Comparison of Outcome of Coronary Artery Bypass Grafting Versus Drug-Eluting Stent Implantation for Non−ST-Elevation Acute Coronary Syndrome

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There is limited data comparing effectiveness of coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) with drug-eluting stents in patients with non−ST-elevation acute coronary syndromes (NSTE-ACS). We compared the long-term outcomes of the 2 revascularization strategies in 1,246 patients presented with NSTE-ACS for left main or multivessel coronary artery disease. Data were pooled from the Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial, the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial, and the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial. The primary outcome was a composite of death from any causes, myocardial infarction, or stroke. The baseline characteristics were similar between the 2 study groups. During the median follow-up of 60 months, the rate of the primary outcome was significantly lower with CABG than with PCI (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.56 to 0.98; p = 0.036). This difference was mainly attributed to a significant reduction in the rate of myocardial infarction (HR 0.50; 95% CI 0.31 to 0.82, p = 0.006). The superiority of CABG over PCI was consistent across the major subgroups. The individual risks of death from any causes or stroke were not different between the 2 groups. In contrast, the rate of repeat revascularization was significantly lower in the CABG group than in the PCI group (HR 0.56; 95% CI 0.41 to 0.75, p <0.001). In this study, among patients with NSTE-ACS for left main or multivessel coronary artery disease, CABG significantly reduces the risk of death from any causes, myocardial infarction, or stroke compared with PCI with drug-eluting stents. **(Am J Cardiol 2017;120:380−386)**

Patients with non−ST-elevation acute coronary syndromes (NSTE-ACS) remain at high risk of recurrent cardiovascular events. In the previous studies, the early risk of major cardiovascular events was found to be higher with coronary artery bypass grafting (CABG), but the revascularization rate was reported to be grater with percutaneous coronary intervention (PCI).[1,2] In this study, we compared the effects of CABG and PCI with drug-eluting stents (DES) on long-term cardiovascular outcomes in patients with NSTE-ACS for left main or multivessel coronary artery disease (CAD) using a pooled database of the Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial, the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial, and the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial.

Methods

We searched for publications from 2005 to 2015 in the COCHRANE, EMBASE, and MEDLINE databases using terms that included "coronary artery bypass surgery," "drug-eluting stent," "left main," and "multivessel coronary artery disease." Seven randomized trials were identified.[3−11] Four trials were not analyzed further: the investigators of the FREEDOM trial did not participate,[8] the CARDia trial used both drug-eluting and bare-metal stents,[9] and 2 small trials

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Table 1
Patient characteristics

Variable	CABG (N=634)	PCI (N=612)	p-value
Age (years)	65.1±9.8	64.1±10.2	0.104
Men	465 (73.3%)	427 (69.8%)	0.167
Body mass index (kg/m^2)	25.8±3.8	26.0±4.3	0.491
Current smoker	157 (24.9%)	138 (22.5%)	0.351
Diabetes mellitus			
Any	207 (32.6%)	225 (36.8%)	0.137
Requiring insulin	47 (7.4%)	50 (8.2%)	0.673
Hypercholesterolemia	351 (55.5%)	365 (59.7%)	0.136
Hypertension	383 (60.4%)	376 (61.4%)	0.728
Clinical presentation			0.907
Unstable angina pectoris	594 (93.7%)	575 (94.0%)	
NSTEMI	40 (6.3%)	37 (6.0%)	
Previous myocardial infarction	145 (22.9%)	135 (22.2%)	0.786
Previous stroke	27 (5.6%)	30 (6.2%)	0.684
Peripheral vascular disease	39 (6.2%)	33 (5.4%)	0.628
Creatinine >200μmol/L	11 (1.7%)	9 (1.5%)	0.823
Left ventricular dysfunction*	24 (4.3%)	36 (7.1%)	0.062
No. of narrowed coronary arteries			0.814
2	59 (9.3%)	57 (9.3%)	0.814
3	326 (51.4%)	316 (51.6%)	
Proximal LAD	401 (63.3%)	382 (62.6%)	
Left main			0.954
isolated	33 (5.2%)	24 (3.9%)	
plus 1	47 (7.4%)	41 (6.7%)	
plus 2	68 (10.7%)	76 (12.4%)	
plus 3	101 (15.9%)	98 (16.0%)	
SYNTAX scores	26.9±10.6	26.8±10.8	0.789
Complete revascularization	403 (64.9%)	343 (56.6%)	0.003

CABG = coronary artery bypass grafting; LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention.

