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【 ORIGINAL ARTICLE 】

Risk Stratification of Cardiovascular Events in Very Elderly Patients with Known or Suspected Coronary Artery Disease Who Had Normal Single-photon Emission Computed Tomographic Myocardial Perfusion Imaging Findings

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Abstract:

Objective We aimed to stratify the risk of major cardiovascular (MCV) events in Japanese patients with known or suspected coronary artery disease (CAD) who had normal single-photon emission computed tomographic myocardial perfusion imaging (SPECT MPI) findings and to compare the risk by generation.

Methods This was a retrospective study. The composite endpoint was the occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Patients The study subjects were 2,035 patients with normal SPECT MPI findings at baseline who had been followed up to confirm their prognosis for 3 years. The patients were categorized into 3 age groups: very elderly (≥80 years old, n=311), elderly (65-79 years old, n=1,097), and younger (<65 years old, n=542).

Results During the follow-up, 68 patients experienced MCV events: cardiovascular death (n=29), non-fatal myocardial infarction (n=15), and non-fatal stroke (n=24). The MCV event rate was significantly higher in very elderly patients than in other patients. Multivariate predictors were age categories, the estimated glomerular filtration rate, atrial fibrillation, and stress left ventricular ejection fraction. The MCV event rate was 6.1% in very elderly patients. However, the MCV event rate in those with normal cardiac and renal functions without atrial fibrillation was 3.3%, which was similar to that in elderly and younger patients.

Conclusion The MCV event rate was high in very elderly patients despite their normal SPECT MPI findings at baseline. Therefore, very elderly patients with multivariate risks should be carefully followed to avoid a poor prognosis.

Key words: prognosis, risk stratification, very elderly patients, coronary artery disease, normal myocardial perfusion imaging

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Introduction

Japan has one of the longest-living populations in the world. The proportion of the population aged ≥65 years is estimated to be nearly 30% in 2025 and 40% in 2060 according to the vital statistics of the Ministry of Health, Labour and Welfare. Aging increases the risk of cardiovascular disease, which is the leading cause of death in elderly people ≥75 years of age and also accounts for one-quarter of diseases requiring nursing care. In addition, cardiovascular disease often progresses asymptomatically in elderly people, which results in a diagnostic delay and ultimately reduces their life expectancy. Therefore, the Japanese Circulation Society has established a five-year plan to reduce the rates of stroke and cardiovascular disease (STOP CVD: Stop Cerebral Cardiovascular Disease) in cooperation with the Japan Stroke Society.

The exercise stress test is useful for diagnosing and screening for cardiovascular disease, and exercise tolerance

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is an important index affecting a patient's prognosis. Treadmill testing is a representative versatile exercise stress test. The Duke treadmill score, which is derived from the duration of exercise, maximum ST deviation on an electrocardiogram, and chest pain index, is known to be a predicator of clinical outcomes (1). However, the Duke treadmill score was reported to fail to predict future cardiac events and to stratify the risk of cardiac events in elderly patients, whereas nuclear cardiology was a superior approach for the prediction and risk stratification of cardiac disease in elderly patients (2).

Single-photon emission computed tomographic myocardial perfusion imaging (SPECT MPI) is a useful imaging methodology for predicting future cardiac events in patients with known or suspected coronary artery disease (CAD) (3, 4). An ischemic evaluation with SPECT MPI is highly recommended by the American College of Cardiology/American Heart Association guideline (5) and Japanese Circulation Society guideline (6). In addition, previous studies reported that patients with known or suspected CAD who had normal SPECT MPI findings are considered to have a low risk of cardiovascular events (<1%/year) (3, 7, 8).

However, only a minority of clinical studies conducted with nuclear cardiology have been focused on elderly patients. In addition, there are few nuclear cardiology studies investigating the risk of CVD in very elderly Japanese patients with normal SPECT MPI findings in particular. Therefore, we conducted this study to stratify the risk of cardiovascular events in Japanese patients with known or suspected CAD who had normal SPECT MPI findings and to compare the risk by generation.

Materials and Methods

Patient population

We retrospectively investigated 2,035 patients with known or suspected CAD who had normal rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin SPECT MPI findings (9-12) documented at Nihon University Itabashi Hospital between April 2009 and March 2013 and followed the patients up to confirm their prognosis for 3 years. We excluded patients ≤20 years of age, those with hypertrophic or dilated cardiomyopathy, those with serious valvular heart disease, those with heart failure being class III or higher New York Heart Association (NYHA) functional classification, and those with onset of acute coronary syndromes within three months. Patients were divided into 3 different age groups: very elderly (VE: ≥80 years old, n=311), elderly (E: 65-79 years old, n=1,097), and younger (Y: <65 years old, n=542) according to the preceding study (13).

