

Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients

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Background—The proven efficacy of transcatheter aortic valve implantation (TAVI) in high-risk patients is leading to the expansion of its indications toward lower-risk patients. However, this shift is not supported by meaningful evidence of its benefit over surgical aortic valve replacement (SAVR). This analysis aims to describe outcomes of TAVI versus SAVR in low-risk patients.

Methods and Results—We compared the outcome after TAVI and SAVR of low-risk patients (European System for Cardiac Operative Risk Evaluation II [EuroSCORE II] <4%) included in the Observational Study of Effectiveness of SAVR—TAVI Procedures for Severe Aortic Stenosis Treatment (OBSERVANT) study. The primary outcome was 3-year survival. Secondary outcomes were early events and major adverse cardiac and cerebrovascular events at 3 years. Propensity score matching resulted in 355 pairs of patients with similar baseline characteristics. Thirty-day survival was 97.1% after SAVR and 97.4% after TAVI ($P=0.82$). Cardiac tamponade, permanent pacemaker implantation, major vascular damage, and moderate-to-severe paravalvular regurgitation were significantly more frequent after TAVI compared with SAVR. Stroke rates were equal in the study groups. SAVR was associated with higher risk of cardiogenic shock, severe bleeding, and acute kidney injury. At 3 years, survival was 83.4% after SAVR and 72.0% after TAVI ($P=0.0015$), whereas freedom from major adverse cardiac and cerebrovascular events was 80.9% after SAVR and 67.3% after TAVI ($P<0.001$).

Conclusions—In patients with low operative risk, significantly better 3-year survival and freedom from major adverse cardiac and cerebrovascular events were observed after SAVR compared with TAVI. Further studies on new-generation valve prostheses are necessary before expanding indications of TAVI toward lower-risk patients. (*Circ Cardiovasc Interv.* 2016;9:e003326. DOI: 10.1161/CIRCINTERVENTIONS.115.003326.)

Key Words: aortic valve replacement ■ aortic valve stenosis ■ EuroSCORE II ■ low-risk ■ surgical ■ TAVI ■ TAVR

Transcatheter aortic valve implantation (TAVI) is a widely accepted procedure for the treatment of severe aortic valve stenosis in patients with high operative risk.¹ The minimally invasive nature and excellent clinical outcome of TAVI have led to a widespread use of this procedure.² However, several early complications after TAVI have been increasingly recognized as major drawbacks of this procedure and may affect the long-term outcome.³ Despite these limitations, clinicians are expanding the use of TAVI also into patients with intermediate- and low-operative risk.^{4,5} A recent randomized trial, the Nordic Aortic Valve Intervention Trial (NOTION), demonstrated that in patients with

a mean European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) of $\approx 2.0\%$, TAVI achieved 1-year results similar to surgical aortic valve replacement (SAVR).⁶ However, this study randomized only 18% of the screened patients and was likely underpowered. Three observational studies showed similar survival after TAVI and SAVR in intermediate-risk patients,⁷⁻⁹ whereas a recent analysis showed lower early mortality after SAVR with sutureless prosthesis compared with TAVI in patients with a mean EuroSCORE II of $\approx 4\%$.¹⁰

See Editorial by Young and Elmariah

Received September 11, 2015; accepted March 15, 2016.

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The Data Supplement is available at <http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.115.003326/-/DC1>.

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Circ Cardiovasc Interv is available at <http://circinterventions.ahajournals.org>

DOI: 10.1161/CIRCINTERVENTIONS.115.003326

WHAT IS KNOWN

- TAVI is widely recognized as an effective treatment method in high-risk patients with severe aortic valve stenosis.
- The excellent results of TAVI are leading to the expansion of its indications toward lower-risk patients, without evidence of any benefit over surgical aortic valve replacement.

WHAT THE STUDY ADDS

- This prospective study showed that surgical aortic valve replacement and TAVI can be performed in patients with EuroSCORE <4% with similar 30-day mortality rates.
- Surgical aortic valve replacement had significantly better 3-year outcomes than TAVI.
- These data suggest that expanding the use of TAVI in low-risk patients may not be justified.

The aim of the present study is to evaluate the early and 3-year outcome after TAVI and SAVR in low-risk patients (EuroSCORE II <4%) from the multicenter nationwide prospective Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment (OBSERVANT) study.

Methods

Study Design and Data Collection

OBSERVANT is a national observational, prospective, multicenter, cohort study that enrolled consecutive patients undergoing TAVI or SAVR for severe aortic valve stenosis at 93 Italian cardiology/cardiac surgery centers between December 2010 and June 2012. Details on the study design, patient eligibility criteria, and data collection modalities have been reported elsewhere.⁹ This study was coordinated by the Italian National Institute of Health and led in cooperation with the Italian Ministry of Health, the National Agency for Regional Health Services, Italian Regions, and Italian scientific societies and federations representing Italian professionals involved in the management of aortic valve stenosis. The complete list of executive working group, participating centers, and investigators is reported in the Appendix in the Data Supplement. In the participating hospitals, both SAVR and TAVI could be offered to patients with aortic valve stenosis. The study protocol has been approved by the Ethical Committee of each participating center, and patients gave their informed consent to participate in this study.

Inclusion Criteria

The study population included consecutive adult patients admitted with a diagnosis of severe aortic valve stenosis (defined as an aortic valve area <1 cm², maximum aortic velocity >4 m/s, or mean pressure gradient >40 mm Hg) and requiring an aortic valve replacement. Data on demographic characteristics, health status before intervention, comorbidities, and complete information on the type of intervention were collected into a standardized online datasheet on a password-protected website. Collected data were stored and analyzed at the Italian National Institute of Health. CoreValve (Medtronic, MN) and Sapien XT (Edwards Lifesciences, Irvine, CA) valve prostheses were implanted in these patients.

Patients with EuroSCORE II <4%¹¹ were the subjects of the present analysis. To evaluate only low-risk patients avoiding any selection

bias in the assignment to TAVI or SAVR, patients with porcelain aorta, hostile chest, active endocarditis, and oxygen therapy and those undergoing any combined procedure (coronary revascularization or intervention on other heart valves), as well as patients who underwent emergency procedure, were excluded from this analysis.

