Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Management of Myocardial Revascularization in Patients With Stable Coronary Artery Disease Undergoing Transcatheter Aortic Valve Implantation

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BACKGROUND: The best management of stable coronary artery disease (CAD) in patients undergoing transcatheter aortic valve implantation (TAVI) is still unclear due to the marked inconsistency of the available evidence.

METHODS: The REVASC-TAVI registry (Management of Myocardial Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation With Coronary Artery Disease) collected data from 30 centers worldwide on patients undergoing TAVI who had significant, stable CAD at preprocedural work-up. For the purposes of this analysis, patients with either complete or incomplete myocardial revascularization were compared in a propensity score matched analysis, to take into account of baseline confounders. The primary and co-primary outcomes were all-cause death and the composite of all-cause death, stroke, myocardial infarction, and rehospitalization for heart failure, respectively, at 2 years.

RESULTS: Among 2407 patients enrolled, 675 pairs of patients achieving complete or incomplete myocardial revascularization were matched. The primary (21.6% versus 18.2%, hazard ratio, 0.88 [95% CI, 0.66–1.18]; *P*=0.38) and co-primary composite (29.0% versus 27.1%, hazard ratio, 0.97 [95% CI, 0.76–1.24]; *P*=0.83) outcome did not differ between patients achieving complete or incomplete myocardial revascularization, respectively. These results were consistent across different prespecified subgroups of patients (< or >75 years of age, Society of Thoracic Surgeons score > or <4%, angina at baseline, diabetes, left ventricular ejection fraction > or <40%, New York Heart Association class I/II or III/IV, renal failure, proximal CAD, multivessel CAD, and left main/proximal anterior descending artery CAD; all *P* values for interaction >0.10).

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CONCLUSIONS: The present analysis of the REVASC-TAVI registry showed that, among TAVI patients with significant stable CAD found during the TAVI work-up, completeness of myocardial revascularization achieved either staged or concomitantly with TAVI was similar to a strategy of incomplete revascularization in reducing the risk of all cause death, as well as the risk of death, stroke, myocardial infarction, and rehospitalization for heart failure at 2 years, regardless of the clinical and anatomical situations.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ myocardial revascularization ■ outcome ■ percutaneous coronary intervention ■ transcatheter aortic valve implantation

See Editorial by Ibrahim and Williams

WHAT IS KNOWN

- This is the largest evidence that patients undergoing transcatheter aortic valve implantation (TAVI) with significant stable coronary artery disease (CAD) at preprocedural work-up, complete myocardial revascularization did not reduce the risk of all cause death, as well as the risk of death, stroke, myocardial infarction, and rehospitalization for heart failure at 2 years.
- A consistent lack of benefit of complete revascularization was confirmed regardless of whether percutaneous coronary intervention in all significant coronary stenoses (performed either staged or concomitantly to the index TAVI procedure) was carried out in younger patients and those presenting with angina, left ventricular dysfunction, and a larger area of myocardium at risk.

WHAT THE STUDY ADDS

- This study supports a highly conservative approach of angiographically significant, stable CAD in patients undergoing TAVI, balancing the risk of eventual difficulties in re-engaging coronary arteries after TAVI.
- The study raises doubts about the impact of revascularization of stable lesions in proximal segments of coronary vessels, which to date have been considered prognostically significant in this setting.
- Validation of functional testing to identify prognostically significant CAD and guide myocardial revascularization in TAVI setting is a priority.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
CABG	coronary artery bypass grafting
CAD	coronary artery disease
LM	left main
MI	myocardial infarction
PCI	percutaneous coronary intervention
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation
VARC-2	Valve Academic Research Consortium-2

The burden of coronary artery disease (CAD) is significant in patients undergoing transcatheter aortic valve implantation (TAVI).[1] With respect to CAD treatment, while coronary artery bypass grafting at the time of surgical aortic valve replacement is considered the gold standard in case of concomitant significant CAD, treatment algorithms of significant CAD in TAVI candidates vary considerably across different institutions.[2] Indeed, TAVI offers the clear advantage of being able to defer the treatment of concomitant CAD, balancing the priority of treatment according to the severity of the diseases and patients' clinical presentation. Current European and American guidelines recommend to consider percutaneous coronary intervention (PCI) in TAVI patients with proximal CAD (Class IIa).[3,4] Nevertheless, indication for treatment of significant CAD in TAVI setting still remains a matter of debate, due to the marked inconsistency of the available evidence, which are mainly based on nonrandomized data.[2,5–12] In fact, whether performing PCI and achieving complete revascularization in patients undergoing TAVI would offer a clinical benefit in patients with significant CAD remains unclear.[13] The randomized, noninferiority ACTIVATION trial (Percutaneous Coronary Intervention Prior to Transcatheter Aortic Valve Implantation) showed that rates of death and rehospitalization at 1 year were similar between PCI and no PCI prior to TAVI.[14] However, the study was prematurely stopped due to slow recruitment and had limitations, including the unmet noninferiority margin and the poor generalizability.[14] The aim of the present analysis from a multicenter registry of real-world patients with significant stable CAD undergoing TAVI was to determine whether complete revascularization would produce similar clinical results when compared with incomplete revascularization.

METHODS

Registry Design

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The REVASC-TAVI (Management of Myocardial Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation With Coronary Artery Disease) is an investigator-initiated registry designed to collect data on patients with severe aortic stenosis (AS) undergoing TAVI and found to have significant untreated CAD at the time of pre-TAVI work-up. A total of 30 centers from Europe, North America, South America, and Japan contributed their patient level data using a dedicated case report form (Supplemental Material). Baseline demographics, clinical and echocardiographic features, medications, coronary angiography, PCI and TAVI procedural details, and follow-up data were collected by the co-investigators at each institution. All inconsistencies were resolved directly by communicating with the local investigators. The management of CAD, including indication for PCI, the use of functional invasive or noninvasive tests for myocardial ischemia and intravascular ultrasound, PCI strategy and duration of antiplatelet therapy were left to the discretion of each local heart team and operating interventional cardiologist.

All baseline diagnostic angiograms and PCI procedures were re-assessed at each center to capture baseline coronary status and postprocedural status in case of PCI. In case of patients with previous coronary artery bypass grafting, completeness of revascularization was assessed by evaluating the native coronary circulation and the respective grafts.

The registry protocol was approved by the institutional review committee at each participating center. All patients included in this study gave their informed consent to the procedure.

