Prognostic Value of Major Cardiac Event Risk Score Estimated With Gated Myocardial Perfusion Imaging in Japanese Patients With Coronary Artery Disease

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SUMMARY

We published a cardiac event risk score (CERS) predicting the risk of major cardiac events (MCEs) within 3 years. The purpose of this study was to verify the prognostic value of the CERS before and after treatment in Japanese patients with coronary artery disease.

We retrospectively investigated 612 patients who underwent rest ²⁰¹Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion single photon emission computed tomography (SPECT) between October 2004 and March 2013 and who had a significant stenosis with $\geq 75\%$ narrowing of the arterial diameter detected by coronary angiography performed after confirmation of $\geq 5\%$ ischemia with the SPECT. The patients underwent treatment including revascularization and medication, and thereafter, were re-evaluated with SPECT during a chronic phase and followed-up to confirm prognosis for ≥ 1 year. The endpoint was the onset of MCEs during the follow-up.

During the follow-up (36.7 ± 14.5 months), 50 patients (8.7%) experienced MCEs comprising cardiac death ($n = 16$), non-fatal myocardial infarction ($n = 4$), and unstable angina pectoris ($n = 30$). The multivariate Cox proportional hazards regression model analysis for the actual occurrence of MCEs showed the summed difference score % and MCE risks estimated with the CERS after treatment to be significant independent variables. Ischemic reduction after treatment contributed significantly to a decrease in the MCE risks. The MCE risks estimated with the CERS after treatment were generally consistent with the incidence of the MCEs actually observed.

The CERS after treatment is a valuable formula for predicting prognosis in Japanese patients with coronary artery disease. (Int Heart J 2016; 57: 408-416)

Key words: Prognosis, Risk stratification, Risk calculator, Ischemic heart disease, SPECT

Prediction of a cardiac event risk is important for decisions concerning an optimal therapeutic strategy in patients with coronary artery disease (CAD). A well-known cardiac event risk score is a prediction algorithm developed in an epidemiological study (Framingham study) in the United States.¹⁾ The algorithm, which is a valuable tool to predict the risk of cardiac events in the 10 subsequent years in Caucasians, is highly recommended in the Guideline on the Assessment of Cardiovascular Risk published by the American College of Cardiology and American Heart Association in 2013.²⁾

Myocardial perfusion single photon emission computed tomography (SPECT) is widely recognized as a useful imaging methodology for the prediction of future cardiac events in patients with known or suspected CAD since the reports of Hachamovitch, *et al.*^{3,4)} Also, in Japan, myocardial perfusion SPECT has commonly been used to predict cardiac events in

patients with CAD. Risk stratification of cardiac events by nuclear cardiology has been demonstrated in some large-scale prognostic studies including the multicenter prospective Japanese Assessment of Cardiac Events and Survival Study in patients with ischemic heart disease (J-ACCESS),⁵⁾ in asymptomatic patients with type 2 diabetes (J-ACCESS 2),⁶⁾ in patients with chronic kidney disease (J-ACCESS 3),⁷⁾ and in another single-center large-scale prospective study.⁸⁾

Nakajima, *et al.*⁹⁾ published a Heart Risk Table, which is the first cardiac event risk score predicting the risk of major cardiac events (MCEs) in Japanese patients with CAD within 3 years, prepared on the basis of predictors obtained from the J-ACCESS database ($n = 2,395$). MCEs predicted with the Heart Risk Table, however, include severe heart failure unlike MCEs defined in non-Japanese studies.^{3,4)}

We, therefore, conducted a single-center large-scale retrospective prognostic study in 2,579 Japanese patients with CAD

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undergoing nuclear cardiology to prepare a cardiac event risk score (CERS) predicting the risk of MCEs excluding severe heart failure within 3 years.¹⁰⁾ In the present study, we attempted to verify the prognostic values of the CERS before and after treatment in Japanese patients with CAD.

METHODS

The Institutional Review Board of Nihon University Itabashi Hospital approved this study, which proceeded in accordance with the ethical standards established in the 1964 Declaration of Helsinki. All study participants provided written informed consent prior to inclusion in the study.

