

Five-year outcomes of the early-generation Intrepid transapical transcatheter mitral valve replacement system

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ABSTRACT

BACKGROUND: Transcatheter mitral valve replacement (TMVR) offers a potential treatment option for select patients with mitral regurgitation (MR) deemed unsuitable for surgery or transcatheter repair, but data are limited on its long-term durability and performance.

AIMS: We evaluated 5-year outcomes from the global Pilot Study with the Intrepid transapical (TA) TMVR system.

METHODS: This multicentre, single-arm study evaluated the early-generation Intrepid TA system in patients with symptomatic \geq moderate-severe MR at high risk for mitral valve (MV) surgery. Echocardiograms and clinical events were independently adjudicated, and patients were followed for up to 5 years.

RESULTS: Ninety-five patients were enrolled at 21 sites between 2015 and 2019. The mean age was 74.0 ± 9.2 years, 43.2% of patients were female, the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was $6.5 \pm 4.8\%$, 57.9% had prior heart failure hospitalisation (HFH), and 88.4% were in New York Heart Association (NYHA) Functional Class III/IV. Secondary MR was present in 78.7%, and 76.6% had a left ventricular ejection fraction $\leq 50\%$. Up to 5 years, all-cause mortality was 66.7% and HFH was 55.4%, with one 30-day MV reintervention (1.1%). Haemodynamic valve deterioration occurred in 1.4%, the median MV mean gradient remained stable at 3.6 mmHg (first and third quartiles: 3.0, 4.8 mmHg), \leq mild MR was present in 100% of patients, and no patient experienced paravalvular leak. NYHA Functional Class I/II was maintained in 84.6%.

CONCLUSIONS: In this 5-year follow-up of the early-generation Intrepid TA TMVR system, we observed sustained MR reduction, durable haemodynamic valve performance, and improved functional status among survivors. The APOLLO (ClinicalTrials.gov: NCT03242642) and APOLLO-EU (NCT05496998) trials using the transfemoral Intrepid system will further determine the role of TMVR in managing this high-risk patient population. ClinicalTrials.gov: NCT02322840

KEYWORDS: durability; haemodynamic performance; long term; mitral regurgitation; TMVR; transapical

Conventional surgical mitral valve (MV) repair or replacement improves longevity and quality of life for patients with MV disease. However, fewer than one-half of patients with \geq moderate-severe mitral regurgitation (MR) are referred for MV surgery, primarily due to high surgical risk^{1,2}. The self-expanding Intrepid transcatheter mitral valve replacement (TMVR) system (Medtronic) is a less invasive investigational technology to treat MR. Data from the pooled analysis of the Pilot Study (ClinicalTrials.gov: NCT02322840) and the initial phase of the APOLLO trial (NCT03242642) using the early-generation transapical (TA) Intrepid system showed excellent device haemodynamics with the ability to eliminate MR up to 2 years³. The device performance data were further confirmed in the next-generation transfemoral system, which demonstrated improved safety outcomes up to 2 years in patients treated under an early feasibility study^{4,6}.

In order to treat severe MR in patients who are ineligible for conventional MV surgery or transcatheter MV repair, two TMVR devices are currently approved for commercial use in Europe (Tendyne [Abbott], SAPIEN M3 [Edwards Lifesciences]). Additionally, the Tendyne system recently received U.S. Food and Drug Administration approval for treating patients with symptomatic severe MV disease associated with severe mitral annular calcification. However, long-term data on device durability and clinical outcomes after TMVR beyond 3 years have not been reported⁷. The present Pilot Study aimed to evaluate the 5-year clinical and echocardiographic outcomes focused on device performance after TMVR with the Intrepid TA TMVR system.

Editorial, see page e133

Methods

STUDY DESIGN AND PATIENT POPULATION

The Intrepid TMVR global Pilot Study is a multicentre, prospective, non-randomised study evaluating the safety and performance of the Intrepid TA TMVR system in patients at high risk for conventional MV surgery. Patients were recruited from 21 hospitals in Australia, Europe, and the US (**Supplementary Table 1**). Key eligibility criteria, study device, procedure-related details, and endpoints of the Pilot Study have been reported previously^{3,8}. Briefly, inclusion criteria were age >18 years, symptomatic \geq moderate-severe MR (3-4+), no or minimal MV calcification, and a left ventricular ejection fraction (LVEF) $\geq 20\%$. Key exclusion criteria were severe pulmonary hypertension, need for coronary revascularisation, haemodynamic instability, need for other surgical valvular therapy, severe renal insufficiency, and prior MV surgery or intervention. The complete inclusion/exclusion criteria are listed in **Supplementary Table 2**. Institutional review board approval was obtained in all centres, and patients provided informed consent for study participation.

Abbreviations

HFH	heart failure hospitalisation	MV	mitral valve	TA	transapical
LVEF	left ventricular ejection fraction	MVARC	Mitral Valve Academic Research Consortium	TEER	transcatheter edge-to-edge repair
MDCT	multidetector computed tomography	PVL	paravalvular leak	TMVR	transcatheter mitral valve replacement
MR	mitral regurgitation				

Impact on daily practice

Intrepid transapical (TA) transcatheter mitral valve replacement (TMVR) was associated with long-term mitral regurgitation (MR) elimination, durable haemodynamic valve performance, and improved functional status among survivors up to 5 years in selected patients with symptomatic \geq moderate-severe MR. The 5-year clinical and echocardiographic outcomes will help Heart Teams in the decision-making process for MR treatment and underscore the need for optimal patient selection and heart failure therapies. With 5-year valve performance of the Intrepid TA TMVR system now available, future studies on transfemoral TMVR and comparison studies with transcatheter edge-to-edge repair will better define the role of TMVR in the management of high surgical risk patients with \geq moderate-severe MR.

The early-generation Intrepid TMVR system comprised a self-expanding, nitinol dual-stent valve and a TA delivery system. A circular inner stent frame houses a 27 mm trileaflet bovine pericardial valve, and a conformable outer stent anchors to the native anatomy without leaflet capture. The valve is delivered transapically via a 35 Fr catheter access sheath. The early-generation system included valves with outer fixation ring diameters of 43, 46, and 50 mm, whereas 42 and 48 mm valves are used in current clinical trials^{3,8}.

Anatomical suitability for TA TMVR was determined using transoesophageal echocardiography and multidetector computed tomography (MDCT). Study eligibility was determined by local Heart Teams at the study sites (including, at the minimum, a cardiac surgeon, an interventional cardiologist, and an echocardiologist) and approved by an independent physician committee. An independent clinical events committee, which also served as the data and safety monitoring board (Stanford University, Stanford, CA, USA), adjudicated endpoint-related adverse events and reviewed the safety results. Echocardiographic endpoints were assessed by an independent echocardiographic core laboratory (Mayo Clinic, Rochester, MN, USA).

STUDY ENDPOINTS AND DEFINITIONS

Clinical and transthoracic echocardiography assessments were performed at discharge, 1 month, 3 months, 6 months, 12 months, and biannually thereafter for up to 5 years. Unscheduled echocardiograms were performed by sites if clinically indicated and reviewed by the echocardiographic core laboratory. The severity of MR was assessed according to American Society of Echocardiography criteria⁹. Moderate haemodynamic valve deterioration was defined according to the Heart Valve Collaboratory 2022 and Mitral Valve

Academic Research Consortium (MVARC) 2015 criteria as an increase in the mean transmural gradient of ≥ 5 mmHg from 30 days/discharge to the last available echocardiogram or transvalvular MR \geq moderate, while severe haemodynamic valve deterioration was defined as a mean transmural gradient of ≥ 10 mmHg or MR \geq moderate-severe^{10,11}.

MDCT was collected per protocol at discharge and 1 year for patients enrolled at US sites. Quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire at baseline and 1 year, as previously reported³. New York Heart Association (NYHA) Functional Class was assessed from baseline to 5 years. Standard definitions for clinical events were used in accordance with the MVARC 2015 criteria¹¹, except for device thrombosis, as described in **Supplementary Appendix 1**. Post-procedure anticoagulation was prescribed per physician discretion but was recommended for at least 3-6 months post-implant, or longer unless there was a clinical indication to discontinue it.

STATISTICAL ANALYSIS

Continuous variables are summarised as mean \pm standard deviation, or median and first (Q1) and third quartiles (Q3), as appropriate. Categorical variables are reported as frequencies and percentages. Adverse event rates were estimated as Kaplan-Meier estimates and reported at 30 days, 1 year, and 5 years. Thrombosis and endocarditis events were also reported as linearised rates with 95% confidence intervals (CIs), expressed per 100 patient-years. All-cause, cardiovascular, and non-cardiovascular mortality were landmarked at 1 year post-procedure to assess the later impact of TMVR by excluding events potentially attributable to the TA approach. Paired echocardiographic analysis was performed using the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Change in NYHA Class from baseline was assessed using the Wilcoxon signed-rank test. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed by the sponsor using SAS software, version 9.4 (SAS Institute).

