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Prognostic table for predicting major cardiac events based on J-ACCESS investigation

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Abstract

Objectives. The event risk of patients with coronary heart disease may be estimated by a large-scale prognostic database in a Japanese population. The aim of this study was to create a Heart Risk Table for predicting the major cardiac event rate.

Methods. Using the J-ACCESS database created by a prognostic investigation involving 117 hospitals and >4000 patients in Japan, multivariate logistic regression analysis was performed. The major event rate over a 3-year period that included cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization was predicted by the logistic regression equation. The algorithm for calculating the event rate was simplified for creating tables.

Results. Two tables were created to calculate cardiac risk by age, perfusion score category and ejection fraction with and without a presence of diabetes. A relative risk table comparing age-matched control subjects was also made. When the simplified tables were compared with the results from original logistic regression analysis, both risk values and relative risks agreed well ($p<0.0001$ for both).

Conclusion. The Heart Risk Table was created for patients suspected of having ischemic heart disease and who underwent myocardial perfusion gated single-photon emission computed tomography. The validity of risk assessment using a J-ACCESS database should be validated in a future study.

Key words: J-ACCESS study, ischemic heart disease, cardiac events, prognosis,

Introduction

Prediction of cardiac events has been considered important for management of patients with ischemic heart disease.[1, 2] In the era of multi-modality cardiac imaging including cardiac echocardiography, x-ray computed tomography and magnetic resonance imaging, nuclear methods have been validated well for estimating cardiac risks of future events. In spite of the well-known role of nuclear cardiology in this field, there has been no definite evidence for a Japanese population based on large-scale multi-center cohort studies. A prognostic study using stress-rest myocardial perfusion single-photon emission computed tomography (SPECT) has thus been performed in Japan to create a Japanese database since 2001.[3] The study design, reliability of the gated SPECT methodology, normal values and major cardiac event rates in a Japanese population have been published.[4-6] The prospective study involved 117 hospitals, and >4600 subjects were registered and followed up for 3 years. The study enabled patients to stratify risks according to the predicted rate of future events. Namely, low-risk patients were indicated for less invasive means or primary preventions, whereas high-risk patients were indicated for coronary revascularization or more invasive approaches.[7]

The purpose of this study was to create practical tables to estimate cardiac event risks based on a multivariate analysis. To make the practical tables from the statistics, a simplified model for calculating event rates was required. We compared the created table and the results of the original regression formula.

Materials and methods

J-ACCESS investigation

The subjects and method have been described elsewhere.[3, 6] Briefly, a total of 4031 patients were analyzed after excluding early revascularization within 60 days of the SPECT study. The inclusion criteria included ≥20 years of age who were undergoing stress and rest ECG-gated SPECT due to suspected or known ischemic heart diseases. 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. During the 3-year follow-up, major cardiac events were defined as cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization.

SPECT data analysis

A myocardial perfusion study was performed using ^{99m}Tc-tetrofosmin using a standard stress-rest protocol. The SPECT images were divided into 17 or 20 segments, and visual perfusion for ^{99m}Tc-tetrofosmin uptake in individual segments was scored as follows: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced and 4, absent.[8] The scores from the 20-segment and 17-segment models were converted using the ratio of 17/20.[8] Summed stress (SSS) and rest (SRS) scores were calculated based on the stress and rest findings. The summed

difference score (SDS) was defined as the difference between SSS and SRS. The severity of myocardial perfusion defects was defined with four grades of categories (O, I, II and III) using summed scores; namely, normal (score 0-3) and mildly reduced (score 4-8), moderately reduced (score 9-13) or severely reduced (score ≥14) in the 20-segment model, respectively.[9, 10] Gated SPECT was quantitatively analyzed by QGS software (Cedars Sinai Medical Center, CA, USA).[11]

Multivariate analysis

In-the J-ACCESS study, major cardiac events developed in 175 patients (4.3%/3 years), which comprised cardiac death, nonfatal myocardial infarction and severe heart failure.[6] Univariate analysis demonstrated significant variables of age, body mass index, diabetes mellitus, hypertension and history of revascularization and myocardial infarction. Multivariate analysis showed selected final variables of age, diabetes, summed stress score and end-systolic volume (ESV) or ejection fraction (EF). Thus, multivariate logistic regression analysis was applied in this study to estimate the event rate.

