

# Outcome of Patients With Severe Aortic Stenosis and Normal Coronary Arteries Undergoing Transcatheter Aortic Valve Implantation



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**Coronary artery disease and severe aortic stenosis (AS) often coexist. This study sought to investigate the impact of normal coronary arteries as negative risk marker in patients undergoing transcatheter aortic valve implantation (TAVI). Consecutive patients with severe AS undergoing TAVI were dichotomized according to the presence or absence of normal coronary arteries, defined as absence of coronary lesions with diameter stenosis  $\geq 30\%$  in vessels  $\geq 1.5$  mm in diameter on coronary angiogram in patients without prior coronary revascularization. The primary end point was 1-year mortality. Out of 987 patients with severe AS undergoing TAVI, 258 (26%) patients had normal coronary arteries. These patients were younger, more likely women, and had lower EuroSCORE II and STS risk scores. Although mortality at 30 days was similar in the normal coronary artery and the coronary atherosclerosis groups (3.1% vs 5.6%,  $p = 0.11$ ), it was lower in those with normal coronary arteries at 1 year (8.9% vs 17%,  $p = 0.003$ ). In multivariable analysis, the presence of normal coronary arteries on coronary angiogram independently predicted 1-year mortality (adjusted HR 0.57, 95% CI 0.37 to 0.90,  $p = 0.02$ ). In conclusion, this study defined normal coronary arteries as negative risk marker in patients with severe AS undergoing TAVI. © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2021;143:89–96)**

Surgical or transcatheter aortic valve implantation (TAVI) represent the standard therapy for severe symptomatic AS,<sup>1–3</sup> as medical options to delay or halt disease progression do not exist. About half of patients with severe AS scheduled for TAVI exhibit significant coronary artery lesions.<sup>4–6</sup> Data on the impact of the presence and extent of coronary artery disease on outcomes after TAVI remain, however, conflicting and optimal management of coronary artery disease in terms of timing and completeness of coronary revascularization in the context of TAVI needs to be determined.<sup>7–12</sup> Characteristics and outcomes of patients presenting with isolated severe AS and normal coronary arteries have not adequately been investigated. An advanced understanding of these patients may extend our knowledge about AS progression and the interplay between degenerative aortic valve disease and coronary atherosclerosis. This study therefore aims at determining clinical characteristics and outcomes of patients with severe AS and

normal coronary arteries in a large, prospective cohort of patients with severe AS undergoing TAVI.

## Methods

A total of 987 patients diagnosed with severe AS and undergoing TAVI at the University Hospital Zurich, Switzerland, between May 2008 and September 2017 were included in the analysis. Data were prospectively entered into a dedicated web-based database (REDCap, Vanderbilt University Medical Center, Nashville), hosted by the Clinical Trial Center at the University Hospital Zurich, Zurich, Switzerland. Regular follow-up was performed by either patient visit or phone call or assessed using available hospital records. Events were categorized according to the updated standardized end point definitions of the Valve Academic Research Consortium (VARC)-2 consensus document.<sup>13</sup> For the purpose of this study, patients were dichotomized according to the presence or absence of normal coronary arteries, with normal coronary arteries defined as  $\leq 30\%$  coronary artery diameter stenosis by visual estimation in at least 2 coronary angiography projections in patients without prior coronary revascularization, in line with the European Society of Cardiology working group position paper on myocardial infarction with non-obstructive coronary arteries.<sup>14</sup> In a sensitivity analysis, patients were categorized as having normal coronary arteries based on multi-detector computed tomography (MDCT, absence of coronary calcium accumulation, Figure 1). The study was approved by the local ethics committee and performed

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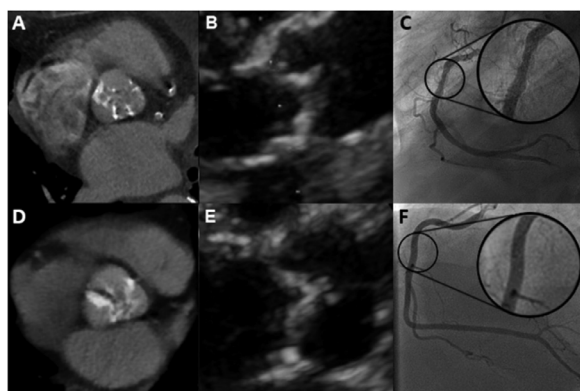


