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Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis

1-Year Results From the All-Comers NOTION Randomized Clinical Trial

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ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) is an option in certain high-risk surgical patients with severe aortic valve stenosis. It is unknown whether TAVR can be safely introduced to lower-risk patients.

OBJECTIVES The NOTION (Nordic Aortic Valve Intervention Trial) randomized clinical trial compared TAVR with surgical aortic valve replacement (SAVR) in an all-comers patient cohort.

METHODS Patients ≥70 years old with severe aortic valve stenosis and no significant coronary artery disease were randomized 1:1 to TAVR using a self-expanding bioprosthesis versus SAVR. The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction (MI) at 1 year.

RESULTS A total of 280 patients were randomized at 3 Nordic centers. Mean age was 79.1 years, and 81.8% were considered low-risk patients. In the intention-to-treat population, no significant difference in the primary endpoint was found (13.1% vs. 16.3%; p = 0.43 for superiority). The result did not change in the as-treated population. No difference in the rate of cardiovascular death or prosthesis reintervention was found. Compared with SAVR-treated patients, TAVR-treated patients had more conduction abnormalities requiring pacemaker implantation, larger improvement in effective orifice area, more total aortic valve regurgitation, and higher New York Heart Association functional class at 1 year. SAVR-treated patients had more major or life-threatening bleeding, cardiogenic shock, acute kidney injury (stage II or III), and new-onset or worsening atrial fibrillation at 30 days than did TAVR-treated patients.

CONCLUSIONS In the NOTION trial, no significant difference between TAVR and SAVR was found for the composite rate of death from any cause, stroke, or MI after 1 year. (Nordic Aortic Valve Intervention Trial [NOTION]; NCT01057173) (J Am Coll Cardiol 2015;65:2184–94) © 2015 by the American College of Cardiology Foundation.

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Aortic valve stenosis is the most prevalent heart valve disease in the Western world, and it has a poor prognosis after symptom onset (1-3). Previously, surgical aortic valve replacement (SAVR) was the only effective treatment, but after being introduced in 2002, transcatheter aortic valve replacement (TAVR) became an option for certain patients with severe symptomatic aortic valve stenosis that was considered inoperable or in patients at high risk for surgical complications (4,5). More recently, observational studies have demonstrated acceptable mortality outcomes in low- and intermediate-risk patients (6–10); however, no randomized clinical trials have been conducted in this patient population.

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Different TAVR systems have been developed, and currently self-expandable or balloon-expandable bioprostheses are used. Patients undergoing TAVR and SAVR procedures experience different spectra of complications related to the different nature of the treatments. After TAVR, more patients have prosthesis regurgitation, conduction disturbances requiring a pacemaker, and vascular complications, whereas SAVR-treated patients have more bleeding, acute kidney injury (AKI), and new-onset atrial fibrillation (AF) (11,12). The impact of these complications on mortality and morbidity has not been firmly established. In high-risk patients, improved survival was demonstrated with TAVR using a self-expanding prosthesis compared with SAVR after 1 year (12), whereas survival was similar to findings with SAVR after 1 and 2 years when a balloon-expandable prosthesis was used (11,13).

The NOTION (Nordic Aortic Valve Intervention) trial is an all-comers trial evaluating the benefits and harms of TAVR using a self-expanding prosthesis versus SAVR in patients with echocardiographically severe aortic valve stenosis.

METHODS

The NOTION trial was an investigator-initiated, multicenter, randomized, nonblinded, superiority trial conducted at 2 centers in Denmark and 1 in Sweden. The trial design has been described in detail previously (14). A total of 280 patients were randomly assigned to TAVR using a self-expanding prosthesis versus SAVR and were followed for 5 years. The primary outcome was evaluated after 1 year.

The regional ethical review board at each site approved the trial protocol, and the trial was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent. The investigators collected and stored all data, which were fully monitored by an independent monitoring unit. An independent clinical events committee adjudicated all clinical events. An independent statistician confirmed the statistical analysis. All authors confirm that the trial was conducted according to the protocol, and they vouch for the accuracy and completeness of the data and analyses.

PATIENT SELECTION. Patients ≥70 years of age with severe degenerative aortic valve stenosis referred for SAVR and also candidates for TAVR were eligible for inclusion regardless of their predicted risk of death after surgery. A heart team consisting of at least an imaging cardiologist, an interventional cardiologist, and a cardiac surgeon evaluated all patients. Severe aortic valve stenosis was defined as an effective orifice area <1 cm^2 or indexed for body surface area <0.6 cm^2/m^2 and a mean aortic valve gradient >40 mm Hg or peak systolic velocity >4 m/s. Symptomatic patients had to have dyspnea, New York Heart Association (NYHA) functional class II or higher, angina pectoris, or cardiac syncope to qualify for the trial. Asymptomatic patients could be included if they had left ventricular posterior wall thickness ≥17 mm, decreasing left ventricular ejection fraction, or new-onset AF. Eligible patients were expected to survive for more than 1 year. Patients were excluded if they had another severe heart valve disease or coronary artery disease (CAD) requiring intervention. Other important exclusion criteria were previous cardiac surgery, myocardial infarction (MI) or stroke within 30 days, severe renal failure requiring dialysis, or pulmonary failure with a forced expiratory volume within 1 s or diffusion capacity <40% of expected.

Trial eligibility, choice of prosthesis size, and arterial access route were based on transthoracic and transesophageal echocardiograms and an aorto-iliofemoral angiogram and were confirmed by the primary interventional and surgical investigator at each site. Supplemental computed tomography (CT) studies were performed in patients with difficult aortic annular measurements or peripheral arterial disease.

