

Original article

Clinical impact of complex percutaneous coronary intervention in the pre-TAVR workup



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ABSTRACT

Introduction and objectives: In patients undergoing percutaneous coronary intervention (PCI) in the workup pre-transcatheter aortic valve replacement (TAVR), the clinical impact of coronary revascularization complexity remains unknown. This study sought to examine the impact of PCI complexity on clinical outcomes after TAVR in patients undergoing PCI in the preprocedural workup.

Methods: This was a multicenter study including consecutive patients scheduled for TAVR with concomitant significant coronary artery disease. Complex PCI was defined as having at least 1 of the following features: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length > 60 mm, or chronic total occlusion. The rates of major adverse cardiac events (MACE), including cardiovascular mortality, myocardial infarction, and coronary revascularization were evaluated.

Results: A total of 1550 patients were included, of which 454 (29.3%) underwent complex PCI in the pre-TAVR workup. After a median follow-up period of 2 [1–3] years after TAVR, the incidence of MACE was 9.6 events per 100 patients-years. Complex PCI significantly increased the risk of cardiac death (HR, 1.44; 95%CI, 1.01–2.07), nonperiprocedural myocardial infarction (HR, 1.52; 95%CI, 1.04–2.21), and coronary revascularization (HR, 2.46; 95%CI, 1.44–4.20). In addition, PCI complexity was identified as an independent predictor of MACE after TAVR (HR, 1.31; 95%CI, 1.01–1.71; $P = .042$).

Conclusions: In TAVR candidates with significant coronary artery disease requiring percutaneous treatment, complex revascularization was associated with a higher risk of MACE. The degree of procedural complexity should be considered a strong determinant of prognosis in the PCI-TAVR population.

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Impacto de la intervención coronaria percutánea compleja en el estudio previo al TAVI

RESUMEN

Palabras clave:

Implante percutáneo de válvula aórtica
Intervención coronaria percutánea
TAVI
ICP
ICP compleja

Introducción y objetivos: Se desconoce el impacto pronóstico asociado con la complejidad de la revascularización coronaria de pacientes que se someten a una intervención coronaria percutánea (ICP) durante el estudio previo al implante percutáneo de válvula aórtica (TAVI). El objetivo de este estudio es evaluar el impacto pronóstico de una ICP compleja realizada durante el estudio pre-TAVI.

Methods: Estudio multicéntrico que incluye a pacientes consecutivos sometidos a TAVI a quienes se había realizado una angioplastia en los 3 meses previos al procedimiento. La ICP se clasificó como compleja cuando cumplía al menos 1 de los siguientes criterios: ≥ 3 vasos tratados, ≥ 3 stents implantados, ≥ 3 lesiones tratadas, bifurcación tratada con 2 stents, más de 60 mm de stent implantados u oclusión crónica total. Se evaluó la tasa de eventos adversos cardíacos mayores (MACE): mortalidad cardiovascular, infarto y necesidad de nueva revascularización coronaria.

Resultados: Se incluyó a 1.550 pacientes sometidos a ICP; 454 (29,3%) de ellas eran ICP complejas. A los 2 años, la incidencia de MACE fue de 9,6 eventos cada 100 pacientes-año. La ICP compleja se asoció con mayor riesgo de muerte cardiovascular (HR = 1,44; IC95%, 1,01–2,07), infarto de miocardio no relacionado con el procedimiento (HR = 1,52; IC95%, 1,04–2,21) y revascularización coronaria (HR = 2,46; IC9%, 1,44–4,20). Asimismo, la ICP compleja se asoció con mayor riesgo de MACE tras el TAVI (HR = 1,31; IC95%, 1,01–1,71; $p = .042$).

Conclusiones: En candidatos a TAVI con enfermedad coronaria significativa, una revascularización compleja se asoció con mayor riesgo de eventos adversos.

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Abbreviations

AS: aortic stenosis
CABG: coronary artery bypass grafting
CAD: coronary artery disease
MACE: major adverse cardiac events
PCI: percutaneous coronary intervention
TAVR: transcatheter aortic valve replacement

INTRODUCTION

The prevalence of coronary artery disease (CAD) in the transcatheter aortic valve replacement (TAVR) population is fairly high, with up to 25% of TAVR candidates undergoing percutaneous coronary intervention (PCI) as a part of the preprocedural workup or at the time of the TAVR procedure.¹ The need for coronary revascularization in TAVR patients remains controversial in such cases, due to the inconsistency of the available evidence, mainly based on nonrandomized data.²

Owing to the shared pathophysiology of aortic stenosis (AS) and CAD, TAVR recipients frequently exhibit multivessel disease and complex coronary lesions.³ Although the presence of concomitant complex CAD has been a common exclusion criterion in most randomized trials comparing TAVR vs surgical aortic valve replacement, evidence from observational studies suggests that the anatomical complexity of CAD and completeness of coronary revascularization might have an impact on the clinical outcomes following TAVR.^{4,5}

Advanced CAD and a challenging subset of lesions usually translate into more complex revascularization strategies. In the TAVR setting, a complex coronary anatomy (SYNTAX score > 22) has been associated with an increased risk of all-cause and cardiovascular mortality at 5-year follow-up.⁶ However, the impact of the complexity of percutaneous revascularization in this population remains largely unknown. Therefore, the aim of the

present study was to evaluate, in a large cohort of patients undergoing PCI during pre-TAVR workup, the impact of PCI complexity on long-term outcomes after TAVR.

METHODS

This multicenter study included consecutive patients with severe AS and concomitant CAD who underwent a PCI as part of their pre-TAVR workup between 2007 and 2022. Data were derived from 15 centers in Canada, Europe, and Brazil. The study was approved by the ethics committee of each participating center and all patients provided informed consent for the procedures.

PCI was performed within 3 months before TAVR or at the time of the TAVR procedure. The management of CAD, including PCI strategy, the use of functional invasive tests for myocardial ischemia and intravascular ultrasound, and duration of antiplatelet therapy were left to the discretion of the physician responsible for the procedure. Significant CAD was assessed either by angiographic assessment ($\geq 70\%$ stenosis in an epicardial coronary vessel or $\geq 50\%$ left main artery stenosis) or fractional flow reserve (≤ 0.80). Revascularization was considered complete when all significant lesions in vessels > 2 mm diameter had been successfully treated. The indications for TAVR, device type and procedural approach were assessed by each Heart Team based on an extensive clinical and anatomical preoperative assessment. The transfemoral approach was the default choice, and alternative access was reserved for patients with unfavorable iliofemoral anatomy.

Data collection and study definitions

Baseline, procedural, and follow-up data were prospectively collected in a dedicated database. Clinical follow-up was performed in each participating center at 1 and 12 months post-TAVR,

and yearly thereafter, either by a medical visit or by telephone. The patient's vital status was updated at each medical contact, recording the date of the last contact for each patient.