Results

BASELINE CHARACTERISTICS

The study cohort included 95 patients who had undergone TA TMVR between 2015 and 2019 and completed 5-year follow-up. Demographics, baseline characteristics, and medical history are presented in **Table 1**. The mean age was 74.0 \pm 9.2 years, 43.2% of patients were female, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score for MV replacement was 6.5 \pm 4.8%, 57.9% had experienced a heart failure hospitalisation (HFH) within the year preceding enrolment, and 88.4% were in NYHA Class III/IV. The predominant mechanism of MR was secondary (78.7%), 70.2% had an LVEF \leq 50%, and nearly all had \geq moderate-severe MR (95.8%). Four patients were initially treated for \geq moderate-severe MR based on the site echocardiogram reading but were later found to have lower MR severity after formal core lab review.

INTRAPROCEDURAL AND 30-DAY CLINICAL OUTCOMES

A summary of the patient flow is provided in **Figure 1**. The Intrepid valve was successfully implanted in 92 (96.8%) of

Table 1. Baseline patient characteristics.

	(n=95)
Age, years	74.0 \pm 9.2
Sex	
Male	56.8 (54)
Female	43.2 (41)
STS-PROM score, %	6.5 \pm 4.8
NYHA III/IV	88.4 (84)
Diabetes	37.9 (36)
Hypertension	78.9 (75)
Prior MI	42.1 (40)
HFH within the past year	57.9 (55)
\geq Moderate chronic lung disease	25.3 (24)
Peripheral artery disease	15.8 (15)
Prior stroke	13.7 (13)
Prior PCI	42.1 (40)
Prior cardiac surgery	47.4 (45)
Prior valve surgery	10.5 (10)
CABG	40.0 (38)
GFR <60 mL/min/1.73 m ²	57.4 (54/94)
Atrial fibrillation/atrial flutter	60.0 (57)
Prior ICD	28.4 (27)
Prior CRT	15.8 (15)
Aetiology of MR	
Primary MR	21.3 (20/94)
Secondary MR	78.7 (74/94)
\geq Moderate-severe MR	95.8 (91)
LVEF, %	45.2 \pm 10.6
LVEF \leq 30%	6.4 (6/94)
LVEF 30-50%	63.8 (60/94)
LVEF >50%	29.8 (28/94)
Valve size deployed	
43, 46, or 50 mm	94.7 (89/94)
42 or 48 mm	5.3 (5/94)

Data are presented as mean \pm standard deviation, % (no. of patients), or % (n/N). CABG: coronary artery bypass graft; CRT: cardiac resynchronisation therapy; GFR: glomerular filtration rate; HFH: heart failure hospitalisation; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

95 patients. In one patient, the procedure was aborted prior to valve deployment because of uncontrolled bleeding around the sutures at the apical incision site. The other two patients underwent conversion to surgical mitral valve replacement during the index procedure due to device malposition/migration. Clinical outcomes for the attempted implant cohort, reported as Kaplan-Meier estimates, are shown in **Table 2**. A total of 18 deaths (18.9%) occurred within 30 days post-procedure; the majority were attributed to cardiovascular causes (n=15, 15.8%).

Eight HFH events occurred within 30 days (9.6%), and 3 patients experienced a disabling ischaemic stroke (3.6%); one was procedure related, while two were both device and procedure related. A total of 20 patients experienced

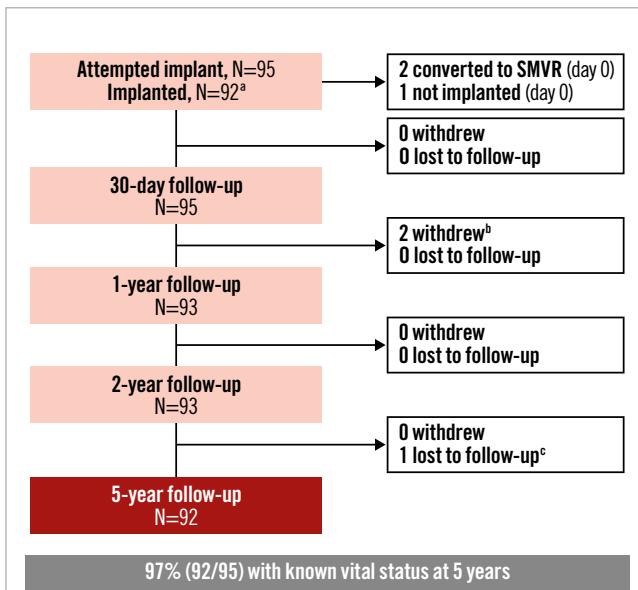


Figure 1. Patient flowchart. Flowchart depicting the number of patients enrolled in the analysis cohort, number of successful implants, and number of patients with known vital status at follow-up. ^aThe analysis of clinical outcomes is based on the attempted implant cohort, and the analysis of echocardiographic outcomes is based on the implanted cohort. ^bOne patient who converted to SMVR at day 0 and one patient who converted to SMVR at day 1 were followed for 30 days then withdrew from the study. ^cOne patient missed the 54- and 60-month visits and was considered lost to follow-up. Each follow-up includes patients who were evaluated, died prior to, or were observed alive at a later timepoint. SMVR: surgical mitral valve replacement

life-threatening (n=16) or fatal bleeding events (n=4) due to access-related apical or intrathoracic bleedings. There was 1 MV (device-related) reintervention (1.1%) due to device malposition within 30 days, with successful percutaneous valve-in-valve implantation. No myocardial infarction, clinically significant device thrombosis, clinical haemolysis, or prosthetic MV endocarditis events were reported within the first 30 days.

ONE-YEAR CLINICAL OUTCOMES

All-cause mortality and HFH at 1 year were 31.9% and 26.0%, respectively (Table 2). A total of 12 patients had their first HFH between 31 days and 1 year. No additional cases of disabling stroke occurred between 31 days and 1 year. Two cases of clinically significant device thrombosis with sequelae (3.0%) were diagnosed. At the time of diagnosis, the first patient was on warfarin but had a subtherapeutic international normalised ratio (INR) value, while the second patient was not on anticoagulation after completing the protocol-recommended 6-month period. In both cases, intensification or reinitiation of anticoagulation therapy led to resolution of thrombosis as confirmed by imaging.

There were 2 cases of MV endocarditis between 31 days and 1 year (observed on post-procedure days 84 and 167). The first resolved following antibiotic therapy, while the second case was fatal. Details on all device thrombosis and endocarditis events can be found in Supplementary Table 3 and Supplementary Table 4, respectively. There were no new MV reinterventions or bleeding events between 31 days and 1 year.

FIVE-YEAR CLINICAL OUTCOMES

At 5 years, 62 patients were deceased, and 2 patients missed their follow-up visit. The remaining 28 patients that were still in contact completed their 5-year follow-up visit

Table 2. Clinical outcomes up to 5 years.

	30 days	1 year	5 years	New patients with events between 1 and 5 years
All-cause mortality	18.9 (18)	31.9 (30)	66.7 (62)	32
Cardiovascular mortality	15.8 (15)	26.1 (24)	51.6 (43)	19
Non-cardiovascular mortality	3.7 (3)	7.9 (6)	31.4 (19)	13
Disabling stroke	3.6 (3)	3.6 (3)	9.1 (6)	3
Myocardial infarction	0 (0)	0 (0)	22.9 (10)	10
Cardiovascular hospitalisation	12.1 (10)	48.2 (37)	79.0 (57)	20
Heart failure hospitalisation	9.6 (8)	26.0 (20)	55.4 (37)	17
Bleeding event ≥major (MVARC definition)	24.3 (23)	24.3 (23)	32.5 (27)	4
Fatal	4.2 (4)	4.2 (4)	4.2 (4)	0
Life-threatening	17.1 (16)	17.1 (16)	21.8 (18)	2
MV reintervention	1.1 (1)	1.1 (1)	1.1 (1)	0
Device thrombosis				
Clinically significant with sequelae	0 (0)	3.0 (2)	10.5 (5)	3
Clinically significant without sequelae	0 (0)	0 (0)	1.7 (1)	1
MV endocarditis	0 (0)	2.9 (2)	4.6 (3)	1
Haemolysis	0 (0)	0 (0)	0 (0)	0

Data are presented as Kaplan-Meier rates (no. of patients with the event). MV: mitral valve; MVARC: Mitral Valve Academic Research Consortium

(**Table 2**). The Kaplan-Meier rates for all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and HFH at 5 years were 66.7%, 51.6%, 31.4%, and 55.4%, respectively (**Central illustration A and B, Table 2**). The composite rate of all-cause mortality or HFH at 5 years was 78.6%. Per the independent clinical events committee, a total of 5 deaths were attributed to the device. One death was deemed definitely related (endocarditis, as described previously), while four were considered possibly related (2 fatal strokes, 1 intracranial bleeding following a fall due to cardiac arrest, and 1 stroke followed by hospital-acquired pneumonia). One-year landmark analyses for all-cause, cardiovascular, and non-cardiovascular mortality are shown in **Supplementary Figure 1**. When excluding 1-year mortality, all-cause, cardiovascular, and non-cardiovascular mortality estimates up to 5 years were 51.2%, 34.5%, and 25.5%, respectively.

