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Prediction of New-Onset Refractory Congestive Heart Failure Using Gated Myocardial Perfusion SPECT Imaging in Patients With Known or Suspected Coronary Artery Disease

Subanalysis of the J-ACCESS Database

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OBJECTIVES The purpose of this study was to evaluate the predictive value of perfusion/function parameters measured by gated myocardial perfusion single-photon emission computed tomography (SPECT) in combination with clinical variables in patients with known or suspected coronary artery disease to predict refractory heart failure (HF).

BACKGROUND The increasing number of HF patients requires the establishment of a prophylactic strategy that can identify patients at high risk of HF due to coronary artery disease.

METHODS We analyzed clinical and stress/rest-gated SPECT data from the multicenter, prospective, and observational J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT) database of 3,835 known or suspected coronary artery disease patients in which new-onset congestive HF symptoms requiring aggressive medical treatment were observed in 71 patients for 3 years.

RESULTS The multivariable Cox hazard model revealed that chronic renal dysfunction (hazard ratio (HR): 6.227 [95% confidence interval (CI): 2.920 to 13.279]), the end-systolic volume index (ESVI) (HR: 1.019 [95% CI: 1.011 to 1.029]), and moderate to high stress summed score (SSS) (HR: 3.012 [95% CI: 1.757 to 5.181]) independently ($p < 0.0001$) predicted HF. In addition to the close ($p < 0.0001$) correlation of ESVI and SSS with HF incidence, the combined tertiles of SSS and ESVI revealed high-risk patients with a maximally 17.3 times greater risk (5.2%/3 years) compared with the minimal risk (0.3%/3 years) at a normal to low SSS and lower ESVI. Chronic renal dysfunction combined with ESVI and SSS categories had the greatest ($p < 0.005$ to 0.001) incremental prognostic value with a global chi-square value (125.0) over single or other combined risks.

CONCLUSIONS Chronic renal dysfunction, greater stress-induced perfusion abnormality, and higher ESVI provide independent and additive information for predicting the risk of refractory HF in known or suspected coronary patients, indicating the efficacy of perfusion/function parameters measured by stress-gated perfusion SPECT for identifying patients at greater risk of future refractory HF. (J Am Coll Cardiol Img 2009;2:1393–1400) © 2009 by the American College of Cardiology Foundation

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Heart failure (HF) due to coronary artery disease (CAD) is a leading cause of cardiac death and disability. Despite recent advances in drug and nonpharmacological treatments, the number of cases of lethal HF has been increasing in developed countries (1,2), indicating the need for a more effective method to identify patients at increased risk of refractory congestive HF. The American College of Cardiology/American Heart Association Guidelines (3) show the efficacy of myocardial stress perfusion tomography for the evaluation of stress-induced ischemia, cardiovascular outcomes, and myocardial viability in CAD patients with a history of HF.

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An electrocardiography-gated approach can improve the prognostic power of a stress perfusion study for predicting cardiac death and nonfatal myocardial infarction (MI) by adding functional measurements (3–7). Although a history of HF is a major determinant of cardiac death and recurrence of HF events, data regarding the value of stress/rest-gated perfusion tomography to predict new-onset refractory HF have been sparse. This issue is important not only for stratification of HF risk but also for establishing a prophylactic strategy against this lethal disease.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CI = confidence interval
ESVI = end-systolic volume index
HF = heart failure
HR = hazard ratio
MI = myocardial infarction
SPECT = single-photon emission computed tomography
SSS = summed stress score

The J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated single-photon emission computed tomography) database using 4,031 patients with known or suspected CAD was prospectively designed to identify the value of clinical and perfusion/function measures by quantitative gated perfusion tomography for predicting major cardiac events (8,9). Despite lower mortality and hard event rates in the Japanese population, clinical risks identified in this population were similar to those reported in North American and European patients (8). Nearly one-half of the major cardiac events observed in the study were congestive HF requiring admission and aggressive medical treatment, but the risks and predictive values of gated perfusion tomography variables were not fully clarified. In the present study, we focused on new-onset refractory congestive HF events with the aim of identifying the event risks and the incremental predictive value of functional/perfusion measurements assessed by gated perfusion tomography over clinical data in patients with known or suspected CAD using the J-ACCESS database.

