SYNTAX Score is associated with worse outcomes after off-pump coronary artery bypass grafting surgery for three-vessel or left main complex coronary disease

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Objective: The SYNergy between percutaneous intervention with TAXus drug eluting stents and cardiac surgery (SYNTAX) Score is a tool for risk stratification of patients according to the complexity of coronary lesions developed during the SYNTAX trial. We examined the influence of the SYNTAX Score on the incidence of major adverse cardiac and cerebrovascular events.

Methods: All patients with de novo left main or 3-vessel disease undergoing coronary artery bypass grafting from January 2005 to December 2008 at our institution (Hospital Clínico San Carlos, Madrid, Spain) were retrospectively assessed, and their SYNTAX Score was calculated. The influence of the SYNTAX Score on post-procedural and follow-up mortality and combined major adverse cardiac and cerebrovascular events (including death, myocardial infarction, cerebrovascular accident, and repeat revascularization) was identified by multivariate analysis. Balancing score analysis was performed to eliminate the effect of potential confounders.

Results: A total of 716 patients were enrolled. Mean SYNTAX Score was 34.5 (standard deviation, 6.7; range, 11.5–76). Three groups of patients were identified according to the score terciles: low (≤33), intermediate (33–37), and high (>37). These terciles scores differed greatly from those reported by the SYNTAX trial investigators. The multivariate analysis identified that the SYNTAX Score was associated with follow-up mortality (hazard ratio = 1.046, $P = .015$) and combined early and follow-up major adverse cardiac and cerebrovascular events (odds ratio = 1.079, $P < .001$; and hazard ratio = 1.034, $P = .026$, respectively). Balancing score-adjusted analyses demonstrated that the SYNTAX Score was independently associated with early and late major adverse cardiac and cerebrovascular events (odds ratio = 1.65, $P < .001$; and hazard ratio = 1.034, $P = .027$, respectively).

Conclusions: SYNTAX Score was remarkably high among patients undergoing surgical off-pump myocardial revascularization at our institution. In this subset of patients, a higher SYNTAX Score was associated with a higher incidence of in-hospital and follow-up major adverse cardiac and cerebrovascular events after coronary artery bypass grafting, but not with early or late mortality. (J Thorac Cardiovasc Surg 2011;142:e123-32)

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Coronary artery bypass grafting (CABG) surgery is currently the treatment of choice for 3-vessel and left main coronary artery (LMCA) disease.[1,2] However, recent developments in percutaneous coronary intervention (PCI) have made its endovascular treatment feasible.[3,4] CABG has also undergone advances, such as less invasive surgical access, use of arterial rather than venous grafts, and off-pump surgery.[5] To reassess and compare the outcomes of both therapeutic options, the SYNergy between percutaneous intervention with TAXus drug eluting stents and cardiac surgery (SYNTAX) trial was initiated in 2005.[6] In this randomized multicenter trial, the outcomes of PCI using paclitaxel-eluting TAXUS stents and CABG for the treatment of 3-vessel and LMCA disease were compared. The SYNTAX Score is a comprehensive angiographic scoring system that assesses coronary lesion complexity within the context of this trial to select patients for one or the other option.[7] In addition to showing acceptable reproducibility, the Syntax score has shown good predictive behavior. Thus, in a report of postprocedural and 1-year outcomes of surgical or PCI revascularization in the patients initially included in the SYNTAX trial stratified by SYNTAX Score, a lower major adverse cardiac and cerebrovascular events (MACCE)-free survival was recorded for the patients with the higher scores in the PCI group.[8] On the other hand, Mohr and colleagues[9] assessed the prognostic value of the SYNTAX Score in the SYNTAX trial CABG group and found no relationship between the

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
CABG	= coronary artery bypass grafting
CI	= confidence interval
CK	= creatine kinase
COPD	= chronic obstructive pulmonary disorder
CPB	= cardiopulmonary bypass
euroSCORE	= European System for Cardiac Operative Risk Evaluation
HR	= hazard ratio
IQR	= interquartile range
LMCA	= left main coronary artery
MACCE	= major adverse cardiac and cerebrovascular events
OR	= odds ratio
PCI	= percutaneous coronary intervention
SD	= standard deviation
SYNTAX	= SYNergy between percutaneous intervention with TAXus drug eluting stents and cardiac surgery

score and 2-year follow-up survival. The predictive value of the score has been also studied in cohorts of patients different from those of the SYNTAX study undergoing PCI[10-12] and surgical revascularization for LMCA disease[13] or 3-vessel disease.[14] The present study was designed to assess the use of the SYNTAX Score to predict MACCE in the postprocedural course of patients undergoing CABG with de novo 3-vessel or LMCA disease.

MATERIALS AND METHODS

Patients

All patients undergoing isolated CABG between January 2005 and December 2008 at the Hospital Clínico San Carlos (Madrid, Spain) were retrospectively assessed. Patients were enrolled if they had de novo 3-vessel, isolated LMCA, or LMCA disease with 1, 2, or 3 coronary vessels requiring surgical revascularization. Patients were excluded if they had undergone prior revascularization or single or 2-vessel disease. These criteria were similar to those of the original design of the SYNTAX trial.[6] Before surgical intervention, written informed consent was obtained from all patients. The study protocol was approved by the institutional review board of our institution. Demographic, anthropometric, clinical, and surgical data were obtained from each patient. Postprocedural risk was estimated using the European System for Cardiac Operative Risk Evaluation (euroSCORE).[15] A list of all analyzed variables is provided in Table 1. The follow-up was completed between April 2009 and June 2009. For this purpose, patients were contacted by telephone calls or office visits during this period of time.

