Autonomic Imaging in the Assessment of Congestive Heart Failure

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The following relationships exist for Mark I. Travin, M.D.

- **Astellas**
  - Speakers Bureau

- **GE**
  - MIBG research study participation
  - Advisory Board

Cardiac $^{123}$I-MIBG is currently an off-label use of an approved radiopharmacuetical
EPIDEMIOLOGY AND APPROACH
CONGESTIVE HEART FAILURE
Epidemiology

- CHF: an “epidemic” in the developed world.
  - Aging population
  - More patients survive acute cardiac events

- Prevalence: 5 million (USA). 550,000 new cases each year

- High mortality: 50% death rate at 5 years.
  - Underlying or contributing cause of death in 286,700 annually.

- Resource Utilization
  - CHF is most common DRG diagnosis. 1 million hospitalizations/year.
  - More Medicare $ spent on CHF than other conditions.

The year in CHF. J Am Coll Cardiol 2005; 46:2125-2133.
"The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return."

E. Braunwald
Contemporary View of Heart Failure

- Myocardial Dysfunction
  - Increased Load
  - Reduced Systemic Perfusion
  - Activation of RAS, SNS, Cytokines
    - Altered Gene Expression
    - Ischemia Energy Depletion
    - Direct Toxicity
      - Cell Death
        - Apoptosis
        - Necrosis
CURRENT PARADIGM OF CHF

“CHF can no longer be considered a simple contractile disorder or a disease of the heart alone. Clinical manifestations are . . . the result of changes to the heart’s cellular and molecular components and to mediators that drive homeostatic control.”

J. Cohn

(J Am Coll Cardiol 2000; 35:569-82.)
Radionuclide imaging can play an important role in assessing the etiology and characteristics of CHF, and in the planning and following of therapeutic management.
<table>
<thead>
<tr>
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<th>Targeting radiotracer</th>
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*FDG, Fluorodeoxyglucose; ICAM, intercellular adhesion molecule; HLA, human leukocyte antigen; BMIPP, beta-methyl-iodophenylpentadecanolic acid; MIBG, metalodobenzylguanidine; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NE, norepinephrine; HED, hydroxyephedrine.*
Table 1. Targeting myocardial pathology

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**CARDIAC AUTONOMIC INNERVATION**

- Heart is richly innervated by autonomic fibers.
- Play a crucial role in regulating cardiac function (in addition to circulating mediators, e.g., NE).
- Complex balance between sympathetic and parasympathetic output:
  - Maintain resting hemodynamic parameters within a narrow range
  - Allow appropriate inotropic and chronotropic cardiac response to increased workload demands
AUTONOMIC DYSFUNCTION IN CV DISEASE

- Cardiac pathology upsets normal balance between sympathetic and parasympathetic function.
- Impaired cardiac response to increased workload:
  - Symptoms
  - Exertional limitations
- Increased susceptibility to adverse events:
  - Remodeling
  - Arrhythmias
  - Death
- Autonomic dysfunction: both a manifestation of cardiac pathology and a contributor to it.
- Nuclear imaging is unique in its ability to visualize the cardiac neuronal condition.
Sympathetic Neuron Synapse

**PRESYNAPSE**

- Axon
- Tyrosine
- Dopa
- Dopamine
- Norepinephrine
- Vesicles
- NE release into synaptic space
- Uptake 1

**SYNAPTIC CLEFT**

- NE
- Post synaptic receptors
- α₁
- β₁
- β₂
- G
- AC
- AMP → cAMP
- Uptake 2

**POSTSYNAPSE**

- Myocyte

Diagram showing the process of neurotransmission in a sympathetic neuron synapse.
$^{123}$I-$m$IBG (meta-iodobenzylguanidine)

A Physiologic Analog of the Sympathetic Nervous System Neurotransmitter Norepinephrine (NE)
Neuronal MIBG uptake consists primarily of active transport sites (uptake-1). MIBG clearance may occur from both vesicular (exocytosis) and extravesicular compartments.