METHODS

Patient selection and follow-up. The design of the J-ACCESS was previously described (9). Briefly, a consecutive series of patients (at least 30 patients and as many as 40 per hospital) referred for stress-gated myocardial perfusion imaging was enrolled after meeting the following entry criteria: 1) 20 years of age or older; 2) written informed consent having been obtained; and 3) no acute coronary syndrome within the past 3 months, no severe valvular disease requiring medications, no idiopathic cardiomyopathy, no serious arrhythmias or HF of New York Heart Association functional class III/IV, and no severe liver or kidney disease. Patients were followed regularly at each hospital for 3 years with the following primary end points: cardiac death, nonfatal acute MI, and admission requiring aggressive medical treatment for severe congestive HF events defined as refractory HF. Cardiac death was defined as death due to any cardiac etiology, including acute coronary syndrome, arrhythmias, and pump failure. The diagnosis of acute MI was established by the following findings: severe prolonged chest pain, acute ST-segment elevation of $\geq$2 mm in some leads of a standard electrocardiogram for >30 min, and definite acute elevation of serum creatine kinase or troponin level during the first 2 days. A clinical diagnosis was established by symptoms and signs along with laboratory data, chest X-ray, 12-lead electrocardiogram, and, if necessary, imaging techniques such as ultrasound, X-ray, computed tomography, and coronary angiography and by excluding noncardiac death due to infection, malignancy, stroke, or other disorders. Registered physicians regularly contacted patients and checked patient records to monitor clinical conditions and finally determined the presence or absence of any cardiac event and then reported it to the J-ACCESS office. Scintigraphic results were reported to each attending physician in the outpatient clinic who managed patients regularly and determined the need for hospitalization requiring aggressive medical treatment when development of HF was suspected. Patient follow-up data were collected from 117 hospitals by the J-ACCESS office regularly at least every year for 3 years or until death. When a patient had multiple cardiac events, only the first event was used as the end point of follow-up. As described previously (8), the data for 4,031 patients were used for the outline analysis because 223 (4.8%) patients were lost during follow-up and 375 patients were excluded due to early coronary revascularization within the first 60 days. Because the present study

focused on new-onset congestive HF requiring admission and aggressive treatment, 196 patients with a history of HF were excluded and data for 3,835 patients were finally analyzed. The diagnosis of new-onset refractory congestive HF was made by several of the following findings and by the need for admission and aggressive medical treatment: findings from a careful history taking, typical symptoms (dyspnea or orthopnea), neck vein distention, peripheral edema, lung rales, S3 gallop, and tachycardia, together with chest X-ray findings (cardiomegaly, bilateral lung congestion, and/or pleural effusion). The final diagnosis of new-onset refractory congestive HF was confirmed after admission using electrocardiography, 2-dimensional echocardiography, and/or chest computed tomography to exclude noncardiac diseases with similar symptoms or signs. There was no sudden cardiac death or noncardiac death in this study.

Stress myocardial perfusion imaging. Most stress and rest technetium-99m–tetrofosmin perfusion studies were performed using a 1-day protocol (98.8%) with a mean initial dose of 305 ± 81 MBq and a mean second dose of 709 ± 132 MBq (8,9). Stress mode was as follows: 68.8% had exercise, 14.6% had dipyridamole, and 13.8% had adenosine triphosphate. Electrocardiography-gated tomographic data were obtained using a multidetector camera system equipped with a high-resolution (58.3%) or other types of collimator and reconstructed using ramp (89.7%) or Shepp-Logan (10.3%) filters (8,9).

Quantification of functional parameters by gated perfusion study. Ejection fraction (percentage), end-diastolic volume (in milliliters), and end-systolic volume (in milliliters) at rest were calculated at each institute using QGS software (Cedars Sinai Medical Center, Los Angeles, California) (9,10). The volumes were corrected by body surface area to provide the end-diastolic volume index (millimeters per square meter) and end-systolic volume index (ESVI) (milliliters per square meter). The precision of the functional parameters or preference-based variability among institutions was investigated before the start of this study, and excellent reproducibilities were confirmed: SD of left ventricular ejection fraction <3.6% and coefficient of variation of the end-diastolic volume <9.3% (11).