Tables for cardiac risk

Since ESV depended on the patient height and weight, we used EF instead of ESV to simplify the table. Then, the predictors included continuous variables of EF and age. EF (0-100%) was classified into ten classes. Age was also classified into each ten-year-old class from 40 to 90 years old; namely 40-49, 50-59 years old, and so on. The presence of diabetes was used as 0 or 1. SSS was classified into four categories as described above, since SSS had an ordinary scale.

In the Heart Risk View, relative risk (unit: folds) was defined as the calculated risk divided by the age-matched normal values in non-diabetic subjects. Since the normal EF value of EF was influenced by factors of age and sex, the EF of control patients was determined accordingly in the Heart Risk View.[5, 6, 12] In this Heart Risk Table, relative risk was similarly calculated, but the control EF was fixed to normal values of 65% for both sexes.

Clinical validation of the Heart Risk Table

The risk values calculated by the equation from original multi-variate logistic analysis were compared with those obtained from values from the Heart Risk Table. A total of 31 consecutive patients with stress-rest SPECT were analyzed by both Heart Risk View and Heart Risk Tables. The average age was 68±11 years old (27 males and 4 females). Diabetes was associated with 16 patients. The 17-segment-based SSS ranged from 0 to 28. The SSS categories were O (SSS 0-2, n=7), I (SSS 3-7, n=10), II (SSS 8-11, n=8) and III (≥12, n=6). The calculated risk vales were classified into low (0 to 3%), intermediate (>3 to 9%), high (>9 to 15%) and very high (>15%) for three years.

Statistics

Multivariate logistic analysis was performed as indicated above. Mean and standard deviations

(SD) were calculated for each parameter. The relationship between the risk value and the relative risk was calculated by linear regression analysis. Contingency table analysis was performed to compare risk severity groups, and the likelihood ratio and Pearson's chi-square were calculated. A p value < 0.05 was considered significant.

Results

Logistic regression analysis

The multivariate regression model determined by diabetes (0-1), age, SSS category (0-3) and EF was determined using a logit function as follows:

$$\text{logit}(p) = -4.8125 + 0.8858\times(\text{diabetes:0, 1}) + 0.0558(\text{age}) + 0.1941\times(\text{SSS category:0-3}) - 0.0475\times(\text{EF})$$

$$p\ (\%/3\ \text{years}) = 1 / (1+e^{-\text{logit}(p)}) \times 100$$

Based on this formula, risk and relative risk values were tabulated with respect to ten-year age classes and 10% EF classes. Figures 1A and 1B show cardiac risks for patients without and with diabetes mellitus. If the patient's age and the presence of diabetes were given, corresponding risk (%) and relative risk (folds) were found from the crossover point of the EF class and age class.

Example of risk estimation

Figure 2 shows an example of a 64-year old male patient with inferior hypoperfusion. The summed stress score of the inferior and septal wall was 9, and it was classified into moderate severity without significantly induced ischemia. The major cardiac event rate estimated in this case was 2.9%/3 years, which was 1.6 fold higher than that of the age-matched control subjects. Risk values determined by Heart Risk Table was 2.5%/3 years which was 1.8 folds of the controls.

Comparison of Heart Risk Table with logistic regression analysis

The estimated cardiac event risk and relative risk are compared (Figure 3). A good correlation between the Heart Risk View and simplified Heart Risk Table was observed. When the severity of risk was classified into four severity groups, complete agreement was observed in 25 of 31 patients (81%), and all patients were within one grade of difference (Table 1)

Discussion

Heart Risk Table, which calculates the three-year major event rate, was created based on a J-ACCESS prognostic investigation. The correlation of risk values calculated by Heart Risk Table and by logistic regression analysis was good. A prognostic chart using a simplified look-up table was the first application in the field of nuclear medicine, and may be applicable to patients suspected of having coronary heart diseases.

