

ORIGINAL RESEARCH

STRUCTURAL

Impact of Extent of Coronary Artery Disease in Transcatheter Aortic Valve Replacement



A PRO-TAVI Substudy

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ABSTRACT

BACKGROUND Coronary artery disease is present in one-half of patients undergoing transcatheter aortic valve replacement (TAVR). The recent randomized controlled PRO-TAVI (Percutaneous Coronary Intervention Before Transcatheter Aortic Valve Implantation) trial indicated that deferral of percutaneous coronary intervention (PCI) is safe in patients with concomitant coronary artery disease at 1-year follow-up. The SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score quantifies the extent of coronary artery disease, which may guide individualized revascularization strategies.

OBJECTIVES The aim of this study was to evaluate the association between SYNTAX score (SS) and clinical outcomes in patients undergoing TAVR.

METHODS This study was a substudy of the PRO-TAVI trial, including 466 patients with significant coronary artery disease undergoing TAVR randomized to deferral of PCI or PCI before TAVR. SS was calculated from preprocedural coronary angiograms, and patients were stratified by SS quartiles. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke, and major bleeding at 1 year. An ischemic composite outcome of all-cause mortality, myocardial infarction, and stroke was also assessed.

RESULTS The primary composite outcome did not differ across SS categories between the deferral and PCI groups at 1-year follow-up, which was completed by all but 1 patient. In patients with SS >17, the ischemic composite outcome occurred more often in the deferral group (30.9% vs 14.8%; adjusted HR: 2.43; 95% CI: 1.04-5.64; $P = 0.04$), driven primarily by all-cause mortality and stroke. Bleeding events were less frequent in the deferral group across all SS subgroups.

CONCLUSIONS In patients with concomitant coronary artery disease undergoing TAVR, deferral of PCI reduced bleeding risk and appeared safe across all SS categories. Deferral of PCI in patients with more complex coronary artery disease (SS >17) was associated with higher risk for the ischemic composite outcome. These post hoc findings require confirmation in randomized trials. (Percutaneous Coronary Intervention Before Transcatheter Aortic Valve Implantation [PRO-TAVI]; [NCT05078619](https://doi.org/10.1016/j.jcin.2026.07.034)) (JACC Cardiovasc Interv. 2026;19:2619-2630) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

ABBREVIATIONS AND ACRONYMS

HR_{adj} = adjusted HR

PCI = percutaneous coronary intervention

rSS = residual synergy between PCI with taxus and cardiac surgery score

SS = synergy between PCI with taxus and cardiac surgery score

TAVR = transcatheter aortic valve replacement

Coronary artery disease frequently coexists in patients undergoing transcatheter aortic valve replacement (TAVR), affecting approximately one-half of the patients.¹ European guidelines state that percutaneous coronary intervention (PCI) should be considered in patients undergoing TAVR with high-grade coronary artery stenoses.² However, the recently published PRO-TAVI (Percutaneous Coronary Intervention Before Transcatheter Aortic Valve Implantation) trial challenged the guidelines by demonstrating that deferral of PCI was noninferior to TAVR with preceding PCI with respect to the composite of all-cause mortality, myocardial infarction, stroke, and major bleeding at 1 year.³ Accordingly, deferral of PCI prior to TAVR may be a safe approach in patients with concomitant coronary artery disease.

Importantly, the severity of a single coronary stenosis does not capture the overall burden and anatomical complexity of coronary artery disease. The SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score was introduced to provide a comprehensive assessment of the extent of coronary artery disease and is an independent predictor of major adverse cardiac and cerebrovascular events in patients without valvular disease undergoing PCI.⁴ Furthermore, prior observational studies have demonstrated an association between higher SYNTAX score (SS) and worse clinical outcomes in patients undergoing TAVR.^{5,6} However, robust prospective evidence to guide individualized revascularization strategies in patients undergoing TAVR remains limited.

Therefore, the aim of this study was to evaluate the association of the extent of coronary artery disease with clinical outcomes in patients undergoing TAVR.

METHODS

STUDY DESIGN AND PARTICIPANTS. The present substudy of the PRO-TAVI trial was a post hoc analysis. In brief, the PRO-TAVI trial was an investigator-initiated, open-label, randomized controlled trial whose design and results have been published previously.^{3,7} The trial enrolled 466 patients across 12 centers in the Netherlands between October 2021 and November 2024. Patients were eligible if they had an indication for TAVR and significant coronary artery disease, defined as at least 1 stenosis of 70% to 99% by visual estimation in a native coronary artery with a minimum diameter of 2.5 mm or in a bypass graft or a stenosis of 40% to 70% by visual estimation accompanied by a positive invasive physiological parameter. Key exclusion criteria were the presence of unprotected left main coronary artery disease or left main equivalent, as well as a solitary chronic total occlusion.

The trial protocol was approved by the national authorities and the ethics committee of the University Medical Centre Utrecht (21/464), and the Institutional Review Board of each participating center. The funder had no role in design of the trial, data collection and analysis, interpretation of the data, or writing of the report. The PRO-TAVI trial is registered with ClinicalTrials.gov (NCT05078619).

RANDOMIZATION AND STUDY PROCEDURES. Participants were randomized in a 1:1 ratio to either deferral of PCI or PCI before TAVR after providing written informed consent. Randomization was stratified according to the presence of coronary artery disease in the proximal left anterior descending artery, defined as segment 6 of the SS.

Patients assigned to the PCI group underwent PCI before TAVR. In the deferral group, patients were not scheduled for routine PCI after TAVR unless clinically

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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indicated. The execution and strategy of both PCI and TAVR procedures were left to the operator's discretion.

Following TAVR, patients received low-dose aspirin or oral anticoagulation, if indicated. After PCI, patients were treated with either dual antiplatelet therapy or single antiplatelet therapy in addition to oral anticoagulation, in accordance with international guidelines.⁸ Oral anticoagulation was routinely interrupted during TAVR, whereas dual antiplatelet therapy was continued.

Follow-up was conducted in person or by telephone at 4 and 12 months after randomization.

