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ORIGINAL RESEARCH

STRUCTURAL

Aortic Valve Replacement in Women

A Pooled Analysis of the RHEIA and PARTNER 3 Trials

Helene Eltchaninoff, MD,[a] Stephan Windecker, MD,[b] Michael J. Mack, MD,[c] Philippe Pibarot, DVM,[d] Vinod H. Thourani, MD,[e] Jeroen J. Bax, MD, MSc,[f] David J. Cohen, MD,[g,h] Nikolaos Bonaros, MD,[i] Raj Makkar, MD,[j] Sabine Bleiziffer, MD,[k] Wilson Y. Szeto, MD,[l] Pierre Berthoumieu, MD,[m] Rebecca T. Hahn, MD,[h,n] Tomas Hovorka, MSc,[o] Jan Mareš, PhD,[p] Jennifer Taylor, MSc, MPhil,[q] Didier Tchetche, MD,[r] Martin B. Leon, MD.[h,s]

ABSTRACT

BACKGROUND In women with severe aortic stenosis, there are limited data regarding outcome differences following transcatheter (TAVR) vs surgical aortic valve replacement (SAVR).

OBJECTIVES The authors sought to examine outcomes of TAVR vs SAVR in a patient-level pooled analysis of women in the RHEIA and PARTNER 3 trials.

METHODS Patients in both trials were randomly allocated to a balloon-expandable SAPIEN 3/Ultra valve or to surgical bioprostheses. Individual patient data of female participants in the 2 trials were pooled. The primary endpoint was all-cause mortality, all stroke, or rehospitalization at 1 year.

RESULTS A total of 376 women were randomized to TAVR and 336 to SAVR. The mean age was ∼73 years, and the mean Society of Thoracic Surgeons (STS) score was 2.1%. Kaplan-Meier estimates of event rates at 1 year with TAVR vs SAVR were 8.5% vs 16.8% for the composite of all-cause mortality, all stroke, or rehospitalization (absolute difference −8.2%; 95% CI: −13.1% to −3.3%; $P < 0.001$), 1.1% vs 2.1% ($P = 0.27$) for all-cause mortality, 2.7% vs 3.9% ($P = 0.35$) for all stroke, and 5.4% vs 11.9% ($P = 0.002$) for rehospitalization. The composite endpoint of all-cause death or stroke was similar between the 2 treatment groups: 3.5% vs 5.4% (absolute difference −1.9%; 95% CI: −5.0% to 1.1%; $P = 0.21$).

CONCLUSIONS Among women with symptomatic severe aortic stenosis, TAVR led to a reduction in the rate of the combined endpoint of all-cause mortality, stroke, or rehospitalization at 1-year follow-up, largely due to a significant reduction in the rate of rehospitalization. (JACC Cardiovasc Interv. 2025;18:1540–1553) © 2025 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Univ Rouen Normandie, Inserm U 1096, CHU Rouen, Department of Cardiology, Rouen, France; [b]Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland; [c]Baylor Scott & White Health, Plano, Texas, USA; [d]Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; [e]Piedmont Heart Institute, Atlanta, Georgia, USA; [f]Leiden University Medical Center, Leiden, the Netherlands; [g]St. Francis Hospital, Roslyn, New York, USA; [h]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York, USA; [i]Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria; [j]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA; [k]Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center North Rhine-Westphalia, Bad Oeynhausen, Germany; [l]Perelman School of Medicine at the University of Pennsylvania, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [m]Department of Cardiac and Thoracic Surgery, Clinic Pasteur, Toulouse, France; [n]Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA; [o]Edwards Lifesciences, Prague, Czech Republic; [p]Department of Data Science, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [q]Edwards Lifesciences, London, United Kingdom; [r]Clinique Pasteur Toulouse, France; and the [s]Columbia University Irving Medical Center, New York, New York, USA.

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Half of all patients with severe aortic stenosis (AS) are women.[1,2] However, women are less likely to be referred for aortic valve replacement (AVR),[3] and less likely to receive AVR treatment.[2] Women have been underrepresented in cardiovascular trials[4] including trials of heart valve devices,[5] which is particularly concerning given that AS has distinct characteristics in women compared with men. Women present with less aortic valve calcification but more valvular fibrosis than men.[6,7] In addition, women have smaller aortic annuli, and are more likely to display concentric left ventricular (LV) remodeling, a larger extent of diffuse myocardial fibrosis, better preservation of left ventricular ejection fraction (LVEF), and more paradoxical low-flow, low-gradient AS.[6,7]

The RHEIA trial (Randomized researcH in womEn all comers wIth Aortic stenosis; NCT04160130), conducted in 12 European countries, was the first prospective, randomized controlled trial comparing outcomes of transcatheter aortic valve replacement (TAVR) with a balloon-expandable valve vs surgical aortic valve replacement (SAVR) exclusively in women with symptomatic severe AS and demonstrated a significant reduction in the composite of death, stroke, or rehospitalization at 1-year follow-up with TAVR compared with SAVR.[8] The PARTNER 3 trial (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114), conducted in the United States, Australia, Canada, Japan, and New Zealand, demonstrated the superiority of TAVR with a balloon-expandable valve compared with SAVR for the composite of death, stroke, or rehospitalization at 1 year in women and men with symptomatic severe AS at low surgical risk.[9] A subgroup analysis of PARTNER 3 suggested that the benefit of TAVR over SAVR might be greater in women compared with men although statistical testing did not reveal a significant interaction.

In order to better understand the outcomes of TAVR vs SAVR in women, we sought to pool individual patient data from RHEIA and the female cohort of PARTNER 3. By conducting analyses in a larger and more diverse population, which has been studied using similar primary endpoint definitions and the same echocardiography core laboratory, the study aimed to provide estimates of event rates and their differences with precision and confidence exceeding those provided by either of the trials alone.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

EOA = effective orifice area

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

PPM = patient-prosthesis mismatch

PVR = paravalvular regurgitation

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

METHODS

RHEIA and PARTNER 3 were prospective, multicenter, randomized controlled trials of TAVR vs SAVR in patients with symptomatic severe AS. The main differences between the 2 trials were that RHEIA enrolled exclusively women across the surgical risk spectrum, whereas PARTNER 3 enrolled men and women at low surgical risk (Society of Thoracic Surgeons [STS] score <4%). In the PARTNER 3 trial, patients were enrolled from March 2016 through October 2017, whereas in the RHEIA trial, patients were enrolled from November 2019 through April 2023. For both trials, all patients provided written informed consent before participation, and the protocol was approved by the institutional review board at each site. The design, baseline characteristics, and primary results of the 2 trials have been published previously.[8-10] Pooling of data from female patients enrolled in the 2 trials was facilitated by several factors: 1) age and surgical risk of enrolled patients were similar between the 2 trials; 2) both trials randomized patients to undergo TAVR with the balloon-expandable SAPIEN 3 or SAPIEN 3 Ultra system (Edwards Lifesciences) or SAVR with any commercially available bioprosthetic valve; 3) endpoint definitions were similar across the 2 trials; and 4) both trials used the Quebec Heart & Lung Institute, Quebec, Canada as an echocardiography core laboratory.

