Impact of Coronary Revascularization in Patients Who Underwent Transcatheter Aortic Valve Implantation

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Coronary artery disease (CAD) is a common co-morbidity in transcatheter aortic valve implantation (TAVI) patients, but the prognostic value of coronary revascularization before TAVI is currently unknown. The aim of the present study was to assess the impact of coronary revascularization in patients who underwent TAVI. Patients underwent TAVI from 2008 to 2016 were included in the study. Baseline SYNTAX score and residual SYNTAX score (rSS) after percutaneous coronary intervention were calculated. Based on rSS, patients were classified as complete revascularization (rSS = 0), reasonably incomplete revascularization (rSS >0 and <8), and incomplete revascularization (rSS ≥8). The primary objective was to evaluate the impact of CAD and rSS on major cardiovascular adverse events (MACEs). The secondary objective was to assess the impact of rSS on hospitalization for heart failure. A total of 349 patients (mean age 82.4 ± 5.7 years, 53% women) were included in the study. A total of 187 patients (53.6%) had CAD (mean baseline SYNTAX score 9.2 ± 8.1). Percutaneous coronary intervention was performed in 29.9% of patients, achieving reasonably incomplete revascularization in 45.4%, and incomplete revascularization in 24.5%. The mean follow-up was 35.2 ± 25.3 months. No differences were observed in MACE rate between the CAD and non-CAD groups, or between the different degrees of revascularization. Differences were also not seen in the different levels of revascularization and hospitalization due to heart failure. In patients who underwent TAVI in this study, no association was found between the presence of CAD or the degree of revascularization in a long-term follow-up. **(Am J Cardiol 2019;123:948−955)**

Between 41% and 75% of patients with aortic stenosis (AS) who underwent transcatheter aortic valve implantation (TAVI) present with concomitant coronary artery disease (CAD).[1-5] In surgical series of aortic valve replacement (SVR), the presence of CAD has been associated with increased surgical risk and complications, as well as worse long-term prognosis and higher mortality.[6−9] However, the influence of CAD and its treatment on prognosis is not clear in patients who underwent TAVI. According to clinical practice guidelines, significant CAD must be treated during SVR, though it increases surgical risk and the duration of the procedure.[10-11] In TAVI patients, percutaneous coronary intervention (PCI) should be considered if there is >70% stenosis in the proximal segment of a main artery (class IIa, level of evidence C).[12] Several studies have dealt with this issue, but with contradictory results. The present study aims to provide new evidence regarding the need for PCI before TAVI in patients with CAD.

Methods

A total of 349 consecutive patients with severe symptomatic AS who underwent TAVI at our center between November 2008 and August 2016 were included in this observational retrospective study. All patients were evaluated by a multidisciplinary team. Severe AS was defined by aortic valve area <1 cm^2 or transvalvular mean gradient >40 mm Hg according to current clinical practice guidelines. The present study was carried out in accordance with the principles of the Declaration of Helsinki.

Coronary angiography was performed on all patients before TAVI. The presence of CAD was defined as the presence of 1 or more lesions in the epicardial coronary arteries, with stenosis ≥50% in vessels with a diameter ≥1.5 mm.[13] The baseline Syntax score (bSS) was evaluated by 2 expert interventionist cardiologists trained in Syntax score evaluation using an online calculator (www.syntaxscore.com, version 2.1) and blinded to outcome data. In case of disagreement, the opinion of a third observer was obtained for final decision. In the group of patients with previous revascularization, if a coronary artery had no significant lesion, it was not considered for calculation of the

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score, but these patients were included in the CAD group. The CABG SYNTAX score was used in patients with previous surgical revascularization.

