing HFpEF,[16] as a consequence of increased LA pressure and LA remodeling.

Prevalence of MR in HFpEF

The prevalence of MR in patient with HFpEF can be extrapolated from echocardiographic analysis of major

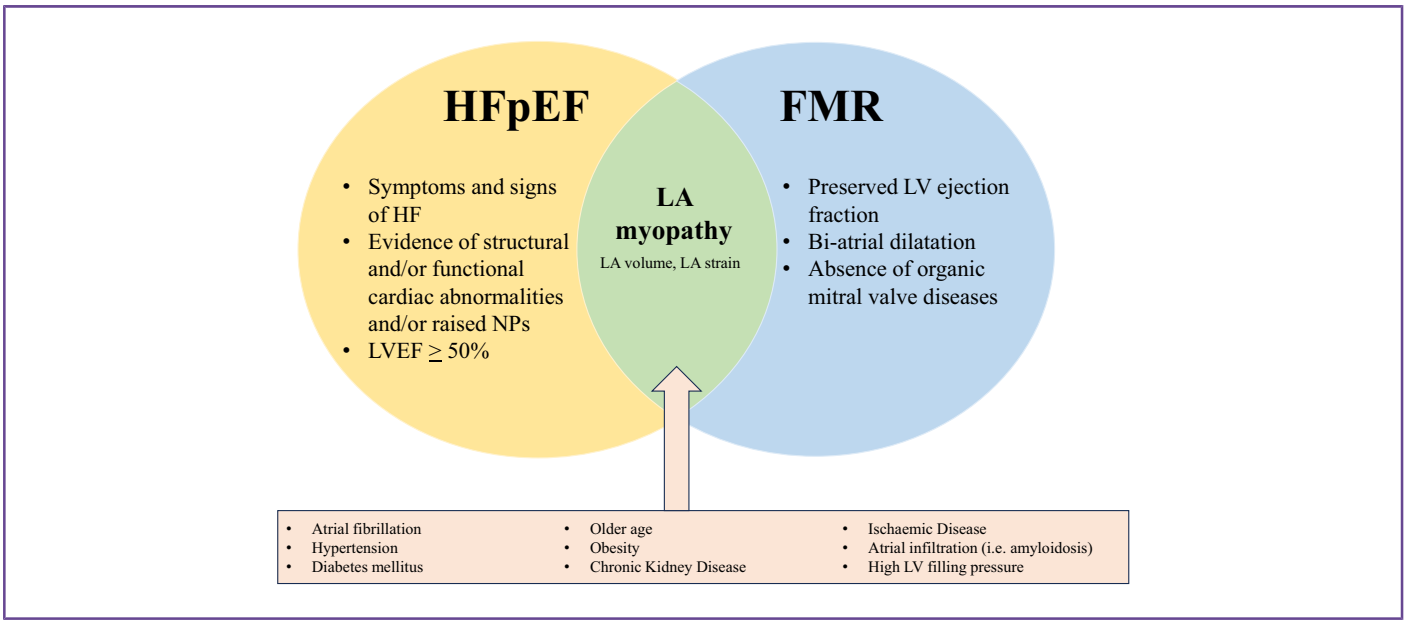


Fig. 1. Common causes leading to the development of LA myopathy, a common feature of FMR and HFpEF.
FMR = functional mitral regurgitation; FNP = natriuretic peptide; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction.

