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REVIEW

Cardiovascular Events in Japan
– Lessons From the J-ACCESS Multicenter Prognostic Study Using Myocardial Perfusion Imaging –

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The multicenter Japanese-Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT (J-ACCESS), which involved 117 institutions and 4,629 patients, was the first attempt to quantify cardiac events and survival using stress-rest-gated single-photon emission computed tomography myocardial perfusion images (MPI) and QGS software in Japan. A 3-year follow-up study showed a relatively lower incidence of hard events than in the USA and some European countries, but a similar role of perfusion and left ventricular (LV) function. A low event risk with normal MPI and a higher incidence of major cardiac events in patients with large perfusion defects and LV dysfunction were defined. MPI was useful even among patients with proven coronary artery stenosis. The association between diabetes and chronic kidney disease (CKD) was an important predictor of cardiac events and the risk was evaluated using new software and risk charts. Additional studies were extended to include asymptomatic diabetes (J-ACCESS 2) and CKD (J-ACCESS 3). Because risk estimation is linked to the national healthcare system and clinical practice, optimal risk stratification and guidance for therapeutic strategies are recommended. (*Circ J* 2012; **76:** 1313–1321)

Key Words: Cardiac event risk; Coronary artery disease; Japanese population; Myocardial perfusion imaging; Multicenter study

During the rapid development of imaging modalities in cardiology, nuclear cardiology has played an important role in direct visualization of myocardial ischemia. Its contribution to prognostic evaluation in the USA and Europe has been established and major predictors of cardiovascular events have been assembled in nuclear cardiology guidelines.[1] The value of prognostic evaluation and risk stratification using myocardial perfusion imaging (MPI) and single-photon emission computed tomography (SPECT) has been recognized in Japan since the 1990s. However, because a large-scale multicenter study has not been conducted in Japan or other Asian countries, the appropriateness of extrapolating the experience in the USA and Europe to a Japanese population remains unknown. In fact, Japanese governmental statistics indicate that the estimated mortality rate of cardiac disease is half or one-third of that in the USA. Nevertheless, cardiac death was the second leading cause of death (15%) followed by malignant neoplasms (29%) in the 65-year-old subgroup in the 2009 Japanese statistics. Thus, the Japanese-Assessment of Cardiac Event and Survival Study by Quantitative Gated SPECT (J-ACCESS) investigation supported by the Japan Cardiovascular Research Foundation created prognostic databases and evaluated the effectiveness of MPI in the Japanese healthcare system and epidemiological backgrounds.[2] The present overview presents the main results of the first Japanese multicenter investigation of coronary artery disease (CAD) using stress myocardial perfusion SPECT, and discusses the role of nuclear cardiology.

J-ACCESS Investigation

The J-ACCESS investigation involved 117 institutions in Japan and 4,629 consecutive patients (male, n=2,989 (65%); age, 65±10 years; female, n=1,640 (35%); age, 67±10 years) with suspected or known CAD if indicated for stress cardiac imaging using ^{99m}Tc-tetrofosmin stress myocardial perfusion SPECT between October 2001 and March 2003. Images acquired from electrocardiographic gated SPECT at all institutions were quantitatively analyzed using QGS software (Cedars Sinai Medical Center, Los Angeles, CA, USA). J-ACCESS was the first large-scale prognostic investigation to use a cardiac imaging modality to investigate CAD in Japan.

Data from at least the gated study of all patients at rest were analyzed using QGS software. Myocardial segmentation was based on a 20-segment model, and summed stress (SSS), summed rest (SRS) and summed difference (SDS) scores were calculated based on 0–4 points in each segment (0, normal to 4, defect). Japanese governmental statistics include death due

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Table 1. Clinical Backgrounds of the Patients

	J-ACCESS (n=4,031)	J-ACCESS 2 (n=485)
Registration	Consecutive (suspected or known CAD)	Asymptomatic type-2 DM
Age	66±10	67±8
Male sex	64%	58%
Body mass index (kg/m²)	24±3	25±4
Diabetes	29%	100%
Diabetic retinopathy	–	25%
Diabetic neuropathy	–	20%
History of cerebrovascular accident	–	11%
Family history of CAD	12%	7%
Currently smoking	16%	19%
Hypertension	55%	82%
Dyslipidemia	47%	80%
Event rate		
Total cardiac events per year	6.5% (263/4,031)	6.5% (33/506)
Major cardiac events per 3 years*	4.3% (175/4,031)	3.5% (17/485)
Hard events per 3 years	2.0% (82/4,031)†	2.9% (14/485)‡
Cardiac death per 3 years	1.1% (45/4,031)	1.0% (5/485)

