Impact of Follow-Up Ischemia on Myocardial Perfusion Single-Photon Emission Computed Tomography in Patients with Coronary Artery Disease

Se Hun Kang[1]*, Hyo In Choi[2]*, Young-Hak Kim[2], Eun Young Lee[2], Jung-Min Ahn[2], Seungbong Han[3], Pil Hyung Lee[2], Jae-Hyung Roh[2], Sung-Han Yun[2], Duk-Woo Park[2], Soo-Jin Kang[2], Seung-Whan Lee[2], Cheol Whan Lee[2], Dae Hyuk Moon[4], Seong-Wook Park[2], and Seung-Jung Park[2]

[1]Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam;
[2]Division of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul;
[3]Department of Applied Statistics, Gachon University, Seongnam;
[4]Department of Nuclear Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

Purpose: Few studies have reported on predicting prognosis using myocardial perfusion single-photon emission computed tomography (SPECT) during coronary artery disease (CAD) treatment. Therefore, we aimed to assess the clinical implications of myocardial perfusion SPECT during follow-up for CAD treatment.

Materials and Methods: We enrolled 1153 patients who had abnormal results at index SPECT and underwent follow-up SPECT at intervals ≥6 months. Major adverse cardiac events (MACE) were compared in overall and 346 patient pairs after propensity-score (PS) matching.

Results: Abnormal SPECT was associated with a significantly higher risk of MACE in comparison with normal SPECT over the median of 6.3 years (32.3% vs. 19.8%; unadjusted $p<0.001$). After PS matching, abnormal SPECT posed a higher risk of MACE [32.1% vs. 19.1%; adjusted hazard ratio (HR)=1.73; 95% confidence interval (CI)=1.27−2.34; $p<0.001$] than normal SPECT. After PS matching, the risk of MACE was still higher in patients with abnormal follow-up SPECT in the revascularization group (30.2% vs. 17.9%; adjusted HR=1.73; 95% CI=1.15−2.59; $p=0.008$). Low ejection fraction [odds ratio (OR)=5.33; 95% CI=3.39−8.37; $p<0.001$] and medical treatment (OR=2.68; 95% CI=1.93−3.72; $p<0.001$) were independent clinical predictors of having an abnormal result on follow-up SPECT.

Conclusion: Abnormal follow-up SPECT appears to be associated with a high risk of MACE during CAD treatment. Follow-up SPECT may play a potential role in identifying patients at high cardiovascular risk.

Key Words: Single-photon emission computerized tomography, prognosis, coronary artery disease

INTRODUCTION

Stress myocardial perfusion imaging using single-photon emission computed tomography (SPECT) is commonly used for risk stratification and therapeutic decision making in patients with coronary artery disease (CAD).[1-3] Since ischemia is a strong predictor of adverse outcomes, such as death or myocardial infarction (MI),[4,5] detecting ischemia is an important part of the diagnostic strategy for patients with stable CAD. In addition to the diagnostic and prognostic utility of myocardial perfusion SPECT, the extent of ischemia is one of the primary measures that drives decisions regarding revascularization.[6-8] Patients

with moderately or severely abnormal myocardial perfusion SPECT have significantly higher mortality rates if treated with medical therapy alone.[5,7] Previous studies on myocardial perfusion SPECT have focused on the prognostic utility of stress imaging as the initial test for patients with CAD.[8,9] However, there are only a few studies that show a relationship between the presence and severity of ischemia and prognosis during CAD treatment.[10-12] Therefore, according to the current guidelines and appropriate use criteria for follow-up of CAD, routine stress imaging is not recommended, except for special high-risk groups after coronary revascularization.[13,14] Hence, in the current study, we aimed to assess the clinical implications of serial myocardial perfusion SPECT in patients with CAD who were receiving either medication or revascularization therapy.

MATERIALS AND METHODS

Study population

We identified consecutive patients who underwent serial myocardial perfusion SPECT, had abnormal results on a first study [which was defined as summed stress score (SSS) ≥3],[15] and had follow-up adenosine stress SPECT at an interval ≥6 months between the two studies that were performed between January 1, 2000 and June 31, 2014. Patients were also excluded if they had MI <3 months before initial SPECT, previous revascularization therapy, serious non-coronary heart disease, including cancer with a life expectancy less than one year, incomplete nuclear data, multiple coronary revascularizations between the two SPECT procedures, and no clinical follow-up information. As a result, a total of 1153 patients with serial SPECT studies were included (Fig. 1). Because of the retrospective nature of the study, a waiver for individual informed consent was granted

by the Institutional Review Board.

Myocardial perfusion imaging

Thallium-201 (Tl-201) SPECT was the default stress myocardial perfusion imaging used during the study period. Images were acquired with a standardized protocol.[16] Adenosine was intravenously administered at a rate of 140 mcg/kg/minute for 6 min. Three minutes after the initiation of the adenosine infusion, a dose of Tl-201 (range=92.5–148 MBq, as determined by the patient's body weight) was intravenously injected. Six minutes after adenosine infusion, post-stress myocardial perfusion images were acquired using two-head gamma cameras equipped with low-energy, all-purpose collimators. The specific acquisition parameters were dependent on the camera.

