Geographical Difference of the Interaction of Sex With Treatment Strategy in Patients With Multivessel Disease and Left Main Disease

A Meta-Analysis From SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery), PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), and BEST (Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease) Randomized Controlled Trials

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Background—The impact of sex on clinical outcomes of percutaneous coronary intervention and coronary artery bypass graft for patients with multivessel coronary disease and unprotected left main disease could be dissimilar between Western and Asian populations.

Methods and Results—To assess clinical outcomes after percutaneous coronary intervention or coronary artery bypass graft in women and men with multivessel coronary disease and unprotected left main disease, a pooled analysis (n=3280) was performed using the patient-level data from 3 large randomized trials: SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery), PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), and BEST (Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trials. The primary end point was all-cause death. Of 3280 patients, 794 patients (24.2%) were women. The median follow-up period was 1806 days (1611–1837 days). In women, a high heterogeneity of the treatment effect among the 3 trials was found for all-cause death (I²>50%), whereas in men, it was consistent across the 3 trials. In the Western trial (SYNTAX), female sex favored coronary artery bypass graft compared with percutaneous coronary intervention (hazard ratio (percutaneous coronary intervention) 2.213; 95% confidence interval, 1.242–3.943; P=0.007), whereas in the Asian women (PRECOMBAT and BEST), the treatment effect was neutral between both strategies. Sex interaction with treatment strategy was evident in the Western trial (Pinteraction=0.019) but not in the Asian trials (PRECOMBAT Pinteraction=0.469 and BEST Pinteraction=0.472; I²=58%).

Conclusions—The present meta-analysis suggested the presence of the heterogeneous sex–treatment interaction across Asian and Western trials. Considering the ongoing globalization of our medical practice, the heterogeneity of the sex–treatment interaction needs to be well recognized and taken into account during the decision making of the treatment strategy.


Key Words: coronary artery bypass ■ meta-analysis ■ percutaneous coronary intervention ■ randomized controlled trial ■ sex
WHAT IS KNOWN
• SYNTAX score II mortality prediction model assists in decision making for patients with multivessel coronary artery disease and unprotected left main disease based on the individual risk assessment with anatomic complexity of coronary disease and baseline characteristics.
• Female sex has a lower predicted mortality rate for CABG than for PCI in the SYNTAX score II model because there was a significant sex–treatment interaction in the SYNTAX trial.

WHAT THE STUDY ADDS
• The present meta-analysis from SYNTAX, PRECOMBAT, and BEST trials suggested the presence of the heterogeneous sex–treatment interaction across Asian and Western trials.
• CABG was favorable in Western women, whereas in Asian women, both revascularization strategies were similar.
• Although the SYNTAX Score II prediction model was valid in the PRECOMBAT and BEST trials, the present results raise a concern of applying the prediction tool to the Asian population.

In patients with multivessel coronary artery disease and unprotected left main disease, the choice of the best revascularization strategy is a rather complex undertaking. SYNTAX score II provides treatment recommendation based on the individual risk assessment with baseline characteristics including sex.1,2 The SYNTAX score II prediction model was created based on the results of SYNTAX trial (Synergy between PCI with Taxus and Cardiac Surgery).3 In the SYNTAX trial, the interaction for treatment effect with sex was present. Accordingly, female sex has a lower predicted mortality rate for coronary artery bypass graft (CABG) than for percutaneous coronary intervention (PCI) in the SYNTAX score II model. However, some doctors in the Asian countries would prefer to choose PCI for female patients because of the risk of surgery. Nevertheless, the recent results of the EXCEL trial (the leading drug eluting stent, Xience for left main disease) also presented the similar results to SYNTAX trial.4,5 These results drove us to evaluate the impact of female sex on clinical outcomes between Western and Asian populations.

Methods
The methods and designs of SYNTAX, PRECOMBAT, and BEST trials have been previously described elsewhere.6–8 Some differences between them are worth noting and are summarized as follows.

