Part I

3-Dimensional echocardiography

Chapter 2

Value of the *'TAVI$_2$-SCORe'* versus Surgical Risk Scores for Prediction of One Year Mortality in 511 Patients Undergoing Transcatheter Aortic Valve Implantation

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ABSTRACT

Objectives

A bed-side available transcatheter aortic valve implantation (TAVI)-dedicated prognostic risk score is an unmet clinical need. We aimed to develop such a risk score predicting 1-year mortality post-TAVI and to compare it to the performance of the logistic EuroSCORE I (LES-I) and II (LES-II) and the Society of Thoracic Surgeons (STS) score.

Methods and Results

Baseline variables of 511 consecutive patients undergoing TAVI that were independently associated with 1-year mortality post-TAVI were included in the *$TAVI_2$-SCORe*. Discrimination and calibration abilities of the novel score were assessed and compared to surgical risk scores. One-year mortality was 17.0% (n=80/471). Porcelain **T**horacic aorta (HR 2.56), **A**nemia (HR 2.03), left **V**entricular dysfunction (HR 1.98), recent myocardial **I**nfarction (HR 3.78), male **S**ex (HR 1.81), **C**ritical aortic valve stenosis (HR 2.46), **O**ld age (HR 1.68) and **Re**nal dysfunction (HR 1.76) formed the *$TAVI_2$-SCORe (all p<0.05)*. According to number of points assigned (1 for each variable and 2 for infarction), patients were stratified into 5 risk categories: 0, 1 (HR 2.6), 2 (HR 3.6), 3 (HR 10.5) and ≥4 (HR 17.6). *$TAVI_2$-SCORe* showed best discrimination ability (Harrells`C statistic 0.715) compared to LES-I, LES-II and STS scores (0.609, 0.633 and 0.50, respectively). Cumulative 1-year survival was 54% versus 88% for patients with *$TAVI_2$-SCORE* ≥3 versus <3 points, respectively (p<0.001). Contrary to surgical risk scores, there was no significant difference between observed and expected 1-year mortality for all *$TAVI_2$-SCORe* risk strata (all p>0.05, Hosmer-Lemeshow statistic 0.304), suggesting superior calibration performance.

Conclusions

The *$TAVI_2$-SCORe* is an accurate, simple and bed-side available score predicting 1-year mortality post-TAVI, outperforming conventional surgical risk scores for this endpoint.

INTRODUCTION

Current guidelines recommend transcatheter aortic valve implantation (TAVI) to improve symptoms and/or survival in symptomatic patients with severe aortic valve stenosis and high or prohibitive risk for surgical aortic valve replacement.[1] Candidate selection for TAVI is based on the heart-team decision.[1] Current surgical risk scores, including the logistic EuroSCORE I (LES-I), the logistic EuroSCORE II (LES-II) or the Society of Thoracic Surgeons (STS) score predict 30 day survival after conventional surgery and are used to identify high or prohibitive surgical risk patients.[1, 2] These risk scores, however, are not designed nor validated to assess mortality risk for TAVI. In particular, a few studies that have evaluated the value of conventional surgical risk scores to predict 1-year mortality after TAVI concluded that the heart-team evaluation remains the cornerstone in decision-making in the absence of a TAVI-dedicated risk score that might have superior discrimination or calibration properties than conventional surgical risk scores.[3-6] Accordingly, a risk score to predict outcome after TAVI and thereby optimize the selection of patients remains an unmet clinical need.[7, 8] The aim of the current study was to test and compare the performance of LES-I, LES-II and STS score to a newly developed TAVI-dedicated clinical risk score to predict 1-year mortality post-TAVI. We hypothesized that a TAVI-dedicated risk score based on baseline preprocedural patient characteristics might be superior to conventional surgical risk scores in predicting survival.

METHODS

Patient population

Patients with symptomatic severe aortic stenosis (valve area <1.0 cm^2 and/or <0.6 cm^2/m^2 and/or mean gradient ≥40 mmHg) who underwent TAVI at the Leiden University Medical Center (Leiden, the Netherlands) and Centro Cardiologico Monzino IRCCS (Milan, Italy) between November 2007 and November 2012 were included. All patients were considered to be at high or prohibitive surgical risk, according to the heart-team decision. Baseline patient demographic data, cardiovascular risk factors, symptoms, medication, laboratory variables and 2-dimensional transthoracic echocardiographic data were retrospectively analyzed.

Echocardiography

Baseline transthoracic 2-dimensional echocardiography was performed using commercially available ultrasound systems (Vivid 7 and E9, GE Medical Systems, Horten, Norway and iE33, Philips Medical systems). Standard gray-scale and Dop-

pler ECG-triggered cine-loop images were acquired and transferred to a workstation for off-line analysis (EchoPAC version 110.0.0 or 112.0.0). Left ventricular (LV) assessment was performed as recommended, including LV linear dimensions measured at the parasternal long-axis view and LV mass calculated using the Devereux's formula and indexed to body surface area.[9] LV volumes and ejection fraction were measured according to the Simpson's method. Similarly, left atrial volume was determined. All volumes were indexed to the body surface area. Early mitral inflow velocity (E) was measured on pulsed wave Doppler recordings with the sample volume located at the tips of the mitral leaflets and the early septal mitral annular velocity (E') was assessed on apical 4-chamber tissue-Doppler acquisitions.[10] Subsequently the E/E' ratio was calculated. Mitral, aortic and tricuspid valve regurgitation were evaluated using spectral and color-Doppler images and semi-quantitatively graded as trivial, mild, moderate and severe, as recommended.[11] Aortic valve area was assessed using the continuity equation and indexed to the body surface area.[12] On continuous wave Doppler acquisitions in the apical 5-chamber view the mean transaortic valve gradient was measured.[12] Maximal tricuspid regurgitant jet velocity combined with inferior caval vein respiratory variation was used to calculate systolic pulmonary arterial pressure.[13]

