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ORIGINAL INVESTIGATIONS

Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Aortic Stenosis

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ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) is now the standard of care for patients with symptomatic severe aortic stenosis who are extreme, high, or intermediate risk for surgical aortic valve replacement (SAVR).

OBJECTIVES The authors sought to evaluate TAVR in a prospective multicenter trial involving low-risk patients.

METHODS The Low Risk TAVR (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis) trial was the first U.S. Food and Drug Administration–approved Investigational Device Exemption trial to enroll in the United States. This investigator-led trial was a prospective, multicenter, unblinded, comparison to historical controls from the Society of Thoracic Surgeons (STS) database. The primary endpoint was all-cause mortality at 30 days.

RESULTS The authors enrolled 200 low-risk patients with symptomatic severe aortic stenosis at 11 centers to undergo TAVR. The authors compared outcomes with an inverse probability weighting–adjusted control cohort of 719 patients who underwent SAVR at the same institutions using the STS database. At 30 days, there was zero all-cause mortality in the TAVR group versus 1.7% mortality in the SAVR group. There was zero in-hospital stroke rate in the TAVR group versus 0.6% stroke in the SAVR group. Permanent pacemaker implantation rates were similar between TAVR and SAVR (5.0% vs. 4.5%). The rates of new-onset atrial fibrillation (3.0%) and length of stay (2.0 ± 1.1 days) were low in the TAVR group. One patient (0.5%) in the TAVR group had >mild paravalvular leak at 30 days. Fourteen percent of TAVR patients had evidence of subclinical leaflet thrombosis at 30 days.

CONCLUSIONS TAVR is safe in low-risk patients with symptomatic severe aortic stenosis, with low procedural complication rates, short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of TAVR patients at 30 days. (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis [Low Risk TAVR; NCT02628899) (J Am Coll Cardiol 2018;72:2095–105) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

CT = computed tomography

HALT = hypoattenuated leaflet thickening

IPW = inverse probability weighting

NYHA = New York Heart Association

PPM = permanent pacemaker

RELM = reduction in leaflet motion

SAVR = surgical aortic valve replacement

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

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

Transcatheter aortic valve replacement (TAVR) is an established therapy for patients with symptomatic severe aortic stenosis who are extreme (1,2), high (3,4), or intermediate (5,6) risk for surgery. Recently, there has been a global trend toward offering TAVR to operable patients who would otherwise undergo surgery (7–10). Operator experience, technical improvements, and TAVR device design enhancements facilitate the desire for expansion of TAVR for patients who are low risk for surgical mortality. The NOTION (Nordic Aortic Valve Intervention) trial was the only randomized trial to date comparing TAVR and surgical aortic valve replacement (SAVR) in mostly low-risk patients, 82% of whom had

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Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) <4% (8). TAVR compared favorably to SAVR with 30-day mortality of 2.1% versus 3.7% with TAVR versus SAVR, respectively, although there were significantly higher rates of permanent pacemaker (PPM) and paravalvular aortic regurgitation with TAVR using an early-generation self-expanding TAVR device. Furthermore, recent concerns of TAVR device leaflet thrombosis and restricted leaflet motion (11) have not been evaluated in a prospective clinical trial in low-risk patients. We report the results from the Low Risk TAVR (LRT) trial, the first U.S. Food and Drug Administration–approved Investigational Device Exemption (IDE) trial in the United States to enroll patients with symptomatic severe aortic stenosis and low surgical risk.

METHODS

TRIAL OVERSIGHT. The LRT trial (NCT02628899) was a prospective multicenter feasibility trial to test the safety of transfemoral TAVR in low-risk patients with symptomatic severe aortic stenosis (12). The trial was an investigator-initiated study and was fully funded and managed by the sponsor (MedStar Health Research Institute, Washington, DC) (Online Table 1). Enrolling centers assumed the cost of all local research activities as well as the research-driven tests. The research protocol was approved by the relevant institutional review boards. All patients gave written informed consent and were evaluated before enrollment by an independent clinical review committee, comprising 1 interventional cardiologist and 1 cardiothoracic surgeon, to ensure low-risk status as well as clinical and anatomical eligibility for transfemoral TAVR. All echocardiographic and computed tomography (CT) imaging studies were analyzed by an independent core laboratory. The primary endpoint of the study was all-cause mortality at 30 days. A composite secondary endpoint of all-cause mortality, stroke, and >mild paravalvular aortic regurgitation was evaluated after adjustment. Secondary endpoints also included individual components of this composite and additional relevant procedural complications (12). All clinical endpoints were adjudicated by an independent clinical events adjudication committee comprising an interventional cardiologist, a cardiothoracic surgeon, and a neurologist using both Valve Academic Research Consortium (VARC 2) and STS definitions (13). The data were fully and independently monitored.

