Impact of Multivessel Coronary Artery Disease With Versus Without Left Main Coronary Artery Disease on Long-Term Mortality After Coronary Bypass Grafting Versus Drug-Eluting Stent Implantation

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Limited data are available on the impact of concomitant left main coronary artery disease (CAD) on mortality after revascularization of multivessel coronary artery disease (MVD) alone or multivessel plus left main coronary artery disease (MVLMD). This study compared long-term mortality between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents in 2,887 patients with MVD or MVLMD. Data were pooled from the BEST, PRECOMBAT, and SYNTAX trials. The primary outcome was death due to any cause. Of the 2,887 patients, 1,975 (68.4%) were classified as having MVD and 912 (31.6%) as having MVLMD. The median follow-up duration was 60.2 months. In the patients with MVD, primary outcome rate after CABG was significantly lower than after PCI (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.49 to 0.89; p = 0.007). In the patients with MVLMD, however, CABG and PCI showed similar primary outcome rates (HR 0.98; 95% CI 0.67 to 1.43; p = 0.896). Among those who underwent CABG, primary outcome rate was lower in the patients with MVD than in those with MVLMD (HR 0.66; 95% CI 0.46 to 0.95; p = 0.024). Kaplan-Meier analysis showed a clear separation between the patients with MVD and those with MVLMD 2.5 years after the index surgery. The risk of death due to any cause was significantly lower after CABG than after PCI with drug-eluting stents in patients with MVD but not in those with MVLMD. The advantage of CABG over PCI for multivessel CAD was significantly attenuated if concomitant left main CAD was present. **(Am J Cardiol 2017;119:225−230)**

Multivessel coronary artery disease (MVD) is often accompanied by left main coronary artery disease (CAD); however, very limited data are available focusing on the impact of concomitant left main CAD after revascularization. In this study, we compared long-term mortality in patients with MVD with versus without left main CAD in patients who underwent coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

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Methods

The data in the present study were pooled from 3 multicenter trials: Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX), Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stents in Patients With Left Main Coronary Artery Disease (PRECOMBAT), and Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease (BEST).[1−5] The SYNTAX trial recruited patients from Europe and the United States, whereas the PRECOMBAT trial and the BEST trial recruited patients from Asia. The SYNTAX trial included 1,800 patients with three-vessel CAD (n = 1,095) or left main CAD (n = 705). The PRECOMBAT trial included 600 patients with left main CAD. The BEST trial included 880 patients with 2- or 3-vessel CAD. In all 3 trials, patients who were eligible for both PCI and CABG were randomized to receive either treatment. Among the patients included in these 3 trials, we

Table 1
Baseline characteristics of the study patients

Variables	CABG (n = 1,432)	PCI (n = 1,455)
Age (years)	64.8 ± 9.6	64.6 ± 9.6
Men	1,113 (77.7%)	1,093 (75.1%)
Body mass index (kg/m^2)	26.5 ± 4.1	26.5 ± 4.3
Current smoker	314 (22.0%)	300 (20.6%)
Diabetes mellitus	489 (34.1%)	494 (34.0%)
Hypercholesterolemia	906 (63.6%)	968 (66.2%)
Hypertension	912 (63.7%)	984 (67.6%)
Clinical presentation		
Stable angina pectoris	862 (60.2%)	8980 (61.2%)
Acute coronary syndrome	570 (39.8%)	565 (38.8%)
Previous myocardial infarction	324 (22.8%)	296 (20.5%)
Previous stroke	68 (5.6%)	69 (5.6%)
Peripheral vascular disease	107 (7.5%)	103 (7.1%)
Chronic kidney disease (serum Cr >200 μmol/L)	23 (1.6%)	17 (1.2%)
Left ventricular ejection fraction <40%	59 (4.1%)	55 (3.8%)
Extent of CAD		
Multivessel without left main	991 (69.2%)	984 (67.6%)
Multivessel with left main	441 (30.8%)	471 (32.4%)
EuroSCORE	3.4 ± 2.5	3.4 ± 2.4
SYNTAX score	28.3 ± 10.3	27.6 ± 10.1
Number of stents		4.3 ± 2.0
Total stented length (mm)		88.7 ± 43.2
Number of total grafts	2.9 ± 0.8	
Number of arterial grafts	1.7 ± 0.8	
Follow-up (years)	4.3 ± 1.4	4.4 ± 1.3

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

identified 2,887 with MVD alone or multivessel plus left main coronary disease (MVLMD); these formed our study population.

