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STATE-OF-THE-ART PAPER

Prediction of Coronary Risk by SYNTAX and Derived Scores

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery

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The introduction of the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score has prompted a renewed interest for angiographic risk stratification in patients undergoing percutaneous coronary intervention. Syntax score is based on qualitative and quantitative characterization of coronary artery disease by including 11 angiographic variables that take into consideration lesion location and characteristics. Thus far, this score has been shown to be an effective tool to risk-stratify patients with complex coronary artery disease undergoing percutaneous coronary intervention in the landmark SYNTAX trial, as well as in other clinical settings. This review provides an overview of its current applications, including its integration with other nonangiographic clinical scores, and explores future applications of the SYNTAX and derived scores. (J Am Coll Cardiol 2013;62:1219–30) © 2013 by the American College of Cardiology Foundation

The SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score (SS) was developed as part of the SYNTAX trial with the object to characterize and objectively quantify the severity and extent of coronary artery disease (CAD) (1). Subsequent assessments of the SS both within the SYNTAX trial and in external datasets have demonstrated the score's ability to predict adverse ischemic events in patients undergoing percutaneous coronary intervention (PCI) (2–4). The application of SS has been extended to a variety of other clinical settings (3–22). Moreover, the integration of clinical variables in the SS has provided a significant improvement in the process of risk stratification (23–30). The purpose of this review is to describe the current and future applications of the SS and other derived scores.

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Before the SYNTAX Score

Prior to the development of the SS, several coronary angiographic-based scores were created to risk-stratify patients with CAD (31–39). Most of these early scores were elaborated around the concept of quantification of myocardium at risk and/or severity of coronary artery stenosis. Among them, the Duke Jeopardy score, first described in 1977 (31) and then validated in 1985 (32), demonstrated that a simple method of estimating the amount of myocardium at risk on the basis of the particular location of coronary artery stenosis gave more prognostic information than the number of diseased coronary arteries did. Furthermore, by including the degree of coronary artery stenosis and by attributing a higher score to the disease of the left anterior descending coronary artery than to other coronary arteries, the prognostic ability of this score was significantly improved. In 1988, the American College of Cardiology/American Heart Association Task Force subcommittee proposed a lesion-specific classification as a guide to estimate the likelihood of a successful balloon angioplasty and the occurrence of complications (40–42). Lesions were classified as types A, B, or C, based on the presence or absence of high-risk angiographic characteristics (such as lesion length, tortuosity, calcification, thrombus, bifurcation, total occlusion, etc.). Each lesion type was associated with an estimated rate of procedural success, defined as freedom of abrupt vessel closure following balloon angioplasty (procedural success with type A lesions: >85%, type B: 60% to 85%, and type C: <60%). Although

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
CSS = clinical SYNTAX score
FFR = fractional flow reserve
FSS = functional SYNTAX score
GRC = global risk classification
LM = left main
MACCE = major adverse cardiovascular and cerebrovascular event(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
rSS = residual SYNTAX score
SS = SYNTAX score
TVR = target vessel revascularization

this score was initially applied to predict outcomes after balloon angioplasty, it was also shown to predict outcomes after bare-metal stent (43) or drug-eluting stent implantation (44). The amount of jeopardized myocardium and lesion high-risk features, as determined by coronary angiography, have been the basis of many contemporary scores, including the SS.

The SYNTAX Score

The SS is an anatomically based tool that quantitatively characterizes the coronary vasculature with respect to the number, location, complexity, and functional impact of angiographically obstructive lesions. The distributions of the coronary arteries are mapped based on the ARTS (Arterial Revascularization Therapies Study) investigators' modification of the American Heart Association classification of coronary tree segments (Fig. 1) (45,46). Each coronary segment is weighted according to the fraction of blood supplied to the left ventricle and the amount of corresponding jeopardized myocardium, as devised by Leaman et al. (47) (Table 1). Each significant lesion (defined as a diameter stenosis of ≥50% in vessels with a minimum diameter of ≥1.5 mm) is visually assessed and analyzed according to the American College of Cardiology/American Heart Association lesion classification system (40). Depending on several angiographic characteristics, the lesion is given a corresponding point value (Table 2), and finally scores of individual lesions are summed to derive the final score. (The detailed method of score calculation is described elsewhere [1], and it is outside the scope of this review.) Whereas the derived score is a semicontinuous variable, it is typically categorized in a tripartite fashion as determined in the SYNTAX trial (low: 0 to 22, intermediate: 23 to 32, high: >32) (2).

