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Original article

The Value of the SYNTAX Score II in Predicting Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation

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ABSTRACT

Introduction and objectives: The predictive value of the SYNTAX score (SS) for clinical outcomes after transcatheter aortic valve implantation (TAVI) is very limited and could potentially be improved by the combination of anatomic and clinical variables, the SS-II. We aimed to evaluate the value of the SS-II in predicting outcomes in patients undergoing TAVI.

Methods: A total of 402 patients with severe symptomatic aortic stenosis undergoing transfemoral TAVI were included. Preprocedural TAVI angiograms were reviewed and the SS-I and SS-II were calculated using the SS algorithms. Patients were stratified in 3 groups according to SS-II tertiles. The coprimary endpoints were all-cause death and major adverse cardiovascular events (MACE), a composite of all-cause death, cerebrovascular event, or myocardial infarction at 1 year.

Results: Increased SS-II was associated with higher 30-day mortality ($P = .036$) and major bleeding ($P = .015$). The 1-year risk of death and MACE was higher among patients in the 3rd SS-II tertile (HR, 2.60; $P = .002$ and HR, 2.66; $P < .001$) and was similar among patients in the 2nd tertile (HR, 1.27; $P = .507$ and HR, 1.05; $P = .895$) compared with patients in the 1st tertile. The highest SS-II tertile was an independent predictor of long-term mortality ($P = .046$) and MACE ($P = .001$).

Conclusions: The SS-II seems more suited to predict clinical outcomes in patients undergoing TAVI than the SS-I. Increased SS-II was associated with poorer clinical outcomes at 1 and 4 years post-TAVI, independently of the presence of coronary artery disease.

Valor de la puntuación SYNTAX II para la predicción de eventos clínicos en pacientes sometidos a implante percutáneo de válvula aórtica

Palabras clave:
Implante percutáneo de válvula aórtica
Cirugía de revascularización aortocoronaria
Intervención coronaria percutánea
Puntuación SYNTAX

RESUMEN

Introducción y objetivos: La puntuación SYNTAX (PS) tiene muy escaso valor predictivo de eventos clínicos tras el implante percutáneo de válvula aórtica (TAVI), pero que podría mejorar con la combinación de variables clínicas y anatómicas, la nueva PS-II. Nuestro objetivo es evaluar el valor de la PS-II en la predicción de eventos en pacientes sometidos a TAVI.

Métodos: Se incluyó en total a 402 pacientes con estenosis aórtica grave sometidos a TAVI. Se revisó la angiografía coronaria antes del procedimiento y se calcularon la PS-I y la PS-II según los algoritmos de la PS. Se estratificó a los pacientes en 3 grupos en función de los terciles de la PS-II. Los objetivos primarios fueron muerte por cualquier causa y los eventos adversos cardiovascular mayores (MACE), un compuesto de muerte, evento cerebrovascular o infarto de miocardio al año de seguimiento.

Resultados: Una PS-II aumentada se asoció con más mortalidad (p = 0,036) y hemorragias mayores (p = 0,015) a los 30 días. Los riesgos de muerte (HR = 2,60; p = 0,002) y MACE (HR = 2,66; p < 0,001) al año de seguimiento fueron mayores en el tercer tercil de la PS-II y similares en el segundo tercil (muerte, HR = 1,27; p = 0,507; MACE, HR = 1,05; p = 0,895) comparados con los pacientes del primer tercil. Pertenecer al tercer tercil de la PS-II fue un predictor independiente de mortalidad (p = 0,046) y MACE (p = 0,001) a largo plazo.

Conclusiones: La PS-II parece más adecuada que la PS-I para predecir eventos clínicos en pacientes sometidos a TAVI. Una mayor PS-II se asoció a más eventos clínicos al año y a los 4 años de la TAVI, independientemente de la presencia de enfermedad coronaria.

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Abbreviations

CABG: coronary artery bypass graft
CAD: coronary artery disease
PCI: percutaneous coronary intervention
SS-I: SYNTAX score I
SS-II: SYNTAX score II
TAVI: transcatheter aortic valve implantation

INTRODUCTION

Aortic stenosis frequently coexists with coronary artery disease (CAD), sharing common risk factors and a similar pathogenesis.[1,2] The risk of surgical aortic valve replacement is increased in the presence of CAD, with coronary artery bypass graft (CABG) generally indicated at the time of valve surgery.[3] Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of intermediate and high-risk patients with severe symptomatic aortic stenosis.[4] The extent and complexity of CAD in these patients is heterogeneous and optimal management remains unknown. Furthermore, with the expansion of TAVI in clinical practice, the ability to predict postprocedural outcomes, particularly in lower-risk patients, is of increasing interest. Previous studies have reported that the presence of CAD in TAVI candidates had no impact on short- and mid-term clinical outcomes. The anatomic SYNTAX score I (SS-I), originally designed to assess the procedural complexity of percutaneous coronary revascularization,[5] has been investigated as a potential tool to predict major cardiovascular events in patients undergoing TAVI.[6,7] However, the predictive value of the SS-I was found to be very limited, potentially as a result of focusing only on coronary anatomy, ignoring the important role of patient comorbidities. A more recent index, the SYNTAX score II (SS-II), which combines anatomic characteristics with clinical variables, has been shown to provide a long-term, individualized risk assessment for patients with complex CAD.[8–10] Although the SS-II was developed to aid in decision-making between CABG and percutaneous coronary intervention (PCI) in patients with complex CAD, we hypothesized that the inclusion of clinical variables, several of which have been identified as predictors of increased mortality in surgical aortic valve replacement[11,12] and TAVI[13,14] may improve the prognostic value over that of the SS-I in predicting outcomes post-TAVI.

