Comparison of a Simple Angiographic Approach With a Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Score–Based Approach for Left Main Coronary Artery Stenting

A Pooled Analysis of Serial PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) Studies

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Background—The applicability of Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery scores to left main coronary artery disease (CAD) has been questioned. A simplified alternative is needed for guiding decision making.

Methods and Results—We evaluated the prognostic value of a simplified angiographic classification in comparison with a Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery score–based approach for patients with left main CAD undergoing drug-eluting stent implantation. The proposed approach classified left main CAD as either extensive (n=819), defined as left main bifurcation lesions with an involvement of ostial left circumflex artery or as any left main lesion plus multivessel CAD, or limited (n=453), defined as ostial/midshaft lesions or left main bifurcation lesions without an involvement of ostium of left circumflex artery, alone or plus 1-vessel disease. The databases from 4 prospective Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease studies were pooled, and the primary outcome was a major adverse cardiac event, defined as death, myocardial infarction, or repeat revascularization. During follow-up (median 38 months; interquartile range, 36–61 months), the risk for major adverse cardiac event was significantly higher with extensive than with limited left main CAD (adjusted hazard ratio, 2.13; 95% confidence interval, 1.54–2.94; $P<0.001$). The risk for a composite outcome of death or myocardial infarction was also higher with extensive left main CAD (adjusted hazard ratio, 1.75; 95% confidence interval, 1.08–2.85; $P=0.02$). However, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery score tertiles did not effectively stratify these 2 outcome measures.

Conclusions—Compared with Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery scores, the simpler angiographic approach provided better discrimination for future cardiovascular events in patients with left main CAD undergoing drug-eluting stent implantation. **(*Circ Cardiovasc Interv*. 2018;11:e005374. DOI: 10.1161/CIRCINTERVENTIONS.117.005374.)**

Key Words: coronary artery disease ■ drug-eluting stents ■ myocardial infarction ■ percutaneous coronary intervention ■ sirolimus

Percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) has been increasingly used to treat left main coronary artery disease (CAD).[1–4] It has been shown that the safety outcomes for PCI are similar to those for coronary artery bypass graft surgery (CABG) despite a higher rate of repeat revascularization.[5–10] However, left main CAD is highly heterogeneous, with considerable variation in disease extent and lesion complexity; a reliable general guide to appropriate

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WHAT IS KNOWN

- The anatomic Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score quantifies complexity of coronary artery disease, taking into account the number and location of significant lesions, as well as parameters that reflect the lesion-independent complexity.
- A single numeric Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score contains no information about technical feasibility.
- Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score calculation is complex and rather difficult to implement in daily clinical practice, and its applicability for left main coronary artery disease has been a matter of debate.

WHAT THE STUDY ADDS

- A simplified angiographic morphology-based classification that incorporates details of left main bifurcation lesions and number of diseased vessels may better predict the complexity of procedure and outcomes after left main intervention than the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery score–based approach.

clinical practice is, therefore, required. The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score is an anatomic scoring system that quantifies angiographic lesion complexity, developed to predict clinical outcomes after PCI or CABG in patients with 3-vessel or left main CAD.[11] The anatomic SYNTAX score is considered an important predictor of future adverse cardiovascular events in patients undergoing PCI (but not CABG), helping in the choice of the optimal revascularization strategy.[6,12] However, SYNTAX score calculation is complex and rather difficult to implement in daily clinical practice. Furthermore, its applicability for left main CAD has been a matter of debate.[13–15] Thus, a simplified reliable guide to left main revascularization may be needed.

In this study, we developed a simplified angiographic morphology-based classification, which incorporates details of left main bifurcation lesions and number of diseased vessels, and compared its prognostic value with that of the SYNTAX score–based approach in patients with left main CAD undergoing DES implantation.

Methods

Study Population

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.

For the present study, databases from the first PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) randomized trial and from 3 subsequent prospective registries (PRECOMBAT 2, 3, and 4) were pooled for a patient-level analysis. The study design, detailed entry criteria, and outcomes of the PRECOMBAT trial have been previously described.[16] Briefly, in the PRECOMBAT trial, patients with significant left main CAD (diameter stenosis ≥50%) and clinical equipoise for both PCI and CABG were randomized to treatment with either strategy. In the PRECOMBAT 2 to 4 trial registries, patients were enrolled using the exact same criteria but were sequentially treated with different types of DES.[17] All studies were multicenter, recruiting patients from 23 sites in Korea. Sirolimus-eluting stents (Cordis Corporation, Miami Lakes, FL) were used in the PRECOMBAT randomized trial. Everolimus-eluting Xience V stents (Abbott Vascular, Santa Clara, CA), everolimus-eluting Promus Element stents (Boston Scientific, Natick, MA), and zotarolimus-eluting Resolute Integrity stents (Medtronic Inc, Santa Rosa, CA) were used in the PRECOMBAT 2, 3, and 4 studies, respectively (Figure 1). From these studies, we identified a study population of 1272 patients with left main CAD treated with PCI using DESs between April 2004 and February 2015. The study protocols were approved by the institutional review board at each participating center, and written informed consent was provided by all patients.

Data Collection and Follow-Up

Each database included a common set of variables comprising patient demographics, risk factors, clinical manifestations, left ventricular function, angiographic findings, and procedural details. All instances of PCI with DES were performed in a standardized manner.[16] All patients were pretreated with aspirin and clopidogrel. Aspirin (100–200 mg/d) was used indefinitely, and clopidogrel (75 mg/d) was used for at least 12 months. All patients were encouraged to undergo optimal medical therapy at the physicians' discretion. Follow-up outcome data were prospectively collected through scheduled outpatient clinic evaluations and telephone interviews. All events were based on clinical diagnoses made by the patients' physicians and were centrally adjudicated by an independent group of clinicians. Final follow-up statuses were ascertained between September and October 2016, and 3-year follow-up was completed for 80% of the eligible patients. Patients lost to follow-up were censored at the date of last contact. Analyses of all angiographic data were performed by 2 independent angiographers in the angiographic core laboratory in Asan Medical Center, Seoul, South Korea. Angiographic variables pertinent to SYNTAX scores were analyzed using dedicated angiographic software (CASS V, Pie Medical Imaging, Maastricht, the Netherlands). The total score was derived from the sum of the points assigned to each coronary lesion that produced ≥50% stenosis in vessels ≥1.5 mm in diameter.[11]

Study Outcomes and Definitions

The primary outcome was a major adverse cardiac event (MACE), defined as a composite of death because of any cause, myocardial infarction, or repeat revascularization. Secondary outcomes were individual components of the primary outcome and a composite of death or myocardial infarction. Previously described definitions from the PRECOMBAT randomized trial were used for the individual clinical outcomes.[16] Briefly, myocardial infarction was defined as new pathological Q waves and an increased creatine kinase–myocardial band concentration >5× the upper reference limit if occurring within 48 hours after index procedure or as new Q waves or an increased creatine kinase–myocardial band concentration above the upper reference limit with ischemic symptoms or signs if occurring after 48 hours.