The residual Syntax score (rSS) was calculated by the same interventional cardiologists after reviewing the angiographic images after PCI. Patients were divided into 3 groups according to the rSS: complete revascularization (CR; rSS = 0), reasonably incomplete revascularization (RIR; 0> rSS <8), and incomplete revascularization (IR; rSS ≥8). The cutoff of 8 points was chosen according to previous studies.[3,14]

The decision to perform PCI before TAVI due to CAD was at the discretion of the heart team, taking into account patient's symptoms, detection of functional myocardial ischemia, viable myocardium at risk, angiographic documentation of significant stenoses (≥50% in TCI, ≥70% in proximal segments of the rest of coronary arteries), and technical complexity. The PCI technique was at the discretion of the interventional cardiologist. In most cases, revascularization was performed at least 1 month before TAVI. After PCI, dual antiplatelet therapy consisting of 100 mg aspirin and 75 mg clopidogrel was maintained for 3 to 6 months depending on the patient's bleeding risk, regardless of the type of stent (bare metal stent or drug-eluting stent).

TAVI was performed under general anesthesia in the first 28 cases and in all procedures by axillary artery approach (7%); in the remaining cases local anesthesia with conscious sedation were used. All procedures were performed using the self-expanding CoreValve (Medtronic, Minneapolis, Minnesota). For a proper assessment of the aortic annulus, prosthesis size, and morphology of the access path, a computed tomography-based evaluation was performed before implantation. The most frequent access route was percutaneous transfemoral, and surgical cutdown for axillary access was performed in 4% of cases. Complications were defined according to the consensus document of the Valve Academic Research Consortium-2.[15]

The objective of this study was to determine the prognostic value of CAD and the degree of revascularization according to the rSS in patients who underwent TAVI. The primary objective was a combination of major cardiovascular adverse events (MACEs), consisting of death from any cause, myocardial infarction (MI), and the need for new revascularization. As a secondary objective, we analyzed the effect of CAD and rSS on hospitalization due to heart failure (HF) after TAVI. Demographic, clinical, interventional, and follow-up data were retrospectively collected from electronic medical records and medical examinations at the hospital.

Categorical variables were analyzed using the chi-squared test and expressed as %. Continuous variables were analyzed by analysis of variance and expressed as mean ± standard deviation. All of the variables were stratified according to the 3 rSS groups to compare the baseline characteristics of the patients in relation to the presence of CR, RIR, or IR. Cox proportional hazard regression models were used, with the months until the first event appeared as the time. The predicted event rates were estimated from the unadjusted Cox regression models. Patients free of events were censored at the time of death or at the time of last medical contact depending on what occurred. Survival curves were constructed based on the Kaplan-Meier method and compared using the log-rank test. To evaluate the additive prognostic value of rSS as a continuous or categorical variable, multivariate models adjusted by the EuroSCORE II or STS score were developed. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Significance was set at $p < 0.05$. All statistical analyses were carried out in SPSS version 22.0 and Stata 14.0.

Results

The mean patient age was 82.4 ± 5.7 years and 53% were women. Of the 349 patients, 187 (54%) had CAD. Within the CAD group, CR was achieved in 56 patients (30%), RIR in 85 (45%), and IR in 46 (25%). The mean follow-up was 35.2 ± 25.3 months (interquartile range 15.6 to 53.3 months). Clinical follow-up was complete for all patients. Baseline characteristics of the patients are provided in Table 1. The group of patients with CAD had more dyslipidemia ($p \leq 0.001$) and left ventricular ejection fraction <50% ($p \leq 0.038$), which was more frequent in the IR group. The mean bSS was 9.2 ± 8.1 for the total population, and 5.6 ± 7.0, 7.1 ± 6.0, and 17.7 ± 8.5 for patients who achieved CR, IRI, and IR, respectively. The bSS strongly correlated with the rSS (Spearman's rho = 0.646, $p < 0.0001$), and patients with more coronary disease had a higher rSS (Figure 1). Figure 2 shows the different rSS groups according to the bSS. Thus, the highest % of CR were obtained in the groups with a lower bSS.

At the end of the follow-up, the total mortality for the total cohort was 40.1% (n = 140). The MACE rate was 43% (n = 151) during the follow-up. All-cause mortality was the most frequent event (40%, n = 140), followed by MI (6%, n = 20), and the need for new revascularization (3%, n = 12). Figure 3 shows the frequency of MACEs according to the rSS. The line representing MACEs increases slightly at the same time as rSS but does not reach significance. Figure 4 shows the Kaplan Meier curves for MACEs; no significant differences were observed between any of the groups. In the separate analyses of each end point of the primary objective (Figure 4), only the need for new revascularization (Log Rank p = 0.032) was more frequent in the group with CAD than the group without CAD. This difference was not reflected in the combined end point or in mortality when analyzed alone.

