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Catheterization and Cardiovascular Interventions 90:177–185 (2017)

CORONARY ARTERY DISEASE

Original Studies

Predictors of Long-Term Outcomes after Bypass Grafting Versus Drug-Eluting Stent Implantation for Left Main or Multivessel Coronary Artery Disease

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Background: We assessed predictors of long-term outcomes after coronary artery bypass grafting (CABG) versus those after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in 3,230 patients with left main or multivessel coronary artery disease (CAD). Methods and Results: Data were pooled from the BEST, PRECOMBAT, and SYNTAX trials. Age, chronic kidney disease, chronic obstructive lung disease, left ventricular dysfunction, and peripheral arterial disease (PAD) were common predictors of all-cause mortality. Diabetes mellitus, previous myocardial infarction (MI), and SYNTAX score were independent predictors of all-cause mortality in the PCI group, but not in the CABG group. In the CABG group, age was the only risk factor for MI; left ventricular dysfunction, hypertension, and PAD were risk factors for stroke. On the other hand, in the PCI group, incomplete revascularization and previous MI were risk factors for MI; age and previous stroke for stroke. In addition, chronic kidney disease significantly correlated with a composite outcome of death, MI, or stroke in the CABG group, and incomplete revascularization and previous MI in the PCI group. Conclusions: Simple clinical variables and SYNTAX score differentially predict long-term outcomes after CABG versus those after PCI with DES for left main or multivessel CAD. Those predictors might help to guide the choice of revascularization strategy. © 2017 Wiley Periodicals, Inc.

Key words: coronary artery bypass grafting; drug-eluting stents; left main coronary artery disease; multivessel coronary artery disease

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

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Contract grant sponsor: CardioVascular Research Foundation, Seoul, Korea.

Conflict of interest: Nothing to report.

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Received 17 October 2016; Revision accepted 19 December 2016

DOI: 10.1002/ccd.26927
Published online 23 January 2017 in Wiley Online Library (wileyonlinelibrary.com)

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INTRODUCTION

Both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents (DES) are effective revascularization strategies for patients with left main or multivessel coronary artery disease (CAD) [1–3]. Over the past decades, both therapies have significantly evolved and improved safety and efficacy. Several randomized controlled trials have compared the relative advantages of both strategies in managing left main or multivessel CAD [4–12]. However, controversy regarding the optimal revascularization strategy for such patients exists, and the choice between CABG and PCI in routine clinical practice is often not straightforward. The identification of variables associated with long-term outcomes after CABG or PCI might aid for the choice of revascularization strategy. In the present study, pooled analysis of data from the BEST, PRECOMBAT, and SYNTAX trials was performed to identify the factors that favor CABG or PCI as the preferred revascularization approach in patients with left main or multivessel CAD.

METHODS

Study Population

A brief summary of the three multicenter trials is presented [4,5,8]. The SYNTAX recruited patients in Europe and the United States. The BEST recruited patients in Asia, and the PRECOMBAT recruited in the Korea. The SYNTAX trial included 1,800 patients with three-vessel and/or left main CAD and used paclitaxel-eluting stents for PCI; the PRECOMBAT trial included 600 patients with left main CAD and used sirolimus-eluting stents for PCI; the BEST trial included 880 patients with two- or three-vessel CAD and used everolimus-eluting stents for PCI. In all three trials, patients eligible for both CABG and PCI were randomized to be treated with either strategy. Among these patients, we identified 3,230 patients who had actually undergone either CABG ($n = 1{,}538$) or PCI with DES ($n = 1{,}692$).

Data Collection and Predictor Variables

Protocol with pre-specified outcomes and a common set of baseline variables were determined by the principal investigators for each trial (SJP and PWS). Data from each trial were merged at the coordinating institution (Asan Medical Center, Seoul, Korea). An independent clinical event committee blinded to the randomization adjudicated all end points in each study. The pooled database was checked for completeness and consistency by responsible investigators (MC and JMA) from the Asan Medical Center.

