



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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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 2020-000,137-40) is a prospective, randomized, multinational, multicenter, open-label, and noninferiority 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 nondisabling), 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 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. (Am Heart J 2021;232:23–38.)

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Over the last 2 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.¹⁻⁷ 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^{3,10-12} showing comparable clinical outcomes to surgery. A role for TAVR in patients at intermediate surgical risk has been subsequently investigated in the PARTNER 2A⁴ and SURTAVI^{5,13} trials, which demonstrated the noninferiority of TAVR with respect to surgical aortic valve replacement (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 3⁶ and Evolut Low Risk⁷ 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 cost competitive to Evolut THV series and more affordable than SAPIEN THV series. In fact, the Myval THV has more 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 vs contemporary THV series in patients with severe symptomatic native AS.

Current evidence of head-to-head tavr device comparison

To date, 6 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 trial¹⁶ 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; $P < .001$ 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 noninferiority criteria of the primary safety endpoint was met (Portico 13.8% vs commercially available valves 9.6%; absolute difference 4.2; 95% CI -0.4-8.8; upper confidence bound 8.1%; $P = .034$ for noninferiority and $P = .071$ for superiority). The primary efficacy endpoint was also met (Portico 14.8% vs commercially available valves 13.4%; difference 1.5%; 95% CI -3.6-6.5; upper confidence bound 5.7%; $P = .0058$ for noninferiority 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%; $P = .037$ for superiority).

The REPRISE-III trial¹⁹ demonstrated noninferiority 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 noninferior for the primary safety endpoint (LOTUS 20.3% vs CoreValve or Evolut R 17.2%; difference 3.1%; Farrington-Manning 97.5% CI, $-\infty$ to 8.3%; $P = .003$ for noninferiority). However, the LOTUS valve, compared with the CoreValve or Evolut R, met the noninferiority for the primary effectiveness endpoint (LOTUS 15.4% vs CoreValve or Evolut R 25.5%; difference -10.1%; Farrington-Manning 97.5% CI, $-\infty$ to -4.4%; $P < .001$ for noninferiority), and furthermore, the superiority analysis for the primary effectiveness endpoint was statistically significant (difference -10.2%; 95% CI -16.3%--4.0%; $P < .001$ for superiority).

The SOLVE-TAVI investigator-driven trial²⁰ 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 2 devices

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-2017/Oct	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	Noninferiority	Noninferiority	Equivalence	Noninferiority	Noninferiority	Noninferiority
Noninferiority 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%	–
Result of the trials	Superiority for the primary endpoint	Noninferiority for the primary endpoint	Noninferiority for the primary endpoint	Equivalence for the primary endpoint	Noninferiority didn't meet for the primary endpoint	Noninferiority didn't meet for the primary endpoint	–

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

*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).

Figure 1

	CHOICE*	PORTICO- IDE	REPRISE-III	SOLVE-TAVI	SCOPE-I	SCOPE-II	LANDMARK
Device success							
All-cause death							
All stroke							
Disabling stroke							
Life threatening or disabling bleeding							
Major vascular complications							
Coronary artery obstruction requiring intervention							
Acute kidney injury (stage 2 or 3)							
Re-hospitalization for valve related symptoms of heart failure							
Valve related dysfunction requiring repeat procedures							
Valve related dysfunction analysed by echocardiography							
Moderate or severe paravalvular regurgitation							
Permanent pacemaker implantation							

*Definitions of the endpoints were derived by the VARC-2 criteria, except for the CHOICE trial, in which the first VARC consensus document was used.

 Primary endpoint

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.

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 - 4.66 ; $P = .04$ for equivalence).

The SCOPE-I trial²¹ 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 noninferiority compared to the SAPIEN 3 (ACURATE neo 24% vs SAPIEN 3 16%; absolute risk difference 7.1%; upper 95% confidence limit 12.0%; $P = .42$ for noninferiority).

