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Randomized Trial of Stents Versus Bypass Surgery for Left Main Coronary Artery Disease

5-Year Outcomes of the PRECOMBAT Study

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ABSTRACT

BACKGROUND In a previous randomized trial, we found that percutaneous coronary intervention (PCI) was not inferior to coronary artery bypass grafting (CABG) for the treatment of unprotected left main coronary artery stenosis at 1 year.

OBJECTIVES This study sought to determine the 5-year outcomes of PCI compared with CABG for the treatment of unprotected left main coronary artery stenosis.

METHODS We randomly assigned 600 patients with unprotected left main coronary artery stenosis to undergo PCI with a sirolimus-eluting stent (n = 300) or CABG (n = 300). The primary endpoint was a major adverse cardiac or cerebrovascular event (MACCE: a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target vessel revascularization) and compared on an intention-to-treat basis.

RESULTS At 5 years, MACCE occurred in 52 patients in the PCI group and 42 patients in the CABG group (cumulative event rates of 17.5% and 14.3%, respectively; hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 0.84 to 1.90; p = 0.26). The 2 groups did not differ significantly in terms of death from any cause, myocardial infarction, or stroke as well as their composite (8.4% and 9.6%; HR, 0.89; 95% CI, 0.52 to 1.52; p = 0.66). Ischemia-driven target vessel revascularization occurred more frequently in the PCI group than in the CABG group (11.4% and 5.5%, respectively; HR: 2.11; 95% CI: 1.16 to 3.84; p = 0.012).

CONCLUSIONS During 5 years of follow-up, our study did not show significant difference regarding the rate of MACCE between patients who underwent PCI with a sirolimus-eluting stent and those who underwent CABG. However, considering the limited power of our study, our results should be interpreted with caution. (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease [PRECOMBAT]; NCT00422968) (J Am Coll Cardiol 2015;65:2198–206) © 2015 by the American College of Cardiology Foundation.

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Patients undergoing revascularization of unprotected left main coronary artery (ULMCA) stenosis are considered at high risk of adverse cardiovascular events. Coronary artery bypass grafting (CABG) had been considered the standard of care for ULMCA stenosis (1). However, over the past 20 years, improvements in stent technology and an accumulation of operator experience have increased the number of elective percutaneous coronary interventions (PCIs) performed to treat UMLCA stenosis (2–4). Subsequently, several large registries and randomized, controlled studies have shown that PCI with a drug-eluting stent and CABG had comparable incidences of death, myocardial infarction (MI), or stroke (5–7). Thus, recent guidelines considered PCI to be a potential alternative to CABG for ULMCA stenosis (8). However, the durable effect of PCI remains in debate, and there are limited existing data from long-term studies comparing PCI and CABG.

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We present the 5-year results of the PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) study.

METHODS

STUDY DESIGN AND PATIENTS. The study design and methods of the PRECOMBAT trial were previously reported (6). In brief, the PRECOMBAT trial was a prospective, open-label, randomized trial conducted at 13 sites in South Korea. Patients considered eligible to participate in the study were older than 18 years of age and had received a diagnosis of stable angina, unstable angina, silent ischemia, or non-ST-segment elevation MI. All patients had newly diagnosed ULMCA stenosis (more than 50% diameter stenosis by visual angiographic estimation) and had been judged to be suitable candidates for either PCI or CABG. A complete list of inclusion and exclusion criteria is provided in the Online Appendix. Patients were randomly assigned to undergo PCI with sirolimus-eluting stents or CABG in a 1:1 ratio. The institutional review board at each hospital approved the protocol, and all patients provided written informed consent.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

PROCEDURES. The procedures for PCI and CABG were described previously (5). Sirolimus-eluting stents were the default drug-eluting stents used during PCI. Use of intravascular ultrasound, adjunctive devices, or glycoprotein IIb/IIIa inhibitors was at the operator's discretion. All patients undergoing PCI took aspirin plus clopidogrel (300-mg loading dose) or ticlopidine (500-mg loading dose) before or during the procedure. After PCI, all patients were prescribed 100 mg/day aspirin indefinitely and 75 mg/day clopidogrel or 250 mg/day ticlopidine for at least 1 year. During CABG, the internal thoracic artery was preferred for bypass of the left anterior descending artery. Medications after CABG were given according to the policy of the institution or the preference of the surgeon. During the index procedure or repeated revascularization, the decision of which lesion was to be revascularized was at the operator's discretion.

