Assessment of long-term mortality in patients with complex coronary artery disease undergoing percutaneous intervention: comparison of multiple anatomical and clinical prognostic risk scores

Bruno L. Janella[1], MD; Carlos M. Campos[1,2]*, MD, PhD; Adriano Caixeta[1], MD, PhD; Breno O. Almeida[1], MD, PhD; Fabio Sandoli Brito Jr[1], MD, PhD; Alexandre Abizaid[1,3], MD, PhD; Marco A. Perin[1], MD, PhD

1. Hospital Israelita Albert Einstein, São Paulo, Brazil; 2. Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; 3. Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil

KEYWORDS

- drug-eluting stent
- left main
- multiple vessel disease

Abstract

Aims: Three-vessel and left main coronary artery disease (CAD) have important prognostic implications. Consequently, numerous risk scores have been developed to stratify patients with complex CAD. The aim of the present study was to compare the predictive performance of six risk scores for occurrence of four-year all-cause mortality.

Methods and results: From March 2008 to December 2012, 348 consecutive patients with complex CAD undergoing percutaneous coronary intervention (PCI) in a tertiary centre in São Paulo, Brazil, were analysed. Four-year mortality was assessed. The scores compared were: baseline SYNTAX score (SS), residual SYNTAX score (rSS), ACEF score, clinical SYNTAX score (cSS), SYNTAX revascularisation index (SRI) and SYNTAX score II (SSII). SSII had the best predictive performance, AUC 0.82, Brier score 0.10, surpassing all the other scores for long-term mortality prediction. Moreover, SSII discriminated well PCI patients in risk groups with p<0.01 for four-year all-cause mortality. The ACEF score (AUC 0.77) and the cSS (AUC 0.78) were significantly better than the SS (AUC 0.65), SRI (AUC 0.60) or the rSS (AUC 0.55).

Conclusions: For patients with complex CAD treated by PCI, the combination of baseline clinical and angiographic factors provided better risk assessment. The SSII demonstrated the most precise predictive performance for long-term mortality.

Corresponding author: Hospital Albert Einstein - Departamento de Hemodinâmica e Cardiologia Intervencionista, Av. Albert Einstein, 627/701 – Morumbi, São Paulo – SP, 05652-900, Brazil. E-mail: carlosacampos1@gmail.com

Abbreviations

ARTS I	Arterial Revascularization Therapies Study Part I
AUC	area under the curve
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
cSS	clinical SYNTAX score
IQR	interquartile range
LVEF	left ventricular ejection fraction
NRI	Net Reclassification Index
PCI	percutaneous coronary intervention
PVD	peripheral vascular disease
rSS	residual SYNTAX score
SRI	SYNTAX revascularisation index
SS	SYNTAX score
SSII	SYNTAX score II
ULMCA	unprotected left main coronary artery

Introduction

Left main and three-vessel coronary artery disease (CAD) have been established as markers of poor prognosis[1,2]. The large amount of myocardium at risk with a higher probability of events classified these conditions as complex CAD[3,4]. Consequently, a number of risk scores have been developed in order to scrutinise complex CAD and decide the best therapeutic option.

With regard to percutaneous coronary intervention (PCI), the severity of baseline CAD, clinical characteristics and the post-revascularisation residual atherosclerotic burden have been shown to be independently related with long-term mortality and are considered in the risk stratification of coronary atherosclerosis[4-8]. For quantification of the atherosclerotic burden, the SYNTAX score (SS) is a combination of the total jeopardised myocardium and anatomical complexity[9]. Among the clinical characteristics, it is worth mentioning that the combination of age, creatinine clearance and ejection fraction is the backbone of risk models in cardiology[7,10]. Moreover, the residual SYNTAX score (rSS) and the SYNTAX revascularisation index (SRI) quantify CAD post revascularisation and the proportion of CAD burden treated[6,11].

