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Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients

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ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) has emerged as a safe and effective therapeutic option for patients with severe aortic stenosis (AS) who are at prohibitive, high, or intermediate risk for surgical aortic valve replacement (SAVR). However, in low-risk patients, SAVR remains the standard therapy in current clinical practice.

OBJECTIVES This study sought to perform a meta-analysis of randomized controlled trials (RCTs) comparing TAVR versus SAVR in low-risk patients.

METHODS Electronic databases were searched from inception to March 20, 2019. RCTs comparing TAVR versus SAVR in low-risk patients (Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score <4%) were included. Primary outcome was all-cause death at 1 year. Random-effects models were used to calculate pooled risk ratio (RR) and corresponding 95% confidence interval (CI).

RESULTS The meta-analysis included 4 RCTs that randomized 2,887 patients (1,497 to TAVR and 1,390 to SAVR). The mean age of patients was 75.4 years, and the mean STS-PROM score was 2.3%. Compared with SAVR, TAVR was associated with significantly lower risk of all-cause death (2.1% vs. 3.5%; RR: 0.61; 95% CI: 0.39 to 0.96; $p = 0.03$; $I^2 = 0\%$) and cardiovascular death (1.6% vs. 2.9%; RR: 0.55; 95% CI: 0.33 to 0.90; $p = 0.02$; $I^2 = 0\%$) at 1 year. Rates of new/worsening atrial fibrillation, life-threatening/disabling bleeding, and acute kidney injury stage 2/3 were lower, whereas those of permanent pacemaker implantation and moderate/severe paravalvular leak were higher after TAVR versus SAVR. There were no significant differences between TAVR versus SAVR for major vascular complications, endocarditis, aortic valve re-intervention, and New York Heart Association functional class ≥II.

CONCLUSIONS In this meta-analysis of RCTs comparing TAVR versus SAVR in low-risk patients, TAVR was associated with significantly lower risk of all-cause death and cardiovascular death at 1 year. These findings suggest that TAVR may be the preferred option over SAVR in low-risk patients with severe AS who are candidates for bioprosthetic AVR.
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Approximately 12% of patients >75 years of age have aortic stenosis (AS), and 3.4% have severe AS; as the population continues to age, the prevalence of AS is anticipated to increase further (1). Transcatheter aortic valve replacement (TAVR) has emerged as a safe and effective therapeutic option for patients with symptomatic severe AS who are at prohibitive, high, or intermediate risk for surgical aortic valve replacement (SAVR), and more than 25,000 TAVRs are now being performed annually across >400 centers in the United States (2). Several recent studies have suggested comparable outcomes with TAVR and SAVR in low-risk patients with severe AS. The NOTION (Nordic Aortic Valve Intervention) randomized controlled trial (RCT) demonstrated no statistical difference in major

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clinical outcomes up to 5 years after TAVR versus SAVR in lower surgical risk patients ≥70 years of age (3–5). The single-arm LRT (Low Risk TAVR) trial was a Food and Drug Administration–approved Investigational Device Exemption study in the United States that found TAVR in low-risk patients was feasible and safe at 1 year (6,7). Recently, 2 pivotal RCTs demonstrated that TAVR with balloon-expandable or self-expanding valves was superior or noninferior to SAVR, respectively, in patients at low risk for surgery (8,9). Although these studies consistently demonstrated at least comparable outcomes of TAVR and SAVR, the possible superiority of TAVR over SAVR has important implications in the management of low-risk patients with severe AS. Moreover, the RCTs used different primary composite endpoints and were not powered for the individual components of the primary endpoints. We therefore sought to perform a systematic review and meta-analysis of RCTs comparing TAVR versus SAVR in low-risk patients.

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METHODS

DATA SOURCES. We searched PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane CENTRAL (Central Register of Controlled Trials), EMBASE (Excerpta Medica Database), and Web of Science from inception through March 20, 2019 for English language, peer-reviewed publications. The following key words and Medical Subject Headings (MeSH) terms were used: "transcatheter aortic valve replacement (MeSH)," "transcatheter aortic valve implantation," "TAVR," "TAVI," and "low risk" (Online Table 1). Reference lists of review articles, meta-analyses, and original studies identified by the electronic search were reviewed to find other potentially eligible studies.

STUDY SELECTION. Studies were included in the meta-analysis if they fulfilled the following criteria: 1) were a RCT (or post hoc analysis of a RCT); 2) compared TAVR versus SAVR; 3) included low-risk patients, defined as Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score <4%; and 4) reported 1-year outcomes. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for the protocol of our meta-analysis (Online Table 2) (10).

