Transcatheter Mitral Valve Replacement in Patients with Heart Failure and Secondary Mitral Regurgitation: From COAPT Trial

Federico M. Asch, MD, Paul A. Grayburn, MD, Robert J. Siegel, MD, Saibal Kar, MD, D. Scott Lim, MD, Jonathan G. Zaroff, MD, Jacob M. Mishell, MD, Brian Whisenant, MD, Michael J. Mack, MD, JoAnn Lindenfeld, MD, William T. Abraham, MD, Gregg W. Stone, MD, Neil J. Weissman, MD, on behalf of the COAPT Investigators

PII: S0735-1097(19)37678-8

DOI: https://doi.org/10.1016/j.jacc.2019.09.017

Reference: JAC 26756

To appear in: *Journal of the American College of Cardiology*

Received Date: 15 September 2019

Accepted Date: 17 September 2019

Please cite this article as: Asch FM, Grayburn PA, Siegel RJ, Kar S, Lim DS, Zaroff JG, Mishell JM, Whisenant B, Mack MJ, Lindenfeld J, Abraham WT, Stone GW, Weissman NJ, on behalf of the COAPT Investigators, Transcatheter Mitral Valve Replacement in Patients with Heart Failure and Secondary Mitral Regurgitation: From COAPT Trial, *Journal of the American College of Cardiology* (2019), doi: https://doi.org/10.1016/j.jacc.2019.09.017.

Transcatheter Mitral Valve Replacement in Patients with Heart Failure and Secondary Mitral Regurgitation: From COAPT Trial

Authors: Federico M. Asch MD [a], Paul A. Grayburn MD [b], Robert J. Siegel MD [c], Saibal Kar MD [c], D. Scott Lim MD [d], Jonathan G. Zaroff MD [e], Jacob M. Mishell MD [e], Brian Whisenant MD [f], Michael J. Mack MD [g], JoAnn Lindenfeld MD [h], William T. Abraham MD [i], Gregg W. Stone MD [j] and Neil J. Weissman MD [a], on behalf of the COAPT Investigators

Affiliations:
[a] FMA, NJW: MedStar Health Research Institute, Washington, DC
[b] PAG: Baylor University Medical Center, Baylor Heart and Vascular Institute, Dallas, TX
[c] RJS, SK: Cedars-Sinai Smidt Heart Institute, Los Angeles, CA
[d] DSL: Division of Cardiology, University of Virginia, Charlottesville, VA
[e] JGZ, JMM: Kaiser Permanente - San Francisco Hospital, San Francisco, CA
[f] BW: Intermountain Medical Center, Murray, UT
[g] MJM: Baylor Scott & White Heart and Vascular Hospital, Plano, TX
[h] JL: Advanced Heart Failure, Vanderbilt Heart and Vascular Institute, Nashville, TN
[I] WTA: Departments of Medicine, Physiology, and Cell Biology, Division of Cardiovascular Medicine, and the Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH
[j] GWS: The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York and The Cardiovascular Research Foundation, New York, NY

Brief Title: COAPT Echocardiographic Outcomes

Funding: The COAPT trial was sponsored by Abbott and designed collaboratively by the principal investigators and the sponsor.

Tweet #1: The COAPT echocardiographic screening algorithm should be used for selection of heart failure patients with secondary MR to identify patients likely to benefit from MitraClip implantation.

Tweet #2: Echocardiography is critical for identifying patients with heart failure and secondary MR who may achieve COAPT-trial consistent results in clinical practice.

Tweet #3: In COAPT, all major echocardiography-based subgroups responded to MitraClip with consistently lower rates of death or HF hospitalization compared with guideline directed medical therapy alone.

Acknowledgements: The authors want to acknowledge the following individuals for their support and expertise in data analysis and presentation: Pooja Singhal, PhD, Jeffrey Ellis, PhD and Kartik Sundareswaran, MD (all from Abbott Structural Heart Global Clinical Affairs); Yu Shu, PhD, Juanjuan Li, PhD, Deepika Morishetti, MS and Hong Nie, PhD (all from Abbott, Global Biometrics).

Disclosure of Potential Conflicts of Interest:
FMA: Director of an academic echocardiography core lab (MedStar Health Research Institute) with Institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, Livanova.
PAG: research grant support from Abbott, Edwards Lifesciences, Medtronic and Boston

Scientific, Consultant for Abbott, Edwards, Medtronic, Neochord, Imaging Core Lab Contracts from Edwards Lifesciences, Neochord, W. L. Gore, Cardiovalve.
RJS: speaker fees from Philips Ultrasound
SK: research grant support from Abbott, Boston Scientific, Edwards Lifesciences, Mitralign; consulting income from Abbott and Boston Scientific
DSL: research grant support from Abbott; consulting income from Abbott
BW: consultant for Edwards Lifesciences and Boston Scientific
JL: research grant support from AstraZeneca; consulting income from Abbott, Edwards Lifesciences, Boston Scientific, Relypsa, Boehringer Ingelheim, V-Wave, CVRx, Impulse Dynamics.
WTA: research grant support from Abbott; consulting income from Abbott
GWS: consulting fees from Neovasc, Valfix, Gore; equity/options/consulting fees from Ancora; Institutional conflict: Columbia University receives royalties from Abbott for sale of the MitraClip.
NJW: Associate director of an academic echocardiographic core lab (MedStar Health Research Institute) with Institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, Livanova.
The other authors report no conflicts.

Corresponding Author:
Federico M. Asch, MD
MedStar Health Research Institute at MedStar
Washington Hospital Center
100 Irving St, NW, Suite EB 5123
Washington, DC 20010
Phone (o):(202) 877-3792
Phone (Cell): (301) 654-5645
Fax: (202) 877-0792
Email: federico.asch@medstar.net
Twitter: @FedericoAsch

Abstract

Background: In the COAPT trial among patients with heart failure (HF) and moderate-to-severe (3+) or severe (4+) secondary mitral regurgitation (SMR), patients treated with the transcatheter mitral valve replacement (TMVR) had reduced rates of HF hospitalization and mortality compared with guideline-directed medical therapy (GDMT) alone.

Objectives: To describe the echocardiographic patient qualification process for COAPT, baseline echocardiographic characteristics, changes over time, and the interaction between treatment group and echocardiographic parameters on clinical outcomes.

Methods: A novel echocardiographic algorithm was implemented for grading MR severity during the screening process. Standardized echocardiograms were obtained at baseline and during regular follow-up intervals through 2 years, and analyzed by a core laboratory.

Results: A total of 614 patients were randomized to TMVR plus maximally- tolerated GDMT or GDMT alone. Mean baseline left ventricular ejection fraction (LVEF) was 31.3±9.3%, LV end-diastolic volume was 192.7±71 ml, and effective regurgitant orifice area was 0.41±0.15 cm^2. The beneficial effect of TMVR compared with GDMT alone was consistent in all echocardiographic subgroups, independent of the severity of LV dysfunction, LV dilatation, pulmonary hypertension, severity of tricuspid regurgitation or individual MR characteristics. The LVEF decreased and the LV volumes progressively increased in both groups during follow-up, although less after TMVR ($P<0.05$).

Conclusions: HF patients in the COAPT trial with 3+ or 4+ SMR, selected using strict echocardiographic criteria, benefitted from TMVR with reduced 2-year rates of death and HF hospitalization. Strict application of these echocardiographic criteria should enable the COAPT results to be translated to clinical practice.

Trial Registration (clinicaltrials.gov): NCT 01626079

Condensed Abstract

In the COAPT randomized clinical trial, treatment of heart failure (HF) patients with 3+ or 4+ secondary mitral regurgitation (MR) had reduced rates of HF hospitalization and mortality. A specific algorithm was developed based on the American Society of Echocardiography recommendations to identify candidate patients. No groups of non-responders were identified based on echocardiography. Strict application of these echocardiographic criteria is essential if the COAPT results are to be duplicated in clinical practice.

Key Words: Secondary mitral regurgitation; heart failure; percutaneous mitral valve repair; mitral valve edge-to-edge repair; MitraClip; echocardiography; clinical outcomes.

