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ORIGINAL ARTICLE

Transcatheter Mitral Valve Replacement Versus Medical Therapy for Secondary Mitral Regurgitation: A Propensity Score–Matched Comparison

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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 (Choice of Optimal Transcatheter Treatment for Mitral Insufficiency) included patients with MR undergoing TMVR using dedicated devices. Patients with MR pathogeneses other than secondary MR were excluded. Patients treated with GDMT alone were derived from the control arm of the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation). We compared outcomes between the TMVR and GDMT groups, using propensity score matching to adjust for baseline differences.

RESULTS: After propensity score matching, 97 patient pairs undergoing TMVR (72.9±8.7 years; 60.8% men; transapical access, 91.8%) versus GDMT (73.1±11.0 years; 59.8% men) were compared. At 1 and 2 years, residual MR was ≤1+ in all patients of the TMVR group compared with 6.9% and 7.7%, respectively, in those receiving GDMT alone (both $P<0.001$). The 2-year rate of heart failure hospitalization was significantly lower in the TMVR group (32.8% versus 54.4%; hazard ratio, 0.59 [95% CI, 0.35–0.99]; $P=0.04$). Among survivors, a higher proportion of patients were in the New York Heart Association functional class I or II in the TMVR group at 1 year (78.2% versus 59.7%; $P=0.03$) and at 2 years (77.8% versus 53.2%; $P=0.09$). Two-year mortality was similar in the 2 groups (TMVR versus GDMT, 36.8% versus 40.8%; hazard ratio, 1.01 [95% CI, 0.62–1.64]; $P=0.98$).

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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 heart failure, and similar mortality compared with GDMT.

REGISTRATION: URL: https://clinicaltrials.gov; Unique identifier: NCT04688190 (CHOICE-MI) and NCT01626079 (COAPT).

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: bioprosthesis ■ heart failure ■ heart valve disease ■ mitral valve ■ mitral valve insufficiency ■ propensity score

WHAT IS KNOWN

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

WHAT THE STUDY ADDS

- For selected patients with secondary mitral regurgitation, transcatheter mitral valve replacement 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 transcatheter mitral valve replacement among established mitral regurgitation therapies.

Nonstandard Abbreviations and Acronyms

CHOICE-MI	Choice of Optimal Transcatheter Treatment for Mitral Insufficiency
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
HR	hazard ratio
LV	left ventricle
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
NYHA	New York Heart Association
PASP	pulmonary artery systolic pressure
PS	propensity score
TEER	transcatheter edge-to-edge repair
TMVR	transcatheter mitral valve replacement

Secondary mitral regurgitation (MR) is a frequent finding in patients with systolic heart failure (HF) and has been associated with increased mortality and HF hospitalization (HFH) rates.[1,2] The COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; NCT01626079) demonstrated significant benefits of transcatheter edge-to-edge repair (TEER) compared with guideline-directed medical therapy (GDMT) alone, with fewer HFHs and improved survival among patients with moderate-to-severe or severe secondary MR who remained symptomatic despite maximally tolerated 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 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 (Choice of Optimal Transcatheter Treatment for Mitral Insufficiency) registry (NCT04688190) and the COAPT trial, we performed a propensity score (PS)–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 registry and COAPT trial.

CHOICE-MI Registry Design

The CHOICE-MI registry design has been described previously.[8] In brief, this retrospective, international, multicenter 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 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 transapical (92.7%) or transfemoral access (7.3%; 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 pathogenesis (n=68), moderate or severe mitral stenosis (n=5), moderate or severe mitral annular calcification (n=14), and severe right ventricular dysfunction (n=26) were excluded (Figure 1). Severe right ventricular dysfunction was defined as tricuspid annular plane systolic excursion <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 ≤70 mm, and the absence of severe pulmonary artery hypertension or symptomatic moderate-to-severe right ventricular 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) 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 End Points

