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Title: First-in-Human Evaluation of Balloon Expandable Transcatheter Heart Valve in the Treatment of Severe Symptomatic Native Aortic Stenosis: The MyVal-1 Study.

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First-in-Human Evaluation of Balloon Expandable Transcatheter Heart Valve in the Treatment of Severe Symptomatic Native Aortic Stenosis: The MyVal-1 Study

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Short running title: First-in-Human MyVal-1 Study

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Conflict of interest:

Dr. Samin K. Sharma and Dr. Ashok Seth are external scientific advisors to Meril Life Sciences Pvt. Ltd., India. Dr. Ravinder Singh Rao and Dr. Praveen Chandra are proctors for Myval THV technology and have received honoraria from Meril Life Sciences Pvt. Ltd., India. The other authors have no conflict of interest to declare.

ABSTRACT

Aims: To demonstrate safety and efficacy of the next-generation balloon-expandable Myval™ transcatheter heart valve (THV) in intermediate or high-risk patient population with severe symptomatic native aortic stenosis.

Methods and Results: MyVal-1 was first-in-human, prospective, multicentre, single-arm, open-label study. Between June 2017 and February 2018, a total of 30 patients were enrolled at 14 sites across India. Mean age was 75.5±6.7 years; 43.3% had coronary artery disease. The mean Society of Thoracic Surgeons score was 6.4±1.8% and 100% patients were in New York Heart Association (NYHA) functional class II/III/IV at pre-procedure. The six-minute walk test and Kansas City Cardiomyopathy Questionnaire (KCCQ) score were recorded. After successful implantation of Myval THV, 96.6% and 100% were in NYHA functional class I/II at 30-day and 12-month follow-up, respectively. Outcomes of six-minute walk test (148.0±87.4 vs. 336.0±202.9meter) and KCCQ score (36.6±11.0 vs. 65.9±11.4) improved from baseline to 12-month follow-up. The effective orifice area (0.6±0.2cm^2 vs. 1.8±0.3cm^2, p<0.0001), mean aortic-valve gradient (47.4±8.8mmHg vs. 12.0±3.3mmHg, p<0.0001), peak aortic-valve gradient (71.7±13.0mmHg vs. 20.3±5.9mmHg, p<0.0001) and trans-aortic velocity (4.5±0.4m/s vs. 2.2±0.4m/s, p<0.0001) improved substantially from baseline to 12-month post-procedure. Four all-cause mortality were reported through 12 months. Moreover, there was no other moderate/severe paravalvular leak, aortic regurgitation or need for new permanent pacemaker (PPM) through 12-month follow-up.

Conclusions: The MyVal-1 study demonstrated the primary safety and efficacy of Myval THV with no new PPM requirement through 12-month follow-up. However, future trials with larger number of patients and long-term follow-up are warranted to establish the safety and efficacy.

Keywords: Aortic regurgitation; Aortic stenosis; Paravalvular leak; Femoral; TAVI

Condensed Abstract

The first-in-human MyVal-1 study enrolled 30 severe aortic stenosis patients at intermediate or high-risk for surgery, and successfully implanted Myval THV in 100% patients. At 12-month follow-up, the study achieved its safety endpoint with four all-cause mortality. Moreover, effective orifice area, mean and peak aortic-valve gradient, and trans-aortic velocity improved significantly from baseline to discharge through 12-month follow-up. Furthermore, NYHA functional class, results of six-minute walk test and KCCQ score improved from baseline to 12-month follow-up. Study outcomes demonstrated the primary safety and efficacy of Myval THV, with no new PPM requirement, in severe symptomatic native aortic stenosis patients.

Abbreviations:

AS	Aortic stenosis
EOA	Effective orifice area
KCCQ	Kansas City Cardiomyopathy Questionnaire
MACCRE	Major adverse cardiac cerebrovascular and renal events
NYHA	New York Heart Association
PVL	Paravalvular leak
PPM	Permanent pacemaker
QoL	Quality of life
STS	Society of Thoracic Surgeons
SAVR	Surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement
THV	Transcatheter heart valve

Introduction

Aortic stenosis (AS) is a common type of valve disorder in the elderly population, and its prevalence is increasing in aging societies.[1] Two decades ago, surgical aortic valve replacement (SAVR) was the only available treatment for AS.[2] In 2002, "proof-of-concept" case of transcatheter aortic valve replacement (TAVR) was performed by Cribier and his colleagues.[3] TAVR was introduced as an alternative treatment for selected patients with severe AS who were not eligible for surgery.[4] Moreover, TAVR was found non-inferior to SAVR with lower rate of mortality and reduced cardiac arrest in intermediate and high-risk patient populations.[5, 6] TAVR has been successfully carried out in more than 200,000 patients across 65 countries, and is currently considered to be the best strategy for treatment of calcific, severe AS in patients with intermediate to high-risk surgical scores.[7]

Some of the approved TAVR systems (SAPIEN 3, SAPIEN XT – Edwards Lifesciences, Lotus – Boston Scientific, and CoreValve, Evolut PRO – Medtronic) are well established. However, some reports demonstrated certain challenges during implantation or post-procedure with low as well as intermediate and high operative risk patients, which includes a requirement of new permanent pacemaker (PPM), paravalvular leak (PVL), increased risk for valve dislocation, annular rupture, aortic regurgitation (AR) and need of second TAVR implantation.[8-12]

The Conformité Européenne (CE) approved Myval™ transcatheter heart valve (THV) (Meril Life Sciences Pvt. Ltd., India) is a next-generation balloon-expandable TAVR system with features that facilitate accurate positioning and favourable clinical outcomes than current generation TAVR systems. The present study aims to demonstrate its safety and efficacy in intermediate or high-risk patient population with severe symptomatic native aortic stenosis.

Methods

Study design

The MyVal-1 was first-in-human, prospective, multicenter, single-arm, open-label study (Clinical Trials Registry-India: CTRI/2016/11/007512) performed at 14 sites across India to evaluate the safety and efficacy of next generation balloon-expandable Myval THV in symptomatic patients with severe AS. The study protocol was approved by institutional ethics committees. All patients received and signed informed consent. There was an independent data safety monitoring board that adjudicated all the adverse events.

Patient population

A total of 36 patients were screened for the study. Out of these, six patients were excluded due to reasons shown in **Figure 1**. All the inclusion and exclusion criteria for the implantation of the study device are mentioned in the supplementary (Supplementary material).

Device description and procedure

Myval THV is a balloon-expandable TAVR system (**Figure 2**). The device is characterized by a nickel-cobalt alloy frame which is composed of a single design element - hexagon. These are arranged in a hybrid honey-comb fashion which allows 53% of the frame to have large open cells towards the aortic end and 47% to have closed cells with higher annular radial force towards the ventricular end. This novel design geometry on crimping gives rise to a unique alternative dark-light band-like pattern which allows precise positioning, placement, and deployment of the THV across the native annulus (**Figure 3**). The valve construction material is decellularised bovine pericardium tissue, which receives an anti-calcification

treatment and is crafted into a tri-leaflet valve, fixed at three equipoise vertical commissural posts (separated at 120°) on the metal frame. The lower closed cell part of the valve frame is covered externally with a protective sealing cuff of polyethylene terephthalate (PET) to form an external buffing. This feature has a significant benefit in terms of minimising or eliminating PVL. The Myval THV is manufactured in diameters of 20mm, 21.5mm, 23mm, 24.5mm, 26mm, 27.5mm, 29mm, and 32mm.

