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Impact of aetiology of mitral regurgitation on outcome after Mitraclip: lessons learned from MitraSwiss Registry.

Short title: Mitral valve repair in a large real-world population

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Abstract

Aims: The Swiss national registry on percutaneous mitral valve interventions was established in 2011 to monitor safety/ efficacy of percutaneous mitral valve repair (PMVR) with MitraClip. We report in-hospital, short and mid-term outcomes of all patients prospectively enrolled.

Methods and results: Since 2011, MitraSwiss enrolled 1212 patients with moderate and severe MR of functional (FMR) or degenerative (DMR) etiology treated with PMVR in 10 centers. Pre-specified endpoints included clinical, echocardiographic and functional parameters with follow up planned up to 5 years. Outcomes are compared according to MR etiology. Acute procedural success was achieved in 91.5% of cases, with no differences between FMR and DMR and sustained good mid-term results. NYHA class and pulmonary pressure improved significantly in both cohorts. Cumulative probability of death at 5 years was 54% (95%CI 45-63) in FMR and 45% (95%CI 37-54) in the DMR (HR=1.15, p=0.009). Age, anemia, impaired renal function and reduced left ventricular ejection fraction resulted as independent predictors of death at 5 years.

Conclusions: In a large contemporary cohort of non-surgical patients with severe MR, PMVR confirms its safety and effectiveness. At a mid-term follow up mortality and MACE are lower in DMR patients, though MR aetiology is not directly and independently associated with outcome.

Key Words: mitral regurgitation, mitral valve repair, chronic heart failure.

Condensed abstract: Mid-term outcomes of 1212 patients enrolled in the Mitraswiss registry and treated with percutaneous mitral valve repair with Mitraclip are reported. Outcomes stratified according to etiology. Safety and efficacy of PMVR is confirmed at 5 years follow up. Age, anemia, impaired renal function and reduced left ventricular ejection fraction resulted as independent predictors of 5 years mortality, while etiology was not associated with outcome.

Abbreviations:

DMR: Degenerative Mitral Regurgitation
FMR: Functional Mitral Regurgitation
LVEF: Left Ventricular Ejection Fraction
MACE: Major Adverse Clinical Event
MR: Mitral Regurgitation
NYHA: New York Heart Association
PMVR: Percutaneous Mitral Valve Repair

Introduction

With a prevalence of 10% in individuals aged ≥75 years, mitral regurgitation (MR) is the most common valvular disease (1,2) with substantial impact on morbidity and mortality (3,4). Gold standard of treatment in eligible patients with degenerative MR (DMR) is surgical mitral valve repair, based on its superior long-term results compared to mitral valve replacement or medical therapy (5). Nonetheless, an increasing number of patients with severe MR, which have been denied surgical mitral valve interventions in the past (6), is currently treated by percutaneous mitral valve repair (PMVR) using the MitraClip system (Abbott, Menlo Park, CA, USA), based on the surgical "double-orifice" technique (7). Initially tested in selected, low risk, US-patients with predominantly DMR, PMVR proved to be non-inferior to surgical repair (8) in the randomized Everest II trial, yielding however a higher rate of recurrence in the mid-long term (9).

Indications of PMVR expanded to patients at high surgical risk presenting with functional MR (FMR) and considered an additional tool in the treatment of chronic heart failure. Regardless of MR

aetiology, it has rapidly shown a significant impact on patients' symptoms and quality of life at short/mid-term follow-up (10-12). To further support the adoption of PMVR in the setting of FMR the MITRA-FR (13) and COAPT (14) trials were conducted. Surprisingly, despite similar study designs, the two trials reported discordant results, with the first not showing any impact on incidence of death or unplanned hospitalization for heart failure at one year while the latter demonstrating a survival benefit of PMVR, opening, rather than closing the discussion.

In Switzerland PMVR is performed since 2009 and from November 2011 PMVR patients using the MitraClip have been prospectively included in the national MitraSwiss registry. Follow-up up to 5 years was planned since its conception.

The aim of this analysis is to report the outcome after PMVR in a real world, all comers population and its predictors after inclusion of more than 1200 patients, stratifying results according to MR aetiology.

METHODS

Since September 2011, we aimed to include all patients undergoing PMVR using the MitraClip NT/NTR in a prospective multicenter longitudinal observational study. To date 10 Swiss centers actively participate in the registry. Local institutional boards approved study protocol, all patients provided consent for treatment and data collection. According to protocol, case report form was designed since conception and data quality constantly ascertained by external monitoring. MitraSwiss enrolls elective patients presenting with moderate (3+) or severe (4+) FMR or DMR with indications for percutaneous treatment (15,16). DMR was defined as MR secondary to diseased mitral valve, while FMR as MR secondary to a diseased left ventricle with anatomically intact valve. Patients were considered for PMVR after Heart Team evaluation confirming suitability for percutaneous approach. Surgical risk was estimated by European System for Cardiac

Operative Risk Evaluation (EuroSCORE and EuroSCORE II), Society of Thoracic Surgeons Risk Model (STS Score) and clinical judgement.

According to registry design a set of prespecified clinical endpoints including all-cause mortality, hospitalizations for heart failure and mitral valve surgery due to failure of PMVR or redo-PMVR were defined. These were grouped into a Major Adverse Clinical Event (MACE) endpoint. Events were reviewed by blinded clinical-event adjudication committee and disagreement solved by consensus. Echocardiographic parameters included left ventricular ejection fraction (LVEF), MR grade, LV-volumes and diameters, LA dimension and estimate of pulmonary pressure. NYHA class assessment was recorded in all patients , 6 minutes walking tests (6MWT) were performed in suitable patients. Primary endpoint of the present analysis is all cause-mortality at five years, while MACE were set as secondary endpoints.

TTE were performed at screening, baseline and follow-up visits and MR graded according to current recommendations (17). LV volumes and function (LVEF) were assessed. Left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD) and left atrial (LA) dimension were measured. Systolic pulmonary pressures estimated from pressure gradient between right ventricle and atrium in systole. TEE was used during PMVR to guide the procedure and to assess procedural success. Clip implantation procedure has been widely described in detail in previous reports (8-10,20-21).