After 1 year, an additional 19 patients died due to cardiovascular causes (**Table 2**). Worsening HF was the main cause of death among these patients (n=12), followed by sudden/unwitnessed death (n=3), death due to a neurological event (n=2), due to myocardial infarction (n=1), and of unknown cause (n=1). There were 17 patients that had their first HFH between 1 and 5 years. Among these, there were 4 patients with progression of other non-MV diseases that contributed to the advancement of HF (3 patients with severe aortic valve disease, and 1 patient with severe tricuspid regurgitation).

Between 1 and 5 years, myocardial infarction occurred in a total of 10 patients, all but two of whom had a history of prior myocardial infarction and/or revascularisation with percutaneous coronary intervention or coronary artery bypass grafting. Three additional patients experienced their first disabling stroke, with two of these events being device related. Additionally, no new fatal bleeds occurred between 1 and 5 years, while 2 patients had their first new life-threatening bleeding event. One life-threatening subdural haematoma occurred on day 1,185, associated with overanticoagulation (INR 9.6), and one life-threatening bleeding following postperipheral stenting occurred on day 1,545.

INTREPID VALVE FUNCTION UP TO 5 YEARS

The rate of significant device thrombosis per 100 patient-years with and without sequelae were 1.95 (95% CI: 0.81-4.69) and 0.39 (95% CI: 0.06-2.77), respectively. Three clinically significant device thrombosis events with sequelae and 1 event without sequelae occurred after 1 year (**Supplementary Table 3**). At the time of the event, 2 patients were receiving warfarin (the INR was 2.1 in one patient and unknown in the other patient), and 2 patients were receiving clopidogrel. Management involved intensifying or adding anticoagulation therapy. Of these 4 cases, two completely resolved per follow-up imaging, one remained of unknown status, and one persisted in the setting of disseminated intravascular coagulation and a COVID-19 infection. Among the total of 6 cases of clinically significant device thrombosis up to 5 years of follow-up, the independent clinical events committee determined that none of the 5 subsequently occurring mortalities was caused by implant thrombosis.

The rate of MV endocarditis per 100 patient-years was 1.17 (95% CI: 0.38-3.63). There was one new case of MV endocarditis between 1 and 5 years (post-procedure day 500), which resolved following antibiotic therapy (**Supplementary Table 4**). There was no new incidence of MV reinterventions between 1 and 5 years.

IMPROVEMENT IN FUNCTIONAL STATUS

At baseline, 88.4% of patients were in NYHA Class III/IV. Significant symptom improvement was observed following Intrepid TMVR, with 77.3%, 89.8%, and 84.6% of surviving patients in Class I/II at the 30-day, 1-, and 5-year follow-ups, respectively (**Central illustration C**).

FIVE-YEAR ECHOCARDIOGRAPHIC OUTCOMES

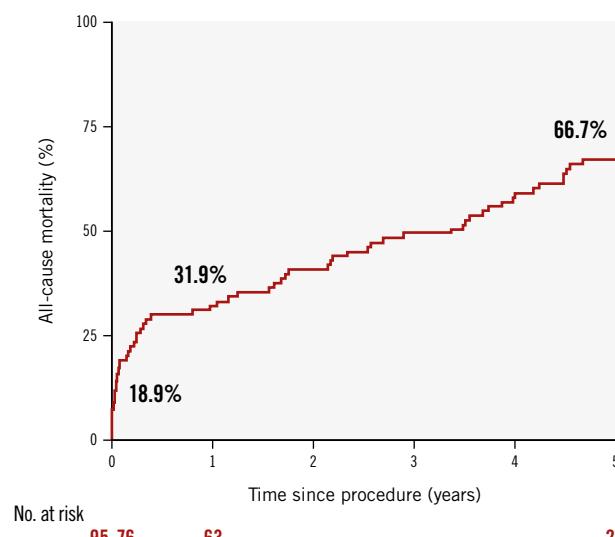
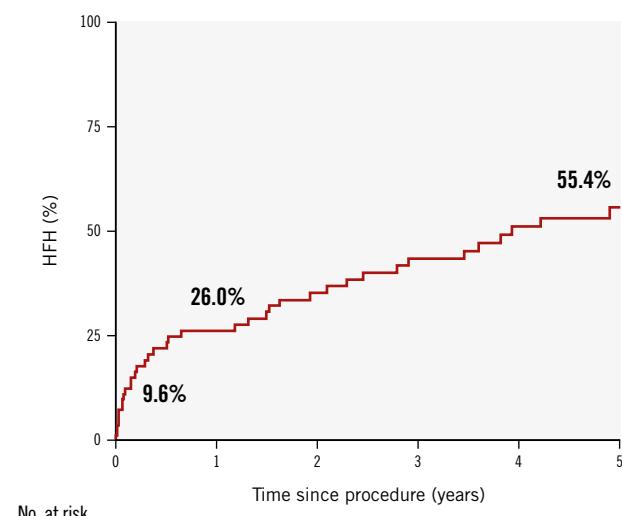
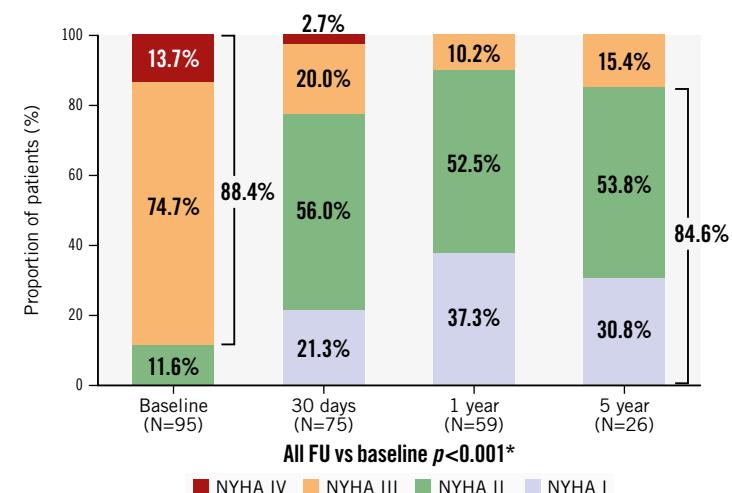
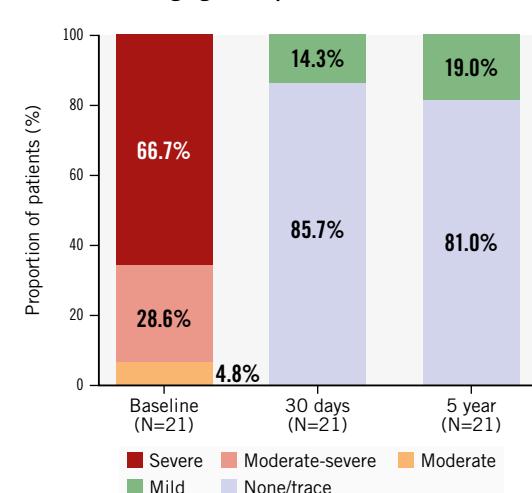
Twenty-one of 28 patients (75%) with 5-year follow-up had transthoracic echocardiographic images for core lab evaluation of MR severity. Among survivors at 5 years, all patients were free from residual MR greater than mild in severity (**Figure 2A**), and no patients had more than trace paravalvular leak (PVL) (**Figure 2B**). Similar findings were observed in a paired MR analysis (**Central illustration D**). A review of all available scheduled and clinically driven unscheduled echocardiograms revealed no MR or PVL greater than mild in severity in the study. The rate of moderate haemodynamic valve deterioration was 1.4% (1/69), while there was no evidence of severe haemodynamic deterioration during the 5 years of follow-up.

The median MV mean gradient at 5 years among survivors was 3.6 mmHg (Q1: 3.0 mmHg, Q3: 4.8 mmHg) (**Figure 3A**), and the median left ventricular (LV) outflow tract peak gradient was 6.6 mmHg (Q1: 3.8 mmHg, Q3: 8.8 mmHg) (**Figure 3B**). A paired comparison of echocardiographic outcomes at baseline and 5 years is shown in **Table 3**. There were no significant changes in the LV end-systolic diameter index, LV end-diastolic diameter index, cardiac output, or tricuspid regurgitation severity. The LVEF decreased from baseline to 5-year follow-up. Although not statistically significant, forward stroke volume increased, while pulmonary artery systolic pressure and right ventricular dysfunction decreased.

