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Impact of SYNTAX Score on 10-Year Outcomes After Revascularization for Left Main Coronary Artery Disease

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the long-term impact of SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) on differential outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for left main coronary artery (LMCA) disease.

BACKGROUND The very long term prognostic effect of SS on mortality and major cardiovascular events after LMCA revascularization is still undetermined.

METHODS In the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry, patients with baseline SS measurements were analyzed. The 10-year rates of all-cause mortality, the composite of death, Q-wave myocardial infarction, or stroke, and target vessel revascularization after PCI or CABG were compared according to baseline SS.

RESULTS Among 1,580 patients with baseline SS, 547 patients (34.6%) had low SS (≤22), 350 (22.2%) had intermediate SS (23 to 32), and 683 (43.2%) had high SS (≥33). In patients with low to intermediate SS, the adjusted 10-year risks for death and serious composite outcome were similar between the PCI group and the CABG group. However, in patients with high SS, PCI with stenting, compared with CABG, was associated with a higher risk for death (hazard ratio: 1.39; 95% confidence interval: 1.00 to 1.92; p = 0.048) and serious composite outcome (hazard ratio: 1.27; 95% confidence interval: 0.94 to 1.74; p = 0.123). In each revascularization group, conventional tertiles of SS had a differential prognostic impact on 10-year clinical outcomes in the PCI arm but not in the CABG arm.

CONCLUSIONS In this 10-year extended follow-up of patients undergoing LMCA revascularization, CABG showed a clear prognostic benefit over PCI in patients with high anatomic complexity measured by SS at baseline. The discriminative capacity of SS on long-term outcomes was relevant in the PCI group but not in the CABG group. (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease [MAIN-COMPARE]; NCT02791412) (J Am Coll Cardiol Intv 2020;13:361–71) © 2020 by the American College of Cardiology Foundation.

Over the past decade, several randomized clinical trials and observational registries have evaluated whether percutaneous coronary intervention (PCI) with stenting is as an effective form of myocardial revascularization as coronary artery bypass grafting (CABG) for the treatment of left main coronary artery (LMCA) disease (1–4). Recent evidence supports that PCI is a safe and effective alternative to CABG in patients with LMCA disease with low to intermediate anatomic complexity (5,6).

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) was developed to assess anatomic complexity and to reflect the overall level of atherosclerotic plaque burden (7,8). On the basis of the

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CAD = coronary artery disease

DES = drug-eluting stent(s)

IPTW = inverse-probability treatment weighting

LMCA = left main coronary artery

MI = myocardial infarction

PCI = percutaneous coronary intervention

SS = SYNTAX score(s)

TVR = target vessel revascularization

clinical utility of the anatomic SS, current U.S. and European guidelines advocate use of the SS for deciding on optimal revascularization strategy for patients with LMCA disease (9,10). However, 2 recent randomized clinical trials, 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), showed limited clinical performance of SS to differentiate comparative outcomes after PCI and CABG (5,11). However, these trials enrolled patients with relatively less complex anatomy (i.e., low to intermediate SS), and thus those results did not reflect a "real-world" population with a diverse spectrum of SS. Furthermore, follow-up duration <5 years is not sufficient to determine the long-term effect of revascularization strategies.

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We therefore sought to investigate the clinical impact of SS on 10-year mortality and major adverse events in an unrestricted, real-world population undergoing PCI or CABG for unprotected LMCA disease using the extended follow-up of the MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) registry (12).

METHODS

STUDY DESIGN AND POPULATION. The design, inclusion criteria, and results of the MAIN-COMPARE study have been published previously (13–15). Briefly, the MAIN-COMPARE study included consecutive patients with unprotected LMCA disease (stenosis >50%) who underwent PCI or CABG at 12 major cardiac centers in Korea between January 2000 and June 2006. Patients with previous CABG, concomitant valve or aortic surgery, or ST-segment elevation myocardial infarction (MI) or cardiogenic shock at presentation were excluded. The final 10-year report of the MAIN-COMPARE study was published recently (12).

Treatment strategy for LMCA disease between either PCI or CABG was at the discretion of attending cardiologists or cardiac surgeons, with careful consideration of clinical and anatomic factors and patient preference. Clinical and anatomic conditions favoring either PCI or CABG were described previously (12–14), and all procedures or surgery were guided by standard techniques and management. Because of device availability, bare-metal stents (BMS) were used between January 2000 and May 2003, while drug-eluting stents (DES) were used between May 2003 and June 2006 in the study population. Antiplatelet therapy and periprocedural anticoagulation were prescribed according to accepted guidelines. During follow-up, patient management, including medical treatment, was performed in accordance with accepted guidelines and established standards of care. There was no industry involvement in the design, conduct, or analysis of this study. Local ethics committees at participating hospitals approved the use of clinical data for this study, and all patients provided written informed consent.

SS CALCULATION AND CATEGORIZATION. The SS for each patient was calculated retrospectively by scoring all coronary lesions with diameter stenosis >50%, in vessels with diameter >1.5 mm, using the SS algorithm, as recommended (7,16). The calculation was done using an openly accessible web-based score calculator (http://www.syntaxscore.com). The core laboratory analysts who calculated SS were blinded to baseline demographics, treatment allocation, and clinical outcomes. The interoperator variability for SS measurement has been previously described in detail (17). Study subjects were categorized into tertiles on the basis of baseline SS, which were low (≤22), intermediate (23 to 32), and high (≥33). To compare treatment effects of PCI and CABG, patients were divided into 2 groups (low to intermediate SS vs. high SS), which was consistent with current guidelines of myocardial revascularization (9,10).

