

Impact of Mitral Regurgitation Severity and Left Ventricular Remodeling on Outcome After Mitraclip Implantation: Results From the Mitra-FR Trial

David Messika-Zeitoun, Bernard Iung, Xavier Armoiry, J.-N. Trochu, Erwan Donal, Gilbert Habib, Eric Brochet, Hélène Thibault, Nicolas Piriou,

Bertrand Cormier, et al.

▶ To cite this version:

David Messika-Zeitoun, Bernard Iung, Xavier Armoiry, J.-N. Trochu, Erwan Donal, et al.. Impact of Mitral Regurgitation Severity and Left Ventricular Remodeling on Outcome After Mitraclip Implantation: Results From the Mitra-FR Trial. JACC: Cardiovascular Imaging, 2021, 14 (4), pp.742-752. 10.1016/j.jcmg.2020.07.021. hal-02959038

HAL Id: hal-02959038 https://hal.science/hal-02959038v1

Submitted on 24 Apr 2023 $\,$

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Impact of Mitral Regurgitation Severity and Left Ventricular Remodeling on Outcome after Mitraclip implantation – Results from the Mitra-FR Trial

David Messika-Zeitoun, MD, PhD 1, Bernard Iung, MD 2,3, Xavier Armory PharmD, PhD 4 Jean-Noël Trochu MD, PhD 5, Erwan Donal MD, PhD 6, Gilbert Habib MD, PhD 7,8, Eric Brochet MD 3, Hélène Thibault MD 9, Nicolas Piriou MD 5, Bertrand Cormier MD 10 Christophe Tribouilloy MD, PhD 11, Patrice Guerin MD, PhD 12, Thierry Lefèvre MD 10, Delphine Maucort-Boulch MD, PhD 13, Alec Vahanian MD 2, Florent Boutitie MD, PhD 13, Jean-Francois Obadia, MD, PhD 14

- 1. Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Canada;
- 2. Université de Paris and INSERM 1148, Paris, France;
- 3. APHP, Hôpital Bichat, DHU FIRE, Paris, France;
- 4. Edouard Herriot Hospital, Pharmacy Department / Claude Bernard University- Laboratoire MATEIS, Lyon, France;
- 5. Université Nantes, CHU Nantes, CNRS, INSERM, l'institut du Thorax, Nantes, France
- 6. CHU de Rennes, Hôpital Pontchaillou, Rennes, France and LTSI UMR1099, INSERM, Universite de Rennes-1, Rennes, France
- 7. APHM, La Timone Hospital, Cardiology Department, Marseille France
- 8. Aix Marseille Univ, IRD, APHM, MEPHI, IHU-Méditerranée Infection, Marseille, France
- 9. Groupement Hospitalier Est, Hospices Civils de Lyon, Service d'Explorations Fonctionnelles Cardiovasculaires, 28 AvenueDoyen Lépine, Bron 69677, France
- 10. Institut Cardiovasculaire Paris Sud, Hôpital Privé Jacques Cartier, Massy, France
- 11. Department of Cardiology, Amiens University Hospital, Amiens, France; EA 7517 MP3CV, Jules Verne University of Picardie, Amiens, France
- 12. CHU Nantes, INSERM UMR 1229, Nantes University, Interventional Cardiology unit, Institut du Thorax, Nantes, France
- Université Lyon 1, Villeurbanne, France; CNRS, UMR5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, Service de Biostatistique - Bioinformatique, Pôle Santé Publique, Hospices Civils de Lyon, Villeurbanne, France;
- 14. Hopital Cardiovasculaire Louis Pradel, Chirurgie Cardio-Vasculaire et Transplantation Cardiaque, Hospices Civils de Lyon and Claude Bernard University, Lyon, France

Address for correspondence:

David Messika-Zeitoun, Department of Cardiology, University of Ottawa Heart Institute, Ottawa, Canada. E-mail: <u>DMessika-zeitoun@ottawaheart.ca</u>. Tel: 613-696-7337; Fax: 613-696-7127

Jean-Francois Obadia, Hôpital Cardiovasculaire Louis Pradel, Chirurgie Cardio-Vasculaire et Transplantation Cardiaque, 28, Avenue Doyen Lépine, 69677 Bron Cedex, France. Email: jean-francois.obadia@chu-lyon.fr. Tel: +33 4 72 11 90 00

FUNDING: Funded by the French Ministry of Health and Research National Program and Abbott Vascular

ACKNOWLEDGEMENTS: None

CONFLICTS OF INTEREST:

- David Messika-Zeitoun received consultant fees from Edwards Lifesciences
- Bernard Iung, has received consultant fees from Edwards Lifesciences and travel fees from Boehringer Ingelheim
- Xavier Armory None
- Jean-Noël Trochu has received speaker's honoraria, travel and grant support from Abbott and Novartis, honoraria for lectures or advisory boards from Amgen, Bayer, Resmed, grants from the EU programme Horizon 2020 and is an unpaid member of the Corvia Medical Scientific Advisory Group outside the submitted work.
- Erwan Donal get research facilities from General Electric Healthcare and consultant fees from Abbott.
- Gilbert Habib none
- Eric Brochet served as proctor for Abbott
- Hélène Thibault none
- Nicolas Piriou received consultant fees from Abbott
- Bertrand Cormier none
- Christophe Tribouilloy none
- Patrice Guerin is consultant for Abbott, Edwards Lifesciences and Boston scientifics
- Thierry Lefèvre served as proctor for Abbott
- Delphine Maucort-Boulch none
- Alec Vahanian is consultant for consultancy Cardiovalve
- Florent Boutitie none
- Jean-Francois Obadia none

Clinical Trial: MITRA-FR ClinicalTrials.gov number, NCT01920698

ABSTRACT

Objectives. We aimed to identify a subset of patients based on echocardiographic parameters that might have benefited from transcatheter correction using the Mitraclip system in the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial.

Background. It has been suggested that differences in the degree of mitral regurgitation (MR) and left ventricular (LV) remodeling may explain the conflicting results between the MITRA-FR and the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trials.

Methods. In a post-hoc analysis, we evaluated the interaction between the intervention and subsets of patients defined based on MR severity (effective regurgitant orifice [ERO], regurgitant volume [RVOL] and regurgitant fraction [RF]), LV remodelling (end-diastolic and end-systolic diameters and volumes) and combination of these parameters with respect to the composite of death from any cause or unplanned hospitalization for heart failure at 24 months.

Results. We observed a neutral impact of the intervention in subsets with the highest MR degree (ERO \geq 30 mm², RVOL \geq 45 ml or RF \geq 50%) as in patients with milder MR degree. The same was seen in subsets with the milder LV remodelling using either diastolic or systolic diameters or volumes. When parameters of MR severity and LV remodelling were combined, there was still no benefit of the intervention including in the subset of patients with an ERO/end-diastolic volume ratio \geq 0.15 despite similar ERO and LV end-diastolic volume compared to COAPT patients.

Conclusions. In the MITRA-FR trial, we could not identify a subset of patients defined based on the degree of the regurgitation, LV remodelling or on their combination, including those deemed as having disproportionate MR, that might have benefited from transcatheter correction using the Mitraclip system.

Funded by the French Ministry of Health and Research National Program and Abbott Vascular; MITRA-FR ClinicalTrials.gov number, NCT01920698.

Key words. Mitral regurgitation. Transcatheter mitral valve therapy, outcomes

ABBREVIATIONS:

COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation ERO: effective regurgitant orifice GDMT: guideline-directed medical therapy LV: left ventricular LVOT: left ventricular outflow tract MR: mitral regurgitation MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation RF: regurgitation fraction RVOL: regurgitant volume TMVR:transcatheter mitral valve repair

INTRODUCTION

Secondary mitral regurgitation (MR) usually develops as a consequence of left ventricular (LV) dilatation and dysfunction.(1,2) While the association between secondary MR and outcome is undisputed (3-6), the beneficial impact of its correction remained debated. The publication of the MITRA-FR trial (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) (7,8) which showed no difference in all-cause mortality or unplanned hospitalization for heart failure at 12 and at 24 months between the control and intervention arms, and of the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) (9), showing a decrease of all-cause mortality and heart failure hospitalizations at 24 months in the percutaneous repair group, has generated a lot of controversies. Differences in procedural expertise between the two groups of investigators were modest and are unlikely to explain divergent results of such magnitude. Differences in the baseline characteristics of the population enrolled in the MITRA-FR and COAPT trials has led to the hypothesis that transcatheter mitral valve repair (TMVR) using the Mitraclip system might be effective in improving outcome in selected patients with secondary MR. However, no clear selection criteria could be derived from the two trials.

In this regard, differences in the degree of MR and of LV remodeling between the two studies have attracted a lot of attention. The importance of these parameters is supported by observational studies showing that the prognostic impact of secondary MR is less prominent in patients with advanced heart failure suggesting that MR correction in these subsets may provide limited benefit.(10) The concept of proportionate / disproportionate MR (ratio of MR severity / LV dimension and whether the degree of MR is expected or not for the observed degree of LV dilatation) has emerged as a framework to predict which patient might benefit from MR correction. The main principle underpinning this concept is that when the degree of MR is significantly higher than what would be expected for the observed degree of LV remodeling (disproportionate), MR is driving the outcome and consequently its correction might be beneficial. In contrast, in patients with proportionate MR, LV remodeling / dysfunction is the main determinant of the outcome so that MR correction would not affect the outcome.

