【 ORIGINAL ARTICLE 】

Prognostic Significance of the Residual SYNTAX Score and Ischemic Reduction Detected with Nuclear Cardiology for Prediction of Major Cardiac Events after Revascularization

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Abstract:

Objective   There is no report on the risk stratification of major cardiac events (MCEs) with a combination of the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score and ischemic reduction detected with rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion single-photon-emission computed tomography (SPECT) after revascularization in Japanese patients with coronary artery disease (CAD).

Methods   This was a retrospective study. The patients were followed up to confirm their prognosis for at least one year. Ischemia was evaluated based on the summed difference scores converted to the percentage of the total myocardium Safety Data Sheet (SDS%). The SYNTAX score and SDS% were calculated before and after revascularization. The endpoint was the occurrence of MCEs.

Patients   Study subjects were 293 patients who had a ≥75% stenotic lesion detected with coronary angiography following confirmation of ≥5% ischemia with SPECT, underwent revascularization, and thereafter received a re-evaluation with SPECT and coronary angiography.

Results   During the follow-up, 25 patients experienced MCEs of cardiac death (n=2), non-fatal myocardial infarction (n=3), and unstable angina pectoris (n=20). A receiver operating characteristic analysis indicated that the best cut-off values of the residual SYNTAX score and ΔSDS% were 12 and 5%, respectively, for the prediction of MCEs. The patients with a low residual SYNTAX score (<12) and high ΔSDS% (≥5%) had the best prognosis, while those with a high residual SYNTAX score (≥12) and low ΔSDS% (<5%) had the worst prognosis.

Conclusion   The combination of the residual SYNTAX score and ischemic reduction detected with nuclear cardiology is useful for predicting MCEs after revascularization.

Key words: risk stratification, residual SYNTAX score, ischemic reduction, coronary artery disease, revascularization, myocardial perfusion SPECT

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Introduction

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score was developed following the SYNTAX trials to evaluate whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is better in patients with coronary artery disease (CAD) requiring revascularization (1). This score is highly recommended under the current guidelines for coronary revascularization prepared by the European Society of Cardiology and European Association for Cardio-Thoracic Surgery (2). In addition, the residual SYNTAX score after revascularization has been reported to be a useful index for quantifying and describing the extent of completeness of revascularization, which is associated with the prog-

nosis (3, 4).

Myocardial perfusion single-photon-emission computed tomography (SPECT) is well recognized as a useful imaging methodology for the prediction of cardiac events in patients with known or suspected CAD (5, 6). An ischemic evaluation with myocardial perfusion SPECT is useful in a wide range of medical management strategies and is highly recommended by the American College of Cardiology/American Heart Association guideline (7). In addition, the ischemic evaluation before and after PCI is considered useful for predicting the prognosis after PCI based on the results of the nuclear sub-study of the COURAGE (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial (8). However, no report on the risk stratification of cardiac events according to the combination of the SYNTAX score and ischemic volume detected with nuclear cardiology has yet been published.

We conducted this retrospective prognostic study in Japanese patients with CAD to investigate the relationship of the residual SYNTAX score and ischemic reduction after revascularization with the prognosis and to stratify the risk of major cardiac events (MCEs) with the combination of the cut-off values of residual SYNTAX score and ischemic reduction.

Materials and Methods

Patient population

We retrospectively investigated 293 patients with CAD who underwent rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT (9-12) at Nihon University Itabashi Hospital between October 2004 and May 2015 and who had significant stenosis, defined as ≥75% narrowing of the coronary arterial diameter based on the American Heart Association classification detected with coronary angiography (CAG) performed after confirmation of ≥5% ischemia with SPECT according to the preceding study (8, 9); who underwent revascularization; and who subsequently received a re-evaluation with SPECT and CAG during the chronic phase. The patients were followed up to confirm their prognoses for at least one year after the second CAG procedure.

The interval between the first SPECT and first CAG procedures was 1.6±3.2 months, that between the first CAG and revascularization procedures was 0.6±2.6 months, that between revascularization and the second SPECT was 8.5±6.5 months, and that between the second SPECT and the second CAG procedure was 3.0±5.5 months. The second SPECT procedure was performed 11.1±8.3 months after the first SPECT procedure.

We excluded patients ≤20 years old, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with heart failure of New York Heart Association (NYHA) functional classification ≥III, those with <5% ischemia detected with the first SPECT procedure, and those with a history of CABG. Follow-up examinations were based on medical records for patients who periodically attended the hospital and responses to a posted questionnaire enclosing a written informed consent form for patients who did not attend. The follow-up was successful for 280 patients (96%) but failed for the remaining 13 patients. Data from these 280 patients were therefore ultimately included in the analysis.

This study was approved by the institutional review board of Nihon University Itabashi Hospital.

Electrocardiogram (ECG)-gated dual-isotope myocardial perfusion SPECT

The procedure of rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin ECG-gated myocardial perfusion SPECT was performed according to a protocol previously reported (9-12). All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq), and a 16-frame gated SPECT image was initiated 10 minutes after injection at rest. An i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was then performed under stress induced by ergometer exercise in 28% of the patients or by adenosine triphosphate in 72% of patients. Sixteen-frame gated SPECT image acquisition was initiated 30 minutes after the exercise or 30 to 60 minutes after the adenosine stress induction. The acquisition was performed first in a supine position and subsequently in a prone position. No attenuation or scatter correction was used. The 12-lead ECG was monitored continuously during stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least three minutes after the stress induction.