Follow-up examinations were based on medical records for patients who periodically attended the hospital and responses to a posted questionnaire enclosing a written informed consent form for patients who did not attend. The follow-up was completed for 1,950 (95.8%) of patients. Consequently, data from the 1,950 patients were retrospectively analyzed.

This study was approved by the institutional review board of Nihon University Itabashi Hospital.

Electrocardiography (ECG)-gated dual-isotope SPECT MPI

The procedure of rest ^{201}Tl and stress ^{99m}Tc-tetrofosmin ECG-gated SPECT MPI was performed according to a previously reported protocol (9-12). All patients received an intravenous (i.v.) injection of ^{201}Tl (111 MBq), and a 16-frame gated SPECT MPI was initiated 10 minutes after injection during rest. The i.v. injection of ^{99m}Tc-tetrofosmin (740 MBq) was then performed under stress induced by ergometer exercise in 22% of the patients, by adenosine triphosphate with low-grade ergometer exercise (vasodilator-exercise stress) in 45%, and adenosine triphosphate alone (vasodilator stress) in 33%. Sixteen-frame gated SPECT MPI acquisition was initiated 30 minutes after the exercise or 30 to 60 minutes after the adenosine stress. The acquisition was performed in a supine position, subsequently in a prone position. No attenuation or scatter correction was used. A 12-lead ECG was monitored continuously during stress tests. Heart rate and blood pressure were recorded at baseline and every minute for at least three minutes after the stress.

The projection data over 360° were obtained with 64×64 matrices and a circular orbit. A triple-detector SPECT MPI system equipped with low-energy high-resolution collimators was used (GCA9300A; Canon Medical Systems, Tokyo, Japan). SPECT MPI scans were reconstructed from the data with a data processor (JETStream Workspace 3.0; Philips North America, Andover, USA) combined with a Butterworth filter of ^{201}Tl (order 5; cut-off frequency 0.42 cycles/cm), that of ^{99m}Tc (order 5; cut-off frequency 0.44 cycles/cm) and a ramp filter.

SPECT MPI interpretation

The SPECT MPI scans were divided into 20 segments (10, 14) on 3 short-axis slices (distal, mid, basal) and 1 vertical long-axis (mid) slice, and the tracer uptake of each segment was visually scored using a 5-point scale (0: normal; 1: slight reduction in the uptake; 2: moderate reduction in the uptake; 3: severe reduction in the uptake; and 4: absence of the uptake). The sum total of the scores of 20 segments in the stress and rest images provided the summed stress score (SSS) and the summed rest score (SRS) respectively. The summed difference score (SDS) was calculated as the difference between the SSS and SRS. A patient who had an SSS <4 was defined as having normal SPECT MPI findings. The visual semi-quantitative scoring was performed by two independent expert interpreters who were not provided with patient's clinical information. Cohen's kappa (κ), which was calculated to determine the inter-observer variability for the summed defect score, was 0.91, indicating

Table 1. MCV Event Rates in Three Age Groups.

Age category	Overall (69±10) (n=1,950)		Younger patients (56±8) (n=542)		Elderly patients (72±4) (n=1,097)		Very elderly patients (83±3) (n=311)		p value for trend
	n	%	n	%	n	%	n	%	
Cardiovascular death	29	1.5	2	0.4	16	1.5	11	3.5	0.0003
Fatal MI	11	0.6	0	0	8	0.7	3	1.0	0.0455
Heart failure death	11	0.6	1	0.2	2	0.2	8	2.5	0.0001
Sudden cardiac death	7	0.3	1	0.2	6	0.6	0	0.0	0.9208
Non-fatal MI	15	0.8	5	0.9	8	0.7	2	0.6	0.6261
Non-fatal stroke	24	1.2	5	0.9	13	1.2	6	1.9	0.2251
Total	68	3.5	12	2.2	37	3.4	19	6.1	0.0043

MCV: major cardiovascular, MI: myocardial infarction

very good reproducibility.

Sixteen-frame quantitative gated SPECT MPI data were analyzed using the QGS™ software program (Cedars-Sinai Medical Center, Los Angeles, USA) to calculate the left ventricular ejection fraction (LVEF, %), end-diastolic volume (LVEDV, mL), and end-systolic volume (LVESV, mL) as described by Germano et al. (15).

Patient follow-up

All patients were followed up for three years (37.9±7.5 months) after the initial stress myocardial perfusion gated SPECT MPI.

