ORIGINAL RESEARCH

Prognostic Effect of the SYNTAX Score on 10-Year Outcomes After Left Main Coronary Artery Revascularization in a Randomized Population: Insights From the Extended PRECOMBAT Trial

Junghoon Lee, MD*; Jung-Min Ahn, MD*; Ju Hyeon Kim, MD; Yeong Jin Jeong, MD; Junho Hyun, MD; Yujin Yang, MD; Ji Sung Lee, PhD; Hanbit Park, MD; Do-Yoon Kang, MD; Pil Hyung Lee, MD, PhD; Duk-Woo Park, MD, PhD; Seung-Jung Park, MD, PhD; on behalf of the PRECOMBAT Investigators†

BACKGROUND: The long-term prognostic effect of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for left main coronary artery disease is controversial.

METHODS AND RESULTS: In the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial, 600 patients with left main coronary artery disease were randomized to undergo PCI with drug-eluting stents (n=300) or CABG (n=300). We compared 10-year outcomes after PCI and CABG according to SS categories and evaluated the predictive value of SS in each revascularization arm. The primary outcome was a major adverse cardiac or cerebrovascular event (composite of death, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) at 10 years. Among 566 patients with valid SS measurement at baseline, 240 (42.4%) had low SS, 200 (35.3%) had intermediate SS, and 126 (22.3%) had high SS. The 10-year rates of major adverse cardiac or cerebrovascular events were not significantly different between PCI and CABG in low (21.6% versus 22.2%, P=0.97), intermediate (31.8% versus 22.2%; P=0.13), and high SS (46.2% versus 35.7%; P=0.31) (P-for-interaction=0.46). There were no significant interactions between SS categories and revascularization modalities for death (P=0.92); composite of death, myocardial infarction, or stroke (P=0.87); and target-vessel revascularization (P=0.06). Higher SS categories were associated with higher risks for major adverse cardiac or cerebrovascular events in the PCI arm but not in the CABG arm.

CONCLUSIONS: Ten-year clinical outcomes between PCI and CABG were not significantly different according to the SS. The SS was predictive of major adverse cardiac or cerebrovascular events after PCI but not after CABG.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03871127.

Key Words: coronary artery bypass graft | coronary artery disease | percutaneous coronary intervention

Correspondence to: Duk-Woo Park, MD, PhD, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea. E-mail: dwpark@amc.seoul.kr

*J. Lee and J.-M. Ahn contributed equally.
†A complete list of the PRECOMBAT Investigators can be found in the Supplementary Material.

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Recent studies reported that percutaneous coronary intervention (PCI) is a safe and effective treatment modality for patients with left main coronary artery (LMCA) disease with low-to-intermediate anatomic complexity in comparison with coronary artery bypass grafting (CABG). 1–5 Specifically, the extended follow-up study of the PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial showed that there was no significant difference between PCI with drug-eluting stents (DES) and CABG with respect to the primary composite outcome of major adverse cardiac or cerebrovascular events (MACCE), mortality, and serious composite outcome of death, myocardial infarction (MI), or stroke at 10 years. 6

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) was developed for use as an objective method for comprehensively defining the anatomic complexity and severity of multivessel coronary artery disease. 7 The SS was shown to be useful in risk stratification and for facilitating decision-making for an optimal revascularization strategy between CABG and PCI for patients with multivessel coronary artery disease. 8 Thus, most revascularization guidelines have advocated that revascularization strategies should be based on risk assessment by the baseline SS. 9,10 However, the specific value of the SS in patients with LMCA disease is not fully determined. Recent clinical trials showed a limited discriminative capacity of the SS for predicting differential outcomes after PCI and CABG, 2,11 as well as the substantial discrepancy between on-site and core-laboratory measurements in patients with LMCA disease. 2 Also, in a recent report of the real-world registry, extreme high-risk patients with high SS who were not equally eligible for both PCI or CABG were substantially included. 12 We herein tested the performance of the SS in patients with LMCA disease who underwent either PCI or CABG by analyzing the extended 10-year follow-up data of the PRECOMBAT trial.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population, Revascularization, and Follow-Up

The protocol, trial design, patient eligibility criteria, and methods of the PRECOMBAT trial have been described previously. 6,13,14 The PRECOMBAT trial was a prospective, multicenter, open-label randomized clinical trial (RCT) in which patients with unprotected LMCA disease were randomly assigned to undergo PCI with DES (n=300) or CABG (n=300) in 13 hospitals in South Korea between April 2004 and August 2009.
Interventional cardiologists and cardiac surgeons at each participating site assessed the patients for clinical and anatomic eligibility for myocardial revascularization, which was considered to be equally suitable for both PCI and CABG. Details of the PCI and CABG procedures have been described previously. First-generation sirolimus-eluting stents (Cypher stent, Cordis/Johnson & Johnson, Miami Lakes, FL, USA) were used in the PRECOMBAT trial, and the interventional cardiologists were encouraged to treat all arteries that were likely to contribute to ischemia or had lesions with >70% diameter stenosis and to achieve complete anatomic revascularization. Dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 12 months after stent implantation. The use of internal mammary conduits was strongly advised for all CABG cases. Medical treatment was performed to keep patients free of angina. The trial was approved by the institutional review board or ethics committee at each participating center. Written informed consent was obtained from all patients.

