Journal of the American Heart Association

ORIGINAL RESEARCH

Outcomes of Transcatheter Edge-to-Edge Repair in Potentially Favorable Candidates for Left Ventricular Assist Device: Evidence From the OCEAN-Mitral Registry

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BACKGROUND: Transcatheter edge-to-edge repair of the mitral valve (M-TEER) has shown promising outcomes in patients with advanced heart failure and significant mitral regurgitation. Similarly, outcomes after left ventricular assist device (LVAD) implantation have improved in advanced heart failure with/without mitral regurgitation. However, the indication of M-TEER in favorable candidates for LVAD therapy remains unclear.

METHODS: Potentially favorable LVAD candidates were defined as patients with advanced heart failure and secondary mitral regurgitation who underwent M-TEER and were considered theoretically suitable for LVAD therapy based on data from the optimized catheter valvular intervention (OCEAN)-Mitral registry. Among this cohort, Cox proportional hazards regression analysis was performed to identify factors associated with cardiovascular death following M-TEER.

RESULTS: A total of 3764 patients who underwent M-TEER were included. Of them, 129 were identified as potentially favorable LVAD candidates (mean age: 67 years; 67% men). Despite advanced heart failure, procedural success was 96%. The 1-year rate of cardiovascular death was 10.1%, increasing to 38.9% at 3 years. Baseline left ventricular end-diastolic diameter was independently associated with cardiovascular death (hazard ratio: 1.07 per 1-mm increase; 95% CI: 1.02–1.12; P=0.01). In patients with markedly enlarged left ventricles, symptom improvement was limited, and reverse remodeling was not achieved.

CONCLUSIONS: M-TEER can be safely performed even in potentially favorable LVAD candidates. However, long-term efficacy appears limited, particularly in those with advanced LV remodeling. Further studies are warranted to establish an optimal strategy, including the role of LVAD therapy versus M-TEER, for this high-risk population.

REGISTRATION: URL: https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000027188.

Key Words: destination therapy ■ left ventricular assist device ■ mitral regurgitation ■ transcatheter edge-to-edge repair

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This manuscript was sent to Amgad Mentias, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.046638

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Transcatheter edge-to-edge repair for mitral valve can be performed with high procedural safety and success rates even in patients who are potentially favorable candidates for left ventricular assist device therapy.
- Among these patients, long-term efficacy of transcatheter edge-to-edge repair for mitral valve appears to be limited in those with markedly enlarged left ventricle.

What Are the Clinical Implications?

- In patients who may be suitable candidates for left ventricular assist device therapy, clinicians should prioritize consideration of left ventricular assist device implantation, and even when transcatheter edge-to-edge repair for mitral valve is performed, ensure careful longitudinal follow-up to avoid missing the optimal timing for left ventricular assist device implantation.

Nonstandard Abbreviations and Acronyms

DT	destination therapy
HFrEF	heart failure with reduced ejection fraction
HMRS	HeartMate Risk Score
MCS	mechanical circulatory support
M-TEER	transcatheter edge-to-edge repair for mitral valve
SMR	secondary mitral regurgitation

Following the publication of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial,[1] transcatheter edge-to-edge repair of the mitral valve (M-TEER) has become a widely accepted procedure for patients with heart failure with reduced ejection fraction (HFrEF) and significant mitral regurgitation (MR). Favorable long-term outcomes following M-TEER have been demonstrated,[2] and the clinical benefits have been observed not only in patients with advanced HF, including those in cardiogenic shock,[3] but also in those with moderate to severe MR, indicating its potential utility even in less severe cases.[4]

Left ventricular (LV) reverse remodeling following the procedure is widely recognized as a prognostic factor in patients with HFrEF.[5] Some patients, particularly individuals with advanced HF, have extremely progressed LV remodeling, accompanying enlarged LV cavity and reduced LV contractility. Reverse remodeling may not necessarily be achieved following M-TEER in all of these patients. LV remodeling rather progresses further despite M-TEER in some patients. Individuals with insufficient reverse remodeling have a higher incidence of mortality and morbidity.[6,7] We should understand that M-TEER is the direct and makeshift therapeutic tool for the mitral valve alone, but not for the LV.

The implantation of a left ventricular assist device as destination therapy (DT) or bridge to transplant is one of the robust therapeutic strategies for patients with advanced HF. In Japan, left ventricular assist device for DT (DT-LVAD) was incorporated into the national health insurance system in April 2021, and its recognition and clinical application have since been spreading gradually. The HeartMate 3, which is currently the most widely used device, has emerged as a favorable option for LVAD implantation because of its significantly lower rates of major complications such as stroke, bleeding, and pump thrombus compared with previous generation devices, thereby offering the potential for improved long-term outcomes after implantation of LVAD.[8]

Patients with advanced HF often have secondary ventricular MR. Notably, durable LVAD therapy can ameliorate most of these MRs via the strong mechanical LV unloading facilitation of reverse remodeling of mitral valve morphology.[9] Thus, durable LVAD implantation is the optimal therapeutic option for individuals with advanced HF and concomitant MR, together with M-TEER.

Nevertheless, compared with M-TEER, LVAD implantation is obviously more invasive and demands substantially more medical resources.[10] While the safety of LVAD implantation following M-TEER has been suggested, concerns remain about the potential delay in optimal timing for LVAD implantation.[11]

Patients with advanced HF often accompany secondary MR (SMR), whereas those with significant MR often accompany severe HF (ie, secondary ventricular MR). In the real-world clinical practice, a subset of patients considered for LVAD implantation because of their advanced HF may also be candidates for M-TEER because of their concomitant MR. Consistently, some potential LVAD candidates may receive M-TEER, instead of LVAD implantation. As mentioned above, such a strategy may cause the delay of LVAD implantation at an appropriate timing or rather the loss of change to receive LVAD implantation, attributable to prolonged insufficient hemodynamic support by M-TEER alone.