Abbreviations

SMR - Secondary mitral regurgitation
LV - left ventricle/ventricular
HF - heart failure
GDMT - guideline-directed medical therapy
PISA - proximal isovelocity surface area
EROA – effective regurgitant orifice area
EF - ejection fraction
TTE - transthoracic echocardiograms
RVSP - Right Ventricular Systolic Pressure

Introduction

Secondary mitral regurgitation (SMR) refers to MR in the absence of structural abnormalities of the mitral valve complex and occurs most frequently in the setting of left ventricular (LV) dysfunction. The interaction between MR and LV dysfunction is complex as both pathologies result in LV volume overload with subsequent disease progression. The presence of substantial SMR in patients with LV dysfunction is associated with worsened quality of life and increased mortality.(1–4) Despite its recognized clinical importance, the diagnosis and treatment of SMR remains challenging. Treatment of heart failure (HF) with medical therapies or ventricular resynchronization may improve the severity of SMR and patient outcomes,(5–7) although surgical repair of SMR has not been demonstrated to improve prognosis.(8–10)
The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial has demonstrated that mitral valve leaflet approximation with transcatheter mitral valve replacement (TMVR) reduces the rate of hospitalizations and improves survival in selected patients with HF and SMR compared to maximally-tolerated guideline-directed medical therapy (GDMT) alone.(11) While COAPT demonstrated unequivocal evidence for clinical improvement with MR reduction, a similar randomized study, the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial was negative, possibly due in large part to differences in the echocardiographic severity of MR and LV dysfunction in the enrolled patient populations.(12) As the shape of the MR regurgitant orifice in SMR is elliptical rather than circular, the use of classic MR parameters such as proximal isovelocity surface area (PISA) or vena contracta (VC) can be problematic. Evaluating SMR severity after TMVR is

especially challenging given the presence of multiple mitral orifices. A lack of consensus among experts has resulted in discordant recommendations from professional societies.(13–16)

To address these issues the COAPT investigators employed a specific echocardiographic core laboratory MR assessment algorithm to qualify patients for the COAPT trial. This methodology and its impact on trial outcomes have not been described. We therefore herein describe the echocardiographic methodology used in the COAPT trial and the echocardiographic features characterizing the eligible population; analyze the effect of intervention on LV remodeling and function; and identify echocardiographic characteristics that predict favorable outcomes after TMVR in HF patients with severe SMR.

Methods

Study Design. The COAPT trial design has been published previously.(17) In brief, COAPT was a multicenter, randomized, controlled, open-label trial of TMVR with the MitraClip device (Abbott, Chicago, Illinois) in patients with HF and moderate-to-severe (3+) or severe (4+) MR who remained symptomatic despite maximally tolerated guideline-directed medical therapies (GDMT). Patients had LV ejection fraction (EF) between 20-50%, LV end-systolic diameter (LVESD) ≤70 mm, and absence of severe pulmonary hypertension (defined as pulmonary artery systolic pressure >70 mmHg despite vasodilator therapy) or moderate or severe right ventricular failure. Patients were randomized to receive TMVR plus GDMT or GDMT alone.

Echocardiographic follow-up was performed at 1, 6, 12, 18, and 24 months after randomization. The primary effectiveness endpoint was all hospitalizations for HF within 24 months, assessed when all patients had completed at least 1-year follow-up. All TTEs were

analyzed by an independent echocardiographic core laboratory (MedStar Health Research Institute, Washington DC).

The protocol was approved by the investigational review board at each participating center, and all patients provided written informed consent. Abbott sponsored the trial and provided statistical support for the present analysis. The investigators had unrestricted access to the data and accept responsibility for the integrity of the present report.

Echocardiographic core laboratory analysis. Among patients who the sites identified as possible trial candidates, the echocardiographic core laboratory was responsible for confirming the presence of 3+ or 4+ SMR and other echocardiographic eligibility parameters from the screening TTEs, rejecting randomization of ineligible subjects. For qualification purposes, MR severity was assessed as 3+ or higher following a pre-specified multiparametric algorithm created for the COAPT trial (**Central Illustration; Supplemental Table 1**), adapted from the criteria recommended by the American Society of Echocardiography (ASE) 2003 Guidelines.(18, 19) This algorithm consisted of 3 tiers of evaluation that were applied in a hierarchical manner; patients qualified for COAPT by meeting at least one of them. Follow-up MR severity was assessed using an integrative approach based on qualitative and quantitative data adapted from the ASE Guidelines. MR was categorized as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate to severe) or 4+ (severe) as detailed in Supplemental Table 1.(19, 20) All other echocardiographic parameters (Table 1) were analyzed based on ASE recommendations.(19, 21) Follow-up echocardiograms did not have PISA evaluation, as the presence of the MitraClip would prevent accurate, reproducible measurements of multiple regurgitant, eccentric jets with non-hemispheric proximal flow convergence. Therefore, MR regurgitant volume (RV) and regurgitant fraction (RF) at follow-up were obtained from Doppler

hemodynamic and volumetric analysis. If more than one regurgitant jet was identified at follow-up, the vena contracta width of the dominant jet was measured or the vena contracta widths of multiple jets were added if more than one was considered significant.

Statistical analysis. Baseline characteristics were summarized with means and standard deviations (SD) for continuous measures and proportions for categorical variables. Between treatment groups, variables were compared with t-test for the continuous measures and proportional odds model for the categorical variables. For time-to-first event analyses, event rates were estimated by the Kaplan-Meier method, and compared with Cox regression. Multivariable analysis was performed to identify the baseline variables which were independent predictors of the 24-month rate of death or HF hospitalization in each treatment group. The variables entered into these models are listed in Table 2. Changes in echocardiographic parameters over time were calculated as the difference between the baseline and follow-up visits. Subjects without an available follow-up echo image who had an adjudicated heart failure death prior to that visit were assigned the worst change from baseline to that visit. For all other subjects who had missing echo values due to other reasons (e.g. death not due to heart failure, withdrawals, missing echoes, etc.), multiple imputation with Markov Chain Monte Carlo was used. The imputations were done within treatment groups up to 12-months of follow-up. For the 18 and 24-month visit, only eligible subjects were included in the analysis. Analysis of covariance (ANCOVA) was performed to compare changes over time adjusted for baseline values. A two-sided p-value <0.05 was considered statistically significant for all superiority tests. All statistical analyses were performed with SAS software, v9.3 (SAS Institute).

Results

Screening echocardiographic assessments and study enrollment. Between December 2012 through June 2017, 1576 subjects were screened at 78 centers in the U.S. and Canada, of whom 911 (57.8%) were ineligible (**Central Illustration**). Principal echocardiographic exclusion criterion included <3+ MR severity, primary or mixed MR etiology, LVESD >70 mm and LVEF <20% or >50%. Among the 665 enrolled patients (including roll-in subjects), 85.7% met the ≥3+ MR severity criteria based on the first tier of the multiparametric algorithm, while the remainder qualified based on tiers 2 or 3 (**Central Illustration**). Among those qualified as tier 1, 41.5% met both the effective regurgitant orifice area (EROA) >0.3 cm^2 and pulmonary vein systolic flow reversal criteria, 54.9% met only the EROA criterion and 3.5% met only the PV flow criterion.

Fifty-one patients were treated with TMVR as roll-ins and 614 were randomized (302 to TMVR plus GDMT, 312 to GDMT alone). Baseline clinical characteristics of the two treatment groups were well matched, as reported elsewhere.(11)

Baseline echocardiographic characteristics. Overall, the feasibility to obtain most baseline echocardiographic measures was high. LV volumes and LVEF by Simpson's rule, PISA-derived EROA, VC and color Doppler MR were all obtained in >93% of cases. Pulmonary vein flow was assessible in 77.2% of cases and right ventricular systolic pressure (RVSP) in 86.0%. Grading of MR severity by the ASE-derived integrative approach was possible in all patients. However, significant limitations were encountered in the assessment of RV and RF by the combined 2D volumes Simpson's rule / Doppler hemodynamics method. These calculations were feasible in only 42.3% of patients at baseline and were available for paired baseline and follow-up analysis in only 11.4% of patients. Furthermore, the volumetric analysis obtained from

2D and Doppler were frequently discrepant due to underestimation by the 2D Simpson's method.(22) Therefore, these variables were excluded from further analysis.

The mean LVEF was 31.3 ± 9.3%, LV end-diastolic volume (LVEDV) was 192.7±71 ml, RVSP was 44.3±13.7 mmHg and 16.4% had tricuspid regurgitation (TR) of moderate or higher severity. MR was graded as 3+ and 4+ in 52.2% and 47.8% of patients respectively. By PISA evaluation, mean EROA was 0.41±0.15 cm^2. The device and control groups had similar baseline echocardiographic characteristics (Table 1), except for pulmonary vein flow (higher incidence of systolic flow reversal in the device group, p=0.02). Baseline echocardiographic characteristics of patients qualified in each of the 3 tiers are presented in Supplemental Table 2.

Baseline characteristics and outcomes. Unadjusted analysis of baseline echocardiographic parameters was performed to identify predictors of first HF hospitalization or death. The salutary effect of TMVR compared with GDMT alone in reducing the time to death or HF hospitalization was consistent in all echocardiographic subgroups at 12 months (Supplemental Table 3) and at 24 months (**Figure 1**). Reduced LVEF, greater EROA and RVSP and the severity of TR were independent predictors of death or HF hospitalization within 24 months in patients randomized to GDMT alone. In contrast, only higher RVSP and STS score were predictive of death or HF hospitalization in TMVR-treated patients (Table 2). The independent predictors of 24-month mortality alone are shown in Supplemental Table 4.