So far, the concept of proportionate/disproportionate MR has not been assessed on individual patient data. We aimed to evaluate in a post-hoc analysis of the MITRA-FR trial whether we could identify a subset of patients based on the degree of MR and of LV remodeling, in isolation or in combination, including patients with so-called disproportionate MR, that might have benefited from TMVR using the Mitraclip system.

METHODS

The MITRA-FR trial

The design of the MITRA-FR trial has been previously published.(11) Briefly MITRA-FR randomized 307 patients enrolled between December 2013 through March 2017 at 37 French centers in a 1:1 ratio, to undergo TMVR in addition to guideline-directed medical therapy (GDMT) including resynchronisation (intervention group) or to receive GDMT alone (control group). The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months. Following the publication of MITRA-FR results at 12 months, results at 24 months were also reported.(7,8) Eligible patients had severe secondary MR with an effective regurgitant orifice (ERO) area \geq 20 mm² or a regurgitant volume (RVOL) \geq 30 ml per beat as assessed by echocardiography,(12) a left ventricular ejection fraction between 15% and 40% and chronic heart failure symptoms (New York Heart Association [NYHA] functional class II, III, or IV). Before enrollment, each investigator was instructed to up-titrate all GDMTs to maximally tolerated doses according to updated European guidelines for medical management of heart failure with reduced left ventricular ejection fraction.(13,14) Randomization was performed in permuted blocks, with stratification according to trial center. The trial was approved by the Ethics committee and written informed consent was obtained from all the patients before the initiation of trial procedures. An independent events validation committee adjudicated all serious adverse events against pre-specified definitions. The members of this committee were blinded to treatment assignment.

Echocardiographic assessment

Before randomization, all patients underwent a transthoracic and transoesophageal echocardiography reviewed by an independent centralized core laboratory (Bichat hospital, Paris, France) according to the European Association of Echocardiography guidelines.(12) All echocardiographic parameters were measured centrally. End-systolic and end-diastolic LV diameters were measured in the parasternal long-axis view. LV end-systolic volume, LV enddiastolic volume and LV ejection fraction were measured using the biplane Simpson method of disk. LA volume was derived from the biplane area-length method. The aortic stroke volume was calculated by multiplying the LV outflow tract (LVOT) area, derived from measurement of the LVOT diameter assuming a circular shape, with the LV outflow tract time-velocity integral measured using pulsed Doppler. Quantification of MR severity and calculation of the ERO and RVOL relied on the PISA method. The regurgitation fraction (RF) was calculated as the ratio of

6

the RVOL divided by the sum of the RVOL and aortic stroke volume. Echocardiographic parameters were indexed to the body surface area.

Study device and procedure

The device used in this trial was the MitraClip (Abbott Vascular). The percutaneous procedure of Mitraclip device implantation has been previously described. After randomization to the study device intervention group, the procedure was performed within a median of 14 days [interquartile range (IQR) [9–18]. All procedures were performed with technical proctoring from Abbott Vascular.

Statistical analysis

For the present study, the outcome was the composite of death from any cause or unplanned hospitalization for heart failure at 24 months. Analyses were performed according to the intention-to-treat principle and repeated according to the per-protocol principle excluding patients who had a protocol deviation, patients in the intervention group in whom the device was not implanted and excluding all events that occurred during the first 21 days after randomization. The present study consisted on non-pre-specified subgroup analyses based on median or commonly accepted thresholds values of the degree of MR, LV remodeling and of their combination. Assessment of the treatment effect (hazard ratio and associated 95% confidence interval) in each subgroup and of the Wald test for interaction between the subgroup and the intervention was performed using a Cox's proportional hazard model with the subgroup, the intervention and the interaction term as covariates. A two-sided P value of less than 0.05 was

7

considered to indicate statistical significance. The SAS software (Windows, Version 9.4) was used for all analyses.

RESULTS

Patients and procedure

Baseline characteristics and clinical outcomes at 1 and 2 years have already been reported. A total of 307 patients with secondary mitral regurgitation underwent randomization, 152 to percutaneous repair in addition to medical treatment (intervention group) and 155 to medical treatment alone (control group). Three patients were excluded from the control group after randomization owing to issues with informed consent and the final control group comprised 152 patients. The demographic, clinical characteristics and guideline-directed medical treatment of the two groups were similar at baseline, with the exception of a history of myocardial infarction, which was more common in the intervention group. Among the 152 patients in the intervention group, implantation was not attempted in eight patients (5.2%); a technical device success was achieved in 138 (95.8%) of the 144 attempted procedures according to the consensus document from the Mitral Valve Academic Research Consortium. The intention to treat analysis involved the 152 patients enrolled in both arms while the per-protocol analysis relied on 109 patients in the intervention arm and 137 in the control arm.

Degree of mitral regurgitation

Average value of quantitative parameters of MR degree are presented in the Table. Overall mean ERO was 31±11 mm² (median 29 mm², IQR [22-37]), mean RVOL 45±14 ml (median 43 ml, IQR [35-53]) and mean RF 0.49±0.10 (median 0.46, IQR [0.42-0.56]) (Table 1). ERO was $\ge 40 \text{ mm}^2$ in 49 patients and RF ≥ 0.50 in 135 patients. Interaction between the degree of MR and the impact of TMVR is presented in Figure 1. In the subsets with the highest degree of MR (defined by an ERO $\ge 30 \text{ mm}^2$, a RVOL $\ge 45 \text{ ml}$ or a RF $\ge 50\%$), the impact of the intervention was neutral and similar to that observed in patients with milder MR degree. Combining parameters of MR severity (ERO $\ge 30 \text{ mm}^2$ and RVOL $\ge 45 \text{ ml}$ or ERO $\ge 30 \text{ mm}^2$ and RF $\ge 50\%$) led to similar results.

Left ventricular remodelling and function

As expected, LV was enlarged in most patients and by design, LVEF was reduced in all patients. Mean end-diastolic and end-systolic diameters were 69±8 mm (median 69, IQR [63-74]) and 58±9 mm (median 58, IQR [52-65]) respectively and mean end-diastolic and end-systolic volumes were 250±75 ml (median 242, IQR [193-300]) and 169±63 ml (median 157, IQR [124-209]) respectively. Mean LVEF was 33±7%. Interactions between trial group and subsets defined based on LV size and function are presented in Figure 2. No benefit of the intervention was observed in subsets with the milder LV remodelling whatever the criteria used (end-diastolic or end-systolic LV diameters or volumes absolute or indexed to BSA). Combining criteria of LV remodelling (quartiles with the lowest end-diastolic and systolic diameters or volumes) failed to identify a subset of patients who might have benefited from the intervention. Only in the quartile of 60 patients with the lowest end-diastolic and end-systolic volumes the intervention was of borderline significance. Similarly, there was no impact of the intervention in patients with the highest LVEF or with the highest aortic stroke volume.

Combination of degree of mitral regurgitation and left ventricular remodelling

9

In an attempt to identify patients with disproportionate MR, different indices and thresholds were tested. These patients were first identified as those with the highest ratio of the ERO divided by various LV size parameters (end-diastolic or end-systolic LV diameters or volumes absolute or indexed to BSA). No subset seems to have benefited from the intervention (Figure 3). More specifically, effect of the intervention was neutral in patients' subsets with both an ERO / LV end-diastolic LV volume ≥ 0.15 or < 0.15 (mean 0.13 ± 0.05 (median 0.12, IQR [0.10-0.16]). Results were similar when LVEF was combined with ERO or combined with RF. We finally identified the quartile of patients with the highest MR degree and the lowest LV remodelling using again both end-diastolic and end-systolic LV diameters and volumes absolute or indexed to BSA (Figure 4). Effect of the intervention was neutral in these quartiles as in the remaining subsets.

In the above mentioned MITRA-FR subsets, when we plotted ERO against LV enddiastolic volume (Central figure), patients with the more severe MR presented with larger LV volumes while patients with an ERO / LV end-diastolic volume ≥ 0.15 (N=92) and patients with an ERO ≥ 30 mm² and a LV end-diastolic volume < 242 ml (N=55) presented with similar ERO and LV volumes than the COAPT overall population (39±12 mm², 201±57 ml and 38±8 mm², 195±33 ml respectively).

Per-protocol analysis

In the per-protocol population (109 patients in the intervention group and 137 in the control arm), analyses led to similar results indicating no impact of the intervention in any subset based on degree of mitral regurgitation, LV remodelling or function or combination of both (Supplementary Figures 1 to 4).

DISCUSSION

In the present study, we aimed to identify, using echocardiographic parameters, a subset of patients enrolled in the MITRA-FR trial that might have benefited from percutaneous repair. There were no significant interactions between trial group and any of the subsets defined based on the degree of the regurgitation, the degree of LV remodelling / dysfunction or the combination of these parameters with respect to the composite of all-cause death or unplanned hospitalization for heart failure at 24 months in both intention-to-treat and per-protocol analyses.

