Circulation

ORIGINAL RESEARCH ARTICLE

Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease

Extended Follow-Up of the PRECOMBAT Trial

Editorial, see p 1447

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BACKGROUND: Long-term comparative outcomes after percutaneous coronary intervention (PCI) with drug-eluting stents and coronary-artery bypass grafting (CABG) for left main coronary artery disease are highly debated.

METHODS: In the PRECOMBAT trial (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), patients with unprotected left main coronary artery disease were randomly assigned to undergo PCI with sirolimus-eluting stents (n=300) or CABG (n=300) in 13 hospitals in Korea from April 2004 to August 2009. The follow-up was extended to at least 10 years for all patients (median, 11.3 years). The primary outcome was the incidence of major adverse cardiac or cerebrovascular events (composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization).

RESULTS: At 10 years, a primary outcome event occurred in 29.8% of the PCI group and in 24.7% of the CABG group (hazard ratio [HR] with PCI vs CABG, 1.25 [95% CI, 0.93–1.69]). The 10-year incidence of the composite of death, myocardial infarction, or stroke (18.2% vs 17.5%; HR 1.00 [95% CI, 0.70–1.44]) and all-cause mortality (14.5% vs 13.8%; HR 1.13 [95% CI, 0.75–1.70]) were not significantly different between the PCI and CABG groups. Ischemia-driven target-vessel revascularization was more frequent after PCI than after CABG (16.1% vs 8.0%; HR 1.98 [95% CI, 1.21–3.21).

CONCLUSIONS: Ten-year follow-up of the PRECOMBAT trial of patients with left main coronary artery disease randomized to PCI or CABG did not demonstrate significant difference in the incidence of major adverse cardiac or cerebrovascular events. Because the study was underpowered, the results should be considered hypothesis-generating, highlighting the need for further research.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT03871127 and NCT00422968.

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Key Words: coronary artery bypass grafting ■ coronary artery disease ■ drug-eluting stents ■ outcome assessment ■ percutaneous coronary intervention ■ survival

Sources of Funding, see page 1444

https://www.ahajournals.org/journal/circ

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Clinical Perspective

What Is New?

- Long-term outcomes (beyond 5 years and up to 10 years) after percutaneous coronary intervention with drug-eluting stents and coronary-artery bypass grafting for left main coronary artery disease are highly debated and still limited.
- In this 10-year follow-up of the PRECOMBAT trial (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), there was no significant difference between percutaneous coronary intervention and coronary-artery bypass grafting in the incidence of major adverse cardiac or cerebrovascular events, composite of death, myocardial infarction, or stroke, and all-cause mortality.

What Are the Clinical Implications?

- This extended follow-up of PRECOMBAT provides important insights on long-term outcomes, which could aid in decision-making for the optimal revascularization strategy in patients with left main coronary artery disease.
- However, our findings should be confirmed or refuted through adequately powered, larger-sized trials with long-term follow-up.

Although coronary-artery bypass grafting (CABG) surgery has traditionally been the mainstay of treatment for patients with left main coronary artery (LMCA) disease, percutaneous coronary intervention (PCI) has undergone considerable evolution.[1,2] Technical improvements in stent placement and the development of drug-eluting stents (DES) led to greater use of PCI, and many studies have reported favorable outcomes after PCI with DES for this complex disease.[3,4] Subsequently, multiple comparisons between the 2 competing revascularization strategies (CABG vs PCI with DES) have been conducted in randomized trials as well as registry studies,[5–9] in most of which the 2 strategies were associated with similar incidence of the composite end point of death, myocardial infarction (MI), stroke, or all-cause mortality.

However, data are still limited on long-term (beyond 5 years) outcomes of PCI or CABG in patients with LMCA disease. Available long-term studies showed conflicting results,[10–14] and some studies reported a trend of late catch-up or crossover in the incidence of the primary composite outcome or all-cause death favoring CABG over PCI during extended follow-up.[11,13,14] Therefore, there remains uncertainty about long-term outcomes warranting additional longer-term follow-up studies.

In the PRECOMBAT trial (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), we randomly assigned patients with LMCA disease to receive either PCI with sirolimus-eluting stents or CABG.[6] This trial showed no significant difference between the 2 strategies in the incidence of major adverse cardiac or cerebrovascular events and mortality at 2 and 5 years.[6,15] To further characterize the long-term outcomes of PCI and CABG in patients with LMCA disease, we now present the 10-year follow-up results of this trial.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The trial design and methods of the PRECOMBAT trial (NCT00422968) have been described previously.[6,15] Briefly, the PRECOMBAT trial was a prospective, open-label, randomized trial that compared PCI with sirolimus-eluting stents with CABG in patients with LMCA disease. It was conducted at 13 hospitals in Korea between April 2004 and August 2009. Details of the trial organization and participating centers are provided in the Data Supplement.

Although the PRECOMBAT trial was initially planned to complete follow-up at 5 years in the original protocol,[6] all participating centers agreed to participate in the extended 10-year follow-up study. This extended 10-year follow-up study was registered at https://www.clinicaltrials.gov as an investigator-driven extension of follow-up of the PRECOMBAT trial (NCT03871127) and was funded by the CardioVascular Research Foundation (Seoul, Korea). The sponsor had no role in the study design nor in the collection, analyses, or interpretation of data. The institutional review board at each hospital approved the protocol, and informed consent to obtain information on 10-year outcomes was waived. Follow-up was performed in accordance with the local law and regulations of each participating site and complied with the Declaration of Helsinki. The principal investigators had unrestricted access to the data, prepared the article, and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Patients, Randomization, and Procedures

Patients were eligible for participation in the trial if they had de novo stenosis of the LMCA of more than 50% (as estimated visually) and had received a diagnosis of stable angina, unstable angina, silent ischemia, or non–ST-segment elevation MI. Clinical and anatomic eligibility of all participants had to be considered by the cardiologists and surgeons at each hospital to be equivalently suitable for both PCI and CABG. A complete list of inclusion and exclusion criteria are provided in Table I in the Data Supplement.

