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Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization

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Objectives This study aimed to validate the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score representing angiographic complexity after unprotected left main coronary artery (ULMCA) revascularization.

Background The validity of the SYNTAX score has been adequately evaluated.

Methods The SYNTAX scores were calculated for 1,580 patients in a large multicenter registry who underwent percutaneous coronary intervention (PCI) (n = 819) or coronary artery bypass graft (CABG) (n = 761) for ULMCA stenosis. The outcomes of interests were 3-year incidences of major adverse vascular events (MAVE), including death, Q-wave myocardial infarction, and stroke and major adverse cardiac and cerebrovascular events (MACCE), including MAVE and target vessel revascularization of ULMCA.

Results The incidence of 3-year MAVE was 6.2% in the lowest (≤23), 7.1% in the intermediate (23 to ~36), and 17.4% in the highest (>36) SYNTAX score tertile groups after PCI (p = 0.010). However, the incidences of MAVE in the CABG group and MACCE in the PCI and CABG groups did not differ among the SYNTAX tertiles. In subgroups, the MAVE (p = 0.005) and MACCE (p = 0.007) rates according to the SYNTAX score tertiles were significantly different in patients receiving drug-eluting stent, not in those receiving bare-metal stent. When compared with the clinical EuroSCORE (European System for Cardiac Operative Risk Evaluation), the C-indexes of SYNTAX score and EuroSCORE were 0.59 and 0.67, respectively, for discrimination of MAVE and 0.53 and 0.57, respectively, for MACCE.

Conclusions The angiographic SYNTAX score seems to play a partial role in predicting long-term adverse events after PCI for ULMCA stenosis. A complementary consideration of patient's clinical risk might improve the predictive ability of risk score. (J Am Coll Cardiol Intv 2010;3:612–23) © 2010 by the American College of Cardiology Foundation

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The introduction of drug-eluting stents (DES), together with advances in peri- and post-procedural adjunctive pharmacotherapies, has improved outcomes of percutaneous coronary interventions (PCI) for unprotected left main coronary artery (ULMCA) stenosis (1–15). Therefore, PCI with stenting is now considered a viable alternative to coronary artery bypass graft (CABG) surgery (2,6,10,16). Standard guidelines, however, still recommend PCI for patients with ULMCA stenosis at high surgical risk or in emergency clinical situations, such as bailout procedures or for treatment of acute myocardial infarction (MI), because recent findings have failed to show that DES placement is superior or at least noninferior to CABG with respect to effectiveness of repeat revascularization (10,17,18).

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Several risk scores have been developed to stratify patients at high risk of revascularization for ULMCA or multivessel stenosis (17,19,20). One such, the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, was formulated to comprehensively represent angiographic complexity, which is considered an important determinant of outcomes after PCI or CABG for treatment of multivessel coronary disease (17,21,22). When the score was intrinsically applied to patients enrolled in the SYNTAX randomized trial, which compared DES with CABG in patients with multivessel disease, a lower incidence of adverse events after CABG was observed only in the highest SYNTAX score tertile group (17). This finding suggested the role of SYNTAX score in predicting differential outcomes of stenting versus CABG for complex coronary lesions. This score, however, should be validated in a large external cohort so that the SYNTAX score can be more widely applied to predict ULMCA revascularization.

We sought to validate the SYNTAX score by measurements of discrimination and calibration for 3-year outcomes of patients enrolled in revascularization procedures for unprotected left main coronary artery stenosis, with the MAIN-COMPARE (COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) registry of patients undergoing PCI or CABG for ULMCA stenosis (10). Furthermore, its discriminatory power was compared with the EuroSCORE (European System for Cardiac Operative Risk Evaluation), which has been considered an important clinical risk score to predict outcomes in patients undergoing CABG or PCI (19,20,23).

Methods

The MAIN-COMPARE study enrolled patients with ULMCA stenosis (>50% narrowing) who underwent either CABG or PCI as the index procedure at 12 major cardiac centers in Korea between January 2000 and June 2006 (10). The left main was considered unprotected if there were no patent grafts to the left anterior descending or circumflex arteries. Patients who had undergone previous CABG, those who underwent concomitant valvular or aortic surgery, and those who had ST-segment elevation MI or presented with cardiogenic shock were excluded. The institutional review board at each hospital approved the use of clinical data for this study, and all patients provided written informed consent. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the report as written.

Procedures and follow-up. The PCI and CABG procedure have been described (10). For PCI, the selection of stent, adjunctive device, and medication was at the operator's discretion. After 2003, DES, either sirolimus- (Cypher, Cordis Corporation, Johnson & Johnson, Miami Lakes, Florida) or paclitaxel-eluting (Taxus, Boston Scientific, Natick, Massachusetts) stents, were used as the default stent in all institutions. For CABG, the internal thoracic artery was first attempted to use for revascularization of the left anterior descending artery. Clinical, angiographic, procedural, and outcome data were collected and adjudicated centrally. Information about vital status was ascertained from the National Population Registry of the Korea National Statistical Office. Routine angiographic follow-up at 6 to 10 months after the procedure was recommended for all patients undergoing PCI, but not CABG. The EuroSCORE, composed of groups of weighted patient-oriented, cardiac-related, and surgery-related factors, was reported in a simple additive form from individual sites and examined centrally (19).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
DES = drug-eluting stent(s)
MACCE = major adverse cardiac and cerebrovascular events
MAVE = major adverse vascular events
MI = myocardial infarction
PCI = percutaneous coronary intervention
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery

The primary end point of the study was the incidence of major adverse vascular events (MAVE), defined as the composite of death, Q-wave MI, and stroke, which reflected the safety of treatment. The secondary end point was the incidence of major adverse cardiac and cerebrovascular events (MACCE), a composite consisting of all the components of MAVE plus target vessel revascularization (TVR) at ULMCA, which reflected the effectiveness of treatment. Death was defined as death from any cause. Q-wave MI was defined as documentation of a new abnormal Q-wave after index treatment. Stroke, indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging analyses. The TVR at ULMCA was defined as repeat revascularization of the treated vessel,

including any segment of the left anterior descending artery, left circumflex artery, or ULMCA.