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

PS 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 PS, 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× the SD of the logit of PSs (Figure S1). Success of matching was assessed by computing the standardized difference for each covariate with a value <20% considered as not significant. PS overlap histograms before and after matching were provided (Figure S2). The inverse propensity weighting method was included as a sensitivity analysis. Continuous variables are reported as mean and SD and were compared with the Student *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables are reported as frequency and percentage and were compared with the χ^2 test or Fisher exact test when the expected cell counts fell below 5. Clinical end points 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% CIs were calculated using Cox proportional-hazards models. Changes in echocardiographic parameters from baseline to follow-up time points were compared with 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 predefined subgroups and treatment groups (TMVR versus 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 before PS matching are presented in Table S3. After 1:1 PS matching, the analytic cohort comprised 97 matched patient pairs with secondary MR treated with TMVR (age, 72.9±8.7 years; 60.8% men; body mass index, 26.5 kg/m^2 [interquartile range, 23.4–30.4]; EuroSCORE II, 5.3% [interquartile range, 3.3–12.4]) or GDMT alone (73.1±11.0

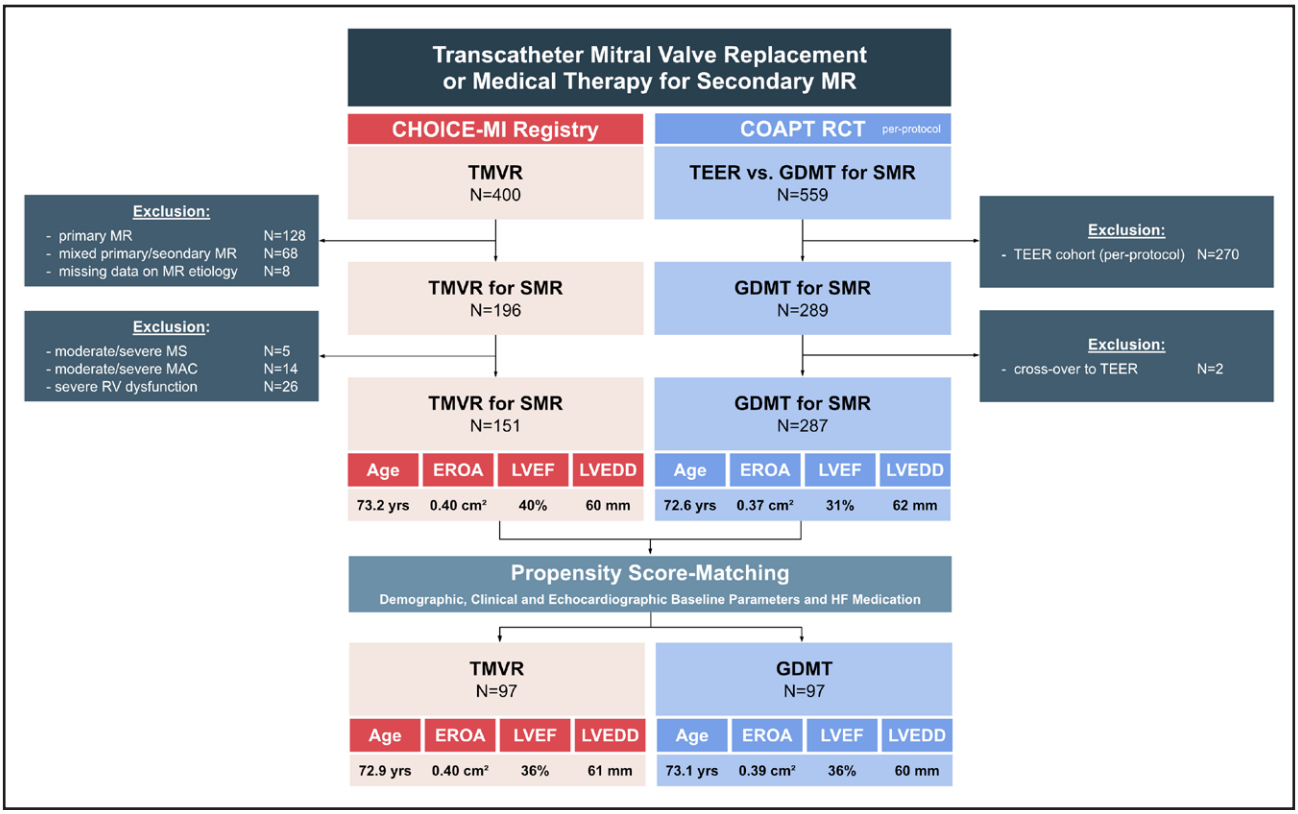

Figure 1. Study flowchart.
CHOICE-MI indicates Choice of Optimal Transcatheter Treatment for Mitral Insufficiency; COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; EROA, effective regurgitant orifice area; 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 ventricle; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; and TMVR, transcatheter mitral valve replacement.

