Outcomes of Coronary Artery Bypass Graft Surgery Versus Drug-Eluting Stents in Older Adults

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OBJECTIVES: Little data are available to compare coronary artery bypass graft surgery (CABG) vs percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in older adults. We evaluate the long-term outcomes of CABG vs PCI with DES in older adults with left main or multivessel coronary artery disease (CAD).

DESIGN: Individual patient-level meta-analysis.

SETTINGS: Databases from the BEST, PRECOMBAT, and SYNTAX trials were combined.

PARTICIPANTS: A total 1,079 adults aged 70 to 89 years were pooled.

MEASUREMENTS: The primary outcome was a composite of death from any causes, myocardial infarction, stroke, or repeat revascularization.

RESULTS: During a total of 6.3 (median, 4.9) years of follow-up, the primary composite outcome of all-cause mortality, myocardial infarction, stroke, or repeat revascularization occurred in 26% (141/550) and 34% (179/529) of patients in the CABG and PCI groups, respectively (hazard ratio (HR), 0.75; 95% confidence interval (CI), 0.60–0.94; $P = .012$). CABG was associated with fewer myocardial infarction (4% vs 8% for PCI; HR, 0.48; 95% CI, 0.29–0.80; $P = .037$); and repeat revascularizations (8% vs 17% for PCI; HR, 044; 95% CI, 0.31–0.64; $P < .001$), but had little association with all-cause mortality or stroke.

CONCLUSION: Older adults age 70 to 89 years with left main or multivessel CAD who participated in the BEST, PRECOMBAT, and SYNTAX trials; compared to PCI, CABG was associated with lower risk of primary outcome which was mostly driven by lower risk of myocardial infarction. **J Am Geriatr Soc 65:625–630, 2017.**

Key words: coronary artery bypass graft surgery; drug-eluting stents; older; left main coronary artery disease; multivessel coronary artery disease

Coronary artery disease (CAD) progresses with advancing age, which leads to an increasing number of older adults with significant CAD. In current clinical practice, older adults often have left main or multivessel CAD that represent a large group of the patient population requiring revascularization.[1,2] These older adults are at higher risk of cardiovascular events after either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) because of comorbid conditions and reduced functional capacity. Over the past decade, both CABG and PCI technologies have continuously advanced with improved patient outcomes. At present, however, little data are available to compare CABG vs PCI with drug-eluting stents (DES) in older adults with left main or multivessel CAD.[3–5] Thus, the appropriate revascularization strategy in these patients remains uncertain.

We investigated the long-term outcomes of CABG vs PCI with DES in older adults with left main or multivessel CAD using a large pooled database from the BEST, PRECOMBAT, and SYNTAX trials.

METHODS

Study Patients

Below is a brief description of three trials.[6–10] All of the trials were multicenter: SYNTAX recruited 1,800 patients (mean age, 65 ± 10 years) with 3-vessel or left main CAD from Europe and the United States.[6,8] This study revealed

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that CABG was superior to PCI with paclitaxel-eluting stents for the rate of major adverse cardio-cerebral event (MACCE) during 5-year of follow-up. PRECOMBAT trial enrolled 600 patients (mean age, 62 ± 10 years) with left main CAD from Korea, and presented non-inferior MACCE outcomes in PCI with sirolimus-eluting stents compared to CABG during 2-year follow-up.[7] BEST recruited 880 patients (mean age, 64 ± 9 years) with 2- or 3-vessel CAD from Asia, and showed that CABG reduced major adverse cardiac events than PCI with everolimus-eluting stents at 2-year follow-up.[9] In all of these trials, patients who were eligible for both PCI and CABG were randomly assigned to receive either strategy. Among these patients, we identified 1,079 adults (32.9% of total cohort) with age 70 to 89 years,[3] comprising the study population.

