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Imaging

Prognostic Value of Normal Stress Myocardial Perfusion Imaging and Ventricular Function in Japanese Asymptomatic Patients With Type 2 Diabetes

– A Study Based on the J-ACCESS-2 Database –

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Background: This study was designed to determine the clinical risk for hard events after normal single-photon emission computed tomography (SPECT) and to identify the predictors of increased risk in asymptomatic patients with diabetes mellitus, based on a Japanese Assessment of Cardiac Events and Survival Studies by quantitative gated SPECT (J-ACCESS)-2 study.

Methods and Results: A total of 513 consecutive asymptomatic patients who underwent stress ^{99m}Tc-tetrofosmin SPECT in Japan were included in this study. Based on SPECT image and QGS data, 319 had a summed stress score ≤3, a summed difference score <2 and normal cardiac function (end-systolic volume ≤60 ml, males, ≤40 ml, females; left ventricular ejection fraction ≥49%, males, ≥50%, females). Myocardial perfusion was normal in 62% of this study population. During a 3-year follow-up, there were a total of 8 cardiac major events (2.5%): 2 cases of sudden death, 5 of acute coronary syndrome, and 1 of hospitalization because of congestive heart failure. The annual major event rate was 0.8%. Subjects undergoing coronary angiography had significantly more major events than those who did not among normal SPECT subjects (P=0.01). Kaplan-Meier analysis showed that the cardiac major events rate was very low, and subjects with normal SPECT can be considered as low risk among asymptomatic patients with diabetes.

Conclusions: An excellent prognosis was associated with a normal SPECT in asymptomatic patients with diabetes, so these patients can be exempted from further invasive procedure. (*Circ J* 2010; **74:** 1916–1921)

Key Words: Prognosis; Radionuclide imaging; SPECT

Patients with type 2 diabetes mellitus (DM) have a higher risk of cardiovascular events and death than those without the disease.[1–6] Coronary artery disease (CAD) in diabetic patients is frequently silent.[7–9] To maximize the effective treatment of cardiovascular disease in patients with DM, it is important to objectively identify CAD in asymptomatic subjects in a noninvasive way as early as possible.[4–6] Risk stratification is essential for the development of evidence-based strategies for improved patient care for those with DM.[5,6]

The evaluation of known or suspected CAD using ECG-gated myocardial perfusion single-photon emission computed tomography (SPECT) imaging has been established for diagnosis and risk assessment by many precedent studies.[10–14] The Japanese Assessment of Cardiac Events and Survival Studies by quantitative gated SPECT (J-ACCESS) is the first large-scale prognostic study using myocardial perfusion imaging (MPI) of an Asian population.[15–17] Cardiac event rates associated with normal or low-risk myocardial perfusion SPECT imaging with ^{99m}Tc-tetrofosmin have been shown.[17] Following the J-ACCESS study, J-ACCESS-2 began focusing on DM.[18] In general, patients with normal SPECT images have a lower risk of death and hard cardiac events, whereas in those with abnormal MPI, the mortality and hard cardiac

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event rates become significantly higher.[15,17,19] J-ACCESS-2 showed that an abnormal perfusion study indicated more cardiovascular events in asymptomatic diabetic patients.[19]

We hypothesized that a normal MPI study in diabetic patients would have prognostic value for predicting a low rate of cardiovascular events. Based on the database of the J-ACCESS-2, the present study was designed to assess clinical risk for major and all cardiovascular events in diabetic patients with normal SPECT images as a subanalysis of the J-ACCESS-2.