years; 59.8% men; body mass index, 26.1 kg/m^2 [interquartile range, 22.5–30.2]; EuroSCORE II, 7.0% [interquartile range, 3.4–10.7]). Baseline differences between matched and unmatched subjects are summarized in 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, body mass index, surgical risk, NYHA functional class, MR severity (assessed by effective regurgitant orifice area), LV function and diameters, severity of tricuspid regurgitation, or PASP. Treatment with HF medications was 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 End Points

Procedural and 30-day outcomes after TMVR according to the Mitral Valve Academic Research Consortium criteria are shown in Table S5. Kaplan-Meier analyses for clinical end points over 2 years in the matched groups are shown in Figure 2 and Figure S3. Clinical study end points 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 with 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 end points of death or HFH (50.6% versus 67.1%; HR, 0.73 [95% CI, 0.49–1.11]; P=0.14; Figure 2C), cardiovascular death (TMVR versus GDMT, 24.9% versus 32.7%; HR, 0.84 [95% CI, 0.45–1.55]; P=0.58; Figure S3A), and cardiovascular death or HFH (46.4% versus 63.7%; HR, 0.70 [95% CI, 0.45–1.08]; P=0.10; Figure S3B). Similar trends were found in a sensitivity analysis using inverse propensity weighting (Figure S4).

The results of 3-month landmark analyses for all clinical end points are shown in Figure 3 and Figure S3.

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, y	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
HFH (within the past 12 mo)	75 (77.3)	50 (51.6)	<0.001	55.61
Noncardiovascular 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				
β-Blocker	89 (91.8)	86 (88.7)	0.47	10.42
ACE inhibitor/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, mm Hg	43.9±16.2	45.2±14.8	0.56	−8.47

Data are presented as mean±SD, median (Q1–Q3), or n (%), where applicable. ACE indicates angiotensin-conversing enzyme; 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; HFH, heart failure hospitalization; 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; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; TMVR, transcatheter mitral valve replacement; and TR, tricuspid regurgitation.

While the exclusion of events within the first 3 months did not have an impact on 2-year all-cause mortality (Figure 3A) or cardiovascular mortality (Figure S3C), 3-month landmark analyses for the end points of HFH (21.3% versus 45.8%; HR, 0.42 [95% CI, 0.21–0.96]; versus *P*=0.01; Figure 3B), death or HFH (38.2% versus 59.7%; HR, 0.58 [95% CI, 0.34–0.98]; *P*=0.04; Figure 3C), and cardiovascular death or HFH (34.5% versus 55.9%; HR, 0.55 [95% CI, 0.31–0.96]; *P*=0.03; Figure S3D) showed significantly lower event rates with TMVR versus GDMT alone.

Subgroup Analysis

The results of TMVR versus GDMT for the 2-year rate of all-cause mortality in different subgroups are shown in Figure S5A. In patients with baseline tricuspid regurgitation ≥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 versus GDMT for the 2-year rate of HFH were consistent in all subgroups (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 body mass index <25 kg/m^2, without diabetes, without chronic obstructive pulmonary disease, without atrial fibrillation, at NYHA functional class III or IV, and with effective regurgitant orifice area <0.4 cm^2, but formal interaction testing was negative.