After TAVI, 32% (n = 112) of patients had at least 1 HF hospitalization at the end of follow-up. No significant differences were found when analyzing the influence of CAD and rSS on HF hospitalization (Log Rank p = 0.748 for the total population and p = 0581 in patients with CAD). No significant difference was found adding HF hospitalization to the MACEs (Log Rank p = 0.971 for total population and p = 0.928 for patients with CAD; Figure 5). After performing an adjustment with multivariable Cox proportional hazards regression, the bSS, CR, RIR, and IR were not associated with an increase in MACEs, even when the results were adjusted by STS score or EuroSCORE II (Table 2). When each of these events was broken down, only a higher incidence of reinfarction was observed in the IR group compared to the non-CAD group (HR 5.97, 95% CI 1.78 to 20.01, p = 0.004), and a greater need for new

Table 1
Baseline characteristics of the study groups

Variable	No CAD (n = 162)	Complete (n = 56)	Reasonably incomplete (n = 85)	Incomplete (n = 46)	p
Age (years)	82.9 ± 6.2	81.2 ± 4.7	82.6 ± 5.4	81.9 ± 6.0	0.277
Women	64.8%	39%	49%	33%	<0.001
BMI (kg/m^2)	29.6 ± 5.4	28.5 ± 4.9	28.2 ± 4.7	27.6 ± 3.6	0.042
Dyslipidemia	49.4%	63%	65%	80%	0.001
Diabetes Mellitus	22.2%	32%	28%	39%	0.111
Hypertension	82.7%	86%	86%	89%	0.722
Peripheral artery disease	4.4%	11%	21%	30%	<0.001
Prior heart failure	56.6%	53%	60%	61%	0.803
NYHA III-IV	95.7%	95%	94%	87%	0.180
LVEF <50%	11.1%	21%	21%	26%	0.038
PAP ≥55 mm Hg	28.4%	26%	18%	26%	0.315
Prior stroke	10.6%	11%	11%	20%	0.353
Atrial fibrillation	35.8%	23%	24%	28%	0.133
Bundle branch block	20.4%	20%	27%	20%	0.602
COPD	34.6%	21%	29%	17%	0.071
MDRD-4 <60 ml/min/1.73 m^2	49.4%	63%	52%	50%	0.393
Anemia	53.1%	57%	66%	54%	0.275
EuroSCORE II (per 1 point)	5.0 ± 4.0	6.2 ± 4.9	6.1 ± 5.1	7.9 ± 5.8	0.001
STS (points)	5.6 ± 3.5	6.8 ± 5.3	6.1 ± 3.6	5.9 ± 3.8	0.217
Syntax score (points)	–	5.6 ± 7.0	7.1 ± 6.0	17.7 ± 8.5	<0.001

BMI = body mass index; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; NYHA = New York Heart Association; PAP = pulmonary artery pressure.

Anemia was defined as a concentration of hemoglobine < 12 g/dL in women and < 13 g/dL in men.

revascularization in the RIR (HR 9.55, 95% CI 1.11 to 82.15, p = 0.040) and IR groups (HR 13.96, 95% CI 1.56 to 124.61, p = 0.018) in relation to the group without CAD.

Discussion

In this study, the presence of CAD and the need for PCI before TAVI had no influence on the development of MACEs. This lack of association was also observed when analyzing the influence of CAD and the rSS on readmission for HF after TAVI, either in isolation or when the HF was added to the combined end point. Our findings suggest that revascularization before TAVI should not be carried out routinely and should be personalized, likely in relation to clinical data and not just anatomical findings.