TAVR PATIENT SELECTION. Between February 16, 2016, and February 8, 2018, 290 patients with symptomatic severe aortic stenosis were screened by the enrolling centers' multidisciplinary heart teams, and a total of 200 patients (Online Table 2) were confirmed to be low risk based on an STS-PROM score ≤3% and absence of comorbidity that would increase surgical risk, including, but not limited to, frailty, porcelain aorta, severe pulmonary hypertension, and advanced liver disease. Severe aortic

Cardiology, MedStar Washington Hospital Center, Washington, DC; and the °Department of Cardiac Surgery, MedStar Washington Hospital Center, Washington, DC. The Low Risk TAVR (NCT02628899) study is funded by MedStar Health Research Institute, Washington, DC. Dr. Waksman has served on advisory boards for Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., and Cardioset; has been a consultant for Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., and Cardioset; has received grant support from Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, and Chiesi; has served on Speakers Bureaus for AstraZeneca and Chiesi; and has been an investor in MedAlliance. Dr. Rogers has been a consultant for Medtronic; and a proctor for Medtronic and Edwards Lifesciences. Dr. Goncalves has been a proctor for Medtronic. Dr. Hanna has been a speaker for Edwards Lifesciences. Dr. Asch has been the director of an academic cardiovascular imaging core lab with institutional contracts with Edwards Lifesciences, Medtronic, Boston Scientific, Biotronik, and Abbott. Dr. Weissman has been the director of an academic cardiovascular imaging core lab with institutional contracts with Boston Scientific, Ancora Heart, LivaNova, and HDL Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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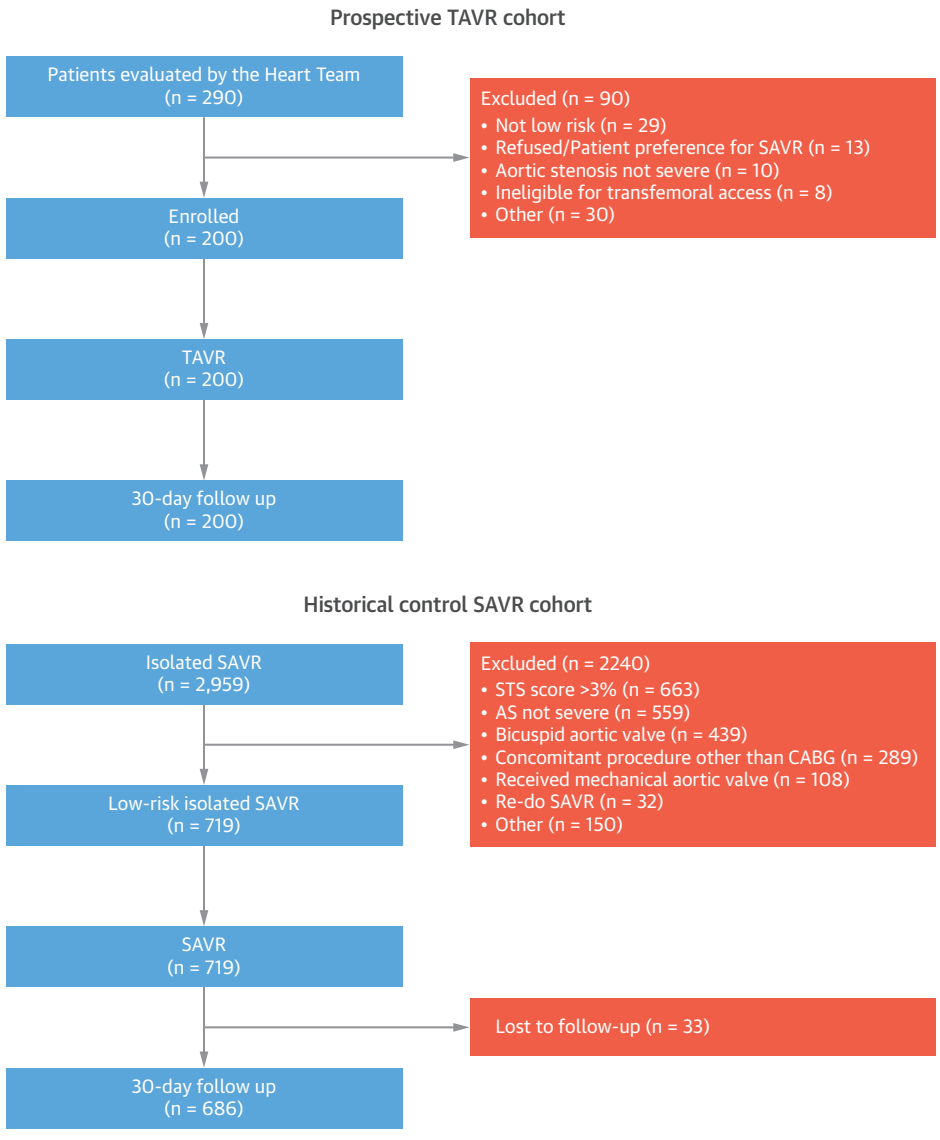
FIGURE 1 Study Design



Historical control group was composed of patients who underwent isolated SAVR at the enrolling centers in the STS database. A full list of exclusions to ensure patients were low risk is included in the Online Appendix. AS = aortic stenosis; CABG = coronary artery bypass grafting; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

stenosis was defined as a mean aortic valve gradient ≥40 mm Hg *or* Vmax ≥4 m/s *and* calculated aortic valve area ≤1.0 cm^2 *or* aortic valve area index ≤0.6 cm^2/m^2. Only patients who were symptomatic with dyspnea (New York Heart Association [NYHA] functional class II or higher), angina pectoris, or cardiac syncope were included. Patients with unrevascularized coronary artery disease or requiring intervention for another heart valve were excluded. Patients with bicuspid aortic stenosis were excluded and enrolled in a separate registry arm of the trial that is not part of this analysis. Eligibility for transfemoral access and TAVR valve sizing were determined by pre-procedural contrast-enhanced CT according to

