

ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

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Percutaneous coronary intervention (PCI) is increasingly used to treat unprotected left main coronary artery stenosis, although coronary-artery bypass grafting (CABG) has been considered to be the treatment of choice.

METHODS

We randomly assigned patients with unprotected left main coronary artery stenosis to undergo CABG (300 patients) or PCI with sirolimus-eluting stents (300 patients). Using a wide margin for noninferiority, we compared the groups with respect to the primary composite end point of major adverse cardiac or cerebrovascular events (death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) at 1 year. Event rates at 2 years were also compared between the two groups.

RESULTS

The primary end point occurred in 26 patients assigned to PCI as compared with 20 patients assigned to CABG (cumulative event rate, 8.7% vs. 6.7%; absolute risk difference, 2.0 percentage points; 95% confidence interval [CI], -1.6 to 5.6; $P=0.01$ for noninferiority). By 2 years, the primary end point had occurred in 36 patients in the PCI group as compared with 24 in the CABG group (cumulative event rate, 12.2% vs. 8.1%; hazard ratio with PCI, 1.50; 95% CI, 0.90 to 2.52; $P=0.12$). The composite rate of death, myocardial infarction, or stroke at 2 years occurred in 13 and 14 patients in the two groups, respectively (cumulative event rate, 4.4% and 4.7%, respectively; hazard ratio, 0.92; 95% CI, 0.43 to 1.96; $P=0.83$). Ischemia-driven target-vessel revascularization occurred in 26 patients in the PCI group as compared with 12 patients in the CABG group (cumulative event rate, 9.0% vs. 4.2%; hazard ratio, 2.18; 95% CI, 1.10 to 4.32; $P=0.02$).

CONCLUSIONS

In this randomized trial involving patients with unprotected left main coronary artery stenosis, PCI with sirolimus-eluting stents was shown to be noninferior to CABG with respect to major adverse cardiac or cerebrovascular events. However, the noninferiority margin was wide, and the results cannot be considered clinically directive. (Funded by the Cardiovascular Research Foundation, Seoul, Korea, and others; PRECOMBAT ClinicalTrials.gov number, NCT00422968.)

A NUMBER OF REGISTRY REPORTS, AS well as a substudy from a large, randomized trial, have indicated that percutaneous coronary intervention (PCI) may be an acceptable alternative to coronary-artery bypass grafting (CABG) in some patients with unprotected left main coronary artery stenosis.¹⁻¹¹ Recent clinical guidelines have accordingly stated that elective PCI can be considered for patients who have unprotected left main coronary artery disease, although they suggest that the aggregated evidence favors CABG.^{12,13} Whether the outcomes after PCI are similar to those after CABG remains uncertain, however, owing to the lack of large, randomized clinical trials. Registry results have an inherent limitation of selection bias, preventing an accurate comparison of the two treatments.¹⁴ The results observed in patients with left main coronary artery stenosis in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery randomized substudy (SYNTAX; ClinicalTrials.gov number, NCT00114972), although hypothesis-generating, nonetheless indicate the need for further randomized studies, owing to the limitations of such subgroup analyses.^{6,15} A recent small, randomized study, which failed to show the noninferiority of PCI as compared with CABG, was limited by inadequate statistical power.¹¹

In the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial, we compared PCI using sirolimus-eluting stents with CABG for revascularization in patients with unprotected left main coronary artery stenosis.

METHODS

STUDY DESIGN

The PRECOMBAT trial was a prospective, open-label, randomized trial conducted at 13 sites in Korea. The trial was designed by the principal investigator, and the protocol was approved by the institutional review board at each participating center (see the trial protocol, available with the full text of this article at NEJM.org). Funding was provided by the Cardiovascular Research Foundation, Seoul, Korea; Cordis; and the Korean Ministry of Health and Welfare. The funders assisted in the design of the protocol but had no role in the conduct of the trial or in the analysis

or interpretation of the data. The principal investigator (the first author) had unrestricted access to the data after the database was locked, prepared all drafts of the manuscript, and made the decision to submit the manuscript for publication. The principal investigator vouches for the completeness and accuracy of the data and the analyses, as well as the fidelity of the study to the trial protocol.

