Myocardial Sympathetic Innervation, Imaging

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Dr. Kenneth McKusick, MD, SNMMI

APC Panel Meeting August 26th, 27th, 2013

Jointly Presented by:
The American Society of Nuclear Cardiology
Merlino Healthcare Consulting Corp.
The Society of Nuclear Medicine & Molecular Imaging

American Society of Nuclear Cardiology
Society of Nuclear Medicine & Molecular Imaging

• The American Society of Nuclear Cardiology is a 4,500 member society comprised of physicians, scientists, technologists, and other personnel who work in the nuclear cardiology field. ASNC provides its members with continuing medical education, promoted accreditation and certification, and is the principal advocacy voice for the profession.

• The Society of Nuclear Medicine & Molecular Imaging is a 19,000 member society representing nuclear and molecular imaging professionals. SNMMI strives to be a leader in unifying, advancing, and optimizing molecular imaging with the ultimate goal of improving human health.
• What is being imaged: Cardiac sympathetic innervation. Tracer taken up/retained in sympathetic nerve terminal

How is it measured: ROI of heart and mediastinum => heart/mediastinal (H/M) ratio of counts
Higher ratio = more preserved innervation, lower risk of arrhythmia, death

SPECT perfusion
SPECT mIBG

• Sept 2008 - indicated for use in the detection of rare neuroendocrine tumors in children and adults

• March 2013 - imaging assessment of sympathetic innervation of the myocardium to assist in the evaluation of adult patients with NYHA class II or III HF and LV EF ≤ 35% to help identify pts with 1- and 2-yr mortality risks as indicated by an H/M ratio ≥ 1.6
Basis for Approval

• “ADMIRE-HF” trial – 985 pts w NYHA II/III HF and EF<35%. H/M ratio >1.6 associated with 1-yr survival 99%, 2-yr survival 97%

Clinical Utility

How will clinicians use this test?
• To identify low risk HF pts when decision making unclear-
  • eg elderly HF pt w low EF, candidate for ICD by guidelines but patient hesitant, need more info to balance risk vs benefit
AMA CPT® Category III Codes
New July 1, 2013

<table>
<thead>
<tr>
<th>CPT Category III</th>
<th>APC Assigned</th>
<th>Status Indicator</th>
<th>Descriptor</th>
<th>July 1, 2013 / Prop. January 1, 2014 Payment Rate</th>
</tr>
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<tbody>
<tr>
<td>0331T</td>
<td>0398</td>
<td>S</td>
<td>Myocardial sympathetic innervation, imaging, planar qualitative and quantitative assessment;</td>
<td>$308.99 / $397.32</td>
</tr>
<tr>
<td>0332T</td>
<td>0398</td>
<td>S</td>
<td>Myocardial sympathetic innervation, imaging, planar qualitative and quantitative assessment; with tomographic SPECT</td>
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</tr>
<tr>
<td>A9582</td>
<td>---</td>
<td>N</td>
<td>Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 millicuries</td>
<td>---</td>
</tr>
</tbody>
</table>

Proposed Rule CY 2014 using 2012 Medicare Claims Data:
A9582 mean cost $1,319.97; median cost is $1,178.52.
G.E. reported to CMS ASP Q2 2013 = $2,696.00

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Description of the CMS 2011 Claims Data

Concentration of A9582 I-123 iobenguane Claims in 2011

Analysis of the 2011 CMS claims data (proposed rule CY 2013) by Direct Research, LLC.
Description of the Data

• An analysis of 2011 Medicare claims data reveals A9582 is found predominantly with tumor imaging claims.

Specifically CPT codes:
• 78075, 78802, 78803, and 78804.

• The APCs associated with these tumor imaging services are 0408 and 0414.

Existing Diagnostic Radiopharmaceutical CMS Data: Cost & ASP

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>A9582</td>
<td>Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 millicuries</td>
<td>$1,319.97</td>
<td>$1,178.52</td>
<td>$2,636.16*</td>
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</tbody>
</table>

The cost of this diagnostic radiopharmaceutical (A9582) is a significant cost to consider for any APC placement:

• Page 271 of Advance Copy of CY 2014 Proposed Rule; “40-percent threshold is a reasonable definition of a significant cost”
### 2011 CMS Claims Data
#### Off-Set File Final Rule CY 2013