Angiographic measurement. To measure each SYNTAX score, a baseline angiogram obtained before the procedure was retrospectively collected for each of 1,580 (70.5%) patients from the overall cohort of the MAIN-COMPARE registry. A calculation of the SYNTAX score was based on the algorithm, which was the sequential morphological evaluation of dominance; number of lesions; segments involved/lesion; and presence of total occlusion, trifurcation, bifurcation, aorto-ostial lesion, severe tortuosity, long lesion (>20 mm), heavy calcification, thrombus, and diffuse/small vessels in the ULMCA and concomitant lesions for each patient (21). The score was independently analyzed with dedicated angiographic software (CASS-5, Pie-Medical, Maastricht, the Netherlands) by 6 angiographers in the angiographic core laboratory (CardioVascular Research Foundation, Seoul, Korea). To decrease interobserver variation, the scores measured by individual angiographers were randomly monitored and reviewed by a senior angiographer. In case of disagreement, consensus was made within the group. Furthermore, to assess the reliability of score measurement in the core lab, we examined interexaminer reliabilities with the intraclass correlation coefficient for quantitative variables of the SYNTAX score. The intraclass correlation coefficient for 20 patients, who were randomly selected from the MAIN-COMPARE registry and were measured by 6 angiographers, was 0.69 before this study. A coefficient <0.4 was considered poor agreement; 0.4 to 0.59 was considered fair; 0.6 to 0.75 was considered good; and >0.75 was considered excellent (24).

Statistical analysis. Baseline demographic, clinical, and angiographic characteristics were reported as medians with interquartile ranges for continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared between 2 groups with the Mann-Whitney *U* test, whereas the Kruskal-Wallis test was used for multiple group comparisons. Categorical variables were compared with the chi-square test or Fisher exact test, as appropriate. The normality assumption for the SYNTAX score was evaluated by the Kolmogorov-Smirnov test.

To validate the SYNTAX score and the ability of the score to predict primary and secondary end points, measures of discrimination and calibration were examined (25). To assess discrimination ability, which refers to the power to distinguish between patients with and without events for 3 years, the C-index method was used (26). A value of 0.5 represents no weighting, whereas values between 0.7 and 0.9 were useful in predictive models (27). We also compared the risk model fit by use of the Akaike Information Criterion, which is a measure based on the log likelihood function, and a low value implies a better fit (28). The slopes of the linear predictors (shrinkage) were separately computed (29) to calibrate the 2 models of SYNTAX score and EuroSCORE. The slope of the predictor is a measure of how well the predicted probability reflected observed probabilities. A score of 1.0 represents full agreement, whereas lower scores represent poorer concordance. Furthermore, to test the additive role of clinical EuroSCORE, we repeated the analyses of calibration and discrimination after adding the term of EuroSCORE into the model for SYNTAX score. The differences in the C-index between the SYNTAX score and EuroSCORE were obtained through bootstrap with percentile method (200 replicates) (30). Moreover, to test the differential effect of PCI versus CABG on long-term outcomes for subgroups stratified by SYNTAX score tertile, we used the Kaplan-Meier method and compared the primary and secondary end points of the 2 strategies with the log-rank test. Interactions between factors associated with treatment type and SYNTAX score tertiles were tested by incorporation of formal interaction terms in a multivariate Cox model. Finally, additional multivariate Cox proportional hazard regression models were created to identify factors independently contributing to outcomes. Proportional hazards assumptions were confirmed by Schoenfeld's tests, and no relevant violation was found. In our multivariate models, the potential confounders were adjusted by backward elimination until variables with only p values <0.1 remained. To avoid overfitting problem caused by the limited number of events, we restricted the number of covariates, including age (year), male sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, prior PCI, previous MI, chronic lung disease, cerebral or peripheral vascular disease, chronic renal failure, congestive heart failure, family history of coronary artery disease, acute coronary syndrome, number of extra-ULMCA diseased vessels, number of diseased segments according to the SYNTAX classification, left anterior descending artery stenosis, left circumflex stenosis, right coronary stenosis, ULMCA bifurcation stenosis, aorto-ostial ULMCA stenosis, ostial left circumflex artery stenosis, treatment type (CABG vs. PCI), EuroSCORE, and SYNTAX score.

All p values were 2-sided, and p values <0.05 were regarded as statistically significant. The SAS software version 9.1 (SAS Institute, Cary, North Carolina) and the R programming language with Design library were used for statistical analysis.

