A New Tool for the Risk Stratification of Patients With Complex Coronary Artery Disease
The Clinical SYNTAX Score

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Background—Presently, no effective risk model exists to predict long-term mortality or other major adverse cardiovascular and cerebrovascular events (MACCE) in those patients undergoing percutaneous coronary intervention (PCI). This study aimed to assess whether the Clinical SYNTAX Score (CSS) calculated by multiplying the SYNTAX Score to a modified ACEF score (age/ejection fraction +1 for each 10 mL the creatinine clearance <60 mL/min per 1.73 m²) would improve the ability of either score to predict mortality and MACCE.

Methods and Results—The CSS was calculated in 512 patients enrolled in the ARTS-II study who had serum creatinine levels, ejection fraction, and body weight recorded at baseline. Clinical outcomes in terms of MACCE and mortality at 1- and 5-year follow-up were stratified according to CSS tertiles: CSSLOW (n=170), 15.6<CSSTMID≤27.5 (n=171), and CSSHIGH>27.5 (n=171). At 1-year follow-up, rates of repeat revascularization and MACCE were significantly higher in the highest tertile group. At 5-year follow-up, CSSHIGH had a comparable rate of myocardial infarction, a trend toward a significantly higher rate of death, and significantly higher rates of repeat revascularization and overall MACCE compared with patients in the lower 2 tertiles. The respective C-statistics for the CSS, SYNTAX Score, and ACEF score for 5-year mortality were 0.69, 0.62, and 0.65 and for 5-year MACCE were 0.62, 0.59, and 0.57.

Conclusions—An improvement in the ability of the SYNTAX Score to predict MACCE and mortality can be achieved by combining the SYNTAX Score with a simple clinical risk score incorporating age, ejection fraction, and creatinine clearance to produce the Clinical SYNTAX score.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00235170.

Key Words: SYNTAX score • complex coronary artery disease • risk stratification

Coronary artery bypass grafting (CABG) has historically been the preferred method of revascularization in patients with complex coronary artery disease (CAD); however, recent evidence indicates that in specific groups of patients, percutaneous coronary intervention (PCI) can offer a safe and suitable alternative.1–4 This expanding use of PCI has consequently increased the importance of developing a systematic approach for risk stratifying these complex patients so that they might receive the appropriate revascularization option. The ability to objectively decide which patients with complex CAD are suitable for PCI has gained new ground recently after the introduction of the SYNTAX Score.6,7 Not only can this lesion-based scoring system quantify coronary anatomic complexity, but studies also demonstrate that it has a role in the short- and long-term risk stratification of patients undergoing PCI.8–11

Clinical Perspective on p 000

One of the limitations of using the SYNTAX Score in this context is that lesion-based scoring systems have been shown to have a lower ability to predict mortality when compared with scoring systems using clinical characteristics.12 In patients undergoing PCI, there are currently only limited data available on the use of risk scores that rely solely on clinical characteristics, such as the euroSCORE.13–15 Moreover, it has been suggested that the use of too many individual variables may reduce the overall accuracy of data.16 The recently introduced ACEF score, for example, uses just age, left ventricular ejection fraction (LVEF), and serum creatinine (Scr) and appears to be as good as more complex scores in predicting mortality in patients undergoing elective CABG.17 An acceptable modification to the ACEF score is to use the
derived creatinine clearance (CrCl) instead of SCr because this not only represents a better estimate of underlying renal function but has also been previously shown to improve the predictive accuracy of cardiac risk models such as the euroSCORE.18

The aim of this study was to investigate whether a Clinical SYNTAX Score (CSS), representing a multiplication of the SYNTAX score with a modified ACEF score (through the incorporation of CrCl), would improve the individual ability of either of these scores to predict mortality in patients with complex CAD undergoing PCI, who were enrolled in the Arterial Revascularization Therapies Study Part II (ARTS-II).

Methods

Study Population

The ARTS-II study has been published previously.19 In brief, the study was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the sirolimus eluting stent (SES) in 607 patients with de novo multivessel CAD, using the surgical group of ARTS-I as historic controls.

Patient Selection

Patients with stable angina, unstable angina, or silent ischemia, who had ≥2 coronary lesions located in different major epicardial vessels and/or their side branches (not including the left main stem [LMS]) that were potentially amenable to stent implantation, were eligible for inclusion. All patients enrolled into the ARTS-II study were required to have a lesion with a diameter stenosis >50% in the left anterior descending artery and ≥1 other major epicardial coronary artery. The goal was to achieve complete anatomical revascularization. Coronary lesions were required to be amenable to stenting using a SES with a diameter of 2.5 to 3.5 mm and length of 13 to 33 mm; there was no restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy, or stenting of side branches were left to the discretion of the operators.