The primary endpoint was cardiovascular death within the three-year follow-up. The secondary composite endpoint was the first occurrence of any one of three major cardiovascular (MCV) events consisting of cardiovascular death, non-fatal MI, and non-fatal stroke within the three-year follow-up. Cardiovascular death was defined as death due to any cardiac cause, including fatal myocardial infarction (MI), heart failure, and sudden cardiac death. Non-fatal stroke was defined as cerebral infarction including ischemic stroke and cardiogenic embolism. A patient who had insufficient data to indicate the occurrence of the MCV events was regarded as a non-event case.

When a patient had several cardiovascular events, only the first event was set as the follow-up endpoint.

Statistical analyses

Continuous variables were calculated as means and standard deviations. Intergroup comparisons of continuous variables were achieved using an unpaired *t*-test for two groups and an analysis of variance for three groups. Intergroup comparisons of categorical variables and global chi-square values were achieved using the chi-square test. A Cox proportional hazards model was used for univariate analyses to identify significant predictors of MCV events. A stepwise Cox proportional hazards model was employed for multivariate analyses with significant predictors as variables in order to determine independent predictors of MCV events.

The Kaplan-Meier survival analysis was used to estimate MCV event-free survivals in three different age groups: very elderly, elderly, and younger patients. A log-rank test was used to analyze the homogeneity of the survival curves between three different age groups. The chi-square for trend test was used to compare the SSS severity derived from the SPECT MPI and MCV event rates during the three-year follow-up between very elderly, elderly, and younger patients, and to compare MCV event rates between subgroups with stepwise exclusion of multivariate independent predictors in very elderly patients.

All data were analyzed using the MedCalc Statistical Software program, Version 18.5 (MedCalc Software, Mariakerke, Belgium). A p value of <0.05 was considered statistically significant.

Results

Cardiovascular death and MCV event rates and patient characteristics

During the follow-up, 68 of 1,950 (3.5%) patients experienced MCV events consisting of cardiovascular death (n=29), non-fatal MI (n=15), and non-fatal stroke (n=24). The number of the patients with cardiovascular death was 11 for death due to fatal MI, 11 for death due to heart failure, and 7 for sudden cardiac death. Table 1 summarizes the incidence of the MCV events in the three age groups. The incidence of the MCV events during the three-year follow-up was 2.2% in the younger patients, 3.4% in the elderly patients, and 6.1% in the very elderly patients and significantly increased with aging (p=0.0043). The overall incidence of cardiovascular death, which was 0.4% in the younger patients, 1.5% in elderly patients, and 3.5% in very elderly patients, tended to significantly increase with aging (p=0.0003). Among all cardiovascular deaths, the incidence of death due to heart failure and fatal MI tended to significantly increase with aging; however, there was no significant trend in the incidence of non-fatal MI and non-fatal stroke.

Table 2 summarizes the background characteristics of the patients in each age group. The three age groups differed in

Table 2. Background Characteristics of Patients in Three Age Groups.

	Younger patients n=542	Elderly patients n=1,097	Very elderly patients n=311	p value for trend
Male patients	350 65%	648 59%	155 50%	<0.001
Age	56 ± 8	72 ± 4	83 ± 3	<0.001
Asymptomatic	249 46%	521 47%	134 43%	0.581
Atypical chest pain	182 34%	349 32%	92 30%	0.227
Typical chest pain	32 6%	56 5%	13 4%	0.269
Shortness of breath	49 9%	119 11%	51 16%	0.002
Chronic atrial fibrillation	26 5%	93 8%	28 9%	0.010
History of MI	42 8%	73 7%	20 6%	0.410
History of revascularization	105 19%	259 24%	62 20%	0.529
Hypertension	361 67%	827 75%	267 86%	<0.001
Diabetes mellitus	140 26%	301 27%	84 27%	0.627
Hyperlipidemia	333 61%	653 60%	170 55%	<0.001
Aspirin	203 37%	480 44%	140 45%	0.015
Statins	219 40%	501 46%	125 40%	0.668
β-blockers	132 24%	253 23%	89 29%	0.286
Ca-antagonists	266 49%	655 60%	193 62%	<0.001
Nitrates	37 7%	152 14%	46 15%	0.001
ARB	230 42%	503 46%	163 52%	0.006
ACE inhibitors	24 4%	69 6%	20 6%	0.162
eGFR	71.8 ± 23.7	63.8 ± 21.0	57.6 ± 18.9	<0.001
Exercise stress	227 42%	194 18%	10 3%	<0.001
Vasodilator-exercise stress	220 41%	549 50%	113 36%	0.860
Vasodilator stress	95 17%	354 32%	188 61%	<0.001
Summed stress score	0.1 ± 0.5	0.1 ± 0.4	0.1 ± 0.3	0.267
Summed rest score	0.1 ± 0.6	0.0 ± 0.3	0.1 ± 0.7	0.214
Summed difference score	0.0 ± 0.7	0.0 ± 0.3	0.0 ± 0.7	0.233
Rest LVEF	65.0 ± 10.0	70.0 ± 9.4	71.9 ± 9.8	<0.001
Rest LVEDV	77.1 ± 24.7	65.1 ± 21.1	58.9 ± 19.5	<0.001
Rest LVESV	28.4 ± 15.1	20.7 ± 11.8	17.7 ± 10.6	<0.001
Stress LVEF	66.0 ± 10.3	69.2 ± 9.5	69.9 ± 10.0	<0.001
Stress LVEDV	87.6 ± 26.5	76.0 ± 23.1	69.6 ± 21.2	<0.001
Stress LVESV	31.5 ± 16.8	24.7 ± 13.5	22.2 ± 12.6	<0.001

