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CME

A Pooled Analysis of Multicenter Cohort Studies of ^{123}I-*m*IBG Imaging of Sympathetic Innervation for Assessment of Long-Term Prognosis in Heart Failure

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CME Objective for This Article: Identified Need: The AHA/ACC guidelines 2009 update state that because of improved treatment of heart failure over the past 10 years, new prognostic models may have to be developed. Desired Result: General cardiologists understand pathophysiological and clinical implications of cardiac autonomic dysfunction and identify high-risk patients with chronic heart failure for lethal cardiac events. Learning Objective: Risk stratification and long-term prognosis assessment of patients with chronic heart failure by using cardiac sympathetic nerve imaging with I-123–labeled metaiodobenzylguanidine (*m*IBG).

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A Pooled Analysis of Multicenter Cohort Studies of ^{123}I-*m*IBG Imaging of Sympathetic Innervation for Assessment of Long-Term Prognosis in Heart Failure

OBJECTIVES The study objectives were to create a cardiac metaiodobenzylguanidine (*m*IBG) database using multiple prospective cohort studies and to determine the quantitative iodine-123–labeled *m*IBG indices for identifying patients with chronic heart failure (HF) at greatest and lowest risk of lethal events.

BACKGROUND Although the prognostic value of cardiac *m*IBG imaging in patients with HF has been shown, clinical use of this procedure has been limited. It is required to define universally accepted quantitative thresholds for high and low risk that could be used as an aid to therapeutic decision-making using a large cohort database.

METHODS Six prospective HF cohort studies were updated, and the individual datasets were combined for the present patient-level analysis. The database consisted of 1,322 patients with HF followed up for a mean interval of 78 months. Heart-to-mediastinum ratio (HMR) and washout rate of cardiac *m*IBG activity were the primary cardiac innervation markers. The primary outcome analyzed was all-cause death.

RESULTS Lethal events were observed in 326 patients, and the population mortality rate was 5.6%, 11.3%, and 19.7% at 1, 2, and 5 years, respectively. Multivariate Cox proportional hazard model analysis for all-cause mortality identified age ($p < 0.0001$), New York Heart Association (NYHA) functional class ($p < 0.0001$), late HMR of cardiac *m*IBG activity ($p < 0.0001$), and left ventricular ejection fraction (LVEF) ($p = 0.0029$) as significant independent predictors. Analysis of the 512-patient subpopulation with B-type natriuretic peptide (BNP) results showed BNP ($p < 0.0001$), greater NYHA functional class ($p = 0.0002$), and late HMR ($p = 0.0011$) as significant predictors, but LVEF was not. The receiver-operating characteristic–determined threshold of HMR (1.68) identified patients at significantly increased risk in any LVEF category. Survival rates decreased progressively with decreasing HMR, with 5-year all-cause mortality rates >7% annually for HMR <1.25, and <2% annually for HMR ≥1.95. Addition of HMR to clinical information resulted in a significant net reclassification improvement of 0.175 ($p < 0.0001$).

CONCLUSIONS Pooled analyses of independent cohort studies confirmed the long-term prognostic value of cardiac *m*IBG uptake in patients with HF independently of other markers, such as NYHA functional class, BNP, and LVEF, and demonstrated that categoric assessments could be used to define meaningful thresholds for lethal event risk. (J Am Coll Cardiol Img 2013;6:772–84) © 2013 by the American College of Cardiology Foundation

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Despite recent advances in pharmacological and nonpharmacological treatment of heart failure (HF), the physiological characteristics that determine the risk profile of an individual patient are often poorly understood. One attribute of cardiac physiology that could have direct application to therapeutic measures used to reduce occurrence of lethal events in patients with HF is the status of the autonomic nervous system.

Autonomic nervous system function is associated with manifestations, progression, and outcomes of chronic HF (1). Despite initial compensatory augmentation for maintenance of systemic hemodynamics and peripheral circulation, long-lasting and excess stimulation of sympathetic nerve function is responsible for adverse events in HF attributable to increased activity of the renin-angiotensin-aldosterone system (2,3). This adrenergic hyperactivity results in increases in tissue oxygen demand, peripheral vascular resistance, plasma volume and oxygen stress, and water–electrolyte imbalance. Other potential consequences of this hyperactivity are myocardial ischemia and arrhythmic events.

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

HF = heart failure

HMR = heart-to-mediastinum ratio

I = iodine

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

***m*IBG** = metaiodobenzylguanidine

NE = norepinephrine

NRI = net reclassification improvement

NYHA = New York Heart Association

ROC = receiver-operating characteristic

VT = ventricular tachycardia

WR = washout rate

Persistent efferent stimulation of sympathetic nerve function in failing hearts impairs efficiency of reuptake, turnover, and storage of norepinephrine (NE) at pre-synaptic nerve endings, resulting in increased spill-over and deficiency of NE stores (4). Cardiac sympathetic function and status of innervation can be assessed noninvasively using neuroimaging with the NE analog, iodine (I)-123–labeled metaiodobenzylguanidine (*m*IBG), which shares uptake, storage, and release system at nerve endings with NE (5). Increased NE turnover and pre-synaptic NE deficits can be identified as an increased *m*IBG washout rate (WR) from the heart and decreased *m*IBG activity quantified as the heart-to-mediastinum ratio (HMR).