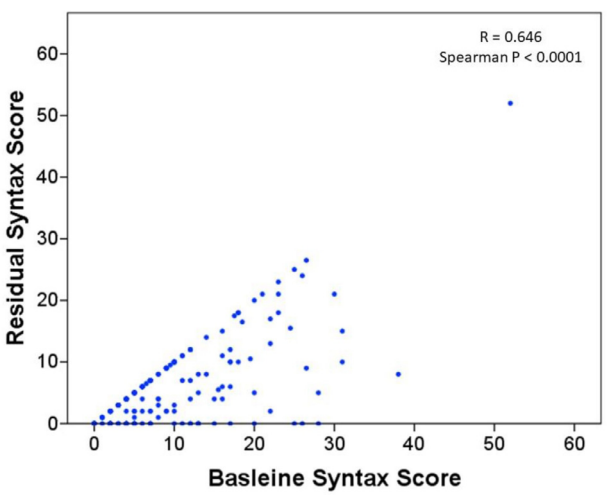

Figure 1. Relation between the baseline SYNTAX score (bSS) and the residual SYNTAX score (rSS) after percutaneous coronary intervention in 187 patients with coronary artery disease who underwent transcatheter aortic valve implantation. *Each point may represent more than one value. A strong correlation was present between bSS and rSS, though for any level of bSS, the range of post-PCI rSS varied considerably.

Although CAD is prevalent in patients who underwent TAVI,[1–5] its prognostic value is unclear and the indication for PCI before TAVI is not validated in this population. Analogous to SVR, PCI is recommended when it affects the proximal segments of the main vessels, with a level of evidence C due to the lack of data.[12] Some published studies point to a higher mortality in these patients,[16,17] whereas others reported no difference in prognosis.[5,18–20] In a meta-analysis of 7 studies including 2,472 patients with a mean follow-up of 452 days, CAD did not behave as a risk factor for higher mortality (OR 1.0, 95% CI 0.67 to 1.5).[21] In our study, with longer follow-up, we also found no prognostic influence of CAD on mortality from any cause.

Regarding PCI before TAVI, previous studies have compared TAVI plus PCI versus TAVI alone, with contradictory results. Recently, a meta-analysis of 9 studies with 3,858 patients (PCI was performed previously in 983) concluded that, in PCI pre-TAVI group, there were more vascular complications and greater mortality at 30 days (OR 1.42, 95% CI 1.08 to 1.87, p = 0.01), but there were no differences in mortality per year (OR 1.05, 95% CI 0.71 to 1.56) or the time of revascularization, regardless of it occurring before the implant or in the same procedure.[22] Our results are in line with what is described in this meta-analysis. However, unlike our

