



**HAL**  
open science

## 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, H el ene 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-02959038>**

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 destin ee au d ep ot et  a la diffusion de documents scientifiques de niveau recherche, publi es ou non,  emanant des  tablissements d'enseignement et de recherche franais ou  trangers, des laboratoires publics ou priv es.



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, H el ene Thibault MD 9, Nicolas Piriou MD 5, Bertrand Cormier MD 10  
Christophe Tribouilloy MD, PhD 11, Patrice Guerin MD, PhD 12, Thierry Lef evre 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. Universit e de Paris and INSERM 1148, Paris, France;
3. APHP, H opital Bichat, DHU FIRE, Paris, France;
4. Edouard Herriot Hospital, Pharmacy Department / Claude Bernard University- Laboratoire MATEIS, Lyon, France;
5. Universit e Nantes, CHU Nantes, CNRS, INSERM, l'institut du Thorax, Nantes, France
6. CHU de Rennes, H opital Pontchaillou, Rennes, France and LTSI UMR1099, INSERM, Universit e de Rennes-1, Rennes, France
7. APHM, La Timone Hospital, Cardiology Department, Marseille France
8. Aix Marseille Univ, IRD, APHM, MEPHI, IHU-M editerran e Infection, Marseille, France
9. Groupement Hospitalier Est, Hospices Civils de Lyon, Service d'Explorations Fonctionnelles Cardiovasculaires, 28 Avenue Doyen L epine, Bron 69677, France
10. Institut Cardiovasculaire Paris Sud, H opital Priv e 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
13. Universit e Lyon 1, Villeurbanne, France; CNRS, UMR5558, Laboratoire de Biom etrie et Biologie  volutive,  quipe Biostatistique-Sant e, Service de Biostatistique - Bioinformatique, P ole Sant e Publique, Hospices Civils de Lyon, Villeurbanne, France;
14. H opital 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: [DMessika-zeitoun@ottawaheart.ca](mailto:DMessika-zeitoun@ottawaheart.ca). Tel: 613-696-7337; Fax: 613-696-7127

Jean-Francois Obadia, H opital Cardiovasculaire Louis Pradel, Chirurgie Cardio-Vasculaire et Transplantation Cardiaque, 28, Avenue Doyen L epine, 69677 Bron Cedex, France. Email: [jean-francois.obadia@chu-lyon.fr](mailto: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 ( $ERO \geq 30 \text{ mm}^2$ ,  $RVOL \geq 45 \text{ ml}$  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.<sup>(11)</sup> 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.<sup>(7,8)</sup> Eligible patients had severe secondary MR with an effective regurgitant orifice (ERO) area  $\geq 20 \text{ mm}^2$  or a regurgitant volume (RVOL)  $\geq 30 \text{ ml}$  per beat as assessed by echocardiography,<sup>(12)</sup> 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 end-diastolic 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

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



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  $31 \pm 11 \text{ mm}^2$  (median  $29 \text{ mm}^2$ , IQR [22-37]), mean RVOL  $45 \pm 14 \text{ ml}$  (median  $43 \text{ ml}$ , IQR [35-53]) and mean RF  $0.49 \pm 0.10$  (median  $0.46$ , IQR [0.42-0.56]) (Table 1).

ERO was  $\geq 40 \text{ mm}^2$  in 49 patients and RF  $\geq 0.50$  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  $\geq 30 \text{ mm}^2$ , a RVOL  $\geq 45 \text{ ml}$  or a RF  $\geq 50\%$ ), the impact of the intervention was neutral and similar to that observed in patients with milder MR degree. Combining parameters of MR severity (ERO  $\geq 30 \text{ mm}^2$  and RVOL  $\geq 45 \text{ ml}$  or ERO  $\geq 30 \text{ mm}^2$  and RF  $\geq 50\%$ ) 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  $69 \pm 8 \text{ mm}$  (median 69, IQR [63-74]) and  $58 \pm 9 \text{ mm}$  (median 58, IQR [52-65]) respectively and mean end-diastolic and end-systolic volumes were  $250 \pm 75 \text{ ml}$  (median 242, IQR [193-300]) and  $169 \pm 63 \text{ ml}$  (median 157, IQR [124-209]) respectively. Mean LVEF was  $33 \pm 7\%$ . 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**