A protocol with prespecified outcomes and a common set of baseline variables were established by the principal investigators of the present study (SJP and PWS). Individual patient data from each trial were sent to the coordinating institution (Asan Medical Center, Seoul, Korea) to be pooled together. An independent clinical event committee, which was blinded to the randomization, adjudicated all end points in each study. The pooled database was checked for completeness and consistency by responsible investigators from the coordinating institution.

The pooled database included demographics, clinical history, risk factors, angiographic and echocardiographic findings, revascularization strategies, medication history, and clinical outcomes during follow-up. Unless specified otherwise, previously reported definitions from each study were used as variables. The primary outcome was death due to any cause. Secondary outcomes included death due to cardiac causes, myocardial infarction, stroke, and any coronary revascularization. Previously reported definitions from each study were used for individual clinical outcomes.[1–5] MVD was defined as 2- or 3-vessel CAD and MVLMD as 2- or 3-vessel CAD with concomitant left main CAD.

Data analysis occurred on an intention-to-treat basis. Data from the 3 trials were combined for an overall analysis. Then, time-to-event outcomes were depicted using Kaplan-Meier methodology and compared using the log-rank test. The stratified Cox proportional hazards model was used to analyze the impact of the revascularization strategy on clinical outcomes. All reported p values were 2 sided; p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, Illinois).

Results

Baseline patient characteristics were similar between the 2 groups (Table 1). The mean age was 64.7 years; 76.4% of the patients were men, and 34.0% had diabetes mellitus. Of the 2,887 patients, 1,975 (68.4%) were classified as having MVD and 912 (31.6%) as having MVLMD; 1,432 (49.6%) underwent CABG and 1,455 (50.4%) underwent PCI. The median follow-up duration was 60.2 months (interquartile range 51.7 to 61.3 months).

The primary outcome occurred in 120 patients (8.4%) in the CABG group compared with 162 patients (11.1%) in the PCI group (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.60 to 0.96; p = 0.023). The 30-day mortality rates after CABG were similar to those after PCI for both the patients with MVD (0.7% vs 1.2%, respectively, log-rank p = 0.241) and those with MVLMD (0.9% vs 2.1%, respectively, log-rank p = 0.133). During the follow-up, the mortality rates in the patients with MVD was significantly lower in those who underwent CABG compared with those who underwent PCI (HR, 0.66; 95% CI 0.49 to 0.89; p = 0.007; Figure 1, Table 2). In contrast, in the patients with MVLMD, the mortality rates were similar for CABG and PCI (HR 0.98; 95% CI 0.67 to 1.43; p = 0.896; Figure 1). Likewise, the rate of death due to cardiac causes in the patients with MVD was lower in those who underwent CABG, but this was not the case in those with MVLMD (Figure 1).

There were 46 cases (3.2%) of myocardial infarction in the CABG group and 104 (7.1%) in the PCI group (HR 0.45; 95% CI 0.32 to 0.64; p <0.001). With the patients with MVD, the rates of myocardial infarction were significantly lower after CABG than after PCI (Table 2). In contrast, the rate of myocardial infarction in patients with MVLMD was numerically lower after CABG than after PCI; however, the difference between the 2 groups was not statistically significant. There was a similar statistically insignificant difference in the rate of stroke, which was lower in those who underwent PCI in both the patient with MVD and those with MVLMD. However, CABG was superior to PCI with regard to repeat revascularization, irrespective of whether there was concomitant left main CAD (Table 2).

In those who underwent CABG, the primary outcome was lower in the patients with MVD than in those with MVLMD (HR 0.66; 95% CI 0.46 to 0.95; p = 0.024; Figure 2). A landmark analysis revealed a significant separation between the Kaplan-Meier curves for the patients with MVD and MVLMD 2.5 years after the index surgery (HR 0.48; 95% CI 0.29 to 0.81; p = 0.006; Figure 2). There were no differences in survival according to the number of bypass grafts performed to the patients with MVD (Figure 2); however, patients with MVLMD who received >4 bypass grafts were more likely to survive than those who received fewer than 4 (Figure 2).

