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

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

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

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

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

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

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

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

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

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

Methods

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

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

Abbreviations and Acronyms

BNP = B-type natriuretic peptide

CE = cardiac event

HF = heart failure

H/M = heart/mediastinum ratio

ICD = implantable cardioverter-defibrillator

^{123}I-*m*IBG = iodine-123 *meta*-iodobenzylguanidine

LVEF = left ventricular ejection fraction

MPI = myocardial perfusion imaging

NE = norepinephrine

NYHA = New York Heart Association

SCD = sudden cardiac death

SPECT = single-photon emission computed tomography

VT = ventricular tachycardia

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

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