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Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation

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Aim The aim of this study was to evaluate whether coronary artery disease (CAD) severity exerts a gradient of risk in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Methods and results A total of 445 patients with severe AS undergoing TAVI were included into a prospective registry between 2007 and 2012. The preoperative SYNTAX score (SS) was determined from baseline coronary angiograms. In case of revascularization prior to TAVI, residual SS (rSS) was also determined. Clinical outcomes were compared between patients without CAD ($n = 158$), patients with low SS (0–22, $n = 207$), and patients with high SS (SS >22, $n = 80$). The pre-specified primary endpoint was the composite of cardiovascular death, stroke, or myocardial infarction (MI). At 1 year, CAD severity was associated with higher rates of the primary endpoint (no CAD: 12.5%, low SS: 16.1%, high SS: 29.6%; $P = 0.016$). This was driven by differences in cardiovascular mortality (no CAD: 8.6%, low SS: 13.6%, high SS: 20.4%; $P = 0.029$), whereas the risk of stroke (no CAD: 5.1%, low SS: 3.3%, high SS: 6.7%; $P = 0.79$) and MI (no CAD: 1.5%, low SS: 1.1%, high SS: 4.0%; $P = 0.54$) was similar across the three groups. Patients with high SS received less complete revascularization as indicated by a higher rSS (21.2 ± 12.0 vs. 4.0 ± 4.4, $P < 0.001$) compared with patients with low SS. High rSS tertile (>14) was associated with higher rates of the primary endpoint at 1 year (no CAD: 12.5%, low rSS: 16.5%, high rSS: 26.3%, $P = 0.043$).

Conclusions Severity of CAD appears to be associated with impaired clinical outcomes at 1 year after TAVI. Patients with SS >22 receive less complete revascularization and have a higher risk of cardiovascular death, stroke, or MI than patients without CAD or low SS.

Keywords Coronary artery disease • Aortic stenosis • Transcatheter aortic valve implantation • SYNTAX score

Introduction

Coronary artery disease (CAD) and aortic valve stenosis (AS) frequently co-exist.[1] The common clinical occurrence is related at least in part to a similar pathogenesis.[2] Beyond age-related degenerative changes, both disease entities are characterized by active lesions with subendothelial accumulation of oxidized low-density lipoproteins and inflammation with lymphocytes and macrophages which are responsible for disease progression.[3,4] Moreover, CAD and AS share several risk factors including age, male gender,

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arterial hypertension, hypercholesterolaemia, diabetes mellitus, and chronic kidney disease.[2] As a result, >50% of patients with severe AS undergoing surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) have concomitant CAD.[5–12]

The presence of CAD increases the risk for peri-procedural complications and impairs long-term clinical outcomes after SAVR.[5–7] Whether CAD and its severity have prognostic implications among elderly patients with severe AS undergoing TAVI is still a matter of debate.[8–13] Of note, the extent and complexity of CAD among patients with severe AS is quite variable. The SYNTAX score (SS) is an anatomical risk score which allows to quantify the extent and complexity of CAD, and has been shown to predict long-term clinical outcomes among patients with CAD undergoing percutaneous coronary intervention (PCI).[14–16] The purpose of the present study was to evaluate the impact of CAD severity as assessed by the SS on clinical outcomes among patients with severe AS undergoing TAVI.

Methods

Patient population

A total of 445 elderly patients with symptomatic severe AS undergoing TAVI were included into a prospective registry at Bern University Hospital (Bern TAVI Registry) between August 2007 and April 2012. Patients referred for TAVI evaluation underwent interdisciplinary discussion within the local, institutional Heart Team consisting of invasive cardiologists, and cardiovascular surgeons. The indication for TAVI was based on patients' clinical history, clinical status, anatomical suitability, and geriatric assessment.[17,18] Patients underwent implantation of the Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis, MN, USA), the Edwards Sapien transcatheter heart valve (Edwards LifeSciences, Irvine, CA, USA), or the Symetis Acurate TA aortic bioprosthesis (Symetis, Ecublens, Switzerland) using the femoral, transapical, or subclavian access route as previously described.[17] The selected access route followed the principle of the least invasive approach, based on the individual anatomical characteristics as determined by contrast enhanced computed tomography, angiography, and transthoracic or transoesophageal echocardiography.[19] Among patients with CAD, complete revascularization of proximal coronary artery segments with a diameter stenosis ≥70% was attempted by PCI. The latter was performed either in a scheduled session prior to TAVI (staged PCI) or at the time of TAVI (concomitant PCI). In case of concomitant PCI, patients underwent PCI followed by TAVI during the same session. Revascularization strategies were based on clinical presentation and coronary angiography findings since functional methods of ischaemia detection have not been validated in patients with severe AS. The study complied with the declaration of Helsinki, and the registry was approved by the local ethics committee. All the patients provided written informed consent to participate in the Bern TAVI Registry with prospective follow-up assessment.

Angiographic analysis

All angiographic analyses were performed at the Core Angiographic Laboratory of the Department of Cardiology at Bern University Hospital, Bern, Switzerland. For the purpose of this study, baseline coronary angiograms of all patients were reviewed by two experienced invasive cardiologists who were trained in the assessment of SS and blinded to clinical outcomes.[20] Coronary artery disease was defined as the presence of one or more lesions of the epicardial coronary arteries with ≥50% diameter stenosis in vessels ≥1.5 mm in diameter. For patients with CAD, SS at baseline—defined as SS prior to any PCI—was calculated by consensus of the two readers using the SS algorithm (available at www.syntaxscore.com).[21] In case of disagreement, the opinion of a third reviewer was obtained and final decision was achieved by consensus. For patients with prior coronary artery bypass surgery (CABG), the CABG SS was applied.[22] For patients undergoing PCI, the extent and complexity of untreated CAD was determined by assessing residual SS (rSS)—defined as SS of remaining CAD after PCI prior to TAVI.[23] For patients not undergoing PCI rSS was considered equivalent to SS at baseline. The SS of 30 randomly selected cases were reassessed by the same readers 4 weeks later, with evidence of a strong correlation in terms of reproducibility ($r = 0.98$).