TABLE 1 Baseline Characteristics

	Observed			IPW Adjusted		
	TAVR	SAVR	p Value	TAVR	SAVR	p Value
Age, yrs	73.6 ± 6.1	70.0 ± 8.3	<0.001	71.7 ± 14.9	70.9 ± 9.2	0.17
Male	123/200 (61.5)	438/719 (60.9)	0.88	119/200 (59.4)	439/719 (61.0)	0.69
Body mass index, kg/m^2	31.1 ± 6.6	30.9 ± 12.9	0.73	32.6 ± 14.7	30.7 ± 13.3	0.002
NYHA functional class III or IV	35/200 (17.5)	145/714 (20.3)	0.38	53/200 (26.0)	148/714 (20.6)	0.12
STS-PROM score, %*	1.8 ± 0.5	1.6 ± 0.6	<0.001	1.7 ± 1.0	1.7 ± 0.7	0.37
Diabetes mellitus	61/200 (30.5)	186/719 (25.9)	0.19	49/200 (24.0)	188/719 (26.1)	0.55
Renal insufficiency†	12/200 (6.0)	52/717 (7.3)	0.54	9/200 (4.3)	56/717 (7.7)	0.06
Hypertension	171/200 (85.5)	574/719 (79.8)	0.07	174/200 (86.8)	585/719 (81.3)	0.05
Peripheral vascular disease	4/200 (2.0)	46/719 (6.4)	0.02	34/200 (16.6)	40/719 (5.5)	<0.001
Cerebrovascular disease	16/200 (8.0)	61/719 (8.5)	0.83	13/200 (6.2)	66/719 (9.1)	0.14
Prior CVA/TIA	19/200 (9.5)	51/719 (7.1)	0.26	11/200 (5.0)	57/719 (7.9)	0.12
Chronic lung disease	16/200 (8.0)	125/719 (17.4)	0.001	25/200 (12.4)	111/719 (15.4)	0.26
LVEF	63.5 ± 7.5	58.7 ± 8.7	<0.001	63.2 ± 15.5	58.7 ± 10.1	<0.001
Prior PCI	42/200 (21.0)	67/719 (9.3)	<0.001	21/200 (10.2)	91/719 (12.6)	0.33
Prior CABG	2/200 (1.0)	22/719 (3.1)	0.11	6/200 (3.0)	19/719 (2.6)	0.78
Pre-existing PPM	7/200 (3.5)	30/713 (4.2)	0.65	5/200 (2.0)	38/713 (5.2)	0.01
Prior myocardial infarction	12/200 (6.0)	51/717 (7.1)	0.58	7/200 (3.3)	56/718 (7.7)	0.006
Arrhythmia	34/200 (17.0)	83/719 (11.5)	0.04	26/200 (12.6)	101/719 (14.0)	0.59

Values are mean ± SD or n/N (%). Adjusted patient counts, both SAVR and TAVR, are rounded up. *The Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) score estimates the rate of death at 30 days among patients undergoing SAVR based on a pre-defined number of baseline demographic and clinical characteristics, and procedural variables. †Renal insufficiency defined as either GFR <60 ml/min/1.73 m^2 or dialysis dependent.

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; IPW = inverse probability weighting; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVD = peripheral vascular disease; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

the TAVR device manufacturers' instructions for use. A complete list of trial inclusion and exclusion criteria is included in Online Table 3.

TAVR PROCEDURES. Patients underwent TAVR via transfemoral access using a commercially available balloon-expandable (Sapien 3, Edwards Lifesciences, Irvine, California) or self-expanding TAVR device (CoreValve, Evolut R, or Evolut PRO, Medtronic, Minneapolis, Minnesota). The choice of TAVR device and use of general anesthesia or moderate sedation was at the discretion of the implanting physicians. Alternate access was not permitted. Every TAVR patient underwent follow-up imaging to evaluate for leaflet thrombosis with 4-dimensional contrast-enhanced cardiac CT at 30 days. Patients with renal dysfunction precluding contrast administration underwent transesophageal echocardiography (TEE) instead.

HISTORICAL STS SAVR COHORT. All patients who underwent isolated SAVR (as defined by STS) at enrolling centers between January 1, 2013, and December 31, 2017, and whose data were recorded in the STS Adult Cardiac Surgery database were included in a deidentified manner. Patients were subsequently excluded from the analysis if they were not low risk according to the STS-PROM score or due to significant comorbidities. The most common reasons for excluding SAVR patients were STS score >3%, aortic stenosis not severe, bicuspid aortic valve, concomitant procedure other than coronary artery bypass graft surgery (CABG), and received mechanical prosthesis (**Figure 1**). A complete list of exclusion criteria is included in Online Table 4.

CARDIAC CT ANALYSIS FOR LEAFLET THROMBOSIS. CT scans were performed using 64-slice or greater multidetector row CT and contrast-enhanced retrospective electrocardiogram-gated acquisitions without dose modulation. Tube potential was set at 120 kV. Images were reconstructed at 10% intervals. Images were reconstructed with <1.0-mm slice thickness and 50% slice overlap. Dedicated 3-dimensional analysis software (Synapse 3D, Fujifilm Medical Systems, Stamford, Connecticut) was used to create 2-dimensional axial and multiplanar reconstruction in valve specific planes. Images were evaluated in systole and diastole for structural abnormalities and leaflet motion. Abnormalities were defined using previously described criteria (14). Hypoattenuated leaflet thickening (HALT) was defined as an area of CT hypoattenuation beginning at the leaflet insertion to the valve frame. Reduction in leaflet motion (RELM) was defined as mild (<50%

