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REVIEW

Transcatheter Approaches to Atrial Functional Mitral Regurgitation: How Far Have We Come?

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ABSTRACT

Functional mitral regurgitation (MR) is associated with increased cardiovascular morbidity and mortality and over the past decade, the diagnosis of atrial functional mitral regurgitation (aFMR) has been increasingly observed in the elderly, especially in those with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). Annular enlargement, perturbations of annular contraction, and atriogenic leaflet tethering distinguish the pathophysiology of aFMR from the one of ventricular origin. However, no consensus provides recommendations regarding the differential diagnosis and the subsequent management of aFMR. The advent of transcatheter mitral valve repair has paved the way for various treatments including edge-to-edge repair (TEER), mitral annuloplasty, and replacement, with optimistic results on short-medium-term outcome provided by preliminary studies. In parallel, rhythm control of AF for paroxysmal and persistent types, should be pursued to induce reverse remodeling and restoring the normal leaflet coaptation. In this setting, catheter ablation aiming for electrical isolation of the pulmonary veins is the most widely recognized and effective strategy for maintaining sinus rhythm. Nevertheless, arrhythmia-free survival is lower in patients with persistent and long-term persistent AF, leading to the adoption of hybrid strategies combining transcatheter endocardial ablation and thoracoscopic epicardial surgical ablation. This review provides an update on the diagnosis and treatment of aFMR, focusing on available transcatheter approaches that can be performed in the catheterization lab and electrophysiology lab.

1 | Introduction

Mitral regurgitation (MR) is the most common valvular heart disease and it is associated with significant morbidity and mortality worldwide [1], being among the most common cause of heart failure (HF) and recurrent arrhythmias [2]. The relationship between MR and sustained supraventricular tachycardia such as atrial fibrillation (AF) has been deeply investigated thorough the last decade. Indeed, independently of MR, AF is the most frequent rhythm disorder, being observed in 2% of the general population and its prevalence is destined to increase with population aging [3]. AF and MR synergistically induce electroanatomic adverse remodeling of left atrium, fibrosis, and increased volume and annular size, leading to a vicious cycle that worsens both MR and AF. This type of atriogenic MR, labeled atrial functional MR (aFMR) [4], is increasingly reported in patients with AF (varying

from 10% to 40%), particularly, in the elderly, obese patients and in those with HF with preserved EF (HFpEF) [5]. However, the true prevalence of aFMR is difficult to establish due to several differences across studies regarding patient selection, methods, definition of MR severity, and lack of longitudinal data [6]. The impact of aFMR on life expectancy is reported as comparable to degenerative MR and ventricular functional MR (vFMR) [6, 7]. AFMR is also related to increased risk for recurrent HF hospitalizations, high surgical risk and increased mortality in patients with HF [8]. Mitral valve repair by surgical annuloplasty was the historically recommended treatment, reporting low rates of reoperation, mortality, and MR recurrence [9, 10]. Compared to vFMR, lower mortality but higher risk of reoperation is reported [11]. Given its high prevalence in the elderly, less invasive strategies may be valuable alternatives to broaden the eligibility criteria for treatment. Transcatheter approaches allow for a minimally invasive valve repair, annuloplasty, or replacement and its use has rapidly spread out in the last decades, in particular for the treatment of vFMR or in patients at high surgical risk, reporting optimistic results, lowering the in-hospital stay and the rate of complications [12]. On the other hand, since preserving sinus rhythm (SR) through aggressive AF treatment is known to be associated with a lower degree of MR regurgitation and left atrial (LA) myopathy [13], catheter ablation (CA) is currently the preferred strategy to treat aFMR without directly intervening on the valve. Despite the conspicuous number of potential treatments available, the management of aFMR is still uncertain, often underestimated and it lacks a clear indication according to universal guidelines. In this review, we provide a transversal update of the current evidence on possible transcatheter intervention of aFMR and discuss about future perspectives.

2 | Pathophysiology

Functional MR is characteristically not primarily caused by structural changes of the valve apparatus being the epiphenomenon of either left ventricle (LV) or LA dysfunction leading, respectively, to vFMR and aFMR. Functional MR is often a mix of vFMR and aFMR, particularly, in patients with HFrEF and dilated LV. VFMR is linked to LV dilatation and dysfunction with subsequent papillary muscle displacement leading to reduced mitral valve systolic closing forces. On the contrary, aFMR alone is mostly described in patients with hypertrophic, non-dilated LV and preserved ejection fraction (EF), underlying its different etiology, mainly related to mitral annular dilatation caused by chronically elevated LA pressure [14]. The etiopathogenetic mechanism through which AF and annular dilatation causes significant MR without LV dysfunction has been controversial for a long time. The advent of three-dimensional echocardiography (3DE) has provided utmost insights on aFMR due to its capability to explore overtime changes of the whole mitral valve apparatus, including the interplay between LA and the mitral annulus dynamics [15].

2.1 | Adverse Atrial Remodeling

Adverse atrial remodeling is defined as a detrimental change in atrial structure or function that promotes atrial arrhythmias [16]. The close interaction between atrial myopathy, AF, and MR involves multiple determinants such as aging, inflammation, oxidative stress, fibrosis, fat infiltration, and both electrical and autonomic remodeling [17], leading to a vicious circle that includes atrial myopathy and an increased risk of sustained AF and MR worsening [18]. AF and HFpEF are strictly associated and share several risk factors such as hypertension, diabetes mellitus, chronic kidney disease, and obesity [19]. Diastolic dysfunction related to cardiac hypertrophy and rate-related left ventricular incompetency are the main cause leading to exacerbation of each other. Moreover, in patients with AF, diagnostic uncertainties may exist for the diagnosis of HFpEF due to their interrelations influencing test results for echocardiography and natriuretic peptides [20]. Anatomical and functional evaluation of the LA is useful to identify patients at higher risk of incidental AF and ischemic stroke [21–23], as well as to predict reverse remodeling after CA in patients with established AF [24, 25]. The increase of MR was positively related to LA size and development of permanent AF over 65 ± 10 months in a study [26] and rhythm control strategy, either medically or by ablation, led to lesser aFMR progression than the rate control one [27]. Finally, improvement of right chambers parameters, as well as tricuspid regurgitation with SR restoration, was reported in several studies [28, 29], underlining once again their involvement in the natural history of AF, as well as the current underestimation of the role of the right chambers in the etiopathogenesis of aFMR [30].

2.2 | Annular Dysfunction

The mitral annulus is a fibrous structure central to the fibrous skeleton of the heart with critical valvular physiologic functions. Normally it has a dynamic shape folding along the intercommissural axis during the LV systole [31] that allows the mitral valve to download stress of increased LV systolic pressure [32]. AF primarily contributes to the loss of both the saddle-shaped deepening of the mitral annulus and the reduction of the physiological atrial annular contraction in late LV diastole, by up to 40% of its potential, resulting subsequently in the loss of leaflet coaptation until early systole [33]. Moreover, the progression of adverse LA remodeling leads to a replacement of the contractile atrial myocardium with interstitial fibrosis and an increased stress on the mitral leaflets due to the increased tethering distance [34]. Recently, considerable attention has been given to atrial contraction capacity as a measure of atrial muscular cell health. Atrial strain performed by speckle tracking echocardiography or cardiac magnetic resonance is the newest method to evaluate LA contraction, demonstrating higher prognostic power compared to LA volume alone in different cardiac diseases, such as HFrEF [35], HFpEF [5], degenerative MR [36], and vFMR [37]. In aFMR, LA strain has emerged as a robust predictor of outcome in terms of death and HF hospitalizations, overcoming LV function and LA volume [38].