However, definitive selection criteria distinguishing between the 2 therapeutic strategies (ie, durable LVAD versus M-TEER) remain unclear. Among the individuals who received M-TEER, LVAD implantation might have been more recommended in some of them. Therefore, in this study, we aimed to propose optimal criteria to

indicate durable LVAD versus M-TEER by analyzing the clinical course following M-TEER in patients who were "theoretically" considered as potential favorable LVAD candidates, using large-scale data from a Japanese multicenter registry of M-TEER.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

The optimized catheter valvular intervention (OCEAN)-Mitral registry, registered with the University Hospital Medical Information Network (UMIN000023653), is a prospective, investigator-initiated, multicenter observational study involving patients with significant MR undergoing M-TEER in Japan. This registry consists of data collected from 21 participating centers nationwide. Approval for the study protocol and the establishment of the registry database was obtained from the institutional review board of all participating centers. The study adheres to the ethical standards set forth in the Declaration of Helsinki, and written informed consent was obtained from all patients before enrollment.

The data analyzed in this study were derived from patients who underwent M-TEER between April 2018 and June 2023. During this period, the MitraClip (Abbott Vascular Inc., Santa Clara, CA, USA) G2 system was initially used, followed by the introduction of the next-generation MitraClip G4 system, which became clinically available after its approval in September 2020.

Patient Selection

From this registry, we identified patients with HFrEF, defined as a left ventricular ejection fraction (LVEF) ≤40%, who underwent M-TEER for SMR. Among them, we identified those considered theoretically potential favorable candidates for LVAD therapy, including patients with New York Heart Association (NYHA) class IV symptoms or those requiring intravenous inotropes or mechanical circulatory support (MCS), corresponding to INTERMACS profiles 1–4.

Patients with advanced age (≥76 years), or severe frailty (clinical frailty scale ≥7) were excluded, as these conditions would generally preclude LVAD implantation. INTERMACS profiles 1 was defined as patients requiring immediate MCS, profile 2 as patients with progressive clinical deterioration despite intravenous inotropic support, profile 3 as patients dependent on intravenous inotropes with stable hemodynamics, and profile 4 as patients with resting symptoms consistent with NYHA class IV. Patients corresponding to profile 5 ("exertion intolerant") were likely excluded because NYHA class IV was defined based on the presence of resting symptoms in this registry.

Of them, patients categorized as high-risk according to the HeartMate Risk Score (HMRS) were excluded from the final analysis, because LVAD is generally not indicated in patients assigned to the HMRS high risk because of their high estimated mortality and morbidity rate following LVAD implantation.

HMRS is a predictive model originally developed to estimate postimplantation outcomes in patients undergoing HeartMate II LVAD implantation.[12] It is calculated using the following, and a score greater than 2.48 is classified as high risk:

$$\begin{aligned}\text{HMRS} = {} & 0.0274 \times \text{age (years)} - 0.723 \times \text{albumin (g/dL)} \\ & + 0.74 \times \text{serum creatinine (mg/dL)} + 1.136 \times \text{PT} - \text{INR} \\ & + 0.807 \text{ (if center volume} < 3 \text{ cases/year)}\end{aligned}$$

For the present analysis, we assumed that all patients who underwent M-TEER, were potentially favorable LVAD candidates, having low or intermediate HMRS (ie, despite theoretically favorable LVAD candidates, they received M-TEER, instead of durable LVAD implantation).

Study Design and our Hypothesis

The final cohort was theoretically assumed to have had acceptable clinical outcomes if they had received LVAD implantation, given their assignment to the low or intermediate risk. There should be a controversial case between LVAD implantation versus M-TEER. Eventually, all of them received M-TEER, instead of LVAD implantation.

We investigated risk factors for cardiovascular mortality during a 3-year observation period following M-TEER. Based on the robust evidence that LVAD therapy is superior to M-TEER in stabilizing hemodynamics and improving mortality and morbidity, patients who encountered the primary outcome might have avoided the events if they had received LVAD instead of M-TEER. In other words, patients with such risk factors may have been theoretically good candidates for LVAD, rather than M-TEER.

M-TEER Indication and Procedure

The indication for M-TEER was determined by multidisciplinary heart teams at each institution, including interventional cardiologists, HF specialists, cardiovascular surgeons, anesthesiologists, and other healthcare professionals. In principle, M-TEER was considered for patients with symptomatic SMR refractory to guideline-directed medical therapy. Echocardiographic

parameters, including the severity of MR and left ventricular function, were assessed by transthoracic echocardiography, while the mitral valve anatomy, which was critical to assessing the feasibility of M-TEER, was evaluated through transesophageal echocardiography conducted by echocardiography specialists at each institution.

The M-TEER procedure using the MitraClip system followed standardized protocols. It was performed under general anesthesia via a transfemoral venous and transseptal approach, utilizing a 24 Fr steerable guide catheter and clip delivery system. Device positioning was mainly guided by transesophageal echocardiography, with additional assessments following the grasping of the mitral valve leaflet. The clip was deployed upon confirmation of adequate bilateral leaflet grasping and reduction of MR. The need for additional clips was considered based on the degree of residual MR and mitral stenosis postdeployment. The procedural end point was defined as acute procedural success, indicated by achieving residual MR of moderate or less.

End Points and Definitions

Data related to the procedure, such as procedural time, number of implanted devices, whether acute procedure success was achieved, and procedure related complications, were collected. Postprocedural data, including in-hospital mortality and the recurrence of MR, were also obtained.

