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Outcomes of transcatheter edge-to-edge repair for atrial functional mitral regurgitation

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KEYWORDS

- Mitral regurgitation
- Mitral valve disease
- Mitral valve repair

Abstract

Background: Prognostic benefits of transcatheter edge-to-edge repair (TEER) remain unclear in patients with atrial functional mitral regurgitation (AFMR).

Aims: We aimed to investigate clinical outcomes of TEER for AFMR.

Methods: We retrospectively classified FMR patients undergoing TEER into AFMR or ventricular FMR (VFMR). Residual MR ≤1+ at discharge was considered as optimal MR reduction, and elevated mean mitral valve pressure gradient (MPG) was defined as MPG ≥5 mmHg at discharge. The primary outcome was a composite of all-cause mortality and hospitalization due to heart failure within one year.

Results: Of 441 FMR patients, 125 patients were considered as AFMR. Residual MR ≤1+ was associated with a lower risk of the composite outcome in both AFMR and VFMR, while MPG ≥5 mmHg was associated with a higher risk of the composite outcome in AFMR but not in VFMR. AFMR patients with residual MR ≤1+ and MPG ≥5 mmHg, as well as those with residual MR >1+, had a higher incidence of the composite outcome than those with residual MR ≤1+ and MPG <5 mmHg (50.7%, 41.8%, and 14.3%, respectively; p<0.001). This association was consistent after adjustment for clinical and echocardiographic characteristics.

Conclusions: MR reduction to ≤1+ by TEER was associated with a lower risk of clinical outcomes in patients with AFMR, while MPG ≥5 mmHg was related to a higher risk of clinical outcomes. Optimal MR reduction by TEER may have potential benefits on prognosis of patients with AFMR, although the prognostic benefit may be attenuated by elevated MPG.

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Running title: Outcomes of TEER for AFMR

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ABSTRACT

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Conclusion: MR reduction to ≤1+ by TEER was associated with a lower risk of clinical outcomes in patients with AFMR, while MPG ≥5 mmHg was related to a higher risk of clinical outcomes. Optimal MR reduction by TEER may have potential benefits on prognosis of patients with AFMR, although the prognostic benefit may be attenuated by elevated MPG.

Keywords: Mitral regurgitation; Mitral valve disease; Mitral valve repair

Condensed abstract

This retrospective observational study showed that residual mitral regurgitation (MR) of ≤1+ at discharge after transcatheter edge-to-edge repair was associated with a lower risk of the composite outcome of all-cause mortality and hospitalization due to heart failure in patients with atrial functional MR (AFMR). In contrast, mean mitral valve pressure gradient (MPG) of ≥5 mmHg at discharge was associated with an increased risk of the composite outcome in patients with AFMR. The prognostic benefit of MR reduction by TEER may be attenuated by elevated MPG in patients with AFMR.

Abbreviations

AFMR = atrial functional mitral regurgitation

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

LA = left atrium

LV = left ventricle

MPG = mean mitral valve pressure gradient

TEER = transcatheter edge-to-edge repair

VFMR = ventricular functional mitral regurgitation

Introduction

Functional mitral regurgitation (FMR) is defined as MR caused mainly by abnormality of the left-sided heart function and geometry as opposed to degenerative MR caused by intrinsic structural valve changes [1]. Growing insights into the pathophysiology of FMR have revealed two subtypes: atrial FMR (AFMR) and ventricular FMR (VFMR) [2,3]. While VFMR is attributed to underlying left ventricular (LV) remodeling or dysfunction, AFMR is caused by left atrial (LA) enlargement and subsequent mitral annulus dilation. According to recent studies, a non-negligible number of FMR patients are considered as AFMR, with increased mortality and morbidities [4,5]. Given the differences in underlying cardiac remodeling, more tailored managements based on the subtype of FMR are needed.

Transcatheter edge-to-edge repair (TEER) is an established alternative option for patients with MR at high risk for cardiac surgery [6,7]. The COAPT trial, a randomized control trial comparing TEER with medical therapy, has revealed the prognostic benefit of TEER in VFMR patients [7]; however, evidence regarding the prognostic impact of TEER for AFMR is still limited. Prior studies suggest the effectiveness of TEER in reducing MR in AFMR patients [8-10]; however, it remains unanswered whether the MR reduction improves clinical outcomes in patients with AFMR.

The reduction in MR by TEER entails the risk for generating relevant mitral stenosis. Elevated mean mitral valve pressure gradient (MPG) after TEER is associated with impaired prognosis in patients with degenerative MR [11,12]. However, this association may be less significant in patients with FMR [12-14], while the prior studies mainly focused on VFMR. Given the differences in underlying cardiac remodeling, the association of elevated MPG with prognosis might differ between AFMR and VFMR.

In the present study, we therefore investigated the association of MR reduction and elevated MPG with clinical outcomes after TEER in patients with AFMR.

Methods

Study population

This study was designed as a retrospective analysis of data from the Bonn registry, which is a prospective, consecutive collection of patient data from the Heart Center Bonn. We identified consecutive symptomatic patients with moderate-to-severe or severe FMR who underwent TEER from September 2010 to March 2022. Patients with a prior history of surgical or transcatheter mitral valve interventions were excluded from this analysis. All included patients were deemed as ineligible or at high risk for conventional surgery. A standard diagnostic workup was performed, including transthoracic and transesophageal echocardiography and left heart catheterization. The decision about the form of treatment for MR was determined by the interdisciplinary heart team at the Heart Center Bonn. The present study was approved by the institutional ethics committee and conducted in concordance with the Declaration of Helsinki. All participants in this study provided written informed consent.

Echocardiographic assessments

All patients underwent transthoracic and transesophageal echocardiography before the TEER procedure. All echocardiographic assessments were performed according to current guidelines [15]. At the apical two- and four-chamber views, LV end-diastolic and end-systolic and LA volumes were evaluated. LV and LA volumes were indexed by body surface area. The severity of MR was determined based on qualitative and quantitative criteria adapted from Mitral Valve Academic Research Consortium guidelines [16]. MR was categorized as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe).

The etiology of MR was evaluated based on the current expert opinion [17]. Before the procedure, the etiology of MR was prospectively classified into degenerative or functional MR by experienced echocardiographers. For the current analysis, FMR was retrospectively classified into AFMR and VFMR with the following definition. AFMR was defined as cases that met all of the following criteria: 1) normal LV systolic function (i.e., LV ejection fraction >50%), 2) no or mild LV enlargement (LV end-diastolic volume index: ≤89 ml/m^2 for male and ≤70 ml/m^2 for female) without segmental LV wall abnormality [18], and 3) moderate or severe LA enlargement (LA volume index: ≥42 ml/m^2) [18]. Patients lacking any one of the criteria were considered to have VFMR.

Residual MR and MPG after TEER were evaluated by transthoracic echocardiography at discharge. Residual MR was assessed using qualitative and semi-quantitative parameters, according to the current guidelines [19]. MPG was measured from continuous-wave doppler of the mitral inflow in diastole by tracing the entire forward flow contour from the apical views [20]. Residual MR ≤1+ was considered as optimal MR reduction, and elevated MPG was defined as MPG ≥5 mmHg [21]. According to residual MR and MPG at discharge, patients were stratified into three groups: 1) residual MR ≤1+ with MPG <5 mmHg, 2) residual MR ≤1+ with MPG ≥5 mmHg, and 3) residual MR >1+.

Procedure

The procedures were performed using the MitraClip system (Abbott Structural Heart, Santa Clara, CA, USA) or PASCAL system (Edwards Lifesciences, Irvine, CA, USA) under general anesthesia with three-dimensional transesophageal echocardiographic and fluoroscopic guidance.

Outcome measures

The primary outcome was a composite of all-cause mortality and hospitalization due to heart failure within one year after TEER. All clinical events, including hospitalization due to heart failure, were independently adjudicated by the local heart team based on the criteria of the Mitral Valve Academic Research Consortium criteria [21]. The occurrence of clinical events was recorded from admission and outpatient medical records, interviews at telephone, or documentation from the referring general practitioners.