STUDY PATIENTS

Eligible study participants were older than 18 years of age and had received a diagnosis of stable angina, unstable angina, silent ischemia, or non-ST-elevation myocardial infarction. All patients had to have newly diagnosed unprotected stenosis of more than 50% of the diameter of the left main coronary artery, as estimated visually, and had to be considered by the physicians and surgeons at each hospital to be suitable candidates for either PCI or CABG. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org. A separate registry was created to allow the follow-up of patients who had unprotected left main coronary artery stenosis but who were not eligible to participate in the trial. All study participants provided written informed consent using documents approved by the local ethics board.

STUDY PROCEDURES

Study participants were randomly assigned, in a 1:1 ratio, with the use of an interactive Web-based response system, to undergo PCI with sirolimus-eluting stents or CABG. The randomization sequence was computer-generated; randomization was performed in permuted block sizes of 6 and 9, with the use of sealed envelopes, and was stratified according to participating center. Details of the PCI and CABG procedures are provided in the Supplementary Appendix.

FOLLOW-UP AND END POINTS

All patients who underwent PCI were asked to return for follow-up angiography 8 to 10 months after the procedure, or earlier if symptoms of angina developed. In contrast, routine follow-up angiography was not recommended for patients who underwent CABG. All other follow-up assessments were conducted in the hospital and at 30 days and 6, 9, and 12 months at a clinic visit or by means of a telephone interview.

The primary end point was a composite of major adverse cardiac or cerebrovascular events, including death from any cause, myocardial infarction, stroke, and ischemia-driven target-vessel revascularization, for the 12-month period after randomization. Secondary end points included the individual components of the primary end point; the composite of death, myocardial infarction, or stroke; and stent thrombosis. Definitions of the end points are provided in the Supplementary Appendix.

All clinical end points were assessed by the event adjudication committee, whose members were unaware of the study-group assignments. Analyses of all angiographic data were performed in the angiographic core laboratory of the Cardiovascular Research Foundation.^{16,17}

STATISTICAL ANALYSIS

The primary analysis was a noninferiority comparison between the two treatments with respect to the primary end point of major adverse cardiac or cerebrovascular events, according to the intention-to-treat principle. On the basis of data from large, randomized clinical trials evaluating the efficacy of CABG in patients with multivessel coronary disease,¹⁸ we estimated that the incidence of the primary end point 1 year after CABG would be 13%. A noninferiority margin of 7 percentage points was chosen for the absolute difference in risk at 1 year.¹⁹ We estimated that with a total of 572 patients (286 per group), the study would have 80% power to show noninferiority, with a one-sided type I error rate of 0.05. Assuming that 5% of patients would be lost to follow-up at 1 year, we determined that the study should have a final sample of 600 patients (300 per group). When the significance level was fixed at 0.025, we estimated that the study would retain 72% power to show noninferiority with this sample size.

Baseline clinical and angiographic characteristics and procedural data for the two trial groups were compared with the use of Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. The Kaplan-Meier method was used to estimate survival for each of the two groups. In addition to the primary analysis, which compared events over the course of 1 year, we performed post hoc survival analyses that compared events in the two groups to 2 years, because the event rate at 1 year did not reach the

anticipated level. For these analyses, data on patient follow-up were censored at 2 years or when the end point occurred. The noninferiority hypothesis was assessed statistically with the use of a *z*-test, which was based on the 95% confidence interval for the absolute difference in the rate of the primary end point at 1 year. Event rates for other end points and 2-year event rates were compared with the use of the log-rank test of time to the first event after randomization. Hazard ratios and 95% confidence intervals were estimated with the use of Cox proportional-hazards models; the proportional-hazards assumption was confirmed for the primary end point.²⁰ We assessed the consistency of treatment effects in prespecified subgroups, using Cox regression models with tests for interaction. All reported *P* values and confidence intervals are two-sided, apart from those for noninferiority testing of the primary end point. No adjustment has been made for multiple testing. SAS software, version 9.1 (SAS Institute), and the R programming language (R Foundation for Statistical Computing) were used for statistical analyses.