All participating centers agreed to participate in the extended 10-year follow-up study. During the long-term follow-up, guideline-directed medical therapy and management of risk factors for secondary prevention were highly recommended for all patients. Information on adverse clinical events and survival data (ie, vital status, cause of death, date of death) was obtained by reviewing the healthcare records and referring to the national death registry of the Korean National Health Insurance Service database, which was merged from the Statistics Korea database. The trial is registered at clinicaltrials.gov (Identifier, NCT03871127). This study is a post hoc analysis of the subjects enrolled in the extended follow-up of the PRECOMBAT trial.

**SYNTAX Score Calculation and Categorization**

Because the SS was developed while the patient recruitment was ongoing in the PRECOMBAT trial, the SS for each patient was measured retrospectively at the core laboratory (Asan Medical Center, Seoul, South Korea) by scoring all coronary lesions with >50% diameter stenosis in vessels with diameters >1.5 mm using the SS algorithm, as described previously. The calculation was done using an openly accessible web-based score calculator (www.syntaxscore.com). The analysts at the core laboratory who calculated the SS were blinded to the baseline demographics, treatment allocation, and clinical outcomes of the patients. The interoperator variabilities on the SS measurement have been previously described in detail. To compare the treatment effects between PCI and CABG, the study subjects were categorized into 3 conventional groups according to the level of baseline SS (low, intermediate, high) with an unequivocal, noncardiovascular cause could be established. Protocol definition of MI was defined as the appearance of both new Q-waves and creatine kinase-myocardial band to >5× the upper reference limit within 48 hours after PCI/CABG (periprocedural MI) or a rise of creatine kinase-myocardial band >1× upper reference limit plus new ischemic symptoms or signs >48 hours after PCI/CABG (spontaneous MI). Stroke was defined as a focal neurological deficit resulting from vascular lesions of the brain lasting >24 hours, as confirmed by a neurologist and imaging. Revascularization events were classified as either ischemia driven or nonischemia driven by prespecified criteria. An independent clinical events committee adjudicated all primary and secondary end points with source document verification.

**Statistical Analysis**

A descriptive analysis was performed by presenting the data as mean (SD) or number (proportion). Continuous variables were compared with Student t test or the Wilcoxon rank-sum test, and categorical variables were compared with the χ² test or Fisher’s exact test (expected frequency: <5). Cumulative event rates were calculated using the Kaplan-Meier estimates, with event or censoring times calculated from the date of randomization. Event rates were based on Kaplan-Meier estimates in time-to-first-event analyses and were compared using the log-rank test.

Outcomes of PCI versus CABG were evaluated after stratification according to the SS categories. Although no formal statistical hypothesis was defined a priori, subgroup analysis according to the SS categories with formal interaction testing was prespecified in the statistical analysis plan in the PRECOMBAT 10-year follow-up study protocol. A Cox proportional-hazards model was used to compare the rates of primary and secondary end points between groups, and hazard ratios (HRs) were calculated and presented with 95% confidence intervals.
The 10-year rates of primary and secondary end points were well balanced between the 2 groups in terms of the primary end point of MACCE across all SS categories (low, 21.6% versus 22.2%, \( P=0.97 \); intermediate, 31.8% versus 22.0%, \( P=0.13 \); high, 47.2% versus 35.7%, \( P=0.31 \)) (Figure 2). Accordingly, there was no significant interaction between the SS categories and the revascularization type on the 10-year primary outcome (\( P \text{-for-interaction}=0.46 \)).

In addition, there were no significant differences in mortality and serious composite outcome of death, MI, or stroke between the 2 revascularization arms, irrespective of the SS category (Figure 3). The 10-year incidence of ischemia-driven TVR was notably higher after PCI than after CABG with increasing levels of SS categories; TVR rates were similar between the 2 revascularization groups in the low SS category but were notably higher after PCI than after CABG in the high SS category. Linear regression showing the likelihood of risk of primary composite outcome according to SYNTAX score is illustrated in Figure S1. Although CIs are wide, the HRs for primary composite outcome seem to be higher according to SYNTAX score; however, there was no statistically significant interaction between the PCI and CABG groups with respect to the risk of primary composite outcome.

