



Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score

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Background

The SYNTAX score (SXscore), an anatomical-based scoring tool reflecting the complexity of coronary anatomy, has established itself as an important long-term prognostic factor in patients undergoing percutaneous coronary intervention (PCI). The incorporation of clinical factors may further augment the utility of the SXscore to longer-term risk stratify the individual patient for clinical outcomes.

Methods and results

Patient-level merged data from >6000 patients in seven contemporary coronary stent trials was used to develop a logistic regression model—the Logistic Clinical SXscore—to predict 1-year risk for all-cause death and major adverse cardiac events (MACE). A core model (composed of the SXscore, age, creatinine clearance, and left ventricular ejection fraction) and an extended model [incorporating the core model and six additional (best performing) clinical variables] were developed and validated in a cross-validation procedure. The core model demonstrated a substantial improvement in predictive ability for 1-year all-cause death compared with the SXscore in isolation [area under the receiver operator curve (AUC): core model: 0.753, SXscore: 0.660]. A minor incremental benefit of the extended model was shown (AUC: 0.791). Consequently the core model alone was retained in the final the Logistic Clinical SXscore model. Validation plots confirmed the model predictions to be well calibrated. For 1-year MACE, the addition of clinical variables did not improve the predictive ability of the SXscore, secondary to the SXscore being the predominant determinant of all-cause revascularization.

Conclusion

The Logistic Clinical SXscore substantially enhances the prediction of 1-year mortality after PCI compared with the SXscore, and allows for an accurate personalized assessment of patient risk.

Introduction

The SYNTAX score^{1–4} (SXscore) has established itself as an important prognostic tool in risk stratifying patients in the Synergy

between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) pioneered Heart Team approach, and has since been validated in patients undergoing percutaneous coronary intervention (PCI) at a short and longer-term follow-

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up.^{5–9} More recently the SXscore has been applied to contemporary ‘All-Comers’ coronary stent trials, and has consistently been shown to be an independent predictor of 1-year mortality and major adverse cardiac events (MACE).^{10–12} In contrast, traditional risk scores for patients undergoing PCI principally allow for the estimation of procedural risk.^{13–18}

The addition of clinical risk factors to the SXscore has been shown to potentially further augment its utility to objectively select the most appropriate revascularization strategy for patients planning to undergo surgical or percutaneous revascularization.^{19–23} These approaches have involved the amalgamation of cardiac surgery-based summary risk scores to the SXscore to form the ‘Global Risk’ (SXscore and additive EuroSCORE)²³ and the ‘clinical SXscore’ (SXscore and the modified ACEF score).^{19–22} As the individual clinical components of the cardiac surgery-based summary risk scores were not incorporated into the development of the combined risk models, and that these risk scores contained redundant information not relevant to the prediction of mortality after PCI—such as the chronic obstructive pulmonary disease and pulmonary hypertension in the EuroSCORE—this may have limited the predictive ability of the final risk models.²³ Furthermore, these approaches categorized patient risk without giving a more personalized risk assessment—with the Clinical SXscore^{19–22} being able to identify a high-risk population only, and the Global Risk²³ a lower-risk population.

The aims of the present study are to combine the individual components of the Clinical SXscore—namely the continuous variables age, creatinine or creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), and the SXscore—to form the Logistic Clinical SYNTAX score (Logistic Clinical SXscore). The underlying hypothesis being that the addition of these ‘Core’ clinical variables would provide the majority of the improvement to the 1-year predictive ability of the SXscore compared with the addition of further clinical variables. The second aim of this study was to allow for a more personalized approach to risk stratification, compared with the categorical approaches of previous risk models.^{19–23}

Methods

Patients

Patient-level data from seven contemporary coronary stent trials^{3,24–29} incorporating 6508 patients with a calculated SXscore were pooled for the present study and have previously been described.¹⁹ An additional trial was excluded from the original database ($n = 187$)³⁰ due to permission being unobtainable from the study sponsor, and a further 12 patients excluded due to missing values for death, leading to a total of 6309 patients in the present analysis. The endpoints for the prognostic analyses were 1-year all-cause death and MACE [a composite of all-cause death, myocardial infarction (MI) and all-cause revascularization].

Predictors and model development

During the development phase, two risk models were defined: (i) a core model that incorporated the SXscore and components of the ACEF and modified ACEF scores³¹ (age, creatinine or CrCl and LVEF); (ii) an extended model that included the core model and the addition of best performing clinical variables that improved the

performance of the core model. The CrCl was defined by the Cockcroft and Gault formula.³² The left ventricular ejection fraction was defined as the percentage LVEF taken by transthoracic echocardiography or left ventriculography taken at the time of the diagnostic coronary angiogram.

