10.1161/CIRCINTERVENTIONS.123.013045

Transcatheter Mitral Valve Replacement versus Medical Therapy for Secondary Mitral Regurgitation: A Propensity Score-Matched Comparison

Running title: *Ludwig et al; TMVR versus GDMT for Secondary MR*

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AHA Journals Subject Terms: Valvular Heart Disease, Heart Failure

**This work was presented as late-breaking clinical data at EuroPCR, May 16-19, 2023

***This manuscript was sent to Charanjit Rihal, MD, MBA, Guest Editor, for review by expert referees, editorial decision, and final disposition.

ABSTRACT

Background: Transcatheter mitral valve replacement (TMVR) is an emerging therapeutic alternative for patients with secondary mitral regurgitation (MR). Outcomes of TMVR versus guideline-directed medical therapy (GDMT) have not been investigated for this population. This study aimed to compare clinical outcomes of patients with secondary MR undergoing TMVR versus GDMT alone.

Methods: The CHOICE-MI registry included patients with MR undergoing TMVR using dedicated devices. Patients with MR etiologies other than secondary MR were excluded. Patients treated with GDMT alone were derived from the control arm of the COAPT trial. We compared outcomes between the TMVR and GDMT groups, using propensity score (PS)-matching to adjust for baseline differences.

Results: After PS-matching, 97 patient pairs undergoing TMVR (72.9±8.7 years, 60.8% male, transapical access 91.8%) versus GDMT (73.1±11.0 years, 59.8% male) were compared. At 1 and 2 years, residual MR was ≤1+ in all patients of the TMVR group compared to 6.9% and 7.7%, respectively, in those receiving GDMT alone (both p<0.001). The 2-year rate of HF hospitalization was significantly lower in the TMVR group (32.8% vs. 54.4%, HR 0.59, 95% CI 0.35-0.99; p=0.04). Among survivors, a higher proportion of patients were in NYHA functional class I or II in the TMVR group at 1 year (78.2% vs. 59.7%, p=0.03) and at 2 years (77.8% vs. 53.2%, p=0.09). Two-year mortality was similar in the two groups (TMVR vs. GDMT, 36.8% vs. 40.8%, HR 1.01, 95% CI 0.62-1.64; p=0.98).

Conclusions: In this observational comparison, over 2-year follow-up, TMVR using mostly transapical devices in patients with secondary MR was associated with significant reduction of MR, symptomatic improvement, less frequent hospitalizations for HF and similar mortality compared with GDMT.

Registration: *ClinicalTrial.gov:* NCT04688190 (CHOICE-MI); *ClinicalTrial.gov:* NCT01626079 (COAPT)

Keywords: transcatheter mitral valve replacement; guideline-directed medical therapy; secondary mitral regurgitation; heart failure; COAPT; CHOICE-MI

Non-standard Abbreviations and Acronyms

CHOICE-MI	Choice of Optimal Transcatheter Treatment for Mitral Insufficiency Registry
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
GDMT	guideline-directed medical therapy
HF	heart failure
HFH	heart failure hospitalization
MR	mitral regurgitation
NYHA	New York Heart Association
PS	propensity score
TEER	transcatheter edge-to-edge repair
TMVR	transcatheter mitral valve replacement

Clinical Perspective

What is Known

- Transcatheter mitral valve replacement (TMVR) is an emerging therapy for patients with secondary mitral regurgitation (MR) providing predictable MR elimination to the majority of treated patients.
- The clinical benefit for patients undergoing TMVR compared to guideline-directed medical therapy alone has not been investigated.

What the Study Adds

- For selected patients with secondary MR, TMVR using dedicated devices represents a safe and effective alternative providing symptomatic improvement and less frequent heart failure hospitalizations compared to medical therapy alone.
- Randomized trials are necessary to determine the future role of TMVR among established MR therapies.

Secondary mitral regurgitation (MR) is a frequent finding in patients with systolic heart failure (HF) and has been associated with increased mortality and HF-related hospitalization rates.[1,2] The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation, NCT01626079) trial demonstrated significant benefits of transcatheter edge-to-edge repair (TEER) compared with GDMT alone, with fewer HF hospitalizations (HFH) and improved survival among patients with moderate-to-severe or severe secondary MR who remained symptomatic despite maximally tolerated guideline-directed medical therapy (GDMT).[3,4] TEER in COAPT was effective in eliminating severe MR in >90% of patients throughout 2-year follow-up, although most treated patients had residual 1+ or 2+ MR.

Transcatheter mitral valve replacement (TMVR) has been developed as a therapeutic alternative for patients with MR, and is under investigation in several US pivotal studies.[5–7] Although a major advantage of TMVR is the near complete resolution of MR in the vast majority of patients, the prognostic advantages of eliminating as compared with reducing secondary MR in patients with left ventricular (LV) dysfunction are uncertain, especially in patients undergoing TMVR using the transapical (TA) approach.[8]

In the absence of results from randomized controlled trials, we sought to provide exploratory data on the potential benefit of TMVR compared with GDMT alone in patients with secondary MR. Using data from the CHOICE-MI Registry (CHoice of OptImal transCatheter trEatment for Mitral Insufficiency Registry, NCT04688190) and the COAPT trial, we performed a propensity score-matched comparison of secondary MR patients undergoing TMVR versus GDMT focusing on clinical, functional and echocardiographic outcomes.

METHODS

Data Transparency and Openness

The data that support the findings of this study may be made available from the corresponding author upon reasonable request with approval by the study leadership of the CHOICE-MI and COAPT trials.

CHOICE-MI Registry Design

The CHOICE-MI Registry design has been described previously.[8] In brief, this retrospective, international, multi-center study included 400 patients in whom TMVR with different dedicated devices was performed at 31 centers between May 2014 and July 2022. All patients were at high or prohibitive surgical risk and considered suboptimal candidates for TEER by local heart team consensus. Reasons for TEER ineligibility are given in **Supplemental Table S1**. According to practice guidelines, patients with secondary MR were supposed to have received maximally tolerated GDMT at the time of TMVR screening. TMVR was performed using either TA (92.7%) or transfemoral (TF) access (7.3%) (**Supplemental Table S2**). Anatomical eligibility for TMVR was assessed by local heart teams and device manufacturers based on local and trial protocols.