Myval THV is recommended to be crimped on its novel specially designed hi-flex, over-the-wire Navigator™ balloon catheter system (Meril Life Sciences Pvt. Ltd., India) prior to insertion within the vessel (**Figure 4**). The Navigator has a unique construction characterized by proximal deep flexion handle and a distal balloon with two counter-opposing soft stoppers within that create a shallow, low profile crimping zone and thus a snug fit that prevents any inadvertent dislocation of Myval THV during negotiation through the sheath or thereafter. Additionally, the delivery system allows for flexion of the distal catheter system which ensures trauma-free negotiation across the aortic arch and minimises or eliminates any threat for a peri-procedural stroke, during arch navigation. The balloon further has two internal expansion ports, which facilitate simultaneous expansion distally, and proximally (similar to a dog-bone) stabilizing the valve during deployment and ensuring precision placement. The crimped THV is inserted via a specially designed 22Fr (THV sizes: 20, 23 and 26mm) or 24Fr (THV size: 29mm) expandable sheath. In situations where the operator is not able to deploy the valve in the desired orthotopic position, the unique sheath design allows valve retraction within the sheath.

All the patients received a loading dose of aspirin (325mg/day) and clopidogrel (300mg/day) before the procedure. In most of the cases, using standard percutaneous techniques, a pre-dilatation was performed using an over-the-wire balloon (Mammoth™, Meril Life Sciences

Pvt. Ltd., India) compatible with 0.035" guide wire. Once the THV was positioned accurately across the annulus, a dry pacing run at 180-200bpm was conducted to ensure the valve positioning. The Myval THV was deployed under fluoroscopic guidance by connecting an inflation device pre-filled with a mixture of saline and contrast (75:25) using controlled emptying of the syringe under rapid pacing. Once the THV was fully deployed, the Navigator THV delivery system balloon was fully deflated, and the temporary pacing was stopped. The delivery system was withdrawn from the implantation site, and the post-procedural echo was recorded to check the accuracy of valve deployment, confirm the absence of any trauma to adjoining zone, to measure the gradients and to check for presence of AR or PVL. **Figure 5** depicts positioning of the Myval THV in the case example of the MyVal-1 study.

After the procedure, anaesthesia/sedation was reversed, and patients were transferred to the intensive care unit. All the patients were prescribed 75mg/day aspirin and clopidogrel for at least 6-12 months post-procedure.

Endpoints and follow-up

Clinical follow-up and echocardiography were performed at post-procedure through 12-month. Thereafter, clinical and echocardiographic follow-up will be performed annually up to 5-year post-procedure. The safety endpoint was Kaplan-Meier survivorship up to 12-month follow-up. Additional safety endpoints were all-cause death and stroke up to 12-month follow-up. The efficacy endpoints were improvement in NYHA functional classification, effective orifice area (EOA), and six-minute walk test from baseline through 12-month follow-up. Additionally, quality of life (QoL) as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ), freedom from major adverse cardiac cerebrovascular and renal event (MACCRE) was assessed at respective follow-up. MACCRE was defined as the composite of

cardiovascular death, evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, or valve migration), stroke, procedure-associated and/or device- associated adverse cardiac events, or kidney dysfunction. Device success, early safety at 30 days, clinical efficacy after 30 days, myocardial infarction, all-cause death and stroke were defined in accordance with Valve Academic Research Consortium-2 (VARC-2) definition.[13] All the MACCRE and VARC-2 definitions are mentioned in the supplementary (Supplementary material).

Statistical analysis

Patient demographics, device performance, risk factors, and clinical outcomes were summarized using descriptive statistics for continuous variables and frequency tables for categorical variable. Continuous variables were reported as mean±standard deviation. Categorical variable were expressed as number and percentages. Moreover, all calculations were performed using SAS version 9.2. Change from baseline for NYHA functional class was assessed using the paired Wilcoxon signed rank test; six-minute walk test was assessed through paired t-test. Time to event analysis for survival was evaluated by Kaplan Meier curve.

Results

Baseline characteristics of study population

Between June 2017 and February 2018, a total of 30 symptomatic patients (73.3% males) with a mean age of 75.5±6.7 years were enrolled in the study. The number of patients enrolled at each participating site is mentioned in the supplementary (Supplementary Table 1). Baseline and demographic characteristics are listed in **Table 1**.

Procedural outcomes

Myval THV was implanted in all 30 patients enrolled in the MyVal-1 study. Procedural details are shown in **Table 2.** There were no cases of coronary obstruction, valve dislocation, annular rupture, or structural damage to the aortic valve apparatus. The placement of a second valve was not required in any of the case.

Echocardiographic findings

As shown in **Figure 6**, EOA (1.7±0.3cm^2 vs. 0.6±0.2cm^2, p<0.0001) and mean aortic-valve gradient (8.0±2.7mmHg vs. 47.4±8.8mmHg; p<0.0001), improved significantly at post-procedure as compared to baseline. These results were sustained at 12-month with EOA of 1.8±0.3cm^2, (p<0.0001) and mean aortic-valve gradient of 12.0±3.3mmHg (p<0.0001) improved significantly from baseline to 12-month follow-up. Moreover, peak aortic-valve gradient (20.3±5.9mmHg vs. 71.7±13.0mmHg; p<0.0001) and trans-aortic velocity (2.2±0.4m/s vs. 4.5±0.4m/s; p<0.0001) remains significantly improved hemodynamically at 12-month follow-up as compared to baseline. Two patients had a mild PVL after Myval THV implantation which was treated by post-dilatation during the procedure itself. This did not result in any patient complication or change in hemodynamic performance.

NYHA functional class and QoL status

NYHA functional class improved significantly (p<0.0001) from baseline to 12-month follow-up (**Figure 7**). The QoL improved from baseline to 12-month follow-up; according to the KCCQ score (36.6±11.0 vs. 65.9±11.4). Outcomes of six-minute walk test (148.0±87.4 vs. 336.0±202.9meter) were improved from baseline to 12-month follow-up.

Clinical follow-up

Clinical outcomes along with MACCRE events at different follow-up periods are depicted in **Table 3**. Cumulative all-cause mortality at 1-month, 6-month, and 12-month follow-up were

1 (3.3%), 2 (6.7%), and 4 (13.3%), respectively. Kaplan-Meier survivorship curve of mortality is shown in **Figure 8.** Out of four all-cause mortality, one patient died due to acute renal failure post-procedure; one patient died due to septicemia at 6-month follow-up; one patient died due to coronary artery disease with hypertension and another patient reported death related to non-cardiac event at 12-month follow-up. Major vascular complications were observed in two patients at post-procedure, and none of the patients reported any stroke, life-threatening bleeding or myocardial infarction, hemolysis, thrombosis, and valve migration. Three patients were re-hospitalized at 30-day follow-up. All the re-hospitalized patients were successfully treated and discharged. None of the patients required any new PPM up to 12-month follow-up.