TABLE 2 Procedural Characteristics

TAVR	
Total procedure time, min	88.2 ± 40.4
General anesthesia	49/200 (24.5)
Transfemoral access	200/200 (100.0)
Implantation of >1 valve	4/200 (2.0)
Conversion to surgery	1/200 (0.5)
Balloon expandable valve	180/204 (88.2)
Self-expanding valve	24/204 (11.8)
Valve size implanted	
20 mm	10/204 (4.9)
23 mm	46/204 (22.5)
26 mm	100/204 (49.0)
29 mm	42/204 (20.6)
31/34 mm	6/204 (2.9)
SAVR	
Valve size implanted	
≤19 mm	76/719 (10.6)
21 mm	216/719 (30.0)
23 mm	261/719 (36.3)
25 mm	123/719 (17.1)
27 mm	37/719 (5.1)
29 mm	6/719 (0.8)

Values are mean ± SD or n/N (%). Denominator for the TAVR valve type and sizes is 204 because 4 patients required implantation of 2 valves during the index procedure.

Abbreviations as in Table 1.

reduction in leaflet excursion), moderate (50% to 70% reduction in leaflet excursion), severe (>70% reduction in leaflet excursion), or immobile (no leaflet motion). Hypoattenuation affecting motion was defined as HALT in combination with at least moderate RELM. All findings of HALT and RELM were confirmed by consensus of 2 independent readers.

STATISTICAL ANALYSIS. Continuous variables are presented as means and standard deviations, categorical variables as percentages. Comparisons between TAVR and SAVR patients were made with unpaired Student's *t*-tests for continuous variables and contingency table chi-square for categorical variables for the observed baseline data. Propensity scores were calculated by logistic regression of TAVR versus SAVR using the following variables: age, male sex, race, hypertension, diabetes, hyperlipidemia, prior stroke or transient ischemic attack, chronic lung disease, arrhythmia (any), cerebrovascular disease, peripheral vascular disease, prior CABG, prior percutaneous coronary intervention, cancer, and STS-PROM score. Inverse probability weighting (IPW) was used to balance TAVR and SAVR patients with respect to potentially confounding variables. Logistic regression, adjusted by IPW, was used to compare TAVR versus SAVR with respect to the composite endpoint of all-cause mortality, stroke, and >mild paravalvular aortic regurgitation. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. A total of 290 patients were screened by the local heart teams, and ultimately, 200 patients underwent TAVR at 11 centers in the United States. The most common reasons for exclusion were the patient not being low risk, declined to participate in research or preferred to undergo SAVR, not meeting echocardiographic criteria for severe aortic stenosis, and not being eligible for transfemoral access (Figure 1). A total of 2,959 patients who underwent isolated SAVR at the enrolling centers were evaluated for the historical control cohort. After exclusions, a

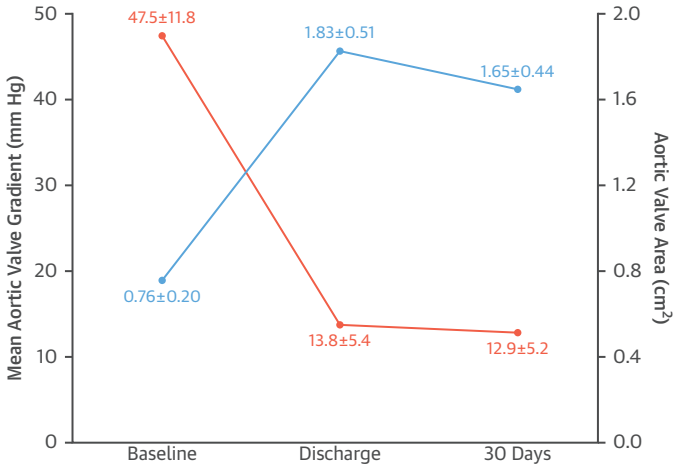
TABLE 3 In-Hospital Procedure-Related Complications

	TAVR	SAVR	p Value	Difference (95% CI)
Length of stay post-procedure, days	2.0 ± 1.1	6.4 ± 3.9	<0.001	−3.6 (−4.95 to −3.85)
VARC 2 life-threatening or major bleeding*	5/200 (2.5)	74/719 (10.3)	<0.001	−7.8 (−0.13 to − 0.02)
VARC 2 major vascular complications	5/200 (2.5)	–	–	–
Acute kidney injury†	0/200 (0.0)	–	–	–
All-cause death	0/200 (0.0)	5/719 (0.7)	0.591	−0.7 (−0.02 to 0.01)
Stroke	0/200 (0.0)	4/719 (0.6)	0.582	−0.6 (−0.02 to 0.01)
MI	0/200 (0.0)	–	–	–
Endocarditis	0/200 (0.0)	–	–	–
New-onset atrial fibrillation	6/200 (3.0)	293/719 (40.8)	<0.001	−37.8 (−0.46 to−0.30)
New PPM implantation	10/200 (5.0)	32/719 (4.5)	0.742	0.5 (−0.04 to 0.05)
Coronary artery obstruction	1/200 (0.5)	–	–	–

Values are mean ± SD or n/N (%), unless otherwise indicated. *VARC 2 major bleeding for SAVR assumed if ≥3 units red blood cell transfusion given during procedure. †Stage 3 acute kidney injury defined as increase in serum creatinine to ≥300% (>3× increase compared with baseline) *or* serum creatinine ≥4.0 mg/dl with an acute increase ≥0.5 mg/dl *or* new requirement for dialysis.