* Left ventricular dysfunction defined as left ventricular ejection fraction < 40% or moderate to severe left ventricular dysfunction. Percentages are based on the number of non-missing values.

Table 2
Medications at discharge and follow-up

Medication	CABG (N=634)	PCI (N=612)	p-value
Aspirin			
At discharge	596 (95.2%)	592 (97.4%)	0.045
1 year after randomization	555 (92.0%)	555 (94.1%)	0.169
5 year after randomization	356 (79.3%)	372 (85.1%)	0.023
$P2Y_{12}$ inhibitors			
At discharge	398 (63.6%)	586 (96.4%)	<0.001
1 year after randomization	315 (52.2%)	476 (80.7%)	<0.001
5 year after randomization	137 (30.6%)	198 (45.3%)	<0.001
ACEI/ARB			
At discharge	235 (37.5%)	340 (55.9%)	<0.001
1 year after randomization	280 (46.4%)	326 (55.3%)	<0.001
5 year after randomization	208 (46.3%)	252 (57.7%)	<0.001
β blockers			
At discharge	343 (54.8%)	446 (73.4%)	<0.001
1 year after randomization	426 (70.6%)	474 (80.3%)	<0.001
5 year after randomization	245 (54.6%)	281 (64.3%)	0.003
Statins			
At discharge	471 (75.2%)	510 (83.9%)	<0.001
1 year after randomization	479 (79.4%)	511 (86.6%)	0.001
5 year after randomization	320 (71.3%)	333 (76.2%)	0.095

Percentages are based on the number of non-missing values.

ACEI = angiotensin-converting-enzyme inhibitors; ARB = angiotensin receptor blockers; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

had not published any long-term outcomes.[10,11] Individual patient-level data were pooled from the BEST (*ClnicalTrials.gov* number, NCT00997828), PRECOMBAT (*ClinicalTrials.gov* number, NCT00422968), and SYNTAX (*ClinicalTrials.gov* number, NCT00114972) trials.[3–7] Protocols, comprising prespecified outcomes and a common set of baseline variables, were established by the principal investigators in each trial (SJP and PWS). Individual patient data from each trial were sent to Asan Medical Center in Seoul, Korea, as the coordinating institution. An independent clinical events committee that was blind to the randomization data adjudicated all the end points in each study.

The merged database included demographics (age, gender, body weight, height), clinical history (chronic kidney disease, previous myocardial infarction, previous stroke, peripheral artery disease, previous PCI), risk factors (diabetes mellitus, hypercholesterolemia, hypertension, current smoking), angiographic and echocardiographic findings (number of diseased vessels, involvement of left main coronary artery or proximal left anterior descending coronary artery, SYNTAX score, left ventricular dysfunction), revascularization strategies, medication history (aspirin, $P2Y_{12}$ inhibitors, antihypertensive drugs, statins, insulin), and clinical outcomes (all-cause death, cardiac death, myocardial infarction, stroke, repeat revascularization). Unless specified, the previously reported definitions from each study were used as variables in our current investigation. The primary outcome of our present study was a composite of death from any causes, myocardial infarction, or stroke from all available follow-up information. The secondary outcomes included the individual components of the primary outcome, any coronary revascularization, and a composite of all-cause death or myocardial infarction.[3–7]

We analyzed data according to the intention to treat principle. The databases for the BEST, PRECOMBAT, and SYNTAX trials were combined for overall pooled analysis, and time-to-event outcomes were displayed using the Kaplan-Meier methodology and compared by the log-rank test. The stratified Cox proportional hazards model was used to analyze the impact of revascularization strategy on clinical outcomes and to determine whether merging of the data from the 3 trials would influence the primary outcome. The treatment effect was estimated separately for each trial, and the estimates were combined to provide an overall estimate of the treatment effect. For the analysis, we used 1-stage approach with random-effect meta-analysis and a likelihood ratio test was performed to assess the homogeneity of the data. The assumption of homogeneity was not violated ($p = 0.237$). The proportional hazards assumption regarding the treatment assignments was confirmed using a Schoenfeld residuals test; no relevant violations of the assumption were found. Analyses were performed by an independent statistician who was unaware of the treatment assignments. All reported p values are 2 sided, and values of $p < 0.05$ were considered to indicate statistical significance.

