Characteristics and Outcomes of Patients Screened for Transcatheter Mitral Valve Implantation: 1-Year Results from the CHOICE-MI Registry

Short title: The CHOICE-MI Registry: Outcomes after TMVI Screening

Authors (Manuscript)

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Abstract

Aims: Transcatheter mitral valve implantation (TMVI) represents a novel treatment option for patients with mitral regurgitation (MR) unsuitable for established therapies. The CHOICE-MI registry aimed to investigate outcomes of patients undergoing screening for TMVI.

Methods and Results: From 05/2014 to 03/2021, patients with MR considered suboptimal candidates for transcatheter edge-to-edge repair (TEER) and at high risk for mitral valve surgery underwent TMVI screening at 26 centres. Characteristics and outcomes were investigated for patients undergoing TMVI and for TMVI-ineligible patients referred to bailout-TEER, high-risk surgery or medical therapy (MT). The primary composite endpoint was all-cause mortality or heart failure hospitalisation after 1 year.

Among 746 patients included (78.5 years [IQR 72.0-83.0], EuroSCORE II 4.7% [IQR 2.7-9.7]), 229 patients (30.7%) underwent TMVI with ten different dedicated devices. At 1 year, residual MR ≤1+ was present in 95.2% and the primary endpoint occurred in 39.2% of patients treated with TMVI. In TMVI-ineligible patients (N=517, 69.3%), rates of residual MR ≤1+ were 37.2%, 100.0% and 2.4% after bailout-TEER, high-risk surgery and MT, respectively. The primary endpoint at 1 year occurred in 28.8% of patients referred to bailout-TEER, in 42.9% of patients undergoing high-risk surgery and in 47.9% of patients remaining on MT.

Conclusion: This registry included the largest number of patients treated with TMVI to date. TMVI with ten dedicated devices resulted in predictable MR elimination and

sustained functional improvement at 1 year. In TMVI-ineligible patients, bailout-TEER and high-risk surgery represented reasonable alternatives, while MT was associated with poor clinical and functional outcomes.

Key words: mitral regurgitation, transcatheter mitral valve implantation, transcatheter edge-to-edge repair, mitral valve surgery, medical therapy.

Abbreviations

CT	computed tomography
MAC	mitral annulus calcification
MR	mitral regurgitation
MT	medical therapy
MV	mitral valve
NYHA	New York Heart Association
PMR	primary mitral regurgitation
SMR	secondary mitral regurgitation
TEER	transcatheter edge-to-edge repair
TMVI	transcatheter mitral valve implantation

Introduction

Current guidelines for the management of valvular heart disease support the use of mitral valve (MV) surgery or mitral transcatheter edge-to-edge repair (TEER) as standard therapies for severe mitral regurgitation (MR).[1,2] However, approximately one half of all patients with severe MR are not referred to surgery, either due to frailty, multiple comorbidities, or prohibitive surgical risk.[3,4] Mortality in untreated patients reaches 50% at 5 years, and up to 90% of surviving patients require hospitalisation for congestive heart failure (HF) within the first 5 years after diagnosis of MR.[3,4] TEER is recommended in patients with severe primary MR (PMR), who are deemed at high or prohibitive surgical risk, and in selected patients with secondary MR (SMR) on optimal guideline-directed medical therapy regardless of surgical risk.[1,2] But despite a favourable safety profile and improving efficacies of TEER, some patients remain unsuitable or suboptimal candidates. Moreover, residual or recurrent MR after TEER is associated with adverse outcome.[5–7] Consequently, a considerable portion of patients with severe MR remains unsuitable for established MR therapies.[8]

Transcatheter mitral valve implantation (TMVI) has demonstrated favourable short- and mid-term outcomes yielding predictable MR elimination and persisting functional improvement with different dedicated devices.[9–12] This novel therapy may represent a potential therapeutic alternative for these patients. However, TMVI faces anatomical challenges currently limiting its widespread adoption.[13,14]

Given the wide spectrum of available therapies for patients with MR, there is an urgent need for a more refined selection process on different treatment strategies for these patients. Moreover, the role of TMVI among established MR therapies has not yet been clearly

defined. The primary aim of the *CHoice of OptImal transCatheter trEatment for Mitral Insufficiency Registry* (CHOICE-MI) registry was to investigate characteristics and outcomes of patients with MR considered unsuitable candidates for established MR therapies, who subsequently underwent screening for TMVI.

Methods

Study design

The CHOICE-MI registry is an investigator-initiated, multicentre, international study evaluating outcomes of MR patients considered unsuitable for established therapies undergoing screening for TMVI. This retrospective study (ClinicalTrials.gov Identifier: NCT04688190) enrolled patients from 26 centres worldwide screened for TMVI from 05/2014 to 03/2021. Baseline clinical, echocardiographic, and computed tomography (CT) characteristics as well as TMVI screening data were collected for all patients. Clinical and echocardiographic results at discharge, 30 days and 1 year were determined and adjudicated separately by each participating centre according to current guidelines. Anonymized data were centrally collected for analysis. All data collection and analyses were performed with the approval of the ethics committees of the respective academic centres, informed consent has been obtained from the patients and the investigation conforms with the principles outlined in the *Declaration of Helsinki*. The data underlying this article will be shared on reasonable request to the corresponding author.

Study population

This study included patients with symptomatic MR ≥2+ that were considered unsuitable for established therapies (i.e., at high at high or prohibitive surgical risk and with suboptimal anatomy for TEER) and underwent TMVI evaluation. Patients with isolated MS or MR <2+ at baseline (N=21) were excluded from this analysis (**Figure 1**).

Patients who underwent TMVI were treated with ten different TMVI devices with transapical or transseptal approach (see **Supplementary Methods** for a list of implanted

devices). Patients received TMVI within compassionate-use programs, clinical trials or as commercial use. Patient suitability for TMVI was adjudicated by multidisciplinary local Heart Teams depending on local and/or clinical trial protocols.

Patients considered TMVI-ineligible were treated based on local institutional protocols and after discussion in the local interdisciplinary Heart Teams by either bailout-TEER with either the MitraClip (Abbott Structural Heart, Santa Clara, CA) or the PASCAL system (Edwards Lifesciences LLC, Irvine, CA), high-risk surgery (MV repair or replacement) or continued medical therapy (MT).

Study endpoints and definitions

The primary study endpoint was a composite endpoint of all-cause mortality or heart failure (HF) hospitalisation at 1 year. Secondary study endpoints were all-cause and cardiovascular (CV) mortality at 1 year, residual MR on transthoracic echocardiography and New York Heart Association (NYHA) functional Class, at discharge and after 1 year. CV mortality was defined as mortality attributable to myocardial ischemia and infarction, HF, cardiac arrest or cerebrovascular accident. HF hospitalisation was defined as new-onset or worsening signs and symptoms of heart failure that required urgent therapy and resulted in hospitalisation. Technical success, procedural success and in-hospital complication rates were reported according to the Mitral Valve Academic Research Consortium (MVARC) criteria.[15] MR elimination was defined as residual MR <1+.