ENDPOINTS AND FOLLOW-UP. The study endpoints were death from any cause; the composite of death, Q-wave MI, or stroke; and target vessel revascularization (TVR). Q-wave MI was defined as the development of any new pathological Q waves after the index treatment. Stroke was confirmed by neurologists with clinical symptoms and neurological imaging. TVR was defined as any repeat revascularization of the treated vessels, including any segments of the left anterior descending coronary artery and/or the left circumflex coronary artery. All clinical events were confirmed by source documentation collected at each hospital and centrally adjudicated by an independent group of clinicians unaware of the type of index procedure.

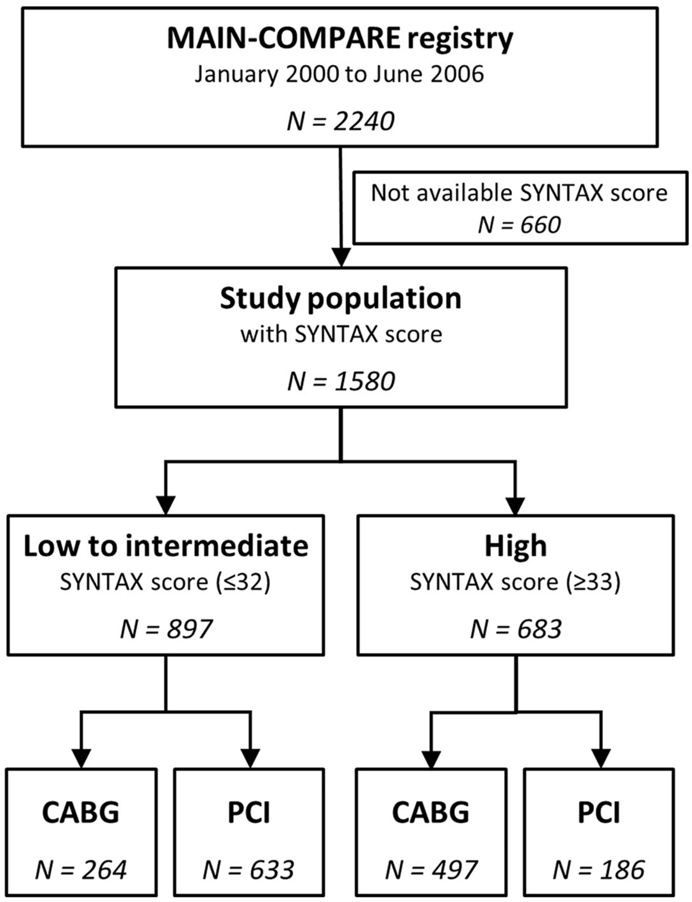
The recommended clinical follow-up was at 1 month, 6 months, 1 year, and annually thereafter. In the 10-year MAIN-COMPARE study, the follow-up period was extended through December 31, 2016, to ensure that all patients had the opportunity to be followed up for at least 10 years. Medical record review and telephone contact were used to complete follow-up data beyond 10 years. Complete information on vital status and date of death were obtained through December 31, 2016, from the National Population Registry of the Korea National Statistical Office on the basis of the unique 13-digit personal identification number all Korean citizens have. Detailed methods for data acquisition and management during extended follow-up have been reported elsewhere (12).

STATISTICAL ANALYSIS. Summary statistics are presented as percentages in the case of categorical variables and as mean ± SD in the case of continuous variables. Baseline characteristics of the patients were compared between treatment groups using the Pearson chi-square test for categorical variables and Student's *t*-test for continuous variables. Event rates were based on Kaplan-Meier estimates in time-to-first event analyses and were compared using the log-rank test.

Inverse-probability treatment weighting (IPTW) based on propensity scores of patients was used as the primary tool to adjust for differences in the baseline characteristics between the PCI and CABG groups (18,19). The separated propensity scores were calculated for each low to intermediate SS group and high SS group. We examined the similarity of the baseline characteristics among treatment groups before and after IPTW (20). The standardized mean differences were analyzed to assess balance between PCI and CABG arms. The cumulative event curves were estimated using a weighted Kaplan-Meier method and with using IPTW (21). All available follow-up data were used for the long-term outcome analyses, without censoring clinical events beyond 10 years.

In addition, to assess the independent prognostic value of the 3 levels of the SS in each treatment arm of PCI and CABG, multivariate Cox regression analyses were used to adjust for clinically relevant covariates. Models were adjusted for wave; age; sex; presence of diabetes, hypertension, dyslipidemia, peripheral vascular disease, restenotic lesion, and chronic kidney disease; current smoking status; history of PCI, MI, and stroke; left ventricular ejection fraction; clinical presentation; extent of disease; and disease location. All reported p values are 2-sided, and p values <0.05 were considered to indicate statistical significance. No adjustments were made for multiple comparisons. All statistical analyses were performed with the use of the R software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 1 Study Flow Diagram

