Incremental Utility of Iodine-123 Meta-Iodobenzylguanidine Imaging Beyond Established Heart Failure Risk Models

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ABSTRACT

Background: Nuclear myocardial imaging with iodine-123 meta-iodobenzylguanidine (^{123}I-*m*IBG) is approved for risk stratification of patients with systolic heart failure (HF). Whether ^{123}I-*m*IBG imaging provides incremental prognostic utility beyond established risk models remains unclear.

Methods and Results: In a multicenter study, 961 patients with moderate systolic HF underwent ^{123}I-*m*IBG imaging and were followed for cardiac death, progressive HF, or life-threatening arrhythmias over 2 years. We constructed 4 multivariable models, using variables from each of 4 published HF risk models, and patient-level scores were calculated both before and after adding the heart-to-mediastinum ratio (H/M) from ^{123}I-*m*IBG imaging. Incremental utility was evaluated by calculating integrated discrimination improvement (IDI), which quantifies the increase in probability of experiencing the primary end point after adding H/M to each model. The composite end point occurred in 25% of patients. After adding H/M, absolute IDI ranged from 2.1% to 3.0%, representing 33%−59% relative improvements in risk stratification. Of note, hazard ratios for H/M were remarkably similar between risk models (0.40−0.44 for predicting the composite end point, 0.10−0.18 for mortality; all $P < .001$).

Conclusions: Despite notable differences in predictor variables, patient populations, and analytic techniques from which each model was initially derived, adding ^{123}I-*m*IBG data to HF risk models consistently identified patients at lower risk of experiencing adverse events. (*J Cardiac Fail 2014;20:577−583*)

Key Words: Risk model, radionuclide imaging, heart failure, prognosis.

Despite improvements in morbidity and mortality over the past several decades, heart failure (HF) remains the most common and costly discharge diagnosis for patients aged ≥65 years.[1] As a result, intensive efforts have been expended in the development of both pharmacologic and nonpharmacologic approaches to managing systolic HF, including implantable cardiac devices.[2−6] With progressive financial pressures on global health care systems, and with increasing numbers of patients living with chronic HF, identifying those patients most likely to benefit from intensive therapies is essential.

To better understand factors affecting prognosis in HF, several clinical risk models have been constructed to identify patients at particularly high or low risk of experiencing adverse events.[7−11] Other studies have supplemented the clinical models with biomarker or imaging results to better stratify patient prognosis.[12,13] One approach, adopted extensively in Japan and several European countries, is the use of the norepinephrine analogue iodine-123 meta-iodobenzylguanidine (^{123}I-*m*IBG) to assess myocardial sympathetic innervation with nuclear imaging. In the Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) multicenter study, the heart-to-mediastinum (H/M) ratio determined with the use of ^{123}I-*m*IBG identified patients at lower risk of cardiac death, progressive HF, or life-threatening arrhythmias during a 2-year follow-up.[14] In a subsequent analysis, the H/M ratio also improved the assessment of mortality risk when applied to the Seattle Heart Failure Model, an established but somewhat complicated clinical risk model for patients with systolic HF.[8,15] Based on these data, ^{123}I-*m*IBG myocardial imaging is used for assessing

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prognosis in patients with left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association (NYHA) functional class II and III symptoms, including recent approval in the United States.

Despite these findings, risk stratification using the H/M ratio as part of other, more simplified, HF risk models has not been reported. Furthermore, the incremental utility of ^{123}I-*m*IBG imaging for predicting cardiovascular events other than mortality has not been studied. To better evaluate the practical use of the H/M ratio in daily clinical practice, we used data from ADMIRE-HF to assess the performance of 4 established HF risk models for predicting the composite clinical end point of cardiac death, progressive HF, or life-threatening arrhythmia. We then quantified the incremental prognostic utility of the H/M ratio when added to each of these individual models.

