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ORIGINAL INVESTIGATIONS

Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis Outside Randomized Trials

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ABSTRACT

BACKGROUND Recent randomized trials including low-risk patients showed positive results for transcatheter aortic valve replacement (TAVR) compared to surgical aortic valve replacement (SAVR), but patients with non-tricuspid aortic valve (NTAV), severe coronary artery disease (SevCAD), and those requiring concomitant mitral/tricuspid valve (CMTV) or concomitant ascending aorta replacement (CAAR) interventions were excluded.

OBJECTIVES This study sought to evaluate the presence and impact of the main clinical variables not evaluated in TAVR versus SAVR trials (NTAV, SevCAD, and CMTV or CAAR intervention) in a large series of consecutive low-risk patients with severe aortic stenosis (SAS) undergoing SAVR.

METHODS Single-center study including consecutive patients with SAS and low surgical risk (Society of Thoracic Surgeons score of $<4\%$) undergoing SAVR. Baseline, procedural characteristics, and 30-day outcomes were prospectively collected.

RESULTS Of 6,772 patients with SAS who underwent SAVR between 2000 and 2019, 5,310 (78.4%) exhibited a low surgical risk (mean Society of Thoracic Surgeons score: $1.94 \pm 0.87\%$). Of these, 2,165 patients (40.8%) had at least 1 of the following: NTAV (n = 1,468, 27.6%), SevCAD (n = 307, 5.8%), CMTV (n = 306, 5.8%), and CAAR (n = 560, 10.5%). The 30-day mortality and stroke rates for the overall low-risk SAS cohort were 1.9% and 2.4%, respectively. The mortality rate was similar in the SevCAD (2.6%) and CAAR (2.1%) groups versus the rest of the cohort (odds ratio [OR]: 1.79; 95% confidence interval [CI]: 0.85 to 3.75, and OR: 1.64; 95% CI: 0.88 to 3.05, respectively), lower in the NTAV group (0.9%; OR: 0.42; 95% CI: 0.22 to 0.81), and higher in the CMTV group (5.9%; OR: 2.61; 95% CI: 1.51 to 4.5).

CONCLUSIONS In a real-world setting, close to one-half of the low-risk patients with SAS undergoing SAVR exhibited at least 1 major criterion not evaluated in TAVR versus SAVR randomized trials. Clinical outcomes were better than or similar to those predicted by surgical scores in all groups but those patients requiring CMTV intervention. These results may help determine the impact of implementing the results of TAVR-SAVR trials in real practice and may inform future trials in specific groups. (J Am Coll Cardiol 2021;77:111-23) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAAR = concomitant ascending aorta replacement

CI = confidence interval

CMTV = concomitant mitral or tricuspid valve

CT = computed tomography

MR = mitral regurgitation

NTAV = non-trileaflet aortic valve

OR = odds ratio

RAMR = risk-adjusted mortality ratio

SAS = severe aortic stenosis

SAVR = surgical aortic valve replacement

SevCAD = severe coronary artery disease

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

TIA = transient ischemic attack

Transcatheter aortic valve replacement (TAVR) is a well-established therapy for treating elderly patients with symptomatic severe aortic stenosis (SAS) (1,2). Currently, clinical guidelines provide the same recommendation grade for TAVR and surgical aortic valve replacement (SAVR) for patients with at least an intermediate surgical risk. The preference of one approach versus the other depends on patient frailty status, comorbidities, the concomitant presence of other cardiac conditions requiring surgical repair, and anatomic issues such as transfemoral access suitability, aortic valve morphology, and calcium burden (3,4).

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For low-risk surgical patients, SAVR is still recommended over TAVR, but recent randomized trials (PARTNER [Placement of Aortic Transcatheter Valves] 3 and Evolut Low Risk [Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low-Risk Patients]) showed positive clinical outcomes in low-risk TAVR recipients, noninferior or even superior to their SAVR counterparts (5,6). Thus, a rapid expansion of TAVR toward the treatment of low-risk patients with SAS is expected in the near future. However, the PARTNER 3 and Evolut Low Risk trials had several exclusion criteria that could preclude their general applicability in the low-risk SAS population. Indeed, no data exist on the prevalence and clinical impact of the main exclusion criteria included in the low-risk TAVR versus SAVR trials, such as non-trileaflet aortic valve (NTAV), severe coronary artery disease (SevCAD), concomitant mitral or tricuspid valve (CMTV) intervention, and concomitant ascending aorta replacement (CAAR). Thus, we sought to evaluate, in a large series of consecutive low-risk SAVR recipients, the presence and clinical impact of the factors (NTAV, SevCAD, CMTV, CAAR) not evaluated in recent TAVR versus SAVR trials.

METHODS

All adult patients with SAS and a low surgical risk who underwent SAVR between January 2000 and January 2019 in our center were included in the study. Data regarding previous medical history, surgical details, and clinical outcomes were recorded prospectively in a dedicated database. The local ethics committee (Quebec Heart and Lung Institute) approved data collection and reporting.

SURGICAL RISK SCORE CALCULATIONS. Based on patient medical records and clinical reports, EuroSCORE II (European System for Cardiac Operative Risk Evaluation, 2011 version) and the Society of Thoracic Surgeons (STS) (Adult Cardiac Surgery Database version 2.9) scores were calculated retrospectively (between January and June of 2020) for all SAVR recipients. Online automatic calculators (EuroSCORE and Online STS Adult Cardiac Surgery Risk Calculator) were used. For patients who underwent concomitant procedures not available for data entry in the STS online calculator sheet (e.g., ascending aorta replacement), the calculation was performed taking into consideration valve disease and coronary revascularization exclusively, when applicable. STS and EuroSCORE calculations were performed by 2 investigators (A.A. and P.V.), and any discrepancies between them were resolved by a third investigator (J.R.-C.). Low risk was defined as an expected 30-day mortality of <4% as determined by the STS score (5).

LOW-RISK TAVR TRIAL EXCLUSION CRITERIA. All exclusion criteria in the low-risk PARTNER 3 trial were verified by using patient medical records. Patients who underwent a previous mechanical aortic valve replacement and those presenting with acute infective endocarditis were directly excluded because they posed an absolute contraindication for TAVR. Four groups that would have been excluded from the PARTNER 3 trial because of features potentially favoring SAVR were evaluated:

- NTAV: all patients exhibiting unicuspid or bicuspid native aortic valves were included in this group.
- SevCAD: SevCAD was considered as either significant (>50%) unprotected left main coronary artery disease or as the presence of a SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score higher than 32 (5). All SYNTAX scores were calculated retrospectively, based on the pre-SAVR coronary angiography. Two investigators (A.A. and J.R-C.) calculated the SYNTAX score values.
- CMTV: CMTV intervention was considered if either a replacement or repair for any of these valves was performed for treating moderate-to-severe or severe regurgitation and/or moderate-severe stenosis.
- CAAR: CAAR was considered when this intervention was performed in the presence of a clinical indication such as ascending aorta dilation or aneurysm (Ross procedures without primary indication for ascending aorta replacement were not included).