Coronary Artery Bypass Grafting Technique

Off-pump CABG surgery was always the first choice. Cardiopulmonary bypass (CPB) was conducted only in patients who showed hemodynamic or electric instability that could not be corrected otherwise during surgery. Internal thoracic artery, saphenous vein, or radial artery grafts were harvested. Heparin was administered to achieve an activated clotting time of 300 to 350 seconds. First, the area of the anterior descending artery was revascularized. Next, distal anastomoses to the lateral, posterolateral, and diaphragmatic aspects were undertaken. Finally, proximal aspects were anastomosed to the ascending aorta with side clamping. Anastomoses were achieved by running suture, using a non-reabsorbable 7-0 monofilament (6-0 for sutures to the aorta). The heparin effect was reversed using protamine.

SYNTAX Score

By using the criteria of the SYNTAX trial,[7] we assessed all stenoses 50% or greater in any coronary vessel with a diameter of 1.5 mm or greater. For each patient, the score was retrospectively calculated by a single team comprising a heart surgeon and an interventional cardiologist (not blindly). The last coronary angiography before CABG procedure was used for score assessment. The SYNTAX Score was divided into 3 terciles according to its distribution in the population of patients included in the study.

Objective

The main aim of this study was to examine the effect of the SYNTAX Score on the outcomes of CABG for 3-vessel or left main disease. We recorded the incidence of the following major events during the postprocedural course (defined as the patient's hospital stay or the 30 days after surgery) and in the follow-up: (1) all cause death; (2) grouped MACCE, including (a) death; (b) acute myocardial infarction (AMI) (troponin I > 15 μg/L in the first 12 hours, troponin I > 20 μg/L in the first 24 hours or creatine kinase [CK]-MB 5 times greater than the upper limit of the normal range after CABG; CK to CK-MB value 5 times the upper limit of normal in the follow-up);[6,16] (c) permanent stroke (focal neurologic defect > 24 hours causing irreversible brain damage or permanent disability);[6] and (d) repeat revascularization (PCI or CABG). Only first event survival was assessed in the follow-up. Thus, repeated events were discarded.

Statistical Analysis

Continuous variables were compared with linear regression. Differences between qualitative variables were assessed using the chi-square test (linear trend if independent variable was ordinal) or Fisher's exact test (for expected frequencies < 5). Student *t* test, Mann–Whitney *U* test, or analysis of variance was used to compare quantitative (dependent) versus qualitative (independent) variables depending on normality and number of categories.

Potential confounding factors associated with the SYNTAX Score were identified using simple linear regression. Then, a balancing score[17] was developed using non-parsimonious multiple linear regression models that included those variables associated with the SYNTAX Score ($P < .10$) and first order interactions. The highest R^2 model was selected to develop the balancing score.

Risk factors for postprocedural events were identified by univariate and multivariate analyses. We performed a non-balanced binary logistic regression analysis including all variables found to be associated with postprocedural events in the univariate analysis ($P < .20$) and those associated with the SYNTAX Score ($P < .05$). The balancing score was included in the multivariate analysis to better discriminate potential confounders.

Event-free survival in the follow-up was assessed including both postprocedural and postdischarge events. Follow-up survival curves were produced according to the Kaplan–Meier method. Mantel–Haenszel log-rank tests were performed to analyze survival differences. Independent predictive factors for outcomes during the follow-up period were detected using a Cox proportional hazard model. Variables included in multivariate Cox model were those associated with the SYNTAX Score ($P < .05$) and those linked to the incidence of events in a univariate Cox model ($P < .20$). Again, to avoid further bias, the balancing score was included in the Cox analysis.

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TABLE 1. Baseline characteristics by SYNTAX Score terciles and SYNTAX Score by number of disease vessels

SYNTAX Score and baseline characteristics

SYNTAX Score	≤33; n = 282	33–37; n = 219	>37; n = 215	*P*
Female gender	74 (26.3%)	45 (20.5%)	31 (14.4%)	.001
Age, y	65.16 (10.9)	68.49 (9.28)	69.51 (9.28)	<.001
Obesity (BMI > 30 kg/m^2)	69 (24.5%)	57 (26%)	34 (15.8%)	.030
Diabetes	78 (28%)	106 (48.4%)	132 (62%)	<.001
Arterial hypertension	175 (62.5%)	164 (74.9%)	163 (75.8%)	.001
Dyslipidemia	179 (64.6%)	154 (70.6%)	150 (70.1%)	.176
PVD	27 (9.6%)	40 (18.3%)	80 (37.2%)	<.001
Smoker	153 (54.8%)	119 (54.8%)	120 (56.1%)	.793
COPD	20 (7.1%)	31 (14.2%)	22 (10.3%)	.186
Prior stroke	6 (2.1%)	17 (7.8%)	23 (10.8%)	<.001
Chronic renal failure	18 (6.4%)	23 (10.5%)	45 (20.9%)	<.001
Previous AMI	131 (46.5%)	109 (49.8%)	115 (53.5%)	.120
AMI < 90 d	92 (32.6%)	77 (35.2%)	72 (33.5%)	.808
LVEF < 60%	61 (21.6%)	53 (24.2%)	67 (31.2%)	.017
Severe PHT*	7 (2.5%)	10 (4.6%)	8 (3.7%)	.416
NYHA III/IV	82 (29.1%)	75 (34.2%)	91 (42.4%)	<.001
Reoperation	7 (2.5%)	7 (3.2%)	12 (5.6%)	.073
Critical preprocedural state†	46 (16.4%)	28 (12.8%)	36 (16.7%)	.985
Incomplete revascularization	32 (11.4%)	50 (22.8%)	46 (21.4%)	<.001
Saphenous graft	152 (54.1%)	149 (68%)	141 (65.6%)	.006
ITA graft	280 (99.6%)	216 (98.6%)	213 (99.1%)	.442
Bilateral ITA graft	76 (27%)	29 (13.2%)	40 (18.6%)	.011
Radial artery graft	39 (13.9%)	23 (10.5%)	20 (9.3%)	.105
Endarterectomy	15 (5.3%)	10 (4.6%)	16 (7.4%)	.353
Conversion to CPB	9 (3.2%)	9 (4.1%)	9 (4.2%)	.399
euroSCORE	4 (IQR 2–6)	5 (IQR 3–7)	5 (IQR 3–8)	<.001
euroSCORE logistic	5 (SD 4.3)	5.7 (SD 3.9)	7.7 (4.9)	.009

