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ORIGINAL ARTICLE

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Coronary artery bypass graft surgery versus drug-eluting stent implantation for high-surgical-risk patients with left main or multivessel coronary artery disease

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Abstract

OBJECTIVES: There are limited data comparing long-term outcomes of coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in patients with high surgical risk. We evaluated 5-year outcomes following CABG versus PCI with DES in 598 patients with left main or multivessel coronary artery disease (CAD) and a high surgical risk [EuroSCORE (European system for cardiac operative risk evaluation) $\geq$ 6].

METHODS: Databases were merged from the BEST, PRECOMBAT and SYNTAX trials. The primary outcome was a major adverse cardio-cerebral event (MACCE), defined as the composite of all-cause death, myocardial infarction, stroke or repeat revascularization.

RESULTS: During 5-year follow-up, the rates of MACCE were 29.4% in the CABG group and 43.8% in the PCI group [hazard ratio (HR), 0.64; 95% confidence interval (CI), 0.49 - 0.84; $P = 0.001$]. The MACCE was significantly better with CABG than with PCI in patients with high and intermediate SYNTAX scores (34.9% vs 46.3%, $P = 0.039$, and 29.7% vs 47.6%, $P = 0.010$, respectively), but comparable between the two groups in those with low SYNTAX scores. The rates of all-cause death and stroke were similar between the two groups. However, CABG was associated with fewer myocardial infarctions (HR, 0.50; 95% CI, 0.27 - 0.93; $P = 0.027$) and repeat revascularizations (HR, 0.32; 95% CI, 0.20 - 0.52; $P < 0.001$).

CONCLUSIONS: Among high surgical risk patients with left main or multivessel CAD, CABG compared to PCI with DES was associated with a lower rate of MACCE.

Keywords: Coronary artery bypass graft surgery • Drug-eluting stents • EuroSCORE • Left main coronary artery disease • Multivessel disease

INTRODUCTION

Left main or multivessel coronary artery disease (CAD) has been treated with either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents (DES) [1–3]. CABG is generally the preferred revascularization therapy for these patients, and PCI with DES can be used in certain subsets of patients. As life expectancy increases, revascularization becomes necessary for greater numbers of patients with high surgical risk. These patients are at a higher risk of morbidity and mortality after surgical intervention [4–7]. In real-world practice, therefore, PCI with DES is often used to treat high surgical risk patients with left main or multivessel CAD [2, 3, 8]. However, little data are available to compare CABG versus PCI with DES for such patients. Therefore, identification of the ideal approach to treat these patients remains a difficult challenge.

In this study, we combined databases from the BEST, PRECOMBAT and SYNTAX trials [11], and compared 5-year outcomes of CABG and PCI with DES in high surgical risk patients with left main or multivessel CAD.

MATERIALS AND METHODS

Study population

A brief description of each of the three trials is as follows [12–14]. All were multicentre trials: SYNTAX recruited 1800 patients with left main or three-vessel disease from Europe and the USA; BEST 880 patients with 2- or 3-vessel CAD from Asia; and PRECOMBAT 600 patients with left main CAD from Korea. The BEST trial used everolimus-eluting stents, the PRECOMBAT trial sirolimus-eluting stents and the SYNTAX trial paclitaxel-eluting stents. In all of these trials, patients who were eligible for both PCI and CABG were randomized to receive treatment with either strategy. Among these patients, we identified 598 patients with EuroSCORE (European system for cardiac operative risk evaluation) ≥6 who were treated with either CABG ($n = 306$) or PCI with DES ($n = 292$); these formed our study population.

Data collection

The principal investigators for each trial (S.-J.P. and P.W.S.) established protocols including prespecified outcomes and a common set of baseline variables [11]. The merged database included information regarding demographics (age, sex, body weight and height), clinical history (chronic kidney disease, prior myocardial infarction, prior stroke and peripheral artery disease), risk factors (diabetes mellitus, hypercholesterolaemia, 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-cause death, cardiac death, myocardial infarction, stroke and repeat revascularization). Unless specifically described, definitions from each study were used for variables [12–14].