Data Collection

The principal investigators for each trial (SJP and PWS) created a protocol with pre-specified outcomes and a common set of baseline variables. The coordinating institution (Asan Medical Center, Seoul, Korea) gathered individual patient data from each trial to be merged. The investigators from Asan Medical Center checked the pooled database for completeness and consistency.

The merged database included demographics (age, sex, body weight, and height), clinical history (chronic kidney disease, previous myocardial infarction, previous stroke, peripheral artery disease, and previous PCI), risk factors (diabetes, hypercholesterolemia, hypertension, and smoking), angiographic and echocardiographic findings (number of diseased vessels, left main CAD, proximal left anterior descending CAD, SYNTAX score, and left ventricular dysfunction), revascularization strategies, medication history (aspirin, $P2Y_{12}$ inhibitors, antihypertensive drugs, and statins), and clinical outcomes during follow-up (all-causes of death, cardiac death, myocardial infarction, stroke, and repeat revascularization). To quantify and evaluated the effect of the anatomical complexity of CAD in older adults, we adopted SYNTAX score which has been widely used to predict the outcome after revascularization. SYNTAX score is an angiographic grading tool to define the complexity of CAD and is categorized as low (<23), intermediate (23–32), and high (≥33) which was also validated by clinical outcomes.[6]

Completeness of revascularization was defined as the treatment of any lesions with more than 50% diameter stenosis in vessels ≥1.5 mm in SYNTAX trial,[6] ≥2.0 mm in BEST trial,[9] and ≥2.5 mm in PRECOMBAT trial[7] as estimated on the diagnostic angiography. Except the definition of complete revascularization, other definitions of variables were same.

Definitions and Outcome Measures

The primary outcome was the composite of MACCE including death from any causes, myocardial infarction, stroke, or repeat revascularization. Secondary outcomes included death from any causes, myocardial infarction, stroke, and any coronary revascularization. We used previously reported definitions from each study for individual clinical outcomes.[6,7,9]

Statistical Analysis

For the analysis, we used one–stage approach with random-effect meta-analysis and performed a likelihood-ratio test to assess the homogeneity of the data.[11] Data were analyzed according to the intention to treat principle. Databases were merged from the three trials, and time-to-event outcomes were analyzed using Kaplan–Meier methodology. The impact of the revascularization strategy on clinical outcomes was analyzed using the stratified Cox proportional hazards model. All reported *P*-values were two-sided; *P*-values <.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 18.0, SPSS Inc.).

RESULTS

Baseline Characteristics

The study population included 1,079 adults with left main or multivessel CAD, who were treated with either CABG (n = 550) or PCI with DES (n = 529). Baseline characteristics were well matched between the two groups (Table 1). The mean age was 74.7 years (minimum 70 to maximum 89), 65.8% of the patients were men, and 31.7% had diabetes mellitus. Left main CAD was present in 411 patients (38.1%), and multivessel CAD in 668 patients (61.9%).

Table 1. Baseline Patient Characteristics

	CABG (N = 550)	PCI (N = 529)	*P*-Value
Age (years)	74.7 ± 3.7	74.8 ± 3.7	0.684
Male sex	367 (66.7)	343 (64.8)	0.513
Body mass index	26.0 ± 4.0	25.7 ± 3.9	0.257
Current smoker	54 (9.9)	50 (9.5)	0.800
Diabetes	187 (34.0)	155 (29.3)	0.097
Requiring insulin	44 (8.0)	32 (6.0)	0.211
Hypercholesterolemia	326 (59.4)	310 (58.8)	0.853
Hypertension	370 (67.3)	381 (72.0)	0.090
Clinical presentation			
Stable angina	315 (57.3)	328 (62.0)	0.113
ACS	235 (42.7)	201 (38.0)	
Previous myocardial infarction	119 (21.8)	109 (20.8)	0.668
Previous stroke	32 (6.8)	24 (5.2)	0.308
Peripheral artery disease	52 (9.5)	46 (8.7)	0.665
CKD (Cr <200 μmol/L)	12 (2.2)	7 (1.3)	0.284
Left ventricular dysfunction[a]	26 (5.9)	19 (4.9)	0.550
Diseased vessels			
Proximal LAD disease	348 (64.0)	314 (59.6)	0.139
Left main disease	212 (38.6)	199 (37.6)	0.754
Multivessel disease	338 (61.4)	330 (62.4)	0.754
SYNTAX score	29.2 ± 10.8	28.1 ± 10.8	0.079
EuroSCORE[b]	5.5 ± 2.1	5.4 ± 2.0	0.202