Over the past 2 decades, numerous single and multicenter studies (6–11) and a recent meta-analysis using published data (12) have demonstrated the efficacy of cardiac *m*IBG sympathetic imaging for identifying symptomatic patients with HF most likely to experience lethal events. However, these studies have not provided data sufficient to establish long-term prognostic values and universally accepted levels of uptake that define high- and low-risk patient cohorts. Such definitions would require analyses of a large cohort database including prognostic *m*IBG markers and other standard clinical variables assessed for HF risk stratification. The present study was designed to create such a cardiac *m*IBG database by combining patient-level data from multiple prospective HF cohort studies (8,13–19), all of which were performed as physician-initiated clinical research in routine cardiology practice in Japan. The objective was to prospectively analyze the database to confirm short- and long-term prognostic values of quantitative ^{123}I-*m*IBG indices on myocardial sympathetic innervation imaging and then define uptake levels that identified patients with HF at highest and lowest risk of all-cause mortality.

METHODS

Study design. The present study was designed as a patient-level analysis combining individual prospectively obtained original datasets from multiple prospective HF cohorts studied independently between 1990 and 2009 in Japan (8,13–19). All patients were participants enrolled in prospective observational studies of *m*IBG cardiac imaging, a procedure that is approved for clinical use in Japan. The entry criteria for the current analyses were as follows: a prospective HF follow-up study; establishment of the HF diagnosis by cardiologists using standard diagnostic criteria (the Framingham criteria); a minimum of 12 months of periodic follow-up for patients who survived; a primary end-point of all-cause mortality; and cardiac *m*IBG imaging performed after stabilization using contemporary drug therapy for the measurement of HMR and WR. In the present study, only definitively confirmed deaths were considered events, but not aborted events such as recovery from resuscitated cardiac arrest or appropriate implantable cardioverter-defibrillator (ICD) shock.

Cardiac *m*IBG imaging is a routinely available clinical procedure in Japan (cost covered by the national medical insurance system of Japan) that is recommended in nuclear cardiology practice guidelines for the management and prognostic assessment of HF (20). Standard imaging procedures performed in Japan are as follows: use of 111 MBq of ^{123}I-*m*IBG with a high specific activity (commercially available in Japan), a gamma camera equipped with a low-energy collimator, and early and delayed imaging, from which HMR and WR are calculated at the time of imaging.

Follow-up protocol. According to guidelines of the ethics committee of each medical center, patient informed consent for participation was obtained in all original cohorts studied. Performance of the

present study also was based on ethical committee guidelines for approval to collect data and personal intelligence protection.

Patients with HF from 6 Japanese medical centers provided data for this study. All patients were regularly followed for the mean follow-up interval of 77.6 (range 1 to 175) months with a median interval of 67 months at the outpatient clinic of each facility by cardiologists who were in charge of HF management. Median follow-up intervals in the 6 institutions were 72.0 (range 1 to 175), 73.0 (range 1 to 115), 58.7 (range 9.5 to 91), 83.1 (range 1.6 to 175), 127 (range 1 to 173), and 31.5 (range 10 to 72) months. The primary endpoint was all-cause death, including cardiac deaths (pump failure death, death due to myocardial infarction, and sudden cardiac death) and noncardiac death. Sudden cardiac death was defined as witnessed cardiac arrest and death within 1 h after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 h. Follow-up data collected as part of the original studies were updated when possible. Clinical outcomes were confirmed regularly by patient medical records or telephone interview in each facility; therefore, follow-up data were available for all patients included in this study.

Patients. A total of 1,360 patients were entered into the original cohort studies, but 32 patients (2.35%) were excluded from the database because they were lost to follow-up thereafter. Data from 1,401 *m*IBG studies in the remaining 1,328 patients were submitted for this study. Six surviving patients were excluded because of a follow-up period <1 year, and results from 73 repeated (not first) *m*IBG studies also were removed from the analysis. Thus, the database for final analysis consisted of results from a total of 1,322 patients, 71% of whom were male, with a mean age of 61 (range 15 to 97) years; 362 (27.4%) had an ischemic HF cause (275 [20.8%] with prior myocardial infarction), 1,322 had a mean left ventricular ejection fraction (LVEF) of 37% (range 6% to 88%), 298 (23.8%) had diabetes mellitus, 388 (31.0%) had hypertension, and 288 (21.8%) had dyslipidemia. The following patients were not submitted for inclusion in the database: patients with end-stage renal failure requiring dialysis therapy; patients with malignant disorders; patients with neurogenic disorders involving the autonomic nervous system; patients having been treated with tricyclic antidepressant drugs or other drugs that are known to have a sympathomimetic action and interfere with cardiac *m*IBG uptake; and patients who were scheduled to undergo any cardiac surgery (typically for revascularization rather than device implantation).