ANGIOGRAPHIC EVALUATION. Preprocedural coronary angiograms obtained during routine work-up of all patients were assessed at an independent core laboratory by experienced interventional cardiologists, who were blinded to treatment allocation and clinical outcomes. Core laboratory assessment included, among other analyses, calculation of the SS. In accordance with SYNTAX methodology, all lesions in vessels with a diameter of at least 2.5 mm were included in the scoring.

RESIDUAL SYNTAX SUBANALYSIS. Incomplete revascularization, characterized by residual SYNTAX score (rSS) >8 after PCI, in patients without valvular disease has been associated with an increased risk for death, myocardial infarction, and stroke.⁹ Therefore, a subanalysis is performed investigating the association of incomplete revascularization with clinical outcomes in patients undergoing TAVR. In the PCI group, coronary angiograms recorded at the completion of the index PCI procedure were used to calculate the rSS.

ENDPOINTS. All endpoints were defined in accordance with the Valve Academic Research Consortium 3 criteria.¹⁰ In accordance with the primary endpoint of the PRO-TAVI trial, the primary outcome of the present substudy was a composite of all-cause mortality, myocardial infarction, stroke, and major bleeding at 1 year from randomization. Major bleeding was defined as Valve Academic Research Consortium 3 types 2 to 4 bleeding. Secondary outcomes included, among others, a composite of all-cause mortality, myocardial infarction, and stroke, as well as the individual components of the primary outcome and revascularization. All potential endpoints were adjudicated by an independent clinical event committee blinded to treatment allocation.

STATISTICAL ANALYSIS. For the SS analysis, patients were stratified into 4 subgroups on the basis of the quartile distribution of the SS among included

patients. For the rSS analysis, patients in the PCI group were divided into 2 subgroups using a predefined cutoff of >8 for the rSS.⁹ All time-to-event analyses were conducted in the intention-to-treat population.

Within each subgroup, differences in the primary and secondary outcomes between the deferral and PCI groups were calculated using Cox proportional hazards regression, and HRs with corresponding 95% CIs are reported. Proportional hazard assumptions were tested using Schoenfeld residuals, and results were presented in case of violation. Patients with incomplete follow-up were censored at the day of last known clinical status. Additionally for the SS analysis, HRs were adjusted for the Society of Thoracic Surgeons Predicted Risk of Mortality score. As a sensitivity analysis, HRs for the composite outcomes were reported across SS subgroups using the conventional cutoff values (≤ 22 , 22–32, and > 32). Kaplan-Meier plots were used for the primary outcome within each subgroup, as well as for the composite of all-cause mortality, myocardial infarction, and stroke.

A restricted cubic spline curve was plotted, using Cox proportional hazards model, to evaluate the continuous association between the SS and HR for the primary outcome between the deferral and PCI group, as well as for the composite of all-cause mortality, myocardial infarction, and stroke. Only patients within the 5th and 95th percentile range of the SS distribution were included in this analysis. Natural cubic splines were used with a prespecified 4 degrees of freedom. Two internal knots were located at the 33rd and 67th percentiles of the SS, as well as 2 boundary knots at the 5th and 95th percentiles.

Categorical variables are reported as frequencies and percentages, and differences were tested using the chi-square test. Continuous variables were visually tested for normality using distribution plots. Accordingly, continuous variables are reported as mean $\pm$ SD or median (Q1–Q3). Differences in continuous variables were tested using Student's *t*-test or the Mann-Whitney *U* test. All statistical tests were 2-tailed, and *P* values <0.05 were considered to indicate statistical significance. Analyses were performed using RStudio version 2024.12.1 (Posit).

RESULTS

POPULATION. All 466 patients enrolled in the PRO-TAVI trial were included in the present substudy. Complete 1-year follow-up was available for 465 of

	Total Cohort (N = 466)	SYNTAX Score ≤5 (n = 120)	5 < SYNTAX Score ≤10 (n = 128)	10 < SYNTAX Score ≤17 (n = 109)	SYNTAX Score >17 (n = 109)
Patient characteristics					
Age, y	81 (78-84)	81 (77-84)	81 (78-84)	81 (78-83)	82 (78-84)
Female	166/466 (35.6)	49/120 (40.8)	58/128 (45.3)	36/109 (33.0)	23/109 (21.1)
Body mass index, kg/m ²	25.9 (23.8-29.2)	26.5 (24.0-29.2)	26.3 (24.2-29.7)	25.3 (23.2-29.4)	25.7 (23.9-28.3)
NYHA functional class III/IV	239/466 (51.3)	73/120 (60.8)	66/128 (51.6)	48/109 (44.0)	52/109 (47.7)
Anginal symptoms	188/466 (40.3)	51/120 (42.5)	44/128 (34.4)	48/109 (44.0)	45/109 (41.3)
Frailty ^a	79/466 (17.0)	24/120 (20.0)	23/128 (18.0)	14/109 (12.8)	18/109 (16.5)
Medical history					
Previous CABG	32/466 (6.9)	7/120 (5.8)	10/128 (7.8)	7/109 (6.4)	8/109 (7.3)
Previous PCI	98/466 (21.0)	29/120 (24.2)	26/128 (20.3)	21/109 (19.3)	22/109 (20.2)
Previous MI	103/466 (22.1)	23/120 (19.2)	22/128 (17.2)	28/109 (25.7)	30/109 (27.5)
Previous stroke	41/466 (8.8)	11/120 (9.2)	9/128 (7.0)	9/109 (8.3)	12/109 (11.0)
Peripheral artery disease	81/466 (17.4)	21/120 (17.5)	19/128 (14.8)	22/109 (20.2)	19/109 (17.4)
Atrial fibrillation	162/466 (34.8)	45/120 (37.5)	42/128 (32.8)	34/109 (31.2)	41/109 (37.6)
Diabetes mellitus	150/466 (32.2)	34/120 (28.3)	37/128 (28.9)	34/109 (31.2)	45/109 (41.3)
Oral anticoagulation	169/466 (36.3)	48/120 (40.0)	45/128 (35.2)	35/109 (32.1)	41/109 (37.6)
Risk scores					
STS-PROM	3.1 (1.9-5.0)	3.5 (2.1-6.0)	2.6 (1.7-4.9)	2.9 (1.8-4.5)	3.3 (2.3-5.0)
EuroSCORE II	2.9 (2.0-4.5)	3.0 (1.9-4.5)	3.0 (2.0-4.9)	2.7 (2.0-4.0)	2.9 (2.1-5.0)
Echocardiographic characteristics					
Peak pressure gradient, mm Hg	68 (55-80)	70 (57-84)	68 (59-80)	65 (55-76)	65 (49-77)
Preserved left ventricular ejection fraction (≥50%)	341/466 (73.2)	98/120 (81.7)	92/128 (71.9)	81/109 (74.3)	70/109 (64.2)
Angiographic characteristics					
90% to 99% stenosis	278/466 (59.7)	67/120 (55.8)	63/128 (49.2)	65/109 (59.6)	83/109 (76.1)
Proximal LAD	100/466 (21.5)	0/120 (0)	30/128 (23.4)	33/109 (30.3)	37/109 (33.9)