Functional Outcomes

Functional status according to NYHA functional class 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 (ie, lower) among patients treated with TMVR than GDMT at both 1 (*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 versus 59.7% with GDMT alone. These proportions were similar at 2-year follow-up (77.8% versus 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 (ie, none/trace MR) in 93.7%, 89.1%, and 64.3% of patients at discharge, 1-year follow-up, and 2-year follow-up, most patients receiving GDMT alone had MR ≥2+ during

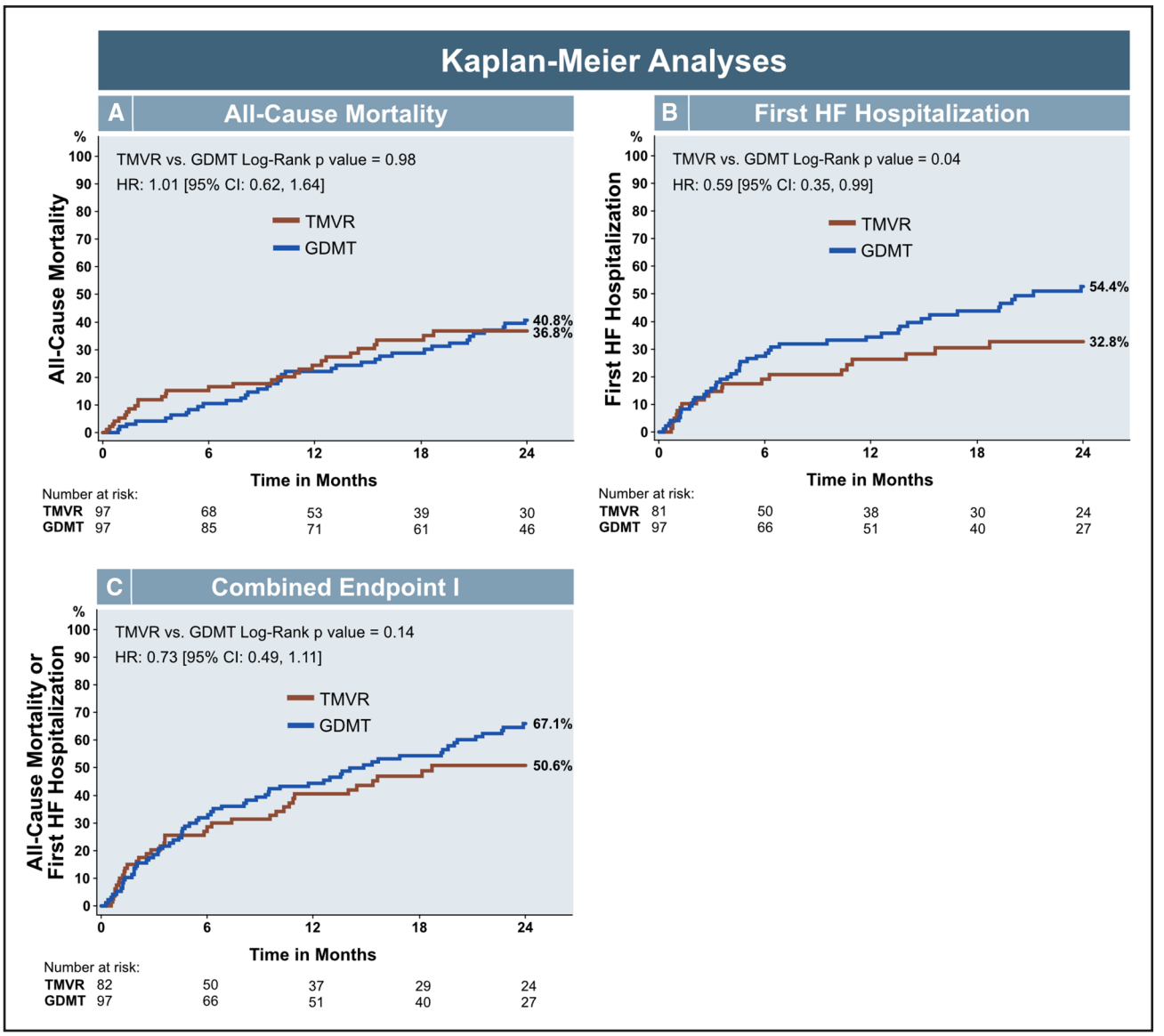

Figure 2. Two-year Kaplan-Meier analyses for study end points in the matched groups.
A, Kaplan-Meier analysis for all-cause mortality. **B**, Kaplan-Meier analysis for heart failure (HF) hospitalization. **C**, Kaplan-Meier analysis for the combined end point of all-cause mortality or HF hospitalization. GDMT indicates guideline-directed medical therapy; HR, hazard ratio; and TMVR, transcatheter mitral valve replacement.

follow-up (93.7%, 93.1%, and 92.2% at discharge, 1 year, and 2 years, respectively).