Secondary MR has been uniformly associated with an increased risk of mortality and cardiovascular events in patients with ischemic or dilated cardiomyopathies. However, whether secondary MR is simply a marker, or the direct cause of the observed increased risk cannot be addressed by measuring MR severity. The only way to assess whether MR directly contributes to the observed worse outcome is to evaluate the impact of its correction. This was the aim of both the MITRA-FR and the COAPT trials, which provided divergent results. A post hoc analysis of the COAPT trial with subgroup defined based on MR severity and LV remodelling suggested that TMVR was less effective in patients with the lowest ERO (\leq 30 mm²) and the largest LV size (LV end-diastolic volume index \geq 96 ml/m²).(15) Mirroring this analysis, we performed a post-hoc analysis based on the MITRA-FR trial population and evaluated whether patients with the highest degree of MR and / or the lowest degree of LV remodelling – including patients with potentially disproportionate MR - might have benefited from TMVR. This analysis has been called by the medical community.(16-18)

We first evaluated whether TMVR had a different impact on outcomes according to the degree of MR. Optimal thresholds to define severe MR are debated. In MITRA-FR we used an

ERO of 20 mm² and a RVOL of 30 ml to define a severe MR and to be enrolled in the trial. These thresholds are based on outcome studies showing that prognosis is markedly impaired above these thresholds(3,4) and they were the thresholds recommended to define severe secondary MR by the European Society of Cardiology and the American College of Cardiology / American Heart Association at the time MITRA-FR was designed (19,20). These thresholds were revised in 2017 by the American College of Cardiology / American Heart Association and by the American Society of Echocardiography with severe secondary MR defined by ERO of 40 mm² and a RVOL of 60 ml as for primary MR.(21,22) Nevertheless, it is mentioned that, to define severe MR, a cut-off value of 20 mm² is more sensitive while a cut-off value of 40 mm² is more specific, and that a lower threshold (30 mm²) could be considered due the frequent elliptic shape of the regurgitant orifice area in secondary MR. The regurgitant fraction (ratio of the RVOL divided by the sum of the RVOL + forward stroke volume) has been proposed as a more robust and discriminative parameter to assess MR severity.(23) We observed a similar and neutral effect of TMVR in all subset of patients defined based on the degree of MR, including in the subset of patients with a $RF \ge 50\%$, which was close to the median RF value in the MITRA-FR population. Thus, even if the subsets with the highest MR degree as defined based on the latest recommendations, we could not identify a subset that might have benefited from the TMVR.

LV remodelling and function are well known critical prognostic parameters in patients with ischemic or dilated cardiomyopathies including patients presenting with secondary MR. We thus investigated whether TMVR might had an impact in patients with the smallest LV size or with the highest LVEF using both systolic and diastolic dimensions, diameters and volumes and absolute and indexed values. We found no interaction between subsets as above defined including forward (aortic) stroke volume and TMVR. It is worth noting that most patients presented with significant LV remodelling and that only 31 patients presented with a LV end-diastolic volume $< 96 \text{ ml/m}^2$.

In patients with secondary MR, the degree of MR should not be solely considered and should be integrated with the severity of the LV remodelling. This concept, nicely developed by Paul Grayburn and colleagues, refers to whether the degree of MR is in agreement or not with the degree of MR that might have been expected based on LV size and function (17). The concept of disproportionate MR has been proposed as a framework to explain the disparities in the outcome observed in MITRA-FR and COAPT trials with patients with disproportionate MR enrolled in COAPT and patients with proportionate MR enrolled in MITRA-FR. To identify patients with disproportionate MR in a quantitative manner, indices based on ratio of MR degree / LV size such as ERO / LV end-diastolic volume have been proposed. Although no clear thresholds have been defined, predictive models suggest that a value of 0.15 is in favor of disproportionate MR. In the present study, we have tested the interaction between TMVR and subsets derived from various MR severity / LV size ratios. We did not observe an impact of TMVR in any of the considered subsets. In particular, impact of TMVR was neutral in patients with an ERO / LV end-diastolic volume above or below the median value (0.12) and above or below 0.15. The ratio of the RVOL / LV end-diastolic volume (also equal to RF x LVEF) has also been proposed to define disproportionate MR.(16,24) A neutral effect of TMVR therapy was also observed above or below 0.20 in MITRA-FR. We finally identified quartiles of patients with the highest degree of MR and the smallest LV enlargement and also observed a neutral effect of the TMVR. Overall, we could not identify any subset of patients defined based on combination of MR severity and LV remodeling / systolic function that might have benefited

from TMVR in the MITRA-FR trial. Interestingly, when we plotted the ERO against the LV end-diastolic volume of the patients with an ERO / LV end-diastolic volume ratio ≥ 0.15 or of the quartile of patients with an ERO \geq 30 mm² and a LV end-diastolic volume < 242 ml (median value), these subsets were close to those of the COAPT Trial (Figure 5). Thus, while COAPT post-hoc analysis suggested that patients with the lowest MR degree and the largest LV size did not derive benefit from TMVR,(18) the reciprocal was not verified in MITRA-FR since we observed a neutral effect of TMVR in patients with the largest ERO and the smallest LV size despite apparent similarities with COAPT patients in term of ERO and LV size. Although these analyses should be viewed cautiously as post-hoc defined and derived from small sample size subsets, they are intriguing and question whether the proportionate / disproportionate framework is the main reason for the divergent clinical outcomes in the two trials. Other parameters such as the right ventricular function, LV fibrosis and LV contractile reserve possibly different between the two trials' populations might also explain the observed divergent outcomes. An individualpatient data meta-analysis of MITRA-FR and COAPT capturing the full spectrum of secondary MR patients may help to identify patients who might benefit from TMVR from those who might not.

Major strengths of the present study need to be emphasized. Evaluation of the impact of TMVR in the various subsets including in those deemed to have disproportionate MR were not derived from observational studies(25) but from one of the only two currently available randomized controlled trials comparing TMVR to 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. Outcomes were prospectively collected; all events were adjudicated

by an independent committee and follow-up was 99% complete at one year and 95% complete at two years. Nevertheless, several limitation deserves comments. First, all analysis presented were post-hoc defined and are based on relatively small subsets with thus inherent bias and limitations of such analysis. However, results were remarkably homogeneous showing the absence of impact of TMVR in all but one subset analyzed. Statistical significant was reached in a subset of 51 patients with an end-diastolic volume < 195 ml and an end-systolic volume < 124 ml in the per-protocol analysis with a very wide confidence interval. Importantly similar analysis based on LV diamters did not show the same trend and thus these results may likely due to chance. Second, we are not claiming that our subsets and the thresholds used in the present study are defining disproportionate MR. Disproportionate MR might be defined by higher degree of MR / LV size ratio than those observed in the MITRA-FR trial and we could not test the 0.20 threshold due to limited sample size. However, in order to perform meaningful statistical analysis with reasonable sample size in all subsets we had to use the median values observed in our population. Again our results were consistent in all subsets while in contrast, in COAPT, the positive effect of TMVR was consistent in most echocardiographic subsets.(26) Nevertheless, we cannot exclude that the MITRA-FR population might have presented with uniformly advanced disease precluding identification of a subset that might have benefited from TMVR. Finally, inconsistencies in measurements of LV volumes and stroke volumes as well as in regurgitant volume in COAPT have been raised.(16,26,27) These inconstancies raise caution when comparing degree of MR and LV remodelling between studies and underline the critical importance of centralized readings.

CONCLUSION

Differences in baseline characteristics and more specifically differences in the degree of MR and of LV remodeling between the MITRA-FR and COAPT trials have been suggested as one main reason to explain the differences in clinical outcomes observed in the two trials. In particular, the concept of proportionate / disproportionate MR has been proposed as a framework to predict which patient might benefit from MR correction. In the MITRA-FR trial, we could not identify a subset of patients defined based on the degree of the regurgitation, LV remodelling / dysfunction or on their combination - including subsets deemed as having disproportionate MR - that might have benefited from transcatheter correction using the Mitraclip system.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The impact of transcatheter mitral valve repair was evaluated in subsets of MITRA-FR patients defined based on MR severity, LV remodeling, isolated or in combination. As in the overall MITRA-FR population, intervention was neutral in patients with the highest MR severity or the smallest LV size including those deemed as having disproportionate MR.

TRANSLATIONAL OUTLOOK: MITRA-FR and COAPT trials have provided divergent results. Additional studies are clearly needed to identify patients that will benefit the most from transcatheter mitral valve repair.

REFERENCES

- Liel-Cohen N, Guerrero JL, Otsuji Y, et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3dimensional echocardiography. Circulation 2000;101:2756-63.
- Yiu S, Enriquez-Sarano M, Tribouilloy C, Seward J, Tajik A. Determinants Of The Degree Of Functional Mitral Regurgitation In Patients With Systolic Left Ventricular Dysfunction: A Quantitative Clinical Study. Circulation 2000;102:1400-6.
- Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. J Am Coll Cardiol 2005;45:260-7.
- 4. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759-64.
- 5. Lamas G, Mitchell G, Flaker G, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Circulation 1997;96:827-33.
- 6. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011;97:1675-80.
- Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med 2018;379:2297-2306.
- Iung B, Armoiry X, Vahanian A, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail 2019;21:1619-1627.

- Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med 2018;379:2307-2318.
- 10. Goliasch G, Bartko PE, Pavo N, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. Eur Heart J 2018;39:39-46.
- Obadia JF, Armoiry X, Iung B, et al. The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation. EuroIntervention 2015;10:1354-60.
- 12. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307-32.
- 13. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.