2.3 | Atriogenic Leaflet Tethering and Maladaptive Growth

aFMR can be considered a mix of the Carpentier Types 1 (normal leaflet motion) and 3b (restricted closure during systole) [39]. The typical atriogenic leaflet tethering of aFMR

is caused by the distortion of the posterior annulus secondary to LA dilatation, as the anterior annulus is not modifiable, being attached to the rigid mitro-aortic curtain [40]. Moreover, since the posterior annulus is located into a crest of the LV inlet, LA wall expansion leads the posterior annulus to tilt upward and outside the myocardium, resulting in asymmetric tethering of the posterior leaflet. With the progression of the LA enlargement and the dislocation of the posterior leaflet against the crista of the LV free wall, the angle formed by the intersection of the annular plane with the line that connects the base of the posterior leaflet with the papillary muscle increases, leading to an asymmetric, posteriorly deviated jet of regurgitation. Despite LA dilatation secondary to AF has always been considered the main cause of aFMR, it is not clear why only some patients with moderate to severe LA dilatation develop significative MR. Histopathological studies demonstrated changes of leaflets structure in response to several stresses, including strain and mitral annulus folding [41]. This remodeling is mediated by several cellular signaling factors such as the transforming growth factor-β (TGF-β) family, which are capable of activating and differentiating mitral pluripotent cells into fibroblasts and mesenchymal cells [42]. Leaflets remodeling appears crucial to gap the cooptation deficit caused by annular dilatation [43], however, patients with aFMR are reported to typically exhibit insufficient leaflet remodeling, characterized by a smaller leaflet-to-closure area ratio compared to controls [44]. This compensatory leaflet dilatation is reported to be variable among individuals and studies exploring predictive factors of leaflet remodeling are lacking. Kim et al. found that an annulus area $> 8\,cm^2/m^2$ led to significant MR despite the occurrence of leaflet remodeling while an area between 5 and $8\,cm^2/m^2$ led to a variable MR degree based on the single individual [45].

3 | Treatment of aFMR

aFMR is a consequence of several mechanisms encompassing electroanatomic impairment of the left atrium, mitral annulus enlargement and distortion, and mitral leaflets remodeling. Therefore, different therapeutic approaches could be considered, depending on the leading cause of the MR. According to current ESC and ACC/AHA guidelines, due to the lack of large, prospective studies, aFMR is without a specific treatment [46, 47]. Unlike vFMR, the medical management of aFMR is limited due to the absence of effective drugs tested in ad-hoc trials [48]. Major studies that explored the effects of renin-angiotensin-aldosterone system-inhibitors (RAAS-I) and neprilysin inhibitors (ARNI) on HFpEF patients such as the PRIME trial and PARAMOUNT reported significant improvement in LA size [49]. Nevertheless, changes in annular size were not reported and most studies assessing ARNI did not differentiate aFMR from ventricular vFMR. In the PARAGON-HF, the subgroup of patients deriving most benefit were women, patients with AF, and those with EF $\leq$ 57%. This benefit may be mediated by a reduction of MR severity, albeit not explicitly assessed. In addition, RAAS-I, ARNI, and sodium-glucose co-transporter 2-inhibitors (SGLT2-I) reported beneficial effects on the degree of regurgitation in dedicated studies on vFMR [49, 50].

3.1 | Surgical Approach

Cardiac surgery is the cornerstone of MV repair, in particular, for degenerative MR. Nevertheless, little is known about the treatment of aFMR and despite the lack of universal consensus, ring annuloplasty remains the most common treatment [10, 51, 52]. Available studies showed significant results on MR recurrence at midterm [53, 54], even though the longest one (median 28 ± 17 months of follow-up) reported MR recurrence in 20% of patients [55]. In this study, adverse prognostic factors were larger preoperative LV size and significant leaflet tethering. Type I MR secondary to homogeneous LV dilatation is usually characterized by a non/low grade of symmetrical leaflets tethering that does not compromise the annuloplasty [56]. Nevertheless, in cases of severely dilated LV, mitral annuloplasty alone may not be sufficient to achieve long-term durability. In this setting, other techniques such as leaflet augmentation may be added to the annuloplasty [57]. Finally, since AF and tricuspid regurgitation are common findings in this population, both Maze procedure and tricuspid valve annuloplasty are often associated to mitral annuloplasty, up to 50% of patients in recent series [10].

3.2 | Percutaneous Approach

The prevailing trend of an aging population, coupled with a higher prevalence of comorbidities among individuals with aFMR, along with the conflicting results of surgical treatment has significantly driven the push for transcatheter treatments. Transcatheter techniques target a specific part of the valvular apparatus, therefore, a comprehensive preprocedural assessment to identify the most effective intervention based on aFMR characteristics is necessary. 3DE is the gold standard for both preprocedural analysis of the MR and guiding transcatheter procedure, providing detailed and real-time imaging of the valve anatomy and MR characteristics [58].

3.2.1 | Edge-to-Edge Repair (TEER)

The current most used approach is the TEER by MitraClip (Abbott Vascular) and PASCAL Mitral Valve Repair System (Edwards Lifesciences), even in the absence of randomized prospective trials. Indeed, available data have been extracted from previous large-scale registries enrolling patients with different types of secondary MR. In the retrospective study MITRA-TUNE, the MitraClip effectively reduced the degree of MR in long term and lead to reverse remodeling of cardiac chambers [59]. The main findings of this analysis were also: (i) a high rate of safety and efficacy of the procedure, (ii) a high rate of technical and procedural success, (iii) residual MR independently associated with all-cause death and HF hospitalization, and (iv) reverse remodeling of LA and mitral annular dimensions after TEER during follow-up, which might indicate a durable reduction in residual MR over time. The analysis of the multicenter Spanish MitraClip registry reported an acute reduction in MR from 3/4+ to $\leq$ 2+ in 94% of patients, associated with improved NYHA functional class, which was evident only in patients with functional MR compared to other

etiologies [60]. Another subanalysis exploring 1-year all-cause mortality and new readmissions due to HF after TEER showed similar event rates among patients with primary MR, secondary MR, and mixed MR [61]. Independent predictors included NYHA class, previous surgical revascularization, EuroSCORE II, diabetes mellitus, and LVEF. Accordingly, the subanalysis of the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation, which included 126 patients with atrial fibrillation and HF with preserved ejection fraction (HFpEF) (7.8% of the whole cohort), reported significant improvement in MR and NYHA class at follow-up [63]. In patients with aFMR, the 2-year survival rate was 70.4%, showing no difference compared to non-aFMR and vFMR groups. Strong adverse independent predictors included NYHA Class IV and right ventricular dysfunction. In the multicenter prospective observational study EXPAND, TEER significantly reduced MR, improved functional status, and showed substantial safety from major adverse cardiovascular events (MACE) over a 1-year follow-up [62]. More recently, a retrospective study by Tanaka et al. [64] showed a reduction in death and HF hospitalization in aFMR patients treated with TEER. More specifically, the lower the MR, the lower the rate of the primary endpoint within 1-year. Intriguingly, an increased residual mean pressure gradient ≥ 5 mmHg at discharge correlated with adverse outcome. So far, only one meta-analysis has assessed the echocardiographic and clinical outcomes between patients with aFMR and vFMR treated with TEER, reporting similar clinical outcomes at both short- and long-term follow-up [65]. No differences regarding the rate of postprocedural MR grade ≥ 2, postprocedural NYHA class ≤ 2, or all-cause mortality were found over the study period. Figure 1 shows a case of annular reverse remodeling after MitraClip implantation in a patient affected by severe aFMR. LA changes after TEER are currently largely unknown and only two, small, retrospective studies with this aim have been published so far. In the first, 25 patients undergoing TEER improved LA reservoir and contraction strain as well as 3D volume without changes in conventional parameters over 1-year follow-up [66]. The second study reported reverse remodeling of both left and right chambers after a median of 5.7 months in 24 patients [67]. Intriguingly, a higher degree in right ventricular reverse remodeling was found in aFMR patients treated with TEER compared to patients with other mechanisms of MR. This finding deserves confirmation in future studies.