Follow-up

The median follow-up duration was 13.4 months (IQR 12.0-15.3) for the overall study population, and 23.2 months (IQR 18.4-25.3), 11.5 months (IQR 9.2-14.2), 7.1 months (IQR 5.7-16.7) and 9.9 months (IQR 8.4-13.7) for the subgroups of TMVI, bailout-TEER, high-risk surgery and MT, respectively.

Statistical analyses

Continuous variables were reported as means with standard deviations or median with interquartile range (IQR, 25th to 75th percentile) depending on distribution of data, while categorical variables were reported as proportions. The paired Mann-Whitney U-test was used to test for differences between time points. Time to event endpoints were assessed using Kaplan-Meier analysis. Kaplan-Meier analysis using the landmark analysis approach with a post-TMVI window of 30 days as T0 was performed. Cox regression for the primary composite endpoint at 1 year was performed applying nested adjustment models for the impact of residual MR ≥1+ and ≥2+. Forest plots display the respective Hazard Ratio (HR) and 95%-confidence interval (CI) of residual MR ≥1+ and ≥2+ after adjustment for age, sex, chronic kidney disease, chronic obstructive pulmonary disease, left ventricular ejection fraction (LVEF). A two-sided $p<0.05$ was considered statistically significant and all statistical analyses were performed using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 746 patients met the inclusion criteria and were included into this analysis. Two hundred twenty-nine patients were considered TMVI-eligible. Anatomical ineligibility was the most common reason for screening failure among 517 (69.3%) patients considered TMVI-ineligible. Specific reasons for TMVI screening failure are demonstrated in **Supplementary Figure 1A**. Compared to all patients screen-failing TMVI, annular dimensions outside the TMVI treatment range and prohibitive leaflet morphology were more present in patients referred to bailout-TEER, while mitral annulus calcification (MAC) was less frequent in these patients (**Supplementary Figure 1B**).

TMVI-eligible patients

Baseline characteristics for all subgroups are summarized in **Table 1**. Patients eligible for TMVI (N=229, 30.7%) (76.0 years [IQR 71.0-81.0], 36.7% female) presented with high rates of cardiac as well as non-cardiac comorbidities resulting in elevated surgical risk (EuroSCORE II 6.3% [IQR 3.6, 13.2]). History of myocardial infarction was found in 43.0% (N=95) of patients. Regarding prior cardiac surgery, 35.8% (N=82) previously underwent coronary artery bypass graft surgery and 10.0% (N=22) had surgical aortic valve replacement. The predominant MR aetiology among TMVI-eligible patients was SMR (58.4%, N=128), while only a minority was diagnosed with PMR (28.8%, N= 63). Echocardiographically, patients were characterised by dilated left ventricles (LV end-diastolic volume [LVEDV] 153.4 mL [IQR 116.5-198.0]), reduced LVEF (40.0% [IQR

35.0-54.0]) and a high rate of tricuspid regurgitation ≥2+ (50.7%, N=111). Moderate or severe MAC, as diagnosed by CT, was present in 27 patients (13.0%).

TMVI-ineligible patients

A total of 216 TMVI-ineligible patients (29.0%) (79.0 years [IQR 73.0-83.0], 42.6% female, EuroSCORE II 4.2% [IQR 2.5-7.7]) were referred to bailout-TEER. The majority of these patients were diagnosed with PMR (47.6%, N=98) and presented with preserved LVEF (55.8% [IQR 40.1-61.9]). Among TMVI-ineligible patients, this subgroup had lowest transvalvular gradients (2.1 mmHg [IQR 1.7-3.6]) and largest LV dimensions (LVEDV 118.2 mL [IQR 90.4-159.4]). The rate of moderate to severe MAC was low (15.3%, N=27) in patients referred to bailout-TEER.

Only few TMVI-ineligible patients (N=61, 8.2%) (77.0 years [IQR 68.7-82.0], 54.1% female) underwent high-risk surgery. Among all patients screened for TMVI, this subgroup was characterised by the lowest rates of comorbidities as well as lowest estimated surgical risk (EuroSCORE II 2.9% [IQR 2.0-5.7]. Thirteen (21.3%) and 7 patients (13.0%) underwent redo cardiac surgery after coronary artery bypass graft surgery or surgical aortic valve replacement, respectively. The vast majority of patients referred to high-risk surgery was diagnosed with PMR (71.7%, N=38), preserved LVEF (59.5% [IQR 50.0-62.7]) and non-dilated LV dimensions (LVEDV 98.8 mL [IQR 78.2-121.0]. Patients undergoing high-risk surgery had the highest rate of moderate to severe MAC (34.7%, N=17) among patients screened for TMVI.

The majority of patients undergoing TMVI screening was declined for both transcatheter and surgical intervention (32.2%, N= 240) consecutively remaining on MT. Median age of

these patients was 80.0 years (IQR 74.0-83.0) and 55.0% (N=132) were female. High rates of concomitant comorbidities resulted in highest estimated surgical risk among TMVI-ineligible patients (EuroSCORE II 4.4% [IQR 2.6-9.4]). PMR was the predominant MR aetiology of patients continuing on MT (58.1%, N=137). Patients in this subgroup presented with highest transvalvular gradients (4.0 mmHg [IQR 2.1-6.0] on echocardiography and a high rate of moderate to severe MAC (33.6%, N=73) on CT.

In-hospital and 1-year outcomes

Outcomes after TMVI

TMVI procedures were performed via transapical or transseptal approach in 89.5% and 10.5% of patients, respectively, yielding high technical success (95.2%) and low procedural mortality (1.8%). Prothesis malposition, left ventricular outflow tract (LVOT) obstruction, and device migration were reported in 8 (3.7%), 7 (3.2%) and 5 (2.3%) patients treated with TMVI, respectively. Conversion to open-heart surgery was necessary in 6 (2.8%) patients. Access site complications and reinterventions for bleeding according to the MVARC criteria occurred in 21 (9.6%) and 12 (7.5%) patients, respectively. At 30-day follow-up, 22 patients had died, the majority from cardiovascular causes (N=19, **Table 2**). At discharge, MR severity was ≤1+ in 95.1% of patients in the TMVI group. Complete MR elimination was achieved in 83.9% of patients. At 1-year follow-up after TMVI, MR ≤1+ was found in 95.2% of patients, while MR remained eliminated in 72.2% of patients (**Figure 2**). Comparable results with TMVI were achieved in the subgroup of patients with moderate or severe MAC (N=27). **Supplementary Figure 2** shows MR severity at baseline, discharge and at 1 year for these patients.