PROCEDURES. Patients were randomized in a 1:1 ratio to treatment with TAVR or SAVR. Randomization was performed at the Copenhagen Trial Unit and was stratified according to trial site, age (70 to 74 years or older), and history of CAD (yes or no). The allocation

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AKI = acute kidney injury

CAD = coronary artery disease

CT = computed tomography

2DE = 2-dimensional transesophageal echocardiography

EuroSCORE = European System for Cardiac Operative Risk Evaluation

MI = myocardial infarction

NYHA = New York Heart Association

SAVR = surgical aortic valve replacement

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

TAVR = transcatheter aortic valve replacement

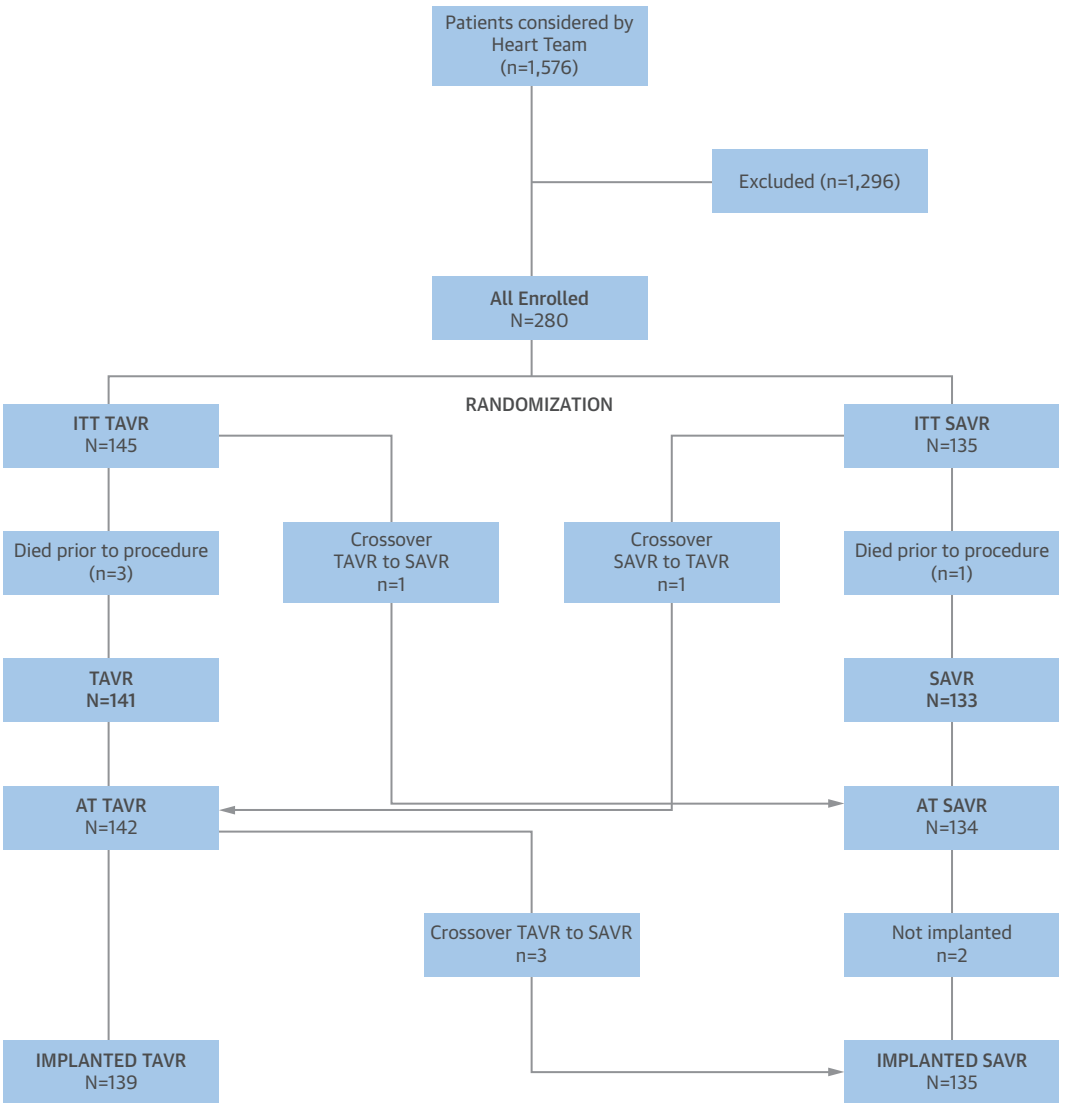
TIA = transient ischemic attack

sequence was arranged in permuted blocks, and block size was unknown to the investigators.

Patients randomized to TAVR received the CoreValve self-expanding bioprosthesis (Medtronic Inc., Minneapolis, Minnesota) in sizes 23, 26, 29, or 31 mm. The preferred route of arterial access was femoral, with left subclavian access as the second choice. The procedure was performed using general or local anesthesia, as described previously (15). Patients received a loading dose of pre-procedural clopidogrel (300 mg) and aspirin (75 mg) and unfractionated heparin during the procedure. Post-procedure, patients continued on a maintenance dose of clopidogrel (75 mg/day) for 3 months and lifelong aspirin (75 mg/day). If warfarin was indicated, this was continued in combination with clopidogrel for the first 3 months, followed by lifelong aspirin.

Patients randomized to SAVR underwent conventional open heart surgery with the use of cardiopulmonary bypass. All patients received a bioprosthesis, with the specific type and size determined during the surgical procedure. Surgical patients received a

FIGURE 1 Patient Flow



After excluding 1,296 of the 1,576 originally considered patients, 280 were enrolled and randomized 1:1 to either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) and were followed for 1 year. AT = as-treated population (patients with an attempted procedure); ITT = intention-to-treat population.