HFpEF trials and registries (Table 1).[17,18] The PARAGON-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF) trial assessed the severity of MR in 908 patients. Of these, 83 patients (9%) had moderate regurgitation, whereas 28 patients (3%) had more than moderate regurgitation.[19] In the TOPCAT trial (Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist), MR severity has been estimated in 935 patients and, among these, a more than moderate MR was present in 71 patients (12%).[20] Regarding the data obtained from large registers, in an analysis of the ESC-HF Long-Term Registry,[1] moderate to severe MR has been identified in 19.5% among 1462 patients with HFpEF. More recently, in another analysis of the same registry including 2022 patients with HFpEF, moderate or severe MR, either isolated or combined with tricuspid regurgitation, has been identified in 19% of patients.[21] Among the ATTEND (Acute Decompensated Heart Failure Syndromes) patients, 53.4% showed mild MR and 18.4% showed moderate to severe MR.[22] In contrast, Balogh et al.,[23] in a retrospective single-center analysis, observed a higher prevalence of more than moderate MR (36.3%) in 270 patients with HFpEF. Bartko et al,[24] in an observational cohort study with data from the Viennese community health care provider network, observed a 61% rate of moderate MR, whereas there was only a 4.5% rate of severe MR in a cohort of 7362 patients with HFpEF. Last, in a retrospective analysis of 280 consecutive patients with HFpEF referred to the Mayo Clinic catheterization laboratory,[16] 42% ($n = 117$) displayed mild or moderate MR and 58% ($n = 163$) displayed no or trivial MR (non−MR-HFpEF).

It is important to highlight that LA myopathy was greater in MR-HFpEF compared with non−MR-HFpEF.[16] Although the reported data cannot be ascribed entirely to FMR, it is reasonable to consider that the MR described in these studies may have functional features. Taken together, the data suggest a significant prevalence of moderate to severe MR in patients diagnosed with HFpEF, highlighting the shared pathological mechanisms of these conditions.

In contrast, it is important to note that the prevalence of HFpEF in patients with FMR is less known and difficult to estimate with the fewer data available to date. Moreover, the prevalence of AFMR has been neglected for decades by surgeons and interventional cardiologists until a few years ago, and this factor has led to a relevant underestimation of diagnosis. Often time, owing to remodeling and fibrosis of the flaps, these forms were misclassified as organic having preserved EF.

Diagnostic tools of MR in HFpEF

Echocardiography is the first line of assessment in both HFpEF and MR.[25] Because FMR and HFpEF share common abnormalities of cardiac structure and function, the differential diagnosis in clinical practice and by cardiac imaging may be challenging in presence of mild MR as well.

The main findings of FMR in the context of HFpEF include[26] (a) preserved LV EF (although LV global longitudinal strain [GLS] may be impaired)[27]; (b) biatrial dilatation; and (c) absence of organic mitral valve diseases. These

Table 1 Prevalence of MR in Patients With HFpEF

Authors	Type of Study	HFpEF Sample (*n*)	Prevalence of MR
Shah et al[19]	PARAGON-HF Trial, multicenter, randomized, double-blind	908	83 (9%) moderate 28 (3%) moderate to severe
Shah et al[20]	TOPCAT Trial, multicenter, randomized, double blind	935	112 (12%) moderate to severe
Chioncel et al[1]	ESC-HF long-term registry prospective, observational	1462	285 (19.5%) moderate to severe
Adamo et al[21]	ESC-HF long-term registry prospective, observational	2022	390 patients (19%) moderate to severe
Kajimoto et al[22]	ATTEND registry prospective, observational	1825	974 (53.4%) mild 336 (18.4%) moderate to severe
Oikawa et al[34]	JASPER registry prospective, observational	341	24 (7%) moderate
Balogh et al[23]	Retrospective, single-center study	270	172 (63.7%) mild-moderate 98 (36.3%) moderate to severe
Tamargo et al[16]	Retrospective analysis	280	117 (42%) mild-moderate
Bartko et al[24]	Prospective, observational study	7 362	4491 (61%) moderate 331 (4.5%) severe
Klapholz et al[18]	Prospective, multicenter registry	619	389 (62.9%) mild-moderate 61 (9.9%) moderate to severe
Katz et al[17]	Prospective, observational study	402	113 (28.1%) mild 58 (14.4%) moderate

HFpEF = Heart failure with preserved ejection fraction; MR = mitral regurgitation.

characteristics typically describe the AFMR. Assessment of the MR severity is achieved by combining several methods. Semiquantitative evaluations include the color flow area of the regurgitant jet, appropriate only to assess the presence of a regurgitation but not suitable to quantify its severity, the evaluation of the vena contracta, and the area of the jet as it leaves the regurgitant orifice. The evaluation of anterograde velocity of mitral inflow, pulmonary venous flow and continuous Doppler density of the MR jet are others useful semiquantitative parameters for assessing the severity of MR. The quantitative criteria include the assessment of the anatomic regurgitant orifice area and the proximal isovelocity surface area method, the most valuable quantitative approach whenever feasible.[28]

Transesophageal echocardiography is eventually recommended in the presence of MR to correctly assess valve anatomy and the feasibility of surgical or transcatheter repair. Three-dimensional echocardiography may complement 2-dimensional conventional echocardiography to study annular and leaflet area as well as leaflet remodeling.