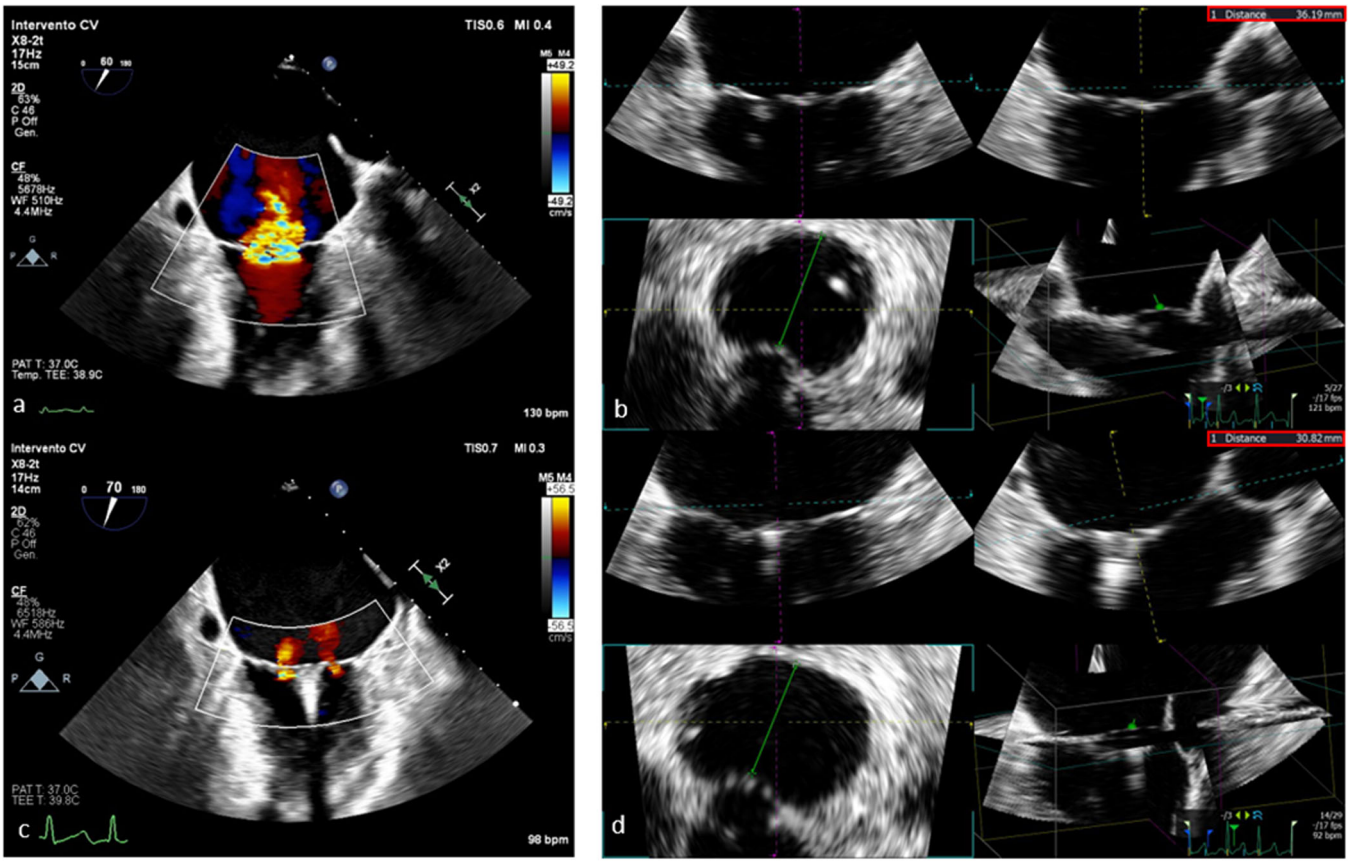


FIGURE 1 | TOE images of a 76-years male affected by severe aFMR due to LA severe dilatation (biplane volume of 85 mL/m^2) and subsequent dilatation of mitral valve annulus (annular area of 14 cm^3, IC diameter of 45 mm, AP diameter of 36 mm). To be noted, leaflet degeneration is frequently encountered in these setting, maybe due to older age and more leaflet stressing. The patient underwent TEER with the implantation of a single MC XTR in central position. (a) IC view of mitral valve during preoperative assessment; (b) shows three-dimensional reconstruction of mitral annulus by using Tomtec-Arena software to measure AP diameter; (c) IC view of mitral valve after implantation of one MC XTR in central position; (d) shows the reconstructed mitral annulus after MC implantation. A significant reduction of AP diameter occurred. aFMR, atrial functional mitral regurgitation; AP, anteroposterior; IC, intercommissural; MC, Mitraclip; MR, mitral regurgitation; TEER, transcatheter edge-to-edge repair, TOE, transesophageal echocardiography. [Color figure can be viewed at wileyonlinelibrary.com]

3.2.2 | Alternative Approaches

In case of anatomical unsuitability for TEER, direct annuloplasty by Cardioband Mitral System (Edwards Lifesciences), Millipede IRIS Ring (Boston Scientific), and indirect annuloplasty by Carillon Mitral Contour System (Cardiac Dimensions) may be valuable alternatives [68, 69]. Direct and indirect annuloplasty are relatively novel techniques compared to TEER with indications limited to specific cases and less clear effectiveness in long-term reduction of MR [17]. Moreover, since the concept of aFMR has only recently gained consideration and interest, few studies have been conducted to evaluate percutaneous annuloplasty in this specific scenario. Rottländer et al. demonstrated a reduction of both anteroposterior mitral valve diameter (4.3 vs. 3.8 cm; $p < 0.05$) and effective regurgitant orifice area in a small group of 15 patients with moderate/severe aFMR [70]. Recently, a comparison between Carillon and MitraClip showed similar reduction of NYHA class at 3- and 12-months in aFMR and whether TEER achieved a lower average MR degree, Carillon obtained a more consistent reverse remodeling of LA, leading to a significant reduction of LA volume [71]. This finding is proof of the feasibility and safety of these devices in HFpEF patients with aFMR but further prospective studies are needed.

3.3 | Rhythm Control Strategy

According to the latest ESC guidelines on AF management, CA is effective in maintaining SR in patients with paroxysmal and persistent AF and it is recommended in symptomatic patients in case of medical therapy failure or as first-line treatment [72]. These recommendations are based on the results of multiple RCTs and metanalysis demonstrating the superiority of AF ablation over antiarrhythmic drugs in terms of freedom from recurrent arrhythmia, improvement in symptoms, exercise capacity, and quality of life [73, 74]. Although the severity of aFMR is commonly mild to moderate, its presence adversely affects the long-term prognosis in patients with AF [75, 76]. As AF is the first cause of aFMR, maintaining SR can improve LA myopathy by contrasting the dilatation of LA and mitral annulus area [14, 77]. Moreover, SR may also carries positive effects directly on the mitral valve complex, including annular contraction and leaflet surface area, contributing to the improvement of regurgitation [79]. Gertz et al. retrospectively compared patients with moderate to severe aFMR and preserved LVEF with a matched AF cohort with trivial and/or mild MR undergoing first AF ablation. Successful CA showed a significant reduction in the severity of MR and LA size [14]. According to another study, CA reduced the severity of both tricuspid and MR and induced 3DE anatomical and functional reverse remodeling of cardiac chambers over 1 year [27]. A case report showed reduction in severity of aFMR after CA ablation [78]. In a study including patients with different MR etiology, CA of paroxysmal AF led to greater improvement in the severity of secondary MR compared to primary MR [80]. Furthermore, patients with functional MR reported lower rate of supraventricular arrhythmias, that was positively associated with the severity of MR, the duration of AF, and LA dimension. Although the relationship between AF and MR progression is even a matter of debate, severe MR is a common cause of AF ablation failure [77]. Therefore, early interventions to preserve SR may lead to better outcomes in preventing the development of aFMR. Recovery of LA electrical and structural functions has been variably described following the resumption of SR [81, 82]. Patients with HF are known to have more advanced atrial remodeling and fibrosis, with a consequent increase in recurrent arrhythmia and poorer prognosis [83]. SR is associated with improved survival in HF but multiple interventions to restore SR may be required [84]. Randomized controlled studies (RCT) of pharmacological rate versus rhythm control strategies in AF and HF have not demonstrated differences, maybe due to the limited efficacy and toxicity of antiarrhythmic medications [85]. This reason may explain why RCT on AF ablation in patients with HF reported improved life expectancy, HF hospitalizations, and functional status [86]. The CAMERA-MRI study explored structural changes of cardiac chambers after AF ablation in patients with tachycardia-induced cardiomyopathy [87]. Compared to medical rate control, AF ablation improved LV function and reduced diffuse fibrosis. Moreover, after 1-year follow-up, significant improvement in right atrium (RA) voltages and reduction of complex atrial electrograms, particularly, in the posterior and septal regions were found in 12 patients [88]. A retrospective study enrolling patients with both aFMR and vFMR (the most part affected by nonischemic cardiomyopathy) reported a lower rate of atrial tachyarrhythmias in patients that improved MR after CA [89]. Interestingly, reverse remodeling after CA encompassed also the LV, while the time of AF, eGFR, and previous stroke were associated with worse results of CA. In another study including patients with both preserved and mildly reduced LVEF, MR improvement after CA was comparable between the aFMR (64%) and vFMR groups (52%, $p = 0.20$) [90]. MR improvement was also related to a reduction in LA volume and mitral annular size in aFMR group and improve in LVEF in vFMR group. Positive predictors were the absence of extensive LA low-voltage areas and small LV diastolic diameter at baseline, respectively. Table 1 reports the main available studies on transcatheter treatment of AF. Since 30%–50% of patients undergoing mitral valve surgery have history of AF [91], concomitant mitral valve surgery and surgical AF ablation by using the MAZE technique is commonly employed and demonstrated safety and efficacy in AF prevention, despite a slight greater risk of needing a permanent pacemaker [92, 93]. In cases of advanced atrial remodeling characterized by severely dilated LA, myocardial fibrosis, valvular AF, significant MR and multiple failure of CA, bipolar ablation by thoracoscopic approach has recently become a valuable option [94]. This hybrid technique combines the advantages of a thoracoscopic surgical ablation (direct visualization of anatomical structures and the possibility to deliver epicardial lesions) and endocardial CA (check line block, confirm pulmonary vein isolation, completing lesions from endocardium or reaching areas not accessible by the surgical ablation). No studies on the effect of hybrid AF ablation on aFMR are available so far. Figure 2 illustrates main characteristics and management of vFMR and aFMR.

