



## Estimation of Cardiac Event Risk by Gated Myocardial Perfusion Imaging and Quantitative Scoring Methods Based on a Multi-Center J-ACCESS Database

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**Background:** Myocardial perfusion imaging (MPI) has been used to estimate cardiac event risk. The aim of the present study is to achieve stable risk estimation based on perfusion scoring and a multi-center prognostic database.

**Methods and Results:** Multivariate logistic regression analysis was performed to estimate cardiac event risk based on a J-ACCESS study. A stress-MPI was performed in 45 patients with coronary artery disease (CAD) and in 25 non-CAD patients. Perfusion defect scoring of summed stress score (SSS) was performed by 5 methods: (1) visual scoring; (2) automatic scoring of 3 short-axis and 1 vertical long-axis slices; (3) visual modification of Method 2; (4) automatic polar map scoring based on a Japanese multi-center database; and (5) visual modification of Method 4. Agreement of SSS between 2 observers was good ( $r=0.87-0.97$ ). Agreement of estimated cardiac event risk between observers and among 5 methods was very good ( $r=0.99-1.00$ ). Regarding diagnostic accuracy for CAD, Method 5 showed optimal diagnostic yields (sensitivity 84%, accuracy 77%).

**Conclusions:** Estimation of cardiac event risk in conjunction with polar map segmentation and common normal databases resulted in stable risk values, and might be used for risk stratification in patients suspected of having CAD. (*Circ J* 2011; **75**: 2417–2423)

**Key Words:** Cardiac event risk; Coronary artery disease; Gated single-photon emission computed tomography; Myocardial perfusion defect scores

An important role of nuclear cardiology is to estimate risks for future cardiovascular events.<sup>1-4</sup> A number of studies have used myocardial perfusion imaging (MPI) in patients with coronary artery disease (CAD), and it has been found that myocardial ischemia, perfusion defect, and left ventricular (LV) function are determinants of cardiac event risks. Quantification of myocardial perfusion defect has been essential to predict risks, and therefore stable and reliable methods for evaluating perfusion defect are required. Based on a Japanese prognostic cohort study to predict future cardiac events using gated MPI (J-ACCESS investigation), cardiac event risks were estimated by perfusion defect during a stress condition or summed stress score (SSS), LV ejection fraction (EF), patient age, and presence of diabetes.<sup>5-7</sup> Because SSS was determined by selected short-axis and long-axis slices and visual interpretation in

this investigation, this might have been the cause of fluctuation of defect scores and final estimated cardiac event risks. The goal of estimating event risk is not simply knowing major predictors, but the predicted risks contribute to management of patients with suspected or known CAD. The event risk in terms of percentage per year should be able to be reproducibly calculated. However, the stability of the calculated risk values including nuclear perfusion imaging has not been evaluated. The purpose of this study is to evaluate several possible methods for perfusion defect quantification and to determine the best method of obtaining stable risk using multi-variate analysis, as well as to detect the culprit lesion of CAD.

Received April 5, 2011; revised manuscript received May 26, 2011; accepted June 7, 2011; released online July 28, 2011 Time for primary review: 13 days

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Financial support: Japan Cardiovascular Research Foundation.

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-0371

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## Editorial p2318

### Methods

#### Logistic Regression Analysis to Estimate Cardiac Event Risk

J-ACCESS databases that were validated by a 3-year follow up study and cardiac event analyses were used.<sup>5</sup> A total of 4,031 patients were analyzed after excluding early revascularization within 60 days of the single-photon emission computed tomography (SPECT) study. The inclusion criteria included subjects  $\geq 20$  years of age who underwent stress and rest electrocardiography (ECG)-gated SPECT with  $^{99m}\text{Tc}$ -tetrofosmin because of suspected or known ischemic heart diseases. During the 3-year follow-up, major cardiac events were defined as cardiac death, non-fatal myocardial infarction, and severe heart failure requiring hospitalization. A gated-SPECT study was performed, and quantitative gated SPECT (QGS) software (Cedars Sinai Medical Center, CA, USA) was used to calculate end-diastolic volume (EDV), end-systolic volume (ESV), and EF.