Statistics

Continuous variables are presented as the mean ± standard deviation or the median with an interquartile range (IQR) were compared with Students' t-tests or Wilcoxon tests. Cross-sectional comparisons among groups were made by either of the ANOVA or Kruskal-Wallis tests. Categorical data are presented as numbers with percentages and were compared by chi-square or Fischer exact tests. New York Heart Association (NYHA) functional class was compared between baseline and the last follow-up using Bowker's test. Time-to-event curves are depicted using the Kaplan–Meier method and compared between groups using the log-rank test. Univariate and multivariable Cox proportional hazard models were used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the outcomes. Covariates in the multivariable model were predefined based on the presumed association with clinical outcomes and were divided into two models, considering the number of the primary outcome. Model 1 included age, male sex, atrial fibrillation, and estimated glomerular filtration rate; and model 2 included LV ejection fraction, LA volume index, systolic pulmonary artery pressure, and severity of tricuspid regurgitation. We depicted three-not spline curves for the relationship between MPG and its hazard risk in AFMR and VFMR. Statistical significance was set as a two-sided $p<0.05$. All analyses were

conducted using Stata/SE 15.1 (StataCorp, College Station, TX, USA) or R version 4.3.1 (R foundation for Statistical Computing).

Results

Study population

A total of 441 patients with FMR who underwent TEER were included in the present analysis. The mean age was 77 ± 8 years, and 56.7% were male. The median EuroSCORE II was 4.14% (IQR: 2.68–7.23%) **(Supplemental Table 1).**

Of these, 125 patients (28.3%) were classified as AFMR. Baseline characteristics of patients with AFMR are shown in Table 1. Patients with AFMR were older and more frequently female than those with VFMR **(Supplemental Table 1)**. The proportion of atrial fibrillation was higher in patients with AFMR. In contrast, prior histories of coronary artery disease and cardiac implantable electronic device were more frequent in patients with VFMR. Patients with VFMR had a higher risk for cardiac surgery than those with AFMR (EuroSCORE II: 4.71% [IQR: 2.86–8.07%] vs. 3.40% [IQR: 2.39–4.97%]; p<0.001).

Echocardiographic assessment at baseline showed that patients with AFMR had a higher LV ejection fraction, smaller LV volumes, larger LA volume than those with VFMR. MPG at baseline was more likely to be higher in patients with AFMR compared to those with VFMR (1.7 mmHg [IQR: 1.3–2.6 mmHg] vs. 1.5 mmHg [IQR: 1.1–2.2 mmHg]; p=0.058), while the severity of MR was comparable between the two groups. Mitral annulus diameter was greater in patients with AFMR than in those with VFMR (38 mm [IQR: 35–43 mm] vs. 37 mm [IQR: 33–40 mm]; p<0.001). Severe or greater tricuspid regurgitation was more frequent in patients with AFMR than in those with VFMR (48.0% vs. 26.3%; p<0.001).

Procedural outcome

The TEER procedures in patients with AFMR were mostly performed by the MitraClip system (92.0%), followed by the PASCAL system (8.0%; **Table 2**). The mean number of implanted clips was 1.4 ± 0.8, and the median procedural time was 80 minutes (IQR: 49–99 minutes). No surgical conversion was required. The procedural data in patients with VFMR is shown in **Supplemental Table 2**.

The echocardiographic assessment at discharge showed that, in patients with AFMR, residual MR ≤1+ was achieved in 96 of 125 patients (76.8%), while MPG ≥5 mmHg was observed in 27 patients (21.6%). Consequently, residual MR ≤1+ with MPG <5 mmHg was achieved in 75 patients (60.0%; **Figure 1**). Residual MR ≤1+ with MPG ≥5 mmHg were observed in 21 patients (16.7%), while residual MR >1+ was recorded in 29 patients (23.2%), respectively.

The rate of residual MR ≤1+ was comparable between patients with AFMR and those with VFMR (76.8% vs. 72.2%; p=0.27), while MPG ≥5 mmHg was more frequent in patients with AFMR than in those with VFMR (21.6% vs. 13.3%; p=0.030).

Clinical and echocardiographic characteristics at baseline according to the procedural results in AFMR are shown in **Table 1**. In AFMR, patients with residual MR ≤1+ and MPG <5 mmHg had a smaller LA volume index compared to those with residual MR >1+ or residual MR ≤1+ and MPG ≥5 mmHg (54.9 ml/m^2 [IQR: 44.9–69.2 ml/m^2], 67.1 ml/m^2 [IQR: 54.3–117.1 ml/m^2], and 57.6 ml/m^2 [IQR: 2.3–84.8 ml/m^2]; p=0.017). In contrast, severity of MR was comparable between the groups.

The clinical and echocardiographic characteristics of patients with VFMR according to the procedural results are shown in **Supplemental Table 3**.

Clinical outcomes

The median follow-up was 422 days (IQR: 173–863 days). Within one year, the composite outcome occurred in 31 of 125 patients with AFMR. In patients with AFMR, residual MR ≤1+ was associated with a lower risk of the composite outcome (HR: 0.43; 95%CI: 0.21–0.90; p=0.025), while MPG ≥5 mmHg was associated with a higher risk of the composite outcome (HR: 2.31; 95%CI: 1.11–4.83; p=0.025; **Figure 2 and Supplemental Table 4**). On the other hand, in patients with VFMR, residual MR ≤1+ was associated with a lower risk of the composite outcome (HR: 0.56; 95%CI: 0.35–0.88; p=0.012), while the association between MPG ≥5 mmHg and the composite outcome was not significant (HR: 0.83; 95%CI: 0.41–1.66; p=0.60) (**Figure 2 and Supplemental Table 4)**.

The spline curves showed a non-linear association between MPG and its hazard rate of the composite outcome in patients with AFMR **(Figure 3)**, and the risk of the composite outcome increased with MPG of >5 mmHg. In contrast, no significant relationship between MPG and the composite outcome was observed in patients with VFMR.

AFMR patients with residual MR ≤1+ and MPG ≥5 mmHg, as well as those with residual MR >1+, had a higher incidence of the composite outcome than those with residual MR ≤1+ and MPG <5 mmHg (50.7%, 41.8%, and 14.3%; p<0.001; **Figure 4**). In the Cox proportional hazard analysis, residual MR ≤1+ with MPG ≥5 mmHg, as well as residual MR >1+, was associated with a higher risk of the composite outcome than residual MR ≤1+ with MPG <5 mmHg (HR: 4.37; 95%CI: 1.82–10.51; p=0.001, and HR: 3.55; 95%CI:1.51–8.36; p=0.004, respectively; **Table 3**). This association was consistent in the multivariable models.

In contrast, the risk of the composite outcome was comparable between residual MR ≤1+ with MPG ≥5 mmHg and <5 mmHg in patients with VFMR (**Figure 4 and Table 3**).

NYHA functional class at follow-up

Data of NYHA functional class at the last follow-up was available in 90 of 125 patients with AFMR (**Supplemental Figure 1**). Patients with residual MR <1+ and MPG ≥5 mmHg were more likely to have NYHA III or IV at the follow-up, compared to those with residual MR <1+ and MPG <5 mmHg (58.8% vs. 31.6%; p=0.042), although an improvement in NYHA functional class between baseline and the follow-up was also observed in patients with residual MR <1+ and MPG ≥5 mmHg. (Central Illustration)

Discussion

In the present study, we investigated the association of residual MR and MPG with clinical outcomes after TEER in patients with AFMR. The main findings of the present study are as follows:

1. Residual MR ≤1+ at discharge was associated with a lower risk of the composite outcome in both AFMR and VFMR. In contrast, MPG ≥5 mmHg at discharge was associated with a higher risk of the composite outcome in AFMR but not in VFMR.
2. In patients with AFMR, residual MR ≤1+ with MPG ≥5 mmHg, as well as residual MR >1+, was associated with a higher risk of the composite outcome than residual MR ≤1+ with MPG <5 mmHg.
3. Patients with AFMR who had residual MR ≤1+ with MPG ≥5 mmHg had a less post-procedural improvement in NYHA functional class than those with residual MR ≤1+ and MPG <5 mmHg.