The major exclusion criteria were patients with previous PCI, LMS disease, overt congestive heart failure, LVEF <30%, history of a cerebrovascular accident, transmural myocardial infarction (MI) in the preceding week, severe hepatic or renal disease, neutropenia or a cerebrovascular accident, any revascularization (percutaneous or surgical), and MI at 1- and 5-year follow-up.

Definitions

Deaths included mortality from any cause. Cerebrovascular accidents included transient ischemic attacks; reversible neurological deficits, intracranial hemorrhage, and ischemic stroke.20 MI was defined in the first 7 days after the intervention, if there was documentation of new abnormal Q waves and either a ratio of serum creatinine kinase MB (CK-MB) isoenzyme to total creatinine kinase (CK) that was ≥0.1, or a CK-MB value that was 5 times the upper limit of normal. Serum CK and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Commencing 8 days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI. An MI was only confirmed after the relevant ECGs had been analyzed by the core laboratory and adjudicated by the clinical events committee. This 2-part method of defining MI was developed for ARTS-I to address the difficulty in diagnosing an MI after cardiac surgery.21 These definitions have been adopted by the ARC Consortium and are applied whenever a comparison between PCI and coronary artery surgery is performed. In the final report, the window of 7 days is not specifically mentioned, and this window has been maintained for the sake of comparison with the historical data from ARTS-I.

Statistical Methods

All variables were stratified according to CSS tertiles. Continuous variables are expressed as mean± SD and were compared using 1-way ANOVA. Categorical data are presented as frequency (percentages) and were compared using the Fisher exact test or the Pearson χ² test. The distribution of the SYNTAX Score, ACEFSCr score, and CSS were assessed before and after logarithmic transformation using the Kolmogorov-Smirnov test. Clinical outcomes are presented as hierarchical and nonhierarchical outcomes, with the hierarchical outcome the worst outcome (following the order death, stroke, MI [Q-wave, followed by non–Q-wave], and repeat revascularization [CABG then PCI]) that the patient experiences. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates and compared by the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression analysis was used to find independent predictors of MACCE, with those variables with a probability value of <0.10 in the univariate analysis being included in the backward stepwise multivariable model. Receiver operator curves (ROC) were used to compare the performance and predictive accuracy of the CSS, SYNTAX Score, ACEFSCr, ACEFCCr, EUROADD, EUROLOG, and the SYNTAX score combined with the euroSCORE (additive and logistic) for MACCE and mortality at 5-year follow-up. A probability value of <0.05 was
considered significant, and all tests were 2-tailed. Data were analyzed with SPSS version 17.0 software (SPSS Inc, Chicago, Ill).

Results
The ARTS-II study recruited 607 patients, of whom 512 (84.3%) had 2- or 3-vessel intervention at the time of the index PCI and had LVEF, SCr, and body weight recorded at baseline. Median (interquartile range, IQR) follow-up was 1800 (IQR, 0) days. The results of analyses performed in the 239 (39.3%) patients in the ARTS-II study who had treatment for only 3VD and had LVEF, SCr, and body weight recorded at baseline are shown in the online Data Supplement.

SYNTAX, ACEFSCr, and CSS Scores
The SYNTAX Score ranged from 4 to 58, with a mean ± SD of 20.8 ± 9.6 and a median of 19 (IQR, 11.9). The ACEFSCr score ranged from 0.5 to 2.3, with a mean ± SD of 1.07 ± 0.27 and a median of 1.1 (IQR, 0.3). The CSS ranged from 4 to 209, with a mean ± SD of 27.2 ± 23.8, and a median of 20.5 (IQR, 18.7). All 3 scores were initially nonparametric (Kolmogorov-Smirnov test, *P* > 0.05) and became normally distributed after logarithmic transformation (Supplementary Figure 1).

In this post hoc analysis, the 512 patients (1645 treated lesions) were divided according to their CSS into tertiles defined as CSSLOW ≤ 15.6 (n = 170), 15.6 < CSSMID ≤ 27.5 (n = 171), and CSSHIGH > 27.5 (n = 171).

Baseline Angiographic and Procedural Characteristics
Baseline angiographic and procedural characteristics of the study population, stratified according to CSS tertiles, are shown in Tables 1 and 2. Patient age and hypertension were both significantly higher in the CSSHIGH tertile, whereas body mass index, family history of CAD, current smoking, and CrCl were all significantly lower in the CSSHIGH. Table 2 demonstrates that indicators of lesion complexity, such as lesion length and lesion type, were significantly greater in the CSSHIGH tertile, reflecting the higher calculated SYNTAX Score for these lesions.