18

- Packer M, Grayburn PA. Contrasting Effects of Pharmacological, Procedural, and Surgical Interventions on Proportionate and Disproportionate Functional Mitral Regurgitation in Chronic Heart Failure. Circulation 2019;140:779-789.
- Gaasch WH, Aurigemma GP, Meyer TE. An Appraisal of the Association of Clinical Outcomes With the Severity of Regurgitant Volume Relative to End-Diastolic Volume in Patients With Secondary Mitral Regurgitation. JAMA Cardiol 2020.
- Grayburn PA, Sannino A, Packer M. Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials. JACC Cardiovasc Imaging 2019;12:353-362.
- Packer M, Grayburn PA. New Evidence Supporting a Novel Conceptual Framework for Distinguishing Proportionate and Disproportionate Functional Mitral Regurgitation.
 JAMA Cardiol 2020.
- 19. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012;33:2451-96.
- 20. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:2440-92.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014
 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A

Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-e1195.

- 22. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-371.
- Bartko PE, Arfsten H, Heitzinger G, et al. A Unifying Concept for the Quantitative Assessment of Secondary Mitral Regurgitation. J Am Coll Cardiol 2019;73:2506-2517.
- 24. Gaasch WH, Meyer TE. Secondary mitral regurgitation (part 1): volumetric quantification and analysis. Heart 2017;104:634-638.
- Bartko PE, Heitzinger G, Arfsten H, et al. Disproportionate Functional Mitral Regurgitation: Advancing a Conceptual Framework to Clinical Practice. JACC Cardiovasc Imaging 2019;12:2088-2090.
- Asch FM, Grayburn PA, Siegel RJ, et al. Echocardiographic Outcomes After
 Transcatheter Leaflet Approximation in Patients With Secondary Mitral Regurgitation:
 The COAPT Trial. J Am Coll Cardiol 2019;74:2969-2979.
- Nishimura RA, Bonow RO. Percutaneous Repair of Secondary Mitral Regurgitation A Tale of Two Trials. N Engl J Med 2018;379:2374-2376.

Figure Legends:

Figure 1. Impact of the intervention according to the severity of the regurgitation

Interaction between the degree of the mitral regurgitation and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months.

Figure 2. Impact of the intervention according to the left ventricular remodelling

Interaction between the degree of left ventricular remodelling and systolic function and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months.

Figure 3. Impact of the intervention according to ratio of severity of the regurgitation / left ventricular remodelling

Interaction between the degree of mitral regurgitation and left ventricular remodelling / systolic function and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months.

Figure 4. Impact of the intervention according to the combination of severity of the regurgitation and left ventricular remodelling

Interaction between quartiles with the highest degree mitral regurgitation and the lowest left ventricular remodelling and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months.

Central figure. Relationship between the effective regurgitant orifice (ERO) and the left ventricular end-diastolic volume (LVEDV) in the MITRA-FR trial overall and in various subsets as well as in the overall COAPT trial.

Illustrating domains define disproportionately severe, proportionately severe, and non-severe functional mitral regurgitation (Modified from Grayburn and al.)(17).

Boxes indicated subsets with an ERO \geq or < 0.3 cm², crosses subsets with a regurgitant volume \geq or < 45 ml, plus signs subsets with a regurgitant fraction \geq or < 50%, stars subsets with a ratio of ERO/LVEDV \geq or < 0.15 and triangles combination of ERO and LVEDV.

Patients with the lowest MR severity / LV remodeling are in blue, those with the most severe MR severity / LV remodeling in red. Orange indicates patients with intermediate phenotype.

Table. Baseline values presented as mean ± standard deviation (SD) and median, 25-75 interquartile range (IQR) of quantitative parameters of the degree of mitral regurgitation and of left ventricular remodelling and function.

Echocardiographic parameter	Mean ± SD	Median, 25-75 IQR
Effective regurgitant orifice area, mm ²	31±11	29 [22-37]
Regurgitant volume, ml	45±14	43 [35-53]
Regurgitant fraction, %	0.49±0.10	0.49 [0.42-0.56]
Left ventricular end-diastolic diameter, mm	69±8	69 [63-74]
Left ventricular end-diastolic diameter index, mm/m ²	38±5	37 [34-41]
Left ventricular end-systolic diameter, mm	58±9	58 [52-65]
Left ventricular end-systolic diameter index, mm/m ²	32±5	32 [28-35]
Left ventricular end-diastolic volume, ml	250±75	242 [193-300]
Left ventricular end-diastolic volume index, ml/m ²	135±35	133 [110-157]
Left ventricular end-systolic volume, ml	169 ± 63	157 [124-209]
Left ventricular end-systolic volume index, ml/m ²	92±30	85 [70-111]
Left ventricular ejection fraction, %	33±7	35 [28-39]
Aortic stoke volume, ml	46±13	44 [37-54]
Aortic stoke volume index, ml/m ²	25±6	24 [20-28]
Effective regurgitant orifice area / left ventricular end-diastolic diameter	0.45±0.16	0.43 [0.33-53]
Effective regurgitant orifice area / left ventricular end-systolic diameter	0.54±0.19	0.51 [0.40-0.62]
Effective regurgitant orifice area / left ventricular end-diastolic volume	0.13±0.05	0.12 [0.10-0.16]
Effective regurgitant orifice area / left ventricular end-systolic volume	0.20±0.09	0.18 [0.14-0.25]
Regurgitant fraction x left ventricular ejection fraction	0.16±0.5	0.16 [0.13-0.20]

* Regurgitant volume was missing in 2 patients, left ventricular diameters and volumes in 2 patients, ejection fraction in 1 patient, stroke volume in 19 patients and regurgitant fraction in 21 patients

Supplementary material

Supplemental Figure 1. Interaction between the degree of the mitral regurgitation and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months (per-protocol analysis).



<--Percut. repair better-- --MT better-->

Supplemental Figure 2. Interaction between the degree of left ventricular remodelling and systolic function and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months (per-protocol analysis).

Subgroup	Percut Events/	. repair /N (%)	Medical 1 Events/N	treatment I (%)	HR (95% CI)	1	P interaction
End-diastolic diameter							0.88
<69 mm	34/54	(63.0)	40/63	(63.5)	1.03 (0.65, 1.62)	F∳ B }	
≥69 mm	36/55	(65.5)	53/73	(72.6)	0.98 (0.64, 1.49)	├─ ─ ■ <mark> </mark> ───	
End-diastolic diameter index							0.29
<37 mm/m2	37/59	(62.7)	41/59	(69.5)	0.83 (0.53, 1.30)	⊢	
≥37 mm / m2	33/50	(66.0)	52/77	(67.5)	1.16 (0.75, 1.80)		
End-systolic diameter							1.00
<58 mm	31/53	(58.5)	35/59	(59.3)	1.01 (0.63, 1.65)	⊢ (
≥58 mm	39/56	(69.6)	58/77	(75.3)	1.02 (0.68, 1.52)	⊢−−− ₩ −−−− 1	
End-systolic diameter index							0.82
<32 mm /m2	45/69	(65.2)	47/69	(68.1)	0.97 (0.64, 1.45)		
≥32 mm / m2	25/40	(62.5)	46/67	(68.7)	1.04 (0.64, 1.69)	}₽(
End-diastolic + end systolic diameter							0.60
End-diastolic diameter < 63 mm and end-systolic diameter < 52 mm	13/19	(68.4)	11/20	(55.0)	1.22 (0.54, 2.71)	⊢ − −	1
End-diastolic diameter ≥ 63 mm or end-systolic diameter ≥ 52 mm	57/90	(63.3)	82/116	(70.7)	0.96 (0.69, 1.35)	⊢	
End-diastolic volume							0.39
<242 ml	31/52	(59.6)	47/71	(66.2)	0.84 (0.54, 1.33)	<u>├────</u> ₩_ <u>├</u> ──┤	
≥242 ml	39/57	(68.4)	47/65	(72.3)	1.11 (0.73, 1.70)	} — }∎	
End-diastolic volume index							0.46
<133 ml / m2	35/56	(62.5)	45/67	(67.2)	0.87 (0.56, 1.35)		
≥133 ml / m2	35/53	(66.0)	49/69	(71.0)	1.10 (0.71, 1.70)	► †	
End-systolic volume							0.68
<157 ml	33/54	(61.1)	44/68	(64.7)	0.91 (0.58, 1.42)	┝───╋┼──┤	
≥157 ml	36/54	(66.7)	50/68	(73.5)	1.03 (0.67, 1.59)	⊢₽ {	
End-systolic volume index							0.23
<85 ml / m2	33/55	(60.0)	46/67	(68.7)	0.80 (0.51, 1.25)	┝───╋─┤─┤	
≥85 ml / m2	36/53	(67.9)	48/69	(69.6)	1.17 (0.76, 1.80)	┝─┼╋──┤	
End-diastolic + end systolic volume						3	0.01
End-diastolic volume < 195 and end-systolic volume < 124 ml	15/28	(53.6)	18/23	(78.3)	0.43 (0.22, 0.85)		
End-diastolic volume ≥ 195 ml or end-systolic volume ≥ 124 ml	55/81	(67.9)	76/113	(67.3)	1.20 (0.85, 1.71)	▶	
LVEF							0.92
<35 %	30/46	(65.2)	51/70	(72.9)	0.97 (0.62, 1.53)	⊢	
≥35 %	40/63	(63.5)	43/66	(65.2)	1.01 (0.65, 1.55)	⊢ i ∎i	
Aortic stroke volume							0.92
<44 ml	35/55	(63.6)	41/58	(70.7)	0.93 (0.59, 1.46)		
≥44 ml	29/47	(61.7)	47/71	(66.2)	0.96 (0.60, 1.53)	⊢∎	
Aortic stroke volume index							0.68
<24 ml / m2	36/57	(63.2)	39/56	(69.6)	0.88 (0.56, 1.38)	<u>}</u>	
≥24 ml / m2	28/45	(62.2)	49/73	(67.1)	1.01 (0.63, 1.60)	·••	
							- <u>-</u>

0.25

0.5

<--Percut. repair better-- --MT better-->

1 1.5 2 3

Supplemental Figure 3. Interaction between the degree of mitral regurgitation and left ventricular remodelling / systolic function and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months (per-protocol analysis).

