Cardiovascular events in Japanese asymptomatic patients with type 2 diabetes: A 1-year interim report of a J-ACCESS 2 investigation using myocardial perfusion imaging

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Abstract

Purpose. Diabetic patients have a high risk for cardiovascular events. The role of myocardial perfusion imaging was investigated in asymptomatic diabetic patients to evaluate short-term prognosis in a Japanese population.

Methods. A total of 506 asymptomatic patients ≥50 years of age who had carotid artery maximum intima-media thickness ≥1.1mm, urinary albumin excretion of ≥30mg/g creatinine, with additional criteria of abdominal obesity, low HDL cholesterol, high triglyceride level and hypertension were enrolled and followed up over a3-year period. Gated SPECT with stress-rest protocol was performed and analyzed by summed defect scores and QGS software. One-year cardiovascular events were analyzed.

Results. Myocardial ischemia was observed in 17% of patients, and abnormal perfusion findings of ischemia and/or scar were observed in 32% of patients. By the end of the one-year follow-up, 33 (6.5%) cardiovascular events occurred including 6 all-cause deaths. Patients with summed stress score (SSS) >8 had a higher incidence of either death or cardiovascular events. Event-free survival rates for SSS 0-3, 4-8, 9-13 and ≥14 were 0.96, 0.95, 0.82 and 0.76, respectively. Multivariate Cox regression analysis showed that significant variables were SSS, history of cerebrovascular accident and electrocardiographic abnormality at rest.

Conclusions. The one-year interim summary showed that cardiovascular events were significantly higher in patients with SPECT abnormality, although hard cardiac event rate was relatively low. Targeted treatment strategy is required for asymptomatic but potentially high-risk diabetic patients.

Introduction

For risk stratification of ischemic heart events, coronary stenosis, myocardial ischemia and baseline cardiac functions are important factors to predict patient prognosis. Various clinical conditions including metabolic syndrome have been investigated using myocardial perfusion imaging (MPI). [1] Among the clinical backgrounds, diabetes mellitus promotes atherosclerosis, resulting in one of the major pathophysiological causes of cerebral infarction and myocardial infarction. [2-4] The risk of patients with diabetes are two- to fourfold higher than non-diabetic patients and are comparable with those with prior myocardial infarction. [5, 6] Since atherosclerosis may progress even in asymptomatic diabetic patients, it is vital to diagnose ischemic heart diseases at an early subclinical stage. [7-9]

The role of MPI for detecting ischemia has been validated well and supported by many precedent single-photon emission computed tomography (SPECT) studies. [10-13] A general consensus has been achieved for detection of ischemia and prognostic evaluation. [3, 14] Although abundant data are available in Western countries, few data are available dealing with the role of MPI in Japanese non-diabetic and diabetic patients. In a Japanese prognostic cohort study using gated SPECT (J-ACCESS study), the hard event rate was relatively lower than that in Western prognostic studies. [6, 15] We therefore began the J-ACCESS 2 prospective cohort study with a three-year follow-up period that focused on asymptomatic patients with type 2 diabetes.

We hypothesized that gated MPI has prognostic values to predict cardiovascular events even in a short-term follow-up. The incidences of stress-induced ischemia and resting perfusion defect, as well as functional abnormalities by gated MPI, were summarized in asymptomatic patients with type 2 diabetes, and the prognostic value was investigated during a one-year follow-up period.

Methods

Patients

The J-ACCESS II prognostic registry was a prognostic cohort study involving 513 patients from 50 institutions. [16] The registration period was from June 2004 through September 2005. All institutions employed certified physicians for diabetes and could participate in a 3-year follow-up after registration. The inclusion criteria included patients with type 2 diabetes, ≥50 years of age, who either had a maximal carotid artery intima-media thickness (max IMT) ≥ 1.1 mm by ultrasonography or a urinary albumin excretion rate of ≥30 mg/g creatinine, or patients who satisfied at least two of the following four conditions: abdominal obesity (body mass index (BMI) ≥ 25 and waist circumference ≥85 cm for men, and ≥90 cm for women) hypo-HDL-cholesterolemia (<40 mg/dL); hypertriglyceridemia (≥150 mg/dL), and hypertension (blood pressure ≥ 130/85 mmHg) (Figure 1). The criteria of waist circumference were in accordance with Japanese guidelines. [17, 18] Exclusion criteria included patients with myocardial infarction, effort angina and unstable angina. Patients with HbA_{1c} ≥10% or evidence of nephropathy (serum cr.
eatinine ≥1.5 mg/dL) within 1 month before enrollment were excluded. Also excluded were patients with valvular heart disease, idiopathic cardiomyopathy, evidence of rest ECG abnormalities such as atrial fibrillation, New York Heart Association Class III or IV heart failure at the time of myocardial perfusion SPECT and arteriosclerosis obliterans. A total of 83% of patients were medically treated, and the remaining patients were controlled by diet, exercise, etc. at the time of registration.