TABLE 1 Baseline Characteristics

	TAVR* (n = 145)	SAVR* (n = 135)
Age, yrs	79.2 ± 4.9	79.0 ± 4.7
Male	78/145 (53.8)	71/135 (52.6)
NYHA functional classification		
I	7/144 (4.9)	3/134 (2.2)
II	67/144 (46.5)	70/134 (52.2)
III	67/144 (46.5)	57/134 (42.5)
IV	3/144 (2.1)	4/134 (3.0)
STS-PROM score, %	2.9 ± 1.6	3.1 ± 1.7
Logistic EuroSCORE, %	8.4 ± 4.0	8.9 ± 5.5
Logistic EuroSCORE II, %	1.9 ± 1.2	2.0 ± 1.3
Additive EuroSCORE, %	7.4 ± 1.4	7.5 ± 1.4
Diabetes mellitus	26/145 (17.9)	28/135 (20.7)
Creatinine level >2 mg/dl	2/145 (1.4)	1/135 (0.7)
History of hypertension	103/145 (71.0)	103/135 (76.3)
Peripheral vascular disease	6/145 (4.1)	9/135(6.7)
Prior cerebrovascular accident	24/145 (16.6)	22/135 (16.3)
Chronic lung disease	17/145 (11.7)	16/135 (11.9)
Cardiac risk factors		
Prior PCI	11/145 (7.6)	12/135 (8.9)
Pre-existing pacemaker	5/145 (3.4)	6/135 (4.4)
Prior MI	8/145 (5.5)	6/135 (4.4)
Prior AF/atrial flutter	40/144 (27.8)	34/133 (25.6)

Values are mean ± SD or n/N (%). *No statistical significant differences between groups were found for any variable.

AF = atrial fibrillation; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; TAVR = transcatheter aortic valve replacement.

TABLE 2 Procedural Characteristics

TAVR	
Procedural success*	139/142 (97.9)
Total procedure time, min	90.3 ± 38.6
Local anesthesia	26/142 (18.3)
Use of inotropes	86/142 (60.6)
Implantation of >1 valve prosthesis	4/142 (2.8)
Conversion to surgery	3/142 (2.1)
Transfemoral access	137/142 (96.5)
Transsubclavian access	5/142 (3.5)
Valve size implanted	
23 mm	2/142 (1.4)
26 mm	57/142 (40.1)
29 mm	69/142 (48.6)
31 mm	14/142 (9.9)
SAVR	
Total procedure time, min	177.2 ± 39.8
Conversion to other procedure†	2/134 (1.5)
Use of inotropes	48/133 (36.1)
Valve size implanted	
19 mm	11/132 (8.3)
21 mm	42/132 (31.8)
23 mm	45/132 (34.1)
25 mm	32/132 (24.2)
27 mm	2/132 (1.5)

Values are n/N (%) or mean ± SD. *Defined as leaving the catheterization room with a functional transcatheter self-expanding prosthesis. †1 apico-aortic conduit and 1 apical TAVR with a balloon-expandable bioprosthesis.

Abbreviations as in Table 1.

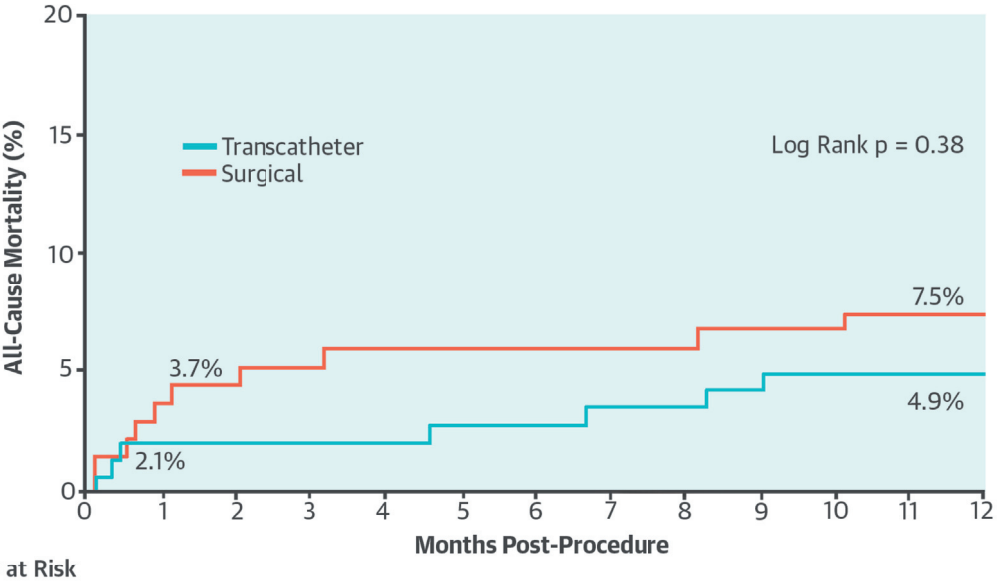
postoperative antiplatelet and anticoagulation regimen similar to that used for the TAVR-treated patients. All patients received prophylactic antibiotics during the procedure, and senior interventional cardiologists or cardiac surgeons performed all procedures.

Follow-up assessments, including a physical examination, documentation of trial-specified outcomes and adverse events, NYHA functional classification, blood sampling, and 12-lead electrocardiography, were done before discharge and 1, 3, and 12 months after the procedure. Specially trained echocardiographic technicians performed transthoracic echocardiograms at baseline and after 3 and 12 months. Experienced cardiologists evaluated all echocardiograms. National electronic medical records confirmed all clinical outcomes. When a neurological lesion was suspected, an independent neurologist conducted a formal neurological examination, and cerebral imaging studies were performed.

