Beyond the SYNTAX Score
– Advantages and Limitations of Other Risk Assessment Systems in Left Main Percutaneous Coronary Intervention –
Davide Capodanno, MD, PhD

Risk stratification is an emerging topic in the modern management of patients with left main disease referred for percutaneous coronary intervention (PCI). Recent years have witnessed an explosive multiplication of risk models for prognostic stratification in complex PCI. Many of this models deal with modification of the angiographic SYNTAX score, or seek to overcome its known pitfalls and limitations, including lack of clinical and functional information, inter- and intra-observer variabilities, and poor calibration. Risk scoring systems beyond the SYNTAX score may be classified into angiographic (residual SYNTAX score, coronary artery bypass grafting SYNTAX score), clinical (EuroSCORE I and II, ACEF score and modified ACEF scores), combined clinical and angiographic (Global Risk Classification, Clinical SYNTAX score, logistic Clinical SYNTAX score, SYNTAX score II) and functional (Functional SYNTAX score). This article reviews current concepts in risk modeling and explores the advantages and limitations of the alternatives to the SYNTAX score in patients undergoing left main PCI. (Circ J 2013; 77: 1131–1138)

Key Words: Left main disease; Risk scores; Risk stratification

A Primer on Assessing the Performance of a Risk Model

Unlike diagnostic models, prognostic models are intrinsically limited by their stochastic and time-dependent nature, thereby making risk stratification more difficult than diagnosis. The best result that can be achieved from prognostic modeling is generally to estimate the risk of future events, classify patients into risk categories and compare treatment modalities within different classes of risk. Ideally, a risk model should feature well-defined characteristics, including prognostic accuracy (Figure 1). Although the statistical performance of a score is a key characteristic in evaluating its validity, a score is not really useful if it does not predict accurately enough for its clinical purpose. Indeed, although statistical invalidity is something that can be remedied, clinical invalidity cannot.

Table 2 lists a series of statistical parameters that characterize the performance of a score. The Brier score is a measure of overall performance that was initially proposed in the 1950s as a means of verifying weather forecasts in terms of probability. It consists only of positive values ranging from 0 (perfect

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Cardiothoracic-Vascular Department, Ferrarotto Hospital, University of Catania, Catania, Italy
Mailing address: Davide Capodanno, MD, PhD, Cardiothoracic-Vascular Department, Ferrarotto Hospital, University of Catania, via Citelli 6, 95124 Catania, Italy. E-mail: dcapodanno@gmail.com
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for individuals with events and the other for individuals without events. For events, +1 is assigned for upward reclassification, –1 for downward and 0 for subjects who do not change their risk category, with the opposite done for non-events. The individual scores are then summed and divided by the number of people in each group. Finally, beyond working properly in a certain population, a risk score must work reasonably in different and/or plausibly related settings. This step, named “validation”, includes a hierarchy of increasingly stringent modalities: (1) internal validation, where derivation and validation procedures are restricted to a single data set; (2) temporal validation, where evaluation is performed on a second data set from the same center; and (3) external validation, where evaluation is performed on data from one or more other centers. External validation offers the best assurance of the reliability of a model.

The SYNTAX Score: Strengths and Weaknesses

The SYNTAX score was introduced in 2005 as a way to facilitate the currently recommended “Heart Team approach” within the landmark SYNTAX trial. By calculating the SYNTAX score, investigators were forced to review the coronary angiogram in detail before making any decision on whether the patients could be randomized, including precise assessment of each lesion ≥50% located in vessels ≥1.5 mm. Ideally, a team of 3 persons should compute the SYNTAX score, with the primary focus on coronary anatomy, which includes defining the coronary dominance and characterizing the presence and features of chronic total occlusions, trifurcations, bifurcations, aorto-ostial lesions, severe tortuosity, long lesions, heavy calcification, thrombus and/or diffuse disease. Several studies have suggested that in ULMCA disease the SYNTAX score carries a significant prognostic role, with higher SYNTAX scores associated with higher burden of long-term mortality and ischemic adverse events in patients undergoing PCI.

The final 5-year results of the SYNTAX trial have confirmed that the SYNTAX score is not only a valid tool for estimating the inherent risk associated with PCI, but also an effective aid in selecting the category of patients with lower burden of coronary artery disease whose outcomes with PCI could be similar, or even numerically superior, to CABG. Whether this concept applies to patients with SYNTAX score ≤32 is the subject of an ongoing large-scale randomized trial (NCT01205776).