Reproducibility of the SYNTAX Score

Assessment of the SS relies on visual quantification of diameter stenosis and a qualitative evaluation of the morphological characteristics of each lesion, a process that carries a well-described degree of variability (48,49). In the study by Serruys et al. (50), overall core laboratory

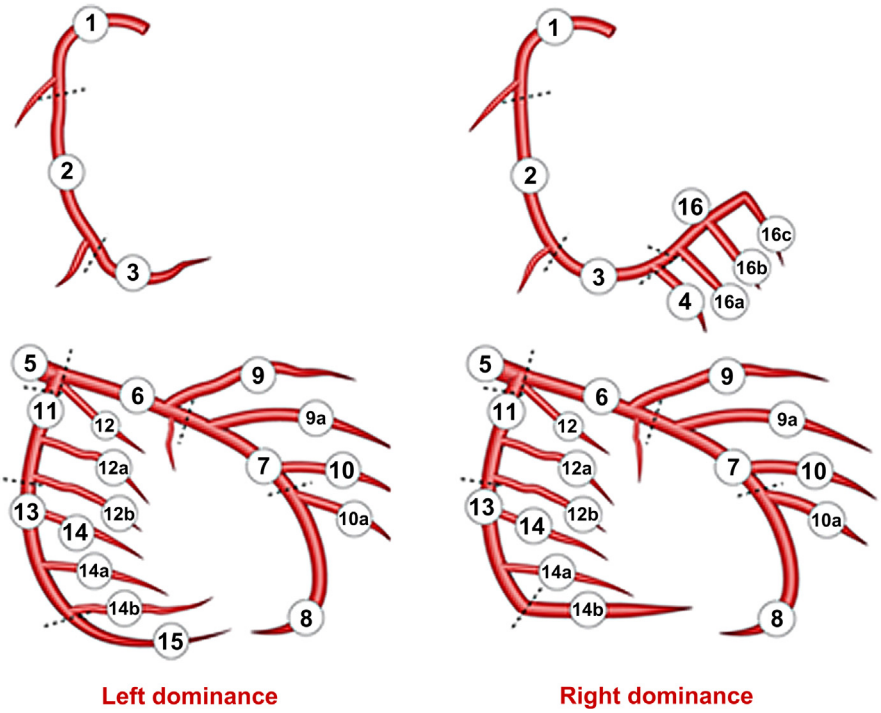

Figure 1 Modified AHA Coronary Segment Classification Used in the SS

Sixteen-segment–based coronary segment classification used in SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score (SS), initially developed by American Heart Association (AHA) and later modified by the ARTS (Arterial Revascularization Therapies Study) investigators. Adapted with permission from Sianos (1).

Table 1 Segmental Weighting Factors Used in SS

Segment	Segment Name	Right Dominance	Left Dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	N/A
16	Posterolateral branch from RCA	0.5	N/A
16a	Posterolateral branch from RCA	0.5	N/A
16b	Posterolateral branch from RCA	0.5	N/A
16c	Posterolateral branch from RCA	0.5	N/A
5	Left Main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonal	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonal	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/anterolateral artery	1	1
12a	Obtuse marginal	1	1
12b	Obtuse marginal	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolateral	0.5	1
14b	Left posterolateral	0.5	1
15	Left Posterior descending	N/A	1

Adapted, with permission, from Leaman et al. (47); and adapted from Sianos et al. (1).

LAD = left anterior descending artery; N/A = not applicable; RCA = right coronary artery; SS = SYNTAX score; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

Table 2 Points for Specific Lesion Characteristics in SS

Aorto ostial stenosis	+1
Bifurcation, Medina classification*	
Type 1-0-0, 0-1-0, 1-1-0	+1
Type 1-1-1, 0-0-1, 1-0-1, 0-1-1	+2
Angulation <70°	+1
Trifurcation	
1 diseased segment	+3
2 diseased segments	+4
3 diseased segments	+5
4 diseased segments	+6
Diameter reduction	
Total occlusion	×5
Significant lesion, 50% to 99%	×2
TO	
Age >3 months or unknown	+1
Blunt stump	+1
Bridging	+1
First segment visible beyond TO	+1/ nonvisible segment
SB	
Yes, SB <1.5 mm	+1
Yes, SB both <1.5 mm & ≥1.5 mm	+1
Severe tortuosity	+2
Length >20 mm	+1
Heavy calcification	+2
Thrombus	+1
Diffuse disease/small vessels	+1/ segment number

*Medina classification: 0 indicates absence of significant lesion; 1 indicates presence of significant lesion. In the 3-digit code, the first and second digits indicate the status of the parent vessel proximal and distal to the side branch, respectively, and the third digit indicates the status of the side branch itself. Adapted from Sianos et al. (1).

SB = side branch; SS = SYNTAX score; TO = total occlusion.

interobserver and intraobserver kappa values were 0.45 and 0.59, respectively, thereby indicating a moderate level of agreement. The level of agreement for each specific SS component (bifurcation, calcification severity, diffuse disease, etc.) varied from 0.41 to 0.85, indicating a moderate to good level of agreement. To better understand the sources of inter- and intraobserver variability, our group demonstrated that an extensive training provided by expert core laboratory technicians can significantly improve the scoring performance and the level of agreement among a group of interventional cardiologists (51). The SS components with the most significant variability were bifurcation lesions, small vessel/diffuse disease, and lesions involving the circumflex territory. In light of these findings, extensive training, beyond the recommended online tutorial (52), is mandatory for optimal clinical application.

Role of the SYNTAX Score in Various Clinical Settings

As shown in Table 3, the prognostic value of the SS has been investigated in various clinical settings, including patients with multivessel CAD, unprotected left main (LM) CAD, non–ST-segment elevation acute coronary syndrome, and ST-segment elevation acute myocardial infarction (MI).