<table>
<thead>
<tr>
<th>APC</th>
<th>Descriptor</th>
<th>CY 2013 APC Payment</th>
<th>APC Off-Set Percentage and Dollar Amount</th>
<th>Theoretical Total Cost Procedure – RP from CMS 2011 Off-Set Data</th>
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<tbody>
<tr>
<td></td>
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<td>Portion of APC Payment Associated with “Policy Packaged” Drugs (Drugs that Are Always Packaged, i.e. Diagnostic Radiopharmaceuticals)</td>
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<tr>
<td>0398</td>
<td>Level I Cardiac Imaging</td>
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<td>0377</td>
<td>Level II Cardiac Imaging</td>
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<td>Nuclear Medicine Oncologic APC</td>
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<tr>
<td>0414</td>
<td>Level II Tumor/Infection Imaging</td>
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<td>$955.60</td>
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### 2012 CMS Claims Data
#### Off-Set File RP dollar from Final Rule CY 2013

<table>
<thead>
<tr>
<th>APC</th>
<th>Descriptor</th>
<th>Proposed CY 2014 APC Payment</th>
<th>APC Off-Set Percentage and Dollar Amount</th>
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<td></td>
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<td>Level I Cardiac Imaging</td>
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<td>$1,159.77</td>
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<td>$623.58</td>
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Assumption, used dollar amount for RP from the 2011 Claims, best proxy. At the time material needed for presentation no other CMS data available.
APC Placement – 0331T & 0332T
New Category III CPT Services

- There are no current nuclear medicine APCs that are representative of similar bundled/packaged costs and resources, as well as clinical similarities for these new services.
  - Placement in Tumor Imaging APCs would violate Clinical Homogeneity
  - Placement in any one of the current nuclear medicine APCs would clearly undervalue these new Category III CPT services.

Recommendation Option 1:
Use Available Existing Costs

<table>
<thead>
<tr>
<th>APC</th>
<th>Descriptor</th>
<th>Theoretical Total Cost Procedure –RP from CMS 2011 Off-Set Data</th>
<th>Last Publicly Available ASP Data</th>
<th>Total Theoretical Packaged Cost</th>
<th>New Technology APC Category</th>
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<tbody>
<tr>
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<td>Level I Cardiac Imaging (Planar) (0331T)</td>
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Assumption, used dollar amount for RP from the 2011 Claims, best proxy. At the time material needed for presentation no other CMS data available.
Recommendation Option 2: Use Available Existing Costs

<table>
<thead>
<tr>
<th>APC</th>
<th>Descriptor</th>
<th>Theoretical Total Cost Procedure –RP from CMS 2011 Off-Set Data</th>
<th>P CY 2014 Mean Cost Data</th>
<th>Total Theoretical Packaged Cost</th>
<th>New Technology APC Category</th>
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<tr>
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<td>Level I Cardiac Imaging (Planar) (0331T)</td>
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Nuclear Medicine Oncologic APC (Violates Clinical Homogeneity)

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<tr>
<th>APC</th>
<th>Descriptor</th>
<th>Theoretical Total Cost Procedure –RP from CMS 2011 Off-Set Data</th>
<th>P CY 2014 Mean Cost Data</th>
<th>Total Theoretical Packaged Cost</th>
<th>New Technology APC Category</th>
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Assumption, used dollar amount for RP from the 2011 Claims, best proxy.
At the time material needed for presentation no other CMS data available.

Joint Society Recommendation

- We request the APC Advisory Panel recommend that CMS utilize existing cost data for a resource based APC placement in one of the new technology APCs.
- Since the off-set file for CY 2014 is not available until the final rule, we would recommend CMS consider and utilize our methodology to obtain the individual costs, added together for appropriate APC placement in new technology to maintain both resource and clinical homogeneity.
Potential Consequences of Not Making the Requested Change

- Inappropriate assumptions about outpatient services costs for new technology will stifle future research and development in this field.

Expected Outcome

- The American Society of Nuclear Cardiology and the Society of Nuclear Medicine and Molecular Imaging expect appropriate placement of these codes will lead to appropriate access to sympathetic innervation imaging and improved treatment for heart failure.
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<th>Presentation Checklist</th>
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<td>Societal descriptions – slide 2</td>
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<tr>
<td>HCPCS codes involved – slide 7</td>
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<tr>
<td>APCs affected – slides 7,9,11&amp;12</td>
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<tr>
<td>Description of the issue – slides 7-15</td>
</tr>
<tr>
<td>Description of the data – slides 7-15</td>
</tr>
<tr>
<td>Clinical example – slides 3-6</td>
</tr>
<tr>
<td>Recommendation/rationale – slide 16</td>
</tr>
<tr>
<td>Expected outcome – slide 18</td>
</tr>
<tr>
<td>Potential consequences of not making the change – slide 17</td>
</tr>
</tbody>
</table>
Cardiac Sympathetic Imaging
With mIBG in Heart Failure