Cardiac death plus *nonfatal MI + severe HF requiring hospitalization, †nonfatal MI and ‡nonfatal ACS.
J-ACCESS, Japanese-Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; HF, heart failure; ACS, acute coronary syndrome.

to heart failure (HF) within cardiac death. Considering this feature of the Japanese health care system, we adopted a primary endpoint that included cardiac death, nonfatal myocardial infarction (MI) and severe HF requiring hospitalization, which we refer to as major adverse cardiac events (MACE). The inclusion of more than 4,600 patients in 117 hospitals indicates that J-ACCESS reflected routine nuclear cardiology practice throughout Japan, and not only that in selected major cardiac centers.

Gated SPECT as a Standard Quantitation Method

The first point requiring clarification was whether or not the quantitative parameters of ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV) were valid and reliable when >100 hospitals were involved in 1 study. Although high EF reproducibility has been already reported, the degree to which different SPECT reconstruction preferences influence the precision of EF and left ventricular (LV) volumes remains unknown.[3,4] Three projection datasets including EF values of approximately 30%, 50% and 70% (large, no or small, and absent defect, respectively) were processed at each institution using their routine processing protocols.[5] The results showed a standard deviation of <3.6% for EF, and the coefficient of variance of the EDV was <9.3% overall. Good precision of the quantitative data allowed further follow-up study and analysis. Defects were scored using visual estimation and quantitative software-based scoring helped the reliability of risk estimation. Normal QGS values for the Japanese population were also defined from the databases to define the appropriate threshold of abnormality.[6]

Major Findings of J-ACCESS

Table 1 shows the demographics of the patients and a list from the J-ACCESS 2 study of asymptomatic diabetic patients. The severity of stress defects using SSS definitely determined the prognosis of the patients.[7] The major event rate was the lowest in patients with SSS 0–3 at 2.3% per 3 years, and increased 4-fold in patients with SSS ≥14 to 9.2% per 3 years (Figure 1). However, the overall cardiac event rate was still lower in Japan at 3.1% per year than in the USA and Europe, even in patients with high SSS. This was not only due to the criteria used to select the patients and definition of cardiac events, but also to differences in composite factors including lifestyle and ethnicity. Differences in the intensive medical care system and indications for percutaneous coronary intervention (PCI) and coronary artery bypass surgery might also be associated. Nevertheless, the dependence on SSS severity category and LV function was similar, and the role of risk stratification by MPI was confirmed.[8–11] The incidence of major cardiac events was >5-fold higher in patients with EF <45% than in those with EF ≥45% (16.55% vs. 2.94% per 3 years, P<0.001). The event rate was also higher in patients with LV dilation according to the EDV and ESV. Multivariate analysis with the Cox proportional hazard model indicated that age, diabetes, ESV, EF and SSS were major predictors of cardiac events (Table 2). We also analyzed total events including death from non-cardiac causes, unstable angina, newly diagnosed angina pectoris, HF, PCI and coronary bypass grafting in addition to the hard events of cardiac death and nonfatal MI.[12] Significant predictors were then age, diabetes, prior revascularization, SDS and EF for total events.

The incidence of major events was generally lower in Japan compared with the USA and some European countries. Among all events, death and nonfatal MI occurred in half of the patients, and the proportion with severe HF was generally high. This was partly due to the exclusion of patients who were treated by revascularization within 60 days, baseline differences in patients' background risks, and variations in medical management of CAD under the Japanese healthcare system.

Normal SPECT and Low Pretest Likelihood

That the prognosis of individuals with a normal MPI is good has reached consensus in the USA and some European coun-

