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Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure

Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study

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Objectives The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study prospectively evaluated iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) imaging for identifying symptomatic heart failure (HF) patients most likely to experience cardiac events.

Background Single-center studies have demonstrated the poorer prognosis of HF patients with reduced ^{123}I-*m*IBG myocardial uptake, but these observations have not been validated in large multicenter trials.

Methods A total of 961 subjects with New York Heart Association (NYHA) functional class II/III HF and left ventricular ejection fraction (LVEF) ≤35% were studied. Subjects underwent ^{123}I-*m*IBG myocardial imaging (sympathetic neuronal integrity quantified as the heart/mediastinum uptake ratio [H/M] on 4-h delayed planar images) and myocardial perfusion imaging and were then followed up for up to 2 years. Time to first occurrence of NYHA functional class progression, potentially life-threatening arrhythmic event, or cardiac death was compared with H/M (either in relation to estimated lower limit of normal [1.60] or as a continuous variable) using Cox proportional hazards regression. Multivariable analyses using clinical, laboratory, and imaging data were also performed.

Results A total of 237 subjects (25%) experienced events (median follow-up 17 months). The hazard ratio for H/M ≥1.60 was 0.40 ($p < 0.001$); the hazard ratio for continuous H/M was 0.22 ($p < 0.001$). Two-year event rate was 15% for H/M ≥1.60 and 37% for H/M <1.60; hazard ratios for individual event categories were as follows: HF progression, 0.49 ($p = 0.002$); arrhythmic events, 0.37 ($p = 0.02$); and cardiac death, 0.14 ($p = 0.006$). Significant contributors to the multivariable model were H/M, LVEF, B-type natriuretic peptide, and NYHA functional class. ^{123}I-*m*IBG imaging also provided additional discrimination in analyses of interactions between B-type natriuretic peptide, LVEF, and H/M.

Conclusions ADMIRE-HF provides prospective validation of the independent prognostic value of ^{123}I-*m*IBG scintigraphy in assessment of patients with HF. (Meta-Iodobenzylguanidine Scintigraphy Imaging in Patients With Heart Failure and Control Subjects Without Cardiovascular Disease, NCT00126425; Meta-Iodobenzylguanidine [123I-mIBG] Scintigraphy Imaging in Patients With Heart Failure and Control Subjects Without Cardiovascular Disease, NCT00126438) (J Am Coll Cardiol 2010;55:2212–21) © 2010 by the American College of Cardiology Foundation

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Increased myocardial sympathetic activity is a prominent feature of heart failure (HF) and is associated with progressive myocardial remodeling, inexorable decline in left ventricular function, and worsening symptoms (1–3). Alterations in myocardial sympathetic nerve activity also play an important role in the generation of ventricular arrhythmias and sudden cardiac death (SCD) (4,5). Increased neuronal release of norepinephrine (NE) is usually accompanied by decreased neuronal NE reuptake due to post-transcriptional downregulation of the cardiac NE transporter (6–8). The resultant increase in NE concentration in the sympathetic synaptic cleft induces desensitization of myocardial beta-adrenoceptors (9,10). Adrenoreceptor inhibitors counter such alterations and improve survival by retarding HF progression and preventing tachyarrhythmias (11,12). Accordingly, interrogation of myocardial sympathetic nervous system activity has been suggested as an aid to assessment of prognosis and clinical management of HF patients (13,14).

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The decrease in the NE reuptake mechanism has been successfully assessed by radionuclide imaging with the iodine-123–labeled NE analog *meta*-iodobenzylguanidine (^{123}I-*m*IBG), which has demonstrated an excellent safety profile during more than 20 years of clinical use (5,13–15). Uptake of ^{123}I-*m*IBG into myocardial sympathetic nerve endings is mediated by the NE transporter, and because the compound is not metabolized, the amount of ^{123}I-*m*IBG retention over several hours after administration is a reflection of neuronal integrity (15). Reduced myocardial ^{123}I-*m*IBG uptake has been demonstrated to be an independent predictor of adverse long-term outcome, and improvement in ^{123}I-*m*IBG uptake is observed in response to effective HF therapy (13,16–21). Although there is extensive literature on ^{123}I-*m*IBG imaging in both ischemic and nonischemic cardiomyopathy, most studies have been conducted at single centers involving relatively small numbers of patients and have not been performed under rigorous clinical trial conditions. As such, the potential usefulness of ^{123}I-*m*IBG imaging in the clinical management of HF patients has remained uncertain.

The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study consisted of 2 identical open-label phase III studies to provide prospective validation of the prognostic role of quantitation of sympathetic innervation of the myocardium using ^{123}I-*m*IBG. This paper presents the combined primary efficacy results from the 2 ADMIRE-HF studies.

Methods

Study design. Ninety-six sites in North America (U.S. and Canada) and Europe participated in ADMIRE-HF. The study was approved by the institutional review boards and ethics committees at each center, and all subjects signed informed consent before performance of any procedures. The first subject was imaged on July 27, 2005; the last subject was imaged on February 20, 2008.

The methods used in the trial have been described in detail previously (22). The primary inclusion criteria were HF (New York Heart Association [NYHA] functional class II or III) due to ischemic or nonischemic cardiomyopathy; left ventricular ejection fraction (LVEF) ≤35%; and guidelines-based optimum pharmacotherapy including beta-blocker, angiotensin-converting enzyme inhibitor, and/or angiotensin receptor blocker (ARB). Major exclusion criteria were functioning ventricular pacemaker; history of defibrillation to treat a previous ventricular arrhythmic event; cardiac revascularization, implantable cardioverter-defibrillator (ICD) implantation or acute myocardial infarction within previous 30 days; and serum creatinine >3.0 mg/dl (265 μmol/l) (22). Within 30 days before imaging, all subjects underwent a complete clinical evaluation, NYHA functional class assessment, echocardiography, and blood draw for plasma B-type natriuretic peptide (BNP) and NE levels. The echocardiographic data and blood work were submitted to separate core laboratories for analysis.

