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SYNTAX score based on coronary computed tomography angiography may have a prognostic value in patients with complex coronary artery disease

An observational study from a retrospective cohort

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Abstract

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score is an invasive coronary angiography (ICA)-based score for quantifying the complexity of coronary artery disease (CAD). Although the SYNTAX score was originally developed based on ICA, recent publications have reported that coronary computed tomography angiography (CCTA) is a feasible modality for the estimation of the SYNTAX score.

The aim of our study was to investigate the prognostic value of the SYNTAX score, based on CCTA for the prediction of major adverse cardiac and cerebrovascular events (MACCEs) in patients with complex CAD.

The current study was approved by the institutional review board of our institution, and informed consent was waived for this retrospective cohort study. We included 251 patients (173 men, mean age 66.0 ± 9.29 years) who had complex CAD [3-vessel disease or left main (LM) disease] on CCTA. SYNTAX score was obtained on the basis of CCTA. Follow-up clinical outcome data regarding composite MACCEs were also obtained. Cox proportional hazards models were developed to predict the risk of MACCEs based on clinical variables, treatment, and computed tomography (CT)-SYNTAX scores.

During the median follow-up period of 1517 days, there were 48 MACCEs. Univariate Cox hazards models demonstrated that MACCEs were associated with advanced age, low body mass index (BMI), and dyslipidemia ($P < .2$). In patients with LM disease, MACCEs were associated with a higher SYNTAX score. In patients with CT-SYNTAX score ≥23, patients who underwent coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention had significantly lower hazard ratios than patients who were treated with medication alone. In multivariate Cox hazards model, advanced age, low BMI, and higher SYNTAX score showed an increased hazard ratio for MACCE, while treatment with CABG showed a lower hazard ratio ($P < .2$).

On the basis of our results, CT-SYNTAX score can be a useful method for noninvasively predicting MACCEs in patients with complex CAD, especially in patients with LM disease.

Abbreviations: BMI = body mass index, CABG = coronary artery bypass graft surgery, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, ICA = invasive coronary angiography, LM = left main, MACCE = major adverse cardiac and cerebrovascular event, MI = myocardial infarction, MPR = multiplanar reformat, PCI = percutaneous coronary intervention, SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery, UA = unstable angina.

Keywords: complex coronary artery disease, coronary computed tomography angiography, prognosis, SYNTAX score

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1. Introduction

The complexity of coronary artery disease (CAD) is one of the main factors influencing the selection of treatment modality in patients with CAD, in addition to the extent of myocardial ischemia, patient and clinician preference, and other patient comorbidities.[1] Coronary artery bypass graft surgery (CABG) has been the standard of care for the revascularization of patients with complex CAD such as multivessel and left main (LM) coronary disease.[1] However, with the advancement of operator ability and device technologies for percutaneous coronary intervention (PCI), the use of PCI has expanded to the treatment of patients with increasingly complex CAD. The optimum method for the revascularization of these patients has been a matter of debate.

The SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) score has been developed to calculate complexity of CAD based on invasive coronary angiography (ICA).[2] The ICA-SYNTAX score can predict major adverse cardiac and cerebrovascular events (MACCEs) in populations with complex CAD (LM disease or 3-vessel disease),[3] and guide the optimal revascularization strategy. Among patients with complex CAD, CABG remains as the standard of care for patients with high (≥33) or intermediate (23–32) SYNTAX scores, whereas PCI is an acceptable alternative in patients with less complex disease (SYNTAX score ≤22).[4] Recent studies have reported the feasibility of coronary computed tomography angiography (CCTA) for the SYNTAX score.[5–9] A previous study demonstrated that the CT-SYNTAX score may have prognostic value for predicting major adverse cardiac events in patients with varying severities of CAD.[8] Nevertheless, the use of the CT-SYNTAX score in patients with complex CAD has not yet been well-established. Considering the high diagnostic accuracy of CT for CAD and the excellent correlation between the CT-SYNTAX score and ICA-SYNTAX score, we hypothesized that the CT-SYNTAX score may have prognostic value in patients with complex CAD.