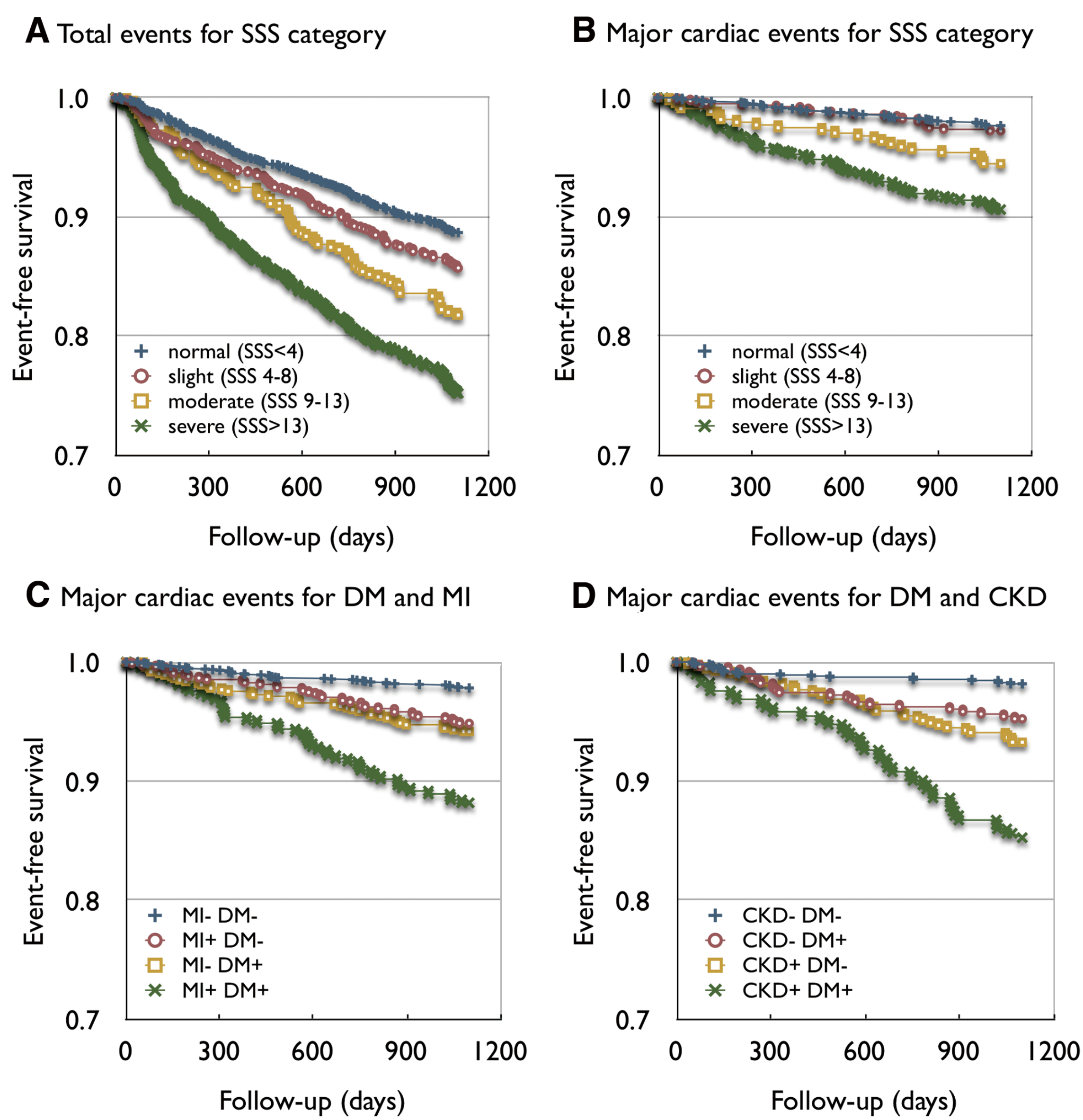

Figure 1. Kaplan-Meier curves. Total events (**A**), major cardiac events based on SSS categories (**B**), diabetes and history of myocardial infarction (**C**), and diabetes and chronic kidney disease (CKD) (**D**). (Adapted from references 7 & 39 with permission.) DM, diabetes mellitus; MI, myocardial infarction; SSS, summed stress score.

tries, and the negative predictive value for cardiac events is generally high,[13,14] which was also confirmed in Japan. The rates of annual major cardiac events was 0.81% and 0.63% per year in patients with a normal SSS (≤3) and in those with the more strict criteria of SSS ≤3, normal EF and normal ESV, respectively.[15,16] The rates of the hard events of cardiac death and nonfatal MI were 0.55% and 0.52%, respectively, in patients classified according to both types of criteria. These findings were confirmed from a study of the pretest likelihood of developing CAD.[17] The pretest likelihood of CAD was determined by age, sex and type of chest pain. The incidence of event rates in patients with SSS >3 and SSS ≤3 in the low-risk group did not differ among patients at low (<15%), intermediate (15–85%) and high (>85%) risk;[18] however, the incidence of cardiac event rates was significantly higher among patients at intermediate or high risk within the group with SSS >3 than ≤3. These findings showed that risk stratification is more meaningful for patients at intermediate to high risk for CAD. A recent study found that normal findings of SPECT MPI using only exercise or pharmacological stress testing indicate an excellent short-term prognosis.[14] Although stress testing alone has not been widely applied in Japan, it might be an option when considering the low incidence of serious outcomes in low-risk patients.