FOLLOW-UP AND ENDPOINTS. After PCI, all patients were asked to undergo follow-up angiography 8 to 10 months after the procedure or earlier if they were experiencing symptoms of angina. However, routine follow-up angiography was not performed for patients who underwent CABG. All other follow-up assessments were performed at 1, 6, 9, and 12 months and yearly thereafter at a clinic visit or via a telephone interview.

The primary endpoint was a major adverse cardiac or cerebrovascular event (MACCE) (a composite of death from any cause, MI, stroke, or ischemia-driven target vessel revascularization [TVR]) after randomization. Secondary endpoints included the individual components of the primary endpoint; a composite of death, MI, or stroke; and clinically driven TVR. Deaths were considered cardiac unless an unequivocal noncardiac cause was established. MI was defined as the appearance of new Q waves and an increase in the creatine kinase-myocardial band concentration to more than 5 times the upper limit of the normal range, if occurring within 48 h after the procedure or as the appearance of new Q waves or an increase in the creatine kinase-myocardial band concentration to greater than the upper limit of the normal range, plus ischemic symptoms or signs, if occurring more than 48 h after the procedure. Stroke was defined as a sudden onset of neurological deficit resulting from vascular lesions of the brain and persisting for more than 24 h. TVR, in which repeat revascularization with either PCI or CABG was performed in the treated vessel, was considered to be driven by

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

HR = hazard ratio

MACCE = major adverse cardiac or cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

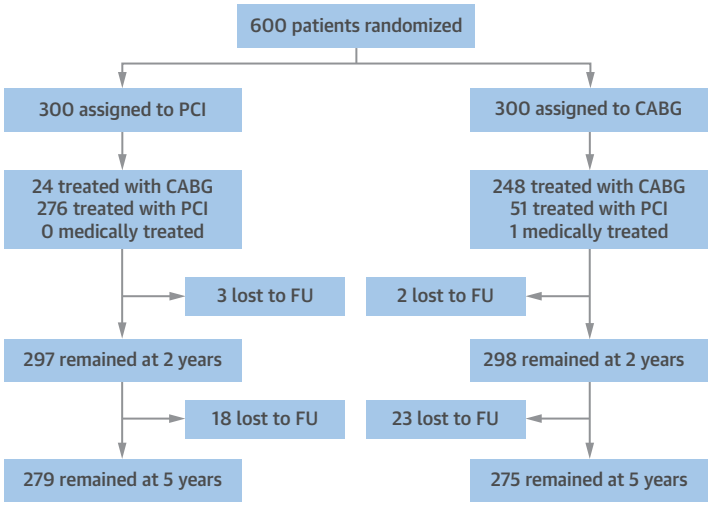
TVR = target vessel revascularization

ULMCA = unprotected left main coronary artery

ischemia if the stenosis of any vessel was at least 50% of the vessel diameter in the presence of ischemic signs or symptoms or if the stenosis was at least 70% of the vessel diameter, even in the absence of ischemic signs or symptoms. Alternatively, TVR was considered clinically driven when the treated vessels had stenosis of at least 50% in the presence of ischemic signs or symptoms. The event adjudication committee, whose members were blind to the study group assignments, assessed all clinical endpoints.

