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The Prognostic Utility of the SYNTAX Score on 1-Year Outcomes After Revascularization With Zotarolimus- and Everolimus-Eluting Stents

A Substudy of the RESOLUTE All Comers Trial

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Objectives This study assessed the ability of the SYNTAX score (SXscore) to stratify risk in patients treated with percutaneous coronary intervention (PCI) using zotarolimus-eluting or everolimus-eluting stents.

Background The SXscore can identify patients treated with PCI who are at highest risk of adverse events.

Methods The SXscore was calculated prospectively in 2,033 of the 2,292 patients enrolled in the RESOLUTE All Comers study (RESOLUTE III All Comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). Clinical outcomes in terms of a patient-oriented composite endpoint (POCE) of all-cause death, myocardial infarction (MI), and repeat revascularization; the individual components of POCE; target lesion failure (TLF) (a composite of cardiac death, target-vessel MI, and clinically driven target lesion revascularization); and stent thrombosis were subsequently stratified according to SXscore tertiles: $SXscore_{LOW} \leq 9$ (n = 698), $9 < SXscore_{MID} \leq 17$ (n = 676); $SXscore_{HIGH} > 17$ (n = 659).

Results At 12-month follow-up, rates of POCE, MI, repeat revascularization, TLF, and the composite of death/MI were all significantly higher in patients in the highest SXscore tercile. Rates of stent thrombosis were all highest in the $SXscore_{HIGH}$ tertile ($p > 0.05$). After multivariate adjustment, the SXscore was identified as an independent predictor of POCE, MI, repeat revascularization, and TLF ($p < 0.05$ for all). At 12-month follow-up, the SXscore, ACEF score, and Clinical SXscore had C-statistics of 0.57, 0.78, and 0.67, respectively, for mortality and of 0.62, 0.56, 0.63, respectively, for POCE. No significant between-stent differences were observed for TLF or POCE in any of the SXscore tertiles.

Conclusions The SYNTAX score is able to stratify risk amongst an all-comers population treated with PCI with second-generation drug-eluting stents (DES); however, improvements can be made with the inclusion of clinical variables. (RESOLUTE III All Comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; NCT00617084) (J Am Coll Cardiol Intv 2011;4:432–41) © 2011 by the American College of Cardiology Foundation

The SYNTAX score (SXscore) is a comprehensive scoring system made up of angiographic variables (1,2). It was originally developed to quantify the complexity of coronary artery disease (CAD); however, subsequent studies have demonstrated its ability to identify patients treated by percutaneous coronary intervention (PCI) who are at highest risk of adverse events (3–8).

Currently, prospective studies assessing its use in patients treated with PCI are limited to the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) study (4), which only enrolled patients with complex CAD (3-vessel and/or left main disease), and the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) study (3), which was more reflective of everyday clinical practice through its all-comers design. Of note, other than the 703 patients treated with the biolimus-eluting stent with a biodegradable polymer in the LEADERS SXscore substudy (3), all other studies evaluating the SXscore have assessed outcomes in patients treated with first-generation drug-eluting stents (DES) (4–9). Second-generation DES were developed on the background of safety concerns with these first-generation devices, and early data suggest significantly improved outcomes (10–12); however, the effect of this on the benefits of using the SXscore to stratify risk remains to be established.

The RESOLUTE All Comers study (RESOLUTE III All Comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) (13) randomized 2,292 patients to treatment with the Resolute zotarolimus-eluting stent (R-ZES) (Medtronic Inc., Santa Rosa, California) or the Xience V everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California). Results demonstrated that R-ZES was noninferior to EES with respect to the 12-month primary clinical endpoint of target lesion failure (TLF) (R-ZES 8.2% vs. EES 8.3%, $p_{noninferiority} < 0.001$), a composite of cardiac death, target-vessel myocardial infarction (MI), and clinically driven target lesion revascularization (TLR) and the 13-month secondary angiographic endpoint of in-stent diameter stenosis (R-ZES 21.65 ± 14.42% vs. EES 19.76 ± 14.64%, $p_{noninferiority} = 0.035$). In this sub-study of the RESOLUTE All Comers trial the prognostic value of the SXscore was assessed in isolation and in comparison with the Age, Creatinine and Ejection Fraction (ACEF score) (14,15) and the clinical SYNTAX score (CSS), (16) in an all-comers population treated with second-generation DES.