AFMR has become a topic of growing interest in the field of FMR. Although the ventricular etiology was traditionally recognized as the mechanism of FMR, recent studies have explored the unique pathophysiology of AFMR and revealed its prevalence, clinical demographics, and prognosis [2,3]. Given the differences in underlying cardiac function and geometry, optimal therapeutic managements may differ between VFMR and AFMR. While TEER is an established

treatment option for VFMR, the evidence of prognostic benefits of TEER in patients with AFMR is still lacking.

In the present study, we identified patients with AFMR upon the database of subjects who underwent TEER. Based on the current expert opinion [17], we defined AFMR as a subtype of FMR that fulfill the following criterion: preserved LV ejection fraction, normal or mildly enlarged LV volume, absence of abnormal LV wall motion, and moderate or severe LA enlargement. As a results, approximately a quarter of FMR patients were considered as AFMR. Patients with AFMR were older and were more likely to be female and to have atrial fibrillation than those with VFMR. In addition, patients with AFMR had a greater mitral annular dilation and more frequently severe or more TR than those with VFMR. These findings were consistent with the characteristics of patients with AFMR that were shown in previous studies [4,8,10].

In the patients with AFMR, residual MR ≤1+ at discharge was achieved in 77.6%, while MPG ≥5 mmHg at discharge was observed in 21.6%. The rate of residual MR ≤1+ at discharge was comparable between AFMR and VFMR, which was in line with previous studies [8-10]. In contrast, MPG ≥5 mmHg was more frequent in patients with AFMR than in those with VFMR. This might be attributable to distinct anatomical and functional features of the mitral valve in patients with AFMR [17]. In addition, due to the more advanced age, degenerative changes in the mitral annulus might be more profound in patients with AFMR than in those with VFMR, affecting post-procedural changes in MPG after TEER.

The present analysis showed that residual MR ≤1+ was associated with a lower risk of the composite outcome in patients with AFMR. This association was consistent after adjusting for baseline clinical and echocardiographic characteristics. Previous observational studies showed that mitral valve surgery may improve prognosis of patients with AFMR compared to conservative therapy [22]. Our finding further infers that TEER is a safe and effective option to reduce MR to ≤1+

and that MR reduction by TEER may lead to better prognosis of patients with AFMR, as shown in patients with degenerate MR or VFMR [11,23].

While there is growing evidence regarding the prognostic benefits of MR reduction by TEER, the association between post-procedural MPG and clinical outcomes remains a subject of debate. Recent studies suggest that the association between MPG and clinical outcomes after TEER can vary based on the etiology of MR: elevated MPG may less impact on the prognosis of patients with FMR, as compared to degenerative MR [11-14]. We expanded the prior evidence by showing the association between elevated MPG and higher risk of the composite outcome in patients with AFMR, but not in VFMR. The relationship between MPG, as a continuous variable, and the composite outcome in patients with AFMR was also confirmed using our spline curve. The effect of elevated MPG on prognosis may be more pronounced in patients with AFMR.

The negative impact of elevated MPG on prognosis of patients with AFMR may go beyond the benefit of MR reduction by TEER. In the present study, residual MR ≤1+ with MPG ≥5 mmHg was associated with a higher risk of the composite outcome than residual MR ≤1+ with MPG <5 mmHg. Moreover, the post-procedural improvement in NYHA functional class was less in patients with elevated MPG, regardless of MR reduction to ≤1+. These findings raise a possibility that the benefits of MR reduction by TEER may be attenuated by elevated MPG in patients with AFMR. Further studies are needed to validate our findings.

The potential explanations for the prognostic impact of elevated MPG in patients with AFMR may be multifactorial. Patients with AFMR are characterized by advanced LA remodeling and atrial arrhythmia. Elevated MPG, indicating an increase in afterload of the LA, might be more critical for advancing the remodeling of LA, such as enlargement and dysfunction. Moreover, concomitant atrial fibrillation could enhance vulnerability of the LA to elevated MPG. Nevertheless, the association between elevated MPG and the composite outcome in patients with

AFMR was consistent even after adjusting for LA volume and atrial fibrillation. Our results are hypothesis generating and need further insights into the different effect of elevated MPG on prognosis between AFMR and VFMR.

Given the prognostic impact of elevated MPG, the therapeutic strategy to achieve optimal MR reduction without elevated MPG may be essential to ensure benefits of MR reduction in patients with AFMR. Appropriate patient selection based on anatomical features of the mitral valve may refine procedural results of TEER for AFMR. Future studies are needed to identify the anatomical predictors of elevated MPG after TEER in patients with AFMR. Also, device selection of transcatheter mitral valve intervention may be important. The PASCAL system is a TEER device characterized by a central spacer and nitinol construction [24]. These features of the PASCAL system may enable optimal MR reduction with minimizing the stress on mitral leaflets and annulus, thereby preventing the risk of mitral stenosis [25]. Furthermore, alternative transcatheter techniques can be potential therapeutic options for patients with AFMR. Direct annuloplasty is reported to be unlikely to increase MPG compared to TEER [26], and transcatheter replacement techniques may achieve a greater reduction of MR without generating relevant mitral stenosis than TEER [27]. Thus, the patient and device selection of transcatheter mitral valve intervention may need to be discussed based on the phenotypes of FMR.

Limitations

Several limitations should be acknowledged when interpreting the results of this study. First, the retrospective design introduces inherent biases associated with patient selection. Despite the multivariable adjustment for potential confounders, unmeasured confounders could influence our results. Second, there is no established definition of AFMR so far, and our echocardiographic assessments were not adjudicated by an external core laboratory. Nevertheless, we defined AFMR

based on the current expert opinion [17], and the characteristics of patients with AFMR were in line with previous reports [4,8,10]. Third, this study included TEER procedures performed from 2010 to 2022. During these years, there have been a lot of developments of the device and technique of TEER and the managements of patients with FMR, which might affect our results. Fourth, we evaluated MPG using echocardiography at discharge and defined a relevant mitral stenosis as MPG >5 mmHg according to the Mitral Valve Academic Research Consortium criteria [21]. MPG is flow depend and can vary depending on the heart rate, loading conditions, and cardiac output at the time of measurements. In addition, MPG may vary between the end of TEER procedures and discharge [12]. Therefore, mitral valve orifice area or MPG indexed by heart rate and cardiac output might precisely assess post-procedural mitral stenosis [28]. However, MPG shows a reasonable surrogate for mitral valve orifice area [29], and the cut-off value of MPG indexed by heart rate and cardiac output is not yet established in patients undergoing TEER. Furthermore, our spline curve showed the risk of the composite outcome increased with MPG of ≥5 mmHg in patients with AFMR, which confirms the robustness of the applied cut-off value of MPG. Fifth, we could not assess left atrial pressure during the TEER procedure. Changes in left atrial pressure after TEER might be valuable for assessing hemodynamical effects of MR reduction and elevated MPG. Finally, we could not assess the durability of MR reduction and the changes in MPG at follow-ups.

Conclusions

MR reduction to ≤1+ by TEER was associated with a lower risk of clinical outcomes in patients with AFMR, while elevated MPG was linked to an increased risk of clinical outcomes. Optimal MR reduction by TEER may have potential benefits on prognosis of patients with AFMR, although the prognostic benefit of MR reduction may be attenuated by elevated MPG.

Impact on daily practice

Transcatheter edge-to-edge repair (TEER) is safe and effective in reducing mitral regurgitation (MR) in patients with atrial functional MR (AFMR). In the present study, MR reduction to ≤1+ by TEER was associated with better prognosis in patients with AFMR; however, the prognostic benefit of MR reduction was attenuated by elevated mean mitral valve pressure gradient (MPG). Optimal MR reduction by TEER may have potential benefits on prognosis of patients with AFMR, although the prognostic benefit of MR reduction may be attenuated by elevated MPG.

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Conflicts of interests

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FIGURE LEGEND

Figure 1. Study flowchart

Abbreviations: TEER = transcatheter edge-to-edge repair; FMR = functional mitral regurgitation; MPG = mean mitral valve pressure gradient.

