SYNTAX Score-II Predicts Long-Term Mortality in Patients Who Underwent Left Main Percutaneous Coronary Intervention Treated With Second-Generation Drug-Eluting Stents

Jiqiang He,1 MD, Hua Zhao,1 MD, Xianpeng Yu,1 MD, Quan Li,1 MD, Shuzheng Lv,1 MD, Fang Chen,1 MD, and Tengyong Jiang,1 MD

Summary

The aim of this study was to evaluate the capacity of the SYNTAX Score-II (SS-II) to predict long-term mortality in patients undergoing left main percutaneous coronary intervention (LM-PCI) treated with second-generation drug-eluting stents (DES).

Data from 487 consecutive patients with de novo left main coronary artery disease undergoing PCI were retrospectively studied. The patients were divided into tertiles according to the SS-II: low SS-II tertile (SS-II ≤ 22), intermediate SS-II tertile (SS-II of 23 to 30), and high SS-II tertile (SS-II ≥ 30). The survival curves were estimated by the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard regression analyses were performed to evaluate the possible associations between the SS-II and the rates of long-term mortality. The predictive ability of the SS-II for mortality was assessed and compared with the SYNTAX score (SS) alone by an area under the receiver operator curve (AUC).

The overall SS-II was 27.3 ± 9.1. At a mean follow-up of 5.1 years, the long-term mortality was 6.0%. The rates of mortality were 2.4%, 3.4%, and 11.6%, respectively (P < 0.0001) in the low, intermediate, and high SS-II tertiles. The cardiac mortality rates were 1.8%, 1.4%, and 8.1%, respectively (P = 0.002) among patients in the 3 groups. By multivariate analysis, SS-II was an independent predictor of the long-term mortality (hazard ratio: 1.56, 95% confidence interval: 1.05 to 2.32; P = 0.03). The AUC demonstrated a substantially higher predictive accuracy of the SS-II for mortality compared with the SS alone (AUC was 0.689 and 0.596, respectively).

In patients with LM-PCI treated with a second-generation DES, the SS-II is an independent predictor of long-term mortality and demonstrates a superior predictability compared with the SS alone. (Int Heart J 2017; 58: 344-350)

Key words: Left main coronary artery disease, Predict

The SYNTAX score II (SS-II) was recently developed by applying a Cox proportional hazards model to the results of the SYNTAX trial data. The SS-II incorporates a combination of two anatomical (anatomical SS and left main coronary artery disease) and 6 clinical variables (age, sex, left ventricular ejection fraction, creatinine clearance, chronic obstructive pulmonary disease, and peripheral vascular disease).1 The SS-II has been shown to provide reliable predictions of 4-year mortality for complex coronary artery disease (CAD), being internally validated in the landmark, all-comers, randomized SYNTAX trial1,2 and externally applied in two real world registries.3,4 Therefore, the SS-II provides an impartial, evidence-based assessment of the decision-making process for clinicians weighing anatomical and clinical factors to establish the optimum revascularization technique for individual patients with complex CAD. However, all previous studies1-5 about the validation of the SS-II have enrolled patients totally or mostly treated with a first-generation DES and some even used a small number of bare metal stents. At present, second-generation DES are widely applied in patients with CAD undergoing PCI in clinical practice. Some studies6-10 have demonstrated that patients treated with second-generation DES showed a significantly low incidence of long-term mortality compared with first-generation DES. Therefore, the performance of the SS-II predicting the mortality in patients undergoing second-generation DES implantation remains unclear, especially among patients with LM PCI only. The purpose of this study was to validate the SS-II for predicting long-term mortality in patients with LM treated with a second-generation DES.

Methods

Study population: Eligible patients with de novo LM CAD only undergoing PCI with a second-generation DES including...
the zotarolimus-eluting stent Endeavor and zotarolimus-eluting stent Resolute (Medtronic Inc., Santa Rosa, CA) and everolimus-eluting stent (Abbott Vascular, Santa Clara, CA) between January 2006 to December 2012 at Beijing An Zhen Hospital, China were consecutively enrolled. Patients who previously underwent PCI or CABG and presented with an acute myocardial infarction (AMI) were excluded. A total of 487 patients were finally retrospectively analyzed. Before stent implantation, all patients received aspirin according to their physicians' normal procedures and either clopidogrel 75 mg/day for 3 days before the procedure or a preprocedural loading dose of clopidogrel ≥ 300 mg. Patients were continued on clopidogrel for at least one year (75 mg/day) and aspirin indefinitely (100 mg/day) after the procedure. All follow-up data were collected by outpatient visits or telephone interview and angiographic follow-up.