Image interpretation

Semi-quantitative visual interpretation was performed by independent expert interpreters, using 17 segments for the severity and extent of abnormalities on stress imaging.[17] Each segment was scored using a 5-point scoring system (0=normal; 1=equivocal; 2=moderate; 3=severe reduction in radioisotope uptake; 4=absence of detectable tracer uptake in a segment), as previously described.[18] The score that was summed from the stress scan was defined as the SSS: SSS was determined by adding the scores of the 17 segments on the stress images. The SPECT study was considered to be abnormal if the SSS was 3 or greater. According to the result of follow-up myocardial perfusion SPECT, patients were categorized into normal and abnormal groups.

Procedure and follow-up

Coronary angiography was recommended for patients on the basis of their clinical presentation and the results of the noninvasive stress test. Significant stenosis on coronary angiogra-
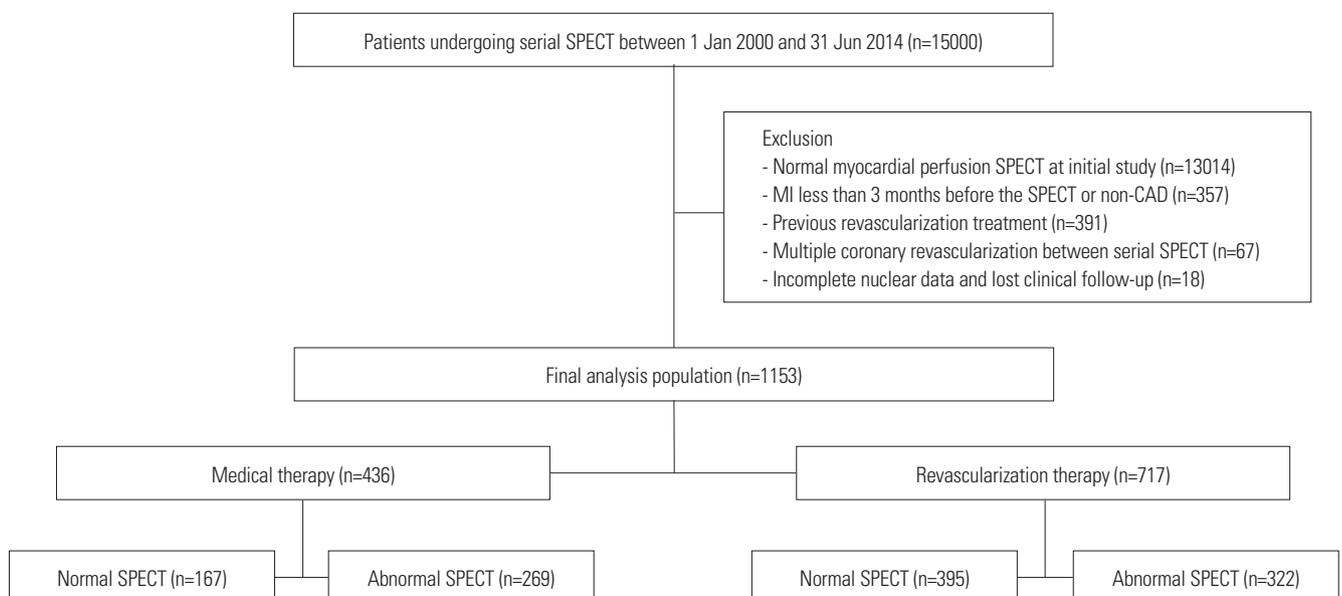
Fig. 1. Patient flow. CAD, coronary artery disease; MI, myocardial infarction; SPECT, single-photon emission computed tomography.

phy was defined as >50% stenosis in an epicardial coronary artery. In patients with significant stenosis, the decision to perform revascularization or medical therapy was at the discretion of the individual cardiologist. Percutaneous coronary intervention (PCI)[19] or coronary artery bypass graft (CABG) surgery was performed using standard techniques.[20] Medical treatment was performed with a medical regimen that consisted of at least antiplatelet, antianginal, and lipid-lowering therapies.[3] After index myocardial perfusion SPECT, patients received either medical treatment or revascularization treatment.

Definitions

The primary outcome of interest was the occurrence of major adverse cardiac events (MACE), which was the composite of all-cause death, nonfatal MI, or unplanned revascularization after follow-up myocardial perfusion SPECT. When patients received multiple serial myocardial perfusion SPECTs, the first follow-up SPECT with an interval of ≥6 months after the index myocardial perfusion SPECT was selected for analysis. An MI was defined as elevated cardiac enzymes (troponin I or myocardial band fraction of creatine kinase) more than the upper limit of the normal value with ischemic symptoms or electrocardiography findings that were indicative of ischemia. After follow-up myocardial perfusion SPECT, any further PCI or CABG (excluding planned staged PCI) was considered an unplanned revascularization. Death, non-fatal MI, and unplanned revascularizations were verified by reviewing medical records.