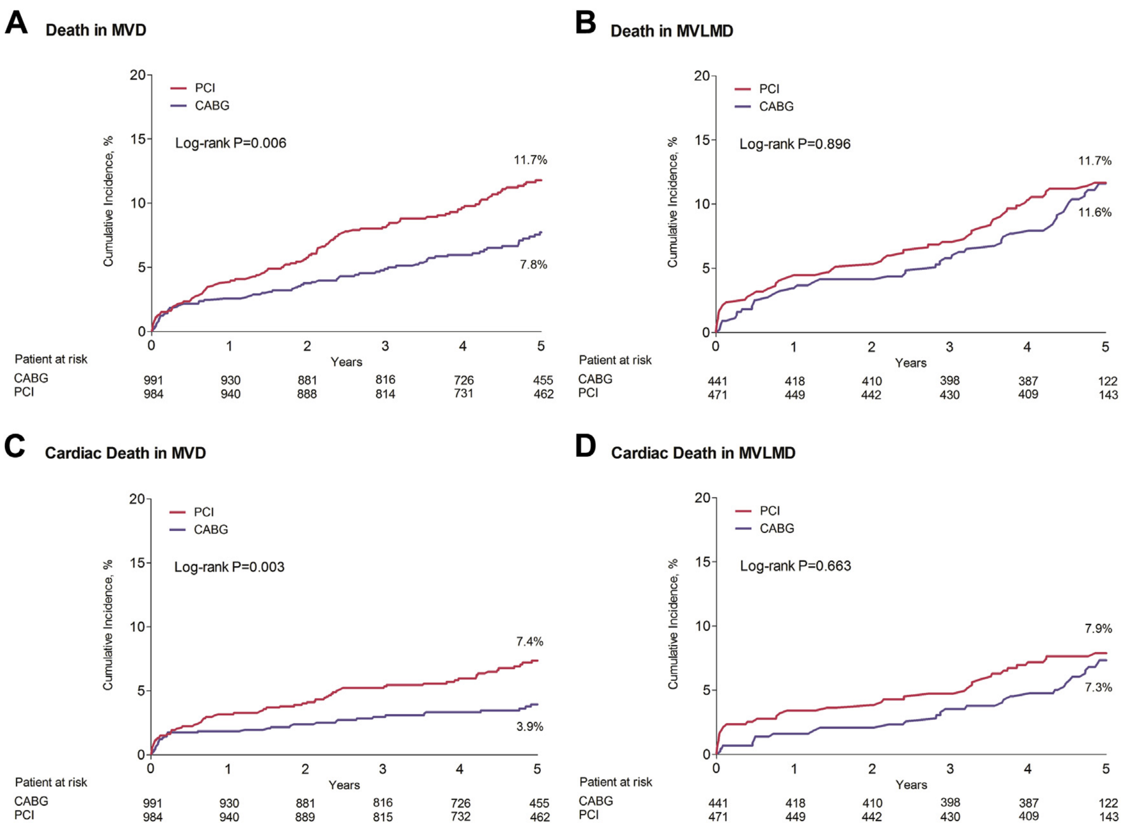

Figure 1. Death due to any cause according to patient subgroup. The cumulative incidences of death due to any cause *(A, B)* and death due to a cardiac cause *(C, D)* according to concomitant left main CAD are shown: (*A* and *C*) MVD and (*B* and *D*) MVLMD. The log-rank test was used to calculate p values using all the available follow-up data. Percentages denote 5-year event rates.

Discussion

Our analysis of the pooled patient-level data revealed that among the patients with MVD, there was significantly lower rate of long-term mortality in those who underwent CABG compared with those who underwent PCI. This was not the case for the patients with MVLMD. Similar patterns were observed in the rates of myocardial infarction and stroke. These findings suggest that concomitant left main CAD may attenuate the relative advantage of CABG over PCI in the management of multivessel CAD.

Percutaneous or surgical revascularization has been used for the treatment of MVD, but the optimal technique to perform revascularization remains controversial. Numerous trials comparing CABG with PCI have reported similar mortality rates between the 2 treatment techniques.[6] However, most trials were performed before the era of DES and were insufficiently powered to detect a small difference in the rate of death due to any cause. Traditionally, CABG has been preferred over PCI for diabetic patients with MVD, but this is largely based on the subgroup analysis of the bypass angioplasty revascularization investigation study, which showed 10-year survival rates of 57.8% for CABG and 45.5% for balloon angioplasty in diabetic patients with MVD ($p = 0.025$).[7] In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease and SYNTAX trials,[4,8] however, CABG significantly decreased long-term mortality in patients with MVD compared with PCI with DES. Similarly, our patient-level meta-analysis showed a lower mortality, with fewer myocardial infarctions, after CABG than after PCI with DES in patients with MVD. There was no significant interaction between this result and the status of diabetes (p-value for interaction = 0.93), demonstrating that CABG is superior to PCI with DES in all-cause mortality for both diabetic and nondiabetic patients with MVD. These findings agree with the ACCF and STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies study, which