Therefore, in decision making for complex CAD, the initial anatomical complexity, whether to attempt complete revascularisation or to follow a reasonable incomplete revascularisation strategy, and also clinical and demographic variables should be considered. However, the impact of each risk model on long-term prognosis in isolation has not been compared and described. The objective of the present study was to test and compare SYNTAX-derived risk models that use clinical variables, baseline and post-PCI atherosclerotic burden for four-year all-cause death in a real-world population of complex CAD.

Methods

STUDY POPULATION

The present study is a registry which enrolled consecutive, real-world patients with complex CAD treated by PCI at the Albert Einstein Hospital, São Paulo, Brazil, from March 2008 to December 2012. Patients with previous coronary artery bypass graft surgery (CABG), ST-segment elevation myocardial infarction, and single or double vessel coronary artery disease were excluded from the study. Among 1,460 patients enrolled in the registry, 589 participants had three-vessel and/or unprotected left main CAD (complex CAD). Of these, 241 met the aforementioned exclusion criteria, and 348 were included in the current analysis.

The data collection was performed in a dedicated electronic database. The follow-up was made by phone or email at 30 days, six months, and annually until five years after PCI. The local ethics committee approved the research protocol, and informed consent was obtained from all patients.

DEFINITIONS

The creatinine clearance (CrCl), a measure of estimated glomerular filtration rate, was calculated using the Cockcroft-Gault equation[12]. Chronic obstructive pulmonary disease (COPD) was defined as the long-term use of bronchodilators or steroids for lung disease (EuroSCORE definition)[13]. Peripheral vascular disease (PVD) was defined as aorta and arteries other than coronaries, with exercise-related claudication, or revascularisation surgery, or reduced or absent pulsation, or angiographic stenosis of more than 50%, or combinations of these characteristics (Arterial Revascularization Therapies Study Part I [ARTS I] definition)[14]. Preprocedural left ventricular ejection fraction (LVEF) was taken by transthoracic echocardiography or diagnostic left ventriculography.

RISK MODELS

The present study compared the predictive performance on long-term all-cause mortality of the following risk scores.

– SYNTAX score: for the present study, experienced interventional cardiologists blinded to clinical outcomes assessed the SS for each angiogram (www.syntaxscore.com).

– ACEF score (age, creatinine, ejection fraction) score[15]: the modified ACEF score ($ACEF_{CrCl}$) was calculated retrospectively using the formula age/ejection fraction+1 point for every 10 mL/min reduction in CrCl below 60 mL/min per 1.73 m^2 (up to a maximum of six points)[16].

– Clinical SYNTAX score (cSS): the cSS was calculated retrospectively for each patient using the formula cSS=(SYNTAX score) × (modified ACEF score).

– SYNTAX score II[7]: this is composed of the combination of two angiographic (SS and three-vessel/left main CAD) and six clinical elements: age, gender, creatinine clearance, COPD, peripheral artery disease and LVEF. Using the actual baseline clinical and angiographic data from every screened patient in the trial, SSII (PCI model) was calculated for each patient using an electronic calculator as previously described[17].

– Residual SYNTAX score[11]: the rSS was defined as the SS recalculated after PCI.
– SYNTAX revascularisation index[18]: the SRI was calculated as: $100 \times (1-[rSS/baseline\ SS])$.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean±SD or median with interquartile range (IQR) based on their distributions. To obtain four-year mortality predictions based on the risk scores, Cox logistic regression analysis was used with each score as a sole linear predictor. The performance of the risk scores was evaluated using four metrics: c-statistics, Brier score, calibration plots, and Kaplan-Meier analyses. Discrimination was studied with the c-statistics and by Kaplan-Meier analyses with focus on a four-year time horizon[19]. The Brier score is a proper score function that measures the accuracy of probabilistic predictions[20]. The Brier score is a quadratic scoring rule, where the squared differences between actual binary outcomes "Y" and predictions "p" are calculated: $Y*(1-p)^2+(1-Y)*p^2$. Therefore, the lower the Brier score, the more precise is the risk model. As not all persons had follow-up completed until four years, our reclassification was based on the expected number of case and control patients calculated by using the Kaplan-Meier estimator[21]. All statistical analyses were performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

