Prediction of Cardiac Mortality and Events by Myocardial Perfusion Imaging: Differences between Japanese and American Populations

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Chapter 14

PREDICTION OF CARDIAC MORTALITY AND EVENTS BY MYOCARDIAL PERFUSION IMAGING: DIFFERENCES BETWEEN JAPANESE AND AMERICAN POPULATIONS

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ABSTRACT

Cardiac diseases are one of the major causes of death both in Western countries and in Japan. Based on various clinical information, identification of myocardial ischemia and contractile function plays a major role in predicting serious cardiac events of death and acute coronary syndromes. Currently, myocardial perfusion imaging provides both kinds of information, and clinical follow-up studies have been performed in the U.S., Europe and Japan. Due to our involvement in a Japanese multi-center prognostic study, we have found similarities and differences between Western and Japanese populations. The most important predictors of cardiac events are myocardial perfusion abnormality and ventricular function. The importance of diabetes and chronic kidney disease should be also emphasized. The trends of cardiovascular events should be carefully investigated because of westernized diets and lifestyles in addition to current progress of therapeutic strategy.

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INTRODUCTION

Ischemic heart disease is one of the major causes of death in Asian countries as well as in Western countries. From the viewpoint of national healthcare, its prevention, early diagnosis and medical examination procedures to guide appropriate treatment have become an important issue. Even after medical or surgical treatments, if the therapeutic effectiveness, recurrence of disease and indications for additional therapy can be evaluated, it would greatly contribute to the management of the patients. This article deals with the similarities and differences between Japan and Western countries with respect to cardiac death and serious events. In this article, we focus on the imaging of coronary artery disease, particularly on the role of perfusion imaging. A prognostic study involving >100 hospitals in Japan has provided us insight into the diagnostic and therapeutic strategies.

UNDERLYING FACTORS OF CORONARY ARTERY DISEASE

The Framingham Heart Study and subsequent cohort studies have shown conclusively that risk of coronary heart disease is related to serum total cholesterol level [1]. The impact has been found to be augmented by adding risk factors. In fact, coronary risk factors include background factors of high age, male gender, family history of coronary artery disease and hypertension, and in addition, factors related to diet and life styles. These may include dyslipidemia, that is, low HDL (high-density lipoprotein) cholesterol and high LDL (low- density lipoprotein) cholesterol, smoking habit, fatty meals, insufficient exercise and obesity.

The tendency is true not only in American and European countries, but also in Japan. As Japanese lifestyles have become westernized, the risk factors have become westernized, although ethnic or genetic differences might be underlying [2]. In Japan, a risk chart of NIPPONDATA 80 (National Integrated Projects for Prospective Observation of Non- communicable Disease and its Trend in the Aged) has been created based on a database of 100,000 Japanese subjects [3, 4]. Based on this prognostic database, the risk level and ten- year mortality rate could be estimated by age, presence of diabetes, smoking, blood pressure and cholesterol level. For example, in male subjects in their 50s with conditions of fasting blood sugar >200 mg/dL, no smoking, systolic blood pressure 140–159 mmHg and cholesterol 260–279 mg/dL, cardiovascular risk level is calculated as the level 3 of 6 (6 is the highest level), and ten-year mortality rate would be 3–7%. Although the mortality rate of patients cannot be exaggerated, appropriate medical care and life-style modifications would surely be beneficial for patients' motivation for treatments.

The mortality rate caused by cardiac diseases is one of the lowest in Japan compared with that of American and European countries, which is about 1/3 of the U.S.. Cardiac death, however, is the

second highest cause of death in Japan, and prevention of cardiovascular events is an important healthcare issue (Figure 1).