Definitions and study outcomes

The additive EuroSCORE predicts the risk of death after heart surgery based on patient, cardiac and operative factors. All of the three trials commonly assumed the clinical risk of each patient based on the same additive EuroSCORE. Possible scores range from 0 to 39, with higher scores indicating greater risk, and high surgical risk is defined by a EuroSCORE ≥6 [4, 5]. The primary outcome was a major adverse cardio-cerebral event (MACCE) defined as the composite of all-cause death, myocardial infarction, stroke or repeat revascularization. Secondary outcomes included death from any cause, myocardial infarction, stroke and any coronary revascularization. Definitions for individual clinical outcomes were previously reported [12–14].

Statistical analysis

All analyses were performed on an intention-to-treat basis. 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 [15]. We presented continuous variables as means ± standard deviations, and categorical variables as frequencies. We merged databases from the three trials for pooled analysis, and used the Kaplan–Meier methodology for time-to-event outcomes, and the log-rank test for comparison. The impact of the revascularization strategy on clinical outcomes was analysed using the stratified Cox proportional hazards model. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA).

Table 1: Patient characteristics

	CABG ($n = 306$)	PCI ($n = 292$)	*P*-value
Age (years)	74.0 ± 6.3	73.7 ± 6.4	0.63
Male sex	175 (57.2)	151 (51.7)	0.18
Body mass index	26.2 ± 4.1	26.4 ± 4.8	0.56
Current smoker	40 (13.3)	26 (8.9)	0.087
Diabetes mellitus			
Any	105 (34.3)	96 (32.9)	0.71
Requiring insulin	34 (11.1)	27 (9.2)	0.45
Hypercholesterolaemia	189 (61.8)	184 (63.0)	0.75
Hypertension	196 (64.1)	195 (66.8)	0.48
Clinical presentation			0.98
Stable angina	104 (34.0)	99 (33.9)	
Acute coronary syndrome	202 (66.0)	193 (66.1)	
Prior myocardial infarction	117 (38.5)	108 (37.4)	0.78
Prior stroke	15 (5.4)	20 (7.3)	0.35
Peripheral artery disease	64 (20.9)	45 (15.4)	0.081
Chronic pulmonary disease	35 (11.4)	40 (13.7)	0.40
Chronic kidney disease[a]	19 (6.2)	13 (4.5)	0.34
Left ventricular dysfunction[b]	29 (9.5)	16 (5.5)	0.11
Diseased vessels			
Proximal LAD disease	182 (59.9)	156 (53.6)	0.12
Left main disease	118 (38.6)	116 (39.7)	0.18
Multivessel disease	188 (61.4)	176 (60.3)	0.18
SYNTAX score	29.8 ± 11.8	29.1 ± 11.8	0.53
EuroSCORE	7.2 ± 1.6	7.2 ± 1.5	0.62
Follow-up (years)	4.0 ± 1.8	4.1 ± 1.6	0.21

CABG: coronary artery bypass graft surgery; LAD: left anterior descending coronary artery; PCI: percutaneous coronary intervention.
[a]Chronic kidney disease defined as serum creatinine >200 μmol/l.
[b]Left ventricular dysfunction defined as left ventricular ejection fraction <40% or moderate-to-severe left ventricular dysfunction.

RESULTS

Baseline characteristics

Baseline characteristics were well-matched between the two groups (Table 1). The mean age was 73.9 years, 54.5% of the patients were men, and 33.6% had diabetes mellitus. Left main CAD was present in 234 patients (39.1%), and multivessel CAD in 364 patients (60.9%). The median follow-up duration was 5.0 years (interquartile range: 3.5–5.0 years). Follow-up was completed for 92.9% of patients, and the remaining patients lost to follow-up were censored at the date of their last contact. Most of the patients were well treated with optimal medical therapy at discharge and follow-up, but it was less given after CABG than after PCI (data not shown).

Primary outcome

The rates of MACCE were 29.4% in the CABG group and 43.8% in the PCI group [hazard ratio (HR), 0.64; 95% confidence interval

Table 2: Clinical outcomes

	CABG (n = 306) No. (%)	PCI (n = 292) No. (%)	Hazard ratio (95% CI)	P-value
Primary outcome				
Death, MI, stroke or RR	90 (29.4)	128 (43.8)	0.64 (0.49–0.84)	0.001
Secondary outcomes				
Death from any cause	57 (18.6)	71 (24.3)	0.79 (0.56–1.12)	0.19
Death from cardiac causes	32 (10.5)	46 (15.8)	0.68 (0.44–1.07)	0.098
Myocardial infarction	15 (4.9)	29 (9.9)	0.50 (0.27–0.93)	0.027
Stroke	13 (4.2)	11 (3.8)	1.18 (0.53–2.63)	0.69
Repeat revascularization	22 (7.2)	63 (21.6)	0.32 (0.20–0.52)	<0.001
Death or myocardial infarction	65 (21.2)	86 (29.5)	0.73 (0.53–1.01)	0.058

The P-values were calculated with all available follow-up data.
CABG: coronary artery bypass graft surgery; CI: confidence interval; PCI: percutaneous coronary intervention; RR: repeat revascularization.