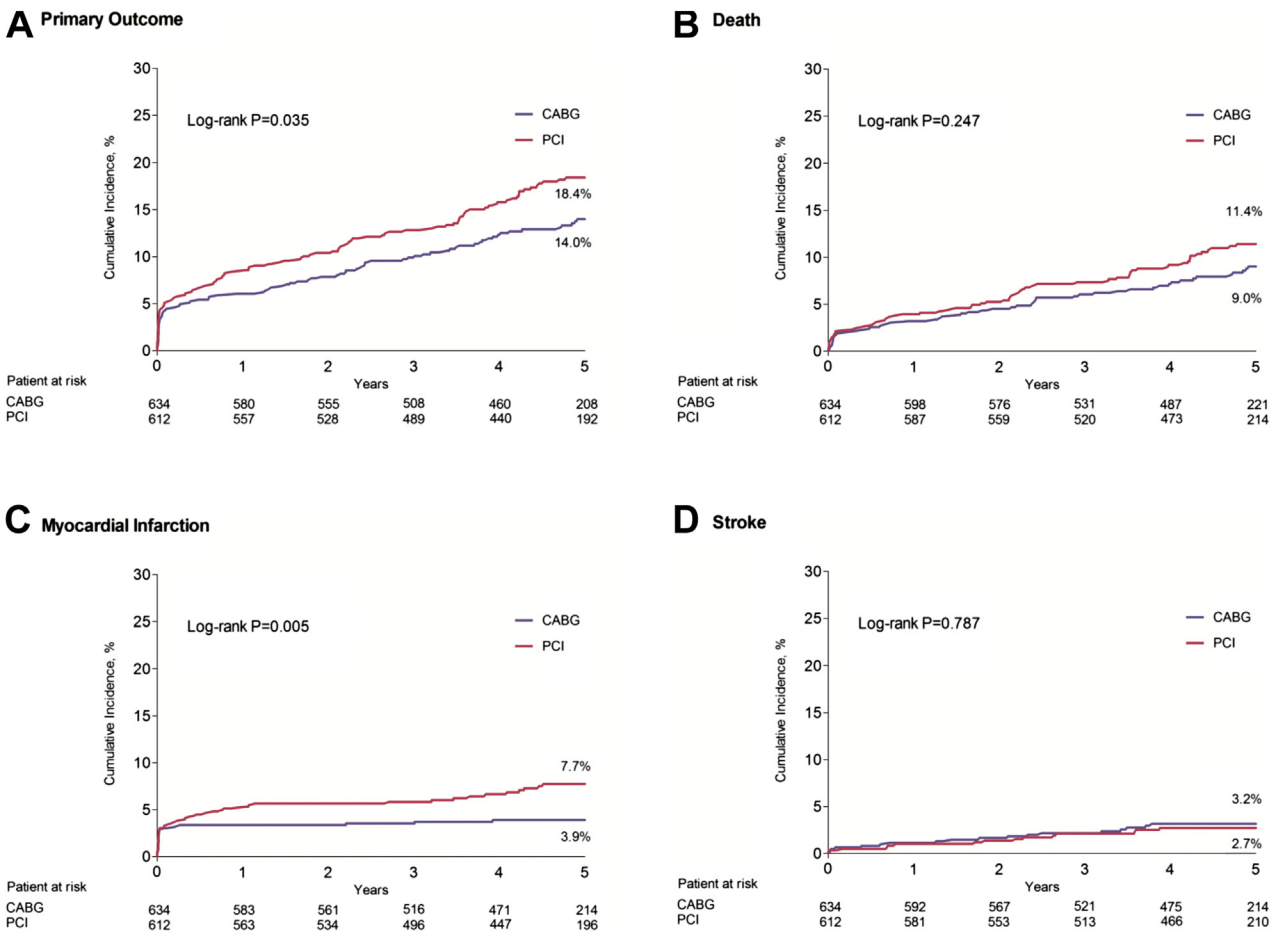

Figure 1. Clinical outcomes among patients with non−ST-elevation acute coronary syndrome. The event rates of death from any causes, myocardial infarction, or stroke *(A)*, death from any causes *(B)*, myocardial infarction *(C)*, and stroke *(D)* are shown. The p values were calculated using the log-rank test with all available follow-up data.