Event rate in the J-ACCESS study

The J-ACCESS investigation was first evidence made in a Japanese population who had undergone myocardial perfusion SPECT. When hard events, defined as cardiac death and non-fatal infarction, were the endpoints, cardiac death (n = 57, 1.4%/3 years) and non-fatal myocardial infarction (n = 39, 1.0%/3 years) occurred in 96 patients (2.4%/3 years) during the 3-year follow-up period. When severe heart failure was included as an endpoint, major cardiac events developed in 175 patients (4.3%/3 years), which comprised cardiac death (n = 45, 1.1%/3 years), non-fatal myocardial infarction (n = 37, 1.0%/3 years) and severe heart failure (n = 93, 2.3%/3 years). Patients with normal and severely abnormal SSS had low (2.3%/3 years) and high (9.2%/3 years) rates of major cardiac events, respectively. Hachamovitch et al. showed that over a mean follow up of 642 days in 5183 patients, 277 hard events (5.3%) occurred, including 3.0% cardiac death rate, 2.3% myocardial infarction rate.[9] Petix et al. showed that during follow-up (median 13 months) of 333 patients, 17 cardiac deaths (5.1%) and 13 nonfatal acute myocardial infarctions (3.9%) occurred.[13] Although the study setting might differ among studies, the event rate was generally lower in Japan compared with those of Western studies.[6, 9, 10, 13, 14] The annual hard event rate in normal myocardial perfusion SPECT was found to be low (0.63%) in the subanalysis.[15] The importance of diabetes mellitus has been emphasized in a Japanese population, which has been also demonstrated in Western studies.[14, 16, 17]

Multivariate analysis for this study

The statistical analysis for predicting events was performed with the Cox proportional hazard model in the first summary,[18] while the present study was based on the multivariate logistic regression model. The merit of the logistic regression model was that the risk values were directly estimated by the regression model, which might be intuitionally understood. A similar approach using a prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy has been reported.[19]

The logistic regression analysis using ESV instead of EF created the equation of

logit p= -8.9333 + 0.9159×(diabetes:0, 1) + 0.0635×(age) + 0.225×(SSS categroy:0-3) + 0.0182×(ESV)

to calculate logit(p). Although the equations were also available in the Heart Risk View, [6, 12] we used only EF in this Table. Since the ESV was influenced by the physique of patients, we needed simplification for generating the table.

Importance of predicting cardiac events

Predicting cardiac mortality risk or major event risk can provide valuable information for management of patients suspected of having ischemic heart disease. Hachamovitch et al demonstrated that revascularization in comparison to medical therapy had greater survival benefit in patients with moderate to large amounts of inducible ischemia.[7] According to their results, a patient diagnosed with no or mild ischemia could be indicated for medication, whereas a patient having moderate to severe myocardial ischemia could be indicated for more aggressive treatment including

coronary intervention and coronary bypass surgery. The extent of the perfusion abnormality was the single most important prognostic predictor, even when coronary angiography was performed.[20] The principal notion that myocardial perfusion abnormality or ischemia was strongly correlated with event rate has been validated even in recent studies. To estimate cardiac event risk, the recommended guidelines of blood pressure, total cholesterol, and low-density-lipoprotein cholesterol to predict coronary heart disease have been published from American Heart Association and the American College of Cardiology.[21] In addition, a simple coronary disease prediction algorithm was developed using categorical variables, which allows physicians to predict cardiac risk in patients without overt coronary artery disease. In Japan, NIPPON DATA80 has been summarized using variables of sex, age, smoking, blood glucose level, blood pressure, total cholesterol, and other factors. The original charts based on the data provided risk for coronary heart disease, stroke, and all cardiovascular death risk among the general Japanese population. The present study also aimed at similar approaches using a myocardial perfusion study, although the number of variables was still limited.

Patients who underwent coronary revascularization within 60 days of the SPECT study were excluded from the study group. In clinical settings, those with moderate or severe stress-induced ischemia will be treated by coronary revascularization after the SPECT study. This sort of selection bias could not be avoided in the prognostic cohort study. However, the estimation of event risks before revascularization based on the prognostic database is meaningful for patient management.

