ORIGINAL ARTICLE

Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

G.W. Stone, A.P. Kappetein, J.F. Sabik, S.J. Pocock, M.-C. Morice, J. Puskas, D.E. Kandzari, D. Karmpaliotis, W.M. Brown III, N.J. Lembo, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P.E. Buszman, A. Bochenek, E. Schampaert, P. Pagé, R. Modolo, J. Gregson, C.A. Simonton, R. Mehran, I. Kosmidou, P. Généreux, A. Crowley, O. Dressler, and P.W. Serruys, for the EXCEL Trial Investigators*

ABSTRACT

BACKGROUND

Long-term outcomes after percutaneous coronary intervention (PCI) with contemporary drug-eluting stents, as compared with coronary-artery bypass grafting (CABG), in patients with left main coronary artery disease are not clearly established.

METHODS

We randomly assigned 1905 patients with left main coronary artery disease of low or intermediate anatomical complexity (according to assessment at the participating centers) to undergo either PCI with fluoropolymer-based cobalt–chromium everolimus-eluting stents (PCI group, 948 patients) or CABG (CABG group, 957 patients). The primary outcome was a composite of death, stroke, or myocardial infarction.

RESULTS

At 5 years, a primary outcome event had occurred in 22.0% of the patients in the PCI group and in 19.2% of the patients in the CABG group (difference, 2.8 percentage points; 95% confidence interval [CI], −0.9 to 6.5; P=0.13). Death from any cause occurred more frequently in the PCI group than in the CABG group (in 13.0% vs. 9.9%; difference, 3.1 percentage points; 95% CI, 0.2 to 6.1). In the PCI and CABG groups, the incidences of definite cardiovascular death (5.0% and 4.5%, respectively; difference, 0.5 percentage points; 95% CI, −1.4 to 2.5) and myocardial infarction (10.6% and 9.1%; difference, 1.4 percentage points; 95% CI, −1.3 to 4.2) were not significantly different. All cerebrovascular events were less frequent after PCI than after CABG (3.3% vs. 5.2%; difference, −1.9 percentage points; 95% CI, −3.8 to 0), although the incidence of stroke was not significantly different between the two groups (2.9% and 3.7%; difference, −0.8 percentage points; 95% CI, −2.4 to 0.9). Ischemia-driven revascularization was more frequent after PCI than after CABG (16.9% vs. 10.0%; difference, 6.9 percentage points; 95% CI, 3.7 to 10.0).

CONCLUSIONS

In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years. (Funded by Abbott Vascular; EXCEL ClinicalTrials.gov number, NCT01205776.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at the Cardiovascular Research Foundation, 1700 Broadway, 8th Fl., New York, NY 10019, or at gstone@crf.org.

*A complete list of investigators, institutions, and research organizations participating in the EXCEL trial is provided in the Supplementary Appendix, available at NEJM.org.

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Percutaneous coronary intervention (PCI) with drug-eluting stents has emerged as an acceptable treatment for selected patients with left main coronary artery disease.[1-8] However, long-term data from randomized trials comparing PCI involving contemporary drug-eluting stents with coronary-artery bypass grafting (CABG) in these patients are lacking. In the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial,[2] which involved patients with left main coronary artery disease of low or intermediate anatomical complexity, PCI with everolimus-eluting stents was noninferior to CABG with respect to the primary composite outcome measure of death, stroke, or myocardial infarction at a median 3-year follow-up. However, although the incidence of periprocedural adverse events (within 30 days) was lower in the PCI group, patients in the CABG group had fewer adverse events between 30 days and 3 years after the procedure. To further characterize the long-term outcomes of PCI as compared with CABG in patients with left main coronary artery disease, we report the final 5-year outcomes from this trial.

Methods

Trial Design

The trial design has been described previously.[2,9] In brief, we performed an international, open-label, multicenter, randomized trial that compared PCI involving thin-strut cobalt–chromium fluoropolymer-based everolimus-eluting stents (XIENCE, Abbott Vascular) with CABG in patients with left main coronary artery disease. The organization of the trial is described and participating centers are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol, also available at NEJM.org, was designed by the principal investigators and trial committees, in which interventional cardiologists and cardiac surgeons were represented equally. The trial was approved by the investigational review board or ethics committee at each participating center, and written informed consent was obtained from all the patients. The trial was sponsored by Abbott Vascular, which participated in the design of the protocol and in the selection and management of the sites but was not involved in the management or analysis of the data or preparation of the manuscript, although it had the right to a nonbinding review of the manuscript. The principal investigators had unrestricted access to the data, prepared the manuscript, and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Enrollment, Randomization, and Follow-up

Patients were eligible to participate in the trial if they had stenosis of the left main coronary artery of 70% or more (as estimated visually) or stenosis of 50% to less than 70% (if determined by means of noninvasive or invasive testing to be hemodynamically significant) and if a consensus among the members of the heart team had been reached regarding eligibility for revascularization with either PCI or CABG (Table S1 in the Supplementary Appendix).[2,9] In addition, eligible patients had low or intermediate anatomical complexity of coronary artery disease, as assessed at the participating center and defined by a Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score of 32 or less.[10] The SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score, and higher scores (no upper limit) indicating more complex coronary anatomy.