Mortality risk factors

Baseline patient data were used to calculate individual values of conventional surgical risk scores that assess the probability of 30 day mortality after cardiac surgery: LES-I, LES-II and STS score. Parameters were entered according to the website definitions. Additional baseline factors, potentially relating to increased risk of mortality after TAVI, were also collected. These included laboratory findings such as hemoglobin, C-reactive protein (CRP), serum albumin, aspartate transaminase (AST), alanin aminotransferase (ALT) and total bilirubin. Poor mobility and neurologic dysfunction were defined in accordance with website definitions applied in the LES-II. Frailty was present when evidence existed of a syndrome of decreased reserve and resistance to stressors, resulting from multiple declines across multiple physiologic systems, leading to vulnerability to adverse outcomes.[14, 15] Cognitive dysfunction or dementia was noted if mentioned in the medical history. Porcelain aorta and hostile chest were defined in accordance with recent VARC-2 consensus definitions.[16] Urgent procedural need comprised patients requiring intervention on current admission for medical reasons.

TAVI procedure

The vast majority of TAVI procedures (n=499, 98%) were performed using a balloon-expandable Edwards-Sapien prosthesis (Edwards Lifesciences, Irvine, CA)

of 23, 26, or 29 mm. A minority of patients (n=12, 2%) received a self-expandable CoreValve prosthesis (Medtronic, Minneapolis, USA), using similar sizes. Prosthesis sizing was based on aortic annulus measurements using 3-dimensional imaging techniques (multidetector row computed tomography [preferably] or transesophageal echocardiography). The transfemoral route was used in 268 patients (52%), while a transapical route was chosen in 243 subjects (48%) because of unsuitable anatomy or intervention/surgery of the arterial vascular tree or in case of porcelain aorta.[7] All procedures were performed during general anaesthesia under fluoroscopic and transesophageal echocardiography guidance.

Study endpoint

All-cause mortality 1-year after TAVI was the primary study endpoint. Survival and causes of death were assessed for all patients by consulting the patient's medical files and the official Dutch National Survival Registry.

Statistical analysis

Continuous variables, reported as mean ± SD if normally distributed and as median with interquartile range if non-normally distributed, were compared with the Student-T test and Mann Whitney U test, respectively. Categorical data are given as percentages and compared by χ^2-test or Fisher exact test as appropriate. First, performance of conventional surgical risk score models to predict 1-year mortality was evaluated.[17, 18] Discrimination (ability to correctly identify high versus low mortality risk) was evaluated by Harrell`s C statistic. The cumulative survival was assessed with the Kaplan Meier method dichotomizing the patients into high versus low mortality risk, using >20% versus ≤20% for LES-I, >8% versus ≤8% for LES-II and >10% versus ≤10% for STS-score, respectively.[19] Calibration (ability to match patients' expected versus observed mortality) was determined by binomial testing of expected versus observed overall mortality and according to risk score quartiles. In addition Hosmer-Lemeshow goodness of fit statistic was calculated for all surgical risk scores. A value <0.05 indicates significant difference in expected versus observed mortality.

Second, a new TAVI-dedicated 1-year mortality risk prediction model was developed, restricted to demographic, clinical, biochemical and echocardiographic patient factors present at baseline. Exploratory categorizing of baseline parameters into nominal variables by different cut-off levels was performed and tested at univariate Cox regression analysis. Categorical baseline parameters available in approximately all study patients and achieving univariate significance level of $p<0.05$, were entered in a multivariate Cox regression model, using a backward elimination approach. Multivariate analysis identified risk factors independently

related to 1-year mortality after TAVI. These risk factors were assigned 1 or 2 points, proportional to their respective hazard ratios, to create a simple scoring system, the *TAVI$_2$-SCORe* (porcelain *T*horacic aorta, *A*nemia, *V*entricular dysfunction, recent myocardial *I*nfarction, male *S*ex category, *C*ritical aortic valve stenosis, *O*ld age and *Re*nal dysfunction). According to the number of points assigned, patients were divided into different risk categories.

Third, the performance of the newly developed *TAVI$_2$-SCORe* model was evaluated using identical discrimination and calibration statistics as described above. In addition internal validation of the model's discriminatory power was performed by bootstrap validation of Harrell`s C statistic on 100 samples drawn from the patient cohort. The mean difference in performance between each bootstrap sample and its corresponding performance in the original patient sample (optimism) was used to correct the initial Harrell's C statistic of the original patient cohort for the *TAVI$_2$-SCORe* model.

Fourth, the performance of the new *TAVI$_2$-SCORe* to predict 1-year mortality after TAVI versus that of the conventional surgical risk scores was evaluated based on available results of discrimination and calibration for the respective scores.

SPSS version 20.0. (SPSS Inc., Chicago, Illinois) was used for statistical analysis. A p-value of <0.05 was considered statistically significant for all tests that were 2-sided.

