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Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease

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ABSTRACT

BACKGROUND

Percutaneous coronary intervention (PCI) involving drug-eluting stents is increasingly used to treat complex coronary artery disease, although coronary-artery bypass grafting (CABG) has been the treatment of choice historically. Our trial compared PCI and CABG for treating patients with previously untreated three-vessel or left main coronary artery disease (or both).

METHODS

We randomly assigned 1800 patients with three-vessel or left main coronary artery disease to undergo CABG or PCI (in a 1:1 ratio). For all these patients, the local cardiac surgeon and interventional cardiologist determined that equivalent anatomical revascularization could be achieved with either treatment. A noninferiority comparison of the two groups was performed for the primary end point — a major adverse cardiac or cerebrovascular event (i.e., death from any cause, stroke, myocardial infarction, or repeat revascularization) during the 12-month period after randomization. Patients for whom only one of the two treatment options would be beneficial, because of anatomical features or clinical conditions, were entered into a parallel, nested CABG or PCI registry.

RESULTS

Most of the preoperative characteristics were similar in the two groups. Rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; P=0.002), in large part because of an increased rate of repeat revascularization (13.5% vs. 5.9%, P<0.001); as a result, the criterion for noninferiority was not met. At 12 months, the rates of death and myocardial infarction were similar between the two groups; stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; P=0.003).

CONCLUSIONS

CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at 1 year. (ClinicalTrials.gov number, NCT00114972.)

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*The other Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) investigators are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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Coronary-artery bypass grafting (CABG) was introduced in 1968 and rapidly became the standard of care for symptomatic patients with coronary artery disease.[1] Advances in coronary surgery (e.g., off-pump CABG, smaller incisions, enhanced myocardial preservation, use of arterial conduits, and improved postoperative care) have reduced morbidity, mortality, and rates of graft occlusion.[2-6]

Percutaneous coronary intervention (PCI) was introduced in 1977.[7] Experience with this approach, coupled with improved technology, has made it possible to treat increasingly complex lesions and patients with a history of clinically significant cardiac disease, risk factors for coronary artery disease, coexisting conditions, or anatomical risk factors.[8,9] Several trials comparing PCI involving bare-metal stents with CABG in patients with multivessel disease (e.g., the Arterial Revascularization Therapies Study Part I [ARTS I], the Medicine, Angioplasty, or Surgery Study for Multivessel Coronary Artery Disease [MASS II; Current Controlled Trials number, ISRCTN66068876], the Argentine Randomized Study of Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease [ERACI-II], and the Angina with Extremely Serious Operative Mortality Evaluation [AWESOME]) showed similar survival rates but higher revascularization rates among patients with bare-metal stents at 5 years. Others have shown a significant long-term survival advantage with surgery (e.g., the Stent or Surgery [SOS] study).[10-12] Studies comparing PCI involving drug-eluting stents with CABG have generally been smaller and nonrandomized.[13-24]

Data from randomized, controlled trials of drug-eluting stents as compared with bare-metal stents have shown significant reductions in the rate of repeat intervention, with similar rates of death and myocardial infarction.[25] These improvements have led to expanded use of PCI in patients with complex coronary anatomical features, though most randomized trials comparing drug-eluting stents and bare-metal stents excluded such patients. According to current guidelines,[26] CABG remains the treatment of choice for patients with severe coronary artery disease, including those with left main coronary artery disease and those with three-vessel disease. There is a lack of data from adequately powered randomized trials of PCI in such patients. Thus, PCI is being performed in this group without adequate support from evidence-based medicine and randomized clinical trials.[27]

In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, we assessed the optimal revascularization strategy for patients with previously untreated three-vessel or left main coronary artery disease and defined the populations of patients for whom only one revascularization method will be effective.

METHODS

STUDY DESIGN

The SYNTAX trial is a prospective, clinical trial conducted in 85 sites and approved by the institutional review board at each participating center. The study had an "all-comers" design involving the consecutive enrollment of all eligible patients with three-vessel or left main coronary artery disease at sites in 17 countries in Europe and the United States. The study design has been described previously.[28] Criteria for study and registry enrollment and outcome data are described in the Supplementary Appendix. The authors designed the study, as part of their role on the steering committee, in collaboration with the sponsor, Boston Scientific. The sponsor was involved in collection and source verification of the data, with oversight by an independent clinical events committee. The sponsor's biostatisticians performed the analyses; however, data analyses were verified independently by a statistician on the data and safety monitoring committee. The authors wrote the manuscript and vouch for the completeness and accuracy of the data gathering and analysis.

SELECTION AND RANDOMIZATION OF PATIENTS

A local interventional cardiologist and cardiac surgeon at each site prospectively evaluated eligible patients with previously untreated three-vessel coronary disease and those with left main coronary artery disease (alone or with one-, two-, or three-vessel disease). Inclusion and exclusion criteria are listed in the Methods section of the Supplementary Appendix. Patients in whom it was determined that equivalent anatomical revascularization could be achieved with either CABG or PCI involving Taxus Express paclitaxel-eluting stents (Boston Scientific) were randomly assigned to undergo one of the two treatment options by means of an interactive voice-responding system. Ran-

domization was stratified at each site according to the presence or absence of left main coronary artery disease and medically treated diabetes (diabetes for which the patient was receiving oral hypoglycemic agents or insulin at the time of enrollment). Patients for whom only one treatment option was suitable were entered into a parallel, nested registry: the PCI registry for CABG-ineligible patients and the CABG registry for PCI-ineligible patients.