Decreased GLS is commonly encountered among patients with HFpEF, ranging from 50% to 60%.[29] A value of less than 16% is considered a minor criterion for HFpEF diagnosis.[25] LV GLS is commonly impaired also in patients with FMR as compared with patients without FMR, despite comparable volumes.[30] In addition, GLS in patients with FMR may also have prognostic implications. In 197 patients with preserved EF and with at least moderate FMR, impaired LV GLS (≤16.3%) had a significantly lower cumulative survival rate at 5 years, as compared with patients with an LV GLS of more than 16.3% (74% vs 93%, $P < 0.001$).[31]

Although the evidence of diastolic dysfunction may be mainly attributable to HFpEF, evidence of high LV filling pressure resulting in high E/e′, LA dilatation and elevated estimated pulmonary artery systolic pressure are also common features of FMR. Last, measures of LA function, such as LA reservoir strain, have been shown to correlate well with the LV filling pressure, representing an early marker of LV diastolic dysfunction and incident HFpEF.[32] However, as mentioned elsewhere in this article, patients with FMR also have altered LA function by strain imaging.[33]

Thus, it is very difficult to distinguish between HFpEF and MR contribution to these pathophysiological changes and echocardiographic features. Indeed, no specific parameters or tools are available and validated to distinguish the 2 conditions accurately.

CMR may be a useful diagnostic tool in patients with poor echocardiographic acoustic window or in cases where myocardial structural characterization is required in suspected cardiomyopathy. Of note, international position papers point out a modest agreement between MR severity by CMR vs quantitative echocardiography and yet large studies on prognostic value of CMR-quantitated MR are lacking.[28]

Prognosis of MR in HFpEF

Little is known about the prognostic value of MR in patients with HFpEF (Table 2). The ATTEND registry[22] found that 53% and 18% of 1825 decompensated patients with HFpEF still showed mild or moderate to severe FMR at discharge, respectively, which was linked to a higher risk of all-cause mortality and readmission for HF (hazard ratio [HR] 1.40; 95% confidence interval (CI) 1.14−1.72, $P = 0.001$ and HR 1.40, 95% CI 1.09−1.81, $P = 0.009$, respectively). Similarly, in the JASPER registry, in

Table 2 Prognostic Value of MR Among Patients With HFpEF

Authors	Type of study	HFpEF sample	Outcomes
Shah et al[19]	PARAGON-HF Trial Multicenter, randomized, double-blind	908	Moderate to severe MR: HR 1.28, 95% CI 0.98−1.66, $P = 0.067$ for HF hospitalization or CV death
Shah et al[20]	TOPCAT Trial Multicenter, randomized, double blind	600	Moderate to severe MR: HR 1.49, 95% CI 0.97−2.28, $P = 0.067$ for HF hospitalization, aborted sudden death, or CV death
Kajimoto et al[22]	ATTEND Registry Prospective, observational	1825	Mild MR: HR 1.40, 95% CI 1.14−1.72, $P = 0.001$ for all-cause mortality or HF hospitalization Moderate to severe MR: HR 1.40, 95% CI 1.09−1.81, $P = 0.009$ for all-cause mortality or HF hospitalization
Oikawa et al[34]	JASPER Registry Prospective, observational	341	Moderate MR: HR 2.256, 95% CI 1.035-4.917, $P = 0.041$ for all-cause mortality
Tamargo et al[16]	Retrospective analysis	280	Mild-moderate MR: log-rank $P = 0.08$ for all-cause death or HF hospitalization
Saito et al[35]	Retrospective analysis	189	Moderate to severe MR: log-rank $P = 0.046$ for cardiac death or HF hospitalization
Bartko et al[24]	Prospective, observational	7362	Moderate MR: univariable model HR 1.15, 95% CI 1.06−1.26, $P < 0.001$; adjusted HR 1.00, 95% CI 0.92−1.10, $P = 0.94$ for long-term mortality Severe MR: univariable model HR 1.52;,95% CI 1.25−1.85, $P < 0.001$; adjusted HR 1.49, 95% CI 1.21−1.84, $P < 0.001$ for long-term mortality