OVERALL PARTNER 3 TRIAL ELIGIBILITY. All PARTNER 3 exclusion criteria were evaluated in a specific subanalysis. Some of the criteria could not be evaluated in the same manner as recommended by the low-risk TAVR trial investigators (e.g., aortic annulus suitability by 3-dimensional image and computed tomography [CT]-based femoral access suitability). In these scenarios, we proceeded as follows:

- For aortic annulus size suitability, all aortic annular dimensions were sized in vivo by the cardiothoracic surgeon. A sizing smaller than 19 mm was considered as the lowest threshold for unsuitability, whereas a sizing higher than 29 mm was considered as the upper cutoff point.
- For vessel characteristics precluding passage of the introducer sheath, we considered previous bilateral bypass, including iliac and/or femoral segments, as severe peripheral artery disease preventing a transfemoral TAVR approach.

MAIN CLINICAL ENDPOINTS: 30-DAY MORTALITY AND CEREBROVASCULAR EVENTS. The 30-day mortality and stroke rates were assessed prospectively and entered in a dedicated database. Stroke was defined as any brain, spinal cord, or retinal cell death attributable to ischemia based on a pathological image (CT and/or magnetic resonance) and/or clinical evidence of ischemic injury based on symptoms persisting at least 24 h. Transient ischemic attack (TIA) was defined as any brain, spinal cord, or retinal ischemia, without acute infarction and without >24 h of persisting disability. All cerebrovascular events were assessed by a neurologist.

The 1-year mortality events were also recorded and entered in a dedicated database.

SUBANALYSIS ACCORDING TO THE TIMING OF SURGERY. To determine the potential effect of surgical timing on clinical outcomes, the study population was divided in 2 subgroups based on the year of surgery (2000 to 2010 and 2011 to 2019). This subanalysis was performed for each subgroup (NTAV, CAAR, CMTV, and SevCAD).

STATISTICAL ANALYSIS. Continuous variables were presented as mean ± SD and categorical variables as absolute numbers and percentages. Mean comparisons were performed using Student's *t*-test. The chi-square test was used to compare proportions. Unadjusted and adjusted logistic regression analyses were performed to compare 30-day mortality, stroke, and TIA rates for patients included in the various subgroups evaluated. The adjusted analysis was performed by using a multivariate logistic regression model (backward stepwise method) including all baseline and procedural characteristics shown in Supplemental Tables 1 to 4 and forcing the presence of the evaluated subgroup within the final model. Unadjusted and adjusted Cox regression analyses were performed to compare 1-year mortality rates, with the adjusted model obtained with a multivariate Cox regression analysis (backward stepwise method) as previously described. Kaplan-Meier survival estimates and the log-rank test were used to compare mortality rates between groups.

The risk-adjusted mortality ratio (RAMR) between observed and expected mortality events was calculated, along with its 95% confidence interval (CI), for

TABLE 1 Baseline Characteristics of the SAS Low-Surgical-Risk Population (STS <4%) (N = 5,310)

Age, yrs	68.2 ± 10.5
Female	1,804 (33.97)
BMI, kg/m^2	28.5 ± 5.3
Smoker	648 (12.20)
Hypertension	3,623 (67.23)
Diabetes mellitus	1,334 (25.12)
Atrial fibrillation	662 (12.47)
PCI	489 (9.21)
CABG	142 (2.67)
Hypertrophic cardiomyopathy	57 (1.12)
Previous SAVR	67 (1.26)
Previous SMVR	0 (0.00)
Previous ascending aortic surgery	17 (0.32)
Stroke	261 (4.92)
Chronic kidney disease	2,167 (31.5)
Clearance (Cockcroft-Gault equation), ml/min	73.5 ± 24.6
PAD	395 (7.44)
COPD	479 (9.02)
Cirrhosis	29 (0.55)
NYHA functional class	
I	632 (11.90)
II	2,571 (48.43)
III	2,028 (38.19)
IV	79 (1.49)
Unicuspid-bicuspid aortic valve	1,468 (27.70)
Aortic mean gradient, mm Hg	45.32 ± 16.35
Aortic valve area, cm^2	0.73 ± 0.18
Severe AR	144 (2.71)
Severe MR	178 (3.35)
Mitral stenosis (moderate or severe)	82 (1.50)
Severe TR	24 (0.46)
LVEF, %	59.2 ± 10.3
STS score, %	1.94 ± 0.86
EuroSCORE II, %	3.1 ± 2.54

Values are mean ± SD or n (%).

AR = aortic regurgitation; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricle ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PAD = peripheric artery disease; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; SMVR = surgical mitral valve replacement; STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation.

TABLE 2 Main Procedural Characteristics of the SAS Low-Risk Cohort (N = 5,310)

Type of SAVR	
Bioprosthesis	4,336 (84.80)
Mechanical	662 (12.47)
Ross procedure	145 (2.73)
Concomitant ascending aorta replacement	560 (10.54)
Homograft	22 (0.43)
Bentall	538 (10.13)
Concomitant mitral valve intervention	296 (5.58)
Mitral valve replacement	248 (4.67)
Mitral valve repair	48 (0.90)
Concomitant tricuspid valve intervention	24 (0.45)
Tricuspid valve replacement	4 (0.08)
Tricuspid valve repair	20 (0.38)
Concomitant CABG	2,044 (38.49)
1-vessel disease	1,054 (19.85)
2-vessel disease	679 (12.79)
3-vessel disease	311 (5.86)
Left main disease	228 (4.29)
Number of bypasses performed (in patients undergoing concomitant CABG)	2.04 ± 1.70
Time of extracorporeal circulation, min	108.3 ± 45.0
Prosthesis size implanted, mm	
17	9 (0.17)
18	8 (0.06)
19	286 (5.39)
20	9 (0.17)
21	1,120 (21.09)
22	22 (0.41)
23	1,705 (32.11)
24	30 (0.56)
25	1,401 (26.38)
27	393 (7.40)
29	79 (1.49)
>29	16 (0.30)

Values are n (%) or mean ± SD.

CABG = coronary artery bypass graft; SAS = severe aortic stenosis; SAVR = surgical aortic valve replacement.

comparing observed and expected surgical mortality, with values of >1.0 meaning higher observed than expected mortality. A p value of <0.05 was considered significant for all statistical tests. All analyses were performed by using Stata, version 14.0 (StataCorp, College Station, Texas).

