ORIGINAL ARTICLE

Fractional Flow Reserve–Guided PCI as Compared with Coronary Bypass Surgery

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ABSTRACT

BACKGROUND

Patients with three-vessel coronary artery disease have been found to have better outcomes with coronary-artery bypass grafting (CABG) than with percutaneous coronary intervention (PCI), but studies in which PCI is guided by measurement of fractional flow reserve (FFR) have been lacking.

METHODS

In this multicenter, international, noninferiority trial, patients with three-vessel coronary artery disease were randomly assigned to undergo CABG or FFR-guided PCI with current-generation zotarolimus-eluting stents. The primary end point was the occurrence within 1 year of a major adverse cardiac or cerebrovascular event, defined as death from any cause, myocardial infarction, stroke, or repeat revascularization. Noninferiority of FFR-guided PCI to CABG was prespecified as an upper boundary of less than 1.65 for the 95% confidence interval of the hazard ratio. Secondary end points included a composite of death, myocardial infarction, or stroke; safety was also assessed.

RESULTS

A total of 1500 patients underwent randomization at 48 centers. Patients assigned to undergo PCI received a mean (±SD) of 3.7±1.9 stents, and those assigned to undergo CABG received 3.4±1.0 distal anastomoses. The 1-year incidence of the composite primary end point was 10.6% among patients randomly assigned to undergo FFR-guided PCI and 6.9% among those assigned to undergo CABG (hazard ratio, 1.5; 95% confidence interval [CI], 1.1 to 2.2), findings that were not consistent with noninferiority of FFR-guided PCI (P=0.35 for noninferiority). The incidence of death, myocardial infarction, or stroke was 7.3% in the FFR-guided PCI group and 5.2% in the CABG group (hazard ratio, 1.4; 95% CI, 0.9 to 2.1). The incidences of major bleeding, arrhythmia, and acute kidney injury were higher in the CABG group than in the FFR-guided PCI group.

CONCLUSIONS

In patients with three-vessel coronary artery disease, FFR-guided PCI was not found to be noninferior to CABG with respect to the incidence of a composite of death, myocardial infarction, stroke, or repeat revascularization at 1 year. (Funded by Medtronic and Abbott Vascular; FAME 3 ClinicalTrials.gov number, NCT02100722.)

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*A full list of the FAME 3 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Large, randomized trials have shown improved outcomes in patients with three-vessel coronary artery disease when coronary revascularization is performed with coronary-artery bypass grafting (CABG) rather than with percutaneous coronary intervention (PCI).[1-3] However, trials have rarely used second-generation drug-eluting stents and have not routinely measured fractional flow reserve (FFR) to guide PCI. Second-generation drug-eluting stents have improved early and late outcomes, leading to lower rates of associated stent thrombosis, procedural and spontaneous myocardial infarction, restenosis, and death than first-generation drug-eluting stents.[4] FFR is an index measured with a coronary pressure wire that provides more accurate assessment of the hemodynamic significance of a coronary stenosis than does an angiogram alone. FFR-guided PCI results in better short-term and long-term outcomes than does angiography-guided PCI or medical therapy alone.[5-7] We sought to evaluate FFR-guided PCI performed with current-generation drug-eluting stents as compared with CABG with respect to the incidence of major adverse cardiac or cerebrovascular events among patients with three-vessel coronary artery disease.

Methods

Trial Design

We conducted the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 3 trial, an investigator-initiated, multicenter, international, randomized, controlled trial, at 48 sites; details regarding the design and conduct of the trial have been published previously and are provided in the protocol and the Supplementary Appendix, available with the full text of this article at NEJM.org.[8,9] The trial was supported by research grants to Stanford University from Medtronic and Abbott Vascular, which had no role in the design or conduct of the trial or in the preparation of the manuscript. Stanford University oversaw the conduct of the trial. The first author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients with angiographically identified three-vessel coronary artery disease not involving the left main coronary artery were randomly assigned in a 1:1 ratio to undergo either CABG or FFR-guided PCI. Randomization was performed with the use of a Web-based system and was stratified according to diabetes status and trial site. The major inclusion criterion was the presence of three-vessel coronary artery disease, defined as at least 50% diameter stenosis as assessed by visual estimation in each of the three major epicardial vessels or major side branches but not involving the left main coronary artery; the stenosis also needed to be amenable to revascularization by means of either PCI or CABG, as determined by the heart team at the trial site. Major exclusion criteria were recent ST-segment elevation myocardial infarction, cardiogenic shock, and a left ventricular ejection fraction of less than 30%. The full list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. The trial protocol was approved by relevant institutional review boards or ethics committees, and all participants provided written informed consent.

