Cardiomyopathies

Predicting Risk Versus Predicting Potential Survival Benefit Using $^{123}$I-mIBG Imaging in Patients With Systolic Dysfunction Eligible for Implantable Cardiac Defibrillator Implantation

Analysis of Data From the Prospective ADMIRE-HF Study

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Background—Cardiac $^{123}$I-metaiodobenzylguanidine ($^{123}$I-mIBG) imaging improves prognostication in patients with left ventricular (LV) dysfunction. Whether $^{123}$I-mIBG can identify optimal candidates for implantable cardiac defibrillator (ICD) placement is unclear. We examined whether $^{123}$I-mIBG enhances risk assessment and identifies patients with enhanced survival with ICD in a patient cohort with reduced LV function who were candidates for ICD implantation.

Methods and Results—We identified 777 patients (66 sites, 12 countries) without ICD at the time of enrollment in Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) and index $^{123}$I-mIBG study. Patients completed prescribed study protocol and follow-up. Heart-to-mediastinum (H/M) ratio was determined from $^{123}$I-mIBG results. Survival modeling used a Cox proportional hazards mixed-effects model, including a propensity score, to adjust for nonrandomized ICD implantation after $^{123}$I-mIBG. All-cause death occurred in 75 patients (9.6%), and 196 (25%) patients had ICD implantation on follow-up. After adjusting for multiple factors, although the H/M ratio added incremental prognostic value and enhanced reclassification, neither H/M results, BNP levels, nor left ventricular ejection fraction interacted with ICD use in the survival model, indicating that these variables did not identify patients with enhanced survival with ICD implantation. Nonetheless, H/M results did identify the number of lives saved by ICD use per 100 treated.

Conclusions—We found that although $^{123}$I-mIBG imaging enhances the risk stratification of patients with left ventricular dysfunction who are ICD candidates, it does not identify which patients may have improved survival with ICD placement. However, $^{123}$I-mIBG identifies the absolute benefit gained with ICD use, thus may play a role in optimizing the cost-effectiveness of this intervention.

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Key Words: defibrillators ■ heart failure ■ prognosis ■ radioisotopes ■ survival
at risk of ventricular dysrhythmia, appropriate ICD discharge, or sudden cardiac death.\textsuperscript{8,10,13,14,17} Whether the use of \textsuperscript{123}I-mIBG results to guide the selection of ICD candidates will enhance patient survival and improve the efficiency of care is unclear.

Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) is a prospective multicenter study designed to validate the prognostic value of quantification of sympathetic innervation of the myocardium using \textsuperscript{123}I-mIBG scintigraphy in patients with LVEF<35\% and New York Heart Association (NYHA) functional class II or III heart failure.\textsuperscript{11,12} To address whether \textsuperscript{123}I-mIBG imaging has a role as a gatekeeper for the identification of the optimal ICD candidate, we identified a subset of the ADMIRE-HF cohort, who did not have an ICD, at the time of their index \textsuperscript{123}I-mIBG test, as our study cohort. We sought to determine whether \textsuperscript{123}I-mIBG results\textsuperscript{1} yield incremental prognostic value for prediction of adverse events in patients without ICD and\textsuperscript{2} identify which patients would have enhanced survival with versus without ICD implantation after their index study.

\textbf{Methods}

The ADMIRE-HF study prospectively evaluated \textsuperscript{123}I-mIBG imaging for identifying adverse cardiac events in patients with symptomatic heart failure. The design and primary results of ADMIRE-HF have been described previously.\textsuperscript{11,12,18} The primary inclusion criteria included NYHA functional class II or III heart failure, LVEF<35\%, and guidelines-based optimum pharmacotherapy. Major exclusion criteria included functioning ventricular pacemaker, history of defibrillation to treat a previous ventricular arrhythmic event, cardiac revascularization, acute myocardial infarction within previous 30 days, and serum creatinine \textgreater{}3.0 mg/dL (265 \textmu mol/L).\textsuperscript{11}

The present study is an analysis of 777 subjects (81\% of original recruited cohort, 66 sites, and 2 regions—North America and Europe [12 countries]), who did not have ICD implantation before their index \textsuperscript{123}I-mIBG study and enrollment into ADMIRE-HF. Study participants completed an informed consent statement approved by their local institutional review board or ethics committee.