Echocardiographic changes over time. At 30-day follow-up only 7.4% of TMVR-treated patients had ≥3+ MR, an effect that was durable throughout the 24-month follow-up period (Supplemental Figure 1). Some patients in the control group also had improved MR severity during follow-up (e.g. 34.3% had ≤2+ MR at 30 days), but much fewer than after TMVR at all timepoints (all P<0.001). Compared to baseline, MR improved by ≥2 grades at 12

months in 84.1% of alive patients in the device group and in 15.9% in the control group ($p<0.001$).

Changes in LV volumes, LVEF and other parameters over time are shown in **Table 3**, **Figure 2,** and **Supplemental Table 5**. LVESV and LVEDV increased over time in both groups, but less so after TMVR. The LVEF also decreased over time in both groups, initially more so after TMVR compared with GDMT alone. However, by 12 months the reduction in LVEF from baseline was less in patients treated with TMVR compared with control.

Discussion

The potential implications of effectively applying the COAPT results to clinical practice are substantial. At least 5.7 million patients in the US have HF,(23) ~15% of whom have 3+ or 4+ SMR.(24) The COAPT trial demonstrates that such patients who remain symptomatic despite maximally-tolerated GDMT may benefit from MR reduction with TMVR, in terms of improved quality of life and exercise capacity, reduced HF hospitalizations and prolonged survival.(11) However, not all HF patients with SMR derive benefit from TMVR. Specifically, patients enrolled in the MITRA-FR trial, who had on average less severe MR and greater LV dilatation, had similar 12-month rates of death or HF hospitalization with and without TMVR (12). The present analysis, representing the formal COAPT trial echocardiographic sub-study, is thus of direct clinical relevance in identifying those patients likely to benefit (and not benefit) by TMVR.

In this regard, the major findings from the present study are: 1) MR severity was assessed in COAPT using a specific integrative multiparametric MR grading algorithm that resulted in enrollment of a homogeneous population that benefitted by TMVR; 2) The relative clinical benefit of TMVR in the COAPT population was consistent across all baseline echocardiographic

parameters, regardless of LV size and function, RVSP or degree of MR or TR; 3) However, despite participation of highly skilled clinical centers with expert echocardiographers in COAPT, nearly 1/3 of patients believed by the sites to meet the protocol echocardiographic criteria did not qualify by core laboratory review, testifying to an ongoing need for specialized echocardiographic training and experience; 4) The improvement in MR severity after TMVR was durable throughout 24 months of follow-up; 5) In GDMT-treated patients, reduced baseline LVEF, greater EROA, RVSP and severity of TR predicted adverse outcomes during follow-up, whereas after TMVR only baseline RVSP and STS score had independent prognostic value; and 6) Over time progressive adverse LV remodeling and deterioration in LV systolic function were mitigated in patients treated with TMVR compared with GDMT only.

Accurately assessing SMR remains problematic even at experienced centers. Challenges include the diversity of regurgitant orifice shapes, dynamic changes throughout the cardiac cycle, suboptimal views and assessment technique, suboptimal reproducibility of MR quantification methods, and lack of uniformity in utilization of the multiple parameters for evaluation of MR severity. Assessment of MR severity is thus often subjective and variable. To minimize such imprecision, COAPT implemented a tiered algorithm for MR severity qualification based on multiple quantitative echocardiographic Doppler parameters based on the general principles espoused by the ASE and ACC.(15, 20) To our knowledge, COAPT is the first randomized trial of MR therapies which utilized such well-defined criteria requiring verification by an independent echocardiographic core laboratory. This algorithm assigned a hierarchical value to individual standard parameters, and its implementation resulted in a fairly homogeneous study population with 86% of patients qualifying by tier 1 (EROA $\geq$0.3 cm^2 or pulmonary vein systolic flow reversal). Moreover, the benefits of TMVR were consistent in patients qualifying as having

≥3+ SMR with any of the 3-tiered criteria. Coupled with the requirement for LVESD ≤7 cm and LVEF of 20-50%, use of this hierarchy provided that the COAPT population had a well-defined and consistent severity of SMR and LV dimensions and function. As a result, 24-month clinical outcomes were consistently favorable after TMVR compared with GDMT alone in all echocardiographic subgroups examined, regardless of baseline LVEF, LV volumes, RVSP, or MR or TR severity, testifying to the uniformity of the enrolled population.

The criteria to identify severe SMR in COAPT were more restrictive than that used in the MITRA-FR trial which required a single measure of EROA >0.2 cm^2 or RV >30 ml, adapted from ESC recommendations.(12,13,16) As a result of the different definitions for MR severity required, patients in COAPT had substantially more severe SMR than those in MITRA-FR (mean EROA 0.41 cm^2 vs. 0.31 cm^2 respectively). The severity of SMR in many patients enrolled in MITRA-FR may not have been severe enough to clinically benefit from TMVR. In this regard, baseline EROA in COAPT was an independent predictor of the 2-year risk of death or HF hospitalization in the control group but not after TMVR. Also, of note, COAPT capped the upper LV dimension that was acceptable to treat (LVESD ≤7 cm), while there was no such limit in MITRA-FR. As a result, the mean indexed LVEDV was substantially larger in MITRA-FR than COAPT (135±35 vs. 101±34 mL/m^2). It is thus likely that the prognosis of MITRA-FR patients was dictated relatively more by their LV dysfunction than MR severity, in contrast to patients enrolled in COAPT, as proposed by Grayburn and Packer.(25) Thus, adoption of the COAPT criteria by heart teams and their recommendation by societal guidelines to select patients with severe SMR for TMVR should increase the likelihood that high-risk HF patients will be identified and benefit from MR reduction, while avoiding treatment in patients whose prognosis is dictated more by advanced LV dysfunction.

MR improvement after TMVR was sustained throughout 24 months, attributable to the fact that TMVR directly addresses the principal structural abnormality in SMR, that is lack of leaflet coaptation. Notably, a modest proportion of control group patients experienced improvement of MR by 1 grade over time, possibly reflecting the dynamic nature of SMR, modifications in medical therapy, or regression to the mean. Ongoing studies from COAPT are examining the impact of achieving ≤1+ vs. 2+ vs. ≥3+ MR whether by device treatment or control.

The LVs in both groups further dilated during follow-up, reflecting the natural history of the underlying cardiomyopathy. Such remodeling, however, was worse in the control group, suggesting that MR-mediated volume overload reduction with TMVR slowed the progression of the underlying disease process. Of note, the LVEF decreased more within 1 month after TMVR compared with in the control group, consistent with the early effects of increased afterload after MR reduction. Nonetheless, patients' symptomatic status and functional class markedly improved after TMVR at all follow-up intervals, including at 30 days (11), likely due to the immediate reduction in left atrial pressure with TMVR. Moreover, at 12 months and beyond the reduction in LVEF was less pronounced in the TMVR group than with GDMT only, reflecting long-term benefits on LV remodeling. Of note, it was during this period (≥12 months) that the survival advantage with TMVR emerged. Nonetheless, while these findings are intriguing, interpretations of the absolute and relative temporal changes in LV volumes and LVEF within and between the groups must be tempered by the risk of survivorship bias. Within 2 years 46% and 29% of patients in the control and device groups respectively died, and it is likely that LV remodeling and progressive LV dysfunction were worse in patients in whom follow-up echocardiographic measures were not available either due to death or disability. To attempt to

account for this bias we utilized a two-stage imputation method that was pre-specified in the statistical analysis plan to account for missing data. There is no perfect method, however, to adjust for this degree of missing data, and these results should thus be considered hypothesis generating. The different imputation methods used in the present versus prior HF studies may also explain differences in observed LV remodeling patterns.(26–28)

Limitations. First, inconsistencies between 2D-derived LV volumes and total stroke volume (SV), and Doppler-derived forward SV and RV and PISA-derived MR severity have been noted.(29) Such observations reflect the use of different echocardiographic techniques to assess these different measures and inherent limitations of echocardiography in grading MR severity and other parameters of interest. Specifically, although PISA is the most widely used and reproducible method to grade MR severity, it assumes a single jet, a round flat orifice and constant flow throughout systole, conditions that are often not present with SMR. LV volumes, total SV and LVEF are most commonly measured by Simpson's method, which under-estimates LV volumes, especially with dilated ventricles.(22) Forward stroke volume is measured by continuous wave Doppler at the LV outflow tract. These three measurement techniques are not inter-changeable, and accurate direct measures of RV and RF were available in a minority of cases. Thus, assuming that total SV from Simpson's method equals the sum of the forward SV from Doppler hemodynamics plus an assumed RV from PISA-derived MR severity is erroneous. For these reasons each reported value should be considered on its own merits, and efforts to reconcile differences between the different methods should be avoided. Second, evaluating MR severity after TMVR is challenging. Multiple regurgitant orifices are present, further complicated by jet eccentricity. Simply adding measurements for each individual jet is not accurate. The parameters that are most reliable after TMVR include evaluation of color Doppler

jet area and direction, pulmonary vein flow and to a lesser extent the VC. The post- TMVR MR grading scale utilized in the COAPT trial was based on these parameters, as detailed in Supplemental Table 1B. Whether newer technologies such as 3D color Doppler offer advantages over those used in COAPT deserves further study. Further study is also required to validate the utility of post- TMVR MR severity as assessed herein or by recent consensus statements.(30) Third, the relationship between echocardiographic characteristics and outcomes has been analyzed in a relatively simplistic manner. The present report focused on subgroup analyses pre-specified at study inception, defined in most cases by the observed median measures (which avoids bias); further exploratory analyses will be carried out in specific subpopulations and to identify non-linear relationships. Finally, longer-term follow-up (currently planned for 5 years) is necessary to determine the durability and long-term impact of TMVR of SMR in HF.