MI: myocardial infarction, ARB: angiotensin receptor blocker, ACE: angiotensin converting enzyme, eGFR: estimated glomerular filtration rate , LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume

the proportions of men. There was a statistically significant trend among the three age groups in the proportion of patients who had shortness of breath, chronic atrial fibrillation, hypertension, hyperlipidemia, and treatment with aspirin, calcium antagonists, nitrates, or angiotensin receptor blockers (p≤0.015). In addition, a statistically significant trend was observed in the proportion of patients undergoing either exercise or vasodilator stress among the three age groups. There was a statistically significant trend in the estimated glomerular filtration rate (eGFR), LVEF, LVEDV, and LVESV at rest or under stress among the three age groups (p<0.001).

Table 3 summarizes the background characteristics of the patients with and without MCV events. There was no significant gender difference between the patients with and without MCV events. Age was significantly higher in the patients with MCV events than in those without such events (73±10 vs. 69±10; p=0.0018). Shortness of breath, chronic atrial fibrillation, a history of MI, hypertension, and diabetes mellitus were more common in the patients who experienced MCV events than in those with no MCV events (p≤0.0395). In addition, a greater proportion of the patients who experienced MCV events underwent vasodilator stress than those with no MCV events (p<0.0001). The patients with MCV events had significantly lower eGFR and LVEF values at rest and under stress (p≤0.0041), and significantly higher LVESV values under stress than the patients without MCV events (p=0.0171).

Cardiovascular death and MCV event rates

Fig. 1 shows the cardiovascular death and MCV event rates during the three-year follow-up in each age group. The cardiovascular death rate was significantly higher in the very elderly patients than in the younger (3.5% vs. 0.4%, p=0.0003) and elderly (3.5% vs. 1.5%, p=0.0184) patients. In addition, there was a significant difference in the cardiovas-

Table 3. Background Characteristics of Patients with and without MCV Events.

	MCV event (+) n=68	MCV event (-) n=1,882	p value
Male patients	45 66%	1,108 59%	0.2289
Age	73 ± 10	69 ± 10	0.0018
Asymptomatic	32 47%	872 46%	0.9062
Atypical chest pain	13 19%	610 32%	0.0209
Typical chest pain	3 4%	98 5%	0.7713
Shortness of breath	17 25%	202 11%	0.0003
Chronic atrial fibrillation	13 19%	134 7%	0.0002
History of MI	10 15%	125 7%	0.0101
History of revascularization	20 29%	406 22%	0.1244
Hypertension	58 85%	1,397 74%	0.0395
Diabetes mellitus	26 38%	499 26%	0.0323
Hyperlipidemia	33 48%	1,123 60%	0.0663
eGFR	51.3 ± 24.4	65.6 ± 21.7	<0.0001
Exercise stress	3 4%	428 23%	0.0003
Vasodilator-exercise stress	23 34%	859 46%	0.0544
Vasodilator stress	42 62%	595 32%	<0.0001
Summed stress score	0.2 ± 0.7	0.1 ± 0.4	0.0373
Summed rest score	0.1 ± 0.6	0.0 ± 0.5	0.0913
Summed difference score	0.0 ± 0.4	0.0 ± 0.5	0.8555
Rest LVEF	65.5 ± 10.4	69.0 ± 9.9	0.0041
Rest LVEDV	67.7 ± 23.5	67.4 ± 22.9	0.9205
Rest LVESV	24.7 ± 13.8	22.3 ± 13.2	0.1413
Stress LVEF	63.5 ± 10.5	68.6 ± 9.9	<0.0001
Stress LVEDV	79.2 ± 23.8	78.2 ± 24.7	0.7403
Stress LVESV	30.4 ± 16.0	26.0 ± 14.7	0.0171

MCV: major cardiovascular, MI: myocardial infarction, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume

cular death rate between elderly and younger patients (1.5% vs. 0.4%, p=0.0465) and a significant increase in the rates with aging was observed (p<0.05; Fig. 1a). The MCV event rate in the very elderly patients was 6.1%, which was significantly higher than that in the younger (2.2%, p=0.0035) and elderly (3.4%, p=0.0293) patients (Fig. 1b).

