Influence of Ejection Fraction on the Prognostic Value of Sympathetic Innervation Imaging With Iodine-123 MIBG in Heart Failure

Amil M. Shah, MD, MPH,* Mikhail Bourgoun, MD,* Jagat Narula, MD, PriD,† Arnold F. Jacobson, MD, PriD,‡ Scott D. Solomon, MD*
Boston, Massachusetts; New York, New York; and Princeton, New Jersey

OBJECTIVES The aim of this study was to determine whether left ventricular ejection fraction (LVEF) influences the relationship between abnormal myocardial sympathetic innervation imaging by iodine 123 meta-iodobenzylguanidine (123I-MIBG) and outcomes in patients with heart failure (HF).

BACKGROUND In systolic HF, both abnormal 123I-MIBG imaging and reduced LVEF are associated with higher risk of cardiovascular events. Whether 123I-MIBG imaging has the same predictive value across the LVEF spectrum is unclear.

METHODS Among 985 patients in the ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial with New York Heart Association functional class II or III HF and site-reported LVEF ≤35%, the core laboratory–determined LVEFs were available for 901 subjects, ranging from 20% to 58% (mean LVEF 34 ± 7%), and was >35% in 386 subjects.

RESULTS The mean age of the study population was 62 ± 12 years, 80% were male, and the majority had New York Heart Association functional class II symptoms and HF of nonischemic etiology. At all levels of LVEF, the 123I-MIBG heart-to-mediastinum ratio of <1.6 was associated with a higher risk of death or potentially lethal arrhythmic event and of the composite of cardiovascular death, arrhythmic event, and HF progression. Comparing subjects with LVEF ≤35% and >35%, there was no evidence of effect modification of LVEF on the risk associated with low heart-to-mediastinum ratio for death or arrhythmic event (adjusted hazard ratio: 2.39 [95% confidence interval (CI): 1.03 to 5.55] vs. 5.28 [95% CI: 1.21 to 23.02]; interaction p = 0.48) and for the composite (adjusted hazard ratio: 1.80 [95% CI: 1.01 to 3.23] vs. 2.41 [95% CI: 1.11 to 5.23]; interaction; p = 0.86). For death or arrhythmic event, the heart-to-mediastinum ratio appeared to improve the risk discrimination beyond clinical and biomarker data among both LVEF groups, with improvement in the model C-statistic (0.67 vs. 0.69, p = 0.03) and integrated discrimination improvement (p = 0.0008).

CONCLUSIONS 123I-MIBG imaging has prognostic value across a spectrum of LVEFs. Further studies may be warranted to prospectively test the prognostic value of 123I-MIBG imaging in patients with HF and an LVEF >35%. (J Am Coll Cardiol Img 2012;5:1139–46) © 2012 by the SIR

From the *Brigham and Women’s Hospital, Boston, Massachusetts; †Mount Sinai School of Medicine, New York, New York; and ‡GE Healthcare, Princeton, New Jersey. Dr. Jacobson is an employee of GE Healthcare and has minor ownership of GE stock. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. H. William Strauss, MD, served as Guest Editor for this paper.

Manuscript received October 24, 2011; revised manuscript received January 24, 2012, accepted February 8, 2012.
Patients with heart failure (HF) are at an increased risk of death secondary to both arrhythmia and HF progression regardless of left ventricular ejection fraction (LVEF) (1,2). When <45%, LVEF is a powerful predictor of adverse events in patients with HF (3). However, few measures are available to risk-stratify HF patients with a normal or mildly reduced LVEF. In particular, although subjects with HF and an LVEF >35% are at an increased risk of sudden death compared with persons without HF, there is currently no widely applicable method to risk-stratify these patients and identify those who may benefit from advanced therapies such as implantable cardioverter-defibrillators (4).

Evaluations of LVEF are often imprecise, related to interobserver variability, differences due to imaging modality, and physiological variation over time related to changes in loading conditions and heart rate (5). The use of experienced core laboratories appears to improve the uniformity of LVEF assessment by echocardiography in multicenter clinical trials, and profession guidelines for their use are now available (6). When LVEF cutoffs are used in multicenter clinical trials, discordance in LVEF results between the enrolling site and a core laboratory is not uncommon (7).

