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Long-Term Mortality After Coronary Revascularization in Nondiabetic Patients With Multivessel Disease

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ABSTRACT

BACKGROUND In diabetic patients with multivessel coronary artery disease (CAD), the survival difference between coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) favors CABG. However, there are few data on the mortality difference between the 2 strategies in nondiabetic patients.

OBJECTIVES This study performed a patient-level meta-analysis to compare the effect of CABG versus PCI with drug-eluting stents on long-term mortality in 1,275 nondiabetic patients with multivessel CAD.

METHODS Individual patient data from the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) and the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trials were pooled. The primary outcome was death from any cause.

RESULTS The median follow-up time was 61 months (interquartile range: 50 months to 62 months). The risk of death from any cause was significantly lower in the CABG group than in the PCI group (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.43 to 0.98; $p = 0.039$). A similar finding was observed for the risk of death from cardiac causes. The superiority of CABG over PCI was consistent across the major clinical subgroups. Likewise, the rate of myocardial infarction was remarkably lower after CABG than after PCI (HR: 0.40; 95% CI: 0.24 to 0.65; $p < 0.001$). However, the rate of stroke was not different between the 2 groups (HR: 1.13; 95% CI: 0.59 to 2.17; $p = 0.714$). The need for repeat revascularization was significantly lower in the CABG group than in the PCI group (HR: 0.55; 95% CI: 0.40 to 0.75; $p < 0.001$).

CONCLUSIONS CABG, as compared with PCI with drug-eluting stents, significantly reduced the long-term risk of mortality in nondiabetic patients with multivessel CAD. (J Am Coll Cardiol 2016;68:29-36)

Both coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) play a major role in the management of multivessel coronary artery disease (CAD) (1-5). Since the introduction of drug-eluting stents (DES), PCI has become a widely used option for the treatment of multivessel CAD.

Several randomized trials comparing the relative outcomes of CABG versus PCI in patients with multivessel CAD have been published (6-11). In

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAD = coronary artery disease

DES = drug-eluting stent(s)

PCI = percutaneous coronary intervention

general, diabetic patients have poorer clinical outcomes than nondiabetic patients and better survival with CABG than PCI (6,7,9). However, controversy still exists as to the optimal revascularization strategy in nondiabetic patients with multivessel CAD. Death from any cause is undoubtedly the most unbiased endpoint to determine treatment strategy, but each randomized trial has shown limited power to assess the clinical equipoise between CABG and PCI regarding mortality. Pooling of patient-level data from these randomized trials might be suggested to increase the statistical power and allow time-to-event analysis of this issue (12).

SEE PAGE 37

Therefore, in the present study, we combined the databases from the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) and the BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trials, and performed a patient-level analysis. The effects of CABG versus PCI with DES on long-term mortality in nondiabetic patients with multivessel CAD and the differences among major clinical subgroups were analyzed.

METHODS

STUDY PATIENTS. Each trial's designs, detailed entry criteria, and outcomes were described previously (8,11). In brief, both trials were multicenter and multinational: SYNTAX recruited patients from Europe and the United States, and BEST recruited from Asia. The SYNTAX trial included 1,800 patients with 3 vessels or left main CAD. The BEST trial included 880 patients with 2- or 3-vessel CAD. In both studies, patients eligible for both CABG and PCI were randomized to treatment with either strategy. PCI was performed using either paclitaxel-eluting stents in the SYNTAX trial or everolimus-eluting stents in the BEST trial. Patients with concomitant left main CAD (n = 705) or diabetes mellitus (n = 700) were excluded from this study.

DATA COLLECTION. The principal investigators of each trial (S.J.P., P.W.S.) programmed a protocol with the pre-specified outcomes and a common set of baseline variables. Individual patient data from each