OUTCOMES. The primary outcome was the composite rate of all-cause death, stroke, or MI 1 year post-procedure. Exploratory outcomes were as follows: the rate of individual components of the composite outcome; the rate of cardiovascular death; prosthesis reintervention; cardiogenic shock; valve endocarditis; conduction abnormalities requiring permanent pacemaker; atrial fibrillation or flutter; and vascular, renal, and bleeding complications after 1 and 12 months. Clinical improvement was assessed according to NYHA functional classification. Echocardiographic outcomes included aortic valve effective orifice area, mean pressure gradient, and degree of total aortic valve regurgitation (graded as none/trace, mild, moderate, and severe) at 3 and 12 months. All outcomes were defined according to Valve Academic Research Consortium-2 definitions (16).

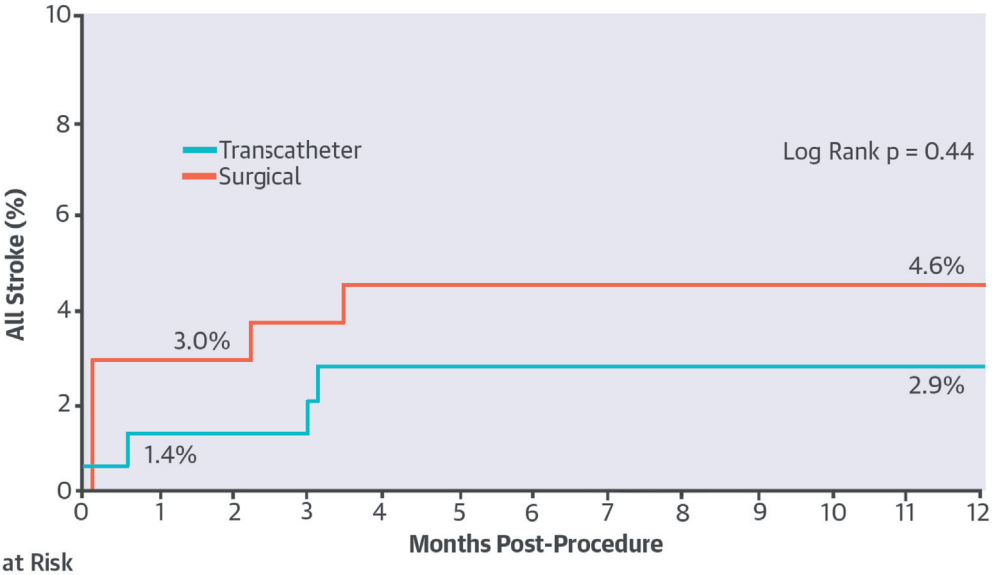
STATISTICAL ANALYSIS. The primary hypothesis was that the rate of the composite outcome of death from any cause, stroke, or MI after 1 year would be lower for patients receiving TAVR versus SAVR. On the basis of available clinical data (17), in-hospital procedure databases, and predicted operative mortality risk (EuroSCORE I [European System for Cardiac Operative Risk Evaluation version I]), we assumed an estimated occurrence of the primary outcome of 5% after TAVR and 15% after SAVR. With a 1:1 ratio in the

CENTRAL ILLUSTRATION **TAVR Versus SAVR in Severe Aortic Valve Stenosis**



Patients at Risk

Transcatheter	142	139	137	126
Surgical	134	128	125	115



Patients at Risk

Transcatheter	142	137	134	123
Surgical	134	124	120	110

Thyregod, H.G.H. et al. J Am Coll Cardiol. 2015; 65(20):2184–94.

An all-comers patient population with severe aortic valve stenosis was randomized 1:1 to transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction at 1 year, and there were no significant difference in the primary outcome between the 2 groups or in its components, including all-cause mortality **(top)** and stroke **(bottom)**.

treatment assignment, we calculated that 140 patients in each group would be required to have 80% power at a 2-sided alpha-level of 5%.

The analysis for the primary outcome was performed in the intention-to-treat population with logistic regression by adjusting for age, trial site, and history of CAD with a 2-sided alpha level of 5%. The primary outcome was also analyzed in the as-treated population. The intention-to-treat population was defined as all patients randomized, the as-treated population as patients in whom 1 of the 2 trial procedures was attempted. All outcomes, apart from the primary outcome, were considered exploratory.

A time-to-event analysis was conducted using Kaplan-Meier estimates, and comparisons between treatment groups were done using the log-rank test. Categorical variables were compared using the Fisher exact test or the chi-square test as appropriate. Continuous variables were presented as means (± SD) and compared with the use of Student *t* test. Ordinal variables were compared using the Mantel-Haenszel test. All testing used a 2-sided alpha level of 0.05. All statistical analyses were performed with the use of SAS software version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

From December 2009 to April 2013, 1,576 patients were evaluated by the Heart Team at participating centers and were pre-screened for trial participation. A total of 1,296 patients were excluded: 79% did not meet inclusion criteria; 8% declined to participate; 1% withdrew informed consent (3 in the transcatheter group and 5 in the surgical group); and 12% were excluded for other reasons. The remaining 280 patients were randomized (145 TAVR and 135 SAVR, the intention-to-treat population). A procedure was attempted in 276 patients (142 TAVR and 134 SAVR, the as-treated population) (**Figure 1**). Four patients died before the procedure (3 TAVR and 1 SAVR), and 2 patients (1 in each group) were crossed over to the other procedure before an attempted procedure. The patient crossing from SAVR to TAVR died 11 days post-procedure.

