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1-Year Outcomes of Novel Balloon-Expandable vs Contemporary Transcatheter Heart Valves in Severe Aortic Stenosis

The LANDMARK Trial

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ABSTRACT

BACKGROUND In the LANDMARK trial, the Myval balloon-expandable transcatheter heart valve (THV) series was noninferior to the most commonly used contemporary SAPIEN and Evolut Series THVs for the 30-day early safety endpoint in participants with symptomatic severe native aortic stenosis.

OBJECTIVES The current report from the LANDMARK trial describes clinical outcomes, hemodynamic performances, and quality of life at 1 year.

METHODS This open-label, noninferiority trial enrolled 768 participants across 31 hospitals in Europe, New Zealand, and Brazil. Participants were randomly assigned (1:1) to receive either a Myval THV series or a contemporary THV (SAPIEN or Evolut series). The composite endpoint at 1 year included all-cause mortality, all strokes, and procedure- or valve-related hospitalizations. Clinical efficacy was defined as freedom from the composite endpoint. As recommended in Valve Academic Research Consortium-3, the previous composite endpoint combined with the assessment of quality of life at baseline and 1 year with the 12-Item Short Form Health Survey was reported as an extended composite endpoint. The noninferiority hypothesis was prespecified for the assessment of the primary endpoint at 30 days. Considering the specific 1-year composite endpoints of Valve Academic Research Consortium-3 and the event rate of 27.23% derived from recent studies, an a posteriori descriptive and exploratory noninferiority hypothesis was introduced with a noninferiority margin of 10.89%. The analysis was performed in the intention-to-treat population.

RESULTS The mean age was 80 years, 48% were women, and the median Society of Thoracic Surgeons Predicted Risk of Mortality score was 2.6%. There was no significant difference in the Kaplan-Meier estimates of freedom from the composite endpoint at 365 days (Myval THV 87.0% vs contemporary THVs 86.9%). The Myval THV series was noninferior to the contemporary THVs for the composite endpoint (difference: −0.1%; 1-sided 95% CI: 3.9%; $P_{\text{noninferiority}} < 0.0001$). Similarly, there were no significant differences in freedom from the extended composite endpoint (80.5% vs 77.3%; difference: 3.2%; 95% CI: −2.9% to 9.2%; $P = 0.33$).

CONCLUSIONS In the treatment of symptomatic severe native aortic stenosis, the clinical and hemodynamic outcomes of the Myval THV series were comparable to those of contemporary THVs for the 1-year composite of all-cause mortality, all strokes, or procedure- or valve-related hospitalizations. (LANDMARK Trial: a Randomised Controlled Trial of Myval THV [LANDMARK]; NCT04275726) (JACC. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

EOA = effective orifice area

KM = Kaplan-Meier

PPI = permanent pacemaker implantation

PPM = prosthesis-patient mismatch

PVR = prosthetic valve regurgitation

QOL = quality of life

SF-12 = 12-Item Short Form Health Survey

STS = Society of Thoracic Surgeons

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

VARC = Valve Academic Research Consortium

Transcatheter aortic valve replacement (TAVR) is recommended for treating symptomatic severe aortic stenosis (AS) in guidelines across the United States and Europe, following randomized trials that confirm its safety and efficiency compared with surgical aortic valve replacement, regardless of patient risk.[1-9] The primary evidence supporting TAVR has been established through pivotal studies using the SAPIEN (Edwards Lifesciences) and CoreValve/Evolut (Medtronic) transcatheter heart valves (THVs), making these TAVR systems the most commonly used THVs for treating AS. To date, several novel TAVR bioprostheses have been evaluated in head-to-head comparisons against these standard valves.[10-14] The Myval (Meril Life Sciences Pvt Ltd) THV series is a novel balloon-expandable bioprosthesis, whose noninferiority at 30 days compared with the SAPIEN and Evolut series has been reported in the LANDMARK trial.[15-17] Here, we report the 1-year clinical and hemodynamic outcomes of the LANDMARK trial.

METHODS

STUDY DESIGN. In this prospective, randomized, open-label, noninferiority trial conducted across 31 hospitals in 16 countries (Germany, France, Sweden, the Netherlands, Italy, Spain, Portugal, Greece, Hungary, Poland, Slovakia, Slovenia, Croatia, Estonia, New Zealand, and Brazil), we compared the Myval THV series with contemporary standard THVs (SAPIEN and Evolut series) in patients with symptomatic severe native AS. The details of the trial design and the primary results at 30 days have been published previously.[15,16,18,19]

The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol, informed consent documents, and other relevant trial documents were approved by the ethics committees of the respective

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trial centers. Echocardiograms and electrocardiograms were analyzed by 2 independent core labs (CORRIB core lab, Galway, Ireland [echocardiogram]; CERC, Paris, France [electrocardiogram]) using analysts blinded to the allocated treatment group. Endpoints were adjudicated by a blinded, independent clinical events committee, which had access to core lab assessments.

P.W.S. had full access to the data and drafted the initial version of the manuscript, which was then reviewed and approved by all authors before submission. The authors vouch for the accuracy and completeness of the data and confirm adherence to the trial protocol.

PATIENTS. Enrollment began in January 2021. The original inclusion and exclusion criteria were modified in October 2021 and published as a supplement to the design paper following updated guidelines from the European Society of Cardiology.[8,18,19] After the primary publication of the 30-day outcomes, the statistical analysis plan and protocol were revised before analyzing the 1-year outcomes to ensure consistency with the Valve Academic Research Consortium (VARC)-3 recommendations.[20] Patients (≥18 years of age) with symptomatic severe native AS who were deemed suitable for transfemoral TAVR with all 3 trial devices were considered for enrollment. Patients who declined to provide informed consent were excluded (Supplemental Table 1). A prescreening committee assessed suitability for transfemoral TAVR with the 3 devices, using preprocedural multislice computed tomography, echocardiography, electrocardiography, and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score. The site's heart team made the final decision regarding subject enrollment. Participants with a mean aortic annulus diameter >29 mm were excluded from the randomized trial but included in the nested registry for extra-large sizes of Myval (30.5 mm and 32 mm). All patients provided written informed consent.

RANDOMIZATION AND MASKING. A total of 768 participants were randomly allocated in a 1:1 ratio to receive the Myval (n = 384) or contemporary (n = 384) THV series, with equal allocation between SAPIEN and Evolut within the contemporary group. To avoid an imbalance in baseline risk across treatment arms, the covariate-adaptive Frane method was used based on the STS-PROM (version 2.9), which categorized patients into low (<4%), intermediate (4%-8%), and high (>8%) risk groups with covariates allocated for each group (low risk: 0.000-3.999; intermediate risk: 4.000-8.000; high risk: 8.001-15.000), so asymptotically the power of testing the treatment effects would be greatest and the selection bias minimal. The randomization code was generated by computer and managed centrally, ensuring that no site had prior knowledge of treatment assignment. Subsequent stratification and a 1:1 allocation of patients in the contemporary arm between the SAPIEN (n = 192) and Evolut (n = 192) THV series were performed using an interactive Web-based randomization system (**Figure 1**, Supplemental Figure 1). A covariate-adaptive randomization process was employed based on simulations in accordance with the Frane method, considering both power and selection bias.[15,18,21]

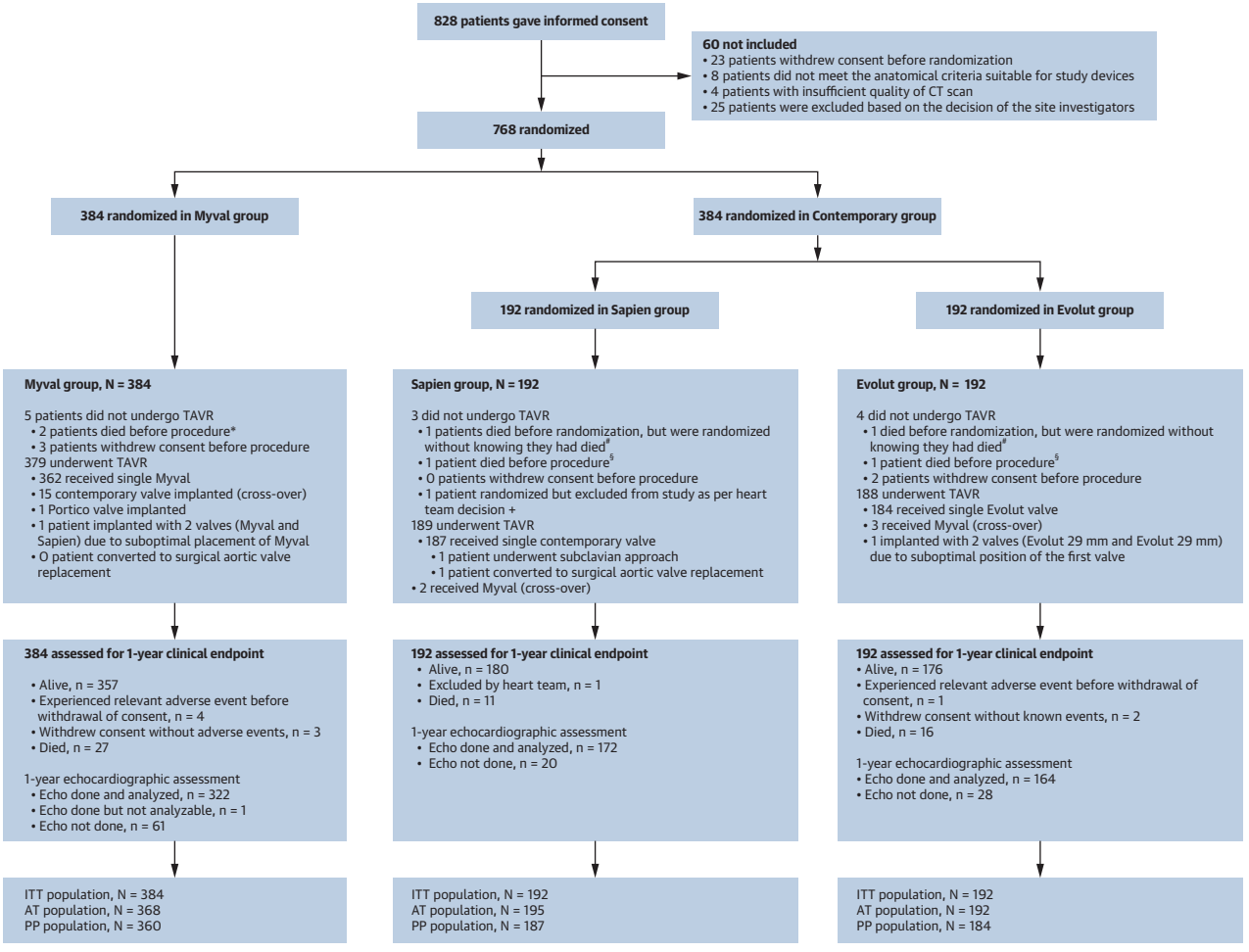
PROCEDURES. The transfemoral approach was specified in the trial protocol. Devices were implanted according to the manufacturer's instructions for use. The choice of angiographic projection during THV deployment, sedation method (local or general anesthesia), predilatation, postdilatation, and femoral access closure (surgical or nonsurgical) were all left to the operator's discretion. The Myval THV series included the Myval and Myval Octacor with sizes 20 mm, 21.5 mm, 23 mm, 24.5 mm, 26 mm, 27.5 mm, and 29 mm. The SAPIEN THV series included the SAPIEN 3 and SAPIEN 3 Ultra with sizes 20 mm, 23 mm, 26 mm, and 29 mm. Last, the Evolut THV series included the Evolut R, Evolut PRO, Evolut PRO+, and Evolut FX with sizes 23 mm, 26 mm, 29 mm, and 34 mm (Supplemental Table 2).