Randomization was performed with the use of an interactive voice-based or Web-based system in block sizes of 16, 24, or 32, with stratification according to the presence or absence of diabetes, SYNTAX score, and trial center. Clinical follow-up was performed at 1 month, 6 months, and 1 year and then annually through 5 years. Guideline-directed medical therapy and management of risk factors were recommended for all the patients, as previously described.[9] Dual antiplatelet therapy was administered before PCI and for a minimum of 1 year thereafter. Aspirin was administered before and after CABG, and the use of clopidogrel during follow-up was allowed but not mandatory. Routine angiographic follow-up was not permitted.

Outcomes

The primary outcome was the composite of death from any cause, stroke, or myocardial infarction at 3 years. Major secondary outcomes included

the primary outcome measure at 30 days and the composite of death, stroke, myocardial infarction, or ischemia-driven revascularization at 3 years. The cause of death was adjudicated as definite cardiovascular, definite noncardiovascular, or undetermined, and undetermined cases were conservatively classified as cardiovascular. Long-term additional secondary outcomes included these measures and their components at 5 years, as well as therapy failure (definite stent thrombosis or symptomatic graft stenosis or occlusion), all revascularizations, and all cerebrovascular events (stroke or transient ischemic attack). Outcomes are defined in Table S2. Trial monitors collected source documents of all primary and secondary outcome events for adjudication by an independent events committee. The extent of disease and SYNTAX score were assessed at an angiographic core laboratory.

STATISTICAL ANALYSIS

The trial was powered to show the noninferiority of PCI to CABG with respect to the primary outcome at 3 years.[2,9] The 5-year secondary outcomes were prespecified but were not explicitly powered or adjusted for multiple comparisons. The principal analyses were performed in the intention-to-treat population, which included all patients according to the group to which they were randomly assigned, regardless of the treatment received. Sensitivity analyses were performed in the per-protocol and as-treated populations,[9] with multiple imputation to account for missing follow-up data.[11]

Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. However, the underlying assumption of proportional hazards in the Cox model for the primary and major secondary outcomes from randomization through 5 years was not met (treatment–time interaction, P<0.001). Principal comparisons between treatments were therefore performed by logistic regression with follow-up time included as a log-transformed offset variable (no other covariates were included), with the use of an estimated standard error for the difference. In a post hoc analysis, we also evaluated piecewise hazards models separately within 0 to 30 days (the periprocedural period), 30 days to 1 year (the major risk period for stent restenosis), and 1 year to 5 years (long-term follow-up) — intervals during which proportional hazards were preserved. Given the presence of nonproportional hazards, net treatment effects were also examined with the use of post hoc milestone and restricted mean survival time analyses (Table S3). For milestone analysis, the percentage of patients with an event in each group was estimated with the Kaplan–Meier method, and Greenwood's formula was used to estimate standard errors. The difference between groups in milestone event rates that occurred each day during the 5-year follow-up period is reported. Restricted mean event-free survival time is the mean time free from an outcome event adjusted for loss to follow-up, reflecting the area under the survival curve.[12] The difference between groups in the restricted mean survival time over the 5-year follow-up period is reported.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with the use of Student's t-test or the Wilcoxon rank-sum test for non-normally distributed data. For superiority, a two-sided P value of less than 0.05 was considered to indicate statistical significance. The 95% confidence intervals for secondary outcomes were not adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND PROCEDURES

From September 29, 2010, to March 6, 2014, a total of 1905 patients with left main coronary artery disease were randomly assigned at 126 sites in 17 countries to PCI (948 patients) or CABG (957 patients) (Fig. S1). Baseline clinical and angiographic characteristics were well balanced between the groups (Tables S4 and S5). The mean (±SD) age of the patients was 66.0±9.6 years, 76.9% of patients were male, and 29.1% had diabetes. The mean SYNTAX score was 20.6±6.2 according to assessment at local sites and 26.5±9.3 according to the angiographic core laboratory analysis, and 80.5% of the patients had distal left main bifurcation disease. Procedural data are shown in Table S6. Adherence to guideline-directed medical therapy was high,

