Prognostic Value of Gated Myocardial Perfusion Imaging for Asymptomatic Patients With Type 2 Diabetes

The J-ACCESS 2 investigation

YOSHIMITSU YAMASAKI, MD, PHD[1]
KENICHI NAKAJIMA, MD, PHD[2]
HIDEO KUSUOKA, MD, PHD[3]
TOHRU IZUMI, MD, PHD[4]
ATSUNORI KASHIWAGI, MD, PHD[5]
RYUZO KAWAMORI, MD, PHD[6]
KAZUAKI SHIMAMOTO, MD, PHD[7]
NOBUHIRO YAMADA, MD, PHD[8]
TSUNEHIKO NISHIMURA, MD, PHD[9]

OBJECTIVE — Individuals with type 2 diabetes are at high risk for cardiovascular events. We evaluated the prognostic value of gated myocardial perfusion single-photon computed tomography (SPECT) for asymptomatic diabetic patients in a Japanese population.

RESEARCH DESIGN AND METHODS — Asymptomatic patients (n = 485) aged ≥50 years with either a maximal carotid artery intima-media thickness of ≥1.1 mm, or a urinary albumin ≥30 mg/g creatinine or who had at least two of the following, abdominal obesity, low HDL cholesterol, high triglyceride levels, and hypertension, were enrolled at 50 institutions. The patients were evaluated using gated SPECT with the stress-rest protocol and followed up for 3 years.

RESULTS — During the follow-up period, 62 (13%) events occurred, including 5 cardiac deaths and 57 cardiovascular events. Patients with summed stress scores (SSS) of ≥9 had a significantly higher incidence (of either death or cardiovascular events) than those with SSS scores of <9 (23 vs. 12%; P = 0.009). Multivariate Cox regression analysis showed that significant variables were SSS ≥9, a low estimated glomerular filtration rate, and being a current smoker. Univariate Cox regression analysis showed that ticlopidine and insulin use are potent medical modulators of cardiovascular events.

CONCLUSIONS — The incidences of cardiovascular events and death were significantly high in a select population of type 2 diabetic patients with SPECT abnormalities. A targeted treatment strategy is required for asymptomatic but potentially high-risk patients with type 2 diabetes.

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Coronary stenosis, myocardial ischemia, and baseline cardiac functions are important factors for the risk stratification of cardiac events and thus are used to predict patient prognosis. Among various clinical factors, diabetes promotes atherosclerosis, resulting in a major pathophysiological cause of cerebral and myocardial infarction (MI) (1). The risk for diabetic patients without prior MI is two- to fourfold higher than that for nondiabetic patients, and it is comparable with the risk for nondiabetic patients with prior MI (2,3). However, because atherosclerosis can progress even in asymptomatic diabetic patients, diagnosing ischemic heart diseases at an early subclinical stage is vital (4).

The role of single-photon emission computed tomography (SPECT) in detecting myocardial ischemia and evaluating prognosis has been validated (1,5–7). A prognostic investigation using gated SPECT (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT [J-ACCESS]) in a Japanese population was started in 2001, and the patients were followed up for 3 years (3). That study revealed that diabetes is the most important predictor of cardiac events in the Japanese population, as has been shown in the Finnish population (2). Therefore, we designed the J-ACCESS 2 prospective cohort study of asymptomatic patients with type 2 diabetes (8). The 1st year interim report clarified the value of gated SPECT for individuals with type 2 diabetes (9). The present final report evaluates the prognostic value of gated SPECT and includes a more detailed stratification of ischemic cardiovascular events in diabetic patients.