For this study, only patients undergoing TMVR for moderate-to-severe (3+) or severe (4+) secondary MR were included. Patients with mixed primary and secondary MR etiology (N=68), moderate or severe mitral stenosis (N=5), moderate or severe mitral annular calcification (N=14), and patients with severe right ventricular (RV) dysfunction (N=26) were excluded (**Figure 1**). Severe RV dysfunction was defined as tricuspid annular plane systolic excursion (TAPSE) <12 mm. Anonymized baseline and follow-up data were centrally collected for analysis. Data collection was approved by the local institutional review boards with waiver of informed consent due to the retrospective nature of the study, and the study was performed in accordance with the Declaration of Helsinki.

COAPT Trial Design

The study design and protocol of the COAPT trial have been described previously.[3] Briefly, a total of 614 patients with moderate-to-severe (3+) or severe (4+) MR were randomized to treatment with TEER plus GDMT (N=302) or GDMT alone (N=312). For this study, we used the per-protocol GDMT control group (N=289) in whom all enrollment criteria were met. Patients receiving TEER treatment during 2-year follow-up were excluded (N=2). By protocol, all patients were required to be on optimized GDMT and in New York Heart Association (NYHA) functional class II, III, or ambulatory IV at the time of enrollment. Key eligibility criteria were an LV ejection fraction (LVEF) between 20% and 50%, LV end-systolic diameter (LVESD) ≤70 mm, and the absence of severe pulmonary artery hypertension or symptomatic moderate to severe RV dysfunction. All patients were determined to be ineligible for surgery by the local heart teams, and successful treatment with the MitraClip™ device (Abbott, Santa Clara, CA, USA) was considered feasible by the MitraClip implanting investigator. All patients in this report have completed 2-year follow-up. The local institutional review boards approved the trial, and all patients provided written informed consent.

Study Endpoints

The aim of this study was to provide an exploratory outcome comparison of TMVR plus GDMT vs. GDMT alone among propensity score-matched patients with HF and 3+ or 4+ secondary MR. Clinical study endpoints included all-cause mortality, cardiovascular (CV) mortality and the rate of HFH over 2 years. Combined endpoints included death or HFH, and CV death or HFH over 2 years. Clinical outcomes were assessed for the overall matched cohorts as well as for predefined subgroups. Functional outcome was assessed according to NYHA functional class at 1- and 2-year follow-up. Echocardiographic endpoints at discharge, 1- and 2-year follow-up included residual MR, LVEF, change in LVEF, LV end-diastolic diameter (LVEDD), change in LVEDD, pulmonary artery systolic pressure (PASP), change in

PASP and tricuspid regurgitation (TR) grade moderate (2+) or less. Since patients in the GDMT group did not have an index hospitalization, 30-day follow-up was used instead of discharge echocardiography.

Statistical Analysis

Propensity score matching was performed to select appropriate controls and to adjust for potential confounding factors between the groups at baseline. A total of 19 baseline variables (including demographics, comorbidities, echocardiographic parameters, and HF medications) were included in the propensity score, which used logistic regression to predict the probability that the patient was in the TMVR group. Multiple imputation was used to account for missing covariate data. Variables with >20% missing data were not included in this study. Subjects were matched using a 1:1 greedy nearest-neighbor matching procedure with a caliper of 0.1 times the standard deviation of the logit of propensity scores (**Supplemental Figure S1**). Success of matching was assessed by computing the standardized difference for each covariate with a value <20% considered as not significant. Propensity score overlap histograms before and after matching were provided (**Supplemental Figure S2**). The inverse propensity weighting (IPW) method was included as a sensitivity analysis. Continuous variables are reported as mean and standard deviation and were compared with Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables are reported as frequency and percent and were compared with the Chi-square test or Fisher's exact test when the expected cell counts fell below five. Clinical endpoints were compared with the log-rank test and are reported as Kaplan-Meier estimates. Kaplan-Meier 3-month landmark analyses were performed excluding early events. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Changes in echocardiographic parameters from baseline to follow-up time points were compared with analysis of covariance (ANCOVA), with adjustment for the baseline value. Subgroup analyses were performed to assess potential differences of treatment effect in various

subgroups by including the interaction term between pre-defined subgroups and treatment groups (TMVR vs. GDMT) in the Cox models. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

Unmatched patient characteristics prior to propensity score-matching are presented in **Supplemental Table S3**. After 1:1 propensity score-matching, the analytic cohort comprised 97 matched patient pairs with secondary MR treated with TMVR (age 72.9±8.7 years, 60.8% male, BMI 26.5 kg/m^2 [interquartile range (IQR) 23.4, 30.4], EuroSCORE II 5.3% [IQR 3.3, 12.4]) or GDMT alone (73.1±11.0 years, 59.8% male, BMI 26.1 kg/m^2 [IQR 22.5, 30.2], EuroSCORE II 7.0% [IQR 3.4, 10.7]). Baseline differences between matched and unmatched subjects are summarized in **Supplemental Table S4**. Baseline clinical and echocardiographic characteristics of the matched cohorts are summarized in **Table 1**. There were no significant differences between the groups regarding age, sex, BMI, surgical risk, NYHA functional class, MR severity (assessed by effective regurgitant orifice area [EROA]), LV function and diameters, severity of TR, or PASP. Treatment with HF medications were comparable in the matched groups except for a higher rate of mineralocorticoid receptor antagonist treatment in the TMVR group. The rates of previous myocardial infarction, previous percutaneous coronary intervention, and prior dialysis were higher in the GDMT group, while HFH within the past 12 months was more frequent in the TMVR group.

Clinical Study Endpoints

Procedural and 30-day outcomes after TMVR according to the Mitral Valve Academic Research Consortium (MVARC) criteria are shown in **Supplemental Table S5**. Kaplan-Meier analyses for clinical endpoints over 2 years in the matched groups are shown in **Figure**

2 and **Supplemental Figure S3**. Clinical study endpoints for the matched groups after 1 and 2 years are summarized in **Table 2**. Thirty-day mortality rate was 5.2% in the TMVR group and 2.1% in the GDMT group (p=0.25). All-cause mortality after 2 years occurred in 36.8% of patients after TMVR and 40.8% of patients in the GDMT alone group (HR 1.01, 95% CI 0.62-1.64, p=0.98) (**Figure 2A**). The rate of HFH was significantly lower in the TMVR group (32.8%) compared to the GDMT alone group (54.4%) (HR 0.59, 95% CI 0.35-0.99, p=0.04; **Figure 2B**). Despite overall numerically higher event rates in the GDMT alone group, there were no statistically significant differences between TMVR and GDMT regarding the 2-year endpoints of death or HFH (50.6% vs. 67.1%, HR 0.73, 95% CI 0.49-1.11, p=0.14; **Figure 2C**), CV death (TMVR vs. GDMT, 24.9% vs. 32.7%, HR 0.84, 95% CI 0.45-1.55, p=0.58; **Supplemental Figure S3A**), and CV death or HFH (46.4% vs. 63.7%, HR 0.70, 95% CI 0.45-1.08, p=0.10; **Supplemental Figure S3B**). Similar trends were found in a sensitivity analysis using IPW (**Supplemental Figure S4**).