Ignasi Carrió, MD,* Martin R. Cowie, MD, MSc,† Junichi Yamazaki, MD,§ James Udelson, MD,‖ Paolo G. Camici, MD‡
Barcelona, Spain; London, United Kingdom; Tokyo, Japan; and Boston, Massachusetts

Cardiac sympathetic imaging with meta-iodobenzylguanidine (mIBG) is a noninvasive tool to risk stratify patients with heart failure (HF). In patients with ischemic and nonischemic cardiomyopathy, cardiac mIBG activity is a very powerful predictor of survival. Cardiac sympathetic imaging can help in understanding how sympathetic overactivity exerts its deleterious actions, which may result in better therapy and outcome for patients with HF. (J Am Coll Cardiol Img 2010;3:92–100) © 2010 by the American College of Cardiology Foundation

Current Challenges in Heart Failure (HF)

The prognosis of HF has improved in the past 20 years, but it remains a serious condition with a markedly increased risk of death in the early period after onset of the syndrome (1). In population studies, there is a 10% mortality by 30 days. For those who survive this early high-risk period, the 5-year mortality is 54% in men and 40% in women (1). Mortality for patients in most recent clinical trials, with a background of appropriate pharmacological neurohormonal blockade, is around 8% to 10% per annum. Device therapy, with cardiac resynchronization with or without an implantable cardioverter-defibrillator further improves the prognosis (2–4), but at a relatively high additional financial cost initially.

In clinical trials of chronic HF therapy, 50% of deaths are due to sudden death, and progressive HF accounts for around 30% of deaths, this latter proportion increasing as symptomatic severity increases (5). In population studies including patients with new-onset HF, progressive HF appears to be the single most common cause of death (52%), with sudden death accounting for only 22% of deaths within the first 6 months of diagnosis (6,7).

Identifying those patients most at risk of death, and those most likely to benefit from currently available treatment technologies, remains a challenge. Identifying the risk of sudden, presumed arrhythmic, death, is particularly difficult. In general, older age, greater functional impairment, poorer systolic function of the left ventricle, lower serum sodium, poorer renal function, broader QRS complex, lower blood pressure, and inability to tolerate disease-modifying drugs such as angiotensin-converting enzyme (ACE) inhibitors are associated with a poorer prognosis and are men-
tioned in guidelines for HF management (8,9). Poorer adherence to evidence-based treatment by the physician has also been shown to be independently associated with a worse prognosis (10). There is a pressing need for improved risk stratification for patients developing HF, with the goal of better identification of those for whom more aggressive therapy is likely to be beneficial.

Pathophysiologic Basis for Cardiac Sympathetic Imaging

Compared with myocardium of healthy controls, the myocardium of patients with chronic left ventricular dysfunction is characterized by a significant reduction of pre-synaptic norepinephrine (NE) uptake and post-synaptic beta-adrenoeceptor density (11,12). There is increased sympathetic activity in the hearts of patients with congestive HF, which is a generalized rather than a regional phenomenon and might contribute to the remodeling process of the whole left ventricle. This concept is consistent with the finding that down-regulation of myocardial beta-adrenoeceptor density, measured using positron emission tomography (PET) with 11C-CGP-12177, soon after acute myocardial infarction is predictive of the occurrence of left ventricular dilatation at follow-up (13). Myocardial beta-adrenoeceptor density appears reduced in patients with HF due to dilated cardiomyopathy (14) and down-regulation of myocardial beta-adrenoeceptor is more pronounced in patients with hypertrophic cardiomyopathy who proceed to left ventricular dilation and HF (15). Therefore, myocardial beta-adrenoeceptor down-regulation may be a general nonspecific response to stress and could be due to a locally increased amount of NE in the synaptic cleft. The sustained hyperactivity of the sympathetic nervous system observed in HF is the consequence of several mechanisms including increased central sympathetic outflow, altered neuronal NE reuptake, and facilitation of cardiovascular response to sympathetic stimulation by angiotensin II.