CI = confidence interval; CV = cardiovascular; HFpEF = Heart failure with preserved ejection fraction; HR = hazard ratio; MR = mitral regurgitation.

hospitalized patients with HFpEF, moderate MR at discharge was associated with an increased risk of all-cause mortality (HR 2.25, 95% CI 1.035−4.917, $P = 0.041$).[34] Tamargo et al[16] showed that there was a tendency toward higher event rates of all-cause death or HF hospitalization in MR-HFpEF as compared with non−MR-HFpEF (log-rank $P = 0.08$), over a median follow-up of 5.4 years. In contrast, in the echocardiographic sub-analysis of PARAGON-HF,[19] moderate or greater MR was modestly associated with cardiovascular (CV) deaths and HF hospitalizations (HR 1.28, 95% CI 0.98−1.66, $P = 0.067$), although measures of the MR jet area/LA area ratio showed a prognostic value even after adjustment for confounders. Similarly, in TOPCAT,[20] MR was slightly associated with the primary composite outcome (HF hospitalization, aborted sudden death, CV death) (HR 1.49, 95% CI 0.97−2.28, $P = 0.067$).

It has been also shown that the presence of moderate MR during a hospitalization for HFpEF leads to a high rate of readmission for HF after discharge (36.7%) during follow-up.[35] Mesi et al[33] observed that mortality at 3 years among patients with preserved EF and severe FMR was more than twice that of a cohort with severe primary MR (41% vs 19%, $P = 0.004$). It is interesting to note that patients with MR with eccentric MR jets show a trend ($P = 0.07$) toward higher mortality and a greater hospitalization rate for HF than patients with central MR jets. Recently, Moonen et al[36] analyzed 5500 patients with MR from the National Echo Database of Australia. Over a median follow-up of 65 months, CV death occurred in 51% in this group with a median survival from the time of echocardiogram of 2.6 years. Freedom from all-cause mortality at 1, 3, and 5 years was 82%, 63%, and 50%, whereas freedom from CV death was 92%, 82%, and 75% for FMR, respectively.

In HFpEF, the presence of AF is associated with increased mortality, thromboembolic risk, and hospitalization rates.[37] It is important to consider the additional role of the presence of AF in patients with HFpEF and MR. In the ARIC (Atherosclerosis Risk in Communities) study, AF was not significantly associated with increased 1-year mortality risk in patients with no/mild MR but was significantly associated with 1-year mortality in patients with HFpEF with moderate/severe MR (adjusted HR 1.91, 95% CI 1.25−2.91).[14]

The available data underline the clinical implications of MR in the context of HFpEF. Attention should be paid to correctly diagnose FMR in patients with HFpEF to stratify patients at a high risk of worse clinical outcomes and to provide effective medical management.

Management

ESC guidelines on the treatment of HF and valvular heart disease do not provide clear recommendations for the management of FMR in patients with HFpEF. On the contrary, the 2022 American guidelines recommend mitral surgery (IIb), in persistently symptomatic patients, after having achieved control of AF, if present, and optimization of medical therapy for HF.[38]

Pharmacological Therapy

Therapies that decrease elevated LA pressure and prevent LA remodeling and fibrosis may limit the risk of AF, HFpEF, and FMR (Fig. 2). There is evidence that in hypertensive patients, blood pressure control obtained with angiotensin II receptor blockers (ARBs) can decrease LA volume and improve LA strain parameters.[39] In addition