RESULTS

A total of 511 patients (median age 82 [77-86] years, 38% male) were included, of which 207 (41%) were treated in Leiden and 304 (59%) in Milan. A total of 36 patients were excluded because of incomplete data to calculate respective conventional surgical risk scores. Baseline characteristics are listed in Table 1. All patients were at high or prohibitive surgical risk as indicated by mean LES-I, LES-II and STS score. No patients were lost to follow-up for evaluation of the study endpoint. Within 30 days, 29 (5.7%) died, mainly from cardiovascular causes (n=25, 86%), as summarized in Table 2. Peri-procedural death occurred in 12 patients. In addition 51 individuals died between 30 days and 1-year, resulting in overall 1-year mortality of 17.0% (n=80/471). Mortality between 30 days and 1-year was attributed to cardiovascular cause in 47% (n=24) of patients. One year mortality rates were similar between both centers (p=0.88). Patients were further dichotomized based on 1-year mortality status, as shown in Table 1. Patients who died within 1-year after TAVI showed significantly higher LES-I and LES-II than patients who survived and tended to have higher STS score.

Table 2.1
Baseline characteristics of overall study population and stratified according to survival status one year post transcatheter aortic valve implantation.

		At One Year		
Variable	Overall n=511	Alive (n=391)	Dead (n=80)	p value
Age (years)	82 (77-86)	82 (77-86)	83 (78-87)	0.28
Men	194 (38%)	135 (35%)	40 (50%)	0.009
Body surface area (m^2)	1.77±0.21	1.76±0.20	1.77±0.23	0.68
Body mass index (kg/m^2)	26±4	26±4	25±4	0.16
Sinus rhythm	393 (77%)	303 (78%)	58 (73%)	0.34
Hypertension	423 (83%)	319 (82%)	66 (83%)	0.85
Diabetes mellitus II	141 (28%)	106 (27%)	23 (29%)	0.76
Smoker	175 (35%)	134 (34%)	23 (30%)	0.34
Hypercholesterolemia	309 (61%)	225 (58%)	50 (63%)	0.41
Medications				
β-blocker	267 (52%)	201 (51%)	42 (53%)	0.86
Diuretics	375 (73%)	285 (73%)	64 (80%)	0.19
Spironolactone	102 (20%)	76 (19%)	21 (26%)	0.17
Angiotenisn converting enzyme inhibitor and/or angiotensin II receptor blocker	302 (59%)	240 (61%)	44 (55%)	050
Statin	247 (48%)	180 (46%)	41 (51%)	0.40
Insulin	77 (15%)	55 (14%)	14 (18%)	0.43
Inotrope(s)	22 (4%)	17 (4%)	4 (5%)	0.77
New York Heart Association class				0.009
I	17 (3%)	14 (4%)	1 (1%)	
II	132 (26%)	106 (27%)	12 (15%)	
III	252 (50%)	196 (50%)	40 (5%)	
IV	109 (21%)	75 (19%)	27 (34%)	
Syncope	105 (21%)	83 (21%)	16 (20%)	0.81
Angina pectoris	180 (35%)	140 (36%)	26 (33%)	0.57
Logistic Euroscore I (%)	18.3 (12.1-27.7)	17.8 (12.1-26.1)	22.6 (14.3-34.5)	0.002
Logistic Euroscore II (%)	6.4 (4.0-10.6)	6.1 (3.9-10.1)	9.1 (5.5-14.1)	<0.001
STS score (%)	16.6 (12.5-22.1)	16.4 (12.5-21.9)	17.8 (12.9-23.5)	0.14
Dialysis	4 (0.8%)	4 (1%)	0 (0%)	1.00
Chronic obstructive pulmonary disease	148 (29%)	107 (27%)	31 (39%)	0.042
Peripheral artery disease	242 (47%)	179 (46%)	44 (55%)	0.13
Porcelain aorta	58 (11%)	36 (9%)	17 (21%)	0.002
Prior stroke/transient ischemic attack	74 (14%)	58 (15%)	9 (11%)	0.40
Recent myocardial infarction (<90 days)	12 (2%)	6 (2%)	5 (6%)	0.025
Prior cardiac surgery	127 (25%)	92 (24%)	22 (28%)	0.45

Table 2.1 (continued)

Variable	Overall n=511	At One Year		p value
		Alive (n=391)	Dead (n=80)	
Prior percutaneous coronary intervention	121 (24%)	90 (23%)	20 (25%)	0.84
Poor mobility	140 (28%)	110 (28%)	24 (30%)	0.75
Neurologic dysfunction	42 (8%)	35 (9%)	7 (9%)	0.95
Frailty	98 (21%)	74 (20%)	20 (26%)	0.22
Cognitive dysfunction/dementia	55 (11%)	43 (11%)	12 (15%)	0.31
Ascites	4 (1%)	2 (1%)	2 (3%)	0.14
Cirrosis	15 (3%)	11 (3%)	4 (5%)	0.30
Hostile chest	93 (18%)	70 (18%)	14 (18%)	0.92
Creatinine clearance (ml/kg/min)	49 (36-61)	49 (36-61)	44 (31-58)	0.07
Hemoglobin (g/dl)	12.1±1.6	12.1±1.6	11.7±1.6	0.047
C reactive protein (mg/dl)	4.0 (2-10)	3.4 (1.8-8.8)	7.0 (2.7-15.1)	0.010
Albumin (g/dl)	3.8±0.5	3.8±0.5	3.6±0.6	0.030
Total bilirubin (μmol/l)	0.81 (0.63-1.20)	0.80 (0.61-1.10)	0.98 (0.67-1.40)	0.009
Aspartate transaminase (U/l)	23 (18-29)	22 (18-28)	25 (20-34)	0.009
Alanin aminotransferase (U/l)	17 (13-23)	17 (13-22)	19 (14-26)	0.06
Left ventricular end-diastolic diameter (mm)	48±8	48±8	48±8	0.78
Left ventricular end-systolic diameter (mm)	31±9	31±9	32±10	0.53
Left ventricular mass index (g/m^2)	145±40	146 ± 40	150±41	0.37
Left ventricular end-diastolic volume index (ml/m^2)	52 (42-68)	53 (42-68)	50 (41-70)	0.45
Left ventricular end-systolic volume index (ml/m^2)	21 (15-34)	21 (15-34)	24 (15-37)	0.37
Left ventricular ejection fraction (%)	58 (46-66)	58 (48-66)	54 (39-61)	0.008
Left atrial volume index (ml/m^2)	54±23	55±24	52±16	0.32
E/e`	26 (18-37)	26 (17-37)	32 (20-40)	0.18
Systolic pulmonary arterial pressure (mmHg)	39 (30-46)	39 (31-46)	42 (32-49)	0.009
Aortic regurgitation ≥ grade 3	25 (5%)	19 (5%)	1 (4%)	1.00
Mitral regurgitation ≥ grade 3	33 (7%)	26 (7%)	5 (7%)	1.00
Tricuspid regurgitation ≥ grade 3	32 (6%)	22 (6%)	7 (9%)	0.29
Aortic valve mean gradient (mmhg)	47±17	48±16	47±20	0.43
Aortic valve area indexed (cm^2/m^2)	0.38±0.10	0.38±0.10	0.38±0.09	0.87
Urgent procedural need	45 (9%)	28 (7%)	14 (18%)	0.003