As a single-photon emission computed tomography (SPECT) tracer whose use does not require availability of an on-site cyclotron, 123I-meta-iodobenzylguanidine (mIBG) has been the most widely used imaging agent for studying causes and effects of cardiac sympathetic hyperactivity. mIBG was developed through a modification of the potent neuron-blocking agent guanethidine that acts selectively on sympathetic nerve endings. Uptake of 123I-mIBG into neurons is achieved mainly through the uptake-1 mechanism, a homeostatic system responsible for the reuptake of NE. Unlike NE, mIBG is not metabolized, allowing it to be imaged. The uptake-1 mechanism is one of the main NE disposal systems, and its malfunction may lead to abnormal catecholamine concentration in the synaptic cleft.

Imaging Techniques and Quantification With mIBG

A complete imaging protocol typically includes planar and SPECT images obtained 15 to 30 min (early) and 3 to 4 h (delayed) after intravenous injection of 111 to 370 MBq (3 to 10 mCi) 123I-mIBG (Fig. 1) (16). Myocardial uptake and distribution is visually assessed. mIBG uptake is semiquantified by calculating a heart-to-mediastinum ratio (HMR) after drawing regions of interest over the heart and mediastinum (Fig. 1). This approach provides a highly reproducible index of cardiac sympathetic activity (16). By comparing early and delayed activities, the mIBG wash-out (WO) rate from the myocardium can be derived, providing a parameter that reflects retention of NE by sympathetic neurons (17).

SPECT images of the heart allow evaluation of the regional sympathetic activity. Polar maps of the myocardium can be constructed from the SPECT images and allow assessment of the defect extent and severity. Such polar maps can be easily compared with those of healthy individuals (Fig. 2). 123I-mIBG SPECT images can also be compared with SPECT myocardial perfusion images to examine differences between regional innervation and perfusion. In making such comparisons, it is important to be aware of differences between normal innervation and perfusion patterns, such as lower uptake of 123I-mIBG seen in the posterior inferior wall, especially in elderly persons (18,19).

Imaging With 123I-mIBG in Ischemic Heart Disease

The sympathetic nervous tissue is more sensitive to the effects of ischemia than the myocardial tissue (20). It has been shown that the uptake of 123I-mIBG is significantly reduced in areas of myocardial infarction (21), and adjacent noninfarcted regions (22) as well as in areas with acute and chronic ischemia (23,24). It is likely that ischemia damages sympathetic neurons
(probably earlier and more severely than cardiac myocytes), which may take a long time to regenerate and that episodes of ischemia result in decreased $^{123}$I-mIBG uptake. Sympathetic nerve trunks course along the same path as the coronary arteries, with the potential of a neuronal defect being present distal to the site of myocardial injury. Immunohistochemistry has demonstrated good correspondence between $^{123}$I-mIBG imaging and the presence or absence of sympathetic cardiac nerves (25). Reinnervation may be incomplete as late as 3 months after acute myocardial infarction, but by 12 months after a first infarction, an increase in activity in the peri-infarcted region without a change in perfusion has been observed (26).

Concordance between the extent of $^{123}$I-mIBG defect at rest and perfusion defect at exercise has been shown in patients with coronary artery disease. This concordance suggests that resting imaging with $^{123}$I-mIBG combined with resting myocardial perfusion imaging (MPI) may be useful as a marker of reversible ischemia in patients unable to exercise and with contraindications to pharmacological stress (27). Another potential role of mIBG imaging at rest is the detection of transient ischemia, which has been shown with metabolic tracers of both fatty acid and glucose analogs, termed “ischemic memory,” that may result in regional decrease in mIBG uptake (28–32). This property of resting $^{123}$I-mIBG imaging also has promise in the evaluation of the area at risk in the subacute phase of acute coronary syndromes by revealing more extensive defects than MPI.

**Imaging With $^{123}$I-mIBG for Risk Stratification and Prognosis**

Impaired cardiac adrenergic innervation as assessed by $^{123}$I-mIBG imaging is strongly related to mortality in patients with HF independently of its cause. The prognostic value of $^{123}$I-mIBG scintigraphy compared with other noninvasive cardiac imaging indices was initially studied in patients with either ischemic or idiopathic cardiomyopathy (33,34). Among all clinical and imaging variables, only the late HMR and left ventricular ejection fraction (LVEF) were independent predictors of mortality, with late HMR being the best predictor of event-free survival. In these studies, a late HMR of $\leq 1.2$ was used to identify reduced $^{123}$I-mIBG uptake. Using this same threshold, it has been shown that reduced late HMR is correlated with other predictors of prognosis such as LVEF, cardiac...
index, pulmonary wedge pressure, and peak oxygen consumption, with late HMR ≤1.2 and peak oxygen uptake also predictive of death or cardiac transplantation over follow-up (35).