Predictor variables included demographics; clinical history (chronic kidney disease [serum creatinine >200 μmol/L], previous myocardial infarction (MI), previous stroke, peripheral artery disease, and previous PCI); risk factors (diabetes mellitus, hypercholesterolemia, hypertension, and smoking status); angiographic and echocardiographic findings (number of diseased vessels, left main CAD, SYNTAX score, and left ventricular ejection fraction); procedural variables (types of DES, number of stents, length of the stented segment, number of grafts), and EuroSCORE. Unless specified, the definitions used for variables in each study were adopted for this analysis.

Definitions and Outcome Measures

Clinical outcomes were death from any cause; MI; stroke; and a composite of death from any cause, MI, or stroke. Previously reported definitions from each study were used for individual clinical outcomes.

Statistical Analyses

Data was analyzed based on the actual treatment that each patient had received. Time-to-event outcomes were analyzed by using Kaplan–Meier method; between-group differences were assessed using log-rank test. The treatment effect was separately estimated for each trial and was combined to provide an overall estimation. A likelihood-ratio test was performed to assess data homogeneity, and the assumption of homogeneity was not violated ($P = 0.248$). The Cox proportional hazards model was adopted to determine predictors of long-term outcomes. Expected predictors were selected from the merged database; most variables were >99% complete. However, left ventricular ejection fraction was missing for 21.8% of patients in the CABG group, and 22.3% in the PCI group. Missing values were imputed with the median value of left ventricular ejection fraction after data stratification by treatment groups and using a combination of other risk factors (sex, hypertension, and previous MI) [13]. All reported P-values are two-sided; P-values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 18.0, SPSS, Chicago, IL).

RESULTS

Study Population

The study population comprised 3,230 patients (98.5% of the total cohort) who were actually treated with either CABG or PCI with DES. Baseline characteristics were well matched between the groups (Table I). The median age was 65.0 years; 75.9% of the patients were men, and 32.3% had diabetes mellitus. The index event was stable angina in 60.7% of the

TABLE I. Baseline Patient Characteristics by Study Group

Variables	CABG ($n = 1,538$)	PCI ($n = 1,692$)
Age (years)	64.4 ± 9.7	64.4 ± 9.7
Men	1,198 (77.9%)	1,255 (74.2%)
Body mass index (kg/m^2)	26.5 ± 4.1	26.5 ± 4.4
Current smoker	342 (22.3%)	356 (21.0%)
Diabetes mellitus	484 (31.5%)	558 (33.0%)
Hypercholesterolemia	983 (64.3%)	1,082 (64.2%)
Hypertension	584 (38.0%)	579 (34.2%)
Clinical presentation		
Stable angina	933 (60.7%)	1,029 (60.8%)
Acute coronary syndrome	605 (39.3%)	663 (39.2%)
Previous PCI	73 (4.7%)	80 (4.7%)
Previous MI	329 (21.5%)	327 (19.4%)
Previous stroke	74 (5.9%)	73 (5.4%)
Peripheral arterial disease	109 (7.1%)	112 (6.6%)
CKD (serum Cr $\geq$ 200 μmol/L)	22 (1.4%)	19 (1.1%)
Chronic obstructive lung disease	91 (5.9%)	88 (5.2%)
Left ventricular ejection fraction	59.3 ± 10.9	59.1 ± 12.0
Extent of CAD		
Left main CAD	679 (40.1%)	614 (39.9%)
Mutivessel CAD	1,013 (59.9%)	924 (60.1%)
EuroSCORE	3.4 ± 2.4	3.3 ± 2.4
SYNTAX score	27.6 ± 10.6	26.4 ± 10.4
Complete revascularization	1,015 (66.8%)	968 (57.2%)
Number of stents		3.9 ± 2.1
Length of stented segment (mm)		81.2 ± 44.8
Number of arterial grafts	1.7 ± 0.8	
Follow-up (years)	4.4 ± 1.3	4.5 ± 1.3

Percentages are based on the number of non-missing values.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; Cr, creatinine; PCI, percutaneous coronary intervention; MI, myocardial infarction.

patients, and acute coronary syndrome in 39.3%. Left main CAD was the site of lesion in 40% of the patients; 60% had multivessel CAD. The median follow-up duration was 59.2 (interquartile range: 53.8 − 60.3) months.

