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Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation

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Aims Transcatheter aortic valve implantation (TAVI) is an established treatment alternative to surgical aortic valve replacement in high-risk and inoperable patients and outcomes among patients with estimated low or intermediate risk remain to be determined. The aim of this study was to assess clinical outcomes among patients with estimated low or intermediate surgical risk undergoing TAVI.

Methods and results Between August 2007 and October 2011, 389 consecutive patients underwent TAVI and were categorized according to the Society of Thoracic Surgeons (STS) score into low (STS $< 3\%$; $n = 41$, 10.5%), intermediate (STS $\geq 3\%$ and $\leq 8\%$, $n = 254$, 65.3%), and high-risk (STS $> 8\%$; $n = 94$, 24.2%) groups for the purpose of this study. Significant differences were found between the groups (low risk vs. intermediate risk vs. high risk) for age (78.2 ± 6.7 vs. 82.7 ± 5.7 vs. 83.7 ± 4.9, $P < 0.001$), body mass index (28.1 ± 6.1 vs. 26.5 ± 4.9 vs. 24.4 ± 4.6, $P < 0.001$), chronic renal failure (34 vs. 67 vs. 90%, $P < 0.001$), all-cause mortality at 30 days (2.4 vs. 3.9 vs. 14.9%, $P = 0.001$), and all-cause mortality at 1 year (10.1 vs. 16.1 vs. 34.5%, $P = 0.0003$). No differences were observed with regards to cerebrovascular accidents and myocardial infarction during 1-year follow-up.

Conclusion In contemporary practice, TAVI is not limited to inoperable or STS-defined high-risk patients and should be guided by the decision of an interdisciplinary Heart Team. Compared with patients at calculated high risk, well-selected patients with STS-defined intermediate or low risk appear to have favourable clinical outcomes.

Keywords Transcatheter aortic valve implantation • TAVI • Aortic stenosis • Risk stratification • Intermediate risk

Introduction

Untreated symptomatic severe aortic stenosis has a dismal prognosis.[1] A pharmacological treatment approach to relieve the mechanical obstruction of the left ventricle or to slow progression of disease has yielded disappointing results.[2] For decades, surgical aortic valve replacement (SAVR) was the only effective therapy to alleviate symptoms and improve prognosis.[3] After the first successful transcatheter aortic valve implantation (TAVI) in 2002, prospective trials[4,5] and numerous observational studies[6–8] have reported improved survival of TAVI compared with medical treatment in inoperable patients[4] and similar outcomes compared with SAVR in selected high-risk patients.[5] Appropriate risk stratification in patients referred for TAVI evaluation remains challenging, as there is no validated risk score for TAVI patients and the currently used surgical risk scores may over- or underestimate the actual risk incurred.[9] As a result, it is recommended to consider comorbidities, and frailty in addition to calculated risk scores such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) or Society of Thoracic Surgeons (STS) score, when

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evaluating the best therapeutic option for patients with severe aortic stenosis.

Current guidelines recommend to perform TAVI in patients considered inoperable or at high risk for SAVR.[10] To appropriately select elderly patients with symptomatic severe aortic stenosis, the judgement of a collaborative group of physicians, including specialists for cardiac surgery, interventional cardiology, cardiac anaesthesia as well as geriatric medicine, is warranted. Different reasons affect the decision-making process and favour a less invasive treatment strategy (TAVI) in contemporary clinical practice. Factors including the general medical condition and frailty of the patient importantly impact on treatment selection beyond the estimated surgical risk as assessed by available risk scores. It is well known that patients at high risk according to the STS score have worse clinical outcome after SAVR compared with patients with lower STS risk.[11] However, little information is available on clinical outcomes among patients undergoing TAVI deemed at low or intermediate risk as assessed by surgical risk scores alone. Thus, the purpose of the present study was to compare clinical outcomes of patients undergoing TAVI considered at intermediate or low risk according to the STS score compared with high-risk patients.

Methods

Patient population

Between August 2007 and October 2011, 389 elderly patients with symptomatic severe aortic stenosis were included into a prospective single centre registry (Bern TAVI Registry). Consecutive patients underwent TAVI with the self-expandable Medtronic CoreValve bioprosthesis (MCV; Medtronic, Minneapolis, MN, USA) or the balloon-expandable Edwards Sapien transcatheter heart valve (ES, Edwards LifeSciences, Irvine, CA, USA), using the femoral, transapical, and subclavian access route, as previously described.[12] Decisions regarding the access site were based on the individual anatomical characteristics as determined by contrast enhanced computed tomography, angiography, and transthoracic- or transoesophageal echocardiography. The preferred access route followed the principle of the least invasive approach. The study complied with the declaration of Helsinki, and the registry was approved by the local ethics committee. All patients provided written informed consent to participate in the registry with prospective follow-up assessment.

The Heart Team decision

Patients referred for TAVI evaluation underwent interdisciplinary discussion in the local, institutional Heart Team consisting of experienced interventional cardiologists and cardiovascular surgeons. The indication to undergo TAVI was based on patients' clinical history (e.g. previous coronary artery bypass graft surgery, previous myocardial infarction, previous cerebrovascular event), clinical status (e.g. body mass index, diabetes mellitus, renal failure, left ventricular ejection fraction, coronary artery disease, chronic obstructive lung disease), and a dedicated geriatric assessment.[13]

Definitions

Clinical risk estimation was followed by prospective calculation of the logistic EuroSCORE[14] and the STS risk score.[11] For the purpose of this analysis, patients were categorized into three groups according to the primarily proposed definition for the European SURTAVI patient population[15,16]: (i) low-risk group (STS risk score < 3); (ii) intermediate risk group (STS risk score ≥ 3 and ≤ 8); and (iii) high-risk group (STS risk score > 8). In addition, patients were subcategorized into time quartiles according to treatment date and baseline clinical characteristics and clinical outcomes subsequently analysed. All events were adjudicated by an independent team of interventional cardiologists and cardiac surgeons according to the endpoint definitions proposed by the Valve Academic Research Consortium (VARC), described in detail elsewhere.[17]