Table 1. Primary and Secondary Clinical Outcomes at 5 Years.*

Outcome	PCI (N=948)		CABG (N=957)		Difference in Event Rates (95% CI)	Odds Ratio (95% CI)
	Events	Event Rate	Events	Event Rate		
	no.	%	*no.*	%	*percentage points*	
Primary outcome						
Death, stroke, or myocardial infarction	203	22.0	176	19.2	2.8 (–0.9 to 6.5)	1.19 (0.95 to 1.50)
Secondary outcomes						
Death, stroke, myocardial infarction, or ischemia-driven revascularization	290	31.3	228	24.9	6.5 (2.4 to 10.6)	1.39 (1.13 to 1.71)
Death from any cause	119	13.0	89	9.9	3.1 (0.2 to 6.1)	1.38 (1.03 to 1.85)
Cardiovascular	61	6.8	49	5.5	1.3 (–0.9 to 3.6)	1.26 (0.85 to 1.85)
Definite cardiovascular	45	5.0	40	4.5	0.5 (–1.4 to 2.5)	1.13 (0.73 to 1.74)
Undetermined cause	16	1.9	9	1.1	0.9 (–0.3 to 2.0)	1.78 (0.78 to 4.06)
Noncardiovascular	58	6.6	40	4.6	2.0 (–0.2 to 4.2)	1.47 (0.97 to 2.23)
Stroke	26	2.9	33	3.7	–0.8 (–2.4 to 0.9)	0.78 (0.46 to 1.31)
Myocardial infarction	95	10.6	84	9.1	1.4 (–1.3 to 4.2)	1.14 (0.84 to 1.55)
Periprocedural	37	3.9	57	6.1	–2.1 (–4.1 to –0.1)	0.63 (0.41 to 0.96)
Nonperiprocedural	59	6.8	31	3.5	3.2 (1.2 to 5.3)	1.96 (1.25 to 3.06)
Ischemia-driven revascularization	150	16.9	88	10.0	6.9 (3.7 to 10.0)	1.84 (1.39 to 2.44)
PCI	125	14.1	80	9.1	4.9 (1.9 to 7.9)	1.65 (1.22 to 2.22)
CABG	38	4.3	8	0.9	3.4 (1.9 to 4.9)	4.90 (2.27 to 10.56)
Additional outcomes						
Any revascularization	153	17.2	92	10.5	6.7 (3.5 to 9.9)	1.79 (1.36 to 2.36)
Stent thrombosis	16	1.8	0	0	—	—
Definite	10	1.1	0	0	—	—
Probable	6	0.7	0	0	—	—
Symptomatic graft stenosis or occlusion	0	0	58	6.5	—	—
Therapy failure†	10	1.1	58	6.5	–5.4 (–7.2 to –3.6)	0.16 (0.08 to 0.32)
Cerebrovascular events‡	29	3.3	46	5.2	–1.9 (–3.8 to 0)	0.61 (0.38 to 0.99)
Transient ischemic attack	3	0.3	14	1.6	–1.3 (–2.2 to –0.4)	0.21 (0.06 to 0.74)

* Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses; thus, the rate is not the same as the ratio of the numerator and denominator. Odds ratios and 95% confidence intervals were estimated from logistic regression with follow-up time included as a log-transformed offset variable. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† Therapy failure was defined as definite stent thrombosis or symptomatic graft stenosis or occlusion.
‡ Cerebrovascular events were stroke or transient ischemic attack.

although medication use differed between the groups during follow-up (Table S7).

PRIMARY OUTCOME

Five-year follow-up was achieved in 93.2% and 90.1% of the PCI and CABG groups, respectively. The primary composite of death, stroke, or myocardial infarction at 5 years occurred in 22.0% of the patients in the PCI group and 19.2% of the patients in the CABG group (difference, 2.8 percentage points; 95% confidence interval [CI], –0.9 to 6.5; P=0.13) (Table 1 and Fig. 1A). The

hazard ratios (PCI vs. CABG) for the primary outcome varied in the three periods between 0 to 30 days (hazard ratio, 0.61; 95% CI, 0.42 to 0.88), 30 days to 1 year (hazard ratio, 1.07; 95% CI, 0.68 to 1.70), and 1 year to 5 years (hazard ratio, 1.61; 95% CI, 1.23 to 2.12) (Table 2 and Fig. S2). Analyses of milestones and restricted mean survival time showed that the early benefit of PCI was gradually diminished over time by increased postprocedural risk (Fig. S3). Mean event-free survival through 5 years was 5.2 days (95% CI, −46.1 to 56.5) longer after PCI than after CABG. The treatment effect for the primary outcome in prespecified subgroups is shown in Figure 2. Results were similar in the per-protocol and as-treated populations and after multiple imputation accounting for missing follow-up data (Tables S8 and S9).