Figure 2. Association of residual MR and MPG with the composite outcome according to etiology of FMR

Incidence of the composite outcome according to residual mitral regurgitation (MR) and mean mitral valve pressure gradient (MPG) in patients with atrial functional MR (A and B) and ventricular functional MR (C and D).

Figure 3. Spline curves for the hazard ratio of MPG in AFMR and VFMR

Spline curves for the relationship between MPG at discharge and its hazard risk are shown in patients with AFMR **(A)** and VFMR **(B)**.

Abbreviations: AFMR = atrial functional mitral regurgitation; VFMR= ventricular functional mitral regurgitation; MPG = mean mitral valve pressure gradient.

Figure 4. Association of procedural results with the composite outcome in AFMR and VFMR

Incidence of the composite outcome according to residual mitral regurgitation (MR) and mean mitral valve pressure gradient (MPG) in patients with atrial functional mitral regurgitation (AFMR) **(A)** and ventricular functional mitral regurgitation (VFMR) **(B)**.

Central illustration: Association of residual MR and MPG with clinical outcome after TEER according to etiology of functional MR

Residual MR>1+ was associated with a higher incidence of the one-year composite outcome, consisting of all-cause mortality and hospitalization due to heart failure, in both atrial and ventricular functional MR. In patients with atrial functional MR, residual MR ≤1+ with MPG ≥5 mmHg also had a higher risk of the composite outcome.

Abbreviations: MR=mitral regurgitation; MPG=mean mitral valve pressure gradient; TEER=transcatheter edge-to-edge repair

Tables

Table 1. Baseline characteristics of patients with AFMR

		Residual MR ≤1+			
	Total	MPG<5mmHg	MPG≥5mmHg	Residual MR>1+	p-value
	n=125	n=75	n=21	n=29	
Age, year	80.0 ± 6.5	80.7 ± 6.0	80.7 ± 7.0	77.9 ± 7.0	0.12
Male	54 (43.2)	30 (40.0)	7 (33.3)	17 (58.6)	0.14
BMI, kg/m^2	27.2 ± 5.6	28.9 ± 6.6	26.3 ± 3.8	24.1 ± 2.5	0.014
EuroSCOREII, %	4.2 ± 2.8	4.0 ± 2.7	4.8 ± 2.6	4.2 ± 3.0	0.48
Diabetes	30 (24.0)	18 (24.0)	6 (28.6)	6 (20.7)	0.81
Hypertension	101 (80.8)	65 (86.7)	16 (76.2)	20 (69.0)	0.10
Coronary artery disease	55 (44.0)	32 (42.7)	10 (47.6)	13 (44.8)	0.92
Prior myocardial infarction	15 (12.0)	8 (10.7)	2 (9.5)	5 (17.2)	0.61
Prior PCI	45 (36.0)	26 (34.7)	8 (38.1)	11 (37.9)	0.93
Prior CABG	19 (15.2)	10 (13.3)	5 (23.8)	4 (13.8)	0.48
Prior stroke	9 (7.2)	5 (6.7)	2 (9.5)	2 (6.9)	0.90
Atrial fibrillation	116 (92.8)	69 (92.0)	19 (90.5)	28 (96.6)	0.65
NYHA functional class					0.30
II	19 (15.2)	11 (14.7)	4 (19.0)	4 (13.8)	
III	91 (72.8)	58 (77.3)	12 (57.1)	21 (72.4)	
IV	15 (12.0)	6 (8.0)	5 (23.8)	4 (13.8)	
COPD	26 (20.8)	15 (20.0)	4 (19.0)	7 (24.1)	0.88
Pacemaker, ICD, or CRT	30 (24.0)	16 (21.3)	6 (28.6)	8 (27.6)	0.69
eGFR, ml/min/m^2	49.3 ± 18.4	50.0 ± 18.1	42.5 ± 13.5	52.6 ± 21.4	0.14
Hemodialysis	1 (0.8)	1 (1.3)	0 (0.0)	0 (0.0)	0.71
NT-proBNP, pg/ml	1986 (1403, 4019)	1954 (952, 3607)	2048 (1561, 3964)	1954 (1691, 7155)	0.17
Beta blockers	98 (78.4)	59 (78.7)	16 (76.2)	23 (79.3)	0.96
RAS inhibitors	84 (67.2)	55 (73.3)	13 (61.9)	16 (55.2)	0.18
MRA	55 (44.0)	33 (44.0)	11 (52.4)	11 (37.9)	0.60
Loop diuretics	108 (86.4)	66 (88.0)	17 (81.0)	25 (86.2)	0.71
Echocardiography					
LVEF, %	59.3 ± 6.2	58.7 ± 5.4	60.9 ± 7.0	59.8 ± 7.2	0.32
LV end-diastolic volume index, ml/m^2	50.3 ± 17.7	49.6 ± 17.4	46.7 ± 17.9	55.1 ± 18.1	0.23
LV end-systolic volume index, ml/m^2	20.3 ± 8.2	20.6 ± 8.0	17.9 ± 8.3	21.6 ± 8.7	0.30
LA volume index, ml/m^2	57.4 (48.2, 78.7)	54.9 (44.9, 69.2)	57.6 (52.3, 84.8)	67.1 (54.3, 117.1)	0.017

EROA, mm^2	33 (30, 44)	34 (28, 40)	30 (29, 40)	35 (30, 40)	0.60
Regurgitant volume, ml	45.0 (35.5, 60.5)	42.5 (32.5, 55.0)	50.0 (42.0, 64.0)	45.0 (42.0, 62.0)	0.32
MPG, mmHg	1.7 (1.3, 2.6)	1.6 (1.1, 2.4)	1.6 (1.4, 3.0)	1.9 (1.6, 3.1)	0.069
Mitral annulus diameter, cm	3.8 (3.5, 4.3)	3.7 (3.5, 4.1)	3.8 (3.5, 4.2)	4.0 (3.6, 4.2)	0.24
SPAP, mmHg	44.4 ± 18.7	45.5 ± 18.1	48.5 ± 21.6	38.9 ± 17.1	0.16
TAPSE, mm	19.1 ± 4.9	19.8 ± 4.7	17.9 ± 4.7	18.5 ± 5.5	0.24
TR ≥severe	60 (48.0)	37 (49.3)	10 (47.6)	13 (44.8)	0.92

Values are either the number (%), mean ± SD, or median (interquartile range).

Abbreviations: MR, mitral regurgitation; MPG, mean mitral valve pressure gradient; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronized therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; EROA, effective regurgitant orifice area; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 2. Procedural data and echocardiography at discharge in patients with AFMR

		Residual MR ≤1+			
	Total	MPG<5mmHg	MPG≥5mmHg	Residual MR>1+	p-value
	n=125	n=75	n=21	n=29	
Procedural data					
Device type					0.41
MitraClip	115 (92.0)	70 (93.3)	20 (95.2)	25 (86.2)	
PASCAL	10 (8.0)	5 (6.7)	1 (4.8)	4 (13.8)	
Number of clips	1.4 ± 0.8	1.3 ± 0.6	1.9 ± 0.7	1.3 ± 1.1	0.021
Procedural time, min	80 (49, 99)	64 (43, 94)	90 (52, 109)	90 (80, 114)	0.002
Echocardiography at discharge					
MR severity					<0.001
0+	15 (12.0)	13 (17.3)	2 (9.5)	0 (0.0)	
1+	81 (65.6)	62 (82.7)	19 (90.5)	0 (0.0)	
2+	19 (14.4)	0 (0.0)	0 (0.0)	19 (65.5)	
3+	4 (3.2)	0 (0.0)	0 (0.0)	4 (13.8)	
4+	6 (4.8)	0 (0.0)	0 (0.0)	6 (20.7)	
MPG, mmHg	4.0 ± 1.6	3.4 ± 1.0	6.4 ± 1.0	4.0 ± 1.8	<0.001

Values are either the number (%), mean ± SD, or median (interquartile range).

Abbreviations: MR, mitral regurgitation; MPG, mean mitral valve pressure gradient.