Methods

Participating Facilities and Patients

The J-ACCESS-2 prognostic registry was a prognostic cohort study involving 513 patients from 50 institutions.[18] The registration period was from June 2004 to September 2005. All institutions employed certified physicians for examination of DM, and the patients could participate in a 3-year follow-up after registration. The inclusion criteria were patients with type 2 diabetes, ≥50 years of age, who had either a maximal carotid artery intima–media thickness (max. IMT) ≥1.1 mm by ultrasonography or a urinary albumin excretion rate ≥30 mg/g creatinine, or patients who satisfied at least 2 of the following 4 conditions: abdominal obesity (body mass index ≥25 and waist circumference ≥85 cm for men, and ≥90 for women), hypo-high-density lipoprotein-cholesterolemia (<40 mg/dl); hypertriglyceridemia (≥150 mg/dl), and hypertension (blood pressure ≥130/85 mmHg). Exclusion criteria were patients with myocardial infarction (MI), unstable angina pectoris or effort angina. Also excluded were patients with hemoglobin A_{1c} ≥10% or evidence of nephropathy (serum creatinine ≥1.5 mg/dl) within 1 month before enrollment. Patients with valvular heart disease, idiopathic cardiomyopathy, severe arrhythmia (such as arterial fibrillation), or heart failure with class III or higher New York Heart Association (NYHA) functional classification, or arteriosclerosis obliterans were also excluded from the study. A total of 83% of the subjects were medically treated, and the remaining patients were controlled by diet, exercise, etc at the time of registration.

The study group consisted of 513 asymptomatic patients (males, 58%; mean age, 67±8 years) with DM (100%). The most frequent complication was hypertension (82%), followed by dyslipidemia (80%).

The following conditions were imposed upon facilities wishing to participate in the J-ACCESS study:[18] stress and rest myocardial perfusion SPECT using ^{99m}Tc-tetrofosmin and quantitative gated SPECT (QGS software, Cedars Sinai Medical Center, Los Angeles, CA, USA) analysis and follow-up surveys for 3 years after registration. The investigators were asked to comply with the Declaration of Helsinki, and their institutional review boards were asked to approve their participation in the study in principle, and to receive the written informed consent of all the patients to participate in the survey.[18]

SPECT Imaging

Stress ^{99m}Tc-tetrofosmin imaging was performed in each institution. A 1-day protocol was used in 94% of the institutions, and a 2-day protocol was used in the remainder. The protocol of the stress scans was the method routinely used at each facility; that is, the exercise equipment, or the pharmaceutical and their administration method to induce stress was not particularly regulated. Exercise, dipyridamole (0.15 mg·kg^{-1}·min^{-1}×4 min), adenosine (0.12 mg·kg^{-1}·min^{-1}×6 min) and adenosine triphosphate (0.16 mg·kg^{-1}·min^{-1}×5 min) were performed in 72%, 16, 6% and 6% of the institutions, respectively.

In patients who underwent sign- and symptom-limited exercise testing, heart rates were continuously monitored with 12-lead ECG. Patients were encouraged to reach 85% of the maximal age-predicted heart rate or more.

Patient Background Data

Age, sex, height, weight, subjective symptoms, history of present illness, medical history, risk factors, obesity and treatment before SPECT examination, including revascularization and medications, were surveyed.

Follow-up Survey

The occurrence and nature of cardiac events were investigated at 1, 2, and 3 years after registration.[18] All cardiac deaths and nonfatal acute coronary syndrome, as well as severe heart failure requiring hospitalization, were defined as major cardiovascular events. Total events further included percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), de novo stable angina, unstable angina, transient ischemic attack of the brain, stroke and arteriosclerosis obliterans. Among 513 subjects, 506 (98.6%) completed the 3 years of follow-up; 7 subjects were excluded because they were unable to be followed or were unwilling to cooperate.

SPECT Image Interpretation

Each hospital used the same semiquantitative scoring system for image interpretation. Each of the 20 segments was scored according to a 5-point scheme to provide a systematic and reproducible method of scan interpretation. The 20-segment scoring system used 3 short-axis slices (apical, mid, and basal) of the left ventricle, with the apex represented by 2 segments visualized on the midvertical long-axis image.[17,20,21] Each segment was scored as follows: 0=normal, 1=slight reduction of uptake, 2=moderate reduction of uptake, 3=severe reduction of uptake, and 4=absence of radiotracer uptake. For each stress image, the segmental scores were summed to derive the summed stress score (SSS). For this analysis, all patients had a low-risk SPECT scan that was defined as a normal SSS of ≤3.[17] The left ventricular ejection fraction (LVEF, %), end-diastolic volume (EDV, ml), and end-systolic volume (ESV, ml) were obtained from the QGS analysis.