Table 1 describes the baseline characteristics of the intention-to-treat population. The 2 groups were well balanced, with a mean age of 79.1 ± 4.8 years, 53.2% male sex, and 47.1% in NYHA functional class III or IV. The comorbidity burden was moderate, with 19.3% having diabetes mellitus, 16.4% prior cerebrovascular disease, and 11.8% chronic obstructive pulmonary disease. Only 5.4% had peripheral vascular disease. When calculating the Society of Thoracic Surgeons Predicted Risk Of Mortality (STS-PROM) and EuroSCORE I and II estimates for 30-day predicted surgical mortality risk, 81.8% were considered low-risk patients (STS-PROM <4, mean ± SD, 3.0 ± 1.7), and mean logistic EuroSCORE I and II values were 8.6 and 2.0, respectively.

TABLE 3 Clinical Outcomes in the As-Treated Population

	Index Hospitalization* or 30 Days†			1 Year		
	TAVR	SAVR	p Value	TAVR	SAVR	p Value
Major, life threatening, or disabling bleeding*	16 (11.3)	28 (20.9)	0.03			
Cardiogenic shock*	6 (4.2)	14 (10.4)	0.05			
Major vascular complications*	8 (5.6)	2 (1.5)	0.10			
Acute kidney injury stage II or III*	1 (0.7)	9 (6.7)	0.01			
All-cause death†	3 (2.1)	5 (3.7)	0.43	7 (4.9)	10 (7.5)	0.38
Cardiovascular death†	3 (2.1)	5 (3.7)	0.43	6 (4.3)	10 (7.5)	0.25
Neurological events†	4 (2.8)	4 (3.0)	0.94	7 (5.0)	8 (6.2)	0.68
Stroke†	2 (1.4)	4 (3.0)	0.37	4 (2.9)	6 (4.6)	0.44
Transient ischemic attack†	2 (1.4)	0 (0)	0.17	3 (2.1)	2 (1.6)	0.71
MI†	4 (2.8)	8 (6.0)	0.20	5 (3.5)	8 (6.0)	0.33
Valve endocarditis†	1 (0.7)	0 (0)	0.33	4 (2.9)	2 (1.6)	0.47
New-onset or worsening AF†	24 (16.9)	77 (57.8)	<0.001	30 (21.2)	79 (59.4)	<0.001
Permanent pacemaker implantation†	46 (34.1)	2 (1.6)	<0.001	51 (38.0)	3 (2.4)	<0.001

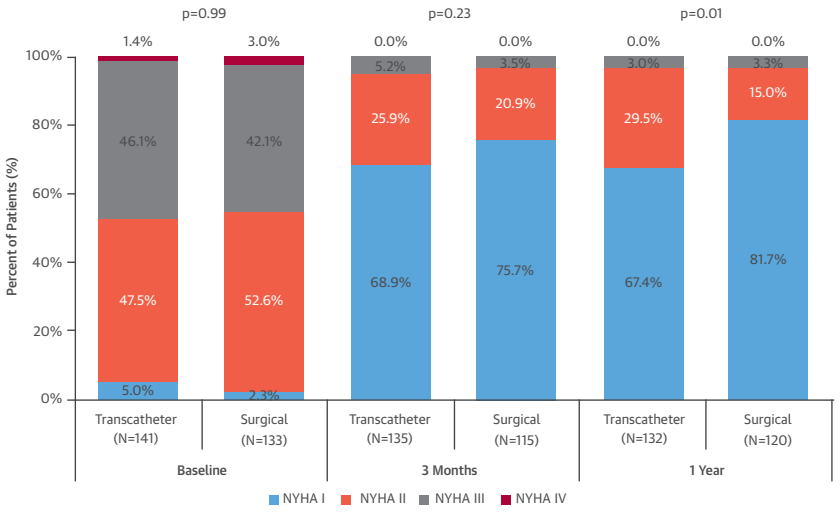
Values are n (%). *Rate during index hospitalization; data reported as number of patients with events (percentage) in each treatment group; p values were calculated by Fisher exact test or chi-square test, as appropriate. †Rates determined at 30 days and 1 year; data reported as number of subjects (Kaplan-Meier estimates) at the specific time point, and they do not equal the number of patients with events divided by the total number of patients in each treatment group; p values were calculated by the log-rank test for all data through 30 days or 1 year.

Abbreviations as in **Table 1**.

In the as-treated population, mean time from randomization to procedure was 32.5 days for TAVR and 40.9 days for SAVR (p = 0.08). Two patients assigned to SAVR were not treated with a trial procedure (1 treated with an apico-aortic conduit and 1 with apical TAVR using a balloon-expandable bioprosthesis); 3 TAVR-treated patients were converted to SAVR because of complications during the procedure. A total of 139 and 135 patients had the trial TAVR and SAVR prosthesis implanted, respectively. The arterial access was femoral in 96.5% of TAVR-treated patients (**Table 2**). No patients were lost to follow-up.

OUTCOMES. In the intention-to-treat analysis, the composite rate of death from any cause, stroke, or MI at 1 year (the primary outcome) was similar in the 2 groups (13.1% vs. 16.3% for TAVR and SAVR, respectively; −3.2% absolute difference; p = 0.43 for superiority). The result did not change in the as-treated analysis (11.3% vs. 15.7%; −4.4 absolute difference; p = 0.30). The composite outcome was primarily driven by death from any cause (Kaplan-Meier rate 4.9% vs. 7.5%; p = 0.38) (**Central Illustration**).

FIGURE 2 NYHA Functional Class



Symptomatic status varied according to New York Heart Association (NYHA) class at baseline, after 3 months, and after 1 year in patients with an attempted procedure. At 1 year, the transcatheter aortic valve replacement group had significantly more dyspnea versus the surgical group ($p = 0.01$).