Results

Baseline and procedural characteristics. We evaluated a total of 1,580 patients, 819 (51.8%) undergoing PCI and 761 (48.2%) undergoing CABG. Clinical and angiographic characteristics are shown in Tables 1 and 2. The SYNTAX score was not normally distributed, and its median value was 30.0 (Fig. 1). When patients were stratified by SYNTAX score tertiles, the cutoff points were 23 and 36. Compared with patients in the lowest SYNTAX score tertile, those in

Table 1. Clinical Characteristics of Patients According to SYNTAX Score Tertiles

Variable	Lowest (≤23)			Intermediate (>23 and ≤36)			Highest (>36)			p Value*	
	PCI (n = 435)	CABG (n = 112)	p Value	PCI (n = 268)	CABG (n = 243)	p Value	PCI (n = 116)	CABG (n = 406)	p Value	PCI Group	CABG Group
Age (yrs)	58.5 (49.0–65.8)	59.7 (53.4–69.4)	0.081	66.6 (58.4–72.2)	63.1 (57.0–67.9)	<0.001	67.1 (57.9–75.5)	65.3 (58.4–70.3)	0.029	<0.001	<0.001
Male sex (%)	288 (66.2)	84 (75.0)	0.075	199 (74.3)	179 (73.7)	0.88	33 (28.4)	109 (26.8)	0.73	0.070	0.93
Diabetes mellitus	96 (22.1)	27 (24.1)	0.65	103 (38.4)	79 (32.5)	0.16	50 (43.1)	155 (38.2)	0.34	<0.001	0.016
Hypertension	185 (42.5)	48 (42.9)	0.95	162 (60.4)	118 (48.6)	0.007	68 (58.6)	216 (53.2)	0.30	<0.001	0.13
Hyperlipidemia	125 (28.7)	26 (23.2)	0.24	87 (32.5)	84 (34.6)	0.61	46 (39.7)	172 (42.4)	0.60	0.073	0.001
Current smoker	117 (26.9)	40 (35.7)	0.066	62 (23.1)	81 (33.3)	0.010	16 (13.8)	104 (25.6)	0.008	0.012	0.035
Previous PCI	72 (16.6)	15 (13.4)	0.42	67 (25.0)	29 (11.9)	<0.001	21 (18.1)	34 (8.4)	0.003	0.021	0.17
Previous MI	27 (6.2)	9 (8.0)	0.49	25 (9.3)	25 (10.3)	0.72	16 (13.8)	48 (11.8)	0.57	0.024	0.50
Previous heart failure	7 (1.6)	3 (2.7)	0.45	5 (1.9)	6 (2.5)	0.64	5 (4.3)	15 (3.7)	0.76	0.19	0.66
Chronic obstructive pulmonary disease	9 (2.1)	4 (3.6)	0.32	6 (2.2)	3 (1.2)	0.51	1 (0.9)	11 (2.7)	0.48	0.65	0.32
Cerebrovascular disease	25 (5.7)	3 (2.7)	0.19	25 (9.3)	19 (7.8)	0.54	14 (12.1)	36 (8.9)	0.30	0.042	0.09
Peripheral vascular disease	6 (1.4)	6 (5.4)	0.010	2 (0.7)	10 (4.1)	0.012	4 (3.4)	29 (7.1)	0.15	0.13	0.28
Chronic renal failure	7 (1.6)	3 (2.7)	0.45	11 (4.1)	5 (2.1)	0.19	5 (4.3)	19 (4.7)	0.87	0.086	0.19
Ejection fraction (%)	63.0 (58.0–68.0)	63.0 (56.0–67.0)	0.33	61.0 (55.0–67.0)	61.0 (55.0–66.0)	0.67	59.5 (52.3–65.0)	58.0 (48.0–64.0)	0.33	<0.001	<0.001
Atrial fibrillation	8 (1.8)	3 (2.7)	0.70	7 (2.6)	10 (4.1)	0.34	3 (2.6)	6 (1.5)	0.42	0.76	0.11
Acute coronary syndrome	288 (66.2)	73 (65.2)	0.84	160 (59.7)	178 (73.3)	0.001	70 (60.3)	337 (83.0)	<0.001	0.17	<0.001
Family history of coronary disease	36 (8.3)	16 (14.3)	0.053	16 (6.0)	28 (11.5)	0.025	7 (6.0)	42 (10.3)	0.16	0.45	0.50
EuroSCORE	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.063	4.0 (2.0–5.0)	4.0 (3.0–5.0)	0.97	4.0 (3.0–6.0)	5.0 (3.0–6.0)	0.086	<0.001	<0.001

Values are presented as median (interquartile range) or n (%). *p Values among 3 groups stratified by SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score tertiles within the stenting or coronary artery bypass graft (CABG) group.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Angiographic Characteristics of Patients According to SYNTAX Score Tertiles

Variable	Lowest (≤23)			Intermediate (>23 and ≤36)			Highest (>36)			p Value*	
	PCI (n = 435)	CABG (n = 112)	p Value	PCI (n = 268)	CABG (n = 243)	p Value	PCI (n = 116)	CABG (n = 406)	p Value	PCI Group	CABG Group
SYNTAX score (total)	15.0 (12.0–19.0)	18.0 (14.0–21.0)	<0.001	29.0 (26.0–32.5)	31.0 (28.0–34.0)	<0.001	42.0 (38.1–45.9)	46.5 (41.0–53.6)	<0.001	<0.001	<0.001
Number of extra left main diseased vessels	0 (0–1.0)	1.0 (0–2.0)	<0.001	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.028	3.0 (2.0–3.0)	3.0 (3.0–3.0)	0.008	<0.001	<0.001
Number of diseased SYNTAX segments	1.0 (1.0–2.0)	2.0 (1.0–3.0)	<0.001	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.021	6.0 (6.8–4.0)	7.0 (5.0–8.0)	<0.001	<0.001	<0.001
Extra left main stenosis											
Left anterior descending	119 (27.4)	37 (33.0)	0.24	253 (94.4)	218 (89.7)	0.049	115 (99.1)	404 (99.5)	0.64	<0.001	<0.001
Left circumflex	69 (15.9)	31 (27.7)	0.004	143 (53.4)	137 (56.4)	0.49	99 (85.3)	353 (86.9)	0.66	<0.001	<0.001
Right coronary	95 (21.8)	43 (38.4)	<0.001	155 (57.8)	178 (73.3)	<0.001	95 (81.9)	373 (91.9)	0.002	<0.001	<0.001
Left main morphology											
SYNTAX score (left main)	12.0 (11.0–14.0)	13.0 (12.0–14.0)	0.007	14.0 (12.0–15.0)	14.0 (12.0–15.0)	0.75	15.0 (13.0–17.0)	14.0 (13.0–16.0)	0.20	<0.001	<0.001
Bifurcation stenosis	272 (62.5)	85 (75.9)	0.008	232 (86.6)	210 (86.4)	0.96	100 (86.2)	368 (90.6)	0.17	<0.001	<0.001
Aorto-ostial stenosis	217 (49.9)	42 (37.5)	0.019	140 (52.2)	126 (51.9)	0.93	74 (63.8)	300 (73.9)	0.033	<0.001	0.15
Side branch stenosis	123 (28.3)	51 (45.5)	<0.001	85 (31.7)	67 (27.6)	0.31	39 (33.6)	118 (29.1)	0.35	<0.001	<0.001