Subgroup	Percut Events	. repair /N (%)	Medical Events/N	treatment I (%)	HR (95% CI)		Ť	P interaction
ERO/End-diastolic diameter								0.41
< median	33/50	(66.0)	48/74	(64.9)	1.11 (0.71, 1.73)		▶ ▶ ₩ ₩ ₩	
≥median	37/59	(62.7)	45/62	(72.6)	0.86 (0.55, 1.33)		⊢	
ERO/End-diastolic diameter index								0.66
< median	34/54	(63.0)	44/69	(63.8)	1.06 (0.68, 1.66)			
≥median	36/55	(65.5)	49/67	(73.1)	0.92 (0.60, 1.42)		↓ ∎↓↓	
ERO/End-systolic diameter								0.58
< median	31/46	(67.4)	47/70	(67.1)	1.08 (0.69, 1.70)		⊢	
≥median	39/63	(61.9)	46/66	(69.7)	0.91 (0.59, 1.39)		⊢	
ERO/End-systolic diameter index								0.94
< median	30/49	(61.2)	47/73	(64.4)	0.96 (0.61, 1.52)			
≥median	40/60	(66.7)	46/63	(73.0)	0.98 (0.64, 1.50)		⊢	
ERO/End-diastolic volume							65 D.	0.65
<0 15	50/78	(64.1)	64/93	(68.8)	1.02 (0.70, 1.48)		⊢i ∎i	
≥0 15	20/31	(64.5)	30/43	(69.8)	0.87 (0.49, 1.53)		⊢	
ERO/End-diastolic volume								0.11
< median	36/54	(66.7)	44/69	(63.8)	1.24 (0.80, 1.93)		⊢	
≥median	34/55	(61.8)	50/67	(74.6)	0.75 (0.48, 1.16)		┝───■──┼─┤	
ERO/End-diastolic volume index								0.46
< median	30/47	(63.8)	50/75	(66.7)	1.07 (0.68, 1.68)		⊢∎ 1	
≥median	40/62	(64.5)	44/61	(72.1)	0.84 (0.55, 1.29)		⊢	
ERO/End-systolic volume								0.12
< median	34/50	(68.0)	47/72	(65.3)	1.22 (0.78, 1.90)			
≥median	35/58	(60.3)	47/64	(73.4)	0.75 (0.48, 1.15)		┝───╋──┼─┤	
ERO/End-systolic volume index								0.31
< median	31/48	(64.6)	49/74	(66.2)	1.11 (0.71, 1.74)		⊦	
≥median	38/60	(63.3)	45/62	(72.6)	0.81 (0.52, 1.24)		F ■ + - 1	
ERO and LVEF								0.68
ERO < 30 or LVEF < 35	52/80	(65.0)	74/105	(70.5)	0.95 (0.67, 1.36)		⊢∎	
ERO ≥ 30 and LVEF ≥ 35	18/29	(62.1)	20/32	(62.5)	1.11 (0.59, 2.10)		⊢	
RVOL / End-diastolic volume								0.93
<20	47/75	(62.7)	66/96	(68.8)	0.96 (0.66, 1.40)		⊢	
≥20	16/26	(61.5)	21/32	(65.6)	0.93 (0.49, 1.78)		⊢	
						-		
						0.25	0.5 1 1.5 2	3

Supplemental Figure 4. Interaction between quartiles with the highest degree mitral regurgitation and the lowest left ventricular remodelling and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months (per-protocol analysis).

