Transcatheter aortic valve replacement in low-risk patients

Reemplazo percutáneo de válvula aórtica en pacientes de bajo riesgo

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Approximately 12.4% of patients >75 years of age have aortic stenosis (AS) and 3.4% have severe AS.[1] The prevalence of AS and its impact on public health and health care resources is expected to increase with the aging population.[2] Since the first human percutaneous balloon-expandable transcatheter aortic valve implantation by Dr. Alain Cribier on April 16, 2002 in Rouen, France, this disruptive technology has evolved rapidly over the past two decades.[3] Approximately 400,000 transcatheter aortic valve replacement (TAVR) procedures have been performed worldwide with an estimated growth of 40% per year, and the annual number of TAVRs have now surpassed the number of surgical aortic valve replacement (SAVR) procedures in some countries.[4,5] The role of TAVR as a safe and effective treatment option in patients with symptomatic severe aortic stenosis who are at prohibitive, high, or intermediate risk for surgery is well established. Recently, based on results of the PARTNER 3 and Evolut Low-Risk trials, the United States Food and Drug Administration expanded indication for TAVR to patients at low risk for SAVR.[6,7] This article will summarize the data on TAVR in low-risk patients, discuss considerations when choosing between TAVR vs. SAVR for low-risk patients, and highlight areas for future research.

TAVR VS. SAVR IN LOW-RISK PATIENTS

Prospective studies of TAVR in low-risk patients are summarized in **Table 1**.

Nordic Aortic Valve Intervention Trial (NOTION)

NOTION was an investigator-initiated, multi-center, non-blinded, superiority trial which randomized all-comer patients ≥70 years with isolated severe aortic valve stenosis to SAVR or TAVR in Denmark and Sweden.[8] The trial included 280 patients, 81.1% of whom were low-risk (Society of Thoracic Surgeons Predicted Risk Of Mortality [STS-PROM] <4%). The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction (MI) at 1 year. There was no significant difference in the rate of the primary endpoint between TAVR vs. SAVR at 1 year (13.1% vs. 16.3%, p=0.43) and 5 years (38.0% vs. 36.3%, p=0.86).[8,9] Compared with patients who underwent SAVR, those who underwent TAVR had significantly higher rates of permanent pacemaker (PPM) implantation and ≥ moderate total aortic regurgitation, and lower rates of major or life-threatening bleeding, acute kidney injury (AKI) stage 2 or 3, and new-onset or worsening atrial fibrillation (AF) at 30 days.[8]

Low Risk TAVR (LRT) Study

The LRT was an investigator-initiated, prospective, multicenter feasibility trial to test the safety of transfemoral TAVR in low-risk patients with symptomatic severe AS.[10] The study enrolled 200 low-risk (STS-PROM ≤3%) patients at 11 centers who underwent transfemoral TAVR and were compared to a historical cohort of 719 patients who underwent isolated SAVR at the same institutions. At 30 days, there was zero all-cause mortality in the TAVR group vs. 1.7% in the SAVR group (p=0.59).[10] PPM implantation rates were similar between TAVR and SAVR (5.0% vs. 4.5%, p=0.74). At 1-year follow-up, mortality was 3.0%, stroke rate was 2.1%, and PPM implantation rate was 7.3% in the TAVR group.[11]

Placement of Aortic Transcatheter Valves (PARTNER) 3 Trial

The PARTNER 3 trial was a multicenter, randomized trial comparing transfemoral TAVR using the third-generation balloon-expandable SAPIEN 3 (Edwards Lifesciences, Irvi ne, CA) valve system with SAVR in low-risk patients (STS-PROM <4%).[6] The primary endpoint was a composite of death, stroke, or rehospitalization at 1 year. Both noninferiority testing (with a prespecified margin of 6%) and superiority testing were performed in the as-treated population (n=950). At 1 year, the rate of the primary endpoint was significantly lower in the TAVR group than in the SAVR group (8.5% vs. 15.1%; absolute difference, −6.6%; 95% confidence interval[CI]: −10.8 to −2.5; p<0.001 for noninferiority; hazard ratio [HR], 0.54; 95%CI: 0.37 to 0.79; p=0.001 for superiority).[8] Results

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TABLE 1. Prospective studies of TAVR in low-risk patients.