Values are presented as median (interquartile range) or n (%). *p Values among 3 groups stratified by SYNTAX score tertiles within the stenting or CABG group.
Abbreviations as in Table 1.

Figure 1. Distribution, Mean, and Median Values of the SYNTAX Score

The score was not normally distributed by Kolmogorov-Smirnov test ($p < 0.001$). Mean: 30.9, standard deviation: 14.2, median 30.0, interquartile range: 19 to 40, tertile group: ≤23, <23 and ≤36, >36. SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

the highest tertile were likely to be elderly persons and to have more coronary risk factors, unstable manifestations, extensive coronary involvement, high EuroSCORE, and bifurcation ULMCA stenosis. In the PCI group, the numbers of patients with the highest, intermediate, and lowest SYNTAX scores were 111, 44, and 19, respectively, in patients receiving bare-metal stent (BMS) and 324, 224, and 97, respectively, in those receiving DES.

When angiographic characteristics were compared between PCI and CABG groups in the 3 SYNTAX score tertiles, we found that the CABG group was more likely to have more extensive coronary involvement than the PCI group. However, the differences in clinical characteristics were heterogeneous between the 2 treatments across the various subgroups.

3-year outcomes. When follow-up was censored at 3 years, follow-up was completed in 1,508 (95.4%) patients. For the 3-year period, the Kaplan-Meier incidence of death, MAVE, and MACCE in the PCI and CABG groups were 6.2% versus 9.2% ($p = 0.021$), 7.1% versus 10.4% ($p = 0.020$), and 17.4% versus 13.1% ($p = 0.016$), respectively. Figure 2 shows the 3-year Kaplan-Meier incidences of MAVE and MACCE for overall patients stratified by the SYNTAX score tertiles. Figure 3 shows the incidences of MAVE and MACCE in patients receiving PCI and CABG, for subgroups stratified by SYNTAX score tertiles. The differences in event rates among the groups stratified by SYNTAX score tertiles were statistically significant for MAVE in the PCI ($p = 0.010$) but not for MAVE in the CABG ($p = 0.293$) and MACCE in the PCI ($p = 0.080$) and CABG ($p = 0.594$) groups. The interaction between

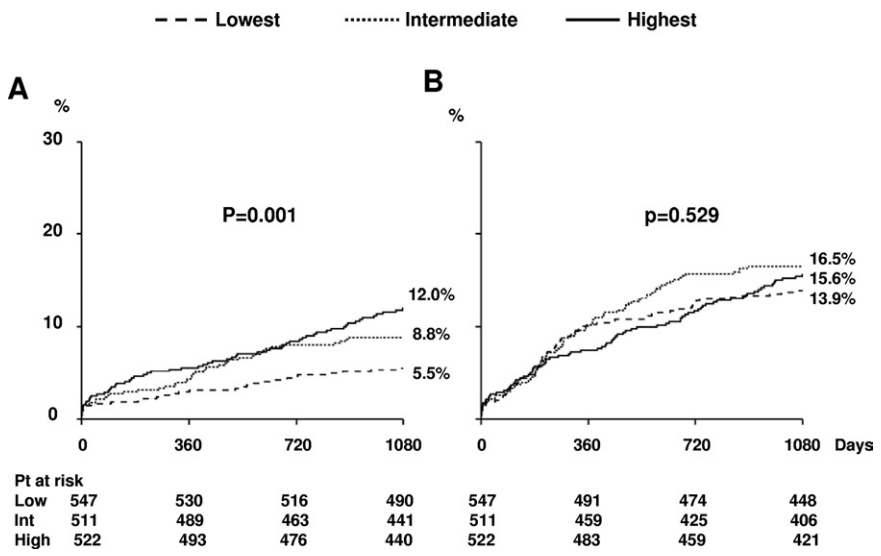

Figure 2. Kaplan-Meier Incidence Curves of Outcomes in Overall Patients

Three-year event rates of death, Q-wave myocardial infarction, or stroke **(A)**; and rates of death, Q-wave myocardial infarction, stroke, or target vessel revascularization **(B)** for patients with the lowest (Low), intermediate (Int), and highest (High) SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score tertile groups.

treatment type and SYNTAX score tertiles was not significant with regard to the risk of MAVE (p = 0.25) or MACCE (p = 0.66).

When the PCI group was separated into patients receiving BMS or DES, the 3-year incidences of MAVE (p = 0.005) and MACCE (p = 0.007) according to the SYNTAX score tertiles were significantly different in the DES group (Fig. 4). However, the difference of MAVE (p = 0.18) or MACCE (p = 0.49) rates did not differ in the BMS group. The interaction between treatment type and SYNTAX score tertiles was not significant with regard to the risk of MAVE (p = 0.20, BMS vs. CABG; p = 0.17, DES vs. CABG) or MACCE (p = 0.39, BMS vs. CABG; p = 0.29, DES vs. CABG).