STATISTICAL ANALYSIS. Assuming 13% incidence of the primary endpoint in the CABG group, a noninferiority margin of 7%, and use of a *Z* test for hypothesis testing, the original PRECOMBAT trial was designed to have 80% power to show the noninferiority of PCI, with a 1-sided type I error rate of 0.05. In this study, unless stated otherwise, all analyses were performed on an intention-to-treat basis. A descriptive analysis was performed by presenting data as the mean ± SD or number (%). Continuous variables were compared with a Student *t* test or Wilcoxon rank sum test, and categorical variables were compared with chi-square or Fisher exact test, as appropriate. Five-year outcomes were defined as events occurring within 1,825 days after randomization. The number of events and their cumulative incidence were presented as number (%), with the latter estimated using the Kaplan-Meier method and compared between the 2 groups using the log-rank test of the time to the first event after randomization. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with the use of Cox proportional hazards models. The proportional hazards assumption was checked with a graphical log-minus-log method. We also compared the primary endpoint between the 2 groups using Cox regression models with robust SEs to account for the clustering effect of sites. The patients lost to follow-up were included in the analyses for all outcomes by censoring at the data of last follow-up. We assessed the consistency of treatment effects in the pre-specified subgroups using Cox regression models with tests for interaction. For more explicit comparison with contemporary studies and guidelines, we added a subgroup analysis according to the SYNTAX tertile from the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial. All statistical analyses were performed using IBM SPSS version 21 (IBM, Chicago, Illinois). A 2-tailed p value <0.05 was considered statistically significant.

FIGURE 1 Patient Distribution in the PRECOMBAT Study at the 5-Year Follow-Up



The number of the patients randomized to each group, those who actually received the assigned treatment, and those who were lost to follow-up are shown. CABG = coronary artery bypass grafting; FU = follow-up; PCI = percutaneous coronary intervention; PRECOMBAT = Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease.

RESULTS

STUDY PATIENTS. Between April 2004 and August 2009, a total of 600 eligible patients were randomly assigned to undergo PCI with sirolimus-eluting stents (n = 300) or CABG (n = 300). Of those, 279 patients (93%) in the PCI group and 275 patients (91.7%) in the CABG group completed 5 years of follow-up (Figure 1).

Baseline demographic and lesion characteristics were previously described (7). In brief, the mean age of patients was 61.8 ± 10.0 years in the PCI group and 62.7 ± 9.5 years in the CABG group; 228 patients (76.0%) in the PCI group and 231 patients (77.0%) in the CABG group were male; 102 patients (34.0%) in the PCI group and 90 patients (30.0%) in the CABG group had medically treated diabetes, of whom 10 (3.3%) and 9 (3.0%), respectively, needed insulin; 223 patients (74.4%) in the PCI group and 213 patients (71.0%) in the CABG group had left main plus multivessel involvement. The mean SYNTAX score was 24.4 ± 9.4 in the PCI group and 25.8 ± 10.5 in the CABG group.

Selected procedural characteristics of the patients are as follows. In the PCI group, intravascular ultrasound was used in 91.2%; the mean number of stents implanted in left main coronary lesions and per-patient was 1.6 ± 0.8 and 2.7 ± 1.4, respectively. In CABG patients, 63.8% underwent

off-pump surgery; 93.6% underwent revascularization of the left anterior descending artery with left internal mammary artery.

Antiplatelet drug use was significantly higher in patients in the PCI group than in the CABG group throughout the study period. At 5 years, significantly more patients in the PCI group were receiving dual-antiplatelet therapy than in the CABG group (Online Table 1).

STUDY ENDPOINTS. The cumulative incidences of the clinical outcomes are described in **Table 1**, the **Central Illustration**, and **Figure 2**. At 5 years, the cumulative incidence of MACCE was 17.5% in the PCI group and 14.3% in the CABG group (HR: 1.27; 95% CI: 0.84 to 1.90; p = 0.26). Analysis after adjustment for between-site variability showed results similar to those from the original analysis (HR: 1.27; 95% CI: 0.83 to 1.93; p = 0.28). The rate of the composite of death from any cause, MI, or stroke was also similar between the 2 groups (8.4% and 9.6%, respectively; HR: 0.89; 95% CI: 0.52 to 1.52; p = 0.66), without significant differences in the individual components (**Central Illustration**). Ischemia-driven TVR was more likely to occur in the PCI group than in the CABG group (11.4% and 5.5%; HR: 2.11; 95% CI: 1.16 to 3.84; p = 0.012) (**Figure 2**). In a landmark analysis (Online Figure 1), the risk of ischemia-driven TVR in the PCI group was more obvious 1 year after randomization. An analysis of an as-treated basis is shown in Online Table 2. Definite or probable stent thrombosis occurred in 2 patients, with a 5-year cumulative incidence of 0.3%.

