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Clinical Research

Impact of procedural success on clinical outcome after MitraClip: Results from the MITRA-FR trial☆

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HIGHLIGHTS

- Different procedural success rates may explain divergent MITRA-FR and COAPT results.
- Optimal procedural result was defined as residual MR grade ≤ 1 + at discharge.
- Controls received guideline-directed medical therapy only.
- Outcomes: 24-month all-cause death or unplanned heart failure hospitalization.
- Patients with an optimal procedural result and controls had similar outcomes.
- Our results do not support this hypothesis.

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ABSTRACT

Background: Differences in procedural success rates have been proposed to explain the divergent results between the MITRA-FR trial (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation).
Aim: To examine whether MITRA-FR patients who had successful clip implantation achieved a better outcome than the control group.

Abbreviations: CI, confidence interval; COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; ERO, effective regurgitant orifice; HR, hazard ratio; LV, left ventricular; MR, mitral regurgitation; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; TMVr, transcatheter mitral valve repair.

☆ Tweet: The present MITRA-FR sub-study does not support the hypothesis that the differences in rates of residual mitral regurgitation at discharge between MITRA-FR and COAPT explain the divergent results between the two trials.

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Methods: Based on the per protocol population of MITRA-FR, we compared the outcome in 71 patients in whom optimal clip implantation was achieved (group 1: mitral regurgitation grade ≤ 1 + at discharge) with that in 23 patients with non-optimal clip implantation (group 2: mitral regurgitation grade ≥ 2 + at discharge) and that in 137 patients in the control group (group 3). The primary endpoint was all-cause death or unplanned hospitalization for heart failure at 24 months.
Results: Event-free survival was not different across the groups (42 ± 6% in group 1, 30 ± 10% in group 2 and 31 ± 4% in group 3; log-rank $P = 0.32$). In multivariable analyses, after adjustment for age, sex, rhythm, aetiology, left ventricular ejection fraction and mitral regurgitation severity, group was not associated with variations in outcome: using Group 3 as reference, hazard ratio 0.86, 95% confidence interval 0.58–1.27 ($P = 0.43$) in group 1; and hazard ratio 0.98 95% confidence interval 0.54–1.76 ($P = 0.94$) in group 2.
Conclusions: The clinical outcome of patients in whom optimal procedural result was achieved at discharge was not different compared with the control group. Our results do not support the hypothesis that the differences in rates of residual mitral regurgitation at discharge between MITRA-FR and COAPT explain the divergent results between the two trials.

1. Background

The discordant results of the two randomized controlled trials that have evaluated the benefit of transcatheter correction of secondary mitral regurgitation (MR) in patients with left ventricular (LV) systolic dysfunction using the MitraClip system (Abbott Vascular, Chicago, IL, USA) have generated significant controversy among the medical community. Whereas the MITRA-FR trial (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) was neutral, showing no difference in all-cause mortality or unplanned hospitalization for heart failure between the intervention and control arms at 12 and 24 months [1,2], the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) [3] showed a significant decrease in all-cause mortality and heart failure hospitalizations at 24 months in the transcatheter mitral valve repair (TMVr) group. Differences in baseline characteristics (lower degree of MR severity with more advanced LV remodelling in MITRA-FR than in COAPT) and the proportionate/disproportionate concept have emerged as a potential framework for identifying which patients might benefit from MR correction [4]. However, recent MITRA-FR subgroup analyses have failed to identify a subset of patients, defined in terms of degree of regurgitation or LV remodelling/dysfunction or their combination–including subsets deemed to have disproportionate MR – that might have benefited from transcatheter correction using the MitraClip system [5]. The presumed lower procedural success rates in MITRA-FR compared with COAPT, as assessed by residual MR severity, has also been proposed to explain the differences in outcomes between the two trials. In order to test the potential impact of procedural success on clinical outcomes in the MITRA-FR trial, we compared the outcomes in patients in whom successful clip implantation was achieved with outcomes in the control group, and we tested the potential interaction with the severity of MR.