RESEARCH DESIGN AND METHODS

— The J-ACCESS 2 prognostic registry is a prognostic cohort study of 513 patients from 50 institutions (8) who were registered between June 2004 and September 2005. Certified physicians specializing in diabetes at all institutions participated in the 3-year follow-up. The inclusion criteria included age ≥50 years with type 2 diabetes and either a maximal carotid artery intima-media thickness (max IMT) of ≥1.1 mm (10) or a urinary albumin level of ≥30 mg/g creatinine (11) or at least two of the following, abdominal obesity (BMI ≥25 kg/m^2 and abdominal circumference ≥85 cm for men and ≥90 cm for women), hypo–HDL cholesterolemia (HDL cholesterol

From the [1]Department of Endocrinology and Metabolism, Osaka University, Suita, Japan; the [2]Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa, Japan; the [3]National Hospital Organization Osaka National Hospital, Osaka, Japan; the [4]Department of Cardiology and Internal Medicine, Kitasato University, Sagamihara, Japan; the [5]Department of Medicine, Shiga University of Medical Science, Ohtsu, Japan; the [6]Department of Medicine, Metabolism and Endocrinology, School of Medicine, Juntendo University, Tokyo, Japan; the [7]Second Department of Internal Medicine, Sapporo Medical University, School of Medicine, Sapporo, Japan; the [8]Division of Metabolism and Endocrinology, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; and the [9]Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan.
Corresponding author: Yoshimitsu Yamasaki, yamasaki@medone.med.osaka-u.ac.jp.
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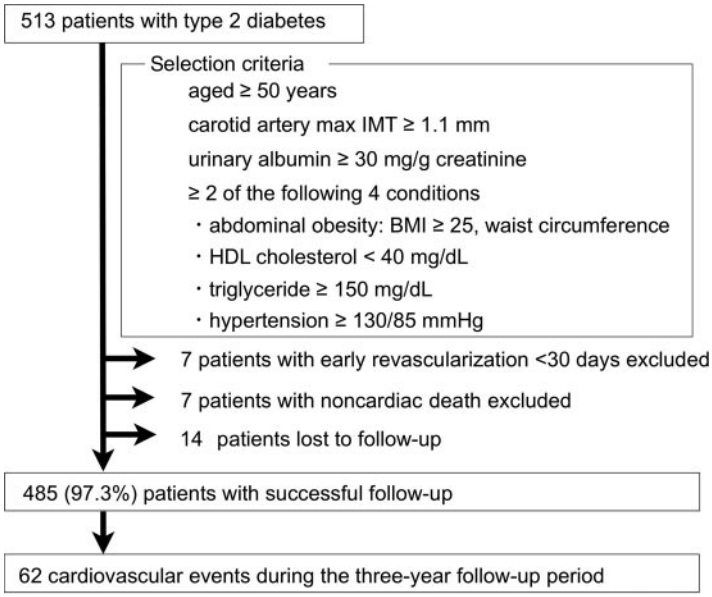

Figure 1—*Study design of J-ACCESS 2 and patient registry.*

level >40 mg/dl), hypertriglyceridemia (triglyceride level ≥150 mg/dl), and hypertension (blood pressure ≥130/85 mmHg). The abdominal circumference criteria conformed to Japanese guidelines. Exclusion criteria comprised MI, effort angina, and unstable angina. Patients with A1C ≥10% within 1 month before enrollment or evidence of nephropathy (serum creatinine measurement ≥1.5 mg/dl within 1 month before enrollment) were excluded. Also excluded were those with valvular disease, idiopathic cardiomyopathy, evidence of abnormalities on rest electrocardiography (ECG) such as atrial fibrillation, NYHA (New York Heart Association) class III or IV heart failure at the time of myocardial perfusion SPECT, and peripheral arterial disease (Fig. 1). Estimated glomerular filtration rates (eGFRs) were calculated according to the equation proposed by Cockcroft and Gault (12). On the basis of these criteria, we selected patients who were asymptomatic in terms of ischemic heart disease but who had potential event risks from diabetes complications.

The institutional review board of each hospital approved the study, which complied with the Ethical Guidelines for Epidemiological Research in Japan. Written informed consent was obtained from all participants before starting the study.

Myocardial perfusion imaging

Stress-rest myocardial perfusion SPECT images were obtained using the 1-day technetium-99m–tetrofosmin protocol at 94% of the institutions and the 2-day protocol at the remainder. Exercise, dipyridamole, adenosine, and adenosine-triphosphate stress tests were performed in 71 15, 7, and 6% of the patients, respectively. The administered dose of technetium-99m–tetrofosmin was 200–400 MBq (average 331 MBq) for the first study and 700–800 MBq (748 MBq) for the second. The gated study proceeded on patients at rest. Standard SPECT image acquisition protocols used 64 × 64 matrices over 360° or 180° rotations.