Values are median (Q1-Q3) or n/N (%). ^aFrailty was assessed using the Edmonton Frailty Scale (range: 0-18), with frailty defined as a score >5.

CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LAD = left anterior descending coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

466 patients (99.8%), with 1 patient lost to follow-up at day 150. The median age was 81 years (Q1-Q3: 78-84 years), and 166 of 466 patients (35.6%) were women. The median Society of Thoracic Surgeons Predicted Risk of Mortality score was 3.1 (Q1-Q3: 1.9-5.0). Baseline characteristics are presented in [Table 1](#), and baseline characteristics of the 4 SS subgroups for the deferral and PCI group are presented in [Supplemental Table 1](#).

A total of 120 of 466 patients (25.8%) had SS ≤5, 128 of 466 patients (27.5%) had SS of >5 to ≤10, 109 of 466 patients (23.3%) had SS of >10 to ≤17, and 109 of 466 (23.3%) patients had SS >17. The distribution of baseline characteristics across these 4 subgroups was heterogeneous. Overall, patients with higher SS were more frequently men and had a higher prevalence of diabetes mellitus. Compared with patients in the SS ≤5 group, those in the SS >17 group less frequently presented with NYHA functional class III or IV symptoms (52 of 109 [47.7%] vs 73 of 120 [60.8%]), less frequently had a preserved left ventricular ejection fraction (70 of 109 [64.2%] vs 98 of 120 [81.7%]), and more frequently demonstrated 90% to 99% coronary stenosis (83 of 109 [76.1%] vs 67 of 120 [55.8%]).

Fluoroscopy time and contrast volume during PCI increased with higher SS categories. Multivessel PCI was performed more frequently in patients in higher SS categories. In addition, balloon-expandable valves were more often implanted in patients with higher SS categories. Use of cerebral embolic protection devices was infrequent overall, with no use in patients with SS >17. Procedural characteristics are presented in [Table 2](#).

OUTCOMES FOR SYNTAX SCORE. The composite outcome of all-cause mortality, myocardial infarction, stroke, and major bleeding did not differ across the 4 SS subgroups and are presented in [Table 3](#) and [Supplemental Figure 1](#). The composite of all-cause mortality, myocardial infarction, and stroke occurred more frequently among patients with SS >17 in the deferral group compared with patients with SS >17 undergoing PCI prior to TAVR (17 of 55 [30.9%] vs 8 of 54 [14.8%]; adjusted HR [HR_{adj}]: 2.43; 95% CI: 1.04-5.64; *P* = 0.04) ([Central Illustration](#)). This difference was driven primarily by higher rates of all-cause mortality (10 of 55 [18.2%] vs 6 of 54 [11.1%]; HR_{adj}: 1.83; 95% CI: 0.66-5.06; *P* = 0.30) and stroke (6 of 55 [10.9%] vs 0 of 54 [0.0%]; HR_{adj} not applicable).

TABLE 2 Procedural Characteristics of the Total Cohort and of the 4 SYNTAX Score Subgroups

	Total Cohort (N = 233)	SYNTAX Score ≤5 (n = 62)	5 < SYNTAX Score ≤10 (n = 62)	10 < SYNTAX Score ≤17 (n = 55)	SYNTAX Score >17 (n = 54)
PCI procedure ^a					
PCI performed	229/233 (98.3)	61/62 (98.4)	61/62 (98.4)	53/55 (96.4)	54/54 (100)
Amount of contrast used, mL	90 (60-126)	75 (50-120)	90 (50-117)	100 (74-143)	100 (73-190)
Fluoroscopy time, min	8.6 (4.1-14.2)	5.0 (3.3-11.9)	6.5 (3.3-11.9)	10.0 (6.1-13.4)	13.4 (8.0-23.3)
Drug-eluting stent	209/229 (91.3)	50/61 (82.0)	56/61 (91.8)	50/53 (94.3)	53/54 (98.1)
Multivessel PCI	63/229 (27.5)	6/61 (9.8)	14/61 (23.0)	19/53 (35.8)	24/54 (44.4)
Residual SYNTAX score	0 (0-6)	0 (0-0)	0 (0-2)	4 (0-8)	7 (3-15)
	Total Cohort (N = 466)	SYNTAX Score ≤5 (n = 120)	5 < SYNTAX Score ≤10 (n = 128)	10 < SYNTAX Score ≤17 (n = 109)	SYNTAX Score >17 (n = 109)
TAVR procedure					
TAVR performed ^b	459/466 (98.5)	119/120 (99.2)	127/128 (99.2)	109/109 (100)	104/109 (95.4)
Transfemoral access route	428/459 (93.2)	110/119 (92.4)	118/127 (92.9)	101/109 (92.7)	99/104 (95.2)
Balloon-expandable valve ^c	242/457 (53.0)	58/118 (49.2)	63/127 (49.6)	56/109 (51.4)	65/103 (63.1)
Cerebral protection	9/459 (2.0)	3/119 (2.5)	4/127 (3.1)	2/109 (1.8)	0/104 (0)
Predilatation	255/459 (55.6)	71/119 (59.7)	65/127 (51.2)	63/109 (57.8)	56/104 (53.8)
Postdilatation	76/459 (16.6)	23/119 (19.3)	20/127 (15.7)	15/109 (13.8)	18/104 (17.3)

Values are n/N (%) or median (Q1-Q3). ^aFour patients did not undergo PCI (1 patient died before PCI, 1 patient chose not to undergo PCI, 1 patient underwent emergent abdominal surgery, and 1 patient had new renal failure). ^bSeven patients did not undergo TAVR (6 died before TAVR, and 1 patient within the deferral group chose not to undergo TAVR). ^cTwo TAVR procedures were not accompanied by the implantation of a transcatheter heart valve because of procedural difficulties.

TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

No significant differences were observed in the other SS subgroups (SS ≤5: 11 of 58 [19.0%] vs 13 of 62 [21.0%] [HR_{adj}: 0.87; 95% CI: 0.39-1.95; *P* = 0.73]; SS >5 to SS ≤10: 12 of 66 [18.2%] vs 10 of 66 [16.1%] [HR_{adj}: 1.12; 95% CI: 0.48-2.60; *P* = 0.79]; SS >10 to SS ≤17: 8 of 54 [14.8%] vs 7 of 55 [12.7%] [HR_{adj}: 1.18; 95% CI: 0.43-3.25; *P* = 0.75]). Kaplan-Meier curves for this ischemic composite are shown in Figure 1.

Major bleeding occurred more frequently in the PCI group within the SS ≤5 subgroup (3 of 58 [5.2%] vs 13 of 62 [21.0%]; HR_{adj}: 0.23; 95% CI: 0.06-0.79; *P* = 0.02). Any bleeding was more frequent in the PCI group across all SS subgroups (SS ≤5: 13 of 58 [22.4%] vs 26 of 62 [41.9%] [HR_{adj}: 0.46; 95% CI: 0.23-0.89; *P* = 0.02]; SS >5 to SS ≤10: 8 of 66 [12.1%] vs 25 of 66 [40.3%] [HR_{adj}: 0.24; 95% CI: 0.11-0.53; *P* < 0.001]; SS >10 to SS ≤17: 11 of 54 [20.4%] vs 21 of 55 [38.2%] [HR_{adj}: 0.46; 95% CI: 0.22-0.95; *P* = 0.03]; SS >17: 8 of 55 [14.5%] vs 26 of 54 [48.1%] [HR_{adj}: 0.26; 95% CI: 0.12-0.58; *P* < 0.001]). No significant differences between the PCI and deferral groups were observed for other outcomes across any SS subgroup. All HR_{adj} are presented in Table 3. HR_{adj} for the composite outcomes between the deferral and PCI groups using the conventional SS cutoffs are presented in Supplemental Table 3. Unadjusted HRs are provided in Supplemental Tables 2 and 3.

When evaluating the SS as a continuous variable in relation to the treatment effect in a purely descriptive manner, no benefit of performing PCI prior to

TAVR, compared with deferral of PCI, was observed for the composite of all-cause mortality, myocardial infarction, stroke, and major bleeding (Figure 2A). No benefit was observed for the composite of all-cause mortality, myocardial infarction, and stroke (Figure 2B). However, a trend toward a more favorable effect of PCI prior to TAVR was observed among patients with the highest SS, with an almost linear pattern across the observed range.

OUTCOMES FOR RESIDUAL SYNTAX SCORE. For the rSS subanalysis, 229 of 233 patients (98.3%) in the PCI group were included. Of the total of 233 patients assigned to PCI prior to TAVR, 3 did not undergo PCI, because of patient preference, emergent abdominal surgery, or new-onset renal failure. One patient died prior to PCI. The median rSS was 0 (Q1-Q3: 0-6). A total of 33 of 299 patients (14.4%) had rSS >8, while 196 of 229 patients (85.5%) had rSS ≤8.

The composite of all-cause mortality, myocardial infarction, stroke, and major bleeding did not differ between patients with rSS >8 and rSS ≤8 (7/33 [21.2%] vs 51/196 [26.0%]; HR: 0.78; 95% CI: 0.35-1.72; *P* = 0.54) (Supplemental Figure 2). No difference was observed for the composite of all-cause mortality, myocardial infarction, and stroke (5 of 33 [15.2%] vs 31 of 196 [15.8%]; HR: 0.97; 95% CI: 0.38-2.50; *P* = 0.96) (Figure 3). Revascularization occurred more frequently in patients with rSS >8 (4 of 33 [12.1%] vs 7 of 196 [3.6%]; HR: 3.58; 95% CI:

TABLE 3 Adjusted HRs of the Outcomes Between the Deferral and PCI Groups Across the 4 SYNTAX Score Subgroups