SYNTAX Score and coronary anatomy

SYNTAX Score	≤33; n = 282	33–37; n = 219	>37; n = 215	*P*
Main coronary artery lesion	153 (54.4%)	24 (11%)	142 (66.4%)	.085
No. affected vessels				<.001
0 vessels	13 (4.6%)	0 (0%)	0 (0%)	
1 vessel	41 (14.6%)	0 (0%)	0 (0%)	
2 vessels	93 (33.1%)	17 (7.8%)	3 (1.4%)	
3 vessels	134 (47.7%)	202 (92.2%)	212 (98.6%)	

No. of diseased vessels	n (%)	SYNTAX Score	*P*
Left main plus 0 vessel	15 (2.1%)	17.5 (IQR 16.8–20.3)	<.001
Left main plus 1 vessel	51 (5.7%)	23.5 (IQR 22.5–25.5)	
Left main plus 2 vessels	113 (15.8%)	30.5 (IQR 28.5–32.5)	
Left main plus 3 vessels	152 (21.2%)	41 (IQR 39.5–43.5)	
3-vessel disease (no left main)	395 (55.2%)	34.5 (IQR 33–37)	

Data expressed as absolute frequencies (n) and percentages (%) or means and SD (or medians and IQR). Only data for valid cases are provided; lost cases were not assessed. Chi-square or Fisher's exact test (depending on the expected frequency) was used to compare qualitative variables. Analysis of variance used to compare means. *CAD,* Coronary artery disease; *AMI,* acute myocardial infarction; *BMI,* body mass index; *PVD,* peripheral vascular disease; *COPD,* chronic obstructive pulmonary disease; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association; *ITA,* internal thoracic artery; *CPB,* cardiopulmonary bypass; *PHT,* pulmonary hypertension; *euroSCORE,* European System for Cardiac Operative Risk Evaluation; *SYNTAX,* SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery. *Considered only if severe: pulmonary artery systolic pressure > 60 mm Hg. †Critical preprocedural state: ventricular tachycardia, ventricular fibrillation or aborted sudden death, cardiac massage, invasive ventilatory support, need for inotropic support or balloon counterpulsation, acute renal failure (anuria or oliguria < 10 mL/h).

TABLE 2. Early outcome frequencies

SYNTAX Score	≤33; n = 282	33–37; n = 219	>37; n = 215	*P*
Postprocedural mortality	10 (3.6%)	7 (3.2%)	19 (8.8%)	.011
Postprocedural stroke	2 (0.7%)	2 (0.9%)	4 (1.9%)	.240
Periprocedural AMI	12 (4.3%)	43 (19.6%)	42 (19.5%)	<.001
Early repeat revascularization	6 (2.1%)	6 (2.7%)	6 (2.8%)	.632
Grouped MACCE	22 (7.8%)	50 (22.8%)	50 (23.3%)	<.001

Data expressed as absolute frequencies (n) and percentages (%). Chi-square (lineal trend) or Fisher's exact test depending on the expected frequency was used to compare qualitative variables. *AMI,* Acute myocardial infarction; *MACCE,* major adverse cardiac and cerebrovascular events; *SYNTAX,* SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery.

Shapiro–Wilk normality tests were used to test normality of continuous variables and multivariate models residuals. PASW 18.0 for Windows (SPSS Inc, Chicago, Ill) was used for statistical analysis.

RESULTS

Baseline Clinical Characteristics

From January 2005 to December 2008, 920 patients consecutively underwent isolated CABG surgery. Of these, 716 patients were enrolled in this study and 204 patients were excluded for the following reasons: 2-vessel disease (n = 137), single-vessel disease (n = 44), or previous revascularization (n = 134).

Clinical and anatomic baseline characteristics by SYNTAX Score terciles are shown in Table 1. These data indicate a significantly older age in the 2 groups with higher scores and a greater prevalence of women in the first 2 score groups. Among the cardiovascular risk factors examined, a higher prevalence of diabetes mellitus, arterial hypertension, peripheral vascular disease, chronic kidney disease, and prior stroke were observed in the top 2 SYNTAX Score groups. A higher prevalence of patients in functional class III or IV was also observed in the 2 higher score terciles.

Revascularization procedure details are also shown in Table 1. Mean mortality predicted by logistic regression of the euroSCORE was 6.1% (standard deviation [SD], 4.3). A total of 110 patients (15.4%) underwent CABG in a critical preprocedural state (according to the euroSCORE definition[14]). In 27 patients (3.8%), the procedure was converted on-pump. A total of 548 patients (76.5%) had 3-vessel disease, and 319 patients (44.6%) had LMCA disease. Some 709 of the patients (99%) received at least 1 internal thoracic artery, 442 patients (61.7%) received at least 1 saphenous vein, and 82 patients (11.4%) received at least 1 radial artery graft. More incomplete revascularizations were observed in the 2 top score groups ($P < .001$).

When the standard euroSCORE was compared with the SYNTAX Score, a positive linear correlation was observed (b = 0.152 euroSCORE points/SYNTAX Score point, 95% confidence interval [CI], 0.064–0.240; $P = .001$).