**SS-II:** The SS-II has been described in detail previously. Briefly, in the present study, the anatomical SS was calculated using dedicated software as previously reported. The SS-II was calculated using a nomogram, with scores assigned for the presence and magnitude of each variable (anatomical SS, LM disease, age, sex, left ventricular ejection fraction, creatinine clearance, chronic obstructive pulmonary disease, and peripheral vascular disease) directly based on the Cox proportional hazards model coefficients, generating different scores for PCI. The anatomical SS for each angiogram was assessed by two experienced investigators who were blinded to the procedural data and clinical outcome. In the case of a disagreement, the opinion of a third observer was obtained and the final decision was made by consensus. The patients were divided into 3 groups according to the tertiles of SS-II for PCI: low SS-II tertile, intermediate SS-II tertile, and high SS-II tertile.

**Study endpoints:** The primary endpoint of the present study was all-cause mortality at follow-up. The secondary endpoints included the occurrence of cardiac death, myocardial infarction (MI), a cerebrovascular event, any repeat revascularization, and major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, cerebrovascular event, MI, and repeated revascularization. Death was defined as any post-procedural death and was considered of cardiac origin unless there was documentation of another cause. Post-PCI MI and AMI during follow-up were defined according to the consensus document on the third universal definition of MI. A cerebrovascular event was defined as an ischemic neurologic deficit lasting more than 24 hours. Repeated revascularization (including both target lesion revascularization and target-vessel revascularization) was defined as a subsequent revascularization procedure by percutaneous intervention or surgery after PCI. All major adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment.

**Statistical analysis:** Categorical variables are expressed as numbers and percentages and are compared with the chi-square or Fisher's exact test. Continuous variables are presented as the mean ± standard deviation (SD) and were compared using the Student t test or the Mann-Whitney rank sum test, as appropriate. 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. In addition to the SS-II risk score, variables historically known to be associated with long-term mortality were investigated with univariate Cox regression models. The statistically significant correlates of worse prognosis identified in univariable analyses were then introduced into a multivariable model using the forced entry method, with a variable entry criterion of 0.05. Receiver operator characteristic (ROC) curves were constructed to assess the predictive accuracy of the SS and SS-II for long-term mortality. The optimal cutoff for the SS-II in predicting the mortality was quantified by ROC curve analysis. All tests were two-tailed, and a P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 17.0 for Windows.

**Results**

Among the entire cohort, the SS-II ranged from 14 to 52, with a mean ± SD of 27.3 ± 9.1 and a median of 24.9 (interquartile range 19.5 to 32.4). In the present analysis, patients were categorized according to tertiles of the SS-II defined as: low tertile (SS-II ≤ 22, n = 168), intermediate SS-II tertile (22 < SS-II < 30, n = 147), and high SS-II tertile (SS-II ≥ 30, n = 172).

**Baseline characteristics:** Baseline characteristics of the study population, stratified according to the tertiles of the SS-II, are summarized in Table I. Patients in the upper tertile were older, more frequently female, and more frequently had a previous MI, peripheral vascular disease, and triple-vessel disease, while patients in the lower tertile had a significantly higher ejection fraction and lower pre-PCI creatinine.

**Clinical follow-up outcomes:** At a mean follow-up of 5.1 years, clinical outcomes stratified according to SS-II tertiles are presented in Table II and Figures 1A to 1E. Overall, the incidences of all-cause death, cardiac death, noncardiac death, MI, any repeat revascularization, stroke, and MACCE were 6.0%, 3.9%, 2.1%, 6.0%, 16.8%, 1.4%, and 23.4%, respectively. Compared with patients with low or intermediate SS-II tertiles, the rates of all-cause death and cardiac death were significantly higher in patients with high SS-II tertile (2.4%, 3.4%, 11.6%, P < 0.0001 and 1.8%, 1.4%, 8.1%, P = 0.002, respectively). Similarly, the incidences of MI, any repeat revascularization, and MACCE were significantly increased among patients with high SS-II tertile. However, there were no significant differences in noncardiac death and stroke among the SS tertiles.

**Univariate and multivariate analysis:** The results of the univariate and multivariate Cox regression analyses are shown in Table III. After adjustment of possible confounders, the SS-II remained an independent predictor of the long-term mortality (hazard ratio: 1.56, 95% confidence interval: 1.05 to 2.32; P = 0.03). The SS also could predict mortality in the present population (hazard ratio: 1.03, 95% confidence interval: 1.01 to 1.06; P = 0.019).

**ROC analysis:** By ROC analysis, the SS-II accurately predicted the mortality with AUC of 0.689 (95% CI 0.631-0.748, P < 0.001). The AUC demonstrated a substantially higher predictive accuracy of the SS-II for mortality, compared with the SS alone (AUC = 0.596, 95% CI 0.533-0.659, P = 0.002). An SS-II of 27 was identified as the optimal cutoff to predict mortality with a sensitivity of 86.2% and specificity of 63.1% as shown in Figure 2. According to the cutoff value, patients with high
SS-II (SS-II > 27) had a significantly higher rate of mortality (12.6%) compared with patients with low SS-II (SS-II ≤ 27) (1.7%, HR 6.63, 95% CI 2.52–17.44, \( P < 0.0001 \)).