Multivessel CAD. The SS was first applied in the SYNTAX trial that enrolled 1,800 patients with multivessel and/or LM CAD (2). At 1-year follow-up, major adverse cardiovascular and cerebrovascular events (MACCE), which included all-cause death, MI, stroke, and target vessel revascularization (TVR), were significantly lower in the coronary artery bypass graft (CABG) group (12.4%) compared with the PCI group (17.8%, p = 0.002). Interestingly, whereas 1-year MACCE rates progressively increased across SS tertiles in patients treated with PCI (MACCE rates in lower SS tertile = 14.7%, intermediate SS tertile = 16.7%, and higher SS tertile = 23.4%), MACCE rates in patients treated with CABG remained similar across all SS tertiles (lower SS tertile = 13.6%, intermediate SS tertile = 12.0%, and higher SS tertile = 10.9%). These results make the SS an effective stratification tool when deciding the optimal strategy of revascularization between CABG and PCI. The recently published 5-year results of the SYNTAX trial reinforced the 1-year findings, with the CABG cohort of patients having significantly lower MACCE rates in patients with SS > 32 and between 23 and 32 compared with the PCI cohort (53).

In contrast, in the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (54), in which 1,900 diabetic patients with multivessel CAD were randomized to

Table 3 SS Use Among Different Populations

First Author (Ref. #)	Year	Type of Study	N	Follow-Up (months)	Tertiles	Outcomes Predicted	Conclusions
Multivessel disease							
Valgimigli et al. (4)	2007	RP, MC	306	12	≤18, >18–26,>26	MACCE	SS identified as independent predictor of 1-yr MACCE; best cutoff value for PCI was SS ≤32
Farkouh et al. (54)	2012	PP, MC	1,900	46	0–22, >22–32, >32	—	—
Left main							
Capodanno et al. (5)	2009	RP, SC	819	24	<34, >34*	Death	SS >34 identified as predictor of 2-yr death and MACE after LM PCI, CABG should be the preferred treatment for SS >34
Kim et al. (7)	2010	RP, MC	1,580	36	≤23, >23–36, >36	MAVE	SS predicted 3-yr MAVE after PCI; highest tertile having significantly greater MAVE
Morice et al. (8)	2010	PP, MC	705	12	0–22, >22–32, >32	MACCE	SS >32 was independent predictor of greater 1-yr MACCE after PCI compared with CABG
Capodanno et al. (6)	2011	RP, SC	556	36	≤32†	MAVE, MACCE	PCI with SS ≤32 had similar MAVE compared with CABG but greater MACCE due to more frequent TVR at 3 yrs
Chakravarty et al. (10)	2011	RP, SC	328	39.5	‡	Death, MACCE	SS ≥36 and >20 were independent predictors of death and MACCE, respectively, in the PCI group at 2.8 yrs
Park et al. (55)	2011	RP, MC	1,146	55.1	0–22, >22–32, >32	Death, MAVE	SS ≤32 had lower or equal MAVE with PCI using DES and those with SS >32 did better with CABG at 5 yrs
Shiomi et al. (11)	2012	RP, MC	1,005	34.2	0–22, >22–32, >32	MAVE	SS ≤32 had equivalent MAVE compared with CABG and those with SS >32 has lower MAVE with CABG at 3 yrs
LM/MVD							
Serruys et al. (2)	2009	PP, MC	1,800	12	0–22, >22–32, >32	MACCE	SS >32 had greater 1-yr MACCE with PCI compared with CABG
STEMI							
Garg et al. (14)	2011	RP, MC	807	12	≤9, >9–≤16, >16	Death, MACE, ST	SS was independent predictor of 1-yr death, MACE, and ST
Magro et al. (12)	2011	PP, MC	669	18	<10, 10–20, >20	Death, MACE	SS was independent predictor of death and MACE at 1.5 yrs
NSTE-ACS							
Palmerini et al. (16)	2011	RP, MC	2,627	12	<7, >7–<13, ≥13	Death, cardiac death, MI, TVR	SS was independent predictor of 1-yr death, MI, and TVR
All-comers							
Wykrzykowska et al. (17)	2010	PP, MC	1,397	12	≤8, >8–≤16, >16	Death, TVR, ST	SS was independent predictor of 1-yr death and MACE
Garg et al. (15)	2011	PP, MC	2,033	12	≤9, 9–≤17, >17	MACE, MI, TVR, TLR	SS was independent predictor of 1-yr MACE, MI, TVR, and TLR. Addition of clinical variables (ACEF score) improved the score's predictability
Garg et al. (13)	2011	RP, MC	6,496	12	≤8, >8–<15, 15–<23, ≥23§	Death, MACE, MI, TVR, ST	SS was independent predictor of 1-yr death, MACE, ST
Girasis et al. (27)	2011	RP, MC	848	60	≤7, >7–≤14, >14	Death, cardiac death, MACE, MI, TLR	SS was independent predictor of MACE at 5 yrs, which was further enhanced by addition of clinical variables (ACEF score)