Coronary artery disease characteristics are shown in Table 1. The mean SYNTAX Score was 34.5 (SD, 6.7; range, 11.5–76). As expected, higher SYNTAX Scores were observed among patients with 3-vessel disease (median 34.5, interquartile range [IQR], 33–37) and LMCA plus 3-vessel (median, 41; IQR, 39.5–43.5). The prevalence of 3-vessel disease was greater in the 2 top score groups ($P < .01$), whereas the prevalence of LMCA disease was greater in the lowest and highest SYNTAX Score groups ($P < .085$).

A balancing score was produced using multiple linear regression including those factors associated with the SYNTAX Score ($P < .10$) and their first order interactions. The highest R^2 model was selected among those obtained. This score included age, obesity, diabetes, high blood pressure, peripheral vascular disease, previous cerebrovascular accident, chronic renal failure, left ventricle ejection fraction less than 50%, incomplete revascularization, saphenous vein grafting, bilateral internal thoracic artery grafting, New York Heart Association III/IV, gender, and first order interactions for gender, age, obesity, diabetes mellitus, high blood pressure, incomplete revascularization, and peripheral vascular disease.

Postprocedural Events

Ninety-seven patients (13.5%) had an AMI, 8 patients (1.1%) had a stroke, 18 patients (2.5%) required a repeat revascularization, and 36 patients (5%) died in the postoperative course. A total of 122 patients (17.0%) had at least 1 adverse event. Table 2 shows the incidence of events by SYNTAX Score terciles.

Univariate binary logistic regression analysis was performed to detect those dependent variables related to the studied events ($P < .20$) (Table 3) to be included in the multivariate analysis. In the multivariate binary logistic regression (Table 3), female gender, age, chronic obstructive pulmonary disorder (COPD), NYHA III/IV class, critical preprocedural state, coronary endarterectomy, and conversion to CPB were independent predictors for in-hospital mortality. The SYNTAX Score was not associated with a higher in-hospital mortality (odds ratio [OR] = 1.049, 95% CI, 0.995–1.106; $P = .077$). After performing the same multivariate analysis adjusted by the balancing score, the SYNTAX Score was not associated with postprocedural mortality (OR = 1.039; 95% CI, 0.977–1.105; $P = .223$).

Female gender, diabetes mellitus, critical preprocedural state, coronary endarterectomy, conversion to CPB, and

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TABLE 3. Univariate and multivariate logistic regression analyses of early events

	Postoperative mortality				Postoperative combined MACCE			
	Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female gender	2.541 (1.267–5.096)	.009	2.924 (1.306– 6.545)	.009	1.45 (0.923–2.278)	.106	1.974 (1.198–3.252)	.008
Age (y)	1.087 (1.041–1.135)	<.001	1.059 (1.011–1.11)	.016	1.032 (1.011–1.054)	.003	1.016 (0.989–1.043)	.251
BMI $\geq$ 30 kg/m^2	0.640 (0.351–1.902)	.640	0.793 (0.298–2.107)	.641	0.631 (0.377–1.057)	.08	0.605 (0.35–1.046)	.072
Diabetes mellitus	1.617 (0.824–3.176	.162	1.156 (0.519–2.576)	.722	0.822 (0.553–1.222)	.333	0.593 (0.379–0.926)	.022
High blood pressure	2.193 (0.899–5.348)	.084	1.141 (0.402–3.241)	.804	1.71 (1.072–2.726)	.024	1.537 (0.929–2.543)	.094
Dyslipidemia	1.428 (0.66–3.088)	.366	—	—	1.127 (0.736–1.726)	.582	—	—
Peripheral vascular disease	2.612 (1.302–5.242)	.007	1.368 (0.566–3.306)	.486	1.189 (0.745–1.897)	.468	0.898 (0.522–1.545)	.698
Smoker	0.634 (0.323–1.245)	.186	0.781 (0.291–1.47)	.45	0.689 (0.465–1.021)	.063	0.981 (0.45–3.211)	.687
COPD	3.203 (1.443–7.108)	.004	3.5 (1.413–8.673)	.007	1.061 (0.563–2.001)	.584	1.13 (0.558–2.285)	.734
Previous stroke	1.334 (0.393–4.526)	.644	0.733 (0.186–2.881)	.656	0.716 (0.297–1.729)	.458	0.574 (0.223–1.478)	.574
Chronic renal failure	2.201 (0.969–5)	.059	1.225 (0.441–3.406)	.697	1.232 (0.696–2.18)	.474	0.573 (0.222–1.474)	.248
Previous AMI	0.903 (0.461–1.767)	.765	—	—	0.981 (0.664–1.448)	.923	—	—
Recent AMI	0.859 (0.415–1.777)	.682	—	—	1.042 (0.691–1.571)	.844	—	—
LVEF < 50%	1.716 (0.85–3.462)	.132	0.852 (0.332–2.184)	.738	1.128 (0.725–1.753)	.594	0.945 (0.56–1.596)	.833
Severe pulmonary hypertension*	5.315 (1.871–15.097)	.002	2.376 (0.606–9.321)	.214	1.965 (0.802–4.813)	.139	1.522 (0.546–4.238)	.422
NYHA III/IV	4.062 (1.995–8.273)	<.001	2.869 (1.327–6.2)	.007	1.322 (0.893–1.988)	.160	1.061 (0.669–1.685)	.8
Previous cardiac surgery	2.593 (0.741–9.076)	.136	1.468 (0.322–6.694)	.62	3.825 (1.712–8.548)	.001	2.414 (0.989–5.895)	.053
Critical preprocedural state†	4.391 (2.187–8.817)	<.001	2.909 (1.352–6.258)	.006	2.245 (1.401–3.599)	.001	2.151 (1.301–3.556)	.003
Incomplete revascularization	1.21 (0.613– 2.388)	.583	0.776 (0.339–1.777)	.548	0.992 (0.67–1.469)	.969	0.759 (0.478–1.206)	.244
Saphenous grafts	0.969 (0.487–1.928)	.929	0.525 (0.220–1.25)	.145	1.307 (0.865–1.975)	.204	0.93 (0.543–1.59)	.79
Radial artery graft	1.261 (0.476–3.339)	.641	—	—	0.824 (0.432–1.573)	.557	—	—
ITA graft	0.26 (0.03–2.283)	.224	—	—	0.2 (0.04–1.001)	.05	0.229 (0.044–1.2)	.081
Bilateral ITA graft	0.621 (0.237–1.626)	.332	0.587 (0.201– 2.56)	.901	0.692 (0.408–1.173)	.171	0.97 (0.471–1.995)	.933
Coronary endarterectomy	2.881 (1.057–7.85)	.039	3.125 (1.016–9.677)	.047	2.748 (1.395–5.411)	.003	2.76 (1.328–5.738)	.007
Conversion to CPB	3.322 (1.381–7.992)	.007	4.762 (1.648–13.762)	.004	3.366 (1.858–6.1)	<.001	2.752 (1.44–5.261)	.002
SYNTAX Score	1.053 (1.007–1.102)	.023	1.049 (0.995–1.106)	.077	1.06 (1.029–1.092)	<.001	1.079 (1.042–1.118)	<.001

