Impact of the Extent of Coronary Artery Disease on Outcomes After Revascularization for Unprotected Left Main Coronary Artery Stenosis

Young-Hak Kim, MD, PhD,* Duk-Woo Park, MD, PhD,* Won-Jang Kim, MD,* Jong-Young Lee, MD,* Sung-Cheol Yun, PhD,† Soo-Jin Kang, MD, PhD,* Seung-Whan Lee, MD, PhD,* Cheol Whan Lee, MD, PhD,* Myeong-Ki Hong, MD, PhD,* Seung-Wook Park, MD, PhD,* Seung-Jung Park, MD, PhD*

Seoul, Korea

Objectives
This study was designed to examine the impact of the extent of coronary disease on long-term outcomes after coronary stenting or coronary artery bypass graft (CABG) surgery for unprotected left main coronary artery (ULMCA) stenosis.

Background
The differential outcome of ULMCA revascularization according to the coronary involvement remains uncertain.

Methods
From the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry, 2,240 patients with ULMCA stenosis who underwent either stenting or CABG were stratified by number of diseased vessels.

Results
Following adjustment with EuroSCORE (European System for Cardiac Operative Risk Evaluation), diabetes mellitus, and bifurcation stenosis, stents and CABG had similar risks of death and major adverse cardiac events including death, Q-wave myocardial infarction, or stroke in all subgroups regardless of the number of diseased vessels over 4 years. In patients with 2-vessel (23.0% vs. 14.2%; hazard ratio [HR]: 1.739; 95% confidence interval [CI]: 1.171 to 2.582; p = 0.006) or 3-vessel (25.0% vs. 17.6%; HR: 1.493; 95% CI: 1.096 to 2.035; p = 0.011) disease, however, stenting was associated with a higher risk of major adverse cardiac and cerebrovascular events including major adverse cardiac events or target vessel revascularization than CABG. Interaction of vascular involvement with type of stent or CABG was not significant.

Conclusions
Stenting appears to be a safe alternative to CABG in patients having ULMCA stenosis combined with additional vascular disease. The advantage of CABG over stenting lies principally in the reduction of repeat revascularization across subgroups stratified by the number of diseased vessels. (J Am Coll Cardiol 2010;55:2544–52)

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Recent clinical studies have compared the initial and long-term safety and effectiveness of percutaneous coronary intervention with coronary artery stents with coronary artery bypass graft (CABG) surgery for unprotected left main coronary artery (ULMCA) stenosis (1–7). Despite coronary stenting showing an increased tendency of target vessel revascularization (TVR), the long-term outcomes of stenting, either with bare-metal stents (BMS) or drug-eluting stents (DES), were comparable to those of CABG, as determined by the occurrence of major adverse cardiac or cerebrovascular events (MACCE). Due to a lack of statistical power, however, the differential outcomes of stents versus CABG in subgroups stratified by the presence of comorbidities related to poor prognosis remain uncertain. In fact, although the extent of extra-ULMCA coronary disease, represented by the number of diseased vessels, has been considered a risk factor predicting adverse outcomes, no study has specifically addressed this issue (8–12). A recent subgroup analysis of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) randomized trial suggested that DES appeared to be comparable to CABG for patients with...
isolated ULMCA stenosis, but inferior for those with multivessel ULMCA stenosis in terms of the risk of MACCE (13). This study, however, had inherent limitations associated with subgroup analyses, in which the probability of false positive might be increased by the multiplicity issue (14).

We have therefore assessed the impact of extra-ULMCA vascular disease on long-term outcomes in revascularization for ULMCA stenosis in patients enrolled in the MAIN-COMPARE (Revascularization for Unprotected Left MAIN Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization) registry. The MAIN-COMPARE registry had shown comparable 3-year risks of death or myocardial infarction and higher risks of TVR with stenting than with CABG in the overall population (5). In this substudy, we extended the follow-up duration to 4 years and compared the outcomes of stenting versus CABG in patients stratified according to the extent of coronary artery disease.