PATIENTS. In both trials, patients were eligible for inclusion if they had symptomatic severe AS and were suitable for transfemoral TAVR with the balloon-expandable SAPIEN 3 or SAPIEN 3 Ultra system (Edwards Lifesciences) or SAVR with any commercially available bioprosthetic valve. Patients with unicuspid, bicuspid, or noncalcified aortic valves, complex coronary artery disease, or other anatomical features that suggested an increased risk of complications with either TAVR or SAVR were excluded

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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from both trials. A full list of inclusion and exclusion criteria has been published previously.[8-10]

RANDOMIZATION AND PROCEDURES. Both trials randomly assigned eligible patients, in a 1:1 ratio, to undergo either transfemoral TAVR with the SAPIEN 3 or SAPIEN 3 Ultra system or SAVR with a commercially available bioprosthetic valve. The SAPIEN 3 and SAPIEN 3 Ultra system and the procedures for TAVR and SAVR have been described previously.[11]

ANALYTIC COHORT AND ENDPOINTS. The primary endpoint for this pooled analysis was the same as the primary endpoint for both trials—the composite of all-cause mortality, all stroke, or rehospitalization at 1 year. Rehospitalization was defined as any hospitalization related to the procedure, the valve, or heart failure. Key secondary endpoints were the composite of all-cause mortality or all stroke at 1 year, and the individual components of the primary endpoint.

Other endpoints included: 1) length of the index hospitalization; 2) Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score[12] at 30 days and 1 year; 3) alive and well, defined as alive with KCCQ ≥75 and no decrease from baseline ≥10 points at 1 year;[13] 4) life-threatening or major bleeding at 1 year; 5) acute kidney injury (stage 2 and 3) at 30 days; and 6) new permanent pacemaker implantation at 1 year. Echocardiographic outcomes were assessed by the central core laboratory at baseline, 30 days, and 1 year, and included: 1) mean aortic valve gradient; 2) effective orifice area (EOA); 3) LVEF; 4) LVEF <50% (LV systolic dysfunction); 5) paravalvular regurgitation (PVR); 6) total aortic regurgitation; and 7) patient-prosthesis mismatch (PPM).

STATISTICAL ANALYSES. All analyses compared patients who were assigned to TAVR vs SAVR. Analyses of baseline characteristics, procedural data, primary outcomes, and additional clinical outcomes (except KCCQ) were performed in the pooled as-treated population, defined as patients in whom the allocated procedure was initiated, whether completed or not. Analyses of KCCQ and echocardiographic outcomes were performed in the valve implant pooled population, defined as patients who successfully received a valve according to the allocated randomization arm.

Variables are summarized as counts and percentages, means with standard deviations, means with standard errors, or medians and quartiles. Confidence limits were computed using the exact binomial distribution for binary variables, and the t-distribution for continuous variables. Groups were compared using Fisher exact test or the chi-square test for categorical variables, *t*-tests for continuous variables (unless otherwise noted), and the Wilcoxon rank sum test for ordinal variables (eg, NYHA functional class and valve regurgitation). Comparisons of follow-up KCCQ scores were performed using analysis of covariance, adjusted for baseline values. Time-to-event outcomes were evaluated using the Kaplan-Meier method with confidence intervals for event rates at given times calculated from the *Z* statistic based on the Greenwood standard error and with log-rank test *P* values.

In addition to the overall comparisons of TAVR vs SAVR in the pooled female population, stratified analyses were performed to assess for heterogeneity of treatment effects among subgroups defined based on age (≤75 and >75 years) and systolic annular area (≤430 mm^2 and >430 mm^2) determined by a computed tomography core lab. These analyses, focused on time-to-event outcomes, were performed by including an interaction term in the Cox model used to perform the overall treatment comparisons.

Analyses were performed using statistical package R (version 4.2.0, R Foundation for Statistical Computing). Data are available upon reasonable request from the corresponding author.

RESULTS

BASELINE CHARACTERISTICS. The pooled analysis included 712 women, enrolled from 17 countries. In the as-treated populations of the 2 trials, 376 were randomized to TAVR (RHEIA n = 215; PARTNER 3 n = 161) and 336 were randomized to SAVR (RHEIA n = 205; PARTNER 3 n = 131). Baseline characteristics of the as-treated population are outlined in **Table 1**. Baseline characteristics were well balanced between the TAVR and SAVR groups. The mean age was ~73 years, and the mean STS score was 2.1%, indicating a largely low surgical risk population.

PROCEDURAL DATA. In the as-treated population, concomitant procedures were performed in 12 of 376 patients (3.2%) in the TAVR arm vs 64 of 336 (19.0%) in the SAVR arm ($P < 0.001$). Implanted valve sizes are listed in Supplemental Table 1. The proportion of valve sizes ≤21 mm was 50.3% in the surgical arm and 5.6% in the TAVR arm.

PRIMARY OUTCOME AND KEY SECONDARY OUTCOMES. One-year follow-up data were available for 95.6% of patients. At 1-year follow-up, the composite primary endpoint of all-cause death, all stroke, or rehospitalization was less frequent among patients

TABLE 1 Baseline Characteristics by Treatment Arm Among the As-Treated Population

	TAVR (n = 376)	SAVR (n = 336)	*P* Value
Age, y	73.4 ± 4.78 (376)	73.3 ± 5.18 (336)	0.81
≤75 y	67.8 (255/376)	64.6 (217/336)	0.38
BMI, kg/m^2	29.9 ± 5.95 (376)	30.2 ± 5.95 (336)	0.52
STS score, %	2.1 ± 0.95 (375)	2.1 ± 1.06 (330)	0.74
EuroSCORE II, %	1.7 ± 1.18 (375)	1.7 ± 1.03 (334)	0.78
NYHA functional class			0.75[a]
I	2.7 (10/376)	1.5 (5/336)	
II	61.2 (230/376)	64.3 (216/336)	
III or IV	36.2 (136/376)	34.2 (115/336)	
Coronary artery disease	14.9 (56/376)	17.9 (60/336)	0.31
Stroke or cerebrovascular accident	4.3 (16/376)	4.8 (16/336)	0.86
Carotid disease[b]	5.6 (21/372)	5.4 (18/333)	>0.99
Peripheral vascular disease	4.0 (15/376)	4.8 (16/335)	0.71
COPD	3.2 (12/376)	4.8 (16/336)	0.34
Creatinine >2 mg/dL	0.0 (0/376)	0.0 (0/336)	>0.99
Diabetes mellitus	25.5 (96/376)	26.6 (89/335)	0.80
Atrial fibrillation[c]	6.1 (23/376)	7.8 (26/333)	0.38
Pulmonary hypertension	3.2 (12/375)	5.1 (17/336)	0.26
Prior permanent pacemaker	1.6 (6/376)	3.6 (12/333)	0.10