Post-procedure, transcatheter patients compared with surgical patients had lower rates of major or life-threatening bleeding (11.3% vs. 20.9%; $p = 0.03$), cardiogenic shock (4.2% vs. 10.4%; $p = 0.05$), and AKI (stage II or III) (0.7% vs. 6.7%; $p = 0.01$) (Table 3). No TAVR-treated patient required percutaneous coronary intervention during the procedure, but 2 such patients had cardiac perforation; 1 SAVR-treated patient required concomitant coronary artery bypass resulting from a right coronary ostium lesion. The mean in-hospital time after the index procedure was shorter for TAVR (8.9 ± 6.2 days vs. 12.9 ± 11.6 days; $p = 0.001$). No difference was found for major vascular complications.

At 30 days in the as-treated population, more TAVR-treated patients had conduction abnormalities requiring a permanent pacemaker (34.1% vs. 1.6%; $p < 0.001$), but they had a lower rate of new-onset or worsening AF (16.9% vs. 57.8%; $p < 0.001$). There was no significant difference between treatment groups in the composite outcome or any of its separate components. In addition, no difference was found in the rate of cardiovascular death or transient ischemic attack (TIA). No patient had prosthesis reintervention.

The rates of death from any cause, cardiovascular death, stroke or TIA, or MI did not differ between treatment groups at 1 year (see Table 3), nor did any patient have significant prosthesis dysfunction requiring intervention after 1 year.

The rate of permanent pacemaker implantation remained higher in TAVR-treated patients (38.0% vs. 2.4% for TAVR and SAVR; $p < 0.001$) at 1 year, whereas the rate of new-onset or worsening AF was lower (21.2% vs. 59.4%; $p < 0.001$) compared with SAVR-treated patients. The number of cardiopulmonary, neurology, vascular, or bleeding-related hospitalizations or the number of days hospitalized during the first year was not different between treatment groups within the first year.

FUNCTIONAL OUTCOMES. Patients in both treatment groups experienced significant improvement in dyspnea as measured by NYHA functional class by 30 days, and this improvement was maintained at 1 year (Figure 2). After 1 year, TAVR-treated patients had more dyspnea compared with SAVR-treated patients (29.5% in NYHA functional class II indicating mild dyspnea vs. 15.0%; $p = 0.01$).

The effective orifice area improved after both procedures and remained constant at 1 year (Figure 3). Compared with SAVR-treated patients, TAVR-treated patients had more improvement in effective orifice area relative to baseline at 3 months and 1 year (change from baseline to 1 year: 1.0 ± 0.5 cm^2 vs. 0.6 ± 0.5 cm^2; $p < 0.001$). The mean pressure gradient decreased as a result of each procedure, although this change did not differ between groups at 1 year (change from baseline to 1 year: −34.8 ± 18.0 mm Hg vs. −32.0 ± 18.3 mm Hg; $p = 0.23$). TAVR-treated patients experienced a

higher rate of relevant total aortic valve regurgitation compared with SAVR-treated patients at 3 months, and this rate remained stable during the first year (for moderate to severe regurgitation at 1 year: 15.7% vs. 0.9%; $p < 0.001$) (Figure 4).

DISCUSSION

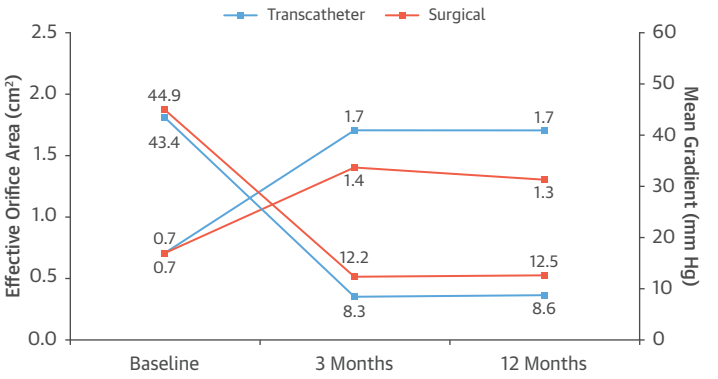
The NOTION trial is a randomized all-comers population with varying degrees of clinical symptoms and echocardiographically severe aortic valve stenosis to TAVR versus SAVR. Although TAVR was not superior to SAVR for the primary outcome, which was the composite rate of death from any cause, stroke, or MI after 1 year, the trial showed that TAVR appeared safe and effective in low- and intermediate-risk patients. There were no differences between treatment groups at any time point for any individual component of the composite outcome or for cardiovascular death, TIA, or prosthesis reintervention.

The results concur with propensity score-matched studies, showing no differences in death from any cause between TAVR and SAVR after 30 days or 1 year for patients with an STS-PROM score ≤4% (8) or in patients with a mean logistic EuroSCORE I of 9.1% after 30 days (9). In an exploratory post-hoc analysis in the current trial, noninferiority could be shown for TAVR compared with SAVR for the primary outcome when using the same noninferiority margin of 7.5% used in the PARTNER (Placement of Aortic Transcatheter Valves) and U.S. CoreValve High Risk trials (11,12).

The NOTION trial was designed to compare TAVR with standard surgical treatment in patients most often referred for treatment in contemporary clinical practice. At the time of trial design, there were no randomized TAVR trials or observational studies including low- and intermediate-risk patients. It was expected that the lower-risk patients would show greater benefit from the less invasive TAVR procedure than their higher-risk counterparts; however, the magnitude of this benefit was uncertain.