Study endpoints and definitions

The pre-specified primary endpoint of the present study was a composite of ischaemic clinical outcomes—cardiovascular death, stroke, or myocardial infarction (MI)—at 1 year. Secondary endpoints were the individual components of the primary endpoint, as well as all-cause death and the composite of all-cause death, stroke, and MI. Acute kidney injury, access site complications, and the Valve Academic Research Consortium (VARC) safety endpoint were assessed. The definition of cardiovascular death involved any death due to a proximate cardiac cause or a death of unknown cause, as well as all procedure-related deaths and death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, or other vascular disease. Peri-procedural MI (≤72 h) was determined as new ischaemic symptoms or signs in the presence of elevated cardiac biomarkers (i.e. two or more post-procedure samples that were >6–8 h apart with a 20% increase in the second sample and a peak value >10× the 99th percentile URL, or a peak value >5× the 99th percentile URL with new pathological Q waves in at least two contiguous leads).[24] Spontaneous MI (>72 h) was determined in case of elevation of cardiac biomarkers (i.e. at least one value >99th percentile URL) together with evidence of ischaemia.[24] Major stroke encompassed a rapid onset of focal or global neurological deficit of ≥24 h duration necessitating therapeutic intervention, or documentation of a new intracranial defect using MRI or CT-scan. Acute kidney injury was defined according to a modified RIFLE classification and was based upon changes in serum creatinine up to 72 h after the procedure. Stage 3 kidney injury was considered in case of an increase in creatinine of ≥300% with an acute increase of at least 44 μmol/L. Moreover, patients receiving any case of renal replacement therapy (haemodialysis, peritoneal dialysis, or haemofiltration) during the index hospitalization or within the first 30 days after the procedure are considered to meet stage 3 kidney injury irrespective of other criteria. All events were adjudicated according to the VARC I definitions[24] by a clinical event committee consisting of invasive cardiologists and cardiac surgeons.

Clinical follow-up

Adverse events were assessed in hospital, and regular clinical follow-up was performed at 1, 6, and 12 months by means of a clinical visit or a standardized telephone interview. All suspected events were adjudicated by the clinical event committee. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) responsible for central data audits and maintenance of the database.

Statistical analysis

Patients were stratified into three groups according to the presence and severity of CAD: patients without CAD, patients with low SS (0–22), and patients with high SS (>22). Baseline characteristics and clinical

outcomes were compared between groups. Discrete data were summarized as counts and frequencies (%) and compared with ANOVAs, whereas continuous data were presented as means ± SD and compared with χ^2 tests.

Clinical outcomes at 30 and 1 year were expressed as counts or incidence rates computed according to Kaplan–Meier analysis. Hazard ratios were derived from Mantel-Cox log-rank for death, cardiovascular death, stroke, MI, and the composites of these endpoints. Risk ratios were computed from Poisson regression with robust error variances for acute renal failure, access site complications, and VARC safety endpoint.

Clinical outcomes at 1 year were also compared between: patients without CAD, patients in the lower rSS tertiles (0–14), and patients in the higher rSS tertile (>14).

A Cox multivariate regression analysis was performed to assess predictors of 1-year risk of the composite primary endpoint of cardiovascular death, stroke, or MI, including in the model baseline SS >22 as well as covariates known to be associated with these adverse events (i.e. age, gender, diabetes, hypercholesterolaemia, peripheral vascular disease, left ventricular ejection fraction). To assess reproducibility of the SS assessment, the Pearson's *r* correlation coefficient was used. Analyses were performed using STATA version 12.1 (StataCorp, College Station, TX, USA). *P*-values <0.05 were considered statistically significant.

Results

Out of 445 elderly patients with severe AS undergoing TAVI between 2007 and 2012, 158 patients (35.5%) had no CAD, 207 patients (46.5%) had a low SS (0–22), and 80 patients (18.0%) had a high SS (>22). Scheduled follow-up was completed in all patients, with a mean follow-up duration of 258 ± 146 days for the overall population and no differences between groups (no CAD: 261 ± 144 days, low SS: 257 ± 146 days, high SS: 254 ± 149 days).

Baseline and procedural characteristics

Baseline clinical characteristics are summarized in *Table 1*. At baseline, patients with higher SS were less frequently female (no CAD: 70%, low SS: 56%, high SS: 28%; $P < 0.001$). Increased CAD severity was associated with diabetes mellitus (no CAD: 20%, low: SS 28%, high SS: 36%; $P = 0.019$), hypercholesterolaemia (no CAD: 43%, low SS: 66%, high SS: 86%; $P < 0.001$), peripheral vascular disease (no CAD: 12%, low SS: 23%, high SS: 31%; $P = 0.001$), and reduced left ventricular ejection fraction (no CAD: 53.7 ± 15.0%, low SS: 52.7 ± 14.6%, high SS: 47.4 ± 14.7%; $P = 0.007$). The mean aortic valve area was larger (no CAD: 0.56 ± 0.24 cm^2, low SS: 0.61 ± 0.22 cm^2, high SS: 0.67 ± 0.21 cm^2; $P = 0.003$) and mean transaortic valvular gradient lower (no CAD: 46.9 ± 18.2 mmHg, low SS: 42.1 ± 15.9 mmHg, high SS: 38.3 ± 15.0 mmHg; $P = 0.001$) among patients with higher SS. The Logistic EuroSCORE (no CAD: 19.5 ± 11.1, low SS: 23.7 ± 13.8, high SS: 30.3 ± 15.7; $P < 0.001$) and the STS score (no CAD: 5.9 ± 4.3, low SS: 7.0 ± 5.5, high SS: 8.6 ± 6.3; $P = 0.001$) were higher with increasing CAD extent and complexity.