TABLE 1 Patient Characteristics

	CABG (n = 638)	PCI (n = 637)
Age, yrs	64.3 ± 9.8	64.8 ± 9.9
Male	512 (80.3)	499 (78.3)
Body mass index, kg/m^2	26.4 ± 3.7	26.4 ± 4.1
Current smoker	142 (22.3)	126 (19.8)
Hypercholesterolemia	411 (64.8)	424 (66.8)
Hypertension	405 (63.5)	430 (67.5)
Clinical presentation		
Stable angina	393 (61.6)	400 (62.8)
ACS	245 (38.4)	237 (37.2)
Previous myocardial infarction	172 (27.1)	144 (22.7)
Previous stroke	32 (5.0)	39 (6.1)
Peripheral vascular disease	37 (5.8)	31 (4.9)
CKD (creatinine >200 μmol/l)	5 (0.8)	5 (0.8)
Left ventricular dysfunction*	24 (4.9)	19 (3.9)
Diseased vessels		
Proximal LAD disease	365 (57.5)	375 (59.1)
2 vessels	65 (10.2)	81 (12.7)
3 vessels	573 (89.8)	556 (87.3)
SYNTAX score	26.7 ± 9.4	25.9 ± 9.1
EuroSCORE†	3.3 ± 2.4	3.3 ± 2.4
Follow-up, yrs	4.4 ± 1.4	4.4 ± 1.3

Values are mean ± SD or n (%). *Left ventricular dysfunction was defined as LVEF <40% or moderate to severe left ventricular dysfunction. †The EuroSCORE is a clinical model for calculating the risk of death after cardiac surgery on the basis of patient, cardiac, and operative factors. Possible scores range from 0 to 39, with higher scores indicating greater risk. Percentages are on the basis of the number of nonmissing values.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CKD = chronic kidney disease; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

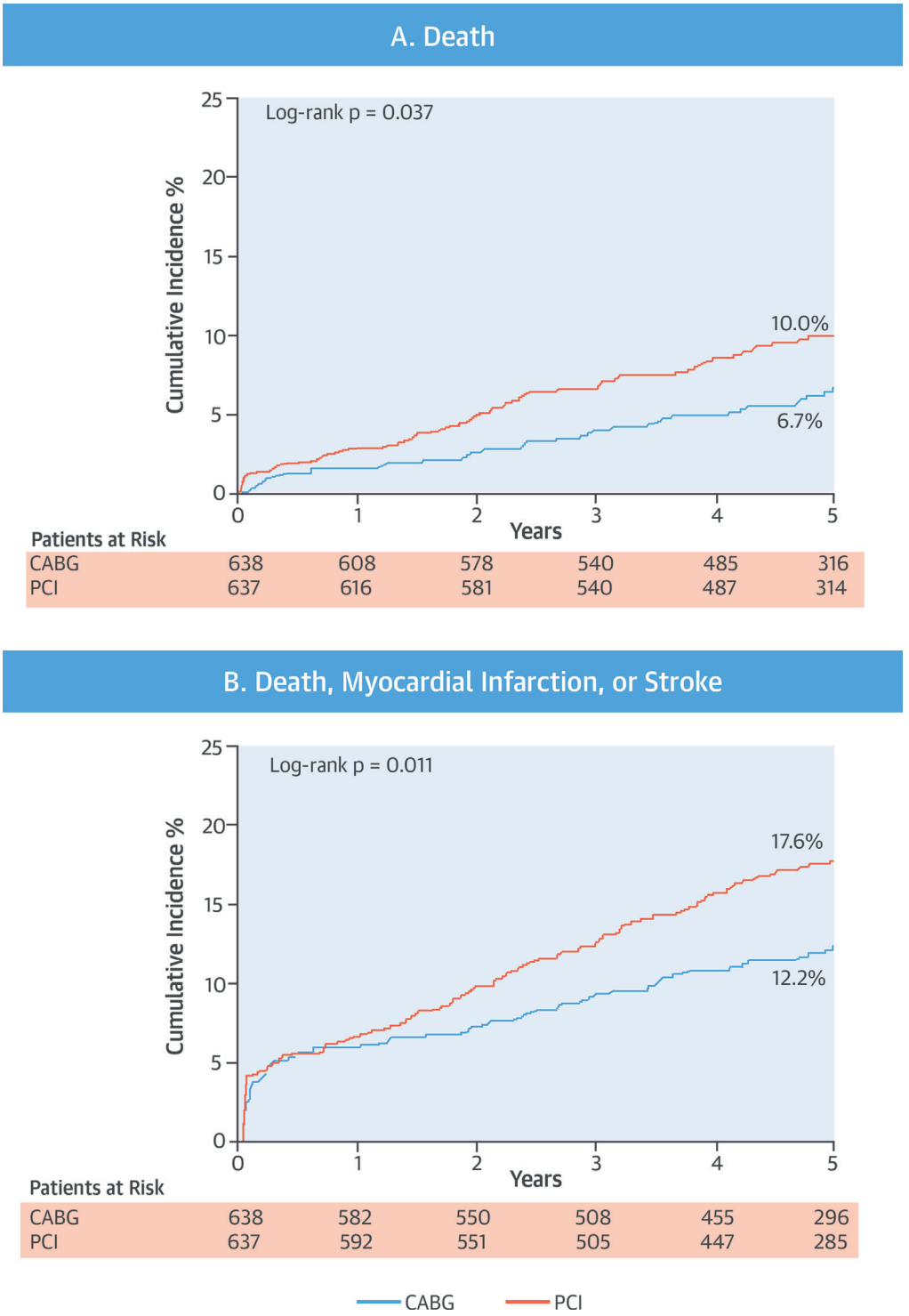
TABLE 2 Medications at Discharge and Follow-Up