Hypertension: history of high blood pressure and/or on antihypertensive treatment. Hypercholesterolemia: history of hypercholesterolemia and/or on statin therapy.

Table 2.2
Causes of death post transcatheter aortic valve implantation.

Variable	first 30 days n=29	30 days - one year n=51	overall n=80
Cardiovascular	25 (86%)	24 (47%)	49 (61%)
Cardiogenic shock/heart failure	11 (38%)	10 (20%)	21 (26%)
Vascular access problems	7 (24%)	0	7 (14%)
iliac dissection	3 (10%)	0	3 (4%)
aortic dissection	4 (14%)	0	4 (5%)
Sudden death	2 (7%)	3 (6%)	5 (6%)
Stroke	0	5 (10%)	5 (6%)
Myocardial infarction	0	1 (2%)	1 (1%)
Aortic annulus rupture	1 (3%)	0	1 (1%)
Left main coronary occlusion	1 (3%)	0	1 (1%)
Interventricular septum rupture	1 (3%)	0	1 (1%)
Acute bowel ischemia	1 (3%)	1 (2%)	2 (3%)
Intestinal bleeding	1 (3%)	2 (4%)	2 (3%)
Pulmonary embolism	0	2 (4%)	2 (3%)
Non cardiovascular	4 (14%)	27 (53%)	31 (39%)
Infection	1 (3%)	6 (12%)	7 (9%)
Traffic accident	1 (3%)	1 (2%)	2 (3%)
Unknown	2 (3%)	11 (22%)	13 (16%)
Renal failure	0	2 (4%)	2 (3%)
Respiratory failure	0	2 (4%)	2 (3%)
Liver failure	0	2 (4%)	2 (3%)
Femur fracture	0	1 (2%)	1 (1%)
Oncologic	0	2 (4%)	2 (3%)

Surgical risk scores and 1-year mortality

The Harrell's C statistic for LES-I, LES-II and STS score to predict 1-year mortality after TAVI was 0.609 (p=0.002), 0.633 (p<0.001) and 0.500 (p=0.14), respectively. Kaplan Meier survival analysis showed significantly worse cumulative 1-year survival in patients with LES-I >20% compared to ≤20% (79 versus 89%, p=0.002) and LES-II >8% versus ≤8% (77 versus 89%, p=0.001), but not when stratified by STS score >10% versus ≤10% (84 % versus 89%, p=0.36) (Figure 1). These results suggest that LES-II has overall reasonable ability to discriminate between patients at high versus low risk for 1-year mortality after TAVI, and better compared to LES-I and STS score.

Overall the STS score showed good calibration with no significant difference between the number of predicted and observed deaths during 1-year follow-up