The aim of our study was to investigate the prognostic value of the CT-SYNTAX score for the prediction of MACCEs in patients with complex CAD.

2. Methods

2.1. Patients

This study was approved by the institutional review board of our institution, and informed consent was waived. For this retrospective cohort study, we included 302 patients from a CCTA database of our institution, who met both of the following 2 criteria: LM or 3-vessel disease documented on dual-source CCTA from February 2010 to July 2011 and no previous PCI or CABG. Fifty-one patients who were lost to follow-up (i.e., a follow-up period shorter than 4 years) were excluded from the study. Finally, a total of 251 patients consisted of our study population (Fig. 1). Of these patients, 92 and 54 were included in previous studies by Suh et al.[8,9] One study evaluated the long-term prognostic value of the CT-SYNTAX score in a population who underwent both CCTA and ICA, and compared the prognostic value of the CT-SYNTAX score and ICA-SYNTAX score.[8] Another study investigated the diagnostic accuracy of CCTA and the CT-SYNTAX score for selection of CABG candidates.[9] Our study focused on the prognostic value of the CT-SYNTAX score in patients with complex CAD as documented on CCTA. Demographic data and information on cardiovascular risk factors were collected from the electronic medical records.

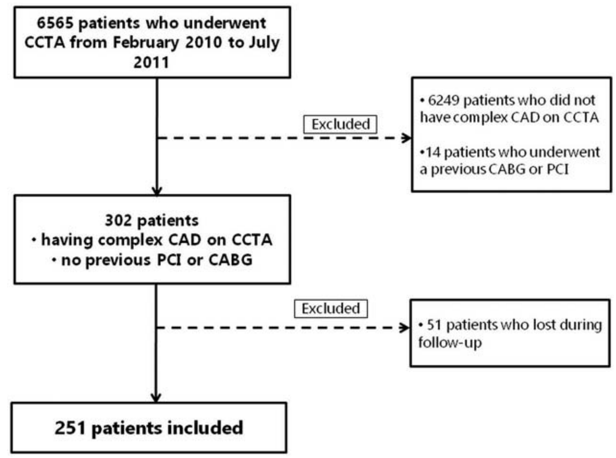

Figure 1. Flow chart of the study population. CCTA = coronary computed tomography angiography; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

2.2. Image acquisition

Computed tomographic (CT) scans were performed using a dual-source CT scanner (SOMATOM Definition Flash; Siemens Health Care, Forchheim, Germany), as described in detail previously.[8] Image reconstructions were conducted as previously described, using filtered back projection with a medium kernel (b36f), and the slice thickness of 0.75 mm with 0.5 mm increments.[8]

2.3. Image analysis

The CCTA images were independently analyzed by 2 reviewers who were blinded to the clinical history, and final diagnosis was made by consensus reading in case of interreader discrepancies. Presence of significant CAD (>50% stenosis in diameter) was analyzed using a 16-segment model from the American Heart Association classification.[10]

2.4. Calculation of the CT-SYNTAX Score

CT-SYNTAX score was obtained using the SYNTAX score calculator version 2.11 (www.syntaxscore.com),[2] as previously described.[5,11] Two reviewers independently calculated the SYNTAX score and the final score was made by a consensus.

2.5. Follow-up data

From the electronic medical records, follow-up data were reviewed and collected. The primary end point was the occurrence of MACCEs, including cardiac death, nonfatal myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization either by PCI or CABG after 90 days from index CCTA, or stroke.