#### Patients

A total of 70 patients (66 $\pm$ 10 years, 36 males and 34 females) who were suspected of having CAD were retrospectively selected at Kanazawa University to examine robustness of risk estimation. To include appropriate range of score distribution for risk analysis, 23 patients with 1-vessel disease ( $\geq 75\%$  stenosis) and 22 with 2-vessel disease, who underwent both coronary angiography and MPI within a month, were selected. Three-vessel disease was excluded from the study because culprit coronary artery could not be strictly defined. Any patients with previous myocardial infarction, after coronary revascularization, cardiomyopathy, and valvular heart disease were excluded. The incidences of diabetes and hypertension were 33% for both. Non-CAD patients (n=25) were also selected, in which 11 patients underwent coronary angiography and the stenosis was  $\leq 25\%$ , and the remaining patients were judged as low-likelihood of CAD based on subsequent clinical workups. In the low-likelihood patients, no patients who required diabetic or hypertensive medication were included.

#### Myocardial Perfusion Imaging

A myocardial perfusion study was conducted using  $^{99m}\text{Tc}$ -tetrofosmin or sestamibi with 300–370 MBq for the stress study and 740–800 MBq for the rest study. The stress type involved symptom-limited or  $>85\%$  of the target heart-rate exercise using a bicycle ergometer (n=47) and pharmacological administration of adenosine (n=20) and dipyridamole (n=3). A dual-headed SPECT system equipped with low-energy collimators (e.cam, Siemens-Asahi Medical Technologies Ltd, Tokyo, Japan) was used for data acquisition with a 360-degree acquisition. Gated-SPECT was performed using a division of 16-frame per cardiac cycle at least at rest. After reconstructing standard short-axis and long-axis images using Butterworth and ramp filters, QGS software was used to calculate LV functional parameters.

#### Perfusion Defect Score

A 17-segment model was used to semiquantify perfusion defects. Individual segments were scored as follows: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent.<sup>8</sup> The severity of myocardial perfusion defects, namely SSS, was defined with four grades of categories (0, I, II, and III) using summed scores of all the segments; namely,

normal (score  $<3$ ) and mildly reduced (score 3–7), moderately reduced (score 8–11), or severely reduced (score  $>11$ ) in the 17-segment model, respectively. The threshold of 3, 8, and 12 corresponded to 4.4%, 11.7%, and 17.6% of the total points of 68 (17 segment $\times$ 4 point), respectively. Two nuclear medicine physicians independently evaluated the segmental scores in the following 5 methods:

**Method 1** Segmental scores were visually made using whole SPECT slices.

**Method 2** Three short-axis slices (base, mid, and apical) and 1 mid-vertical long-axis were selected by using Heart Risk View software (Nihon Medi-Physics Co Ltd, Japan).<sup>6,9</sup> This software was designed to calculate risk values based on the 4 selected slices as mentioned above. The location of the slices was manually adjusted. Regarding the automatic scoring, a Japanese Society Nuclear Medicine working group (JSNM-WG) database was used as a guide of normal distribution patterns, which was made for  $^{99m}\text{Tc}$  sestamibi and tetrofosmin in each gender.<sup>10</sup>