Conclusions.

In the COAPT trial patients with HF and 3+ or 4+ SMR who remained symptomatic despite maximally tolerated GDMT benefitted from MitraClip implantation, regardless of their degree of LV dysfunction, LV dilatation, pulmonary hypertension, severity of TR or individual MR characteristics. Only higher baseline RVSP and STS score predicted the risk of death or HF hospitalization after TMVR. The improvement in MR severity was dramatic and durable through at least 24 months. Echocardiography is of critical importance in determining the etiology and severity of MR and LV dimensions and function to identify those patients most likely to benefit from percutaneous leaflet approximation, while avoiding treatment of patients less likely to benefit. Advanced echocardiographic expertise specific to this technology and population is imperative to ensure that the results of COAPT (and MITRA-FR) are translated to “real-world”

clinical practice to provide clinical benefit to a population that is at extremely high-risk of death and HF hospitalization.

Perspectives

Medical Knowledge and Patient Care: Identification of appropriate patients with HF and SMR who may benefit from MR reduction is challenging due to the lack of uniform definitions and the conflicting results of COAPT and MITRA-FR. The multiparametric echocardiographic algorithm used in COAPT to grade MR severity during the screening process should be adopted in clinical practice as it has been proven to identify patients that obtain substantial clinical benefit from transcatheter mitral valve replacement (TMVR). In the COAPT trial, all echocardiography-based subgroups analyzed had lower rates of death or HF hospitalization after TMVR compared with GDMT alone. No groups of "non-responders" were identified. Thus, all symptomatic HF patients with 3+ or 4+ SMR meeting COAPT criteria should be considered for TMVR, as the clinical benefits were profound in eligible patients.

Translational Outlook: Further study is required to understand the varying results from the COAPT and MITRA-FR trials. While differences in MR severity and LV dilatation in the patients enrolled in the two studies may underlie this discordance, further insights may be gleaned by an individual patient data pooled analysis of the two databases, complemented by analysis of all echocardiograms at the same central core laboratory.

References

1. Agricola E, Ielasi A, Oppizzi M et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. Eur J Heart Fail. 2009;11:581–87.
2. Nasser R, Van Assche L, Vorlat A et al. Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed Heart Failure Patients With Reduced Ejection Fraction. JACC Heart Fail. 2017;5:652–59.
3. 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.
4. Sannino A, Smith RL, Schiattarella GG, Trimarco B, Esposito G, Grayburn PA. Survival and Cardiovascular Outcomes of Patients With Secondary Mitral Regurgitation: A Systematic Review and Meta-analysis. JAMA Cardiol. 2017;2:1130–39.
5. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–49.
6. Di Biase L, Auricchio A, Mohanty P et al. Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. Europace. 2011;13:829–38.
7. van Bommel RJ, Marsan NA, Delgado V et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. Circulation. 2011;124:912–19.
8. Goldstein D, Moskowitz AJ, Gelijns AC et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med. 2016;374:344–53.

9. Michler RE, Smith PK, Parides MK et al. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. N Engl J Med. 2016;374:1932–41.
10. Smith PK, Puskas JD, Ascheim DD et al. Surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med. 2014;371:2178–88.
11. Stone GW, Lindenfeld J, Abraham WT et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018;379:2307–18.
12. Obadia JF, Messika-Zeitoun D, Leurent G et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018;379:2297–306.
13. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–91.
14. Nishimura RA, Otto CM, Bonow RO et al. 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 Practice Guidelines. J Am Coll Cardiol. 2014;63:e57–185.
15. 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. J Am Coll Cardiol. 2017;70:252–89.
16. 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 J Cardiothorac Surg. 2012;42:S1–44.

17. Mack MJ, Abraham WT, Lindenfeld J et al. Cardiovascular Outcomes Assessment of the MitraClip in Patients with Heart Failure and Secondary Mitral Regurgitation: Design and rationale of the COAPT trial. Am Heart J. 2018;205:1–11.

18. Grayburn PA, Weissman NJ, Zamorano JL. Quantitation of mitral regurgitation. Circulation. 2012;126:2005–17.

19. Zoghbi WA, Enriquez-Sarano M, Foster E et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16:777–802.

20. 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;30:303–71.

21. Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–63.

22. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;59:1799–808.

23. Mozaffarian D, Benjamin EJ, Go AS et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133:e38–360.

24. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003;91:538–43.

25. 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. 2018

26. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. J Am Coll Cardiol. 1997;29:1060–66.

27. St John Sutton MG, Plappert T, Abraham WT et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107:1985–90.

28. Wong M, Staszewsky L, Latini R et al. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure trial (Val-HeFT) echocardiographic data. J Am Coll Cardiol. 2004;43:2022–27.

29. Hagendorff A, Doenst T, Falk V. Echocardiographic assessment of functional mitral regurgitation: opening Pandora's box? ESC Heart Fail. 2019;6:678-685.

30. Zoghbi WA, Asch FM, Bruce C et al. Guidelines for the Evaluation of Valvular Regurgitation After Percutaneous Valve Repair or Replacement: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2019;32:431–75.

Figure Legends

Figure 1. Subgroup analysis of baseline echocardiographic parameters as predictors of time to death or first heart failure hospitalization through 24 months of follow-up. Values in the TMVR plus GDMT and GDMT alone columns are Kaplan-Meier estimated % (n) of cases reaching the endpoint at 24 months. Abbreviations as in the **Central Illustration**.

Figure 2. LV remodeling and systolic function during 24-month follow-up. Paired analysis of LV volumes and LVEF by echocardiography from baseline to 1, 6, 12, 18 and 24 months of follow-up. Subjects without an available follow-up echo image who had an adjudicated heart failure death prior to that visit were assigned the worst change from baseline to that visit. For all other subjects who had missing echo values due to other reasons (e.g. death not due to heart failure, withdrawals, missing echoes, etc.), multiple imputation with Markov Chain Monte Carlo was used. Analysis of covariance was performed for paired analysis of change over time adjusted for baseline values. Abbreviations as in the **Central Illustration**.

Central Illustration. Echocardiographic inclusion flowchart. This multiparametric screening algorithm was used by the COAPT trial echocardiography core laboratory to determine if baseline MR severity was 3+ or higher for qualification purposes. The 3 tiers of evaluation were applied in a hierarchical manner (from tier 1 to 3); patients qualified for COAPT by meeting criteria of at least one of them. MR severity was subsequently graded as 3+ vs. 4+ based on the integrative evaluation of multiple parameters recommended by the ASE guidelines (as listed in Table 2). HF= heart failure; MR= mitral regurgitation; DMR= degenerative mitral regurgitation; GDMT= guideline directed medical therapies; TTE= transthoracic echocardiography; EROA= effective regurgitant orifice area; PV= pulmonary vein; RV= regurgitant volume; RF=

regurgitant fraction; VC= vena contracta; PISA= proximal isovelocity surface area; CW= continuous wave Doppler; LA= left atrium.