Table 2
Clinical outcomes by treatment group

Variables	CABG (n = 1,432)	PCI (n = 1,455)	Hazard ratio (95%CI)	*P*-value
Death due to any cause				
MVD	70 (7.1%)	107 (10.9%)	0.66 (0.49−0.89)	0.007
MVLMD	50 (11.3%)	55 (11.7%)	0.98 (0.67−1.43)	0.896
Myocardial infarction				
MVD	29 (2.9%)	76 (7.7%)	0.38 (0.25−0.58)	<0.001
MVLMD	17 (3.9%)	28 (5.9%)	0.65 (0.35−1.18)	0.156
Stroke				
MVD	30 (3.0%)	26 (2.6%)	1.17 (0.69−1.97)	0.568
MVLMD	12 (2.7%)	5 (1.1%)	2.59 (0.91−7.36)	0.073
Repeat revascularization				
MVD	85 (8.6%)	180 (18.3%)	0.45 (0.35−0.58)	<0.001
MVLMD	50 (11.3%)	104 (22.1%)	0.49 (0.35−0.68)	<0.001

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

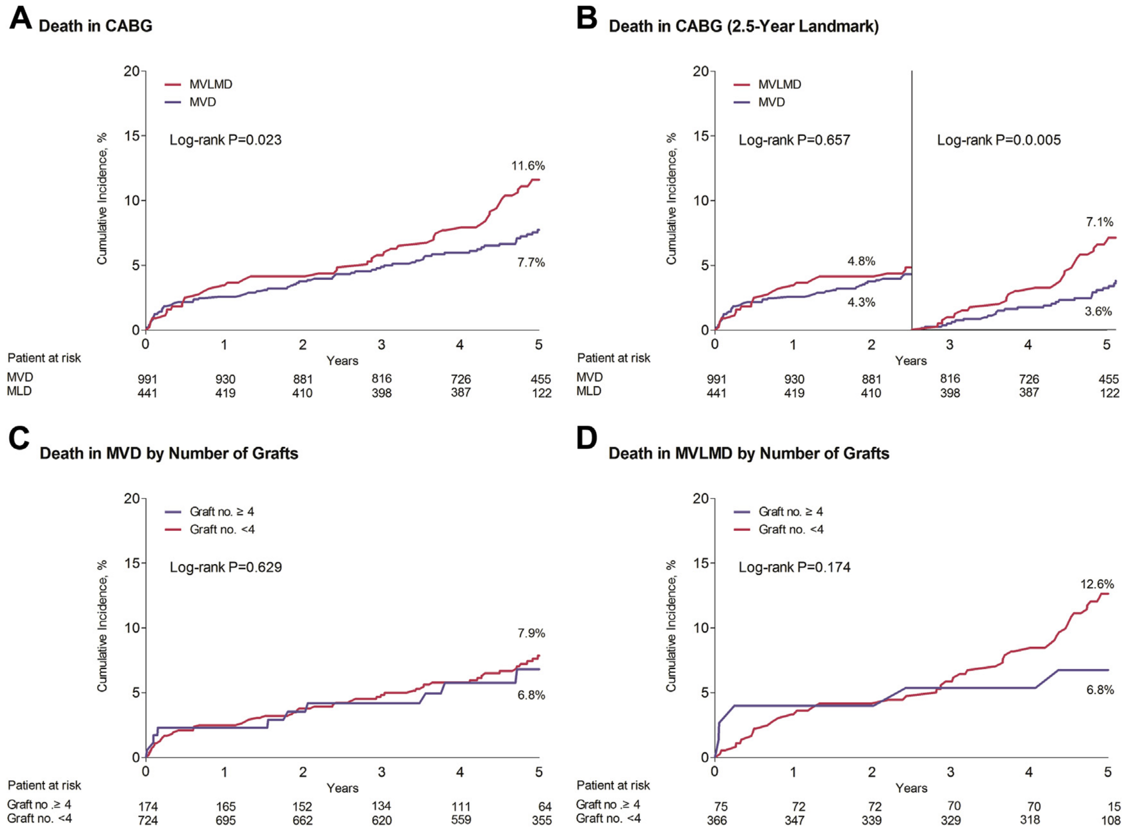

Figure 2. CABG subgroup and landmark analysis. Time-to-event curves in patients with CABG are shown: *(A)* all-cause mortality through 5 years; *(B)* all-cause mortality through 2.5 years and from 2.5 through 5 years (landmark analysis); *(C)* all-cause mortality in patients with MVD according to the number of grafts; *(D)* all-cause mortality in patients with MVLMD according to the number of grafts. The log-rank test was used to calculate p values using all the available follow-up data. Percentages denote 5-year event rates.