Projection data over 360° were obtained with 64×64 matrices and a circular orbit. A triple-detector SPECT system equipped with low-energy high-resolution collimators was used (GCA9300A; Canon Medical Systems, Tokyo, Japan). SPECT images were reconstructed from the data with a data processor (JETStream Workspace 3.0; Philips North America, Milpitas, USA) combined with a Butterworth filter of ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), that of ^{99m}Tc (order 5; cut-off frequency 0.44 cycles/cm) and a ramp filter.

SPECT MPI interpretation

The SPECT images were divided into 20 segments (10) on 3 short-axis slices (distal, mid, basal) and 1 vertical long-axis (mid) slice, and the tracer uptake of each segment was visually scored using a 5-point scale (0: normal; 1: slight reduction of uptake; 2: moderate reduction of uptake; 3: severe reduction of uptake; and 4: absence of uptake). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS), respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. The respective summed scores were converted to a percentage of the total myocardium (visual % myocardium). The visual % myocardium was derived from a summed score divided by the maximum potential score (4× 20) and multiplied by 100. When the SDS was 8, the visual ischemic % myocardium was 10% (13). A difference be-

tween SDS% derived from the first and second SPECT (ΔSDS%) was used for evaluation of improvement in ischemia.

Visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided patients' clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.90, indicating very good reproducibility.

Sixteen-frame quantitative gated SPECT data were analyzed using the QGS™ software program (Cedars-Sinai Medical Center, Los Angeles, USA) to calculate the left ventricular ejection fraction (LVEF, %), end-diastolic volume (LVEDV, mL), and end-systolic volume (LVESV, mL), as described by Germano et al. (14).

SYNTAX score calculation

Coronary angiography was performed according to Judkin's method. Angiographic results were visually interpreted by two experienced angiographers who were unaware of the SPECT image interpretation. Coronary lesions were graded according to their anatomy, including the number, location, and length of lesions, dominance, total occlusion, trifurcation/bifurcation, aorto ostial, severe tortuosity, calcification, thrombus, and diffuse disease. Each coronary lesion with luminal narrowing ≥50% in vessels ≥1.5 mm in diameter was separately scored using the SYNTAX score calculator and then summed to provide an overall SYNTAX score (http://www.syntaxscore.com).

Cohen's kappa (κ) for the SYNTAX score was 0.88, indicating very good reproducibility. Baseline and residual SYNTAX scores were estimated at the first and second CAG procedure, respectively.

Patient follow-up

All 280 patients were followed for 28.8±14.5 months after the second CAG procedure. The primary endpoint was the onset of MCEs, consisting of cardiac death, non-fatal myocardial infarction (MI), and unstable angina pectoris (UAP), during the follow-up. A diagnosis of UAP was provided for patients who required unscheduled hospitalization for the management of UAP occurring within 24 hours of the most recent symptoms and who had worsening ischemic discomfort, ischemic ECG changes without ST elevation, and negative troponins.

Patients undergoing scheduled PCI, including additional PCI after the second CAG procedure, were not included among those who experienced MCEs and were continuously followed to confirm their prognoses. Patients who had insufficient data indicating the occurrence of MCEs were regarded as non-event cases. When patients had several MCEs, only the first event was considered the follow-up endpoint.

Statistical analyses

Continuous variables were calculated as means and stan-

dard deviations. Intergroup comparisons of continuous variables were achieved with an unpaired t-test. The chi-square test was used for intergroup comparisons of categorical variables and global chi-square values. A paired t-test was used to analyze the significance of differences in visual % myocardium, the left ventricular function on quantitative gated SPECT, the SYNTAX score, and the number of chronic total occlusion (CTO) vessels before and after revascularization. A Cox proportional hazards model was used for the univariate analysis to identify significant predictors of MCEs. A stepwise Cox proportional hazards model was used for the multivariate analysis with significant predictors as variables to identify independent predictors of MCEs.

The Kaplan-Meier survival analysis was used to estimate the MCE-free survival in the patients grouped according to the best cut-off values of the residual SYNTAX score and ΔSDS% for the prediction of MCEs calculated with the receiver operating characteristic (ROC) analysis. A log-rank test was used to analyze the homogeneity of the survival curves between the groups.

All data were analyzed using MedCalc Statistical Software program, version 17.9.7 (Mariakerke, Belgium). A p value of <0.05 was considered statistically significant.

Results

Cardiac event rates and best cut-off values of residual SYNTAX score and ΔSDS%

During the follow-up, 25 of 280 (8.9%) patients experienced MCEs of cardiac death (n=2), non-fatal MI (n=3), and UAP (n=20).
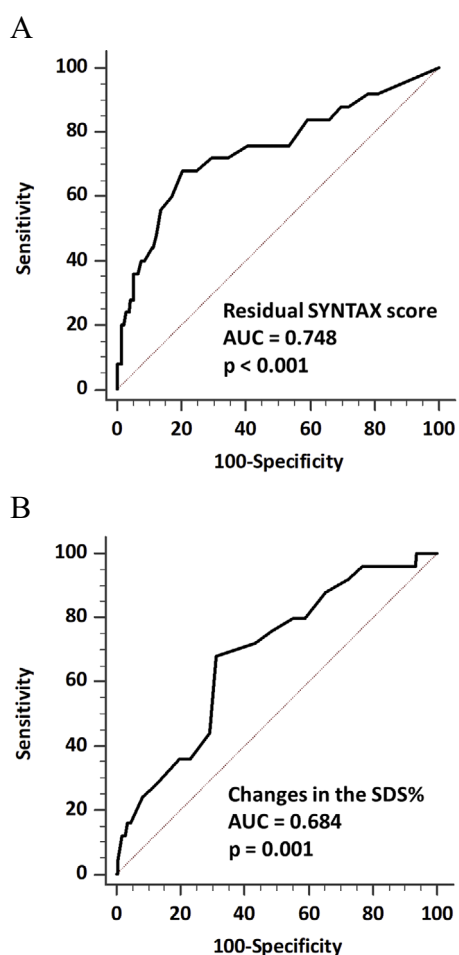
Fig. 1 shows the ROC curves of the residual SYNTAX score (A) and ΔSDS% (B) for the detection of MCEs. The best cut-off value of the residual SYNTAX score was 12, which had a sensitivity and specificity of 68% and 80%, respectively. The best cut-off value of the ΔSDS% was 5%, which had a sensitivity and specificity for the detection of MCEs of 68% and 69%, respectively.