Acute procedural success (APS) was defined as placement of 1 or more clips resulting in a post interventional MR severity of ≤2+ according to the EVEREST I protocol (8).

Statistical analysis

Data were described as median and 25th-75th percentiles if continuous, counts and percentages if categorical. Data distribution was assessed graphically with the q-q plot. Given the presence of skewed distribution and/or outliers, non-parametric methods were used. Comparisons between FMR and DMR were performed using Mann-Whitney U and Fisher's exact tests. Cumulative and event-free survival were described with the Kaplan Meier estimator. Comparisons were made with

Cox regression models and hazard ratios (HR) and 95% confidence intervals (95%CI) were computed. To adjust for potential confounders, a multivariable model including MR etiology, age, gender, cardiac function procedure and laboratory findings was fitted. Huber White robust standard errors were computed to account for clustering within center. Regression models (linear, logistic or ordinal logistic, depending on the variable) for repeated measures were used to assess changes over time. Robust standard errors were computed to account for intra-patient correlation of measures. Interaction of MR type and time was tested to assess whether FMR and DMR had different behaviors over time. Stata 15.1 (Stata Corp, College Station, TX, USA) was used for computation. A 2-sided p-value <0.05 was considered statistically significant. As this is a national registry designed to enrol all-comer subjects who underwent mitraclip implant for a long period of time, no sample size was computed a priori. A-posteriori calculation showed that the power for the univariable comparison of survival rates between DMR and FMR, was 0.87 (with alpha 2-sided 5%).

RESULTS

Patient sample and baseline characteristics

Between September 1st,2011 and December 31st,2018, 1265 patients were enrolled. Baseline, procedural and short term follow-up data completeness was ascertained in 1212 patients (95.8%), while 53 excluded for data missing regarding mechanism of MR **Figure 1** reports rate of recruitments per year. Baseline clinical characteristics by MR etiology are available in **Table 1 while supplementary figure 1** reports patient's flow. MR was functional in 560 (46.2%) and degenerative in 652 (53.8%). FMR were younger, more frequently males, with a higher BMI and higher burden of coronary artery disease than DMR. While baseline hemoglobin were equal in FMR and DMR, renal function was significantly lower in FMR.

At echocardiography**,** patients with FMR showed a moderate to severe degree of left ventricular dysfunction, significantly lower than in DMR (p<0.001).

Procedural results

Acute procedural success was achieved 91.5% of cases, without differences between FMR and DMR (**Table 2**). Number of clips implanted per patients did not differ according to etiology. While no significant differences between FMR and DMR within the peri-procedural measurements were observed, patients with FMR had a significantly lower median trans-mitral gradient at discharge (3.2 vs. 4.0 mmHg; p=0.002).

In-hospital outcomes

Periprocedural death was 0.5% for both DMR and FRM (1 device related and 5 non device related deaths). No differences observed for non-fatal procedure-related complications.

ICU/CCU stay were longer for FMR (p <0.001), while length of hospitalization comparable among groups.

MR grade 3+ or 4+ decreased from 99% at baseline to about 18% at discharge. A similar proportion of patients, 64% with FMR and 59% with DMR, were discharged with MR grade of 1+.

30-day Outcomes

Thirty-day mortality was 2.1% (95%CI:1.2-3.6%) in DMR and 3.3 (95%CI:2.0-5.2; p=0.125) in FMR. Rate of mitral surgical intervention/*redo* PMVR within 30 days was 1.3% (95%CI:0.6-2.6%) and 0.5% (95%CI:0.1-1.5; p=0.158), rehospitalization for heart failure occurred in 1.9% (95%CI:1.0-3.3%) and 1.9% (95%CI:1.0-3.5; p=1.00) respectively. Rate of MACE was 5.2% (95%CI:3.6-7.2%) in DMR and 5.9% (95%CI:4.0-8.1%; p=0.616) in FMR .

Functional changes over long term follow-up

As shown in **Figure 2** (upper panels), MR grade markedly decreased at discharge and with minimal changes thereafter (p<0.001 for both FMR and DMR); at 6 months still 50% of the FMR patients and 43% of the DMR patients had MR grade 1+. Although the rate of MR 3+ and 4+ was slightly higher in the DMR than in FMR over the entire follow-up, no significant difference was shown (test for interaction p=0.507). A similar behavior was observed for NYHA class (**Figure 2,** lower panels), with a marked reduction at discharge and minimal changes thereafter (p<0.001 for both). While more than 70% of patients were in NYHA class III/ IV before treatment in both cohorts, the rate remained consistently below 35%, with no difference between cohorts at follow-up (test for interaction p=0.963). **Figure 3**, reports changes over time of echocardiographic parameters (additional data on the supplementary appendix).

Clinical follow-up

Follow-up was available in 1153 patients (95,1%) with a median duration of 13 months (25^{th}-75^{th} 6-35). A total of 265 died and 310 experienced MACE, corresponding to a cumulative probability of death of 50% (95%CI:44-57) and MACE of 54% (95%CI:47-61) at 5-years.

139 died in the FMR and 126 in the DMR cohorts, corresponding to a mortality of 18 (95%CI:15-21) and 15 per 100 person-year (95%CI:13-18), respectively. The cumulative probability of death at 5-years was 54% (95%CI:45-63) in the FMR, and 45% (95%CI:37-54) in the DMR cohort (p<0.001).

166 experienced MACE in the FMR and 144 in the DMR cohorts. MACE rate was 25 (95%CI:21-29) and 20/100 person-year (95%CI:17-23), respectively and MACE probability at 5-years was 59% (95%CI:49-69) and 50% (95%CI:41-60, p=0.015).