Table 1. Baseline Characteristics of the Study Patients with Normal and Abnormal Follow-Up SPECT Results

Variables	Total population			Medication group			Revascularization group		
	Normal (n=562)	Abnormal (n=591)	p value	Normal (n=167)	Abnormal (n=269)	p value	Normal (n=395)	Abnormal (n=322)	p value
Age, yr	61.4±9.6	61.7±10.0	0.564	61.6±10.4	61.1±10.3	0.611	61.3±9.3	62.2±9.8	0.191
Male	380 (67.6)	435 (73.6)	0.030	110 (65.9)	199 (74.0)	0.089	270 (68.4)	236 (73.3)	0.174
BMI, kg/m²	25.1±3.0	25.2±3.5	0.447	25.3±2.9	25.0±3.8	0.421	25.0±3.0	25.4±3.3	0.109
Hypertension	340 (60.5)	395 (66.8)	0.030	98 (58.7)	191 (71.0)	0.011	242 (61.3)	204 (63.4)	0.620
Diabetes mellitus	179 (31.9)	233 (39.4)	0.009	44 (26.3)	94 (34.9)	0.077	135 (34.2)	139 (43.2)	0.017
Hyperlipidemia	201 (35.8)	207 (35.0)	0.841	59 (35.3)	110 (40.9)	0.290	142 (35.9)	97 (30.1)	0.117
Current smoker	162 (28.8)	184 (31.1)	0.149	54 (32.3)	83 (30.9)	0.770	108 (27.3)	101 (31.4)	0.482
Chronic renal failure	23 (4.1)	33 (5.6)	0.298	13 (7.8)	25 (9.3)	0.713	10 (2.5)	8 (2.5)	1.000
Chronic lung disease	15 (2.7)	10 (1.7)	0.349	9 (5.4)	7 (2.6)	0.214	6 (1.5)	3 (0.9)	0.715
Laboratory data									
Total cholesterol, mg/dL	180.6±42.5	181.2±41.2	0.801	182.1±40.2	181.2±38.9	0.825	178.0±43.4	181.2±43.0	0.703
Serum creatinine, mg/dL	1.1±1.0	1.3±1.7	0.009	1.2±1.2	1.5±2.2	0.071	1.1±0.9	1.2±1.2	0.217
LV EF, %	59.0±8.1	53.1±11.6	<0.001	57.5±8.6	53.0±11.6	<0.001	59.7±7.8	53.2±11.7	<0.001
LV EF <50%	36 (6.4)	175 (29.6)	<0.001	13 (7.8)	78 (29.0)	<0.001	23 (5.8)	97 (30.1)	<0.001
Medications									
Beta-blocker	424 (75.4)	464 (78.5)	0.243	116 (69.5)	208 (77.3)	0.087	308 (78.0)	256 (79.5)	0.685
CCB	512 (91.1)	489 (82.7)	<0.001	126 (75.4)	192 (71.4)	0.412	386 (97.7)	297 (92.2)	0.001
ACEi or ARB	164 (29.2)	280 (47.4)	<0.001	53 (31.7)	138 (51.3)	<0.001	111 (28.1)	142 (44.1)	<0.001
Statin	340 (60.5)	339 (57.4)	0.307	55 (32.9)	116 (43.1)	0.044	285 (72.2)	223 (69.3)	0.443
Coronary angiography	463 (82.4)	442 (74.8)	0.002	91 (54.5)	144 (53.5)	0.923	398 (100.0)	324 (100.0)	1.000
Disease extent			<0.001			<0.001			<0.001
1 vessel	129 (23.0)	105 (17.8)		24 (14.4)	49 (18.2)		85 (21.4)	56 (17.4)	
2 vessel	111 (19.8)	110 (18.6)		16 (9.6)	39 (14.5)		95 (23.9)	71 (22.0)	
3 vessel	207 (36.8)	229 (38.7)		11 (6.6)	35 (13.0)		196 (49.2)	194 (60.2)	
Left main disease	83 (14.8)	72 (12.2)	0.048	3 (1.8)	4 (1.5)	0.365	80 (20.3)	68 (21.1)	0.520
SPECT results									
Interval between 2 tests, days	734.2±723.9	817.6±705.7	0.048	1237.0±802.2	1082.8±724.8	0.039	521.6±567.9	596.1±607.1	0.091
SSS at baseline	8.3±4.3	9.9±5.2	<0.001	7.2±4.0	8.2±4.2	0.011	8.8±4.4	11.3±5.4	<0.001
SSS at follow-up	0.8±1.2	7.8±3.9	<0.001	0.9±1.2	7.6±3.7	<0.001	0.8±1.1	8.0±4.0	<0.001
Angina at follow-up	114 (20.3)	124 (21.0)	0.770	41 (24.6)	61 (22.7)	0.653	73 (18.5)	63 (19.0)	0.713

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body-mass index; CCB, calcium channel blocker; LV EF, left ventricular ejection fraction; SPECT, single-photon emission computed tomography; SSS, summed stress score.
Values are presented as a n (%) or mean±SD.

Statistical analysis

The continuous and categorical covariates are summarized as a mean±standard deviation or count (%). According to the follow-up myocardial perfusion SPECT results, all patients were divided into normal and abnormal groups. The baseline patient characteristics were compared between the two groups using the t test or Fisher exact test for continuous and categorical variables, respectively. The cumulative incidence of MACE for the normal and the abnormal groups was obtained using the Kaplan-Meier method and compared between the two groups using the log-rank test. To examine the effect of abnormal results on MACE and its individual events, the unadjusted and adjusted Cox proportional hazards regression models were fitted. Covariates that were statistically significant in univariate analysis and/or those that were clinically relevant were considered candidate variables for multivariate models. In the Cox model, the proportionality assumptions were assessed using the Schoenfeld residual test, and no relevant violations were detected.