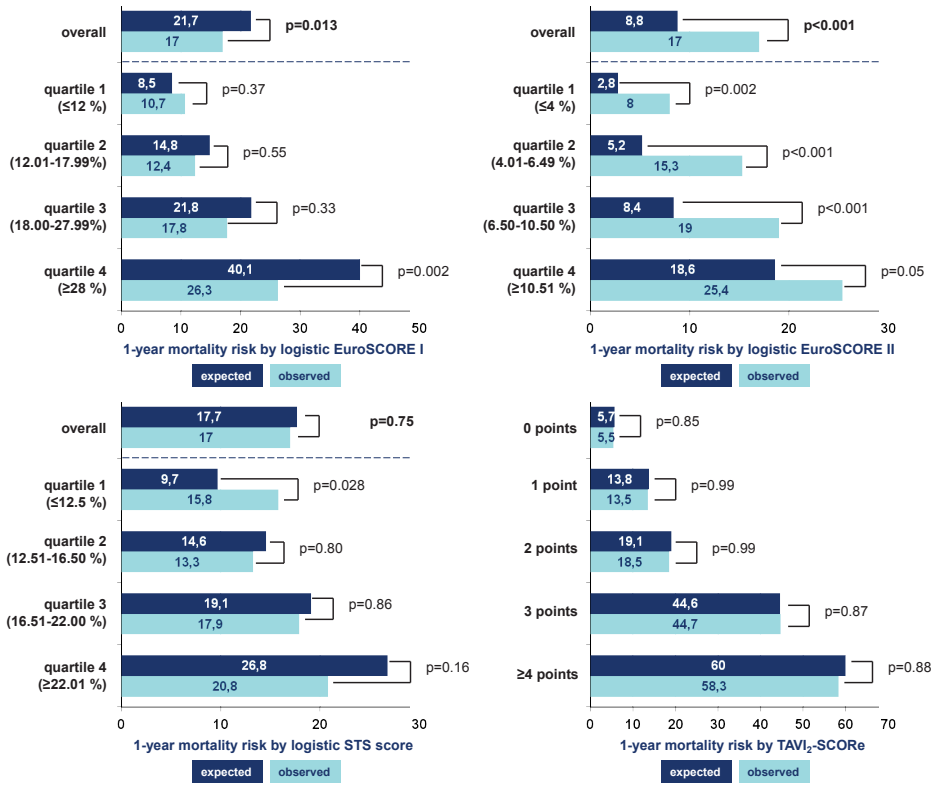


Figure 2.1
Percentage of expected versus observed mortality 1-year after TAVI for surgical risk scores (and quartiles) and *$TAVI_2$-SCORe* risk strata (calibration ability). See text for details.

(Figure 2). The STS-score however, significantly overestimated 1-year mortality for the lowest risk category (first STS score quartile). In contrast, the LES-I and LES-II showed significant differences in predicting 1-year mortality compared to the observed deaths. In particular, LES-I overestimated mainly high risk patients (fourth quartile) and LES-II significantly overestimated survival within all risk categories (all 4 quartiles). Hosmer-Lemeshow statistics (8 degrees of freedom) confirmed the superior calibration ability of the STS score (0.844) compared to the LES-I (0.457) versus LES-II (0.185).

Development of the *$TAVI_2$-SCORe*

Several baseline parameters that are included in the conventional surgical risk scores were associated with 1-year mortality after TAVI (Table 3 and in supplemental Table 1). Interestingly, other baseline parameters, not included in LES-I, LES-II or STS score, were also associated with 1-year mortality post-TAVI: porcelain

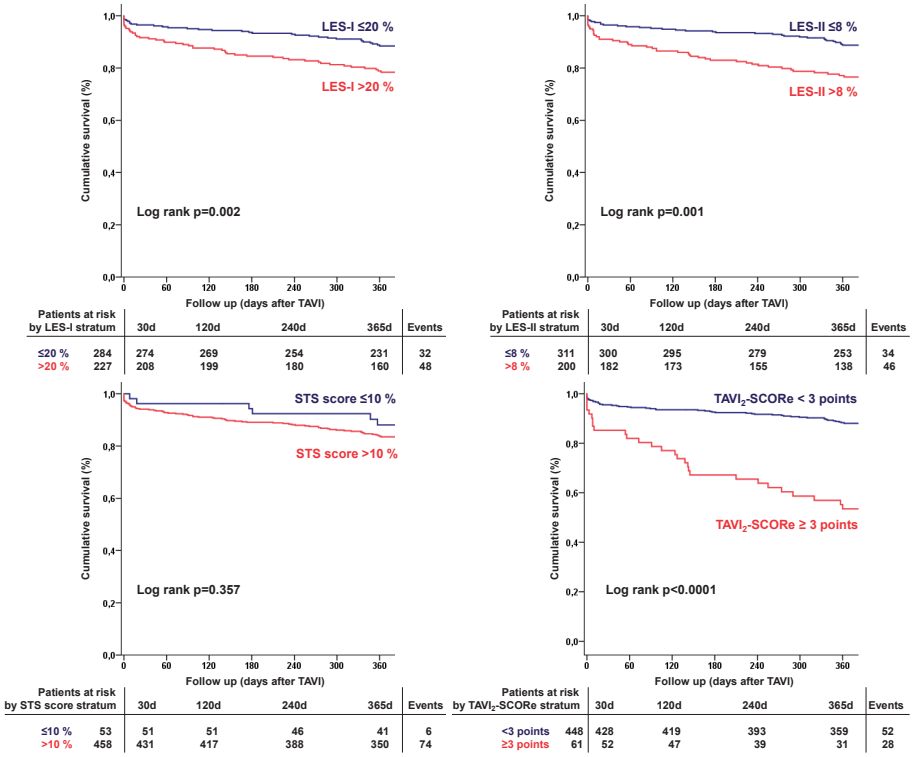


Figure 2.2
Cumulative 1-year survival after TAVI stratified into high versus low risk categories of surgical risk scores and *$TAVI_2$-SCORe* (discrimination ability).

thoracic aorta, hemoglobin <10 g/dl (anemia), CRP >10 mg/dl, serum albumin <3.0 g/dl, total bilirubin level and mean aortic valve gradient ≥70 mmHg (critical aortic valve stenosis). Univariate baseline predictors available in the vast majority of the study population (509/511 patients) were entered in the multivariate analysis that identified 8 baseline parameters with independent relation to 1-year mortality after TAVI: porcelain *T*horacic aorta, *A*nemia, *V*entricular dysfunction (LV ejection fraction <35%), recent myocardial *I*nfarction (<90 days prior to TAVI), male *S*ex category, *C*ritical aortic valve stenosis, *O*ld age (>85 years) and *Re*nal dysfunction (creatinine clearance <30 ml/kg/min). These parameters comprise the *$TAVI_2$-SCORe*. All parameters were individually weighted by assignment of 1 point for the majority of the variables and 2 points for recent myocardial infarction, proportional to hazard ratios noted. According to the number of points assigned (0, 1, 2, 3 or ≥4), patients were divided into 5 different risk categories (Figure 3).