Statistical analysis

Patient demographics and follow-up data were prospectively collected and entered into a dedicated database held at the Clinical Trials Unit, University of Bern, Switzerland. All statistical analyses were performed by a statistician of an academic clinical trials unit (D.H. and P.J., Department of Clinical Research and Clinical Trials Unit Bern, Bern University Hospital, Switzerland) using Stata 12 (StataCorp LP, College Station, TX, USA). We report risk ratios (RR) (95% CI) from Mantel–Cox log-rank tests of time to first event for death, cardiovascular death, cerebrovascular accidents, and myocardial infarction up to 30-day and 1-year follow-up separately. We report RR (95% CI) from Poisson regressions with robust error variances for bleeding, acute renal failure, access site complications, VARC safety endpoint, and any composite involving these outcomes, occurring within 30 days follow-up. We report RR (95% CI) derived from estimated probabilities using exact logistic regressions in pair wise comparisons when zero outcomes occurred in one of the risk groups. Overall *P*-values show a test for a linear effect from the low to the intermediate to the high STS risk groups, except Fisher's test in case of zero outcome in any risk group. The effect of STS risk score on all-cause mortality at 1 year was analysed using logistic regression. Continuous variables are presented as means $\pm$ SD and are compared by means of analysis of variance *F*-tests. Categorical data are expressed as frequencies and percentages and are compared using χ^2 and Fisher's exact tests.

Results

Patient population

Out of 389 TAVI patients, 94 (24.2%) patients were categorized as high risk (STS > 8), 254 patients (65.3%) as intermediate risk (STS ≥ 3 and ≤ 8), and 41 (10.5%) patients as low risk (STS < 3). Baseline clinical characteristics according to the risk group are summarized in *Table 1*. Patients in the high-risk group were older, and presented with lower body mass index compared with patients at intermediate and low risk. Diabetes, arterial hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, and renal failure were more prevalent among high risk compared with intermediate and low-risk patients. There were no differences with respect to previous myocardial infarction, previous coronary artery bypass graft surgery, previous stroke, and atrial fibrillation between the different patient groups. Left ventricular ejection fraction was lower among high risk compared with intermediate and low-risk patients (48.2 ± 15 vs. 52.0 ± 15 vs. 59.1 ± 11, $P < 0.001$). Although we observed no differences in aortic valve area, there was a trend towards a lower mean transaortic gradient (41.6 ± 19 vs. 44.4 ± 16 vs. 48.6 ± 16, $P = 0.08$) and higher systolic pulmonary arterial pressure (54.0 ± 17 vs. 50.5 ± 17 vs. 46.8 ± 17,

Table 1 Baseline clinical characteristics

	All patients, N = 389	STS risk group			P-value
		Low, N = 41	Intermediate, N = 254	High, N = 94	
Age (years)	82.5 ± 5.8	78.2 ± 6.7	82.7 ± 5.7	83.7 ± 4.9	<0.001
Female gender, *n* (%)	224 (58%)	20 (49%)	145 (57%)	59 (63%)	0.31
Body mass index (kg/m^2)	26.2 ± 5.1	28.1 ± 6.1	26.5 ± 4.9	24.4 ± 4.6	<0.001
Cardiac risk factors					
Diabetes mellitus, *n* (%)	105 (27%)	5 (12%)	66 (26%)	34 (36%)	0.01
Hypercholesterolaemia, *n* (%)	236 (61%)	25 (61%)	156 (62%)	55 (59%)	0.87
Hypertension, *n* (%)	303 (78%)	25 (61%)	203 (80%)	75 (80%)	0.02
Current smoker, *n* (%)	48 (12%)	6 (15%)	31 (12%)	11 (12%)	0.89
Past medical history					
Previous myocardial infarction, *n* (%)	64 (16%)	5 (12%)	40 (16%)	19 (20%)	0.45
Previous coronary artery bypass graft, *n* (%)	72 (19%)	5 (12%)	43 (17%)	24 (26%)	0.10
Previous percutaneous coronary intervention, *n* (%)	94 (24%)	7 (17%)	59 (23%)	28 (30%)	0.24
Previous stroke, *n* (%)	30 (8%)	4 (10%)	17 (7%)	9 (10%)	0.59
Peripheral vascular disease, *n* (%)	87 (22%)	2 (5%)	52 (20%)	33 (35%)	<0.001
Chronic obstructive pulmonary disease, *n* (%)	72 (19%)	3 (8%)	43 (17%)	26 (28%)	0.01
Clinical features					
Pulmonary artery hypertension (PAPs in mmHg)	51.0 ± 17.0	46.8 ± 16.7	50.5 ± 16.9	54.0 ± 17.2	0.06
Renal failure (GFR < 60mL/min/1.73 m^2)	268 (69%)	14 (34%)	169 (67%)	85 (90%)	<0.001
Coronary artery disease, *n* (%)	238 (61%)	19 (46%)	155 (61%)	64 (68%)	0.06
Atrial fibrillation, *n* (%)	103 (27%)	6 (15%)	69 (27%)	28 (31%)	0.13
Echocardiographic variables					
Left ventricular ejection fraction (%)	51.9 ± 14.8	59.1 ± 10.9	52.0 ± 14.8	48.2 ± 15.0	<0.001
Aortic valve area (cm^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.97
Mean transaortic gradient (mmHg)	44.2 ± 16.8	48.6 ± 16.1	44.4 ± 16.0	41.6 ± 18.7	0.08
Symptoms					
New York Heart Association (NYHA) Functional Class					<0.001
I, *n* (%)	22 (6%)	8 (20%)	11 (4%)	3 (3%)	<0.001
II, *n* (%)	109 (28%)	20 (49%)	71 (28%)	18 (19%)	0.002
III, *n* (%)	206 (53%)	11 (27%)	146 (58%)	49 (53%)	0.001
IV, *n* (%)	49 (13%)	2 (5%)	24 (10%)	23 (25%)	<0.001
Heart Team decision					<0.001
Anatomical reasons, *n* (%)	12 (3%)	4 (10%)	7 (3%)	1 (1%)	0.02
Comorbidities with poor prognosis, *n* (%)	21 (5%)	2 (5%)	12 (5%)	7 (7%)	0.60
Intermediate surgical risk, *n* (%)	172 (44%)	25 (61%)	125 (49%)	22 (23%)	<0.001
Excessive surgical risk, *n* (%)	180 (46%)	10 (24%)	110 (43%)	60 (64%)	<0.001
Emergency intervention, *n* (%)	4 (1%)	0 (0%)	0 (0%)	4 (4%)	0.01
Risk assessment					
Logistic EuroSCORE (%)	24.3 ± 14.2	13.2 ± 7.5	22.1 ± 11.9	35.1 ± 15.7	<0.001
STS score (%)	6.8 ± 5.3	2.1 ± 0.5	5.1 ± 1.4	13.3 ± 7.1	<0.001
Antithrombotic therapy at baseline					
Aspirin, *n* (%)	237 (62%)	23 (56%)	152 (61%)	62 (67%)	0.45
Clopidogrel, *n* (%)	69 (18%)	4 (10%)	45 (18%)	20 (22%)	0.26
Oral anticoagulation, *n* (%)	106 (28%)	10 (24%)	68 (27%)	28 (30%)	0.77

PAPs, systolic pulmonary artery pressure.
Depicted are means ± SD with *P*-values from ANOVAs, or counts (%) with *P*-values from Chi-square (for multiple categories) or Fisher's tests (for binary categories).