DATA EXTRACTION AND QUALITY ASSESSMENT. Two physician reviewers (D.K. and S.E.) evaluated independently the study eligibility and quality, and performed data extraction using standardized data collection sheets. Disagreements were resolved by consensus. Data on study characteristics, patient and procedural characteristics, and outcomes were extracted. Study quality was evaluated using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (11).

OUTCOMES. The primary outcome of interest was death from any cause. Secondary outcomes included cardiovascular death, stroke, myocardial infarction (MI), valve/heart failure rehospitalization, new/worsening atrial fibrillation, permanent pacemaker (PPM) implantation, major vascular complications, life-threatening/disabling bleeding, acute kidney injury (AKI) stage 2/3, endocarditis, aortic valve reintervention, moderate/severe paravalvular leak (PVL), and New York Heart Association (NYHA) functional class ≥II. All outcomes were assessed at 1-year follow-up.

STATISTICAL ANALYSIS. Random-effects models of DerSimonian and Laird were used to calculate pooled risk ratio (RR) and corresponding 95% confidence interval (CI) for primary and secondary outcomes. Heterogeneity was assessed using the Higgins I^2 statistic, with values <25% and >75% considered indicative of low and high heterogeneity, respectively. Publication bias was assessed visually by asymmetry in funnel plots and formally using Egger's regression test. Sensitivity analysis was performed using fixed-effect models. We also performed a sensitivity analysis after excluding the post hoc analysis of the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial. All tests were 2-tailed with a p value of <0.05 considered significant. Analyses were performed using Review Manager version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration Copenhagen, Denmark) and Meta-Essentials version 1.4 (12).

