



Cardiac Event Risk in Japanese Subjects Estimated Using Gated Myocardial Perfusion Imaging, in Conjunction With Diabetes Mellitus and Chronic Kidney Disease

Kenichi Nakajima, MD; Shinro Matsuo, MD; Chio Okuyama, MD; Tsuguru Hatta, MD;
Kazumasa Tsukamoto, PhD; Shigeyuki Nishimura, MD; Akira Yamashina, MD;
Hideo Kusuoka, MD; Tsunehiko Nishimura, MD

Background: Cardiac event risk is estimated using quantitative gated myocardial perfusion imaging (MPI) and clinical background in patients with ischemic heart disease. The aim of the present study was to calculate major cardiac event risk and tabulate it in the Heart Risk Table for clinical use of risk stratification.

Methods and Results: Multivariate logistic regression was performed based on a multicenter prognostic database (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated Single-photon emission computed tomography [J-ACCESS investigation]) using MPI (n=2,395). The risk of major cardiac events (cardiac death, non-fatal myocardial infarction and heart failure requiring hospitalization) was estimated using age, ejection fraction (EF), estimated glomerular filtration rate (eGFR) and presence of diabetes mellitus (DM). Age-matched standard eGFR was determined in 77 subjects. Major cardiac event risk was calculated using the equation: $\text{risk (\%/3 years)} = 1 / (1 + \text{Exp}(-(-4.699 - 0.0151 \times \text{eGFR} + 0.7998 \times \text{DM} + 0.0582 \times \text{age} + 0.697 \times \text{SSS} - 0.0359 \times \text{EF}))) \times 100$, where SSS refers to summed stress scores. Risk was determined without eGFR (the initial version) and using the present formula with eGFR (revised version), with consistent results. DM and chronic kidney disease were major determinants of cardiac events.

Conclusions: Cardiac event risk was estimated using MPI defect score and left ventricular EF in conjunction with eGFR and the presence of DM. The risk table might be used for risk evaluation in Japanese patients undergoing MPI. (*Circ J* 2012; **76**: 168–175)

Key Words: Cardiac event; Chronic kidney disease; Diabetes mellitus; Myocardial perfusion imaging; Risk stratification

Estimation of cardiovascular events has been considered important for evaluating the severity of coronary artery disease (CAD) as well as to determine therapeutic strategy.^{1–3} To stratify risk, myocardial perfusion imaging (MPI) has been effective both in Western countries and in Japan.^{4–7} Although a number of prognostic studies have been conducted in the USA and Europe, only a few multi-center studies have been performed in Japan. Although the incidences of cardiac mortality and hard events were relatively low in the Japanese studies, similar prognostic factors have been found in both Japanese and Western subjects but with some differences, such as obesity.^{8,9} According to the prognostic database of the

Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated Single-photon emission computed tomography (J-ACCESS investigation), larger perfusion defects, cardiac dysfunction and older age were principal predictors of cardiac events.^{4,10} Among various clinical backgrounds, only the presence of diabetes mellitus (DM) was selected on multivariate analysis to predict major cardiac events. Therefore, the diagnostic algorithm to predict major cardiac events included quantitative analysis of perfusion, left ventricular (LV) function and DM for the risk estimation.¹¹ Subsequently, in a sub-analysis of the J-ACCESS study, chronic kidney disease (CKD) was found to be one of the main predictors of major cardiac

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Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa (K.N., S.M.); Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto (C.O., T.N.); Division of Nephrology, Department of Medicine, Ohmihachiman Community Medical Center, Shiga (T.H.); Department of Environment and Occupational Health, Graduate School of Medicine, Toho University, Tokyo (K.T.); Second Department of Internal Medicine, Tokyo Medical University Hospital, Tokyo (A.Y.); Department of Cardiology, Saitama Medical School Hospital, Saitama (S.N.); and Osaka National Hospital, Osaka (H.K.), Japan

Mailing address: Kenichi Nakajima, MD, Department of Nuclear Medicine, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa 920-8641, Japan. E-mail: nakajima@med.kanazawa-u.ac.jp or Tsunehiko Nishimura, MD, Department of Radiology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: nisimura@koto.kpu-m.ac.jp

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events.¹² The result was essentially in agreement with that of a US study dealing with CKD and cardiac death rate.¹³

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The purpose of the present study was to create a risk calculation method using a Japanese prognostic database and also to present a risk chart for clinical use. The consistency between the previous version of risk calculation¹¹ and this new version including both DM and CKD was investigated.

Methods

J-ACCESS Investigation

The subjects and the method of the J-ACCESS study have been described elsewhere.^{4,11} Briefly, a total of 4,031 patients were analyzed after excluding early revascularization within 60 days of single-photon emission computed tomography (SPECT). According to the inclusion criteria, subjects aged ≥ 20 years who underwent stress-and-rest electrocardiography (ECG)-gated SPECT because of suspected or known ischemic heart disease, were enrolled. Patients with onset of myocardial infarction or unstable angina pectoris within 3 months, valvular heart disease, idiopathic cardiomyopathy, severe arrhythmia, heart failure with class III or higher New York Heart Association classification, and severe liver or renal disorders were excluded. Patients were followed up for 3 years. Primary endpoints included cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization. The study was approved by the institutional review boards or ethics committees in all participating hospitals.