EO 1 Edu - Edu		Percut. repair Events/N (%)		Percut. repair Med Events/N (%) Ever		ercut. repair Medical treatment ents/N (%) Events/N (%)		HR (95% CI)	1	P interaction
100 - 21 mm2 and End-disabolic diameter > 62 mm 1201 - 61/14 abolic diameter + 64 mm 1201 - 61/14 abolic diameter + 61/14 abolic diam	EPO + End-diastolic diameter							0.58		
EPC 0- 20 mm 2 and End-distatic diameter - 69 mm 0 = FR0 2 30 and End-distatic diameter : 69 mm 4486 (60,2) 20.00 (67,7) 0.66 (0.4, 17,7) (67,7) 0.66 (0.4, 17,7) EPC 0- End-distatic diameter index 2 37 mm/m2 1523 (62,2) 24.07 (84,7) 0.67 (0.4, 1.40) (61,7) 0.66 (0.4, 17,7) EPC 0- End-distatic diameter index 2 37 mm/m2 1523 (62,2) 24.07 (84,6) 0.57 (0.4, 1.40) (61,7) 0.66 (0.4, 17,7) (61,7) 0.66 (0.4, 17,7) (61,7) 0.67 (0.4, 1.40) (61,7) 0.67 (0.4, 1.40) (61,7) 0.54 EPC 0- End-static diameter index 2 37 mm/m2 1705 (61,7) 170 (76, 1, 10,7) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (61,7) 0.70 (0.4, 1.40) (71,7) 0.70 (0.4, 1.40) (71,7) (0.	ERO < 30 mm2 and End-diastolic diameter \geq 69 mm	13/21	(61.9)	24/32	(75.0)	0.78 (0.40, 1.54)	F			
EPO 2.0.30 mm2 and End-distolic diameter (69 mm H223 (66.7) 0.86 (0.4.1,70) Image: Constraint of Constraint	ERO < 30 mm2 and End-diastolic diameter < 69 mm or ERO ≥ 30 and End-diastolic diameter ≥ 69 mm	43/65	(66.2)	49/74	(66.2)	1.14 (0.76, 1.72)	F → B → 1			
END - End-dilusticial climater index 2 37 mm/m2 1503 6627 2493 667 108 (0.55, 2.65) 109 (0.55, 2.65) 109 (0.55, 2.65) 109 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 100 (0.55, 2.65) 1	ERO \ge 0.30 mm2 and End-diastolic diameter < 69 mm	14/23	(60.9)	20/30	(66.7)	0.86 (0.43, 1.70)	F			
END 4 sum 2 and End distabilic diameter index 2 3 mm/m2 (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2000) (2	ERO + End-diastolic diameter index	15/23	(65.2)	24/36	(66.7)	1.08 (0.56, 2.05)		0.90		
ERO 2 0.30 mm2 and End-diastolic diameter index 37 mm/m2 1725 (80,0) 1724 (70,8) 0.87 (0.41, 170) ERO 4 End-systolic diameter index 37 mm/m2 1725 (80,0) 1724 (70,8) 0.87 (0.41, 170) 0.54 ERO 4 End-systolic diameter index 37 mm/m2 1725 (80,0) 1724 (70,8) 0.87 (0.41, 170) 0.54 ERO 4 End-systolic diameter index 37 mm/m2 1725 (80,0) 1724 (70,8) 0.87 (0.41, 170) 0.54 ERO 4 End-systolic diameter index 32 mm/m2 1777 (80,0) 1772 (70,0) 0.88 (0.41, 170) 0.54 ERO 4 S0 mm2 and End-diastolic diameter index 42 mm/m2 1777 1863 0.568 0.56 0.56 0.56 0.54 ERO 4 S0 mm2 and End-diastolic diameter index 42 mm/m2 1777 0.86 (0.42, 1.82) 0.54 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.56 0.5	ERO < 30 mm2 and End-diastolic diameter index \geq 37 mm/m2 ERO < 30 mm2 and End-diastolic diameter index < 37 or ERO > 30 and End-diastolic diameter index > 37 mm/m2	38/61	(62.3)	52/76	(68.4)	0.97 (0.64, 1.48)	· · · · · · · · · · · · · · · · · · ·			
ERO + End-systolic diameter 2 SB mm 16/23 64.0 30.33 78.0 43.14.61 ERO + SD mm2 and End-diastolic diameter > SB mm or ERO ≥ 30 and End-diastolic diameter > SB mm 14/24 (63.3) 19/20 (65.5) 0.80 (0.41, 17.6) 14/24 0.54 ERO + SD mm2 and End-diastolic diameter index > 32 mm/m2 11/17 (64.7) 18/28 (64.3) 1.18 (0.56, 2.49) 14/24 0.54 ERO + End-systolic diameter index > 32 mm/m2 20.90 72.40 172.6 (65.4) 1.24 (0.65, 2.35) 14/24 0.54 ERO + End-diastolic diameter index > 32 mm/m2 20.90 72.40 172.6 (65.4) 1.24 (0.65, 2.35) 14/44 0.54 ERO + End-diastolic diameter index > 32 mm/m2 11/17 (64.7) 11/18 (57.7) 0.88 (0.42, 1.82) 14/44 0.56 0.56 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.56 0.56 0.57 0.56 0.57 0.56 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.57 0.56 0.57 0	$ERO \ge 0.30$ mm2 and End-diastolic diameter index < 37 or ErO \ge 30 and Erd-diastolic diameter index \ge 37 mm/m2	17/25	(68.0)	17/24	(70.8)	0.87 (0.44, 1.70)	<u>⊢</u>			
ERO + End-systolic diameter 1675 (# 40) 30/38 (75.9) 0.79 0.4.3.1.49) ERO + Sind Fard-diastolic diameter > 58 mm or ERO ≥ 30 and End-diastolic diameter > 58 mm 14060 (# 67.7) 4469 (# 63.8) 1.117 (0.76, 1.80) ERO + End-systolic diameter index 32 mm/r2 (# 4469 (# 63.8) 1.118 (0.56, 2.49) 0.564 ERO + So 10.3 mm Z and End-diastolic diameter index ≥ 32 mm/r0.2 20/29 (7 2.4) 17/26 (# 65.4) 1.124 (0.65, 2.49) ERO + End-systolic diameter index < 32 mm/r0.2								0.54		
ERO < 30 mm2 and End-diastolic diameter < 58 mm	ERO + End-systolic diameter ERO < 30 mm2 and End-diastolic diameter > 58 mm	16/25	(64.0)	30/38	(78.9)	0.79 (0.43, 1.45)	F			
ERO 2 0.30 mm2 and End-diastolic diameter index 58 mm 14/24 (68.3) 19/29 (65.5) 0.88 (0.44, 1.76) 0.54 ERO 4 End-systolic diameter index 20 mm/2 and End-diastolic diameter index < 32 mm/m2	ERO < 30 mm2 and End-diastolic diameter < 58 mm or ERO \ge 30 and End-diastolic diameter \ge 58 mm	40/60	(66.7)	44/69	(63.8)	1.17 (0.76, 1.80)	F - } ⊞ 1			
ER0 + End-systolic diameter index ER0 < 30 mm2 and End-diastolic diameter index ≤ 32 mm/m2 ER0 < 30 mm2 and End-diastolic diameter index < 32 mm/m2 or ER0 ≥ 30 and End-diastolic diameter index ≥ 32 mm/m2 ER0 < 30 mm2 and End-diastolic diameter index < 32 mm/m2 or ER0 ≥ 30 and End-diastolic diameter index ≥ 32 mm/m2 ER0 < 30 mm2 and End-diastolic volume index < 32 mm/m2 or ER0 ≥ 30 and End-diastolic diameter index ≥ 32 mm/m2 ER0 < 30 mm2 and End-diastolic volume ≥ 42 ml ER0 < 30 mm2 and End-diastolic volume < 242 or ER0 ≥ 30 and End-diastolic volume ≥ 242 ml	ERO \geq 0.30 mm2 and End-diastolic diameter < 58 mm	14/24	(58.3)	19/29	(65.5)	0.88 (0.44, 1.76)				
ERO < 30 mm2 and End-diastolic diameter index = 32 mm/m2	ERO + End-systolic diameter index	11/17	(64.7)	19/29	(64.3)	1 18 (0 56 2 49)		0.54		
ERO < 30 mm2 and End-diastolic diameter index < 32 mm/m2 or ERO ≥ 30 and End-diastolic diameter index ≥ 32 mm/m2	ERO < 30 mm2 and End-diastolic diameter index ≥ 32 mm/m2	20/02	(04.7)	10/20	(04.3)	1.16 (0.56, 2.49)				
ERO + End-diastolic volume 21/3 (72.4) 11/28 (82.4) 12/4 (0.69, 2.39) ERO + End-diastolic volume 21/3 (67.7) 0.88 (0.42, 1.82) 0.66 ERO < 30 mm2 and End-diastolic volume < 242 ml	ERO < 30 mm2 and End-diastolic diameter index < 32 mm/m2 or ERO \ge 30 and End-diastolic diameter index \ge 32 mm/m2 ERO \ge 0.30 and End diastolic diameter index \le 32 mm/m2	30/03	(00.3)	17/06	(70.7)	0.05 (0.56, 1.27)				
ERO + End-diastolic volume 11/19 (57.9) 21/31 (67.7) 0.88 (0.42, 1.82) ERO < 30 mm2 and End-diastolic volume > 242 or ERO > 30 and End-diastolic volume > 242 ml 52/76 (68.4) 54/76 (71.1) 1.05 (0.72, 1.53) ERO > 0.30 mm2 and End-diastolic volume < 242 ml		21/29	(72.4)	17/20	(65.4)	1.24 (0.65, 2.35)		0.66		
ERO < 30 mm2 and End-diastolic volume < 242 ml	ERO + End-diastolic volume	11/19	(57.9)	21/31	(67.7)	0.88 (0.42, 1.82)	►			
ERO ≥ 0.30 mm2 and End-diastolic volume < 242 ml	ERO < 30 mm2 and End-diastolic volume < 242 mile ERO < 30 mm2 and End-diastolic volume < 242 or ERO \geq 30 and End-diastolic volume \geq 242 ml	52/76	(68.4)	54/76	(71.1)	1.05 (0.72, 1.53)	F			
ERO + End-diastolic volume index 0,98 ERO < 30 mm2 and End-diastolic volume index < 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2 or ERO ≥ 30 and End-diastolic volume ≥ 157 ml	ERO \ge 0.30 mm2 and End-diastolic volume < 242 ml	7/14	(50.0)	19/30	(63.3)	0.69 (0.29, 1.64)	F			
ERO < 30 mm2 and End-diastolic volume index ≤ 133 ml/m2 10/16 (62.5) 22/33 (66.7) 1.02 (0.48, 2.16) ERO < 30 mm2 and End-diastolic volume index < 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2 5078 (64.1) 54/76 (71.1) 0.94 (0.64, 1.39) ERO < 30 mm2 and End-diastolic volume index < 133	ERO + End-diastolic volume index							0.98		
ERO < 30 mm2 and End-diastolic volume index < 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2	ERO < 30 mm2 and End-diastolic volume index ≥ 133 ml/m2	10/16	(62.5)	22/33	(66.7)	1.02 (0.48, 2.16)	F			
ERO ≥ 0.30 mm2 and End-diastolic volume ≥ 157 ml 10/15 (66.7) 18/28 (64.3) 0.99 (0.46, 2.15) ERO + End-systolic volume 11/19 (57.9) 22/32 (68.8) 0.88 (0.43, 1.82) 0.86 ERO < 30 mm2 and End-diastolic volume ≥ 157 ml	ERO < 30 mm2 and End-diastolic volume index < 133 ml/m2 or ERO ≥ 30 and End-diastolic volume index ≥ 133 ml/m2	50/78	(64.1)	54/76	(71.1)	0.94 (0.64, 1.39)	⊢∎ 1			
ERO + End-systolic volume 11/19 (57.9) 22/32 (68.8) 0.88 (0.43, 1.82) 0.86 ERO < 30 mm2 and End-diastolic volume < 157 ml	ERO ≥ 0.30 mm2 and End-diastolic diameter index < 133	10/15	(66.7)	18/28	(64.3)	0.99 (0.46, 2.15)	⊢ • I			
ERO < 30 mm2 and End-diastolic volume ≤ 157 ml 11/19 (67.6) 53/75 (70.7) 1.03 (0.70, 1.51) ERO < 30 mm2 and End-diastolic volume ≤ 157 ml 50/74 (67.6) 53/75 (70.7) 1.03 (0.70, 1.51) ERO < 2.0.30 mm2 and End-diastolic volume ≤ 157 ml 9/16 (56.3) 19/30 (63.3) 0.83 (0.37, 1.83) ERO + End-systolic volume index 12/19 (63.2) 23/35 (65.7) 1.05 (0.52, 2.11) 10/17 0.85 ERO < 30 mm2 and End-diastolic volume index < 85 ml/m2	ERO + End-systolic volume	14/40	(57.0)	22/22	(69.9)	0.00 /0.42 4.02		0.86		
ERO < 30 mm2 and End-diastolic volume < 157 ml	ERO < 30 mm2 and End-diastolic volume ≥ 157 ml	50/74	(57.9)	22/32	(00.0)	0.00 (0.43, 1.02)				
ERO + End-systolic volume index 85 ml/m2 12/19 (63.2) 23/35 (65.7) 1.05 (0.52, 2.11) 0.85 ERO < 30 mm2 and End-diastolic volume index < 85 ml/m2	ERO < 30 mm2 and End-diastolic volume < 157 of ERO 2 30 and End-diastolic volume 2 157 ml FRO > 0.30 mm2 and End-diastolic volume < 157 ml	50/74	(67.6)	53/75	(70.7)	1.03 (0.70, 1.51)				
ERO + End-systolic volume index 12/19 (63.2) 23/35 (65.7) 1.05 (0.52, 2.11) ERO < 30 mm2 and End-diastolic volume index < 85 ml/m2		9/16	(56.3)	19/30	(63.3)	0.83 (0.37, 1.83)		0.85		
$ERO < 30 \text{ mm2} and End-diastolic volume index < 85 \text{ ml/m2}} = 4873 (65.8) 51/72 (70.8) 1.00 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67, 1.48) = 100 (0.67,$	ERO + End-systolic volume index	12/19	(63.2)	23/35	(65.7)	1.05 (0.52, 2.11)		0.00		
ERO ≥ 0.30 mm2 and End-diastolic volume index < 85 ml/m2 10/17 (58.8) 20/30 (66.7) 0.80 (0.37, 1.70)	ERO < 30 mm2 and End-diastolic volume index < 85 ml/m2 or ERO \ge 30 and End-diastolic volume index > 85 ml/m2	48/73	(65.8)	51/72	(70.8)	1.00 (0.67, 1.48)	· ⊢_∎			
	ERO ≥ 0.30 mm2 and End-diastolic volume index < 85 ml/m2	10/17	(58.8)	20/30	(66.7)	0.80 (0.37, 1.70)	⊢ -			