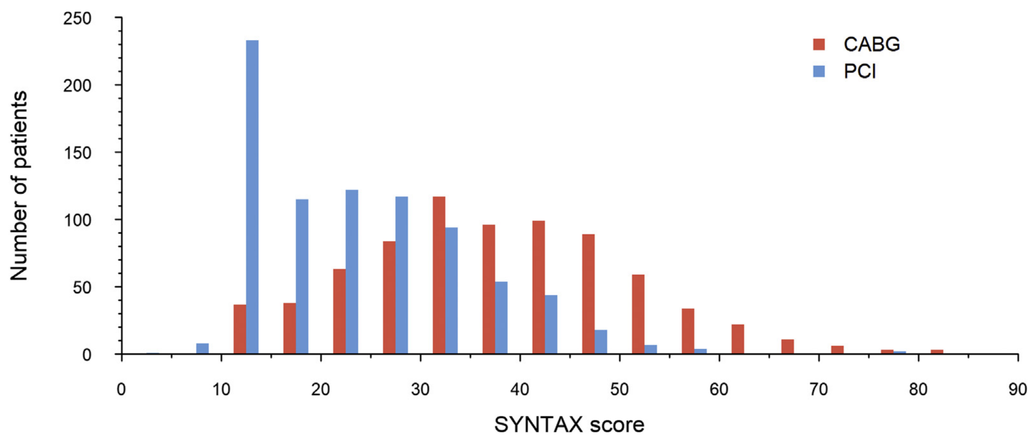


CABG = coronary artery bypass grafting; MAIN-COMPARE = Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

RESULTS

STUDY POPULATION AND SS. A total of 2,240 patients with unprotected LMCA disease were enrolled in the MAIN-COMPARE registry between January 2000 and June 2006. The SS was not available in 660 patients. Ultimately, a total of 1,580 patients were analyzed in this study (Figure 1). Of them, 897 patients (56.8%) were categorized into the low-to-intermediate SS group (547 [34.6%] with low SS [≤22] and 350 [22.2%] with intermediate SS [23 to 32]), and 683 (43.2%) patients were categorized into the high SS (≥33) group. In 897 patients with low to intermediate SS, 633 (71%) underwent PCI, and 264 (29%) underwent CABG. Among 683 patients with

FIGURE 2 The Distribution of SYNTAX Score in the Study Population



Abbreviations as in Figure 1.

high SS, 186 (27%) underwent PCI, and 497 (73%) underwent CABG.

The distribution of SS in study subjects is illustrated in Figure 2. The graph shows the right-skewed distribution of SS in the PCI arm, and bell-shaped distribution in the CABG arm. The median SS was 23.0 (interquartile range: 14.0 to 31.2) in patients who underwent PCI and 37.5 (interquartile range: 29.0 to 47.5) in patients who underwent CABG ($p < 0.001$).

CHARACTERISTICS OF THE STUDY POPULATION. The baseline clinical, anatomic, and procedural characteristics of PCI and CABG patients according to SS group are shown in Table 1 and Online Table 1. In general, patients undergoing CABG were more likely to have a higher risk for clinical and anatomic risk factors profiles (i.e., a higher incidence of current smoking, peripheral artery disease, or acute coronary syndrome, lower ejection fraction, and higher anatomic complexities involving distal LMCA involvement and more advanced extent of coronary artery disease [CAD]). This pattern was more prominent in the high SS group than in the low to intermediate SS group.

After adjustment with the use of IPTW, all the clinical covariates were well balanced (Table 2). The standardized mean differences were <0.1 for almost all variables, indicating that the PCI and CABG arms were balanced after adjustment.

COMPARATIVE 10-YEAR CLINICAL OUTCOMES ACCORDING TO SS GROUPS. The median follow-up duration was 11.8 years (interquartile range: 10.4 to 13.1 years) for the study population. The Kaplan-Meier event curves of clinical outcomes after PCI and CABG according to the SS groups are shown in Table 3 and Online Figure 1. Observed 10-year rates of mortality and the composite of death, Q-wave MI, or stroke were similar between patients who underwent CABG or PCI in the low to intermediate SS group. However, 10-year rates of death and serious composite outcome were significantly higher after PCI than after CABG in the high SS group. The rate of TVR was consistently higher after PCI than after CABG, in which the rate difference was more prominent in the high SS group.

The IPTW Kaplan-Meier event rates and curves for clinical outcomes are shown in Table 3 and the Central Illustration. In the low to intermediate SS group, the adjusted 10-year risks for death and composite of death, Q-wave MI, or stroke were similar between the PCI group and the CABG group. In the high SS group, PCI was associated with a significantly higher risk for 10-year mortality and tended toward a higher risk for serious composite outcome of death, Q-wave MI, or stroke. The risk for TVR was significantly higher after PCI, with a higher magnitude of risk in the high SS group. When stratified analyses were performed in each time period of BMS era and DES era, the adjusted risks for death and serious composite outcome were higher after DES implantation than after concurrent CABG (Online Table 2). This trend was not evident in the comparison of BMS and concurrent CABG.