Resting gated SPECT was quantitatively analyzed with QGS software at each institution. For data analysis, the QGS program was applied to process short-axis tomograms to determine LVEF and ESV, EDV.[17,20,21] The reproducibility of LVEF and volumes within each work station was validated,[22] even though the gated SPECT preferences varied. Manual adjustment was performed if automatic edge tracing was inappropriate. Normal limits for gated SPECT and QGS software were determined based on the J-ACCESS database.[17,20] For this study, we defined ESV in the normal range when it was ≥60 ml in males, or when it was ≥40 ml in females. We therefore defined gated SPECT images as normal when LVEF in males was ≥49%, or ≥55 in females.[17,20]

Data Analysis and Statistics

The mean, standard deviation (SD) was calculated in each group. Differences between clinical status and cardiac events were compared by chi-square test.

We used the Wilcoxon rank sum test to compare results

Table 1. Number of Subjects Who Met the Normal Criteria

	n
Total subjects	513
SSS<4	364
SDS<2	425
Normal ESV	500
Normal LVEF	491
Subjects who meet all criteria	319

Subjects who meet all criteria have SSS≤3, normal ESV, normal LVEF.
Normal criteria: ESV≤60 ml in males, ESV≤40 ml in females; LVEF≥49% in males, LVEF≥55% in females.
SSS, summed stress score; SDS, summed difference score; ESV, end-systolic volume; LVEF, left ventricular ejection fraction.

from patients with and without cardiac events and the chi-square test to categorical data. Descriptive statistics were calculated for each prognostic variable. Further estimation of risk was performed using Cox proportional hazard models to determine the independent predictors of cardiac events. The probability of survival was calculated with the Kaplan-Meier method. A P-value <0.05 was considered significant.

Results

Of the 513 registered patients in the J-ACCESS-2 study, 319 were defined as normal, and had a SSS ≤3, a summed difference score (SDS) <2, normal cardiac function (ESV ≤60%, males, ≤40%, females; LVEF ≥49%, males, ≥50%, females).

Table 2. Major Cardiovascular Events During 3-Year Follow-up

Major event	Cardiac death	Sudden death	ACS	HF
1st year	0	1	2	0
2nd year	0	1	3	0
3rd year	0	0	0	1

ACS, acute coronary syndrome; HF, heart failure.

Table 1 shows the number of subjects who met the criteria for normal. There were 425 subjects who showed a SDS <2. QGS functional data revealed 500 subjects were defined as normal based on criteria of ESV ≤60 ml in males and ESV ≤40 ml in females. In addition, 491 subjects were found to be normal based on the criterion of LVEF ≥49% in males and ≥55% in females. Myocardial perfusion was normal in 62% of this study population.

Definite ECG abnormalities were observed in 22 subjects, including right bundle-branch block (8), left ventricular hypertrophy (7), negative T wave (6), and ventricular premature complex (1).

Among 319 normal subjects, 248 performed exercise stress testing and of them 222 (90%) achieved the target heart rate.

Major Cardiovascular Events and All Events

Among the 319 subjects who met all the normal criteria in terms of major cardiovascular events, there were a total of 8 cardiac major events (2.5%) during the 3-year follow-up: 2 cases of sudden death, 5 of acute coronary syndrome, and 1 of hospitalization because of congestive heart failure.