Discrimination and calibration. The median EuroSCORE was 4.0 (interquartile range: 2 to ~6). Table 3 summarizes the results of discrimination and calibration of the SYNTAX score as compared with the EuroSCORE. In discriminating between CABG and PCI with a primary end point of MAVE, the SYNTAX score was less predictive than the EuroSCORE, as indicated by the lower C-indexes in all subgroups (p = 0.0123 in overall patients, p = 0.89 in the PCI group, and p < 0.001 in CABG group). Consequently, the Akaike Information Criterion was lower with the EuroSCORE than the SYNTAX score, indicating that the former is a better predictive model. The slope of the linear predictor was closer to 1.00 when using EuroSCORE rather than SYNTAX score, indicating that the former model was better calibrated. Regarding the secondary end point of MACCE, both the SYNTAX score and the EuroSCORE had C values lower than 0.6 in the PCI group, indicating that their predictive abilities were weak. The differences of C values between the 2 scores were statistically significant in the CABG group (p < 0.001), but not in the PCI group (p = 0.18) and overall patients (p = 0.083). When the EuroSCORE and SYNTAX score were combined, the values of the C-index and the Akaike Information Criterion for the risk of MAVE and MACCE were slightly increased, indicating an improvement of predictive ability.

Multivariable analysis. When multivariate Cox regression models were formulated, clinical characteristics of patients and EuroSCORE were independent predictors of MAVE or MACCE (Table 4). However, the SYNTAX score was not an independent predictor in any model.

Discussion

A good risk-scoring model is considered to be valuable in predicting outcomes and guiding a selection of appropriate treatment strategies for patients with complex coronary lesions. However, because of the lack of clinical studies relevant to development of a risk model applicable to PCI, EuroSCORE—which was created for patients undergoing open-heart surgery—has often been used as a clinical risk index to represent clinical complexity of patients receiving PCI or CABG for ULMCA stenosis (1,15,20,31). Application of EuroSCORE to PCI procedures, however, is inherently limited because the score was designed to assess surgical risk. As a result, new risk scores, such as the Mayo

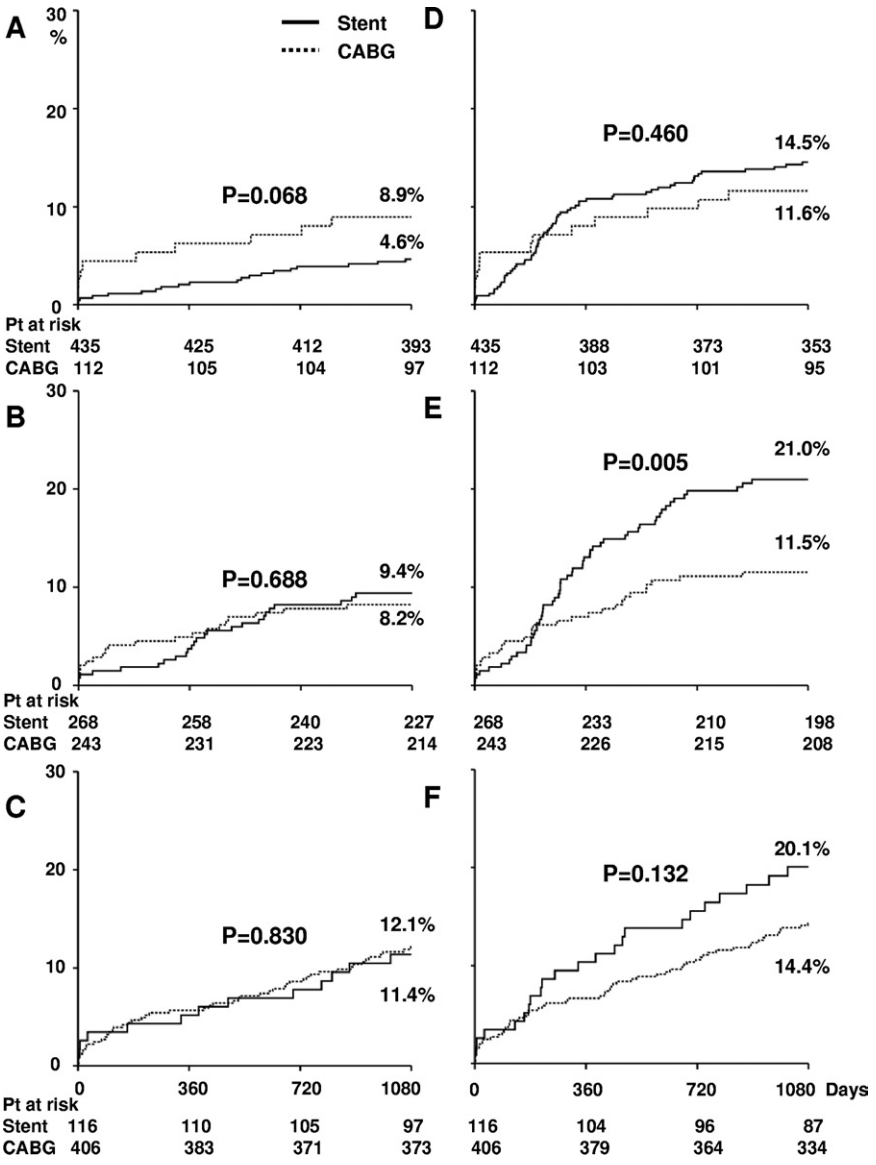

Figure 3. Kaplan-Meier Incidence Curves of Outcomes

Three-year event rates of death, Q-wave myocardial infarction, or stroke for patients with the lowest **(A)**, intermediate **(B)**, and highest **(C)** SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score tertile groups between the stent and coronary artery bypass graft (CABG) groups. Three-year event rates of death, Q-wave myocardial infarction, stroke, or target vessel revascularization for patients with the lowest **(D)**, intermediate **(E)**, and highest **(F)** SYNTAX score tertile groups between the stent and CABG groups.