PREDICTIVE VALUE OF SS IN EACH TREATMENT ARM. The 10-year rates of clinical outcomes stratified by SS tertile in each CABG and PCI arm are shown in

TABLE 1 Baseline Characteristics of Patients According to SYNTAX Score Category

	Low to Intermediate SYNTAX Score			High SYNTAX Score		
	CABG (n = 264)	PCI (n = 633)	p Value	CABG (n = 497)	PCI (n = 186)	p Value
Wave			<0.001			<0.001
BMS era (January 2000 to May 2003)	99 (37.5)	143 (22.6)		161 (32.4)	31 (16.7)	
DES era (May 2003 to June 2006)	165 (62.5)	490 (77.4)		336 (67.6)	155 (83.3)	
Age, yrs	61.0 ± 10.1	60.1 ± 11.6	0.270	63.9 ± 8.9	66.3 ± 10.1	0.004
Male	196 (74.2)	432 (68.2)	0.088	364 (73.2)	138 (74.2)	0.878
Diabetes	77 (29.2)	169 (26.7)	0.501	184 (37.0)	80 (43.0)	0.179
Hypertension	115 (43.6)	305 (48.2)	0.234	267 (53.7)	110 (59.1)	0.238
Dyslipidemia	77 (29.2)	188 (29.7)	0.937	206 (41.4)	70 (37.6)	0.414
Current smoker	92 (34.8)	167 (26.4)	0.014	133 (26.8)	28 (15.1)	0.002
Previous PCI	30 (11.4)	119 (18.8)	0.009	48 (9.7)	41 (22.0)	<0.001
Previous MI	25 (9.5)	47 (7.4)	0.372	57 (11.5)	21 (11.3)	>0.99
Previous CHF	7 (2.7)	11 (1.7)	0.530	17 (3.4)	6 (3.2)	>0.99
Chronic lung disease	6 (2.3)	13 (2.1)	>0.99	12 (2.4)	3 (1.6)	0.732
Cerebrovascular disease	12 (4.5)	45 (7.1)	0.199	46 (9.3)	19 (10.2)	0.815
Peripheral arterial disease	10 (3.8)	8 (1.3)	0.028	35 (7.0)	4 (2.2)	0.023
Renal failure	7 (2.7)	13 (2.1)	0.761	20 (4.0)	10 (5.4)	0.577
Ejection fraction	59.6 ± 11.1	61.1 ± 10.2	0.057	56.6 ± 12.2	59.1 ± 11.0	0.017
Clinical indication			0.203			<0.001
Silent ischemia	11 (4.2)	17 (2.7)		8 (1.6)	7 (3.8)	
Chronic stable angina	70 (26.5)	209 (33.0)		84 (16.9)	68 (36.6)	
Unstable angina	157 (59.5)	352 (55.6)		356 (71.6)	87 (46.8)	
NSTEMI	26 (9.8)	55 (8.7)		49 (9.9)	24 (12.9)	
Left main disease location			0.007			0.033
Ostium or shaft	110 (41.7)	328 (51.8)		245 (49.3)	74 (39.8)	
Distal bifurcation	154 (58.3)	305 (48.2)		252 (50.7)	112 (60.2)	
Extent of diseased vessel			<0.001			<0.001
Left main only	36 (13.6)	191 (30.2)		6 (1.2)	7 (3.8)	
Left main plus 1-vessel disease	52 (19.7)	163 (25.8)		24 (4.8)	28 (15.1)	
Left main plus 2-vessel disease	92 (34.8)	155 (24.5)		108 (21.7)	58 (31.2)	
Left main plus 3-vessel disease	84 (31.8)	124 (19.6)		359 (72.2)	93 (50.0)	
Restenotic lesion	6 (2.3)	20 (3.2)	0.615	3 (0.6)	5 (2.7)	0.064

Values are n (%) or mean ± SD.

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CHF = congestive heart failure; DES = drug-eluting stent; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

Figure 3 and Online Table 3. Increasing SS categories were associated with increased risks for mortality and composite outcome in the PCI arm but not in the CABG arm.

After multivariate adjustment of relevant clinical covariates, the adjusted predictive risks for outcomes according to increasing SS levels are shown in **Table 4**. In patients who underwent CABG, the SS categories were not significantly associated with increased risks for mortality, composite of death, Q-wave MI, or stroke, and TVR. By contrast, in the PCI arm, there was incremental prognostic value of SS categories for predicting long-term clinical outcomes. Compared with patients with low SS, the adjusted 10-year risks for death, composite outcome, and TVR were significantly higher in patients with high SS.

DISCUSSION

Using the longest follow-up cohort to date of patients who underwent LMCA revascularization, we assessed the long-term clinical impact of SS on 10-year comparative outcomes after PCI and CABG. The major findings of the present analysis are that: 1) in patients with low to intermediate SS, the 10-year risks for death and the composite of death, Q-wave MI, or stroke were similar between PCI and CABG; 2) in contrast, CABG showed a clear prognostic benefit over PCI in patients with high SS with respect to mortality and serious composite outcome; 3) TVR occurred more often in the PCI arm regardless of SS, but the risk was prominent in the high SS group; and 4) SS had incremental prognostic value on 10-year

TABLE 2 Adjusted Baseline Characteristics of Patients Using Inverse Probability Weighting