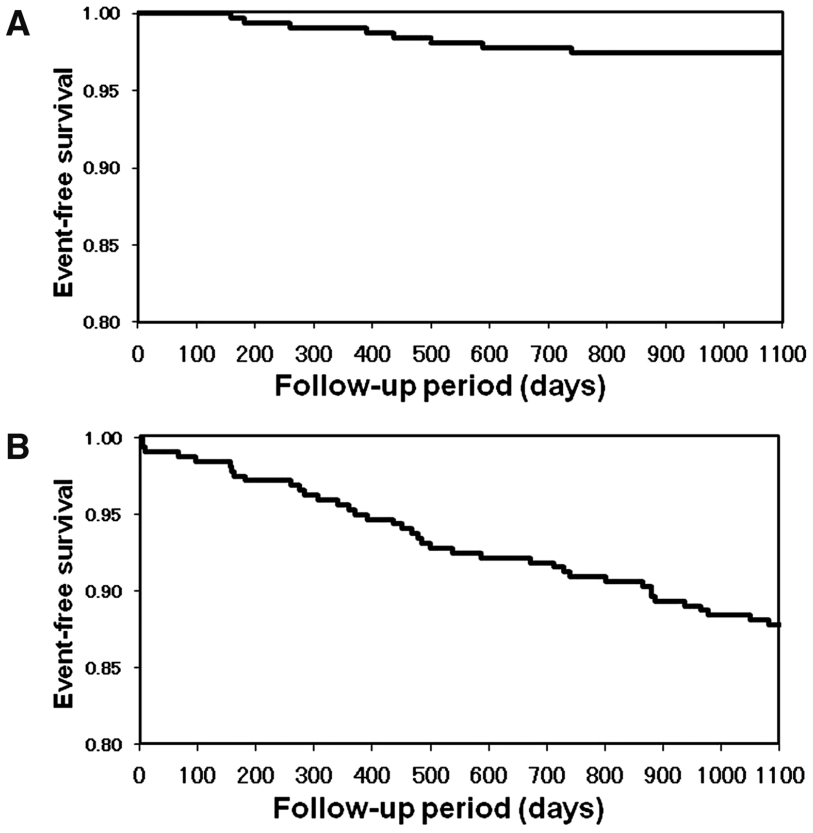

Figure. Kaplan-Meier survival curves for major cardiovascular events (**A**) and all events (**B**) after normal cardiac scintigraphy in patients with diabetes (n=319).

Table 3. Demographic Data According to Major Cardiovascular Events

	Cardiac event	No cardiac event	P value
n	8	311	
CAG	2 (25%)	8 (3%)	0.010
Hypertension	6 (75%)	265 (85%)	0.77
Dyslipidemia	7 (88%)	248 (80%)	0.94
Laboratory data			
HDL-C (mg/dl)	53.4±8.1	51.0±14.8	0.39
TG (mg/dl)	153.1±62.4	163.9±104.7	0.92
Creatinine (mg/dl)	0.89±0.19	0.77±0.24	0.15
ECG abnormalities			
Present	2 (25%)	58 (19%)	0.84
Absent	4 (50%)	214 (69%)	
Unknown	2 (25%)	39 (13%)	
Scintigraphic data			
SSS	0.50±1.1	0.48±0.9	0.94
LVEF (%)	69.8±5.3	69.7±8.9	0.81
EDV (ml)	64.3±15.2	69.8±19.4	0.43
ESV (ml)	19.0±6.8	22.1±10.6	0.43

CAG, coronary angiography; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; EDV, end-diastolic volume. Other abbreviations see in Table 1.

Table 4. Demographic Data According to All Events Rate

	Cardiac event	No cardiac event	P value
n	39	280	
CAG	3 (8%)	7 (3%)	0.21
Hypertension	35 (90%)	236 (84%)	0.51
Dyslipidemia	30 (77%)	225 (80%)	0.94
Laboratory data			
HDL-C (mg/dl)	51.9±12.5	51.0±14.9	0.49
TG (mg/dl)	158.1±83.5	164.3±106.4	0.81
Creatinine (mg/dl)	0.84±0.28	0.76±0.23	0.12
ECG abnormalities			
Present	11 (28%)	49 (18%)	0.078
Absent	20 (51%)	198 (71%)	
Unknown	8 (21%)	33 (12%)	
Scintigraphic data			
SSS	0.38±0.88	0.49±0.9	0.36
LVEF (%)	69.8±10.3	69.7±8.6	0.71
EDV (ml)	68.6±20.3	69.8±19.2	0.66
ESV (ml)	21.6±12.0	22.1±10.3	0.52

Abbreviations see in Tables 1,3.