Patient population: We retrospectively investigated 612 patients with CAD who underwent rest ²⁰¹Tl and stress ^{99m}Tc-tetrofosmin myocardial perfusion SPECT^{8,10-16)} at Nihon University Itabashi Hospital between October 2004 and March 2013 and who had a significant stenosis with 75% or greater narrowing of the arterial diameter detected by coronary angiography (CAG) performed after confirmation of at least 5% ischemia by the SPECT. The patients underwent treatment including revascularization and medication, and thereafter, were re-evaluated with the SPECT during a chronic phase and followed up to confirm prognosis for at least one year. The interval between the first SPECT and the CAG was 1.6 ± 3.2 months, that between the CAG and revascularization was 0.8 ± 3.9 months, and that between the revascularization and the second SPECT was 8.3 ± 8.2 months. The second SPECT was performed at 13.3 ± 10.6 months after the first SPECT. We excluded patients aged ≤ 20 years, as well as those with hypertrophic or dilated cardiomyopathy, with serious valvular heart disease, with heart failure with class III or higher New York Heart Association (NYHA) functional classification, and with less than 5% ischemia detected by the first SPECT. Patients were diagnosed as hypertensive if they had systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg within the past 3 months or were currently under medication to lower blood pressure; as having diabetes mellitus if they had fasting blood glucose > 126 mg/dL and/or casual blood glucose > 200 mg/dL within the past 3 months or were under medication to control hyperglycemia, or were already diagnosed with diabetes mellitus; as having hyperlipidemia if they had low-density lipoprotein cholesterol > 140 mg/dL within the past 3 months or were currently under medication to normalize hypercholesterolemia; as having typical chest pain if they had substernal chest pain or discomfort that was provoked by exertion or emotional stress and was relieved by rest and/or nitroglycerin. Follow-up examinations were based on medical records for patients who periodically attended the hospital and responded to a mailed questionnaire for patients who did not attend. The follow-up was successful for 572 patients (93%) but unsuccessful for the remaining 40 patients. Data from all 572 patients were finally included in the analysis. All 612 patients enrolled in this study were a different population from the patients ($n = 2,579$) enrolled in the previous study conducted to prepare the CERS.¹⁰⁾

ECG-gated dual-isotope myocardial perfusion SPECT: The rest ²⁰¹Tl and stress ^{99m}Tc-tetrofosmin ECG-gated myocardial perfusion SPECT procedure was performed according to a previously reported protocol.^{8,10-16)} All patients received an in-

travenous injection of ²⁰¹Tl (111 MBq) and a 16-frame gated SPECT image was initiated 10 minutes after the injection during rest. Next, an intravenous injection of ^{99m}Tc-tetrofosmin (740 MBq) was administered under stress induced by ergometer exercise in 23% of the patients or by adenosine triphosphate in 77% of the patients. Sixteen-frame gated SPECT image acquisition was initiated 30 minutes after the exercise or 30 to 60 minutes after the adenosine triphosphate stress. The acquisition was performed with the patient in a supine position and then in a prone position. No attenuation or scatter correction was used. A 12-lead ECG was monitored continuously during the stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least 3 minutes after the stress.

The 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 (Toshiba, GCA9300A, Tokyo). SPECT images were reconstructed from the data with a data processor (Philips North America, JETStream Workspace 3.0, MA, USA) combined with Butterworth filters of ²⁰¹Tl (order 5; cut-off frequency 0.42 cycles/cm) and ^{99m}Tc (order 5; cut-off frequency 0.44 cycles/cm) and a ramp filter.

SPECT image interpretation: The SPECT images were divided into 20 segments¹²⁾ on 3 short-axis (distal, mid, basal) and one vertical long-axis (mid) slices, 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 percent of the total myocardium (visual % myocardium). Visual % myocardium was derived from a summed score divided by the maximum potential score (4×20) and multiplied by 100. When the SSS score was 4, the visual % myocardium was 5%. A change in SDS% (Δ SDS%) was a difference between SDS% estimated by the first and second SPECT. The visual semi-quantitative scoring was performed by two independent expert interpreters who were not aware of any clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.92, indicating very good reproducibility. Sixteen-frame quantitative gated SPECT data were analyzed with QGSTM software (Cedars-Sinai Medical Center, Los Angeles, CA, 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.*¹⁷⁾

Evaluation of eGFR: The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels at the time of SPECT for each patient with the Modification of Diet in Renal Disease Equation for Japanese Patients proposed by the Japanese Society of Nephrology¹⁸⁾ as follows:

$$\text{eGFR} = A \times 194 \times (\text{Serum Creatinine})^{-1.094} \times (\text{Age})^{-0.287},$$
where A is 1 for men and 0.739 for women and eGFR is expressed as mL/minute/1.73 m².

Patient follow-up: The study endpoint was the onset of MCEs during the follow-up, consisting of cardiac death, non-fatal