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CE = cardiac event
HF = heart failure
H/M = heart/mediastinum ratio
ICD = implantable cardioverter-defibrillator
^{123}I-*m*IBG = iodine-123 *meta*-iodobenzylguanidine
LVEF = left ventricular ejection fraction
MPI = myocardial perfusion imaging
NE = norepinephrine
NYHA = New York Heart Association
SCD = sudden cardiac death
SPECT = single-photon emission computed tomography
VT = ventricular tachycardia

Radionuclide imaging and analysis procedures. Imaging procedures are described in detail in the Online Appendix. Briefly, all subjects received 10 mCi (370 MBq; ±10%) of ^{123}I-*m*IBG (AdreView, GE Healthcare) and underwent anterior planar and single-photon emission computed tomography (SPECT) imaging of the thorax beginning at 15 min ("early") and 3 h 50 min ("late") post-injection (Fig. 1). On a separate day, myocardial perfusion imaging (MPI) with technetium-99m (^{99m}Tc)-tetrofosmin (MyoView, GE Healthcare) was performed as previously described (22). All images were processed by certified nuclear medicine technologists and interpreted at an independent core laboratory (Icon Medical Imaging, Warrington, Pennsylvania). All planar and SPECT images were reviewed by 3 expert independent nuclear cardiologists who were blinded to clinical data.

The heart/mediastinum ratio (H/M) was determined from the counts/pixel in a visually drawn heart region of interest divided by the counts/pixel in a 7×7 pixel mediastinum region of interest in the mid-line upper chest positioned to reflect the location with lowest activity (i.e., nonspecific background). Each reader validated the H/M determined for each planar image and scored all SPECT image sets employing a 17-segment model and a scale of 0 to 4 (23).

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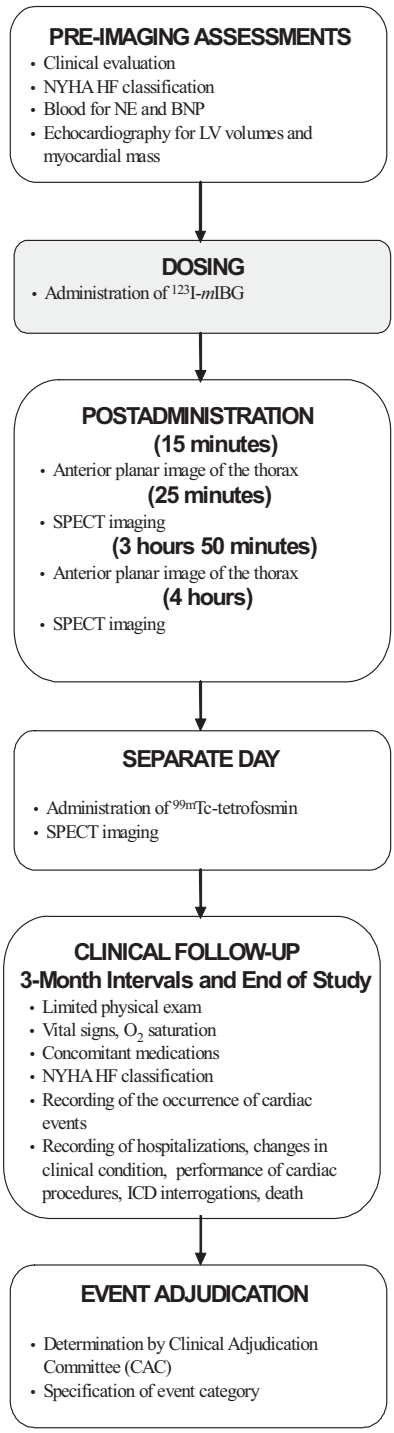

Figure 1 **The ADMIRE-HF Study Scheme**

Flow diagram of the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study procedures, including pre-iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) clinical assessments, ^{123}I-*m*IBG and technetium-99m (99mTc)-tetrofosmin imaging studies, and in-person assessments at 3-month intervals for 2 years. BNP = B-type natriuretic peptide; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; NE = norepinephrine; NYHA = New York Heart Association; SPECT = single-photon emission computed tomography.

Clinical follow-up and event adjudication. All subjects received standard clinical care and were followed up until: 1) the subject completed a 2-year period after the ^{123}I-*m*IBG study; 2) subject death was confirmed; 3) the subject withdrew from the study or was lost to follow-up; or 4) the trial was terminated because the protocol-specified number of cardiac events (CEs) had been confirmed. Complete details are provided in the Online Appendix.

The Clinical Adjudication Committee reviewed data from case report forms and source documents to confirm occurrence of CEs, specifically: 1) HF progression: increase in symptomatic status from NYHA functional class II to III or IV, or increase from NYHA class III to class IV; 2) potentially life-threatening arrhythmic event, including documented episode of spontaneous sustained (>30 s) ventricular tachyarrhythmia, resuscitated cardiac arrest, or appropriate ICD discharge (antitachycardia pacing or defibrillation); or 3) cardiac death (further classified as due to HF progression, sudden cardiac death [SCD], or other causes).

Statistical analysis. Statistical analyses were performed at the University of California, Irvine (by V.A.L. and N.D.W.). The univariate primary and secondary analyses were performed on the pooled ADMIRE-HF dataset using consensus H/M results for each subject. The pre-specified primary end point was the late H/M in relation to time-to-occurrence of the first CE in trial subjects. This single ^{123}I-*m*IBG value was selected for the primary analysis because of the extensive literature supporting its prognostic significance (24,25). Complete ^{123}I-*m*IBG and MPI SPECT data were collected for exploratory evaluations, and these data were included in preplanned secondary analyses for each of the 2 trials. Complete details of statistical analyses are provided in the Online Appendix.

The primary analysis was based on subjects classified into 2 pre-specified groups, late H/M <1.6 and ≥ 1.6 (22). The analysis employed a univariate Cox proportional hazards model fitted to the time to first occurrence of a CE (composite of 3 CE categories) (26). Secondary Cox proportional hazards analyses were performed using the continuous numerical H/M rather than the binary division. Additional Cox proportional hazards analyses were performed for each of the 3 event categories, providing estimates of the hazard ratios for occurrence of each event category independent of the others (e.g., comparing subjects who had an HF progression CE vs. those who did not). Only the time to occurrence of the first event in a category for a given subject was used. Kaplan-Meier survival analyses were also performed on the primary and secondary end point data.