RESULTS

TRIAL PARTICIPANTS

Between April 2004 and August 2009, a total of 1454 patients with unprotected left main coronary artery stenosis were enrolled (Fig. 1 in the Supplementary Appendix). We randomly assigned 600 of these patients to PCI with sirolimus-eluting stents (300 patients) or to CABG (300 patients). The remaining 854 patients did not undergo randomization for the reasons indicated in Table 1 in the Supplementary Appendix but were included in the registry.

The baseline clinical characteristics of the PCI and CABG groups were similar (Table 1). The mean age of the trial participants was 62 years, and 76.5% were men. As assessed according to the European System for Cardiac Operative Risk Evaluation (euroSCORE),²¹ 6.0% of patients in the PCI group and 8.0% of those in the CABG group were at high operative risk (euroSCORE of 6 or greater, on a scale ranging from 0 to 39, with higher scores indicating greater risk) (*P*=0.34). The baseline angiographic characteristics of the two groups were also similar (Table 2 in the Supplementary Appendix).

Table 3 in the Supplementary Appendix shows

Table 1. Baseline Clinical Characteristics of the Patients, According to Study Group.*

Characteristic	PCI (N=300)	CABG (N=300)	P Value
Age — yr	61.8±10.0	62.7±9.5	0.24
Male sex — no. (%)	228 (76.0)	231 (77.0)	0.77
Body-mass index†	24.6±2.7	24.5±3.0	0.74
Medically treated diabetes — no. (%)			
Any	102 (34.0)	90 (30.0)	0.29
Insulin-dependent	10 (3.3)	9 (3.0)	0.82
Hypertension — no. (%)	163 (54.3)	154 (51.3)	0.46
Hyperlipidemia — no. (%)	127 (42.3)	120 (40.0)	0.56
Current smoker — no. (%)	89 (29.7)	83 (27.7)	0.59
Previous PCI — no. (%)	38 (12.7)	38 (12.7)	1.00
Previous myocardial infarction — no. (%)	13 (4.3)	20 (6.7)	0.21
Previous congestive heart failure — no. (%)	0	2 (0.7)	0.16
Chronic renal failure — no. (%)	4 (1.3)	1 (0.3)	0.37
Peripheral vascular disease — no. (%)	15 (5.0)	7 (2.3)	0.08
Chronic obstructive pulmonary disease — no. (%)	6 (2.0)	10 (3.3)	0.31
Clinical presentation — no. (%)			0.12
Stable angina or no symptoms	160 (53.3)	137 (45.7)	
Unstable angina	128 (42.7)	144 (48.0)	
Unstable angina and recent acute myocardial infarction	12 (4.0)	19 (6.3)	
Ejection fraction — %	61.7±8.3	60.6±8.5	0.12
Electrocardiographic findings — no./total no. (%)			0.77
Sinus rhythm	286/296 (96.6)	289/297 (97.3)	
Atrial fibrillation	5/296 (1.7)	5/297 (1.7)	
Other	5/296 (1.7)	3/297 (1.0)	
EuroSCORE value‡	2.6±1.8	2.8±1.9	0.16

* Plus–minus values are means ±SD. The percentages shown are the incidences as estimated with the use of a Kaplan–Meier survival analysis of data from the intention-to-treat population. P values were calculated with the use of the log-rank test. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