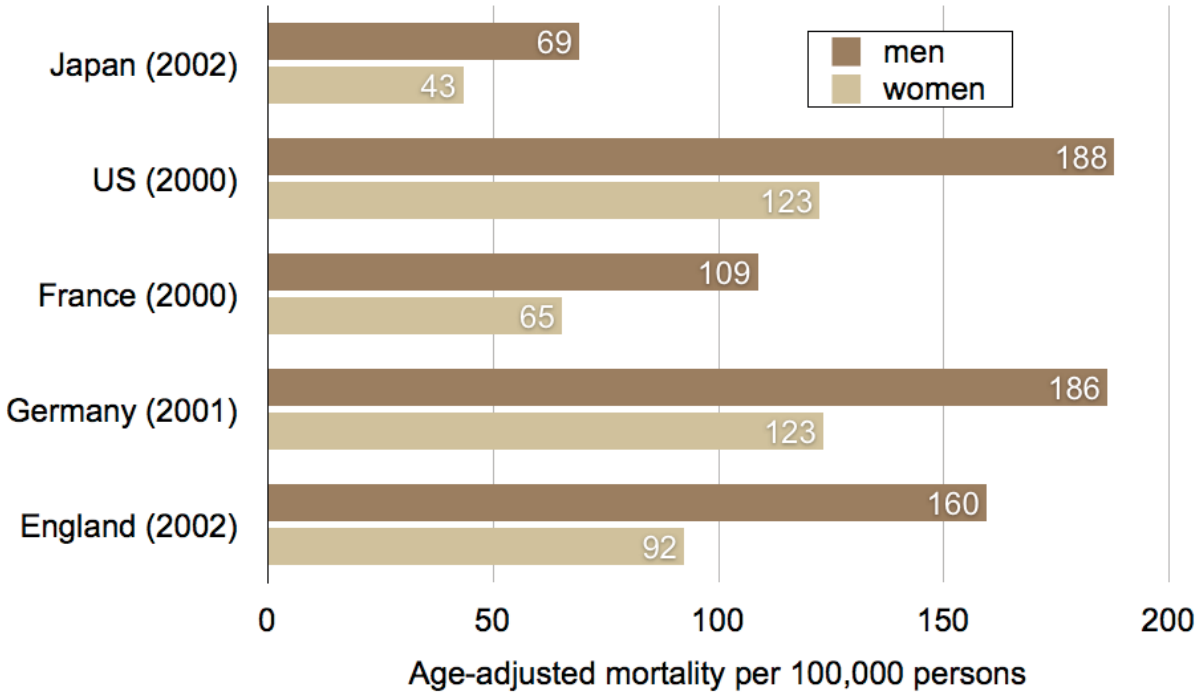

Figure 1. Comparison of age-adjusted mortality rate per 100,000 persons due to cardiac diseases. The data are from the statistics of the Ministry of Health, Labor and Welfare of Japan and WHO Statistical Annual. The Japanese statistics included pulmonary embolism and other pulmonary vascular diseases in the cardiac disease

NUCLEAR IMAGING AND PROGNOSTIC STUDIES

Current technological development for imaging coronary artery disease is extremely advanced and includes X-ray computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, as well as nuclear cardiology studies of single-photon emission computed tomography (SPECT) and positron emission tomography (PET). In an outpatient department setting, approaches to coronary artery disease may start from typical chest symptoms and electrocardiography (ECG). Rest ECG can detect myocardial injury and infarction, and stress ECG has been used to identify exercise-induced ischemia, typically found in angina pectoris. Echocardiography can be used as a bedside imaging modality to evaluate cardiac morphology and ventricular contractility. X-ray CT based coronary imaging using contrast media has been developed due to technical advances of high-speed multi- detector CT systems. MRI is also a promising technology to evaluate myocardial damage or coronary artery stenosis. In the era of multi-modality imaging, nuclear cardiology has been used since the 1970s to visualize myocardial perfusion using thallium-201. The development of new technetium-99m (^{99m}Tc) myocardial imaging radiopharmaceuticals and computer technology to support the ECG gating and quantification of myocardial perfusion has enhanced the availability of nuclear cardiology as a non-

invasive reliable method (Figure 2). Academic societies of the American Heart Association and American College of Cardiology summarized the guidelines for radionuclide imaging in 1995 and revised these guidelines in 2003, and they have made recommendations for appropriate use of radionuclide imaging [5].