Among patients with CAD, those with high SS had more frequently prior MI, previous CABG and PCI, and where characterized by more complex CAD in terms of number of vessels involved, presence of small vessel disease, long lesions, bifurcation lesions, and type B2/C lesions compared with patients with low SS. Procedural characteristics were similar among all groups as summarized in *Table 2*. Noteworthy, patients with high SS at baseline had higher rSS compared with patients with low SS (4.0 ± 4.4 vs. 21.2 ± 12.0, $P < 0.001$).

Clinical outcomes

Clinical outcomes through 1 year after TAVI are reported in *Table 3*. At 30 days, similar findings were observed across the three groups with respect to the primary endpoint (no CAD: 7.0%, low SS: 7.2%, high SS: 10.0%; $P = 0.54$), as well as the individual components cardiovascular death (no CAD: 3.8%, low SS: 5.4%, high SS: 7.5%; $P = 0.22$), stroke (no CAD: 5.1%, low SS: 2.0%, high SS: 2.6%; $P = 0.19$), and MI (no CAD: 0.6%, low SS: 0.5%, high SS: 0%).

At 1 year, increased CAD severity was associated with higher rates of the primary endpoint (no CAD: 12.5%, low SS: 16.1%, high SS: 29.6%; $P = 0.016$). This was mainly driven by a difference in cardiovascular death (no CAD: 8.6%, low SS: 13.6%, high SS: 20.4%; $P = 0.029$), whereas the risk of stroke (no CAD: 5.1%, low SS: 3.3%, high SS: 6.7%; $P = 0.79$) and MI (no CAD: 1.5%, low SS: 1.1%, high SS: 4.0%; $P = 0.54$) was similar in all three groups. Rates of all-cause mortality (no CAD: 16.9%, low SS: 19.6%, high SS: 26.1%; $P = 0.16$), and of the composite of all-cause mortality, stroke, and MI (no CAD: 19.4%, low SS: 21.5%, high SS: 33.5%; $P = 0.071$), were numerically higher with increasing CAD severity, although statistically not significant. Cumulative event rates of the primary endpoint and cardiovascular mortality among patients without CAD, patients with low SS, and patients with high SS are shown in *Figures 1* and *2*. Of note, the 1-year risk of the primary endpoint was higher among patients with high SS (HR: 2.24, 95% CI: 1.18–4.23, $P = 0.013$) and similar among patients with low SS (HR: 1.23, 95% CI: 0.68–2.21, $P = 0.49$) compared with patients without CAD.

Using multivariate analysis (*Figure 3*), left ventricular ejection fraction (HR: 1.29, 95% CI: 1.11–1.51) emerged as the only independent predictor of the primary endpoint at 1 year. Coronary artery disease with SS >22 was associated with an increased risk of the primary endpoint without reaching statistical significance (HR: 1.68, 95% CI: 0.94–3.02, $P = 0.079$).

Since 48.4% of patients with CAD underwent PCI prior to TAVI, clinical outcomes were also compared according to rSS post-PCI (*Table 4*). Although the range of rSS varied considerably for any value of SS, a strong correlation was observed between SS and rSS (*Figure 4*; Spearman's rho = 0.84, $P < 0.001$), indicating that patients with high SS received less complete revascularization and therefore had a higher extent and complexity of CAD after PCI prior to TAVI compared with patients with low SS. The primary endpoint occurred more frequently among patients in the higher rSS tertile (26.3%) compared with patients in the lower rSS tertiles (16.5%) and patients without CAD (12.5%, $P = 0.043$).

Discussion

To the best of our knowledge, this is the first study to assess the impact of CAD severity as quantified by the angiographic SS on clinical outcomes among elderly patients with severe AS undergoing TAVI, and has the following principal findings:

Table 1 Baseline clinical characteristics

	Overall (n = 445)	No CAD (n = 158)	CAD by SYNTAX-score		P-value
			Low (0–22) (n = 207)	High (>22) (n = 80)	
Age, years	82.5 ± 5.8	83.0 ± 5.9	82.4 ± 5.9	81.9 ± 5.2	0.36
Female gender (%)	249 (56)	111 (70)	116 (56)	22 (28)	<0.001
Body mass index, kg/m^2	26.1 ± 4.9	25.7 ± 4.9	26.4 ± 5.1	25.9 ± 4.2	0.38
Cardiac risk factors (%)					
Diabetes mellitus	117 (26)	31 (20)	57 (28)	29 (36)	0.019
Insulin-treated	41 (9)	10 (6)	23 (11)	8 (10)	0.28
Hypercholesterolaemia	273 (61)	67 (43)	137 (66)	69 (86)	<0.001
Hypertension	362 (81)	122 (77)	173 (84)	67 (84)	0.25
Current smoker	44 (10)	14 (9)	22 (11)	8 (10)	0.85
Past medical history (%)					
Previous stroke	35 (8)	10 (6)	20 (10)	5 (6)	0.42
PVD	92 (21)	19 (12)	48 (23)	25 (31)	0.001
Chronic obstructive pulmonary disease	79 (18)	31 (20)	34 (16)	14 (18)	0.71
Clinical features					
Systolic pulmonary pressure, mmHg	51.3 ± 17.2	50.7 ± 17.2	52.0 ± 17.3	50.6 ± 17.0	0.73
Renal failure (%)	301 (68)	113 (72)	135 (65)	53 (66)	0.43
Atrial fibrillation (%)	128 (29)	53 (34)	59 (29)	16 (20)	0.10
LVEF, %	52.1 ± 14.9	53.7 ± 15.0	52.7 ± 14.6	47.4 ± 14.7	0.007
Aortic valve area, cm^2	0.60 ± 0.23	0.56 ± 0.24	0.61 ± 0.22	0.67 ± 0.21	0.003
Mean transaortic gradient, mmHg	43.1 ± 16.9	46.9 ± 18.2	42.1 ± 15.9	38.3 ± 15.0	0.001
Symptoms (%)					
NYHA I or II	154 (35)	54 (35)	74 (36)	26 (33)	0.90
NYHA III or IV	288 (65)	102 (65)	133 (64)	53 (67)	0.90
Coronary artery disease (%)					
Prior MI	67 (15)	0 (0)	41 (20)	26 (33)	<0.001
Prior CABG	75 (17)	0 (0)	28 (14)	47 (59)	<0.001
Prior PCI	109 (24)	0 (0)	70 (34)	39 (49)	<0.001
Vessels diseased (%)					
Left main	25 (9)	–	6 (3)	19 (24)	<0.001
Left anterior descending	220 (79)	–	141 (71)	79 (99)	<0.001
Left circumflex	159 (57)	–	87 (44)	72 (90)	<0.001
Right coronary artery	170 (61)	–	97 (49)	73 (91)	<0.001
Vein graft	38 (13)	–	6 (3)	32 (40)	<0.001
Small vessel disease	16 (12)	–	4 (4)	12 (29)	<0.001
Bifurcation lesions	53 (38)	–	28 (29)	25 (60)	0.001
Long lesions	59 (42)	–	34 (35)	25 (60)	0.009
Type B2 or C lesions	102 (73)	–	64 (66)	38 (90)	0.003
Risk assessment					
Baseline SYNTAX score	16.5 ± 12.5	–	10.1 ± 6.5	33.2 ± 7.9	<0.001
Logistic EuroSCORE	23.4 ± 13.8	19.5 ± 11.1	23.7 ± 13.8	30.3 ± 15.7	<0.001
STS score	6.9 ± 5.3	5.9 ± 4.3	7.0 ± 5.5	8.6 ± 6.3	0.001
Antithrombotic therapy (%)					
Aspirin	270 (61)	68 (43)	138 (67)	64 (81)	<0.001
Clopidogrel	86 (20)	13 (8)	50 (24)	23 (29)	<0.001
Oral anticoagulation	121 (27)	45 (29)	57 (28)	19 (24)	0.75

Values are n (%) or means ± SD. CABG,coronary artery bypass graft; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STS, Society of Thoracic Surgeons.

Table 2 Procedural characteristics

	Overall (n = 445)	No CAD (n = 158)	CAD by SYNTAX-score		P-value
			Low (0–22) (n = 207)	High (>22) (n = 80)	
Access route (%)					0.44
Femoral	348 (78)	130 (82)	158 (76)	60 (75)	0.29
Apical	92 (21)	27 (17)	47 (23)	18 (23)	0.38
Subclavian	5 (1)	1 (1)	2 (1)	2 (3)	0.42
Valve type (%)					0.53
Medtronic core valve	240 (54)	91 (58)	106 (51)	43 (54)	0.48
Edwards Sapien valve	202 (45)	65 (41)	100 (48)	37 (46)	0.39
Symetis acurate TA	3 (1)	2 (1)	1 (0.5)	0 (0)	–
Procedural specifications (%)					
General anaesthesia	178 (42)	55 (37)	92 (46)	31 (41)	0.24
PCI	139 (31)	–	97 (47)	42 (53)	0.43
Concomitant PCI	75 (17)	–	58 (28)	17 (21)	0.43
Staged PCI	63 (14)	–	38 (18)	25 (31)	0.41
New-onset of atrial fibrillation	33 (7)	12 (8)	16 (8)	5 (6)	0.91
Post TAVI—need for PPM	107 (24)	42 (27)	43 (21)	22 (28)	0.32
Valve in series	9 (2)	4 (3)	2 (1)	3 (4)	0.28
Revascularization (%)					
PCI	139 (31)	–	97 (47)	42 (53)	0.43
Vessels treated					
Left main	10 (7)	–	4 (4)	6 (14)	0.07
Left anterior descending	83 (60)	–	60 (62)	23 (55)	0.46
Left circumflex	25 (18)	–	15 (16)	10 (24)	0.34
Right coronary artery	53 (38)	–	36 (37)	17 (40)	0.71
Vein graft	5 (4)	–	1 (1)	4 (10)	0.029
Residual SYNTAX score	9.2 ± 10.9	–	4.0 ± 4.4	21.2 ± 12.0	<0.001

Values are n (%). CAD, coronary artery disease; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium.

(1) coronary artery disease is present in two-thirds of elderly patients with severe AS undergoing TAVI in routine clinical practice;
(2) severity of CAD is associated with higher risk profiles at baseline and impaired ischaemic clinical outcomes at 1 year among elderly patients with severe AS undergoing TAVI;
(3) patients with CAD and SS >22 undergoing TAVI are associated with a higher risk of cardiovascular death, stroke, or MI at 1 year, owing to a two-fold increased risk of cardiovascular mortality compared with patients without CAD.