Trial Procedures

CABG was performed according to the standard practice at each participating center, with complete arterial revascularization strongly recommended. Assessment of the FFR to guide CABG was not mandated, but if it was performed at the time of the diagnostic angiogram, the information could be used by the surgeon. All patients assigned to undergo PCI first underwent FFR assessment with a coronary pressure wire (Abbott Vascular) and intravenous or intracoronary adenosine. The protocol specified that only stenoses with an FFR of 0.80 or lower were to be treated with PCI, which was performed with durable polymer zotarolimus-eluting stents (Resolute Integrity or Resolute Onyx, Medtronic). Post-PCI FFR measurement was encouraged. Intravascular imaging was performed as deemed necessary by the treating physicians. All the patients in both groups were to receive aspirin and a high-dose statin, as well as guideline-directed medical therapy. Patients undergoing PCI were to receive a second antiplatelet medication for at least 6 months after PCI. Follow-up was performed at hospital discharge and at 1, 6, and 12 months.

End Points

The primary end point was the occurrence within 1 year of a major adverse cardiac or cerebrovas-

cular event, defined as death from any cause, myocardial infarction, stroke, or repeat revascularization. Myocardial infarction was defined as procedural or spontaneous. In both groups, the biomarker threshold used to define a procedural myocardial infarction was any elevation of the cardiac troponin level to more than 10 times the 99th percentile of the upper reference limit within 72 hours after the procedure in patients who had normal levels at baseline or an increase in the cardiac troponin level of more than 20% in patients who had elevated levels at baseline. In addition, at least one of the following criteria needed to be met: new pathologic Q waves or new left bundle-branch block, angiographic documentation of new graft or major native coronary occlusion, or imaging evidence of new loss of viable myocardium or a new regional wall-motion abnormality. This definition is in line with a type 5 myocardial infarction (post-CABG procedural myocardial infarction) according to the Third and Fourth Universal Definitions of Myocardial Infarction.[10,11] Spontaneous myocardial infarction was defined as an increase or decrease in the cardiac troponin level with at least one value above the 99th percentile of the upper reference limit in addition to evidence of myocardial ischemia with at least one of the following findings: symptoms of ischemia, electrocardiographic changes indicative of new ischemia, development of pathologic Q waves, or imaging evidence of new loss of viable myocardium or a new regional wall-motion abnormality. Prespecified secondary end points are listed in Table S2. An independent clinical events committee adjudicated events in a blinded fashion.

STATISTICAL ANALYSIS

The primary analysis was conducted in accordance with the intention-to-treat principle. We initially assumed that 12% of the patients who were randomly assigned to undergo CABG would have a primary end-point event within 1 year; we also hypothesized that patients who were randomly assigned to undergo PCI would not have a higher risk of a primary end-point event than those assigned to undergo CABG.[3,12,13] With an upper boundary of less than 1.45 for the 95% confidence interval of the hazard ratio prespecified as indicating noninferiority and with a one-sided 2.5% significance level, we calculated that a sample of 712 patients per group (1424 for the entire trial) would be required in order to achieve 90% power to claim noninferiority. To account for patients who were anticipated to be either lost to follow-up or withdrawn from the trial, we enrolled 1500 patients. During recruitment and without knowledge of event rates, the trial steering committee decided to increase the noninferiority margin to an upper boundary of less than 1.65 for the 95% confidence interval of the hazard ratio because it was thought to be more appropriate on the basis of newly published clinical trials comparing CABG with PCI, which reported major adverse cardiac or cerebrovascular events occurring in no more than 10% of the patients randomly assigned to undergo CABG and used noninferiority margins similar to a hazard ratio of 1.65.[9] With this change, a sample of 645 patients per group (1290 for the entire trial) was required to achieve 90% power to claim noninferiority; however, the steering committee elected to complete the scheduled enrollment of 1500 patients.

