



HAL
open science

Characteristics and outcomes of patients screened for transcatheter mitral valve implantation: 1-year results from the CHOICE-MI registry

W. Ben Ali, S. Ludwig, A. Duncan, J. Weimann, G. Nickenig, T. Tanaka, A. Coisne, A. Vincentelli, R. Makkar, J. G. Webb, et al.

► **To cite this version:**

W. Ben Ali, S. Ludwig, A. Duncan, J. Weimann, G. Nickenig, et al.. Characteristics and outcomes of patients screened for transcatheter mitral valve implantation: 1-year results from the CHOICE-MI registry. *European Journal of Heart Failure*, 2022, 24 (5), pp.887-898. 10.1002/ejhf.2492 . inserm-03754197

HAL Id: inserm-03754197

<https://inserm.hal.science/inserm-03754197>

Submitted on 19 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Characteristics and outcomes of patients screened for transcatheter mitral valve implantation: 1-year results from the CHOICE-MI registry

Walid Ben Ali^{1†}, Sebastian Ludwig^{2,3,4†}, Alison Duncan⁵, Jessica Weimann², Georg Nickenig⁶, Tetsu Tanaka⁶, Augustin Coisne⁷, Andre Vincentelli⁷, Raj Makkar⁸, John G. Webb⁹, Mariama Akodad⁹, David W.M. Muller¹⁰, Fabien Praz¹¹, Mirjam G. Wild^{11,12}, Jörg Hausleiter¹², Sachin S. Goel¹³, Moritz Wyler von Ballmoos¹³, Paolo Denti¹⁴, Omar Chehab¹⁵, Simon Redwood¹⁵, Gry Dahle¹⁶, Stephan Baldus¹⁷, Matti Adam¹⁷, Hendrik Ruge¹⁸, Rüdiger Lange¹⁸, Tsuyoshi Kaneko¹⁹, Lionel Leroux²⁰, Nicolas Dumonteil²¹, Didier Tchetché²¹, Hendrik Treede²², Michele Flagiello²³, Jean-Francois Obadia²³, Thomas Walther²⁴, Maurizio Taramasso²⁵, Lars Søndergaard²⁶, Sabine Bleiziffer²⁷, Tanja K. Rudolph²⁷, Neil Fam²⁸, Joerg Kempfert²⁹, Juan F. Granada⁴, Gilbert H.L. Tang³⁰, Ralph Stephan von Bardeleben^{22*}, Lenard Conradi^{2,3}, and Thomas Modine²⁰, CHOICE-MI Investigators[‡]

¹Montreal Heart Institute, Montreal, Quebec, Canada; ²University Heart and Vascular Center Hamburg, Hamburg, Germany; ³German Center for Cardiovascular Research (DZHK): Partner site Hamburg/Kiel/Lübeck, Hamburg, Germany; ⁴Cardiovascular Research Foundation, New York City, NY, USA; ⁵Royal Brompton Hospital, London, UK; ⁶Heart Center Bonn, Bonn, Germany; ⁷Centre Hospitalier Universitaire de Lille, Lille, France; ⁸Cedars-Sinai Medical Center, Los Angeles, CA, USA; ⁹St. Paul's Hospital, Vancouver, BC, Canada; ¹⁰St. Vincent's Hospital, Sydney, NSW, Australia; ¹¹Bern University Hospital, Bern, Switzerland; ¹²Ludwig Maximilian University of Munich, Munich, Germany; ¹³Houston Methodist Hospital, Houston, TX, USA; ¹⁴Ospedale San Raffaele, Milan, Italy; ¹⁵St. Thomas' Hospital, London, UK; ¹⁶Oslo University Hospital, Oslo, Norway; ¹⁷University Hospital of Cologne, Cologne, Germany; ¹⁸German Heart Center Munich, Munich, Germany; ¹⁹Brigham and Women's Hospital, Boston, MA, USA; ²⁰Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; ²¹Clinique Pasteur, Toulouse, France; ²²Heart Valve Center, Heart and Vascular Center, Universitätsmedizin Mainz, Mainz, Germany; ²³Department of Cardiac Surgery, Louis Pradel Cardiologic Hospital, Lyon, France; ²⁴Frankfurt University Hospital, Frankfurt, Germany; ²⁵HerzZentrum Hirslanden Zürich, Zürich, Switzerland; ²⁶Rigshospitalet, Copenhagen, Denmark; ²⁷Heart and Diabetes Center NRW, Bad Oeynhausen, Germany; ²⁸St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; ²⁹German Heart Center Berlin, Berlin, Germany; and ³⁰Mount Sinai Hospital, New York City, NY, USA

Received 24 January 2022; revised 21 March 2022; accepted 21 March 2022; online publish-ahead-of-print 17 April 2022

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 May 2014 to March 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,

*Corresponding author. Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Kardiologie I, Heart Valve Center, Langenbeckstr. 1, 55 131 Mainz, Germany. Tel: +49 6131 172892, Fax: +49 6131 176692, Email: stephan.von_bardeleben@unimedizin-mainz.de

[†]These authors contributed equally to this manuscript.