Table 1. Baseline echocardiographic characteristics

Echo parameter	Device Group (N=302)	Control Group (N=312)	P-value
LVEF, %	31.3 ± 9.1 (281)	31.3 ± 9.6 (295)	0.96
LVEDV, ml	194.4 ± 69.2 (281)	191.4 ± 73.0 (295)	0.61
LVESV, ml	135.5 ± 56.1 (281)	134.6 ± 60.4 (295)	0.85
LVEDD, cm	6.17 ± 0.73 (301)	6.19 ± 0.75 (308)	0.77
LVESD, cm	5.28 ± 0.86 (301)	5.30 ± 0.88 (307)	0.81
LA volume, ml	91.7 ± 36.3 (292)	91.0 ± 44.8 (303)	0.84
MR severity, n (%)			0.13
Moderate to severe (3+)	49.0% (148/302)	55.1% (172/312)	
Severe (4+)	51.0% (154/302)	44.9% (140/312)	
PISA radius, cm	0.89 ± 0.17 (293)	0.88 ± 0.18 (308)	0.62
EROA, PISA, cm^2	0.41 ± 0.15 (289)	0.40 ± 0.15 (303)	0.41
Vena contracta, cm	0.58 ± 0.12 (277)	0.58 ± 0.12 (293)	0.88
Peak E, cm/sec	110.6 ± 28.7 (280)	109.4 ± 24.9 (286)	0.60
Pulmonary vein flow			0.02
None (0)	0.0% (0/240)	0.0% (0/234)	
Mild (1+)	0.4% (1/240)	0.9% (2/234)	
Moderate (2+)	12.9% (31/240)	12.4% (29/234)	
Moderate to severe (3+)	30.0% (72/240)	42.7% (100/234)	
Severe (4+)	56.7% (136/240)	44.0% (103/234)	
MR color flow jet			0.18

None (0)	0.0% (0/302)	0.0% (0/312)	
Mild (1+)	0.0% (0/302)	0.0% (0/312)	
Moderate (2+)	6.0% (18/302)	6.7% (21/312)	
Moderate to severe (3+)	43.0% (130/302)	47.8% (149/312)	
Severe (4+)	51.0% (154/302)	45.5% (142/312)	
TR severity, n (%)			0.16
None (0)	2.7% (8/299)	1.3% (4/300)	
Mild (1+)	82.6% (247/299)	80.7% (242/300)	
Moderate (2+)	14.0% (42/299)	16.7% (50/300)	
Moderate to severe (3+)	0.7% (2/299)	1.0% (3/300)	
Severe (4+)	0.0% (0/299)	0.3% (1/300)	
RVSP mmHg	44.0 ± 13.4 (253)	44.6 ± 14.0 (275)	0.60

LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; LVEDD= left ventricular end diastolic diameter; LVESD= left ventricular end systolic diameter; LA= left atrial; MR= mitral regurgitation; PISA= proximal isovelocity surface area; EROA= effective regurgitant orifice area; PV= pulmonary vein; TR= tricuspid regurgitation; RVSP= right ventricular systolic pressure.

Table 2. Predictors of 24-month all-cause mortality or heart failure hospitalization by multivariable cox regression

	Hazard Ratio [95% CI]	**P-Value**
GDMT-treated patients		
RVSP (per mmHg)	**1.01 [1.00, 1.02]**	**0.03**
STS replacement score (per point)	1.07 [0.98, 1.18]	0.14
LVEDV (per mL)	1.00 [1.00, 1.00]	0.84
Sex (female vs male)	0.97 [0.64, 1.46]	0.87
EROA, PISA (per cm^2)	**3.15 [1.08, 9.21]**	**0.04**
Etiology of cardiomyopathy (ischemic vs non-ischemic)	0.92 [0.62, 1.36]	0.66
STS repair score (per point)	0.96 [0.87, 1.07]	0.47
LVEF (per %)	**0.98 [0.96, 1.00]**	**0.03**
Age (per year)	0.99 [0.97, 1.01]	0.24
Tricuspid regurgitation grade (≥2+ vs ≤1+)	**1.60 [1.07, 2.39]**	**0.02**
TMVR-Treated Patients		
RVSP (per mmHg)	**1.02 [1.01, 1.04]**	**0.005**
STS replacement score (per point)	**1.12 [1.02, 1.23]**	**0.02**
LVEDV (per mL)	1.00 [1.00, 1.01]	0.07

Sex (female vs male)	0.64 [0.37, 1.08]	0.09
EROA, PISA (per cm^2)	2.56 [0.79, 8.26]	0.12
Etiology of cardiomyopathy (ischemic vs non-ischemic)	0.70 [0.43, 1.13]	0.15
STS repair score (per point)	0.95 [0.88, 1.04]	0.26
LVEF (per %)	1.01 [0.98, 1.03]	0.56
Age (per year)	1.01 [0.98, 1.03]	0.57
Tricuspid regurgitation grade (≥2+ vs ≤1+)	0.90 [0.51, 1.61]	0.73

RVSP= right ventricular systolic pressure; STS= Society of Thoracic Surgeons; EROA= effective regurgitant orifice area; PISA= proximal isovelocity surface area; LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; GDMT= Guideline-directed medical therapy.

Table 3. Adjusted changes in echocardiographic parameters from baseline to 12 months

Echo Parameter	Device Group (12 months minus baseline)	Control Group (12 months minus baseline)	Difference (Device - Control)	p-value
LVEF (%)	-5.6 ± 1.2 (281)	-8.8 ± 1.1 (295)	3.2 ± 1.6	0.048
LVEDV (ml)	-5.1 ± 4.5 (281)	4.8 ± 4.8 (295)	-9.8 ± 6.8	0.16
LVESV (ml)	6.5 ± 3.9 (281)	12.8 ± 4.2 (295)	-6.3 ± 5.8	0.29
LVEDD (cm)	0.04 ± 0.06 (301)	0.24 ± 0.08 (308)	-0.21 ± 0.11	0.07
LVESD (cm)	0.15 ± 0.08 (301)	0.43 ± 0.08 (307)	-0.28 ± 0.11	0.02
LA volume (ml)	9.7 ± 2.4 (292)	12.6 ± 2.5 (303)	-2.9 ± 3.4	0.40
Vena contracta (cm)	-0.09 ± 0.02 (277)	0.03 ± 0.02 (293)	-0.12 ± 0.02	<0.001
Peak E (cm/sec)	27.85 ± 2.92 (280)	4.34 ± 2.92 (286)	23.50 ± 4.12	<0.001
RVSP (mmHg)	-1.2 ± 1.2 (253)	1.7 ± 1.43 (275)	-2.9 ± 1.94	0.14

Data are expressed as least square mean ± standard error, adjusted for the baseline value. Unadjusted baseline values for LVEDV, LVESV and LVEF are shown in Supplementary Table 5. Subjects without an available follow-up echo image who had an adjudicated heart failure death prior to that visit were assigned the worst change from baseline to that visit. For all other subjects who had missing echo values due to other reasons (e.g. death not due to heart failure, withdrawals, missing echoes etc.), multiple imputation with Markov Chain Monte Carlo was used. Analysis of covariance (ANCOVA) was performed for paired analysis of changes overtime adjusted for baseline values. P-value calculated from analysis of covariance (ANCOVA);

LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; LVEDD= left ventricular end diastolic diameter; LVESD= left ventricular end systolic diameter; LA= left atrial; RVSP= right ventricular systolic pressure.