SUBGROUP. Formal testing for interactions showed that the results of the comparison of the 5-year rate of MACCE between PCI and CABG were consistent across multiple subgroups except for those defined according to angiographic left main coronary artery stenosis (>70% vs. 50% to 70%) (**Figure 3**). Across the 3 subgroups defined by SYNTAX score tertiles, the rates of MACCE and the composite of death from any cause, MI, or stroke were not significantly different between the 2 groups (Online Table 3, Online Figure 2). In the high SYNTAX score (≥33) group, the rate of ischemia-driven TVR was significantly higher in the PCI group than in the CABG group.

TABLE 1 Study Outcomes at the 5-Year Follow-Up

Endpoint	PCI (n = 300)	CABG (n = 300)	Hazard Ratio (95% CI)	p Value
MACCE	52 (17.5)*	42 (14.3)	1.27 (0.84–1.90)	0.26
Death from any cause	17 (5.7)	23 (7.9)	0.73 (0.39–1.37)	0.32
Cardiac	11 (3.8)	20 (6.9)	0.54 (0.26–1.13)	0.098
Noncardiac	6 (2.0)	3 (1.1)	1.98 (0.49–7.91)	0.33
Myocardial infarction	6 (2.0)	5 (1.7)	1.20 (0.37–3.93)	0.76
Q-wave MI	4 (1.4)	3 (1.0)	1.33 (0.30–5.95)	0.71
Non-Q-wave MI	2 (0.7)	2 (0.7)	0.99 (0.14–7.06)	1.00
Stroke	2 (0.7)	2 (0.7)	0.99 (0.14–7.02)	0.99
Death, MI, or stroke	25 (8.4)	28 (9.6)	0.89 (0.52–1.52)	0.66
Repeat revascularization	38 (13.0)	21 (7.3)	1.86 (1.09–3.17)	0.020
TVR	36 (12.4)	18 (6.3)	2.05 (1.17–3.62)	0.011
Ischemia driven	33 (11.4)	16 (5.5)	2.11 (1.16–3.84)	0.012
Clinically driven	27 (9.3)	15 (5.2)	1.83 (0.97–3.44)	0.057
Death, MI, or ischemia-driven TVR	50 (16.8)	40 (13.7)	1.28 (0.85–1.94)	0.24

Values are n (%) unless otherwise indicated. *Percentages are Kaplan-Meier estimates from the intention-to-treat analysis. A log-rank test was used to calculate p values. Ischemia-driven TVR was defined as any repeat revascularization with either PCI or CABG in the treated vessel having at least 50% diameter stenosis in the presence of ischemic signs or symptoms or at least 70% diameter stenosis in the absence of ischemic signs or symptoms. Clinically driven TVR excluded lesions without ischemic symptoms or signs from the ischemia-driven TVR.