Similar Predictors

Predictors of long-term outcomes on univariate and multivariate analyses are presented in Tables II and III, and Supporting Information Tables SI−SIV. Several predictive variables were common in both the CABG and PCI groups. Age, chronic kidney disease, chronic obstructive lung disease, left ventricular dysfunction (left ventricular ejection fraction <40%), and peripheral artery disease were independent predictors of death from any cause in both groups. Similarly, these variables, except for chronic kidney disease, were independently related to a composite outcome of death, MI, or stroke in both groups (Table III). There were no common predictors of MI and stroke in the CABG and PCI groups.

Disparate Predictors

Diabetes mellitus, previous MI, and the SYNTAX score were independently related to death from any cause in the PCI group, but not in the CABG group (Table II, Fig. 1). Chronic kidney disease was an independent predictor of a composite outcome of death, MI, or stroke in the CABG group and complete revascularization and previous MI in the PCI group (Table III). A composite outcome was similar between the two groups in patients with chronic kidney disease but favored CABG over PCI in those without chronic kidney disease (Fig. 2A). In the CABG group, age was the only risk factor for MI; left ventricular dysfunction, hypertension, and PAD accounted for the risk of stroke (Table II). On the other hand, in the PCI group, incomplete revascularization and previous MI were the risk factors for MI (Fig. 2B); age and previous stroke were predictors of stroke. The incidence of stroke was numerically higher after CABG than after PCI in patients without previous stroke, whereas an inverse association was observed among patient with previous stroke (Fig. 2C).

EuroSCORE Versus SYNTAX Score

In the CABG group, death from any cause was significantly related to the EuroSCORE (hazard ratio [HR]: 1.32; 95% confidence interval [CI], 1.24–1.40; $P < 0.001$), but not to the SYNTAX score ($P = 0.541$). In the PCI group, however, both the EuroSCORE (HR: 1.27; 95% CI, 1.21 − 1.33; $P < 0.001$) and the SYNTAX score ($P = 0.004$) were independent predictors of death from any cause. In patients with high SYNTAX scores, all-cause mortality was significantly lower with CABG than with PCI (HR: 0.66; 95% CI, 0.45 − 0.97; $P = 0.034$) (Fig. 1). The difference in all-cause mortality between the two groups decreased in patients with intermediate SYNTAX scores (HR: 0.80; 95% CI, 0.55 − 1.16; $P = 0.237$) and reversed in those with low SYNTAX scores (HR: 1.25; 95% CI, 0.81–1.93; $P = 0.307$).

DISCUSSION

Among patients with left main or multivessel CAD, some clinical variables such as age, chronic obstructive lung disease, left ventricular dysfunction, or peripheral artery disease were common predictors of long-term outcomes in both CABG and PCI groups. The others appeared to differentially influence the long-term outcomes after CABG compared to those after PCI with DES. Diabetes mellitus, previous MI, and the SYNTAX score were significantly related to the long-term mortality after PCI with DES. Previous MI was a key determinant of MI after PCI with DES. Similarly,

TABLE II. Multivariate Predictors of Death, Myocardial Infarction, or Stroke

	CABG			PCI with DES		
Variables	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Death from any cause						
Age	1.07	1.05–1.10	<0.001	1.07	1.05–1.09	<0.001
CKD	3.87	1.87–8.10	<0.001	2.74	1.26–5.95	0.011
Chronic obstructive lung disease	2.14	1.28–3.57	0.004	1.93	1.20–3.09	0.007
LVEF ≥ 40%	0.42	0.23–0.76	0.004	0.45	0.25–0.80	0.007
PAD	2.84	1.85–4.37	<0.001	2.38	1.56–3.63	<0.001
Diabetes mellitus				1.47	1.08–2.02	0.015
Previous MI				1.86	1.34–2.57	<0.001
SYNTAX scores						0.018
low vs. high				0.58	0.39–0.88	0.010
intermediate vs. high				0.96	0.68–1.37	0.819
Myocardial infarction						
Age	1.04	1.00-1.07	0.027			
Complete revascularization				0.64	0.44–0.93	0.020
Previous MI				2.48	1.68–3.67	<0.001
Stroke						
Age				1.07	1.03–1.12	0.001
Previous stroke				3.26	1.26–8.44	0.015
LVEF ≥ 40%	0.32	0.12–0.92	0.033			
Hypertension	3.20	1.34–7.66	0.009			
PAD	2.69	1.19-6.12	0.018			