2. Methods

2.1. The MITRA-FR trial

The design of the MITRA-FR trial has been published previously [6]. Briefly, from December 2013 to March 2017, at 37 French centres, MITRA-FR randomized 307 patients with severe secondary MR, who were symptomatic despite guideline-driven medical therapies, in a 1:1 ratio, to undergo percutaneous mitral valve repair in addition to optimized medical therapy (intervention group) or to receive medical therapy alone (control group). The primary endpoint was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months, which was subsequently extended to 24 months [1,2]. Eligible patients had severe secondary MR, with a regurgitant volume ≥ 30 mL/beat or an effective regurgitant orifice (ERO) area ≥ 20 mm^2 [7], an LV ejection fraction between 15% and 40% and chronic heart failure symptoms (assessed as New York Heart Association functional class II, III or IV). Before enrolment (as well as during follow-up), each investigator was instructed to up-titrate all guideline-driven medical therapies to maximally tolerated doses, according to updated European guidelines for the medical management of heart failure with reduced LV ejection fraction [8,9].

Randomization was performed in permuted blocks, with stratification according to trial centre. The trial was approved by the ethics committee, and written informed consent was obtained from all the patients before the initiation of trial procedures. A steering committee designed the trial protocol, and an independent data and safety monitoring board oversaw the safety of the trial. An independent events validation committee blindly adjudicated all serious adverse events to be classified in the corresponding clinical outcomes according to the prespecified definition of events.

There was no patient or public involvement in the design, conduct, choice of outcome measures and recruitment of the study. The trial is registered on ClinicalTrials.gov (identifier: NCT01920698).

2.2. Echocardiographic assessment

Before randomization, all patients underwent transthoracic and transoesophageal echocardiography, reviewed by an independent centralized core laboratory (Bichat Hospital, Paris, France), according to the European Association of Echocardiography guidelines [7]. All echocardiographic variables were measured centrally. End-systolic and end-diastolic LV diameters were measured in the parasternal long-axis view. LV end-systolic volume, LV end-diastolic volume and LV ejection fraction were measured using the biplane Simpson's method of disk. Left atrial volume was derived from the biplane area-length method. Quantification of MR severity at baseline and calculation of the ERO and regurgitant volume relied on the PISA (proximal isovelocity surface area) method. Echocardiography was repeated at discharge for patients in the intervention arm. The degree of MR at discharge was semi-quantitatively graded by the centralized core laboratory as grade 0+ (none or trace), 1+ (mild), 2+ (mild to moderate), 3+ (moderate to severe) or 4+ (severe), based on a multiparametric approach, as recommended [7].

2.3. Study device and procedure

The device used in the trial, namely the MitraClip system, and the related percutaneous procedure have been described

Table 1
Comparison of baseline characteristics according to group.

Characteristics	Successful clip implantation ($n = 71$)	Non-successful clip implantation ($n = 23$)	Control arm ($n = 137$)	*P*
Age (years)	69 ± 10	73 ± 8	71 ± 10	0.28
Male sex	57 (80)	20 (87)	96 (70)	0.11
Ischaemic cardiomyopathy	51 (72)	13 (57)	77 (57)	0.09
Previous myocardial infarction	41 (58)	11 (48)	48 (35)	< 0.01
Previous coronary revascularization	40 (56)	11 (48)	58 (43)	0.17
Atrial fibrillation	22 (33)	11 (52)	43 (32)	0.21
Diabetes	25 (39)	5 (22)	38 (29)	0.23
Severe renal insufficiency	6 (9)	4 (17)	17 (13)	0.56
NYHA class III or IV	45 (63)	16 (70)	101 (74)	0.28
Systolic blood pressure (mmHg)	110 ± 15	111 ± 20	108 ± 17	0.74
Heart rate (beats/min)	72 ± 14	76 ± 11	73 ± 13	0.47
EuroSCORE II[a]	6 (3–12)	7 (5–15)	6 (4–10)	0.50
LV ejection fraction (%)	33 ± 6	34 ± 6	33 ± 7	0.99
LV end-diastolic diameter (mm)	68 ± 8	71 ± 8	69 ± 8	0.09
LV end-diastolic diameter index (mm/m^2)	37 ± 5	38 ± 4	38 ± 5	0.07
LV end-systolic diameter (mm)	57 ± 9	61 ± 8	59 ± 9	0.09
LV end-systolic diameter index (mm/m^2)	31 ± 5	33 ± 5	32 ± 5	0.07
LV end-diastolic volume (mL)	247 ± 80	272 ± 69	249 ± 75	0.17
LV end-diastolic volume index (mL/m^2)	132 ± 38	145 ± 31	135 ± 34	0.16
LV end-systolic volume (mL)	166 ± 68	182 ± 56	168 ± 64	0.25
LV end-systolic volume index (mL/m^2)	89 ± 33	97 ± 27	91 ± 30	0.20
Systolic pulmonary pressure (mmHg)	53 ± 16	55 ± 15	54 ± 14	0.77
Effective regurgitant orifice area (mm^2)	29 ± 8	37 ± 13	31 ± 12	0.01
Effective regurgitant orifice area ≥ 30 mm^2	27 (38)	15 (65)	65 (47)	0.08
Regurgitant volume (mL)	43 ± 14	51 ± 11	46 ± 15	0.01
NT-proBNP (ng/L)	2,884 (1,778–5,180)	6790 (3,231–14,551)	3484 (2091–6276)	0.03
BNP (ng/L)	726 (310–1,105)	875 (712–1251)	842 (497–1349)	0.30
Glomerular filtration rate (mL/min)	49 ± 20	43 ± 13	50 ± 20	0.46

