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SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial

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Aims To investigate the ability of SYNTAX score and Clinical SYNTAX score (CSS) to predict very long-term outcomes in an all-comers population receiving drug-eluting stents.

Methods and results The SYNTAX score was retrospectively calculated in 848 patients enrolled in the SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization (SIRTAX) trial. The CSS was calculated using age, and baseline left ventricular ejection fraction and creatinine clearance. A stratified *post hoc* comparison was performed for all-cause mortality, cardiac death, myocardial infarction (MI), ischaemia-driven target lesion revascularization (TLR), definite stent thrombosis, and major adverse cardiac events (MACE) at 1- and 5-year follow-up. Tertiles for SYNTAX score and CSS were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$ and $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$ and $CSS_{HIGH} > 17.0$, respectively. Major adverse cardiac events rates were significantly higher in SS_{HIGH} compared with SS_{LOW} at 1- and 5-year follow-up, which was also seen at 5 years for all-cause mortality, cardiac death, MI, and TLR. Stratifying outcomes across CSS tertiles confirmed and augmented these results. Within CSS_{HIGH}, 5-year MACE increased with use of paclitaxel- compared with sirolimus-eluting stents (34.7 vs. 21.3%, $P = 0.008$). SYNTAX score and CSS were independent predictors of 5-year MACE; CSS was an independent predictor for 5-year mortality. Areas-under-the-curve for SYNTAX score and CSS for 5-year MACE were 0.61 (0.56–0.65) and 0.62 (0.57–0.67), for 5-year all-cause mortality 0.58 (0.51–0.65) and 0.66 (0.59–0.73) and for 5-year cardiac death 0.63 (0.54–0.72) and 0.72 (0.63–0.81), respectively.

Conclusion SYNTAX score and to a greater extent CSS were able to stratify risk for very long-term adverse clinical outcomes in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year all-cause mortality was improved using CSS. Trial Registration Number: NCT00297661.

Keywords Percutaneous coronary intervention • Drug-eluting stents • Clinical outcome • Angiography • SYNTAX score • Clinical SYNTAX score

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Introduction

The SYNTAX score is a lesion-based angiographic scoring system originally devised to grade the complexity of coronary artery disease[1] and thereby facilitate consensus in the study of a diagnostic angiogram between surgeons and interventional cardiologists. In the SYNTAX trial,[2] it proved effective in predicting clinical outcomes after elective percutaneous coronary intervention (PCI) procedures in patients with three-vessel and/or left main coronary artery disease.[3] The score's predictive ability for a number of clinical outcomes has subsequently been assessed in patient cohorts with a varying extent of coronary artery disease undergoing both elective and emergent PCI procedures.[4–13] Several of these studies have suggested that, being solely based on angiographic variables, the SYNTAX score cannot account for the variability related to clinical factors which are widely acknowledged to impact on long-term outcomes, such as a patients' age,[14] left ventricular ejection fraction,[15] and renal function.[16]

A clinical score incorporating the aforementioned variables, the ACEF score, has been retrospectively validated in patients undergoing elective coronary artery bypass grafting (CABG) operations.[17] Integration of this score, modified through the replacement of serum creatinine with creatinine clearance, with the SYNTAX score, in the Clinical SYNTAX score (CSS), has been shown to improve the predictive ability for adverse clinical outcomes after PCI.[10,11,18] However, information regarding the very long-term performance of either SYNTAX score or CSS in an all-comers population is currently lacking.

The SIRolimus-eluting stent compared with pacliTAXel-Eluting Stent for coronary revascularization (SIRTAX) trial[19] was a prospective, observer-blind, randomized controlled study comparing the safety and efficacy of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in 1012 patients undergoing PCI for either stable angina or an acute coronary syndrome. This study design offers a convenient setting for describing the distribution of the SYNTAX score and CSS in an all-comers population. Furthermore, the availability of 5-year follow-up data permits a more robust evaluation of both scores, in order to confirm their potential to risk stratify clinical outcomes at very long-term after the implantation of drug-eluting stents.

Methods

Patient population and coronary intervention

The design of the SIRTAX trial has been previously described.[19] Patients were eligible to participate if they presented at least one lesion with percentage diameter stenosis ≥50%, in a vessel with a reference diameter between 2.25 and 4.00 mm that was suitable for stent implantation. There were no limitations on the number of lesions treated, number of vessels diseased or on the length of the lesions. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at the participating centres. Written informed consent was obtained from each patient before enrollment. There was no industry involvement in the design, conduct or analysis of the study.

Patients were randomly assigned on a 1:1 basis to treatment with SES (Cypher®; Cordis, Warren, NJ, USA) or PES (Taxus®, Boston Scientific, Natick, MA, USA). No mixture of drug-eluting stents was allowed within a given patient. All procedures were performed according to interventional standards at the time. Before or at the time of the procedure, patients received at least 100 mg of aspirin, a 300 mg loading dose of clopidogrel, and unfractionated heparin (70–100 U/kg of body weight). After the procedure, all patients were advised to maintain aspirin lifelong, and clopidogrel therapy was prescribed for 12 months irrespective of stent type.

SIRTAX endpoints and definitions

All adverse events were adjudicated by an independent clinical events committee throughout 5 years and have been reported separately.[20] The pre-specified primary endpoint was a composite of major adverse cardiac events (MACE) including death from cardiac causes, myocardial infarction (MI), and ischaemia-driven target lesion revascularization (TLR). The diagnosis of MI was based on the presence of new Q waves of at least 0.4 s duration in ≥2 contiguous leads and an elevated creatine kinase MB fraction. In the absence of pathologic Q waves, the diagnosis of MI was based on an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase MB or troponin I. Target lesion revascularization was defined as an intervention (either surgical or percutaneous) to treat a stenosis within the stent or within the 5-mm borders adjacent to the stent. Revascularization was considered to be driven by ischaemia, if percentage diameter stenosis was ≥50% on the basis of quantitative coronary angiography in the presence of ischaemic signs or symptoms, or ≥70% even in the absence of ischaemic signs or symptoms.

Stent thrombosis was diagnosed as an acute coronary syndrome with angiographic documentation of either target vessel occlusion or thrombus within or adjacent to the previously stented segment; applying Academic Research Consortium recommendations,[21] definite stent thrombosis was documented.

SYNTAX score and angiographic analysis

The SYNTAX score algorithm, which is described in full elsewhere and is available on the SYNTAX score website (www.syntaxscore.com), was employed to retrospectively score all coronary lesions deemed to have a percentage diameter stenosis ≥50%, in vessels ≥1.5 mm. All angiographic variables pertinent to SYNTAX score calculation were computed by two experienced interventional cardiologists (C.G., S.G.) on diagnostic angiograms obtained before the procedure. In case of disagreement, the opinion of a third analyst (G.S.) was obtained and the final decision was made by consensus. Analysts were blinded to procedural data and clinical outcome. The final score was calculated on a patient basis from the individual lesion scores, which were saved in a dedicated database, and was not made available to the analysts until after the completion of the study.