SECONDARY OUTCOMES

The secondary composite outcome of death, stroke, myocardial infarction, or ischemia-driven revascularization at 5 years occurred in 31.3% of the patients in the PCI group and 24.9% of the patients in the CABG group (difference, 6.5 percentage points; 95% CI, 2.4 to 10.6) (Table 1 and Fig. 1B). The incidences of the individual components of the primary and secondary composite outcomes are shown in Table 1 and Figure 3. Death from any cause occurred in 13.0% of the patients in the PCI group and 9.9% of the patients in the CABG group (difference, 3.1 percentage points; 95% CI, 0.2 to 6.1). Eighteen of the 30 excess deaths in the PCI group were adjudicated as noncardiovascular deaths, 5 as definite cardiovascular deaths, and 7 as being of undetermined cause (Table S10). The results were similar after accounting for patients who were lost to follow-up (Table S9). The incidences of stroke and myocardial infarction at 5 years did not differ significantly between the PCI group and the CABG group. Ischemia-driven revascularization within 5 years was performed more frequently after PCI than after CABG, whereas the incidences of all cerebrovascular events and definite stent thrombosis or symptomatic graft stenosis or occlusion at 5 years were less frequent with PCI than with CABG. The hazard ratios for the secondary outcomes between 0 to 30 days, 30 days to 1 year, and 1 year to 5 years are provided in Table 2.

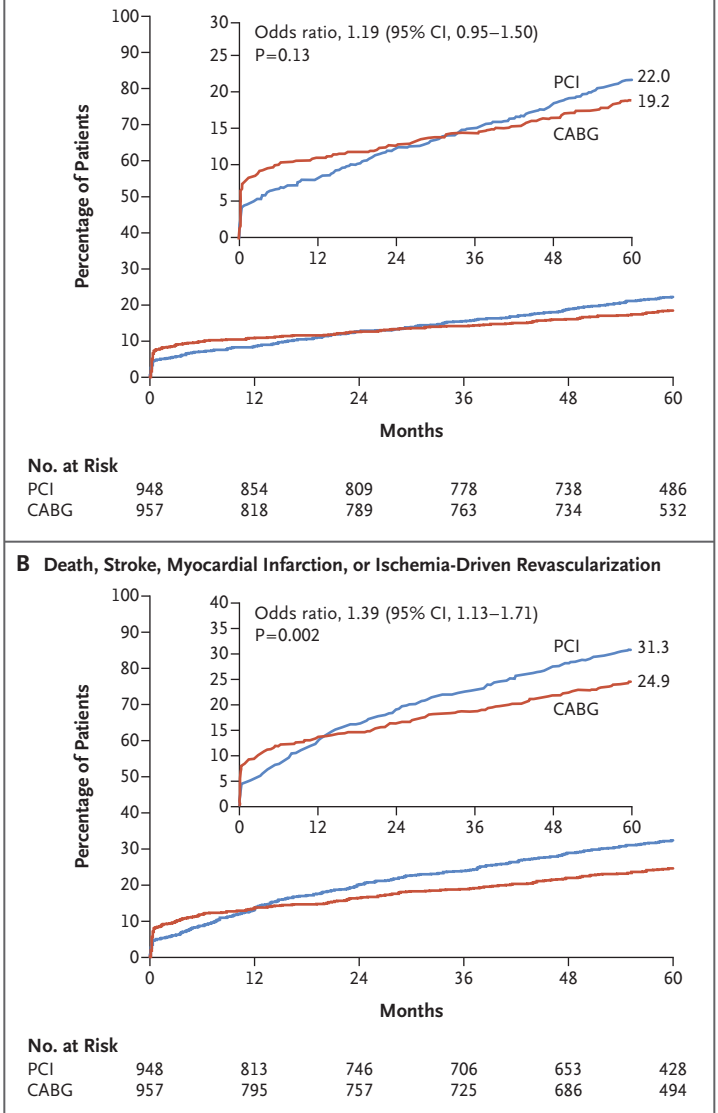

Figure 1. Time-to-First-Event Curves for the Primary and Secondary Composite Outcomes through 5-Year Follow-up.

Panel A shows the results of the primary composite outcome of death from any cause, stroke, or myocardial infarction. Panel B shows the results of the secondary composite outcome of death from any cause, stroke, myocardial infarction, or ischemia-driven revascularization. Event rates were based on Kaplan–Meier estimates. Given nonproportional hazards during the follow-up period, logistic regression with follow-up time included as a log-transformed offset variable was used to calculate the odds ratios with 95% confidence intervals. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. In each panel, the inset shows the same data on an enlarged y axis. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

