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ORIGINAL RESEARCH

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 is limited on long-term durability and performance.

AIMS: We evaluated 5-year outcomes from the global Pilot study (NCT02322840) with the Intrepid transapical (TA) TMVR system.

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

RESULTS: Ninety-five patients were enrolled at 21 sites between 2015 and 2019. Mean age was 74.0±9.2 years, 43.2% female, mean STS-PROM 6.5±4.8%, 57.9% had prior heart failure hospitalization (HFH), and 88.4% were in NYHA Class III/IV. Secondary MR was present in 78.7%, and 76.6% had a left ventricular ejection fraction ≤50%. Through 5 years, all-cause mortality was 66.7% and HFH 55.4%, with one 30-day MV reintervention (1.1%). Hemodynamic valve deterioration occurred in 1.4%, median MV mean gradient remained stable at 3.6 mmHg (Q1, Q3: 3.0, 4.8 mmHg), with ≤ mild MR in 100% of patients, and none had paravalvular leak. NYHA Class I/II was maintained at 84.6%.

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

KEYWORDS: Mitral regurgitation; transapical; TMVR; long-term; durability, hemodynamic performance

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DISCLOSURES

Dr. Tang has received speaker's honoraria 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's honoraria and served as a physician proctor, consultant, advisory board member, ENVISION trial screening committee member, and TRILUMINATE trial anatomic eligibility and publications committee member for Abbott Structural Heart, has served as an advisory board member for Boston Scientific, a consultant for Shockwave Medical, Anteris, Philips, Edwards Lifesciences, Peija Medical and Shenqi Medical Technology, and has received speaker's honoraria from Siemens Healthineers. Dr. Rajagopal has received personal fees for speaking from Medtronic, Boston Scientific, and Abbott Vascular; is on the screening committee for the APOLLO trial sponsored by Medtronic; and has equity stake and is Chief Medical Officer of Opus Medical Therapies. Dr. Sorajja has served as consultant for Medtronic, 4C Medical, Abbott, Adona, Arcos, Boston Scientific, ConKay, Coramaze, CroiValve, Cultiv8, Edwards Lifesciences, Egg Medical, EvolutionMed, Foldax, GE Medical, Haemonetics, InQ8, Laguna Tech, LAZA, Mirus, Phillips, Polares, Tricares, WL Gore, vDyne, Unorthodox Ventures, Valcare, and xDot. Dr. Bajwa has received personal and institutional consulting fees from Medtronic. Dr. Gooley has received consulting fees from Medtronic, Boston Scientific, Abbott Vascular and Teleflex. Dr. Walton has served as a physician proctor, advisory board member, and received institutional research grant support from Medtronic, Edwards Lifesciences, and Abbott. Dr. 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. Dr. Ng has received institutional grant support from and is a proctor for Edwards Lifesciences and Abbott. Dr. Williams has nothing to declare. Dr. Zajarias is a consultant for Medtronic, Edwards Lifesciences, and Anteris. Dr. Hildick-Smith has received speaker's honoraria and served as a physician proctor for Medtronic, Edwards Lifesciences, Terumo, Abbott, and Boston Scientific. Dr. Tchétché has served as a consultant to Medtronic, Abbott, Boston Scientific, and Edwards Lifesciences. Dr. Spargias has served as a physician proctor and consultant for Medtronic, Edwards Lifesciences and Abbott. Dr. Rajani has nothing to declare. Dr. Bapat is a consultant for Medtronic, Edwards Lifesciences, Abbott, and Reniva. Dr. De Backer has received institutional research grant support and consulting fees from Medtronic, Abbott, and Boston Scientific. Dr. Blackman is a consultant and proctor for Medtronic and JenaValve technologies, is a consultant and speaker for Abbott Vascular, and has received an institutional research grant support from Medtronic. Dr. McCarthy has received speaking fees and royalties from Edwards Lifesciences; speaking fees from Atricure; served on the advisory board for Arthrex; received royalties from Genesee; and served as the surgical primary investigator for the REPAIR-MR Trial (unpaid) and on the advisory board for Abbott. Dr. Laine has nothing to declare. Dr. Jain is a consultant for Medtronic, Edwards Lifesciences, Phillips HealthCare, and GE Healthcare, and is an advisory board member of Medtronic.Dr. 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. Dr. Thaden reports research support for the echocardiographic core laboratory from Medtronic. Nicholas Marka is an employee and shareholder of Medtronic. Dr. Mack is on the executive board for the APOLLO trial sponsored by Medtronic; and is coprincipal investigator for the PARTNER 3 and COAPT trials sponsored by Edwards Lifesciences and Abbott Vascular. Dr. 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. Dr. Leon has received personal and institutional grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Dr. Reardon reports receiving personal consulting fees from Abbott, Boston Scientific, Gore Medical and Medtronic outside of the submitted work.

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STRUCTURED 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 is limited on long-term durability and performance.

Aims: We evaluated 5-year outcomes from the global Pilot study (NCT02322840) with the Intrepid transapical (TA) TMVR system.