The SCOPE-II trial²² was an investigator initiated, prospective, multicenter, noninferiority, 1:1 RCT (ACURATE neos 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 noninferiority 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%; $P = .055$ for noninferiority). 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 - -2.60 ; $P = .003$ for superiority). Cardiac death at 30 days (2.8% vs 0.8%; $P = .03$ for superiority) and 1 year (8.4% vs 3.9%; $P = .01$ for superiority), and moderate or severe PVR at 30 days (10% vs 3%; $P = .002$ for superiority) were significantly increased in the ACURATE neo group compared to the Evolut THV series group. Patients were followed up to 1-year postprocedure only.

Methods

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Myval THV system

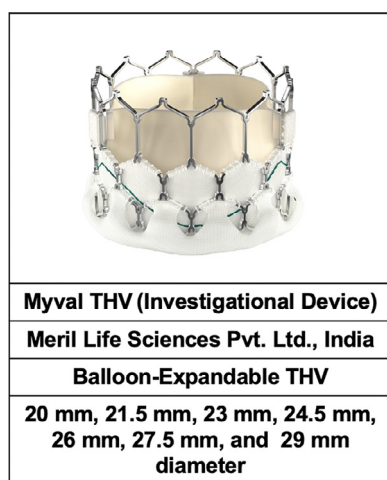
The investigational device in the LANDMARK trial is the Myval THV, a balloon-expandable THV system. The Myval THV system is indicated for replacing the aortic valve in patients with severe symptomatic native AS who have been determined by the heart team to be eligible

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

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

Figure 2



Investigational device in the LANDMARK trial. THV: transcatheter heart valve.

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 20 mm, 21.5 mm, 23 mm, 24.5 mm, 26 mm, 27.5 mm, and 29 mm in diameter (Table 2 and Fig. 2).

Control arm THV system

SAPIEN THV series (Edwards Lifesciences, CA) 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) 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 20 mm,

23 mm, 26 mm, and 29 mm in diameter and those of Evolut THV series include 23 mm, 26 mm, 29 mm, and 34 mm in diameter.

The selection of the control arm in the trials comparing head-to-head TAVR devices is important to achieve noninferiority or superiority of novel TAVR technologies, compared with current TAVR technologies. In the previous 6 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^{16,18-21}. The contemporary “standard” TAVR devices have been selected in the control arm to convince clinicians and cardiologists of the noninferiority 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 nondisabling),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 noninferiority trial. Clinical data of the primary endpoint will be adjudicated by an independent Clinical Event Committee, 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^{4-7,18-21,27,28}. Assuming noninferiority 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 (ie, 346:346) are required at 93% power, with 5% level of significance. Considering 10% dropout rate, a total of 768 patients (ie, 384:384) will be required to be enrolled into the LANDMARK trial.

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				X						
	• 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										
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		X		X		X		X	X	X
	• NYHA functional classification										
	• Six-minute walk test		X		X						
16	Echocardiographic End Points	X	X		X		X		X	X	X
	• EOA										
	• iEOA										
	• Mean aortic valve gradient										
	• Peak aortic valve gradient										
	• Peak aortic velocity										
	• Total aortic regurgitation, transvalvular regurgitation (except baseline) and paravalvular regurgitation (except baseline)										
	• Left ventricular ejection fraction										
	• Valve calcification										
	• Cardiac output and cardiac index										

(continued on next page)

Table 3. (continued)

		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
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		