Patients

In order to calculate event risk, 2,453 patients for whom estimated glomerular filtration rate (eGFR) data were available were selected initially.¹² Subsequently, based on the univariate analysis as previously performed,⁴ a total of 2,395 patients having complete information for eGFR, presence of DM and history of myocardial infarction were selected. The definition of CKD was $\text{eGFR} < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. Patients with end-stage renal disease, that is, those who had undergone hemodialysis or who were candidates for renal transplantation, were excluded. $\text{eGFR} (\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2})$ was calculated using the following equation modified for Japanese subjects:¹⁴

$$\text{eGFR} = 194 \times (\text{creatinin}^{-1.094}) \times (\text{age}^{-0.287})$$

for male subjects and

$$\text{eGFR} = \text{eGFR}_{\text{male}} \times 0.739$$

for female subjects. In the J-ACCESS study protocol, the presence of DM was recorded as a risk factor based on the institutional definitive diagnosis including blood sugar, hemoglobin A_{1c} and other clinical manifestations. Patients on diabetic medication or insulin were also included. The clinical characteristics of the subjects are given in **Table 1**.

MPI

Of the 2,395 patients, stress–rest ^{99m}Tc-tetrofosmin SPECT was performed on 2,361 patients (98.6%) using a 1-day protocol and on 34 (1.4%) using a 2-day protocol. The stress test was applied as exercise in 1,668 patients (69.6%), and as pharmacological stress (dipyridamole, adenosine and adenosine triphosphate) for the remaining patients.

Table 1. Clinical Characteristics and MPI Results

	Mean \pm SD
n	2,395
Male (%)	64.0
Age (years)	66.1 \pm 10.0
Body mass index (kg/m ²)	23.7 \pm 3.3
Typical chest pain (%)	46.3
Past history of MI (%)	30.7
Past history of revascularization (%)	36.8
Current smoking (%)	15.8
Hypertension (%)	55.8
Diabetes mellitus (%)	32.8
Dyslipidemia (%)	51.4
Family history of CAD	11.0
eGFR ($\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)	67.3 \pm 30.7
eGFR $< 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (%)	33.4
MPI parameters	
LVEF (%)	61.2 \pm 13.9
End-diastolic volume (ml)	85.3 \pm 38.0
End-systolic volume (ml)	37.0 \pm 30.9
SSS	9.0 \pm 11.5
Summed rest score	7.6 \pm 11.0
Summed difference score	1.5 \pm 3.8

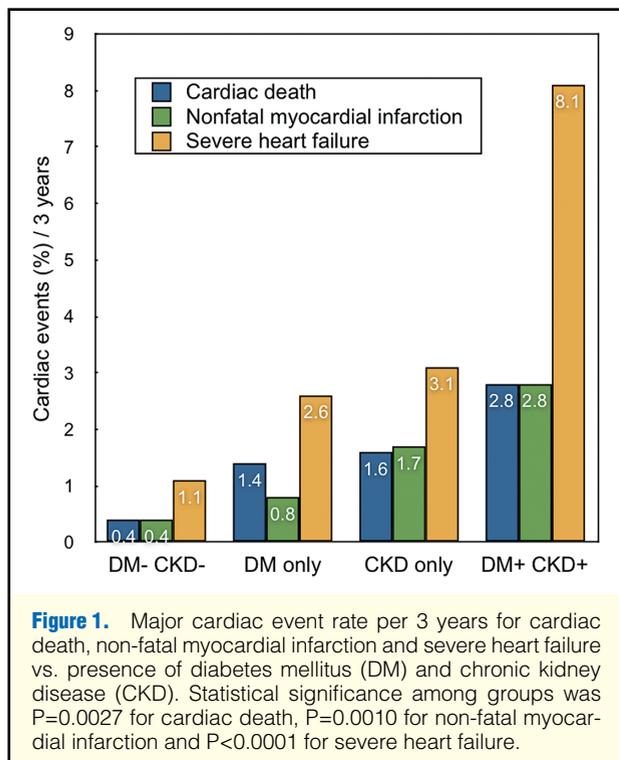
MPI, myocardial perfusion imaging; MI, myocardial infarction; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SSS, summed stress score.