Predictors of future MCV events

Table 4 summarizes the results of the univariate and multivariate Cox proportional hazards regression analyses in all the patients. Univariate predictors of MCV events were age, age category, shortness of breath, vasodilator stress test, chronic atrial fibrillation, history of MI, hypertension, diabetes mellitus, rest LVEF, stress LVEF and LVESV, and eGFR. Among those predictors, the multivariate predictors were age category, chronic atrial fibrillation, stress LVEF, and eGFR in all patients.

Correlation between MCV event rates and independent predictors in very elderly patients

Fig. 2 shows the MCV event rates in the very elderly patients who did not have one or more multivariate risks. The MCV event rate was 6.1% in the very elderly patients who had normal SPECT MPI findings as mentioned above. Furthermore, the MCV event rate was 3.3% in the very elderly patients who had no chronic atrial fibrillation, ≥45% of stress LVEF, and ≥60 mL/min/1.73 m^2 of eGFR in addition to having normal SPECT MPI findings. The MCV event rates showed a significant downward trend with a decreasing number of multivariate risks (p<0.0001).

Fig. 3 shows the Kaplan-Meier curves of the MCV event-free survival in the younger and elderly patients and in the very elderly patients with and without the multivariate risks (chronic atrial fibrillation, stress LVEF <45%, and eGFR < 60 mL/min/1.73 m^2). The very elderly patients with the multivariate risks experienced a poor prognosis, which was significantly different from the prognosis in the younger and elderly patients (p<0.05). However, the prognosis in the very elderly patients who had no multivariate risks was similar to that in the younger and elderly patients (p>0.05).

Discussion

This study compared the risk of MCV events in the very elderly, elderly, and young Japanese patients with known or suspected CAD who had normal SPECT MPI findings. Aging led to an increase in the incidence of MCV events, including cardiovascular death, in this population. The very

