Rationale and design of a randomized clinical trial comparing safety and efficacy of Myval transcatheter heart valve versus contemporary transcatheter heart valves in patients with severe symptomatic aortic valve stenosis: the LANDMARK trial

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Rationale and design of a randomized clinical trial comparing safety and efficacy of Myval transcatheter heart valve versus contemporary transcatheter heart valves in patients with severe symptomatic aortic valve stenosis: the LANDMARK trial

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Highlights

- The LANDMARK is a randomized trial comparing head-to-head TAVR devices.
- The trial evaluates safety and efficacy of Myval versus contemporary approved THVs.
- Myval is a balloon-expandable THV with additional intermediate and extra-large sizes.
- Myval unique design aims to mitigate both PVR and conduction disturbances.
- Clinical follow-up of the LANDMARK trial will be up to 10 years.

Abstract

Background

The recent approval of transcatheter aortic valve replacement (TAVR) in patients with low operative risk has paved the way for the introduction of novel and potentially improved technologies. The safety and efficacy of these novel technologies should be investigated in randomized control trials against the contemporary TAVR devices. The objective of the LANDMARK trial is to compare the balloon-expandable Myval transcatheter heart valve (THV) series with contemporary THV (SAPIEN THV and Evolut THV series) series in patients with severe symptomatic native aortic stenosis.

Methods/Design

The LANDMARK trial (ClinicalTrials.govNCT04275726, EudraCT number 2020-000137-40) is a prospective, randomized, multinational, multicenter, open-label, non-inferiority trial of approximately 768 patients treated with TAVR via the transfemoral approach. Patients will be allocated in a 1:1 randomization to Myval THV series (n=384) or to contemporary THV (n=384) (either of SAPIEN THV or Evolut THV series). The primary combined safety and efficacy endpoint is a composite of all-cause mortality, all stroke (disabling and non-disabling), bleeding (life-threatening or disabling), acute kidney injury (stage 2 or 3), major vascular complications, prosthetic valve regurgitation (moderate or severe), and conduction system disturbances (requiring new permanent pacemaker implantation), according to the Valve Academic Research Consortium-2 criteria at 30-day follow-up. All patients will have follow-up up to 10 years following TAVR.

Summary

The LANDMARK trial is the first randomized head-to-head trial comparing Myval THV series to commercially available THVs in patients indicated for TAVR. We review prior data on head-to-head comparisons of TAVR devices and describe the rationale and design of the LANDMARK trial.

Keywords

aortic stenosis, balloon-expandable valve, paravalvular regurgitation, permanent pacemaker implantation, randomized trial, transcatheter aortic valve replacement, transcatheter heart valve.

Introduction

Over the last two decades, transcatheter aortic valve replacement (TAVR) has emerged as a valuable alternative to surgery in an increasingly wide spectrum of patients with severe symptomatic AS[1,2,3,4,5,6,7]. The safety and efficacy of TAVR was initially established in patients at high surgical risk in the PARTNER 1A[2,8,9] and US CoreValve high-risk trials[3,10,11,12] showing comparable clinical outcomes to surgery. A role for TAVR in patients at intermediate surgical risk has been subsequently investigated in the PARTNER 2A[4] and SURTAVI[5,13] trials, which demonstrated the non-inferiority of TAVR with respect to SAVR in this patient population. Furthermore, these trials have demonstrated the superiority of TAVR over surgery when performed via transfemoral approach[5,14]. These data were generated from properly designed randomized clinical trials (RCTs) comparing TAVR with surgery over short and intermediate follow-up periods.

The recent approval of TAVR for patients at low operative risk, based on the results of the randomized PARTNER 3[6] and Evolut Low Risk[7] trials, has opened a new avenue of wider TAVR expansion into lower surgical risk population as well as the introduction of novel and potentially improved technologies into patient care. Recently, the safety and efficacy of Myval™ (Meril Life Sciences Pvt. Ltd., India), a novel balloon-expandable transcatheter heart valve (THV), was shown in the MyVal-1 first-in-human trial, with particularly low rates of paravalvular regurgitation (PVR) and new permanent pacemaker implantation (PPI)[15]. Furthermore, one of the strong assets of the Myval THV is that its cost is around 15-20% cheaper than SAPIEN THV series and fairly close to Evolut THV series. In fact, the Myval THV has similar features compared to SAPIEN THV series. If the non-inferiority of the Myval THV is proved, it might be

an attractive alternative in the global market for operators that privilege a balloon expandable system.

We review prior data on head-to-head comparisons of TAVR devices, and describe the rationale and design of the LANDMARK trial, an RCT comparing safety and efficacy of Myval THV series versus contemporary THV series in patients with severe symptomatic native AS.

Current evidence of head-to-head TAVR device comparison

To date, six RCTs of head-to-head TAVR device comparison have been published and are summarized in **Table 1**. The primary endpoints at 30 days are shown in **Figure 1**.

The CHOICE trial[16] demonstrated a superior device success at 30 days in patients treated with a second-generation balloon-expandable valve (SAPIEN XT) via transfemoral approach compared to a first-generation self-expanding valve (CoreValve) in 241 patients with severe AS at intermediate-to-high risk for surgery (SAPIEN XT 95.9% vs CoreValve 77.5%; relative risk 1.24; 95% confidence interval [CI] 1.12-1.37; P<0.001 for superiority). At 5-year follow-up, clinical outcomes with the SAPIEN XT and CoreValve were not significantly different, although the statistical power was limited[17].

In the PORTICO-IDE trial[18], the first-generation Portico valve was compared with the other commercially available valves (SAPIEN, SAPIEN XT, SAPIEN 3, CoreValve, Evolut R, or Evolut PRO). The primary safety endpoint was a composite of all-cause mortality, disabling stroke, life-threatening bleeding requiring transfusion, acute kidney injury (AKI) requiring dialysis, and major vascular complication at 30 days. The primary efficacy endpoint was all-cause mortality and disabling stroke at 1 year. The pre-specified non-inferiority criteria of the primary safety endpoint was met (Portico 13.8% vs commercially available valves 9.6%;

absolute difference 4.2; 95% CI -0.4 to 8.8; upper confidence bound 8.1%; P=0.034 for non-inferiority and P=0.071 for superiority). The primary efficacy endpoint was also met (Portico 14.8% vs commercially available valves 13.4%; difference 1.5%; 95% CI -3.6 to 6.5; upper confidence bound 5.7%; P=0.0058 for non-inferiority and P=0.50 for superiority). However, post-hoc superiority tests showed that commercially available valves were superior to the Portico valve for the primary safety endpoint in the as-treated population (commercially available valves 9.4% vs Portico 14.4%; absolute difference: 5.0%; 95% upper confidence bound 8.9%; P=0.037 for superiority).

The REPRISE-III trial[19] demonstrated non-inferiority of a mechanically expanded valve (LOTUS) compared to self-expanding valves (CoreValve or Evolut R) in 912 patients with severe AS at high surgical risk with respect to the composite primary safety endpoint of all-cause death, stroke, life-threatening and major bleeding, advance stages of AKI, and major vascular complications at 30 days and the composite of primary effectiveness endpoint of all-cause death, disabling stroke, and moderate-or-severe PVR at 1 year. Use of the LOTUS valve compared with the CoreValve or Evolut R was non-inferior for the primary safety endpoint (LOTUS 20.3% vs CoreValve or Evolut R 17.2%; difference 3.1%; Farrington-Manning 97.5% CI, -∞ to 8.3%; P=0.003 for non-inferiority). However, the LOTUS valve, compared with the CoreValve or Evolut R, met the non-inferiority for the primary effectiveness endpoint (LOTUS 15.4% vs CoreValve or Evolut R 25.5%; difference -10.1%; Farrington-Manning 97.5% CI, -∞ to -4.4%; P<0.001 for non-inferiority), and furthermore, the superiority analysis for the primary effectiveness endpoint was statistically significant (difference -10.2%; 95% CI -16.3% to -4.0%; P<0.001 for superiority).