Each hospital approved the study by the institutional review board, and the whole study was conducted in compliance with the Ethical Guidelines For Epidemiological Research in Japan. Written informed consent was obtained from all participants.

Myocardial perfusion imaging

Stress-rest MPI was performed with ^{99m}Tc-tetrofosmin. A 1-day protocol was used in 94% of the institutions, and a two-day protocol in the remaining institutions. Regarding the stress types, exercise, dipyridamole (0.15 ml/min/kg x 4 min), adenosine (0.12 ml/min/kg x 6 min) and adenosine triphosphate (0.16 ml/min/kg x 5 min) were performed in 72%, 16%, 6%

and 6% of the institutions, respectively. The average dose of ^{99m}Tc-tetrofosmin administered was 331 MBq for the initial study and 748 MBq for the second study. The exercise study was performed at 36±20 minutes after tetrofosmin injection, and the resting study was similarly performed at 47±20 minutes after injection. The interval between the stress and rest studies was 60-120 minutes. A gated study was performed at least at rest. SPECT imaging was performed with standard acquisition protocols with 360 or 180-degree rotations. Gating was performed by 16, 8, 12 and 32 frames per cardiac cycle in 44%, 40%, 12% and 4% of the institutions. According to the preceding J-ACCESS substudy in patients with low-likelihood of ischemic heart disease and no events, EF with the 16-frame study was significantly higher than that with the 8-frame study by 4% only in men.[19]

Myocardial segmentation and quantification

Myocardial perfusion images of short-axis, vertical long-axis and horizontal long-axis images were generated with a standard acquisition protocol, which was verified by J-ACCESS study. [6, 19, 20] All SPECT images were interpreted using a 20-segment model by experienced physicians. The use of 20-segment model was to compare results with the precedent J-ACCESS study, which showed good correlation with 17-segment model. [21] Each of the myocardial segments was visually scored using a 5-point scoring system: 0= normal, 1=mildly reduced, 2=moderately reduced, 3=severely reduced and 4=absent. Total scores in 20 segments were calculated as the sum of stress, rest and difference scores (SSS, SRS and SDS). Four SSS severity categories were used for risk-based groups of 0-3 (normal), 4-8 (mild), 9-13 (moderate) and ≥14 (severe).

Procedures for quantification of gated SPECT are described elsewhere [6, 20]. Gated SPECT was analyzed by QGS software (Cedars Sinai Medical Center, CA, USA) of each institution.[19] Manual adjustment was performed when automatic edge tracing was inappropriate. The left ventricular ejection fraction (LVEF, %), end-diastolic volume (EDV, mL), and end-systolic volume (ESV, mL) were obtained.

Follow-up survey

The cardiovascular events were investigated at 1, 2, and 3 years after the registration, and this interim report was based on the results of the one-year follow-up. Follow-up was completed in 100% of the patients by the end of one year. After excluding 7 patients who had early revascularization <30 days of registration, 506 patients were finally selected for prognostic analysis. Events of all-cause death and non-fatal acute coronary syndrome were defined as hard events. Total events further included the percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), *de novo* stable angina, unstable angina, severe heart failure requiring hospitalization, transient ischemic attack of the brain, stroke and arteriosclerosis obliterans.