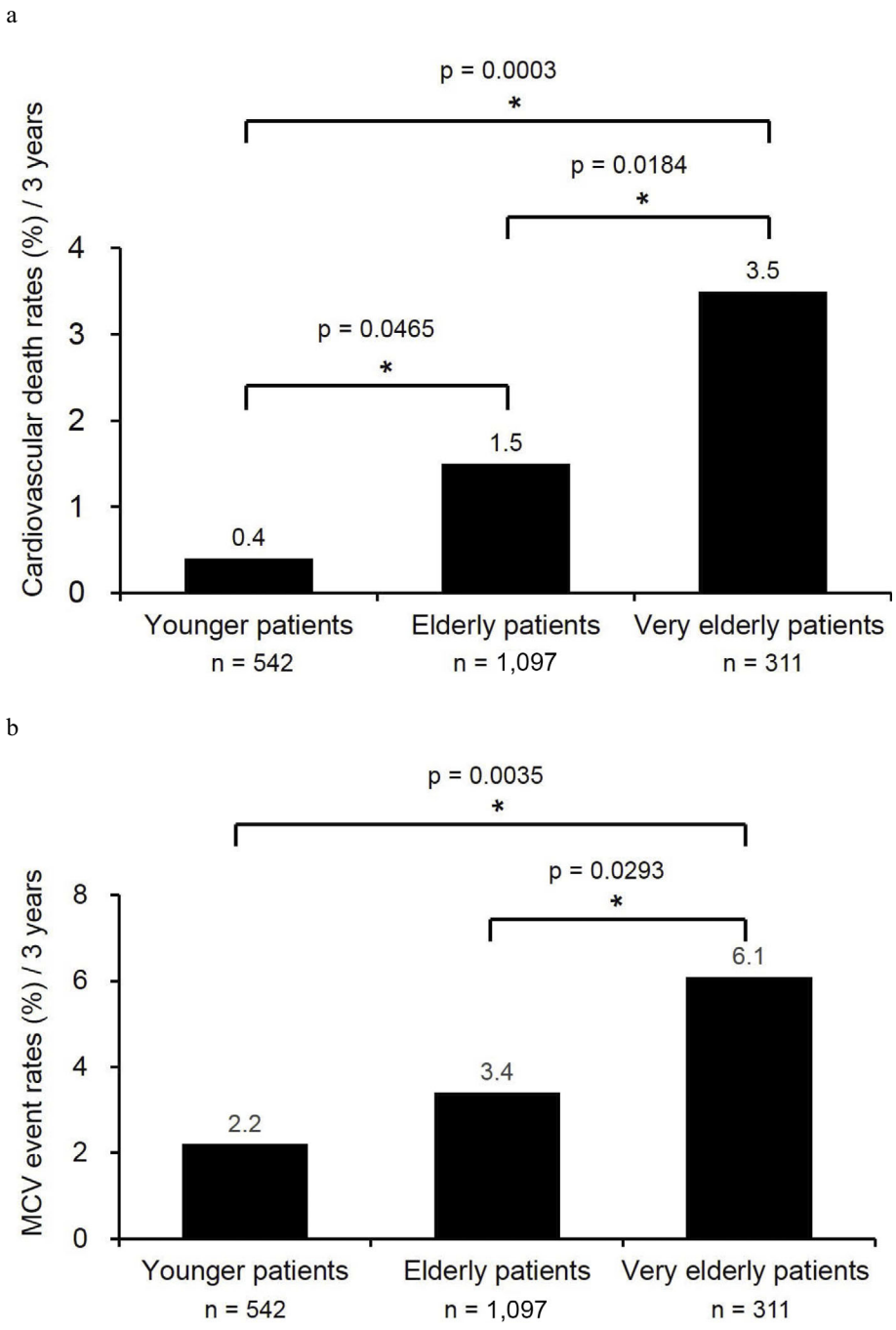

Figure 1. **Difference in cardiovascular death and MCV event rates with normal SPECT MPI findings among the three age groups. a: cardiovascular death rates. b: MCV event rates. *: statistically significant intergroup difference (p<0.05). MCV: major cardiovascular, SPECT MPI: single-photon emission computed tomographic myocardial perfusion imaging**

elderly patients ≥80 years of age had a poorer prognosis than the young and elderly patients. In addition, the results of the multivariate analysis indicated that important factors predicting future MCV events were age category, chronic atrial fibrillation, stress LVEF <45%, and eGFR <60 mL/min/1.73 m^2. The clinical course of very elderly patients with such multivariate risks should be carefully followed, even if they have normal SPECT MPI findings, because they have a high risk of MCV events. This study's results also suggested that the elimination of those multivariate risks might reduce the MCV event rate in very elderly patients with normal SPECT MPI findings.

In the present study in patients with normal SPECT MPI findings, as expected, the MCV event rate was significantly higher in the very elderly patients than in the younger and elderly patients. The results of a study in patients with suspected CAD who had no history of CAD conducted by Nair et al. (13) demonstrated that very elderly patients (≥80 years of age) with normal SPECT MPI findings had significantly more cardiac events than younger patients; indeed, the inci-

Table 4. Univariate and Multivariate Cox Proportional Hazards Regression Analyses.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Age	1.0446	1.0172 - 1.0727	0.0013			
Age category	1.7321	1.2009 - 2.4982	0.0033	1.7000	1.1705 - 2.4691	0.0053
Male gender	1.3657	0.8264 - 2.2570	0.2240			
Shortness of breath	2.7467	1.5864 - 4.7559	0.0003			
Vasodilator stress test	6.4311	2.0212 - 20.4622	0.0016			
Chronic atrial fibrillation	3.0417	1.6618 - 5.5675	0.0003	1.8898	1.0120 - 3.5290	0.0458
History of MI	2.3798	1.2163 - 4.6561	0.0113			
History of revascularization	1.4904	0.8846 - 2.5110	0.1338			
Hypertension	1.9979	1.0212 - 3.9086	0.0433			
Diabetes mellitus	1.7077	1.0471 - 2.7850	0.0320			
Hyperlipidemia	0.6309	0.3921 - 1.0150	0.0576			
eGFR	0.9740	0.9647 - 0.9833	<0.0001	0.9796	0.9697 - 0.9896	0.0001
Rest LVEF	0.9664	0.9445 - 0.9888	0.0035			
Rest LVEDV	1.0003	0.9900 - 1.0107	0.9569			
Rest LVESV	1.0119	0.9958 - 1.0282	0.1480			
Stress LVEF	0.9512	0.9297 - 0.9733	<0.0001	0.9586	0.9357 - 0.9821	0.0006
Stress LVEDV	1.0014	0.9919 - 1.0110	0.7698			
Stress LVESV	1.0171	1.0031 - 1.0313	0.0165			