2.6. Statistical analysis

Categorical variables were expressed as numbers with percentages, and continuous variables are expressed as means with standard deviations. Differences between groups were analyzed using the Chi-square or Fisher exact tests for categorical variables, and using the Student *t* test or Mann–Whitney *U* test for continuous variables. We set 2 subgroups according to the extent of anatomical CAD: patients with LM disease (with or without additional vessel involvement), and those with 3-vessel disease in the absence of LM disease. Moreover, patients were divided according to the CT-SYNTAX score into 3 categories: score < 22, 23 to 32, or ≥33. Cumulative event rates were demonstrated using Kaplan–Meier survival curve for the CT-SYNTAX score groups and compared using the log-rank test. Cox regression analyses were used to identify predictors of MACCEs. Hazard ratios were assessed as an estimation of risk with 95% confidence intervals (95% CIs). The predictive ability of Cox regression was assessed using Harrell c statistics.[12] A *P* value of less than .05 was considered statistically significant, although a *P* value of less than .2 was the cutoff for statistical significance in the Cox regression analyses. All analyses were performed with R (version 3.2.4.; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

The study population consisted of 251 patients (173 men, mean age 66.0 ± 9.29 years). The clinical characteristics are demonstrated in Table 1. One hundred eighty-seven patients (74.5%) had 3-vessel disease without LM disease, and 37 patients (14.7%) had LM disease without 3-vessel disease. Twenty-seven patients (10.8%) showed LM disease with 3-vessel disease.

3.2. SYNTAX score based on CCTA

The CT-SYNTAX score had a median of 17 (25th to 75th percentile, 12.3–23). When patients were divided into 3 subsets based on SYNTAX score, the number of patients in each group was as follows: SYNTAX score group 1 (≤22, n = 182), group 2 (23–32, n = 50), and group 3 (≥33, n = 19).

3.3. Follow-up data and clinical and CT variables associated with MACCEs

During the median follow-up period of 1517 days (25th to 75th percentile, 1312–1674 days), there were a total of 48 MACCEs (event rate 19.1%). The 48 composite MACCEs included 23 cardiac deaths, 1 nonfatal MI, 2 episodes of UA requiring hospitalization, 12 revascularizations after 90 days of index test, 3 cases of nonfatal MI and late revascularization, 3 cases of UA requiring hospitalization and late revascularization, and 4 strokes. Early revascularization (less than 90 days after index CT) was performed in 149 patients (106 PCI and 43 CABG).

Figure 2 depicts the Kaplan–Meier estimates of the cumulative probability of MACCEs as stratified by the SYNTAX score based on CCTA. Kaplan–Meier survival curves showed that cumulative events did not significantly increase with CT-SYNTAX score in the overall study group and in patients without LM disease (log-rank test, $P > .05$). However, the cumulative events showed a significant increase with increasing CT-SYNTAX scores in patients with LM disease ($P = .037$). Figure 3 demonstrates the Kaplan–Meier estimates of the cumulative probability of MACCEs according to the treatment methods. In the overall study group, no significant difference was observed in the cumulative events between the treatment methods. In patients with a low SYNTAX score (0–22), the cumulative event rate was not different according to the treatment, whereas patients with an intermediate or high SYNTAX score (≥23) showed a significant difference between groups ($P = .028$).

In univariate Cox regression analysis, advanced age, low BMI, and dyslipidemia were predictors of MACCEs among the clinical variables ($P < .2$, Table 2). Sex, hypertension, diabetes, smoking, and Framingham risk score were not associated with increasing hazard ratios for MACCEs. Patients with a high SYNTAX score (≥33) showed an increased hazard ratio (2.054, 95% CI 0.857–4.93) for MACCEs compared with patients with a low

Table 1

Baseline characteristics of the study group according to the SYNTAX score category on CCTA.

	SYNTAX group 1 (n = 182)	SYNTAX group 2 (n = 50)	SYNTAX group 3 (n = 19)	*P*
Male	120	38	15	.197
Age	65.4 ± 9.41	67.0 ± 8.97	68.2 ± 8.79	.310
BMI	24.2 ± 3.43	24.3 ± 2.97	23.9 ± 2.21	.917
Diabetes	57	11	6	.375
Hypertension	111	32	14	.373
Dyslipidemia	29	14	3	.168
Current smoker	**29**	**7**	**7**	**.026**
Chest pain				.219
Typical	27	6	1	
Atypical	46	7	6	
Nonanginal	41	17	2	
Asymptomatic	68	21	9	
LVEF	**65.4 ± 10.9 (n = 145)**	**60.4 ± 12.8 (n = 41)**	**40.9 ± 13.0 (n = 18)**	**.026**
Pretest probability				.838
Very low	2	2	0	
Low	63	18	8	
Intermediate	88	24	9	
High	20	5	1	
Nonapplicable	9	2	0	

Data are numbers of patients with percentages in parentheses.
BMI = body mass index, CCTA = coronary computed tomography angiography, LVEF = left ventricular ejection fraction.
Bold values indicate statistical significance.