Semiquantitative analysis of perfusion images. Tomographic images were divided according to a standard 20-segment model and scored visually using a 5-point

Table 1. Comparison of HF and Non-HF Groups With No History of HF

Variables	HF Group (n = 71)	Non-HF Group (n = 3,764)	p Value
Age (yrs)	70.5 ± 9.6	65.6 ± 10.0	<0.0001
Sex (male)	56.3%	63.8%	0.2426
Previous myocardial infarction	45.1%	27.9%	0.0019
History of PAD	15.5%	2.8%	<0.0001
History of revascularization	40.8%	35.7%	0.3487
History of stroke	14.1%	7.8%	0.0727
Chronic renal dysfunction	11.3%	1.4%	<0.0001
Diabetes mellitus	56.3%	27.6%	<0.0001
Hypertension	67.6%	54.1%	0.0375
Hyperlipidemia	47.9%	46.8%	1.0000
Current smoker	15.5%	14.9%	1.0000
EDVI at rest (ml/m^2)	65.4 ± 30.9	50.0 ± 17.2	<0.0001
ESVI at rest (ml/m^2)	34.5 ± 28.1	20.0 ± 13.8	<0.0001
LVEF at rest (%)	53.0 ± 14.3	63.0 ± 12.6	<0.0001
Summed stress score	15.4 ± 13.7	8.0 ± 10.5	<0.0001
0–8 (low)	33.8%	68.0%	<0.0001
9–13 (moderate)	19.7%	10.8%	0.0288
≥14 (high)	46.5%	21.2%	<0.0001
Summed rest score	12.5 ± 13.6	6.7 ± 9.8	<0.0001
Summed difference score	3.2 ± 5.1	1.4 ± 3.7	0.0043
Digitalis	11.3%	3.2%	0.0008
Aspirin	77.5%	57.7%	0.0013
Beta-blocker	35.2%	22.3%	0.0169
Angiotensin receptor blocker	47.9%	32.1%	0.0072

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HF = heart failure; LVEF = left ventricular ejection fraction; PAD = peripheral artery disease.

scoring system by trained nuclear cardiologists and nuclear medicine physicians at each hospital as follows: 0, normal; 1, slightly reduced; 2, moderately reduced; 3, severely reduced; and 4, absent (12). Myocardial perfusion abnormality was assessed by summation of scores of 20 segments as follows: summed stress score (SSS), summed rest score, and summed difference score, which is the difference between the stress and rest tests. Before the study, visual assessment was standardized to minimize institutional bias in all participating hospitals, and the Image Evaluation Committee confirmed excellent agreement of SSS and summed rest score: kappa = 0.85 and lax agreement within 1 grade of summed score category (89%) (11). Based on previous risk stratification by perfusion score (5 to 7), the SSS was categorized into 3 subgroups: normal to low (SSS 0 to 8) as a low risk, moderate (SSS 9 to 13) as an intermediate risk, and high (SSS $\geq$ 14) as a high risk.

Statistical analysis. Continuous variables are shown as mean $\pm$ SD. The mean differences between the 2 groups and the prevalence of variables were compared using an unpaired *t* test and 2 $\times$ 2 chi-square test, respectively. Differences between scintigraphic (nonparametric) scores were examined by Wilcoxon rank-sum testing. For the identification of significant predictors, univariable analysis with a Cox model was performed using the variables listed in Table 1. Then multivariable analysis with a Cox proportional hazard model was performed using the statistically appropriate number of significant variables identified by the univariable analysis, which depends on incidence of HF events. Blood tests were done before or at least at the time of scintigraphic study to identify chronic renal dysfunction, which was defined in this study as a baseline serum creatinine concentration over the upper limit of normal in each laboratory (generally 1.2 mg/ml for men and 1.0 mg/ml for women) or estimated glomerular filtration rate <60 ml/min/1.73 m^2. The Kaplan-Meier method was used to determine cumulative event-free survival by key parameters for identifying a patient category at greater risk of new-onset refractory HF and were compared using the log-rank test. For the assessment of incremental prognostic values of significant predictors, global chi-square values were calculated after adding in several independent predictors identified by multivariable analy-