Table I. Characteristics of Patients With and Without Major Cardiac Events

	Major cardiac event (+) <i>n</i> = 50		Major cardiac event (-) <i>n</i> = 522		<i>P</i>
Male gender	42	84%	422	81%	0.7220
Age	68 ± 12		67 ± 9		0.4424
Typical chest pain	18	36%	195	37%	0.9710
History of MI	23	46%	195	37%	0.2938
History of revascularization	32	64%	244	47%	0.0289
Hypertension	40	80%	414	79%	0.9459
Diabetics	31	62%	239	46%	0.0408
Hyperlipidemia	29	58%	391	75%	0.0156
Smoking	19	38%	196	38%	0.9285
Aspirin	48	96%	503	96%	0.9569
Statins	23	46%	323	62%	0.0411
β-blockers	18	36%	205	39%	0.7631
Ca-antagonists	24	48%	246	47%	0.9760
Nitrates	17	34%	204	39%	0.5804
ARB	24	48%	255	49%	0.9736
ACE	9	18%	49	9%	0.0925
eGFR	57.3 ± 26.3		61.4 ± 23.4		0.2488
Angiographic CAD					
1 Vessel	12	24%	176	34%	0.2151
2 Vessels	20	40%	169	33%	0.3485
3 Vessels	18	36%	177	34%	0.8092
Treatment					
PCI	38	76%	395	76%	0.9039
POBA	(2)	(5%)	(15)	(4%)	0.9944
BMS	(7)	(18%)	(79)	(20%)	0.9839
DES	(29)	(76%)	(301)	(76%)	0.8542
CABG	1	2%	44	8%	0.1808
Medication	11	22%	83	16%	0.3617

MI indicates myocardial infarction; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; BMS, bare-metal stent; DES, drug-eluting stent; and CABG, coronary artery bypass grafting.

myocardial infarction (MI), and unstable angina pectoris (UAP) identified from medical records or from responses to a mailed out questionnaire. A diagnosis of UAP was provided for a patient who required unscheduled hospitalization for the management of UAP, occurring within 24 hours of the most recent symptoms, and who had worsening ischemic discomfort, objective evidence of myocardial ischemia, and negative cardiac biomarkers. All 572 patients were followed up for at least one year (36.7 ± 14.5 months) after the second SPECT. When a patient had multiple MCEs, only the first event was taken as the study endpoint.

Estimated MCE risks within 3 years with the CERS: MCE risk (%) within 3 years before and after treatment was estimated with the following formula¹⁰⁾ predicting the risk of MCEs except severe heart failure on the basis of 4 predictors consisting of age, diabetes mellitus (DM), SSS, and eGFR:

$$\text{MCE risk (\%/3 years)} = 1 / \{1 + \text{Exp}[-(3.176 + 0.018 \times \text{age} + 0.602 \times \text{DM} - 0.022 \times \text{eGFR} + 0.051 \times \text{SSS})]\} \times 100$$

where age is in years, DM is 1 for presence or 0 for absence, eGFR is mL/minute/1.73 m², and SSS is continuous variables. Estimated MCE risk reduction (%) was defined as a difference in MCE risk (%) between before and after treatment.

Statistical analysis: Continuous variables were calculated as the mean and standard deviation. Intergroup comparisons of continuous and categorical variables were achieved with the unpaired *t* test and the chi-square test, respectively. The paired *t* test was used to compare MCE risks estimated before and af-

ter treatment. Univariate analyses used the Cox proportional hazards regression model and multivariate analyses the stepwise Cox proportional hazards regression model. Linear regression analysis of ΔSDS% as an independent variable and estimated MCE risk reduction within 3 years with the CERS as a dependent variable was performed by the least squares method to calculate a correlation coefficient (*r*) suggesting a relationship between the two variables. Kaplan-Meier survival analysis was used to compare between MCE risks estimated with the CERS after treatment and actual MCE risks. The chi-square for trend test was used to detect any differences between 3 categories divided by tertile. All data were analyzed with MedCalc Software Version 13.1.2.0 (Mariakerke, Belgium). A *P* value of < 0.05 was considered statistically significant.

RESULTS

Major cardiac event rates and patient characteristics: During the follow-up, 50 (8.7%) of 572 patients experienced MCEs including cardiac death (*n* = 16), non-fatal MI (*n* = 4), and UAP (*n* = 30). CAG, which was performed in all 34 patients with non-fatal MI and UAP, indicated severe stenosis. Of those, 33 patients underwent percutaneous coronary intervention (PCI) for culprit lesions and the remaining patient underwent coronary artery bypass grafting (CABG). Major causes of UAP were progression of residual non-culprit stenosis (*n* =

Table II. Summary of Visual % Myocardium, Ischemic Reduction, Left Ventricular Ejection Fraction and Volume, and MCE Risk Estimated With the Cardiac Event Risk Score