	SYNTAX Score ≤5 (n = 120) Deferral: n = 58; PCI: n = 62	5 < SYNTAX Score ≤10 (n = 128) Deferral: n = 66; PCI: n = 62	10 < SYNTAX Score ≤17 (n = 109) Deferral: n = 54; PCI: n = 55	SYNTAX Score >17 (n = 109) Deferral: n = 55; PCI: n = 54
Primary outcome				
All-cause mortality, myocardial infarction, stroke, or major bleeding	13; 19 0.66 (0.33-1.34)	14; 15 0.81 (0.39-1.67)	11; 12 0.90 (0.40-2.04) ^d	18; 14 1.34 (0.67-2.69)
Secondary outcomes				
All-cause mortality, myocardial infarction, or stroke	11; 13 0.87 (0.39-1.95)	12; 10 1.12 (0.48-2.60)	8; 7 1.18 (0.43-3.25)	17; 8 2.43 (1.04-5.64)
All-cause mortality	4; 8 0.53 (0.16-1.78)	9; 6 1.43 (0.51-4.03)	5; 5 1.03 (0.30-3.57)	10; 6 1.83 (0.66-5.06)
Cardiovascular mortality	2; 5 0.42 (0.08-2.16)	4; 6 0.63 (0.18-2.23)	3; 3 1.03 (0.21-5.11)	8; 2 4.56 (0.96-21.56)
Myocardial infarction	3; 2 1.53 (0.26-9.18)	5; 6 0.75 (0.23-2.48)	1; 1 1.02 (0.06-16.28)	4; 3 1.48 (0.33-6.64)
Stroke	4; 5 0.90 (0.24-3.37)	2; 3 0.63 (0.10-3.75)	2; 2 1.14 (0.16-8.17)	6; 0 NA
Major bleeding (VARC-3 types II-IV)	3; 13 0.23 (0.06-0.79)	3; 7 0.38 (0.10-1.47)	4; 6 0.66 (0.19-2.34)	4; 8 0.51 (0.15-1.70)
Any bleeding (VARC-3 types I-IV)	13; 26 0.46 (0.23-0.89)	8; 25 0.24 (0.11-0.53)	11; 21 0.46 (0.22-0.95)	8; 26 0.26 (0.12-0.58)
I	10; 16 0.62 (0.28-1.37)	5; 21 0.19 (0.07-0.50)	7; 17 0.37 (0.15-0.90)	4; 19 0.18 (0.06-0.54)
II	1; 6 0.17 (0.02-1.44)	1; 3 0.31 (0.03-2.96)	1; 3 0.33 (0.03-3.17)	1; 3 0.36 (0.04-3.45)
III	2; 7 0.30 (0.06-1.44)	2; 4 0.45 (0.08-2.48)	2; 2 1.02 (0.14-7.23) ^d	2; 5 0.40 (0.08-2.09)
IV	0; 2 NA	0; 0 NA	1; 1 1.10 (0.07-17.76)	1; 0 NA
Revascularization ^a	7; 3 2.55 (0.66-9.88)	7; 2 3.39 (0.70-16.34)	2; 1 2.06 (0.19-22.72)	8; 5 1.54 (0.50-4.73) ^d
Urgent revascularization ^b	3; 2 1.53 (0.26-9.18)	5; 1 4.78 (0.56-41.04)	1; 1 1.02 (0.06-16.30)	4; 3 1.47 (0.33-6.58)
Study lesion revascularization ^c	5; 1 5.69 (0.66-49.03)	4; 2 1.86 (0.34-10.20)	2; 0 NA	7; 4 1.75 (0.51-6.00)
Hospitalization	20; 25 0.74 (0.41-1.34)	20; 16 1.21 (0.62-2.33)	15; 19 0.74 (0.38-1.46)	17; 19 0.92 (0.48-1.77)

Values are number of events in deferral group; number of events in PCI group, with HR (95% CI) beneath. The number of events was based on time-to-first event analyses. ^aExcluding index PCI procedures (1 procedure because of protocol violation in the deferral group, 229 procedures in the PCI-before-TAVR group). ^bUrgent revascularization included all procedures that were done in an urgent, an emergent, or a salvage setting, adjudicated in accordance with the American College of Cardiology's and American Heart Association's Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. ^cStudy lesion was defined as the study segment including the 5-mm margin proximal and distal to stent. In the deferral group, study lesion revascularization was defined as a PCI of the study lesion. In the PCI group, study lesion revascularization was defined as (recurrent) PCI of the study lesion. ^dThe HR should be interpreted as exploratory given that the proportional hazard assumption was violated.

NA = not applicable; VARC-3 = Valve Academic Research Consortium 3; other abbreviations as in [Table 1](#).

1.05-12.22; $P = 0.04$), as did urgent revascularization and study lesion revascularization. No significant differences were observed for the other outcomes. Number of events and HRs for all outcomes are presented in [Supplemental Table 4](#).

DISCUSSION

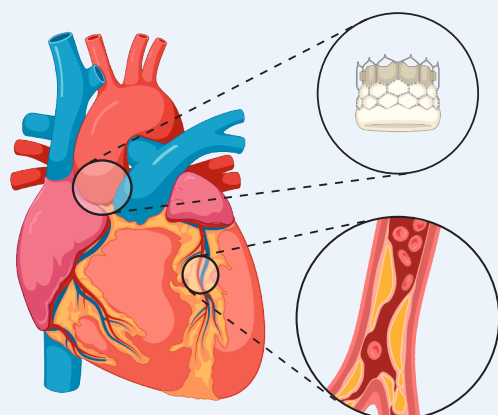
The main findings of the present substudy of the PRO-TAVI trial are that: 1) deferral of PCI prior to TAVR appeared safe and reduced bleeding risk in patients across all SS categories; 2) patients with SS >17 who did not undergo PCI reported higher rates of the composite of all-cause mortality, myocardial infarction, and stroke compared with those undergoing PCI before TAVR; and 3) incomplete

revascularization, defined as rSS >8, increased the rates of repeat revascularization.

EXTENT OF CORONARY ARTERY DISEASE IN TAVR PATIENTS. The SS is an angiographic tool that quantifies the anatomical complexity of coronary artery disease on the basis of various lesion characteristics, such as location, length, and calcification, and does not depend on grade of stenosis. Several single-center observational studies have investigated the impact of the SS on clinical outcomes in patients undergoing TAVR. Most studies have reported an association between increased mortality and intermediate to severe coronary artery disease complexity, defined as SS >22.^{5,6,11,12} However, other observational studies have failed to demonstrated a

CENTRAL ILLUSTRATION Overview and Main Findings of the PRO-TAVI Substudy

Impact of Extent of Coronary Artery Disease in Patients Undergoing TAVR



PRO-TAVI Trial

Patients with concomitant CAD
undergoing TAVR
(n = 466)

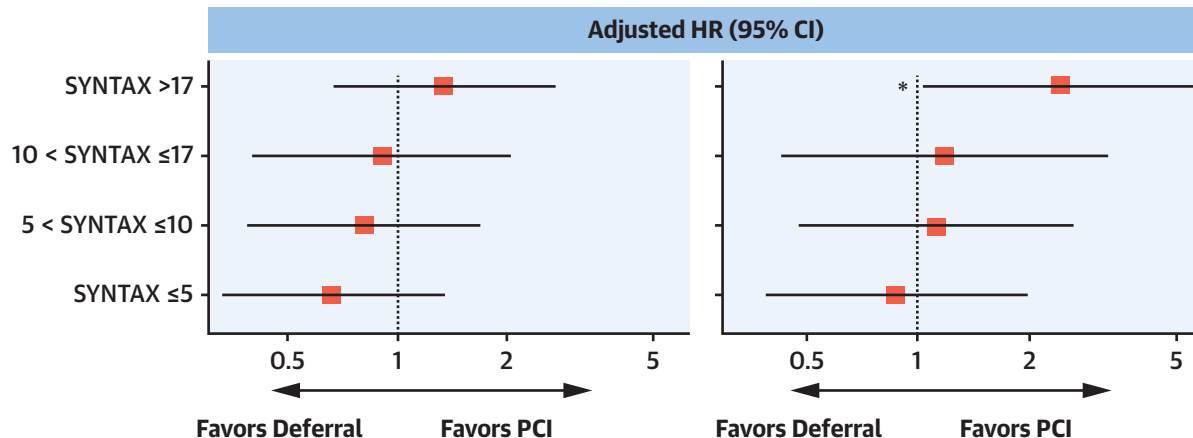
Deferral of PCI
(n = 233)