METHODS

Patient Population

A total of 402 consecutive patients with severe symptomatic aortic stenosis undergoing transfemoral TAVI at our institution were included. The indication for TAVI was reviewed in the context of the institutional Heart Team meeting, including at least 1 cardiac surgeon and interventional, imaging and clinical cardiologists, based on the patient's clinical history, anatomical suitability and frailty assessment. Severe aortic stenosis was defined as a mean transaortic pressure gradient of > 40 mmHg or valve area of < 1.0 cm^2 using transthoracic, transoesophageal or dobutamine stress echocardiography, as appropriate. All patients underwent routine coronary angiography prior to TAVI. The decision to perform coronary revascularization was made at the Heart Team meeting, based on the location and extent of the CAD and complexity of PCI. In general, proximal and mid severe lesions with a large amount of myocardium at risk were revascularized and lesions in distal segments or secondary vessels were not treated. Patients underwent replacement of the Edwards Sapien transcatheter heart valve (Edwards Lifesciences, Irvine, California, United States) or the Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis, Minnesota, United States) using the transfemoral route, as previously described.[15] Electrocardiogram and cardiac markers were monitored every 8 hours during the first 24 hours and daily afterwards, in all patients as part of our standard TAVI protocol. Antithrombotic treatment after TAVI consisted of aspirin (indefinitely) plus clopidogrel (3-6 months) unless contraindicated. If anticoagulation was indicated for any other reason, oral anticoagulant therapy was administrated (with or without single antiplatelet therapy). All patients provided informed consent for the procedure and follow-up.

Angiographic Analysis

Preprocedural angiograms were analyzed in the angiographic core laboratory of our institution by an interventional cardiologist expert in the assessment of the SS-I and blinded to clinical outcomes.[16] CAD was defined as the presence of 1 or more lesions of the epicardial coronary arteries with $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm in diameter.[17] The SS-I was calculated using the SS-I algorithm.[17] In patients with previously revascularized lesions, which remained patent at the time of the pre-TAVI coronary angiogram, these lesions were considered to be nonsignificant in the calculation of the SS-I, but these patients were included in the CAD group. When previous revascularization was carried out surgically, the SS-I score was calculated using the CABG SYNTAX score.[18] A residual SYNTAX score was calculated in patients who underwent PCI prior to TAVI.[19] The SS-II was calculated for all patients using the SS-II algorithm,[8] which includes the anatomical SS-I and baseline clinical variables such as age, sex, creatinine clearance, left ventricle ejection fraction, left main disease, chronic obstructive pulmonary disease, and peripheral vascular disease. In patients who underwent PCI in the 30 days prior to TAVI, the pre-PCI SS-I was used and, in patients without coronary lesions, an SS-I value of 0 was entered.

Study Endpoints and Definitions

The coprimary endpoints of this study were all-cause death and major adverse cardiovascular events, a composite of all-cause death, nonfatal cerebrovascular event, or nonfatal myocardial infarction at 1 year. Secondary endpoints were the individual components of the primary endpoint at 1 year, as well as cardiovascular death. Major adverse cardiovascular events and their components were assessed at 30 days, 1 year, and 4 years. Cardiovascular death was defined as any death due to a cardiac cause or death of unknown cause, all procedure-related deaths (defined as all-cause mortality within 30 days or during the index procedure hospitalization if longer than 30 days), and deaths due to cerebrovascular disease, pulmonary embolism, or vascular disease.[20] Cerebrovascular events included transient ischemic attack and stroke defined according to symptom duration, persistent neurological dysfunction, and/or evidence of cerebral infarction on imaging.[20] Myocardial injury was defined as evidence of new Q waves on the electrocardiogram or new regional wall motion abnormalities at echocardiography. Biochemical markers of myocardial injury were defined as a rise in troponin > 35 upper limit normal (ULN) or creatinine kinase-isoenzyme MB > 5 ULN.

Clinical Follow-up

Adverse events were assessed in hospital and at clinical follow-up. Baseline clinical and procedural characteristics and adverse events were prospectively entered into the dedicated institutional database. Patients were followed up at 1 month, 6 months, and 1 year postprocedure and yearly thereafter.