Notations for using Heart Risk Table

The table contains the characteristics of the J-ACCESS database. Selection biases are the same as those of the original J-ACCESS investigation. Although the patients were registered consecutively in 117 hospitals, relatively low risk patients for cardiac disease might have been included. However, this inclusion implied that the database reflected ordinary nuclear cardiology practice in Japan. Caution should be exercised for the application of Heart Risk Table, since the number of patients <40 years old are few, and baseline cardiac diseases such as cardiomyopathy and severe heart failure as shown in the Method section were excluded. It has been generally accepted that the cardiac event rate is less than 1%, when myocardial perfusion SPECT was normal.[15, 22] However, radionuclide distribution throughout the myocardium, increased tracer lung uptake, transient ventricular dilatation after stress and balanced perfusion reduction in multi-vessel disease should also be considered to estimate patient disease severity and prognosis, which are not included in this table. Insufficient exercise level could also underestimate the ischemia. Moreover, we used only predictors defined by multivariate analysis. The occurrence of soft events may include history of revascularization, hypertension and dyslipidemia. The diagnosis of diabetes mellitus was made clinically in each institute, and the relationship of the severity of diabetes and event risks could not be analyzed in this study. The importance of diabetes will be clarified by the subsequent J-ACCESS 2 study, which focused specifically on diabetes mellitus.[23]

However, even considering these limitations, this Heart Risk Table does not contradict

previously published reports or guidelines. The idea for risk estimation should be taken into account for patient management for ischemic heart diseases. A further follow-up study would be valuable for the validity of the application of this table in the future.

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Heart Risk Table

A. Patient without diabetes

Major events / 3 years (%)

Age			SSS category O	I	II	III
40-49	LVEF	10%	5.9	7.0	8.4	10.0
		20%	3.7	4.5	5.4	6.5
		30%	2.4	2.8	3.4	4.1
		40%	1.5	1.8	2.2	2.6
		50%	0.9	1.1	1.4	1.6
		60%	0.6	0.7	0.8	1.0
		70%	0.4	0.4	0.5	0.6
		80%	0.2	0.3	0.3	0.4
		90%	0.1	0.2	0.2	0.2
50-59			O	I	II	III
	LVEF	10%	9.8	11.7	13.8	16.3
		20%	6.3	7.6	9.1	10.8
		30%	4.0	4.9	5.8	7.0
		40%	2.5	3.1	3.7	4.5
		50%	1.6	1.9	2.3	2.8
		60%	1.0	1.2	1.5	1.8
		70%	0.6	0.8	0.9	1.1
		80%	0.4	0.5	0.6	0.7
		90%	0.2	0.3	0.4	0.4
60-69			O	I	II	III
	LVEF	10%	16.0	18.7	21.9	25.4
		20%	10.6	12.5	14.8	17.5
		30%	6.8	8.2	9.8	11.6
		40%	4.4	5.3	6.3	7.6
		50%	2.8	3.3	4.0	4.8
		60%	1.7	2.1	2.5	3.1
		70%	1.1	1.3	1.6	1.9
		80%	0.7	0.8	1.0	1.2
		90%	0.4	0.5	0.6	0.8
70-79			O	I	II	III
	LVEF	10%	24.9	28.7	32.9	37.3
		20%	17.1	20.0	23.3	27.0
		30%	11.4	13.5	15.9	18.7
		40%	7.4	8.8	10.5	12.5
		50%	4.7	5.7	6.8	8.2
		60%	3.0	3.6	4.4	5.2
		70%	1.9	2.3	2.8	3.3
		80%	1.2	1.4	1.7	2.1
		90%	0.7	0.9	1.1	1.3
80-89	LVEF		O	I	II	III
		10	36.7	41.3	46.1	50.9
		20	26.5	30.5	34.7	39.2
		30	18.3	21.4	24.9	28.7
		40	12.2	14.5	17.1	20.0
		50	8.0	9.5	11.3	13.4
		60	5.1	6.1	7.4	8.8
		70	3.2	3.9	4.7	5.7
		80	2.0	2.5	3.0	3.6
		90	1.3	1.6	1.9	2.3

Relative risk vs. age-matched controls (folds)

SSS category	O	I	II	III
10%	12.9	15.5	18.5	22.1
20%	8.2	9.9	11.9	14.3
30%	5.2	6.2	7.5	9.1
40%	3.2	3.9	4.8	5.7
50%	2.0	2.5	3.0	3.6
60%	1.3	1.5	1.9	2.3
70%	0.8	1.0	1.2	1.4
80%	0.5	0.6	0.7	0.9
90%	0.3	0.4	0.5	0.5