The present study included 348 patients with complex CAD treated by PCI. Patients' baseline characteristics are listed in **Table 1**. The median age was 68.8 years (IQR 60-77), 79.3% were male, 39.7% had diabetes, and the median LVEF was 57% (IQR 49.1-64.2%). The median SYNTAX score was 30 (IQR 22.0-39.0). After four years of follow-up, the rate of all-cause death in the studied population was 17.8%.

PREDICTIVE PERFORMANCE OF RISK SCORE MODELS: DISCRIMINATION

The discriminative performance of the risk scores is shown in **Table 2**. The SSII had the best predictive accuracy for four-year all-cause mortality (c-statistics 0.82; 95% confidence interval [CI]: 0.76-0.88). The cSS and the ACEF performed well with no significant difference

Table 1. Baseline characteristics (n=348).

Age, years	68.8 (60.0-77.0)
Male, %	79.3
Family history of CAD, %	35.1
Current smokers, %	15.5
Hypertension, %	75.6
Diabetes mellitus, %	39.7
Insulin-requiring diabetes mellitus, %	11.8
Dyslipidaemia, %	68.4
Stable CAD, %	48.6
UA/non-STEMI, %	51.4
LVEF, %	57.0 (49.1-64.2)
Creatinine clearance, mL/min	85.6 (60.3-114.0)
SYNTAX score	30.0 (22.0-39.0)
ACEF score	1.3 (1.0-2.3)
Clinical SYNTAX score	50.6 (24.4-126.0)
SYNTAX score II	32.4 (25.5-43.3)
Residual SYNTAX score	12.3 (6.0-20.0)
SYNTAX revascularisation index	58.6 (26.7-81.7)

CAD: coronary artery disease; LVEF: left ventricular ejection fraction; STEMI: ST-elevation myocardial infarction; UA: unstable angina

between these two models (c-statistics 0.78; 95% CI: 0.71-0.83, and c-statistics 0.77; 95% CI: 0.71-0.84, respectively). The performance of purely anatomical characteristics (both baseline and residual) had significantly lower predictive accuracy. Additionally, the SS, ACEF, cSS, and SSII were able to separate low-, medium-, and high-risk tertiles (p<0.01 for all) **(Figure 1)**, while the rSS and SRI were not.

CALIBRATION

The score with the smallest difference between the predicted and the observed four-year all-cause mortality was the SSII. **Figure 2** illustrates the calibration of the scores tested in the present analysis.

Discussion

The findings of the present study can be summarised as follows: (1) the scores with baseline characteristics (both clinical and anatomical) had better performance than the assessment of complete revascularisation scores; (2) the combination of baseline clinical

Table 2. C-statistics and *p*-values for comparison of each risk score.

	C-statistics	95% CI	*p*-values					
			ACEF	cSS	SRI	rSS	SS	SSII
ACEF	0.77	0.71 to 0.84	–	0.54	<0.01	<0.01	0.01	0.03
cSS	0.78	0.71 to 0.83	0.54	–	<0.01	<0.01	<0.01	0.01
SRI	0.60	0.53 to 0.67	<0.01	<0.01	–	0.09	0.16	<0.01
rSS	0.55	0.48 to 0.63	<0.01	<0.01	0.09	–	0.05	<0.01
SS	0.65	0.58 to 0.73	0.01	<0.01	0.16	0.05	–	<0.01
SSII	0.82	0.76 to 0.88	0.03	0.01	<0.01	<0.01	<0.01	–