Exercise Tolerance and ECG Changes

Exercise tolerance and ECG changes during stress testing can estimate the severity of ischemic heart disease. The 3-year major event rates in patients with SSS <4 who achieved target

Table 2. Multivariate Cox Proportional Analyses in J-ACCESS Study

	HR	P value
Total events		
Age	1.031	<0.0001
SDS	1.071	<0.0001
EF	0.969	<0.0001
Diabetes	1.315	0.0331
History of revascularization	1.582	0.0002
Major events		
Age	1.056	<0.0001
SSS	1.222	0.0081
EF	0.981	0.0378
ESV	1.009	<0.0001
Diabetes	2.242	<0.0001
Hard events		
Age	1.052	<0.0001
EF	0.972	0.0171
ESV	1.008	0.0176
Diabetes	2.085	0.0008

See Table 1 for definitions of major and hard events.
J-ACCESS, Japanese-Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT; HR, hazard ratio; SDS, summed difference score; EF, ejection fraction; SSS, summed stress score; ESV, end-systolic volume.

heart rates or not were 1.4% and 2.4%, respectively, compared with 4.0% and 5.4%, respectively, in those with SSS ≥4.[19] The absolute peak exercise capacity in a treadmill test of 6,213 consecutive men was a powerful predictor of the risk of death.[20] Similarly, patients with positive ischemic ECG changes and reversible perfusion abnormalities had higher rates of hard and major events.[21] Thus, subsidiary information collected during stress studies is of additional prognostic value.

Additive Value of SPECT for Patients Who Undergo Coronary Angiography (CAG)

Patients who undergo CAG have potentially higher risks for cardiac events and the role of MPI should be investigated. As supposed from the clinical courses of multivessel disease, the number of stenotic arteries is a significant predictor of events.[22] Univariate analysis of patients with CAG showed that the number of stenotic vessels determined by CAG (>75%), SSS, SDS, EDV, ESV, EF and presence of diabetes were significant predictors (**Figure 2A**). However, multivariate Cox regression analysis revealed only ESV and SDS as significant variables. ESV was a particularly powerful prognostic marker of major cardiac events because the major events included severe HF. The event rate irrespective of the presence of ischemia was low among patients with none or 1-vessel disease. Ischemia and LV dysfunction were predictors of cardiac events among patients with multivessel disease, but the event rate was relatively low among those without ischemia and with good LV function. An additive value of LV functional parameters using both stress- and rest-gated MPI were also confirmed to evaluate post-ischemic stunning, which was a marker of poor prognosis.[23]

Early Revascularization and Prognosis

Hachamovitch et al found that >10% of ischemia in the myocardium is an indication for more aggressive treatment with PCI.[24] The J-ACCESS study included 375 patients who had undergone early revascularization within 60 days. Cardiac event rates relative to the amount of ischemic myocardium were compared after matching propensity scores between patients with and without early revascularization (n=316 per group).[25] The cardiac event rates among patients with ≤5%, 6–10% and >10% ischemic myocardium who underwent early revascularization were 8.0%, 3.0% and 0%, respectively, compared with rates of 4.5%, 6.1%, and 12.3%, respectively, among those who did not. The cardiac event rates increased among patients without revascularization with increasing ischemia. In contrast, the event rates were lower in those who were referred for early revascularization, particularly among those with >10% ischemia (P=0.0062). These findings were comparable to those of another Japanese (J-SAP) study of the outcomes of patients with stable low-risk CAD who underwent medical-preceding and PCI-preceding therapies.[26] The study found overall rates of cardiac death and acute coronary syndrome (ACS) were 2.1% in medical group and 4.7% in PCI group, respectively (P=NS).[26] The prospective COURAGE trial also demonstrated a persistent prognostic benefit of revascularization in patients with an ischemic myocardium that improved by >5%.[27]

Risk for Severe HF

Identification of patients at high risk for severe HF before LV function worsens is very important. The proportion of HF in major hard events was generally large in this J-ACCESS series. Follow-up of patients who developed HF in the first year showed that 9 of 41 (22.0%) died of cardiac death within the next 3 years.[12] It is known that reversible myocardial ischemia is an important predictor of ACS, but not of HF. The J-ACCESS subanalysis of refractory HF proved that abnormal myocardial perfusion, the ESV index and chronic kidney disease (CKD) stage ≥4 are independent predictors and have additive prognostic significance (**Figure 2B**).[28]

Asymptomatic Type 2 Diabetes Mellitus and Cardiac Events

The J-ACCESS study showed that diabetes mellitus is one of the most important predictors among various clinical backgrounds. The 3-year major event rates between nondiabetic patients with, and diabetic patients without prior MI were notably comparable at 5.06% and 5.73%, respectively (**Figure 1C**).[7] These results were similar to those of a Finnish study indicating that diabetes imposed a similar risk to prior MI.[29] In addition, combining SSS with these backgrounds provided better risk stratification.