Data expressed as OR, 95% CI, and *P* value. Binary logistic regression was performed for univariate and multivariate analyses. Variables to be included in multivariate analysis: univariate analysis ($P < .2$) and those associated with SYNTAX Score ($P < .05$). *AMI,* Acute myocardial infarction; *MACCE,* major adverse cardiac and cerebrovascular events. *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *LVEF,* left ventricular ejection fraction; *ITA,* internal thoracic artery; *CPB,* cardiopulmonary bypass; *NYHA,* New York Heart Association; *SYNTAX,* SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery. *Pulmonary hypertension considered only if severe: pulmonary artery systolic pressure > 60 mm Hg. †Critical preprocedural state: ventricular tachycardia, ventricular fibrillation or aborted sudden death, cardiac massage, invasive ventilatory support, need for inotropic support or balloon counterpulsation, acute renal failure (anuria or oliguria < 10 mL/h).

SYNTAX Score were associated with postoperative MACCE in a multivariate binary logistic regression. Once adjusted by the balancing score, the SYNTAX Score remained independently associated with a higher risk of postprocedural MACCE (OR = 1.065, 95% CI, 1.03–1.1; $P < .001$).

Follow-up

One patient was lost to follow-up. Median follow-up was 26.68 months (IQR, 10.97–39.52).

Survival at 1, 2, and 4 years for each SYNTAX Score tercile was as follows: low score ($\leq$33): 95%, 93%, and 92%, respectively; medium (33–37): 91%, 91%, 82%, respectively; and high (>37): 87%, 85%, 73%, respectively. Log-rank tests for each period demonstrated statistically significant differences ($P = .015$, $P = .009$, and $P = .032$, respectively) (Figure 1, *A*). Survival free from combined MACCE for each tercile were as follows: low score ($\leq$33): 91%, 86%, and 79%, respectively; medium (33–37): 85%, 81%, 54%, respectively; and high (>37): 79%, 78%, and 67%, respectively. Again, log-rank tests for each period demonstrated statistically significant survival differences ($P = .011$, $P < .001$, and $P = .009$, respectively) (Figure 1, *B*). Figure 1, *C–E* shows survival curves for AMI, acute cerebrovascular accident, and repeat revascularization. Survival differences were statistically significant when comparing survival free from AMI (Mantel–Haenszel log-rank test $P = .001$), but not for acute cerebrovascular accident or repeat revascularization ($P = .582$ and $P = .289$, respectively).

Table 4 shows the univariate and unadjusted multivariate Cox analysis for mortality and incidence of MACCE in the follow-up. Age, female gender, COPD, pulmonary systolic pressure greater than 60 mm Hg, NYHA III/IV, critical preprocedural state, conversion to CPB, and SYNTAX Score were associated with a worse survival in the follow-up. When adjusting the multivariate Cox analysis with the balancing score, SYNTAX Score was no longer associated with a higher follow-up mortality (hazard ratio [HR],