In other large cohorts of patients (36,37) with HF studied with 123I-mIBG, a reduced late HMR has been the most powerful predictor of cardiac mortality. A late HMR ≤1.74, age ≥60 years, a history of myocardial infarction, and New York Heart Association (NYHA) functional class III or IV strongly indicated poor clinical outcomes (36). However, 123I-mIBG imaging was the most powerful independent long-term prognostic indicator for ischemic or idiopathic cardiomyopathy patients. Late HMR was the most powerful independent predictor of cardiac mortality in both groups of patients, superior to the early HMR and the WO rate, with an identical threshold for both groups for identifying patients at risk of cardiac death when LVEF ≤50% (37).

The incremental prognostic implications of cardiac 123I-mIBG imaging have been assessed as well. Plasma brain natriuretic peptide (BNP) level significantly, but roughly, correlated with cardiac sympathetic nerve imaging results in a series of patients with HF (38). Univariate analysis identified BNP level, HMR, chronic renal dysfunction, diabetes mellitus, age, and use of nitrates as significant predictors of fatal pump failure. Using a plasma BNP threshold of 172 pg/ml and a late HMR threshold of 1.74 together, the hazard ratio was 34.4. Prevalence of fatal pump failure significantly increased from 22% to 62.5% when diabetes mellitus and chronic renal dysfunction were present with a higher BNP level and low cardiac 123I-mIBG activity.

The largest body of prognostic results is based on the late HMR from planar 123I-mIBG imaging (Fig. 3). Further confirmation of the strong prognostic value of this parameter was presented in the results of a recent retrospective multicenter European study (39), which included blind review and prospective quantitative reanalysis of the late HMR of 290 patients with ischemic and nonischemic HF (NYHA functional class II to IV, 262 patients with LVEF <50%) with follow-up data for 2 years. A standardized method for drawing heart and mediastinum region of interests on planar chest images was evaluated by 3 independent blinded readers. The analysis technique was robust, with 95% to 98% agreement among the readers regarding the HMR results obtained. The mean HMR was significantly different between patients with and without events (1.51 vs. 1.97). Based on receiver operating characteristic curve analysis, a threshold value for HMR of 1.75 yielded a sensitivity of 84% with a specificity of 60% to predict events (2-year event-free survival 62% for late HMR ≤1.75 vs. 95% for late HMR ≥1.75). Logistic regression showed late HMR and LVEF as the only significant predictors of major cardiac events (Fig. 4).
Besides the late HMR, the prognostic value of other $^{123}$I-$m$IBG parameters has also been reported. The WO rate was evaluated in patients with LVEF <40% during a follow-up of 52 months (40). A WO rate <27% was a strong predictor of survival. In another series of outpatients with HF (mean LVEF 29%), of whom 48 had abnormal WO rate (≥27%), sudden cardiac death was significantly more frequent in patients with an abnormal WO rate (41). $^{123}$I-$m$IBG WO rate and both early and late HMR were significantly associated with sudden cardiac death. The prognostic value of cardiac $^{123}$I-$m$IBG imaging together with that of time and frequency domain parameters of HRV in patients with mild-to-moderate chronic HF has been prospectively evaluated (42). On univariate analysis, WO rate, late HMR, and normalized very-low-frequency power showed a significant association with the cardiac events at follow-up. Multivariate analysis showed that WO rate was the only independent predictor of cardiac events.

A recent meta-analysis (43) performed on 18 studies with a total of 1,755 patients provided further confirmation that patients with HF and decreased cardiac $^{123}$I-$m$IBG uptake or increased WO rate have a worse prognosis as compared with patients with normal $^{123}$I-$m$IBG parameters.

**Imaging With $^{123}$I-$m$IBG for Assessment of Treatment**

Cardiac $^{123}$I-$m$IBG imaging can demonstrate drug-induced changes in cardiac adrenergic activity. Enalapril improved cardiac sympathetic activity but did
not affect plasma NE levels in a group of patients with HF (44), supporting the concept that restoration of cardiac neuronal uptake of NE is one of the beneficial effects of ACE treatment. Similar increases in cardiac \textsuperscript{123}I-\textit{mIBG} uptake have been observed after treatment with other ACE and angiotensin receptor blocker (ARB) (45,46) in patients with chronic HF.