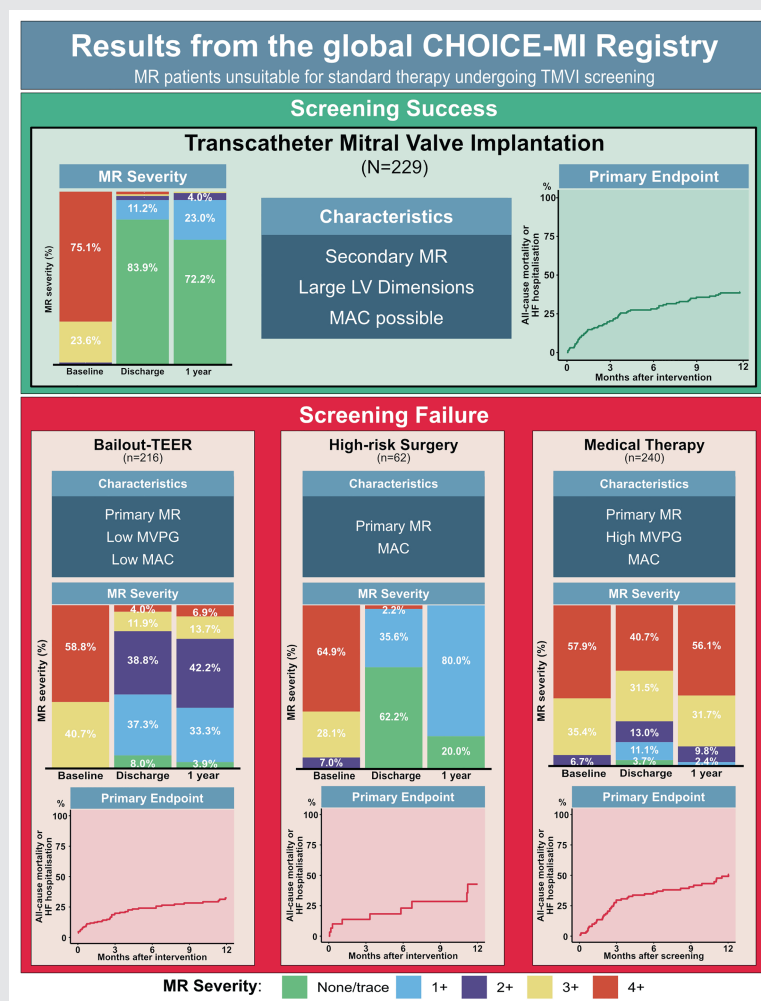
[‡]The full list of all investigators is given in the online supplementary Appendix S1.

high-risk surgery or medical therapy (MT). The primary composite endpoint was all-cause mortality or heart failure hospitalization after 1 year. Among 746 patients included (78.5 years, interquartile range [IQR] 72.0–83.0, EuroSCORE II 4.7% [IQR 2.7–9.7]), 229 patients (30.7%) underwent TMVI with 10 different dedicated devices. At 1 year, residual MR $\leq 1+$ 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 $\leq 1+$ 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 10 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.

Graphical Abstract



Results from the global CHOICE-MI registry. CHOICE-MI, CHoice of Optimal transCatheter trEatment for Mitral Insufficiency; HF, heart failure; MAC, mitral annulus calcification; MR, mitral regurgitation; MVPG, mitral valve pressure gradient; TEER, transcatheter edge-to-edge repair.

Keywords

- Mitral regurgitation • Transcatheter mitral valve implantation • Transcatheter edge-to-edge repair • Mitral valve surgery • Medical therapy

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 hospitalization 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 (MT) 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 (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 May 2014 to March 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 was 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 $\geq 2+$ that were considered unsuitable for established therapies (i.e. at high or prohibitive surgical risk and with suboptimal anatomy for TEER) and underwent TMVI evaluation. Patients with isolated mitral stenosis or MR $< 2+$ at baseline ($n = 21$) were excluded from this analysis (Figure 1).

Patients who underwent TMVI were treated with 10 different TMVI devices with transapical or transseptal approach (see online supplementary Appendix S1 for a list of implanted devices). Patients received TMVI within compassionate-use programmes, 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 ineligible for TMVI 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, USA) or the PASCAL system (Edwards Lifesciences LLC, Irvine, CA, USA), high-risk surgery (MV repair or replacement) or continued MT.