As shown in **Figure 4** and in **supplementary Table 1**, FMR had a 15% excess risk for death and 28% for MACE (HR=1.15,95% CI:1.04-1.28; p=0.009 and HR=1.28,95% CI:1.05-1.66; p=0.015) vs DMR. However, when adjusting in a multivariable Cox model for age, gender, preoperative cardiac function, laboratory and procedural findings, death and MACE excess risk for FMR was

not confirmed. Independent predictors of death at 5-years were age (HR=1.04,95% CI:1.02-1.07; p=0.001), lower hemoglobin (HR=0.81,95%CI:0.74-0.89; p<0.001), impaired renal function (log creatinine, HR=1.45,95%CI:1.10-1.93; p=0.009), reduced LVEF (HR=0.98,95% CI:0.97-0.99; p=0.009). NYHA class III-IV resulted marginally non-significant (HR=1.38,95% CI:0.95-1.99; p=0.083). Independent predictors of 5-years MACE were lower hemoglobin (HR=0.87,95%CI: 0.80-0.95; p=0.002) and reduced LVEF (HR=0.97, 95% CI:0.96-0.98;p<0.001) while NYHA III-IV marginally not significant (HR=1.37,95% CI:0.98-1.92;p=0.067).

DISCUSSION

This analysis derived from MitraSwiss registry is, to the best of our knowledge, the largest prospectively cohort of PMVR patients with clinical and echocardiographic mid-term follow-up stratified according to MR etiology.

Main findings are: (1) FMR and DMR represent two entities with peculiar characteristics. In our cohort, DMR were older but substantially healthier than FMR. Conversely in younger FMR patients, presence of MR mirrored the valvular involvement of congestive heart failure, a disease with systemic implications. (2) Procedural safety and short-term outcomes are excellent in FMR and DMR with APS exceeding 90% in both groups and low rate of procedural complications. Reduction of MR is associated with hemodynamic consequences such as a significant and stable decrease of pulmonary pressure with beneficial impact on symptoms and functional capacity (3). While mid-term outcomes in DMR are different from FMR, MR etiology *per se* is not an independent predictor of mortality or MACE, both being driven by markers of systemic involvement such as anemia and impaired renal function.

So far only the Everest trial and long term analysis of TRAMI registry reported on long term data about safety and efficacy after PMVR with a pooled numerosity well below 1000 patients. Our data add on the knowledge by confirming previous finding and opening new perspectives.

Overall, baseline characteristics of MitraSwiss patients are comparable to TRAMI population in terms of age and sex distribution, while significantly older than in the EVEREST trial. Moreover, distribution between FMR and DMR in our registry is well balanced as compared to TRAMI (FMR 69.3%) or EVEREST II (DMR 73%), allowing to sustain comparisons between groups.

Patients with FMR showed a greater burden of comorbidities with cardiac and systemic implications as compared to DMR. Conversely, DMR patients were older clearly highlighting the intrinsic differences between the functional, mirroring the mitral involvement in a systemic disease, and the degenerative aetiology, marker of valvular disease with cardiac, but often without systemic, involvement.

Despite baseline differences, safety of PMVR was confirmed with risk of procedural mortality or complications well below 1%, being in line with previous reports (8,9,11-13,14,20-22). An extremely low periprocedural (0.5%) and 30 days (2.7%) mortality, low rate of periprocedural complications, immediate and deferred surgical conversion was observed.

Efficacy was confirmed, with APS of >90% , in line with TRAMI registry data (21). The beneficial effect at mid-term and the functional benefit of PMVR as demonstrated by the improvement in the NYHA class and 6MWT and by the reduction in pulmonary pressure, was maintained in both groups. A relative decrease in LVEF, already evident in the EVEREST II (18) population was seen in our DMR patients, associated with an increase in LVESV. This finding is probably justified by a significant reduction in left ventricular preload and increased afterload after MR reduction (19).

It is well known from real time left ventricular pressure-volume loops recorded during PMVR that an improvement in hemodynamics after PMVR resulted in reverse LV remodeling by reducing LV preload while preserving contractility (23).

Overall 5-years mortality was 50%, comparable to TRAMI (53.8% at 4 years) (23) but significantly higher than in EVEREST II trial (32%) (20), confirming the clinical significance of MR as a marker of poor long term prognosis in a real life scenario.. Interestingly, 5-years mortality in our cohort is in line to that observed in patients with of congestive heart failure (24), furtherly supporting the

concept that MR is just an aspect of a more complex picture. Of note, despite an older age and its independent association with outcome, 5-years survival of DMR was significantly higher than in FMR, pointing up once more the intrinsic differences between the two etiologies.

For what relates prognostic factors associated with outcome, our data do not support previous findings derived from the EVEREST II trial in which functional etiology was independently associated with long term mortality together with COPD, diabetes, peripheral artery disease and age. In line TRAMI and Spanish registry, etiology did not show any prognostic role (25). In our population, independent predictors of 5-years mortality and MACE reflect substantially the clinical conditions at the time of repair, which are ultimately among the factors that led to the decision to prefer PMVR over surgery. Interestingly, a good procedural result, which predicted 1-year and 2-years mortality (26), lost is significance in our population at a longer follow-up, as observed in other cohorts (20,21). This might be justified as a hierarchical role of age, anemia or renal impairment resulting as determinants of long term prognosis, nonetheless with a minor impact on short term outcomes.

Obviously, our data do not add adjunctive evidences to solve the debate derived from the publication of Mitra-FR and COAPT trials. While confirming the benefit in term of symptoms, the Mitral-FR study, failed to show any impact on the survival in advanced disease (13). In patients at an earlier disease stage, with more pronounced MR and less dilated LV an impressive benefit over medical treatment was seen in the COAPT trial (14), leaving open the question on which patient with FMR should be selected for PMVR. As for the nature of registry data, the lack of a comparator does not allow us to draw any conclusion upon the prognostic impact of PMVR. Reassuringly, the median LVEDV in our FMR population is 163 ml, identifying patients with clinically significant MR but smaller ventricles when compared to MITRA-FR and COAPT trials. This places our FMR population in the newly defined group of “disproportionate” or “tertiary” mitral regurgitation (27,28) in which the amount of MR exceeds the degree of left ventricular dysfunction, a class of

patients in which PMVR proved to reduce the risk of death and hospitalization for heart failure according to COAPT results (14).

Limitations

Data derive from an observational registry, thus intrinsic inaccuracies to the dataset apply. Moreover, as a limitation of all dynamic cohorts, 5 years follow up is available only for a limited percentage of patients. Although a critical event committee reviewed all events at 30 days, risk of under-reporting of later events remains. While clinical and echocardiographic follow-up was a condition required from registry, representing a unique feature of the present analysis, echocardiographic data were site-reported and not core lab adjudicated. Finally, no data are available regarding evolution of medical treatment over time.