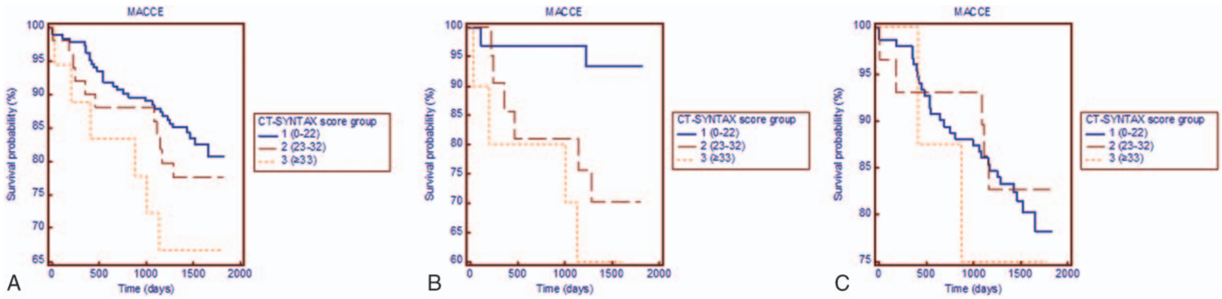

Figure 2. Kaplan–Meier curves for the prediction of MACCEs according to the CT-based SYNTAX score (A) in the entire population, (B) patients with LM disease, and (C) patients with 3-vessel disease without LM involvement. All patients (n=251, P=.222), patients with LM disease (n=64, P=.037), (c) patients with 3-vessel disease without LM involvement (n=187, P=.899). CT = computed tomography; LM = left main coronary artery; MACCE = major adverse cardiac and cerebrovascular event.

SYNTAX score (0–22) (P=.107). In patients with LM disease, MACCEs tended to increase with higher SYNTAX scores (P<.2). With regard to treatment method, patients who underwent CABG showed decreased hazard ratios for MACCEs compared with patients who received medical treatment (0.352, 95% CI 0.123–1.01; P=.0528). In the subgroup analysis of patients with intermediate to high SYNTAX scores (≥23), patients with PCI and CABG showed decreased hazard ratios for MACCEs compared with patients who received medical treatment (hazard ratio 0.489, 95% CI 0.167–1.431, P=.192 for PCI; hazard ratio 0.158, 95% CI 0.0345–0.721, P=.0172 for CABG). In multivariate analysis, patients with advanced age, low