4 | Future Perspectives

4.1 | Unclear Fields

The clinical impact of aFMR will escalate overtime and worldwide due to the aging population, the ongoing obesity, and the AF epidemic [95]. However, several aspects of the

TABLE 1 | Main studies that evaluated interventional approaches for aFMR treatment.

Study	Strategy	Year	Type	Aim of study	primary endpoints	secondary endpoints	Results
Wagner et al [10]	Mitral Annuloplasty	2022	Retrospective, observational	Long-term outcome of aFMR population	Recurrence of MR, need for mitral valve re-intervention, and mortality	/	− 75% 5-year survival − 5% MR recurrence (≥ 2+)
MITRA-TUNE (Multicenter Italian Registry Of Transcatheter Treatment Of Atrial Functional Mitral Regurgitation) [59]	TEER	2021	Retrospective, observational, multicentric	Long-term outcome of aFMR population	Technical success, cumulative freedom from all-cause death, cardiac death, HF hospitalization, and the combined all-cause death/HF hospitalization	−Technical success and 30-day device and procedural success. −Change in MR and NYHA class −Entity of LA and mitral annular remodeling	−97% technical success − Residual MR ≥ 2+ and mitral IC annular diameter ≥ 35 mm were independently associated with combined all-cause death/HF hospitalization at the follow-up − Positive reverse remodeling of LA and MVA dimensions
Spanish MitraClip Multicenter Registry [60]	TEER	2021	Prospective, observational, multicentric	Clinical and echocardiographic outcomes in aFMR compared to vFMR, primitive MR, mixed MR	Postprocedural and 12-month MR	− Postprocedural changes in TR and PSAP at 12 months. − Changes in NYHA functional class at 6 and 12 months. − 1-year rates of reintervention − 1-year survival free of all-cause mortality and readmission for HF	− Significant aFMR reduction at 12 months − Nonsignificant decrease of sPAP and TR - Improvement in NYHA functional class at 6- and 12-month -— 1.2% of 1-year MV surgery or TEER redo − 74.9% of 1-year survival free for HF admission
EuroSMR subanalysis [62]	TEER	2022	Prospective, observational, multicentric	Evaluate aspects and outcomes of aFMR patients undergoing TEER and analyze impact of RV dysfunction	MR severity and NYHA class improvement	Comparison of procedural and long-term outcomes according to RV dysfunction	− Significant reduction of MR severity

(Continues)

TABLE 1 | (Continued)

Study	Strategy	Year	Type	Aim of study	primary endpoints	secondary endpoints	Results
							− 87.2% procedural success and 62.4% MR ≤ 1+ − 50% reduction of NYHA functional class III/IV
Expand (Experience of Performance and Safety for the Next Generation of MitraClip Devices) [64]	TEER	2022	Prospective, observational, multicenter	Assess the safety, echocardiographic outcomes, and clinical effectiveness	MR severity < 2+ at 30-day follow-up	30-day and 1-year MR severity, NYHA functional class, KCCQ overall score, HF hospitalization, all-cause mortality, 30-day major adverse events, and 1-year leaflet adverse events	− 100% 1-year MR reduction − 26.6% 1-year KCCQ increase − improvements in NYHA − Rare MACE at 30 days and leaflet adverse events at 1 year
Hamada et al. [65]	TEER	2023	Meta-analysis of observational	Clinical outcomes of TEER in aFMR versus vFMR	//	//	No difference in the rates of post-procedural MR grade ≥ 2, NYHA class ≤ 2, and all-cause mortality at short- and long-term follow-up
Tanaka et al. [63]	TEER	2024	Observational, retrospective	Clinical outcomes of TEER in AFMR	Composite of all-cause mortality and HF hospitalization at 1-year follow-up	/	MPG ≥ 5 mmHg or residual MR > 1+ were related to a higher incidence of the composite outcome
Rottlander et al. [71]	Indirect Annuloplasty versus TEER	2022	Retrospective single-center study	Compare indirect mitral annuloplasty using the Carillon Mitral Contour System and edge-to-edge repair via MitraClip in aFMR	Reduction of regurgitant volume after 12 months in patients with successful Carillon implantation	/	− Comparable reduction of NYHA at 3- and 12-month − Lower average FMR with TEER − Significant reduction of iLAV
Gertz et al. [77]	AF ablation	2011	Retrospective cohort study	Explore aFMR improvement after sinus rhythm restoration	MR reduction at 1-year follow-up	/	Reduction in LA size, annular dimension, and significant MR in SR

(Continues)

TABLE 1 | (Continued)

Study	Strategy	Year	Type	Aim of study	primary endpoints	secondary endpoints	Results
							restoration group (24% vs 82%, $p = 0.005$)
Zhao et al. [75]	AF ablation	2014	Prospective cohort study	Role of MR on long-standing persistent AF ablation	Recurrence of MR and atrial tachycardia	/	Atrial tachycardia recurrence associated with organic MR and regurgitation severity
Sugumar et al. [88]	AF ablation	2019	Subanalysis	Long term follow-up of a subgroup CAMERA MRI trial	Reverse atrial remodeling at 2-year follow-up	/	Reverse electrical and structural atrial remodeling associated with LV reverse remodeling and improved systolic function

Abbreviations: AF, atrial fibrillation; aFMR, atrial functional mitral regurgitation; HF, heart failure; ILAV, indexed left atrial volume; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrium; LV, Left ventricle; MACE, major adverse cardiovascular events; MR, mitral regurgitation; MPG, mitral valve pressure gradient; MVA, mitral valve annulus; PSAP, pulmonary systolic artery pressure; RV, right ventricle; TEER, transcatheter edge-to-edge repair; TR, tricuspidal regurgitation; VFMR, ventricular functional mitral regurgitation.

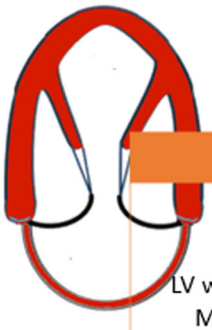
disease are still unclear and potentially suitable for study. Gender differences are even more reported in the natural history of AF-related LA myopathy, characterized by faster and more severe adverse remodeling in females [96]. Further studies are needed to verify if this gender difference is applicable also for aFMR. Moreover, the involvement of the right chambers, in particular, the RA and the tricuspid valve, in the natural history of aFMR deem further investigations, since they might be involved in the risk of AF recurrence after CA.

4.2 | Transcatheter Approaches for Mitral Valve Repair

In recent years, potential therapeutic options including medical therapy, transcatheter mitral valve repair/replacement, or transcatheter/hybrid AF ablation have emerged [97]. Despite several limitations and small sample sizes of available studies, promising results on medium-term effects of transcatheter aFMR repair have been provided. Similarly to AF, the response of aFMR to treatment seems to be time-dependent. For this reason, it is crucial to develop an optimized, universally accepted workflow encompassing early diagnosis and management to prevent LA and annular remodeling. Successful simultaneous direct mitral annuloplasty and TEER were reported in a case report by Braun et al. The author also underlined the capability of the annuloplasty to facilitate clip implantation by approximating the anterior and posterior mitral leaflet [98]. So far, numerous concerns need to be considered in patients with aFMR treated with transcatheter approaches, including the inability to completely eliminate the regurgitation, operator dependency, and lack of long-term durability data. Transcatheter annuloplasty and mitral valve replacement are also valuable alternatives but still not sufficiently investigated for the treatment of aFMR.