	NOTION[8,9]	Low-Risk TAVR Study[10,11]	PARTNER 3[6]	Evolut Low Risk[7]
Year	2015	2018	2019	2019
Study Design	RCT, superiority	Prospective, single-arm	RCT, non-inferiority and superiority	RCT, non-inferiority
N	280	200	950	1,403
Key inclusion criteria	≥70 years of age; severe AS; heart team evaluation; symptomatic; asymptomatic with LVPWT ≥17 mm, decreasing LVEF, or new onset atrial fibrillation; >1 year survival.	Severe AS, symptomatic (NYHA functional class ≥2, angina pectoris, or syncope); STS ≤3%; eligible for transfemoral access; candidate for SAVR if offered; elective procedure; estimated life-expectancy >24 months.	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.	Bicuspid aortic valve; concomitant disease of another heart valve or aorta that requires intervention; ESRD on dialysis or CrCl<20 cc/min; LVEF <20%; recent (<6 months) stroke/TIA; recent (<30 days) AMI; symptomatic carotid/vertebral artery disease; severe unrevascularized CAD; recent (<30 days) or ongoing bleeding; uncontrolled atrial fibrillation; severe COPD (FEV1 <750 cc); liver failure with Child's class C or D; ongoing sepsis or infective endocarditis; preprocedural shock, inotropes, mechanical assist device, or cardiac arrest.	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 (FEVI <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 prior to trial procedure; percutaneous coronary/peripheral intervention with BSM within 30 days or DES within 180 days prior to randomization; recent (<2 months) stroke/TIA; severe dementia; estimated life-expectancy <24 months.
TAVR Valve Type	CoreValve (Medtronic Inc., Minneapolis, MN)	Sapien 3 (Edwards Lifesciences, Irvine, CA) or CoreValve, Evolut R, or Evolut PRO (Medtronic Inc., Minneapolis, MN)	Sapien 3 (Edwards Lifesciences, Irvine, CA)	CoreValve, Evolut R, or Evolut PRO (Medtronic Inc., Minneapolis, MN)
Primary Endpoint	Composite of all-cause death, stroke, or MI at 1 year.	All-cause death at 30 days.	Composite of all-cause death, stroke, or rehospitalization at 1 year.	Composite of all-cause death or disabling stroke at 24 months.

Adapted and modified from Kolte et al. ***J Am Coll Cardiol.***2019;74:1532-1540 (reference 13).

were consistent at 2-year follow-up (11.5% vs. 17.4%; absolute difference, −5.9%; HR, 0.63; 95%CI: 0.45 to 0.88; p=0.007).[12] TAVR resulted in a lower rate of stroke than SAVR at 30 days (0.6% vs. 2.4%, p=0.02) and 1 year (1.2% vs. 3.3%; p=0.03); however, this difference narrowed and was no longer statistically significant at 2 years (2.4% vs. 3.6%; p=0.28).[6,12] There were no significant differences in PPM implantation rates between TAVR vs. SAVR at 1- and 2-year follow-up. At 2 years, Valve Academic Research Consortium (VARC)-2 defined valve thrombosis rates were higher in the TAVR groups compared with the SAVR group (2.6% vs. 0.7%, p=0.02).[12]

Evolut Low Risk Trial

The Evolut Low Risk Trial was a multinational, randomized, noninferiority trial comparing the safety and efficacy of TAVR with one of the three self-expanding, supraannular bioprostheses (CoreValve, Evolut R, or Evolut PRO; Medtronic, Minneapolis, MN) with that of SAVR in low-risk patients (STS-PROM ≤3%).[7] The primary endpoint was a composite of death from any cause or disabling stroke at 24 months. The trial used Bayesian adaptive statistical methods with non informative prior distributions to assess the primary endpoint when 850 patients had reached 12-month follow-up. The prespecified noninferiority margin for the primary endpoint was 6%. The 24-month estimated incidence of the primary endpoint was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, −1.4%; 95% Bayesian credible interval for difference, −4.9 to 2.1; posterior probability of noninferiority >0.999).[7] At30 days, patients who had undergone TAVR, as compared with SAVR, had lower rates of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), AKI stage 2 or 3 (0.9% vs. 2.8%), and AF (7.7% vs. 35.4%), and higher rates of ≥ moderate aortic regurgitation (3.5% vs. 0.5%) and PPM implantation (17.4% vs. 6.1%).[7]