Quantitative gated SPECT

Myocardial perfusion images of short-axis, vertical long-axis, and horizontal long-axis images were generated using prefiltering (mainly Butterworth) and ramp filters. All SPECT images were interpreted by experienced physicians using a 20-segment model, as in the J-ACCESS study (3). The results of the segmentation were comparable with estimations based on the 17-segment model (13). Each of the myocardial segments was visually scored using a 5-point system: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent. Totals were calculated as summed stress, rest, and difference scores (SSS, SRS, and SDS) as validated by precedent prognostic studies (7). The maximum score was 80 points (20 segments × 4 points/segment). Risk-based grouping was based on two SSS severity categories: <9 (normal or mildly abnormal) and ≥9 (moderately or severely abnormal) as categorized in the J-ACCESS study (3).

Quantitative gated SPECT proceeded as described (3,14). SPECT slices were reconstructed using the standard software provided by the manufacturer. Gated SPECT images were analyzed at each institution using QGS software (Cedars-Sinai Medical Center, Los Angeles, CA) with automated processing. Inappropriate edge tracing was manually adjusted. Values for left ventricular ejection fraction (LVEF, %), end-diastolic volume (EDV, ml), and end-systolic volume (ESV, ml) were obtained.

Follow-up survey

Cardiovascular events were investigated at 1, 2, and 3 years after registration, and the present final prognostic analysis was based on 3-year follow-up data from 485 of the 513 patients because 7 who underwent revascularization within 30 days of registration, 7 who died because of noncardiac causes, and 14 who did not attend the hospital were excluded. The end point of the follow-up was hard events defined as sudden or cardiac death and acute coronary syndrome. Total events additionally included severe heart failure requiring hospitalization, percutaneous coronary intervention, coronary artery bypass grafting, de novo stable angina, unstable angina, nonsevere heart failure, transient ischemic attack of the brain, as well as stroke, and peripheral artery disease.

Statistics

Continuous variables are expressed as means ± SD. We applied the Wilcoxon rank sum test to compare results from patients with and without cardiovascular events and applied the χ^2 test to categorical data. The independent variables in the univariate Cox proportional hazard model included age, sex, cardiac risk factors (chest pain, BMI, hypertension, dyslipidemia, diabetes, history of smoking, family history of coronary artery disease, and ECG abnormalities), summed perfusion defect scores, quantitative gated SPECT parameters of ejection fraction (EF), and volumes. Medications before the follow-up were also included. The dependent variable was the occurrence of total events. The threshold value for events was an EF of 45% and male and female subject ESV values of 60 and 40 ml, respectively (13). The relative hazard ratios (HRs) and 95% CIs were calculated. The multivariate Cox pro-

Table 1—*Comparison of parameters between patients with and without events and low (<9) and high (≥9) SSS*

