

## Surveillance study for creating the national clinical database related to ECG-gated myocardial perfusion SPECT of ischemic heart disease: J-ACCESS study design

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**Background:** ECG-gated myocardial perfusion SPECT is widely applied to diagnose ischemic heart disease, and such findings are useful to predict patient prognosis. However, Japan does not have a database that correlates SPECT image findings with the prognosis of patients who have ischemic heart disease. **Methods:** A large-scale clinical study involving 117 medical facilities throughout Japan was established to survey the clinical background and image findings of patients who have undergone ECG-gated stress perfusion SPECT. These patients were followed up for three years to investigate the occurrence of cardiac events. **Results:** The 4,629 registered patients comprised 2,989 males (age  $64.9 \pm 10.3$  y, mean  $\pm$  SD) and 1,640 females (age  $67.2 \pm 9.7$  y). The most frequent complication was hypertension (54.5%), followed by hyperlipidemia (47.2%) and diabetes (29.4%). Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was conducted on 1,925 of the patients. SPECT examinations were ordered for further examination of chest pain (32.8%), periodic follow-up after coronary artery intervention (24.2%), screening for coronary artery disease (15.1%), follow-up of old myocardial infarction (14.9%), more detailed investigation of ECG or echocardiographic abnormalities (13.1%), etiological assessment of heart failure (1.6%), and further inspection for acute coronary syndrome (0.3%). The method of inducing stress was most often exercise loading at 68.8%, and infusion of either dipyridamole (14.6%) or adenosine triphosphate (ATP, 13.8%). The most frequently applied amount of  $^{99m}\text{Tc}$ -tetrofosmin was an initial dose of 200 to 300 MBq combined with a second dose of 700 to 800 MBq (37.7%). The mean doses were  $305 \pm 81$  at the initial and  $709 \pm 132$  MBq at the second administration. A history of angina pectoris (41.2%) was the most frequent, followed by myocardial infarction (29.5%). **Conclusions:** During the two years of follow-up after registration, 46 of the 4,629 subjects have discontinued or dropped out, 134 have died, and 4,449 (97.8%) continue to undergo follow-up investigations. A complete report will be presented when the follow-up data for 3 years have been compiled and analyzed.

**Key words:** ischemic heart disease, ECG-gated SPECT,  $^{99m}\text{Tc}$ -tetrofosmin, prognostication, J-ACCESS

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### INTRODUCTION

ECG-gated myocardial perfusion SPECT imaging can simultaneously evaluate blood flow and wall motion in the myocardium, and it is widely used to diagnose ischemic heart disease. Furthermore, the AHA/ACC guidelines<sup>1,2</sup> also recommend SPECT imaging as a primary technique to detect abnormal myocardial perfusion.

The findings obtained by ECG-gated SPECT imaging are useful for estimating the prognosis of patients with ischemic heart disease, especially when predicting the likelihood of subsequent coronary events. Hachamovitch et al.<sup>3</sup> conducted SPECT scans in 5,183 patients with coronary artery disease and surveyed the number of cardiac deaths and myocardial infarctions during follow-up. They demonstrated that the annual incidences of cardiac death and of myocardial infarction were 0.3% and 0.5%, respectively, among individuals with normal uptake, 0.8% and 2.7% in those with mildly reduced uptake, 2.3% and 2.9% in those with moderate reduction, and 2.9% and 4.2% in those with severe reduction, indicating that the incidence closely correlated with the degree of stenosis in coronary arteries. Sharir et al.<sup>4</sup> reported that the ejection fraction and end-systolic volume calculated by ECG-gated SPECT are additional factors predictive of the incidence of cardiac death and myocardial infarction. Furthermore, many studies<sup>5-8</sup> have verified the correlation between SPECT image findings and prognosis in patients with ischemic heart disease. In North America and Europe, evidence-based medicine (EBM) for the diagnosis and prognosis of ischemic heart disease using SPECT imaging has been established based on the accumulation of large amounts of data.<sup>9-11</sup>

Over 300,000 cardiac nuclear perfusion scans are performed annually in Japan and this technique is currently an essential means of diagnosing ischemic heart disease. Several studies<sup>12-15</sup> of the diagnosis by SPECT imaging as well as the correlation between findings and prognosis have been performed, but all of them included only a small number of patients. Thus, EBM in Japan relating the prognosis prediction of ischemic heart disease by cardiac SPECT has not yet been established because large-scale studies have not been conducted. Some reports<sup>16-21</sup> have indicated that ischemic heart disease, in particular acute myocardial infarction, often occurs at a lower incidence and is often milder in Japan compared with the rest of the world, and that it progresses more slowly than in the US and Europe. Therefore, more data targeting Japanese are necessary.