Baseline characteristics of patients

Table 1 shows the baseline characteristics of the patients divided into two groups according to the best cut-off value of residual SYNTAX score after revascularization. There was no significant difference in the baseline characteristics, except for the estimated glomerular filtration rate (eGFR), between the patients with low (<12) and high (≥12) residual SYNTAX scores. The eGFR was significantly higher in the patients with a low residual SYNTAX score than in those with a high score (65±19 vs. 53±29, p=0.0001).

The inter-group comparison of the visual ischemic % myocardium, cardiac functions, angiographic findings, vessel characteristics, SYNTAX scores, and MCE rates

Table 2 shows the visual ischemic % myocardium, cardiac

A

B

Figure 1.   ROC curves of the residual SYNTAX score for the detection of MCEs (A) and of ΔSDS% for the detection of MCEs (B). ΔSDS%: the difference between the summed difference scores converted to a percentage of the total myocardium derived from the first and second single-photon-emission computed tomography procedures, MCE: major cardiac event, ROC: receiver operating characteristic, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

Table 1.   Baseline Characteristics of Patients with a Low (<12) or High (≥12) Residual SYNTAX Score.

	Residual SYNTAX score<12 n=211		Residual SYNTAX score ≥12 n=69		p value
Male gender	173	82%	56	81%	0.8768
Age	66 ± 10		67 ± 10		0.3973
History of MI	72	34%	27	39%	0.4509
History of Revasc	96	45%	40	58%	0.0724
Hypertension	170	81%	60	87%	0.2299
Diabetes mellitus	100	47%	31	45%	0.7221
Hyperlipidemia	176	83%	52	75%	0.1362
Smoking	73	35%	29	42%	0.2663
Aspirin	207	98%	66	96%	0.2583
Thienopyridines	202	96%	65	94%	0.6003
Statins	151	72%	47	68%	0.5855
β-blockers	79	37%	30	43%	0.3728
Calcium channel blocker	103	49%	34	49%	0.9472
Nitrates	66	31%	27	39%	0.2302
ARB	98	46%	41	59%	0.0618
ACE Inhibitors	30	14%	9	13%	0.8071
Insulin users	15	7%	6	9%	0.6646
eGFR (mL/min/1.73m^2)	65 ± 19		53 ± 29		0.0001

SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, MI: myocardial infarction, Revasc: revascularization, ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme, eGFR: estimated glomerular filtration rate

functions, angiographic findings, vessel characteristics, SYNTAX score, and MCE rates in the patients with a low or high residual SYNTAX score. The mean SSS% values before and after revascularization were 18.2% and 9.4%, respectively, in the patients with a low residual SYNTAX score and 18.8% and 13.6%, respectively, in those with a high score. The difference between the SSS% derived from the first and second SPECT procedures (ΔSSS%) was significantly higher in the patients with a low residual SYNTAX score than in those with a high score (8.9%±9.5% vs. 5.2%±11.7%; p=0.0101). The ΔSDS% significantly differed between the 2 groups: 8.8%±9.0% in the patients with a low residual SYNTAX score and 5.5%±10.4% in those with a high score (p=0.0118). The proportion of patients with ΔSDS% ≥5% was significantly higher in the group with a low residual SYNTAX score than in that with a high score (70% vs. 52%; p=0.0064). There was no significant differ-

ence in the cardiac function, except for the stress LVEF after revascularization, between the two groups.

There was no significant difference in the proportions of patients who had ischemia in the region of left anterior descending artery (LAD), right coronary artery, (RCA), or left circumflex artery (LCA) between the two groups. The proportions of patients who had 1-, 2-, and 3-vessel disease were 39%, 42%, and 19%, respectively, in the group with a low residual SYNTAX score and 16%, 38%, and 46%, respectively, in the group with a high score; there was a significant difference between the 2 groups in the proportions of patients with 1- and 3-vessel disease. The proportion of patients with complete revascularization for the target vessels at the first CAG procedure was higher in the group with a low residual SYNTAX score than in that with a high score (76% vs. 57%; p=0.0016). The proportions of patients who underwent repeat-revascularization at the second CAG procedure and who had in-stent restenosis at the PCI site were significantly higher in the group with a high residual SYNTAX score than in that with a low score (26% vs. 74% and 10% vs. 42%, respectively; p<0.0001). The proportion of the patients who had CTO vessels was significantly higher in the group with a high residual SYNTAX score than in that with a low score both before and after revascularization (27% vs. 46% and 12% vs. 45%, respectively; p<0.004).