The index \textsuperscript{123}I-mIBG study (Adreview, GE Healthcare, Princeton, NJ; 370 MBq [10 mCi±10\%]) included a 10-minute planar anterior chest image performed at 15 minutes (early image) and again at 3 hours and 50 minutes (late image). Separately, resting myocardial perfusion single-photon emission computed tomography (SPECT) imaging with \textsuperscript{99m}Tc-tetrofosmin (Myoview, GE Healthcare) was performed as previously described.\textsuperscript{11,12} All images were reviewed and interpreted at an independent core laboratory by 3 expert nuclear cardiologists, who were blinded to clinical data.\textsuperscript{11,12} Heart/mediastinum (H/M) uptake ratios were calculated from the late images. Summed rest scores were determined from myocardial perfusion imaging data using a standard 5-point, 17-segment model.\textsuperscript{19}

\textbf{End Points and Metrics}

The primary end point of our analysis was all-cause death, and our secondary end point was the composite of sudden cardiac death or life-threatening arrhythmia. These end points were defined by the criteria of, and identified and adjudicated by, the ADMIRE-HF trial. Life-threatening arrhythmia was defined as an event with significant hemodynamic or respiratory compromise necessitating urgent medical or electric therapy, including ventricular tachycardia, resuscitated cardiac arrest, antitachycardia pacing, ICD discharge, or defibrillation.\textsuperscript{11} All-cause death was selected to reduce issues of misclassification bias associated with assigning cause of death,\textsuperscript{20} and the secondary end point was selected because of its closer association with the therapy examined.

\textsuperscript{123}I-mIBG results were represented by consensus late H/M. Rest \textsuperscript{99m}Tc-tetrofosmin myocardial perfusion imaging results were represented by summed rest scores.

\textbf{Statistical Methods}

Numeric variables were summarized using mean±1 SD, when distributions seemed to be normal; otherwise, medians and interquartile ranges were used. Histograms and normal QQ plots were used to evaluate normality. Categorical variables were summarized by frequency and percentage. Univariable comparisons were made using t tests for apparently normally distributed data; Wilcoxon’s rank sum test for skewed data; and \chisq tests for categorical data. Fisher test was used when >20\% of the cross-tabulated table cell frequencies were ≤5.

\textbf{Multivariable Modeling}

To address the first goal of the study, whether \textsuperscript{123}I-mIBG results yield incremental prognostic value for the prediction of adverse events in patients without ICD, we used a mixed-effects model to take into account the effects of variability introduced by differences between regions of patient recruitment and sites of patient recruitment. Thus, the random effects of this model were recruitment site nested within region of recruitment (Nested random factors are sometimes also referred to as hierarchical random factors). Hence, survival modeling was performed using a mixed effects Cox proportional hazards model to determine the association of \textsuperscript{123}I-mIBG results with survival time free of all-cause death after adjusting for baseline covariates and potential confounders.\textsuperscript{21–23} In all instances in the current article, modeling of survival end points used this modeling approach.

Given the limited number of outcomes available, to maximize the number of variables we could consider in the model, we decided to initially develop a risk model that would include those covariates we felt were important to correct for but that were not part of the central question of the article (can MIBG results identify which patients may have an enhanced survival with ICD versus no ICD implantation). Thus, the variables we included in this model to summarize baseline clinical risk included age, race, body mass index (BMI), sex, diabetes mellitus, smoking history, NYHA classification, hypertension, MI history, BNP, LVEF, and heart failure cause. As in the other survival analyses in this study, we used a Cox proportional hazards mixed-effects model. The predicted risk of each individual patient based on this model was used as a clinical risk score to inform our model of the variables listed above without excessive overfitting. Overfitting has the potential to inflate the SEs of the estimated coefficients, which reduces the level of precision and confidence we may have in making interpretations. Although the use of a propensity score is not ideal, we feel it was the best compromise for acknowledging the known risk factors with the finite data available.

In the current article, we are evaluating the impact of an intervention (ICD use) performed after the initial noninvasive test. As this is an observational study and treatment assignment was not randomized, we have attempted as best possible to take these biases into account. To this end, we felt it was necessary to include a propensity score to take this nonrandomized treatment assignment into account; hence, we modeled post-testing use of ICD. It was our intention to determine the probability or risk of each patient who have been referred to ICD (based on this model) and to use this estimated risk as a propensity score to adjust our final survival model (a Cox proportional hazards mixed model).