Thus, we started to collect data regarding clinical background, image findings, and the nature of cardiac events in patients who have undergone ECG-gated stress SPECT scans. We will perform a stratified analysis to evaluate the actual use of this procedure in Japan and the accuracy of prognoses based on the findings. This study, which will establish a database of the diagnosis and treatment of ischemic heart disease, was named J-ACCESS based on the English, "Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT." This paper describes the aim and the design of the J-ACCESS study.

## MATERIALS AND METHODS

### *Participating facilities and patients*

The following conditions were imposed upon facilities wishing to participate in the study; stress/rest myocardial perfusion SPECT using <sup>99m</sup>Tc-tetrofosmin and quantitative gated SPECT (QGS) analysis at least 30 patients registered during a defined period, and follow-up surveys for 3 years after registration. The inclusion criteria for the patients were:  $\geq 20$  years of age, and scheduled to undergo stress/rest ECG-gated SPECT due to suspected or extant ischemic heart disease. Patients with onset of myocardial infarction or unstable angina pectoris within 3 months, valvular heart disease, idiopathic cardiomyopathy, severe arrhythmia, or heart failure with class III or higher New York Heart Association (NYHA) classification, or severe liver or renal disorders were excluded from the study.

The registration period was from October 1, 2001 to March 31, 2002, and aimed to accumulate over 3,000 patients. The investigators were asked to comply with the Declaration of Helsinki, and for their Institutional Review Boards (IRB) to approve their participation in the study in principle, and to receive the written informed consent of all patients to participate in the survey.

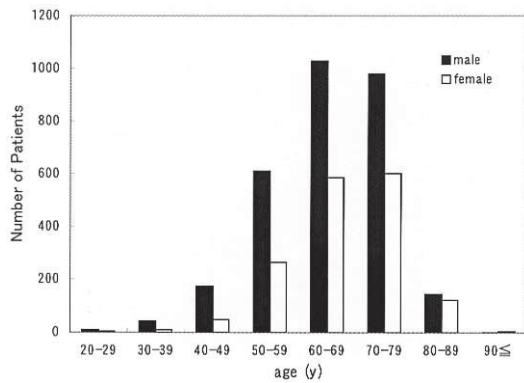
### *Study protocol*

The registered patients underwent stress/rest myocardial perfusion SPECT. The image data, patient background, treatment before SPECT, treatment undergone within 60 days after registration, and examinations other than SPECT were determined. The patients were followed up for 3 years thereafter. The nature of cardiac events if they occurred was described at 1, 2 and 3 years after the registration.

### *SPECT imaging*

Stress/rest SPECT scans used <sup>99m</sup>Tc-tetrofosmin. QGS analysis was also performed at rest. The protocol of the stress scans was whatever method was routinely used at each facility, that is, the exercise equipment, or the pharmaceutical and its administration method to induce stress were not particularly regulated. QGS analysis under stress was not obligatory, and when it was accomplished, data regarding the stress method and the analytical results were compiled. The imaging conditions and image processing procedures were separately surveyed.

The SPECT images were divided into 20 segments, and visual perfusion scores for <sup>99m</sup>Tc-tetrofosmin uptake in individual segments were scored in five stages as described by Berman et al.<sup>3</sup> as follows: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced and 4, absent uptake. The left ventricular ejection fraction (LVEF, %), end-diastolic volume (EDV, ml), and end-systolic volume (ESV, ml) were obtained from the QGS analysis. The heart rate and ECG findings during the stress test were also surveyed.



**Fig. 1** Distribution of patients by age and gender. Closed and open bars represent males and females, respectively.

#### Patient background data

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

#### Findings of other examinations

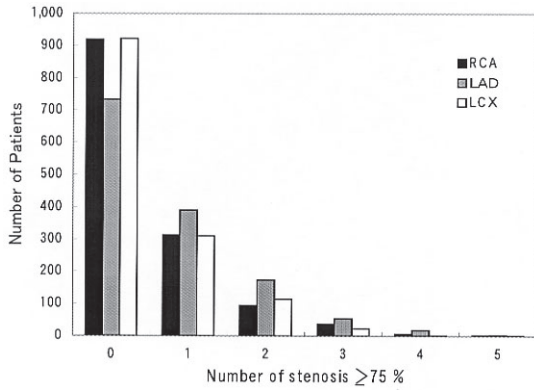
The survey documented whether or not ECG at rest, ECG under exercise stress, chest X-rays, echocardiography, coronary angiography (CAG) and left ventriculography (LVG) had been conducted, and if so, the findings were recorded. If hematological or blood biochemistry tests had been conducted within two months before or after SPECT imaging, then the date and the results were recorded.