4.3 | Atrial Fibrillation Treatment

So far, rhythm control of AF has been demonstrated to be superior to rate control in preventing LA remodeling and MR progression to an irreversible stage and should be the first choice whenever applicable. Given the worldwide epidemic of AF, the need to break down the waiting lists for AF ablation is of paramount importance. Therefore, single-shot techniques have been developed providing promising results in term of effectiveness, procedure times, and rate of complications compared to point-by-point CA. To date, radiofrequency (RF) and cryoablation are the most used techniques and have demonstrated similar results regarding the long-term efficacy and safety [99]. Pulsed field ablation (PFA) is a novel single-shot technique with similar efficacy profile to RF and cryoablation but higher safety [100]. However, no comparisons among different energy sources have been performed to investigate their potential effects on LA myopathy and aFMR. It is logical to think that the most effective technology in aFMR prevention is the one that keeps SR longer. In cases of persistent AF, pulmonary vein isolation effectiveness is significantly reduced, and further techniques to compartmentalize the LA (i.e., posterior wall and LA appendage isolation) or functional mapping to identify driver regions [101].



vFMR		aFMR
LVEF <50% LV dilatation LV wall motion abnormalities Mitral annulus dilatation Papillary muscle displacement Single/Bileaflet tethering Central/eccentric jet Increased leaflets tenting	**IMAGING CHARACTERISTICS**	LVEF >50%, Normal LV volume LA dilatation Mitral annulus dilatation Bileaflet tethering Central Jet Flattened leaflets Reduced leaflets tenting
HFrEF	**HEART FAILURE**	HFpEF
DCM	**UNDERLYING PATHOLOGY**	NON DCM AF
Four pillars Diuretics	**MEDICAL THERAPY**	Antiarrhythmic drugs SGLT2i Diuretics
TEER ✓Improved functional class ✓Reduced HF hospitalization ✓Improved mortality ✓Reverse remodeling ANNULOPLASTY (controversial data) TMVR (more data are needed)	**TRANSCATHETER TREATMENT**	TEER ✓Improved functional class ✓Reduced HF hospitalization **X** Improved mortality ✓Reverse remodeling ANNULOPLASTY (No data) TMVR (No data) AF ABLATION

FIGURE 2 | Comparison between vFMR and aFMR. [Color figure can be viewed at wileyonlinelibrary.com]

5 | Conclusions

AFMR diagnosis is increasing and is associated with worse outcome of HF, persistency of AF, and reduced quality of life. A number of potential treatments are currently available, encompassing medical management, mitral valve repair, and AF prevention. This condition highlights that the interplay of different figures within the cardiological team including cardiologists specialized in HF, interventional cardiologists, and cardiac surgeons is deemed necessary to establish the best personalized approach for each patient.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. E. J. Benjamin, P. Muntner, A. Alonso, et al., "Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association," *Circulation* 139 (2019): e56–e528, https://doi.org/10.1161/cir.0000000000000659.

2. E. Anter, M. Jessup, and D. J. Callans, "Atrial Fibrillation and Heart Failure," *Circulation* 119 (2009): 2516–2525, https://doi.org/10.1161/CIRCULATIONAHA.108.821306.

3. M. Zoni-Berisso, F. Lercari, T. Carazza, and S. Domenicucci, "Epidemiology of Atrial Fibrillation: European Perspective," *Clinical Epidemiology* 6 (2014): 213–220, https://doi.org/10.2147/clep.S47385.

4. W. A. Zoghbi, R. A. Levine, F. Flachskampf, et al., "Atrial Functional Mitral Regurgitation: A JACC: Cardiovascular Imaging Expert Panel Viewpoint," *JACC. Cardiovascular imaging* 15 (2022): 1870–1882, https://doi.org/10.1016/j.jcmg.2022.08.016.

5. M. Tamargo, M. Obokata, Y. N. V. Reddy, et al., "Functional Mitral Regurgitation and Left Atrial Myopathy in Heart Failure With Preserved Ejection Fraction," *European Journal of Heart Failure* 22 (2020): 489–498, https://doi.org/10.1002/ejhf.1699.

6. V. Dziadzko, M. Dziadzko, J. R. Medina-Inojosa, et al., "Causes and Mechanisms of Isolated Mitral Regurgitation in the Community: Clinical Context and Outcome," *European Heart Journal* 40 (2019): 2194–2202, https://doi.org/10.1093/eurheartj/ehz314.

7. C. Saito, Y. Minami, K. Arai, et al., "Prevalence, Clinical Characteristics, and Outcome of Atrial Functional Mitral Regurgitation in

Hospitalized Heart Failure Patients With Atrial Fibrillation," *Journal of Cardiology* 72 (2018): 292–299, https://doi.org/10.1016/j.jjcc.2018.04.002.

8. O. Mesi, M. M. Gad, A. D. Crane, et al., "Severe Atrial Functional Mitral Regurgitation," *JACC: Cardiovascular Imaging* 14 (2021): 797–808, https://doi.org/10.1016/j.jcmg.2021.02.008.

9. F. Nappi, S. S. Avatar Singh, O. Santana, and C. G. Mihos, "Functional Mitral Regurgitation: An Overview for Surgical Management Framework," *Journal of Thoracic Disease* 10 (2018): 4540–4555.

10. C. M. Wagner, A. A. Brescia, T. Watt, et al., "Surgical Strategy and Outcomes for Atrial Functional Mitral Regurgitation: All Functional Mitral Regurgitation Is Not the Same!," *Journal of Thoracic and Cardiovascular Surgery* 167 (2024): 647–655, https://doi.org/10.1016/j.jtcvs.2022.02.056.

11. S. A. Hirji, C. L. Cote, H. Javadikasgari, A. Malarczyk, S. McGurk, and T. Kaneko, "Atrial Functional Versus Ventricular Functional Mitral Regurgitation: Prognostic Implications," *Journal of Thoracic and Cardiovascular Surgery* 164 (2022): 1808–1815.e4, https://doi.org/10.1016/j.jtcvs.2020.12.098.

12. A. Alperi, J. F. Granada, M. Bernier, F. Dagenais, and J. Rodés-Cabau, "Current Status and Future Prospects of Transcatheter Mitral Valve Replacement," *Journal of the American College of Cardiology* 77 (2021): 3058–3078, https://doi.org/10.1016/j.jacc.2021.04.051.

13. S. Nishino, N. Watanabe, K. Ashikaga, et al., "Reverse Remodeling of the Mitral Valve Complex After Radiofrequency Catheter Ablation for Atrial Fibrillation," *Circulation: Cardiovascular Imaging* 12 (2019): e009317, https://doi.org/10.1161/CIRCIMAGING.119.009317.

14. Z. M. Gertz, A. Raina, L. Saghy, et al., "Evidence of Atrial Functional Mitral Regurgitation Due to Atrial Fibrillation," *Journal of the American College of Cardiology* 58 (2011): 1474–1481, https://doi.org/10.1016/j.jacc.2011.06.032.

15. G. Valocik, O. Kamp, and C. Visser, "Three-Dimensional Echocardiography in Mitral Valve Disease," *European Journal of Echocardiography* 6 (2005): 443–454, https://doi.org/10.1016/j.euje.2005.02.007.

16. S. Nattel and M. Harada, "Atrial Remodeling and Atrial Fibrillation," *Journal of the American College of Cardiology* 63 (2014): 2335–2345, https://doi.org/10.1016/j.jacc.2014.02.555.

17. M. J. Shen, R. Arora, and J. Jalife, "Atrial Myopathy," *JACC. Basic to Translational Science* 4 (2019): 640–654, https://doi.org/10.1016/j.jacbts.2019.05.005.

18. Y. C. Chen, A. Voskoboinik, A. L. Gerche, T. H. Marwick, and J. R. McMullen, "Prevention of Pathological Atrial Remodeling and Atrial Fibrillation," *Journal of the American College of Cardiology* 77 (2021): 2846–2864, https://doi.org/10.1016/j.jacc.2021.04.012.

19. I. C. Van Gelder, M. Rienstra, K. V. Bunting, et al., "2024 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration With the European Association for Cardio-Thoracic Surgery (EACTS)," *European Heart Journal* 45 (2024): 3314–3414, https://doi.org/10.1093/eurheartj/ehae176.

20. T. A. McDonagh, M. Metra, M. Adamo, et al., "2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure," *European Heart Journal* 42 (2021): 3599–3726, https://doi.org/10.1093/eurheartj/ehab368.

21. D. J. Lim, B. Ambale-Ventakesh, M. R. Ostovaneh, et al., "Change in Left Atrial Function Predicts Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis," *European Heart Journal - Cardiovascular Imaging* 20 (2019): 979–987, https://doi.org/10.1093/ehjci/jez176.