RESULTS

Trial Population and SYNTAX Score

A total of 600 patients with unprotected LMCA disease were enrolled in the PRECOMBAT trial between April 2004 and August 2009. Among them, the SS was not available in 34 (5.7%) patients, and a total of 566 (94.3%) patients were analyzed in this study (291 patients in the PCI group and 275 patients in the CABG group). The mean SS was 24.3±9.6 in the PCI group and 25.3±10.9 in the CABG group (\( P=0.22 \)). The distribution of SS was bell-shaped in both the PCI and CABG arms (Figure 1), and the proportions of the SS categories were similar between the PCI arm and the CABG arm (low, 45.0% versus 39.6%; intermediate, 35.1% versus 35.6%; high, 19.9% versus 24.7%, respectively). Generally, patients in higher SS categories were older and had higher-risk profiles of baseline characteristics (eg, diabetes mellitus, hypertension, distal LMCA bifurcation, and the extent of the diseased vessel) (Table S1). The baseline clinical and angiographic characteristics of the PCI and CABG groups according to the SS categories are summarized in Table 1. Most of the baseline characteristics were well balanced between the 2 groups in each SS category.

Long-Term Outcomes According to SS Categories

The median follow-up duration was 11.2 years (interquartile range, 10.1–13.0; 11.1 years in the PCI group and 11.4 years in the CABG group, \( P=0.71 \)). The 10-year rates of primary and secondary end points between the PCI and CABG groups stratified by the SS categories at baseline are shown in Table 2. There were no statistically significant differences between the PCI group and the CABG group in terms of the primary end point of MACCE across all SS categories (low, 21.6% versus 22.2%, \( P=0.97 \); intermediate, 31.8% versus 22.0%, \( P=0.13 \); high, 47.2% versus 35.7%, \( P=0.31 \)).

DISCUSSION

In this extended follow-up of the PRECOMBAT trial specifically targeting patients with LMCA disease, we evaluated the very long-term clinical impact of SS on
the relative long-term treatment effect between PCI with DES and CABG. We did not find a significant difference between PCI with sirolimus-eluting stents and CABG in the primary composite end point of MACCE at 10 years according to the SS categories (ie, low, intermediate, high). Likewise, the 10-year incidences of mortality and composite of death, MI, or stroke were also similar between the 2 groups irrespective of the SS category. The rates of TVR and repeat revascularization were consistently higher after PCI than after CABG. There was no significant interaction between the SS categories and treatment with DES compared with CABG on the relative risk of 10-year primary and secondary outcomes. The increasing levels of SS were predictive of MACCE after PCI but not after CABG. The discriminative capacity of the SS for predicting 10-year outcomes was limited in both the PCI arm and the CABG arm.

The SS was developed for use as an objective method for evaluating the prognostic impact of the severity of multivessel coronary artery disease and for guiding the optimal revascularization strategy of CABG or PCI.18 However, data on the clinical value and utility of the SS in patients with LMCA disease were still limited. Two landmark RCTs of the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial and
### Table 1. Baseline Characteristics of the Patients by Treatment and SYNTAX Categories

| SYNTAX Categories | Low | Intermediate | High |
|-------------------|-----|--------------|------|
| **PCI (n=131)**   |     |              |      |
| **CABG (n=109)**  |     |              |      |
| **P Value**       | 0.51 | 0.073        | 0.065|
| **Age, y**        | 59.8±10.7 | 62.0±9.5 | 65.4±8.3 |
| **Sex**           | >0.99 | >0.87        | >0.99 |
| **Male**          | 101 (77.1) | 78 (76.5) | 45 (77.6) |
| **Female**        | 30 (22.9) | 24 (23.5) | 13 (22.4) |
| **Body mass index, kg/m²** | 24.4±2.5 | 24.6±2.8 | 24.6±2.6 |
| **Diabetes mellitus** |     |              |      |
| **Any**           | 31 (23.7) | 42 (41.2) | 27 (46.6) |
| **Requiring insulin** | 2 (1.5) | 5 (4.9) | 3 (5.2) |
| **Hypertension**  | 60 (45.8) | 58 (56.9) | 38 (65.5) |
| **Hyperlipidemia**| 47 (35.9) | 46 (46.9) | 21 (36.2) |
| **Current smoker**| 42 (32.1) | 27 (26.5) | 18 (31.0) |
| **Previous PCI**  | 16 (12.2) | 17 (16.7) | 4 (6.9) |
| **Previous MI**   | 7 (5.3) | 6 (5.9) | 4 (6.9) |
| **Previous congestive heart failure** | 0 (0) | 2 (2) | 1 (1.5) |
| **Chronic kidney disease** | 4 (3.1) | 5 (4.9) | 3 (5.2) |
| **Peripheral arterial disease** | 6 (4.6) | 5 (4.9) | 4 (6.9) |
| **Chronic lung disease** | 2 (1.5) | 2 (2.0) | 1 (1.5) |
| **LMCA disease location** | 0.68 | 0.68 | 0.68 |
| **Distal bifurcation** | 75 (57.3) | 78 (76.5) | 59.6±8.5 |
| **Ostium or shaft** | 56 (42.7) | 24 (23.5) | 60.4±7.8 |
| **Extent of diseased vessels** | 0.082 | 0.54 | 0.39 |
| **LM only**       | 25 (19.1) | 2 (2.0) | 0 (0.0) |
| **LM+1-vessel disease** | 33 (25.2) | 13 (12.7) | 13 (13.3) |
| **LM+2-vessel disease** | 43 (32.8) | 42 (41.2) | 38 (65.5) |
| **LM+3-vessel disease** | 30 (22.9) | 45 (44.1) | 43 (74.1) |
| **Euroscore**     | 2.6±1.8 | 2.5±1.8 | 2.9±1.8 |
| **SYNTAX Score**  | 15.6±4.5 | 27.5±2.8 | 38.0±4.9 |
| **Complete revascularization** | 97 (74.0) | 68 (66.7) | 42 (61.8) |