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

Results: Ninety-five patients were enrolled at 21 sites between 2015 and 2019. Mean age was 74.0±9.2 years, 43.2% female, mean STS-PROM 6.5±4.8%, 57.9% had prior heart failure hospitalization (HFH), and 88.4% were in NYHA Class III/IV. Secondary MR was present in 78.7%, and 76.6% had a left ventricular ejection fraction ≤50%. Through 5 years, all-cause mortality was 66.7% and HFH 55.4%, with one 30-day MV reintervention (1.1%). Hemodynamic valve deterioration occurred in 1.4%, median MV mean gradient remained stable at 3.6 mmHg (Q1, Q3: 3.0, 4.8 mmHg), with ≤ mild MR in 100% of patients, and none had paravalvular leak. NYHA Class I/II was maintained at 84.6%.

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

Keywords: Mitral regurgitation; transapical; TMVR; long-term; durability, hemodynamic performance

ABBREVIATIONS

HFH = heart failure hospitalization

LVEF = left ventricular ejection fraction

MDCT = Multidimensional computed tomography

MR = mitral regurgitation

MV = mitral valve

MVARC = Mitral Valve Academic Research Consortium

PVL = paravalvular leak

TMVR = Transcatheter mitral valve replacement

TA = Transapical

TEER = Transcatheter edge-to-edge repair

INTRODUCTION

Conventional surgical mitral valve (MV) repair or replacement improves longevity and quality of life for patients with MV disease. However, less than one-half of patients with ≥ 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 (NCT02322840) and the initial phase of the APOLLO Trial (NCT03242642) using the early-generation transapical (TA) Intrepid system showed excellent device hemodynamics with the ability to eliminate MR through 2 years [3]. The device performance data was further confirmed in the next generation transfemoral system, which demonstrated improved safety outcomes out to 2 years in patients treated under an early feasibility study [4-6].

Two TMVR devices to treat severe MR in patients ineligible for conventional MV surgery or transcatheter MV repair are currently approved for commercial use in Europe (Tendyne [Abbott Structural Heart], SAPIEN M3 [Edwards Lifesciences]). Additionally, the Tendyne system recently received FDA 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 reported [7]. 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.

METHODS

STUDY DESIGN AND PATIENT POPULATION

The Intrepid TMVR global Pilot study is a multi-center, prospective, non-randomized 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 U.S. (**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 ≥ moderate-severe MR (3-4+), no or minimal MV

calcification, and a left ventricular ejection fraction (LVEF) ≥20%. Key exclusion criteria were severe pulmonary hypertension, need for coronary revascularization, hemodynamic instability, need for other surgical valvular therapy, severe renal insufficiency, and prior MV surgery or intervention. Complete inclusion/exclusion criteria are listed in **Supplementary Table 2.** Institutional review board approval was obtained in all centers, and patients provided informed consent for study participation.

The early-generation Intrepid TMVR system is comprised of 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 35Fr 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].

Anatomic suitability for TA TMVR was determined using transesophageal echocardiography and multidetector computed tomography (MDCT). Study eligibility was determined by local heart teams at study sites (including, at minimum, a cardiac surgeon, 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, California), adjudicated endpoint-related adverse events and reviewed the safety results. Echocardiographic endpoints were assessed by an independent echocardiographic core laboratory (Mayo Clinic, Rochester, Minnesota).

STUDY ENDPOINTS AND DEFINITIONS

Clinical and transthoracic echocardiography assessments were performed at discharge, 1 month, 3 months, 6 months, 12 months, and biannually thereafter through 5 years. Unscheduled echocardiograms were performed by sites if clinically indicated and reviewed by the echocardiographic core laboratory. Severity of MR was assessed according to American Society of Echocardiography criteria [9]. Moderate hemodynamic valve deterioration was defined according to the Heart Valve Collaboratory 2022 and Mitral Valve Academic Research Consortium (MVARC) 2015 criteria as an increase in mean transmitral gradient of ≥ 5 mmHg from 30-day/discharge to last available echocardiogram, or transvalvular MR ≥ moderate, while

severe hemodynamic valve deterioration was defined as mean transmitral gradient of ≥ 10 mmHg or MR ≥ moderate-severe [10,11].

MDCT was collected per protocol at discharge and 1 year for patients enrolled at U.S. sites. Quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire at baseline and 1 year, as previously reported [3]. NYHA functional class was assessed from baseline through 5 years. Standard definitions for clinical events were used in accordance with MVARC 2015 criteria [11], except for device thrombosis, as described in **the Supplementary Appendix.** Post-procedure anticoagulation was prescribed per physician discretion, but was recommended for at least 3-6 months post-implant and longer unless there was a clinical indication to discontinue it.

STATISTICAL ANALYSIS

Continuous variables are summarized as mean ± standard deviation, or median and first (Q1) and third (Q3) quartiles, 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 linearized 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 Inc., Cary, NC).

RESULTS

BASELINE CHARACTERISTICS

The study cohort included 95 patients who underwent TA TMVR between 2015 and 2019 and reached 5-year follow-up. Demographics, baseline characteristics, and medical history are