All multivariable analyses employed Cox proportional hazards methods with backwards elimination. For each phase III study, separate multivariable analyses were performed using the SPECT interpretations for each blinded reader. Additional multivariable analyses were performed on the pooled ADMIRE-HF data using only the planar (early and late) ^{123}I-*m*IBG results; clinical variables such as age, sex, serum creatinine, systolic blood pressure; and cardiac risk factors such as hypertension, dyslipidemia, and diabetes. In the protocol-

Table 1 Clinical Characteristics of the Heart Failure Subjects

n	961
Sex, male (%)	80.1
Race, white (%)	74.9
Body mass index (kg/m^2)	29.2 ± 6.1
ACE inhibitors/ARBs (%)	94.2
Beta-blockers (%)	91.9
Lipid-lowering agents (%)	74.6
Aldosterone antagonist (%)	38.9
Diabetes (%)	36.0
Hypertension (%)	64.5
Smoker, current or past (%)	73.9
Dyslipidemia (%)	72.4
Heart failure: NYHA functional class II, III (%)	82.7, 17.3
Heart failure: ischemic, nonischemic (%)	66.0, 34.0
LVEF (%)	27.1 ± 6.1

ACE-I = angiotensin-converting enzyme inhibitor; ADMIRE-HF = AdreView Myocardial Imaging for Risk Evaluation in Heart Failure; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

specified multivariable analyses, myocardial washout was not included because it is derived from the same data used in calculating early and late H/M. However, as the prognostic significance of washout is widely cited in the literature (24,25), additional analyses examining the impact of this variable were performed.

Statistical significance for the univariate Cox proportional hazards analyses of the composite primary end point was set at $p < 0.025$ (alpha = 0.05 split between the analyses using H/M divided at 1.60 and as a continuous variable). All other analyses used a significance level of $p < 0.05$.

Results

Study participants. ^{123}I-*m*IBG studies were performed in 985 subjects (453 and 532 subjects in the 2 phase III trials). Of these 985 subjects, 21 subjects were withdrawn because of protocol violations (only discovered post-dosing; n = 17), adverse events (n = 3; nausea; hypoglycemia secondary to insulin administration; acute myocardial infarction in subject with ischemic electrocardiography changes before ^{123}I-*m*IBG dosing), or subject request on the day of dosing (n = 1). In addition, images from 2 subjects were not submitted for central reading, and planar images from 1 subject were considered nondiagnostic by the readers. Therefore, the evaluable efficacy population consisted of 961 subjects. The demographic information for those subjects is summarized in Table 1.

During the follow-up period of 2 days to 30.4 months (median 17 months), 237 first CEs were observed: HF progression in 163 subjects, arrhythmic events in 50 subjects, and cardiac death in 24 subjects. Fifty-two subjects had CEs in more than 1 category during follow-up, resulting in the following subject totals in each CE category: HF progression, n = 176; arrhythmic events, n = 64; cardiac death, n = 53. The total number of deaths during the trial was 81 (8%; 28 noncardiac). Characteristics of subjects based on occurrence of CEs are compared in Table 2. There was no difference in the age, sex, and medication usage of subjects who did and did not experience CEs. Subjects who experienced events were more likely to have NYHA functional class III symptoms, HF of nonischemic etiology, lower LVEF, and higher levels of BNP and NE.

The mean late H/M was 1.44 (standard deviation 0.20), and the distribution of this parameter was symmetric (first, second, and third quartiles of 1.30, 1.42, and 1.57, respectively). A total of 201 subjects (21%) had H/M ≥1.60 (protocol-defined binary division) (22).

Primary analyses. The CE risk (primary end point) was significantly lower for subjects with H/M ≥1.60, with hazard ratio of 0.40 (97.5% CI: 0.25 to 0.64; $p < 0.001$). Survival analysis showed 2-year event rates of 38% versus 15% for the 2 H/M groups (Fig. 2). The Cox proportional hazards analysis based on the continuous numerical H/M

Table 2 Comparison of Characteristics of Subjects With and Without Cardiac Events

Characteristic	Subjects With Events (n = 237)	Subjects Without Events (n = 724)	p Value
Male sex (%)	83.5	79.0	0.129
Age (yrs)	61.5 ± 13.5	62.7 ± 11.3	0.243
LVEF (%)	25.0 ± 6.6	27.8 ± 5.8	<0.001
ACE-I or ARB (%)	93.3	94.5	0.484
Beta-blocker (%)	91.6	92.0	0.834
Aldosterone antagonist (%)	43.5	37.4	0.095
HF class: NYHA II, III (%)	75.1, 24.9	85.2, 14.8	<0.001
HF etiology: ischemic, nonischemic (%)	60.3, 39.7	67.8, 32.2	0.035
BNP (ng/l) (n = 926)	393.1 ± 472.9	217.1 ± 339.2	<0.001
Plasma NE (pg/ml) (n = 913)	721.9 ± 408.1	641.7 ± 344.6	0.003
Early H/M	1.53 ± 0.19	1.58 ± 0.20	0.003
Late H/M	1.39 ± 0.18	1.46 ± 0.21	<0.001
Washout (%)	41.8 ± 17.3	36.1 ± 17.2	<0.001

BNP = B-type natriuretic peptide; HF = heart failure; H/M = heart/mediastinum ratio; NE = norepinephrine; Washout = ([early heart (H) counts/pixel (cpi) − early mediastinum (M) cpi] − [late H cpi* − late M cpi*])/(early H cpi − early M cpi) (*decay-corrected); other abbreviations as in Table 1.