Table 1. Comparison of Clinical Data Between Survivors and Nonsurvivors

	Survived (n = 996)	Dead (n = 326)	p Value
Age, yrs	60 ± 14	64 ± 12	<0.001
Men	70.1	75.2	0.0074
NYHA functional class			<0.0001
I	30	15	
II	42	33	
III	25	40	
IV	3	12	
LVEF, %	38 ± 14	33 ± 14	<0.0001
Ischemic cause of HF	27.4	27.3	0.969
Prior myocardial infarction	19.9	21.1	0.658
Diabetes mellitus	22.7	27.1	0.116
Hypertension	33.1	24.8	0.0065
Dyslipidemia	27.1	17.4	0.0090
Sustained ventricular tachycardia history	21.6	35.3	<0.0001
Brain natriuretic peptide, pg/ml*	300 ± 366	584 ± 494	<0.0001
Cardiac *m*IBG study			
HMR (late)‡	1.80 ± 0.35	1.59 ± 0.29	<0.0001
WR, %	37.5 ± 13.9	44.2 ± 14.6	<0.0001
Medications			
Diuretics	65.3	83.1	<0.0001
ACE-I and/or ARB	65.5	64.1	0.657
Beta-blockers	55.1	48.8	0.0458
Aldosterone antagonists†	47.8	46.3	0.757

Values are mean ± SD or %. *n = 512. †n = 539. ‡HMR (late) indicates HMR which is obtained from late *m*IBG scan and equal to late HMR.
ACE-I = angiotensin-converting enzyme-inhibitor; ARB = angiotensin-receptor blocker; HF = heart failure; HMR = heart-to-mediastinum ratio; LVEF = left ventricular ejection fraction; *m*IBG = metaiodobenzylguanidine; NS = not significant; NYHA = New York Heart Association; WR = washout rate.

Thirteen patients (1.2%) had ICDs at the time of *m*IBG imaging. Plasma B-type natriuretic peptide (BNP) data were available for 512 patients (39%).

Cardiac *m*IBG imaging. Cardiac *m*IBG imaging was performed using standard procedures after administration of 111 MBq of high specific activity ^{123}I-*m*IBG (commercially available in Japan, Daiichi Radioisotope/Fujifilm RI Pharma, Tokyo, Japan) with patients in fasting and resting condition (8,13–19). Anterior planar *m*IBG images of the chest were obtained using a gamma camera equipped with a low-energy collimator 15 to 30 min (early image) and 3 to 4 h (late image) after the intravenous tracer injection. Cardiac ^{123}I-*m*IBG activity was quantified as HMR by manually drawing regions of interest on the upper mediastinum

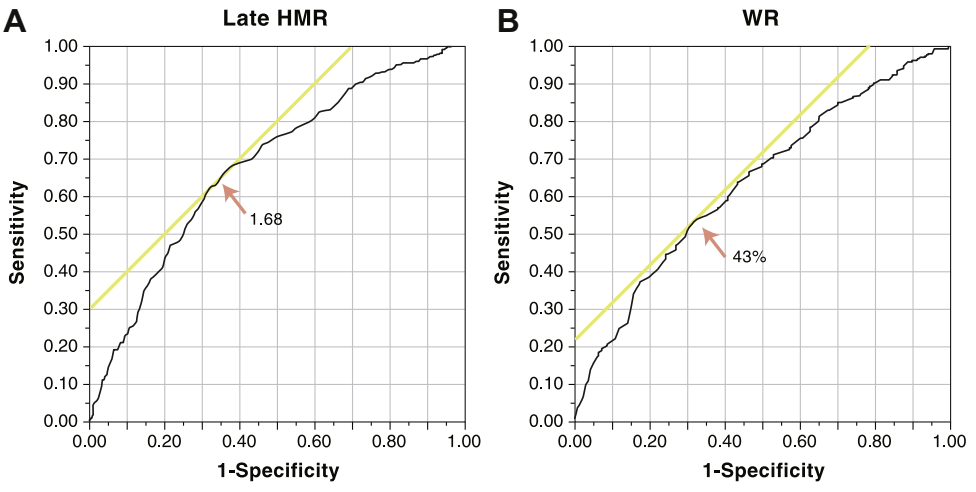


Figure 1. ROC Analysis of Late HMR and WR

Receiver-operating characteristic (ROC) analysis of late heart-to-mediastinum ratio (HMR) and washout rate (WR) of cardiac meta-iodobenzylguanidine (*m*IBG) activity, indicating that optimal cutoff values for identifying lethal events are 1.68 for late HMR **(A)** and 43% for WR **(B)**.

and the whole cardiac region by an experienced nuclear medicine technician who was unaware of any clinical data. ^{123}I-*m*IBG WR from the heart, based on count differences between early and late images, also was calculated (11).

Statistical analysis. Analysis of the combined database was performed by independent statistical experts (K.N. and S.M.) without participation of the other investigators. Summary values for numeric variables are shown as mean ± SD. Mean values were compared between the 2 groups (fatal events and survivors) using the unpaired *t* test, and prevalence values were compared using the chi-square test. Receiver-operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of an independent significant parameter.

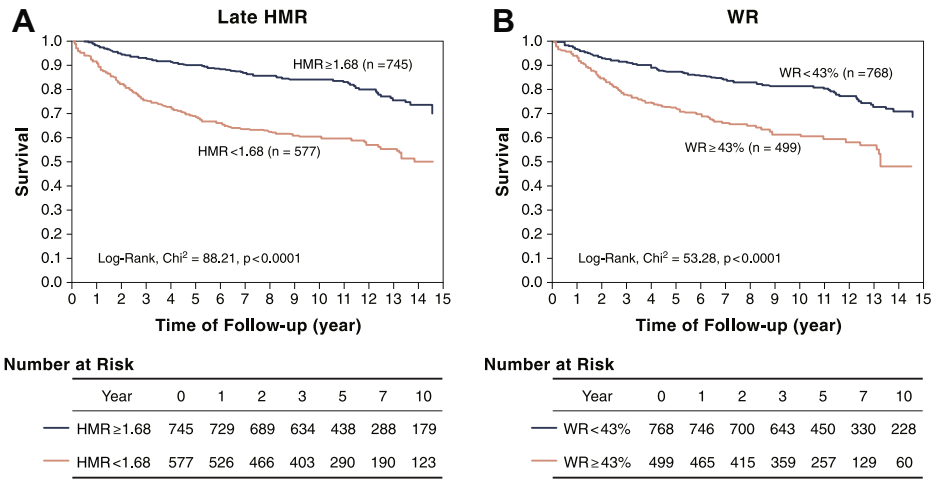


Figure 2. Kaplan-Meier Event-Free Curves of 2 Groups Classified by Late HMR and WR