presented in **Table 1**. Mean age was 74.0 ± 9.2 years, 43.2% of patients were female, STS-PROM for MV replacement was 6.5 ± 4.8%, 57.9% had a heart failure hospitalization (HFH) within the year preceding enrollment, and 88.4% were in NYHA Class III/IV. The predominant mechanism of MR was secondary (78.7%), 70.2% had an LVEF ≤ 50%, and nearly all had ≥ moderate-severe MR (95.8%). Four patients were initially treated for ≥ moderate-severe MR based on site echocardiogram reading, but 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 95 patients. In one patient, the procedure was aborted prior to valve deployment due to 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 three patients experienced a disabling ischemic stroke (3.6%); one was procedure-related, while two were both device- and procedure-related. A total of 20 patients experienced life-threatening (n=16) or fatal bleeding events (n=4) due to access-related apical or intrathoracic bleedings. There was one 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 hemolysis, 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 sub-therapeutic 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 case, while the second case was fatal. Details on all device thrombosis and endocarditis events can be found in **Supplementary Tables 3 and 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**). 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 Panels A-B, Table 2**). The composite rate of all-cause mortality or HFH at 5 years was 78.6%. Per 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 4 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 through 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 neurological event (n=2), myocardial infarction (n=1), and death of unknown cause (n=1). There were 17 patients that had their first HFH between 1-5 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 1-5 years, myocardial infarction occurred in a total of 10 patients, all but two of whom had a history of prior myocardial infarction and/or revascularization with PCI or CABG. 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 two patients had their first new life-threatening bleeding event. One life-threatening subdural hematoma occurred on day 1185 associated with over-anticoagulation (INR 9.6), and one life-threatening bleeding following post peripheral stenting occurred on day 1545.

INTREPID VALVE FUNCTION THROUGH 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 one event without sequelae occurred after 1 year (**Supplementary Table 3**). At the time of the event, 2 patients were receiving warfarin (INR was 2.1 in one patient and unknown in another patient) and 2 patients were receiving clopidogrel. Management involved intensifying or adding anticoagulation therapy. Of these four 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. Of the total 6 cases of clinically significant device thrombosis through 5 years, the independent clinical events committee determined that none of 5 subsequently occurring mortalities were 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 at NYHA Class III/IV. Significant symptom improvement was observed following Intrepid TMVR, with 77.3%, 89.8%, and 84.6% of surviving patients at Class I/II at 30 days, 1-, and 5-year follow-up, respectively (**Central Illustration Panel C**).

FIVE-YEAR ECHOCARDIOGRAPHIC OUTCOMES

Twenty-one (75%) of 28 patients 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 Panel 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 hemodynamic valve deterioration was 1.4% (1/69), while there was no evidence of severe hemodynamic deterioration through 5 years of follow-up.

The median MV mean gradient at 5 years among survivors was 3.6 mmHg (Q1, Q3: 3.0, 4.8 mmHg) (**Figure 3A**), and the median left ventricular outflow tract peak gradient was 6.6 mmHg (Q1, Q3: 3.8, 8.8 mmHg) (**Figure 3B**). 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 (LVESDi), LV end-diastolic diameter index (LVEDDi), cardiac output, and 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 (PASP) and right ventricular (RV) dysfunction decreased.

DISCUSSION

The major findings in this study are **(Central Illustration)**: 1) Intrepid TA TMVR resulted in near elimination of MR through 5- years among survivors, with durable hemodynamic valve performance and a low rate of hemodynamic valve deterioration; 2) there was one 30-day MV reintervention and none thereafter; 3) device-related complications (thrombosis and endocarditis) were infrequent through 5- years, with no apparent clustering of events and no cases of hemolysis; 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 hospitalized for HF within 5 -years. These findings highlight the complex comorbid patient population evaluated in this Pilot study, and the need for systematic optimization of patient selection, guideline directed medical therapy for HF, and a less-invasive transfemoral delivery system.

Durable Valve Performance of the Intrepid TMVR System

Building on previously published 2-year Intrepid TA TMVR data [3], 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 transmitral gradients, both of which have been associated with adverse clinical outcomes [12-17]. Similar to other Intrepid studies [5,6], the Pilot study showed that among survivors, 100% had ≤mild MR and no PVL, with stable transmitral gradients through 5-years. 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 mid-term TMVR [7] 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 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 favored over Transapical approach in TMVR

TA transcatheter aortic valve replacement 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 rates [5]. The most recent ENCIRCLE trial (NCT04153292) data on the Sapien M3 system (Edwards Lifesciences) further confirms the safety of transfemoral TMVR over a TA approach [24]. Transfemoral TMVR is now the only approach with the latest generation 29Fr Intrepid system in the APOLLO and APOLLO EU trials, with other TMVR systems also

evolving to the transfemoral approach (e.g. Cephea [Abbott Structural Heart], InnoValve [Edwards Lifesciences], Alta Valve [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 was 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 system [25], at 2 years with the CHOICE-MI registry with 11 different TMVR devices [26], at 3-years with other TA TMVR systems [7], and at 5-years with TEER [27,28]. Indeed, the Pilot study population was truly a high-risk patient cohort, with a mean STS-PROM of 6.5% for MV replacement, nearly 50% had prior cardiac surgery, 28.4% had an implantable cardioverter defibrillator, 15.8% had an implantable cardiac resynchronization therapy device, almost 80% had secondary MR, 70% had an LVEF ≤ 50%, and almost 60% had prior HFH within the year preceding enrollment. Whether the high mortality rates relate to MR etiology (primary MR vs secondary MR) remain unclear, given the relatively small sample sizes in the above studies and the limited ability to compare outcomes based on MR etiology. However, TA TMVR with the Tendyne system had lower 1-year mortality in two real-world series with fewer secondary MR patients [25,29]. Results from the larger registries (e.g. ENCIRCLE, APOLLO, SUMMIT) will provide a more robust comparison in outcomes between primary and secondary MR patients undergoing TMVR.