Discussion

The major findings in this study are as follows (**Central illustration**): (1) Intrepid TA TMVR resulted in near-elimination of MR during 5-year follow-up among survivors, with durable haemodynamic valve performance and a low rate of haemodynamic valve deterioration; (2) there was one 30-day MV reintervention and none thereafter; (3) device-related complications (thrombosis and endocarditis) were infrequent during 5-year follow-up, with no apparent clustering of events and no cases of haemolysis; and (4) there was sustained improvement in functional status in survivors. In this high-risk patient population treated with the early-generation Intrepid TA TMVR system, 78.6% of the patients either died or were hospitalised for heart failure (HF) within 5 years. These findings highlight the complex comorbid patient population evaluated in this Pilot Study and the need for systematic optimisation of patient selection, guideline-directed medical therapy for HF, and a less invasive transfemoral delivery system.

Five-year clinical outcomes with the Intrepid transapical TMVR system.

A All-cause mortality**B Heart failure hospitalisation****C New York Heart Association Class****D Mitral regurgitation (paired)**

Five-year outcomes in the Pilot Study with the early-generation Intrepid TA TMVR system demonstrated the following in survivors:

- Sustained elimination of MR
- Durable haemodynamic valve performance
- One MV reintervention within 30 days, and none thereafter
- Low rates of thrombosis and endocarditis, and no cases of haemolysis
- Continued improvement in Functional Class

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A) Kaplan-Meier estimate of all-cause mortality up to 5 years; (B) Kaplan-Meier estimate of heart failure hospitalisation up to 5 years; (C) symptom status (NYHA Functional Class) at baseline, 30 days, 1 year, and 5 years; *Wilcoxon signed-rank test; (D) mitral regurgitation severity over time (paired, N=21). FU: follow-up; HFH: heart failure hospitalisation; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; TA: transapical; TMVR: transcatheter mitral valve replacement

DURABLE VALVE PERFORMANCE OF THE INTREPID TMVR SYSTEM

Building on previously published 2-year Intrepid TA TMVR data³, the elimination of MR and low transvalvular gradients seen at 5 years are important factors when considering

TMVR as an alternative treatment option to surgery or transcatheter repair. Despite an excellent safety profile, the Achilles' heel of transcatheter edge-to-edge repair (TEER) is residual or recurrent MR, as well as elevated transmитral gradients, both of which have been associated with adverse

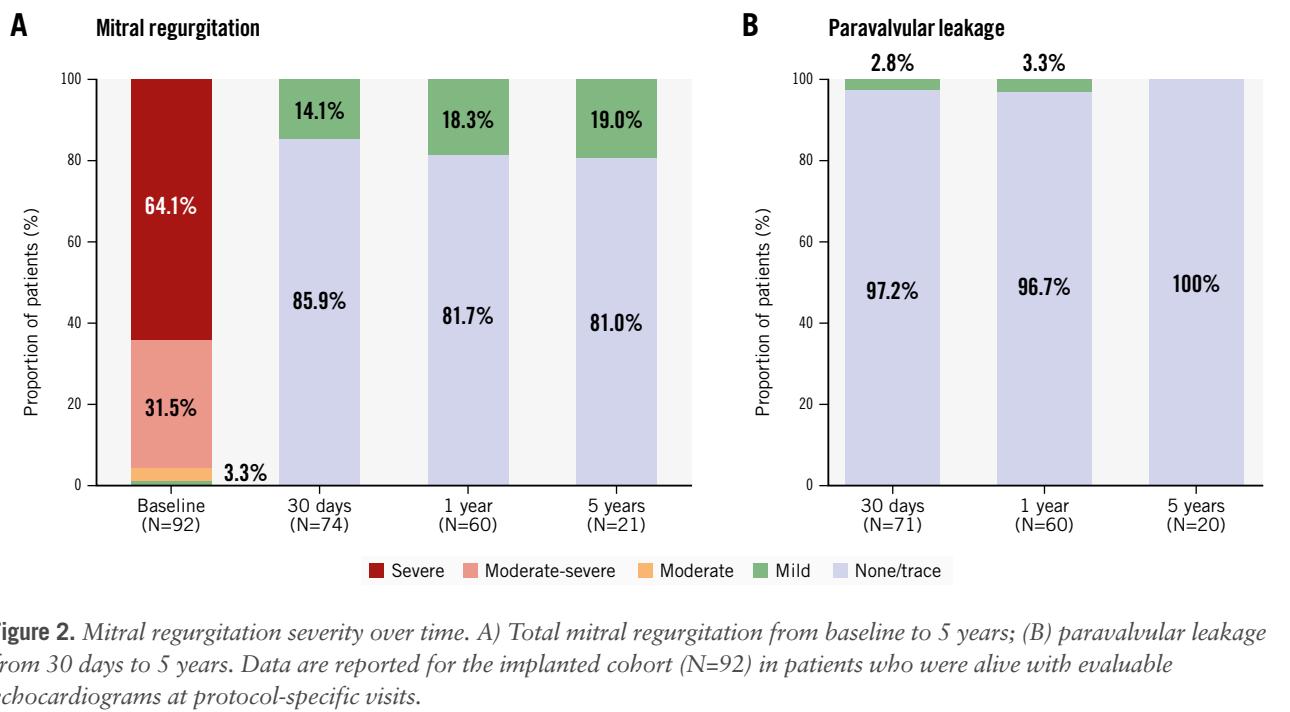


Figure 2. Mitral regurgitation severity over time. A) Total mitral regurgitation from baseline to 5 years; (B) paravalvular leakage from 30 days to 5 years. Data are reported for the implanted cohort (N=92) in patients who were alive with evaluable echocardiograms at protocol-specific visits.

clinical outcomes¹²⁻¹⁷. Similar to other Intrepid studies^{5,6}, the Pilot Study showed that among survivors, 100% had \leq mild MR and no PVL, with stable transmural gradients for up to 5 years of follow-up. Clinically significant device thrombosis with sequelae, a concern for TMVR, was observed in this study, with no distinct pattern in the timing of events post-procedure, while MV endocarditis events remained infrequent (1.17 [95% CI: 0.38-3.6] per 100 patient-years). These findings align with other midterm TMVR⁷ and conventional MV replacement studies^{18,19} and reinforce the importance of valve performance as a key factor, supporting the continued use of the Intrepid TMVR system. Extending anticoagulation beyond 6 months after TMVR should be strongly considered in patients deemed at high risk for thrombosis (e.g., with a history of hypercoagulability, and/or severe left ventricular dysfunction) and at acceptable risk for bleeding. Further studies will be necessary to evaluate this hypothesis, given the balance between valve thrombosis and bleeding in this high-risk population.

TRANSFEMORAL FAVOURED OVER TRANSAPICAL APPROACH IN TMVR

TA transcatheter aortic valve implantation has largely been replaced by a transfemoral approach due to increased safety and better patient recovery^{20,21}. Similarly, we have seen significant access site-related complications with TA TMVR, both with the Intrepid system and other systems^{22,23}. However, there were almost no device-related events beyond the first year in the Pilot Study. The next-generation Intrepid transfemoral TMVR system has demonstrated improved procedural safety compared to the TA system reported in this study, with 0% 30-day and 6.7% 1-year mortality rates⁵. The most recent ENCIRCLE trial (ClinicalTrials.gov: NCT04153292) data on the SAPIEN M3 system further confirm the safety of

transfemoral TMVR over a TA approach²⁴. Transfemoral TMVR is now the only approach with the latest-generation 29 Fr Intrepid system in the APOLLO and APOLLO EU trials, with other TMVR systems also evolving to the transfemoral approach (e.g., Cephea [Abbott], InnoValve [Edwards Lifesciences], AltaValve [4C Medical]).

IMPACT OF PATIENT RISK PROFILE ON LONG-TERM OUTCOMES AFTER TMVR

This long-term study showed that both all-cause and cardiovascular mortality after TA TMVR were relatively high at 5 years, at 66.7% and 51.6%, respectively. The HFH rate was 55.4%. These findings paralleled those reported at 1 year in the TENDER registry with the Tendyne system²⁵, at 2 years with the CHOICE-MI registry with 11 different TMVR devices²⁶, at 3 years with other TA TMVR systems⁷, and at 5 years with TEER^{27,28}. Indeed, the Pilot Study population was a truly high-risk patient cohort: the mean STS-PROM score was 6.5% for MV replacement, nearly 50% had prior cardiac surgery, 28.4% had an implantable cardioverter defibrillator, 15.8% had an implantable cardiac resynchronisation therapy device, almost 80% had secondary MR, 70% had an LVEF \leq 50%, and almost 60% had a prior HFH within the year preceding enrolment. Whether the high mortality rates relate to MR aetiology (primary MR vs secondary MR) remains unclear, given the relatively small sample sizes in the above studies and the limited ability to compare outcomes based on MR aetiology. However, TA TMVR with the Tendyne system had lower 1-year mortality in 2 real-world series with fewer secondary MR patients^{25,29}. Results from the larger registries (e.g., ENCIRCLE, APOLLO, SUMMIT [ClinicalTrials.gov: NCT03433274]) will provide a more robust comparison in outcomes between primary and secondary MR patients undergoing TMVR.