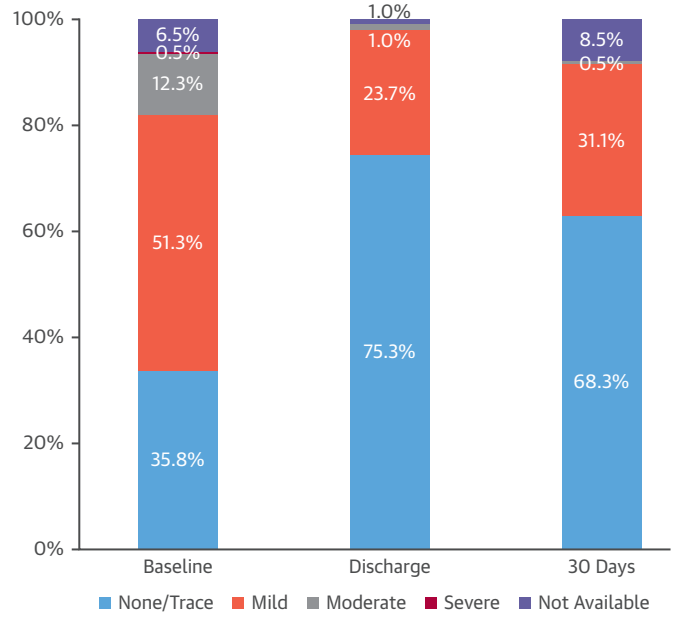
CI = confidence interval; MI = myocardial infarction; all other abbreviations as in Table 1.

FIGURE 2 TAVR Hemodynamics



Complete echocardiographic studies were obtained in TAVR patients at baseline, before hospital discharge and at 30-day follow up. Results are from the core lab analysis. TAVR = transcatheter aortic valve replacement.

FIGURE 3 Total Aortic Regurgitation in the TAVR Cohort



Complete echocardiographic studies were obtained in TAVR patients at baseline, before hospital discharge, and at 30-day follow-up. Total aortic regurgitation includes transvalvular and paravalvular regurgitation. Reasons why data were not available included uninterpretable echocardiographic images and patients lost to follow-up. Results are from the core lab analysis. TAVR = transcatheter aortic valve replacement.

total of 719 SAVR patients were included in the historical control cohort for the final analysis (Figure 1). Unadjusted and adjusted baseline demographic and clinical characteristics are provided in Table 1. Before adjustment, SAVR patients were younger with a lower mean STS-PROM score, lower mean left ventricular ejection fraction, higher prevalence of peripheral vascular disease and chronic obstructive pulmonary disease, and lower rates of prior percutaneous coronary intervention or arrhythmia. After IPW adjustment, there was no longer any difference between the 2 groups with regard to age and STS-PROM score. There remained a difference in mean left ventricular ejection fraction, but both were within normal limits.

PROCEDURAL AND 30-DAY OUTCOMES. Most TAVR procedures were performed under moderate sedation with a balloon-expandable TAVR valve, and all were performed via transfemoral access (Table 2). The rate of vascular and bleeding complications was low (Table 3). No TAVR patient crossed over to SAVR, but 1 TAVR patient required emergency CABG for coronary artery obstruction and made a full recovery. A total of 4 TAVR patients required implantation of a second valve during the index procedure (1 received 2 self-expanding valves, and 3 received 2 balloon-expandable valves). A total of 40.6% of SAVR patients received a 21-mm bioprosthesis or smaller, and only 4.3% of patients underwent aortic annular enlargement before SAVR. By comparison, only 4.9% of TAVR patients received a 20-mm valve. Mean aortic valve gradients decreased significantly and aortic valve area increased significantly after TAVR (Figure 2). Two TAVR patients (1.0%) had moderate or severe paravalvular regurgitation at hospital discharge (Figure 3). Ninety-nine percent of patients were in NYHA functional class II or higher before TAVR, and 98.5% were in NYHA functional class I or II at 30-day follow-up (Figure 4).

Hospital length of stay was significantly shorter after TAVR. The rate of PPM implantation was low in both cohorts. The rate of post-operative atrial fibrillation was higher after SAVR. For the composite endpoint of all-cause mortality, disabling stroke, and >mild aortic regurgitation at hospital discharge, after adjustment, there was no difference between TAVR and SAVR (odds ratio: 0.49 [95% confidence interval: 0.19 to 1.2]; p = 0.127).

Unadjusted 30-day all-cause mortality was 0.0% versus 1.7%; p = 0.079 (95% confidence interval: −0.038 to 0.003), for TAVR versus SAVR, respectively. All 200 TAVR patients were discharged alive within 30 days of the TAVR procedure, and there was zero mortality and zero disabling stroke at