	Major cardiac event (+) <i>n</i> = 50	Major cardiac event (-) <i>n</i> = 522	<i>P</i>
SSS% before treatment	18.3 ± 11.9	19.0 ± 11.0	0.6510
SRS% before treatment	6.3 ± 8.3	5.0 ± 7.9	0.2721
SDS% before treatment	12.0 ± 6.3	14.0 ± 7.6	0.0673
SSS% after treatment	14.9 ± 12.4	10.9 ± 11.4	0.0200
SRS% after treatment	7.5 ± 10.9	5.3 ± 8.8	0.0948
SDS% after treatment	7.4 ± 7.7	5.6 ± 6.3	0.0700
ΔSDS%	4.6 ± 7.9	8.4 ± 9.0	0.0044
5% ≥ ischemic reduction	23 46%	353 68%	0.0035
Rest LVEF before treatment	52.5 ± 15.5	57.2 ± 14.2	0.0262
Rest LVEDV before treatment	103.4 ± 59.8	92.3 ± 42.8	0.0923
Rest LVESV before treatment	56.8 ± 54.4	44.3 ± 36.5	0.0284
Stress LVEF before treatment	50.1 ± 14.6	54.7 ± 13.8	0.0242
Stress LVEDV before treatment	122.7 ± 60.6	109.3 ± 47.3	0.0631
Stress LVESV before treatment	69.1 ± 55.2	54.9 ± 41.0	0.0236
Rest LVEF after treatment	52.9 ± 15.8	59.2 ± 13.9	0.0024
Rest LVEDV after treatment	104.1 ± 56.7	89.2 ± 40.4	0.0173
Rest LVESV after treatment	56.8 ± 54.4	41.0 ± 34.3	0.0035
Stress LVEF after treatment	50.3 ± 15.2	57.8 ± 13.6	0.0002
Stress LVEDV after treatment	121.2 ± 60.6	103.3 ± 45.4	0.0103
Stress LVESV after treatment	68.7 ± 57.7	48.5 ± 38.0	0.0007
Estimated MCE risk (%/3 years) with CERS before treatment	14.1 ± 11.1	11.5 ± 8.6	0.0417
Estimated MCE risk (%/3 years) with CERS after treatment	13.9 ± 10.8	9.4 ± 8.0	0.0003
Estimated MCE risk reduction (%/3 years) with CERS	0.2 ± 6.3	2.0 ± 4.7	0.0126

The treatment mentioned in this table consists of percutaneous coronary intervention, coronary artery bypass grafting, and medication. SSS indicates summed stress score; SRS, summed rest score; SDS, summed difference score; ΔSDS%, the difference in SDS% between the first and second SPECT; LVEF, left ventricular ejection fraction; LVEDV, left ventricular ejection end-diastolic volume; LVESV, left ventricular ejection end-systolic volume; MCE, major cardiac event; and CERS, cardiac event risk score.

13), new stenotic lesions (*n* = 3), re-stenosis at the revascularization site (*n* = 3), progression of stenosis at regions adjacent to the revascularization site (*n* = 6), and progression of stenosis at jailed branches of the revascularization site (*n* = 5).

Table I summarizes the characteristics of the patients with and without MCEs. Mean age of the patients with and without MCEs was 68 and 67 years old, respectively, and 84% and 81% of the patients with and without MCEs were males. The proportions of patients with typical chest pain, a history of MI, hypertension, or a smoking habit were not significantly different between the two groups with and without MCEs. The proportions of patients with a history of revascularization and those with DM were significantly higher in the group with than without MCEs (*P* < 0.041). The proportions of patients with hyperlipidemia and those treated with statins were significantly lower in the group with than without MCEs (*P* < 0.042). The proportions of patients treated with other medications including aspirin, β-blockers, calcium antagonists, nitrates, angiotensin II receptor blockers, or angiotensin converting enzyme inhibitors were not significantly different between the two groups. The eGFR of patients with MCEs was 57.3 ± 26.3 mL/minute/1.73 m², which was similar to that of patients without MCEs (61.4 ± 23.4 mL/minute/1.73 m²). The severity of CAD detected by CAG was similar between the two groups. The proportion of patients undergoing PCI was 76% (38/50) in the group with MCEs and 76% (395/522) in the group without MCEs. As a breakdown of PCI, the proportions of patients treated with plain old balloon angioplasty were 5% (2/38) in the group with MCEs and 4% (15/395) in the group without MCEs; those treated with a bare-metal stent were 18% (7/38)

in the group with MCEs and 20% (79/395) in the group without MCEs; those treated with a drug-eluting stent were 76% (29/38) in the group with MCEs and 76% (301/395) in the group without MCEs. One of the patients with MCEs and 44 of the patients without MCEs underwent CABG. The remaining patients (11 and 83 in the groups with and without MCEs, respectively) received medication alone, mainly due to an inappropriate lesion for revascularization.