Methods

Study population. The methods of the RESOLUTE All Comers study have been published previously (13). In brief, the study applied an all-comers approach to recruit 2,292 patients with chronic stable CAD or acute coronary syndromes including ST-segment elevation myocardial infarction that were eligible for enrollment if they had ≥1 lesion with diameter stenosis (DS) ≥50% and a reference vessel diameter between 2.25 and 4.0 mm. No restriction was placed on the number of lesions or vessels treated or the number of stents implanted. Principal exclusion criteria were: allergy to study medication, metal alloys, or contrast media; planned surgery within 6 months of PCI unless the dual antiplatelet therapy could be maintained throughout the perioperative period; pregnancy; participation in another trial before reaching the primary endpoint; and lastly, inability to give informed consent. The study complied with the Declaration of Helsinki and was approved by all institutional ethics commit-

Abbreviations and Acronyms

ACEF score = **Age, Creatinine and Ejection Fraction**
CAD = **coronary artery disease**
CEC = **clinical events committee**
CSS = **clinical SYNTAX score**
DES = **drug-eluting stent(s)**
ECG = **electrocardiograph**
EES = **everolimus-eluting stent(s)**
MI = **myocardial infarction**
PCI = **percutaneous coronary intervention**
POCE = **patient-oriented composite endpoint**
R-ZES = **Resolute zotarolimus-eluting stent(s)**
ST = **stent thrombosis**
SXscore = **SYNTAX score**
TLF = **target lesion failure**
TLR = **target lesion revascularization**

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tees. All patients provided written informed consent for participation in the trial.

Randomization and procedures. Patients were randomly allocated on a 1:1 basis to treatment with R-ZES or EES and to 12-month clinical follow-up only or in addition to active angiographic follow-up at 13-months, on a 1:4 basis with a factorial design. A blinded independent clinical events committee (CEC) adjudicated all endpoints, and independent study monitors verified all case reports from data on-site. The operators were by necessity aware of the assigned study stent during PCI and angiographic follow-up, but patients and staff involved in follow-up assessment were blinded to the allocated stent type.

The R-ZES were available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 30 mm, whereas EES were available in diameters of 2.25 to 4.0 mm and in lengths of 8 to 28 mm. Balloon angioplasty and stent implantation were performed according to standard technique, and direct stenting was allowed. The aim was to obtain full lesion coverage with 1 or several stents. No mixture of DES was permitted within a given patient, unless the operator was unable to insert the study stent, in which case crossover to another nonstudy device of the operator's choice was possible.

Procedural anticoagulation was achieved with unfractionated heparin 5,000 IU or 70 to 100 IU/kg, whereas the use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Before the procedure, all patients enrolled into the study received ≥75 mg of acetylsalicylic acid, whereas the 300- to 600-mg loading dose of clopidogrel was only given if no clopidogrel had been administrated in the previous 7 days. All patients were discharged on ≥75 mg of acetylsalicylic acid indefinitely and clopidogrel 75 mg for >6 months after the index procedure. In the case of intercurrent revascularization procedures needing stent implantation, treating cardiologists were encouraged to use study stents.

Follow-up. Adverse events were assessed in hospital, and clinical follow-up was performed at 1, 6, and 12 months. Additional clinical follow-up is planned at yearly intervals to 5 years. One in 5 patients was asked to return for angiographic follow-up at 13 months.

SXscore. The SXscore for each patient was calculated prospectively by scoring all coronary lesions with a DS ≥50%, in vessels ≥1.5 mm, with the SXscore algorithm that is described in full elsewhere (1,2) and available at the SYNTAX Score website (17). All angiographic variables pertinent to SXscore calculation were computed by 2 core laboratory analysts (Cardialysis B.V., Rotterdam, the Netherlands), who were blinded to all clinical data, presentation, and outcomes. In the event of disagreement, the opinion of a third analyst was sought, and the final decision was established by consensus. Patients with occluded infarct-related arteries were scored as occlusions of unknown duration in a similar manner as any chronically occluded artery. In addition, those patients with lesions due to restenosis or in-stent restenosis were scored in the same manner as if the lesion were a de novo lesion. Although this methodology was not described in the original description of the SXscore, it has previously been applied to other all-comers (3,6) and ST-segment elevation myocardial infarction populations (9).

ACEF score and CSS. The ACEF score was calculated with the combination of the patient's age, left ventricular ejection fraction, and serum creatinine as described elsewhere (14). Similarly, the CSS was calculated with the combination of the SXscore and the patient's age, left ventricular ejection fraction, and creatinine clearance as described in the primary manuscript (16).

Study endpoints. The primary endpoint of this analysis was a patient-oriented composite endpoint (POCE) of all-cause death, any MI, and any repeat revascularization. Secondary endpoints included the individual components of the POCE, together with 1-year rates of cardiac death, target vessel MI, clinically indicated TLR, a safety composite of death/MI, TLF (a composite of cardiac death, target-vessel MI, and TLR), and definite, definite/probable, and any stent thrombosis (ST).