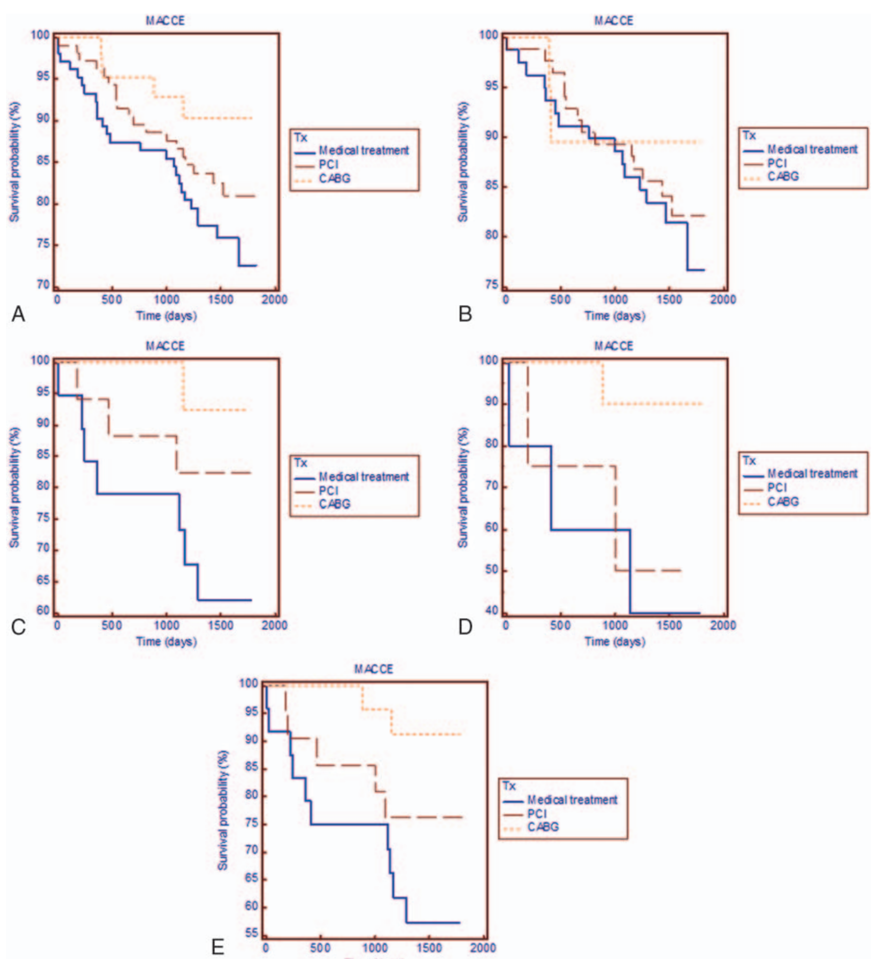

Figure 3. Kaplan–Meier curves for the prediction of MACCEs according to the treatment methods, all patients (n=251, P=.113), SYNTAX score group 1 (0–22; n=182, P=.708), SYNTAX score group 2 (23–32; n=50, P=.118), SYNTAX score group 3 (≥33; n=19, P=.0989), SYNTAX score group 2 and 3 (≥33, n=69, P=.028), CABG = coronary artery bypass graft surgery; MACCE = major adverse cardiac and cerebrovascular event; PCI = percutaneous coronary intervention.

Table 2

Univariate Cox regression analysis for the prediction of MACCEs.

Variables	HR	95% CI	*P*
Clinical variables			
Sex			
Male	1		Reference
Female	0.7154	0.3722–1.375	.315
Age	**1.0561**	**1.0215–1.0919**	**.0014**
BMI	**0.9121**	**0.8566–0.9712**	**.0041**
Hypertension			
No	1		Reference
Yes	1.188	0.652–2.166	.573
Diabetes			
No	1		Reference
Yes	0.8776	0.4643–1.659	.6876
Dyslipidemia			
No	1		
Yes	**0.4961**	**0.1964–1.253**	**.1381**
Smoke			.9343
Never smoker	1		Reference
Former smoker	0.9998	0.5191–1.923	.998
Current smoker	1.1460	0.5347–2.455	.727
FRS	1.022	0.9879–1.058	.205
LVEF	1.001	0.9741–1.03	.936
CT-SYNTAX score (continuous)	1.026	0.992–1.061	.136
CT-SYNTAX score (group)			
Entire group			.2489
Group 1 (SYNTAX score 0–22)	1		Reference
Group 2 (SYNTAX score 23–32)	1.299	0.6526–2.584	.457
Group 3 (SYNTAX score ≥33)	**2.054**	**0.8569–4.925**	**.107**
Patients with LM disease			
Group 1 (SYNTAX score 0–22)	1		Reference
Group 2 (SYNTAX score 23–32)	**4.946**	**0.9969–24.54**	**.0504**
Group 3 (SYNTAX score ≥33)	**6.769**	**1.2384–37.00**	**.0273**
Patients without LM disease			
Group 1 (SYNTAX score 0–22)	1		Reference
Group 2 (SYNTAX score 23–32)	0.8236	0.3185–2.129	.689
Group 3 (SYNTAX score ≥33)	1.3018	0.3104–5.461	.718
Treatment			
Entire group			
Medical treatment	1		Reference
PCI	0.6903	0.3800–1.254	.2236
CABG	**0.3524**	**0.1226–1.012**	**.0528**
Group 1 (SYNTAX score 0–22)			
Medical treatment	1		Reference
PCI	0.8339	0.4023–1.729	.625
CABG	0.5643	0.1290–2.468	.447
Group 2 and 3 (SYNTAX score ≥23)			
Medical treatment	1		Reference
PCI	**0.4889**	**0.1670–1.4311**	**.1916**
CABG	**0.1577**	**0.0345–0.7207**	**.0172**