Data Quality Assessment

Data auditing was performed by independent observers after specific standard operating procedures. They monitored the participating hospitals to assess the completeness of the enrolled cohort and compared the collected data with those of the original clinical records.

Outcomes and Follow-Up

Three-year survival was the primary outcome of this analysis. Secondary outcomes were 30-day mortality and in-hospital adverse events, such as stroke, vascular complications, severe bleeding, and acute kidney injury. Stroke was defined as any focal deficit lasting >24 hours or focal deficit lasting <24 hours with positive neuroimaging studies. Vascular complications were defined as any access site complication requiring surgical or percutaneous vascular intervention. Severe bleeding was defined as bleeding requiring >4 red blood cell units.¹² Acute kidney injury was classified into 3 stages according to the Acute Kidney Injury Network (AKIN) definition criteria and taking into consideration only the baseline and postoperative serum creatinine levels.¹³ Other secondary outcomes were major adverse cardiac and cerebrovascular events (MACCE) at 3 years. MACCE were defined as the composite end point including any of the following adverse events: death from any cause, stroke, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass graft. An administrative follow-up has been set up for each enrolled patient through a record linkage with the National Hospital Discharged Records database for in-hospital events and with the Tax Registry Information System for information on survival.

Statistical Analysis

Continuous variables are presented as the mean±standard deviation and were compared using the Student *t* test. Categorical variables are presented as counts and percentages and were compared with the χ^2 test or Fisher exact test when appropriate. As observational studies do not provide randomization, a propensity score–matching method was used to select 2 groups of patients undergoing SAVR and TAVI, respectively, with similar baseline characteristics. The propensity score was estimated using a nonparsimonious logistic regression model with the treatment method as the dependent variable.¹⁴ The following variables have been included as covariates: age; sex; frailty status; previous percutaneous coronary intervention; previous balloon aortic valvuloplasty; previous cardiac surgery; previous operation on the aorta; chronic dialytic treatment; diabetes mellitus; chronic obstructive pulmonary disease; previous myocardial infarction; peripheral arteriopathy; estimated glomerular filtration rate; critical preoperative state; unstable angina; neurological dysfunction; pulmonary hypertension (systolic pulmonary arterial pressure >60 mm Hg); chronic liver disease; active neoplastic disease; New York Heart Association class; left ventricular ejection fraction; coronary artery disease; urgent operation; and mitral valve regurgitation.

One-to-one propensity score matching was performed using the nearest neighbor method and a caliper of 0.2 of the standard deviation of the logit of the propensity score.¹⁵ When a patient of a pair is lost to follow up and the matched patient is still alive (or free from events when considering the MACCE outcome), the time of observation of both patients is truncated at the time of the last observation of the lost patient to guarantee the comparability between the 2 groups.

To evaluate the balance between the matched groups, the *t* test for paired sample for continuous variables, the McNemar test for dichotomous variables, the Stuart–Maxwell test for categorical variables, and the analysis of the standardized differences after matching have been used (Table 1). The same tests have been used to test differences in the early adverse events of propensity score–matched groups. Differences in the outcomes of matched pairs at 3 years

Table 1. Baseline Clinical Characteristics of Propensity Score–Matched Pairs of Patients With EuroSCORE II <4%

	SAVR, n=355	TAVI, n=355	P Value
Age, y ±SD	80.0±5.1	80.1±6.4	0.81
Male, n (%)	209 (58.9)	206 (58.0)	0.83
BMI, kg/m ² ±SD	27.0±4.3	27.1±5.2	0.88
Diabetes mellitus, n (%)	57 (16.1)	53 (14.9)	0.67
eGFR, mg/min per 1.73 m ² ±SD	66.6±19.0	66.3±20.6	0.84
Chronic dialytic treatment, n (%)	4 (1.1)	8 (2.3)	0.24
Smoking history, n (%)	38 (10.7)	37 (10.4)	0.91
Neurological dysfunction, n (%)	15 (4.2)	15 (4.2)	1.00
Chronic liver disease, n (%)	19 (5.4)	13 (3.7)	0.29
Active neoplastic disease, n (%)	16 (4.5)	20 (5.6)	0.49
Peripheral arteriopathy, n (%)	31 (8.7)	36 (10.1)	0.53
Pulmonary disease, n (%)	70 (19.7)	65 (18.3)	0.62
Pulmonary hypertension, n (%)	23 (6.5)	18 (5.1)	0.42
Previous cardiac surgery, n (%)	5 (1.4)	9 (2.5)	0.29
Previous op. on the aorta, n (%)	8 (2.3)	10 (2.8)	0.64
Previous BAV, n (%)	9 (2.5)	15 (4.2)	0.18
Previous AMI, n (%)	29 (8.2)	26 (7.3)	0.67
Previous PCI, n (%)	61 (17.2)	58 (16.3)	0.77
Coronary artery disease, n (%)	45 (12.7)	56 (15.8)	0.23
One-vessel disease	29 (8.2)	37 (10.4)	0.65
Two-vessel disease	11 (3.1)	12 (3.4)	
Three-vessel disease	5 (1.4)	7 (2.0)	
NYHA classes, n (%)			
I	29 (8.2)	23 (6.5)	0.78
II	144 (40.1)	152 (42.8)	
III	164 (46.2)	160 (45.1)	
IV	18 (5.1)	20 (5.6)	
Unstable angina, n (%)	2 (0.6)	4 (1.1)	0.41
Frailty score (moderate–severe), n (%)	49 (13.8)	52 (14.6)	0.74
Urgent procedure, n (%)	5 (1.4)	6 (1.7)	0.76
Logistic EuroSCORE I, % ±SD	6.3±3.0	6.3±2.7	0.97
Logistic EuroSCORE II, % ±SD	2.5±0.8	2.6±0.8	0.60

P values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables and *t* test for paired sample for continuous variables. AMI indicates acute myocardial infarction; BAV, balloon aortic valvuloplasty; BMI, body mass index; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

have been evaluated by the Kaplan–Meier method with the Klein–Moeschberger stratified log-rank test.¹⁶

A subgroup analysis of the 3-year mortality among SAVR and TAVI propensity-matched patients has been made stratifying by the following variables: sex, age (≤80 versus >80), previous cardiac surgery, mitral valve regurgitation, left ventricular ejection function,

paravalvular leak, new pacemaker, and chronic obstructive pulmonary disease. A Cox model able to account for propensity score matching has been used for each stratified analysis. In case of discordant classification of patients within a pair, because of residual variation in baseline variables, we gave precedence to the characteristics of the TAVI patient.⁸ The risk of experiencing a morbid event has been presented by subgroup as hazard ratio with 95% confidence interval. These hazard ratios have been accompanied by test for interaction between treatment and patient characteristics from Cox model.