Based on the J-ACCESS findings, the J-ACCESS 2 study that involved 513 patients with asymptomatic type 2 diabetes was started in 2004.[30] The inclusion criteria included patients with either a maximal carotid artery intima–media thickness ≥1.1 mm on ultrasonography or a urinary albumin excretion rate ≥30 mg/g creatinine, or who satisfied at least 2 of the following 4 criteria: abdominal obesity (body mass index ≥25 and waist circumference criteria), hypo-high-density lipoprotein-cholesterolemia, hypertriglyceridemia and hypertension. Although the patients had a high incidence of hypertension (82%) and dyslipidemia (80%), the average SSS was 2.7±4.3% and EF was 67±10%; that is, a low-risk profile for CAD (**Table 1**). Even in these patients, MPI indicated 17% of ischemia and 22% scarring (6% for both), and approximately

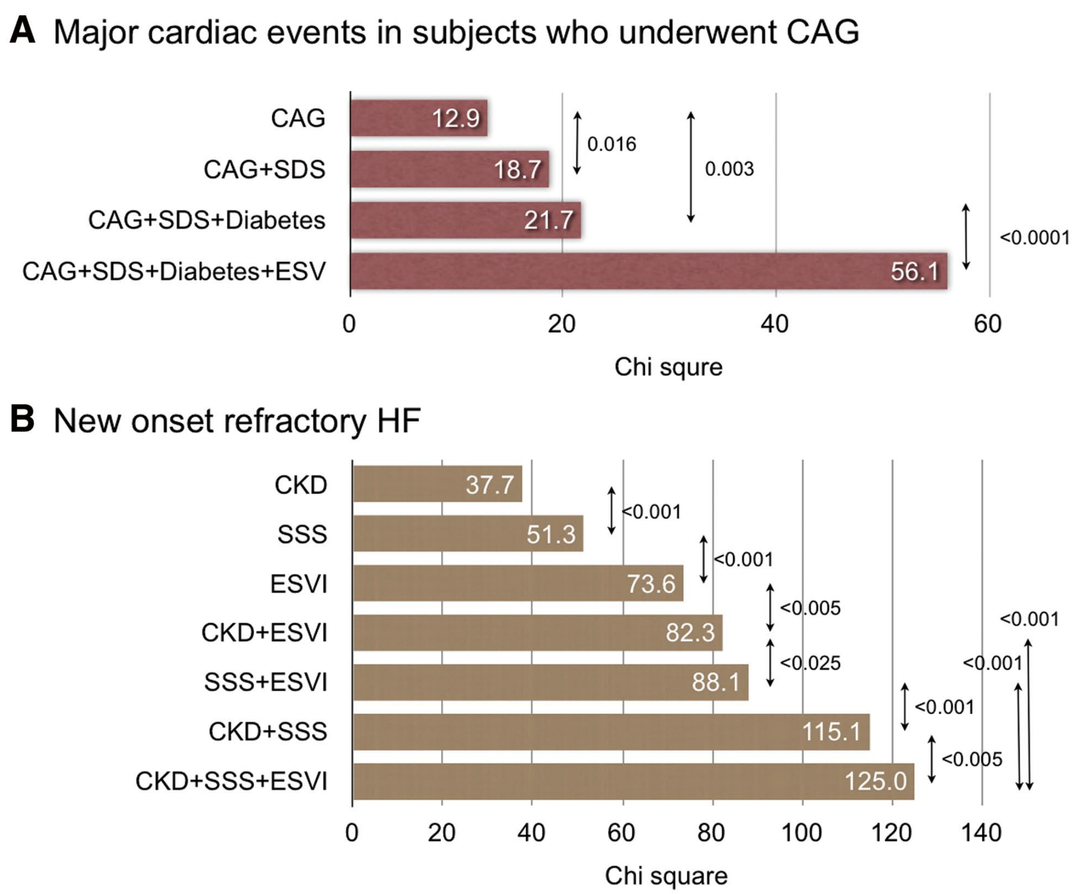

Figure 2. Statistical chi-square results of incremental prognostic values. Prediction of major cardiac events in patients after CAG (**A**) and in patients with new-onset refractory HF (**B**). (Adapted from references 12, 22 & 28 with permission.) CAG, coronary angiography; CKD, chronic kidney disease; ESV, end-systolic volume; ESVI, ESV index/m^2 body surface area; HF, heart failure; SDS, summed stress score; SSS, summed stress score.