	CABG (n = 638)	PCI (n = 637)	p Value
Aspirin			
At discharge	577 (91.6)	613 (96.5)	<0.001
1 yr after randomization	541 (88.7)	570 (92.5)	0.021
5 yrs after randomization	373 (81.3)	382 (82.5)	0.624
$P2Y_{12}$ inhibitors			
At discharge	310 (49.2)	611 (96.2)	<0.001
1 yr after randomization	218 (35.7)	464 (75.3)	<0.001
5 yrs after randomization	86 (18.8)	165 (35.6)	<0.001
Statins			
At discharge	494 (78.4)	544 (85.7)	0.001
1 yr after randomization	508 (83.3)	548 (89.0)	0.004
5 yrs after randomization	374 (81.5)	387 (83.6)	0.400
Beta-blockers			
At discharge	412 (65.4)	481 (75.7)	<0.001
1 yr after randomization	497 (81.5)	514 (83.4)	0.365
5 yrs after randomization	307 (66.9)	320 (69.1)	0.468
ACE inhibitors or ARBs			
At discharge	247 (39.2)	352 (55.4)	<0.001
1 yr after randomization	318 (52.1)	340 (55.2)	0.282
5 yrs after randomization	255 (55.6)	267 (57.7)	0.518

Values are n (%). Percentages are on the basis of the number of nonmissing values.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Surgery Versus Stents for Nondiabetic Multivessel Disease: Mortality for Overall Patients and SYNTAX Score Subgroups**



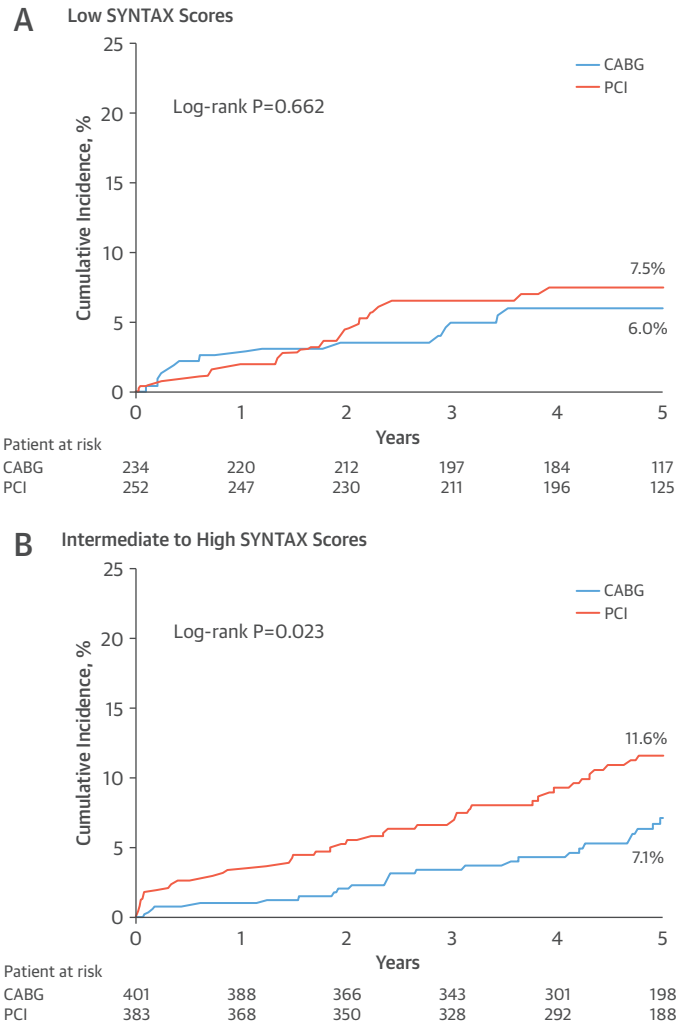
Chang, M. et al. J Am Coll Cardiol. 2016;68(1):29–36.