Outcomes at 12 Months
Hierarchical and nonhierarchical clinical outcomes at 12 months are shown in Table 3. Overall the primary end point of mortality was comparable among each CSS tertile. MACCE (18.7% CSSHIGH versus 7.6% CSSMID versus 6.5% CSSLOW, *P* = 0.001) and repeat revascularization (15.8% CSSHIGH versus 6.4% CSSMID versus 5.3% CSSLOW, *P* = 0.002) were both significantly higher in the CSSHIGH tertile, compared with the lower 2 groups.

Long-Term Outcomes
Figure 1 demonstrates the rates of death, MI, repeat revascularization, and MACCE according to CSS tertiles during...
There were no significant differences in events (death/MI/repeat revascularization/MACCE) between patients in the low and mid CSS tertiles. Patients in the CSSHIGH tertile had significantly higher rates of repeat revascularization and MACCE when compared with the lower 2 tertiles. In addition, mortality was significantly higher with CSSHIGH compared with CSSLOW, whereas the rate of MI was comparable for all 3 groups.

### Multivariable Analysis

The results of the Cox multivariable analysis are shown in Table 4. The log CSS, log SYNTAX Score, and log ACEFScr score were all univariate predictors of long-term MACCE. After multivariable adjustment, the independent predictors of MACCE at 5-year follow-up were the log CSS and the presence of incomplete revascularization, diabetes, or peripheral vascular disease.

### CSS Versus SYNTAX Score Versus ACEFScr

The ROC curves for mortality and MACCE at 5-year follow-up are shown in Figure 2. The respective C-statistics for the CSS, SYNTAX Score, and ACEFScr score for 5-year mortality were 0.69, 0.62, and 0.65 and for 5-year MACCE were 0.62, 0.59, and 057 (P<0.05 for all).

### CSS Versus MCRS Versus EUROADD Versus EUROLOG

The Kaplan-Meier curves for 5-year mortality and MACCE-free survival stratified according to tertiles of the CSS, MCRS, EUROADD, and EUROLOG are shown in Figure 3. Overall, there were no significant differences between corresponding tertiles for the CSS, MCRS, EUROADD, and EUROLOG. For each score, patient mortality and MACCE among those in the lowest tertile were significantly better than those in the highest tertile and comparable with the intermediate tertile. A significant difference in mortality was observed between the intermediate and highest tertile with the use of the MCRS and EUROADD but not the EUROLOG or CSS. Conversely, the significant difference in MACCE between the intermediate and highest tertile observed with the CSS was not observed with the other 3 scores.

The ROC curves for mortality and MACCE at 5-year follow-up for the CSSCrCl, CSSScr, ACEFCrCl, SYNTAX score, MCRS, EUROADD, EUROLOG, and SYNTAX score combined with the euroSCORE (additive and logistic) are shown in Figure 4, and Table 5.

The results of these analyses performed specifically in patients with 3VD can all be found in the online Data Supplement.
Discussion

To the best of our knowledge, this is the first description of the CSS that represents a risk score combining both clinical and angiographic variables. The main findings from this study are that the CSS has an ability superior to either the SYNTAX Score or ACEFScr score alone in the prediction of MACCE and mortality at 5-year follow-up in patients with complex CAD undergoing PCI. Furthermore, the log CSS is an independent predictor of long-term MACCE in this group of patients.

Risk stratification and the assessment of risk-benefit are 2 important aspects of clinical medicine, and should form an integral part of the patient informed consent process. Technological advances mean that the majority of coronary lesions are amendable to PCI; however, this may not always be the most appropriate treatment for an individual patient. The final decision of whether to perform PCI or CABG in patients with complex CAD is no longer simply based only on the views of the interventional cardiologist and cardiac surgeon; patient choice now plays an important part in the decision. Consequently, to enable patients to make the most appropriate informed decision for them as an individual, a suitable method of quantifying risk is essential. The importance of risk stratification in these patients is further emphasized when considering the escalating complexity of CAD being treated with PCI and the increasing age of patients undergoing PCI. The recently introduced SYNTAX Score offers the potential to meet this unmet clinical need.