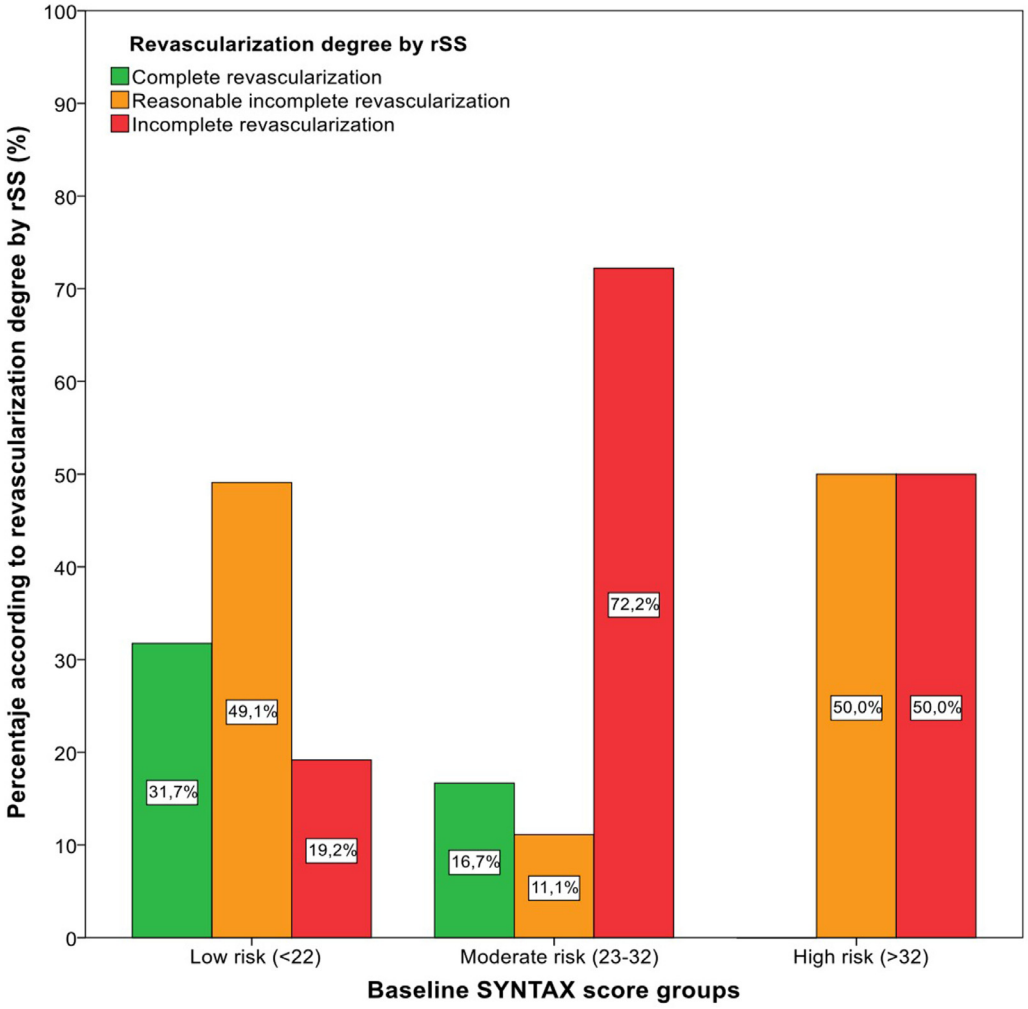

Figure 2. Completeness of revascularization stratified by residual SYNTAX score (rSS) according to the baseline SYNTAX score (bSS). Complete revascularization was frequent in the 2 upper-risk groups of the bSS.
rSS = residual SYNTAX score.

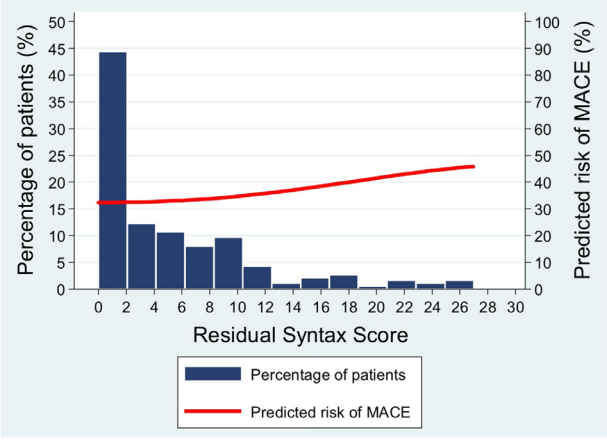

Figure 3. Histogram of the frequency of residual Syntax scores (dark blue bars) and mean predicted probability of MACEs (solid red line) (Color version of figure is available online.)
MACEs = major cardiovascular adverse events.

study, those studies did not take the revascularization result into account; thus, whether the degree of revascularization assessed by rSS had prognostic influence could not be determined. The data in the literature are contradictory in this sense. Paradis et al[5] studied the impact of the degree of revascularization on 377 TAVI patients and found no significant differences between the rSS <8 and rSS >8 groups for mortality from any cause at 30 days and 1 year, and for a combined end point of death, MI, and strokes per year. Van Mieghem et al[3] reported similar results, finding no difference in mortality per year between the CR and IR groups. These studies add validity to previous results.[23-25] In contrast to these studies, our study differentiated 3 groups according to the rSS in order to better discriminate the effect of revascularization, and the follow-up time was >1 year. Despite this, we did not find any prognostic impact of the different degrees of revascularization. Furthermore, Witberg et al[14] used method similar to ours and reported an increase in mortality in patients with severe CAD (Syntax score >22; OR 2.092, 95% CI