All diagnostic angiograms and electrocardiograms were reviewed by staff at an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) who were unaware of the treatment assignments. Diagnostic angiograms were scored, according to the SYNTAX score algorithm,[29] at the site and at the core laboratory. In addition, staff at an independent central chemistry laboratory (Covance, Indianapolis and Geneva) who were unaware of treatment assignments assessed selected variables.

The institutional review board at each site approved the protocol, and all patients provided written informed consent. The protocol and consent forms were consistent with the Food and Drug Administration's Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki, the International Conference on Harmonisation, and all local regulations, as appropriate.

REVASCULARIZATION AND PHARMACOLOGIC TREATMENT

Patients were treated with the intention of achieving complete revascularization of all vessels at least 1.5 mm in diameter with stenosis of 50% or more, as identified by the local interventional cardiologist and cardiac surgeon. The surgical technique for CABG, the approaches used for stent implantation, and the postprocedure medication regimen were chosen according to local clinical practice. In patients who underwent PCI, antiplatelet medication was prescribed on the basis of the directions for use of the Taxus Express stent and local clinical practice. In most centers, thienopyridines were continued even after 6 months, with 71.1% of patients receiving them at 12 months. Aspirin was prescribed indefinitely for all patients who underwent randomization. Use of the standard of postintervention care was recommended.[30] Procedural details are described in the Methods section of the Supplementary Appendix.

PRIMARY END POINT

The primary clinical end point was a composite of major adverse cardiac and cerebrovascular events (i.e., death from any cause, stroke, myocardial infarction, or repeat revascularization) throughout the 12-month period after randomization. An independent clinical events committee (including cardiologists, cardiac surgeons, and a neurologist; see the list in the Supplementary Appendix) adjudicated all primary clinical end points, staged procedures, and cases in which the sternum was reopened.

STATISTICAL ANALYSIS

The primary analysis was a noninferiority comparison of the two treatments for the primary end point of adverse binary cardiac or cerebrovascular events in all patients who underwent randomization (on an intention-to-treat basis). If the one-sided 95% upper confidence limit for the difference was less than the prespecified delta value (6.6%), PCI with the drug-eluting stents would be considered to be noninferior to CABG in the overall randomized cohort. The noninferiority margin was based on historical data (see the Methods section in the Supplementary Appendix). We calculated the means (±SD) for continuous variables in each of the two groups and compared them using Student's t-test. Binary variables are reported as counts and percentages, and differences between the two groups were assessed by means of the chi-square or Fisher's exact test. Cumulative event rates were estimated by means of the Kaplan–Meier method. In addition, the 12-month rates of major adverse cardiac or cerebrovascular events were analyzed on the basis of the SYNTAX score and compared with the use of a chi-square test. The SYNTAX score reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33 (see the Supplementary Appendix for details).

RESULTS

STUDY PARTICIPANTS

From March 2005 through April 2007, a total of 4337 patients with previously untreated three-vessel or left main coronary artery disease (or both) were screened (Fig. 1). After consideration by the local

interventional cardiologist and cardiac surgeon and after written informed consent was obtained, 3075 patients (70.9%) were included in the study. Of these, 1800 patients were randomly assigned to undergo CABG (897 patients) or PCI with drug-eluting stents (903 patients) at sites in the United States (245 patients) and in Europe (1555 patients). The reasons for exclusion of the remaining 1262 patients are listed in Figure 1. Only one treatment option was suitable in 1275 patients (29.4%), who were enrolled in the nested registry for CABG (1077 patients) or PCI (198 patients).

Patients in the two groups were well balanced with regard to most of the baseline demographic and clinical characteristics (Table 1). The proportion of patients with blood pressure of 130/80 mm Hg or higher was significantly larger in the PCI group. The numbers of current smokers, patients with elevated triglyceride levels (≥150 mg per deciliter [1.7 mmol per liter]), and patients with reduced high-density lipoprotein cholesterol levels (<40 mg per deciliter [1.0 mmol per liter] for men or <50 mg per deciliter [1.3 mmol per liter] for women) were higher in the CABG group. A total of 38.8% of patients in the CABG group and 39.5% of those in the PCI group had left main coronary artery disease, with or without additional diseased vessels. Approximately 25% of patients had medically treated diabetes, of whom about one third required insulin. Moreover, nearly half the patients (45.8%) met the criteria for the metabolic syndrome.[33] More than 20% of patients in both groups were considered to be at high surgical risk, on the basis of a European System for Cardiac Operative Risk Evaluation (euroSCORE)[31] value of 6 or more (24.9% in the CABG group and 24.7% in the PCI group, P=0.94) and a Parsonnet score[32] of 15 or more (20.2% and 20.5%, respectively; P=0.87).

Overall, more than 4 clinically significant coronary lesions were treated per patient (mean, 4.4 for CABG and 4.3 for PCI); among all patients in both groups, total occlusion was identified in 23.1%, and 72.8% had a bifurcation lesion (Table 1). These results, together with other lesion characteristics, resulted in an average raw SYNTAX score of 29.1 in the CABG group and 28.4 in the PCI group (P=0.19) (Table 1).