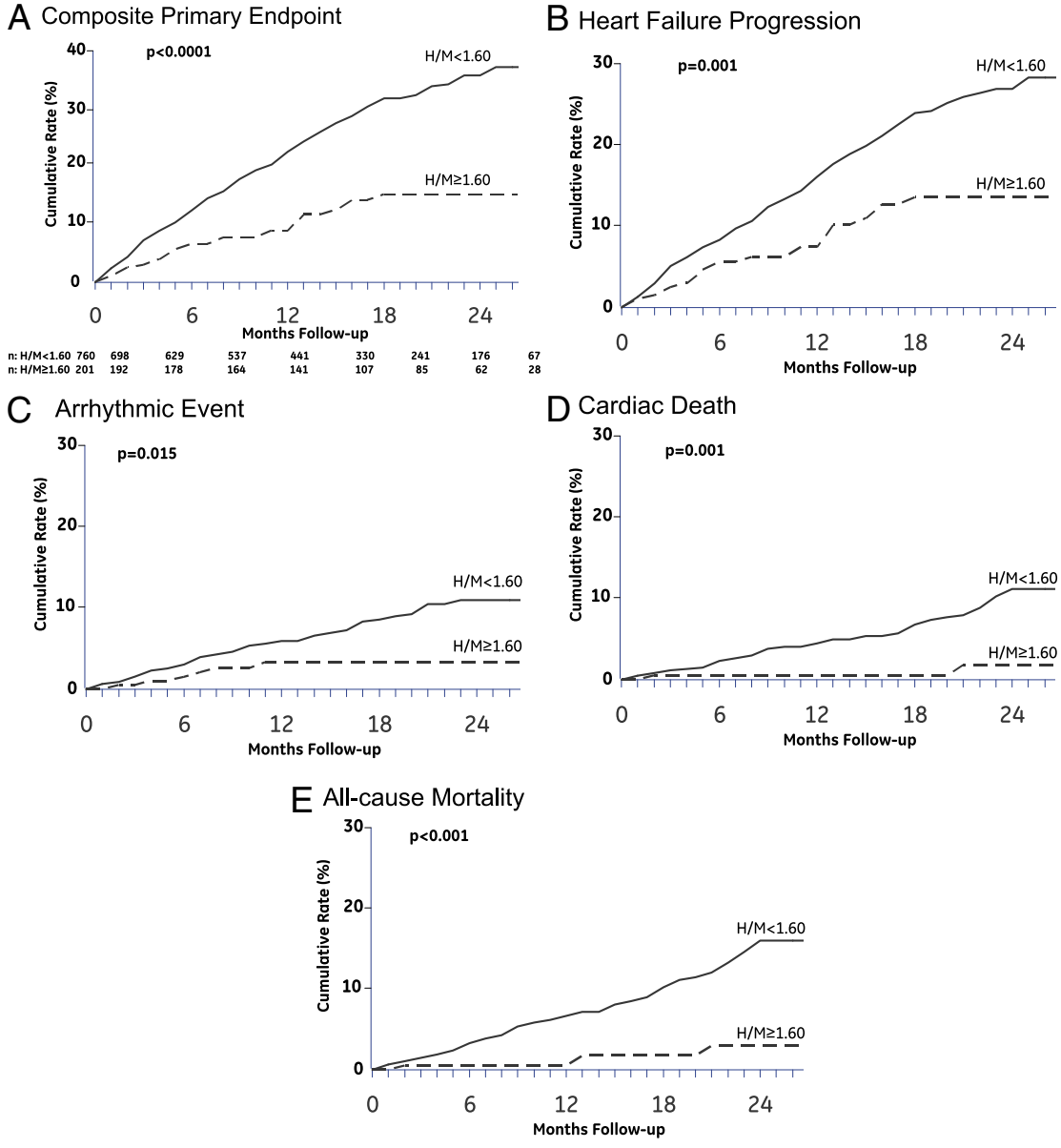

Figure 2 **Cumulative Event Curves Comparing Subjects With H/M <1.60 Versus ≥1.60**

(A) Composite primary end point; **(B)** heart failure progression; **(C)** arrhythmic event; **(D)** cardiac death; **(E)** all-cause mortality. For each analysis, the former group has a significantly higher event rate. H/M = heart/mediastinum ratio.

demonstrated an even lower hazard ratio (0.22; 97.5% CI: 0.10 to 0.47; $p < 0.001$). The analyses based on the individual event categories showed significant differences for all 3, with the lowest hazard ratio for subjects with high H/M being for cardiac death (0.14; 95% CI: 0.03 to 0.58; $p = 0.006$) (Fig. 2, Table 3).

Additional analyses considering cardiac death and all-cause mortality are presented in Figures 2 and 3 and Table 4. For H/M <1.60, 2-year probabilities of cardiac death and all-cause mortality were 11.2% and 16.1% versus 1.8% and 3.0% for the group with H/M ≥1.60. Treated as a continuous variable, there was a progressive decline in both cardiac and all-cause mortality from >20% for H/M <1.10 to 0% for H/M ≥1.80. The 2-year cardiac death rate in the total population was 9.1%, compared with the rate in the first decile (H/M <1.20; n = 92) of 19.1%.

Secondary analyses. The multivariable analyses from the individual phase III studies demonstrated a consistently significant contribution for the late H/M across blinded readers. These same analyses showed no consistent contribution to event prediction for the ^{123}I-*m*IBG and 99mTc-

Table 3 Results of Cox Proportional Hazards Model for H/M Threshold of 1.60 on Cardiac Events Categories

Event Category	N	Total Events n	Total Events %	Hazard Ratio (95% CI)	p Value
Heart failure progression	961	176	18.3	0.49 (0.32–0.77)	0.002
Potentially life-threatening arrhythmia	961	64	6.7	0.37 (0.16–0.85)	0.020
Cardiac death	961	53	5.5	0.14 (0.03–0.58)	0.006

CI = confidence interval; H/M = heart/mediastinum ratio.

tetrofosmin SPECT results. The multivariable analysis of the pooled ADMIRE-HF data using only the planar ^{123}I-*m*IBG imaging results produced a model with 4 independent variables contributing to the prediction of the primary outcome events: late H/M, LVEF, NYHA functional class, and plasma BNP (Table 5). In univariate Cox proportional hazards analyses, the early and late H/M and washout all were significantly associated with risk of CEs. In multivariable analyses with these 3 parameters, the late H/M was consistently the only parameter that retained statistical significance.