Statistical analyses were conducted with the SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

The study population comprised 1,246 patients (38.0% of the total cohort) who presented with NSTE-ACS and underwent randomization to either CABG (n = 634) or PCI (n = 612) treatment group. The 2 groups were well matched for baseline characteristics, except for complete revascularization (Table 1). The mean age was 64.0 years; 71.6% of the patients were men and 34.7% had diabetes mellitus. The index event was unstable angina in 93.8% of the patients and NSTE myocardial infarction in 6.2% of cases. Most of the patients received optimal medical therapy at discharge and follow-up, which was less frequently prescribed in the CABG group than in the PCI group (Table 2). The median follow-up duration was 60.0 months (interquartile range 49.8 to 61.2 months) for the CABG group and 60.0 months (interquartile range 51.1 to 61.2 months) for the PCI group, respectively.

During the follow-up, the primary outcome of death from any causes, myocardial infarction, or stroke occurred in 85 patients (13.4%) in the CABG group versus 110 patients (18.0%) in the PCI group (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.56 to 0.98; p = 0.036) (Figure 1, Table 3). This difference was mainly attributed to a significant reduction in the rate of myocardial infarction (Table 3). In addition, the incidence of primary outcome was significantly lower in the CABG group than the PCI group for patients with multivessel CAD (Figure 2) but not for those with left main CAD. Similar findings were observed according to the SYNTAX score.

The secondary outcome, death from any or cardiac causes, occurred similar in both groups during the follow-up (HR 0.81; 95% CI 0.57 to 1.16, p = 0.248, HR 0.86; 95% CI 0.56 to 1.32, p = 0.498, respectively) (Table 3, Figure 1). On the contrary, the incidence of myocardial infarction was significantly lower in the CABG group (HR 0.50; 95% CI 0.31 to 0.82, p = 0.006). Numerically, more patients had a stroke after CABG than after PCI; there was no statistical significance (HR 1.10; 95% CI 0.56 to 2.15, p = 0.788). Conversely, fewer repeat revascularizations were required with CABG than with PCI (HR 0.56; 95% CI 0.41 to 0.75, p <0.001).

In the subgroup analyses, there was no significant interaction between treatment effect and any of the subgroup variables other than gender (Figure 3). Although the

Table 3
Overall clinical outcomes by treatment group

	CABG (N=634)	PCI (N=612)	Hazard ratio (95%CI)	p-value
	no. (%)			
Primary outcome: death, MI, or stroke	85 (13.4%)	110 (18.0%)	0.74 (0.56-0.98)	0.036
Secondary outcomes				
Death from any causes	55 (8.7%)	66 (10.8%)	0.81 (0.57-1.16)	0.248
Death from cardiac causes	40 (6.3%)	45 (7.4%)	0.86 (0.56-1.32)	0.498
MI	24 (3.8%)	46 (7.5%)	0.50 (0.31-0.82)	0.006
Stroke	18 (2.8%)	16 (2.6%)	1.10 (0.56-2.15)	0.788
Repeat revascularization	67 (10.6%)	113 (18.5%)	0.56 (0.41-0.75)	<0.001
Death, or MI	73 (11.5%)	99 (16.2%)	0.71 (0.52-0.96)	0.024

The p-values were calculated with all available follow-up data.
CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention.