ACEF: age, creatinine, and ejection fraction; cSS: clinical SYNTAX score; rSS: residual SYNTAX score; SRI: SYNTAX revascularisation index; SS: SYNTAX score; SSII: SYNTAX score II
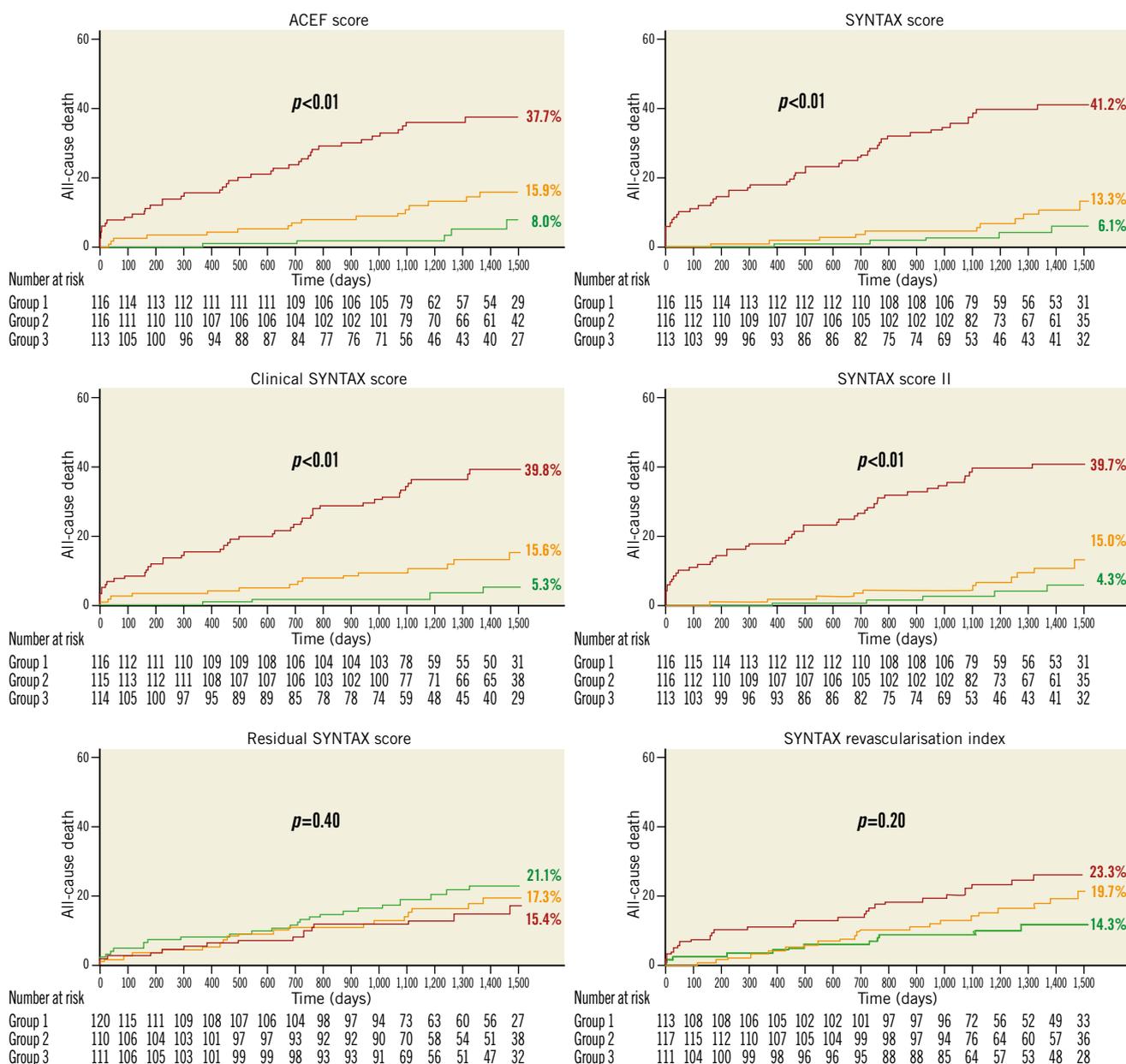
Figure 1. *Kaplan-Meier curves of four-year all-cause mortality according to each risk score discrimination by terciles (p-values obtained from log-rank test). The colours of the survival curves are shown according to each score terciles values in points: high=red; intermediate=orange; low=green.*

and anatomical characteristics improved the prediction of long-term all-cause mortality; (3) the SSII had the best overall accuracy for risk stratification of complex CAD.