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). BNP: brain natriuretic peptide; LV: left ventricular; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association.

[a] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation, and ranges from 0% to 100%, with higher scores indicating greater risk.

previously. After randomization to the intervention group, the procedure was performed within a median of 14 (interquartile range 9–18) days. All procedures were performed with technical proctoring from Abbott Vascular.

2.4. Statistical analysis

The primary endpoint was the composite of all-cause death or unplanned hospitalization for heart failure at 24 months. The secondary outcomes measures were individual components of the primary outcome at 24 months. Analyses were carried out according to the per protocol principle, excluding patients who had a protocol deviation and patients in the intervention group in whom the device was not implanted, and excluding all events that occurred during the first 21 days.

For the purpose of the present post-hoc analysis, the per protocol population was divided into three groups: patients who had optimal procedural clip implantation, defined as a residual MR grade ≤ 1+ at discharge (group 1); patients who had a non-optimal procedural clip implantation, defined as a residual MR grade ≥ 2+ at discharge (group 2); and patients in the control arm (group 3). Events rates by groups are presented on the basis of the Kaplan-Meier estimates in time to first event analysis, and were compared using the log-rank test. Comparisons between groups were performed using the Kruskal-Wallis test for quantitative variables, and Fisher's exact test for binary or ordinal variables. As the group definitions did not follow the randomization rule, and groups were likely to differ in term of baseline characteristics, the impact of procedural success was assessed using Cox proportional-hazards analysis, after adjustment for age, rhythm, aetiology (ischaemic versus dilated cardiomyopathy), LV ejection fraction, systolic pulmonary artery pressure and ERO. To evaluate the interaction between the degree of MR at baseline and outcomes, comparisons of event-free survival curves between the three groups were also performed separately in patients with an ERO ≥ 30 mm^2 and in patients with an ERO < 30 mm^2. A two-sided *P*-value < 0.05 was considered to indicate statistical significance. SAS software for Windows, version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

3. Results

3.1. Population

The per protocol population consisted of 246 patients (109 patients in the intervention group and 137 in the control arm). Of the 109 patients in the intervention group, MR grade could not be evaluated at discharge in 15 patients; as a result, these patients were excluded. For completeness, a comparison of the baseline characteristics of these 15 patients with those of the rest of the intervention group is presented in Online material Table A.1. Of the 94 remaining patients, MR grade at discharge was ≤ 1+ in 71 patients (group 1) and ≥ 2+ (group 2) in 23 patients, including eight patients with an MR grade of 3+/4+. Patients in group 1 tended to present more often with ischaemic heart disease, whereas patients in group 2 presented with a more severe degree of regurgitation and LV remodelling (Table 1).

3.2. Primary outcome

Overall, at 2 years, 151 patients died or had unplanned hospitalization for heart failure: 41 patients in group 1; 16 patients in group 2; and 94 patients in group 3. Event-free survival rates at 24 months were 42 ± 6% in group 1, 30 ± 10% in group 2 and 31 ± 4% in group 3, and did not differ statistically across the three groups (log-rank *P* = 0.32) (Fig. 1, central illustration). In multivariable analysis, after adjustment for age, rhythm, aetiology (ischaemic versus