With the TA TMVR system, the KM 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 at 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%, respectively [27]. The 5-year results of the EuroSMR registry showed a similar all-cause mortality of 65% in patients with secondary MR [28]. 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 had less blood transfusion and shorter hospital stay [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 optimizing 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 I/II. This is consistent with the sustained improvements observed with other TMVR systems [7]. Although left ventricular dimensions and cardiac output were unchanged over time in this 5-year study, similar to other mid-term TMVR series [31], 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 approach [6]. 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 post-procedural 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 in discussing treatment options with patients with symptomatic MR at high risk for open surgery.

STUDY 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 time points. Thus, paired comparisons for 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 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 rate of continuation or discontinuation was 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 through 5-years 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.

IMPACT ON DAILY PRACTICE

Intrepid TA TMVR was associated with long-term MR elimination, durable hemodynamic valve performance, and improved functional status among survivors up to 5-years in selected patients with symptomatic ≥ 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 HF therapies.

With favorable 5-year valve performance of the Intrepid TA TMVR system, future studies on transfemoral TMVR and comparison studies to TEER will better define the role of TMVR in the management of high surgical risk patients with ≥ moderate-severe MR.

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FIGURE LEGENDS

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

Caption. A) Kaplan-Meier estimate of all-cause mortality to 5 years; B) Kaplan-Meier estimate of heart failure hospitalization to 5 years; C) Symptom status (NYHA functional class) at baseline, 30 days, 1 year, and 5 years; D) Mitral regurgitation severity over time (paired, N=21)

Figure 1 Title. Patient flow chart

Caption. Flow chart depicting number of patients enrolled in the analysis cohort, number of successful implants, and number of patients with known vital status at follow-up. [a] Analysis of clinical outcomes is based on attempted implant cohort, and analysis of echocardiographic outcomes is based on implanted cohort. [b] One patient converted to SMVR at day 0 and one patient converted to SMVR at day 1 were followed through 30-days and withdrew from the study. [c] One 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 time point. SMVR = surgical mitral valve replacement

Figure 2 Title. Mitral regurgitation severity over time

Caption. A) Total mitral regurgitation from baseline to 5 years; B) Paravalvular leakage from 30 days to 5 years. Data reported on implanted cohort (N=92) in patients alive with evaluable echocardiograms at protocol specific visits

Figure 3 Title. Gradients over time

Caption. A) Mitral valve mean gradient over time; B) Left ventricular outflow tract (LVOT) peak gradient over time. Data reported on implanted cohort (N=92) in patients alive with evaluable echocardiograms at protocol specific visits. Values reported as median (Q1, Q3). CW = continuous wave.

Table 1: Baseline Patient Characteristics

	(n=95)
Age, years	74.0 ± 9.2
Sex	
Male	56.8% (54)
Female	43.2% (41)
STS Score – PROM, %	6.5 ± 4.8
NYHA III/IV	88.4% (84)
Diabetes	37.9% (36)
Hypertension	78.9% (75)
Prior MI	42.1% (40)
HFH within past year	57.9% (55)
≥ 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)
Etiology of MR	
Primary MR	21.3% (20/94)
Secondary MR	78.7% (74/94)
≥ Moderate-severe MR	95.8% (91)
LVEF, %	45.2 ± 10.6
LVEF ≤30%	6.4% (6/94)
LVEF 30-50%	63.8% (60/94)
LVEF >50%	29.8% (28/94)
Valve size deployed	
43, 46 & 50 mm	94.7% (89/94)
42 & 48 mm	5.3% (5/94)

Data presented as mean ± standard deviation, % (no. of patients), or % (n/N). CABG = coronary artery bypass graft; ICD = implantable cardioverter defibrillator; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PROM = Predicted Risk of Mortality; STS = Society of Thoracic Surgeons; HFH = heart failure hospitalization; MR = mitral regurgitation.

Table 2: Clinical Outcomes Through 5 Years

	30 days	1 year	5 years	New patients with events from 1-5 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% (0)	22.9% (10)	10
Cardiovascular hospitalization	12.1% (10)	48.2% (37)	79.0% (57)	20
Heart failure hospitalization (HFH)	9.6% (8)	26.0% (20)	55.4% (37)	17
Bleeding event ≥major, MVARC	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 sequalae	0.0% (0)	3.0% (2)	10.5% (5)	3
Clinically significant without sequelae	0.0% (0)	0.0% (0)	1.7% (1)	1
MV endocarditis	0.0% (0)	2.9% (2)	4.6% (3)	1
Hemolysis	0.0% (0)	0% (0)	0% (0)	0