Values are n (%) or mean±SD. CABG indicates coronary artery bypass grafting; LMCA, left main coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
Table 2. Ten-Year Clinical Outcomes According to SYNTAX Score Categories and Revascularization Treatment*

| 10-y Outcome | SYNTAX Categories | P Interaction Value† |
|--------------|------------------|----------------------|
|               | Low (PCI n=131)  |            | Intermediate (PCI n=101) |            | High (PCI n=58) |            |
|               | CABG (n=109)     | Log-Rank P Value | CABG (n=98) | Log-Rank P Value | CABG (n=68) | Log-Rank P Value |
| Primary outcome | MACCE‡ | 27 (21.6) | 0.97 | 32 (31.8) | 0.13 | 27 (47.2) | 0.31 | 0.46 |
| Secondary outcomes | Death from any cause | 13 (10.5) | 0.68 | 17 (16.9) | 0.19 | 12 (21.0) | 0.76 | 0.92 |
|                  | Cardiac death | 7 (5.7) | 0.85 | 7 (7.3) | 0.69 | 8 (14.5) | 0.99 | 0.90 |
|                  | Noncardiac cause | 4 (3.4) | 0.99 | 6 (6.1) | 0.06 | 1 (1.9) | 0.38 | 0.76 |
|                  | Undetermined | 2 (1.9) | 0.50 | 4 (4.5) | 0.09 | 3 (5.8) | 0.93 | 0.63 |
|                  | MI | 4 (3.3) | 0.43 | 2 (2.0) | 0.57 | 2 (3.6) | 0.54 | 0.99 |
|                  | Q-wave MI | 2 (1.6) | 0.20 | 1 (1.0) | 0.33 | 1 (1.7) | 0.4 | 0.02 |
|                  | Non Q-wave MI | 2 (1.7) | 0.11 | 1 (1.0) | >0.99 | 1 (1.9) | 0.89 | 0.29 |
|                  | Stroke | 2 (1.6) | 0.70 | 2 (2.3) | 0.65 | 1 (2.1) | 0.35 | 0.39 |
|                  | Death, MI, or stroke | 18 (14.5) | 0.59 | 19 (18.9) | 0.29 | 15 (26.2) | 0.49 | 0.87 |
|                  | Ischemia-driven target-vessel revascularization | 13 (10.7) | 0.52 | 15 (15.6) | 0.19 | 17 (31.6) | <0.01 | 0.06 |
|                  | Any revascularization | 21 (17.4) | 0.10 | 20 (21.4) | 0.17 | 18 (33.4) | <0.01 | 0.29 |
|                  | Stent thrombosis (definite) or symptomatic graft occlusion | 3 (2.4) | 0.27 | 0 (0.0) | 0.04 | 1 (1.8) | 0.38 | 0.12 |

CABG indicates coronary artery bypass grafting; MACCE, major adverse cardiac or cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

*Event rates (%) shown are the incidences estimated in Kaplan-Meier survival analysis of data from the intention-to-treat population.
†Formal interaction testing was performed to determine whether the SYNTAX score category influenced the relative risk of PCI vs CABG for the occurrence of primary or secondary end points at 10 years.
‡The primary end point of MACCE was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