The SYNTAX Score is derived entirely from the coronary anatomy and lesion characteristics and is calculated using dedicated software, enabling complex coronary artery anatomy to be quantified. The score, which was an integral part of the SYNTAX trial design, was initially devised as a method to ensure that both the cardiologist and cardiac surgeon accurately reviewed the angiogram of patients with complex CAD, enabling a consensus regarding the optimal method and completeness of revascularization to be reached. Importantly, the SYNTAX Score was calculated a priori, before the outcome of revascularization was known. The results of the SYNTAX trial have subsequently demonstrated that the score has an important role in stratifying patients with complex CAD to aid revascularization decisions. Further evaluation of the score has also indicated its ability to predict clinical outcomes. In patients with 3VD, the SYNTAX Score has been shown to be an independent predictor of MACCE at both 1-year and 5-year follow-up. Similarly, in patients with LMS disease, Capodanno et al reported that the SYNTAX Score was able to predict both cardiac death (P<0.001) and MACCE (P=0.04) at short-term follow-up. More recently, analysis of SYNTAX scores collected prospectively in the LEADERS study and retrospectively in the SIRTA study indicates that risk stratification using the SYNTAX Score can be expanded to include all patients with CAD, irrespective of severity.

The SYNTAX Score is independent of a patient’s clinical characteristics, some of which, for example, patient age, have been consistently shown to be an independent predictor of mortality. Furthermore, previous studies have demonstrated the superior performance of clinical based risk models, such as the MCRS, in the prediction of morbidity and mortality when compared with lesion-based scores such as the Amer-
Therefore, the absence of any clinical characteristics in the calculation of the SYNTAX Score is a potential limitation to its use in risk stratification. The CSS described in the present study for the first time represents a modification of the SYNTAX Score to accommodate for these inherent limitations. The present study has indicated that the inclusion of patient characteristics does

### Table 4. Univariate and Multivariable Predictors of MACCE at 5-Year Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Predictors of MACCE at 5 Years</th>
<th>Multivariable Predictors of MACCE at 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[95% CI]</td>
<td>[95% CI]</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 [1.00–1.04]</td>
<td>1.55 [1.09–2.19]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.80 [1.28–2.54]</td>
<td>1.97 [1.14–3.41]</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.01 [1.18–3.44]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log ACEF</td>
<td>7.11 [1.56–32.45]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log clinical SYNTAX score</td>
<td>1.81 [1.42–2.29]</td>
<td>1.77 [1.02–3.07]</td>
</tr>
<tr>
<td>No. of diseased lesions</td>
<td>1.43 [1.17–1.73]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incomplete revascularization</td>
<td>1.56 [1.12–2.17]</td>
<td>1.43 [1.01–2.02]</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
improve the ability of the score, as indicated by the ROC curves, to predict MACCE and mortality compared with the original score.

Intuitively, the use of multiple clinical variables should improve the accuracy of a risk model; however, this accuracy may ultimately be contaminated by the desire to create the “perfect model.” In practice, Ranucci et al illustrated this by demonstrating that a simple scoring method using just age, LVEF, and SCr (ACEFSCr score) is as good as complex scores such as the euroSCORE (17 clinical variables) and Parsonnet score in predicting mortality in patients undergoing elective CABG. These 3 variables are known to affect the risk of both CABG and PCI; and therefore even though the score has not previously been validated in patients undergoing PCI, it was considered acceptable to use as a basis for the development of the CSS. Retrospective justification for using the ACEF score as an integral part of the CSS come in part from the comparable C-statistics for MACCE and mortality between the validated MCRS and the ACEFSCr (Table 5, Figure 4, and Supplementary Figure 2). Of note, the combination of the SYNTAX score with the euroSCORE only offered an advantage over the CSS in the prediction of mortality among those patients with 2- and 3VD (Table 5, Figure 4, and Supplementary Figures 2 and 3).

Figure 2. ROC curve for the SYNTAX score, ACEFSCr, and CSS for mortality (A) and MACCE (B). The use of the CSS leads to an improvement in the C-statistic for both outcomes.

![Figure 2](image)

**Table 5.** Area under the curve (95% CI) and P Value

<table>
<thead>
<tr>
<th>Score</th>
<th>Area under the curve (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTAX score</td>
<td>0.62 [0.62-0.73]</td>
<td>0.03</td>
</tr>
<tr>
<td>ACEFSCr score</td>
<td>0.65 [0.54-0.76]</td>
<td>0.007</td>
</tr>
<tr>
<td>CSS</td>
<td>0.69 [0.56-0.80]</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier curve showing the 5-year mortality (A) and MACCE-free survival (B) stratified according to tertiles of the CSS, Mayo Clinic Risk Score (MCRS), Additive euroSCORE (EUROADD) and Logistic euroSCORE (EUROLOG). No significant difference was observed between outcomes in Tertiles 1 and 2 (probability values not shown). *P (log-rank) values.