ECHOCARDIOGRAPHIC ANALYSIS. The protocol mandated echocardiographic acquisition preprocedure and at discharge, 30 days, and 1 year. In the core lab, image analysis and quantification were performed according to the American Society of Echocardiography and European Association of Echocardiography guidelines using TOMTEC-ARENA TTA 2.51 (Philips).[22-24] For details of the core lab analysis and reproducibility, see Supplemental Appendix 1.

OUTCOMES. The composite endpoint at 1 year was defined as all-cause mortality, all strokes, or hospitalizations for procedure- or valve-related causes. The clinical efficacy was defined as freedom from the composite endpoint.[25] Hospitalization for procedure- or valve-related causes included hospitalization for new complications, exacerbation of previous in-hospital periprocedural complications, bioprosthetic valve dysfunction, bleeding complications related to oral anticoagulation or antiplatelet therapy, or heart failure-related hospitalizations.

The extended composite endpoint was defined as all-cause mortality, all strokes, hospitalization for

FIGURE 1 Trial Profile



*2 participants died before the procedure and were included in the population for endpoint analysis. #1 patient signed informed consent and was randomized; however, the investigators were unaware that the patient had died in the meantime, and therefore the patient was included in the endpoint analysis. §1 patient died before the procedure and was included in the population for endpoint analysis. +1 patient was excluded after randomization by the investigator due to rapid progression of his Alzheimer's disease. AT = as treated; CT = computed tomography; ITT = intention to treat; PP = per protocol; TAVR = transcatheter aortic valve replacement.

procedure- or valve-related causes, or decline in quality of life (QOL). The extended clinical efficacy was defined as freedom from the extended composite endpoint. VARC-3 recommends a comprehensive QOL assessment such as the Kansas City Cardiomyopathy Questionnaire or the 12-Item Short Form Health Survey (SF-12). Decline in QOL was defined as a decrease of ≥2.5 points in both the physical and mental components of the SF-12 compared with preprocedural baseline.[26] Multiple imputation by the chained equation method was used to handle missing SF-12 assessments at 1 year in patients who were alive and had not withdrawn their consent (Supplemental Appendix 2).[27] This extended composite endpoint was assessed as a binary outcome in the intention-to-treat population. A sensitivity analysis was performed for extended clinical efficacy using an alternative definition of decline in QOL, defined as a decrease of ≥2.5 points in either the physical or mental components of the SF-12.

Other secondary endpoints included the individual components of the composite endpoint, deterioration in QOL assessed by SF-12, bioprosthetic valve dysfunction, deterioration, and failure.[25]

Hemodynamic bioprosthetic valve deterioration was categorized into 3 stages. Stage 1 included

structural valve deterioration, nonstructural valve dysfunction (other than paravalvular regurgitation or prosthesis-patient mismatch [PPM]), leaflet thrombosis, or endocarditis without significant hemodynamic changes. Stage 2 was defined as an increase in mean transvalvular gradient ≥10 mm Hg resulting in a mean gradient ≥20 mm Hg, accompanied by a decrease in effective orifice area (EOA) of ≥0.3 cm^2 or ≥25% and/or a decrease in Doppler velocity index of ≥0.1 or ≥20% compared with 30-day echocardiographic measurements. Stage 2 was also considered present in cases with new onset or an increase of ≥1 grade in transvalvular regurgitation resulting in moderate or greater regurgitation. Stage 3 hemodynamic deterioration was defined as an increase in mean transvalvular gradient of ≥20 mm Hg, resulting in a mean gradient of ≥30 mm Hg, with a concomitant decrease in EOA of ≥0.6 cm^2 or ≥50%, and/or a decrease in Doppler velocity index of ≥0.2 or ≥40%, compared with 30-day echocardiographic measurements. Stage 3 was also considered present in cases with new onset or an increase of ≥2 grades in transvalvular bioprosthetic regurgitation resulting in severe regurgitation.

Stages of clinical bioprosthetic valve failure were defined as follows. Stage 1 was defined as any bioprosthetic dysfunction associated with new or worsening symptoms, or with irreversible stage 3 hemodynamic bioprosthetic valve deterioration. Stage 2 was defined as the need for aortic valve reintervention. Stage 3 was defined as valve-related death.

For the adjudication of moderate or severe prosthetic valve regurgitation (PVR), the clinical events committee reviewed all potential moderate or severe PVR events, including scheduled (predischarge, 30 days, and 1 year) and unscheduled echocardiography, triggered either by the echo core lab reading or site reporting. Whenever there existed a discrepancy in the reading of the degree of moderate or severe PVR between the site and the echo core lab, the clinical events committee adjudicated the echocardiographic images and clinical context. This adjudication overruled the site or core lab reading, was considered as a "first-time event" by reaching the endpoint of moderate or severe PVR, and is reported in a cumulative rate.

PPM was defined according to the VARC-3 criteria. For patients with a body mass index <30 kg/m^2, moderate and severe mismatch were defined as an indexed EOA ≤0.85 cm^2/m^2 and ≤0.65 cm^2/m^2, respectively. For patients with body mass index ≥30 kg/m^2, the corresponding thresholds were ≤0.70 cm^2/m^2 and ≤0.55 cm^2/m^2, respectively.

TABLE 1 Baseline Characteristics

	Myval THV Series (n = 384)	Contemporary THV Series (n = 384)
Age, y	80.0 ± 5.7	80.4 ± 5.4
Sex		
Female	193 (50.3)	176 (45.8)
Male	191 (49.7)	208 (54.2)
Body mass index, kg/m^2	28.2 ± 4.9	28.0 ± 4.9
STS score, %	2.6 (1.7-4.0)	2.6 (1.7-4.0)
Low risk (<4%)	290 (75.5)	289 (75.3)
Intermediate risk (4%-8%)	78 (20.3)	78 (20.3)
High risk (>8%)	16 (4.2)	17 (4.4)
Diabetes	111 (28.9)	114 (29.7)
Dyslipidemia	42 (10.9)	36 (9.4)
History of hypertension	256 (66.7)	254 (66.2)
Estimated glomerular filtration rate		
<60 mL/min/1.73 m^2	171/362 (47.2)	176/360 (48.9)
<30 mL/min/1.73 m^2	53/362 (14.6)	54/360 (15.0)
Chronic obstructive pulmonary disease	42 (10.9)	40 (10.4)
History of atrial fibrillation or flutter	94 (24.5)	99 (25.8)
Previous stroke	13 (3.4)	8 (2.1)
Permanent pacemaker	11 (2.9)	18 (4.7)
Previous MI	26 (6.8)	23 (6.0)
Previous CABG	13 (3.4)	21 (5.4)
Previous percutaneous coronary intervention	30 (7.8)	25 (6.5)
Previous cerebrovascular accident or a transient ischemic attack in last 6 mo	5 (1.3)	1 (0.3)
Echocardiogram		
LVEF, %	58.3 ± 10.7	57.3 ± 10.0
Mean pressure gradient, mm Hg	39.9 ± 14.0	38.7 ± 13.6
Peak velocity, m/s	4.0 ± 0.7	3.9 ± 0.6
CT		
Annular area, mm^2	470.5 ± 80.0	471.4 ± 78.4
Annular perimeter, mm	77.8 ± 6.7	77.9 ± 6.5
Small annulus (aortic annulus area ≤430 mm^2)	125 (32.6)	120 (31.3)
Bicuspid valve	23 (6.0)	29 (7.6)

Values are mean ± SD, n (%), median (Q1-Q3), or n/N (%).

CABG = coronary artery bypass grafting; CT = computed tomography; LVEF = left ventricular ejection fraction; MI = myocardial infarction; STS = Society of Thoracic Surgeons; THV = transcatheter heart valve.

For detailed definitions of all endpoints, see Supplemental Table 3.

STATISTICAL ANALYSIS. The demographic, baseline characteristics, echocardiographic and electrocardiographic assessment, QOL, and 6-minute walk test were summarized using descriptive statistics. For continuous variables, summary statistics included mean ± SD and median (Q1-Q3), as appropriate. *P* values were calculated by 2-sample *t* test between the 2 groups. Categorical variables are presented as frequency and percentage. Pearson's chi-square test or Fisher exact test was used to compare categorical variables between the Myval THV series and the contemporary THV series as appropriate (**Tables 1 and 2**, Supplemental Tables 4 to 12).