	Total	SSS < 9	SSS ≥ 9	*P*	Total events	No events	*P*
Age (years)	66.8 ± 7.7	66.9 ± 7.7	66.1 ± 7.8	0.428	68.8 ± 7.7	66.5 ± 7.7	0.050
Male sex	280/485 (57.7)	246/438 (56.2)	34/47 (72.3)	0.048	36/62 (59.4)	244/423 (57.7)	0.999
BMI (kg/m^2)	24.8 ± 3.6	24.8 ± 3.6	24.7 ± 3.6	0.845	24.3 ± 3.1	24.8 ± 3.7	0.465
Max IMT (mm)	1.6 ± 0.8	1.7 ± 0.8	1.5 ± 0.7	0.145	1.7 ± 0.6	1.6 ± 0.8	0.604
Complications							
Retinopathy	122/485 (25.2)	113/438 (25.8)	9/47 (19.1)	0.411	17/62 (27.5)	105/423 (24.8)	0.777
Neuropathy	95/485 (19.6)	82/438 (18.7)	13/47 (27.7)	0.203	11/62 (17.7)	84/423 (19.9)	0.825
Cerebrovascular accident	49/459 (10.7)	43/414 (10.4)	6/45 (13.3)	0.724	9/58 (15.5)	40/401 (9.9)	0.293
Family history of CAD	27/397 (6.8)	24/358 (6.7)	3/39 (7.7)	0.999	3/48 (6.3)	24/349 (6.9)	1.000
Current smoking	85/458 (18.6)	77/415 (18.6)	8/43 (18.6)	1.000	16/55 (29.1)	69/403 (17.1)	0.050
Medication							
Sulfonylurea	218/485 (44.9)	199/438 (45.4)	19/47 (40.4)	0.616	26/62 (41.9)	192/423 (45.4)	0.708
α-glucosidase inhibitor	131/485 (27.0)	115/438(26.3)	16/47 (34.0)	0.332	14/62 (22.6)	117/423 (27.7)	0.491
Biguanide	89/485 (18.4)	76/438 (17.4)	13/47 (27.7)	0.124	9/62 (14.5)	80/423 (18.9)	0.510
Pioglitazone	41/485 (8.5)	38/438 (8.7)	3/47 (6.4)	0.794	2/62 (3.2)	39/423 (9.2)	0.180
Glinide	13/485 (2.7)	11/438 (2.5)	2/47 (4.3)	0.819	3/62 (4.8)	10/423 (2.4)	0.480
Insulin	145/485 (29.9)	127/438 (29.0)	18/47 (38.3)	0.248	29/69 (41.9)	119/423 (28.1)	0.039
ACE inhibitor	73/485 (15.1)	71/438 (16.2)	2/47 (4.3)	0.050	8/62 (12.9)	65/423 (15.4)	0.752
Angiotensin II receptor blocker	180/485 (37.1)	157/438 (35.8)	23/47 (48.9)	0.108	23/62 (37.1)	157/423 (37.1)	1.000
Calcium antagonist	207/485 (42.7)	189/438 (43.2)	18/47 (38.3)	0.628	31/62 (50.0)	176/423 (41.6)	0.267
Diuretic	42/485 (8.7)	35/438 (8.0)	7/47 (14.9)	0.185	6/62 (9.7)	36/423 (8.5)	0.950
α-blocker	25/485 (5.2)	24/438 (5.5)	1/47 (2.1)	0.521	4/62 (6.5)	21/423 (5.0)	0.852
β-blocker	36/485 (7.4)	33/438 (7.5)	3/47 (6.4)	0.999	3/62 (4.8)	33/423 (7.8)	0.568
Statin	169/485 (34.8)	157/438 (35.8)	12/47 (25.5)	0.212	15/62 (24.2)	154/423 (36.4)	0.080