Kaplan-Meier event-free curves of 2 groups classified by the cutoff values of late HMR (1.68) and WR (43%) showing significantly lower survival rate of patients with late HMR <1.68 or WR >43% **(pink)** than the counterparts **(blue)**. Abbreviations as in Figure 1.

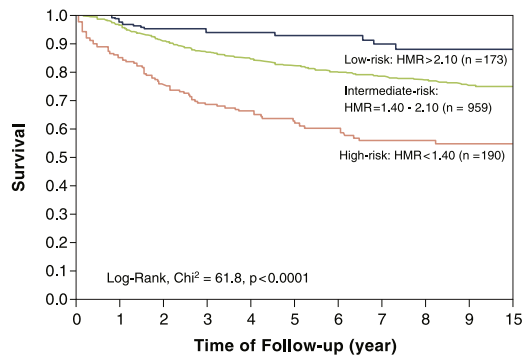
Table 2. Kaplan-Meier Analysis for Sudden Cardiac Death and Pump Failure Death at 5 Years

	Late HMR ≥1.68	Late HMR <1.68	Log Rank	p Value
All-cause death	10.2	31.7	88.2	<0.0001
Sudden cardiac death	2.9	8.6	24.8	<0.0001
Pump failure death	5.0	18.9	57.0	<0.0001
	WR, ≥43	**WR, <43**	**Log Rank**	**p Value**
All-cause death	28.2	13.2	53.3	<0.0001
Sudden cardiac death	9.6	2.7	25.5	<0.0001
Pump failure death	15.4	7.2	28.6	<0.0001

Values are %.
Abbreviations as in Table 1.

Univariate and multivariate analyses using a Cox proportional hazards model were performed. The multivariate model for time to all-cause mortality was evaluated using a stepwise forward elimination procedure and categorized variables such as age (<30 to ≥80 years, 10-year unit), greater New York Heart Association (NYHA) functional class (I/II vs. III/IV), late HMR (<1.1 to ≥2.0, 0.1 unit), LVEF (<20% to ≥50%, 10% unit), and BNP (<200, 200 to 399, ≥400). Factors considered included demographic data (age, sex), medical history (e.g., diabetes mellitus, hypertension), cardiac medications (e.g., angiotensin-converting enzyme inhibitors, beta-blockers), and measured parameters (LVEF, BNP, HMR). Factors significant at the $p < 0.05$ level were retained in the model. Survival curves of patient subgroups were created by the Kaplan-Meier method and compared using the log-rank test. Analyses based on sequential HMR subgroups were used to define thresholds for different mortality rates to 5 years.

Models without and with inclusion of HMR were compared using ROC curve and net reclassification improvement (NRI) methods for more

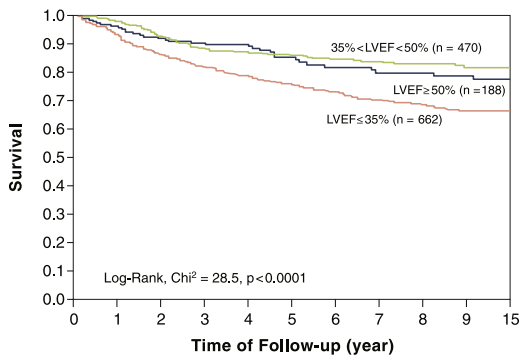


Number at Risk

Year	0	1	2	3	5	7	10
HMR>2.10	173	170	161	148	78	56	38
HMR1.4 - 2.10	959	926	854	770	571	368	227
HMR<1.4	190	163	142	120	81	56	39

Figure 3. Kaplan-Meier Event-Free Curves of 3 Subgroups Classified Using Late HMR

Kaplan-Meier event-free curves of 3 subgroups classified using the mean ± SD value (1.75 ± 0.35) of late HMR in the total population. The event-free curves were significantly separated into 3 categories as low-, intermediate-, and high-risk subgroups. Abbreviation as in Figure 1.



Number at Risk

Year	0	1	2	3	5	7	10
EF≥50%	188	180	172	160	98	83	56
35%<EF<50%	470	458	424	379	281	185	112
EF≤35%	662	615	557	496	348	209	133

Figure 4. Kaplan-Meier Event-Free Curves of 3 Subgroups Classified by LVEF Categories

Kaplan-Meier event-free curves of 3 subgroups classified by left ventricular ejection fraction (LVEF) categories ≤35%, 36% to 49%, and ≥50% showing significantly lower survival for the patient group with LVEF of ≤35% compared with that of the other 2 groups. EF = ejection fraction.