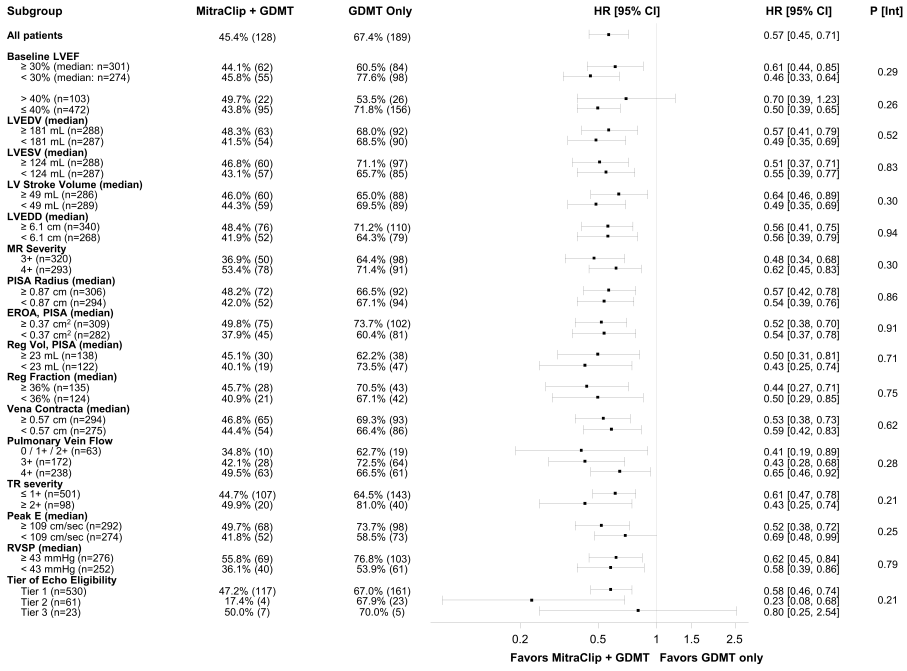
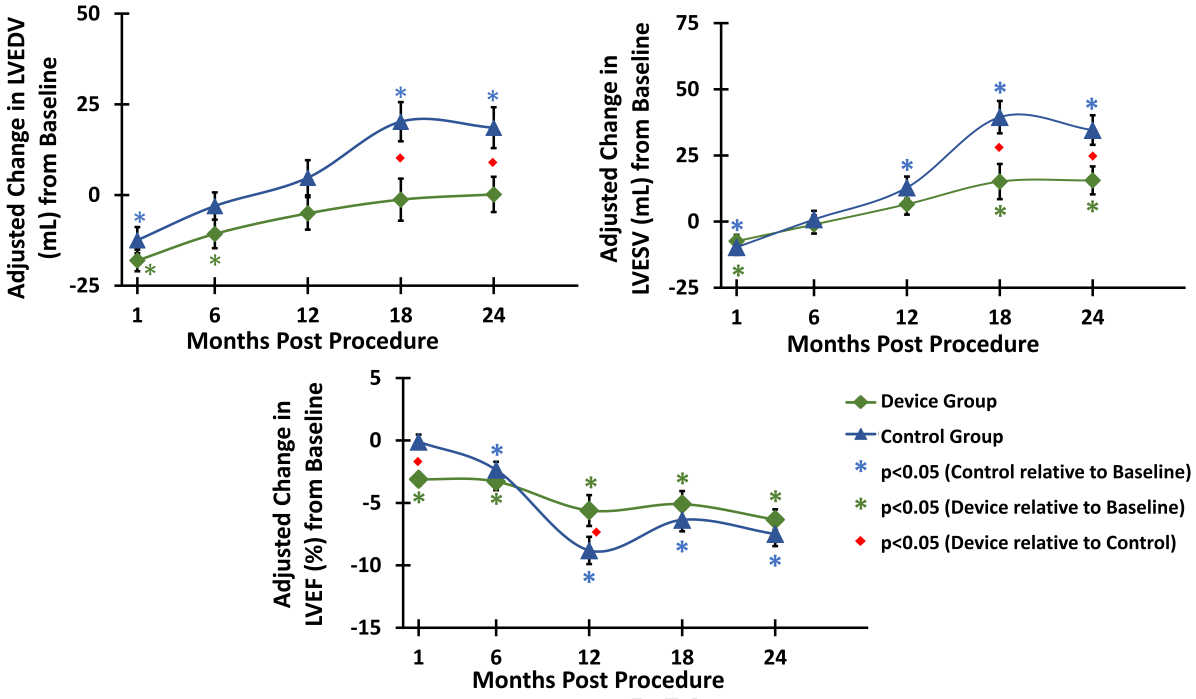
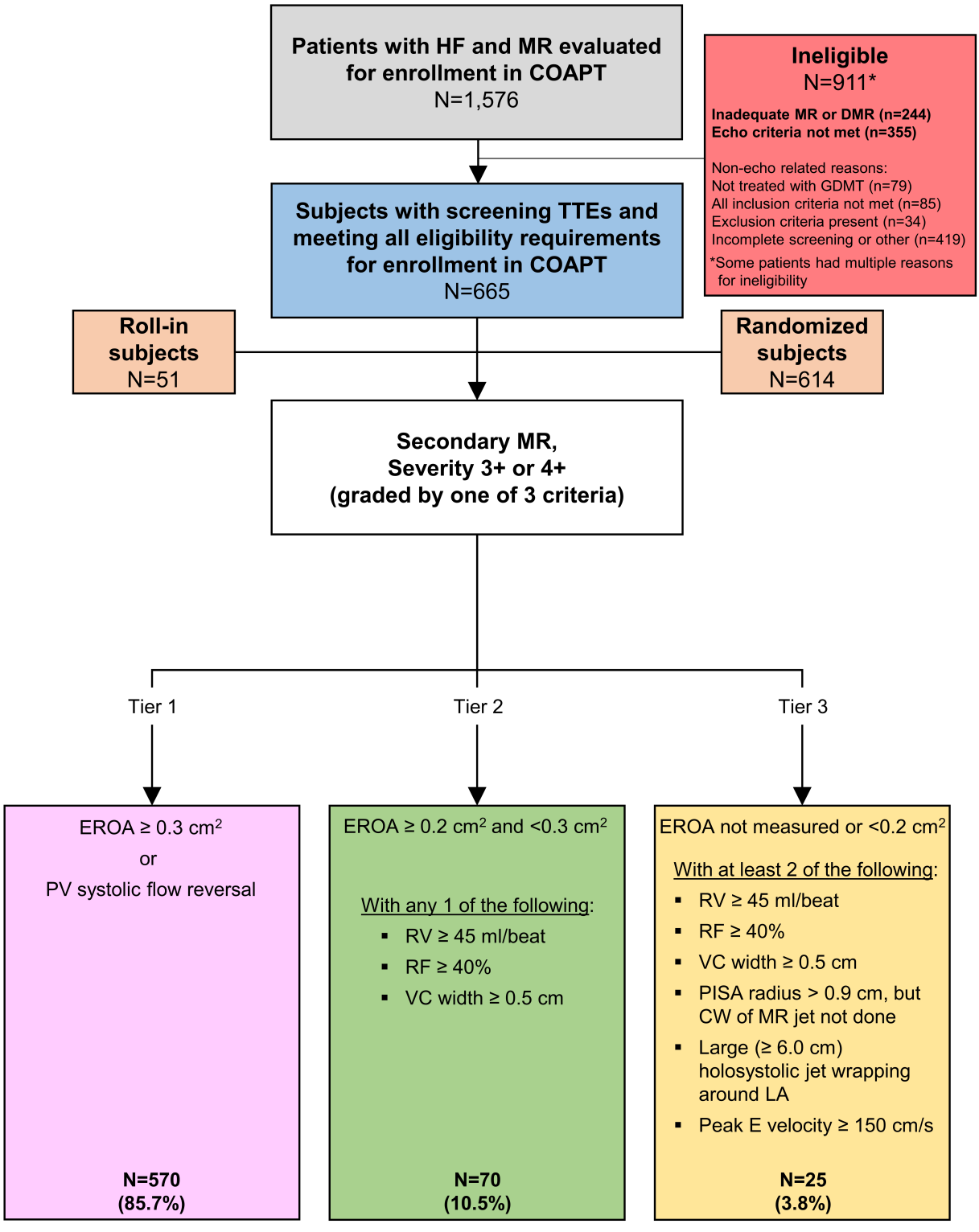


Figure 2. Subgroup analysis of baseline echocardiographic parameters as predictors of time to death or first HF hospitalization through 24 months of follow-up




Patients with HF and MR evaluated for enrollment in COAPT
N=1,576
Ineligible
N=911*
Inadequate MR or DMR (n=244)
Echo criteria not met (n=355)
Non-echo related reasons:
Not treated with GDMT (n=79)
All inclusion criteria not met (n=85)
Exclusion criteria present (n=34)
Incomplete screening or other (n=419)
*Some patients had multiple reasons for ineligibility
Subjects with screening TTEs and meeting all eligibility requirements for enrollment in COAPT
N=665
Roll-in subjects
N=51
Randomized subjects
N=614
Secondary MR,
Severity 3+ or 4+
(graded by one of 3 criteria)
Tier 1
Tier 2
Tier 3
EROA ≥ 0.3 cm2
or
PV systolic flow reversal
N=570
(85.7%)
EROA ≥ 0.2 cm2 and <0.3 cm2
With any 1 of the following:
RV ≥ 45 ml/beat
RF ≥ 40%
VC width ≥ 0.5 cm
N=70
(10.5%)
EROA not measured or <0.2 cm2
With at least 2 of the following:
RV ≥ 45 ml/beat
RF ≥ 40%
VC width ≥ 0.5 cm
PISA radius > 0.9 cm, but CW of MR jet not done
Large (≥ 6.0 cm) holosystolic jet wrapping around LA
Peak E velocity ≥ 150 cm/s
N=25
(3.8%)

MitraClip Implantation in Patients with Heart Failure and Secondary Mitral Regurgitation: Echocardiographic Outcomes from the COAPT Trial

Authors: Federico M. Asch, Paul A. Grayburn, Robert J. Siegel, Saibal Kar, D. Scott Lim, Jonathan G. Zaroff, Jacob M. Mishell, Brian Whisenant, Michael J. Mack, JoAnn Lindenfeld, William T. Abraham, Gregg W. Stone and Neil J. Weissman, on behalf of the COAPT Investigators

Supplemental material

Supplemental Table 1: COAPT criteria for grading mitral regurgitation severity. Hierarchical algorithm for study screening and criteria used at all study timepoints.

1. **Mitral regurgitation severity inclusion criteria for COAPT trial**

Inclusion: MR severity was assessed as ≥3+ by the echocardiographic core laboratory if any of the following 3 sets of criteria (tiers) were met:		
Tier 1	**Tier 2**	**Tier 3**
EROA ≥0.3 cm^2 or PV systolic flow reversal	EROA ≥0.2 cm^2 and <0.3 cm^2 With any 1 of the following: ▪ RV ≥45 ml/beat ▪ RF ≥40% ▪ VC width ≥ 0.5 cm	EROA not measured or <0.2 cm^2 With at least 2 of the following: ▪ RV ≥ 45 ml/beat ▪ RF ≥ 40% ▪ VC width ≥ 0.5 cm ▪ PISA radius > 0.9 cm, but CW of MR jet not done ▪ Large (≥ 6.0 cm) holosystolic jet wrapping around LA ▪ Peak E velocity ≥ 150 cm/s

This multiparametric algorithm, adapted from the criteria recommended by the American Society of Echocardiography 2003 Guidelines, [17, 18] was used for qualification purposes to determine if MR was 3+ or higher. The 3 tiers of evaluation were applied in a hierarchical manner and patients qualified for COAPT by meeting the criteria of at least one of them. For MR grading purposes, MR severity was subsequently graded as 3+ or 4+ based on the integrative evaluation of multiple parameters recommended by the ASE guidelines (parameters are listed in Table 1).