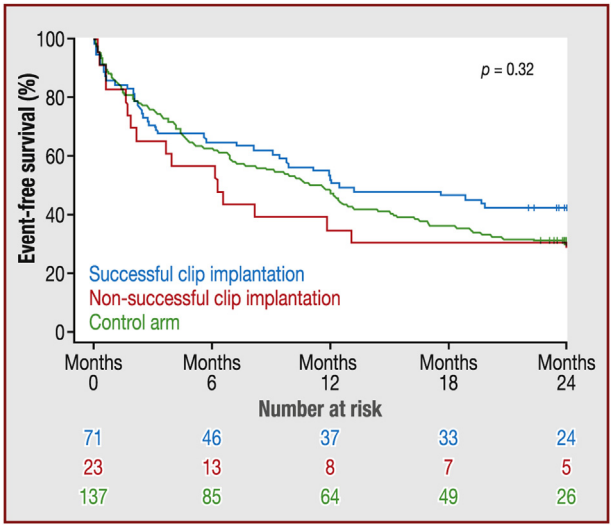


Fig. 1. Kaplan-Meier estimates of survival without a primary outcome event (all-cause death or unplanned hospitalization for heart failure) according to group. Group 1 in blue: patients from the intervention arm with optimal successful clip implantation (residual mitral regurgitation grade ≤ 1 + at discharge). Group 2 in red: patients from the intervention arm with non-successful clip implantation (residual mitral regurgitation grade ≥ 2 + at discharge). Group 3 in green: control or medical arm. The number of patients at risk in each group is presented at the bottom of the figure.

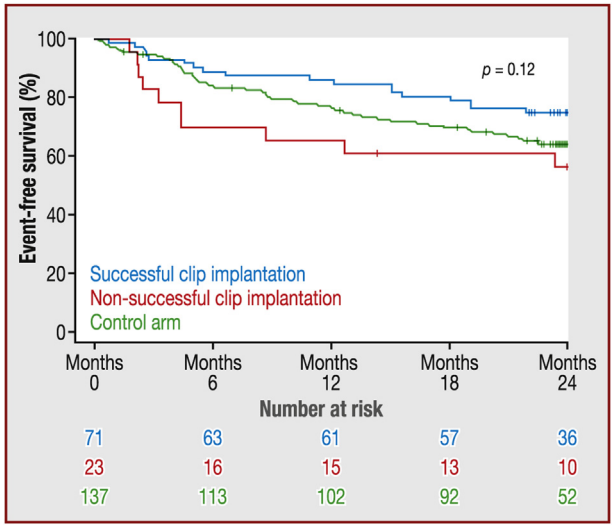


Fig. 2. Kaplan-Meier estimates of survival according to group. Group 1 in blue: patients from the intervention arm with optimal successful clip implantation (residual mitral regurgitation grade ≤ 1 + at discharge). Group 2 in red: patients from the intervention arm with non-successful clip implantation (residual mitral regurgitation grade ≥ 2 + at discharge). Group 3 in green: control or medical arm. The number of patients at risk in each group is presented at the bottom of the figure.

dilated cardiomyopathy), LV ejection fraction and ERO, group was not associated with differences in outcomes (using group 3 as reference: hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.58–1.27 [$P = 0.43$] in group 1; and HR 0.98, 95% CI 0.54–1.76 [$P = 0.94$] in group 2). Adding systolic pulmonary pressure into the model (available in 197 patients) did not change our conclusions (using group 3 as reference: HR 0.94, 95% CI 0.60–1.47 [$P = 0.77$] in group 1; and HR 0.99, 95% CI 0.51–1.98 [$P = 0.99$] in group 2). Also, our results remained unchanged when adding sex, history of myocardial infarction or LV end-systolic indexed volume into the model (all $P > 0.40$).

3.3. Secondary outcomes

Event-free survival curves for each component of the primary endpoint are presented in Fig. 2 (all-cause death) and Fig. 3 (unplanned hospitalization for heart failure). There were 73 death events during follow-up: 18 in group 1; 10 in group 2; and 48 in group 3. Overall survival rates were not different across groups (75 ± 5% in group 1, 56 ± 10% in group 2 and 64 ± 4% in group 3; log-rank $P = 0.12$). In multivariable analysis, group was not associated with differences in mortality rates (using group 3 as reference: HR 0.72, 95% CI 0.40–1.29 [$P = 0.27$] in group 1; and HR 1.25, 95% CI 0.57–2.74 [$P = 0.57$] in group 2).

In addition, 140 patients had unplanned hospitalization for heart failure during follow-up: 38 in group 1; 15 in group 2; and 87 in group 3. Event-free survival rates were also not different across groups (45 ± 6% in group 1, 32 ± 10% in group 2 and 34 ± 4% in group 3; log-rank $P = 0.34$). In multivariable analysis, no differences were seen (using group 3 as reference: HR 0.86, 95% CI 0.57–1.30 [$P = 0.48$] in group 1; and HR 1.07, 95% CI 0.59–1.95 [$P = 0.82$] in group 2).