Clinical outcomes were prospectively monitored for up to 3 years after the procedure through scheduled outpatient visits and review of medical records within the OCEAN-Mitral registry, with follow-up censored in June 2024. Patients lost to follow-up were censored at the time of the last available contact. The primary outcome of interest was cardiovascular death, selected as a clinically meaningful end point to evaluate appropriateness of M-TEER in high-risk patients who might otherwise be considered for advanced therapies such as LVAD. The secondary outcome was HF hospitalization.

Statistical Analyses

Statistical analyses were conducted using JMP Pro 18 (SAS Institute Inc., Cary, NC, USA), except for the competing risk analysis, which was conducted using EZR (Jichi Medical University, Tochigi, Japan). Two-sided *P* values <0.05 were considered statistically significant. Continuous variables were reported as medians with interquartile ranges, while categorical variables were presented as frequencies and percentages. Comparisons of continuous variables were performed using either Student *t* test or the Mann–Whitney U test, depending on data distribution. For categorical variables, Pearson χ^2 test or Fisher's exact test was employed as appropriate. As missing data were minimal, complete-case analyses were performed.

Kaplan–Meier curve was constructed from the date of the procedure to assess cardiovascular mortality and the differences between groups were assessed using log-rank test. In addition, as an exploratory subgroup analysis, we examined factors associated with cardiovascular death in patients who were potential candidates for LVAD, to better understand the risk factors in this high-risk group. Cox proportional hazards regression analysis was conducted to identify factors associated with cardiovascular death following M-TEER. Candidate variables were prespecified based on clinical relevance and their availability prior to the procedure. Candidate variables were evaluated in univariate analysis, with variables showing *P* values <0.05 and/or considered clinically relevant were included in the multivariable analysis using a forced-entry method. All continuous variables were analyzed as continuous variables in the Cox models. The proportional hazards assumption was evaluated by testing time-dependent effects using interaction terms between each covariate and log-transformed time. When non-proportionality was suggested, landmark analysis was prespecified to separately assess early and late hazards. Procedural variables were not included in the primary multivariable analysis because the aim of the study was to identify pre-procedural prognostic criteria. We further compared longitudinal changes in left ventricular dimension and LVEF based on the cutoff values of variables identified by multivariable analysis using receiver operating characteristic curve analysis. Longitudinal trajectories were analyzed using mixed-effects models with patient-level random intercepts to account for repeated measurements over time.

RESULTS

Baseline Characteristics

Among 3764 patients who underwent M-TEER between April 2018 and June 2023 and were enrolled in the OCEAN-Mitral registry, 129 patients were potentially favorable candidates for durable LVAD implantation after applying the careful selection criteria described in the Methods section. In other words, these patients received M-TEER despite having a good indication of LVAD therapy (ie, conflicting cases between LVAD implantation and M-TEER). The patient selection flowchart was presented in Figure 1.

Baseline characteristics of the included patients were shown in Table 1 and Table S1. The mean age was 67 years, and 67% were male. More than 90% of patients had a history of hospitalization for HF, and more than 70% of the cohort required inotropes before undergoing M-TEER. The mean systolic blood

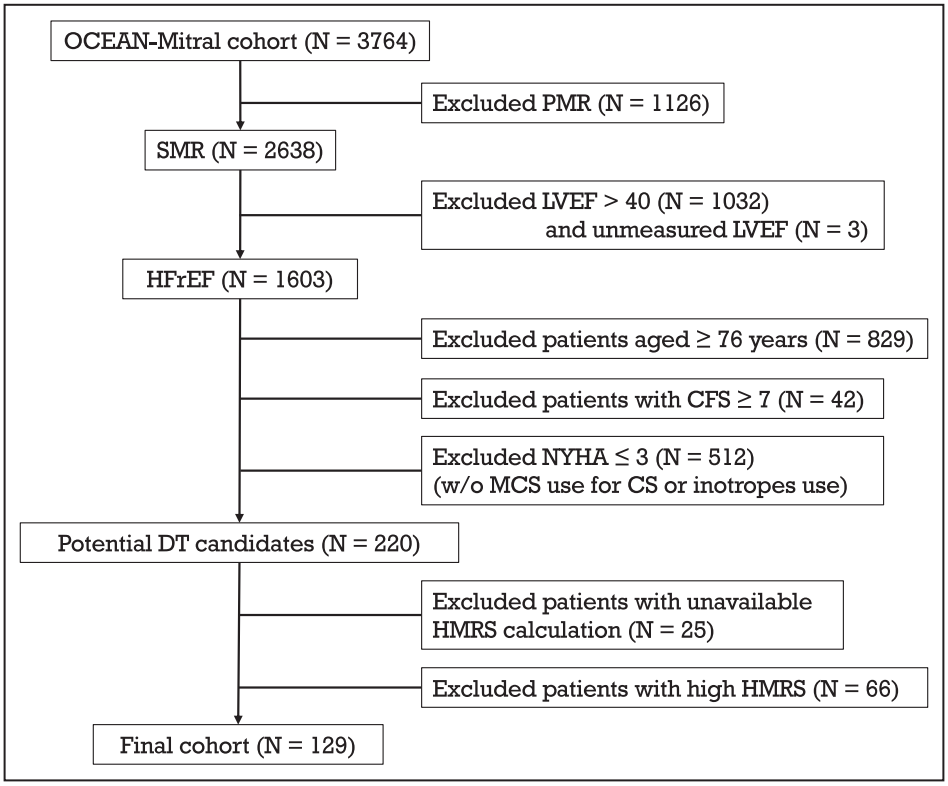

Figure 1. Flow diagram of patient selection for DT candidates.
CFS indicates clinical frailty scale; CS, cardiogenic shock; DT, destination therapy; HFrEF, heart failure with reduced ejection fraction; HMRS, HeartMate Risk Score; LVEF, left ventricular ejection; MCS, mechanical circulatory support; NYHA, New York Heart Association; PMR, primary mitral regurgitation; and SMR, secondary mitral regurgitation.

pressure was 93 mm Hg, reflecting their compromised hemodynamic status. The mean HMRS was 1.56, being assigned to low or intermediate risk. Beta blockers were administered in >80% of the cases, whereas renin-angiotensin system inhibitors were introduced in <70%, possibly attributable to hypotension. Plasma B-type natriuretic peptide levels were above 500 pg/mL. Echocardiography demonstrated advanced cardiac remodeling, with many cases presenting with severe MR.