Definitions. Definitions of all endpoints are provided in the primary manuscript (13). All deaths were considered cardiac unless an undisputed noncardiac cause was present. Myocardial infarction was defined according to an extended historical protocol definition and according to Academic Research Consortium definitions (18,19). A Q-wave MI required, in the absence of cardiac enzyme data, a history of chest pain or other acute symptoms consistent with myocardial ischemia together with new pathological Q waves in ≥2 contiguous electrocardiograph (ECG) leads as assessed by the core laboratory or CEC. In the presence of elevated cardiac enzymes, new pathological Q waves in ≥2 contiguous ECG leads as assessed by the core laboratory or CEC were sufficient to diagnose a Q-wave MI. In the absence of an ECG, a Q-wave MI could be adjudicated on the basis of the clinical scenario and appropriate cardiac enzyme data.

A TLR was considered clinically indicated if angiography during follow-up showed a DS ≥50% (core laboratory quantitative coronary angiography assessment) and if 1 of the following occurred: 1) a positive history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; 3) abnormal results of any invasive functional diagnostic test (e.g., fractional flow reserve); or 4) a TLR with a DS ≥70% even in the absence of the aforementioned ischemic signs or symptoms. An ST was defined according to the Academic Research Consortium definitions (18).

Statistical methods. All patients with a calculated SXscore were included in the analysis. All variables were stratified according to SXscore tertiles. Discrete data were summarized as frequencies (%), whereas continuous data were expressed as mean ± SD. Testing for (linear) trends was

done with generalized linear models with SYNTAX tertiles as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical data. The Fisher exact test was used to analyze differences in outcome between stents. Survival curves were constructed for time-to-event variables with Kaplan-Meier estimates and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. A Cox multivariate model was performed with the covariates sex, age >65 years, presence of diabetes, presentation with acute MI, stent type, and SXscore. C-statistics from receiver operator characteristic curves were used to compare the discrimination of the SXscore, ACEF score, and CSS score. A p value of <0.05 was considered significant, and all tests were 2-tailed. Data were analyzed with SAS software (SAS, version 9.2, Cary, North Carolina) by a dedicated statistician.

Results

The SXscore was available for 2,033 (88.7%) of 2,292 patients enrolled in the study, with the presence of coronary artery bypass grafts (224 patients) as the major reason for inability to calculate the score. The SXscore ranged from 0 to 54.5, with a mean ± SD of 14.6 ± 9.2 and a median of 13.0 (interquartile range 7 to 20). In this analysis patients were categorized according to tertiles of the SXscore defined as: $SXscore_{LOW}$ ≤9 (n = 698); 9 <$SXscore_{MID}$ ≤17 (n = 676); $SXscore_{HIGH}$ >17 (n = 659).

Baseline clinical characteristics. Baseline clinical parameters stratified according to SXscore tertiles are presented in Table 1. Advanced patient age, male sex, the presence of diabetes mellitus and multivessel disease, and presentation with an acute MI were all significantly more common in the $SXscore_{HIGH}$ tertile. Conversely, hypercholesterolemia and presentation with stable angina were significantly more frequent in the $SXscore_{LOW}$ tertile.

Baseline angiographic characteristics. Baseline lesion and procedural characteristics are shown in Table 2. The frequency of triple-vessel disease and all markers of increased lesion complexity such as the presence of bifurcation lesions and total occlusions were all significantly higher in the $SXscore_{HIGH}$ tertile, in line with its method of derivation. Correspondingly the number of treated lesions, stents implanted, and mean stent length were also higher in the $SXscore_{HIGH}$ tertile.

Clinical outcomes. Clinical outcomes at 1 year are shown in Table 3, whereas cumulative survival curves are displayed in Figure 1. Overall, the POCE, the safety endpoint of death/MI, and the rates of MI and repeat revascularization were all significantly higher in the $SXscore_{HIGH}$ tertile. No trends were noted among rates of death and definite, definite/probable, or any ST and the SXscore tertile of the patient.

Table 1. Baseline Clinical Characteristics

Variable	SXscore ≤9 (n = 698)	9 <SXscore ≤17 (n = 676)	SXscore >17 (n = 659)	p Value
Baseline characteristics				
Male	71.2% (497)	76.9% (520)	78.8% (519)	0.001
Age, yrs	63.0 ± 10.9	63.0 ± 10.8	65.5 ± 11.0	<0.001
Risk factors				
Previous MI	26.5% (182)	24.8% (164)	28.7% (185)	0.37
Diabetes mellitus	19.3% (135)	23.2% (157)	24.7% (163)	0.02
Arterial hypertension	70.6% (493)	71.3% (482)	68.3% (450)	0.35
Hypercholesterolemia	65.6% (458)	64.1% (433)	59.8% (394)	0.03
Premature CAD in first-degree relative	36.0% (214)	37.7% (218)	30.7% (169)	0.07
Current smoker	25.5% (178)	29.3% (198)	29.1% (192)	0.13
Previous PCI	31.2% (218)	26.6% (180)	29.9% (197)	0.57
Creatinine clearance, ml/1.73 m^2	96.2 ± 34.4	96.6 ± 34.7	90.9 ± 34.3	0.006
Left ventricular ejection fraction <30%	2.0% (8)	2.4% (8)	1.6% (6)	0.69
Multivessel disease	32.4% (226)	57.0% (385)	78.8% (519)	<0.0001
SXscore	5.7 ± 2.4	13.3 ± 2.3	25.5 ± 6.7	N/A
Indication for treatment				
Revascularization for angina or MI	86.8% (606)	88.9% (601)	89.4% (589)	0.14
Stable angina	37.5% (262)	31.8% (215)	30.2% (199)	0.004
Unstable angina	21.6% (151)	19.7% (133)	14.9% (98)	0.002
Acute MI	27.7% (193)	37.4% (253)	44.3% (292)	<0.0001