**DISCUSSION**

The main findings of the present study are the following: 1) SS-II was an independent predictor of long-term mortality (HR: 1.56, 95% CI: 1.05 to 2.32; \( P = 0.03 \)) in patients with LM-PCI treated with a second-generation DES, and as the tertile of the SS-II increased, the mortality increased. An SS-II of 27 was identified as the optimal cutoff to predict a higher rate of mortality. 2) SS-II indicated a superior predictability for long-term mortality among a population with LM-PCI compared with the anatomical SS alone.

The present study is the first to assess the ability of SS-II to predict the long-term mortality in patients with LM only treated entirely with a second-generation DES. SS-II was developed and internally validated in the SYNTAX trial \(^1\), \(^2\) and externally validated in the DELTA \(^3\) and CREDO-Kyoto registries, \(^4\) but the above study populations included patients with LM and/or 3-vessel disease undergoing PCI, and the patients totally or mostly were treated with a first-generation DES. Although Xu, et al\(^5\) reported that the SS-II was able to risk-stratify patients and predict long-term mortality in patients undergoing LM-PCI only, patients in their study were also mostly treated with a first-generation DES (62.3%), and only 33.5% of the patients underwent implantation with a second-generation DES (33.5%), and even a small number of bare metal stents (4.2%) were used. At present, second-generation DES are widely applied in patients with CAD undergoing PCI in...
Figure 1. Kaplan-Meier curves showing event rates stratified by the SS-II. All-cause death (A); cardiac death (B); myocardial infarction (C); repeated revascularization (D); and MACCE (E), defined as a composite of all-cause death, cerebrovascular event, MI, and repeated revascularization.
clinical practice. Some previous studies\textsuperscript{6-10} have demonstrated that patients treated with a second-generation DES were found to have superior safety and efficacy compared with first-generation DES. Therefore, it is possible that the performance of SS-II in predicting the prognosis after PCI will be affected by the type of stent used. The current study shows that SS-II can independently predict the long-term mortality in patients treated with a second-generation DES, which provides further evidence to support the more routine use of SS-II in contemporary practice. However, in comparison with the study of Xu, et al,\textsuperscript{5} the present study showed slightly higher long-term mortality (6.0\% versus 5.0\%) despite using second-generation DES which are supposed to have better clinical outcomes. The probable reasons for the difference include: 1) different numeric value of the SS-II. The mean SS-II for PCI of the entire cohort in the Xu, et al study\textsuperscript{5} was 25.6 ± 7.8, and the calculated SS-II

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate Cox Regression Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>0.34</td>
<td>1.19</td>
<td>0.83-1.70</td>
</tr>
<tr>
<td>Male</td>
<td>0.51</td>
<td>1.33</td>
<td>0.57-3.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.07</td>
<td>2.30</td>
<td>0.94-5.66</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.93</td>
<td>1.04</td>
<td>0.48-2.23</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.07</td>
<td>2.00</td>
<td>0.94-4.24</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.13</td>
<td>0.55</td>
<td>0.26-1.20</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.37</td>
<td>1.55</td>
<td>0.59-4.07</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>&lt; 0.0001</td>
<td>6.38</td>
<td>2.67-15.24</td>
</tr>
<tr>
<td>LVEF (per 10% increase)</td>
<td>&lt; 0.0001</td>
<td>0.93</td>
<td>0.90-0.95</td>
</tr>
<tr>
<td>Creatinine (per 10% increase)</td>
<td>&lt; 0.0001</td>
<td>1.04</td>
<td>1.03-1.05</td>
</tr>
<tr>
<td>Baseline SS (per 10-point increase)</td>
<td>0.01</td>
<td>1.46</td>
<td>1.11-1.93</td>
</tr>
<tr>
<td>SS-II (per 10-point increase)</td>
<td>&lt; 0.0001</td>
<td>2.36</td>
<td>1.66-3.35</td>
</tr>
<tr>
<td><strong>Multivariable Cox Regression Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>0.41</td>
<td>0.85</td>
<td>0.57-1.26</td>
</tr>
<tr>
<td>Male</td>
<td>0.51</td>
<td>1.38</td>
<td>0.53-3.60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.82</td>
<td>1.12</td>
<td>0.40-3.15</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.53</td>
<td>1.34</td>
<td>0.54-3.33</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.69</td>
<td>0.76</td>
<td>0.19-2.99</td>
</tr>
<tr>
<td>LVEF (per 10% increase)</td>
<td>0.01</td>
<td>0.94</td>
<td>0.90-0.99</td>
</tr>
<tr>
<td>Creatinine (per 10% increase)</td>
<td>&lt; 0.0001</td>
<td>1.04</td>
<td>1.02-1.05</td>
</tr>
<tr>
<td>Baseline SS (per 10-point increase)</td>
<td>0.019</td>
<td>1.03</td>
<td>1.01-1.06</td>
</tr>
<tr>
<td>SS-II (per 10-point increase)</td>
<td>0.03</td>
<td>1.56</td>
<td>1.05-2.32</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; SS, SYNTAX score; SS-II, SYNTAX score II; HR, hazard ratio; and CI, confidence interval.