[a] Left ventricular dysfunction defined as left ventricular ejection fraction <40% or moderate to severe left ventricular dysfunction.

[b] 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 based on the number of non-missing values.

CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction; LAD = left anterior descending coronary artery; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

The median follow-up duration was 4.9 years (interquartile range: 3.8–5.0 years). Most of the patients were well treated with optimal medical therapy at discharge and follow-up, but it was less used after CABG than after PCI (data not shown).

Primary Outcome

The primary outcome occurred in 141 (25.6%) patients in the CABG group and 179 (33.8%) patients in the PCI group (hazard ratio (HR), 0.75; 95% confidence interval (CI), 0.60–0.94; $P = .012$) (Table 2). In patients with low SYNTAX scores (<23), the rate of primary outcome tended to be higher with CABG than with PCI (HR, 1.19; 95% CI, 0.78–1.83; $P = .418$; Figure 1B). Conversely, in those individuals with intermediate SYNTAX scores (23–32), it tended to be lower with CABG than with PCI (HR, 0.76; 95% CI, 0.53–1.09; $P = .137$; Figure 1C). For patients with high SYNTAX scores (≥33), however, the rate of primary outcome was significantly lower with CABG than with PCI (HR, 0.49; 95% CI, 0.34–0.72; $P < .001$; Figure 1D). By multivariate analysis, revascularization strategy (CABG vs PCI with DES), peripheral artery disease, completeness of revascularization, SYNTAX scores, and EuroSCORE were independent predictors of primary outcome (Table S1).

Secondary Outcomes

Death from any causes occurred in 77 (14.0%) patients in the CABG group and 95 (18.0%) patients in the PCI group (HR, 0.80; 95% CI, 0.60–1.09; $P = .153$) (Figure S1A, Table 2). A similar trend was observed regarding death from cardiac causes (Table 2). The rate of myocardial infarction was significantly lower in the CABG group compared with the PCI group (HR, 0.48; 95% CI, 0.29–0.80; $P = .037$) (Figure S1B). Likewise, the composite outcome of death from any causes or myocardial infarction significantly favored CABG over PCI (Table 2). There were numerically more strokes among CABG patients than among PCI patients (HR, 1.49; 95% CI, 0.76–2.92; $P = .252$) (Figure S1C). Conversely, the need for repeat revascularization was remarkably less common in the CABG group than in the PCI group (HR, 044; 95% CI, 0.31–0.64; $P < .001$) (Figure S1D).

Subgroup Analysis

There was no significant interaction between treatment effects and major clinical subgroups regarding the primary outcome except SYNTAX scores (Figure S2). We also found no significant interaction for the primary outcome of the 3 trials ($P = .361$ for interaction). However, a significant interaction was observed between treatment effects and the primary outcome according to the SYNTAX scores ($P = .008$ for interaction).

DISCUSSION

In this pooled patient-level analysis, we found that adults in their age 70 to 89 with left main or multivessel CAD had lower rates of MACCE in the CABG group than in the PCI group. The advantage of CABG was particularly pronounced in patients with high SYNTAX scores, but not in those with low-to-intermediate SYNTAX scores. In addition, the two groups had similar rates of death from any causes and stroke. Although CABG did not show mortality benefit over PCI, CABG had better outcomes in a composite of death or myocardial infarction.