The results of 3-month landmark analyses for all clinical endpoints are shown in **Figure 3** and **Supplemental Figure S3**. While the exclusion of events within the first 3 months did not have an impact on 2-year all-cause mortality (**Figure 3A**) or CV mortality (**Supplemental Figure S3C**), 3-month landmark analyses for the endpoints of HFH (21.3% vs. 45.8%, HR 0.42, 95% CI 0.21-0.96, p=0.01, **Figure 3B**), death or HFH (38.2% vs. 59.7%, HR 0.58, 95% CI 0.34-0.98, p=0.04, **Figure 3C**), and CV death or HFH (34.5% vs. 55.9%, HR 0.55, 95% CI 0.31-0.96, p=0.03, **Supplemental Figure S3D**) showed significantly lower event rates with TMVR vs. GDMT alone.

Subgroup Analysis

The results of TMVR vs. GDMT for the 2-year rate of all-cause mortality in different subgroups are shown in **Supplemental Figure S5A**. In patients with baseline TR ≥2+, event rates tended to be lower in the TMVR group ($p_{interaction}$=0.017), whereas female patients showed lower mortality when treated with GDMT alone ($p_{interaction}$=0.022). The results of

TMVR vs. GDMT for the 2-year rate of HFH were consistent in all subgroups (**Supplemental Figure S5B**). There was a suggestion of a greater benefit of TMVR in patients ≥75 years of age, at high surgical risk (EuroSCORE II ≥10%), with BMI <25 kg/m^2, without diabetes, without chronic obstructive pulmonary disease, without atrial fibrillation, at NYHA functional class III or IV, and with EROA <0.4 cm^2, but formal interaction testing was negative.

Functional Outcomes

Functional status according to NYHA functional was assessed among survivors at 1- and 2-year follow-up (**Figure 4**). There were no differences in NYHA functional class at baseline, with 71.1% and 68.0% of patients at NYHA class III or IV in the TMVR and GDMT groups, respectively. Among surviving patients, NYHA class was better (i.e., lower) among patients treated with TMVR than GDMT at both 1-year (p=0.002) and 2-years (p=0.035). At 1-year, the proportion of surviving patients who were in NYHA Class I or II was 78.2% with TMVR vs. 59.7% with GDMT alone. These proportions were similar at 2-year follow-up (77.8% vs. 53.2%).

Echocardiographic Outcomes

MR severity according to treatment group at baseline, discharge, 1-year and 2-year follow-up is summarized in **Figure 5**. While the majority of patients treated with TMVR showed complete MR elimination (i.e., none/trace MR) in 93.7%, 89.1% and 64.3% of patients at discharge, 1-year and 2-year follow-up, most patients receiving GDMT alone had MR ≥2+ during follow-up (93.7%, 93.1% and 92.2% at discharge, 1 year and 2 years, respectively).

Echocardiographic endpoints at discharge, and at 1- and 2-year follow-up are shown in **Table 3**. No significant differences between TMVR and GDMT alone were found in the follow-up measures of LVEF or TR. Patients undergoing GDMT alone showed greater LVEDD reduction at discharge (1.3 ± 8.4 mm vs. -9.1 ± 20.5 mm, p=0.001). The impact of TMVR on PASP was significantly greater compared with GDMT alone at discharge (-

6.1 ± 14.9 mmHg vs. -0.2 ± 12.3 mmHg, p=0.001) and at 2-year follow-up (-16.9 ± 18.1 mmHg vs. 2.1 ± 15.4 mmHg, p=0.004).

DISCUSSION

The present propensity-matched comparison has provided initial insights into the potential benefits of TMVR in patients with severe secondary MR treated with GDMT. The main results of our analysis can be summarized as follows: 1) MR was eliminated in most patients undergoing TMVR, while the severity of MR remained unchanged in patients receiving GDMT alone. This finding was accompanied by a sustained reduction of PASP in patients undergoing TMVR; 2) TMVR was associated with a significant reduction in the rate of HF-related hospitalizations through 2-year follow-up, although no significant difference in mortality was observed between TMVR and GDMT alone; 3) Subgroups with potentially improved outcomes after TMVR were identified; and 4) Functional improvement according to NYHA functional class at 1- and 2-year follow-up was greater after TMVR compared with GDMT alone.

By including a matched GDMT control group, our study expands upon insights from prior single arm studies of TMVR. Several prior reports have shown that in appropriately selected patients, TMVR can provide predictable and durable MR elimination.[6,7,9–12] The two largest single-arm studies of TMVR using the Tendyne (Abbott, Santa Clara, CA, USA) and the Intrepid device (Medtronic, Santa Rosa, CA, USA) both showed functional improvement compared with baseline and a significant reduction in pulmonary artery pressures at follow-up.[6,7] In addition, Muller et al. demonstrated that the rate of HFH was lower after TMVR compared with the immediate pre-TMVR period.[6] Our study confirms and extends these results by providing the first evidence that outcomes following TMVR in patients with HF

and severe secondary MR may be improved compared with GDMT alone. The greatest benefits of TMVR were in the reduction of HFH and improved functional class.