A Cox regression analysis on the overall low-risk population, adjusting by propensity score, has been performed to assess the robustness of the findings from the propensity-matched SAVR/TAVI groups.

Tests were 2-sided, and a *P*<0.05 was considered statistically significant. Statistical analyses were performed using the SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC).

Results

The OBSERVANT study includes 7618 patients who underwent either isolated TAVI or isolated SAVR. For the purposes of this study, 3402 patients (44.7%) fulfilled the inclusion criteria and were the subjects of this analysis. Their baseline characteristics are summarized in Table in the Data Supplement. From this cohort of patients with EuroSCORE II <4%, 2871 (84%) underwent SAVR and 531 (15.6%) patients underwent TAVI. Transfemoral access was used in 484 patients (91.1%), whereas a transapical approach was used in 47 patients (8.9%). As expected, significant differences in the baseline variables and operative risk were observed between SAVR and TAVI groups (EuroSCORE II, TAVI 2.7±0.8% versus SAVR 1.7±0.9%; *P*<0.001; Table in the Data Supplement).

Propensity score matching resulted in 355 pairs of patients whose baseline and echocardiographic characteristics are summarized in Tables 1 and 2. Figure 1 shows the changes in standardized differences in baseline covariates between

Table 2. Preoperative Echocardiographic Parameters of Propensity Score–Matched Pairs of Patients With EuroSCORE II <4%

	SAVR, n=355	TAVI, n=355	P Value
LVEF, n (%)			
>50%	304 (85.6)	304 (85.6)	0.94
30%–50%	46 (13.0)	47 (13.2)	
<30%	5 (1.4)	4 (1.1)	
Mitral valve regurgitation, n (%)			
Mild	206 (58.0)	193 (54.4)	0.64
Moderate	66 (18.6)	67 (18.9)	
Severe	3 (0.8)	2 (0.6)	
Aortic valve pattern			
Aortic valve area, cm ² ±SD	0.71±0.25	0.67±0.26	0.048
Peak gradient, mm Hg ±SD	86±22	84±21	0.37
Mean gradient, mm Hg ±SD	53±15	53±15	0.64
Annulus diameter, mm ±SD	21±2	22±2	<0.001

P values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables, and *t* test for paired sample for continuous variables. EuroSCORE II indicates European System for Cardiac Operative Risk Evaluation II; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

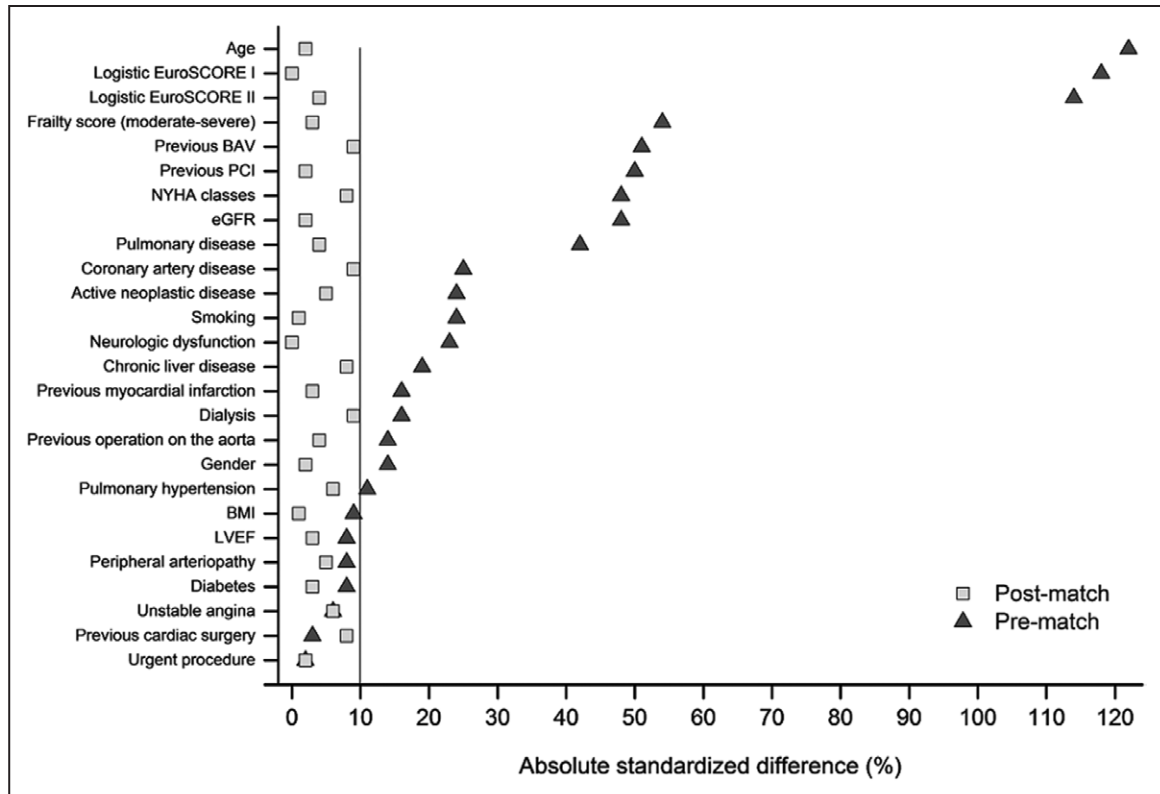


Figure 1. Absolute standardized differences in baseline covariates between patients undergoing transcatheter aortic valve implantation and those undergoing surgical aortic valve replacement before and after propensity score matching. Post-match standardized difference <10% indicates excellent covariate balance. BAV indicates balloon aortic valvuloplasty; BMI, body mass index; eGFR, estimated glomerular filtration rate; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

patients undergoing TAVI and those undergoing SAVR after one-to-one propensity score matching. None of the covariates had a postmatch standardized difference >10%, which indicates an excellent covariate balance.