Left main CAD was classified as extended or limited left main CAD according to the complexity of the lesion and CAD extent (Figure 2). Significant stenosis extending beyond the left main stem but confined within 5 mm of the proximal segment of left anterior descending or left circumflex artery was regarded as a continuum of the left main lesion. Extended left main CAD was defined as left main bifurcation lesions with an involvement of >50% narrowing in the ostium of left circumflex artery or as any left main lesion plus multivessel disease (nonleft main lesions with ≥70% stenosis in vessels ≥2.5 mm in diameter). Limited left main CAD was defined as ostial/midshaft lesions or left main bifurcation lesions without an involvement

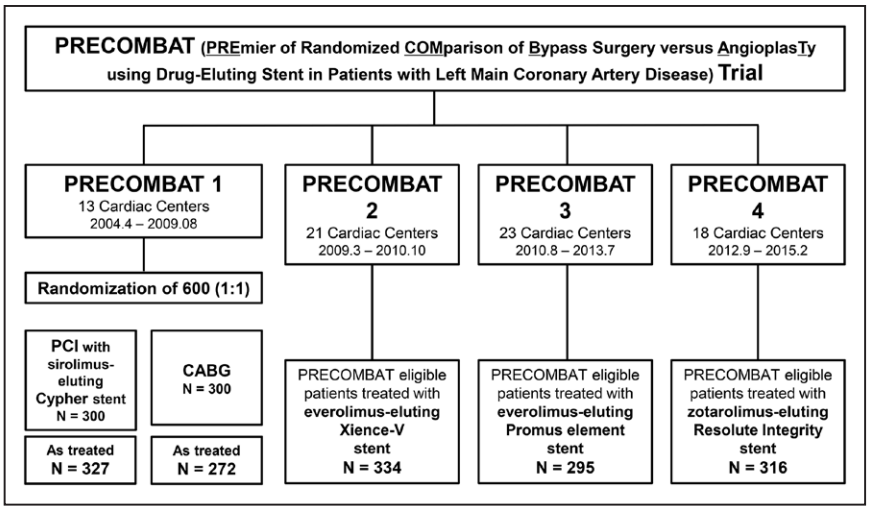

Figure 1. Overview of the PRECOMBAT study series. CABG indicates coronary artery bypass graft surgery; and PCI, percutaneous coronary intervention.

of ostium of left circumflex artery, alone or plus 1-vessel disease. All these angiographic assessments were made by visual estimation.

Statistical Analysis

Databases from the 4 studies were pooled and were analyzed according to the actual treatment received. Time-to-event outcomes were determined from the index procedure date to the final follow-up date. Cumulative event rates and survival curves were generated using the Kaplan–Meier method and were compared with the log-rank test. Cox proportional hazards regression analyses were conducted to estimate the risk associated with extensive left main CAD relative to that of limited left main CAD and the risk associated with a high (>32) or intermediate (23–32) SYNTAX score relative to that of a low (≤22) SYNTAX score. Variables with a $P \leq 0.1$ in the univariate analyses or with clinical relevance were included in the multivariable Cox regression model. The following variables were tested: age, body mass index, diabetes mellitus, hypertension, hypercholesterolemia, history of myocardial infarction, history of heart failure, chronic kidney disease, peripheral vascular disease, clinical diagnosis, left ventricular ejection fraction, atrial fibrillation, and use of intravascular ultrasound. Considering that each registry differed by type of stent and by calendar time, we included a variable classified by study type as a confounder in each multivariable model. The final multivariable models were determined by backward stepwise elimination procedures, sequentially discarding the least significant variables from the full model (Table I in the Data Supplement). Discrimination ability of the final models was assessed by Harrell c-index, and the optimism-corrected c-index was obtained using 1000 bootstrap resamples.[18] Data analyses were performed using survival and rms package in R software version 3.2.2 13 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). All reported P values are 2 sided, and $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

The baseline clinical and angiographic characteristics are presented in Table 1. The mean age was 64.0 years, 75.6%

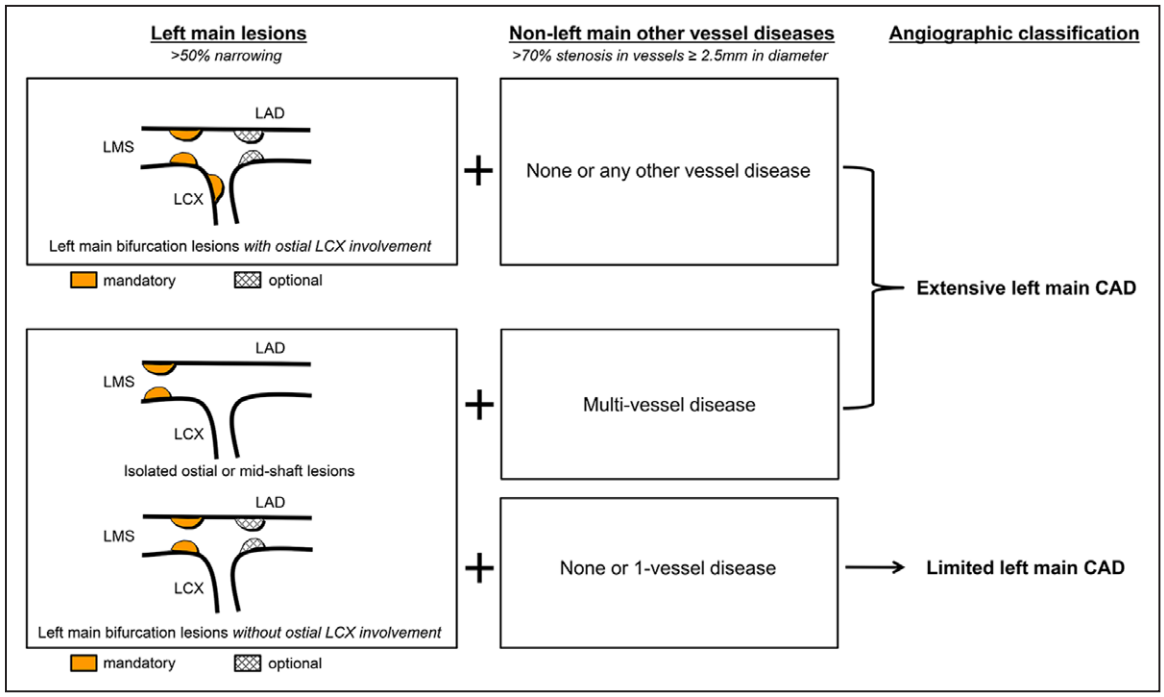

Figure 2. Angiographic classification. CAD indicates coronary artery disease; LAD, left anterior descending coronary artery; LCX, left circumflex artery; and LMS, left main stem.

of the patients were men, and 33.0% had diabetes mellitus. In addition, 348 patients (27.4%) had 3-vessel disease and 903 patients (71.0%) had distal left main bifurcation involvement, of which 333 (26.2%) had significant involvement in the ostium of left circumflex artery. According to the angiographic classification, 453 patients (35.6%) were identified as having limited left main CAD and the remaining 819 (64.4%) as having extensive left main CAD. Stratified by the SYNTAX score, 718, 369, and 185 patients were included in the low, intermediate, and high score groups, respectively. The patients with extensive left main CAD or high SYNTAX score were older and were more likely than