22. M. Schaaf, P. Andre, M. Altman, et al., "Left Atrial Remodelling Assessed By 2D and 3D Echocardiography Identifies Paroxysmal Atrial Fibrillation," *European Heart Journal—Cardiovascular Imaging* 18 (2017): 46–53, https://doi.org/10.1093/ehjci/jew028.

23. F. Pathan, E. Sivaraj, K. Negishi, et al., "Use of Atrial Strain to Predict Atrial Fibrillation After Cerebral Ischemia," *JACC. Cardiovascular imaging* 11 (2018): 1557–1565, https://doi.org/10.1016/j.jcmg.2017.07.027.

24. I. E. Hof, B. K. Velthuis, S. M. Chaldoupi, et al., "Pulmonary Vein Antrum Isolation Leads to a Significant Decrease of Left Atrial Size," *Europace* 13 (2010): 371–375, https://doi.org/10.1093/europace/euq464.

25. J. V. Wylie, D. C. Peters, V. Essebag, W. J. Manning, M. E. Josephson, and T. H. Hauser, "Left Atrial Function and Scar After Catheter Ablation of Atrial Fibrillation," *Heart rhythm: the official journal of the Heart Rhythm Society* 5 (2008): 656–662, https://doi.org/10.1016/j.hrthm.2008.02.008.

26. L. Pype, L. Embrechts, B. Cornez, et al., "Long-Term Effect of Atrial Fibrillation on the Evolution of Mitral and Tricuspid Valve Regurgitation," *Acta Cardiologica* 75 (2020): 639–647, https://doi.org/10.1080/00015385.2019.1649339.

27. L. Soulat-Dufour, S. Lang, K. Addetia, et al., "Restoring Sinus Rhythm Reverses Cardiac Remodeling and Reduces Valvular Regurgitation in Patients With Atrial Fibrillation," *Journal of the American College of Cardiology* 79 (2022): 951–961, https://doi.org/10.1016/j.jacc.2021.12.029.

28. L. Welikovitch, G. Lafreniere, G. W. Burggraf, and A. J. Sanfilippo, "Change in Atrial Volume Following Restoration of Sinus Rhythm in Patients With Atrial Fibrillation: A Prospective Echocardiographic Study," *Canadian Journal of Cardiology* 10 (1994): 993–996.

29. A. T. M. Gosselink, H. J. G. M. Crijns, H. P. M. Hamer, H. Hillege, and K. I. Lie, "Changes in Left and Right Atrial Size After Cardioversion of Atrial Fibrillation: Role of Mitral Valve Disease," *Journal of the American College of Cardiology* 22 (1993): 1666–1672, https://doi.org/10.1016/0735-1097(93)90593-p.

30. E. Xie, R. Yu, B. Ambale-Venkatesh, et al., "Association of Right Atrial Structure With Incident Atrial Fibrillation: A Longitudinal Cohort Cardiovascular Magnetic Resonance Study From the Multi-Ethnic Study of Atherosclerosis (MESA)," *Journal of Cardiovascular Magnetic Resonance* 22 (2020): 36, https://doi.org/10.1186/s12968-020-00631-1.

31. J. J. Silbiger and R. Bazaz, "Contemporary Insights into the Functional Anatomy of the Mitral Valve," *American Heart Journal* 158 (2009): 887–895, https://doi.org/10.1016/j.ahj.2009.10.014.

32. I. S. Salgo, J. H. Gorman, R. C. Gorman, et al., "Effect of Annular Shape on Leaflet Curvature in Reducing Mitral Leaflet Stress," *Circulation* 106 (2002): 711–717, https://doi.org/10.1161/01.cir.0000025426.39426.83.

33. Z. Tang, Y. T. Fan, Y. Wang, C. N. Jin, K. W. Kwok, and A. P. W. Lee, "Mitral Annular and Left Ventricular Dynamics in Atrial Functional Mitral Regurgitation: A Three-Dimensional and Speckle-Tracking Echocardiographic Study," *Journal of the American Society of Echocardiography* 32 (2019): 503–513, https://doi.org/10.1016/j.echo.2018.11.009.

34. B. Li, F. Luo, X. Luo, et al., "Effects of Atrial Fibrosis Induced By Mitral Regurgitation on Atrial Electrophysiology and Susceptibility to Atrial Fibrillation in Pigs," *Cardiovascular Pathology* 40 (2019): 32–40, https://doi.org/10.1016/j.carpath.2019.01.006.

35. E. Carluccio, P. Biagioli, A. Mengoni, et al., "Left Atrial Reservoir Function and Outcome in Heart Failure With Reduced Ejection Fraction," *Circulation: Cardiovascular Imaging* 11 (2018): e007696, https://doi.org/10.1161/CIRCIMAGING.118.007696.

36. J. Stassen, A. L. van Wijngaarden, S. C. Butcher, et al., "Prognostic Value of Left Atrial Reservoir Function in Patients With Severe Primary Mitral Regurgitation Undergoing Mitral Valve Repair," *European Heart Journal—Cardiovascular Imaging* 24 (2022): 142–151, https://doi.org/10.1093/ehjci/jeac058.

37. J. Stassen, F. Namazi, P. van der Bijl, et al., "Left Atrial Reservoir Function and Outcomes in Secondary Mitral Regurgitation," *Journal of the American Society of Echocardiography* 35 (2022): 477–485.e3, https://doi.org/10.1016/j.echo.2022.01.007.

38. D. Cramariuc, H. Alfraidi, Y. Nagata, et al., "Atrial Dysfunction in Significant Atrial Functional Mitral Regurgitation: Phenotypes and Prognostic Implications," *Circulation: Cardiovascular Imaging* 16 (2023): e015089, https://doi.org/10.1161/circimaging.122.015089.

39. Y. Abe, Y. Takahashi, and T. Shibata, "Functional Mitral Regurgitation, Updated: Ventricular or Atrial?," *Journal of Echocardiography* 18 (2020): 1–8, https://doi.org/10.1007/s12574-019-00453-w.

40. J. J. Silbiger, "Does Left Atrial Enlargement Contribute to Mitral Leaflet Tethering in Patients With Functional Mitral Regurgitation? Proposed Role of Atriogenic Leaflet Tethering," *Echocardiography* 31 (2014): 1310–1311, https://doi.org/10.1111/echo.12629.

41. J. P. Dal-Bianco, E. Aikawa, J. Bischoff, et al., "Active Adaptation of the Tethered Mitral Valve: Insights Into a Compensatory Mechanism for Functional Mitral Regurgitation," *Circulation* 120 (2009): 334–342, https://doi.org/10.1161/circulationaha.108.846782.

42. E. J. Armstrong and J. Bischoff, "Heart Valve Development: Endothelial Cell Signaling and Differentiation," *Circulation Research* 95 (2004): 459–470, https://doi.org/10.1161/01.RES.0000141146.95728.da.

43. L. Ring, D. P. Dutka, F. C. Wells, S. P. Fynn, L. M. Shapiro, and B. S. Rana, "Mechanisms of Atrial Mitral Regurgitation: Insights Using 3D Transoesophageal Echo," *European Heart Journal—Cardiovascular Imaging* 15 (2014): 500–508, https://doi.org/10.1093/ehjci/jet191.

44. N. Kagiyama, A. Hayashida, M. Toki, et al., "Insufficient Leaflet Remodeling in Patients With Atrial Fibrillation," *Circulation: Cardiovascular Imaging* 10 (2017): e005451, https://doi.org/10.1161/CIRCIMAGING.116.005451.

45. D. H. Kim, R. Heo, M. D. Handschumacher, et al., "Mitral Valve Adaptation to Isolated Annular Dilation," *JACC: Cardiovascular Imaging* 12 (2019): 665–677, https://doi.org/10.1016/j.jcmg.2017.09.013.

46. A. Vahanian, F. Beyersdorf, F. Praz, et al., "2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease," *European Heart Journal* 43 (2022): 561–632, https://doi.org/10.1093/eurheartj/ehab395.

47. C. M. Otto, R. A. Nishimura, R. O. Bonow, et al., "2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation* 143 (2021): e72–e227, https://doi.org/10.1161/cir.0000000000000923.

48. T. A. McDonagh, M. Metra, M. Adamo, et al., "2023 Focused Update of the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure," *European Heart Journal* 44 (2023): 3627–3639, https://doi.org/10.1093/eurheartj/ehad195.

49. D.-H. Kang, S. J. Park, S. H. Shin, et al., "Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation," *Circulation* 139 (2019): 1354–1365, https://doi.org/10.1161/CIRCULATIONAHA.118.037077.