The cumulative incidences of death from any cause **(A)** and of a composite of death from any cause, myocardial infarction, or stroke **(B)** for all patients are shown. CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

trial was sent to the coordinating board of Asan Medical Center in Seoul, Korea, and merged for analysis. The pooled database was checked for completeness and consistency by investigators at the Asan Medical Center. A committee blinded to randomization adjudicated all clinical endpoints of each study. Unless specified, previously reported definitions from each study were used for variables.

STUDY OUTCOMES. The primary outcome was death from any cause. The secondary outcomes were a composite of death, myocardial infarction, or stroke; myocardial infarction; stroke; or any repeat revascularization. Previously reported definitions from each study were used for individual clinical outcomes (8,11). Briefly, in the SYNTAX trial, myocardial infarction was defined as any myocardial infarction occurring after randomization, and its detailed definition was described elsewhere (8). In the BEST trials, myocardial infarction was defined as new Q waves and increase in the creatine kinase-MB concentration to >5 times the upper limit of the normal range, if occurring within 48 h after the procedure, or as new Q waves or an increase in creatine kinase MB concentration to greater than the upper limit of the normal range, plus ischemic symptoms or signs, if occurring more than 48 h after the procedure (11).

FIGURE 1 Primary Outcomes for SYNTAX Score Subgroups



The cumulative incidences of death from any cause for the low **(A)** and the intermediate to high **(B)** SYNTAX score subgroups are shown. The p values were calculated using the log-rank test with all available follow-up data. Percentages denote 5-year event rates. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

STATISTICAL ANALYSIS. All analyses were performed according to the intention-to-treat principle. Time-to-event outcomes were displayed using Kaplan-Meier methodology, compared by the log-rank test. Stratified Cox proportional hazards models were used to analyze the impact of revascularization strategy on clinical outcomes and to determine whether the merged data from each trial would influence the primary outcome. The treatment effect was estimated separately for each trial, and the estimates were combined to provide an overall treatment effect. A likelihood-ratio test was performed to assess the homogeneity of data, and the assumption of homogeneity was not violated ($p = 0.914$). The proportional-hazards assumption regarding the treatment assignments was confirmed through the Schoenfeld residuals test; no relevant violations of the assumption were found. An independent statistician who was unaware of the treatment assignments performed analyses. All reported p values were 2-sided, and values of $p < 0.05$ were considered to indicate statistical significance. Statistical analyses were performed with SPSS software (version 18.0, SPSS Inc., Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS. A total of 1,275 patients were randomly assigned to CABG (n = 638) or PCI (n = 637). The 2 groups were well balanced on baseline characteristics (Table 1). The median age of patients in the study was 65 years (interquartile range: 58 to 72 years); 79.3% of the patients were men. At discharge, 91.6% and 96.5% ($p < 0.001$) of patients received aspirin and 78.4% and 85.7% received statins ($p = 0.001$) in the PCI and CABG groups, respectively (Table 2). Other medications were also less commonly used in the CABG group than in the PCI group.