TABLE 2 Clinical Efficacy and Other Key Secondary Outcomes at 365 Days

Events	Myval THV Series (n = 384)	Contemporary THV Series (n = 384)	Difference (95% CI) (%)	*P* Value
Clinical efficacy (freedom from all-cause death, all stroke, procedure- or valve-related hospitalization)	335 (87.0)	334 (86.9)	0.1 (−4.7 to 4.9)	1.00
All-cause mortality	27 (7.2)	27 (7.1)	0.1 (−3.5 to 3.7)	1.00
Cardiovascular mortality	22 (5.8)	21 (5.6)	0.2 (−3.1 to 3.5)	1.00
Noncardiovascular mortality	5 (1.4)	6 (1.6)	−0.2 (−1.9 to 1.5)	1.00
Death occurring ≤30 d after the index procedure	9 (2.4)	9 (2.4)	0 (−2.2 to 2.2)	1.00
Death occurring >30 d after the index procedure	18 (4.9)	18 (4.9)	0 (−3.1 to 3.1)	1.00
All stroke (neuro ARC type 1)	21 (5.7)	13 (3.4)	2.3 (−0.6 to 5.2)	0.22
Ischemic	18 (4.9)	12 (3.2)	1.7 (−1.1 to 4.5)	0.35
Hemorrhagic	2 (0.6)	1 (0.3)	0.3 (−0.6 to 1.2)	1.00
Stroke, not otherwise specified	1 (0.3)	0 (0.0)	0.3 (−0.2 to 0.8)	1.00
Stroke disability				
Fatal stroke[a]	5 (1.3)	2 (0.5)	0.8 (−0.5 to 2.1)	0.45
Stroke with disability[b]	11 (3.0)	4 (1.1)	1.9 (−0.1 to 3.9)	0.12
Stroke without disability[c]	5 (1.3)	7 (1.9)	−0.6 (−2.4 to 1.2)	0.77
Stroke without disability assessment	0 (0)	0 (0)	–	
Procedure- or valve-related hospitalization	16 (4.3)	20 (5.4)	−1.1 (−4.1 to 1.9)	0.61
Hospitalization for new complications	9 (2.5)	9 (2.4)	0.1 (−2.1 to 2.3)	1.00
Heart failure-related hospitalizations	4 (1.1)	8 (2.2)	−1.1 (−2.9 to 0.7)	0.38
Exacerbation or deterioration of previous in-hospital periprocedural complication	1 (0.3)	1 (0.3)	0 (−0.8 to 0.8)	1.00
Bioprosthetic valve dysfunction	2 (0.6)	2 (0.6)	0 (−1.1 to 1.1)	1.00
Decrease of ≥2.5 points of both physical and mental domains of SF-12 using multiple imputation[d]	29/329 (8.8)	38/333 (11.4)	−2.6 (−7.5 to 2.3)	0.33
Decrease of ≥2.5 points of either physical or mental domains of SF-12 using multiple imputation[d]	127/329 (38.6)	133/333 (39.9)	−1.3 (−9.1 to 6.4)	0.78
Extended clinical efficacy with QOL outcomes (freedom from all-cause mortality, all stroke, procedure- or valve-related hospitalization, a decrease of ≥2.5 points in both physical and mental domains of SF-12)[d]	309 (80.5)	297 (77.3)	3.2 (−2.9 to 9.2)	0.33
Extended clinical efficacy with QOL outcomes (freedom from all-cause mortality, all stroke, procedure- or valve-related hospitalization, a decrease of ≥2.5 points in either physical or mental domains of SF-12)[d]	217 (56.5)	211 (54.9)	1.6 (−5.7 to 8.8)	0.72
Bioprosthetic valve dysfunction as adjudicated events	41 (11.1)	48 (13.0)	−1.9 (−6.5 to 2.7)	0.50
Structural valve deterioration[e]	0 (0)	1 (0.3)	−0.3 (−0.8 to 0.2)	1.00
Nonstructural valve dysfunction[f]	36 (9.7)	45 (12.2)	−2.5 (−6.9 to 1.9)	0.35
Valve thrombosis	4 (1.2)	5 (1.3)	−0.1 (−1.7 to 1.5)	1.00
Endocarditis	4 (1.1)	1 (0.3)	0.8 (−0.4 to 2.0)	0.37
Hemodynamic bioprosthetic valve deterioration	9 (2.6)	6 (1.6)	1.0 (−1.0 to 3.0)	0.60
Stage 1 (morphological valve deterioration without significant hemodynamic deterioration)[g]	7 (1.9)	4 (1.1)	0.8 (−0.9 to 2.5)	0.54
Stage 2 (moderate hemodynamic valve deterioration)[h]	2 (0.7)	2 (0.5)	0.2 (−0.9 to 1.3)	1.00
Stage 3 (Severe hemodynamic valve deterioration)[i]	0 (0.00)	0 (0.00)	–	
Clinical bioprosthetic valve failure	3 (0.8)	10 (2.8)	−2.0 (−3.9 to −0.1)	0.09
Stage 1 (bioprosthetic valve dysfunction with clinically expressive criteria OR irreversible stage 3 hemodynamic valve deterioration)	1 (0.3)	3 (0.9)	−0.6 (−1.7 to 0.5)	0.62
Stage 2 (aortic valve reintervention)	0 (0.00)	5 (1.4)	−1.4 (−2.6 to −0.2)	0.07
Stage 3 (valve-related death)	2 (0.6)	2 (0.5)	0.1 (−0.9 to 1.1)	1.00

Values are n (%) or n/N (%), unless otherwise indicated. All percentages are Kaplan-Meier estimates at 365 days otherwise specified. *P* values are calculated by Pearson's chi-square test or Fisher exact test. [a]Death resulting from a stroke. [b]Modified Rankin scale of ≥2 at 90 days and increase of ≥1 from prestroke baseline. [c]Modified Rankin scale of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 days or no increase in modified Rankin scale category from prestroke baseline. [d]Percentages calculated using a simple proportion. The SF-12 obtained at the 1-year follow-up visit was used. Imputation was performed only for missing SF-12 at 1 year. A total of 65 missing SF-12 values were imputed. [e]Intrinsic permanent changes to the prosthetic valve, including wear and tear, leaflet disruption, flail leaflet, leaflet fibrosis and/or calcification, or strut fracture or deformation. [f]Any abnormality, not intrinsic to the prosthetic valve, resulting in valve dysfunction. Examples include residual intra- or paraprosthetic aortic regurgitation; leaflet entrapment by pannus, tissue, or suture; inappropriate positioning or sizing; dilatation of the aortic root after stentless prostheses or aortic valve sparing operations; prosthesis-patient mismatch; and embolization. In the LANDMARK trial, only para- or intravalvular regurgitation and patient prosthesis mismatch were observed in this category. [g]Evidence of structural valve deterioration, nonstructural valve dysfunction (other than paravalvular regurgitation or prosthesis-patient mismatch), thrombosis, or endocarditis without significant hemodynamic changes. [h]Increase in mean transvalvular gradient ≥10 mm Hg resulting in mean gradient ≥20 mm Hg with concomitant decrease in effective orifice area ≥0.3 cm^2 or ≥25% and/or decrease in Doppler velocity index ≥0.1 or ≥20% compared with echocardiographic assessment performed 1 to 3 months postprocedure, OR new occurrence or increase of ≥1 grade of intraprosthetic aortic regurgitation resulting in ≥ moderate aortic regurgitation. [i]Increase in mean transvalvular gradient ≥20 mm Hg resulting in mean gradient ≥30 mm Hg with concomitant decrease in effective orifice area≥0.6 cm^2 or ≥50% and/or decrease in Doppler velocity index ≥0.2 or ≥40% compared with echocardiographic assessment performed 1 to 3 months postprocedure, OR new occurrence, or increase of ≥2 grades, of intraprosthetic aortic regurgitation resulting in severe aortic regurgitation.

ARC = Academic Research Consortium; QOL = quality of life; other abbreviations as in Table 1.

The trial was designed in 2019 using data from randomized head-to-head comparisons of THVs available at that time; a sample size of 768 participants was calculated as necessary to demonstrate that the Myval THV series was noninferior to contemporary THVs for the 30-day safety and effectiveness endpoint (a composite of all-cause mortality, all stroke, bleeding [VARC type 3 and 4], acute kidney injury [stages 2, 3, and 4], major vascular complications, moderate or severe PVR, or new permanent pacemaker implantation [PPI]).[15,18] The prespecified 1-year clinical efficacy endpoint was the composite of all-cause mortality, all strokes, and hospitalizations for procedure- or valve-related causes. In the current exploratory analysis, clinical efficacy was defined as freedom from the clinical efficacy endpoint.

Following publication of the 30-day primary endpoint results, a noninferiority comparison between the 2 arms for the composite endpoint at 1 year was added as a descriptive and exploratory analysis in the updated statistical analysis plan and trial protocol in January 2025, and published in April 2025.[20] The expected event rate of the 1-year clinical efficacy composite endpoint was 27.23%, based on previous and more recent head-to-head randomized THV comparisons.[10,12,28] The noninferiority margin was set at 10.89% (40% of the expected event rate). The current a posteriori, descriptive, and exploratory noninferiority hypothesis would provide a 94% power. To avoid censoring of patients who came at the early time window of 1-year follow-up (335 days to 395 days), noninferiority was also assessed at 335 days.

Clinical endpoints were assessed using Kaplan-Meier estimates at day 365, unless specified. The results are reported as point estimates and 95% CI for the risk difference. Additionally, in the figures with Kaplan-Meier (KM) curves, HRs, and log-rank *P* values at 365 days are provided as post hoc analysis, while KM curves were extended up to 395 days to capture late events within the time window of 1-year follow-up. To include the echocardiographic findings obtained between 365 and 395 days, additional supplemental tables report bioprosthetic valve dysfunction, deterioration, and failure up to 395 days.

For a post hoc exploratory analysis, comparisons between the Myval THV series vs the SAPIEN THV series and the Myval THV series vs the Evolut THV series were performed and are reported in Supplemental Tables 13 to 24. *P* values were not corrected for multiple testing.

The missing SF-12 data at 1 year for patients who were alive and had not withdrawn their consent were imputed using multiple imputation by the chained equation method (Supplemental Appendix 2). No imputation for missing echocardiographic parameters was performed, considering the high availability (94%) of echocardiograms in patients who were alive and had not withdrawn consent at 1 year.

Statistical analyses were performed using R software, version 4.3.3 (R Foundation for Statistical Computing).