Table 2. Primary and Secondary Outcomes over Three Periods.*

Variable	PCI		CABG		Hazard Ratio (95% CI)
	Events	Event Rate	Events	Event Rate	
	no./no. of patients	%	*no./no. of patients*	%	
Outcomes at 30 days					
Death, stroke, or myocardial infarction	46/948	4.9	75/957	8.0	0.61 (0.42–0.88)
Death	9/948	1.0	10/957	1.1	0.90 (0.37–2.21)
Stroke	6/948	0.6	12/957	1.3	0.50 (0.19–1.32)
Myocardial infarction	37/948	3.9	59/957	6.3	0.63 (0.42–0.94)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	46/948	4.9	80/957	8.5	0.57 (0.40–0.82)
Ischemia-driven revascularization	6/948	0.6	13/957	1.4	0.46 (0.17–1.21)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	3/948	0.3	11/957	1.2	0.27 (0.08–0.97)
Outcomes from 30 days to 1 yr					
Death, stroke, or myocardial infarction	38/948	4.1	35/957	3.8	1.07 (0.68–1.70)
Death	22/948	2.4	23/957	2.5	0.94 (0.53–1.69)
Stroke	5/948	0.5	7/957	0.8	0.71 (0.22–2.23)
Myocardial infarction	16/948	1.7	10/957	1.1	1.58 (0.72–3.48)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	83/948	8.9	56/957	6.1	1.48 (1.05–2.07)
Ischemia-driven revascularization	59/948	6.4	28/957	3.1	2.10 (1.34– 3.30)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	0/948	0	22/957	2.4	—
Outcomes from 1 yr to 5 yr					
Death, stroke, or myocardial infarction	133/933	15.1	83/929	9.7	1.61 (1.23–2.12)
Death	88/933	10.0	56/929	6.6	1.57 (1.12–2.19)
Stroke	16/933	1.9	15/929	1.8	1.06 (0.52–2.15)
Myocardial infarction	43/933	5.1	20/929	2.4	2.16 (1.27–3.67)
Death, stroke, myocardial infarction, or ischemia-driven revascularization	198/933	22.4	118/929	13.8	1.74 (1.38–2.18)
Ischemia-driven revascularization	100/933	11.6	49/929	5.8	2.10 (1.49–2.95)
Definite stent thrombosis or symptomatic graft stenosis or occlusion	7/933	0.8	25/929	3.0	0.28 (0.12–0.64)

* Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses; thus, the rate is not the same as the ratio of the numerator and denominator. The landmark period from 30 days to 5 years includes all randomly assigned patients at day 30 except those who died before day 30. Thus, some patients with a stroke, myocardial infarction, or ischemia-driven revascularization within 30 days may have had a second event between 30 days and 5 years. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

DISCUSSION

Patients with left main coronary artery disease have a poor prognosis because of the large amount of myocardium at risk.[13] Survival among patients with left main coronary artery disease is longer after revascularization with either PCI or CABG than with medical therapy alone.[14] In six randomized trials involving patients with left main coronary artery disease, PCI with drug-eluting stents was associated with more favorable outcomes at 1 year than CABG, with fewer periprocedural adverse events and more rapid recovery.[3,4,15] Conversely, conflicting long-term

Subgroup	PCI (N=948) Events/total patients no.	PCI (N=948) Event rate %	CABG (N=957) Events/total patients no.	CABG (N=957) Event rate %	Odds Ratio (95% CI)
All patients	203/948	22.0	176/957	19.2	1.19 (0.95–1.50)
Age (median cutoff)					
≥67 yr	123/466	27.2	98/472	21.8	1.39 (1.02–1.89)
<67 yr	80/482	16.9	78/485	16.6	1.00 (0.71–1.40)
Sex					
Male	145/722	20.6	134/742	18.7	1.12 (0.86–1.46)
Female	58/226	26.3	42/215	21.1	1.39 (0.88–2.20)
Diabetes mellitus, medically treated					
Yes	72/256	29.0	62/249	25.5	1.24 (0.83–1.86)
No	131/692	19.4	114/707	16.9	1.17 (0.89–1.55)
Chronic kidney disease					
Estimated GFR ≤60 ml/min	54/164	34.0	37/144	27.6	1.44 (0.86–2.39)
Estimated GFR >60 ml/min	147/770	19.5	135/791	17.6	1.13 (0.87–1.47)
Left ventricular ejection fraction					
≥50%	158/782	20.6	144/796	18.7	1.14 (0.88–1.46)
<50%	33/111	31.5	26/115	24.2	1.35 (0.73–2.49)
Geographic region					
North America	89/381	24.2	61/371	17.3	1.57 (1.09–2.26)
Europe	111/534	21.1	102/541	19.6	1.09 (0.81–1.48)
Other	3/33	9.6	13/45	29.6	0.24 (0.06–0.96)
Non–left main diseased coronary arteries (core laboratory assessment)					
0	33/163	20.7	23/167	14.3	1.55 (0.86–2.78)
1	60/292	21.2	61/292	21.9	0.94 (0.62–1.40)
2	79/325	25.0	50/295	17.8	1.58 (1.06–2.36)
3	31/162	19.2	37/182	20.7	0.93 (0.54–1.59)
Left main bifurcation or trifurcation stenosis ≥50% (core laboratory assessment)					
Yes	171/771	22.7	136/741	19.0	1.24 (0.96–1.60)
No	32/171	19.2	35/195	18.9	1.05 (0.62–1.79)
SYNTAX score (site reported)					
≤22	119/560	21.9	106/588	18.7	1.21 (0.90–1.62)
23–32	84/386	22.2	70/366	20.0	1.16 (0.81–1.67)
SYNTAX score (core laboratory assessment)					
≤22	49/294	17.2	58/364	16.7	0.99 (0.65–1.51)
23–32	91/392	23.7	69/346	20.7	1.22 (0.85–1.74)
≥33	56/228	25.0	42/216	20.0	1.36 (0.86–2.15)

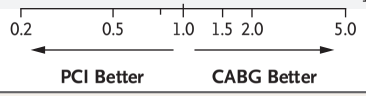

Figure 2. Subgroup Analyses of the Primary Composite Outcome at 5 Years.