Methods

Subjects. The MAIN-COMPARE study enrolled patients with ULMCA stenosis who underwent either CABG or stenting as the index procedure at 12 major cardiac centers in Korea between January 2000 and June 2006 (5). The left main coronary artery was considered unprotected if there were no patent grafts to the left anterior descending artery or circumflex artery. Patients who had undergone previous CABG, those who underwent concomitant valvular or aortic surgery, and those who had ST-segment elevation myocardial infarction or presented with cardiogenic shock were excluded. The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

Procedures. In the institutions involved in this study, CABG has been formally recommended as the standard therapy for patients having ULMCA stenosis. On the other hand, stenting for such a lesion was performed according to the preference of the patient or physician, as well as in patients with high risks associated with CABG, when the patients had suitable coronary anatomy for stenting. From January 2000 through May 2003, all coronary stenting was performed with BMS, whereas from May 2003 through June 2006, stenting was exclusively performed with DES. For DES, sirolimus-eluting stents (Cypher, Cordis Corporation, Miami Lakes, Florida) or paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts) were selected at the discretion of the operator. Procedures for ULMCA and other vessels were performed using standard interventional techniques. All patients undergoing stenting were prescribed aspirin plus clopidogrel (loading dose: 300 or 600 mg) or ticlopidine (loading dose: 500 mg) before or during the procedure, and aspirin was continued indefinitely after the procedure. Patients treated with BMS were prescribed clopidogrel or ticlopidine for at least 6 months. Surgical revascularization was performed using standard bypass techniques. Whenever possible, the internal thoracic artery was used preferentially for revascularization of the left anterior descending artery.

Follow-up and end points. Clinical, angiographic, procedural, and outcome data were collected using a dedicated Internet-based reporting system. All outcomes of interest were adjudicated by the central events committee. In addition, information about vital status was ascertained from the National Population Registry of the Korea National Statistical Office. Clinical follow-up was recommended at 1 month, 6 months, 1 year, and annually thereafter. Routine angiographic follow-up for all patients treated with stenting was recommended at 6 to 10 months after the procedure. However, for patients who underwent CABG, angiographic follow-up was recommended only if there were ischemic symptoms or signs during follow-up.

The primary end point of the study was the major adverse cardiac events (MACE), defined as the composite of death, Q-wave myocardial infarction, or stroke. The other outcomes such as death, stroke, TVR, or MACCE including MACE or TVR were considered as secondary end points. Death was defined as death from any cause. Q-wave myocardial infarction was defined as documentation of a new abnormal Q-wave after the index treatment. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging analyses. Target lesion revascularization (TLR) was defined as any repeat revascularization with percutaneous coronary intervention or CABG surgery in the target ULMCA or within the adjacent 5 mm. TVR was defined as repeat revascularization of the treated ULMCA, including any segments of the left anterior descending artery, left circumflex artery, or ULMCA. Extra-ULMCA extent and elsewhere of coronary disease was defined as the presence of significant narrowing (>50% diameter stenosis) in a major epicardial vessel, including the left anterior descending artery, left circumflex artery, and right coronary artery. Ostial stenosis of the left anterior descending artery or circumflex artery was regarded as part of the bifurcation ULMCA stenosis and was therefore not considered as extra-ULMCA extent.

To compare angiographic complexity in both treatment groups, the SYNTAX scores were retrospectively calculated for 1,580 (70.5%) patients from the overall cohort at the Angiographic Core Laboratory in CardioVascular Research Foundation, Seoul, Korea, according to the algorithm (8).

Statistical analysis. The main purpose of this study, which was pre-specified in the initial protocol, was to compare the
incidence of outcomes following stenting versus CABG in patients stratified by the extra-ULMCA extent and elsewhere of coronary artery disease. In addition, to identify the impact of stent design on clinical outcomes, comparisons between stent versus CABG were stratified into the first wave (Wave #1), comparing BMS and contemporary CABG, and the second wave (Wave #2), comparing DES and contemporary CABG, as described (5). We also assessed the impact of extra-ULMCA coronary artery disease on outcomes within each treatment strategy.