The length of time between randomization and performance of the study procedure, the duration of the procedure, and the duration of the postprocedural hospital stay were significantly greater with CABG than with PCI (Table 1). A higher proportion of patients had complete revascularization after CABG than after PCI (63.2% vs. 56.7%, P=0.005). Medical management at discharge differed between the CABG and PCI groups: patients who underwent CABG received less pharmacologic treatment, whereas those who underwent PCI were consistently treated with antiplatelet medications (Table 2). In the CABG group, off-pump surgery was performed in 15.0% of patients, one or more arterial grafts were used in 97.3% of patients, and an average of 2.8 conduits and 3.2 distal anastomoses per patient were performed. In the PCI group, 14.1% of patients underwent staged procedures, 63.1% had at least one bifurcation or trifurcation treated, more than four stents on average were implanted per patient, and a third of patients had placement of stents with a total length of more than 100 mm.

A greater proportion of patients in the CABG registry had characteristics of severe lesions — including large proportions of patients with total occlusion (56.4%), bifurcation (80.8%), lesions that were more than 20 mm in length (31.5%), and heavy calcification (32.7%) — than in either randomized group or the PCI registry (Table 2 in the Supplementary Appendix). Together with other anatomical characteristics, these features resulted in an average raw SYNTAX score of 37.8±13.3 among the patients in the CABG registry (Table 2 in the Supplementary Appendix). In contrast, the prevalence of cardiac risk factors and the prevalence of coexisting conditions were increased among patients enrolled in the PCI registry. A total of 30.2% of these patients had diabetes, 40.4% had previously had a myocardial infarction, 19.3% had a diagnosis of chronic obstructive pulmonary disease, 14.1% had a history of transient ischemic attacks or stroke, and 4.7% were dependent on pacemakers — leading to average surgical scores that were higher than in the other groups of patients (euroSCORE value, 5.8±3.1; and Parsonnet score, 14.4±9.5) (Table 2 in the Supplementary Appendix).

PRIMARY OUTCOME

Preprocedural rates of major adverse cardiac or cerebrovascular events were low and did not differ significantly between the two groups (0.9% in the CABG group and 0.3% in the PCI group, P=0.13) (Table 6 in the Supplementary Appendix), as was the case for in-hospital rates. The preprocedural