The modelling of the propensity score was nonparsimonious, included a variety of factors, and used a conventional Cox proportional hazards model. Because the ICD was placed at varying times after the initial test, this was modeled using ICD as a time-dependent covariate. The calculation of this score was performed by determining the estimated risk of each individual for experiencing the outcome and using this as the propensity score.

Subsequently, a second, predefined survival model was developed that included medical risk and ICD propensity score (from the first models), summed rest scores, H/M ratio (as a continuous variable), and ICD placement. Random factors again consisted of site nested within region. Subsequently, we also re-examined this model treating H/M ratio as a binary variable, dichotomized at the value 1.6. The results of these models were represented graphically by calculating the predicted probability of an event over the range of H/M ratios based on the survival model. Values of other, nonplotted, values were
Results

Baseline Characteristics

The baseline characteristics of the 777 patients in this study are shown in Table 1. Patients were predominantly middle-aged, white, and male with BMI at the upper range of overweight. The majority of patients were current or prior smokers had hypertension, and just over a third were diabetics. The majority of patients had prior MI and prior revascularization. Two-thirds of patients had ischemic heart failure. Of the overall cohort, 177 (23%) patients had H/M ratios ≥1.6, and 597 (77%) had H/M ratios <1.6.

Outcomes

The median duration of follow-up was 17 months (2 days to 30.4 months). All-cause death occurred in 75 patients (9.6%). Of these deaths, 48 (6.2%) occurred in the United States and 27 (3.5%) in Europe. Furthermore, 49 were cardiac death (6.3%), of which 23 were sudden cardiac death (3.0%), and 26 patients experienced life-threatening arrhythmias (3.3%). After the index 123I-mIBG study, 196 (25%) patients had an ICD implanted. Of these, 87 (11%) were placed in the first 60 days after testing and 109 (14%) after this time point.

Survival Modeling Results

Baseline Medical Risk

The Cox proportional hazards mixed-effects model summarizing pretest medical risk is shown in Table 2. Patient age and BMI had significant nonlinear components (both main effect plus main effect squared), and BNP was modeled with a transformation. Significant inter-site variability was present that was better modeled with the random-effects model. Site location was also associated with outcome. Predicted probability of death for each subject was extracted from the model and used to represent the medical risk for death at the time of enrollment in subsequent survival modeling.

Propensity Score

Of the covariates included in modeling post-123I-mIBG ICD implantation—age, race, BMI, sex, diabetes mellitus, smoking, NYHA class, hypertension, MI history, heart failure cause, and site—only age, BMI, and diabetes mellitus were significant in this model (Table 3). Based on this model, ICD implantation probability was determined for each patient as the propensity score.

Overall Survival

The overall prognostic model (Table 4) included the medical risk summary variable, the propensity score for receiving an ICD (from the models above), the summed rest scores, the H/M ratio (as a continuous variable), and whether an ICD was placed after the index study. The overall model χ² was 99.0 (P<0.001). H/M ratio as a continuous variable was an independent and incremental predictor of all-cause death. Even after adjusting for other information available, H/M ratio results significantly risk stratified the cohort (Figure 1). The use of ICD was also an independent predictor of outcome, adding incrementally at all values of H/M (Figure 2). Importantly, the number of lives saved per 100 treated with ICD placement (absolute benefit) increased with decreasing values of H/M until a value of ~1.5.

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.0±11.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.0±6.3</td>
</tr>
<tr>
<td>Male sex</td>
<td>79% (617)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65% (506)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>15% (119)</td>
</tr>
<tr>
<td>Prior</td>
<td>58% (452)</td>
</tr>
<tr>
<td>Never</td>
<td>26% (206)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36% (277)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75% (579)</td>
</tr>
<tr>
<td>Black</td>
<td>13% (102)</td>
</tr>
<tr>
<td>Other</td>
<td>12% (96)</td>
</tr>
<tr>
<td>Prior myocardal infarction</td>
<td>56% (431)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>57% (433)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>84% (652)</td>
</tr>
<tr>
<td>III</td>
<td>16% (125)</td>
</tr>
<tr>
<td>BNP*</td>
<td>237.1±260.2</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>27.4±6.0</td>
</tr>
<tr>
<td>Nonischemic heart failure cause</td>
<td>35% (275)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LV, left ventricular; and NYHA, New York Heart Association.