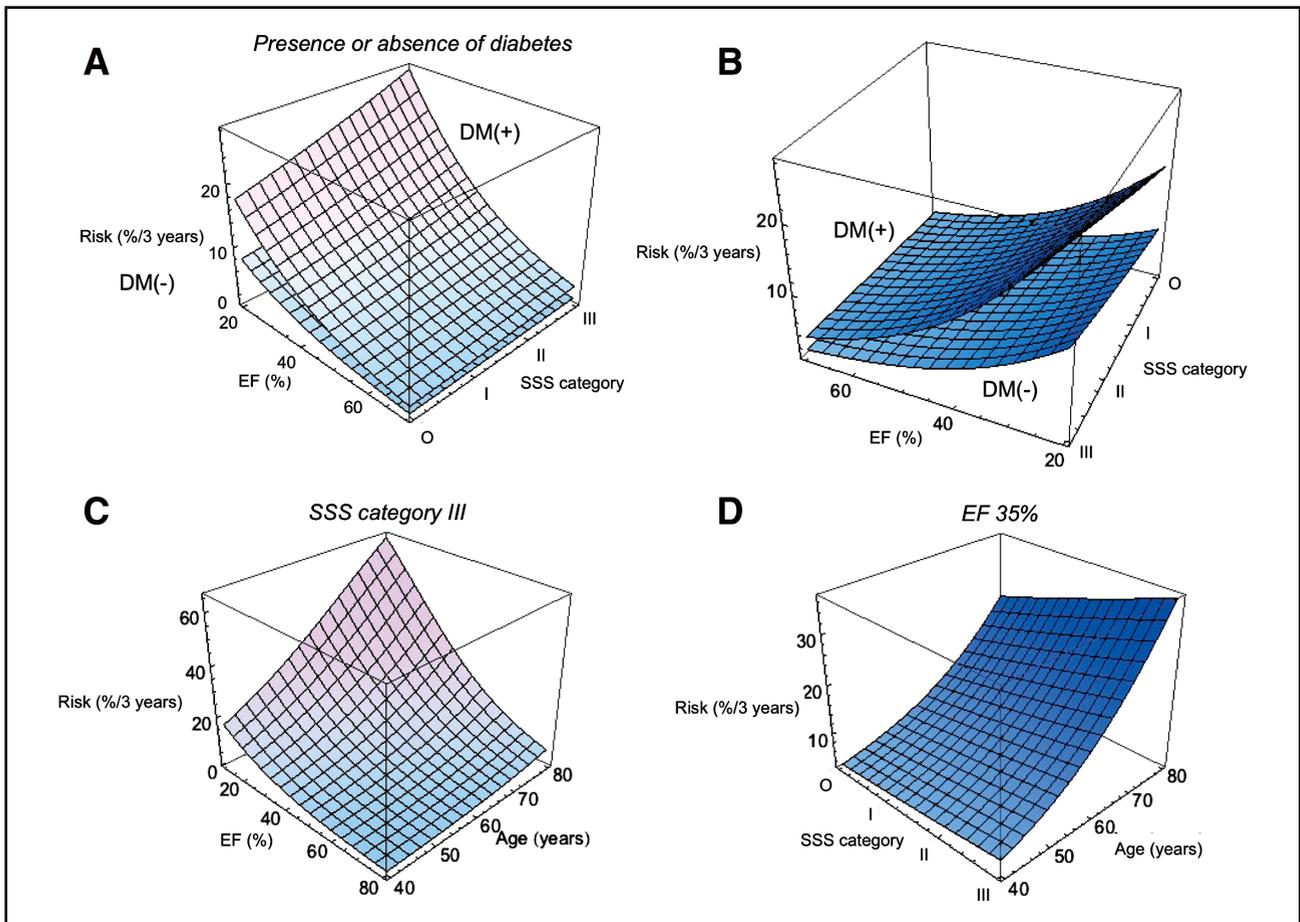
**Method 3** Following the scoring of Method 2, the scoring was visually modified to appropriate values. In this manual correction, female breast and male diaphragmatic attenuation artifacts were modified, if judged inappropriate. A normal variant of the low count in the basal inferior to septal segments was also taken into consideration.

**Method 4** An automatic segmental scoring method based on quantification of polar map was used (Heart Score View, Nihon Medi-Physics Co Ltd). Using this software, stress and rest short-axis SPECT slices were transferred by digital imaging and communication in medicine format from a dedicated nuclear medicine computer system. Two image sets of stress and rest were automatically co-registered using an algorithm of maximization of mutual information.<sup>11</sup> The adequacy of co-registration was confirmed visually. After roughly setting a circumference of the myocardium, myocardial maximal counts on the radial directions were searched with a model of cylinder (base to mid slices) plus sphere (apical slices and the apex) shapes. The regional counts were plotted on a polar map, and a 17-segment model was applied to calculate each segmental average count (%). To calculate the segmental scores, the same gender- and tracer-based JSNM-WG database was used. The threshold values of each segment for scoring were adjusted so that a moderate decrease (score 2) corresponded to approximately 50% of the maximum count.

**Method 5** After the scoring by Method 4, inappropriate scores were corrected visually in conjunction with whole SPECT slices. The modification was performed, if required, in the attenuation artifacts and inclusion of basal segments, which was similar to the modification of Method 3.

#### Diagnostic Accuracy of Each Method

The diagnostic accuracy for coronary stenosis  $\geq 75\%$  was calculated. Each coronary artery territory was assigned as follows: left anterior descending artery to anteroseptal and apical segments, left circumflex artery to lateral segments, and right coronary artery to inferior and inferoseptal segments. In patient-based analysis, any abnormality identified on the map was considered positive. In coronary artery-based analysis, the score was considered positive when perfusion abnormality was detected on the stenotic coronary territory. In 2-vessel disease, 2 stenotic coronary territories were combined, and summed regional scores were calculated. In the CAD group, each study therefore had 1 stenotic coronary territory and 1 non-stenotic territory. In the non-CAD group, all areas were judged as a non-stenotic territory. Regarding the threshold of SSS between nor-



**Figure 1.** Three-dimensional plots of the logistic regression equation. (A, B) Relationship between summed stress score (SSS) and ejection fraction (EF) at age 60 with and without diabetes mellitus (DM). Panels B and A are viewed from different angles. (C) Relationship between age and EF with SSS category III and diabetes. (D) Relationship between age and SSS with diabetes as an example of EF=35%.