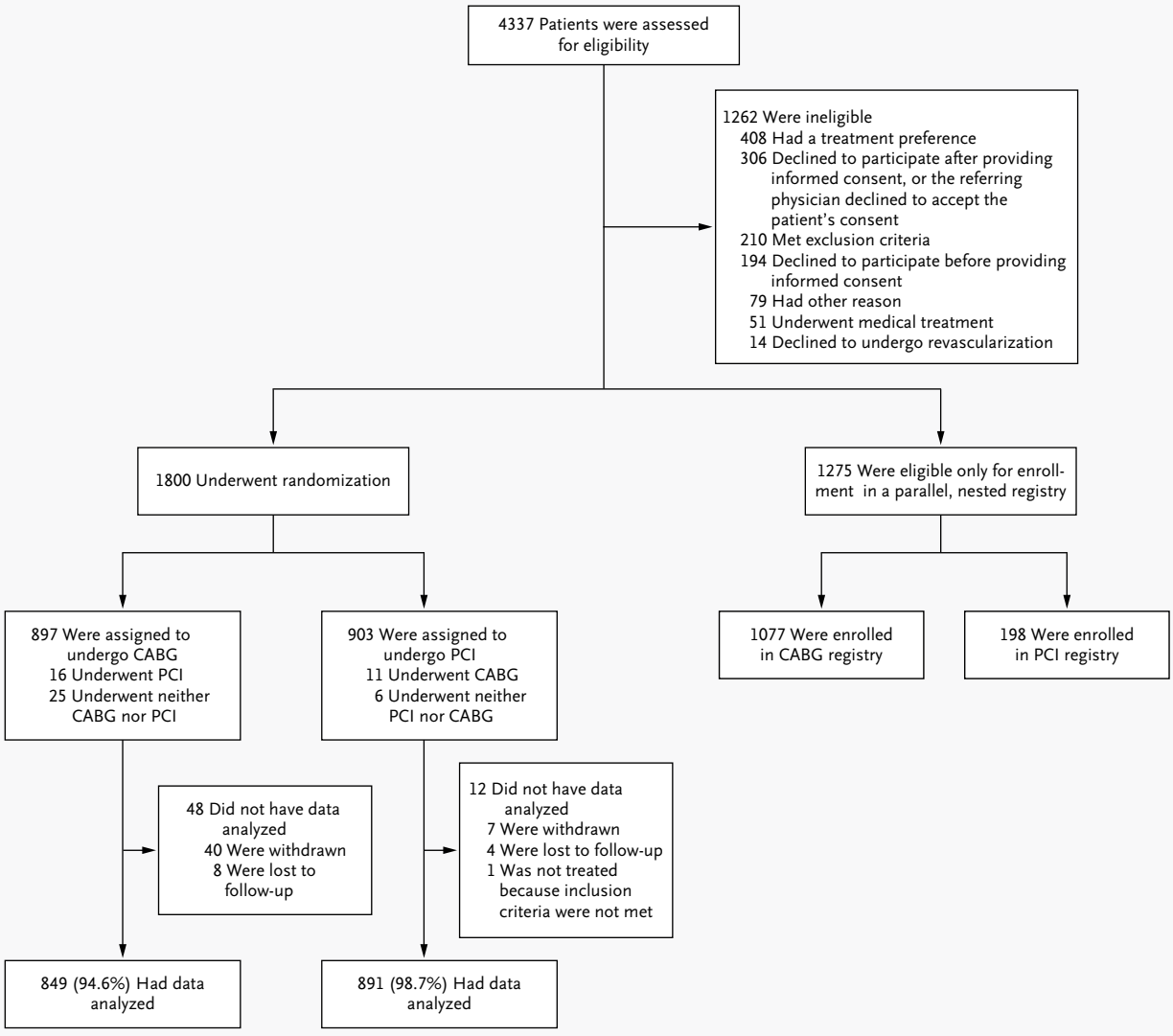

Figure 1. Enrollment and Randomization of Patients with Previously Untreated Three-Vessel or Left Main Coronary Artery Disease in the SYNTAX Trial.

The trial used an "all-comers" design. Exclusion criteria were previous intervention, acute myocardial infarction, and concomitant surgery. Patients meeting either of the first two exclusion criteria were, according to the trial design, excluded without consultation of the local interventional cardiologist and cardiac surgeon. The need for concomitant surgery was discussed with the local interventional cardiologist and cardiac surgeon. Data for patients who were assigned to one treatment but underwent the other and for those who did not undergo either revascularization procedure were analyzed in an intention-to-treat manner. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

rates of two of the individual components of the primary outcome, stroke and myocardial infarction, were similar in the two groups (Table 2 in the Supplementary Appendix). At 12 months, the incidence of major adverse cardiac or cerebrovascular events was lower in the CABG group (12.4%) than in the PCI group (17.8%, P=0.002) (Fig. 2 and Table 3). Thus, the absolute difference in the 12-month rate of major adverse cardiac or cerebrovascular events between the two groups was 5.5 percentage points, with an upper 95% confidence interval of 8.3 percentage points. The results of an as-treated analysis were similar: the 12-month rate of major adverse cardiac or cerebrovascular events was 12.3% with CABG and 17.6% with PCI (P=0.002).

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

Characteristic	PCI (N=903)	CABG (N=897)	P Value
Age — yr	65.2±9.7	65.0±9.8	0.55
Male sex — %	76.4	78.9	0.20
Body-mass index†	28.1±4.8	27.9±4.5	0.37
Medically treated diabetes — %‡			
Any	25.6	24.6	0.64
Requiring insulin	9.9	10.4	0.72
Metabolic syndrome — %	46.0	45.5	0.86
Current smoker — %	18.5	22.0	0.06
Previous myocardial infarction — %	31.9	33.8	0.39
Previous stroke — %	3.9	4.8	0.33
Previous transient ischemic attack — %	4.3	5.1	0.46
Blood pressure ≥130/85 mm Hg — %	68.9	64.0	0.03
Congestive heart failure — %	4.0	5.3	0.18
Carotid artery disease — %	8.1	8.4	0.83
Hyperlipidemia — %	78.7	77.2	0.44
Triglycerides ≥150 mg/dl (1.7 mmol/liter) — %	32.3	38.7	0.007
HDL cholesterol <40 mg/dl (1.0 mmol/liter) for men or <50 mg/dl (1.3 mmol/liter) for women — %	46.2	52.5	0.01
Angina — %			
Stable	56.9	57.2	0.91
Unstable	28.9	28.0	0.66
Ejection fraction <30% — %	1.3	2.5	0.08
euroSCORE value	3.8±2.6	3.8±2.7	0.78
Parsonnet score	8.5±7.0	8.4±6.8	0.76
SYNTAX score	28.4±11.5	29.1±11.4	0.19
No. of lesions	4.3±1.8	4.4±1.8	0.44
Total occlusion — %	24.2	22.2	0.33
Bifurcation — %	72.4	73.3	0.67
Time to procedure — days	6.9±13.0	17.4±28.0	<0.001
Procedure duration — hr	1.7±0.9	3.4±1.1	<0.001
Postprocedural hospital stay — days	3.4±4.5	9.5±8.0	<0.001
Complete revascularization — %	56.7	63.2	0.005

* Plus–minus values are means ±SD. Data are given for the intention-to-treat population. P values, the average SYNTAX score, the average number of lesions, and the percentages of patients with total occlusion and bifurcation were calculated at the core laboratory. The European System for Cardiac Operative Risk Evaluation (euroSCORE) value could range from 0 to 18, with increasing values reflecting a higher predicted operative mortality.[31] The Parsonnet score could range from 0 to 47, with increasing values reflecting a higher predicted in-hospital mortality.[32] The SYNTAX score reflects a comprehensive anatomical assessment, with scores ranging from 0 to 83 and higher scores indicating more complex coronary disease (see the Supplementary Appendix for details). CABG denotes coronary-artery bypass grafting, HDL high-density lipoprotein, and PCI percutaneous coronary intervention.

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

‡ Medically treated diabetes was defined as diabetes for which the patient was receiving oral hypoglycemic agents or insulin at the time of enrollment.