BMI = body mass index, CABG = coronary artery bypass graft surgery, CI = confidence interval, FRS = Framingham risk score, HR = hazard ratio, LM = left main coronary artery, LVEF = left ventricular ejection fraction, MACCE = major adverse cardiac and cerebrovascular event, PCI = percutaneous coronary intervention.
Bold values indicate statistical significance.

BMI, and higher SYNTAX scores had an increased hazard ratio, and treatment with CABG resulted in a lower hazard ratio (Table 3, $P < .2$; Harrell C statistic = 0.675).

4. Discussion

Our study shows that the CT-based SYNTAX score has prognostic value for predicting MACCEs and for guiding optimal treatment methods in patients with complex CAD on CCTA. Patients with a high SYNTAX score (≥33) showed an increased hazard ratio for MACCEs compared with patients with a low SYNTAX score (0–22). In particular, MACCEs tended to increase with higher SYNTAX scores in patients with LM disease. In patients with a CT-SYNTAX score ≥23, those who underwent CABG and PCI showed significantly lower hazard ratios than patients who were treated with medication alone. In the multivariate analysis, clinical factors such as advanced age and low BMI in addition to higher SYNTAX scores resulted in higher hazard ratios for MACCES, while treatment with CABG resulted in lower hazard ratios.

The prognostic value of the SYNTAX score calculated from ICA has been well-established, indicating that a high SYNTAX

Table 3

Multivariate Cox regression analysis for the prediction of MACCEs.

Variables	HR	95% CI	P
Clinical variables			
Age	**1.0388**	**1.0035–1.0753**	**.0311**
BMI	**0.9358**	**0.8715–1.0048**	**.0676**
Dyslipidemia	0.5786	0.2235–1.4982	.2597
Treatment			
Medical treatment	1 (Reference)		
PCI	0.9233	0.4959–1.7190	.8013
CABG	**0.3279**	**0.1089–0.9873**	**.0474**
CT-SYNTAX score			
Group 1 (SYNTAX score 0–22)	1 (Reference)		
Group 2 (SYNTAX score 23–32)	**1.6052**	**0.7900–3.2615**	**.1907**
Group 3 (SYNTAX score ≥33)	**2.7442**	**1.0976–6.8614**	**.0308**

BMI = body mass index, CABG = coronary artery bypass graft surgery, CI = confidence interval, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular event, PCI = percutaneous coronary intervention.
Bold values indicate statistical significance.

score is an independent predictor of worse outcome after revascularization (PCI or CABG).[4,13–19] A recent randomized clinical trial reported that among patients with complex CAD, the low (0–22) SYNTAX score group did not have significantly different rates of MACCEs between treatment groups (CABG vs PCI). In contrast, patients with intermediate (23–32) or high SYNTAX scores (≥33) had significantly increased MACCEs with PCI than with CABG.[4] Outcomes based on the overall results of this trial at 5 years suggest that CABG should remain the standard of care for patients with high or intermediate SYNTAX scores, while PCI is an acceptable alternative for patients with low SYNTAX scores.[4] Consistently, CABG is recommended for improving survival in patients with significant LM disease or 3-vessel disease as class I recommendation, whereas PCI is considered as a reasonable alternative to CABG in case of significant LM disease with low SYNTAX score (≤22) as class IIa recommendation, and low-intermediate SYNTAX score (<33) as class IIb recommendation.[1] Similarly, in our study, hazard ratios for the occurrence of MACCEs were different according to treatment methods in patients with intermediate or high CT-SYNTAX scores (≥23), but not in patients with low CT-SYNTAX scores (0–22). This result may suggest that CCTA can be a useful modality to calculate the complexity of CAD and stratify patients for appropriate treatment planning.