Patients were randomly assigned, in a 1:1 ratio, to undergo PCI with sirolimus-eluting stents or CABG. Central

randomization was performed using an interactive web-based response system in permuted block sizes of 6 and 9, with stratification according to the participating center. Details of the PCI and CABG procedures have been described previously.[6,15] PCI was performed with standard interventional techniques according to local practice, and sirolimus-eluting stents were used as the default device. Surgical revascularization was performed with standard bypass techniques, and the internal-thoracic-artery graft was preferentially used for the left anterior descending coronary artery. Dual antiplatelet therapy (aspirin and clopidogrel) was administered before PCI, and for at least 1 year thereafter. Aspirin was indefinitely used after CABG, and concomitant use of clopidogrel was at the discretion of the operators. During follow-up, guideline-directed medical therapy and management of risk factors for secondary prevention were highly recommended for all patients.[6,15]

Outcome and Follow-Up

The primary outcome was a composite of major adverse cardiac and cerebrovascular events (ie, death from any cause, nonfatal MI, nonfatal stroke, or ischemia-driven target vessel revascularization). Major secondary outcomes included the individual components of the primary composite outcome; a composite of death, MI, or stroke; any revascularization; and definite stent thrombosis or symptomatic graft occlusion. Outcome definitions are provided in Table II in the Data Supplement. All primary and secondary outcome events were centrally adjudicated by an independent clinical-events committee, with source documents at each hospital. The extent of disease and a SYNTAX score (Synergy between PCI with Taxus and Cardiac Surgery; which was developed while the current trial was ongoing and thus measured as post hoc) was independently assessed by an angiographic core laboratory, in which members were blinded to randomization.[6] The SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with higher SYNTAX scores indicating more complex coronary artery disease.

According to the original protocol recommendation, clinical follow-up was performed at 1, 6, 9, and 12 months and then annually through 5 years.[6] Ten years after the index treatment, all participants in this trial were invited to participate in 10-year follow-up evaluations. During the extended follow-up, if a patient was unwilling or unable to return to the enrolling center, follow-up was maintained by the enrolling investigators through telephone contact or medical records obtained from other hospitals, as necessary. Information on adverse clinical events and survival data (vital status, cause of death, and date of death) was obtained through (electronic) healthcare record review and national death registry checks of the Korean National Health Insurance Service database, which was merged from the Statistics Korea database. The National Health Insurance Service is a single-payer program of a universal health coverage system in Korea and provides mandatory health care for all Korean citizens, with an enrollment rate of more than 97%.[16,17]

Statistical Analysis

This report provides descriptive information on all end point events that occurred during 10-year follow-up. Therefore, we did not perform formal hypothesis testing for the noninferiority comparison between PCI and CABG with respect to the primary end point of major adverse cardiac or cerebrovascular events.[6] All principal analyses were performed according to the intention-to-treat principle, in other words, treatment groups were defined according to the original randomization. A descriptive analysis was performed by presenting data as mean (SD) or number (proportion). Continuous variables were compared with Student *t* test or the Wilcoxon rank-sum test, and categorical variables were compared with the χ^2 test or Fisher exact test. Cumulative event rates were calculated using the Kaplan-Meier estimates, with event or censoring times calculated from the date of randomization. Risk differences and corresponding 95% CIs with the Wald approach were reported. We also compared the primary and secondary outcomes between the 2 groups using Cox regression models with robust standard errors to account for the clustering effect of participating site. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years. Patients lost to follow-up were included in the analyses for all outcomes by censoring at the date of last follow-up. The proportional-hazards assumption was confirmed using the Schoenfeld residuals test and graphical log-minus-log method;[18] no relevant violations of the underlying assumption were found.

Sensitivity analyses were conducted with the use of the as-treated analyses (in which patients were compared based on the treatment they actually received) and the per-protocol analyses (which included only patients who actually received their randomly assigned treatment). We also assessed the consistency of treatment effects in the prespecified subgroups using Cox regression models with tests for interaction: age (<65 vs ≥65 years), sex (male vs female), diabetes mellitus (yes vs no), acute coronary syndrome (yes vs no), left main disease location (ostium or shaft vs distal bifurcation), extent of combined diseased vessels (isolated LMCA disease, or LMCA disease in combination with 1-vessel, 2-vessel, or 3-vessel disease), SYNTAX score category (scores of ≤22 defined as low, 23–32 as intermediate, and ≥33 as high),[5,8,9] and complete revascularization (yes vs no). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Patients and Treatment

From April 2004 through August 2009, a total of 600 of patients with unprotected LMCA disease were randomly assigned to PCI with sirolimus-eluting stents (300 patients) or to CABG (300 patients). The baseline clinical and angiographic characteristics are summarized in Table 1 and well balanced between the PCI and CABG groups. The mean (±SD) age of the trial participants was 62.3±9.7 years, 76.5% were men, and 32.0% had medically treated diabetes mellitus. Distal left main bifurcation disease was present in 64.6% of the patients, and the mean SYNTAX score was 24.8±10.3 (low in 42.4%, intermediate in 35.3%, and high in 22.3%). Complete revascularization was achieved in 68.3% in the PCI group and 70.3% in the CABG group.