Table 1. Clinical and Angiographic Characteristics

	Limited Disease Group (n=453)	Extensive Disease Group (n=819)	*P* Value	SYNTAX Score ≤22 (n=718)	SYNTAX Score 23–32 (n=369)	SYNTAX Score >32 (n=185)	*P* Value
Age	61.4±10.7	64.8±10.0	<0.001	61.9±10.7	65.4±9.6	66.6±9.7	<0.001
Sex, male	338 (74.6)	623 (76.1)	0.61	551 (76.7)	263 (71.3)	147 (79.5)	0.06
Body mass index, kg/m^2	24.6±2.8	24.4±2.9	0.31	24.5±2.8	24.4±3.0	24.4±2.8	0.97
Current smoker	94 (20.8)	219 (26.7)	0.02	182 (25.3)	83 (22.5)	48 (25.9)	0.53
Diabetes mellitus	127 (28.0)	293 (35.8)	0.01	197 (27.4)	148 (40.1)	75 (40.5)	<0.001
Hypertension	258 (57.0)	525 (64.1)	0.01	413 (57.5)	243 (65.9)	127 (68.6)	0.003
Hypercholesterolemia	214 (47.2)	412 (50.3)	0.32	341 (47.5)	193 (52.3)	92 (49.7)	0.32
Prior PCI	60 (13.2)	113 (13.8)	0.85	94 (13.1)	57 (15.4)	22 (11.9)	0.43
History of myocardial infarction	25 (5.5)	44 (5.4)	>0.99	36 (5.0)	25 (6.8)	8 (4.3)	0.37
History of heart failure	8 (1.8)	13 (1.6)	0.99	15 (2.1)	5 (1.4)	1 (0.5)	0.29
Chronic kidney disease	12 (2.6)	23 (2.8)	>0.99	22 (3.1)	11 (3.0)	2 (1.1)	0.32
Peripheral vascular disease	11 (2.4)	51 (6.2)	0.004	28 (3.9)	22 (6.0)	12 (6.5)	0.18
Chronic lung disease	7 (1.5)	25 (3.1)	0.15	14 (1.9)	15 (4.1)	3 (1.6)	0.08
Clinical diagnosis			0.05				0.12
Stable angina	215 (47.5)	426 (52.0)		352 (49.0)	193 (52.3)	96 (51.9)	
Unstable angina	192 (42.4)	291 (35.5)		293 (40.8)	125 (33.9)	65 (35.1)	
NSTEMI	46 (10.2)	102 (12.5)		73 (10.2)	51 (13.8)	24 (13.0)	
LVEF, %	61.2±8.4	59.4±9.7	0.001	61.2±8.9	59.0±9.4	57.7±9.9	<0.001
Atrial fibrillation	17 (3.7)	30 (3.7)	>0.99	24 (3.3)	18 (4.9)	5 (2.7)	0.33
Disease extent			<0.001				<0.001
Left main lesion only	174 (38.4)	5 (0.6)		151 (21.0)	28 (7.6)	0	
Left main lesion plus 1VD	279 (61.6)	58 (7.1)		217 (30.2)	94 (25.5)	26 (14.1)	
Left main lesion plus 2VD	0	408 (49.8)		208 (29.0)	136 (36.9)	64 (34.6)	
Left main lesion plus 3VD	0	348 (42.5)		142 (19.8)	111 (30.1)	95 (51.4)	
RCA involvement	48 (10.6)	471 (57.5)	<0.001	194 (27.0)	191 (51.8)	134 (72.4)	<0.001
Distal bifurcation involvement	257 (56.7)	646 (78.9)	<0.001	468 (65.2)	291 (78.9)	144 (77.8)	<0.001
SYNTAX score	18.3±6.8	24.6±8.9	<0.001	15.9±3.7	27.2±2.8	37.5±4.7	<0.001
Study stratum			<0.001				0.004
PRECOMBAT 1	92 (20.3)	235 (28.7)		156 (21.7)	111 (30.1)	60 (32.4)	
PRECOMBAT 2	165 (36.4)	169 (20.6)		188 (26.2)	104 (28.2)	42 (22.7)	
PRECOMBAT 3	92 (20.3)	203 (24.8)		176 (24.5)	81 (22.0)	38 (20.5)	
PRECOMBAT 4	104 (23.0)	212 (25.9)		198 (27.6)	73 (19.8)	45 (24.3)	
Extensive disease	NA	NA	NA	381 (53.1)	272 (73.7)	166 (89.7)	<0.001

Data are shown as medians (interquartile ranges) or numbers (%). LVEF indicates left ventricular ejection fraction; NA, not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RCA, right coronary artery; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery Study; and VD, vessel disease.

their counterparts to have diabetes mellitus, hypertension, peripheral vascular disease, and a lower left ventricular ejection fraction.

Angiographic Classifications and Procedural Characteristics

The distributions of the individual SYNTAX scores according to the angiographic classifications are depicted in Figure 3. Of the patients with limited left main CAD, 116 (25.6%) were in the intermediate and high SYNTAX score tertiles; of those with extensive left main CAD, 381 (46.5%) were classified in the low SYNTAX score tertile. The 2-stent strategy was used in only 1 patient with limited left main CAD but was used in 41.1% of those with extensive left main CAD. In contrast, the 2-stent strategy was used to a similar degree across all of SYNTAX score tertiles (Table 2). Complete revascularization (ie, successful stenting of all vessels ≥2.5 mm in diameter with stenosis ≥70%) was more frequently achieved in patients with both limited left main CAD and low SYNTAX scores.

Clinical Outcomes

During the follow-up period (median, 38 months; interquartile range, 36–61 months), MACE occurred in 239 patients (18.8%). There were 96 deaths (7.5%), 24 myocardial infarctions (1.9%), and 19 strokes (1.5%). Repeat revascularization was performed in 148 patients (11.6%), of whom 98 received target-lesion revascularization and 53 received new-lesion revascularization.

The Kaplan–Meier 3-year survival estimates for MACE and hard clinical outcomes are shown in Figure 4. The cumulative rates of MACE considerably differed between patients with low and those with intermediate or high SYNTAX score but did not differ between patients with intermediate and those with high SYNTAX score. A similar finding was observed for the composite outcome of death or myocardial infarction. In contrast, there was a significantly higher rate of MACE in patients with extensive left main CAD than in those with limited left main CAD (16.0% versus 8.5% at 3 years; $P<0.001$). Similarly, the rates of a composite of death or myocardial infarction differed significantly between these 2 groups (9.3% versus 3.6%; $P<0.001$). In addition, compared with patients with limited left main CAD, those with extensive left main CAD had significantly higher cumulative rates of mortality (9.6% versus 3.8%; $P<0.001$) and repeat revascularization (14.5% versus 6.4%; $P<0.001$). There was also a strong trend toward a higher rate of myocardial infarction in the extensive left main CAD group (2.4% versus 0.9%; $P=0.07$).