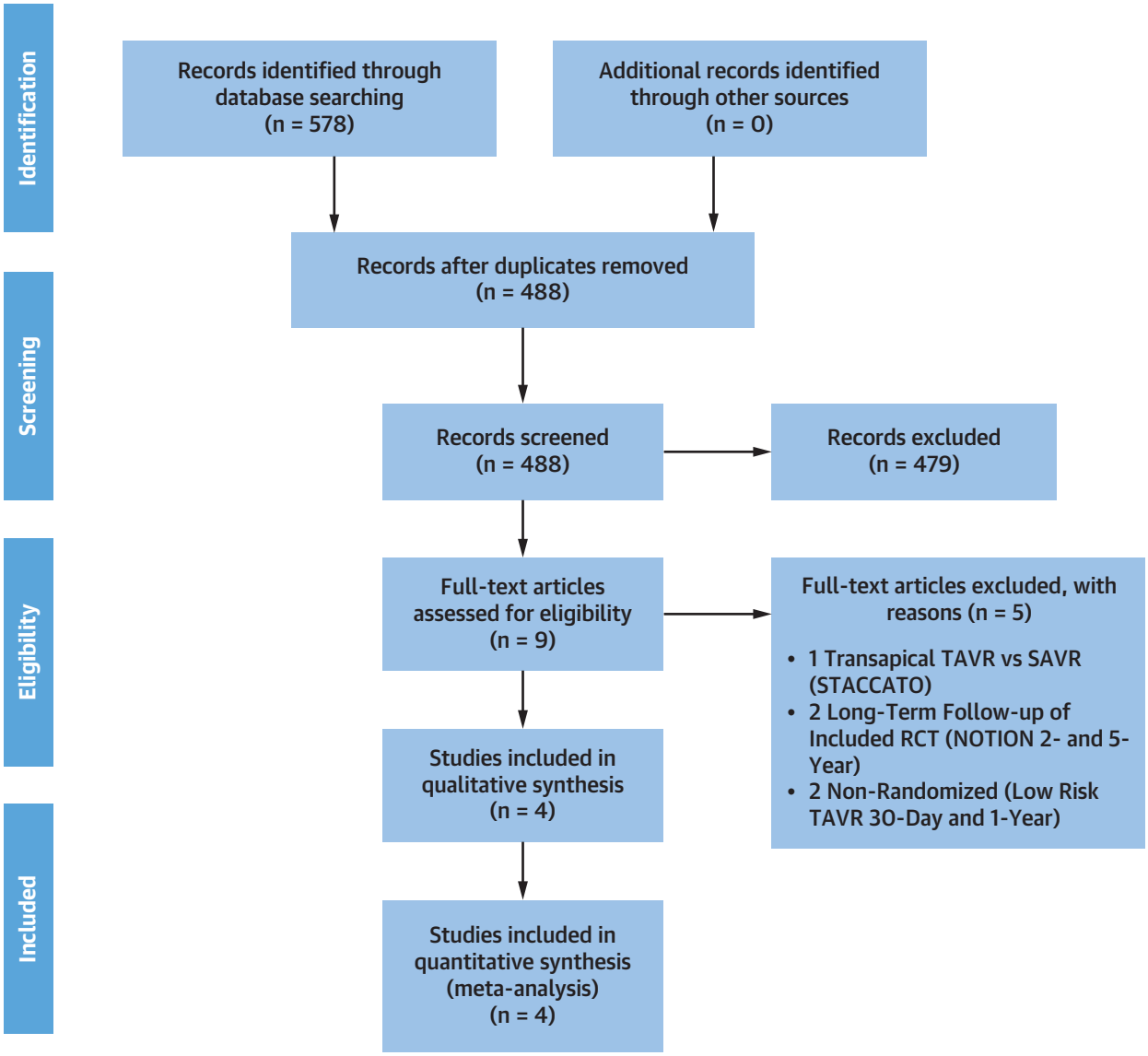
RESULTS

The database search yielded 578 articles. After excluding duplicates, 488 articles were screened at the title/abstract level, and 479 were excluded for various reasons (e.g., review articles, meta-analysis, observational studies, included low- and intermediate-risk patients). Nine full-text articles were assessed for eligibility (**Figure 1**) of which 4 were included in the final meta-analysis (3,8,9,13). The characteristics of the included studies are shown in **Table 1**. Of the 4 studies included in this

ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury
AS = aortic stenosis
CI = confidence interval
MI = myocardial infarction
NYHA = New York Heart Association
PPM = permanent pacemaker
PVL = paravalvular leak
RCT = randomized controlled trial
RR = risk ratio
SAVR = surgical aortic valve replacement
SVD = structural valve deterioration
TAVR = transcatheter aortic valve replacement

FIGURE 1 PRISMA Study Selection Flow Diagram



Electronic database search yielded 578 articles. After excluding duplicates, 488 articles were screened at the title/abstract level and 479 were excluded for various reasons. Nine full-text articles were assessed for eligibility of which 4 were included in the final meta-analysis. NOTION = Nordic Aortic Valve Intervention Trial; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

meta-analysis, 3 were RCTs and 1 was a post hoc analysis of a RCT. The studies included a total of 2,887 patients (1,497 randomized to TAVR and 1,390 randomized to SAVR). Three studies used self-expanding valves and 1 used balloon-expandable valves. Of the 1,497 patients randomized to TAVR, a self-expanding valve was used in 1,001 (66.9%) and a balloon-expandable valve in 496 (33.1%) patients. Risk-of-bias assessment demonstrated "low risk" of overall bias for 3 studies and "some concerns" for 1 study (post hoc analysis of a RCT) (Online Table 3). Baseline patient and procedural characteristics of the 2 groups in each study are summarized in Online Table 4. The mean age of patients was 75.4 years. The proportion of male patients ranged from 53.2% to 69.3%. The mean STS-PROM score was 2.3%.