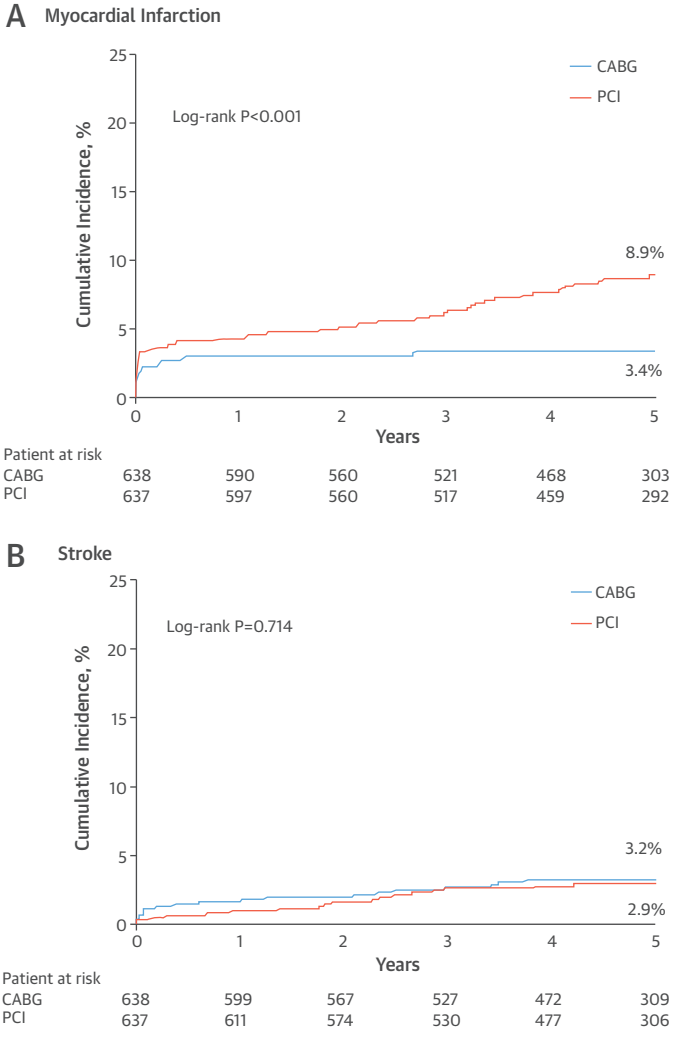
PRIMARY OUTCOME

The median length of follow-up after randomization was 61 months (interquartile range: 50 months to 62 months). The primary outcome of death from any cause occurred in 38 patients (6.0%) in the CABG group and 59 (9.3%) in the PCI group (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.43 to 0.98; p = 0.039) (**Central Illustration**). Similarly, the rate of death from cardiac causes was significantly lower in the CABG group compared with the PCI group (HR: 0.41; 95% CI: 0.25 to 0.78; p = 0.005). The statistical difference between 2 groups was pronounced after 2 years of randomization for both all-cause and cardiac mortality. The benefit of CABG over PCI was notably greater in patients with intermediate (23 to 32) to high (≥33) SYNTAX scores than in those with low (0 to 22) SYNTAX scores (**Figure 1**).

SECONDARY OUTCOMES. A composite of death, myocardial infarction, or stroke occurred in 72 patients (11.3%) in the CABG group and 106 (16.6%) in the PCI group (HR: 0.68; 95% CI: 0.50 to 0.92; p = 0.012) (**Central Illustration**). There were fewer myocardial infarctions in the CABG group (3.3%) than in the PCI group (8.3%) (HR: 0.40; 95% CI: 0.24 to 0.65; p < 0.001) (**Figure 2A**). The rate of stroke was numerically higher, but not significantly different between the 2 groups (HR: 1.13; 95% CI: 0.59 to 2.17; p = 0.714) (**Figure 2B**). In contrast, the rate of repeat revascularization was significantly lower in the CABG group than in the PCI group (HR: 0.55; 95% CI: 0.40 to 0.75; p < 0.001).

SUBGROUP ANALYSES. Subgroup analyses showed the consistent superiority of CABG over PCI on the primary outcome across all major subgroups (**Figure 3**). There was no interaction of treatment effect concerning the primary outcome between 2 trials (p = 0.913 for interaction). There was also no significant interaction observed between treatment effect and types of DES for the primary outcome.