Aspirin	102/485 (21.0)	86/438 (19.6)	16/47 (34.0)	0.034	18/62 (29.0)	84/423 (19.9)	0.137
Ticlopidine	21/485 (4.3)	18/438 (4.1)	3/47 (6.4)	0.726	7/62 (11.3)	14/423 (3.3)	0.011
Biochemical data							
Total cholesterol (mg/dl)	200.1 ± 34.7	199.6 ± 34.8	204.4 ± 33.4	0.324	208.9 ± 28.8	198.8 ± 35.3	0.020
LDL cholesterol (mg/dl)	117.5 ± 31.2	116.7 ± 31.1	126.5 ± 30.6	0.133	125.1 ± 26.6	116.6 ± 31.6	0.083
HDL cholesterol (mg/dl)	51.1 ± 14.7	51.2 ± 14.8	50.0 ± 13.4	0.643	51.6 ± 14.3	51.0 ± 14.7	0.672
Triglycerides (mg/dl)	168.6 ± 114.8	169.3 ± 117.9	162.5 ± 82.3	0.988	176.1 ± 117.2	167.6 ± 114.6	0.974
Fasting blood glucose (mg/dl)	157.9 ± 54.7	157.3 ± 54.6	164.1 ± 56.7	0.218	171.4 ± 65.4	155.9 ± 52.8	0.065
A1C (%)	7.5 ± 1.2	7.5 ± 1.2	7.5 ± 1.3	0.873	7.3 ± 1.0	7.5 ± 1.2	0.363
Blood urea nitrogen (mg/dl)	16.8 ± 5.1	16.7 ± 5.0	18.2 ± 5.2	0.032	18.7 ± 6.7	16.5 ± 4.7	0.065
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.3	0.173	0.8 ± 0.3	0.8 ± 0.2	0.356
Urinary albumin (mg/g Cre)	159.1 ± 408.0	154.7 ± 415.1	200.6 ± 337.5	0.017	201.7 ± 323.5	154.3 ± 416.8	0.140
Log[urinary albumin (mg/g Cre)]	3.9 ± 1.4	3.9 ± 1.4	4.5 ± 1.2	0.018	4.3 ± 1.5	3.9 ± 1.4	0.148
eGFR (ml/min)	82.3 ± 27.7	82.1 ± 27.6	84.5 ± 29.3	0.633	73.5 ± 22.8	83.6 ± 28.2	0.014
ECG							
ECG abnormality at rest	89/426 (20.9)	79/381 (20.7)	10/45 (22.2)	0.969	16/54 (29.6)	73/372 (19.6)	0.131
Ischemia on stress ECG	50/180 (27.8)	41/156 (26.3)	9/24 (37.5)	0.342	6/24 (25.0)	44/156 (28.2)	0.342
Wall motion abnormality	8/178 (4.5)	4/153 (2.6)	4/25 (16.0)	0.013	3/26 (11.5)	5/152 (3.3)	0.172
Nuclear studies							
EDV (ml)	73.6 ± 22.1	71.6 ± 19.9	92.1 ± 31.2	<0.001	73.6 ± 23.9	73.6 ± 21.8	0.839
ESV (ml)	25.2 ± 13.1	23.9 ± 11.7	37.7 ± 18.6	<0.001	26.9 ± 14.0	24.9 ± 13.0	0.429
LVEF (%)	67.4 ± 9.8	68.1 ± 9.5	60.4 ± 9.1	<0.001	64.8 ± 10.8	67.8 ± 9.6	0.090
SSS	2.8 ± 4.6	1.6 ± 2.3	14.1 ± 5.4	<0.001	3.6 ± 5.0	2.7 ± 4.5	0.364
SSS ≥9	47/485 (9.7)	—	—		11/62 (17.7)	36/423 (8.5)	0.039
SRS	2.1 ± 3.7	1.4 ± 2.3	9.3 ± 6.2	<0.001	2.4 ± 3.9	2.1 ± 3.7	0.875
SDS	0.7 ± 2.8	0.3 ± 1.5	4.8 ± 6.5	<0.001	1.2 ± 3.5	0.6 ± 2.7	0.202