The SOLVE-TAVI investigator-driven trial[20] enrolled 447 patients at intermediate-to-high surgical risk, who underwent transfemoral TAVR using a newer-iteration of self-expanding valve (Evolut R) compared to a newer-iteration of balloon-expandable valve (SAPIEN 3). The study demonstrated the equivalence of the two devices with regard to the primary efficacy composite endpoint of all-cause death, stroke, moderate-to-severe PVR, and PPI at 30 days (Evolut R 28.4% vs SAPIEN 3 26.1%; rate difference -2.39; 90% CI -9.45 to 4.66; P=0.04 for equivalence).

The SCOPE-I trial[21] enrolled 739 patients at low risk, who underwent TAVR using the self-expanding valve (ACURATE neo) compared to the balloon-expandable SAPIEN 3 valve. The combined primary safety and efficacy endpoint was a composite of all-cause death, any stroke, life-threatening or disabling bleeding, major vascular complications, coronary artery obstruction requiring intervention, AKI (stage 2 or 3), rehospitalization for valve-related symptoms or congestive heart failure, valve-related dysfunction requiring repeat procedure, moderate or severe PVR, and prosthetic valve stenosis at 30 days. The ACURATE neo valve did not meet non-inferiority compared to the SAPIEN 3 (ACURATE neo 24% vs SAPIEN 3 16%; absolute risk difference 7.1%; upper 95% confidence limit 12.0%; P=0.42 for non-inferiority).

The SCOPE-II trial[22] was an investigator initiated, prospective, multicenter, non-inferiority, 1:1 RCT (ACURATE neo vs Evolut THV series) including 796 patients. The primary endpoint was a composite of all-cause mortality or stroke rates at 1 year. The key secondary endpoint, powered for superiority of the ACURATE neo valve, was new PPI at 30 days. The ACURATE neo did not meet non-inferiority compared to Evolut THV series in terms of the primary endpoint of a composite of all-cause mortality or stroke rates at 1 year (ACURATE neo 15.8% vs Evolut THV series 13.9%; absolute risk difference 1.8%, upper 95% confidence limit

6.1%; P=0.055 for non-inferiority). The ACURATE neo was associated with a lower incidence of the key secondary endpoint of new PPI at 30 days (ACURATE neo 10.5% vs Evolut THV series 18.0%; absolute risk difference -7.5%; 95% CI -12.4 to -2.60; P=0.003 for superiority). Cardiac death at 30 days (2.8% vs 0.8%; P=0.03 for superiority) and 1 year (8.4% vs 3.9%; P=0.01 for superiority), and moderate or severe PVR at 30 days (10% vs 3%; P=0.002 for superiority) were significantly increased in the ACURATE neo group compared to the Evolut THV series group. Patients were followed up to 1-year post-procedure only.

Methods

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Myval THV system

The investigational device in the LANDMARK trial is the Myval THV, a balloon-expandable THV system. The Myval THV system is indicated for replacing the aortic valve in patients with severe symptomatic native AS who have been determined by the heart team to be eligible for TAVR. The MyVal-1 first-in-human trial demonstrated a low rate of new PPI in addition to excellent clinical and hemodynamic outcomes[23, 24]. The Myval THV was granted the CE mark in April 2019. The specifications of the device are described in detail in the **Supplemental materials**. Myval THV series will include Myval THVs or any subsequent advanced version commercially available at the study site. Device sizes of Myval THV include 20mm, 21.5mm, 23mm, 24.5mm, 26mm, 27.5mm, and 29mm in diameter (**Table 2 and Figure 2**).

Control arm THV system

SAPIEN THV series (Edwards Lifesciences, CA, USA) will consist of SAPIEN 3/SAPIEN 3 Ultra THVs or any subsequent advanced version commercially available at the study site. Evolut THV series (Medtronic, MN, USA) will include Evolut R/Evolut PRO THVs or any subsequent advanced version commercially available at the study site. Device sizes of SAPIEN THV series include 20mm, 23mm, 26mm, and 29mm in diameter and those of Evolut THV series include 23mm, 26mm, 29mm, and 34mm in diameter.

The selection of the control arm in the trials comparing head-to-head TAVR devices is important to achieve non-inferiority or superiority of novel TAVR technologies, compared with current TAVR technologies. In the previous six RCTs of head-to-head TAVR device comparison, SAPIEN THV series or CoreValve/Evolut THV series were selected as the valves in the control arm[16,18,19,20,21]. The contemporary "standard" TAVR devices have been selected in the control arm to convince clinicians and cardiologists of the non-inferiority or superiority of the study device with respect to current generation devices. In the LANDMARK trial, Myval THV will also be compared to the contemporary "standard" TAVR devices (SAPIEN THV series or Evolut THV series).

Primary and secondary endpoints

The primary combined safety and efficacy endpoint is a composite of all-cause mortality, all stroke (disabling and non-disabling)[25], bleeding (life-threatening or disabling), AKI (stage 2 or 3), major vascular complications, PVR (moderate or severe) analyzed by echocardiography, and conduction system disturbances (requiring a new PPI), according to the Valve Academic

Research Consortium (VARC)-2 criteria at 30-day follow-up[26]. The secondary endpoints are summarized in **Table 3.**

Study design

The LANDMARK trial is a prospective, randomized, multinational, multicenter, open-label, and non-inferiority trial. Clinical data of the primary endpoint will be adjudicated by an independent Clinical Event Committee (CEC), and ongoing safety monitoring will be performed by an independent Data and Safety Monitoring Board (DSMB) (**Supplemental materials**). Each patient must provide written informed consent as approved by the ethical committee of the respective clinical site in order to participate in the LANDMARK study.

Statistical Considerations

Sample Size Calculation

The event rate for primary composite safety and efficacy endpoint at 30 days is assumed at 26.1% in both groups based on the data of different trials[4,5,6,7,18,19,20,21,27,28]. Assuming non-inferiority margin of 10.44% (40% of the assumed event rate) with allocation ratio of 1:1 (Myval THV series: contemporary THV [SAPIEN THV series and Evolut THV series]) a sample size of 692 patients (i.e. 346:346) are required at 93% power, with 5% level of significance. Considering 10% dropout rate, a total of 768 patients (i.e. 384:384) will be required to be enrolled into the LANDMARK trial.

Randomization

Patients will be allocated in a 1:1 to Myval THV and contemporary THV series (stratification and equal allocation for each valve will be done within the contemporary THV series, i.e. 50% SAPIEN THV series and 50% Evolut THV series) (**Figure 3**). Approximately 768 patients with severe symptomatic native AS will be enrolled in this trial. Considering the power and selection bias simultaneously, we will use a covariate-adaptive randomization procedure based on the simulation (**Supplemental materials**) according to the Frane method[29]. Using this randomization procedure, the covariate (STS-PROM Risk Score version 2.9 [low risk (<4%), intermediate risk (4% to 8%), and high risk (>8%)]) imbalances within each treatment group will be small enough such that asymptotically the power of testing the treatment effects would be the largest and the selection bias would be optimal. To achieve this, the patient will be assigned to the treatment group that would minimize the imbalance in the groups based on risk. A Chi-squared goodness-of-fit test for categorical covariates will measure the imbalance in risk group[30]. Depending on the findings, new patient will be assigned to that risk group which would show minimum imbalance in the Chi-Squared test.