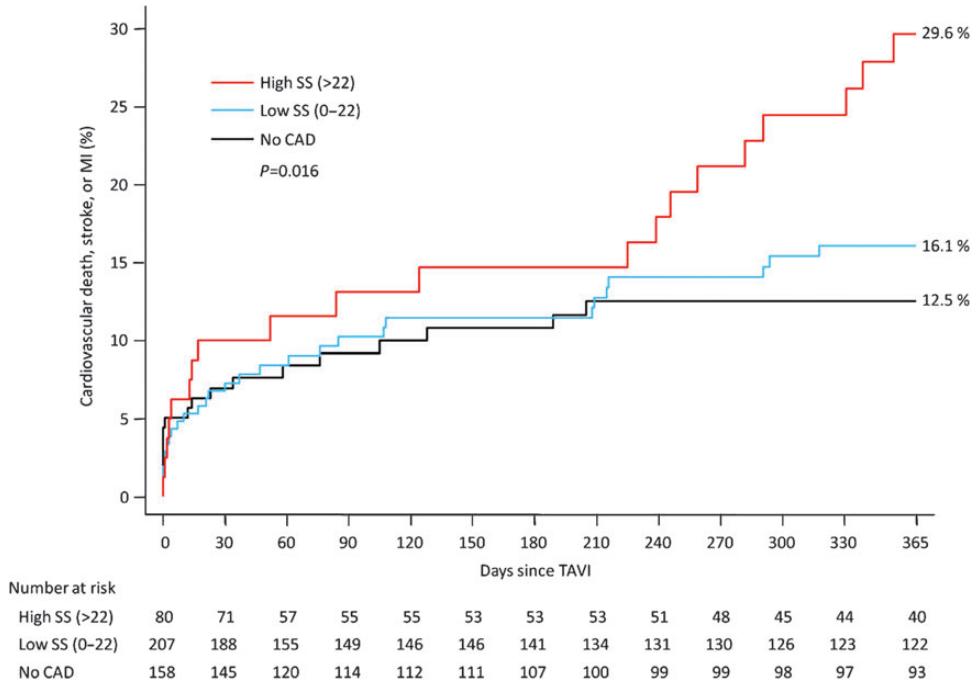
Coronary artery disease and AS share several pathophysiological mechanisms which contribute to the coexistence of both disease entities. Initiating factors of CAD and AS are similar and include the subendothelial accumulation of oxidized low-density lipoprotein, and recruitment of lymphocytes and macrophages resulting in local inflammatory reactions.[3,25] These processes lead to extracellular matrix formation, calcification, fibrosis, and endothelial dysfunction which are accentuated by mechanical stress in both CAD and AS. However, the larger accumulation of extracellular calcification and the absence of smooth-muscle cells distinguish AS from CAD.[4] Moreover, AS is characterized by gradual but continuous progression with subsequent clinical events resulting from left ventricular outflow obstruction due to immobile leaflets.[1] Conversely, CAD does not follow a continuous and linear fashion but is characterized by periods of relative quiescence followed by episodes of clinically apparent or silent plaque rupture.[26] Clinical events in patients with CAD are related to myocardial ischaemia, typically as a consequence of atherosclerotic plaque instability.[26]

In this series of 445 elderly patients with severe AS undergoing TAVI, almost two-thirds (65%) of patients had evidence of CAD. Interestingly, the severity of CAD was associated with major comorbidities at baseline. Similar findings were recently reported in a study investigating CAD among patients with severe AS undergoing SAVR.[5] In the present study, we observed that the extent and complexity of CAD correlated with baseline risk profiles reflecting a higher burden of atherosclerotic disease. Indeed, patients with more severe CAD—as indicated by higher SS—had more frequently prior ischaemic events, peripheral vascular disease, hypercholesterolaemia, diabetes mellitus, and impaired left ventricular function at baseline. The correlation of

Table 3 Clinical outcomes through 1 year according to baseline SYNTAX-score

	Overall (n = 445)	No CAD (n = 158)	CAD by SYNTAX-score		Low (0–22) vs. No CAD		High (>22) vs. No CAD		Overall *P*-value
			Low (0–22) (n = 207)	High (>22) (n = 80)		*P*-value	RR (95% CI)	*P*-value	
Events at 30 days									
Cardiovascular death, stroke, or MI	34 (7.6)	11 (7.0)	15 (7.2)	8 (10.0)	1.04 (0.48–2.26)	0.93	1.44 (0.58–3.58)	0.43	0.47
All-cause death, stroke, or MI	38 (8.5)	12 (7.6)	18 (8.7)	8 (10.0)	1.14 (0.55–2.37)	0.73	1.32 (0.54–3.23)	0.54	0.54
All-cause death	28 (6.3)	8 (5.1)	14 (6.8)	6 (7.5)	1.35 (0.57–3.23)	0.49	1.52 (0.53–4.39)	0.44	0.41
Cardiovascular death	23 (5.2)	6 (3.8)	11 (5.4)	6 (7.5)	1.42 (0.52–3.83)	0.49	2.03 (0.65–6.29)	0.22	0.22
Stroke	14 (3.2)	8 (5.1)	4 (2.0)	2 (2.6)	0.38 (0.11–1.26)	0.12	0.50 (0.11–2.33)	0.37	0.19
Major stroke	13 (3.0)	8 (5.1)	3 (1.5)	2 (2.6)	0.28 (0.08–1.07)	0.06	0.50 (0.11–2.33)	0.37	0.15
Minor stroke	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	–	–	–	–	–
Myocardial infarction	2 (0.5)	1 (0.6)	1 (0.5)	0 (0.0)	0.76 (0.05–12.21)	0.85	–	–	–
Acute kidney injury	17 (3.8)	6 (3.8)	6 (2.9)	5 (6.3)	0.76 (0.25–2.32)	0.64	1.65 (0.52–5.24)	0.40	0.54
Major access site complications	38 (8.5)	14 (8.9)	20 (9.7)	4 (5.0)	1.09 (0.57–2.09)	0.89	0.56 (0.19–1.66)	0.30	0.39
VARC safety endpoint	114 (25.6)	38 (24.1)	54 (26.1)	22 (27.5)	1.08 (0.76–1.55)	0.66	1.14 (0.73–1.80)	0.56	0.54
Events at 1 year									
Cardiovascular death, stroke, or MI	67 (17.3)	18 (12.5)	29 (16.1)	20 (29.6)	1.23 (0.68–2.21)	0.49	2.24 (1.18–4.23)	0.013	0.016
All-cause death, stroke, or MI	89 (23.0)	27 (19.4)	39 (21.5)	23 (33.5)	1.10 (0.68–1.80)	0.69	1.73 (0.99–3.01)	0.054	0.07
All-cause death	76 (19.9)	23 (16.9)	35 (19.6)	18 (26.1)	1.18 (0.70–2.00)	0.53	1.58 (0.85–2.94)	0.14	0.16
Cardiovascular death	50 (13.1)	12 (8.6)	24 (13.6)	14 (20.4)	1.55 (0.78–3.10)	0.22	2.36 (1.09–5.10)	0.029	0.029
Stroke	18 (4.5)	8 (5.1)	6 (3.3)	4 (6.7)	0.57 (0.20–1.65)	0.30	1.00 (0.30–3.32)	1.00	0.79
Major stroke	17 (4.3)	8 (5.1)	5 (2.9)	4 (6.7)	0.48 (0.16–1.46)	0.19	1.00 (0.30–3.32)	1.00	0.74
Minor stroke	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	–	–	–	–	–
Myocardial infarction	6 (1.8)	2 (1.5)	2 (1.1)	2 (4.0)	0.77 (0.11–5.47)	0.80	2.00 (0.28–14.21)	0.49	0.54