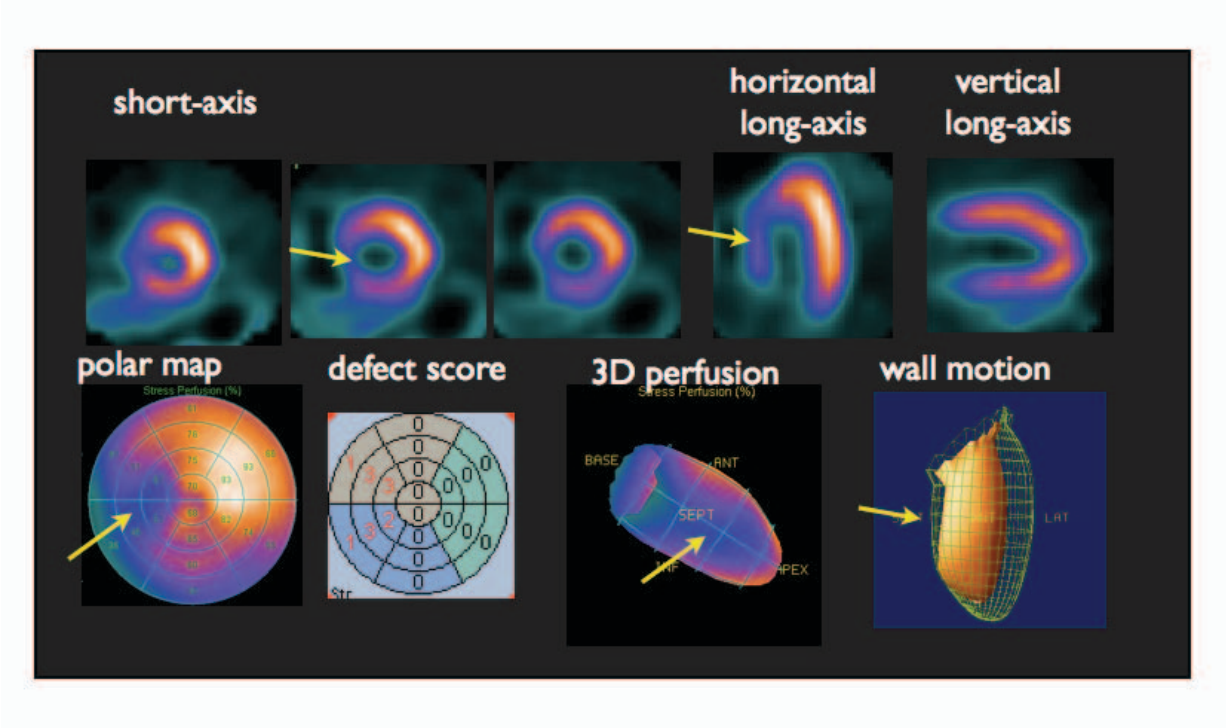

Figure 2. Quantification of myocardial perfusion imaging at stress. Septal segment showed decreased perfusion at stress condition (arrows). In this patient, summed stress defect score was 13 (intermediate- high), and ejection fraction was calculated as 62%. The diagnosis of exercise-induced ischemia was made by comparing it with resting condition

Nuclear Imaging to Detect Myocardial Ischemia

Nuclear medicine is an imaging modality using principles of a tracer. A radiotracer that has characteristics of accumulating myocardium emits gamma rays, which are used to reconstruct three-dimensional myocardial images. The sliced myocardium images reflect the shape of the myocardium, but more importantly they are functional images of perfusion. Namely, if the patient had chest pain during a stress study, the myocardial hypoperfusion in the relevant area would be visualized on the SPECT image. Current computer technology further enables visibility of a beating heart by electrocardiographic gating. The degree of perfusion can be quantified by sophisticated software using a three-dimensional display or a polar map display [6, 7]. The segmentation of the myocardial wall, automatic division of the coronary artery territory and fusion technique of CT angiography and perfusion are current advances of computer technology.