Values are mean ± SD (n) or % (n/N). [a]Wilcoxon rank sum test. [b]Defined as history of carotid disease in PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis), or carotid artery stenosis (>50%) comorbidity in RHEIA (Randomized researcH in womEn all comers wIth Aortic stenosis). [c]Defined as a history of atrial fibrillation in PARTNER 3, or a rhythm category on baseline electrocardiogram (ECG) assessment in RHEIA.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

randomized to TAVR vs SAVR (8.5% vs 16.8%; absolute difference −8.2%; 95% CI: −13.1% to −3.3%; $P < 0.001$). One-year event rates with TAVR vs SAVR were 5.4% vs 11.9% for rehospitalization (absolute difference −6.5%; 95% CI: −10.7% to −2.3%; $P = 0.002$), with no significant differences between groups for the composite of all-cause mortality or all stroke; the composite of all-cause death or disabling stroke; all-cause mortality; or all stroke (**Table 2**, **Figure 1**).

OTHER OUTCOMES. The mean length of the index hospitalization was significantly shorter with TAVR vs SAVR (4.4 ± 4.0 days vs 9.3 ± 4.7 days, respectively; $P < 0.001$). Changes from baseline in NYHA functional class, the KCCQ overall summary score, and the alive and well outcome at 1 year are shown in **Figure 2** and Supplemental Tables 2 and 3. Patients in the TAVR group had a significantly lower incidence of life-threatening or major bleeding compared with the SAVR group at 30 days (2.4% vs 15.8%; $P < 0.001$) and 1 year (3.5% vs 16.7%; $P < 0.001$) (**Table 2**). No statistically significant differences were observed between groups in the incidences of acute kidney injury stage 2/3 or new permanent pacemaker implantation at either time point (new permanent pacemaker at 1 year: 6.8% vs 5.0% with TAVR vs SAVR; $P = 0.31$) (**Table 2**).

ECHOCARDIOGRAPHIC OUTCOMES. Mean transvalvular gradient was significantly higher with TAVR than SAVR at 30 days (13.4 ± 0.3 mm Hg vs 11.4 ± 0.3 mm Hg; $P < 0.001$) and 1 year (14.5 ± 0.3 mm Hg vs 12.0 ± 0.3 mm Hg, respectively; $P < 0.001$) (**Figure 3A**, Supplemental Table 4). EOA was significantly smaller with TAVR compared with SAVR at 30 days (1.7 ± 0.0 cm^2 vs 1.8 ± 0.0 cm^2; $P = 0.03$) and 1 year (1.6 ± 0.0 cm^2 vs 1.7 ± 0.0 cm^2; $P = 0.04$) (**Figure 3A**, Supplemental Table 4). The incidence of moderate or severe PVR with TAVR vs SAVR was 0.6% vs 0.0% ($P = 0.50$) at 30 days, and 0.9% vs 0.4% ($P = 0.63$) at 1 year (**Figure 3B**, Supplemental Table 4). The incidence of mild PVR with TAVR vs SAVR was 20.3% vs 2.6% ($P < 0.001$) at 30 days and 19.5% vs 1.8% ($P < 0.001$) at 1 year (**Figure 3B**, Supplemental Table 4). At 30 days, severe PPM was observed in 3.4% with TAVR and 5.6% with SAVR ($P = 0.24$), whereas moderate PPM was observed in 22.3% and 17.5% of patients, respectively ($P = 0.16$) (**Figure 3C**, Supplemental Table 4).

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TABLE 2 Key Clinical Outcomes Among the As-Treated Population

Event	30 Days				1 Year			
	TAVR (n = 376)	SAVR (n = 336)	Difference[a] of KM Rate, % (TAVR − SAVR)	*P* Value[b]	TAVR (n = 376)	SAVR (n = 336)	Difference[a] of KM Rate, % (TAVR − SAVR)	*P* Value[b]
All-cause death, all stroke, or rehospitalization[c]	18 (4.8)	32 (9.5)	−4.7 [−8.6 to −0.9]	0.01	32 (8.5)	56 (16.8)	−8.2 [−13.1 to −3.3]	<0.001
All-cause death, disabling stroke, or rehospitalization[c]	14 (3.7)	26 (7.7)	−4.0 [−7.5 to −0.6]	0.02	26 (6.9)	49 (14.7)	−7.7 [−12.3 to −3.2]	<0.001
All-cause death or all stroke	7 (1.9)	11 (3.3)	−1.4 [−3.8 to 0.9]	0.23	13 (3.5)	18 (5.4)	−1.9 [−5.0 to 1.1]	0.21
All-cause death or disabling stroke	3 (0.8)	4 (1.2)	−0.4 [−1.9 to 1.1]	0.60	6 (1.6)	10 (3.0)	−1.4 [−3.6 to 0.8]	0.21
All-cause death	2 (0.5)	4 (1.2)	−0.7 [−2.0 to 0.7]	0.34	4 (1.1)	7 (2.1)	−1.0 [−2.9 to 0.8]	0.27
Cardiovascular death	2 (0.5)	4 (1.2)	−0.7 [−2.0 to 0.7]	0.34	3 (0.8)	4 (1.2)	−0.4 [−1.9 to 1.1]	0.59
Noncardiovascular death	0 (0.0)	0 (0.0)	0.0 [0.0 to 0.0]	>0.99	1 (0.3)	3 (0.9)	−0.6 [−1.8 to 0.5]	0.26
All stroke	5 (1.3)	8 (2.4)	−1.0 [−3.1 to 1.0]	0.29	10 (2.7)	13 (3.9)	−1.2 [−3.9 to 1.4]	0.35
Disabling stroke	1 (0.3)	1 (0.3)	0.0 [−0.8 to 0.8]	0.94	2 (0.5)	5 (1.5)	−1.0 [−2.5 to 0.5]	0.20
Nondisabling stroke	4 (1.1)	7 (2.1)	−1.0 [−2.9 to 0.8]	0.27	8 (2.2)	8 (2.4)	−0.2 [−2.4 to 2.0]	0.80
Rehospitalization[c]	11 (3.0)	22 (6.7)	−3.7 [−6.9 to −0.5]	0.02	20 (5.4)	39 (11.9)	−6.5 [−10.7 to −2.3]	0.002
Aortic valve reintervention	2 (0.5)	0 (0.0)	0.5 [−0.2 to 1.3]	0.18	2 (0.5)	1 (0.3)	0.2 [−0.7 to 1.2]	0.63
Endocarditis	0 (0.0)	1 (0.3)	−0.3 [−0.9 to 0.3]	0.29	1 (0.3)	1 (0.3)	0.0 [−0.8 to 0.8]	0.93
Valve thrombosis	3 (0.8)	0 (0.0)	0.8 [−0.1 to 1.7]	0.10	5 (1.3)	1 (0.3)	1.0 [−0.3 to 2.3]	0.13
New onset atrial fibrillation[d]	9 (2.6)	72 (23.3)	−20.7 [−25.7 to −15.7]	<0.001	14 (4.0)	73 (23.6)	−19.6 [−24.8 to −14.5]	<0.001
New permanent pacemaker implantation[d]	23 (6.2)	14 (4.3)	1.9 [−1.4 to 5.2]	0.27	25 (6.8)	16 (5.0)	1.8 [−1.7 to 5.3]	0.31
Life-threatening or major bleeding	9 (2.4)	53 (15.8)	−13.4 [−17.6 to −9.2]	<0.001	13 (3.5)	56 (16.7)	−13.2 [−17.6 to −8.8]	<0.001
Acute kidney injury - stage 2/3	2 (0.5)	7 (2.1)	−1.6 [−3.3 to 0.1]	0.06	3 (0.8)	8 (2.4)	−1.6 [−3.5 to 0.3]	0.09
Myocardial infarction	1 (0.3)	5 (1.5)	−1.2 [−2.6 to 0.2]	0.08	1 (0.3)	6 (1.8)	−1.5 [−3.1 to 0.0]	0.04

