Inter- and Intra-Observer Variability for Assessment of the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) Score and Association of the SYNTAX Score With Clinical Outcome in Patients Undergoing Unprotected Left Main Stenting in the Real World

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Background: The Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) score was proposed as a method to evaluate the complexity of coronary anatomy. However, the reproducibility of assessment for the SYNTAX score in unprotected left main coronary artery (ULMCA) disease has not yet been adequately evaluated. The purpose of this study is to assess inter- and intra-observer variability for the assessment of the SYNTAX score in patients undergoing ULMCA stenting in daily clinical practice.

Methods and Results: The SYNTAX score of 101 consecutive patients who underwent ULMCA stenting with sirolimus-eluting stent was independently assessed by 2 experienced interventional cardiologists. One of the 2 cardiologists evaluated all the cases again 6 months after the initial assessment. The κ value for inter-observer variability in estimating the SYNTAX score was 0.62 according to the dichotomized analysis (≥ 33 , < 33) and 0.58 according to the tertile analysis (< 23 , $23 \leq < 33$, ≥ 33), while the intra-observer variability was 0.78 and 0.69, respectively. Patients with a high SYNTAX score (≥ 33 , $n=55$) compared with those with low or intermediate score (< 33 , $n=46$) had a significantly higher rate of target-lesion revascularization (TLR) of the ULMCA lesion at 2 years (24% vs. 4.4%, $P=0.01$).

Conclusions: Both inter- and intra-observer variability for estimating the SYNTAX score were within an acceptable range and a high SYNTAX score showed a higher rate of TLR in patients undergoing ULMCA stenting in daily clinical practice. (*Circ J* 2011; **75**: 1130–1137)

Key Words: Coronary disease; Percutaneous coronary intervention; Revascularization; SYNTAX score

Percutaneous coronary intervention (PCI) has been considered as a contraindication in patients with unprotected left main coronary artery (ULMCA) disease. Recently, however, several studies reported favorable clinical outcomes in patients undergoing ULMCA stenting using a drug-eluting stent.^{1–7} Therefore, PCI with drug-eluting stent

for left main disease is emerging as a possible alternative treatment for coronary artery bypass grafting (CABG). However, appropriate criteria in selecting coronary revascularization procedures, such as PCI or CABG, has not been established in patients with ULMCA disease. The Synergy Between Percutaneous Coronary Intervention With TAXUS

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and Cardiac Surgery (SYNTAX) score was proposed as a method to evaluate the complexity of coronary anatomy.^{8,9} In the SYNTAX trial, the SYNTAX score has shown good discriminative ability between patients suitable for either CABG or PCI, and the reproducibility of estimation of the SYNTAX score has indicated an acceptable degree of agreement.^{9,10} However, the reproducibility of estimation for the SYNTAX score and the predictive ability of the SYNTAX score for clinical outcome have not yet been adequately evaluated in real world clinical practice.

The aim of this study was to evaluate inter- and intra-observer variability for estimating the SYNTAX score in patients undergoing ULMCA stenting with sirolimus-eluting stent (SES) in real world clinical practice. As an exploratory analysis, 2-year clinical outcomes were also assessed according to the SYNTAX score.

Methods

Patient Population

The study population consisted of 101 consecutive patients who underwent PCI with SES for de novo ULMCA disease at Kyoto University Hospital between September 2004 and December 2008. The left main coronary artery lesion was regarded as unprotected if there was no patent bypass graft to the left anterior descending coronary artery or left circumflex coronary artery. PCI was performed in patients who preferred PCI rather than CABG and in patients who were considered to have an unacceptably high risk for CABG. All procedures, including stenting techniques, were left to the discretion of the operators. The recommended antiplatelet regimen included aspirin (81 mg/day) indefinitely and thienopyridine (200 mg of ticlopidine or 75 mg of clopidogrel daily) for at least 3 months. The loading dose and the duration of dual-antiplatelet therapy was left to the discretion of each attending physician.

Written informed consent on the procedure and follow-up protocol was obtained from all patients before the procedure was carried out. The study protocol was approved by the ethical committee of Kyoto University.