Patients with acute MIs were not included in the SYNTAX trial. In the context of our study the culprit lesions were scored using the angiographic views of the infarct-related arteries before any intervention; in the absence of flow these were scored as total occlusions of <3-months' duration.[9] Patients with prior CABG operation were excluded from the analysis; a dedicated amendment for calculating the score in the presence of grafts has not been made available yet. Finally, in-stent restenosis lesions were scored as *de novo* ones.

Clinical SYNTAX score

The modified ACEF score was retrospectively calculated,[18] based on the patients' left ventricular ejection fraction, age, and creatinine clearance derived using the Cockcroft–Gault equation.[22] Respective methodology has been amply described elsewhere. Values for variables included in the modified ACEF score were recorded before the index PCI. Clinical SYNTAX score was calculated multiplying the value of SYNTAX score by the modified ACEF score.

Statistics

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Patient characteristics and outcome measures were stratified according to score tertiles among all patients with a calculated CSS. Continuous variables are presented as mean ± 1 standard deviation (SD) or median values (25th to 75th percentile) as appropriate; categorical variables are displayed as counts and/or percentages. Comparisons were performed with one-way analysis of variance (ANOVA) for continuous variables following a normal distribution and with the χ^2 test for categorical variables. The normality assumption was evaluated by the Kolmogorov–Smirnov test. Spearman's rank correlation coefficient was used to measure the strength of the association of SYNTAX score with CSS.

Cumulative event rates through all 5-years of follow-up were estimated by means of the Kaplan–Meier method. Testing for trends in event rates across score tertiles was done with the Cochran–Armitage test in SAS software (SAS, version 9.2, Cary, NC, USA). All-cause mortality, MACE, cardiac death, TLR, MI, and definite stent thrombosis rates were compared across SYNTAX score and CSS tertiles according to the Cox proportional-hazards model; the assumption of proportional hazards was verified by visual inspection of the log-minus-log curves. Independent predictors of 5-year MACE, all-cause mortality, and cardiac death were sought among variables significant beyond the level of $P = 0.10$ in univariable analysis. Potential predictors were checked for collinearity before entering a multivariable backward stepwise model; variables with a variance inflation factor >2.5 were disqualified. Crude and adjusted hazard ratios and corresponding 95% confidence intervals are reported for qualifying variables.

SYNTAX score, CSS, and multivariable models were also evaluated in terms of calibration and discrimination for 5-year MACE, cardiac, and all-cause mortality. Calibration was evaluated with the Hosmer–Lemeshow (H–L) goodness-of-fit test, wherein a lower χ^2 statistic and a higher corresponding *P*-value implied a better match between the estimated probabilities and the actual events. Discrimination was explored with the areas under the receiver-operating characteristics (ROC) curves; an area of 1.0 would indicate perfect discrimination, whereas an area of 0.5 indicates the total absence of discriminatory power. Areas-under-the-curves (AUCs) for SYNTAX score, CSS, and multivariable models were compared with the DeLong method[23] using MedCalc for Windows, version 11.6.0.0 (MedCalc Software, Mariakerke, Belgium). Finally, in order to formally assess, whether CSS improved the risk stratification over the SYNTAX score, a net reclassification improvement (NRI) analysis was performed.[24]

To complete our analysis, a stratified comparison of clinical outcomes between SES and PES was also performed across SYNTAX score and CSS tertiles using Cox regression analysis. To determine whether there was an interaction between treatment arm and scores' tertiles, likelihood ratio tests were used.

All statistical tests were two-sided and a *P*-value < 0.05 was considered statistically significant.

Results

Analysis was performed for 848 patients (1792 lesions). Scores were not evaluable in 91 cases due to prior CABG; another 57 angiograms were either not available or not fully evaluable in the acquired views. Finally in 16 cases, data on creatinine clearance could not be retrieved, consequently CSS could not be calculated; clinical outcomes of these 164 patients excluded from the analysis are shown in Supplementary material online, *Table S1*.

The SYNTAX score ranged from 1 to 42, with a mean ± SD of 11.7 ± 7.3, and a median of 10 (6.0–16.0). The CSS ranged from 0.7 to 272.2, with a mean + SD of 17.4 ± 20.5, and a median of 11.6 (6.4–21.2); expectedly, there was a strong correlation between the two scores ($r = 0.87$, $P < 0.001$). Both scores were non-parametric and their distribution was skewed to the right (*Figure 1*). Tertiles for SYNTAX score and CSS were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$ and $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$ and $CSS_{HIGH} > 17.0$, respectively.

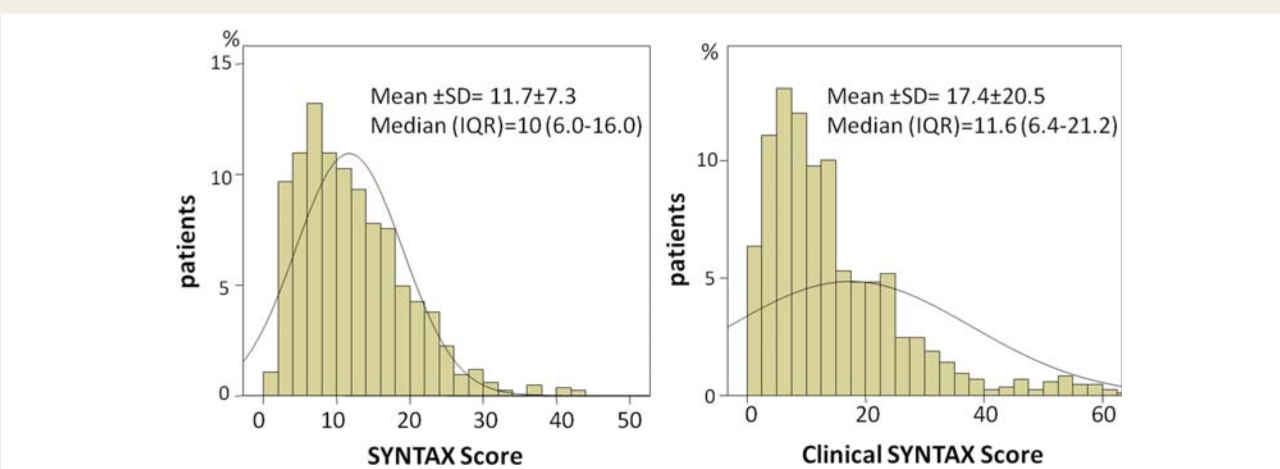

Figure 1 Scores' distribution in the SIRTAX trial population. Histograms of SYNTAX score (left side) and Clinical SYNTAX score (right side) with superimposed normal curves; in both cases the distribution is skewed to the right. Histogram for Clinical SYNTAX score is truncated at the 98th percentile value. Mean ± SD values and median values plus inter-quartile range (IQR) are reported.