Statistics

Continuous variables are expressed as mean ± standard deviation (SD). We applied the Wilcoxon rank sum test to compare results from patients with and without cardiac events, and the χ^2 test to categorical data. The differences in cardiovascular event rates among SSS severity groups were compared using Kaplan-Meier estimates. The independent variables in the univariate Cox proportional hazard model included age, gender, cardiac risk factors, summed scores, QGS parameters of EF and volumes. The relative hazard ratios, 95% confidence intervals and Wald χ^2 values were calculated. The multivariate Cox proportional model was applied using a forward stepwise method based on selected independent variables with the univariate Cox proportional hazard model. Statistical significance was defined as P < 0.05.

Results
Clinical backgrounds

Among the criteria for patient registry, the criteria of maximum IMT $\geq$1.1 mm and urinary albumin excretion rate of $\geq$30 mg/g of creatinine, were satisfied in 37% and 35 % of patients, respectively.

Table 1 shows patient characteristics in 506 subjects. Common risk factors were hypertension (82%) and dyslipidemia (80%). Regarding other risk factors, 17% and 26 % of patients had current and past smoking, respectively, and 6% had family history of CAD. BMI of $\geq$30 kg/m^2 was observed in 40 (8%) patients. Regarding medications, hypoglycemic drugs were most often used (83%). Coronary angiography was performed in 45 patients (9%). Coronary artery stenosis $\geq$75% was observed in 19 patients: single, double and triple-vessel diseases in 9, 8, and 2 patients, respectively.

SPECT findings of perfusion defects and ischemia

Myocardial ischemia without fixed defects (scarring) defined as SDS $\geq$2 and SRS<4 was observed in 54 patients (11%), and fixed perfusion defect without ischemia defined as SRS $\geq$4 and SDS <2 was observed in 80 patients (16%) (Figure 1). Fixed perfusion defect associated with ischemia defined as SRS $\geq$4 and SDS $\geq$2 was observed in 30 patients (6%). The remaining normal findings were observed in 342 patients (68%).   Stress-induced ischemia with and without scarring was observed in 84 patients (17%).

Death and cardiovascular events by the end of one year

During the one-year follow-up period, 6 patients died, including 2 from sudden death, 1 from severe heart failure and double-vessel disease, 2 from cancer and 1 from complication of pneumonia (Table 2). One of the cancer patients experienced stable angina and PCI before death. Two patients who showed EF <50% had severe heart failure; one died and the other had CABG.

Regarding non-fatal cardiovascular events, *de novo* stable angina pectoris was diagnosed in 11 patients, of whom 8 of them had PCI, and the remaining patients were medically treated. Either cerebrovascular accident or transient ischemia attack was observed in 7 patients. PCI was performed in 12, CABG in 1 and both PCI and CABG in 1.

The following events were summarized based on all-cause death and non-fatal cardiovascular events. Patients with and without events are compared in Table 3. Patients with events had a significantly higher incidence of ECG abnormality at rest (p=0.02) and significant coronary stenosis ($\geq$75%) in at least one vessel than those without events (24% vs. 2%, p=0.005). Regarding medication, in patients with events, medications for dyslipidemia were less frequent in the event group (p=0.03). Although EF and volumes did not differ significantly, patients with cardiac events showed higher SSS (p=0.005) and SDS (p=0.02). When patients with SSS $\leq$8 and >8 were compared, cardiac event rates were 5% for the low SSS group and 20% for the high SSS group (p=0.0002). The high SSS group showed a higher LDL cholesterol (p=0.03), a lower incidence of dyslipidemic medication (p=0.02), a higher blood urea nitrogen (p=0.04), a higher urinary albumin excretion rate (p=0.02) and a higher incidence of segmental wall motion abnormality (p=0.009). Myocardial perfusion defect scores of SRS and SDS were higher in the high SSS group (p<0.0001 for all). The higher EDV, higher ESV and lower EF were observed in the high SSS group (p<0.0001 for all).

The Kaplan-Meier curve for the event-free survival is shown in Figure 2. At the end of the 1-year follow-up, the event-free rate was 0.96, 0.95, 0.82 and 0.76 for the SSS group of 0-3, 4-8, 9-13 and 14 or more, respectively. Since the curves were divided into two groups of SSS $\leq$8 and >8 and differed significantly (p<0.0001), the following analysis was performed using two groups of high and low SSS values.