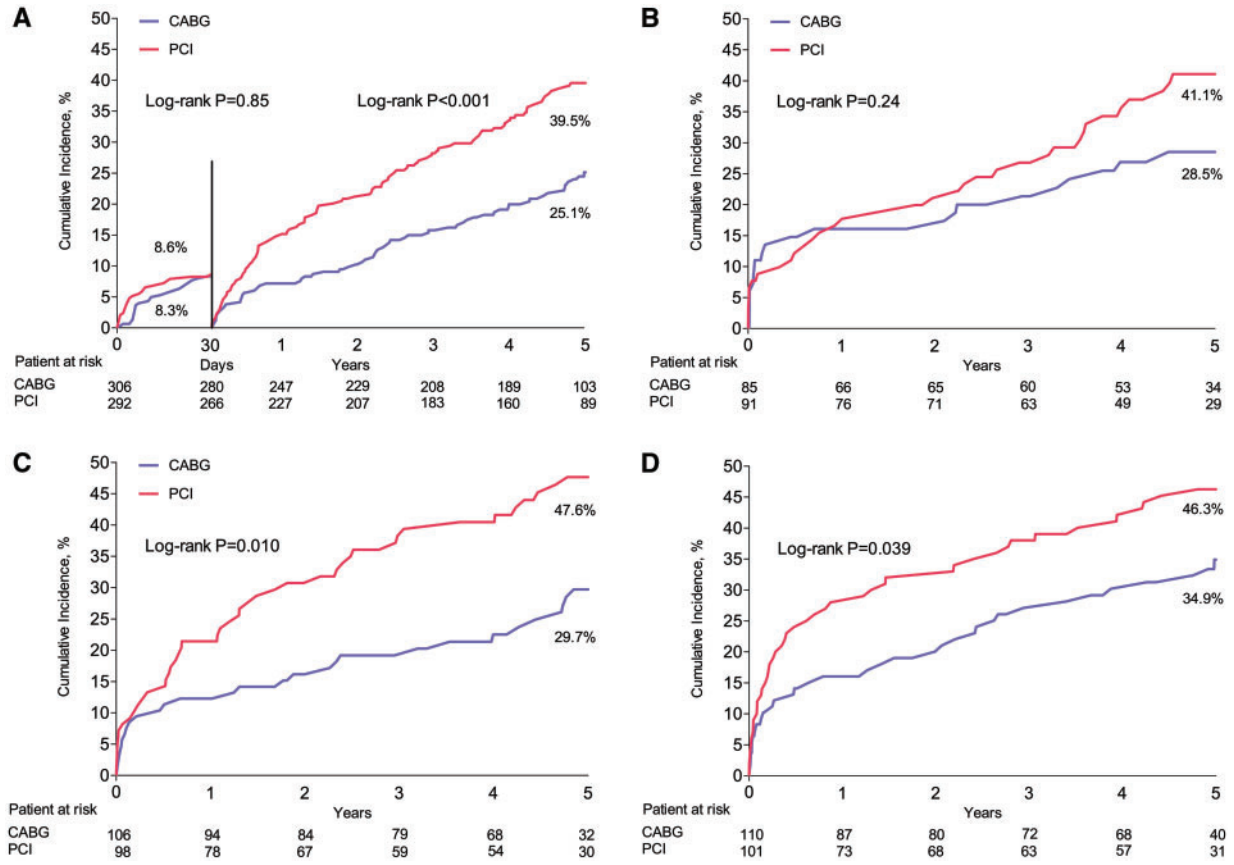

Figure 1: Primary outcome for the overall patient population and SYNTAX subgroups. The incidence of the composite of all-cause death, myocardial infarction, stroke or repeat revascularization in the overall patient population with 30-day landmark analysis (**A**), patients with low SYNTAX scores (**B**), intermediate SYNTAX scores (**C**) and 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.