Statistical Analysis

The demographic and baseline characteristics will be summarized using descriptive statistics. For continuous variables, summary statistics will include means, standard deviations, medians, and quartiles. For continuous variables, comparisons will be performed using the ANOVA or Kruskal-Wallis test. Pearson's chi-square test will be used to compare categorical variables. For pairwise testing, multiple Student's t-tests or Mann-Whitney U tests will be used. The categorical variables will be presented as frequency and percentage. Survival analysis will be

309 performed with Kaplan-Meier survivorship curves and comparisons will be made amongst the
310 three groups using log-rank test.
311 The primary objective of this study is to prove that Myval THV is non-inferior to
312 contemporary THV series (SAPIEN THV series and Evolut THV series). Subsequently, the
313 secondary objective is to show that Myval THV is non-inferior to SAPIEN THV series and
314 Evolut THV series. The differences in rate of composite clinical endpoint for all comparisons
315 will be determined at 95% confidence interval (CI). The primary and subsequent secondary
316 objective of non-inferiority will be claimed if upper limit of the 95% CIs (or 97.5% CIs, when
317 adjustment for multiplicity is required) is smaller than the non-inferiority margin (10.44%). The
318 Bonferroni-based gatekeeping method, which controls the false discovery rate at significance
319 level, will be used to correct for multiplicity of hypothesis testing.
320 All statistical tests will be conducted at the 5% significance level unless otherwise
321 indicated. All statistical analyses will be done using SAS version 9.4.
322
323 **Patient population**
324 Patient aged ≥65 years with symptomatic severe AS with any surgical risk status, and who meet
325 all the inclusion criteria and none of the exclusion criteria presented in **Table 4**, will be eligible
326 for participation in the study. All patients will be recruited at approximately 60 sites globally
327 which may include sites across Australia, Austria, Belgium, Bulgaria, Croatia, the Czech
328 Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands,
329 New Zealand, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and
330 the United Kingdom.
331

Device implantation

The index procedure will occur within 30 days of the subject baseline visit. Based on the baseline computed tomography (as per pre-defined criteria), the size of the device to be implanted will be determined (**Table 2**). At index procedure (on the day of procedure), aortography will be performed as per the standard procedure. The transfemoral approach will be used for device insertion for all patients in this study[31]. All device implantation procedures will be followed as per their respective instructions for use and best practices defined by each technology.

Follow-up

After the THV implantation, the patient will be followed up at 30 days, one year, three years, five years, seven years, and ten years at the clinic. Intermediate telephonic follow-up will be carried out at six months, two years, and four years after the implantation. The interim analysis of the primary and secondary endpoints, based on DSMB's recommendation, will be performed at the 30-day, 1-year, 3-year, and 5-year time-points after the procedure (**Table 5**). All patients lost to follow-up will be included in the last observation carried forward population and will be evaluated for efficacy. All injuries and/or deaths will be reported as an adverse event or serious adverse event.

Data collection

Investigators and their teams will be responsible for recruitment and ethical conduct of the study. All data will be collected in the Electronic Case Report Form with a unique patient ID only. All data used in the analysis and reporting will be without identifiable reference to the patient. The

12-lead ECG will be performed at baseline, pre-discharge, 30 days, 1-year, 3-year, and 5-year. Echocardiography will be performed at baseline, pre-discharge, 30 days, 1, 3, 5, 7 and 10 years.

Independent data adjudication

All echocardiographic, angiographic, and electrocardiographic data of this study will undergo independent adjudication. Echocardiography will be sent to an independent core lab (CORRIB, Galway, Ireland) for analysis purpose at baseline, pre-discharge, 30 days, 1 year and 5 years. Echocardiography at 3, 7, and 10 years clinic visit may be assessed by a cardiologist/expert independent of site or it will be site reported. The 12-lead ECG will be sent to an independent core lab (CERC, Paris, France) for analysis purpose at baseline, pre-discharge, 30 days, 1 year and 5 years. The 12-lead ECG at 3-year clinic visit may be assessed by the cardiologist/expert independent of site. An independent core lab (CORRIB, Galway, Ireland) will analyze contrast aortography imaging after THV implantation to evaluate PVR (videodensitometric analysis[32,33]), implantation depth after TAVR, and association between final device position and rates of conduction system disturbances (requiring a new PPI) and PVR. Core lab procedures manual including imaging acquisition protocols and site training will be provided to the participating sites before enrollment.

Discussion

The objective of the LANDMARK trial is to prove non-inferiority of Myval THV series to FDA approved and commercially available THVs in patients with severe symptomatic native AS indicated for TAVR in RCT design. Furthermore, this trial will investigate incremental value of

improved design features and the availability of the intermediate sizes in Myval THV series in achieving superior outcomes as determined one or more of the aforementioned secondary endpoints. In the present study, a 1:1 randomization design will be used to treat 384 patients with Myval THV series and 384 patients with contemporary THV series (192 patients with SAPIEN THV series and 192 patients with Evolut THV series). Overall, previously published RCTs comparing head-to-head TAVR devices were conducted with a 1:1 randomization to the investigational device versus control devices, except the REPRISE-III trial[19] in which patients were randomized in a 2:1 fashion to the investigational LOTUS valve versus the self-expanding CoreValve/Evolut R valve.

Currently, there is an increasing tendency to compare TAVR devices performance in head-to-head randomization in lower-operative risk population as exemplified by the decreasing mean STS score among population included in the six trials, with the SCOPE-I trial having the lowest mean STS score of 3.4%. In the LANDMARK trial, all operative risks will be included and depending on the prevalence and distribution of STS categories, an exploratory analysis will be subsequently performed.

The estimated event rate in the LANDMARK trial is set at 26.1%, which is based upon published data on the incidence of the components of the composite primary endpoint at 30 days among all operative risk categories[7,20]. However, if the majority of included patients in the LANDMARK trial have a low operative risk, the observed event rate might be lower than expected.

Three of head-to-head TAVR device comparative studies adopted a non-inferiority design except for the CHOICE[16] and SOLVE-TAVI[20] trials. There is no consensus on the optimal width of a non-inferiority margin in non-inferiority trials[34]. In the PORTICO-IDE[18], REPRISE-

III[19], SCOPE-I[21], and SCOPE-II[22] trials, the non-inferiority margins for the primary endpoint at 30 days were 8.5% (risk ratio: 1.27), 10.5% (risk ratio: 1.26), 7.7% (risk ratio: 1.35), and 6.0% (risk ratio: 1.50), respectively, although the components of the composite primary endpoint varied among the trials. In the LANDMARK trial, a non-inferiority margin of 10.4% (relative risk ratio of 1.40) for the primary safety and efficacy endpoint at 30 days will be used; a relative risk ratio usually recommended by the Food and Drug Administration (FDA)[35].

The selection of the primary as well as secondary endpoints in all head-to-head trials was based on the VARC-2 criteria[26] except for the CHOICE trial[16], in which the first VARC consensus document[36] was used. Basically, the primary endpoint in the various head-to-head TAVR device trials was a composite of multiple individual VARC-2 endpoints, consistently including death and stroke rates[26]. The only exception was the CHOICE trial[16], in which device success was considered as a primary endpoint. The other components of the composite primary endpoint varied from one trial to another, and included additional endpoints such as PVR, PPI, vascular complications, bleeding, AKI, and rehospitalization. The rationale behind inclusion of these components of the primary endpoint in different studies is probably based on the investigator's preference. However, we believe that the composite primary endpoint of the LANDMARK trial reflects increasing scientific community towards intolerance for higher PVR and PPI rates, particularly when TAVR is considered in a younger and lower risk population.