Table 1 Baseline clinical characteristics and risk factors

Characteristic	SS ≤7 (*n* = 293)	7< SS ≤14 (*n* = 287)	SS >14 (*n* = 268)	*P*-value
Age (years ± SD)	60.7 ± 10.6	61.4 ± 11.2	63.7 ± 11.3	0.004
Male gender, *n* (%)	218 (74.4)	219 (76.3)	211 (78.7)	0.48
Body mass index ±SD	27.4 ± 4.2	27.4 ± 4.0	27.0 ± 3.8	0.41
Diabetes mellitus, *n* (%)	45 (15.4)	50 (17.4)	66 (24.6)	0.04
Hypertension, *n* (%)	171 (58.4)	175 (61.0)	160 (59.7)	0.85
Hyperlipidaemia, *n* (%)	176 (60.1)	159 (55.4)	146 (54.5)	0.66
Current smoking, *n* (%)	124 (42.3)	100 (34.8)	93 (34.7)	0.41
Previous MI, *n* (%)	73 (24.9)	78 (27.2)	73 (27.2)	0.56
Previous PCI, *n* (%)	51 (17.4)	51 (17.8)	48 (17.9)	0.94
Peripheral vascular disease, *n* (%)	19 (6.5)	17 (5.9)	13 (4.9)	0.84
Stable angina pectoris, *n* (%)	163 (55.6)	115 (40.1)	108 (40.3)	<0.001
Acute coronary syndromes, *n* (%)	130 (44.4)	172 (59.9)	160 (59.7)	<0.001
Unstable angina, *n* (%)	14 (4.8)	23 (8.0)	12 (4.5)	
Non ST-segment elevation MI, *n* (%)	74 (25.3)	61 (21.3)	63 (23.5)	
ST-segment elevation MI, *n* (%)	42 (14.3)	88 (30.7)	85 (31.7)	
Multi-vessel coronary artery disease, *n* (%)	96 (32.8)	107 (58.2)	209 (78.0)	<0.001
Left ventricular ejection fraction (% ±SD)	60.2 ± 9.4	56.8 ± 11.4	53.3 ± 12.6	<0.001
Serum creatinine (mg/dL ±SD)	0.93 ± 0.33	0.95 ± 0.54	1.02 ± 0.83	0.14
Creatinine clearance (mL/min/1.73 m^2 ±SD)	98.6 ± 34.9	99.5 ± 35.8	91.6 ± 34.8	0.02

MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; SS, SYNTAX score.

Table 2 Procedural characteristics and lesions adjudicated in SYNTAX score

Characteristics per patient	SS ≤7 (*n* = 293)	7 <SS ≤14 (*n* = 287)	SS >14 (*n* = 268)	*P*-value
Mean number of lesions ±SD	1.4 ± 0.6	2.1 ± 0.9	2.9 ± 1.2	<0.001
Bifurcation-trifurcation lesions ±SD	0.1 ± 0.3	0.6 ± 0.6	0.9 ± 0.8	<0.001
Total occlusions ±SD	0.1 ± 0.3	0.3 ± 0.5	0.6 ± 0.6	<0.001
Lesions treated ±SD	1.2 ± 0.5	1.4 ± 0.6	1.5 ± 0.6	<0.001
One lesion treated, *n* (%)	237 (80.9)	180 (62.7)	150 (56.0)	<0.001
Two lesions treated, *n* (%)	49 (16.7)	91 (31.7)	99 (36.9)	
Three lesions treated, *n* (%)	7 (2.4)	16 (5.6)	19 (7.1)	
Mean number of stents ±SD	1.1 ± 0.3	1.2 ± 0.4	1.2 ± 0.6	<0.001
Total stent length ±SD	20.5 ± 11.4	26.9 ± 14.8	30.0 ± 16.8	<0.001
SES usage, *n* (%)	139 (47.4)	150 (52.3)	137 (51.1)	0.48
PES usage, *n* (%)	154 (52.6)	137 (47.7)	131 (48.9)	0.48

PES, paclitaxel-eluting stents; SD, standard deviation; SES, sirolimus-eluting stents; SS, SYNTAX score.

Baseline characteristics and risk factors stratified across SYNTAX score tertiles are reported in *Table 1* and data pertinent to the procedure and the score calculation are reported in *Table 2*.

Stratified clinical outcomes

One-year outcomes across SYNTAX score tertiles are reported in Supplementary material online, *Table S2*; 5-year outcomes across SYNTAX score tertiles are shown in *Figure 2*. Five-year MACE rates were significantly higher in SS_{HIGH} compared with SS_{LOW} [24.2 vs. 12.5%, HR: 2.10 (1.40–3.16), $P < 0.01$], which was also the case for 5-year all-cause mortality, cardiac death, MI, and TLR rates; for all these endpoints there was a significant trend ($P \leq 0.03$) for higher event rates with increasing SYNTAX score tertiles.

Stratifying outcomes across CSS tertiles (*Table 3* and see Supplementary material online, *Table S3*) led to similar results for the comparisons between high and low score tertiles. However, in contrast to the SYNTAX score analysis, event rates for MACE and TLR were significantly higher in CSS_{HIGH} compared with both CSS_{MID} and CSS_{LOW} at 1- and 5-year follow-up; this held