Complex PCI included interventions with at least 1 of the following features: 3 vessels treated, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation with 2 stents implanted, total stent length > 60 mm, or chronic total occlusion as target lesion.⁷ The information on the PCI procedure was obtained by procedural reports which were revised by 2 interventional cardiologists.

Clinical outcomes

The primary outcome was a composite of major adverse cardiac events (MACE), including cardiac death, nonprocedural myocardial infarction, and need for new coronary revascularization at follow-up. The secondary outcomes included the individual components of the combined primary endpoint, all-cause death, definite or probable stent thrombosis or restenosis, stroke, and bleeding. All adverse events were collected and adjudicated according to Valve Academic Research Consortium-2 criteria and acute coronary syndrome guidelines.^{8,9}

Statistical analysis

Qualitative variables were reported as percentages and continuous data as mean $\pm$ standard deviation or median (interquartile range [IQR]), depending on their distribution. Continuous variables were compared using the Student t-test (2-tailed) or Mann-Whitney U rank sum test, as appropriate. Qualitative variables were

compared with the chi-square or Fisher exact tests. Survival curves were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Cox multivariable regression analysis was performed to identify the independent predictors of MACE and all-cause and cardiovascular mortality in the whole PCI-TAVR cohort. Variables with clinical interest and with $P < .10$ on the univariable analysis were entered in a multivariable analysis. The multivariable analysis was performed using backward stepwise Cox regression. All analyses were performed using a hierarchical method to account for between-center variability. A 2-sided alpha level of 0.05 was used for all statistical testing. All statistical analyses were performed using SAS version 9.4 (SAS Institute, United States).

RESULTS

A total of 1550 patients treated with PCI in the work-up pre-TAVR were included. Among them, 454 (29.3%) had at least 1 of the complex PCI criteria. Baseline clinical characteristics according to procedural complexity are reported in [table 1](#). The mean age of the patients was 81.2 ± 7 years, 42.0% were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 6.1% [3.1% to 6.9%]. Patients who underwent complex PCI were more frequently male and exhibited higher rates of previous PCI and chronic obstructive pulmonary disease.

Procedural characteristics (for PCI and TAVR), and in-hospital outcomes of the study population stratified by PCI complexity are shown in [table 2](#) and [table 3](#). The median time between PCI and TAVR was 31 [8 to 68] days. Most (94.3%) PCI procedures were staged before TAVR, and a minority (5.7%) were performed

Table 1
Baseline characteristics according to PCI complexity

	Overall (n = 1550)	Complex PCI (n = 454)	Noncomplex PCI (n = 1096)	P
<i>Baseline characteristics</i>				
Age, y	81.2 $\pm$ 7.4	80.9 $\pm$ 7.4	81.3 $\pm$ 7.4	.322
Female	651 (42.0)	161 (35.5)	490 (44.7)	< .001
BMI, kg/m ²	27.2 $\pm$ 5.1	27.5 $\pm$ 5.6	27.1 $\pm$ 4.9	.195
Hypertension	1301 (83.9)	391 (86.1)	910 (83.0)	.131
Diabetes Mellitus	569 (36.7)	164 (36.1)	405 (36.9)	.758
History of smoking	140 (9.6)	43 (9.5)	97 (8.9)	.805
Previous MI	361 (23.4)	118 (25.9)	243 (22.2)	.116
Previous PCI	1052 (68.1)	332 (73.1)	720 (65.7)	.006
Previous CABG	215 (13.9)	71 (15.7)	144 (13.1)	.199
Peripheral artery disease	369 (23.9)	116 (25.5)	253 (23.1)	.482
COPD	318 (20.6)	108 (23.8)	210 (19.2)	0.038
Atrial fibrillation or flutter	410 (26.5)	127 (28.0)	283 (25.8)	.478
Chronic renal disease (eGFR (< 60 mL/min))	845 (54.5)	235 (51.8)	610 (55.7)	.161
NYHA class III/IV	1081 (12.0)	325 (71.6)	756 (68.9)	.309
Previous pacemaker	186 (12.0)	53 (11.7)	133 (12.2)	.801
STS-PROM	6.1 $\pm$ 6.5	6.2 $\pm$ 8.9	6.0 $\pm$ 5.1	.622
<i>Echocardiography findings</i>				
LVEF, %	54.3 $\pm$ 13.1	53.2 $\pm$ 12.9	54.7 $\pm$ 13.1	.041
Mean aortic gradient, mmHg	44.2 $\pm$ 14.7	42.2 $\pm$ 14.8	44.9 $\pm$ 14.7	.001
Aortic valve area, cm ²	0.69 $\pm$ 0.21	0.71 $\pm$ 0.22	0.68 $\pm$ 0.20	.046

BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Data are expressed as mean $\pm$ SD, n (%).

Table 2

Angiographic characteristics of coronary angiograms and PCI performed before TAVR according to PCI complexity

	Overall (n = 1550)	Complex PCI (n = 454)	Noncomplex PCI (n = 1096)	P
<i>Vessel disease</i>				
1	750 (48.4)	93 (20.5)	657 (59.9)	< .001
2	501 (32.3)	188 (41.4)	313 (28.6)	
3	299 (19.3)	173 (38.1)	126 (11.5)	
<i>Number of vessels treated</i>				
1	1082 (69.8)	151 (33.3)	931 (84.9)	< .001
2	384 (24.8)	219 (48.2)	165 (15.1)	
3	84 (5.4)	84 (18.5)	0 (0)	
<i>PCI distribution</i>				
LM	249 (16.1)	106 (23.4)	143 (13.1)	< .001
LAD	945 (60.9)	347 (76.4)	598 (54.6)	< .001
LCx	652 (42.1)	267 (58.8)	385 (35.1)	< .001
RCA	808 (52.1)	289 (63.7)	519 (47.4)	< .001
SVG	95 (6.1)	37 (8.2)	58 (5.3)	.033
LIMA	19 (1.2)	9 (1.9)	10 (0.9)	.082
<i>Number of lesions treated</i>				
		2.3 ± 0.9	1.2 ± 0.4	< .001
SYNTAX score	12.1 ± 9.0	19.2 ± 9.7	9.7 ± 7.4	< .001
<i>PCI timing</i>				
Staged	1461 (94.3)	442 (97.4)	1019 (92.9)	< .001
Concomitant	89 (5.7)	12 (2.6)	77 (7.0)	
Complete revascularization	1148 (74.1)	326 (71.8)	822 (75.0)	.192
Residual SYNTAX score	2.6 ± 5.3	3.0 ± 5.8	2.4 ± 5.2	< .001
<i>Periprocedural complications</i>				
Major/life-threatening bleeding	53 (3.4)	18 (3.9)	35 (3.2)	.449
Stroke	3 (0.2)	0 (0)	3 (0.3)	.560
Heart failure	45 (2.9)	21 (4.6)	24 (2.3)	.013
Acute kidney injury	72 (4.7)	26 (5.7)	46 (4.2)	.195
Bifurcation	461 (29.7)	226 (49.8)	235 (21.4)	< .001
Ostial location	403 (26.0)	173 (38.1)	230 (20.9)	< .001
Calcification	761 (49.1)	291 (64.1)	470 (42.9)	< .001
Chronic total occlusion	96 (6.2)	96 (21.2)	0 (0)	< .001
Use of FFR	86 (5.6)	31 (6.8)	55 (5.0)	.157
Use of cutting balloon	138 (8.9)	52 (11.5)	86 (7.9)	.023
Use of rotational atherectomy	111 (7.2)	65 (14.3)	46 (4.2)	< .001
<i>Device</i>				
DES	1242 (80.1)	405 (89.2)	837 (76.4)	< .001
BMS	309 (19.9)	66 (14.5)	243 (22.2)	< .001
BRS	1 (0.1)	0 (0)	1 (0.1)	.999
DEB	16 (1.0)	3 (0.7)	13 (1.2)	.422
POBA	21 (1.4)	2 (0.4)	19 (1.7)	.045
Number of stents implanted	1.79 ± 1.14	3.18 ± 1.10	1.22 ± 0.48	< .001