	Low to Intermediate SYNTAX Score			High SYNTAX Score		
	CABG (n = 264)	PCI (n = 633)	SMD	CABG (n = 497)	PCI (n = 186)	SMD
Wave			0.01			0.07
BMS era (January 2000 to May 2003)	0.26	0.26		0.28	0.26	
DES era (May 2003 to June 2006)	0.74	0.74		0.72	0.75	
Age	60.91	60.37	0.05	64.54	64.92	0.04
Male	0.73	0.70	0.05	0.74	0.73	0.02
Diabetes	0.27	0.27	0.01	0.38	0.40	0.04
Hypertension	0.43	0.46	0.06	0.55	0.55	0.003
Dyslipidemia	0.28	0.29	0.03	0.41	0.39	0.04
Current smoker	0.31	0.29	0.04	0.24	0.22	0.04
Previous PCI	0.17	0.17	0.01	0.13	0.16	0.09
Previous MI	0.08	0.08	0.004	0.12	0.13	0.04
Previous CHF	0.02	0.02	0.02	0.03	0.03	0.01
Chronic lung disease	0.02	0.02	0.03	0.02	0.01	0.08
Cerebrovascular disease	0.05	0.06	0.07	0.09	0.08	0.04
Peripheral arterial disease	0.02	0.02	0.01	0.06	0.05	0.03
Renal failure	0.03	0.02	0.05	0.04	0.04	0.04
Ejection fraction	60.70	60.71	0.002	57.38	58.46	0.09
Clinical indication			0.04			0.11
Silent ischemia	0.03	0.03		0.02	0.03	
Chronic stable angina	0.29	0.31		0.23	0.25	
Unstable angina	0.58	0.57		0.65	0.59	
NSTEMI	0.10	0.09		0.11	0.13	
Left main disease location			0.01			0.05
Ostium or shaft	0.49	0.49		0.48	0.45	
Distal bifurcation	0.51	0.51		0.53	0.55	
Extent of diseased vessel			0.02			0.07
Left main only	0.25	0.25		0.01	0.02	
Left main plus 1-vessel disease	0.25	0.24		0.09	0.09	
Left main plus 2-vessel disease	0.27	0.28		0.23	0.25	
Left main plus 3-vessel disease	0.23	0.23		0.67	0.64	
Restenotic lesion	0.03	0.03	0.01	0.01	0.01	0.03

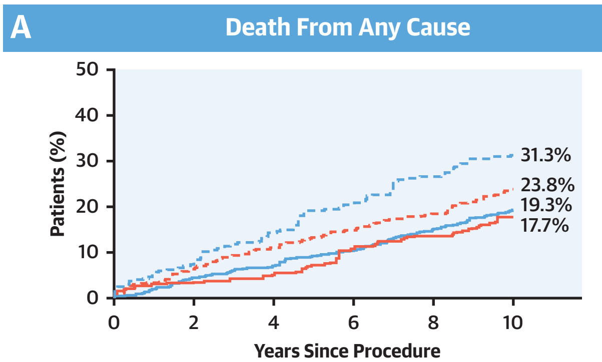
Abbreviations as in Table 1.

TABLE 3 Unadjusted and Adjusted Risks for 10-Year Outcomes After PCI or CABG, According to SYNTAX Score Category

	Unadjusted Outcomes					Adjusted Outcomes With the Use of Inverse-Probability Treatment Weighting				
	Event Rates at 10 yrs		Unadjusted Risks			Event Rates at 10 yrs		Adjusted Risks		
	CABG	PCI	HR (95% CI)*	p Value	p Value for Interaction†	CABG	PCI	HR (95% CI)*	p Value	p Value for Interaction†
Death					0.021					0.323
Low to intermediate SYNTAX score (≤32)	19.1	17.5	0.90 (0.65–1.26)	0.544		17.7	19.3	1.10 (0.78–1.54)	0.589	
High SYNTAX score (≥33)	23.8	34.1	1.53 (1.13–2.08)	0.006		23.8	31.3	1.39 (1.00–1.92)	0.048	
Death, Q-wave MI, or stroke					0.066					0.694
Low to intermediate SYNTAX score (≤32)	20.6	20.0	0.96 (0.70–1.32)	0.790		18.8	21.6	1.17 (0.84–1.62)	0.352	
High SYNTAX score (≥33)	27.7	37.4	1.43 (1.07–1.91)	0.016		27.5	33.7	1.27 (0.94–1.74)	0.123	
Target vessel revascularization					0.094					0.208
Low to intermediate SYNTAX score (≤32)	5.7	19.4	3.67 (2.11–6.39)	<0.001		4.5	19.7	4.78 (2.59–8.85)	<0.001	
High SYNTAX score (≥33)	4.2	27.9	7.32 (4.27–12.55)	<0.001		4.0	29.2	8.29 (4.79–14.34)	<0.001	

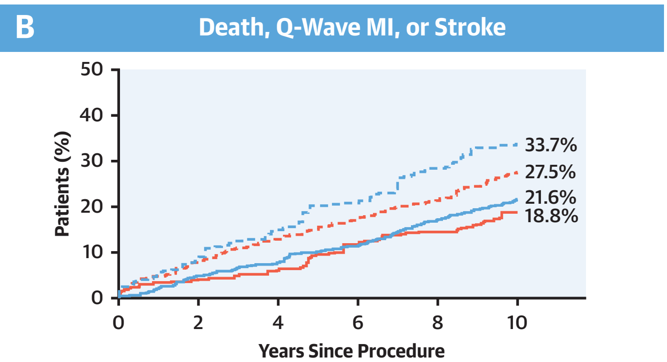
*HR is the risk of PCI for different outcomes compared with CABG. †P value for interaction for clinical presentation (ACS vs. non-ACS) and revascularization strategy (PCI vs. CABG).
ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION Adjusted 10-Year Kaplan-Meier Curves of PCI or CABG With the Use of Inverse Probability Weighting According Low to Intermediate and High SYNTAX Score Groups