50. Y. W. Lin, C. Y. Chen, J. Y. Shih, et al., "Dapagliflozin Improves Cardiac Hemodynamics and Mitigates Arrhythmogenesis in Mitral Regurgitation-Induced Myocardial Dysfunction," *Journal of the American Heart Association* 10 (2021): e019274, https://doi.org/10.1161/JAHA.120.019274.

51. Y. Fan, S. Wan, R. H. L. Wong, and A. P. W. Lee, "Atrial Functional Mitral Regurgitation: Mechanisms and Surgical Implications," *Asian Cardiovascular and Thoracic Annals* 28 (2020): 421–426, https://doi.org/10.1177/0218492320941388.

52. A. Amabile, S. Fereydooni, M. Mori, et al., "Variable Definitions and Treatment Approaches for Atrial Functional Mitral Regurgitation: A Scoping Review of the Literature," *Journal of Cardiac Surgery* 37 (2022): 1182–1191, https://doi.org/10.1111/jocs.16312.

53. H. A. Vohra, R. N. Whistance, A. Magan, S. A. Sadeque, and S. A. Livesey, "Mitral Valve Repair for Severe Mitral Regurgitation Secondary to Lone Atrial Fibrillation," *European Journal of Cardio-Thoracic Surgery* 42 (2012): 634–637, https://doi.org/10.1093/ejcts/ezs029.

54. Y. Takahashi, Y. Abe, Y. Sasaki, et al., "Mitral Valve Repair for Atrial Functional Mitral Regurgitation in Patients With Chronic Atrial Fibrillation," *Interactive Cardiovascular and Thoracic Surgery* 21 (2015): 163–168, https://doi.org/10.1093/icvts/ivv119.

55. T. Sakaguchi, T. Totsugawa, K. Orihashi, et al., "Mitral Annuloplasty for Atrial Functional Mitral Regurgitation in Patients With Chronic Atrial Fibrillation," *Journal of Cardiac Surgery* 34 (2019): 767–773, https://doi.org/10.1111/jocs.14136.

56. T. Salvatore, F. Ricci, G. D. Dangas, et al., "Selection of the Optimal Candidate to MitraClip for Secondary Mitral Regurgitation: Beyond Mitral Valve Morphology," *Frontiers in Cardiovascular Medicine* 8 (2021), https://doi.org/10.3389/fcvm.2021.585415.

57. A. P. W. Lee, M. Acker, S. H. Kubo, et al., "Mechanisms of Recurrent Functional Mitral Regurgitation After Mitral Valve Repair in Non-ischemic Dilated Cardiomyopathy: Importance of Distal Anterior Leaflet Tethering," *Circulation* 119 (2009): 2606–2614, https://doi.org/10.1161/circulationaha.108.796151.

58. E. Agricola, F. Meucci, F. Ancona, A. Pardo Sanz, and J. L. Zamorano, "Echocardiographic Guidance in Transcatheter Structural Cardiac Interventions," *EuroIntervention* 17 (2022): 1205–1226, https://doi.org/10.4244/eij-d-21-00582.

59. A. Popolo Rubbio, L. Testa, C. Grasso, et al., "Transcatheter Edge-To-Edge Mitral Valve Repair in Atrial Functional Mitral Regurgitation: Insights From the Multi-Center MITRA-TUNE Registry," *International Journal of Cardiology* 349 (2022): 39–45, https://doi.org/10.1016/j.ijcard.2021.11.027.

60. T. Benito-González, F. Carrasco-Chinchilla, R. Estévez-Loureiro, et al., "Clinical and Echocardiographic Outcomes of Transcatheter Mitral Valve Repair in Atrial Functional Mitral Regurgitation," *International Journal of Cardiology* 345 (2021): 29–35, https://doi.org/10.1016/j.ijcard.2021.09.056.

61. I. Pascual, D. Arzamendi, F. Carrasco-Chinchilla, et al., "Reparación Mitral Transcatéter Según La Etiología De La Insuficiencia Mitral: Datos De La Vida Real Procedentes Del Registro Español De Mitraclip," *Revista española de cardiología* 73 (2020): 643–651, https://doi.org/10.1016/j.rec.2019.07.018.

62. P. Doldi, L. Stolz, M. Orban, et al., "Transcatheter Mitral Valve Repair in Patients With Atrial Functional Mitral Regurgitation," *JACC: Cardiovascular Imaging* 15 (2022): 1843–1851, https://doi.org/10.1016/j.jcmg.2022.05.009.

63. N. Sodhi, F. M. Asch, T. Ruf, et al., "Clinical Outcomes With Transcatheter Edge-to-Edge Repair in Atrial Functional MR From the EXPAND Study," *JACC: Cardiovascular Interventions* 15 (2022): 1723–1730, https://doi.org/10.1016/j.jcin.2022.07.023.

64. T. Tanaka, A. Sugiura, J. Vogelhuber, et al., "Outcomes of Transcatheter Edge-to-Edge Repair for Atrial Functional Mitral Regurgitation," *EuroIntervention* 20 (2024): e250–e260, https://doi.org/10.4244/eij-d-23-00819.

65. S. Hamada, H. Ueyama, T. Aikawa, et al., "Outcomes of Transcatheter Edge-to-Edge Repair for Atrial Functional Mitral Regurgitation: A Meta-Analysis of Observational Studies," *Catheterization and Cardiovascular Interventions* 102 (2023): 751–760, https://doi.org/10.1002/ccd.30806.

66. C. Toprak, G. Kahveci, A. Kilicgedik, et al., "Left Atrial Remodeling in Patients Undergoing Percutaneous Mitral Valve Repair With the Mitraclip System: An Advanced Echocardiography Study," *Echocardiography* 33 (2016): 1504–1511, https://doi.org/10.1111/echo.13288.

67. A. Albini, M. Passiatore, J. F. Imberti, et al., "Ventricular and Atrial Remodeling After Transcatheter Edge-to-Edge Repair: A Pilot Study,"

Journal of Personalized Medicine 12 (2022): 1916, https://doi.org/10.3390/jpm12111916.

68. M. Ali, S. S. Shreenivas, D. N. Pratt, D. R. Lynch, and D. J. Kereiakes, "Percutaneous Interventions for Secondary Mitral Regurgitation," *Circulation: Cardiovascular Interventions* 13 (2020): e008998, https://doi.org/10.1161/CIRCINTERVENTIONS.120.008998.

69. S. Deferm, P. B. Bertrand, F. H. Verbrugge, et al., "Atrial Functional Mitral Regurgitation," *Journal of the American College of Cardiology* 73 (2019): 2465–2476, https://doi.org/10.1016/j.jacc.2019.02.061.

70. D. Rottländer, M. Gödde, H. Degen, A. Ögütcü, and M. Haude, "Percutaneous Coronary Sinus–Based Mitral Valve Annuloplasty in Atrial Functional Mitral Regurgitation," *JACC: Cardiovascular Interventions* 13 (2020): 2947–2949, https://doi.org/10.1016/j.jcin.2020.09.019.

71. D. Rottländer, M. Golabkesh, H. Degen, A. Ögütcü, M. Saal, and M. Haude, "Mitral Valve Edge-to-Edge Repair Versus Indirect Mitral Valve Annuloplasty in Atrial Functional Mitral Regurgitation," *Catheterization and Cardiovascular Interventions* 99 (2022): 1839–1847, https://doi.org/10.1002/ccd.30157.

72. G. Hindricks, T. Potpara, N. Dagres, et al., "2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration With the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed With the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC," *European Heart Journal* 42 (2021): 373–498, https://doi.org/10.1093/eurheartj/ehaa612.

73. M. K. Turagam, D. Musikantow, W. Whang, et al., "Assessment of Catheter Ablation or Antiarrhythmic Drugs for First-Line Therapy of Atrial Fibrillation: A Meta-Analysis of Randomized Clinical Trials," *JAMA Cardiology* 6 (2021): 697–705, https://doi.org/10.1001/jamacardio.2021.0852.

74. D. L. Packer, D. B. Mark, R. A. Robb, et al., "Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial," *Journal of the American Medical Association* 321 (2019): 1261–1274, https://doi.org/10.1001/jama.2019.0693.

75. L. Zhao, W. Jiang, L. Zhou, et al., "The Role of Valvular Regurgitation in Catheter Ablation Outcomes of Patients With Long-Standing Persistent Atrial Fibrillation," *Europace* 16 (2014): 848–854, https://doi.org/10.1093/europace/eut252.