Study endpoints and definitions

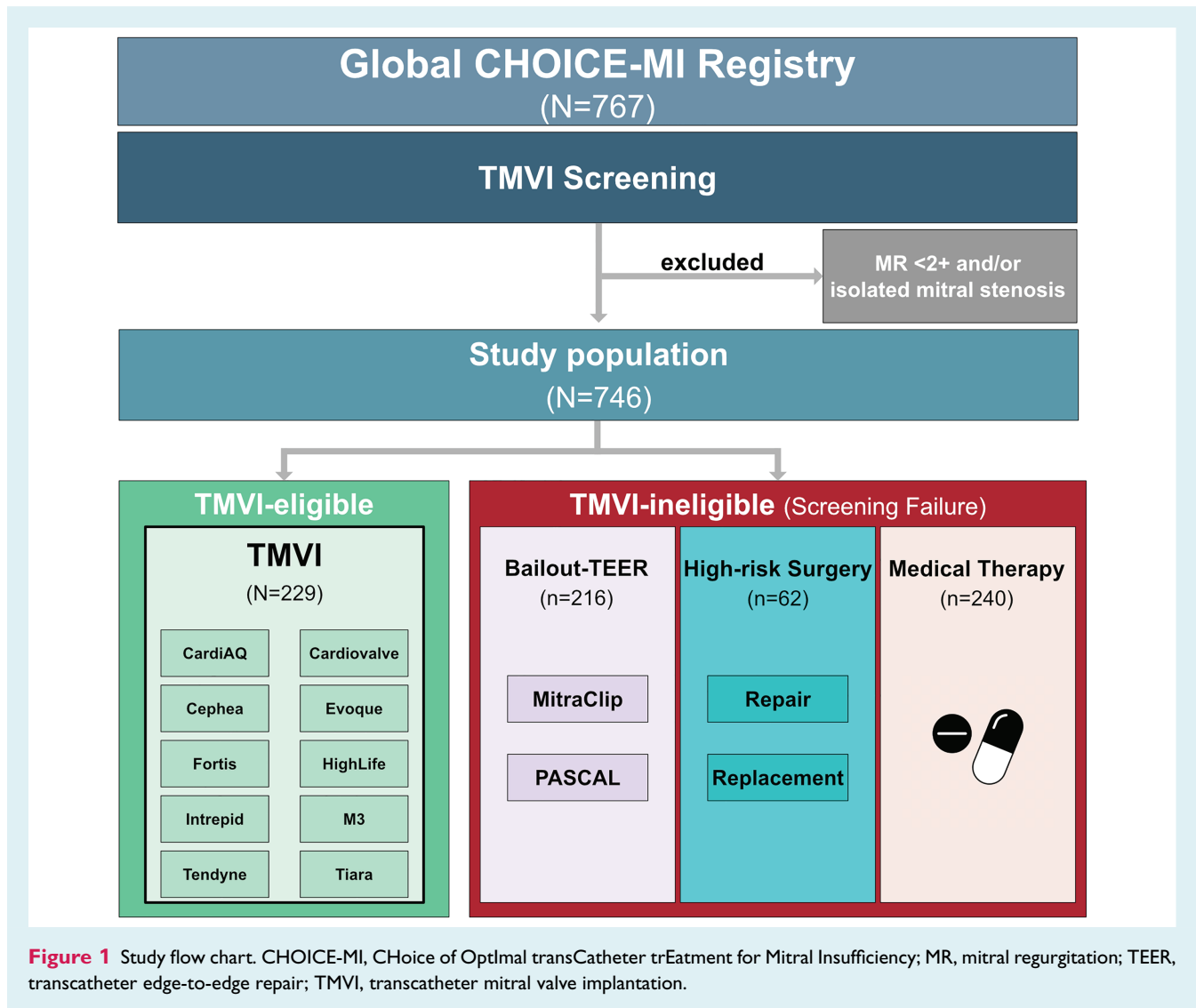
The primary study endpoint was a composite endpoint of all-cause mortality or HF hospitalization at 1 year. Secondary study endpoints were all-cause and cardiovascular (CV) mortality at 1 year, residual MR on transthoracic echocardiography and New York Heart Association (NYHA) functional class, at discharge and after 1 year. CV mortality was defined as mortality attributable to myocardial ischaemia and infarction, HF, cardiac arrest, or cerebrovascular accident. HF hospitalization was defined as new-onset or worsening signs and symptoms of HF that required urgent therapy and resulted in hospitalization. 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 (interquartile range [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 IQR (25th–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 $\geq 1+$ and $\geq 2+$. Forest plots display the respective hazard ratio (HR) and 95% confidence interval (CI) of residual MR $\geq 1+$ and $\geq 2+$ after adjustment for age, sex, chronic kidney disease, chronic obstructive pulmonary disease, and 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. Overall, 229 patients were considered eligible for TMVI. Anatomical ineligibility was the most common reason for screening failure among 517 (69.3%) patients considered ineligible for TMVI. Specific reasons for TMVI screening failure are shown in online supplementary Figure S1A. 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 (online supplementary Figure S1B).