Table 1. Baseline Characteristics of the Patients

Characteristic	PCI Group (N=300)	CABG Group (N=300)
Age, y	61.8±10.0	62.7±9.5
Male sex, No. (%)	228 (76.0)	231 (77.0)
Body mass index*	24.6±2.7	24.5±3.0
Diabetes mellitus, No. (%)		
Any diabetes mellitus	102 (34.0)	90 (30.0)
Requiring insulin	10 (3.3)	9 (3.0)
Hypertension, No. (%)	163 (54.3)	154 (51.3)
Hyperlipidemia, No. (%)	127 (42.3)	120 (40.0)
Current smoker, No. (%)	89 (29.7)	83 (27.7)
Previous PCI, No. (%)	38 (12.7)	38 (12.7)
Previous myocardial infarction, No. (%)	13 (4.3)	20 (6.7)
Previous congestive heart failure, No. (%)	0	2 (0.7)
Chronic renal failure, No. (%)	4 (1.3)	1 (0.3)
Peripheral arterial disease, No. (%)	15 (5.0)	7 (2.3)
Chronic obstructive pulmonary disease, No. (%)	6 (2.0)	10 (3.3)
Family history of coronary artery disease, No. (%)	31 (10.3)	19 (6.3)
Clinical presentation, No. (%)		
Stable angina or silent ischemia	160 (53.3)	137 (45.7)
Unstable angina	128 (42.7)	144 (48.0)
Recent myocardial infarction	12 (4.0)	19 (6.3)
Left ventricular ejection fraction (%)	61.7±8.3	60.6±8.5
Electrocardiographic findings, No./total No. (%)		
Sinus rhythm	286/296 (96.6)	289/297 (97.3)
Atrial fibrillation	5/296 (1.7)	5/297 (1.7)
Other	5/296 (1.7)	3/297 (1.0)
EuroSCORE†	2.6±1.8	2.8±1.9
Left main disease location, No./total No. (%)		
Ostium or shaft	99/299 (33.1)	111/294 (37.8)
Distal bifurcation	200/299 (66.9)	183/294 (62.2)
Extent of diseased vessel, No. (%)		
Left main only	27 (9.0)	34 (11.3)
Left main plus 1-vessel disease	50 (16.7)	53 (17.7)
Left main plus 2-vessel disease	101 (33.7)	90 (30.0)
Left main plus 3-vessel disease	122 (40.7)	123 (41.0)
SYNTAX score by core-laboratory assessment‡		
Mean	24.3±9.6	25.3±10.9
Category, No./total No. (%)		
Low (≤22)	131/291 (45.0)	109/275 (39.6)
Intermediate (23 to 32)	102/291 (35.1)	98/275 (35.6)
High (≥33)	58/291 (19.9)	68/275 (24.7)
Complete revascularization	205 (68.3)	211 (70.3)

Plus–minus values are mean±SD. Percentages may not total 100 because of rounding. CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*Body mass index is the weight in kilograms divided by the square of the height in meters.

†The EuroSCORE (European System for Cardiac Operative Risk Evaluation) is a clinical model for calculating the risk of death after cardiac surgery based on patient, cardiac, and operative factors. Possible scores range from 0 to 39, with higher scores indicating greater risk.

‡The SYNTAX score (Synergy between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) reflects a comprehensive angiographic assessment of the coronary vasculature, with a score of 22 or less indicating low anatomical complexity and scores of 23 to 32 indicating intermediate anatomical complexity (0 is the lowest score and there is no upper limit).[5] The SYNTAX score was measured by angiographic core laboratory assessment and was available for 291 patients in the PCI group and 275 patients in the CABG group who had available angiograms of sufficient image quality to make the assessment accurately.

Procedural or operative data are provided in Table III in the Data Supplement. In the PCI group, intravascular ultrasound was used in 91.2% of the patients and a mean of 2.7 stents were implanted per patient. In the CABG group, 63.8% underwent off-pump surgery and 93.6% underwent revascularization of the left anterior descending artery with an internal-thoracic-artery graft.

Follow-Up and Outcomes

The median duration of follow-up in all patients was 11.3 years (interquartile range, 10.2 to 13.0; maximum follow-up, 14.7 years). The flow of patients through the trial up to 10 years of follow-up are provided in Figure I in the Data Supplement. Ten-year follow-up for all clinical end point events was achieved in 288 patients (96.0%) randomized to PCI and 288 patients (96.0%) randomized to CABG, respectively. Vital status was verified in all patients.

The primary end point of major adverse cardiac or cerebrovascular events at 10 years occurred in 29.8% of the patients in the PCI group and 24.7% of the patients in the CABG group (HR with PCI vs CABG, 1.25 [95% CI, 0.93–1.69]; Table 2 and Figure 1A). There was also no significant between-group difference with respect to the secondary composite outcome of death, MI, or stroke (18.2 vs 17.5%; HR 1.00 [95% CI, 0.70–1.44]) and death from any cause (14.5% vs 13.8%; HR 1.13 [95% CI, 0.75–1.70]) at 10 years (Table 2; Figure 1B and 1C, respectively). The incidence of MI and stroke at 10 years did not significantly differ between the 2 groups. However, the 10-year incidences of ischemia-driven target-vessel revascularization and any revascularization were higher after PCI than after CABG (Table 2 and Figure 1D).

Sensitivity and Subgroup Analyses

We performed an as-treated analysis comparing 327 patients who were actually treated with PCI and 272 patients who were actually treated with CABG (Figure I in the Data Supplement); the HR for the primary outcome with PCI was 1.51 (95% CI, 1.11–2.06; Table IV in the Data Supplement). We also performed a per-protocol comparison of 276 patients randomly assigned to PCI who actually received PCI and 248 patients assigned to CABG who actually underwent CABG; the HR for the primary outcome with PCI was 1.51 (95% CI, 1.09 to 2.10; Table V in the Data Supplement). In addition, when we estimated the risks of cause-specific mortality and nonmortality related outcomes in competing-risks framework, overall results were consistent (Table VI in the Data Supplement).