Statistical Analysis

Because the SS-II produces estimates of mortality for both PCI and CABG, a C statistic for 30-day mortality and 1-year mortality was carried out using binary logistic regression analyses. Receiver operating characteristic (ROC) curves were constructed and pairwise comparison of ROC curves among SS-I, SS-II PCI, and SS-II CABG was performed to assess the best score for the identification of the primary endpoint. In addition, time-dependent ROC curves for censored survival data were also created to assess the predictive value of both SS-II PCI and CABG for 1-year mortality.[21] The SS-II for PCI proved the best fit and therefore all further analysis was carried out using this score. Patients were stratified into 3 groups according to SS-II PCI tertiles. Baseline characteristics and clinical outcomes were compared between groups. Categorical variables are summarized as counts and frequencies and continuous data are presented as means ± standard deviation or median [interquartile range (IQR), 25th-75th percentile] when not normally distributed, using the Shapiro-Wilk test. Clinical outcomes at 30 days, 1 year, and 4 years are expressed as counts or incidence rates using Kaplan-Meier analysis and compared between patients in the 1st SS-II tertile, 2nd SS-II tertile, and 3rd SS-II tertile. Analyses were also tested in patients with and without CAD according to SS-II PCI tertiles. *P* values < .05 were considered statistically significant. The analyses were performed using SPSS 19.0 for Windows (SPSS, Inc, Chicago, Illiniois, United States) and R statistical software, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline and Procedural Characteristics

Baseline clinical characteristics are summarized in Table 1. Overall, the median age was 84 [IQR 80-87] years with a high prevalence of diabetes (34%), atrial fibrillation (39%), and renal failure (47%). A total of 193 (48.0%) patients had CAD with a median SS-I and residual SS-I of 4 [IQR, 0-9] and 2 [IQR, 0-7], respectively.

Table 1
Baseline Clinical and Echocardiographic Characteristics According to SYNTAX Score II Tertiles

		SYNTAX score II			
	Overall (n = 402)	First tertile (SS-II < 37.4) (n = 134)	Second tertile (SS-II, 37.4-44.0) (n = 134)	Third tertile (SS-II > 44.0) (n = 134)	*P*
Baseline characteristics					
Age, y	84 [80-87]	81 [76-84]	85 [81-87]	86 [83-88]	.001
Female sex	247 (61.4)	54 (40.3)	95 (70.9)	98 (73.1)	.001
BMI, kg/m^2	27 [25-30]	29 [26-32]	27 [25-29]	27 [23-30]	.001
Diabetes mellitus	135 (33.8)	47 (35.6)	43 (32.3)	45 (33.6)	.851
Hypertension	334 (83.7)	106 (80.9)	115 (85.8)	113 (84.3)	.542
CAD	193 (48.0)	62 (46.3)	50 (37.3)	81 (60.4)	.001
Prior cardiac surgery	47 (11.7)	22 (16.4)	13 (9.7)	12 (9.0)	.112
Atrial fibrillation	158 (39.3)	59 (44.0)	49 (36.6)	50 (37.3)	.387
Previous pacemaker	44 (10.9)	10 (7.5)	16 (11.9)	18 (13.4)	.265
COPD	85 (21.1)	39 (29.1)	18 (13.4)	28 (20.9)	.007
Previous stroke	49 (12.2)	16 (11.9)	17 (12.7)	16 (11.9)	.977
Peripheral vascular disease	28 (7.0)	1 (0.7)	4 (3.0)	23 (17.2)	.001
eGFR, mL/min	64.1 ± 24.3	81.3 ± 23.0	61.3 ± 19.7	49.8 ± 18.6	.001
eGFR < 60 mL/min	188 (46.8)	21 (15.7)	70 (52.2)	97 (72.4)	.001
Logistic EuroSCORE	14.8 [10.0-22.0]	11.0 [7.0-17.0]	13.6 [10.0-18.0]	19.8 [14.0-29.0]	.001
SYNTAX score	0 [0-4]	0 [0-2]	0 [0-1]	2 [0-8]	.001
PCI before TAVI	35 (8.7)	8 (6.0)	5 (3.7)	22 (16.4)	.001
SYNTAX score II CABG	41.6 [37.9-48.1]	40.0 [34.0-44.0]	40.0 [37.0-47.0]	45.8 [41.0-53.1]	.001
SYNTAX score II PCI	40.8 [35.4-45.7]	33.0 [30.0-35.4]	40.8 [39.1-42.9]	48.0 [45.7-52.0]	.001
Echocardiographic characteristics					
Left ventricular ejection fraction, %	56.7 ± 18.7	58.7 ± 16.2	60.8 ± 17.5	50.5 ± 20.6	.001
Mean aortic gradient, mmHg	47.7 ± 15.7	43.7 ± 14.5	50.9 ± 15.3	48.3 ± 16.6	.001
Aortic valve area, cm^2	0.60 [0.50-0.70]	0.60 [0.50-0.70]	0.60 [0.40-0.70]	0.60 [0.50-0.70]	.144
Moderate to severe MR	33 (8.2)	10 (7.5)	11 (8.2)	12 (9.0)	.906
Moderate to severe AR	55 (13.8)	17 (12.8)	17 (12.8)	21 (15.8)	.647

AR, aortic regurgitation; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; PCI, percutaneous coronary intervention; SS-II, SYNTAX score II; TAVI, transcatheter aortic valve implantation. Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

