Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease
– Analysis of CREDO-Kyoto Registry –

Carlos M. Campos, MD; David van Klaveren; Javaid Iqbal, MD, PhD; Yoshinobu Onuma, MD, PhD; Yao-Jun Zhang, MD, PhD; Hector M. Garcia-Garcia, MD, PhD; Marie-Angele Morel, BSc; Vasim Farooq, MD, PhD; Hiroki Shiomii, MD; Yutaka Furukawa, MD; Yoshihisa Nakagawa, MD; Kazushige Kadota, MD; Pedro A. Lemos, MD, PhD; Takeshi Kimura, MD; Ewout W. Steyerberg, PhD; Patrick W. Serruys, MD, PhD

Background: SYNTAX score II (SSII) provides individualized estimates of 4-year mortality after coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in order to facilitate decision-making between these revascularization methods. The purpose of the present study was to assess SSII in a real-world multicenter registry with distinct regional and epidemiological characteristics.

Methods and Results: Long-term mortality was analyzed in 3,896 patients undergoing PCI (n=2,190) or CABG (n=1,796) from the Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2. SSII discriminated well in both CABG and PCI patient groups (concordance index [c-index], 0.70; 95% CI: 0.68–0.72; and 0.75, 95% CI: 0.72–0.78) surpassing anatomical SYNTAX score (SS; c-index, 0.50; 95% CI: 0.47–0.53; and 0.59, 95% CI: 0.57–0.61). SSII had the best discriminative ability to separate low-, medium- and high-risk tertiles, and calibration plots showed good predictive performance for CABG and PCI groups. Use of anatomical SS as a reference improved the overall reclassification provided by SSII, with a net reclassification index of 0.5 (P<0.01).

Conclusions: SSII has robust prognostic accuracy, both in CABG and in PCI patient groups and, compared with the anatomical SS alone, was more accurate in stratifying patients for late mortality in a real-world complex coronary artery disease Eastern population. (Circ J 2014; 78: 1942–1949)

Key Words: Coronary artery bypass grafting; Percutaneous coronary intervention; Risk stratification; SYNTAX score; SYNTAX score II

Percutaneous coronary intervention (PCI), until recently, has been considered a class III indication (ie, potentially harmful) for patients with unprotected left main (ULMCA) and 3-vessel coronary artery disease (CAD). Coronary artery bypass grafting (CABG) has been the standard treatment for these patients with complex CAD for more than 50 years. Over the last decade, PCI has undergone a number of technical and technological advancements and hence has challenged the superiority of CABG. Consequently, every advancement in PCI technology has been scrutinized and compared against CABG, generating debate as to whether a patient should be referred to CABG or PCI, with advantages for one or the other depending on context. Therefore, the accurate risk estimation of multivessel CAD remains a fundamental step in the decision-making process.

Editorial p1832
Presently, for patients with ULMCA or complex CAD, the prevailing guidelines recommend a multidisciplinary approach referred to as the heart team. These guidelines also advise the heart team to use synergy between PCI with taxus and cardiac surgery (SYNTAX) score alone or combined with the Society of Thoracic Surgeons (STS) score as a tool to make an objective risk stratification. The SYNTAX score II (SSII) has been recently developed by applying a Cox proportional hazards model to the results of the SYNTAX trial, obtaining a combination of clinical and anatomical predictors. Given that the SSII has been derived from an all-comers randomized trial of PCI vs. CABG, it has the potential to assess individual risk estimation between these revascularization strategies and facilitate multidisciplinary decision-making.

SSII has been shown to provide reliable predictions of 4-year mortality for complex CAD in an external validation of the Drug Eluting stent for LefT main coronary Artery disease (DELTA) registry. The DELTA registry consisted of predominantly Western patients with ULMCA disease. In patients with 3-vessel disease and no left main involvement, however, SYNTAX score (SS) would represent more complex downstream coronary anatomical disease. This may be a signal of a more adverse risk profile, in patients who have evidence of systemic atherosclerosis and therefore are at greater long-term cardiovascular risk.

The purpose of the present study was therefore to assess SSII in patients with 3-vessel and/or ULMCA disease in a real-world multicenter registry with distinct regional and epidemiological characteristics.

**Methods**

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG registry cohort-2 has been previously described in detail. Briefly, this was a physician-initiated non-industry-sponsored multicenter registry enrolling consecutive patients undergoing first coronary revascularization among 26 centers in Japan between January 2005.
and December 2007. The relevant ethics committees in all participating centers approved the research protocol. Because of retrospective enrolment, written informed consent from the patients was waived, excluding those patients who refused participation in the study when contacted for follow-up.