In the PORTICO-IDE[18] and REPRISE-III[19] trials, the primary safety endpoint was analyzed at 30 days post TAVR, and the primary efficacy endpoint was analyzed at 1 year. The primary safety and efficacy endpoint of the LANDMARK trial according to the VARC-2 criteria[26] will be assessed at 30 days post TAVR as in the SOLVE-TAVI[20] and SCOPE-I[21] trials.

The SOLVE-TAVI trial demonstrated that the Evolut R and SAPIEN 3 were equivalent for the primary endpoint including moderate or severe PVR and PPI.

The design configuration of Myval THV allows for well-controlled placement across the native aortic annulus with a propensity to avoid excessively deep implantation within the left ventricular outflow tract (**Figure 2**). The internal skirt on the valve frame prevents the bioprosthetic valve from inadvertent damage caused by native calcium spicules and also minimizes propensity for PVR. Additionally, the external skirt further contributes in minimizing PVR by facilitating the plugging of micro-channels at the THV anchor site. Furthermore, Myval THV has additional intermediate and extra-large sizes to traditional sizes (20mm, 21.5mm, 23mm, 24.5mm, 26mm, 27.5mm, 29mm, 30.5mm, and 32mm). One of the exclusion criteria in the LANDMARK trial states native aortic annulus size <18 mm or >28 mm (as per measured perimeter-derived diameter for self-expanding or area-derived diameter for balloon-expandable valves by CT). We did not include the extra-large sizes THV sizes in the trial because there are no appropriate Edwards or Medtronic comparator valves. The broader size-matrix of Myval THV ensures optimal sizing of THV to patient's CT-derived annulus diameter. This aids in preserving the geometry of the bioprosthetic valve while respecting the patient's aortic root complex. Notably, all sizes of Myval THV are compatible with 14 Fr Python™ introducer sheath (Meril Life Sciences Pvt. Ltd., India). The Python introducer sheath allows full retrieval of undeployed Myval THV in cases of unsuccessful deployment.

When deployed, Myval THV is expanded by dilatation of the Navigator balloon in such a manner that 85% of the bioprosthetic valve lies in the aorta and 15% in the sub-annular space leading to 3.0-3.5 mm sub-annular depth of Myval THV. This shallow deployment of Myval THV and the avoidance of excessive oversizing relative to the native anatomy, made possible by

the additional valve sizes, aim to prevent damage to the cardiac conduction system and hence reduce the risk of new conduction system disturbances and the need for a new PPI. The choice of valve size including the additional intermediate sizes and depth of implantation traditionally involve a trade-off between the potential development of PVR and the requirement for a new PPI[37,38,39]. We expect that the Myval THV design will mitigate both PVR and conduction disturbances.

Follow-up duration after TAVR varies in the designs of each study, and there are very few data regarding very long-term valve durability. Assessments of valve function in the early RCT cohorts and registries have consistently shown preserved valve function up to 5 years after TAVR[9,17,40,41,42,43]. Between 5 and 10 years after TAVR using data from the U.K. TAVI registry, long-term transcatheter aortic valve function was shown to remain free of structural valve degeneration in 91% of patients[44]. Clinical follow-up of the LANDMARK trial is up to 10 years, whereas the longest follow-up period of the previous six head-to-head TAVR device comparison RCTs is up to 5 years in the REPRISE-III[19] and SOLVE-TAVI[20] trials. The LANDMARK trial will provide useful information on the long-term durability of the Myval THV series as well as SAPIEN THV series or Evolut THV series.

Conclusion

The LANDMARK trial is the first randomized head-to-head TAVR device trial comparing Myval THV to FDA approved and commercially available THVs in patients with severe symptomatic native AS indicated for TAVR. The unique features of Myval THV might mitigate PVR and reduce the need for PPI via optimized valve sizing, controlled depth of implantation and thereby result in improved device-host interaction. Clinical follow-up up to 10 years will

provide useful information with respect to the long-term durability of the Myval THV series as well as SAPIEN THV series or Evolut THV series.

Study Organization

The LANDMARK trial was designed by personnel at Meril Life Sciences Pvt. Ltd., India in collaboration with a team of interventional cardiologists including the members of the Study Leadership. The LANDMARK trial is the sponsor-initiated trial and funded by Meril Life Sciences Pvt. Ltd., India.

Figure legends

Figure 1. The components of the primary endpoint at 30 days in six published head-to-head TAVR device RCTs and LANDMARK trial.

TAVR: transcatheter aortic valve replacement; RCT: randomized control trial; VARC: Valve Academic Research Consortium

Figure 2. Investigational device in the LANDMARK trial.

THV: transcatheter heart valve

Figure 3. Flow chart of the study design.

THV: transcatheter heart valve

Figure 1. The components of the primary endpoint at 30 days in six published head-to-head TAVR device RCTs and LANDMARK trial.

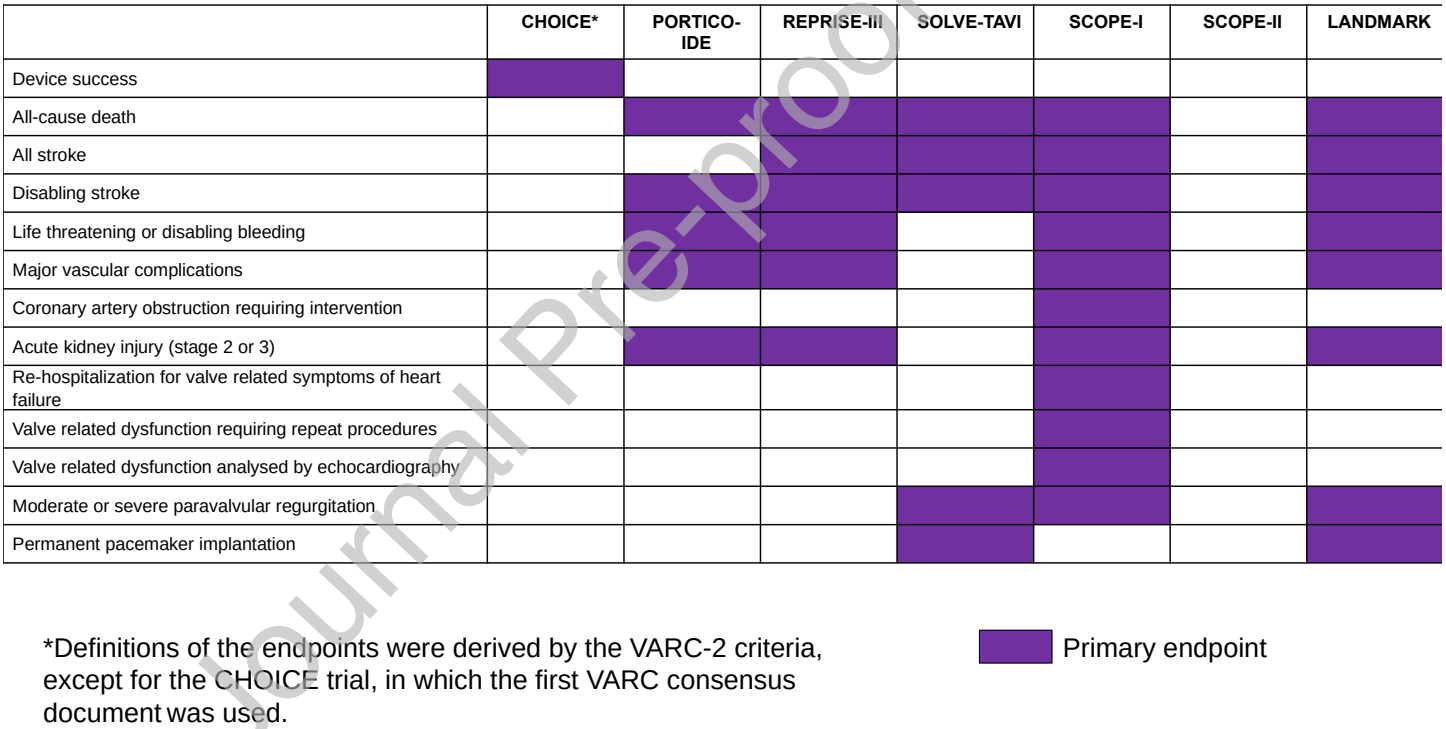

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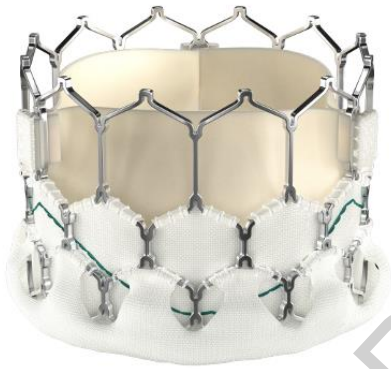
Figure 2. Investigational device in the LANDMARK trial.