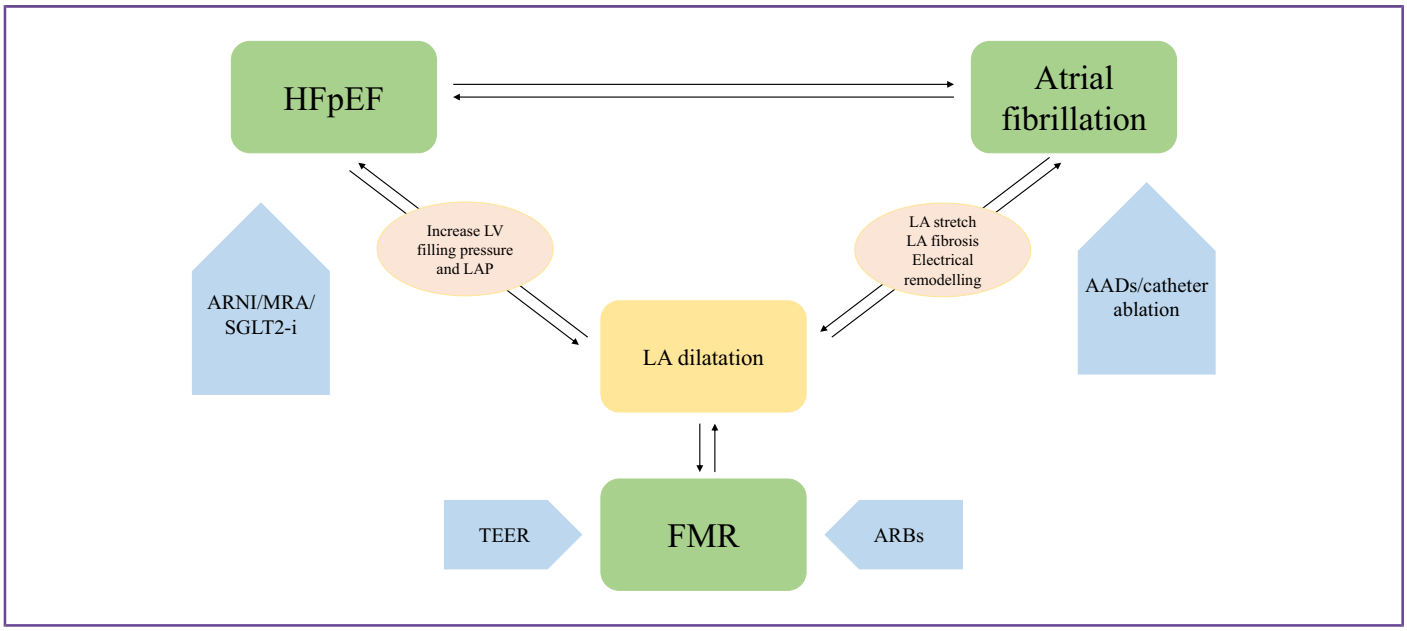


Fig. 2. Pathophysiology and treatment options of FMR and HFpEF.
AADs = anti-arhythmic drugs; ARNI = angiotensin receptor neprilysin inhibitor; LA = left atrial; LAP left atrial pressure; MRA = mineralocorticoid receptor antagonists; RAASi = renin–angiotensin system inhibitors; TEER = percutaneous edge-to-edge mitral valve repair; other abbreviations as in Fig. 1.

to this mechanism, ARBs have been reported to modulate profibrotic changes in the process of mitral valve leaflet remodeling after myocardial infarction, suppressing excess cellular proliferation, valve thickening, and matrix remodelling.[40] In this regard, Kim et al[41] analyzed directly the effect of ARBs in patients with MR. The patients who were taking these drugs had a lower vena contracta width (4.56 ± 0.56 vs 5.58 ± 1.43 mm, $P = 0.038$) compared with the control group. These results are preliminary, but suggest that these drugs may have a prophylactic effect on MR.[41] When compared with valsartan, sacubitril/valsartan seems to be even more effective on atrial remodeling. In fact, in patients undergoing radiofrequency catheter ablation (CA), sacubitril/valsartan treatment displayed significant decrease in the LA diameter (4.3 ± 0.5 cm to 3.8 ± 0.5 cm, $P < 0.001$) and LA volume index (48.0 ± 6.4 mL/m^2 to 41.7 ± 7.0 mL/m^2, $P < 0.001$) from baseline to 24 weeks. There was also a numerical decrease in AF recurrence rate in the sacubitril/valsartan group, compared with the valsartan group (9.4% vs 15.6%), although this difference did not attain statistical significance ($P = 0.708$).[42]