MIBG IMAGING
Parameters Assessed

- **Global cardiac uptake of tracer (planar)**
  - Heart/mediastinal ratio. $2.5 \pm 0.3$ (<1.2 has particularly poor prognosis).

- **Global washout (planar)**
  - Measures ability of myocardium to retain MIBG. Normal pts: $10\% \pm 9\%$. Higher values correlate with disease, such as CHF. (>27%: dramatically increased mortality). May have some correlation with increased sympathetic tone - but complexity of this relationship has not been fully elucidated.

- **Regional uptake of tracer (SPECT)**
  - Heterogeneous uptake may indicate regional denervation, i.e., autonomic imbalance, and possibly increased susceptibility to arrhythmia.
  - BUT: normal variants include decreased inferior uptake, particularly with aging and in men.

ANALYSIS OF MIBG PLANAR IMAGES

**HMR Ratio**
ROI’s drawn around heart and mediastinum, counts per pixel determined for each, and ratio calculated.

**Myocardial Washout**
\[(\text{Early-late counts corrected for } I-123 \text{ decay}) \times 100] / \text{early counts}\n
H/M ratio = 2.24
WO = 10.64
H/M ratio = 1.29
WO = 23.35
Potential Clinical Uses of Cardiac MIBG/Neuronal Imaging

- **Congestive Heart Failure**
  - Prognosis
  - Assess response to standard medical therapy
  - Find pts who would benefit from mechanical interventions (CRT, LVAD, Transplant)

- **Cardiac Arrhythmias**
  - Assess risk for sudden cardiac death
  - Better identify patients who would benefit from ICD
  - Assess patients with primary arrhythmias

- **Monitor recovery & complications post Cardiac Transplant**

- **Assess patients with Ischemic Heart Disease**
  - Increased sensitivity to detect disease
  - Ischemic memory

- **Identify higher risk patients with Diabetes Mellitus**

- **Assess toxic effects of Chemotherapy**
MIBG IMAGING AND CONGESTIVE HEART FAILURE
CHF AND THE AUTONOMIC NERVOUS SYSTEM

- Increased adrenergic activity occurs in CHF
- Initially favorable, but eventually deleterious:
  - Arrhythmias
  - Decreased myocardial catecholamine levels
  - Down regulation of β-receptors
  - Elevated plasma NE levels
  - Activation of renin-angiotensin.

- Unfavorable myocardial remodeling:
  - Myocyte hypertrophy
  - Myocyte apoptosis
  - Changes in extracellular matrix

- Patients with dilated cardiomyopathy - ischemic and idiopathic - have MIBG image abnormalities.
  - Reduced and/or heterogeneous uptake
  - Increased washout

**Figure 4.** Diagrammatic representation of pathophysiologic changes induced by myocardial injury in acute and chronic HF. In the latter, the persistently activated sympathetic adrenergic system (SAS) includes arterial and venous constriction by release of vasoactive substances, activation of the renin-angiotensin-aldosterone system (RAAS) with salt and water retention, and increased myocardial wall stress, oxygen consumption, and energy requirements, culminating in ventricular remodeling and myocardial fibrosis.

PROPOSED STAGES OF AUTONOMIC DYSFUNCTION IN CHF AS MEASURED BY MIBG

- **EARLY**: increase in NET-1 uptake.

- **MID**: Increased MIBG washout when NET-1 system is overwhelmed by increased endogenous NE concentration.

- **LAST STAGE**: diminished pre-synaptic function (loss of neurons or down-regulation of NET-1). Decreased delayed MIBG uptake (decreased H/M ratio).

123I-MIBG Imaging and Prognosis in CHF/LV Dysfunction

90 pts. with CHF and EF < 45%
(24 CAD, 66 no CAD)

Survival Rate (%)

H/M > 120%
H/M = heart mediastinal ratio 4 hrs after injection

$^{123}$I-MIBG Washout is a Predictor of Prognosis

79 pts. with CHF, EF < 40%.