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 (left ventricular 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 $\geq 2+$ (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 74.0–83.0], 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 left ventricular 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 characterized by the lowest rates of comorbidities as well as the 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 left ventricular 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

Transcatheter mitral valve implantation 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 $\leq 1+$ 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 $\leq 1+$ 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 ($n = 27$). Online supplementary Figure S2 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; online supplementary Figure S3).

According to Kaplan–Meier analysis, the primary combined endpoint of all-cause mortality or HF hospitalization 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 (online supplementary Figure S4). 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 online supplementary Table S1.

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 seven patients (3.4%) and one patient (0.7%), respectively. At 30 days after bailout-TEER, a total of nine patients had died (CV death: $n = 6$) (Table 2).

At discharge and after 1 year, the rates of residual MR $\leq 1+$ were 45.3% and 37.2%, respectively (Figure 2). Functional improvement was present both at discharge and 1 year after bailout-TEER (online supplementary Figure S3). 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 online supplementary Figure S5.

Outcomes after high-risk surgery

The majority of TMVI-ineligible patients referred to high-risk surgery underwent MV replacement (63.0%, $n = 34$), while 20 patients (37.0%) were treated with MV repair. Technical success was reported for 50 patients (98.0%) with procedural mortality in one patient (2.0%). Overall postprocedural and 30-day complication rates were low with the highest rate reported for acute renal

Echocardiographic Outcome

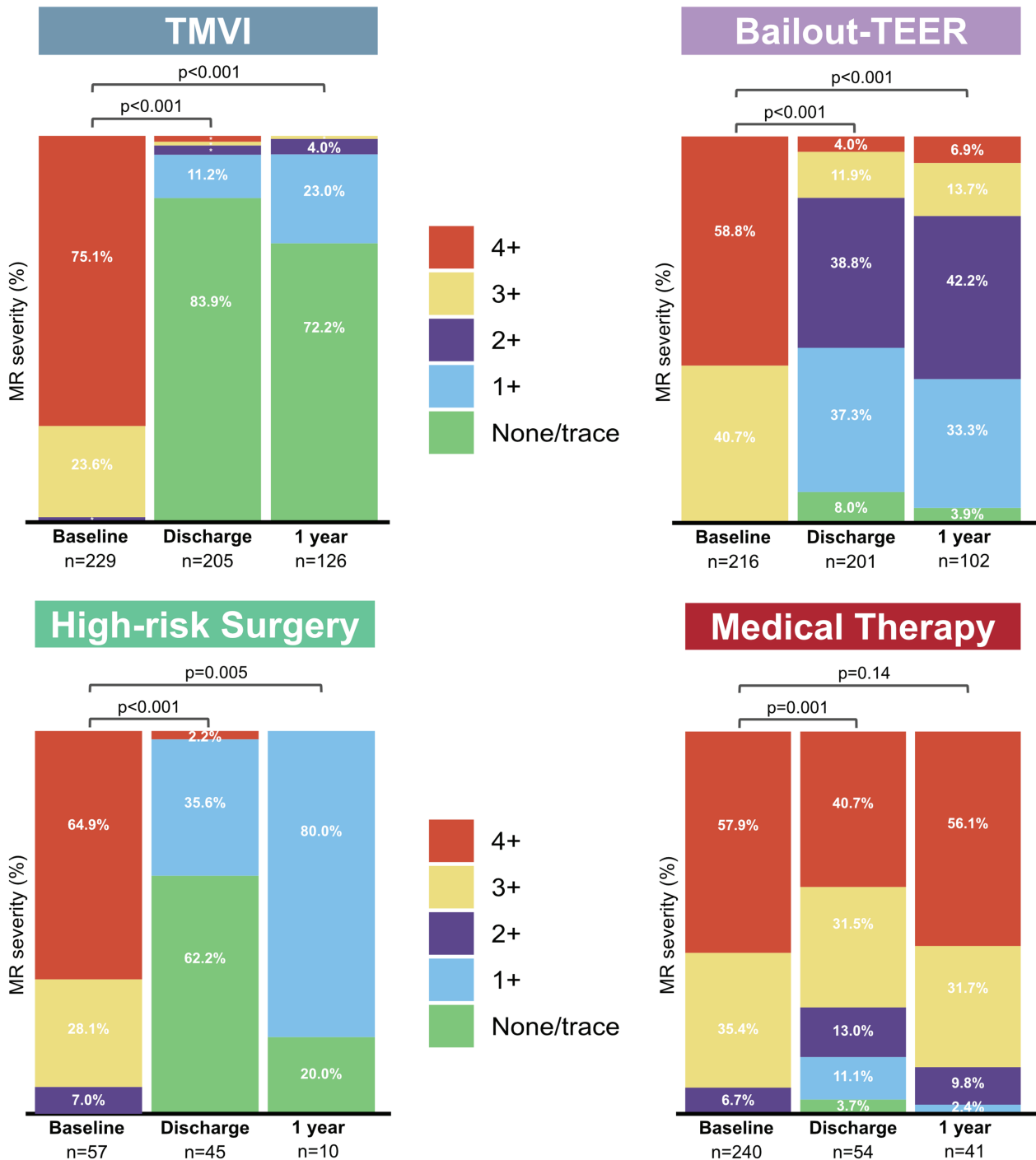


Figure 2 Echocardiographic outcome. Mitral regurgitation (MR) at baseline and residual MR at discharge and after 1 year (*p*-values are given for comparisons between baseline and discharge or baseline and 1 year). Frequencies smaller 2% are indicated by *. TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation.