Among 15,939 patients enrolled in the registry, 3,986 participants had 3-vessel and/or ULMCA and were included in current analyses.

**SSII**

The SSII has been described in detail previously. Briefly, SSII uses the 2 anatomical variables (anatomical SS and ULMCA disease) and 6 clinical variables (age, creatinine clearance, left ventricular ejection fraction [LVEF], sex, chronic obstructive pulmonary disease, and peripheral vascular disease) to predict 4-year mortality after revascularization with CABG or PCI.

For the present study, SSII was calculated using a nomogram, with scores assigned for the presence and magnitude of each predictor directly based on the Cox proportional hazards model coefficients (Figure 1), generating different scores for PCI and CABG. The 4-year mortality estimates were obtained in accordance with the revascularization procedure that each patient underwent: PCI or CABG.

**Statistical Analysis**

Categorical variables are presented as numbers and percentages and were compared using the chi-squared test. Continuous variables are expressed as mean±SD or median with interquartile range (IQR), and were compared using Student’s t-test or Wilcoxon rank-sum test based on their distributions.

SSII predictor data were all present in at least 90% of the patients. Multiple imputation (5×) of missing data was undertaken using an imputation strategy that takes into account the correlation between all potential predictors. To obtain 4-year mortality predictions based on anatomical SS alone, Cox logistic regression analysis was used with anatomical SS as a sole linear predictor.

SSII for PCI (in patients undergoing PCI) and for CABG (in patients undergoing CABG) was evaluated using 4 metrics: c-statistics; calibration plots; reclassification tables; and net reclassification index (NRI). Outcome was analyzed using Kaplan-Meier curves with a 4-year time horizon. Discrimination was studied with the concordance index (c-index).

Calibration was assessed by plotting the observed 4-year mortality by quintiles of the predicted 4-year mortality. Comparison between the anatomical and II SYNTAX scores was further quantified using a reclassification table and its NRI.

The NRI uses reclassification tables constructed separately for participants with and without events, and quantifies the correct movement in categories: upwards for events and downwards for non-events as follows: NRI=[(percentage of events moved to higher risk category in event group)−(percentage of events moved to lower risk category in event group)]−[(percentage of non-events moved to higher risk category in non-event group)−(percentage of non-events moved to lower risk category in non-event group)]. Given that not all persons had follow-up completed to 4 years, the present reclassification was based on the expected number of case and control patients calculated using the Kaplan-Meier estimator. All statistical analysis was done

### Table 1. Subject Baseline Characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>PCI (n=2,190)</th>
<th>CABG (n=1,796)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>71 (63–77)</td>
<td>70 (63–75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>1,554 (71)</td>
<td>1,336 (74.4)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>23.7 (21.5–25.8)</td>
<td>23.3 (21.1–25.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1,066 (48.7)</td>
<td>935 (52.1)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>On insulin therapy</strong></td>
<td>287 (13.1)</td>
<td>309 (17.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1,907 (87.1)</td>
<td>1,514 (84.3)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td>541 (24.7)</td>
<td>437 (24.3)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>454 (20.7)</td>
<td>387 (21.5)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>415 (18.9)</td>
<td>396 (22)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Prior symptomatic stroke</strong></td>
<td>346 (15.8)</td>
<td>248 (13.8)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Hemodialysis</strong></td>
<td>124 (5.7)</td>
<td>119 (6.6)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>70 (3.2)</td>
<td>60 (3.3)</td>
<td>1</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>227 (12.6)</td>
<td>256 (11.7)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>60 (50–67)</td>
<td>60 (49–68)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Creatinine clearance (mg/dl)</strong></td>
<td>61.7 (44.2–80.9)</td>
<td>61.4 (43.7–78.9)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural characteristics</th>
<th>PCI (n=2,190)</th>
<th>CABG (n=1,796)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAD extension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>1,825 (83.3)</td>
<td>1,156 (64.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LM isolated</td>
<td>57 (3.2)</td>
<td>31 (1.4)</td>
<td></td>
</tr>
<tr>
<td>LM and 1-vessel disease</td>
<td>89 (4.1)</td>
<td>108 (6)</td>
<td></td>
</tr>
<tr>
<td>LM and 2-vessel disease</td>
<td>132 (6)</td>
<td>182 (10.1)</td>
<td></td>
</tr>
<tr>
<td>LM and 3-vessel disease</td>
<td>113 (5.2)</td>
<td>293 (16.3)</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>24 (17–30)</td>
<td>29 (23–37)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data given as median (IQR) or n (%).