Continued on the next page

Table 3 Continued

First Author (Ref. #)	Year	Type of Study	N	Follow-Up (months)	Tertiles	Outcomes Predicted	Conclusions
Residual disease							
Généreux et al. (69)	2012	RP, MC	2,686	12	0 –≤2, >2–≤8, >8	Death, cardiac death, MACE, MI, TVR	rSS >8 was predictor of increased death, cardiac death, MACE, MI, and TVR at 30 days and 1 yr in NSTE-ACS patients
Capodanno et al. (72)	2013	RP, SC	400	24	0, 1–8, >8	Death	rSS was independent predictor of cardiac death at 2 yrs in LM PCI
Malkin et al. (70)	2012	RP, SC	353	36	0, >0	Death	rSS was significant predictor of 3-yr death in LM PCI
Malkin et al. (73)	2013	PP, SC	240	30	<1, 1–8, >8	Death	rSS was independent predictor of death in MVD PCI at 2.6 yrs
Farooq et al. (71)	2013	PP, MC	903	60	0, >0–4, >4–8, >8	Death, cardiac death, MACCE, stent thrombosis	rSS was an independent predictor of 5-yr mortality after DES PCI of complex coronary disease, with a similar effect among LM PCI, diabetes, and poor ejection fraction.
CABG							
Birim et al. (18)	2009	RP, SC	148	12	≤19, 19–25, >25	MACCE	SS was independent predictor of 1-yr MACCE and SS >36.5 was the best discriminating cutoff
Lemesle et al. (59)	2009	RP, SC	320	12	<24.5, 24.5–34, >34	—	SS was unable to predict 1-yr MAVE after CABG
Mohr et al. (19)	2011	PP, MC	1,541	24	0–22, 22–32, >32	—	SS was unable to predict 2-yr MACCE after CABG
Carnero-Alcazar et al. (20)	2011	RP, SC	716	26.68	<33, 33–37, >37	MACCE	SS was independent predictor of 2-yr MACCE
Head et al. (21)	2012	PP, MC	836	36	0–22, 22–32, >32	—	SS >32 showed a trend toward increasing 3-yr MACCE

*This study used 2 cutoff values rather than tertiles. †This study included all patients with SS ≤32. ‡In this study, patients were divided in quartiles. PCI group: quartile 1: 10 to 19; quartile 2: 19.5 to 24; quartile 3: 26 to 35; and quartile 4: 36 to 68.5. CABG group: quartile 1: 10 to 21; quartile 2: 22 to 27; quartile 3: 27 to 34; and quartile 4: 35 to 49. §Patients were divided in quartiles rather than tertiles.

ACEF = Age, Creatinine, and Ejection Fraction score; CABG = coronary artery bypass graft; DES = drug-eluting stent(s); LM = left main coronary artery disease; MACE = major adverse cardiac event(s); MACCE = major adverse cardiovascular and cerebrovascular event(s); MAVE = major adverse vascular event(s); MC = multicenter; MI = myocardial infarction; MVD = multiple vessel disease; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PP = prospective; RP = retrospective; rSS = residual SYNTAX score; SC = single center; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

either PCI or CABG, no significant interaction was apparent between the strategy of revascularization and the SS for 1- and 5-year clinical outcomes (p for interaction = 0.28 and 0.58, respectively). However, the interaction analysis in the FREEDOM trial may have been underpowered. Moreover, patients were stratified using the same tertile cutoff value as in the SYNTAX trial; therefore, whether different cutoff values could be associated with different outcomes remains undetermined. Finally, a trend was apparent, suggesting that the benefit of CABG over PCI was less evident in patients in the lowest SS tertile than in the upper 2 tertiles. Further studies are warranted to determine the prognostic value of the SS in patients with multivessel CAD and diabetes.

The largest pooled analysis investigating the prognostic value of the SS, including 7 contemporary trials (n = 6,508), demonstrated that the SS was an independent predictor of mortality, stent thrombosis, and combined ischemic endpoints at 1 year, regardless of the clinical presentation (13). The rates of these adverse events were significantly greater in the highest SS quartile.

Left main CAD. The prognostic value of the SS has been extensively studied in patients with unprotected LM CAD undergoing PCI (3,5–11,55). In most of these studies, rates of composite ischemic endpoints (death, MI, target lesion revascularization TLR, or TVR) were significantly greater in the highest tertile of SS than in the lower 2 tertiles (3,6,8–10). In a recent report, Capodanno et al. (5) demonstrated that SS >34 was associated with significantly higher rates of ischemic events in patients undergoing PCI than in those undergoing CABG. Interestingly, only the baseline SS, and not even the lesion location in the LM (ostial, shaft, or bifurcation) or number of stents implanted, had a prognostic value. SS, therefore, currently has a central role in selecting the most appropriate strategy of revascularization between PCI and CABG in patients with unprotected LM CAD (56–58). Of note, SS is a key element in the process of patient randomization in the ongoing pivotal multicenter randomized EXCEL (Evaluation of Xience Prime or Xience V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, which is randomizing patients with unprotected LM CAD and SS <32 to either PCI or CABG.

Non–ST-segment elevation acute coronary syndrome. Palmerini et al. (16) were the first to assess the prognostic value of the SS in 2,627 patients with non–ST-segment elevation acute coronary syndrome treated with PCI in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. In that study, patients in the upper tertile of SS had significantly higher rates of ischemic events than did patients in the lower 2 tertiles, and at 1 year, the SS was an independent predictor of all-cause death, cardiac death, and MI. These findings confirm the prognostic value of the SS also for ranges of SS significantly lower than those present in the SYNTAX trial, and extend the prognostic value of the SS to patients with acute coronary syndromes.