NYHA functional class after TMVI improved significantly with 72.6% and 82.7% of followed-up patients in NYHA functional class I or II at discharge and at 1 year, respectively (both <0.001 compared to 14.4% at baseline, **Supplementary Figure 3**).

According to Kaplan-Meier analysis, the primary combined endpoint of all-cause mortality or HF hospitalisation at 1 year occurred in 39.2% of the TMVI group. In a 30-day landmark analysis for the primary endpoint excluding all events occurring within 30 days after TMVI, this rate decreased to 32.1% at 1 year (**Figure 3**). The secondary endpoints of all-cause and CV mortality after 1 year occurred in 28.2% and 19.3% of patients undergoing TMVI, respectively (**Supplementary Figure 4**). Kaplan-Meier estimated outcomes according to transapical or transseptal access route are demonstrated in **Figure 4** showing numerically, yet not statistically, lower rates of the primary combined endpoint (transapical 41.3% vs. transseptal 26.8%, p=0.22) as well as all-cause mortality (transapical 29.6% vs. transseptal 17.3%, p=0.23) after 1 year for patients treated with transseptal compared to transapical TMVI. Baseline characteristics and procedural data according to transapical or transseptal TMVI are given in **Supplementary Table 1**.

Outcomes after bailout-TEER

In TMVI-ineligible patients undergoing bailout-TEER, technical success was achieved in 164 patients (86.3%) and no procedural mortality was reported. Post-procedural complication rates were overall low with access site complications or reinterventions for bleeding in 7 patients (3.4%) and 1 patient (0.7%), respectively. At 30-days after bailout-TEER, a total of 9 patients had died (CV death: N=6) (**Table 2**).

At discharge and after 1 year, the rates of residual MR ≤1+ were 45.3% and 37.2%, respectively (**Figure 2**). Functional improvement was present both at discharge and 1 year after bailout-TEER (**Supplementary Figure 3**). The primary composite endpoint occurred in 28.8% of patients within 1 year after bailout-TEER (**Figure 5**). Kaplan-Meier analyses for all-cause and CV mortality in TMVI-ineligible patients are given in **Supplementary Figure 5**.

Outcomes after high-risk surgery

The majority of TMVI-ineligible patients referred to high-risk surgery underwent MV replacement (63.0%, N=34), while twenty patients (37.0%) were treated with MV repair. Technical success was reported for 50 patients (98.0%) with procedural mortality in 1 patient (2.0%). Overall postprocedural and 30-day complication rates were low with the highest rate reported for acute renal failure (11.1%, N=5). After 30 days a total of 5 patients had died (CV death: N=4).

Residual MR at discharge was ≤1+ in the majority of patients undergoing high-risk surgery (97.8%), of whom MR was completely eliminated in 62.2%. Rates of MR elimination at discharge were numerically higher after surgical MV replacement (72.0%) compared to MV repair (52.6%). In patients followed-up after 1 year, residual MR was ≤1+ in all patients (**Figure 2**). In patients undergoing high-risk surgery, the primary endpoint occurred in 42.9% after 1 year (**Figure 5**).

Outcomes under medical therapy

The rate of residual MR ≤1+ in patients remaining on MT and receiving follow-up echocardiography was 14.8% at discharge and 2.4% at 1 year. The majority of patients on MT remained at MR ≥3+ (baseline: 93.3%, discharge: 72.2%, 1 year: 87.8%) (**Figure 2**). Compared to baseline NYHA functional class, medically managed patients with available clinical follow-up showed significant functional improvement at discharge, but not after 1 year (**Supplementary Figure 3**). The primary endpoint after 1 year occurred in 47.9% of patients remaining on MT (**Figure 5**).

Prognostic impact of residual MR

The impact of residual MR ≥1+ and ≥2+ on the primary composite endpoint was evaluated by using multivariable adjustment for the groups of TMVI and bailout-TEER (**Supplementary Figure 6**). While residual MR ≥1+ did not predict outcome in patients undergoing TMVI or bailout-TEER, residual MR ≥2+ was an independent predictor of the primary endpoint after 1 year both in patients undergoing TMVI (HR 2.86 [95%-CI 1.04, 7.86], p=0.042) and bailout-TEER (HR 2.38 [1.11, 5.10], p=0.026).

Discussion

The global, multicentre CHOICE-MI registry investigated characteristics and outcomes of MR patients considered unsuitable for established MR therapies undergoing TMVI screening. Among a total of 746 included patients, this study comprises the so far largest cohort of patients treated with TMVI (N=229) involving ten different TMVI devices. These are the main findings regarding the different treatment strategies following TMVI screening success or failure:

1. Patients undergoing TMVI with ten different dedicated devices showed high rates of comorbidities and elevated surgical risk. These patients were mostly treated for SMR, had dilated LV dimensions and reduced LVEF. Few patients underwent TMVI for moderate to severe MAC. TMVI was associated with high technical success, predictable MR elimination and functional improvement in the majority of patients. Event rates at 1 year were numerically lower with transseptal compared to transapical TMVI.

2. A considerable portion of TMVI-ineligible patients was referred to bailout-TEER despite anatomies initially considered unfavourable for a TEER procedure. The predominant MR aetiology of these patients was PMR. Most patients presented with preserved LVEF, low transvalvular gradients and a low rate of MAC. Although these patients showed elevated rates of significant residual MR (residual MR ≥2+ 54.7% at discharge), bailout-TEER yielded functional improvement and satisfactory clinical outcomes.

3. Only few TMVI-ineligible patients were referred to high-risk surgery. The vast majority of these patients was treated for PMR, with preserved LVEF and a high rate of MAC. In eligible patients, high-risk surgery was associated with acceptable echocardiographic, functional and clinical outcomes.

4. The majority of TMVI-ineligible patients remained unsuitable for any MV intervention and continued on MT. These patients are characterised by high surgical risk, high rates of comorbidities, predominantly PMR with high transvalvular gradients and a high prevalence of MAC. Outcomes of these medically managed patients were poor.

5. While residual MR ≥1+ was not associated with outcome, residual MR ≥2+ was an independent predictor of the primary composite endpoint for patients undergoing TMVI and bailout-TEER.