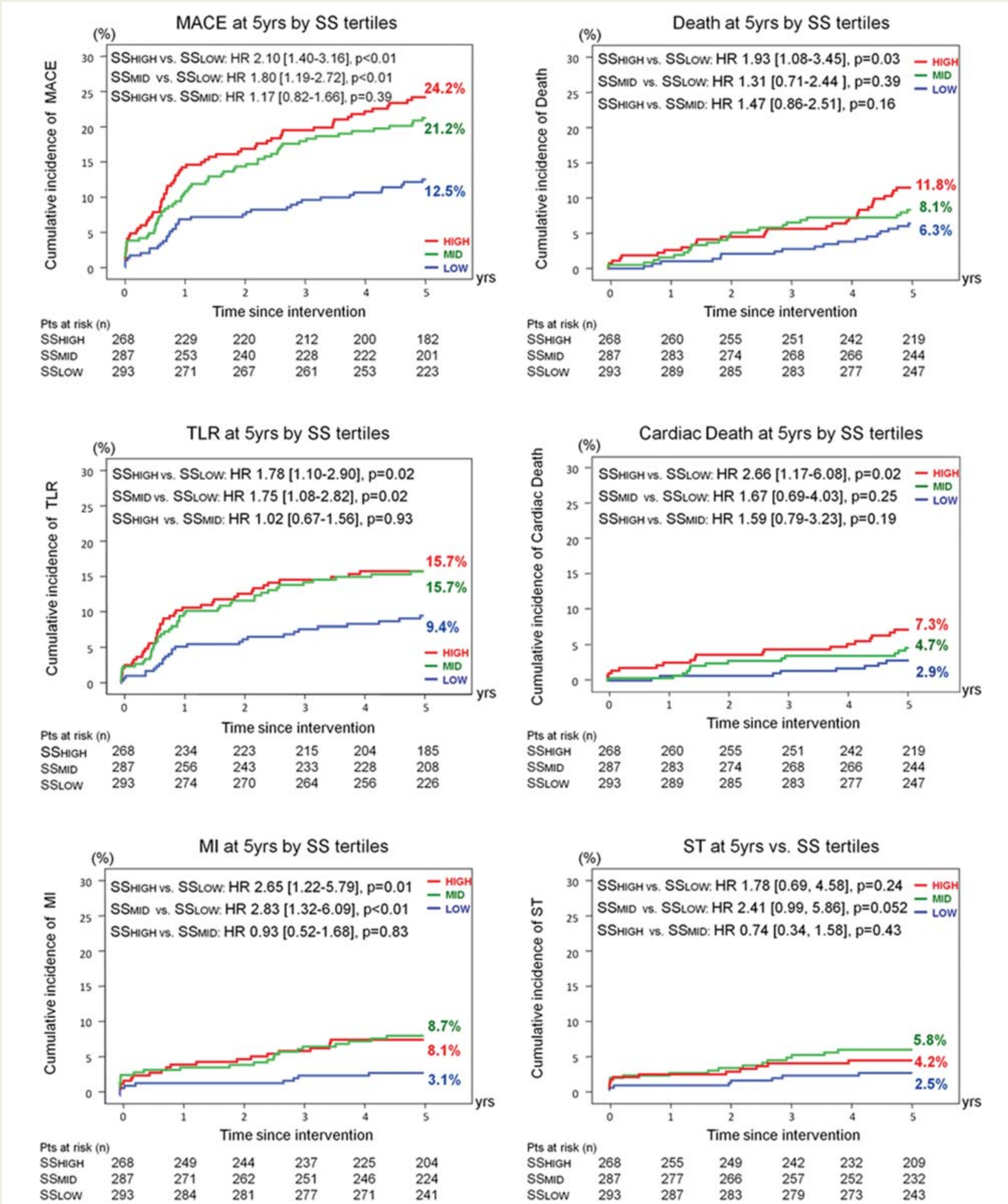

Figure 2 Clinical outcomes at 5-year follow-up stratified across SYNTAX score tertiles. Kaplan–Meier curves are presented for major adverse cardiac events, ischaemia-driven target lesion revascularization, myocardial infarction, all-cause mortality (death), cardiac death and definite stent thrombosis. Tertiles for SYNTAX score were defined as $SS_{LOW} \leq 7$, $7 < SS_{MID} \leq 14$, $SS_{HIGH} > 14$. Pairwise comparison results are presented as hazard ratios plus 95% confidence intervals and respective *P*-values.

Table 3 Clinical outcomes at 5-year follow-up stratified across CSS tertiles (univariable analysis)

	CSS_{LOW}, $n = 282$, %	CSS_{MID}, $n = 283$, %	CSS_{HIGH}, $n = 283$, %	HR (95% CI) CSS_{HIGH} vs. CSS_{LOW}	*P*-value	HR (95% CI) CSS_{MID} vs. CSS_{LOW}	*P*-value	HR (95% CI) CSS_{HIGH} vs. CSS_{MID}	*P*-value	*P*-value trend*
Death	5.8	4.6	15.5	2.82 (1.59–5.00)	<0.001	0.80 (0.39–1.67)	0.56	3.51 (1.89–6.54)	<0.001	<0.001
Cardiac death	2.2	2.5	10.0	4.71 (1.94–11.40)	0.001	1.15 (0.39–3.43)	0.80	4.08 (1.78–9.35)	0.001	<0.001
MI	5.1	4.7	9.9	2.02 (1.06–3.85)	0.03	0.93 (0.44–1.97)	0.85	2.18 (1.12–4.22)	0.02	0.03
TLR (ID)	11.3	11.4	17.9	1.71 (1.09–2.67)	0.02	1.03 (0.63–1.69)	0.90	1.65 (1.06–2.58)	0.03	0.03
MACE	14.1	15.3	28.0	2.18 (1.48–3.20)	<0.001	1.10 (0.72–1.70)	0.66	1.97 (1.36–2.87)	<0.001	<0.001
Stent thrombosis (definite)	3.6	3.2	5.5	1.56 (0.70–3.48)	0.27	0.90 (0.37–2.21)	0.82	1.74 (0.76–3.97)	0.19	0.29

CI, confidence interval; CSS, Clinical SYNTAX score; HR, hazard ratio; ID, ischaemia driven; MACE, major adverse cardiac events; MI, myocardial infarction; TLR, target lesion revascularization.
CSS tertiles defined as $CSS_{LOW} < 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$.
*Cochran-Armitage trend test.

also for all-cause mortality, cardiac death, and MI at 5 years. Definite stent thrombosis rates were directionally but not significantly higher in CSS_{HIGH} compared with both CSS_{MID} and CSS_{LOW} at 1-and 5-year follow-up.

SYNTAX Score vs. Clinical SYNTAX score

The ROC curves for MACE, all-cause mortality, and cardiac death at 5-year follow-up are shown in *Figure 3*. The AUC for CSS was significantly larger compared with the one for SYNTAX score regarding cardiac death [0.72 (0.63–0.81) vs. 0.63 (0.54–0.72), $P = 0.002$] and all-cause mortality [0.66 (0.59–0.73) vs. 0.58 (0.51–0.65), $P < 0.001$]. The AUC for MACE was decreased for both scores, being not significantly larger for CSS [0.62 (0.57–0.67) vs. 0.61 (0.56–0.65), $P = 0.24$].