For the surgical group, the mean 30-day risk of mortality in NOTION was estimated to be 3.1% using the STS-PROM score and 8.6% and 2.0% using the logistic EuroSCORE I and EuroSCORE II, whereas the observed 30-day mortality rate was 3.7%. The NOTION patient population was therefore different from those in the 2 other randomized trials comparing TAVR and SAVR. In the PARTNER trial, using a balloon-expandable prosthesis, the mean STS-PROM was 11.7% for the surgical group (11) versus 7.5% in the surgical group of the U.S. CoreValve High Risk trial using the same self-expanding prosthesis as in NOTION trial (12).

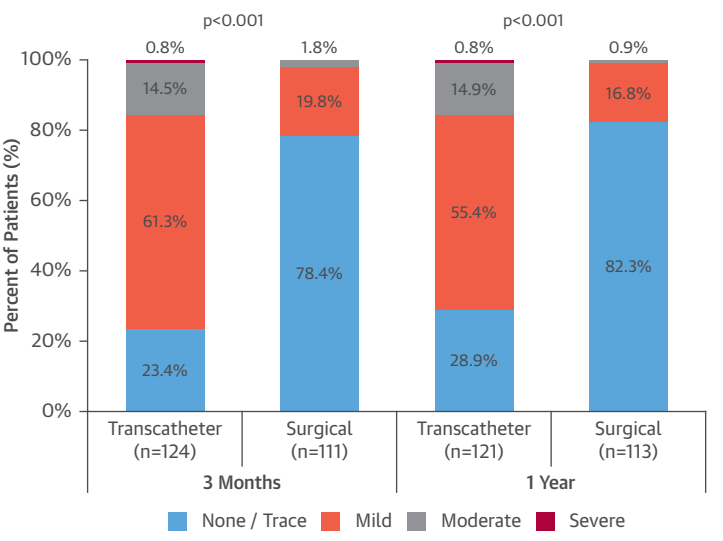
FIGURE 3 Aortic Valve Hemodynamics



Aortic valve hemodynamics were measured as mean effective orifice area (in cm^2) and mean aortic valve gradient (in mm Hg) according to implanted valve prosthesis at baseline, at 3 months, and at 1 year. The transcatheter aortic valve replacement group had significantly greater improvement in effective orifice area versus the surgical group at each time point ($p < 0.001$).

The actual mortality at 30 days was 8.0% and 4.5% in those 2 trials, respectively. We found better agreement in particular between the STS-PROM estimate and observed 30-day mortality compared with other studies with high-risk patients (18,19). In an observational study of TAVR in low-risk patients (STS-PROM score <4%), the mortality rates at 30 days and 1 year were similar to ours (10).

FIGURE 4 Total Aortic Valve Regurgitation



Although improved at 1 year from 3 months, the transcatheter aortic valve replacement group had significantly more regurgitation versus the surgical group at each time point ($p < 0.001$).

The mortality rate post-TAVR in the NOTION trial was one of the lowest ever reported for transcatheter therapy, and stroke rates after both treatments were also low compared with any previously reported series. In particular, TAVR-treated patients did not have a higher rate of neurological events, which has been a concern related to catheter manipulation of the calcified aorta and balloon valvuloplasty (20). Aortic valve regurgitation was more prevalent in TAVR-treated patients (15.7% had moderate or severe regurgitation after 1 year) and did not improve over time. This prevalence was higher than seen in the U.S. CoreValve High Risk trial (6.1% at 1 year) (12), but it was similar to other observational studies also using a self-expanding prosthesis (21,22). Both mild (13) and moderate-severe aortic valve regurgitation have been associated with increased mortality after TAVR (21,22). This difference in aortic valve regurgitation may partly explain the difference seen in NYHA functional class at 1 year, with more TAVR-treated patients experiencing mild dyspnea. However, no difference between groups could be demonstrated in the rate of death or hospitalization during the first year.

The inherent differences between TAVR and SAVR, with regard to procedures and valve designs, were seen in the procedure-related outcomes. TAVR-treated patients had more conduction abnormalities requiring a permanent pacemaker and minor vascular complications, whereas SAVR-treated patients had more bleeding complications, cardiogenic shock, AKI, and new-onset or worsening AF, and they also had a longer post-procedure hospital stay. Well documented in other trials (11,12), these differences reflect the less invasive nature of transcatheter treatment.

The NOTION trial was initiated only 2 years after TAVR was widely introduced, and experience with the procedure was limited. Furthermore, because this trial was designed in 2009, numerous improvements to the TAVR procedure were subsequently introduced. At the time when patients were enrolled in the NOTION trial, 2-dimensional transesophageal echocardiography (2DE) was the standard of care for annular sizing, whereas the U.S. CoreValve High Risk trial relied on CT for sizing (12). Since that time, 2DE has been shown to cause systematic valve undersizing and aortic valve regurgitation compared with CT (23–25). Moreover, using CT studies to measure the distance from annulus to coronary ostia and the degree of valvular and access vessel calcification may potentially reduce the risk of coronary artery obstruction, aortic annulus rupture, stroke, conduction abnormalities, and vascular complications (26).

We found no signs of prosthesis deterioration during the first year, and no patient had prosthesis reintervention. Favorable long-term durability data (up to 3 and 6 years) for TAVR prostheses are emerging (27,28), but more randomized long-term data are needed. In addition, the clinical significance of aortic valve regurgitation and ventricular pacing on morbidity and mortality must be better understood, or these complications must be avoided in newer generations of transcatheter valves, before broadening the indications for TAVR in lower-risk patients.

STUDY LIMITATIONS. The NOTION trial used centralized randomization stratified for relevant prognostic factors (29,30). The trial methodologies have been described in detail, including the plans for statistical analyses (14). Moreover, 2 independent teams analyzed and validated the results.