As the Logistic Clinical SXscore was to be developed for predicting future longer-term (1-year) clinical outcomes, relatively weaker predictors (of borderline significance) were selected and retained in the extended model only if there was an appropriate increase in AUC when added to the core model in the multivariable logistic regression model, in line with work described by Harrell and others.^{33,34}

Within all the coronary stent trials predictor values generally were >90% complete if the predictor was recorded. Multiple imputation of missing values in the trials with predictors recorded was undertaken using an advanced imputation strategy that takes the correlation between all potential predictors into account [method of chained equations (MICE algorithm in R software)].^{35–37}

Statistical analysis

Logistic regression analyses were performed to examine individual and joint relations between the core model, other clinical characteristics (extended model), and the binary outcome of 1-year all-cause death and MACE. Interaction terms between predictors were examined with likelihood ratio tests, but none was of sufficient relevance to extend the models beyond the main effects for each predictor. All analyses were stratified by the coronary stent trial.

Determining how the variables should be modelled was a vital step in identifying which variables were most strongly related to 1-year clinical outcomes. For the continuous predictors, possible non-linearity with clinical outcomes was assessed with restricted cubic spline functions. These are flexible functions that can accommodate curves in the form of the association to assess the assumption that patient characteristics are linearly related to the log odds of the outcome event.^{33,34} To allow for a direct comparison of the prognostic value of predictors recorded in different units or scales, the odds ratios (ORs) for continuous predictors were scaled to correspond to a change from the 25th to 75th percentile of the predictor distribution.³⁷ Pooled ORs were estimated over the imputed data set, and repeated using only the complete data, which gave similar results (unpublished data). Statistical analyses were performed with R software³⁷ and SPSS Version 17.0 (SPSS, Inc., Chicago IL, USA).

Validation

The predictive performance of the model was cross-validated by the omission of each of the coronary stent trials in turn, with the model fitted on the remaining pooled population, and the resulting fit tested on the omitted trial.^{38–40} This methodology allowed for the estimation of the extent to which the predictive accuracy of the model (based on the entire sample) was affected by any differences between the seven coronary stent trials.^{3,24–29} This form of cross-validation by trial was hence a stronger test of validity than if, for example, the study population had been divided at random into a development and validation cohort.^{34,41,42}

The measure of predictive discrimination used to characterize the model performance in the original and the validation samples, was by the area under the receiver operating characteristic curve (AUC), and is equal to the *c*-statistic (the ability to distinguish a patient with and without a clinical outcome—and ranges from 0.50 (no better than flipping a coin) to 1.0 (model is 100% correct). Calibration—the agreement between observed and predicted risks—was assessed with the Hosmer–Lemeshow test and validation plots.^{33,40}

Model presentation

The final model is presented in a score chart with the scores based on the original logistic regression coefficients and can be used to obtain approximate predictions for individual patients.^{34,40} Scores were based on rounding of the regression coefficients. A constant was subtracted or added to rescale the scores in positive integers. The sum scores were related to the risks of 1-year mortality with logistic regression. The score chart can be used to obtain approximate predictions for individual patients.

Results

Development of the model

Within the analysed data set 175 all-cause deaths (2.8%) and 797 MACE (15.8%) were observed. The univariate associations of the SXscore and clinical variables to 1-year all-cause death and MACE are shown in *Table 1*. Creatinine clearance was

demonstrated to be a stronger univariate predictor of 1-year all-cause death compared with serum creatinine and was therefore incorporated into the core model (CrCl, OR: 2.2; 95% CI: 1.8–2.8; creatinine, OR: 1.4; 95% CI: 1.2–1.6). Linear relationships were a good approximation for the SXscore, age, CrCl, and LVEF with 1-year mortality, except that constant risk was evident at higher values for the LVEF ($\geq 50\%$) and CrCl (≥ 90 mL/min) (Supplementary material online, Appendix). The four factors (SXscore, age, CrCl, and LVEF) were entered into a multivariable logistic regression model (*Table 2*) and confirmed to be strong independent predictors of 1-year mortality, thus forming the core model.

Similar analyses were repeated with the core model and the best performing clinical variables (six clinical variables: presentation, body mass index (BMI), peripheral vascular disease, diabetes, previous MI, smoking) for 1-year mortality to form the extended model.

Table 1 Univariate associations between predictors of 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials

Characteristics	Coding	Death (n = 6309)		MACE (n = 5048) ^a	
		Number (%)	Univariate ^b	Number (%)	Univariate ^b
Core model					
SYNTAX score ^c	23 vs. 8	—	1.7 (1.6–1.8)	—	1.8 (1.7–1.8)
Age (years) ^c	72 vs. 56	—	2.9 (2.7–3.1)	—	1.2 (1.2–1.2)
CrCl ^c	67 vs. 109	—	2.2 (1.8–2.6)	—	1.2 (1.1–1.3)
Ejection fraction ^d	40 vs. 50	—	2.2 (1.8–2.8)	—	1.3 (1.1–1.5)
Extended model					
Presentation (%)					
Stable		72 (2.4)	1.0	386 (15.1)	1.0
UA		32 (2.5)	1.0 (0.7–1.6)	185 (15.2)	1.0 (0.8–1.2)
NSTEMI		25 (3.1)	1.8 (1.1–2.9)	102 (16.5)	1.1 (0.8–1.4)
STEMI		46 (3.6)	1.7 (1.1–2.9)	97 (14.9)	1.0 (0.8–1.3)
Female		58 (3.7)	1.5 (1.1–2.1)	215 (17.1)	1.2 (1.0–1.4)
BMI ^c	30 vs. 25	—	1.1 (1.0–1.1)	—	1.0 (1.0–1.1)
PVD		20 (6.9)	2.5 (1.5–4.1)	49 (20.6)	1.3 (0.9–1.8)
Diabetes (%)					
Non-insulin treated		32 (3.8)	1.8 (1.2–2.8)	146 (17.4)	1.3 (1.1–1.6)
Insulin treated		27 (6.8)	3.1 (2.0–4.8)	101 (25.4)	2.1 (1.6–2.6)
Hypertension (%)		134 (3.1)	1.5 (1.1–2.2)	579 (16.1)	1.2 (1.0–1.5)
Hyperlipidaemia (%)		95 (2.3)	0.6 (0.5–0.9)	523 (15.3)	1.0 (0.9–1.2)
Glycoprotein 2b3a use (%)		57 (3.3)	1.2 (0.8–1.9)	173 (16.3)	1.1 (0.9–1.4)
Previous smoking (%)		48 (2.3)	0.8 (0.6–1.2)	259 (13.9)	1.0 (0.8–1.2)
Current smoking (%)		37 (2.2)	0.8 (0.5–1.1)	178 (14.3)	0.9 (0.7–1.1)
Previous MI (%)		68 (3.9)	1.8 (1.3–2.4)	250 (16.8)	1.2 (1.0–1.4)
Previous PCI (%)		23 (1.9)	0.7 (0.4–1.1)	179 (16.9)	1.2 (0.9–1.4)
TIA or CVA (%)		10 (5.5)	1.5 (0.7–2.8)	33 (22.8)	1.4 (0.9–2.1)
Stent generation (%)	Newer generation	58 (2.1)	0.9 (0.5–1.6)	382 (14.1)	0.8 (0.6–1.1)

CrCl, creatinine clearance; Yrs, years; UA, unstable angina; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; BMI, body mass index; PVD, peripheral vascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; CVA, cerebrovascular accident.

^an = 5048 without STRATEGY/MULTI-STRATEGY^{24,28} and SIRTAX²⁶ trials secondary to all-cause revascularization not being recorded in the trials.

^bOdds ratio (95% confidence interval).

^cOdds ratios for continuous variables are given for the inter-quartile range.

^dOdds ratio for a decrease in 10% for values below 50%.

Table 2 Multivariable associations [odds ratio (95% CI)], between the individual components of the core model, for 1-year death and 1-year major adverse cardiac events in the pooled database of seven contemporary coronary stent trials

Characteristics	Coding	Death (n = 6309)	MACE (n = 5048) ^a
Core model			
SYNTAX Score ^b	23 vs. 8	1.41 (1.15–1.73)	1.72 (1.54–1.91)
Age (years) ^b	72 vs. 56	2.06 (1.51–2.82)	1.06 (0.92–1.22)
CrCl (ml/min) ^b	67 vs. 109	1.53 (1.12–2.09)	1.11 (0.94–1.31)
LVEF (%) ^c	40 vs. 50	1.97 (1.61–2.41)	1.10 (0.93–1.30)

CrCl, creatinine clearance, LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events.

^an = 5048 without STRATEGY/MULTI-STRATEGY^{24,28} and SIRTAX²⁶ trials secondary to all-cause revascularization not being recorded in the trials.

^bOdds ratios for continuous variables are given for the inter-quartile range (indicated in coding column).

^cOdds ratio for a decrease in 10% for values <50%.

Table 3 Performances of the Logistic Clinical SYNTAX score (core model) at cross-validation

Study	Death		MACE	
	SYNTAX score	Core model	SYNTAX score	Core model
ARTS II ²⁵	0.69	0.75	0.69	0.70
LEADERS ²⁷	0.63	0.74	0.62	0.61
STRATEGY ²⁴ /MULTI-STRATEGY ²⁸	0.62	0.84	—	—
RESOLUTE ²⁹	0.57	0.77	0.63	0.63
SIRTAX ²⁶	0.64	0.71	—	—
SYNTAX ³	0.67	0.73	0.58	0.59
Overall ^a	0.660	0.753	0.605 ^b	0.609 ^b

The core model was developed by omitting each study in turn, with the model fitted on the remaining pooled population, and validated by testing the resulting fit on the omitted trial.^{38–40} Values shown are c-statistics for testing the resulting fit on the omitted trial (cross-validation).