Prognostic Evaluation for Adverse Cardiac Events

One of the most useful approaches of nuclear cardiology is to assess future risks for cardiac events [8]. In low-risk patients for cardiac events, a less invasive examination would be recommended, and it might be followed by diets and exercise, or if necessary, medication. On the other hand, higher-risk patients might require a more active or invasive examination which might be justified. The judgment for admission and interventional treatment is an important point from an economical viewpoint.

A nuclear medicine examination is known to be valuable for intermediate-risk patients [5]. It has been understood that the results of nuclear cardiology has an impact on the risk stratification of the patient risk for future cardiovascular events. The hard cardiac events usually denote cardiac death and non-fatal myocardial infarction. Many investigators have unanimously demonstrated that normal nuclear studies indicate a 0.6% of cardiac event rate per year [5, 9]. In contrast, patients with an abnormal nuclear study, such as those with a significant degree of myocardial ischemia, resting perfusion defects and left ventricular dysfunction had more than ten times the risk of cardiac events. Therefore, in these high-risk patients, a more aggressive treatment strategy would be recommended to achieve a better outcome.

J-ACCESS Japanese Prognostic Study

In the Japanese population, it has been reported that coronary artery disease is less frequent and more mild in its severity. In fact, life expectancy in the Japanese population is one the highest in the world. According to the statistics from the Health Ministry, life expectancy for Japanese women — already the longest in the world — has risen by nearly 1.5 years, and it increased to 86.05 years in 2008 from 84.60 years in 2000. For men, life expectancy rose to 79.29 years from 77.72 years. Eating habits, obesity and ethnic differences may be background causes of this higher life expectancy.

Whether myocardial perfusion imaging is similarly beneficial for risk stratification in the Japanese population has not been verified. Since no background database has been created, the J-ACCESS prognostic study, which utilized a nuclear cardiology examination and long- term follow-up, was initiated in 2001 [10]. The study registered patients who were suspected of having coronary artery disease and who underwent myocardial perfusion imaging using Tc-99m tetrofosmin. More than 4,500 patients were registered from 117 hospitals in Japan. The participation of a large number of hospitals was the characteristic of this study and reflected the clinical practice of nuclear cardiology in Japan. The degree of perfusion abnormality was scored semi-quantitatively. Cardiac function, such as ventricular volumes and ejection fraction, was computed by the QGS software (Cedars Sinai Medical Center, CA, USA) (Figure 2). The reliability of the software was confirmed separately and found to be very good. The error of ejection fraction was less than 5% even when more than 100 hospitals were involved in the study [11]. The use of population-specific normal database also enhances the diagnostic accuracy [12].

CHARACTERISTICS OF CARDIAC EVENTS IN JAPAN

Based on a follow-up of 3 years, the major cardiac event rates including cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization, were 4.3% per every three-year period [10]. Moreover, when only hard cardiac events (excluding severe heart failure) were used as endpoints, the rate decreased to 2.4%. The incidence of hard event rate was generally lower compared to that of the American studies (Figure 3). However, the study demonstrated a higher event rate in patients who had stress myocardial perfusion defects and ventricular dysfunction, which were similar between US and Japan. Notable differences included lower event rates in cardiac death and non-fatal myocardial infarction in comparison to that in the US population. These differences may also have been related to somewhat different therapeutic strategies between the US and Japan, such as indications to aggressive medical treatments, percutaneous coronary intervention and coronary bypass surgery. Notably, of the various background factors, only diabetes was the major predictor of cardiac events based on multivariate analysis for both hard events and total events [10, 13]. Diabetes has been regarded as a coronary-artery disease equivalent in Western countries. Similarly, in Japan, diabetic patients without prior myocardial infarction showed a comparable event rate to non-diabetic patients with prior myocardial infarction (Figure 4).