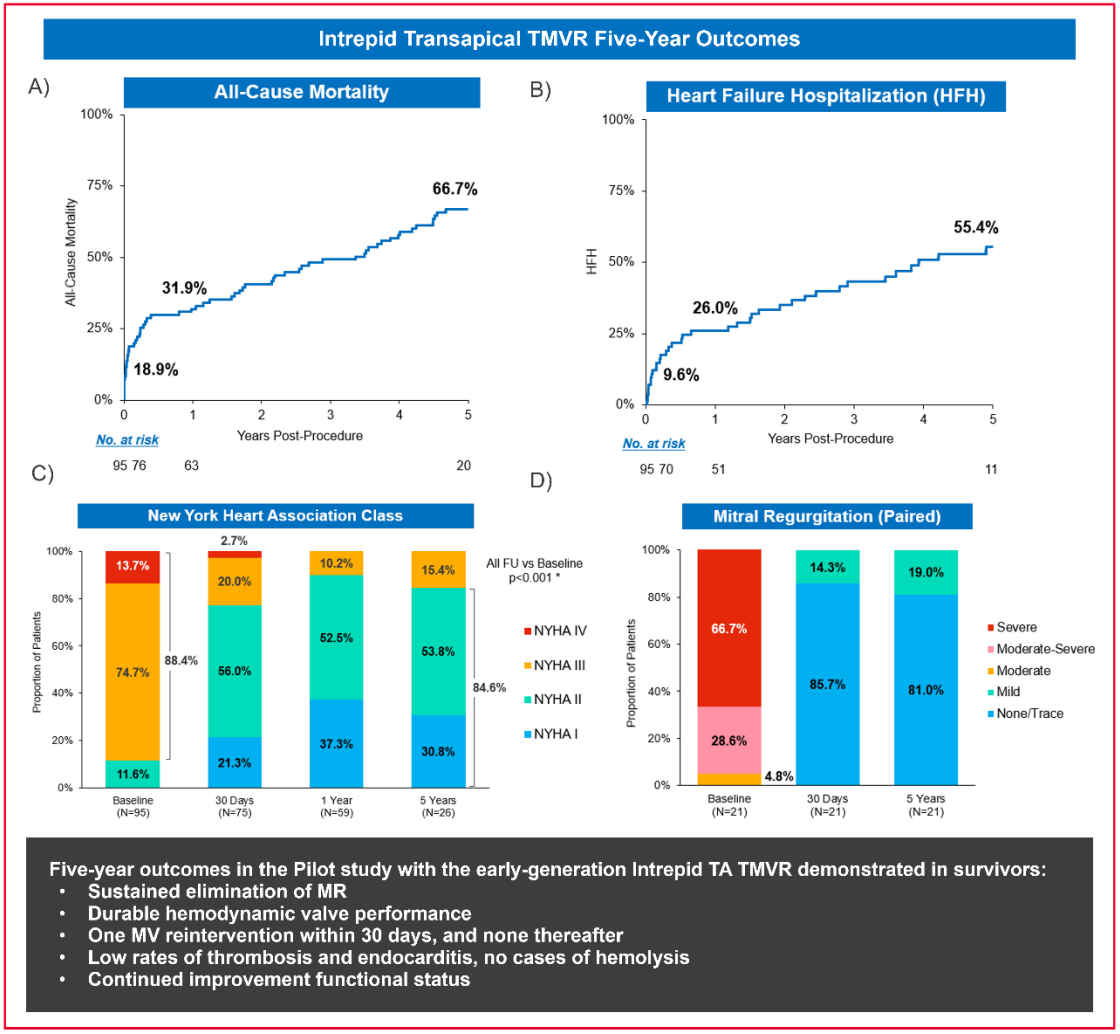
Data presented as Kaplan-Meier rate (no. of patients with event). MV = mitral valve; MVARC = mitral valve academic research consortium.

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

Central Illustration



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

- **Sustained elimination of MR**
- **Durable hemodynamic valve performance**
- **One MV reintervention within 30 days, and none thereafter**
- **Low rates of thrombosis and endocarditis, no cases of hemolysis**
- **Continued improvement functional status**