ST-segment elevation MI. Two studies have investigated the prognostic utility of the SS in patients with ST-segment elevation MI (12,14). In both studies, patients had significantly lower SS values than in the SYNTAX trial, demonstrating the rarity of this practice outside of the SYNTAX trial (2). In both studies, SS was an independent predictor of 1-year death, major adverse cardiac events (MACE), and stent thrombosis, with the highest tertile showing significantly higher rates of ischemic events compared with the lower 2 tertiles. Interestingly, the SS determined before PCI had a similar predictive value as the SS determined after revascularization of the culprit artery. Further studies are warranted to determine the role of SS in this particular setting.

CABG population. In contrast to patients undergoing PCI, SS seems not to influence clinical outcomes after CABG. Several studies (2,19,59) have shown that both mortality and composite ischemic outcomes in patients undergoing CABG are independent from SS. Recently, the CABG nested registry analysis of the SYNTAX trial confirmed no apparent association between high SS and an adverse prognosis after CABG (21). One potential explanation for these results is the fact that surgical revascularization, bypassing coronary lesions, is not affected by the negative impact that lesion complexity in the proximal site of the coronary tree may have in case PCI is performed. However, 2 studies have recently suggested that the SS may be associated with an adverse prognosis in patients with unprotected LM CAD undergoing CABG, or in those treated with off-pump CABG (18,20), Notwithstanding these possible exceptions, demographic and clinical risk factors seem to have a greater impact than angiographic variables do in patients undergoing CABG.

SYNTAX-Derived Risk Scores

One important limitation of SS is that it does not integrate clinical variables in the scoring algorithm. Patients with equivalent scores may have different short- and long-term outcomes, depending on the presence of comorbidities (60). To overcome these limitations, attempts have been made to combine clinical-based scores with SS (Fig. 2, Table 4).

Global risk classification. The global risk classification (GRC), a combination of SS and EuroSCORE (European System for Cardiac Operative Risk Evaluation), was developed to improve the predictive ability of SS (Fig. 3) (25). Capodanno et al. (25) were the first to demonstrate that the GRC had significantly better discriminative power for risk prediction of cardiac mortality than did SS alone in patients with multivessel CAD. Indeed, among patients with LM CAD undergoing PCI, the GRC had a net reclassification improvement of 26%. In contrast to SS alone, GRC had a better ability for discriminating patients at intermediate risk of cardiac mortality.

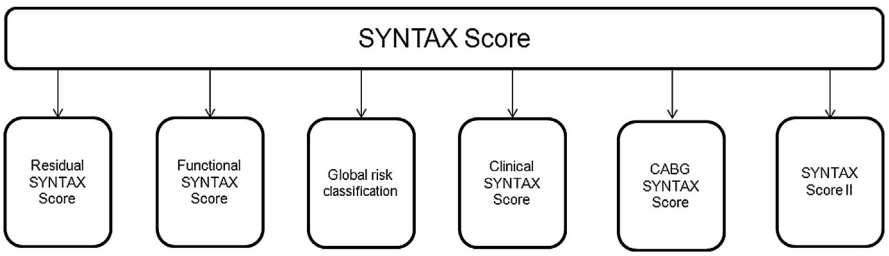

Figure 2 Scores Evolving From SS

CABG = coronary artery bypass graft; other abbreviations as in Figure 1.

Similar results were reported by Serruys et al. (61), who showed that GRC has a better predictive ability than either SS alone or EuroSCORE both in patients with unprotected LM CAD and in those with multivessel CAD. Additionally, GRC identified a low-risk cohort of patients that could be safely treated with PCI.

Clinical SYNTAX score. The clinical SYNTAX score (CSS) integrates SS with the modified ACEF (Age, Creatinine clearance and Ejection Fraction) score. Using only 3 clinical variables, the ACEF score has been shown to predict outcomes with comparable accuracy as that of EuroSCORE in patients undergoing CABG (62). CSS is determined by multiplying the SS and modified ACEF score values. In the study by Garg et al. (26), the CSS had a better discriminatory power for 5-year mortality and MACE than either SS alone or modified ACEF score did. Patients in the highest tertile of CSS had significantly higher rates of mortality, MACE, and repeat revascularization than did those in the lower 2 tertiles. Moreover, CSS was an independent predictor of MACE at 5 years. Girasis et al. (27) reported that CSS had a better discriminatory power and at least equivalent calibration than SS for all-cause mortality and cardiac mortality. However, the main limitations of CSS is represented by the fact that it has a poor discriminative power for ischemic outcomes in the lower 2 tertiles and that its prognostic performance is poorer for pooled patients with double- and triple-vessel CAD than for patients with only triple-vessel CAD (26).

Logistic clinical SYNTAX score. In order to overcome the above-mentioned limitations of the SS and CSS, the logistic CSS was developed. SS and consequently CSS were not developed by selecting variables in multivariable logistic models, but rather on an arbitrary ranking of lesion site and complexity. The logistic CSS variables were selected on the basis of logistic regression coefficients, thus developing score charts for individual risk assessment (Fig. 4). This score demonstrated a substantial improvement in the predictive ability for 1-year all-cause death compared with SS, but not for MACE. The predominant role of angiographic variables over clinical factors in determining the risk of TVR is a possible explanation (63). The logistic CSS has recently been externally-validated in a different population of patients with acute coronary syndrome (64).