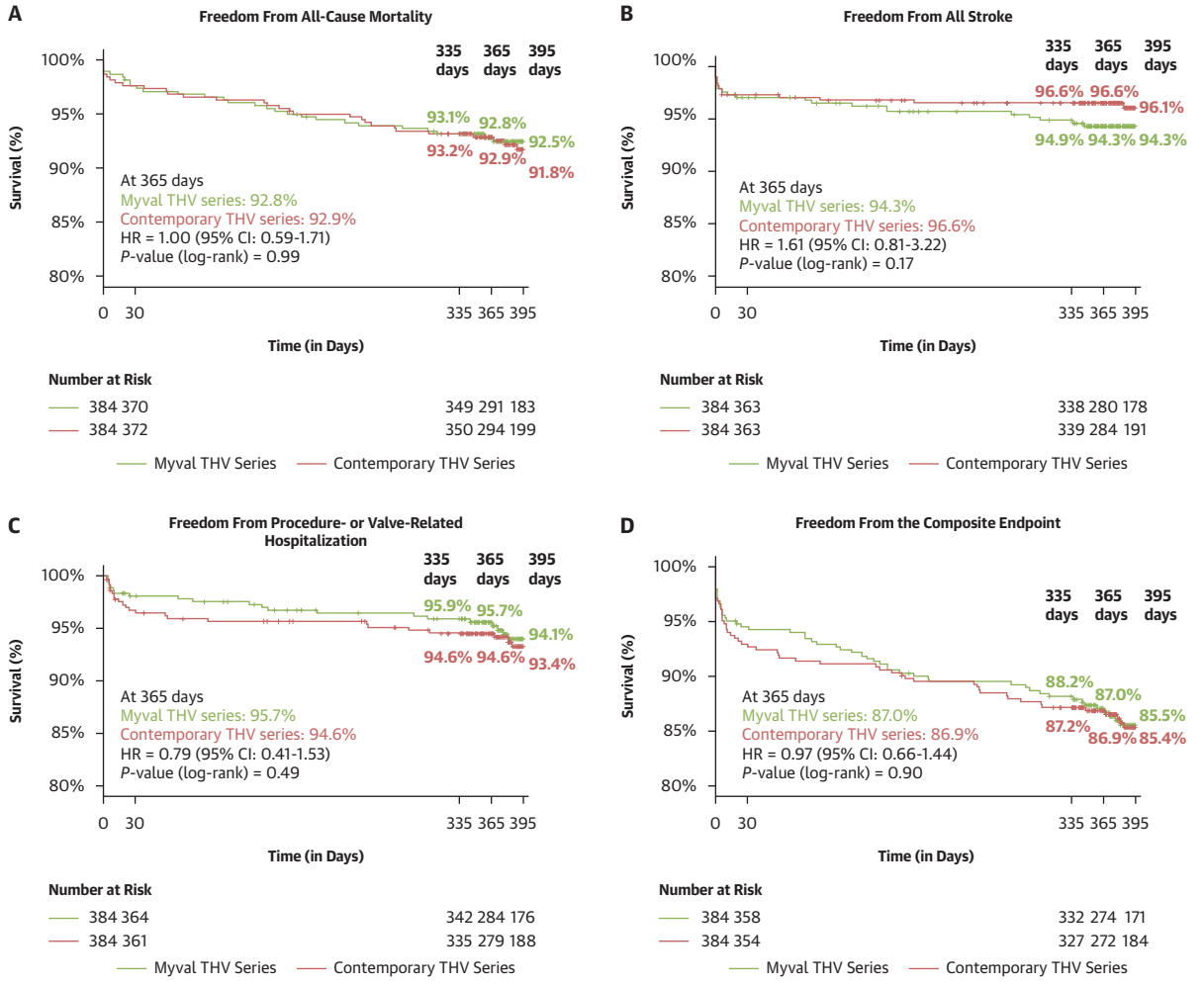
RESULTS

TRIAL PROFILE. Between January 6, 2021, and December 5, 2023, 768 patients were enrolled (**Figure 1**), with 384 patients randomly assigned to Myval THVs and 384 to contemporary THVs. The mean age was 80.2 ± 5.6 years, and 369 (48%) of 768 patients were female (**Table 1**). The median STS-PROM score was 2.6 (Q1-Q3: 1.7-4.0). Procedural characteristics are shown in Supplemental Table 4. In the intention-to-treat population of the Myval THV series arm (n = 384), 379 patients underwent TAVR, with 362 receiving a single Myval series THV (Myval [n = 330] or Myval Octacor [n = 32]). In the contemporary THV group (n = 384), 192 patients were assigned to each SAPIEN and Evolut group. In the SAPIEN group, 189 patients underwent TAVR, with 187 receiving a single SAPIEN valve. In the Evolut group, 188 patients underwent TAVR, with 184 receiving a single Evolut valve (**Figure 1**, Supplemental Figure 1). The type and size of valves used are tabulated in Supplemental Table 2.

Compared with patients with complete follow-up, those with incomplete clinical follow-up or echocardiographic assessment had higher Society of Thoracic Surgeons (STS) scores, a lower prevalence of low-risk (<4%) STS scores, a higher prevalence of a lower estimated glomerular filtration rate <30 mL/min/1.73 m^2, more frequent atrial fibrillation, lower left ventricular ejection fraction, and a larger annular area. Patients without SF-12 assessment were older, had a significantly higher STS score, had a lower prevalence of low-risk (<4%) STS scores, had more frequent hypertension, had a lower occurrence of an estimated glomerular filtration rate <30 mL/min/1.73 m^2, had more frequent atrial fibrillation, had lower left ventricular ejection fraction, had lower mean pressure gradient, and had a higher prevalence of preimplanted pacemaker (Supplemental Table 25).

CLINICAL OUTCOMES. **Figure 2** shows freedom from all-cause mortality (**Figure 2A**), all strokes (**Figure 2B**), procedure- or valve-related hospitalizations (**Figure 2C**), and the composite endpoint (**Figure 2D**). The Kaplan-Meier estimates at 365 days for clinical

FIGURE 2 Kaplan-Meier Curves of Clinical Efficacy Composite and the Individual Components (Myval and Contemporary Groups)

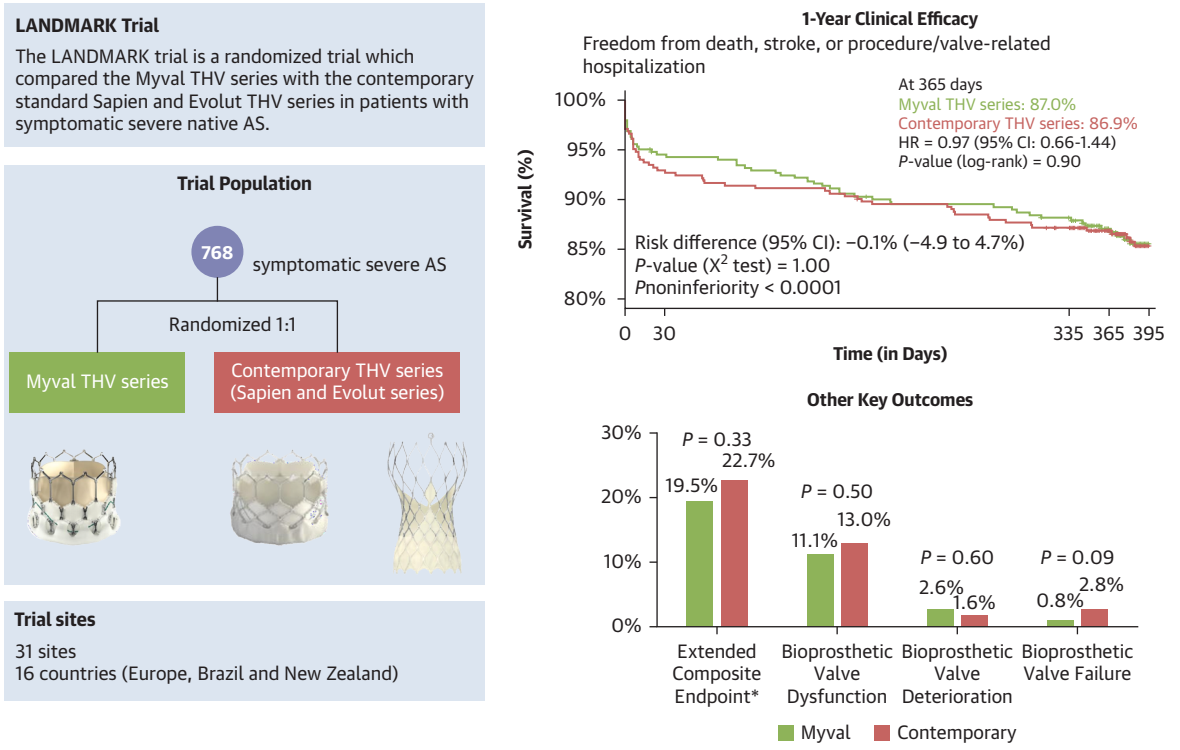


Kaplan-Meier curves of freedom from (A) all-cause mortality, (B) all stroke, (C) procedure- or valve-related hospitalization, and (D) the composite of all-cause mortality, all stroke or procedure- or valve-related hospitalization. THV = transcatheter heart valve.

efficacy (freedom from the composite endpoint) were 87.0% in the Myval arm and 86.9% in the contemporary arm (**Table 2**). Similar results were observed in analyses using the per-protocol and as-treated populations (Supplemental Table 5). Supplemental Figure 2 shows the KM curve of clinical efficacy with overlaying symbols indicating the type of events. The KM curves of the clinical efficacy in a landmark analysis from 30 days up to 1 year show respective KM estimates for the Myval and contemporary THV series of 92.1% and 93.5% (log-rank $P = 0.50$) (Supplemental Figure 3). The exploratory noninferiority analysis confirmed noninferiority of the Myval and contemporary THV series at 335 days (difference: −1.0%, 1-sided 95% CI: 2.9%, Pnoninferiority < 0.001) and at 365 days (difference: −0.1%, 1-sided 95% CI: 3.9%; Pnoninferiority < 0.0001) (**Central Illustration**).

Because 9.2% (n = 65 of 703) of SF-12 assessments could not be obtained in patients who were alive and had not withdrawn their consent at 1 year, multiple imputation was used (Supplemental Figure 4). The extended clinical efficacy (freedom from the extended composite endpoint) was 80.5% and 77.3% in the Myval and contemporary arms, respectively (difference: 3.2%; 95% CI: −2.9% to 9.2%; $P = 0.33$) (**Table 2**). The sensitivity analysis of the extended clinical efficacy using an alternative definition of decline in QOL (a decrease of ≥2.5 points in either the physical or mental components of SF-12) also showed

CENTRAL ILLUSTRATION **1-Year Outcomes of the LANDMARK Trial**



Serruys PW, et al. JACC. 2025;■(■):■-■.

The randomized LANDMARK Trial demonstrated noninferiority for clinical efficacy of Myval THV series (n = 384) compared to the contemporary THV series (Sapien and Evolut series, n = 384) at 1 year for the treatment of symptomatic severe aortic stenosis. *Composite of all-cause mortality, all stroke, hospitalization for procedure- or valve-related causes, or decline in quality of life (QOL). Decline in QOL was defined as a decrease of ≥2.5 points in both the physical and mental components of the SF-12 at 1 year compared with the preprocedural baseline. AS = aortic stenosis; SF-12 = 12-Item Short Form Health Survey; THV = transcatheter heart valve.

no significant difference between the 2 arms (56.5% vs 54.9%; difference: 1.6%; 95% CI: −5.7% to 8.8%; $P = 0.72$) (Table 2).

At 365 days, there were no between-group differences in the incidence of all-cause mortality, cardiovascular death, all stroke, hospitalizations due to procedure- or valve-related causes, or all-cause hospitalization (Table 2, Supplemental Table 6).