Table 2.3
Univariate and multivariate cox regression analysis. Baseline parameters available in the majority of study patients (n=509/511) and reaching significance level <0.05 at univariate level only are shown. Results of univariate analysis including all factors tested is available as supplemental file.

	Univariate			Multivariate		
	HR	p value	95% CI	HR	p value	95% CI
Age >85 years	1.63	0.035	1.04-2.56	1.68	0.030	1.05-2.69
Male gender	1.70	0.018	1.10-2.64	1.81	0.012	1.14-2.87
New York Heart Association class III or IV	2.24	0.008	1.23-4.05	1.82	0.06	0.98-3.38
Chronic obstructive pulmonary disease	1.62	0.037	1.03-2.53	1.54	0.08	0.96-2.47
Porcelain aorta	2.39	0.001	1.34-4.08	2.56	0.001	1.46-4.48
Recent myocardial infarction (<90 days)	3.58	0.006	1.15-8.87	3.78	0.005	1.50-9.54
Creatinine clearance <30 ml/kg/min	1.95	0.011	1.16-3.26	1.76	0.036	1.04-2.97
Hemoglobin <10 g/dl	1.89	0.031	1.06-3.36	2.03	0.022	1.11-3.73
Left ventricular ejection fraction <35 %	2.05	0.015	1.15-3.66	1.98	0.028	1.08-3.63
Systolic pulmonary arterial pressure >45 mmHg	1.58	0.049	1.01-2.49	1.39	0.19	0.85-2.28
Aortic valve mean gradient ≥70 mmHg	2.10	0.012	1.18-1.73	2.46	0.004	1.33-4.56
Urgent procedure	2.22	0.007	1.25-3.96	1.67	0.10	0.91-3.05

Abbreviations: CI: confidence interval; HR: hazard ratio

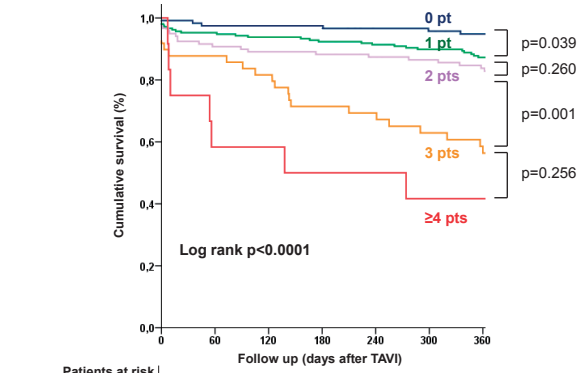
TAVI$_2$-SCORe and 1-year mortality

The Harrell's C statistic for prediction of 1-year mortality after TAVI in the original patient cohort applying the *TAVI$_2$-SCORe* was 0.720 (p<0.001). Internal bootstrap validation indicated limited optimism of the model (0.005), an expected low value for a single predictor model. The final corrected Harrell's C statistic therefore was 0.715, indicating high discriminatory performance. In addition, the Kaplan Meier analysis indicated highly significant differences in cumulative survival for patients when stratified according to different *TAVI$_2$-SCORe* risk strata (Figure 3). In particular, a *TAVI$_2$-SCORe* of ≥3 points versus <3 indicates significantly worse 1-year cumulative survival after TAVI (54 versus 88%, p<0.0001). Figure 4 indicates that a *TAVI$_2$-SCORe* of 3 or ≥4 points, compared to 0 points, was associated with a respective 10-fold and 17-fold increased mortality risk within 1-year after TAVI. These data indicate that the *TAVI$_2$-SCORe* is accurate in discriminating patients at high versus low risk for 1-year mortality after TAVI.

In addition, no significant difference in expected versus observed mortality 1-year after TAVI was observed for the *TAVI$_2$-SCORe*, stratified according to the different risk categories. Hosmer-Lemeshow statistic for the *TAVI$_2$-SCORe* was 0.304 (2 degrees of freedom). These data underscore accurate calibration of the *TAVI$_2$-SCORe* model.

TAVI$_2$-SCORe versus LES-I, LES-II and STS score

Higher bootstrap validation corrected Harrell`s C statistic and the Kaplan Meier survival analyses showed that the *TAVI$_2$-SCORe* had better discriminatory performance to predict 1-year mortality after TAVI than conventional surgical risk scores. Moreover, no significant difference between observed and expected 1-year mortality for all *TAVI$_2$-SCORe* risk strata suggested better calibration performance compared to LES-I, LES-II and STS score.



Patients at risk by TAVI$_2$-SCORe stratum		30d	120d	240d	365d	Events
0 points	119	118	116	108	103	6
1 points	210	200	197	185	167	26
2 points	119	110	106	100	90	20
3 points	49	43	40	33	26	21
≥4 points	12	9	7	6	5	7

Figure 2.3
Cumulative 1-year survival after TAVI, stratified according to the different *TAVI$_2$-SCORe* risk strata. Different risk strata were compared by Cox regression. Pt(s): point(s).

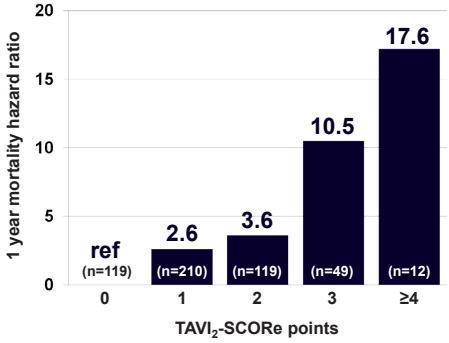


Figure 2.4
Hazard ratio for 1-year mortality after TAVI according to different *TAVI$_2$-SCORe* risk strata. Ref: reference category.