In terms of calibration, CSS was more robust compared with SYNTAX score for all-cause mortality ($\chi^2 = 6.148$, $P = 0.63$ vs. $\chi^2 = 7.674$, $P = 0.36$) and slightly less robust for cardiac death ($\chi^2 = 9.695$, $P = 0.29$ vs. $\chi^2 = 7.377$, $P = 0.39$). Similar to discrimination, calibration for MACE was worse for SYNTAX score and CSS when compared with that for mortality ($\chi^2 = 9.968$, $P = 0.19$ and $\chi^2 = 15.619$, $P = 0.05$).

When reclassifying patients with all-cause mortality from SS into CSS tertiles, 14/72 (19.5%) patients with events were moved to higher risk categories (upward) and 3/72 (4.2%) to lower risk categories (downward), thus resulting in a net gain of 15.3% (*Table 4*). In patients without events, 95 were moved downward and 99 upward, on aggregate a net loss of 0.5%; consequently the NRI was 14.7% ($z = 2.46$, $P = 0.014$). Following the same procedure, NRI for cardiac mortality was more pronounced 19.1% ($z = 2.36$, $P = 0.018$); on the other hand, NRI for patients with MACE was negligible (0.6%, $P = 0.88$) (see Supplementary material online, *Tables S4* and *S5*).

Multivariable analysis

Independent predictors for MACE, all-cause mortality and cardiac death at 5-year follow-up are reported in *Tables 5* and *6*. Because of the strong correlation between SYNTAX score and CSS, each score was entered separately in the multivariable analysis together with other variables significant in univariable analysis. There were no collinearity issues among potential predictors, even when CSS was tested together with left ventricular ejection fraction, age, and creatinine clearance (variance inflation factor <1.76 for all parameters). Nevertheless, the latter three variables being components of ACEF and hence of CSS, were left out of models including CSS, in order to minimize collinearity.

Both scores were independent predictors of MACE (in separate models) next to the number of treated lesions. Addition of diabetes did not significantly impact discrimination for either the CSS ($P = 0.68$) or the SYNTAX score model ($P = 0.88$); calibration improved for the former but got worse for the latter. Regarding all-cause mortality, CSS was an independent predictor next to diabetes. Addition of diabetes to CSS resulted in a model with larger AUC ($P = 0.36$) but worse calibration compared with stand-alone CSS. Similar to all-cause mortality, CSS was an independent predictor for cardiac death next to diabetes. Addition

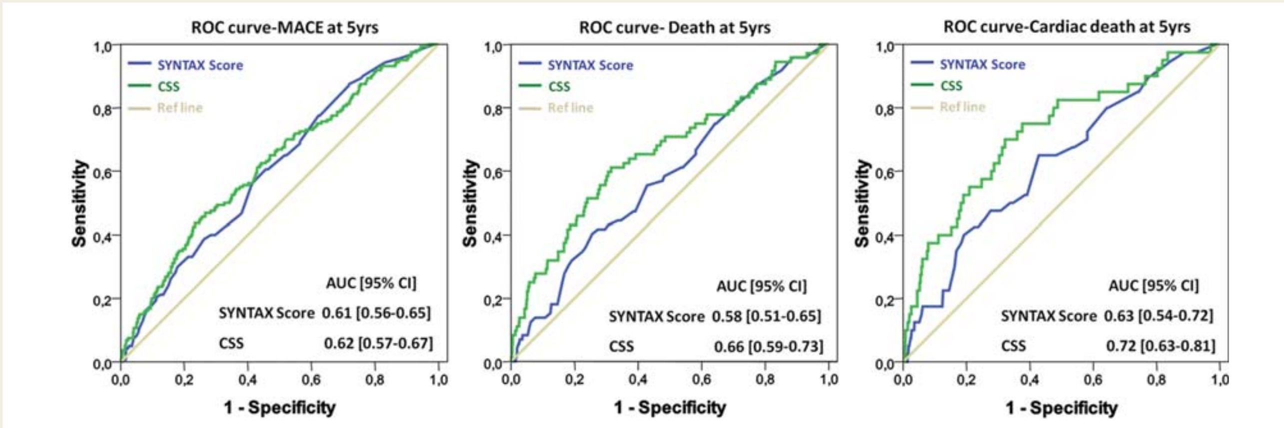

Figure 3 Receiver operating characteristic (ROC) curves for SYNTAX score and Clinical SYNTAX score. Left: 5-year major adverse cardiac events. Middle: 5-year all-cause mortality (death). Right: 5-year cardiac death. AUC, area-under-the-curve, CI, confidence interval, CSS, Clinical SYNTAX score.

Table 4 Five-year all-cause mortality reclassification into CSS tertiles

		CSS tertiles			
		CSS_{LOW}	CSS_{MID}	CSS_{HIGH}	Total
Patients with events					
SS tertiles	SS_{LOW}	14	**1**	**3**	18
	SS_{MID}	**2**	11	**10**	23
	SS_{HIGH}	**0**	**1**	30	31
	Total	16	13	43	72
Patients without events					
SS tertiles	SS_{LOW}	227	**40**	**8**	275
	SS_{MID}	**39**	174	**51**	264
	SS_{HIGH}	**0**	**56**	181	237
	Total	266	270	240	776

SS, Clinical SYNTAX score; SS, SYNTAX score.
Score tertiles as defined in text.
Patients indicated in bold were moved to higher risk (above the diagonal) and lower risk (below the diagonal) categories respectively, when reclassified.

of diabetes to CSS resulted in a model with slightly larger AUC ($P = 0.52$) and better calibration compared with stand-alone CSS.

Stratified analysis of drug-eluting stents performance

Overall adverse clinical event rates for each treatment arm are reported in *Table 7* for the 848 patients included in this substudy. Stratified comparisons of PES vs. SES across CSS tertiles for clinical outcome measures at 1- and 5-year follow-up are shown in *Figures 4* and *5*, respectively. Among patients in the higher CSS tertile, there was an increase in MACE rates with PES compared with SES at 1-year follow-up [23.9 vs. 8.6%, HR: 3.02 (1.56–5.83), $P = 0.001$], which was mainly driven by increased TLR rates in the PES arm [18.1 vs. 6.5%, HR: 2.91 (1.36–6.25), $P = 0.004$]. Higher MACE rates for the PES arm persisted at 5 years [34.7 vs. 21.3% for SES, HR: 1.85 (1.17–2.93), $P = 0.008$], whereas differences in TLR rates were no longer significant [22.0 vs. 14.0%, HR: 1.70 (0.96–3.02), $P = 0.07$]. The interaction term between treatment arm and CSS tertiles for 5-year MACE had a $P = 0.050$, suggesting a genuine effect, whereas for 1-year MACE, $P = 0.10$. Interaction term *P*-values for all-cause mortality, MI and TLR were 0.76, 0.26, 0.29 at 1-year and 0.43, 0.18, 0.39 at 5-year follow-up, respectively.