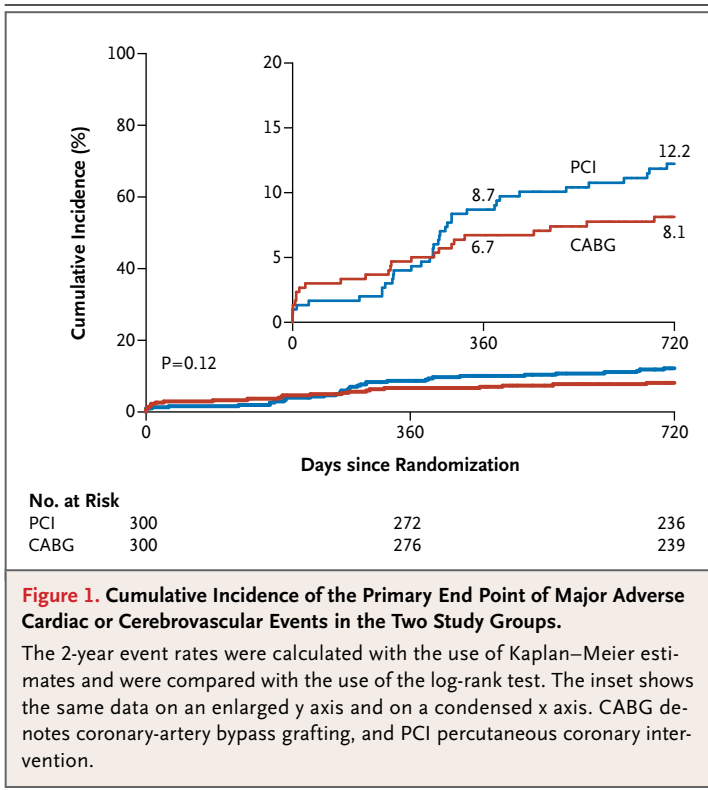
‡ The EuroSCORE is a clinical model for calculating the risk of death after cardiac surgery on the basis of patient, cardiac, and operative factors. Possible scores range from 0 to 39, with higher scores indicating greater risk.

the procedural characteristics of the study groups. Complete revascularization was achieved in 205 patients (68.3%) in the PCI group and 211 (70.3%) in the CABG group ($P=0.60$). The mean (\pm SD) duration of the hospital stay after the procedure was 8.4 ± 14.5 days in the CABG group and 3.1 ± 5.8 days in the PCI group ($P<0.001$). At the time of discharge, patients in the PCI group more consistently received some medications, including antiplatelet medications, beta-blockers, and calcium-channel blockers, than did patients in the CABG group (Table 4 in the Supplementary Appendix).

Follow-up angiography at 8 to 10 months was performed more frequently in the PCI group than in the CABG group (in 75.3% of patients vs. 24.7%, $P<0.001$). Table 5 in the Supplementary Appendix shows the baseline characteristics of patients in the PCI group in whom follow-up angiography was performed and those in whom follow-up angiography was not performed.

TRIAL END POINTS

The median follow-up period was 24.0 months in both the PCI and CABG groups. The primary end point of major adverse cardiac or cerebrovas-



cular events at 12 months occurred in 26 patients assigned to PCI as compared with 20 patients assigned to CABG (cumulative event rate, 8.7% vs. 6.7%; absolute risk difference, 2.0 percentage points; 95% confidence interval [CI], -1.6 to 5.6 ; $P=0.01$ for noninferiority) (Fig. 1). When noninferiority was tested at the one-sided 0.025 level, the 97.5% CI was -2.3 to 6.3 . The 1-year cumulative event rates for the primary end point in an analysis of patients according to the treatment received (as-treated analysis) were 9.2% and 5.9%, respectively (absolute risk difference, 3.3 percentage points; 95% CI, -0.2 to 6.8 ; $P=0.04$ for noninferiority) (see Table 6 in the Supplementary Appendix).

There were no significant between-group differences in the cumulative incidence rates of the individual components of the primary end point at 1 year, including death, myocardial infarction, stroke, ischemia-driven target-vessel revascularization, and the composite of death, myocardial infarction, or stroke (Fig. 2, and Fig. 2 in the Supplementary Appendix). When the follow-up analysis was extended to 2 years, there were no significant differences in the incidence rates of the primary composite end point or the individual end points of death, myocardial infarction, or stroke (Table 2, and Fig. 2 in the Supplementary Appendix). However, the 2-year rate of ischemia-driven target-vessel revascularization was significantly lower in the CABG group than in the PCI group. The rates of clinically driven target-vessel revascularization did not differ significantly between the groups (Table 7 in the Supplementary Appendix).