one-third of them had some type of abnormality. Multivariate Cox regression analysis of the 3-year follow-up data showed that significant variables for predicting total events, including death, ACS and cerebrovascular events, were a high SSS (≥9), a low estimated glomerular filtration rate (eGFR) and being a current smoker.[31] Table 1 shows comparable total event rates between J-ACCESS and J-ACCESS 2, and a higher contribution of diabetes to cardiovascular events. The higher hard event rate in J-ACCESS 2 was partly due to the inclusion of ACS instead of nonfatal MI in addition to cardiac death. The DIAD study involving asymptomatic diabetes did not find a significant role of MPI screening and the annual hard event rate was only 0.6%.[32,33] However, the event rate was definitely higher among patients with MPI abnormalities. General screening for asymptomatic diabetic patients were hence not indicated, but recruiting potentially higher risk patients was considered essential for the effective use of MPI. Multiple risk factors increased the risk for cardiac events among patients with metabolic syndrome, and diabetic patients requiring combined oral and insulin therapy carried a higher risk.[34] The effect of medication significantly affected the outcome in J-ACCESS. Although the apparent incidence of dyslipidemia was lower in patients with than without cardiac events (47% vs. 56%, P=0.02), those with events were treated more frequently with insulin or digitalis, but less frequently with statins.[35] However, a European study involving consecutive diabetic patients, the IDIS prospective multicenter study, demonstrated that MPI provided a significantly enhanced prediction model for cardiac events compared with traditional risk factors and ECG stress test.[36] The diagnostic indications for MPI should be defined and amended.

CKD and Cardiac Events

Deteriorating renal function suggested by the eGFR and proteinuria is closely associated with the occurrence of cardiovascular events. The association with CAD is higher among patients with CKD, particularly those who require hemodialysis, and this could be a cause of hard events.[37,38] The J-ACCESS subanalysis found that complication with CKD estimated from the eGFR is a major predictor of cardiac events (Figure 1D).[39,40] These findings are compatible with those of Hakeem et al, who demonstrated that both MPI and CKD had incremental power for cardiac death prediction over baseline risk factors and LV dysfunction.[37] Although renal dysfunction caused by diabetes and other causes such as hypertensive nephrosclerosis could not be differentiated, complication with both diabetes and CKD apparently increased cardiac event rates. Accord-

Major cardiac event per 3 years

Age	EF	SSS<9, DM (-) eGFR ≥90	60-89	45-59	30-44	<30	SSS≥9, DM (-) ≥90	60-89	45-59	30-44	<30	SSS<9, DM (+) ≥90	60-89	45-59	30-44	<30	SSS≥9, DM (+) ≥90	60-89	45-59	30-44	<30
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

Relative risk versus age-matched control subjects

Age	EF	SSS<9, DM (-) eGFR ≥90	60-89	45-59	30-44	<30	SSS≥9, DM (-) ≥90	60-89	45-59	30-44	<30	SSS<9, DM (+) ≥90	60-89	45-59	30-44	<30	SSS≥9, DM (+) ≥90	60-89	45-59	30-44	<30
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

Figure 3. Heart risk table to predict major cardiac events in conjunction with diabetes and chronic kidney disease (CKD). (Section for 60–69-year-olds is cited from reference 44 with permission.) Major cardiac events for 3 years and relative risk values (folds) vs. age-matched control are shown. DM, diabetes mellitus; EF, ejection fraction (%); eGFR, estimated glomerular filtration rate ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$); SSS, summed stress score.

ing to the Japanese Society for Dialysis Therapy, the incidence of patients with end-stage renal disease starting chronic dialysis therapy has been >2,000 per million population since 2005, and populations in Japan have a higher prevalence of CKD than those in the USA.[41] Because eGFR is commonly determined in routine clinical practice together with urinalysis, early detection of high-risk populations and appropriate indications for MPI might potentially decrease the risk for serious cardiac events nationwide.