As for the primary outcome, results remained unchanged when systolic pulmonary pressure was entered into the model (using group 3 as reference: HR 0.82, 95% CI 0.43–1.58 [$P = 0.56$] in group 1 and HR 1.11, 95% CI 0.43–2.91 [$P = 0.83$] in group 2 for all-cause death; and HR 0.94, 95% CI 0.59–1.51 [$P = 0.81$] in group 1 and HR

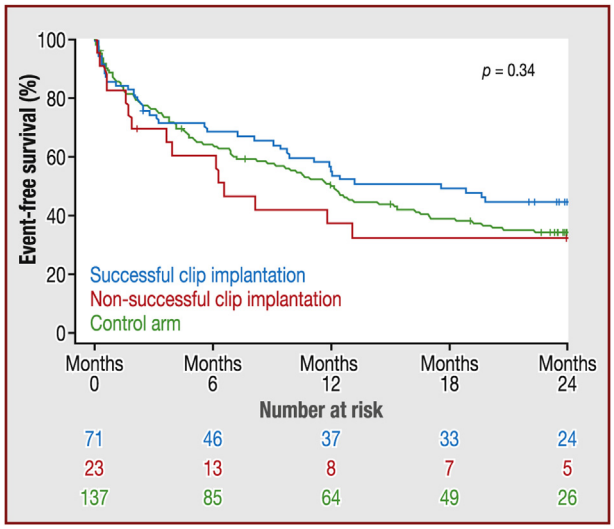


Fig. 3. Kaplan-Meier estimates of survival without unplanned hospitalization for heart failure according to group. Group 1 in blue: patients from the intervention arm with optimal successful clip implantation (residual mitral regurgitation grade ≤ 1 + at discharge). Group 2 in red: patients from the intervention arm with non-successful clip implantation (residual mitral regurgitation grade ≥ 2 + at discharge). Group 3 in green: control or medical arm. The number of patients at risk in each group is presented at the bottom of the figure.

1.10, 95% CI 0.56–2.18 [$P = 0.78$] in group 2 for unplanned hospitalization for heart failure).

3.4. Interaction with baseline MR severity

Event-free survival rates by group for the primary endpoint and its components were also evaluated separately in the subset of patients with an ERO ≥ 30 mm^2 ($n = 107$) and in the subset of patients with an ERO < 30 mm^2 ($n = 124$). No difference in outcome was observed for the primary endpoint and both of its components per group in both subsets (all $P > 0.20$).

4. Discussion

In MITRA-FR, the outcomes (composite of all-cause death or unplanned hospitalization for heart failure at 24 months, or each of its components) were not different between patients in whom an optimal procedural result (defined as residual MR grade ≤ 1+ at discharge) was achieved and patients in the control arm (guideline-directed medical therapy only).

TMVr using the MitraClip is a complex intervention that requires close collaboration within a multidisciplinary team, and a unique skillset for both the operator and the echocardiographer guiding the intervention. As with surgery, residual MR after TMVr has been shown to be an important prognostic factor, associated with higher readmission rates and lower survival [10–14]. Therefore, the goal of TMVr, as for surgery, should be to achieve a residual MR that is no more than mild for each procedure. Factors associated with higher procedural success rate include the experience of the operator and of the team. Both operator and institutional volumes are associated with higher rates of optimal results and, consequently, outcomes, as well as lower complication rates [15,16]. In addition, appropriate patient selection is critical in order to be able to achieve optimal procedural success and probably improve patient outcome.