Myval THV (Investigational Device)
Meril Life Sciences Pvt. Ltd., India
Balloon-Expandable THV
20 mm, 21.5 mm, 23 mm, 24.5 mm, 26 mm, 27.5 mm, and 29 mm diameter

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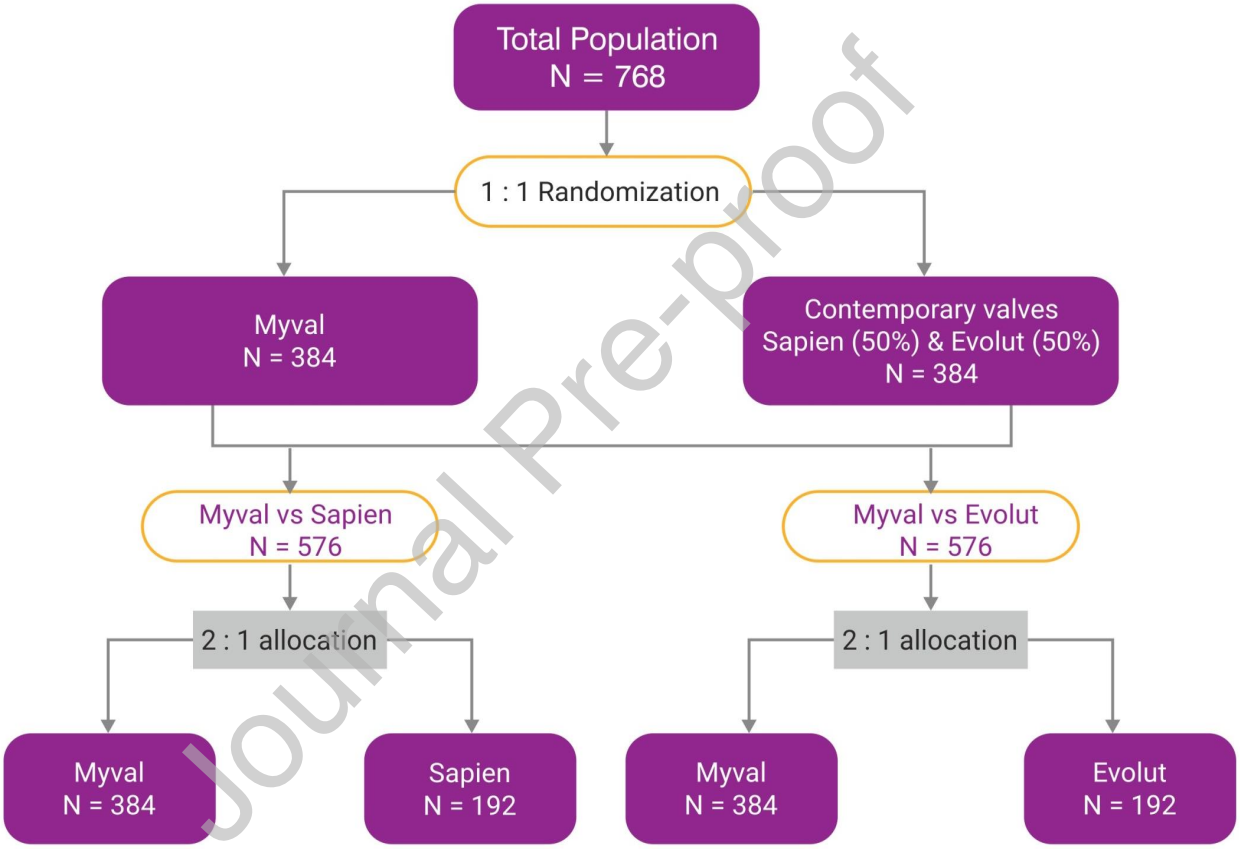
494 **Figure 3. Flow chart of the study design.**



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496 **Table 1. Summary of six published head-to-head device comparison RCTs and LANDMARK trial**

Name of trial	CHOICE	PORTICO-IDE	REPRISE-III	SOLVE-TAVI	SCOPE-I	SCOPE-II	LANDMARK
Year of design	2012	2014	2014	2016	2017	2017	2019
Enrollment period	2012/Mar-2013/Dec	2014/May-2017Oct	2014/Sep-2015/Dec	2016/Apr-2019/Jan	2017/Feb-2019/Feb	2017/Apr-2019/Apr	2020/Oct-
Year of publication	2014 (JAMA)	2020 (Lancet)	2018 (JAMA)	2020 (European Heart Journal)	2019 (Lancet)	2020 (Circulation)	-
Study device	SAPIEN XT	Portico	LOTUS	Evolut R	ACURATE neo	ACURATE neo	Myval
Control device	CoreValve	Commercially available valves	CoreValve/ Evolut R	SAPIEN 3	SAPIEN 3	Evolut R/PRO	SAPIEN THV series and Evolut THV series
Randomization, Study device: Control device	1:1	1:1	2:1	1:1	1:1	1:1	1:1
Patient population, Study device vs Control device	121 vs 120	381 vs 369	607 vs 305	225 vs 222	372 vs 367	398 vs 398	384:384*
Trial design	Superiority	Non-inferiority	Non-inferiority	Equivalence	Non-inferiority	Non-inferiority	Non-inferiority
Non-inferiority margin for the primary endpoint at 30 days	-	8.5%	10.5%	-	7.7%	6.0%	10.4%
Risk ratio	-	1.27	1.26	-	1.35	1.50	1.40
STS score, Study device/Control device	5.6%/6.2%	6.4%/6.6%	6.7%/6.9%	4.9%/4.7%	3.7%/3.4%	4.6%/4.5%	-

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Result of the trials	Superiority for the primary endpoint	Non-inferiority for the primary endpoint	Non-inferiority for the primary endpoint	Equivalence for the primary endpoint	Non-inferiority didn't meet for the primary endpoint	Non-inferiority didn't meet for the primary endpoint	-

* In the LANDMARK trial, a 1:1 randomization design will be used to treat 384 patients with Myval THV and 384 patients with contemporary THV series (192 patients with SAPIEN THV series and 192 patients with Evolut THV series).

RCT: randomized control trial: STS score: Society of Thoracic Surgery score.