Interestingly, current guidelines suggest that a clinical equipoise between PCI and CABG is possible in ULMCA disease when the SYNTAX score is ≤32, whether a lower threshold for referring a patient to CABG (>22) is recommended in the case of multivessel disease. This is likely because among...
Risk Stratification of ULMCA

From a statistical standpoint, the SYNTAX score has been associated with acceptable discrimination for cardiac mortality and major adverse cardiac events (MACE). However, it can suffer from poor calibration, with intermediate predictions that systematically do not correspond to observations. Finally, the SYNTAX score lacks clinical or ischemia information, and it does not account for presentations commonly seen in daily cath-lab routine, such as in-stent restenosis, bypass grafts or less common presentations such as coronary aneurysms, congenital anomalies, and muscular bridges. Some of these limitations have been recently addressed, as noted later.

Other Angiographic Models Based on the SYNTAX Score

The CABG SYNTAX score, a modification of the SYNTAX score, has been recently introduced. Essentially, it is the SYNTAX score of the native coronary vessels with points deducted based on the vessel-segment weighting of the bypassed coronary vessel. In such a way, it allows for a feasible and plausible calculation of the SYNTAX score in patients with prior CABG, and for the incorporation of CABG patients into contemporary trials measuring coronary complexity. On the dedication of the reader.
The residual SYNTAX score (rSS) is calculated as the SYNTAX score of lesions left untreated after a revascularization procedure, as described by Genereux et al. A criticism of the traditional methods for defining complete revascularization is that they do not take into account the relative role of each coronary artery in supplying the left ventricle. Against this background, the rSS was conceived and used as a standardized quantitative measure of incomplete revascularization after ULMCA PCI, with potentially important and practical prognostic implications. In patients with incomplete revascularization, for example, a cut-off of rSS=8 has been suggested to separate the outcomes of patients at higher risk of future events and those at lower risk, but prospective validation is necessary. In the CUSTOMIZE registry of 400 patients undergoing ULMCA PCI, the baseline SYNTAX score and the rSS were linearly related (R²=0.73, P<0.001) but approximately 33% of patients were assigned to different categories of risk on the basis of the 2 models. In terms of cardiac mortality at 2 years, the rSS was associated with similar discrimination compared with the baseline SYNTAX score, but better calibration. Intriguingly, the difference between the baseline SYNTAX score and the rSS, which may be considered an indirect quantification of the extent of PCI, was not significantly associated with cardiac mortality (Figure 2). Possible explanations for this finding include that the anticipated benefit of an extensive revascularization (ie, >5 stents) may be counterbalanced by PCI complications, especially when stents are placed on non-ischemia-producing lesions (ie, acute kidney injury, periprocedural myocardial infarction, stent thrombosis, restenosis). In addition, subsets typically represented in the highest tertiles of rSS may not be ideal candidates to PCI (ie, chronic total occlusions, calcified lesions, complex bifurcations and trifurcations, small vessels). Repeating the risk assessment in the peri-PCI period (ie, calculating both the baseline SYNTAX score and the rSS to define new classes of risk) was found to improve prediction, compared with a single risk assessment, and accurately reclassified a proportion of patients into more appropriate risk categories (NRI=14%).

### Clinical Risk Scores for ULMCA Disease

The Parsonnet score is an operative model consisting of 14 clinical variables that was shown to significantly predict ischemic outcomes after ULMCA revascularization in multiple registries, not merely limited to CABG. The EuroSCORE (European System for Cardiac Operative Risk Evaluation) was originally intended to be a risk calculator of predicted operative mortality in the setting of cardiac surgery. The score was derived and validated in a dataset of nearly 20,000 consecutive patients from 128 hospitals in 8 European countries. The most important and reliable predictive patient-, cardiac- and procedure-related factors of operative mortality were combined to prepare the scoring system, which proved subsequently to be highly transportable and valid elsewhere. The EuroSCORE is available in 2 versions: (1) logistic, where clinical variables enter a complex logistic formula for the estimation of percent predicted mortality or (2) additive, an approximation to the logistic formula easier to use at the bedside, where a weight or number is assigned to each risk factor present in the patient. Both models are now well established and have been validated in many populations across different countries and local realities. In very high-risk patients, the simpler additive model was found to underestimate the risk when certain combinations of variables coexist. Recently, an updated version of the logistic EuroSCORE derived from a more contemporary dataset was launched. The new model, dubbed EuroSCORE II, has been preliminarily validated by the EuroSCORE Project Group and awaits further validation by users worldwide. Because many factors included in the EuroSCORE are also established predictors of early and long-term cardiac mortal-
ity, regardless of the treatment received, it is intuitive that such a model may also work well in the context of PCI. In a study by Romagnoli et al, the EuroSCORE was prospectively and systematically assessed in 1,173 patients undergoing PCI, showing consistency in predicting in-hospital mortality across many subgroups and levels of risk.54 In ULMCA PCI, the EuroSCORE has been proven to be associated with good discrimination for early and moderate discrimination for long-term cardiac mortality.55,56 Whether the new EuroSCORE II will further improve the prognostic ability of the EuroSCORE in ULMCA PCI is currently unexplored.