(CI), 0.49 - 0.84; P = 0.001] (Table 2). Within 30 days of the index procedure, there was no difference in the rates of MACCE between two groups (Fig. 1A). In addition, in patients with low SYNTAX scores (<23), the rate of MACCE did not differ between the two groups (HR, 0.73; 95% CI, 0.44 - 1.24; P = 0.24; Fig. 1B). However, in those individuals with intermediate SYNTAX scores (23–32), and high SYNTAX scores (≥33), there were lower rates of MACCE in the CABG group compared with the PCI group (HR, 0.55; 95% CI, 0.35 - 0.87; P = 0.011; Fig. 1C and HR, 0.64; 95% CI, 0.41 - 0.98; P = 0.040; Fig. 1D, respectively).

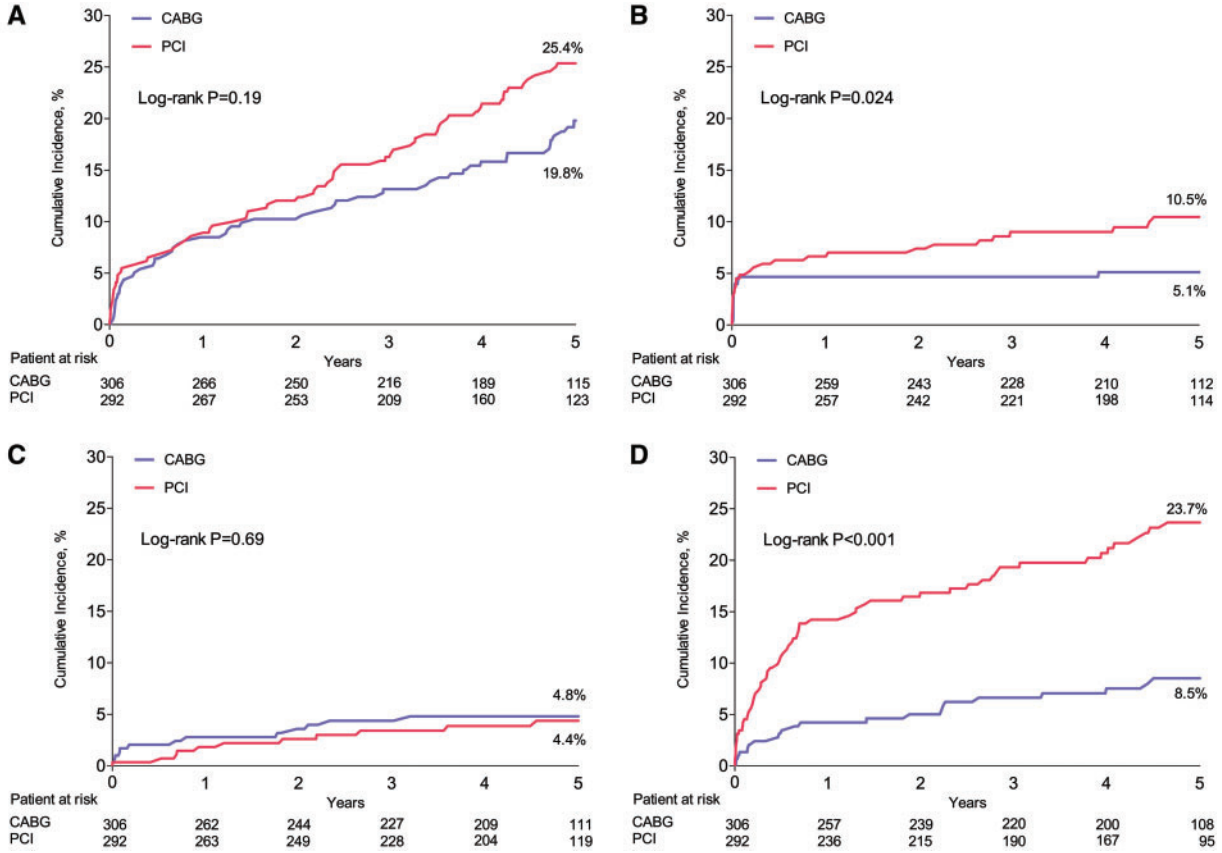

Figure 2: Secondary outcomes for the overall patient population. The incidence of all-cause death (**A**), myocardial infarction (**B**), stroke (**C**) and repeat revascularization (**D**) are shown. *P*-values were calculated using the log-rank test with all available follow-up data. Percentages denote 5-year event rates. CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention.