Discussions

The first-in-human MyVal-1 study demonstrated the safety and efficacy of next-generation balloon-expandable Myval THV implanted using percutaneous transfemoral approach. The Myval THV was successfully implanted in all 30 patients with a lower incidence of 30-day as well as 12-month all-cause mortality (4 out of 30 patients). The results of this study support the use of Myval THV in intermediate and high-risk patients with severe symptomatic native AS. No new PPM required during and after the implantation of Myval THV. Also, no moderate/severe PVL, hemolysis, thrombosis and valve migration were reported at 12-month follow-up.

Several randomized studies have demonstrated the effectiveness of TAVR over SAVR for symptomatic patients with AS (at low as well as high to intermediate operative risk) with lower 30-day postoperative mortality rate.[4, 5, 12, 14, 15] The TAVR procedure is generally associated with a risk of acute kidney injury due to variety of factors such as diabetes

mellitus, chronic kidney disease, low glomerular filtration rates, peripheral vascular disease, hemodynamic instability during rapid pacing, previous stroke, and contrast agent volume.[16] In our study, one death was reported in a patient due to acute renal failure who was diabetic, hypertensive and had renal insufficiency. The analysis of SWISS-TAVI registry, which comprised of 3491 consecutive patients, demonstrated the lower rate of in-hospital (2.9%) and 30-day mortality (3.8%) after TAVR procedure.[17] The present study reported similar findings at 30-day with a mortality rate of 3.3%.

TAVR is frequently associated with moderate/severe paravalvular regurgitation (10-12%), which may require repeat intervention.[15, 18, 19] In the MyVal-1 study, prosthetic aortic regurgitation was not seen in any patient up to 12-month follow-up. Mild PVL was seen in 7.1% of the patient without any hemodynamic affects. Our data is in accordance with the recently published low-risk PARTNER 3 trial using SAPIEN 3 valve were mild PVL seen in higher rate with TAVR than with surgery (29.4% vs. 2.1%).[20] Moreover, there was a substantial improvement in aortic valve hemodynamic from baseline in terms of EOA, mean aortic-valve gradient, peak aortic-valve gradient, and trans-aortic velocity through 12-month follow-up.

Other major concerns after TAVR are the neurological complications including stroke. Earlier studies have shown a greater risk of stroke within 30 days in TAVR than surgical replacement.[18, 21] In PARTNER-1 trial, the 30-day stroke rate was 3.6%.[21] Studies have suggested that in-hospital stroke events, both major and minor, were commonly seen in nonagenarian patients following TAVR.[19] In this study, none of the patients reported any stroke during the 12-month follow-up. Moreover, a recent study has favoured TAVR over SAVR with shorter hospital stay (3 days vs. 7 days).[20] Our procedural data in accordance with the study for a shorter hospital stay.

The overall objective of TAVR in AS is to improve QoL and prolong the life expectancy in patients, and improvement in NYHA functional class and six-minute walk test.[18, 22] The QoL outcomes from recent studies have shown significant improvements after TAVR through 1-month, 6-month, and 1-year.[23-25] Our results are in line with these observations with significant improvements in QoL as well as NYHA and six-minute walk test from baseline to 12-month follow-up till.

New pacemaker implantation is a predictor of increased 30-day mortality following TAVR in low-flow AS and occurs due to arterio-ventricular block associated with deeper implantation of valve.[26, 27] The rates were shown to decrease with newer THV designs and advanced knowledge of predictors of pacemaker implantation.[28] The lowest pacemaker rate among the currently available valve is reported with SAPIEN 3 (7.3%) in PARTNER 3 trial.[20] Moreover, in the SURTAVI trial (25.9%) and Evolut low-risk trial (17.4%) patients were required implantation of PPM in TAVR patients at 30-day follow-up.[12, 15] Out of 30 patients evaluated in the MyVal-1 study, no new PPM was implantation through 12-month follow-up. This may be attributed to the fact that the design of Myval THV allows 75:25 for aorta:ventricle positioning across the annular landing zone leading to marginal foreshortening of the frame from ventricular end and thus resulting into the reduced depth of valve implantation within the left ventricular outflow tract.

Limitations

The limitation of this study is that it is a first-in-human experience, with smaller sample size. The present study warrants the need for future trials with a larger population and adequate power to validate the outcomes. Another limitation of the study is the assessment of safety and efficacy at short-term follow-up. Although pre-specified in the study protocol, our study

was not statistically powered for clinical endpoints at 12-month, so the results should be considered for hypothesis generation only.

Conclusion

The results of this first-in-human study demonstrated the primary safety and efficacy of Myval THV in patients with severe AS, who were at intermediate or high-risk for surgery. Higher rate of device success was achieved without the need for a new PPM implant. The preliminary observations of MyVal-1 study will serve as a basis for the future trials with larger number of patients and long-term follow-up to further establish the safety and efficacy of Myval THV.

Impact on daily practice

The MyVal-1 study provided acceptable safety and efficacy of Myval THV with no need for new PPM implant through 12-month follow-up. Besides this, there was no event of stroke observed during the 12-month follow-up. Moreover, the results are encouraging without any device-related adverse events. The MyVal-1 study thus demonstrates that implantation of Myval THV is safe in severe AS patients with intermediate or high-risk for surgery.

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Appendix

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Table 1: Characteristics of the patients at baseline.

Characteristics	Myval THV (N=30)
Age (Years) (mean±SD)	75.5±6.7
Male	22 (73.3)
Society of Thoracic Surgeons score (mean±SD), (%)	6.4±1.8
New York Heart Association functional class	
I	0 (0.0)
II	9 (30.0)
III	16 (53.3)
IV	5 (16.7)
Previous intervention and history	
Coronary artery bypass grafting	5 (16.7)
Percutaneous coronary intervention	4 (13.3)
Cerebral vascular disease	1 (3.3)
Coronary artery disease	13 (43.3)
Previous myocardial infarction	4 (13.3)
Peripheral vascular disease	3 (10.0)
Chronic obstructive pulmonary disease	14 (46.7)
Extensively calcified aorta	2 (6.7)
Pulmonary hypertension	5 (16.7)
Computed Tomography Data	
Aortic root analysis, (mm)	
Left ventricular outflow tract	21.8±2.0
Annulus diameter, (mm)	
Perimeter derived	24.0±1.9
Area derived	23.6±1.9
Sinus of valsalva, (mm)	
Left	28.8±1.8
Right	28.7±1.5
Non	31.1±2.4
Height of coronary ostia, (mm)	
Left	13.6±1.4
Right	12.9±1.6
Sinotubular junction, (mm)	29.3±2.4
Ascending aorta, (mm)	34.9±3.5
Horizontal annulus	2 (6.9)
Echocardiographic Data	
Valve pathophysiology	
Effective orifice area, cm^2	0.6±0.2
Mean aortic-valve gradient, mmHg	47.4±8.8
Peak aortic-valve gradient, mmHg	71.7±13.0
Left ventricular ejection fraction (mean±SD), (%)	45.5±11.5
Aortic regurgitation, (Moderate/severe)	0 (0.0)
Mitral regurgitation, (Moderate/severe)	2 (6.7)

Values are n (%) or mean±SD

Table 2: Procedural characteristics.