Figure 1. Representative MDCT (A), echocardiography (B), and coronary angiography (C) of a patient with severe aortic stenosis and concomitant coronary atherosclerosis. Representative MDCT (D), echocardiography (E), and coronary angiography (F) of a patient with severe aortic stenosis and normal coronary arteries. MDCT = multi-detector computed tomography.

according to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Transthoracic echocardiography studies were performed using commercially available ultrasound systems (Philips iE33 or Epic, Philips Healthcare, Andover, Massachusetts; GE Vivid 7 or E9 or E95, GE Healthcare, Milwaukee, Wisconsin). Two-dimensional and Doppler echocardiographic images were acquired in parasternal long-axis and apical views and obtained in accordance with the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.<sup>15</sup> Aortic stenosis severity was quantified based on peak jet velocity, mean transvalvular pressure gradient, and effective orifice area as calculated by the continuity equation.<sup>15,16</sup>

Biplane conventional coronary angiography was performed according to current guidelines and standard techniques. Baseline coronary angiograms of all patients were reviewed by experienced physicians. Normal coronary arteries were defined as absence of epicardial coronary artery lesions with a diameter stenosis  $\geq 30\%$  by visual estimation in vessels  $\geq 1.5$  mm in diameter in patients without prior coronary revascularization. Ambiguous results were assessed using quantitative coronary angiography (QCA, Xcelera Philips, Eindhoven, The Netherlands).

Multi-detector computed tomography was performed using a 128-slice dual-source computed tomography system (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) with the following parameters: a quality reference tube current time product of 130 mAS/rotation using automatic tube current modulation (CAREDose; Siemens), a reference tube voltage of 100 kVp using automated attenuation-based tube voltage selection (pitch 3.2, gantry rotation time 0.25 s). The reconstructed slice thickness was 0.6 mm with an increment of 0.4 mm using a soft tissue convolution kernel (Bv36). For image acquisition, a bolus of 45 mL Iopromide (Ultravist 300, 300 mg/mL, Bayer Schering Pharma, Berlin, Germany) was injected at a flow rate of 5 mL/s, followed by a second bolus of 35 mL at a flow rate of 2.5 mL/s. Then, 60 mL saline solution was injected at the same flow rate. Bolus tracking in the ascending aorta was performed with a signal attenuation threshold

of 100 Hounsfield Units at 120 kVp. Coronary arteries without any calcium accumulation and without any wall irregularities were considered as unaffected. The quantification of aortic valve calcium was performed in a semi-automatic manner using «calcium scoring» application as previously described (Syngo.via, Siemens Healthcare, Forchheim, Germany).<sup>17,18</sup>

Continuous variables are presented as mean  $\pm$  standard deviation or median and interquartile range as appropriate, and categorical variables as number and percentages. The Shapiro Wilk test was used to test for normality distribution, and the Levene's test to assess the homogeneity of variance. Pairwise comparison was performed using the Student's *t*-test or the Mann-Whitney *U*-test as appropriate. Categorical variables were analyzed by the Pearson's Chi-square test or the Fischer's Exact test. The probability of death at one year was calculated using the Kaplan-Meier method with the Log Rank test used for comparisons among groups. Cox proportional hazard models were used to assess independent predictors of death at 1 year. The following prespecified variables known to be associated with mortality in AS patients were included in the multivariable models: age, gender, peripheral artery disease, cerebrovascular disease, arterial hypertension, type 2 diabetes, dyslipidemia, overweight and/or obesity (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>), smoking status, chronic obstructive pulmonary disease, and estimated glomerular filtration rate (eGFR). The proportionality assumption was assessed by correlation testing based on Schoenfeld residuals. A 2-sided *p*-value of 0.05 was considered statistically significant. All analyses were performed with SPSS for Windows 25.0 (Chicago, Illinois).