Table 2 summarizes the types of major events that occurred during the 3-year follow-up. The major cardiovascular event rate during the follow-up period in patients with normal SSS, ESV and LVEF was 2.5%, and the major cardiovascular event rate during the 3-year follow up period in patients with only a normal SSS was 2.9%. There were no significant statistical differences in the cardiovascular event rate between normal SSS, and normal SSS, ESV and LVEF (P=NS). The annual major event rate in patients with normal SPECT who met all criteria was 0.8%. Subjects undergoing CAG had significantly more major events than those who did not (P=0.01).

Table 5. Variables for All Events Based on Cox Multivariate Analysis

	HR (95%CI)	P value
Age	1.041 (0.99–1.10)	0.12
Sex	0.86 (0.36–2.06)	0.74
Hypertension	2.64 (0.62–11.3)	0.19
Dyslipidemia	0.64 (0.28–1.47)	0.29
Abnormal ECG	1.78 (0.83–3.82)	0.14
SSS	0.99 (0.64–1.57)	0.96
LVEF	1.04 (0.93–1.17)	0.47
EDV	0.96 (0.91–1.03)	0.27
ESV	1.09 (0.92–1.29)	0.33

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,3.

There were 10 subjects who underwent CAG and 7 had positive ECG results on their examination. When the backgrounds of the patients who underwent CAG were studied, 9 out of 10 had hypertension (90%), and 9 of 10 had dyslipidemia (90%).

In total, 5 patients died of non-cardiac reasons, 2 underwent PCI, 6 had de novo stable angina, 1 had a transient ischemic attack of the brain, 11 had a stroke and 3 had arteriosclerosis obliterans.

In 248 patients with exercise stress, there were 6 in the major cardiovascular events group (2.4%) and 26 in the all events group (10.5%) during the 3-year follow-up. In 71 patients with pharmacological stress, there were 2 cases of major cardiovascular events (2.6%) and 13 of all events (16.9%) during the 3-year follow-up. There were no significant differences in major cardiovascular events between exercise and pharmacological stress test groups (P=NS).

Prognosis in Subjects With Normal SPECT

For the subjects with normal scintigraphic results among the patients with DM, Figure A shows the Kaplan-Meier analysis curves for major cardiovascular events, and Figure B shows the curves for all events. There were a total of 39 all events in the study population. This analysis showed that the cardiac major events rate is very low, and subjects with normal SPECT could be considered as low risk in this study group.

Relationship Between Clinical Status and Cardiac Events

The relationship between clinical status and major cardiac events is shown in Table 3. There were no statistical significant differences between subjects with and without major cardiac events. There were more significant major cardiac events in patients who underwent CAG than in those who did not (P=0.01). Table 4 shows the demographic data of the all events group.

The ability of the prognostic variables to predict all cardiac events was examined by multivariate Cox proportional hazard analysis. As indicated in Table 5, there was no independent predictor of all cardiac events in asymptomatic patients with DM.

Discussion

This study has demonstrated the low risk associated with normal MPI, even though patients with type 2 DM have a higher risk of cardiovascular events and death than those without

diabetes. Moreover, cardiac functional analysis by ECG-gated SPECT may enhance incremental prognostic information.[15]

A risk-based approach is essential in the management of diabetic patients with atherosclerosis.[23] Screening for CAD in diabetic patients using SPECT may be beneficial for determining the therapeutic strategy, because the symptoms in the majority of patients with DM are silent. Therefore, when we recognize clinical symptoms such as chest pain or dyspnea, the disease can be at an advanced stage. Microvascular and macrovascular complications occur at the onset of hyperglycemia during the initial diagnosis of DM. The incidence of silent MI in diabetic patients is reported to be higher than that in nondiabetic patients.[24] Physicians should use MPI more often to objectively evaluate silent myocardial ischemia in diabetes.[9] Risk stratification in asymptomatic diabetic patients could be achieved by nuclear cardiology testing.[19] Focusing on cardiovascular disease in diabetes, this J-ACCESS-2 study is the first large-scale prospective study of diabetic patients in Asia to evaluate the prognostic value of ECG-gated SPECT imaging.[18,19] Patients enrolled in this study were all asymptomatic with type 2 DM and no clinical evidence of CAD. To maximize the effective treatment of cardiovascular disease in patients with DM, it is important to identify CAD in asymptomatic patients as early as possible.[24–26]