*Median, 142.8 (25th percentile, 75th percentile: 57.8, 316.1).
at which point the absolute benefit approximately plateaued across abnormal H/M values (Figure 3).

The net reclassification index for H/M ratio in this model was 0.1756 (SE, 0.1179; \( P = 0.1363 \)). The overall integrated discrimination improvement was 0.01103 (SE, 0.0045; \( P = 0.0146 \)).

This modeling was repeated using H/M as a dichotomous variable (threshold \( \geq 1.6 \)). The overall model was significant (overall model: \( \chi^2 = 106.3; P < 0.001 \)). After adjusting as above, H/M as a dichotomous variable remained an independent and incremental predictor of all-cause death and enhanced risk stratification (hazard ratio, 0.14; 95% confidence interval, 0.03–0.60), as did ICD implantation (hazard ratio, 0.32; 95% confidence interval, 0.16–0.64).

In this model, the net reclassification index for dichotomous H/M ratio was 0.4040 (SE, 0.1179; \( P = 0.0006 \)). The overall integrated discrimination improvement was 0.00305 (SE, 0.00733; \( P = 0.000031 \)).

### Identification of Potential Benefit With ICD Use

Finally, we examined whether H/M ratio, LVEF, or BNP levels predicted which patients may have enhanced survival with versus without ICD implantation. Beginning with the model shown in Table 4, the addition of H/M ratio×ICD implantation (\( \chi^2 = 0.22; P = 0.97 \)), LVEF×ICD implantation (\( \chi^2 = 1.0, P = 0.80 \)), or BNP×ICD implantation (\( \chi^2 = 0.32, P = 0.85 \)) did not improve the model, indicating that none of these 3 metrics could identify which patients would have enhanced survival with versus without ICD use (within the limitations of this model and cohort).

### Secondary End Points

We also examined the models presented above using the secondary end point of sudden cardiac death and life-threatening arrhythmia (as a composite end point.) After adjusting for the medical risk score, Myoview summed rest score, and an ICD use propensity score, the H/M ratio as a continuous variable was not significant (\( P = 0.90 \)) but the use of ICD was (\( P = 0.039 \)). When dichotomous H/M was used in this model, it was more predictive, but not significant (\( P = 0.067 \)). Interactions between ICD use and H/M ratio, LVEF, or BNP levels were all not significant. However, the interpretation of these models was problematic because of the bias introduced by the occurrence of life-threatening arrhythmia predominantly being diagnosed by ICD interrogation.

### Conventional Cox Proportional Hazards Modeling

We repeated the analysis of the primary end point using a conventional (nonmixed effects) Cox proportional hazards model. The results of his model were largely similar to that of the mixed-effects model in that medical risk score was a significant predictor of outcome, whereas propensity score
for ICD implantation and Myoview summed score were not significant. H/M ratio remained significantly associated with reduced risk, but ICD use was only of borderline significance (hazard ratio, 0.60; 95% confidence interval, 0.33–1.09; \( P = 0.92 \)). Region of patient recruitment, used as a random effect in the primary analysis, was entered as a covariate and was not significant. Site of recruitment was not considered in the model because of insufficient power.

We also examined the interaction between H/M ratio and ICD implantation and found this not to be significant (\( P = 0.73 \)), again indicating the inability of these test results to identify which patients would have improved outcomes with this intervention (Table 5).

### Discussion

In the current study of patients without ICDs enrolled in ADMIRE-HF, we found that the results of \(^{123}\)I-mIBG imaging yielded incremental and independent prognostic value for prediction of all-cause mortality over baseline clinical, historical, and demographic information, as well as myocardial perfusion imaging, LVEF, and BNP data. This was the case whether the H/M results were considered as a continuous or categorical (dichotomous) variable, as well as whether the added value was demonstrated using nested models, enhanced stratification, or improved reclassification. Furthermore, we identified that on the basis of the ADMIRE-HF study, it seems that all patients who are ICD candidates (on the basis of the guideline recommendations at the time of the study design and enrollment) benefitted from ICD implantation irrespective of \(^{123}\)I-mIBG H/M ratio.