Baseline demographic, clinical, and angiographic characteristics were reported as median and interquartile range (IQR) for continuous variables and number and percentage for categorical variables. Continuous variables were compared using the Mann-Whitney U test for 2 groups and the Kruskal-Wallis test for multiple groups. Categorical variables were compared using the chi-square test or Fisher exact test, when appropriate. Unadjusted cumulative incidences of events were analyzed using Kaplan-Meier methods and compared using the log-rank test. All patients were censored at the time of an event or at a fixed interval of 4 years. When the cumulative incidence of composite outcomes was analyzed, the patient was censored at the first event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with Cox proportional hazard models. Due to the limited number of events in each subgroup, adjustment was performed using 3 fixed covariates including the standard EuroSCORE (European System for Cardiac Operative Risk Evaluation), the presence of diabetes mellitus, and bifurcation ULMCA involvement, which were traditionally considered as important risk factors of revascularization therapy for ULMCA disease (15-17). In addition, an accessory Cox model was also created to adjust angiographic complexity using the SYNTAX score and EuroSCORE without imputation method. Interactions between factors associated with the extent of coronary artery disease and treatment strategy were tested by incorporation of formal interaction terms in the multivariable Cox model.

All reported p values are 2-sided, and p < 0.05 was considered statistically significant. SPSS software version 11 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

Results

Patient characteristics. A total of 2,240 patients were included in our analysis; their demographic, clinical, and angiographic characteristics are listed in Table 1. Within either the stent or the CABG group, patients having multivessel disease plus ULMCA stenosis were likely to be older; have a greater prevalence of diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular disease, bifurcation ULMCA involvement, and right coronary artery stenosis; and have lower left ventricular ejection fraction and higher EuroSCORE than patients having isolated ULMCA or 1-vessel disease. Compared with patients undergoing CABG, those undergoing stenting had a higher prevalence of prior percutaneous coronary intervention, less involvement of bifurcation ULMCA and right coronary artery stenosis, and lower ejection fraction; this was particularly true in subgroups having multivessel disease. The SYNTAX score was significantly higher with extensive coronary artery involvement in either stent or CABG groups. In addition, the score was higher in patients undergoing CABG than those undergoing stenting in all subgroups.

Unadjusted event rate at 4 years. When the follow-up was censored at 4 years, the mean duration of follow-up was 45.4 months (IQR 38.8 to 48.0 months) in the stent group and 48.0 months (IQR 44.8 to 48.0 months) in the CABG group (p < 0.001). In the stent group, patients receiving BMS were followed for the median of 48.0 months (IQR 46.7 to 48.0 months) and those receiving DES for 42.8 months (IQR 38.2 to 48.0 months) (p < 0.001).

The observed incidences of unadjusted outcomes are listed in Table 2. Figure 1 shows the Kaplan-Meier incidences of MACE and MACCE in the subgroups. For all subgroups, the incidence of death, stroke, or MACE did not differ between the stent and CABG groups. Among the subgroups with 2- or 3-vessel plus ULMCA disease, however, the incidence of MACCE was significantly higher in the stent group than in the CABG group, which was driven by increased incidence of TVR. The difference of TLR or TVR rates between the stent and CABG groups was consistently observed in patients with isolated ULMCA; 1-, 2-, or 3-vessel disease in the overall patients; and in Wave #1 including patients receiving BMS. However, in Wave #2, including patients receiving DES, TLR or TVR did not statistically differ between the stent and CABG groups. Among the subgroups with isolated ULMCA stenosis or 1-vessel plus ULMCA disease, the incidence of MACCE did not statistically differ between the stent and CABG groups. However, in patients with 2- or 3-vessel plus ULMCA disease, the MACCE rate was higher in the stent group than in the CABG group in either Waves #1 or #2. The Kaplan-Meier incidence of revascularization for extra-ULMCA coronary artery disease, between the stent and CABG groups, was 1.0% versus 0% (p = 0.435) in isolated ULMCA, 3.2% versus 1.8% (p = 0.485) in 1-vessel, 5.5% versus 2.1% (p = 0.040) in 2-vessel, and 4.6% versus 2.9% (p = 0.086) in 3-vessel plus ULMCA stenoses. At 4 years, angiographic stent thrombosis occurred in 11 patients (1.5 ± 0.4%) receiving DES and 1 patient (0.7 ± 0.3%) receiving BMS (log-rank p = 0.120).