PCI before TAVR
(n = 233)

Study aim
Evaluating the association of extent of CAD
with clinical outcomes in patients with
concomitant CAD undergoing TAVR

All-Cause Mortality, Myocardial Infarction, Stroke, and Major Bleeding

All-Cause Mortality, Myocardial Infarction, and Stroke

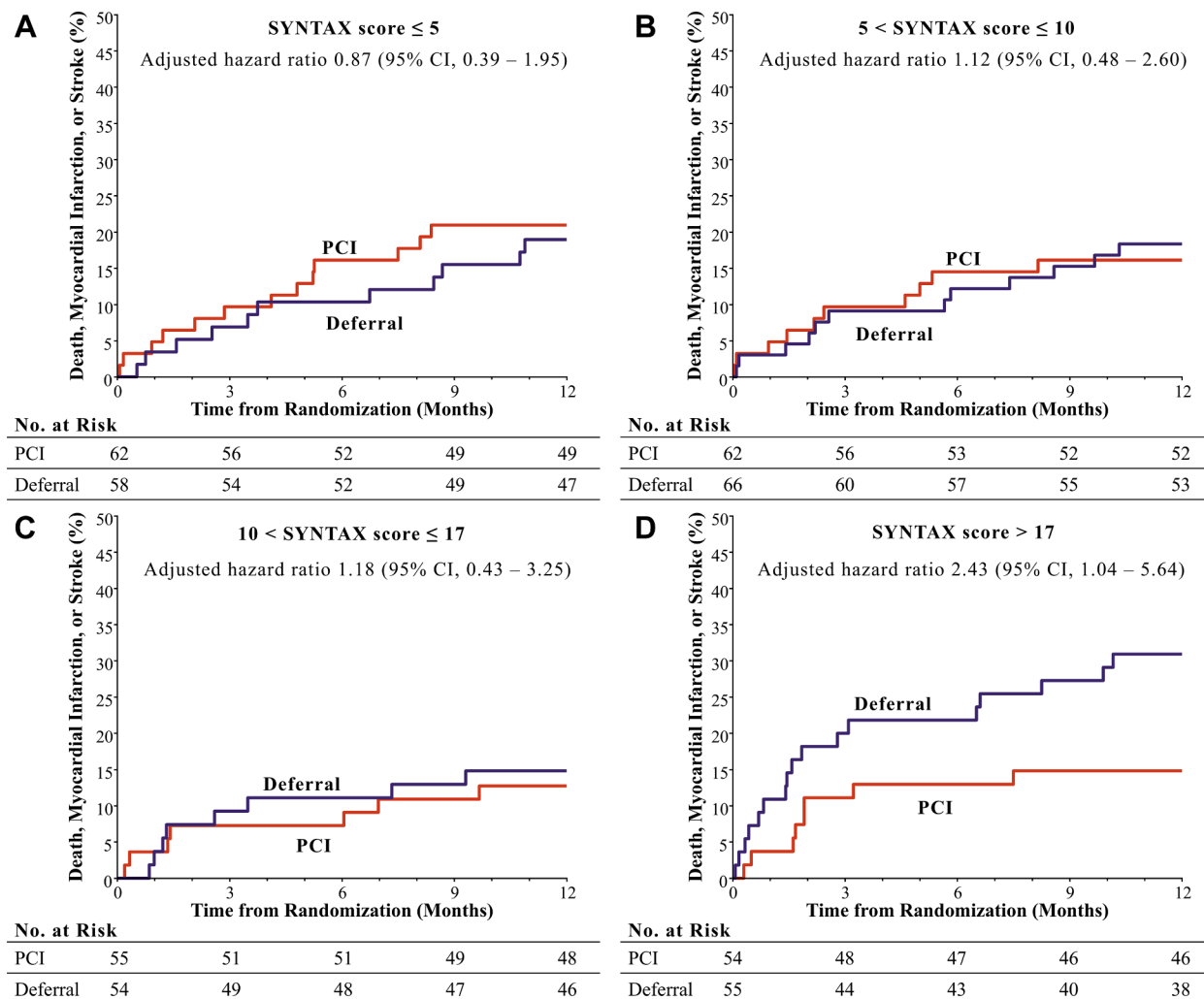


- In patients undergoing TAVR with concomitant CAD, an initial conservative strategy reduced the risk of bleeding and appeared safe in patients across all SYNTAX scores.
- Patients with a SYNTAX score >17 had a lower incidence of the composite of all-cause mortality, myocardial infarction, and stroke when undergoing PCI before TAVR.

Broeze GM, et al. JACC Cardiovasc Interv. 2026;19(19):2619-2630.

CAD = coronary artery disease; PCI = percutaneous coronary intervention; PRO-TAVI = Percutaneous Coronary Intervention Before Transcatheter Aortic Valve Implantation; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TAVR = transcatheter aortic valve replacement.