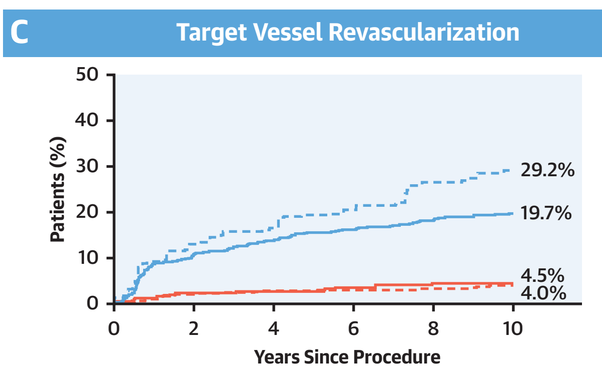
Number at risk

High SS						
PCI	186	159	146	135	125	117
CABG	497	464	440	419	402	375
Low-Intermediate SS						
PCI	633	603	584	561	532	505
CABG	264	252	246	231	224	212



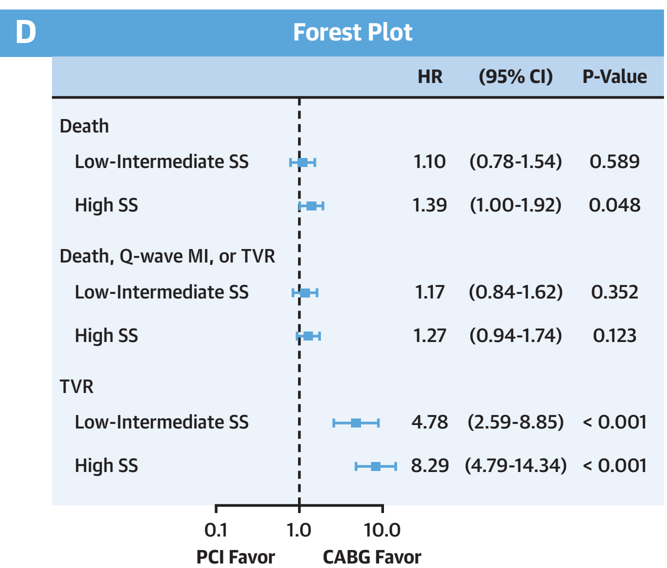
Number at risk

High SS						
PCI	186	157	145	135	122	113
CABG	497	457	431	408	388	356
Low-Intermediate SS						
PCI	633	601	580	555	519	490
CABG	264	250	244	229	221	210



Number at risk

High SS						
PCI	186	139	126	111	94	84
CABG	497	454	430	409	392	363
Low-Intermediate SS						
PCI	633	540	507	477	444	418
CABG	264	246	241	225	216	206



Low-Intermediate SS: — PCI — CABG
High SS: - - - PCI - - - CABG

Low-Intermediate SYNTAX score

Mortality : PCI ≈ CABG
Serious events : PCI ≈ CABG
Revascularization : PCI > CABG

High SYNTAX score

Mortality : PCI > CABG
Serious events : PCI > CABG
Revascularization : PCI > CABG

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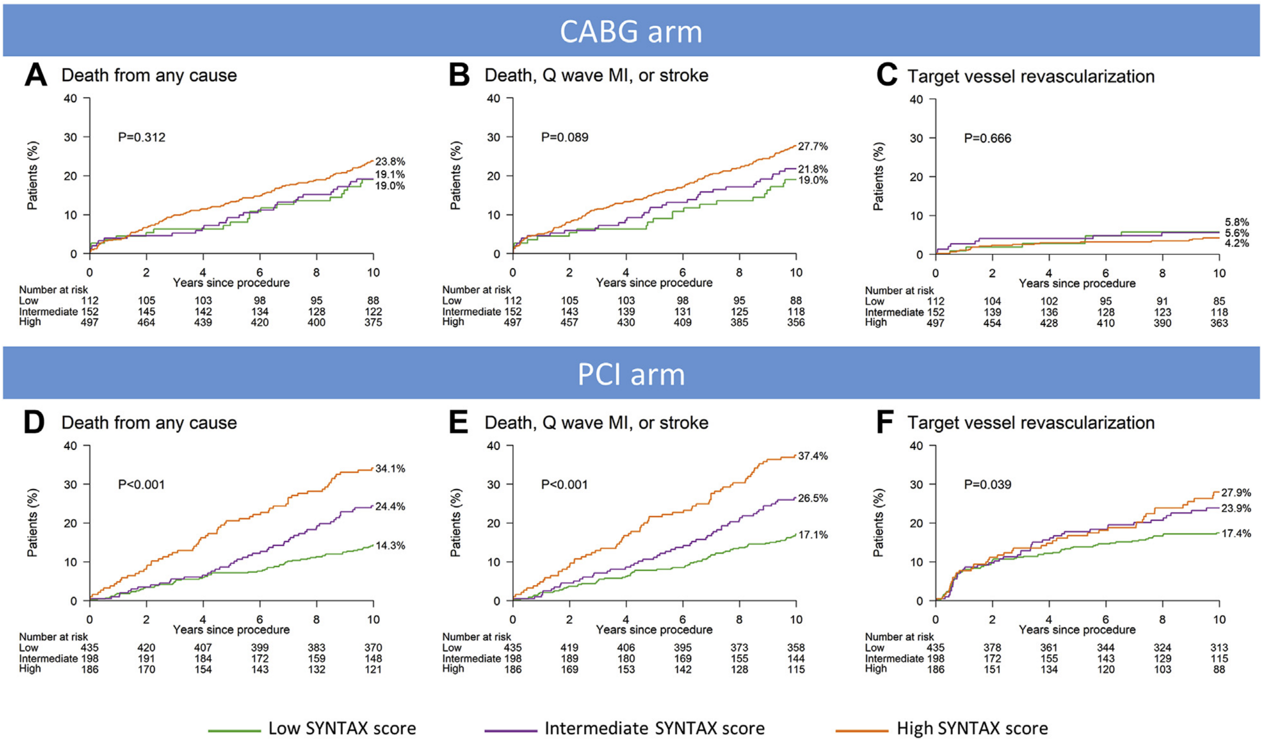
(A) Death from any cause in the low to intermediate and high SYNTAX score (SS) groups. **(B)** The composite of death, Q-wave myocardial infarction (MI), and stroke in the low to intermediate and high SS groups. **(C)** Target vessel revascularization (TVR) in the low to intermediate and high SS groups. **(D)** Forest plot for 10-year events. CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