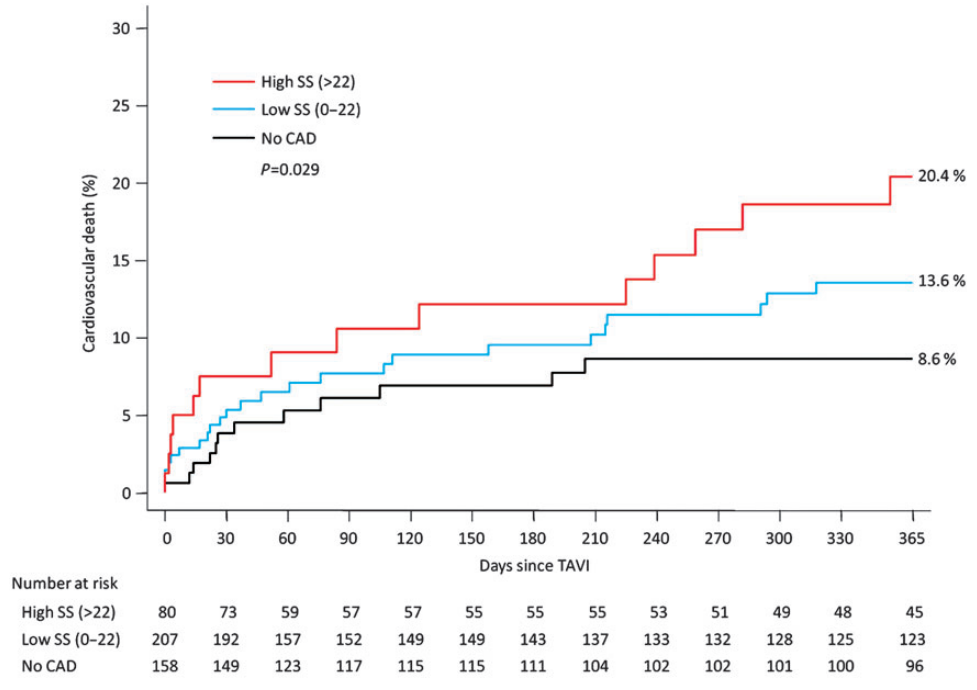
Values are n (%). CAD, coronary artery disease; MI, myocardial infarction; RR, risk ratio; VARC, Valve Academic Research Consortium.



Number at risk

High SS (>22)	80	71	57	55	55	53	53	53	51	48	45	44	40
Low SS (0–22)	207	188	155	149	146	146	141	134	131	130	126	123	122
No CAD	158	145	120	114	112	111	107	100	99	99	98	97	93

Figure 1 Cardiovascular death, stroke, or myocardial infarction through one year according to coronary artery disease (CAD) severity. Cumulative event curves of the primary endpoint—the composite of cardiovascular death, stroke, and myocardial infarction—in patients without CAD, patients with low SYNTAX score (SS; 0–22), and patients with high SS (>22).



Number at risk

High SS (>22)	80	73	59	57	57	55	55	55	53	51	49	48	45
Low SS (0–22)	207	192	157	152	149	149	143	137	133	132	128	125	123
No CAD	158	149	123	117	115	115	111	104	102	102	101	100	96

Figure 2 Cardiovascular death through one year according to CAD severity. Cumulative event curves of cardiovascular death in patients without CAD, patients with low SYNTAX score (SS; 0–22), and patients with high SS (>22).