BMS, bare-metal stent; BRS, bioresorbable scaffold; DEB, drug-eluting balloon; DES, drug-eluting stent; FFR, fractional flow reserve; LAD, left anterior descending artery; LCx, left circumflex artery; LIMA, left internal mammary artery; LM, left main artery; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; RCA, right coronary artery; SVG, saphenous vein graft; SYNTAX, SYnergy between PCI with TAXUS and Cardiac Surgery; TAVR, transcatheter aortic valve replacement.

Data are expressed as n (%) or mean ± SD.

simultaneously (at the same time as TAVR). Complete revascularization was achieved in 1148 (74.1%) patients. Procedural PCI features were largely unbalanced between complex and noncomplex PCI groups. Patients undergoing complex PCI exhibited more advanced CAD, as evidenced by a higher number of diseased and treated vessels, a higher baseline and residual mean SYNTAX score, a higher prevalence of chronic total occlusions, coronary calcification, ostial coronary lesions, and bifurcation lesions. The frequency of the complex PCI components in the overall population is shown in [figure 1](#). Rates of periprocedural PCI complications did not differ

between complex and noncomplex PCI, except for a higher occurrence of heart failure in the complex PCI group (4.6% vs 2.3%; $P = .013$).

In TAVR procedures, transfemoral access was the approach of choice for most patients (79.2%). The adoption of nontransfemoral access was most frequent in the complex PCI group (26.2% vs 18.6%; $P < .001$). Balloon- and self-expanding transcatheter valves were used in 987 (63.7%) and 562 (36.3%) patients, respectively. No differences were observed between the 2 groups regarding postprocedural TAVR complications. At hospital discharge, 58.3%

Table 3

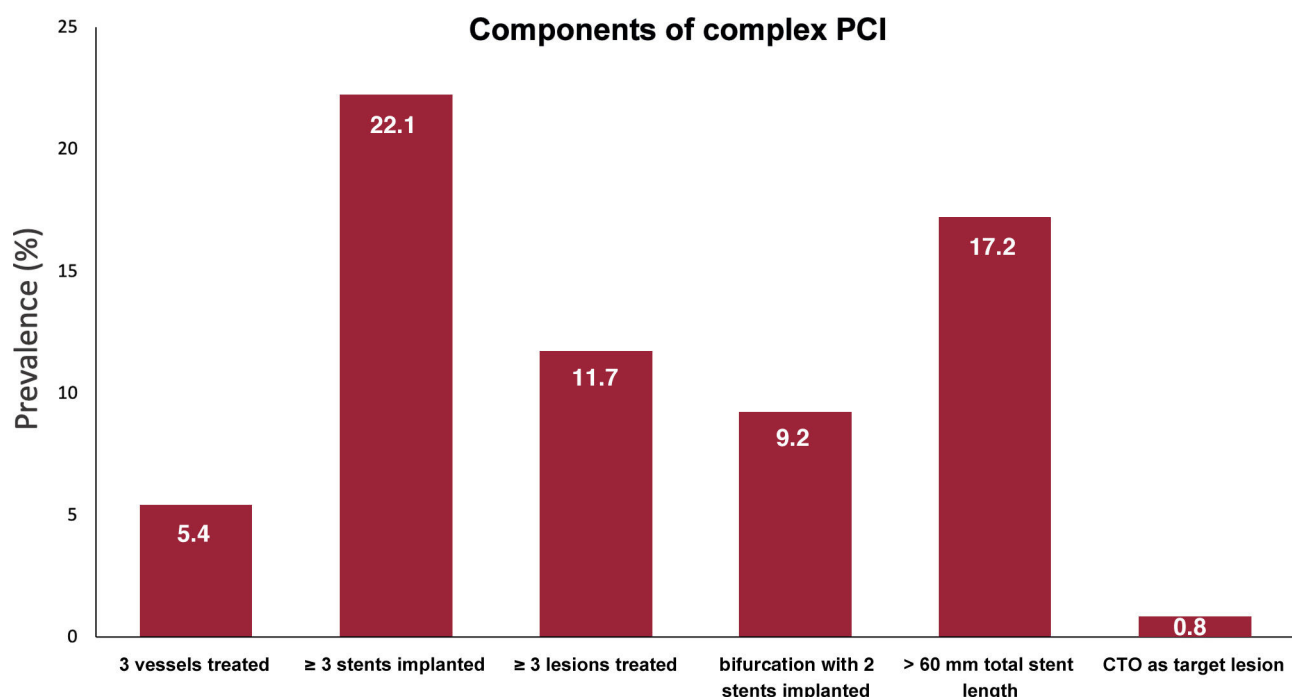
TAVR procedural characteristics, and early outcomes according to the PCI complexity