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the NOBLE study (Nordic-Baltic-British Left Main Revascularization Study) showed a limited clinical value of SS for differentiating the comparative outcomes after PCI and CABG.¹⁹,²⁰ In EXCEL, the rate of the primary composite of death, MI, or stroke was similar between PCI and CABG in different levels of core laboratory-measured SS and there was no significant interaction between the SS categories and the relative treatment effect (P_{interaction}=0.49),¹⁹ which was also consistently shown in its 5-year report.² Similarly, in the NOBLE trial, the anatomical SS did not have a significant impact on the relative clinical outcomes after PCI and CABG (P_{interaction}=0.16), thus limiting the clinical utility of the SS in LMCA revascularization.¹¹,²⁰ Also, a pooled meta-analysis showed that the 5-year mortality between PCI and CABG for LMCA disease did not significantly differ in patients according to the SS tertiles.¹ This phenomenon was also consistently shown in this 10-year follow-up of the PRECOMBAT trial. This collective body of clinical evidence thus far seems to highlight the limited clinical utility of SS for treatment selection in patients with LMCA disease and thus clinical use of SS may be better focused on patients with multivessel disease in whom the score was first developed. Also, presence of LMCA disease automatically confers a SS of 5 or 6 before other disease is included, so that the requirement for this lesion may skew the distribution of SS to include less severe form of coronary artery disease compared with other multivessel disease without LMCA disease. This phenomenon might account for some of the lack of clinical impact of SS.

Follow-up duration of <5 years might not be sufficient to determine the long-term effect of revascularization strategies. In a recent long-term follow-up report of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease), the 10-year adjusted rates of mortality and serious composite outcome were similar between the PCI group and the CABG group in the low-to-intermediate SS

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**Figure 2.** Ten-year event curves for primary end point of major adverse cardiac or cerebrovascular events according to the SYNTAX score categories and revascularization treatment.

The primary end point of major adverse cardiac or cerebrovascular events was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization. CABG indicates coronary artery bypass grafting; HR, hazard ratio; PCI, percutaneous coronary intervention; SS, SYNTAX score; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
category. However, CABG showed better clinical outcomes over PCI in patients in the high SS category. When compared with the MAIN-COMPARE registry, the paucity of high SS was observed in PRECOMBAT trial (43% and 22% respectively) and the mean score in PRECOMBAT was very similar to that reported in EXCEL, which expressly excluded patients with scores >33. Such discrepancy between RCTs and registries might be explained by the fact that the MAIN-COMPARE registry included “real-world” extremely high-risk population with higher SS values who were not fairly eligible for both PCI and CABG. In PRECOMBAT trial, because the high SS group accounts for only a small percentage, interpretation of the results may be limited. Most of RCTs excluded patients with extremely high anatomic complexity.

Similar to several prior studies, the current study demonstrated that the SS has a prognostic value in predicting differential clinical outcomes in patients who received PCI but not in patients who underwent CABG. The mechanistic basis for this discrepancy should be clarified. With PCI, higher SS is associated with a higher proportion of complex high-risk procedures (such as higher stent number, longer stents, and more use of complex stent techniques), which are closely associated with worse clinical outcomes during follow-up. By contrast, the event rate remained stable across different SS categories with CABG treatment. Coronary grafting effectively “bypasses” the diseased proximal diseased segments; thus, with a satisfactory anastomosis on the mid-to-distal site of coronary artery, SS reflecting lesion length, heavy calcification, or angulation might not be directly related.

**Figure 3.** Ten-year event curves for key secondary outcomes according to the SYNTAX score categories and revascularization treatment.

**A.** All-cause mortality. **B.** Composite of death, MI, or stroke. **C.** Ischemia-driven target-vessel revascularization. CABG indicates coronary artery bypass grafting; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; SS, SYNTAX score; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
to poorer outcomes. In addition, the progression of downstream coronary atherosclerotic disease might be higher after PCI than after CABG. 28 Accordingly, patients with the highest SS are funneled to CABG, whereas those with the lowest SS are deemed reasonable candidates for PCI. 25

Coronary heart teams can play an important role in guiding the optimal revascularization strategy for patients with LMCA disease. 29 However, on the basis of the current RCT-based studies that tested the performance of the SS score in this particular scenario, the clinical utility of SS might be limited for identifying patients with LMCA disease for whom PCI may be equivalent to surgical revascularization. Also, SS showed a modest discrimination capability for predicting long-term outcomes in patients with LMCA disease. Therefore, a more integrative approach with clinical factors such as operative risks, expected longevity, and patient preferences as well as more applicable and practical risk-score tools may be required to tailor the optimal decision-making process of revascularization strategy for patients with significant LMCA disease. 30-32

**Study Limitations**

First, the PRECOMBAT trial was an RCT with strict inclusion and exclusion criteria. Therefore, results would not be entirely applicable to real-world population in which the high SS could have a significant interaction with the results. Second, this study was not statistically powered to make comparisons between subgroups of SS for MACCE or its individual components. In addition, a limited number of patients especially in the high SS might suffer from the lack of statistical power. Therefore, our findings should be confirmed or refuted via subsequent clinical trials that are adequately powered for this purpose. Also, given that this trial was not originally randomized with SS criteria, observed findings in the current analyses are exploratory and hypothesis-generating only. Third, we cannot capture the detailed information on concurrent cardiovascular medications during the extended long-term follow-up, which could influence the relative long-term outcomes after PCI and CABG. Fourth, the progression of the disease over 10 years reduces the value of SS that reflects the degree of disease at the time of revascularization. Finally, the PRECOMBAT trial used first-generation DES; thus, the PCI arm could be better with current second-generation DES for the same score range. Therefore, the current findings in PRECOMBAT should be further confirmed or refuted via longer-term (beyond 5 years) follow-up of EXCEL and NOBLE trials using contemporary DES.