Transcatheter Mitral Valve Implantation

The role that TMVI will take among all available treatment options for severe MR is yet to be defined. The present study adds valuable real-world data that may contribute to a more precise definition of advantages and disadvantages of this novel transcatheter therapy. In accordance with published data, MR elimination was achieved in almost all surviving patients with the high rates of NYHA functional class I/II at follow-up.[12,16] Thus, effective, predictable and durable elimination of MR, irrespective of the underlying MV pathology, together with significant symptom relief may be considered the central benefit

from TMVI therapy. This includes the challenging subgroup of patients with moderate or severe MAC showing similar echocardiographic results in this study. However, 1-year mortality was the elevated in the TMVI group (28.2% 1-year all-cause mortality, 19.3% 1-year CV mortality), which may be partly explained by patients' high-risk profiles with highest estimated surgical risk in the TMVI group. The use of novel systems and devices in compassionate-use programs or early feasibility studies may also have triggered higher mortality rates. Moreover, most patients were treated via large-bore delivery sheaths and transapical access (89.5%) partially accounting for elevated 30-day mortality rates. Prospectively, the transition of TMVI to completely transseptal procedures and an improved selection process might reduce procedural risk and improve short- and mid-term outcomes. In fact, most device manufacturers are currently focusing on developing transseptal devices for TMVI and preliminary results with dedicated devices are promising.[11,17,18] While 1-year event rates in patients treated via transseptal access in the present study were numerically, yet not statistically, lower compared to those treated transapically, further studies are warranted comparing both access routes. In summary, TMVI may potentially become a complementary alternative to TEER in anatomically suitable patients, especially those in whom effective MR reduction (<2+ MR) may not be possible with TEER. Regarding the subset of patients with MAC, TMVI with dedicated mitral valve devices might represent a feasible alternative to valve-in-MAC with balloon-expandable transcatheter heart valves.[19,20] The long-term impact of complete MR elimination by TMVI on functional outcome and survival will require further investigation with longer follow-up.

Bailout-Transcatheter Edge-to-edge Repair

Although patients included in the present registry were initially considered suboptimal candidates for TEER, a considerable portion of TMVI-ineligible patients subsequently underwent bailout-TEER. Patients referred to bailout-TEER were characterised by PMR aetiology with low transvalvular gradients and a low prevalence of MAC. Despite technical success reported in <90% of bailout-TEER procedures, the rate of all-cause mortality or HF hospitalisation after 1 year was low and patients experienced significant functional improvement at 1 year. Nevertheless, residual MR at discharge remained ≥2+ in over half of the patients (54.7%). In contrast to recent data from the Global EXPAND study of MR patients treated with a next generation device (predominantly primary MR, residual MR ≥2+: 10.8% at 1 year), our findings further strengthen the fact that these patients in our study were indeed suboptimal candidates for TEER.[21] Although reasons for TEER ineligibility were not investigated in the present study, it may be assumed that suboptimal leaflet morphology (e.g., significant leaflet tethering, short and/or calcified posterior MV leaflet, leaflet clefts or indentations) was present in a significant portion of patients resulting in an elevated rate of significant residual MR and implying reliability of the screening for TEER-eligibility at the individual centres. However, given the low 30-day and 1-year-mortality for TEER even in the presence of presumably unfavourable MV anatomy for the procedure, bailout-TEER can be considered a safe and feasible alternative therapy among selected patients ineligible for TMVI.

High-risk Surgery

Surgical intervention, whether repair or replacement, remains a cornerstone for treatment of patients with severe MR, particularly in patients with PMR.[1,22] As expected, since the present study population consists of patients considered at high or prohibitive surgical risk, only few patients with predominantly PMR underwent high-risk MV surgery after TMVI screening failure. These patients were characterised by the highest prevalence of MAC, though as expected had fewer comorbidities and lower estimated surgical risk compared to other subgroups. The majority of patients underwent surgical MV replacement (63.0%), suggesting suboptimal anatomy for surgical repair. However, MR was effectively reduced to ≤1+ in almost all patients and NYHA functional class improved significantly. Elevated event rates after high-risk surgery at 1 year might be partially explained by the procedural impact of cardiac surgery via a more traumatic sternotomy approach chosen in the majority of patients (81.8%) in an overall elderly and comorbid patient population with high rates of prior cardiac surgery. However, the high rate of the composite endpoint was mainly driven by HF hospitalisations, while estimated all-cause mortality after 1 year remained low (9.4%). Although the present study lacks sufficient follow-up of surgically treated patients limiting any drawn conclusions, our results support the inclusion of MV surgery as part of a multidisciplinary approach to manage MV disease even in surgical high-risk patients.

Medical Therapy

Patients who were continued on MT represent the largest subgroup among all TMVI-ineligible patients, and in fact among all patients unsuitable for established MR therapies included in this study. The poor outcomes of these patients have been reported previously

and are confirmed by the present study.[23,24] Yet, they represent an important group with unmet clinical need, given they are not suitable candidates for any MV intervention. These patients had high rates of MAC, highest transvalvular pressure gradients and smallest annular diameters as measured by CT. While guideline-directed MT is strongly recommended for patients with SMR and impaired LV function, the majority of patients on MT in this study suffered from PMR and had preserved systolic LV function.[1,25] Due to the degenerative aetiology of MR in most of these patients, the benefit of guideline-directed MT is limited since it fails to address the underlying pathology. Consequently, MR severity or NYHA functional class did not improve during follow-up. Driven particularly by a high rate of HF hospitalisations, almost 50% of the patients in the MT group either died or were re-admitted to hospital for congestive HF within 1 year after screening. Future innovations and transcatheter solutions should focus on expanding therapeutical alternatives to this subset of MR patients ineligible for any MV intervention.

Study Limitations

Several limitations need to be addressed regarding this study. First, the retrospective nature of this study has inherent biases, including time bias as different TMVI devices and generations were included. Therefore, all drawn conclusions can only be hypothesis-generating. Second, the ineligibility of patients for TEER resulting in subsequent treatment with TMVI, bailout-TEER, MV surgery or MT was assessed independently by the local Heart Teams, which might have introduced patient selection biases. Third, echocardiographic results were not core laboratory adjudicated. Fourth, follow-up of patients was incomplete (especially in the high-risk surgery and MT subgroups) limiting

conclusions particularly regarding echocardiographic and functional outcomes. Fifth, information on the implementation of guideline-directed MT was not available. Prospective randomized trials are certainly warranted to define the individual role of each therapy within the spectrum of treatment options for MR, such as the SUMMIT trial (NCT03433274) randomizing between TMVI and TEER in eligible patients.

Conclusions

This registry of patients undergoing TMVI screening included the so far largest cohort of patients treated with TMVI. TMVI with ten different dedicated devices offered high procedural success and predictable elimination of MR, accompanied with sustained functional improvement after 1 year. However, TMVI screening failure was common and usually occurred due to anatomical ineligibility. Despite suboptimal anatomy, bailout-TEER remains a valid treatment option in TMVI-ineligible patients, and was associated with low rates of mortality and HF hospitalisation at 1 year in this study. Although feasible in only few patients, high-risk surgery represents a reasonable option in operable candidates. MT alone was associated with poor outcomes, mostly in patients with PMR and MAC, further emphasizing the unmet need for adequate therapeutic alternatives in a considerable portion of patients with MR.