MPI Data Analysis

MPI was performed using ^{99m}Tc-tetrofosmin with a standard stress–rest protocol. The SPECT images were divided into 20 segments, and visual perfusion defects in individual segments were scored as follows: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced, and 4, absent. Although the 20-segment model was used for the initial analysis to utilize the original J-ACCESS data, the score of a 17-segment model was also used for calculating risk tables and creating calculation software.^{15,16} The conversion of 2 segmentation models was done using a coefficient of 17/20. Summed stress scores (SSS) and summed rest scores (SRS) were calculated based on stress and rest findings, respectively, and the summed difference score was defined as the difference between SSS and SRS. The severity of total MPI defects was categorized into 4 grades (O, I, II and III) using summed scores in the 20-segment model: namely, normal, score 0–3; slightly abnormal, score 4–8; moderately abnormal, score 9–13; or severely abnormal, score ≥ 14 . In the 17-segment model the categories O–III corresponded to 0–3, 4–7, 8–11 and > 11 , respectively. Gated SPECT was quantitatively analyzed using QGS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA). LV end-diastolic volume, end-systolic volume (ESV) and ejection fraction (EF) were calculated.

Multivariate Analysis

In the J-ACCESS study, major cardiac events occurred in 175 patients (4.3%/3 years), and these consisted of cardiac death, non-fatal myocardial infarction, and severe heart failure.⁴ After selecting significant variables on univariate analysis ($P < 0.05$), the selected final variables on multivariate analysis included age, presence of DM, SSS and ESV or EF. Thus, similarly in the present study multivariate logistic regression analysis was applied to estimate the event rate using age, SSS,



EF, presence of DM and eGFR. The variable of history of myocardial infarction was not included because it was found to be not significant.

Standard eGFR

To estimate age-matched eGFR, patients who had no history of cardiac disease, no ECG abnormality, normal SSS (0–3), normal SRS (0–3), normal LVEF and ESV (LVEF >50% and ESV <60 ml for men, and LVEF >55% and ESV <40 ml for women¹⁷), no cardiac risk factors (ie, family history of CAD, DM, dyslipidemia and smoking), no history of renal failure or arteriosclerosis obliterans were selected from the J-ACCESS database. A total of 77 patients (28 men and 49 women, mean age 61 ± 13 years, range 21–80 years) were selected. The eGFR was calculated using the Japanese equation given in the previous section.¹⁴

Risk Charts for Cardiac Events

Because ESV in ml depended on the patient height and weight, we used EF instead to simplify the risk table. Because the predictors included continuous variables of EF and age, the EF (0–100%) was classified into 10 classes and age was also classified by decade. The absence or presence of DM was noted

as 0 or 1. SSS was classified into 1 of 2 categories of low (SSS <9) and high (SSS ≥ 9). The control EF was set at 65% for both sexes. The eGFR was classified into <30, 30–44, 45–59, 60–89 and ≥ 90 ml \cdot min⁻¹ \cdot 1.73 m⁻² for the risk table. Subdivision of the class of 30–59 ml \cdot min⁻¹ \cdot 1.73 m⁻² into 2 subgroups was consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) report.¹⁸ A relative risk value (unit: fold) was defined as the calculated risk divided by the age-matched normal risk in non-diabetic subjects with standard eGFR.

Statistical Analysis

Mean \pm SD was calculated for each parameter. The difference in event rate among each group was examined on chi-square test and Steel-Dwass non-parametric multiple comparison tests. Using statistically significant independent variables with the univariate Cox proportional hazard model, the multivariate Cox proportional model was applied using a forward stepwise method. Multivariate logistic analysis was performed as described here. To calculate event risk and for graphical comparison among methods, Mathematica (version 8.0 on Mac OS-X, Wolfram Research, Champaign, IL, USA) was used. $P<0.05$ was considered to be significant.

Results

Age-Matched eGFR

Because age-matched eGFR after correction did not differ significantly between men and women, the linear regression line was calculated for all patients as follows: $eGFR = 111.4 - 0.618 \times \text{age}$ ($P<0.0001$).

Cardiac Events

Major cardiac events of cardiac death, non-fatal myocardial infarction and severe heart failure occurred in 27 patients (1.1%), 25 patients (1.0%) and 64 patients (2.7%), respectively. The event rates are summarized in **Figure 1**. When the patients were classified according to DM and CKD, the major event rate was 20/1,094 (1.8%) for neither CKD nor DM, 24/501 (4.8%) for only DM, 33/516 (6.4%) for only CKD, and 39/284 (13.7%) for both CKD and DM ($P<0.0001$).

Logistic Regression Analysis

Based on the J-ACCESS investigation summary ($n=4,031$), the major event rate was estimated using the following equation:¹¹

$$\text{Major event risk (\%/3 years)} = 1 / (1 + \text{Exp}[-(-4.8125 + 0.8858 \times \text{DM} (0 \text{ or } 1) + 0.0558 \times \text{age} + 0.1941 \times \text{SSS category} (0, 1, 2 \text{ or } 3) - 0.0475 \times \text{EF} (\%))]) \times 100,$$

... Equation 1

where age is given in years. Similarly, when multivariate logistic regression analysis was performed in the present study,

	Estimate	Standard error	χ^2	P value
Intercept	-4.699	1.0776	19.0154	<0.0001
Age (years)	0.0582	0.0128	20.7291	<0.0001
Diabetes (presence or absence)	0.7998	0.2001	15.9681	<0.0001
LVEF (%)	-0.0359	0.00742	23.4257	<0.0001
SSS (high or low)	0.697	0.2326	8.9802	0.0027
eGFR (ml \cdot min ⁻¹ \cdot 1.73 m ⁻²)	-0.0151	0.00488	9.567	0.0020

J-ACCESS, Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated Single-photon emission computed tomography. Other abbreviations see in Table 1.