Group 1: WO > 27%, Group 2: WO < 27%.
Based on normal control group showing WO 9.6 ± 8.5%. 2SD = 27%.
Endpoints: Death, admission for worsening CHF

123I-MIBG Imaging for Risk of Major Cardiac Event
(Retrospective European Multicenter Study)

290 CHF pts. In 6 European Centers during 10 yr. period.

MCE: Cardiac death, transplant, potentially fatal arrhythmia (including ICD discharge)

ADMIRE-HF: Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (MBG 311/312)

- 2 multicenter studies involving a total of 57 centers in USA, 35 centers in Europe, 4 centers in Canada (over 2-2½ yrs.).
  - 961 CHF patients (94 controls) available for analysis.

- Phase III trial to investigate clinical utility of $^{123}$I-MIBG imaging in patients with Class II-III CHF, LVEF $\leq$ 35%.

- **Primary endpoint**
  - Correlate abnormally low H/M ratio ($< 1.6$) with adverse cardiac events:
    - Heart failure progression (II to III or IV, III to IV)
    - Potentially life-threatening arrhythmia (sustained VT, ICD discharge, aborted arrest)
    - Cardiac death

- **Secondary endpoints**
  - Correlate numerical H/M ratio with cardiac events
  - Correlate MIBG SPECT image findings with cardiac events
  - Characterize the safety profile of $^{123}$I-MIBG

Primary Efficacy Analysis

Event-free Survival Probability

H/M ≥ 1.60: 2-year event-free survival 85%

H/M < 1.60: 2-year event-free survival 63%*

*p < 0.0001 vs H/M ≥ 1.60

Time (days)

n: H/M ≥ 1.60: 201
n: H/M < 1.60: 760

313 195
179 658
157 562
136 462
109 356
79 265
52 149

Jacobson AF. Presented at American College of Cardiology
Cardiac Death Events

H/M ≥ 1.60: 2-year event-free survival 98%

H/M < 1.60: 2-year event-free survival 89%

*p = 0.002 vs H/M ≥ 1.60
Cardiac Death vs. H/M

2-Year Cardiac Mortality Rate (%)

- N = 92 for H/M Ratio < 1.20
- N = 668 for H/M Ratio 1.20 - 1.59
- N = 201 for H/M Ratio > 1.60

Statistical significance:
- p < 0.01 for H/M Ratio 1.20 - 1.59 compared to < 1.20
- p < 0.01 for H/M Ratio > 1.60 compared to < 1.20
- p < 0.00001 for H/M Ratio > 1.60 compared to 1.20 - 1.59

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Cardiac Mortality vs LVEF & H/M Ratio

Survival Probability

Time (days)

LVEF<30%, H/M \geq 1.60^* \quad (n = 81)

LVEF<30%, H/M<1.60 \quad (n = 409)

*p=0.034 vs LVEF<30%, H/M<1.60
Imaging of Myocardial Sympathetic Innervation for Prediction of Cardiac and All-Cause Mortality in Heart Failure Patients: Analyses from the ADMIRE-HF Trial (Presented at AHA 2009)

STUDY OBJECTIVE

Evaluate the contribution of heart mediastinal ratio (H/M) to multivariate prediction models for cardiac and all-cause mortality.

Mark I. Travin, MD, Karthik Ananthasubramaniam, MD, Milena J. Henzlova, MD, Ian P. Clements, MD, Aman Amanullah MD, Arnold F. Jacobson, MD.
# Variables Assessed

<table>
<thead>
<tr>
<th>Age</th>
<th>CHF etiology</th>
<th>H/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>NYHA Class (baseline)</td>
<td>LVEF</td>
</tr>
<tr>
<td>Race</td>
<td>Body mass index</td>
<td>NE</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ACE-I or ARB use</td>
<td>BNP</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>β-blocker use</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Lipid lowering med use</td>
<td></td>
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<tr>
<td>Diabetes</td>
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<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Hazard Ratio (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>----------</td>
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<td>---------</td>
</tr>
<tr>
<td>H/M</td>
<td>0.18 (0.03, 0.97)</td>
<td>0.046</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.94 (0.90, 0.98)</td>
<td>0.004</td>
</tr>
<tr>
<td>BNP</td>
<td>1.00 (1.00, 1.00)*</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age</td>
<td>1.03 (1.01, 1.06)</td>
<td>0.013</td>
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*Numbers truncated; all values > 1.0000
2 yr Cardiac Mortality in Relation to LVEF and H/M