511 **Table 2. Size chart of Myval THV**

Myval THV size (mm)	TEE annulus size (mm)	MSCT derived Native annulus area (mm^2)	MSCT Area-derived diameter (mm)
20.0	16.0–19.0	270–330	18.5–20.5
21.5	17.5–20.5	314–380	20.0–22.0
23.0	18.0–22.0	360–440	21.4–23.7
24.5	19.5–23.5	410-500	22.8–25.2
26.0	21.0–25.0	460–560	24.2–26.7
27.5	22.5–26.5	510–630	25.5–28.3
29.0	24.0–28.0	570–700	26.9–29.9

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513 THV: transcatheter heart valve; TEE: Transesophageal Echocardiogram; MSCT: multi-slice computed tomography

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521 **Table 3. Summary of the secondary endpoints**

		Pre-discharge	At 30 days	At 6 months	At 1 year	At 2 years	At 3 years	At 4 years	At 5 years	At 7 years	At 10 years
1	A composite of • all-cause mortality • all stroke • life-threatening or disabling bleeding • AKI (stage 2 or 3) • major vascular complications • moderate or severe prosthetic valve regurgitation • conduction system disturbances resulting in a new permanent pacemaker implantation [26]				X						
2	All-cause mortality [26]	X	X	X	X	X	X	X	X	X	X
3	All stroke [26]	X	X		X		X		X		
4	AKI stage 2 or 3 [26]	X	X		X						
5	Life-threatening or disabling bleeding [26]	X	X		X		X		X		
6	Moderate or severe prosthetic valve regurgitation	X	X		X		X		X	X	X
7	New Permanent pacemaker implantation	X	X		X		X		X	X	X
8	Conduction disturbances and arrhythmias[# 26]	X	X		X		X		X		
9	Device success [26]	X	X								
10	Early safety [26]		X								
11	Clinical efficacy [26]		X								
12	Time-related valve safety [26]		X		X		X		X		
13	Vascular and access-related complications [26]	X	X		X						
14	Major vascular complications [26]	X	X		X						
15	Functional improvement from baseline as measured per • NYHA functional classification		X		X		X		X	X	X
	• Six-minute walk test		X		X						
16	Echocardiographic End Points • EOA • iEOA • Mean aortic valve gradient • Peak aortic valve gradient • Peak aortic velocity • Total aortic regurgitation, transvalvular regurgitation (except baseline) and	X	X		X		X		X	X	X

	paravalvular regurgitation (except baseline) • Left ventricular ejection fraction • Valve calcification • Cardiac output and cardiac index										
17	Prosthetic valve dysfunction [26]	X	X		X		X		X		
18	Patient-prosthesis mismatch* [26]	X	X		X						
19	Length of index hospital stay	X									
20	Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA 3 or 4)		X		X		X		X		
21	Health status as evaluated by the SF-12 Health Questionnaire		X		X						
22	Valve thrombosis † [26]		X		X		X		X		
23	Coronary obstruction requiring intervention [26]	X									
24	Valve malpositioning [26]	X									
25	Conversion to open surgery	X									
26	Unplanned use of cardiopulmonary bypass [26]	X									
27	Ventricular septal perforation [26]	X									
28	New onset of atrial fibrillation or atrial flutter	X	X		X		X		X		
29	Endocarditis [26]		X		X		X		X		
30	Major bleeding event [26]		X		X		X		X		

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523 # Any variation from the normal heart rhythm requiring medical intervention as per investigator's discretion.

524 * Severity of patient-prosthesis-mismatch will be based on followings:

525 • For patients with BMI <30kg/m^2, iEOA 0.85 – 0.65cm^2/m^2 considered as moderate and <0.65cm^2/m^2 considered as severe

526 • For patients with BMI ≥30kg/m^2, iEOA 0.90 – 0.60cm^2/m^2 considered as moderate and <0.60cm^2/m^2 considered as severe

527 BMI=weight (kg)/ [height (m)] ^{2}

† Valve thrombosis is defined as per VARC-2 criteria as any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment [26]. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis [26].

AKI: acute kidney injury; NYHA: New York Heart Association; EOA: effective orifice area; iEOA: index effective orifice area; BMI: body mass index; VARC: Valve Academic Research Consortium

Table 4. Inclusion-exclusion criteria for the LANDMARK trial

Inclusion criteria

- Patient must be ≥65 years of age and he/she and/or their legal representative has provided a written informed consent to participate in the study as approved by the institutional review board/ethics committee of the investigational site
- The patient is eligible for treatment with all three study devices considering individual's vascular anatomy and morphology – especially the aortic root complex and the vascular access site
- Patient meets the echocardiographic criteria according to ACC/AHA guidelines for TAVR [45]:
    - Stage D1 (severe high-gradient AS) – mean gradient ≥40 mmHg or jet velocity ≥4.0 m/s AND aortic valve area (AVA) of <1.0 cm^2 or indexed aortic valve area of ≤0.6 cm^2 /m^2,
    - Stage D2 (severe symptomatic low-flow low-gradient severe AS) – low left ventricular (LV) ejection fraction (<50%) with an AVA ≤1.0 cm^2. Aortic velocity is <4.0 m/s at rest but increases to at least 4.0 m/s on low dose dobutamine, or
    - Stage D3 (severe symptomatic low-flow low-gradient severe AS) – Normal LVEF (>50%), aortic valve area ≤1.0 cm^2 (or indexed aortic valve area of ≤0.6 cm2/m2) with an aortic velocity <4.0 m/s and mean gradient <40 mmHg and a stroke volume index <35 ml/m^2 [46,47,48]

Exclusion criteria

- Patients who are not willing to provide an informed consent form, or whose legal heirs object to their participation in the study
- Evidence of an acute myocardial infarction ≤30 days before the trial procedure
- Mixed aortic valve disease (AS with predominant aortic regurgitation >3+)
- Pre-existing prosthetic heart valve in any position, or prosthetic ring, or any type of mitral repair device
- Patients undergoing concomitant procedures on the pulmonic valve, mitral valve, tricuspid valve or the ascending aorta
- Severe mitral annular calcification, or severe (greater than 3+) mitral insufficiency

- Blood dyscrasias as defined: leukopenia (WBC<3000 cell/mL), acute anaemia (Hb <9 g/dL), thrombocytopenia (platelet count <50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states
- Significant coronary artery disease requiring revascularization as per Heart Team assessment
- Need for emergency surgery for any reason within 30 days of index procedure
- Any planned surgical or peripheral procedure to be performed within the 30 days follow-up from the index procedure
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 1 month of randomization
- Active peptic ulcer or upper gastrointestinal bleeding within 90 days before index procedure
- Hemodynamic instability requiring inotropic support or mechanical heart assistance before index procedure
- Hypertrophic cardiomyopathy with or without obstruction
- Severe ventricular dysfunction with LVEF <30%
- Intracardiac mass, thrombus or vegetation as evident from echocardiography, CT or MRI
- A known hypersensitivity or contraindication to cobalt, chromium, nickel, nitinol, heparin, aspirin, ticlopidine (ticlid), or P2Y12 inhibitors or coumadin derivatives (warfarin) or Factor X or A inhibitors, contrast media, which cannot be adequately premedicated
- Native aortic annulus size <18mm or >28mm (as per measured perimeter-derived diameter for self-expanding or area-derived diameter for balloon expanding valves by CT scan)
- Unicuspid or bicuspid aortic valve as evident from echocardiography or CT or MRI
- Cardiogenic shock (low cardiac output, vasopressor dependence, or mechanical hemodynamic support)
- Cerebrovascular accident or a transient ischemic attack within 6 months prior to the procedure
- Origin of coronary ostia <10 mm from annular plane as measured on CT scan and cannot be protected by standard techniques
- Renal insufficiency and/or end stage renal disease requiring chronic dialysis with serum creatinine >3.0 mg/dl (265.2 mmol/L)

- Life expectancy <24 months due to non-cardiac co-morbid conditions due carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease
- Significant aortic disease or peripheral artery disease (including disease of the upper and lower extremity arteries, renal arteries, and abdominal or thoracic aortic systems which as per heart team assessment is significant and unsuitable to perform TAVR procedure) including aneurysm defined as maximal luminal diameter ≥5 cm; marked tortuosity (hyperacute bend), thrombus, prior aortic graft, aortic arch atheroma [particularly if thick (>5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta
- Ilio-femoral vessel characteristics such as severe tortuosity, calcification or stenosis, aneurysm of iliofemoral origin to the entire aorta (including common femoral, external iliac, common iliac and the origin of common iliac), which in investigator’s opinion would be improper for safe vascular access or implantation of the device
- Currently participating in an investigational drug or another device study
- Active bacterial endocarditis within 6 months of procedure
- Active infection requiring antibiotic treatment

TAVR: transcatheter aortic valve replacement; AS: aortic stenosis; LVEF: left ventricular ejection fraction; WBC: white blood cell; HB: hemoglobin; PCI: percutaneous coronary intervention; CT: computed tomography; MRI: magnetic resonance imaging.