	Overall (n = 1550)	Complex PCI (n = 454)	Noncomplex PCI (n = 1096)	P
Procedural characteristics				
<i>Primary access</i>				
Transfemoral	1227 (79.2)	335 (73.8)	892 (81.4)	< .001
Nontransfemoral	323 (20.8)	119 (26.2)	204 (18.6)	
<i>Valve type</i>				
Balloon-expandable	987 (63.7)	300 (66.1)	687 (62.7)	.187
Self-expandable	562 (36.3)	153 (33.7)	409 (37.3)	
Valve-in-valve procedure	70 (4.5)	21 (4.6)	49 (4.5)	.894
Echocardiography postprocedure				
LVEF, %	55.7 ± 1.6	55.2 ± 11.9	55.8 ± 11.5	.650
Mean aortic gradient, mmHg	10.3 ± 5.1	10.4 ± 4.6	10.3 ± 5.1	.886
Moderate/severe AR	128 (8.4)	40 (8.9)	88 (8.2)	.686
30-day complications				
All-cause mortality	42 (2.7)	12 (2.6)	30 (2.7)	.917
Bleeding	196 (12.7)	58 (12.8)	138 (12.6)	.921
Minor bleeding	65 (4.2)	24 (5.3)	41 (3.7)	.167
Major bleeding	83 (5.4)	20 (4.4)	63 (5.8)	.285
Life-threatening bleeding	57 (3.7)	19 (4.2)	38 (3.5)	.494
Major vascular complication	129 (8.3)	29 (6.4)	100 (9.1)	.076
Stroke	49 (3.2)	9 (1.9)	40 (3.7)	.089
Acute kidney injury	144 (9.3)	33 (7.3)	111 (10.1)	.079
Myocardial infarction*	10 (0.6)	6 (1.3)	4 (0.4)	.455
Antithrombotic treatment at discharge				
Single antiplatelet therapy	92 (5.9)	21 (4.6)	71 (6.5)	.160
Dual antiplatelet therapy	904 (58.3)	254 (55.9)	650 (59.3)	.222
Anticoagulation therapy	47 (3.0)	13 (2.9)	34 (3.1)	.803
Antiplatelet + anticoagulation	482 (31.1)	157 (34.6)	325 (29.7)	.056

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

Data are expressed as mean ± SD, n (%).

* Myocardial infarction refers to spontaneous myocardial infarction (type 1).

**Figure 1.** Rate of complex PCI components in the overall population. CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

of patients received dual antiplatelet therapy, 34.1% were on an oral anticoagulant (monotherapy: 3.0%; in combination with antiplatelet therapy: 31.1%), and 5.9% received single antiplatelet therapy, with no differences between the complex and noncomplex PCI groups.

Long-term outcomes according to PCI complexity

The median length of follow-up of the study population was of 2 [1–3] years. A total of 82 patients (5.3%) were lost to follow-up, 486 patients (31.4%) died during the study period, 169 (11.1%) of them from cardiovascular causes.

Long-term outcomes following TAVR stratified according to PCI complexity are summarized in [table 4](#). The incidence of MACE (primary endpoint) was 9.6 events per 100 patients-years (hazard ratio [HR] for complex PCI, 1.31; 95% confidence interval [95%CI], 1.01–1.71; $P = .042$). The estimated event-free survival was 79.8 months in the complex PCI group vs 87.4 months in the noncomplex PCI group ($P < .01$). Patients in the complex PCI group had higher rates of cardiac death, myocardial infarction, coronary revascularization, target vessel revascularization, target lesion revascularization, restenosis, and stent thrombosis. Complex PCI was not associated with an increased risk of all-cause mortality, stroke, and bleeding events at adjusted analyses.

The Kaplan-Meier estimates for MACE at 4-year follow-up after TAVR are shown in [figure 2](#). The 4-year follow-up MACE rates were 31.1% and 19.6% in the complex and noncomplex PCI groups, respectively (log-rank $P < .005$). Complex PCI significantly increased the risk for cardiac death, myocardial infarction, and coronary revascularization at 4-year follow-up (log-rank, $P < .001$). The complexity of PCI did not affect all-cause death rates ([figure 3](#)). Similar rates of bleeding events were observed, irrespective of PCI complexity.

Adjusted risks for the cardiac ischemic endpoints (MACE and its individual components) according to the type of high-risk procedural features are shown in [figure 4](#). PCI with ≥ 3 stents implanted and bifurcations with the 2-stent strategy were the angiographic subsets most strongly associated with increased ischemic risk.

Predictors of MACE after TAVR

The risk of MACE following TAVR was 8.6%, 19.4%, and 29.7% at 1-, 3-, and 5-year follow-up. The univariable and multivariable analyses of the factors associated with the occurrence of MACE after TAVR are shown in [table 5](#). In the multivariable model, previous myocardial infarction, previous coronary artery bypass graft (CABG), chronic kidney disease, nontransfemoral access, incomplete revascularization, and complex PCI were independently associated with an increased risk of MACE.

DISCUSSION

The main findings of our study can be summarized as follows: 1) among patients referred for PCI in the pre-TAVR workup, about 1 out of 3 patients underwent complex coronary revascularization; 2) complex PCI was associated with higher rates of MACE after a median follow-up period of 2 years; 3) patients undergoing complex PCI exhibited a greater risk of cardiac death, coronary revascularization, myocardial infarction, and coronary thrombotic events, with similar rates of all-cause mortality; and 4) on multivariable analysis, PCI complexity emerged as independent predictor of MACE following TAVR, along with incomplete revascularization, previous myocardial infarction, previous CABG, nontransfemoral access and chronic kidney disease ([figure 5](#)).

Table 4
Long-term outcomes of the study population according to PCI complexity^a

	Complex PCI (n = 454)	Noncomplex PCI (n = 1096)	Univariable HR (95%CI)	P	Adjusted ^b HR (95%CI)	P
MACE	89 (19.6)	158 (14.4)	1.41 (1.09–1.84)	.010	1.36 (1.03–1.79)	.029
Cardiac death	62 (13.7)	107 (9.8)	1.43 (1.03–2.00)	.035	1.44 (1.01–2.07)	.048
Myocardial infarction	50 (11.0)	72 (6.6)	1.73 (1.21–2.49)	.003	1.52 (1.04–2.21)	.029
STEMI	10 (2.2)	6 (0.6)	4.17 (1.51–11.47)	.006	4.36 (1.41–13.5)	.011
NSTEMI type 1	16 (3.5)	25 (2.3)	1.64 (0.88–3.08)	.121	1.47 (0.76–2.84)	.248
NSTEMI type 2	12 (2.6)	22 (2.0)	1.37 (0.68–2.77)	.379	1.21 (0.59–2.47)	.603
Unstable angina	12 (2.6)	17 (1.6)	1.76 (0.84–3.68)	.136	1.53 (0.72–3.26)	.269
Coronary revascularization	31 (6.8)	29 (2.7)	2.67 (1.61–4.44)	<.001	2.46 (1.44–4.20)	.001
All-cause mortality	140 (30.8)	346 (31.6)	1.01 (0.83–1.23)	.894	0.95 (0.78–1.19)	.741
Target vessel revascularization	22 (4.9)	19 (1.7)	2.89 (1.57–5.35)	<.001	2.51 (1.31–4.83)	.006
Target lesion revascularization	21 (4.6)	18 (1.6)	2.92 (1.55–5.48)	<.001	2.55 (1.30–4.99)	.006
Restenosis	17 (3.7)	17 (1.5)	2.50 (1.27–4.89)	.008	2.27 (1.14–4.52)	.019
Stent thrombosis	5 (1.1)	1 (0.1)	12.5 (1.46–107.1)	.021	13.8 (1.6–119.7)	.018
Stable angina	5 (1.1)	11 (1.0)	1.12 (0.39–3.22)	.834	1.07 (0.37–3.11)	.905
Stroke	25 (5.5)	71 (6.5)	0.85 (0.54–1.33)	.470	0.98 (0.62–1.57)	.945
Bleeding	89 (19.6)	213 (19.4)	0.99 (0.78–1.28)	.975	0.98 (0.76–1.26)	.977
Minor bleeding	39 (8.6)	56 (5.1)	1.66 (1.10–2.51)	.016	1.48 (0.98–2.25)	.065
Major bleeding	32 (7.1)	106 (9.7)	0.72 (0.48–1.07)	.106	0.74 (0.49–1.11)	.147
Life-threatening bleeding	28 (6.2)	58 (5.3)	1.16 (0.73–1.84)	.524	1.17 (0.73–1.88)	.515