In contemporary clinical practice, a large proportion of patients requiring revascularization is older adults in accordance to their increased longevity.[1,2] Until now, there are no specific randomized trials comparing CABG versus PCI with DES in older adults with left main or multivessel CAD. In the New York State's clinical registry, a total of 1,932 older adults (≥75 years) with multivessel CAD receiving CABG and DES were compared and mean follow-up duration was 18 months.[4] The rates of death from any causes, myocardial infarction, or stroke were similar for the two groups, but the rates of repeat revascularization were significantly higher for patients who underwent DES. Similarly, in our present analysis, CABG compared to PCI with DES significantly decreased the rate of MACCE. Also, a significant interaction was observed between treatment effects and SYNTAX scores. MACCE did not differ between CABG and PCI with DES in patients with low or intermediate SYNTAX scores. In contrast, the rate of MACCE was significantly lower with CABG than with PCI with DES in those with high SYNTAX scores. These findings suggest that PCI with DES

Table 2. Clinical Outcomes

	CABG (N = 550)	PCI (N = 529)		
	No. (%)		Hazard Ratio (95% CI)	*P*-Value
Primary outcome: death, MI, stroke, or RR	141 (25.6)	179 (33.8)	0.75 (0.60–0.94)	0.012
Secondary outcomes				
Death from any causes	77 (14.0)	95 (18.0)	0.80 (0.60–1.09)	0.153
Death from cardiac causes	38 (6.9)	58 (11.0)	0.65 (0.43–0.98)	0.037
MI	22 (4.0)	44 (8.3)	0.48 (0.29–0.80)	0.005
Stroke	21 (3.8)	14 (2.6)	1.49 (0.76–2.92)	0.252
Repeat revascularization	43 (7.8)	91 (17.2)	0.44 (0.31–0.64)	<0.001
Death or MI	92 (16.7)	120 (22.7)	0.75 (0.57–0.98)	0.036

The *P* values were calculated with all available follow-up data.

CABG = coronary artery bypass graft surgery; CI = confidence interval; MI = myocardial infarction; RR = repeat revascularization; PCI = percutaneous coronary intervention.