CI, confidence interval; CKD, chronic kidney disease; DES, drug-eluting stent; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

TABLE III. Multivariate Predictors of a Composite Outcome of Death, Myocardial Infarction, or Stroke

	CABG			PCI with DES		
Variables	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.06	1.04–1.08	<0.001	1.05	1.03–1.06	<0.001
Chronic obstructive lung disease	1.74	1.10–2.74	0.018	1.67	1.10–2.53	0.016
LVEF ≥ 40%	0.49	0.29–0.82	0.007	0.50	0.31–0.81	0.011
PAD	2.21	1.50–3.24	<0.001	1.68	1.13–2.49	0.011
CKD	2.78	1.41–5.51	0.003			
Complete revascularization				0.78	0.61–0.99	0.043
Previous MI				1.96	1.51–2.54	< 0.001

CI, confidence interval; CKD, chronic kidney disease; DES, drug-eluting stent; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

previous stroke was an important predictor of stroke after PCI with DES. In contrast, chronic kidney disease was an independent predictor of a composite outcome of death, MI, or stroke after CABG. These findings suggest that simple clinical variables and the SYNTAX score can help guide the revascularization strategy for patients with left main or multivessel CAD.

Age and major organ dysfunction are well-established predictors of mortality in patients with significant CAD undergoing CABG or PCI [4–17]. Likewise, in the present study, age, chronic kidney disease, chronic obstructive lung disease, and left ventricular dysfunction were independent predictors of long-term mortality after both CABG and PCI with DES. In fact, these variables are included in the EuroSCORE [14], and the EuroSCORE was validated for a reliable predictor of long-term mortality in both groups [18]. Major organ failure is undoubtedly the most powerful predictor of mortality irrespective of revascularization strategy, highlights the importance of comprehensive medical care for such patients. In this study, peripheral artery disease was also an independent predictor of the long-term mortality in both groups. It is certainly linked to cardiovascular morbidity and mortality, and even mild, asymptomatic peripheral artery disease has been shown to increase the risk of cardiovascular events [19,20]. Indeed, peripheral artery disease seems to be a marker of heavy atherosclerotic burden and is associated with an increased risk of mortality in both CABG and PCI groups, which calls for aggressive preventive and therapeutic interventions.

Robust data to guide the choice between CABG and PCI with DES among patients with left main or