On the basis of the Academic Research Consortium classification,²² definite or probable stent thrombosis occurred in two patients in the PCI group over the course of 2 years. Symptomatic graft occlusion occurred in four patients in the CABG group, of whom two died during the index hospitalization and two underwent successful target-vessel revascularization.

Formal testing for interactions showed that the results of the comparison of the 2-year rate of major adverse cardiac or cerebrovascular events between PCI and CABG were consistent across multiple subgroups (Fig. 3).

REGISTRY PARTICIPANTS AND END POINTS

Among the patients who did not undergo randomization but were included in the registry group, more patients underwent PCI than CABG (55.6% vs. 44.3%). The patients in the CABG registry

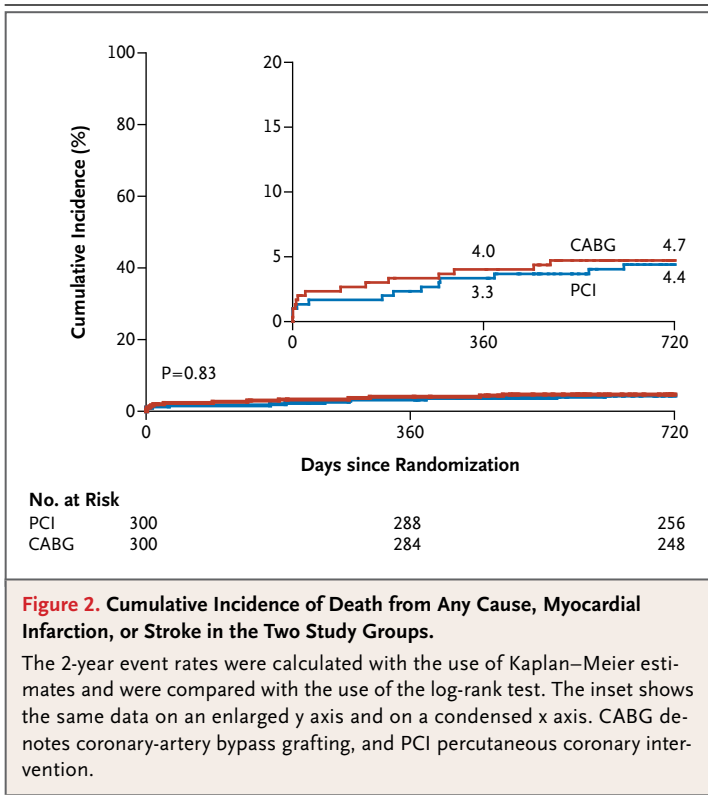


Table 2. Clinical End Points.*

End Point	PCI (N=300)		CABG (N=300)		Hazard Ratio with PCI (95% CI)	P Value
	no. of patients	cumulative event rate (%)	no. of patients	cumulative event rate (%)		
Primary end point: major adverse cardiac or cerebrovascular events†						
30 Days after procedure	4	1.3	9	3.0		
6 Mo after randomization	9	3.0	11	3.7		
12 Mo after randomization	26	8.7	20	6.7		
24 Mo after randomization	36	12.2	24	8.1	1.50 (0.90–2.52)	0.12
Secondary end points						
Death, myocardial infarction, or stroke						
12 Mo after randomization	10	3.3	12	4.0		
24 Mo after randomization	13	4.4	14	4.7	0.92 (0.43–1.96)	0.83
Death						
12 Mo after randomization	6	2.0	8	2.7		
24 Mo after randomization	7	2.4	10	3.4	0.69 (0.26–1.82)	0.45
From cardiac causes	3	1.0	8	2.7		
From noncardiac causes	4	1.4	2	0.7		
Myocardial infarction						
12 Mo after randomization	4	1.3	3	1.0		
24 Mo after randomization	5	1.7	3	1.0	1.66 (0.40–6.96)	0.49
Q wave	3	1.0	3	1.0		
Non-Q wave	2	0.7	0	0		
Stroke						
12 Mo after randomization	0	0	2	0.3		
24 Mo after randomization	1	0.4	2	0.7	0.49 (0.04–5.40)	0.56
Ischemia-driven target-vessel revascularization‡						
12 Mo after randomization	18	6.1	10	3.4		
24 Mo after randomization	26	9.0	12	4.2	2.18 (1.10–4.32)	0.02
Stent thrombosis or symptomatic graft occlusion§						
12 Mo after randomization	0	0	3	1.0		
24 Mo after randomization	1	0.3	4	1.4	0.25 (0.03–2.22)	0.25