Table 1. Correlation of Summed Stress Score Among Visual and Software Scoring Methods			
Methods	R	P value	
<b>A. Method 1 (visual) vs.</b>			
Method 2 (3 SA+1 mid VLA slices)	0.84	<0.0001	
Method 3 (Method 2+visual modification)	0.93	<0.0001	
Method 4 (polar map method)	0.84	<0.0001	
Method 5 (Method 4+visual modification)	0.84	<0.0001	
<b>B. Inter-observer reproducibility</b>			
Method 1	0.88	<0.0001	
Method 2	0.88	<0.0001	
Method 3	0.87	<0.0001	
Method 4	0.97	<0.0001	
Method 5	0.90	<0.0001	

SA, short-axis; VLA, vertical long-axis

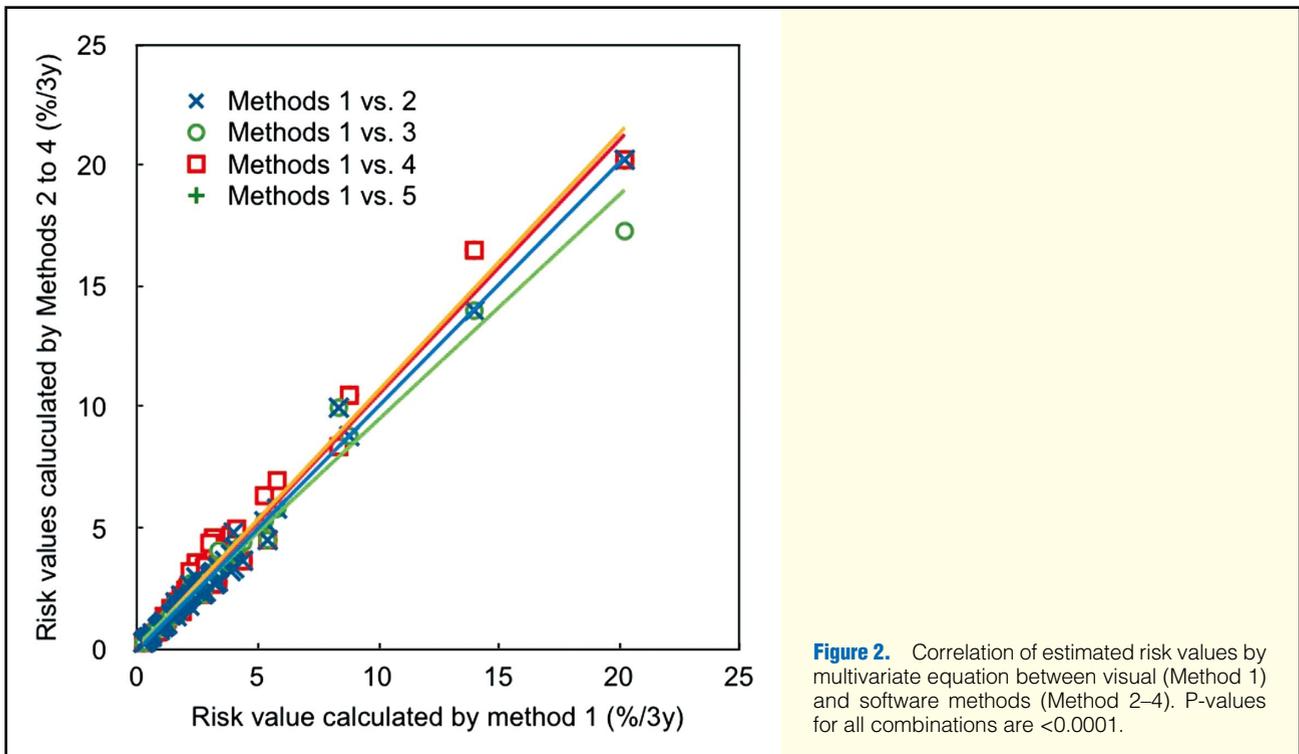
Table 2. Correlation of Estimated Cardiac Risk (%/3 Years) Among Visual and Software Scoring Methods			
Methods	R	P value	
<b>A. Method 1 (visual) vs.</b>			
Method 2 (3 SA+1 mid VLA slices)	0.99	<0.0001	
Method 3 (Method 2+visual modification)	0.99	<0.0001	
Method 4 (polar map method)	0.99	<0.0001	
Method 5 (Method 4+visual modification)	0.99	<0.0001	
<b>B. Inter-observer reproducibility</b>			
Method 1	0.99	<0.0001	
Method 2	0.99	<0.0001	
Method 3	0.99	<0.0001	
Method 4	1.00	<0.0001	
Method 5	1.00	<0.0001	