95%CI, confidence interval; HR, hazard Ratio; MACE, major adverse cardiac events; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Data are expressed as n (%).

^a Median follow-up of 2 [interquartile range: 1 to 3] years posttranscatheter aortic valve replacement.

^b Adjusted for gender, dyslipidemia, previous CAD, previous PCI, non-transfemoral approach.

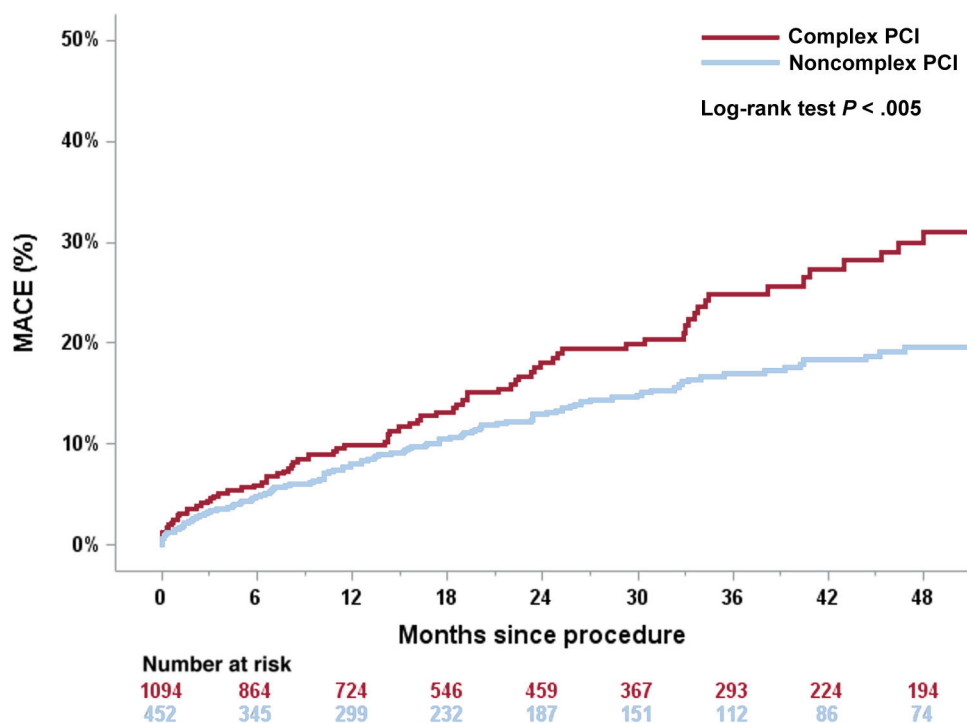


Figure 2. Kaplan-Meier curves for MACE according to the PCI complexity. Kaplan-Meier estimates demonstrate higher rates of MACE (cardiac death, nonprocedural myocardial infarction, and need for new coronary revascularization) in the complex PCI group (red line) compared with noncomplex PCI (blue line) over 4 years of follow-up. MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

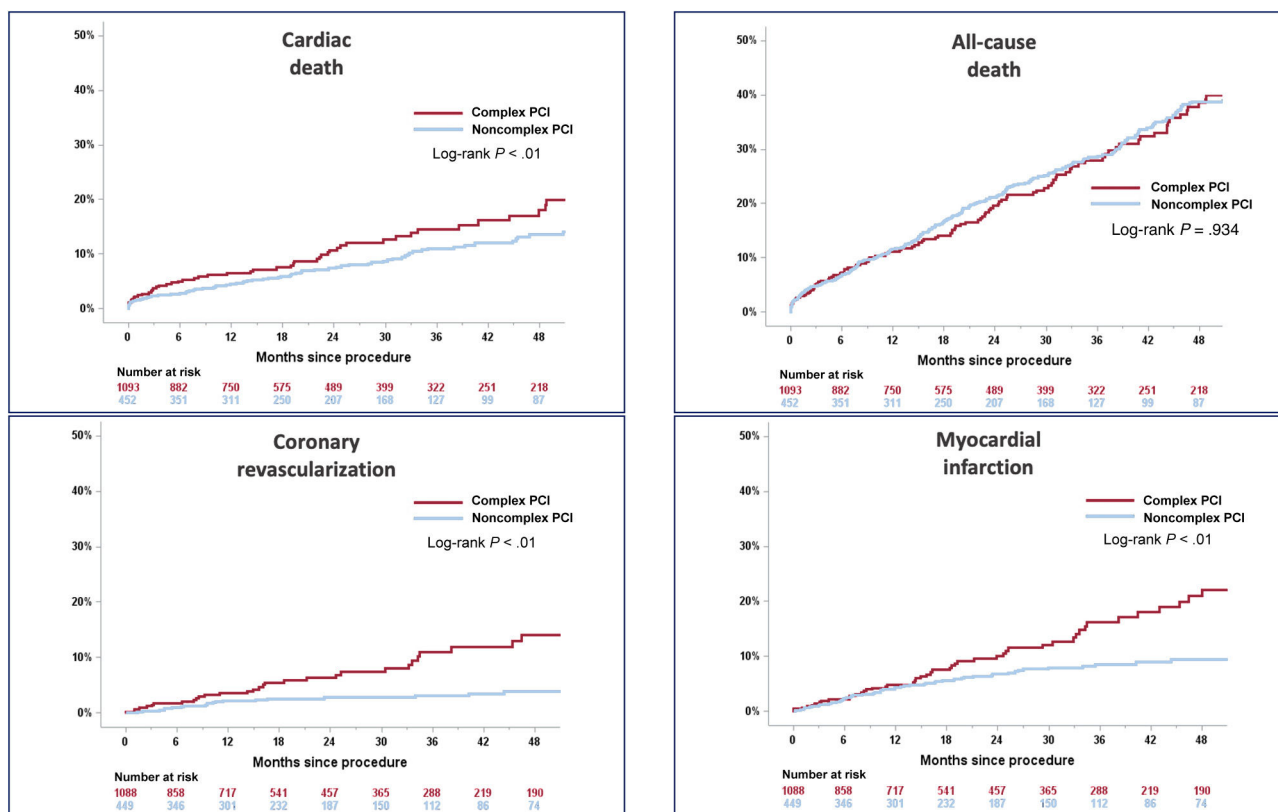


Figure 3. Effect of procedural complexity on ischemic and bleeding outcomes. Cumulative hazard curves for cardiac death, all-cause death, coronary revascularization, and myocardial infarction, stratified according to PCI complexity. PCI, percutaneous coronary intervention.