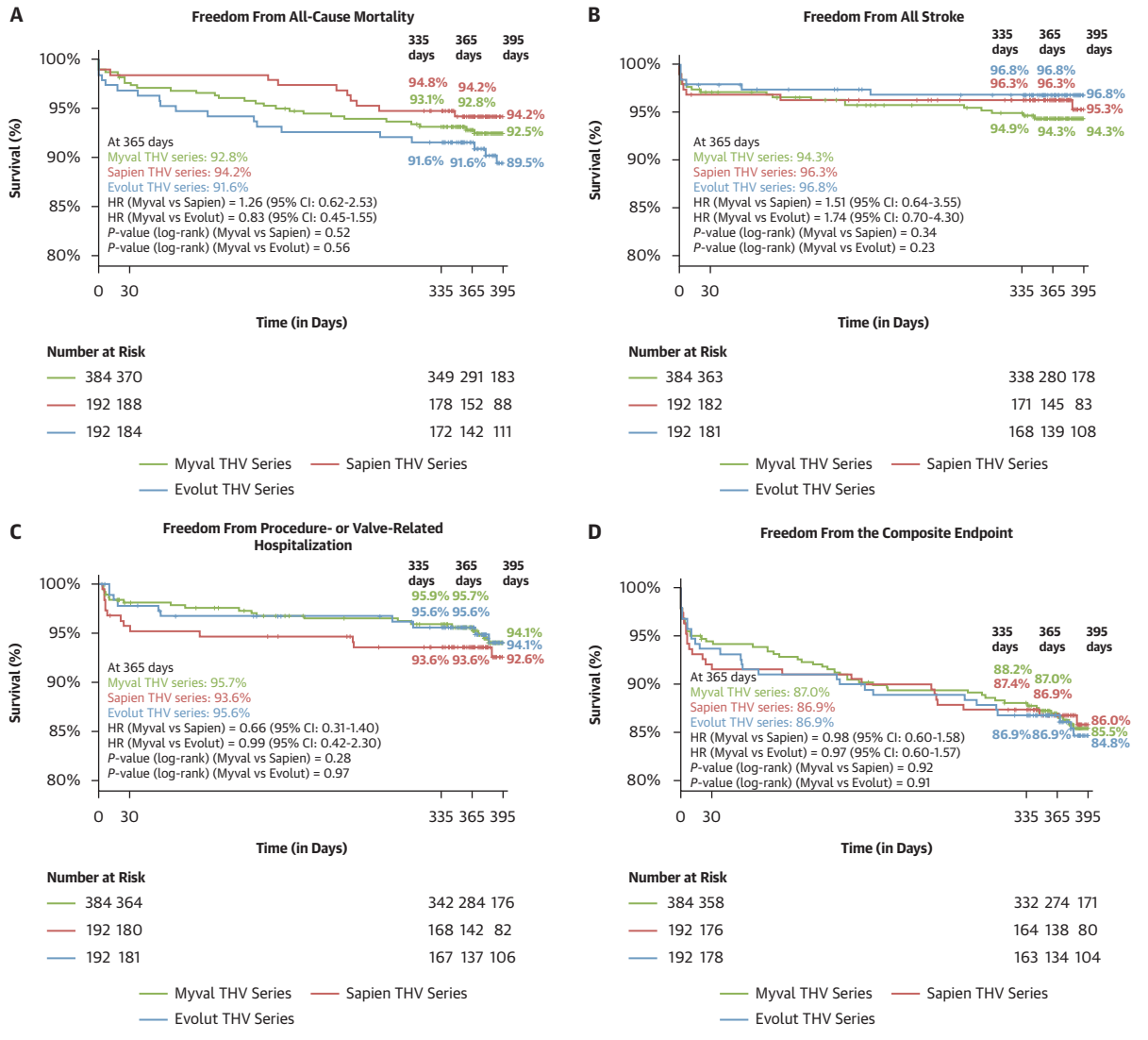
Likewise, there were no significant differences in clinical efficacy or its components in the post hoc comparisons between the Myval and the SAPIEN THV series, and between the Myval and Evolut THV series (Figure 3, Supplemental Tables 15 to 17).

The incidence of new PPI in patients without a pacemaker at baseline was 17.6% (n = 64) in the Myval arm and 19.1% (n = 68) in the contemporary arm (difference: -1.5%; 95% CI: -7.1% to 4.1%; $P = 0.68$) (Supplemental Table 6). Rates in the SAPIEN (19.2%) and Evolut (18.9%) groups were comparable to the Myval group ($P = 0.71$ and $P = 0.82$, respectively) (Supplemental Table 17). The incidence of new left bundle branch block did not differ significantly between the Myval and contemporary groups, nor in the individual comparisons with SAPIEN and Evolut (Supplemental Tables 7 and 18).

Figure 4 and Supplemental Figure 5 display the forest plot of 12 predefined subgroups, showing no significant interactions. This suggests a similar treatment effect across these specific patient groups.

BIOPROSTHETIC VALVE DYSFUNCTION, DETERIORATION, AND FAILURE. Structural valve deterioration occurred in 1 patient in the contemporary arm at 365 days (Table 2). Nonstructural valve dysfunction occurred in 36 patients in the Myval arm and 45 in the contemporary THV arm (9.7% vs 12.2%; difference: −2.5%; 95% CI: −6.9% to 1.9%; $P = 0.35$).

FIGURE 3 Kaplan-Meier Curves of Clinical Efficacy Composite and the Individual Components (Myval, SAPIEN, and Evolut Groups)



Kaplan-Meier curves of freedom from (A) all-cause mortality, (B) all stroke, (C) procedure- or valve-related hospitalization, and (D) the composite of all-cause mortality, all stroke or procedure- or valve-related hospitalization. THV = transcatheter heart valve.

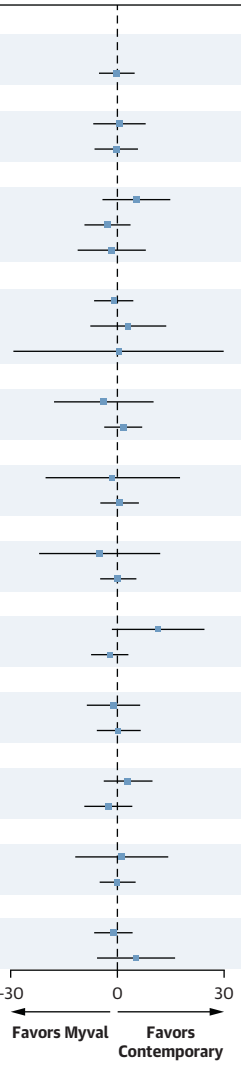
Valve thrombosis was observed in 9 patients (Myval arm, n = 4 [1.2%]; contemporary arm, n = 5 [1.3%]); however, only 1 case was adjudicated as clinically significant. In the Myval group, there were 4 (1.1%) cases of endocarditis, with 2 endocarditis-related deaths, compared with 1 (0.3%) case of endocarditis in the contemporary THV group who died.

Hemodynamic bioprosthetic valve deterioration at 365 days was identified on echocardiography in 9 Myval patients and 6 contemporary arm patients (2.6% vs 1.6%; difference: 1.0%; 95% CI: −1.0% to 3.0%; P = 0.60) (Table 2). Stage 2 hemodynamic deterioration was seen in 2 patients in each group (0.7% vs 0.5%; difference: 0.2%; 95% CI: −0.9% to 1.3%; P = 1.00). Between 365 and 395 days, stage 2 hemodynamic deterioration occurred in 5 of the Myval arm and 2 of the contemporary arm, and stage 3 hemodynamic deterioration occurred in 2 of the Myval arm and 0 of the contemporary arm (Supplemental Table 8).

At 365 days, clinical bioprosthetic valve failure was seen in 13 patients (Myval, n = 3 [0.8%] vs contemporary n = 10 [2.8%]; difference: −2.0%; 95% CI:−3.9% to −0.1%; P = 0.09) (Table 2). Stage 2

FIGURE 4 Subgroup Analyses of the Clinical Efficacy in the Predefined 12 Subsets

Subgroup	No. of Subjects	Events, n/N (%) Myval THV Series	Events, n/N (%) Contemporary THV Series	Risk Difference, % (95% CI)
Age (Year)				
<65	5	0/2 (0.0%)	0/3 (0.0%)	
≥65	763	49/382 (13.0%)	50/381 (13.2%)	-0.2% (-5.0 to 4.6)
Gender				
Male	399	31/191 (16.5%)	33/208 (15.9%)	0.6% (-6.7 to 7.8)
Female	369	18/193 (9.5%)	17/176 (9.8%)	-0.3% (-6.4 to 5.7)
BMI (kg/m^2)				
<25	217	17/99 (17.3%)	14/118 (12.0%)	5.3% (-4.2 to 14.7)
25-30	312	12/159 (7.6%)	16/153 (10.5%)	-2.9% (-9.2 to 3.5)
>30	236	19/124 (15.6%)	19/112 (17.2%)	-1.6% (-11.1 to 7.9)
STS Risk Score				
Low	579	34/290 (11.9%)	37/289 (12.9%)	-1.0% (-6.4 to 4.3)
Intermediate	156	11/78 (14.6%)	9/78 (11.6%)	3.0% (-7.5 to 13.6)
High-risk	33	4/16 (25.0%)	4/17 (24.7%)	0.3% (-29.2 to 29.8)
LVEF				
<50%	129	10/56 (18.0%)	16/73 (21.9%)	-3.9% (-17.7 to 10.0)
≥50%	575	36/293 (12.4%)	30/282 (10.8%)	1.6% (-3.6 to 6.8)
Low Flow-Low Gradient				
Yes	66	5/29 (17.5%)	7/37 (18.9%)	-1.4% (-20.1 to 17.4)
No	619	41/314 (13.2%)	38/305 (12.6%)	0.6% (-4.7 to 5.9)
Bicuspid subset Analysis				
Yes	52	2/23 (8.7%)	4/29 (13.8%)	-5.1% (-22.1 to 11.9)
No	716	47/361 (13.2%)	46/355 (13.1%)	0.1% (-4.8 to 5.1)
Coronary Artery Disease				
Yes	113	11/55 (20.2%)	5/58 (8.8%)	11.4% (-1.5 to 24.3)
No	655	38/329 (11.7%)	45/326 (13.9%)	-2.2% (-7.3 to 2.9)
Annulur Area				
Small annuli (≤430 mm^2)	245	11/125 (9.1%)	12/120 (10.2%)	-1.1% (-8.5 to 6.3)
Nonsmall annulus (>430 mm^2)	523	38/259 (14.8%)	38/264 (14.5%)	0.3% (-5.7 to 6.4)
Baseline NYHA				
Class I, Class II	364	24/177 (13.7%)	20/187 (10.8%)	2.9% (-3.8 to 9.7)
Class III, Class IV	402	25/206 (12.3%)	29/196 (14.9%)	-2.6% (-9.3 to 4.1)
Atrial Fibrillation				
Yes	145	14/71 (20.2%)	14/74 (19.0%)	1.2% (-11.7 to 14.2)
No	612	33/305 (10.9%)	33/307 (10.9%)	0.0% (-4.9 to 5.0)
SF-12 (Baseline)				
<50	617	38/307 (12.5%)	42/310 (13.7%)	-1.2% (-6.5 to 4.2)
≥50	103	6/53 (11.3%)	3/50 (6.1%)	5.2% (-5.6 to 16.0)



Subgroup analyses of the clinical efficacy composite endpoint of all-cause death, all stroke, or hospitalization for procedure- or valvular-related causes. All percentages are Kaplan-Meier estimates at 365 days. BMI = body mass index; LVEF = left ventricular ejection fraction; SF-12, 12-Item Short Form Health Survey; STS = Society of Thoracic Surgeons.

clinical bioprosthetic valve failure (aortic valve reintervention) occurred in 5 patients, all in the contemporary group (0% vs 1.4%; difference: −1.4%; 95% CI: −2.6% to −0.2%; $P = 0.07$), while stage 3 failure (valve-related death) occurred in 2 patients in each group (0.6% vs 0.5%; difference: 0.1%; 95% CI: −0.9% to 1.1%; $P = 1.00$).

Supplemental Table 8 presents the same data at 395 days, to include late echocardiographic follow-up within the 1-year follow-up window. Individual comparisons of Myval, SAPIEN, and Evolut THVs are shown in Supplemental Tables 15 and 19.

ECHOCARDIOGRAPHIC OUTCOMES. Echocardiograms were analyzed in 93.6% (n = 658 of 703) of

surviving patients who did not withdraw their consent before 1 year follow-up (Supplemental Figure 6). The rate of moderate or severe total PVR at the scheduled 1-year echocardiographic follow-up was 1.6% (n = 5 of 322) in the Myval arm vs 3.3% (n = 11 of 336) in the contemporary arm ($P = 0.07$) (Supplemental Table 9, Supplemental Figure 7), with a rate of 2.3% (n = 4 of 172) in the SAPIEN group and 4.3% (n = 7 of 164) in the Evolut group. There were no significant differences between the Myval and SAPIEN groups (1.6% vs 2.3%; $P = 0.10$) or between the Myval and Evolut groups (1.6% vs 4.3%; $P = 0.11$) (**Figure 5**, Supplemental Table 20).