LEADERS, biolimus-eluting stent with biodegradable polymer vs. sirolimus-eluting stent with durable polymer for coronary revascularization trial;²⁷ MACE, major adverse cardiac events; RESOLUTE, RESOLUTE all-comers trial;²⁹ SIRTAX, the sirolimus-eluting vs. paclitaxel-eluting stents for coronary revascularization trial;²⁶ SYNTAX, Synergy between PCI with Taxus and cardiac surgery trial;³ ARTS II, the arterial revascularization therapies study part II trial;²⁵ STRATEGY, the single high-dose bolus tirofiban and sirolimus-eluting stent vs. abciximab and bare metal stent in myocardial infarction trial;²⁴ MULTISTRATEGY, comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction trial.²⁸

^aPooled population (combining all trials).

^bn = 5048 without STRATEGY/MULTI-STRATEGY and SIRTAX secondary to all-cause revascularization not being recorded in the trial.

Model performances

1-Year all-cause death (death)

The core model (SXscore, age, CrCl, and LVEF) demonstrated a significantly better predictive ability for 1-year all-cause death compared with the SXscore in isolation (Table 3). Within the pooled population (combining all trials), the AUC was substantially higher for the core model compared with the SXscore in isolation (core model: 0.753, SXscore 0.660). A minor incremental benefit of the extended model (AUC: 0.791) compared with the core model was evident. Consequently, the core model was retained in the final Logistic Clinical SXscore, and the extended model excluded. The Hosmer–Lemeshow test confirmed that there was no evidence of poor calibration for the core model in pooled analyses of the seven trials ($P = 0.55$). Validation plots of the core model indicated a good agreement between the observed and predicted risks in the three largest coronary stent trials

($n > 1000$) (Figure 1). Within the SYNTAX trial recalibration of the validation plots was necessary to prevent generalized under-estimation of predicted risk, and involved resetting the intercept of the calibration slope to zero.

1-Year major adverse cardiac events

For the outcome of 1-year MACE, the core and extended models added little incremental increase in predictive ability compared with the SXscore in isolation (AUC core model: 0.609, AUC extended model: 0.618, SXscore: 0.605) (Tables 2 and 3). Further analyses indicated that all-cause revascularization least benefited from the addition of clinical variables compared with death or MI (Supplementary material online, Appendix). Since the Logistic Clinical SXscore conferred no major additional benefit to the SXscore in predicting MACE, further analyses for this endpoint are not reported.

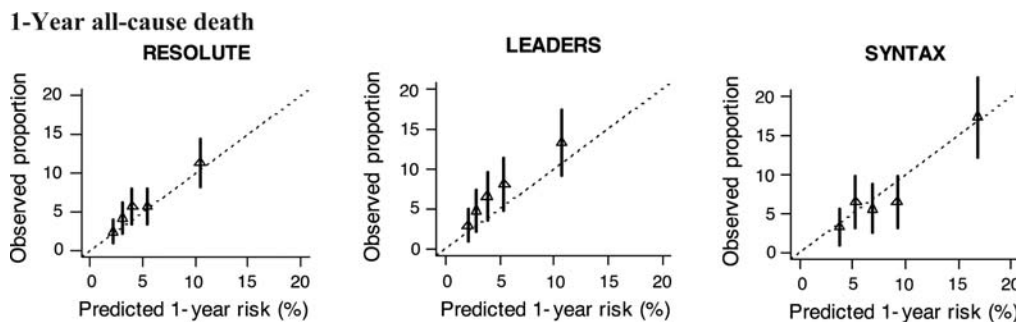


Figure 1 Validation plots at cross-validation for the three largest coronary stent trials ($n > 1000$). Plots are shown for the core model predicting 1-year all-cause death. The triangles indicate the observed frequencies by quintile of predicted probabilities with a 95% confidence interval. Good agreement was evident between observed and predicted risks, indicating that the core model did not over or under-estimate 1-year mortality (i.e. good calibration).