Table 3. Association of procedural results with the composite outcome

	Univariate analysis			Multivariable analysis: Model 1			Multivariable analysis: Model 2		
	HR	**95%CI**	**p value**	**HR**	**95%CI**	**p value**	**HR**	**95%CI**	**p value**
AFMR									
Residual MR ≤1+ / MPG <5 mmHg	1 (reference)			1 (reference)			1 (reference)		
Residual MR ≤1+ / MPG ≥5 mmHg	4.37	1.82–10.51	0.001	4.37	1.79–10.66	0.001	5.11	2.07–12.58	<0.001
Residual MR >1+	3.55	1.51–8.36	0.004	3.36	1.41–8.00	0.006	4.00	1.64–9.74	0.002
VFMR									
Residual MR ≤1+ / MPG <5 mmHg	1 (reference)			1 (reference)			1 (reference)		
Residual MR ≤1+ / MPG ≥5 mmHg	1.01	0.45–2.25	0.99	1.12	0.50–2.51	0.79	1.09	0.45–2.63	0.84
Residual MR >1+	1.80	1.12–2.89	0.015	1.98	1.23–3.20	0.005	1.75	1.03–2.99	0.039

Multivariable model 1 included age, male, atrial fibrillation, and eGFR. Model 2 included LVEF, LA volume index, SPAP, and TR severity.

Abbreviations are shown in Table 1.