As described in the Methods, according to the clinical event committee adjudication, the cumulative rate of moderate or severe PVR was 4.2% (n = 15) in the Myval arm vs 7.1% (n = 26) in the contemporary arm (difference: −2.9%; 95% CI: −6.2% to 0.4%; $P = 0.11$) (Supplemental Table 6). Although rates were similar between Myval and SAPIEN (4.2% vs 3.7% [n = 7]; $P = 0.82$), they were higher with Evolut (10.5% [n = 19]) compared with Myval ($P = 0.02$) (Supplemental Table 17).

Figures 5 and 6 and Supplemental Figure 7 show temporal changes in the EOA and mean pressure gradients. There were substantial improvements from preprocedure to discharge, and stable parameters between 30 days and 1 year. At 1 year, compared with the SAPIEN group, the Myval group had lower mean pressure gradients (9.51 ± 5.26 mm Hg vs 10.54 ± 5.46 mm Hg; difference: -1.03; 95% CI: -2.04 to -0.02; $P = 0.047$), and larger EOA (2.11 ± 0.56 cm^2 vs 1.95 ± 0.58 cm^2; difference: 0.16; 95% CI: 0.046 to 0.26; $P = 0.0056$). Conversely, compared with the Evolut group, the Myval group had higher mean pressure gradients (9.51 ± 5.26 mm Hg vs 6.53 ± 2.99 mm Hg; difference: 2.98; 95% CI: 2.23 to 3.71; $P < 0.0001$) and smaller EOA (2.11 ± 0.56 cm^2 vs 2.25 ± 0.51 cm^2; difference: -0.14; 95% CI: -0.40 to -0.24; $P = 0.0075$) (Supplemental Table 20, Supplemental Figure 8).

At 1 year, patients with a small annulus (≤430 mm^2) had significantly lower rates of combined moderate and severe PPM in the Myval group compared with the SAPIEN group (17.3% vs 33.9%; $P = 0.029$). In comparison, there was no significant difference between the Myval and Evolut groups (17.3% vs 8.3%; $P = 0.22$) (Supplemental Table 21).

FUNCTIONAL AND QOL OUTCOMES. The physical and mental domains of SF-12 (with or without multiple imputation), and other functional assessments, including NYHA functional class and 6-minute walk tests at 1 year, were similar between the 2 arms (Supplemental Tables 10 to 12, Supplemental Figure 9). These findings were also consistent in the individual comparisons among the 3 types of THVs (Supplemental Tables 22-24). Both Myval and contemporary groups showed highly significant improvements in the physical and mental QOL components between baseline preprocedure and 30 days. From 30 days to 1 year, there were no significant changes in QOL with Myval, whereas a significant decline in physical component was observed in the contemporary group (Supplemental Figure 10).

DISCUSSION

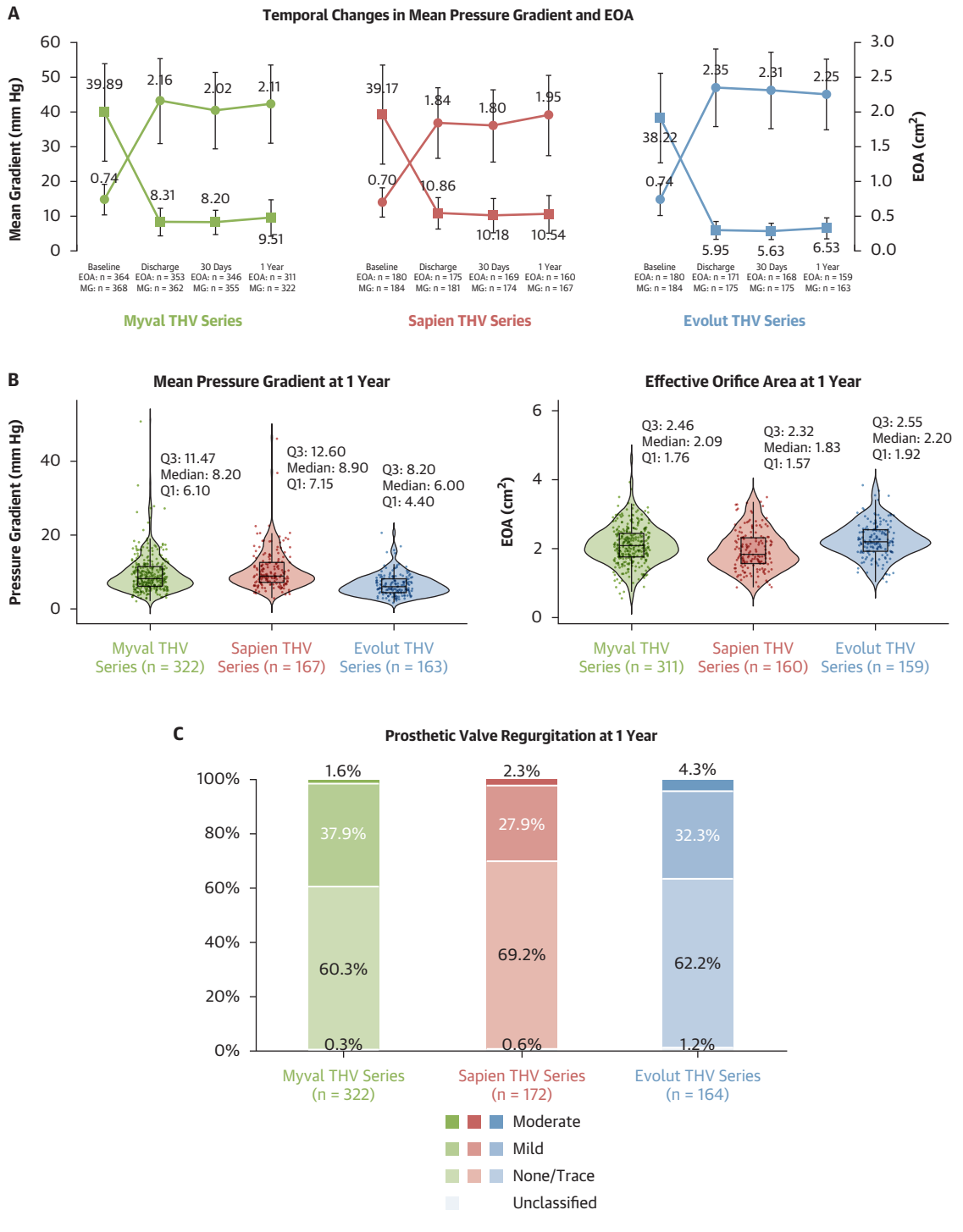
PRINCIPAL FINDINGS. The main finding of this trial is that there were no significant differences in 1-year clinical efficacy, defined as freedom from all-cause mortality, all strokes, and hospitalizations for procedure- or valve-related causes between the Myval THV series and the contemporary THV series. No significant differences were observed in the individual components. Furthermore, the rate of clinical efficacy combined with QOL assessment did not differ significantly between the 2 groups, no matter what the definitions of deterioration of QOL were.

APPLICATION OF VARC-3 RECOMMENDATIONS. The current trial closely followed the recommendations of VARC-3.[25] For 1-year outcome assessment, VARC-3 recommends a composite endpoint comprising 4 components: all-cause mortality, all stroke, hospitalization for procedure- or valve-related causes, and deterioration in QOL. To date, no randomized head-to-head TAVR trial has reported the composite rate of these 4 components, which combine historical events and patient-reported outcomes assessed at a fixed time point. Therefore, we selected the first 3 components as the clinical efficacy composite endpoint, while recognizing the importance of QOL assessment in an extended composite endpoint incorporating QOL deterioration, measured by the SF-12, with multiple imputations applied to address the 9.2% of missing follow-up SF-12 reports.

The 3 levels of assessment for bioprosthetic valve abnormality (dysfunction, deterioration, and failure) in the VARC-3 consensus are structural, hemodynamic, and clinical. The interplay between these 3 components is highly complex for clinical events committees, as well as for scientific reports that must comply with these VARC recommendations, meet regulatory requirements and be clear to readers of the medical literature.

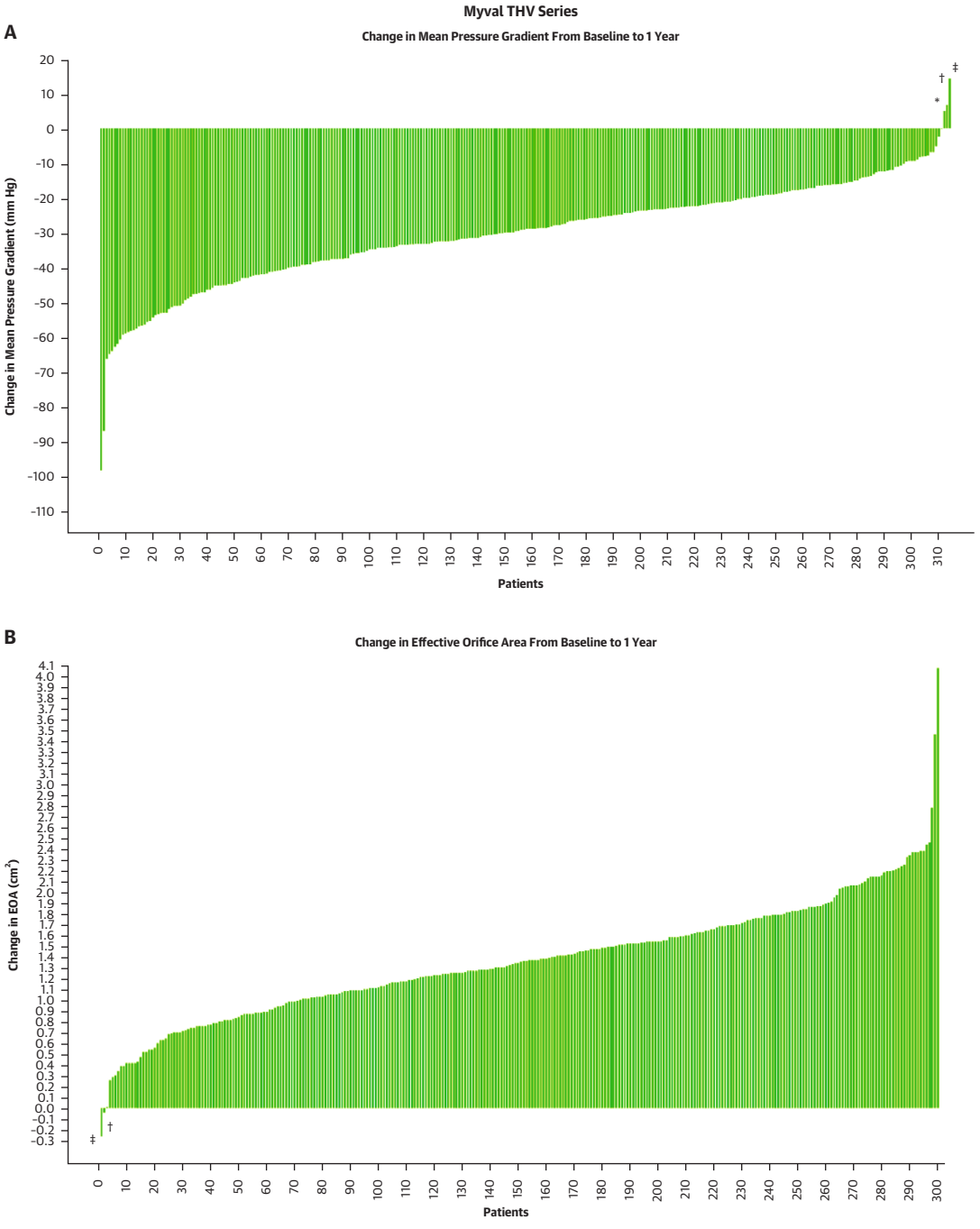
CLINICAL OUTCOMES. The recently reported COMPARE-TAVI trial compared the SAPIEN 3 or SAPIEN 3 Ultra THVs with the Myval or Myval Octacor