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615 **Table 5. Schedule for assessment of different parameters during the trial**

Schedule of events Parameters	Baseline (Pre-procedure)	Index procedure (within 30-day of baseline)[ii]	Post-procedure (< 24 hours after index procedure)	Pre-discharge[♣]	30 ± 7 days follow-up	Telephonic follow-up (6 months) ± 14 days*	1 year ± 30 days follow-up	Telephonic follow-up 2 (years) ± 30 days*	3 years ± 30 days follow-up	Telephonic follow-up (4 years) ± 30 days*	5 years ± 30 days follow-up	7 years ± 30 days follow-up	10 years ± 30 days follow-up	Unscheduled clinical visit
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Randomization		X[#]												
Physical Assessment														
Physical Examination	X			X	X		X		X		X	X	X	X[iii]
NYHA Classification	X			X	X		X		X		X	X	X	X[iii]
Current medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCS Angina	X			X	X		X		X		X	X	X	X[iii]
Modified Rankin Scale[i]	X			X	X		X		X		X			
NIH Stroke Scale	X			X	X		X		X		X			
STS-PROM risk score a EuroSCORE II	X													
Six Minute Walk Test	X			X			X							
Frailty Index	X													
Lab Measurements														
COVID-19 testing	X[iii]			X[iii]	X[iii]		X[iii]		X[iii]		X[iii]	X[iii]	X[iii]	
CBC with Differential and Platelet Count	X		X[iii]	X[iii]	X[iii]		X[iii]							X[iii]
Troponins or CK, CK-MB[i]	X[iv]		X[iv]	X[iv]										X[iii]
Complete Metabolic Panel (Liver Function Test, Albumin, Kidney function test, Lipid profile)	X			X[iii]	X[iii]		X[iii]		X[iii]		X[iii]			X[iii]

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Schedule of events Parameters	Baseline (Pre-procedure)	Index procedure (within 30-day of baseline)[ii]	Post-procedure (< 24 hours after index procedure)	Pre-discharge[♣]	30 ± 7 days follow-up	Telephonic follow-up (6 months) ± 14 days*	1 year ± 30 days follow-up	Telephonic follow-up 2 (years) ± 30 days*	3 years ± 30 days follow-up	Telephonic follow-up (4 years) ± 30 days*	5 years ± 30 days follow-up	7 years ± 30 days follow-up	10 years ± 30 days follow-up	Unscheduled clinical visit
PTT or PT/INR	X		X[iii]	X	X		X		X[iii]		X[iii]			X[iii]
Serum Creatinine	X		X[iii]	X	X		X		X[iii]		X[iii]			X[iii]
Non-Invasive Tests														
12-lead ECG[Ψ]	X[v]		X[iii]	X[v]	X[v]		X[v]		X[vi]		X[v]			X[iii]
Echocardiogram–TTE or TEE[¥]	X[vii]			X[vii]	X[vii]		X[vii]		X[viii]		X[vii]	X[viii]	X[viii]	X[iii]
Invasive Tests														
CT angiogram of Thorax and Abdomen	X[ix]													
Aortic root angiogram (Fluoroscopy imaging)		X[x]												
Valve implant		X												
Quality of Life Measures														
SF-12 Health Questionnaire	X				X		X							
Other														
AE /SAE		X	X	X	X	X	X	X	X	X	X	X	X	X
Device Deficiency		X	X	X	X	X	X	X[iii]	X[iii]	X[iii]	X[iii]	X[iii]	X[iii]	X[iii]
Survival status		X	X	X	X	X	X	X	X	X	X	X	X	X

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617 [#] Once the eligibility is confirmed at baseline, the patient will be randomized in the IWRS, anytime before the index procedure.

618 [♣] Pre-discharge = Test done within 24 hours prior to hospital discharge or maximum of 7 days after index procedure, whichever is

619 earlier.

i. As per VARC-2 criteria, the assessment of the modified Rankin Scale should be done at all scheduled visits in a trial and at 90 days after the onset of any stroke.

ii. The gap between baseline and index procedure can be ≤30 days.

iii. At investigator's discretion.

iv. Biomarkers of troponin or CK, CK-MB should be tested in local laboratory prior to the Index procedure (≤ 72 hour), within 12−24 hour after the procedure, at 24 hour thereafter, at 72 hour or at discharge, and, if still elevated, repeat the test daily until values show a decline as per the VARC-2 criteria.

v. ECG data will be assessed by independent core lab at baseline, pre-discharge, 30-day, 1-year, and 5-year.

vi. ECG collected at 3-year clinic visit will be assessed by the independent core lab.

[Ψ]ECG procedure will be done as per ECG manual applicable for the trial.

vii. ECHO data will be assessed by independent core lab at baseline, pre-discharge, 30-day, 1-year and 5-year.

viii. ECHO collected at 3, 7, and 10-year clinic visit will be assessed by the independent core lab.

[¥]ECHO procedure will be done as per echo manual applicable for the trial.

ix. All trial patients should have baseline thoracic and abdominal CT angiograms with complete visualization of both iliacs and femorals to the aorta done 1 month prior to index procedure.

x. Aortic root angiogram will be performed on the day of procedure, which includes pre- and immediate post-procedural angiogram outcomes without the need for additional intervention. The angiogram must be performed as per

videodensitometry acquisition guidelines for all patients [49,50]. For angiography performed, the clinical findings and the copy of angiographic film (redacting the patient's identity) will be collected for analysis by the independent core lab.

AE: adverse event; CBC: complete blood count; CK: creatine kinase; CCS: Canadian cardiovascular Society; CT: computed tomography; ECG: electrocardiography; ECHO: echocardiography; IWRS: interactive web response system; NYHA: New York Heart Association; PT/INR: Prothrombin time/international normalized ratio; PTT: partial thromboplastin time; SAE: serious adverse event; STS-PROM, Society of Thoracic Surgery-Predicted Risk Of Mortality; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; VARC: Valve Academic Research Consortium

Reference

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597-607.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364(23):2187-98.
3. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370(19):1790-8.
4. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374(17):1609-20.
5. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376(14):1321-1331.
6. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019;380(18):1695-1705.
7. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019;380(18):1706-1715.
8. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366(18):1686-95.
9. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385(9986):2477-84.
10. Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, et al. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2015;66(2):113-21.
11. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, et al. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2016;67(22):2565-74.
12. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. J Am Coll Cardiol 2018;72(22):2687-2696.
13. Serruys PW, Modolo R, Reardon M, Miyazaki Y, Windecker S, Popma J, et al. One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial. EuroIntervention 2018;14(8):877-883.
14. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J 2016;37(47):3503-3512.