Outcomes

Early outcome end points are reported in Table 3. Thirty-day mortality was 2.9% after SAVR and 2.6% after TAVI ($P=0.82$). Stroke rate was rather low and similar in the 2 study groups (SAVR 1.1% versus TAVI 1.1%; $P=1.00$). The rates of cardiac tamponade (4.3% versus 1.7%; $P=0.049$), permanent pacemaker implantation (12.7% versus 2.6%; $P<0.001$), major vascular damage (7.6% versus 0%; $P<0.001$), mild-to-severe paravalvular regurgitation (48.2% versus 11.3%; $P<0.001$), and moderate-to-severe paravalvular regurgitation (9.7% versus 1.5%; $P<0.001$) were significantly higher after TAVI compared with SAVR. On the other hand, TAVI was associated with significantly lower risk of cardiogenic shock (1.7% versus 4.6%; $P=0.025$), severe bleeding (4.4% versus 15.2%; $P<0.001$), and acute kidney injury (AKIN stages 1–3: 26.0% versus 43.7%; $P<0.001$) compared with SAVR. TAVI was associated with lower mean transvalvular gradient (10.6 versus 14.4 mmHg; $P<0.001$).

One-, 2-, and 3-year survival were 92.2%, 87.2%, and 83.4% after SAVR and 88.6%, 80.4%, and 72.0% after TAVI, respectively (stratified log-rank test; $P<0.001$; Figure 2). One-, 2-, and 3-year freedom from MACCE were 89.6%,

84.6%, and 80.9% after SAVR and 84.6%, 75.9%, and 67.3% after TAVI, respectively (stratified log-rank test; $P<0.001$; Figure 2). Incidence of adverse events (stroke, myocardial infarction, and coronary revascularization) at 3-year follow-up is reported in Table 4.

Results from stratified analyses are shown in Figure 3. Treatment effects in terms of 3-year mortality were similar across all subgroups.

Furthermore, a propensity score–adjusted analysis performed on the overall low-risk population showed that TAVI was associated with significantly lower 3-year survival than SAVR ($P=0.002$, hazard ratio =1.59, 95% confidence interval: 1.18–2.13); this result confirms the findings of the propensity score analysis performed on the matched groups ($P=0.002$, hazard ratio =1.70, 95% confidence interval: 1.22–2.37; Figure 3).

Discussion

The results of this study indicate that a rather large number of low-risk patients are treated by TAVI. The data from the OBSERVANT study suggest that the decision not to perform SAVR in such a large number of patients was made without any evident contraindication to conventional surgery. Indeed, the availability of information on the frailty status and on other important preoperative risk factors along with data on risk factors contraindicating SAVR made feasible the identification and matching of patients without prohibitive surgical risk.

Table 3. Early Outcome End Points in Propensity Score–Matched Pairs of Patients With EuroSCORE II <4%

Adverse Events	SAVR, n=355	TAVI, n=355	P Value
30 days mortality, n (%)	10 (2.8)	9 (2.5)	0.82
Stroke, n (%)	4 (1.1)	4 (1.1)	1.00
Valve migration, n (%)	0	7 (2.0)	<0.001
Cardiogenic shock, n (%)	16 (4.6)	6 (1.7)	0.025
Cardiac tamponade, n (%)	6 (1.7)	15 (4.3)	0.049
Permanent pacemaker, n (%)	9 (2.6)	44 (12.7)	<0.001
Major vascular damage, n (%)	0	25 (7.6)	<0.001
Infection	21 (6.2)	16 (4.7)	0.40
Wound, n (%)	6 (1.8)	4 (1.2)	0.24
Lung or other organs, n (%)	9 (2.7)	11 (3.3)	
Sepsis, n (%)	6 (1.8)	1 (0.3)	
Emergency PCI, n (%)	0	2 (0.6)	<0.001
Severe bleeding, n (%)*	48 (15.2)	14 (4.4)	<0.001
Paravalvular regurgitation, n (%)			
Mild	32 (9.8)	126 (38.7)	<0.001
Moderate	5 (1.5)	29 (8.9)	
Severe	0	2 (0.6)	
Acute kidney injury, n (%)†	146 (43.7)	87 (26.0)	<0.001
AKIN stages			
Stage 1†	96 (28.7)	62 (18.6)	<0.001
Stage 2†	22 (6.6)	11 (3.3)	
Stage 3†	28 (8.4)	14 (4.2)	
De novo dialysis, n (%)*	26 (7.6)	10 (2.9)	0.006
Mean transvalvular gradient, mmHg ±SD	14.4±6.9	10.6±6.0	<0.001
Peak transvalvular gradient, mmHg ±SD	25.7±11.2	19.4±8.5	<0.001
ICU stay, days ±SD	2.9±3.4	2.5±2.9	0.12

P values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables, and *t* test for paired sample for continuous variables. AKIN indicates Acute Kidney Injury Network; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; ICU, intensive care unit; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

*Bleeding requiring transfusion of more than 4 U of red blood cells.

†Excluding patients with previous dialysis.

Although there is not yet enough evidence on the efficacy of this approach,¹⁷ the decision to offer TAVI to these patients was likely based on Institutional policies of choosing TAVI instead of SAVR even if this indication drift was not supported by clear evidence of any benefit in low-risk patients. Furthermore, the minimally invasive nature of TAVI is attractive in elderly patients, and we suspect that several lower-risk patients might have denied SAVR and asked to be treated by TAVI.