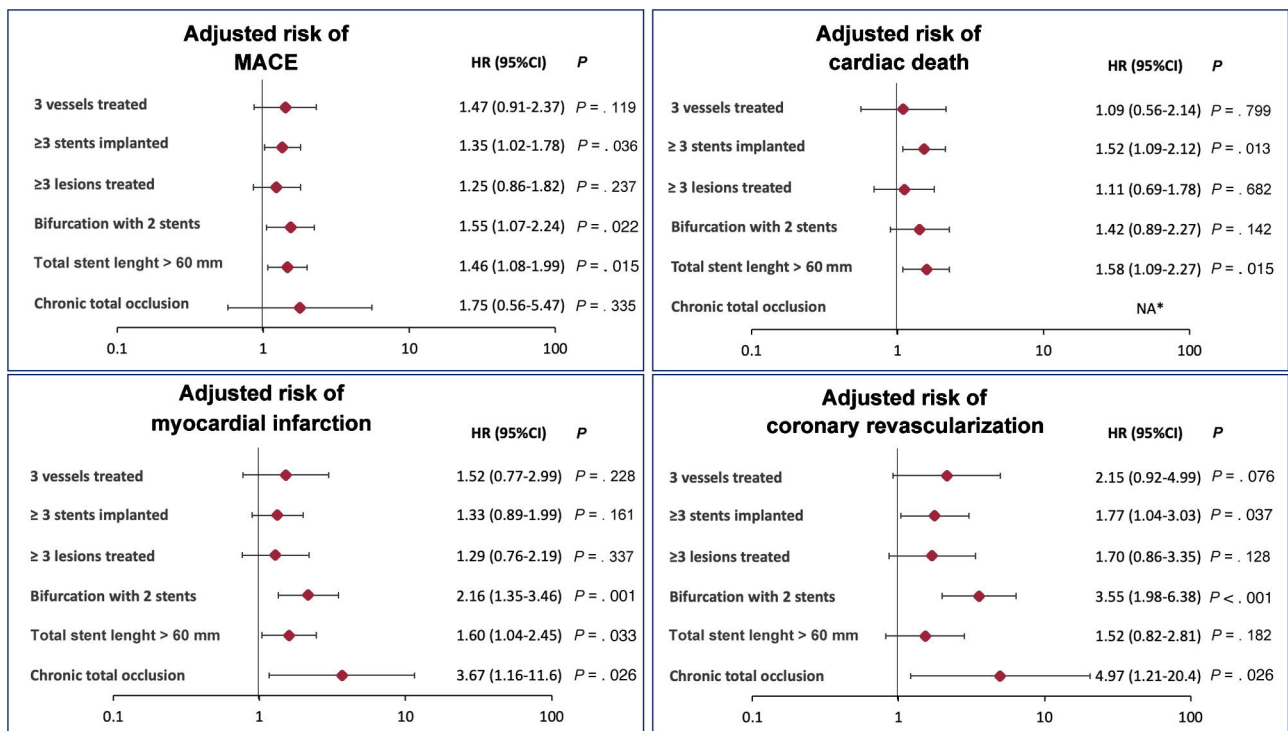


Figure 4. Effect of high-risk procedural subsets on ischemic outcomes. Adjusted risk of MACE, cardiac death, myocardial infarction, and coronary revascularization among high-risk procedural subsets. 95%CI, 95%confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; NA, not applicable. No cardiac death occurred in the chronic total occlusion group.

Table 5

Independent predictors of major adverse cardiac events after transcatheter aortic valve replacement

Variable	Univariable model		Multivariable model	
	HR (95%CI)	P	HR (95%CI)	P
Hypertension	1.59 (1.08-2.34)	.018	-	-
Diabetes	1.46 (1.13-1.88)	.004	-	-
Previous MI	1.54 (1.18-2.01)	.001	1.35 (1.03-1.77)	.032
Previous CABG	1.57 (1.16-2.12)	.003	1.50 (1.10-2.05)	.004
eGFR < 60 mL/min	1.37 (1.05-1.77)	.019	1.33 (1.02-1.73)	.030
Nontransfemoral approach	1.96 (1.52-2.54)	< .001	1.79 (1.37-2.34)	< .001
Incomplete revascularization	1.64 (1.27-2.13)	< .001	1.43 (1.09-1.88)	.01
Complex PCI	1.44 (1.11-1.87)	.006	1.31 (1.01-1.71)	.042

95%CI, 95% confidence interval; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The management of concomitant CAD in TAVR candidates remains a largely unresolved issue. Although coronary revascularization in the preprocedural workup is routine practice in most TAVR centers, there is no evidence of its appropriateness, due to inconsistent data on the impact of CAD, its complexity, and the completeness of revascularization on outcomes.

Outside the TAVR population, several randomized trials failed to show any prognostic benefit of PCI in patients with stable ischemic heart disease.¹⁰ In the TAVR field, the only evidence from randomized studies has come from the ACTIVATION trial, showing that angiography-guided PCI pre-TAVR conferred no benefit in terms of reduced rates of mortality and rehospitalization at 1 year compared with conservative management, and, in contrast, increased bleeding risk.¹¹ Nonetheless, the study was prematurely interrupted due to the slow recruitment rate and did not meet the

formal noninferiority margin, thus precluding the drawing of definite conclusions on this topic. In addition, most of the patients included in that trial had single lesions and underwent simple PCI procedures. Moreover, a recent analysis investigated the impact of untreated chronic obstructive CAD on outcomes after TAVR, reporting relatively low rates of unplanned coronary revascularization and acute coronary syndrome at 1 year (0.7% and 0.5%, respectively),¹² with a rise in incidence with increasing severity of CAD. Therefore, performing TAVR first in patients with concomitant significant CAD could be a safe option, and PCI could be considered post-TAVR in patients with residual symptom despite optimal medical therapy.