Values are given as % (n) or mean ± SD.
CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; SXscore = SYNTAX score.

Table 2. Baseline Lesion and Procedural Characteristics

Variable	SXscore ≤9 (n = 698)	9 <SXscore ≤17 (n = 676)	SXscore >17 (n = 659)	p Value
Extent of disease				
No. of disease lesions	1.5 ± 0.7	2.5 ± 1.1	4.0 ± 1.6	<0.0001
1-vessel disease	67.6% (472)	26.9% (182)	7.4% (49)	0.005
2-vessel disease	29.1% (203)	54.3% (367)	36.1% (238)	<0.0001
3-vessel disease	2.1% (15)	18.8% (127)	56.4% (372)	<0.0001
Lesion location				
Left main stem	0.0% (0)	0.6% (4)	5.8% (38)	<0.0001
Right coronary artery	46.8% (327)	60.7% (410)	75.9% (500)	<0.0001
Circumflex artery	34.1% (238)	53.3% (360)	74.5% (491)	<0.0001
LAD artery	51.3% (358)	77.4% (523)	95.1% (627)	<0.0001
Proximal LAD involvement	8.7% (61)	21.0% (142)	44.9% (296)	<0.0001
All de novo lesions	89.3% (620)	92.5% (620)	90.6% (591)	0.39
Lesion characteristics				
≥1 bifurcation lesion	25.9% (181)	56.2% (380)	75.6% (498)	<0.0001
≥1 trifurcation lesion	0.6% (4)	3.6% (24)	6.4% (42)	<0.0001
≥1 ostial lesion	1.6% (11)	3.0% (20)	4.9% (32)	0.0005
≥1 occlusion	3.6% (25)	25.3% (171)	49.3% (325)	<0.0001
≥1 tortuous lesion	24.8% (171)	45.0% (304)	62.7% (413)	<0.0001
≥1 lesion ≥20 mm	8.0% (55)	29.6% (200)	53.0% (349)	<0.0001
≥1 calcified lesion	3.0% (21)	10.4% (70)	21.5% (142)	<0.0001
≥1 lesion with thrombus	5.8% (40)	6.5% (44)	10.9% (72)	0.0004
≥1In-stent restenosis lesion	9.1% (63)	5.5% (37)	7.7% (50)	0.30
Off-label indication*	49.9% (348)	67.2% (454)	80.9% (533)	<0.0001
Procedural characteristics				
No. of treated lesions	1.2 ± 0.4	1.5 ± 0.6	1.9 ± 1.0	<0.0001
No. of stents implanted	1.5 ± 0.8	1.9 ± 1.1	2.6 ± 1.6	<0.0001
Total stent length, mm	25.7 ± 16.3	35.3 ± 22.9	48.1 ± 30.3	<0.0001
Mean duration of DAPT, days	315 ± 97	319 ± 90	308 ± 102	0.20

Values are given as mean ± SD or % (n). *Off-label use included patients with at least 1 of the following clinical and lesion characteristics: renal insufficiency (≥140 μmol/l), ejection fraction <30%, acute myocardial infarction (≤72 h), >1 lesion/vessel, ≥2 vessels stented; lesions >27 mm, bifurcations, bypass grafts, in-stent restenosis, unprotected left main, lesions with thrombus, or total occlusion.
DAPT = dual antiplatelet therapy; LAD = left anterior descending artery; SXscore = SYNTAX score.

Multivariate analysis. The results of the Cox multivariable analysis are shown in Table 4. The SXscore remained an independent predictor, after adjustment of confounding factors, of clinical outcomes such as MI, repeat revascularization, TLF, and POCE.

SXscore versus ACEF score versus CSS. Table 5 reports the respective C-statistics for the SXscore, ACEF score, and CSS for a range of clinical outcomes at 12-month follow-up. The discriminatory ability of the SXscore was best for repeat revascularization, poorest for the assessment of mortality, and comparable to the CSS for the composite endpoints of TLF and POCE.