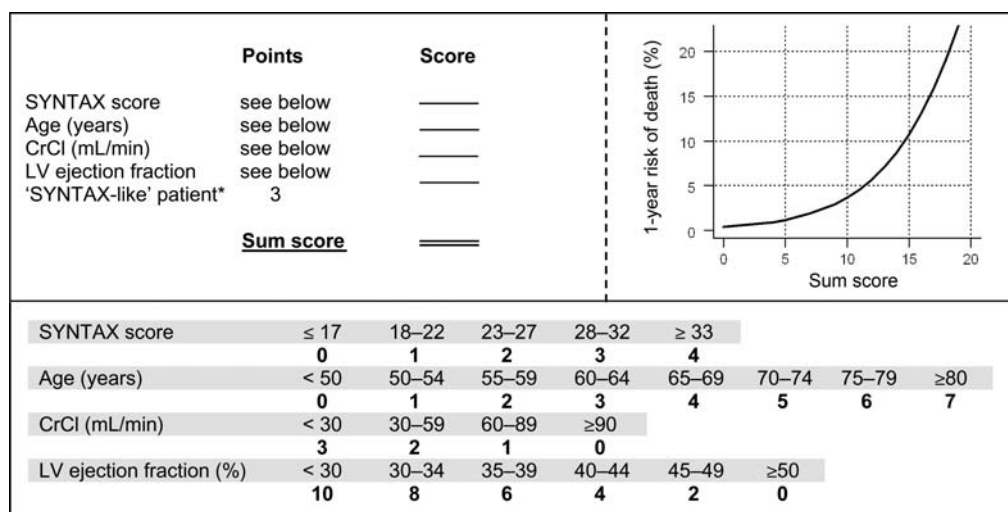


Figure 2 The Logistic Clinical SYNTAX score for the prediction of 1-year death. *SYNTAX-like patient defined as fulfilling the enrolment criteria for the SYNTAX All-Comers trial, i.e. left main stem (isolated or associated with one-, two-, or three-vessel disease) or three-vessel disease alone. CrCl, creatinine clearance, LV ejection fraction, left ventricular ejection fraction.

Score charts for 1-year all-cause death

A simple score chart for the bedside application of the final Logistic Clinical SXscore for predicting 1-year all-cause death after PCI is illustrated (Figure 2). An extra score is included for a “SYNTAX-like” patient, i.e. a patient presenting with left main disease (isolated or associated with 1, 2, or 3-vessel disease) or 3-vessel disease, due to the need to recalibrate risks to the SYNTAX trial patients as described previously. One-year mortality can be accurately estimated by the summation of scores. Similar charts for the extended model are enclosed in the Supplementary material online, Appendix.

Discussion

The main findings from this study are that: (i) the Logistic Clinical SXscore—consisting of four continuous variables (SXscore, age,

CrCl, LVEF)—substantially enhances the risk stratification of PCI patients for the outcome of 1-year all-cause death compared with the SXscore in isolation; (ii) the Logistic Clinical SXscore was able to accurately distinguish patients with or without a clinical outcome (discrimination) and could accurately predict individual patient risk (calibration) without under or over-estimating risk; (iii) the addition of further clinical variables to the four key predictors of the Logistic Clinical SXscore (SXscore, age, CrCl, and LVEF) did not substantially increase its predictive ability; (iv) an individualized approach to the longer-term (1-year) risk stratification of patients after PCI was achievable utilizing the SXscore and (v) the SXscore in isolation was the predominant determinant of 1-year MACE with little additional predictive benefit of clinical variables, predominantly secondary to the SXscore being the main determinant of all-cause revascularization.

The logistic clinical SYNTAX score: predicting 1-year death

The findings of the Logistic Clinical SXscore, namely that a few strongly predictive clinical variables leading to the accurate prediction of 1-year all-cause death after PCI, are consistent with the concepts of the “law of parsimony” or “Occam’s razor.” Age, CrCl, and LVEF are objectively measured continuous clinical variables in line with the ACEF methodology, which has previously been shown to match or even surpass the EuroSCORE (consisting of 17 clinical variables) in predicting in-hospital mortality after elective coronary artery bypass graft surgery.^{31,43,44} Explanations for this comparability have included that the clinical variables of the ACEF score were objectively defined and continuous.³¹

Notably the addition of a further six clinical variables to the Logistic Clinical SXscore to form the extended model lead to a minor incremental increase in its predictive ability. This is likely related to the inter correlation between the core model and the additional clinical variables. Clear correlations were evident (Pearson correlation coefficient 0.2 or greater, $P < 0.001$) for age and gender/hypertension; CrCl and gender/BMI; LVEF and MI; SXscore and prior PCI; BMI and diabetes mellitus. In addition the presence of diabetes has historically been associated with adverse outcomes after PCI.^{45,46} It is however likely that patients with more severe diabetes were captured by the continuous variables in the Logistic Clinical SXscore, in particular a reduced CrCl. Both a reduced CrCl and proteinuria—a marker of diabetic nephropathy—have previously been shown to be significant determinants of adverse risk following PCI.^{47–49} Furthermore diabetics without evidence of proteinuria have also previously been reported to have a similar survival compared with non-diabetics.⁴⁷

SYNTAX score

The SXscore calculation has previously been reported to have moderate inter-observer variability when performed by interventional cardiologists,^{4,50} which may be perceived as a limitation of the Logistic Clinical SXscore. Appropriate training of SXscore reporting has, however, been shown to substantially reduce inter-observer variability.^{1,2,50} It has previously been suggested that the SXscore is a reflection of the underlying co-morbidity of the patient,²³ for which the present study provides further supportive evidence. This notion is also supported by the 10-year predicted Framingham risk scores being recently shown to have a significant and direct relationship with the prevalence and magnitude of coronary artery calcium scores.⁵¹