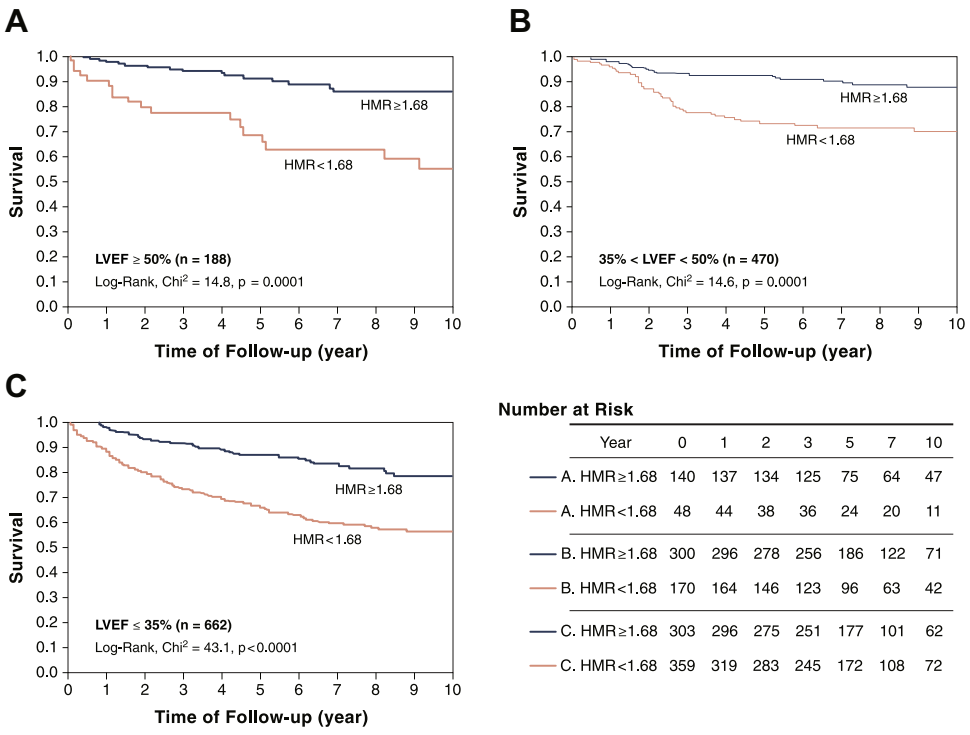


Figure 5. Kaplan-Meier Event-Free Curves According to 3 LVEF Categories

Kaplan-Meier event-free curves according to the 3 left ventricular ejection fraction (LVEF) categories: **(A)** LVEF of 50% or more, **(B)** LVEF >35% and <50%, and **(C)** LVEF of ≤35%. The cutoff value of late heart-to-mediastinum ratio (HMR) (1.68) shows significantly lower survival of the subgroup with late HMR <1.68 compared with those with HMR >1.68 in each LVEF category.

appropriate identification of low and/or high-risk categories. All analyses were performed using the SAS statistical program package (JMP version 9, SAS, Cary, North Carolina).

RESULTS

During follow-up, 326 patients (24.7%) died. Of these deaths, 263 (81%) were judged to be of cardiac cause as part of the original studies or during the current data review. Table 1 compares clinical backgrounds between groups with and without lethal events. The event group was older and more frequently male, had a history of sustained ventricular tachycardia (VT) and diuretic use, had greater NYHA functional class, had greater BNP level, and had lower LVEF. The event group less frequently had hypertension or dyslipidemia, and used beta-blocking agents. On *m*IBG imaging, the deceased group had significantly lower late HMR and greater WR than the survivors. There was no significant difference in the prevalence of ischemic cause of HF, diabetes mellitus, or use of renin-angiotensin-aldosterone system inhibitors between the groups.

ROC analysis identified 1.68 and 43% as optimal thresholds of HMR and WR, respectively (Fig. 1), for dichotomizing the population into higher- and lower-risk patients for lethal outcomes. Patients with late HMR <1.68 or WR >43% had significantly ($p < 0.0001$) lower survival rates (Fig. 2). Likewise, the late HMR and WR values differentiated the high- from the low-risk patients both for sudden cardiac death and for pump failure death at 5 years (Table 2).

According to the mean ± SD value (1.75 ± 0.35) of late HMR in the total population, patients were classified into 3 subgroups that could be characterized as low-, intermediate-, and high-risk (Fig. 3). Patients also could be classified into 3 subgroups using LVEF categories: ≤35%, 36% to 49%, and ≥50%. The subgroup with LVEF ≤35% had significantly poorer survival than the other 2 subgroups (Fig. 4). The late HMR threshold of 1.68 identified high-risk patients in each LVEF-categorized subgroup (Fig. 5).

Univariate Cox analysis identified significant variables, including age, LVEF, BNP, and *m*IBG parameters (HMR and WR), listed in Table 3. Ischemic cause, renin-angiotensin-aldosterone system inhibitors, and diabetes mellitus were not significant. Multivariate Cox proportional hazards analysis using categorized variables demonstrated age (<30 to ≥80 years, 10-year unit), greater NYHA functional class (I/II vs. III/IV), late HMR (<1.1 to ≥2.0, 0.1 unit), and LVEF (<20% to ≥50%, 10% unit) for the total population as independent significant predictors of lethal events (Table 4). When the subpopulation with BNP was analyzed, categoric BNP (<200, 200 to 399, ≥400), greater NYHA functional class (I/II vs. III/IV), and late HMR (<1.1 to ≥2.0, 0.1 unit) were identified to be significant, but LVEF (<20% to ≥50%, 10% unit) was not.