Major cardiac event (%) / 3 years

		SSS<9, DM (-)					SSS≥9, DM (-)					SSS<9, DM (+)					SSS≥9, DM (+)				
		eGFR																			
Age	EF	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30
40-49	10%	2	3	4	5	6	4	5	7	9	11	5	6	8	10	13	9	11	15	18	22
	20%	2	2	3	3	4	3	4	5	6	8	3	4	6	7	9	7	8	11	13	17
	30%	1	1	2	2	3	2	3	4	5	6	2	3	4	5	7	5	6	8	10	12
	40%	1	1	1	2	2	2	2	3	3	4	2	2	3	4	5	3	4	6	7	9
	50%	1	1	1	1	2	1	1	2	2	3	1	1	2	3	3	2	3	4	5	6
	60%	0	0	1	1	1	1	1	1	2	2	1	1	1	2	2	2	2	3	4	5
	70%	0	0	0	1	1	1	1	1	1	1	1	1	1	1	2	1	1	2	3	3
	80%	0	0	0	0	1	0	0	1	1	1	0	1	1	1	1	1	1	1	2	2
50-59	10%	4	5	7	8	10	7	9	12	15	19	8	10	14	16	20	15	18	24	28	34
	20%	3	3	5	6	7	5	7	9	11	14	6	7	10	12	15	11	14	18	22	26
	30%	2	2	3	4	5	4	5	6	8	10	4	5	7	9	11	8	10	13	16	20
	40%	1	2	2	3	4	3	3	5	6	7	3	4	5	6	8	6	7	10	12	15
	50%	1	1	2	2	3	2	2	3	4	5	2	3	4	4	6	4	5	7	9	11
	60%	1	1	1	1	2	1	2	2	3	4	1	2	3	3	4	3	4	5	6	8
	70%	0	1	1	1	1	1	1	2	2	3	1	1	2	2	3	2	3	4	4	6
	80%	0	0	1	1	1	1	1	1	1	2	1	1	1	2	2	1	2	2	3	4
60-69	10%	7	8	11	14	17	13	15	20	24	29	14	17	22	26	31	24	29	36	41	48
	20%	5	6	8	10	13	9	11	15	18	22	10	12	16	20	24	18	22	28	33	39
	30%	3	4	6	7	9	7	8	11	13	17	7	9	12	15	18	14	16	22	26	31
	40%	2	3	4	5	7	5	6	8	10	12	5	6	9	11	14	10	12	16	19	24
	50%	2	2	3	4	5	3	4	6	7	9	4	5	6	8	10	7	9	12	14	18
	60%	1	1	2	3	3	2	3	4	5	6	3	3	4	6	7	5	6	9	11	13
	70%	1	1	1	2	2	2	2	3	4	5	2	2	3	4	5	4	4	6	8	10
	80%	1	1	1	1	2	1	1	2	3	3	1	2	2	3	4	3	3	4	5	7
70-79	10%	7	8	11	14	17	13	15	20	24	29	14	17	22	26	31	24	29	36	41	48
	20%	5	6	8	10	13	9	11	15	18	22	10	12	16	20	24	18	22	28	33	39
	30%	3	4	6	7	9	7	8	11	13	17	7	9	12	15	18	14	16	22	26	31
	40%	2	3	4	5	7	5	6	8	10	12	5	6	9	11	14	10	12	16	19	24
	50%	2	2	3	4	5	3	4	6	7	9	4	5	6	8	10	7	9	12	14	18
	60%	1	1	2	3	3	2	3	4	5	6	3	3	4	6	7	5	6	9	11	13
	70%	1	1	1	2	2	2	2	3	4	5	2	2	3	4	5	4	4	6	8	10
	80%	1	1	1	1	2	1	1	2	3	3	1	2	2	3	4	3	3	4	5	7
80-89	10%	19	22	29	34	40	32	37	45	50	57	34	39	47	53	60	51	56	64	69	75
	20%	14	17	22	26	32	24	29	36	42	48	26	31	39	44	51	42	47	56	61	67
	30%	10	12	16	20	24	18	22	28	33	39	20	24	31	36	42	33	39	47	53	59
	40%	7	9	12	15	18	14	16	22	26	31	15	18	23	28	33	26	30	38	44	50
	50%	5	6	9	11	14	10	12	16	20	24	11	13	18	21	26	20	23	30	35	41
	60%	4	5	6	8	10	7	9	12	14	18	8	10	13	16	20	15	18	23	27	33
	70%	3	3	4	6	7	5	6	9	11	13	6	7	9	12	15	11	13	17	21	26
	80%	2	2	3	4	5	4	4	6	8	10	4	5	7	8	11	8	9	13	16	19

Figure 2. Risk charts for major cardiac events (%)/3 years. Summed stress score (SSS) <9 without diabetes mellitus (DM), SSS ≥9 without DM, SSS <9 with DM and SSS ≥9 with DM from left to right. Yellow, 3.0–11.9%; pink, 12.0–35.9%; red, ≥36.0%.