TABLE 1 Characteristics of the Included Trials

	NOTION (3)	SURTAVI (STS <3%) (13)	PARTNER 3 (8)	Evolut Low Risk (9)
Year	2015	2018	2019	2019
Study design	RCT, superiority	Post hoc analysis of RCT	RCT, noninferiority and superiority	RCT, noninferiority
N	280	254*	950	1,403
Key inclusion criteria	≥70 yrs of age; severe AS; heart team evaluation; symptomatic; asymptomatic with LVPWT ≥17 mm, decreasing LVEF, or new onset atrial fibrillation; >1 yr survival.	Symptomatic severe AS; STS 3% to 15% and intermediate risk of operative mortality per heart team.	Severe calcific AS and NYHA functional class ≥2, exercise tolerance test demonstrating a limited exercise capacity, abnormal BP response, or arrhythmia, or asymptomatic with LVEF <50%; STS <4% and low risk of operative mortality per heart team; eligible for transfemoral access.	Severe AS; symptomatic or asymptomatic with very severe AS, exercise tolerance test demonstrating a limited exercise capacity, abnormal BP response, or arrhythmia, or LVEF <50%; STS <3% and low risk of operative mortality per heart team.
Key exclusion criteria	Concomitant severe valve disease; CAD requiring intervention; prior cardiac surgery; MI or stroke within 30 days; ESRD on dialysis; pulmonary failure with FEV1 or diffusion capacity <40% of expected.	Unicuspid or bicuspid aortic valve; severe AR/MR/TR; severe MS; multivessel CAD with SYNTAX score >22 and/or UPLM; MI ≤30 days before trial procedure; percutaneous coronary/peripheral intervention within 30 days before randomization; recent (<6 months) stroke/TIA; LVEF <20%; ESRD on dialysis or CrCl <20 ml/min; liver failure (Child C); severe COPD (FEV1 <750 ml); pulmonary artery systolic pressure >80 mm Hg; severe dementia; clinical frailty; estimated life expectancy <24 months.	Unicuspid, bicuspid, or non-calcified aortic valve; severe AR/MR (>3+), ≥moderate MS; pre-existing bioprosthetic or mechanical valve in any position; complex CAD; MI within 30 days before randomization; stroke/TIA within 90 days of randomization; active bacterial endocarditis within 180 days of randomization; LVEF <30%; eGFR <30 or dialysis; severe lung disease (FEV1 <50% predicted) or home oxygen; severe pulmonary hypertension; cirrhosis or active liver disease; clinical frailty; estimated life expectancy <24 months.	Bicuspid aortic valve; severe MR/TR; moderate or severe MS; pre-existing prosthetic heart valve in any position; multivessel CAD with SYNTAX score >22 and/or UPLM; MI ≤30 days before trial procedure; percutaneous coronary/peripheral intervention with BMS within 30 days or DES within 180 days before randomization; recent (<2 months) stroke/TIA; severe dementia; estimated life expectancy <24 months.
TAVR valve type	CoreValve (100%) (Medtronic, Dublin, Ireland)	CoreValve (84%) or Evolut R (16%) (Medtronic, Dublin, Ireland)	Sapien 3 (100%) (Edwards Lifesciences, Irvine, California)	CoreValve (3.6%), Evolut R (74.1%), or Evolut PRO (22.3%) (Medtronic, Dublin, Ireland)
Primary endpoint	Composite of all-cause death, stroke, or MI at 1 yr.	Composite of all-cause death or disabling stroke at 24 months.	Composite of all-cause death, stroke, or rehospitalization at 1 yr.	Composite of all-cause death or disabling stroke at 24 months.

*Included in current meta-analysis.

AR = aortic regurgitation; AS = aortic stenosis; BMS = bare-metal stent; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; DES = drug-eluting stents; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FEV1 = forced expiratory volume in 1 s; LVEF = left ventricular ejection fraction; LVPWT = left ventricular posterior wall thickness; MI = myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; NOTION = Nordic Aortic Valve Intervention Trial; NYHA = New York Heart Association; PARTNER = Placement of Aortic Transcatheter Valves; RCT = randomized controlled trial; STS = Society of Thoracic Surgeons; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; TIA = transient ischemic attack; TR = tricuspid regurgitation; UPLM = unprotected left main coronary artery.

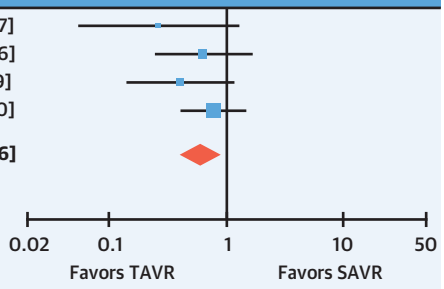
In low-risk patients with severe AS, TAVR was associated with significantly decreased risk of death from any cause at 1 year compared with SAVR (2.1% vs. 3.5%; RR: 0.61; 95% CI: 0.39 to 0.96; p = 0.03; I^2 = 0%) (**Central Illustration**). For the secondary outcomes studied, TAVR was associated with significantly lower risk of cardiovascular death (1.6% vs. 2.9%; RR: 0.55; 95% CI: 0.33 to 0.90; p = 0.02; I^2 = 0%) (**Central Illustration**), with no statistically significant differences in stroke (3.0% vs. 4.2%; RR: 0.68; 95% CI: 0.43 to 1.07; p = 0.10; I^2 = 17%), MI (1.7% vs. 2.1%; RR: 0.78; 95% CI: 0.46 to 1.34; p = 0.37; I^2 = 0%), or valve/heart failure rehospitalization (5.2% vs. 7.9%; RR: 0.72; 95% CI: 0.42 to 1.23; p = 0.23; I^2 = 62%), compared with SAVR (**Figure 2**). Rates of new/worsening atrial fibrillation (10.0% vs. 39.4%; RR: 0.27; 95% CI: 0.20 to 0.32; p < 0.001; I^2 = 63%), life-threatening/disabling bleeding (3.9% vs. 11.2%; RR: 0.37; 95% CI: 0.24 to 0.55; p < 0.001; I^2 = 42%), and AKI stage 2/3 (0.7% vs. 2.9%; RR: 0.26; 95% CI: 0.13 to 0.52; p < 0.001; I^2 = 0%) were significantly lower, whereas those of PPM implantation (17.4% vs. 5.5%; RR: 3.85; 95% CI: 1.73 to 8.58; p = 0.001; I^2 = 85%) and moderate/severe PVL (3.6% vs. 1.7%; RR: 2.16; 95% CI: 1.03 to 4.54; p = 0.04; I^2 = 18%) were significantly higher with TAVR versus SAVR. There were no significant differences between TAVR versus SAVR for major vascular complications (3.6% vs. 2.4%; RR: 1.66; 95% CI: 0.89 to 3.11; p = 0.11; I^2 = 30%), endocarditis (0.4% vs. 0.6%; RR: 0.73; 95% CI: 0.24 to 2.20; p = 0.58; I^2 = 0%), aortic valve reintervention (1.1% vs. 0.6%; RR, 0.75; 95% CI, 0.67 to 4.59; p = 0.25; I^3=3%), and NYHA functional class ≥II (21.2% vs. 17.6%; RR: 1.24; 95% CI: 0.96 to 1.61; p = 0.11; I^2 = 45%) (Online Figure 1). Visual assessment of funnel plots showed asymmetry suggesting potential risk of publication bias; however, formal assessment using Egger's regression test demonstrated no evidence of publication bias for the outcomes studied with the exception of major vascular complications (p = 0.025) (Online Figure 2).