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  $\geq 0.15$  or  $< 0.15$  (mean  $0.13 \pm 0.05$  (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 end-diastolic volume (Central figure), patients with the more severe MR presented with larger LV volumes while patients with an ERO / LV end-diastolic volume  $\geq 0.15$  (N=92) and patients with an ERO  $\geq 30$  mm<sup>2</sup> and a LV end-diastolic volume  $< 242$  ml (N=55) presented with similar ERO and LV volumes than the COAPT overall population ( $39 \pm 12$  mm<sup>2</sup>,  $201 \pm 57$  ml and  $38 \pm 8$  mm<sup>2</sup>,  $195 \pm 33$  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 ( $\leq 30 \text{ mm}^2$ ) and the largest LV size (LV end-diastolic volume index  $\geq 96 \text{ ml/m}^2$ ).<sup>(15)</sup> 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.<sup>(16-18)</sup>

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 mm<sup>2</sup> 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 mm<sup>2</sup> 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 mm<sup>2</sup> is more sensitive while a cut-off value of 40 mm<sup>2</sup> is more specific, and that a lower threshold (30 mm<sup>2</sup>) 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  $\geq$  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  $\text{RF} \times \text{LVEF}$ ) 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  $\geq 0.15$  or of the quartile of patients with an ERO  $\geq 30$  mm<sup>2</sup> 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 individual-patient 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 limitations deserve comments. First, all analyses 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 significance 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 diameters did not show the same trend and thus these results may likely be 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 inconsistencies 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

1. 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 3-dimensional echocardiography. *Circulation* 2000;101:2756-63.
2. 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.
3. 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.
7. 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.
8. 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.

9. 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. Goliash 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.
11. 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.
14. 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.

15. 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.
16. 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.
17. 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.
18. 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.
21. 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.
  23. 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.
  25. 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.
  26. 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.
  27. 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 cm<sup>2</sup>, 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.

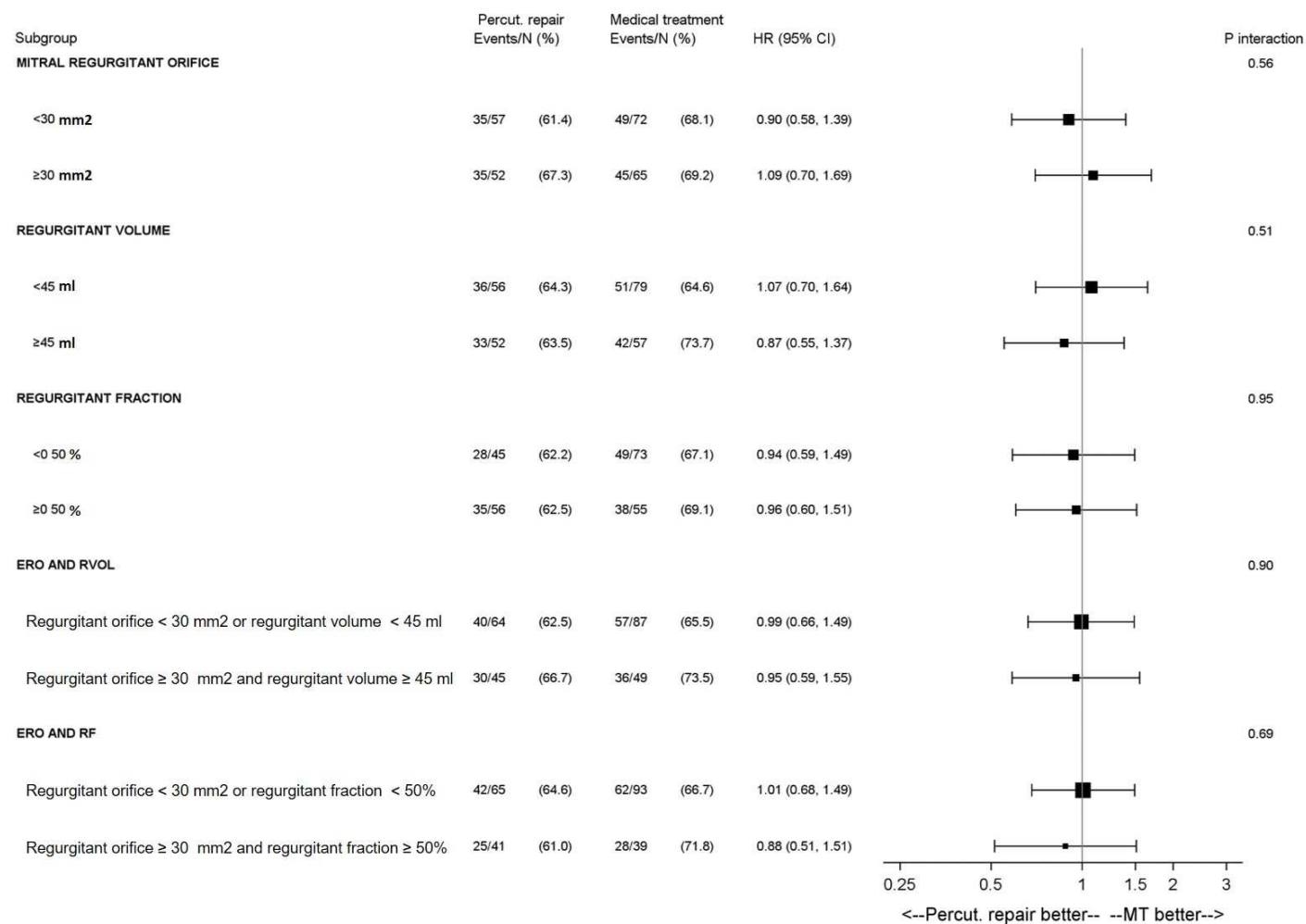
**Table.** Baseline values presented as mean  $\pm$  standard deviation (SD) and median, 25-75 interquartile range (IQR) of quantitative parameters of the degree of mitral regurgitation and of left ventricular remodelling and function.