![Bar chart showing 2 yr Cardiac Mortality in Relation to LVEF and H/M. The chart compares mortality rates between different EF ranges and H/M ratios.](chart.png)
2-Year Cardiac Mortality Rate in Patients with Low BNP

BNP <100 ng/l

2-year Rate (%) vs. H/M

LVEF:
- <20%
- 20-29%
- ≥30%

H/M:
- 1: <1.20
- 2: 1.20-1.39
- 3: 1.40-1.59
- 4: ≥1.60
2 yr Cardiac Mortality in Relation to BNP and H/M

- H/M < 1.6
- H/M >= 1.6

| BNP 100-300 | N = 257
| BNP 300-500 | N = 108
| BNP >500    | N = 119

- H/M < 1.6: 69, 10, 5
- H/M >= 1.6: 25, 10, 11
Interaction of BNP, LVEF, H/M

- 242 patients with BNP $\geq$ 300 ng/l
  - 32 cardiac deaths
  - No cardiac deaths in patients with H/M $\geq$ 1.60, 28 of whom had LVEF <30%

- Patients with BNP $\geq$ 100 ng/dl
  - No cardiac deaths in 84 patients with H/M $\geq$ 1.60
All-Cause Mortality

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<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
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DATA SUMMARY

- Four predictors of cardiac mortality:
  - Age
  - LVEF
  - BNP
  - H/M

- Patients with LVEF $\leq 30\%$ and BNP $> 300$ ng/l had no cardiac deaths when H/M was $\geq 1.6$

- All persisted in predicting all-cause mortality, except LVEF.
ROLE OF MIBG IN GUIDING AND FOLLOWING THERAPY OF CHF
Effect of Metoprolol on MIBG Uptake (H/M%)

18 patients with dilated CM, 6 controls

Effect of Carvedilol on Cardiac $^{123}$I-MIBG Uptake in Patients with Dilated CM

22 patients Class II, III, IV CHF

Figure 3. Patient with cardiomegaly and relatively advanced baseline impairment of cardiac sympathetic nerve function, as demonstrated by a 4-hour heart-mediastinum ratio of I-123 MIBG activity of 1.38 (A). Subjectively, I-123 heart activity is similar to adjacent lung activity. Improvement in the 4-hour heart-mediastinum I-123 MIBG ratio to 1.67 with carvedilol treatment (B). Subjectively, the heart is less dilated and I-123 myocardial activity is now more clearly greater than adjacent lung activity.

Therapy Related to Improvement in MIBG Parameters

- β-blockers
- ACE-I
- ARB
- Spironolactone
- Amiodarone
Potential Role of MIBG Imaging in Guiding CHF Therapy

- May have a role in evaluation of potential and actual responses to neurohumoral antagonists.
  - Symptomatic response sometimes unclear.
  - Exercise/HR improvement may be masked by $\beta$-blockers.

- Patients not showing MIBG improvement may need to be considered for other therapies.
  - Change in medications
  - CRT and/or LVAD
  - Transplant

Prognostic Value of $^{123}$I-MIBG Before and After Optimized Treatments in CHF

85 pts. with idiopathic dilated CM, LVEF < 45%


Fig 2. (Left) Changes in the heart to mediastinum (H/M) ratio and washout rate between before and 6 months after optimized additional treatment in nonsurvivors (*, †). (Right) Changes in the H/M ratio and washout rate between before and 6 months after optimized additional treatment in survivors (*, ‡). †† mean value in nonsurvivors. †‡ mean value in survivors. *p<0.01 vs before additional treatment for dilated cardiomyopathy.
Prognostic Value of $^{123}\text{I}$-MIBG Before and After Optimized Treatments in CHF

85 pts. with idiopathic dilated CM, LVEF < 45%

High plasma BNP (after 6 months) and absolute changes in delayed H/M ratio were independent predictors of mortality.