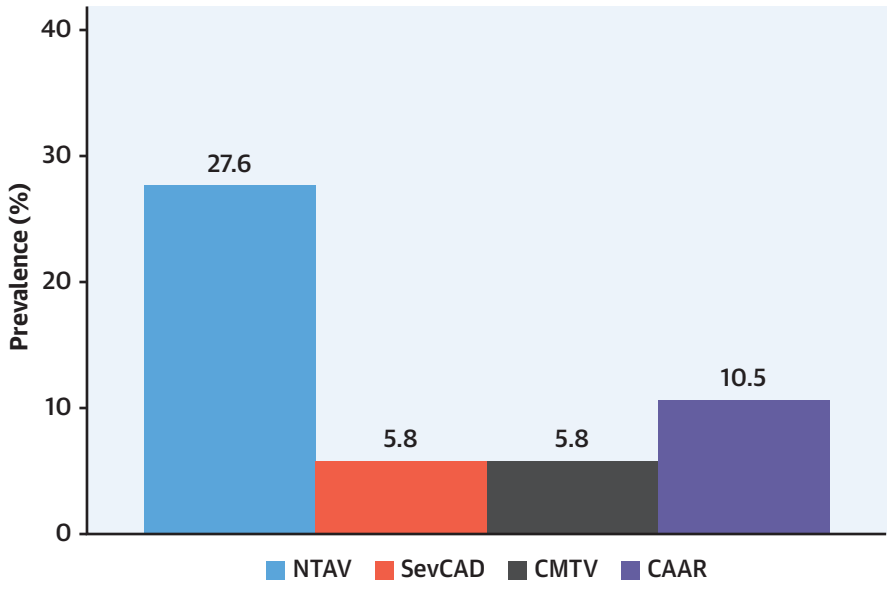
RESULTS

Between January 2000 and January 2019, 8,934 patients underwent SAVR at our center. Of these, SAS was present in 6,772 (75.8%) patients, and a low surgical risk as estimated by STS score (<4%) was found in 5,388 patients (79.6% of low-risk patients with SAS). After excluding those cases with acute infective endocarditis and previous mechanical aortic valve replacement, a total of 5,310 low-risk patients with SAS (78.4% of the overall SAS population) were included in the analysis. The 30-day clinical status was known for all of them. The main baseline characteristics of the study population are shown in Table 1, and the main procedural details of the SAVR intervention are summarized in Table 2. The mean age of the patients was 68 ± 11 years, and most patients (66%) were men. The mean STS and EuroSCORE II were 1.94 ± 0.86% and 3.10 ± 2.54%, respectively. The presence of NTAV, SevCAD, CMTV, and CAAR were observed in 27.6%, 5.8%, 5.8%, and 10.5% of patients, respectively, with up to 40.8% of patients exhibiting at least 1 of the 4 aforementioned clinical variables (Figure 1).

A total of 1,468 (27.6%) patients presented with native NTAV, with an increasing incidence in younger patients (Figure 2). The main clinical outcomes are shown in Table 3. In this group, the observed 30-day mortality was 0.9%, which was lower than the mortality risk estimated by EuroSCORE II (RAMR: 0.32; 95% CI: 0.19 to 0.55), and tended to be lower than that estimated by STS (RAMR: 0.59; 95% CI: 0.34 to 1.02). The 30-day stroke and TIA rates in this subgroup were of 1.6% and 0.3%, respectively. The main characteristics of the NTAV and trileaflet aortic valve groups are summarized in Supplemental Table 1. Compared to their trileaflet valve counterparts, patients with NTAV exhibited a lower 30-day mortality rate (adjusted odds ratio [OR]: 0.42; 95% CI: 0.22 to 0.81; log-rank test: 0.001) (Figure 3) but similar stroke (adjusted OR: 0.90; 95% CI: 0.54 to 1.49; p = 0.69), and TIA (adjusted OR: 2.28; 95% CI: 0.74 to 7.01; p = 0.15) rates. The 1-year mortality rate was lower than that observed for patients with trileaflet valve (adjusted hazard ratio [HR]: 0.59; 95% CI: 0.38 to 0.93; p = 0.02) (Table 4). In the subanalysis by surgical date, a lower observed than expected mortality (both by STS and EuroSCORE II) was observed for the late (vs. early) cohort of NTAV patients (Supplemental Table 5).

A total of 307 (5.8%) patients had concomitant SevCAD, left main disease was present in 228 (4.3%) patients, and a coronary disease leading to a SYNTAX score over 32 without left main involvement in 79 (1.5%) patients. The incidence of SevCAD according to age is shown in Figure 2, and the main clinical outcomes are shown in Table 3. The observed 30-day mortality was 2.6%, which was similar to that estimated by STS and EuroSCORE II (Table 3). The 30-day stroke and TIA rates for this group were 3.3% and 0.3%, respectively. The main baseline characteristics of the SevCAD and non-SevCAD groups are summarized in Supplemental Table 2. Compared to their non-SevCAD counterparts, patients with SevCAD exhibited similar rates of 30-day mortality (adjusted

FIGURE 1 Prevalence of the Main Clinical Variables Not Evaluated in Low-Risk TAVR Versus SAVR Trials



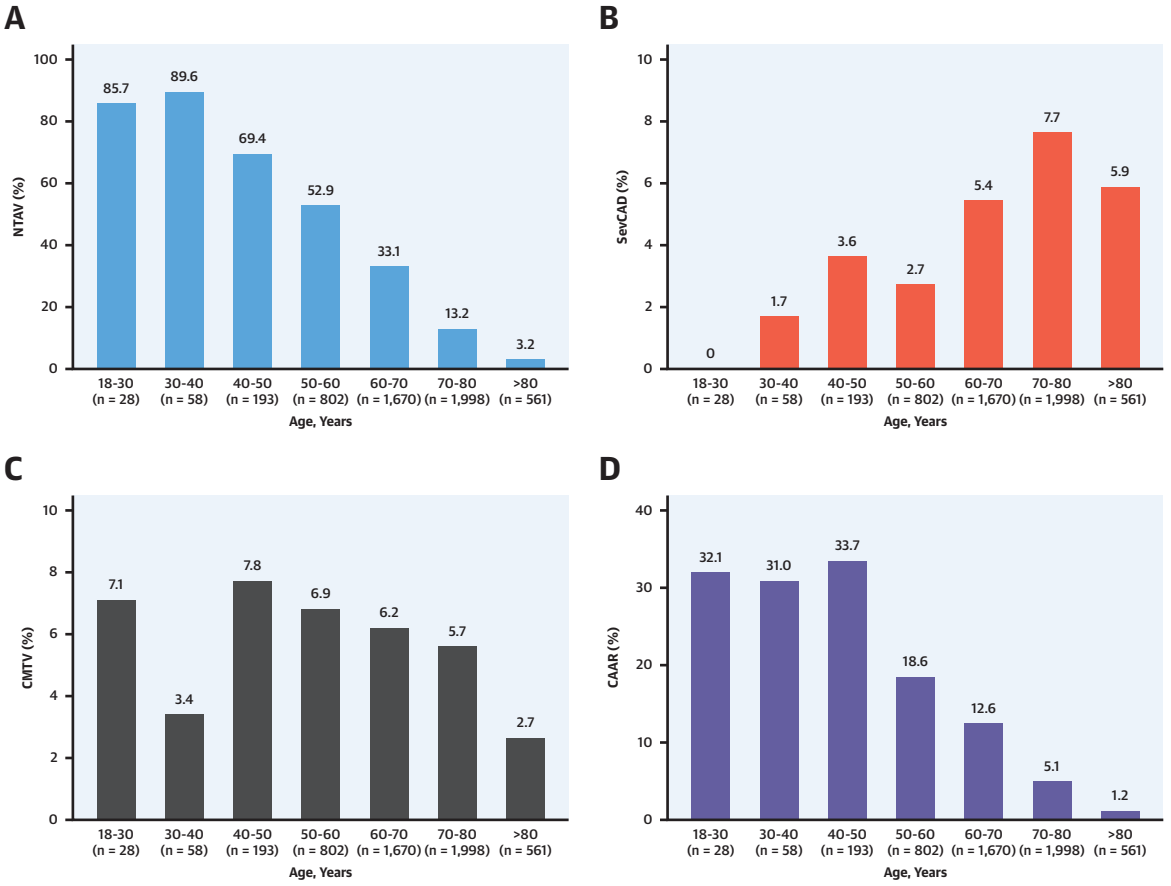
Bar chart representing the percentage of patients in the SAS low-risk cohort (n = 5,310) included in each of the subgroups evaluated: NTAV, SevCAD, CMTV, and CAAR. Up to 40.8% of the low-risk patients with SAS who underwent SAVR exhibited at least 1 of the previous conditions, most commonly an NTAV. CAAR = concomitant ascending aorta replacement; CMTV = concomitant mitral or tricuspid/valve disease; NTAV = non-trileaflet aortic valve; SAS = severe aortic stenosis; SAVR = surgical aortic valve replacement; SevCAD = severe coronary artery disease; TAVR = transcatheter aortic valve replacement.