FIGURE 1 Kaplan-Meier Curves for the Ischemic Composite Outcome Across SYNTAX Score Categories



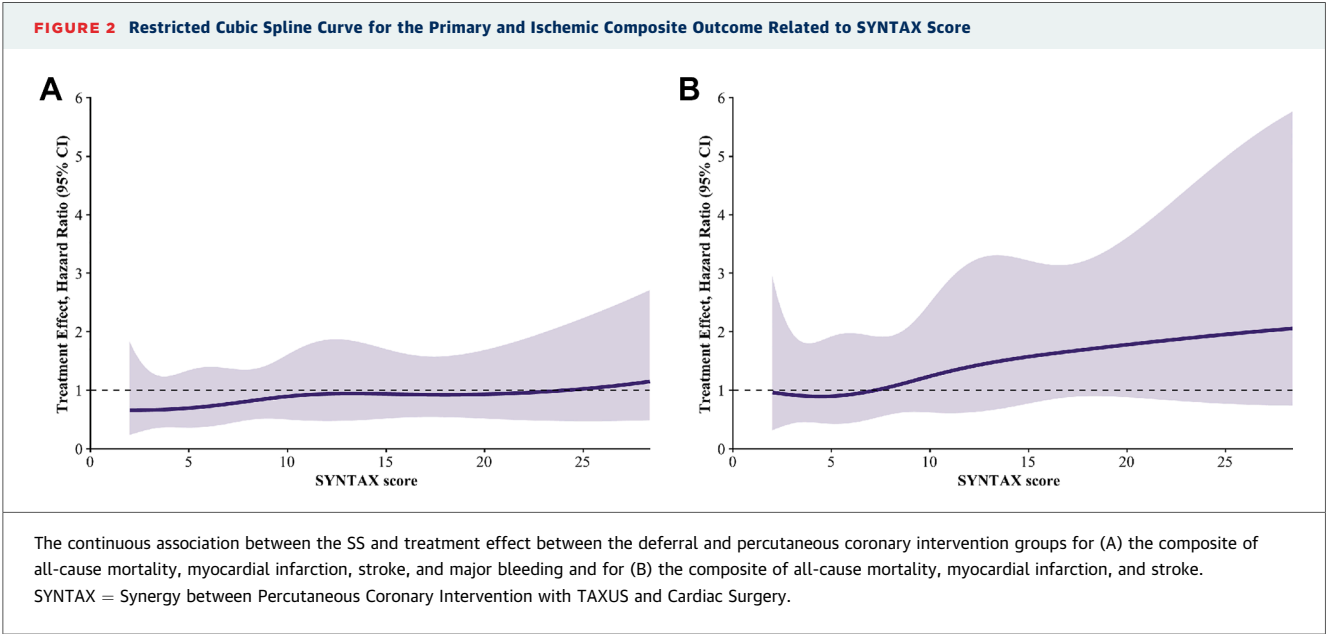
The outcome is a composite of all-cause mortality, myocardial infarction, and stroke at 1 year after randomization. Subgroups are based on quartile distribution of the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score. PCI = percutaneous coronary intervention.

significant relationship between SS and mortality.^{13,14} No differences in stroke or myocardial infarction have been observed in all studies. It is important to note that these studies differ in PCI strategies.

Importantly, a meta-analysis showed that the TAVR population is characterized by a relatively low coronary artery disease complexity, with a median SS of 14.¹² The NOTION-3 (Nordic Aortic Valve Intervention-3) trial reported a median SS of 9,¹⁵ whereas patients in the PRO-TAVI trial exhibited a slighter higher median SS of 10. These findings suggest that the conventional SS stratification thresholds (≤ 22 , 23–32, and > 32) are less applicable in the

TAVR population. In this context, in the present study we evaluated the SS using quartiles of this score within the PRO-TAVI cohort, aiming to provide a more applicable assessment of the impact of the extent of coronary artery disease on clinical outcomes.

In the present substudy of the PRO-TAVI trial, no differences were found in the primary composite outcome across all SS categories, consisting of all-cause mortality, myocardial infarction, stroke, and major bleeding. Additionally, bleeding rates were lower in the deferral group across all SS categories. However, within the SS > 17 subgroup, the composite of all-cause mortality, myocardial infarction, and

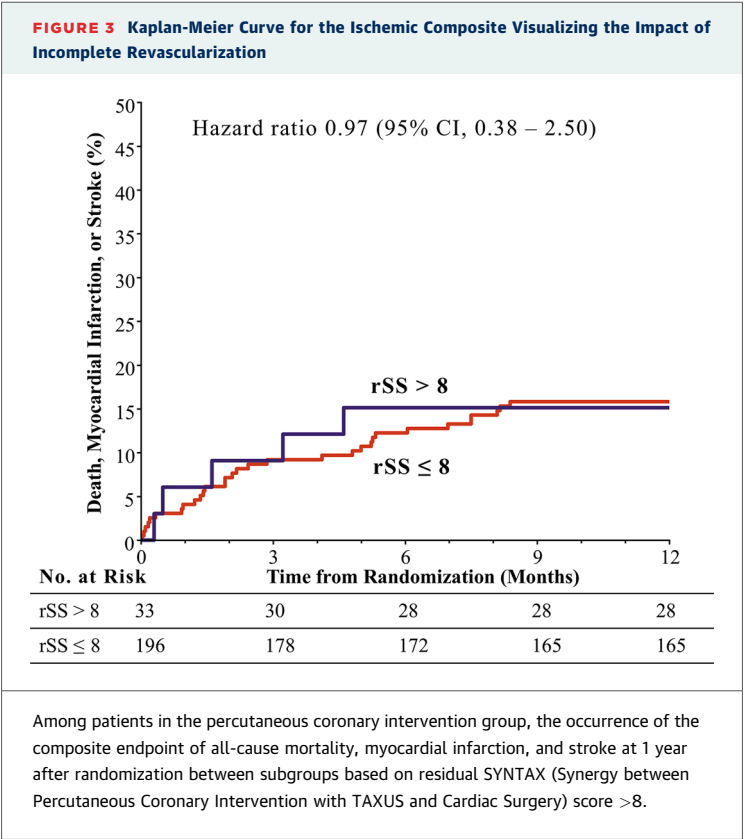


stroke occurred more often in the deferral group. This difference was driven primarily by all-cause mortality and stroke, without an increased risk for myocardial infarction with deferral of PCI. These findings may reflect the potential benefit of dual antiplatelet therapy in patients with high atherosclerotic burden. Although this observation may support a strategy of PCI in patients with more complex coronary artery disease, it should be interpreted with caution as the current substudy was a post hoc analysis. Therefore, confirmation in adequately powered randomized controlled trials is warranted.