	O	I	II	III
10%	12.4	14.7	17.5	20.6
20%	8.0	9.6	11.5	13.6
30%	5.1	6.1	7.4	8.8
40%	3.2	3.9	4.7	5.7
50%	2.0	2.4	3.0	3.6
60%	1.3	1.5	1.9	2.2
70%	0.8	1.0	1.2	1.4
80%	0.5	0.6	0.7	0.9
90%	0.3	0.4	0.5	0.5

	O	I	II	III
10%	11.6	13.6	15.9	18.5
20%	7.7	9.1	10.8	12.7
30%	5.0	6.0	7.1	8.5
40%	3.2	3.8	4.6	5.5
50%	2.0	2.4	2.9	3.5
60%	1.3	1.5	1.8	2.2
70%	0.8	1.0	1.2	1.4
80%	0.5	0.6	0.7	0.9
90%	0.3	0.4	0.5	0.5

	O	I	II	III
10%	10.5	12.1	13.8	15.7
20%	7.2	8.4	9.8	11.4
30%	4.8	5.7	6.7	7.9
40%	3.1	3.7	4.4	5.3
50%	2.0	2.4	2.9	3.4
60%	1.3	1.5	1.8	2.2
70%	0.8	1.0	1.2	1.4
80%	0.5	0.6	0.7	0.9
90%	0.3	0.4	0.5	0.6

	O	I	II	III
10%	9.0	10.1	11.3	12.5
20%	6.5	7.5	8.5	9.6
30%	4.5	5.2	6.1	7.0
40%	3.0	3.5	4.2	4.9
50%	2.0	2.3	2.8	3.3
60%	1.3	1.5	1.8	2.2
70%	0.8	1.0	1.2	1.4
80%	0.5	0.6	0.7	0.9
90%	0.3	0.4	0.5	0.6

B. Patient with diabetes

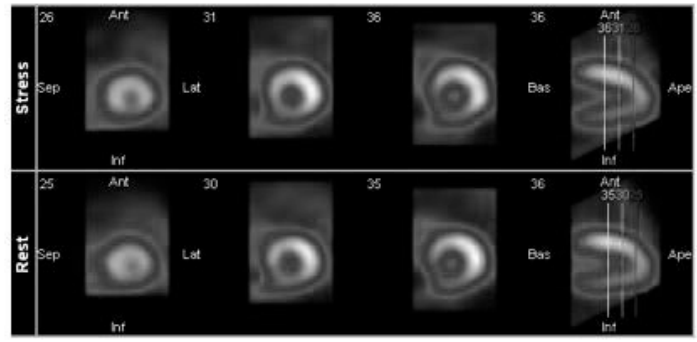
Major events / 3 years (%)

Age	LVEF	SSS category O	I	II	III
40-49	10%	13.1	15.5	18.2	21.3
	20%	8.6	10.2	12.2	14.4
	30%	5.5	6.6	7.9	9.5
	40%	3.5	4.2	5.1	6.1
	50%	2.2	2.7	3.2	3.9
	60%	1.4	1.7	2.0	2.5
	70%	0.9	1.0	1.3	1.5
	80%	0.5	0.7	0.8	1.0
	90%	0.3	0.4	0.5	0.6
50-59	10%	20.9	24.3	28.0	32.1
	20%	14.1	16.6	19.5	22.7
	30%	9.3	11.0	13.1	15.4
	40%	6.0	7.2	8.6	10.2
	50%	3.8	4.6	5.5	6.6
	60%	2.4	2.9	3.5	4.2
	70%	1.5	1.8	2.2	2.7
	80%	0.9	1.1	1.4	1.7
	90%	0.6	0.7	0.9	1.0
60-69	10%	31.5	35.9	40.5	45.2
	20%	22.3	25.8	29.7	33.9
	30%	15.1	17.8	20.8	24.2
	40%	10.0	11.9	14.0	16.6
	50%	6.4	7.7	9.2	11.0
	60%	4.1	4.9	5.9	7.1
	70%	2.6	3.1	3.8	4.6
	80%	1.6	2.0	2.4	2.9
	90%	1.0	1.2	1.5	1.8
70-79	10%	44.6	49.4	54.3	59.0
	20%	33.4	37.8	42.5	47.3
	30%	23.7	27.4	31.5	35.8
	40%	16.2	19.0	22.2	25.7
	50%	10.7	12.8	15.1	17.7
	60%	7.0	8.3	9.9	11.8
	70%	4.5	5.4	6.4	7.7
	80%	2.8	3.4	4.1	4.9
	90%	1.8	2.1	2.6	3.1
80-89	10%	58.5	63.1	67.5	71.6
	20%	46.7	51.5	56.3	61.0
	30%	35.2	39.8	44.5	49.3
	40%	25.3	29.1	33.3	37.7
	50%	17.4	20.3	23.7	27.4
	60%	11.6	13.7	16.2	19.0
	70%	7.5	9.0	10.7	12.7
	80%	4.8	5.8	6.9	8.3
	90%	3.1	3.7	4.4	5.3