Figure 1

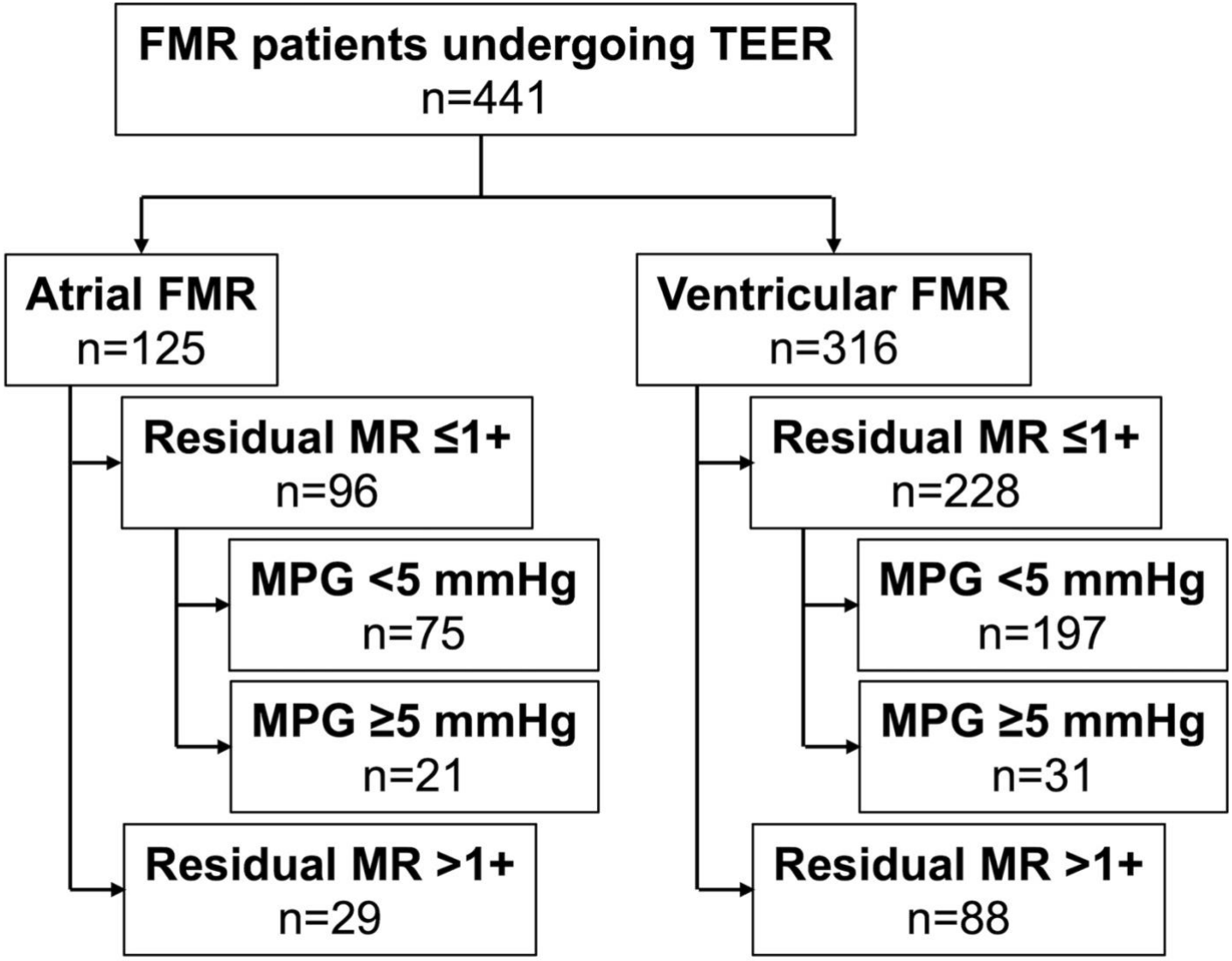


Figure 2

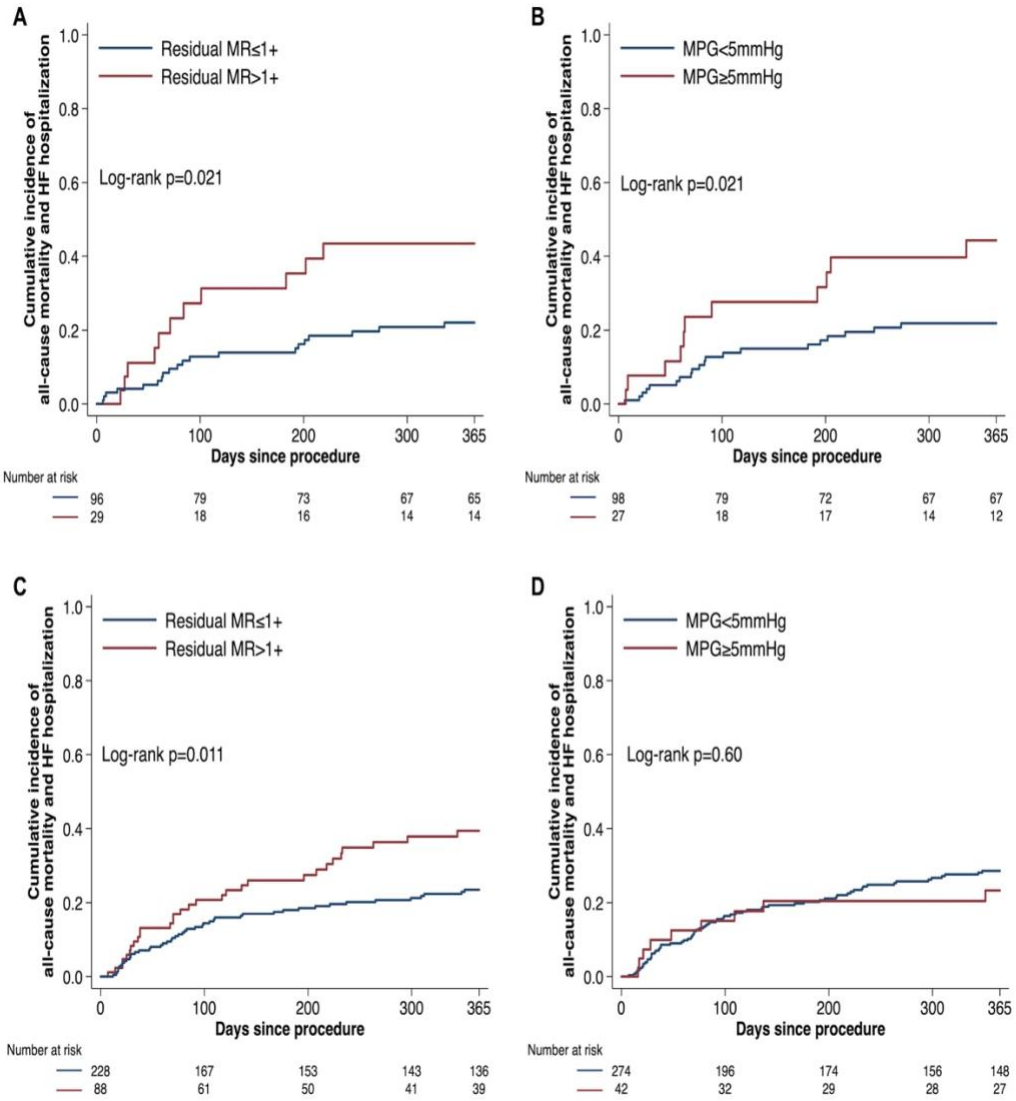


Figure 3

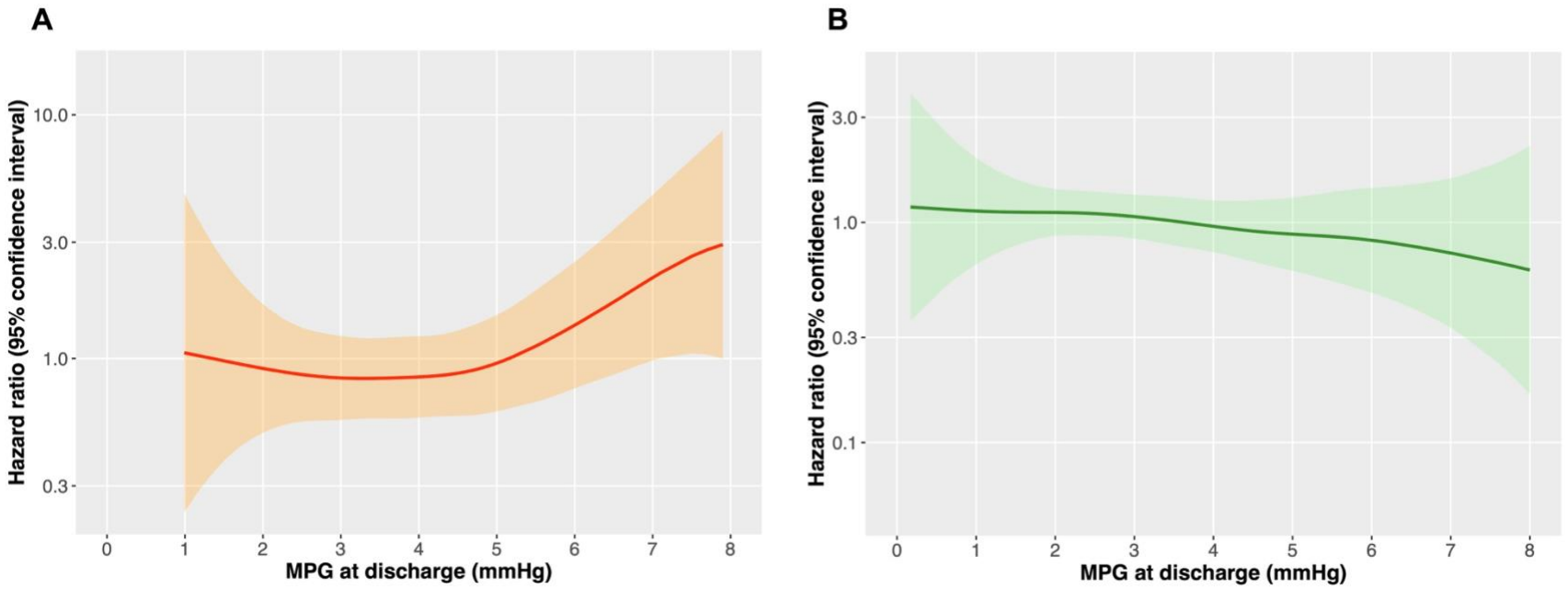
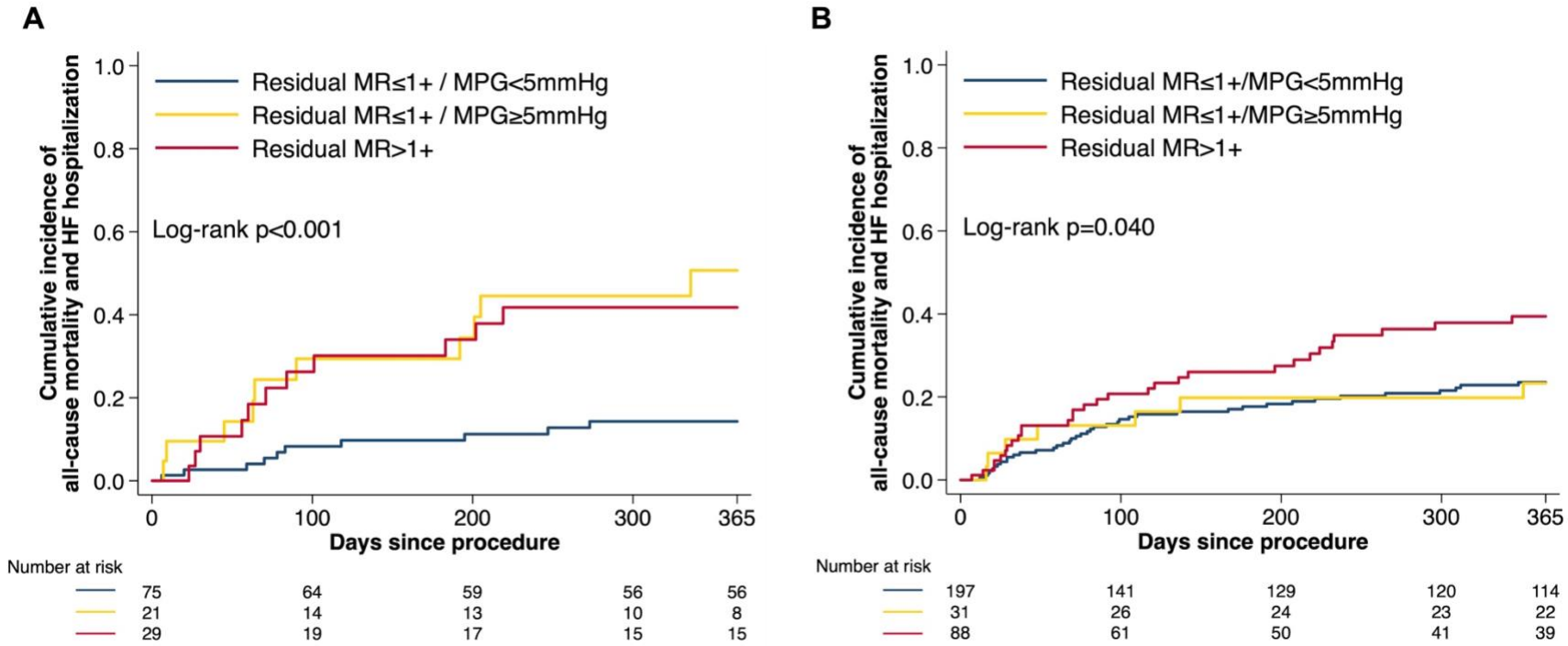
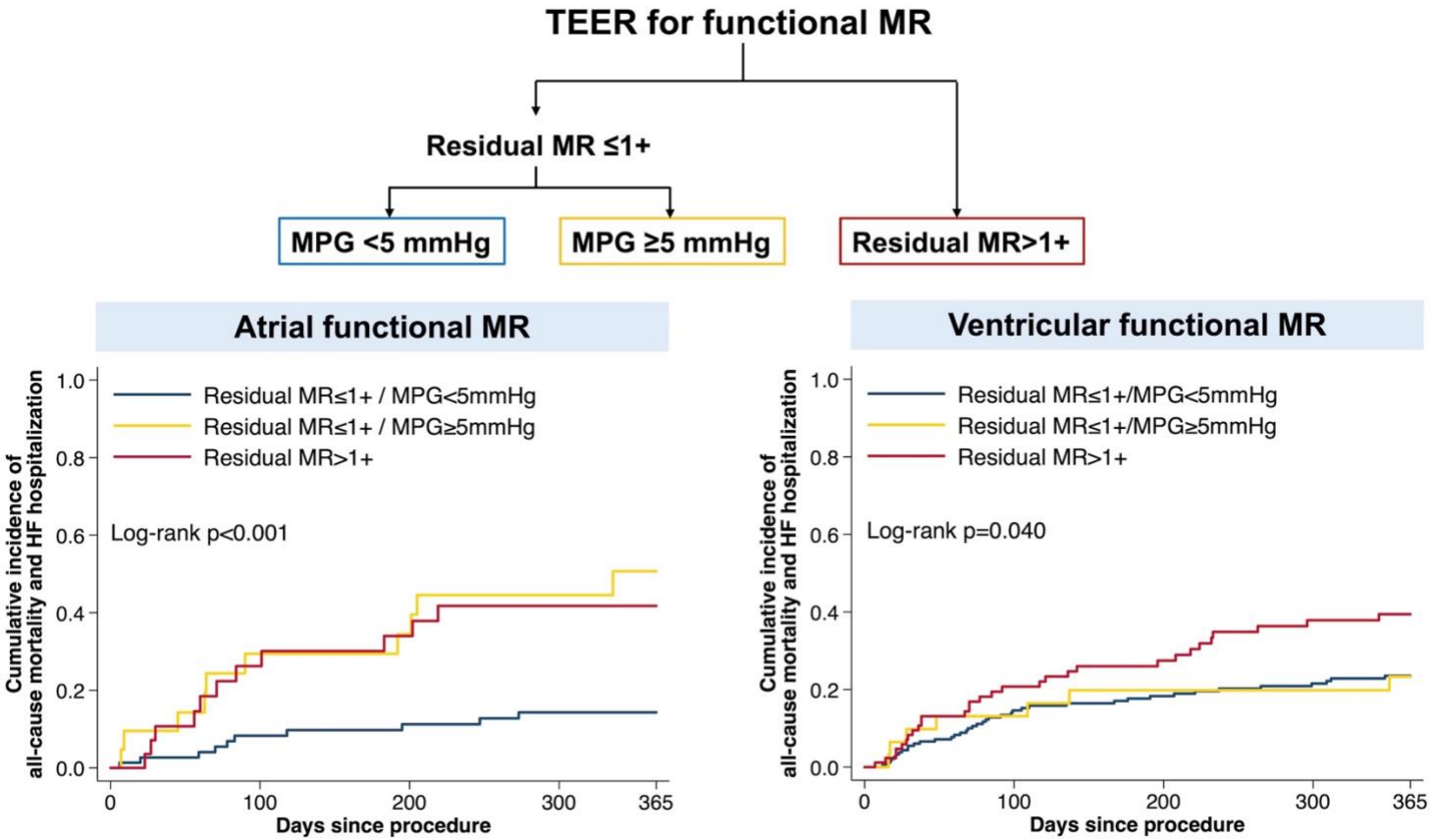