Univariate analysis showed that the significant variables were HDL cholesterol, blood urea nitrogen, creatinine, ECG abnormality at rest, significant coronary stenosis, SRS, SDS and SSS (Figure 3). When the multivariate Cox regression analysis was applied, SSS (>8 vs. $\leq$8, χ^2=16.9, p<0.0001), rest ECG abnormality (χ^2=6.1, p=0.013) and cerebrovascular accident (χ^2=5.7, p=0.017) were the independent predictor of cardiovascular events, but the HDL cholesterol was not selected as a significant predictor.

Discussion

In the J-ACCESS 2 population with asymptomatic type 2 diabetes, which was strictly defined by the selection criteria of carotid maximum IMT, microalbuminuria, abdominal obesity, dyslipidemia and hypertension, stress-induced ischemia was observed in 17% of patients. The cardiovascular event rate was four-fold higher in high-SSS patients (>8) than in low-SSS (≤8) patients. The total event rate was 33 of 506 (6.5%) including 6 deaths (1.2%). Patients with events had higher SSS and SDS, ECG abnormality at rest and significant coronary artery stenosis found by coronary angiography than those without.

Among patients with diabetes, CAD is a leading cause of death, as well as extensive deterioration of macrovascular and microvascular components of multiple organs. The prevalence of diabetes in the Japanese population, however, has been considered to be lower than that in Western population, but it is rapidly increasing with westernizing lifestyles, as revealed by recent epidemiological surveys of Hisayama and the Japanese Diabetes Society. [22-24] Therefore, by recognizing the differences in baseline lifestyles between Western and Japanese populations, the cardiovascular event rate in Japanese asymptomatic diabetic patients was of great concern.

The high prevalence of diabetes was also confirmed by the J-ACCESS study, which included 30% of diabetic patients by consecutive registration of 4629 patients. [6] The impact of diabetes was equivalent to that of prior myocardial infarction when the cardiac major cardiac event rate of cardiac death, non-fatal myocardial infarction and severe heart failure requiring hospitalization was analyzed. The finding in the Japanese population was in accordance with the study by Haffner et al. and also consistent with a statement "diabetes is a cardiovascular disease" by the American Heart Association. [5, 25]

A high incidence of abnormal scans has been noted in asymptomatic patients. Miller et al. found that abnormal scans were present in ~60% of asymptomatic diabetic patients, approximately equal to the percentage in symptomatic diabetic. [26] In addition, a DIAD study indicated silent myocardial ischemia occurred in as high as 22% of asymptomatic patients with type 2 diabetes. [27] In another European study involving 120 asymptomatic patients, 33% had an abnormal stress study, including myocardial perfusion abnormalities in 25% of patients. [28] The present J-ACCESS 2 study demonstrated a relatively lower incidence (17%) of induced ischemia. This was probably caused by the difference in criteria of patient entry, and partly due to baseline ethnic differences among America, European and Japanese populations.

The incidence of ischemia and cardiovascular events is thought to be influenced by the selection criteria. Screening all diabetic patients is not justified from a practical point of view. It is imperative to identify the best candidate for screening diabetic patients to obtain the high diagnostic yield from MPI. [29] In the DIAD study, careful exclusion criteria were used to avoid the possibility of ischemic heart diseases, namely to select truly asymptomatic patients. In the J-ACCESS 2 study, to register the patients with appropriate diagnostic yields, we decided to select the patients who had metabolic status of possible ischemia, although they had no chest symptom and evidence of CAD at the time of entry. The DIAD study patients showed a mean HbA_{1c} of 7.1±1.5%, LDL cholesterol of 113±32 mg/dL and 85% of either insulin or oral agent treatment, whereas the J-ACCESS II showed 7.5±1.2%, 118±31 mg/dL and 83%, respectively. Moreover, BMI was higher in the DIAD study (31±6 kg/m^2) than in the J-ACCESS 2 study (25±4 kg/m^2). Albuminuria of >30 mg/g creatinine was observed in 21% of the patients in the DIAD study, whereas in the J-ACCESS 2 study the average albuminuria was 175±505 mg/g.