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 sex	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)	123.2 (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

Values are given as median (interquartile range), or n (%).

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; 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; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; SAVR, surgical aortic valve replacement; SL, septal-lateral; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation.

failure (11.1%, $n = 5$). After 30 days a total of five patients had died (CV death: $n = 4$).

Residual MR at discharge was $\leq 1+$ 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 $\leq 1+$ 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 $\leq 1+$ 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 $\geq 3+$ (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 (online supplementary Figure S3). The primary endpoint after 1 year occurred in 47.9% of patients remaining on MT (Figure 5).

Table 2 Procedural and 30-day outcomes

	TMVI (n = 229)	Bailout-TEER (n = 216)	High-risk surgery (n = 61)
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-TEER			
No. of clips		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)

Values are given as n (%), mean ± standard deviation, median (interquartile range).

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

Prognostic impact of residual mitral regurgitation

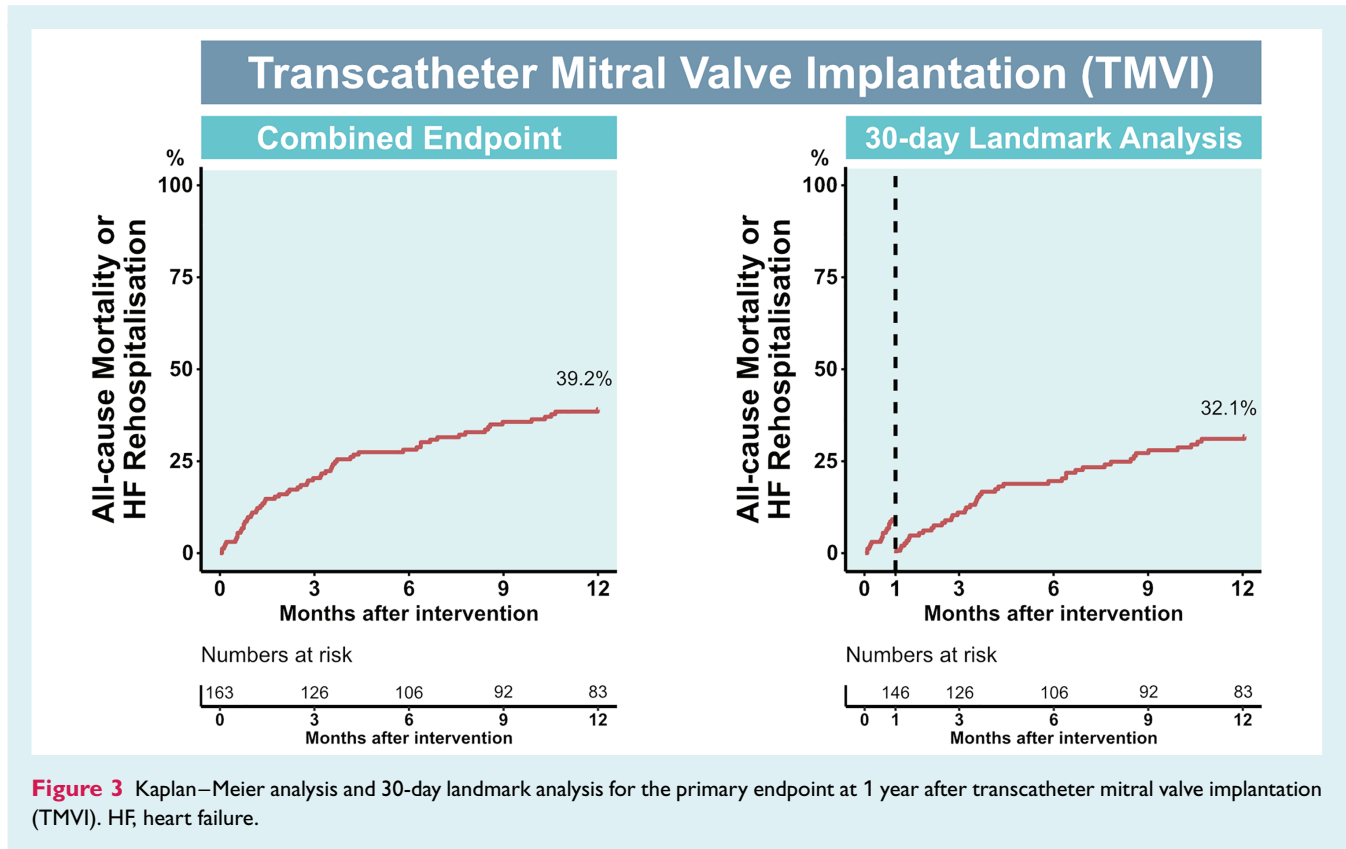
The impact of residual MR ≥1+ and ≥2+ on the primary composite endpoint was evaluated by using multivariable adjustment for the groups of TMVI and bailout-TEER (online supplementary Figure S6). While residual MR ≥1+ did not predict outcome in patients undergoing TMVI or bailout-TEER, residual MR ≥2+ 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 [95% CI 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 10 different TMVI devices. These are the main findings regarding the different treatment strategies following TMVI screening success or failure:

1. Patients undergoing TMVI with 10 different dedicated devices showed high rates of comorbidities and elevated surgical risk. These patients were mostly treated for SMR, had dilated left ventricular 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 number 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



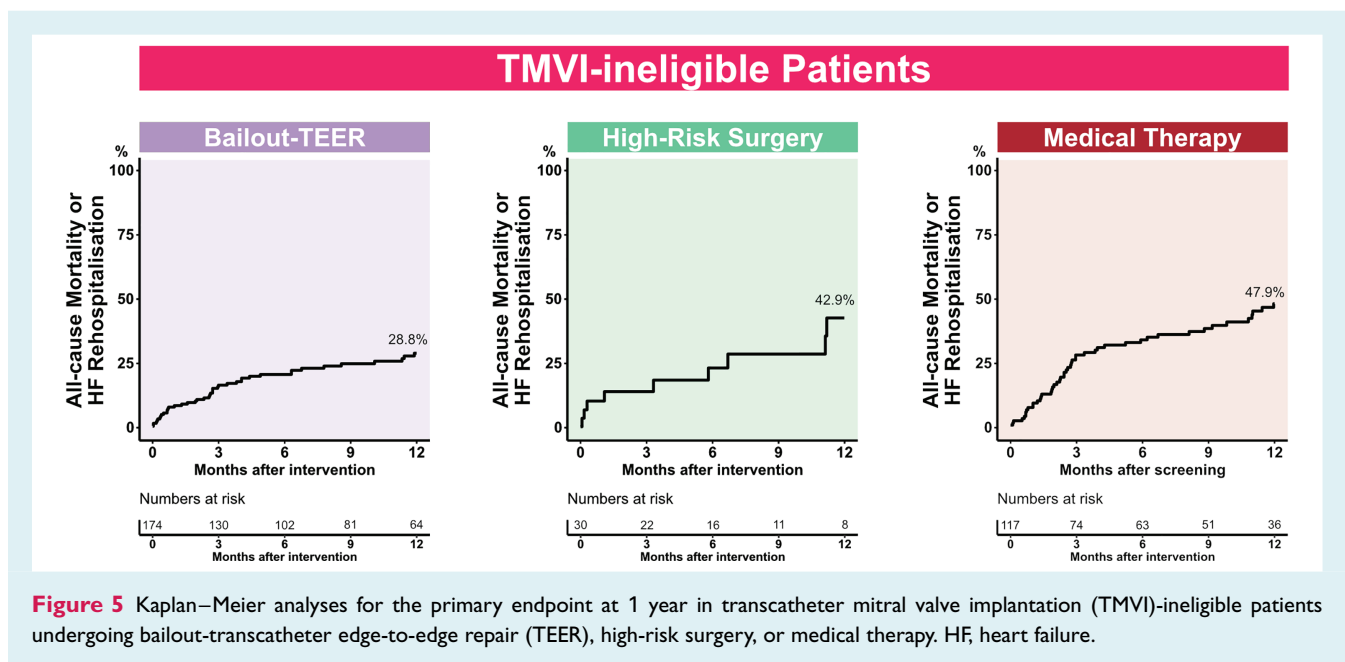
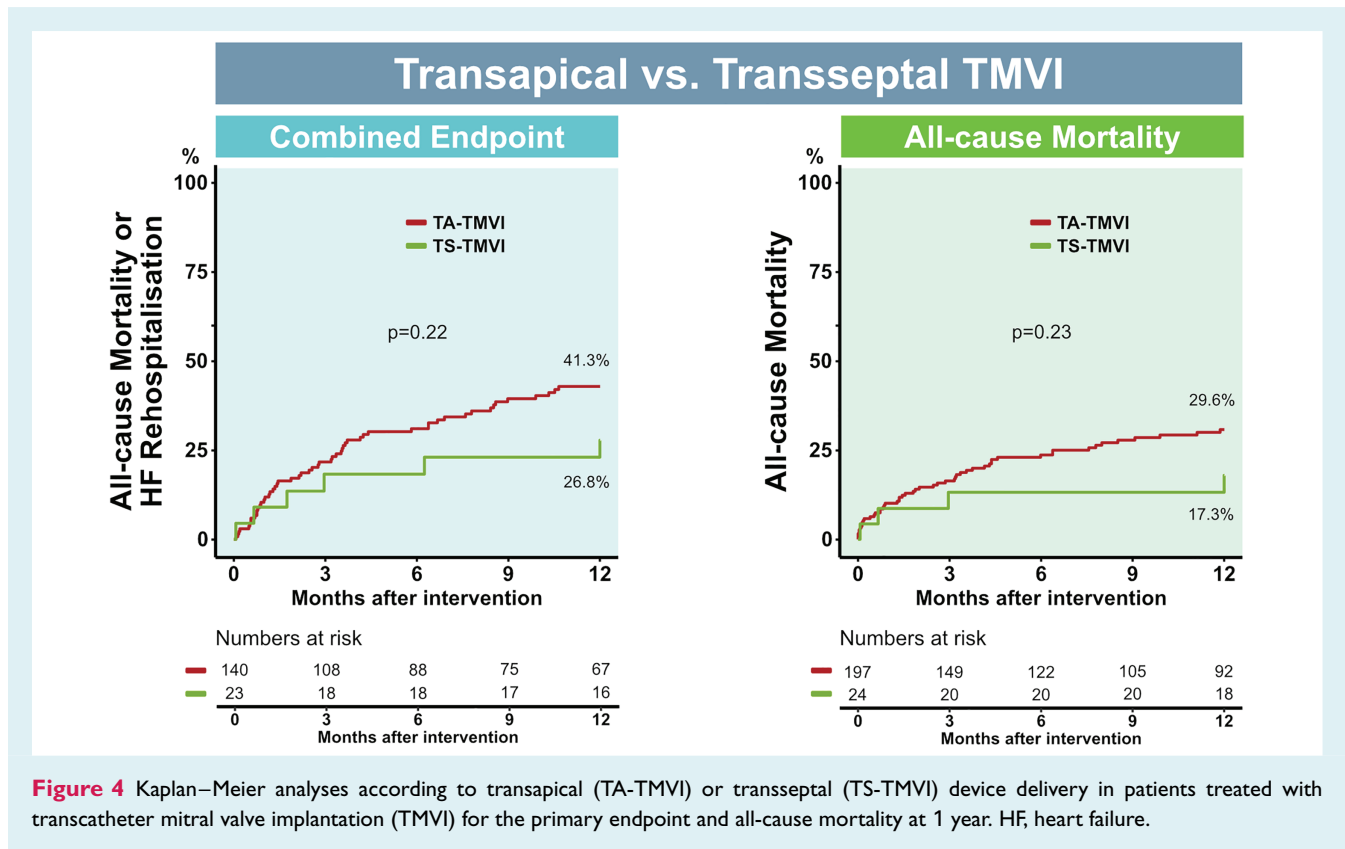
presented with preserved LVEF, low transvalvular gradients and a low rate of MAC. Although these patients showed elevated rates of significant residual MR (residual MR $\geq 2+$ 54.7% at discharge), bailout-TEER yielded functional improvement and satisfactory clinical outcomes.