Parameters	Myval (N=30)
Implanted Myval size	
20 mm	2 (6.7)
23 mm	13 (43.3)
26 mm	11 (36.7)
29 mm	4 (13.3)
Pre-dilatation with mammoth balloon	
16 mm	7 (23.3)
20 mm	15 (50.0)
23 mm	3 (10.0)
25 mm	1 (3.3)
Post-dilatation	6 (20.0)
Access site	
Right common femoral artery	22 (73.3)
Left common femoral artery	8 (26.7)
Procedural anaesthesia	
General anaesthesia	18 (60.0)
Conscious deep sedation	12 (40.0)
Average hospital stay, (days)	4.4±1.4
Device success	30 (100.0)
Procedure success	29 (96.7)

Values are n (%) or mean±SD

Table 3: Cumulative clinical outcomes up to 12-month follow-up.

Events	Post-procedure (N=30)	30-day follow-up (N=30)	6-month follow-up (N=30)	12-month follow-up (N=30)
All-cause mortality	[#]1 (3.3)	1 (3.3)	2 (6.7)	4 (13.3)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney dysfunction	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)
Device associated and/or procedure-associated adverse cardiac events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Major vascular complications	2 (6.7)	2 (6.7)	2 (6.7)	2 (6.7)
Repeat hospitalization	0 (0.0)	*3 (10.0)	3 (10.0)	3 (10.0)
New permanent pacemaker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Early safety (at 30 days)	-	3 (10.0)	-	-
Clinical efficacy (after 30 days)	-	-	2 (6.7)	4 (13.3)

Values are n (%). [#]patient died due to kidney dysfunction *one patient reported gastroenteritis, one patient had access site complications and one patient reported fracture in left femur.

Figure Legends

Figure 1: Patients enrolment and disposition.

Figure 2: Design of Myval THV.

Figure 3: Positioning of Myval THV.

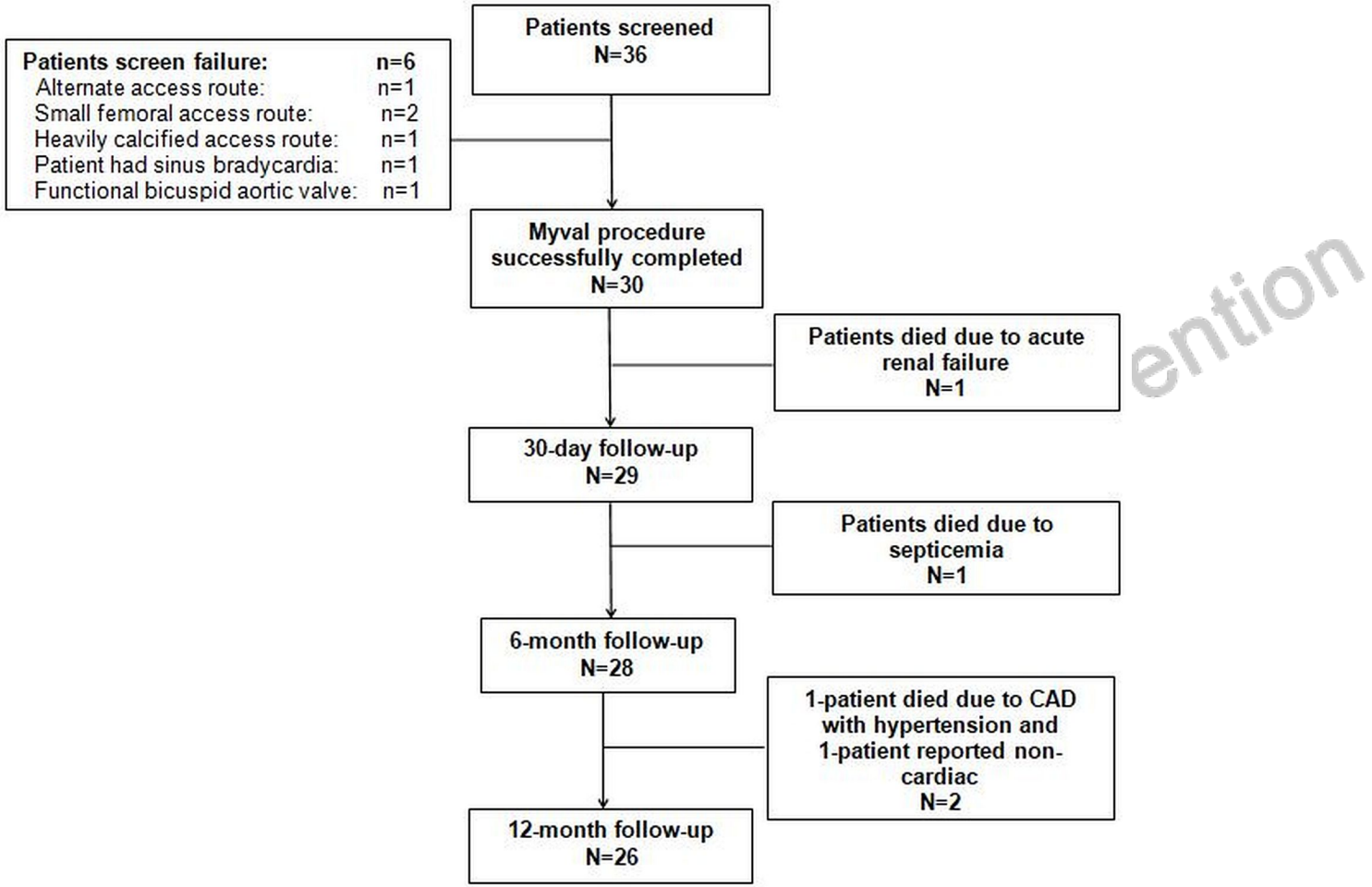
Figure 4: Navigator of Myval THV delivery system.