All-cause mortality progressively decreased with increasing HMR. All-cause mortality rates at 1 year, 2 years, and 5 years for the total population were 5.6%, 11.3%, and 19.7%, respectively (Fig. 6). When late HMR was <1.7, mortality rates at these 3 times were greater than the average, whereas those with HMR >1.7 had below average mortality rates, confirming the findings of the earlier ROC analysis (HMR threshold 1.68). For 5-year mortality, patients with HMR ≤1.2 had an annual death rate >7%, whereas patients with HMR ≥2.0 had an annual death rate <2%.

Table 5 shows the results of NRI analysis of the models using age (decile), LVEF (decile), and NYHA functional class (I/II vs. III/IV) with and without late HMR data at 3 5-year mortality categories of <10%, 10% to 30%, and >30%. Compared with the baseline model without HMR, the model with HMR had net gains in reclassification of 0.073 for patients who died ($p = 0.0415$), 0.102 for surviving patients ($p < 0.0001$), and NRI = 0.175 ($p < 0.0001$).

Table 3. Results of Univariate Cox Analysis for All-Cause Mortality

	Chi-Square	Hazard Ratio	95% CI Lower–Upper	p Value
Age (<30–≥80 yrs, 10-yr unit)	20.76	1.23	1.12–1.34	<0.0001
Men	3.88	1.28	1.00–1.66	0.049
Ischemic cause	0.01	0.99	0.94–1.77	0.943
NYHA functional class	96.02	5.38	3.51–8.19	<0.0001
NYHA functional class (I/II vs. III/IV)	83.17	2.81	2.26–3.51	<0.0001
ACE-I and/or ARB	0.72	0.91	0.72–1.14	0.399
Beta-blockade	8.42	0.72	0.58–0.90	0.0037
Diuretics	46.17	2.50	1.89–3.38	<0.0001
LVEF (<20%–≥50%, 10% unit)	40.19	0.72	0.65–0.80	<0.0001
HMR, early (<1.1–≥2.0, 0.1 unit)	12.78	0.93	0.89–0.97	0.0004
HMR, late (<1.1–≥2.0, 0.1 unit)	91.79	0.82	0.79–0.85	<0.0001
WR (<30%–≥60%, 10% unit)	78.94	1.52	1.39–1.67	<0.0001
Diabetes mellitus	2.11	1.21	0.94–1.54	0.146
Hypertension	5.10	0.75	0.58–0.96	0.024
Dyslipidemia	13.12	0.59	0.43–0.79	0.0003
Sustained VT history	8.39	1.41	1.12–1.77	0.0038
BNP (<200, 200–399, ≥400)	63.00	2.76	2.12–3.63	<0.0001

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BNP = B-type natriuretic peptide; CI = confidence interval; HMR = heart-to-mediastinum ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VT = ventricular tachycardia; WR = washout rate.

DISCUSSION

The present study using multiple cohort studies demonstrated the independent prognostic value of altered cardiac sympathetic function as assessed by categorical and numeric HMR data from cardiac *m*IBG imaging. Compared with earlier investigations (6–11), including the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study, the present results showed the long-term efficacy of risk assessment by HMR for more than 10 years. The results derived from a large number of patients not only support previous *m*IBG data, but also strengthen the value of quantitative *m*IBG markers to identify all-cause mortality risk in patients with HF. The present data also reflect the consistent, high-quality imaging procedures using high specific activity ^{123}I-*m*IBG in the prospective cohort studies. More important, the results suggest that the HMR could be used to define suitable thresholds for high and low risk to facilitate therapeutic decision making.

Patient-level pooled analysis. Unlike a previous *m*IBG meta-analysis, which only included calculations based on published aggregate imaging and

Table 4. Multivariate Cox Proportional Hazards Model for Time to All-Cause Mortality

	Hazard Ratio	95% CI Lower–Upper	p Value
Total population (N = 1,320)			
Age (<30–≥80 yrs, 10-yr unit)	1.21	1.10–1.33	<0.0001
NYHA (I/II vs. III/IV)	2.07	1.64–2.60	<0.0001
HMR, late (<1.1–≥2.0, 0.1 unit)	0.85	0.82–0.89	<0.0001
LVEF (<20%–≥50%, 10% unit)	0.85	0.77–0.95	0.0029
Subpopulation with BNP data (n = 512)			
BNP (<200, 200–399, ≥400)	2.19	1.65–2.93	<0.0001
NYHA (I/II vs. III/IV)	2.05	1.41–3.05	0.0002
HMR, late (<1.1 –≥2.0, 0.1 unit)	0.87	0.80–0.95	0.0011

Abbreviations as in Table 3.

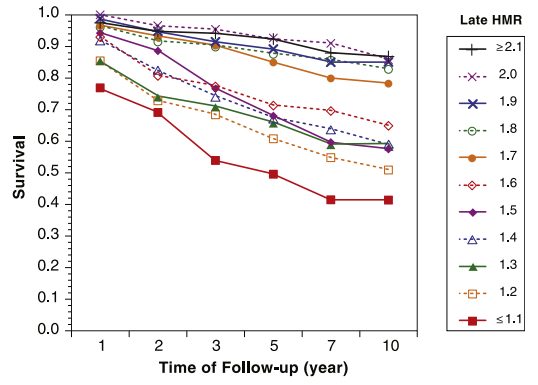


Figure 6. All-Cause Mortality Rates at 1 Year, 2 Years, and 5 Years in the 11 HMR-Categorized Groups