Although the results of \(^{123}\)I-mIBG were prognostically significant, \(^{123}\)I-mIBG results did not identify a relative survival benefit—that is, which patients would have an enhanced survival with versus without ICD placement. Although \(^{123}\)I-mIBG–defined ICD candidates could not be identified, it does seem that the number of lives saved per 100 treated (absolute benefit) of ICD was identified by \(^{123}\)I-mIBG testing varied across values of H/M results, thus, identifying a potential role of \(^{123}\)I-mIBG in optimizing the cost-effectiveness of this intervention. When repeating this analysis using nonmixed effects Cox proportional hazards, and not accounting for site effects or nesting site in the region, ICD use was of only borderline significance, whereas dichotomized H/M remained significant, but the interaction between test result and ICD use also remained nonsignificant.

### Comparison With Previous Studies

Previous studies have supported the prognostic value of sympathetic innervation imaging in patients with left ventricular dysfunction, whether using \(^{123}\)I-mIBG\(^{6,8-15,17,24}\) or PET quantification of \(^{11}\)C-HED,\(^{16}\) finding that this approach predicted cause-specific mortality from sudden cardiac death.
independently of LVEF and infarct volume. These results have been further supported by both prospective and retrospective cohort studies, as well as the recent, large, prospective multicenter ADMIRE-HF registry,11,18 from which the current cohort were drawn. Meta-analyses of previous studies have also shown similar results.15 The current study extends these results to patients with left ventricular systolic dysfunction, who are ICD candidates, but have not yet received this potentially beneficial intervention. Although previous studies have used H/M ratio as a dichotomous variable, we think that maintaining H/M as a continuous variable is more robust. By doing so, our analyses suggest that 1.5 is a superior prognostic threshold than 1.6 if H/M is to be used as a dichotomous variable.

The current results, unlike previous studies, also examines whether the results of testing can identify which patients have enhanced survival with versus without ICD implantation using an approach similar to that previously used to assess the value of revascularization in the setting of inducible ischemia.24–27 Previous studies examining the prognostic value of $^{123}$I-mIBG, including those from the ADMIRE-HF study, have not considered ICD data in their analyses. Despite the incremental prognostic value and enhanced reclassification provided by these test results, although $^{123}$I-mIBG results do not determine which patients may have improved survival with ICD implantation, the number of lives saved per 100 treated with ICD varies with H/M values. Thus, $^{123}$I-mIBG may be a tool to determine the cost-effectiveness of ICD in a patient population. These results further support the paradigm that identification of risk and identification of potential benefit with a specific intervention is different phenomenon. These results also point to the need to combine multiple sources of information—imaging and otherwise—to enhance the ability to identify candidate patients for specific interventions.

**Incremental Prognostic Value Versus Identification of Treatment Benefit**

The results of the current study introduce the importance of an alternative paradigm defining the value of noninvasive testing. To date, the assessment and valuation of noninvasive testing has been focused on various methodological approaches demonstrating that the results of testing yield incremental and independent prognostic value over previously available information.28 In the current era where numerous sources of risk assessment are available—clinical, historical, demographic, biochemical, imaging, genetic, etc—whether additional risk stratification is clinically meaningful is unclear. Furthermore, whether the additional test results will result in improved patient management is also unclear, since a change in treatment is not necessarily correct if it does not result in improved patient outcome or patient benefit. Importantly, in the current era where enhanced patient benefit is the standard by which medical care will be judged, it will be important to identify a

### Table 4. Predictors of All-Cause Mortality: Results of Survival Modeling (H/M as a Continuous Variable)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical risk score</td>
<td>...</td>
<td>10.68 (5.11–22.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICD propensity score</td>
<td>...</td>
<td>1.03 (0.72–1.46)</td>
<td>0.890</td>
</tr>
<tr>
<td>Myoview summed rest score</td>
<td>...</td>
<td>1.12 (0.73–1.70)</td>
<td>0.600</td>
</tr>
<tr>
<td>H/M ratio (continuous variable)</td>
<td>...</td>
<td>0.14 (0.03–0.60)</td>
<td>0.008</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>No ICD (reference)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>ICD</td>
<td></td>
<td>0.32 (0.16–0.64)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Integrated log likelihood $\chi^2$: 99.0. Site by region (intercept): 0.693. Site (intercept): 0.581. H/M indicates heart/mediastinum ratio; and ICD, implantable cardiac defibrillator.