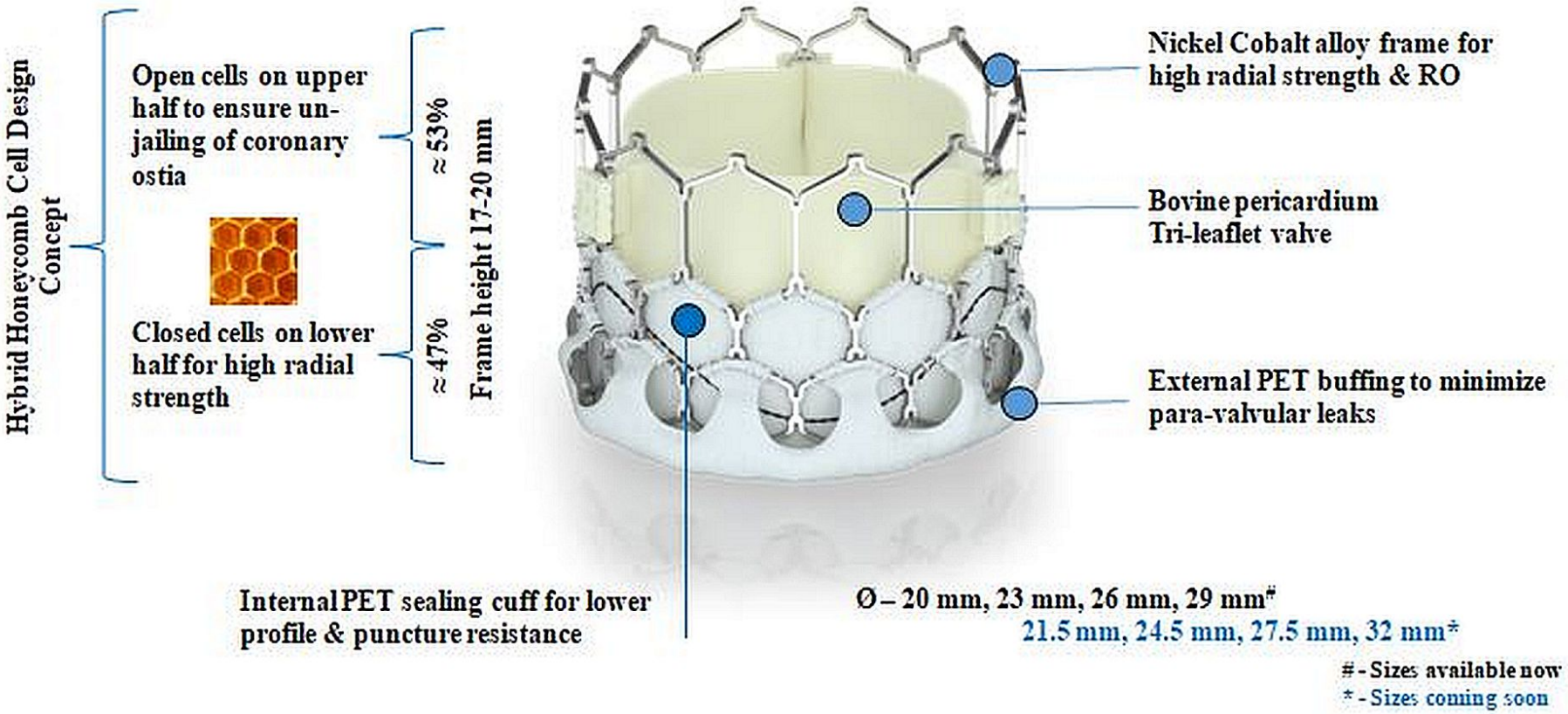
Figure 5: Case example, a) Baseline aortogram. b) Pre-dilatation. c) Navigator flexion avoids scrapping against contralateral arch-wall. d) Valve positioning. e) Precise placement and deployment. f) Final orthotopic deployment.

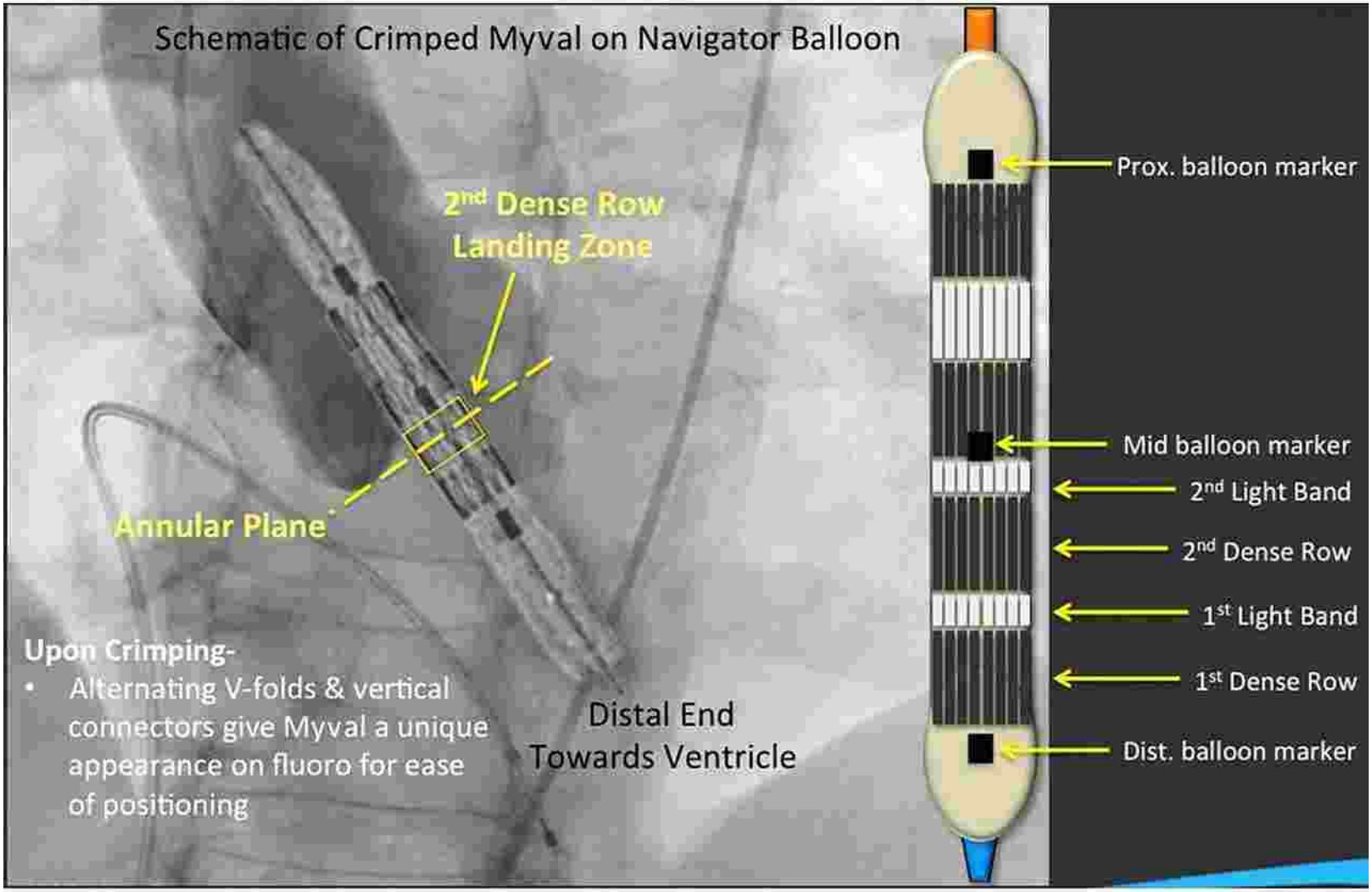
Figure 6: Mean aortic-valve gradient and effective orifice area by echocardiography.