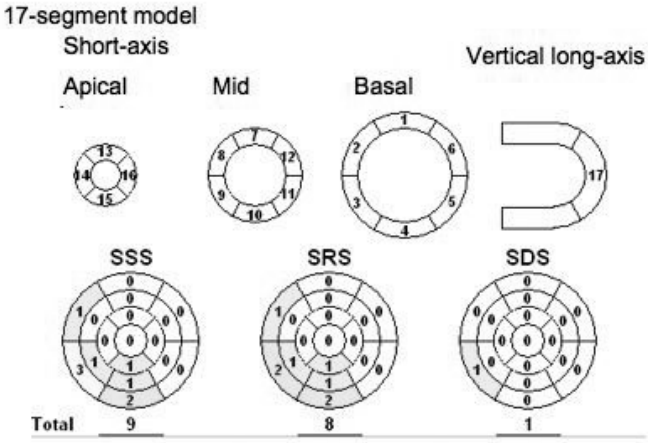
Relative risk vs. age-matched controls (folds)

LVEF	SSS category O	I	II	III
10%	28.9	34.1	40.0	46.8
20%	18.9	22.5	26.7	31.7
30%	12.1	14.6	17.4	20.8
40%	7.7	9.3	11.2	13.4
50%	4.9	5.9	7.1	8.5
60%	3.0	3.7	4.5	5.4
70%	1.9	2.3	2.8	3.4
80%	1.2	1.4	1.7	2.1
90%	0.7	0.9	1.1	1.3
10%	26.4	30.6	35.4	40.5
20%	17.8	21.0	24.6	28.7
30%	11.7	13.9	16.5	19.5
40%	7.5	9.0	10.8	12.9
50%	4.8	5.8	6.9	8.3
60%	3.0	3.7	4.4	5.3
70%	1.9	2.3	2.8	3.4
80%	1.2	1.4	1.7	2.1
90%	0.7	0.9	1.1	1.3
10%	22.9	26.1	29.4	32.9
20%	16.2	18.8	21.6	24.7
30%	11.0	12.9	15.1	17.6
40%	7.3	8.6	10.2	12.0
50%	4.7	5.6	6.7	8.0
60%	3.0	3.6	4.3	5.2
70%	1.9	2.3	2.8	3.3
80%	1.2	1.4	1.7	2.1
90%	0.7	0.9	1.1	1.3
10%	18.8	20.8	22.8	24.8
20%	14.0	15.9	17.9	19.9
30%	10.0	11.5	13.2	15.1
40%	6.8	8.0	9.3	10.8
50%	4.5	5.4	6.3	7.5
60%	2.9	3.5	4.2	5.0
70%	1.9	2.3	2.7	3.2
80%	1.2	1.4	1.7	2.1
90%	0.7	0.9	1.1	1.3
10%	14.3	15.5	16.5	17.5
20%	11.4	12.6	13.8	15.0
30%	8.6	9.7	10.9	12.1
40%	6.2	7.1	8.2	9.2
50%	4.3	5.0	5.8	6.7
60%	2.8	3.4	4.0	4.6
70%	1.8	2.2	2.6	3.1
80%	1.2	1.4	1.7	2.0
90%	0.7	0.9	1.1	1.3

Figure 1 Cardiac event rate for three years estimated by age, EF and SSS category. Charts A and B indicate risk values for patients without and with diabetes mellitus. Color-coding from light to dark corresponds to low (0 to 3%), intermediate (>3 to 9%), high (>9 to 15%) and very high (>15%) risks.