The SYNTAX trial[4,22] left a number of legacies for risk assessment and decision making in the treatment of complex CAD since it was an all-comers randomised trial of PCI versus CABG. The SYNTAX-based scores tell a good part of the story of the contemporary risk assessment of complex CAD. Most of these risk scores are herewith tested and compared in a "real-world" population.

The anatomical SS was developed as a tool to force the Heart Team to analyse the coronary angiogram systematically and assess

the risk for anatomical revascularisation by CABG and PCI. It was first reported to be useful for decision making between CABG and PCI in the SYNTAX trial in 2009[22]. The anatomical SS was then implemented in multiple medical guidelines and tested in numerous populations[23,24]. The SS had the limitation of classifying patients into categories or terciles. The expanding use of PCI has consequently increased the importance of developing a systematic approach for risk stratifying complex patients so that they might not be restricted by terciles or arbitrary cut-offs. Doctors should have individual risk estimation for an adequate dialogue with the patient and a meaningful comparison of performance between
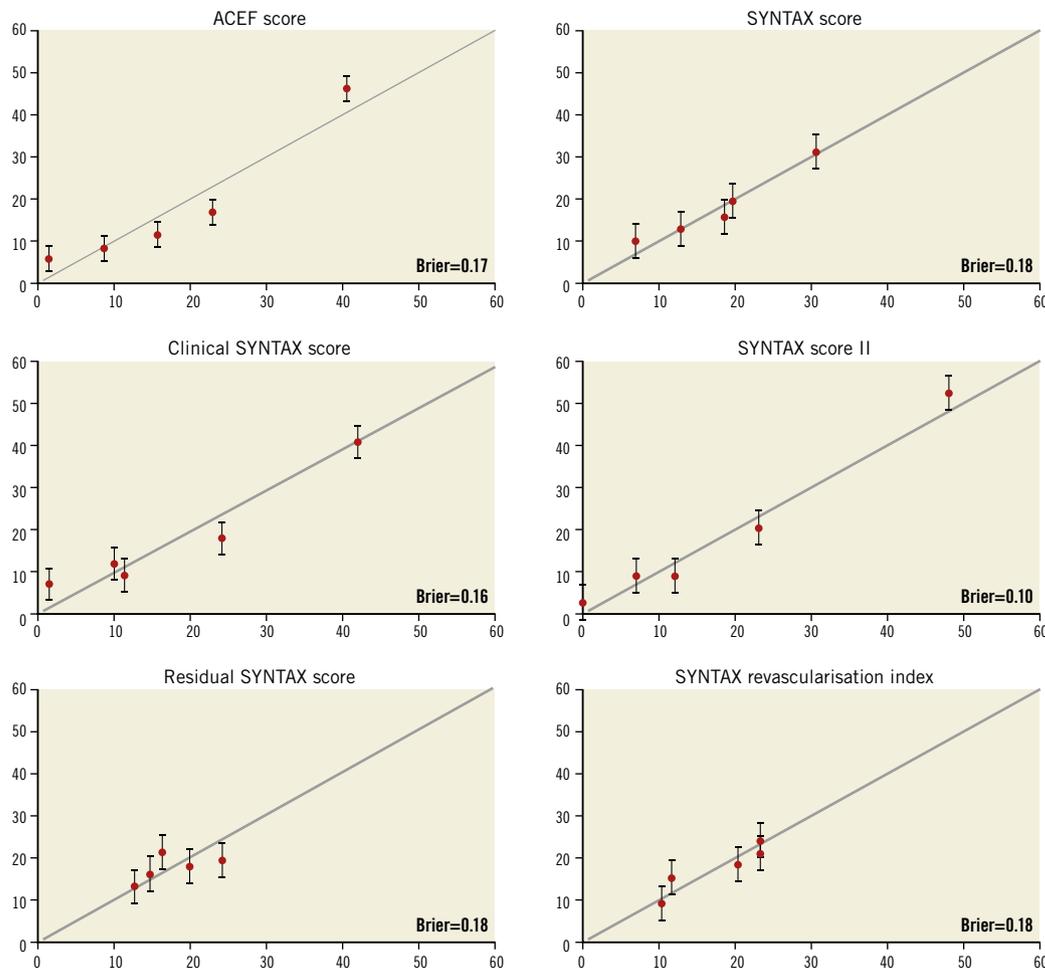
Figure 2. *Calibration plot risk scores for observed and predicted mortalities. The circles demonstrate the Kaplan-Meier estimates of four-year mortality (vertical axis) by quintiles and the predicted four-year risk (horizontal axis).*