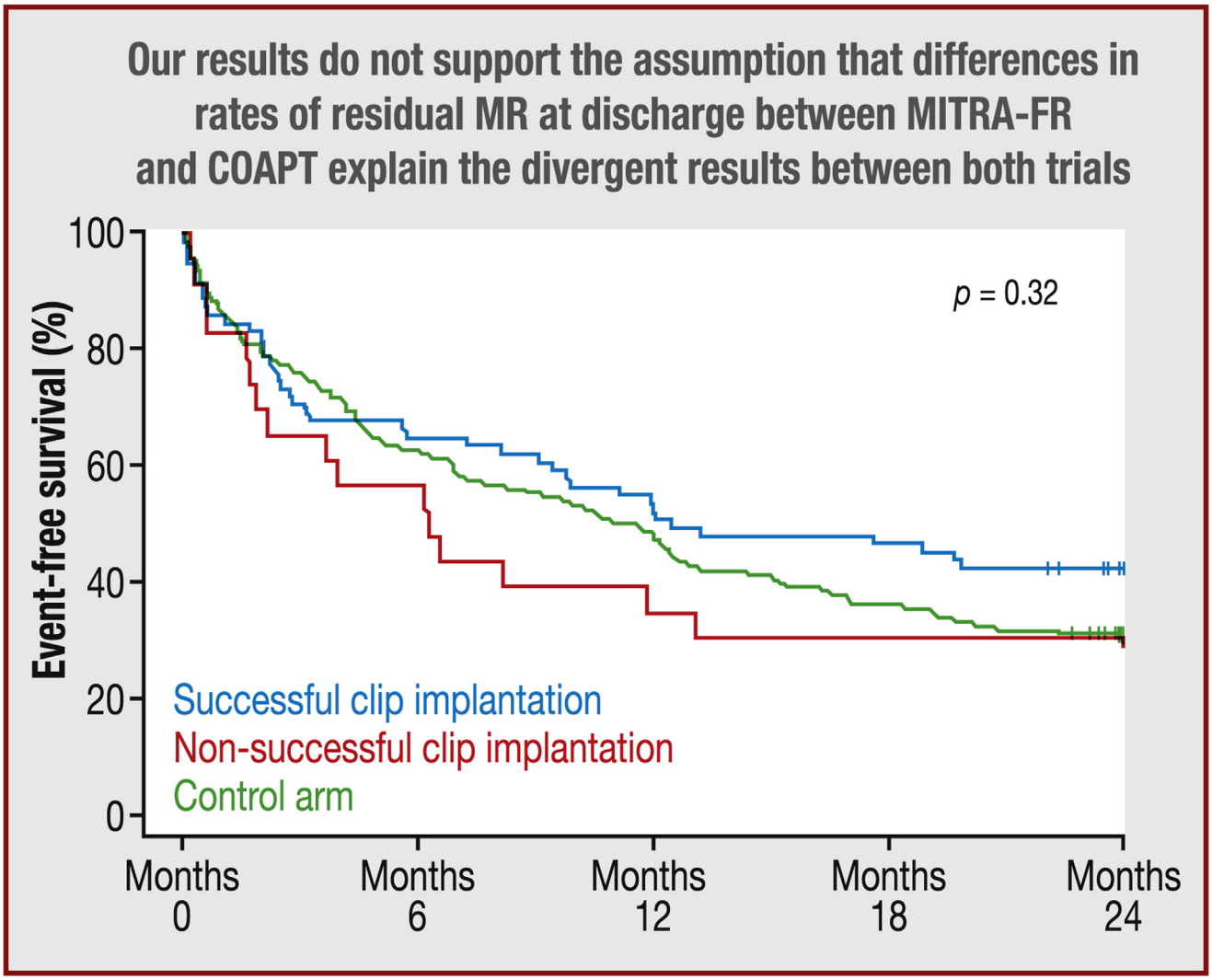
As procedural success rates were slightly higher in COAPT than in MITRA-FR (82% vs. 76%, respectively, in patients in whom MR degree was available at discharge in both trials), it has been suggested that this difference in residual MR severity contributed to the divergent results observed in these two trials. However, it is worth noting that the difference was of small magnitude, and that the overall procedural results of the intervention compared well with contemporary registries in both trials [12,16]. In addition, this difference should be interpreted cautiously because of the difficulty in quantifying residual MR on a double orifice, and the possible heterogeneity of the assessments between the core laboratories of the two trials. The lower optimal procedural success rate could have been the consequence of patient selection and differences in patients' baseline characteristics, with enrolment of patients at a more advanced disease stage in MITRA-FR and/or a lower level of experience of the operators/teams. Regarding the former, in a MITRA-FR subanalysis we were unable to identify a subset of patients based on MR severity, LV remodelling or their combination who may have benefited from the intervention. Although the presence of a learning curve for this intervention is indubitable, in MITRA-FR there was no interaction between centre size (high/low enrolling centres) as a surrogate for centre experience and the impact of the intervention (HR 1.50, 95% CI 0.80–2.9 in centres that enrolled > 15 patients, and HR 0.90, 95% CI 0.50–1.70 in centres that enrolled ≤ 15 patients for the primary endpoint) [1]. Nevertheless, in an attempt to reconcile MITRA-FR and COAPT divergent results, we compared the outcomes of patients with optimal procedural success with the remaining population and, more specifically, the control group (who received guideline-driven medical therapy only). In this per protocol analysis, the outcomes in patients with an optimal procedural result and in the control group were not different as measured by the primary endpoint or each of its components at 24 months. The absence of difference was observed in univariate analysis and in multivariable analysis, as baseline characteristics of the groups were slightly different and the group definitions did not follow the randomization rules. Thus, the slightly lower procedural success rate in MITRA-FR than in COAPT is unlikely to explain the different results between the two trials, especially of such magnitude. Importantly, we are certainly not implying that procedural success rate has no impact on outcome, but that in MITRA-FR we did not observed a difference in outcomes between patients in whom an optimal procedural result was achieved and the control arm, suggesting that MR may not be the main driver of outcome in this population. In addition, it is worth noting that the number of patients with grade 3+/4+ residual MR in our study was small, and in a recent subanalysis of COAPT, if degree of residual MR predicted outcome, there was no difference between patients who achieved 0/1+ and 2+ residual MR [17].