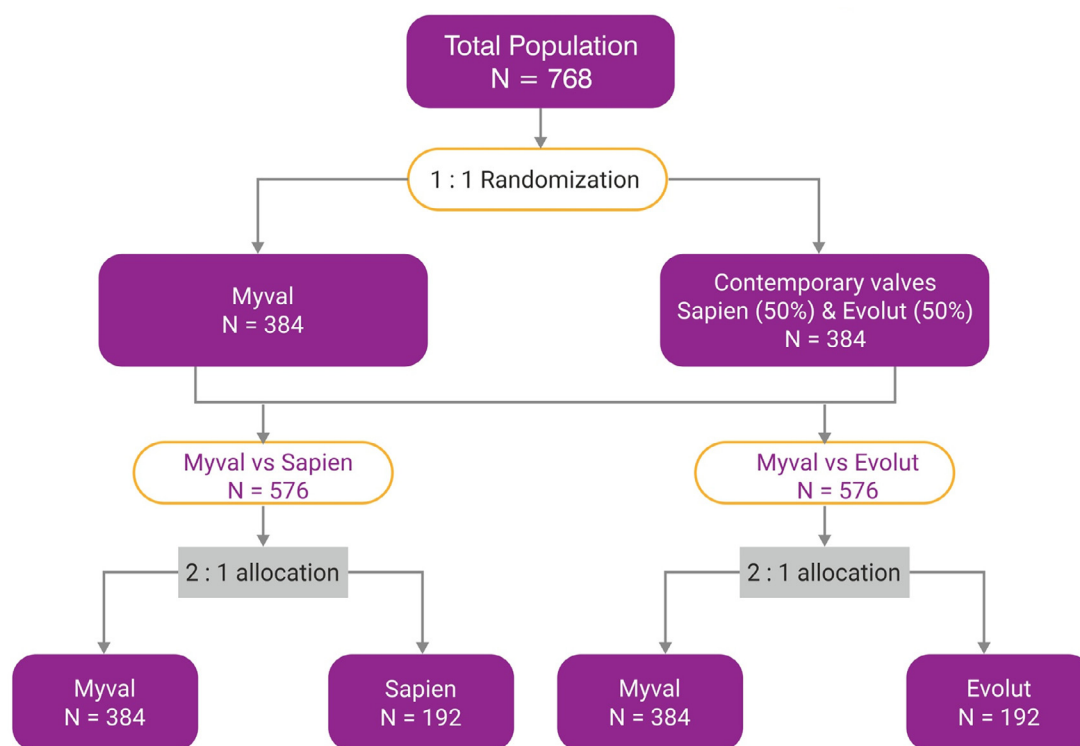
AKI: acute kidney injury; BMI: body mass index; EOA: effective orifice area; iEOA: index effective orifice area; NYHA: New York Heart Association; VARC: Valve Academic Research Consortium.

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

[†] Severity of patient-prosthesis-mismatch will be based on followings: For patients with BMI <30 kg/m², iEOA 0.85-0.65cm²/m² considered as moderate and <0.65cm²/m² considered as severe. For patients with BMI ≥30 kg/m², iEOA 0.90-0.60cm²/m² considered as moderate and <0.60cm²/m² considered as severe. 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.

Figure 3

Flowchart of the study design. THV: transcatheter heart valve.

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, that is, 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%-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.²⁹ 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 performed with Kaplan-Meier survivorship curves and comparisons will be made amongst the 3 groups using log-rank test.

The primary objective of this study is to prove that Myval THV is noninferior to contemporary THV series (SAPIEN THV series and Evolut THV series). Subsequently, the secondary objective is to show that Myval THV is noninferior to SAPIEN THV series and Evolut THV series. The differences in rate of composite clinical endpoint for all comparisons will be determined at 95% confidence interval (CI). The primary and subsequent secondary objective of noninferiority will be claimed if upper limit of the 95% CIs (or 97.5% CIs, when adjustment

for multiplicity is required) is smaller than the noninferiority margin (10.44%). The Bonferroni-based gatekeeping method, which controls the false discovery rate at significance level, will be used to correct for multiplicity of hypothesis testing.

All statistical tests will be conducted at the 5% significance level unless otherwise indicated. All statistical analyses will be done using SAS version 9.4.