Peri-Procedural Findings

Procedural data were displayed in Table 2. The acute procedure success rate was above 95%, which was comparable to that observed in the overall patient population.[13] The anesthesia time, procedural time, and device time were 144 minutes, 75 minutes, 52 minutes, respectively. The number of implanted clips was one in two-thirds of the cases, while 2 clips were required in the remaining one-third.

Procedure-related complications were infrequent, though postoperative acute kidney disease and a requirement for iatrogenic atrial septal defect closure were observed in approximately 3% of total cases. The number of in-hospital deaths was 5 cases (3.9%). The proportion of patients receiving guideline-directed medical therapy, including renin-angiotensin system inhibitor and beta blockers, was reduced after the procedure compared with the pre-procedural period.

Clinical Outcomes Following M-TEER and Associated Baseline Factors

The median follow-up period was 476 (interquartile range 337–838) days. The 1-year mortality rate after M-TEER was relatively low (10.1%), but it increased substantially to 38.9% at 3 years (Figure 2A). The 1- and 3-year cumulative incidences of HF hospitalization, with death as a competing risk, were also considerably high at 26.9% and 43.8%, respectively (Figure 2B).

In univariate analysis, higher C-reactive protein (CRP), larger LV end-diastolic dimension (LVDd), and lower LVEF were associated with the development of cardiovascular death. In a multivariable analysis including these 3 factors, higher C-reactive protein and larger LV dimension were independently associated

Table 1. Baseline Characteristics

	Overall
No.	129
Age, y	67 (60, 71)
Men, n (%)	87 (67.4)
BMI, kg/m^2	20.8 (18.6, 23.1)
Systolic BP, mm Hg	93 (85, 102)
Heart rate, /min	80 (70, 90)
Ischemic heart disease, n (%)	48 (37.2)
History of stroke, n (%)	12 (9.3)
History of VT or VF, n (%)	37 (28.7)
Clinical frailty scale, degree	3 (3, 4)
AF or AT, n (%)	32 (24.8)
CRT implantation, n (%)	37 (28.7)
STS score for MVR, %	5.8 (3.4, 10.4)
INTERMACS profile 1–2 (MCS use for cardiogenic shock), n (%)	4 (3.1)
INTERMACS profile 3 (Inotropes before M-TEER), n (%)	87 (67.4)
INTERMACS profile 4 (Resting symptom), n (%)	38 (29.5)
HMRS	1.56 (1.19, 1.97)
HMRS (low/intermediate/high)	65 (50.4)/64 (49.6)/0 (0)
Medications	
RAS inhibitor, n (%)	89 (69.0)
Beta blocker, n (%)	104 (80.6)
MRA, n (%)	105 (81.4)
SGLT2 inhibitor, n (%)	46 (35.7)
Dose of furosemide, mg	40 (20, 40)
Laboratory data	
Hemoglobin, g/dL	12.1 (10.6, 13.6)
Albumin, g/dL	3.6 (3.3, 3.9)
Creatinine, mg/dL	1.14 (0.91, 1,55)
BNP, pg/mL	536 (320, 1137)
CRP, mg/dL	0.30 (0.10, 0.90)
Echocardiogram	
LA volume index, mL/m^2	78 (60, 106)
LV end-diastolic diameter, mm	68 (54, 68)
LV end-systolic diameter, mm	60 (54, 68)
LV ejection fraction, %	26.4 (22.2, 30.7)
E/e′	16.6 (12.8, 21.0)
MR severity (mild/moderate/moderate–severe/severe)	0 (0)/0 (0)/20 (15.5)/33 (25.6)/76 (58.9)
EROA, cm^2	0.37 (0.28, 0.50)
MVA, cm^2	5.4 (4.5, 6.5)
TR severity (NA/none/mild/moderate/moderate–severe/severe)	1 (0.8)/24 (18.6)/58 (44.9)/40 (31.0)/5 (3.9)/1 (0.8)

Continuous variables are presented as median (interquartile range). AF indicates atrial fibrillation; AT, atrial tachycardia; BMI, body mass index; BNP, type B natriuretic peptide; BP, blood pressure; CRP, C reactive protein; CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; HF, heart failure; HMRS, heartmate risk score; LA, left atrium; LV, left ventricle; M-TEER, transcatheter edge-to-edge repair for mitral valve; MCS, mechanical circulatory support; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; MVA, mitral valve area; MVR, mitral valve replacement; RAS, renin-angiotensin-aldosterone; SGLT2, sodium-glucose co-transporter 2; TR, tricuspid regurgitation; VT, ventricular tachycardia; and VF, ventricular fibrillation.

with cardiovascular death (P<0.05 for both) (Table 3). Because the proportional hazards assumption was violated for both CRP and LVDd in the time-dependent interaction analysis, a prespecified 1-year landmark Cox proportional hazards analysis were performed. In this model, larger LVDd remained significantly associated with cardiovascular death, whereas CRP and LVEF were not. Details results are shown in Table 4.

Although LVDd was analyzed as a continuous variable in all Cox models, patients were stratified according to the statistically derived cutoff value of 69 mm for descriptive illustration only. Using this illustrative stratification, the group with LVDd ≥69 mm showed a higher rate of cardiovascular mortality compared with the group with LVDd <69 mm (hazard ratio: 2.65, 95% CI: 1.17–5.98, P=0.013) (Figure 3).