$P = 0.06$) among high risk compared with intermediate and low-risk patients.

Baseline clinical characteristics were further analysed according to time quartiles. STS risk assessment of patients was significantly higher in the first quartile (Q1) compared with Q2 (7.5 ± 5.9 vs. 5.6 ± 4.7) but not different to Q3 and Q4 (Q3: 6.7 ± 4.2; Q4: 7.3 ± 5.8) (see Supplementary material online, *Table S1*).

Procedural results

Procedural characteristics and results are presented in *Table 2*. The majority of patients underwent TAVI using the transfemoral access route with either the Medtronic CoreValve (58%) or the Edwards Sapien valve (42%) with no differences between the three risk groups. Concomitant coronary revascularization tended to be more frequently performed in high risk compared with the intermediate and low surgical risk groups (22 vs. 15 vs. 7%, $P = 0.08$). As a result, the duration of the procedure (96.6 ± 47 vs. 79.5 ± 30 vs. 70.5 ± 23, $P < 0.001$) and fluoroscopy time (22.8 ± 13 vs. 19.2 ± 9 vs. 16.6 ± 8, $P = 0.002$) was highest among high-risk patients.

Procedural characteristics according to time quartiles are depicted in Supplementary material online, *Table S2*. Procedure time (Q1 91.4 ± 42 vs. Q4 70.7 ± 28 min, $P = 0.001$) as well as the need for general anaesthesia (Q1 47 vs. Q4 26%, $P = 0.002$) significantly decreased over time. The VARC Device success steadily increased (Q1 74 vs. Q4 97%, $P < 0.001$), which was mainly related to a reduction in post-TAVI aortic regurgitation ≥ 2 (Q1 24 vs. Q4 2%, $P < 0.001$).

Clinical outcomes

Clinical outcomes at 30 days and at 1 year are summarized in *Table 3*. All-cause mortality at 30 days was highest in the high-risk group (14.9 vs. 3.9 vs. 2.4%, $P = 0.001$), mainly driven by an increased cardiovascular mortality (12.9 vs. 3.2 vs. 0%, $P = 0.003$). Major adverse events including acute renal failure (8.5 vs. 2.8 vs. 0%, $P = 0.03$) and major access site complications (12.8 vs. 7.1 vs. 0%, $P = 0.03$) were also more frequent in high risk compared with intermediate and low-risk patients. There were no differences with respect to cerebrovascular accidents, myocardial infarction, and bleeding complications between the groups undergoing TAVI at 30 days of follow-up.

At 1 year of follow-up, all-cause mortality was highest among high risk followed by intermediate and low-risk patients (34.5 vs. 16.1 vs. 10.1%, $P = 0.0003$). The inter-group comparison demonstrated a significant difference between the three groups (all-cause mortality: low vs. high risk RR 0.27, 95%CI 0.09–0.77, intermediate vs. high risk RR 0.41, 95% CI 0.24–0.67, $P < 0.001$; cardiovascular mortality: low vs. high risk RR 0.16, 95% CI 0.04–0.70, intermediate vs. high risk RR 0.35, 95% CI 0.19–0.62, $P = 0.0001$) (*Figure 1*). All-cause mortality in this TAVI population followed a sigmoid function with low rates of death in the low-risk group and an exponential increase up to the STS predicted risk of 25% (*Figure 2*, logistic regression, STS risk score effect per 1 unit increase: OR 1.088, 95% CI 1.039–1.139, $P = 0.0003$). No significant differences with regards to cerebrovascular accidents and myocardial infarction between the different risk groups were observed throughout 1 year of follow-up.

Clinical outcomes at 30 days of follow-up per treatment quartile are displayed in Supplementary material online, *Table S3*. The inter-quartile group comparison showed no significant difference for all-cause and cardiovascular death, major stroke, myocardial infarction, and acute renal failure; however, there was a significant reduction in life-threatening (Q1 23.5 vs. Q4 9.3%, RR 0.76, 95% CI 0.62–0.93, $P = 0.01$) and major bleeding complications (Q1 41.8 vs. Q4 18.6%, RR 0.78, 95% CI 0.68–0.88, $P < 0.001$).

Transfemoral transcatheter aortic valve implantation

Out of 389 patients, 308 (79%) underwent TAVI via transfemoral, 76 (20%) patients via transapical, and 5 (1%) patients via transsubclavian access. Patients undergoing transfemoral TAVI were also categorized into high risk, intermediate and low risk with baseline clinical characteristics (*Table 4*) and clinical outcomes (*Table 5*) shown separately. Among low-risk patients undergoing transfemoral TAVI, the 30-day rate of all-cause mortality, cerebrovascular accidents, myocardial infarction, and acute renal failure was 0%. Compared with the overall patient population, there was a linear increase in all-cause (low vs. high risk RR 0.26, 95% CI 0.08–0.90, intermediate vs. high risk RR 0.39, 95% CI 0.22–0.71, $P = 0.0013$) and cardiovascular mortality (low vs. high risk RR 0.21, 95% CI 0.05–0.91, intermediate vs. high risk RR 0.30, 95%CI 0.15–0.60, $P = 0.0005$) at 1 year of follow-up.

Discussion

The present analysis of patients undergoing TAVI in the framework of contemporary European practice has the following principal findings:

- A substantial proportion of patients undergoing TAVI in contemporary clinical practice are at high-risk when calculating the logistic EuroSCORE but only at intermediate risk when applying the STS score.
- Clinical outcomes among carefully selected patients considered at low or intermediate risk according to the STS score are favourable and superior compared with high-risk patients.
- Transfemoral TAVI among patients with low STS score is associated with the lowest rate of peri-procedural complications and short-term mortality.