76. Y. Abe, K. Akamatsu, K. Ito, et al., "Prevalence and Prognostic Significance of Functional Mitral and Tricuspid Regurgitation Despite Preserved Left Ventricular Ejection Fraction in Atrial Fibrillation Patients," *Circulation Journal* 82 (2018): 1451–1458, https://doi.org/10.1253/circj.CJ-17-1334.

77. Z. M. Gertz, A. Raina, S. E. Mountantonakis, et al., "The Impact of Mitral Regurgitation on Patients Undergoing Catheter Ablation of Atrial Fibrillation," *Europace* 13 (2011): 1127–1132, https://doi.org/10.1093/europace/eur098.

78. S. Nishino, N. Watanabe, K. Ashikaga, et al., "Reverse Remodeling of the Mitral Valve Complex After Radiofrequency Catheter Ablation for Atrial Fibrillation: A Serial 3-Dimensional Echocardiographic Study," *Circulation: Cardiovascular Imaging* 12 (2019): e009317, https://doi.org/10.1161/CIRCIMAGING.119.009317.

79. E. O. Udo and R. J. Hassink, "Pulmonary Vein Isolation as a Treatment for Severe Atrial Functional Mitral Regurgitation in a Patient With Atrial Fibrillation," *International Journal of Cardiology* 175 (2014): 578–579, https://doi.org/10.1016/j.ijcard.2014.05.025.

80. M. Takigawa, T. Kuwahara, A. Takahashi, et al., "The Mechanism of Mitral Regurgitation Assessed by Preprocedural Echocardiography Is Associated With the Outcome of Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation," *Journal of Interventional Cardiac Electrophysiology* 46 (2016): 299–306, https://doi.org/10.1007/s10840-016-0123-8.

81. A. W. Teh, P. M. Kistler, G. Lee, et al., "Electroanatomic Remodeling of the Left Atrium in Paroxysmal and Persistent Atrial Fibrillation Patients Without Structural Heart Disease," *Journal of Cardiovascular Electrophysiology* 23 (2012): 232–238, https://doi.org/10.1111/j.1540-8167.2011.02178.x.

82. A. W. Teh, P. M. Kistler, G. Lee, et al., "Long-Term Effects of Catheter Ablation for Lone Atrial Fibrillation: Progressive Atrial Electroanatomic Substrate Remodeling Despite Successful Ablation," *Heart Rhythm* 9 (2012): 473–480, https://doi.org/10.1016/j.hrthm.2011.11.013.

83. S. Prabhu, A. Voskoboinik, A. J. A. McLellan, et al., "Biatrial Electrical and Structural Atrial Changes in Heart Failure," *JACC: Clinical Electrophysiology* 4 (2018): 87–96, https://doi.org/10.1016/j.jacep.2017.08.012.

84. M. Talajic, P. Khairy, S. Levesque, et al., "Maintenance of Sinus Rhythm and Survival in Patients With Heart Failure and Atrial Fibrillation," *Journal of the American College of Cardiology* 55 (2010): 1796–1802, https://doi.org/10.1016/j.jacc.2010.01.023.

85. D. Roy, M. Talajic, S. Nattel, et al., "Rhythm Control Versus Rate Control for Atrial Fibrillation and Heart Failure," *New England Journal of Medicine* 358 (2008): 2667–2677, https://doi.org/10.1056/NEJMoa0708789.

86. N. F. Marrouche, J. Brachmann, D. Andresen, et al., "Catheter Ablation for Atrial Fibrillation With Heart Failure," *New England Journal of Medicine* 378 (2018): 417–427, https://doi.org/10.1056/NEJMoa1707855.

87. S. Prabhu, B. T. Costello, A. J. Taylor, et al., "Regression of Diffuse Ventricular Fibrosis Following Restoration of Sinus Rhythm With Catheter Ablation inPatients With Atrial Fibrillation and Systolic Dysfunction," *JACC: Clinical Electrophysiology* 4 (2018): 999–1007, https://doi.org/10.1016/j.jacep.2018.04.013.

88. H. Sugumar, S. Prabhu, A. Voskoboinik, et al., "Atrial Remodeling Following Catheter Ablation for Atrial Fibrillation-Mediated Cardiomyopathy," *JACC: Clinical Electrophysiology* 5 (2019): 681–688, https://doi.org/10.1016/j.jacep.2019.03.009.

89. J. T. Wu, J. A. B. Zaman, H. Y. Yakupoglu, et al., "Catheter Ablation of Atrial Fibrillation in Patients With Functional Mitral Regurgitation and Left Ventricular Systolic Dysfunction," *Frontiers in Cardiovascular Medicine* 7 (2020): 596491, https://doi.org/10.3389/fcvm.2020.596491.

90. M. Masuda, K. Sekiya, M. Asai, et al., "Influence of Catheter Ablation for Atrial Fibrillation on Atrial and Ventricular Functional Mitral Regurgitation," *ESC Heart Failure* 9 (2022): 1901–1913, https://doi.org/10.1002/ehf2.13896.

91. R. Lee, P. M. McCarthy, E. C. Wang, et al., "Midterm Survival in Patients Treated for Atrial Fibrillation: A Propensity-Matched Comparison to Patients Without a History of Atrial Fibrillation," *Journal of Thoracic and Cardiovascular Surgery* 143 (2012): 1341–1351, discussion 1350-1341, https://doi.org/10.1016/j.jtcvs.2012.02.006.

92. A. M. Gillinov, A. C. Gelijns, M. K. Parides, et al., "Surgical Ablation of Atrial Fibrillation during Mitral-Valve Surgery," *New England Journal of Medicine* 372 (2015): 1399–1409, https://doi.org/10.1056/NEJMoa1500528.

93. J. Chen, Y. Wang, M. Lv, et al., "Mitral Valve Repair and Surgical Ablation for Atrial Functional Mitral Regurgitation," *Annals of Translational Medicine* 8 (2020): 1420, https://doi.org/10.21037/atm-20-2958.

94. M. Marini, L. Pannone, D. G. Della Rocca, et al., "Hybrid Ablation of Atrial Fibrillation: A Contemporary Overview," *Journal of Cardiovascular Development and Disease* 9 (2022): 302, https://doi.org/10.3390/jcdd9090302.

95. A. Preda, F. Carbone, A. Tirandi, F. Montecucco, and L. Liberale, "Obesity Phenotypes and Cardiovascular Risk: From Pathophysiology

to Clinical Management," *Reviews in Endocrine and Metabolic Disorders* 24 (2023): 901–919, https://doi.org/10.1007/s11154-023-09813-5.

96. A. Preda, F. Giordano, V. Giani, F. Guarracini, and P. Mazzone, "Accelerated Adverse Atrial Remodeling in Women With Atrial Fibrillation: Results From Studies Using Electroanatomic Mapping Systems," *American Journal of Cardiology* 203 (2023): 524–525, https://doi.org/10.1016/j.amjcard.2023.07.124.

97. S. Farhan, J. J. Silbiger, J. L. Halperin, et al., "Pathophysiology, Echocardiographic Diagnosis, and Treatment of Atrial Functional Mitral Regurgitation," *Journal of the American College of Cardiology* 80 (2022): 2314–2330, https://doi.org/10.1016/j.jacc.2022.09.046.

98. D. Braun, M. Näbauer, S. Massberg, and J. Hausleiter, "One-Stop Shop: Simultaneous Direct Mitral Annuloplasty and Percutaneous Mitral Edge-To-Edge Repair in a Patient With Severe Mitral Regurgitation," *Catheterization and Cardiovascular Interventions* 93 (2019): E318–e319, https://doi.org/10.1002/ccd.27848.

99. S. S. Balasubramanian, S. Siddamsetti, and S. Gautam, "Abstract 12646: Cryoablation vs. Radiofrequency Ablation in Persistent AFib: An Updated Meta-Analysis," *Circulation* 144 (2021): A12646, https://doi.org/10.1161/circ.144.suppl_1.12646.

100. R. V. Davalos, L. M. Mir, and B. Rubinsky, "Tissue Ablation With Irreversible Electroporation," *Annals of Biomedical Engineering* 33 (2005): 223–231, https://doi.org/10.1007/s10439-005-8981-8.

101. A. Verma, C. Jiang, T. R. Betts, et al., "Approaches to Catheter Ablation for Persistent Atrial Fibrillation," *New England Journal of Medicine* 372 (2015): 1812–1822, https://doi.org/10.1056/NEJMoa1408288.