* The percentages shown are Kaplan–Meier estimates from the intention-to-treat analysis. Hazard ratios and 95% confidence intervals were assessed for the events over the course of 2 years. P values were calculated with the use of the log-rank test. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† 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.

‡ Ischemia-driven target-vessel revascularization was defined as any repeat revascularization with the use of either PCI or CABG in the treated vessel in which there was stenosis of at least 50% of the diameter in the presence of ischemic signs or symptoms or at least 70% stenosis in the absence of ischemic signs or symptoms. Clinically driven target-vessel revascularization was defined as revascularization of lesions for which ischemic symptoms or signs were present.

§ Stent thrombosis or graft occlusion was adjudicated according to the definition used in the SYNTAX trial.¹⁵

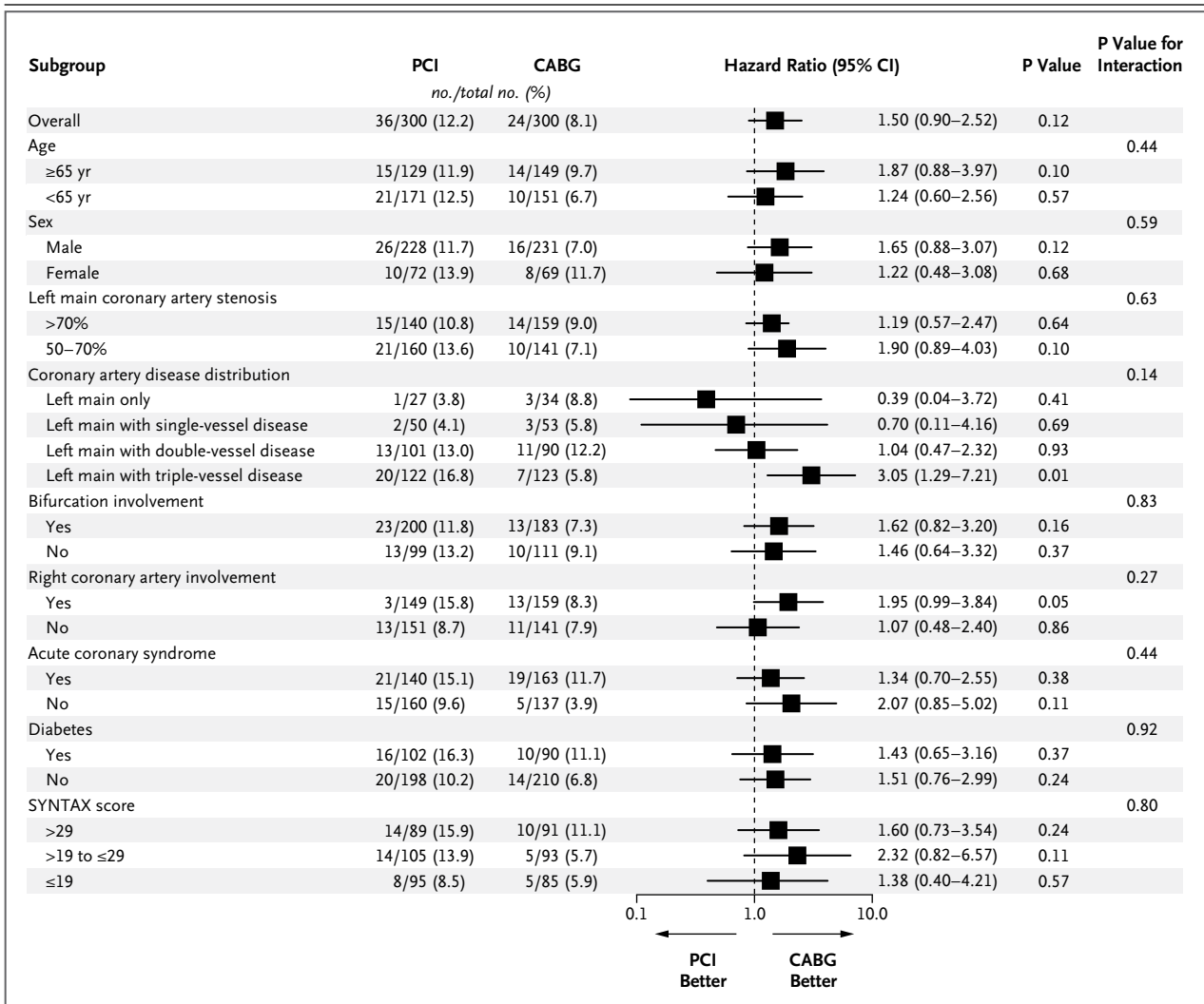


Figure 3. Subgroup Analyses of the Primary End Point at 2 Years.

Hazard ratios, with 95% confidence intervals, are shown for the primary end point of major adverse cardiac or cerebrovascular events (a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) at 2 years, according to subgroups of patients randomly assigned to the percutaneous coronary intervention (PCI) group or the coronary-artery by-pass grafting (CABG) group. The percentages shown are Kaplan–Meier estimates from the intention-to-treat analysis. The P value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. The SYNTAX score ranges from 0 to 83, with higher scores indicating more complex disease.

group had more complex clinical and angiographic characteristics than did the patients in the PCI registry group. The characteristics of the registry cohort, as compared with those of the randomized cohort, are shown in Tables 8, 9, 10, and 11 in the Supplementary Appendix.