Despite the favorable outcomes of TMVR in our study cohort, there was no evidence of a survival benefit in patients with secondary MR undergoing TMVR compared with GDMT alone in the present study. Female patients even showed lower all-cause mortality when treated medically, which could be explained by commonly smaller LV size in female patients conferring a higher risk of peri-procedural complications during TMVR (e.g., LV outflow tract obstruction). These findings are contrast with those seen with mitral TEER in the COAPT trial and may reflect several factors (3). First, the analytic cohort for our study was <1/3 the size of the COAPT trial and was therefore underpowered for all-cause mortality. Treating secondary MR does not improve the underlying LV dysfunction, and even in COAPT, TEER only mitigated but did not halt adverse LV remodeling.[13,14] Finally, the impact of the procedural learning curve and TMVR access-related complications (especially from TA access) on mortality may have contributed to high rates of 30-day mortality in the TMVR group. In the future, larger randomized trials of TMVR (with TF access) and GDMT alone will be necessary to determine the extent to which TMVR impacts long-term survival in patients with severe secondary MR. In interpreting our findings, it is important to note that in an elderly population with few treatment options, the reduction of HFH and the symptomatic improvement is often an equally (or even more) important treatment goal than increasing longevity. The present results thus support a potential role for TMVR as a treatment option for selected HF patients with secondary MR patients, especially for those who are not suitable for TEER.[15,16] Studies evaluating the optimal anatomies and other conditions for TEER and TMVR treatment would be useful to provide further guidance for device selection. The COAPT inclusion criteria seem to have identified a subset of patients with secondary MR, who substantially benefit from a TEER procedure, whereas such criteria do not exist for TMVR.[17] Therefore, a comparison of mostly TEER-ineligible patients undergoing TMVR to

the device arm of the COAPT trial did not seem appropriate for our study. A recent study compared outcomes of patients with secondary MR undergoing TMVR to a matched real-world TEER cohort showing superior MR reduction and functional improvement, but higher early post-procedural mortality after TMVR.[18] In line with our study, these results highlight the need for a reduction in procedure-related adverse events after TMVR and warrant randomized controlled trials comparing TMVR versus TEER.

Importantly, the results of the present study reflect the outcomes of TMVR predominantly with TA access. More than 1,000 patients have been treated to date with the TA Tendyne device (Abbott Vascular), which is the only commercially-available TMVR system in Europe and the most widely used device in CHOICE-MI.[19] However, several transfemoral/transseptal (TF) TMVR systems are currently under clinical investigation, and the TMVR landscape is expected to transition to a predominance of devices using the TF approach.[20,21] Similar to the experience with transcatheter aortic valve implantation, it seems likely that this technological change will make an impact on short-term outcomes.[22] Early experience with the TF Intrepid device (Medtronic Inc., Redwood City, CA, USA) have demonstrated promising results with low rates of short-term mortality and complications.[12] By reducing peri-procedural complications and mortality, the prognostic benefits of TMVR might be further improved. In our study, the number of patients undergoing TF-TMVR was too small to determine potential differences between TA and TF access. Ongoing dedicated studies will demonstrate whether a transition to TF-TMVR can meet these expectations.

Study Limitations

Our study should be interpreted in the context of several limitations. First, the present study is an exploratory, post-hoc comparison of two highly selected patient populations. By design, all patients were anatomically appropriate for TMVR in CHOICE-MI and for TEER in COAPT. Although the analytic cohort for our study was selected based on propensity score matching, this approach did not account for anatomic differences in valve morphology (which was not

available in either dataset). In particular, the fact that patients referred for TMVR are usually considered suboptimal TEER candidates while patients included in COAPT were explicitly determined to be suitable for TEER suggests that not all differences in mitral valve anatomy and cardiac structure and function were accounted for in our study. By excluding patients with mixed MR etiology, mitral stenosis and mitral annular calcification from the TMVR cohort, we sought to achieve anatomical comparability, yet some inherent selection bias remains. However, medical comorbidities and the degree of HF are more important drivers of outcomes in secondary MR than mitral valve anatomy. Given the similar LVEF, LV dimensions, and comorbidities in the matched cohorts, we believe to have achieved reasonable comparability between the study groups. In addition, echocardiographic follow-up in the TMVR group was incomplete and there was no data on the evolution of medical HF treatment. Given these important limitations, our results cannot be considered to be a substitute for a high-quality randomized comparison and will remain relevant only until such data become available.

Conclusions

In the present propensity score-matched analysis comparing outcomes of patients with HF and secondary MR undergoing TMVR or GDMT alone, TMVR using mostly transapical devices was associated with a lower rate of HFH, greater symptomatic improvement, with elimination of MR in most patients, effects that were durable through 2 years. No difference between TMVR and GDMT was observed in 2-year mortality. In the absence of randomized controlled trials in this population, these results provide important preliminary evidence on the benefits of TMVR in patients with HF and severe secondary MR.

Acknowledgements: We would like to thank all the CHOICE-MI and COAPT Investigators for their invaluable contributions to this study.

Sources of Funding: This work was supported by a grant from the German Heart Foundation (DHS) [grant number S/04/21] to Dr. Ludwig. The COAPT trial was funded by Abbott (Santa Clara, CA, USA).

Disclosures:

SL: travel compensation: Edwards; speaker honoraria: Abbott; advisory fees: Bayer

LC: advisory board: Abbott, Medtronic, Boston Scientific; personal fees: Edwards

DJC: research grant and consulting: Abbott, Edwards Lifesciences, Boston Scientific, Medtronic AC: proctor: Abbott; speaker: Abbott, GE

AS: consultant: NeoChord

WTA: research grant: National Institutes of Health – National Heart, Lung, and Blood Institute (National Institutes of Health 1 UG3 / UH3 HL140144-01, 08/01/18 - 07/31/22, "Impact of Low Flow Nocturnal Oxygen Therapy on Hospital Readmission/Mortality in Patients with Heart Failure and Central Sleep Apnea (LOFT-HF)"; consulting: Abbott, Boehringer-Ingelheim, Zoll; honoraria: Impulse Dynamics; salary: V-Wave Medical.

WBA: grants: Medtronic, Edwards

SK: grants and consulting: Abbott, Boston Scientific, Edwards, 4TECH; stock: 4TECH.

DSL: grants: Abbott, Boston Scientific, Corvia, Edwards, Medtronic, Trisol, V Wave; consultant: Ancora, Philips, Valgen, Venus.

AD: consultant: Abbott, Edwards, Medtronic.

MAdamo: personal fees: Edwards, Boston Scientific; grants and honoraria: Medtronic

DWMM: advisory board: Abbott, Medtronic, Edwards

ASP: consultant: Medtronic, Boston Scientific, Abbott.

HR: advisory board: Abbott; proctor: Abbott, Edwards.

LS: grants and consulting: Edwards, Medtronic.

MAdam: grants and honoraria: Medtronic; personal fees: Boston Scientific, Edwards

GD: proctor/speaker: Abbott, Edwards.

JK: honoraria: Edwards, Medtronic, Abbott, CryoLife.