The presence of severe CAD represents an important factor that may influence the clinical decision-making process in AS patients. Patients with complex CAD were excluded from the randomized

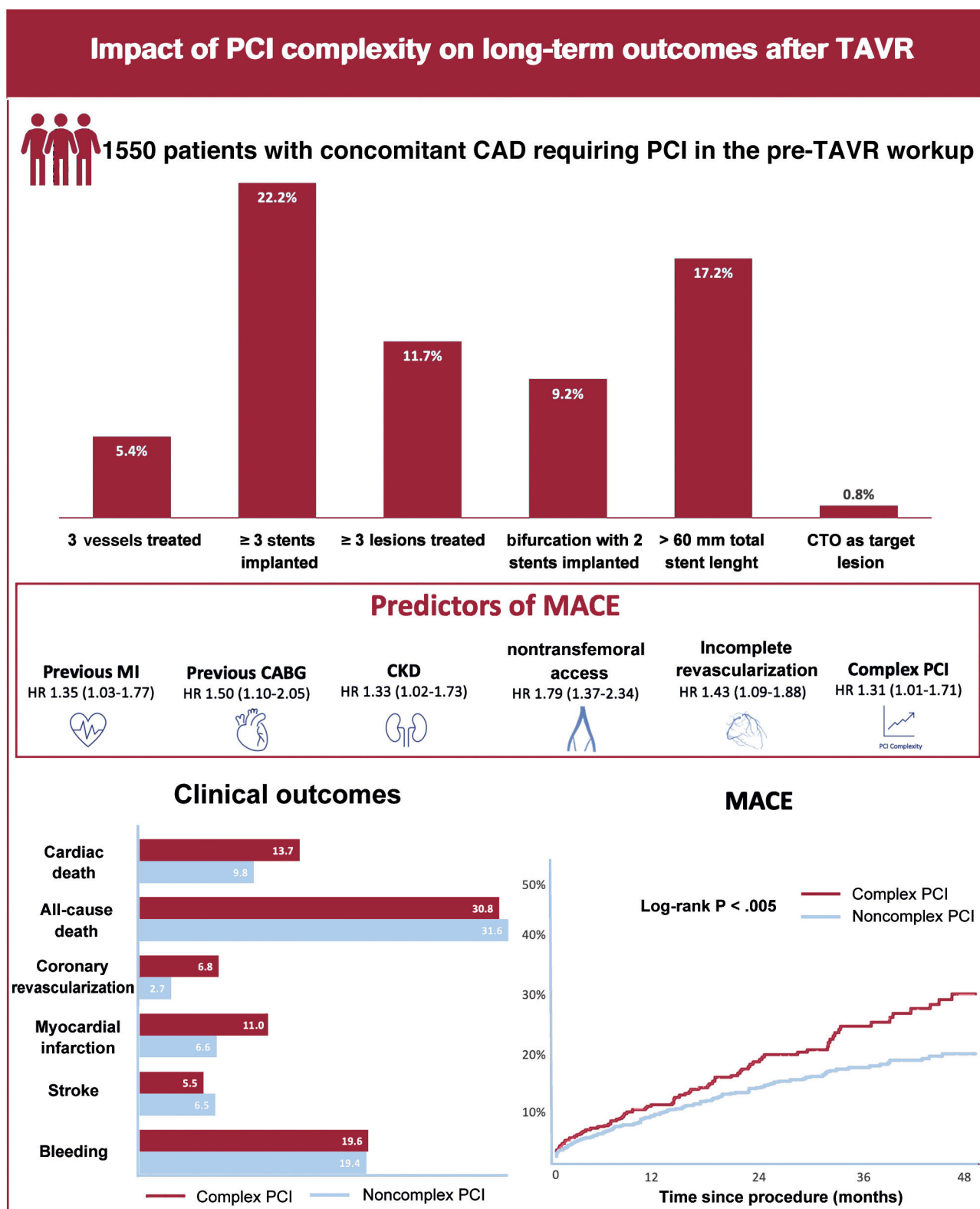


Figure 5. Long-term outcomes of complex PCI in the TAVR population. Rate of complex PCI components in the PCI-TAVR population (top). Predictors of MACE following TAVR (middle). Clinical outcomes of the study population stratified according to PCI complexity (bottom, left), and Kaplan-Meier curve for MACE up to 4 years following TAVR (bottom, right). CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CTO, chronic total occlusion; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

trials comparing TAVR and surgical aortic valve replacement, affecting the generalizability of the results to the general AS population.^{13,14} In a propensity-matched study, Alperi et al.⁴ showed that in patients with complex CAD (SYNTAX score > 22 or unprotected left main disease), the percutaneous approach (PCI + TAVR) was associated with a similar risk of MACCE (all-cause mortality, myocardial infarction, coronary revascularization, and stroke) compared with a combined surgical intervention (surgical aortic valve replacement + CABG) after a median follow-up of 3 years. Nevertheless, a higher risk for repeat coronary revascularization was observed in TAVR + PCI recipients.

To date, few studies have investigated the impact of coronary lesion complexity on outcomes post-TAVR. In a study including 604 patients, the anatomical complexity of coexisting CAD was associated with a 2-fold increased risk of cardiovascular mortality after TAVR (SYNTAX score > 22; HR, 1.84; $P = .041$).⁶ The presence of complex CAD emerged as an independent predictor for cardiac death, suggesting that it is not simply a marker of atherosclerotic burden, but rather a critical ischemic risk factor in AS patients. However, the study was limited by its small sample size, based on a single-center experience.

To the best of our knowledge, the present study is the first to show the impact of coronary revascularization complexity on long-term outcomes in a large, multicenter cohort of TAVR patients undergoing PCI during the preprocedural workup. This is noteworthy for 2 reasons: first, PCI complexity usually reflects that of CAD and, second, it provides a practical insight into the effect of revascularization techniques on clinical results. In our cohort, the complexity of PCI was significantly associated with poorer long-term outcomes. Having at least 1 of the complex PCI criteria conferred a higher risk of cardiac death, myocardial infarction, coronary revascularization, stent thrombosis, and restenosis after TAVR. Overall mortality did not differ between complex and noncomplex PCI patients. However, the baseline risk profile and the comorbidity burden, which mostly impacts the prognosis in TAVR patients, were similar among the 2 groups, which could explain the comparable outcomes in terms of all-cause mortality. In contrast, the differences were marked regarding the complexity of CAD and procedural features. About one-half of patients exhibited multivessel disease, and coronary lesions were frequently complex (B2/C type, calcified, ostial location), likely defining the excess cardiac mortality risk related to complex PCI. Moreover, the association between PCI complexity and ischemic risk is likely multifactorial. Patients undergoing more complex procedures usually have more advanced CAD, implying higher risk for atherothrombosis due to the natural progression of CAD.¹⁵ Treating more complex lesions (ie, bifurcations, calcified lesions) may increase the risk of incomplete stent apposition and delayed endothelialization, which may act as a trigger for platelet activation and subsequent intracoronary thrombosis.^{16,17}