Study Population
The SYNTAX trial was a randomized trial conducted at 85 sites in 17 countries in Europe and the United States that included 1800 patients with previously untreated 3-vessel or left main coronary artery disease.9 PRECOMBAT trial was a randomized trial conducted at 13 sites in Korea that included 600 patients with documented unprotected left main disease.10 The BEST trial was a randomized trial conducted at 27 sites in South Korea, China, Malaysia, and Thailand that included 880 patients with multivessel coronary artery disease (multivessel disease, 2 or 3 vessels) and without left main involvement.11

In all studies, patients deemed eligible for both PCI and CABG by an interventional cardiologist and a cardiac surgeon were prospectively enrolled and randomized in a 1:1 ratio to undergo either PCI or CABG. In the PCI arm, paclitaxel-eluting TAXUS stents were used in the SYNTAX trial, sirolimus-eluting CYHER stents were used in the PRECOMBAT trial, and everolimus-eluting XIENCE stents were used in the BEST trial. The other details of the procedure and data collection were previously described elsewhere.6–8 In all 3 trials, the institutional review board at each site approved the protocol, and all patients provided written informed consent.

Database Pooling
The principal investigators in each trial (S.-J.P., P.W.S.) set up a protocol with the prespecified outcomes and a common set of baseline variables. Individual patient data from each trial were sent for merging to the coordinating Asan Medical Center in Seoul, Korea. An independent clinical events committee adjudicated all end points in each study. We used the original adjudications for each trial. The pooled database was checked for completeness and consistency by responsible investigators in Asan Medical Center.

The merged database included demographics (age, sex, body weight, and height), clinical history (chronic kidney disease, previous myocardial infarction, previous stroke, peripheral artery disease, and previous PCI), risk factors (diabetes mellitus, hypercholesterolemia, hypertension, and smoking), angiographic and echocardiographic findings (number of diseased vessels, left main coronary artery disease, proximal left anterior descending coronary artery disease, SYNTAX score, and left ventricular dysfunction), revascularization strategies, medication history (aspirin, P2Y12 inhibitors, and statins), and clinical outcomes during follow-up (all-cause death, cardiac death, myocardial infarction, stroke, and repeat revascularization).

Clinical End Point and Definitions
The primary clinical end point of the SYNTAX trial was a composite of major adverse cardiac and cerebrovascular events (ie, all-cause death, stroke, myocardial infarction, or repeat revascularization). The primary end point of the BEST trial was a composite of all-cause death, myocardial infarction, or target- vessel revascularization. The primary end point of the PRECOMBAT trial was the composite of all-cause death, myocardial infarction, stroke, and ischemia-driven target-vessel revascularization. The definitions of events were described elsewhere.6–8 In all trials, an independent clinical events committee (including cardiologists, cardiac surgeons, and a neurologist) adjudicated all end points.

In the present study using the merged database, the primary end point was all-cause death. Secondary end points included a composite of major adverse cardiac and cerebrovascular events (all-cause
### Table 1. Baseline Characteristics of Women and Men in 3 Trials

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Women (n=402)</th>
<th>Men (n=141)</th>
<th>P Value Across Trials</th>
<th>Women (n=251)</th>
<th>Men (n=629)</th>
<th>P Value Across Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.1±9.6</td>
<td>62.5±10.1</td>
<td>&lt;0.001</td>
<td>68.7±7.6</td>
<td>62.8±9.5</td>
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<td>Height, cm</td>
<td>160.2±6.5</td>
<td>154.7±5.7</td>
<td>&lt;0.001</td>
<td>152.3±5.4</td>
<td>166.6±5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>72.7±15.3</td>
<td>58.9±8.7</td>
<td>&lt;0.001</td>
<td>56.3±8.0</td>
<td>69.4±9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anatomic SYNTAX score</td>
<td>27.2±12.0</td>
<td>24.6±10.7</td>
<td>&lt;0.001</td>
<td>24.8±7.2</td>
<td>24.8±7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>73.9±28.1</td>
<td>75.1±23.8</td>
<td>&lt;0.001</td>
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</tbody>
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(Continued)
death, stroke, myocardial infarction, or repeat revascularization); its individual components; and a composite of all-cause death, stroke, or myocardial infarction as a safety end point. The previously reported definitions from each study were used for individual clinical outcomes.6–8

Statistical Analysis

The databases for the SYNTAX, PRECOMBAT, and BEST trials were combined for the present analysis. All analyses were performed based on the intention-to-treat principle. Patients were stratified according to trials (SYNTAX versus PRECOMBAT versus BEST).

Categorical variables are expressed as counts (percentages) and compared with χ² or Fisher exact test. Continuous variables are expressed as mean±SD or median (interquartile range) and compared using Student t test, Mann–Whitney U test, or ANOVA as appropriate. Outcomes were assessed in a time-to-first-event fashion with the Kaplan–Meier method and compared with the log-rank test.