Definitions

Significant CAD was defined according to the latest guidelines on myocardial revascularization.[3,4] In details, it was defined as the presence of visual angiographic stenosis ≥70% (≥50% if protected left main [LM] or vein graft), instantaneous wave-free ratio value ≤0.89, fractional flow reserve value ≤0.80, in 1 or more coronary arteries of at least 2.5 mm of diameter, not revascularized by patent coronary stents or bypass grafts, found at the coronary angiography performed during the pre-TAVI work-up or LM minimal lumen area<6 mm^2 at intravascular ultrasound assessment. Staged PCI before TAVI was defined as PCI procedures planned and performed after the indication to TAVI and before the index procedure (PCI for acute coronary syndromes were excluded by definition). Staged PCI after TAVI was defined as PCI procedures planned and performed intentionally after TAVI in a different setting (the diagnosis of significant CAD was made prior to TAVI). Concomitant PCI was defined as planned PCI procedures performed concomitantly during the index TAVI (either before or after transcatheter aortic valve deployment). Unplanned PCI was defined as PCI procedures performed due to recurrent angina, acute coronary syndrome, or coronary occlusion after TAVI.

Complete revascularization was defined as the absence of residual significant coronary stenosis after TAVI and the planned PCI timing (before or after the index TAVI).

All outcomes were defined according to the Valve Academic Research Consortium-2 (VARC-2) definitions (5).

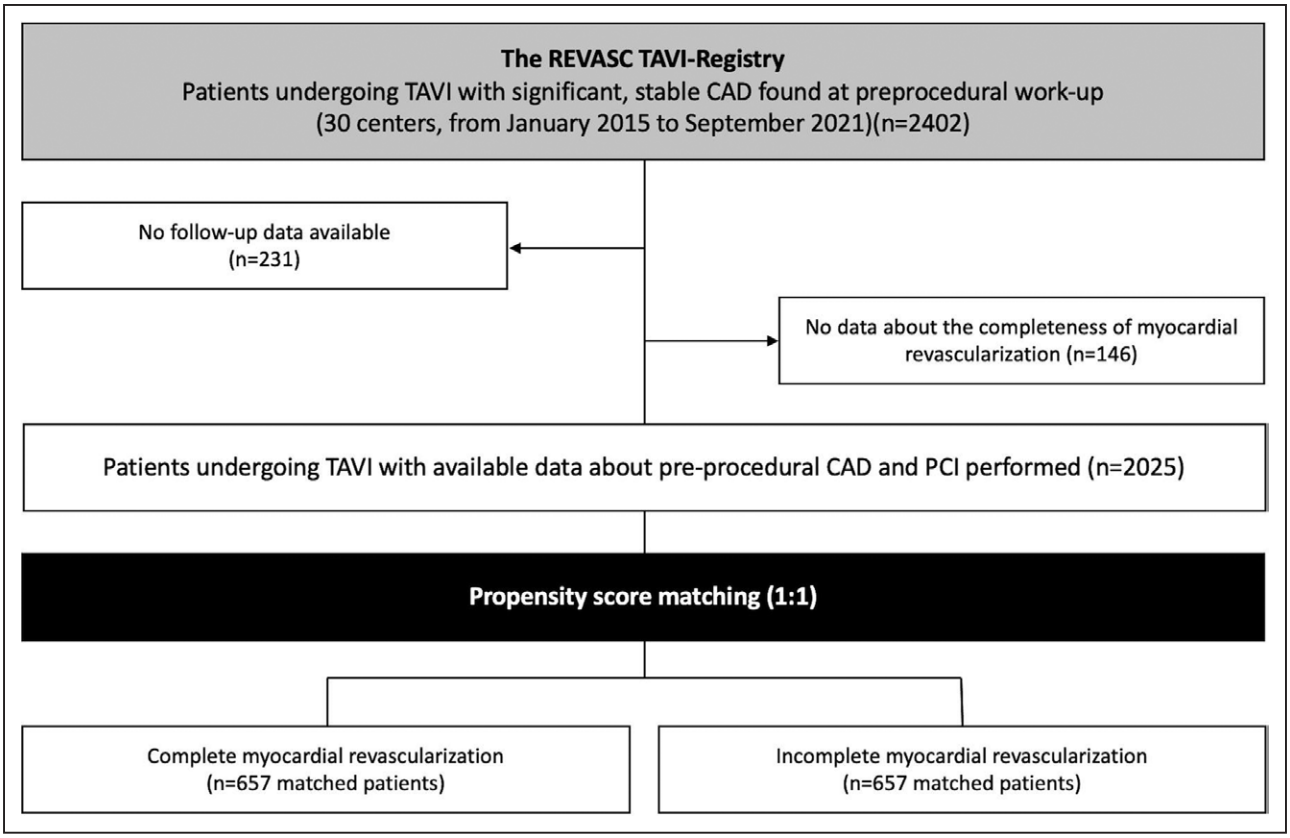

Figure 1. Study flowchart.
CAD indicates coronary artery disease; PCI, percutaneous coronary intervention; REVASC-TAVI, Management of Myocardial Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation With Coronary Artery Disease; and TAVI, transcatheter aortic valve intervention.

Table 1. Baseline Characteristics of the Matched Population

	Overall (n=1314)	Complete revascularization (n=657)	Incomplete revascularization (n=657)	SMD
Sex, n (%)				0.055
Male	777 (59.1)	381 (58.0)	396 (60.3)	
Female	534 (40.7)	274 (41.7)	260 (39.6)	
NA	3 (0.2)	2 (0.3)	1 (0.1)	
Age, median [IQR]	82.6 [78.1–85.8]	82.2 [78.1–85.1]	83.0 [78.0–86.0]	0.004
BMI, median [IQR]	26.3 [23.7–29.4]	26.3 [23.7–29.1]	26.3 [23.7–29.4]	0.006
Hypertension, n (%)				0.032
No	201 (15.3)	100 (15.2)	101 (15.4)	
Yes	1110 (84.5)	555 (84.5)	555 (84.5)	
NA	3 (0.22)	2 (0.33)	1 (0.1)	
Diabetes, n (%)				0.025
No	880 (67.0)	437 (66.5)	443 (67.4)	
Yes	425 (32.3)	215 (32.7)	210 (32.0)	
NA	9 (0.7)	5 (0.8)	4 (0.6)	
PAD, n (%)				0.033
No	1084 (82.5)	542 (82.5)	542 (82.5)	
Yes	218 (16.6)	108 (16.4)	110 (16.7)	
NA	12 (0.9)	7 (1.1)	5 (0.8)	
COPD, n (%)				0.032
No	1096 (83.4)	547 (83.2)	549 (83.6)	
Yes	206 (15.7)	103 (15.7)	103 (15.7)	
NA	12 (0.9)	7 (1.1)	5 (0.8)	
eGFR, mL/min median [IQR]	55.1 [40.5–64.0]	55.0 [40.0–64.0]	55.1 [41.0–64.0]	0.009
Prior CABG, n (%)				0.035
No	1165 (88.7)	583 (88.7)	582 (88.6)	
Yes	137 (10.4)	67 (10.2)	70 (10.6)	
NA	12 (0.9)	7 (1.1)	5 (0.8)	
Prior PCI, n (%)				0.019
No	806 (61.4)	404 (61.5)	402 (61.2)	
Yes	497 (37.8)	247 (37.6)	250 (38.0)	
NA	11 (0.8)	6 (0.9)	5 (0.8)	
Prior MI, n (%)				0.039
No	1008 (76.7)	501 (76.3)	507 (77.2)	
Yes	296 (22.5)	150 (22.8)	146 (22.2)	
NA	10 (0.8)	6 (0.9)	4 (0.6)	
Prior stroke, n (%)				0.022
No	1199 (91.2)	599 (91.2)	600 (91.3)	
Yes	89 (6.8)	44 (6.7)	45 (6.9)	
NA	26 (2.0)	14 (2.1)	12 (1.8)	
Prior pacemaker, n (%)				0.035
No	1170 (89.0)	585 (89.0)	585 (89.1)	
Yes	117 (8.90)	57 (8.7)	60 (9.1)	
NA	27 (2.1)	15 (2.3)	12 (1.8)	
Prior SAVR, n (%)				0.018
No	1223 (93.1)	611 (93.0)	612 (93.2)	
Yes	19 (1.4)	9 (1.4)	10 (1.5)	
NA	72 (5.5)	37 (5.6)	35 (5.3)	