This analysis is based on a single-centre experience with consecutive patients undergoing TAVI. All patients were considered to be at increased risk for SAVR during the Heart Team discussion, but were found to be at estimated intermediate risk when applying the STS score. Significant comorbidities and high-risk features that are not accounted for in the STS risk and EuroSCORE contribute to this difference. This suggests that patient selection based on risk score calculation only is not sufficient to assess the 'true' risk of a patient undergoing SAVR. Thus, careful patient selection based on the Heart Team model is required for appropriate treatment allocation.[10]

Since the early stages of TAVI, the logistic EuroSCORE was recommended as one of the surgical risk scores widely used in Europe with a cut-off value of 20% considered as high risk. With

Table 2 Procedural characteristics

	All patients, N = 389	STS risk group			P-value
		Low, N = 41	Intermediate, N = 254	High, N = 94	
Procedure time (min)	82.7 ± 35.4	70.5 ± 23.1	79.5 ± 30.2	96.6 ± 47.2	<0.001
Fluoroscopy time (min)	19.8 ± 10.3	16.6 ± 7.8	19.2 ± 9.3	22.8 ± 13.1	0.002
Amount of contrast (mL)	252.2 ± 96.7	226.0 ± 82.0	255.9 ± 94.1	254.0 ± 108.1	0.18
General anaesthesia, *n* (%)	164 (42%)	17 (41%)	102 (40%)	45 (48%)	0.43
Access route					
Transfemoral, *n* (%)	308 (79%)	33 (80%)	200 (79%)	75 (80%)	0.94
Transapical, *n* (%)	76 (20%)	8 (20%)	50 (20%)	18 (19%)	
Transsubclavian, *n* (%)	5 (1%)	0 (0%)	4 (2%)	1 (1%)	
Valve type					
Medtronic CoreValve, *n* (%)	224 (58%)	25 (61%)	148 (58%)	51 (54%)	0.72
Edwards Sapien valve, *n* (%)	165 (42%)	16 (39%)	106 (42%)	43 (46%)	
Revascularization					
Concomitant PCI, *n* (%)	63 (16%)	3 (7%)	39 (15%)	21 (22%)	0.08
Staged PCI, *n* (%)	35 (9%)	1 (2%)	25 (10%)	9 (10%)	0.30
Procedural specifications					
VARC device success, *n* (%)	330 (85%)	37 (90%)	216 (85%)	77 (82%)	0.46
Post TAVI—need for permanent pacemaker, *n* (%)	97 (25%)	10 (24%)	67 (26%)	20 (21%)	0.62
Post TAVI—aortic regurgitation ≥2	52 (13%)	4 (10%)	33 (13%)	15 (16%)	0.60
Valve in series, *n* (%)	7 (2%)	0 (0%)	4 (2%)	3 (3%)	0.40

Depicted are means ± SD with *P*-values from ANOVAs or counts (%) with *P*-values from Chi-square (for multiple categories) or Fisher's tests (for binary categories).

growing experience in patient selection and in performing the procedure, it was recognized that the logistic EuroSCORE overestimates the effective risk for adverse clinical outcomes.[9] This dilemma has led to inconsistent inclusion criteria across different studies in the past. More recently initiated studies such as the PARTNER 2 and the SURTAVI trial rely on a STS- rather than EuroSCORE-based risk estimate. In the absence of a validated risk score for patients undergoing TAVI, numerous factors including comorbidities, clinical status, individual anatomical characteristics, and frailty need to be carefully assessed and considered prior to treatment allocation. The discussion of these factors in a dedicated Heart Team is helpful to guide the most appropriate patient selection and treatment allocation. In the present analysis, we categorized patients into three different risk groups according to the initial European inclusion criteria of the SURTAVI trial comparing TAVI with SAVR among intermediate risk patients (low-risk STS score <3%, intermediate risk 3–8%, high risk >8%). Considering the estimated risk of the overall population, this is well in line with previous observational studies[6,18] and reflects contemporary practice in Europe. More recently, a single surgical centre in Germany reported on a shift towards the treatment of lower risk patients undergoing TAVI.[19] Among 420 patients undergoing TAVI at this institution, the overall calculated peri-operative risk according to the STS score was 7.1 ± 5.4% (EuroSCORE 25.4% ± 16) in the first quartile but only 4.8 ± 2.6% (EuroSCORE 17.8 ± 12%) in the last quartile of their experience. The trend towards inclusion of lower risk patients is further substantiated by a recent publication of the UK TAVI Registry investigators.[20] Using the logistic EuroSCORE, the authors report an estimated peri-operative risk of 18.5% (11.7–27.9), which is comparable with the intermediate risk group [logistic EuroSCORE 19.6% (12.8–28.7)] of the present patient population.

The present analysis revealed significantly better short- and mid-term clinical outcomes of low and intermediate risk patients compared with the high-risk group. All-cause and cardiovascular mortality correlated well with the predicted risk according to the STS score. Mortality followed a linear function at 30 days and 1 year for cardiovascular and all-cause death in favour of low and intermediate risk patients. Considering the VARC combined safety endpoint, the low-risk group had a 59% and the intermediate risk group a 45% lower risk to reach this endpoint compared with the high-risk group. Moreover, the improved clinical outcome for lower risk patients was sustained over time, demonstrating a 71 and 59% relative risk reduction, respectively. Similar results were reported from the German Heart Center in Munich, with better clinical outcomes over time related to the inclusion of lower risk and younger patients. The 30-day and 6-month mortality rates decreased from 11.4 to 3.8% and from 23.5 to 12.4%,