Conclusions

Our data confirms mid-term safety and efficacy of PMVR using MitraClip system in an all-comer population.

Treatment leads to significant reduction of MR and to several significant clinical and functional benefits in a high proportion of the patients. Although patients with DMR and FMR are intrinsically distinct populations, short-term outcomes do not differ. Mortality and MACE are lower at a mid-term follow up in DMR patients, nonetheless etiology of MR is not associated with outcome.

Impact on daily practice: PMVR with Mitraclip is a valuable therapeutic option both in FMR and in DMR patients not suitable for surgery able to provide symptomatic benefit and functional improvements. Mid-term outcomes are worse in FMR than in DMR patients. Nonetheless MR etiology isn't associated with five-years mortality, while significant associations were evident with markers of systemic involvement such as anemia, renal impairment and left ventricular ejection, highlighting the clinical and prognostic interdependence between MR and congestive heart failure.

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Appendix:
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Figure legends:

Figure 1: Frequency of patient's recruitment in the Mitraswiss registry per year (2011-2018).

Figure 2: Evolution of MR class and NYHA grade after PMVR at follow up according to MR aetiology.

Figure 3: Evolution of echocardiographic parameters at follow up according to MR aetiology.

Figure 4: Kaplan Meier survival estimates for mortality and MACE by MR aetiology.

Table 1. Baseline characteristics

	DMR (n=652)	FMR (n=560)	p	All patients (n=1212)
*Age, years**	81.0 (76.0-85.0)	76.0 (69.0-81.5)	<0.001	79.0 (73.0-84.0)
*BMI, kg/m^2 **	24.5 (21.8-27.3)	25.3 (22.3-28.3)	<0.001	24.8 (22.0-27.7)
Male, n(%)	377 (57.8)	356 (63.6)	0.045	733 (60.5)
CV risk factors				
Hypertension, n(%)	461 (74.3)	421 (77.4)	0.244	882 (75.7)
Hyperlipidemia, n(%)	253 (41.1)	300 (55.1)	<0.001	553 (47.7)
Diabetes mellitus, n(%)	81 (13.5)	135 (25.7)	<0.001	216 (19.3)
Coronary artery disease, n(%)	251 (40.9)	353 (65.5)	<0.001	604 (52.4)
Comorbities				
myocardial infarction, n(%)	79 (12.8)	225 (41.9)	<0.001	304 (26.4)
PCI, n(%)	144 (23.5)	244 (45.3)	<0.001	388 (33.7)
CABG, n(%)	67 (10.9)	142 (26.5)	<0.001	209 (18.2)
Valve surgery, n(%)	70 (11.2)	44 (8.0)	0.075	114 (9.7)
TAVI, n(%)	33 (5.3)	22 (4.0)	0.334	55 (4.7)
Hospitalization for heart failure, n(%)	174 (28.6)	198 (37.2)	0.002	372 (32.6)
Atrial fibrillation, n(%)	343 (55.4)	306 (56.5)	0.723	649 (55.9)
PM/ICD, n(%)	84 (13.5)	177 (32.6)	<0.001	261 (22.4)
CRT, n(%)	29 (4.4)	107 (19.1)	<0.001	136 (11.2)
Clinical presentation				
*Heart rate, beats/min**	74 (64-83)	72 (63-82)	0.162	73 (64-82)
NYHA class,n(%)			0.034	
I/II	197 (31.7)	139 (25.4)		336 (28.7)
III	350 (56.2)	324 (59.2)		674 (57.6)
IV	75 (12.0)	84 (15.3)		159 (13.6)
*Hemoglobin, (g/dl) **	12.6 (11.2-13.7)	12.5 (11.1-13.6)	0.424	12.6 (11.2-13.7)
*Creatinine, μmol/*l*	102 (83-139)	121 (95-157)	<0.001	110 (88-148)
*GFR ml/min/1.73 m^2**	45 (34-60)	43 (31-58)	0.010	44 (33-60)
*Logistic Euroscore, %**	6.6 (4.2-13.2)	8.4 (4.1-20.7)	0.003	7.2 (4.2-16.0)
*Euroscore II, %**	3.4 (2.0-5.5)	4.9 (2.8-9.5)	<0.001	4.1 (2.3-6.9)
*STS score, %**	3.7 (2.0-6.5)	3.7 (1.9-8.0)	0.787	3.7 (1.9-7.38)
Echocardiography				
MR grade			<0.001	
Moderate (3+)	75 (11.7)	124 (22.3)		199 (16.6)
Severe (4+)	568 (88.3)	431 (77.7)		1000 (83.4)
*LVEF, %**	60 (50-65)	36 (28-50)	<0.001	50 (35-61)
*LVEDV, ml**	121 (92-160)	163 (117-214)	<0.001	137 (101-190)
*LVESV, ml**	46 (34-78)	112 (67-159)	<0.001	76 (42-159)
*LA volume, ml**	62 (47-79)	60 (47-77)	0.301	61 (47-78)
RV gradient > 30 mmHg, n (%)	375 (77.3)	341 (80.0)	0.332	716 (77.2)

* : values reported as median (25th-75th) .BMI: body mass index; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; PM: pacemaker; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; NYHA: New York Heart Association class; GFR: Glomerular Filtration Rate; STS: Society of Thoracic Surgeons; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume, LA: left atrial volume