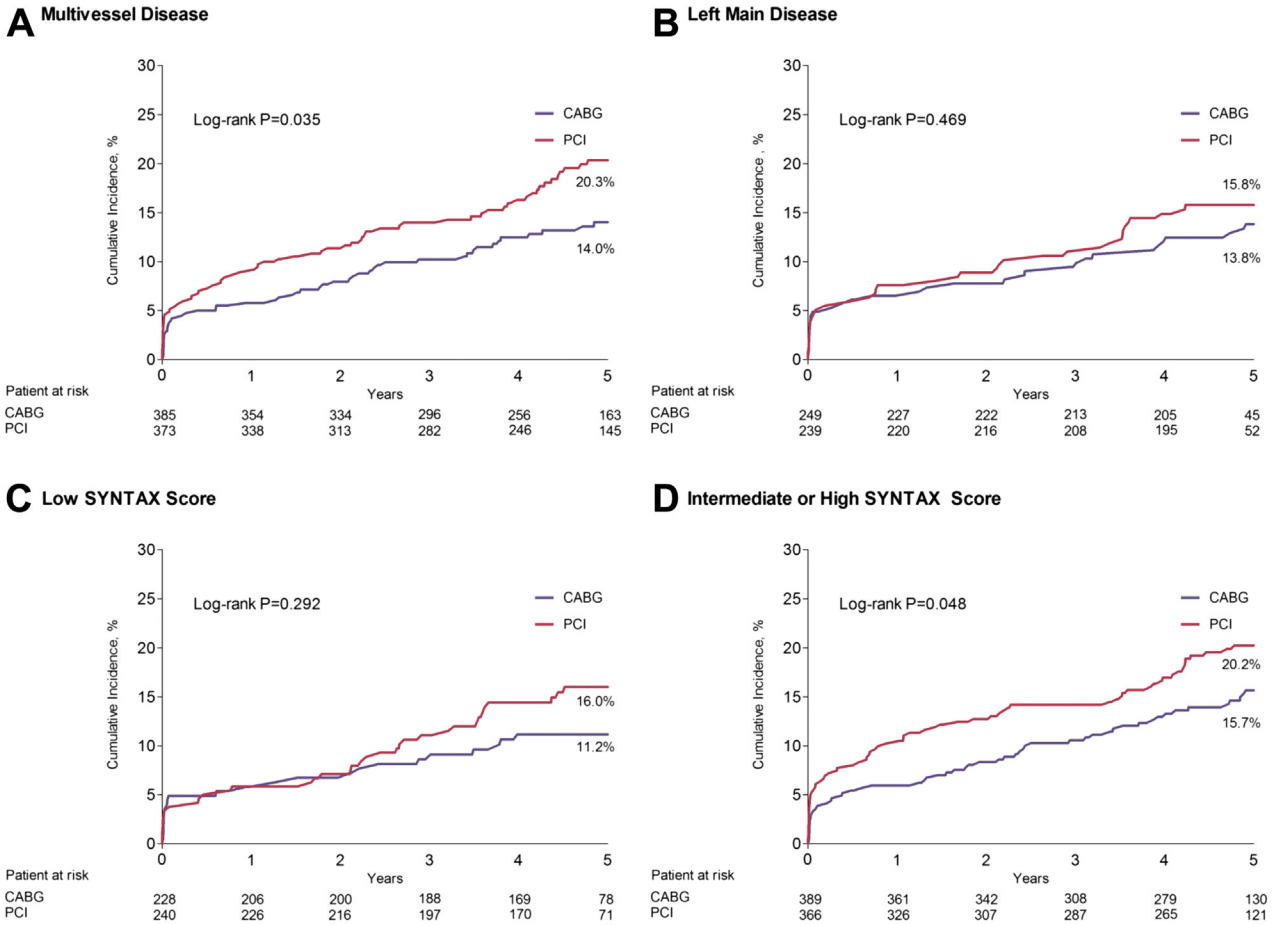

Figure 2. Primary outcome according to subgroup. The cumulative incidences of death from any causes, myocardial infarction, or stroke in patients with multivessel coronary artery disease *(A)*, left main coronary artery disease *(B)*, low SYNTAX scores *(C)*, and intermediate or high SYNTAX scores *(D)* are shown. The p values were calculated using the log-rank test with all available follow-up data. The percentages denote 5-year event rates.

interaction between treatment efficacy and clinical presentation of CAD was not significant for the primary outcome, the difference between CABG and PCI was statistically significant in patients with multivessel CAD but not in those with left main CAD. Those similar patterns were observed for involvement of proximal left anterior descending artery and scales of SYNTAX scores.

Discussion

Our current analysis has revealed that among patients with NSTE-ACS for left main or multivessel CAD, CABG significantly reduced the composite rate of death from any causes, myocardial infarction, or stroke compared with PCI with DES. This benefit was consistent across most major