Between-group differences in the incidence of the primary end point were visualized with the use of cumulative-incidence curves and estimated with a Cox proportional hazards model that adjusted for stratification factors (through inclusion of baseline diabetes status as a term in the model and by allowing the baseline hazard for each trial site to vary). Each component of the primary end point was similarly compared between the treatment groups, and safety end points were compared with the use of a chi-square or Fisher's exact test, as appropriate. The proportional hazards assumption was evaluated for the primary analysis with a two-sided score test of the scaled Schoenfeld residuals over time at the 0.05 level. Noninferiority was assessed with a Wald test at the 0.025 level of significance.

Subgroup analyses were performed under the same Cox proportional hazards framework as the primary analysis, and results were visualized as a forest plot for the following prespecified characteristics: age group (<65 years or ≥65 years), sex, presence or absence of diabetes, presence or absence of acute coronary syndrome, left ventricular ejection fraction (>50% or ≤50%), previous PCI, and core laboratory–assessed Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (an angiography-based score evaluating the severity of the coronary artery disease; lower scores indi-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PCI (N=757)	CABG (N=743)
Age — yr	65.2±8.6	65.1±8.3
Male sex — no. (%)	616 (81.4)	619 (83.3)
White race — no. (%)†	711 (93.9)	686 (92.3)
Body-mass index‡	28.6±4.5	28.7±4.3
Diabetes — no. (%)	214 (28.3)	214 (28.8)
Insulin-dependent	55 (7.3)	61 (8.2)
Non–insulin-dependent	159 (21.0)	153 (20.6)
Hypertension — no./total no. (%)	538/756 (71.2)	556/741 (75.0)
Dyslipidemia — no./total no. (%)	521/756 (68.9)	531/741 (71.7)
Smoking status — no./total no. (%)		
Current tobacco user	145/756 (19.2)	136/741 (18.4)
Previous tobacco user	296/756 (39.2)	296/741 (39.9)
Family history of coronary artery disease — no./total no. (%)	246/756 (32.5)	213/740 (28.8)
Previous myocardial infarction — no./total no. (%)	252/756 (33.3)	248/741 (33.5)
Previous PCI — no./total no. (%)	98/756 (13.0)	104/741 (14.0)
History of TIA or CVA — no./total no. (%)	49/756 (6.5)	56/741 (7.6)
Kidney disease — no./total no. (%)§	37/756 (4.9)	44/741 (5.9)
Noninvasive test for ischemia — no./total no. (%)	311/756 (41.1)	301/741 (40.6)
LVEF ≤50% — no./total no. (%)	137/753 (18.2)	130/740 (17.6)
Hospitalized with NSTE-ACS — no./total no. (%)	300/756 (39.7)	287/741 (38.7)

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, CVA cerebrovascular accident, LVEF left ventricular ejection fraction, NSTE-ACS non–ST-segment elevation acute coronary syndrome, PCI percutaneous coronary intervention, and TIA transient ischemic attack.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Kidney disease was defined as an estimated glomerular filtration rate (calculated with the Modification of Diet in Renal Disease Study equation) of less than 60 ml per minute per 1.73 m^2 of body-surface area.

cate less complexity of coronary artery disease and predict a better outcome with PCI [the lowest score is 0, and there is no upper limit]).[1] A post hoc sensitivity analysis was performed with the use of an alternative definition proposed by the Society for Cardiovascular Angiography and Interventions to identify procedure-related clinically relevant myocardial infarction.[14] Analyses were independently reproduced within the statistical team and conducted with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.0.[15]

RESULTS

PATIENTS

Of the 1500 patients enrolled, 757 were randomly assigned to undergo PCI and 743 to undergo CABG (Fig. S1). The mean age of the patients was 65 years, 29% had diabetes, 39% presented with an acute coronary syndrome, and 13% had undergone previous PCI (Table 1). On average, patients had 4.3 lesions; 22% of the patients had at least one vessel with chronic total occlusion, and 68% had at least one bifurcation lesion. The mean SYNTAX score was 26.