(*Continued*)

Table 1. Continued

	Overall (n=1314)	Complete revascularization (n=657)	Incomplete revascularization (n=657)	SMD
Bicuspid aortic valve, n (%)				0.064
NA	71 (5.4)	36 (5.5)	35 (5.3)	
0	1193 (90.8)	592 (90.1)	601 (91.5)	
1	50 (3.8)	29 (4.4)	21 (3.2)	
CCS class, n (%)				0.063
1	876 (66.6)	436 (66.4)	440 (67.0)	
2	150 (11.4)	74 (11.2)	76 (11.6)	
3	106 (8.1)	50 (7.6)	56 (8.5)	
4	22 (1.7)	11 (1.7)	11 (1.7)	
NA	160 (12.2)	86 (13.1)	74 (11.2)	
NYHA class, n (%)				0.053
I	32 (2.4)	17 (2.6)	15 (2.3)	
II	407 (31.0)	204 (31.1)	203 (30.9)	
III	767 (58.4)	385 (58.6)	382 (58.1)	
IV	105 (8.0)	49 (7.4)	56 (8.5)	
NA	3 (0.2)	2 (0.3)	1 (0.2)	
AF, n (%)				0.035
No	949 (72.2)	473 (72.0)	476 (72.5)	
Yes	342 (26.0)	171 (26.0)	171 (26.0)	
NA	23 (1.8)	13 (2.0)	10 (1.5)	
STS mortality score, % median [IQR]	4.8 [3.0–5.7]	5.0 [3.0–5.5]	4.5 [2.9–5.7]	0.009
LVEF, % median [IQR]	55.0 [45.0–60.0]	55.0 [45.0–60.0]	55.0 [44.0–60.0]	0.002
Aortic mean gradient, mmHg, median [IQR]	44.0 [36.0–51.0]	44.0 [35.0–51.0]	44.0 [36.0–51.0]	0.022
AVA, cm^2 median [IQR]	0.7 [0.6–0.8]	0.7 [0.6–0.8]	0.7 [0.6–0.8]	0.004
Aspirin, n (%)	872 (70.4)	465 (76.1)	407 (64.9)	0.247
Clopidogrel, n (%)	513 (41.4)	337 (55.2)	176 (28.1)	0.571
Ticagrelor, n (%)	9 (0.9)	4 (0.7)	5 (1.1)	0.040
Prasugrel, n (%)	15 (1.5)	8 (1.5)	7 (1.6)	0.008
DOAc, n (%)	167 (13.4)	89 (14.6)	78 (12.4)	0.063
Vitamin K antagonist, n (%)	137 (11.1)	56 (9.2)	81 (12.9)	0.121
DAPT*, n (%)	455 (34.6)	298 (45.4)	157 (23.9)	0.507
DAT*, n (%)	95 (7.2)	53 (8.1)	42 (6.4)	0.133
TAT*, n (%)	71 (5.4)	46 (7.0)	29 (4.4)	0.245

AF indicates atrial fibrillation; AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; DAT, dual anti-thrombotic therapy; DAPT, dual antiplatelet therapy; DOAc, direct-acting oral anticoagulants; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; PAD, peripheric artery disease; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SMD, standardized mean difference; STS, Society of Thoracic Surgeon; TAT, triple anti-thrombotic therapy; and TAVI, transcatheter aortic valve implantation.

*Data on anti-thrombotic therapy at the time of TAVI not available for 75 patients.

Registry Outcomes

The primary outcome of the study was all-cause death at 2 years. The co-primary outcome was the composite of all-cause death, stroke, myocardial infarction (MI), and heart failure (HF) rehospitalization at 2 years. Secondary outcomes included in-hospital complications and stroke, MI, rehospitalization for HF, and unplanned PCI at 2 years.

Statistical Analysis

Categorical variables are reported as counts and percentages. Continuous variables are reported as medians and interquartile ranges. Continuous variables were compared with the *t*-test or Mann-Whitney *U* test for paired samples, and categorical variables were compared with the χ^2 statistics, Fischer exact, or McNemar tests for paired samples as appropriate.

To account for the nonrandomized design of our study, adjustment with propensity score matching (PSM) was used. The propensity score was estimated using a logistic regression model according to a nonparsimonious approach.

Variables included in the PSM were sex, age, body mass index, diabetes, hypertension, peripheral artery disease, chronic obstructive pulmonary disease, renal failure (defined as estimated glomerular filtration rate<30 mL/min), prior coronary artery bypass grafting, prior PCI, prior MI, prior stroke, prior pacemaker implantation, New York Heart Association classification, Canadian

cardiovascular society (CCS) classification, prior surgical aortic valve replacement, atrial fibrillation (AF), Society of Thoracic Surgeons mortality score, left ventricle ejection fraction, aortic mean gradient, and aortic valve area (Figure S1). One-to-one PSM with the nearest neighbor method with a caliper width of 0.1 of the standard deviation of propensity score logit was used.

Time-to-event curves for the primary and co-primary outcomes were estimated using Kaplan-Meier method. Cumulative incidence functions of stroke, MI, HF rehospitalization, and unplanned PCI were estimated using Fine and Gray method considering all-cause death as a competing event.