Table 3 Clinical outcomes at 30 days and 1 year of follow-up

	All patient, *N* = 389	STS risk group			Low vs. high	Intermediate vs. high	Overall *P*-value
		Low, *N* = 41	Intermediate, *N* = 254	High, *N* = 94	RR (95% CI)	RR (95% CI)	
30 days follow-up							
All-cause death, *n* (%)	24 (6.4)	1 (2.4)	10 (3.9)	13 (14.9)	0.16 (0.02–1.27)	0.27 (0.12–0.61)	0.001
Cardiovascular death, *n* (%)	19 (5.2)	0 (0.0)	8 (3.2)	11 (12.9)	0.06 (0.00–2.67)	0.25 (0.10–0.63)	0.003
Cerebrovascular accidents, *n* (%)	14 (3.6)	1 (2.4)	10 (4.0)	3 (3.4)	0.73 (0.08–7.07)	1.22 (0.34–4.43)	0.95
Major stroke, *n* (%)	12 (3.1)	1 (2.4)	8 (3.2)	3 (3.4)	0.73 (0.08–7.07)	0.97 (0.26–3.65)	0.83
Minor stroke, *n* (%)	2 (0.5)	0 (0.0)	2 (0.8)	0 (0.0)		2.14 (0.04–108.59)	1.00
Transient ischaemic attack, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Myocardial infarction, *n* (%)	2 (0.5)	0 (0.0)	1 (0.4)	1 (1.1)	0.50 (0.00–50.35)	0.37 (0.02–5.91)	0.57
Bleeding							
Life-threatening, *n* (%)	64 (16.5)	6 (14.6)	36 (14.2)	22 (23.5)	0.63 (0.27–1.43)	0.61 (0.38–0.97)	0.10
Major, *n* (%)	125 (32.2)	12 (29.3)	79 (31.1)	34 (36.3)	0.81 (0.47–1.40)	0.86 (0.62–1.19)	0.35
Acute renal failure, *n* (%)	15 (3.9)	0 (0.0)	7 (2.8)	8 (8.5)	0.08 (0.00–3.40)	0.32 (0.12–0.87)	0.03
Access site complications							
Major, *n* (%)	30 (7.7)	0 (0.0)	18 (7.1)	12 (12.8)	0.19 (0.03–1.30)	0.56 (0.28–1.11)	0.03
Minor, *n* (%)	42 (10.8)	8 (19.5)	27 (10.6)	7 (7.5)	2.62 (1.02–6.75)	1.43 (0.64–3.17)	0.06
VARC combined safety endpoint, *n* (%)	104 (26.8)	7 (17.1)	58 (22.8)	39 (41.6)	0.41 (0.20–0.84)	0.55 (0.40–0.77)	0.0004
All-cause death or stroke, *n* (%)	32 (8.2)	2 (4.9)	15 (5.9)	15 (16.0)	0.29 (0.07–1.27)	0.36 (0.18–0.74)	0.01
All-cause death, stroke, or MI, *n* (%)	34 (8.7)	2 (4.9)	16 (6.3)	16 (17.1)	0.27 (0.06–1.17)	0.36 (0.18–0.72)	0.004
1-year follow-up							
All-cause death, *n* (%)	66 (19.6)	4 (10.1)	35 (16.1)	27 (34.5)	0.27 (0.09–0.77)	0.41 (0.24–0.67)	0.0003
Cardiovascular death, *n* (%)	48 (14.2)	2 (5.3)	24 (10.8)	22 (28.6)	0.16 (0.04–0.70)	0.35 (0.19–0.62)	0.0001
Cerebrovascular accidents, *n* (%)	18 (5.2)	3 (8.7)	12 (5.0)	3 (3.4)	2.00 (0.36–11.11)	1.42 (0.40–5.08)	0.38
Major stroke, *n* (%)	15 (4.3)	3 (8.7)	9 (3.6)	3 (3.4)	2.00 (0.36–11.11)	1.07 (0.29–3.99)	0.42
Minor stroke, *n* (%)	2 (0.5)	0 (0.0)	2 (0.8)	0 (0.0)	na	2.14 (0.04–108.59)	1.00
Transient ischaemic attack, *n* (%)	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)	na	0.01 (0.00–0.08)	1.00
Myocardial infarction, *n* (%)	5 (1.6)	1 (3.1)	1 (0.4)	3 (4.3)	0.56 (0.05–6.31)	0.12 (0.01–1.04)	0.23
All-cause death or stroke, *n* (%)	77 (22.6)	7 (18.2)	41 (18.5)	29 (36.9)	0.44 (0.19–1.01)	0.45 (0.28–0.73)	0.0037
All-cause death, stroke, or MI, *n* (%)	79 (23.1)	8 (21.0)	41 (18.4)	30 (37.7)	0.48 (0.22–1.06)	0.43 (0.27–0.69)	0.0041

Depicted are counts (incidence rates %) and *P*-values for an overall linear effect.
Risks ratios (RR) (95% CI) from Mantel–Cox log rank for death, cardiovascular death, cerebrovascular events, myocardial infarction, and their composites.
Risk ratios (RR) (95% CI) derived from estimated probabilities using exact logistic regression in pair wise comparisons involving zero outcomes.
Overall *P*-values for linear effect low vs. intermediate vs. high STS risk groups, except Fisher's test in case of zero outcome in any group.