Procedural details for both groups are provided in Table 2. In the FFR-guided PCI group, the mean number of lesions per patient was 4.3, the mean number of drug-eluting stents implanted per patient was 3.7, and the median stented length was 80 mm. FFR was measured in 82% of lesions. The most common reasons for not measuring FFR were subtotally or completely occluded vessels. The mean FFR was 0.70, and 24% of the lesions intended for treatment had an FFR greater than 0.80. FFR was measured after PCI in 60% of treated lesions, with a

Table 2. Angiographic and Procedural Characteristics.*

Characteristic	PCI (N=757)	CABG (N=743)
Median time to procedure (IQR) — days	4 (1–13)	13 (6–26)
Median procedure duration (IQR) — min	87 (67–113)	197 (155–239)
Median length of hospital stay (IQR) — days	3 (1–7)	11 (7–16)
No. of lesions	4.3±1.3	4.2±1.2
At least one chronic total occlusion — no./total no. (%)	157/755 (20.8)	171/739 (23.1)
At least one bifurcation lesion — no./total no. (%)	522/755 (69.1)	491/739 (66.4)
SYNTAX score†	26.0±7.1	25.8±7.1
SYNTAX score category — no./total no. (%)†		
Low, 0 to 22	237/734 (32.3)	245/710 (34.5)
Intermediate, 23 to 32	365/734 (49.7)	343/710 (48.3)
High, >32	132/734 (18.0)	122/710 (17.2)
PCI characteristics		
Staged procedure — no./total no. (%)	166/750 (22.1)	NA
No. of stents	3.7±1.9	NA
Median total length of stents placed (IQR) — mm	80 (52–116)	NA
Intravascular imaging used — no./total no. (%)	87/744 (11.7)	NA
CABG characteristics		
Multiple arterial grafts — no./total no. (%)	NA	173/705 (24.5)
No. of distal anastomoses	NA	3.4±1.0
LITA used as graft — no./total no. (%)	NA	684/705 (97.0)
Off-pump surgery — no./total no. (%)	NA	168/698 (24.1)
FFR used before CABG — no./total no. (%)	NA	72/718 (10.0)

* Plus–minus values are means ±SD. Data on time to procedure were missing for 11 patients in the PCI group and 37 in the CABG group, data on procedure duration were missing for 12 patients in the PCI group and 77 patients in the CABG group, data on length of hospital stay were missing for 8 patients in the PCI group and 15 patients in the CABG group, and data on number of lesions were missing for 2 patients in each group. In the PCI group, data on number of stents were missing for 12 patients, and data on total length of stents were missing for 30 patients. In the CABG group, data on the number of distal anastomoses were missing for 51 patients. FFR denotes fractional flow reserve, IQR interquartile range, LITA left internal thoracic artery, and NA not applicable.

† The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiography-based score evaluating the severity of the coronary artery disease; lower scores indicate less complexity of coronary artery disease and predict a better outcome with PCI (the lowest score is 0, and there is no upper limit). Scores were calculated by the core laboratory. Data were missing for 23 patients in the PCI group and 33 patients in the CABG group.

mean value of 0.88. Intravascular imaging was used in 12% of cases.

Patients undergoing CABG had a mean of 4.2 lesions and received a mean of 3.4 distal anastomoses; 97% received a left internal thoracic-artery graft, and 25% received multiple arterial grafts. FFR was measured before CABG in 10% of patients.

END POINTS

Follow-up at 1 year was completed in 99.7% of the patients. FFR-guided PCI did not meet the criterion set in this trial for noninferiority with respect to the primary end point. At 1 year, the incidence of the primary end point was 10.6% in the FFR-guided PCI group and 6.9% in the CABG group (hazard ratio, 1.5; 95% confidence interval, 1.1 to 2.2; P=0.35 for noninferiority) (Table 3 and Fig. 1). There was no clear evidence of between-group differences in the incidence of each individual component of the primary end point or the composite of death, myocardial infarction, or stroke (Table 3 and Fig. S2).

There were no obvious differences between the groups with respect to medical therapy at 1 year, with the exception of a higher percentage

Table 3. End Points at 1 Year.