Patient population

Patient aged ≥ 65 years with symptomatic severe AS with any surgical risk status, and who meet all the inclusion criteria and none of the exclusion criteria presented in [Table 4](#), will be eligible for participation in the study. All patients will be recruited at approximately 60 sites globally which may include sites across Australia, Austria, Belgium, Bulgaria, Croatia, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom.

Device implantation

The index procedure will occur within 30 days of the subject baseline visit. Based on the baseline computed tomography (as per predefined 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.³⁰ 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, 1 year, 3 years, 5 years, 7 years, and 10 years at the clinic. Intermediate telephonic follow-up will be carried out at 6 months, 2 years, and 4 years after the implantation. The interim analysis of the primary and secondary endpoints, based on Data and Safety Monitoring Board'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, predischARGE, 30 days, 1-year, 3-year, and 5-year. Echocardiography will be performed at baseline, predischARGE, 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, predischARGE, 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, predischARGE, 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^{31,32}), 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 Food and Drug Administration (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 vs control devices, except the REPRISE-III trial¹⁹ in which patients were randomized in a 2:1 fashion to the investigational LOTUS valve vs 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 6 trials, with the SCOPE-I trial having the

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 3 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 TAVR⁴⁴:
 - 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 cm² or indexed aortic valve area of ≤ 0.6 cm²/m²,
 - Stage D2 (severe symptomatic low-flow low-gradient severe AS) – low left ventricular (LV) ejection fraction ($< 50\%$) with an AVA ≤ 1.0 cm². 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 cm² (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/m²⁴⁵⁻⁴⁷

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 $> 3+$)
- Preexisting 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 $< 3,000$ cell/mL), acute anemia (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 < 18 mm or > 28 mm (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 noncardiac comorbid 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

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

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.

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

Schedule of events Parameters	Baseline (Preprocedure)	Index procedure (within 30-day of baseline) ⁱⁱ	Postprocedure (< 24 h 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	Xⁱⁱⁱ
NYHA Classification	X			X	X		X		X		X	X	X	Xⁱⁱⁱ
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	Xⁱⁱⁱ
Modified Rankin Scale [‡]	X			X	X		X		X		X			
NIH Stroke Scale	X			X	X		X		X		X			
STS-PROM risk score and EuroSCORE II	X													
Six Minute Walk Test	X				X		X							
Frailty Index	X													
Lab Measurements														
COVID-19 testing	Xⁱⁱⁱ			Xⁱⁱⁱ	Xⁱⁱⁱ		Xⁱⁱⁱ		Xⁱⁱⁱ		Xⁱⁱⁱ	Xⁱⁱⁱ	Xⁱⁱⁱ	Xⁱⁱⁱ
CBC with Differential and Platelet Count	X		Xⁱⁱⁱ	Xⁱⁱⁱ	Xⁱⁱⁱ		Xⁱⁱⁱ							Xⁱⁱⁱ
Troponins or CK, CK-MB [‡]	X^{iv}		X^{iv}	X^{iv}										Xⁱⁱⁱ
Complete Metabolic Panel (Liver Function Test, Albumin, Kidney function test, Lipid profile)	X			Xⁱⁱⁱ	Xⁱⁱⁱ		Xⁱⁱⁱ		Xⁱⁱⁱ		Xⁱⁱⁱ			Xⁱⁱⁱ

(continued on next page)

Table 5. (continued)

Schedule of events Parameters	Baseline (Preprocedure)	Index procedure (within 30-day of baseline) ⁱⁱ	Postprocedure (< 24 h after index procedure)	Pre- discharge ⁱ	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

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.

* Once the eligibility is confirmed at baseline, the patient will be randomized in the IWRS, anytime before the index procedure.