## Results

Out of 987 patients with severe AS undergoing TAVI, a total of 258 (26%) patients had normal coronary arteries based on coronary angiography (Figure 2). When defining normal coronary arteries as absence of coronary calcification on MDCT, 160 (16%) patients had normal coronary arteries (Figure 2). Baseline characteristics are given in Table 1 and procedural outcomes according to the updated standardized end point definitions of the VARC-2 consensus document in Table 2, respectively. In the coronary atherosclerosis group, a total of 212 (29%) patients had prior percutaneous coronary intervention (PCI) and a total of 139 (19%) patients prior coronary artery bypass grafting (CABG). In 59 (8.1%) patients, concomitant PCI was performed during TAVI and in 2 patients, PCI was performed after TAVI.

At 12 months, a total of 143 patients had died, 104 patients from cardiovascular causes (Table 3). Although mortality at 30 days was similar in the normal coronary artery and the coronary atherosclerosis groups (3.1% vs 5.6%, *p* = 0.11), it was lower in those with normal coronary arteries at 1 year (8.9% vs 17%, *p* = 0.003, Figure 3). Similar trends were observed when defining normal coronary arteries by MDCT (Figure 3). In multivariable analysis, the presence of normal coronary arteries on coronary angiogram independently predicted 1-year mortality (adjusted HR 0.57, 95% CI 0.37 to 0.90, *p* = 0.02). Defining normal

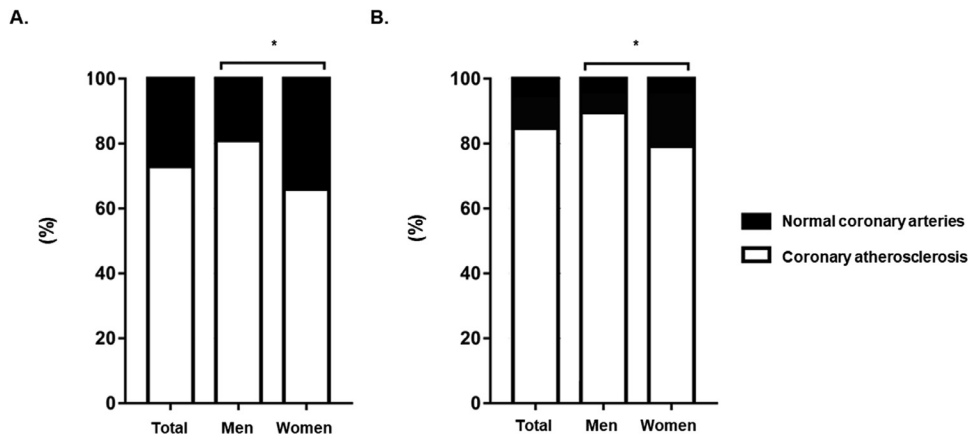


Figure 2. (A) Percentage of patients with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by coronary angiography. (B) Percentage of patients with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by MDCT. MDCT = multi-detector computed tomography.

coronary arteries by MDCT, normal coronary arteries were not predictive for 1-year mortality (adjusted HR 0.78, 95% CI 0.46 to 1.33,  $p=0.37$ ). Predictors of mortality by multivariable analysis are summarized in Table 4. When medication at discharge was incorporated individually into the

multivariable model, neither aspirin (adjusted HR 1.17, 95% CI 0.67 to 2.02,  $p=0.58$ ), nor  $P_2Y_{12}$  inhibitors (adjusted HR 0.86, 95% CI 0.52 to 1.40,  $p=0.54$ ), statins (adjusted HR 0.98, 95% CI 0.62 to 1.53,  $p=0.92$ ), beta blockers (adjusted HR 1.18, 95% CI 0.78 to 1.78,  $p=0.43$ ), angiotensin