Table 2. Procedural results

	DMR	FMR	p	All patients
Number of clips implanted			0.282	
Procedure attempted, clip not implanted	12 (1.8)	6 (1.0)		18 (1.5)
1 clip	262 (40.8)	218 (39.2)		480 (40.1)
2 clips	289 (45.0)	278 (50.0)		567 (47.3)
3 clips	68 (10.5)	45 (8.1)		113 (9.4)
4 clips	11 (1.7)	8 (1.4)		19 (1.6)
***Post procedural transmitral gradient**, mmHg**	4.0 (3.0-5.0)	3.2 (2.0-5.0)	0.002	3.5 (2.6-5.0)
***Procedural time,** min**	62 (40-85)	75 (44-104)	0.182	70 (41-102)
Acute procedural success	564 (91.4)	494 (91.6)	0.916	1058 (91.5)
Procedural complications				
Periprocedural mortality,n(%)	3 (0.5)	3 (0.5)	1.000	6 (0.5)
Mechanical ventilation > 48 hours,n(%)	4 (0.6)	4 (0.7)	1.000	8 (0.6)
Left ventricular Assist Device,n(%)	5 (0.8)	3 (0.5)	0.730	8 (0.6)
Bleeding requiring transfusion,n(%)	7 (1.1)	6 (1.1)	1.000	13 (1.1)
Transseptal puncture related complication,n(%)	12 (1.9)	4 (0.7)	0.128	16 (1.3)
Stroke,n(%)	2 (0.3)	1 (0.1)	1.000	3 (0.2)
In hospital outcomes				
*ICU/CCU stay**	1 (1-2)	2 (1-4)	<0.001	2 (1-3)
*Total hospital stay**	5 (4-7)	5 (4-8)	0.080	5 (4-7)
30 days Outcomes				
MACE,n(%)	34 (5.2)	33 (5.9)	0.616	67 (5.5)
Heart failure hospitalizations,n(%)	13 (1.9)	11 (1.9)	1.000	24 (1.9)
Cardiac surgery/redo PMVR,n(%)	9 (1.3)	3 (0.5)	0.158	12 (0.9)
Mortality,n(%)	14 (2.1)	19 (3.3)	0.125	33 (2.7)

*: values reported as median(25^{th}-75^{th}).ICU/CCU: intensive care t/coronary care unit. HF: Heart Failure; PMVR: percutaneous mitral valve repair. Transeptal puncture related complication defined as conversion to surgery or pericardial effusion requiring drainage.

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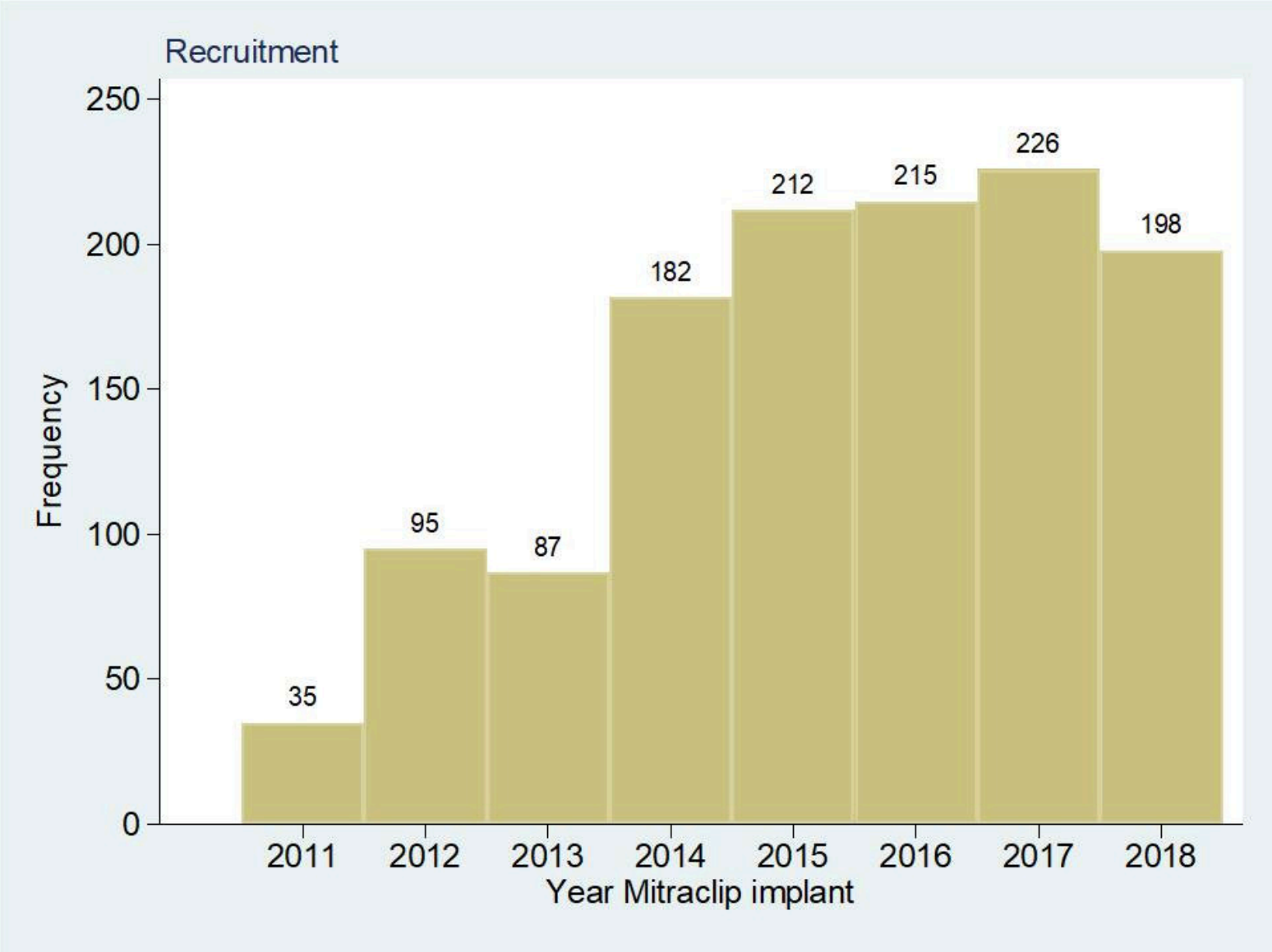
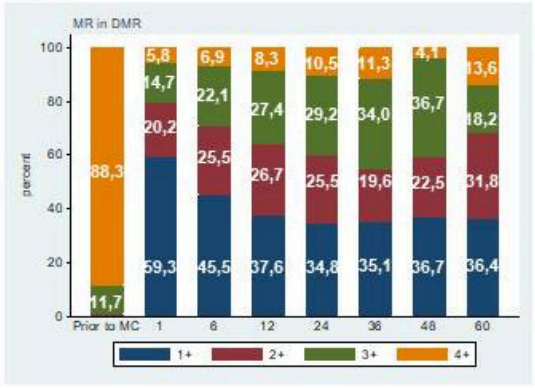
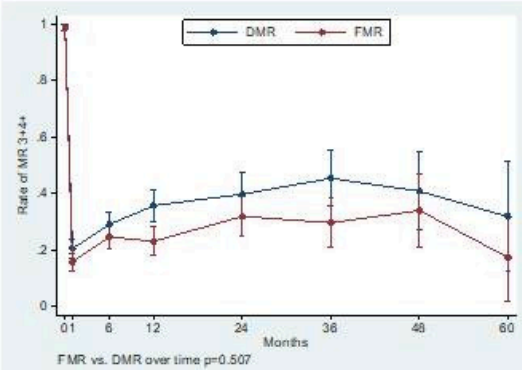