Methods

Data Source

The design and principal findings of ADMIRE-HF have been described previously.[14,16] In brief, from July 2005 to February 2008, ADMIRE-HF prospectively enrolled 961 patients with LVEF ≤35%, NYHA functional class II or III due to ischemic or nonischemic etiologies, and optimal pharmacotherapy. Major exclusion criteria were history of pacemaker placement; prior defibrillation for ventricular arrhythmia; serum creatinine >3.0 mg/dL; recent coronary revascularization; acute myocardial infarction; or placement of an implantable cardiac defibrillator (ICD) within the previous 30 days. All subjects underwent complete clinical evaluation, including NYHA functional class assessment, echocardiography, and laboratory assessments at baseline. After receiving a standard intravenous bolus of ^{123}I-*m*IBG (Adreview; GE Healthcare, Princeton, New Jersey), each subject underwent anterior planar and single-photon-emission computed tomographic imaging of the thorax beginning at 15 minutes (''early'') and 3 hours 50 minutes (''late'') after injection. The H/M ratio was determined from the counts per pixel in the heart region of interest divided by the counts per pixel in a 7 × 7 pixel mediastinal region with the lowest activity. Patients were followed for a maximum of 2 years to assess for the primary composite end point: HF progression necessitating hospital admission, life-threatening arrhythmia, or cardiac death. Statistical analysis of ADMIRE-HF suggested that H/M ratio <1.6 was most discriminative for identifying patients at higher risk of the composite primary end point and each of its individual components.[14]

HF Risk Models

In the present analysis, 4 established risk models were selected based on the variety of patient populations studied, differences in study end points and analytic techniques, and the simple clinically feasible predictor variables in each model (Table 1). The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study was a retrospective multicenter analysis of patients with HF diagnosed on initial hospital presentation, in which multivariable predictors of 30-day and 1-year all-cause mortality were identified.[7] The Cardiac Resynchronization−Heart Failure (CARE-HF) risk model was derived from a multicenter randomized trial comparing the effects of cardiac resynchronization therapy with standard pharmacologic therapy in patients with NYHA functional class III−IV symptoms and LVEF ≤35%.[9] The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II risk model was a post hoc analysis from a multicenter randomized trial that compared the impact of ICD placement versus conventional medical therapy in patients with NYHA functional class I−III HF and LVEF ≤30%.[10] Peripheral Arterial Disease, Age, Creatinine, and Ejection Fraction (PACE) was a prospective registry of patients with systolic HF receiving clinically indicated ICDs, in which clinical predictors of 1-year mortality were identified.[11]

Statistical Approach

Using the predictor variables from each published risk model, we calculated individual patient risk estimates for the ADMIRE-HF study's composite primary end point. When predictor variables from each model were not collected in ADMIRE-HF, multivariable models were constructed with the remaining risk factors from each published model (see Table 1). Four separate logistic regression analyses were performed using the variables from the EFFECT, CARE-HF, MADIT-II, and PACE risk models, with c-statistics calculated for each model and hazard ratios calculated for each predictor variable within each model. We then added H/M ratio <1.6 or ≥1.6 as a dichotomous variable, as previously described,[14] and recalculated the c-statistic for each model. Because 3 of the 4 established risk models were initially derived with the use of mortality as the dependent variable, as a secondary analysis we reran all risk models with the use of all-cause mortality as the end point of interest.

To quantify the incremental utility of adding the H/M ratio to each risk model, we used the integrated discrimination improvement (IDI) statistic—a measure of the change in predicted probability of experiencing events after adding variables to an existing multivariable model.[17] The IDI is a validated statistical technique that combines the increase in calculated probability for patients who experience the primary end point, plus the decrease in probability for patients who do not experience the end point, after adding the additional variable (ie, after adding H/M ratio to each multivariable regression model).

The authors had direct access to the ADMIRE-HF study data; statistical analyses were performed independently from the study sponsor with the use of SAS software (version 8.2; SAS Institute, Cary, North Carolina). *P* values of ≤.05 were considered to be statistically significant unless otherwise specified. Patients had provided informed consents when enrolled in ADMIRE-HF, and the present research protocol using existing deidentified data was granted exempt status by the Institutional Review Board of Saint Louis University.

Results

Baseline Characteristics

In ADMIRE-HF, European centers enrolled 363 patients (38%), Canadian centers enrolled 18 patients (2%), and the United States represented the remaining 580 patients (60%). The overall study population was largely white (75%) and male (80%), with HF symptoms predominantly classified as NYHA functional class II (83%). The mean LVEF was 27% and two-thirds of the patients had ischemic etiology. In this population, H/M ratio ≥1.6 demonstrated consistently high specificity and negative predictive values for each of the clinical events studied (ranging from 72% to