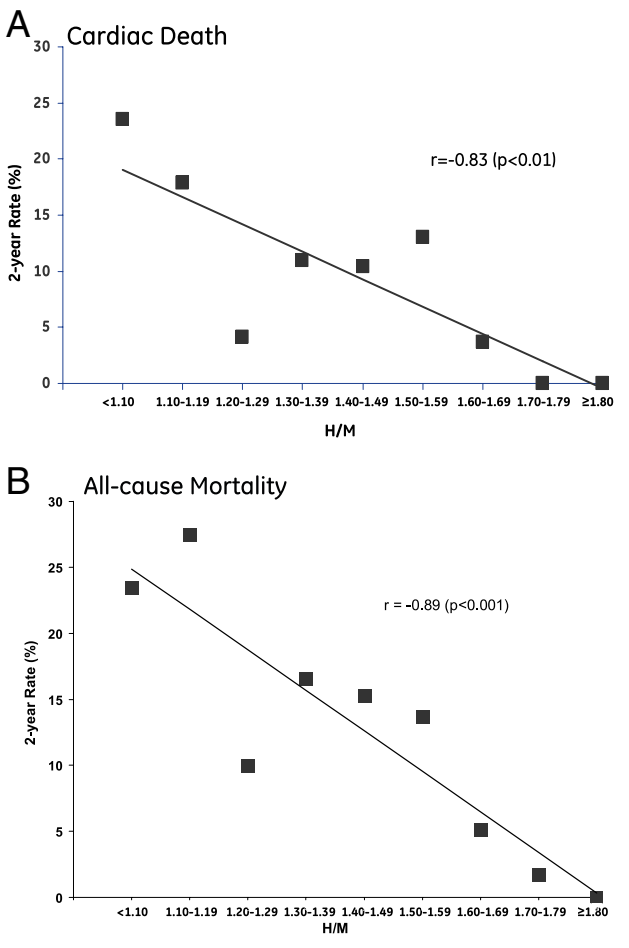

Figure 3 2-Year Cardiac Death and All-Cause Mortality Rates Versus H/M

Two-year cardiac death **(A)** and all-cause mortality **(B)** rates show progressive decline from >20% for heart/mediastinum ratio (H/M) <1.10 to 0% for H/M ≥1.80.

Comparison with other prognostic markers. The utility of addition of the H/M to 2 frequently used markers of prognosis in HF patients, BNP and LVEF, was examined in subanalyses. The median BNP level in the 926 subjects with adequate blood samples was 140 ng/l, and there was a small but statistically significant negative correlation between plasma BNP and H/M (Online Fig. 1). There were highly significant differences in the total CE and cardiac death rates between subjects with BNP levels below and above the population median (Figs. 4A and 4B). Addition of the binary H/M result provided further stratification for total CEs and cardiac death in the high-risk BNP population and a difference of borderline significance for total CEs in subjects with BNP <140 ng/l (Figs. 4C and 4D). The 2-year CE rate for subjects with BNP >140 ng/l was 42%, but among the subset with H/M ≥1.60, the rate was 20.5%. There were no cardiac deaths among the 57 subjects with BNP >140 ng/l and ^{123}I-*m*IBG H/M ≥1.60, compared with 42 cardiac deaths among the 406 subjects (10.3%) with above-median BNP and H/M <1.60.

Median LVEF in the 961 subjects was 29%, and there was a modest but statistically significant positive correlation between LVEF and H/M (Online Fig. 2). There were highly significant differences in total event and cardiac death rates between subjects with LVEF levels below and above the population median (Figs. 4E and 4F). Addition of the binary H/M result provided further stratification for HF subjects in both LVEF groups (Figs. 4G and 4H). The 2-year CE rate for subjects with LVEF <30% and H/M ≥1.60 was less than half that of all subjects with LVEF <30% (17.6% vs. 40.3%). There were 2 cardiac deaths among the 81 subjects (2.5%) with LVEF <30% and H/M ≥1.60 as compared with 39 cardiac deaths among the 409 (9.5%) with LVEF <30% and H/M <1.60. There were no

Table 4 Proportions of Subjects With Cardiac and All-Cause Death in Relation to H/M Threshold of 1.60

H/M	N	Cardiac Deaths n	Cardiac Deaths %	All Deaths n	All Deaths %	p Value
<1.60	760	51	6.7	77	10.1	<0.002
≥1.60	201	2	1.0	4	2.0	<0.002

H/M = heart/mediastinum ratio.

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Table 5 Results of Multivariable Cox Proportional Hazards Analysis of Time to Cardiac Events

Variable	Hazard Ratio (95% CI)	p Value
H/M	0.36 (0.17–0.75)	0.006
LVEF	0.95 (0.93–0.97)	<0.001
NYHA functional class	1.48 (1.08–2.02)	0.015
BNP	1.00 (1.00–1.00)*	<0.001

n = 903 subjects with complete data; 224 cardiac events. *Value represents incremental hazard for 1 unit change (1 ng/l) and is rounded from 1.0004 (1.0002 to 1.0007).

BNP = B-type natriuretic peptide; H/M = heart/mediastinum ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; CI = confidence interval.

cardiac deaths among the 120 subjects with LVEF ≥30% and H/M ≥1.60.

Further analyses examined the interaction of H/M, LVEF, and BNP in the 926 subjects with BNP results. Among the 273 subjects with above-median values for BNP and below-median LVEF values, there were significantly lower 2-year primary event and cardiac death rates for subjects with H/M ≥1.60 compared with H/M <1.60 (Fig. 5A). Considering values of all 3 parameters in the most abnormal quartile (H/M ≤1.30, LVEF ≤23%, BNP >311.4 ng/l), the highest and lowest rates of primary events and cardiac deaths were among the 38 and 456 subjects with all 3 parameters or none in the most abnormal quartile, respectively (Figs. 5B and 5C).

Among the 10% of subjects with the lowest LVEF (<20%; n = 98), H/M values still discriminated between higher- and lower-risk subpopulations. Thirty-five of 61 subjects (57%) with H/M <1.40 had outcome events, compared with 10 of 37 (27%) with H/M ≥1.40 (p = 0.004). Considering this low LVEF decile in conjunction with subjects in the highest-risk deciles for H/M (<1.20) and BNP (>595.9 ng/l), 31 cardiac deaths (58% of the study total) occurred among the 233 subjects (24%) with at least 1 such high-risk value (p < 0.001 compared with 22 cardiac deaths among the remainder of the population [n = 727]). Each of the 3 parameters alone identified a subset of the subjects who experienced cardiac death (BNP, n =18; H/M, n = 13; LVEF, n = 13).

Arrhythmic events. A total of 86 subjects (9%) experienced either nonfatal arrhythmic events (self-limited ventricular tachycardia [VT], n = 12; resuscitated cardiac arrest, n = 6; appropriate ICD discharges, n = 45) or SCD (n = 23). These combined "arrhythmic" events were significantly more common in subjects with H/M <1.60 (79 of 760 [10.4%] vs. 7 of 201 [3.5%]; p < 0.01). The highest prevalence of arrhythmic events was in the H/M range 1.30 to 1.39 (27 of 206; 13.1%). The highest H/M in a subject who experienced a fatal arrhythmic event was 1.60. Only 5 arrhythmic events occurred in the 191 subjects with H/M >1.60 (2.6%); 2 of 137 subjects with no ICD experienced self-limited episodes of VT, whereas 3 of 54 subjects with ICDs had device activations (2 antitachycardia pacing, 1 direct current shock).