CENTRAL ILLUSTRATION **All-Cause and Cardiovascular Death at 1 Year After TAVR Versus SAVR in Low-Risk Patients**

A

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
SURTAVI (STS Below 3%)	2	131	7	123	8.4%	0.27 [0.06, 1.27]
NOTION	7	145	10	135	23.2%	0.65 [0.26, 1.66]
PARTNER 3	5	496	11	454	18.5%	0.42 [0.15, 1.19]
Evolut Low Risk	17	725	20	678	49.9%	0.79 [0.42, 1.50]
Total (95% CI)		**1,497**		**1,390**	**100.0%**	**0.61 [0.39, 0.96]**
Total events	31		48			

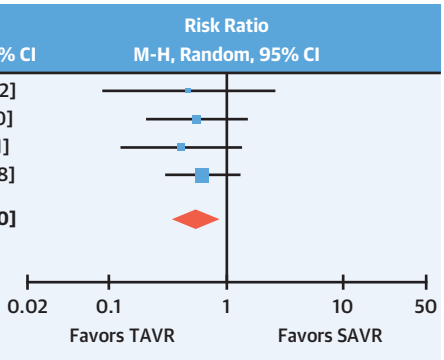
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.28$, df = 3 (p = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 2.12 (p = 0.03)



B

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
SURTAVI (STS Below 3%)	2	131	4	123	8.8%	0.47 [0.09, 2.52]
NOTION	6	145	10	135	25.6%	0.56 [0.21, 1.50]
PARTNER 3	4	496	9	454	18.1%	0.41 [0.13, 1.31]
Evolut Low Risk	12	725	18	678	47.5%	0.62 [0.30, 1.28]
Total (95% CI)		**1,497**		**1,390**	**100.0%**	**0.55 [0.33, 0.90]**
Total events	24		41			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 3 (p = 0.94); $I^2 = 0\%$
Test for overall effect: Z = 2.37 (p = 0.02)



Kolte, D. et al. J Am Coll Cardiol. 2019;74(12):1532–40.

All-cause death **(A)** and cardiovascular death **(B)** at 1 year after TAVR versus SAVR in low-risk patients are shown. In low-risk patients with severe aortic stenosis, TAVR was associated with significantly lower risk of all-cause death (2.1% vs. 3.5%; RR: 0.61; 95% CI: 0.39 to 0.96; p = 0.03; $I^2 = 0\%$) and cardiovascular death (1.6% vs. 2.9%; RR: 0.55; 95% CI: 0.33 to 0.90; p = 0.02; $I^2 = 0\%$) at 1 year as compared with SAVR. CI = confidence interval; M-H = Mantel-Haenszel; NOTION = Nordic Aortic Valve Intervention Trial; PARTNER = Placement of Aortic Transcatheter Valves; RR = risk ratio; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVR = transcatheter aortic valve replacement.

Sensitivity analysis using fixed-effect models showed similar results (Online Table 5). Sensitivity analysis after excluding the post hoc analysis of the SURTAVI trial showed similar results except for all-cause death, which was no longer statistically significant (RR: 0.66; 95% CI: 0.41 to 1.06; p = 0.09; $I^2 = 0\%$) and valve/heart failure rehospitalization, which was significantly lower with TAVR versus SAVR (RR: 0.59; 95% CI: 0.43 to 0.81; p = 0.001; $I^2 = 0\%$) (Online Table 6).