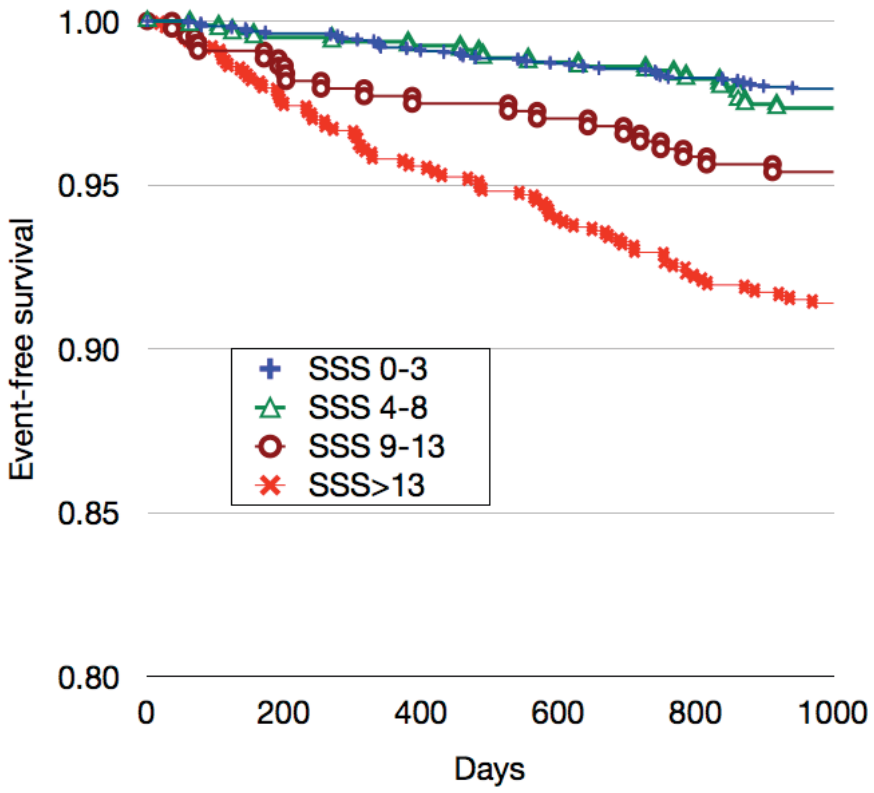

Figure 3. Kaplan-Meier estimates for major cardiac events according to stress myocardial perfusion. The myocardial perfusion image at stress was scored as summed stress score (SSS) of <4 (normal), 4-8 (mildly

abnormal), 9-13 (moderately abnormal) and >13 (severely abnormal). Significant differences among groups (P <0.0001 by χ^2 trend test). Adapted from Eur J Nucl Med 2009. [10]

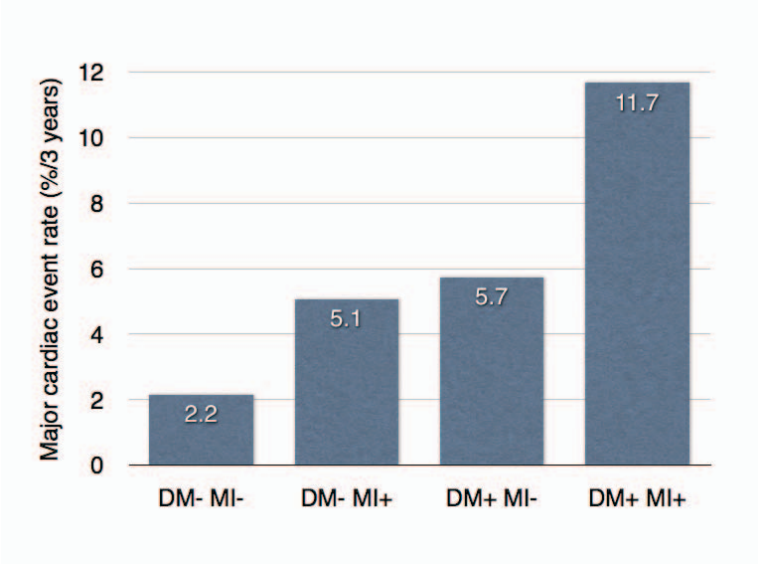

Figure 4. Major cardiac event rate per 3-year period classified by diabetes mellitus (DM) and history of myocardial infarction (MI). Diabetic patients without prior MI showed comparable event rate to non- diabetic patients with prior MI

When the annual cardiac event rate was observed regarding total and hard events, the event rate differed significantly due to the stress-induced ischemia and left ventricular function. Figure 5 shows patients classified by summed difference score (summed stress defect score minus summed rest defect score) ≥2 and <2, and ejection fraction of ≥45% and <45%.