Data are means ± SD or *n*/total (%). CAD, coronary artery disease.

portional model was applied using a forward stepwise method based on statistically significant independent variables excluding medication in the univariate Cox proportional hazards model. Two prognostic severity categories based on SSS values of <9 or ≥9 were included in the multivariate analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical background

Among the criteria for patient registry, IMT ≥1.1 mm and urinary albumin ≥30

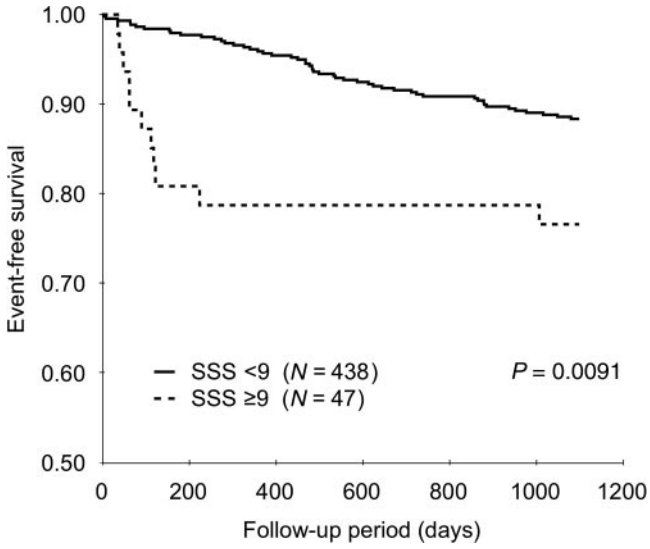

Figure 2—*Event-free survival in low (<9) and high (≥9) SSS groups.*

mg/g of creatinine were satisfied in 37 and 36% of the patients, respectively. The frequency of the other criteria was hypertension (blood pressure ≥130/85 mmHg or taking hypotensive drugs) in 81%, hypertriglyceridemia (triglyceride level ≥150 mg/dl, HDL cholesterol level <40 mg/dl, or taking hypolipidemic drugs) in 80%, and abdominal obesity in 21%. BMI was 24.8 ± 3.6 kg/m^2, and IMT was 1.6 ± 0.8 mm. With respect to other risk factors, 19% of patients were current smokers, and 7% had a family history of coronary artery disease. Rest ECG findings were atypical in 89 (21%) of 426 (88%) of the patients. Exercise ECG findings suggested myocardial ischemia in 50 (28%) of 180 (37% of the total) patients (Table 1).

Death and cardiovascular events during follow-up

Five patients died during the 3-year follow-up, three due to sudden death and two to cardiac death. 9 patients were diagnosed with nonfatal acute coronary syndrome, 3 developed heart failure requiring hospitalization, 10 were diagnosed with stable angina pectoris, and 3 were diagnosed with nonsevere heart failure. Cerebrovascular accidents and transient ischemic attacks occurred in 15 and 2 patients, respectively, and 6 patients were diagnosed with peripheral artery disease. Recurrent and initial percutaneous coronary intervention proceeded in one and six patients, respectively. Other cardiovascular accidents occurred in two patients.

Figure 2 shows Kaplan-Meier curves for event-free survival for cardiac events. At the end of follow-up, the event-free rates were 0.88 and 0.77 for the groups with low and high SSS, respectively (P = 0.009). The urinary excretion rate of albumin was higher in the high SSS group (P = 0.017). ECG revealed a higher incidence of segmental wall motion abnormalities (P = 0.013) and the myocardial perfusion defect scores of SRS and SDS were higher (both $P < 0.0001$) in the high SSS group. Both EDV and ESV were higher, whereas EF was lower in the high SSS group (all $P < 0.0001$; Table 1).

The following event summary is based on sudden or cardiac death and nonfatal cardiovascular events. Table 1 compares patients with and without events. Patients with events were older (P = 0.05) and had higher total cholesterol levels (P = 0.020). They also had a significantly lower eGFR (P = 0.014) and were frequently medicated with ticlopidine (P = 0.011) or insulin (P = 0.039). The results of nuclear studies did not significantly differ.

Univariate analysis showed that the significant variables for total events were age, current smoking, use of insulin or ticlopidine, high total cholesterol level, low eGFR, low LVEF, and SSS ≥9 (Table 2). Multivariate Cox regression analysis applied using these significant variables but excluding medication revealed that SSS ≥9 (HR 3.385 [95% CI 1.783–6.426]; P = 0.0002), eGFR (0.982 [0.971–0.992]; P = 0.0008), and current smoking (2.083 [1.194–3.632]; P = 0.0097) were independent predictors of cardiac events.

CONCLUSIONS — Coronary artery disease is a leading cause of death among Western and Japanese patients with diabetes. The prevalence of diabetes in the Japanese population is rapidly increasing as the lifestyle becomes more Westernized. Therefore, the cardiovascular event rate among asymptomatic diabetic Japanese patients is a matter of considerable concern.

The rate of cardiac deaths and cardiovascular events among patients with type 2 diabetes in the J-ACCESS 2 population during the 3-year follow-up was 13%. Scholte et al. (15) found a comparable rate of cardiovascular events in 6 (5%) of 120 patients during a follow-up period of 12 months, whereas the Detection of Ischemia in Asymptomatic Diabetics (DIAD)-2 study identified a 0.6% annual cardiovascular event rate among asymptomatic diabetic patients (16). The offsetting factors of healthier patients capable of exercise testing and more intensive therapy might have been associated with the rather low cardiac event rate in the DIAD-2 study. Asymptomatic patients were selected in the J-ACCESS 2 investigation from the viewpoint of coronary artery disease but with potential event risks included in the selection criteria. In addition, because the patients were indicated for myocardial perfusion imaging by a physician, patients with relatively higher risk might have been included.