J-ACCESS 2 study demonstrated that significant predictors of cardiovascular events were defect score during stress, rest ECG abnormality and cerebrovascular accidents by multivariate analysis. In contrast, Scholte et al. demonstrated that current smoking, duration of diabetes and the cholesterol/HDL ratio to predict an abnormal study. [28] During their one-year follow-up, 5% (6 of 120) had cardiac events. Although the predictors may differ between the studies, our study endpoint was cardiovascular events, not perfusion abnormality. Our study showed a comparable event rate of 6.5% (33 of 506) to this European study. In the J-ACCESS 2 population, LDL cholesterol differed between high and low SSS groups, but the event rates did not differ significantly between them. The event group, however, showed a tendency of lower HDL cholesterol (p=0.06). Smoking was not significant predictors for ischemia and cardiac events in this study and preceding J-ACCESS study with regards to major cardiac events and

total events. [6, 15]

The outcome of the diabetic patient with SPECT abnormality was worse than those without SPECT abnormality. A study of asymptomatic diabetic patients without known CAD demonstrated a 2.2% annual critical event rate of myocardial infarction and cardiac deaths. [30] Another study demonstrated that 8.6% of patients with diabetes had cardiac events (cardiac deaths and myocardial infarction) compared with 4.5% in the nondiabetic cohort. [12] The critical event rate seemed lower in our study as long as one-year interim results were observed. Even in our study, however, the incidence of sudden death, PCI, CABG, severe heart failure was in 3.6% of asymptomatic patients and cerebrovascular accident and transient ischemic attack in 1.4%. Interestingly, Wackers et al. found that majority of asymptomatic patients with type 2 diabetes demonstrated resolution of ischemia on repeat stress imaging after 3 years.[31] Therefore, appropriate or aggressive management of these patients would modify the outcome, and further follow-up has continued for three years in our study group.

Conclusion

When asymptomatic diabetic patients were followed up in a Japanese population, the incidence of cardiovascular events with SPECT abnormality was higher than that without SPECT abnormality even in the one-year interim summary. To avoid potential outcome of hard events in these patients, targeted efforts would be required for those who have clinical conditions of micro-albuminuria, increased carotid max IMT, dyslipidemia, hypertension and abdominal obesity.

Acknowledgment

Figure Legends

Figure 1
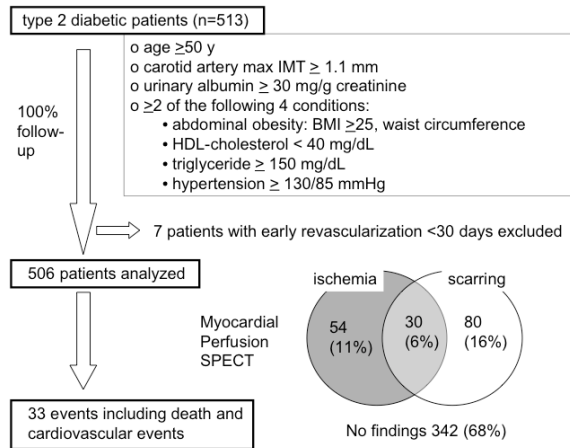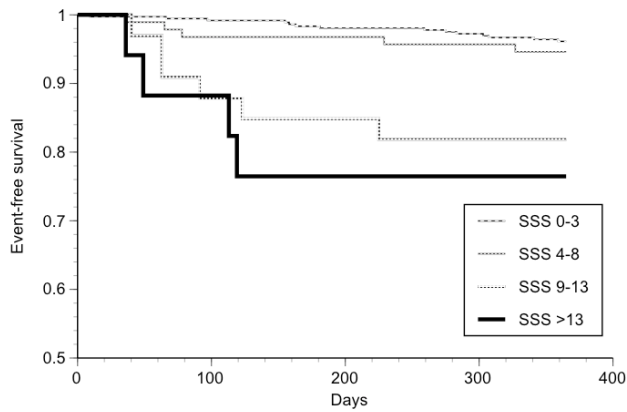Study design of J-ACCESS 2 and results of myocardial perfusion imaging