Temporal Change in Clinical Parameters Stratified by LV Size

Changes in clinical parameters following M-TEER are shown in Figure 4. All patients were in NYHA class IV before the procedure, but the majority improved to below class II after M-TEER (Figure 4A). Notably, in the group with LVDd <69 mm, over 90% of patients

Table 2. Procedural Data

	Overall
No.	129
Procedural data	
Anesthesia time, min	144 (122, 189)
Procedural time, min	75 (59, 110)
Device time, min	52 (35, 74)
No. of implanted clips (1/2/3)	86 (66.7)/42 (32.6)/1 (0.8)
Acute procedure success, n (%)	124 (96.1)
Procedure related complications	
Major pericardial effusion, n (%)	0 (0)
Access site complication, n (%)	1 (0.8)
TEE associated complication, n (%)	0 (0)
Pulmonary complication, n (%)	0 (0)
Acute kidney injury, n (%)	4 (3.1)
SLDA, n (%)	0 (0)
Leaflet tear, n (%)	1 (0.8)
Clip embolization, n (%)	0 (0)
Requirement of IASD closure n (%)	4 (3.1)
Postprocedural adverse event	
Recurrence of MR, n (%)	9 (7.0)
In-hospital death, n (%)	5 (3.9)

Continuous variables are presented as median (interquartile range). IASD indicates iatrogenic atrial septal defect; MR, mitral regurgitation; SLDA, single leaflet device attachment; and TEE, transesophageal echocardiography;

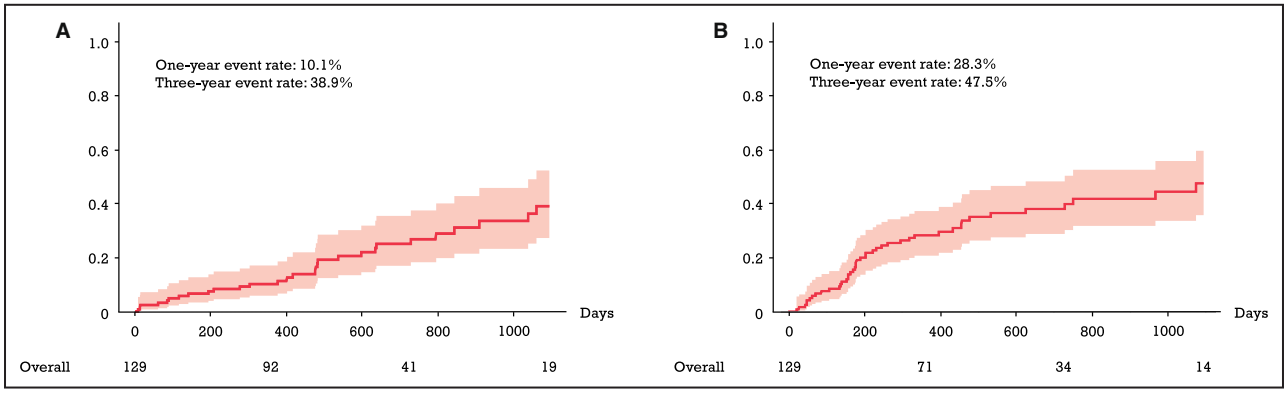

Figure 2. A, Kaplan–Meier curve for cardiovascular death following M-TEER, (B) Kaplan–Meier curve for heart failure hospitalization.
M-TEER indicates transcatheter edge-to-edge repair of the mitral valve.

maintained NYHA class below II even at 1 year. The distribution of MR severity at 1 year was not favorable even in patients with LVDd <69 mm (Figure 4B). A noteworthy finding was that the group with LVDd <69 mm demonstrated a modest tendency toward reverse remodeling in LV dimension (Figure 4C) and clear improvement in LVEF over time (Figure 4D), whereas the group with LVDd ≥69 mm exhibited no meaningful improvement in either parameter (P>0.05 for the time effect in the mixed-effect model).

DISCUSSION

In this study, we attempted to identify optimal candidates for VAD implantation versus M-TEER. For the clarification of our aim, we investigated the risk factors

Table 3. Univariable and Multivariable Cox Proportional Hazards Model for Cardiovascular Death

	Univariate analysis			Multivariable analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age, per 1 y	1.02	0.97–1.08	0.3920			
Men	1.29	0.57–2.92	0.5368			
SBP, per 5 mm Hg	0.74	0.52–1.03	0.0748			
CFS, per 1 grade	1.37	0.98–1.88	0.0678			
IHD	0.70	0.31–1.58	0.3790			
History of VT or VF	0.87	0.37–2.04	0.7427			
Prior stroke	2.50	0.95–6.58	0.0641			
Use of inotropes	1.48	0.63–3.48	0.3645			
Use of MCS	3.25	0.76–13.9	0.1120			
Hemoglobin, per 1 g/dL	0.96	0.78–1.16	0.6446			
Albumin, per 1 g/dL	0.55	0.26–1.18	0.1243			
Creatinine, per 1 mg/dL	1.35	0.63–2.71	0.4232			
BNP, per 100 pg/mL	1.03	0.98–1.07	0.2107			
CRP, per 1 mg/dL	1.16	1.04–1.25	0.0121	1.16	1.05–1.26	0.0084
LAVI, per 10 mL/m^2	1.00	0.89–1.11	0.9951			
LVDd, per 1 mm	1.07	1.02–1.12	0.0035	1.07	1.02–1.12	0.0099
LVEF, per 1%	0.93	0.87–0.99	0.0208	0.95	0.89–1.01	0.1118
MR severity, per 1 grade	1.34	0.79–2.52	0.2969			

BNP indicates type B natriuretic peptide; CFS, clinical frailty scale; CRP, C-reactive protein; EF, ejection fraction; IHD, ischemic heart disease; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic diameter; MCS, mechanical circulatory support; MR, mitral regurgitation; SBP, systolic blood pressure; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 4. Multivariable Cox Proportional Hazards Model for Cardiovascular Death in the 1-Year Landmark Analysis

	Hazard ratio	95% CI	*P* value
CRP, per 1 mg/dL	0.94	0.51–1.34	0.7789
LVDd, per 1 mm	1.09	1.03–1.16	0.0028
LVEF, per 1%	0.99	0.92–1.08	0.8864

CRP indicates C-reactive protein; EF, ejection fraction; and LVDd, left-ventricular end-diastolic diameter.

for cardiovascular mortality following M-TEER in patients with advanced HF who were potentially favorable candidates for LVAD therapy (satisfying indication of durable LVAD implantation with low- or intermediate-risk), using a large-scale cohort in Japan. The main findings are as follows (Central illustration).