Zotarolimus versus everolimus. For illustrative purposes, a comparison of outcomes amongst patients in each SXscore tertile stratified according to stent type was performed. Overall rates of TLF, the device-oriented primary endpoint of the Resolute All Comers study, and the POCE were comparable between R-ZES and EES in all 3 SXscore groups ($p > 0.05$). Notably, in 659 patients with the most complex CAD, mortality was significantly higher in patients treated with EES (R-ZES 1.3% vs. EES 4.1%, $p = 0.03$), whereas rates of clinically indicated TLR (7.2% vs. 3.5%, $p = 0.04$) and definite ST (2.2% vs. 0.0%, $p = 0.006$) were significantly higher in those treated with R-ZES.

Discussion

This study, which represents the largest assessment of the SXscore in patients treated with PCI and is the first to assess its ability to stratify risk in patients treated entirely with second-generation DES, demonstrates a consistent ability of the SXscore to identify patients at highest risk of adverse events after PCI.

A key to optimizing outcomes in patients undergoing PCI is the ability to reliably identify those patients at highest risk of undesired events. With respect to this, the SXscore has been consistently shown to be an important tool for risk stratification; however, prior assessments of the

Table 3. Clinical Outcomes at 12 Months on an Intention-To-Treat Basis

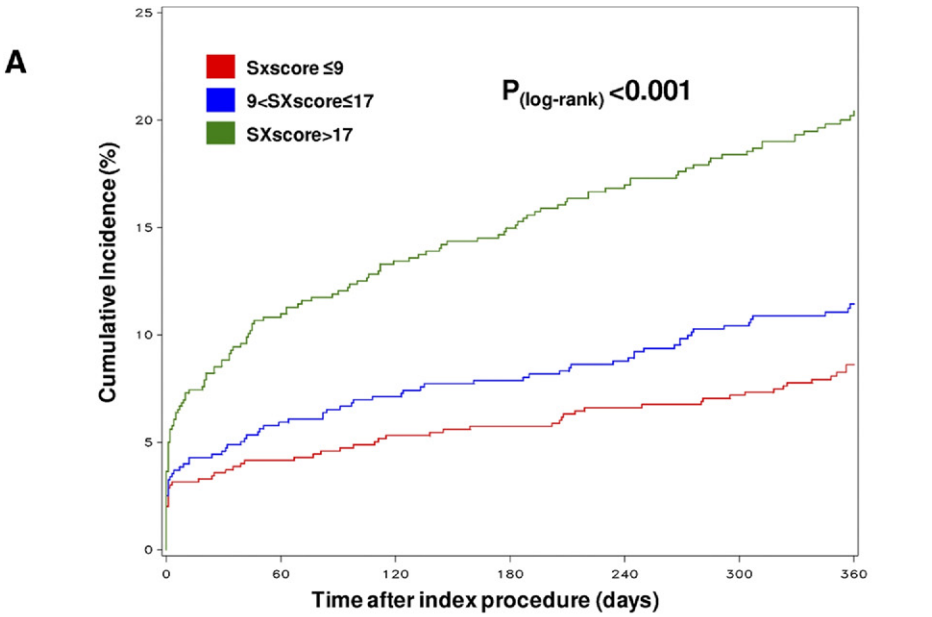
Variable	SXscore ≤9 (n = 698)	9 <SXscore ≤17 (n = 676)	SXscore >17 (n = 659)	p Value
Death	1.9% (13)	1.0% (7)	2.7% (18)	0.25
Cardiac death	1.0% (7)	0.4% (3)	2.1% (14)	0.06
Any MI*	8.0% (56)	12.1% (82)	18.2% (120)	<0.0001
Any MI†	3.2% (22)	3.8% (26)	5.3% (39)	0.01
Target vessel MI†	2.7% (19)	3.6% (24)	5.6% (37)	0.006
Any repeat revascularization	5.0% (35)	7.7% (52)	13.7% (90)	<0.0001
Clinically indicated TLR	2.0% (14)	2.7% (18)	5.3% (35)	0.0007
Death or MI	4.7% (33)	4.7% (32)	8.2% (54)	0.01
Target lesion failure‡	5.2% (36)	5.9% (40)	11.7% (77)	<0.0001
Patient-oriented composite endpoint§	8.5% (59)	11.2% (76)	20.0% (132)	<0.0001
ARC definite stent thrombosis	0.4% (3)	0.6% (4)	1.1% (7)	0.16
ARC definite/probable stent thrombosis	0.9% (6)	0.7% (5)	1.7% (11)	0.15
ARC any stent thrombosis	1.4% (10)	0.9% (6)	2.6% (17)	0.10

Values are given as % (n). *Defined according to the Academic Research Consortium (ARC) (18). †Extended historical definition (19). ‡Target lesion failure: cardiac death, MI† (not clearly attributable to a nontarget vessel) and clinically indicated target lesion revascularization (TLR). §Patient-oriented composite endpoint: a composite of all-cause mortality, MI (Q- and non–Q-wave), or any revascularization.
Abbreviations as in Table 1.