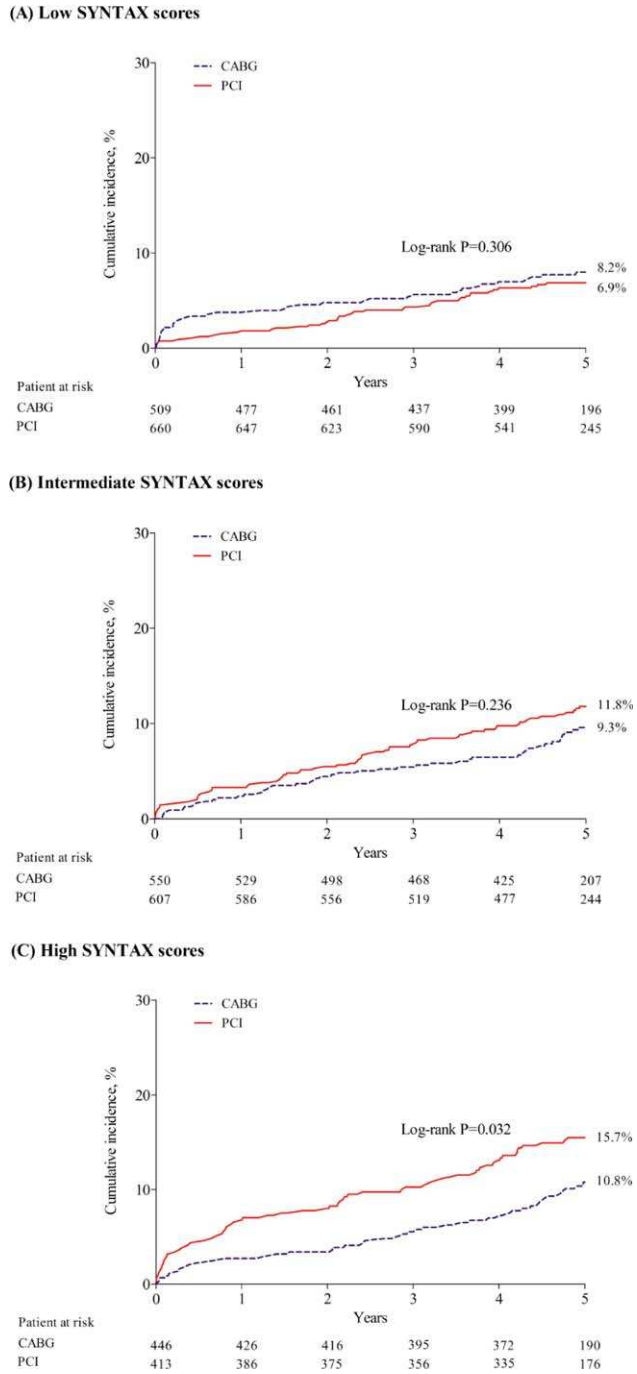

Fig. 1. Time-to-event curves for death from any cause by the SYNTAX subgroups. The cumulative incidence of death from any cause in patients with low SYNTAX scores (A), intermediate SYNTAX scores (B), and high SYNTAX scores (C) are shown. *P*-values were calculated using the log-rank test with all available follow-up data. Percentages denote 5-year event rates. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. [Color figure can be viewed at wileyonlinelibrary.com]