SA, short-axis; VLA, vertical long-axis

mal and abnormal values, 5% of the total point of the 17 segment model was 3.4 points (17×4×5%).<sup>1,8</sup> Therefore, possible thresholds of 3 and 4 were compared for total myocardial segmental scores. As for regional scores of the coronary territories, a relatively smaller threshold value of 2 or 3 was used, considering the limited area of 1 or 2 coronary artery territories.

**Statistics**

All values were expressed as mean±standard deviation. Multivariate logistic regression analysis was performed as indicated above. Correlation coefficients and regression lines were calculated between interpreters and between 2 methods. Differences in sensitivity and specificity were evaluated by



**Figure 2.** Correlation of estimated risk values by multivariate equation between visual (Method 1) and software methods (Method 2–4). P-values for all combinations are <0.0001.

McNemar's test. A P-value <0.05 was considered significant.

## Results

### The Multivariate Model to Calculate Cardiac Event Risk

Based on the multivariate logistic regression analysis, the estimated event rate was created as follows:

$$\text{logit}(p) = a + b \times (\text{diabetes: 0, 1}) + c \times (\text{age}) + d \times (\text{SSS category 0–III: 0–3}) + e \times (\text{EF})$$

$$p (\%/3 \text{ years}) = 1 / (1 + \text{Exp}[-\text{logit}(p)]) \times 100,$$

$$\text{where } a = -4.8125, b = 0.8858, c = 0.0558, d = 0.1941, \text{ and } e = -0.0475.$$

The effects of age, SSS category (0–III), EF, and the presence of diabetes on the risk values (event rates in percent per 3 years) were plotted on three-dimensional charts (Figure 1). Because 4 parameters were included to estimate the risk value, the relationship of 2 parameters were plotted when 2 other parameters were fixed. The higher the age and the SSS categories, and the lower the EF, the more significantly increased were risk values. The presence of diabetes almost doubled risk values. The effect of SSS category on event risk was particularly larger in patients with lower EF and higher age.

### Agreement of Stress Defect Scores

When visual scores (Method 1) by expert interpretation was compared with software methods (Methods 2–5), the correlation coefficient of SSS was from 0.84 to 0.93, in which the combination of Methods 1 and 3 showed the highest correlation ( $r=0.93$ ,  $P<0.0001$ ) (Table 1A). The P-values for all combination were equally high ( $P<0.0001$ ). When SSS calculated by 2 observers was compared, correlation coefficients ranged from 0.87 to 0.97, in which Method 4 using the automatic polar map display showed the highest correlation ( $r=0.97$ ,  $P<0.0001$ ) (Table 1B).