In the intention-to-treat population, 19 patients would need to be treated with CABG to avoid the primary outcome in 1 patient; the numbers needed to treat to avoid specific components of the outcome were 14 for revascularization, 119 for death, and 71 for myocardial infarction. The number needed to treat with PCI to avoid stroke in 1 patient was 60.

SECONDARY OUTCOME

The rate of repeat revascularization at 12 months was significantly higher among patients in the PCI group than among those in the CABG group (13.5% vs. 5.9%, P<0.001) (Table 3). Most patients who underwent repeat revascularization were treated with PCI rather than CABG. The rate of stroke was significantly higher with CABG than with PCI at 12 months, even though the two groups were well balanced with regard to carotid artery disease and other risk factors for stroke (Table 3). At 12 months, the two groups had similar rates of death from any cause or myocardial infarction and of the combined end point of death from any cause, stroke, or myocardial infarction (Table 3). The rate of death from cardiac causes was greater with PCI than with CABG (3.7% vs. 2.1%, P=0.05); the rate of death from noncardiac causes, although not significant, was higher with CABG (1.4% vs. 0.7%, P=0.13). The 12-month rates of symptomatic graft occlusion (in the CABG group) and stent thrombosis (in the PCI group) were similar (P=0.89) (Table 3).

OUTCOMES ACCORDING TO THE SYNTAX SCORE

In the CABG group, the binary 12-month rates of major adverse cardiac or cerebrovascular events were similar among patients with low SYNTAX scores (0 to 22, 14.7%), those with intermediate scores (23 to 32, 12.0%), and those with high scores (≥33, 10.9%) (Fig. 3). In contrast, in the PCI group, the rate of major adverse cardiac or cerebrovascular events was significantly increased among patients with high SYNTAX scores (23.4%) as compared with those with low scores (13.6%) or intermediate scores (16.7%) (P=0.002 for high vs. low scores; P=0.04 for high vs. intermediate scores) (Fig. 3). There was a significant interaction between SYNTAX score and treatment group (P=0.01); patients with low or intermediate scores in the CABG group and in the PCI group had similar rates of major adverse cardiac or cerebrovascular events, whereas among patients with high scores, the event rate was significantly increased in the PCI group (Fig. 3).

Table 2. Cardiac-Related Medications Given after the Study Procedure.*

Medication	PCI	CABG	P Value
	percent		
Any	98.9	98.6	0.62
Aspirin			
At discharge	96.3	88.5	<0.001
1 Mo after procedure	93.5	85.4	<0.001
6 Mo after randomization	93.2	82.7	<0.001
12 Mo after randomization	91.2	84.3	<0.001
Thienopyridine			
At discharge	96.8	19.5	<0.001
1 Mo after procedure	95.5	18.4	<0.001
6 Mo after randomization	91.3	16.1	<0.001
12 Mo after randomization	71.1	15.0	<0.001
Any antiplatelet drug			
At discharge	97.0	23.7	<0.001
1 Mo after procedure	95.8	21.2	<0.001
6 Mo after randomization	91.4	18.4	<0.001
12 Mo after randomization	72.8	17.2	<0.001
Nonthienopyridine antiplatelet drug	1.9	4.8	<0.001
Warfarin derivative	2.6	7.1	<0.001
Statin	86.7	74.5	<0.001
Beta-blocker	81.3	78.6	0.17
ACE inhibitor	55.1	44.6	<0.001
Calcium-channel blocker	25.8	18.4	<0.001
Angiotensin II–receptor antagonist	13.3	7.0	<0.001
Amiodarone	1.5	12.8	<0.001
H_2-receptor blocker	14.5	21.7	<0.001

* Percentages are from the intention-to-treat analysis. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

OUTCOMES IN SUBGROUPS

The subgroups of patients with left main or three-vessel coronary artery disease were prespecified, and the study had a statistical power of 80% for each subgroup. However, the overarching statistical test was a noninferiority assessment of data from all patients with either left main coronary artery disease or three-vessel coronary disease (or both). Since noninferiority was not proven in this