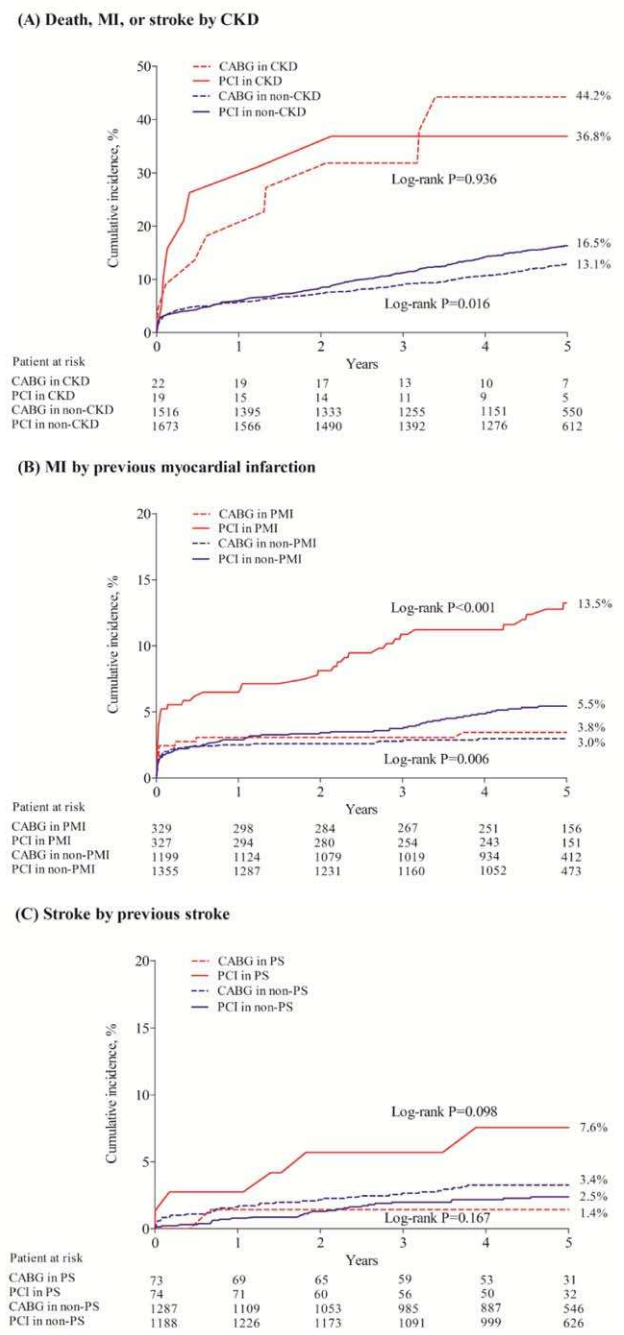

Fig. 2. Clinical outcomes by major clinical subgroups. Cumulative incidence of a composite outcome of death, MI, or stroke by chronic kidney disease (A), MI by previous MI (B), and stroke by previous stroke (C) are shown. *P*-values were calculated using the log-rank test with all available follow-up data, indicating significant difference between CABG and PCI. Percentages denote 5-year event rates. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; MI, myocardial infarction; PS, previous stroke. [Color figure can be viewed at wileyonlinelibrary.com]

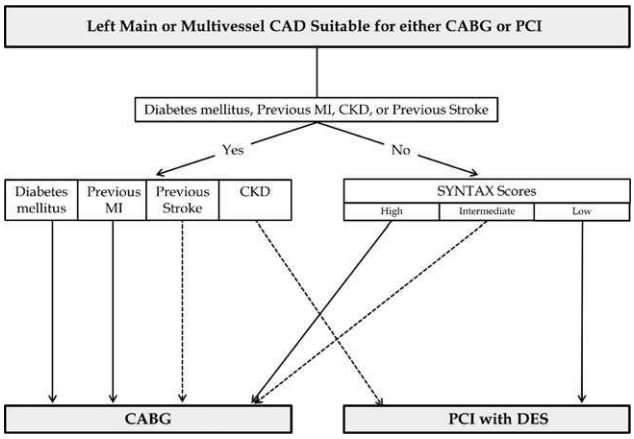

Fig. 3. Proposed algorithm of revascularization strategy for patients with left main or multivessel coronary artery disease. Solid lines indicate the preferred choice, and dotted lines indicate the better choice. CAD, coronary artery disease; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DES, drug-eluting stents; MI, myocardial infarction; PCI, percutaneous coronary intervention.

multivessel CAD are rather limited [15,16]. In the present analysis, diabetes mellitus, previous MI, and the SYNTAX score were differentially predictive of the long-term mortality after CABG and PCI with DES. These variables were independent determinants of long-term mortality in the PCI group but not in the CABG group, which may merit a more central role to guide the revascularization strategy. Diabetic patients have a greater burden of atherosclerosis and tend to have worse clinical outcomes following revascularization procedures than non-diabetic patients. CABG has been accepted as the preferred method of revascularization for multivessel disease over PCI, reflecting the results of the Bypass Angioplasty Revascularization Investigation trial [21] and the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial [9]. In this regard, our findings are consistent with those of previous trials and support the survival advantage of CABG over PCI in diabetic patients with severe CAD. In addition, patients with previous MI remain at high risk of recurrent events and mortality [22,23]. CABG offers greater protection against MI than PCI [9,24]. In the present study, previous MI was an independent predictor of all-cause mortality as well as of MI in the PCI group but not in the CABG group. These findings suggest that just like diabetic multivessel disease, CABG is the preferred strategy for patients with previous MI and left main or multivessel CAD. The SYNTAX score was introduced to measure the complexity of CAD; higher SYNTAX scores are indicative of a more complex CAD [4,25–27]. In recent studies on the treatment of left main CAD, PCI compared with CABG had similar rates of death, MI, or stroke at 3 years in the EXCEL trial [28], but higher rates of death, MI, stroke, or repeat revascularization at 5 years in the NOBLE trial [29]. Although the results were discordant with each other, these findings suggest that both treatments are valid options for patients with left main CAD. There were no significant interactions between SYNTAX scores and treatment effect regarding primary outcome in both trial. However, these findings were based on medium-term follow-up (median, 3 years) with different primary outcomes, and it should be cautiously interpreted. In our present analysis, the SYNTAX score was associated with worse long-term outcomes after PCI, but not after CABG, which is consistent with results from previous studies that showed that it did not affect the long-term outcomes after CABG [25–27]. Furthermore, in patients with high SYNTAX scores, CABG offered a survival advantage over PCI with DES. In those with low SYNTAX scores, however, the relative risk of all-cause death was reversed, suggesting that PCI with DES is the preferred strategy in such patients.