Figure 4



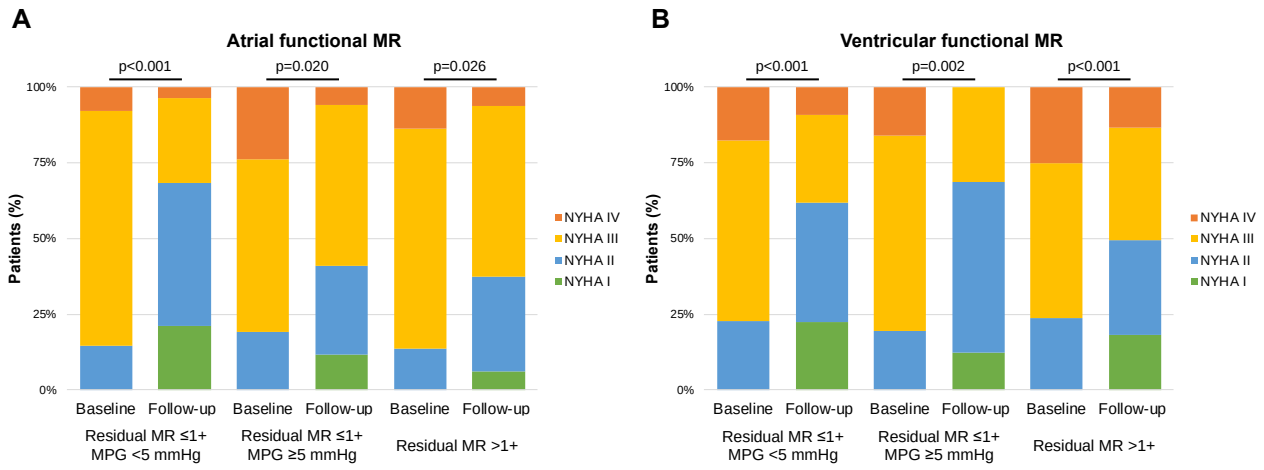
Central Illustration



SUPPLEMENTAL MATERIAL

List of contents

Supplemental Figure 1. New York Heart Association functional class at the last follow-up



Changes in New York Heart Association (NYHA) functional class from baseline to the last follow-up in patients with atrial functional mitral regurgitation (MR) (A) and ventricular functional MR (B).

Abbreviations: MPG = mean mitral valve pressure gradient.

Supplemental Table 1. Baseline characteristics of patients with AFMR and VFMR

	Total n=441	VFMR n=316	AFMR n=125	p-value
Age, year	77 ± 8	76 ± 8	80 ± 6	<0.001
Male	250 (56.7)	196 (62.0)	54 (43.2)	<0.001
BMI, kg/m^2	26.3 ± 5.1	26.0 ± 4.8	27.2 ± 5.6	0.13
EuroSCOREII, %	4.14 (2.68, 7.23)	4.71 (2.86, 8.07)	3.40 (2.39, 4.97)	<0.001
Diabetes	121 (27.4)	91 (28.8)	30 (24.0)	0.31
Hypertension	336 (76.2)	235 (74.4)	101 (80.8)	0.15
Coronary artery disease	246 (55.8)	191 (60.4)	55 (44.0)	0.002
Prior myocardial infarction	144 (32.7)	129 (40.8)	15 (12.0)	<0.001
Prior PCI	184 (41.7)	139 (44.0)	45 (36.0)	0.13
Prior CABG	109 (24.7)	90 (28.5)	19 (15.2)	0.004
Prior stroke	47 (10.7)	38 (12.0)	9 (7.2)	0.14
Atrial fibrillation	347 (78.7)	231 (73.1)	116 (92.8)	<0.001
Pacemaker, ICD, or CRT	191 (43.3)	161 (50.9)	30 (24.0)	<0.001
NYHA class				0.012
II	91 (20.6)	72 (22.8)	19 (15.2)	
III	273 (61.9)	182 (57.6)	91 (72.8)	
IV	77 (17.5)	62 (19.6)	15 (12.0)	
COPD	75 (17.0)	49 (15.5)	26 (20.8)	0.18
eGFR, ml/min/m2	46.1 (34.3, 59.8)	45.8 (32.1, 58.4)	47.5 (36.5, 61.1)	0.30
Hemodialysis	8 (1.8)	7 (2.2)	1 (0.8)	0.32
NT-proBNP	3396 (1691, 6935)	3756 (2082, 8482)	1986 (1403, 4019)	<0.001
Beta blockers	380 (86.2)	282 (89.2)	98 (78.4)	0.003
RAS inhibitors	329 (74.6)	245 (77.5)	84 (67.2)	0.025
MRA	217 (49.2)	162 (51.3)	55 (44.0)	0.17
Loop diuretics	389 (88.2)	281 (88.9)	108 (86.4)	0.46
Echocardiography				
LVEF, %	44.3 ± 14.9	38.4 ± 13.1	59.3 ± 6.2	<0.001
LV end-diastolic volume index, ml/m^2	52.1 (37.5, 68.7)	58.2 (40.3, 86.9)	46.9 (36.3, 63.4)	0.007
LV end-systolic volume index, ml/m^2	36.7 (20.9, 62.0)	48.4 (32.3, 69.9)	19.1 (14.1, 26.1)	<0.001
LA volume index, ml/m^2	51.9 (41.2, 69.5)	48.6 (36.6, 65.5)	57.4 (48.2, 78.7)	<0.001
EROA, mm^2	33 (30, 41)	33 (30, 44)	33 (30, 40)	0.74
Regurgitant volume, ml	66 (60, 71)	66 (60, 71)	65 (54, 75)	0.73
MPG, mmHg	1.6 (1.1, 2.4)	1.5 (1.1, 2.2)	1.7 (1.3, 2.6)	0.058
Mitral annulus diameter, mm	3.7 (3.3, 4.0)	3.7 (3.3, 4.0)	3.8 (3.5, 4.3)	<0.001

SPAP, mmHg	42.6 ± 15.3	41.8 ± 13.8	44.4 ± 18.7	0.13
TAPSE, mm	17.8 ± 5.3	17.4 ± 5.4	19.1 ± 4.9	0.002
TR ≥severe	143 (32.4)	83 (26.3)	60 (48.0)	<0.001

Values are either the number (%), mean ± SD, or median (interquartile range).