The H/M ratio change before and after optimized treatment predicts mortality independent of clinical and neurohumoral factors associated with a poor prognosis.

Cardiac Sympathetic Activity Pre and Post CRT Evaluated by $^{123}$I-MIBG Myocardial Scintigraphy

- 30 patients with chronic CHF (NYHA Class III or IV)
- Studied before and >3 months after CRT
- Responder = improving to Class I or II (21 pts.)
- H/M ratio was the only independent predictor of CRT response
  (NS: QRS width, echo dimensions, EF, NYHA, age, etc.)

MIBG IMAGING AND ARRHYTHMIAS
Ability to Assess at Risk Patients Who Need an ICD
**SUDDEN CARDIAC DEATH**

- Major cause of death in U.S.: 300,000-400,000/year. 1/2 of all CV deaths
- Most (3/4) are from ventricular tachyarrhythmias. VT to VF.
- Problem: difficult to accurately identify patients at risk
- Better identification of patients at risk for SCD would allow more effective use of ICD, potentially decreasing incidence of SCD.

*Natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms. Preexisting heart disease may or may not have been known to be present, but the time and mode of death are unexpected. (Myerburg and Castellanos, Braunwald, Heart Disease 5th Edition, p. 742)*
What Causes Sudden Cardiac Death in CHF?

- Of CHF deaths: **50% are sudden and unexpected** (6-9x general population)
- Presumption: **mostly VT/VF, but increasing % from bradyarrhythmias and EMD**
  - Medical therapy for CHF may be lessening disposition to VT/VF

**PATHOPHYSIOLOGY**
- Myocardial ischemia
- Action potential prolongation/dispersion of repolarization
  - Disruption of K, Na, Ca channels
- Altered conduction
  - Inexcitable barriers and tissue discontinuities
- Genetic predisposition
- **Altered neurohormonal signaling**
  - RAAS activation
  - Autonomic abnormalities: Global disruption, regional heterogeneities of sympathetic innervation
  - Denervated, viable myocardium may be most at risk.

Multi-hit hypothesis of the development of SCD. Heart failure serves to enhance the risk by the associated alterations in the myocardial substrate and increasing the frequency/intensity of triggers of malignant arrhythmias.

Mechanisms of SCD are complex and incompletely understood.

- Underlying disease is variable: 80% CAD, 10-15% CM, 5-10% miscellaneous (valve disease, infiltrative disease, congenital, primary electrical without structural abnormalities)
- Potential common end pathway related to autonomic dysfunction.

Autonomic nervous system likely plays a role: trigger and sustaining milieu.

Denervated but viable myocardium may be most at risk.
123I-MIBG Imaging After MI

- **Stanton et al. (Zipes) (JACC 1989;14:1519-26)**
  - 19 men > 1 week following Q wave MI, 4 normal volunteers
  - MIBG defect area frequently > than area of infarction (rest TI defects).
  - Pts. with “mismatch” had more ventricular arrhythmias (Holter monitor).

- **McGhie AI, Corbett JR et al. (Willerson) (AJC 1991; 67:236-242)**
  - 27 pts. 10 ± 4 days after Q wave MI.
  - MIBG images showed defects more extensive than TI defects.
  - MIBG defect scores were higher in patients with ventricular arrhythmias on Holter.
Sympathetically Denervated Myocardium Post MI

67 pts. < 14 days after MI

Sympathetically Denervated Myocardium Post MI


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**Fig. 2** Scatter plot illustrating the positive correlation between mismatch defect size (% of left ventricle surface) and QTc interval duration (ms).