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Conflicts of interest

WBA received research grants from Medtronic and Edwards Lifesciences. SL was supported by a grant from the German Heart Foundation (DHS) and received travel compensation by Edwards Lifesciences. AD is a consultant for and has and received honoraria from Abbott Laboratories, Edward Lifesciences and Medtronic. GHLT is a physician proctor and consultant for Medtronic, consultant and TAVR physician advisory board member for Abbott Structural Heart, consultant for NeoChord and advisory board member for JenaValve. LC is advisory board member for Abbott, Medtronic and BostonScientific and has received personal fees from Edwards Lifesciences. The remaining authors have declared no conflicts of interest with regard to this manuscript.

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Legends

Figure legends

Graphical Abstract: Results from the global CHOICE-MI Registry

Abbreviations:

CHOICE-MI = *CHoice of OptImal transCatheter trEatment for Mitral Insufficiency Registry*, HF = heart failure, MAC = mitral annulus calcification, MR = mitral regurgitation, MVPG = mitral valve pressure gradient, TEER = transcatheter edge-to-edge repair

Figure 1: **Study flow chart**

Abbreviations:

CHOICE-MI = *CHoice of OptImal transCatheter trEatment for Mitral Insufficiency Registry*, MR = mitral regurgitation, TEER = transcatheter edge-to-edge repair, TMVI = transcatheter mitral valve implantation

Figure 2: **Echocardiographic outcome**

Mitral regurgitation (MR) at baseline and residual MR at discharge and after 1 year (p-values are given for comparisons between baseline and discharge or baseline and 1 year). Frequencies smaller 2 % are indicated by *.

Abbreviations:

MR = mitral regurgitation, TEER = transcatheter edge-to-edge repair, TMVI = transcatheter mitral valve implantation

Figure 3: **Kaplan-Meier analysis and 30-day landmark analysis for the primary endpoint at 1 year after Transcatheter Mitral Valve Implantation (TMVI)**

Abbreviations:

HF = heart failure

Figure 4: **Kaplan-Meier analyses according to transapical (TA-TMVI) or transseptal (TS-TMVI) device delivery in patients treated with TMVI for the primary endpoint and all-cause mortality at 1 year**

Abbreviations:

HF = heart failure

TA = transapical

TMVI = transcatheter mitral valve implantation

TS = transseptal

Figure 5: **Kaplan-Meier analyses for the primary endpoint at 1 year in TMVI-ineligible patients undergoing bailout-TEER, high-risk surgery or medical therapy**

Abbreviations:

HF = heart failure, TEER = transcatheter edge-to-edge repair, TMVI = transcatheter mitral valve implantation

Tables

Table 1: **Baseline characteristics**

	All patients (N=746)	TMVI (N=229)	Bailout-TEER (N=216)	High-Risk Surgery (N=61)	MT (N=240)	p-value
Clinical Baseline Parameters						
Age (years)	78.5 (72.0, 83.0)	76.0 (71.0, 81.0)	79.0 (74.0, 83.0)	77.0 (68.7, 82.0)	80.0 (74.0, 83.0)	<0.001
Female gender	341 (45.7)	84 (36.7)	92 (42.6)	33 (54.1)	132 (55.0)	<0.001
EuroSCORE II (%)	4.7 (2.7, 9.7)	6.3 (3.6, 13.2)	4.2 (2.5, 7.7)	2.9 (2.0, 5.7)	4.4 (2.6, 9.4)	<0.001
STS PROM (%)	5.0 (2.9, 7.8)	5.7 (3.2, 8.6)	4.1 (3.0, 6.7)	3.7 (2.1, 5.8)	5.2 (2.8, 8.1)	0.002
NYHA class III	479 (64.6)	142 (62.0)	143 (66.5)	44 (73.3)	150 (63.3)	0.36
NYHA class IV	133 (17.9)	54 (23.6)	44 (20.5)	4 (6.7)	31 (13.1)	0.002
Arterial hypertension	550 (74.6)	160 (72.4)	159 (73.6)	42 (68.9)	189 (79.1)	0.23
Diabetes	173 (23.3)	57 (24.9)	35 (16.2)	11 (18.0)	70 (29.5)	0.006
COPD	133 (17.9)	41 (17.9)	41 (19.0)	6 (9.8)	45 (19.1)	0.38

Prior stroke	87 (12.0)	30 (13.1)	26 (12.5)	4 (7.4)	27 (11.4)	0.69
Extracardiac Arteropathy	140 (19.3)	47 (20.5)	40 (19.2)	6 (11.1)	47 (20.0)	0.45
Prior myocardial infarction	192 (26.7)	95 (43.0)	38 (18.3)	9 (16.7)	50 (21.2)	<0.001
Prior CABG	188 (25.2)	82 (35.8)	44 (20.4)	13 (21.3)	49 (20.5)	<0.001
Prior SAVR	67 (9.3)	22 (10.0)	14 (6.7)	7 (13.0)	24 (10.1)	0.43
Prior TAVI	74 (10.6)	19 (8.6)	15 (8.0)	3 (5.7)	37 (15.7)	0.018
Chronic kidney disease	339 (49.1)	119 (55.3)	94 (45.4)	15 (29.4)	111 (51.2)	0.005
Dialysis	24 (3.3)	9 (4.1)	4 (1.9)	1 (1.9)	10 (4.2)	0.45
Baseline Echocardiography						
Primary MR	336 (47.1)	63 (28.8)	98 (47.6)	38 (71.7)	137 (58.1)	<0.001
Secondary MR	294 (41.2)	128 (58.4)	83 (40.3)	8 (15.1)	75 (31.8)	<0.001

Mixed primary /secondary MR	84 (11.8)	28 (12.8)	25 (12.1)	7 (13.2)	24 (10.2)	0.82
MR 2+	24 (3.2)	3 (1.3)	1 (0.5)	4 (7.0)	16 (6.7)	<0.001
MR 3+	243 (32.7)	54 (23.6)	88 (40.7)	16 (28.1)	85 (35.4)	<0.001
MR 4+	475 (64.0)	172 (75.1)	127 (58.8)	37 (64.9)	139 (57.9)	<0.001
EROA (cm^2)	0.35 (0.23, 0.47)	0.35 (0.23, 0.45)	0.34 (0.26, 0.44)	0.35 (0.25, 0.47)	0.35 (0.23, 0.50)	0.96
Mean gradient (mmHg)	3.0 (2.0, 4.5)	3.0 (2.0, 4.0)	2.1 (1.7, 3.6)	3.5 (2.0, 7.0)	4.0 (2.1, 6.0)	<0.001
LVEF (%)	50.0 (38.1, 60.0)	40.0 (35.0, 54.0)	55.8 (40.1, 61.9)	59.5 (50.0, 62.7)	55.0 (40.1, 60.0)	<0.001
LVEF <30%	47 (6.5)	18 (8.2)	13 (6.1)	1 (1.7)	15 (6.4)	0.33
LVESV (mL)	63.9 (41.2, 102.0)	88.0 (55.2, 121.8)	54.0 (36.9, 78.7)	34.2 (27.8, 50.0)	71.6 (40.0, 104.6)	<0.001
LVEDV (mL)	134.0 (97.6, 175.5)	153.4 (116.5, 198.0)	118.2 (90.4, 159.4)	98.8 (78.2, 121.0)	134.6 (89.2, 173.8)	<0.001
LVESD (mm)	40.0 (33.0, 50.0)	45.5 (40.0, 54.0)	38.0 (32.0, 46.3)	37.5 (30.0, 44.6)	36.0 (32.0, 47.0)	<0.001