DISCUSSION

This study indicates that *TAVI$_2$-SCORe* is a simple and novel risk model for accurate prediction of 1-year mortality after TAVI, based on preprocedural baseline patient characteristics. Moreover, the *TAVI$_2$-SCORe* outperforms discriminatory and calibration abilities of conventional surgical risk scores, including LES-I, LES-II and STS-score.

Surgical risk scores and TAVI outcome

Cumulative 30 day and 1-year mortality observed in our registry is in line with the respective mortality of 7.4-9.7% and 24% reported in the 2 largest real-world registries including >3000 patients treated with TAVI.[19, 20] In addition, the high LES-I and STS scores in our series, comparable to the scores previously reported, reflect appropriate selection of patients for TAVI that were at high or prohibitive surgical risk.[1, 8, 19, 20] Estimation of operative risk with the LES-I, LES-II, and STS scores are used worldwide.[21-23] These scores however, have not been developed to predict the operative risk of elderly patients with symptomatic severe aortic stenosis and associated co-morbidities who are currently referred for TAVI. In addition, these scores, and recently more TAVI-dedicated risk scores, are intended to predict 30 day mortality.[8] Although this is an important acute clinical endpoint, 1-year mortality might be preferred for purposes of patient selection and evaluation of cost-benefits for a given treatment. A limited number of studies have reported on the value of conventional surgical risk scores to predict 1-year mortality after TAVI and have compared the performance of different surgical risk scores.[3-6, 19] Predictive performance of a risk model relies both on discrimination (ability to identify patients at high versus low mortality risk) and calibration (ability to match observed versus expected mortality).[17, 18] Both characteristics are not mutual exclusive and should be reported to assess the value of a prognostic risk model.[17] In patients undergoing TAVI, higher LES-I and STS score have been associated with increased 1-year mortality risk.[6, 19] Another study including 426 TAVI patients suggested that STS score but not LES-I or LES-II were independently related to this endpoint.[3] Furthermore, Sedaghat et al. reported on model performance statistics of different conventional surgical risk scores to predict 1-year mortality after TAVI in 206 patients undergoing TAVI with CoreValve prosthesis.[4] The authors showed better discrimination abilities for LES-I compared to LES-II and STS score with Harrell's C statistic of 0.72, 0.70 and 0.70 respectively. In addition both LES-I and LES-II were well calibrated for 1-year mortality contrary to STS score with a Hosmer-Lemeshow statistic of 0.36, 0.32 and 0.08, respectively. In contrast, the present study showed reasonable discrimination abilities for LES-II score (≤8 % low risk versus >8 % high risk) and superior and good calibration for STS score, despite mortality underestimation for the lowest risk category.

TAVI$_2$-SCORe and TAVI outcome

Based on preprocedural patients' baseline characteristics that showed independent association with 1-year mortality after TAVI, we developed the *TAVI$_2$-SCORe*. LV systolic dysfunction, recent myocardial infarction, sex, age and renal dysfunction, incorporated in conventional surgical risk scores, also showed a relation to outcome after TAVI in several reports.[14, 21-27] Porcelain thoracic aorta and anemia might represent risk factors more specifically related to outcome after TAVI.[28] Interestingly, several additional factors such as hypoalbuminemia and a rise of inflammatory markers (CRP) were related to the study endpoint. These factors should be explored in larger patient cohorts and might prove to be useful to further refine the *TAVI$_2$-SCORe*. The present study demonstrated accurate and superior discrimination and calibration properties of the *TAVI$_2$-SCORe* compared to conventional surgical risk scores.

LIMITATIONS

Some important limitations should be acknowledged. First, prospective validation of the *TAVI$_2$-SCORe* in a large external cohort of patients treated with TAVI is needed. Second, the current study findings cannot be extrapolated to patients treated with TAVI prosthesis other than the Edwards SAPIEN system. Third, procedural and postprocedural factors, including the access (transfemoral versus transapical, direct aortic or transsubclavian) and paravalvular leak post-TAVI also determine outcome post-TAVI and might further improve predictive performance, but do not allow for clinical decision making prior to the TAVI procedure.[20, 26, 29, 30] Finally, frailty, a potential key factor in TAVI outcome, did not relate to the study endpoint in the current series. A more objective definition to define frailty by using multidimensional geriatric assessment including prospective assessment of mobility, cognitive function, nutritional status and instrumental and basic daily live activities might be more appropriate.

CONCLUSION

TAVI$_2$-SCORe is a risk score predicting 1-year mortality after TAVI, based on preprocedural baseline patient characteristics. Simplicity, bed-side availability and better predictive ability compared to conventional surgical risk scores are the main strengths. Awaiting prospective external validation, *TAVI$_2$-SCORe* might become a valuable clinical tool for decision making and patient selection for TAVI.

SUPPLEMENTAL TABLE

Univariate 1-year mortality cox regression analysis for all baseline parameters tested and categorized to their best performing cut-off values.