Visual % myocardium, left ventricular function, and estimated MCE risks: Table II summarizes visual % myocardium (SSS%, SRS% or SDS%) for myocardial defects detected by the SPECT as well as LVEF, LVEDV, and LVESV estimated with the quantitative gated SPECT before and after the treatment in the patients with and without MCEs; ΔSDS% and the number of patients having ≥ 5% ischemic reduction in patients with and without MCEs; MCE risks estimated with CERS before and after the treatment in the patients with and without MCEs. The visual % myocardium before the treatment was not different between the patients with and without MCEs. After the treatment, the SSS% was significantly higher in the patients with than without MCEs (14.9 ± 12.4 versus 10.9 ± 11.4; *P* = 0.0200). The ΔSDS% was significantly higher in the patients without than with MCEs (8.4 ± 9.0 versus 4.6 ± 7.9; *P* = 0.0044). The proportions of patients having ≥ 5% ischemic reduction after the treatment were 46% and 68% in the patients with and without MCEs, respectively (*P* = 0.0035). The rest and stress LVEF were generally higher while the rest and stress LVEDV and LVESV were smaller in the patients without than with MCEs, irrespective of whether it was estimated before or after the treatment. The MCE risk within 3 years estimated

Table III. Univariate Cox Proportional Hazards Regression Analysis

	Chi-Square	Hazard ratio	95% Confidence interval	P
Age	0.9739	1.0156	0.9850 - 1.0472	0.3237
Male sex	0.3513	1.2569	0.5924 - 2.6669	0.5534
History of MI	1.1904	1.3629	0.7837 - 2.3704	0.2752
History of revascularization	5.0678	1.9415	1.0928 - 3.4492	0.0244
Hypertension	0.0313	1.0647	0.5342 - 2.1217	0.8594
Diabetes mellitus	4.2452	1.8228	1.0327 - 3.2175	0.0394
Hyperlipidemia	5.4910	0.5129	0.2942 - 0.8940	0.0191
Statin use	4.6018	0.5440	0.3128 - 0.9461	0.0319
eGFR	1.8697	0.9922	0.9812 - 1.0033	0.1715
SSS% before treatment	0.2783	0.9930	0.9677 - 1.0190	0.5978
SRS% before treatment	1.0506	1.0161	0.9857 - 1.0474	0.3054
SDS% before treatment	3.4762	0.9579	0.9157 - 1.0020	0.0623
SSS% after treatment	5.5894	1.0242	1.0042 - 1.0447	0.0181
SRS% after treatment	3.0708	1.0225	0.9975 - 1.0481	0.0797
SDS% after treatment	3.4063	1.0355	0.9980 - 1.0743	0.0649
Δ SDS%	8.6103	0.9465	0.9125 - 0.9817	0.0033
5% $\geq$ ischemic reduction	4.7610	0.5217	0.2916 - 0.9332	0.0291
Rest LVEF after treatment	9.3817	0.9734	0.9569 - 0.9903	0.0022
Rest LVEDV after treatment	5.5690	1.0060	1.0010 - 1.0110	0.0183
Rest LVESV after treatment	8.2202	1.0075	1.0024 - 1.0126	0.0041
Stress LVEF after treatment	13.7102	0.9664	0.9492 - 0.9840	0.0002
Stress LVEDV after treatment	6.5929	1.0059	1.0014 - 1.0104	0.0102
Stress LVESV after treatment	11.0891	1.0078	1.0032 - 1.0124	0.0009
Estimated MCE risk (%/3 years) with CERS before treatment	5.0420	1.0291	1.0038 - 1.0550	0.0247
Estimated MCE risk (%/3 years) with CERS after treatment	15.5913	1.0456	1.0228 - 1.0689	0.0001
Estimated MCE risk reduction (%/3 years) with CERS	8.3334	0.9363	0.8955 - 0.9789	0.0039

The treatment mentioned in this table consists of percutaneous coronary intervention, coronary artery bypass grafting, and medication. MI indicates myocardial infarction; eGFR, estimated glomerular filtration rate; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; Δ SDS%, the difference in SDS% between the first and second SPECT; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MCE, major cardiac event; and CERS, cardiac event risk score.

Table IV. Multivariate Cox Proportional Hazards Regression Analysis

	Hazard ratio	95% Confidence interval	P
Δ SDS%	0.9559	0.9559 - 0.9917	0.0167
Estimated MCE risk (%) with CERS after treatment	1.0399	1.0160 - 1.0644	0.0010

The treatment mentioned in this table consists of percutaneous coronary intervention, coronary artery bypass grafting and medication. SDS indicates summed difference score; Δ SDS%, a difference between SDS% by the first and second SPECT; MCE, major cardiac event; and CERS, cardiac event risk score.

with the CERS was significantly higher in the patients with than without MCEs, irrespective of whether it was estimated before or after the treatment. The MCE risk reduction within 3 years estimated with the CERS was significantly lower in the patients with than without MCEs (0.2 ± 6.3 versus 2.0 ± 4.7 ; $P = 0.0126$).

Prediction of MCEs: The results of univariate Cox proportional hazards regression analysis showed a history of revascularization, DM, hyperlipidemia, statin use, SSS% after treatment, Δ SDS%, 5% $\geq$ ischemic reduction, left ventricular function after treatment, MCE risks estimated with the CERS before and after treatment, and MCE risk reduction within 3 years estimated with the CERS to be significant predictors for MCEs (Table III). Among these variables, Δ SDS% ($P = 0.0167$) and the MCE risk estimated with CERS after treatment ($P = 0.0010$) were extracted as independent predictors for MCEs in multivariate Cox proportional hazards regression analysis (Table IV).