At 1 year, among patients in the registry cohort, major adverse cardiac or cerebrovascular events had occurred in 45 of the 475 patients who had undergone PCI and in 24 of the 335 patients who had undergone CABG (cumulative event rate, 9.9%

vs. 7.6%) (Table 12 and Fig. 3 in the Supplementary Appendix). As in the randomized cohort, there were no significant differences between the PCI and CABG groups in the registry cohort with respect to the rates of most of the major trial end points at 1 or 2 years. The exception was the end point of ischemia-driven target-vessel revascularization, which occurred significantly more frequently in the PCI group than in the CABG group (Table 12 and Fig. 3 in the Supplementary Appendix).

DISCUSSION

In this prospective, randomized trial involving patients with unprotected left main coronary artery stenosis, PCI with sirolimus-eluting stents was noninferior to CABG with respect to the primary composite end point of major adverse cardiac or cerebrovascular events at 1 year. In addition, the two groups had similar rates of the individual components of death, myocardial infarction, and stroke. However, the rate of ischemia-driven target-vessel revascularization at 2 years was lower in the CABG group than in the PCI group.

Our major finding, that event rates after PCI and CABG did not differ significantly in this clinical setting, was in agreement with the results of the SYNTAX substudy involving patients with left main coronary artery stenosis; however, the event rates at 1 year in the SYNTAX substudy were higher than those in our study (15.8% in the PCI group and 13.7% in the CABG group, $P=0.44$).⁶ In both the SYNTAX substudy and our study, the incidence of ischemia-driven target-vessel revascularization was higher after PCI than after CABG.