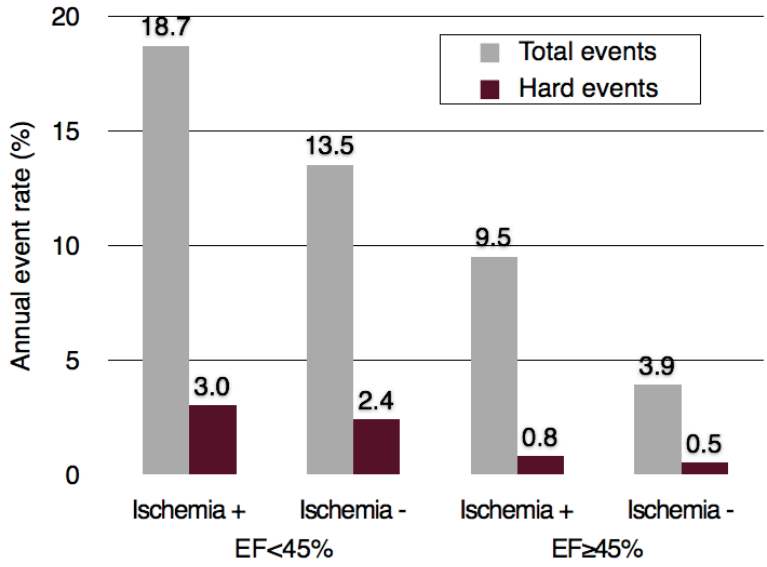

Figure 5. Annual event rate for total and hard cardiac events. Hard cardiac events include cardiac death and non-fatal myocardial infarction. Ischemia is determined by summed difference score (defined as the difference between stress and rest perfusion defect score) ≥2. Ejection fraction (EF) was calculated by gated SPECT. Statistics: p<0.0001 for total events, p=0.0003 for hard events