DISCUSSION

In this meta-analysis of RCTs comparing TAVR versus SAVR in patients with severe AS who are at low risk of operative mortality, TAVR was associated with significantly lower risk of all-cause death and cardiovascular death at 1 year. TAVR was also associated with lower rates of new/worsening atrial fibrillation, life-threatening/disabling bleeding, and AKI stage 2/3 compared with SAVR. There were no significant differences between TAVR versus SAVR for stroke, MI, valve/heart failure rehospitalizations, major vascular complications, endocarditis, aortic valve reintervention, or NYHA functional class. Rates of PPM implantation and moderate/severe PVL were significantly higher after TAVR versus SAVR. To our knowledge, this is the first meta-analysis of RCTs comparing TAVR versus SAVR in low-risk patients.

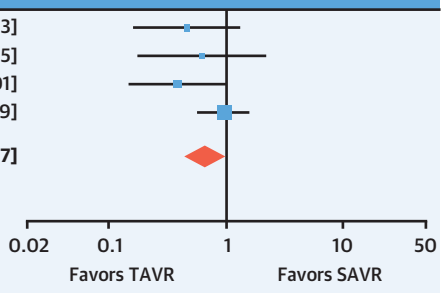
Since the initial Food and Drug Administration approval in November 2011 for patients at prohibitive risk for surgery, the use of TAVR has rapidly expanded over the past few years to patients at high and intermediate risk for SAVR. However, in patients

FIGURE 2 Stroke, MI, and Valve/Heart Failure Rehospitalization at 1 Year After TAVR Versus SAVR in Low-Risk Patients

A

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
SURTAVI (STS Below 3%)	5	131	10	123	16.7%	0.47 [0.17, 1.33]
NOTION	4	145	6	135	12.3%	0.62 [0.18, 2.15]
PARTNER 3	6	496	14	454	19.8%	0.39 [0.15, 1.01]
Evolut Low Risk	30	725	29	678	51.2%	0.97 [0.59, 1.59]
Total (95% CI)		**1497**		**1390**	**100.0%**	**0.68 [0.43, 1.07]**
Total events	45		59			

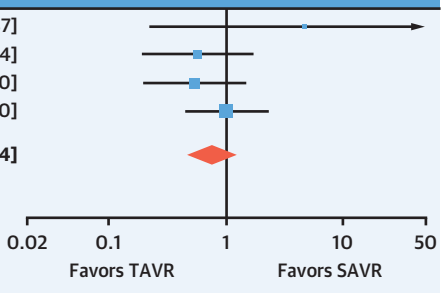
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.62$, df = 3 (P = 0.30); $I^2 = 17\%$
Test for overall effect: Z = 1.66 (P = 0.10)



B

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
SURTAVI (STS Below 3%)	2	131	0	123	3.2%	4.70 [0.23, 96.87]
NOTION	5	145	8	135	24.2%	0.58 [0.20, 1.74]
PARTNER 3	6	496	10	454	28.7%	0.55 [0.20, 1.50]
Evolut Low Risk	12	725	11	678	43.9%	1.02 [0.45, 2.30]
Total (95% CI)		**1497**		**1390**	**100.0%**	**0.78 [0.46, 1.34]**
Total events	25		29			

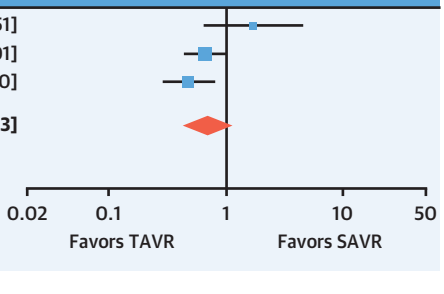
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.53$, df = 3 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 0.89 (P = 0.37)



C

Study or Subgroup	TAVR Events	TAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
SURTAVI (STS Below 3%)	11	131	6	123	19.9%	1.72 [0.66, 4.51]
PARTNER 3	36	496	49	454	42.1%	0.67 [0.45, 1.01]
Evolut Low Risk	23	725	44	678	38.0%	0.49 [0.30, 0.80]
Total (95% CI)		**1352**		**1255**	**100.0%**	**0.72 [0.42, 1.23]**
Total events	70		99			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 5.23$, df = 2 (P = 0.07); $I^2 = 62\%$
Test for overall effect: Z = 1.21 (P = 0.23)