Iodine 123 meta-iodobenzylguanidine (123I-mIBG) is a radiopharmaceutical that is selectively taken up into pre-synaptic sympathetic nerve endings via the norepinephrine reuptake system but is not metabolized (8,9). Reductions in 123I-mIBG uptake therefore may represent abnormalities of pre-synaptic norepinephrine reuptake or sustained hyperactivity of the sympathetic nervous system in HF with pre-synaptic norepinephrine depletion. Abnormal cardiac sympathetic innervation imaging using 123I-mIBG is associated with a higher risk of mortality and morbidity among patients with HF and an LVEF ≤35% (10). Data regarding the prognostic utility of 123I-mIBG in HF with an LVEF >35% are limited (11).

We hypothesized that the association of lower heart-to-mediastinum ratio (H/M ratio) with mortality and potentially lethal arrhythmic events will be equivalent among HF patients across the spectrum of left ventricular (LV) systolic function. To gain greater insight into the utility of 123I-mIBG imaging in HF with EF >35%, we performed a retrospective analysis of the ADMIRE-HF (Adre-View Myocardial Imaging for Risk Evaluation in Heart Failure) trial database using LVEF determined by a core laboratory in which a subset of patients had an LVEF >35%. Specifically, we sought to assess for the presence of effect modification of LVEF on the relationship between H/M ratio and the risk of death or potentially lethal arrhythmic event and of cardiovascular death, arrhythmic event, or HF progression.

METHODS

Patient population. The ADMIRE-HF trial was the combination of 2 identical open-label, multicenter trials designed to provide prospective validation of the prognostic role of cardiac sympathetic innervation imaging using 123I-mIBG in patients with HF (12). The study enrolled 985 HF subjects who met the following inclusion criteria: New York Heart Association (NYHA) functional class II or III symptoms, an ischemic or nonischemic cardiomyopathy with a site-reported LVEF ≤35%, and receiving evidence-based medical therapy including a beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. All enrolled patients underwent planar imaging of the anterior thorax at 15 min and 4 h after 123I-mIBG injection. Subjects were followed for a median of 17 months to the primary composite endpoint of cardiac death, potentially life-threatening arrhythmic event, or HF progression. The extent of 123I-mIBG uptake was quantified at a core reading facility, and clinical events were adjudicated by an endpoint adjudication committee as previously described (13). A potentially life-threatening arrhythmic event was defined as an episode of spontaneous ventricular tachycardia >30 s, resuscitated cardiac arrest, or appropriate implantable cardioverter-defibrillator discharge (antitachycardia pacing or defibrillation). HF progression was defined as an increase in NYHA functional class from II to III or IV or from III to IV. The primary results of the ADMIRE-HF trial were previously presented and published (12).

Echocardiographic analysis. For trial inclusion, a site-reported LVEF could be based on assessment by echocardiography, radionuclide ventriculography, electrocardiography-gated single-photon emission computed tomography myocardial perfusion imaging, contrast ventriculography, or cardiac magnetic resonance. For quality assurance purposes, sites also submitted echocardiograms to an independent core laboratory for quantitative assessment.
of LV volumes and LVEFs. All echocardiograms were evaluated in a core laboratory blinded to both H/M ratio and clinical status. Ventricular volumes were determined by the Simpson method in the apical 4-chamber view, and LVEF was calculated from volumes in the standard manner (14).

Of 901 patients with a core laboratory–determined LVEF, 813 (90%) had site LVEF measured by echocardiography. Of these 813 patients, the same echocardiogram was used for site assessment and core laboratory analysis in 707 (87%). In the remaining 106 patients (13%), the study used for site LVEF assessment and core laboratory analysis were separated by a mean of 32 days (range, 1 to 439 days). In 88 patients (10%), the site-reported LVEF was based on a modality other than echocardiography, and in 59 (67%) of these patients, the study used for site assessment of LVEF was performed on a different day from the echocardiogram analyzed by the core laboratory (mean difference, 26 days; range, 1 to 50 days).