### Correlation of Cardiac Risk Values Compared With Visual Scoring

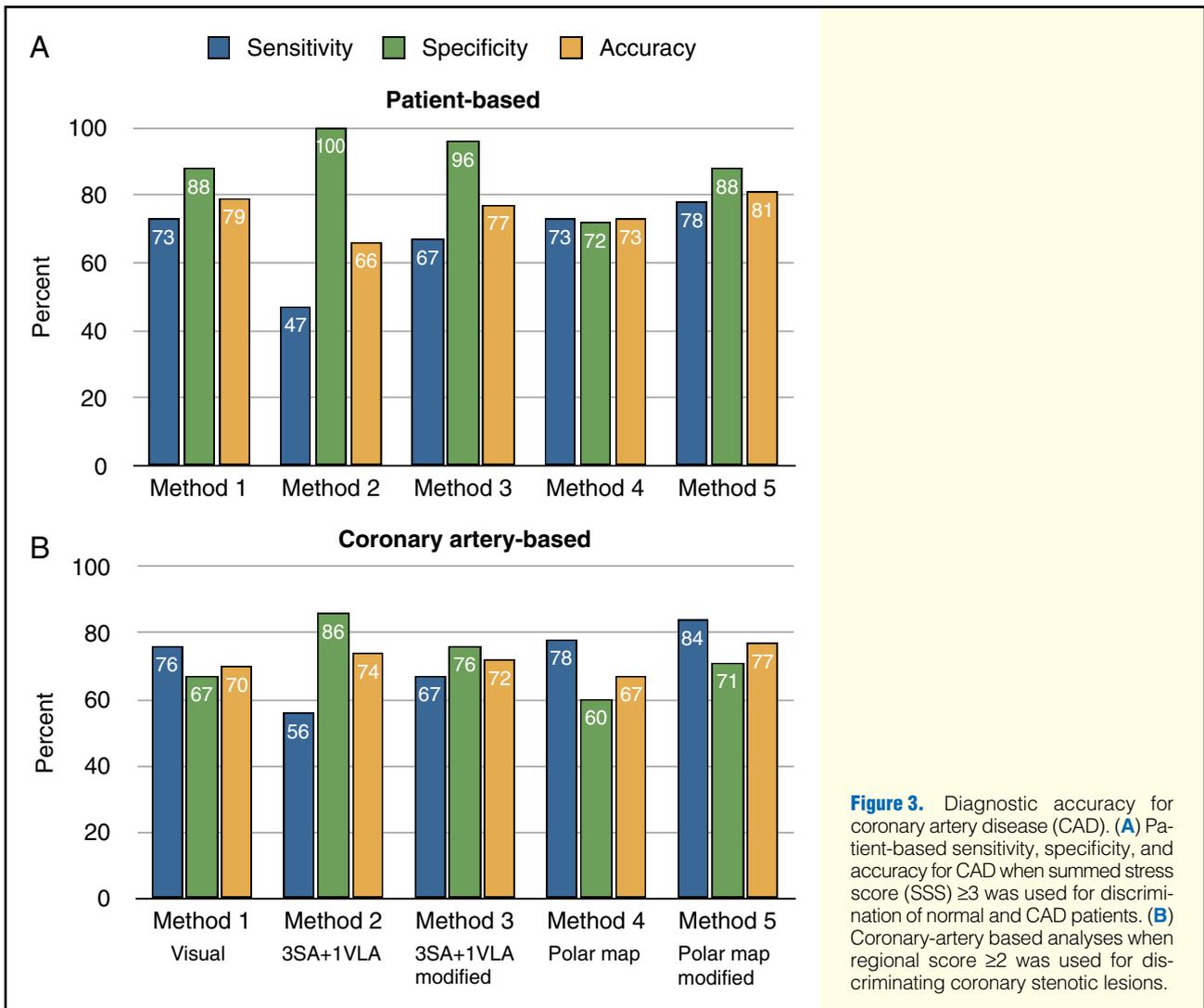
When estimated cardiac event rates were compared with that by visual scoring (Method 1),  $r=0.99$  between Methods 1 vs. 2–5 (Table 2A). Interobserver correlation coefficients between observers were 0.99–1.00 for Methods 1–5 (Table 2B). A high correlation was observed between visual and the other 4 methods (Figure 2). All the P-values showed that the risk calculation was highly reproducible if based on the 4 SSS categories.

### Diagnostic Accuracy of CAD

The SSS values of 3 and 4 were compared as the possible threshold between normal and abnormal results. The average diagnostic accuracy was slightly higher for  $\text{SSS} \geq 3$  (0.78) compared with that for  $\text{SSS} \geq 4$  (0.76). In patient-based analysis, when  $\text{SSS} \geq 3$  was defined as abnormal, sensitivity, specificity, and accuracy are shown in Figure 3. Sensitivity was the highest (78%) in Method 5 and the lowest (47%) in Method 2 ( $P=0.0002$ ). Overall accuracy was 81% for Method 5. In coronary artery-based analysis, a summed regional score  $\geq 2$  was similarly defined as abnormal. The sensitivity by Methods 2 and 5 was 56% and 84%, respectively ( $P=0.0009$  between Methods 2 and 5). Specificity was the lowest (60%) in Method 4 and the highest (86%) in Method 2. The accuracy for detecting the coronary artery stenotic lesion was the highest by Method 5 (77%).

## Discussion

Estimating cardiovascular event risk based on MPI has been considered as an important role of nuclear cardiology. The results of this study indicated that integration of myocardial polar-map quantification with a multi-center normal databases and multi-center prognostic databases could shed light on possible future event risks using multivariate analysis. The reproducibility of the estimated event risk was high based on gated



perfusion imaging.