Most previous studies on the SYNTAX score based on CCTA have focused on the feasibility and reproducibility of CT-based SYNTAX scoring by using ICA-based SYNTAX score as a reference standard, and showed both a positive correlation and moderate-to-good agreement between CT-SYNTAX score and ICA-SYNTAX score.[5,7,11,20,21] A previous study reported high diagnostic accuracy (sensitivity 80% and specificity 83%) of CT-STYNAX score for detecting patients with high SYNTAX score (≥33) categories.[7] CCTA offers advantages over ICA in calculating SYNTAX score in case of assessing the length of the occluded segment, as well as for evaluating LM ostial lesion, as LM lesions by ICA is difficult to assess due to vessel overlap and foreshortening.[7,9,22] CT-SYNTAX score can have various clinical applications for classifying patients with CAD, predicting complex PCI, and selecting CABG candidates. [7,9,22–24] As of now, only 1 study has reported the prognostic value of CT-SYNTAX score in patients who underwent both CCTA and ICA.[8] Interestingly, on both CCTA and ICA, high SYNTAX scores increased hazard ratios compared with low SYNTAX scores.[8] However, the SYNTAX score was initially designed to quantify the complexity of LM or 3-vessel disease, and calculating the SYNTAX score is considered to be more valuable in complex CAD. As the study population of the previous study included patients with varying extents of CAD, patients with complex CAD consisted of only 21.9% of the overall population. In contrast, all of our study population had complex CAD on CCTA, and the result of multivariate Cox hazard model demonstrated that increasing CT-SYNTAX score was an independent predictor for MACCEs in patients with complex CAD. Such result may support the hypothesis that the SYNTAX score based on CCTA has prognostic value in patients with complex CAD.

In addition to the CT-SYNTAX score and treatment methods, clinical risk factors such as age and BMI were revealed to be independent predictors for MACCEs in our study. Advanced age and obesity are considered as risk factors of CAD. However, lower BMI was associated with higher MACCEs in our study. In fact, the impact of BMI on the occurrence of MACCEs is controversial. Previous studies have reported that overweight or obesity was related with similar or lower mortality and MACCE after coronary revascularization.[25] This gives rise to the "obesity paradox" and can be explained by selection bias in previous investigations, the effect of increased metabolic reserve due to obesity, and improved outcomes after revascularization because of larger vessel size and easier stent placement in patients with large body size.[26,27]

Our study had some limitations. First, as the current study was a retrospective study performed at a single institution, the number of patients was relatively small and selection bias was possible. In particular, the loss of a substantial number (51 of 302 patients, 16.9%) of patients during follow-up could have been a considerable limitation. Second, among 48 MACCEs that occurred in our study population, only 24 cases (50%) had a hard outcome (23 cardiac deaths and 1 nonfatal MI). Third, CT-based SYNTAX score may be different from ICA-based SYNTAX score, which may result in different SYNTAX group categories between the 2 modalities. However, previous studies reported a good correlation between CT-based and ICA-based SYNTAX scores in patients with complex CAD, and a good agreement for classifying the SYNTAX score categories.[7] Although the CT-SYNTAX scores may be valuable for noninvasively stratifying patients based on clinical outcomes and providing information about the optimal treatment strategy, the importance of ICA should not be overlooked, considering further information by ICA with fractional flow reserve and intracoronary imaging for corrective diagnosis and appropriate treatment. Finally, we did not consider other factors that can affect treatment selection and prognosis, such as myocardial ischemia and coronary plaque characteristics. We believe that a future prospective study using a larger population may be able to address this issue.

In conclusion, the CT-SYNTAX score can be a useful method for noninvasively predicting MACCEs and for guiding treatment methods in patients with complex CAD. A higher SYNTAX score was associated with increasing MACCEs and treatment with CABG was associated a lower hazard ratio for MACCEs.

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