The areas under the ROC curves for SS-I and residual SS-I were 0.520 (95%CI, 0.404–0.636; $P = .732$) and 0.510 (95%CI, 0.398–0.623; $P = .856$) for 30-day mortality and 0.551 (95%CI, 0.473–0.629; $P = .185$) and 0.524 (95%CI, 0.448–0.601; $P = .527$) for 1-year mortality, respectively. The overall median SS-II for PCI and CABG was 40.8 [IQR, 35.4-45.7] and 41.6 [IQR, 37.9-48.1], respectively. The SS-II for PCI proved a better fit than the SS-II for CABG for both 30-day (C statistic, 0.632; 95%CI, 0.524-0.740; $P = .022$; C statistic, 0.480; 95%CI, 0.380-0.580; $P = .728$, respectively, $P = .032$ for comparison of both ROC curves) and 1-year mortality (C statistic 0.625; 95%CI, 0.552-0.699; $P = .001$; C statistic, 0.539; 95%CI, 0.466-0.612; $P = .309$, respectively, $P = .075$ for comparison of both ROC curves) (Figure 1 of the supplementary material). The time-dependent area under curve (AUC) also showed better fit with SS-II for PCI compared with the SS-II for CABG within 1 year (Figure 2 of the supplementary material). Therefore all further analysis was carried out using the SS-II for PCI according to its tertiles: 1st SS-II tertile (< 37.4), 2nd SS-II tertile (37.4-44.0), and 3rd SS-II tertile (> 44).

All baseline clinical characteristics included in the SS-II were more frequent in the 3rd SS-II tertile ($P < .001$), except chronic pulmonary disease ($P < .007$), which was more frequent in patients in the 1st tertile. Consequently, patients with a higher SS-II were older, more commonly female, had more peripheral vascular disease, lower renal and left ventricular function and less complete revascularization prior to TAVI (higher residual SS-I) ($P < .001$ for all comparisons). Other clinical variables not included in the SS-II, including diabetes, atrial fibrillation, previous stroke, and hypertension were similarly distributed across SS-II tertiles. Logistic EuroSCORE (1st tertile, 13.58 ± 8.4; 2nd tertile, 15.84 ± 8.99; 3rd tertile, 22.05 ± 10.59; $P < .001$) was higher with increasing SS-II. Procedural characteristics were similar among all groups (Table 2).

Clinical Outcomes

In-hospital clinical outcomes after TAVI are reported in Table 3. Increased SS-II was associated with higher 30-day mortality (1st tertile, 5 [3.7%]; 2nd tertile, 7 [5.2%]; 3rd tertile: 15 [11.2%]; $P = .036$) and more life-threatening or major bleeding complications ($P = .015$). There was a trend toward increased acute kidney injury in the highest tertile (1st tertile, 30 [23.3]; 2nd tertile, 25 [19.5]; 3rd tertile, 40 [32.5]; $P = .051$). The presence of CAD alone had no impact on the rate of the combined primary endpoint or on all-cause mortality at 30 days and 1 year.

As shown in Table 4, the 1-year risk of major adverse cardiovascular events, all-cause death, and cardiac death was higher among patients in the 3rd SS-II tertile (HR, 2.66; 95%CI, 1.46-4.84; $P < .001$; HR, 2.60; 95%CI, 1.40-4.84; $P = .002$, HR, 3.81; 95%CI, 1.54-9.38; $P = .004$) and was similar among patients in the 2nd tertile (HR, 1.05; 95%CI, 0.52-2-12; $P = .895$; HR, 1.27; 95%CI, 0.63-2.55; $P = .507$; HR, 1.99; 95%CI, 0.75-5.30; $P = .168$) compared with patients in the 1st tertile. There was no significant difference in risk of readmission or cardiac readmission among the groups. At 4 years, a higher SS-II was associated with higher rates of all-cause mortality ($P = .017$), cardiac mortality ($P = .012$), and major adverse cardiovascular events ($P = .002$) (Figure 1). On multivariable analysis, the 3rd SS-II tertile was an independent predictor of 4-year mortality and major adverse cardiovascular events (Table 5). When the population was stratified into patients with and without CAD, the highest SS-II tertile continued to be associated with long-term mortality (Figure 2).

DISCUSSION

This study analyzed for the first time the impact of the SS-II on clinical outcomes among patients with severe symptomatic aortic stenosis undergoing TAVI. SYNTAX score II, which adds clinical variables to CAD severity quantified by the angiographic SS-I, was superior to the SS-I in predicting 30-day and 1-year mortality in patients with aortic stenosis undergoing TAVI. Increasing SS-II was associated with increased major adverse cardiovascular events, all-cause death, and cardiac death in the TAVI population independently of the presence of CAD. Patients with an SS-II > 44 had an independent ~2-fold increased risk of major adverse cardiovascular events and all-cause mortality at 1 year and 4 years compared with patients with an SS-II < 37.4.