Comparison of estimated MCE risks before and after treat-

ment: MCE risks within 3 years estimated with the CERS after treatment were not different from those estimated before treatment in the patients with MCEs ($13.9\% \pm 10.8\%$ versus $14.1\% \pm 11.1\%$; $P = 0.8018$) but were significantly lower in the patients without MCEs ($9.4\% \pm 8.0\%$ versus $11.5\% \pm 8.6\%$; $P < 0.0001$).

MCE risks within 3 years estimated with the CERS in patients having $\geq 5\%$ ischemic reduction were significantly lower after than before treatment ($8.9\% \pm 7.9\%$ versus $12.3\% \pm 9.5\%$; $P < 0.0001$). In contrast, MCE risks within 3 years estimated with CERS in patients having no $\geq 5\%$ ischemic reduction were significantly higher after than before treatment ($11.7\% \pm 8.8\%$ versus $10.6\% \pm 7.4\%$; $P = 0.0007$).

Correlation between estimated MCE risks reduction and Δ SDS%: Figure 1 shows a positive correlation between the MCE risk reduction (%) within 3 years estimated with CERS and the Δ SDS% ($r = 0.6242$; $P < 0.001$). A greater Δ SDS% was associated with a greater increase in the MCE risk reduction estimated with the CERS.

Figure 1. Correlation between MCE risk reduction within 3 years estimated with CERS and Δ SDS%. CERS indicates cardiac event risk score; Δ SDS%, percent change in summed difference score; and r , correlation coefficient.

Figure 2. Kaplan-Meier curves for the actual MCE risks in patients divided into 3 categories with tertile. The data shown in parentheses indicate MCE risks estimated with the CERS. MCE indicates major cardiac event; and CERS, cardiac event risk score.

Comparison of MCE risks estimated after treatment with actual occurrences of MCEs: The patients were divided into 3 categories on the basis of the MCE risks estimated with the CERS. Figure 2 illustrates Kaplan-Meier curves for the actual MCE risks and Figure 3 shows a comparison between the actual MCE risks and the MCE risk estimated with CERS in the 3 categories. The proportions of patients who actually experienced MCEs were 5.1% (10/198) in the 1st tertile, 8.1% (15/186) in the 2nd tertile, and 13.3% (25/188) in the 3rd tertile. The tertile division was significant stratification ($P = 0.0095$). The actual MCE risk was significantly higher in the 3rd tertile than in the 1st tertile ($P = 0.0082$) and was also significantly different between the 3 categories ($P = 0.0042$).

Figure 3. Comparison between the actual MCE risks (closed column) and the MCE risks estimated with the CERS (open column) in patients divided into 3 categories with tertile. MCE indicates major cardiac event; and CERS, cardiac event risk score.

MCE risks within 3 years estimated with the CERS after treatment, which were $3.5\% \pm 1.0\%$ for the 1st tertile, $7.7\% \pm 1.5\%$ for the 2nd tertile, and $18.7\% \pm 9.1\%$ for 3rd tertile, almost included each of the actual MCE risks.

Typical images in a patient having good prognosis: Figure 4 illustrates serial polar maps obtained from a typical patient having good prognosis after undergoing PCI.

The patient was a 69-year-old male with stable effort angina. The first SPECT showed extensive ischemia in the region of the left anterior descending artery (LAD) in October 2009. He underwent CAG, which revealed 90% stenosis in the proximal region of the LAD, and then PCI for the stenosis in the LAD. No ischemia was detected in the LAD region by the second SPECT in April 2010. Thereafter, he experienced no cardiac events and had a good prognosis. His MCE risk within 3 years estimated with CERS was 31.4% before PCI but definitely decreased to 6.0% after PCI on the basis of his data: eGFR was 63 mL/minute/1.73 m²; DM was present; and SSS was 38 and zero before and after PCI, respectively.

DISCUSSION

This is the first report demonstrating the prognostic value of a CERS predicting the risk of MCEs (except severe heart failure) within 3 years in Japanese patients with CAD, which was evaluated on the basis of the results from a retrospective single-center nuclear cardiology study. This report has considerable significance because the prognostic value of the CERS was verified on the basis of comparison between MCE risks estimated with the CERS and the actual occurrences of MCEs in patients who were not involved in the previous study on preparation of the CERS. MCE risks estimated with the CERS after treatment were selected as an independent predictor based on the results of the multivariate analysis, and were consistent with the actual occurrences of MCEs demonstrated by tertile-divided Kaplan-Meier analysis and the chi-square for trend

Figure 4. Serial polar maps of stress (upper), rest (middle), and ischemic (bottom) QPS images in a typical patient having good prognosis after undergoing PCI. QPS indicates quantitative perfusion single photon emission computed tomography; and PCI, percutaneous coronary intervention.

test. The results of this verification indicate that the CERS has a high significance for prediction of MCE risks and is a useful clinical tool for a prognosis of patients with CAD.