Echocardiographic end points at discharge, 1-year follow-up, 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 tricuspid regurgitation. Patients undergoing GDMT alone showed greater LV end-diastolic diameter reduction at discharge (1.3±8.4 versus −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 versus −0.2±12.3 mm Hg; P=0.001) and at 2-year follow-up (−16.9±18.1 versus 2.1±15.4 mm Hg; 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 HFHs through 2-year follow-up, although no significant difference in mortality was observed between TMVR and GDMT alone; (3) subgroups

Table 2. Clinical Study End Points in the Matched Groups

Study end points	TMVR (n=97)	GDMT (n=97)	HR (95% CI)	*P* value
Study end points after 1 y				
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 end points after 2 y				
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 end points are given as Kaplan-Meier estimated event rates (n events) or n/total n (%), where applicable. GDMT indicates guideline-directed medical therapy; HFH, heart failure hospitalization; HR, hazard ratio; NYHA, New York Heart Association; and TMVR, transcatheter mitral valve replacement.

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 2 largest single-arm studies of TMVR using the Tendyne (Abbott, Santa Clara, CA) and the Intrepid device (Medtronic, Redwood City, CA) 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[6] demonstrated that the rate of HFH was lower after TMVR compared with the immediate pre-TMVR period. 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 periprocedural complications during TMVR (eg, LV outflow tract obstruction). These findings are in 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 transapical 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 transfemoral 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 postprocedural 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 transapical access. More than 1000 patients have been treated to date with the transapical Tendyne device (Abbott, Santa Clara, CA), which is the only commercially available TMVR system in Europe and the most widely used device in CHOICE-MI.[19] However, several transfemoral/transseptal TMVR systems are currently under clinical investigation, and the TMVR landscape is expected to