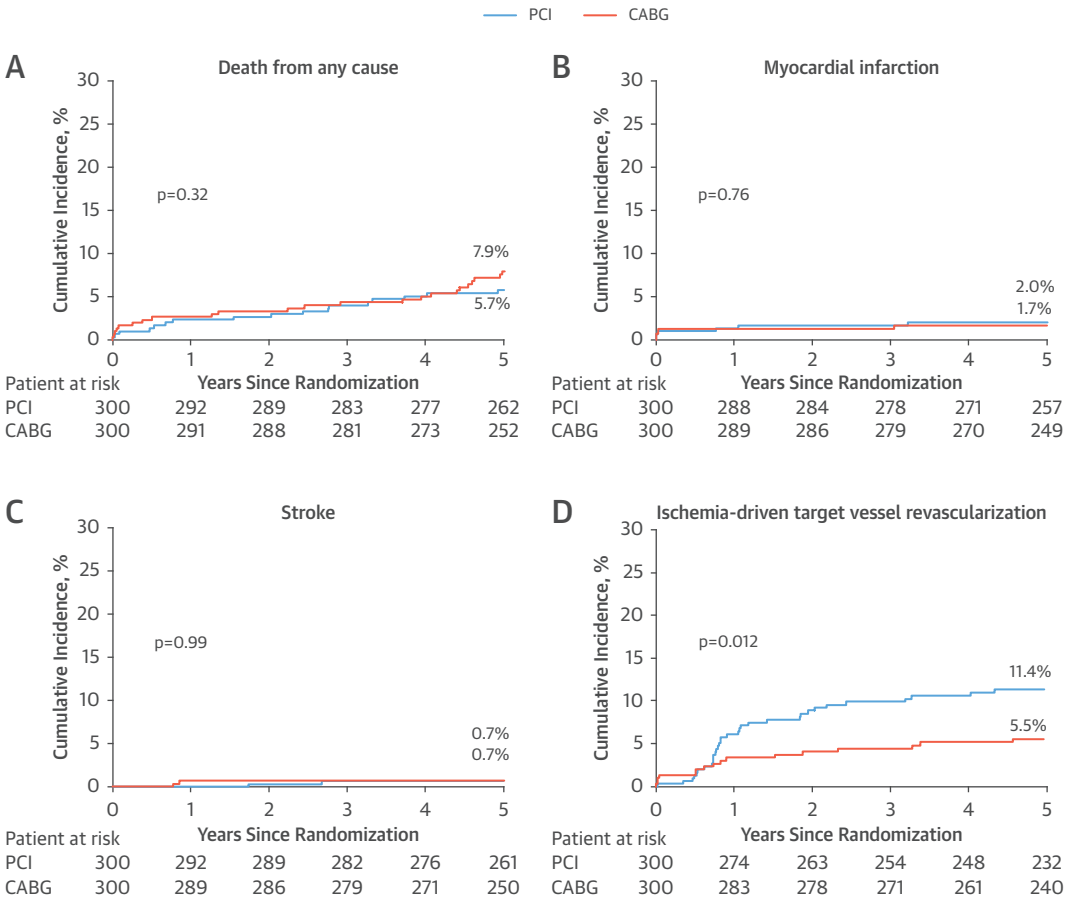
CABG = coronary artery bypass grafting; CI = confidence interval; MACCE = major adverse cardiac or cerebrovascular event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization.

DISCUSSION

The PRECOMBAT study was a randomized trial comparing PCI with drug-eluting stents and CABG, focusing on patients with ULMCA stenosis. The 1-year outcomes of the study showed the noninferiority of PCI to CABG with respect to MACCE (7). The current 5-year results of the study showed that there were no significant differences in the rate of MACCE between patients assigned to PCI with sirolimus-eluting stents and those assigned to CABG, which confirmed and extended the results observed at 1 year (**Central Illustration**). In addition, the rate of the composite of death, MI, or stroke was similar between the 2 groups. However, ischemia-driven TVR occurred more frequently in the PCI group than in the CABG group. These results are supported by data from observational studies (9–12), a small randomized study (13), and a meta-analysis of patients with long-term follow-up (14). Recently, 5-year outcomes of the left main subgroup in the SYNTAX study also showed a similar trend, with no differences in the rate of MACCE between the PCI and CABG groups (15).

The rates of overall adverse events in our study were lower than those reported in the SYNTAX study. The main differences were that we used sirolimus-eluting stents as the default stent, and we used intravascular ultrasound in more than 90% of patients for stent optimization (16–18). We considered reasonably incomplete, but functionally adequate stent implantation in the non-left main coronary artery stenosis to avoid an excess of stent and related events (19). In addition, differences in patient characteristics, presentation, and lesion complexity may be possible contributing factors. Nevertheless, the

FIGURE 2 Kaplan-Meier Cumulative Event Curves for the Individual Clinical Events at the 5-Year Follow-Up



Shown are rates of the death of any cause **(A)**, myocardial infarction **(B)**, stroke **(C)**, and ischemia-driven target vessel revascularization **(D)**. Abbreviations as in Figure 1.