Clinical outcomes after adjusting for possible confounders using the Cox regression model are summarized in Table 3. The risk of MACE was significantly higher in patients with extensive disease than those with limited left main CAD (adjusted hazard ratio, 2.13; 95% confidence interval [CI], 1.54–2.94; $P<0.001$). The adjusted risks for the composite of death or myocardial infarction were also significantly higher in patients with extensive left main CAD (adjusted hazard ratio, 1.75; 95% CI, 1.08–2.85; $P=0.02$), which was largely attributable to higher risk of death (adjusted hazard ratio, 1.79; 95% CI, 1.04–3.07; $P=0.04$). Although there was a significant trend (P for trend=0.03) of the adjusted risk of MACE according to the SYNTAX score–stratified subgroups, the risk was significantly higher in patients with intermediate SYNTAX score but not in patients with high SYNTAX score, compared with those with low SYNTAX score. Overall, the risks of secondary outcomes did not significantly differ between groups stratified by SYNTAX score tertiles. The results were obvious when patients were divided into 2 groups by SYNTAX scores (low to intermediate [0–32] versus high [≥32]; Table II in the Data Supplement). For the primary outcome of MACE, the optimism-corrected c-index of the final model including only clinical risk factors was 0.638 (95% CI, 0.597–0.678). Adding SYNTAX score tertiles and simple angiographic

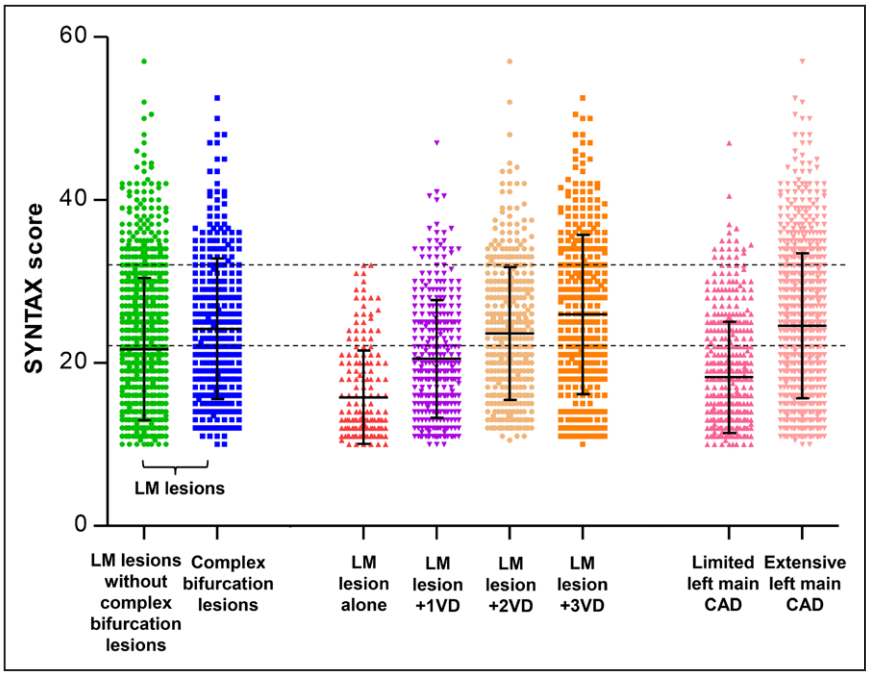

Figure 3. Distribution of individual SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Study) scores. Upper and lower dotted line correlates with SYNTAX score of 32 and 22, respectively. Complex bifurcation lesions refer to left main bifurcation lesions with a significant involvement in the ostium of left circumflex artery. CAD indicates coronary artery disease; LM, left main; and VD, vessel disease.

Table 2. Procedural Characteristics

	Limited Disease Group (n=453)	Extensive Disease Group (n=819)	*P* Value	SYNTAX Score ≤22 (n=718)	SYNTAX Score 23–32 (n=369)	SYNTAX Score >32 (n=185)	*P* Value
Stent technique			<0.001				<0.001
Left main stenting only	145 (32.0)	98 (12.0)		188 (26.2)	44 (11.9)	11 (5.9)	
Simple crossover technique	307 (67.8)	384 (46.9)		365 (50.8)	214 (58.0)	113 (61.1)	
Two-stent technique	1 (0.2)	337 (41.1)		165 (23.0)	111 (30.1)	61 (33.0)	
Final kissing balloon	64 (14.1)	420 (51.3)	<0.001	235 (32.7)	156 (42.3)	93 (50.3)	<0.001
No. of stents in LMCA	1.3±0.6	1.9±0.9	<0.001	1.4±0.7	1.9±0.8	2.1±1.1	<0.001
Stent length in LMCA	30.2±19.1	47.5±26.2	<0.001	32.5±19.1	50.6±26.4	57.0±30.0	<0.001
Total stent number per patient	1.6±0.9	2.7±1.2	<0.001	1.8±1.0	2.7±1.1	3.2±1.5	<0.001
Use of intravascular ultrasound	415 (91.6)	708 (86.4)	0.008	645 (89.8)	319 (86.4)	159 (85.9)	0.15
Complete revascularization	373 (82.3)	458 (55.9)	<0.001	517 (72.0)	218 (59.1)	96 (51.9)	<0.001

LMCA indicates left main coronary artery; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Study.

classification to clinical risk factors resulted in an increase in the c-index by 0.01 (0.648; 95% CI, 0.609–0.688) and 0.026 (0.664; 95% CI, 0.626–0.701), respectively. The optimism-corrected c-index of the model involving simple angiographic classification (0.753; 95% CI, 0.707–0.799) was also higher than that involving SYNTAX score tertiles (0.742; 95% CI, 0.695–0.789) for the composite outcome of death or myocardial infarction.

Comparison With CABG Patients

A total of 272 patients who underwent CABG for left main CAD were identified in the pooled databases of