Table 1  
Baseline characteristics

Variable	Total (n=987)	Coronary arteries		p-value
		Normal (n=258)	Abnormal (n=729)	
Age (years)	81.3 $\pm$ 7.2	80 $\pm$ 8.1	81.8 $\pm$ 6.8	0.001
Women	488 (49%)	162 (63%)	326 (45%)	<0.001
Body mass index (kg/m <sup>2</sup> )	26.8 $\pm$ 4.9	27.2 $\pm$ 5.6	26.7 $\pm$ 4.6	0.17
Previous coronary bypass	139 (14%)	0 (0%)	139 (19%)	<0.001
Previous percutaneous coronary intervention	212 (22%)	0 (0%)	212 (29%)	<0.001
Peripheral artery disease	225 (23%)	40 (16%)	185 (25%)	0.001
Cerebrovascular disease	175 (18%)	33 (13%)	142 (20%)	0.02
Family history of coronary artery disease	102 (14%)	16 (8.9%)	86 (16%)	0.02
Arterial hypertension	785 (80%)	183 (71%)	602 (83%)	<0.001
Type 2 diabetes mellitus	243 (25%)	48 (19%)	195 (27%)	0.009
Dyslipidemia	506 (51%)	120 (47%)	386 (53%)	0.08
Overweight or obesity	586 (59%)	153 (59%)	433 (59%)	1.0
Smoker	377 (38%)	80 (31%)	297 (41%)	0.006
Chronic obstructive pulmonary disease	154 (16%)	50 (19%)	104 (14%)	0.052
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	56.7 $\pm$ 21.2	58.9 $\pm$ 22.8	55.9 $\pm$ 20.6	0.053
Total cholesterol (mg/dl)	179.1 $\pm$ 50.6	190.8 $\pm$ 58.4	175.2 $\pm$ 50.6	0.002
Low-density lipoprotein cholesterol (mg/dl)	101.6 $\pm$ 43.2	109 $\pm$ 46.7	97.3 $\pm$ 42.8	0.02
High-density lipoprotein (mg/dl)	54.5 $\pm$ 15.6	58.4 $\pm$ 19.5	50.6 $\pm$ 15.6	<0.001
Left ventricular ejection fraction (%)	54.6 $\pm$ 13.5	57.2 $\pm$ 12.6	53.7 $\pm$ 13.6	<0.001
Mean transaortic pressure gradient (mmHg)	41.7 $\pm$ 16.4	44.3 $\pm$ 17.8	40.9 $\pm$ 15.8	0.005
Aortic valve area (mm <sup>2</sup> )	0.75 $\pm$ 0.21	0.74 $\pm$ 0.22	0.75 $\pm$ 0.21	0.43
Indexed aortic valve area, (mm <sup>2</sup> /m <sup>2</sup> )	0.41 $\pm$ 0.12	0.41 $\pm$ 0.12	0.41 $\pm$ 0.12	0.68
Aortic valve Agatston score	2493 (1525-3649)	2326.0 (1477-3653)	2512.5 (1549-3654)	0.39
EuroSCORE II	4.2 (2.5-7.8)	3.2 (1.9-5.2)	4.7 (2.9-8.3)	<0.001
STS Score	4.6 (3.0-6.9)	3.7 (2.6-5.7)	4.8 (3.2-7.3)	<0.001
Medications at discharge				
Aspirin	778 (83%)	198 (80%)	580 (85%)	0.13
$P_2Y_{12}$ inhibitor	760 (82%)	180 (73%)	580 (85%)	<0.001
Statin	606 (65%)	111 (45%)	495 (72%)	<0.001
Beta blocker	457 (49%)	110 (45%)	347 (51%)	0.06
Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers	593 (64%)	145 (59%)	448 (65%)	0.045
Calcium channel blocker	213 (23%)	40 (16%)	173 (25%)	0.005

Values are given as numbers and percentages, median (interquartile range), or mean (standard deviation).

Table 2

Thirty-day procedural outcomes according to the criteria of the Valve Academic Research Consortium (VARC)-2.