OR: 1.79; 95% CI: 0.85 to 3.75; log-rank test: 0.37) (**Figure 3**), stroke (adjusted OR: 1.40; 95% CI: 0.73 to 2.76; p = 0.30), TIA (adjusted OR: 0.84; 95% CI: 0.11 to 6.08; p = 0.87), and 1-year mortality (adjusted HR: 1.37; 95% CI: 0.74 to 2.41; p = 0.34) (**Table 4**). Observed mortality rates were similar to those expected by STS in both the early and late study cohorts (Supplemental Table 5). In the subgroup of 228 patients with left main disease, the observed 30-day mortality was 1.8% (vs. estimated mortality by STS of 2.5%), whereas in the subgroup of 79 patients with high SYNTAX score without left main involvement, the observed mortality was 5.1% (vs. STS estimated mortality of 2.6%).

A total of 306 (5.8%) patients underwent CMTV intervention: 237 (4.5%) isolated mitral valve replacement, 45 (0.9%) isolated mitral valve repair, 1 (0.1%) isolated tricuspid valve replacement, 8 (0.2%) isolated tricuspid valve repair, and 14 (0.3%) concomitant mitral and tricuspid valve intervention. The rate of CMTV according to age is shown in **Figure 2**, and the main clinical outcomes are shown in **Table 3**. The observed 30-day mortality was 5.9%, which was higher than that estimated by STS (RAMR: 2.27; 95% CI: 1.41 to 3.70) and similar to that estimated by EuroSCORE II (RAMR: 1.14; 95% CI: 0.71 to 1.81). The 30-day stroke rate for this group was 2.3%, and the TIA rate was 0.98%. The main characteristics of the CMTV intervention and no-CMTV intervention groups are summarized in Supplemental Table 3. Compared to patients who had no concomitant mitral or tricuspid intervention, those with CMTV intervention exhibited a higher 30-day mortality (adjusted OR: 2.61; 95% CI: 1.51 to 4.5; log-rank test: <0.001) (**Figure 3**), with no significant differences in stroke (adjusted OR: 0.94; 95% CI: 0.43 to 2.04; p = 0.87) and TIA (adjusted OR: 2.57; 95% CI: 0.75 to 8.82; p = 0.13). The 1-year mortality rate for this subgroup was higher than that observed for patients without CMTV intervention (adjusted HR: 2.5; 95% CI: 1.65 to 3.80; p < 0.001) (**Table 4**). In the subanalysis by procedural date, a higher observed mortality than that estimated by STS (Supplemental Table 5) was found for the late CMTV cohort. In addition, in the overall late study cohort, patients with CMTV had a higher 30-day mortality than their non-CMTV counterparts (adjusted OR: 10.2; 95% CI: 4.74 to 21.9) (Supplemental Table 6).

A total of 560 (10.5%) patients underwent CAAR, with a much higher rate among patients younger than

FIGURE 2 Main Clinical Variables Not Evaluated in Low-Risk TAVR Versus SAVR Trials According to Age



Histograms representing the prevalence of the main conditions not evaluated in trials of TAVR versus SAVR (NTAV, SevCAD, CMTV, and CAAR) according to age at the time of surgery: **(A)** NTAV, **(B)** SevCAD, **(C)** CMTV intervention, and **(D)** CAAR. The prevalence of NTAV and CAAR progressively increased as patients underwent SAVR at younger ages. Abbreviations as in Figure 1.

50 years (Figure 2). The main clinical outcomes are shown in Table 3. In this group, the observed 30-day mortality was 2.1%, which was similar to the mortality estimated by STS (RAMR: 1.16; 95% CI: 0.66 to 2.04) and lower than that estimated by EuroSCORE II (RAMR: 0.41; 95% CI: 0.23 to 0.72). The 30-day stroke rate was 2.3%, and there were no TIA events. The main characteristics of the CAAR and non-CAAR

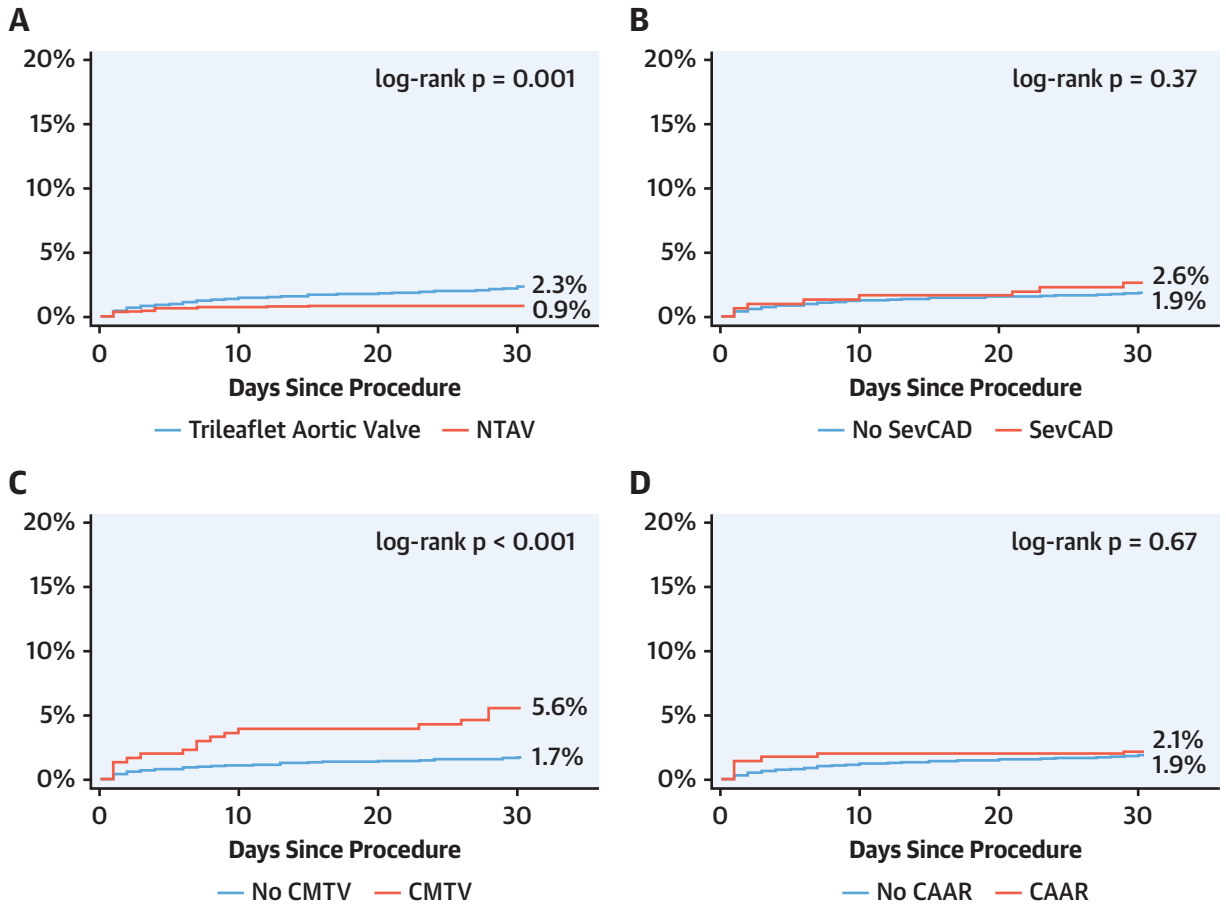
TABLE 3 Main 30-Day Outcomes, According to the Presence of Different Clinical/Procedural Variables