Regarding HF therapies, in patients with HFpEF, values of circulating biomarkers that may reflect a profibrotic state had been reported.[43] Mineralocorticoid receptor antagonists decrease extracellular matrix turnover and myocardial collagen, one of the mechanisms of atrial disease.[39] For this reason, it was postulated that they could have a benefit on LA remodeling in HFpEF. However, in the TOPCAT echocardiographic substudy, spironolactone was not associated with significant change in LA structure over time.[44] The IMPRESS-AF (Spironolactone in Atrial Fibrillation) (NCT02673463) trial is investigating whether spironolactone improves diastolic function in patients with HFpEF with permanent AF.

In the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) trial,[43] LA size and volume significantly decreased after 36 weeks in patients treated with sacubitril/valsartan. In this study, patients with less fibrosis have responded more quickly, with a decrease in overall chamber compliance and a resultant decrease in LA volume, whereas patients with more fibrosis required more than 6–9 months to respond to sacubitril/valsartan.

Recently, treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors has been shown to be a cornerstone in the treatment of HFpEF. Reassuring data on atrial remodeling with SGLT2 inhibitors were already available in HF with reduced EF patients.[45] Recently, the DAPA-MODA (Impact on Atrial Remodeling of Dapaglifozin in Patients With Heart Failure) trial showed a significant decrease in LA volume (−6.6%, 95% CI −11.1 to −1.8, $P = 0.008$) in patients with HF treated with dapagliflozin, irrespective of LVEF and diabetes status.[46] Similarly, in a systematic review and meta-analysis, the use of SGLT2 inhibitors was associated with an improvement in the LA volume index, confirming the importance of SGLT2 inhibition toward the reversal of cardiac remodeling.[47] In addition, dapagliflozin was shown to decrease the incidence of reported episodes of AF/atrial flutter adverse events in high-risk patients with type 2 diabetes mellitus. This

effect was consistent, regardless of the patient's previous history of AF, atherosclerotic CV disease, or HF.[48]

Adoption of guideline-recommended medical therapies for HF provides promising results to favor LA reverse remodeling.[49] Sacubitril/valsartan and SGLT2 inhibitors are the drugs that have so far shown the greatest benefit in the treatment of HFpEF. By acting on atrial remodeling and AF rate reduction, these drugs have the potential to contribute to favor MR reduction in HFpEF. ARBs have also been shown to be effective in atrial remodeling and in decreasing the severity of MR, albeit in a minor way compared with sacubitril/valsartan. Negative evidence exists instead currently with mineralocorticoid receptor antagonists. Yet the clinical implications on subsequent reduction of FMR need to be assessed by future studies.

Role of Rhythm Control

Rhythm control has been proposed as a means of decreasing FMR by promoting atrial/annular reverse remodeling and restoring atrial and ventricular contributions to annular contraction. In this regard, several studies have reported improvements in LA volume, peak atrial longitudinal strain, and consequently a decrease in FMR either after cardioversion or CA.[50–52] Preferably, a rhythm control strategy should be adapted in early stages of the disease because AF duration is inversely linked to the ability to maintain sinus rhythm (SR).[27]

Early rhythm control treatment is also the strategy of choice in patients with HFpEF. In a meta-analysis of five studies including 16,825 patients,[53] rhythm control for AF in patients with HFpEF was associated with lower all-cause mortality as compared with rate control (odds ratio [OR] 0.735, 95% CI 0.665–0.813, $P < 0.001$). CA was used as part of the rhythm control strategy in 4 of the 5 studies included in this meta-analysis, and the results were confirmed even after removing the study that used anti-arhythmic drugs as the exclusive method of rhythm control (OR 0.538, 95% CI 0.325–0.892, $P = 0.01$). The role of CA was confirmed in another meta-analysis of 7 trials with 1696 patients.[54] CA was effective in maintaining SR in patients with HFpEF and noninferior for patients without HF (risk ratio (RR) 0.92, 95% CI 0.76–1.10, $P = 0.34$). Additionally, CA tended to significantly maintain SR (RR 4.73, 95% CI 1.86–12.03, $P = 0.001$) and reduce rehospitalization for HF compared with medical therapy (RR 0.36, 95% CI 0.19–0.71, $P = 0.003$). However, no significant differences were found between 2 groups regarding the mortality rate ($P = 0.59$), unlike another previous meta-analysis that included 1505 patients from 6 studies where patients with HFpEF experienced significantly less mortality after CA.[55]