AG: proctor: Abbott

TS: honoraria and travel: Abbott, Cardiovalve

GHLT: proctor/consultant: Medtronic; consultant/advisory board: Abbott; consultant: NeoChord; advisory board: JenaValve; honoraria: Siemens, EastEnd Medical

SR: proctor and personal fees: Edwards; advisory board: Medtronic

MT: consultant: Abbott, Edwards, Boston Scientific, Shenqi Medical, Simulands, Occlufit, MTEx, MEDIRA, 4tech and CoreMedic; personal fees: Cardiovalve.

FP: consultant: Edwards

NF: consultant: Edwards, Abbott, Cardiovalve

ND: consultant/proctor: Abbott, Boston Scientific, Edwards, Medtronic

RSVB: consulting/honoraria: Abbott, Edwards, Medtronic; research grants to university: Abbott, Edwards

TKR: honoraria: Abbott

MJR: consultant: Medtronic, Boston, Abbott, Gore (all funds to department)

MM: personal fees: Actelion, Amgen, Livanova, Servier, Vifor pharma as member of Executive or Data Monitoring Committeees of sponsored clinical trials; Astra-Zeneca, Abbott, Bayer, Boheringer Ingelhelm and Edwards Therapeutics for participation to advisory boards and/or speeches at sponsored meetings

PD: personal fees: Abbott, Edwards

MJM: co-PI PARTNER Trial (Edwards) and COAPT trial (Abbott); study chair: APOLLO trial (Medtronic)

JH: consulting fees, speaker honoraria, and research support to institution: Abbott, Edwards

FMA: institutional contracts: Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, Livanova

AL: advisory board: Medtronic, Boston Scientific, Philips, Edwards, Abbott

JL: grant: AstraZeneca; consulting: Abbott, Alleviant, AstraZeneca, Cordio, CVRx, Edwards, Boehringer Ingelheim, Merck, Medtronic, Vascular Dynamics, V-Wave

TM: consultant: Abbott, Edwards, Medtronic

GWS: honoraria: Medtronic, Pulnovo, Infraredx; consultant: Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical, Millennia Biopharma; equity/options: Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, Xenter. Dr. Stone's daughter is an employee at Medtronic. Institutional disclosure: Dr. Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, Pulnovo and V-wave.

JG is the President and CEO of Cardiovascular Research Foundation

The remaining authors have nothing to disclose regarding this manuscript.

Supplemental Material

Figure S1-S5

Table S1-S5

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Tables

Table 1. Baseline Clinical and Echocardiographic Parameters in the Matched Groups

Parameters	TMVR (N=97)	GDMT (N=97)	p value	Standardized Difference (%)
Demographic Parameters				
Age - years	72.9 ± 8.7	73.1 ± 11.0	0.94	-1.14
Sex - male	59 (60.8)	58 (59.8)	0.88	2.11
BMI - kg/m^2	26.5 [23.4, 30.4]	26.1 [22.5, 30.2]	0.91	1.70
EuroSCORE II - %	5.3 [3.3, 12.4]	7.0 [3.4, 10.7]	0.47	-10.40
Cardiovascular Comorbidities				
Atrial fibrillation	55 (56.7)	47 (48.5)	0.25	16.57
Coronary artery disease	66 (68.0)	73 (75.3)	0.26	-16.06
Previous MI	47 (48.5)	58 (59.8)	0.11	-22.91
Previous PCI	40 (41.2)	55 (56.7)	0.03	-31.31
Previous CABG	30 (30.9)	33 (34.0)	0.65	-6.61
Prior TAVR or SAVR	5 (5.2)	8 (8.3)	0.57	-12.39
Previous stroke/TIA	12 (12.4)	17 (17.5)	0.31	-14.49
Peripheral vascular disease	17 (17.5)	21 (21.7)	0.47	-10.41
NYHA Functional Class III/IV	69 (71.1)	66 (68.0)	0.64	6.73
Hospitalization for HF (within past 12 months)	75 (77.3)	50 (51.6)	<0.001	55.61
Non-Cardiovascular Comorbidities				

Diabetes	27 (27.8)	27 (27.8)	1.00	0.00
COPD	18 (18.6)	23 (23.7)	0.38	-12.65
Serum albumin <3.3 g/dL	11 (11.3)	8 (8.3)	0.47	10.42
eGFR - mL/min	48.9 ± 18.6	46.5 ± 19.0	0.38	12.73
Prior Dialysis	1 (1.0)	5 (5.2)	0.21	-23.99
Heart Failure Medication				
Betablocker	89 (91.8)	86 (88.7)	0.47	10.42
ACEI/ARB/ARNI	72 (74.2)	70 (72.2)	0.75	4.66
MRA	59 (60.8)	45 (46.4)	0.04	29.25
Echocardiographic Parameters				
MR 3+ or 4+	97 (100)	97 (100)	1.00	0.00
EROA - cm^2	0.40 [0.25, 0.54]	0.39 [0.31, 0.51]	0.43	11.29
LVESD - mm	51.3 ± 11.9	49.7 ± 8.5	0.30	15.06
LVEDD - mm	61.0 ± 8.9	60.0 ± 7.2	0.39	12.47
LVEF - %	36.0 ± 8.7	36.2 ± 10.2	0.87	-2.38
TR ≥3+	2 (2.1)	3 (3.1)	1.00	-6.51
PASP - mmHg	43.9 ± 16.2	45.2 ±14.8	0.56	-8.47

Data presented as mean ± standard deviation, median [Q1, Q3], or no (%), where applicable. Abbreviations: ACEI: angiotensin-conversing enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, BMI: body mass index, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, EROA: effective regurgitant orifice area, GDMT: guideline-directed medical therapy, HF: heart failure, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, MI: myocardial infarction, MR: mitral regurgitation, MRA: mineralocorticoid receptor antagonist, NYHA: New York Heart Association, PASP: pulmonary artery systolic pressure, PCI: percutaneous coronary intervention, SAVR: surgical aortic valve replacement, TIA: transient ischemic attack, TAVR: transcatheter aortic valve replacement, TR: tricuspid regurgitation