All-cause mortality rates at 1 year **(closed circles)**, 2 years **(open diamonds)**, and 5 years **(closed squares)** in the 11 HMR-categorized groups; total population mortality rates **(dotted lines)** are 5.6% at 1 year, 11.3% at 2 years, and 19.7% at 5 years. For late HMR <1.7, mortality rates tended to exceed the population mortality rates at 1, 2, and 5 years, indicating high-risk patients. Abbreviation as in Figure 1.

outcome results (12), this study involved collection of the individual data records for each patient with HF, thereby permitting detailed analyses of the full combined population and selected relevant subpopulations. A particular strength of the present study was the use of multiple different analysis techniques, including ROC curve, Kaplan-Meier survival, Cox proportional hazards, and NRI. Multivariate Cox analysis demonstrated independent prognostic value for *m*IBG imaging findings beyond that of demographic and medical history variables. NRI confirmed appropriate reclassification of patients who did and did not have lethal events. Examined from these multiple statistical perspectives, the merged data from the participating sites provided consistent evidence of efficacy for cardiac *m*IBG imaging equivalent to that typically obtained from a multicenter prospective trial. A further measure of the success of the analyses was the consistency of the results for subsets, including those based on different LVEF ranges. Despite the expected limitations inherent in aggregating data originally collected over a 20-year period, the consistency of the results provides validation of the methods used in performance of this pooled patient-level analysis.

Table 5. Net Reclassification Analysis for All-Cause Mortality at Risk Levels of 10% and 30% per 5 Years

Model Without HMR	Model With HMR			
Frequency and Row %	**<10%**	**10%–30%**	**>30%**	**Total**
Patients with events				
<10%	10 (34.50)	19 (65.50)	0 (0.00)	29
10%–30%	11 (8.60)	88 (68.80)	29 (22.70)	128
>30%	0 (0.00)	19 (21.10)	71 (78.90)	90
Total	21 (8.50)	126 (51.00)	100 (40.50)	247
Patients without events				
<10%	235 (82.20)	51 (17.80)	0 (0.00)	286
10%–30%	160 (25.20)	415 (65.30)	61 (9.60)	636
>30%	0 (0.00)	61 (40.70)	89 (59.30)	150
Total	395 (36.80)	527 (49.20)	150 (14.00)	1,072

Values are n (%) or n.
Abbreviation as in Table 1.

Mechanisms of impaired cardiac sympathetic innervation. Cardiac sympathetic imaging can help in understanding the pathophysiological and prognostic implications of alterations of cardiac sympathetic nerve function and innervation in HF. Given that abnormalities of cardiac sympathetic innervation are common in most forms of heart disease, including ischemic and nonischemic causes (6–9,21,22), and medications affecting this system (particularly beta-blockers) are among the most effective therapies for patients with HF and ischemic heart disease, a quantitative assessment of this system should have obvious value as an additional piece of relevant medical information. Although the *m*IBG imaging technique has been readily available in Japan for 2 decades, the new insights provided by this pooled analysis should expand understanding of the importance of the sympathetic nerve findings. In the same way that assessment of myocardial perfusion provides functional insights to supplement the information about coronary artery disease provided by angiographic procedures, assessment of myocardial sympathetic innervation augments the morphological and mechanical indices on left ventricular dimensions and systolic and diastolic function provided by methods such as echocardiography and cardiac magnetic resonance.

Several investigations have shown that impaired cardiac *m*IBG activity can improve in response to current medical management using beta-adrenoceptor blockers and inhibitors of the renin-angiotensin-aldosterone system in selected patients (23,24). Therefore, this imaging technique can help to monitor response to therapy and is also likely to predict the effectiveness of such drug treatment and nonpharmacological device therapy in patients with HF (25–28). However, decreased late cardiac *m*IBG activity and increased WR can reflect the aggregate effect of a number of processes that cannot be

individually assessed in vivo, such as reduced number of sympathetic nerve terminals, decreased tyrosine hydroxylase activity, decreased function of NE and vesicular monoamine transporters, and increased neuronal stimulation with increased NE turnover. Impaired sympathetic pre-synaptic activity in conjunction with excess and long-lasting activation of central excitatory inputs not only limits compensatory action to maintain cardiac inotropy, but also induces dysregulation of post-synaptic adrenoceptor signal transduction, potentially producing denervation supersensitivity that may contribute to lethal arrhythmogenicity in failing hearts (29).

Impact on clinical management of patients with HF. Precise risk stratification of patients with HF can contribute to implementation of prophylactic medical therapy against lethal events and appropriate selection of candidates who can benefit most from nonpharmacological device therapy using ICDs (26–28) and/or cardiac resynchronization therapy. LVEF provides little prognostic information for the one-third to one-half of patients with HF with preserved LV systolic function, and the prognostic limitations of LVEF for the prediction of sudden cardiac/arrhythmic death have been noted (30). In this study, the prognostic value of LVEF was reduced when other powerful prognosis indicators such as BNP and cardiac *m*IBG activity were available, whereas the prognostic value of cardiac *m*IBG activity was successfully demonstrated in patients with HF with reduced and normal LVEF. It is unlikely but needed in the foreseeable future to establish specific treatments for impaired cardiac sympathetic innervation independently of LVEF. Nevertheless, identification of neuronal deficiencies using *m*IBG neuroimaging should contribute to more effective use of currently available therapies and therefore better outcomes for patients with HF.