To reduce treatment selection bias and potential confounding, propensity score (PS)-matching analysis was performed. The PS of obtaining the abnormal myocardial perfusion SPECT results was estimated using the nearest-neighbor matching method with a caliper width of 0.2. The considered variables for the PS were age, sex, body mass index, hypertension, diabetes mellitus, current smoking, hyperlipidemia, prior revascularization treatment, chronic pulmonary disease, chronic renal failure, creatinine, total cholesterol, left ventricular (LV) ejection fraction <50%, and the use of beta blockers, calcium channel blockers (CCB), angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) agents, or statins, which are listed in Table 1. In general, covariate balancing was considered to be achieved as long as the absolute standardized dif-

ference of the means or proportions was <0.25. In the PS analyses, no violations of covariate balancing were detected (Supplementary Fig. 1, only online). For the PS-matched cohorts, continuous variables were compared using the paired t test or the Wilcoxon signed-rank test, as appropriate, and the categorical variables were compared using the McNemar's or Bowker's test of symmetry, as appropriate. A subgroup analysis was performed according to the treatment groups. Furthermore, univariate and multivariate logistic regression analyses were performed to identify independent clinical predictors of having abnormal results on follow-up myocardial perfusion SPECT. In the multivariable logistic regression, we employed a backward variable selection approach based on the *p* values. The significance level for staying in the model was set to 0.05. All statistical analyses were performed using SPSS (version 19.0 software; IBM Corp., Armonk, NY, USA) and R software (version 2.13; R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). Additionally, the R package MatchIt was used to conduct the PS analysis.[21] All tests were two-tailed, and *p*<0.05 was considered statistically significant.

RESULTS

Overall population

Baseline characteristics

The median follow-up interval between the index and follow-up myocardial perfusion SPECT procedures was 474 days [interquartile range (IQR)=243–1107 days]. Abnormal results on follow-up myocardial perfusion SPECT were noted in 591 patients (51.3%). The baseline clinical characteristics and myo-
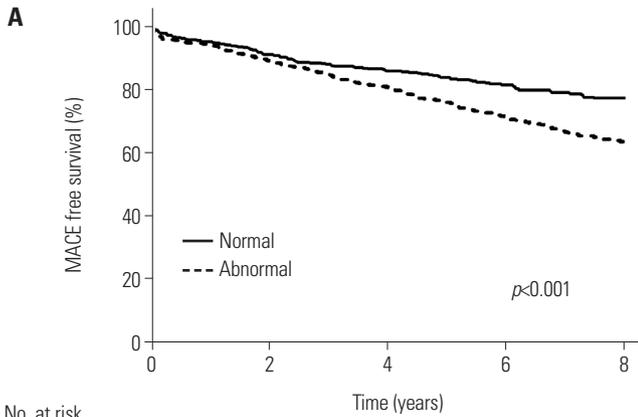
Table 2. Clinical Outcomes in Patients with Abnormal Follow-Up SPECT in Comparison with Normal SPECT in the Overall Population

Variables	Normal	Abnormal	Unadjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)*	*p* value
Overall population[†]						
MACE	111 (19.8)	191 (32.3)	1.735 (1.373–2.193)	<0.001	1.595 (1.249–2.038)	<0.001
Death	74 (13.2)	114 (19.3)	1.472 (1.098–1.972)	0.010	1.235 (0.907–1.681)	0.180
Myocardial infarction	22 (3.9)	48 (8.1)	2.114 (1.276–3.502)	0.004	1.697 (0.997–2.888)	0.051
Unplanned revascularization	37 (6.6)	56 (9.5)	1.477 (0.975–2.237)	0.066	1.634 (1.060–2.517)	0.026
Medication group[‡]						
MACE	36 (21.6)	87 (32.3)	1.492 (1.012–2.201)	0.044	1.472 (0.979–2.211)	0.063
Death	32 (19.2)	54 (20.1)	0.974 (0.629–1.509)	0.907	0.978 (0.616–1.550)	0.923
Myocardial infarction	5 (3.0)	23 (8.6)	2.667 (1.013–7.021)	0.047	2.134 (0.770–5.915)	0.145
Unplanned revascularization	5 (3.0)	20 (7.4)	2.309 (0.864–6.168)	0.095	2.118 (0.764–5.872)	0.149
Revascularization group[§]						
MACE	75 (19.0)	104 (32.3)	1.772 (1.316–2.384)	<0.001	1.662 (1.218–2.269)	0.001
Death	42 (10.6)	60 (18.6)	1.720 (1.159–2.552)	0.007	1.409 (0.930–2.133)	0.106
Myocardial infarction	17 (4.3)	25 (7.8)	1.791 (0.967–3.317)	0.064	1.613 (0.847–3.072)	0.146
Unplanned revascularization	32 (8.1)	36 (11.2)	1.414 (0.878–2.277)	0.154	1.602 (0.980–2.620)	0.060