First, among all patients who underwent M-TEER for SMR, 4.9% were theoretically potential favorable candidates for durable LVAD therapy, and this cohort had severely impaired LV function (ie, they received M-TEER despite being good candidates for durable LVAD therapy). Second, M-TEER could be performed safely even in patients with advanced HF, such as those in the present study, and their outcomes—particularly short-term outcomes—were relatively acceptable. Third, largely remodeled LV and elevated inflammatory markers were identified as potential risk factors for cardiovascular death following M-TEER (despite they were assumed to be good LVAD candidates). Finally, patients with largely remodeled LV had a higher incidence of cardiovascular death after M-TEER, and they showed a tendency toward progressive deterioration of LV function.

Current Indication of M-TEER in Critically Ill Patients

In case of severe SMR, excluding those with extremely reduced LVEF or right ventricle failure, M-TEER is recommended as a class IIa indication according to the current guidelines, provided the patients meet the inclusion criteria of the COAPT trial.[14] For patients not meeting these criteria, M-TEER may still be considered to improve patients' symptoms and quality of life when other therapeutic options are unavailable. In those with severely impaired ventricular function, cardiac replacement therapy, including heart transplantation and LVAD therapy, is considered. Importantly, any types of valve intervention are not recommended in patients with an LVEF of less than 15%. Other challenging situations include patients receiving intravenous inotropes or requiring temporary MCS. In the real-world clinical practice, eventual indication of M-TEER is at the discretion of the attending clinicians.

In the present study, we included several potentially favorable LVAD candidates, who eventually received M-TEER: patients with extremely impaired LV function were included, with 20% having an LV end-systolic diameter ≥ 70 mm and 15% having an LVEF <20%, both of which were beyond the COAPT criteria, representing real-world clinical practice.

On the other hand, requiring intravenous inotropes or temporary MCS, which were likewise excluded in the COAPT trial, may not completely be the contraindication for M-TEER, as seen also in the present study (70.5%). Recent study suggested that prior reduction

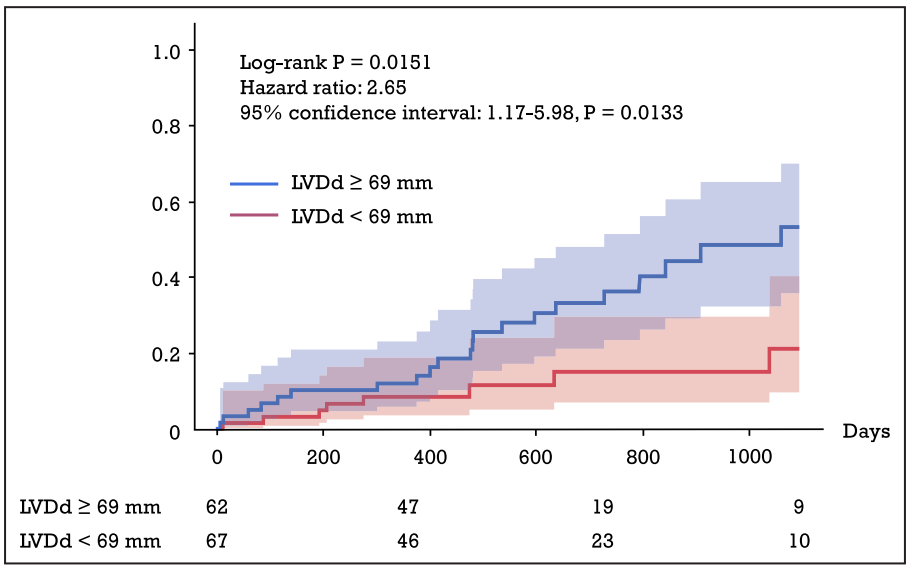

Figure 3. Kaplan–Meier curve for cardiovascular death following M-TEER stratified by the LV size.
LV indicates left ventricle; LVDd, LV end-diastolic dimension; and M-TEER, transcatheter edge-to-edge repair of the mitral valve.