Event rates were based on Kaplan–Meier estimates; thus, the rate is not the same as the ratio of the numerator and denominator. There were no significant differences between the relative risks of the treatment effects in any of the subgroups. The estimated glomerular filtration rate (GFR) was calculated by means of the Cockcroft–Gault equation. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score, and higher scores (no upper limit) indicating more complex coronary anatomy. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

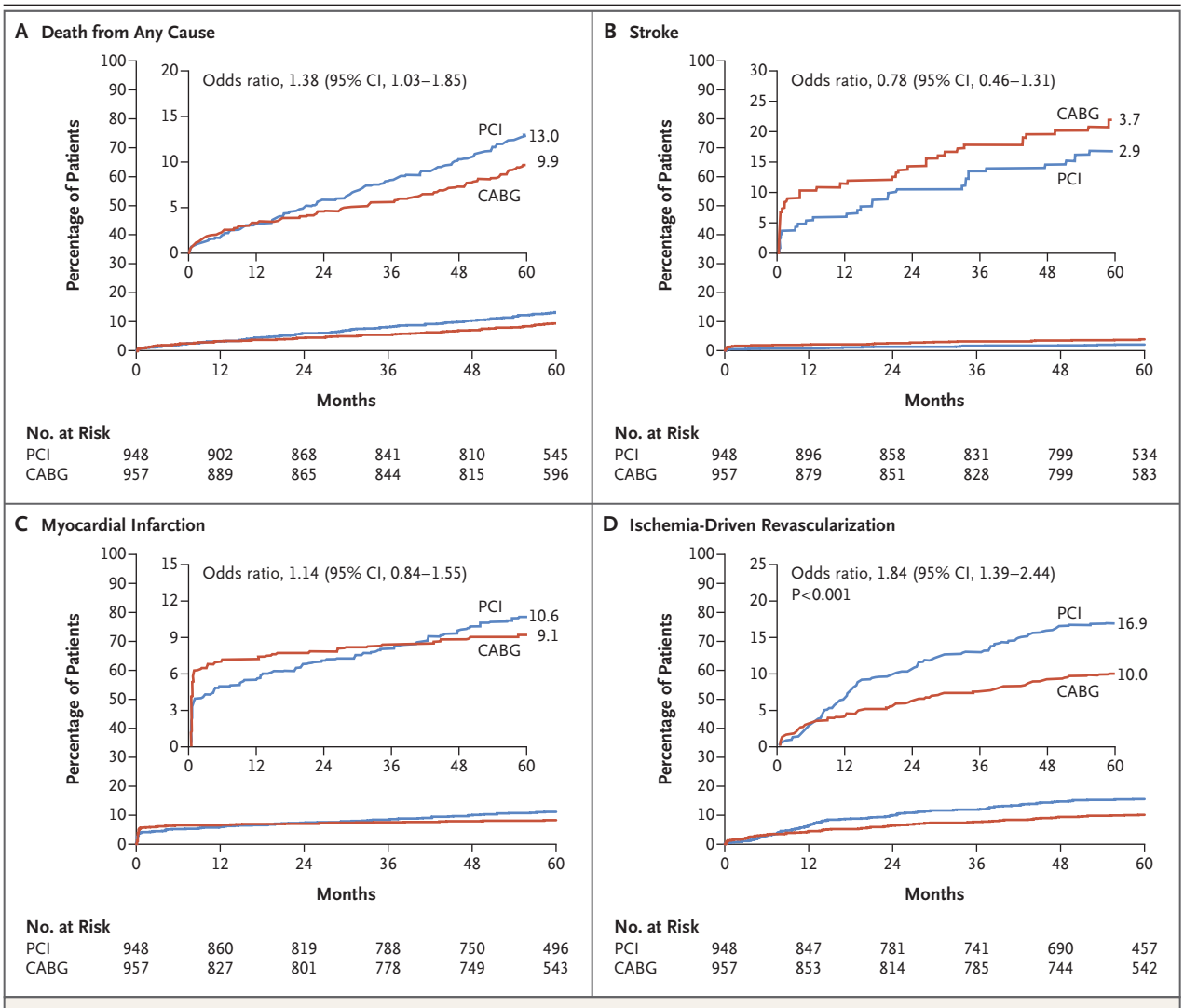

Figure 3. Time-to-First-Event Curves for the Components of the Primary and Secondary Composite Outcomes through 5-Year Follow-up.