15. Sharma SK, Rao RS, Chandra P, Goel PK, Bharadwaj P, Joseph G, et al. First-in-Human Evaluation of Balloon Expandable Transcatheter Heart Valve in the Treatment of Severe Symptomatic Native Aortic Stenosis: The MyVal-1 Study. EuroIntervention 2019.
16. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tolg R, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311(15):1503-14.
17. Abdel-Wahab M, Landt M, Neumann FJ, Massberg S, Frerker C, Kurz T, et al. 5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves: Results From the CHOICE Randomized Clinical Trial. JACC Cardiovasc Interv 2020;13(9):1071-1082.
18. Makkar RR, Cheng W, Waksman R, Satler LF, Chakravarty T, Groh M, et al. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. Lancet 2020.
19. Feldman TE, Reardon MJ, Rajagopal V, Makkar RR, Bajwa TK, Kleiman NS, et al. Effect of Mechanically Expanded vs Self-Expanding Transcatheter Aortic Valve Replacement on Mortality and Major Adverse Clinical Events in High-Risk Patients With Aortic Stenosis: The REPRISE III Randomized Clinical Trial. JAMA 2018;319(1):27-37.
20. Thiele H, Kurz T, Feistritzer HJ, Stachel G, Hartung P, Eitel I, et al. Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve implantation: the randomized SOLVE-TAVI trial. Eur Heart J 2020.
21. Lanz J, Kim WK, Walther T, Burgdorf C, Mollmann H, Linke A, et al. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. Lancet 2019;394(10209):1619-1628.
22. Tamburino C, Bleiziffer S, Thiele H, Scholtz S, Hildick-Smith D, Cunnington M, et al. Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients with Symptomatic Severe Aortic Stenosis: The SCOPE 2 Randomized Clinical Trial. Circulation 2020.
23. Sharma SK, Rao RS, Chopra M, Sonawane A, Jose J, Sengottuvelu G. Myval transcatheter heart valve system in the treatment of severe symptomatic aortic stenosis [published online ahead of print, 2020 Jul 6]. Future cardiology 2020.
24. Sharma SK, Rao RS, Chopra M, Sonawane A, Jose J, Sengottuvelu G. Myval transcatheter heart valve system in the treatment of severe symptomatic aortic stenosis. Future cardiology 2020.
25. Lees KR, Bath PM, Schellinger PD, Kerr DM, Fulton R, Hacke W, et al. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. Stroke 2012;43(4):1163-70.
26. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33(19):2403-18.

27. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. J Am Coll Cardiol 2015;65(20):2184-94.
28. Forrest JK, Mangi AA, Popma JJ, Khabbaz K, Reardon MJ, Kleiman NS, et al. Early Outcomes With the Evolut PRO Repositionable Self-Expanding Transcatheter Aortic Valve With Pericardial Wrap. JACC Cardiovasc Interv 2018;11(2):160-168.
29. FRANE JW. A METHOD OF BIASED COIN RANDOMIZATION, ITS IMPLEMENTATION, AND ITS VALIDATION. Drug Information Journal, 1998;32:423-432.
30. Frane JW. A Method of Biased Coin Randomization, its Implementation, and its Validation. Drug Information Journal 1998;32(2):423-432.
31. Kawashima H, Watanabe Y, Kozuma K, Nara Y, Hioki H, Kataoka A, et al. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. EuroIntervention 2017;12(16):1954-1961.
32. Modolo R, Chang CC, Onuma Y, Schultz C, Tateishi H, Abdelghani M, et al. Quantitative aortography assessment of aortic regurgitation. Insight into a novel technique. EuroIntervention 2019.
33. Modolo M CC, Abdelghani M, Kawashima H, Ono M, Tateishi H, Miyazaki Y, Pighi M, Wykrzykowska JJ, de Winter RJ, Ruck A, Chieffo A, van Mourik MS, Yamaji K, Richardt G, de Brito FS Jr, Lemos PA, Al-Kassou B, Piazza N, Tchetche D, Sinning JM, Abdel-Wahab M, Soliman O, Søndergaard L, Mylotte D, Onuma Y, Van Mieghem NM, Serruys PW. Quantitative Assessment of Acute Regurgitation Following TAVR - A Multicenter Pooled Analysis of 2,258 Valves. JACC Cardiovasc Inverv 2020.
34. Althunian TA, de Boer A, Klungel OH, Insani WN, Groenwold RHH. Methods of defining the non-inferiority margin in randomized, double-blind controlled trials: a systematic review. Trials 2017;18(1):107-107.
35. Services USDoHaH, Administration FaD, (CDER) CfDEaR, (CBER) CfBEaR. Non-Inferiority Clinical Trials to Establish Effectiveness -Guidance for Industry-. 2016.
36. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32(2):205-17.
37. Falk V, Wohrle J, Hildick-Smith D, Bleiziffer S, Blackman DJ, Abdel-Wahab M, et al. Safety and efficacy of a repositionable and fully retrievable aortic valve used in routine clinical practice: the RESPOND Study. Eur Heart J 2017;38(45):3359-3366.
38. Dumonteil N, Meredith IT, Blackman DJ, Tchetche D, Hildick-Smith D, Spence MS, et al. Insights into the need for permanent pacemaker following implantation of the repositionable LOTUS valve for transcatheter aortic valve replacement in 250 patients: results from the REPRISE II trial with extended cohort. EuroIntervention 2017;13(7):796-803.
39. Sinning JM, Grube E. Two sides to every story: the trade-off between paravalvular leakage and the occurrence of conduction disturbances in transcatheter heart valves. EuroIntervention 2017;13(7):777-779.

40. Daubert MA, Weissman NJ, Hahn RT, Pibarot P, Parvataneni R, Mack MJ, et al. Long-Term Valve Performance of TAVR and SAVR: A Report From the PARTNER I Trial. JACC Cardiovasc Imaging 2016.
41. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385(9986):2485-91.
42. Kovac J, Schuler G, Gerckens U, Muller R, Serruys PW, Bonan R, et al. Four-year experience with the CoreValve transcatheter heart valve. EuroIntervention 2016;12(8):e1039-e1046.
43. Sawaya F, Kappetein AP, Wisser W, Nataf P, Thomas M, Schachinger V, et al. Five-year haemodynamic outcomes of the first-generation SAPIEN balloon-expandable transcatheter heart valve. EuroIntervention 2016;12(6):775-82.
44. Blackman DJ, Saraf S, MacCarthy PA, Myat A, Anderson SG, Malkin CJ, et al. Long-Term Durability of Transcatheter Aortic Valve Prostheses. J Am Coll Cardiol 2019;73(5):537-545.
45. Aortic Stenosis Writing G, Bonow RO, Brown AS, Gillam LD, Kapadia SR, Kavinsky CJ, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for the Treatment of Patients With Severe Aortic Stenosis: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Soc Echocardiogr 2018;31(2):117-147.
46. Otto CM, Baumgartner H. Updated 2017 European and American guidelines for prosthesis type and implantation mode in severe aortic stenosis. Heart 2018;104(9):710-713.
47. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-2791.
48. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70(2):252-289.
49. Modolo R, Serruys PW, Chang CC, Wohrle J, Hildick-Smith D, Bleiziffer S, et al. Quantitative Assessment of Aortic Regurgitation After Transcatheter Aortic Valve Replacement With Videodensitometry in a Large, Real-World Study Population: Subanalysis of RESPOND and Echocardiogram Association. JACC Cardiovasc Interv 2019;12(2):216-218.
50. Modolo R, Chang CC, Tateishi H, Miyazaki Y, Pighi M, Abdelghani M, et al. Quantitative aortography for assessing aortic regurgitation after transcatheter aortic valve

819 implantation: results of the multicentre ASSESS-REGURGE Registry. EuroIntervention
820 2019;15(5):420-426.
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