Stratifying outcome across SYNTAX score tertiles led to similar results regarding the performance of PES vs. SES (see Supplementary material online, *Figures S1* and *S2*). However, the interaction term between treatment arm and SYNTAX score tertiles for all endpoints at 1- and 5-year follow-up had a *P*-value consistently >0.05; thus conclusions drawn from these results should be interpreted with caution.

Discussion

The main findings of this study indicate that the SYNTAX score, and to a greater extent the CSS, have an important role to play in the risk stratification of very long-term clinical outcomes in an all-comers population receiving drug-eluting stents. Both scores were identified as independent predictors of 5-year MACE, nevertheless having modest discriminatory power and calibration for this endpoint. Clinical SYNTAX score was also an independent predictor of 5-year all-cause mortality and cardiac death; its superior discriminatory power and calibration compared with SYNTAX score resulted in a significant improvement in risk stratification. An additional potential role of the CSS in the assessment of stent performance was also identified.

Although the current study employed comparable inclusion criteria to the two most recent all-comers studies, the mean SYNTAX score of 11.7 was lower than the 13.5 and 14.6 seen in the LEADERS and RESOLUTE studies, respectively[7,11]; similarly CSS tertile values in our study were lower compared with the

Table 5 Independent predictors of adverse events at 5-year follow-up (models including SYNTAX score)

Variables	HR (95% CI)[a]	*P*-value	AUC (95% CI)[c]	H–L χ^2 (*P*-value)[c]
MACE				
SYNTAX score[b]	1.03 (1.01–1.05)	0.003	0.63 (0.58–0.68)	7.78 (0.46)
Number of lesions treated	1.54 (1.21–1.96)	<0.001		
All-cause mortality				
Age[b]	1.06 (1.04–1.09)	<0.001	0.71 (0.65–0.78)	10.967 (0.20)
Diabetes mellitus	2.14 (1.32–3.46)	0.002		
Cardiac death				
Age[b]	1.07 (1.03–1.11)	<0.001	0.75 (0.67–0.83)	5.425 (0.71)
Diabetes mellitus	2.01 (1.05–3.85)	0.04		
LVEF[b]	0.97 (0.94–0.99)	0.006		

AUC, area under the curve; CI, confidence interval; H–L, Hosmer–Lemeshow; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.
[a]After adjustment for confounding factors.
[b]Per unit increase.
[c]For the entire model.

Table 6 Independent predictors of adverse events at 5-year follow-up (models including CSS)

Variables	HR (95% CI)[a]	*P*-value	AUC (95% CI)[c]	H–L χ^2 (*P*-value)[c]
MACE				
CSS[b]	1.009 (1.005–1.013)	<0.001	0.65 (0.60–0.69)	10.214 (0.25)
Number of lesions treated	1.58 (1.24–2.01)	<0.001		
All-cause mortality				
CSS[b]	1.011 (1.006–1.015)	<0.001	0.68 (0.61–0.75)	7.576 (0.48)
Diabetes mellitus	2.21 (1.34–3.66)	0.002		
Cardiac death				
CSS[b]	1.012 (1.006–1.018)	<0.001	0.74 (0.65–0.82)	5.614 (0.69)
Diabetes mellitus	2.23 (1.13–4.39)	0.02		

AUC, area under the curve; CI, confidence interval; CSS, Clinical SYNTAX score; H–L, Hosmer–Lemeshow; HR, hazard ratio; MACE, major adverse cardiac events.
[a]After adjustment for confounding factors.
[b]Per unit increase.
[c]For the entire model.

RESOLUTE (0–11.2, >11.2–24.7, >24.7). This observation is not surprising considering the differing time periods when patients were enrolled in the three studies (SIRTAX 2003–2004, LEADERS 2006–2007, RESOLUTE 2008), and the increasing number of co-morbidities now seen in patients presenting for revascularization. On the other hand, the ARTS II trial enrolled patients during a similar time to the SIRTAX study; however, inclusion criteria required patients to have at least two-vessel coronary artery disease.[25] The prevalence of multi-vessel disease in SIRTAX was close to 60%,[19] and therefore the lower mean and tertile cut-off values, seen for the SYNTAX score and CSS in the current study are entirely expected.

As mean SYNTAX score values decrease in patient cohorts with less complex disease compared with the seminal SYNTAX trial, one would hypothesize that differences in clinical outcomes between individuals would go increasingly undetected by a score solely based on angiographic parameters; clinical variables may therefore compensate for this possible decrease in sensitivity of the SYNTAX score. This hypothesis has been explored in diverse patient populations by integrating clinical information together with angiographic parameters into hybrid risk scores, such as the CSS,[11,18] the Global risk classification (GRC)[10,26] and the New Risk Stratification (NERS).[27] In our study, we chose CSS as the most parsimonious of these hybrid scores to assess the incremental value of clinical data in risk stratification over stand-alone SYNTAX score; thereby we tried to limit statistical over-fitting and multiple collinearity between potential predictors.[28]

The discriminatory power for MACE was similar for SYNTAX score and CSS in our study; *C*-statistics were comparable with the findings for 5-year MACE in the ARTS II (AUC: 0.57 and 0.62)[18] and for 1-year MACE in the RESOLUTE (AUC: 0.59 and

Table 7 Clinical outcomes at 1- and 5-year follow-up by treatment arm (univariable analysis)

	PES, *n* = 422, %	SES, *n* = 426, %	HR (95% CI) PES vs. SES	*P*-value
1-year outcome				
Death	2.1	1.4	1.53 (0.54–4.29)	0.42
Cardiac death	1.4	0.9	1.52 (0.43–5.40)	0.51
Myocardial infarction	4.1	2.8	1.44 (0.69–3.02)	0.33
TLR (ID)	10.8	5.7	1.95 (1.19–3.20)	0.008
MACE	13.6	7.5	1.86 (1.20–2.86)	0.005
Stent thrombosis (definite)	1.7	1.9	0.88 (0.32–2.44)	0.81
5-year outcome				
Death	8.4	8.8	0.97 (0.61–1.54)	0.89
Cardiac death	5.1	4.6	1.13 (0.61–2.10)	0.70
Myocardial infarction	7.3	5.8	1.28 (0.75–2.20)	0.36
TLR (ID)	14.8	12.3	1.26 (0.87–1.82)	0.23
MACE	20.7	17.7	1.22 (0.90–1.67)	0.20
Stent thrombosis (definite)	4.2	4.1	1.02 (0.52–2.00)	0.96

CI, confidence interval; HR, hazard ratio; ID, ischaemia driven; MACE, major adverse cardiac events; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; TLR, target lesion revascularization.