Values are n (%) of subjects with the Kaplan-Meier estimate. Imputed dates are used for events with incomplete onset dates. [a]The 95% CI for the difference is calculated from the Z-statistic based on the Greenwood standard error. [b]*P* value is calculated from log-rank statistic. [c]Rehospitalization (valve-related or procedure-related or worsening congestive heart failure). [d]Subjects with the medical condition at baseline were excluded.

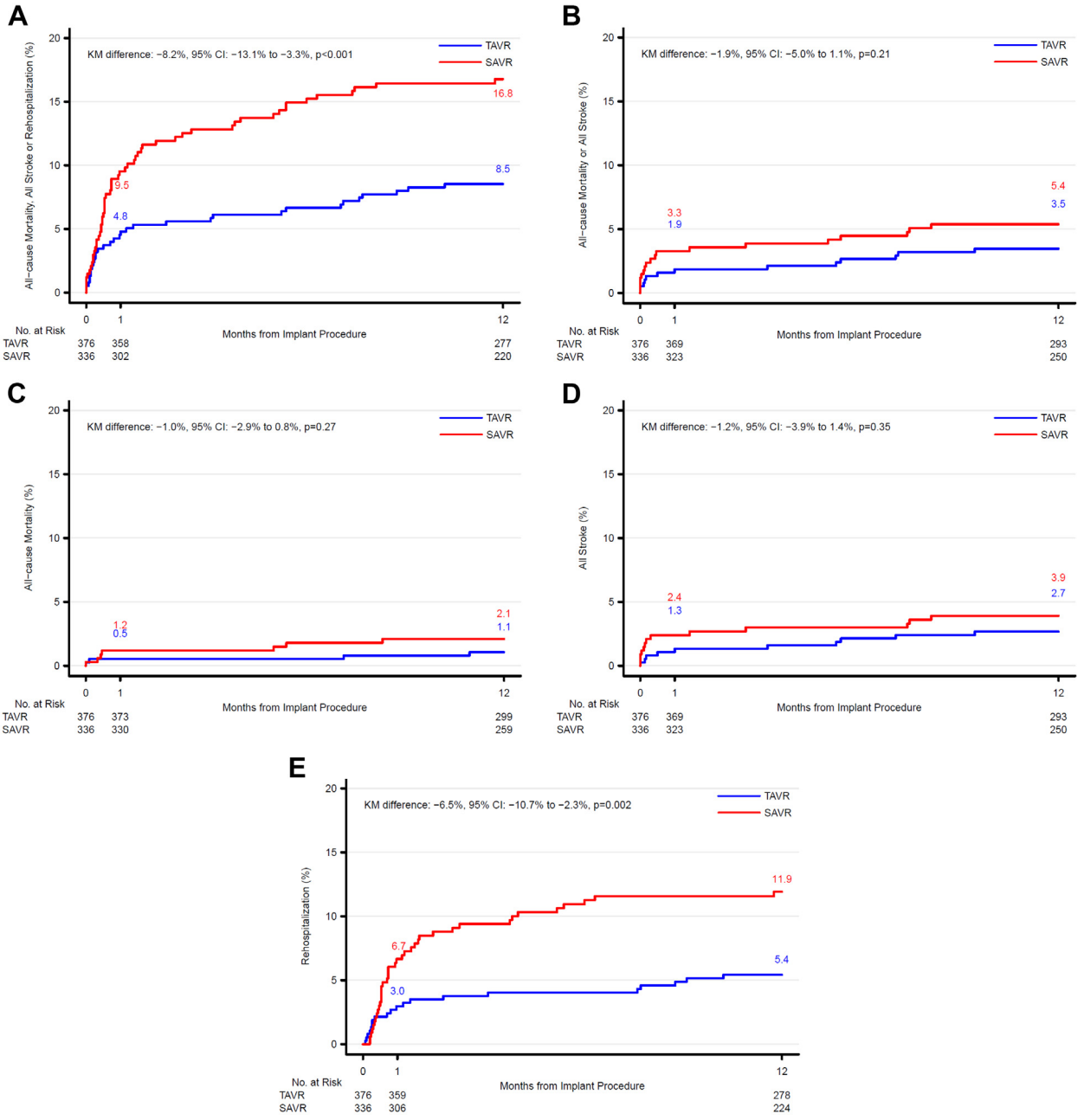
KM = Kaplan-Meier; other abbreviations as in Table 1.

SUBGROUP ANALYSES. Subgroup analyses of the primary endpoint at 1 year showed no heterogeneity of treatment effect in any of the subgroups examined (**Figure 4A**, Supplemental Figure 1A). Subgroup analyses of the composite of all-cause mortality or all stroke at 1 year showed heterogeneity of treatment effect by systolic annular area; *P* for interaction = 0.01 (**Figure 4B**, Supplemental Figure 1B). For the composite of all-cause death or all stroke, Kaplan-Meier estimates of event rates at 1 year with TAVR vs SAVR were 2.4% vs 6.5% (absolute difference −4.1%; 95% CI: −7.9% to −0.3%) in women with systolic annular area ≤430 mm^2 (n = 466/694; 67.1%) and 6.0% vs 0.9% (absolute difference 5.1%; 95% CI: 0.5% to 9.8%) in women with systolic annular area >430 mm^2 (n = 228/694; 32.9%) (**Table 3**, Supplemental Figure 1).