demonstrated that the survival advantage of CABG over PCI was observed regardless of age, gender, diabetes mellitus, and left ventricular ejection fraction.[9]

MVD is often associated with concomitant left main CAD, and CABG has been the treatment of choice for patients with this combination of conditions. The surgical mortality for left main CAD has been shown to range from 2% to 3%[10]; in contrast, the 30-day mortality in our study was 0.9%. There is limited data regarding long-term mortality after CABG for left main CAD. Sabik et al[11] reported that in 3,803 patients with CABG with left main CAD, the survival rate was 97.6% at 30 days, 93.6% at 1 year, and 83% at 5 years. In the present analysis, the 5-year survival rate after CABG was 89.2% in the patients with MVLMD and 92.3% in those with MVD. There was a trend toward better survival in patients with MVLMD who received >4 grafts than in those who received fewer grafts. In addition, a landmark analysis revealed that the survival curves for patients with MVD and patients diverge 2.5 years after an index surgery. In a comparison study of CABG for left main versus other lesions, left main CAD was found to be a predictor of surgical and follow-up mortality (odds ratio, 2.05; 95% CI 1.29 to 3.25; $p = 0.002$).[12] These findings suggest that concomitant left main CAD may increase the risk of long-term mortality after CABG for multivessel CAD. Although the underlying mechanisms for this remain unclear, there are several potential explanations.

Myocardial ischemia is an important determinant of adverse clinical events, and revascularization is known to improve the patient's prognosis.[13,14] However, residual ischemia after revascularization is not uncommon[15] and also increases the risk of cardiovascular events after either CABG or PCI.[16,17] PCI restores antegrade blood flow to the whole distribution of a major epicardial artery, whereas bypass grafts may allow antegrade blood flow to the distal territory, leaving areas proximal to the anastomosis site to be relatively ischemic.[18,19] Atherosclerotic plaque progression is up to 10 times more frequent in bypassed arteries than in comparable arteries without bypass because low and oscillating shear stress leads to endothelial dysfunction and accelerates atherosclerosis.[20–22] The proximal portion of the left anterior descending coronary artery is often buried under epicardial fat, requiring its tedious dissection for graft anastomosis. Therefore, in real-world practice, the graft on the left anterior descending coronary artery is usually placed in the distal part of its course, where the surgeons are easily accessible. However, the proximal portion of the myocardium is retrogradely perfused in a nonphysiological manner and can be more vulnerable to ischemia during stress conditions. Furthermore, the complete occlusion of a native coronary vessel is also common with a proximal stenosis >90% on the preoperative angiogram.[20–22] Therefore, left main CAD with tight stenosis is more likely to progress to total occlusion after CABG, rendering graft failure more catastrophic because of a large ischemic burden. This also limits future revascularization options because of the lower PCI success rate.[23] In this situation, placing the graft as proximally as possible on the left anterior descending coronary artery may be optimal to minimize the area at risk of residual ischemia. In addition, as our study suggests, multiple bypass grafts may decrease the ischemic island proximal to the graft anastomosis site after occlusion of the left main coronary artery. Despite our findings, however, additional studies are needed to further investigate the best site for graft anastomosis to the left anterior descending coronary artery, the optimal number of bypass grafts, or a hybrid approach to achieve functionally durable complete revascularization of MVLMD.

Several limitations of this study need to be considered and addressed in future studies. First, this was a post hoc analysis evaluating the long-term mortality after CABG, comparing patients with MVD and those with MVLMD. Therefore, our findings should be interpreted with caution, requiring confirmation by ongoing randomized clinical trials (such as the currently ongoing trials Evaluation of XIENCE PRIME™ or XIENCE V® Everolimus Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization [EXCEL] [NCT01205776] and Nordic-Baltic-British Left Main Revascularization Study [NOBLE] [NCT01496651]). Second, previous DESs were used in both the PRECOMBAT and SYNTAX trials. There may be room for further improvements from newer generation DES in patients with PCI. However, our study focused on outcomes in patients who received CABG through contemporary surgical technique.

Disclosures

All authors have no commercial relationships relevant to the contents of this report to disclose.

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