There was a difference in the impact of extra-ULMCA coronary artery disease involvement on long-term outcomes between the 2 treatment strategies. In the CABG group, the incidence of MACE or MACCE did not statistically differ between patients with isolated ULMCA disease and those with 1-, 2-, or 3-vessel disease. Similarly, in the stent group, the incidences of composite outcomes did not differ between patients with isolated ULMCA disease and those with 1- or 2-vessel disease. However, the incidences of MACE (12.9%
### Table 1  Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isolated LM</th>
<th>LM With 1 Vessel</th>
<th>LM With 2 Vessels</th>
<th>LM With 3 Vessels</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Stent</td>
<td>CABG</td>
<td>p Value</td>
<td>Stent</td>
</tr>
<tr>
<td>Patients, n</td>
<td>278</td>
<td>71</td>
<td></td>
<td>264</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>55 (47–64)</td>
<td>55 (48–63)</td>
<td>0.47</td>
<td>60 (52–67)</td>
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<td>Male sex, %</td>
<td>61.5</td>
<td>69</td>
<td>0.24</td>
<td>75.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any diabetes</td>
<td>20.1</td>
<td>18.3</td>
<td>0.73</td>
<td>27.7</td>
</tr>
<tr>
<td>Requiring insulin</td>
<td>2.5</td>
<td>7.0</td>
<td>0.06</td>
<td>6.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.1</td>
<td>31.0</td>
<td>0.34</td>
<td>47.7</td>
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<tr>
<td>Hyperlipidemia</td>
<td>20.9</td>
<td>19.7</td>
<td>0.83</td>
<td>25.0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18.0</td>
<td>26.8</td>
<td>0.10</td>
<td>21.6</td>
</tr>
<tr>
<td>Prior angioplasty</td>
<td>9.7</td>
<td>9.9</td>
<td>0.97</td>
<td>18.2</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>2.5</td>
<td>4.2</td>
<td>0.44</td>
<td>9.5</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>1.4</td>
<td>4.2</td>
<td>0.15</td>
<td>1.9</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2.5</td>
<td>0.35</td>
<td>0.35</td>
<td>2.3</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3.2</td>
<td>1.4</td>
<td>0.69</td>
<td>6.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.4</td>
<td>2.8</td>
<td>0.11</td>
<td>0.8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.4</td>
<td>2.8</td>
<td>0.11</td>
<td>0.4</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64 (59–68)</td>
<td>64 (59–67)</td>
<td>0.79</td>
<td>62 (57–68)</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>3.0 (2.0–4.3)</td>
<td>3.0 (2.0–5.0)</td>
<td>0.16</td>
<td>3.0 (2.0–5.0)</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>13 (11–16)</td>
<td>17 (13–25)</td>
<td>0.001</td>
<td>19 (14–27)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.4</td>
<td>5.6</td>
<td>0.06</td>
<td>2.7</td>
</tr>
<tr>
<td>Clinical indication, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>2.5</td>
<td>2.6</td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>Stable angina</td>
<td>32.7</td>
<td>23.9</td>
<td></td>
<td>36.0</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>58.6</td>
<td>63.4</td>
<td></td>
<td>52.7</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>6.1</td>
<td>7.0</td>
<td></td>
<td>9.1</td>
</tr>
<tr>
<td>Bifurcation LM stenosis</td>
<td>21.7</td>
<td>33.8</td>
<td>0.037</td>
<td>49.4</td>
</tr>
<tr>
<td>Right coronary disease</td>
<td>0.7</td>
<td>1.00</td>
<td></td>
<td>15.2</td>
</tr>
<tr>
<td>Restenotic lesion</td>
<td>2.9</td>
<td>5.6</td>
<td>0.27</td>
<td>3.8</td>
</tr>
</tbody>
</table>

The values are presented with median (interquartile range) and number (percentage). *The p values among 4 groups stratified by extra left main coronary artery involvement within the stenting or CABG group.