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 characterized 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 $\geq 1+$ was not associated with outcome, residual MR $\geq 2+$ 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 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 programmes 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 characterized 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 hospitalization after 1 year was low and patients experienced significant functional improvement at 1 year. Nevertheless, residual MR at discharge remained $\geq 2+$ 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 $\geq 2+$: 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 characterized 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 $\leq 1+$ 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 hospitalizations, 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 left ventricular 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 hospitalizations, 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 10 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 hospitalization 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

We would like to thank all the CHOICE-MI investigators for their invaluable contributions to this study. Open Access funding enabled and organized by Projekt DEAL.

Funding

This research was supported by a grant from the German Heart Foundation (DHS).

Conflict of interest: W.B.A. received research grants from Medtronic and Edwards Lifesciences. S.L. was supported by a grant from the German Heart Foundation (DHS) and received travel compensation by Edwards Lifesciences. A.D. is a consultant for and has and received honoraria from Abbott Laboratories, Edward Lifesciences and Medtronic. G.H.L.T. is a physician proctor and consultant for Medtronic, consultant and TAVR physician advisory board member for Abbott Structural Heart, consultant for Neo-Chord and advisory board member for JenaValve. L.C. is advisory board member for Abbott, Medtronic and BostonScientific and has received personal fees from Edwards Lifesciences. All other authors have nothing to disclose.