				Estimated Mortality				
	N	Stroke	TIA	STS Score	EuroSCORE II	Observed Mortality	RAMR for STS (95% CI)	RAMR for EuroSCORE II (95% CI)
Overall	5,310	128 (2.41)	21 (0.40)	1.94 ± 0.86	3.09 ± 2.54	102 (1.92)	0.99 (0.82-1.20)	0.62 (0.51-0.75)
NTAV	1,468	23 (1.57)	5 (0.34)	1.49 ± 0.7	2.77 ± 2.36	13 (0.89)	0.59 (0.34-1.02)	0.32 (0.19-0.55)
SevCAD	307	10 (3.30)	1 (0.33)	2.52 ± 0.8	3.39 ± 2.05	8 (2.61)	1.03 (0.52-2.08)	0.77 (0.38-1.54)
CMTV	306	7 (2.29)	3 (0.98)	2.84 ± 0.8	4.48 ± 3.3	18 (5.88)	2.27 (1.41-3.70)	1.14 (0.71-1.81)
		6 (2.13)*	3 (1.06)*			18 (6.4)*		
CAAR	560	13 (2.32)	0 (0.00)	2.04 ± 0.7	5.25 ± 3.5	12 (2.14)	1.16 (0.66-2.04)	0.41 (0.23-0.72)

Values are n (%) or mean ± SD, unless otherwise indicated. *Values considering exclusively mitral procedures without tricuspid valve intervention.

CAAR = concomitant ascending aorta replacement; CI = confidence interval; CMTV = concomitant mitral or tricuspid/valve disease; NTAV = non-trileaflet aortic valve; OR = odds ratio; RAMR = risk-adjusted mortality ratio; SevCAD = severe coronary artery disease; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

FIGURE 3 Kaplan-Meier Estimates for 30-Day Mortality



Kaplan-Meier curves for 30-day mortality according to the presence of **(A)** NTAV, **(B)** SevCAD, **(C)** CMTV intervention, and **(D)** CAAR in our cohort of low-risk patients with SAS undergoing SAVR. Statistical differences between groups were assessed by means of the log-rank test. The NTAV group presented less 30-day mortality than the rest of the cohort, whereas a higher mortality rate was observed for the CMTV group. Abbreviations as in Figure 1.

groups are summarized in Supplemental Table 4. No significant differences in 30-day mortality (adjusted OR: 1.64; 95% CI: 0.88 to 3.05; log-rank test: 0.67) (Figure 3), stroke (adjusted OR: 1.54; 95% CI: 0.84 to 2.84; p = 0.16), or 1-year mortality (adjusted HR: 0.67; 95% CI: 0.34 to 1.33; p = 0.25) were found between patients with and without CAAR (Table 4). In the subanalysis by procedural date, the late cohort of CAAR patients exhibited similar observed 30-day mortality (0.94%) to that estimated by STS (RAMR: 0.51; 95% CI: 0.16 to 1.59) and lower than that estimated by EuroSCORE II (RAMR: 0.19; 95% CI: 0.06 to 0.59) (Supplemental Table 5), whereas there were no differences between CAAR versus no-CAAR patients regarding 30-day mortality in both the early and late study cohorts (Supplemental Table 6).

SUBANALYSIS OF THE PATIENTS FULFILLING THE PARTNER 3 CRITERIA. After applying all PARTNER 3 inclusion and exclusion criteria, only 2,727 patients (51.4%) of the initial 5,310 SAS low-risk population would have been eligible for the trial. The main features precluding patient inclusion were a bicuspid aortic valve (27.6%) and thoracic aortic disease needing ascending aorta replacement (10.5%). A flow diagram of different exclusion criteria is presented in Figure 4. The absolute and relative numbers of patients within the SAS low-risk cohort presenting with any condition that may have excluded them for trial participation are displayed in Supplemental Table 7. In the group fulfilling the PARTNER 3 criteria, the observed 30-day mortality was 1.6%, whereas the estimated STS mortality was 2.0%, and the estimated

TABLE 4 Unadjusted and Adjusted Regression Analysis for Patients Included in the Various Subgroups Versus the Rest of the Cohort (Primary and Secondary Endpoints)

	NTAV				SevCAD			
	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
30-day mortality	0.37 (0.21-0.66)	0.001	0.42 (0.22-0.81)	0.01	1.37 (0.66-2.84)	0.4	1.79 (0.85-3.75)	0.13
Stroke	0.57 (0.36-0.90)	0.01	0.90 (0.54-1.49)	0.69	1.39 (0.72-2.69)	0.32	1.40 (0.73-2.76)	0.30
TIA	0.82 (0.30-2.23)	0.64	2.28 (0.74-7.01)	0.15	0.81 (0.11-6.08)	0.84	0.84 (0.11-6.08)	0.87
	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
1-yr mortality	0.39 (0.26-0.60)	<0.001	0.59 (0.38-0.93)	0.02	1.15 (0.64-2.08)	0.63	1.37 (0.74-2.41)	0.34

Variables included for adjusted OR values: all baseline characteristics significantly unbalanced between groups (Supplemental Tables 1 to 4).
HR = hazard ratio; NA = not applicable; other abbreviations as in Table 3.