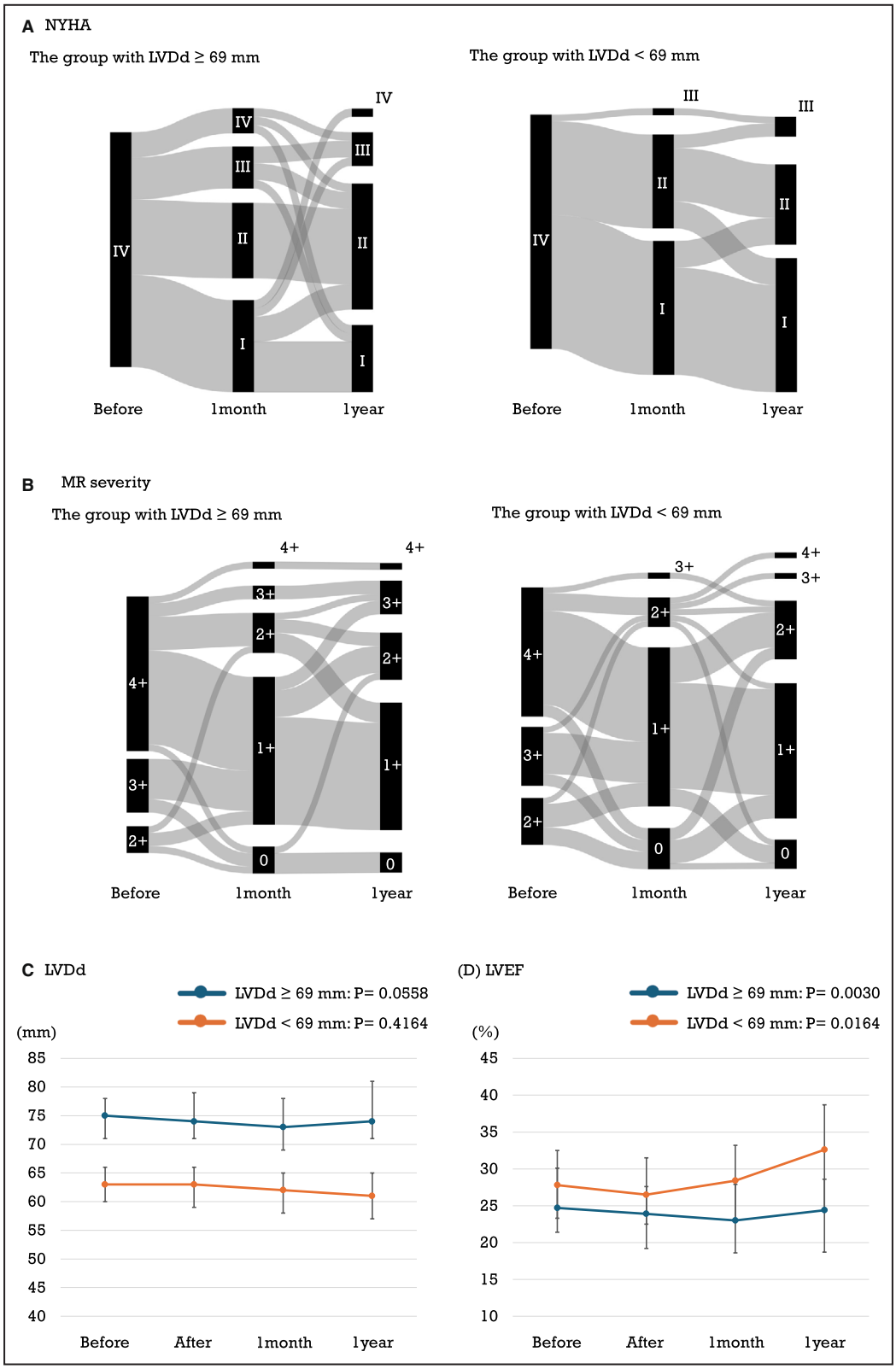

Figure 4. Changes in parameters following M-TEER according to LV size.
A, NYHA, **(B)** MR severity, **(C)** LVDd, and **(D)** LVEF. LV indicates left ventricle; LVDd, LV end-diastolic diameter; LVEF, left ventricular ejection fraction; M-TEER, transcatheter edge-to-edge repair of the mitral valve; MR, mitral regurgitation; and NYHA, New York Heart Association.

in MR by these intensive interventions, followed by M-TEER, may lead to favorable outcomes in carefully selected patients.[3]

Indication for LVAD Implantation as DT or Bridge to Transplantation

The optimal candidates for LVAD implantation are patients with stage D HFrEF who exhibit progressive symptoms despite receiving optimal medical therapy, corresponding to NYHA IV, after excluding those with significant comorbidity or unfavorable social conditions. Of note, this indication also encompasses patients who are dependent on inotropic support or temporary MCS for hemodynamic stabilization. In recent years, DT-LVAD has become increasingly prevalent, particularly among patients who are not candidates for heart transplantation owing to advanced age, psychosocial factors, or other contraindications.[15]

More than 40% of patients with HFrEF have significant SMR.[16] Given the accumulating evidence that durable LVAD implantation alone can ameliorate significant SMR without concomitant intervention to the mitral valve, some candidates of M-TEER, particularly when they have advanced HF and SMR, can be overlapped with the therapeutic targets of LVAD implantation.

The HeartMate 3 (Abbott Vascular Inc., Santa Clara, CA, USA), a centrifugal-flow LVAD that obtained CE mark in 2015 and FDA approval in 2017, has become the mainstream device in current practice. The MOMENTUM 3 trial demonstrated that HeartMate 3 was associated with fewer LVAD-related complications and improved long-term survival compared with conventional HeartMate II.[8] In addition to prolonging survival, LVAD implantation markedly improves symptoms, exercise tolerance, and quality of life, with these effects being maintained over extended periods.[17]

Despite the benefits of LVAD implantation, device-related complications, including bleeding, ischemic stroke, and pump thrombosis, as well as right ventricular failure, driveline infections, and the burden on patients and caregivers, remain challenges.[18–20] In addition, the high cost necessitates careful consideration of LVAD indication.[21]

Optimal Therapeutic Strategy for Patients With Advanced HF With SMR

M-TEER may be considered an alternative therapeutic option for patients who are potential LVAD candidates, but for whom LVAD implantation poses concerns related to surgical risk, device management, or social circumstances. However, given the relatively high mortality, M-TEER cannot be considered universally beneficial for all such patients, underscoring the critical importance of careful patient selection.