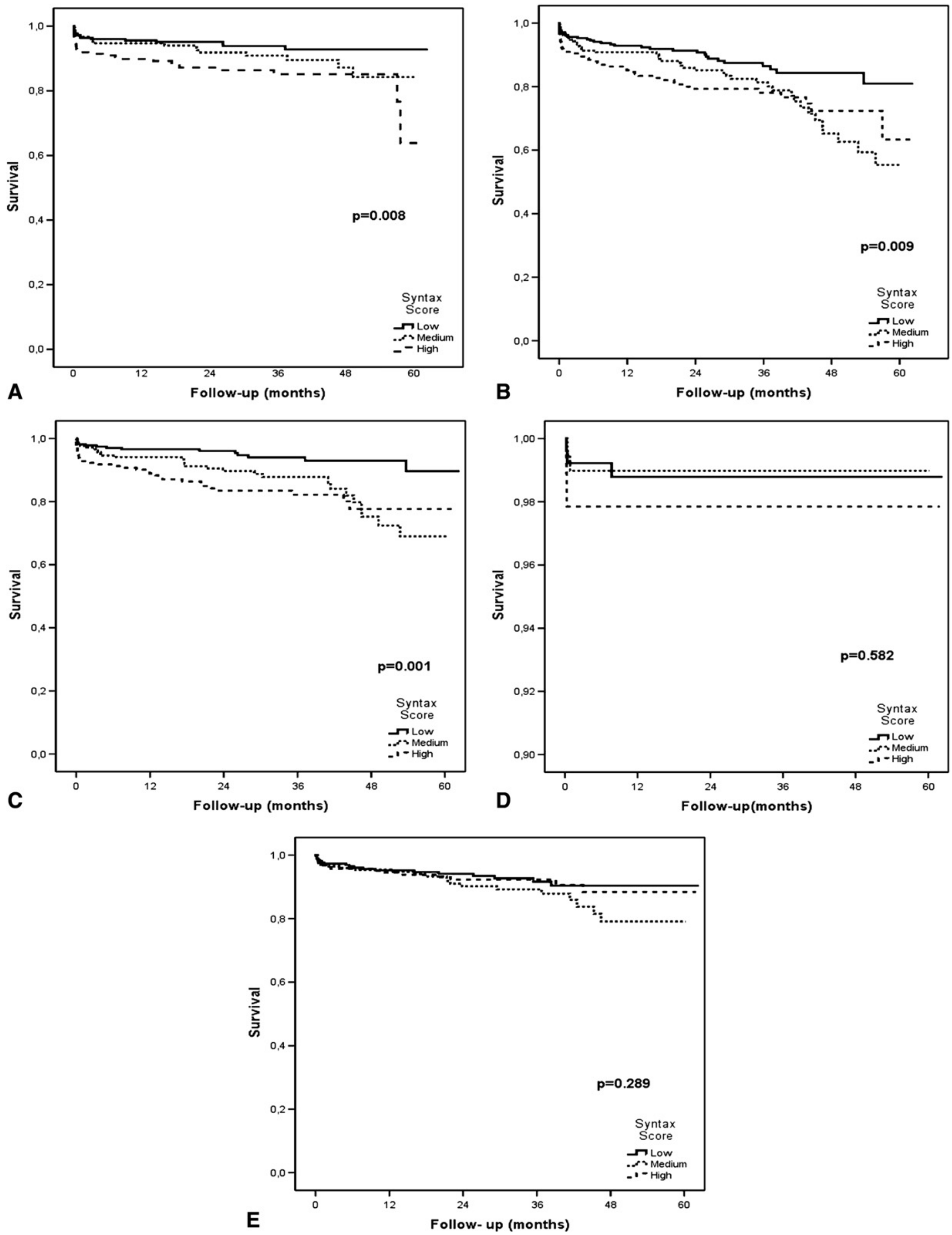

FIGURE 1. Survival curves for follow-up MACCE. A, Survival. B, Survival free from MACCE. C, Survival free from AMI. D, Survival free from acute cerebrovascular accident. E, Survival free from repeat revascularization. Mantel–Haenszel log-rank tests. Statistically significant differences: $P < .05$. *SYNTAX,* SYNergy between percutaneous intervention with TAXus drug eluting stents and cardiac surgery.

TABLE 4. Univariate and multivariate Cox proportional hazard models of follow-up events

	Mortality				Combined MACCE			
	Univariate analyses		Multivariate analyses		Univariate analyses		Multivariate analyses	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (y)	1.078 (1.046–1.112)	<.001	1.058 (1.024–1.093)	.001	1.033 (1.013–1.053)	.001	1.019 (0.998–1.041)	.076
Female gender	2.253 (1.352–3.756)	.002	2.301 (1.311– 4.039)	.004	1.531 (1.025–2.287)	.038	1.583 (1.02–2.457)	.041
BMI ≥ 30 kg/m^2	0.879 (0.478–1.616)	.677	1.03 (0.521–2.035)	.933	0.974 (0.63–1.505)	.905	1.003 (0.628–1.601)	.992
Diabetes mellitus	1.421 (0.87–2.321)	.161	1.05 (0.602–1.83)	.864	1.484 (1.035–2.128)	.032	1.302 (0.88–1.925)	.187
High blood pressure	1.645 (0.894–3.025)	.109	0.948 (0.483–1.86)	.876	1.193 (0.792–1.797)	.398	0.871 (0.559–1.357)	.54
Dyslipidemia	1.319 (0.757–2.297)	.328	—	—	1.297 (0.865–1.945)	.209	—	—
Peripheral vascular disease	2.456 (1.48–4.078)	.001	1.282 (0.696–2.363)	.425	1.818 (1.228–2.69)	.003	1.287 (0.83–1.995)	.26
Smoker	0.806 (0.494–1.316)	.39	—	—	0.993 (0.692–1.424)	.968	—	—
COPD	2.851 (1.598–5.086)	<.001	2.785 (1.483–5.23)	.001	2.35 (1.49–3.707)	<.001	2.143 (1.311–3.502)	.002
Previous stroke	1.269 (0.509–3.164)	.609	0.72 (0.272–1.906)	.509	1.103 (0.538–2.26)	.79	0.658 (0.308–1.303)	.279
Chronic renal failure	2.843 (1.631–4.955)	<.001	1.343 (0.699–2.580)	.375	2.13 (1.37–3.313)	.001	1.369 (0.829–2.258)	.219
Previous AMI	0.967 (0.591–1.583)	.894	—	—	1.117 (0.778–1.602)	.549	—	—
Recent AMI (< 90dd)	0.985 (0.584–1.66)	.954	—	—	1.117 (0.766–1.627)	.565	—	—
LVEF < 50%	2.379 (1.447–3.911)	.001	0.918 (0.483–1.763)	.796	1.723 (1.177–2.522)	.005	1.04 (0.66–1.64)	.865
Severe pulmonary hypertension*	6.336 (3.307–12.138)	<.001	2.675 (1.293–5.536)	.008	3.87 (2.174–6.888)	<.001	2.34 (.246–4.396)	.008
NYHA III/IV	3.701 (2.219–6.17)	<.001	2.192 (1.266–3.796)	.005	2.001 (1.396–2.869)	<.001	1.503 (1.023–2.209)	.038
Previous cardiac surgery	1.34 (0.43–4.274)	.621	—	—	0.923 (0.34–2.502)	.875	—	—
Critical preprocedural state†	4.206 (2.561–6.909)	<.001	2.436 (1.422–4.173)	.001	2.039 (1.354–3.07)	.001	1.531 (0.993–2.36)	.054
Incomplete revascularization	1.865 (1.106–3.145)	.019	1.341 (0.754–2.384)	.317	1.512 (1.043–2.191)	.029	1.139 (0.757–1.714)	.531
Saphenous graft	1.069 (0.645–1.771)	.797	0.733 (0.393–1.369)	.33	0.994 (0.688–1.435)	.973	0.739 (0.494–1.104)	.139
Radial artery graft	0.735 (0.331–1.639	.448	—	—	0.71 (0.403–1.252)	.237	—	—
ITA graft	0.296 (0.041–2.153)	.229	—	—	0.198 (0.048–0.811)	.024	0.236 (0.057–0.98)	.047
Bilateral ITA graft	0.479 (0.218– 1.050)	.066	1.371 (0.508–3.698)	.533	0.694 (0.421–1.147)	.201	—	—
Coronary endarterectomy	1.752 (0.756–4.063)	.191	1.909 (0.786–4.64)	.153	1.506 (0.787–2.879)	.216	1.552 (0.791–3.044)	.201
Conversion to CPB	2.637 (1.342–5.181)	.005	3.536 (1.688–7.407)	.001	1.649 (0.908–2.996)	.101	1,871 (1.002–3.493)	.049
SYNTAX Score	1.054 (1.02–1.088)	.001	1.046 (1.009–1.085)	.015	1.037 (1.01–1.064)	.007	1.034 (1.004–1.065)	.026