Figure 2
Event-free survival in 4 severity groups: SSS 0-3 (n=363), 4-8 (n=93), 9-13 (n=33) and >13 (n=17). A significant difference was observed between groups between SSS 0-8 and SSS ≥9 (p<0.0001).
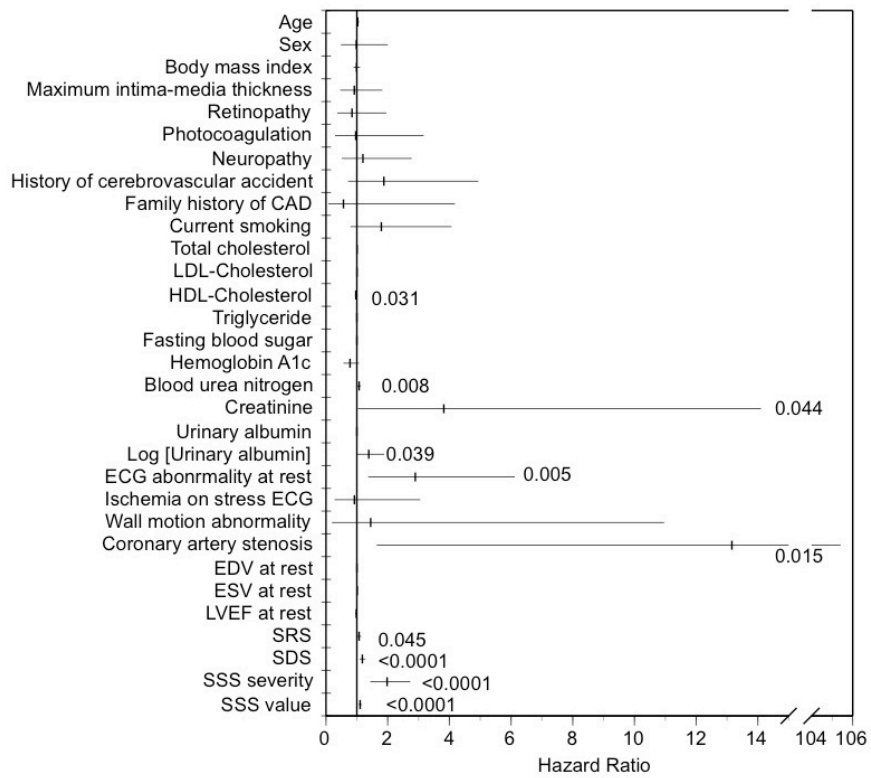
Figure 3 Hazard ratios by univariate Cox regression analysis. Bars indicate the hazard ratio and 95% confidence intervals. P values <0.05 are shown.

Table 1. Patient characteristics (n=506)

	number, mean±SD, %
Number of patients	506
Age (years), male gender (%)	67±8, 58%
Body weight (kg)	63±11
Body mass index (kg/m^2)	25±4
Waist circumference (cm)	89±11
Maximum IMT (mm)	1.7±0.8
Complications and history	
Retinopathy	25%
Neuropathy	20%
Cerebrovascular accident	10%
Family history of CAD	6%
Current and past smoking	17%, 26%
Hypertension	82%
Dyslipidemia	80%
Medications	
for diabetics (insulin use)	83% (30%)
for hypertension	66%
for dyslipidemia	41%
Biochemical data	
Total cholesterol (mg/dL)	200±35
LDL cholesterol (mg/dL)	118±31
HDL cholesterol (mg/dL)	51±15
Triglyceride (mg/dL)	168±114
Fasting blood sugar (mg/dL)	158±55
Hemoglobin A1c (%)	7.5±1.2
Blood urea nitrogen (mg/dL)	16.7±5.1
Creatinine (mg/dL)	0.78±0.24
Urinary microalbumin (mg/g Cre)	175±505 (range 0-5272)
ECG, echocardiography, coronary angiography	
ECG abnormality at rest	95/444 (21%)
Ischemia on stress ECG	129/167 (67%)
Wall motion abnormality	8/181 (4%)
0, 1, 2, and 3 vessel diseases	26, 9, 8, 2
Nuclear study	
EDV (mL), EDVI (mL/m^2)	74±22, 44±11
ESV (mL), ESVI (mL/m^2)	25±13, 15±7
LVEF (%)	67%±10%
SSS	2.7±4.3
SRS	2.1±3.7
SDS	0.60±2.4

IMT, intima-media thickness; CAD, coronary artery disease
EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction
EDVI, end-diastolic volume index; ESVI, end-systolic volume index
SSS, summed stress score; SRS, summed rest score; SDS, summed difference score