0.62)[11] and better compared with the CUSTOMIZE registry left main PCI population (AUC for 2-year MACE 0.52 and 0.50 for SYNTAX score and CSS, respectively).[10] Nevertheless, risk stratification was not very well balanced between score tertiles; specifically, CSS showed diminished ability to discriminate between patients at low and intermediate risk, reflecting findings of earlier studies.[10,18] SYNTAX score was recently shown to have higher discriminatory power for repeat revascularization[11]; since MACE rates were mainly driven by TLR rates in our study, the lack in reclassification improvement with CSS can be explained.

On the other hand, for harder endpoints, such as the all-cause and cardiac mortality, significantly better discrimination and equivalent or better calibration compared with SYNTAX score translated into more refined risk stratification with the CSS. Interestingly, whereas *C*-statistics for both scores regarding mortality were comparable with respective measures in the ARTS II and CUSTOMIZE populations, calibration measures were improved in our study. This refinement in stratification resulted in CSS being an independent predictor for mortality, contrary to SYNTAX score, as also demonstrated in similar studies.[11,13] Very long-term mortality is expected to be dependent on well-known predictors of outcome after PCI, such as age and diabetes mellitus; age is included in the CSS, while diabetes mellitus is known to impact on renal function. Similarly, the EuroSCORE,[29,30] which has also been shown to be effective in risk stratifying patients, either as a stand-alone score or integrated in GRC,[10,26] does not include assessment of diabetic status, but renal function. Diabetes was an independent predictor for all-cause and cardiac mortality next to CSS in our study; nevertheless a model incorporating CSS and diabetes did not significantly improve discrimination or calibration for these outcomes. We may assume that to a certain extent the effect of diabetes has translated into higher angiographic complexity and diminished creatinine clearance.

An added finding of our study is the differential performance of PES and SES for patients in the highest SYNTAX score and CSS tertiles. In the original SIRTAX trial publication,[19] there was a significant increase in the primary endpoint at 9-month follow-up in patients allocated to PES compared with SES; this difference in MACE was mainly driven by the increased TLR rates in the PES treatment arm and was attributed to increased angiographic or procedural complexity. In successive reports from the same group, similarly significant differences in 2-year MACE have been reported between PES and SES, when implanted in vessels with a reference size $<$2.75 mm,[31] or when studied separately in diabetic patients.[32] In both analyses, differences in MACE were driven by significantly decreased TLR rates with SES. Not unexpectedly, in our study, significantly increased MACE rates with PES were observed within the subgroup of patients with increased angiographic complexity. It has already been suggested in the LEADERS[33] and the RESOLUTE[11] trials, that SYNTAX score could identify a subgroup of patients, where there is a difference in clinical outcomes between devices. Nevertheless, in our study respective hazard ratios were inflated, when MACE was stratified across the CSS tertiles; more importantly, the respective interaction term between treatment arm and CSS tertiles reached statistical significance for 5-year MACE, indicating a potential role of CSS-based stratification in device selection. However, it should be recognized that this was a subgroup analysis, not pre-specified in the original study, thus the superiority seen with SES could be the result of a type I error.

Limitations

The current study is limited by its *post hoc* nature. As the cardiologists adjudicating the diagnostic angiograms were blinded to procedural data, and taking into account the modest reproducibility of SYNTAX score even among experienced cardiologists,[34] a discrepancy in results cannot be ruled out, would the scores have been

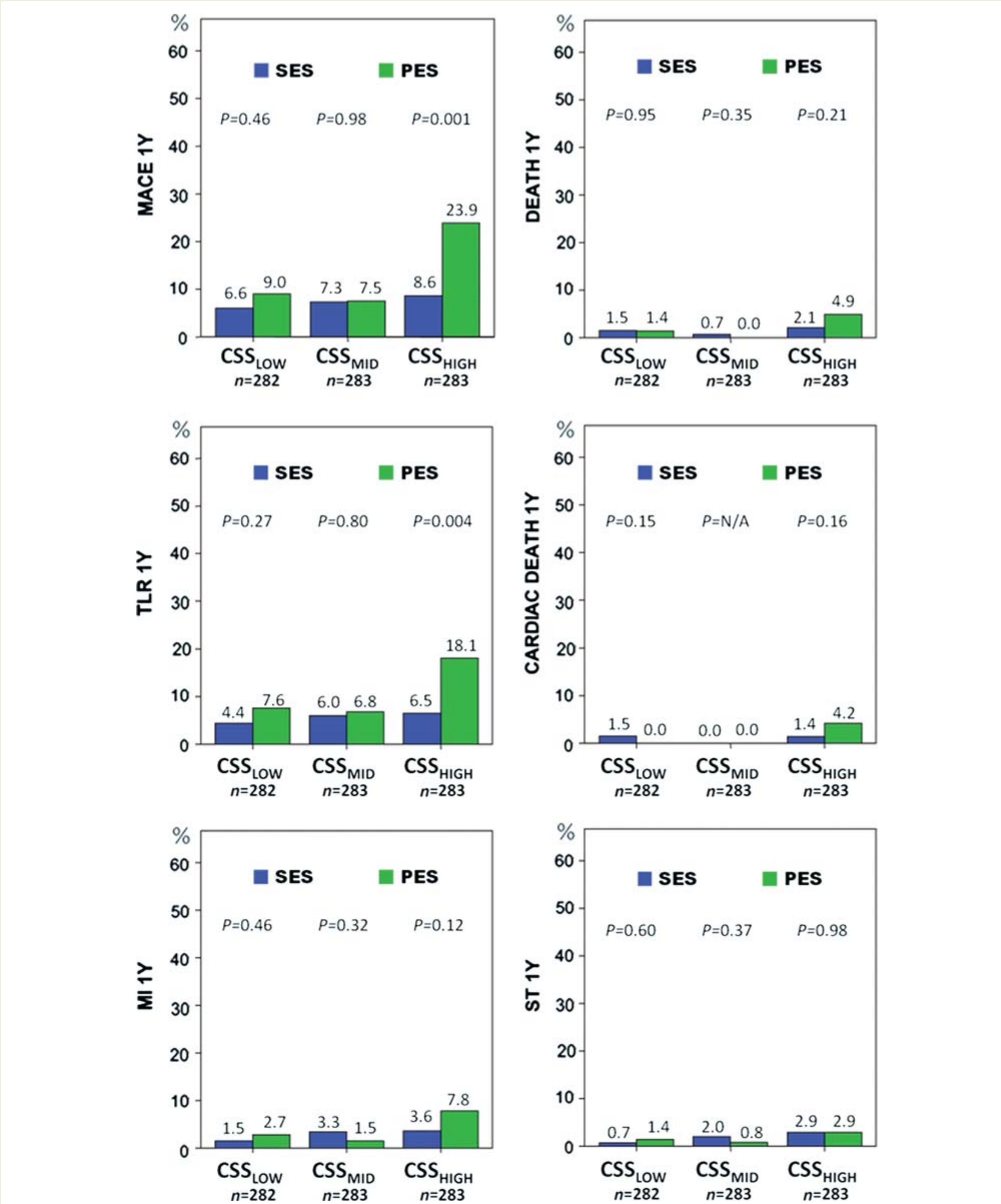

Figure 4 Stratified comparison between treatment arms for clinical outcomes at 1-year follow-up. Events are stratified across Clinical SYNTAX score tertiles defined as $CSS_{LOW} \leq 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$. Clinical outcomes' abbreviations as defined in text. PES, paclitaxel-eluting stents, SES, sirolimus-eluting stents, N/A, non-applicable.