![Figure 1](http://circimaging.ahajournals.org/)

**Figure 1.** Risk-adjusted event-free survival as a function of heart/mediastinum ratio (H/M) results. Patients with 25th, 50th, 75th, and 90th percentiles of H/M ratio as continuous variable are shown (based on survival model shown in Table 4). Survival estimates fixed to values of 475 for Myoview summed rest score (median) and US/Canada region. $P$ value for H/M as shown in Table 4. Censoring data are shown in the table beneath figure.
direct relationship between a test result, specific patient treatment, and subsequent patient outcome. In the current study, we show that the results of $^{123}$I-mIBG both add incremental prognostic value and, by identifying the number of lives saved per 100 patients treated with ICD, may identify when ICD use is cost effective.

Methodological Considerations

To adequately address the potential issues and limitations of the data used in the current study, the statistical analysis used in the current study was relatively more involved. The challenges associated with the current data set included various geographic sources of patient recruitment, the varying time post index test that ICDs were implanted, the need to ascertain the treatment effect of the intervention, issues of model overfitting, the nonrandomized use of ICD, and the use of the primary metric (H/M ratio) as a continuous versus dichotomous variable.

To address the potential variability introduced by geographic variability, we used a mixed effects version of the Cox proportional hazards model, a widely used and accepted solution to this challenge. The varying time to ICD implantation necessitated the use of an extended Cox proportional hazards model with time-dependent covariates. To assess the treatment effect of this intervention, we examined interactions between important clinical metrics (H/M, LVEF, and BNP) and this intervention, a commonly used statistical approach. To minimize or avoid overfitting, we began our analysis by creating a composite variable to take into account a number of important variables that we would otherwise not been able to adjust for. Finally, although H/M has been widely used as a dichotomous variable in the literature, we have not identified a previous study that examined the relative characteristics and value of this metric in this form versus as a continuous variable. We thought this to be an important consideration in light of potential nonlinearity issues and the general belief that the dichotomization of a continuous variable tends to result in a loss of information.

Limitations

The current study was based on information collected as part of a large prospective multicenter study. However, despite the advantages of this study design, patients were not randomized to strategies with versus without $^{123}$I-mIBG or to strategies of randomized postimaging treatment. Thus, many of the limitations commonly associated with observational studies are still present necessitating the use of complex multivariable modeling techniques.

We modeled ICD referral with a propensity score to adjust for nonrandomized treatment. Although we considered all available data in this process, sites did not specifically seek information about this referral. The inclusion of the variables used in the calculation of the propensity scores in the primary survival modeling may make the results of the analysis difficult to interpret. It is possible that unmeasured covariates existed that may have influenced this model (eg, patient insurance
status, socioeconomic status). Despite this, given the extensive information collected, whether additional data would have changed the results of this modeling is unclear. Finally, and most importantly, the inclusion criteria of ADMIRE-HF were specifically tailored to identify patients who were ICD candidates on the basis of current guidelines.

A mixed-effects Cox proportional hazards model was used to permit us to take into account the nonhomogeneity of patients recruited from 66 sites in 3 geographic regions. Conventional modeling would not have permitted this to be considered. The results of our modeling suggest that these factors significantly influenced the results. The use of these risk-adjustment techniques to account for region- and site-dependent referral and time-to-ICD placement biases is a major strength of our study. Indeed, the failure of prior multicenter analyses to account for both the intersite and interregion patient heterogeneity, as well as adjustment for ICD use, is a weakness of previous studies.

In the current study, we used all-cause death rather than cardiac death as the primary end point because of the well-recognized issues associated with defining cause of death and the high frequency of misclassification (25% to 50% or more).

As shown previously, extending the primary end point to type of cardiovascular death (eg, arrhythmic versus nonarrhythmic) would be associated with worsened error rates. Currently, as autopsies are performed in <9% of deaths and ≈9 of 10 of these are accounted for by external causes of death, this problem is worsening. Although we think that cardiovascular death would be a clinically more satisfying end point, its validity is problematic. The use of life-threatening arrhythmias as an end point was also problematic as this end point would be predominantly assessed by examination of the ICD device, thus, largely limited to the ICD population. Care was taken to minimize or avoid overfitting in the modeling process, thus, our use of an aggregate medical risk model. Our primary findings may have been limited by the number of events in the current study.