Based on the “law of parsimony” or “Occam’s razor”, the ACEF score comprises only 3 variables (age, creatinine, ejection fraction) and deliberately excludes some of the confounders that could bias the other clinical scores. Because the number of variables that can be included in a multivariable analysis depends on the number of events (with a ratio of 10 events for each independent variable), this simplified approach is ideally transportable across sites with different case-mixes and event rates. In the context of ULMCA PCI, the ACEF score was found to have a good calibration, but its discrimination did not exceed significantly that of the EuroSCORE for predicting long-term cardiac mortality, and was lower than that of the SYNTAX score (Figure 3).55 A theoretical caveat of the ACEF score is the inclusion of preoperative renal dysfunction as a mortality risk factor only in a range higher than 2.0 mg/dl. Interestingly, the use of creatinine clearance or glomerular filtration rate as a semicontinuous variable in the so-called “modified ACEF score” was found to increase the accuracy of the model, although estimating serum creatinine clearance according to the MDRD (Modification of Diet in Renal Disease) or Cockcroft-Gault equations may introduce a mathematical coupling and a colinearity bias into the ACEF risk model, because age is counted twice (first alone, and secondly within the MDRD and Cockcroft-Gault equations).57,58

From a theoretical standpoint, the EuroSCORE and ACEF score might be not as useful as the SYNTAX score in decision making. In fact, although the SYNTAX score significantly stratifies the outcomes of patients undergoing PCI, its efficacy is suboptimal in patients undergoing CABG, because CABG bypasses the lesion and is less sensitive to the complexity of coronary artery disease than PCI.56 Given this premise, an angiographic score such as the SYNTAX score will likely be associated with significant differences between PCI and CABG as far as the score category increases, thereby being helpful in deciding the appropriate revascularization procedure. Differently, scores including clinical variables may optimally stratify the outcomes of both PCI and CABG, thereby lowering their ability to display differences between the 2 revascularization procedures in any of the increasing risk strata.

### SYNTAX Score Combined With Clinical Risk Models for ULMCA PCI

Being solely based on angiographic variables, the SYNTAX score cannot account for interindividual variability related to the clinical factors that are widely acknowledged to effect long-term outcomes of PCI, such as age, renal impairment or cardiogenic shock. On the other hand, clinical risk scores cannot account for PCI-related outcomes that are inherently linked to angiographic complexity at presentation. In a series of 255 patients undergoing ULMCA PCI, there was a weak, yet significant, linear relationship between the EuroSCORE and the SYNTAX score (R²=0.201, P=0.001), indicating that the 2 models, although with some areas of overlap, also include different and possibly complementary information.55,56 This notion corroborates the rationale for clinical and angiographic scores to be merged into a single classification system (Table 3).

The Global Risk Classification (GRC) is a combined scheme encompassing different strata of the EuroSCORE and SYNTAX score.55 The GRC was found to refine the prognostic ability of the EuroSCORE and the SYNTAX score taken in isolation and led to NRI of ~25% of patients undergoing ULMCA PCI into more coherent risk categories.55,56,59 In a recent validation study, Serruys et al60 investigated the ability of the GRC to improve the identification of low-risk patients with ULMCA or 3-vessel disease who would achieve comparable 3-year outcomes between PCI and CABG. In their pooled analysis of ULMCA patients with low GRC undergoing revascularization by either revascularization modality in the SYNTAX trial (n=701), CABG resulted in significantly higher 3-year mortality compared with PCI (7.5% vs. 1.2%, P=0.0054).

Incremental value in the addition of clinical variables to the SYNTAX score model was confirmed by Garg et al, who described the Clinical SYNTAX Score (CSS) as a multiplication of the SYNTAX and ACEF scores.57 In a head-to-head comparison of the GRC and the CSS in ULMCA PCI, ~33% of patients were differently categorized on the basis of the 2 models.60 The cumulative incidences of 2-year cardiac mortality were 0.6%, 8.7%, and 24.2% in the low-, intermediate- and high-risk GRC groups (P<0.001), and 2.6%, 1.0%, and 25.6% in the low-, intermediate- and high-risk CSS groups (P<0.001), respectively. Table