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LM = left main; NSTEMI = non–ST-segment elevation myocardial infarction; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.
vs. 5.5%, p = 0.003) or MACCE (25.0% vs. 17.0%, p = 0.016) were significantly higher in patients with 3-vessel plus ULMCA disease than in those with isolated ULMCA disease.

**Adjusted HRs. IMPACT OF VASCULAR DISEASE.** After adjusting for differences in EuroSCORE, diabetes mellitus, and bifurcation ULMCA stenosis, the risks of death, MACE, or MACCE were not associated with the number of extra-ULMCA coronary artery disease in either stent or CABG groups (Fig. 2). Similarly, when the patients receiving stents were separated into those receiving DES and BMS, risk of MACE or MACCE was not associated with the number of diseased vessels.

**STENT VERSUS CABG ACCORDING TO VASCULAR DISEASE.** Figure 3 shows the HRs and CIs of outcomes following the use of stents or CABG in patient subgroups stratified by the number of extra-ULMCA coronary artery disease. Stenting and CABG showed comparable risks of death and MACE across subgroups stratified by vascular disease, both for the overall patient population and for Waves #1 and #2. However, the risk of MACCE was significantly higher with stenting than with CABG for patients having 2-vessel (HR: 1.739; 95% CI: 1.171 to 2.582; p = 0.006) or 3-vessel (HR: 1.493; 95% CI: 1.096 to 2.035; p = 0.011) disease in the overall patient population. When the patients were separated into Waves #1 and #2, the HRs of MACCE were significantly higher with stenting for patients with isolated ULMCA (HR: 3.113; 95% CI: 1.069 to 9.062; p = 0.037) and 3-vessel disease (HR: 2.152; 95% CI: 1.309 to 4.456; p = 0.039) in Wave #1, and those with 2-vessel disease (HR: 2.384; 95% CI: 1.329 to 4.277; p = 0.004) in Wave #2. Interactions of extra-ULMCA coronary artery involvement with treatment type were not significant in all subgroups.

In other Cox models, when the outcomes were adjusted with the SYNTAX score and EuroSCORE for 1,580 patients, the HRs of MACCE were still less favorable to stenting in patients with isolated ULMCA stenosis (HR: 2.970; 95% CI: 0.878 to 10.043; p = 0.080), those with 1-vessel (HR: 1.482; 95% CI: 0.664 to 3.309; p = 0.337), 2-vessel (HR: 1.667; 95% CI: 0.978 to 2.840; p = 0.060), and 3-vessel (HR: 1.505; 95% CI: 1.007 to 2.250; p = 0.046) disease. However, with regard to the MACE, the
HRs of stenting were 0.865 (95% CI: 0.519 to 1.443; \( p = 0.579 \)) in isolated left main coronary artery stenosis, 1.037 (95% CI: 0.389 to 2.763; \( p = 0.942 \)) in 1-vessel, 0.804 (95% CI: 0.358 to 1.805; \( p = 0.597 \)) in 2-vessel, and 0.865 (95% CI: 0.519 to 1.443; \( p = 0.579 \)) in 3-vessel disease, as compared with CABG.

**Discussion**

Despite DES showing feasible outcomes for ULMCA in several registries, concerns remain regarding the long-term safety of DES in high-risk patients with complex coronary anatomies. In particular, for ULMCA disease (18–20), the frequent occurrence of multivessel disease may show greater benefits with CAGB, enabling more complete revascularization than with percutaneous coronary intervention (21). Subgroup analysis of the SYNTAX trial showed a tendency toward a higher event rate with DES than with CAGB in patients with multivessel disease, but not in those with isolated ULMCA or 1-vessel disease (13). To date, however, no study in large numbers of patients has assessed the long-term clinical outcomes following revascularization for ULMCA stenosis in patients with extra-ULMCA coronary artery disease. Therefore, this study has an advantage, in which it specifically addresses this issue in a relatively large patient population taken from a nation-based registry enrolling all patients consecutively revascularized with stenting or CAGB for ULMCA disease. Of our patients, 75% receiving stents and 94% receiving CAGB had extra-ULMCA coronary artery disease.