The treatment effect for the primary outcome in prespecified subgroups is shown in Figure 2. The 10-year rate of primary outcome between PCI and CABG were

Table 2. Primary and Secondary Outcomes at 10 Years

Outcomes	PCI Group (N=300)	CABG Group (N=300)	Risk Difference (95% CI)	Hazard Ratio (95% CI)*
	No. of Events (%) at 10 Years		Percentage Points	
Primary outcome				
Major adverse cardiac or cerebrovascular events†	87 (29.8)	72 (24.7)	5.2 (–2.1 to 12.4)	1.25 (0.93–1.69)
Secondary outcomes				
Death, myocardial infarction, or stroke	53 (18.2)	51 (17.5)	0.7 (–5.6 to 6.9)	1.00 (0.70–1.44)
Death from any cause	42 (14.5)	40 (13.8)	0.7 (–5.0 to 6.4)	1.13 (0.75–1.70)
Cardiovascular cause	22 (7.8)	25 (8.7)	–0.9 (–5.5 to 3.6)	0.96 (0.56–1.65)
Noncardiovascular cause	11 (3.9)	8 (2.9)	1.0 (–2.0 to 4.0)	1.55 (0.63–3.81)
Undetermined cause	9 (3.4)	7 (2.7)	0.8 (–2.2 to 3.7)	1.27 (0.50–3.22)
Myocardial infarction	9 (3.2)	8 (2.8)	0.4 (–2.4 to 3.2)	0.76 (0.32–1.82)
Q-wave	4 (1.4)	4 (1.4)	–0.02 (–1.9 to 1.9)	0.82 (0.22–3.06)
Non-Q-wave	5 (1.8)	4 (1.4)	0.4 (–1. to 2.5)	0.71 (0.22–2.26)
Stroke	5 (1.9)	6 (2.2)	–0.3 (–2.7 to 2.1)	0.71 (0.22–2.23)
Ischemia-driven target-vessel revascularization	45 (16.1)	22 (8.0)	8.1 (2.8 to 13.5)	1.98 (1.21–3.21)
Any revascularization	59 (21.3)	29 (10.6)	10.7 (4.6 to 16.7)	2.04 (1.33–3.11)
Stent thrombosis or symptomatic graft occlusion	4 (1.4)	10 (3.7)	–2.3 (–4.9 to 0.3)	0.56 (0.20–1.55)

Event rates (%) shown are the incidences as estimated with the use of a Kaplan-Meier survival analysis of data from the intention-to-treat population. CABG denotes coronary-artery bypass grafting; and PCI, percutaneous coronary intervention.

*Hazard ratios are for the PCI group as compared with the CABG group. For these models, all available follow-up data were used for long-term outcome analyses without censoring clinical events beyond 10 years. The CIs that are reported in this table have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects.

†The primary end point of major adverse cardiac or cerebrovascular events was a composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization.

consistent across multiple subgroups, except for those stratified by the extent of concomitant coronary artery disease in which the event rate was higher after PCI than after CABG in patients with left main and 3-vessel disease.

Primary and key secondary outcomes, according to the SYNTAX score tertiles, are shown in Figures II and III in the Data Supplement. There was no notable trend across the ordered SYNTAX score tertiles in the incidence of the primary outcome; composite of death, MI, or stroke; and death from any cause. The rate of ischemia-driven target-vessel revascularization was significantly higher after PCI than after CABG in the high SYNTAX score group.

DISCUSSION

PRECOMBAT was a randomized trial specifically targeting patients with LMCA disease. In this longest extended follow-up, we did not detect significant difference between PCI with sirolimus-eluting stents and CABG in the primary composite endpoint of major adverse cardiac or cerebrovascular events at 10 years. In addition, the 10-year incidence of composite of death, MI, or stroke, and all-cause mortality were also similar between the 2 groups. The 10-year rate of ischemia-driven target-vessel revascularization was 8 percentage points higher with PCI than with CABG.

Although cumulative evidence have suggested that PCI with DES is an acceptable alternative to CABG in patients with LMCA disease,[1–3] the relative benefit of CABG and PCI has been substantially different over time,[9,11,13,14] but longer-term studies beyond 5 years were still limited. Limited follow-up could penalize the CABG group because the long-term benefits of CABG might not be fully evident until 5 to 10 years after revascularization.[19,20] Therefore, the extended follow-up of PRECOMBAT provides important insights on long-term outcomes, which could aid in decision-making for the optimal revascularization strategy in patients with LMCA disease.

Recently, conflicting long-term findings from several studies have been reported.[11–14] The 10-year report of the MAINCOMPARE registry (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) showed a benefit of CABG over PCI with DES on mortality and a composite of death, Q-wave MI, or stroke after 5 years.[11] The SYNTAX trial showed similar 10-year incidence of all-cause death with PCI and CABG for LMCA disease.[12] The 5-year follow-up of the EXCEL trial (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) reported no significant difference between PCI and CABG in the rate of the primary composite of death, stroke, or