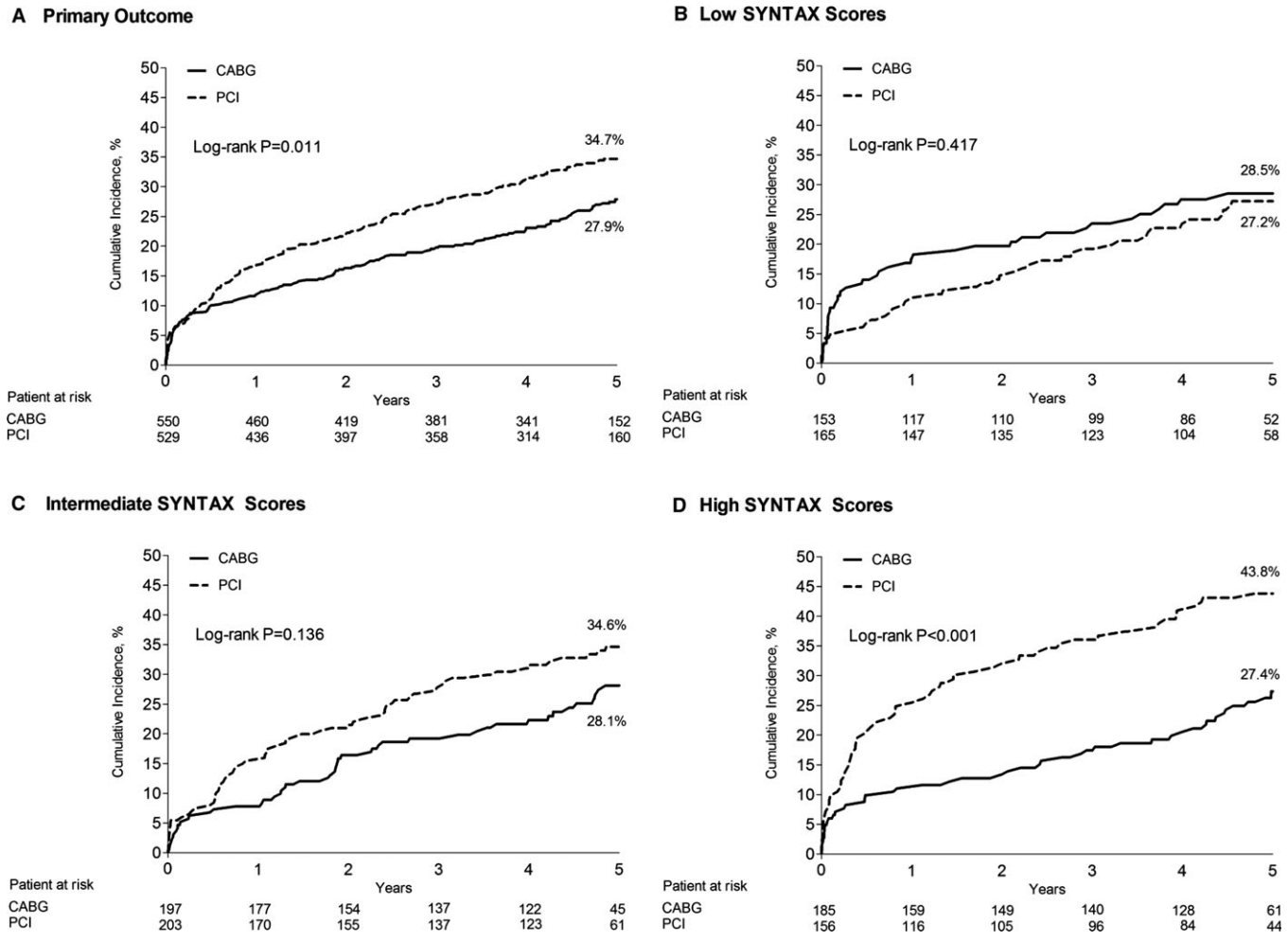

Figure 1. The primary outcome for overall patients and SYNTAX subgroups. The cumulative incidence of a composite of death, myocardial infarction, stroke, or repeat revascularization in overall patients: (A) in low SYNTAX scores, (B) in intermediate SYNTAX scores, and (C) high SYNTAX scores (D) are shown. *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 surgery; PCI = percutaneous coronary intervention.

might be a valid option for older adults with anatomically less complex left main or multivessel CAD. These data also support that, even for patients aged 70 to 89 years old who have left main or multivessel CAD and high anatomical risk scores (SYNTAX scores ≥33), CABG may be an optimal treatment.

In most observation studies, the survival difference between CABG and PCI favored CABG.[5,12,13] In the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry that included >6,000 patients older than 70 years,[12] the survival rate in those aged 70 to 79 years was 87.3% and 83.9%, respectively ($P < .010$); for patients older than 80 years 77.4% and 71.6%, respectively ($P < .010$). Furthermore, a greater absolute risk reductions associated with revascularization was observed in older patients than in younger patients, suggesting that revascularization therapies might be beneficial for certain subsets of patients in older age groups. A large meta-analysis of 66 trials[13] revealed that in patients with 80 to 89 years, there was a trend to a higher 30-day mortality after CABG than after PCI and comparable 1-year and 3-year mortality between the two groups. At 5 years, there was a trend towards improved survival in the CABG group compared with the PCI group. However, many of these trials were outdated with little use of stents.