With regard to beta-blocker therapy, patients with improvement of LVEF of \(\geq 5\%\) after 3 months of treatment with metoprolol demonstrate a decrease in regional WO rate of \textsuperscript{123}I-\textit{mIBG} after 1 month of beta-blocker therapy compared with baseline rates (45). The effect of chronic carvedilol treatment in patients with HF and cardiac sympathetic nerve dysfunction of varying severity due to idiopathic cardiomyopathy has been studied (47–49). Most patients showed a favorable response in left ventricular function to the treatment, regardless of the baseline level of cardiac sympathetic nervous system function, as assessed by cardiac \textsuperscript{123}I-\textit{mIBG} imaging. Patients with severely depressed HMR (<1.40) had a higher likelihood to achieve an improvement in cardiac sympathetic nervous system function in response to carvedilol treatment. In patients treated with bisoprolol a late HMR >1.7 had a sensitivity of 91\% and specificity of 92\% for predicting response to beta-blocker therapy (48).

The influence of aldosterone treatment on cardiac sympathetic nerve activity has been assessed comparing 2 groups of patients treated with an ACE inhibitor and a loop diuretic, 1 with the addition of spironolactone. After 6 months of treatment with spironolactone, the late HMR of \textsuperscript{123}I-\textit{mIBG} and LVEF significantly increased, and the late total defect score as well as the WO rate of \textsuperscript{123}I-\textit{mIBG} significantly decreased, with parallel reduction of the left ventricular end-diastolic volume (50). A prospective study comparing amiodarone versus beta-blockers in the treatment of patients with idiopathic cardiomyopathy (51) reported similar improvement in cardiac symptoms, function, and sympathetic nerve activity with both drugs.

\textsuperscript{123}I-\textit{mIBG} studies for prognostication in 208 patients under combination therapy and with stabilized mild-to-moderate HF and LVEF <45\%, of both ischemic and nonischemic origin have been analyzed (52). \textsuperscript{123}I-\textit{mIBG} and echocardiographic studies were performed at baseline and after 6 months of treatment, which included ACE inhibitors, ARB, beta-blockers, loop diuretics, and spironolactone. The variation in the WO rate between the sequential \textsuperscript{123}I-\textit{mIBG} studies was significantly lower in the noncardiac death group than that in the cardiac death group and was the only independent predictor of cardiac death.

**Newer Multicenter Clinical Trials**

Almost all cardiac \textsuperscript{123}I-\textit{mIBG} studies reported in the past 20 years represented single-center experiences. However, during the past 5 years, a series of multicenter trials were performed to demonstrate the robustness of quantification of \textsuperscript{123}I-\textit{mIBG} cardiac uptake as a prognostic marker in HF patients.

**Prognosis in HF: MBG311 and MBG312.** MBG311 and MBG312 are 2 prospective trials initiated in 2005 to validate the prognostic capability of quantification of sympathetic innervation of the myocardium using \textsuperscript{123}I-\textit{mIBG}. These trials have now been designated as part of the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) program. The hypothesis tested was that patients with HF and abnormal HMR ratios have earlier and more frequent events (HF progression, potentially life-threatening arrhythmia, or cardiac death) than those with HMR within the normal range. Event status was monitored for 24 months, with final determinations made by an independent clinical adjudication committee of cardiologists. Secondary efficacy analyses employed a multiparameter Cox proportional hazards model fitted to multiple imaging and clinical variables, including early and late HMR, total and segmental \textsuperscript{123}I-\textit{mIBG} SPECT defect scores, total and segmental cardiac \textsuperscript{99mTc}Tetrofosmin SPECT MPI defect scores, LVEF, NYHA functional class, BNP, and NE levels, \textsuperscript{123}I-\textit{mIBG}/\textsuperscript{99mTc}Tetrofosmin SPECT mismatch score, and echocardiography left ventricular end-diastolic volume and left ventricular mass. All primary and secondary analyses were performed on the composite end point (first occurrence of any specified adverse cardiac event) and on each individual event category (Table 1). Results of the trials were recently presented at the American College of Cardiology scientific sessions, in March 2009, and the publication of the manuscript is expected to follow soon.

**Prediction of inducibility of ventricular tachycardia: MBG203.** MBG203 was a prospective pilot study to determine whether alterations in cardiac sympathetic innervation as measured by \textsuperscript{123}I-\textit{mIBG} were related to inducibility of ventricular tachyarrhythmias during electrophysiology (EP) testing in patients with previous myocardial infarction. The primary objective was to evaluate results on planar
$^{123}$I–mIBG imaging and the combination of SPECT $^{123}$I–mIBG innervation and $^{99m}$Tc-tetrofosmin MPI in comparison with results on EP testing (positive or negative for inducible sustained ventricular tachycardia as determined by a clinical adjudication committee of 3 EP specialists). Primary inclusion criteria were history of myocardial infarction, left ventricular dysfunction, and referral for a clinically indicated cardiac EP study because of syncope or nonsustained ventricular tachycardia (Table 2).