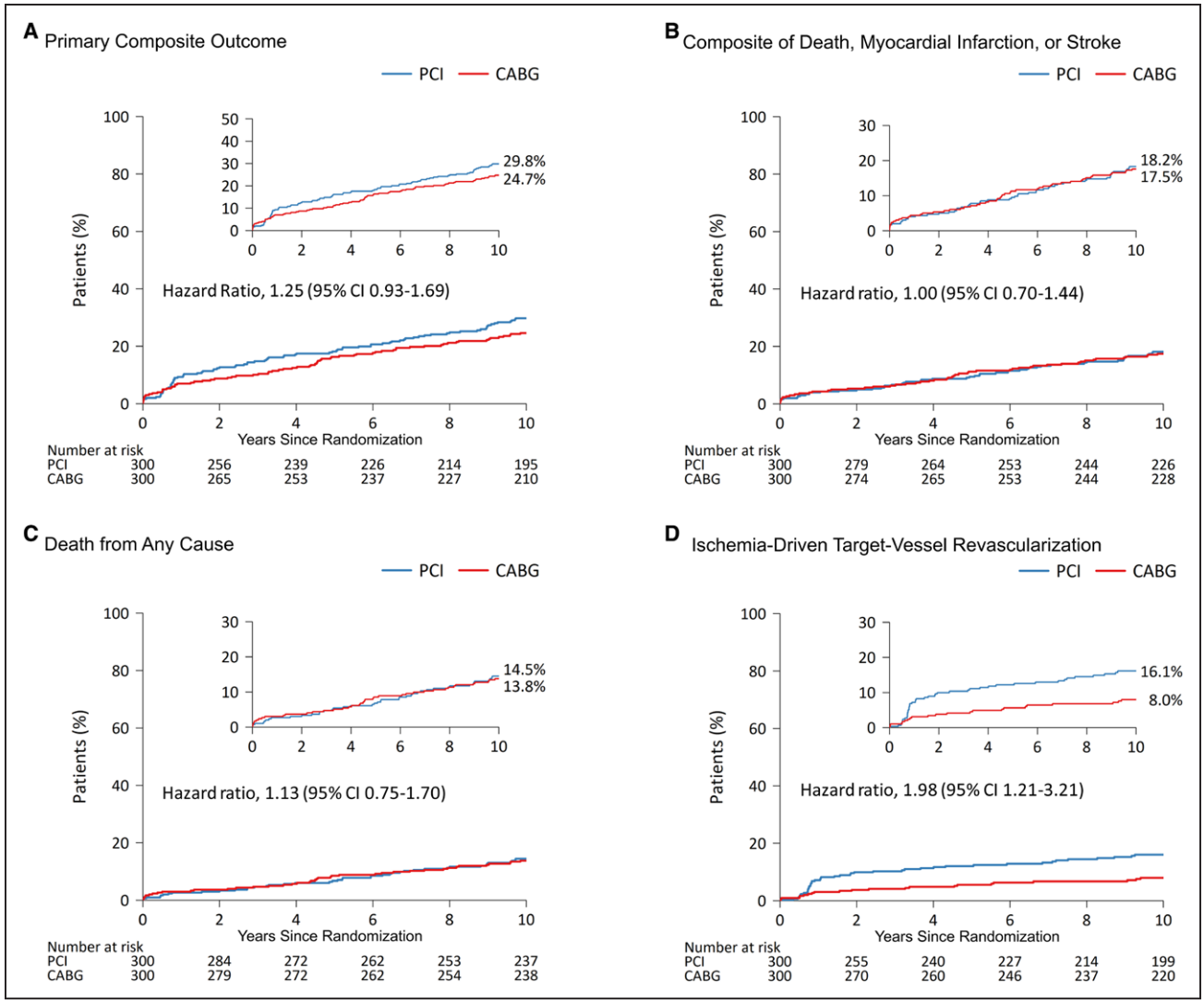

Figure 1. Time-to-event curves for the primary and key secondary outcomes through 10-year follow-up.
A, Results of the analysis of the primary composite outcome of death from any cause, myocardial infarction, stroke, or ischemic-driven target-vessel revascularization at 10 years. The results of the analyses for key secondary outcomes are shown: (**B**) composite of death from any cause, myocardial infarction, or stroke; (**C**) death from any cause; and (**D**) ischemia-driven target-vessel revascularization. Event rates were based on Kaplan-Meier estimates. The hazard ratios are for the percutaneous coronary intervention (PCI) group as compared with the coronary artery bypass grafting (CABG) group. In each panel, the inset shows the same data on an enlarged *y* axis.

MI.[13] However, the 5-year incidence of all-cause death was significantly higher after PCI than after CABG. By contrast, updated 5-year report of the NOBLE trial (Nordic-Baltic-British Left Main Revascularisation Study) showed that PCI was associated with inferior primary composite outcome compared with CABG, which was mainly driven by higher rates of nonprocedural MI and repeat revascularization, but all-cause mortality was similar.[14] In this extended report of the PRECOMBAT trial, we did not detect a significant difference between PCI and CABG in the rates of primary composite of major adverse cardiac or cerebrovascular events and all-cause mortality at 10 years. Recently, the discrepancy in the long-term incidence of all-cause mortality between trials has been highly debated. Given that all-cause deaths were consistently similar after PCI and CABG in several trials and meta-analyses,[9,12,21,22] the excess of all-cause mortality in EXCEL might be because of chance mainly driven by noncardiovascular deaths. Nonetheless, further studies are required to resolve this conflicting issue, because all-cause mortality is the most robust and unbiased index for clinical assessment, and which is less likely influenced by ascertainment bias.[23]

In the present trial, contrary to the intention-to-treat analysis, the as-treated and the per-protocol analyses showed that PCI was associated with a higher 10-year incidence of primary endpoint compared with CABG, which was mainly driven by repeat revascularization. The recent study showed that need for repeat revascularization was independently associated with increased risk for all-cause mortality and cardiovascular mortality