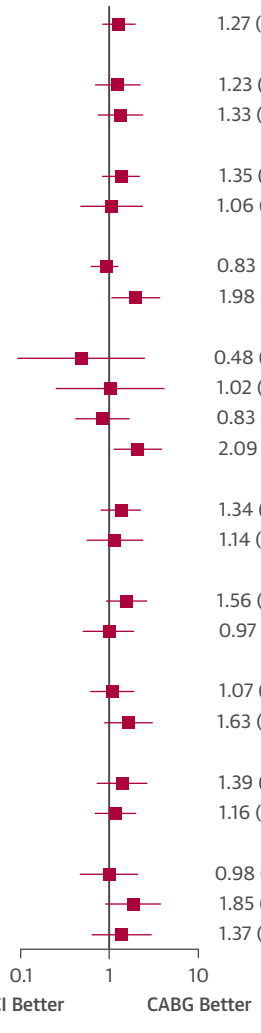
rate of TVR significantly increased in the PCI group at 5 years compared with the CABG group. Given a higher rate of repeat revascularization, even after the use of second-generation drug-eluting stents for ULMCA stenosis, frequent repeat revascularization could be an inherent weakness of stent-related treatments (20). However, the observed increase in repeat revascularization in the PCI group did not appear to translate into an increase in hard endpoints, such as death, MI, or stroke, although a further study with longer follow-up and larger number of subjects will be needed.

With respect to the occurrence of stroke, there was no significant difference between PCI and CABG in our study. However, in the SYNTAX study, although the rate of repeat revascularization was significantly higher in the PCI group, this was offset by a significantly higher rate of stroke in the CABG group. Consequently, the rate of MACCE was similar between groups. Although the absence of any difference between the groups in our study is not easily explained, possible causes are our study's low event rates and limited statistical power. In addition, the different ethnicities in our study and the SYNTAX study could be another contributing factor.

Unlike the situation in multivessel disease (21,22), both PCI and CABG showed similar rates of the composite of death, MI, or stroke in patients with ULMCA stenosis. The reason for this difference in outcomes between ULMCA stenosis and multivessel stenosis is unclear, but ULMCA stenosis might be a more attractive target for PCI because of its larger caliber, shorter lesion length, and lack of tortuosity compared with multivessel disease. The ongoing EXCEL (Evaluation of Xience Prime or Xience V Versus

FIGURE 3 Subgroup Analysis

Subgroup	MACCE		Hazard Ratio (95% CI)	P value	P value for Interaction
	PCI	CABG			
	n / total n. (%)				
Overall	52/300 (17.5)	42/300 (14.3)	1.27 (0.84-1.90)	0.26	-
Age					0.86
≥65 yr	24/129 (18.8)	23/149 (15.8)	1.23 (0.70-2.18)	0.47	
<65 yr	28/171 (16.5)	19/151 (12.8)	1.33 (0.74-2.38)	0.33	
Sex					0.60
Male	39/228 (17.3)	30/231 (13.3)	1.35 (0.84-2.17)	0.21	
Female	13/72 (18.1)	12/69 (17.5)	1.06 (0.48-2.31)	0.89	
Left main coronary artery stenosis					0.043
>70%	20/140 (14.4)	27/159 (17.4)	0.83 (0.47-1.48)	0.53	
50-70%	32/160 (20.2)	15/141 (10.9)	1.98 (1.07-3.65)	0.027	
Coronary artery disease distribution					0.14
Left main only	2/27 (7.4)	5/34 (14.8)	0.48 (0.09-2.47)	0.37	
Left main with single-vessel disease	4/50 (8.0)	4/53 (7.7)	1.02 (0.25-4.07)	0.98	
LM with double-vessel disease	16/101 (16.0)	17/90 (19.2)	0.83 (0.42-1.64)	0.59	
LM with triple-vessel disease	30/122 (24.8)	16/123 (13.3)	2.09 (1.14-3.84)	0.015	
Bifurcation involvement					0.71
Yes	37/200 (18.7)	26/183 (14.7)	1.34 (0.81-2.22)	0.25	
No	15/99 (15.2)	15/111 (13.6)	1.14 (0.56-2.33)	0.73	
Right coronary artery involvement					0.27
Yes	33/149 (22.3)	24/159 (15.5)	1.56 (0.92-2.64)	0.095	
No	19/151 (12.7)	18/141 (13.0)	0.97 (0.51-1.85)	0.93	
Acute coronary syndrome					0.35
Yes	25/140 (17.9)	27/163 (16.8)	1.07 (0.62-1.85)	0.79	
No	27/160 (17.1)	15/137 (11.4)	1.63 (0.87-3.06)	0.13	
Diabetes					0.66
Yes	23/102 (22.7)	15/90 (16.9)	1.39 (0.73-2.67)	0.32	
No	29/198 (14.8)	27/210 (13.2)	1.16 (0.69-1.96)	0.58	
Syntax score					0.49
0-22	16/129 (12.5)	13/104 (13.0)	0.98 (0.47-2.05)	0.97	
23-32	22/102 (21.7)	12/97 (12.6)	1.85 (0.91-3.73)	0.083	
≥33	14/58 (24.2)	13/68 (19.2)	1.37 (0.64-2.91)	0.41	