Estimates of the hazard ratios and subdistributional hazard ratios (SHR) with their 95% CI were calculated with the use of Cox proportional and Fine-Gray hazard models, respectively. Ten subgroups of patients were prespecified: age younger or older than 75 years, Society of Thoracic Surgeons mortality score higher or lower than 4%, angina at baseline, diabetes, left ventricular ejection fraction higher or lower than 40%, New York Heart Association class I/II or III/IV, renal failure, proximal CAD, multivessel CAD, and left main/proximal anterior descending artery CAD. The prespecified subgroups were tested for interaction considering primary and co-primary outcomes. All statistical tests were performed 2-tailed, and *P* value <0.05 was considered as the threshold for statistical significance (*P* value <0.10 for interaction tests). All statistical analyses were performed with R software version 3.6.3 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics of the Prematching Population

A total of 2404 patients with significant, stable CAD undergoing TAVI from January 2015 to September 2021 were enrolled in the REVASC-TAVI registry. After excluding 377 patients with no data at follow-up and in which the completeness of revascularization was unknown, 2025 patients formed the prematching population, and their baseline demographic and clinical characteristics are listed in Table S1. Among these, complete and incomplete myocardial revascularization was achieved in 1310 (64.7%) and 715 (35.3%) patients, respectively (Figure 1).

Propensity-Matched Groups - Patient Population

After adjusting for baseline confounders using the propensity score method, a total of 675 pairs of patients

Table 2. CAD Characteristics of the Matched Population

	Overall (n=1314)	Complete revascularization (n=657)	Incomplete revascularization (n=657)	*P* value
CAD characteristics				
Diseased vessels				<0.001
1, n (%)	668 (50.8)	434 (66.1)	234 (35.6)	
2, n (%)	382 (29.1)	150 (22.8)	232 (35.3)	
≥3, n (%)	264 (20.1)	73 (11.1)	191 (29.1)	
Right dominance, n (%)	1051 (82.5)	516 (82.3)	535 (82.7)	0.883
Coronary segment involved				
LM, n (%)	160 (12.2)	91 (13.8)	69 (10.5)	0.076
Proximal LAD, n (%)	409 (31.1)	198 (30.1)	211 (32.1)	0.475
Mid LAD, n (%)	506 (38.5)	249 (37.9)	257 (39.1)	0.692
Distal LAD, n (%)	106 (8.1)	42 (6.4)	64 (9.7)	0.033
Diagonal, n (%)	215 (16.4)	64 (9.7)	151 (23.0)	<0.001
Proximal LCx, n (%)	262 (19.9)	99 (15.1)	163 (24.8)	<0.001
Mid LCx, n (%)	163 (12.4)	57 (8.7)	106 (16.1)	<0.001
Distal LCx/PDA, n (%)	73 (5.6)	26 (4.0)	47 (7.2)	0.015
Obtuse marginal, n (%)	207 (15.8)	53 (8.1)	154 (23.4)	<0.001
Proximal RCA, n (%)	373 (28.4)	160 (24.4)	213 (32.4)	0.001
Mid RCA, n (%)	285 (21.7)	112 (17.0)	173 (26.3)	<0.001
Distal RCA/PL/PDA, n (%)	184 (14.0)	52 (7.9)	132 (20.1)	<0.001
Venous/arterial graft, n (%)	50 (3.8)	25 (3.8)	25 (3.8)	1.000
Calcific disease, n (%)	296 (25.0)	132 (22.4)	164 (27.5)	0.044
Bifurcation involved, n (%)	289 (26.4)	151 (29.0)	138 (24.0)	0.074
Multivessel CAD, n (%)	646 (49.2)	223 (33.9)	423 (64.4)	<0.001
Proximal CAD, n (%)	834 (63.5)	408 (62.1)	426 (64.8)	0.330
LM/proximal LAD CAD, n (%)	485 (36.9)	240 (36.5)	245 (37.3)	0.819

CAD indicates coronary artery disease; LCx, left circumflex artery; LAD, left anterior descending; LM, left main; PL, posterolateral; PDA, posterior descending artery; and RCA, right coronary artery.

having or not complete myocardial revascularization were matched, with all standardized mean differences (SMDs) of baseline confounders taken into account for PSM below 10% (Table 1).

Patients had a median age of 82.6 years with a median Society of Thoracic Surgeons mortality risk of 4.8%. Patients achieving complete revascularization had higher rates of dual anti-platelet therapy (DAPT; 45.4% versus 23.9%), dual (8.1% versus 6.4%) and triple (7.0% versus 4.4%) anti-thrombotic (DAT and TAT) therapies before TAVI.

Coronary Artery Disease Characteristics

Details of CAD distribution and severity found at the time of coronary angiogram for TAVI work-up are reported in Table 2. Patients achieving incomplete revascularization had more frequently multivessel (33.9% versus 64.4%, *P*<0.01), 3-vessel (11.1% versus 29.1%, *P*<0.01), and calcific CAD (22.4% versus 27.5%, *P*=0.04). No differences in terms of CAD involving proximal segments (62.1% versus 64.8%, *P*=0.33), LM or proximal LAD (36.5% versus 37.3%, *P*=0.82),and bifurcations (29.0 versus 24.0, *P*=0.07) were reported between patients achieving complete or incomplete revascularization.

Percutaneous Coronary Intervention Characteristics

A total of 1225 coronary lesions were treated with PCI in the matched population. Staged and concomitant PCI procedures were performed in 72.1% and 26.3% of matched patients, respectively, with no difference between groups (*P*=0.630). Staged PCI procedures were performed before TAVI in the majority of patients (n=579/681, 85.0%), at a median time of 35 days from TAVI. Invasive assessment of lesion severity with the use of intravascular ultrasound or optical coherence tomography (n=55, 5.5%), fractional flow reserve, or instantaneous wave-free ratio (n=74, 7.5%) was infrequent. Rates of proximal vessel PCI were comparable among matched patients achieving complete or incomplete revascularization (59.7% versus 65.5%, *P*=0.10). PCI of LM/proximal LAD and multivessel PCI were performed more frequently in patients achieving incomplete revascularization (33.8% versus 40.8% and 22.5% versus 34.2%, respectively; *P*=0.05 and *P*<0.01, respectively; Table 3). Details of PCI procedures performed are reported in Table S2.

TAVI Procedure Characteristics

TAVI procedures were performed mainly through a transfemoral approach (n=1238, 94.9%), under local anesthesia (n=1103, n=84.6%). The balloon-expandable Edwards SAPIEN 3/Ultra (Edwards LifeSciences, Irvine, CA) (n=494, 37.8%) and the self-expanding Evolut R/PRO/PRO+ (Medtronic Inc, Marlborough, MA; n=493, 37.7%) were the most frequently used TAVI devices. Details of TAVI procedures were reported in Table S3.