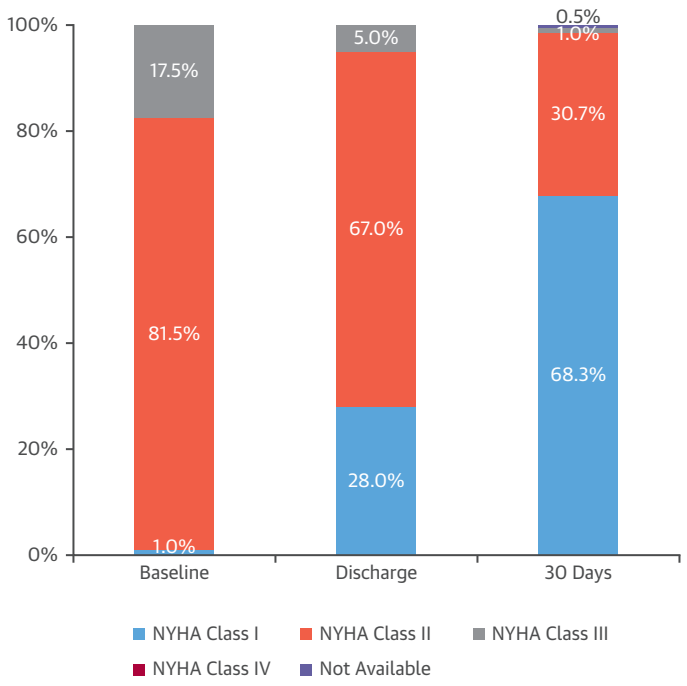
30 days. Of the 719 SAVR patients, 686 (95.4%) had 30-day follow-up, of which 12 (1.7%) had died. Six SAVR patients were still in the hospital at 30 days, and of these, 1 died on post-operative day 51, and the remaining 5 were eventually discharged alive. At 30 days, 1 TAVR patient sustained a nondisabling stroke; the rate of major vascular complications and life-threatening or major bleeding with TAVR was 3.0%; the rate of PPM implantation was 6.5%, and the rate of new-onset atrial fibrillation was 4.5%. No TAVR patients developed stage 3 acute kidney injury or required renal replacement therapy. Hemodynamics remained excellent at 30 days, and only 1 TAVR patient had residual ≥mild paravalvular aortic regurgitation (Figures 2 and 3).

30-DAY FOLLOW-UP IMAGING. At 30 days, 4-dimensional contrast-enhanced cardiac CT was performed in 192 patients and TEE in 2 patients. Six patients refused or were unable to undergo CT or TEE imaging. CT images were partially or fully uninterpretable in 6 patients, most commonly due to motion artifact. Figure 5 stratifies the findings according to evidence of HALT, RELM, and hypoattenuation affecting motion. No leaflet thrombosis was observed with a self-expanding TAVR device. There was no association with cerebrovascular events. Only 1 patient in the LRT trial had a nondisabling stroke at 30 days, but this patient did not have leaflet thrombosis. At 30 days, among patients with an interpretable CT or TEE, 152 of 193 (78.8%) of patients were taking antiplatelet therapy only (aspirin, thienopyridine, or dual antiplatelet therapy) and 39 of 193 (20.2%) of patients were taking oral anticoagulation (warfarin or direct oral anticoagulant). The incidence of HALT was 24 of 152 (15.8%) versus 3 of 39 (7.7%) ($p = 0.302$) in patients taking antiplatelet therapy only versus anticoagulation, respectively.

DISCUSSION

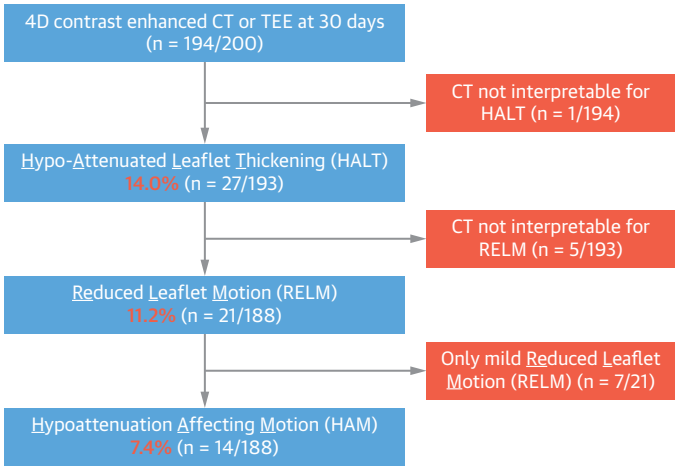
The LRT trial is the first U.S. TAVR trial in low-risk patients with symptomatic severe aortic stenosis. The key findings can be summarized as follows: TAVR in low-risk patients was safe, with zero mortality and zero disabling stroke at 30 days (Central Illustration). The rates of procedural complications, including moderate and higher paravalvular leak, PPM, life-threatening and major bleeding, and vascular complications, were very low with TAVR and SAVR. The rates of new-onset atrial fibrillation and hospital length of stay were significantly lower with TAVR compared with SAVR. Finally, leaflet thrombosis was observed in a minority of TAVR patients at 30 days, but there was no association with cerebrovascular events.