Discussion

^{123}I-*m*IBG has been in clinical use in Japan and Europe for 2 decades, and a large number of published reports have documented abnormalities of myocardial sympathetic innervation in various cardiovascular diseases (13,14,16–21, 24,25). A recent meta-analysis of 18 studies and 1,755 patients confirmed that HF patients with reduced late H/M or increased ^{123}I-*m*IBG washout rate have a worse prognosis as compared with patients with normal ^{123}I-*m*IBG uptake and washout parameters (24). In addition to prediction of HF progression and death, abnormal ^{123}I-*m*IBG uptake and washout have also been shown to be associated with increased incidence of SCD and appropriate ICD discharges (27,28). These reports have supported the usefulness of ^{123}I-*m*IBG imaging for predicting potentially fatal outcomes in HF patients over follow-up periods of months to years. ADMIRE-HF provides the first large, prospective confirmation of the strong prognostic value of quantitation of cardiac adrenergic neuronal activity in HF patients. The current results also suggest a potential beneficial application for the ^{123}I-*m*IBG imaging procedure for identifying HF patients at very low and very high risks for near-term morbidity and mortality.

Role of neurohormonal regulation in HF. Observations that patients with HF have increased circulating catecholamines and downregulation of beta-adrenergic receptors (6–10) have focused particular attention on the potential for molecular imaging of in vivo myocardial NE kinetics to provide improved risk stratification for the HF patient population (24,25). Direct examination of cardiac neuronal status may be more informative than assessment of systemic adrenergic activity in that the ^{123}I-*m*IBG H/M uptake ratio was a significant contributor to the ADMIRE-HF multivariable risk model, but plasma NE was not.

Preserved neuronal uptake of ^{123}I-*m*IBG identified a very low-risk HF population, with late H/M ≥1.60 (21% of trial subjects) associated with <1%/year incidence of cardiac death. In contrast, among the 10% of subjects with H/M <1.20, annual rate of cardiac mortality (9.6%) was 10-fold greater. The results of the ^{123}I-*m*IBG imaging procedure could therefore potentially identify approximately one-third of the HF population studied as either at substantial risk for near-term mortality or to be at low risk on the current level of therapy.

Clinical implications of ADMIRE-HF. ADMIRE-HF did not directly evaluate the potential benefit of ^{123}I-*m*IBG imaging as an aid to clinical management of HF patients, but the study suggests that in appropriately selected patients, this imaging procedure could alert clinicians to the potential need for considering additional treatments. For example, there were 74 ADMIRE-HF subjects who were <50 years old and had BNP <100 ng/l. Forty-seven of these subjects had H/M <1.60, of whom 13 developed CE, including 3 ICD activations, 1 episode of sustained VT, and 1 SCD. Nine of these subjects had HF progression (including 1