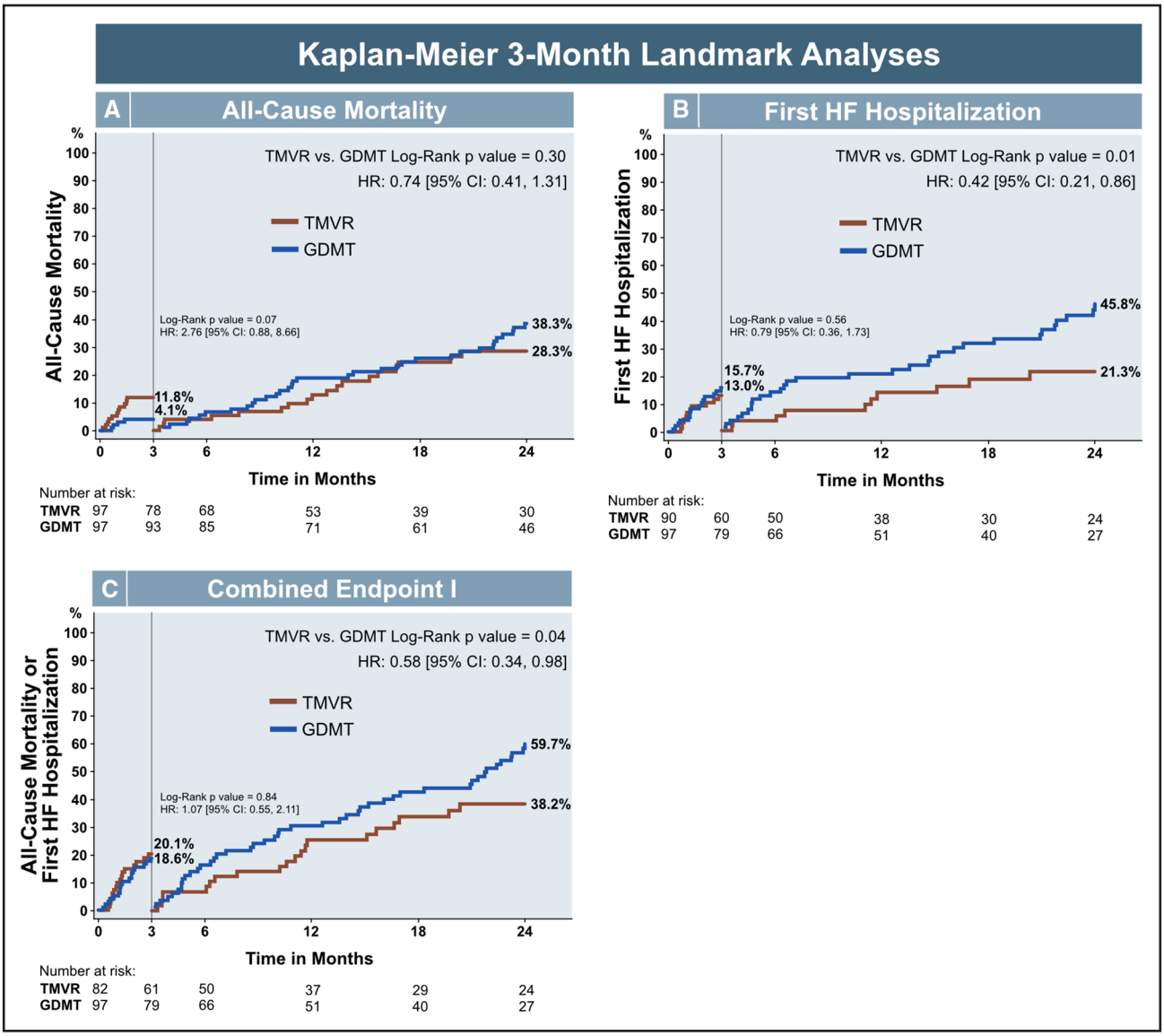

Figure 3. Two-year Kaplan-Meier analyses with landmark analyses after 3 mo for study end points in the matched groups. **A**, Kaplan-Meier analysis with 3-mo landmark analysis for all-cause mortality. **B**, Kaplan-Meier analysis with 3-mo landmark analysis for heart failure (HF) hospitalization. **C**, Kaplan-Meier analysis with 3-mo landmark analysis for the combined end point of all-cause mortality or HF hospitalization. GDMT indicates guideline-directed medical therapy; HR, hazard ratio; and TMVR, transcatheter mitral valve replacement.

transition to a predominance of devices using the transfemoral 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 transfemoral Intrepid device (Medtronic Inc, Redwood City, CA) has demonstrated promising results with low rates of short-term mortality and complications.[12] By reducing periprocedural complications and mortality, the prognostic benefits of TMVR might be further improved. In our study, the number of patients undergoing transfemoral TMVR was too small to determine the potential differences between TA and transfemoral access. Ongoing dedicated studies will demonstrate whether a transition to transfemoral 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 2 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 PS matching, this approach did not account for anatomic differences in valve morphology (which was not available in either data set). 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