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
SYNTAX Score II in CREDO-Kyoto Registry

Figure 2. Kaplan-Meier curves for tertiles of anatomical SYNTAX score and SYNTAX score II for the percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) groups.
Patient Characteristics
Out of 3,986 patients included in the current study, 2,190 patients received PCI and 1,796 patients underwent CABG.
Baseline characteristics of these patients are listed in Table 1. Patients in the PCI group were older, and more often had hypertension, while patients in the CABG group more often had smaller body mass index, diabetes and prior myocardial infarction. Participants treated with CABG had more complex anatomical characteristics and a higher prevalence of associated ULMCA-triple vessel disease and higher anatomical SS. Overall Kaplan-Meier estimated mortality at 4-year follow-up was 14.7% (15.9% for PCI and 12.6% for CABG).

Predictive Performance of SSII

Discrimination The c-index of SSII was 0.70 (95% CI: 0.68–0.72) in the CABG group and 0.75 (95% CI: 0.72–0.78) in the PCI group. On comparison of discrimination, anatomical SYNTAX showed a significant improvement for CABG and PCI groups (c-index, 0.50; 95% CI: 0.47–0.53 and 0.59; 95% CI: 0.57–0.61, respectively). Additionally, the SSII model was able to separate low-, medium- and high-risk tertiles better than anatomical SS for both groups (Figure 2).

Calibration The validation plots (Figure 3) of SSII indicated a reasonably good agreement between the observed and predicted risks for both the CABG and PCI groups. The anatomical SS showed disparity between predicted and observed mortality.

Reclassification Reclassification for all patients (both PCI and CABG patient groups), with and without events is summarized in Table 2. SSII showed a significant improvement in risk stratification (NRI, 0.5; P<0.01). This was also observed when analyzing the PCI and CABG groups separately (Table S1).

Discussion In this study, SSII was assessed in a large all-comers registry of Eastern patients with predominantly high-risk CAD. The findings can be summarized as follows: (1) SSII showed agreement between observed outcomes and predictions; (2) the metrics used showed similar risk stratification for both treatment cohorts (PCI and CABG); and (3) SSII substantially improved the predictive accuracy of long-term mortality predictions if compared with the anatomical SS alone.

SSII was developed from comparison between CABG and PCI in the SYNTAX trial. Its concept permits the composition of 1 single score to predict – based on randomized data – mortality if a patient is assigned to either CABG or PCI. Indeed, in the present study, SSII had similar and consistent predictive performance for both revascularization strategies in a real world population. In contrast, the current guidelines advise the heart team to use the anatomical SS alone or combined with the STS score as a tool to make objective risk stratification in the decision-making process between CABG and PCI. This concept, however, does not allow unified risk assessment.

The metrics used to perform the present analysis reinforce the importance of comprehensive assessment with a combination of angiographic and key clinical characteristics for patients with complex CAD. SSII had a significantly higher accuracy compared to anatomical SS for all-cause death measured by the c-statistic. It has been argued, however, that c-statistic is insensitive to systematic errors in calibration such as differences in average outcome. Therefore, we studied calibration using a graphical representation where predicted risk matched observed risk. In this comparison the SSII also had a more refined pattern (Figure 2). Indeed, a better discriminating model has more spread between quintiles of predicted risk than a poorly discriminating model.

Additionally, it is important for risk prediction as to whether a model can accurately stratify individuals into higher or lower risk categories. Therefore, we used the methodology described previously, which balances the reclassification of a new score, subtracting, from a better risk grouping, a penalty if it lowers the estimated risk category of a patient with event or raises the estimated risk category of a patient without event. The overall NRI of 0.5 (P<0.01) indicates that 50% of patients had a net better classification for higher and lower risk categories using the SSII vs. the anatomical SS. Also, when reclassified separately for type of revascularization – PCI or CABG – the reclassification of SSII was more accurate, indicating its potential as an integrated prediction tool (Table S1). Grouping patients in tertiles according to SSII, a separation of the Kaplan-Meier curves for the occurrence of deaths is evident (Figure 2). The same approach for anatomical SS showed a poor risk stratification (Figure 2).