FIGURE 2 Secondary Outcomes for the Overall Population



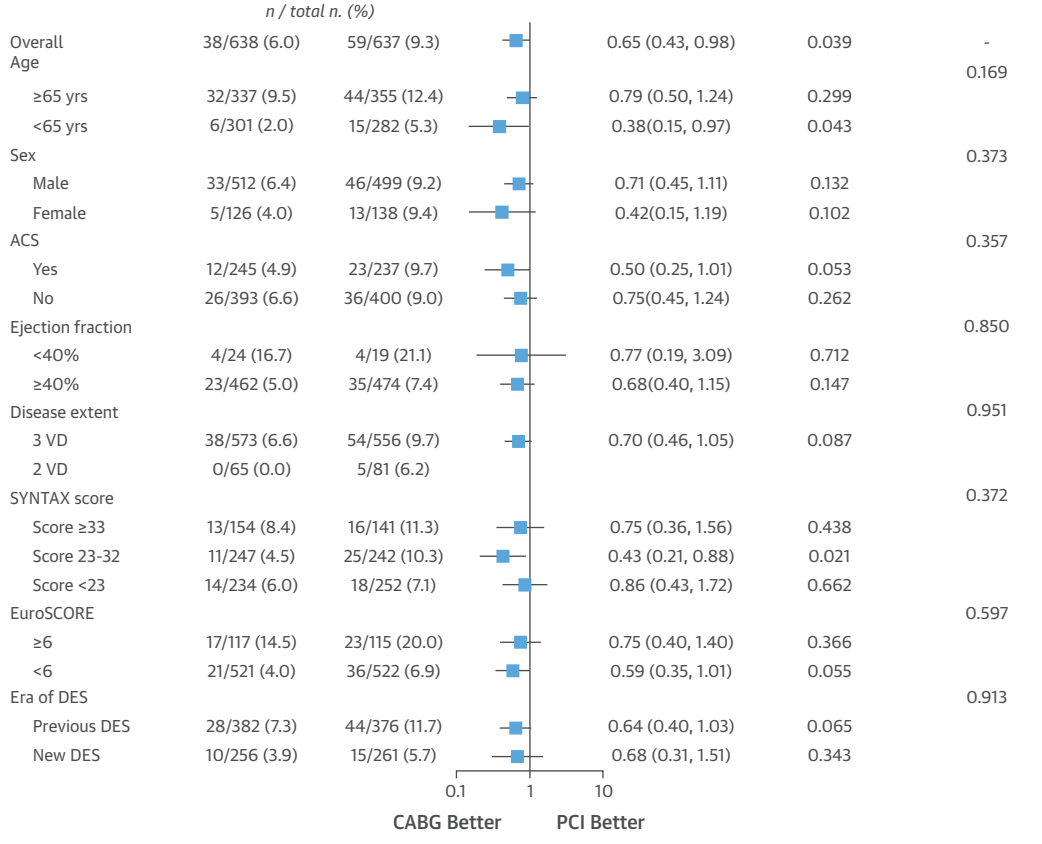
Cumulative incidences of myocardial infarction **(A)** and stroke **(B)** are shown. The p values were calculated using the log-rank test with all available follow-up data. Percentages denote 5-year event rates. Abbreviations as in **Figure 1**.

DISCUSSION

Among nondiabetic patients with multivessel CAD, those who received CABG had a lower rate of death from any cause than those who underwent PCI with DES (**Central Illustration**). Furthermore, the rate of myocardial infarction was remarkably lower after CABG than after PCI with DES. These benefits on both the primary outcome and myocardial infarction were consistent across all major clinical subgroups. In contrast, the risk of stroke linked to CABG was relatively small.

Understanding long-term mortality may help physicians to decide the best treatment strategy for a particular patient. In addition, all-cause mortality may be the most reliable endpoint because it is not affected by bias in classifying the cause of death. However, previous randomized trials were typically not powered to detect a small difference in all-cause mortality. In the present study, therefore, databases from 2 randomized trials were merged to overcome the power limitation of the individual studies. Five-year survival was found to be significantly better in the CABG group than the PCI group in nondiabetic patients with multivessel CAD. There was no between-group difference within the first few months after randomization, but the difference progressively increased over time,