In addition to the MCE risks estimated with the CERS after treatment, the multivariate analysis extracted Δ SDS%, which is an index for improvement of ischemia, as an independent predictor. Furthermore, the greater improvement of ischemia was associated with a greater increase in the MCE risk reduction estimated with the CERS. The MCE risks within 3 years were significantly lower after than before treatment in the patients having at least 5% ischemic reduction while they were significantly higher after than before treatment in the patients having less than 5% ischemic reduction. The results of the nuclear substudy of the COURAGE trial¹⁹⁾ also showed that patients having at least 5% ischemic reduction after treatment could have a significantly better prognosis in comparison with those having less than 5% ischemic reduction. The extent of ischemic reduction after treatment is considered to change or affect the prognosis in patients with CAD. We previously reported a significantly preferable prognosis in patients having at least 5% ischemic reduction in comparison with patients having less than 5% ischemic reduction.²⁰⁾ The significance of ischemic reduction for predicting the prognosis was endorsed

by the results obtained from the present study.

The Heart Risk Table reported by Nakajima, *et al*⁹⁾ is another CERS predicting the risk of MCEs on the basis of data regarding age, DM, LVEF, SSS categories, and eGFR in Japanese patients with CAD. This is similar to our CERS with respect to the use of patient demographic and baseline characteristics as well as data on ischemic quantification obtained from nuclear cardiology. However, their MCEs included severe heart failure; of the total of 116 MCEs, 64 (55.2%) were severe heart failure requiring hospitalization. Therefore, the Heart Risk Table may be a suitable model for predicting the risk of severe heart failure, but might not be applicable to the prediction of risk of acute coronary syndrome. Furthermore, the prognostic value of the Heart Risk Table is unclear because there is no practical report regarding the predictive accuracy of MCE risks estimated with the Table and the risk reduction after treatment.

Many reports have indicated that LVEF is an important predictor of cardiac events.^{5,21)} LVEF is one of the predictors useful in the estimation of MCE risks with the Heart Risk Table. However, in a previous study,¹⁰⁾ we found that LVEF was an independent significant predictor of cardiac death but not of MCEs. Therefore, we have separately prepared two different equations to predict the risks of MCEs and cardiac death. The discrepancy between our equations and the Heart Risk Table may be based on the definition of whether to include severe heart failure in MCEs. In our study, severe heart failure was not included in the MCEs. We consider LVEF or LVEDV to be a significant predictor of cardiac death and severe heart failure. Actually, the correlations were moderate between SSS and stress LVEF ($r = 0.6331$) or LVEDV ($r = 0.5457$) after treatment in this study. The equation incorporating LVEF for prediction of cardiac death will be verified in a future study because the aim of the present study was to verify the equation of MCE risks and also the number of patients with cardiac death observed was too small ($n = 16$) in this study to verify the equation of cardiac death risks.

Determination of a therapeutic strategy and the prediction of prognosis in patients with CAD could also be performed with fractional flow reserve, which is a physiological ischemic variable, measured before and after revascularization.²²⁻²⁴⁾ However, it is difficult to measure the fractional flow reserve in all stenotic vessels and measurement entails the risks associated with an invasive operation. Therefore, the CERS obtained from nuclear cardiology, which is a non-invasive operation, are preferable to determine a therapeutic strategy for improving the prognosis in Japanese patients with CAD.

Study limitations: Our CERS may involve selection bias because it was created on the basis of data from a retrospective single-center investigation. Also, the timings of treatment and evaluation of its effect to examine MCE risk reduction varied from patients to patients because it was a retrospective study. However, the CERS is a useful index with which to predict the risk of MCEs, with the exception of severe heart failure, because they cannot be predicted with the version of the Heart Risk Table that is currently available in Japan. Because this study verified the prognostic value of the CERS as a unique risk equation for predicting coronary events in Japanese patients with CAD, CERS has significance clinically. In addition, this CERS is easily calculated with general spreadsheet software and provides the rate of MCEs within 3 years. Therefore,

we believe the CERS will be confirmed by other institutes.

Most of the MCEs were UAP in this study. The most frequent cause for UAP was identified as progression of residual non-culprit stenosis, which is considered to be possibly associated with a low frequency of statin treatment.