Variable	Total (n=987)	Normal coronary arteries (n=258)	Coronary atherosclerosis (n=729)	p-value
Mortality	49 (5%)	8 (3.1%)	41 (5.6%)	0.11
Device success	850 (86%)	219 (85%)	631 (87%)	0.49
Myocardial infarction	12 (1.2%)	2 (0.8%)	10 (1.4%)	0.74
Stroke	43 (4.4%)	4 (1.6%)	39 (5.3%)	0.01
Major bleeding	70 (7.1%)	17 (6.6%)	53 (7.3%)	0.71
Acute kidney injury	127 (13%)	28 (11%)	99 (14%)	0.26
Major vascular complications	83 (8%)	20 (8%)	63 (9%)	0.66
Permanent pacemaker implantation	194 (20%)	41 (16%)	153 (21%)	0.08
Valve-related dysfunction requiring repeat procedure	16 (1.6%)	6 (2.3%)	10 (1.4%)	0.39

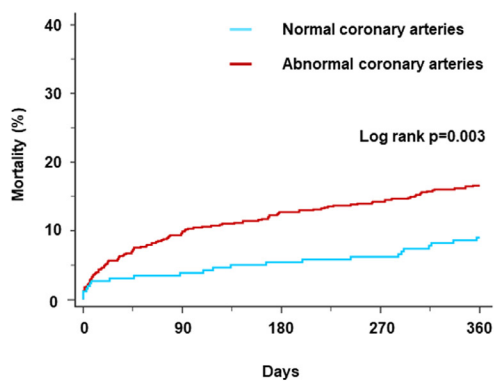
Values are given as numbers and percentages.

Table 3

Causes of death.

Causes of death	Total (deaths=143)	Coronary arteries	
		Normal (deaths=23)	Abnormal (deaths=120)
Procedure-related	29 (20.3%)	5 (21.7%)	24 (20.0%)
Heart failure	30 (21%)	4 (17%)	26 (22%)
Myocardial infarction	5 (3.5%)	0 (0%)	5 (4.2%)
Cardiac arrest due to arrhythmia	2 (1.4%)	0 (0%)	2 (1.7%)
Cerebrovascular events	10 (7.0%)	1 (4.3%)	9 (7.5%)
Mesenteric ischemia	1 (0.7%)	1 (4.3%)	0 (0%)
Gastrointestinal bleeding	2 (1.4%)	0 (0%)	2 (1.7%)
Pulmonary disease	3 (2.1%)	0 (0%)	3 (2.5%)
Infection/systemic inflammatory response syndrome	20 (14%)	5 (22%)	15 (12%)
Renal failure	4 (2.7%)	2 (8.7%)	2 (1.7%)
Cancer	6 (4.2%)	2 (8.7%)	4 (3.3%)
Unknown (including cardiac arrest of unknown origin)	27 (19%)	3 (13%)	24 (20%)
Other	4 (2.8%)	0 (0%)	4 (3.3%)

A.



No of patients at risk

Normal coronary arteries

258

246

241

237

230

Abnormal coronary arteries

729

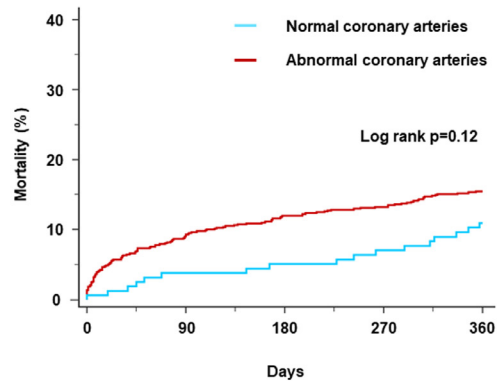
649

626

615

594

B.



No of patients at risk

Normal coronary arteries

160

149

146

143

137

Abnormal coronary arteries

820

739

714

702

680

Figure 3. (A) Kaplan-Meier survival curve of patients with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by coronary angiography. (B) Kaplan-Meier survival curve of patients with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by MDCT. MDCT = multi-detector computed tomography.

Table 4  
Predictors of 1-year mortality.