The baseline and residual SYNTAX scores were 12.4±5.9 and 4.8±3.6, respectively, in the patients with a low residual SYNTAX score and 18.3±6.2 and 18.2±6.4, respectively, in

Table 2. Comparison of Visual Ischemic % Myocardium, Cardiac Functions, Angiographic Findings, Vessel Characteristics, SYNTAX Score, and MCE Rates in Patients with a Low or High Residual SYNTAX Score.

	Residual SYNTAX score<12 n=211		Residual SYNTAX score ≥12 n=69		p value
SSS% before Revasc	18.2 ± 10.3		18.8 ± 10.9		0.6796
SRS% before Revasc	4.1 ± 6.7		4.7 ± 6.9		0.5557
SDS% before Revasc	14.1 ± 7.9		14.2 ± 8.2		0.9643
SSS% after Revasc	9.4 ± 9.4		13.6 ± 12.6		0.0033
SRS% after Revasc	4.1 ± 7.0		5.0 ± 8.2		0.3807
SDS% after Revasc	5.3 ± 5.7		8.6 ± 8.0		0.0002
ΔSSS%	8.9 ± 9.5		5.2 ± 11.7		0.0101
ΔSDS%	8.8 ± 9.0		5.5 ± 10.4		0.0118
ΔSDS% ≥5%	148	70%	36	52%	0.0064
Rest LVEF before Revasc (%)	58.6 ± 14.2		56.0 ± 12.1		0.1763
Rest LVEDV before Revasc (mL)	92.0 ± 41.1		93.4 ± 34.0		0.7981
Rest LVESV before Revasc (mL)	42.6 ± 36.0		44.1 ± 26.8		0.7605
Stress LVEF before Revasc (%)	55.7 ± 13.0		53.3 ± 12.0		0.1919
Stress LVEDV before Revasc (mL)	108.8 ± 45.4		110.9 ± 37.3		0.7288
Stress LVESV before Revasc (mL)	52.7 ± 38.7		54.8 ± 30.4		0.6792
Rest LVEF after Revasc (%)	60.0 ± 13.3		57.0 ± 12.9		0.1030
Rest LVEDV after Revasc (mL)	89.2 ± 37.6		91.3 ± 36.1		0.6760
Rest LVESV after Revasc (mL)	39.8 ± 32.2		42.9 ± 30.9		0.4787
Stress LVEF after Revasc (%)	58.6 ± 12.6		55.3 ± 12.0		0.0395
Stress LVEDV after Revasc (mL)	103.2 ± 41.9		108.6 ± 42.5		0.3540
Stress LVESV after Revasc (mL)	46.7 ± 34.6		52.3 ± 35.0		0.2434
ΔStress LVEF (%)	3.2 ± 7.7		1.9 ± 8.1		0.2457
Ischemia in the region of LAD	96	45%	40	58%	0.0724
Ischemia in the region of RCA	88	42%	34	49%	0.2719
Ischemia in the region of LCX	66	31%	21	30%	0.8955
Angiographic CAD and Revasc					
1-vessel CAD	82	39%	11	16%	0.0005
2-vessels CAD	88	42%	26	38%	0.5554
3-vessels CAD	41	19%	32	46%	<0.0001
POBA	10	5%	2	3%	0.5130
BMS	19	9%	11	16%	0.1064
DES	182	86%	56	81%	0.3042
Multivessel Revasc	53	25%	20	29%	0.5261
Complete Revasc on the1st CAG	161	76%	39	57%	0.0016
Target vessel Revasc on the1st CAG	184	87%	57	83%	0.3394
Revasc on the 2nd CAG	55	26%	51	74%	<0.0001
ISR as target lesion on the 2nd CAG	22	10%	29	42%	<0.0001
CTO vessels before Revasc	58	27%	32	46%	0.0036
CTO vessels after Revasc	26	12%	31	45%	<0.0001
Baseline SYNTAX score	12.4 ± 5.9		18.3 ± 6.2		<0.0001
Residual SYNTAX score	4.8 ± 3.6		18.2 ± 6.4		<0.0001
ΔSYNTAX score	7.6 ± 5.8		0.1 ± 7.5		<0.0001
MCE rates	8	4%	17	25%	<0.0001
Cardiac death	0	0%	2	3%	0.0132
Non-fatal MI	2	1%	1	2%	0.7259
UAP	6	3%	14	20%	<0.0001

SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, MCE: major cardiac event, Revasc: revascularization, SSS: summed stress score, SRS: summed rest score, SDS: summed difference score, ΔSSS%: a difference between summed stress scores converted to the percentage of the total myocardium derived from the first and second single photon emission computed tomography, ΔSDS%: a difference between summed difference scores converted to the percentage of the total myocardium derived from the first and second single photon emission computed tomography, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, ΔStress LVEF: a difference between stress left ventricular ejection fraction derived from the first and second single photon emission computed tomography, LAD: Left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, CAD: coronary artery disease, POBA: percutaneous old balloon angioplasty, BMS: bare-metal stent, DES: drug-eluting stent, CAG: coronary angiography, ISR: in stent restenosis, CTO: chronic total occlusion, ΔSYNTAX score: a difference between baseline and residual SYNTAX scores, MI: myocardial infarction, UAP: unstable angina pectoris

Table 3.   Visual % Myocardium, Cardiac Functions, SYNTAX Score, and CTO Vessels before and after Revascularization in Patients with and without MCEs.