LVEDD (mm)	56.0 (49.0, 63.0)	59.5 (53.0, 65.0)	54.0 (49.0, 61.0)	55.0 (47.7, 65.0)	53.0 (47.0, 60.0)	<0.001
Tricuspid regurgitation ≥2+	360 (50.1)	111 (50.7)	111 (53.4)	28 (51.9)	110 (46.4)	0.52
PASP (mmHg)	49.0 (38.0, 60.0)	50.0 (40.0, 59.0)	45.0 (34.7, 59.3)	47.5 (39.4, 57.6)	50.0 (39.9, 60.0)	0.12
TAPSE (mm)	17.0 (14.0, 20.0)	15.0 (12.0, 19.0)	18.0 (14.0, 21.0)	18.0 (15.0, 21.6)	18.0 (15.0, 21.0)	<0.001
Baseline Computed Tomography						
Annulus perimeter (mm)	126.0 (113.3, 139.3)	125.5 (117.3, 132.1)	136.1 (125.5, 150.0)	117.6 (98.2, 146.6)	115.0 (102.8, 128.0)	<0.001
Annulus area (cm^2)	12.1 (10.0, 14.5)	11.8 (10.3, 13.0)	13.6 (11.5, 16.3)	12.0 (8.1, 16.3)	10.5 (8.4, 13.4)	<0.001
SL Diameter (mm)	34.7 (30.9, 39.8)	33.7 (31.0, 37.7)	38.9 (34.6, 42.6)	33.1 (26.0, 40.2)	32.5 (27.8, 37.4)	<0.001
IC diameter (mm)	40.1 (36.2, 43.8)	40.0 (37.6, 42.5)	43.0 (38.7, 47.6)	39.9 (33.6, 50.1)	37.3 (33.0, 42.2)	<0.001
Aorto-mitral angle (°)	128.3 (122.1, 135.0)	130.0 (123.2, 136.1)	128.1 (122.9, 133.3)	123.5 (115.3, 131.8)	126.2 (120.4, 135.0)	0.058
≥Moderate MAC	144 (22.1)	27 (13.0)	27 (15.3)	17 (34.7)	73 (33.6)	<0.001

Abbreviations:
CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary pressure, EROA = effective regurgitant orifice area, IC = inter-commissural, LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection

fraction, LVESD = left ventricular end-systolic diameter, LVESV = left ventricular end-systolic volume, MAC = mitral annulus calcification, MR = mitral regurgitation, MT = medical therapy, PASP = pulmonary arterial systolic pressure, SAVR = surgical aortic valve replacement, SL = septal-lateral, TAVI = transcatheter aortic valve implantation, STS PROM = Society of Thoracic Surgeons predicted risk of mortality, NYHA = New York Heart Association, TAPSE = tricuspid annular plane systolic excursion, TEER = transcatheter edge-to-edge repair, TMVI = transcatheter mitral valve implantation

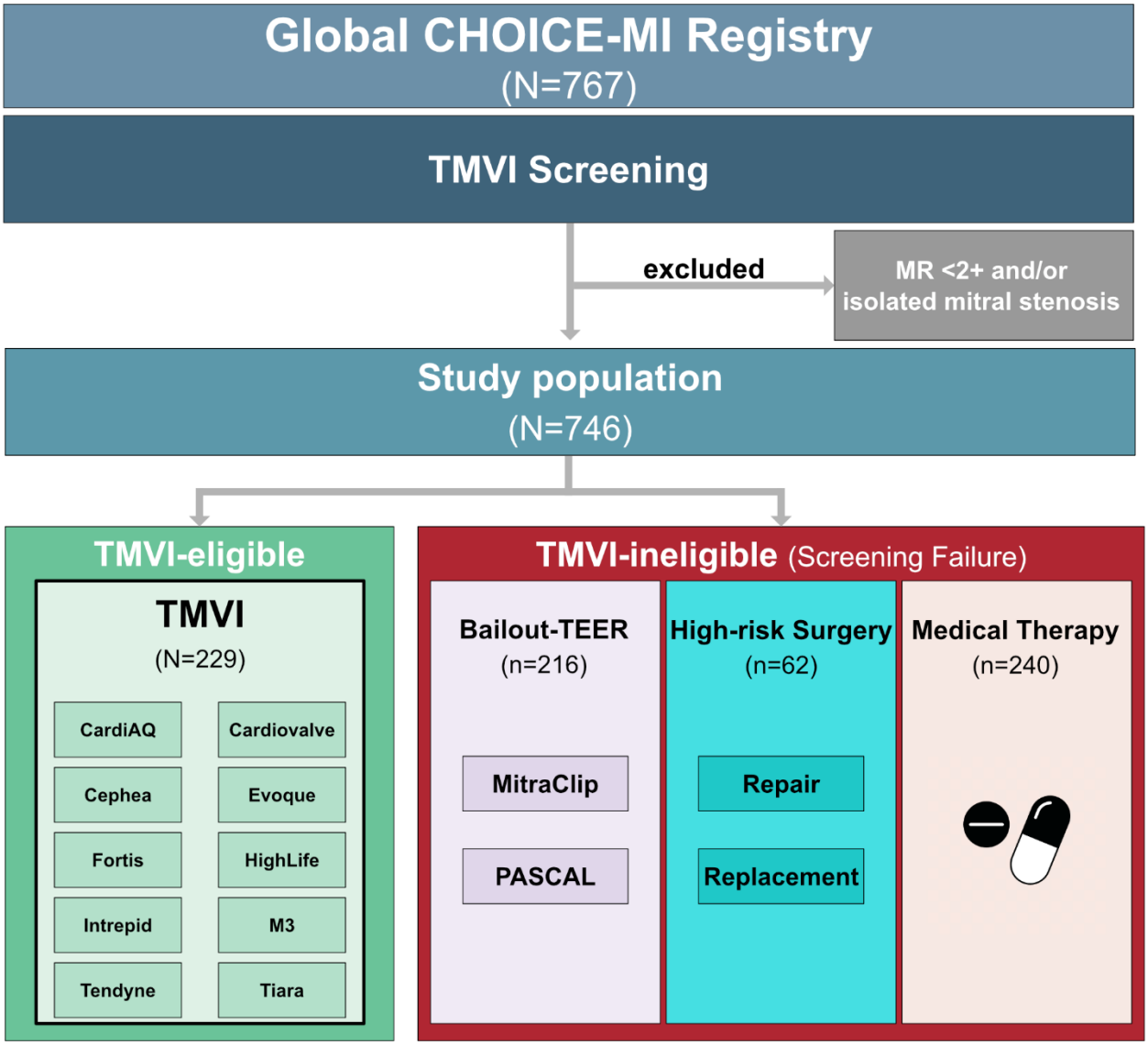
Table 2: **Procedural and 30-day outcomes**