Figure 1

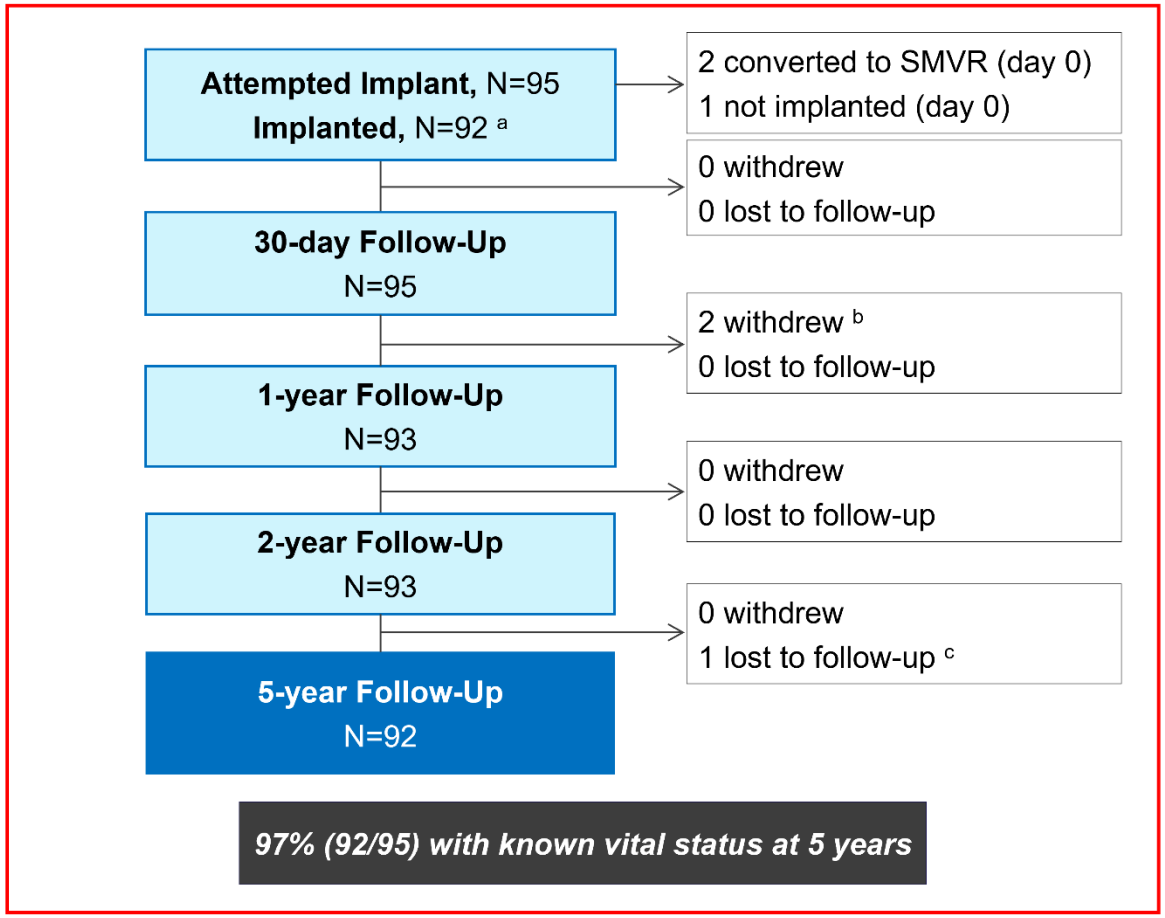

Attempted Implant, N=95
Implanted, N=92 a
2 converted to SMVR (day 0)
1 not implanted (day 0)
0 withdrew
0 lost to follow-up
30-day Follow-Up
N=95
2 withdrew b
0 lost to follow-up
1-year Follow-Up
N=93
0 withdrew
0 lost to follow-up
2-year Follow-Up
N=93
0 withdrew
1 lost to follow-up c
5-year Follow-Up
N=92
97% (92/95) with known vital status at 5 years

Figure 2

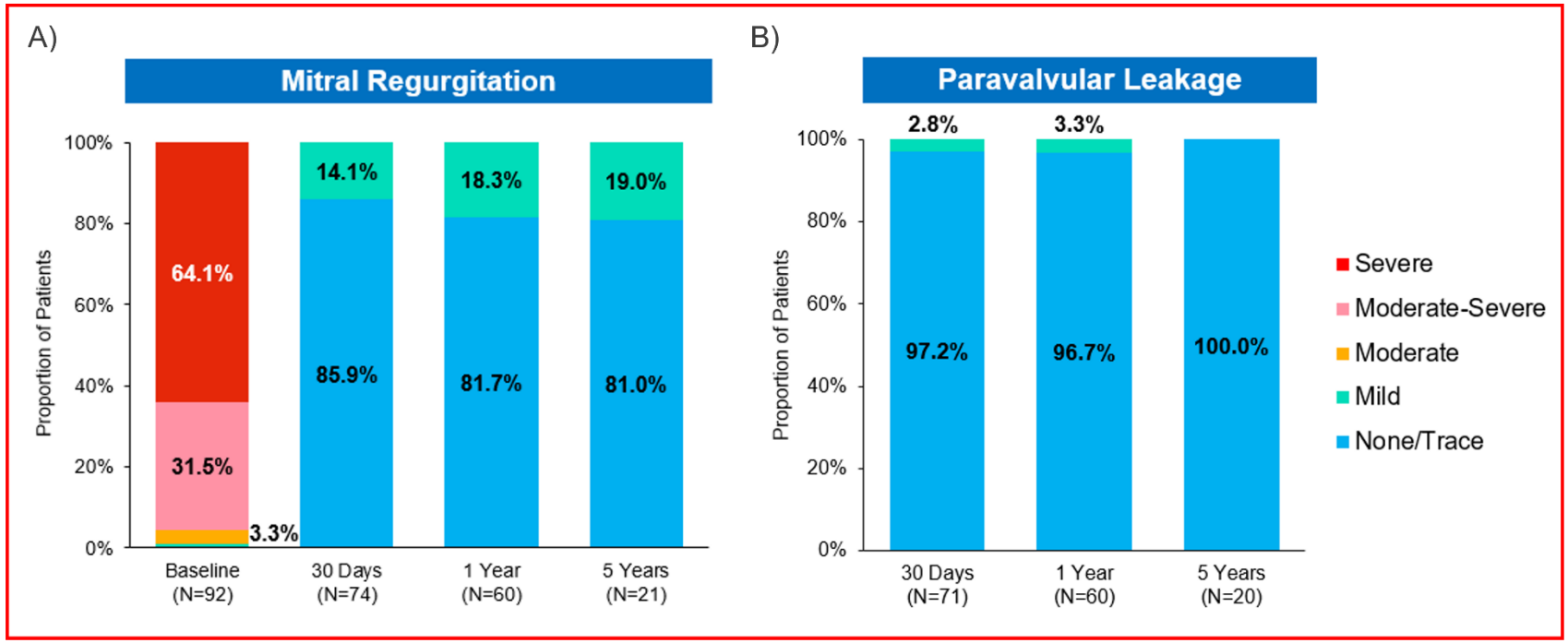
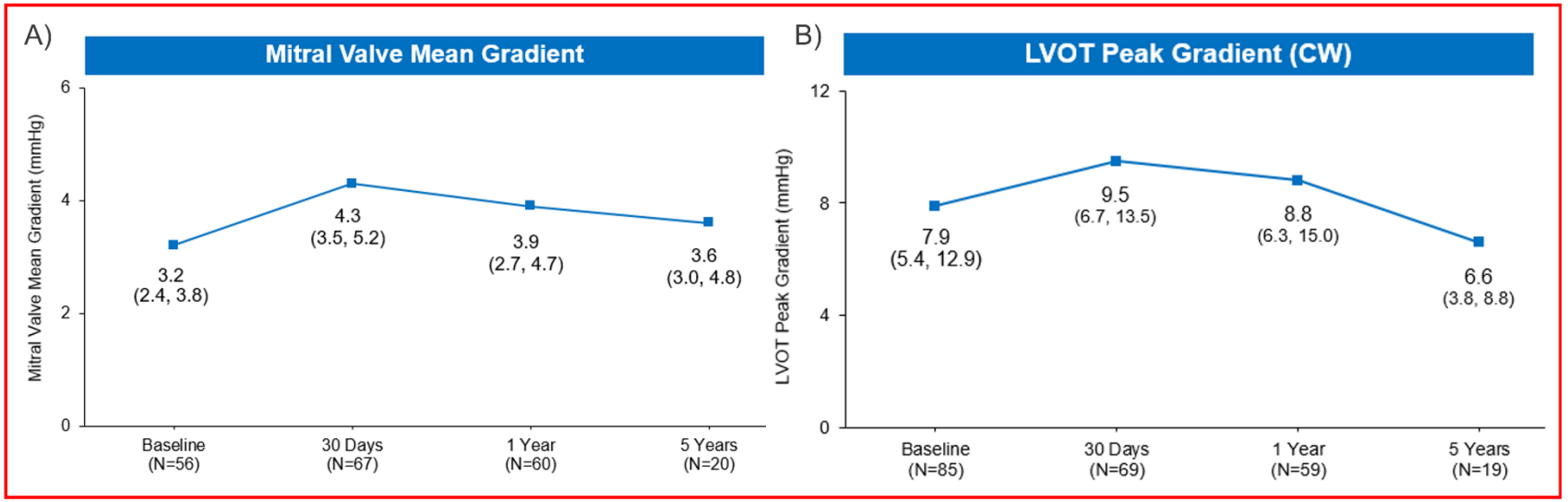