Variable	Multivariable model 1		Multivariable model 2	
	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age (years)	1.03 (1.00-1.06)	0.048	1.03 (1.00-1.06)	0.03
Female sex	0.86 (0.60-1.23)	0.40	0.81 (0.56-1.15)	0.23
Hypertension	1.23 (0.74-2.03)	0.41	1.29 (0.78-2.12)	0.32
Type 2 diabetes mellitus	1.14 (0.78-1.66)	0.51	1.16 (0.80-1.70)	0.43
Dyslipidemia	1.29 (0.92-1.82)	0.14	1.31 (0.93-1.85)	0.12
Obesity	0.85 (0.61-1.19)	0.34	0.84 (0.60-1.18)	0.32
Smoker	1.36 (0.96-1.93)	0.09	1.42 (1.00-2.00)	0.049
Peripheral arterial disease	1.52 (1.06-2.18)	0.02	1.58 (1.10-2.26)	0.01
Cerebrovascular disease	0.92 (0.61-1.41)	0.72	0.93 (0.61-1.43)	0.75
Chronic obstructive pulmonary disease	1.99 (1.34-2.94)	0.001	1.88 (1.27-2.77)	0.001
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Normal coronary arteries	0.57 (0.37-0.90)	0.02	0.78 (0.46-1.33)	0.37

Models were adjusted for all variables shown. Model 1: definition of normal coronary arteries based on coronary angiography. Model 2: definition of normal coronary arteries based on multi-detector computed tomography.

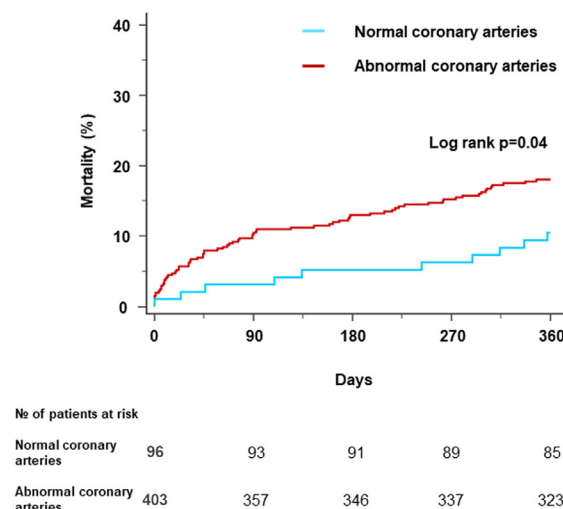
converting enzyme inhibitors and/or angiotensin receptor blockers (adjusted HR 1.00, 95% CI 0.65 to 1.54,  $p=0.99$ ), and calcium channel blockers (adjusted HR 0.66, 95% CI 0.38 to 1.14,  $p=0.13$ ) were associated with 1-year mortality.

Although cardiovascular mortality at 30 days was similar in the normal coronary artery and the coronary atherosclerosis groups (2.7% vs 4.9%,  $p=0.16$ ), it was lower in those with normal coronary arteries at 1 year (5.4% vs 12%,  $p=0.001$ ). Similar results were observed when defining normal coronary arteries by MDCT. In multivariable analysis, independent predictors of 1-year cardiovascular mortality were normal coronary arteries based on coronary angiography (adjusted HR 0.45, 95% CI 0.26 to 0.79,  $p=0.006$ ), chronic obstructive pulmonary disease (adjusted HR 1.69, 95% CI 1.06 to 2.70,  $p=0.001$ ,  $p=0.03$ ) and estimated glomerular filtration rate (adjusted HR 0.98, 95% CI 0.97 to 0.99,  $p<0.001$ ). In the sensitivity analysis defining normal coronary arteries by MDCT, normal coronary arteries tended to be predictive for

1-year cardiovascular mortality (adjusted HR 0.51, 95% CI 0.26 to 1.02,  $p=0.056$ ).