Registry Outcomes

The primary (21.6% versus 18.2%, hazard ratio 0.88 [95% CI, 0.66–1.18]; *P*=0.38) and co-primary composite (29.0% versus 27.1%, hazard ratio 0.97 [95% CI, 0.76–1.24]; *P*=0.83) outcomes did not differ between complete and incomplete revascularization groups (Figure 2). These results did not differ when incomplete revascularization group was further split considering patients receiving PCI or treated conservatively (21.6% versus 18.5% versus 18.0%, and 29.0% versus 27.3% versus 26.9% for primary and co-primary outcome, respectively; *P*=0.63 and *P*=0.94, respectively; Figure 3).

Table 3. PCI Characteristics of the Matched Population

	Overall (n=1314)	Complete revascularization (n=657)	Incomplete revascularization (n=657)	*P* value
PCI, n (%)	944 (71.8)	657 (100.0)	287 (43.7)	<0.001
PCI timing, n (%)				0.027
NA	11 (1.2)	4 (0.6)	7 (2.4)	
Staged before TAVI	579 (61.3)	408 (62.1)	171 (59.6)	
Staged after TAVI	102 (10.8)	73 (11.1)	29 (10.1)	
Concomitant to TAVI, before valve deployment	190 (20.1)	124 (18.9)	66 (23.0)	
Concomitant to TAVI, after valve deployment	59 (6.2)	47 (7.2)	12 (4.2)	
Unplanned PCI	3 (0.3)	1 (0.2)	2 (0.7)	
PCI in proximal vessels*, n (%)	580 (61.4)	392 (59.7)	188 (65.5)	0.095
Multivessel PCI*, n (%)	246 (26.1)	148 (22.5)	98 (34.2)	<0.001
LM/proximal LAD PCI*, n (%)	339 (35.9)	222 (33.8)	117 (40.8)	0.046

LAD indicates left anterior descending; LM, left main; NA, not available; PCI, percutaneous coronary intervention; and TAVI, transcatheter aortic valve implantation.

*Percentages are referred to the total number of PCI performed (n=944).

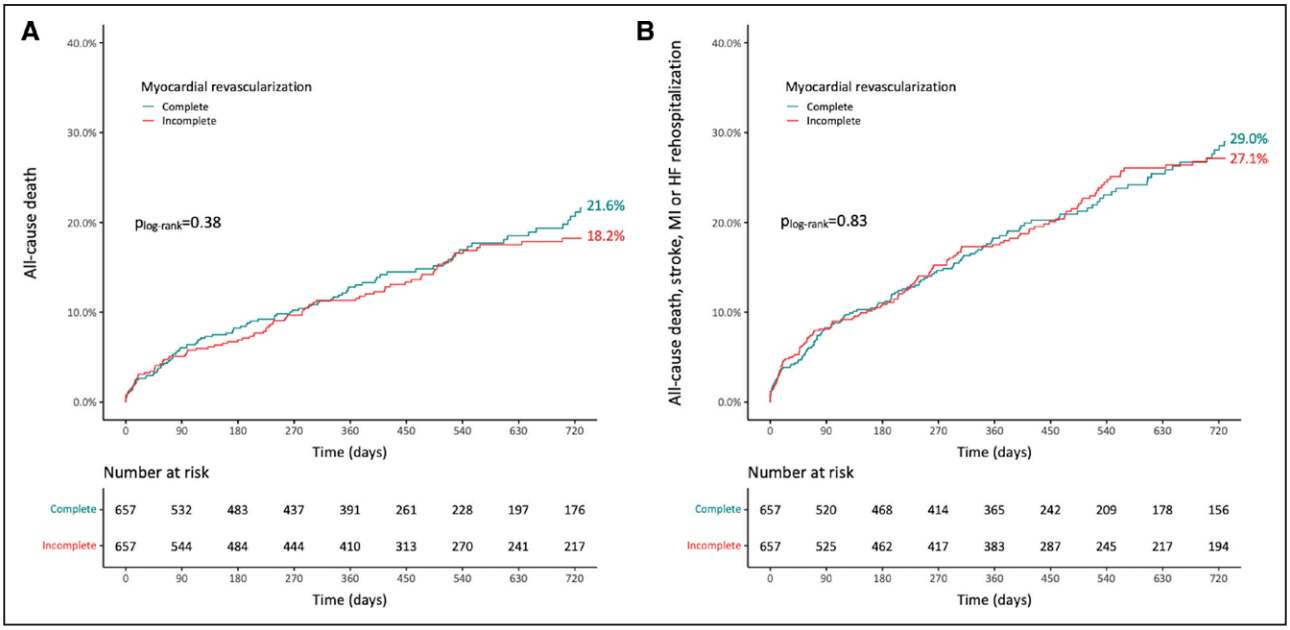

Figure 2. Time-to-event curves of registry outcomes.
A, Primary outcome; **B**, co-primary outcome. HF indicates heart failure; and MI, myocardial infarction.

No differences in stroke (3.2% versus 4.2%, SHR 1.35, [95% CI, 0.70–2.62]; *P*=0.37), MI (2.4% versus 2.7%, SHR 1.27, [95% CI, 0.53–3.00]; *P*=0.59), HF rehospitalization (6.5% versus 7.3%, SHR 1.17 [95% CI, 0.73–1.87]; *P*=0.51), and unplanned PCI (2.6% versus 2.8%, SHR 1.14 [95% CI, 0.53–2.47]; *P*=0.74) were reported between matched patients achieving either complete or incomplete revascularization (Figure 4).

No differences of in-hospital outcomes between patients achieving complete or incomplete revascularization were reported (Table 4).

In-hospital outcomes of patients according to the PCI strategy are reported in Table S4.