Calculation of the SYNTAX Score and Assessment for Inter- and Intra-Observer Variability

The SYNTAX score was calculated by using the SYNTAX score calculator (available at <http://www.syntaxscore.com>). The total SYNTAX score was composed of the individual scores for each separate lesion with a diameter stenosis of $\geq 50\%$ in a vessel of ≥ 1.5 mm in diameter by visual assessment. The details of the SYNTAX score calculation were previously reported.⁹

To assess inter-observer variability, the SYNTAX score was calculated independently by 2 experienced interventional cardiologists, who were blinded to the procedural results and clinical outcomes. Furthermore, one of the 2 observers calculated all the cases again 6 months after the initial calculation to assess intra-observer variability. The observer was blinded to the results of the initial calculation.

Evaluation of the Correlation Between SYNTAX Score and Clinical Outcomes

As an exploratory analysis, 2-year clinical outcomes were also assessed according to the SYNTAX score. To assess the correlation between SYNTAX score and clinical outcomes, we divided the patients into 2 groups: low–intermediate score group (SYNTAX score < 33) and high score group (SYNTAX

Table 1. Quantitative Classification of κ Value

κ value	Degree of agreement
< 0.01	Less than chance agreement
0.01–0.20	Slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Almost perfect agreement

score ≥ 33). The cutoff point of 33 was set according to the SYNTAX trial result, which suggested that compared with CABG, PCI was associated with a higher rate of major cardiac and cerebrovascular events (MACCE) in patients with a SYNTAX score of ≥ 33 , but not in patients with a SYNTAX score of < 33 .⁸ In the case of disagreement between observers on the assessment of the SYNTAX score, the decision of a third observer was obtained after the assessment of inter- and intra-observer variability was completed.

Data on clinical, lesion, and procedural characteristics were obtained from medical records. Follow-up information was obtained either from a review of the hospital record or by telephone contacts with the patients, the family members, or the primary care physician.

The endpoints assessed included all-cause death, cardiac death, sudden cardiac death, myocardial infarction (MI), stent thrombosis (ST), stroke, target lesion revascularization (TLR), and any coronary revascularization. Two combined endpoints were also assessed including a composite of death, MI, or stroke, and a composite of death, MI, stroke, or any coronary revascularization (MACCE). Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was adjudicated according to the definition in the Arterial Revascularization Therapy Study.¹⁰ ST was defined according to the Academic Research Consortium (ARC) definition.¹¹ Stroke was defined as a symptomatic cerebrovascular event confirmed by imaging studies. TLR was defined as either PCI or CABG due to restenosis or thrombosis of the ULMCA lesion that included the proximal and distal edge segments as well as the ostium of the side branches.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD unless otherwise indicated and were compared with Student's t-test or Wilcoxon rank sum test on the basis of their distribution. Categorical variables were presented as numbers and/or percentages, and were compared with the chi-square test or Fisher's exact test, as appropriate. Cumulative incidences of adverse events were estimated by the Kaplan-Meier method and compared using the log-rank test.

The degree of agreement was measured as a percentage of the total agreement using the κ statistic to evaluate inter- and intra-observer variability. The κ statistic is the most commonly used statistic for the evaluation of an agreement between 2 or more observations.¹² A κ value of 1 means perfect agreement, whereas a κ value of 0 means agreement equivalent to chance. The quantitative classification of the κ value is shown in Table 1.^{12–14} The κ statistic was calculated for the SYNTAX score dichotomies (< 33 , ≥ 33), and for the tertiles (< 23 , $23 \leq < 33$, ≥ 33). Regarding the components of scoring, the κ values for the presence of ostial lesion, true bifurcation, long lesion, and severe calcification in the ULMCA lesions were also evaluated.

All statistical tests were 2-tailed. P-values of less than 0.05

Table 2. SYNTAX Score Variability					
	Initial calculation	Inter-observer	κ value	Intra-observer	κ value
Total SYNTAX score (mean ±SD)	34.1±8.8	33.8±8.6	—	33.4±8.5	—
Dichotomies (Low-Intermediate/High: %)	45/56 (45/55)	46/55 (46/54)	0.62	44/57 (44/56)	0.78
Tertiles (Low/Intermediate/High: %)	8/37/56 (8/37/55)	11/35/55 (11/35/54)	0.58	14/30/57 (14/30/56)	0.69
Components of scoring in left main lesion					
True bifurcation	54 (53%)	59 (58%)	0.50	59 (58%)	0.74
Aorto ostial lesion	17 (17%)	18 (18%)	0.48	12 (12%)	0.56
Long lesion (>20 mm)	65 (64%)	55 (54%)	0.23	68 (67%)	0.27
Severe calcification	48 (48%)	21 (21%)	0.12	61 (60%)	0.47

Values are mean ±SD or n (%).

were considered statistically significant. Statistical analysis was performed with JMP 7.0.1 software (SAS Institute Inc, Cary, NC, USA).