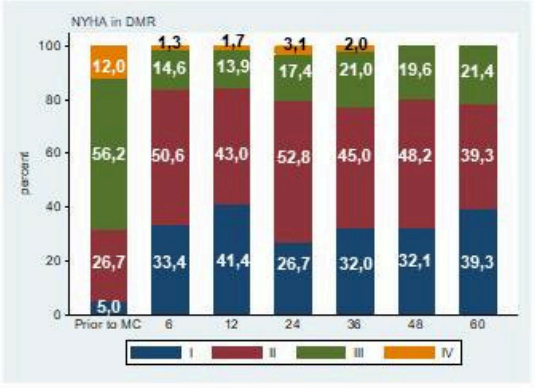
MR

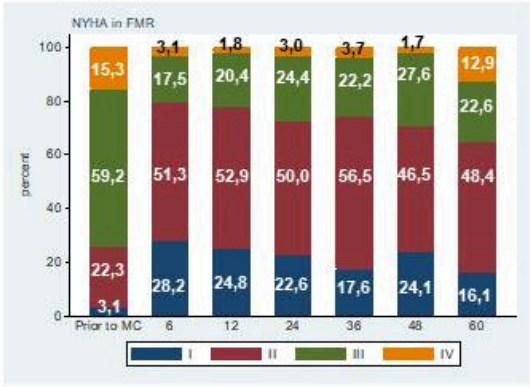


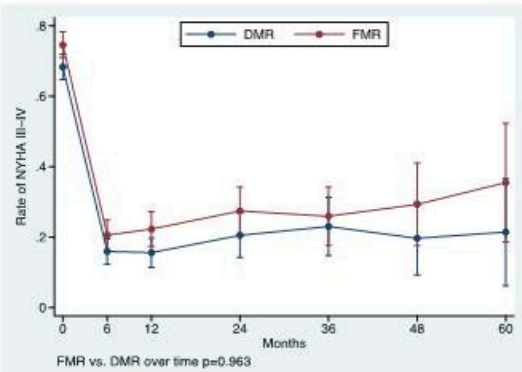


Patients with available obervations at each time point						
	6 M	12 M	24M	36M	48M	60M
DMR	420	277	161	97	49	22
FMR	356	268	166	108	50	23