References

- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2021;**77**:e25–e197.
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;**43**:561–632.
- Mirabel M, lung B, Baron G, Messika-Zeitoun D, Détaint D, Vanoverschelde JL, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J*. 2007;**28**:1358–65.
- Goel SS, Bajaj N, Aggarwal B, Gupta S, Poddar KL, Ige M, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of mitralclip for this unmet need. *J Am Coll Cardiol*. 2014;**63**:185–6.
- Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR, Stebbins A, et al. Outcomes with transcatheter mitral valve repair in the United States: an STS/ACC TVT Registry report. *J Am Coll Cardiol*. 2017;**70**:2315–27.
- Chiarito M, Pagnesi M, Martino EA, Pighi M, Scotti A, Biondi-Zoccai G, et al. Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: a systematic review and meta-analysis. *Heart*. 2018;**104**:306–12.
- Reichart D, Kalbacher D, Rübsamen N, Tigges E, Thomas C, Schirmer J, et al. The impact of residual mitral regurgitation after MitraClip therapy in functional mitral regurgitation. *Eur J Heart Fail*. 2020;**22**:1840–8.
- Ludwig S, Sedighian R, Weimann J, Koell B, Waldschmidt L, Schäfer A, et al. Management of patients with mitral regurgitation ineligible for standard therapy undergoing TMVI screening. *EuroIntervention*. 2022. <https://doi.org/10.4244/EIJ-D-21-00708>.
- Ben-Ali W, Ibrahim R, Rodès-Cabeau J, von Bardeleben RS, Mylotte D, Granada J, et al. Transcatheter mitral valve implantation systematic review: focus on transseptal approach and mitral annulus calcification. *Curr Cardiol Rep*. 2021;**23**:37.
- Muller DWM, Sorajja P, Duncan A, Bethea B, Dahle G, Grayburn P, et al. 2-year outcomes of transcatheter mitral valve replacement in patients with severe symptomatic mitral regurgitation. *J Am Coll Cardiol*. 2021;**78**:1847–59.
- Zahr F, Song HK, Chadderdon SM, Gada H, Mumtaz M, Byrne T, et al. Thirty-day outcomes following transfemoral transseptal transcatheter mitral valve replacement: Intrepid TMVR Early Feasibility Study results. *JACC Cardiovasc Interv*. 2022;**15**:80–9.
- Bapat V, Rajagopal V, Meduri C, Farivar RS, Walton A, Duffy SJ, et al. Early experience with new transcatheter mitral valve replacement. *J Am Coll Cardiol*. 2018;**71**:12–21.
- Ludwig S, Ruebsamen N, Deuschl F, Schofer N, Kalbacher D, Schaefer A, et al. Screening for transcatheter mitral valve replacement: a decision tree algorithm. *EuroIntervention*. 2020;**16**:251–8.
- Coisne A, Pontana F, Tchétché D, Richardson M, Longère B, Vahdat O, et al. Transcatheter mitral valve replacement: factors associated with screening success and failure. *EuroIntervention*. 2019;**15**:e983–9.
- Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 2: Endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol*. 2015;**66**:308–21.
- Sorajja P, Moat N, Badhwar V, Walters D, Paone G, Bethea B, et al. Initial feasibility study of a new transcatheter mitral prosthesis: the first 100 patients. *J Am Coll Cardiol*. 2019;**73**:1250–60.
- Mark H, Brown RA, Lal S, Sathananthan J, Ye J, Cheung A, et al. Transcatheter mitral valve replacement: an update on current techniques, technologies, and future directions. *JACC Cardiovasc Interv*. 2021;**14**:489–500.
- Blackstone EH, Suri RM, Rajeswaran J, Babaliaros V, Douglas PS, Fearon WF, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement. *Circulation*. 2015;**131**:1989–2000.
- Gössl M, Thourani VH, Babaliaros V, Conradi L, Chehab B, Dumonteil N, et al. Early outcomes of transcatheter mitral valve replacement with the Tendyne system in severe mitral annular calcification. *EuroIntervention*. 2021. <https://doi.org/10.4244/EIJ-D-21-00745>.
- Sorajja P, Gössl M, Babaliaros V, Rizik D, Conradi L, Bae R, et al. Novel transcatheter mitral valve prosthesis for patients with severe mitral annular calcification. *J Am Coll Cardiol*. 2019;**74**:1431–40.
- Global EXPAND: Next-Gen MitraClipCuts MR, Boosts QoL at 1 Year. October 16, 2020. <https://www.tctmd.com/news/global-expand-next-gen-mitraclip-cuts-mr-boosts-qol-1-year>. Accessed 30 March 2022.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;**38**:2739–91.
- Niikura H, Gössl M, Kshetry V, Olson S, Sun B, Askew J, et al. Causes and clinical outcomes of patients who are ineligible for transcatheter mitral valve replacement. *JACC Cardiovasc Interv*. 2019;**12**:196–204.
- Ludwig S, Koell B, Sedighian R, Weimann J, Schofer N, Schaefer A, et al. Characteristics and outcomes of patients ineligible for transcatheter mitral valve replacement (TMVR): implications for future device innovation. *J Invasive Cardiol*. 2021;**33**:E294–301.
- Coats AJS, Anker SD, Baumbach A, Alfieri O, von Bardeleben RS, Bauersachs J, et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur Heart J*. 2021;**42**:1254–69.