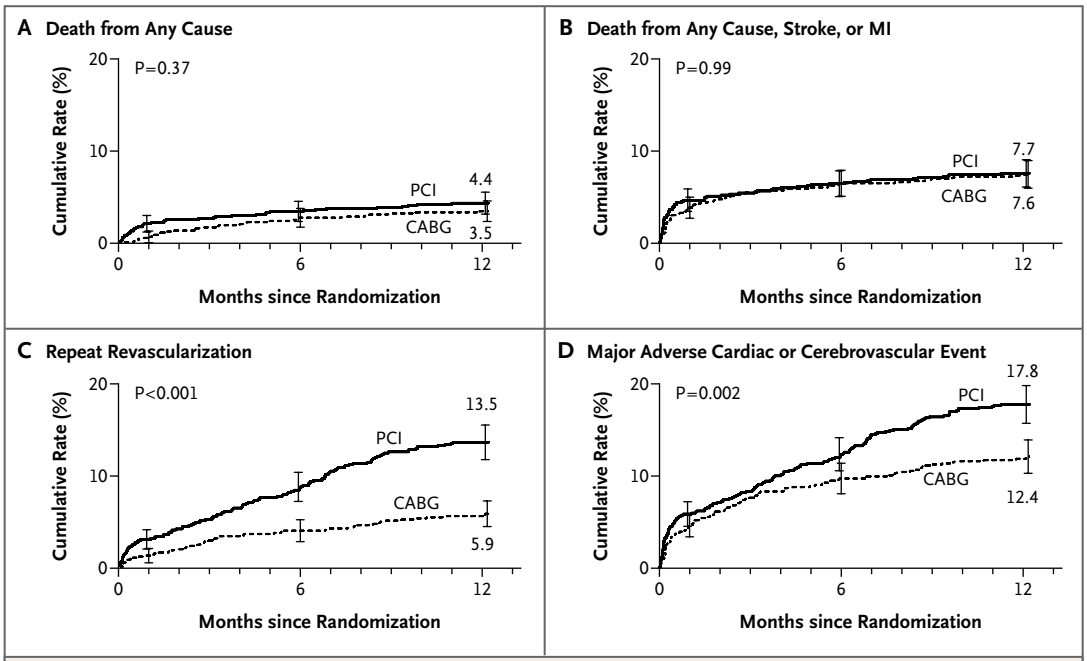

Figure 2. Rates of Outcomes among the Study Patients, According to Treatment Group.

Kaplan–Meier curves are shown for the percutaneous coronary intervention (PCI) group and the coronary-artery bypass grafting (CABG) group for death from any cause (Panel A); death, stroke, or myocardial infarction (MI) (Panel B); repeat revascularization (Panel C); and the composite primary end point of major adverse cardiac or cerebrovascular events (Panel D). The two groups had similar rates of death from any cause (relative risk with PCI vs. CABG, 1.24; 95% confidence interval [CI], 0.78 to 1.98) and rates of death from any cause, stroke, or MI (relative risk with PCI vs. CABG, 1.00; 95% CI, 0.72 to 1.38). In contrast, the rate of repeat revascularization was significantly increased with PCI (relative risk, 2.29; 95% CI, 1.67 to 3.14), as was the overall rate of major adverse cardiac or cerebrovascular events (relative risk, 1.44; 95% CI, 1.15 to 1.81). The I bars indicate 1.5 SE. Relative risks were calculated from the binary rates. P values were calculated with the use of the chi-square test.

cohort, specific information for each subgroup is of an observational nature and is hypothesis generating. The 12-month rate of major adverse cardiac or cerebrovascular events among patients with left main coronary artery disease was similar in the CABG and PCI groups (13.7% and 15.8%, respectively; P=0.44). Although the rate of repeat revascularization among patients with left main coronary artery disease was significantly higher in the PCI group (11.8%, vs. 6.5% in the CABG group; P=0.02), this result was offset by a significantly higher rate of stroke in the CABG subgroup of patients with left main coronary artery disease (2.7%, vs. 0.3% in the corresponding PCI subgroup; P=0.01). A total of 36.6% of patients with left main coronary artery disease also had three-vessel disease. A post hoc analysis of the rates of major adverse cardiac or cerebrovascular events in the subgroups of patients with left main coronary artery disease revealed a higher rate among those who also had two- or three-vessel disease than among those with left main coronary artery disease alone or in combination with one-vessel disease (Fig. 6 in the Supplementary Appendix).

The 12-month rate of major adverse cardiac or cerebrovascular events among patients with three-vessel disease in the absence of left main coronary artery disease was significantly increased in the PCI group as compared with the CABG group (19.2% vs. 11.5%, P<0.001) (Fig. 6 in the Supplementary Appendix), as was the rate of repeat revascularization (14.6% vs. 5.5%, P<0.001). The rate of death from any cause, stroke, or myocardial infarction in this subgroup was similar with PCI and CABG (8.0% and 6.6%, respectively; P=0.39).

Comparisons of data for the cohort with left main coronary artery disease and the cohort with three-vessel disease showed that the cohort with three-vessel disease had higher rates of previous

Table 3. Clinical End Points Occurring in the Hospital or after Discharge, According to Study Group.*

Variable	PCI	CABG	P Value	Relative Risk with PCI (95% CI)
	no./total no. (%)			
Major adverse cardiac or cerebrovascular event				
In hospital	39/896 (4.4)	47/870 (5.4)	0.31	0.81 (0.53–1.22)
30 Days after procedure	54/895 (6.0)	45/866 (5.2)	0.45	1.16 (0.79–1.71)
6 Mo after randomization	111/893 (12.4)	85/860 (9.9)	0.09	1.26 (0.96–1.64)
12 Mo after randomization	159/891 (17.8)	105/849 (12.4)	0.002	1.44 (1.15–1.81)
Death, stroke, or MI	68/891 (7.6)	65/849 (7.7)	0.98	1.00 (0.72–1.38)
Death	39/891 (4.4)	30/849 (3.5)	0.37	1.24 (0.78–1.98)
From cardiac causes	33/891 (3.7)	18/849 (2.1)	0.05	1.75 (0.99–3.08)
From cardiovascular causes	1/891 (0.1)	3/849 (0.4)	0.36†	0.32 (0.03–3.05)
From noncardiovascular causes	5/891 (0.6)	9/849 (1.1)	0.24	0.53 (0.18–1.57)
Stroke	5/891 (0.6)	19/849 (2.2)	0.003	0.25 (0.09–0.67)
MI	43/891 (4.8)	28/849 (3.3)	0.11	1.46 (0.92–2.33)
Repeat revascularization‡	120/891 (13.5)	50/849 (5.9)	<0.001	2.29 (1.67–3.14)
CABG	25/891 (2.8)	11/849 (1.3)	0.03	2.17 (1.07–4.37)
PCI	102/891 (11.4)	40/849 (4.7)	<0.001	2.43 (1.71–3.46)
Graft occlusion or stent thrombosis§	28/848 (3.3)	27/784 (3.4)	0.89	0.96 (0.57–1.62)
Acute (at ≤1 day)	2/896 (0.2)	3/870 (0.3)	0.68†	0.65 (0.11–3.86)
Early (within 2–30 days)	18/893 (2.0)	3/868 (0.3)	0.001	5.83 (1.72–19.73)
Late (within 31–365 days)	9/874 (1.0)	21/854 (2.5)	0.02	0.42 (0.19–0.91)