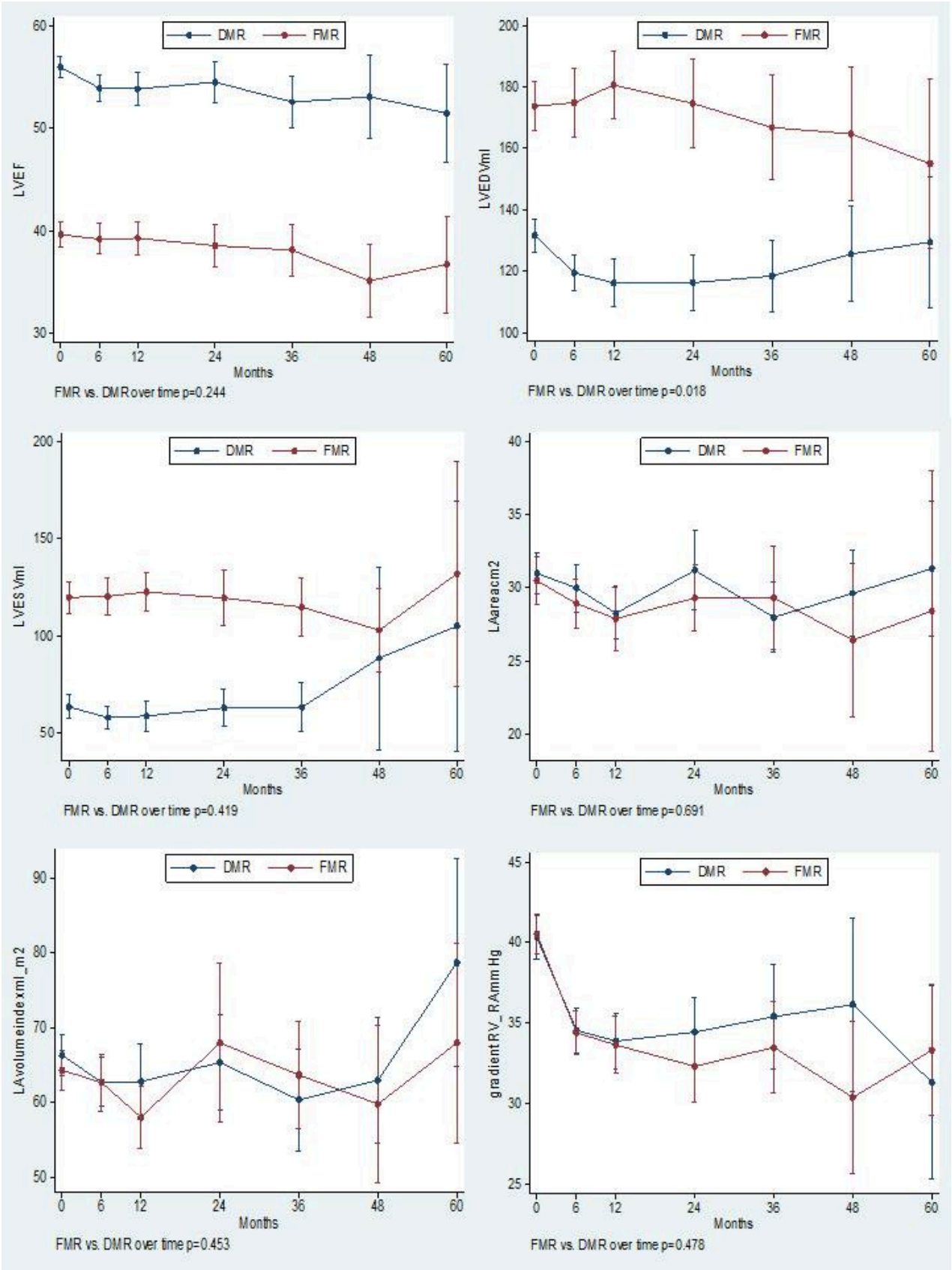
NYHA

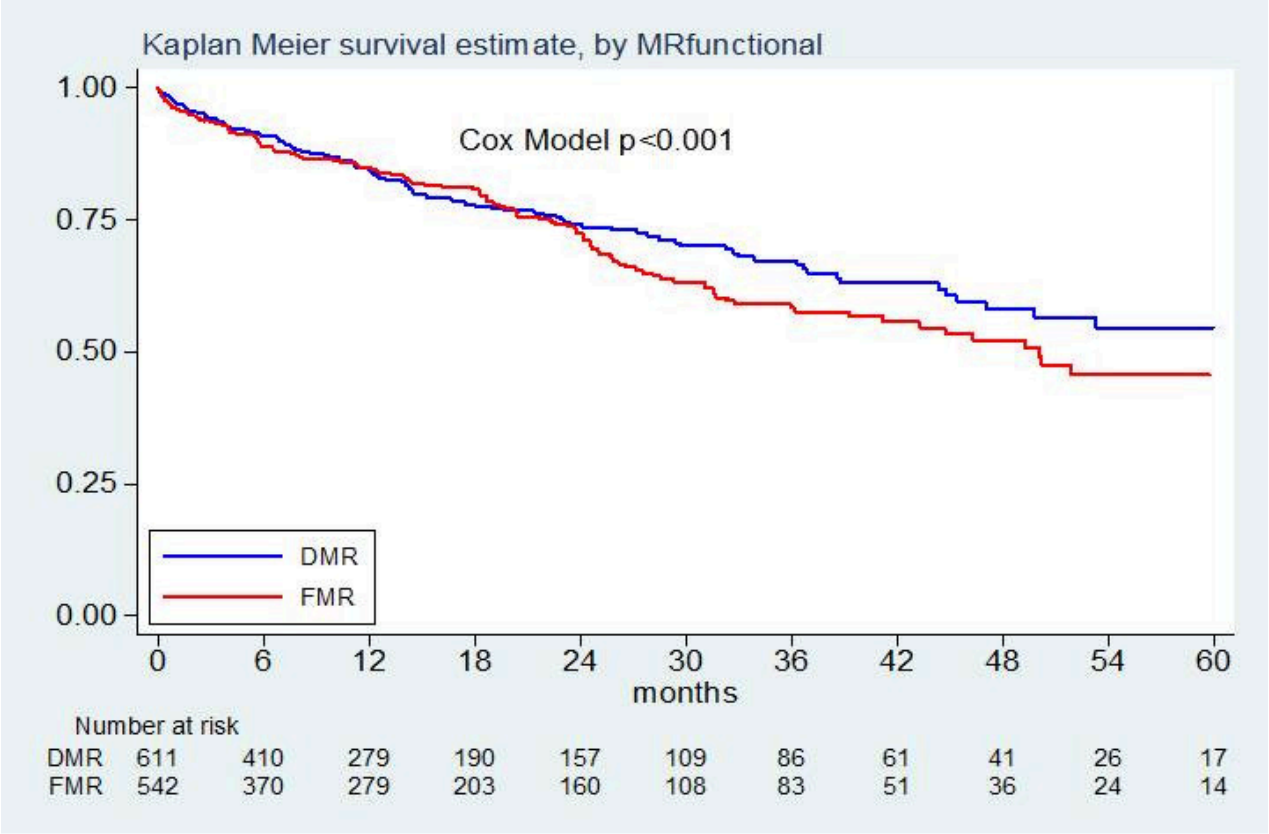


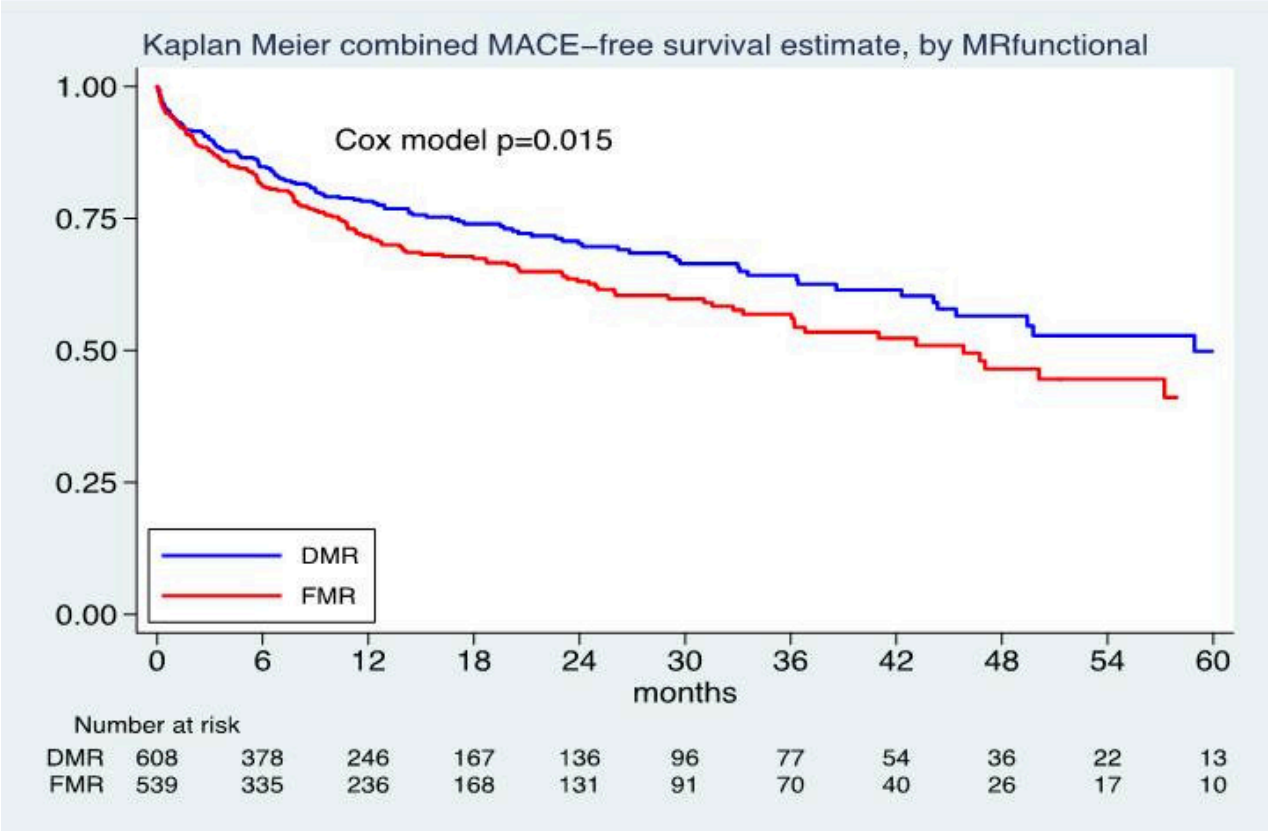




Patients with available obervations at each time point						
	6 M	12 M	24M	36M	48M	60M
DMR	389	295	161	100	56	28
FMR	355	274	164	108	58	31







Supplementary material

Statystical analysis.

As this is a national registry designed to enrol all-comer subjects who underwent mitraclip implant for a long period of time, no sample size was computed a priori. A-posteriori calculation showed that the power for the univariable comparison of survival rates between DMR and FMR, was 0.87 (with alpha 2-sided 5%).

Changes over time of echocardiographic parameters

As compared to FMR, DMR patients presented with a preserved ventricular function prior to treatment. A slight but significant decrease in LVEF was evident in DMR (p=0.003) but not in the FMR cohort (p=0.375), though no significant differences were evident over time between the two cohorts (p for interaction=0.244).

Conversely some difference in the behavior over time was observed for LVEDV (p for interaction=0.018) but not for LVESV (p for interaction=0.419). No overall significant change over time for LVESV was observed in FMR (p=0.580), while a significant increase was evident for DMR patients (p<0.001). LVEDV did not change significantly over time neither in the FMR (p=0.742) nor in the DMR (p=0.299) patients. No changes were also observed among groups for LA area and volume (p=0.691 and 0.453) the RV-RA gradient (p=0.478). Small significant decreases in LA area and volumes were observed within the DMR (p=0.041 and 0.023) but not the FMR patients (p=0.441 and 0.078), whereas the RV-RA gradient showed a marked decrease, stable over time, within both cohorts (p for trend <0.001, for both FMR and DMR).