Table 2. Clinical Study Endpoints in the Matched Groups

Study Endpoints	TMVR (N=97)	GDMT (N=97)	Hazard Ratio (95% CI)	p value
Study Endpoints after 1 Year				
All-cause mortality	24.4 (21)	22.1 (21)	1.18 (0.64, 2.16)	0.59
Cardiovascular mortality	17.4 (14)	17.5 (16)	1.05 (0.51, 2.16)	0.89
HFH	24.4 (18)	34.3 (32)	0.67 (0.37, 1.19)	0.17
All-cause mortality or HFH	40.3 (30)	44.4 (43)	0.89 (0.56, 1.41)	0.61
Cardiovascular mortality or HFH	35.2 (25)	42.0 (40)	0.81 (0.49, 1.34)	0.42
NYHA Functional Class I or II	43/55 (78.2)	37/62 (59.7)	-	0.03
Study Endpoints after 2 Years				
All-cause mortality	36.8 (29)	40.8 (37)	1.01 (0.62, 1.64)	0.98
Cardiovascular mortality	23.2 (17)	32.7 (28)	0.79 (0.43, 1.45)	0.45
HFH	32.8 (21)	54.4 (46)	0.59 (0.35, 0.99)	0.04
All-cause mortality or HFH	50.6 (36)	67.1 (63)	0.73 (0.49, 1.11)	0.14
Cardiovascular mortality or HFH	46.4 (31)	63.7 (58)	0.70 (0.45, 1.08)	0.11
NYHA Functional Class I or II	14/18 (77.8%)	25/47 (53.2%)	-	0.09

Rates for clinical endpoints are given as Kaplan-Meier estimated event rates (n events) or no./total no. (%), where applicable. Abbreviations: GDMT: guideline-directed medical therapy, HFH: heart failure hospitalization, NYHA: New York Heart Association, TMVR: transcatheter mitral valve replacement

Table 3. Echocardiographic Endpoints in the Matched Groups

Echocardiography Endpoints	TMVR (N=97)	GDMT (N=97)	Mean Difference (95% CI)	p value
Echocardiographic Endpoints at Discharge				
MR ≤2+	94/95 (99.0)	25/95 (26.3)	-	<0.001
MR ≤1+	93/95 (97.9)	6/95 (6.3)	-	<0.001
LVEF - %	36.7 ± 11.1	37.0 ± 11.4	0.1 (-2.4, 2.6)	0.92
Change in LVEF (baseline to discharge) - %	0.9 ± 10.3	0.6 ± 6.9	0.1 (-2.4, 2.6)	0.92
LVEDD - mm	61.3 ± 8.9	50.7 ± 20.6	10.65 (4.26, 17.05)	0.001
Change in LVEDD (baseline to discharge) - mm	1.3 ± 8.4	-9.1 ± 20.5	10.65 (4.26, 17.05)	0.001
PASP - mmHg	37.5 ± 12.5	44.9 ± 15.2	-6.8 (-10.8, -2.8)	0.001
Change in PASP (baseline to discharge) - mmHg	-6.1 ± 14.9	-0.2 ± 12.3	-6.8 (-10.8, -2.8)	0.001
TR ≤2+ - no./total no. (%)	62/64 (96.9)	93/95 (97.9)	-	1.00
Echocardiographic Endpoints at 1 Year				
MR ≤2+ - no./total no. (%)	55/55 (100)	24/58 (41.4)	-	<0.001
MR ≤1+ - no./total no. (%)	55/55 (100)	4/58 (6.9)	-	<0.001
LVEF - %	33.2 ± 10.3	34.2 ± 10.7	0.5 (-3.1, 4.1)	0.78
Change in LVEF (baseline to 12 months) - %	-1.7 ± 11.1	-3.1 ± 8.2	0.5 (-3.1, 4.1)	0.78
LVEDD - mm	60.6 ± 7.4	59.4 ± 6.7	-0.9 (-3.3, 1.6)	0.48
Change in LVEDD (baseline to 12 months) - mm	-2.3 ± 7.2	-0.5 ± 4.5	-0.9 (-3.3, 1.6)	0.48
PASP - mmHg	37.6 ± 10.3	39.9 ± 11.7	-2.9 (-8.1, 2.4)	0.28
Change in PASP (baseline to 12 months) - mmHg	-6.2 ± 20.4	-2.7 ± 13.3	-2.9 (-8.1, 2.4)	0.28

TR ≤2+	35/35 (100)	58/59 (98.3)	-	1.00
Echocardiographic Endpoints at 2 Years				
MR ≤2+	14/14 (100)	16/39 (41.0)	-	<0.001
MR ≤1+	14/14 (100)	3/39 (7.7)	-	<0.001
LVEF - %	33.1 ± 8.4	38.0 ± 13.3	-0.7 (-8.9, 7.6)	0.87
Change in LVEF (baseline to 24 months) - %	1.2 ± 11.0	-1.1 ± 11.8	-0.7 (-8.9, 7.6)	0.87
LVEDD - mm	63.6 ± 7.5	58.9 ± 8.4	2.1 (-2.1, 6.3)	0.32
Change in LVEDD (baseline to 24 months) - mm	0.5 ± 5.6	-1.1 ± 6.2	2.1 (-2.1, 6.3)	0.32
PASP - mmHg	30.3 ± 10.1	45.3 ± 16.3	-17.1 (-28.3, -5.8)	0.004
Change in PASP (baseline to 24 months) - mmHg	-16.9 ± 18.1	2.1 ± 15.4	-17.1 (-28.3, -5.8)	0.004
TR ≤2+	13/13 (100)	36/38 (94.7)	-	1.00

*Echocardiographic follow-up at 30 days was used for the GDMT group. Data presented as mean ± standard deviation, or no./total no. (%), where applicable. Abbreviations: CI: confidence interval, GDMT: guideline-directed medical therapy, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, MR: mitral regurgitation, PASP: pulmonary artery systolic pressure, TMVR: transcatheter mitral valve replacement, TR: tricuspid regurgitation

Figure Legends

Figure 1. **Study flow chart**

Abbreviations: EROA: effective regurgitant orifice area, GDMT: guideline-directed medical therapy, HF: heart failure, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, MAC: mitral annular calcification, MR: mitral regurgitation, MS: mitral stenosis, RCT: randomized-controlled trial, RV: right ventricular, SMR: secondary MR, TEER: transcatheter edge-to-edge repair, TMVR: transcatheter mitral valve replacement

Figure 2. **Two-year Kaplan-Meier analyses for study endpoints in the matched groups**.

A) Kaplan-Meier analysis for all-cause mortality; B) Kaplan-Meier analysis for HF hospitalization; C) Kaplan-Meier analysis for the combined endpoint of all-cause mortality or HF hospitalization

Abbreviations: GDMT: guideline-directed medical therapy, HF: heart failure, TMVR: transcatheter mitral valve replacement

Figure 3. **Two-year Kaplan-Meier analyses with landmark analyses after 3 months for study endpoints in the matched groups**.