FIGURE 3 **10-Year Kaplan-Meier Curves for Clinical Events Stratified by SYNTAX Score Category in CABG and PCI Groups**



(A) Death from any cause in the low to intermediate SYNTAX score group of the CABG arm. **(B)** The composite of death, Q-wave myocardial infarction (MI), and stroke in the low to intermediate SYNTAX score group of the CABG arm. **(C)** Target vessel revascularization in the low to intermediate SYNTAX score group of the CABG arm. **(D)** Death from any cause in the high SYNTAX score group of the PCI arm. **(E)** The composite of death, Q-wave MI, and stroke in the high SYNTAX score group of the PCI arm. **(F)** Target vessel revascularization in the high SYNTAX score group of the PCI arm. Abbreviations as in Figure 1.

outcomes in the PCI group but not in the CABG group.

Results of randomized clinical trials comparing PCI and CABG should be interpreted carefully, as these studies have mostly excluded patients with high anatomic complexity (5,6,11). Because the beneficial effect of CABG over PCI is apparent in the high SS group, the conflicting results of those studies might be from lack of power due to a small number of patients with high SS. We analyzed a large-scale multicenter registry including a large proportion of patients with high SS up to 43%. In addition, the advantages of CABG over PCI may become evident beyond at least 5 years because of the late catch-up phenomenon observed in prior studies (5,11,12). In these clinical viewpoints, our extended follow-up study may provide a relevant clinical message on the very long term effect of each revascularization strategy stratified by baseline SS in real-world patients with LMCA disease.

The SS was a powerful predictor for adverse outcomes in patients with multivessel and/or LMCA disease in the SYNTAX trial (8). Several subsequent studies and meta-analyses also confirmed the clinical utility of SS in multivessel CAD (6,22,23). However, until recently, the clinical utility and prognostic impact of SS for LMCA revascularization is not fully determined. In EXCEL and NOBLE, the anatomic SS did not have an impact on relative clinical outcomes after PCI and CABG, limiting the clinical utility of the SS in LMCA revascularization (5,11). Similarly, a recent pooled analysis of 11 trials found that 5-year mortality between PCI and CABG for LMCA disease did not differ in patients according to SS tertile (6). However, this provocative claim should be argued. First, in EXCEL and NOBLE, high anatomic complexity without equipoise for both revascularization methods was a key exclusion criterion, as these patients might have a clear prognostic benefit for CABG, as shown in our study. Therefore, the SS in

TABLE 4 Multivariate Analyses for 10-Year Clinical Outcomes in Each CABG or PCI Arm, According to SYNTAX Score Tertile Categories

	CABG Arm (n = 761)		PCI Arm (n = 819)	
	Adjusted HR (95% CI)*	p Value	Adjusted HR (95% CI)*	p Value
Death				
Low SYNTAX score (≤22)	Reference		Reference	
Intermediate SYNTAX score (23-32)	1.17 (0.63–2.16)	0.627	1.14 (0.76–1.72)	0.526
High SYNTAX score (≥33)	1.09 (0.61–1.93)	0.770	1.59 (1.06–2.38)	0.026
Death, Q-wave MI, or stroke				
Low SYNTAX score (≤22)	Reference		Reference	
Intermediate SYNTAX score (23-32)	1.31 (0.72–2.38)	0.376	1.10 (0.74–1.62)	0.643
High SYNTAX score (≥33)	1.34 (0.77–2.34)	0.301	1.59 (1.08–2.32)	0.018
Target vessel revascularization				
Low SYNTAX score (≤22)	Reference		Reference	
Intermediate SYNTAX score (23-32)	0.61 (0.20–1.85)	0.387	1.36 (0.90–2.07)	0.149
High SYNTAX score (≥33)	0.38 (0.13–1.07)	0.068	1.57 (1.01–2.44)	0.045

*HRs are for the PCI group compared with the CABG group. HRs are adjusted for wave, age, sex, diabetes, hypertension, dyslipidemia, current smoking, previous PCI, previous MI, previous stroke, peripheral vascular disease, chronic kidney disease, left ventricular ejection fraction, clinical presentation, extent of disease, disease location, and restenotic lesion.