End Point	PCI (N=757)	CABG (N=743)	Hazard Ratio (95% CI)	P Value
	*no. of patients (%)**			
Primary end point				
Death from any cause, myocardial infarction, stroke, or repeat revascularization	80 (10.6)	51 (6.9)	1.5 (1.1–2.2)	0.35†
Secondary end points‡				
Death	12 (1.6)	7 (0.9)	1.7 (0.7–4.3)	
Death from cardiac causes	6 (0.8)	4 (0.5)		
Myocardial infarction	39 (5.2)	26 (3.5)	1.5 (0.9–2.5)	
Spontaneous	25 (3.3)	17 (2.3)		
Procedural	13 (1.7)	9 (1.2)		
Stroke	7 (0.9)	8 (1.1)	0.9 (0.3–2.4)	
Death, myocardial infarction, or stroke	55 (7.3)	39 (5.2)	1.4 (0.9–2.1)	
Repeat revascularization	45 (5.9)	29 (3.9)	1.5 (0.9–2.3)	
PCI	39 (5.2)	26 (3.5)		
CABG	6 (0.8)	3 (0.4)		
Safety end points§				
BARC type 3–5 bleeding¶	12 (1.6)	28 (3.8)		<0.01
Acute kidney injury‖	1 (0.1)	7 (0.9)		<0.04
Atrial fibrillation or clinically significant arrhythmia	18 (2.4)	105 (14.1)		<0.001
Definite stent thrombosis	6 (0.8)	NA		
Definite symptomatic graft occlusion	NA	10 (1.3)		
Rehospitalization within 30 days	42 (5.5)	76 (10.2)		<0.001

* Percentages are crude values based on an intention-to-treat analysis.
† This P value was obtained from a test of noninferiority with respect to the primary end point.
‡ Confidence intervals (CIs) were not adjusted for multiplicity and should not be interpreted to inform definitive treatment effects.
§ P values were obtained from chi-square or Fisher's exact tests. Patients who were lost to follow-up before the end of the first year were excluded from comparisons with respect to safety end points.
¶ Bleeding Academic Research Consortium (BARC) type 3–5 indicates severe bleeding.
‖ Acute kidney injury was defined as an increase in serum creatinine level by at least 0.3 mg per deciliter (≥26.5 μmol per liter) within 48 hours, an increase in serum creatinine level to at least 1.5 times the baseline level that was known or presumed to have occurred within the previous 7 days, or a urine volume of less than 0.5 ml per kilogram of body weight per hour for 6 hours.

of patients in the FFR-guided PCI group receiving dual antiplatelet and nitrate therapy (Table S3). Patients randomly assigned to undergo CABG had longer hospital stays and higher incidences of major bleeding, arrhythmia, acute kidney injury, and rehospitalization within 30 days (Table 3). Results for other secondary end points are provided in Table S4. Results of prespecified subgroup analyses are shown in Figures 2 and S3. A post hoc sensitivity analysis evaluating the effect of using a different definition of procedural myocardial infarction resulted in an incidence of this outcome of 14.5% in the CABG group and 10.3% in the FFR-guided PCI group.[14]

DISCUSSION

The main finding of our trial is that in patients with angiographically identified three-vessel coronary artery disease, FFR-guided PCI did not meet the criterion we set for noninferiority with respect to the primary composite end point. CABG resulted in a lower incidence of the composite of death, myocardial infarction, stroke,

or repeat revascularization at 1 year than FFR-guided PCI in which current-generation zotarolimus-eluting stents were used. The incidence of the secondary composite end point of death, myocardial infarction, or stroke and of each individual component of the primary end point did not differ significantly between the two groups. Incidences of procedural complications such as major bleeding, acute kidney injury, arrhythmia, and rehospitalization within 30 days were higher and the mean length of hospital stay longer among the patients randomly assigned to undergo CABG.

These findings are consistent with those of previous trials comparing CABG with PCI, but there are important differences between those trials and the current trial.[1,3] The current trial involved routine measurement of FFR to guide PCI, with the expectation that the use of FFR would lead to more judicious stenting — that is, an FFR-guided strategy would result in PCI being used to treat only functionally significant lesions, which have been shown to be associated with higher rates of adverse events when treated with medications alone, and would avoid unnecessary stenting of non–flow-limiting lesions, which respond as well to medical therapy alone as they do to PCI (and may even respond better to medical therapy alone).[5,7] As anticipated, patients in our trial received fewer stents than those in the SYNTAX trial (3.7 vs. 4.6), which compared PCI (without FFR guidance) with CABG, although the number of coronary lesions was similar.[1] Although these trials are not directly comparable, patients assigned to undergo PCI in our trial also had a lower incidence of repeat revascularization (4.9% vs. 13.5%) and lower mortality (1.6% vs. 4.4%) than those in the SYNTAX trial, despite similar patient characteristics and risk profiles in the two trials (Table S5). Plausible explanations for these findings include the lower number of stents placed (with reduced risk of stent-related complications such as thrombosis or restenosis), improved stent technology, and high levels of adherence to recommended medical therapy. Moreover, the incidence of major adverse cardiac or cerebrovascular events among patients assigned to undergo either FFR-guided PCI (10.6%) or CABG (6.9%) in our trial was lower than that among patients assigned to undergo CABG in the SYNTAX trial (12.4%).[1] Among the patients assigned to undergo CABG, the better outcomes in our trial may be due to improvements in operative techniques or more effective medical therapy. For example, the percentages of the patients assigned to undergo CABG who were using statins or beta-blockers at 1 year were 94% and 83%, respectively, in our trial, as compared with approximately 70% and 75%, respectively, in the SYNTAX trial.[16]