	Percut.	repair	Medical	treatment			
Subgroup	Events/	N (%)	Events/N	l (%)	HR (95% CI)		
End disabilis discustor							
<69 mm	44/72	(61.1)	46/73	(63.0)	1.01 (0.67, 1.52)		
369 mm	53/80	(66.3)	55/78	(70.5)	0.99 (0.68, 1.45)		
End-diastolic diameter index	55/00	(00.0)	55/70	(70.0)	0.00 (0.00, 1.40)		
<37 mm/m2	46/77	(59.7)	47/71	(66.2)	0.86 (0.58, 1.30)	L	
>37 mm/m2	51/75	(68.0)	54/80	(67.5)	1 14 (0 78 1 68)	1	
End-systolic diameter	• • • •	(00.0)	0 11 0 0	(0110)			
<58 mm	42/69	(60.9)	42/70	(60.0)	1.06 (0.69, 1.63)		
>58 mm	55/83	(66.3)	59/81	(72.8)	0.95 (0.66, 1.38)		
End-systolic diameter index		(0010)		()	0.00 (0.00) 1.00)		
<32 mm /m2	56/90	(62.2)	54/81	(66.7)	0.94 (0.65, 1.36)		
≥32 mm / m2	41/62	(66.1)	47/70	(67.1)	1.10 (0.72, 1.67)		
End diactalis + and systelis diameter		()		()	,		
End-diastolic diameter < 63 mm and end-systolic diameter < 52 mm	17/26	(65.4)	13/26	(50.0)	1.34 (0.65, 2.76)		
End-diastolic diameter ≥ 63 mm or end-systolic diameter ≥ 52 mm	80/126	(63.5)	88/125	(70.4)	0.95 (0.70, 1.29)		
End-diastolic volume		()			,		
<242 ml	40/71	(56.3)	52/79	(65.8)	0.81 (0.54, 1.22)	⊢	
≥242 ml	57/81	(70.4)	50/72	(69.4)	1.16 (0.79, 1.70)		
End-diastolic volume index							
<133 ml / m2	43/75	(57.3)	51/76	(67.1)	0.79 (0.53, 1.19)		
≥133 ml / m2	54/77	(70.1)	51/75	(68.0)	1.21 (0.83, 1.78)		
End-systolic volume							
<157 ml	44/74	(59.5)	48/75	(64.0)	0.90 (0.60, 1.36)	F	
≥157 ml	52/77	(67.5)	54/76	(71.1)	1.06 (0.72, 1.55)		
End-systolic volume index							
<85 ml / m2	42/74	(56.8)	52/75	(69.3)	0.75 (0.50, 1.13)		
≥85 ml/m2	54/77	(70.1)	50/76	(65.8)	1.24 (0.85, 1.83)		
End-diastolic + end systolic volume							
End-diastolic volume < 195 and end-systolic volume < 124 ml	20/35	(57.1)	19/25	(76.0)	0.53 (0.28, 1.00)		
End-diastolic volume ≥ 195 ml or end-systolic volume ≥ 124 ml	77/117	(65.8)	83/126	(65.9)	1.13 (0.83, 1.54)		
LVÉF							
<35 %	45/70	(64.3)	58/81	(71.6)	0.96 (0.65, 1.42)		
≥35 %	52/82	(63.4)	44/70	(62.9)	1.04 (0.70, 1.56)		
Aortic stroke volume							
<44 ml	46/73	(63.0)	45/65	(69.2)	0.97 (0.64, 1.46)		
≥44 ml	44/71	(62.0)	49/76	(64.5)	0.95 (0.64, 1.43)		
Aortic stroke volume index							
<24 ml / m2	46/75	(61.3)	44/63	(69.8)	0.87 (0.57, 1.31)	⊢	
≥24 ml / m2	44/69	(63.8)	50/78	(64.1)	1.05 (0.70, 1.57)		



1.5 2

3

1 <--Percut. repair better-- --MT better-->

0.5

0.25

Events/N 43/71 54/81 44/75 53/77 41/71 56/81 42/71 55/81	(%) (60.6) (66.7) (58.7) (68.8) (57.7) (69.1)	Events/N 51/80 50/71 48/77 53/74 52/81 49/70	(%) (63.8) (70.4) (62.3) (71.6) (64.2)	HR (95% Cl) 0.96 (0.64, 1.44) 1.01 (0.69, 1.49) 0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		P interactio 0.85 0.69 0.57
43/71 54/81 44/75 53/77 41/71 56/81 42/71 55/81	(60.6) (66.7) (58.7) (68.8) (57.7) (69.1)	51/80 50/71 48/77 53/74 52/81 49/70	(63.8) (70.4) (62.3) (71.6) (64.2)	0.96 (0.64, 1.44) 1.01 (0.69, 1.49) 0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		0.85 0.69 0.57
43/71 54/81 44/75 53/77 41/71 56/81 42/71 55/81	(60.6) (66.7) (58.7) (68.8) (57.7) (69.1)	51/80 50/71 48/77 53/74 52/81 49/70	(63.8) (70.4) (62.3) (71.6) (64.2)	0.96 (0.64, 1.44) 1.01 (0.69, 1.49) 0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		0.69
54/81 44/75 53/77 41/71 56/81 42/71 55/81	(66.7) (58.7) (68.8) (57.7) (69.1)	50/71 48/77 53/74 52/81 49/70	(70.4) (62.3) (71.6) (64.2)	1.01 (0.69, 1.49) 0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		0.69
44/75 53/77 41/71 56/81 42/71 55/81	(58.7) (68.8) (57.7) (69.1)	48/77 53/74 52/81 49/70	(62.3) (71.6) (64.2)	0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		0.69
44/75 53/77 41/71 56/81 42/71 55/81	(58.7) (68.8) (57.7) (69.1)	48/77 53/74 52/81 49/70	(62.3) (71.6) (64.2)	0.94 (0.63, 1.42) 1.06 (0.72, 1.55)		0.57
53/77 41/71 56/81 42/71 55/81	(68.8) (57.7) (69.1)	53/74 52/81 49/70	(71.6)	1.06 (0.72, 1.55)	⊢_ ∎1	0.57
41/71 56/81 42/71 55/81	(57.7) (69.1)	52/81 49/70	(64.2)	0.00 (0.00 4.00)		0.57
41/71 56/81 42/71 55/81	(57.7) (69.1)	52/81 49/70	(64.2)	0.00 (0.00 1.00)		
56/81 42/71 55/81	(69.1)	49/70		0.90 (0.60, 1.36)	⊢∎	
42/71 55/81	(59.2)		(70.0)	1.06 (0.72, 1.56)	⊢	
42/71 55/81	(59.2)					0.34
55/81	(00.0)	53/81	(65.4)	0.86 (0.58, 1.29)		
	(67.9)	48/70	(68.6)	1.13 (0.77, 1.67)	⊢	
						0.88
67/106	(63.2)	70/105	(66.7)	1.00 (0.71, 1.40)	⊢ ₩1	
30/46	(65.2)	32/46	(69.6)	0.95 (0.58, 1.57)	⊢	
						0.17
47/72	(65.3)	49/79	(62.0)	1.17 (0.79, 1.75)	⊢∎ 1	
50/80	(62.5)	53/72	(73.6)	0.80 (0.54, 1.17)	∎	
						0.35
44/70	(62.9)	51/81	(63.0)	1.09 (0.73, 1.64)	⊢∎ 1	
53/82	(64.6)	51/70	(72.9)	0.84 (0.57, 1.23)	⊢ ∎1	
						0.25
47/72	(65.3)	50/79	(63.3)	1.13 (0.76, 1.69)	⊢	
49/79	(62.0)	52/72	(72.2)	0.82 (0.56, 1.21)	⊢	
						0.44
45/71	(63.4)	51/80	(63.8)	1.07 (0.72, 1.60)	⊢	
51/80	(63.8)	51/71	(71.8)	0.86 (0.58, 1.27)	▶	
						0.40
73/114	(64.0)	82/118	(69.5)	0.93 (0.68, 1.28)	⊢∎(
24/38	(63.2)	20/34	(58.8)	1.25 (0.69, 2.26)	F	
						0.54
67/110	(60.9)	72/106	(67.9)	0.92 (0.66, 1.28)	⊢≣ 1	
22/33	(66.7)	21/34	(61.8)	1.14 (0.63, 2.07)		
3 4 5 4 5 4 4 5 7 2 5 7 2 5 7 2	0/46 7/72 0/80 4/70 3/82 7/72 9/79 5/71 1/80 3/114 4/38 7/110 2/33	0/46 (65.2) 7/72 (65.3) 0/80 (62.5) 4/70 (62.9) 3/82 (64.6) 7/72 (65.3) 9/77 (65.3) 1/80 (63.4) 1/80 (63.4) 1/80 (63.2) 3/114 (64.0) 4/38 (63.2) 7/110 (60.9) 2/33 (66.7)	0446 (65.2) 32/46 7772 (65.3) 4979 0080 (62.5) 53/72 4/70 (62.9) 51/81 3/82 (64.6) 51/70 7/72 (65.3) 50/79 9/79 (62.0) 52/72 5/71 (63.8) 51/70 1/114 (64.0) 51/80 1/114 64.0) 52/118 3/83 (63.2) 20/34 7/110 (60.9) 72/106 2/33 (66.7) 21/34	0.46 (65.2) 32.46 (69.6) 7/72 (65.3) 49.79 (62.0) 0.80 (62.5) 53.72 (73.6) 4/70 (62.9) 51.81 (63.0) 3182 (64.6) 51.70 (72.9) 7772 (65.3) 50.79 (63.3) 9179 (62.0) 52.72 (72.2) 55/1 (63.4) 51.80 (63.8) 51414 (64.0) 82/118 (65.5) 4/38 (63.2) 20.164 (68.8) 7/110 (60.9) 72/106 (67.9) 2/33 (66.7) 21/124 (61.8)	0446 (65.2) 32/46 (69.6) 0.95 (0.58, 1.57) 7772 (65.3) 49/79 (62.0) 1.17 (0.79, 1.75) 080 (65.5) 5372 (73.6) 0.80 (0.54, 1.17) 470 (62.9) 51/81 (63.0) 1.09 (0.73, 1.64) 382 (64.6) 51/70 (72.9) 0.84 (0.57, 1.23) 7772 (65.3) 50/79 (63.3) 1.13 (0.76, 1.69) 979 (62.0) 52/72 (72.2) 0.82 (0.56, 1.21) 57/1 (63.4) 51/80 (63.8) 1.07 (0.72, 1.60) 180 (63.8) 51/71 (71.8) 0.86 (0.58, 1.27) 8/114 (64.0) 82/118 (69.5) 0.93 (0.68, 1.28) 4/38 (63.2) 20/34 (58.8) 1.25 (0.69, 2.26) 7/110 (60.9) 72/106 (67.8) 1.42 (0.68, 2.26) 7/203 (66.7) 21/34 (61.8) 1.44 (0.8, 2.07)	0446 (65.2) 32.466 (69.6) 0.95 (0.58, 1.57) 7772 (65.3) 4979 (62.0) 1.17 (0.79, 1.75) 0400 (62.5) 537/2 (73.6) 0.80 (0.54, 1.17) 4700 (62.5) 537/2 (73.6) 0.80 (0.54, 1.17) 4700 (62.9) 51/61 (63.0) 1.09 (0.73, 1.64) 4779 (65.3) 50/79 (63.3) 1.13 (0.76, 1.69) 9779 (65.2) 52/72 (72.2) 0.82 (0.56, 1.21) 57/1 (65.8) 51/70 (71.8) 0.86 (0.58, 1.27) 1180 (63.8) 51/71 (71.8) 0.86 (0.58, 1.27) 1141 (64.0) 82/118 (69.5) 0.93 (0.68, 1.28) 1/110 (60.9) 72/106 (67.79) 0.92 (0.66, 1.26) 1/110 (60.9) 72/106 (67.9) 0.92 (0.66, 1.26)