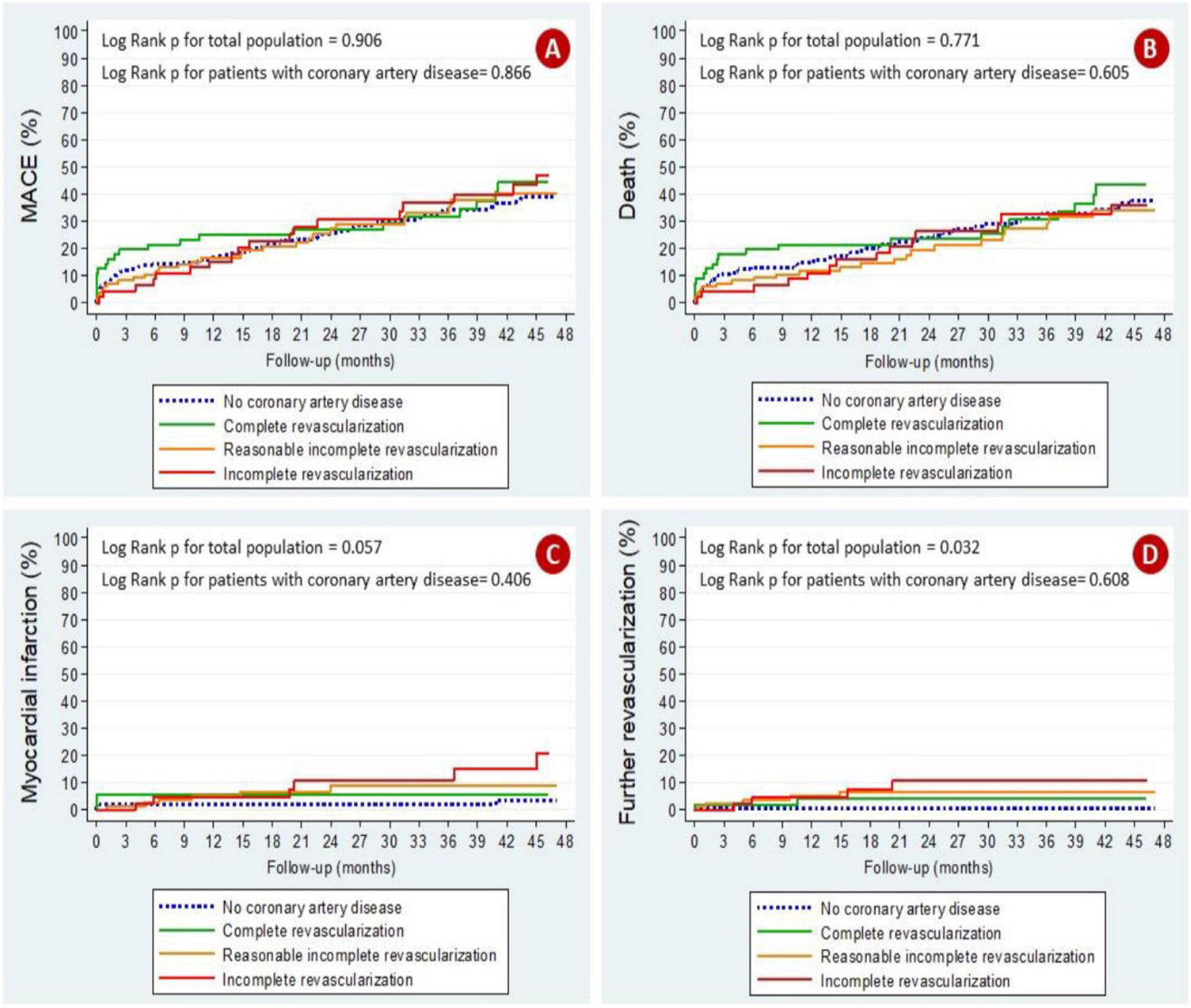

Figure 4. Kaplan-Meier curves showing cumulative event rates through 4 years MACE (*A*), death (*B*), myocardial infarction (*C*), and further revascularization (*D*), stratified by tertiles of rSS score. Adverse ischemic events were similar in incomplete revascularization compared with complete revascularization.
MACEs = major cardiovascular adverse events.