A) Kaplan-Meier analysis with 3-month landmark analysis for all-cause mortality; B) Kaplan-Meier analysis with 3-month landmark analysis for HF hospitalization; C) Kaplan-Meier analysis with 3-month landmark analysis for the combined endpoint of all-cause mortality or HF hospitalization

Abbreviations: GDMT: guideline-directed medical therapy, HF: heart failure, TMVR: transcatheter mitral valve replacement

Figure 4. **NYHA Functional Class at baseline, 1- and 2-year follow-up after TMVR versus medical therapy in the matched groups**.

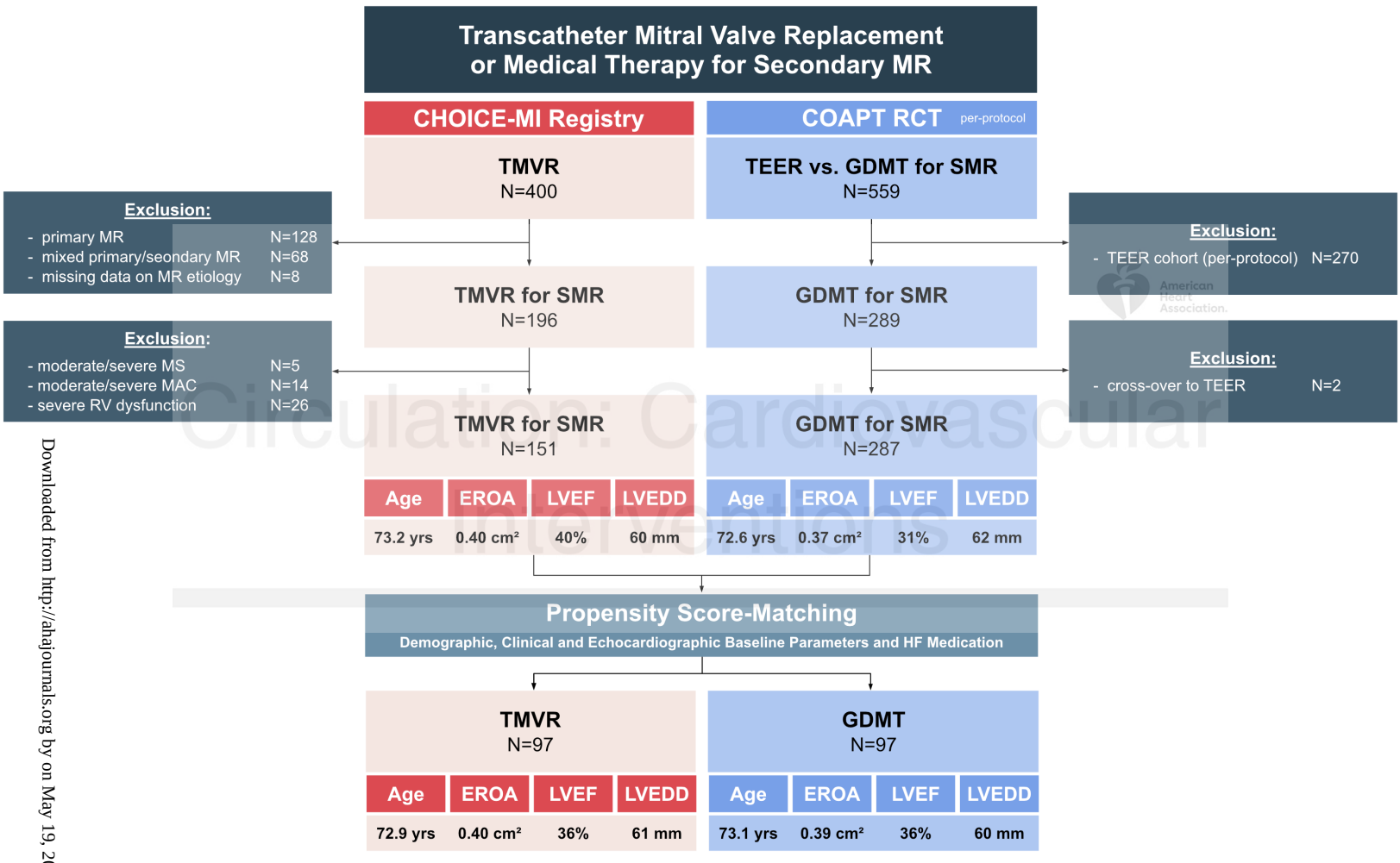
Abbreviations: GDMT: guideline-directed medical therapy, NYHA: New York Heart Association, TMVR: transcatheter mitral valve replacement

Figure 5. **Mitral regurgitation at baseline, discharge, 1- and 2-year follow-up after TMVR versus medical therapy in the matched groups**.

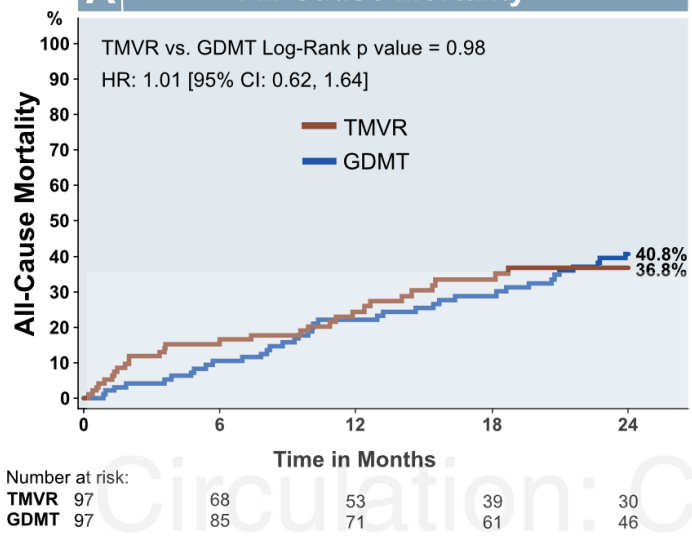
Asterisks (*) indicate percentages below 2.0%.