Chronic kidney disease was a predictor of a composite outcome of death, MI, or stroke after CABG, but not after PCI. There was no difference with respect to a composite outcome of death, MI, or stroke between CABG and PCI in patients with chronic kidney disease. In a recent study conducted in patients with chronic kidney disease, CABG was associated with higher short-term risk of death, stroke, and repeat revascularization, whereas PCI with everolimus-eluting stent was related to a higher long-term risk of repeat revascularization and a similar risk of long-term mortality [30]. These findings suggest that PCI with DES is a better strategy than CABG for those with chronic kidney disease in left main or multivessel CAD. On the other hand, previous stroke was an independent predictor of stroke after PCI but not after CABG. In contrast to those without previous stroke, the incidence of stroke was a little bit higher in the PCI group than in the CABG group in patients with previous stroke. The reasons for this difference remain unclear, but it may be related to prolonged dual antiplatelet therapy after DES implantation. In general, potent antiplatelet therapy significantly increases the risk of stroke in patients with previous stroke [31–34]. Our findings suggest that CABG might be the better strategy than PCI with DES in patients with previous stroke. Incomplete revascularization was independently related to MI after PCI, but not after CABG. It may reflect higher atherosclerotic plaque burden and more advanced coronary artery disease that is less amenable to complete revascularization by PCI. However, the underlying mechanisms remain unclear and require further studies.

Selection of the optimal revascularization strategy is a clinical challenge. Several risk models have addressed

this issue, but they are often not used in real-world practice perhaps due to their perceived complexity with multiple variables [35]. Current guideline recommendations are based on the extent of CAD or anatomical lesion complexity (the SYNTAX score) for selecting the revascularization strategy [1–3]. In the present pooled analysis of case-based data, we identified easily that clinical variables and the SYNTAX score may potentially aid decision making for the revascularization strategy. As proposed in Fig. 3, CABG may be preferred in patients with diabetes mellitus, previous MI, or high SYNTAX scores and can be considered for a better strategy in patients with previous stroke and intermediate SYNTAX scores. In contrast, PCI with DES may be preferred for patients with low SYNTAX scores and a better strategy for those with chronic kidney disease. However, our conclusions are based on indirect evidence, and the inferences drawn do not necessarily represent causal associations. Further studies are needed to draw definitive recommendations on the choice of the revascularization strategy for individual patients.

Several limitations of this study are noteworthy. First, the present analysis was derived from a broad population of patients with left main or multivessel CAD who were suitable for both CABG and PCI with DES, which may limit the generalizability of our findings. Further studies may be needed in selected patients with isolated left main CAD. Second, DES used in the PRECOMBAT and SYNTAX trials differs from the newer-generation DES used in the BEST trial. However, the type of DES was not found to be an independent predictor of long-term outcomes. Third, the definition of certain variables was slightly different across trials. However, this will not influence the results because patients were randomized to receive either strategy. Finally, the definition used for chronic kidney disease was serum creatinine level of >200 μmol/L because of the lack of data on the estimated glomerular filtration, and its effect on outcomes was based on small sample size. In addition, disaggregated data on previous stroke (ischemic or hemorrhagic) was unavailable. Nevertheless, the present analysis is the first to identify common and differential predictors of long-term outcomes after CABG and PCI with DES, in a similar patient population with left main or multivessel CAD.

CONCLUSION

In conclusion, simple clinical variables and the SYNTAX score were differentially predictive of long-term outcomes after CABG and PCI with DES in patients who had left main and multivessel CAD. These variables seem to be useful in decision-making regarding the revascularization strategy.

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