The NOTION-3 trial, alongside the PRO-TAVI trial, is the other randomized controlled trial that also investigated the impact of PCI deferral. In short, the NOTION-3 trial demonstrated the superiority for PCI on the basis of a composite primary endpoint of all-cause mortality, myocardial infarction, and urgent revascularization at a median follow-up of 2 years.¹⁵ No significant differences were observed between patients with SS ≤ 9 and those with SS > 9 , with event rates being nearly identical between treatment groups. However, these analyses were only performed for the primary composite endpoint, and more granular stratification according to SS was not yet assessed. An important methodological difference compared with the PRO-TAVI trial is that NOTION-3 measured fractional flow reserve for all lesions $< 90\%$ stenosis on visual estimation, whereas in PRO-TAVI, physiology assessment was used in lesions with 40% to 70% stenosis on visual estimation. Nevertheless, the proportion of patients with

coronary artery lesions exceeding 90% stenosis was comparable between the 2 trials.

IMPACT OF INCOMPLETE REVASCULARIZATION ON CLINICAL OUTCOMES. Many observational studies have reported that incomplete revascularization,



commonly defined as rSS >8, is associated with increased mortality.^{12,13,16,17} No differences were observed in other clinical outcomes. In contrast, results of the current substudy do not support these findings, neither for all-cause mortality nor cardiovascular mortality. However, higher rates of repeat revascularization were observed in the patients with incomplete revascularization, suggesting that these patients remain symptomatic or experience a more rapid recurrence of symptoms. Despite potential coronary access difficulties related to the transcatheter heart valve, repeat interventions were technically feasible in all patients and were performed without major complications.

CLINICAL IMPLICATIONS. The findings of the present substudy of the PRO-TAVI trial support an initial conservative strategy of PCI deferral in patients undergoing TAVR across all SS categories. Deferral of PCI appears to be safe in these patients and reduces the risk for bleeding. However, patients with SS >17 undergoing PCI before TAVR had a lower incidence of the composite outcome of all-cause mortality, myocardial infarction, and stroke, suggesting that an individualized assessment by the local heart team on the basis of the extent of coronary artery disease is warranted. These findings, however, originate from exploratory subgroup analyses and should therefore be interpreted cautiously.

Optimal timing of the PCI procedure in patients who may benefit is still to be elucidated. Performing PCI before TAVR may increase bleeding risk because of dual antiplatelet therapy,¹⁸ highlighting the need to balance ischemic and bleeding risks when planning PCI in relation to the TAVR procedure. Data from trials, such as the ongoing TAVI PCI (Optimal Timing of Transcatheter Aortic Valve Implantation and Percutaneous Coronary Intervention) trial, may further inform the optimal timing of PCI.¹⁹ In addition, evidence from the ASCOP (Aortic Stenosis With Complex PCI) registry, which evaluated the association between timing of high-risk PCI with outcomes in patients with severe aortic stenosis undergoing TAVR, suggested a strategy of staged PCI before TAVR, as it was associated with better clinical outcomes compared with a concomitant strategy.²⁰

As the reduction in major bleeding reached statistical significance only in patients with SS ≤5, bleeding burden due to dual antiplatelet therapy may be most clinically relevant in those with less complex coronary artery disease. In contrast, patients with more extensive coronary disease may

potentially derive more net clinical benefit from PCI through mitigation of ischemic risk. This interpretation remains speculative and should be viewed in the context of subgroup analyses with limited power.

In addition, the higher use of short-frame balloon-expandable valves in patients with higher SS likely reflects procedural planning aimed at preserving coronary access in the context of more complex coronary anatomy.

In patients with severe aortic stenosis and severe concomitant coronary artery disease, the optimal revascularization strategy remains uncertain. Although coronary artery bypass grafting is traditionally preferred, it is often not feasible in older patients with multiple comorbidities. TCW (Transcatheter Valve and Vessels Trial) suggested favorable outcomes for PCI but was underpowered because of early termination.²¹ Therefore, further randomized data are needed.

In the present substudy, incomplete revascularization did not increase the risk for mortality, myocardial, stroke, and bleeding. However, it was linked to a higher need for repeat revascularization.

STUDY LIMITATIONS. First, patients with unprotected left main coronary artery disease were excluded from the PRO-TAVI trial. The presence of left main coronary artery disease strongly influences the SS. Therefore, the results of this substudy cannot be extrapolated to this population. However, a previous meta-analysis reported a median SS of 14, which is only modestly higher than the median SS of 10 observed in the present study, despite exclusion of left main coronary artery disease.¹²

Second, stratification into 4 subgroups reduced statistical power, increasing the risk for both type I and type II errors. In addition, baseline imbalances between subgroups may have influenced the observed outcomes, as for example illustrated by differences in outcomes between frail and nonfrail patients in the NOTION-3 trial.²²

Third, the present substudy was a post hoc analysis and was not prespecified. Consequently, the results should be interpreted with caution and considered hypothesis-generating.

Finally, the analysis was restricted to outcomes up to 1 year after randomization, and longer term effects remain unknown.

CONCLUSIONS

In patients undergoing TAVR with concomitant coronary artery disease, an initial conservative strategy

reduces the risk for bleeding and appears safe across all SS categories. Patients with higher coronary artery disease complexity (SS >17) had a lower incidence of the composite of all-cause mortality, myocardial infarction, and stroke when undergoing PCI before TAVR compared with those in whom PCI was deferred.

DATA SHARING Data collected for this substudy of the PRO-TAVI trial will not be made publicly available. The study team will consider reasonable collaboration requests, which can be directed to the corresponding author.

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PERSPECTIVES

WHAT IS KNOWN? The recent PRO-TAVI trial indicated that deferral of PCI is a safe approach in patients with concomitant coronary artery disease undergoing TAVR.

WHAT IS NEW? In this substudy, deferral of PCI was associated with reduced bleeding risk and appeared safe across all extents of coronary artery disease. In patients with more complex coronary artery disease, deferral of PCI was associated with a higher risk for ischemic events.

WHAT IS NEXT? These findings suggest that the extent of coronary artery disease should be incorporated into decision-making for TAVR patients with concomitant coronary disease, but confirmation from randomized studies is needed.

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KEY WORDS coronary artery disease, percutaneous coronary intervention, transcatheter aortic valve replacement

APPENDIX For supplemental tables and figures and a list of the PRO-TAVI investigators, please see the online version of this paper.