Comparisons with the clinical SYNTAX score

The Clinical SXscore, on which the Logistic Clinical SXscore is based, multiplied a variant of the surgical-based ACEF (age, creatinine, and ejection fraction) score (modified ACEF score) to the SXscore. In doing so the Clinical SXscore was shown to overestimate predicted risks (i.e. relatively poor calibration) despite modest increases in the discriminative ability of the Clinical SXscore being obtained.^{20,23} The application of the Clinical SXscore to the present study (full data not shown) showed that it was able to identify a high-risk population only (mortality: 6.6%

of the study population), compared with the intermediate- and low-risk groups (mortality: 2.3 and 1.1% of the study population, respectively) consistent with the previously reported literature.^{19–23} Comparatively the Logistic Clinical SXscore within the present study was demonstrated to accurately predict risk across all risk groups (i.e. well calibrated) and importantly was able to provide an individualized risk assessment.

Comparisons with other risk models

The recently reported Functional SXscore (FSS)—a fractional flow reserve (FFR)-guided SYNTAX scoring methodology—has been shown to potentially improve the predictive accuracy of the SXscore.⁵² Within this study, the more objective assessment of coronary stenoses compared with visual assessment (to form the FSS) lead to incremental increases in the predictive accuracies for the outcomes of 1-year MACE (AUC: SXscore, 0.630; FSS, 0.677), 1-year death or MI (AUC: SXscore, 0.621; FSS, 0.676) and 1-year all-cause revascularization (AUC: SXscore, 0.627; FSS, 0.657).⁵² Notably, improvements in the predictive accuracy for 1-year death were not reported with the FSS. Comparatively the Logistic Clinical SXscore in the present study demonstrated a substantial increase in the prediction of 1-year death (AUC: SXscore, 0.660; core model, 0.753), and improvements in the prediction of 1-year death or MI (AUC: SXscore, 0.594; core model, 0.657, extended model 0.666—Supplementary material online, Appendix) without the need for invasive pressure-wire coronary assessment.

The longer-term (1-year) mortality predictions provided by the Logistic Clinical SXscore are the principle differences compared with other reported risk scores, namely the National Cardiovascular Data Registry¹⁶ score, the Mayo Clinical Risk score,^{13,15} the EuroHeart PCI score,¹⁸ and the New York PCI risk score,¹⁴ in that they report in-hospital Death^{14,16,18} or in-hospital MACE,^{50,51} or at the most 30-day mortality¹⁶ after PCI. Other risk scores that longer-term risk stratify patients include the New Risk Stratification score (NERS).⁵³ As previously described with the Clinical SXscore, NERS categorized patients into levels of risk (high and low risk) without giving an individualized assessment of patient risk, which was achievable with the Logistic Clinical SXscore. Furthermore NERS is a more complicated score that consists of 17 clinical variables, 33 anatomical factors, and 4 procedural details, and was developed for patients with left main coronary artery disease undergoing PCI.⁵³

Potential clinical application

Although the patient and clinician may wish to know the short-term risk of procedural complications associated with PCI, a longer-term perspective may also be beneficial. Not only would this appropriately inform the patient, but may also prove to be of benefit in determining whether surgical or percutaneous revascularization would be more appropriate as part of the Heart Team consensus. As recently reported, high co-morbidity patients may confer prognostic and morbidity benefits from undergoing surgical revascularization compared with PCI provided a certain threshold of operative risk is not exceeded.²³

Limitations

Although the Logistic Clinical SXscore was derived from ‘All-Comers’ types patients in contemporary stent trials, each trial still retained certain inclusion and exclusion criteria.¹¹ These criteria were, however, minimal which should legitimize the application of the Logistic Clinical SXscore to contemporary clinical practice. The authors recognize that further external validation of the Logistic Clinical SXscore in ‘real-world’ ‘unrestricted’ registry populations is necessary when these registries reporting the SXscore become available. This would further strengthen the results of this study, although the present analyses were already undertaken in a pooled analysis of seven different contemporary stent trials and internally validated with a cross-validation procedure. Comparisons of the Logistic Clinical SXscore with the Global Risk²³ were not possible since the EuroSCORE was not collected in the seven contemporary stent trials.

Cardiogenic shock is a risk variable that has consistently been shown to be a powerful predictor of in-hospital mortality.^{13–18} This important subset of patients, although not an exclusion criteria in the ‘All-Comers’ trials, by practice lead to the under-recruitment of these patient types predominantly due to the inability to gain appropriate informed consent or refusal to participate.⁵⁴ Consequently, the Logistic Clinical SXscore should at present not be applied to these patients where other risk scores would be better suited.^{13–18}

Future directions

Potentially the integration of the Logistic Clinical SXscore into an online algorithm with the currently available SXscore¹ may serve to simultaneously allow for risk stratification of patients based on anatomical and clinical variables. In addition, the application of the Logistic Clinical SXscore in place of the SXscore to aid in determining the optimal revascularization modality in patients with complex coronary disease is a potential future application. The incorporation of the FSS as previously described,⁵² to allow for a more objective assessment of the coronary anatomy, may enhance the predictive accuracy of the Logistic Clinical SXscore even further. Future direction with non-invasive imaging and FFR calculation⁵⁵—utilizing computational fluid dynamics applied to coronary computed tomography angiography—may be feasible. The expansion of other risk variables to the Logistic Clinical SXscore such as the haemodynamic status as previously discussed may expand the use of this risk score to other patient types.