FIGURE 5 Echocardiographic Hemodynamic Outcomes



(A) Change of aortic valve mean pressure gradient and effective orifice area (EOA). (B) Violin plot of mean pressure gradient and EOA at 1-year echocardiographic follow-up. (C) Total aortic regurgitation at the scheduled 1-year echocardiographic follow-up. Patients whose echocardiographic data were unavailable were excluded from the denominator. MG = mean pressure gradient; THV = transcatheter heart valve.

FIGURE 6 Waterfall Plots of Mean Pressure Gradient and EOA From Preprocedural Baseline to 1 Year



Waterfall plots of (A) mean pressure gradient and (B) effective orifice area (EOA) from preprocedural baseline to 1 year in the Myval group. In 3 cases, mean pressure gradient increased from baseline to 1 year: *5.1, †6.7 and ‡14.3 mm Hg). These patients received transcatheter aortic valve replacement for low-gradient severe aortic stenosis: baseline gradients were *22.2 mm Hg (indexed aortic valve area [AVAi] 0.33 cm^2/m^2), †26.9 mm Hg (AVAi 0.51 cm^2/m^2), and ‡36.6 mm Hg (AVAi 0.42 cm^2/m^2). The patient with the highest gradient increase (‡) received Portico valve after randomization to the Myval transcatheter heart valve arm. In 2 (‡†) out of 3 cases, EOA decreased by ‡0.26 cm^2 and †0.04 cm^2. (C, D) Waterfall plots in the SAPIEN group. In 1 case (§), mean pressure gradient increased from baseline to 1 year by 12.0 mm Hg. (E, F) Waterfall plots in the Evolut group. In 1 case (#), the mean pressure gradient increased by 9.5 mm Hg and EOA decreased by 0.18 cm^2 from baseline to 1 year. These patients received transcatheter aortic valve replacement for low-gradient severe aortic stenosis (baseline gradient §8.5 mm Hg [AVAi 0.40 cm^2/m^2 and left ventricular ejection fraction 24%] and ‡11.1 mm Hg [AVAi 0.53 cm^2/m^2]).

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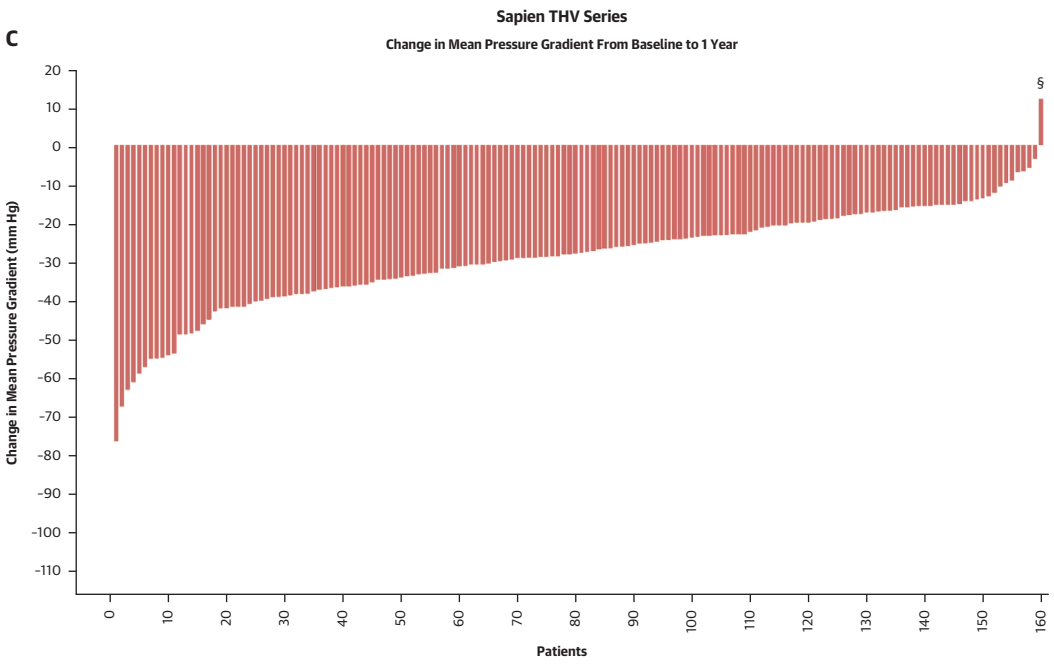
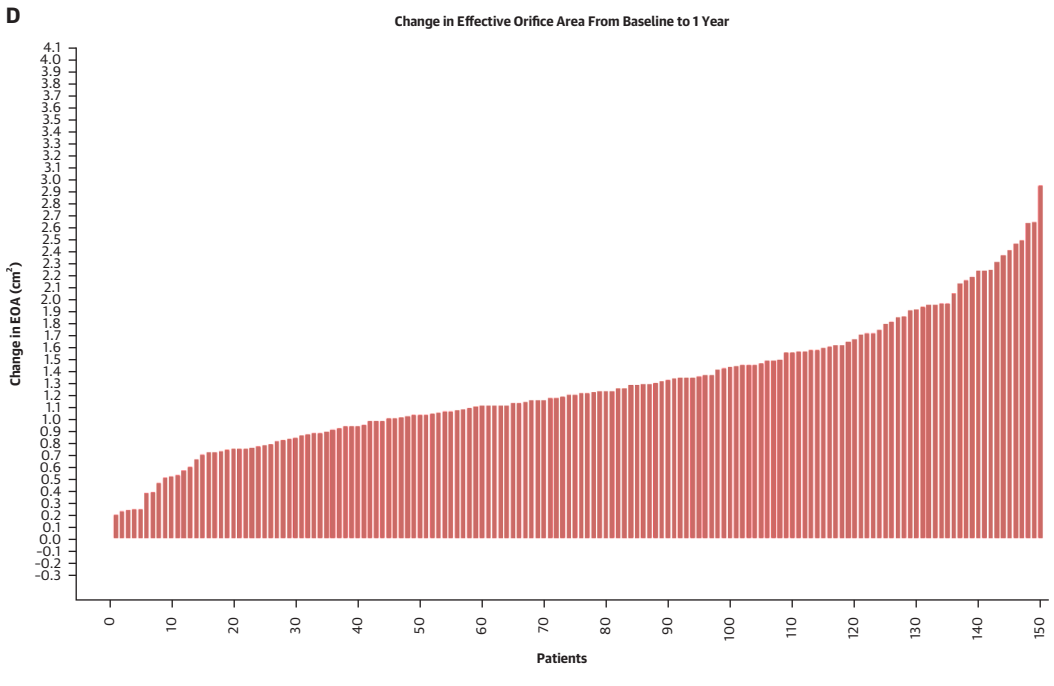
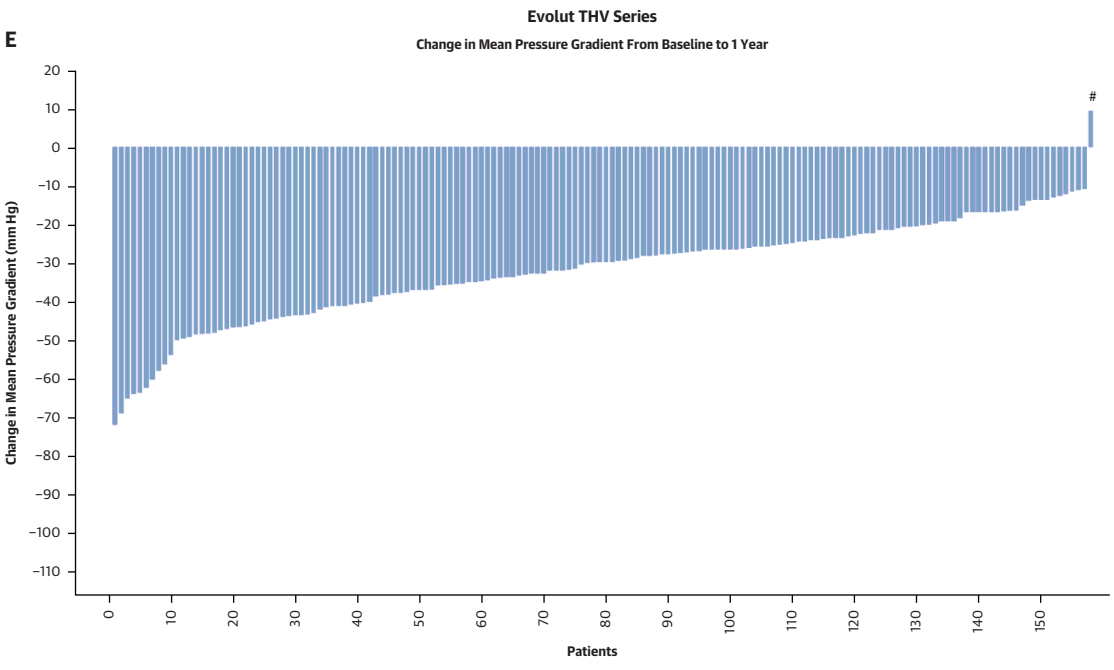
FIGURE 6 Continued