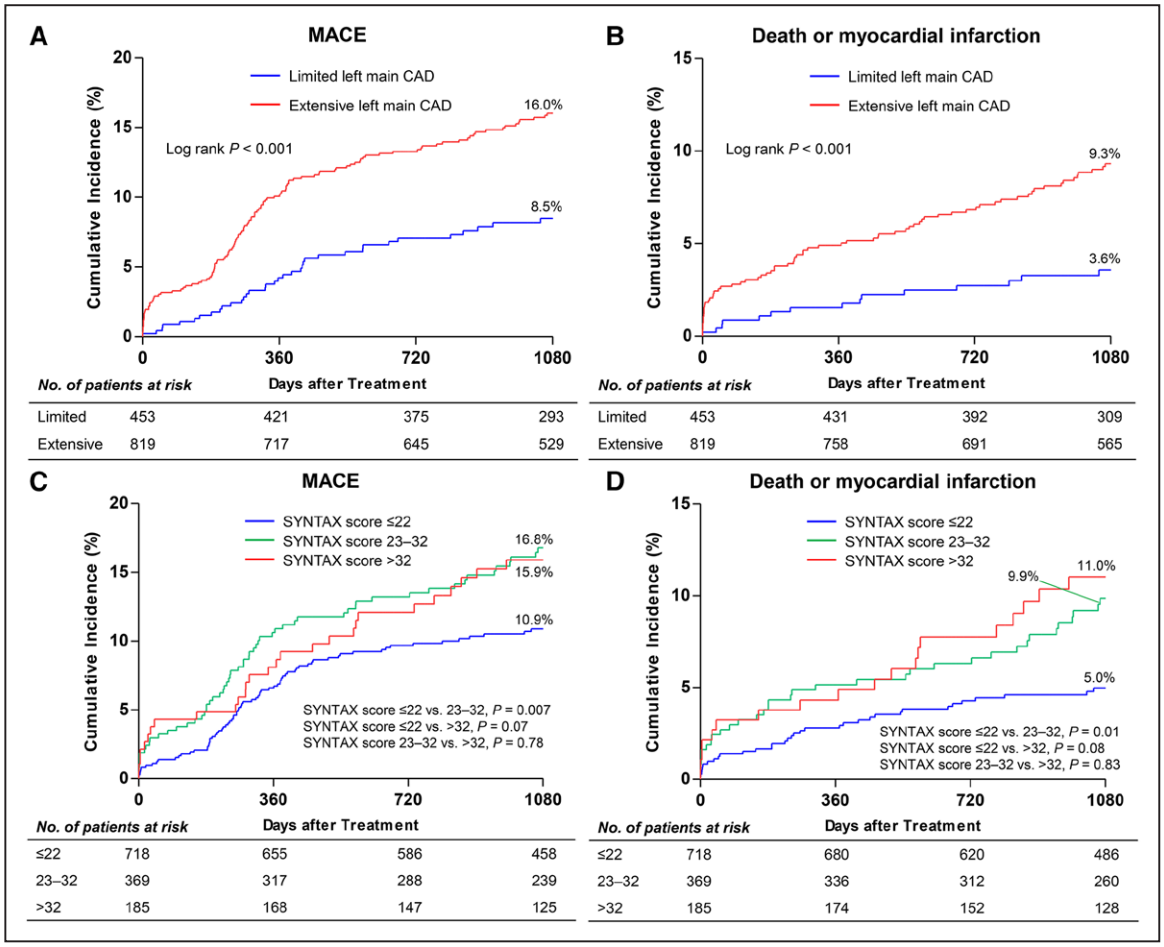

Figure 4. Kaplan–Meier curves for clinical outcomes. The cumulative incidences of major adverse cardiac event (MACE) and a composite of death or myocardial infarction are shown according to the classification of left main coronary artery disease (CAD) as limited or extensive (**A** and **B**) and the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score tertiles (**C** and **D**). *P* values were calculated using the log-rank test with all available follow-up data. Percentages denote 3-year event rates.

Table 3. Crude and Adjusted Hazard Ratios for Clinical Outcomes

Outcome	Subgroup	Rates (%) at 3 y	Crude		Adjusted	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
MACE	Limited CAD	8.5	1		1	
	Extensive CAD	16.0	2.18 (1.59–3.00)	<0.001	2.13 (1.54–2.94)	<0.001
Death or MI	Limited CAD	3.6	1		1	
	Extensive CAD	9.3	2.35 (1.46–3.77)	<0.001	1.75 (1.08–2.85)	0.02
Death	Limited CAD	2.9	1		1	
	Extensive CAD	8.1	2.51 (1.49–4.24)	<0.001	1.79 (1.04–3.07)	0.04
MI	Limited CAD	0.7	1		1	
	Extensive CAD	2.1	2.70 (0.92–7.89)	0.07	2.63 (0.88–7.82)	0.08
Repeat revascularization	Limited CAD	5.0	1		1	
	Extensive CAD	8.3	2.26 (1.50–3.39)	<0.001	2.60 (1.71–3.93)	<0.001
MACE	SYNTAX score ≤22	10.9	1	0.02*	1	0.03*
	SYNTAX score 23–32	16.8	1.47 (1.11–1.95)	0.01	1.45 (1.08–1.93)	0.01
	SYNTAX score >32	15.9	1.39 (0.98–1.98)	0.06	1.36 (0.95–1.96)	0.10
Death or MI	SYNTAX score ≤22	5.0	1	0.02*	1	0.43*
	SYNTAX score 23–32	9.9	1.71 (1.13–2.58)	0.01	1.35 (0.89–2.06)	0.16
	SYNTAX score >32	11.0	1.60 (0.95–2.68)	0.08	1.14 (0.66–1.95)	0.65
Death	SYNTAX score ≤22	4.3	1	0.02*	1	0.37*
	SYNTAX score 23–32	8.2	1.67 (1.07–2.61)	0.03	1.25 (0.79–1.97)	0.35
	SYNTAX score >32	9.8	1.71 (0.99–2.95)	0.06	1.24 (0.70–2.23)	0.46
MI	SYNTAX score ≤22	1.0	1	0.68*	1	0.69*
	SYNTAX score 23–32	2.8	2.21 (0.95–5.13)	0.06	2.18 (0.93–5.11)	0.07
	SYNTAX score >32	1.3	0.72 (0.16–3.30)	0.67	0.73 (0.16–3.39)	0.69
Repeat revascularization	SYNTAX score ≤22	6.8	1	0.34*	1	0.10*
	SYNTAX score 23–32	8.3	1.27 (0.89–1.83)	0.19	1.46 (1.01–2.12)	0.05
	SYNTAX score >32	5.7	1.16 (0.74–1.83)	0.52	1.35 (0.84–2.15)	0.22

Hazard ratios are for extensive left main CAD vs limited left main CAD.

CAD indicates coronary artery disease; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Study.

**P* for trend.

PRECOMBAT trials. The mean SYNTAX score for these patients was 26.3±10.3, with 96 (35.3%), 103 (37.9%), and 73 (26.8%) of the patients classified as having low, intermediate, and high SYNTAX scores, respectively. When categorized according to the proposed angiographic classification, 232 patients (85.3%) and 40 patients (14.7%) were classified as having extensive and limited left main CAD, respectively. The cumulative MACE rate in the CABG patients was closer to that in the PCI patients with limited left main CAD than in those with low SYNTAX scores (Figure I in the Data Supplement). The risk for the composite of death or myocardial infarction was lower, although not significantly so, in those with limited left main CAD compared with the CABG patients and higher in those with the extensive disease; in contrast, the risks were numerically higher in all 3 SYNTAX score–stratified subgroups (Table III in the Data Supplement).

Discussion

In this pooled patient-level analysis, the proposed simple angiographic classification provided better discrimination than the SYNTAX score with regard to future MACE in patients with left main CAD undergoing DES implantation. Limited left main CAD was associated with a significantly lower rate of both MACE and the composite safety outcome compared with extensive left main CAD. In contrast, although there was a trend toward higher rates of MACE according to the SYNTAX score–stratified groups, significant difference remained only between patients with low and intermediate SYNTAX score. There was no significant difference between the SYNTAX score tertile groups in the rates of the composite outcome of death or myocardial infarction. These findings suggest that our simple anatomic classification could be used to separate patients with left main CAD into low-risk and high-risk PCI groups, which could help guide the revascularization strategy for such patients.