LVEF, age, presence or absence of DM, high or low SSS (≥9 or <9), and eGFR were found to be significant variables (Table 2). The odds ratio and 95% confidence interval were 1.060 (1.034–1.087) for age, 2.225 (1.503–3.294) for DM, 0.965 (0.951–0.979) for LVEF, 2.008 (1.273–3.167) for SSS and 0.985 (0.976–0.994) for eGFR. Based on multivariate regression analysis, the major cardiac event risk (P, %/3 years) was calculated as:

$$\text{Major event risk (\%/3 years)} = 1 / (1 + \text{Exp}(-(-4.699 - 0.0151 \times \text{eGFR} + 0.7998 \times \text{DM} + 0.0582 \times \text{age} + 0.697 \times \text{SSS} - 0.0359 \times \text{EF}))) \times 100,$$

... Equation 2

where DM is given as 0 or 1, eGFR in ml · min⁻¹ · 1.73 m⁻², age in years, SSS as 0 or 1, and EF in %.

Creation of Risk Tables

On the basis of this formula, risk and relative risk were tabulated with respect to decade of age and 10%-increment EF classes as the Heart Risk Table (Figure 2 and 3). eGFRs of 20, 37.5, 52.5, 75 and 90 ml · min⁻¹ · 1.73 m⁻² were used to calculate risk for the classes <30, 30–44, 45–59, 60–89 and ≥90 ml · min⁻¹ · 1.73 m⁻², respectively. The average age and EF were used for calculation of tables. Age-matched risk was calculated using the parameters DM=0, CKD=0, EF=65%, SSS=0 and age-matched normal eGFR, and relative risk was defined as calculated risk divided by the age-matched risk.

The Heart Risk Table can be used for patients with and without DM and CKD. If the patient's age, eGFR and the presence of DM are known, corresponding risk (%/3 years) and relative risk (folds) of major cardiac events can be determined from the cross-over point of the eGFR class and EF class.

Relative cardiac event risk (folds)

		SSS<9, DM (-)					SSS≥9, DM (-)					SSS<9, DM (+)					SSS≥9, DM (+)				
		eGFR																			
Age	EF	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30	≥90	60-89	45-59	30-44	<30
40-49	10%	6	8	11	14	18	13	16	22	26	34	14	17	24	29	37	27	33	44	53	65
	20%	5	6	8	10	13	9	11	15	19	24	10	12	17	21	27	19	24	32	39	49
	30%	3	4	6	7	9	6	8	11	14	17	7	9	12	15	19	14	17	23	29	36
	40%	2	3	4	5	6	4	6	8	10	12	5	6	9	11	14	10	12	17	21	26
	50%	2	2	3	3	4	3	4	5	7	9	3	4	6	7	10	7	8	12	15	19
	60%	1	1	2	2	3	2	3	4	5	6	2	3	4	5	7	5	6	8	10	13
	70%	1	1	1	2	2	2	2	3	3	4	2	2	3	4	5	3	4	6	7	9
	80%	1	1	1	1	2	1	1	2	2	3	1	1	2	3	3	2	3	4	5	7
50-59	10%	6	7	10	12	15	11	14	19	23	28	12	15	20	25	31	23	27	36	42	51
	20%	4	5	7	9	11	8	10	13	17	21	9	11	15	18	23	17	20	27	32	40
	30%	3	4	5	6	8	6	7	10	12	15	6	8	11	13	17	12	15	20	24	30
	40%	2	3	4	4	6	4	5	7	9	11	4	5	8	9	12	9	11	15	18	22
	50%	1	2	2	3	4	3	4	5	6	8	3	4	5	7	9	6	8	10	13	16
	60%	1	1	2	2	3	2	2	3	4	6	2	3	4	5	6	4	5	7	9	12
	70%	1	1	1	2	2	1	2	2	3	4	2	2	3	3	4	3	4	5	7	8
	80%	0	1	1	1	1	1	1	2	2	3	1	1	2	2	3	2	3	4	5	6
60-69	10%	5	6	9	10	13	10	12	16	18	22	11	13	17	20	24	19	22	28	32	37
	20%	4	5	6	8	10	7	9	12	14	17	8	9	13	15	19	14	17	22	25	30
	30%	3	3	4	5	7	5	6	8	10	13	6	7	9	11	14	10	13	17	20	24
	40%	2	2	3	4	5	4	4	6	7	9	4	5	7	8	10	8	9	12	15	18
	50%	1	2	2	3	4	3	3	4	5	7	3	3	5	6	8	5	7	9	11	14
	60%	1	1	2	2	3	2	2	3	4	5	2	2	3	4	5	4	5	7	8	10
	70%	1	1	1	1	2	1	2	2	3	4	1	2	2	3	4	3	3	5	6	7
	80%	0	1	1	1	1	1	1	2	2	2	1	1	2	2	3	2	2	3	4	5
70-79	10%	4	5	7	9	11	8	10	12	14	17	9	10	13	15	18	14	17	20	22	25
	20%	3	4	5	7	8	6	7	10	11	13	7	8	10	12	14	11	13	16	19	21
	30%	2	3	4	5	6	4	5	7	9	10	5	6	8	9	11	9	10	13	15	18
	40%	2	2	3	3	4	3	4	5	6	8	4	4	6	7	9	6	8	10	12	14
	50%	1	1	2	2	3	2	3	4	5	6	3	3	4	5	6	5	6	8	9	11
	60%	1	1	1	2	2	2	2	3	3	4	2	2	3	4	5	3	4	6	7	8
	70%	1	1	1	1	2	1	1	2	2	3	1	2	2	3	3	2	3	4	5	6
	80%	0	1	1	1	1	1	1	1	2	2	1	1	2	2	2	2	2	3	4	5
80-89	10%	4	5	6	7	8	7	8	9	10	12	7	8	10	11	12	10	12	13	14	15
	20%	3	3	5	5	7	5	6	7	9	10	5	6	8	9	10	9	10	11	13	14
	30%	2	3	3	4	5	4	5	6	7	8	4	5	6	7	9	7	8	10	11	12
	40%	1	2	2	3	4	3	3	4	5	6	3	4	5	6	7	5	6	8	9	10
	50%	1	1	2	2	3	2	2	3	4	5	2	3	4	4	5	4	5	6	7	8
	60%	1	1	1	2	2	1	2	2	3	4	2	2	3	3	4	3	4	5	6	7
	70%	1	1	1	1	1	1	1	2	2	3	1	1	2	2	3	2	3	4	4	5
	80%	0	0	1	1	1	1	1	1	2	2	1	1	1	2	2	2	2	3	3	4