Secondary outcomes

The rate of all-cause death was 18.6% in the CABG group and 24.3% in the PCI group (HR, 0.79; 95% CI, 0.56 - 1.12; $P = 0.19$) (Fig. 2A, Table 2). A similar trend was observed in the incidence of death from cardiac causes (Table 2). However, the rate of myocardial infarction was significantly lower after CABG than after PCI (HR, 0.50; 95% CI, 0.27 - 0.93; $P = 0.027$) (Fig. 2B). Similarly, the composite outcome of all-cause death or myocardial infarction tended to be in favour of CABG (Table 2). There were numerically more strokes among CABG patients than among PCI patients (HR, 1.18; 95% CI, 0.53 - 2.63; $P = 0.69$) (Fig. 2C). Conversely, repeat revascularization was remarkably less required in the CABG group than in the PCI group (HR, 0.32; 95% CI, 0.20 - 0.52; $P < 0.001$) (Fig. 2D).

Subgroup analysis

No significant interaction was found between treatment effects and major clinical subgroups regarding the primary outcome except peripheral artery disease (Fig. 3). There was also no interaction for the primary outcome among three trials ($P = 0.262$ for interaction).

DISCUSSION

The major findings of this study are that MACCE occurred less frequently after CABG than after PCI with DES in high-surgical-risk patients with left main or multivessel CAD, and the difference was mainly attributable to reduced rates of myocardial infarction and repeat revascularization. The advantage of CABG was consistently noted across major clinical subgroups, but not in those with peripheral arterial disease. In addition, the two groups had similar rates of death from any cause and stroke.

Atherosclerosis progresses with advancing age, and CAD remains a major public health problem. Furthermore, the number of patients with comorbid illnesses has increased in accordance with advances in health care and medical science, and will represent a greater proportion of patients treated by cardiac surgeons [8–10]. These patients are at a higher risk for postoperative morbidity and mortality, and are more likely to shift the risk/benefit ratio of CABG over PCI towards PCI. In real-world practice, PCI has been empirically considered a good alternative to CABG in high-surgical-risk patients who are suitable for either strategy. Ideally, decision-making between CABG and PCI should be guided by the current best medical evidence. The EuroSCORE and the Society of Thoracic Surgeons (STS) score are commonly used for cardiac operative risk evaluation [4–7]. Both scores are well established and have good predictive accuracy for operative mortality. Accordingly, the 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend to use numerous models for the risk stratification of myocardial revascularization [1]. In general, a EuroSCORE value ≥ 6 reflects a high level of risk in patients with severe CAD. In these situations, CABG often produces poor results leading to significant mortality and morbidity [16].