**Table 1** Clinical background of patients

Background factor		Number of patients	(%)	Total	
Chest pain	None	2,423	52.3	4,629	
	Typical angina	746	16.1		
	Atypical angina	1,087	23.5		
	Non-angina	340	7.3		
	Unknown	33	0.7		
Heart failure	None	4,405	95.2	4,629	
	NYHA Class I	101	2.3		
	NYHA Class II	117	2.5		
Medical history	Angina	1,908	41.2		
	Myocardial infarction	1,366	29.5		
	Cerebrovascular disease	373	8.1		
	COPD	96	2.1		
	Liver disorder	180	3.9		
	Malignant tumor	233	5.0		
	ASO	149	3.2		
	Renal failure	96	2.1		
	Pulmonary vascular disease	11	0.2		
Risk factors	Family history of current disease	472	10.2		
	Smoking (current)	727	15.7		
	Smoking (past)	1,582	34.2		
	Diabetes	1,361	29.4		
	Hypertension	2,525	54.5		
	Hyperlipidemia	2,186	47.2		
BMI	< 18.5	Male	95	3.2	186
		Female	91	5.5	
	≥ 18.5 < 25	Male	1,858	62.2	2,827
		Female	969	60.1	
	≥ 25 < 30	Male	867	29.0	1,298
		Female	431	26.3	
	≥ 30 < 40	Male	87	2.9	158
		Female	71	4.3	
	≥ 40	Male	2	0.1	11
		Female	9	0.5	
Unknown	Male	80	2.7	132	
	Female	52	3.2		

The average BMI was  $23.8 \pm 3.0$  for males and  $23.6 \pm 3.6$  for females.

NYHA, New York Heart Association; COPD, Chronic obstructive pulmonary disease; ASO, Arteriosclerosis obliterans; BMI, body mass index.



**Fig. 2** Distribution of numbers of coronary artery stenoses and location. Open, hatched and closed bars represent location of stenosis in right coronary artery (RCA), left descending artery (LAD), and left circumflex coronary artery (LCX), respectively.

**Table 2** Test intervals and the order of stress/rest SPECT imaging

Protocol	Scan order				Total	
	Stress		Rest			
	N	%	N	%	N	%
1 day	4,214	91.0	359	7.8	4,573	98.8
2 days	16	0.3	40	0.9	56	1.2
<b>Total</b>	<b>4,230</b>	<b>91.3</b>	<b>399</b>	<b>8.7</b>	<b>4,629</b>	<b>100</b>

N, Number of patients

#### Treatment after registering for this survey

Revascularization that was performed within 60 days after the registration was recorded.

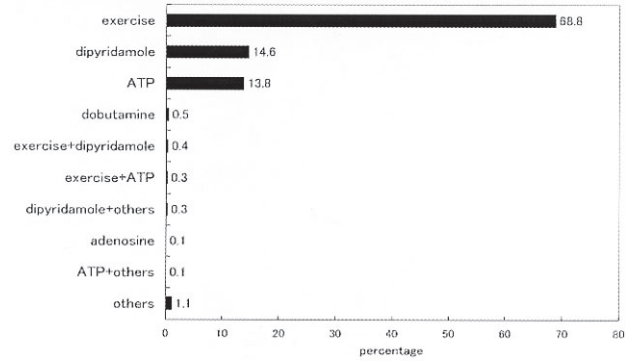
#### Follow-up survey

The occurrence and nature of cardiac events were investigated at 1, 2, and 3 years after the registration. Percutaneous coronary intervention (PCI) including plain old balloon angioplasty (POBA), stenting, directional coronary atherectomy (DCA), and rotablator atherectomy, as well as coronary artery bypass grafting (CABG), recurrent angina and non-severe heart failure were classified as soft events, and death (cardiac death and non-cardiac death), myocardial infarction, and heart failure requiring hospitalization were classified as hard events.