The rate of cardiac deaths and cardiovascular events in the J-ACCESS 2 study was 2.7-fold higher than that of recent epidemiological surveys conducted by the Japanese Diabetes Society (17). The rate of cardiovascular events excluding noncardiac death and heart failure in the J-ACCESS 2 study of 56 events over a period of 3 years was also 2.3-fold higher than that (1.7% per annum) of the non-aspirin group in the more recent Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study of asymptomatic Japanese patients with type 2 diabetes (18). Furthermore, this high cardiovascular event rate was quite comparable with those of groups given intensive and standard treatment (22.1 and 22.4% over a period of 5 years, respectively) in the ADVANCE trial and with the findings of the ACCORD trial (19,20). The J-ACCESS study demonstrated remarkably low cardiovascular risk among Japanese, even among those with type 2 diabetes (3). Asymptomatic patients with type 2 diabetes were enrolled for the J-ACCESS 2 study, and we validated mark-

Table 2—*Univariate Cox regression model for all cardiovascular events*

	HR (95% CI)	*P*
Age	1.037 (1.003–1.073)	0.031
Male sex	0.984 (0.594–1.629)	0.950
BMI (kg/m^2)	0.960 (0.893–1.031)	0.263
Max IMT (mm)	1.008 (0.633–1.605)	0.973
Complications		
Retinopathy	1.061 (0.796–1.413)	0.688
Neuropathy	0.897 (0.467–1.720)	0.743
Cerebrovascular accident	1.612 (0.792–3.281)	0.188
Family history of CAD	0.901 (0.280–2.900)	0.862
Current smoking	1.850 (1.034–3.310)	0.038
Medications		
Sulfonylurea	0.880 (0.531–1.458)	0.620
α-glucosidase inhibitor	0.783 (0.432–1.421)	0.422
Biguanide	0.725 (0.358–1.469)	0.372
Pioglitazone	0.349 (0.086–1.429)	0.143
Glinide	2.152 (0.675–6.862)	0.195
Insulin	1.781 (1.075–2.949)	0.025
ACE inhibitor	0.819 (0.390–1.720)	0.598
Angiotensin II receptor blocker	1.012 (0.605–1.695)	0.963
Calcium antagonist	1.356 (0.824–2.231)	0.230
Diuretic	1.155 (0.497–2.679)	0.738
α-blocker	1.314 (0.477–3.617)	0.598
β-blocker	0.611 (0.192–1.949)	0.405
Statin	0.572 (0.320–1.023)	0.060
Aspirin	1.608 (0.929–2.782)	0.090
Ticlopidine	3.237 (1.474–7.108)	0.003
Biochemical data		
Total cholesterol (mg/dl)	1.007 (1.000–1.014)	0.041
LDL cholesterol (mg/dl)	1.008 (0.997–1.019)	0.152
HDL cholesterol (mg/dl)	1.002 (0.985–1.020)	0.794
Triglycerides (mg/dl)	1.000 (0.999–1.002)	0.634
Fasting blood glucose (mg/dl)	1.004 (1.000–1.008)	0.059
A1C (%)	0.877 (0.707–1.089)	0.234
Blood urea nitrogen (mg/dl)	1.064 (1.022–1.107)	0.002
Creatinine (mg/dl)	2.114 (0.773–5.784)	0.145
Urinary albumin (mg/g Cre)	1.000 (1.000–1.001)	0.534
Log[urinary albumin (mg/g Cre)]	1.223 (0.950–1.575)	0.119
eGFR (ml/min)	0.986 (0.975–0.996)	0.009
ECG		
ECG abnormality at rest	1.680 (0.937–3.014)	0.082
Ischemia on stress ECG	1.093 (0.729–1.638)	0.667
Wall motion abnormality	2.847 (0.855–9.487)	0.088
Nuclear studies		
SSS	1.036 (0.992–1.083)	0.114
SSS ≥ 9	2.322 (1.210–4.455)	0.011
SRS	1.020 (0.959–1.085)	0.530
SDS	1.060 (0.995–1.129)	0.073
LVEF at rest	0.971 (0.946–0.996)	0.023
EDV at rest	1.000 (0.989–1.012)	0.970
ESV at rest	1.010 (0.993–1.027)	0.263