A normal MPI result necessitates a watchful waiting approach to patient care.[17] We have shown that MPI was normal in 62% of this study population of asymptomatic diabetic patients. The finding of a low cardiovascular event risk in patients with normal SPECT has important clinical implications because these patients can be exempted from further invasive procedures.[27,28] When MPI and cardiac function are normal, a policy of proceeding directly to CAG exposes patients to higher risk of cardiac events.[29,30] Why did CAG seem to increase the incidence of major cardiovascular events in the diabetic patients in this study? The precise mechanism is unknown. The patients who underwent angiography might have include a higher number of those with vasospastic angina or advanced atherosclerosis. The increase in major cardiovascular events in the angiography group of patients may be related to selection bias, because there might be a clinical background of suspected CAD in patients who undergo CAG.

In several prior multicenter series and large observational studies, normal stress MPI was associated with an average annual cardiovascular event rate of 0.6–0.9%.[8,17,29] The risk for patients with DM was 2- to 4-fold higher than for nondiabetic patients and is comparable to the risk for patients with a prior MI.[2,3,15] Therefore, the annualized hard event rate of 0.8% in this study population was as low as that of a study conducted in the USA.[3] J-ACCESS-2 did not include patients with prior MI, CABG or PCI; however, J-ACCESS-1 includes these subjects. In spite of this difference in the patients' backgrounds, the cardiac event rate for subjects in the J-ACCESS-2 study who had a normal SPECT was as low as that in J-ACCESS-1.[17] According to the results of this study, asymptomatic diabetic patients with normal MPI are low risk and would be good candidates for intensive risk factor modification using primary and secondary prevention guidelines.[12] The therapeutic focus is not on predicting which patient has anatomic CAD, but on identifying patients at risk for cardiac death or nonfatal MI.[30–32] Normal scintigraphy has to be defined as normal perfusion and normal cardiac function. In this study the cardiovascular event rate was low, even when it was combined with functional analysis. A previous report showed incremental prognostic information with quantitative gated SPECT in subjects with CAD.[15] The very low event rate in the asymptomatic patients in this study could not show the incremental prognostic value of functional analysis.

A watchful waiting approach in the management of patients with normal SPECT will result in cost efficiencies and substantial cost savings compared with a more aggressive, invasive diagnostic workup strategy that includes diagnostic cardiac catheterization.[33–35] For patients with normal SPECT images, no additional testing is required because of the projected benign course. This does not mean a long-term cardiac-event-free period, especially in diabetic patients, because studies of long-term outcome after a normal stress radionuclide study are scarce. These studies assume that patients would undergo no further testing after a normal SPECT study. Because of a greater frequency in atypical presentation, physicians should rely heavily on imaging results to guide their management decisions.[29,36–39] Our present results indicate that the use of stress myocardial SPECT imaging could be a key component of the evaluation of diabetic patients beyond an assessment of clinical features. Such a risk-based approach could result in cost reductions.[33–35]

It is generally accepted that patients with pharmacologically induced stress are more heavily diseased than patients with exercise-induced stress. The present study included both types of stress testing in diabetic patients at the early stage. There were no significant differences in major cardiovascular events between exercise and pharmacological testing in this study, because the event rate for both stress types was very low. On the other hand, an attenuated heart rate response to exercise might predict cardiovascular events.[40] Although most of the subjects in this study achieved the target heart rate, if a patient cannot achieve an adequate work load it should not be considered as a normal result.

Conclusion

For those DM patients undergoing stress SPECT, a low-risk ^{99m}Tc-tetrofosmin scan is associated with an annualized hard event rate of 0.8%. Results from J-ACCESS-2 provide further supportive evidence of the excellent prognosis associated with a normal SPECT scan and patients do not require further invasive therapy.

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