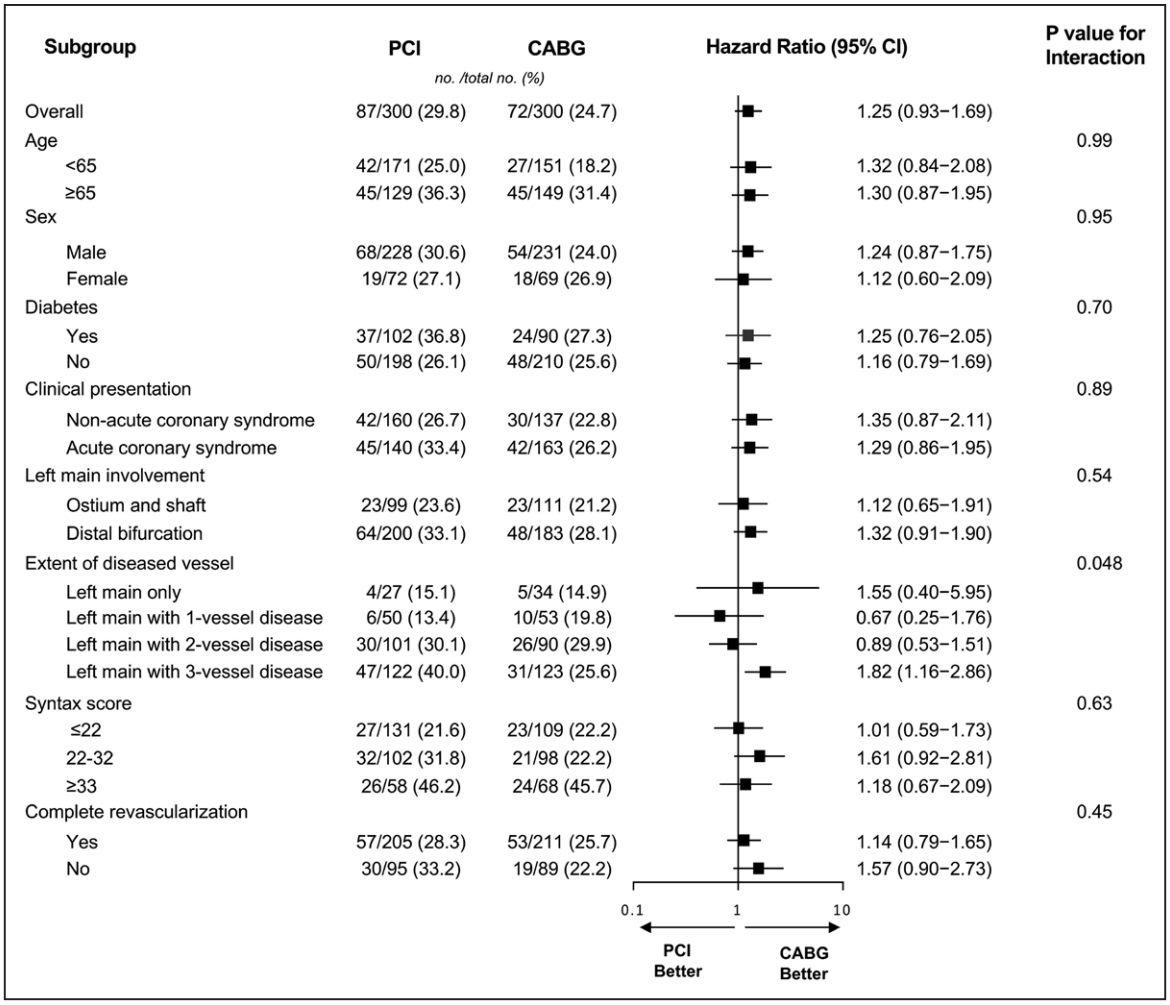

Figure 2. Subgroup analyses of the primary composite outcome at 10 years.
Data are shown as the number of primary composite outcome (ie, composite of death from any cause, myocardial infarction, stroke, or ischemic-driven target-vessel revascularization) events per total number of patients in that subgroup and the event rate. Event rates were based on Kaplan-Meier estimates; thus, the rate is not the same as the ratio of the numerator and denominator. The hazard ratios are for the percutaneous coronary intervention (PCI) group as compared with the coronary artery bypass grafting (CABG) group. The confidence intervals that are reported in this figure have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects. The *P* value for interaction represents the likelihood of interaction between the subgroups and the treatment.

after LMCA revascularization.[24] In this context, it warrants further studies to determine the potential clinical implications of a higher risk of repeat revascularization after PCI than after CABG. However, per-treatment analyses showed that the imbalance in crossover rates between groups modified the results of the primary intention-to-treat analysis. Particularly, a relatively high rate of crossover from the PCI group to the CABG group could have biased our findings toward a neutral effect on outcomes. Therefore, this interpretation should be considered in a provisional and conservative manner. Nevertheless, the per-treatment analyses might be informative as they closely mirror real-world clinical decision making.

Current guidelines have adopted the SYNTAX score to aid the choice of the appropriate revascularization strategy in patients with LMCA disease.[25,26] However, in our trial, SYNTAX score tertiles did not discriminate the more appropriate revascularization strategy with respect to primary and secondary outcomes. Similar findings were also identified in other recent clinical trials.[8,9,12–14,27] Although it is further determined whether the SYNTAX score should be central to the decision-making process for LMCA revascularization, comprehensive approaches combining clinical and anatomic factors could be helpful for enhanced personalized assessment of patient risk.[28] Furthermore, a more integrated PCI approach that incorporates coronary physiology and imaging may substantially improve PCI outcomes in patients with multivessel or LMCA disease.[29]

The overall rates of adverse events and mortality in our trial were substantially lower than the event rates in other trials.[12–14] Although this disparity is not fully elucidated, it may be partly explained by the differences in clinical or lesion characteristics, procedural practice, or race or ethnicity. For instance, intravascular

ultrasound was performed in >90% of patients for stent optimization and the proportion of off-pump surgery was high in our study. Also, the mean SYNTAX and EuroSCORE (European System for Cardiac Operative Risk Evaluation) were lower in our study than in the SYNTAX left main substudy.[6,30] Nevertheless, the relative effect of PCI and CABG might be fairly tested in each trial setting. In addition, clinical practice standards at the institutions participating in this trial, as well as the expertise of the interventional cardiologists and cardiac surgeons who performed the procedures, may differ from those of other institutions and practitioners, potentially limiting the reproducibility of these results in other settings.