hospitals and operators[16]. The cSS was then developed to provide an individualised assessment of risk.

Despite major advances in PCI technology and technique, complete revascularisation is often not achieved in multivessel CAD due to technical or clinical reasons. The prognostic impact of incomplete revascularisation after PCI was inconsistent between studies because they lacked standardised definitions. The residual SS was then developed to quantify the amount of atherosclerotic burden and disease complexity that was not treated by PCI[6,11]. However, it is a matter of considerable debate whether complete revascularisation is always necessary. A novel index was then proposed, namely the SYNTAX revascularisation index (SRI). The SRI considers the relationship between the baseline CAD and the residual CAD after PCI, determining the proportion of CAD that has been treated[11,18]. For complex CAD, an rSS <8 and an SRI >70% were the best cut-off to show reduction in mortality[6,8].

Another advance in terms of risk scores obtained from the SYNTAX trial was the SYNTAX score II. The SYNTAX score II (SSII) was built with the ACEF as its backbone, with the addition of risk factors that were shown to affect decision making

between CABG and PCI directly[7]. The SSII estimates the individual four-year mortality for both revascularisations. As it provides an objective risk prediction for CABG and PCI, the SSII could be implemented in the Heart Team decision-making process between CABG and PCI[17].

Last but not least, the extended model of the logistic clinical SYNTAX score has to be mentioned. It uses logistic regression analyses to explore the independent association of death with a relevant set of prognostic predictors. The logistic clinical SYNTAX score was not tested in the current work because it was originally developed for one- and three-year mortality[10,25] and we used a four-year time horizon.

There were numerous reasons why all-cause death was chosen as the main outcome of the present study. It is important to mention that all-cause death is a hard, reproducible endpoint, not subject to adjudication bias or definitional variation. As was well summarised by Stephen S. Gottlieb, "Dead is dead—artificial definitions are no substitute"[26]. These characteristics make death a very good outcome measure in registries. Also, we would like to mention that all the scores we tested have been shown to be independent

predictors of long-term mortality[6,8,27-29]. Therefore, all-cause death is an excellent metric to compare the performance of these scores.

The present work demonstrated using four metrics that the SSII had the most robust predictive performance. The c-statistic was 0.82 which indicates an accurate predictive score for long-term all-cause death. The SSII was able to classify patients better into low-, intermediate- and high-risk groups **(Figure 1)**. The precision of the predictions of the SSII can also be seen in **Figure 2**. In a good score, the predicted risk matches the observed risk. Also, a better discriminating model has more spread between quintiles of predicted risk than a poorly discriminating model. The improved statistical performance was not obtained through additional computational complexity. Only one angiographic (left main or three-vessel disease) and three clinical (gender, PVD, COPD) variables were added to the cSS[7].

The aforementioned findings reinforce the consistency of the SSII as an adjuvant tool in daily clinical practice, helping in the precise, critical and individual assessment of patients undergoing PCI[17]. The main limitation of the SSII is the relatively small number of external validation studies[23,27,30-32]. Our work validates the SSII in a Brazilian population, known to have profound miscegenation and genomic heterogeneity[33].