The authors had full access to the data and took responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Variability for Assessment of the SYNTAX Score

Inter-Observer Variability The mean SYNTAX score calculated by Observer 1 was 34.1±8.8 (range 10–53.5), whereas that calculated by Observer 2 was 33.8±8.6 (range 11–56) (Figure 1A). The mean difference in the SYNTAX score between the 2 observers was 4.7±6.6. The κ values in the evaluation of inter-observer variability were 0.62 for the SYNTAX score dichotomies (<33, ≥33), and 0.58 for the SYNTAX score tertiles (<23, 23≤–<33, ≥33). Regarding the components of scoring, the κ values for the evaluation of inter-observer variability were 0.48 for ostial lesion, 0.50 for true bifurcation, 0.23 for long lesion and 0.12 for severe

calcification (Table 2).

Intra-Observer Variability The mean SYNTAX scores in the first and second calculation performed by Observer 1 were 34.1±8.8 (range 10–53.5), and 33.4±8.5 (range 11–52), respectively (Figure 1B). The mean difference in the SYNTAX score between the first and second calculation was 4.0±5.2. The κ value for the evaluation of intra-observer variability was 0.78 for the SYNTAX score dichotomies (<33, ≥33), and 0.69 for the SYNTAX score tertiles (<23, 23≤–<33, ≥33). Regarding the components of scoring, the κ values for the evaluation of intra-observer variability were 0.56 for ostial lesion, 0.74 for true bifurcation, 0.27 for long lesion, and 0.47 for severe calcification (Table 2).

SYNTAX Score and Clinical Outcomes

Baseline Characteristics Among 101 consecutive patients undergoing ULMCA stenting with SES, 46 patients had a low–intermediate SYNTAX score and 55 patients had a high SYNTAX score. The mean SYNTAX score was 40.6±5.4 in the high score group and 26.3±5.3 in the low–intermediate score group.

Table 3. Patient, Lesion, and Procedural Characteristics

Characteristics	Low-intermediate SYNTAX score (n=46)	High SYNTAX score (n=55)	P value
(A) Patient characteristics			
Age (years)	71.0±10.0	71.4±9.7	NS
Age ≥80 years, %	17	20	NS
Female gender, %	22	20	NS
Body mass index ≥25, %	26	31	NS
Ejection fraction	58.1±15.3	58.1±13.4	NS
Ejection fraction <30%, %	4.8	2.0	NS
Heart failure, %	8.7	16	NS
Prior myocardial infarction, %	13	20	NS
Prior percutaneous coronary intervention, %	35	31	NS
Angina pectoris (symptom), %	63	78	0.09
ACS, %	13	13	NS
Diabetes mellitus, %	41	56	NS
History of hypertension, %	74	62	NS
Dyslipidemia, %	65	64	NS
Current smoker, %	22	20	NS
Chronic kidney disease (GFR <30), %	11	13	NS
Dialysis, %	6.5	9.1	NS
(B) Lesion characteristics			
Distal bifurcation involvement, %	76	96	0.02
Left dominance, %	35	35	NS
Extent of coronary artery disease			<0.001
Isolated ULMCA, %	11	1.8	
ULMCA + 1 vessel disease, %	41	9.1	
ULMCA + 2 vessel disease, %	39	62	
ULMCA + 3 vessel disease, %	8.7	27	
Total occlusion, %	2.2	22	0.001
Total SYNTAX score	26.3±5.3	40.6±5.4	<0.001
(C) Procedural characteristics			
Number of stents implanted (per patient)	2.1±1.1	3.7±1.6	<0.001
Total stent length, mm (per patient)	45.3±29.4	88.3±39.0	<0.001
Stent diameter/left main, mm	3.5±0.1	3.5±0.1	NS
Elective two-stent, %	8.7	22	0.07
Two-stent (final), %	11	31	0.01
Two-stent technique			0.04
Classical T stenting, %	8.7	18	
Modified T stenting, %	0	7.3	
Crash stenting, %	2.2	1.8	
Culotte stenting, %	0	0	
Y stenting, %	0	3.6	
Final kissing balloon technique, %	82	75	NS

Values are percentages or mean±SD.

ACS, acute coronary syndrome; GFR, glomerular filtration rate (ml·min⁻¹·1.73mm⁻¹).