DISCUSSION

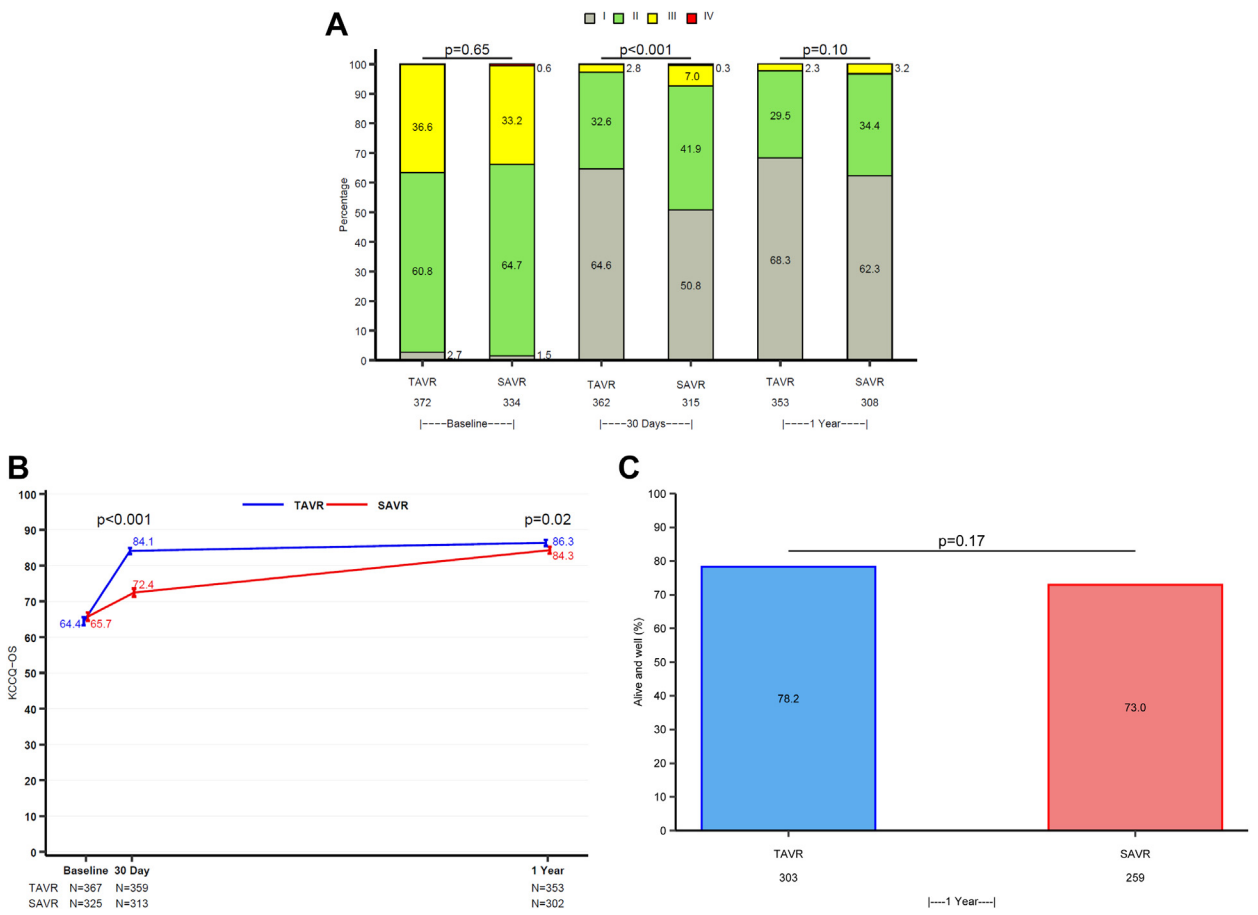
In this patient-level pooled analysis of women with symptomatic severe AS who were randomized to TAVR with the balloon-expandable SAPIEN 3 or SAPIEN 3 Ultra system, or SAVR, the principal results were as follows. First, there was a significantly lower incidence of the primary endpoint of all-cause mortality, all stroke, or rehospitalization with TAVR vs SAVR, driven mainly by a lower rate of rehospitalization during the first 30 days of follow-up (**Central Illustration**). Second, in small and large annulus patients, clinical outcome findings were discordant. Women with a small annulus, who represented approximately two-thirds of the whole cohort, had a lower incidence of the composite of death and stroke with TAVR vs SAVR, whereas women with a large annulus had a significantly higher incidence of the composite of mortality and stroke with TAVR vs SAVR (*P* for interaction = 0.01). Third, women undergoing TAVR spent less time in hospital, and had significantly better early quality of life compared with those receiving SAVR with no clinically meaningful difference seen at 1 year. Fourth, women receiving TAVR had lower rates of bleeding and similar rates of new permanent pacemaker implantation compared with those undergoing SAVR. Last, rates of moderate or severe

FIGURE 1 **Cumulative Incidence of the Primary Endpoint and Key Secondary Endpoints**



Kaplan-Meier (KM) estimated cumulative incidence with KM difference, 95% CI and *P* value of the primary endpoint, which was all-cause mortality, all stroke, or rehospitalization (A),and key secondary endpoints, which were all-cause mortality or all stroke (B), all-cause mortality (C), all stroke (D), and rehospitalization for valve-related or procedure-related symptoms or congestive heart failure (E) in patients who underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). Imputed dates are used for events with incomplete onset dates. Incomplete onset dates were imputed by procedure date if the partial date aligned with the procedure or onset year was missing; otherwise, the earliest possible date (1st of January or first of the onset month) was used.

FIGURE 2 Functional and Quality-of-Life Outcomes



NYHA functional class at baseline, 30 days, and 1 year in patients who underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) is shown in A. The mean Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) scores at baseline, 30 days, and 1 year are shown in B, and the percentage of patients who were alive with a KCCQ-OS score of 75 or higher and no decrease from baseline ≥10 points at 1 year (alive and well endpoint) are shown in C. KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status.