Figure 3. Relative risk given in units of fold. Light blue, 3.0–9.9%; blue, 10.0–19.9%; dark blue, ≥20.0%. EF, ejection fraction; eGFR, estimated glomerular filtration rate.

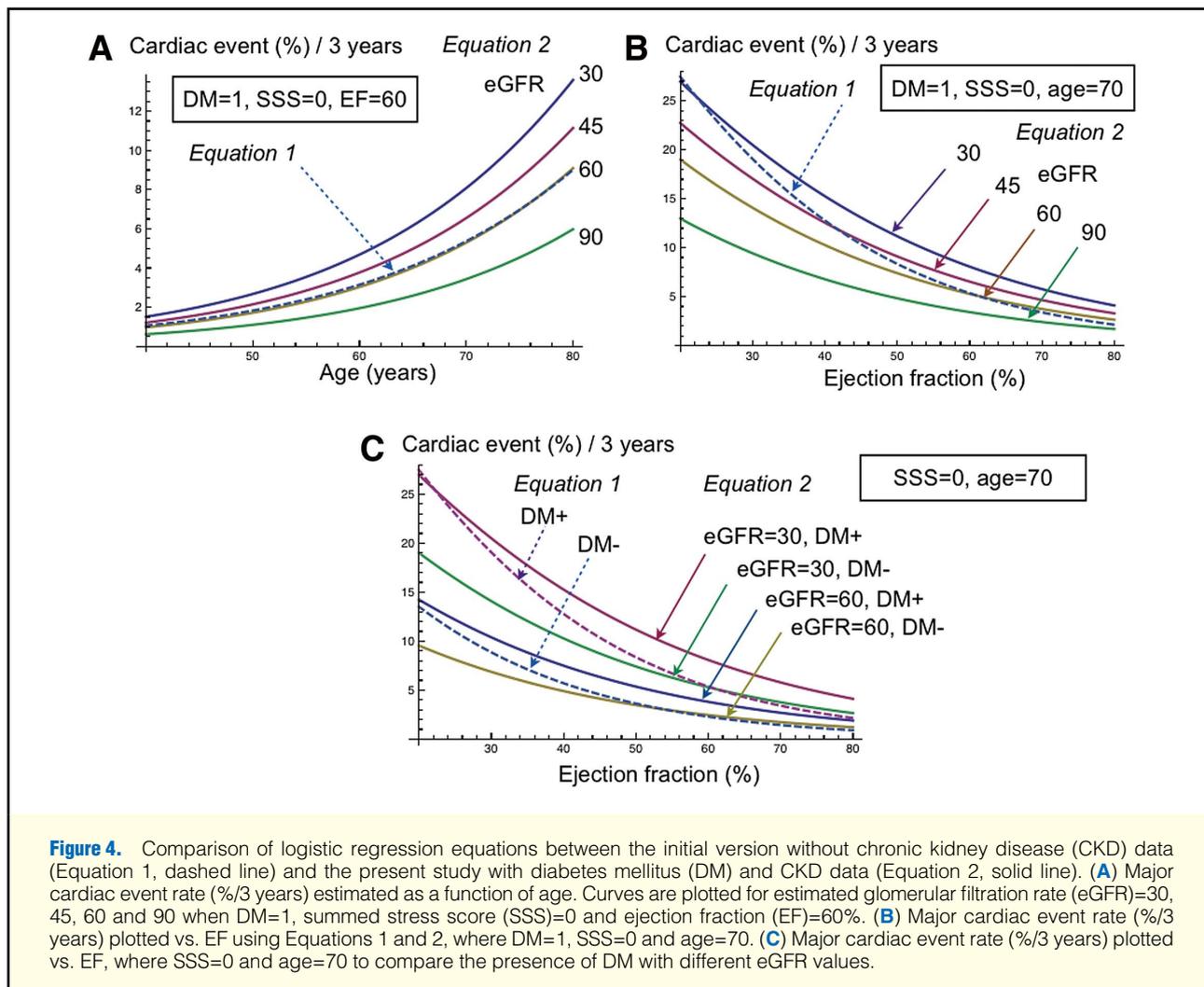
Calculation of Risk With and Without CKD