* Percentages are from the intention-to-treat analysis. P values were calculated with the use of the chi-square test, unless otherwise noted. CABG denotes coronary-artery bypass grafting, MI myocardial infarction, and PCI percutaneous coronary intervention.
† The P value was calculated with the use of Fisher's exact test.
‡ One patient randomly assigned to undergo CABG and seven patients randomly assigned to undergo PCI underwent both repeat PCI and repeat CABG.
§ Stent thrombosis was adjudicated according to the protocol definition.

myocardial infarction, diabetes, poor left ventricular ejection fraction, and lesions with adverse characteristics (lesions that were totally occluded, bifurcated, or long). In addition, the cohort with three-vessel disease had increased numbers of treated vessels and lesions per patient.

DISCUSSION

The SYNTAX trial was designed to compare current surgical and percutaneous techniques in patients with three-vessel or left main coronary artery disease (or both). For the primary end point, the 12-month rate of major adverse cardiac or cerebrovascular events, the noninferiority of PCI as compared with CABG was not demonstrated; CABG proved to be superior. Therefore, the findings with regard to components of the primary end point and subgroup analyses can only be considered as hypothesis-generating. Rates of death and myocardial infarction at 1 year were similar between patients who underwent CABG and those who underwent PCI with drug-eluting stents, whereas the rate of stroke was increased in the CABG group and the rate of repeat revascularization was increased in the PCI group.

Rates of repeat revascularization at 12 months were low in the PCI group, given the high rates of several known predictors of restenosis: lesions characterized by bifurcation or trifurcation (>80%), multivessel disease (>60%), diabetes (>25%), and lesions that were long (>20 mm in length, 20%) or totally occluded (>25%). This rate of repeat revascularization is lower than the rates reported

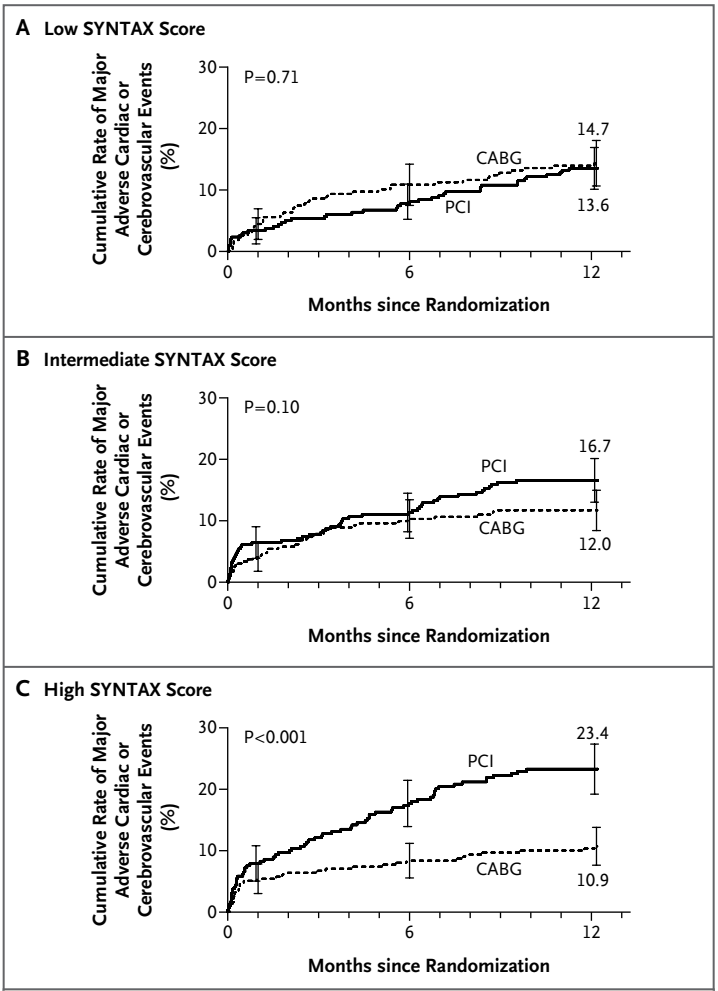

Figure 3. Rates of Major Adverse Cardiac or Cerebrovascular Events among the Study Patients, According to Treatment Group and SYNTAX Score Category.