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

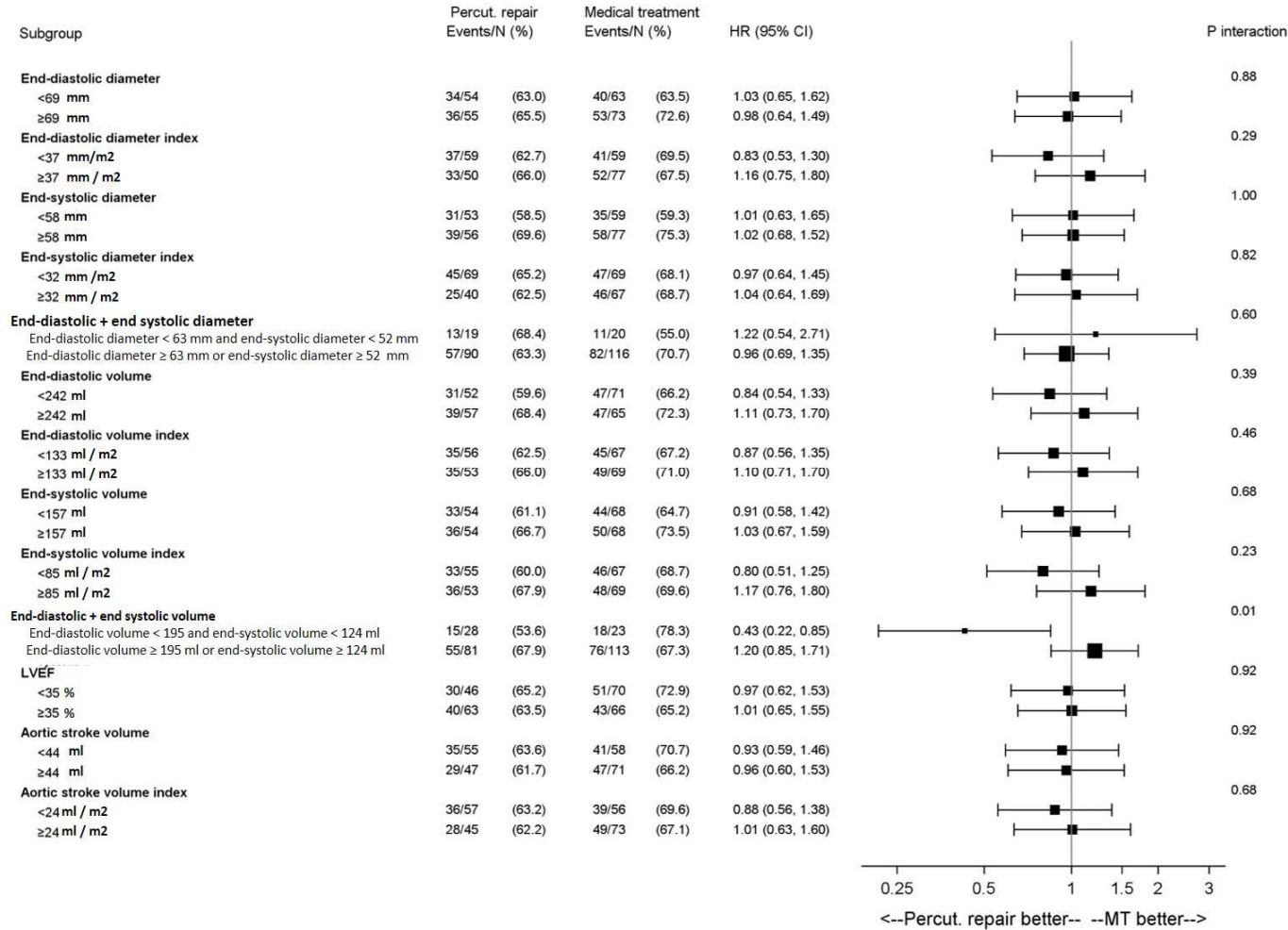
## Supplementary material

**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).

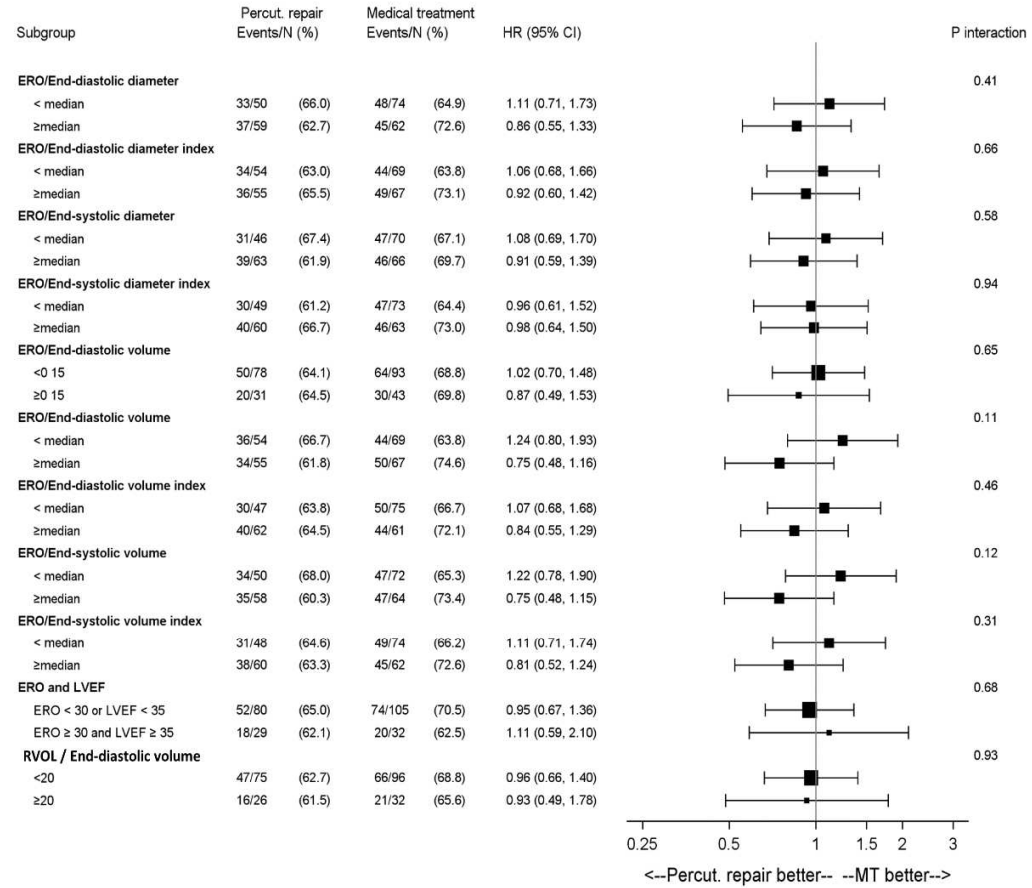




**Supplemental Figure 2.** Interaction between the degree of left ventricular remodelling and systolic function and the Mitraclip on the composite of all-cause death or unplanned hospitalization for heart failure at 24 months (per-protocol analysis).



**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).



**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).