Clinic Risk Score or Texas Heart Institute Risk Score, were created for a better prediction of outcomes after complex PCI (32,33). In the meantime, the SYNTAX score, which was basically developed to characterize angiographic complexity, has been proposed to predict outcomes and select an optimal treatment strategy, whether PCI or CABG (22,34).

The effectiveness of the SYNTAX score was firstly assessed in the ARTS II (Arterial Revascularization Therapies Study part II) trial, which enrolled patients with multivessel coronary disease (34). The SYNTAX score showed a better ability to predict the initial and long-term risks of MACCE when compared with the previous angiographic classification of the American College of Cardiology/American Heart Association. Subsequently, studies in patients with ULMCA stenosis supported the effectiveness of the SYNTAX score in predicting mortality after PCI or CABG (35,36) or myonecrosis after PCI (37). The other studies, however, found that the SYNTAX score was poor when used to predict long-term mortality or TVR after CABG or DES implantation (38). Generalization of these

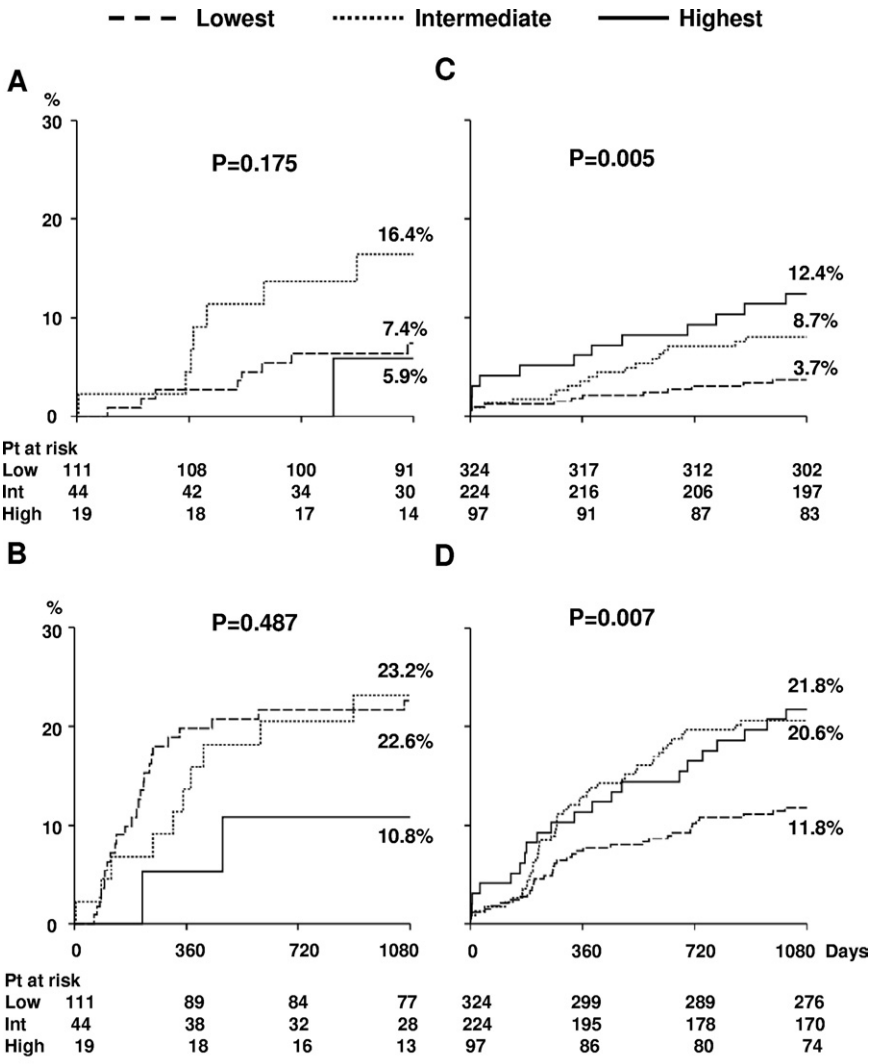

Figure 4. Kaplan-Meier Incidence Curves of Outcomes

Three-year event rates of death, Q-wave myocardial infarction, or stroke for patients with the lowest (Low), intermediate (Int), and highest (High) SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score tertile groups in patients receiving bare-metal stent **(A)** and drug-eluting stent **(C)**. Three-year event rates of death, Q-wave myocardial infarction, stroke, or target vessel revascularization according to the SYNTAX score tertile groups in patients receiving bare-metal stent **(B)** and drug-eluting stent **(D)**.

results assessing the role of the SYNTAX score, however, is limited by small sample sizes, variations in follow-up time, or selected patient enrollment. In this regard, the present study is unique in seeking to validate the scoring system with the largest available external database on consecutive patients undergoing PCI or CABG for ULMCA stenosis, with information filed in a national multicenter registry.