The presence of CAD and the need for concomitant CABG in patients undergoing surgical aortic valve replacement has been associated with increased rates of periprocedural myocardial

Table 2
Procedural Characteristics According to SYNTAX Score II Tertiles

		SYNTAX score II			
	Overall (n = 402)	First tertile (SS-II < 37.4) (n = 134)	Second tertile (SS-II, 37.4-44.0) (n = 134)	Third tertile (SS-II > 44.0) (n = 134)	*P*
General anesthesia	196 (48.8)	69 (51.5)	56 (41.8)	71 (53.0)	.138
Prior balloon valvuloplasty	180 (55.2)	69 (51.5)	72 (53.7)	81 (60.4)	.308
Prothesis type					.172
Balloon-expandable	270 (67.2)	84 (62.7)	88 (65.7)	98 (73.1)	
Self-expandable	132 (32.8)	50 (37.3)	46 (34.3)	36 (26.9)	
Balloon postdilation	66 (16.4)	21 (15.7)	27 (20.1)	18 (13.4)	.319
Prosthesis size					.001
20 or 23 mm	139 (34.6)	31 (23.1)	52 (38.8)	56 (41.8)	
26 mm	172 (42.8)	54 (40.3)	58 (43.3)	60 (44.8)	
29 or 31 mm	91 (22.6)	49 (36.6)	24 (17.9)	18 (13.4)	
Contrast, mL	150 [104-200]	150 [109-203]	150 [100-200]	150 [110-200]	.780
Procedure time, minutes	105 [90-131]	100 [75-130]	105 [90-122]	113 [90-150]	.211

SS-II, SYNTAX score II.
Data are expressed as No. (%) or median [interquartile range].

Table 3
In-hospital Clinical Outcomes According to SYNTAX Score II Tertiles

		SYNTAX score II			
	Overall (n = 402)	First tertile (SS-II < 37.4) (n = 134)	Second tertile (SS-II, 37.4-44.0) (n = 134)	Third tertile (SS-II > 44.0) (n = 134)	*P*
30-day mortality	27 (6.7)	5 (3.7)	7 (5.2)	15 (11.2)	.036
Stroke	9 (2.2)	4 (3.0)	3 (2.2)	2 (1.5)	.711
Myocardial injury					
Increase troponin × 35 ULN (ULN 0.05 ng/dL)	149 (39.9)	44 (35.5)	51 (41.8)	54 (42.5)	.459
Increase creatinine kinase-isoenzyme MB × 5 ULN (ULN 5 ng/dL)	30 (8.4)	6 (5.0)	10 (8.5)	14 (11.6)	.190
Vascular complications					
Major	46 (11.5)	15 (11.3)	14 (10.5)	17 (12.7)	.854
Minor	94 (23.6)	34 (25.6)	29 (21.8)	31 (23.3)	.768
Bleeding complications					
Life-threatening or major	65 (16.5)	17 (12.9)	16 (12.4)	32 (24.1)	.015
Minor	64 (16.2)	24 (18.0)	19 (14.6)	21 (15.8)	.744
Acute kidney injury					
Stage 1, 2 and 3	95 (25.0)	30 (23.3)	25 (19.5)	40 (32.5)	.051
Stage 2 and 3	16 (4.2)	4 (3.1)	5 (3.9)	7 (5.7)	.579
New permanent pacemaker replacement	60 (15.1)	20 (15.3)	21 (15.8)	19 (14.3)	.941
Need for a second valve	13 (3.2)	4 (3.0)	7 (5.2)	2 (1.5)	.221
Significant aortic regurgitation	24 (6.5)	8 (6.2)	11 (8.9)	5 (4.3)	.349
Length of CCU stay, d	1 [1-2]	1 [1-2]	1 [1-2]	1 [1-3]	.816
Length of hospital stay, d	6 [5-9]	6 [5-7]	6 [4-7]	6 [5-7]	.678
Treatment at hospital discharge[*]					.537
None	7 (1.9)	4 (3.1)	1 (0.8)	2 (1.7)	
Single antiplatelet therapy	24 (6.4)	4 (3.1)	10 (7.9)	10 (8.4)	
Dual antiplatelet therapy	207 (55.5)	67 (52.3)	71 (56.3)	69 (58)	
Single anticoagulation therapy	55 (14.7)	21 (16.4)	17 (13.5)	17 (14.3)	
Single antiplatelet + anticoagulation therapy	68 (18.2)	29 (22.7)	22 (17.5)	17 (14.3)	
Triple therapy	12 (3.2)	3 (2.3)	5 (4.0)	4 (3.4)	

CCU, coronary care unit; SS-II, SYNTAX score II; ULN, upper limit normal.
Values are expressed as No. (%) or median [interquartile range].
[*] Excluding patients with in-hospital mortality.