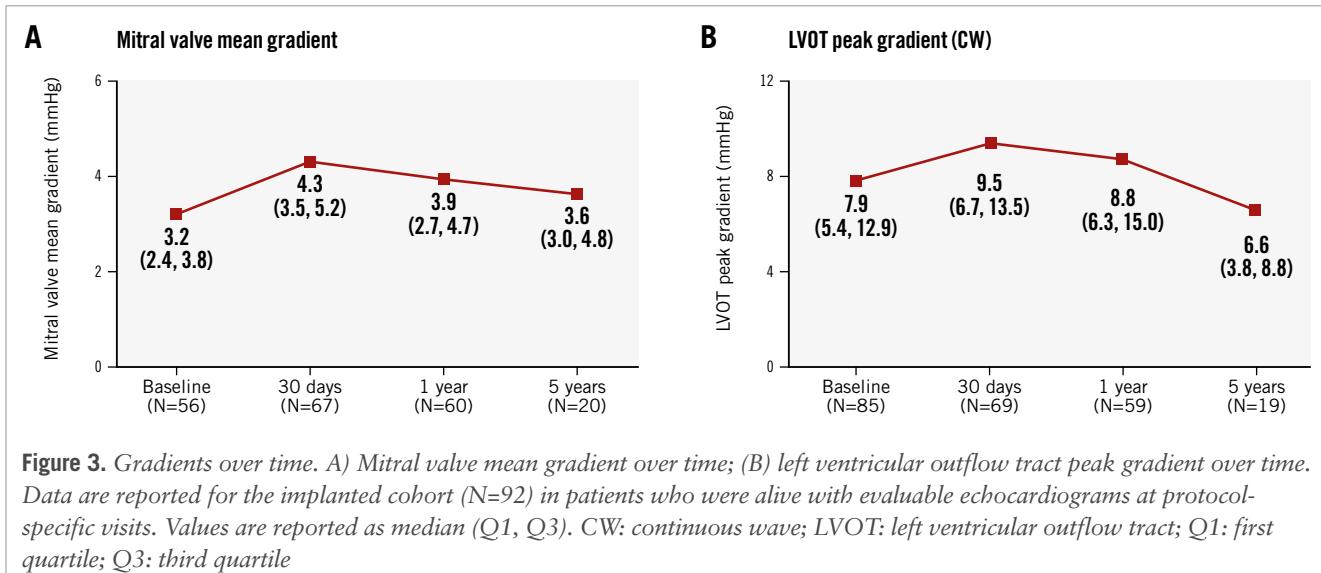


Figure 3. Gradients over time. A) Mitral valve mean gradient over time; (B) left ventricular outflow tract peak gradient over time. Data are reported for the implanted cohort (N=92) in patients who were alive with evaluable echocardiograms at protocol-specific visits. Values are reported as median (Q1, Q3). CW: continuous wave; LVOT: left ventricular outflow tract; Q1: first quartile; Q3: third quartile

With the TA TMVR system, the Kaplan-Meier analysis appeared to show an elevated risk of early mortality from day 0 to 6 months, followed by a plateau from 6 months to 1 year. After the first year, landmark analysis did reveal an ongoing mortality risk after TA TMVR, with 5-year cardiovascular and non-cardiovascular mortality rates of 34.5% and 25.5%, respectively. These findings suggest residual MR is not the main factor after TMVR with Intrepid; rather, mortality appears to be more influenced by patient comorbidities and progressive cardiomyopathy.

Interestingly, 5-year outcomes after TEER in the COAPT Trial were also sobering, with all-cause mortality, cardiovascular mortality, and HFH at 57.3%, 49.0%, and 61.0%, respectively²⁷. The 5-year results of the EuroSMR registry showed a similar all-cause mortality of 65% in patients with secondary MR²⁸. These similar findings, regardless of whether MR reduction or elimination was successful, suggest that we are treating a patient population with severe illness and advanced heart disease. This holds true despite the fact that the two study groups come from different patient populations and time periods. Interestingly, two recent propensity-matched studies between TA TMVR with Tendyne and surgical MV replacement showed no significant outcome differences, but TMVR patients had fewer blood transfusions and shorter hospital stays^{29,30}. A less invasive strategy to eliminate MR may be beneficial in this high-risk population. Nevertheless, implementing a more precise patient selection strategy and optimising HF medical therapy after a successful procedure will be crucial to better address this high-risk patient group beyond just treating their MR.

FUNCTIONAL IMPROVEMENT OVER TIME IN TA TMVR SURVIVORS

Despite a relatively high early mortality after TA TMVR with the Intrepid system, patients who survived to 5 years did exhibit sustained functional improvement, with 84.6% remaining at NYHA Class I/II. This is consistent with the sustained improvements observed with other TMVR systems⁷. Although left ventricular dimensions and cardiac output were unchanged

over time in this 5-year study, similar to other midterm TMVR series³¹, forward stroke volume, right ventricular dysfunction, and pulmonary arterial systolic pressure showed improvements following Intrepid TA TMVR, consistent with the improvements observed in the early feasibility study using a transfemoral approach⁶. The Intrepid APOLLO and APOLLO EU trials will show whether improvements in these cardiac function metrics are observed in a larger patient cohort.

By paired analysis, LVEF numerically declined from 44% at baseline to 40% at 5 years in this study; however, it is unclear whether this decrease is clinically meaningful. Given that approximately 40% of our patients had a history of coronary artery bypass grafting, percutaneous coronary intervention, and myocardial infarction, underlying myocardial dysfunction could be a contributing factor. A similar postprocedural decline in LVEF has been reported with surgery^{32,33}, TEER^{27,34}, and TA TMVR^{31,35}. It is likely that outcomes may continue to improve with the routine use of a transfemoral approach, device iterations, and procedural maturity in TMVR. Seeing durable valve performance at 5 years, even with this early-generation Intrepid system, is important information for discussing treatment options with patients with symptomatic MR at high risk for open surgery.

Limitations

The current work describes the longest follow-up of patients treated to date by TA TMVR. Nonetheless, it remains a relatively small, single-arm study of the early experience with a new TMVR device using a TA approach and may reflect the initial learning curve associated with the procedure and site experience. The lack of a control group limits conclusions with regard to the comparison to other MR therapies. Although clinical follow-up was comprehensive in surviving patients, echocardiograms were not obtained in all patients at all timepoints. Thus, paired comparisons of parameters of cardiac function could only be performed for a subset of patients. Furthermore, results are limited by the competing risk of mortality and reflect outcomes in a minority of surviving patients. Kansas City Cardiomyopathy

Table 3. Paired comparison of echocardiographic outcomes at 5 years.

	n	Baseline	5 years	p-value
MV mean gradient, mmHg	14	3.2 (2.3, 3.9)	3.7 (3.0, 4.7)	0.08
LVOT peak gradient, mmHg	17	6.1 (4.5, 6.6)	6.0 (3.8, 8.8)	0.94
LVESD index	7	2.4 (2.1, 2.9)	2.3 (1.9, 3.1)	0.84
LVEDD index	15	3.1 (2.9, 3.4)	3.1 (2.7, 3.5)	0.46
LVEF, %	20	44.0 (36.0, 55.0)	39.5 (26.5, 46.5)	0.008
Forward stroke volume, mL	14	56.1 (47.4, 65.1)	64.5 (47.4, 69.1)	0.15
Cardiac output, L/min	14	4.7 (3.2, 4.7)	4.4 (3.9, 5.1)	0.33
RV dysfunction ≥mild	17	76.5 (13/17)	47.1 (8/17)	0.06
PASP, mmHg	11	46.0 (33.0, 59.0)	39.0 (32.0, 54.0)	0.42
TR ≥moderate	21	38.1 (8/21)	38.1 (8/21)	>0.99

Data are presented as median (Q1, Q3) or % (n/N). Paired comparisons were made using the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVOT: left ventricular outflow tract; MV: mitral valve; PASP: pulmonary artery systolic pressure; Q1: first quartile; Q3: third quartile; RV: right ventricular; TR: tricuspid regurgitation

Questionnaire assessment was not collected in the Pilot Study, which restricts our ability to assess patient-reported quality-of-life outcomes. Anticoagulation therapy was recommended for at least 3-6 months, but the rates of continuation or discontinuation were unknown. Perioperative management of this high-risk population and long-term medical therapy were not captured by the study protocol. Rigorous and intensive medical therapy with input from HF specialists might have led to improved longer-term outcomes.

Conclusions

In the longest follow-up series of TA TMVR using the early-generation Intrepid system in a high-risk patient population, we observed 5 years of sustained MR elimination and durable valve performance, along with sustained functional improvement among survivors, despite predictable mortality and HFH. Ongoing clinical trials using the less invasive transfemoral approach will help define the patient population most likely to benefit from TMVR.