Several outcomes were assessed unblinded as to procedure; accordingly, assessments of all outcomes apart from death could be subject to bias (29,30). It is, however, difficult to know the direction of such bias. Our sample size may have been too small to detect a potential difference in treatment effect on the primary outcome. Because experience with TAVR was limited when NOTION was initiated, most operators were comfortable using only a single TAVR system. Differences between self-expanding and balloon-expandable valves with regard to aortic valve regurgitation and pacemaker requirement, for example, have been well described (31). External validity was limited in our trial because only 3 centers recruited patients. The current trial results may therefore not be extrapolated to TAVR in general. The NOTION trial did not recruit patients with significant concomitant CAD, and outcomes for this large patient population cannot necessarily be inferred from the current trial. Formal neurological assessments were not performed in all patients, and more subtle neurological symptoms (e.g., cognitive dysfunction) could have been overlooked. The difficulties in determining the degree of aortic valve regurgitation after replacement are well known, and independent echocardiographic evaluations were not made.

CONCLUSIONS

The NOTION trial was an all-comers trial in patients with aortic valve stenosis who were randomized to transcatheter versus surgical aortic valve replacement. No significant differences were found between the 2 procedures regarding the primary outcome death from any cause, stroke, or MI or the exploratory outcomes of cardiovascular mortality or prosthesis reintervention after 1 year. The transcatheter group

did significantly better than the surgical group regarding rates of bleeding, cardiogenic shock, AKI, new-onset or worsening AF, effective orifice area, and number of days hospitalized. The surgical group appeared significantly better in terms of conduction abnormalities requiring a permanent pacemaker, NYHA functional class at 1 year, and aortic valve regurgitation. Therefore, at present we are not able to recommend or refute 1 procedure over the other in lower-risk patients. More randomized clinical trials in this patient population are needed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a randomized comparison of TAVR versus SAVR, TAVR was associated with more frequent requirement for pacemaker implantation, larger improvement in effective valve orifice, more aortic valve regurgitation, and more residual exertional dyspnea at 1 year, whereas SAVR was more often associated with major or life-threatening bleeding, cardiogenic shock, acute kidney injury, and early post-procedural AF.

TRANSLATIONAL OUTLOOK: Further studies are needed to compare the safety, efficacy, and long-term clinical outcomes of TAVR versus SAVR in lower-risk patients with severe aortic valve stenosis.

REFERENCES

1. Ross J Jr., Braunwald E. Aortic stenosis. Circulation 1968;38:61–7.

2. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.

3. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373:956–66.

4. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

5. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

6. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. J Am Coll Cardiol 2012;59:280–7.

7. Latib A, Maisano F, Bertoldi L, et al. Transcatheter vs surgical aortic valve replacement in intermediate-surgical-risk patients with aortic stenosis: a propensity score-matched case-control study. Am Heart J 2012;164:910–7.

8. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. J Am Coll Cardiol Intv 2013;6:443–51.

9. D'Errigo P, Barbanti M, Ranucci M, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis: results from an intermediate risk propensity-matched population of the Italian OBSERVANT study. Int J Cardiol 2013;167:1945–52.

10. Wenaweser P, Stortecky S, Schwander S, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. Eur Heart J 2013;34:1894–905.

11. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

12. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

13. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

14. Thyregod HG, Sondergaard L, Ihlemann N, et al. The Nordic Aortic Valve Intervention (NOTION) trial comparing transcatheter versus surgical valve implantation: study protocol for a randomised controlled trial. Trials 2013;14:11.

15. Grube E, Schuler G, Buellesfeld L, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol 2007;50:69–76.

16. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

17. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2-isolated valve surgery. Ann Thorac Surg 2009;88 1 Suppl:S23–42.

18. Durand E, Borz B, Godin M, et al. Performance analysis of EuroSCORE II compared to the original logistic EuroSCORE and STS scores for predicting 30-day mortality after transcatheter aortic valve replacement. Am J Cardiol 2013;111:891–7.

19. Wendt D, Thielmann M, Kahlert P, et al. Comparison between different risk scoring algorithms on isolated conventional or transcatheter aortic valve replacement. Ann Thorac Surg 2014;97:796–802.

20. Rodes-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol 2011;57:18–28.

21. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585–95.

22. Van Belle E, Juthier F, Susen S, et al. Post-procedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of

predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation 2014;129:1415–27.

23. Lehmkuhl L, Foldyna B, Von Aspern K, et al. Inter-individual variance and cardiac cycle dependency of aortic root dimensions and shape as assessed by ECG-gated multi-slice computed tomography in patients with severe aortic stenosis prior to transcatheter aortic valve implantation: is it crucial for correct sizing? Int J Cardiovasc Imaging 2013;29:693–703.

24. Binder RK, Webb JG, Willson AB, et al. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. J Am Coll Cardiol 2013;62:431–8.

25. Mylotte D, Dorfmeister M, Elhmidi Y, et al. Erroneous measurement of the aortic annular diameter using 2-dimensional echocardiography resulting in inappropriate CoreValve size selection: a retrospective comparison with multislice computed tomography. J Am Coll Cardiol Intv 2014;7:652–61.

26. Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). J Cardiovasc Comput Tomogr 2012;6:366–80.

27. Ussia GP, Barbanti M, Petronio AS, et al. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969–76.

28. Bouleti C, Himbert D, Iung B, et al. Long-term outcome after transcatheter aortic valve implantation. Heart 2015 Feb 5 [Epub ahead of print].

29. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. Br Med J 2008;336:601–5.

30. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med 2012;157:429–38.

31. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–14.

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