2. **Criteria for MR grading post MitraClip.**

	Color Doppler area size	**PV flow**	**Vena Contracta**
1+, Mild	Central and small, (<4 cm^2 or <10% of the LA area)	Systolic dominant	<0.5 cm
2+, Moderate	Central and moderate (4-6 cm^2 or 10-30% of the LA area)	Diastolic dominant	
3+, Moderate to Severe	Central, large (6-8 cm^2 or 30-40% of the LA area) or excentric reaching 1 PV.	All diastolic (systolic blunting)	≥0.5 cm
4+, Severe	Excentric, large (≥8 cm^2 or ≥40% of the LA area), or eccentric reaching the second PV	Systolic flow reversal	

Note: While post MitraClip regurgitant volume and fraction by volumetric analysis were performed, they were unevaluable in more than 50% of cases (irrespective of the MR severity) and are therefore not

reliable or reported. Vena contracta was available in most cases with significant MR (3+ or 4+) but not in those with less severity. If more than one regurgitant jet was identified at follow-up, the vena contracta width of the dominant jet was measured or the vena contracta widths of multiple jets were added if more than one was considered significant. MR= mitral regurgitation; EROA= effective regurgitant area; PV= pulmonary vein; RV= regurgitant volume; RF= regurgitant fraction; VC= vena contracta; LA= left atrial.

Supplemental Table 2. Baseline echocardiographic characteristics according to screening tiers used for qualification of mitral regurgitation as 3+ or higher.

Echo parameter	Tier 1	Tier 2	Tier 3
LVEF, %	31.38 ± 9.26 (500)	31.1 ± 10.2 (56)	30.0 ± 8.3 (20)
LVEDV, ml	195.4 ± 70.7 (500)	179.1 ± 78.6 (56)	168.7 ± 50.6 (20)
LVESV, ml	136.4 ± 57.7 (500)	127.9 ± 66.7 (56)	119.2 ± 43.9 (20)
LVEDD, cm	6.21 ± 0.75 (525)	5.99 ± 0.69 (61)	5.97 ± 0.57 (23)
LVESD, cm	5.31 ± 0.88 (524)	5.13 ± 0.87 (61)	5.09 ± 0.68 (23)
LA volume, ml	93.25 ± 42.19 (515)	80.1 ± 29.2 (59)	76.68 ± 24.80 (21)
MR severity, n (%)			
Moderate to severe (3+)	46.0% (244/530)	95.1% (58/61)	78.3% (18/23)
Severe (4+)	54.0% (286/530)	4.9% (3/61)	21.7% (5/23)
PISA radius, cm	0.91 ± 0.17 (528)	0.75 ± 0.08 (61)	0.74 ± 0.27 (12)
EROA, PISA, cm^2	0.43 ± 0.15 (524)	0.26 ± 0.03 (61)	0.15 ± 0.03 (7)
Vena contracta, cm	0.59 ± 0.12 (489)	0.57 ± 0.10 (59)	0.54 ± 0.12 (22)
Peak E, cm/sec	111.41 ± 27.14 (488)	99.98 ± 22.60 (56)	103.93 ± 24.43 (22)
Pulmonary vein flow			
None (0)	0.0% (0/416)	0.0% (0/46)	0.0% (0/12)
Mild (1+)	0.0% (0/416)	6.5% (3/46)	0.0% (0/12)
Moderate (2+)	10.1% (42/416)	37.0% (17/46)	8.3% (1/12)
Moderate to severe (3+)	32.5% (135/416)	56.5% (26/46)	91.7% (11/12)
Severe (4+)	57.5% (239/416)	0.0% (0/46)	0.0% (0/12)
MR color flow jet			
None (0)	0.0% (0/530)	0.0% (0/61)	0.0% (0/23)
Mild (1+)	0.0% (0/530)	0.0% (0/61)	0.0% (0/23)
Moderate (2+)	5.8% (31/530)	11.5% (7/61)	4.3% (1/23)
Moderate to severe (3+)	40.8% (216/530)	80.3% (49/61)	60.9% (14/23)
Severe (4+)	53.4% (283/530)	8.2% (5/61)	34.8% (8/23)
TR severity, n (%)			
None (0)	1.7% (9/519)	5.1% (3/59)	0.0% (0/21)
Mild (1+)	80.5% (418/519)	88.1% (52/59)	90.5% (19/21)
Moderate (2+)	16.6% (86/519)	6.8% (4/59)	9.5% (2/21)
Moderate to severe (3+)	1.0% (5/519)	0.0% (0/59)	0.0% (0/21)
Severe (4+)	0.2% (1/519)	0.0% (0/59)	0.0% (0/21)
RVSP mmHg	44.83 ± 13.79 (457)	39.93 ± 11.61 (51)	42.47 ± 15.06 (20)

LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; LVEDD= left ventricular end diastolic diameter; LVESD= left ventricular end systolic diameter; LA= left atrial; MR= mitral regurgitation; PISA= proximal isovelocity surface area; EROA= effective regurgitant orifice area; PV= pulmonary vein; TR= tricuspid regurgitation; RVSP= right ventricular systolic pressure.

Supplemental Table 3. Subgroup analysis of baseline echocardiographic parameters as predictors of time to death or first HF hospitalization through 12 months of follow-up

	MitraClip + GDMT Event Rate	GDMT only Event Rate	HR [95% CI]	P-value for interaction
All patients	33.5% (100)	46.2% (142)	0.63 [0.49, 0.82]	
Baseline LVEF				
≥ 30% (median: n=301)	30.9% (46)	44.3% (66)	0.60 [0.41, 0.88]	0.81
< 30% (median: n=274)	33.5% (43)	49.8% (70)	0.56 [0.38, 0.82]	
> 40% (n=103)	24.1% (12)	42.8% (22)	0.49 [0.24, 0.98]	0.62
≤ 40% (n=472)	33.9% (77)	47.9% (114)	0.60 [0.45, 0.80]	
LVEDV (median)				
≥ 181 mL (n=288)	33.8% (47)	46.7% (68)	0.62 [0.43, 0.90]	0.58
< 181 mL (n=287)	30.4% (42)	47.2% (68)	0.54 [0.36, 0.79]	
LVESV (median)				
≥ 124 mL (n=288)	33.0% (45)	48.8% (72)	0.56 [0.39, 0.81]	0.83
< 124 mL (n=287)	31.2% (44)	45.1% (64)	0.60 [0.41, 0.88]	
LV Stroke Volume (median)				
≥ 49 mL (n=286)	37.5% (51)	43.0% (63)	0.80 [0.55, 1.16]	0.09
< 49 mL (n=289)	30.7% (44)	50.5% (71)	0.50 [0.34, 0.73]	
LVEDD (median)				
≥ 6.1 cm (n=340)	36.1% (60)	48.9% (83)	0.62 [0.44, 0.86]	0.93
< 6.1 cm (n=268)	30.4% (40)	44.5% (59)	0.62 [0.41, 0.92]	
MR Severity				
3+ (n=320)	26.0% (38)	40.7% (69)	0.56 [0.38, 0.84]	0.53
4+ (n=293)	40.7% (62)	53.5% (73)	0.65 [0.46, 0.91]	
PISA Radius (median)				
≥ 0.87 cm (n=306)	36.3% (56)	52.0% (77)	0.57 [0.40, 0.80]	0.68
< 0.87 cm (n=294)	29.6% (40)	41.6% (64)	0.65 [0.44, 0.96]	
EROA, PISA (median)				
≥ 0.37 cm^2 (n=309)	36.7% (57)	53.7% (80)	0.55 [0.39, 0.78]	0.79
< 0.37 cm^2 (n=282)	26.9% (35)	39.9% (59)	0.61 [0.40, 0.92]	
Regurgitant Volume, PISA (median)				
≥ 23 mL (n=138)	26.4% (19)	51.5% (33)	0.40 [0.22, 0.70]	0.49
< 23 mL (n=122)	28.4% (14)	47.3% (33)	0.54 [0.29, 1.02]	
Regurgitant Fraction (median)				
≥ 36% (n=135)	26.8% (18)	53.1% (35)	0.39 [0.22, 0.69]	0.41
< 36% (n=124)	28.2% (15)	45.7% (31)	0.56 [0.30, 1.04]	
Vena Contracta (median)				
≥ 0.57 cm (n=294)	34.3% (50)	51.3% (74)	0.57 [0.40, 0.81]	0.46
< 0.57 cm (n=275)	34.3% (44)	43.4% (62)	0.69 [0.47, 1.02]	
PV Flow				
0 / 1+ / 2+ (n=63)	25.0% (8)	51.6% (16)	0.40 [0.17, 0.93]	0.19
3+ (n=172)	28.1% (20)	50.2% (49)	0.45 [0.27, 0.76]	
4+ (n=238)	37.5% (50)	44.7% (45)	0.75 [0.50, 1.12]	
TR severity				
≤ 1+ (n=501)	32.7% (83)	44.1% (107)	0.66 [0.50, 0.88]	0.41
≥ 2+ (n=98)	38.3% (16)	59.4% (31)	0.52 [0.28, 0.95]	
Peak E (median)				
≥ 109 cm/sec (n=292)	36.1% (52)	52.9% (75)	0.55 [0.38, 0.78]	0.09
< 109 cm/sec (n=274)	32.6% (43)	36.3% (51)	0.87 [0.58, 1.31]	
RVSP (median)				
≥ 43 mmHg (n=276)	44.4% (56)	51.3% (75)	0.75 [0.53, 1.06]	0.42
< 43 mmHg (n=252)	24.3% (30)	37.1% (46)	0.60 [0.38, 0.95]	
Tier of Echo Eligibility				
Tier 1 (n=530)	34.6% (90)	47.7% (125)	0.62 [0.47, 0.81]	0.36
Tier 2 (n=61)	17.4% (4)	40.4% (15)	0.40 [0.13, 1.20]	
Tier 3 (n=23)	40.0% (6)	25.0% (2)	1.63 [0.33, 8.11]	