Statistical methods. We dichotomized subjects based on core laboratory–adjudicated LVEFs $\leq 35\%$ or $> 35\%$ to describe baseline clinical and imaging parameters. Continuous variables are presented as mean and SD unless otherwise specified, and between-group comparisons were performed using a Fisher exact test for categorical variables and a $t$ test for continuous variables. Two-sided $p$ values $<0.05$ were considered significant. Sample size was allowed to float.

We assessed for effect modification using 2 methods. First, multivariable Cox proportional hazard models were used to evaluate for effect modification of LVEF on the relationship between H/M ratio and the following outcomes: arrhythmic event or death and a composite of cardiac death, HF progression, and arrhythmic event. All models adjusted for age, sex, baseline NYHA functional class, HF etiology (ischemic or nonischemic), diabetes status, history of hypertension, baseline B-type natriuretic peptide level, and core laboratory–adjudicated LVEF. The area under the receiver–operating characteristic curve was expressed as the C-statistic and tested whether $p_{\text{event}} > p_{\text{nonevent}}$, where $p_{\text{event}}$ is the model predicted probability of an event from the logistic regression model containing the H/M ratio data among individuals who experienced an event and $p_{\text{nonevent}}$ is the model predicted probability of an event among individuals who did not experience an event. The model C-statistic was compared among models with versus without H/M ratio. C–statistics were compared using the Delong test (16). The integrated discrimination improvement (IDI) was calculated as $\text{IDI} = \left( p_{\text{with H/M, event}} - p_{\text{without H/M, event}} \right) - \left( p_{\text{with H/M, nonevent}} - p_{\text{without H/M, nonevent}} \right)$, where $p_{\text{with H/M, event}}$ is the predicted probability of an event from the logistic regression model containing the H/M ratio data among individuals who experienced an event, $p_{\text{without H/M, event}}$ is the predicted probability of an event from the logistic regression model not containing the H/M ratio data among individuals who experienced an event, $p_{\text{with H/M, nonevent}}$ is the predicted probability of an event from the logistic regression model containing the H/M ratio data among individuals who did not experience an event, and $p_{\text{without H/M, nonevent}}$ is the predicted probability of an event from the logistic regression model not containing the H/M ratio data among individuals who did not experience an event (17).

RESULTS

Baseline characteristics. Of 985 subjects enrolled in the ADMIRE-HF trial, $^{123}$I-mIBG imaging results, core laboratory–determined LVEFs, and complete follow-up were available for 901 subjects (91.5% of enrolled subjects) who were included in this analysis. The mean site–reported LVEF was...
and of death or arrhythmic event compared with subjects with an LVEF $>$35%. An H/M ratio $<$1.6 was associated with an increased relative risk of both endpoints without evidence of significant effect modification by LVEF category ($\leq$35% or $>$35%). Figure 2 illustrates the rate of death or arrhythmic event by H/M ratio among 4 categories of core laboratory LVEF, demonstrating consistent trends toward higher event rates with an H/M ratio $<$1.6 in all categories. As demonstrated in Figure 3, no significant heterogeneity of the relative risk associated with an H/M ratio $<$1.6 was detected across the continuum of LVEF for either of the clinical endpoints.

Incremental value of H/M ratio beyond clinical characteristics and LVEF in predicting clinical outcomes in patients with HF and LVEF $\leq$35% and $>$35%. For the cardiovascular composite endpoint, information on H/M ratio did not significantly affect the model C-statistic (Table 3). A small but significant improvement in the IDI was noted, the magnitude of which was most prominent in the LVEF $>$35% group. For the outcome of death or arrhythmic event, the addition of H/M ratio led to significant improvement in both the C-statistic and the IDI. For both measures, the magnitude of effect