Although there was no significant difference in baseline clinical characteristics between the 2 groups, the high SYNTAX score group tended to have more patients with heart failure and diabetes. The high SYNTAX score group had a higher prevalence of left main distal bifurcation lesions, and multi-vessel coronary artery disease. The total number of stents and total stent length per patient were significantly greater in the high SYNTAX score group than in the low-intermediate SYNTAX score group. The 2-stent technique (stenting of both main- and side-branches) was more frequently used in the high SYNTAX score group than in the low-intermediate SYNTAX score group (Table 3).

Clinical Outcomes

Angiographic success was obtained 100% in both groups. The mean clinical follow-up period was 794±315 days, and the clinical follow-up rate was 99.0% at 1 year and 93.1% at 2 years. Angiographic follow-up was performed in 82.2% of patients.

There was no significant difference in the rate of any clinical events between the 2 groups at the time of hospital discharge (Table 4). There was also no difference in the incidence of all-cause death and cardiac death within the 2 years between the low-intermediate score group and the high score group (15% vs. 9.2%, P=0.36 and 3.0% vs. 7.3%,

Table 4. Clinical Outcome at Hospital Discharge and After 2 Years

Characteristic	N of events (Incidence)		P value
	Low-intermediate SYNTAX score (n=46)	High SYNTAX score (n=55)	
At hospital discharge			
All-cause death	1 (2.2%)	1 (1.8%)	NS
Cardiac death	0 (0%)	1 (1.8%)	NS
Sudden cardiac death	0 (0%)	0 (0%)	NS
Myocardial infarction	1 (2.2%)	1 (1.8%)	NS
Stent thrombosis (definite)	0 (0%)	1 (1.8%)	NS
Stroke	1 (2.2%)	0 (0%)	NS
Target lesion revascularization	0 (0%)	1 (1.8%)	NS
Any revascularization	0 (0%)	1 (1.8%)	NS
Death/MI/stroke	3 (6.5%)	2 (3.6%)	NS
MACCE	3 (6.5%)	2 (3.6%)	NS
At 2 years after procedure			
All-cause death	6 (15%)	5 (9.2%)	NS
Cardiac death	1 (3.0%)	4 (7.3%)	NS
Sudden cardiac death	0 (0%)	2 (3.7%)	NS
Myocardial infarction	2 (5.3%)	3 (6.0%)	NS
Stent thrombosis (definite)	1 (3.0%)	2 (4.1%)	NS
Stroke	4 (9.1%)	2 (3.8%)	NS
Target lesion revascularization	2 (4.4%)	12 (24%)	0.01
Any revascularization	5 (11%)	14 (28%)	0.07
Death/MI/stroke	8 (19%)	8 (15%)	NS
MACCE	12 (28%)	19 (36%)	NS

Values are n (%).

MI, myocardial infarction; MACCE, major adverse cardiac or cerebrovascular event.

	High score	baseline	1 year	2 years
Incidence			7.3%	9.2%
N of events			4	5
N of patients at risk	55	55	51	41
Low-intermediate score				
Incidence			4.4%	15.0%
N of events			2	6
N of patients at risk	46	46	44	31

Figure 2. Unadjusted Kaplan-Meier curves for cumulative incidence of all-cause death (A), and cardiac death (B) between the low-intermediate score group and high score group.

Figure 3. Unadjusted Kaplan-Meier curves for cumulative incidence of target lesion revascularization (A) and any revascularization (B) between the low-intermediate score group and high score group.

Figure 4. Unadjusted Kaplan-Meier curves for cumulative incidence of death, MI, or stroke (A) and MACCE (B) between the low-intermediate score group and high score group. MI, myocardial infarction; MACCE, major adverse cardiac and cerebrovascular events.

P=0.26, respectively) (Figure 2; Table 4). The incidence of TLR was significantly higher in the high score group than in the low–intermediate score group (24.3% vs. 4.4%, P=0.01, respectively) (Figure 3A). The incidence of any revascularization tended to be higher in the high score group than in the low–intermediate group (28.2% vs. 11.3%, P=0.07, respectively) (Figure 3B). The incidences of a composite of death, MI, or stroke, and MACCE were not different between the low–intermediate score group and the high score group (18.9% vs. 14.9%, P=0.53 and 27.6% vs. 35.8%, P=0.53, respectively) (Figure 4).