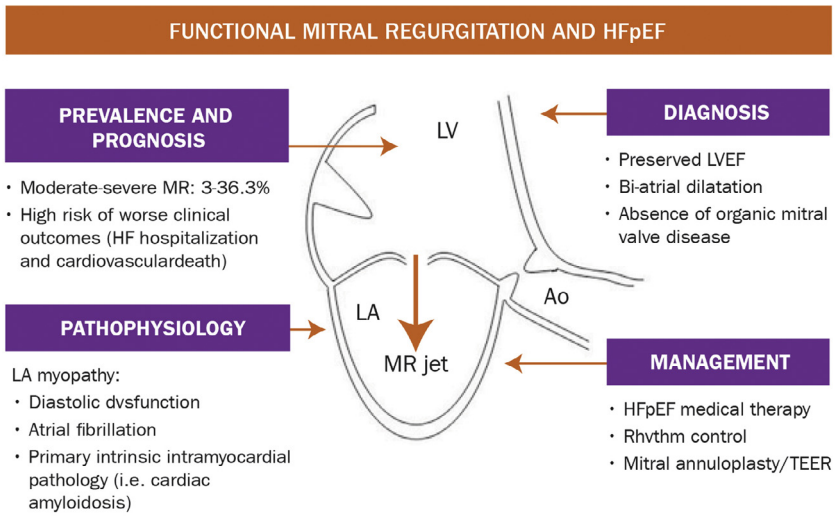
More data are needed in this context. For this reason, the effect of rhythm control with CA is being tested in an ongoing trial, Ablation Versus Medical Management of Atrial Fibrillation in HFpEF (AMPERE) (NCT04282850), to test the difference on mortality and hospitalization.

Surgical Therapy

Surgical mitral annuloplasty may be the most reliable surgical treatment for FMR, but reports from small studies must be confirmed.[50,56] Carino et al[56] selected 20 patients with AFMR and 25 with VFMR. There were no differences between the 2 groups in terms of mortality and reoperation rate. At 2 years, the cumulative incidence of recurrence of MR of 3+ or higher and 2+ or higher was significantly higher in patients with ventricular FMR (VFMR) compared with patients with AFMR (20.8 ± 8.29% vs 5.9 ± 5.71% and 45.8 ± 10.17% vs 5.9 ± 5.71%).[56] Similarly, Deferm et al[50] analyzed 216 patients, of whom 97 had AFMR as opposed to 119 with VFMR. At a median follow-up of 3.3 years, recurrence of moderate or greater MR was significantly lower in AFMR versus VFMR (7% vs 25% at 2 years, overall log-rank $P = 0.001$). Moreover, AFMR was associated with better overall survival compared with VFMR (adjusted HR 0.43, 95% CI 0.22–0.82, $P = 0.011$).[50] Concomitant AF surgical ablation during mitral valve repair could be an option to further reduce the risk of recurrent MR.[57,58]

Small studies have evaluated the role of percutaneous edge-to-edge mitral valve repair treatment in patients with AFMR.[59–67] The prevalence of AFMR in patients with FMR enrolled in these studies ranges from 4.5% to 28.0%. As mentioned elsewhere in this article, the exact prevalence of HFpEF in patients with FMR is not known. Analyzing the characteristics of AFMR patients in the GIse registry Of Transcatheter treatment of MR (GIOTTO), 33 of 79 patients (49%) had prior HF hospitalization and the median N-terminal prohormone of brain natriuretic peptide levels was 540 (interquartile range 280–1271).[67] Similarly, in Multicenter Italian Registry of TRanscatheter TreAtment of ATrial FUnctioNal Mitral REgurgitation (MITRA-TUNE Registry) and in the Spanish MitraClip multicenter registry, 59.0% and 69.8% of patients had an history of HF hospitalization, with a mean N-terminal prohormone of brain natriuretic peptide levels of 894 (interquartile range 326–2734) and 1785 (interquartile range 857–3495), respectively.[61,62] These data suggest that the possible percentage of HFpEF in this category of patients may be very high. After percutaneous edge-to-edge mitral valve repair, the procedural success, defined as MR of 2+ or greater, was achieved in a very high percentage of patients ranging from 87.0% to 99.5%.[59–67]