Also, radiation exposure from cardiac imaging has become an important topic recently. The level of radiation exposure from the ^{201}Tl + $^{99\text{m}}\text{Tc}$ -tetrofosmin dual isotope SPECT received by the patients in this study was nearly 30 mSv, which was higher than that from $^{99\text{m}}\text{Tc}$ -tetrofosmin rest-stress SPECT (8.6 mSv).^{25,26)} However, we used this protocol because the patients were not restricted for a long time due to the short procedural length and the patients were informed of the imaging results immediately after completion of the procedure. Our risk score may be applicable to the $^{99\text{m}}\text{Tc}$ -tetrofosmin rest-stress SPECT protocol because the prediction of prognosis or diagnostic accuracy with ^{201}Tl is generally similar to that with $^{99\text{m}}\text{Tc}$ -tetrofosmin.²⁷⁾

The CERS after treatment is a valuable formula for predicting prognosis in Japanese patients with CAD.

DISCLOSURE

Conflict of interest: All authors declare that they have no conflict of interest.

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REFERENCES

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837-47.
2. Goff DC Jr, Lloyd-Jones DM, Bennett G, *et al*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA Guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129: S49-73.
3. Hachamovitch R, Berman DS, Shaw LJ, *et al*. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; 97: 535-43.
4. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; 107: 2900-7.
5. Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008; 35: 319-28.
6. Nakajima K, Yamasaki Y, Kusuoka H, *et al*. Cardiovascular events in Japanese asymptomatic patients with type 2 diabetes: a 1-year interim report of a J-ACCESS 2 investigation using myocardial

perfusion imaging. *Eur J Nucl Med Mol imaging* 2009; 36: 2049-57.

7. Joki N, Hase H, Kawano Y, *et al*. Myocardial perfusion imaging for predicting cardiac events in Japanese patients with advanced chronic kidney disease: 1-year interim report of the J-ACCESS 3 investigation. *Eur J Nucl Med Mol Imaging* 2014; 41: 1701-9.
8. Matsumoto N, Sato Y, Suzuki Y, *et al*. Prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of future cardiac events in a Japanese population: a middle-term follow-up study. *Circ J* 2007; 71: 1580-5.
9. Nakajima K, Matsuo S, Okuyama C, *et al*. Cardiac event risk in Japanese subjects estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. *Circ J* 2012; 76: 168-75.
10. Yoda S, Nakanishi K, Tano A, *et al*. Major cardiac event risk scores estimated with gated myocardial perfusion imaging in Japanese patients with coronary artery disease. *J Cardiol* 2016; 67: 64-70.
11. Yoda S, Nakanishi K, Tano A, *et al*. Risk stratification of cardiovascular events in patients at all stages of chronic kidney disease using myocardial perfusion SPECT. *J Cardiol* 2012; 60: 377-82.
12. Berman DS, Kiat H, Friedman JD, *et al*. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. *J Am Coll Cardiol* 1993; 22: 1455-64.
13. Yoda S, Sato Y, Matsumoto N, *et al*. Incremental value of regional wall motion analysis immediately after exercise for the detection of single-vessel coronary artery disease – Study by separate acquisition, dual-isotope ECG-gated single-photon emission computed tomography. *Circ J* 2005; 69: 301-5.
14. Yoda S, Nakanishi K, Tano A, *et al*. Diagnostic value of automated quantification of nuclear cardiology in Japanese patients with single vessel coronary artery disease: comparison between Japanese and American normal databases. *J Cardiol* 2013; 62: 224-9.
15. Yoda S, Nakanishi K, Tano A, *et al*. Validation of automated quantification of nuclear cardiology in Japanese patients using total perfusion deficits: comparison with visual assessment. *J Cardiol* 2013; 63: 350-7.
16. Yoda S, Nakanishi K, Tano A, *et al*. Usefulness of automated assessment of nuclear cardiology for prediction of major cardiac events in Japanese patients with known or suspected coronary artery disease: comparison with conventional visual assessment in a large-scale prognostic study. *J Cardiol* 2014; 64: 395-400.
17. Germano G, Kiat H, Kavanagh PB, *et al*. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138-47.
18. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982-92.
19. Shaw LJ, Berman DS, Maron DJ, *et al*. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008; 117: 1283-91.
20. Hori Y, Yoda S, Nakanishi K, *et al*. Myocardial ischemic reduction evidenced by gated myocardial perfusion imaging after treatment results in good prognosis in patients with coronary artery disease. *J Cardiol* 2015; 65: 278-84.
21. Sharir T, Germano G, Kavanagh PB, *et al*. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999; 100: 1035-42.
22. Tonino PA, Fearon WF, De Bruyne B, *et al*. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; 55: 2816-21.
23. De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Eng J Med* 2012; 367: 991-1001.
24. Pijls NH, van Schaardenburgh P, Manoharan G, *et al*. Percutane-

- ous coronary intervention of functionally nonsignificant stenosis 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007; 49: 2105-11.
25. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. *Circulation* 2007; 116: 1290-305. (Review)
26. ICRP. Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007. *Ann ICRP* 2008; 38: 1-197.
27. Gibbons RJ, Chatterjee K, Daley J, *et al.* ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 1999; 33: 2092-197.