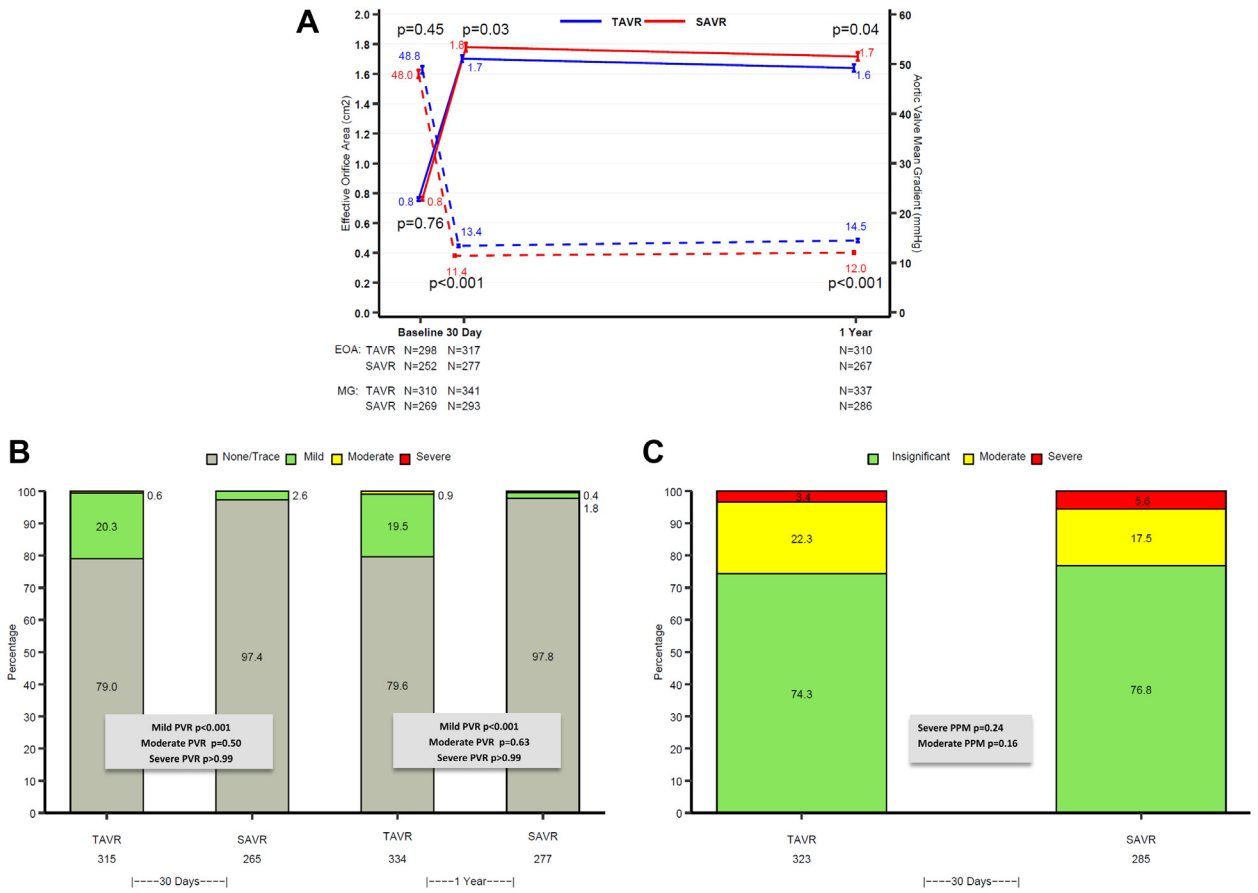
PVR were low and similar although there was a significantly higher incidence of mild PVR with TAVR.

There have been limited data on the outcomes of medical devices in women, a gap raised by the U.S. Food and Drug Administration (FDA) as being important to address.[14] This study was conducted to generate further knowledge on outcome differences following TAVR vs SAVR in women with severe AS. The study pooled together female patients in the RHEIA trial, which enrolled exclusively women across the surgical risk spectrum, and the PARTNER 3 trial, which enrolled men and women at low surgical risk. The findings of this study reflect the excellent outcomes that can be achieved in contemporary clinical practice with both TAVR and SAVR. Despite being performed in different regions of the world with heterogeneous practice patterns and at varying time points, the RHEIA and PARTNER 3 trials demonstrated consistent results in patients of a similar age and surgical risk profile, which are aligned with the results of the current pooled analysis in women.

In this study, the significant difference in clinical endpoints between TAVR and SAVR was for rehospitalization, where TAVR was superior to SAVR at both 30 days and 1 year, with the majority of benefit occurring in the first month after the procedure. Rehospitalization is a substantial contributor to health care costs,[15] and is an important priority for young patients with active lifestyles.

Our finding that TAVR and SAVR performed equally well on the composite outcome of all-cause death or all stroke is at variance with the DEDICATE

FIGURE 3 Echocardiographic Parameters



Echocardiographic parameters assessed by an echocardiography core laboratory are shown, including the aortic valve mean gradients (MGs) and mean effective orifice areas (EOAs) (A), paravalvular regurgitation (PVR) rates (B), and patient-prosthesis mismatch (PPM) at 30 days (C) in patients who underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).

trial (Randomized, Multicenter, Event-Driven Trial of TAVI versus SAVR in Patients with Symptomatic Severe Aortic-Valve Stenosis), which enrolled intermediate- and low-risk patients with a mean age of 74 years and median STS score = 1.8%.[16] In a subgroup analysis in women (who comprised 43% of participants), the incidence of all-cause death or fatal/nonfatal stroke at 1 year in the intention-to-treat population was 16 of 306 (5.2%) with TAVR vs 33 of 298 (11.1%) with SAVR, for a hazard ratio of 0.46 (95% CI: 0.25-0.81). In the current pooled analysis, the incidence of all-cause death or all stroke at 1 year was 3.5% with TAVR and 5.4% with SAVR. The much lower incidence in the SAVR arm of our analysis compared with that of DEDICATE may explain the discrepancy in these results. In fact, the good performance of SAVR in our pooled analysis is in line with contemporary surgical data in young, low-risk patients in the STS registry.[17] The STS analysis enrolled 42,586 patients undergoing SAVR between 2011 and 2019, with a mean age of 74.3 years and mean STS score of 1.9%, of whom 44.2% were female. The overall Kaplan-Meier time-to-event analysis for all-cause mortality at 1 year was 2.6%, whereas in our pooled analysis, it was 2.1%.