Functional SYNTAX score. The rationale of integrating fractional flow reserve (FFR) measurements to SS is supported by 2 concepts highlighted by recent studies: 1) there is a significant discrepancy between lesion severity assessed by visual estimation and their functional correlates as determined by FFR (65,66); and 2) FFR-guided PCI is associated with lower rates of adverse ischemic events in patients with multivessel CAD compared with angiography-guided PCI (67,68). In a recent study, the functional SS (FSS) reclassified 39% of patients from the highest tertile to the lower 2 tertiles, resulting in an improvement in the discrimination power for 1-year adverse cardiovascular events (MI, TVR, and MACE) (28). FSS was also associated with a better inter- and intraobserver reproducibility than SS was. Whereas FSS has the potential to be an important tool in risk-stratification and selection of revascularization strategy, the lack of prospective validation, especially in

Table 4 Comparison of SS and Derived SS Systems

Score Type	Anatomical Variables	Clinical Variables	Predictor of Death	Predictor of MACE	Discrimination Between Lower and Intermediate Tertiles
SYNTAX score	Yes	No	Yes	Yes	No
Global risk classification	Yes	Yes	Yes	Yes	Yes
Clinical SYNTAX score	Yes	Yes	Yes	Yes	No
Logistic clinical SYNTAX score	Yes	Yes	Yes	Yes	Yes
Functional SYNTAX score	Yes	No	N/A	Yes	No
SYNTAX score II	Yes	Yes	Yes	Yes	Yes

N/A = not applicable; other abbreviations as in Tables 1 and 3.

EuroSCORE	SYNTAX Score		
	1st tertile	2nd tertile	3rd tertile
0-2	L	L	I
3-6	L	L	I
>6	I	I	H

Figure 3 Nomogram Describing the Global Risk Classification

Groups are divided as low risk (L), intermediate risk (I), and high risk (H). The SS tertiles varied in various studies. In the study by Capodanno et al. (25), high (EuroSCORE [European System for Cardiac Operative Risk Evaluation] >6 and SS >27), intermediate (EuroSCORE >6 or SS >27), and low (EuroSCORE <6 and SS ≤27). In the study by Serruys et al. (61), low (SS <33 and EuroSCORE <6), intermediate (SS <33 and EuroSCORE ≥6 or SS ≥33 and EuroSCORE <6), and high (SS ≥33 and EuroSCORE ≥6). Adapted with permission from Capodanno et al. (25). Abbreviations as in Figure 1.

LM and multivessel CAD, the limited discrimination power, and the fact that it may be time-consuming to perform, limit the broad applicability of this score in daily clinical practice.

Residual SYNTAX score. Some studies have suggested that incomplete revascularization is among the main factors associated with an increased risk of adverse ischemic outcomes after PCI in patients with high SS (5). The residual SYNTAX score (rSS) was recently proposed as a method to systemically characterize and quantify residual CAD after PCI (69). The rSS calculation is similar to the SS calculation in every respect, except that it is computed after PCI. Among the patients presenting with acute coronary syndrome undergoing PCI, rSS was found to be an independent predictor of mortality, cardiac mortality, MI, unplanned revascularization, and MACE at 1 year (Fig. 5) (69). The predictive and discriminative abilities of rSS were similar to the baseline SS for all outcomes except MI, for which the baseline SS was superior. In an all-comers population undergoing LM CAD revascularization, rSS was also shown to be an independent predictor of mortality at 1 year (70). Recently, the rSS was also validated in the randomized SYNTAX trial, where the rSS was shown to be a strong independent predictor of 5-year mortality, with similar effects among different subgroups (unprotected left main, diabetes, poor ejection fraction) (71). In this analysis, the rSS demonstrated greater discrimination and predictive value for adverse events including death, cardiac death, stent thrombosis, and major adverse cardiac and cerebrovascular events, compared to baseline SS. Similar to the baseline SS, rSS aims to offer uniform and standardized characterization of residual CAD to help patient risk stratification, appropriate groups comparison, and potential revascularization strategy selection (72,73).

CABG SYNTAX score. As the SS was initially validated for patients with native CAD (1,2), it cannot be implemented in patients with CABG. To help address this issue, the CABG SS was developed (74). This score can be calculated by computing first the baseline SS of native vessels and then subtracting points on the basis of graft functionality. The score was evaluated in a pilot study of 115 patients with acceptable reproducibility (k = 0.74; 95% confidence interval: 0.53 to 0.95, p < 0.001) (74). Despite the limited power of the study, it suggested a trend toward higher all-cause death and MACE in patients with high CABG SS. One major limitation of this score is that it does not take into consideration the type of graft used. At this infant stage, the score still requires external validation in larger studies to prove its prognostic capabilities.