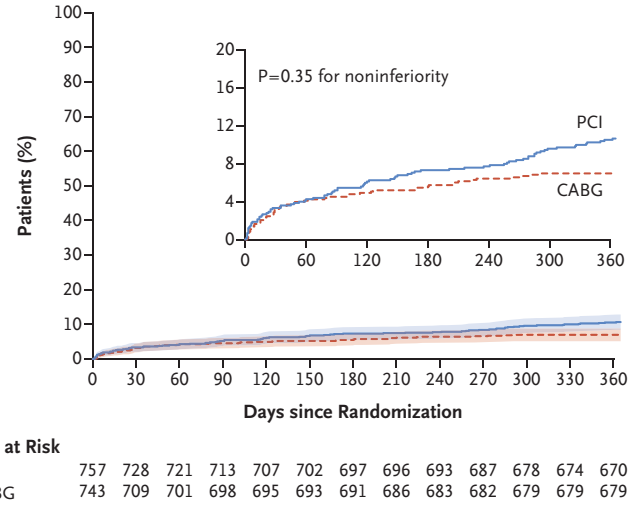

Figure 1. Kaplan–Meier Curves for the Primary End Point.

The primary end point was the occurrence within 1 year of a major adverse cardiac or cerebrovascular event, defined as death from any cause, myocardial infarction, stroke, or repeat revascularization. The inset shows the same data on an enlarged y axis. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

In our trial, FFR was measured in 82% of the lesions in the PCI group and was found to be greater than 0.80 in 24% of the lesions. These percentages were lower than those in a previous trial comparing FFR-guided PCI with angiography-guided PCI in patients with multivessel coronary artery disease (in which FFR was measured in 95% of lesions and was >0.80 in 37% of lesions).[5] The benefit of FFR guidance is primarily related to avoiding unnecessary stents and their inherent complications. In cases in which the FFR measurement and deferral rates are higher, one might anticipate better outcomes with an FFR-guided PCI approach.

FFR was measured before CABG in 10% of patients. Presumably, these patients all had functionally significant three-vessel coronary artery disease. It is likely that a proportion of the can-