Software and Charts for Risk Estimation

Clinical application of the results of J-ACCESS study involves the creation of software for heart risk estimation (Heart Risk View) and a simplified risk chart (Heart Risk Table). Multivariate nominal logistic regression analyses have been based on the importance of SSS, EF or ESV derived from MPI and clinical factors.[42,43] The risk estimation formula was created from SSS, EF, age and the presence of diabetes, and then version 2 added the variable of eGFR.[44] The software and chart have been clinically applied in Japan, and post-test risk classification can be included as part of nuclear cardiology reporting. **Figure 3** is an extract from the risk charts of 60–69-year-olds with respect to EF and eGFR. The presence of diabetes and CKD independently increased the risk of major events by approximately 2-fold and having both increased the risk by 4-fold. As with the large-scale cohorts in the Framingham study in the USA, the findings of the Hisayama-cho and NIPPONDATA studies have been used to understand risk and create risk charts for Japanese.[45,46] Risk estimation using imaging modalities might also provide insight into therapeutic decision-making and prognostic evaluation.

Differences in Cardiac Event Risk Between North American and Japanese Populations

Although the risk for serious cardiovascular event seems lower in Japan than in the USA and Europe, strict comparisons among nations is not simple because many factors such as the backgrounds of the patients, clinical indications for imaging and medical care systems are considerably different. At a cholesterol level of around 5.45 mmol/L (210 mg/dl), coronary heart disease mortality rates vary from 4% to 5% in Japan and Mediterranean Southern Europe to approximately 15% in northern Europe.[47] Hachamovitch et al showed that among 5,183 consecutive patients included in their study, cardiac death and MI occurred at rates of 3.0% and 2.3% during 1991–1993.[8] The J-ACCESS study found a 3-year event rate of 1.41%, and a cardiac death/MI rate of 0.97% (0.47% and 0.32% per year, respectively) in consecutive patients during 2001.

Shaw et al created nomograms for CAD prognosis by classifying patients into low-, intermediate- and high-risk groups.[48] This type of estimation is useful for the clinical management of patients with suspected ischemic heart disease. For example, assuming a 65-year-old patient at intermediate risk with moderate ischemia (12%), no prior MI and EF 40%, the nomogram generated from exercise or adenosine studies would show a 2-year cardiac event rate of 25–35% whereas the Heart Risk Table (**Figure 3**) indicates that the major event rates for non-diabetics with eGFR values of 70 and 35 are 6% and