**Table 1. Baseline Characteristics by Core Laboratory–Adjudicated LVEF**

<table>
<thead>
<tr>
<th>Category</th>
<th>LVEF $\leq$35% (n = 515)</th>
<th>LVEF $&gt;$35% (n = 386)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>29.5 $\pm$ 3.7</td>
<td>40.4 $\pm$ 5.0</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>61.6 $\pm$ 12.0</td>
<td>62.8 $\pm$ 11.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Male</td>
<td>423 (82)</td>
<td>296 (77)</td>
<td>0.04</td>
</tr>
<tr>
<td>White race</td>
<td>381 (74)</td>
<td>292 (76)</td>
<td>0.59</td>
</tr>
<tr>
<td>NYHA functional class III</td>
<td>89 (17)</td>
<td>62 (16)</td>
<td>0.65</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>321 (62)</td>
<td>267 (69)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>29.6 $\pm$ 6.3</td>
<td>28.7 $\pm$ 5.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>193 (37)</td>
<td>137 (35)</td>
<td>0.58</td>
</tr>
<tr>
<td>Hypertension</td>
<td>326 (63)</td>
<td>257 (67)</td>
<td>0.32</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>381 (74)</td>
<td>275 (71)</td>
<td>0.37</td>
</tr>
<tr>
<td>Smoking</td>
<td>384 (75)</td>
<td>281 (73)</td>
<td>0.59</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>483 (94)</td>
<td>358 (93)</td>
<td>0.59</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>475 (92)</td>
<td>350 (91)</td>
<td>0.47</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>376 (73)</td>
<td>291 (75)</td>
<td>0.44</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m$^2$</td>
<td>58.2 $\pm$ 18.2</td>
<td>60.3 $\pm$ 18.0</td>
<td>0.10</td>
</tr>
<tr>
<td>BNP, pg/ml$^*$</td>
<td>170 (69–363)</td>
<td>107 (41–232)</td>
<td>$&lt;$0.0001</td>
</tr>
</tbody>
</table>

Values are mean $\pm$ SD or n (%). *Median and interquartile range and Kruskal-Wallis nonparametric test reported. Continuous variables are expressed as mean $\pm$ SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
DISCUSSION

Of 901 subjects enrolled in the ADMIRE-HF trial with H/M ratio data and core laboratory LVEFs, 384 (43%) had an LVEF $\leq 35\%$. We found no evidence of effect modification of LVEF on the relationship between H/M ratio and risk, either of death or arrhythmic event or of the composite endpoint of cardiac death, arrhythmic event, and worsening HF. For the outcome of death or arrhythmic event, information on H/M ratio appeared to improve discrimination of predictive models beyond clinical, biomarker, and LVEF data, particularly among subjects with an LVEF $\leq 35\%$.

Multiple single-center studies have demonstrated an association between abnormal cardiac sympathetic innervation imaging, reflected in a low H/M ratio, and worse outcomes among patients with HF (10). However, the majority of studies evaluated patients with HF and low LVEF, and only limited data exist regarding the performance of this test in HF patients with normal or only slightly reduced LVEF ($>45\%$) (3). Given the role of the risk of sudden death is especially pronounced among HF patients with significant LV dysfunction, it is also the most common cause of cardiovascular death among patients with HF and normal or slightly reduced systolic function, accounting for 26% to 28% of total mortality (1,2). However, the ability to effectively risk-stratify these patients is limited. Although LVEF is a powerful predictor of mortality and sudden death when significantly reduced, it is less useful in risk-stratifying those patients with normal or only slightly reduced LVEF ($\geq 45\%$) (3). Given the role of LVEF in determining the risk of cardiovascular events.

Table 2. Cumulative Incidence of Cardiovascular Events Among Patients With Core Laboratory–Adjudicated LVEF $\leq 35\%$ Versus $>35\%$ by H/M Ratio Category

<table>
<thead>
<tr>
<th>LVEF $\leq 35%$ (n = 515)</th>
<th>LVEF $&gt;35%$ (n = 386)</th>
<th>p Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>H/M Ratio $\leq 1.6$</td>
</tr>
<tr>
<td>Death</td>
<td>52 (10)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>CV death</td>
<td>33 (6)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Arrhythmic event</td>
<td>48 (9)</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>117 (23)</td>
<td>106 (24)</td>
</tr>
<tr>
<td>Arrhythmic event or death</td>
<td>95 (18)</td>
<td>89 (21)</td>
</tr>
<tr>
<td>CV composite</td>
<td>156 (30)</td>
<td>143 (33)</td>
</tr>
</tbody>
</table>

Values are n (%) or n (range). $^*$Adjusted for age, sex, heart failure etiology, NYHA functional class, diabetes status, hypertension, and B-type natriuretic peptide level.