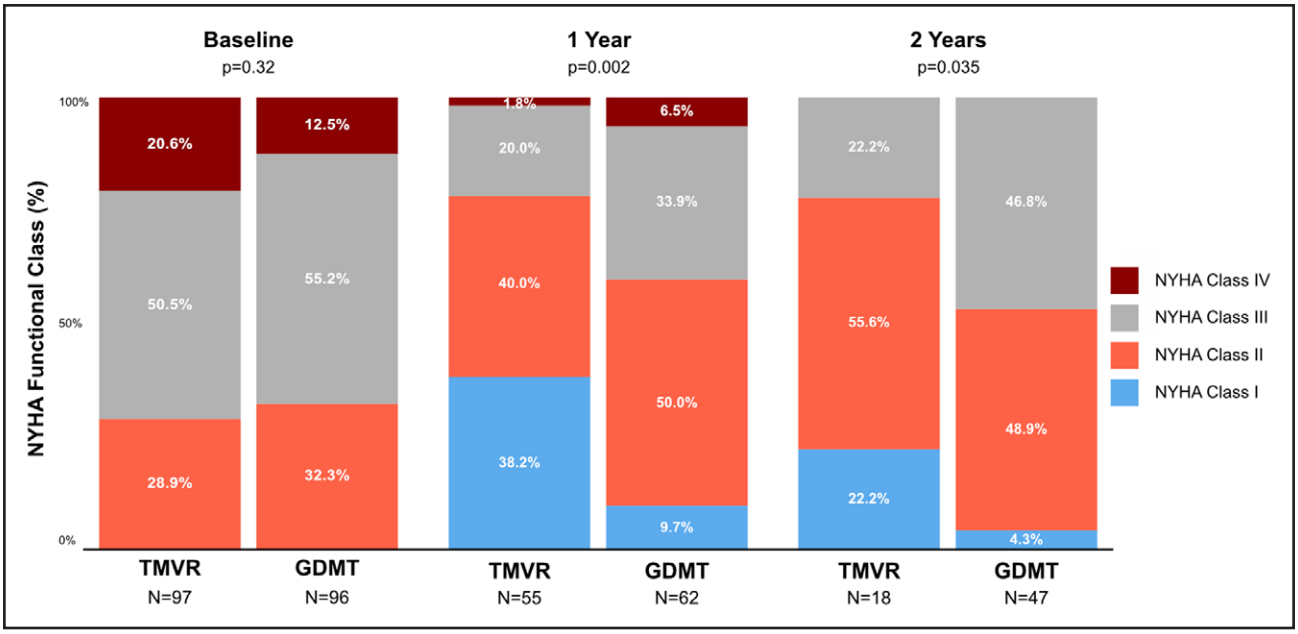

Figure 4. New York Heart Association (NYHA) functional class at baseline, 1-y, and 2-y follow-up after transcatheter mitral valve replacement (TMVR) vs medical therapy in the matched groups.
GDMT indicates guideline-directed medical therapy.

mitral valve anatomy and cardiac structure and function were accounted for in our study. By excluding patients with mixed MR pathogenesis, 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 were 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.