	Subgroup		Events/N (%)		treatment V (%)	HR (95% CI)		P interaction
FDC - Ford Party Party Party								0.26
ERO < 30 mm2 and End-diastolic diameter > 69 mm		17/31	(54.8)	24/33	(72.7)	0.66 (0.36, 1.23)	F	
ERO < 30 mm2 and End-diastolic diameter < 69 mm or ERO ≥ 30 and End-diast	olic diameter ≥ 69 mm	60/88	(68.2)	55/85	(64.7)	1.19 (0.83, 1.72)	⊢	-
ERO ≥ 0.30 mm2 and End-diastolic diameter < 69 mm		20/33	(60.6)	22/33	(66.7)	0.93 (0.51, 1.70)		-
								0.97
ERO + End-diastolic diameter index		22/34	(64.7)	25/38	(65.8)	1.01 (0.57, 1.80)	F	
ERO < 30 mm2 and End-diastolic diameter index < 37 mm/m2 ERO < 30 mm2 and End-diastolic diameter index < 37 or ERO > 30 and End-dia	stolic diameter index > 37 mm/m2	52/84	(61.9)	56/83	(67.5)	0.96 (0.66, 1.41)	⊢_ ∎ i	
ERO ≥ 0.30 mm2 and End-diastolic diameter index < 37 mm/m2		23/34	(67.6)	20/30	(66.7)	1.05 (0.58, 1.91)		
								0.08
ERO + End-systolic diameter		19/35	(54.3)	30/39	(76.9)	0.61 (0.34, 1.08)	⊢	
ERO < 30 mm2 and End-diastolic diameter ≥ 58 mm ERO < 30 mm2 and End diastolic diameter < 58 mm as ERO > 30 and End dias	tolis dismoster > F.9 mm	60/86	(69.8)	49/79	(62.0)	1.32 (0.90, 1.92)	⊢ ⊢ ,	
$ERO \ge 0.30 \text{ mm}^2$ and $End-diastolic diameter < 58 \text{ mm}$ or $ERO \ge 50 \text{ and }End-diastolic diameter < 58 \text{ mm}$	tone diameter 2.58 mm	18/31	(58.1)	22/33	(66.7)	0.87 (0.47, 1.62)		-
								0.67
ERO + End-systolic diameter index		15/25	(60.0)	18/29	(62.1)	1.03 (0.52, 2.05)		
ERO < 30 mm2 and End-diastolic diameter index ≥ 32 mm/m2 ERO < 30 mm2 and End diastolic diameter index < 32 mm/m2 or ERO > 30 and	d End diactolic diameter index > 32 mm/m2	56/89	(62.9)	63/91	(69.2)	0.91 (0.63, 1.30)	⊢_ ≣	
$ERO \ge 0.30$ and $Erd-diastolic diameter index < 32 mm/m2 of ERO \ge 30 and ERO \ge 0.30 and Erd-diastolic diameter index < 32 mm/m2$	a End-diastolic diameter index 2 52 mm/m2	26/38	(68.4)	20/31	(64.5)	1.23 (0.69, 2.21)		
								0.66
ERO + End-diastolic volume		16/29	(55.2)	21/33	(63.6)	0.87 (0.45, 1.66)	F	-
ERO < 30 mm2 and End-diastolic volume ≥ 242 ml ERO < 30 mm2 and End-diastolic volume < 242 or ERO > 30 and End-diastolic	volume > 242 ml	70/100	(70.0)	61/87	(70.1)	1.07 (0.76, 1.51)	⊢_∎	1
ERO ≥ 0.30 mm2 and End-diastolic volume < 242 ml	volume 2 242 mi	11/23	(47.8)	20/32	(62.5)	0.76 (0.36, 1.59)		-
								0.97
ERO + End-diastolic volume index		16/26	(61.5)	22/35	(62.9)	1.01 (0.53, 1.92)		
ERO < 30 mm2 and End-diastolic volume index \ge 133 ml/m2 ERO < 30 mm2 and End-diastolic volume index < 133 ml/m2 or ERO \ge 30 and 1	End-diastolic volume index > 133 ml/m2	67/102	(65.7)	60/86	(69.8)	0.99 (0.70, 1.40)	⊢ 	
$ERO \ge 0.30 \text{ mm2}$ and $End-diastolic diameter index < 133$		14/24	(58.3)	20/31	(64.5)	0.91 (0.46, 1.79)		
								0.82
ERO + End-systolic volume		15/28	(53.6)	23/35	(65.7)	0.82 (0.43, 1.57)		4
ERO < 30 mm2 and End-diastolic volume ≥ 157 ml ERO < 30 mm2 and End diastolic volume < 157 or ERO > 30 and End diastolic	volume > 157 ml	68/99	(68.7)	59/85	(69.4)	1.04 (0.73, 1.47)	· i∎ i	
$ERO \ge 0.30 \text{ mm2}$ and $End-diastolic volume < 157 \text{ of }ERO \ge 50 \text{ and }End-diastolic ERO \ge 0.30 \text{ mm2}$ and $End-diastolic volume < 157 \text{ ml}$	volume 5 137 mi	14/25	(56.0)	20/32	(62.5)	0.95 (0.48, 1.89)		
								0.84
ERO + End-systolic volume index		18/30	(60.0)	23/38	(60.5)	1.02 (0.55, 1.88)		
ERO < 30 mm2 and End-diastolic volume index ≥ 85 ml/m2		64/95	(67.4)	57/81	(70.4)	1.02 (0.71, 1.46)	·	
EKU < 30 mm2 and End-diastolic volume index < 85 ml/m2 or ERO \ge 30 and Er ERO \ge 0.30 mm2 and End-diastolic volume index < 85 ml/m2	ia-alastolic volume index ≥ 85 ml/m2	15/27	(55.6)	22/33	(66.7)	0.82 (0.43, 1.58)	F	4
							0.25 0.5 1 1	5 2 3