Stroke **(A)**, myocardial infarction **(B)**, and valve/heart failure rehospitalization **(C)** at 1 year after TAVR versus SAVR in low-risk patients are shown. In low-risk patients with severe aortic stenosis, there were no statistically significant differences between TAVR versus SAVR for stroke (3.0% vs. 4.2%; RR: 0.68; 95% CI: 0.43 to 1.07; p = 0.10; $I^2 = 17\%$), myocardial infarction (1.7% vs. 2.1%; RR: 0.78; 95% CI: 0.46 to 1.34; p = 0.37; $I^2 = 0\%$), and valve/heart failure rehospitalization (5.2% vs. 7.9%; RR: 0.72; 95% CI: 0.42 to 1.23; p = 0.23; $I^2 = 62\%$) at 1 year. CI = confidence interval; M-H = Mantel-Haenszel; MI = myocardial infarction; NOTION = Nordic Aortic Valve Intervention Trial; PARTNER = Placement of Aortic Transcatheter Valves; RR = risk ratio; STS = Society of Thoracic Surgeons; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation; other abbreviations as in Figure 1.

who are at low risk for operative mortality and in younger patients, SAVR remains the standard therapy in current clinical practice (14). Observational studies comparing TAVR versus SAVR in low-risk patients have produced conflicting results (15-17). The NOTION trial was the first RCT to demonstrate that in lower surgical risk patients ≥70 years of age (>80% with STS-PROM <4%), TAVR was noninferior to SAVR for the primary composite endpoint of death, MI, or stroke at 1 year, with similar results seen at 5-year follow-up (3-5). Recently, 2 pivotal RCTs demonstrated noninferiority/superiority of TAVR versus SAVR in patients at low risk for surgery (8,9). In the PARTNER 3 trial, which randomized 1,000 low-risk

patients to TAVR with a balloon-expandable valve or SAVR, TAVR was superior to SAVR for the primary endpoint (composite of death, stroke, or rehospitalization) at 1 year (8). Similarly, in the Evolut Low Risk trial of 1,468 low-risk patients, TAVR with a self-expanding bioprosthesis was noninferior to surgery with respect to the composite endpoint of death or disabling stroke at 24 months (9). Although the overall results of these trials are consistent, these studies used different primary composite endpoints and were not powered for the individual components of the primary endpoints.

In our meta-analysis focused on individual endpoints, TAVR was associated with a 39% relative risk reduction in all-cause death and a 45% relative risk reduction in cardiovascular death compared with SAVR in low-risk patients with severe AS. Although all-cause death was statistically nonsignificant ($p = 0.09$) in the sensitivity analysis excluding post hoc analysis of the SURTAVI trial, the effect size (RR: 0.66) was comparable to results of the primary analysis in favor of TAVR and suggested that the lack of statistical significance may be due to a decrease in power to detect a significant difference. The magnitude of relative risk reduction for all-cause death and cardiovascular death with TAVR versus SAVR at 1 year is consistent with that seen in the PARTNER 3 (1.0% vs. 2.5% and 0.8% vs. 2.8%, respectively) and Evolut Low Risk (2.4% vs. 3.0% and 1.7% vs. 2.6%, respectively) trials; however, the individual trials were not powered for these endpoints (8,9). A number of factors may contribute to the survival benefit observed with TAVR. These include the less invasive nature of TAVR and more rapid mobilization and recovery as compared with SAVR, coupled with the lower rates of complications including new/worsening atrial fibrillation, life-threatening/disabling bleeding, and AKI, all of which are known to be associated with worse outcomes (18–21).

In our meta-analysis of low-risk patients, rates of stroke were similar after TAVR and SAVR. However, TAVR was associated with higher rates of PPM implantation and moderate/severe PVL as compared with SAVR at 1 year. Need for PPM and moderate/severe PVL after TAVR are higher with self-expanding versus balloon-expandable valves, particularly with the older generations of transcatheter heart valves (22–24). Three of the 4 studies included in the current meta-analysis used self-expanding valves. The original CoreValve (Medtronic, Dublin, Ireland) was used in all patients randomized to TAVR in the NOTION trial, which also had the highest rates of PPM implantation (38.0%) and moderate/severe aortic regurgitation (15.7%) at 1 year among the trials included in this meta-analysis (3). Thus, the higher rates of PPM implantation and moderate/severe PVL with TAVR versus SAVR in our study are likely driven by the use of self-expanding valves in the majority of patients. Due to the small number of trials, and because each trial exclusively used either self-expanding or balloon-expandable valves, we were unable to perform meta-regression analysis to formally assess whether the risk of PPM or moderate/severe PVL with TAVR versus SAVR is modified by the transcatheter valve type in low-risk patients. Of note, in the PARTNER 3 trial, there were no significant differences between TAVR versus SAVR in rates of PPM implantation (7.3% vs. 5.4%) and moderate/severe PVL (0.6% vs. 0.5%) (8).