### Table 3. Ten-Year Clinical Outcomes According to SYNTAX Score Categories in Each Arm*

| 10-y Outcomes                              | PCI Arm | CABG Arm |
|--------------------------------------------|---------|----------|
|                                            | Low     | Intermediate | High | Low     | Intermediate | High     | P for Trend† |
| Primary outcome                            |         |            |       |         |            |         |              |
| MACCE‡                                     | 27 (21.6) | 32 (31.8) | 27 (47.2) | <0.01  | 23 (22.2) | 21 (22.0) | 24 (35.7) | 0.12 |
| Secondary outcomes                         |         |            |       |         |            |         |              |
| Death from any cause                       | 13 (10.5) | 17 (16.9) | 12 (21.0) | 0.13   | 14 (13.7) | 10 (10.5) | 15 (22.3) | 0.21 |
| Cardiac death                              | 7 (5.7) | 7 (7.3) | 8 (14.5) | 0.16   | 7 (6.7) | 8 (8.5) | 9 (13.8) | 0.22 |
| Noncardiac cause                           | 4 (3.4) | 6 (6.1) | 1 (1.9) | 0.73   | 4 (4.2) | 1 (1.1) | 3 (4.7) | 0.93 |
| Undetermined                               | 2 (1.9) | 4 (4.5) | 3 (5.8) | 0.15   | 3 (3.3) | 1 (1.1) | 3 (5.5) | 0.59 |
| MI                                         | 4 (3.3) | 2 (2.0) | 2 (3.6) | >0.99  | 3 (2.9) | 1 (1.1) | 2 (3.2) | 0.87 |
| Q-wave MI                                  | 2 (1.6) | 1 (1.0) | 1 (1.7) | >0.99  | 0 (0.0) | 0 (0.0) | 2 (3.2) | 0.01 |
| Non Q-wave MI                              | 2 (1.7) | 1 (1.0) | 1 (1.9) | >0.99  | 3 (2.9) | 1 (1.1) | 0 (0.0) | 0.13 |
| Stroke                                     | 2 (1.6) | 2 (2.3) | 1 (2.1) | 0.89   | 0 (0.0) | 3 (3.3) | 3 (5.1) | 0.13 |
| Death, MI, or stroke                       | 18 (14.5) | 19 (18.9) | 15 (26.2) | 0.15  | 16 (15.5) | 13 (13.6) | 19 (28.3) | 0.09 |
| Ischemia-driven target-vessel revascularization | 13 (10.7) | 15 (15.6) | 17 (31.6) | <0.01 | 8 (8.0) | 8 (8.8) | 5 (8.3) | 0.72 |
| Any revascularization                      | 21 (17.4) | 20 (21.4) | 18 (33.4) | 0.07 | 10 (10.1) | 12 (13.2) | 6 (10.1) | 0.99 |
| Stent thrombosis (definite) or symptomatic graft occlusion | 3 (2.4) | 0 (0.0) | 1 (1.8) | 0.92   | 1 (0.9) | 4 (4.5) | 5 (8.5) | 0.02 |

*Event rates (%) shown are the incidences estimated in Kaplan-Meier survival analysis of data from the intention-to-treat population.

| P for Trend† was calculated to determine whether there was a differential trend for outcomes after PCI or CABG according to increasing levels of the SYNTAX score.

‡The primary end point of MACCE was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

CABG indicates coronary artery bypass grafting; MACCE, major adverse cardiac or cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
Figure 4. Ten-year Kaplan-Meier curves for primary and secondary outcomes according to the SYNTAX score categories in each arm of CABG and PCI. Kaplan-Meier curve for primary composite outcome; death from any cause; composite of death, myocardial infarction, and stroke; and ischemia-driven target vessel revascularization in the CABG arm (A) and the PCI arm (B). CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.
CONCLUSIONS

In this 10-year report of the PRECOMBAT trial, we did not find differential comparative outcomes after PCI and CABG according to different SS categories with respect to MACCE, mortality, and a serious composite outcome of death, MI, or stroke. An interaction between the strategy of revascularization and the SS was not found for important clinical outcomes. The SS was predictive of MACCE in the PCI arm but not...
in the CABG arm. The prognostic value and clinical application of SS in patients with LMCA for use in coronary heart-team discussions regarding the optimal revascularization strategy would need further validation.