Because the initial risk chart did not include eGFR, the multivariate logistic equations for the present version (Equation 2) and the initial version (Equation 1) were compared. **Figure 4A** shows the effects of eGFR on risk values (%/3 years) when the graphs were plotted with respect to risk vs. age. Increased risk depended on the eGFR, and an age-related increase was clearly observed. Equation 1 was nearly identical to the curve of eGFR=60 in this condition. **Figure 4B** shows the effects of eGFR on the risk values (%/3 years) when the graphs are plotted as risk vs. EF. Equation 1 was comparable with Equation 2 when EF is high, whereas it crossed the curves of eGFR=60, 45 and 30 when EF was decreased. **Figure 4C** shows the effects of the presence of DM and CKD. The risk values were plotted vs. EF. Risk increased in the order of eGFR=30 with DM, eGFR=30 without DM, eGFR=60 with DM and

eGFR=60 without DM based on Equation 2. Equation 1 with and without DM also showed a similar tendency to that shown in **Figure 4B**.

Discussion

Multivariate regression analysis was performed based on perfusion defect and LV function as determined on MPI; age, eGFR and DM. The cardiac event risk was then tabulated as a heart risk table. DM and CKD were important predictors of serious cardiac events in addition to MPI and LV function. Moreover, compared with the initial Heart Risk Table using the logistic regression equation without CKD (version 1),¹¹ the characteristics of the revised regression equation (version 2) were reasonably consistent between versions.



Factors for Risk Evaluation

Epidemiological investigations such as the Framingham study, Hisayama study and NIPPONDATA80 study have determined major prognostic predictors for future cardiovascular events, which have been used as a basis of clinical practice.¹⁹⁻²¹ In addition, the role of MPI in prognostic evaluation has been recognized. In the Japan Circulation Society guidelines for nuclear cardiology, prognosis assessment and risk stratification are included as Class I and Level B.²² Using MPI, in general, perfusion defects extending to multiple coronary territories and larger anterior perfusion defects were one of the high-risk observations, in addition to reduced LVEF and ventricular dilatation.²³ Increased lung tracer uptake and transient ischemic dilatation were also included. Regarding clinical background and variables relating to metabolic syndrome (ie, abdominal obesity, dyslipidemia and hypertension), cardiovascular prognosis was affected by the degree of metabolic dysfunction and stress-induced perfusion abnormality.²⁴ When the J-ACCESS databases were analyzed, variables relating to metabolic syndrome were also included,^{4,10} but because only the background factors of DM and CKD were selected on multivariate analysis, the present logistic regression study was based on the selected variables.

Role of Risk Evaluation

Evaluation of cardiovascular event risk plays an important role in therapeutic decision making. The American Heart Association/American College of Cardiology guidelines for percutaneous coronary intervention emphasize the importance of assessing cardiovascular event risk for revascularization decision making.²³ It has also been noted that induced ischemia was one of the major determinants for patient management.^{3,25} In other words, low-risk patients were considered to be suitable for medical treatment, and high-risk patients required more aggressive treatment including coronary revascularization. Hachamovitch et al found that patients with >10% ischemia could expect more beneficial effects from coronary revascularization.²⁶ We have calculated event risk as a percentage in the present study. The important point, however, is not simply to determine the precise risk, but to understand the relationship between the related variables and to apply the risk to planning of examinations and therapeutic decision making.

DM and CKD

It is known that the presence of DM increases cardiac event rate and is comparable to prior myocardial infarction.²⁷ In our J-ACCESS investigation, DM similarly increased major cardiac event rate, and it has been considered as a common risk factor in all nations. Another study recently showed that the

presence of prior myocardial infarction was a greater factor than DM.²⁸ The reason for the differences probably depended on patient selection bias in addition to the ethnic differences. Moreover, in asymptomatic type 2 DM, the incidence of major cardiac events was relatively low; namely, <1% in 1 year (2.9%/3 years including cardiac death 1.0%/3 years and non-fatal acute coronary syndrome 1.9%/3 years), and low eGFR and smoking were additional predictors.^{29,30} Hakeem et al demonstrated that renal dysfunction was an important independent predictor of cardiac death in patients undergoing MPI.¹³ A J-ACCESS sub-study also showed that eGFR and DM were major predictors of cardiac events.^{12,31} Because the prevalence of CKD is higher in Japan than in other Asian countries and the USA, early detection and treatment are required for decreasing end-stage renal disease and cardiovascular diseases.³² The rate of decline in eGFR was significantly higher in participants with an initial eGFR <50 ml · min⁻¹ · 1.73 m⁻² among the younger groups in the general Japanese population.³³ Therefore, risk estimation using MPI, together with DM and CKD, is considered very important and to have practical value for patient management.