Our findings have important clinical implications. The lower rates of all-cause and cardiovascular death with TAVR suggest that it should be the preferred option over SAVR in low-risk patients (STS-PROM score <4%) with severe AS who are candidates for bioprosthetic AVR, transfemoral access, and who meet the inclusion criteria of the individual RCTs. It is important to note that patients with unicuspid, bicuspid, or noncalcified aortic valve, pre-existing bioprosthetic or mechanical valve, significant valve lesion in addition to aortic stenosis, or any other anatomic feature that increased the risk of complications associated with either TAVR or SAVR were excluded from the PARTNER 3 and Evolut Low Risk trials (8,9). Thus, the results of our meta-analysis do not apply to low-risk patients with any of these anatomic exclusion criteria. Moreover, although formal age criteria were not used for enrollment in the SURTAVI, PARTNER 3, and Evolut Low Risk trials, patients were required to be good candidates for SAVR with a bioprosthetic valve, inherently selecting for an elderly patient population. Results of the low-risk TAVR trials should therefore not be used to justify TAVR in young patients in whom a mechanical aortic valve prosthesis is the preferred strategy.

Long-term valve durability of transcatheter heart valves remains uncertain. In the UK TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry, among 241 patients who underwent TAVR between 2007 and 2011, the incidence of moderate and severe structural valve deterioration (SVD) between 5 and 10 years post-implantation (median 5.8 years) was 8.7% and 0.4%, respectively (25). Similarly, in the FRANCE-2 (French Aortic National CoreValve and Edwards) registry, among 4,201 high-risk patients who underwent TAVR between 2010 and 2012, the rates of moderate/severe SVD and severe SVD at 5 years were 13.3% and 2.5%, respectively (26). In the NOTION trial through

6 years, the rate of moderate/severe SVD was higher for SAVR versus TAVR (24.0% vs. 4.8%; $p < 0.001$) (27). Long-term echocardiographic follow-up to 10 years is planned within the PARTNER 3 and Evolut Low Risk trials, and will hopefully provide definitive guidance regarding the comparative long-term valve durability of surgical and transcatheter valve prostheses in low-risk patients.

STUDY LIMITATIONS. First, this meta-analysis used study-level data as we did not have access to individual patient-level data. Second, although 2- and 5-year outcomes from the NOTION trial have been reported, we used 1-year outcomes for our meta-analysis in keeping with the original trial design as well as for consistency with follow-up duration of other included trials (3-5). Third, the event rates in the Evolut Low Risk trial were derived from the estimated incidence (median of the posterior probability distribution as calculated by Bayesian analysis) as opposed to the true observed incidence (9). Fourth, timing of events was not available thus precluding time-to-event analyses and competing risk models. Last, due to the small number of studies in the meta-analysis, we were unable to perform meta-regression analysis to determine the influence of specific variables/effect modifiers (e.g., age, valve type, etc.) on the association between TAVR versus SAVR and outcomes in low-risk patients (28).

CONCLUSIONS

In this meta-analysis of RCTs comparing TAVR versus SAVR in low-risk patients, TAVR was associated with significantly lower risk of all-cause death and cardiovascular death at 1 year. Rates of new/worsening atrial fibrillation, life-threatening/disabling bleeding, and AKI stage 2/3 were lower, whereas those of PPM implantation and moderate/severe PVL were higher after TAVR versus SAVR at 1 year. Our findings are complementary to the recent pivotal RCTs and provide further evidence suggesting that TAVR may be the preferred option over SAVR in low-risk patients with severe AS who are candidates for bioprosthetic AVR. Long-term follow-up data on outcomes and valve durability remain critical.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: By meta-analysis, in low-risk patients with severe AS meeting the inclusion criteria of the randomized trials, TAVR is associated with a lower risk of all-cause death and cardiovascular death at 1 year compared with SAVR.

TRANSLATIONAL OUTLOOK: Longer-term follow-up of low-risk patients enrolled in the trials will improve understanding of the comparative benefits and risks of TAVR versus SAVR, on mortality, valve durability, and other outcomes.

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KEY WORDS death, low risk, surgical aortic valve replacement, transcatheter aortic valve implantation, transcatheter aortic valve replacement

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