Table 4
One-year Clinical Outcomes According to SYNTAX Score II Tertiles

	1st tertile	2nd tertile	3rd tertile	2nd tertile vs 1st tertile		3rd tertile vs 1st tertile		Overall
	(n = 134)	(n = 134)	(n = 134)	HR (95%CI)	*P*	HR (95%CI)	*P*	*P* value
MACE[*]	18 (13.4)	20 (14.9)	42 (31.3)	1.05 (0.52-2.12)	.895	2.66 (1.46-4.84)	.001	.001
All-cause death	14 (10.4)	18 (13.4)	35 (26.1)	1.27 (0.63-2.55)	.507	2.60 (1.40-4.84)	.002	.003
Cardiac death	6 (4.5)	12 (9.0)	22 (16.4)	1.99 (0.75-5.30)	.168	3.81 (1.54-9.38)	.004	.009
Cerebrovascular event	5 (3.7)	5 (3.7)	9 (6.7)	1.00 (0.29-3.47)	.994	1.89 (0.63-5.65)	.252	.384
Myocardial infarction	1 (0.7)	1 (0.7)	6 (4.5)	1.00 (0.06-16.0)	.999	6.15 (0.74-51.1)	.093	.084
Readmission	36 (27.9)	39 (30.7)	52 (42.6)	1.03 (0.66-1.63)	.887	1.29 (0.84-1.98)	.235	.408
Cardiac readmission	16 (12.4)	23 (18.1)	21 (17.2)	1.23 (0.76-2.00)	.403	1.17 (0.72-1.91)	.524	.690

95%CI, 95% confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
Unless otherwise indicated, data are expressed as No. (%).
[*] Composite of death, cerebrovascular event or myocardial infarction.

infarction and early postoperative mortality.[22,23] Concomitant CAD in the typically elderly TAVI population is frequent, at up to 60%.[6,24–27] However in this scenario, the evidence demonstrating the influence of pre-existing CAD on procedural outcomes and mid-term survival after TAVI is inconclusive.[24,26] While some studies have reported a significant impact on mortality,[27,28] others have found no effects on outcomes.[7,25,29] A meta-analysis of 7 studies including 2472 patients showed that the presence of CAD does not increase the risk of death (OR, 1.0; 95%CI, 0.67-1.5).[30] The anatomic SS-I has been demonstrated to be a useful tool to predict

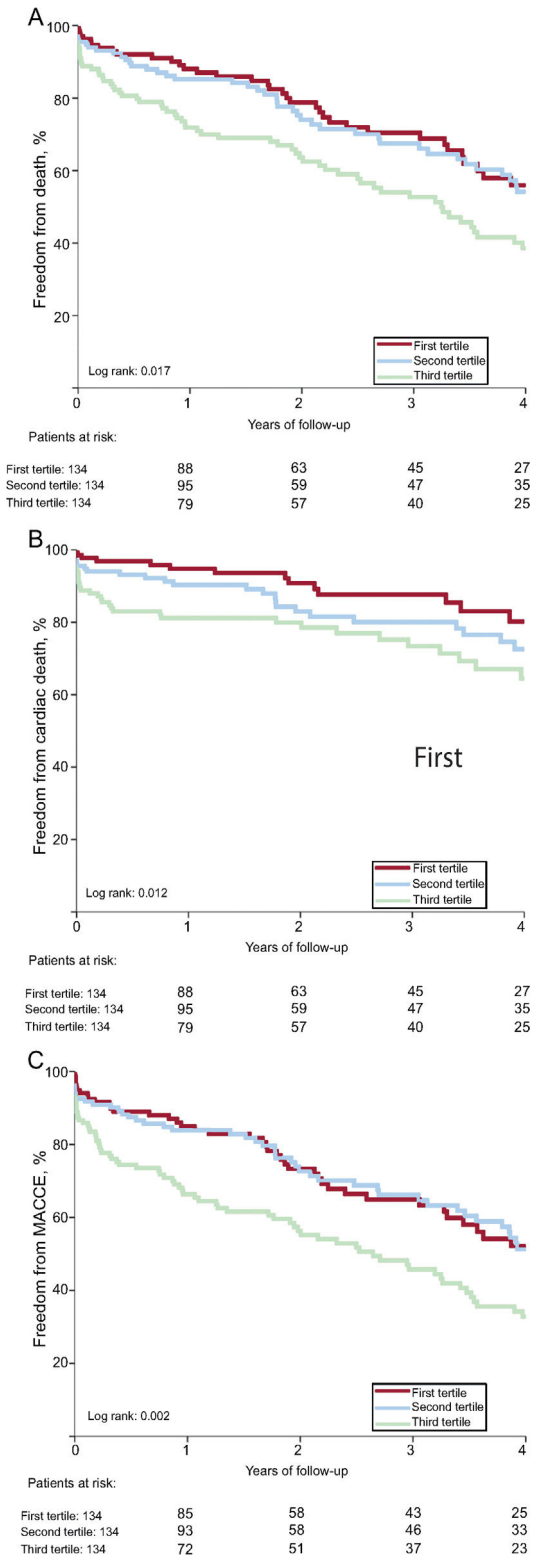

Figure 1. Long-term outcomes according to SYNTAX score II percutaneous coronary intervention. MACE, major adverse cardiovascular events.