The present analysis demonstrated that either TAVI or SAVR can be performed with similar 30-day mortality and stroke. TAVI seems to offer a clear advantage in terms of reduction of acute kidney injury and need of blood transfusion, but

it was associated with a higher risk of permanent pacemaker implantation, moderate-to-severe paravalvular regurgitation, vascular damage, and cardiac tamponade. The occurrence of paravalvular regurgitation and risk of permanent pacemaker implantation occurring after TAVI is of particular concern in low-risk patients. The risk of such complications may likely be reduced by the current transcatheter technology,¹⁸ but still they may have negative prognostic implications in low-risk patients in view of their longer expectancy of life.³ This applies also to octogenarians without significant comorbidities because a pooled analysis of octogenarians undergoing SAVR, mostly from pre-TAVI era, showed that their 5-year survival is 65%.¹⁹ The risk of complications typically associated with SAVR should be reduced as well by a strategy avoiding major bleeding through a minimally invasive approach and by decreasing myocardial ischemia time and duration of cardiopulmonary bypass using sutureless valves.¹⁰

A few studies have previously reported on similar mid-term outcome after TAVI and SAVR in patients with intermediate operative risk.^{7–9} Another study reported on better operative survival with sutureless SAVR compared with TAVI.¹⁰ However, these study populations still belong to a gray area of uncertainty. Taking into consideration that patients with such an operative mortality risk may have an even higher risk of significant postoperative adverse events, it is reasonable to justify a less-invasive approach in these intermediate-risk patients. On the contrary, patients randomized in the NOTION trial had a much lower operative risk (mean Society of Thoracic Surgeons score was ≈3%; mean EuroSCORE II was ≈2%), and the decision to perform TAVI in these patients should take into consideration the low risk of early adverse events occurring after SAVR and, even more importantly, the proven durability of conventional aortic valve prostheses. The present analysis included patients with an operative risk similar to that of NOTION patients, but opposite to the NOTION trial, subjects with coronary artery disease, on chronic dialytic treatment, with history of cardiac surgery and coronary revascularization, and prior stroke were not excluded in this subanalysis of the OBSERVANT study. Furthermore, the lack of power is a clear limitation of the NOTION trial. The observational nature, the limited exclusion criteria, and a longer follow-up are the main differences between the present analysis and the NOTION trial and, to some extent, may explain the differences in terms of survival of these 2 studies. However, both studies showed an increased risk of bleeding, cardiogenic shock, and acute kidney injury with SAVR and an increased risk of paravalvular regurgitation, permanent pacemaker implantation, and vascular complications with TAVI.

Current development of transcatheter technology focuses on facilitating rapid and accurate implantation of the prosthesis and on reducing the risk of vascular injury and paravalvular regurgitation. New transcatheter heart valve prostheses have been recently introduced and showed a potential for reducing such risks and may significantly improve the results of their predecessors.²⁰ Therefore, the present results may be affected by the disadvantages of using second-generation prostheses, and the value of next-generation prostheses in low-risk patients should be reassessed in the near future.