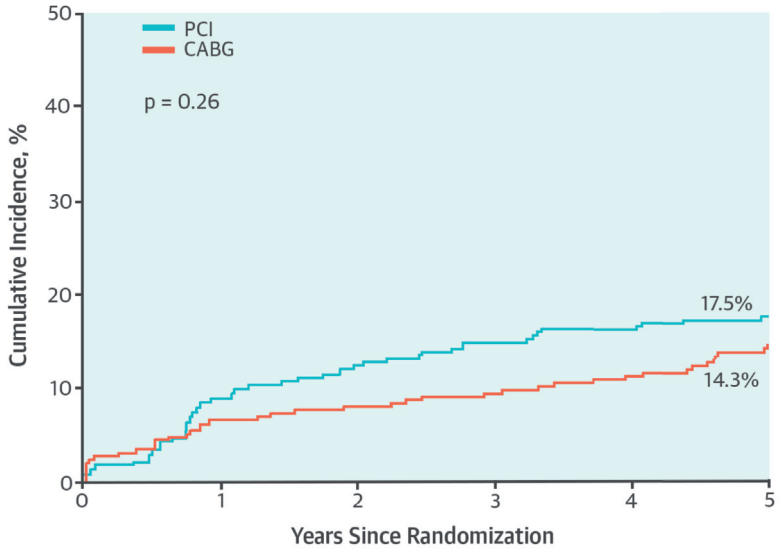


Subgroup analyses with hazard ratios and 95% confidence intervals are shown for the primary endpoint of the composite of death of any cause, myocardial infarction, stroke, or ischemia-driven target vessel revascularization among subgroups of patients randomized to undergo PCI or CABG. The p value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. CI = confidence interval; LM = left main; MACCE = major adverse cardiac or cerebrovascular event(s); other abbreviations as in Figure 1.

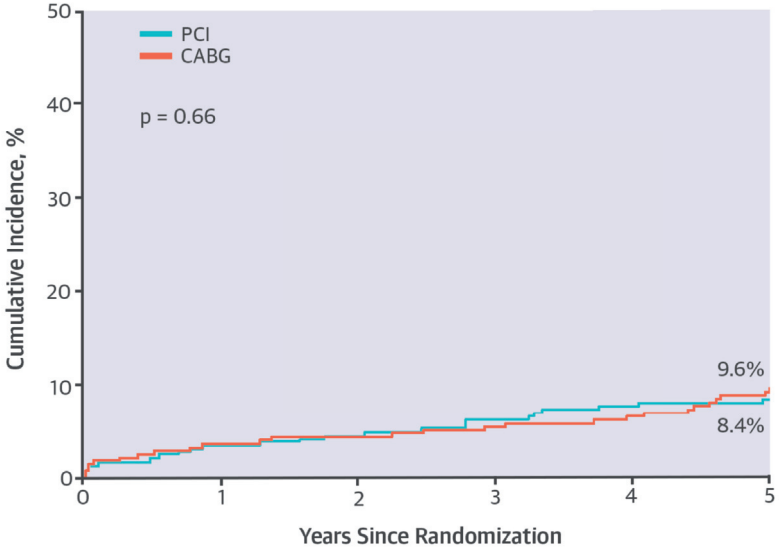
CABG for Effectiveness of Left Main Revascularization) trial comparing a 3-year composite endpoint of death, MI, or stroke in patients treated with PCI using second-generation drug-eluting stents and CABG will provide important information in this regard.