Women had a higher prevalence of normal coronary arteries as compared with men ( $p<0.001$ , Figure 2). Baseline characteristics according to gender are given in Supplementary Table 1. In the coronary atherosclerosis group, besides a similar prevalence of type 2 diabetes among women and men, baseline differences between gender were consistent with those of the whole TAVI cohort (Supplementary Table 2). Women had a lower incidence of new permanent pacemaker implantation (16% vs 24%,  $p=0.001$ ), while other procedural outcomes according to the updated standardized end point definitions of the VARC-2 consensus document were similar in women and men. In men, 1-year mortality was 10% and 18% in the normal coronary artery and the coronary atherosclerosis groups ( $p=0.09$ , Figure 4), and the corresponding rates for cardiovascular mortality were 5.2% and 13% ( $p=0.02$ ), respectively. In women, 1-year mortality was 8.0%

A.



B.

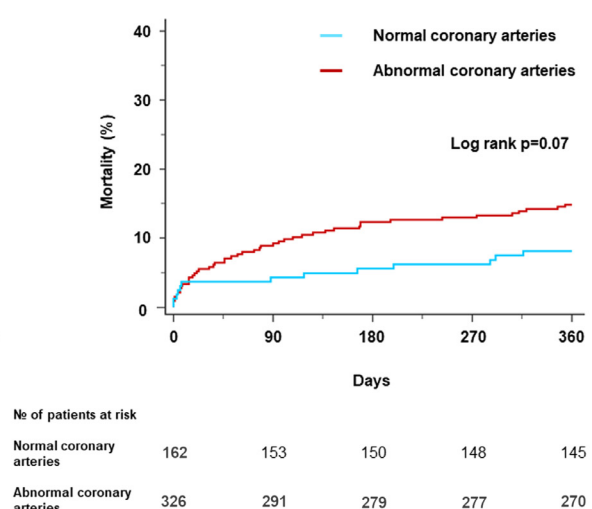


Figure 4. (A) Kaplan-Meier survival curve of men with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by coronary angiography. (B) Kaplan-Meier survival curve of women with severe aortic stenosis and normal coronary arteries or coronary atherosclerosis as defined by coronary angiography.



and 15% in the normal coronary artery and the coronary atherosclerosis groups ( $p=0.04$ , Figure 4), and the corresponding rates for cardiovascular mortality were 5.6% and 11% ( $p=0.07$ ), respectively.

## Discussion

This study demonstrates that patients with severe AS and normal coronary arteries have a different risk profile and improved outcomes after TAVI. Patients with normal coronary arteries are younger, mostly women, and have a lower burden of cardiovascular risk factors including hypertension, type 2 diabetes mellitus and smoking, although they develop a virtually identical aortic valve calcification and AS severity.

Coronary artery disease and calcific AS share common risk factors and pathophysiological pathways and thus, often coexist. Nevertheless, a quarter of patients with severe AS undergoing TAVI in this study had normal coronary arteries based on coronary angiography. The prevalence of patients with normal coronary arteries observed in this patient cohort is in line with previously reported data,<sup>4,5,9,19</sup> and differences among studies are at least in part due to differences in age, baseline risk, and nonuniform definitions of coronary artery disease. The existence of a population with severe calcific AS and completely normal coronary arteries was confirmed by MDCT where 16% of patients displayed coronary arteries devoid of any calcium accumulation. Patients with normal coronary arteries were younger, mostly women, and had a lower baseline risk. Despite these differences in the presence of cardiovascular risk factors, the severity of AS as assessed by echocardiography and aortic valve calcium scoring was comparable among patients with normal coronary arteries and those with coronary atherosclerosis. Although AS and coronary artery disease are characterized by common pathophysiological pathways such as inflammation, lipoprotein accumulation and tissue calcification,<sup>20-24</sup> this observation supports the concept of distinct pathophysiological factors playing an important role in the development of AS but not coronary atherosclerosis. It is conceivable that these hypothetical pathophysiological factors are triggered by a different set or a different combination of cardiovascular risk factors as could be observed in patients with normal versus atherosclerotic coronary arteries in this study. In line with this interpretation, only weak to modest correlations between calcific AS and coronary, carotid and aortic atherosclerosis were observed in other studies;<sup>25-28</sup> furthermore, cholesterol-lowering therapies failed to halt the progression of AS in randomized trials.<sup>29-31</sup>