Previously, SSII was predominantly evaluated in Western patients. Therefore, doubts may have existed over the utility of this tool in other populations. The present analysis confirms the potential to apply this model globally, given that we have now validated it in a population with unique epidemiological characteristics. Japan has the longest life expectancy at birth worldwide and a substantially lower proportion of mortality from cardiovascular diseases, compared with Western countries. Despite recent changes in the lifestyle and dietary habits of Japanese people, the incidence of myocardial infarction in Japan is still much lower than in other industrialized countries. Furthermore, even after revascularization – by either PCI or CABG – Japanese patients have been shown to have better long-term outcomes than US patients and, regarding PCI, a significantly lower definite stent thrombosis than in Western countries. All the aforementioned reasons could suggest that a score developed and validated mainly in Western populations may be less appropriate for global use. In the present cohort SSII discriminated well in both CABG and PCI patient groups (c-index, 0.70; 95% CI: 0.68–0.72 and 0.75, 95% CI: 0.72–0.78, respectively), a performance similar to its internal (c-index, 0.72) and external validations (DELTA registry; c-index, 0.71) in mainly Western patients.

Once more, the SSII predictions were consistent despite the fact that it does not include in its model diabetes mellitus. This could be questioned as a paradox because in the exclusively diabetic patients of the FREEDOM trial, CABG was superior to PCI by significantly reducing rates of death and myocardial infarction. Diabetes, however, was not a useful variable in the SSII, despite medically treated diabetes being stratified at randomization in the SYNTAX trial and reported in 26% of patients. Numerous arguments might explain this apparent divergence. First, diabetes was not an independent predictor of mortality in the SYNTAX trial. Second, diabetes did not have an interaction effect (P=0.67) with CABG or PCI for long-term mortality. Diabetes is a systemic disease, the severity and duration of which have a specific effect on organs such as the heart (detected on complex coronary anatomy and LVEF); peripheral vascular disease (a sign of systemic atherosclerosis); kidney (detected on creatinine clearance); and age (older patients are representative of a longer diabetes multi-organ effect). These arguments may be exemplified by a large population-based cohort study and meta-analysis involving 128,505 individuals with diabetes in which patients without diabetes but with chronic kidney disease and proteinuria had a stronger as-
association with risk of myocardial infarction, and a higher rate of mortality, compared with those with diabetes. Finally, it must be acknowledged that no risk-scoring system is perfect and that careful multidisciplinary clinical reasoning remains vital for decision-making. SSII, however, can be a useful instrument in this process.

Study Limitations
This study has the inherent limitations of a retrospective analysis. The ultimate goal of SSII is to assist the heart team in the decision-making process between CABG and PCI. Thus, a prospective study would be needed to achieve true validation of SSII, where the decision between CABG and PCI is randomized. The present analysis, being retrospective, cannot assess the treatment recommendation based on SSII for the simple fact that the decision was likely made based on a combination of measured variables (as included in SSII) and unmeasured variables (eg, bleeding risk, duration of dual antiplatelet therapy, frailty etc). Presently, validation of SSII is a pre-specified endpoint in the ongoing randomized EXCEL trial (NCT01205776), and SYNTAX trial II, which will use SSII to recruit participants based on patient safety. In the latest trial, functional lesion assessment was added to improve late PCI outcomes and it is plausible that this approach may improve the discrimination of anatomical SS.

In the PCI cohort of the CREDO-Kyoto registry patients were treated mainly with first-generation drug-eluting stent (DES). It is possible that its performance will be affected by the use of newer generation DES. SSII, however, focuses on 4-year overall mortality, an outcome that, apparently, is not affected by the type of stent used. For instance, in a recent meta-analysis of 20 clinical trials that included 20,005 patients, stent type did not alter the overall mortality, unlike late-lumen loss and stent thrombosis rate. Therefore, we do not expect that the type of DES prescribed will affect the predictions made by the PCI model of SSII.

Conclusions
SSII has robust prognostic accuracy, both in CABG and PCI patient groups and – compared with the anatomical SS alone – was able to stratify patients for late mortality in a real-world complex CAD Eastern population.

Acknowledgments
H.M.G.-G. and M.-A.M. are employees of Cardialysis (an academic Clinical Research Organization). The other authors report no conflicts of interest.

References


### Supplementary Files

**Supplementary File 1**

**Table S1.** Reclassification table: 4-year risk strata for PCI vs. CABG

Please find supplementary file(s):