In patients with CAD, risk stratification for cardiovascular events is essential for determining therapeutic strategy and patient management. Recent studies using MPI have unanimously shown that patients with perfusion defects in multiple coronary territories and a larger perfusion defect in the anterior walls have high risks.<sup>12,13</sup> Along these lines, MPI has been utilized as an effective non-invasive test for determining indication of percutaneous coronary intervention.<sup>14</sup> The finding of perfusion defects in the stress imaging, corresponding to SSS in this study, has been considered as one of the predictors of acute ischemic events. The extent of the perfusion abnormality was one of the most important prognostic predictors, even when coronary angiography was performed.<sup>15,16</sup> As for cardiac function, the addition of functional data to perfusion data yielded an incremental value for predicting hard events.<sup>17,18</sup> A decrease in EF and an increase in LV volume contributed to occurrence of cardiac events including severe heart failure.<sup>5,19</sup> In a Japanese population using MPI, a study demonstrated that advanced age, SSS, and summed difference score were independent predictors of cardiac death.<sup>20,21</sup>

The equation for predicting cardiac events was based on multi-variate analysis of J-ACCESS investigation. Based on a 3-year follow-up study of 4,629 patients, major cardiac events

including cardiac death, non-fatal myocardial infarction, and severe heart failure requiring hospitalization could be estimated.<sup>5</sup> The predictors of major cardiac events were then found to be SSS, EF or ESV, age, and presence of diabetes. Because the multi-factorial contribution to event rates was complicated, it is illustrated in **Figure 1**. The risk table for estimating cardiac events during the 3-year period was also proposed.<sup>6</sup> A similar approach using a prognostic score for prediction of cardiac mortality risk after adenosine stress MPI has been reported.<sup>22</sup> They found that the Cox proportional hazards model most predictive of cardiac death included age, percentage myocardium ischemic and fixed, early revascularization, dyspnea, diabetes mellitus, rest and peak stress heart rates, and abnormal rest electrocardiogram. Regarding therapeutic strategy after MPI, Hachamovitch et al demonstrated that coronary revascularization provided greater survival benefit to patients with moderate to large amounts of inducible ischemia in comparison to that of medical therapy.<sup>23</sup> In a Japanese population, prognostic value of ECG-gated rest <sup>201</sup>Tl/stress <sup>99m</sup>Tc-tetrofosmin myocardial perfusion SPECT for the prediction of acute coronary syndrome was investigated in 1,895 patients, and the combination of significant ischemia and low EF showed the highest predictive value for future events.<sup>24</sup>

The reliability of the multiple factors affecting the risk esti-

mation, which was used in this study, is discussed below. First, in the J-ACCESS study, perfusion defect quantification was based on visual estimation based on 20- or 17-segment models using representative 3 short-axis images and mid vertical long-axis image. Inter-individual variation for defect scoring might directly influenced the estimated risk values. Although some threshold values could be used as an auxiliary for quantification, the myocardial perfusion count was not a uniform percentage value to the maximum value. To achieve more stable results, we then used a quantification method derived from all slices throughout the myocardium. As a result, objectivity was enhanced compared with that when using the method for selecting only several slices.<sup>25</sup> Second, reliability of cardiac functional evaluation should be confirmed. The results of using both gated-SPECT and QGS software demonstrated that LV functional parameters were precise even in multiple institutions were involved.<sup>26</sup> In 5 typical workstations currently used in nuclear cardiology, variability of EF was 3.6% and the coefficient of variance of EDV was <10%. In this relatively small preference-based variability, the nuclear method seemed to be appropriate for objective evaluation. Although the reproducibility of risk value was very high in this study, the reason for the high correlation coefficient was that it was affected only by SSS category as indicated by the multivariate logistic equation. The use of reliable quantification software for calculating scores would further enhance the reproducibility.