Table 2. Univariate Analysis for New-Onset HF Events

Variables	Wald Chi-Square	Hazard Ratio	95% Confidence Interval	p Value
Age	17.0581	1.061	1.032–1.091	<0.0001
Previous myocardial infarction	10.0238	2.137	1.336–3.421	0.0015
History of revascularization	1.1268	1.295	0.803–2.089	0.2885
History of stroke	4.0872	1.996	1.021–3.902	0.0432
History of PAD	31.4031	6.285	3.304–11.953	<0.0001
Chronic renal dysfunction	34.6532	9.116	4.367–19.026	<0.0001
Diabetes mellitus	24.6487	3.281	2.052–5.244	<0.0001
Hypertension	4.7758	1.741	1.059–2.861	0.0289
Hyperlipidemia	0.0000	1.001	0.628–1.594	0.9969
Current smoker	0.0179	1.045	0.547–1.999	0.8936
EDVI at rest (ml/m^2)	54.4255	1.027	1.019–1.034	<0.0001
ESVI at rest (ml/m^2)	69.1874	1.029	1.022–1.036	<0.0001
LVEF at rest (%)	44.4212	0.947	0.932–0.962	<0.0001
Summed stress score	31.8972	1.044	1.028–1.059	<0.0001
0–8 (low)	31.9803	0.242	0.148–0.396	<0.0001
9–13 (moderate)	5.4178	2.002	1.116–3.593	0.0199
≥14 (high)	24.1849	3.223	2.021–5.138	<0.0001
Summed rest score	22.3955	1.039	1.022–1.055	<0.0001
Summed difference score	16.2158	1.088	1.044–1.134	0.0001
Digitalis	11.8041	3.631	1.740–7.577	0.0006
Aspirin	10.3174	2.49	1.427–4.345	0.0013
Beta-blocker	6.1107	1.848	1.136–3.008	0.0134
Angiotensin receptor blocker	7.5675	1.922	1.207–3.062	0.0059

Abbreviations as in Table 1.

sis on the basis of increases in the overall likelihood ratio (13). A p value <0.05 was considered statistically significant.

RESULTS

New-onset refractory HF events were documented in 71 patients, including 10 patients in whom cardiac death occurred due to pump failure, with a mean interval of 532 ± 307 days, and 276 (7.2%) of the 3,835 patients underwent later coronary revascularization with a mean interval of 442 ± 319 days during follow-up. The data for 71 HF patients were compared with data for the remaining 3,764 patients, including 28 patients who had cardiac non-HF death and 41 patients who had acute MI. HF patients were significantly older; had a higher prevalence of hypertension, diabetes mellitus, and chronic renal dysfunction; had a history of MI/peripheral artery disease; and had significantly greater left ventricular cavity sizes, abnormal perfusion scores, and lower ejection fraction than non-HF patients (Table 1). Based on the results of univariable analysis (Table 2) and the fact that refractory HF events were observed in 71 patients, the following top 7 parameters that had the greatest Wald chi-square values among 23 variables were used for multivariable Cox hazard models: history of peripheral artery disease, chronic renal dysfunction, end-diastolic volume index, ESVI, ejection fraction, SSS, and no SSS 0–8 category (i.e., moderate to high SSS category). Chronic renal dysfunction, ESVI, and SSS category were identified as independent significant predictors of new-onset refractory HF: chronic renal dysfunction, hazard ratio (HR): 6.227 (95% confidence interval (CI): 2.920 to 13.279); ESVI, HR: 1.019 (95% CI: 1.011 to 1.029); and moderate to high SSS, HR: 3.012 (95% CI: 1.757 to 5.181) (Table 3). Additionally, multivariable analysis with a Cox proportional hazard model was performed excluding 276 patients who underwent coronary revascularization and showed that age, ESVI, and ejection fraction were identified as independent significant predictors of new-onset refractory HF (Table 4).

The moderate and high SSS subgroups (intermediate and high-risk categories) had significantly ($p < 0.0001$) lower event-free rates than the subgroup with normal to low SSS (low-risk category) (Fig. 1). According to ESVI tertile, patients were divided into lower (≤13 ml/m^2, n = 1,276), moderate (14 to 22 ml/m^2, n = 1,306), and higher (≥23 ml/m^2, n = 1,132) ESVI subgroups. The higher ESVI subgroup had a significantly ($p \leq 0.0001$) lower event-free rate than did the low or moderate ESVI subgroup (Fig. 2).