Table 5
Multivariate Predictors of 4-year All-cause Mortality and Major Adverse Cardiovascular Events After Transcatheter Aortic Valve Implantation

	Mortality		MACE	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age[a]	1.02 (0.98-1.07)	.232	1.14 (0.95-1.37)	.147
Female	0.55 (0.35-0.86)	.009	0.59 (0.40-0.87)	.006
COPD	1.15 (0.71-1.86)	.571	1.25 (0.81-1.91)	.308
Peripheral vascular disease	1.07 (0.49-2.34)	.874	1.60 (0.75-3.42)	.226
eGFR, mL/min[b]	1.00 (0.99-1.01)	.702	0.97 (0.88-1.06)	.503
LVEF, mmHg[c]	1.01 (1.00-1.02)	.089	1.05 (1.00-1.11)	.042
Acute kidney injury 2-3	3.35 (1.58-7.10)	.002	2.78 (1.34-5.80)	.006
Paravalvular AR	1.02 (0.44-2.36)	.968	1.00 (0.48-2.06)	.999
SS-II tertiles				
2nd vs 1st tertile SS-II	0.86 (0.51-1.46)	.572	0.97 (0.61-1.53)	.887
3rd vs 1st tertile SS-II	1.68 (1.01-2.81)	.046	2.08 (1.34-3.24)	.001

95%CI, 95% confidence interval; AR, aortic regurgitation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; SS-II, SYNTAX score II.
[a] For each increase of 5 years.
[b] For each decrease of 10 mL/min.
[c] For each decrease of 5%.

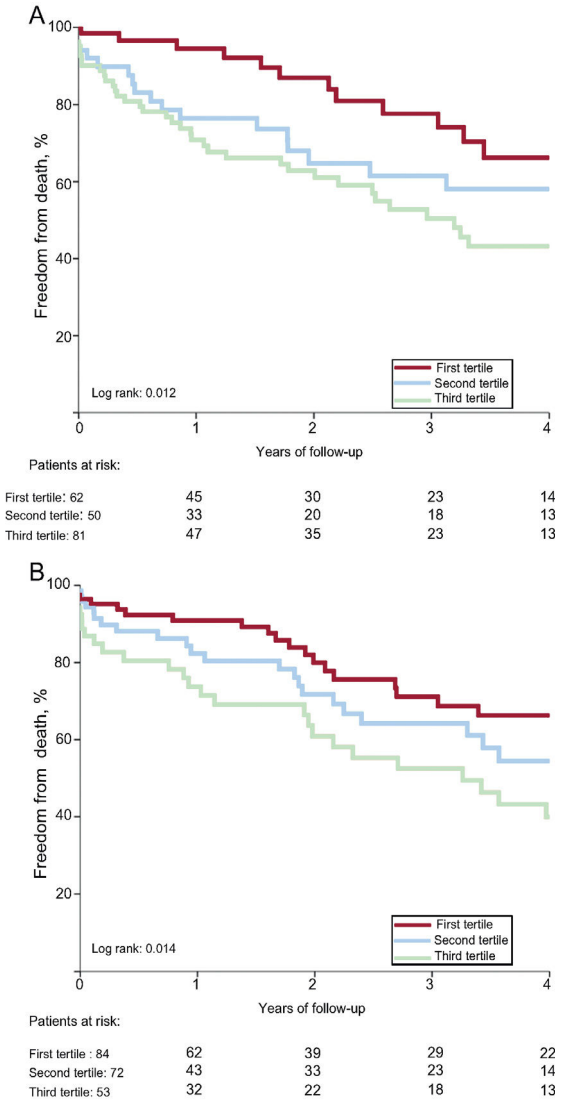

Figure 2. Long-term mortality according to SYNTAX score II percutaneous coronary intervention in patients with coronary artery disease (A) and without coronary artery disease (B).

clinical outcomes in patients undergoing revascularization and several randomized trials for both PCI and TAVI are based on or included SS-I in their algorithms,[8,30] including PARTNER-2[31] and SURTAVI.[32] A more detailed description of the complexity of CAD in TAVI patients, rather than dichotomous CAD status, has been reported using the SS-I.[6,7] While in 1 single-center study, SS-I > 9 was shown to be predictive of mortality in patients undergoing TAVI with the Edwards Sapiens valve,[7] Stefanini et al.[6] demonstrated that patients with an SS-I > 22 had a higher risk of cardiovascular death, stroke, and myocardial infarction. Furthermore the extent and complexity of CAD assessed by SS-I was associated with baseline risk profiles in both TAVI and surgical aortic valve replacement populations.[6,31] The SS-II was developed by combining anatomical variables (anatomic SS-I and the presence of unprotected left main CAD) with clinical variables: age, creatinine clearance, left ventricular ejection fraction, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease. Further validation in the DELTA[32] and CREDO-Kyoto[33] registries showed that the SS-II can better guide decision-making than the original SS-I in patients with CAD. Given that the presence of CAD is only 1 component of the SS-II and CAD and aortic stenosis have a similar pathophysiology,[1,2] it would appear that the SS-II may prove a useful tool in predicting outcomes even in patients without CAD. In our study, we showed an additional predictive value of SS-II, compared with the SS-I and residual SS-I, on 30-day and 1-year mortality in patients undergoing TAVI. This may be explained by the fact that all of the clinical variables included in the SS-II are important factors related to outcomes after TAVI,[34,35] and they have more impact on outcomes than the presence or absence of CAD. Poor renal function and left ventricular ejection fraction, age, chronic obstructive pulmonary disease, and peripheral vascular disease have been associated with worse outcomes in the TAVI population. Female sex is the only contradictory variable, being a protective factor in both the SS-II CABG and TAVI studies (“female paradox”) and a predictor of increased risk in the SS-II PCI. It appears that, in this elderly population, comorbidities may play a more important role in clinical outcome than the extent of CAD. When endpoints were assessed in patients with and without CAD using the SS-II, there were no significant differences between the groups, indicating that the SS-II can be used in the entire TAVI population independent of CAD status. Future studies with the expansion of TAVI to lower risk profile patients will determine whether the extent and complexity of CAD plays a more predominant role in clinical outcomes in this setting.