Table 2. Death and cardiovascular events within a year

Events	N	Total
Death		6
Heart failure, 2VD	1	
Stable Angina, PCI, cancer	1	
Sudden death	1	
Sudden death, 2VD	1	
Cancer	1	
Pneumonia, death from suffocation	1	
Cardiovascular accident		27
ACS, PCI	3	
PCI	1	
PCI, CABG	1	
Stable Angina, PCI	7	
Stable Angina, ASO, PCI	1	
Stable Angina	3	
Severe heart failure, CABG	1	
VSA	1	
CVA	5	
TIA	2	
ASO	2	
Total		33

VD, vessel disease; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome, CABG, coronary artery bypass grafting; VSA, vasospastic angina; CVA, cerebrovascular accident; TIA, transient ischemic attack of the brain; ASO, arteriosclerosis obliterans

Table 3.
Comparison of parameters between patient with and without events and high and low SSS

	Total events	No events	p values	SSS 0-8	SSS >8	p values
N	33	473		456	50	
Cardiovascular events and death				5%	20%	0.0002
Age (years)	69±9	67±8	0.3	67±8	67±8	0.6
Male gender	58%	58%	1.0	43%	30%	0.09
Body mass index (kg/m^2)	25±4	25±4	0.8	25±4	25±5	0.7
Maximum IMT (mm)	1.6±0.6	1.7±0.8	0.7	1.7±0.8	1.6±0.7	0.2
Complications						
Retinopathy	24%	26%	0.3	26%	20%	0.4
Neuropathy	21%	20%	0.8	19%	26%	0.3
Cerebrovascular accident	18%	10%	0.7	10%	12%	0.9
Family history of CAD	3%	6%	0.3	5%	8%	0.6
Current smoking	24%	17%	1.0	17%	18%	1.0
Medications						
Medication for diabetics	94%	82%	0.1	83%	88%	0.4
Insulin	42%	29%	0.2	29%	38%	0.3
Medication for hypertension	82%	65%	0.08	66%	66%	1.0
Medication for dyslipidemia	21%	42%	0.03	43%	24%	0.02
Anti-platelet medication	42%	26%	0.06	26%	34%	0.3
Biochemical data						
Total cholesterol (mg/dL)	208±32	199±35	0.1	199±35	205±33	0.2
LDL cholesterol (mg/dL)	122±27	117±31	0.3	117±31	130±29	0.03
HDL cholesterol (mg/dL)	46±9	51±15	0.06	51±15	51±14	0.8
Triglyceride (mg/dL)	181±104	167±115	0.5	169±118	155±77	0.7
Fasting blood sugar (mg/dL)	163±66	158±54	0.8	158±55	161±56	0.4
Hemoglobin A1c(%)	7.1±1.2	7.5±1.2	0.09	7.5±1.2	7.4±1.3	0.6
Blood urea nitrogen (mg/dL)	19±6	16±5	0.08	16±5	18±5	0.04
Creatinine (mg/dL)	0.85±0.31	0.78±0.23	0.3	0.78±0.23	0.84±0.29	0.2
urinary albumin (mg/g Cre)	300±402	168±511	0.08	174±521	192±333	0.02
Log [urinary albumin (mg/g Cre)]	4.7±1.7	3.9±1.4	0.08	3.9±1.5	4.5±1.2	0.02
ECG, echocardiography, coronary angiography						
ECG abnormality at rest	36%	18%	0.02	19%	20%	1.0
Ischemia on stress ECG	12%	12%	1.0	12%	16%	1.0
Wall motion abnormality	3%	1%	1.0	1%	8%	0.009
1VD, 2VD, 3VD	24%	2%	0.005	2%	18%	0.6
Nuclear studies						
EDV (mL)	74±28	74±22	0.6	72±20	92±32	<0.0001
ESV (mL)	26±16	25±13	0.9	24±12	37±19	<0.0001
LVEF (%)	66±12	68±10	0.5	68±10	61±9	<0.0001
SSS	5.5±6.0	2.5±4.0	0.005	-	-	
SRS	3.3±4.7	2.0±3.6	0.2	1.3±2.2	9.2±6.0	<0.0001
SDS	2.2±4.5	0.5±2.1	0.02	0.2±1.44	3.9±5.2	<0.0001

Abbreviations are the same as in Table 1

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