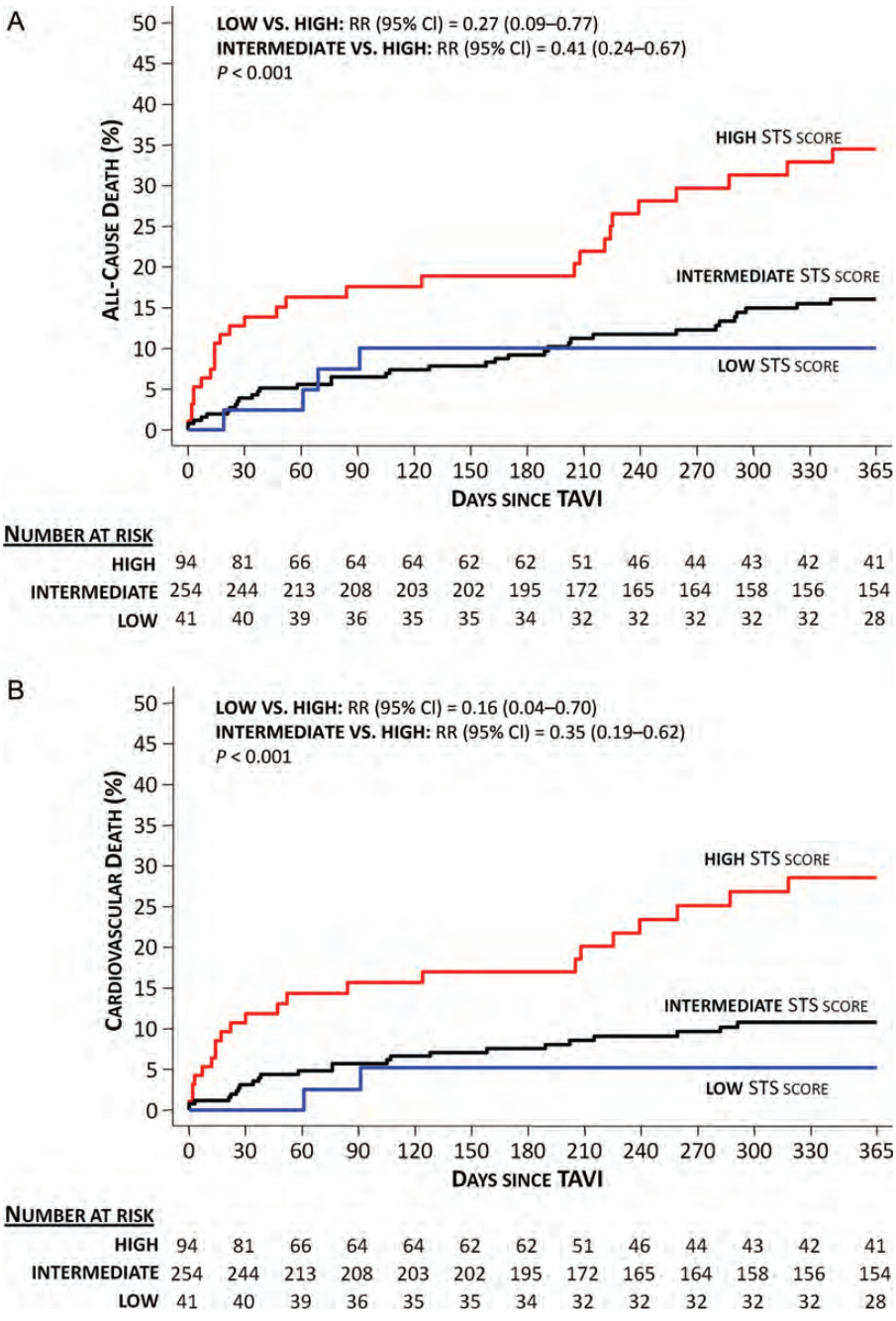

Figure 1 Cumulative incidence of all-cause mortality (*A*) and cardiovascular mortality (*B*) among patients with low (red line, STS score <3), intermediate (black line, STS score 3–8), and high surgical risk (red line, STS score > 8).

respectively, in a crude analysis comparing the first quartile treating higher risk (STS 7.1%) vs. the last quartile with lower risk patients (STS 4.8%). After adjustment for baseline differences, a trend towards a more favourable 30-day clinical outcome was reported.

The treatment of severe aortic stenosis in low and intermediate risk patients was recently addressed by the OBSERVANT research group.[21] Focusing on clinical outcomes, the authors performed a propensity-score matched analysis of 266 patients undergoing SAVR or TAVI. In this group, the preoperative risk assessment was performed by using the logistic EuroSCORE which amounted to 9.4 ± 10.4% for SAVR and 8.9 ± 9.5% among TAVI patients. Mortality at 30 days amounted to 3.8% in patients undergoing TAVI and SAVR and was similar when compared with the intermediate risk patient population included into the present study. Another single-centre study reported clinical outcomes of patients categorized according to the logistic EuroSCORE and observed a low 30-day mortality of 0.9% in the lowest risk patient population (EuroSCORE < 15%).[22]

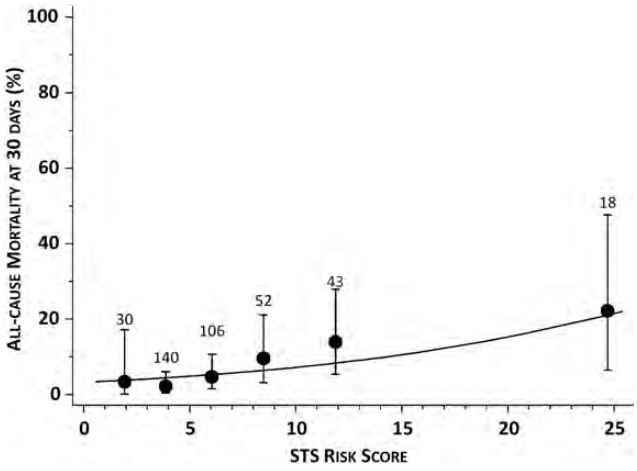

Figure 2 Logistic regression curve for all-cause mortality at 30 days of follow-up depending on the STS risk score assessment.

The findings of the present and previous studies suggest that patients with low or intermediate risk as assessed by the STS score may undergo TAVI with a 30-day mortality of <5%. These results may be attributed to the continuous refinement of technique, equipment, and increasing operator experience.

Young patients at low surgical risk undergoing SAVR have 30-day mortality rates as low as 0%,[23] whereas elderly patients undergoing isolated SAVR have mortality rates up to 6.7% in patients aged 80–84 years, and up to 11.7% in those aged >85 years.[24–26] Clinical outcomes of the present study compare favourably with published results of SAVR. Of note, all patients included into this study were considered to be at increased surgical risk after multi-disciplinary Heart Team discussion.

Apart from the low mortality among patients with low or intermediate surgical risk according to the STS risk score, peri-procedural complications including the VARC combined safety endpoint were also less common. Compared with high-risk patients, patients at low-or intermediate risk had significantly lower rates of major bleeding, major vascular complications, and deterioration of renal function. Especially, the rates of access site and bleeding complications after TAVI have been a matter of debate, and numerous efforts have aimed to minimize these risks. Important advances in the pre-procedural assessment, including semi-automated, CT-scan-based, post-processing software to assist in device and access site selection, a further reduction in vascular delivery sheath diameter, and refinements in suture-based vascular closure devices have contributed to the favourable results. Another matter of concern has been the high rate of permanent pacemaker implantation and paravalvular aortic regurgitation after TAVI, which is not described after SAVR. While recent evidence suggest that the need for permanent pacemaker implantation after TAVI is not associated with worse clinical outcomes,[27] post-procedural aortic regurgitation ≥2 is considered to have an impact on mortality.[28] Whether future generation TAVI prosthesis with improved frame and valve designs as well as refinements in implantation and positioning techniques might reduce the need of a permanent pacemaker implantation and further reduce the rate of relevant residual aortic regurgitation needs to be investigated in the near future.