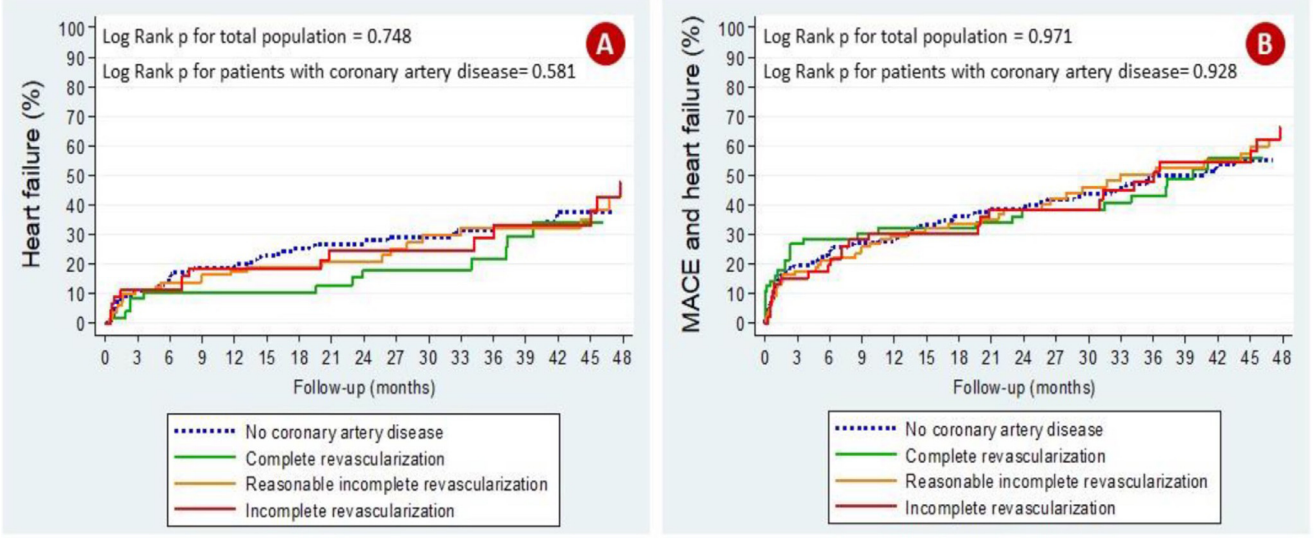

Figure 5. Kaplan-Meier curves showing cumulative event rates through 4 years for heart failure. Adverse ischemic events were similar in incomplete revascularization compared with complete revascularization.
MACEs = major cardiovascular adverse events.