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Conflict of interest statement

G.H.L. Tang has received speaker honoraria from and served as a physician proctor, consultant, advisory board member, TAVR publications committee member, RESTORE study steering and screening committee member, APOLLO trial screening committee member, and IMPACT MR steering committee member for Medtronic; has received speaker honoraria from and served as a physician proctor, consultant, advisory board member, ENVISION trial screening committee member, and TRILUMINATE trial anatomical eligibility and publications committee member for Abbott; has served as an advisory board member for Boston Scientific; a consultant for Shockwave Medical, Anteris, Philips, Edwards Lifesciences, Pejia Medical, and Shenqi Medical Technology; and has received speaker honoraria from Siemens Healthineers. V. Rajagopal has received personal fees for speaking from Medtronic, Boston Scientific, and Abbott; is on the screening committee for the APOLLO trial sponsored by Medtronic; and has equity stake in and is Chief Medical Officer of Opus Medical Therapies. P. Sorajja has served as a consultant for Medtronic, 4C Medical, Abbott, Adona, Arcos, Boston Scientific, ConKay, Coramaze, CroiValve, Cultiv8, Edwards Lifesciences, Egg Medical, Evolution-Med, Foldax, GE HealthCare, Haemonetics, inQB8, Laguna Tech, Laza Medical, Mirus, Philips, Polares, Tricaires, W.L. Gore & Associates, VDyne, Unorthodox Ventures, Valcare, and xDot. T. Bajwa has received personal and institutional consulting fees from Medtronic. R. Gooley has received consulting fees from Medtronic, Boston Scientific, Abbott, and Teleflex. A. Walton

has served as a physician proctor and an advisory board member for and has received institutional research grant support from Medtronic, Edwards Lifesciences, and Abbott. T. Modine is a consultant for Abbott, Boston Scientific, Cephea, Edwards Lifesciences, GE HealthCare, Medtronic, and MicroPort; and is a proctor for and receives speaker fees from Medtronic. M.K. Ng has received institutional grant support from and is a proctor for Edwards Lifesciences and Abbott. A. Zajarias is a consultant for Medtronic, Edwards Lifesciences, and Anteris. D. Hildick-Smith has received speaker honoraria from and served as a physician proctor for Medtronic, Edwards Lifesciences, Terumo, Abbott, and Boston Scientific. D. Tchétché has served as a consultant for Medtronic, Abbott, Boston Scientific, and Edwards Lifesciences. K. Spargias has served as a physician proctor and consultant for Medtronic, Edwards Lifesciences, and Abbott. V.N. Bapat is a consultant for Medtronic, Edwards Lifesciences, Abbott, and Reniva. O. De Backer has received institutional research grant support and consulting fees from Medtronic, Abbott, and Boston Scientific. D. Blackman is a consultant and proctor for Medtronic and JenaValve Technology; is a consultant and speaker for Abbott; and has received institutional research grant support from Medtronic. P. McCarthy has received speaker fees and royalties from Edwards Lifesciences; speaker fees from Atricure; served on the advisory board for Arthrex; received royalties from Genesee; served as the surgical primary investigator for the REPAIR-MR trial (unpaid); and served on the advisory board for Abbott. R. Jain is a consultant for Medtronic, Edwards Lifesciences, Philips Healthcare, and GE HealthCare; and is an advisory board member for Medtronic. R. Martin is on the executive steering committee for the APOLLO trial sponsored by Medtronic; and on the steering committee of REPAIR MR sponsored by Abbott. J.J. Thaden reports research support for the echocardiographic core laboratory from Medtronic. N.A. Marka is an employee and shareholder of Medtronic. M. Mack is on the executive board for the APOLLO trial sponsored by Medtronic; and is co-principal investigator for the PARTNER 3 and COAPT trials sponsored by Edwards Lifesciences and Abbott. D.H. Adams has served as the national co-principal investigator of the Medtronic APOLLO Food and Drug Administration pivotal trial, the NeoChord ReChord Food and Drug Administration pivotal trial, the Medtronic CoreValve US pivotal trial, and the Abbott TRILUMINATE pivotal trial. M.B. Leon has received personal and institutional grant support from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. M.J. Reardon reports receiving personal consulting fees from Abbott, Boston Scientific, W.L. Gore & Associates, and Medtronic, outside of the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study definitions.

Supplementary Table 1. Participating investigators, sites, and personnel.

Supplementary Table 2. Inclusion and exclusion criteria.

Supplementary Table 3. Summary of clinically significant device thrombosis up to 5 years.

Supplementary Table 4. Summary of mitral valve endocarditis up to 5 years.

Supplementary Figure 1. Landmark analysis at 1 year.

The supplementary data are published online at:
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Supplementary data

Supplementary Appendix 1. Study definitions.

Mortality

Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015).

Cardiovascular Mortality: Any death due to the following causes:

- o Heart failure (left or right ventricular dysfunction)
- o Myocardial infarction
- o Major bleeding
- o Thromboembolism
- o Stroke
- o Arrhythmia and conduction disturbances
- o Cardiovascular infection or sepsis (e.g., mediastinitis, endocarditis)
- o Cardiac tamponade
- o Sudden unexpected death
- o Other cardiovascular causes
- o Device failure
- o Death of unknown cause (adjudicated as cardiovascular)

Non-Cardiovascular Mortality: Any death clearly related to non-cardiovascular conditions:

- o Non-cardiovascular infection or sepsis (e.g., pneumonia)
- o Renal failure
- o Liver failure
- o Cancer
- o Trauma
- o Homicide
- o Suicide
- o Other non-cardiovascular causes

Stroke

Disabling Stroke: Defined as a modified Rankin Scale (mRS) score ≥ 2 at 90 days, with an increase of ≥ 1 point from the prestroke baseline.

Myocardial Infarction (MI)

Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015).

Periprocedural MI (<48 hours post-procedure): Criteria based on biomarker elevation (CK-MB or cTn), ECG changes, and timing.

Spontaneous MI (>48 hours post-procedure): Includes biomarker rise and at least one of: ischemic symptoms, ECG changes, or imaging evidence of new myocardial damage.

MI with Sudden Cardiac Death: Sudden death with ST changes or angiographic/autopsy evidence of thrombus.

Pathological MI Findings: Confirmed at autopsy or surgery. High-sensitivity troponins recommended for Type II MI diagnosis, standard assays for Type I.

Elevations not meeting MI criteria = “Myonecrosis not meeting MI criteria.”

Hospitalizations

Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015).

Cardiovascular Hospitalization: Admission due to:

- Coronary artery disease
- Acute MI
- Hypertension
- Cardiac arrhythmias
- Cardiomegaly
- Pericardial effusion
- Atherosclerosis
- Stroke
- Peripheral vascular disease (excluding HF)

Heart Failure Hospitalization (HFH): Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015).

Both criteria must be present:

1. Clinical or laboratory signs of HF worsening
2. Administration of IV or mechanical HF therapies

Subcategories:

- IA. Primary HF hospitalization (cardiac-related)
- IB. Secondary HF hospitalization (non-cardiac-related)

Bleeding Events

Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015). MVARC Bleeding Severity Scale

Major:

Overt bleeding with hemoglobin drop ≥ 3 g/dL or ≥ 3 units transfusion, not life-threatening/extensive

Extensive:

Hb drop ≥ 4 g/dL or ≥ 4 units in 24h, or Hb drop ≥ 6 g/dL within 30 days

Life-threatening:

Bleeding in a critical organ (e.g., intracranial, pericardial), or associated with shock, vasopressors, or surgery

Fatal:

Bleeding is a proximate or contributing cause of death

“Overt” includes clinical signs or excessive chest tube output as specified in MVARC.

Reintervention

Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based

interventions for valve-related complications are also considered reintervention. Reintervention is further subdivided into surgical and percutaneous.

Mitral valve (MV) Reintervention: Device-related reintervention. Required due to device malfunction or failure.

Classification of Relationship to Device or Procedure

Adverse events (AEs) or serious adverse events (SAEs) will be classified based on their relationship to the investigational device or procedure:

- Not Related: Clearly due to other causes
- Remotely Related: Cannot be ruled out but unlikely
- Possible: Temporal relationships exist; alternative causes equally or less likely
- Probable: Strong temporal relationship; alternative causes unlikely
- Definite: Attributable only to the device or procedure
- Not Assessable: Relationship cannot be determined

Device Thrombosis

Diagnosis of clinical device thrombosis requires visualization of thrombus by echo or by MDCT or presence of hypoattenuated leaflet thickening $\geq 50\%$ by MDCT. Thrombosis is further stratified as “significant with clinical sequelae” or “significant without clinical sequelae” based on evidence of arterial embolism or new/worsening HF. Diagnosis of significant thrombosis without sequelae required ≥ 6 mm Hg absolute value of mean transprosthetic mitral gradient and increment of ≥ 5 mm Hg in mean gradient compared with baseline value (at hospital discharge) and initiation or intensification of anticoagulation.