	TMVI (N=229)	**Bailout-TEER** (N=216)	**High-risk Surgery** (N=61)
Transcatheter Mitral Valve Implantation (TMVI)			
Transapical access	205 (89.5)		
Transseptal access	24 (10.5)		
LVOT obstruction	7 (3.2)		
Valve malposition	8 (3.7)		
Valve migration	5 (2.3)		
Bailout-Transcatheter Edge-to-Edge Repair (TEER)			
No. of clips (mean)		1.5 ± 0.9	
≥1 clip implanted		94 (46.1)	
NTR		100 (64.9)	
XTR		53 (34.4)	
SLDA		3 (1.5)	
High-Risk Surgery			
Mitral valve repair			20 (37.0)
Mitral valve replacement			34 (63.0)
Sternotomy approach			36 (81.8)
Right thoracotomy approach			8 (18.2)
CPB time (min)			142.0 (124.3, 178.8)

Cross clamp time (min)			93.5 (76.2, 121.3)
Procedural and 30-day Outcomes			
Technical success	217 (95.2)	164 (86.3)	50 (98.0)
Procedural mortality	4 (1.8)	0 (0)	1 (2.0)
Conversion to surgery	6 (2.8)	1 (0.5)	0 (0)
Access site complications	21 (9.6)	7 (3.4)	1 (2.4)
Reintervention for bleeding	12 (7.5)	1 (0.7)	1 (2.6)
Acute renal failure	30 (15.4)	5 (2.6)	5 (11.1)
Disabling stroke	6 (3.0)	3 (1.5)	3 (6.3)
30-day all-cause mortality	22 (9.9)	9 (4.3)	5 (8.8)
30-day CV mortality	19 (8.7)	6 (3.0)	4 (7.0)

Abbreviations:
AKIN = Acute Kidney Injury Network, CV = cardiovascular, LVOT = left ventricular outflow tract, TMVI = transcatheter mitral valve implantation, TEER = transcatheter edge-to-edge repair, SLDA = single leaflet device attachment, CPB = cardiopulmonary bypass

Figure 1



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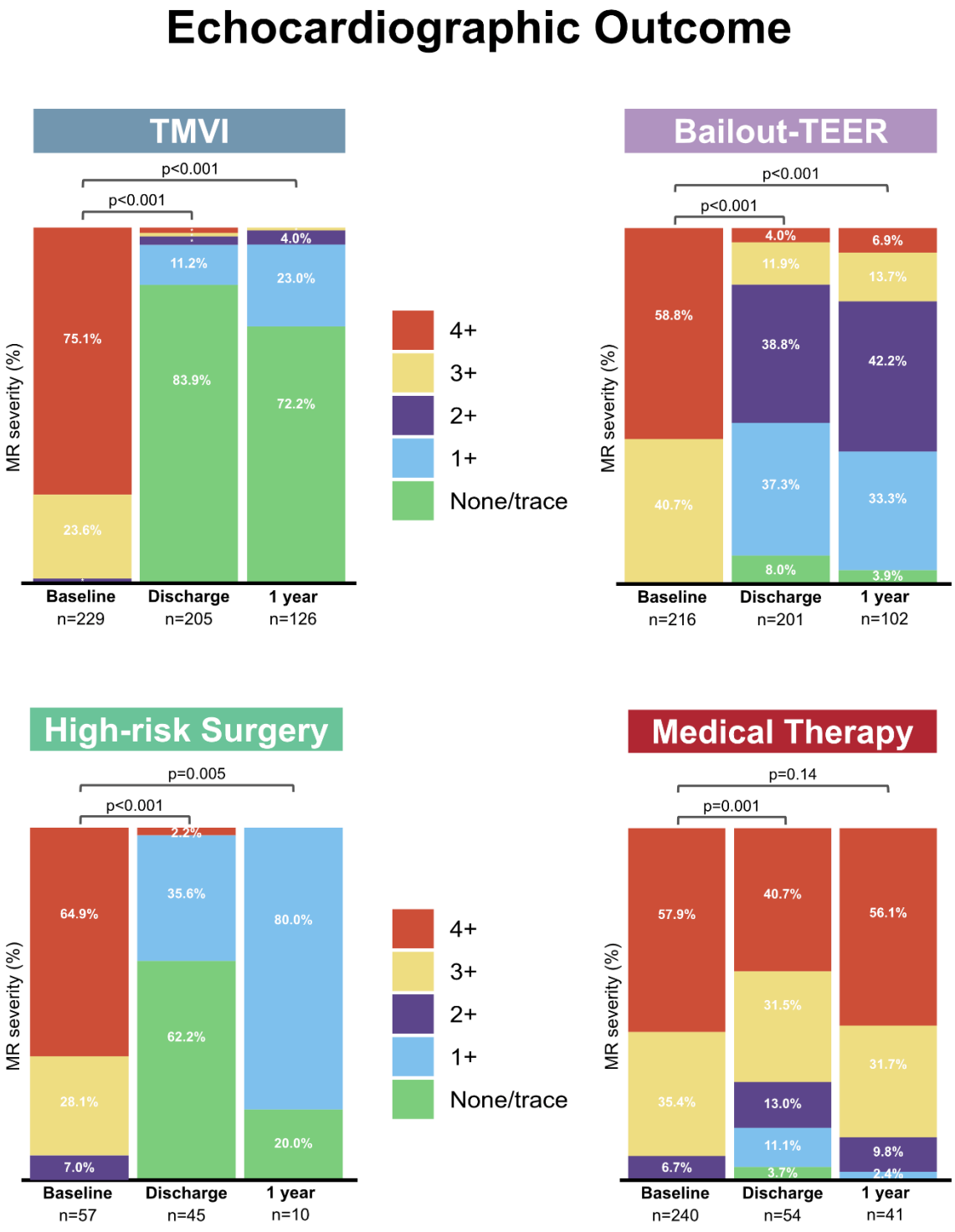