In a subgroup of patients undergoing transfemoral TAVI, the 30-day complication rate was remarkably low. Low-risk patients undergoing transfemoral TAVI showed the most favourable results with no events in terms of all-cause mortality, cerebrovascular accidents, myocardial infarction, major access site complications, and acute renal failure 30 days after the intervention. However, the relatively small patient number as well as the primary intention to treat patients with the transfemoral access route needs to be acknowledged when interpreting these results. Nevertheless, transfemoral access is considered the least invasive approach to perform TAVI, and can be performed as fully percutaneous procedure under local anaesthesia with mild sedation in experienced centres.[29] While the low rates of peri-procedural complications in low and intermediate risk patients are promising, the issue of cerebrovascular adverse events has been a matter of concern.[5] While several coexisting conditions such as atrial fibrillation, concomitant cerebrovascular disease, and aortic arch atheroma may increase the risk of stroke independent of the procedure among elderly patients undergoing TAVI, the procedure itself is associated with a certain risk of thromboembolic complications. Various factors have been identified to contribute to the risk of cerebral injury including the retrograde passage of the calcified aortic valve,[30] the advancement of the large bore catheter through the aortic arch and the ascending aorta as well as the balloon aortic valvuloplasty, and the deployment of the prosthesis.[31]

At this point in time, two clinical trials currently recruit intermediate risk patients to directly compare outcomes of patients undergoing SAVR or TAVI. The PARTNER II trial randomly assigns patients at intermediate surgical risk to undergo either SAVR or TAVI with the Edwards Sapien XT bioprosthesis (ClinicalTrials.gov identifier NCT01314313). In addition, the SURTAVI Trial presently recruits intermediate risk patients to undergo treatment by SAVR or TAVI with the Medtronic CoreValve bioprosthesis and

Table 4 Baseline clinical characteristics: TransFemoral transcatheter aortic valve implantation patients

	All patients, *N* = 308	STS risk group			*P*-value
		Low, *N* = 33	Intermediate, *N* = 200	High, *N* = 75	
Age (years)	83.3 ± 4.8	79.5 ± 4.3	83.5 ± 4.7	84.1 ± 4.8	<0.001
Female gender, *n* (%)	188 (61%)	18 (55%)	122 (61%)	48 (64%)	0.65
Body mass index (kg/m^2)	26.1 ± 4.8	27.9 ± 6.1	26.4 ± 4.5	24.5 ± 4.7	0.001
Cardiac risk factors					
Diabetes mellitus, *n* (%)	80 (26%)	4 (12%)	50 (25%)	26 (35%)	0.04
Hypercholesterolaemia, *n*(%)	179 (58%)	18 (55%)	115 (57%)	46 (61%)	0.77
Hypertension, *n* (%)	239 (78%)	21 (64%)	158 (79%)	60 (80%)	0.12
Current smoker, *n* (%)	29 (9%)	3 (9%)	18 (9%)	8 (11%)	0.92
Past medical history					
Previous myocardial infarction, *n* (%)	47 (15%)	4 (12%)	28 (14%)	15 (20%)	0.41
Previous coronary artery bypass graft, *n* (%)	51 (17%)	4 (12%)	29 (14%)	18 (24%)	0.13
Previous percutaneous coronary intervention, *n* (%)	71 (23%)	3 (9%)	44 (22%)	24 (32%)	0.03
Previous stroke, *n* (%)	23 (7%)	3 (9%)	13 (7%)	7 (9%)	0.68
Peripheral vascular disease, *n* (%)	51 (17%)	1 (3%)	29 (14%)	21 (28%)	0.002
Chronic obstructive pulmonary disease, *n* (%)	56 (18%)	2 (6%)	32 (16%)	22 (29%)	0.006
Clinical features					
Pulmonary artery hypertension (PAPs in mmHg)	51.4 ± 16.8	46.4 ± 16.4	50.9 ± 16.4	54.9 ± 17.3	0.04
Renal failure (GFR < 60mL/min/1.73 m^2)	213 (69%)	13 (39%)	133 (67%)	67 (89%)	<0.001
Coronary artery disease, *n* (%)	176 (57%)	13 (39%)	115 (57%)	48 (64%)	0.06
Atrial fibrillation, *n* (%)	84 (28%)	5 (15%)	56 (28%)	23 (33%)	0.17
Echocardiographic variables					
Left ventricular ejection fraction (%)	52.3 ± 14.6	59.8 ± 10.4	52.6 ± 14.5	48.4 ± 15.0	0.001
Aortic valve area (cm^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.94
Mean transaortic gradient (mmHg)	44.5 ± 16.9	48.6 ± 16.3	45.0 ± 16.3	41.3 ± 18.6	0.09
Symptoms					
New York Heart Association (NYHA) Functional Class					
NYHA I, *n* (%)	20 (7%)	7 (21%)	10 (5%)	3 (4%)	<0.001
NYHA II, *n* (%)	84 (27%)	16 (48%)	55 (28%)	13 (18%)	
NYHA III, *n* (%)	165 (54%)	8 (24%)	118 (59%)	39 (53%)	
NYHA IV, *n* (%)	37 (12%)	2 (6%)	16 (8%)	19 (26%)	
Heart Team decision					
Anatomical or technical reasons, *n* (%)	1 (0%)	0 (0%)	1 (1%)	0 (0%)	<0.001
Comorbidities with poor prognosis, *n* (%)	16 (5%)	2 (6%)	8 (4%)	6 (8%)	
Intermediate surgical risk, *n* (%)	151 (49%)	23 (70%)	110 (55%)	18 (24%)	
Excessive surgical risk, *n* (%)	135 (44%)	8 (24%)	81 (41%)	46 (61%)	
Emergency intervention, *n* (%)	4 (1%)	0 (0%)	0 (0%)	4 (5%)	
Risk assessment					
Logistic EuroSCORE (%)	23.8 ± 14.5	13.1 ± 6.4	21.4 ± 12.0	35.1 ± 16.3	<0.001
STS score (%)	6.9 ± 5.4	2.3 ± 0.4	5.2 ± 1.4	13.5 ± 7.3	<0.001
Antithrombotic therapy					
Aspirin, *n* (%)	185 (60%)	16 (48%)	120 (60%)	49 (66%)	0.22
Clopidogrel, *n* (%)	53 (17%)	3 (9%)	31 (16%)	19 (26%)	0.06
Oral anticoagulation, *n* (%)	84 (27%)	8 (24%)	55 (28%)	21 (28%)	0.90

PAPs, systolic pulmonary artery pressure.
Depicted are means ± SD with *P*-values from ANOVAs or counts (%) with *P*-values from Chi-square (for multiple categories) or Fisher's tests (for binary categories).