Abbreviations as in Tables 1 and 3.

EXCEL and NOBLE might have a limited prognostic impact on differential outcomes, because most enrolled patients were at lower risk with a lesser extent of atherosclerotic disease burden. Second, unexpectedly, paradoxical poor PCI outcome of low tertile SS in NOBLE has not yet been fully elucidated; this might be due to a higher proportion of distal bifurcation disease or a chance effect. Last, different stent types (i.e., second-generation DES in EXCEL and NOBLE vs. a mixture of BMS and first-generation DES in this registry) could partly explain the different impact of SS.

In the EXCEL trial, there was a difference in SS measurement and categorization between site assessments and angiographic core laboratory assessments (5). Nearly a quarter of enrolled patients in EXCEL actually had high SS by core laboratory measurement. However, the reality might be that if the participating site chose a patient as an intermediate (23 to 32) SS and the core laboratory assessment actually showed that SS was high (>32), the difference in anatomic complexity might be actually low, probably representing a single or few lesions, which might have a limited impact on clinical outcomes. In EXCEL, inappropriately enrolled patients with high SS were distributed toward the lower end of the high SS tertile (around 32), and such findings were also applied to NOBLE (5,11).

Prior studies showed that the SS has prognostic value in predicting clinical outcomes in patients undergoing PCI, although it is not predictive in patients undergoing CABG (16,24–26). With CABG treatment, graft vessels usually bypass the entire diseased lesion. Therefore, if there is a disease-free point at the mid to distal site of the coronary artery with a satisfactory anastomosis, SS reflecting lesion length, heavy calcification, or angulation cannot be related to adverse outcomes in the CABG group. In contrast, high baseline SS in PCI treatment is associated with the use of more stents, longer stents, and bifurcation stent techniques, which were usually associated with worse clinical outcomes (25,27,28). In addition, the progression of downstream coronary atherosclerotic disease might be higher after PCI than after CABG (29). Thus, the large atherosclerotic burden encountered in the high SS group can promote this phenomenon, especially in PCI treatment.

A recent report from the FREEDOM trial suggests limited clinical utility in patients with diabetes and multivessel CAD (30). As shown in our study, the SS was shown to have prognostic value in the PCI arm but not in the CABG arm. The incidence of major adverse cardiac and cerebrovascular events was consistently higher for PCI compared with CABG in all SS categories. Thus, the investigators claimed that SS should not be used to guide the choice of coronary revascularization in patients with diabetes and multivessel CAD. However, given that CABG showed a consistent benefit over PCI in patients with multivessel CAD, particularly those with diabetes (6), and the discriminative capacity of diabetes mellitus for optimal revascularization choice for LMCA disease is still limited (31), the clinical and practical utility of the SS should not be abandoned in patients with LMCA disease who have a diverse range of concomitant atherosclerotic plaque burden.

STUDY LIMITATIONS. First, our study was observational and had inherent methodological limitations; thus, its overall findings must be considered hypothetical and hypothesis generating only.

Second, because the treatment choice was left to the physician or patient, our findings are subject to selection bias. Although the propensity score analyses were performed to adjust for potential selection bias and baseline differences, the possibility of other unmeasured confounders having affected the results cannot be excluded. Also, the proportion of PCI patients who were surgical turndowns (i.e., frailty, excess comorbidity) was not exactly captured in our registry. Such confounding factors could influence the comparative outcomes.

Third, about 30% of the total study population was excluded because baseline SS measurement was not available in the overall patients. Baseline characteristics of patients with or without baseline SS are shown in Online Table 4.

Finally, we evaluated clinical outcomes of BMS or first-generation DES for the treatment of LMCA disease in the PCI arm. Therefore, our findings should be further evaluated through extended follow-up of the EXCEL and NOBLE trials using contemporary-generation DES.

CONCLUSIONS

In the longest follow-up of patients with LMCA disease who are more representative of clinical practice, the adjusted 10-year rates of mortality and serious composite outcome were similar after PCI and CABG in patients with low to intermediate anatomic complexity measured by baseline SS. However, CABG showed a clear 10-year long-term benefit over PCI in patients with high anatomic complexity. This study also demonstrates that the SS has a significant correlation with mortality and major adverse events in patients who underwent PCI but not in those who underwent CABG.

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PERSPECTIVES

WHAT IS KNOWN? There were conflicting results from recent randomized trials regarding the prognostic impact and clinical implications of SS in patients with LMCA disease.

WHAT IS NEW? With extended 10-year follow-up, PCI was associated with similar mortality and serious composite outcomes in the low to intermediate SS group. By contrast, there was a clear prognostic benefit for CABG over PCI in the high SS group.

WHAT IS NEXT? Further additional evidence from large, randomized trials EXCEL and NOBLE, may provide more compelling evidence on the long-term effect of contemporary PCI and CABG in patients with LMCA disease according to anatomic complexity measured by SS.

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KEY WORDS coronary artery bypass grafting surgery, left main coronary artery disease, percutaneous coronary intervention, SYNTAX score

APPENDIX For supplemental tables and a figure, please see the online version of this paper.