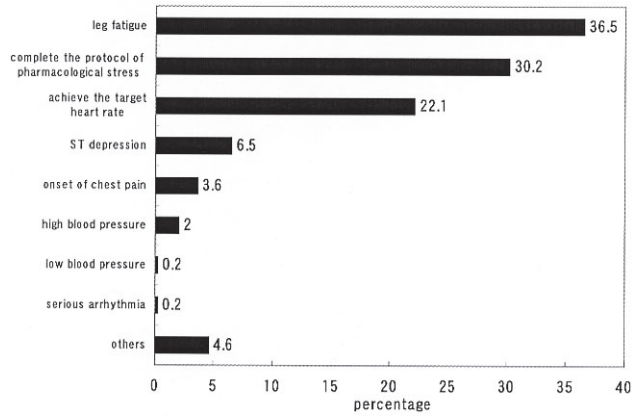
## RESULTS

#### Participating facilities and study population

A total of 117 medical facilities across Japan participated in this study including 4 in Hokkaido, 9 in Tohoku, 39 in Kanto, 17 in Chubu, 31 in Kinki, 10 in Chugoku and Shikoku, and 7 in Kyushu. Among 4,670 registered individuals, 41 were excluded because they did not fulfill the selection criteria leaving 4,629 for follow-up investigations.



**Fig. 3** Method of stress. ATP, Adenosine triphosphate.



**Fig. 4** End point of stress test.

#### Patient background

Figure 1 shows the gender and age distribution of the 2,989 male (65%; age 21–90 years, 64.9 ± 10.3 (mean ± SD)) and 1,640 female (35%; age 20–93 years, 67.2 ± 9.7) patients. Table 1 summarizes current symptoms, medical history, risk factors, and obesity. Among them, 47.6% complained of chest pain, and 4.8% had heart failure (NYHA class I and II). The most frequent illness revealed by the medical history was angina pectoris (41.2%), followed by myocardial infarction (29.5%), cerebrovascular disorder, chronic obstructive pulmonary disease (COPD), liver disorder, malignant tumor, arteriosclerosis obliterans (ASO), renal failure, and pulmonary vascular disease. A family history of the current condition was found in 10.2% of the patients. Smokers comprised 15.7% of the enrolled patients and 34.2% had smoked at some time in the past. Hypertension was the most common complication (54.5%), followed by hyperlipidemia (47.2%) and diabetes (29.4%). Over 60% were within the standard weight range, while 29.0% of the males and 26.3% of the females had class 1 obesity.

PCI or CABG was conducted before SPECT imaging on 1,925 of the patients: 1,614 (83.3%) underwent PTCA, 1,117 of them (58.0%) had stents, 77 (4.0%) underwent DCA, 58 (3.0%) had atherectomy using a rotablator and 400 underwent CABG (20.8%). Among those who under-

**Table 3** <sup>99m</sup>Tc-tetrofosmin doses

2nd dose (MBq)	Initial dose (MBq)				
	Less than 200	200 to 300	300 to 400	400 to 500	500 or more
	433 patients	2,730 patients	1,217 patients	133 patients	433 patients
Less than 500	1.3	2.5	0.0	0.0	0.2
500 to 600	5.9	14.3	1.1	0.1	0.0
600 to 700	0.0	3.5	1.0	0.6	0.0
700 to 800	1.1	37.7	19.3	0.4	1.0
800 to 900	0.0	0.8	1.9	0.9	0.1
900 to 1,000	1.1	0.2	1.3	0.2	0.1
1,000 or more	0.0	0.0	1.7	0.6	1.1

Number of patients and initial dose are shown. Numbers represent % of all patients.

went PCI, 1,678 patients received only this procedure; 991 (59.1%), 401 (23.9%), 157 (9.4%), 65 (3.9%) and 64 (3.8%) patients underwent the procedure once, twice, three, four and five or more times, respectively. The most recent PCI was applied within 1 y in 785 (46.8%) patients, within 1 to 2 y in 240 (14.3%), within 2 to 3 y in 167 (10.0%) and at over 3 years previously in 464 (27.7%). The most recent CAGB was applied within 1 year in 93 (23.3%) patients, between 1 and 2 years in 49 (12.3%), between 2 and 3 years in 38 (9.5%), and at over 3 years previously in 213 (53.3%).

#### Findings of other examinations

The following examinations were conducted within two months before or after SPECT imaging: ECG at rest in 94.3% of the patients, stress ECG in 40.1%, echocardiography in 63.4%, chest X rays in 74.1%, CAG in 48.0%, and LVG in 36.6%. Findings were abnormal in 2,604 (59.6%) of the 4,367 patients who underwent ECG at rest. The abnormalities comprised old myocardial infarction (31.3%) and non-specific ST-T changes (28.6%) followed by left ventricular hypertrophy with strain pattern (12.0%), atrial fibrillation (3.6%), left bundle branch block (1.8%) and ventricular pacemaker rhythm (1.0%). Of the 1,857 patients undergoing stress ECG, 648 (34.9%) had ischemia, 257 (13.8%) were false positives, and 863 were (46.5%) negative. Most of the patients (1,139, 61.4%) underwent stress ECG within 0 to 10 days of SPECT imaging.