Table 5 Clinical outcomes of transfemoral transcatheter aortic valve implantation patients at 30 days and 1 year of follow-up

	All patients, *N* = 308	STS risk group			Low vs. high	Intermediate vs. high	Overall *P*-value
		Low, *N* = 33	Intermediate, *N* = 200	High, *N* = 75	RR (95% CI)	RR (95% CI)	
30 days follow-up							
All-cause death, *n* (%)	17 (5.8)	0 (0.0)	7 (3.5)	10 (14.7)	0.05 (0.00–2.96)	0.24 (0.09–0.65)	0.006
Cardiovascular death, *n* (%)	14 (4.9)	0 (0.0)	5 (2.5)	9 (13.4)	0.03 (0.00–6.16)	0.19 (0.06–0.58)	0.004
Cerebrovascular events, *n* (%)	12 (3.9)	0 (0.0)	9 (4.5)	3 (4.2)	0.50 (0.05–5.17)	1.11 (0.30–4.12)	0.60
Major stroke, *n* (%)	10 (3.3)	0 (0.0)	7 (3.5)	3 (4.2)	0.36 (0.02–5.77)	0.86 (0.22–3.32)	0.78
Minor stroke, *n* (%)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)		2.13 (0.04–105.43)	1.00
Transient ischaemic attack, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Myocardial infarction, *n* (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.3)	0.23 (0.00–149.78)	37.50 (5.33–264.05)	0.35
Bleeding							
Life-threatening, *n* (%)	40 (13.0)	4 (12.1)	21 (10.5)	15 (20.1)	0.61 (0.22–1.69)	0.53 (0.29–0.96)	0.14
Major, *n* (%)	97 (31.5)	9 (27.3)	62 (31.0)	26 (34.8)	0.79 (0.42–1.49)	0.89 (0.62–1.30)	0.42
Acute renal failure, *n* (%)	10 (3.2)	0 (0.0)	3 (1.5)	7 (9.4)	0.02 (0.00–44.54)	0.16 (0.04–0.61)	0.007
Access site complications							
Major, *n* (%)	26 (8.4)	0 (0.0)	15 (7.5)	11 (14.7)	0.16 (0.02–1.38)	0.51 (0.25–1.06)	0.025
Minor, *n* (%)	41 (13.3)	8 (24.2)	26 (13.0)	7 (9.4)	2.60 (1.03–6.58)	1.39 (0.63–3.08)	0.06
VARC combined safety endpoint, *n* (%)	77 (25.0)	4 (12.1)	41 (20.5)	32 (42.8)	0.28 (0.11–0.74)	0.48 (0.33–0.70)	0.0001
All-cause death or stroke, *n* (%)	23 (7.5)	0 (0.0)	11 (5.5)	12 (16.1)	0.08 (0.00–1.49)	0.34 (0.15–0.76)	0.005
All cause death, stroke, or MI, *n* (%)	24 (7.8)	0 (0.0)	11 (5.5)	13 (17.4)	0.07 (0.00–1.45)	0.31 (0.14–0.69)	0.002
1-year follow-up							
All-cause death, *n* (%)	48 (18.2)	3 (9.3)	25 (14.8)	20 (32.3)	0.26 (0.08–0.90)	0.39 (0.22–0.71)	0.0013
Cardiovascular death, *n* (%)	35 (13.2)	2 (6.3)	16 (9.3)	17 (27.7)	0.21 (0.05–0.91)	0.30 (0.15–0.60)	0.0005
Cerebrovascular events, *n* (%)	14 (5.0)	2 (7.7)	9 (4.5)	3 (4.2)	1.20 (0.16–8.81)	1.11 (0.30–4.12)	0.76
Major stroke, *n* (%)	12 (4.3)	2 (7.7)	7 (3.5)	3 (4.3)	1.20 (0.16–8.81)	0.86 (0.22–3.32)	0.84
Minor stroke, *n* (%)	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)		2.13 (0.04–105.43)	1.00
Transient ischaemic attack, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Myocardial infarction, *n* (%)	4 (1.7)	1 (3.8)	0 (0.0)	3 (5.3)	0.54 (0.05–6.11)	0.34 (0.05–2.43)	0.018
All-cause death or stroke, *n* (%)	56 (21.0)	5 (16.3)	29 (16.7)	22 (35.2)	0.38 (0.14–1.04)	0.42 (0.24–0.74)	0.0053
All-cause death, stroke, or MI, *n* (%)	58 (21.7)	6 (19.8)	29 (16.7)	23 (36.0)	0.43 (0.17–1.10)	0.39 (0.23–0.68)	0.0058

Depicted are counts (incidence rates %) and *P*-values for an overall linear effect.
Risks ratios (RR) (95% CI) from Mantel–Cox log rank for death, cardiovascular death, cerebrovascular events, myocardial infarction, and their composites.
Risk ratios (RR) (95% CI) from Poisson regression with robust error variances for bleeding, acute renal failure, access site complications, VARC safety endpoint, and any composite involving these outcomes.
Risk ratios (RR) (95% CI) derived from estimated probabilities using exact logistic regression in pair wise comparisons involving zero outcomes.
Overall *P*-values for linear effect low vs. intermediate vs. high STS risk groups, except Fisher's test in case of zero outcome in any group.

will provide additional important information regarding this issue (ClinicalTrials.gov identifier NCT01586910).

Limitations

When interpreting the results of this study, a number of limitations need to be acknowledged. First, patients underwent treatment in a single, tertiary care referral centre and results may not be generalizable to all institutions. Second, patients were retrospectively categorized into three different risk groups (low, intermediate, and high surgical risk) based on the STS score. This categorization ignores the clinical judgment as well as treatment allocation based on recommendations of the Heart Team introducing an important element of selection bias. Third, differences in baseline characteristics including age and comorbidities outweigh the importance of procedural outcomes during the longer term follow-up. Forth, the study population is small and these findings require confirmation in larger, prospective studies. Finally, the lack of long-term follow-up data does not allow to draw conclusions about valve durability which constitutes an important issue for lower risk and especially younger patients.

Conclusion

In contemporary practice, TAVI is not limited to inoperable or STS-defined high-risk patients and should be guided by the decision of an interdisciplinary Heart Team. Compared with patients at calculated high risk, well-selected patients with STS-defined intermediate or low risk appear to have favourable clinical outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: P.W. is proctor and receives honoraria from Medtronic CoreValve and Edwards Lifesciences. S.W. has received honoraria and consultant fees from Edwards LifeSciences and Medtronic CoreValve. All other authors have no relationships relevant to the contents of this paper to disclose. Supported by an unrestricted research grant of Medtronic to the University of Bern.

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