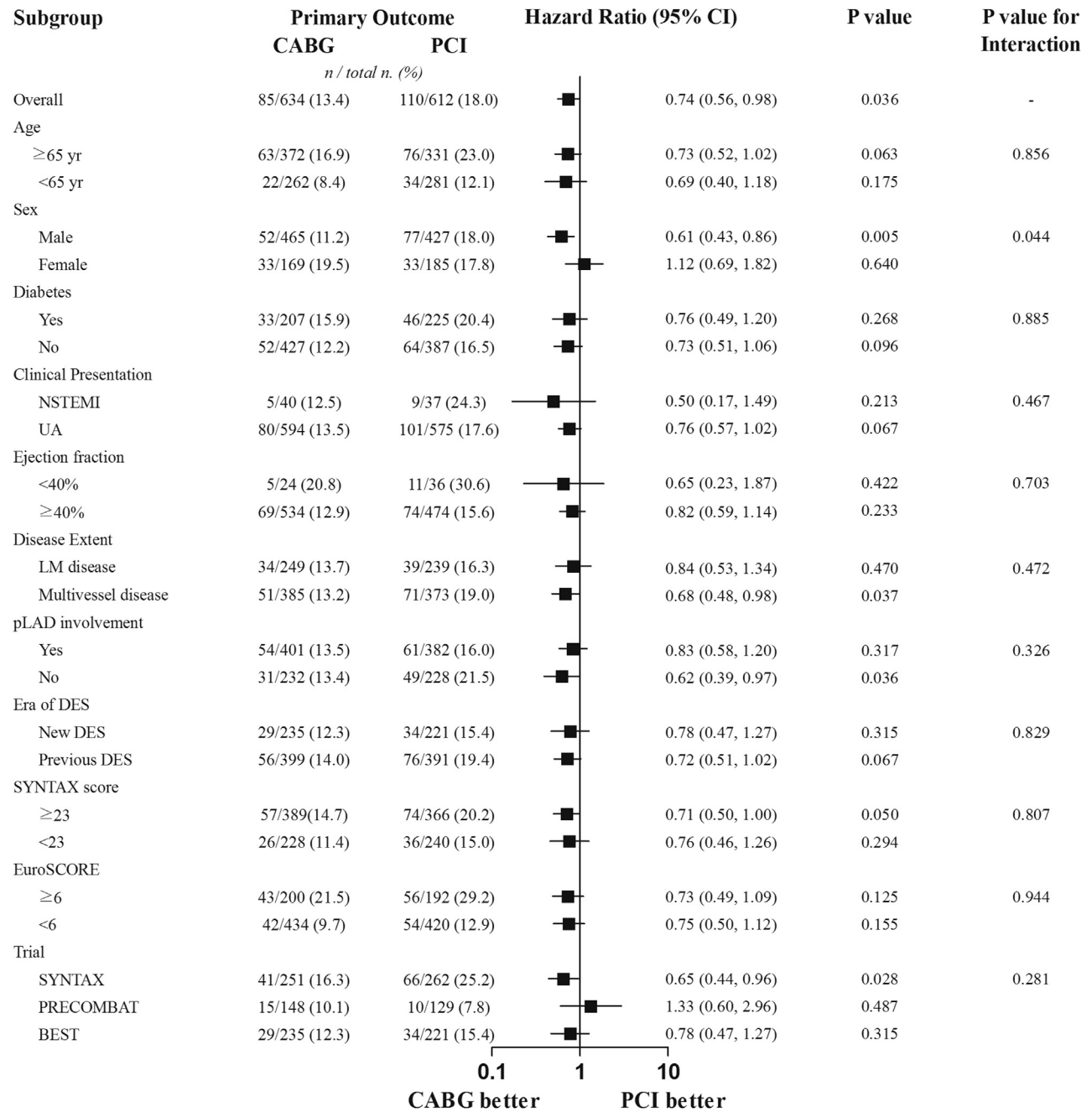

Figure 3. Forest plot of the treatment effect with respect to the primary outcome. Subgroup analyses were performed using Cox proportional hazards regression. NSTEMI = non−ST-elevation myocardial infarction; pLAD = proximal left anterior descending coronary artery; UA = unstable angina.

subgroups and was mainly driven by a reduction in myocardial infarction. However, no significant differences were found in the rates of death or stroke between both groups.