We found that the SYNTAX score was weakly predictive of a risk of 3-year MAVE—a composite of safety end points—in patients undergoing PCI, as indicated by the C-index value of 0.63. In particular, the score showed a stronger predictability when applied to patients receiving DES, having the higher C-index value of 0.66. Likewise, regarding a risk of MACCE, the score was still weakly predictive after DES treatment but not after BMS treatment. This finding was in good agreement with the previous studies showing the benefit of SYNTAX score in predicting long-term outcomes after PCI with DES for multivessel or ULMCA stenosis (34,36). On the contrary, the SYNTAX score lost even the slight predictive ability for patients undergoing CABG, as shown by the C-index value of 0.53. Because the grafts are bypassed downstream of the lesions in CABG surgery, angiographic complexity might have little clinical impact (17,38). Furthermore, in comparison of the

Table 3. Comparison of Discrimination, Calibration, and Global Fit Models for Prediction of Outcomes

Models	Death, Q-Wave MI, or Stroke			Death, Q-Wave MI, Stroke, or TVR		
	Discrimination			Discrimination		
	C-Index (95% CI)	AIC	Calibration Slope of the Linear Predictor	C-Index (95% CI)	AIC	Calibration Slope of the Linear Predictor
Overall patients						
SYNTAX score	0.59 (0.55–0.64)	1,993.9	1.12	0.53 (0.48–0.55)	3,511.0	0.93
EuroSCORE	0.67 (0.62–0.71)	1,949.6	1.02	0.57 (0.53–0.60)	3,493.9	1.09
SYNTAX score/EuroSCORE	0.68 (0.63–0.72)	1,948.5	1.00	0.57 (0.53–0.60)	3,495.7	1.02
Tertile of SYNTAX score	0.58 (0.54–0.63)	1,994.3	1.00	0.52 (0.48–0.55)	3,512.0	0.37
PCI patients receiving any stent						
SYNTAX score	0.63 (0.57–0.70)	765.4	1.07	0.57 (0.52–0.61)	1,874.3	1.00
EuroSCORE	0.64 (0.56–0.72)	752.5	1.06	0.53 (0.48–0.58)	1,876.5	1.16
SYNTAX score/EuroSCORE	0.67 (0.59–0.74)	750.2	1.02	0.57 (0.52–0.61)	1,874.6	0.97
Tertile of SYNTAX score	0.60 (0.54–0.67)	767.8	1.05	0.55 (0.50–0.59)	1,876.6	0.84
PCI patients receiving BMS						
SYNTAX score	0.61 (0.50–0.71)	163.7	0.81	0.48 (0.40–0.56)	374.9	0.34
EuroSCORE	0.52 (0.36–0.69)	164.1	0.41	0.53 (0.42–0.56)	373.6	1.35
SYNTAX score/EuroSCORE	0.59 (0.46–0.72)	165.3	0.46	0.53 (0.42–0.63)	375.5	0.59
Tertile of SYNTAX score	0.61 (0.49–0.73)	163.6	0.76	0.54 (0.47–0.61)	375.1	0.62
PCI patients receiving DES						
SYNTAX score	0.66 (0.58–0.74)	532.3	1.15	0.60 (0.55–0.65)	1,333.4	1.09
EuroSCORE	0.68 (0.60–0.77)	517.5	1.05	0.53 (0.47–0.58)	1,340.1	0.88
SYNTAX score/EuroSCORE	0.71 (0.63–0.79)	515.7	0.96	0.60 (0.55–0.65)	1,334.8	0.97
Tertile of SYNTAX score	0.63 (0.55–0.71)	534.2	0.94	0.58 (0.53–0.63)	1,333.9	0.97
CABG patients						
SYNTAX score	0.53 (0.47–0.59)	1,040.2	0.78	0.51 (0.46–0.57)	1,301.3	0.89
EuroSCORE	0.67 (0.61–0.73)	1,010.7	0.99	0.64 (0.58–0.69)	1,277.2	1.05
SYNTAX score/EuroSCORE	0.68 (0.62–0.73)	1,012.7	0.99	0.64 (0.58–0.69)	1,279.1	1.01
Tertile of SYNTAX score	0.54 (0.49–0.60)	1,040.8	0.78	0.52 (0.43–0.57)	1,302.6	0.50

AIC = Akaike Information Criterion; BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); TVR = target vessel revascularization; other abbreviations as in Table 1.

2 scores, the EuroSCORE was more effective in predicting the risk of MAVE after PCI and CABG and the risk of MACCE after CABG, whereas the SYNTAX score was more effective in predicting the risk of MACCE only after DES treatment. Accordingly, in another analysis with multivariate Cox models, the SYNTAX score was excluded from factors predictive of MAVE or MACCE, after adjusting for baseline clinical and angiographic characteristics.

In addition to the assessment of predictability, an interaction between the treatment type—whether CABG or PCI—and SYNTAX score tertiles was examined to find its role in helping a selection of the appropriate treatment strategy. A recent SYNTAX trial of patients with multivessel or ULMCA disease showed that the risk of MACCE differed between patients in the highest SYNTAX score tertile who underwent PCI or CABG, but no differences were found in patients in the lowest or intermediate tertiles (17). Consequently, the interaction test between the treatment type and SYNTAX score groups was statistically significant. This study suggested that the SYNTAX score could be used to assist physicians in selecting an optimal treatment strategy, depending on the value of the score (17). However, in our study, the interaction between type of treatment and SYNTAX score tertile was not significant with regard to the risk of MAVE or MACCE. In our survival analysis, the pattern of differential outcomes between PCI and CABG was not significantly influenced according to the SYNTAX score tertiles. This finding indicates that the SYNTAX score might not be validated as a useful guidance to select an appropriate strategy in ULMCA revascularization.