Altogether, this subanalysis, as well as those published previously [5,18], consistently shows a neutral effect of TMVr on all-cause death or unplanned hospitalization for heart failure at 24 months in all MITRA-FR subsets. This greatly contrasts with COAPT findings that consistently report a beneficial effect of TMVr in all subsets [19–21]. The present analyses illustrate the critical need to better identify the subsets of patients that will benefit from TMVr. Although rarely mentioned, such identification is also critical to identify patients who will not benefit from TMVr, because the disease is already too advanced or because they may improve under medical therapy. Thus, in COAPT, 25–30% of patients on guideline-directed medical therapy improved, in terms of both MR degree and outcomes, and were considered as responders or super-responders [11,17].

The present study deserves several comments. First, it is a post-hoc analysis, with the inherent bias and limitations of such an analysis. Second, our sample size was relatively small, and there was a trend towards a better outcome in group 1. We cannot exclude that a difference between groups might have been observed with a larger sample size and/or longer follow-up (ongoing). However, evaluation of the impact of TMVr was derived from one of the only two currently available randomized controlled trials comparing TMVr with optimal medical treatment. MITRA-FR enrolled a contemporary and well-defined population of patients with secondary MR and guideline-directed optimal medical heart failure therapy. All measurements were performed by a centralized core laboratory, although no variables evaluating right ventricular function were collected. Outcomes were collected prospectively; all events were adjudicated by an independent committee, and follow-up was 99% complete at 1 year and 95% complete at 2 years. Third, the 15 patients excluded from the present study because of lack of evaluation of residual MR tended to present with more severe MR at baseline, and a selection bias cannot be excluded. Finally, we only assessed procedural success at discharge, and durability of the results during follow-up could not be assessed in MITRA-FR. Whether a higher MR recurrence rate in MITRA-FR compared with COAPT as a result of more advanced disease severity and LV remodelling, as shown for surgical MV repair [22], explains (at least partially) the divergent results between the two trials cannot be excluded. The impact of MR recurrence on top of MR severity at discharge after TMVr has recently been reported in a single-centre observational study [12].

5. Conclusions

In the MITRA-FR trial, the outcome (measured in terms of all-cause death or unplanned hospitalization for heart failure at 24 months) in patients in whom an optimal procedural result was achieved at discharge (defined as an MR grade ≤ 1 +) was not different compared with the control group. Our results do not support the hypothesis that the differences in rates of residual MR at discharge between MITRA-FR and COAPT explain the divergent results between the two trials. The present study, showing a neutral effect of TMVr in patients with optimal procedural results, as in all MITRA-FR subsets investigated so far, strongly suggests that MR in this population was not the primary driver of outcome, and further emphasizes the critical need to better identify patients with functional MR who may benefit from TMVr as opposed to those who will not (Central illustration).



Central illustration. Our results do not support the hypothesis that the differences in rates of residual mitral regurgitation at discharge between MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) explain the divergent results between the two trials.

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Disclosure of interest

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P. G.: consultant for the companies Abbott, Edwards Lifesciences and Boston Scientific.

T. L.: proctor for the company Abbott.

A. V.: consultant for the company Cardiovalve.

The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2022.05.013.

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