The value of accurate risk stratification should be greatest for patients identified as being of high or low risk for adverse outcomes. In that regard, patients with preserved myocardial sympathetic innervation (HMR $\geq$1.95) had an annual death rate <2%, whereas those with substantially reduced innervation (HMR <1.25) had an annual death rate >7%, demonstrating the degree of difference in prognosis that can be determined with *m*IBG imaging. The important observation is that user-defined high and low event rate HMR thresholds can be developed using data appropriate for specified populations. For example, in the Japanese population, an HMR threshold of 1.15 defined an even higher annual mortality rate of >10%. Given that patients with HF are considered for many drugs and invasive and expensive device treatments, there is a great need for flexible prognostic procedures to identify the highest- and lowest-risk patient groups.

Prediction of mode of death is another important clinical issue in HF management. The presented *m*IBG results did not predict mode of death, but rather identified high and low risk for each mode of death using late HMR or WR, suggesting the mechanistic relevance of impaired cardiac innervation and inappropriately augmented cardiac sympathetic stimulation to HF progression and sudden cardiac events. However, the present results cannot be used to indicate which mode of death will affect a particular high-risk patient. Sudden death per se is an outcome resulting from multifactorial pathologies and several triggers that could be modulated by interaction in various clinical conditions, including diabetic state, kidney function, and anemia (31). Hemodynamic instability enhances tachyarrhythmias via augmentations of afferent and efferent autonomic neuronal regulation and the renin-angiotensin-aldosterone system, leading to ischemia and myocyte injury, all of which in turn produce a vicious cycle resulting in pump failure and lethal arrhythmic events.

The present study did not directly address the influence of ischemia on arrhythmogenicity as a mechanism of sudden death. However, the possibility is supported by our previous findings (28) that impairment of myocardial perfusion is related to lethal arrhythmic events/ICD shocks independently of and in addition to altered cardiac sympathetic innervation. From the previous (26–28) and the present findings, further prospective large-cohort investigations are justified for more precise identification of patients with HF at low or high probability of sudden cardiac death and for establishing more appropriate indication for prophylactic or therapeutic use of ICDs in patient populations categorized by LVEF and background cardiac diseases.

Study limitations. Because only baseline data collected at the time of the original studies were available, the individual datasets did not always include complete records of patient demographics, medical history, concomitant medications, and profiles of excluded patients before enrollment in each original database. Likewise, because of the age of some studies, more recently introduced biomarkers such as BNP were only available for a minority (512 [39%]) of the 1,322 patients. A limitation of the VT classification was that history of "sustained" VT was independently confirmed at each institution, and at the time of *m*IBG imaging,

few patients (n = 13) had ICDs that would have provided more accurate documentation of rhythm disturbances. There is also a lack of sufficient information on ICD therapy during long-term follow-up, which could affect the outcome analyses.

The prevalence of ischemic HF cause was as much as 50% lower than in many western countries (32), but this is representative of the 25% to 35% prevalence of ischemic cause in Japanese patients with HF reported in many cohorts. Nevertheless, the proportion of patients with ischemic HF was nearly identical (27%) in the dead and surviving groups, and HF cause was not significant in the multivariate analyses. The high proportion of patients with nonischemic cardiomyopathy also may have contributed to the lower than expected mortality rate compared with other clinical HF trials (32). Overall, the results are consistent with our previous study (13) and a recent prospective trial (11) that demonstrated comparable prognostic value of cardiac *m*IBG activity in patients with ischemic HF cause and patients with nonischemic HF cause.

Because almost all the original studies were observational, the new analyses can provide information about prognosis but not the therapeutic implications of these observations. The consistency of the aggregate results does support the desirability of a prospective interventional study to establish appropriate therapeutic strategies in patients with HF identified to be at greatest risk for lethal events by cardiac *m*IBG imaging. However, even without such a study, the results of the present analyses, in conjunction with those of the recent prospective *m*IBG trial (11), indicate that HMR values from cardiac *m*IBG imaging can identify patients with HF who might not be identified from conventional clinical and laboratory assessments as requiring more aggressive or more conservative treatment.

As presented in previous publications and in this study, cardiac *m*IBG parameters (delayed HMR and WR) have been used to monitor patient outcome and response to medical treatment. However, HMR has not been standardized among publications from various institutions and countries, primarily because of patient-based and methodology-based reasons (33,34). Fortunately, in this study consisting of multiple Japanese prospective cohorts, imaging protocols (including collimator used), dose, and specific activity of ^{123}I-*m*IBG were nearly uniform (8,11,13–19). Nevertheless, the exact numeric HMR values cannot be readily applied to studies performed in other geographies and using other methodologies. Finally, a cost–benefit analysis is needed to identify specific patients in whom cardiac *m*IBG imaging in combination with conventional clinical and laboratory information would be most beneficial.

CONCLUSIONS

A patient-level pooled analysis combining 6 prospectively obtained HF databases, with 1,322 Japanese patients, clearly demonstrated the long-term prognostic value of altered cardiac sympathetic function as assessed by cardiac *m*IBG imaging. The continuous numeric and categorical assessment of cardiac *m*IBG activity using HMR provides information on the probability of survival in patients with HF independently of plasma BNP level and LVEF. By using the HMR values, the cardiologist can define the particular level of risk at which specific therapeutic interventions are deemed appropriate or unnecessary.

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Key Words: cardiac sympathetic nerve function ■ heart failure ■ metaiodobenzylguanidine ■ pooled analysis ■ prognosis.