Mortality rates of patients with severe AS and normal coronary arteries tended to separate at 30 days after TAVI from those with severe AS and coronary atherosclerosis, with significant differences observed at 1 year. The absence of coronary artery disease was associated with a 2-fold lower mortality rate at 1 year after TAVI. Chronic obstructive pulmonary disease, peripheral arterial disease, and impaired kidney function were independently associated with mortality, while normal coronary arteries emerged as independent negative predictor of 1-year mortality. The existing data regarding the relationship of coronary artery

disease with mortality after TAVI are conflicting. In some studies, severe coronary artery disease and incomplete revascularization but not the presence of coronary artery disease per se were related with worse outcomes after TAVI.<sup>32,33</sup> Patients with a Syntax Score >22 received less complete revascularization and exhibited a higher risk of cardiovascular events as compared with patients with a lower Syntax Score.<sup>34</sup> Other studies, however, failed to show an association between coronary artery disease and outcomes in TAVI patients.<sup>7,12,35</sup> Our findings support the concept that the extent and severity of coronary artery disease rather than the mere presence are related with worse outcomes after TAVI. In line with this concept, this study identified a lower risk population of mostly female patients with severe AS and normal coronary arteries.

Sex-related baseline differences in patients with severe AS undergoing TAVI have previously been reported. In line with these studies,<sup>36,37</sup> women with severe AS undergoing TAVI were older, less often smokers, and had higher cholesterol levels and an higher left ventricular ejection fraction,<sup>36,37</sup> irrespective of the presence of coronary atherosclerosis. In this study, sex-related baseline differences in manifestations of atherosclerosis such as a lower prevalence of peripheral artery disease and cerebrovascular disease in women were observed in the coronary atherosclerosis group. In contrast, this effect could not be demonstrated in patients with normal coronary arteries. This observation indicates that patients suffering from atherosclerosis exhibit sex-related differences in the coexistence of coronary, peripheral, and cerebral atherosclerosis.

Two thirds of patients with severe AS and normal coronary arteries were women. We therefore speculate that women may be protected from coronary atherosclerosis although they are affected by AS. However, future studies are needed to further investigate potential sex-related differences in disease expression and the underlying pathophysiological mechanisms. Trends towards lower mortality rates were observed in both women and men with normal coronary arteries.

Some limitations need to be considered. The study including a large cohort of patients with severe AS undergoing TAVI is limited by its single-center observational design. Further, although possible confounding variables were incorporated into the multivariable models, we cannot exclude that unmeasured factors may have affected the results.

In conclusion, this contemporary study identified normal coronary arteries as negative risk marker in patients with severe AS undergoing TAVI. Patients with normal coronary arteries were mostly women, had a different baseline risk profile and a lower comorbidity burden. Despite these differences in patient characteristics, the severity of AS and aortic valve calcification were absolutely comparable. Hence, coronary atherosclerosis should be incorporated into the risk stratification of patients with severe AS and personalized revascularization strategies need to be defined.

## Author Agreement

All authors have read and approved submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere in whole or

part in any language except as an abstract. All authors contributed significantly to this work. None of the authors has any conflict of interest. Submission of the manuscript has been approved by all the authors.

## Authorship

**N Kuzo:** – conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript; final approval of the manuscript submitted. **BE Stähli:** – conception and design of the study; collection, analysis and interpretation of data; statistical analysis, drafting of the manuscript; final approval of the manuscript submitted. **L. Erhart:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **S Anwer:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **M Schindler:** – interpretation of data; analysis, revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **J Kebernik:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **S Mathys:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **TDL Nguyen-Kim:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **M Eberhard:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **F Ruschitzka:** – interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted. **FC Tanner:** – conception and design of study; collection, analysis and interpretation of data; revising the manuscript critically for important intellectual content; final approval of the manuscript submitted.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

## Supplementary materials

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