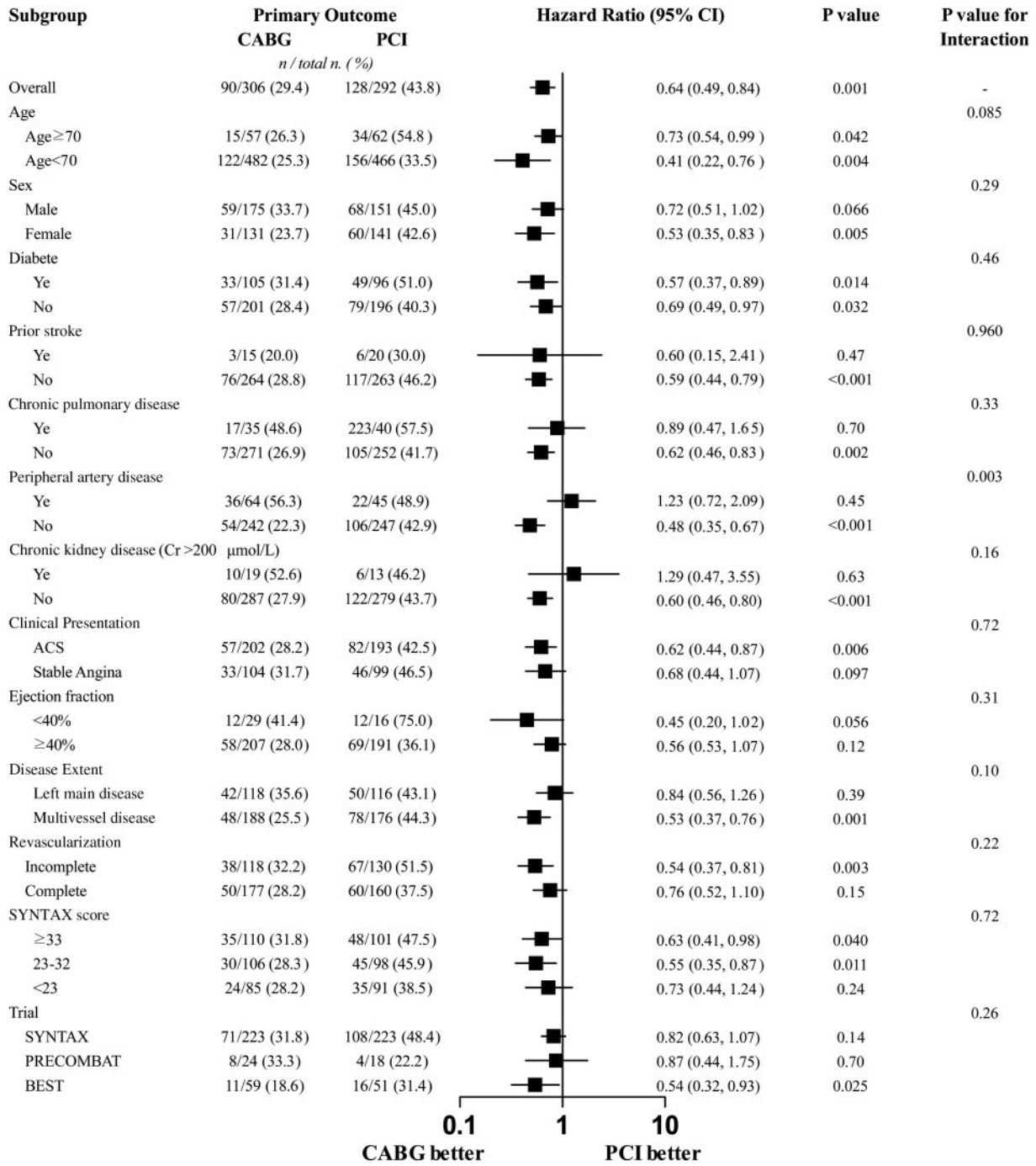

Figure 3: Forest plot of subgroup analysis for primary outcome. Subgroup analyses were performed using Cox proportional-hazards regression. CABG: coronary artery bypass graft surgery; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome.

In fact, current guidelines allow a choice of PCI over CABG for patients with left main or multivessel CAD, who have favourable coronary anatomy for PCI, and for whom operative mortality is >5% by STS score [2, 3]. However, this is an arbitrary number that is not based on data from clinical trials, and the appropriate revascularization strategy in such patients is still unknown.

In this study, we directly compared CABG and PCI with DES in high-surgical-risk patients with left main or multivessel CAD, who were suitable for either strategy. We found that these patients benefit more from CABG than from PCI with DES and the 30-day MACCE rates were similar between the groups. These findings were consistent across most major clinical subgroups. However, in patients with peripheral arterial diseases, the MACCE rates were not different between the two groups. Peripheral arterial disease is a marker of heavy atherosclerotic burden, which significantly increases the risk of cardiovascular events [17, 18]. Our findings suggest that PCI might be the preferred approach in a subgroup of patients with advanced systemic atherosclerosis. In addition, the rates of MACCE between CABG and PCI did not

differ in patients with low SYNTAX scores, indicating that PCI is a reasonable therapeutic option in high-surgical-risk patients with less complex CAD. The incidence of all-cause death was numerically lower (~4%/year) in the CABG group than in the PCI group (~5%/year), suggesting that CABG is at least as good as PCI in terms of all-cause mortality, even in high-surgical-risk patients. Furthermore, the rate of myocardial infarction was markedly lower after CABG than after PCI, being consistent with previous studies demonstrating that CABG is better than PCI for prevention of myocardial infarction [19–21]. Moreover, stroke was relatively rare with no difference between the two groups, suggesting that CABG may not significantly increase the risk of stroke in high-surgical-risk patients. Although the risk of early stroke appears to be higher with CABG than with PCI, off-pump and minimally invasive CABG may contribute to reducing the risk of postoperative stroke [22, 23].