Exercise capacity as evaluated by the 6MWT at 6 months increased significantly both in FMR (by 37 m, 95%CI 18-56, p<0.001; from a median of 350 m, 25^{th}-75^{th} 249-415, to 372 m, 25^{th}-75^{th} 296-477) and DMR cohort (by 27 m, 95%CI 10-43, p=0.002; from a median of 370 m 25^{th}-75^{th} 240-450 to 385 m, 25^{th}-75^{th} 300-483), with no difference between cohorts (p for interaction =0.418).

Supplementary table 1. Association of etiology of mitral regurgitation with mortality and MACE at 60 months.

Univariable and multivariable analyses (the effect of etiology adjusted for potential confounders)

Variable	***Mortality***		***MACE***	
Univariable analysis	***HR (95%CI)***	***p-value***	***HR (95%CI)***	***p-value***
Etiology of MR		**0.009**		**0.015**
DMR	**1**		**1**	
FMR	**1.15 (1.04-1.28)**		**1.28 (1.05-1.66)**	
Multivariable analysis	**Adjusted HR (95%CI)**	**p-value**	**Adjusted HR (95%CI)**	**p-value**
Etiology of MR		**0.283**		**0.163**
DMR	**1**		**1**	
FMR	**0.80 (0.55-1.19)**		**0.78 (0.55-1.10)**	
Age (cont.)	1.04 (1.02-1.07)	0.001	1.01 (0.99-1.03)	0.079
Gender		0.417		0.491
Female	1		1	
Male	1.15 (0.81-1.64)		1.11 (0.82-1.50)	
NYHA class		0.083		0.067
I/II	1		1	
III / IV	1.38 (0.95-1.99)		1.37 (0.98-1.92)	
Preoperative Hb value (cont.)	0.81 (0.74-0.89)	<0.001	0.87 (0.80-0.95)	0.002
Preoperative Creatinine value (log.)	1.45 (1.10-1.93)	0.009	1.11 (0.86-1.44)	0.396
Preoperative LVEF (cont.)	0.98 (0.97-0.99)	0.009	0.97 (0.96-0.98)	<0.001
Preoperative RV/RA gradient		0.410		0.989
< 30 mmHg	1		1	
≥30 mmHg	1.16 (0.81-1.67)		1.01 (0.71-1.40)	
Number of Clips implanted		0.684		0.118
<2	1		1	
≥2	0.93 (0.68-1.28)		1.26 (0.94-1.69)	
Post Mitraclip MR		0.610		0.181
Grade 1-2	1		1	
Grade 3-4	1.10 (0.75-1.60)		1.25 (0.90-1.75)	
Multivariable model p-value	***p<0.001***		***p<0.001***	
Harrel's c (model discrimination)	***0.71***		***0.67***	
Interaction of postop MR & etiology	***p=0.65***		***p=0.99***	

Supplementary figure 1. Patient's flow chart.