In this study, women with a small annulus, who represented two-thirds of the total cohort, had a significantly lower incidence of mortality and stroke at 1 year with TAVR compared with SAVR. Furthermore, in the SAVR arm, the proportion of small

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FIGURE 4 Subgroup Analyses of Clinical Endpoints at 1 Year

A

Subgroups:	No. of Patients	TAVR KM (%)	SAVR KM (%)	Hazard Ratio (95% CI)	Interaction P value[a]
Age					0.60
Age > 75	240	9.2	15.2	0.60 [0.30 - 1.22]	
Age ≤ 75	472	8.2	17.6	0.47 [0.28 - 0.77]	
Systolic Annular Area[b]					0.71
Systolic annular area > 430mm²	228	8.6	18.1	0.48 [0.23 - 0.97]	
Systolic annular area ≤ 430mm²	466	8.8	15.4	0.57 [0.34 - 0.95]	
STS Score					0.92
STS score > 4	29	13.3	28.6	0.47 [0.10 - 2.16]	
STS score ≤ 4	676	8.4	16.6	0.50 [0.33 - 0.77]	
Aortic Valve Mean Gradient					0.28
AoV mean gradient < 40mmHg	150	7.8	23.3	0.33 [0.14 - 0.80]	
AoV mean gradient ≥ 40mmHg	435	8.0	13.8	0.58 [0.34 - 1.02]	
Left Ventricular Ejection Fraction					0.86
LVEF < 50%	20	9.1	22.2	0.41 [0.04 - 3.82]	
LVEF ≥ 50%	540	8.6	16.7	0.52 [0.32 - 0.82]	

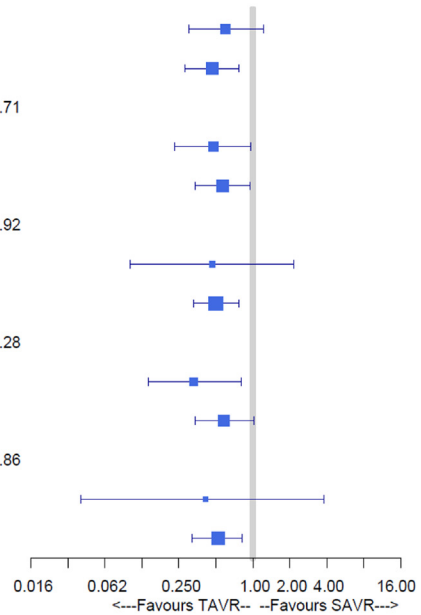

TABLE 3 Primary Endpoint and Key Secondary Endpoints According to Annulus Size Among the Valve Implant Population

Systolic Annular Area	Event at 1 Year	TAVR ($n_{\leq 430}$ = 251, $n_{>430}$ = 116)	SAVR ($n_{\leq 430}$ = 215, $n_{>430}$ = 112)	Difference[a] of KM Rate, % (TAVR − SAVR)
≤430 mm² (n = 466)	All-cause death, all stroke, or rehospitalization[b]	22 (8.8)	33 (15.4)	−6.6 [−12.6 to −0.6]
	All-cause death or all stroke	6 (2.4)	14 (6.5)	−4.1 [−7.9 to −0.3]
	All-cause death	3 (1.2)	5 (2.3)	−1.1 [−3.6 to 1.3]
	All stroke	4 (1.6)	10 (4.7)	−3.1 [−6.3 to 0.2]
	Rehospitalization[b]	16 (6.5)	19 (9.1)	−2.6 [−7.6 to 2.3]
>430 mm² (n = 228)	All-cause death, all stroke, or rehospitalization[b]	10 (8.6)	20 (18.1)	−9.5 [−18.3 to −0.7]
	All-cause death or all stroke	7 (6.0)	1 (0.9)	5.1 [0.5 to 9.8]
	All-cause death	1 (0.9)	0 (0.0)	0.9 [−0.8 to 2.5]
	All stroke	6 (5.2)	1 (0.9)	4.3 [−0.1 to 8.7]
	Rehospitalization[b]	4 (3.5)	20 (18.1)	−14.6 [−22.5 to −6.7]

Values are n (%) of subjects with the Kaplan-Meier estimate. Imputed dates are used for events with incomplete onset dates. [a]The 95% CI for the difference is calculated from the Z statistic based on the Greenwood standard error. [b]Rehospitalization (valve-related or procedure-related or worsening congestive heart failure).

Abbreviations as in Tables 1 and 2.

surgical bioprosthetic valves (≤21 mm) was high (50.3%) and even more (63.7%) in the subgroup with a small annulus, which may negatively impact the long-term management of these patients. Indeed, several studies reported a higher incidence of mortality following valve-in-valve procedures in patients with failed surgical bioprosthetic valves of small size and/or with pre-existing severe PPM.[18,19] However, in the current analysis, in women with a small annulus, observed rates of rehospitalization at 1 year were similar with TAVR and SAVR. By contrast, the incidence of the all-cause death or all stroke endpoint was significantly higher with TAVR vs SAVR in women with a larger annulus. The large annulus subgroup in this all-female population was relatively small with limited statistical power; therefore, these findings should be interpreted with caution and corroborated in larger populations.

A number of recent TAVR trials have focused on patients with a small annulus, of which the majority were women. In the VIVA trial (Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement for Treating Elderly Patients With Severe Aortic Stenosis and Small Aortic Annuli) of patients with a small annulus (93% women, mean age 75.5 years, median STS score 2.5%), rates of death, stroke, and the composite of death or stroke were similar for TAVR and SAVR at 30 days and a median follow-up of 2 years.[20] Patients undergoing TAVR had a significantly lower incidence of major/life-threatening bleeding at 30 days compared with SAVR (9.1% vs 21.6%; $P = 0.03$) and demonstrated a more rapid improvement in quality of life, with a significant benefit over SAVR at 30 days that disappeared at 1- and 2-year follow-up. In our women-only study, it was reassuring to find that rates of permanent pacemaker implantation in the TAVR arm remained low and single-digit at both 30 days (6.2%) and 1 year (6.8%), with no statistical difference with SAVR at either time point. In contrast to our study, the SMART trial (SMall Annuli Randomized To Evolut or SAPIEN Trial) in patients with a small annulus (mean age 80 years, mean STS score = 3.3%), which enrolled 87% women, reported double-digit 30-day and 1-year permanent pacemaker implantation rates of 12.1% and 14% with self-expanding Evolut PRO/PRO+/FX valves compared with 7.8% and 9.3% with SAPIEN 3/SAPIEN 3 Ultra valves.[21]

In this study, women who received TAVR had a shorter hospital stay (4.4 days with TAVR vs 9.3 days with SAVR) and had a more rapid improvement in quality of life compared with those undergoing SAVR. Although there was a statistically significant difference in KCCQ overall summary scores at 1 year, it is unlikely to be clinically different. The categorical alive and well endpoint was similar between treatment arms at 1 year.