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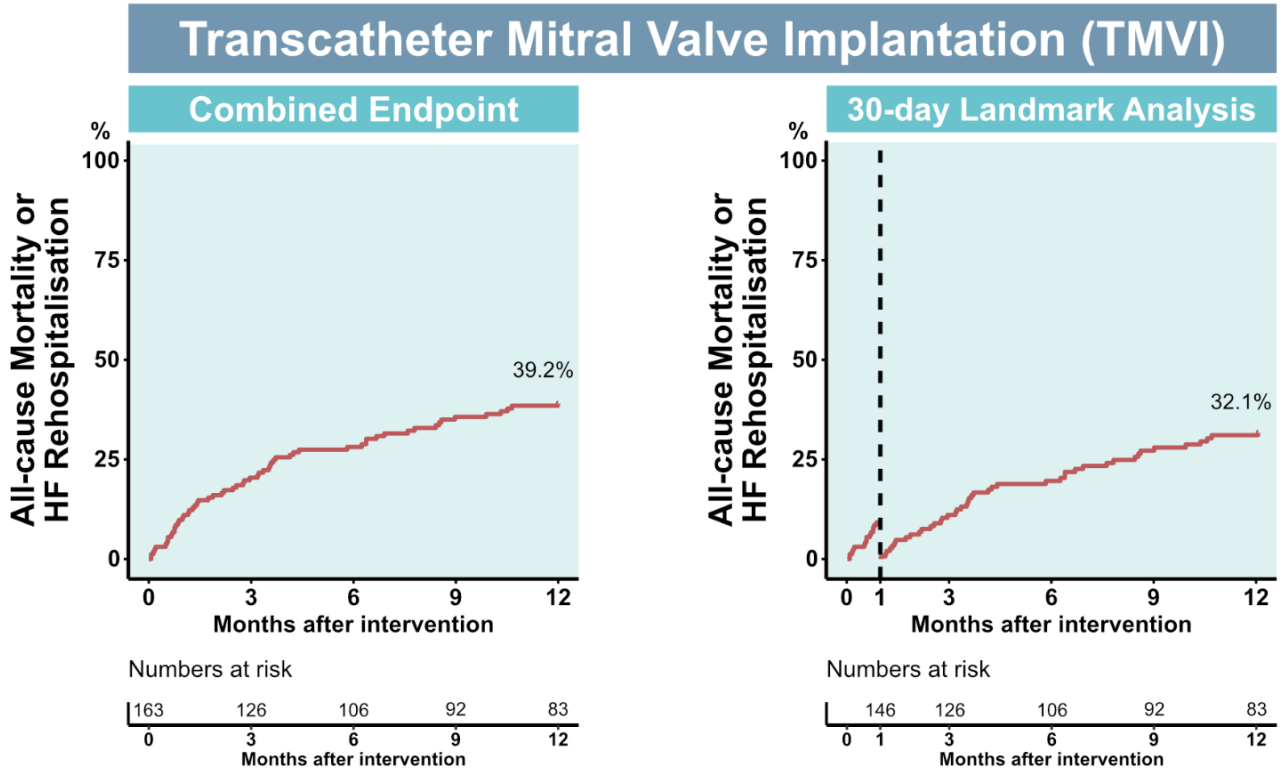

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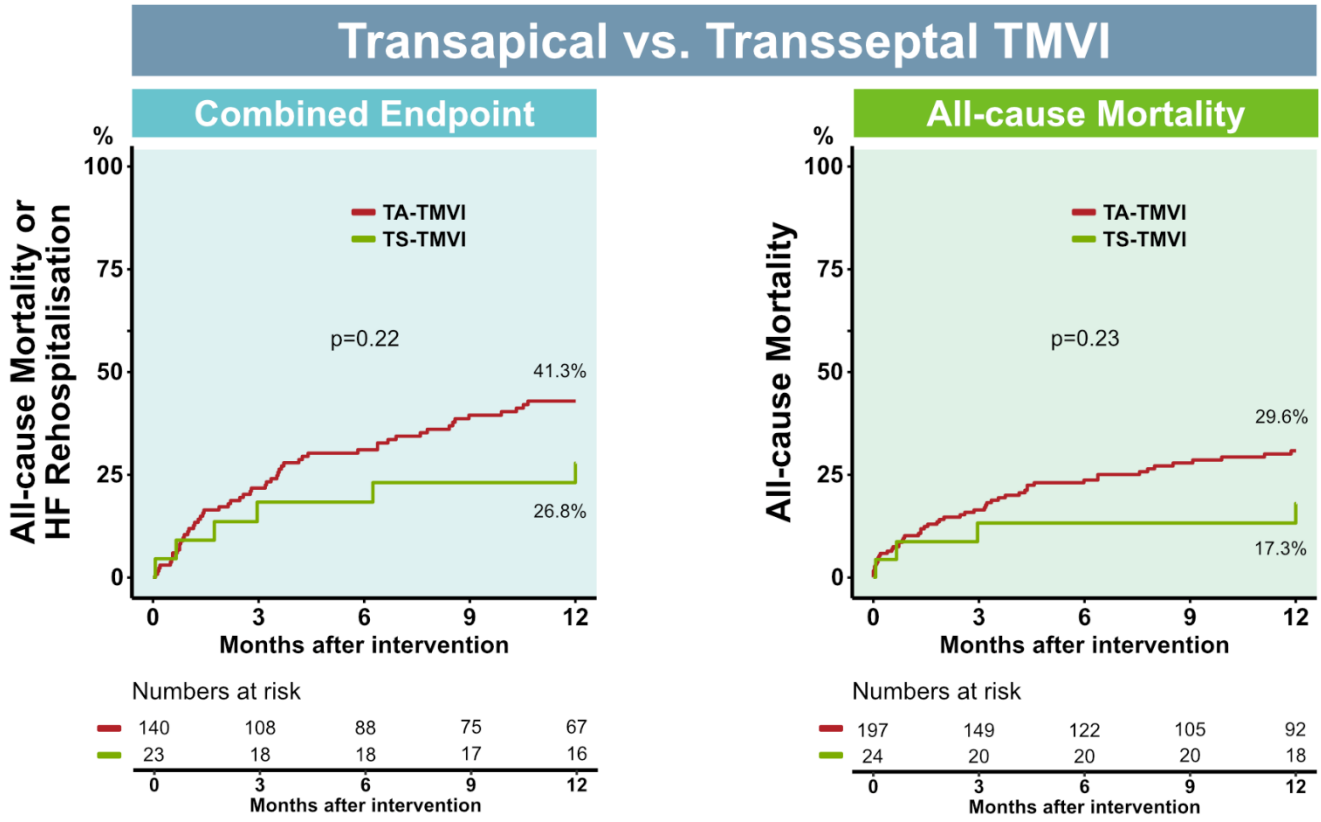

Figure 5