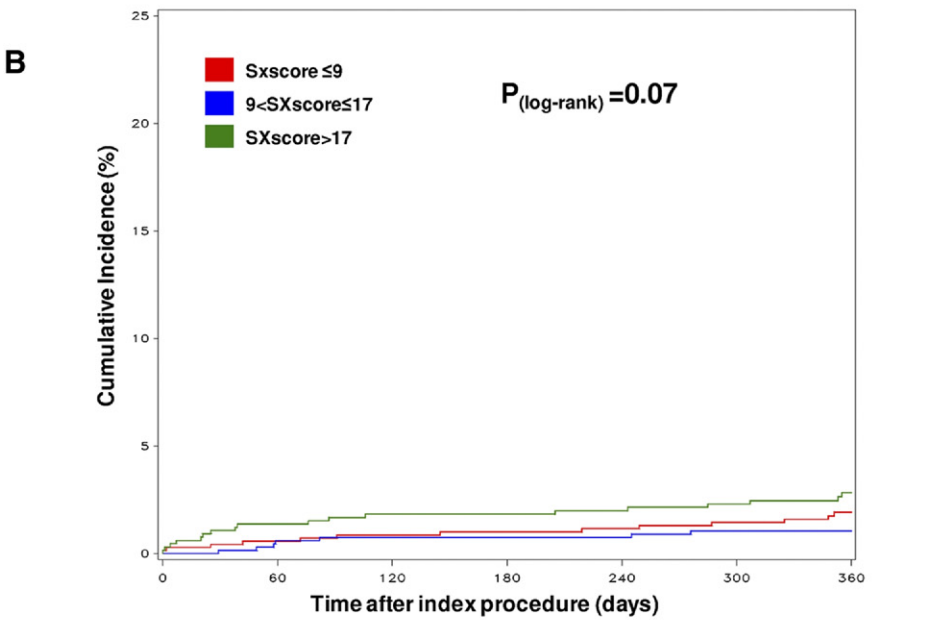
score in PCI populations have been limited by being retrospective (5–9,20) and largely including only those patients with the most complex CAD (4,7,8,20). In addition, other than the LEADERS study (3), all other studies have enrolled patients treated with first-generation DES (4–9). The current prospective study had an all-comers design, such that any patient with symptomatic CAD suitable for PCI who consented to enrollment could be included, thereby ensuring that the patient cohort provided a good reflection of those patients routinely seen in "real-world" contemporary practice. Furthermore, all patients received second-generation DES, which have been shown to have superior safety and efficacy, compared with earlier devices (10–12). Therefore the confirmation of the ability of the SXscore to independently predict adverse clinical outcomes in any patient presenting for PCI treated with second-generation DES is important evidence to support the routine use of the SXscore in everyday practice. This ability to identify those patients at greatest risk of adverse events facilitates appropriate informed consent and counseling while also prompting increased surveillance and aggressive secondary preventive therapy and lifestyle modifications in those at highest risk.

Analysis of the SXscore distribution in the current study clearly indicates that patients with very complex CAD are being treated with PCI—a consequence of the increasing age and comorbidities of patients presenting for revascularization (21) and the advancements in PCI technology. Objective evidence of this increase is reflected in the mean SXscores of the SIRTAX (Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization) and LEADERS studies, which were 11.7 ± 7.3 and 13.5 ± 8.7 (3,6), respectively, compared with 14.6 ± 9.2 in the current study. Moreover, the percentage of patients with SXscores >32, a group with the most complex CAD and previously identified in the SYNTAX trial as the threshold above which surgical revascularization provided the optimal outcome, is also increasing with respective rates of 1.0% and 2.9% in the SIRTAX and LEADERS studies, compared with 4.4% in the present analysis. The current study lacked a surgical control arm, and it is therefore not possible to state whether PCI was appropriate for those patients in the highest SXscore tertile. Moreover, at present, no data are available comparing outcomes in patients randomized to treatment with PCI with second-generation DES or coronary artery bypass grafting; however, the utility of using EES compared with coronary artery bypass grafting in patients with complex CAD is currently being assessed in the ongoing EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) study.