The SYNTAX score quantifies CAD complexity, taking into account several angiographic factors, including the number and location of significant lesions, as well as parameters that reflect the lesion-independent complexity.[11] This scoring system was originally developed because the pre-existing classifications were relatively simplistic. Its predictive value for left main CAD was assessed by a subgroup analysis of the SYNTAX trial and other nonrandomized studies, showing conflicting results.[6,14,19,20] Although it represents a valuable tool for optimizing revascularization strategy decisions, several practical issues have been raised in the current PCI era. First, calculation of a patient's SYNTAX score is complicated and time consuming and requires a certain degree of expertise, making it impractical for clinical use. Furthermore, interobserver agreement in the visual SYNTAX score assessment is poor although this improves with extensive training. In the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial, which was intended for patients with a site-determined SYNTAX score ≤32, 24% of the patients had SYNTAX scores ≥33 according to the angiographic core laboratory analysis.[15] Furthermore, a considerable number of patients were reclassified to different SYNTAX score tertiles (41% of patients with low SYNTAX scores were reclassified as having intermediate or high SYNTAX score tertiles, and 40% of patients with intermediate SYNTAX scores were reclassified as having high SYNTAX scores); this suggests that SYNTAX scores may have limited clinical applicability. Second, PCI practices have significantly changed since the time that the SYNTAX scoring system was developed. Small vessels, generally those with a diameter ≤2.0 mm, are currently not considered large enough for stenting. In addition, stenting in lesions with diameter stenosis of 50% to 70% has become less frequent because these lesions are now commonly known to have functional insignificance.[21] However, SYNTAX scores are still used for vessels >1.5 mm and for all lesions with diameter stenosis >50%, which are defined as significant. Third, although various angiographic parameters that imply lesion complexity are considered in the SYNTAX score calculation, a single numeric SYNTAX score contains no information about technical feasibility. In the present study, there was a considerable overlap in SYNTAX scores between patients with and without complex left main bifurcation lesions and thus poor discrimination of outcomes after DES implantation. This is of particular importance for distal left main CAD because the single-stent crossover technique is associated with more favorable outcomes than the more complex 2-stent technique.[22] In recent large randomized trials,[13,15] there were no significant interactions between treatment effects and the SYNTAX score, indicating that the SYNTAX scoring system may not be sufficiently accurate for guiding the revascularization strategy for left main CAD.

The angiographic morphology-based classification investigated in this study was developed according to accumulated evidence that the key anatomic predictors of future cardiovascular events after PCI are the total extent of other CAD and the presence of distal left main bifurcation lesions that would require a 2-stent approach.[22–25] Extensive left main CAD combines these 2 sets of adverse factors, and the risk of MACE for extensive left main CAD was double that for limited left main CAD. In contrast, SYNTAX scores did not effectively stratify the outcome measures evaluated in our study. A possible explanation may be the differences between the groups in each classification in the need for complex bifurcation stenting and the probability of achieving complete revascularization.[26] The 2-stent technique was frequently used for patients with extensive left main CAD; only 1 patient with limited left main CAD underwent this technique. In contrast, the frequency of the 2-stent approach did not differ significantly across the SYNTAX score subgroups. Furthermore, the difference in the complete revascularization rate was greater between the groups according to the simplified angiographic classification than between the SYNTAX score–based groups. In the analyses that included the PRECOMBAT trial CABG patients, PCI and CABG showed similar outcomes for patients with limited left main CAD, indicating that PCI could be considered a reasonable alternative to CABG for this specific anatomic subset. However, CABG may be the preferred revascularization strategy for patients with extensive left main CAD. Indeed, this concept was partially supported by a recent analysis of pooled data from SYNTAX and PRECOMBAT randomized trials.[25] Finally, complex risk models are often not used in real-world practice because of their perceived complexity involving multiple variables.[24] In this regard, our simple anatomic approach could be useful for guiding the choice of revascularization strategy for patients with left main CAD.

This study had several limitations. First, it was an observational study, and the influences of unmeasured confounding factors and selection bias could not be eliminated even after statistical adjustments; these may have contributed to the observed differences. However, the series of 4 PRECOMBAT studies used the same inclusion/exclusion criteria with prospective enrollment, contributing to a reduction in serious selection bias. Second, progressive improvements in procedural techniques, devices, and medical treatments throughout the long enrollment period should be considered; these may have introduced differences between the groups. Third, although our post hoc analyses were according to lesion anatomy and complexity predicting PCI outcomes but not surgical outcomes well, the usefulness of each classification for guiding revascularization strategy should be tested with subgroups of CABG counterparts. This was not possible in our study because of the small number of CABG patients. Finally, ≈3 years of clinical follow-up may not be sufficient for evaluating the overall performance of PCI.

Conclusions

Compared with the SYNTAX score–based approach, a simplified angiographic morphology-based approach that incorporated details of left main bifurcation lesions and the number of diseased vessels better predicted the complexity of procedure and outcomes after DES implantation. Our approach may offer a simple and practical guide to inform decisions about revascularization strategies for left main CAD.

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Disclosures

None.

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Comparison of a Simple Angiographic Approach With a Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Score–Based Approach for Left Main Coronary Artery Stenting: A Pooled Analysis of Serial PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) Studies

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SUPPLEMENTAL MATERIAL

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I. Supplemental Tables

Supplemental Table 1: **Final models for Table 3**

		P value	HR	95% LL	95% UL
Death					
	Extensive CAD (vs. Limited CAD)	0.035	1.788	1.043	3.066
	Age	<0.001	1.060	1.036	1.085
	Diabetes	0.002	1.900	1.261	2.862
	Hypercholesterolemia	0.062	0.677	0.450	1.020
	Chronic kidney disease	<0.001	3.571	1.938	6.580
	Left ventricular ejection fraction	<0.001	0.955	0.939	0.972
	Atrial fibrillation	0.038	2.123	1.044	4.316
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.464	0.777	0.396	1.526
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.445	1.246	0.709	2.190
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.223	1.462	0.794	2.692
MI					
	Extensive CAD (vs. Limited CAD)	0.083	2.626	0.882	7.821
	Hypertension	0.019	4.283	1.272	14.419
	Hypercholesterolemia	0.189	0.577	0.254	1.312
	History of heart failure	0.014	6.388	1.452	28.114
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.501	1.553	0.432	5.586
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.229	2.045	0.638	6.555
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.281	2.020	0.563	7.247
Repeat Revascularization					
	Extensive CAD (vs. Limited CAD)	<0.001	2.595	1.714	3.929
	Age	<0.001	0.970	0.954	0.985
	Left ventricular ejection fraction	0.407	0.992	0.974	1.011
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.036	1.586	1.031	2.441
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.069	1.587	0.965	2.609
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.016	1.940	1.131	3.328
Death or MI					
	Extensive CAD (vs. Limited CAD)	0.024	1.750	1.076	2.849
	Age	<0.001	1.054	1.032	1.076
	Diabetes	0.011	1.632	1.119	2.380
	Hypercholesterolemia	0.037	0.669	0.458	0.977