	MCEs (+) n=25		p value	MCEs (-) n=255		p value
	1st SPECT	2nd SPECT		1st SPECT	2nd SPECT	
SSS%	16.0±9.8	12.9±9.8	0.1617	18.6±10.5	10.2±10.5	<0.0001
SRS%	4.1±5.5	3.8±4.6	0.7715	4.3±6.8	4.3±7.5	0.7135
SDS%	11.9±6.1	9.1±8.7	0.0865	14.4±8.1	5.8±6.2	<0.0001
0%	0 0%	3 12%		0 0%	88 34%	
1-4.9%	0 0%	5 20%		0 0%	25 10%	
≥5%	25 100%	17 68%		255 100%	142 56%	
LVEF						
Rest	54.9±11.7	55.2±12.5	0.8823	58.2±13.9	59.6±13.3	0.0122
Post Stress	53.4±12.2	53.0±12.9	0.8504	55.2±12.9	58.5±12.4	<0.0001
LVEDV						
Rest	95.0±36.0	93.8±34.2	0.8434	92.0±39.7	89.3±37.5	0.0427
Post Stress	114.5±38.3	109.6±40.6	0.4764	108.8±44.0	104.1±42.2	0.0023
LVESV						
Rest	46.4±28.3	45.3±29.4	0.8269	42.6±34.4	40.1±32.1	0.0357
Post Stress	57.2±32.5	55.4±33.1	0.7413	52.8±37.2	47.4±34.8	0.0001
	1st CAG Baseline	2nd CAG Residual		1st CAG Baseline	2nd CAG Residual	
SYNTAX score	17.8±7.1	15.7±10.5	0.3384	13.4±6.3	7.4±6.5	<0.0001
CTO vessels	10 40%	11 44%	0.7767	80 31%	46 18%	0.0005

MCE: major cardiac event, SPECT: single photon emission computed tomography, SSS: summed stress score, SRS: summed rest score, SDS: summed difference score, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, CAG: coronary angiography, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, CTO: chronic total occlusion

those with a high score. The difference between the baseline and residual SYNTAX scores (ΔSYNTAX score) was significantly higher in the patients with a low residual SYNTAX score than in those with a high score (7.6±5.8 vs. 0.1± 7.5; p<0.0001).

There was a significant difference in MCE rates between the patients with low and high residual SYNTAX scores (4% vs. 25%; p<0.0001). The MCEs observed in the group with a low residual SYNTAX score were non-fatal MI (n=2) and UAP (n=6), while those in the group with a high score were cardiac death (n=2), non-fatal MI (n=1), and UAP (n= 14).

The visual % myocardium, cardiac functions, SYNTAX score, and CTO vessels before and after revascularization in patients with and without MCEs

Table 3 shows the visual % myocardium (SSS%, SRS%, and SDS%), LVEF, LVEDV, LVESV, SYNTAX score, and the number of patients with CTO vessels before and after revascularization among the patients with and without MCEs. There were no significant differences in any parameters after revascularization in the patients who experienced MCEs. In the patients without MCEs, significant differences were observed in all parameters except for the SRS% after revascularization.

Predictors for MCEs

Table 4 shows the results of the univariate analysis with a Cox proportional hazards model and the multivariate analysis with a stepwise Cox proportional hazards model. The univariate analysis showed that the SDS% after revascularization (p=0.0071), ΔSSS% (p=0.0052), ΔSDS% (p=0.0018), stress LVEF after revascularization (p=0.0179), Δstress LVEF (p=0.0200), CTO vessels after revascularization (p= 0.0004), baseline SYNTAX score (p=0.0031), residual SYNTAX score (p<0.0001), and ΔSYNTAX score (p=0.0010) were variables predicting MCEs. Of those variables, ΔSDS% (p=0.0317) and the residual SYNTAX score (p<0.0001) were significant independent predictors according to the multivariate analysis.

Fig. 2 shows the changes in the global chi-square values for the prediction of MCEs using combinations of the independent predictors identified by the multivariate analysis. The global chi-square values for MCE prediction were 4.7 for the clinical value, 21.2 for the clinical + residual SYNTAX score, and 32.2 for the clinical + residual SYNTAX score + ΔSDS%. The global chi-square values significantly increased with the increasing number of independent predictors used in combination (p<0.05).

Table 4. Univariate and Multivariate Cox Proportional Hazards Regression Analyses.