Table 2
Cox survival models for MACE and MACE plus heart failure

	Variable		HR	95% CI	p
MACE	bSS (continuous variable)		1.02	0.99-1.04	0.217
	rSS (continuous variable)		1.02	0.99-1.05	0.272
	rSS adjusted by STS		1.02	0.99-1.05	0.154
	rSS adjusted by EuroSCORE II		1.01	0.98-1.04	0.480
	Degree of revascularization by rSS (reference: complete revascularization)	Reasonably incomplete	0.99	0.61-1.62	0.979
		Incomplete	1.20	0.71-2.03	0.506
	Degree of revascularization by STS-adjusted rSS (reference: complete revascularization)	Reasonably incomplete	1.02	0.63-1.67	0.923
		Incomplete	1.26	0.74-2.14	0.397
	Degree of revascularization by EuroSCORE II-adjusted rSS (reference: complete revascularization)	Reasonably incomplete	0.99	0.61-1.61	0.965
		Incomplete	1.07	0.62-1.84	0.805
	Degree of revascularization by rSS (reference: no coronary artery disease)	Complete	1.26	0.79-2.00	0.338
		Reasonably incomplete	1.25	0.84-1.95	0.273
		Incomplete	1.50	0.97-2.33	0.071
	Degree of revascularization by STS-adjusted rSS (reference: no coronary artery disease)	Complete	1.16	0.73-1.86	0.527
		Reasonably incomplete	1.19	0.80-1.78	0.392
		Incomplete	1.46	0.94-2.28	0.090
	Degree of revascularization by EuroSCORE II-adjusted rSS (reference: no coronary artery disease)	Complete	1.23	0.77-1.97	0.389
		Reasonably incomplete	1.22	0.82-1.82	0.332
		Incomplete	1.32	0.83-2.08	0.238
MACE and heart failure	bSS (continuous variable)		1.00	0.98-1.02	0.689
	rSS (continuous variable)		1.01	0.98-1.04	0.550
	rSS adjusted by STS		1.01	0.99-1.04	0.270
	rSS adjusted by EuroSCORE II		1.00	0.98-1.03	0.845
	Degree of revascularization by rSS (reference: complete revascularization)	Reasonably incomplete	1.12	0.72-1.74	0.627
		Incomplete	1.20	0.73-1.95	0.476
	Degree of revascularization by STS-adjusted rSS (reference: complete revascularization)	Reasonably incomplete	1.17	0.76-1.80	0.467
		Incomplete	1.30	0.81-2.10	0.277
	Degree of revascularization by EuroSCORE II-adjusted rSS adjusted (reference: complete revascularization)	Reasonably incomplete	1.15	0.74-1.78	0.531
		Incomplete	1.14	0.70-1.86	0.595
	Degree of revascularization by rSS (reference: no coronary artery disease)	Complete	1.00	0.66-1.53	0.986
		Reasonably incomplete	1.12	0.80-1.57	0.509
		Incomplete	1.20	0.81-1.78	0.367
	Degree of revascularization by STS-adjusted rSS (reference: no coronary artery disease)	Complete	0.90	0.60-1.36	0.628
		Reasonably incomplete	1.06	0.75-1.49	0.747
		Incomplete	1.18	0.79-1.75	0.415
	Degree of revascularization by EuroSCORE II-adjusted rSS (reference: no coronary artery disease)	Complete	0.95	0.62-1.45	0.820
		Reasonably incomplete	1.10	0.78-1.53	0.596
		Incomplete	1.09	0.73-1.62	0.683

bSS = baseline SYNTAX score; EuroSCORE II = European System for Cardiac Operative Risk Evaluation; rSS = residual SYNTAX score; STS = Society of Thoracic Surgeons.

1140 to 3.841, p = 0.017) and in those with IR (rSS >8; OR 1720, 95% CI 1051 to 2814, p = 0.031). Shamekhi et al identified high bSS (>24) and high rSS (>8) as predictors of 3-year mortality.[26]

The lack of impact of CAD and its intervention on mortality in these patients could be explained by the high prevalence of other co-morbidities, which have been associated with a higher rate of adverse events.[27,28] Another relevant aspect due to its prognostic implication, not studied previously, is the relation between CAD and its degree of revascularization with HF after TAVI. In our study, neither the presence of CAD nor the degree of revascularization influenced hospitalizations for HF, neither when studied in isolation nor when added to the MACEs. Although awaiting the results of the ACTIVATION study,[29] in which patients with CAD who are going to be subjected to TAVI, to PCI

as opposed to medical treatment, a detailed evaluation must be carried out by the Heart Team for each patient.

Our results suggest that neither the existence of CAD nor routine coronary revascularization before TAVI, regardless of the final rSS, is associated with changes in mortality, MI, or the need for revascularization or hospitalization for HF in long-term follow-up. Our results suggest that percutaneous aortic valve implantation without previous PCI in patients with CAD is a safe option, with no deterioration of clinical results.

Our study presents some limitations. This was a single-center, observational, retrospective study subject to confounding and bias factors, even after using multivariate models to adjust the results, and that may be limited by the limited sample size. Second, although 2 expert interventionist cardiologists evaluated the Syntax score, it is based purely on angiograph interpretation.

Disclosures

Ramiro Trillo Nouche is a proctor for Medtronic. The other investigators have no conflicts of interest to declare.

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