	Chronic kidney disease	<0.001	3.190	1.755	5.796
	Left ventricular ejection fraction	<0.001	0.956	0.941	0.972
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.555	0.834	0.456	1.524
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.554	1.171	0.694	1.977
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.172	1.473	0.845	2.570
MACE					
	Extensive CAD (vs. Limited CAD)	<0.001	2.129	1.542	2.939
	Hypertension	0.041	1.331	1.012	1.752
	Hypercholesterolemia	0.005	0.691	0.533	0.896
	History of heart failure	0.014	2.295	1.185	4.443
	Chronic kidney disease	<0.001	2.724	1.594	4.656
	Left ventricular ejection fraction	<0.001	0.974	0.961	0.986
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.164	1.298	0.899	1.873
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.082	0.399	0.958	2.042
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.008	1.731	1.155	2.596
Death					
	SYNTAX G1 (vs. SYNTAX G0)	0.346	1.246	0.789	1.969
	SYNTAX G2 (vs. SYNTAX G0)	0.462	1.244	0.695	2.225
	Age	<0.001	1.061	1.036	1.086
	Diabetes	0.003	1.883	1.248	2.841
	Hypercholesterolemia	0.044	0.656	0.435	0.989
	Chronic kidney disease	<0.001	3.572	1.901	6.709
	Left ventricular ejection fraction	<0.001	0.955	0.938	0.972
	Atrial fibrillation	0.033	2.177	1.066	4.450
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.260	0.682	0.350	1.327
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.458	1.241	0.702	2.193
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.201	1.495	0.808	2.767
MI					
	SYNTAX G1 (vs. SYNTAX G0)	0.074	2.176	0.926	5.114
	SYNTAX G2 (vs. SYNTAX G0)	0.691	0.733	0.159	3.387
	Hypertension	0.023	4.118	1.215	13.963
	Hypercholesterolemia	0.158	0.551	0.241	1.260
	History of heart failure	0.022	5.789	1.293	25.923
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.694	1.289	0.363	4.574
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.234	2.040	0.631	6.597
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.277	2.038	0.564	7.362

Repeat Revascularization					
	SYNTAX G1 (vs. SYNTAX G0)	0.047	1.461	1.005	2.124
	SYNTAX G2 (vs. SYNTAX G0)	0.218	1.345	0.840	2.153
	Age	<0.001	0.973	0.957	0.988
	Left ventricular ejection fraction	0.354	0.991	0.973	1.010
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.139	1.384	0.900	2.127
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.050	1.654	0.999	2.738
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.015	1.961	1.137	3.382
Death or MI					
	SYNTAX G1 (vs. SYNTAX G0)	0.156	1.354	0.891	2.060
	SYNTAX G2 (vs. SYNTAX G0)	0.646	1.135	0.660	1.952
	Age	<0.001	1.055	1.033	1.078
	Diabetes	0.011	1.636	1.120	2.391
	Hypercholesterolemia	0.026	0.650	0.444	0.950
	Chronic kidney disease	<0.001	3.073	1.666	5.666
	Left ventricular ejection fraction	<0.001	0.956	0.940	0.972
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.308	0.734	0.404	1.331
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.577	1.162	0.685	1.971
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.168	1.486	0.847	2.607
MACE					
	SYNTAX G1 (vs. SYNTAX G0)	0.013	1.446	1.080	1.934
	SYNTAX G2 (vs. SYNTAX G0)	0.097	1.361	0.946	1.957
	Hypertension	0.065	1.299	0.984	1.716
	Hypercholesterolemia	0.004	0.679	0.523	0.882
	History of heart failure	0.017	2.253	1.159	4.381
	Chronic kidney disease	<0.001	2.634	1.530	4.536
	Left ventricular ejection fraction	<0.001	0.973	0.961	0.986
	PRECOMBAT 2 (vs. PRECOMBAT 1)	0.476	1.141	0.793	1.643
	PRECOMBAT 3 (vs. PRECOMBAT 1)	0.054	1.456	0.994	2.133
	PRECOMBAT 4 (vs. PRECOMBAT 1)	0.006	1.782	1.185	2.681

SYNTAX G0 indicates group of SYNTAX score≤22, SYNTAX G1 indicates group of SYNTAX score 23–32, and SYNTAX G2 indicates group of SYNTAX score >32

Supplemental Table 2: **Crude and adjusted hazard ratios according to groups stratified by SYNTAX scores of 0−32 and ≥32**

Outcome	Subgroup	Rates (%) at 3 years	Crude		Adjusted	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Death or MI	Limited CAD	3.6	1		1	
	Extensive CAD	9.3	2.35 (1.46–3.77)	<0.001	1.75 (1.08–2.85)	0.02
MACE	Limited CAD	8.5	1		1	
	Extensive CAD	16.0	2.18 (1.59–3.00)	<0.001	2.13 (1.54–2.94)	<0.001
Death or MI	SYNTAX score 0–32	6.7	1		1	
	SYNTAX score >32	11.0	1.27 (0.79–2.05)	0.32	1.01 (0.61–1.63)	0.98
MACE	SYNTAX score 0–32	12.9	1		1	
	SYNTAX score >32	15.9	1.19 (0.86–1.64)	0.30	1.15 (0.82–1.61)	0.41

CAD indicates coronary artery disease; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery study

Supplemental Table 3: **Crude and adjusted hazard ratios for the clinical outcomes (with CABG patients as the reference)**

	Subgroup	Crude		Adjusted	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
MACE	CABG	1		1	
	Limited left main CAD	1.40 (0.89–2.19)	0.14	1.21 (0.74–1.97)	0.46
	Extensive left main CAD	3.07 (2.11–4.47)	<0.001	2.58 (1.70–3.92)	<0.001
Death or myocardial infarction	CABG	1		1	
	Limited left main CAD	0.74 (0.41–1.35)	0.32	0.77 (0.39–1.53)	0.45
	Extensive left main CAD	1.74 (1.10–2.77)	0.02	1.34 (0.77–2.31)	0.30
MACE (by SYNTAX scores)	CABG	1		1	
	0–22	2.03 (1.37–3.02)	<0.001	1.77 (1.13–2.77)	0.01
	23–32	2.98 (1.99–4.45)	<0.001	2.56 (1.65–3.99)	<0.001
	≥33	2.87 (1.83–4.52)	<0.001	2.45 (1.51–3.97)	<0.001
Death or myocardial infarction (by SYNTAX scores)	CABG	1		1	
	0–22	1.06 (0.64–1.76)	0.82	1.05 (0.58–1.91)	0.87
	23–32	1.82 (1.09–3.02)	0.02	1.43 (0.79–2.59)	0.24
	≥33	1.71 (0.94–3.10)	0.08	1.18 (0.61–2.27)	0.63

CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MACE, *major* adverse cardiac event (the composite of death, myocardial infarction, or repeat revascularization); SYNTAX = Synergy Between Percutaneous Coronary

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Supplemental Table 4: **Final Cox models including both the simple angiographic and SYNTAX score based classification as a variable**