It is reassuring that no significant differences in mortality were noted across SXscore tertiles, despite the more complex patient population in the current study—a finding at variance with the LEADERS study, which did identify the SXscore as an independent predictor of mortality (3). Furthermore, although both studies indicated significantly higher rates of their respective primary study endpoints and repeat revascularization in patients in the highest SXscore tertile, the same was not true for MI in the LEADERS study or ST in the current study. This variation in the ability of the SXscore to predict "hard" clinical endpoints is not clearly explained. Without doubt, it could be the consequence of underpowered sub-group analyses (22,23); however, it might also reflect the limitations of using a risk model assessing only 1 type of variable. Consistent with previous studies (15,16), there were variations in the dis-



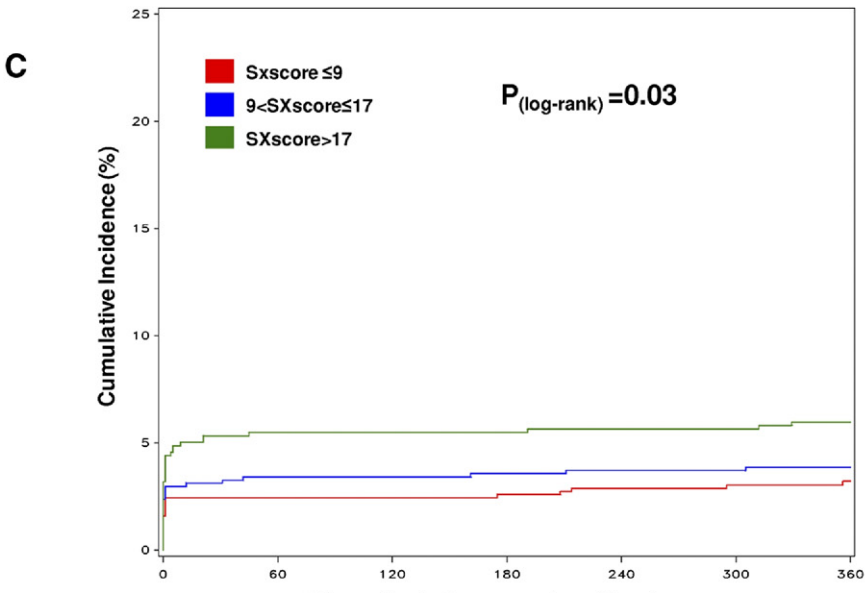
Days	0	60	120	180	240	300	360
Sxscore ≤9	698	666	658	653	646	642	476
9<SXscore≤17	676	630	622	616	607	595	433
SXscore>17	659	580	564	554	534	524	378



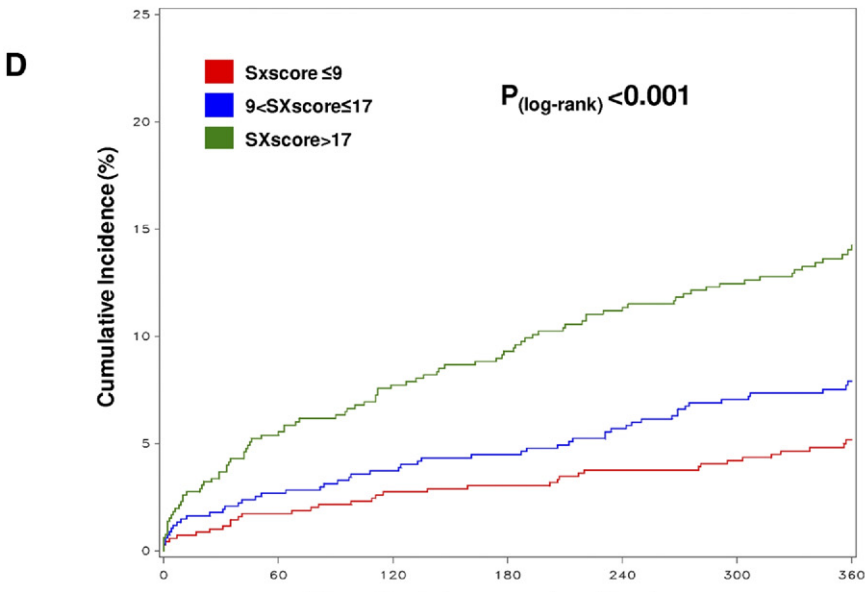
Days	0	60	120	180	240	300	360
Sxscore ≤9	698	691	689	686	683	680	508
9<SXscore≤17	676	666	665	663	659	656	486
SXscore>17	659	643	639	639	630	626	460

Figure 1. Kaplan-Meier Curves

Kaplan-Meier survival curves for **(A)** the patient-oriented composite endpoint (a composite of all-cause death, any myocardial infarction, and any repeat revascularization; **(B)** any death; **(C)** any myocardial infarction; **(D)** any repeat revascularization out to 12-month follow-up. SXscore = SYNTAX score.



Days	0	60	120	180	240	300	360
Sxscore ≤9	698	674	673	669	664	661	496
9<SXscore≤17	676	644	643	640	635	632	465
SXscore>17	659	609	605	605	595	591	433



Days	0	60	120	180	240	300	360
Sxscore ≤9	698	680	671	666	659	654	485
9<SXscore≤17	676	649	641	635	624	612	449
SXscore>17	659	607	590	580	559	549	396

Figure 1. *Continued.*

criminatory ability of the SXscore, ACEF score, and CSS, which represent an anatomical, clinical, and combination clinical/anatomical risk model, respectively, depending on the outcome measure being assessed. The C-statistic for mortality was highest for the ACEF score, reflecting the heavy influence of pre-morbid characteristics on this outcome. Similarly, the C-statistic for repeat revascularization was highest for the SXscore. One of the previous valid concerns with using the SXscore is the absence of clinical variables in its calculation, a deficiency that can be corrected through its combination with a clinically based score as reported previously (16,24) and highlighted in the present study through the improved C-statistics for all outcomes, apart from repeat revascularization, when using the CSS compared with the SXscore.