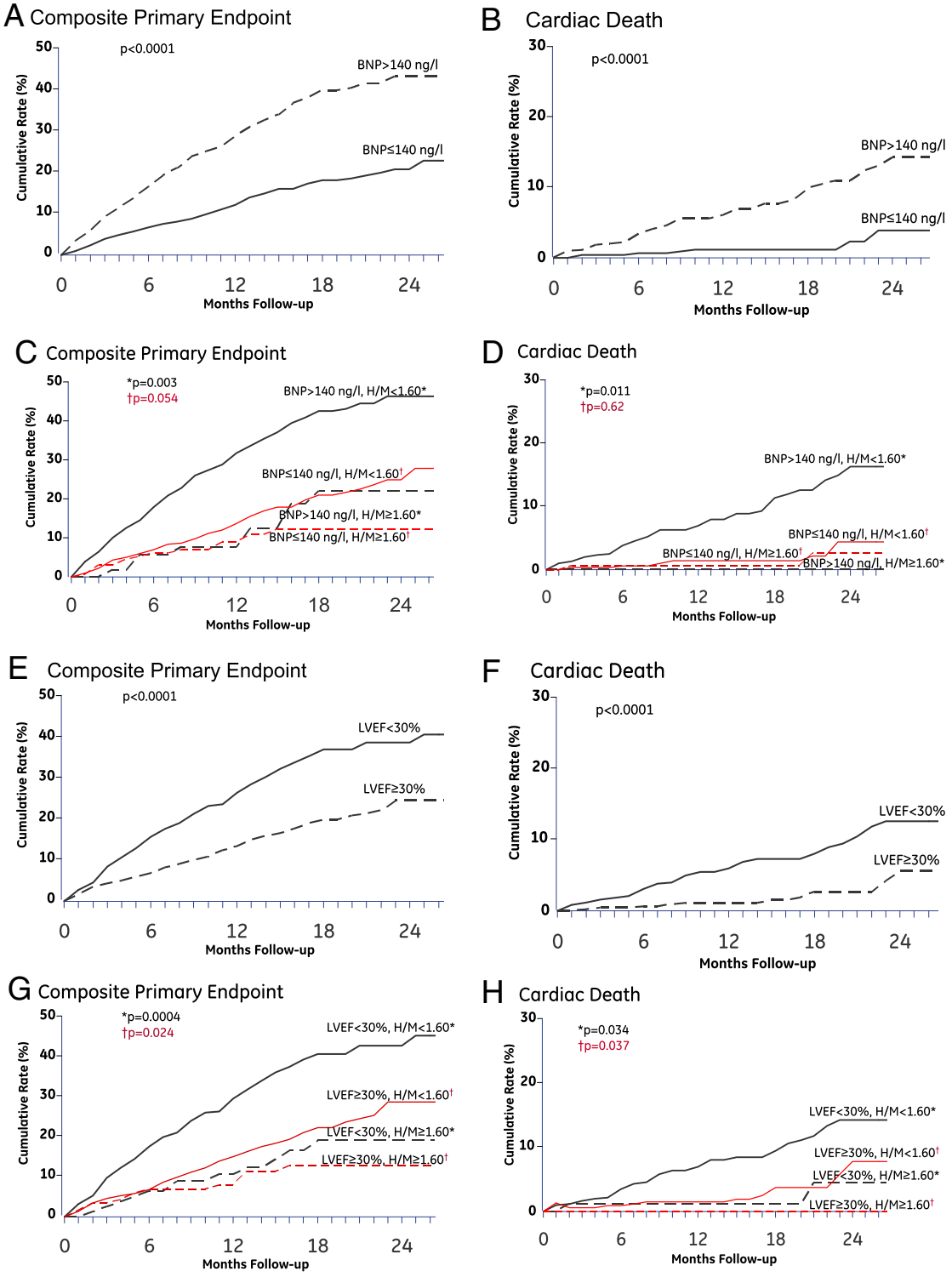

Figure 4 **Cumulative Event Curves in Relation to BNP, LVEF, and H/M**

There is a highly significant difference in primary event **(A)** and cardiac death rates **(B)** between subjects with B-type natriuretic peptide (BNP) below and above the median value of 140 ng/l. Addition of the heart/mediastinum ratio (H/M) (<1.60 vs. ≥1.60) further stratifies subjects with high BNP **(C, D)**. There is a highly significant difference in primary event **(E)** and cardiac death rates **(F)** between subjects divided at the median left ventricular ejection fraction (LVEF) of 29%. Addition of the H/M (<1.60 vs. ≥1.60) further stratifies subjects in both LVEF groups **(G, H)**.

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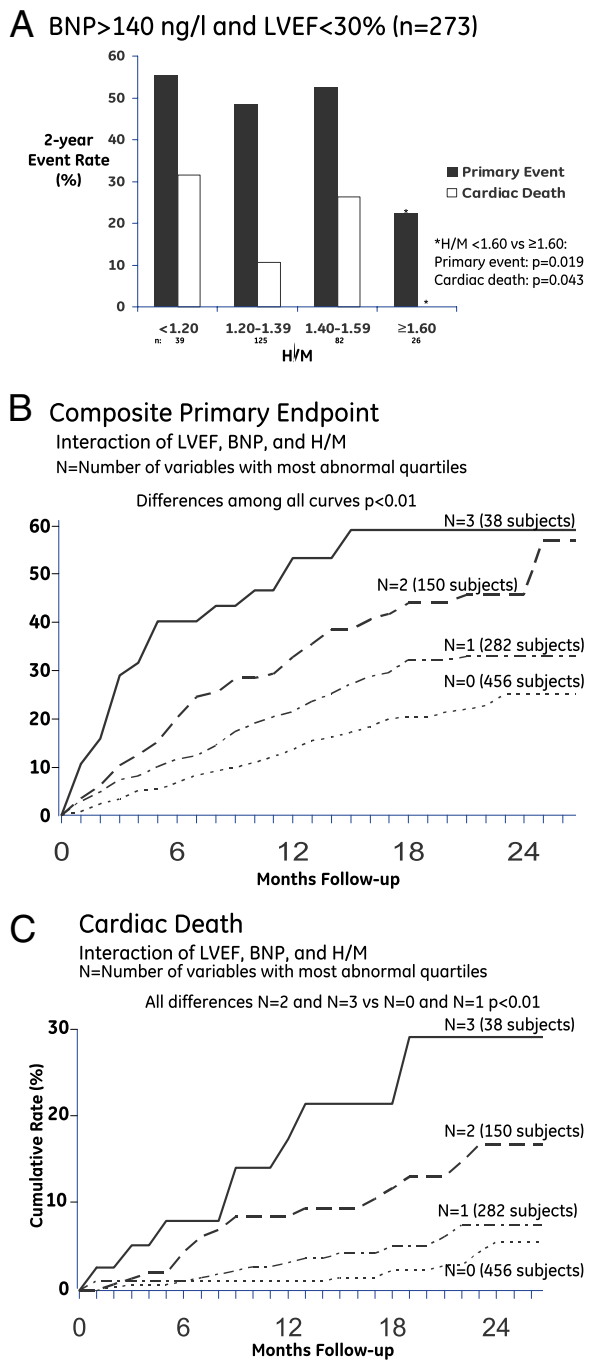

Figure 5 2-Year Primary Event and Cardiac Death Rates and Cumulative Event Curves in Relation to BNP, LVEF, and H/M Values

(A) Among the 273 subjects with both BNP >140 ng/l and LVEF <30%, event rates are significantly lower among subjects with H/M ≥1.60. Highest event rates are in subjects with H/M <1.20. **(B, C)** In relation to the most abnormal quartiles of BNP (>31 ng/l), LVEF (≤23%), and H/M (≤1.30), there is a highly significant difference in primary event rates **(B)** between subjects with 0, 1, 2, and 3 of these high-risk values. Although the same progression is seen for cardiac death **(C)**, the differences between the N = 0 and N = 1 curves and the N = 2 and N = 3 curves do not reach statistical significance. Abbreviations as in Figure 4.

who had previously experienced an ICD shock). Twenty-seven of these 47 subjects did not have ICDs, including the subject who died suddenly. Knowledge of the higher risk associated with abnormal cardiac innervation might have facilitated consideration of more aggressive treatment (such as earlier use of resynchronization therapy) in these subjects.

As a marker of adverse prognosis and cardiac death, BNP had the strongest predictive power (highest chi-square value) in the multivariable analyses. However, as demonstrated in those analyses and in the analyses restricted to H/M, BNP, and LVEF, the H/M provided significant information to complement BNP for identifying subjects at the highest risk for CEs and cardiac death. H/M also stratified risk among subjects with the lowest LVEF values (<20%), including identifying a small low-risk cohort with H/M ≥1.60 (12 of 98; 12%). The likelihood of cardiac death was more than 4 times greater in the subpopulation of subjects with extreme deciles for at least 1 of the 3 parameters of BNP, H/M, and LVEF compared with the remainder of the trial population (13.4% vs. 3.0%).