Among the total, 2,220 patients underwent coronary angiography, and most of these underwent SPECT imaging within one month (42.2% of all patients). Coronary arterial lesions were evident in 1,371 patients; 503 (36.7%) had no significant lesions (75% or more stenosis) in any branches (0 branches), 384 (28.0%) had lesions in 1 branch, 288 (21.0%) in 2 branches and 196 (14.3%) in 3 branches. Figure 2 shows the numbers of stenoses and their locations in the right coronary artery (RCA), left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCX). Moreover, 84 (6.1%) of the 1,371 patients had 50% or more stenosis in the left

main trunk (LMT).

#### SPECT imaging

The reasons for SPECT imaging were further examination of chest pain (32.8%), periodic follow-up after coronary arterial intervention (24.2%), screening for coronary artery disease (15.1%), follow-up of old myocardial infarction (14.9%), further examination of abnormalities in ECG or echocardiography (13.1%), etiological examination of heart failure (1.6%) and further examination of acute coronary syndrome (0.3%).

SPECT imaging at rest after imaging under stress on the same day (1-day protocol) was the most frequent procedure at 91.0% (Table 2). Exercise alone was the most common stress method at 68.8%, followed by dipyridamole infusion (14.6%) and adenosine triphosphate (ATP) infusion (13.8%) (Fig. 3). The endpoint of the stress examination was most often lower limb fatigue (36.5%), followed by completion of the pharmacological stress protocol (30.2%) and achievement of the target heart rate at 22.1% (Fig. 4). The most frequent <sup>99m</sup>Tc-tetrofosmin doses applied were an initial 200 to 300 MBq (148–740 MBq) and a second dose of 700 to 800 MBq (37.7%; 290–1400 MBq, Table 3). The mean initial dose was 305 ± 81 MBq and that of the second was 709–132 MBq.

## DISCUSSION

The rationale for this survey was to establish a database regarding the background, imaging findings, and subsequent cardiac events that arose in patients who had undergone ECG-gated myocardial perfusion SPECT. We will perform a stratified analysis of the prognosis based on the clinical and imaging findings.

This prospective study did not plan to perform new medical procedures on the enrolled patients, but rather collected clinical data from those who had undergone diagnostic examinations required for medical care. Nevertheless, from the perspective of patient protection based on the Declaration of Helsinki, the investigators were



asked to receive approval for the research protocol from each IRB in principle, as well as written informed consent from each patient. In fact, this study started before the enactment of the "Ethical Guidelines for Epidemiological Research,"<sup>22</sup> but conformed to the Declaration of Helsinki.

Because the major objective of this study was to establish a database of cardiac nuclear medicine in Japanese based on ECG-gated myocardial perfusion SPECT images obtained to diagnose ischemic heart disease, only facilities that could register at least 30 successive patients were selected so as to maintain image data stability and the accuracy of image interpretation, and to collect quality data. Moreover, to improve the reliability of data in a multicenter survey, the radiopharmaceutical was limited to <sup>99m</sup>Tc, which provides stable data in ECG-gated perfusion SPECT. Taking into consideration the wide variety of stress methods and SPECT data collection protocols among facilities, QGS analysis of ECG-gated perfusion SPECT imaging was determined to be essential only at rest. However, if QGS analysis after stress was obtained, data regarding the stress method and its end point were collected and tallied.

The current diagnostic criteria in Japan for nuclear cardiology are data from multicenter studies in the USA. However, the incidence of ischemic heart disease is lower, the clinical course is milder and the disease is less progressive among Japanese than American or European patients.<sup>16-21</sup> These results suggest that diagnosis, treatment and prognosis based on the US database may not be suitable for Japanese patients. The data from myocardial perfusion SPECT image findings and the prognosis of patients with ischemic heart disease collected in this study will be the basis for establishing a reliable and accurate database for the Japanese population.

Follow-up investigations associated with this survey have been completed up to the second year, and currently the final results for up to 3 years after registration are being collected and analyzed. Within two years of follow-up, 46 of the 4,629 patients discontinued or dropped out, 134 died and 4,449 (97.8%) continue to undergo follow-up. The complete report including the stratification analysis with the risk for ischemic heart disease will be presented when all follow-up data for 3 years have been compiled and analyzed.

## APPENDIX

The J-ACCESS study was supported by a grant from the Japan Cardiovascular Research Foundation. We acknowledge the work of all investigators.

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