![Figure 3](image)
The modification to the ACEF score to incorporate CrCl has also not previously been validated. Notably, in previous PCI studies that have identified renal dysfunction as a marker of adverse outcome either SCr or CrCl has been used, not both.\(^3\) Conversely, CrCl has been shown to be a better predictor when compared with SCr of risk in patients undergoing surgical revascularization.\(^1\) Incorporation of CrCl into the ACEF score can therefore be justified prospectively by extrapolation of these previous results and retrospectively by the improvements in the C-statistic for MACCE (0.60 versus 0.62) and mortality (0.67 versus 0.69) observed in this study when the CSS was calculated using the ACEF\(_{\text{CrCl}}\) instead of ACEF\(_{\text{SCr}}\) (Figure 4 and Table 5).

This study demonstrates a superior ability of the CSS to predict long-term MACCE and mortality when compared with the individual SYNTAX and ACEF scores. Importantly, after calculating the SYNTAX Score, which remains an important aid to deciding the appropriate revascularization strategy, the CSS can be derived quickly, using easily available variables that are not subject to any interobserver

### Table 5. Comparison of C-Statistics Between 3VD and 2VD/3VD Patient Cohorts

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Mortality</th>
<th>MACCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2VD and 3VD (512 Patients)</td>
<td>2VD and 3VD (512 Patients)</td>
</tr>
<tr>
<td>ACEF, creatinine clearance</td>
<td>0.69</td>
<td>0.60</td>
</tr>
<tr>
<td>ACEF, serum creatinine</td>
<td>0.65</td>
<td>0.57</td>
</tr>
<tr>
<td>Clinical SYNTAX score, creatinine clearance</td>
<td>0.69</td>
<td>0.62</td>
</tr>
<tr>
<td>Clinical SYNTAX score, serum creatinine</td>
<td>0.67</td>
<td>0.60</td>
</tr>
<tr>
<td>euroSCORE, additive</td>
<td>0.71</td>
<td>0.57</td>
</tr>
<tr>
<td>euroSCORE, logistic</td>
<td>0.73</td>
<td>0.57</td>
</tr>
<tr>
<td>Mayo Clinic Risk Score</td>
<td>0.71</td>
<td>0.59</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>0.62</td>
<td>0.59</td>
</tr>
<tr>
<td>SYNTAX-euroSCORE, additive</td>
<td>0.71</td>
<td>0.60</td>
</tr>
<tr>
<td>SYNTAX-euroSCORE, logistic</td>
<td>0.73</td>
<td>0.61</td>
</tr>
</tbody>
</table>
variability. The current analysis also indicates that whereas the CSS has a similar ability to predict mortality when compared with the MCRS and euroSCORE, it offers an additional advantage in the prediction of ischemic end points, which, as suggested by the C-statistics, are a somewhat harder end point to predict than mortality. Clearly, additional research is required to evaluate the potential of this new score in more diverse patient populations undergoing PCI.

Limitations
The current study is limited by its post hoc nature. In addition, the ROC method of analysis, although well suited for diagnostic purposes, may not be appropriate for prognostic models because these models must incorporate the dimension of time, which adds a stochastic element.14 It has therefore been suggested that ROC analysis methods are not well validated for the assessment of time-censored data; however, in the current study the same methods have been used to assess both scoring systems, and these methods are consistent with previous published studies evaluating these risk models.17

Other potential limitations include that lack of validation of the ACEF score in patients having PCI and the lack of any external validation in patients having either PCI or CABG. We accept that the current population may be too small to make definitive conclusions; however, at present, in view of its recent introduction, only select patient populations with complex disease have a SYNTAX score calculation and adjudicated long-term outcomes. The small sample size may account for the similar outcomes between low- and intermediate-risk groups when using the CSS, MCRS, EUROADD, EUROLOG, SYNTAX-euroSCORE (logistic), and MCRS (Figures 1 and 3 and Supplementary Figures 3 and 4). It must also be acknowledged that there is a reduction in the predictive ability of the CSS when it is used in patients with 2VD and 3VD, as opposed to when it is used in only patients with 3VD. Importantly, however, this same observation is seen with both the established scores such as the MCRS and 2VD and 3VD, as opposed to when it is used in only patients with complex coronary artery disease: triple vessel disease or left main coronary artery disease. Yes? No? Don’t Know? Rev Esp Cardiol. 2009;62:719–725.


Conclusion
An improvement in the ability of the SYNTAX Score to predict MACCE and mortality can be achieved by combining the SYNTAX Score with a simple clinical risk score incorporating age, ejection fraction, and creatinine clearance to produce the Clinical SYNTAX Score.

Disclosures
Dr Dawkins is a full-time employee and holds stock in Boston Scientific.

References