Postprocedural and postdischarge MACCE included. Data expressed as HR and 95% CI. Univariate and multivariate binary logistic regression was performed. Variables to be included in multivariate analysis: $P < .2$; and those associated with SYNTAX Score ($P < .05$). *AMI,* Acute myocardial infarction; *MACCE,* major adverse cardiac and cerebrovascular events. *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *LVEF,* left ventricular ejection fraction; *HR,* hazard ratio; *ITA,* internal thoracic artery; *CPB,* cardiopulmonary bypass; *NYHA,* New York Heart Association; *SYNTAX,* SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery. *Severe pulmonary hypertension: pulmonary systolic pressure > 60 mm Hg. †Critical preprocedural state: ventricular tachycardia, ventricular fibrillation or aborted sudden death, cardiac massage, invasive ventilatory support, need for inotropic support or balloon counterpulsation, acute renal failure (anuria or oliguria < 10 mL/h).

1.029; 95% CI, 0.985–1.074; $P = .198$). Female gender, COPD, pulmonary systolic pressure greater than 60 mm Hg, NYHA III/IV, conversion to CPB, and SYNTAX Score were associated with a higher incidence of follow-up MACCE, whereas internal thoracic artery grafting was associated with a lower rate. Once the balancing score was added, SYNTAX Score remained associated with a higher risk for late MACCE (HR, 1.034; 95% CI, 1.004–1.066; $P = .027$).

DISCUSSION

The SYNTAX study is a randomized, multicenter, noninferiority clinical trial that was designed to compare the outcomes of PCI using drug-eluting stents and CABG to treat 3-vessel and LMCA disease.[6] The SYNTAX Score[7] objectively assesses the technical difficulty of PCI such that a higher score indicates more complex coronary lesions.

The validity of the SYNTAX Score within the trial itself was recently examined by the trial's researchers.[8] After a 1-year follow-up, no significant correlation was detected between the SYNTAX Score and the incidence of MACCE in the cohort of patients who underwent CABG surgery ($P = .38$). However, a significant link between SYNTAX Score and MACCE ($P = .007$) was observed in the PCI group. Mohr and colleagues[9] investigated whether the SYNTAX Score affected CABG outcomes among the 1541 patients undergoing CABG included in the SYNTAX trial and found no significant influence. In 2007, Valgimigli and colleagues[10] reported that in patients undergoing PCI, the SYNTAX Score was able to better discriminate the incidence of MACCE. In 2 recent studies addressing the impact of the SYNTAX Score in patients undergoing coronary surgery for LMCA[13] and 3-vessel disease,[14] results have not been consistent. Birim and colleagues,[13] in their study of 148 patients with LMCA disease who underwent surgery, observed that the SYNTAX Score was related to MACCE-free survival and showed excellent discriminatory power (c-index 0.88). In contrast, Lemesle and colleagues[14] found no correlation between the SYNTAX Score ($P = .754$) and the incidence of MACCE in 320 patients with 3-vessel disease undergoing CABG. Serruys and colleagues[12] reported the impact of SYNTAX Score on clinical outcomes in 1205 patients from the ARTS-I trial and 607 patients from the ARTS-II trial. They found that the SYNTAX Score was an independent predictor (OR, 1.68; 95% CI, 1.22–2.28) of MACCE in a 5-year follow-up. Our study assessed the influence of the SYNTAX Score in a series of 716 patients with 3-vessel or LMCA disease on the incidence of MACCE during the postoperative course and follow-up of CABG. For this purpose, we performed a multivariate analysis adjusted by a balancing score[17] and found a significant association between SYNTAX Score and early and midterm combined MACCE.

Another important issue that may explain the differences between the present study and others is that surgical coronary revascularization was performed off-pump in the majority of patients in the current study, whereas CABG was performed on-pump in previous studies.[9,12,13,14] Off-pump CABG is more technically demanding than on-pump CABG,[18] and, in this scenario, a more complex coronary disease may affect outcomes more directly and strongly.