Application to Japanese Patients

The risk charts applicable to Japanese patients were presented in a J-ACCESS study for the first time with DM in 2008 and with DM and CKD in the present study.¹¹ The risk tables would be fitted to clinical practice in Japan and would be suitable for those patients thought to have CAD and who undergo MPI. A US study used prognostic scores to estimate event risks based on a stress myocardial perfusion, but the authors did not use a risk chart.³⁴ When the event rates and underlying disease conditions are determined in non-Japanese nations, they might be comparable with the Japanese table with respect to incidence of events and possible effects of risk factors.

Revised Heart Risk Table

An overview of the Heart Risk Table is valuable to understand the tendency of event risks.¹¹ Although the initial and revised versions of the Heart Risk Table depended on analyses of 4,031 subjects (variable of DM only) and on 2,432 subjects (variables of DM and CKD), respectively, reasonable consistency of event risks was confirmed. To create risk tables, we used each 10%-increment class in EF and 10-year class in age in both versions. SSS was classified into 4 groups (normal, slight, moderate, and severe abnormalities) in the initial version, and into 2 groups (normal–mild and moderate–severe abnormalities) in the revised version. The differences in SSS classification were due to statistical significance depending on the number of patients and multivariate analysis. In addition, the threshold of SSS=9 corresponded to the result that patients undergoing medical therapy had a survival advantage over patients undergoing revascularization in the setting of no or mild amounts of inducible ischemia.²⁶ The subdivision of the class of eGFR of 30–59 ml · min⁻¹ · 1.73 m⁻² into 2 subgroups was proposed in the KDIGO report.¹⁸ Because a steep rise in risk with lower eGFR (30–44) was observed in the meta-analyses, we also used the suggested classification in the Heart Risk Table. When the effect of eGFR was considered, the condition of eGFR=50–60 ml · min⁻¹ · 1.73 m⁻² approximately corresponded to that of the initial version that did not have CKD information. We could thus understand the relationship among EF, eGFR and estimated risk (Figure 4). Interestingly, when we did not use eGFR, the risk for normal EF was near that for high eGFR, but the risk for low EF was near that for low eGFR. Thus, eGFR should be considered as an important

determinant for risk.

Definition of Cardiac Events

Major cardiac events in the present study included cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization, which are all in agreement with the main analysis of the J-ACCESS study.⁴ Although the definition of cardiovascular event may differ among prognostic studies, approximate rates for cardiac death and non-fatal myocardial infarction could be estimated. When the J-ACCESS patients (n=4,031) were classified by SSS category into normal, slight, moderate and severe abnormalities, the cardiac death rate was 25%, 28%, 27% and 28% of the major cardiac events, respectively. The hard events defined as cardiac death and non-fatal myocardial infarction were similarly 57%, 52%, 50% and 44% of the major cardiac events, respectively. Thus, to compare the present study with other prognostic studies in Japan and Western countries, the hard event rate is approximately 1/2, and cardiac death is approximately 1/4 of the major cardiac events.

Limitations and Future Directions

In this logistic regression analysis, DM was categorized as 0 or 1. More precise classification and effect of medical treatment need to be clarified in further studies. Diabetic nephropathy could not be differentiated from DM with non-diabetic nephropathy; predominantly chronic glomerulonephritis, hypertensive nephrosclerosis and unknown etiology. Although the differentiation is clinically important, further studies are required including more detailed patient history and renal biopsy. The calculation of eGFR was based on Japanese equations, but these equations used the variables age, sex and creatinine. The factors affecting creatinine concentration such as muscle mass, muscle disease, patient stature and diet could potentially influence the calculated risk.³² Information on proteinuria, which is a manifestation of CKD, was not available in all patients and could not be included.

The relationship between estimated risk and actual events should be evaluated in future prospective studies. The modification of prognosis by medical treatment or revascularization should also be carefully interpreted in further studies. The utility of the risk table as presented here can be tested in clinical practice, and the value of risk stratification using MPI and patient background should be validated.

Conclusion

The cardiac event risk was estimated using a Japanese multi-center J-ACCESS study and tabulated as charts in the Heart Risk Table. The risk was based on myocardial perfusion defect during stress, EF, age, eGFR and presence of DM. The risk for major cardiac events was more precisely obtained compared with that using the initial version of the Heart Risk Table. Application to clinical practice for risk stratification is expected.

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