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Affiliations
Department of Cardiology (J.L., J.-M.A., J.H.K., Y.J.J., J.H., Y.Y., H.P., D.-Y.K., P.H.L., D.-W.P., S.-J.P.) and Division of Clinical Epidemiology and Biostatistics (U.S.L.), Center for Medical Research and Information, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

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Disclosures
None.

Supplementary Material
Appendix S1
Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL
Appendix

PRECOMBAT Investigators

Trial Investigators, Participating Centers, and Organization

The following persons participated in the enrollment of patients, data collection, or study coordination.

Trial Investigators: DW Park, JM Ahn, HB Park, SC Yun, DY Kang, PH Lee, YH Kim, SJ Choo, CH Chung, JW Lee, SJ Park (Asan Medical Center, Seoul, Korea); DS Lim and HS Son (Korea University Anam Hospital, Seoul, Korea); SW Rha and HJ Kim (Korea University Guro Hospital, Seoul, Korea); GM Park, SG Lee and JP Jung (Ulsan University Hospital, Ulsan, Korea); HC Gwon and YT Kim (Samsung Medical Center, Seoul, Korea); HS Kim and GB Kim (Seoul National University Hospital, Seoul, Korea); IH Chae and GH Park (Seoul National University Hospital, Bundang, Korea); Y Jang and KJ Yoo (Yonsei University Severance Hospital, Seoul, Korea); MH Jeong and BH Ahn (Chonnam National University Hospital, Gwangju, Korea); SJ Tahk and SH Lim (Ajou University Medical Center, Suwon, Korea); KB Seung and GH Go (Catholic University of Korea, St. Mary’s Hospital, Seoul, Korea).

Author Contributions: conception and design — DW Park, JM Ahn, SJ Park; analysis and interpretation of data — DW Park, JM Ahn, SC Yun, SJ Park; drafting of the manuscript — DW Park, JM Ahn, SC Yun, DY Kang, HB Park, SJ Park; critical revision of the manuscript for important intellectual content — DW Park, JM Ahn, HB Han, SC Yun, DY Kang, PH Lee, YH Kim, DS Lim, SW Rha, GM Park, HC Gwon, HS Kim, IH Chae, Y Jang, MH Jeong, SJ Tahk, KB Seung, SJ Park; final approval of the manuscript — DW Park, JM Ahn, HB Han, SC
Data and Safety Monitoring Board: MS Lee (University of Ulsan College of Medicine), KY Cho (Hallym University Sacred Heart Hospital); JY Yang (National Health Insurance Corporation Ilsan Hospital); UC Kang (Daejeon University).

Event-Adjudication Committee: JJ Kim (University of Ulsan College of Medicine, Asan Medical Center), OS Kwon (The Catholic University of Korea, Eunpyeong St. Mary's Hospital), SW Park (University of Ulsan College of Medicine, Ulsan University Hospital), TO Kim (University of Ulsan College of Medicine, Asan Medical Center)
| SYNTAX Categories | Low (N=240, 42.4%) | Intermediate (N=200, 35.3%) | High (N=126, 22.3%) | P Value |
|-------------------|--------------------|-------------------------------|---------------------|---------|
| Age               | 60.1 ± 10.0        | 62.3 ± 9.2                    | 65.8 ± 9.0          | <0.01   |
| Sex               |                    |                               |                     | 0.92    |
| Male              | 185 (77.1%)        | 151 (75.5%)                  | 97 (77.0%)          |         |
| Female            | 55 (22.9%)         | 49 (24.5%)                   | 29 (23.0%)          |         |
| Body-mass index (kg/m2) | 24.4 ± 2.9   | 24.5 ± 2.7                   | 24.6 ± 2.9          | 0.49    |
| Diabetes mellitus |                    |                               |                     |         |
| Any               | 60 (25.0%)         | 73 (36.5%)                   | 48 (38.1%)          | 0.01    |
| Requiring insulin| 3 (1.2%)           | 8 (4.0%)                     | 5 (4.0%)            | 0.15    |
| Hypertension      | 111 (46.2%)        | 107 (53.5%)                  | 75 (59.5%)          | 0.05    |
| Hyperlipidemia    | 84 (35.0%)         | 104 (52.0%)                  | 47 (37.3%)          | <0.01   |
| Current smoker    | 79 (32.9%)         | 55 (27.5%)                   | 30 (23.8%)          | 0.16    |
| Variable                                    | Group 1 | Group 2 | Group 3 | p-value |
|---------------------------------------------|---------|---------|---------|---------|
| Previous PCI                                | 30 (12.5%) | 29 (14.5%) | 11 (8.7%) | 0.30    |
| Previous MI                                 | 11 (4.6%)  | 12 (6.0%)  | 8 (6.3%)  | 0.72    |
| Previous congestive heart failure           | 0 (0.0%)   | 2 (1.0%)   | 0 (0.0%)  | 0.16    |
| Chronic kidney disease                       | 5 (2.1%)   | 0 (0.0%)   | 0 (0.0%)  | 0.03    |
| Peripheral arterial disease                  | 7 (2.9%)   | 7 (3.5%)   | 5 (4.0%)  | 0.86    |
| Chronic lung disease                         | 4 (1.7%)   | 9 (4.5%)   | 3 (2.4%)  | 0.19    |
| LV ejection fraction                         | 58.4 ± 16.6 | 60.9 ± 8.2 | 60.0 ± 8.1 | 0.13    |
| Clinical presentation                        |         |         |         | 0.13    |
| Stable angina or silent ischemia             | 115 (47.9%) | 106 (53.0%) | 64 (50.8%) |         |
| Unstable angina                              | 115 (47.9%) | 79 (39.5%)  | 59 (46.8%) |         |
| Recent MI                                    | 10 (4.2%)  | 15 (7.5%)  | 3 (2.4%)  |         |
| Left main disease location                   |         |         |         | <0.01   |
| Distal bifurcation                           | 133 (55.6%) | 147 (73.5%) | 85 (67.5%) |         |
| Ostium or shaft                              | 106 (44.4%) | 53 (26.5%)  | 41 (32.5%) |         |
| Extent of diseased vessel                    |         |         |         | <0.01   |
|                | n (%)      |       |       |
|----------------|------------|-------|-------|
| LM only        | 59 (24.6%) | 2 (1.0%) | 0 (0.0%) |
| LM + 1-vessel disease | 64 (26.7%) | 26 (13.0%) | 8 (6.3%) |
| LM + 2-vessel disease | 68 (28.3%) | 80 (40.0%) | 27 (21.4%) |
| LM + 3-vessel disease | 49 (20.4%) | 92 (46.0%) | 91 (72.2%) |
| Euroscore      | 2.6 ± 1.8  | 2.6 ± 1.9 | 3.2 ± 1.9 | <0.01 |
| SYNTAX Score   | 15.1 ± 4.7 | 27.3 ± 2.8 | 39.2 ± 5.3 | <0.01 |
| Complete revascularization | 189 (78.8%) | 128 (64.0%) | 75 (59.5%) | <0.01 |