The SS-II was developed to aid in the decision-making process for coronary revascularization in patients with multivessel CAD, and thus generates a probability of mortality for PCI and CABG. In our study, SS-II PCI better predicted 30-day and 1-year mortality. Further analysis will need demonstrate whether this effect continues over a longer period of follow-up. In the present study, SS-II PCI provided a useful stratification of TAVI patients in predicting short-term complications. Importantly, the 3rd tertile had significantly high 30-day mortality, bleeding and acute kidney injury rates (~12%, 24%, and 32%, respectively), which may classify these patients in the group for whom the intervention is considered futile. This provides an additional tool when discussing the risk and benefits of the intervention. In addition, the SS-II PCI differentiated patients in the highest tertile with a higher risk of 4-year major adverse cardiovascular events and all-cause and cardiovascular death. This stratification continued to be relevant after adjustment for other significant baseline differences and known predictive factors of mortality in the TAVI population.

Several surgical risk scores (especially the Society of Thoracic Surgeons score and EuroSCORE) are used in daily clinical practice for risk assessment in TAVI candidates.[36] Although used as part of the Heart Team discussion, they are suboptimal for the assessment of high-risk valvular disease patients.[37–39] New TAVI-specific risk scores have also been developed with variable limitations and prognostic capacity[40–43] and less penetration than traditional surgical risk scores in current practice.[36] Thus, the optimal score for TAVI patients has not yet been developed. In the present study, the predictive ability of the SS-II PCI for 30-day and 1-year mortality was an AUC of 0.632 and 0.619, respectively ($P < .05$). Silaschi et al.[38] reported a nonsignificant AUC for several surgical risk factors in a cohort of 457 patients undergoing TAVI. Although in our study, the association was statistically significant, the predictive value continued to be modest and further efforts should be made to improve clinical risk assessment in this special population. In addition, the impact and management of CAD in patients undergoing TAVI should be addressed in randomized clinical trials. Meanwhile, clinical assessment, risk prediction, and the revascularization strategy before TAVI should be individualized in each patient. The SS-II is an additional, readily available, and useful tool to predict clinical outcomes in patients with aortic stenosis undergoing TAVI.

Limitations

This is a single-center, observational study and indluded only the transfemoral approach. Therefore, our results need to be confirmed by future larger multicenter studies and with different approaches. However, calculation of the SS-II in a real-world cohort may extrapolate the results to other cohorts. Coronary revascularization was performed according to the Heart Team decision, so it may introduce bias into the analysis and results. The SS-II was developed in an entirely different patient population to those undergoing TAVI and was not specifically designed to assess outcomes in this scenario, which limits the analysis. However, most the risk scores currently used are not designed for TAVI candidates.

CONCLUSIONS

The SS-II PCI appears to be a useful tool in predicting outcomes post-TAVI. Increased SS-II was associated with poorer clinical outcomes at 1 and 4 years post-TAVI. Patients with an SS-II > 44 have a higher risk of cardiovascular death, stroke, or MI than patients with an SS-II < 44, independently of the presence of CAD.

CONFLICTS OF INTEREST

L. Nombela-Franco has served as a proctor for Abbott.

WHAT IS KNOWN ABOUT THE TOPIC?

- Aortic stenosis frequently coexists with CAD, and surgical aortic valve replacement in combination with CABG increases periprocedural mortality and morbidity. The impact of CAD in patients undergoing TAVI remains inconclusive. The anatomic SYNTAX score has been investigated as a potential tool to predict major cardiovascular events in patients undergoing TAVI, but its predictive value was found to be very limited

WHAT DOES THIS STUDY ADD?

- The SS-II, which adds clinical variables to CAD severity quantified by the angiography, is superior to the SYNTAX score in predicting 30-day and 1-year mortality in patients with symptomatic aortic stenosis undergoing TAVI. Increasing SS-II was associated with increased major adverse cardiovascular events, all-cause death, and cardiac death in the TAVI population independently of the presence of CAD. Patients with an SS-II $>$ 44 had an independent $\sim$2-fold increased risk of major adverse cardiovascular events and all-cause mortality at 1 year and 4 years compared with patients with a SYNTAX score II $<$ 37.4. SYNTAX score II is a readily available and easily calculable score, which may be a useful addition to risk assessment in patients undergoing TAVI.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at http://dx.doi.org/10.1016/j.rec.2017.10.014.

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