Kaplan–Meier curves are shown for the percutaneous coronary intervention (PCI) group and the coronary-artery bypass grafting (CABG) group for major adverse cardiac or cerebrovascular events at 12 months. The 12-month event rates were similar between the two treatment groups for patients with low SYNTAX scores (0 to 22) (Panel A) or intermediate SYNTAX scores (23 to 32) (Panel B). Among patients with high SYNTAX scores (≥33, indicating the most complex disease), those in the PCI group had a significantly higher event rate at 12 months than those in the CABG group. SYNTAX scores were calculated at the core laboratory. The I bars indicate 1.5 SE. P values were calculated with the use of the chi-square test.

in previous comparative trials involving patients with less-complex clinical profiles and lesions.[10] The increase in the rate of repeat revascularization with PCI as compared with CABG did not appear to translate into a significant overall increase in the rate of death or myocardial infarction, although longer-term follow-up is needed. The risk of repeat revascularization after PCI needs to be balanced against the invasiveness of CABG and the risk of stroke, as previously reported in a meta-analysis of 23 studies comparing CABG and PCI, in which procedure-related strokes were found to be more common after CABG (in 1.2% of patients, vs. 0.6% of those undergoing PCI; P<0.001), without a concomitant decrease in survival.[34]

Recently, concern has been expressed about the possibility of an increased risk of late stent thrombosis with drug-eluting stents. In the SYNTAX trial, most cases of stent thrombosis occurred within 30 days after the procedure, and the 12-month rate of stent thrombosis in the PCI group was similar to the rate of symptomatic graft occlusion in the CABG group. However, as described in the literature, stent thrombosis often has more serious consequences for patients (rate of death, approximately 30%; rate of myocardial infarction, >60%)[35,36] than does graft occlusion, which often results only in angina leading to revascularization.

The use of antiplatelet medication was high among patients in the PCI group (with 71.1% receiving a thienopyridine at 12 months). There was an imbalance between the two groups with regard to general medical management apart from thienopyridine use. Thienopyridine therapy was not mandated beyond 6 months in the PCI group, since the study was designed to compare current CABG and PCI practices, including medication regimens. The low rate of stroke among patients who underwent PCI may have resulted from the use of highly effective dual-antiplatelet therapy, which prevents thromboembolic events; additional treatment with antiplatelet drugs might therefore benefit patients undergoing CABG. In addition, more patients in the CABG group than in the PCI group declined to participate after providing consent; in general, this imbalance was due to the greater invasiveness of CABG.

The SYNTAX score was designed to predict outcomes related to anatomical characteristics and, to a lesser extent, the functional risk of occlusion for any segment of the coronary-artery bed (as reflected by the Leaman score[37]). In our study, the raw SYNTAX score was predictive of outcomes in patients who underwent PCI. In particular, among patients in the PCI group with high SYNTAX scores, not only was the overall rate of major adverse cardiac or cerebrovascular events significantly increased, but also the rate of the composite components of death, stroke, and myocardial

infarction was slightly raised (11.9%, vs. 7.6% in the CABG group; P=0.08). This finding suggests that a percutaneous approach should be avoided in patients with high SYNTAX scores. Similar results were reported after the stratification of patients with three-vessel disease in the ARTS II registry.[38] Retrospective analysis of the ability of the SYNTAX score to predict outcome is currently being performed and is anticipated to be used to evaluate the relative weight of the individual score components. Additional validation of the score in other populations of patients is also needed. Outcomes in the surgical group of our randomized cohort were not influenced by the SYNTAX score.

The completeness of revascularization (i.e., whether all identified lesions were treated) was determined after the procedure by the investigator. The rate of complete revascularization was lower in both treatment groups in our study than in previous studies.[14,15,21,23,39] This result is most likely due to a different definition of completeness of treatment used in the earlier trials and the more complex anatomical characteristics of the patients in our trial.

Although our study provides important information about current treatment of coronary artery disease, there are limitations. First, the 12-month follow-up period may not be sufficient to reflect the true long-term effect of CABG as compared with PCI with drug-eluting stents on cardiac-related health. However, our early results in terms of major adverse cardiac or cerebrovascular events are similar to those of a meta-analysis[34] of trials comparing CABG and PCI with predominantly bare-metal stents. The meta-analysis showed that the rate of major adverse cardiac or cerebrovascular events was lower with CABG than with PCI and that patients who underwent CABG had fewer repeat revascularization procedures than patients who underwent PCI. After 5 years of follow-up, the meta-analysis did not show any significant differences in rates of survival between the CABG and PCI groups,[34] although other studies have shown differences in mortality.[10-12]

Second, the use of medication differed between the groups in our study, reflecting variations in standard care of patients between the two treatment groups. Third, more patients withdrew, after randomization, from the CABG group than from the PCI group. Fourth, although randomization was conducted in a blinded manner, with clinicians and participants unaware of future treatment assignments, it was not possible to blind the performance of the treatment. Finally, the definition of myocardial infarction was based on a surgical definition (the finding of a new Q-wave on electrocardiography, in association with a value for the creatine kinase MB fraction that was five times the upper limit of the normal range), which may have resulted in less severe cases of myocardial infarction being overlooked.

In conclusion, the results of our trial show that CABG, as compared with PCI, is associated with a lower rate of major adverse cardiac or cerebrovascular events at 1 year among patients with three-vessel or left main coronary artery disease (or both) and should therefore remain the standard of care for such patients.

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