The intraobserver reliability for the rest SPECT studies was not available. It is possible that the variability of this

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**Figure 3.** Estimated number of lives saved per 100 treated with implantable cardiac defibrillator (ICD) versus no ICD as a function of heart/mediastinum ratio (H/M) ratio. Results based on model are shown in Table 4.

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**Table 5. Predictors of All-Cause Mortality: Results of Survival Modeling Using Conventional Cox Proportional Hazards (H/M as a Dichotomous Variable)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical risk score</td>
<td>...</td>
<td>9.25 (5.03–17.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICD propensity score</td>
<td>...</td>
<td>1.03 (0.6–1.76)</td>
<td>0.930</td>
</tr>
<tr>
<td>Myoview summed rest score</td>
<td>...</td>
<td>0.97 (0.68–1.37)</td>
<td>0.841</td>
</tr>
<tr>
<td>H/M ratio (dichotomous)</td>
<td>...</td>
<td>0.16 (0.04–0.67)</td>
<td>0.012</td>
</tr>
<tr>
<td>Region</td>
<td>Europe (reference)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>North America</td>
<td>1.15 (0.58–2.27)</td>
<td>0.683</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>No ICD (reference)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>0.60 (0.33–1.09)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

H/M ratio×ICD implantation hazard ratio 0.08 (0–152 000); P=0.73. Effects of site not considered in this model. H/M indicates heart/mediastinum ratio; and ICD, implantable cardiac defibrillator.
measure was greater than expected and was the reason behind why this variable was not predictive in our models.

Finally, although the mixed-effects Cox proportional hazards model has been frequently used and is available for R and Stata, its availability for SAS is problematic.

Conclusions

This analysis of data from ADMIRE-HF reveals that in patients who are ICD candidates but have not yet received these devices, quantitative assessment of sympathetic innervation using 123I-mIBG imaging enhances patient risk assessment. Although this approach does not seem to identify which patients have improved survival with ICD placement, it does identify the absolute benefit with ICD use, thus may play a role in optimizing the cost-effectiveness of this intervention.

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Disclosures

Dr Cerqueira is a consultant for GE Healthcare. The other authors report no conflicts.

References


25. Hachamovitch R, Rozanski A, Hayes SW, Thomson LE, Germain G, Friedman JD, Cohen I, Berman DS. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both

**CLINICAL PERSPECTIVE**

Patients with heart failure and reduced left ventricular ejection fraction represent an enormous and growing healthcare challenge in the United States. In this population, implantable cardiac defibrillators (ICDs) are a therapeutic option shown to affect survival, but their cost-effectiveness has been questioned. \(^{123}\)I-methylodobenzylguanidine (\(m\)IBG), a radionuclide that images myocardial sympathetic nervous system activity, has been shown to risk stratify these patients. The proposed paradigm is that this tracer will enhance the identification of optimal candidates for ICD implantation, thus, enhancing the clinical and cost-effectiveness of ICD use. We explored this paradigm’s validity, examining whether \(^{123}\)I-\(m\)IBG results can identify patients more likely to accrue a survival benefit with ICD implantation. In a patient cohort (without prior ICD implantation) enrolled in Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF), a prospective multicenter study examining the prognostic value of \(^{123}\)I-\(m\)IBG in New York Heart Association class II to III heart failure patients with reduced left ventricular ejection fraction, survival modeling revealed that both \(^{123}\)I-\(m\)IBG results and ICD implantation were prognostically predictive after controlling for potential confounding factors. However, \(^{123}\)I-\(m\)IBG results did not identify which patients may benefit from ICD implantation. Although this challenges the above paradigm, our results also revealed that the number of lives saved per 100 treated with ICD implantation in this cohort varied with the \(^{123}\)I-\(m\)IBG results. This suggests that although \(^{123}\)I-\(m\)IBG testing does not identify which patients will benefit from ICD implantation, it may play a role in enhancing the cost-effectiveness of the selection of patients for ICD use. Further studies, however, will be needed to confirm this finding.
Predicting Risk Versus Predicting Potential Survival Benefit Using $^{123}$I-$m$IBG Imaging in Patients With Systolic Dysfunction Eligible for Implantable Cardiac Defibrillator Implantation: Analysis of Data From the Prospective ADMIRE-HF Study
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