A multivariate regression analysis of factors associated with 2-years all-cause death, and outcomes of patients receiving different PCI strategies, including staged PCI versus concomitant PCI, multivessel versus

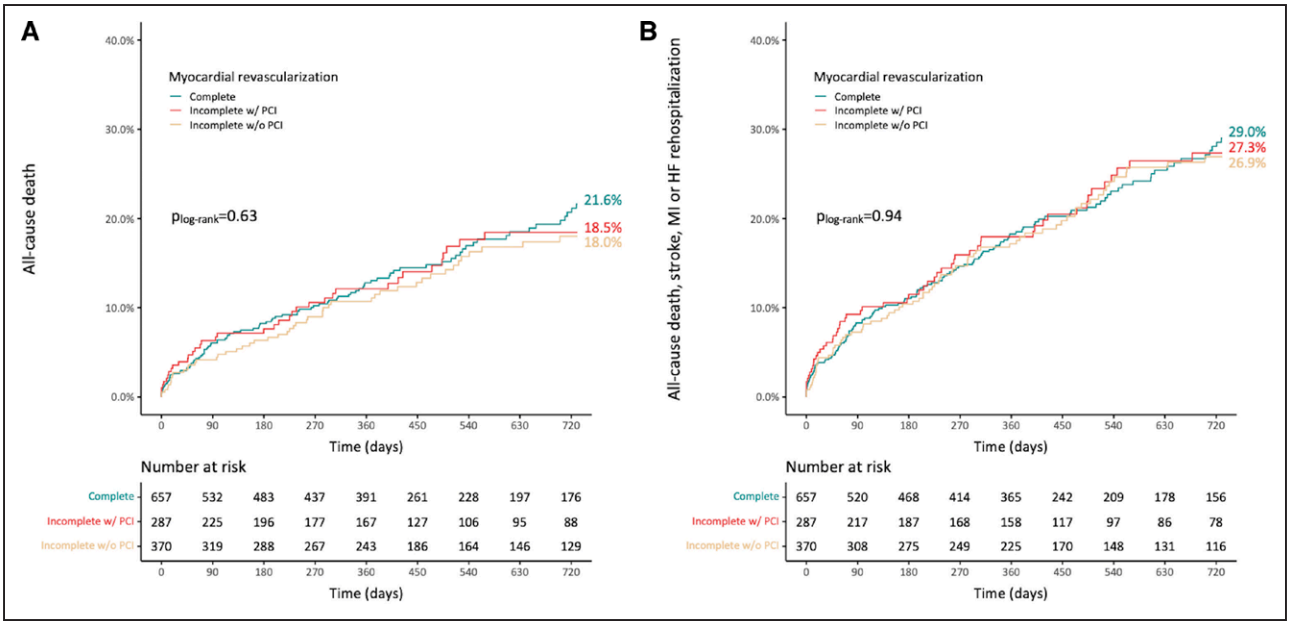

Figure 3. Time-to-event curves of registry outcomes considering patients receiving percutaneous coronary intervention (PCI) or medical therapy among those achieving incomplete myocardial revascularization.
A, Primary outcome; **B**, co-primary outcome. HF indicates heart failure; and MI, myocardial infarction.

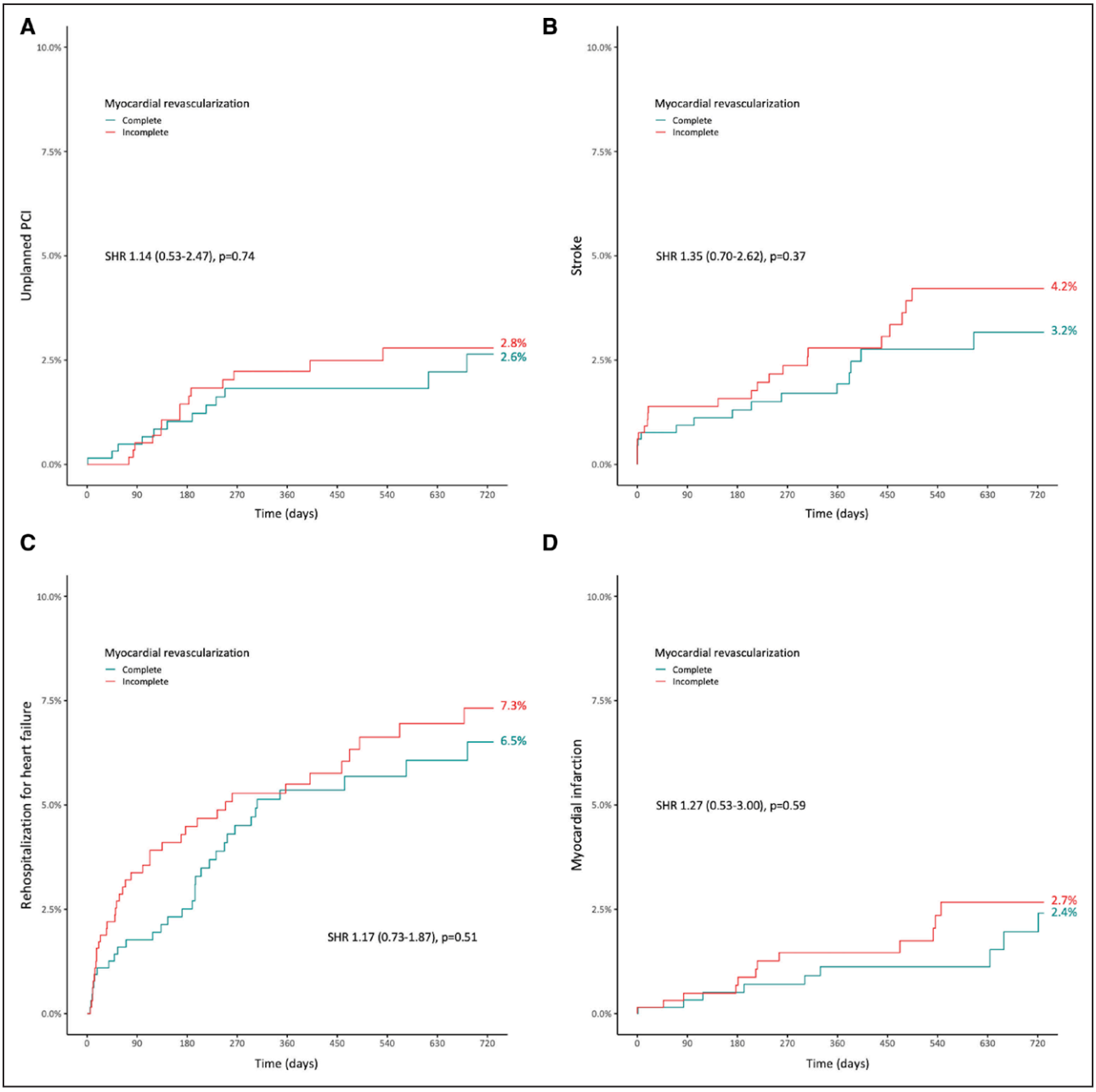

Figure 4. Cumulative incidence of secondary outcomes and subdistributional hazard ratios (SHR) according to the Fine and Gray method.

A, Unplanned percutaneous coronary intervention (PCI); **B**, stroke; **C**, rehospitalization for heart failure; **D**, myocardial infarction.

single-vessel PCI, proximal vessel or mid-distal PCI, and LM/proximal LAD PCI or other-vessel PCI, are provided in Table S5, and Figures S2 and S3, respectively.