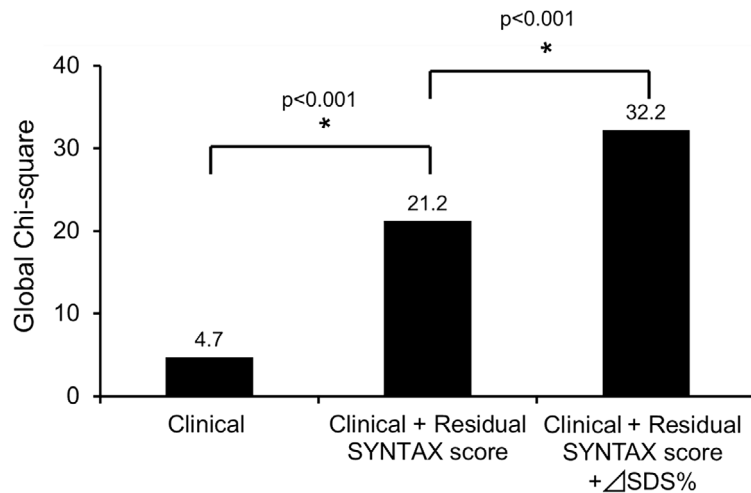|	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% CI		p value	Hazard ratio	95% CI		p value
Age	0.9965	0.9554 -	1.0393	0.8703				
Male sex	0.8728	0.3238 -	2.3525	0.7879				
History of MI	1.2295	0.5317 -	2.8432	0.6290				
History of Revasc	2.1222	0.9082 -	4.9592	0.0823				
Hypertension	1.2351	0.4165 -	3.6623	0.7034				
Diabetes mellitus	1.2396	0.5469 -	2.8096	0.6070				
Hyperlipidemia	0.7260	0.3181 -	1.6569	0.4469				
Smoking	0.9643	0.5428 -	2.2067	0.9315				
eGFR	0.9896	0.9724 -	1.0072	0.2454				
Dual antiplatelet therapy	0.4539	0.0611 -	3.3720	0.4401				
Statins	0.6137	0.2742 -	1.3735	0.2348				
β-blockers	0.7989	0.3415 -	1.8689	0.6046				
Insulin users	0.4809	0.0648 -	3.5707	0.4742				
SSS% before Revasc	0.9758	0.9349 -	1.0185	0.2645				
SRS% before Revasc	1.0038	0.9435 -	1.0680	0.9047				
SDS% before Revasc	0.9532	0.8956 -	1.0146	0.1324				
SSS% after Revasc	1.0293	0.9935 -	1.0664	0.2360				
SRS% after Revasc	0.9986	0.9393 -	1.0615	0.9630				
SDS% after Revasc	1.0782	1.0207 -	1.1390	0.0071				
ΔSSS%	0.9334	0.8893 -	0.9796	0.0052				
ΔSDS%	0.9158	0.8665 -	0.9679	0.0018	0.9437	0.8950 -	0.9949	0.0317
Rest LVEF after Revasc	0.9757	0.9490 -	1.0030	0.0810				
Rest LVEDV after Revasc	1.0056	0.9960 -	1.0140	0.2525				
Rest LVESV after Revasc	1.0063	0.9964 -	1.0164	0.2128				
Stress LVEF after Revasc	0.9648	0.9366 -	0.9938	0.0179				
Stress LVEDV after Revasc	1.0053	0.9965 -	1.0091	0.2377				
Stress LVESV after Revasc	1.0074	0.9985 -	1.0163	0.1036				
ΔStress LVEF	0.9287	0.8726 -	0.9884	0.0200				
Revasc on the 2nd CAG	2.2684	0.9794 -	5.2540	0.0560				
ISR as target lesion on the 2nd CAG	2.1575	0.9133 -	5.0966	0.0796				
CTO vessels before Revasc	1.6075	0.7113 -	3.6332	0.2539				
CTO vessels after Revasc	4.4607	1.9626 -	10.1385	0.0004				
Baseline SYNTAX score	1.0949	1.0311 -	1.1627	0.0031				
Residual SYNTAX score	1.1168	1.0738 -	1.1616	<0.0001	1.1079	1.0633 -	1.1543	<0.0001
ΔSYNTAX score	0.9158	0.8691 -	0.9650	0.0010				

CI: confidence interval, MI: myocardial infarction, Revasc: revascularization, eGFR: estimated glomerular filtration rate, Dual antiplatelet therapy: oral administration of aspirin concomitant with thienopyridines, SSS: summed stress score, SRS: summed rest score, SDS: summed difference score, ΔSSS%: a difference between summed stress scores converted to the percentage of the total myocardium derived from the first and second single photon emission computed tomography, ΔSDS%: a difference between summed difference scores converted to the percentage of the total myocardium derived from the first and second single photon emission computed tomography, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end-systolic volume, ΔStress LVEF: a difference between stress left ventricular ejection fraction derived from the first and second single photon emission computed tomography, CAG: coronary angiography, ISR: in stent restenosis, CTO: chronic total occlusion, SYNTAX: Synergy between, Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, ΔSYNTAX score: a difference between baseline and residual SYNTAX scores

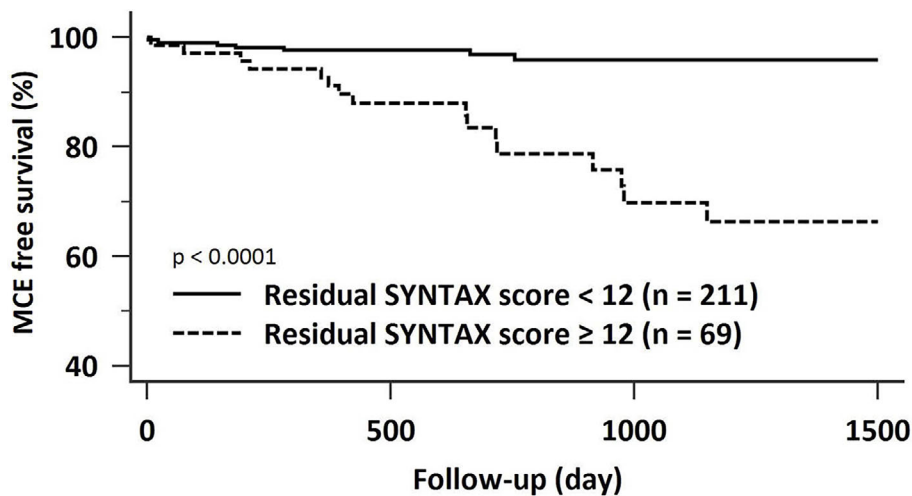### Prediction of MCEs based on residual SYNTAX score and/or ΔSDS% after revascularization

Fig. 3 shows the Kaplan-Meier curves for the proportions of patients without MCEs in groups with low (<12) and high (≥12) residual SYNTAX scores. Patients with a SYNTAX score <12 had a significantly better prognosis than those whose score was ≥12 (p<0.0001).