The rates of cardiac and cerebrovascular events in our study were substantially lower than anticipated. We predicted a 1-year event rate for the primary end point of 13% after CABG, but the observed rates were only 6.7% in the CABG group and 8.7% in the PCI group. In addition, the incidence of stent thrombosis was less than 1% at 2 years. The low event rates in our study were similar to those in the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization study (MAIN-COMPARE)¹ but lower than those in some previous randomized and nonrandomized studies.^{7,9-11,16}

The low event rate may have been the consequence of a number of possible factors. First, our patients may have had less complex coronary morphologic characteristics and clinical presentations than did patients in other studies. The angiographic severity of coronary disease was assessed, in both our trial and the SYNTAX substudy, with the use of the SYNTAX score (a scale with possible values ranging from 0 to 83, with higher scores indicating more complex disease). The mean SYNTAX score in the SYNTAX substudy was 30, whereas in our study it was 25. Similarly,

the clinical risk of death after cardiac surgery was assessed in both studies with the use of the euroSCORE. The mean euroSCORE in the SYNTAX substudy was 3.8, whereas in our study it was 2.7.

Second, our study was a randomized study specifically focusing on the treatment of patients with unprotected left main coronary artery stenosis, whereas such patients were only a subgroup in the SYNTAX trial. Third, the devices and techniques used during PCI or CABG procedures may have influenced the results. Our extensive use of intravascular ultrasonography, single stents in bifurcation lesions, off-pump surgery, and internal thoracic artery for grafting onto the left anterior descending artery may have improved the outcomes reported here.²³⁻²⁵ Furthermore, although the relative efficacy of different drug-eluting stents remains unclear,⁷ the incidence of repeat revascularization or stent thrombosis in the PCI group in our study may have been low owing to the use of sirolimus-eluting stents as compared with the use of paclitaxel-eluting stents in the SYNTAX trial.²⁶⁻²⁹ Finally, our study involved an Asian population, whereas the SYNTAX study involved a U.S. and European population, and there may be a racial or ethnic difference in the propensity for ischemic or thrombotic complications.^{30,31}

Our study had several limitations. First, although PCI was shown to be noninferior to CABG in the analysis of the primary end point, the study was underpowered as a result of the unexpectedly low event rates. In fact, the noninferiority margin of 7 percentage points was almost equivalent to a 100% increase in the observed event rate of the primary end point in the CABG group at 1 year. For this reason, the findings of our trial cannot be considered to be clinically directive. Second, a relatively high incidence of crossover from the PCI group to the CABG group could have biased our findings toward a neutral effect on outcomes. However, the prespecified criterion for noninferiority of PCI was met in the as-treated analysis. Third, the systematic performance of repeat angiography in the PCI group may have increased the rate of target-vessel revascularization in that group. Notably, the between-group difference in the rate of clinically driven target-vessel revascularization, which was reported only in patients with ischemic symptoms or signs, appeared to be smaller than the difference in the rate of ischemia-driven target-

vessel revascularization and was not significant. Fourth, 2 years of follow-up may not be sufficient to assess the late results after PCI with drug-eluting stents as compared with CABG.³² Fifth, owing to the restricted sample size, we cannot fully investigate treatment effects in various subpopulations. Finally, because the design of our trial required that patients meet certain prespecified criteria, our findings may not be generalizable to the entire population of patients with unprotected left main coronary artery stenosis. Larger, ongoing randomized trials, such as the Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial (EXCEL, NCT01205776), in which the outcomes of PCI with a second-generation drug-eluting stent are compared with those of CABG in patients with unprotected left main coronary artery stenosis, may provide further information.

In conclusion, our randomized trial comparing PCI with CABG for the management of unprotected left main coronary artery stenosis showed that at 1 year, the rates of major adverse cardiac or cerebrovascular events were similar in the two treatment groups and met the prespecified criterion for noninferiority of PCI to CABG in this setting. However, because the power of the trial was lower than anticipated and because the noninferiority margin was wide, these results cannot be considered to be clinically directive.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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