Subgroup Analysis

For the primary and co-primary outcomes, there was no differential treatment effect in a number of prespecified subgroups (Figure 5; Figure S4). Among all, the lack of benefit of complete revascularization was consistently observed among younger and older patients (cut-off value 75 years) (P=0.39 and P=0.65 for interaction for the primary and co-primary outcomes, respectively), and among those presenting with and without angina (P=0.81 and P=0.98 for interaction for the primary and co-primary outcomes, respectively).

DISCUSSION

The main findings of this analysis of the multicenter REVASC-TAVI registry were as follows: (1) Completeness of myocardial revascularization in elderly, intermediate-risk

Table 4. In-Hospital Outcomes After TAVI of the Matched Population

	Overall (n=1314)	Complete revascularization (n=657)	Incomplete revascularization (n=657)	*P* value
Death, n (%)	34 (2.6)	17 (2.6)	17 (2.6)	1.000
Cardiovascular death, n (%)	22 (1.7)	13 (2.0)	9 (1.4)	0.520
Disabling stroke, n (%)	15 (1.2)	7 (1.2)	8 (1.2)	1.000
Not disabling stroke, n (%)	18 (1.5)	7 (1.3)	11 (1.7)	0.481
MI, n (%)	7 (0.6)	4 (0.6)	3 (0.5)	0.725
PPI, n (%)	163 (13.8)	81 (13.7)	82 (13.9)	0.933
New onset LBBB, n (%)	177 (15.0)	91 (15.3)	86 (14.6)	0.745
New onset AF, n (%)	33 (3.0)	20 (3.5)	13 (2.4)	0.293
Life-threatening bleeding, n (%)	25 (1.9)	14 (2.2)	11 (1.7)	0.553
Major bleeding, n (%)	72 (5.5)	39 (6.0)	33 (5.1)	0.469
Minor bleeding, n (%)	100 (7.7)	50 (7.7)	50 (7.7)	1.000
Major vascular complication, n (%)	62 (4.8)	33 (5.1)	29 (4.5)	0.605
Minor vascular complication, n (%)	96 (7.4)	51 (7.9)	45 (6.9)	0.526
AKI, n (%)				0.786
Stage 1	86 (6.7)	46 (7.2)	40 (6.2)	
Stage 2	19 (1.5)	8 (1.3)	11 (1.7)	
Stage 3	22 (1.7)	10 (1.6)	12 (1.9)	
Aortic mean gradient, median [IQR]	8.0 [6.0–11.0]	8.0 [6.0–11.0]	8.0 [6.0–10.0]	0.700
PVR grade, n (%)				0.110
None/trivial	565 (46.4)	272 (44.4)	293 (48.4)	
Mild	576 (47.3)	308 (50.3)	268 (44.3)	
Moderate/severe	76 (6.3)	32 (5.2)	44 (7.3)	
Length of stay, median [IQR]	4.0 [2.0–7.0]	5.0 [2.0–7.0]	4.0 [2.0–6.7]	0.026

AF indicates atrial fibrillation; AKI, acute kidney injury; IQR, interquartile range; LBBB, left bundle branch block; MI, myocardial infarction; PPI, permanent pacemaker implantation; PVR, paravalvular regurgitation; and TAVI, transcatheter aortic valve implantation.

TAVI patients did not impact on all-cause death as well as a composite of all-cause death, stroke, MI, and rehospitalization for HF at 2 years; (2) The equipoise between the 2 revascularization strategies in terms of 2-year outcomes was consistent across different prespecified subgroups, including younger patients (<75 years) and those presenting with angina, stenoses on proximal vessel segments, and left ventricular dysfunction.

The possibility to offer patients affected by severe AS and concomitant CAD a proven, transcatheter alternative to surgery has opened new questions about the need to revascularize coronary artery lesions at the time of TAVI. Indeed, if complete myocardial revascularization is recommended in case of surgical aortic valve replacement, less invasive transcatheter treatments offer the opportunity to defer the treatment of either CAD or aortic valve stenosis, balancing the sequence of the treatment according to patients' clinical status and presentation.

The main obstacle in evaluating the need of stable CAD revascularization in patients affected by symptomatic, severe AS lies in the fact that commonly used noninvasive myocardial ischemia testing are contraindicated or affected by presence of this valvopathy.[2,15] Besides, data regarding the applicability of invasive functional testing (instantaneous wave-free ratio/fractional flow reserve) in this setting are sparse, based on nonrandomized studies, and warrant further validation.[16–18]

To date, the benefit of coronary revascularization in the setting of TAVI has been mainly investigated in small, nonrandomized studies, and results are contradictory.[5,6,8,10] The ACTIVATION study is the only randomized clinical trial that explored the benefit of PCI in patients undergoing TAVI with significant CAD.[14] The trial showed similar rates of the primary composite end point of all-cause death and rehospitalization at 1 year in patients receiving PCI or not (41.5% versus 44.0%). However, the study was interrupted prematurely due to the slow recruitment and did not meet the pre-established noninferiority margin (*P*=0.067), thus preventing the authors to draw definite conclusions on this topic. In addition, the trial excluded patients with LM disease or anginal symptoms (CCS≥3).

The present study showed that, among TAVI patients found to have significant CAD during the TAVI work-up, a strategy of complete revascularization did not confer a clinical benefit compared with an incomplete revascularization with respect to all-cause death and the composite of all-cause death, stroke, MI, and rehospitalization for HF at 2 years. These findings are in line with those reported by previous