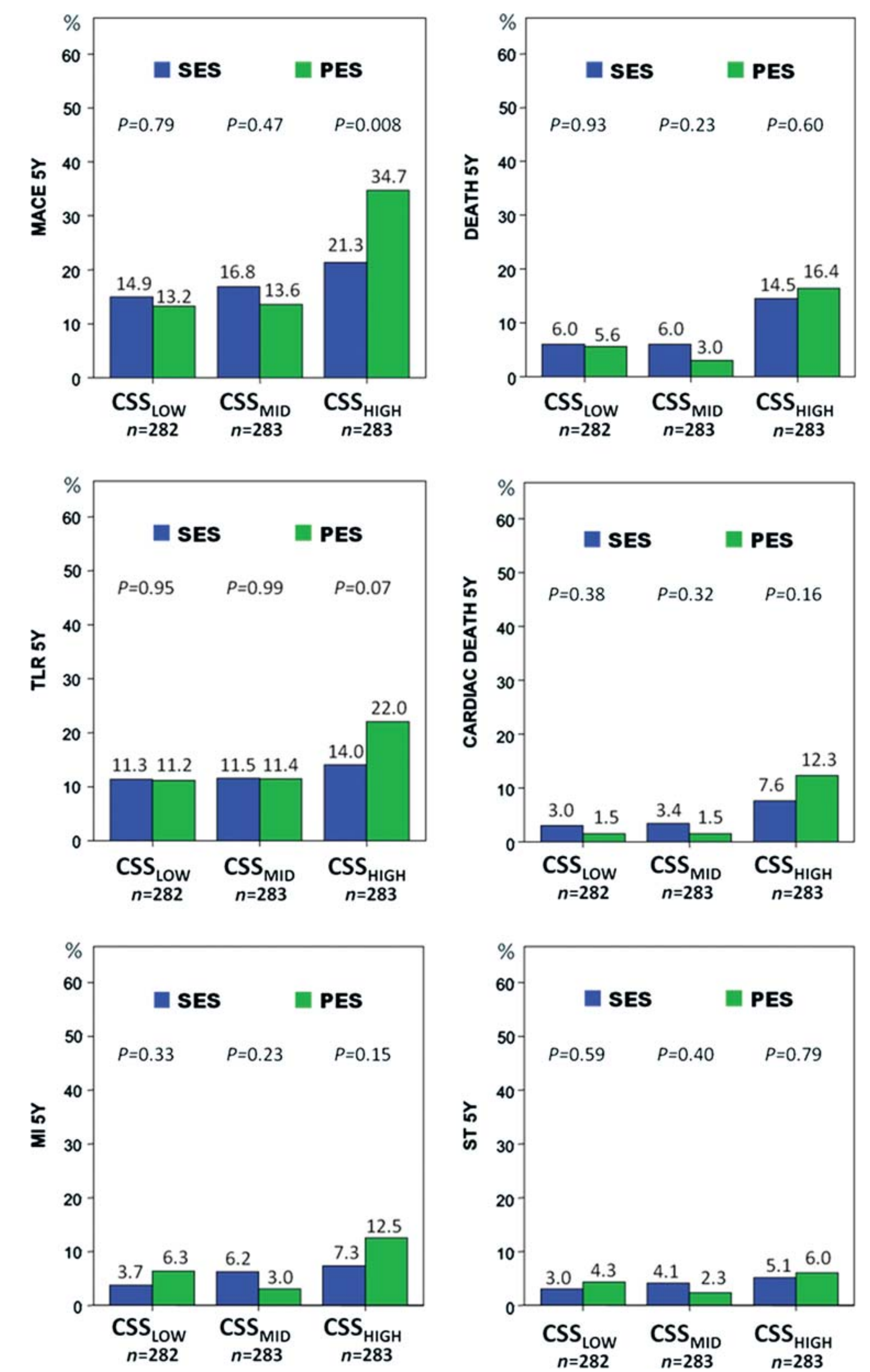

Figure 5 Stratified comparison between treatment arms for clinical outcomes at 5-year follow-up. Events are stratified across Clinical SYNTAX score tertiles defined as $CSS_{LOW} < 8.0$, $8.0 < CSS_{MID} \leq 17.0$, $CSS_{HIGH} > 17.0$. Clinical outcomes' abbreviations as defined in text. PES, paclitaxel-eluting stents, SES, sirolimus-eluting stents.

collected prospectively. However, in the case of the SIRTAX trial, this is purely hypothetical, as the SYNTAX score algorithm had not been developed at the time of patient enrolment.

Well-known limitations of the SYNTAX score should also be acknowledged. Patients with prior CABG had to be excluded from the study; moreover, scoring acute coronary occlusions as total occlusions may have resulted in an inflation of the individual scores overestimating the complexity of recanalization. However, it has been recently shown that SYNTAX score values derived after the instrumentation of the infarct-related artery and therefore probably lower compared with the values derived with the standard method, could have resulted in an erroneous risk stratification; it should not be overlooked that the absence of flow itself holds an adverse impact on long-term outcome.[9] Moreover, irrespective of the method used, SYNTAX score for acute MI patients was proven to improve the discriminatory power of models solely based on clinical variables, such as the TIMI risk score.[35] Lastly, in our study, multivariable analysis adjusted for clinical presentation, rendering SYNTAX score and CSS as independent predictors of MACE and CSS as independent predictor of mortality.

Conclusions

The SYNTAX score and to a greater extent the CSS were able to stratify risk for very long-term adverse clinical outcomes in an all-comers population receiving drug-eluting stents. Predictive accuracy for 5-year mortality was improved using the CSS. Within the highest score tertiles 5-year MACE increased with use of paclitaxel- compared with sirolimus-eluting stents. This study is yet another step to map the performance of SYNTAX score and CSS in the entire range of coronary artery disease seen in daily clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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