Clinical outcomes from individual studies were pooled in a meta-analysis using RevMan 5.3 software. Estimates of hazard ratio with 95% confidence interval were pooled using DerSimonian and Laird random-effect models in which the studies were weighted using the generic inverse-variance approach. χ² statistics was used to measure the difference between subgroups, and evidence of heterogeneity among studies was assessed using I² values of <25%, 25% to 50%, or >50% indicated low, moderate, or high heterogeneity, respectively.

We assessed the interaction of sex with treatment strategy for all-cause death in each trial. Cox proportional-hazards models were used for multivariable analyses. In women and men, hazard ratio of PCI as compared with CABG was calculated. Sex–treatment interaction was assessed in each trial, and its heterogeneity was examined by meta-analysis.

A 2-sided P value <0.05 was considered statistically significant. All analyses were undertaken using R software version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria), SPSS 24.0 (IBM Corporation, Armonk, NY), and RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Patient Characteristics

Of 3280 patients randomized in the pooled database from 3 randomized trials, 794 patients (24.2%) were women; and 2486 patients (75.8%) were men. The median follow-up period was 1806 days (1611–1837 days). Patient demographics and procedural characteristics in women and men are indicated in Table 1.

Clinical Outcomes

Impact of treatment strategy (PCI compared with CABG) on all the outcomes in women and men in the 3 trials were assessed by study-level meta-analysis (Figure 1). In the overall cohort, patients treated with PCI had a higher risk of myocardial infarction, repeat revascularization, and major adverse cardiac and cerebrovascular events than patients treated with CABG both in female and male subgroups. The comparison of women with men demonstrated the similarity of relative PCI risk to CABG for overall clinical outcomes. Only in women, high heterogeneity among 3 trials was found for all-cause death and death/stroke/myocardial infarction (I²>50%). In other words, all-cause mortality was improved with CABG only in Western women, but not in Asian women. In contrast, myocardial infarction and repeat revascularization were consistently improved with CABG regardless of sex or geographical difference.

The Kaplan–Meier analysis for all-cause death in women and men stratified by trials are indicated in Figure 2. In men, PCI and CABG had comparable outcomes in both in Western (SYNTAX) and Asian (PRECOMBAT and BEST) trials. In women, CABG had better outcome than PCI in the Western (SYNTAX) trial, whereas in the Asian (PRECOMBAT and BEST) trials, no significant difference was observed between both revascularization strategies.

Heterogeneity of the Sex Interaction in SYNTAX, PRECOMBAT, and BEST Trials

PCI hazards compared with CABG in women and men were assessed in 3 trials (Table 2). In the Western trial (SYNTAX), female sex favored CABG compared with PCI (hazard ratioPCI versus CABG 2.213 [1.242–3.943]; P=0.007), whereas in the Asian women (PRECOMBAT and BEST), the treatment effect was neutral between both strategies. Sex interaction with treatment strategy was evident in the Western trial (Pinteraction=0.019) but not in the Asian trials (PRECOMBAT Pinteraction=0.469 and BEST Pinteraction=0.472). Meta-analysis of the sex–treatment interaction demonstrated I² of 58%, suggesting the presence of high heterogeneity of sex–treatment interaction across the 3 trials.

Discussion

The main findings of this study are as follows: (1) in women, meta-analysis showed that there was heterogeneity among 3 trials in the effect of PCI versus CABG regarding all-cause mortality and safety end point, whereas in men, there was no such heterogeneity; (2) the heterogeneous interaction of female sex with treatment strategy in Western and Asian populations indicated that in the Western trial (SYNTAX trial),
Figure 1. Risk estimates of clinical outcomes for percutaneous coronary intervention (PCI) vs coronary artery bypass grafting (CABG) in woman and man. Forest plots show results for all-cause death (A), myocardial infarction (B), stroke (C), death or stroke or myocardial infarction (D), repeat revascularization (E), and major adverse cardiac and cerebrovascular events (MACCE; F). BEST indicates Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease; CI, confidence interval; IV, inverse-variance method; PRECOMBAT, Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.
female sex favors CABG compared with PCI, whereas in the Asian trials (PRECOMBAT and BEST), sex does not affect the decision making of the treatment strategy.