The protocol definition of MI considerably varied among trials[5,8,9] and specific criteria of various definitions can penalize a specific treatment group.[31] We used the original protocol definition of MI;[6] among several criteria for MI, this definition may be the most stringent (which included only new pathologic Q-wave after procedure MI during the index hospitalization and clinically-driven spontaneous MI during follow-up). It might partly explain the lower rates of MI in our study. To diminish uncertainty and to minimize ascertainment bias for MI, further research and consensus are warranted to implement a more applicable definition of periprocedural MI not penalizing a specific revascularization group.[31]

Our study had several limitations. First, as PRECOMBAT was an open-label trial, nonfatal outcomes could have been influenced by the knowledge of the treatment received (ie, ascertainment bias). Second, the limited reproducibility of trial findings in real-world settings should be considered. Third, owing to the limited number of patients and low event rates, this trial did not have sufficient statistical power to detect a clinically significant difference in end points. Also, we cannot exclude the possibility that clinical events were underreported because of the nonprespecified 10-year follow-up and lack of yearly follow-up between 5 and 10 years. Fourth, long-term medication use after PCI and CABG varied, which reflects differences in practice with respect to the 2 different treatments. Unfortunately, we did not capture detailed information on concurrent cardiovascular medications during long-term follow-up. Although the extent to which variability in medication use contributed to the present results is uncertain, unmeasured confounding owing to differences in subsequent medication care cannot be ruled out. Finally, because we evaluated the first-generation sirolimus-eluting stents in comparison with CABG, our findings should be confirmed or refuted through 10-year (or longer) follow-up of the recent EXCEL and NOBLE trials involving contemporary DES. Newer-generation DES were not only more effective but also safer than first-generation DES and bare-metal stents.[32,33]

Conclusions

In this 10-year follow-up of the PRECOMBAT trial that enrolled patients with LMCA disease, there was no significant difference between PCI and CABG in the incidence of major adverse cardiac or cerebrovascular events, composite of death, MI, or stroke, and all-cause mortality. However, the study had insufficient statistical power to allow for a firm conclusion, hence further research is needed in this area.

ARTICLE INFORMATION

Received January 28, 2020; accepted March 2, 2020.

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The Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.120.046039.

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Acknowledgments

The authors thank the staff of the PRECOMBAT trial, the other members of the cardiac catheterization laboratories and the cardiovascular surgery departments at the participating centers, and the study coordinators for their efforts in collecting clinical data and ensuring the accuracy and completeness of the data.

Sources of Funding

This study was partly supported by the CardioVascular Research Foundation (Seoul, Korea). The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or decision to submit the article for publication.

Disclosures

Dr D.W. Park reports grants from Daiichi-Sankyo, ChongKunDang Pharm, and Daewoong Pharm, personal fees from Edwards, grants and personal fees from Abott Vascular, and personal fees from Medtronic, all outside the submitted work. Dr G.-M. Park reports grants from Yuhan Pharm outside the submitted work. Dr S.-J. Park reports grants and personal fees from Abott Vascular, grants from Daiichi-Sankyo, grants from ChongKunDang Pharm and Daewoong Pharm, grants and personal fees from Edwards, all outside the submitted work. The other authors report no conflicts.

Supplemental Materials

Appendix (Trial Investigators, Participating Centers, and Organization)
Data Supplement Tables I–VI
Data Supplement Figures I–III