Abbreviations: VFMR, ventricular functional mitral regurgitation; AFMR, atrial functional mitral regurgitation; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronized therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; EROA, effective regurgitant orifice area; MPG, mean mitral valve pressure gradient; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Supplemental table 2. Procedural data and echocardiography at discharge in patients with VFMR

		Residual MR ≤1+			
	Total	MPG<5mmHg	MPG≥5mmHg	Residual MR>1+	p-value
	N=316	N=197	N=31	N=88	
Procedural data					
Device					0.89
MitraClip	300 (94.9)	187 (94.9)	30 (96.8)	83 (94.3)	
PASCAL	16 (5.1)	10 (5.1)	1 (3.2)	5 (5.7)	
Number of clips	1.5 ± 0.7	1.5 ± 0.6	1.5 ± 0.6	1.3 ± 0.9	0.13
Procedural time	66 (48, 91)	63 (47, 86)	76 (56, 87)	70 (48, 103)	0.075
Echocardiography at discharge					
MR severity					<0.001
0+	22 (7.0)	19 (9.6)	3 (9.7)	0 (0.0)	
1+	206 (64.2)	178 (90.4)	28 (90.3)	0 (0.0)	
2+	69 (22.8)	0 (0.0)	0 (0.0)	69 (78.4)	
3+	13 (4.1)	0 (0.0)	0 (0.0)	13 (14.8)	
4+	6 (1.9)	0 (0.0)	0 (0.0)	6 (6.8)	
MPG, mmHg	3.4 ± 1.6	2.9 ± 1.1	6.3 ± 1.0	3.4 ± 1.7	<0.001

Values are either the number (%), mean ± SD, or median (interquartile range).

Abbreviations: MR, mitral regurgitation; MPG, mean mitral valve pressure gradient.

Supplemental Table 3. Baseline characteristics according to procedural results in patients with VFMR

	Residual MR ≤1+			
	MPG<5mmHg	MPG≥5mmHg	Residual MR>1+	p-value
	N=197	N=31	N=88	
Age, year	76.9 ± 7.6	77.0 ± 6.9	73.9 ± 9.4	0.015
Male	130 (66.0)	13 (41.9)	53 (60.2)	0.034
BMI, kg/m^2	26.1 ± 4.4	28.3 ± 5.3	25.2 ± 5.3	0.062
EuroSCOREII, %	6.6 ± 5.1	6.2 ± 4.5	5.3 ± 3.9	0.090
Diabetes	53 (26.9)	11 (35.5)	27 (30.7)	0.56
Hypertension	147 (74.6)	27 (87.1)	61 (69.3)	0.15
Coronary artery disease	118 (59.9)	17 (54.8)	56 (63.6)	0.67
Prior myocardial infarction	78 (39.6)	10 (32.3)	41 (46.6)	0.32
Prior PCI	88 (44.7)	13 (41.9)	38 (43.2)	0.94
Prior CABG	58 (29.4)	10 (32.3)	22 (25.0)	0.66
Prior stroke	67 (34.0)	12 (38.7)	22 (25.0)	0.22
Atrial fibrillation	147 (74.6)	23 (74.2)	61 (69.3)	0.64
NYHA class				0.57
II	45 (22.8)	6 (19.4)	21 (23.9)	
III	117 (59.4)	20 (64.5)	45 (51.1)	
IV	35 (17.8)	5 (16.1)	22 (25.0)	
COPD	27 (13.7)	6 (19.4)	16 (18.2)	0.52
Pacemaker, ICD, or CRT	111 (56.3)	8 (25.8)	42 (47.7)	0.005
eGFR, ml/min/m^2	46.1 ± 19.0	46.1 ± 18.8	50.0 ± 21.7	0.30
Hemodialysis	1 (0.5)	2 (6.5)	4 (4.5)	0.024
NT-proBNP, pg/ml	3754 (2079, 8055)	3412 (1654, 7364)	4495 (2706, 11681)	0.38
Beta blockers	177 (89.8)	27 (87.1)	78 (88.6)	0.88
RAS inhibitors	152 (77.2)	22 (71.0)	71 (80.7)	0.53
MRA	94 (47.7)	17 (54.8)	51 (58.0)	0.26
Loop diuretics	177 (89.8)	27 (87.1)	77 (87.5)	0.80
Echocardiography				
LVEF, %	38.1 ± 13.0	43.2 ± 12.4	37.4 ± 13.3	0.090
LV end-diastolic volume index, ml/m^2	84.8 ± 36.1	80.7 ± 47.1	97.5 ± 46.4	0.046
LV end-systolic volume index, ml/m^2	53.2 ± 29.2	48.1 ± 36.3	63.6 ± 39.0	0.033
LA volume index, ml/m^2	46.9 (34.6, 63.3)	46.9 (37.8, 57.4)	55.8 (40.0, 76.0)	0.025
EROA, mm^2	32 (29, 45)	31 (29, 46)	30 (36, 40)	0.25
Regurgitant volume, ml	45.7 (36.0, 60.0)	46.2 (35.0, 66.0)	47.0 (36.4, 60.0)	0.94

MPG, mmHg	1.4 (1.0, 2.0)	2.1 (1.7, 3.1)	1.6 (1.2, 2.7)	<0.001
Mitral annulus diameter, cm	3.7 (3.3, 4.0)	3.6 (3.3, 3.8)	3.7 (3.3, 4.0)	0.43
SPAP, mmHg	40.7 ± 12.9	40.3 ± 12.3	45.1 ± 15.7	0.047
TAPSE, mm	17.2 ± 5.3	17.0 ± 4.4	17.8 ± 5.8	0.61
TR ≥severe	49 (24.9)	10 (32.3)	24 (27.3)	0.66

Values are either the number (%), mean ± SD, or median (interquartile range).

Abbreviations: MR, mitral regurgitation; MPG, mean mitral valve pressure gradient; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronized therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAS, renin angiotensin system; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; EROA, effective regurgitant orifice area; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Supplemental Table 4. Association of residual MR and MPG with the composite outcome

	Univariate analysis			Multivariable analysis: Model 1			Multivariable analysis: Model 2		
	HR	**95%CI**	**p value**	**HR**	**95%CI**	**p value**	**HR**	**95%CI**	**p value**
AFMR									
Residual MR ≤1+	0.43	0.21–0.90	0.025	0.44	0.21–0.94	0.033	0.42	0.19–0.90	0.025
MPG ≥5 mmHg	2.31	1.11–4.83	0.025	2.48	1.16–5.29	0.019	2.79	1.27–6.11	0.01
VFMR									
Residual MR ≤1+	0.56	0.35–0.88	0.012	0.51	0.32–0.81	0.005	0.58	0.34–0.97	0.038
MPG ≥5 mmHg	0.83	0.41–1.66	0.60	0.86	0.43–1.73	0.68	0.99	0.48–2.10	0.99

Multivariable model 1 included age, male, atrial fibrillation, and eGFR. Model 2 included LVEF, LA volume index, SPAP, and TR severity.

Abbreviations are shown in Table 1.