A)
Mitral Regurgitation
Proportion of Patients
100%
80%
60%
40%
20%
0%
64.1%
31.5%
3.3%
14.1%
85.9%
18.3%
81.7%
19.0%
81.0%
Baseline (N=92)
30 Days (N=74)
1 Year (N=60)
5 Years (N=21)
B)
Paravalvular Leakage
2.8%
3.3%
97.2%
96.7%
100.0%
30 Days (N=71)
1 Year (N=60)
5 Years (N=20)
Severe
Moderate-Severe
Moderate
Mild
None/Trace

Figure 3


A)
Mitral Valve Mean Gradient
Mitral Valve Mean Gradient (mmHg)
6
4
2
0
3.2
(2.4, 3.8)
4.3
(3.5, 5.2)
3.9
(2.7, 4.7)
3.6
(3.0, 4.8)
Baseline
(N=56)
30 Days
(N=67)
1 Year
(N=60)
5 Years
(N=20)
B)
LVOT Peak Gradient (CW)
LVOT Peak Gradient (mmHg)
12
8
4
0
7.9
(5.4, 12.9)
9.5
(6.7, 13.5)
8.8
(6.3, 15.0)
6.6
(3.8, 8.8)
Baseline
(N=85)
30 Days
(N=69)
1 Year
(N=59)
5 Years
(N=19)

Appendix for

Five-Year Outcomes of the Early-Generation Intrepid Transapical Transcatheter Mitral Valve Replacement System

Content:

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

Non-Cardiovascular Mortality: Any death clearly related to non-cardiovascular conditions:
- Non-cardiovascular infection or sepsis (e.g., pneumonia)
- Renal failure
- Liver failure
- Cancer
- Trauma
- Homicide
- Suicide
- 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 ≥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:

- 2 major criteria, or
- 1 major + 3 minor, or
- 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°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