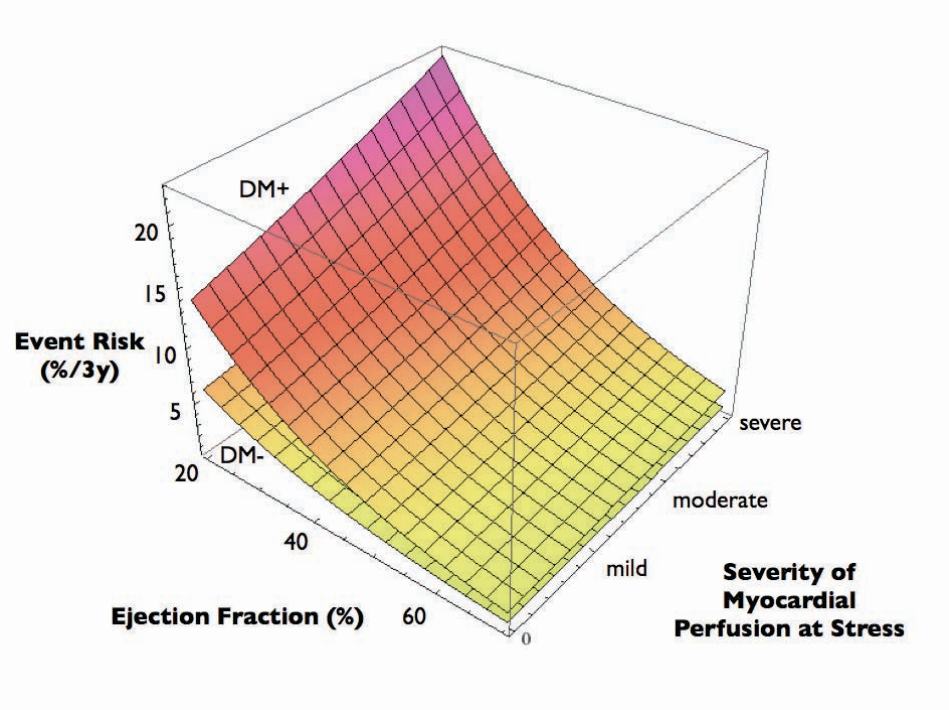

Figure 6. Three-dimensional plot showing effects of EF and severity category of stress myocardial perfusion defect on estimated cardiac risks. The patient's age is assumed to be 55 years old. A difference between the presence and absence of diabetes (DM+ and DM-) is observed

In patients with a normal myocardial perfusion study, the annual hard event rate was 0.5%, comparable with 0.6% in the US [9, 14]. Even when major events including severe heart failure were analyzed, the rate was 0.8% per year.

The relationship among ejection fraction (left ventricular contractility), severity of perfusion defects (0, normal; 1, mild; 2, severe; 3, severe) and age can be plotted as a three- dimensional graph (Figure 6). In particular, when ejection fraction is low, cardiac event risk increased significantly with an increase in perfusion defect category. The impact of diabetes on the increase in the event rate can be visualized in the display. The risk table (Heart Risk Table) was also created [15]. The sample of risk values and relative risks compared with age- matched control is shown in 60-69 year-old patients (Figure 7).

In the substudy focusing on patients who had coronary angiography, parameters derived from nuclear imaging revealed significant additional values on coronary stenosis confirmed by invasive coronary angiography [16]. Therefore, although the number of stenotic vessels is important for predicting event, the existence of myocardial ischemia or perfusion defect was found to be determinant of cardiac events. Recently, more attention is being paid to chronic kidney disease in relation to accompanying cardiac diseases [17]. A J-ACCESS substudy also has shown that the incidence of cardiac events was higher in the group with a lower estimated glomerular filtration rate (eGFR) [18]. The renal dysfunction evaluated by eGFR is one of the major predictors of cardiac events based on multivariate analysis in addition to myocardial perfusion abnormality, left ventricular dysfunction and diabetes. Cardiac event rate was significantly higher in patients with reduced eGFR and high summed stress score (Figure 8).

Age 60-69

		Major events (%) / 3 years — SSS category				Relative risk vs. age-matched controls (folds) — SSS category			
	LVEF	O	I	II	III	O	I	II	III
without diabetes	10%	16.0	18.7	21.9	25.4	11.6	13.5	15.9	18.5
	20%	10.6	12.5	14.8	17.5	7.7	9.1	10.8	12.7
	30%	6.8	8.2	9.8	11.6	5.0	6.0	7.1	8.5
	40%	4.4	5.3	6.3	7.6	3.2	3.8	4.6	5.5
	50%	2.8	3.3	4.0	4.8	2.0	2.4	2.9	3.5
	60%	1.7	2.1	2.5	3.1	1.3	1.5	1.8	2.2
	70%	1.1	1.3	1.6	1.9	0.8	1.0	1.2	1.4
	80%	0.7	0.8	1.0	1.2	0.5	0.6	0.7	0.9
	90%	0.4	0.5	0.6	0.8	0.3	0.4	0.5	0.5
with diabetes		O	I	II	III	O	I	II	III
	10%	31.5	35.9	40.5	45.2	22.9	26.1	29.4	32.9
	20%	22.3	25.8	29.7	33.9	16.2	18.8	21.6	24.7
	30%	15.1	17.8	20.8	24.2	11.0	12.9	15.1	17.6
	40%	10.0	11.9	14.0	16.6	7.3	8.6	10.2	12.0
	50%	6.4	7.7	9.2	11.0	4.7	5.6	6.7	8.0
	60%	4.1	4.9	5.9	7.1	3.0	3.6	4.3	5.2
	70%	2.6	3.1	3.8	4.6	1.9	2.3	2.8	3.3
	80%	1.6	2.0	2.4	2.9	1.2	1.4	1.7	2.1
	90%	1.0	1.2	1.5	1.8	0.7	0.9	1.1	1.3