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography.
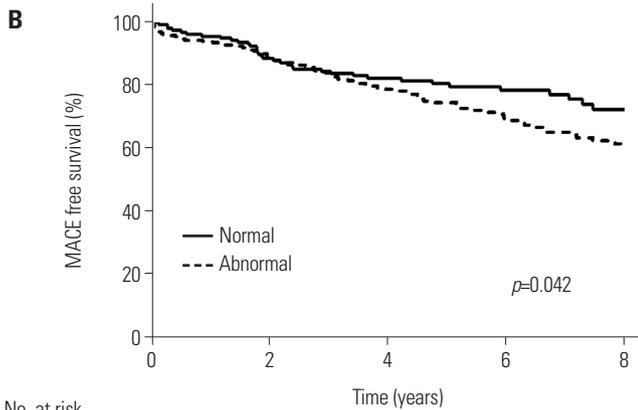*The adjusted covariates included age, diabetes mellitus, chronic renal failure, chronic lung disease, use of ACEi or ARB, use of statins, and left ventricular ejection <50%, [†]Nomal: n=562, abnormal: n=591, [‡]Nomal: n=167, abnormal: n=269, [§]Nomal: n=395, abnormal: n=322.

cardial perfusion SPECT results, according to the results of the follow-up myocardial perfusion SPECT procedures and treatment strategy, are presented in Table 1. The patients in the ab-
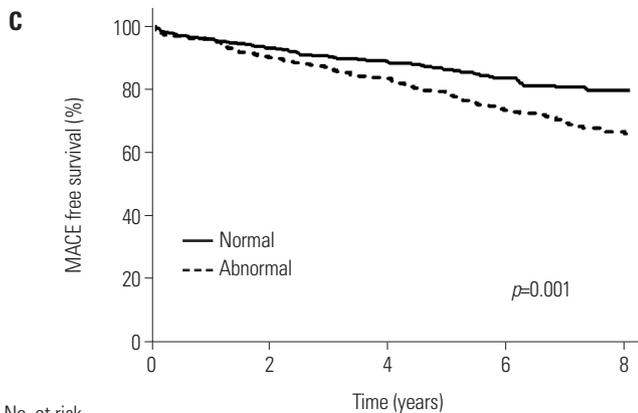
normal group were more likely to be male and have a higher incidence of hypertension, diabetes mellitus, and a low ejection fraction. On myocardial perfusion SPECT, the abnormal group had greater baseline perfusion defects than the normal group. The revascularization therapy group was older and more likely to have diabetes mellitus, greater extent of CAD, and high perfusion defect on the initial myocardial perfusion SPECT (Supplementary Table 1, only online).

Clinical outcomes

Patients were followed for a median of 6.3 years (IQR=3.7–9.1 years) after the follow-up myocardial perfusion SPECT. During the follow-up period, 188 patients died, 70 patients developed nonfatal MI, and 93 patients underwent unplanned revascularization (Table 2). The incidence of MACE was significantly higher in the abnormal group in the overall population and both treatment groups (Fig. 2), and there was also a significant difference in the clinical outcomes of patients according to the result of serial SPECT (Fig. 3). There was also a tendency for a higher risk of events in patients with abnormal follow-up SPECT in comparison with normal SPECT in all subgroups after adjustment using the multivariate Cox model, as indicated in Table 2.

Propensity-matched population

Baseline characteristics

After performing PS matching, 346, 112, and 212 matched pairs of patients in the overall population, medication alone, and revascularization groups were created, respectively (Table 3). There were no significant differences in the baseline clinical characteristics of the PS-matched patients, except the extent of CAD and the results of SPECT.
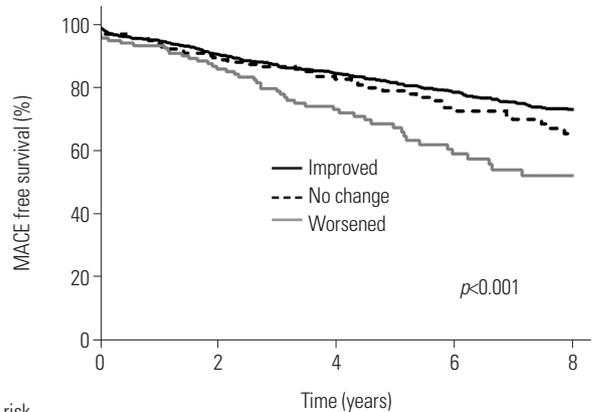
Fig. 2. Kaplan-Meier curves of the cumulative incidence of MACE in patients with normal follow-up SPECT (solid line) versus abnormal follow-up SPECT (dashed line) in the (A) overall population, (B) medication group, and (C) revascularization group. MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography.

Fig. 3. Kaplan-Meier curves of the cumulative incidence of MACE in patients with improved (black solid line), no change (dashed line), and worsened (gray solid line) in the result of serial SPECT. MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography.

Table 3. Baseline Characteristics between the Patients with Normal and Abnormal Follow-Up SPECT Results in the Propensity Score-Matched Population