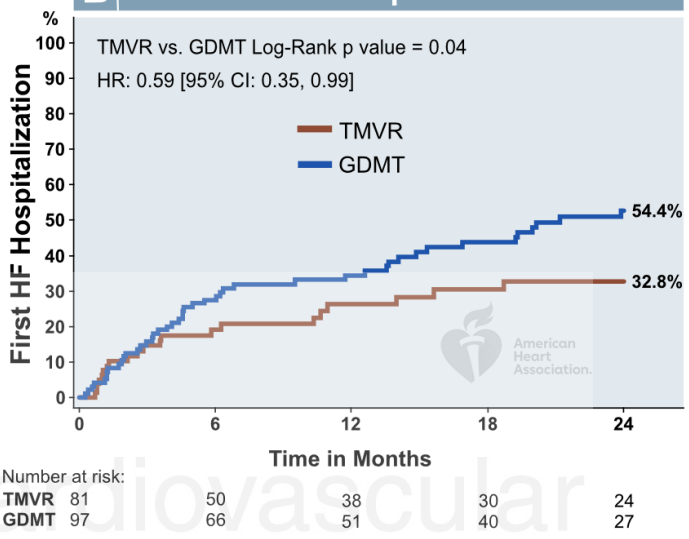
Discharge: Echocardiographic follow-up at 30-days was used for the GDMT group.

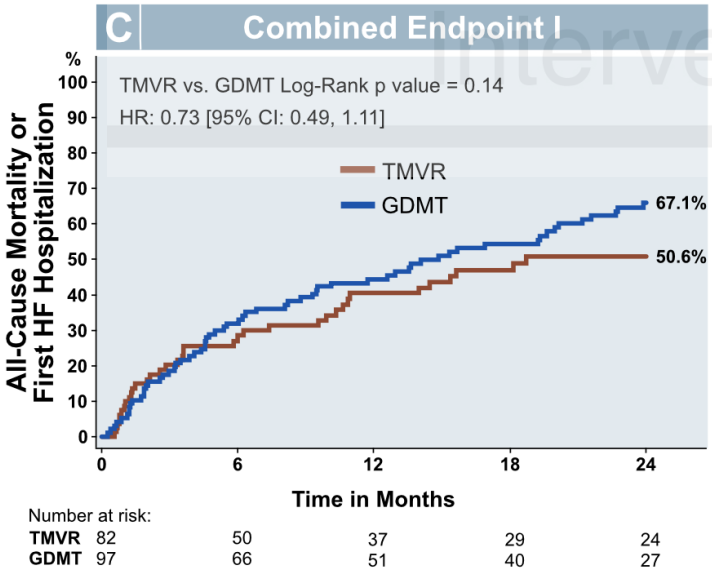
Abbreviations: GDMT: guideline-directed medical therapy, MR: mitral regurgitation, TMVR: transcatheter mitral valve replacement



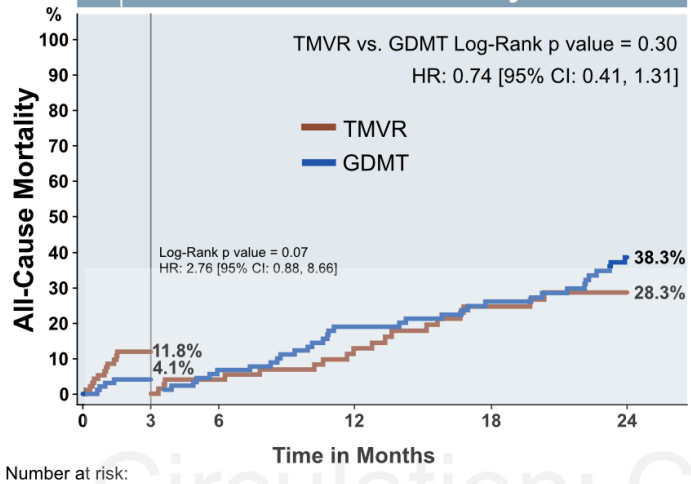
Kaplan-Meier Analyses





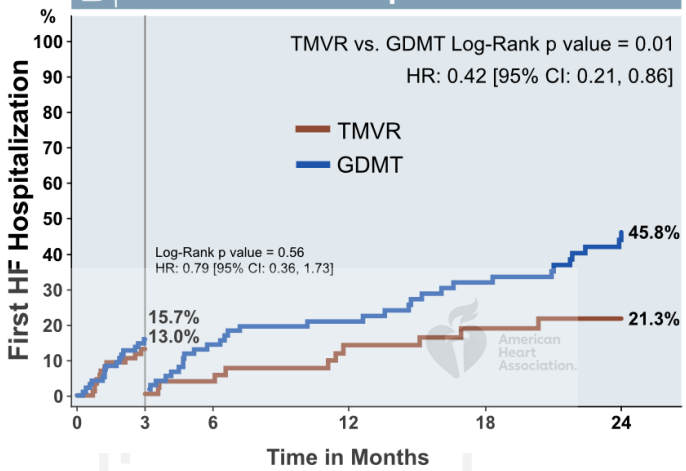


Kaplan-Meier 3-Month Landmark Analyses



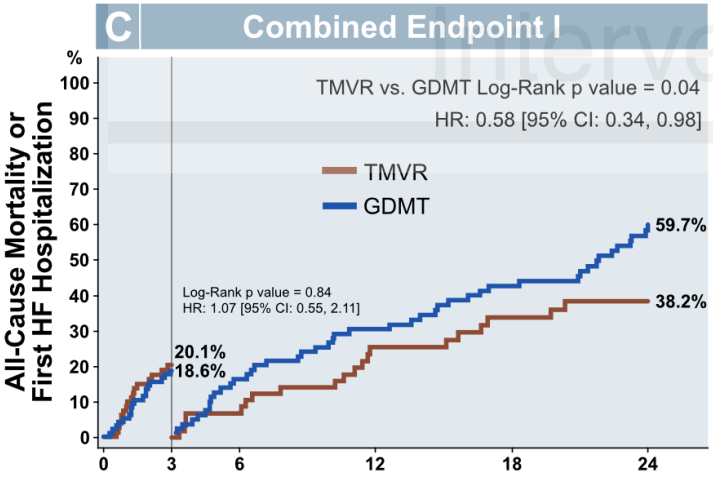
Number at risk:

TMVR	97	78	68	53	39	30
GDMT	97	93	85	71	61	46



Number at risk:

TMVR	90	60	50	38	30	24
GDMT	97	79	66	51	40	27



Number at risk:

TMVR	82	61	50	37	29	24
GDMT	97	79	66	51	40	27