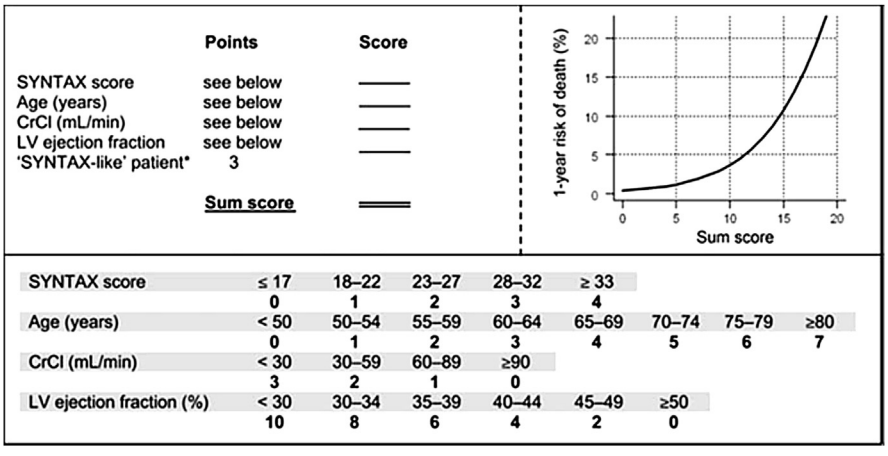

Figure 4 The Logistic CSS for 1-Year All-Cause Mortality Prediction

*SYNTAX-like patient defined as patient having stable multivessel disease and/or left main disease. Adapted with permission from Farooq et al. (63). CrCl = creatinine clearance; CSS = clinical SYNTAX score; LV = left ventricular; other abbreviations as in Figure 1.

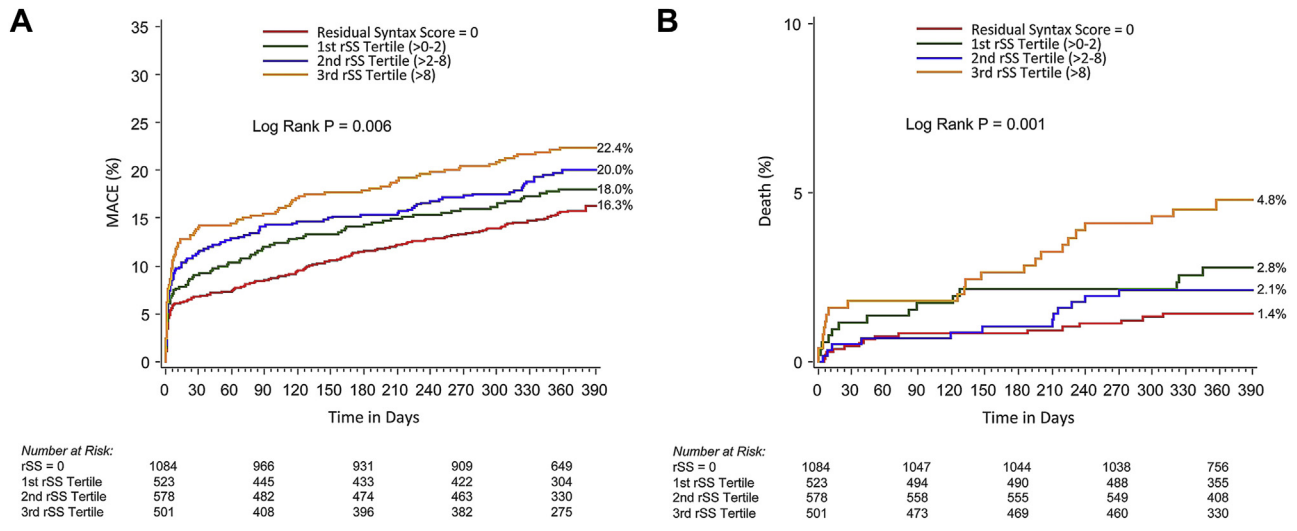

Figure 5 Kaplan-Meier Curves Showing Events Through 1 Year

Both Kaplan-Meier curves show the significant relation of incomplete revascularization (indicated by residual SYNTAX score [rSS]) with **(A)** major adverse cardiac events (MACE) rates and **(B)** all-cause death. Adapted with permission from Généreux et al. (69). Abbreviations as in Figure 1.

SYNTAX score II. The SS II was recently developed to better guide decision-making between CABG and PCI compared to the anatomical SS in patients with complex CAD (29). The SS II combines the anatomical SS with anatomical and clinical variables that were shown to alter the threshold value of the anatomical SS so that equipoise was achieved between CABG and PCI for long-term mortality. These included the presence of age, creatinine clearance, left ventricular ejection fraction, presence of unprotected LM CAD, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease (Fig. 6). In addition the SS II allowed for the individualized assessment of long-term mortality in patients with LM/multivessel CAD undergoing either PCI or CABG, compared to the grouping of risk (low, intermediate, high) with the anatomical SS. The SS II was developed in the randomized SYNTAX Trial and validated in the DELTA (Drug-eluting stent for left main coronary artery disease) registry. The proposed nomogram for bedside application of the SS II is shown in Figure 6.