Fig. 4 shows the Kaplan-Meier curves for the proportions of the patients without MCEs in groups with low (<12) or high (≥12) residual SYNTAX score and with low (<5%) or high (≥5%) ΔSDS% after revascularization. Group 1 consisted of the patients with a low residual SYNTAX score (<12) and a high ΔSDS% (≥5%), group 2 consisted of those with a low residual SYNTAX score (<12) and a low ΔSDS% (<5%), group 3 consisted of those with a high residual SYNTAX score (≥12) and a high ΔSDS% (≥5%), and group 4 consisted of those with a high residual SYNTAX score (≥12) and a low ΔSDS% (<5%). The patients in group 1 had the best prognosis, while those in group 4 had the

Figure 2. Changes in global chi-square values for the prediction of MCEs using a combination of the independent predictors identified by the multivariate analysis. ΔSDS%: the difference between the summed difference scores converted to a percentage of the total myocardium derived from the first and second single-photon-emission computed tomography procedures, MCE: major cardiac event, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, Clinical: the total sum of the chi-square values for older age, male sex, a history of myocardial infarction, a history of revascularization, hypertension, diabetes mellitus, and lower estimated glomerular filtration rate.

Figure 3. Kaplan-Meier curves for proportions of patients without MCEs in groups divided by the best cut-off value of the residual SYNTAX score. MCE: major cardiac event, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

worst prognosis. There were significant differences in the prognosis between group 1 and groups 2, 3, or 4 (p<0.05) and between groups 4 and 2 (p<0.05).

Discussion

This is the first report from Japan to demonstrate the prediction of MCEs based on the residual SYNTAX score and improvement in ischemia following revascularization in patients with CAD. The patients with a low residual SYNTAX score (<12) and ≥5% ischemic reduction after revasculariza-

tion had the best prognosis, while those with a high residual SYNTAX score (≥12) and no such improvement in ischemic volume had the worst prognosis. In addition, the multivariate analysis indicated that the ΔSDS% and residual SYNTAX scores were significant independent variables for the prediction of MCEs. A combination of the ΔSDS% and residual SYNTAX score significantly improved the goodness of fit for the logistic regression model for predicting MCEs in comparison with the residual SYNTAX score alone. Furthermore, the present results suggested that the best cut-off values of both variables might be useful for risk stratifica-
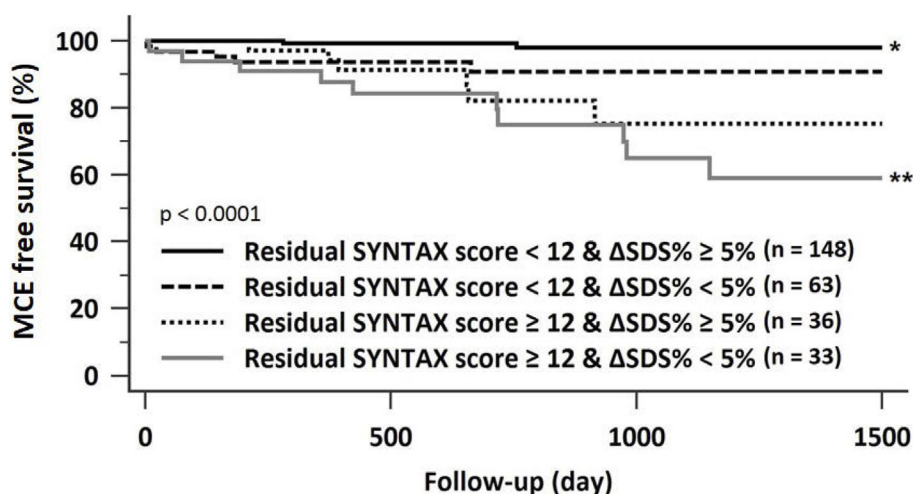
Figure 4. Kaplan-Meier curves for proportions of patients without MCEs in groups divided by the combination of the best cut-off values of the residual SYNTAX score and the ΔSDS% after revascularization. ΔSDS%: the difference between the summed difference scores converted to a percentage of the total myocardium derived from the first and second single-photon-emission computed tomography procedures, MCE: major cardiac event, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery, *: statistically significant difference between group 1 and groups 2, 3, or 4. **: statistically significant difference between groups 4 and 2.

tion of future MCEs.

We compared prognoses between the patients classified into two groups according to the best cut-off value of the residual SYNTAX score. There were differences in the proportions of complete revascularization against the target vessel, in-stent restenosis, and revascularization at the second CAG procedure between the two groups. These differences were based on a high proportion of the patients having three-vessel disease including CTO lesions in the group with a high residual SYNTAX score (≥12), which probably influenced the incidence of future MCEs. In general, complication of target vessels and in-stent restenosis are considered to be associated with a poor prognosis after revascularization. However, it is impossible to perform complete revascularization against all ischemic vessels in patients who have multivessel disease with CTO lesions associated with a higher residual SYNTAX score. In the group with a high residual SYNTAX score (≥12), a high proportion of patients had CTO lesions and/or complicated target lesions that required difficult PCI. Such patients have a high incidence of in-stent restenosis and frequently require revascularization at the second CAG procedure. Some patients with in-stent restenosis develop UAP. Therefore, we should consider the application of optimal medical treatment, including CABG, in patients who have CTO lesions or complicated target lesions.