The third factor involved associated diseases including diabetes mellitus and chronic kidney disease (CKD). The associated condition of diabetes significantly enhanced cardiac event risks. The finding of the J-ACCESS study was comparable to that of a Finnish study, which also demonstrated that history of myocardial infarction had nearly an equivalent risk to the presence of diabetes.<sup>27</sup> Recent multi-center prospective cohort study in the southern Europe demonstrated that patients with previous myocardial infarction had a greater risk than those who had diabetes, suggesting non-equivalence in coronary disease risk for diabetic and myocardial infarction patients.<sup>28</sup> Although the difference in tendency might be related to patient selection criteria and even life-style or dietary habits, further studies including a Japanese population would be required. Another important background affecting the risk value is CKD.<sup>29</sup> The J-ACCESS substudy also demonstrated that decreased estimated glomerular filtration rate (eGFR) was an important predictor of cardiac events.<sup>30</sup> Because the logistic regression analysis was performed by the main study (n=4,031), not from the substudy of CKD patients (n=820), we did not include the factor of eGFR in this study. However, participants with low eGFR (15–29 ml/min) showed >2 times higher event rate than those with eGFR of 30–59 ml/min. The effect of CKD or decreased eGFR on the event risk was therefore considered clinically important, and we are revising the algorithm to include the parameter of renal function as the subsequent software version.

To quantify polar map scores, several kinds of software have been used with somewhat different algorithms of searching myocardial counts, surface models, and quantification methods. Moreover, each software program used standard databases for comparing normal and abnormal patterns and grading the severity of abnormality. The characteristics of a normal database significantly affect the diagnostic accuracy, which includes radionuclide types, radiopharmaceutical types, gender differences, and SPECT acquisition protocols.<sup>10</sup> Even differences in American and Japanese databases significantly influenced the diagnostic ability for CAD.<sup>31</sup> We therefore used JSNM-WG databases to determine appropriate thresholds for

scoring from 4 (complete defect) to 0 (normal). As a result, the scoring into 4 grades by the software was nearly the same as that of the expert reading of the whole images. Regarding evaluation of coronary territories, use of the 3 short-axis and 1 long-axis slices showed lower sensitivity than that of the polar map. It was anticipated that a limited number of slices could not cover all the myocardial surface, and therefore diagnostic sensitivity was better using the polar maps. In addition, a relatively lower inferoseptal count was more reliably quantified by polar maps than by the method using selected slices.

A limitation was that we used both <sup>99m</sup>Tc-tetrofosmin and sestamibi, although the J-ACCESS investigation was performed with only <sup>99m</sup>Tc-tetrofosmin. However, no significant differences between the tracers with regard to sensitivity and specificity were observed in the ROBUST study,<sup>32</sup> and JSNM normal databases did not differ significantly in all segments between sestamibi and tetrofosmin.<sup>10,31</sup> Although in this regression analysis dichotomic variables of presence (1) or absence (0) was used, a further prognostic study might enable us to use a more segmentalized definition. The selection of patients was intended to cover various degrees of perfusion defects for software validation, and not to evaluate their actual event rates in the future. Since the major event rate was 4.3% per 3 years in a population comparable with the J-ACCESS investigation, hundreds or thousands of patients should be registered for the prognostic evaluation. Although many studies have shown various predictors for future events, the actual number of events following the risk prediction have not been examined. When this type of software is used in clinical situations in many institutions, the relationship between prediction (risk) and outcome (events) would be more clearly understood in the future. Severe heart failure was included as one of the major events. Severe heart failure of New York Heart Association classes 3 and 4 requiring hospitalization was an important event in the J-ACCESS population.<sup>19,33</sup> When the patients who had heart failure in the first year were followed up, 9 of 41 (22%) experienced cardiac death in the subsequent 3-year follow-up period.<sup>7</sup> We therefore decided to include only severe heart failure in the major cardiac events. Finally, the reason for excluding 3-vessel disease from the study group was that this study was intended to compare the severity of perfusion defect among 5 methods to calculate risk values and not to validate the diagnostic effectiveness in multivessel disease. Since a large perfusion defect with SSS>11 was classified as the severe group (SSS category III), the estimated risk value was not influenced by the higher scores.

In conclusion, the reliability of predictive variables was enhanced using a quantitative polar map approach compared with an approach using visual analysis of myocardial perfusion defects. The cardiovascular event risks estimated by MPI and LV function could provide stable results as well as good diagnostic ability for CAD. The risk stratification provided by this type of software should be further validated by a long-term follow-up study in a prospective manner.

### Acknowledgment

This work was mainly supported by the Japan Cardiovascular Research Foundation, and in part by Grants-in-Aid for Scientific Research in Japan. The Heart Risk View and Heart Score View software were used as a collaborative research work with Nihon Medi-Physics, Co Ltd, Japan. We thank Mr. Ronald G. Belisle for his editorial assistance in the preparation of manuscript.

### Disclosure

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

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