FIGURE 4 NYHA Functional Class in the TAVR Cohort



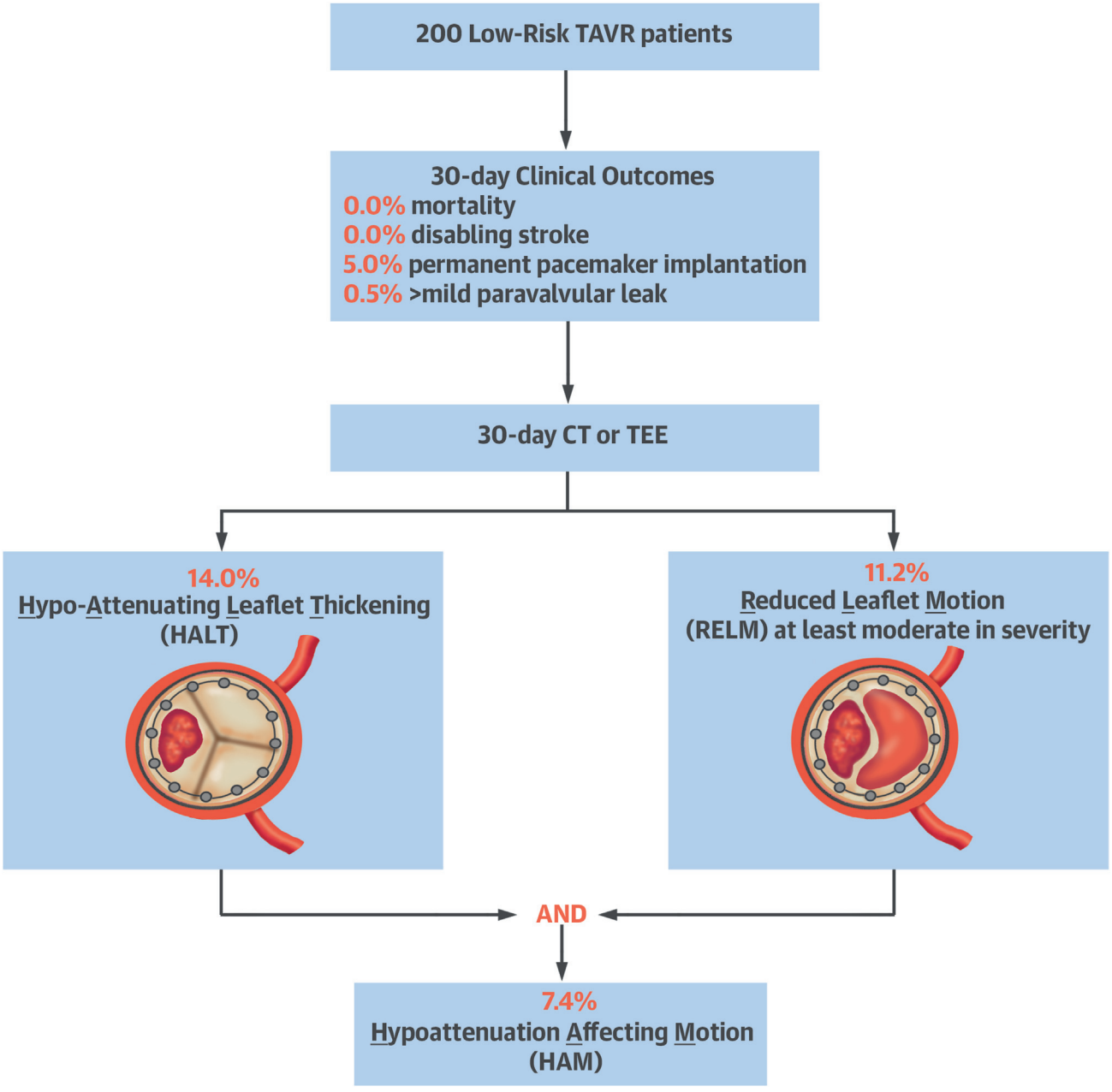
New York Heart Association (NYHA) functional class was recorded in TAVR patients at baseline, before hospital discharge, and at 30-day follow up. One patient did not attend 30-day follow-up. TAVR = transcatheter aortic valve replacement.

FIGURE 5 Subclinical Leaflet Thrombosis in the TAVR Cohort



Four-dimensional (4D) contrast-enhanced CT or TEE was performed in TAVR patients at 30-day follow-up. TAVR leaflet findings were defined according to Jilaihawi et al. (14). All imaging studies were analyzed in an independent core lab. CT = computed tomography; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiography.

CENTRAL ILLUSTRATION **Transcatheter Aortic Valve Replacement (TAVR) in Low-Risk Patients: Clinical Outcomes**



Waksman, R. et al. J Am Coll Cardiol. 2018;72(18):2095–105.

CT = computed tomography; TEE = transesophageal echocardiography.

The finding of zero mortality and zero disabling stroke at 30 days demonstrates the excellent safety of TAVR in low-risk patients. It is important to highlight that except for the sponsor, enrolling centers in the LRT trial were not high-volume centers or experienced centers in clinical trials. As such, these results truly represent contemporary real-world TAVR practice in the United States. The expected mortality rate in the SAVR cohort according to STS-PROM score was 1.6%, and the observed 30-day mortality was 1.7%. Thus, STS-PROM appears to be an accurate predictor of mortality in low-risk patients undergoing SAVR. By

contrast, the expected mortality in the TAVR cohort was 1.8% and the observed 30-day mortality rate was 0%. Thus, STS-PROM appeared to overestimate mortality in TAVR patients, which is consistent with prior observations (15).