Figure 7. A part of prognostic table (Heart Risk Table) based on presence of diabetes mellitus, age, severity category of stress myocardial perfusion defect (SSS category) and left ventricular ejection fraction (EF). Values are estimated as major cardiac event rate for three years (left), and relative risk (folds) compared with that of the age-matched control group (right)

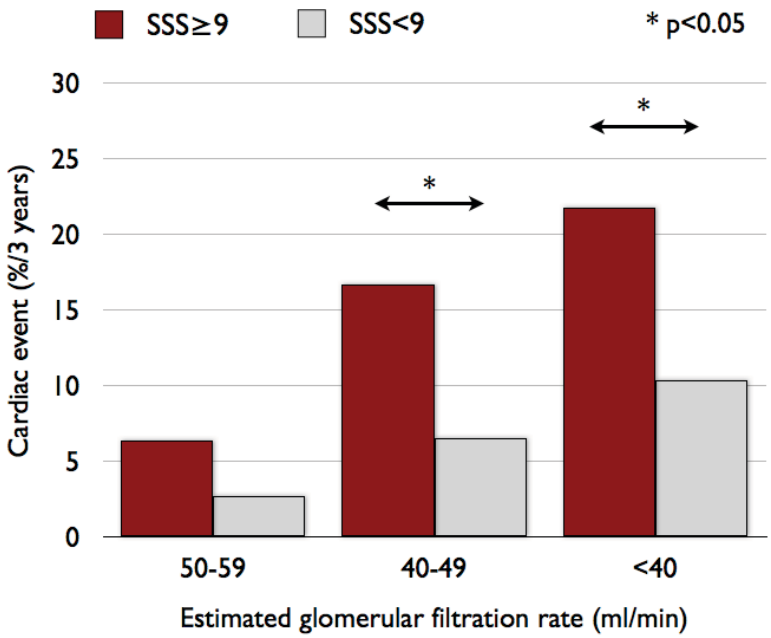

Figure 8. Incremental values of perfusion defect score at stress (SSS) and cardiac event rates for 3 years in patients with CKD. Adapted from Eur J Nucl Med 2009, reference [18]

FUTURE DIRECTIONS

Since diabetes was the major predictor of major events, we started our J-ACCESS 2 investigation focusing on asymptomatic type-2 diabetic patients. The one-year interim summary has just been published [19]. The interim summary showed that cardiovascular events were significantly higher in patients with SPECT abnormality, although the hard cardiac event rate was relatively low. Silent myocardial ischemia occurred in 22% of asymptomatic patients with type 2 diabetes in the DIAD study in the U.S. and in 17% in the J-ACCESS 2 study [20, 21]. A targeted treatment strategy is required for asymptomatic but potentially high-risk diabetic patients. Since hard events are relatively low in the asymptomatic diabetic patients, screening all diabetic patients is not justified from a practical point of view. It is imperative to identify the best candidates for screening diabetic patients to obtain a high diagnostic yield from myocardial perfusion imaging.

CONCLUSION

In this article, we have asserted that cardiac disease is less frequent in Japan than in the U.S. However, cardiac death is still the second leading cause of death (cancer is the highest) in Japan. Although Japan has long been touted as having one of the world's longest-living populations, changing eating patterns, from the traditional fish and rice-based diet to high- cholesterol and high-calorie diets, and life-style changes might enhance the morbidity and mortality in the near future. Further studies should be continued to estimate the risk to appropriately guide treatments and prevent possible future serious events. Noninvasive imaging, such as nuclear cardiology, can identify ischemic myocardium, demonstrate physiological significance of the coronary artery stenosis and guide appropriate therapy. Such prognostic information can be valuable for estimating future events, and would preferably prevent hard events by reducing the risk factors.

ACKNOWLEDGEMENT

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