Use of SS in daily practice and clinical research. The SS has many potential applications both in daily clinical practice and for research purposes. First, it provides the interventional cardiology community a powerful stratification tool, allowing uniform, standardized assessment of CAD extent and severity. Second, the SS may guide clinicians who are deciding upon the most appropriate revascularization modality, especially in complex CAD, and this fact has been recently endorsed in both American and European coronary revascularization guidelines (Class IIa recommendation) (56–58). This clearly justifies the score's integration in the routine clinical practice when facing a complex CAD dilemma. Third, as in the multinational EXCEL trial, it

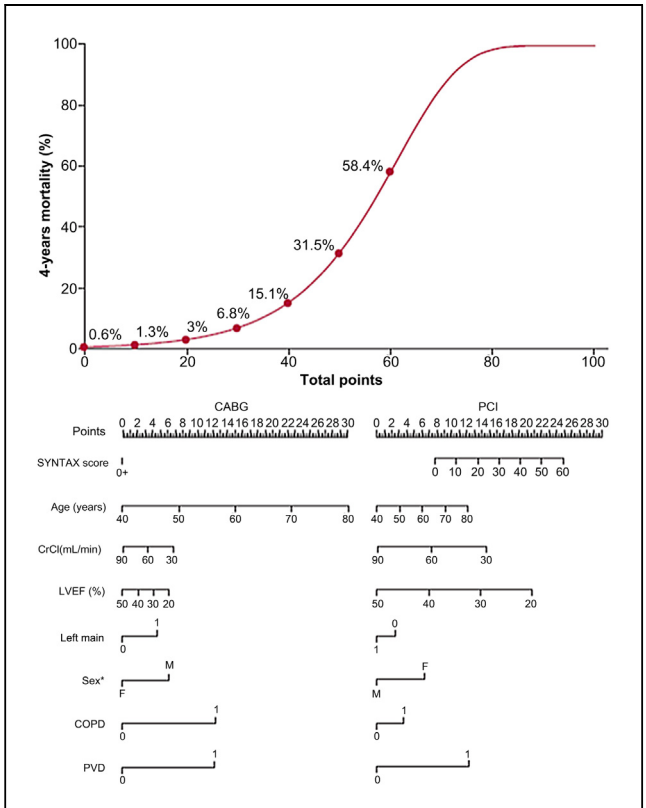

Figure 6 Nomogram for Calculation of SS II

COPD = chronic obstructive pulmonary disease; F = female; LVEF = left ventricular ejection fraction; Left main = unprotected left main coronary artery disease; M = male; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; other abbreviations as in Figures 1, 2, and 4. Adapted with permission from Farooq et al. (29).

may be used as a standardized tool in identifying and stratifying patients to be enrolled in randomized controlled trials. Finally, its ability to predict post-procedural outcomes has important clinical implications, especially when informing patients and family regarding potential adverse outcomes associated with a given revascularization strategy (75).

Current Limitations

As one would expect with any scoring system, the angiographic SS does have limitations. First, the SS is a purely angiographic score and it does not integrate clinical variables that may be relevant for risk stratification of patients undergoing PCI. Nonetheless, by focusing precisely on angiographic characteristics, the SS score can adequately summarize in a quantitative manner the complexity of coronary anatomies that may exist across different patients. Additionally, SS can be combined with other clinical parameters, thereby improving its discriminatory power. Second, SS suffers interobserver variability inherent to visual estimation of vessel stenosis. Online quantitative coronary angiography measurement or physiological assessment using FFR may overcome this issue. Third, the SS score bears other limitations inherent to angiographic characterization of coronary lesions, such as the inability to estimate precisely coronary plaque burden or to identify vulnerable plaques. Whether other modalities, such as intravascular ultrasound, optical coherence tomography, or near-infrared spectroscopy may improve the prognostic power of SS deserves further investigation. Fourth, SS, or any other derived scores, lacks the capacity to take into consideration variation in patient coronary anatomy (vessel diameter, presence and localization of major side branches, myocardium area perfused, etc.) or the impact of presence or absence of viability beyond stenosis. Fifth, these scores suffer from the incapacity to appropriately weigh major differences in operator skills, experience in realization of complex procedures, and the impact of novel revascularization techniques or improvement in device technology. Finally, whereas SS seems to successfully predict several ischemic adverse events in different clinical settings, the predictive power of individual SS components is not known. Indeed, SS integrates heterogeneous angiographic variables that may have a different weight in relation to different ischemic outcomes. For example, it is possible that calcifications or lesion length are associated with TVR more than with other ischemic outcomes, whereas the amount of jeopardized myocardium may be a better predictor of cardiac death. By integrating all-important angiographic variables together with the amount of myocardium at risk, SS represents the most powerful angiographic tool to predict any relevant cardiac endpoints.

Conclusions

The introduction of SS represented a substantial advancement in the quest for better risk stratification and prognostication of patients with CAD undergoing PCI. Although further prospective studies are needed to better determine SS cutoff values for risk-stratifying patients in different clinical scenarios, the possibility of combining clinical and anatomic variables, such as in SS II, represents a major improvement. The role of FSS, with the possibility of determining FFR in a noninvasive fashion using computed tomography angiography (76), may help to overcome current limitations of SS, but this possibility warrants further investigation.

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Key Words: coronary risk stratification ■ percutaneous coronary intervention ■ risk score ■ SYNTAX score.