Study limitations. Failure of the ^{123}I-*m*IBG and 99mTc-tetrofosmin SPECT results to contribute to the multivariable risk models may have been a direct consequence of the rigorous design of the phase III clinical trials. The readers scored all ^{123}I-*m*IBG SPECT exams without reference to either the planar images (and the calculated H/Ms) or the 99mTc-tetrofosmin SPECT studies. The blinded mixture of ischemic and nonischemic cardiomyopathy subjects also made it more challenging for the readers to assign defect severity to the myocardial segments based on global versus regional reduction in ^{123}I-*m*IBG uptake. Determination of the potential value of MPI SPECT, included in this study to assess whether quantitation of innervation/perfusion mismatch would augment prediction of arrhythmic CEs (10,19), was also affected by the inconsistency in the visual ^{123}I-*m*IBG SPECT assessments. The planar H/M succeeded because it was a reproducible quantitative result; it is likely that similar success with SPECT will require use of automated quantitative analysis procedures.

As the present study involved only a single ^{123}I-*m*IBG imaging procedure, short-term reproducibility of the H/M determinations was not assessed. Most published studies that included replicate ^{123}I-*m*IBG exams were examining the effect of medications or devices and involved inter-scan intervals of 6 to 12 months (20,21). However, even modest intra-subject variability in the H/M measurements would be unlikely to change the highly significant results obtained in this study, particularly for individuals with either severely abnormal or normal cardiac uptake.

Conclusions

The ADMIRE-HF demonstrated the capacity of quantitation of sympathetic innervation of the myocardium, measured by the H/M on ^{123}I-*m*IBG scintigraphy, for predicting prognosis for significant cardiac events in subjects with HF and significant left ventricular dysfunction. This is the

population to which guidelines for use of implanted devices for management of HF and arrhythmic event risk usually apply (29). ADMIRE-HF showed a highly significant relationship between time to HF-related events and the H/M, which was independent of other commonly measured parameters such as LVEF and BNP, as well as demographic parameters such as age and renal function, in an HF population on guidelines-based contemporary therapy. The study also showed a clear association between severity of myocardial sympathetic neuronal dysfunction and risk for subsequent cardiac death.

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REFERENCES

1. Brunner-La Rocca HP, Esler MD, Jennings GL, Kay DM. Effect of cardiac nervous activity on mode of death in congestive heart failure. Eur Heart J 2001;22:1136–43.
2. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
3. Leimbach WN Jr., Wallin BG, Victor RG, Aylward PE, Sundlof G, Mark AL. Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 1986;73:913–9.
4. Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation 1990;82 Suppl:I103–13.
5. Paul M, Schafers M, Kies P, et al. Impact of sympathetic innervation on recurrent life-threatening arrhythmias in the followup of patients with idiopathic ventricular fibrillation. Eur J Nucl Med Mol Imaging 2006;33:866–70.
6. Bohm M, La Rosee K, Schwinger RH, Erdmann E. Evidence for reduction of norepinephrine uptake sites in the failing human heart. J Am Coll Cardiol 1995;25:146–53.
7. Ungerer M, Hartmann F, Karoglan M, et al. Regional *in vivo* and *in vitro* characterization of autonomic innervation in cardiomyopathic human heart. Circulation 1998;97:174–80.
8. Backs J, Haunstetter A, Gerber SH, et al. The neuronal norepinephrine transporter in experimental heart failure: evidence for a post-transcriptional downregulation. J Mol Cell Cardiol 2001;33:461–72.
9. Mardon K, Montagne O, Elbaz N, et al. Uptake-1 carrier downregulates in parallel with the beta-adrenergic receptor desensitization in rat hearts chronically exposed to high levels of circulating norepinephrine: implications for cardiac neuroimaging in human cardiomyopathies. J Nucl Med 2003;44:1459–66.
10. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med 1982;307:205–11.
11. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784–94.
12. Abdulla J, Køber L, Christensen E, Torp-Pedersen C. Effect of beta-blocker therapy on functional status in patients with heart failure: a meta-analysis. Eur J Heart Fail 2006;8:522–31.
13. Merlet P, Benvenuti C, Moyse D, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. J Nucl Med 1999;40:917–23.
14. Simoes MV, Barthel P, Matsunari I, et al. Presence of sympathetically denervated but viable myocardium and its electrophysiologic correlates after early revascularised, acute myocardial infarction. Eur Heart J 2004;25:551–7.
15. Sisson JC, Wieland DM. Radiolabeled meta-iodobenzylguanidine: pharmacology and clinical studies. Am J Physiol Imaging 1986;1:96–103.
16. Wakabayashi T, Nakata T, Hashimoto A, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. J Nucl Med 2001;42:1757–67.
17. Merlet P, Valette H, Dubois-Rande JL, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med 1992;33:471–7.
18. Cohen-Solal A, Esanu Y, Logeart D, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. J Am Coll Cardiol 1999;33:759–66.
19. Nakata T, Miyamoto K, Doi A, et al. Cardiac death prediction and impaired cardiac sympathetic innervation assessed by MIBG in patients with failing and nonfailing hearts. J Nucl Cardiol 1998;5:579–90.
20. Kasama S, Toyama T, Kumakura H, et al. Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. J Nucl Med 2002;43:1279–85.
21. Agostini D, Belin A, Amar MH, et al. Improvement of cardiac neuronal function after carvedilol treatment in dilated cardiomyopathy: a 123I-MIBG scintigraphic study. J Nucl Med 2000;41:845–51.
22. Jacobson AF, Lombard J, Banerjee G, Camici P. 123I-*m*IBG scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: design of two prospective multicenter international trials. J Nucl Cardiol 2009;16:113–21.
23. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.
24. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J 2008;29:1147–59.
25. Yamashina S, Yamazaki JI. Neuronal imaging using SPECT. Eur J Nucl Med Mol Imaging 2007;34:939–50.
26. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd edition. New York, NY: John Wiley & Sons, 2000:116–28.
27. Nagarahara D, Nakata T, Hashimoto A, et al. Predicting the need for an implantable cardioverter defibrillator using cardiac metaiodobenzylguanidine activity together with plasma natriuretic peptide concentration or left ventricular function. J Nucl Med 2008;49:225–33.
28. Tamaki S, Yamada T, Okuyama Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction. J Am Coll Cardiol 2009;53:426–35.
29. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol 2009;53:e1–90.

Key Words: sympathetic nervous system ■ radionuclide imaging ■ heart failure ■ prognosis ■ cardiomyopathy ■ *m*IBG.

APPENDIX

For an expanded Methods section, supplementary figures, and Acknowledgments, please see the online version of this article.