In a multivariable analysis, the only variable that showed a significant difference between EP-positive and EP-negative patients was the 4-h $^{123}$I–mIBG SPECT defect score. A 4-h $^{123}$I–mIBG SPECT defect score of ≥37 yielded a sensitivity of 77% and specificity of 75% for predicting EP results (53). The results of this pilot study suggest that the simple index of $^{123}$I–mIBG cardiac uptake represented by the HMR ratio will not be sufficiently sensitive to categorize levels of arrhythmic risk in ischemic heart disease patients. However, the extent of denervated myocardium, as assessed by $^{123}$I–mIBG SPECT imaging, does appear to correlate with inducibility of ventricular tachyarrhythmias during EP testing.

### Cardiac $^{123}$I–mIBG imaging in 2009

Despite the extensive research on cardiac $^{123}$I–mIBG imaging performed over the past 20 years, the exact role of this procedure in diagnosis and management of patients with heart disease remains uncertain. Although the importance of the sympathetic innervation of the heart is unquestioned, and the benefits of therapies that ameliorate the effects of neurohormonal imbalance are well established, doubt lingers about the manner in which quantitative assessment of adrenergic neuronal status should be used. Particularly for HF medical therapies, the conventional reasoning is that all appropriate medications will be used as tolerated and as dictated by symptom improvement, so a monitoring tool such as $^{123}$I–mIBG imaging offers no additional benefit. From a medical and economic point of view, it is easier to treat all patients with moderately priced drugs that have been shown to benefit the large majority than to attempt to individualize treatment based upon a physiological assessment that might produce equivocal results in a subset of the patients. $^{123}$I–mIBG imaging can provide an estimate of prognosis and can demonstrate whether therapies are producing the desired effect on cardiac pre- and post-synaptic function, but other readily available methods already inform the clinician regarding the success of his/her treatment approach. It is thus unlikely that $^{123}$I–mIBG imaging will become a routine clinical procedure for monitoring heart disease status or treatment response. It is in the realm of device therapy that $^{123}$I–mIBG imaging is likely to have its greatest impact in the next few years.

Most of the patients who have a Class I indication for receiving an implantable cardioverter-defibrillator will never experience an appropriate discharge, and about one-third of patients who receive cardiac resynchronization therapy do not improve. For both these patient groups, $^{123}$I–mIBG imaging holds promise as a technique capable of identifying both high and low risk for the adverse outcomes the devices are intended to prevent or at least forestall. The results from the ADMIRE-HF study should provide additional impetus for the development of...
criteria for use of 123I-mIBG imaging (alone or more likely in combination with other procedures) to identify those HF patients at highest and lowest risk for potentially fatal arrhythmic events.

Conclusions

123I-mIBG imaging provides a noninvasive tool for the investigation of cardiac sympathetic innervation. Although defining the exact criteria to be used for clinical decision-making will depend on the results of currently ongoing trials, it appears that 123I-mIBG imaging will soon be added to the resources available to the clinical cardiologist. In the future, imaging of the cardiac sympathetic system will aid in quantifying the functional severity of myocardial injury and remodeling associated with ischemic and nonischemic cardiomyopathy, judging the likely response to medical and device therapy for HF, and identifying the substrate that places the patient at the highest risk for arrhythmic sudden cardiac death.

Acknowledgment

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REFERENCES


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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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Princeton, New Jersey; London, United Kingdom; Cleveland, Ohio; Irvine, California; Caen, France; Roseville, California; and Victoria, Texas

Objectives
The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study prospectively evaluated iodine-123 meta-iodobenzylguanidine (123I-mIBG) 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 123I-mIBG 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 123I-mIBG 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 < 0.001); 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. 123I-mIBG 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 123I-mIBG 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). Adrenoceptor 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).

The decrease in the NE reuptake mechanism has been successfully assessed by radionuclide imaging with the iodine-123–labeled NE analog meta-iodobenzylguanidine (123I-mIBG), which has demonstrated an excellent safety profile during more than 20 years of clinical use (5,13–15). Uptake of 123I-mIBG into myocardial sympathetic nerve endings is mediated by the NE transporter, and because the compound is not metabolized, the amount of 123I-mIBG retention over several hours after administration is a reflection of neuronal integrity (15). Reduced myocardial 123I-mIBG uptake has been demonstrated to be an independent predictor of adverse long-term outcome, and improvement in 123I-mIBG uptake is observed in response to effective HF therapy (13,16–21). Although there is extensive literature on 123I-mIBG 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 123I-mIBG 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 123I-mIBG. 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 optimal 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.