	P value	HR	95% LL	95% UL
MACE				
Extensive CAD (vs. Limited CAD)	<0.001	2.036	1.468	2.825
SYNTAX G1 (vs. SYNTAX G0)	0.199	1.211	0.904	1.623
SYNTAX G2 (vs. SYNTAX G0)	0.832	1.041	0.719	1.507
Hypertension	0.026	1.367	1.038	1.799
Hypercholesterolemia	0.011	0.715	0.552	0.925
History of heart failure	0.008	2.435	1.259	4.708
Chronic kidney disease	<0.001	2.888	1.693	4.926
Left ventricular ejection fraction	<0.001	0.973	0.960	0.985
Death or MI				
Extensive CAD (vs. Limited CAD)	0.017	1.813	1.111	2.960
SYNTAX G1 (vs. SYNTAX G0)	0.328	1.235	0.809	1.883
SYNTAX G2 (vs. SYNTAX G0)	0.942	0.980	0.564	1.703
Age	<0.001	1.054	1.032	1.076
Diabetes	0.010	1.640	1.124	2.392
Hypercholesterolemia	0.031	0.659	0.452	0.962
Chronic kidney disease	<0.001	3.177	1.735	5.818
Left ventricular ejection fraction	<0.001	0.956	0.941	0.972
Study stratum	0.136	1.153	0.956	1.391

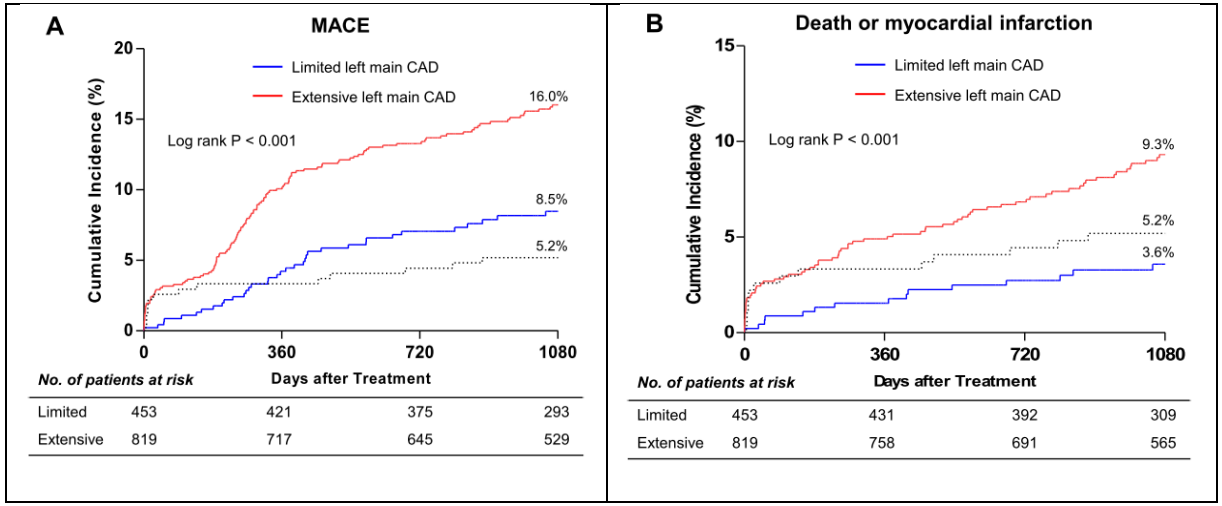
SYNTAX G0 indicates group of SYNTAX score ≤22, SYNTAX G1 indicates group of SYNTAX score 23–32, SYNTAX G2 indicates group of SYNTAX score >32

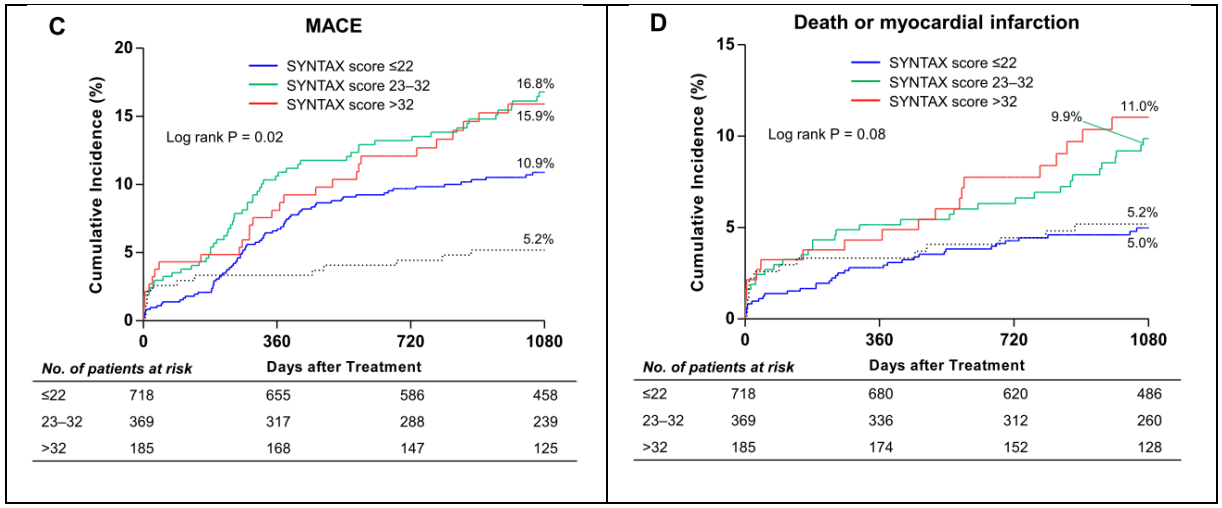
II. Supplemental Figure

Supplemental Figure 1: Kaplan–Meier curves for clinical outcomes including CABG patients from the PRECOMBAT trial.

The cumulative incidences of MACE and a composite of death or myocardial infarction are shown according to the classification of left main CAD as limited or extensive (A, B) and the SYNTAX score tertiles (C, D). P-values were calculated using the log-rank test with all available follow-up data. Percentages denote 3-year event rates. The black dashed line shows the event curves for CABG patients enrolled in the PRECOMBAT trial.

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MACE = major adverse cardiac events; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery study




C
MACE
Cumulative Incidence (%)
SYNTAX score ≤22
SYNTAX score 23–32
SYNTAX score >32
Log rank P = 0.02
16.8%
15.9%
10.9%
5.2%
0
5
10
15
20
0
360
720
1080
No. of patients at risk
Days after Treatment
≤22 718 655 586 458
23–32 369 317 288 239
>32 185 168 147 125
D
Death or myocardial infarction
Cumulative Incidence (%)
SYNTAX score ≤22
SYNTAX score 23–32
SYNTAX score >32
Log rank P = 0.08
11.0%
9.9%
5.2%
5.0%
0
5
10
15
0
360
720
1080
No. of patients at risk
Days after Treatment
≤22 718 680 620 486
23–32 369 336 312 260
>32 185 174 152 128

Supplemental Figure 2: Kaplan-Meier curves according to patients stratified by SYNTAX scores of 0−32 and ≥32

The cumulative incidences of endpoints are shown according to groups of low/intermediate (0−32) and high (≥32) SYNTAX scores. P-values were calculated using the log-rank test with all available follow-up data. Percentages denote 3-year event rates. The black dashed line shows the event curves for CABG patients enrolled in the PRECOMBAT trial.

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MACE = major adverse cardiac events (a composite of death, MI, or RR); SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery study.