CI: confidence interval, MI: myocardial infarction, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume

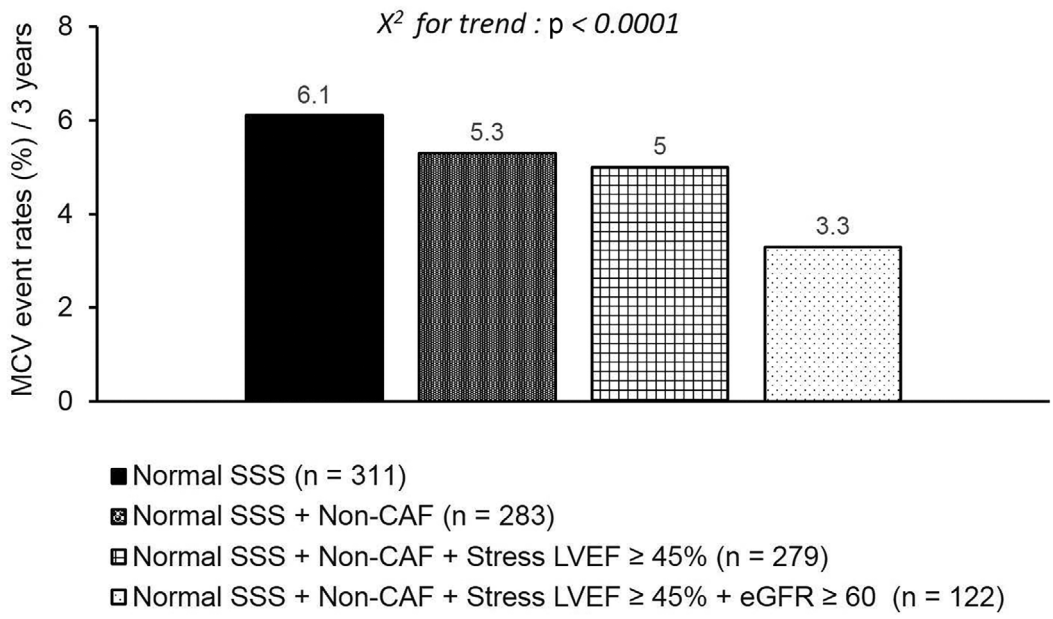

Figure 2. MCV event rates in very elderly patients with normal SPECT MPI findings who did not have one or more multivariate risks. CAF: chronic atrial fibrillation, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, MCV: major cardiovascular, SPECT MPI: single-photon emission computed tomographic myocardial perfusion imaging, SSS: summed stress score

dence of cardiac death was 1.8% in patients ≥80 years of age, 0.6% in patients 65 to 79 years of age, and 0.3% in patients 50 to 64 years of age; consequently, there was a significant correlation between aging and cardiovascular event risks. These findings were the same as those obtained from our present study in very elderly Japanese patients with known or suspected CAD who had normal SPECT MPI findings. An increase in cardiovascular event risks with aging is a common issue in developed nations. Therefore, risk reduction and stratification of cardiovascular events are becoming increasingly frequently required in very elderly patients, even if they have normal SPECT MPI findings. A