Event rates are expressed as Kaplan-Meier estimates with the number of events occurring within 12 months. GDMT= guideline-directed medical therapy; LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; LV= left ventricular; LVEDD= left ventricular end diastolic diameter; MR= mitral regurgitation;

PISA= proximal isovelocity surface area; EROA= effective regurgitant orifice area; PV= pulmonary vein; TR= tricuspid regurgitation; RVSP= right ventricular systolic pressure.

Supplemental Table 4. Predictors of 24-month All-Cause Mortality by Multivariable Cox Regression.

A. MitraClip-Treated Patients

	Hazard Ratio [95% CI]	P-Value
RVSP (mmHg)	1.03 [1.01, 1.05]	0.004
Sex (Female vs Male)	0.40 [0.19, 0.85]	0.016
STS Replacement Score	1.20 [1.03, 1.40]	0.020
Etiology of Cardiomyopathy (Ischemic vs Non-Ischemic)	0.62 [0.34, 1.15]	0.13
STS Repair Score	0.91 [0.79, 1.06]	0.23
EROA, PISA (cm^2)	1.89 [0.41, 8.78]	0.42
LVEF (%)	1.01 [0.98, 1.04]	0.42
LVEDV (mL)	1.00 [1.00, 1.01]	0.69
Age (years)	1.00 [0.97, 1.04]	0.83
Tricuspid Regurgitation Grade (≥ 2+ vs ≤ 1+)	0.94 [0.47, 1.88]	0.87

B. GDMT-Treated Patients

	Hazard Ratio [95% CI]	P-Value
RVSP (mmHg)	1.02 [1.01, 1.03]	0.005
EROA, PISA (cm^2)	5.28 [1.43, 19.50]	0.012
STS Replacement Score	1.12 [1.00, 1.26]	0.053
Tricuspid Regurgitation Grade (≥ 2+ vs ≤ 1+)	1.55 [0.96, 2.52]	0.08
LVEF (%)	0.98 [0.96, 1.01]	0.13
Age (years)	1.01 [0.99, 1.04]	0.27
LVEDV (mL)	1.00 [1.00, 1.01]	0.31
Etiology of Cardiomyopathy (Ischemic vs Non-Ischemic)	0.77 [0.46, 1.30]	0.33
Sex (Female vs Male)	0.79 [0.45, 1.37]	0.39
STS Repair Score	0.96 [0.85, 1.10]	0.57

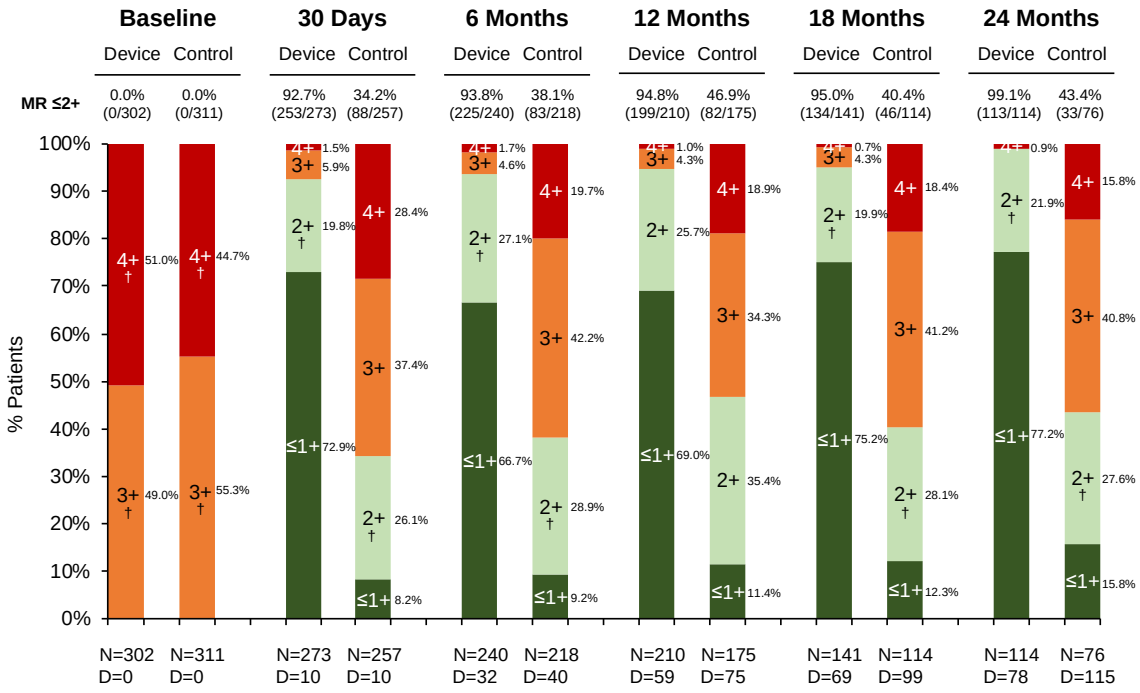
RVSP= right ventricular systolic pressure; STS= Society of Thoracic Surgeons; EROA= effective regurgitant orifice area; PISA= proximal isovelocity surface area; LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; GDMT= Guideline-directed medical therapies.

Supplemental Table 5. Mean LVEF and volumes at baseline and during follow-up.

Echo parameter	Timepoint	Device Group (N=281)	Control Group (N=295)	P-value
LVEDV, ml	Baseline	194.4 ± 4.1	191.4 ± 4.3	0.61
	30 days	175.9 ± 4.0	179.4 ± 4.7	0.59
	6 months	183.1 ± 4.5	188.8 ± 5.0	0.41
	12 months	188.9 ± 5.0	196.6 ± 6.0	0.34
	18 months	192.6 ± 5.9	212.0 ± 6.6	0.03
	24 months	194.1 ± 5.2	210.4 ± 6.8	0.06
LVESV, ml	Baseline	135.5 ± 3.3	134.6 ± 3.5	0.85
	30 days	127.9 ± 3.3	125.0 ± 3.9	0.59
	6 months	134.2 ± 4.1	135.5 ± 4.3	0.84
	12 months	141.9 ± 4.4	147.5 ± 5.2	0.42
	18 months	150.5 ± 6.3	174.1 ± 7.4	0.02
	24 months	150.9 ± 5.3	169.2 ± 6.7	0.03
LVEF, %	Baseline	31.3 ± 0.5	31.3 ± 0.6	0.96
	30 days	28.2 ± 0.6	31.2 ± 0.7	0.005
	6 months	28.0 ± 0.8	28.9 ± 0.8	0.45
	12 months	25.7 ± 1.2	22.5 ± 1.3	0.06
	18 months	26.2 ± 1.0	24.9 ± 1.1	0.37
	24 months	25.0 ± 0.7	23.8 ± 1.1	0.39

Data are mean ± standard error. LVEF= left ventricular ejection fraction; LVEDV= left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume. Subjects without an available follow-up echo image who had an adjudicated heart failure death prior to that visit were assigned the worst change from baseline to that visit. For all other subjects who had missing echo values due to other reasons (e.g. death not due to heart failure, withdrawals, missing echoes etc.), multiple imputation with Markov Chain Monte Carlo was used.

Supplemental Figure 1: Overall MR severity at baseline and follow-up



†Denotes non-significant between-group differences for the same category of MR severity. All other between-group differences were statistically significant for corresponding categories of MR severity.
'N' denotes number of subjects with MR severity data available.
'D" denotes subject deaths which occurred by the upper end of the visit window, whether or not the TTE was performed.

MR = mitral regurgitation; N = number of patients with echocardiographic core lab measurement; D = deaths.