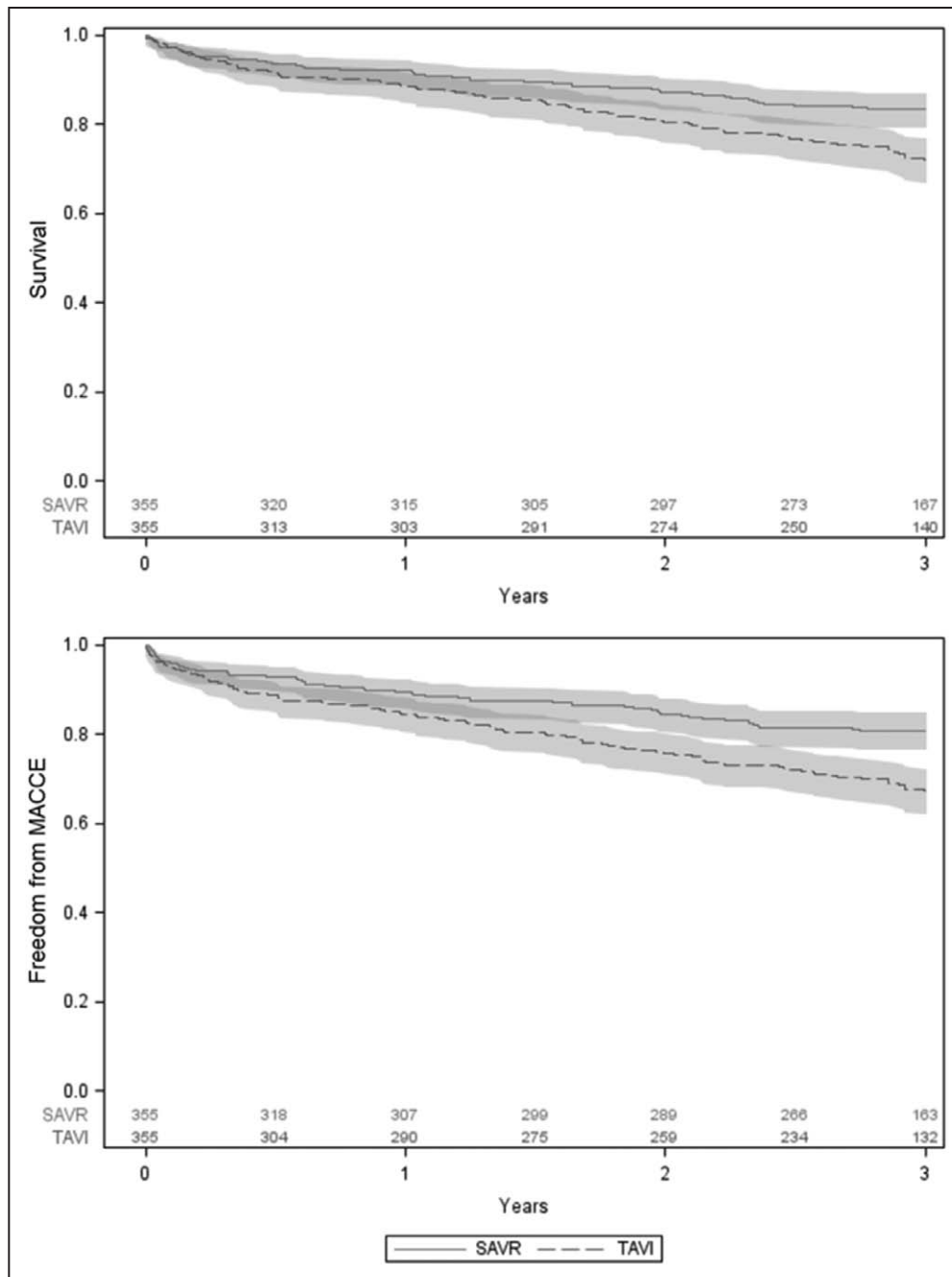


Figure 2. Intermediate survival (log-rank test by Klein–Moeschberger: $P=0.0075$) and freedom from major adverse cardiac and cerebrovascular events (MACCE; log-rank test by Klein–Moeschberger: $P=0.0023$) in propensity score–matched pairs of patients with low operative risk (European System for Cardiac Operative Risk Evaluation II [EuroSCORE II] $<4\%$) after transcatheter (TAVI; red line) or surgical aortic valve replacement (SAVR; blue line) for severe aortic valve stenosis.

Study Limitations

Several limitations related with this study should be acknowledged. First, OBSERVANT is a multicenter, prospective observational study, and the lack of randomization may introduce a selection bias. To compensate for the potential selection and evident baseline imbalance between the study groups, propensity score matching was performed and provided a well-balanced and rather large study population. The results of propensity score matching may still be biased by confounders not taken into account in this analysis. However, the OBSERVANT is a prospective study including a quite large

number of variables which are of significance in risk stratification of patients with aortic valve stenosis. Importantly, conditions contraindicating SAVR were collected prospectively, and these patients were excluded from this analysis. Furthermore, these findings were confirmed at subgroup analyses, which showed no significant interactions and an increased risk of mortality in patients without significant comorbidities.

Second, we recognize that the definition of low operative risk among these patients can be difficult. We adopted a cut off of 4% for EuroSCORE II for defining low-risk patients because these are the patients who are currently accepted

Table 4. Adverse Events at 3-Year Follow-Up

Late Events	SAVR, n=355		TAVI, n=355	
	n	IR, %	n	IR, %
Death from any cause	56	16.6	91	28.0
Stroke	13	3.0	33	9.4
Acute myocardial infarction	5	1.7	6	1.9
Coronary revascularization	3	1.6	5	1.6
MACCE	67	19.1	114	32.7

Incidence rates are computed as actuarial estimates at the specific time point and reported as percentage. IR indicates incidence rates; MACCE, major adverse cardiac and cardiovascular events (defined as the composite of death from any cause, stroke, acute myocardial infarction, and coronary revascularization); SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

for SAVR.²¹ Furthermore, early experience showed that EuroSCORE II seems to be accurate in predicting early mortality in patients undergoing SAVR.²¹ Third, the outcomes were not defined according to the Valve Academic Research Consortium criteria.²² The reason is that such definitions are specifically designed to define complications after TAVI and, therefore, may be misleading to illustrate complications after SAVR, likely resulting in their overestimation. Furthermore,

the OBSERVANT study was started on before these guidelines were published. Fourth, the 3-year follow-up prevents conclusive results on the long-term durability of these methods in these low-risk patients. Fifth, the OBSERVANT registry does not contain data on antithrombotic regimens at discharge. This limitation prevents the analysis of stroke events at 3 years, which in this series occurred more frequently after TAVI than SAVR. Although the optimal antithrombotic therapy after TAVI is a matter of debate, oral anticoagulation is usually administered after SAVR with a bioprosthesis for at least 3 months followed by single antiplatelet therapy. In view of the recently reported subclinical valve thrombosis after TAVI,²³ we speculate that suboptimal antithrombotic therapy may partly explain the increased risk of stroke after TAVI herein observed. Finally, this analysis included only patients who underwent isolated SAVR or TAVI, and it is unknown whether these results also applies to patients requiring concomitant coronary revascularization.

Conclusions

The results of this multicenter observational study showed that in patients with low operative risk, TAVI and SAVR achieve comparable early survival, whereas TAVI increases the risk of paravalvular regurgitation and implantation of pacemaker. Furthermore, significantly better 3-year survival and freedom