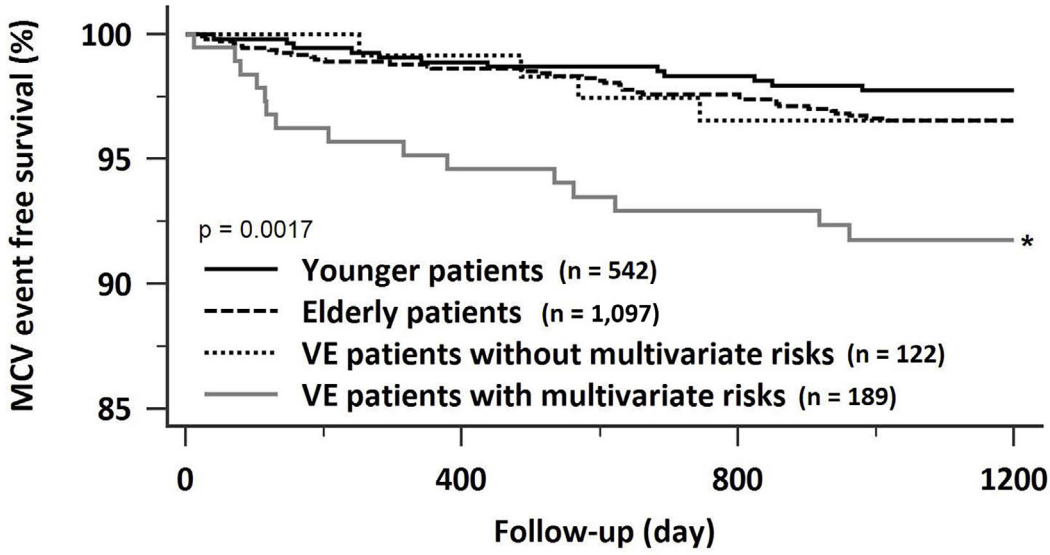

Figure 3. **Kaplan-Meier curves of the MCV event-free survival in patients with normal SPECT MPI findings. MCV: major cardiovascular, SPECT MPI: single-photon emission computed tomographic myocardial perfusion imaging, VE: very elderly, *: statistically significant difference versus the younger and elderly patients.**

prospective multicenter trial investigating the prediction of the prognosis and risk stratification in very elderly patients who have undergone SPECT MPI for suspected CAD would be useful.

In general, patients with suspected CAD who have normal SPECT MPI findings are considered to have a good prognosis (cardiovascular event rate: <1%/year) (3, 7, 8). In Japanese patients, the annual cardiovascular event rate was 0.81%, which was lower than that in western patients, according to the results of a sub-analysis of the Japanese-Assessment of Cardiac Event and Survival Study by Quantitative Gated SPECT (J-ACCESS) study (16). That study indicated that the cardiovascular event rates were higher in patients ≥70 years of age than in those <70 years of age but did not focus on very elderly patients. Hachamovitch et al. investigated the prognostic value of SPECT MPI in elderly patients with known or suspected CAD and reported that the annual cardiac death rate was 3.3% in patients ≥85 years of age and 1.0% in those 75 to 84 years of age who had normal SPECT MPI findings (17). These previous studies therefore indicate that the risk of cardiovascular events is not necessarily low in elderly patients with normal SPECT MPI findings.

In addition, in the present study, MCV event and cardiovascular death rates during the 3-year follow-up were higher in the very elderly patients (6.1% and 3.5% respectively) than in the younger and elderly patients who had normal SPECT MPI findings. However, the very elderly patients who had no multivariate risk factors (i.e., normal stress LVEF values and renal function without chronic atrial fibrillation) had a low risk of MCV events and the same prognosis as the younger and elderly patients, which is a new finding that has never been reported. This finding is considered to be highly useful for clinical decision-making in very elderly patients. Therefore, since not all very elderly patients have a poor prognosis, it is important that predictions of their prognosis are based on a comprehensive evaluation with a combination of multivariate risk analyses and SPECT MPI data. In addition, proper management of the multivariate risks may lead to improvement in the prognosis of elderly patients and consequently an extension of their healthy lifetime.

In the present study, chronic atrial fibrillation was also a significant predictor. This was considered to be associated with non-fatal cardiogenic cerebral embolism, which was a secondary composite endpoint. Among symptoms, shortness of breath was frequently observed (25%) among the patients with MCV events and was a significant univariate predictor. Shortness of breath was reported to be associated with an increase in the risk of cardiac death, regardless of the history of CAD (18). The results of the present study also suggested that shortness of breath might increase the incidence of MCV events, as the patients with that symptom had concurrent heart failure or multi-symptoms, including chronic pulmonary disease and anemia.

Limitations

This observational study was limited by its retrospective nature and single-center setting. In addition, the cardiovascular event rate obtained from this study was considered to be relatively high because the study subjects included high-risk patients with a history of myocardial infarction or coronary revascularization who had been referred to our university hospital.

In the present study, the type of stress was selected at the discretion of the cardiologist who performed SPECT; thus,

there was the potential for selection bias, which may have affected the study results. There was also the potential for institutional bias in the optimal treatment with medication to prevent cardiovascular events, as this was an observational single-center study.

We performed ^{201}Tl+^{99m}Tc-tetrofosmin dual-isotope SPECT to improve throughput in this study, as in previous studies (9-12). Dual-isotope SPECT provides higher radiation exposure than ^{99m}Tc-tetrofosmin rest-stress SPECT. Because the prognostic prediction and diagnostic accuracy of ^{201}Tl are generally the same as those of ^{99m}Tc (19), the ^{99m}Tc-tetrofosmin rest-stress SPECT protocol is expected to provide the same results as in this study.

Conclusion

The incidence of MCV events, including cardiovascular death, was high in very elderly patients, even if they had normal SPECT MPI findings. Therefore, very elderly patients with multivariate risk factors should be carefully followed in order to prevent them from suffering a poor prognosis.

The authors state that they have no Conflict of Interest (COI).

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