Variables	Total population			Medication group			Revascularization group		
	Normal (n=346)	Abnormal (n=346)	p value	Normal (n=112)	Abnormal (n=112)	p value	Normal (n=212)	Abnormal (n=212)	p value
Age, yr	61.8±9.2	61.8±9.6	0.952	60.5±10.6	61.5±9.4	0.480	61.0±9.5	62.4±10.0	0.140
Male	389 (70.1)	404 (72.8)	0.340	74 (66.1)	74 (66.1)	1.000	148 (69.8)	144 (67.9)	0.753
BMI, kg/m^2	25.1±2.8	25.2±3.0	0.880	25.3±2.5	25.2±3.1	0.698	24.9±3.2	25.1±2.9	0.477
Hypertension	217 (62.7)	216 (62.4)	1.000	68 (60.7)	78 (69.6)	0.207	132 (62.3)	138 (65.1)	0.614
Diabetes mellitus	112 (32.4)	119 (34.4)	0.629	28 (25.0)	29 (25.9)	1.000	77 (36.3)	82 (38.7)	0.688
Hyperlipidemia	119 (34.4)	113 (32.7)	0.687	39 (34.8)	42 (37.5)	0.781	66 (31.1)	66 (31.1)	1.000
Current smoker	93 (27.5)	97 (29.0)	0.723	38 (33.9)	33 (29.5)	0.712	67 (31.8)	59 (27.8)	0.438
Chronic renal failure	14 (4.0)	12 (3.5)	0.842	9 (8.0)	7 (6.2)	0.795	3 (1.4)	4 (1.9)	1.000
Chronic lung disease	8 (2.3)	7 (2.0)	1.000	8 (7.1)	3 (2.7)	0.216	2 (0.9)	3 (1.4)	1.000
Laboratory data									
Total cholesterol, mg/dL	183.0±42.1	182.6±42.7	0.902	185.2±40.4	181.6±34.9	0.480	179.5±44.0	180.9±43.8	0.739
Serum creatinine, mg/dL	1.1±0.0	1.1±1.1	0.876	1.2±1.3	1.1±1.2	0.663	1.1±1.1	1.1±1.1	0.872
LV EF, %	59.2±8.4	58.3±7.9	0.170	58.5±8.0	59.2±6.7	0.496	58.9±7.9	58.2±7.7	0.297
LV EF <50%	24 (6.9)	23 (6.6)	1.000	7 (6.2)	5 (4.5)	0.767	17 (8.0)	18 (8.5)	1.000
Medications									
Beta-blocker	271 (78.3)	272 (78.6)	1.000	80 (71.4)	84 (75.0)	0.651	168 (79.2)	172 (81.1)	0.715
CCB	313 (90.5)	301 (87.0)	0.186	85 (75.9)	84 (75.0)	1.000	206 (97.2)	202 (95.3)	0.445
ACEi or ARB	108 (31.2)	98 (28.3)	0.454	29 (25.9)	30 (26.8)	1.000	74 (34.9)	64 (30.2)	0.351
Statin	200 (57.8)	199 (57.5)	1.000	34 (30.4)	29 (25.9)	0.552	144 (67.9)	146 (68.9)	0.917
Coronary angiography	292 (84.4)	288 (83.2)	0.757	67 (59.8)	69 (61.6)	0.891	196 (92.5)	196 (92.5)	1.000
Disease extent			0.016			0.008			0.025
1 vessel	63 (18.2)	43 (12.4)		19 (17.0)	21 (18.8)		42 (19.8)	22 (10.4)	
2 vessel	67 (19.4)	75 (21.7)		13 (11.6)	19 (17.0)		52 (24.5)	46 (21.7)	
3 vessel	136 (39.3)	152 (43.9)		9 (8.0)	19 (17.0)		102 (48.1)	127 (59.9)	
Left main disease	51 (14.7)	47 (13.6)	0.893	3 (2.7)	2 (1.8)	0.327	37 (17.5)	41 (19.3)	0.854
SPECT results									
Intervals between 2 tests, days	728.6±699.0	752.7±657.5	0.640	1230.1±794.9	1056.6±713.0	0.087	507.8±612.9	617.7±577.9	0.058
SSS at baseline	8.1±4.0	9.3±4.9	<0.001	7.0±3.6	7.4±3.6	0.367	8.8±4.5	10.7±5.0	0
SSS at follow-up	0.8±1.1	7.3±3.7	<0.001	0.7±1.1	6.5±2.8	<0.001	0.8±1.2	7.4±3.7	0
Angina at follow-up	71 (20.5)	77 (22.3)	0.643	30 (26.8)	26 (23.2)	0.643	42 (19.8)	48 (22.6)	0.553

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body-mass index; CCB, calcium channel blocker; LV EF, left ventricular ejection fraction; SPECT, single-photon emission computed tomography; SSS, summed stress score.
Values are presented as a n (%) or mean±SD.

Clinical outcomes
In the matched patients, there were 177 MACE events within the median follow-up period of 6.6 years. With respect to the MACE in the matched cohorts, the abnormal group was associated with worse clinical outcomes in the overall population and the revascularization groups (Fig. 4). We noted a consistent pattern in that the abnormal follow-up SPECT group was at a higher risk of MACE and its individual events than the normal group in PS-matched overall patients, medication alone and revascularization groups (Table 4).

Predictors of abnormal follow-up SPECT
Table 5 lists the independent predictors of abnormal results on follow-up SPECT. The variables considered for inclusion in

the multivariate models were sex, hypertension, diabetes mellitus, body mass index ≥25 kg/m^2, current smoking, chronic kidney disease, history of previous revascularization therapy, LV ejection fraction <50%, treatment with CCB, ACEi, or ARB, and the treatment method. Low ejection fraction was a predictor of abnormal follow-up SPECT, the overall population, medication alone and revascularization groups. Revascularization therapy was a protective factor of abnormal SPECT.