In contrast to concerns regarding the long-term safety of DES in patients with complex coronary lesions (18,19,22), our results indicate that stenting and CAGB for ULMCA stenosis were of comparable safety, regardless of extra-ULMCA coronary artery disease. The long-term risks of death, stroke, or MACE were almost identical following stenting and CAGB in all subgroups stratified by the number of diseased vessels. In all subgroups, the observed 4-year incidence of MACE was within a narrow range, from 7% to 16%. This result is in agreement with the recent large randomized ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study or the registry of the DELFT (Drug Eluting Stent for Left Main) study, which enrolled ULMCA disease treated with DES and showed approximately 10% mortality over 2 years (11,12). Moreover, safety performance of both treatment strategies was also in agreement with the results of randomized studies comparing BMS and CAGB, which showed no significant differences in long-term mortality or myocardial infarction in patients with multivessel disease (23–27). A meta-analysis of 4 randomized controlled trials comparing CAGB and BMS found that, for patients with multivessel disease, the 1-year combined incidences of death, myocardial infarction, or stroke were 9.1% and 8.7%, respectively, rates that did not differ significantly (27). More recent studies also showed that DES and CAGB are of comparable safety in patients with multivessel disease (9,10,13,28,29). The recent randomized SYNTAX trial reported that the
1-year incidences of death, myocardial infarction, or stroke were 7.7% for CABG and 7.6% for stenting ($p = 0.98$) (13).

The safety of ULMCA revascularization was further evidenced by analysis of multivariable Cox models within the CABG or stent group. The risk of safety outcomes was not associated with the number of extra-ULMCA coronary artery involvement. In both unadjusted and adjusted analyses, the HRs of MACE in patients with extra-ULMCA coronary artery disease, even those having 3-vessel disease, did not differ significantly from the HRs in patients with isolated ULMCA or 1-vessel disease, CABG showed lower risks, although the differences were not statistically significant due to the small sample distribution. This finding is in agreement with the previous randomized or registry studies for patients with multivessel disease, which reported a higher incidence of TVR following percutaneous coronary intervention than CABG (24–27,30). Stenting with DES was also associated with a higher incidence of TVR than CABG for multivessel disease (9,10,13,30). In fact, in our unadjusted and adjusted analyses, the number of diseased vessels did not significantly influence the long-term outcomes with use of CABG. However, in the stent group, there was a tendency toward an increased crude rate of MACE or MACCE for patients with 3-vessel disease than those with isolated ULMCA stenosis, either in the stent or CABG group. This finding, combined with the results of our previous study, showing that a EuroSCORE integrating clinical risk profiles was the strongest predictor of long-term mortality or myocardial infarction (15), indicates that clinical factors other than angiographic extent of extra-ULMCA coronary artery disease may contribute more significantly to long-term clinical outcomes.

Our results suggest that a major finding of the MAIN-COMPARE study, showing a greater tendency of TVR with stenting than with CABG, may be broadly applicable to subgroups of patients with or without extra-ULMCA coronary artery stenosis (5). Particularly, for patients with 2- or 3-vessel disease, the risk of MACCE was approximately 50% higher with stenting than with CABG, driven by the increased TVR rate. Even in patients with isolated ULMCA or 1-vessel disease, CABG showed lower risks, although the differences were not statistically significant due to the small sample distribution. This finding is in agreement with the previous randomized or registry studies for patients with multivessel disease, which reported a higher incidence of TVR following percutaneous coronary intervention than CABG (24–27,30). Stenting with DES was also associated with a higher incidence of TVR than CABG for multivessel disease (9,10,13,30). In fact, in our unadjusted and adjusted analyses, the number of diseased vessels did not significantly influence the long-term outcomes with use of CABG. However, in the stent group, there was a tendency toward an increased crude rate of MACE or MACCE for patients with 3-vessel disease than those with isolated ULMCA stenosis, either in the stent or CABG group. This finding, combined with the results of our previous study, showing that a EuroSCORE integrating clinical risk profiles was the strongest predictor of long-term mortality or myocardial infarction (15), indicates that clinical factors other than angiographic extent of extra-ULMCA coronary artery disease may contribute more significantly to long-term clinical outcomes.
isolated ULMCA or 1-vessel disease. Given this result, our study supports the recent consensus statement that CABG surgery can be considered as the first-line therapy for ULMCA stenosis before a large randomized trial comparing stenting and CABG for ULMCA stenosis is performed (31). However, in contrast to our study, the left main substudy of the SYNTAX trial suggested that the effect of these 2 treatment strategies was dependent on vascular stenosis (13). For instance, the incidence of MACCE was likely to be higher for stenting than CABG in patients with ULMCA plus 2- or 3-vessel disease, but was lower for stenting in patients with isolated ULMCA or 1-vessel disease.