	Available in N patients	HR	p value	95% CI
Age (years)	511	1.01	0.56	0.98-1.05
Age >85 years	511	1.63	0.035	1.04-2.56
Male gender	511	1.70	0.018	1.10-2.64
Body surface area (m^2)	511	1.13	0.82	0.39-3.31
Body mass index (kg/m^2)	511	0.96	0.17	0.91-1.02
Body mass index >25 kg/m^2	511	0.76	0.22	0.49-1.18
Sinus rhythm	511	0.78	0.32	0.48-1.27
Hypertension	511	1.01	0.97	0.57-1.80
Diabetes mellitus II	511	1.09	0.73	0.67-1.77
Smoker	500	0.78	0.32	0.48-1.27
Hypercholesterolemia	511	1.13	0.59	0.72-1.78
β-blocker	511	1.04	0.88	0.67-1.60
Diuretics	511	1.48	0.16	0.86-2.56
Spironolactone	511	1.44	0.15	0.87-2.37
Angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker	511	0.81	0.36	0.52-1.26
Statin	511	1.19	0.45	0.76-1.84
Insulin	510	1.26	0.44	0.71-2.24
Inotrope(s)	511	1.17	0.76	0.73-3.21
New York Heart Association class III-IV	511	2.24	0.008	1.23-4.05
Syncope	511	0.94	0.82	0.54-1.62
Angina	511	0.89	0.63	0.58-1.42
Angina pectoris class IV	511	1.46	0.52	0.46-4.64
Dialysis	511	0.05	0.58	0.00-1882
Chronic obstructive pulmonary disease	511	1.62	0.037	1.03-2.53
Peripheral artery disease	511	1.39	0.14	0.89-2.16
Porcelain aorta	510	2.39	0.001	1.34-4.08
Prior stroke/transient ischemic attack	511	0.73	0.37	0.36-1.46
Recent myocardial infarction (<90 days)	511	3.58	0.006	1.15-8.87
Prior cardiac surgery	511	1.20	0.74	0.73-196
Prior percutaneous coronary intervention	511	1.10	0.72	0.66-1.82
Poor mobility	510	1.11	0.67	0.69-1.79
Neurologic dysfunction	511	1.07	0.86	0.49-2.33
Frailty	478	1.38	0.22	0.83-2.30
Cognitive dysfunction/dementia	511	1.52	0.18	0.82-2.81
Ascites	511	3.09	0.12	0.76-12.6
Cirrosis	511	1.63	0.34	0.60-4.45

(continued)

	Available in N patients	HR	p value	95% CI
Hostile chest	509	0.92	0.77	0.52-1.64
Creatinine clearance (ml/kg/min)	511	0.99	0.13	0.98-1.01
Creatinine clearance ≤ 30 ml/kg/min	511	1.95	0.011	1.16-3.26
Hemoglobin (g/dl)	510	0.87	0.038	0.76-0.99
Hemoglobin <10 g/dl	510	1.89	0.031	1.06-3.36
C reactive protein (mg/dl)	327	1.01	0.38	0.99-1.01
C reactive protein >10 mg/dl	327	2.03	0.013	1.16-3.53
Albumin (g/dl)	373	0.63	0.023	0.43-0.94
Albumin <3.0 g/dl	373	3.45	0.001	1.71-7.13
Total bilirubin (µmol/l)	433	1.45	0.021	1.06-2.00
Total bilirubin >2.0 µmol/l	433	1.95	0.12	0.84-4.49
Aspartate transaminase (U/l)	464	1.01	0.19	0.99-1.01
Aspartate transaminase >70 U/l (2x ULN)	464	2.66	0.06	0.97-7.29
Alanin aminotransferase (U/l)	464	1.01	0.62	0.96-1.01
Alanin aminotransferase >90 U/l (2x ULN)	464	1.74	0.44	0.73-7.08
Left ventricular end-diastolic diameter (mm)	502	0.99	0.91	0.97-1.03
Left ventricular end-systolic diameter (mm)	429	1.01	0.47	0.99-1.03
Left ventricular mass index (g/m^2)	502	1.01	0.30	0.99-1.01
Left ventricular mass index >130 g/m^2	502	1.43	0.15	0.88-2.31
Left ventricular end-diastolic volume index (ml/m^2)	511	0.99	0.67	0.99-1.01
Left ventricular end-diastolic volume index ≥75 ml/m^2	511	1.24	0.46	0.71-2.17
Left ventricular end-systolic volume index (ml/m^2)	511	1.01	0.30	0.99-1.02
Left ventricular end-systolic volume index ≥31 ml/m^2	511	1.43	0.13	0.90-2.25
Left ventricular ejection fraction (%)	511	0.98	0.004	0.96-0.99
Left ventricular ejection fraction <35 %	511	2.05	0.015	1.15-3.66
Left atrial volume index (ml/m^2)	505	0.99	0.38	0.98-1.01
Left atrial volume index >34 ml/m^2	505	1.41	0.38	0.65-3.07
E/e`	185	1.01	0.26	0.99-1.02
Systolic pulmonary artery pressure (mmHg)	511	1.02	0.039	1.01-1.04
Systolic pulmonary artery pressure >45 mmhg	511	1.58	0.049	1.01-2.49
Aortic regurgitation ≥grade 3	511	0.74	0.61	0.23-2.35
Mitral regurgitation ≥grade 3	511	1.03	0.95	0.42-2.55
Tricuspid regurgitation ≥grade 3	511	1.52	0.29	0.70-3.30
Aortic valve mean gradient (mmHg)	511	0.99	0.48	0.98-1.01
Aortic valve mean gradient >70 mmhg	511	2.10	0.012	1.18-1.73
Aortic valve index (cm^2/m^2)	511	0.58	0.65	0.06-5.78
Aortic valve index <0.6 cm^2/m^2	511	20.7	0.41	0.02-2.63
Urgent procedural need	511	2.22	0.007	1.25-3.96

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