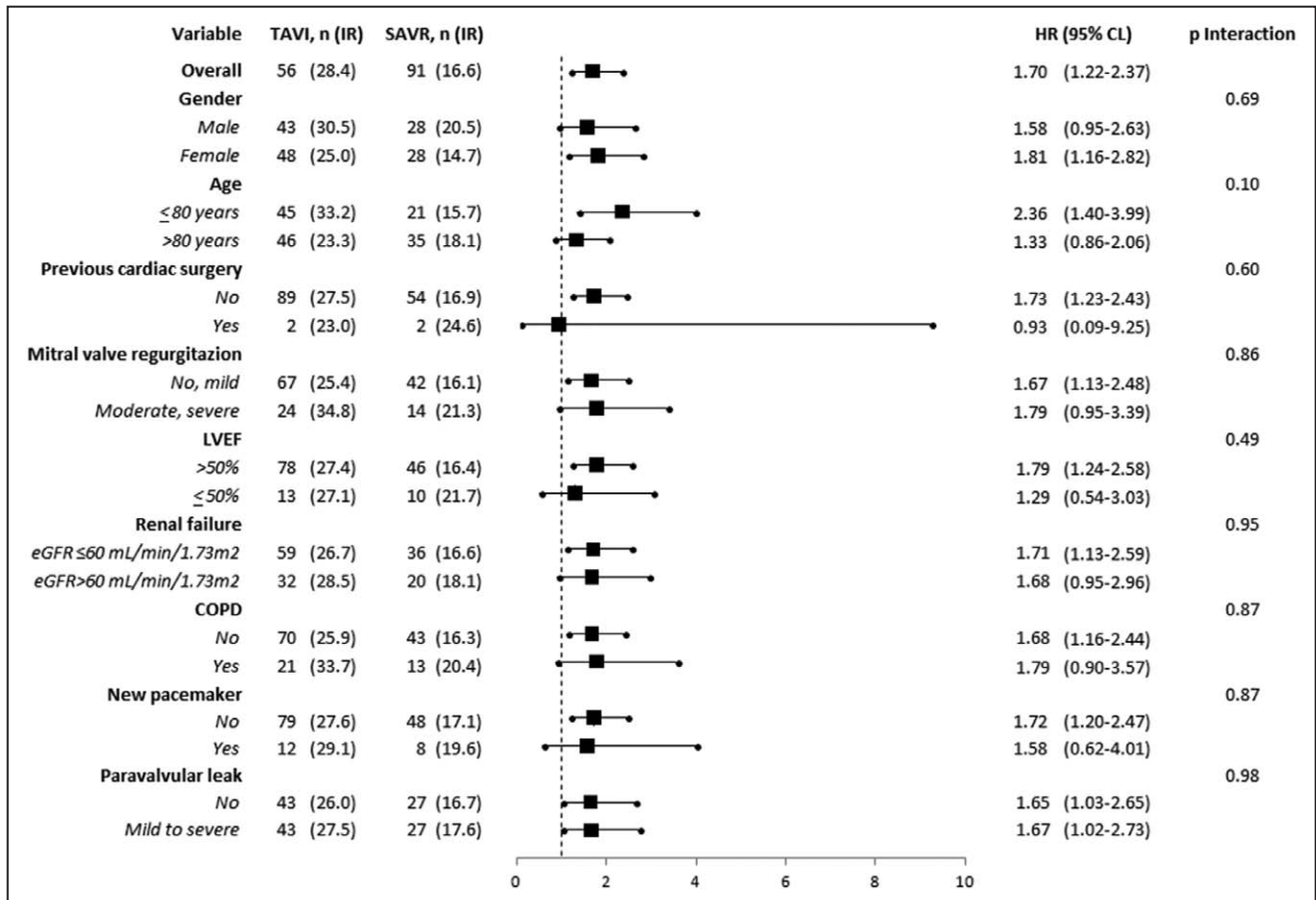


Figure 3. Analysis of the 3-year mortality in different subgroups of patients with testing for interaction. CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IR, incidence rate; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

from MACCE were observed after SAVR compared with TAVI. These results suggest that, at this stage, expanding the indications of TAVI toward lower-risk patients may not be justified. Because next generation transcatheter heart valve prostheses may decrease the risk of paravalvular regurgitation, permanent pacemaker implantation, and access site complications, further studies on the results with these new valve prostheses are necessary to support this approach in patients with low operative risk.

Acknowledgments

The authors thank Gabriella Badoni for her technical support in the organizational phases of the study.

Sources of Funding

The OBSERVANT study was supported by a grant (Fasc. 1M30) from the Italian Ministry of Health and Istituto Superiore di Sanità.

Disclosures

Dr Tamburino receives honorary fees from Medtronic and Abbott. Dr Barbanti is a consultant for Edwards Lifesciences. The other authors report no conflicts.

References

- Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliarios V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. doi: 10.1016/S0140-6736(15)60308-7.
- Walther T, Hamm CW, Schuler G, Berkowitsch A, Kötting J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Möllmann H; GARY Executive Board. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY Registry. *J Am Coll Cardiol*. 2015;65:2173–2180. doi: 10.1016/j.jacc.2015.03.034.
- Kappetein AP, Osnabrugge RL, Head SJ. Patient selection for TAVI in 2014: is there a justification for treating low- or intermediate-risk patients? The surgeon's view. *EuroIntervention*. 2014;10(suppl U):U11–U15. doi: 10.4244/EIJV10SUA2.
- Cribier A, Durand E, Eltchaninoff H. Patient selection for TAVI in 2014: is it justified to treat low- or intermediate-risk patients? The cardiologist's view. *EuroIntervention*. 2014;10(suppl U):U16–U21. doi: 10.4244/EIJV10SUA3.
- Lange R, Bleiziffer S, Mazzitelli D, Elhmidy Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol*. 2012;59:280–287. doi: 10.1016/j.jacc.2011.10.868.
- Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engström T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184–2194. doi: 10.1016/j.jacc.2015.03.014.
- Latib A, Maisano F, Bertoldi L, Giacomini A, Shannon J, Cioni M, Ielasi A, Figini F, Tagaki K, Franco A, Covello RD, Grimaldi A, Spagnolo P, Buchannan GL, Carlino M, Chieffo A, Montorfano M, Alfieri O, Colombo A. 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;164:910–917. doi: 10.1016/j.ahj.2012.09.005.
- Piazza N, Kalesan B, van Mieghem N, Head S, Wenaweser P, Carrel TP, Bleiziffer S, de Jaegere PP, Gahl B, Anderson RH, Kappetein AP, Lange R, Serruys PW, Windecker S, Jüni P. 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. *JACC Cardiovasc Interv*. 2013;6:443–451. doi: 10.1016/j.jcin.2013.01.136.
- Tamburino C, Barbanti M, D'Errigo P, Ranucci M, Onorati F, Covello RD, Santini F, Rosato S, Santoro G, Fusco D, Grossi C, Seccareccia F; OBSERVANT Research Group. 1-Year outcomes after transfemoral transcatheter or surgical aortic valve replacement: results from the Italian OBSERVANT study. *J Am Coll Cardiol*. 2015;66:804–812. doi: 10.1016/j.jacc.2015.06.013.
- Biancari F, Barbanti M, Santarpino G, Deste W, Tamburino C, Gulino S, Immè S, Di Simone E, Todaro D, Pollari F, Fischlein T, Kasama K, Meuris B, Dalén M, Sartipy U, Svenarud P, Lahtinen J, Heikkinen J, Juvonen T, Gatti G, Pappalardo A, Mignosa C, Rubino AS. Immediate outcome after sutureless versus transcatheter aortic valve replacement. *Heart Vessels*. 2016;31:427–433. doi: 10.1007/s00380-014-0623-3.
- Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41:734–744, discussion 744. doi: 10.1093/ejcts/ezs043.
- Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M, Murphy GJ, Sellke FW, Shore-Lesserson L, von Heymann C, Ranucci M. Universal definition of perioperative bleeding in adult cardiac surgery. *J Thorac Cardiovasc Surg*. 2014;147:1458–1463.e1. doi: 10.1016/j.jtcvs.2013.10.070.
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31. doi: 10.1186/cc5713.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
- Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161. doi: 10.1002/pst.433.
- Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data*. New York: Springer Verlag; 1997.
- Tuzcu EM, Kapadia SR, Svensson LG. Well-intended NOTION, ahead of practice. *J Am Coll Cardiol*. 2015;65:2195–2197. doi: 10.1016/j.jacc.2015.03.560.
- Wendt D, Al-Rashid F, Kahlert P, Eißmann M, El-Chilali K, Jánosi RA, Pasa S, Tsagakis K, Liakopoulos O, Erbel R, Jakob H, Thielmann M. Low incidence of paravalvular leakage with the balloon-expandable Sapien 3 transcatheter heart valve. *Ann Thorac Surg*. 2015;100:819–825, discussion 825. doi: 10.1016/j.athoracsur.2015.03.079.
- Vasques F, Messori A, Lucenteforte E, Biancari F. Immediate and late outcome of patients aged 80 years and older undergoing isolated aortic valve replacement: a systematic review and meta-analysis of 48 studies. *Am Heart J*. 2012;163:477–485. doi: 10.1016/j.ahj.2011.12.005.
- Webb J, Gerosa G, Lefèvre T, Leipsic J, Spence M, Thomas M, Thielmann M, Treede H, Wendler O, Walther T. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol*. 2014;64:2235–2243. doi: 10.1016/j.jacc.2014.09.026.
- Biancari F, Juvonen T, Onorati F, Faggian G, Heikkinen J, Airaksinen J, Mariscalco G. Meta-analysis on the performance of the EuroSCORE II and the Society of Thoracic Surgeons Scores in patients undergoing aortic valve replacement. *J Cardiothorac Vasc Anesth*. 2014;28:1533–1539. doi: 10.1053/j.jvca.2014.03.014.
- Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253–269. doi: 10.1016/j.jacc.2010.12.005.
- Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, de Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelmin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB, Søndergaard L. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024. doi: 10.1056/NEJMoa1509233.

Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients

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Circ Cardiovasc Interv. 2016;9:e003326

doi: 10.1161/CIRCINTERVENTIONS.115.003326

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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SUPPLEMENTAL MATERIAL

Supplemental Table. Baseline characteristics of unmatched patients with EuroSCORE II < 4%

	SAVR n=2871	TAVR n=531	p-value
Age (years±SD)	71.3±9.9	81.3±6.1	<0.0001
Male, n (%)	1367 (47.6)	290 (54.6)	0.003
BMI (kg/m ² ±SD)	27.4±4.5	26.9±5.3	0.07
Diabetes mellitus, n (%)	520 (18.1)	80 (15.1)	0.09
eGFR (mg/min/1.73 m ² ±SD)	75.0±20.2	65.2±20.8	<0.0001
Chronic dialysis, n (%)	18 (0.6)	14 (2.6)	<0.0001
Smoking history, n (%)	559 (20.0)	59 (11.3)	<0.0001
Neurologic dysfunction, n (%)	40 (1.4)	29 (5.5)	<0.0001
Chronic liver disease, n (%)	37 (1.3)	23 (4.3)	<0.0001
Active neoplastic disease, n (%)	31 (1.1)	28 (5.3)	<0.0001
Peripheral arteriopathy, n (%)	221 (7.7)	53 (10.0)	0.07
Pulmonary disease, n (%)	243 (8.5)	124 (23.4)	<0.0001
Pulmonary hypertension, n (%)	95 (3.3)	29 (5.5)	0.01
Previous cardiac surgery, n (%)	53 (1.8)	12 (2.3)	0.52
Previous op. on the aorta, n (%)	35 (1.2)	17 (3.2)	0.0006
Previous BAV, n (%)	21 (0.7)	72 (13.6)	<0.0001
Previous AMI, n (%)	132 (4.6)	45 (8.5)	0.0002
Previous PCI, n (%)	194 (6.8)	130 (24.5)	<0.0001
Coronary artery disease, n (%)	288 (10.0)	100 (18.8)	<0.0001
One-vessel disease	186 (6.5)	63 (11.9)	
Two-vessels disease	39 (1.4)	13 (2.4)	<0.0001
Three-vessels disease	63 (2.2)	24 (4.5)	
LVEF, n (%)			
> 50%	2525 (87.9)	456 (85.9)	
30-50%	330 (11.5)	68 (12.8)	0.15
< 30%	18 (0.6)	7 (1.3)	
NYHA classes, n (%)			
I	461 (16.1)	28 (5.3)	<0.0001
II	1444 (50.3)	217 (40.9)	

III	851 (29.6)	249 (46.9)	
IV	111 (3.9)	29 (5.5)	
Unstable angina, n (%)	58 (2.0)	7 (1.3)	0.28
Frailty score (moderate-severe), n (%)	103 (3.7)	110 (20.7)	<0.0001
Urgent procedure, n (%)	40 (1.4)	6 (1.1)	0.63
Logistic EuroSCORE I (% \pm SD)	3.6 \pm 2.3	6.9 \pm 3.3	<0.0001
Logistic EuroSCORE II (% \pm SD)	1.7 \pm 0.9	2.7 \pm 0.8	<0.0001

Abbreviations: SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; BMI, body mass index; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; BAV, balloon aortic valvuloplasty; NYHA, New York Heart Association. P-values refer to McNemar test for dichotomous variables, Stuart-Maxwell test for categorical variables and t-test for paired sample for continuous variables.

Supplemental Appendix

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