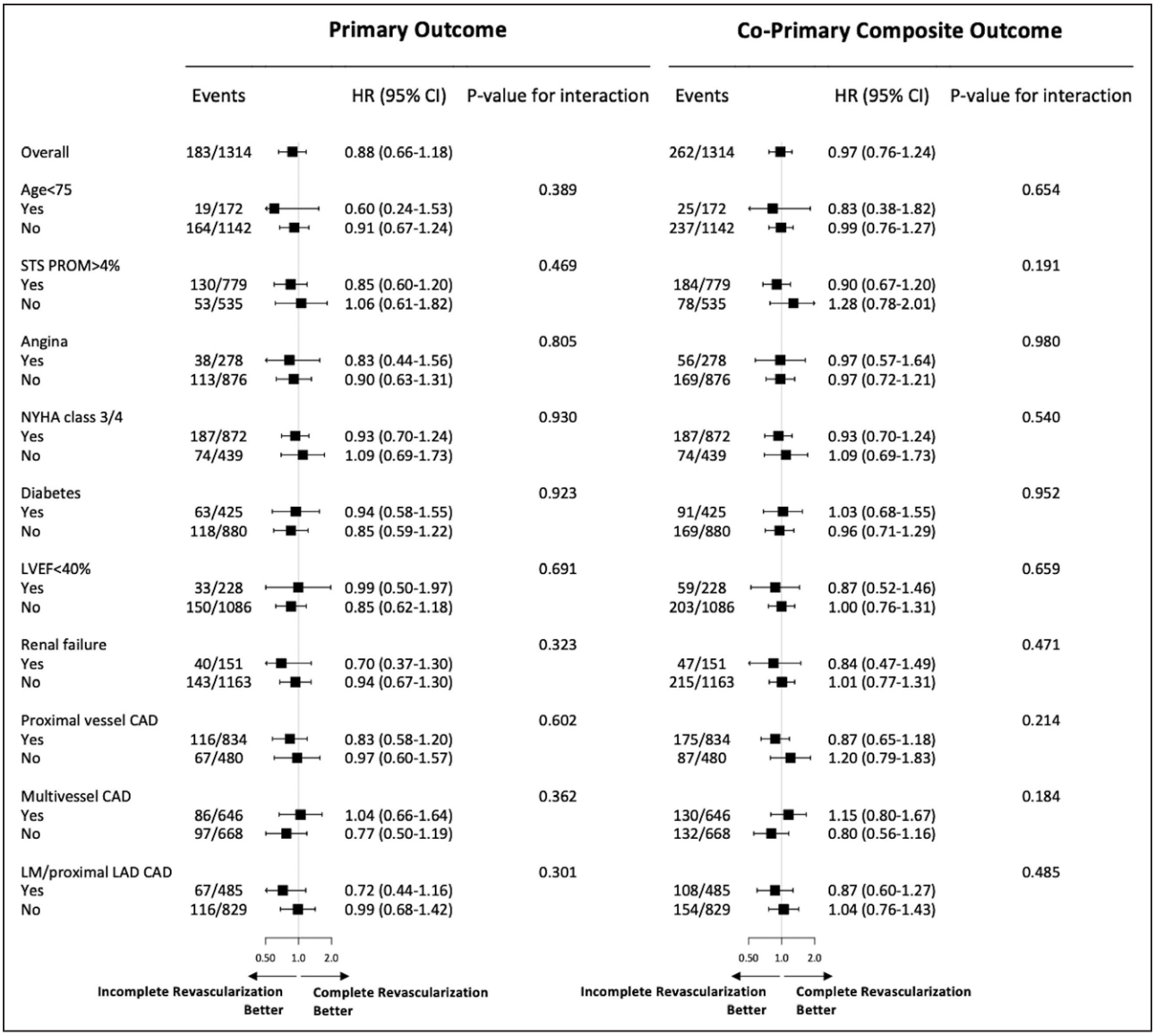

Figure 5. Subgroups analysis of primary and co-primary composite outcomes.
CAD indicates coronary artery disease; HR, hazard ratio; LAD, left anterior descending; LM, left main; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and STS PROM, Society of Thoracic Surgeons predicted risk of mortality.

studies and meta-analyses that evaluated a complete-revascularization strategy in TAVI patients.[13,19] However, these series were smaller and did not provide enough granularity of information regarding CAD severity, distribution, and PCI details.

Of note, the median age of the REVASC-TAVI registry population was 82.6 years. This key aspect recommends a cautious generalization of these findings: in fact, we might argue that the impact of nonrevascularized CAD may be more relevant in younger patients with longer life span. However, the current evidence in the setting of isolated, stable ischemic heart disease in younger populations showed a lack of benefit of PCI over medical therapy in terms of hard outcomes.[20–23]

In the attempt to further address this issue, a subgroup analysis was performed.

Interestingly, we found a consistent lack of benefit of complete revascularization regardless of whether PCI in all significant coronary stenoses was performed in younger patients and those presenting with angina, left ventricular dysfunction, and a larger area of myocardium at risk.

The results of the present analysis tend to support a highly conservative approach of significant, stable CAD in TAVI setting, particularly when dealing with patients ≥80 years. Given the limitations of ischemia testing in the setting of severe AS, the possibility to offer TAVI first and then stratify the need of revascularization in patients with stable CAD by proper testing should be carefully evaluated by local Heart Teams in presence of combined CAD and severe AS. Nevertheless, possible difficulties in accessing the coronary arteries after TAVI should be carefully evaluated, especially when using transcatheter

aortic valves with tall stent frame and small cell design.[24] In this view, an accurate transcatheter valve selection for each patient is mandatory. Future improvements in TAVI devices with the possibility to obtain a safe and more predictable bioprosthetic commissural alignment are particularly awaited to improve coronary access after TAVI.[25] Finally, also the impact of coronary revascularization (PCI) on anti-thrombotic therapy (dual antiplatelet therapy)—and a possible concomitant higher bleeding risk—should be taken into account and balanced against other clinical outcomes such as need for urgent revascularization, MI, or death.

Limitations

This was an observational study without independent adjudication of events or an independent core laboratory imaging analysis. First, although PSM adjustment have resulted into 2 comparing groups with homogeneous baseline characteristics, unmeasured confounders might remain and have affected the results due to the nonrandomized nature of the study. Besides, we cannot exclude a potential bias from mixing the patients with both established CAD and those with newly diagnosed CAD through TAVI workup. Second, due to the retrospective nature of the study, the decision to perform PCI as revascularization versus medical management for CAD was at the discretion of the Heart Team of each participating center and without consistent selection criteria. Third, the use of functional invasive or noninvasive tests to guide coronary revascularization with PCI was particularly low in the REVASC-TAVI registry (<10%), but this reflects the current practice; recent small series showed that incomplete functional revascularization was associated with adverse clinical outcomes after TAVI, but this hypothesis needs to be validated by larger and randomized studies. Therefore, although it is possible that a higher adoption of an fractional flow reserve/instantaneous wave-free ratio-based approach to guide PCI could have improved the appropriateness of revascularization, it is unclear how this strategy might have influenced the effect on hard clinical outcomes. Fourth, the registry did not collect data regarding symptoms at follow-up. Finally, data on antithrombotic therapy duration and compliance at follow-up had a lot of missing; therefore, it was decided to not include this information in the article.

Conclusions

The present analysis of the REVASC-TAVI registry showed that, among elderly, intermediate-risk TAVI patients found to have significant stable CAD during the TAVI work-up, completeness of myocardial revascularization achieved either staged or concomitantly with TAVI was similar to a strategy of incomplete revascularization in reducing the risk of all cause death, as well as the risk of death, stroke, MI, and rehospitalization for HF at 2 years. Randomized controlled trials are needed to determine the role of routine revascularization in patients with significant CAD undergoing TAVI.

ARTICLE INFORMATION

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Supplemental Material

Participating centers
Registry case report form
Enrollment criteria
Tables S1–S5
Figures S1–S4

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