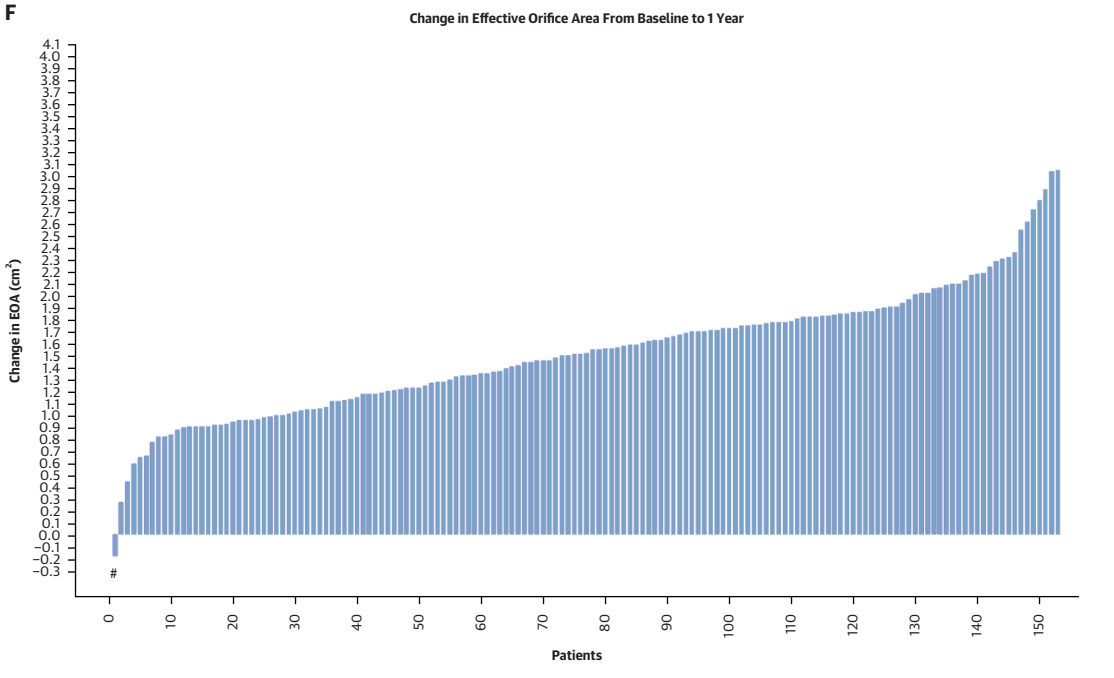




THVs in 1,031 patients with a baseline profile similar to the LANDMARK trial.[14] At 1 year, the Myval THVs were noninferior to the SAPIEN THVs (event rate: SAPIEN 13% vs Myval 14%; risk difference: −0.9%, 1-sided upper 95% CI: 4.4%; $P_{\text{noninferiority}} = 0.019$) for the primary composite endpoint of death, stroke, moderate or severe aortic regurgitation, or moderate or severe hemodynamic THV deterioration. Notably, both the COMPARE-TAVI and LANDMARK trials demonstrated the comparable performance of Myval THVs to reference THVs in terms of 1-year clinical outcomes. Despite these overall similar outcomes, it

FIGURE 6 Continued





must be emphasized that the scientific value of the LANDMARK trial is that the Myval THV series was compared with the 2 archetypes of percutaneous THVs, which are currently the most widely used balloon-expandable and self-expanding THVs in contemporary practice.

PERMANENT PACEMAKER IMPLANTATION. In the LANDMARK trial, the 1-year rate of new PPI in pacemaker-naïve patients was 17.6%, 19.2%, and 18.9% in the Myval, SAPIEN, and Evolut groups, respectively, and there were no significant differences between groups.

In comparison, in the COMPARE-TAVI trial, the rate of new PPI at 1 year was significantly higher with the Myval THV series compared with the SAPIEN THV series (Myval 21%, SAPIEN 12%; $P = 0.00024$).[14] One possible explanation for this discrepancy with the current trial is the different proportions of Myval and Myval Octacor used. In the COMPARE-TAVI trial, Myval was used in 36% and Myval Octacor in 63%, with respective PPI rates at 1 year of approximately 18.6% and 22.5%. In the LANDMARK trial, Myval was the main device used in 86%, with Myval Octacor used in only 8% in the intention-to-treat population, with respective new PPI rates of 17.2% and 22.2%.

The Cleveland group retrospectively compared high vs conventional implantation in 1,028 patients receiving a SAPIEN THV. High implantation reduced implantation depth under the noncoronary cusp from 3.2 ± 1.9 mm to 1.5 ± 1.6 mm, and concomitantly decreased the 30-day PPI rate from 13.1% to 5.5%.[29] In the LANDMARK trial, implantation depths under the noncoronary cusp were 4.3 ± 2.4 mm and 4.6 ± 2.4 mm for the Myval and SAPIEN series, respectively, which were both larger than in recent series, possibly contributing to the higher and comparable pacemaker rates between the 2 balloon-expandable valves.

In contrast, the PPI rate observed in the Evolut group of the LANDMARK trial (18.9%) is comparable to that reported in other trials and registries.[12,30,31] In the Swiss transcatheter aortic valve implantation (TAVI) registry, the rate of new PPI was 14.2% and 18.7% in those who received balloon-expandable and self-expanding THV, respectively.[31] These heterogeneous results indicate the need for further investigations to understand better the factors influencing PPI rates.

ECHOCARDIOGRAPHIC OUTCOMES. Compared with other head-to-head studies, echocardiographic assessment at 1 year was available in a high proportion of surviving patients without withdrawal (93.6%).[10,12,13,28,30,32,33] Given this, no attempt was made to impute missing values, and the results offer robust conclusions about the stable hemodynamic performance of the 2 groups over a year. The incidence of moderate or severe PVR did not differ significantly between the 2 groups, when using data from scheduled 1-year echocardiograms analyzed by core lab.

We also reported the adjudicated cumulative rate of moderate or severe prosthetic valve regurgitation as an event based on all scheduled and unscheduled echocardiograms up to 1 year. Notably, these also did not differ significantly between the 2 groups (Myval THV series: 4.2% vs contemporary THVs series: 7.1%; $P = 0.11$).

Evolut showed a higher cumulative rate of moderate or severe PVR (4.2% vs 10.5%; $P = 0.02$). This may be attributed to the fact that in the Evolut group, several iterations of device with (Pro/Pro+/FX) or without outer skirt (R) have been used in the trial. Indeed, the cumulative rate of moderate or severe PVR was 7.8% (n = 9 of 115) in the Evolut Pro/Pro+/FX and 14.3% (n = 10 of 70) in the Evolut R.

We applied the methodological approach in the COMPARE-TAVI trial[14]: "the most recently available echocardiography images were used to ascertain the degree of aortic regurgitation (at 1 year, 30 days, or postprocedure) to account for potential missing aortic regurgitation data." Notably, using this methodology in the LANDMARK trial gives respective rates of moderate and severe PVR at 1 year after TAVR with Myval of 1.9% and 0%, 2.1% and 0% with SAPIEN, and 6.0%, and 0% with Evolut, respectively (Supplemental Table 26). These results confirm that there is no significant difference in moderate or severe PVR between Myval and SAPIEN (1.9% vs 2.1%) in the LANDMARK trial.

In the LANDMARK trial, the incidence of mild PVR was similar across the 3 THVs; however, a significant difference in paravalvular regurgitation was observed between Myval and SAPIEN ($P = 0.04$) (Supplemental Table 20). Myval patients exhibited a greater rate of moderate or severe calcification on quantitative computed tomography compared with SAPIEN patients ($P = 0.019$) (Supplemental Table 13). These differences might explain the higher incidence of mild paravalvular regurgitation with Myval. However, the prognostic impact of mild paravalvular regurgitation on long-term mortality is controversial in the literature.[34-37]

Myval THVs showed a lower mean pressure gradient and higher EOA than SAPIEN THVs, with similar results at 30 days.[16] Compared with Evolut THVs, Myval THVs had a significantly higher mean pressure gradient, lower EOA, and higher incidence of moderate/severe PPM. Supra-annular self-expanding THVs generally exhibit lower mean pressure gradients and higher EOA than intra-annular balloon-expandable THVs,[38] though echocardiography may overestimate pressure gradients vs catheter measurements. While Doppler echocardiography measures the pressure gradient at the vena contracta, where the pressure reaches its nadir, catheterization measures it distal to the vena contracta, where pressure recovery occurs.[39] Both in vitro and in vivo studies have reported lower pressure gradients when measured by catheterization compared with Doppler

echocardiography.[40-42] This discrepancy is more pronounced in supra-annular self-expanding THVs than in intra-annular balloon-expandable THVs.[41,42] Therefore, a catheter-based pressure gradient study comparing these 3 different types of THVs is warranted.

PROSTHESIS-PATIENT MISMATCH. The rate of ≥moderate PPM at 1 year is significantly higher in SAPIEN than in Myval and Evolut, especially in patients with a small annulus, in which rates are higher in SAPIEN than Myval and similar between Myval and Evolut. A better and more appropriate fitting of the nominal size of the prosthesis with respect to the aortic orifice area (fitting index based on 2 objective measurements = nominal THV size diameter implanted / aortic annulus area-derived diameter) was observed in Myval when compared with SAPIEN, which is a direct consequence of the availability of intermediate valve nominal sizes.[16] While PPM is an established predictor of mortality after surgical aortic valve replacement, its impact in TAVR remains controversial, with studies reporting conflicting associations with mortality.[43] The LANDMARK trial plans to follow up patients for up to 10 years, and future analyses will provide the long-term prognostic impact of PPM.

STUDY LIMITATIONS. When assessing valve replacements, a 1-year follow-up may not detect rare but critical events related to the durability of the bioprosthetic material used. The exploratory noninferiority analysis of 1-year clinical efficacy was planned after the primary 30-day endpoint but was not prespecified in the original trial design. The noninferiority margin of 10.89% was determined based on the sum of event rates for components of clinical efficacy from previous and more recent literature; however, event rates may have been overestimated because these studies did not include the VARC-3-defined clinical efficacy endpoint. No adjustment for multiple testing was performed, and results of secondary and exploratory analyses should therefore be interpreted with caution.

Although a decrease in SF-12 was considered an unfavorable QOL outcome and included in the extended composite endpoint, an absolute cutoff value was not specified, because no established cutoff values exist for SF-12 in elderly patients undergoing TAVR.

The LANDMARK trial did not include the SAPIEN 3 Ultra Resilia, the latest generation of the SAPIEN series, because it was not available in Europe during the enrollment phase. In contrast, the Evolut R, which lacks an outer sealing skirt, was included. One inherent limitation of head-to-head comparisons between THV devices is the rapid pace of device iteration that requires repeated head-to-head comparisons.[44]

The low inclusion rate (15% [n = 768 of 5,109]) may limit generalizability. Early enrollment took place during COVID-19 restrictions, and Myval was temporarily unavailable in some countries due to litigation, which reduced the number of eligible/consented patients. Nevertheless, randomization resulted in well-balanced baseline clinical and valve characteristics between groups.

CONCLUSIONS

The lack of difference in the 3 robust 1-year endpoints—all-cause mortality, all strokes, and procedure- or valve-related hospitalizations—demonstrates that Myval compares favorably in safety and efficacy with 2 contemporary gold standard THVs. The interpretation of these results may warrant caution, as the current 1-year analyses of the LANDMARK trial, including the noninferiority assessment, are exploratory in nature.

DATA AVAILABILITY. The LANDMARK trial plans to continue follow-up for up to 10 years. Patient-level data collected for this trial will not be made publicly available but can be shared upon request after the final long-term follow-up is published.

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APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.