Our findings are in line with those previously reported in PCI studies, showing the harmful impact of procedural complexity.^{7,18,19} Giustino et al.⁷ showed that complex PCI was associated with a higher risk of ischemic but no bleeding events, also pointing out the protective role of prolonged dual antiplatelet therapy (≥ 1 year) in reducing the risk compared with a shorter dual antiplatelet therapy regimen. In a recent meta-analysis, PCI complexity increased the risk of both ischemic and bleeding events.¹⁹ Interestingly, in our study, the frequency of complex (vs simple) PCI was higher compared with previous PCI cohorts (29.3% vs 18%, respectively), as well as the rate of coronary events at follow-up, highlighting the pronounced high-risk profile of the TAVR population requiring PCI.⁷ However, it must be noted that the rates of stent thrombosis and restenosis after a median follow-up of 2 years were as low as 1.2 and 5.2%, respectively, providing

reassuring evidence regarding the long-term results of pre-TAVR PCI.

Previous myocardial infarction, previous CABG, chronic kidney disease, and nontransfemoral access were identified as independent predictors of MACE after TAVR, and these results were in accordance with prior evidence reporting the detrimental effect of patient comorbidities after both PCI and TAVR.²⁰ Of note, complex PCI and incomplete revascularization were also associated with an increased risk of MACE in the multivariable model. The clinical impact of revascularization completeness remains controversial. While some studies did not report a clear clinical benefit,^{21,22} revascularization incompleteness and residual SYNTAX score have been associated with poorer post-TAVR outcomes, supporting a complete revascularization strategy in the pre-TAVR workup.^{3,5} Randomized trials are needed to determine the strategy (conservative approach vs complete revascularization) that translates into the most favorable results after TAVR. Likewise, the potential role of physiologic assessment (fractional flow reserve, instantaneous wave-free ratio) in TAVR candidates should be elucidated. Even if physiology-guided PCI has been associated with better outcomes than angiography-guided PCI,²³ data on the applicability of invasive functional testing in the AS setting are scarce, and warrant further validation of optimal threshold values.

Less invasive transcatheter treatments provide the opportunity to delay the management of either CAD or AS, balancing the sequence of the treatment according to patient's clinical status and centers' practice. Nevertheless, considering the unfavorable impact of angiographic factors (number of diseased vessels), and procedural factors (stent number, stent length, bifurcation with 2 stent strategy), the revascularization strategy (whether and how) should be planned ahead and individualized. The decision to revascularize or not should be balanced according to the severity and location of coronary stenosis, patient's life expectancy, and risk of jeopardizing coronary reaccess after TAVR. How to revascularize remains more difficult due to the narrow tradeoff between avoiding procedural complexity and achieving complete revascularization.

The findings of this study highlight the central role of angiographic features and PCI complexity as an important risk factor for major adverse events that should be considered by the Heart Team when choosing the treatment strategy (regarding both AS and CAD) in patients with significant CAD. Further randomized studies are awaited to provide definitive evidence regarding the potential (un)benefit of routine revascularization in TAVR patients with stable ischemic heart disease and the prognostic meaning of the extent of myocardial revascularization.

Limitations

This study has some limitations. First, the study design was observational and, although the data were collected prospectively, the present analysis was not prespecified and was retrospective. Although the risk for MACE was adjusted for relevant covariates, there might have been residual confounders due to unmeasured factors. The decision to perform PCI and the revascularization strategy were left to the discretion of the operator responsible for the procedure in each participating center, without predefined selection criteria. Even if data about the pharmacological regimen were prospectively collected, we were not able to perform a subanalysis evaluating the impact of different antithrombotic strategies on ischemic and bleeding outcomes, essentially due to the relatively small number of events at follow-up. In addition, almost one-third of our population required concomitant oral anticoagulation therapy,

determining many possible therapeutic combinations. Finally, although clinical events were categorized according to standardized definitions, events were not adjudicated by an independent event adjudication committee.

CONCLUSIONS

In patients with severe CAD undergoing PCI in the pre-TAVR workup, those with complex PCI features exhibited poorer long-term outcomes, including a much higher risk for cardiac death, myocardial infarction and stent thrombosis up to the 4-year follow-up. In addition, PCI complexity emerged as an independent correlate of MACE after TAVR. Our study extends prior findings on complex PCI to the TAVR population, supporting the hypothesis that procedural complexity should be considered as an indicator for risk stratification during the pre-TAVR workup, which could potentially impact the treatment strategy. Further studies are warranted to better define the optimal management of CAD in patients with severe AS mainly concerning the need for routine revascularization, the extent of its completeness, and the type and duration of antithrombotic treatment.

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ETHICAL CONSIDERATIONS

This study was conducted according to the ethics committee of each participating center, and all patients provided signed informed consent for the procedures. This study was conducted in accordance with the SAGER (Sex and Gender Equity in Research) guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this study.

AUTHORS' CONTRIBUTIONS

M. Avvedimento and J. Rodés-Cabau conceived and designed the study. M. Avvedimento and J. Nuche merged local databases from all participating centers and were responsible for quality of data control. M. Côté performed the statistical analysis. M. Avvedimento wrote the first draft of the manuscript. All authors participated in the design and completion of local databases. All authors approved the final version of the manuscript and ensured the accuracy and integrity of the work. All authors had access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. J. Rodés-Cabau is responsible for the overall content of the study as guarantor.

CONFLICTS OF INTEREST

J. Rodés-Cabau has received institutional research grants and speaker/consultant fees from Edwards Lifesciences and Medtronic. The other authors report no conflicts with respect to the content of this manuscript.

WHAT IS KNOWN ABOUT THE TOPIC?

- The prevalence of CAD in the TAVR population is fairly high, with up to 25% of TAVR candidates undergoing PCI as a part of the preprocedural workup or at the time of the TAVR procedure.
- TAVR recipients frequently have multivessel disease and complex coronary lesions.
- Previous evidence suggests that the anatomical complexity of CAD and completeness of coronary revascularization might have an impact on the clinical outcomes following TAVR.

WHAT DOES THIS STUDY ADD?

- The degree of procedural complexity is a strong determinant of prognosis in the PCI-TAVR population.
- Patients undergoing complex PCI exhibit poorer long-term outcomes, including a higher risk of cardiac death, myocardial infarction, and coronary revascularization.
- In patients with significant CAD requiring coronary revascularization in the pre-TAVR workup, PCI complexity should be considered by the Heart Team as an indicator for risk stratification when choosing the treatment strategy.

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