The limited applicability of the SYNTAX score in our study might be explained with several possible mechanisms. Firstly, a significant number of predictors might be based more on clinical and procedural factors than on angiographic morphologies. In several previous risk models, clinical risk profiles were more closely related with the immediate and long-term outcomes after either PCI or CABG (23,32,33). In fact, the partial role of SYNTAX score in predicting MAVE in our study might be attributed

Table 4. Multivariate Predictors of Outcomes

Outcomes	Hazard Ratio	95% CI	p Value
Death, Q-wave MI, or stroke			
Overall patients			
EuroSCORE	1.25	1.16–1.34	<0.001
Chronic lung disease	2.14	1.07–4.29	0.032
Chronic renal failure	2.67	1.54–4.63	<0.001
Atrial fibrillation	2.21	1.11–4.42	0.024
PCI patients			
EuroSCORE	1.17	1.05–1.31	0.004
Prior congestive heart failure	3.86	1.58–9.44	0.003
Chronic renal failure	6.15	2.90–13.01	<0.001
CABG patients			
EuroSCORE	1.27	1.16–1.39	<0.001
Diabetes mellitus	1.76	1.13–2.75	0.013
Chronic lung disease	4.03	1.79–9.05	<0.001
Prior cerebrovascular disease	2.36	1.29–4.31	0.005
Hyperlipidemia	0.60	0.36–0.99	0.043
Death, Q-wave MI, stroke, or TVR			
Overall patients			
EuroSCORE	1.10	1.04–1.16	<0.001
CABG	0.71	0.54–0.92	0.010
Chronic renal failure	2.32	1.40–3.85	0.001
Prior cerebrovascular disease	1.58	1.08–2.33	0.020
Use of intra-aortic balloon pump	2.00	1.09–3.64	0.024
PCI patients			
Prior congestive heart failure	2.98	1.44–6.16	0.003
Use of intra-aortic balloon pump	2.25	1.23–4.10	0.008
Chronic renal failure	4.17	2.27–7.64	<0.001
CABG patients			
EuroSCORE	1.22	1.12–1.33	<0.001
Chronic lung disease	2.52	1.15–5.49	0.021
Prior MI	1.76	1.06–2.94	0.030
Prior cerebrovascular disease	2.32	1.36–3.99	0.002

Abbreviations as in Tables 1 and 3.

to the comorbidities in patients having extensive coronary artery stenosis. However, the SYNTAX score was conceptually created by a combination and modification of previous angiographic scoring systems, which had not themselves been validated on the patient cohort. Therefore, the SYNTAX score might have inherent limitations in its applicability to real-world practice. Secondly, significant interobserver variation in SYNTAX score, attributable to differences in measurements of complex coronary anatomies, might have resulted in heterogeneous outcomes across studies. For example, the scoring system considers "countable segment" as a lesion >1.5 mm in diameter; visual angiographic interpretation might introduce a measurement bias. Furthermore, "angiographic-importance," as determined by vessel size, might not always reflect "clinical-importance," as determined by the requirement for revascularization. As a result, the interobserver variability of scores might be fairly exaggerated in patients with multiple coronary lesions. Finally, the disparities in follow-up duration, patient characteristics, and practice pattern across the various study cohorts might lead to the different results. Although the previous studies showing a strong predictability of the SYNTAX score had follow-up duration of <2 years (17,34), in our present study, more than 95% of patients were followed up for 3 years. Indeed, we found that the event curves for MACCE, when PCI and CABG were compared, gradually diverged beyond 1 year in the SYNTAX score groups. In addition, a higher rate of angiographic follow-up in our study might inflate the need of repeat revascularization, especially for patients undergoing PCI (10).

It is noteworthy, however, that the SYNTAX score is still a novel method to systemically represent angiographic complexity of each patient with a single numerical value. No previous angiographic scoring system can represent a patient-based morphology but a lesion-based morphology (34). Therefore, to improve its clinical performance while maintaining the unique advantage, our study suggested a modification of the SYNTAX score with consideration of clinical risk profiles. When the EuroSCORE was merged with the SYNTAX score in our analysis of discrimination and calibration, the C-index for MAVE was somewhat improved in PCI and CABG groups.

Several limitations of the present study should be addressed. First, the current prediction model was derived from large-volume referral hospitals in 1 Asian country. This might have affected the applicability of the risk score (25), indicating a need for further studies on calibration and discrimination ability of the SYNTAX score in geographically and temporally different populations. However, because our study included a wide range of patients who received BMS, DES, and contemporary CABG, our validation model might have been adequate for testing the effectiveness of risk scores in patients undergoing current revascularization therapies. Second, our validation cohort excluded patients with acute ST-segment elevation MI or cardiogenic shock who underwent emergency procedures. Previous risk models for patients undergoing PCI have shown different discriminative powers when elective and emergency procedures were compared (33). Third, our study was retrospectively performed for a selected population. Therefore, although angiographic analysis is independently performed in the core laboratory, a bias in assessing lesion morphology might be introduced. For instance, the decision of the angiographer about the presence of "disease" in each segment might be influenced by the procedures captured on the analytic angiograms. Furthermore, we need more tests to assess the reliability of measurements across diverse patient subsets. Finally, because our study exclusively enrolled patients with ULMCA stenosis, the validity of the SYNTAX score for other patients and lesions should be further examined in other prospective design studies.

Conclusions

Our validation test of the SYNTAX score suggested that this novel scoring model to present angiographic complexity might play a partial role in predicting long-term outcomes after PCI, not after CABG, in patients with ULMCA stenosis. An integration of a clinical risk prediction based on physician knowledge and experience and patient clinical characteristics might be required for better clinical performance of the SYNTAX score. Therefore, additional research on a useful risk stratification model is still warranted for the widespread and systemic application of a validated risk score.

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Key Words: coronary artery bypass graft surgery ■ coronary artery disease ■ prediction ■ stent.