REFERENCES

1. Lee PH, Ahn JM, Chang M, Baek S, Yoon SH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, et al. Left main coronary artery disease: secular trends in patient characteristics, treatments, and outcomes. *J Am Coll Cardiol.* 2016;68:1233–1246. doi: 10.1016/j.jacc.2016.05.089
2. Park DW, Ahn JM, Park SJ, Taggart DP. Percutaneous coronary intervention in left main disease: SYNTAX, PRECOMBAT, EXCEL and NOBLE-combined cardiology and cardiac surgery perspective. *Ann Cardiothorac Surg.* 2018;7:521–526. doi: 10.21037/acs.2018.04.04
3. Park DW, Park SJ. Percutaneous coronary intervention of left main disease: pre- and post-EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization Study) era. *Circ Cardiovasc Interv*. 2017;10:e004792. doi: 10.1161/circinterventions.117.004792.
4. Lee PH, Kwon O, Ahn JM, Lee CH, Kang DY, Lee JB, Kang SJ, Lee SW, Kim YH, Lee CW, et al. Safety and effectiveness of second-generation drug-eluting stents in patients with left main coronary artery disease. *J Am Coll Cardiol*. 2018;71:832-841. doi: 10.1016/j.jacc.2017.12.032.
5. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* 2009;360:961–972. doi: 10.1056/NEJMoa0804626
6. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med.* 2011;364:1718–1727. doi: 10.1056/NEJMoa1100452
7. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med.* 2008;358:1781–1792. doi: 10.1056/NEJMoa0801441
8. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice MC, Lembo N, Brown WM 3rd, et al; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med.* 2016;375:2223–2235. doi: 10.1056/NEJMoa1610227
9. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T, et al; NOBLE study investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet.* 2016;388:2743–2752. doi: 10.1016/S0140-6736(16)32052-9
10. Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, Milewski KP, Żurakowski A, Orlik B, Konkolewska M, Trela B, Janas A, Martin JL, et al. Left main stenting in comparison with surgical revascularization: 10-year outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial. *JACC Cardiovasc Interv.* 2016;9:318–327. doi: 10.1016/j.jcin.2015.10.044
11. Park DW, Ahn JM, Yun SC, Yoon YH, Kang DY, Lee PH, Lee SW, Park SW, Seung KB, Gwon HC, et al. 10-year outcomes of stents versus coronary artery bypass grafting for left main coronary artery disease. *J Am Coll Cardiol*. 2018;72(23 Pt A):2813–2822. doi: 10.1016/j.jacc.2018.09.012
12. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR Jr, Curzen N, Davierwala P, Noack T, et al; SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet.* 2019;394:1325–1334. doi: 10.1016/S0140-6736(19)31997-X
13. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice MC, Puskas J, Kandzari DE, Karmpaliotis D, Brown WM 3rd, Lembo NJ, et al; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. *N Engl J Med.* 2019;381:1820–1830. doi: 10.1056/NEJMoa1909406
14. Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, Trovik T, Kellerth T, Kalinauskas G, Mogensen LJH, et al; NOBLE investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet.* 2020;395:191–199. doi: 10.1016/S0140-6736(19)32972-1
15. Ahn JM, Roh JH, Kim YH, Park DW, Yun SC, Lee PH, Chang M, Park HW, Lee SW, Lee CW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease: 5-year outcomes of the PRECOMBAT study. *J Am Coll Cardiol.* 2015;65:2198–2206. doi: 10.1016/j.jacc.2015.03.033
16. Son JS, Choi S, Kim K, Kim SM, Choi D, Lee G, Jeong SM, Park SY, Kim YY, Yun JM, et al. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/American Heart Association guidelines with subsequent cardiovascular disease events. *JAMA*. 2018;320:1783-1792. doi: 10.1001/jama.2018.16501.
17. Yun JE, Kim YJ, Park JJ, Kim S, Park K, Cho MS, Nam GB, Park DW. Safety and effectiveness of contemporary P2Y12 inhibitors in an east Asian population with acute coronary syndrome: a nationwide population-based cohort study. *J Am Heart Assoc.* 2019;8:e012078. doi: 10.1161/JAHA.119.012078
18. Cain KC, Lange NT. Approximate case influence for the proportional hazards regression model with censored data. *Biometrics.* 1984;40:493–499.
19. Alexander JH, Smith PK. Coronary-artery bypass grafting. *N Engl J Med.* 2016;375:e22. doi: 10.1056/NEJMc1608042
20. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, et al; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374:1511–1520. doi: 10.1056/NEJMoa1602001
21. Head SJ, Milojevic M, Daemen J, Ahn JM, Boersma E, Christiansen EH, Domanski MJ, Farkouh ME, Flather M, Fuster V, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *Lancet.* 2018;391:939–948. doi: 10.1016/S0140-6736(18)30423-9
22. Palmerini T, Serruys P, Kappetein AP, Genereux P, Riva DD, Reggiani LB, Christiansen EH, Holm NR, Thuesen L, Makikallio T, et al. Clinical outcomes with percutaneous coronary revascularization vs coronary artery bypass grafting surgery in patients with unprotected left main coronary artery disease: a meta-analysis of 6 randomized trials and 4,686 patients. *Am Heart J.* 2017;190:54–63. doi: 10.1016/j.ahj.2017.05.005
23. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol.* 1999;34:618–620. doi: 10.1016/s0735-1097(99)00250-8
24. Giustino G, Serruys PW, Sabik JF 3rd, Mehran R, Maehara A, Puskas JD, Simonton CA, Lembo NJ, Kandzari DE, Morice MC, et al. Mortality after repeat revascularization following PCI or CABG for left main disease: the EXCEL trial. *JACC Cardiovasc Interv.* 2020;13:375–387. doi: 10.1016/j.jcin.2019.09.019
25. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2014;130:1749–1767. doi: 10.1161/CIR.0000000000000095
26. Windecker S, Neumann FJ, Juni P, Sousa-Uva M, Falk V. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:204-212. doi: 10.1093/eurheartj/ehy532.
27. Esper RB, Farkouh ME, Ribeiro EE, Hueb W, Domanski M, Hamza TH, Siami FS, Godoy LC, Mathew V, French J, et al. SYNTAX score in patients with diabetes undergoing coronary revascularization in the FREEDOM trial. *J Am Coll Cardiol.* 2018;72(23 Pt A):2826–2837. doi: 10.1016/j.jacc.2018.09.046
28. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Jr., Mack M, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639-650. doi: 10.1016/s0140-6736(13)60108-7.
29. Park DW, Park SJ. Contemporary state-of-the-art PCI with functional and imaging concepts: forethoughts on the FAME 3 trial. *EuroIntervention.* 2019;15:e219–e221. doi: 10.4244/EIJV15I3A40
30. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Choi JW, Ruzyllo W, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with

taxus and cardiac surgery trial. *Circulation.* 2014;129:2388–2394. doi: 10.1161/CIRCULATIONAHA.113.006689
31. Cho MS, Ahn JM, Lee CH, Kang DY, Lee JB, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, et al. Differential rates and clinical significance of periprocedural myocardial infarction after stenting or bypass surgery for multivessel coronary disease according to various definitions. *JACC Cardiovasc Interv.* 2017;10:1498–1507. doi: 10.1016/j.jcin.2017.05.051
32. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, Vlachojannis GJ, Jensen LO, Christiansen EH, Berencsi K, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol.* 2015;65:2496–2507. doi: 10.1016/j.jacc.2015.04.017
33. Piccolo R, Bonaa KH, Efthimiou O, Varenne O, Baldo A, Urban P, Kaiser C, Remkes W, Räber L, de Belder A, et al; Coronary Stent Trialists' Collaboration. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet.* 2019;393:2503–2510. doi: 10.1016/S0140-6736(19)30474-X