CAD, coronary artery disease.

ers of high risk such as a max IMT of ≥1.1 mm (10), a urinary albumin level of >30 mg/g creatinine (11), and at least two of the four relevant conditions to ensure the registration of those with appropriate diagnostic yields. Considering the substantial difference in cardiovascular event rates between Western and Japanese diabetic patients, we consider that these conditions for enrolment into J-ACCESS 2 might have specifically selected diabetic patients at high risk for cardiovascular diseases.

The role of SPECT for detecting myocardial ischemia has been validated (5,6), and general consensus has also been reached regarding prognostic evaluation. Because the risk of cardiac death and MI increases with increasing degrees of scan abnormalities, the summed score is now widely accepted as described in the guidelines of the American Cardiology Society (7). The rate of sudden or cardiac deaths and cardiovascular events in the J-ACCESS 2 population with asymptomatic type 2 diabetes was 1.9-fold higher among individuals with high than with low SSS. The cardiac event rate (including hospitalization and sudden or cardiac death) was 1.9-fold higher among diabetic patients with than without myocardial ischemia evaluated by myocardial perfusion scintigraphy in the MERIDIAN (Multicentre Trial of Early Revascularisation In Patients with Diabetes Mellitus Type 2 and Mild Anginal Symptoms) trial (21).

To apply the multivariate model, the total numbers of patients and events were limited from the final analysis. We therefore used five variables with the smallest *P* values according to the univariate Cox proportional hazards model. Current smoking and a low eGFR, as well as a high SSS, were found to be independently associated with the increased rate of cardiovascular events in the present study. A large-scale community-based population study revealed an independent, graded association between a reduced eGFR and the risk of death and cardiovascular events (22). Irie et al. (23) also found in a 10-year prospective cohort study that individuals with a reduced eGFR had a 1.65- or 1.81-fold higher risk of cardiovascular diseases . Univariate Cox hazard analysis revealed a higher incidence of cardiovascular events among patients treated with insulin or ticlopidine at baseline. Further analyses on possible affection of baseline medication or additional medication on total events in the J-ACCESS 2 study might clarify the clinical meaning of these observations.

Limitations

Each patient was scored at one of the 50 participating institutions because collecting and evaluating all images at a core center was unfeasible. However, variability of SSS and SRS scores among these institutions was acceptable, and the pre-

cision of the quantitative gated SPECT parameters regarding EF and volumes was excellent (14).

The frequency of a high SSS was lower in the J-ACCESS 2 (10%) than in the J-ACCESS study (34%). The incidence of major cardiac events including sudden or cardiac death, acute coronary syndrome, and severe heart failure requiring hospitalization during a 3-year follow-up in J-ACCESS 2 was 3.5% (17 of 485), which is a little lower than that of diabetic patients without prior MI in the J-ACCESS study (5.7%). Ongoing analysis of the treatment modality might support the decreased rate of major cardiac events in J-ACCESS 2.

In conclusion, the cardiovascular event rate was high and comparable among asymptomatic Japanese and Western diabetic patients. Abnormal myocardial perfusion images might be prognostic for a further twofold higher risk of cardiovascular disease among asymptomatic diabetic patients with conventional cardiovascular risks such as dyslipidemia, hypertension, and abdominal obesity, as well as high carotid atherosclerosis or microalbuminuria. A reduced eGFR and current smoking were other independent predictors for identifying high-risk groups among asymptomatic diabetic patients. The present data indicate that myocardial ischemia would be useful for risk stratification of cardiovascular events in asymptomatic diabetic patients.

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