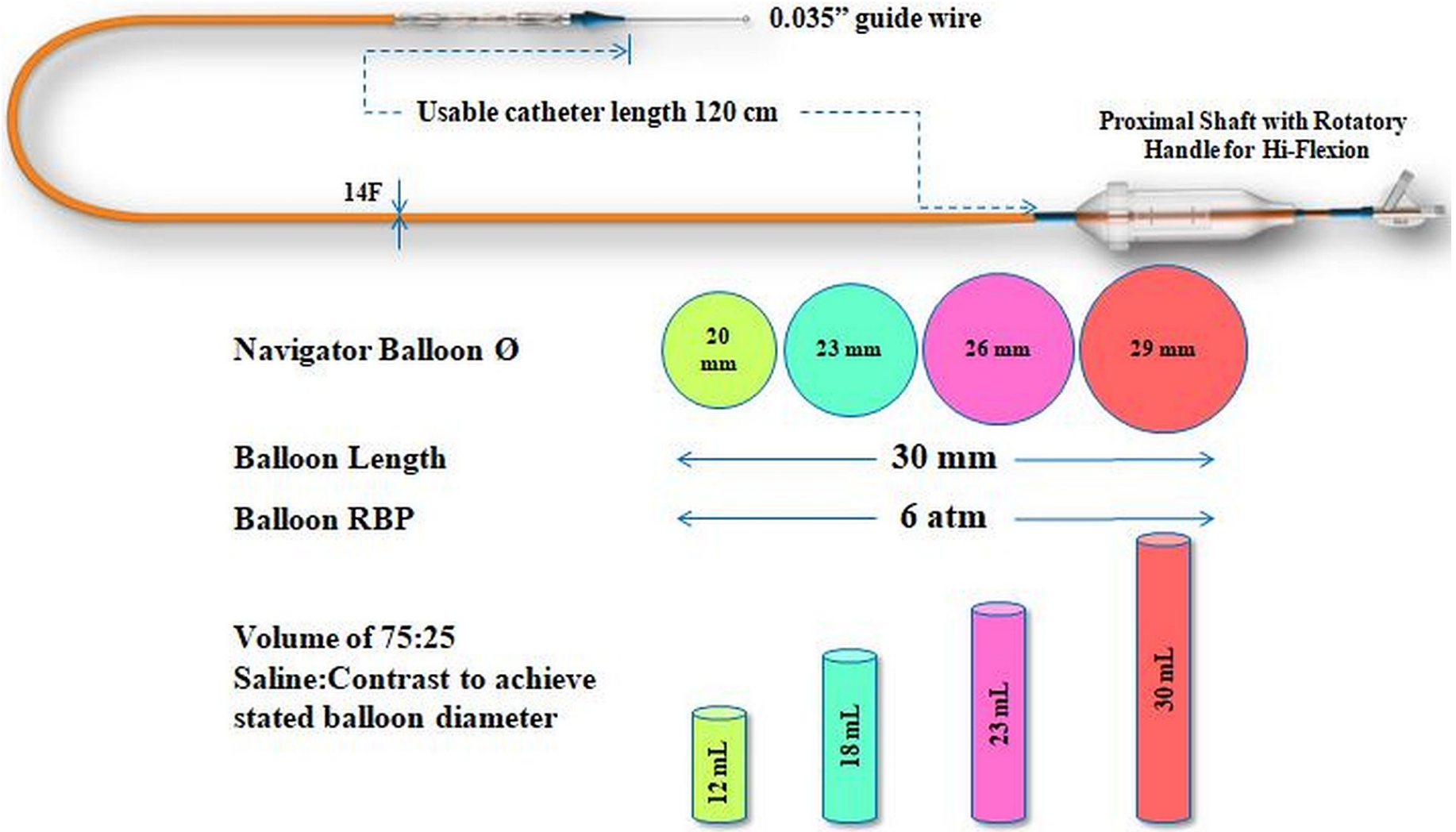
Figure 7: Improvement in NYHA functional class.

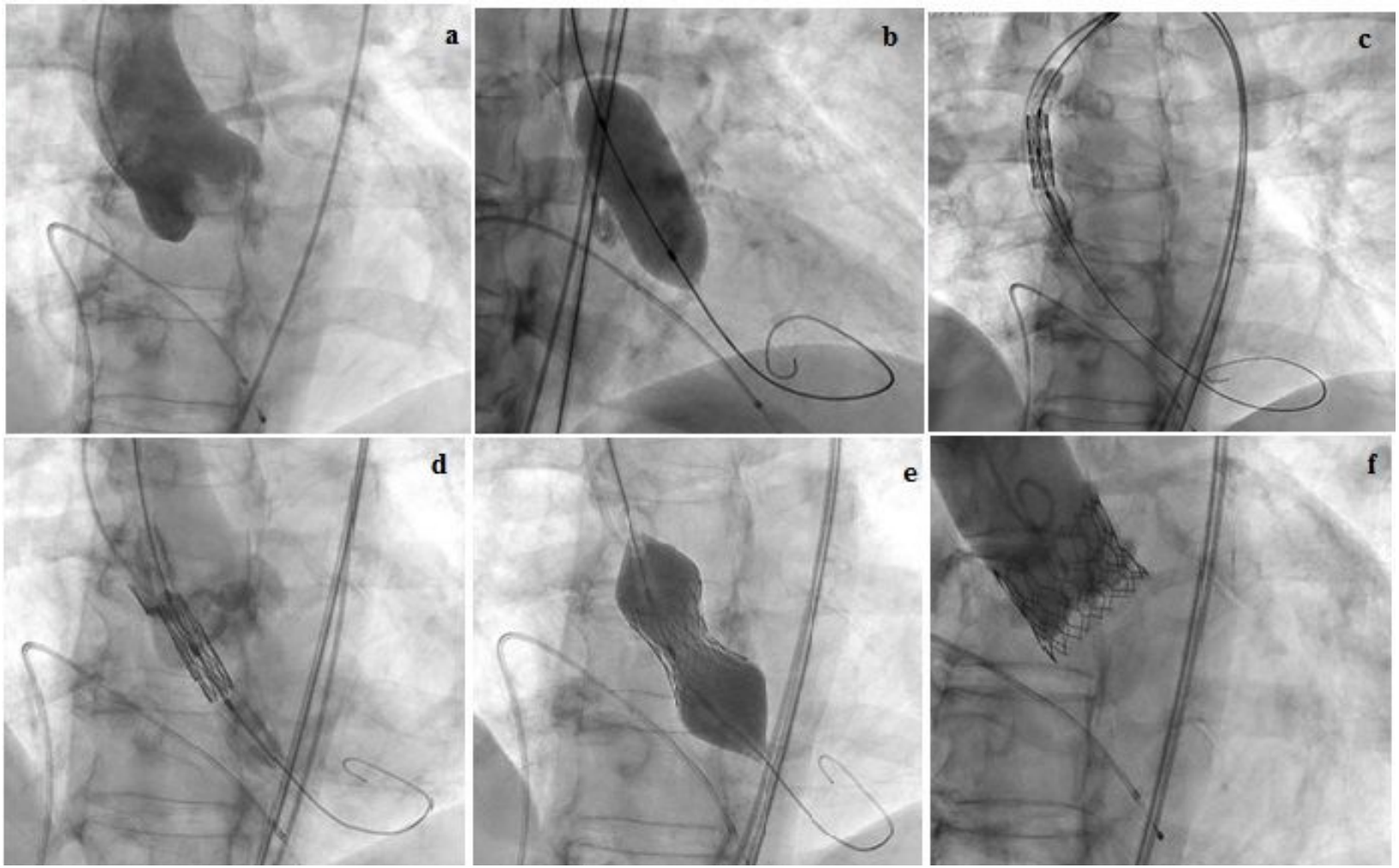
Figure 8: Kaplan-Meier survivorship curve.