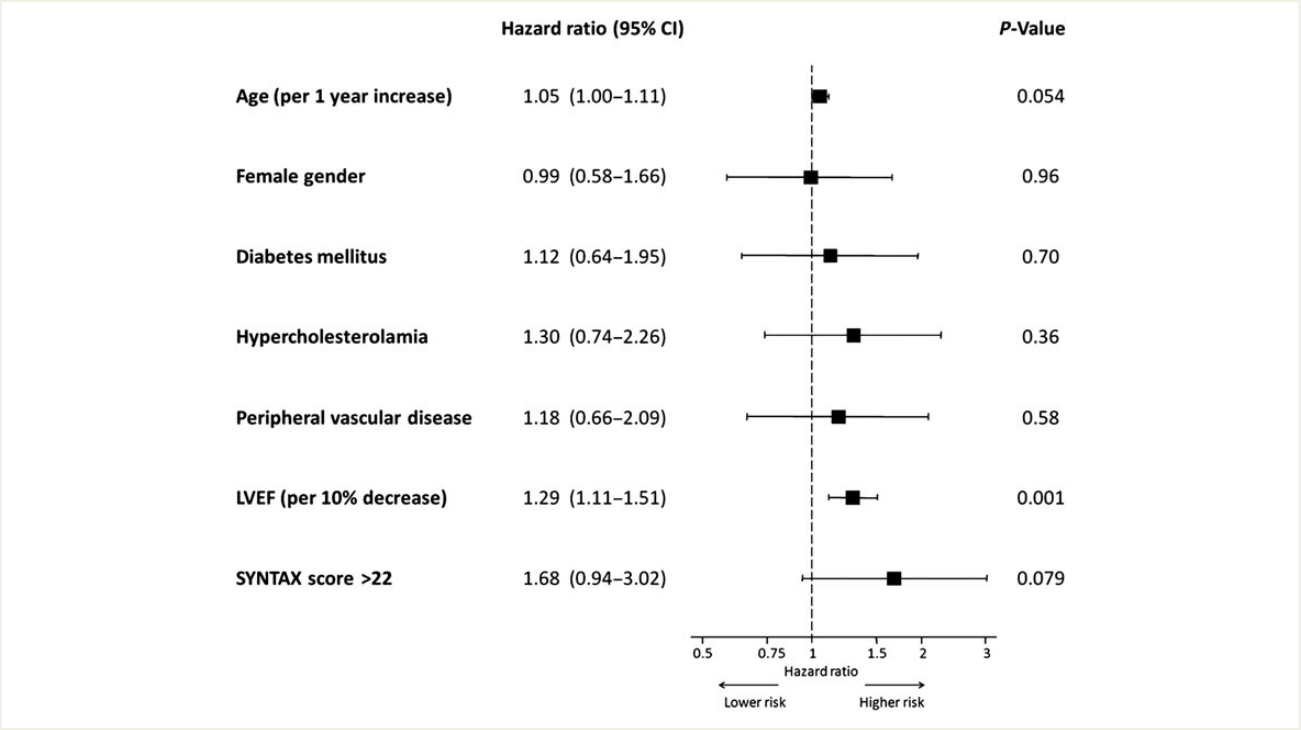


Figure 3 Predictors of cardiovascular death, stroke, or myocardial infarction at one year. LVEF, left ventricular ejection fraction.

higher baseline risk and degree of CAD severity was paralleled by a gradient in the logistic EuroSCORE and STS score ranging from 19.5 and 5.9, respectively, in patients without CAD, up to 30.3 and 8.6 in patients with high SS. Of note, patients with more severe CAD had a greater aortic valve area and a lower mean transaortic gradient at baseline. Similar findings have been reported among patients with severe AS undergoing SAVR.[5] It is tempting to speculate that more advanced CAD is responsible for an earlier manifestation of clinical symptoms resulting in earlier valve replacement therapy among patients with severe AS. Future studies will need to confirm whether this hypothesis holds true in larger patient populations.

Coronary artery disease and need for concomitant CABG has been shown to adversely influence short- and long-term outcomes of patients with severe AS undergoing SAVR.[5,6] However, elderly patients with severe AS undergoing TAVI are frequently not considered suitable candidates for SAVR due to a high or excessive baseline risk.[27,28] It is therefore debated whether CAD extent and complexity has an impact on clinical outcomes among these patients, or whether the valvular disease and comorbid conditions play a predominant role, camouflaging any prognostic impact of CAD. Dewey *et al.*[8] reported a significantly higher 1-year mortality among 84 patients with CAD compared with 87 patients without CAD after TAVI (35.7 vs. 18.4%, $P = 0.01$). Similarly, the presence of CAD has been identified as an independent predictor of death (HR: 1.38, 95% CI: 1.07–1.76) in the large-scale multicentre post-approval SOURCE XT TAVI registry.[29] Conversely, Masson *et al.*[10] reported no impact of CAD on survival among 136 patients undergoing TAVI during 1-year follow-up, despite numerically higher event rates in patients with than in those without CAD (27.7 vs. 18.8%, $P = 0.63$). Along this line, D'Ascenzo *et al.*[12] performed a meta-analysis of seven observational studies, suggesting that CAD does not increase the risk of death in patients undergoing TAVI (OR: 1.0, 95% CI: 0.67–1.50). It is noteworthy that the anatomic extent and complexity of CAD—as systematically quantified by the use of the SS—and its impact on ischaemic outcomes has not been previously assessed in this patient population. Therefore, the present study represents the first analysis evaluating the impact of CAD extent and complexity among elderly patients with severe AS undergoing TAVI, and our findings suggest that CAD severity is associated with more frequent ischaemic events at 1 year. Event rates of the primary endpoint, of all-cause death, of cardiovascular death, and of the composite of all-cause death, stroke, and MI, increased along with CAD severity. Specifically, patients with SS >22 had a markedly higher risk of the composite of cardiovascular death, stroke, and MI at 1 year, primarily due to a two-fold increased risk of cardiovascular death. Of note, the threshold of 22 for SS, as described in the SYNTAX trial,[14] is currently used as key exclusion criteria in the SURgical replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial, in which TAVI is compared with SAVR among patients with severe AS at intermediate surgical risk (ClinicalTrials.gov identifier NCT01586910). Similarly, SS is used for exclusion in the ongoing Placement of AoRTic TraNscathetER Valves 2 (PARTNER-2) trial (ClinicalTrials.gov identifier NCT01314313), with a higher threshold of SS >32.