DISCUSSION

In the present study, we evaluated the long-term clinical implications of follow-up SPECT during CAD treatment with com-

Table 4. Clinical Outcomes in Patients with Abnormal Follow-Up SPECT Compared with Normal SPECT in a Propensity-Matched Population

Variables	Normal group	Abnormal group	Adjusted HR* (95% CI)	p value
Overall population (346 pairs)				
MACE	66 (19.1)	111 (32.1)	1.727 (1.273–2.344)	<0.001
Death	44 (12.7)	59 (17.1)	1.230 (0.830–1.821)	0.302
Myocardial infarction	15 (4.3)	26 (7.5)	1.694 (0.896–3.202)	0.105
Unplanned revascularization	25 (7.2)	38 (11.0)	1.566 (0.945–2.595)	0.082
Medication group (112 pairs)				
MACE	25 (22.3)	34 (30.4)	1.374 (0.801–2.358)	0.248
Death	22 (19.6)	17 (15.2)	0.701 (0.359–1.367)	0.297
Myocardial infarction	3 (2.7)	12 (10.7)	5.370 (1.401–20.583)	0.014
Unplanned revascularization	5 (4.5)	8 (7.1)	1.488 (0.457–4.842)	0.509
Revascularization group (212 pairs)				
MACE	38 (17.9)	64 (30.2)	1.730 (1.154–2.594)	0.008
Death	22 (10.4)	32 (15.1)	1.274 (0.734–2.208)	0.389
Myocardial infarction	7 (3.3)	15 (7.1)	2.094 (0.850–5.160)	0.108
Unplanned revascularization	18 (8.5)	27 (12.7)	1.571 (0.863–2.861)	0.140

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography.
*Adjusted covariates included age, diabetes mellitus, chronic renal failure, chronic lung disease, use of ACEi or ARB, use of statin, and left ventricular ejection <50%; adjusted HRs represent the risk of each clinical outcome comparing abnormal follow-up SPECT with normal follow-up SPECT.

Table 5. Independent Predictors of an Abnormal Follow-Up SPECT*

Variables	Total population			Medication group			Revascularization group		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Male	1.342	0.968–1.860	0.077	2.147	1.133–4.069	0.019	1.161	0.788–1.710	0.449
BMI ≥25 kg/m²	1.124	0.851–1.486	0.410	0.854	0.499–1.464	0.567	1.262	0.905–1.759	0.170
LV EF <50%	5.330	3.393–8.374	<0.001	3.499	1.462–8.373	0.005	6.041	3.558–10.256	<0.001
ACEi or ARB	1.240	0.905–1.699	0.181	1.352	0.735–2.485	0.332	1.234	0.847–1.796	0.273
Medical therapy	2.683	1.934–3.721	<0.001	-	-	-	-	-	-

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body-mass index; CI, confidence interval; LV EF, left ventricular ejection fraction; OR, odds ratio; SPECT, single-photon emission computed tomography.
*Adjusted covariates included male sex, hypertension, diabetes mellitus, current smoking, chronic renal failure, BMI ≥25 kg/m², LV EF <50%, treatment with ACEi or ARB, and medication therapy.

parisons of the clinical outcomes between patients with normal and abnormal follow-up SPECT results. The major findings of this study included the following: 1) abnormal results on follow-up SPECT were associated with worse clinical outcomes, as indicated by an increased risk of death, MI, or unplanned revascularization in the overall study population, and 2) low ejection fraction and medical treatment were independent clinical predictors of having an abnormal result on follow-up SPECT.
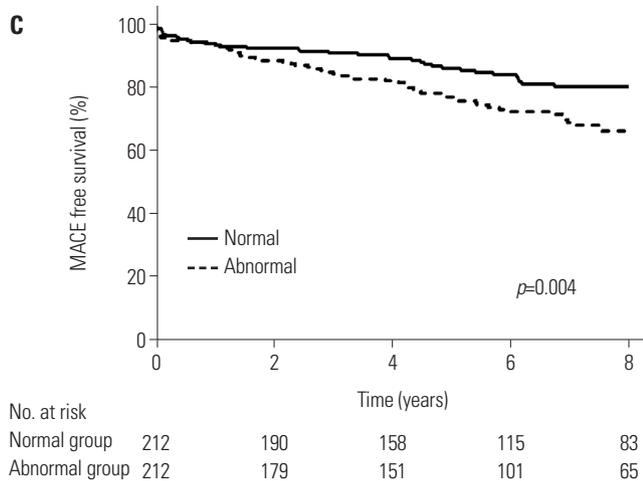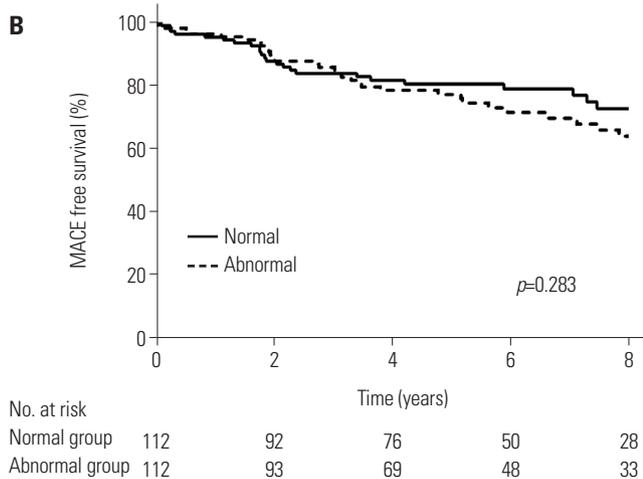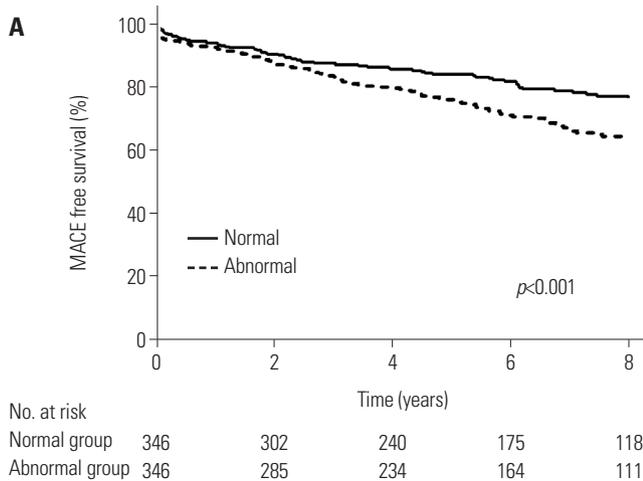
Previous randomized studies of serial myocardial perfusion SPECT demonstrated significant reductions in myocardial ischemia after diverse interventions, including the administration of medical therapy or coronary revascularization.[22,23] In the COURAGE sub-study, residual ischemia was an unadjusted predictor of events, although the noted association was not significant when adjusted for the treatment arm.[10] Recent studies have further suggested that a reduction in ischemia on myocardial perfusion SPECT with either medical or coronary revascularization therapy may identify a patient at lower risk for a sub-