\[\text{Figure 2.} \text{ Receiver operating characteristic curve analyses comparing the SS with the SS-II for the predictability of long-term mortality. The diagonal represents the line of no effect (AUC = 0.50), with curves above this line representing increasing diagnostic accuracy. The circle represents the optimal cutoff (SS-II = 27) to predict mortality with a sensitivity of 86.2\% and specificity of 63.1\%}.\]
among the entire cohort in our study was 27.3 ± 9.1. The mean SS-II of the present study was higher than that of Xu, et al., and the rate of mortality in this analysis was also higher than theirs, which importantly illustrates the predictive capability of the SS-II among patients undergoing LM-PCI only, and 2) different duration of follow-up. The mean duration of follow-up in the present study was longer than that of Xu, et al. (5.1 versus 4.4 years).

A key to optimizing outcomes in patients undergoing PCI is the ability to reliably and accurately identify those patients at highest risk of undesired events, especially hard clinical endpoints such as all-cause death. In this regard, the anatomical SS has been consistently shown to be an important tool for risk stratification. However, one of the most significant limitations of the SS is the omission of clinical variables in its calculation, which has been identified as a major effect in its capacity to accurately stratify patients with complex CAD. The SS-II, by incorporating both the anatomical SS and clinical variables theoretically ensures a more accurate and individualized clinical outcome prediction. However, a limited number of studies have assessed the power of the SS-II. Thus, in the present study we compared the predictability of the SS-II and the SS for long-term mortality in patients undergoing LM-PCI. The results demonstrate that the SS-II has a superior predictability for long-term mortality after PCI compared with the SS alone, which suggests that clinical factors added to the angiographic factors may result in a better system of event scoring. This finding was in good agreement with previous results. This ability of the SS-II to more accurately identify patients at higher risk of death has important clinical implications. It enables physicians to more adequately inform or counsel their patients regarding the potential risk of adverse events and in the choice of revascularization procedure while also prompting increased surveillance and aggressive secondary preventive therapy and lifestyle modifications in those at highest risk after PCI.

Development and validation of the SS-II was initially evaluated in Western patients. Therefore, doubts may have existed over the utility of this tool in other populations, such as in Asian populations. Campos, et al. reported that the SS-II has robust prognostic accuracy compared with the anatomical SS alone, and was more accurate in stratifying patients for late mortality in a real-world complex coronary artery disease in Japanese populations undergoing PCI. The report of Xu, et al. and the present analysis demonstrated that the SS-II was able to risk-stratify patients and predicted the long-term mortality in Chinese populations after LM-PCI. All the aforementioned studies could suggest that the SS-II may be clinically applied in predicting adverse cardiovascular events in Asian populations.

The main difference between the current study and previous studies is the type of DES used. Patients in the present study were all treated with a second-generation DES only, which is one of the most widely used DES in current day practice. Therefore, the results of our study are more clinically significant in guiding the decision-making process to select the most appropriate revascularization strategy among patients with LM. Another difference is the disparity in follow-up duration. The previous studies had follow-up durations of 4 or 4.4 years, and our study had a mean follow-up of 5.1 years. To date, the duration of follow-up in the current study is the longest among the studies on the SS-II.

**Study limitations:** Several limitations of the present study should be addressed. First, this was not a randomized study, but rather a retrospective study and therefore the data acquired may not have been scrutinized to the levels expected in randomized studies. Second, it represents a single-center experience, which may affect the generalizability of our findings. Third, the limited number of patients may have limited the power of the statistical analysis and the ability to find statistical significance for many of the comparisons. Fourth, our validation cohort excluded patients with acute ST-segment elevation MI who underwent emergency procedures. Previous risk models for patients undergoing PCI have shown different discriminative powers when elective and emergency procedures were compared. Fifth, there is always the limitation of interobserver and intraobserver variabilities when calculating the anatomical SS. Finally, the absence of a CABG comparator arm limits the complete interpretation of the outcomes.

**Conclusions:** In patients with LM only undergoing PCI with a second-generation DES, the SS-II is an independent predictor of long-term mortality, and shows a superior predictability compared with the anatomical SS alone.

**References**

10. Wu G, Sun G, Zhao R, Sun M. Clinical outcomes of second- ver-