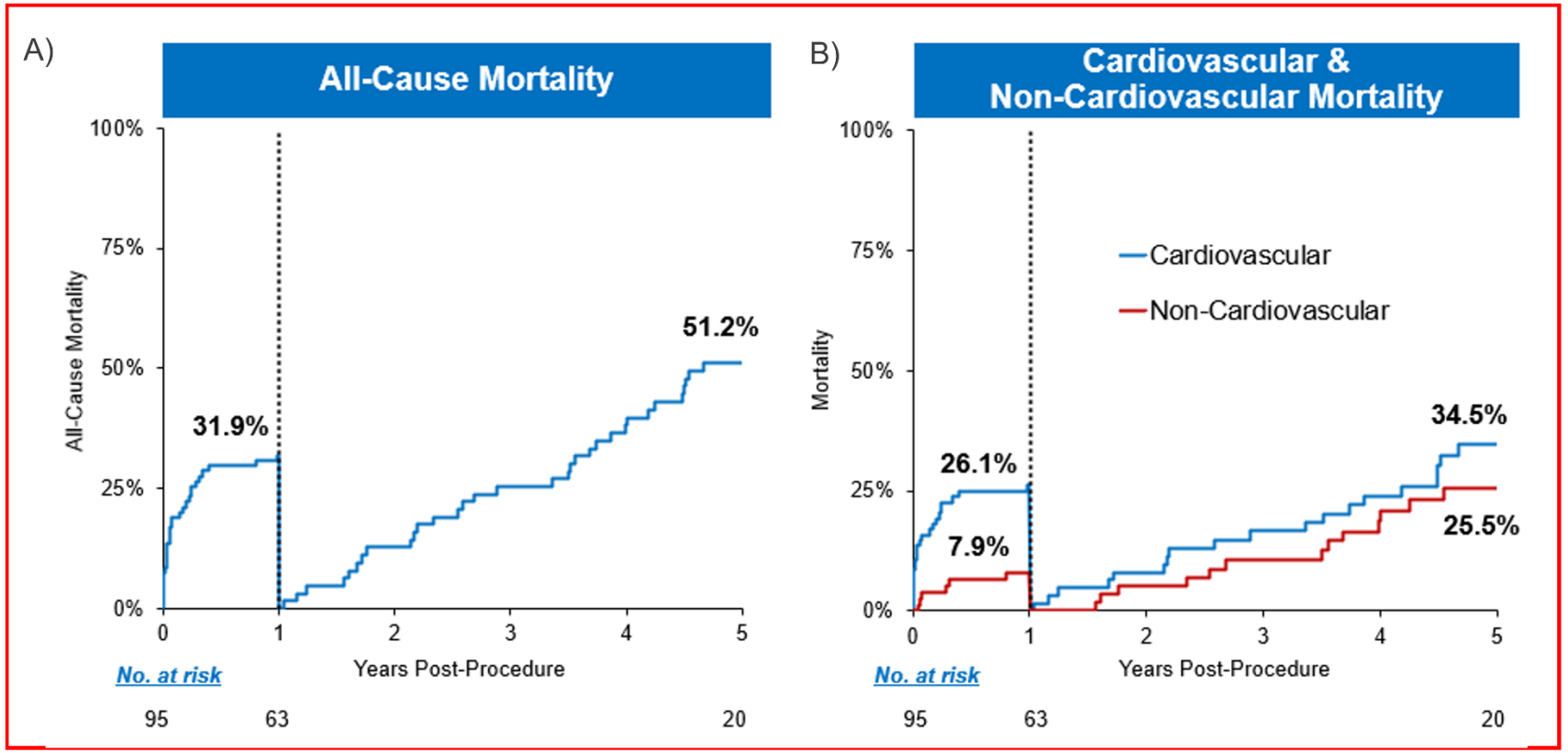
Events meeting 1 major + 1–2 minor or 3–4 minor = "Possible Endocarditis"
Subclassification: By organism and timing: Early (<1 year post-implant) vs. Late (≥1 year)

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

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

Diagnosis should be confirmed by a hematologist.

Supplementary Figure 1. 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



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 Mittnacht, 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 Hebeler 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	
	Hassan Sayegh, Raul Blanco,Vibhar Rangarajan, Peter Flueckiger, Benjamin DeMoss, Roshin Mathew Research Coordinators: Shelley Holt, Elisa Amoroso, Kashaine Gray, Brittney Truss, Denise Whyte, Nita Cadic, Heather Signler, Kimi Wang, Claire Tucker
New York University/Langone Medical Center New York, NY	Principal Investigators: Mathew Williams, Hasan Jilaihawi Co-investigators: Aubrey Galloway, Cezar Staniloae, Muhamed Saric 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
Abbott Northwestern Minneapolis, MN	Principal Investigators: Paul Sorajja, Robert Farivar Co-investigators: Richard Bae, Mario Goessl, Judah Askew Research Coordinators: Kate Jappe, Pam Morley, Aisha Ahmed, Kari Thomas, Brittany Fitzpatrick, Sara Olson, Karen Meyer
Columbia University Medical Center New York, NY	Principal Investigators: Martin Leon, Isaac George Co-investigators: Susheel Kodali, Rebecca Hahn, Torsten Vahl, Tamim Nazif, Michael Borger, Omar Khalique, Vinayak Bapat 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,
Barnes Jewish St. Louis, MO	Principal Investigators: Alan Zajarias, Hersh Maniar Co-investigators: Majesh Makan, Spencer Melby Research Coordinators: Michelle Myers, Kelly Koogler
Northwestern Chicago, IL	Principal Investigators: Patrick McCarthy, Charles Davidson

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 Tchetche 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**
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 ≥ 18 yrs 5. Native mitral valve geometry and size compatible with the Intrepid™ TMVR 6. No or minimal mitral valve calcification 7. Willing to sign Informed Consent for participation in the study and return for all required post-procedure follow-up visits	1. Left ventricular ejection fraction (LVEF) < 20% 2. Evidence of intracardiac mass, thrombus, or vegetation 3. 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/procedure 6. Any endovascular therapeutic interventional or surgical procedure performed within 30 days prior to enrollment 7. Prior stroke within 30 days 8. Need for coronary revascularization 9. Need for emergent surgery 10. History of, or active, endocarditis 11. GI bleeding within 6 months 12. History of bleeding diathesis or coagulopathy or patient will refuse blood transfusion 13. Hemodynamic instability 14. Platelet count of <75,000 cells/mm3 15. 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**
	17. Contraindication to transesophageal echocardiography (TEE) 18. Known hypersensitivity or contraindication to study or procedure medications/contrast which cannot be adequately managed medically. 19. Pregnant, nursing or planning to be pregnant. (Female participants of childbearing potential must have a negative pregnancy test prior to enrollment).

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 vulnerable” per French legislation, including protected adults and prisoners.

Supplementary Table 3: Summary of clinically significant device thrombosis through 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 through 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