Results of analyses of the components of the primary and secondary composite outcomes are shown in Panel A (death from any cause), Panel B (stroke), Panel C (myocardial infarction), and Panel D (ischemia-driven revascularization). Event rates were based on Kaplan–Meier estimates. Given nonproportional hazards during the follow-up period, logistic regression with follow-up time included as a log-transformed offset variable was used to calculate the odds ratios with 95% confidence intervals. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. In each panel, the inset shows the same data on an enlarged y axis.

findings from these trials have been reported.[1,3-5] However, to achieve adequate power, these trials relied on differences in the incidence of repeat revascularization, an outcome of lesser importance to physicians and patients than death, stroke, and myocardial infarction.[16] The degree of deterioration in health status that triggers repeat revascularization is also greater after CABG than after PCI; this calls into question the parity of this outcome.[17,18] In addition, previous trials did not use contemporary drug-eluting stents, which have a better safety profile than that of earlier devices.

The present trial was powered to examine the composite rate of death, stroke, or myocardial infarction. Current-generation fluoropolymer-based thin-strut cobalt–chromium everolimus-eluting stents, which are associated with a low incidence of stent thrombosis, were used,[19,20] and contemporary CABG techniques were incorpo-

rated.[2,9] We did not detect a significant difference in the composite rate of death, stroke, or myocardial infarction at 5 years between patients with left main coronary artery disease and low or intermediate anatomical complexity (as defined by a site-reported SYNTAX score of ≤32) who underwent PCI and those who underwent CABG. This finding was consistent across important subgroups, including patients with diabetes and those without diabetes and patients with lower and higher SYNTAX scores. However, interpreting these results as showing no difference between treatments is simplistic. As shown by the piecewise hazards analysis, three distinct periods of relative risk were present: from 0 to 30 days, when PCI resulted in fewer primary outcome events than CABG; from 30 days to 1 year, when the incidence of the events was similar among patients in each treatment group; and from 1 to 5 years, when primary outcome events were less common after CABG than after PCI. Consideration of the differential timing of risk is clinically relevant, since earlier exposure to adverse events has a more profound influence on the long-term burden of disease than exposure to events occurring later. As shown by the analysis of milestones and restricted mean survival time, by 5 years, the early benefit of PCI due to reduced periprocedural risk was attenuated by the greater number of events that occurred during follow-up than with CABG, such that the cumulative mean time free from adverse events was similar in the two treatment groups.

There were numerical differences between PCI and CABG in several nonpowered secondary outcomes. The event rates of death from any cause (a 3.1-percentage-point difference between the groups) and repeat revascularization (a 6.9-percentage-point difference) favored CABG, whereas event rates of cerebrovascular events (a 1.9-percentage-point difference) and therapy failure (a 5.4-percentage-point difference) favored PCI. Rates of myocardial infarction at 5 years were similar in the two groups, but they favored PCI in the periprocedural period and CABG during long-term follow-up. Although some of these findings may indicate true treatment effects, they must be interpreted cautiously, since more than 20 secondary outcomes were assessed and analyses were not adjusted for multiple comparisons. Nonetheless, several findings warrant comment.

Although the cause of death can sometimes be ambiguous, rates of adjudicated definite cardiovascular death were similar among patients who underwent PCI and those who underwent CABG, consistent with the similar rates of myocardial infarction at 5 years. The difference in all-cause mortality between the groups was driven by noncardiovascular deaths, especially those from cancer and infection, which occurred more commonly after PCI during late follow-up. The finding of a possible excess of deaths from any cause after PCI is at odds with the similar rates of death at 5 years among patients who underwent PCI and among those who underwent CABG in the contemporary Nordic–Baltic–British Left Main Revascularization (NOBLE) trial,[3] an individual patient-data pooled analysis of six randomized trials involving 4478 patients with left main coronary artery disease, and in other meta-analyses[4,21] and with the similar mortality at 10 years after PCI and CABG among patients with left main coronary artery disease in the SYNTAX trial.[22]

Whereas previous studies have shown higher rates of stroke after CABG than after PCI,[23] the excess of cerebrovascular events after CABG in the present trial was driven more by transient ischemic attacks than by strokes. The greater observed incidence of repeat revascularization after the use of drug-eluting stents than after CABG is consistent with previous analyses, but most revascularization events were repeat PCI procedures; only 1 of 25 patients initially treated with everolimus-eluting stents underwent CABG within 5 years. Nonetheless, repeat revascularization procedures may be associated with myocardial infarction and death.[24] These considerations notwithstanding, the absolute 5-year differences between the groups with respect to all the secondary outcomes were relatively modest, and some may have been due to chance. This perspective should be considered in discussions between the heart team and the patient when weighing the pros and cons of the different therapies.[25]