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EuroSCORE II mortality 2.7%. The 30-day stroke and TIA rates for this group were 2.9% and 0.5%, respectively. The 30-day mortality and stroke rates for the early cohort were 2.4% and 3.5%, respectively, and for the late cohort were 0.7% and 2.3%, respectively.

DISCUSSION

The main findings of our study can be summarized as follows (**Central Illustration**): 1) in a large cohort of consecutive patients with SAS undergoing SAVR, most patients exhibited a low surgical risk, and close to one-half had at least 1 major clinical or procedural variable not evaluated in the TAVR versus SAVR low-risk trials, with the presence of an NTAV accounting for the majority of cases, followed by CAAR, SevCAD, and CMTV; 2) the NTAV group had a very low (<1%) mortality rate, whereas those patients with concomitant mitral or tricuspid disease exhibited a higher risk; 3) the observed mortality rate was lower than or similar to that estimated by surgical risk scores (STS or EuroSCORE II) in all patients but those with CMTV; and 4) the observed stroke rate was 2.4%, with no significant differences between groups.

BICUSPID AORTIC VALVE. The use of TAVR for treating patients with NTAV (mainly bicuspid aortic valves) remains controversial. The vast majority of randomized trials comparing TAVR and SAVR have excluded bicuspid and unicuspid aortic valve patients (5–9), and no specific analysis was reported in the only trial including such patients to date (10). Data from a large registry with more than 80,000 patients with TAVR (2,726 of them with bicuspid aortic valve) showed, using a propensity-matched analysis, the lack of differences in mortality and paravalvular leaks between patients with bicuspid and tricuspid aortic valve. However, patients with bicuspid aortic valve experienced higher rates of 30-day stroke and procedural-related complications requiring conversion to open heart surgery compared to their trileaflet valve counterparts (11). On the other hand, the results of a recent TAVR study including low-risk patients with bicuspid aortic valve showed very positive clinical outcomes, with no mortality or disabling stroke at 30 days (12). Still, these results should be interpreted with caution because of the small number of patients (n = 61) and the absence of a control SAVR group.

In our low-risk cohort, the prevalence of bicuspid aortic valve progressively increased as patients underwent SAVR at younger ages. Furthermore, patients with bicuspid aortic valve represented one of the largest subgroups excluded from trials with a plausible option of being treated with TAVR: 945 out of 5,310 patients exhibited a bicuspid aortic valve as the only characteristic precluding trial participation, thus representing approximately one fifth of the entire SAS low-risk population. Of note, the mortality rate in this subgroup was very low (0.9% overall and 0.4% for the most contemporary cohort of NTAV patients), lower than that estimated by surgical risk scores, along with a relatively low (<2%) stroke rate. Future randomized studies comparing SAVR and TAVR are needed to provide more insight into this population. In light of our findings, TAVR results must be outstanding to mimic those obtained by SAVR in this important group of patients.

CORONARY ARTERY DISEASE. The presence of concomitant CAD in patients included in trials of SAVR versus TAVR has progressively decreased in parallel with the reduction of the global risk of the TAVR population (13). In fact, only 27% and approximately 15% of patients included in the PARTNER 3 and Evolut Low Risk trials, respectively, exhibited CAD, compared to approximately 75% of patients in PARTNER A and the Corevalve US extreme risk studies (13). Moreover, the rates of concomitant revascularization in recent low-risk TAVR trials was low (approximately 10%) (5,6).

TABLE 4 Continued

	CMTV				CAAR			
	Unadjusted OR (95% CI)	**p Value**	**Adjusted OR (95% CI)**	**p Value**	**Unadjusted OR (95% CI)**	**p Value**	**Adjusted OR (95% CI)**	**p Value**
30-day mortality	3.57 (2.12-6.0)	<0.001	2.61 (1.51-4.50)	0.001	1.1 (0.60-2.01)	0.74	1.64 (0.88-3.05)	0.12
Stroke	0.95 (0.44-2.06)	0.90	0.94 (0.43-2.04)	0.87	0.97 (0.54-1.73)	0.91	1.54 (0.84-2.84)	0.16
TIA	2.74 (0.80-9.36)	0.11	2.57 (0.75-8.82	0.13	NA	NA	NA	NA
	Unadjusted HR (95% CI)	**p Value**	**Adjusted HR (95% CI)**	**p Value**	**Unadjusted HR (95% CI)**	**p Value**	**Adjusted HR (95% CI)**	**p Value**
1-yr mortality	2.83 (1.87-4.29)	<0.001	2.5 (1.65-3.80)	<0.001	0.44 (0.23-0.86)	0.02	0.67 (0.34-1.33)	0.25

Patients presenting with left main disease represented a small proportion (5%) of our SAS low-risk cohort undergoing SAVR. In this setting, revascularization is mandatory pre-TAVR or during SAVR, because left main involvement directly affects patient prognosis. Controversial results exist regarding surgical versus percutaneous left main revascularization, and clinical guidelines recommend both therapies in cases of low SYNTAX scores (<23), with a surgical approach favored for more complex scenarios (SYNTAX score of >23) (14). Data regarding left main revascularization and TAVR are limited. Although 1 observational study reported the feasibility of left main percutaneous revascularization pre-TAVR, this was based on a high-risk cohort (mean STS of 8.1) with a limited follow-up (15). Therefore, caution would be important when considering left main angioplasty in low-risk TAVR patients, because no randomized data are available, and ulterior coronary ostia access after TAVR could be technically demanding.