The rates of definite ST in the current study were lower than those seen in corresponding tertiles of the SXscore in the LEADERS study, differences that might partly explain the lack of association between ST and SXscore tertile in the present study. It must be acknowledged that the current study is underpowered to assess for this outcome; however, the numerically different rates of ST according to SXscore tertiles—despite comparable duration of DAPT—suggest that there might be an additional role for the SXscore in helping tailor antiplatelet therapy on an individual level. However, confirmation of this hypothesis requires adequately powered randomized trials.

The 12-month outcomes from the RESOLUTE All Comers study demonstrated that R-ZES was noninferior to EES with respect to the primary clinical endpoint of TLF. The present study reassuringly indicates that comparable outcomes with respect to TLF were also maintained between both stents irrespective of the severity of underlying CAD. Of note, although the between-stent differences in mortality and definite ST amongst patients in the highest SXscore tertile followed the trends seen in the full patient cohort, the same was not true for the differences seen in clinically indicated TLR. Similarly, in the LEADERS study, a significant between-stent difference in cardiac death was observed amongst patients in the highest SXscore tertile, which was not seen in the full patient cohort (25). Although these observations might suggest potential differences in stent performance with different severities of CAD, they should be regarded in the first instance as being underpowered, hypothesis-generating analyses and should ultimately be used as a stimulus for further more-directed and adequately powered studies. Nevertheless, these observations do serve to highlight a new potential application of the SXscore as a means to further assess and compare the performance of new coronary devices.

Table 4. Cox Multivariate Analysis

Clinical Outcome	Hazard Ratio for SYNTAX Score* (95% Confidence Interval)	p Value
Death	1.19 (0.80–1.76)	0.40
MI†	1.52 (1.17–1.99)	0.002
Any repeat revascularization	1.75 (1.44–2.13)	<0.001
Target lesion failure‡	1.68 (1.36–2.06)	<0.001
Patient-oriented composite endpoint§	1.68 (1.43–1.96)	<0.001
Any stent thrombosis	1.39 (0.89–2.15)	0.15

*After adjustment of confounding factors: age >65 years, sex, presentation with an acute myocardial infarction (MI), presence of diabetes, and stent type. †Extended historical definition (19). ‡Target lesion failure: cardiac death, MI† (not clearly attributable to a nontarget vessel) and clinically indicated target lesion revascularization (TLR). §Patient-oriented composite endpoint: a composite of all-cause mortality, MI (Q- and non–Q-wave), or any revascularization.

Table 5. Comparison of Discriminatory Ability of SXscore, ACEF Score, and Clinical SYNTAX Score

Variable	C-Statistic		
	SXscore (n = 2,033)	ACEF Score (n = 1,218)	CSS (n = 1,098)
Death	0.57	0.78	0.67
Cardiac death	0.61	0.84	0.71
Any myocardial infarction*	0.60	0.58	0.65
Any repeat revascularization	0.63	0.50	0.59
Target lesion failure†	0.62	0.59	0.63
Patient-oriented composite endpoint‡	0.62	0.56	0.63
ARC any stent thrombosis	0.60	0.72	0.68

Extended historical definition (19). †Target lesion failure: cardiac death, myocardial infarction (MI) (not clearly attributable to a nontarget vessel), and clinically indicated target lesion revascularization (TLR). ‡Patient-oriented composite endpoint: a composite of all-cause mortality, MI (Q- and non–Q-wave), or any revascularization.

ACEF score = Age, Creatinine and Ejection Fraction; CSS = clinical SYNTAX score; SXscore = SYNTAX score.

Study limitations. The SXscore has several limitations, including intraobserver and interobserver variability (2,26)—which is inherent to its subjective derivation with coronary angiography—and the absence of specific algorithms for patients with prior percutaneous or surgical revascularization. Specifically, the current analysis might have limitations, such as underpowered results and chance findings, which are inherent to the use of sub-group analysis (22,23). Missing quantitative values for the ejection fraction and serum creatinine also lead to the ACEF score and CSS being available in only approximately one-half of the study population.

Conclusions

The SXscore is able to stratify risk amongst an all-comers population treated with PCI with second-generation DES; however, improvements can be made with the inclusion of clinical variables.

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Key Words: everolimus-eluting stent(s) ■ resolute zotarolimus-eluting stent(s) ■ SYNTAX score.