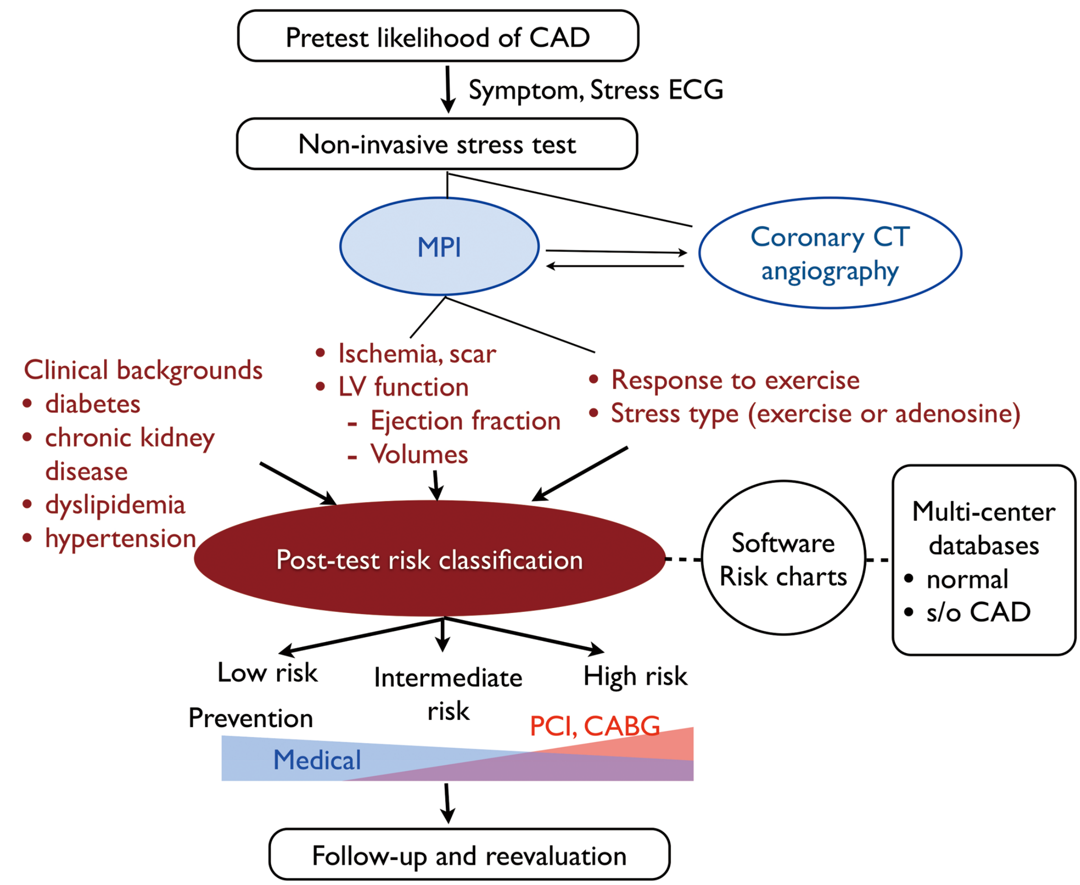

Figure 4. Prediction of cardiac events and risk stratification. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAG, coronary angiography; CT, computed tomography; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention.

10%, respectively and that diabetes increases these values to 12% and 19%, respectively. Considering that cardiac death and nonfatal MI account for approximately half of the major events, a range of 6–19% (major events) per 3 years corresponds to 2–6% (hard events) per 2 years. Although the comparison is a very rough approximation, the differences in hard event risk would be approximately 4–6-fold. Appropriate estimation is thus closely associated with the patients' backgrounds in various countries, and cannot be simply extrapolated even if the annual event rates are given under specific conditions.

Epidemiological Changes in Japan

Life expectancy according to the 2010 statistics of the Japan Ministry of Health, Labour and Welfare in the Japanese population is 79.64 and 86.39 years for men and women, respectively, whereas in the USA it was 75.4 and 80.4, respectively, during 2007 [http://www.mhlw.go.jp/toukei/saikin/hw/life/life10/index.html]. The reasons are multifactorial, but differences in lifestyles and nutrition might be related. Coronary heart disease mortality rates in post-war birth cohorts of Japanese men in Japan and Japanese-American men in Hawaii remain lower than among Caucasian men in the USA.[49] Although the "lag time" between exposure to risk factors and disease occurrence might be somewhat involved, nutritional and genetic differences such as enzymes might be associated with the development of atherosclerosis and the progress of coronary heart disease. The recent increase in diabetes and CKD are important issues in Japanese health care, as well as in many other developed countries. However, westernization of the Japanese lifestyle might influence future longevity trends.[50]

From Risk Stratification to Personalized Medicine

Although cardiovascular event risk as a whole population is important, individual patient outcomes are the result of complex factors, and hence personalized medical practice is required (Figure 4). Screening by MPI would generally not be recommended for individuals at low risk for CAD, because the event rate is usually <1%. However, MPI can be an important option if any one of diabetes, hypertension, dyslipidemia, a combination of risk factors, or a history of arteriosclerotic obliterans of the lower extremities, cerebrovascular accident and ischemic heart disease is identified. The use of coronary computed tomography angiography (CCTA) has rapidly spread in Japan, and it currently exceeds the number of MPI studies. Considering that the advantage of CCTA is high negative predictive values, the role of MPI and CCTA should be determined in further studies.[51–53] Noninvasive tests are generally indicated for patients at intermediate risk and MPI has been the most popular choice. The Japanese Society of Circulation has established guidelines for nuclear cardiology and a noninvasive diagnostic approach to CAD.[54,55] The latter guidelines recommend CCTA and MPI for patients at intermediate risk after estimating the pretest likelihood, and CCTA with the prerequisite of radiation reduction for women aged <50 years, without renal dysfunction determined by serum creatinine, eGFR and microalbuminuria, and without severe coronary calcification. The presence of inducible ischemia should be determined by stress MPI, which will be mainstream stress echocardiography or perfusion magnetic resonance imaging. Although the use of CCTA is increasing in clinical practice, particularly for low- or intermediate-risk patients in the next decade, CTTA and MPI are not simply competitive. To understand the different roles of CCTA and MPI in the decision-making process will become more important, from such viewpoints as anatomical stenosis vs. physiological ischemia, plaque characterization, and effective post-test risk stratification. Moreover, how the optimal therapeutic choice reduces actual event risks in high-risk patients should be investigated in conjunction with the estimation of the severity of risk and prognosis.

The primary purpose of J-ACCESS was to create databases with which to evaluate the incidence of cardiovascular events in Japanese clinical cardiology practice. The J-ACCESS 2 investigation focused on asymptomatic diabetes and J-ACCESS 3 is currently investigating patients with CKD.[56] The J-ACCESS investigation was the first step towards a risk-based approach to patients, and therefore how far nuclear cardiology contributes to reducing the incidence of cardiovascular events should be investigated in conjunction with designing optimal therapeutic strategies.

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