#### 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 123I-mIBG (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 (99mTc)-tetrofosmin (Mycview, 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).
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-mIBG 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 tachyrhythmia, 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-mIBG value was selected for the primary analysis because of the extensive literature supporting its prognostic significance (24,25). Complete $^{123}$I-mIBG 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-mIBG 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-
Results

Study participants. 123I-mIBG 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 123I-mIBG 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 1 Clinical Characteristics of the Heart Failure Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>n</td>
<td>961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>901</td>
<td>82.8</td>
<td></td>
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<tr>
<td>Race, white (%)</td>
<td>759</td>
<td>78.5</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>60.5</td>
<td>59.5</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>ACE inhibitors/ARBs (%)</td>
<td>94.2</td>
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<tr>
<td>Beta-blockers (%)</td>
<td>91.9</td>
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<tr>
<td>Lipid-lowering agents (%)</td>
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<td>Aldosterone antagonist (%)</td>
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<td>Diabetes (%)</td>
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<td>Hypertension (%)</td>
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<tr>
<td>Smoker, current or past (%)</td>
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<tr>
<td>Dyslipidemia (%)</td>
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<td>Heart failure: NYHA functional class II, III (%)</td>
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<tr>
<td>Heart failure: Ischemic, nonischemic (%)</td>
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<tr>
<td>LVEF (%)</td>
<td>27.1</td>
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<td><strong>Values:</strong></td>
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<td>n</td>
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<tr>
<td>LVEF (%)</td>
<td>27.1</td>
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</table>

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.

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

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

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.
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 \(\geq 1.60\).

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 \(\geq 1.80\). 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-mIBG and 99mTc-
tetrofosmin SPECT results. The multivariable analysis of the pooled ADMIRE-HF data using only the planar $^{123}$I-mIBG 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.

**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 (Fig. 4C). The 2-year CE rate for subjects with BNP $>$140 ng/l was 42%, but among the subset with H/M $\geq$1.60, the rate was 20.5%. There were no cardiac deaths among the 57 subjects with BNP $>$140 ng/l and H/M $\geq$1.60, compared with 42 cardiac deaths among the 406 subjects (10.3%) with above-median BNP and H/M $\leq$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 $\geq$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 $\geq$1.60 as compared with 39 cardiac deaths among the 409 (9.5%) with LVEF $<$30% and H/M $<1.60$. There were no

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

<table>
<thead>
<tr>
<th>Event Category</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure progression</td>
<td>961</td>
<td>176</td>
<td>18.3</td>
<td>0.49 (0.32–0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>Potentially life-threatening arrhythmia</td>
<td>961</td>
<td>64</td>
<td>6.7</td>
<td>0.37 (0.16–0.85)</td>
<td>0.020</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>961</td>
<td>53</td>
<td>5.5</td>
<td>0.14 (0.03–0.58)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>H/M</th>
<th>N</th>
<th>Cardiac Deaths</th>
<th>All Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>$&lt;$1.60</td>
<td>760</td>
<td>51 6.7</td>
<td>77 10.1</td>
</tr>
<tr>
<td>$\geq$1.60</td>
<td>201</td>
<td>2 1.0</td>
<td>4 2.0</td>
</tr>
</tbody>
</table>

H/M = heart/mediastinum ratio.
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

123I-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 123I-IBG washout rate have a worse prognosis as compared with patients with normal 123I-IBG uptake and washout parameters (24). In addition to prediction of HF progression and death, abnormal 123I-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 123I-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 123I-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 123I-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 123I-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 123I-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 123I-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

### Table 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M</td>
<td>0.36 (0.17–0.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (0.93–0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.48 (1.08–2.02)</td>
<td>0.015</td>
</tr>
<tr>
<td>BNP</td>
<td>1.00 (1.00–1.00)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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.
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).
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 123I-mIBG 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 123I-mIBG 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 123I-mIBG 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 123I-mIBG 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 123I-mIBG imaging procedure, short-term reproducibility of the H/M determinations was not assessed. Most published studies that included replicate 123I-mIBG 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 123I-mIBG 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


Key Words: sympathetic nervous system • radionuclide imaging • heart failure • prognosis • cardiology • mIBG.

APPENDIX

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