Mitral Valve (MV) Endocarditis

Defined and classified according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015) using Modified Duke Criteria:

Definite Endocarditis: Requires histologic/microbiologic evidence, or:

- o 2 major criteria, or
- o 1 major + 3 minor, or
- o 5 minor criteria

Major Criteria:

- Positive blood cultures for typical IE organisms (e.g., Viridans strep, S. aureus, HACEK)
- Persistent bacteremia
- Positive echocardiographic findings (vegetation, abscess, prosthesis dehiscence)
- New valvular regurgitation

Minor Criteria:

- Predisposition (e.g., IV drug use, valve disease)
- Fever $>38^{\circ}\text{C}$
- Vascular phenomena (e.g., Janeway lesions)
- Immunologic signs (e.g., Osler nodes, Roth spots)
- Microbiologic evidence not fulfilling major criteria

- Echo findings not meeting major criteria

Events meeting 1 major + 1–2 minor or 3–4 minor = "Possible Endocarditis"

Subclassification: By organism and timing: Early (<1 year post-implant) vs. Late (≥ 1 year)

Hemolysis

Defined according to the Mitral Valve Academic Research Consortium (MVARC) Part 2: Endpoint Definitions; (JACC, 2015):

Evidence includes:

- o Paravalvular leak (on TTE or TEE)
- o Anemia requiring transfusion
- o Decreased haptoglobin and/or increased LDH

Diagnosis should be confirmed by a hematologist.

Supplementary Table 1. Participating investigators, sites, and personnel.

Participating Investigational Sites & Personnel	
United States	
Houston-Methodist-DeBakey Heart and Vascular Center/ The Methodist Hospital Houston, TX	Principal Investigators: Michael Reardon, Neal S. Kleiman Co-investigators: Stephen Little, Colin Baker, Ross Reul, Mahesh Ramchandi, Tanush Gupta, Research Coordinators: Pamela Hazen, LaShawna Green, Jeannie Arrendondo, Patricia Brinegar, Lisa Green, Amber Jacobs, Saba Khan, Mary Mata, Wesley Oglesby, Carol Underwood, Kurt White, Meagan Griffin, Tammara Moore, Tia McGaughy, Danielle Gee, Melissa(Iris) Alanis, Adam Daniels, Paulamy Ganguly, Annalise Brisco
The Mount Sinai Medical Center New York, NY	Principal Investigators: David H. Adams, Barry Love Co-investigators: George Dangas, Anelechi Anyanwu, Ahmed El-eshmawi, Julie Swain, Barry Love, Alexander Mitnacht, Menachem Weiner, Himani Bhatt, Gilbert Tang, Farooq Chaudry Research Coordinators: Michael Fusilero, Jerome Tonog, Vanessa Coulibaly, Deniz Akkoc
St. Luke's Medical Center Aurora Health Center Milwaukee, WI	Principal Investigators: Tanvir Bajwa, Daniel O'Hair Co-investigators: Reuka Jain, Bijoy Khandheria Research Coordinators: Wendy Dunaj, Michelle Bennett, Deb Waller, Kathleen Behrens, Tonya Hollrith
Baylor Heart and Vascular Hospital Dallas, TX	Principal Investigators: Paul Grayburn, Robert Hebelter Co-investigators: Michael Mack, Robert Stoler, Research Coordinators: Emily Labile, Kim Waters, Leslie Willcott, Angela Mendez
Piedmont Heart Institute Atlanta, GA	Principal Investigators: Vivek Rajagopal, James Kauten Co-investigators: Christopher Meduri, Mani Vannan, Federico Milla, Randolph Martin, Robi Goswami, John Gott, Sarah Rihehart, Christopher Meduri, Morris Brown David Dean, Sarah Mobasseri, Venkateshwar Polsani,

Participating Investigational Sites & Personnel	
	<p>Hassan Sayegh, Raul Blanco, Vibhar Rangarajan, Peter Flueckiger, Benjamin DeMoss, Roshin Mathew</p> <p>Research Coordinators: Shelley Holt, Elisa Amoroso, Kashaine Gray, Brittney Truss, Denise Whyte, Nita Cadic, Heather Signler, Kimi Wang, Claire Tucker</p>
New York University/Langone Medical Center New York, NY	<p>Principal Investigators: Mathew Williams, Hasan Jilaihawi</p> <p>Co-investigators: Aubrey Galloway, Cezar Staniloae, Muhamed Saric</p> <p>Research Coordinators: Jessie Van Daele, Zachary Taylor, Eleonora Vapheas, Raissa Nunes, Namrata Nepal, Tonya Robin, Pascale Houanche, Saniye Bavbekova, Divya Tenneti, Liora Rafailova, Lucy Lannan, Sam Lo, Tanushi Upadhyay, Katelyn Bastert, Jonathan Lehn</p>
Abbott Northwestern Minneapolis, MN	<p>Principal Investigators: Paul Sorajja, Robert Farivar</p> <p>Co-investigators: Richard Bae, Mario Goessl, Judah Askew</p> <p>Research Coordinators: Kate Jappe, Pam Morley, Aisha Ahmed, Kari Thomas, Brittany Fitzpatrick, Sara Olson, Karen Meyer</p>
Columbia University Medical Center New York, NY	<p>Principal Investigators: Martin Leon, Isaac George</p> <p>Co-investigators: Susheel Kodali, Rebecca Hahn, Torsten Vahl, Tamim Nazif, Michael Borger, Omar Khaliq, Vinayak Bapat</p> <p>Research Coordinators: Alex Kantor, Deniz Akkoc, Kate Dalton, Juan Mendez, Andy Morales, Jeimy Rosado, Dave Hargrove, Parisha Masud, Nikolas Bietnitsky, Nicole Marshall, Ellie James, Flori Rosales,</p>
Barnes Jewish St. Louis, MO	<p>Principal Investigators: Alan Zajarias, Hersh Maniar</p> <p>Co-investigators: Majesh Makan, Spencer Melby</p> <p>Research Coordinators: Michelle Myers, Kelly Koogler</p>
Northwestern Chicago, IL	<p>Principal Investigators: Patrick McCarthy, Charles Davidson</p>

Participating Investigational Sites & Personnel	
	Co-investigators: James Thomas, Mark Ricciardi, Chris Malaisrie, Jyothy Puthumana Research Coordinator: Caitlyn Brady
Australia	
The Alfred, Melbourne, Australia	Principal Investigators: Antony Walton Co-investigators: Stephen Duffy, Silvana Marasco, Helen Thomson, Dion Stub Research Coordinators: Rox Johnston, Samantha Holland, Brianna Davidson
Monash Heart, Melbourne, Australia	Principal Investigators: Robert Gooley Co-investigators: Aubrey Almeida, Siobhan Lockwood, Liam McCormick, Phillip Mottram Research Coordinators: Mary-Anne Austin, Wendy Wallace-Mitchell
Royal Prince Alfred Hospital, Sydney, Australia	Principal Investigators: Martin Ng Co-investigators: Michael Wilson, Bruce Cartwright, Lisa Simmons Research Coordinators: Jun Wu, Mel Wilson, Yuen Yuen Ng, Jessica-Rose Tait
Denmark	
Rigshospitalet Copenhagen, Denmark	Principal Investigator: Ole De Backer Co-investigators: Sten Lyager Nielsen, Nikolaj Ihlemann Research Coordinators: Rikke Bige Sorensen, Line Harboe Kristensen
Europe	
Hygeia Hospital, Athens, Greece	Principal Investigators: Konstantinos Spargias Co-investigators: Nick Boumpoulis, Stratis Pattakos, Spyros Skardoutsos, Michael Chrissoheris, Konstantinos Papadopoulos Research Coordinators: Evgenia Dafnomili

Participating Investigational Sites & Personnel	
Helsinki University Hospital, Helsinki, Finland	Principal Investigators: Mika Laine Co-investigators: Antero Sahlman, Tommi Vahasilta, Suvi Tuohinen, Helena Haenninen, Janne Rapola, Seppo Hiippala Research Coordinator: Christina Salmen
Centre Hospitalier Regional Univeritaire de Lille, Lille, France	Principal Investigators: Thomas Modine Co-investigators: Arnaud Sudre, Augustine Coisne, Emmanuel Robin Research Coordinator: Justine Lerooy
Clinique Pasteur, Toulouse, France	Principal Investigators: Didier Tchétché Co-investigators: Pascal Chambran, Laurent Sidobre Research Coordinator: Frederic Petit
Brighton and Sussex University Hospitals, Brighton, United Kingdom	Principal Investigators: David Hildick-Smith Co-investigators: Uday Trivedi, Arionilson Gomes Research Coordinator: Jessica Parker
Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom	Principal Investigators: Daniel Blackman Co-investigators: Betsy Evans, Christopher Malkin, Dominik Schlosshan, Christopher Munsch Research Coordinator: Kathryn Somers, Helen Reed, Natalie Burtonwood
St. Thomas' Hospital, United Kingdom	Principal Investigators: Ronak Rajani Co-investigators: Bernard Prendergast, Simon Redwood, Jane Hancock Research Coordinator: Karen Wilson, Megan Smith, Sophie Jones

Supplementary Table 2. Inclusion and exclusion criteria.