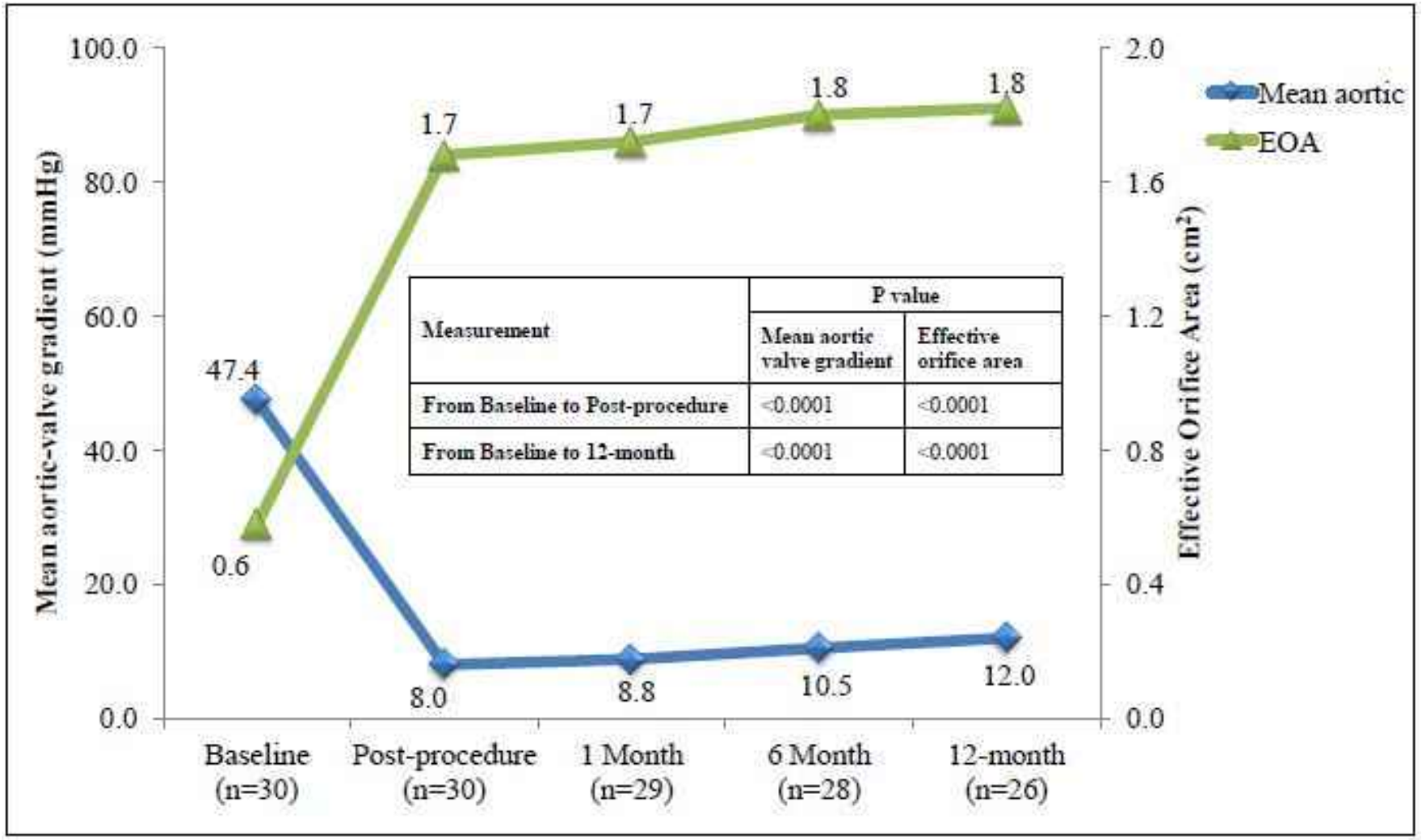




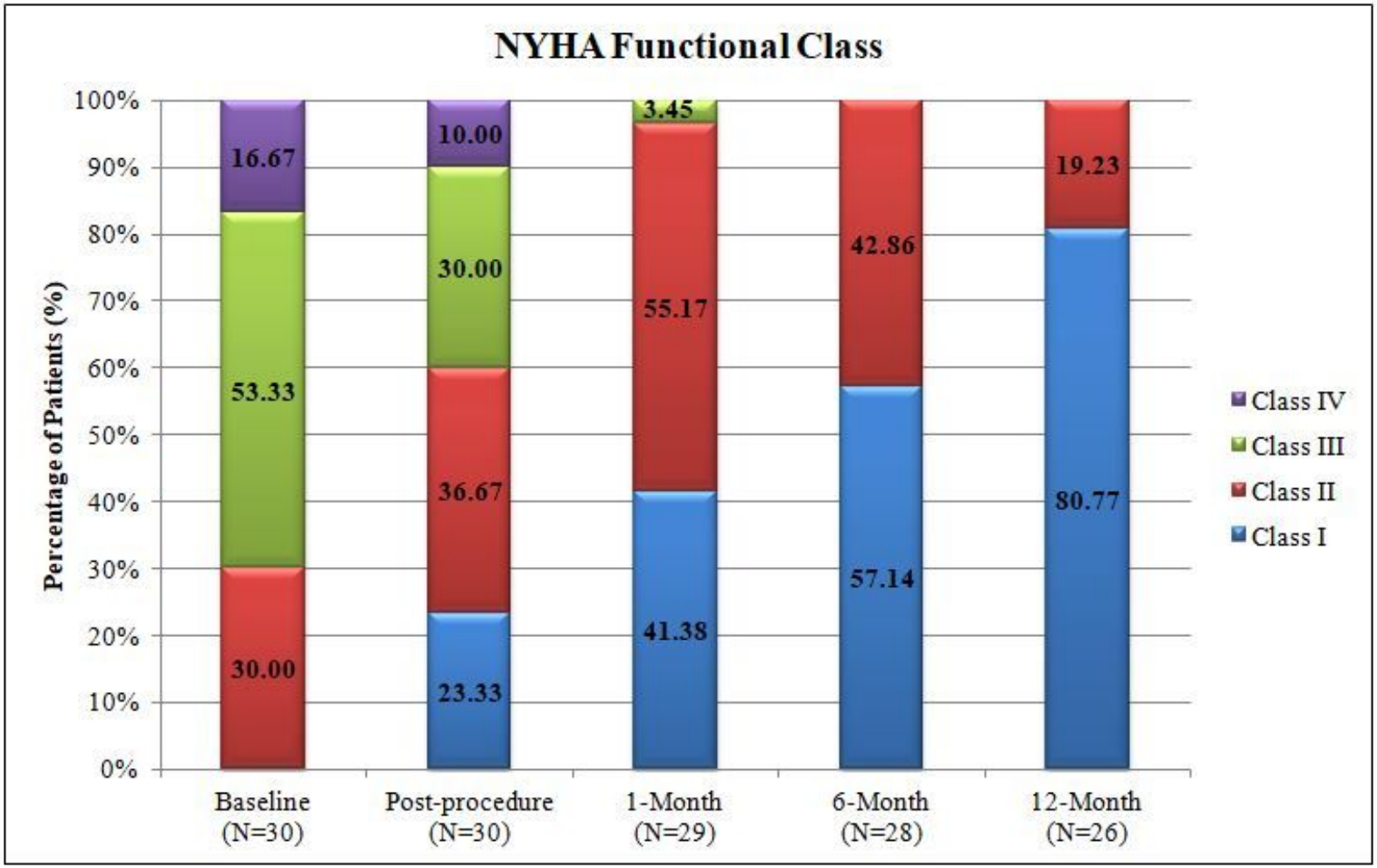


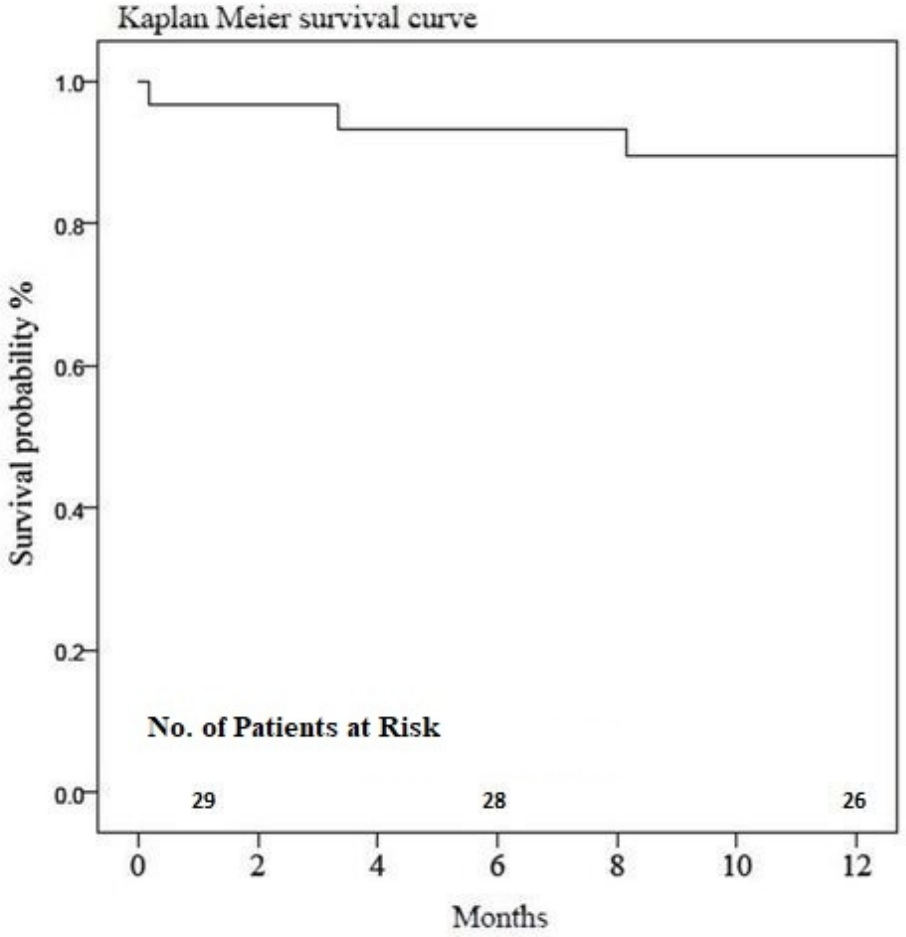






Measurement	P value	
	Mean aortic valve gradient	Effective orifice area
From Baseline to Post-procedure	<0.0001	<0.0001
From Baseline to 12-month	<0.0001	<0.0001





Supplementary Material

Inclusion and exclusion criteria of the MyVal-1 study

Inclusion Criteria:

All patients of this study must meet all of the following inclusion criteria:

1. Patient above 18 years of age who or whose legal representative are willing to sign informed consent form to participate in the study.
2. Patient must have co-morbidities such that the heart team concur that the predicted risk of operative mortality is ≥15% and/or a STS score of ≥4.
3. Patient must have senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area (AVA) of < 0.8 cm^2.
4. Patient should be symptomatic from his/her aortic valve stenosis, as demonstrated by the New York Heart Association (NYHA) Functional Class ≥ II.
5. The patient or the patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
6. The patient agreed for all required post-procedure follow-up visits.

Exclusion Criteria

Patients were excluded from the study if any of the following conditions are present:

1. Patients who are not willing to provide informed consent form, or whose legal heirs object to participate in the study.
2. Pregnant and lactating female patients.
3. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment.
4. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
5. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).

6. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent/scaffold implantation).
7. Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification (MAC), severe (greater than 3+) mitral insufficiency, or Gorlin syndrome.
8. Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb<9mg/dl, thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
9. Untreated clinically significant coronary artery disease requiring revascularization.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery other than aortic valve replacement with the study device.
12. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
13. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20.
14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
15. Active peptic ulcer or upper GI bleeding within the prior 3 months
16. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, or sensitivity to contrast media, which cannot be adequately premedicated.
17. Native aortic annulus size < 18mm or > 28mm as measured by echocardiogram.
18. Recent (within 6 months) cerebrovascular accident (CVA) or a Transient Ischemic Attack.
19. Renal insufficiency and/or end stage renal disease requiring chronic dialysis.
20. Life expectancy < 12 months due to non-cardiac co-morbid conditions.
21. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
22. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter (applicable for transfemoral patients only).