Based on our findings, the calculated cutoff of LV diameter was 69 mm, which is approximately equivalent to the COAPT indication. M-TEER is a focal intervention to the mitral valve alone, and may not be sufficient to compensate extremely remodeled LV. This concept aligns with the framework of disproportionate versus proportionate MR. Patients with disproportionate MR, in which MR severity exceeds the degree of LV dilatation, are more likely to benefit from M-TEER, whereas those with proportionate MR and advanced LV remodeling show limited response because of predominant LV dysfunction. In this study, the group with LVDd ≥69mm corresponded to proportionate MR, characterized by advanced LV remodeling and limited MR severity relative to LV dilation.

Although elevated CRP levels were also associated with adverse outcomes, CRP was not a determinant for selecting LVAD over M-TEER, as higher CRP reflects systemic inflammation and frailty that are unfavorable in both contexts. Therefore, our additional analysis only focused on LV size.

In addition, optimal medical therapy is paramount in HF management. However, in patients with end-stage HF, as represented by the present study cohort, the feasibility of further intensifying medical therapy is often limited, thereby restricting its potential to improve clinical outcomes.

The indication of M-TEER is expanding in real-world clinical practice, as shown in the present study, but we alert to focus on the LV diameter for optimal patient selection. If remodeling is excessively advanced, consideration of LVAD implantation may be warranted, given their relatively worse clinical outcomes following M-TEER despite their low or intermediate LVAD risk. However, this is just our hypothesis. Prospective randomized controlled trials are warranted to compare clinical outcomes between LVAD therapy and M-TEER in this cohort and to conclude the superiority of LVAD therapy over M-TEER.

When we choose M-TEER rather than LVAD, we may still have a chance to implant LVAD following M-TEER, if indicated, as also suggested by the findings from the MitraBridge registry.[22] Although LVAD implantation after M-TEER is technically feasible, concerns remain that changes in mitral valve inflow dynamics, such as reduced valve area, may negatively affect outcomes after LVAD implantation.[23] While some studies have shown that LVAD implantation can be safely performed after M-TEER with comparable outcomes,[24] more progressed hemodynamic deterioration and advanced systemic impairment may let us miss the optimal surgical timing because of prolonged inappropriate LV unloading by M-TEER. Importantly, careful post–M-TEER surveillance is essential to avoid missing the optimal timing for LVAD implantation, and further

studies are warranted to better define the optimal therapeutic sequencing in this high-risk population.

Limitations

This study has several limitations. First, although this is the largest Japanese observational study, the number of potentially favorable candidates for LVAD implantation is relatively small. Because of this limited sample size, the statistical power to detect small-to-moderate differences in clinical outcomes may have been insufficient, and the possibility of type II error cannot be excluded. It is noteworthy that approximately 5% of patients with SMR treated with M-TEER were eligible for LVAD implantation. All participants in the present study underwent M-TEER, despite also having a potential indication of LVAD implantation. This was because the DT strategy has been approved in Japan since 2021 and only very carefully selected patients underwent LVAD implantation as a destination therapy.

Second, we assumed patients to be potentially favorable LVAD candidates when they had indication of durable LVAD therapy and were assigned to low- or intermediate-risk in the HMRS. The cohort may not accurately represent general LVAD candidates, as all patients in the present study were actual M-TEER candidates.

Third, HMRS was used to evaluate the risk of LVAD implantation in this study. Currently, the HeartMate 3 has become the mainstream implantable LVAD, and the HMRS may overestimate the risk in the contemporary era. The HeartMate 3 Risk Score has been proposed as a new risk assessment model.[25] However, it has not yet been validated in Japanese patients. Therefore, we used HMRS, as it remains the reference indicator for patient selection in Japan.

Fourth, the use of guideline-directed medical therapy decreased after M-TEER. Potential contributing factors may include postprocedural hypotension, worsening renal function and hemodynamic instability associated with withdrawal of inotropic support. It is possible that outcomes might have differed if adequate guideline-directed medical therapy had been maintained or further intensified after M-TEER.

Finally, the study population included patients on inotropic support and those who underwent MCS, which may have contributed to heterogeneity in clinical outcomes.

CONCLUSIONS

Despite its procedural safety and short-term benefits, the long-term outcomes of M-TEER remain limited in patients with advanced HF and SMR who are theoretically potential favorable candidates for LVAD therapy, particularly when they have extremely remodeled LV. Further investigation is warranted to clarify the optimal therapeutic approach, including the potential role of LVAD therapy versus M-TEER, in the population with a high risk for M-TEER.

ARTICLE INFORMATION

Received September 17, 2025; accepted February 16, 2026.

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Acknowledgments

The authors thank the investigators and institutions that contributed to the OCEAN-Mitral registry.

Sources of Funding

No funding was obtained for this study.

Disclosures

The OCEAN-Mitral registry which is part of OCEAN-SHD registry is supported by Edwards Lifesciences, Medtronic Japan, Boston Scientific, Abbott Medical Japan, and Daiichi-Sankyo Company. Dr Ueno, Dr Kubo, Dr Izumi, Dr Saji, Dr Izumo, Dr Watanabe, Dr Amaki and Dr Kodama are clinical proctors of transcatheter edge-to-edge repair for Abbott Medical and have received consultant fees from Abbott Medical. Dr Asami and Dr Kodama are clinical proctors of transcatheter edge-to-edge repair for Abbott Medical and have received speaker fees from Abbott Medical. Dr Yamamoto is a clinical proctor of transcatheter edge-to-edge repair for Abbott Medical and has received lecture fees from Abbott Medical. Dr Otsuki has received lecture fees and a scholarship donation from Abbott Medical. Dr Ohno has received consultant, advisor, and speaker fees from Abbott Medical. Dr Hayashida, Dr Enta, Dr Shirai, Dr Mizuno, and Dr Bota are clinical proctors of transcatheter edge-to-edge repair for Abbott Medical. The other authors have no relationships relevant to the content of this article.

Supplemental Material

Table S1
List of OCEAN-Mitral Investigators
STROBE Checklist

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