ⁱ Pre-discharge = Test done within 24 h prior to hospital discharge or maximum of 7 days after index procedure, whichever is earlier. 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. The gap between baseline and index procedure can be ≤30 days. At investigator's discretion. Biomarkers of troponin or CK, CK-MB should be tested in local laboratory prior to the Index procedure (≤ 72 hour), within 12-24 hours 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. ECG data will be assessed by independent core lab at baseline, pre-discharge, 30-day, 1-year, and 5-year. ECG collected at 3-year clinic visit will be assessed by the independent core lab. ^ψECG procedure will be done as per ECG manual applicable for the trial. ECHO data will be assessed by independent core lab at baseline, pre-discharge, 30-day, 1-year, and 5-year. 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. 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. 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 ^{48,49}. 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.

Three of head-to-head TAVR device comparative studies adopted a noninferiority design except for the CHOICE¹⁶ and SOLVE-TAVI²⁰ trials. There is no consensus on the optimal width of a noninferiority margin in noninferiority trials.³³ In the PORTICO-IDE,¹⁸ REPRISE-III,¹⁹ SCOPE-I,²¹ and SCOPE-II²² trials, the noninferiority 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 noninferiority 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 FDA.³⁴

The selection of the primary as well as secondary endpoints in all head-to-head trials was based on the VARC-2 criteria²⁶ except for the CHOICE trial,¹⁶ in which the first VARC consensus document³⁵ 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 1 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-IDE¹⁸ and REPRISE-III¹⁹ 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 criteria²⁶ will be assessed at 30 days post TAVR as in the SOLVE-TAVI²⁰ and SCOPE-I²¹ 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 microchannels at the THV anchor site. Furthermore, Myval

THV has additional intermediate and extra-large sizes to traditional sizes (20 mm, 21.5 mm, 23 mm, 24.5 mm, 26 mm, 27.5 mm, 29 mm, 30.5 mm, and 32 mm). 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 subannular space leading to 3.0-3.5 mm subannular 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.³⁶⁻³⁸ 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.^{9,17,39-42} 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.⁴³ Clinical follow-up of the LANDMARK trial is up to 10 years, whereas the longest follow-up period of the previous 6 head-to-head TAVR device comparison RCTs is up to 5 years in the REPRISE-III¹⁹ and SOLVE-TAVI²⁰ 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 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.

Disclosure

Dr. Soliman and Dr. Onuma report institutional research grants related to their work as the chairman of cardiovascular imaging core labs of several clinical trials and registry sponsored by industry, for which they receive no direct compensation. Dr. Bedogni reports personal fees from Medtronic, personal fees from Boston Scientific, personal fees from Abbott, personal fees from Terumo, personal fees from Meril Life Sciences. Dr. Neumann reports personal fees from Amgen, personal fees from Boehringer Ingelheim, personal fees from Daiichi Sankyo, grants and personal fees from Pfizer, grants and personal fees from Biotronic, grants and personal fees from Edwards Lifesciences, grants from Medtronic, grants and personal fees from Bayer Healthcare, personal fees from Novartis, grants from GlaxoSmithKline, grants and personal fees from Boston Scientific, personal fees from Ferrer, outside the submitted work. Dr. Abdel-Wahab reports other from Boston Scientific, other from Medtronic, outside the submitted work. Dr. Webster has received institutional research grants from Edwards Lifesciences, Medtronic, Boston Scientific, Biotronic, Emboliner and Medeon Biodesign. Dr. Morice is a minor shareholder of electrocuder. Dr. Mylotte is a consultant for Medtronic, Boston Scientific, and Microport. Dr. Wijns reports grants and personal fees from MicroPort, outside the submitted work; and co-founder of Argonauts, an innovation facilitator. Dr. Baumbach reports Institutional Research Support from Abbott Vascular and honoraria from Astra Zeneca, Sinomed, Microport, Abbott Vascular, Cardinal Health, KSH, outside the submitted work. Dr. Serruys reports personal fees from Biosensors, Medtronic, Micel Technologies, Sinomedical Sciences Technology, St. Jude Medical, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. All other authors have no conflict of interest to declare.

Supplementary materials

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