Table 3. Multivariable Analysis With a Cox Proportional Hazard Model for New-Onset HF Events

Variables	Wald Chi-Square	Hazard Ratio	95% Confidence Interval	p Value
Chronic renal dysfunction	22.4111	6.227	2.920–13.279	<0.0001
ESVI at rest (ml/m^2)	18.3374	1.019	1.011–1.029	<0.0001
SSS (moderate to high) (no low SSS)	16.0865	3.012	1.757–5.181	<0.0001

SSS = summed stress score; other abbreviations as in Table 1.

Among the SSS-categorized subgroups, patients with a higher ESVI (≥23 ml/m^2) tended to have higher HF event rates. Combined assessment of SSS and ESVI tertile revealed high-risk patients with a maximally 17.3 times greater risk (5.2%/3 years) compared with the minimal risk (0.3%/3 years) observed at a normal to low SSS and lower ESVI (Fig. 3). Figure 4 compares the global chi-square values of each significant predictor and their combinations (37.7 for chronic renal dysfunction, 51.3 for SSS, and 73.6 for ESVI) and revealed that the combination of chronic renal dysfunction, SSS, and ESVI had the greatest incremental prognostic value for new-onset refractory HF events, with a global chi-square value of 125.0 ($p < 0.005$ to 0.001).

DISCUSSION

The present results provide new insights into the initial development of severe congestive HF in suspected or known coronary patients; chronic renal dysfunction and perfusion/function measures of stress/rest-gated perfusion imaging have independent predictive values of admission due to new-onset congestive HF and aggressive care. The prevalence of CAD is lower, and the prognosis is better in Japanese patients than in patients in other developed countries (14): the hard cardiac event rate of Japanese patients (8) was less than half (9.2%/3 years) that of North American patients (7,8). Refractory congestive HF events are major cardiac events for Japanese patients (7) and have become important for estab-

Table 4. Multivariable Analysis With a Cox Proportional Hazard Model for New-Onset HF Events When Excluding 276 Patients Who Underwent Coronary Revascularization

	Wald Chi-Square	Hazard Ratio	95% Confidence Interval	p Value
Age (yrs)	31.5325	1.112	1.071–1.154	<0.0001
LVEF (%)	6.1304	0.961	0.931–0.992	0.0133
ESVI at rest (ml/m^2)	5.3539	1.018	1.003–1.033	0.0207

Abbreviations as in Table 1.

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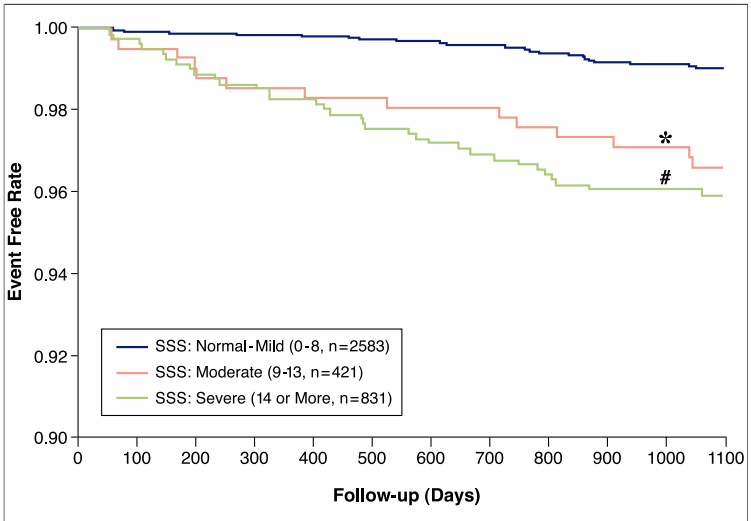

Figure 1. Kaplan-Meier Event-Free Curves of the 3 Subgroups Based on the SSS

The severe summed stress score (SSS) subgroup (SSS ≥14) and the moderate SSS subgroup (SSS 9–13) had significantly lower event-free rates than did the normal to low SSS subgroup (SSS 0–8). *#Versus normal-low, $p < 0.0001$.

lishing an early risk assessment and prophylactic strategy.