Both CABG and PCI with DES play a major role in the management of left main or multivessel CAD. DES have dramatically altered the management of CAD and are increasingly used to treat complex CAD, including left main or multivessel CAD. Patients with high surgical risk tend to prefer PCI over CABG because of a shorter hospital stay, a quicker recovery time and a potentially lower incidence of stroke. However, our study suggests that CABG compared to PCI with DES significantly reduced the risk of MACCE with similar rates of stroke in patients with left main or multivessel CAD. However, further study may be necessary to directly compare CABG and PCI with DES in this specific population.

Limitations

Several limitations of this study need to be addressed. First, this was a sub-study of individual patient-level data from three randomized trials. Therefore, our results should be confirmed by further study. Second, although EuroSCORE predicts both surgical and periprocedural mortality, it has been shown to overestimate the risk, and therefore EuroSCORE II has been used as an update for current practice. Third, the number of patients was too small to analyse hard clinical outcomes (18.2% of the total cohort). Forth, optimal medical therapy was less used in CABG patients compared with PCI patients. The rate of cardiovascular events may be further decreased by standard medical therapies in CABG patients.

CONCLUSION

In conclusion, in high-surgical-risk patients with left main or multivessel CAD, CABG compared to PCI with DES resulted in a lower rate of MACCE.

FUNDING

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Conflict of interest: none declared.

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EDITORIAL COMMENT

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Myocardial revascularization in patients with left main or multivessel coronary artery disease at high surgical risk: conventional wisdom versus risk prediction model

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Keywords: Coronary artery bypass grafting • Coronary artery disease • Guidelines • Heart Team • Percutaneous coronary intervention • Risk scores

Risk prediction models applied to patients with coronary artery disease constitute an indispensable resource for the multidisciplinary decision-making process in the Heart Team as they allow estimating the risk–benefit ratio associated with different treatment options [1]. Among patients with left main or advanced multivessel disease, coronary artery bypass grafting (CABG) has represented the standard of care, whereas percutaneous coronary intervention (PCI) was reserved to less complex anatomical settings until recently [2]. However, when the operative mortality risk is factored in, common sense suggests that the pendulum between CABG and PCI has to shift towards the less invasive percutaneous approach as cardiac surgical risk increases.

In this issue of the Journal, Chang and colleagues challenged the conventional wisdom by providing an individual participant data analysis of 3 randomized trials comparing CABG vs PCI among patients with multivessel disease (BEST trial), left main disease (PRECOMBAT trial) or with either of these 2 conditions (SYNTAX trial) [3]. Using the additive European System for Cardiac Operative Risk Evaluation (EuroSCORE), the authors evaluated the long-term safety and efficacy of CABG compared with PCI among 598 patients at high risk of perioperative surgical death (EuroSCORE $\geq$6). Major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause death, myocardial infarction, stroke or repeat revascularization, were decreased through 5 years among patients assigned to CABG compared with those who underwent PCI (29.4% vs 43.8%, $P = 0.001$). The difference was largely related to a 50% and 70% relative reduction in the risk of myocardial infarction and repeat revascularization, respectively, associated with CABG. Interestingly, at 30 days, the rate of MACCE was similar between CABG and PCI (8.3% vs 8.6%), while cumulative event curves for MACCE began to diverge thereafter (25.1% vs 39.5%, $P < 0.001$).

The study findings pose the question whether the EuroSCORE should be considered as a treatment modifier in the selection between CABG and PCI. To solve this issue, we used published data from a recent pooled analysis of the same 3 trials [4], derived with very close approximation the hazard ratios with 95% confidence intervals for patients with a EuroSCORE <6 and, finally, calculated the *P*-value for interaction in the treatment effect of CABG vs PCI between low-to-moderate risk (EuroSCORE <6) and high-risk (EuroSCORE $\geq$6) patients. The results are summarized in Fig. 1. Of note, the risk-by-treatment interaction did not reveal significant differences for any of the tested clinical outcomes, suggesting the lack of heterogeneity in the treatment effect between CABG and PCI according to surgical