Patients with NSTE-ACS include heterogeneous populations with varying risks of cardiovascular events. In general, high-risk patients are referred for an early invasive strategy and low-risk patients are considered for a conservative strategy. Initial trials found no differences between the 2 approaches in terms of clinical outcomes, but subsequent studies have shown that the early invasive strategy reduces cardiovascular events in high-risk patients compared with a conservative management approach.[12−15] Ad hoc PCI of the culprit vessel responsible for NSTE-ACS is regarded as an appropriate treatment for most patients with single-vessel CAD, particularly those with high-risk features.[16,17] Among patients with NSTE-ACS, however, a substantial proportion (∼50%) has a left main or multivessel CAD.[18−21] In real-world practice, these patients are frequently treated with ad hoc or staged PCI because of the difficulties in balancing ischemic and bleeding risks. PCI may offer the advantages of a faster revascularization, a lower risk of stroke and early discharge; CABG allows a complete revascularization, and therefore,

less need for a repeat revascularization. Thus, whether to perform CABG or PCI in stabilized patients with NSTE-ACS needs to be discussed within the heart team.

There have been no specific randomized trials comparing CABG to PCI with DES in patients with NSTE-ACS. In patients with unstable angina, the Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Multi-Vessel Disease (ERACI) II trial reported that all-cause mortality and myocardial infarction were higher in patients who underwent CABG, but repeat revascularization was higher in those who underwent PCI.[1] A post hoc analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial showed that after propensity score matching, there were no differences in mortality among 1,056 patients at 1 year (4.4% for CABG vs 5.7% for PCI; $p = 0.58$). In addition, the risk of stroke was reported to be higher among patients with CABG compared with those with PCI; otherwise, unplanned revascularization was lower among those with CABG.[2] Those 2 trials were limited by the use of bare-metal stents or nonrandomized patient selection.

In our present study, CABG was superior to PCI with DES in patients with NSTE-ACS with left main or multivessel CAD regarding the composite outcome of death from any causes, myocardial infarction, or stroke. These results suggest that the benefit of CABG over PCI with DES is not different for patients with NSTE-ACS compared with stable patients with CAD. Interestingly, in subgroup analysis, the advantage of CABG over PCI with DES was more prominent in men than in women, suggesting a gender difference in the therapeutic benefit of revascularization. Although this finding may well be subject to chance, women who underwent CABG do seem to have poorer outcomes than men.[22] In addition, we found a more striking benefit of CABG in patients with multivessel CAD, although the interaction p value between treatment effect and the extent of CAD was not significant. As our study presented that the difference between CABG and PCI was greater in patients with intermediate or high SYNTAX scores, the SYNTAX scores may be a helpful guide even for patients with NSTE-ACS.

Although our present study did not have the power to detect small differences in mortality, the incidence of myocardial infarction was remarkably lower after CABG than after PCI with DES, and the difference between these 2 groups continued to diverge over time. The advantage of CABG over PCI in reducing myocardial infarction has been a consistent finding in most studies to date, regardless of the stent types, supporting the hypothesis that CABG may bypass the vulnerable arterial segments and decrease the risk of future myocardial infarction.[23] Stroke remains the major concern for physicians when dealing with CABG because of its critical impact on quality of life. Most stroke episodes occur early after CABG, whereas the incidence of late stroke (>30 days) is generally similar to that of PCI. In our present analysis, the rate of stroke was numerically but not statistically higher after CABG than after PCI with DES. Currently, off-pump CABG is performed increasingly, which may contribute to lessen perioperative complications, especially stroke.[24] Repeat revascularization was required less frequently after CABG than after PCI with DES in our study subjects, which has been a universal finding across studies comparing CABG with PCI. Therefore, a gap between these 2 strategies still exists, and an excess of repeat revascularizations remains the major limitation of PCI even in the DES era. Taken together, the results of our present study demonstrate that in stabilized patients with NSTE-ACS for left main or multivessel CAD, CABG is better than PCI with DES for reducing the risk of death from any causes, myocardial infarction, or stroke.

Several limitations of this study are noteworthy. First, this was a substudy of individual patient-level data from 3 randomized trials. Based on each trials' inclusion criteria, limited number of patients with NSTE-myocardial infarction are analyzed in this study; thus, it may have limited application for the real world. Second, the timing of CABG could not be specified in our present study. Our findings were derived from stabilized patients with NSTE-ACS and may not be fully applicable to emergent patients with NSTE-ACS. Third, although there was no interaction between previous and newer generation DES, each trial used different generations of DES. Fourth, the rate of complete revascularization was significantly higher in CABG group, which may strengthen the benefit of CABG. Finally, standard medications were less frequently used in the CABG group compared with the PCI group; therefore, the patients in our CABG group may have been disadvantaged regarding protection against cardiovascular events.

Disclosures

All other authors declare that they have no conflict of interest with this study.

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