23. Currently participating in an investigational drug or another device study.

24. Active bacterial endocarditis or other active infections.
25. Bulky calcified aortic valve leaflets in close proximity to coronary ostia.

Valve Academic Research Consortium (VARC-2) definition

Device Success:

- Absence of procedural mortality
- Correct positioning of a single prosthetic heart valve into the proper anatomical location
- Intended performance of the prosthetic heart valve (no prosthesis– patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation.

Myocardial infarction:

- Peri-procedural MI (≤72 h after the index procedure)
- New ischaemic symptoms (e.g. chest pain or shortness of breath), or new ischaemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, haemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
- Elevated cardiac biomarkers (preferable CK-MB) within 72 hours after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB. If cardiac biomarkers are increased at baseline (.99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Stroke:

- *Disabling stroke:* an modified Rankin Scale score of 2 or more at 90 days and an increase in at least one modified Rankin Scale category from an individual's pre-stroke baseline.
- *Non-disabling stroke:* an modified Rankin Scale score of 2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline.

Early safety (at 30 days)

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening bleeding

- Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
- Coronary artery obstruction requiring intervention
- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

Clinical efficacy (after 30 days)

- All-cause mortality
- All stroke (disabling and non-disabling)
- Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure
- NYHA class III or IV
- Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm^2 and/or DVI <0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation)

MACCRE definition

Cardiovascular death:

Any of the following criteria

- Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
- Sudden or unwitnessed death
- Death of unknown cause.

Procedure-associated and/or device- associated adverse cardiac events :

- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events

Kidney dysfunction (AKIN Classification):

Stage 1 Increase in serum creatinine to 150-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR

Urine output <0.5 mL/kg/hours for >6 but <12 hours

Stage 2

Increase in serum creatinine to 200-299% (2.0-2.99 × increase compared with baseline) OR

Urine output <0.5 mL/kg/hours for >12 but <24 hours

Stage 3

Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0mg/dL (≥354mmol/L) with an acute increase of at least 0.5mg/dL (44mmol/L) OR

Urine output <0.3ml/kg/hours for ≥24 hours OR Anuria for ≥12 hours

Supplementary table 1

Number of Procedures in Each Participating Site

Site Code	Number of Procedures
001	3
002	7
003	1
004	1
005	4
006	2
007	1
008	1
009	1
010	1
011	1
012	1
013	2
014	4
Total	**30**