Impaired renal function or chronic kidney disease has now been recognized as an independent risk for cardiovascular outcomes, not only in patients with chronic HF (15,16) or CAD (17) but also in patients without overt sclerotic disease (18). Recently, stress myocardial perfusion defect provides useful additional information on cardiac death across the entire spectrum of renal dysfunction in suspected coronary patients (18). The present study showed that low to moderate chronic renal dysfunction was associated with an increased risk of new-onset refractory HF and was independently predictive of future development of HF requiring aggressive care even after adjustment for important confounders. This is probably because chronic renal dysfunction affects ventricular function and HF manifestation due to increases in fluid retention, myocardial stress and stiffness, and resistance to diuretics. Furthermore, endothelial dysfunction and the sclerotic process at arteriole levels, which cannot be angiographically estimated, are likely to progress subclinically and preferentially in renal and coronary arteries.

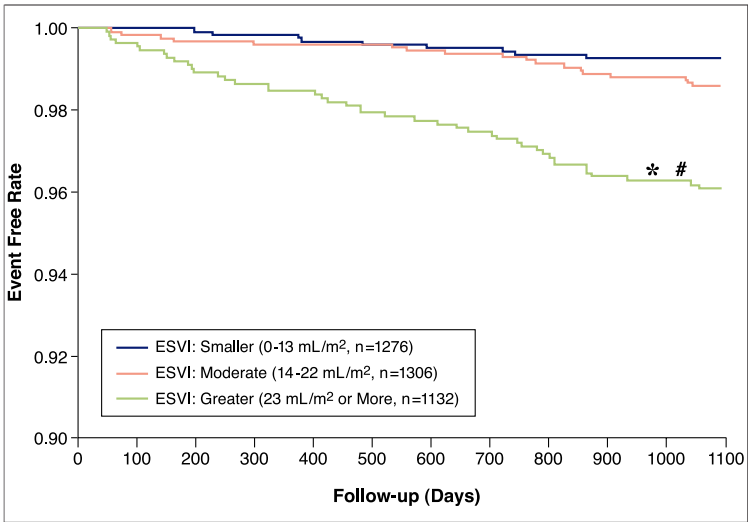

Figure 2. Kaplan-Meier Event-Free Curves Based on End-Systolic Volume Index

Kaplan-Meier event-free curves of the 3 subgroups based on end-systolic volume index (ESVI) (ml/m^2). The higher ESVI subgroup had a significantly lower event-free rate than did the moderate or lower ESVI subgroup. *Versus normal-low, $p < 0.0001$; #versus moderate, $p = 0.0001$.

SSS and ESVI assessed by quantitative gated perfusion imaging had independent and incremental prognostic values over the clinical risk in identifying patients at a greater risk of future refractory HF. The previous J-ACCESS analysis failed to correlate SSS with hard cardiac events (8), probably because of a low hard event rate (2.4%/3 years). Earlier studies (4–7) demonstrated that an intermediate to high risk SSS category is associated with hard cardiac events, and post-stress ejection fraction and volume on gated study have incremental value over perfusion information. Compared with SSS itself, the moderate to high SSS category was more clearly identified as an independent greater risk status in this study. Sharir et al. (5,6) showed that post-stress ESV is dependently and incrementally associated with hard and overall coronary events but not with HF worsening. In this study, ESV was measured at rest and used after correction by body surface area to cancel physical difference, and the present study focused specifically on new-onset refractory congestive HF requiring admission and aggressive treatment. It is also known that nearly half of HF patients have preserved ejection fractions. These observations may explain the prognostic values of ESVI independently of ejection fraction. Additional multivariable Cox analysis revealed that in the case of excluding revascularized patients, age, ESVI, and ejection fraction were independent predictors of new-onset refractory HF. Thus, perfusion abnormality assessed by stress myocardial perfusion imaging and the remodeling process before an overtly impaired ejection fraction are closely associated with future admission due to refractory

congestive HF, particularly in patients with chronic renal dysfunction.