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of variables</th>
<th>Validated outcomes in ULMCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Risk Classification</td>
<td>17</td>
<td>Clinical Angiographic Cardiac death after PCI at 2-year follow up (CUSTOMIZE registry)66 All-cause death after PCI at 3-year follow up (SYNTAX trial ULMCA cohort)59</td>
</tr>
<tr>
<td>Clinical SYNTAX score</td>
<td>3</td>
<td>11 (per lesion)</td>
</tr>
<tr>
<td>Logistic clinical SYNTAX score (core model)</td>
<td>3</td>
<td>11 (per lesion)+1 (SYNTAX-like patient)</td>
</tr>
<tr>
<td>Logistic clinical SYNTAX score (extended model)</td>
<td>11</td>
<td>11 (per lesion)+1 (SYNTAX-like patient)</td>
</tr>
<tr>
<td>SYNTAX score II</td>
<td>6</td>
<td>11 (per lesion)+1 (ULMCA lesion)</td>
</tr>
</tbody>
</table>

MACCE, Major adverse cardiac and cerebrovascular events. Other abbreviations as in Table 1.
respectively. Both combined risk models were associated with superior discrimination compared with other stand-alone tools, including the ACEF score, the EuroSCORE and the SYNTAX score in isolation, but the CSS was associated with lower calibration than the GRC, and the estimates of risk in the low and intermediate CSS groups were not in the anticipated order. There is, therefore, some evidence that the GRC could be associated with the best balance in terms of discrimination and calibration for hard clinical outcomes after ULMCA PCI. 56,60

A method of improving the clinical applicability of the CSS has been recently proposed. 61 The logistic CSS has the theoretical advantage of providing an estimate of risk at the individual level instead of stratifying patients into risk categories. 16 To fulfill this aim, a logistic formula was developed, complemented by an additive version to simplify its calculation into daily practice. Formal external validation of the logistic CSS in the setting of ULMCA PCI, however, is necessary, and whether the additive and logistic versions have similar performances within all classes of risk remains uncertain.

The SYNTAX score II is another evolution of the SYNTAX score incorporating clinical predictors and taking an individualized approach to risk stratification, which enables a direct comparison of long-term estimates of mortality for patients with ULMCA or 3-vessel disease referred for PCI or CABG. 62 Similar to the logistic CSS, the rationale behind the development of the SYNTAX score II is the notion that categorical models such as the SYNTAX score may hide lower risk patients in the higher SYNTAX score groups, and vice versa. The SYNTAX score II displayed superior discrimination (c statistic 0.72) than the SYNTAX score and was externally validated. 62 A nomogram is available that allows for prediction of 4-year mortality in ULMCA or 3-vessel disease patients referred to PCI or CABG, and other website disseminates.

**Functional Scores**

PCI of a functionally nonsignificant stenosis is not beneficial to the patient, either from a prognostic or a symptomatic point of view. 63,64 The Functional SYNTAX score (FSS) has been introduced as the SYNTAX score of only ischemia-producing lesions with fractional flow reserve (FFR) ≤ 0.80. 65 This approach was found to decrease the number of higher-risk patients classified according to the traditional SYNTAX score-based approach and to better discriminate the risk for 1-year MACE in patients undergoing PCI for multivessel disease (Figure 4). 65 Adding to the incorporation of functional information, the FSS has the theoretical advantage of improving the reproducibility of the SYNTAX score because there is less chance for disagreement. On the downside, the FSS has been retrospectively validated in low-risk coronary artery disease, and no validation in ULMCA PCI is presently available. In addition, performing the FFR of all intermediate lesions beyond the ULMCA adds complexity and costs compared with calculation of the SYNTAX score. In this regard, the modification of the residual SYNTAX score into a so-called “residual FSS” is a working hypothesis that warrants further investigation as a standardized measure of the emerging concept of “reasonably incomplete revascularization”.

Calculation of noninvasive FFR derived from coronary computed tomography angiography has been proven to achieve high diagnostic performance for the detection and exclusion of coronary lesions that cause ischemia. 66 The availability and future implementation of this technology may create the premises for calculating a noninvasive FSS, as speculated by Serruys et al. 67

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**Figure 4.** Prognostic accuracy of the functional SYNTAX score (FSS) in the FAME trial. 65 AUC, area under the receiver-operating characteristic curve (see text for details); MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization. (Adapted from Nam et al with permission. 65)
Conclusions

Risk stratification in ULMCA disease aims to govern the unpredictability of random variation, but cannot be used as a substitute for clinical judgment and Heart Team consensus on a case-by-case basis. A wide array of risk scoring systems beyond the SYNTAX score is currently available for prognostic stratification or individual risk assessment in patients with ULMCA disease. It is the author’s view that risk estimation and classification in this scenario are best achieved by integrating clinical, angiographic and functional information. Indeed, with the multiplication of risk scoring systems and modifications of existing models, head-to-head comparisons in large prospective series and standardization by expert consensus of each score’s characteristics (ie, definitions, cut-offs, outcomes to be predicted, timing to outcome prediction) are required to identify which model fits best with the clinical needs specific to ULMCA intervention.

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Circulation Journal 2011; 4: 553–564.