Besides the comparison of these risk scores, it was not clear what was the best means of assessing the risk of a patient with complex CAD for long-term prognosis: the baseline clinical profile in isolation, the baseline anatomy, the combination of anatomy and clinical characteristics or the residual atherosclerotic burden. The present study quantifies with four metrics the benefits of each risk model. We showed that the combination of baseline clinical and angiographic factors provided the best score on this matter. Interestingly, both rSS and SRI did not perform well. Previously, these scores have been shown to be independent predictors of mortality[6,8,18]. Actually, in the study of Capodanno et al, the rSS had better performance than the SS. This discrepancy may have been affected by the presence or not of ischaemia in the unrevascularised territories[34].

Limitations

The present study has the inherent limitations of a single-centre retrospective analysis. The ultimate goal of the SYNTAX score II is to assist the Heart Team in the decision-making process between CABG and PCI. Thus, a prospective study would be needed to achieve a true validation of the SYNTAX score II, where the decision between CABG and PCI is randomised[30]. We did not have detailed data of a CABG group to propose a validation of the SSII also in a group treated by surgery.

Conclusions

In patients with complex CAD treated by PCI, the combination of baseline clinical and angiographic factors provided better risk assessment than either factor alone or post-PCI atherosclerotic burden. The SSII provided the most precise predictive performance for long-term mortality.

Impact on daily practice

Numerous risk scores have been developed to assess the long-term risk of patients with complex CAD. The present work provided a detailed comparison of each component (baseline angiography, clinical factors, residual atherosclerotic burden) of SYNTAX-derived risk scores. The SSII substantially enhances the prediction of four-year mortality after PCI compared with the other scores, and allows an accurate personalised assessment of patient risk.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol.* 1983;51:606.

2. Sullivan DR, Marwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. *Am Heart J.* 1990;119:1262-7.

3. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation.* 1981;63:285-99.

4. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr, Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.

5. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, Religa G, Huang J, Roy K, Dawkins KD, Mohr F. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation.* 2014;129:2388-94.

6. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation.* 2013;128:141-51.

7. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making

between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.

8. Généreux P, Campos CM, Farooq V, Bourantas CV, Mohr FW, Colombo A, Morel MA, Feldman TE, Holmes DR Jr, Mack MJ, Morice MC, Kappetein AP, Palmerini T, Stone GW, Serruys PW. Validation of the SYNTAX revascularization index to quantify reasonable level of incomplete revascularization after percutaneous coronary intervention. *Am J Cardiol.* 2015;116:174-86.

9. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention.* 2005;1:219-27.

10. Farooq V, Vergouwe Y, Räber L, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, de Vries T, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. *Eur Heart J.* 2012;33:3098-104.

11. Généreux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, Xu K, Parise H, Mehran R, Serruys PW, Stone GW. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol.* 2012;59:2165-74.

12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

13. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg.* 2012;41:734-44.

14. 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. *EuroIntervention.* 2005;1:147-56.

15. 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;119:3053-61.

16. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW; ARTS-II Investigators. A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv.* 2010;3:317-26.

17. Campos CM, Stanetic BM, Farooq V, Walsh S, Ishibashi Y, Onuma Y, Garcia-Garcia HM, Escaned J, Banning A, Serruys PW; SYNTAX II Study Group. Risk stratification in 3-vessel coronary artery disease: Applying the SYNTAX Score II in the Heart Team Discussion of the SYNTAX II trial. *Catheter Cardiovasc Interv.* 2015;86:E229-38.

18. Généreux P, Campos CM, Yadav M, Palmerini T, Caixeta A, Xu K, Francese DP, Dangas GD, Mehran R, Leon MB, Serruys PW, Stone GW. Reasonable incomplete revascularisation after percutaneous coronary intervention: the SYNTAX Revascularisation Index. *EuroIntervention.* 2015;11:634-42.

19. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA.* 1982;247:2543-6.

20. Brier GW. Verification of forecasts expressed in terms of probability. *Monthly Weather Review.* 1950;78:1-3.

21. Steyerberg EW, Pencina MJ. Reclassification calculations for persons with incomplete follow-up. *Ann Intern Med.* 2010;152:195-6; author reply 196-7.

22. 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; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961-72.

23. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention.* 2015;10:1024-94.

24. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2012;126:3097-137.

25. Iqbal J, Vergouwe Y, Bourantas CV, van Klaveren D, Zhang YJ, Campos CM, Garcia-Garcia HM, Morel MA, Valgimigli M, Windecker S, Steyerberg EW, Serruys PW. Predicting 3-year mortality after percutaneous coronary intervention: updated logistic clinical SYNTAX score based on patient-level data from 7 contemporary stent trials. *JACC Cardiovasc Interv.* 2014;7:464-70.

26. Gottlieb SS. Dead is dead--artificial definitions are no substitute. *Lancet.* 1997;349:662-3.

27. Campos CM, Garcia-Garcia HM, van Klaveren D, Ishibashi Y, Cho YK, Valgimigli M, Räber L, Jonker H, Onuma Y, Farooq V, Garg S, Windecker S, Morel MA, Steyerberg EW, Serruys PW. Validity of SYNTAX score II for risk stratification of

percutaneous coronary interventions: A patient-level pooled analysis of 5,433 patients enrolled in contemporary coronary stent trials. *Int J Cardiol.* 2015;187:111-5.

28. Farooq V, Serruys PW, Bourantas C, Vranckx P, Diletti R, Garcia Garcia HM, Holmes DR, Kappetein AP, Mack M, Feldman T, Morice MC, Colombo A, Morel MA, de Vries T, van Es GA, Steyerberg EW, Dawkins KD, Mohr FW, James S, Stahle E. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J.* 2012;33: 3105-13.

29. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Stahle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet.* 2013;381:639-50.

30. Campos CM, van Klaveren D, Farooq V, Simonton CA, Kappetein AP, Sabik JF 3rd, Steyerberg EW, Stone GW, Serruys PW; EXCEL Trial Investigators. Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II. *Eur Heart J.* 2015;36:1231-41.

31. Sotomi Y, Cavalcante R, van Klaveren D, Ahn JM, Lee CW, de Winter RJ, Wykrzykowska JJ, Onuma Y, Steyerberg EW, Park SJ, Serruys PW. Individual Long-Term Mortality Prediction Following Either Coronary Stenting or Bypass Surgery in Patients With Multivessel and/or Unprotected Left Main Disease: An External Validation of the SYNTAX Score II Model in the 1,480 Patients of the BEST and PRECOMBAT Randomized Controlled Trials. *JACC Cardiovasc Interv.* 2016;9:1564-72.

32. Xu B, Généreux P, Yang Y, Leon MB, Xu L, Qiao S, Wu Y, Yan H, Chen J, Zhao Y, Zhao Y, Palmerini T, Stone GW, Gao R. Validation and comparison of the long-term prognostic capability of the SYNTAX score-II among 1,528 consecutive patients who underwent left main percutaneous coronary intervention. *JACC Cardiovasc Interv.* 2014;7:1128-37.

33. de Araújo JD. [Epidemiological Polarization in Brazil]. [Article in Portuguese]. *Epidemiol. Serv. Saúde.* 2012;21:533-538. http://scielo.iec.pa.gov.br/pdf/ess/v21n4/v21n4a02.pdf

34. Kobayashi Y, Nam CW, Tonino PA, Kimura T, De Bruyne B, Pijls NH, Fearon WF; FAME Study Investigators. The Prognostic Value of Residual Coronary Stenoses After Functionally Complete Revascularization. *J Am Coll Cardiol.* 2016;67:1701-11.