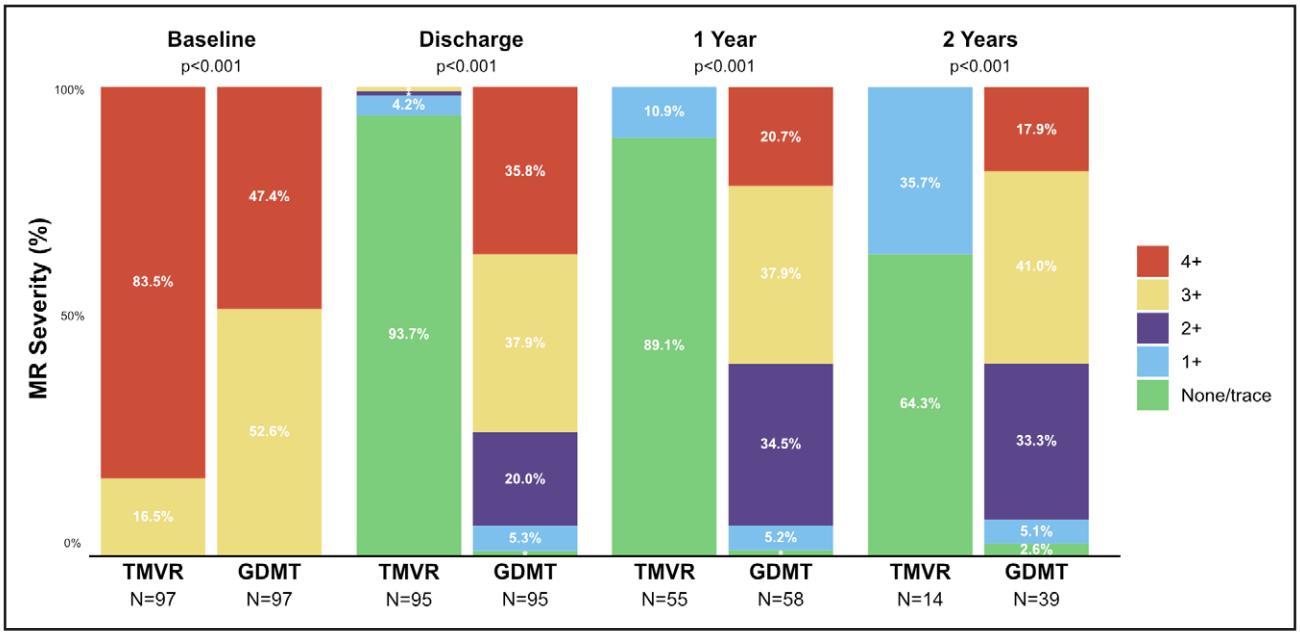

Figure 5. Mitral regurgitation (MR) at baseline, discharge, 1-y, and 2-y follow-up after transcatheter mitral valve replacement (TMVR) vs medical therapy in the matched groups.
*Percentages <2.0%. Discharge: echocardiographic follow-up at 30-d was used for the guideline-directed medical therapy (GDMT) group.

Table 3. Echocardiographic End Points in the Matched Groups

Echocardiography end points	TMVR (n=97)	GDMT (n=97)	Mean difference (95% CI)	*P* value
Echocardiographic end points 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 to 2.6)	0.92
Change in LVEF (baseline to discharge), %	0.9±10.3	0.6±6.9	0.1 (−2.4 to 2.6)	0.92
LVEDD, mm	61.3±8.9	50.7±20.6	10.65 (4.26 to 17.05)	0.001
Change in LVEDD (baseline to discharge), mm	1.3±8.4	−9.1±20.5	10.65 (4.26 to 17.05)	0.001
PASP, mm Hg	37.5±12.5	44.9±15.2	−6.8 (−10.8 to −2.8)	0.001
Change in PASP (baseline to discharge), mm Hg	−6.1±14.9	−0.2±12.3	−6.8 (−10.8 to −2.8)	0.001
TR ≤2+, n/total n (%)	62/64 (96.9)	93/95 (97.9)	…	1.00
Echocardiographic end points at 1 y				
MR ≤2+, n/total n (%)	55/55 (100)	24/58 (41.4)	…	<0.001
MR ≤1+, n/total n (%)	55/55 (100)	4/58 (6.9)	…	<0.001
LVEF, %	33.2±10.3	34.2±10.7	0.5 (−3.1 to 4.1)	0.78
Change in LVEF (baseline to 12 mo), %	−1.7±11.1	−3.1±8.2	0.5 (−3.1 to 4.1)	0.78
LVEDD, mm	60.6±7.4	59.4±6.7	−0.9 (−3.3 to 1.6)	0.48
Change in LVEDD (baseline to 12 mo), mm	−2.3±7.2	−0.5±4.5	−0.9 (−3.3 to 1.6)	0.48
PASP, mm Hg	37.6±10.3	39.9±11.7	−2.9 (−8.1 to 2.4)	0.28
Change in PASP (baseline to 12 mo), mm Hg	−6.2±20.4	−2.7±13.3	−2.9 (−8.1 to 2.4)	0.28
TR ≤2+	35/35 (100)	58/59 (98.3)	…	1.00
Echocardiographic end points at 2 y				
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 to 7.6)	0.87
Change in LVEF (baseline to 24 mo), %	1.2±11.0	−1.1±11.8	−0.7 (−8.9 to 7.6)	0.87
LVEDD, mm	63.6±7.5	58.9±8.4	2.1 (−2.1 to 6.3)	0.32
Change in LVEDD (baseline to 24 mo), mm	0.5±5.6	−1.1±6.2	2.1 (−2.1 to 6.3)	0.32
PASP, mm Hg	30.3±10.1	45.3±16.3	−17.1 (−28.3 to −5.8)	0.004
Change in PASP (baseline to 24 mo), mm Hg	−16.9±18.1	2.1±15.4	−17.1 (−28.3 to −5.8)	0.004
TR ≤2+	13/13 (100)	36/38 (94.7)	…	1.00

GDMT indicates guideline-directed medical therapy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; TMVR, transcatheter mitral valve replacement; and TR, tricuspid regurgitation.

*Echocardiographic follow-up at 30 d was used for the GDMT group. Data are presented as mean±SD or n/total n (%), where applicable.

Conclusions

In the present PS-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.

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Supplemental Material

Figures S1–S5
Tables S1–S5

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