J-ACCESS was not an interventional investigation and did not provide information on an appropriate preventive strategy against refractory HF. Further study is required to establish a prophylactic or therapeutic strategy, including beta-blockers, renin-angiotensin-aldosterone system inhibitors, and/or coronary interventions for patients at increased risk of future refractory HF. It is also important to determine the appropriate timing of prophylactic treatment during long-term observation. In this study, refractory HF events newly developed with a mean interval of 532 days and later coronary revascularization was performed with a mean interval of 442 days during follow-up. In patients at high risk of reversible myocardial ischemia and HF, coronary intervention may be indicated with appropriate timing before refractory HF occurs.

Study limitations. One of the limitations in the J-ACCESS is a loss to follow-up rate of 4.8%. In addition to unknown reasons, it was not determined how the loss rate affected the results. Quality control of the semiquantitative and quantitative methods is essential for a multicenter study, and good reproducibility was guaranteed in this study by training and standardization of quantitative assessment as follows (11): Results of sample data sent back to the J-ACCESS office were excellent in terms of the precision of functional parameters or preference-based variability among institutions (9–11). Although bias in data analysis was not completely eliminated, the excellent results were due to the fact that visual and QGS (Cedars Sinai Medical Center) analyses were performed routinely by trained nuclear cardiologists and nuclear medicine physicians to minimize interobserver errors. A core center system for data analysis, which has been used in other multicenter studies, however, was not used in this study because of technical difficulties in data collection and personal information protection in 117 hospitals. Based on the original study design determined in 2001, a 20-segment model was used for tomographic perfusion image analysis. The 20-segment data can be converted to data using a 17-segment model, which is currently recommended, and the prognostic implications of both models are known to be basically identical (12).

CONCLUSIONS

In addition to chronic renal dysfunction, stress-induced perfusion abnormality and ESVI at rest are significant independent predictors of future admission for new-onset refractory congestive HF and aggressive treatment. By combining perfusion/function measures by gated single-photon

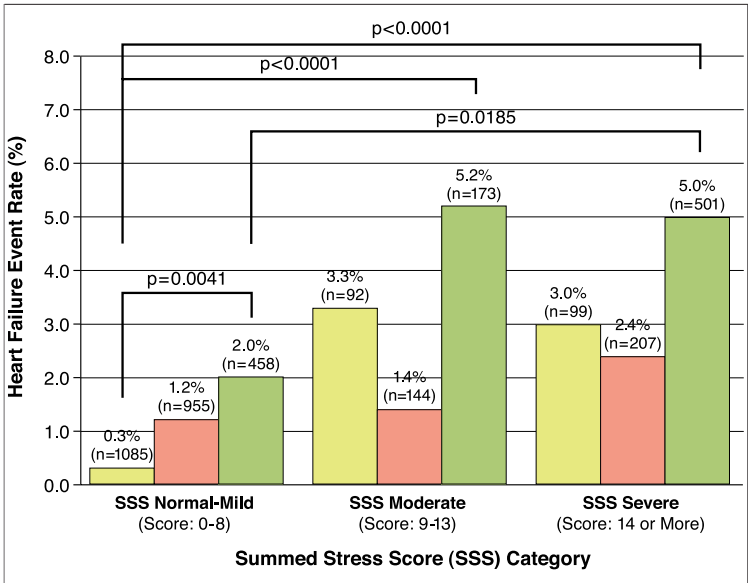

Figure 3. Event Rates of Refractory HF in Each SSS Category

Event rates of new-onset refractory heart failure (HF) in each SSS category tend to increase with the end-systolic volume index (ESVI); based on the ESVI tertile, patients were classified as either lower (≤13 ml/m^2, **yellow columns**), moderate (14 to 22 ml/m^2, **pink columns**), or greater (≥23 ml/m^2, **green columns**). The minimal risk (0.3%/3 years) at a normal to low SSS and lower ESVI increases to the approximately 17 times greater risk (5.0% to 5.2%/3 years) at a moderate to high SSS with a moderate to higher ESVI.