Regarding outcomes compared with patients with VFMR, in the GIOTTO Registry, AFMR had a lower incidence of the composite of CV death and hospitalization for HF that was about half the rate observed for the VFMR groups at the 3-year follow-up.[67] Similarly, in Belgian MitraClip database, the major adverse CV events rate, defined as combined end point of all-cause mortality and



Central Illustration. Prevalence, pathophysiology, diagnosis, prognosis, and management of FMR in patients with HFpEF

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; TEER = transcatheter edge-to-edge mitral valve repair.

hospitalization for HF, was significantly lower in AFMR vs VFMR (adjusted OR 0.46, 95% CI 0.24−0.88). This improved outcome was mainly caused by a lower rate of HF hospitalizations (adjusted OR 0.38, 95% CI 0.16−0.90), whereas all-cause mortality did not differ significantly (adjusted OR 0.8, 95% CI 0.4−1.67).[60] There are also neutral data regarding possible differences in outcomes in the 2 forms of FMR.[62,63] In the EXPAND study, at 1 year, all-cause mortality was 14.1% in patients with AFMR, compared with 18.2% in those with VFMR ($P = 0.41$), HF hospitalization occurred in 18.1% of patients with AFMR compared with 27.2% of those with VFMR at 1 year ($P = 0.16$).[65] Similarly, in the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR), 2-year survival did not differ between AFMR and VFMR patients (HR 1.21, 95% CI 0.85−1.72; $P = 0.300$).[64]

Conclusions

HFpEF and FMR are clinical entities often encountered in clinical practice. Differential diagnosis may be challenging owing to common pathophysiological features, including preserved EF, diastolic dysfunction, LA dilatation and functional impairment, and AF. Clinical studies revealed a significant proportion of moderate to severe MR in the context of HFpEF, identifying a subgroup of patients at increased risk of worse outcomes. Yet, little is known about the proper treatment of these 2 concomitant conditions. The prevention and treatment of atrial dysfunction and dilation by medical therapy for HF and restoration of SR may have a major role. Future studies are needed to better characterize these patients and provide tailored therapies.

Lay summary

Common pathophysiological mechanisms are observed in HFpEF and FMR, such as diastolic dysfunction, preserved EF, atrial dilation and dysfunction, and annular remodeling. However, less is known about the prevalence and clinical value of FMR in the context of HFpEF. The true prevalence of FMR has been overlooked for decades until a few years ago, and this factor has led to a significant underestimation of the diagnosis. This review aims to provide an overview of the known association between MR and HFpEF, discuss underlying mechanisms common to these diseases, and summarize potential targeted pharmacological treatments.

Declaration of competing interest

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CRediT authorship contribution statement

Mauro Riccardi: Writing – original draft, Writing – review & editing. **Maja Cikes:** Writing – original draft. **Marianna Adamo:** Writing – original draft. **Matteo Pagnesi:** Writing – review & editing. **Carlo Mario Lombardi:** Writing – review & editing. **Scott David Solomon:** Writing – review & editing. **Marco Metra:** Writing – review & editing. **Riccardo Maria Inciardi:** Conceptualization, Writing – original draft, Writing – review & editing.

Authors' contribution

Dr. Riccardi and Dr. Inciardi designed the review. Dr. Riccardi and Dr. Inciardi performed manuscript drafting. Dr. Riccardi, Dr. Cikes, Dr. Adamo, Dr. Pagnesi, Dr. Lombardi, Dr. Solomon, Dr. Metra, and Dr. Inciardi performed manuscript revision and provided value intellectual contribution.

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