	Patient	Age-matched control
diabetes	no	no
SSS category	II moderate	O normal
EDV (mL)	71	86 (64-108)
ESV (mL)	28	32 (19-45)
EF (%)	61%	63% (51-75)



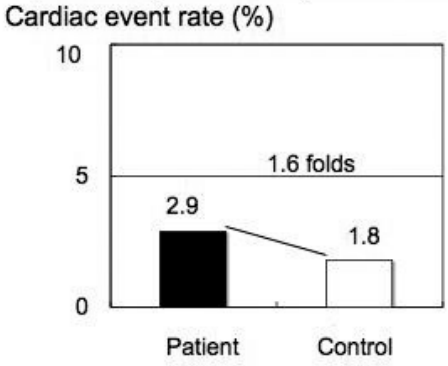


Figure 2 An example of Heart Risk View results. Risk values determined by Heart Risk Table in this patient was 2.5%/3 years, which was 1.8 fold higher than that of the controls.

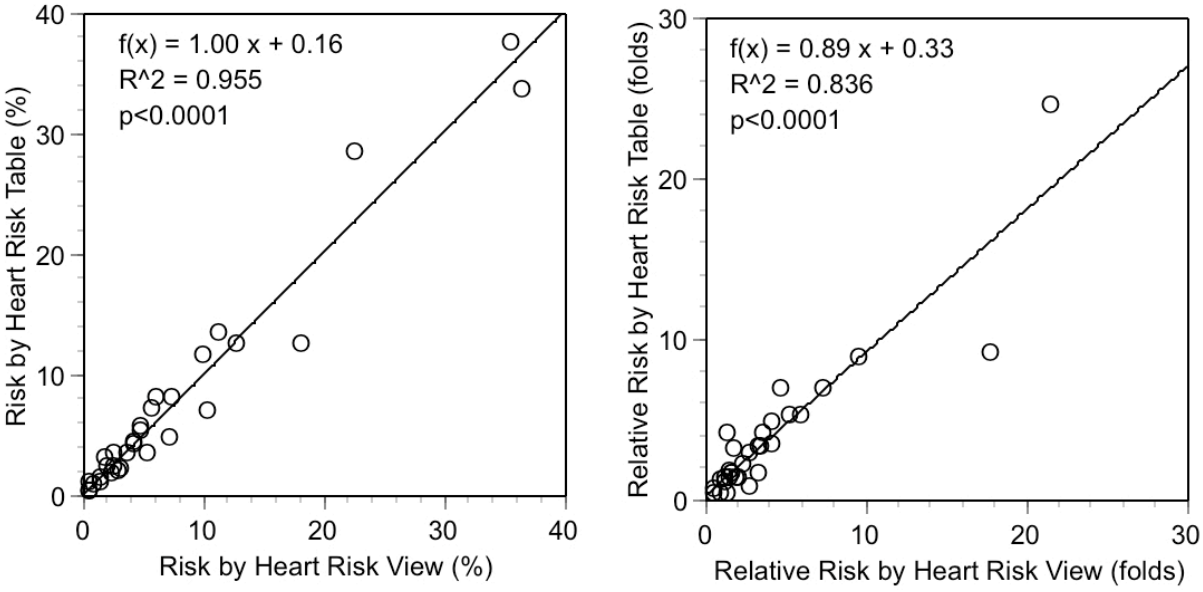


Figure 3 Comparison of risk values (%/3 years) and relative risk to control patients (folds) between Heart Risk Table and Heart Risk View.

Table 1. Comparison of grade of risks estimated by Heart Risk View and Heart Risk Table

	Heart Risk Table				
	low	intermediate	high	very high	total
Heart Risk View					
low	10	2	0	0	12
intermediate	1	10	1	0	12
high	0	1	2	0	3
very high	0	0	1	3	4
total	11	13	4	3	31

likelihood ratio：Chi square 43.1, $p<0.0001$

Pearson: Chi square 50.3, $p<0.0001$

Risks were defined as low risk (0-3%), intermediate risk (>3 to 9%), high risk (>9% to 15%) and very high risk (>15%) for three years.