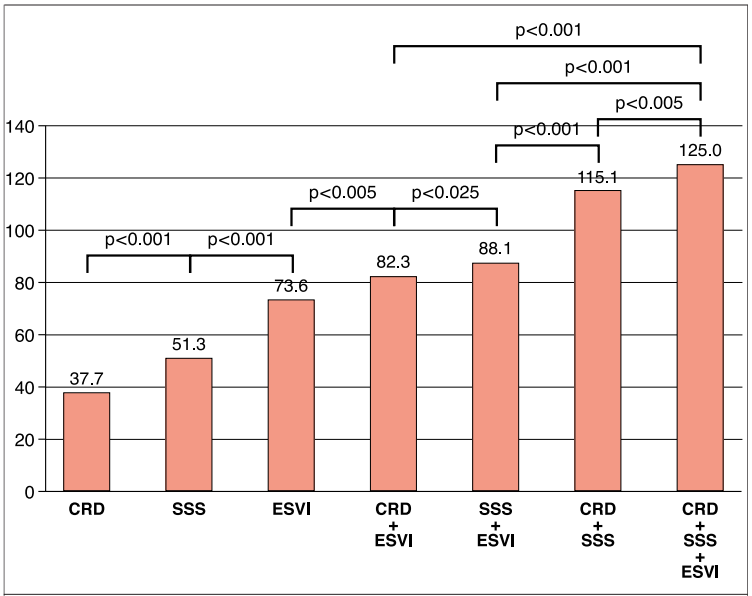

Figure 4. Global Chi-Square Values for Predicting New-Onset Refractory HF

Global chi-square values for predicting new-onset refractory heart failure (HF) significantly and incrementally increase when chronic renal dysfunction (CRD), end-systolic volume index (ESVI), and summed stress score (SSS), all of which were determined by multivariable Cox analysis, are combined.

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emission computed tomography (SPECT) study with renal function, a 3-year HF event risk can be more precisely evaluated in patients with known or suspected CAD, contributing to appropriate selection and prophylactic management of patients at increased risk of refractory congestive HF.

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REFERENCES

1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
2. Cleland JG, Daubert JC, Erdmann E, et al. Long-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006;27:1928–32.
3. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging-executive summary; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318–33.
4. Palmas W, Friedman JD, Diamond GA, et al. Incremental prognostic value of simultaneous assessment of myocardial function and perfusion with technetium-99m sestamibi for prediction of extent of coronary artery disease. J Am Coll Cardiol 1995;25:1024–31.
5. Sharir T, Germano G, Kavanagh PB, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation 1999;100:1035–42.
6. Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. J Nucl Med 2001;42:831–7.
7. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535–43.
8. Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. Eur J Nucl Med Mol Imaging 2008;35:319–28.
9. Kusuoka H, Nishimura S, Yamashina A, Nakajima K, Nishimura T. Surveillance study for creating the national clinical database related to ECG-gated myocardial perfusion SPECT of ischemic heart disease: J-ACCESS study design. Ann Nucl Med 2006;20:195–202.
10. Nakajima K, Kusuoka H, Nishimura S, Yamashina A, Nishimura T. Normal limits of ejection fraction and volumes determined by gated SPECT in clinically normal patients without cardiac events: a study based on the J-ACCESS database. Eur J Nucl Med Mol Imaging 2007;34:1088–96.
11. Nakajima K, Nishimura T. Inter-institution preference-based variability of ejection fraction and volumes using quantitative gated SPECT with 99mTc-tetrofosmin: a multicentre study involving 106 hospitals. Eur J Nucl Med Mol Imaging 2006;33:127–33.
12. Berman DS, Abidov A, Kang X, et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. J Nucl Cardiol 2004;11:414–23.
13. Pollock SG, Abbott RD, Boucher CA, Beller AG, Kaul S. Independent and incremental prognostic value of tests performed in hierarchical order to evaluate patients with suspected coronary artery disease—validation of models based on these tests. Circulation 1992;85:237–48.
14. Verschuren WM, Jacobs DR, Bloemberg BP, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA 1995;274:131–6.
15. Tokmakova MP, Skali H, Kenchaiah S, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival And Ventricular Enlargement (SAVE) study. Circulation 2004;110:3667–73.
16. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8.
17. Hakeem A, Bhatti S, Dillie KS, et al. Predictive value of myocardial perfusion single-photon emission computed tomography and the impact of renal function on cardiac death. Circulation 2008;118:2540–9.
18. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 2003;41:47–55.

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