The Intrepid TMVR Pilot Study Inclusion and Exclusion Criteria	
Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none">1. Severe mitral regurgitation (MR Grade 3-4+)2. Symptomatic mitral regurgitation (NYHA Class II-IV)3. Deemed to be at high risk for conventional mitral valve surgery by the local heart team (including, at minimum, a cardiac surgeon, interventional cardiologist, and an echocardiologist)4. Age \geq 18 yrs5. Native mitral valve geometry and size compatible with the Intrepid™ TMVR6. No or minimal mitral valve calcification7. Willing to sign Informed Consent for participation in the study and return for all required post-procedure follow-up visits	<ol style="list-style-type: none">1. Left ventricular ejection fraction (LVEF) $< 20\%$2. Evidence of intracardiac mass, thrombus, or vegetation3. Pulmonary hypertension (> 70 mmHg systolic)4. Hypertrophic Obstructive Cardiomyopathy (HOCM)5. Prior mitral valve surgery or endovascular procedure, any currently implanted mechanical prosthetic valve, or need for other valve surgery/procedure6. Any endovascular therapeutic interventional or surgical procedure performed within 30 days prior to enrollment7. Prior stroke within 30 days8. Need for coronary revascularization9. Need for emergent surgery10. History of, or active, endocarditis11. GI bleeding within 6 months12. History of bleeding diathesis or coagulopathy or patient will refuse blood transfusion13. Hemodynamic instability14. Platelet count of $< 75,000$ cells/mm³15. Renal insufficiency (Creatinine > 2.5 mg/dL)16. Active infections requiring current antibiotic therapy (if temporary illness, patients may enroll 2 weeks after discontinuation of antibiotics)

The Intrepid TMVR Pilot Study Inclusion and Exclusion Criteria	
Inclusion Criteria	Exclusion Criteria
	<p>17. Contraindication to transesophageal echocardiography (TEE)</p> <p>18. Known hypersensitivity or contraindication to study or procedure medications/contrast which cannot be adequately managed medically.</p> <p>19. Pregnant, nursing or planning to be pregnant. (Female participants of childbearing potential must have a negative pregnancy test prior to enrollment).</p>

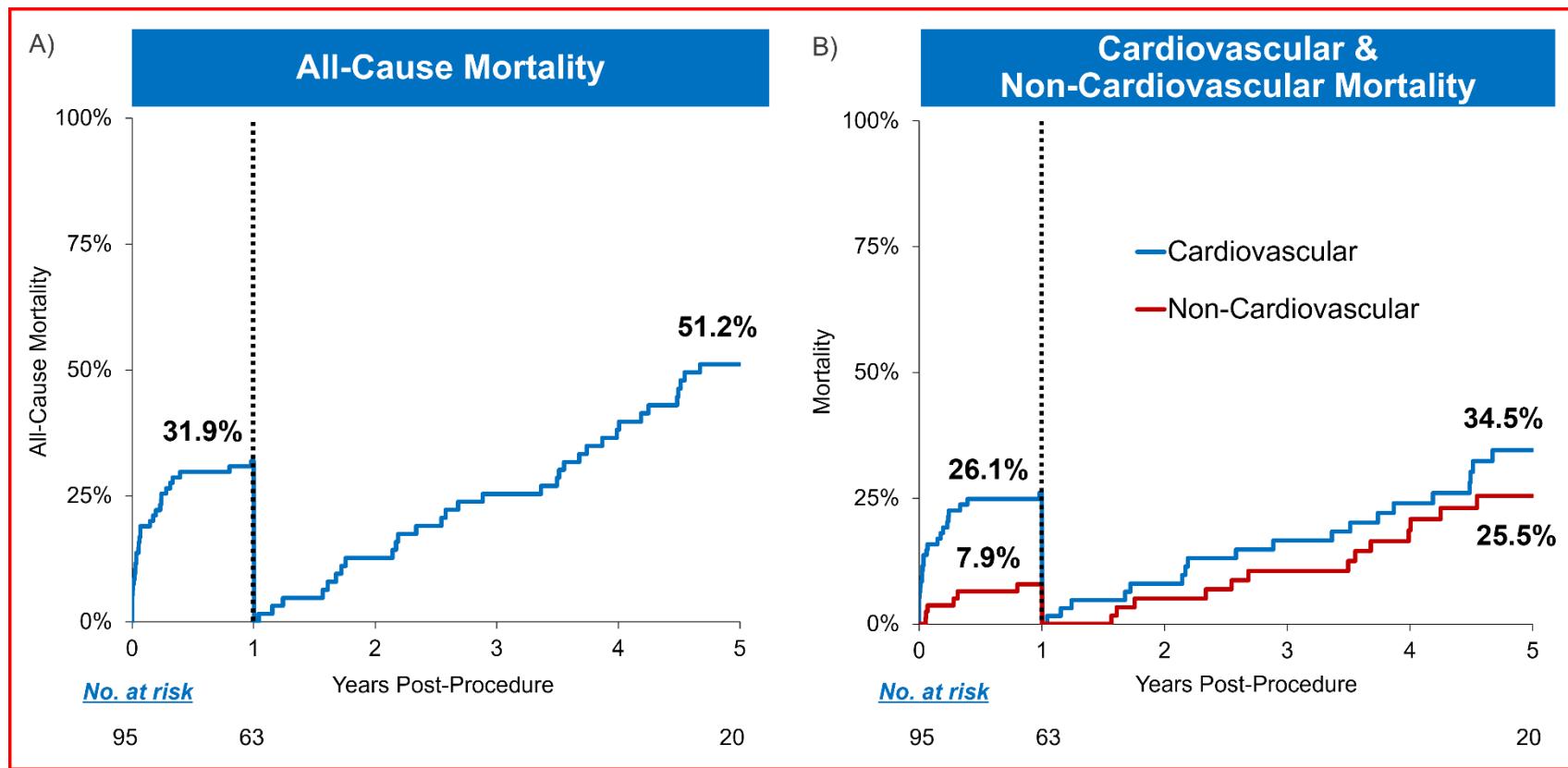
Inclusion criteria differences - France only: 1) Deemed to be at high risk for conventional mitral valve surgery [STS Score > 8 or EuroSCORE > 15, or by agreement by the local heart team (i.e., surgeon, cardiologist & anesthesiologist)]; 2) Subject must be entitled to French social security. Exclusion criteria difference - France only: Any subject who is a “personne vulnérable” per French legislation, including protected adults and prisoners.

Supplementary Table 3. Summary of clinically significant device thrombosis up to 5 years.

Patient	Days after TMVR	With sequelae?	Echo data	Anticoagulant at time of event?	Management	Outcome	Vital status
Within 1st year							
1	97	Yes, HFH	Mitral stenosis	Warfarin, INR<2.0	Intensification of Warfarin	Resolved	Died, day 1637
2	268	Yes, Worsening HF	Mitral stenosis	None	Reinitiation of Warfarin	Resolved	Alive
Between 1st and 2nd years							
3	558	No	Mitral stenosis	Clopidogrel	Apixaban added, Clopidogrel continued	Resolved	Died, day 1053
Between 2nd and 3rd years							
4	1043	Yes, arterial embolism, HITT diagnosed	Mitral stenosis	Clopidogrel	Unfractionated Heparin discontinued and replaced with Bivalirudin; Warfarin started	Unknown	Died, day 1366
Between 3rd and 4th years							
5	1127	Yes, Worsening HF	Mitral stenosis & LAA thrombus	Warfarin, Aspirin, INR unknown	Unfractionated Heparin followed by Warfarin, Aspirin continued	Resolved	Died, day 1706
Between 4th and 5th years							
6	1727	Yes, HFH	Mitral stenosis LAA and LA thrombus	Warfarin, INR 2.1	Intensification of Warfarin	Not resolved	Died, day 1833

Supplementary Table 4. Summary of mitral valve endocarditis up to 5 years.

Patient	Days after TMVR	Pathogen	Vegetation on implant?	Outcome	Vital status
1	84	Staph aureus	Yes	Not recovered	Died, day 87
2	167	Staph epidermidis	Yes	Recovered	Died, day 1297
3	500	Strep viridans	Yes	Recovered	Alive



Supplementary Figure 1. Landmark analysis at 1 year.

A) Kaplan-Meier landmark analysis at 1 year of all-cause mortality; B) Kaplan-Meier landmark analysis at 1 year of cardiovascular mortality and non-cardiovascular mortality