Additional limitations of this trial should be considered. First, bias in event ascertainment cannot be ruled out given the open-label trial design. Second, although the trial excluded patients with high SYNTAX scores, approximately 25% of the patients met this criterion according to the core laboratory analysis. Although the primary outcome results were consistent in this

subgroup, further studies are needed to determine the most appropriate treatment for patients with left main coronary artery disease and high anatomical complexity. Third, a specific biomarker-based definition of large periprocedural myocardial infarction was used in the present trial[2,6]; this definition differs from the criteria used in the Third Universal Definition of Myocardial Infarction[26] (which was developed while the current trial was ongoing) and the Fourth Universal Definition of Myocardial Infarction[27] (which was developed subsequently). The definition used in the EXCEL trial is based on previously established criteria that have been shown to be prognostically relevant after PCI and after CABG and that minimize ascertainment bias.[28] As previously reported, the occurrence of periprocedural myocardial infarction according to this protocol definition was independently predictive of late death from cardiovascular causes and death from any cause after PCI and after CABG, whereas lesser degrees of elevated levels of biomarkers were not.[29] Fourth, patients who underwent PCI, as compared with those who underwent CABG, more commonly received dual antiplatelet therapy and inhibitors of the renin–angiotensin axis during follow-up, whereas patients who underwent CABG more commonly received oral anticoagulants, beta-blockers, diuretics, and antiarrhythmic agents; these differences reflect inherent differences between the procedures and their resulting complications. The extent to which variability in medication use contributed to the present results is uncertain. Finally, follow-up was limited to 5 years, and at this time point the hazard curves were continuing to diverge. Ten-year (or longer) follow-up is needed to characterize the very late safety profiles of PCI and CABG, since both stents and bypass grafts progressively fail over time.

In conclusion, in the present trial we did not find a significant difference between PCI and CABG with respect to rates of the composite outcome of death, stroke, or myocardial infarction at 5 years among patients with left main coronary artery disease and low or intermediate anatomical complexity (as defined by the SYNTAX score) according to assessment at the participating centers.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Gregg W. Stone, M.D., A. Pieter Kappetein, M.D., Ph.D., Joseph F. Sabik, M.D., Stuart J. Pocock, Ph.D., Marie-Claude Morice, M.D., John Puskas, M.D., David E. Kandzari, M.D., Dimitri Karmpaliotis, M.D., W. Morris Brown III, M.D., Nicholas J. Lembo, M.D., Adrian Banning, M.D., Béla Merkely, M.D., Ferenc Horkay, M.D., Piet W. Boonstra, M.D., Ad J. van Boven, M.D., Imre Ungi, M.D., Gabor Bogáts, M.D., Samer Mansour, M.D., Nicolas Noiseux, M.D., Manel Sabaté, M.D., Jose Pomar, M.D., Mark Hickey, M.D., Anthony Gershlick, M.D., Pawel E. Buszman, M.D., Andrzej Bochenek, M.D., Erick Schampaert, M.D., Pierre Pagé, M.D., Rodrigo Modolo, M.D., Ph.D., John Gregson, Ph.D., Charles A. Simonton, M.D., Roxana Mehran, M.D., Ioanna Kosmidou, M.D., Philippe Généreux, M.D., Aaron Crowley, M.A., Ovidiu Dressler, M.D., and Patrick W. Serruys, M.D., Ph.D.

The authors' affiliations are as follows: the Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai (G.W.S., R. Mehran), the Cardiovascular Research Foundation (G.W.S., D.K., N.J.L., R. Mehran, I.K., P.G., A.C., O.D.), Mount Sinai Heart at Mount Sinai Saint Luke's (J. Puskas), and New York–Presbyterian Hospital and Columbia University Medical Center (D.K., N.J.L., I.K.) — all in New York; Erasmus Medical Center, Rotterdam (A.P.K.), Medisch Centrum Leeuwarden, Leeuwarden (P.W.B., A.J.B.), and Academic Medical Center, University of Amsterdam, Amsterdam (R. Modolo) — all in the Netherlands; University Hospitals Cleveland Medical Center, Cleveland (J.F.S.); the London School of Hygiene and Tropical Medicine (S.J.P., J.G.) and the International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London (P.W.S.), London, John Radcliffe Hospital, Oxford (A. Banning), and University Hospitals of Leicester NHS Trust, Leicester (M.H., A.G.) — all in the United Kingdom; Hôpital Privé Jacques Cartier, Ramsay Générale de Santé, Massy, France (M.-C.M.); Piedmont Heart Institute, Atlanta (D.E.K., W.M.B.); Semmelweis University, Budapest (B.M., F.H.), and the University of Szeged, Szeged (I.U., G.B.) — both in Hungary; Centre Hospitalier de l'Université de Montréal (S.M., N.N.) and Hôpital du Sacré-Coeur de Montréal (E.S., P.P., P.G.), Montreal; Hospital Clinic, Barcelona (M.S., J. Pomar); Medical University of Silesia, Katowice, and American Heart of Poland, Ustron — both in Poland (P.E.B., A. Bochenek); University of Campinas, Campinas, Brazil (R. Modolo); Abbott Vascular, Santa Clara, CA (C.A.S.); and Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, NJ (P.G.).

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