Meta-Analysis of TAVR vs. SAVR in Low-Risk Patients

In a meta-analysis that included 3 randomized controlled trials (NOTION, PARTNER 3, and Evolut Low Risk) and 1 *post hoc* analysis of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial, we found that TAVR was associated with significantly lower risk of all-cause death (2.1% vs. 3.5%; risk ratio [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 (**Figure 1**).[13] Rates of new or worsening AF, life-threatening or disabling bleeding, and AKI stage 2 or 3 were lower, whereas those of PPM implantation and ≥moderate paravalvular leak were higher after TAVR vs. SAVR.[13]

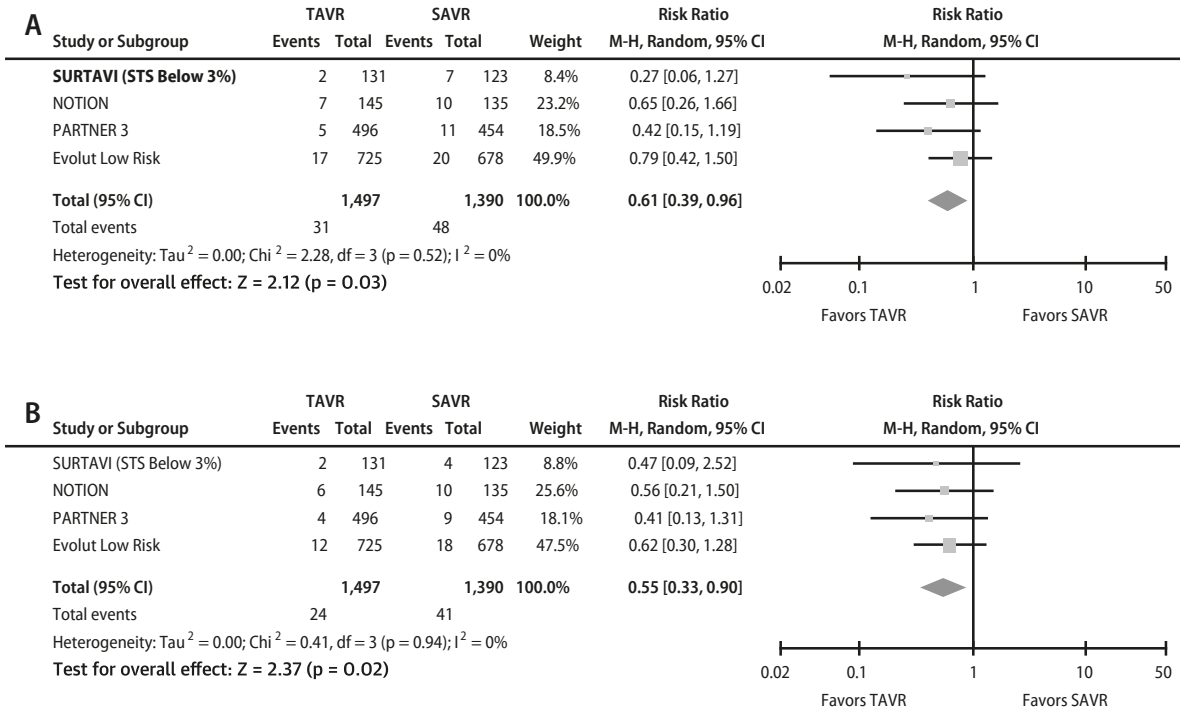

Figure 1. *All-Cause and Cardiovascular Death at 1 Year After TAVR vs. SAVR in Low-Risk Patients. All-cause death (A) and cardiovascular death (B) at 1 year after TAVR versus SAVR in low-risk patients are shown. In low-risk patients with severe aortic stenosis, TAVRwas associated withsignificantly lower risk of all-cause death (2.1% vs. 3.5%; RR, 0.61; 95% CI, 0.39 to 0.96;p=0.03; I2=0%) and cardiovascular death (1.6% vs.2.9%; RR, 0.55; 95% CI, 0.33 to 0.90;p=0.02; I2=0%) at 1 year as compared with SAVR. Adapted from Kolte et al. J Am Coll Cardiol.2019;74:1532-1540 (reference 13). CI = confidence interval; M-H = Mantel-Haenszel; NOTION = Nordic AorticValve Intervention Trial; PARTNER = Placement of Aortic Transcatheter Valves; RR = risk ratio; SAVR = surgicalaortic valve replacement; STS = Society of ThoracicSurgeons; SURTAVI = SurgicalReplacement and Transcatheter Aortic Valve Implantation; TAVR = transcatheter aortic valve replacement.*

CONSIDERATIONS WHEN CHOOSING BETWEEN TAVR VS. SAVR IN LOW-RISK PATIENTS

The choice between TAVR vs. SAVR for patients with symptomatic severe AS, particularly low-risk patients, should involve a Heart Team and a shared-decision making approach to ensure incorporation of patient goals and preferences into the final decision making.[14] It is important to note that the average age of patients in the pivotal low-risk trials was ~74 years, and patients not suitable for transfemoral access, with bicuspid aortic valves, prior bioprosthetic or mechanical valves in any position, severe aortic or mitral regurgitation, ≥ moderate mitral stenosis, low coronary height, severe aortic valve calcification, left ventricular outflow tract (LVOT) calcification were excluded from these trials (**Table 1**).[13] Similarly, patients with multivessel coronary artery disease with SYNTAX score >22 were also excluded. Patients who do not fulfill the strict inclusion and exclusion criteria for the trials may potentially be better served with SAVR.[15]