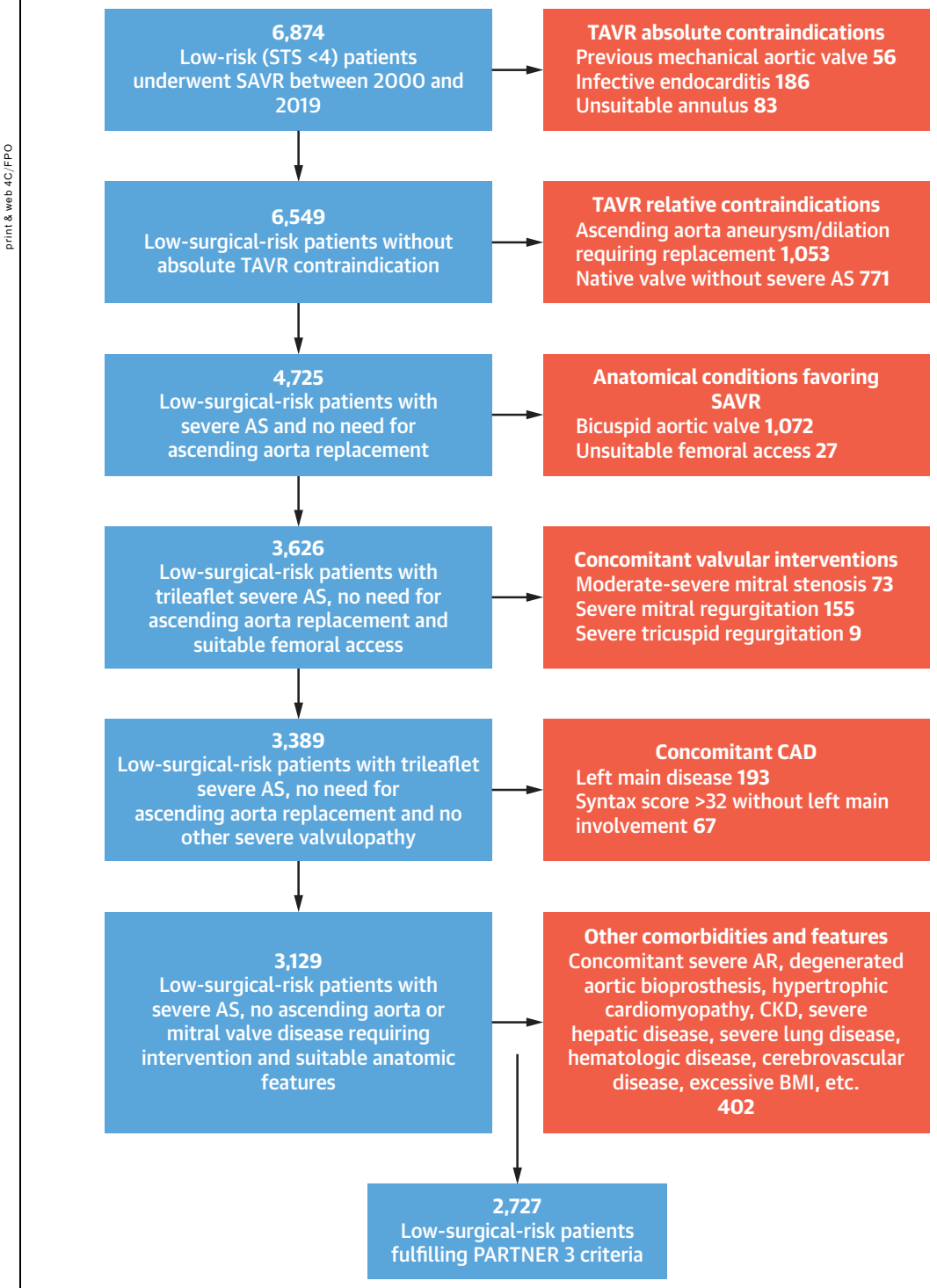
In cases of severe, stable CAD not involving the left main coronary artery, the need for revascularization remains controversial, even outside of the TAVR setting (16). However, a meta-analysis evaluating the prognostic value of the residual SYNTAX score pre-TAVR and after incomplete percutaneous revascularization showed a detrimental prognosis with higher residual SYNTAX scores (17). In our SAS low-risk cohort of 5,310 patients, only 79 (1.4%) presented with high SYNTAX scores (>32) without left main disease. Lack of randomized data in low-risk patients with SAS with complex CAD without left main involvement, along with the uncertainty of reaching a complete percutaneous revascularization in some cases, would favor a surgical approach as the first option for most of these patients, despite the higher procedural risk.

CONCOMITANT MITRAL AND/OR TRICUSPID VALVE INTERVENTION. Numerically, this group did not represent a significant proportion (approximately 6%) of the entire SAS low-risk cohort, because patients basically shifted to the intermediate- or high-risk population owing to the increased estimated risk conferred by the presence of multivalvular disease. Despite the pre-SAVR estimated low risk, we observed a notable increase in mortality associated with mitral and tricuspid disease requiring either replacement or repair at the time of SAVR. In fact, this was the only subgroup in which the observed mortality (5.9%) exceeded numerically the mortality risk estimated by both surgical risk scores, and this increased risk was maintained even after excluding those patients with concomitant tricuspid interventions.

In this setting, transcatheter treatment represents a less invasive alternative to open heart surgery for mitral and tricuspid valvular disease. Although scarce evidence is yet available for percutaneous tricuspid repair, robust clinical data exist for transcatheter repair techniques in mitral regurgitation (MR) patients. The prognostic implication of moderate or severe MR has been well established in multiple clinical scenarios, including TAVR (18,19). Of note, it has been reported that approximately 50% of the patients presenting with significant MR before TAVR experienced an improvement in MR severity after the procedure (20,21). Randomized trials investigating different therapeutic strategies and timing of intervention for patients presenting with SAS and concomitant mitral/tricuspid valve disease are lacking. Whether concomitant MR should be treated medically or addressed in combined or staged procedures is poorly defined. In this setting, individualized strategies based on comorbidity burden, individual valvular anatomic features, and the estimated procedural risk are advisable.

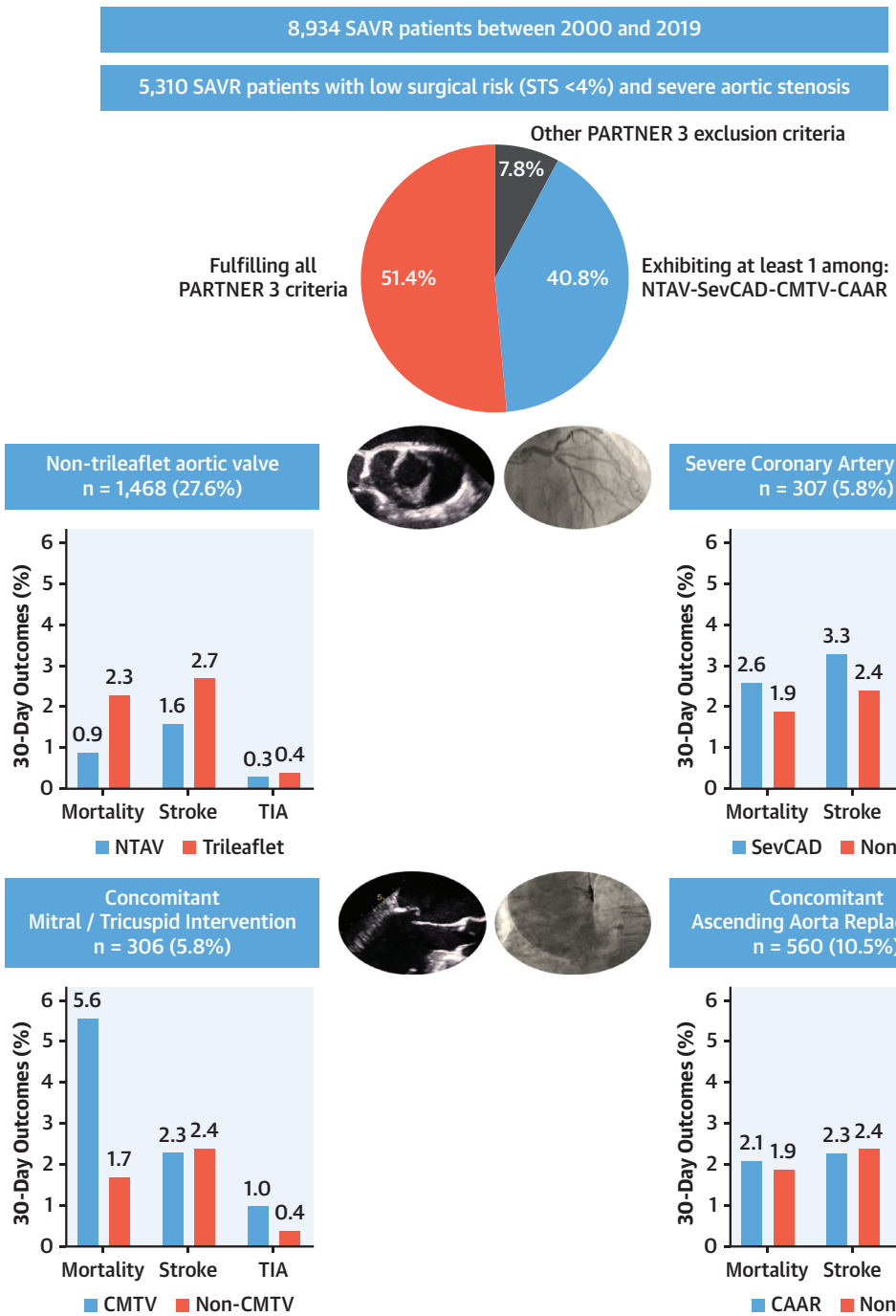
CONCOMITANT ASCENDING AORTA REPLACEMENT. This concomitant feature accounted for approximately 10.5% of the low-risk patients with SAS failing to fulfill PARTNER 3 criteria. Despite the variety in ascending aorta dilatation severity and patient comorbidity burden, a dichotomic pre-procedural decision would need to be taken in a case-by-case clinical scenario: whether to concomitantly replace the aorta by means of open heart surgery or to limit the procedure to an aortic valve replacement, thus offering