Values are n (%) or mean ± SD.

PCI: Percutaneous coronary intervention, CAGB: Coronary artery bypass grafting, MI: myocardial infarction, LM: Left main disease, LV: left ventricular, SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
| 10-Year Outcomes | PCI group | CABG group |
|------------------|-----------|------------|
|                  | HR (95% CI) | p Value | HR (95% CI) | p Value |
| MACCE \[\textit{Low}\] | Reference | Reference | Reference | Reference |
| Intermediate | 1.40 (0.87-2.26) | 0.17 | 0.94 (0.54-1.63) | 0.83 |
| High | 2.10 (1.26-3.49) | <0.01 | 1.58 (0.92-2.72) | 0.10 |
| Death from any cause \[\textit{Low}\] | Reference | Reference | Reference | Reference |
| Intermediate | 1.56 (0.80-3.04) | 0.19 | 0.84 (0.39-1.79) | 0.65 |
| High | 1.70 (0.80-3.59) | 0.17 | 1.63 (0.80-3.33) | 0.18 |
| Death, MI, or stroke \[\textit{Low}\] | Reference | Reference | Reference | Reference |
| Intermediate | 1.29 (0.71-2.37) | 0.40 | 0.78 (0.40-1.52) | 0.47 |
| High | 1.62 (0.83-3.14) | 0.16 | 1.76 (0.95-3.24) | 0.07 |
| Ischemia-driven TVR \[\textit{Low}\] | Reference | Reference | Reference | Reference |
| Intermediate | 1.25 (0.62-2.54) | 0.53 | 0.94 (0.38-2.31) | 0.89 |
| High | 2.72 (1.37-5.38) | <0.01 | 0.82 (0.28-2.40) | 0.72 |
|                | Low       | Reference | High       | Reference |
|----------------|-----------|-----------|------------|-----------|
| Intermediate   | 1.06 (0.59-1.91) | 0.85      | 1.14 (0.52-2.51) | 0.74      |
| High           | 1.83 (1.00-3.35)   | 0.05      | 0.96 (0.38-2.45)   | 0.94      |

CABG: Coronary artery bypass grafting, MI: myocardial infarction, MACCE: major adverse cardiac or cerebrovascular events, PCI: Percutaneous coronary intervention, TVR: target-vessel revascularization.
Figure S1. Linear Regression Showing the Likelihood of Risk of Primary Composite Outcome According to SYNTAX Score.

Cox proportional hazards regression analysis of primary composite outcome. The primary endpoint of major adverse cardiac or cerebrovascular events (MACCE) was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

CABG: Coronary artery bypass graft, PCI: Percutaneous coronary intervention, CI: Confidence interval.