Discussion

The main findings in the present study are as follows: (1) both inter- and intra-observer variability for estimating the SYNTAX score were within the acceptable range in patients undergoing ULMCA stenting in daily clinical practice; and (2) the incidence of TLR was significantly higher in the high SYNTAX score group than in the low–intermediate SYNTAX score group.

Reproducibility of Estimation for the SYNTAX Score

Both inter- and intra-observer variability for estimation of the SYNTAX score in the present study indicated a moderate to substantial degree of agreement beyond chance (the κ value of inter- and intra-observer variability: 0.62, and 0.78, respectively). The degree of agreement in the current analysis in real world clinical practice was consistent with previous results evaluating the SYNTAX score variability in patients enrolled in SYNTAX trial.^{15,16}

Contrary to a previous report suggesting poor reproducibility of estimation of the SYNTAX score in patients with ULMCA disease,¹⁶ the agreement for estimation of the SYNTAX score in the present study was revealed to be of a moderate to substantial degree. One of the reasons why we could obtain such a result was that the analysis was performed retrospectively on the premise that the significant stenosis existed in the left main coronary artery, although observers were blinded to the procedural results and clinical outcomes. Indeed, angiographic evaluation of the significance of the intermediate stenosis in the left main coronary artery was reported to be more difficult compared with lesions in other locations, although the impact of the decision is clinically greater in left main coronary artery lesions.^{17–19}

The present study also evaluated the variability for estimation of the components of scoring, such as the presence of true bifurcation or long lesion in the ULMCA lesions. As shown in Table 2, the reproducibility of estimation for the components of scoring was relatively poor compared with that for the total SYNTAX score. This result highlighted the difficulty in assessing individual components of scoring reproducibility as suggested by previous studies.^{20,21} However, the total extent of atherosclerotic changes and anatomic complexities, which were reflected by the total SYNTAX score, would be more predictive of clinical outcomes after PCI than the individual components of scoring. A moderate to substantial degree of agreement for the total SYNTAX score would provide support for clinical applicability of the SYNTAX score.

Association of the SYNTAX Score With Clinical Outcomes

In the SYNTAX trial, there were incremental differences between PCI and CABG in the incidences of MACCE as the SYNTAX score increased.⁶ In a sub-analysis of left main

disease in the SYNTAX trial, the patients undergoing PCI had a significantly higher rate of MACCE compared with the patients receiving CABG in patients with a high SYNTAX score (≥ 33), but not in those with a low–intermediate score.²² Capodanno et al reported that a higher SYNTAX score was significantly associated with cardiac mortality and MACE in 255 patients who underwent PCI for left main disease in a single center.²³ The same group of investigators also reported that PCI resulted in a similar risk of 2-year mortality compared with CABG in patients with a SYNTAX score of ≤ 34 and in a significantly higher risk in patients with a SYNTAX score of >34 in 819 patients with left main disease undergoing revascularization in 2 Italian centers.²⁴

In the present study, we made an exploratory analysis for the correlation between the SYNTAX score and clinical outcomes. There was no significant difference between the 2 groups not only in all-cause death or cardiac death, but also in the composite endpoints such as MACCE. On the other hand, the incidence of TLR in the high score group was significantly higher compared to the low–intermediate score group. Also, the trend for a higher incidence of any coronary revascularization was consistent with the result from the SYNTAX trial. Obviously, the present analysis was not able to evaluate the incidence of death or cardiac death. Future studies with adequate statistical power would be needed to elucidate the correlation between the SYNTAX score and mortality after ULMCA stenting.

Study Limitations

The present study has several important limitations. First, as already mentioned, variability for the assessment of the SYNTAX score was retrospectively evaluated in a population with a known history of ULMCA stenting. Therefore, it would not be appropriate to extrapolate the current result to the broader patient population with severe coronary disease without ULMCA disease. Second, the reproducibility for assessing the SYNTAX score would be profoundly influenced by the experiences in SYNTAX score calculation and the efforts to reach the consensus between the observers before actual calculation. Finally, the study was limited by the retrospective single center study. The sample size was too small to evaluate clinical endpoints and no adjustment was made for the clinical characteristics.

Conclusions

Both inter- and intra-variability for estimating the SYNTAX score were acceptable and a high SYNTAX score showed a higher rate of TLR in patients who underwent ULMCA stenting in daily clinical practice.

Disclosures

Conflict of interest: Takeshi Kimura is an advisory board member, speaker, and recipient of research grants from Cordis Cardiology Japan, Johnson and Johnson. The remaining authors reported no conflicts.

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