sequent cardiac event.[10,24] Despite the potential advantages of follow-up myocardial perfusion SPECT, clinical practice guidelines and appropriate use criteria do not recommend routine serial testing due to the lack of evidence that supports the benefit of follow-up myocardial perfusion SPECT.[13,25] A report suggested that >5% worsening ischemia is an independent predictor of death or MI, irrespective of the treatment arm, such as medical therapy or revascularization.[26] However, these previous studies were limited by small study populations or case-control designs. Our study, despite its retrospective, single-center, observational study design, is relatively stronger, because it includes a larger study population that was treated at a real-world practice with a longer follow-up period.

The present study demonstrates that follow-up ischemia is associated with adverse outcomes, such as death, MI, and unplanned revascularization. The association between mortality and follow-up ischemia is in line with a previous study that reported that revascularization reduces mortality in patients with an ischemic burden ≥10% on baseline myocardial perfusion

SPECT.[7,27] In our study, among the overall population and the revascularization group, abnormal results on follow-up SPECT demonstrated an increased risk of MACE, death, and MI. In

A

No. at risk

Normal group	346	302	240	175	118
Abnormal group	346	285	234	164	111

B

No. at risk

Normal group	112	92	76	50	28
Abnormal group	112	93	69	48	33

C

No. at risk

Normal group	212	190	158	115	83
Abnormal group	212	179	151	101	65

Fig. 4. Kaplan-Meier curves of the cumulative incidence of MACE in patients with normal follow-up SPECT (solid line) versus abnormal follow-up SPECT (dashed line) in the (A) overall population, (B) medication group, and (C) revascularization group in the PS-matched population. MACE, major adverse cardiac events; SPECT, single-photon emission computed tomography; PS, propensity score.

the medical group, abnormal SPECT was also associated with a higher risk of MACE and unplanned revascularization. Due to the observational study design, unfavorable clinical factors, such as male sex and lower LV ejection fraction, may contribute to worse clinical outcomes in patients with abnormal follow-up SPECT. However, consistent findings after rigorous adjustment with PS matching support our hypothesis that the prognostic benefit of baseline myocardial perfusion SPECT could be applied to follow-up perfusion SPECT in order to predict long-term clinical prognosis. These results indicate that serial myocardial SPECT after receiving either medication alone or revascularization therapy may be helpful for predicting prognosis and subsequently determining the need for more aggressive treatment.

According to current guidelines, myocardial perfusion SPECT is considered appropriate when symptom recurrence, suspected incomplete revascularization, or ≥5 years after CABG.[13,28] Therefore, it is of interest to select appropriate patients who can receive myocardial SPECT as a risk assessment modality when they demonstrate the ambiguous presentation of symptoms. Our present findings indicate that abnormal myocardial SPECT results are common in patients with low LV ejection fraction and treatment with medication only. These factors may be indirectly associated with abnormal follow-up SPECT due to the risk of revascularization or decompensated symptoms of CAD.[29,30] Therefore, our analysis implies that patients with the risk factors for abnormal SPECT are potential candidates who could benefit from receiving follow-up SPECT in order to determine the appropriate treatment strategy.

Our study had some limitations. This was a single-center, observational, retrospective study with the biases that are inherent to this type of analysis. There were also significant baseline differences between patients with normal and abnormal follow-up myocardial SPECT. In addition, patients did not routinely receive serial myocardial perfusion SPECT; rather SPECT was performed at the discretion of the individual physician. Even after statistical adjustment therefore, unobserved confounders might have influenced the results. However, the patients in this study may be representative of a real-world population in daily clinical practice. Finally, due to the small study population, an ischemic threshold on follow-up SPECT for determining clinical prognosis was not evaluated.

In conclusion, abnormal follow-up SPECT results appear to have prognostic implications during CAD treatment in patients receiving either medication alone or revascularization therapy.

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