The SYNTAX Score obtained in our cohort of patients (mean, 34.5; SD, 6.7) is notably higher than that reported by the authors of the SYNTAX trial (mean 29.1 in the CABG group and 28.4 in the PCI group)[8] or Birim and colleagues[13] (mean, 24.9). This difference may be attributed to several factors: (1) First, the creators of the SYNTAX Score themselves warn of the system's low interobserver (weighted Kappa 0.45) and intraobserver (weighted Kappa 0.59) reproducibility.[8] To minimize the error of low reproducibility in our study, 2 observers interpreted the angiographs of each patient. (2) In addition, patients randomized in the SYNTAX trial had to be suitable for the same completeness of both PCI and CABG revascularization. Therefore, only patients who were less technically demanding for PCI were selected for randomization. Mohr and colleagues[9] reported a mean SYNTAX Score of 29.1 (SD, 11.4) for those patients undergoing CABG who were randomized in the SYNTAX trial and 37.8 (SD, 13.3) for those enrolled in the SYNTAX trial CABG registry (similar to the mean score found in the present study). This inclusion/selection bias makes it difficult to ascertain whether the mean SYNTAX Score in the trial represents that of the entire population with LMCA or 3-vessel disease. (3) Finally, most of our candidates for coronary surgery had been previously rejected for a PCI procedure by our center's team of interventional cardiologists. All these factors could explain the higher scores obtained in our patients. According to previous articles and this one, it is highly probable that the SYNTAX Score may predict outcomes after CABG only for those patients with highly complex coronary lesions, whereas it does not for those with low or medium scores.[13]

The data reported in this article reveal a clear relation between the prevalence of cardiovascular risk factors and the complexity and extent of coronary disease. Thus, when we divided the SYNTAX Scores obtained into terciles, a higher prevalence of peripheral arterial disease, diabetes, renal failure, and stroke, and an older age were observed in the 2 top terciles (Table 1). In large population studies, such as Framingham[19] or INTERHEART,[20] a higher prevalence of cardiovascular risk factors has been linked to a greater risk of cardiovascular events. It has also been reported that the severity and extent of atherosclerotic lesions are related to the prevalence of risk factors.[10,21-23] In the present study, this relation has been observed once more. On the other hand, previous studies[13,14] failed to demonstrate this fact. The reason for this could be that SYNTAX Scores were considerably lower than those observed in our population, meaning that those previous studies likely included an insufficient number of patients with scores high enough to detect such a relationship. We also noticed a greater predicted risk (by euroSCORE scale) in the 2 top terciles ($P < .001$). A linear correlation was observed between the SYNTAX Score and the euroSCORE punctuations (b = 0.152 euroSCORE points/SYNTAX Score point, $P < .001$).

In the present study, the SYNTAX Score was independently associated with postprocedural MACCE ($P < .001$, OR = 1.08), which was confirmed after adjustment by the balancing score ($P < .001$, OR = 1.065) (Table 4). This link may be attributed to a greater mortality ($P = .011$) and incidence of AMI ($P < .001$) produced in the groups of patients awarded the highest scores (Table 3). The relationship between higher SYNTAX Scores and poorer postoperative outcomes were reported by Birim and colleagues,[13] who found this to be an independent predictor of postoperative MACCE (relative risk, 1.2; 95% CI, 1.1–1.3). Although no statistically significant relation was detected between in-hospital mortality and SYNTAX Score ($P = .077$), we did observe a higher mortality among the patients showing the higher SYNTAX Scores (8.8% [score > 37] vs 3.2% [score 33–37] or 3.6% [score ≤ 33]). The high incidence of myocardial infarction observed in the population of this study might be explained by the definition we used (see "Materials and Methods" section for events definition).

In the follow-up (mean, 26.7 months; ranking, 0–62), we found that patients with higher SYNTAX Scores had a higher risk of death ($P = .008$) and MACCE ($P = .009$) (Figure 1, *A, B*). On a multivariate analysis adjusted by a balancing score, SYNTAX Score was not independently associated with mortality (HR, 1.029; $P = .198$), but it did show

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an independent association with MACCE (HR, 1.034; $P = .027$). The SYNTAX investigators[8] did not find a significant difference in the incidence of MACCE at 1 year among the 3 terciles ($\leq$22: 10.7%; 23–32: 11.7%; and >33: 14.4%) of the CABG cohort in the SYNTAX study ($P = .38$). Lemesle and colleagues[14] studied a cohort of 320 patients with 3-vessel disease undergoing CABG. SYNTAX Score terciles were less than 24.5, 24.5 to 34, and greater than 34. They did not find a significant difference in the composite event death/myocardial infarction/stroke among the 3 groups at 1 year ($P = .754$). To date, only Birim and colleagues[13] have reported the SYNTAX Score as an independent predictor of MACCE at 1 year (HR, 1.3; 95% CI, 1.1–1.2). We believe that other studies have failed to prove the prognostic value of the SYNTAX Score for outcomes in the follow-up for 3 possible reasons: (1) the follow-up was not long enough, (2) events might be more frequent in those with higher scores than reported in these studies, or (3) the size of the sample was too small.

The SYNTAX Score was created in the setting of the SYNTAX trial to help select a surgical or interventionist therapeutic option based on the severity and extent of atherosclerotic disease in patients with LMCA or 3-vessel disease. Beyond the intended objectives, that trial and others have demonstrated the relation between the SYNTAX Score and major adverse cardiac and cerebrovascular events after PCI or CABG. This study provides objective support for the intuitive idea that the severity and extent of atherosclerotic coronary vessel damage will affect the short and midterm outcomes of surgical coronary revascularization.

LIMITATIONS

This retrospective study was conducted at a single center; thus, the results may not be reproducible or consistent with those of other studies. Although we precisely followed the heart team decision algorithm provided by the SYNTAX investigators, retrospective SYNTAX Score assessment may generate further bias. Future studies need to address the mid- and long-term predictive and MACCE-discriminating capacity of the SYNTAX Score in patients undergoing CABG to corroborate the conclusions of this study.

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