Conclusion

Compared with the SXscore in isolation, the Logistic Clinical SXscore substantially enhances the risk stratification of PCI patients for death at 1-year and allows for an accurate individualized assessment of patient risk. The use of the Logistic Clinical SXscore may also further aid in the Heart Team consensus in determining the optimal revascularization modality.

Supplementary material

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

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References

1. SYNTAX score calculator. <http://www.syntaxscore.com>. SYNTAX working-group. Launched 19th May 2009.
2. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Dyck NV, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *Euro Intervention* 2005;**1**:219–227.
3. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
4. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50–56.
5. Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K, de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 2007;**99**:1072–1081.
6. Capodanno D, Capranzano P, Di Salvo ME, Caggegi A, Tomasello D, Cincotta G, Miano M, Patane M, Tamburino C, Tolaro S, Patane L, Calafiore AM. Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2009;**2**:731–738.
7. Kim Y-H, Park D-W, Kim W-J, Lee J-Y, Yun S-C, Kang S-J, Lee S-W, Lee CW, Park S-W, Park S-J. Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. *J Am Coll Cardiol Interv* 2010;**3**:612–623.
8. Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 2011;**57**:2152–2159.
9. Chakravarty T, Buch MH, Naik H, White AJ, Doctor N, Schapira J, Mirocha JM, Fontana G, Forrester JS, Makkar R. Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol* 2011;**107**:360–366.
10. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter

- LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol* 2010;**56**:272–277.
11. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Raber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score on 1-year clinical outcomes in 6508 patients enrolled in contemporary coronary stent trials. *JACC. Cardiovasc Interv* 2011;**4**: 645–653.
 12. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol* 2011;**57**: 2389–2397.
 13. Singh M, Rihal CS, Selzer F, Kip KE, Detre K, Holmes DR. Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute dynamic registry. *J Am Coll Cardiol* 2003;**42**:1722–1728.
 14. Wu C, Hannan EL, Walford G, Ambrose JA, Holmes DR Jr, King SB III, Clark LT, Katz S, Sharma S, Jones RH. A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol* 2006;**47**:654–660.
 15. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR Jr. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. *Mayo Clin Proc* 2007;**82**:701–708.
 16. Peterson ED, Dai D, DeLong ER, Brennan JM, Singh M, Rao SV, Shaw RE, Roe MT, Ho KK, Klein LW, Krone RJ, Weintraub WS, Brindis RG, Rumsfeld JS, Spertus JA. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588 398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2010;**55**:1923–1932.
 17. Farooq V, Brugaletta S, Serruys PW. Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart* 2011;**97**:1902–1913.
 18. de Mulder M, Gitt A, van Domburg R, Hochadel M, Seabra-Gomes R, Serruys PW, Silber S, Weidinger F, Wijns W, Zeymer U, Hamm C, Boersma E. EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 2011;**32**:1398–1408.
 19. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 2010;**3**: 317–326.
 20. Capodanno D, Caggigi A, Miano M, Cincotta G, Dipasqua F, Giacchi G, Capranzano P, Ussia G, Di Salvo ME, La Manna A, Tamburino C. Global risk classification and clinical SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score in patients undergoing percutaneous or surgical left main revascularization. *J Am Coll Cardiol Interv* 2011;**4**:287–297.
 21. Girasis C, Garg S, Raber L, Sarno G, Morel MA, Garcia-Garcia HM, Luscher TF, Serruys PW, Windecker S. 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. *Eur Heart J* 2011;**32**:3115–3127.
 22. Wykrzykowska JJ, Garg S, Onuma Y, de Vries T, Goedhart D, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klaus V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. *Circ Cardiovasc Interv* 2011;**4**:47–56.
 23. Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, Holmes DR, Jr., Kappetein AP, Mack MJ, Feldman T, Morice MC, Stahle E, James S, Colombo A, Pereda P, Huang J, Morel MA, Van Es GA, Dawkins KD, Mohr FW, Steyerberg EW. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention. The SYNTAX trial at 3 years. *JACC Cardiovasc Interv* 2012;**5**:606–617.
 24. Valgimigli M, Percoco G, Malagutti P, Campo G, Ferrari F, Barbieri D, Cicchitelli G, McFadden EP, Merlini F, Ansani L, Guardigli G, Bettini A, Parrinello G, Boersma E, Ferrari R. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 2005;**293**:2109–2117.
 25. Serruys PW, Ong AT, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, O'Malley AJ, Bressers M, Donohoe D. Arterial revascularisation therapies study part II - Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Euro Intervention* 2005;**1**:147–156.
 26. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, Togni M, Billinger M, Tuller D, Seiler C, Roffi M, Corti R, Sutsch G, Maier W, Luscher T, Hess OM, Egger M, Meier B. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005;**353**:653–662.
 27. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klaus V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Juni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008;**372**:1163–1173.
 28. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, de Cesare N, Rodriguez AE, Ferrario M, Moreno R, Piva T, Sheiban I, Pasquetto G, Prati F, Nazzaro MS, Parrinello G, Ferrari R. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 2008;**299**:1788–1799.
 29. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, KelbÄik H, van Boven AJ, Hofma SH, Linke A, Klaus V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 2010;**363**:136–146.
 30. Serruys PW, Garg S, Abizaid A, Ormiston J, Windecker S, Verheye S, Dubois C, Stewart J, Hauptmann KE, Schofer J, Stangl K, Witzensbichler B, Wiemer M, Barbato E, de Vries T, den Drijver AM, Otake H, Meredith L, Toyloy S, Fitzgerald P. A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study. *Euro Intervention* 2010;**6**:195–205.
 31. Ranucci M, Castelvecchio S. The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *Euro Intervention* 2010;**6**:549–553.
 32. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
 33. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis (Springer Series in Statistics)* New York: Springer-Verlag, Inc. 2001.
 34. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating (Statistics for Biology and Health)*. New York: Springer Science+Business Media, LLC, 2009.
 35. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;**10**:585–598.
 36. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002;**7**:147–177.
 37. R Development Core Team. *A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna (Austria) 2006. Available: <http://www.R-project.org/>. Accessed 1 August 2011.
 38. Efron B, Gong G. A leisurely look at the bootstrap, the jackknife, and cross-validation. *Am Statistician* 1983;**37**:36–48.
 39. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Calif RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41 021 patients. GUSTO-I Investigators. *Circulation* 1995;**91**:1659–1668.
 40. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128–138.
 41. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999;**130**:515–524.
 42. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;**19**:453–473.
 43. Ranucci M, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 2009;**119**:3053–3061.
 44. Ranucci M, Castelvecchio S, Conte M, Megliola G, Speziale G, Fiore F, Guarracino F, Scolletta S, Escobar RM, Falco M, Bignami E, Landoni G. The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29 659 patients undergoing elective cardiac surgery. *J Thorac Cardiovasc Surg* 2011;**142**:581–586.
 45. Weber FD, Schneider H, Wiemer M, Pfannebecker T, Tebbe U, Hamm CW, Senges J, Schneider S, Nienaber CA. Sirolimus eluting stent (Cypher) in patients with diabetes mellitus: results from the German Cypher Stent Registry. *Clin Res Cardiol* 2008;**97**:105–109.
 46. Mack MJ, Banning AP, Serruys PW, Morice MC, Taeymans Y, Van Nooten G, Possati G, Crea F, Hood KL, Leadley K, Dawkins KD, Kappetein AP. Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or metabolic syndrome. *Ann Thorac Surg* 2011;**92**:2140–2146.

47. Marso SP, Ellis SG, Tuzcu M, Whitlow PL, Franco I, Raymond RE, Topol EJ. The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics. *J Am Coll Cardiol* 1999;**33**:1269–1277.
48. Mercado N, Brugts JJ, Ix JH, Shlipak MG, Dixon SR, Gersh BJ, Lemos PA, Guarneri M, Teirstein PS, Wijns W, Serruys PW, Boersma E, O'Neill WW. Usefulness of proteinuria as a prognostic marker of mortality and cardiovascular events among patients undergoing percutaneous coronary intervention (data from the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events [EXCITE] trial). *Am J Cardiol* 2008;**102**:1151–1155.
49. Shaw JA, Andrianopoulos N, Duffy S, Walton AS, Clark D, Lew R, Sebastian M, New G, Brennan A, Reid C, Ajani AE. Renal impairment is an independent predictor of adverse events post coronary intervention in patients with and without drug-eluting stents. *Cardiovasc Revasc Med* 2008;**9**:218–223.
50. Genereux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, Lazar D, Jankovic I, Corral MD, Dressler O, Fahy MP, Parise H, Lansky AJ, Stone GW. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv* 2011;**4**:553–561.
51. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;**57**:1838–1845.
52. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, De Bruyne B, Pijls NH, Fearon WF. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011;**58**:1211–1218.
53. Chen S-L, Chen JP, Mintz G, Xu B, Kan J, Ye F, Zhang J, Sun X, Xu Y, Jiang Q, Zhang A, Stone GW. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *J Am Coll Cardiol Interv* 2010;**3**:632–641.
54. de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;**32**:2161–2167.
55. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, Defrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011;**58**:1989–1997.