Current clinical guidelines have adopted the SYNTAX score to aid in selection of the appropriate revascularization strategy for ULMCA stenosis (8). However, our study showed that the SYNTAX score tertile did not discriminate the more appropriate strategy between treatments. Even in patients with the highest baseline SYNTAX scores (≥33), no significant difference between treatment groups for the primary endpoint was reported. Although this might be primarily due to insufficient statistical power, the utility of the SYNTAX score for this purpose still needs to be evaluated (21,23-25). Recent approaches combining anatomic and clinical factors could be promising for a more accurate personalized assessment of patient risk (25).

CENTRAL ILLUSTRATION **Stenting Versus CABG for Left Main Stenosis: Kaplan-Meier Cumulative Event Curves of the Primary Endpoint and the Major Secondary Endpoint at the 5-Year Follow-Up**



Patients at Risk						
PCI	300	272	261	252	246	231
CABG	300	279	274	267	256	235



Patients at Risk						
PCI	300	288	284	277	270	256
CABG	300	287	284	277	268	247

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(Top) The cumulative incidence of major adverse cardiac or cerebrovascular events (the composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target vessel revascularization). **(Bottom)** The composite of death of any cause, myocardial infarction, or stroke. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

In the subgroup analysis, there was a significant interaction between angiographic stenosis of the left main coronary artery and treatment strategies for the primary endpoint. The reason was unclear, and this unexpected finding is likely due to the play of chance. In addition, patients with left main disease plus 3-vessel disease showed better outcomes with CABG than with PCI, suggesting caution in the use of PCI for left main disease in patients with 3-vessel coronary artery disease or advanced coronary artery disease.

STUDY LIMITATIONS. First, although we tried to enroll all comers, as in other randomized studies, it was possible that we enrolled selected patients with relatively low-risk profiles. Second, crossovers, particularly from PCI to CABG, may have introduced bias. Third, this study did not have adequate power to compare hard endpoints, such as death, MI, and stroke. Fourth, owing to the limited sample size, the results of our subgroup analyses should be considered hypothesis generating at best. Fifth, the systematic performance of follow-up angiography in the PCI group may have increased the rate of TVR. Smaller and statistically insignificant HR for clinically driven TVR, compared with that for ischemia-driven TVR, probably supports this hypothesis. Finally, clinical outcomes may have been affected by unequal use of antiplatelet agents between the 2 groups (Online Table 1).

CONCLUSIONS

During the 5-year follow-up, our study did not show a significant difference in the rate of MACCE between patients who underwent PCI with a sirolimus-eluting stent and those who underwent CABG, supporting current guidelines stating that left main stenting is a feasible revascularization strategy for patients with suitable coronary anatomy. However, considering the limited power of our study, our results should be interpreted with caution.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Over 5 years, outcomes of revascularization for patients with LMCA stenosis managed by PCI did not differ significantly in terms of the composite endpoint of all-cause mortality, MI, stroke, or target vessel revascularization from those in patients undergoing CABG surgery.

TRANSLATIONAL OUTLOOK: Additional studies of a larger number of patients and longer follow-up are needed to provide adequate statistical power to establish the optimal revascularization strategy for the prevention of death, MI, and stroke in patients with LMCA stenosis.

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KEY WORDS coronary artery bypass grafting, long-term outcome, percutaneous coronary intervention

APPENDIX For an expanded Methods section, a list of the participating investigators, and supplemental tables and figures, please see the online version of this article.