Using multivariate analysis, CAD with SS >22 was associated with a nominal 70% increase in the risk of cardiovascular death, stroke, or MI at 1 year, however, without reaching statistical significance. This

Table 4 Clinical outcomes through one year according to residual SYNTAX-score

	Overall (n = 445)	No CAD (n = 158)	Residual SYNTAX-score		Low (0–14) vs. No CAD		High (>14) vs. No CAD		Overall P-value
			Low (0–14) (n = 192)	High (>14) (n = 95)	RR (95% CI)	P-value	RR (95% CI)	P-value	
Events at 1 year									
Cardiovascular death, stroke, or MI	67 (17.3)	18 (12.5)	28 (16.5)	21 (26.3)	1.30 (0.72–2.34)	0.39	1.92 (1.02–3.61)	0.042	0.043
All-cause death, stroke, or MI	89 (23.0)	27 (19.4)	38 (22.4)	24 (29.6)	1.18 (0.72–1.93)	0.52	1.47 (0.85–2.55)	0.17	0.18
All-cause death	76 (19.9)	23 (16.9)	34 (20.3)	19 (23.6)	1.26 (0.74–2.14)	0.39	1.36 (0.74–2.49)	0.33	0.31
Cardiovascular death	50 (13.1)	12 (8.6)	24 (14.3)	14 (17.7)	1.70 (0.85–3.40)	0.13	1.91 (0.89–4.14)	0.10	0.09

Values are n (%). CAD, coronary artery disease; MI, myocardial infarction; RR, risk ratio.

Figure 4 Correlation between the SYNTAX-score at baseline (x-axis) and residual SYNTAX-score (y-axis). Residual SYNTAX-score was defined as SYNTAX-score remaining after percutaneous coronary interventions prior to transcatheter aortic valve implantation. For patients not undergoing percutaneous coronary interventions, residual SYNTAX score was equivalent to SYNTAX score at baseline.

may be explained by the extent of comorbid conditions among patients with severe CAD and other risk factors, particularly impaired left ventricular function which was identified as the only independent predictor of the composite primary endpoint at 1 year in our study.

In the present study, patients with higher baseline SS undergoing TAVI received less complete revascularization as indicated by higher rSS, and experienced less favourable clinical outcomes at 1 year. Although concomitant CABG among patients undergoing SAVR is associated with increased peri-operative mortality, complete revascularization is usually performed bypassing all lesions with a diameter stenosis >50–70%. In this context, a recent propensity-score-matched comparison between patients undergoing CABG plus SAVR and patients undergoing isolated SAVR reported similar short- and long-term survival, suggesting that CABG with complete revascularization at the time of SAVR offsets the adverse effects associated with CAD among patients with otherwise similar comorbidities.[5] Conversely, van Mieghem *et al.*[30] recently reported that completeness of revascularization did not impact clinical outcomes in a series of 124 TAVI patients with significant CAD who underwent PCI in 32% of cases based on Heart Team decision. This study indicated that a judicious revascularization strategy can generate favourable mid-term outcome obviating the need for complete coronary revascularization among appropriately selected TAVI patients. Along this line, our findings suggest that incomplete revascularization with high rSS (>14) impairs long-term clinical outcomes after TAVI, whereas lower rSS (0–14)—indicating an acceptable extent of residual CAD after PCI—may be associated with outcomes comparable with complete revascularization. It is also important to note that patients undergoing SAVR are typically younger and suffer from fewer comorbidities than patients undergoing TAVI and that the long-term benefit derived from additional revascularization therapy may be more relevant in

younger patients. However, randomized trials with prospective planning of revascularization strategy are required to address the optimal revascularization strategy among patients undergoing TAVI.

Several limitations need to be considered when interpreting our study. First, this is a single-centre, observational study and therefore our results need to be considered as hypothesis generating. However, the close correlation of CAD with baseline characteristics and well-established risk factors for CAD together with the size of the study and the event rates lend strength to the analysis. Secondly, patients were stratified into three groups based on the presence and severity of CAD as assessed by the SS. This retrospective stratification neglects that treatment allocation was based on clinical judgement, therefore introducing a source of performance bias. Thirdly, SS is an anatomical risk score based on visual estimation of coronary angiograms with inherent limitations.[31] For the purpose of the present analysis, SS were calculated by consensus of two experienced invasive cardiologists trained for SS assessment with evidence of good reproducibility and blinded to clinical outcomes. It cannot be excluded, however, that results may have varied if less experienced readers had determined SS.[20] Finally, it needs to be pointed out that the objective of the present study was to evaluate whether the extent and complexity of CAD at baseline had an impact on ischaemic clinical outcomes after TAVI, irrespective of coronary revascularization. However, we observed that patients with higher SS received less complete revascularization and therefore had a higher extent and complexity of CAD also after PCI prior to TAVI compared with patients with low SS. Patients with less complete revascularization (i.e. those with higher rSS) had a higher risk of cardiovascular death, stroke, or MI at 1 year. This observation corroborates that more severe and complex CAD impairs clinical outcomes after TAVI.

Conclusions

Severity of CAD appears to be associated with impaired clinical outcomes at 1 year after TAVI. Patients with SS >22 receive less complete revascularization and have a higher risk of cardiovascular death, stroke, or MI than patients without CAD or low SS.

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Conflicts of interest: L.B. is a consultant and proctor for Medtronic. A.A.K. has received speaker honoraria and proctor fees from Medtronic CoreValve and Edwards Lifesciences. F.N. is a proctor for Edwards Lifesciences. C.H. is proctor for Edwards Lifesciences and receives consultant fees from Medtronic. B.M. has received has received educational and research support to the institution from Abbott, Cordis, Boston Scientific, and Medtronic. 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. The other authors report no conflicts of interest.

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