There was a significant interaction between sex and mortality risk of PCI relative to CABG in the Western population but not in the Asian population. In the meta-analysis for all-cause death (Figure 1A), men had no heterogeneity of the treatment effect among 3 trials, whereas women had high heterogeneity ($I^2=61\%$). In women enrolled in the SYNTAX trial, CABG was associated with more favorable outcome than PCI, and in women enrolled in the PRECOMBAT and BEST trials, the treatment effect was neutral between both strategies. Kaplan–Meier analysis presented in Figure 2 also supported these findings. The observed high heterogeneity of the treatment effect in women could result from multiple factors. Physical frames, racial distribution, and procedural strategy are significantly different in Europe/the United States and Asia. Zindrou et al reported a significantly higher CABG mortality rate in South Asians as compared with whites. The regional difference of the PCI procedure between Western countries and Asia was also reported. There could be other unknown confounders in addition to sex and geographical difference. These speculations need to be further explored and confirmed in the future global trials.

In Asian trials (BEST and PRECOMBAT), outcomes after CABG and PCI were comparable in women, whereas in Western trial (SYNTAX), CABG was more favorable than PCI in women. One of the concerns was that different drug-eluting stents were used in the Asian trials (Cypher and Xience) and the Western trial (Taxus). However, the most recent results of the EXCEL trial have demonstrated similar results to the SYNTAX trial. PCI in women had worse clinical outcomes compared with CABG in women. This heterogeneity between Asian and Western women has not been reported to date.

Sex is one of the parameters of SYNTAX Score II prediction model. In the algorithm of SYNTAX Score II, sex is in favor of CABG. However, the current results would suggest that this concept should not be applied directly to Asian populations. This fact is important in our daily clinical practice when deciding a treatment strategy and could have a significant impact in the cardiology community taking into account the ongoing globalization of our medical practice. The SYNTAX Score II model was created based on the Western trials. Although the good validity of the prediction model was proved in the entire population of the PRECOMBAT and BEST trials, the recalibration for the Asian populations needs to be considered.

**Strength and Limitations**

The main advantages of the present analysis are as follows: (1) this study includes the largest randomized population treated
either with PCI or CABG in Europe/the United States and Asia in the drug eluting stent era and (2) this is the first report focusing on the interaction difference of sex with treatment strategy (PCI or CABG) for patients with unprotected left main disease and multivessel coronary disease in a context of randomized populations in Europe/the United States and Asia.

Table 2. Hazard of PCI as Compared With CABG for 5-Y All-Cause Death in Women and Men

<table>
<thead>
<tr>
<th>Trial</th>
<th>Women</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>p Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTAX</td>
<td>2.213</td>
<td>(1.242–3.943)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.001</td>
<td>(0.736–1.361)</td>
<td>0.995</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.192</td>
<td>(1.140–4.218)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>PRECOMBAT</td>
<td>0.462</td>
<td>(0.115–1.847)</td>
<td>0.275</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.827</td>
<td>(0.408–1.678)</td>
<td>0.598</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.563</td>
<td>(0.119–2.668)</td>
<td>0.469</td>
<td></td>
</tr>
<tr>
<td>BEST</td>
<td>1.010</td>
<td>(0.390–2.618)</td>
<td>0.984</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.536</td>
<td>(0.776–3.042)</td>
<td>0.218</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.651</td>
<td>(0.202–2.100)</td>
<td>0.472</td>
<td></td>
</tr>
</tbody>
</table>

BEST indicates Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PRECOMBAT, Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.
Some limitations need to be mentioned. First, although the current pooled database is the largest randomized population, the number of women was only one quarter of the whole population, which could result in the insufficient statistical power. Second, the current analysis revealed the different interaction of female sex between CABG and PCI in Western and Asian population but did not seek to elucidate the reason. Last, although sex was a prespecified subgroup in the 3 trials, post hoc nature during the decision making of the treatment strategy. The interaction needs to be well recognized and taken into account in our medical practice, the heterogeneity of the sex–treatment interaction, which could result in the insufficient statistical power. The present results would also raise a concern of the direct application of the Western prediction tool (SYNTAX score II) to the Asian population.

Conclusions
The present meta-analysis suggested the presence of the heterogeneous sex–treatment interaction across Asian and Western trials. CABG was favorable in Western women, whereas in Asian women, there was no difference between both revascularization strategies. Considering the ongoing globalization of our medical practice, the heterogeneity of the sex–treatment interaction needs to be well recognized and taken into account during the decision making of the treatment strategy. The present results would also raise a concern of the direct application of the Western prediction tool (SYNTAX score II) to the Asian population.

Disclosures
None.

References

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Circ Cardiovasc Interv. 2017;10:
doi: 10.1161/CIRCINTERVENTIONS.117.005027

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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http://circinterventions.ahajournals.org/content/10/5/e005027