CV = cardiovascular; HF = heart failure; H/M ratio = heart-to-mediastinum ratio; HR = hazard ratio; LVEF = left ventricular ejection fraction; other abbreviation as in Table 1.
of cardiac autonomic innervation in the pathogenesis of ventricular arrhythmias (22), sympathetic innervation imaging has the potential to identify subjects at increased risk of life-threatening arrhythmia, although data regarding the relationship between H/M ratio and spontaneous arrhythmias in patients with implantable cardioverter-defibrillators (23) or inducible arrhythmias on electrophysiological testing (24) has been inconsistent. Our findings suggest that a low H/M ratio is associated with a higher risk of death or arrhythmic event across the spectrum of LVEFs, including HF patients with an LVEF >35%. Also, although limited by power, our exploratory analysis of the impact of H/M ratio data on model performance (C-statistic) and reclassification indexes (IDI) suggests that for the outcome of death or arrhythmic event, information on the H/M ratio improves risk discrimination beyond clinical, biomarker, and LVEF data. These findings suggest that 123I-mIBG imaging may hold promise to improve risk stratification among HF patients with an LVEF >35% if future adequately powered prospective studies can confirm these hypothesis-generating findings.

**Study limitations.** All patients had a site-reported LVEF of ≥35%. Although we noted a quantitative core laboratory LVEF >35% in 386 patients (43% of the trial population), the core laboratory LVEF was still <40% in the majority of these (n = 229, 59%) and was <45% in a large majority (n = 324, 84%). These differences may partly relate to a difference in timing and/or modality of study used by site and core laboratory in nearly one-fourth of subjects because the confidence limits for serial assessments of the LVEF in an individual at 2 time points are approximately 10% (25). Differences in the remainder of cases may partly relate to inter-reader variability, which approximates 7%, even when both assessments are measured quantitatively (5,25). Finally, in multicenter clinical trials using LVEF cutoffs for inclusion, discordance between enrolling site and core laboratory assessment is not unusual (7). Although this analysis provides information on the performance of sympathetic innervation imaging in HF patients with lesser degrees of impairment in LV systolic function, it does not represent the HF with preserved ejection fraction population. The timing between performance of the echocardiogram read by the core laboratory and the 123I-mIBG imaging varied. The relationship between appropriate implantable cardioverter-defibrillator therapy and sudden death is unclear. HF progression determined by increased NYHA functional class is subjective, although this endpoint was centrally adjudicated. The analyses were underpowered to detect an interaction by LVEF on the relationship between the H/M ratio and clinical events. They were similarly underpowered to detect incremental benefit of the H/M ratio beyond LVEF, biomarkers, and clinical data, especially when stratified by LVEF. For the LVEF >35% subgroup, adjusted effect estimates for death or ar-

---

**Figure 3. Risk of H/M Ratio <1.6 Across the LVEF Continuum**

Local regression plots of the adjusted HR associated with an H/M ratio <1.6 by LVEF as a continuous measure using multivariable Cox proportional hazards models. Refer to the Methods section for details of plot derivation. All HR point estimates are adjusted for age, sex, heart failure etiology, NYHA functional class, diabetes status, hypertension, and BNP level. (A) Clinical cardiovascular composite of cardiovascular death, arrhythmic event, or heart failure progression; (B) death or arrhythmic event. CI = confidence interval; other abbreviations as in Figure 2.
rhythmic event may be overfitted, although results were qualitatively similar as observed in unadjusted analyses. However, this population is the largest to our knowledge with data on the H/M ratio and clinical outcomes in HF patients with an LVEF ≤35%.

CONCLUSIONS

Myocardial sympathetic innervation imaging with $^{123}$I-mIBG has prognostic value across a broad spectrum of LVEFs for death or arrhythmic event and for cardiovascular death, arrhythmic event, and HF progression. For the outcome of death or arrhythmic event in particular, $^{123}$I-mIBG imaging appears to improve risk discrimination beyond clinical and biomarker data regardless of the LVEF. These findings suggest that further prospective studies may be warranted to evaluate the prognostic value of $^{123}$I-mIBG imaging in patients with HF and an LVEF >35%.

REFERENCES


14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.


Key Words: ejection fraction \[ \text{heart failure} \text{metaiodobenzylguanidine} \text{prognosis} \text{sympathetic nervous system.} \]