In the ACCF and STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) trial,[5] 86,244 CABG patients and 103,549 PCI consecutive patients who were ≥65 years and stable multivessel CAD were compared. Mortality at 1 year was the same in both groups. At 4 years, the adjusted hazard ratio for all-cause mortality was significantly lower in the CABG group compared with the PCI group (relative risk 0.78; 95% CI 0.74–0.82). The survival benefit of CABG increased over time, showing the long-term advantage of CABG over PCI with DES. In addition, a similar difference was observed regardless of age, gender, diabetes status, and left ventricular ejection fraction. As with all observational studies, however, unmeasured confounders may bias the results, and these findings might be considered exploratory until confirmed in randomized trials. In our patient-level meta-analysis, death from any causes was similar between CABG and PCI, but our study was not large

enough to compare a minor difference of all-cause mortality.

Myocardial infarction is a common cause of morbidity and mortality in older adults with advanced CAD. In our study, the incidence of myocardial infarction was significantly lower in CABG patients than in PCI patients, supporting the idea that CABG offers more durable protection against myocardial infarction in patients with severe CAD.[14,15] PCI with DES treats the focal area of tight stenosis and often results in incomplete revascularization in patients with complex CAD.[14] In contrast, CABG is related to a complete revascularization, and may provide greater protection of the myocardium below the vulnerable areas because the grafts are connected to their branches. In our study, incomplete revascularization was also independently related to recurrent cardiovascular events, highlighting the importance of achieving complete revascularization.

Older adults are considered to have more perioperative strokes after CABG than after PCI, which remains a major concern in those undergoing CABG.[16] In recent years, however, the risk of strokes after CABG has significantly decreased with improvements in perioperative management and procedural techniques.[17,18] In the Coronary Revascularization Demonstrating Outcomes Study-Kyoto (CREDO-Kyoto) registry, there was no difference in the stroke incidence between off-pump CABG and PCI.[19] The rate of stroke was numerically higher in our study, but not statistically different after CABG than after PCI with DES. More refined operative techniques including minimally invasive CABG may further reduce the risk of perioperative stroke, enhancing the safety of CABG in older adults.[20]

There are a growing number of older adults requiring coronary revascularization across the world. In real-world clinical practice, however, older adults more frequently choose PCI over CABG because of concerns about postoperative morbidities and mortality.[21] If physical performance is acceptable, CABG might be a better option for older adults with severe left main or multivessel CAD. However, large randomized trials in specific older populations might be needed to help appropriately guiding the management.

Several limitations of this study need to be addressed. First, this was a subgroup analysis of three randomized clinical trials for patients with left main or multivessel CAD. Despite a well-founded statistical method, this cannot exclude the idea that the BEST trial mainly affects the results of this study. Second, optimal medical therapy was less frequently used after CABG than after PCI, which may be disadvantaged to CABG patients in terms of protection against cardiovascular events. Finally, our analysis addressed primarily age and coronary anatomical factors as risk factors and predictors of outcome. We acknowledge that there are many other variables that can potentially impact patient selection and outcomes, including frailty, cognitive dysfunction, and multiple comorbidities. In addition, participants who enroll in trials can differ in meaningful ways from average community patients.

In conclusion, CABG compared to PCI with DES may reduce the risk of MACCE in older adults (≥70) with left main or multivessel CAD.

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Author Contributions: Dr. SJP, CWL, MC and PWS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JMA, RC, YS, and YO: acquisition, analysis of data. CWL, MC, and SJP: interpretation of data and drafting of the manuscript. All authors: critical revision of the manuscript for important intellectual content.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Predictors of the Primary Outcome by Cox Regression Analyses

Figure S1. Secondary outcomes for overall patients. The cumulative incidence of death (A) myocardial infarction, (B) stroke, and (C) repeat revascularization (D) are shown. *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 surgery; PCI = percutaneous coronary intervention.

Figure S2. Forest plot of subgroup analysis for the primary outcome. Subgroup analyses were performed using Cox proportional-hazards regression. DES = drug-eluting stents; ACS = acute coronary syndrome; pLAD = proximal left anterior descending coronary artery.