FIGURE 4 Patients Fulfilling PARTNER 3 Inclusion and Exclusion Criteria



Flow diagram representing the low-risk SAS cohort of patients fulfilling PARTNER 3 inclusion and exclusion criteria. After applying the established criteria for PARTNER 3 trial selection, a total of 2,727 patients from the initial 6,874 patients constituting the low-risk cohort would have fulfilled inclusion/exclusion criteria for this randomized trial of TAVR versus SAVR. AR = aortic regurgitation; AS = aortic stenosis; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; PARTNER = Placement of Aortic Transcatheter Valves; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Clinical Outcomes Following Surgical Aortic Valve Replacement in Low-Risk Patients Ineligible for Randomized Trials of Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement**



Alperi, A. et al. J Am Coll Cardiol. 2021;77(2):111–23.

The **top pie chart** shows the prevalence of patients fulfilling PARTNER (Placement of Aortic Transcatheter Valves) 3 inclusion and exclusion criteria, according to the presence of the main clinical exclusion criteria evaluated in the present study. The **bar charts** show 30-day outcomes (mortality, stroke, and transient ischemic attack) according to the presence of nontricuspid aortic valve **(upper left)**, severe coronary artery disease **(upper right)**, concomitant mitral/tricuspid valve disease **(lower left)**, and concomitant ascending aorta replacement **(lower right)**. Data are expressed as percentages. CAAR = concomitant ascending aorta replacement; CMTV = concomitant mitral/tricuspid valve disease; NTAV = non-tricuspid aortic valve; SAVR = surgical aortic valve replacement; SevCAD = severe coronary artery disease; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

the patient the possibility of a percutaneous approach. It should be highlighted that in our series, CAAR was mainly performed in the younger subset of patients (>30% of those younger than 50 years vs. <5% in those older than 70 years). The longer life expectancy in this younger population increases the risk for aneurysm progression and related complications. Thus, we believe that CAAR should be performed in young patients with SAS with significant ascending aorta dilation, with TAVR not playing any significant role in this scenario. However, the need for CAAR in older patients, even if their estimated surgical risk is low, remains controversial. In the lack of randomized trials, observational studies have demonstrated a mild progression of aorta dilation post-TAVR in both patients with bicuspid and with trileaflet aortic valve, without differences between groups (22). Besides, post-TAVR short- and midterm outcomes in patients with ascending aorta dilation were positive, with the presence of aorta dilation not influencing overall survival (23). Hence, we believe that in older (>70 years) patients presenting with a noncomplicated ascending aorta dilation that does not preclude a safe passage of the percutaneous valve, an individualized approach should be considered after careful evaluation of absolute risk and available alternatives.

STUDY LIMITATIONS. Although data were collected prospectively in a dedicated database, the analysis was of a retrospective nature. Also, some variables that may play a role in patient surgical risk, such as frailty status, were not addressed. Some anatomic conditions such as left ventricle outflow tract calcium burden and femoral access suitability might have been underestimated because of the lack of systematic CT performance. However, given the increasing experience of TAVR in severely calcified valves, as well as with alternative percutaneous arterial routes (i.e., transcarotid and transsubclavian), we believe that their effect on the final results would likely be marginal. Aortic annulus suitability and sizing were evaluated by direct surgical measurements, and the correlation between these measures and CT sizing was not determined. However, previous studies have shown a very good correlation between CT and direct surgical sizing (24). Furthermore, updated risk scores were used, and this may have led to an underestimation of the real surgical risk of inpatients who underwent surgery over the first years of our inclusion period. However, the subanalysis considering the timing of surgery showed the temporal consistency of the main findings. The results of this study were obtained in a high-volume surgical center and may not be extrapolated to other centers and health care systems. A trend toward a higher mortality was observed in some subgroups (SevCAD and CAAR), and sample size limitations may have prevented us from finding more robust and significant associations. Although all cerebrovascular events were diagnosed by a neurologist, there was no systematic neurological evaluation in the absence of symptoms, and this may have underestimated the real incidence of stroke-TIA events. Data regarding the cause of death were available at 30-day follow-up (Supplemental Table 8), but not from there on. Finally, it is important to note that the outcomes post-SAVR may not apply to those observed post-TAVR in patients with similar characteristics.

CONCLUSIONS

Close to one-half of the low-risk patients with SAS exhibited at least 1 clinical variable that had not been evaluated in TAVR versus SAVR randomized trials. In these cases, SAVR was associated with similar results to the rest of the low-risk SAVR recipients, and the observed mortality was even lower than that estimated by surgical risk scores, with the exception of those patients with concomitant mitral/tricuspid valve disease, which exhibited an increased risk. These results should be considered in the expansion of TAVR toward the treatment of low-risk patients and may inform future randomized trials according to specific clinical variables, particularly in the presence of NTAV, CMTV, and SevCAD.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In clinical practice, nearly one-half of low-risk patients with severe aortic stenosis undergoing SAVR have at least 1 characteristic prompting exclusion from randomized comparisons to TAVR. Clinical outcomes are generally better than predicted by surgical risk scores, except for patients undergoing concomitant tricuspid or mitral valve interventions, in whom adverse events are more frequent.

TRANSLATIONAL OUTLOOK: More inclusive randomized trials are warranted to compare various methods of intervention in patients with severe aortic stenosis who have bicuspid aortic valves, severe coronary artery disease, ascending aorta dilation, or concomitant mitral or tricuspid valve disease.

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KEY WORDS aortic stenosis, low surgical risk, transcatheter aortic valve replacement

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