Echocardiographic outcomes were excellent in the surgical and TAVR arms of this study, especially in the context of a female-only population. There was a statistically significant difference in EOA, mean gradient, and mild paravalvular regurgitation, whereas absolute differences were small and unlikely clinically meaningful. It has been reported that mild PVR using a 3-class grading system is not associated with worse clinical outcomes including mortality, although mild-moderate PVR using a 5-class grading system has been associated with impaired outcomes but was not

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CENTRAL ILLUSTRATION **Aortic Valve Replacement in Female Patients**

1-Year Outcomes of Women Randomized to Transcatheter (n = 376) or Surgical (n = 336) Aortic Valve Replacement in a Pooled Analysis of the RHEIA and PARTNER 3 Trials

Study Population

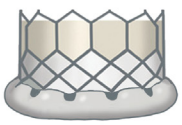
- All comers
- Enrolled from 17 countries
- Mean age ~73 years
- Mean Society of Thoracic Surgeons score 2.1%

♀ 712

Randomized 1:1

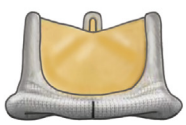
TAVR

Third-generation balloon-expandable system

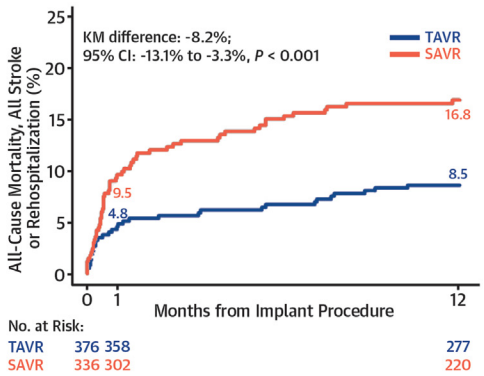


SAVR

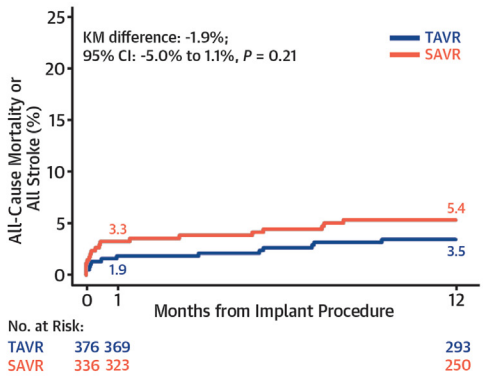
Any commercially available bioprosthetic valve



Primary Composite Endpoint: Death, Stroke, or Rehospitalization at 1 Year



Key Secondary Endpoint: Death or Stroke at 1 Year



- Among women with symptomatic, severe AS, TAVR was associated with a lower rate of the combined endpoint of all-cause mortality, stroke, or rehospitalization at 1 year, compared with SAVR (8.5% vs 16.8%; $P < 0.001$).
- The difference observed in the primary composite endpoint was largely due to a significantly lower rate of rehospitalization with TAVR (5.4% vs 11.9% with SAVR; $P = 0.002$).

Eltchaninoff H, et al. JACC Cardiovasc Interv. 2025;18(12):1540-1553.

1-year outcomes of women randomized to transcatheter aortic valve replacement (TAVR) (n = 376) or surgical aortic valve replacement (SAVR) (n = 336) aortic valve replacement in a pooled analysis of the RHEIA (Randomized researcH in womEn all comers wIth Aortic stenosis) and PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis) trials. AS = aortic stenosis.

assessed in the present study.[22,23] Rates of moderate or severe PVR were very low with both TAVR and SAVR (<1.0%) in this study, which is reassuring, given the impact of this endpoint on clinical outcomes.[22]

In this study, the comparative treatment effects of TAVR vs SAVR were consistent regardless of age; *P* for interaction = 0.60 (**Figure 4A**). The 2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery Guidelines (EACTS)[24] and 2020 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines[25] for the management of severe AS endorse different age cutoff values for TAVR vs SAVR, despite limited evidence.[26] ESC/EACTS guidelines recommend SAVR for patients <75 years at low risk for surgery and TAVR for patients 75 years or older.[24] By contrast, the ACC/AHA guidelines recommend SAVR for patients <65 years, TAVR for patients ≥80 years, and shared decision-making for those for aged 65 to 80 years.[25] Updated ESC/EACTS guidelines are due to be published in 2025. Although this pooled analysis is limited to 1-year follow-up, it is worth noting that with additional data from the current pooled analysis and the RHEIA, NOTION-2 (Nordic Aortic Valve Intervention), and DEDICATE trials,[8,16,27] the totality of evidence suggests that TAVR as an alternative to SAVR in younger patients deserves reconsideration in upcoming guidelines. TAVR has demonstrated rates of mortality, stroke, and rehospitalization equivalent to SAVR with lower rates of bleeding and new-onset atrial fibrillation, earlier improvement in quality of life, and a shorter hospital stay compared with SAVR. The current study also demonstrated that low, and similar, rates of permanent pacemaker implantation and moderate or severe PVR can be achieved with TAVR and SAVR.

STUDY LIMITATIONS. First, it excluded women with unicuspid and bicuspid valves, or other anatomical or clinical factors that increase the risk of complications associated with either TAVR or SAVR. Second, the findings relate to a third-generation balloon-expandable valve system and cannot be extrapolated to other valve types or to newer balloon-expandable iterations. Third, the analysis was not prespecified before the trials being conducted; therefore, the findings should be considered hypothesis generating. Fourth, this study pooled together patients in the all-female RHEIA trial and the female subset of patients in the PARTNER 3 trial. Finally, outcomes are only reported at 1 year, which may not adequately reflect longer term outcomes as are available for the PARTNER 3 trial. Longer-term data will provide further insights on the comparative effectiveness of TAVR vs SAVR in female patients.

CONCLUSIONS

At 1 year, in women with symptomatic severe AS receiving TAVR vs SAVR, there was a significant difference in the combined endpoint of all-cause mortality, all stroke, or rehospitalization, largely due to a significant difference in rehospitalization rate.

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ADDRESS FOR CORRESPONDENCE: Dr Helene Eltchaninoff, Univ Rouen Normandie, Inserm U 1096, CHU Rouen, Department of Cardiology, F-76000 Rouen, France. E-mail: helene.eltchaninoff@chu-rouen.fr.

PERSPECTIVES

WHAT IS KNOWN? The all-female RHEIA trial demonstrated a significant reduction in the composite of death, stroke, or rehospitalization at 1-year follow-up with TAVR compared with SAVR.

WHAT IS NEW? This pooled analysis of RHEIA and the female population of the PARTNER 3 trial demonstrated, in a larger cohort of female patients, a significant difference in the combined endpoint of all-cause mortality, all stroke, or rehospitalization at 1 year, largely due to a significant reduction in the rate of rehospitalization.

WHAT IS NEXT? Longer follow-up of the PARTNER 3 trial will provide more insights into the comparative effectiveness of TAVR vs SAVR in female patients. In addition, substudies will provide in-depth information on specific anatomies and echocardiographic results.

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KEY WORDS aortic stenosis, female patients, SAVR, TAVR

APPENDIX For a supplemental figure and tables, please see the online version of this paper.