The difference between the SYNTAX trial and ours regarding the impact of extra-ULMCA coronary artery involvement may be explained by several factors. First, in contrast to the restricted population in the randomized trial, our nation-based registry reflected an overall population treated in real-world practice. Second, the 1-year follow-up period in the SYNTAX trial may not be sufficient to compare the effectiveness of CABG and stenting. Because the benefit of CABG over medical therapy has been reported to become apparent after 1 year, longer follow-up may be necessary (21). Third, our mandatory practice of angiographic follow-up after stenting might increase the unnecessary need for TVR (32,33). Because angiographic surveillance is generally recommended after stenting but not after CABG, angiographic follow-up was performed in 73% of the stent group and 15% of the CABG group (34). A previous angiographic substudy of a randomized trial suggested that angiographic surveillance approximately doubled the risk of repeat revascularization (33). Moreover, because revascularization treatment was greatly influenced by the practice pattern of country, institution, and operator, a post hoc comparison of TVR across the studies is very difficult. Finally, a lack of information regarding the interaction test in the SYNTAX trial limits our ability to compare the results of the 2 studies (14). We observed no significant interaction between treatment type and vascular involvement in the overall study period, as well with BMS or DES. This analysis indicates that the differences between CABG and stenting may be homogenously maintained across all subgroups stratified in our study. Nonetheless, it is noteworthy that the effectiveness gap between the stent and CABG is gradually decreasing by advancement of stenting technique and use of DES. In our analysis, the incidence of TVR was much lower with use of DES as compared with BMS.

Study limitations. First, although we included a relatively large study population based on a national registry, it is still underpowered to detect small differences between stenting and CABG in multiple comparisons. In fact, the negative results with insufficient sample size and event counts may be misinterpreted due to the unstable estimates of effect, incongruous patterns of results across subgroups, inability to employ a sufficient number of control variables to remove potential biases, intergroup differences or interactions in baseline parameters, and underpowered main effects tests (35). Therefore, an impact of important clinical risks, such as diabetes mellitus, on the differential outcomes between stenting and CABG could not be adequately assessed. To evaluate the power of observed effect, post-hoc power analysis may play a role after completion of study (36). Nevertheless, given the exploratory purpose of this substudy, our result may provide useful information for further clinical researches. Second, despite our multivariable Cox adjustments, observational and nonrandomized study design has inherent limitations for excluding potential biases. Furthermore, due to the small sample size and rare event rate in each subgroup, more rigorous adjustments with propensity-score or inverse-probability-of-treatment weighting could not be tried (37,38). However, any bias may not be serious, inasmuch as the pattern of significance was consistently observed in unadjusted and adjusted outcomes. Third, a lack of full angiographic adjustment may be a residual bias in interpreting the outcomes because angiographic analysis was performed for 71% of patients. Nonetheless, the pattern of HRs of MACE or MACCE after stenting, as compared with CABG, was consistent after adjustments with either EuroSCORE or SYNTAX score (15).

Conclusions

A percutaneous approach with stenting appears to be a safe alternative to CABG in patients with ULMCA and vascular disease. The advantage of CABG over percutaneous intervention seems to lie principally in the reduction of repeat revascularization across the subgroups analyzed in our study. However, additional randomized studies, using a sufficient sample size, are required to provide stronger evidence.

Reprint requests and correspondence: Dr. Seung-Jung Park, Department of Cardiology, University of Ulsan College of Medicine, Cardiac Center, Asan Medical Center, 388-1 Poongnapdong, Songpa-gu, Seoul 138-736, South Korea. E-mail: sjpark@amc.seoul.kr.

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