FIGURE 3 Subgroup Analyses for the Primary Outcome



Subgroup analyses were performed using Cox proportional hazards regression. ACS = acute coronary syndrome; CI = confidence interval; DES = drug-eluting stent(s); VD = vessels diseased; other abbreviations as in Figure 1.

demonstrating a clear survival advantage for CABG. This finding is consistent with the results of previous randomized trials (7,9,13,14). In the largest observational study, ACCF and STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) (15), the adjusted mortality at 1 year was similar between the 2 groups (risk ratio: 0.95; 95% CI: 0.90 to 1.00). In contrast, mortality at 4 years was significantly lower after CABG than after PCI (risk ratio: 0.79; 95% CI: 0.76 to 0.82). The long-term survival advantage after CABG was the same for all patient subgroups, including nondiabetics. In contrast, a recent observational study reported a similar risk of death after CABG versus PCI with everolimus-eluting stents during a 2.9-year follow-up period (16). Despite the use of sophisticated statistical techniques, observational data are confounded by selection biases, often yielding mixed outcomes. In our study, the results were derived from a large pooled population of randomized studies and showed that CABG was associated with progressively better survival than PCI with DES. We also found that in patients with low SYNTAX scores, the 2 strategies were comparable with respect to mortality, but in those with intermediate or high SYNTAX scores, CABG was distinctly superior to PCI with DES. These findings support that CABG is the preferred approach for patients with multivessel CAD, and that PCI may be a valid option for selected low-risk patients with multivessel CAD.

For secondary outcomes, the incidence of myocardial infarction was markedly different between CABG and PCI. The cumulative incidence of myocardial infarction tended to reach a plateau soon after CABG, whereas it continued to accrue over time after PCI with DES. These findings are compatible with those from previous studies (17), supporting the

idea that CABG may bypass the vulnerable segments of a coronary artery. Whereas DES treats the focal area of tight stenosis, CABG avoids touching risky sites and builds healthy connections that prevent future coronary events (18). Considering that more than 90% of CABG cases utilize the left internal thoracic artery graft, the left ventricular myocardium is almost fully protected from future thrombotic occlusion of the proximal and midportion of the left anterior descending coronary artery.

Post-operative stroke is a devastating complication with high morbidity and mortality. Previously, the risk of early stroke was shown to be greater with CABG than with PCI, but the incidence of late stroke was similar (19). On the contrary, we found that stroke rarely occurred, and there was no significant difference between the 2 strategies. A similar finding was observed by other investigators, which should provide some reassurance to patients undergoing CABG (20). The reason for these discrepancies remains unclear, but differences in study design, patients, and medical therapies may have influenced the rates of post-operative stroke. Overall, CABG significantly reduced the risks of death from any cause and myocardial infarction, but carried a small risk of stroke compared with PCI with DES.

STUDY LIMITATIONS. First, this study contains a mixture of generations of DES. Newer-generation DES are reported to improve clinical outcomes, which may narrow the gap between CABG and PCI. However, in our study, there was no significant interaction between previous and newer-generation DES regarding the primary outcome. In addition, neoatherosclerosis, a major cause of late DES failure, occurs over time, irrespective of the type of DES (21,22). In this regard, CABG seems to maintain a comparative advantage over PCI, even in the era of newer-generation DES. Second, the present pooled analysis may have limited power to elucidate differences in primary outcome and subgroups, including SYNTAX score. An ongoing randomized trial (FAME 3, NCT02100722) is expected to reinforce our findings about the relative merits of both strategies. Finally, optimal medical therapy was used substantially less after CABG than after PCI, which may have been disadvantageous for prevention of cardiovascular events patients who underwent CABG.

CONCLUSIONS

CABG, as compared with PCI with DES, significantly reduced the long-term risk of mortality in nondiabetic patients with multivessel CAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In nondiabetic patients with multivessel CAD, CABG is associated with a lower risk of death than percutaneous intervention with DES. Surgery offers greater protection against myocardial infarction, but carries a slightly greater risk of postoperative stroke.

TRANSLATIONAL OUTLOOK: Future comparisons of CABG versus DES should incorporate optimal medical therapy and functional assessments of coronary lesions to guide selection of the optimal method of revascularization.

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KEY WORDS coronary artery bypass graft surgery, drug-eluting stents, multivessel coronary artery disease