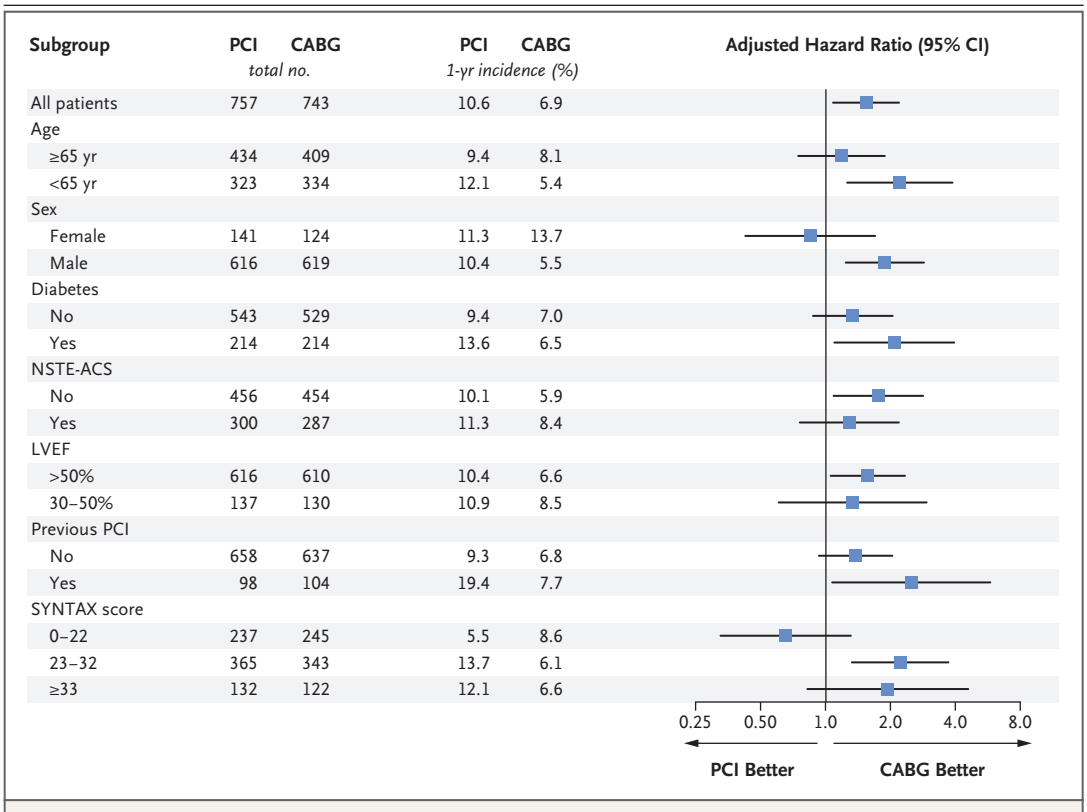

Figure 2. Subgroup Analyses of the Primary End Point.

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiography-based score evaluating the severity of coronary artery disease; lower scores indicate less complexity of coronary artery disease and predict a better outcome with PCI (the lowest score is 0, and there is no upper limit). Scores were calculated by the core laboratory. CI denotes confidence interval, LVEF left ventricular ejection fraction, and NSTE-ACS non–ST-segment elevation acute coronary syndrome.

didates for the trial had FFR measured before randomization and were found to have only one or two vessels with functionally significant disease and therefore were not included in the trial but instead were treated immediately with PCI. This could have skewed the population in this trial toward more severe coronary artery disease.

The definition of procedural myocardial infarction remains controversial. In our primary analysis, we defined procedural myocardial infarction in the CABG and PCI groups using a definition almost identical to the Third Universal Definition of CABG-related myocardial infarction, which resulted in low percentages of patients being classified as having procedural myocardial infarction. Because data on symptoms suggestive of ischemia or new ischemic electrocardiographic changes were not routinely recorded after PCI, we could not apply the Third or Fourth Universal Definition of PCI-related myocardial infarction. If we had been able to calculate the incidence of procedural myocardial infarction according to these definitions, which require lower levels of biomarker elevation (troponin elevation more than 5 times the 99th percentile of the upper reference limit) in conjunction with only symptoms of ischemia or ischemic electrocardiographic changes, we probably would have seen a higher incidence of procedural myocardial infarction in the FFR-guided PCI group. A post hoc sensitivity analysis in which a more liberal definition, including a biomarker-elevation-only criterion, was used resulted in higher incidences of procedural myocardial infarction, particularly among the patients randomly assigned to undergo CABG.[14]

Other limitations of the current analysis also warrant consideration. First, follow-up for this

analysis was only 1 year. Previous trials have shown a greater benefit with CABG than with PCI during longer-term follow-up, particularly with respect to late myocardial infarction and repeat revascularization. Follow-up for 3 and 5 years is ongoing in our trial and will be critical to assessing longer-term effects of these two treatment strategies. Second, the current report does not include information on changes in quality of life and cost-effectiveness, although data have been collected to address these outcomes. Third, FFR was not routinely measured in the patients assigned to undergo CABG; however, trials comparing FFR-guided CABG with angiography-guided CABG have not shown the same benefit as seen with FFR-guided PCI.[17,18] Fourth, intravascular imaging was used in only 12% of the patients treated with PCI; previous data indicate that repeat revascularization is less common when intravascular imaging is routinely performed, although the incidence of repeat revascularization at 1 year in a study in which intravascular imaging was used for 84% of patients undergoing PCI in a similar population was not lower than that in our trial.[19,20] Fifth, the completeness of revascularization in both groups has not yet been analyzed. Sixth, women and persons of color were underrepresented in our trial (Table S6). Future trials involving a more diverse patient population will be necessary before these findings can be generalized.

In our trial, we found that in patients with three-vessel coronary artery disease, FFR-guided PCI was not noninferior to CABG with respect to the composite of death, myocardial infarction, stroke, or repeat revascularization at 1 year.

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

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

APPENDIX

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