The greatest mortality benefit for TAVR over SAVR is in high-risk patients (3,4). In low-risk patients, there may not be a significant mortality benefit. Rather the benefit may be in shorter hospital length of stay, swifter recovery, and superior prosthesis hemodynamics. In the LRT trial, hospital length of stay was >4 days longer with SAVR. In the SAVR cohort, 41% of patients received a 21-mm bioprosthesis or smaller, and <5% of patients underwent annular enlargement surgery. This observation is consistent with the surgical arms of the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) and PARTNER 2 (Placement of Aortic Transcatheter Valves 2) randomized trials in intermediate-risk patients, 34% and 44% of whom received a 21-mm bioprosthesis or smaller (5,6). Post-SAVR valve hemodynamics are not captured in the STS database and therefore could not be compared with TAVR. However, the mean gradients and valve areas in the LRT trial were comparable with those observed in the TAVR arm of the PARTNER 2 S3IR (Sapien 3 Intermediate-Risk) study (16), which is the best available comparator because 88.2% of patients in the LRT trial received a Sapien 3 balloon-expandable valve. At 30 days, mean aortic valve area was 1.7 ± 0.4 cm^2 versus 1.7 ± 0.4 cm^2, and mean gradient was 12.9 ± 5.2 mm Hg versus 11.4 ± 5.0 mm Hg for the LRT trial versus the S3IR trial, respectively. Paravalvular aortic regurgitation and need for PPM implantation have historically been the Achilles' heel of TAVR compared with SAVR. In the TAVR arm of the NOTION trial, these were 15.3% and 34.1%, respectively, at initial follow-up (8). However, in the LRT trial, the rates of moderate or severe paravalvular leak (0.5%) and new PPM implantation (6.5%) at 30 days were the lowest of all of the major TAVR studies. This may be explained by the use of predominantly newer-generation balloon-expandable TAVR devices in younger patients with less aortic annular calcification and less pre-existing conduction system disease, and improved implantation techniques. The mean age of TAVR patients in the LRT trial was 74 years, which is approximately 6 years younger than the intermediate-risk populations in PARTNER 2 and SURTAVI (5,6).

Leaflet thrombosis affects both transcatheter and surgical bioprosthetic valves. A mostly subclinical phenomenon, it may lead to increased transvalvular gradients and may be associated with increased risk of stroke and transient ischemic attacks. The best available data on this still poorly-understood phenomenon hail from the SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional Computed Tomography) and RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation) observational registries, in which the rates of TAVR leaflet thrombosis were 15% in patients on antiplatelet drugs and 4% in patients on oral anticoagulation (either direct oral anticoagulant or warfarin) (17). However, the time interval between TAVR and imaging in these registries varied widely (median 58 days, interquartile range 32 to 236 days). Our data demonstrate that this phenomenon affects low-risk patients with comparable prevalence (**Figure 5**) and is detectable as early as 30 days after TAVR. Similar to the 2 registries, the rate was lower in patients on oral anticoagulation. Leaflet thrombosis was not observed with self-expanding TAVR devices, although only 11.8% of patients in this study received a self-expanding valve. Larger studies are required to evaluate whether this phenomenon affects particular TAVR devices more than others. The rate of stroke was extremely low in the LRT TAVR population, so it is not possible to correlate with leaflet thrombosis. Extended follow-up will determine whether leaflet thrombosis impacts long-term prosthesis hemodynamics and durability. The lower rate of leaflet thickening in patients who were taking vitamin K inhibitors is intriguing but warrants a dedicated study due to the small number of patients on this regimen in the TAVR group.

STUDY LIMITATIONS. This study is the first prospective study of TAVR in low-risk patients conducted in the United States utilizing an historical cohort from a major national database as the control group. Using a nonadjudicated registry for the control group imposes certain limitations. Relevant to this trial, the SAVR patients were not prospectively screened to ensure low-risk status. Rather, we relied on STS-PROM score and absence of high-risk comorbidities to assume low-risk status. Nontraditional baseline characteristics that affect surgical risk such as frailty are not captured in the STS database. Selection bias cannot be excluded despite IPW adjustment. Specific outcomes such as vascular complications and major or life-threatening bleeding are not collected in the STS database either and therefore could not be compared. We therefore used the number of red blood cell transfusions as a surrogate for bleeding. Finally, the STS database does

not capture any data beyond 30 days. Extending routine follow-up data capture to at least 1 year and including data from echocardiography would allow the STS database to serve as a much more useful control for future studies. There is a precedent for using historical controls to evaluate a new TAVR device for commercial approval. The Edwards Sapien 3 transcatheter heart valve was approved in the United States on the basis of the results of a propensity score analysis comparing clinical outcomes in patients who underwent TAVR in a prospective nonrandomized registry with patients who underwent SAVR in the randomized arm of the PARTNER 2A trial (16). Using a dataset from a randomized controlled trial rather than a registry as the control group increases the reliability of the control data. Two large randomized trials of TAVR in low-risk patients have completed enrollment but have not yet reported their findings (18,19). If the LRT trial results match those from these 2 trials, then this will lend further support to this novel study methodology. Moreover, it will become more and more difficult to randomize patients to surgery in the future; therefore, this methodology is likely to become more widespread to evaluate new TAVR devices. Improving data collection quality and adding 1-year outcomes to the STS database are warranted to overcome the limitations of using this methodology for future studies. Finally, long-term follow up is needed to evaluate durability of TAVR devices.

CONCLUSIONS

TAVR is safe in low-risk patients with symptomatic severe aortic stenosis, with low procedural complications rates, short hospital length of stay, zero mortality, and zero disabling stroke at 30 days. Subclinical leaflet thrombosis was observed in a minority of TAVR patients at 30 days but was not associated with clinical events.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with severe, symptomatic aortic stenosis at relatively low surgical risk undergoing TAVR as an alternative strategy may develop subclinical thrombosis of the prosthetic valve leaflets within 30 days after implantation. This phenomenon can also occur after surgical valve replacement, but the mechanisms responsible, predictors and prognostic implications are not well understood.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare the long-term durability of bioprosthetic valves deployed by transcatheter versus surgical techniques, to determine the optimum antithrombotic medication regimen to prevent leaflet thrombosis, and to assess the impact of leaflet thrombosis on prosthesis durability.

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

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