The relationship between the prognosis and ΔSDS%, which is an index of improvement in ischemia after revascularization, has been already reported. The results of a sub-analysis in the COURAGE trial demonstrated that patients with improvement in ischemia (ΔSDS%: ≥5%) had a better prognosis within 5 years than those without such improvement (8). In addition, our preceding study (9) and the

Japanese-Assessment of Cardiac Event and Survival Study by Quantitative Gated SPECT (J-ACCESS) 4 study (15), which was a Japanese multicenter investigation, reported similar results, wherein patients with improvement in ischemia (ΔSDS%: ≥5%) had a better prognosis within 3 years than those without such improvement. The best cut-off value of ΔSDS% was estimated to be 5% in the present study. Therefore, a ΔSDS% of ≥5% is recommended as the target value for ischemic reduction after revascularization, and attaining this was considered to help improve the prognosis in patients with CAD.

Several previous reports have also described the relationship between the prognosis and residual SYNTAX score reflecting incomplete revascularization (3, 4). The residual SYNTAX score was shown to be an important variable for the prediction of short- and long-term prognoses after revascularization, and the incidence of MCEs increased when the score was nine or more. Those results were based on the occurrence of MCEs stratified by residual SYNTAX score tertiles. In the present study, the best cut-off value of the residual SYNTAX score was estimated to be 12 based on an ROC analysis. This cut-off value is useful for predicting MCEs after revascularization and is probably a more definite value than the previous value based on tertiles. In addition, this cut-off value is considered to provide a more accurate prediction and risk stratification of future MCEs in Japanese patients with CAD because the incidence of MCEs after revascularization has been reported to be lower in Japanese than in American patients (15, 16).

The risk of MCEs was stratified by the combination of the ΔSDS% and residual SYNTAX score in the present study. The residual SYNTAX score alone cannot reflect quantitative ischemic reduction, but its combination with

ΔSDS% is considered to accurately predict MCEs after revascularization in Japanese patients with CAD.

Tanaka et al. investigated the relationship between the SYNTAX score and ischemic volume derived from myocardial perfusion SPECT in Japanese patients with CAD and reported that those with a high SYNTAX score and small ischemic volume were likely to have three-vessel disease (17). However, there is a possibility of underestimating the severity of disease in patients with multivessel stenotic lesions because of balanced ischemia (18, 19). In the present study, the ischemic volume (SDS%) before revascularization was 13.5%±7.5% in 1-vessel disease, 15.0%±9.0% in 2-vessel disease, and 13.7%±6.8% in 3-vessel disease; therefore, underestimation of the ischemic volume was not considered to influence the prediction of MCEs in this study.

Some studies have been performed to determine the most appropriate treatment strategy for CTO lesions (20, 21). Although a recent study reported no significant difference in the cardiac death rate between patients with CTO who underwent optimal medical therapy and PCI in the drug-eluting stent era (22), the rate of successful PCI for CTO was significantly higher in patients without MCEs than in those with MCEs in the present study. In addition, CTO vessels after revascularization were a significant predictor of MCEs based on the results of the univariate analysis. Ninety patients had CTO before revascularization, and 40 of them experienced recanalization of CTO after revascularization. Ischemic reduction was significantly greater in patients with recanalization of CTO than in those without it (10.8%± 10.0% vs. 2.7%±6.8%; p<0.0001). The residual ischemic volume was significantly lower in patients with recanalization of CTO than in those without it (5.3%±6.2% vs. 10.3% ±6.7%; p=0.0004). The present study included high-risk patients who had CTO with <5% improvement and ≥10% residual ischemic volume. Such background characteristics may have been associated with a poor prognosis.

Limitations

First, this study was a retrospective, single-center investigation with a relatively small sample size. This small sample size may have biased the type of MCEs that occurred. Second, the study subjects were only those who were able to undergo both SPECT and CAG before and after revascularization and did not include patients with a history of CABG in whom the SYNTAX score could not be calculated. Such a selection bias limits the applicability of the present results to all patients with CAD requiring revascularization. Third, the SYNTAX score II and functional SYNTAX score were recently developed to select appropriate revascularization approaches and predict the clinical outcomes in patients with complicated CAD (23, 24). In this retrospective study, however, it was difficult to compute the SYNTAX score II and functional SYNTAX score because of insufficient data on peripheral vascular disease and chronic obstructive pulmonary disease and insufficient fractional flow reserve data. The usefulness of the combination of each score and ischemic reduction detected with myocardial perfusion SPECT for the prediction and risk stratification of MCEs will need to be investigated in a future study. Fourth, although it is important to perform sufficient medical therapy to help avoid MCEs after revascularization, some patients received insufficient medical treatment, including a low frequency of statin use, because of this study's retrospective design. In addition, the therapeutic strategy had a single-center bias. Finally, we used ^{201}Tl + ^{99m}Tc-tetrofosmin dual isotope SPECT to improve the throughput in this study, as in preceding studies (9-12). Dual isotope SPECT results in more radiation exposure than ^{99m}Tc-tetrofosmin rest-stress SPECT, and it is quite expensive to perform, so it is not recommended for use in a general clinical setting. Because the prognostic prediction and diagnostic accuracy of ^{201}Tl are generally the same as those of ^{99m}Tc (25), the ^{99m}Tc-tetrofosmin rest-stress SPECT protocol is expected to provide the same results as this study.

Conclusion

The combination of the residual SYNTAX score and ischemic reduction detected with nuclear cardiology was useful for predicting MCEs after revascularization.

The authors state that they have no Conflict of Interest (COI).

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