Another important consideration is valve durability and the possible need for a second AVR in the future. Although studies have shown that >90% of patients remain free of structural valve degeneration between 5 and 10 years post-TAVR, longer-term data are not yet available.[16] Similarly, while outcomes of valve-in-valve TAVR in patients with failed SAVR are comparable to native valve TAVR, data on TAVR-in-TAVR (or redo TAVR) are limited.[17,18] These aspects should be discussed with patients/families as part of the shared-decision making process when choosing between TAVR vs. SAVR in low-risk patients.[14]

Severe AS due to bicuspid anatomy is now encountered more frequently with the expansion of TAVR to younger low-risk patients. The Evolut Low Risk Bicuspid Study was a multicenter, prospective, single-arm study to assess the safety and efficacy of TAVR with one of the two self-expanding, supraannular bioprostheses (Evolut R or Evolut PRO; Medtronic, Minneapolis, MN) in low-risk patients with bicuspid aortic stenosis.[19] Patients <60 years, SYNTAX score >22, ascending aortic diameter >4.5 cm, aortopathy requiring surgical intervention, prohibitive LVOT calcification, and anatomic dimensions outside the recommended range were excluded. The primary safety endpoint of all-cause death or disabling stroke at 30-days occurred in 1.3% of patients.[19] The primary efficacy endpoint of device success (defined as absence of procedural mortality, correct position of 1 valve in the proper anatomical location, and absence of >mild aortic regurgitation) occurred in 95.3% of patients.[19] Although these short-term results are promising, longer-term data including randomized trials of TAVR vs. SAVR in low-risk patients with bicuspid aortic stenosis are needed.

CONCLUSION

TAVR has rapidly evolved as a safe and effective treatment option for patients with symptomatic severe AS across the entire spectrum of surgical risk. The choice between TAVR vs. SAVR for patients with symptomatic severe AS, particularly low-risk patients, should involve a Heart Team and a shared-decision making approach to ensure incorporation of patient goals and preferences into the final decision making. Patients who do not fulfill the strict inclusion and exclusion criteria for the pivotal low-risk trials may potentially be better served withSAVR. Further data on long-term durability of TAVR bioprostheses, redo TAVR, and TAVR in bicuspid anatomy are needed.

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