**Fig. 3** Scatter plot illustrating the negative correlation between mismatch defect size (% of left ventricle surface) and RMS40 (root mean square of the amplitude (µV) of the terminal 40 ms of the filtered QRS). Reduced values of this variable indicate the presence of ventricular late potentials.
Abnormal Sympathetic Innervation of Viable Myocardium and the Substrate of VT After MI

11 pigs with LAD occlusion induced MI

*Figure 6* Study Results in a Representative Animal With Inducible VT

Positron emission tomography polar maps (left) show regional distribution of $^{13}$N-ammonia and $^{11}$C-epinephrine retention (top), along with perfusion (white) and innervation defects (blue; bottom). Segmental analysis (bottom right) shows that innervation defect exceeds perfusion defect predominantly in the distal anterior wall segment, highlighted in yellow. Three-dimensional electroanatomical maps, depicted in anterior view on top right, show reduced bipolar endocardial voltage in apex and distal septum/anterior wall. Propagation maps show earliest activation of VT in the infarct borderzone in the distal anterior wall (red arrow). Abbreviations as in Figures 1, 2, and 4.

Abnormal Sympathetic Innervation of Viable Myocardium and the Substrate of VT After MI

11 pigs with LAD occlusion induced MI

Figure 5
PET Defect Sizes in Animals With and Without Inducible VT

Defects are measured in percentage of left ventricular myocardium, which shows tracer retention below 2.5 SDs from the mean of healthy control animals. PET = positron emission tomography; VT = ventricular tachycardia.

Sasano et al., Bengel. J Am Coll Cardiol 2008;51: 2266-75.
Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure


METHODS
We randomly assigned 2521 patients with New York Heart Association (NYHA) class II or III CHF and a left ventricular ejection fraction (LVEF) of 35 percent or less to conventional therapy for CHF plus placebo (847 patients), conventional therapy plus amiodarone (845 patients), or conventional therapy plus a conservatively programmed, shock-only, single-lead ICD (829 patients). Placebo and amiodarone were administered in a double-blind fashion. The primary end point was death from any cause.

CONCLUSIONS
In patients with NYHA class II or III CHF and LVEF of 35 percent or less, amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23 percent.
Relative and Absolute Benefits: Main Results Should be Reported in Absolute Terms

JOHN D. FISHER, M.D. * and HUGO E. ECTOR, M.D.†

Figure 5. Number needed to treat to save one life. NNTs from several device and pharmacologic trials [modified from a Medtronic slide (Minneapolis, MN, USA) with permission].
Limitations of Ejection Fraction for Prediction of Sudden Death Risk in Patients With Coronary Artery Disease

Lessons From the MUSTT Study

Alfred E. Buxton, MD, FACC,* Kerry L. Lee, PhD,† Gail E. Hafley, MS,‡ Luis A. Pires, MD,¶
John D. Fisher, MD,§ Michael R. Gold, MD,|| Mark E. Josephson, MD,#
Michael H. Lehmann, MD,** Eric N. Prystowsky, MD,†† for the MUSTT Investigators

Providence, Rhode Island; Durham, North Carolina; Detroit and Ann Arbor, Michigan; Bronx, New York;
Charleston, South Carolina; Boston, Massachusetts; and Indianapolis, Indiana

Conclusions

Multiple variables influence arrhythmic death and total mortality risk. Patients with EF ≤30% but no other risk factor have low predicted mortality risk. Patients with EF >30% and other risk factors may have higher mortality and a higher risk of sudden death than some patients with EF ≤30%. Thus, risk of sudden death in patients with coronary disease depends on multiple variables in addition to EF. (J Am Coll Cardiol 2007;50:1150–7) © 2007 by the American College of Cardiology Foundation

EF: bears no direct relation to mechanisms of arrhythmias responsible for SCD. SCD accounts for a smaller proportion of deaths in pts. with lowest EF.
A Critical Appraisal of Implantable Cardioverter-Defibrillator Therapy for the Prevention of Sudden Cardiac Death

Roderick Tung, MD, Peter Zimetbaum, MD, Mark E. Josephson, MD

*Boston, Massachusetts*

The indications for implantable cardioverter-defibrillators (ICDs) for the prevention of sudden cardiac death have rapidly expanded over the past 10 years. Clinical trial data have quickly been implemented into guidelines without critical reassessment of the strengths and limitations of the evidence. ICD therapy has inherent risks including infection, unnecessary shocks, potential for proarrhythmia, device malfunction, highly publicized manufacturer advisories, and procedural complications, which can adversely affect morbidity and quality of life. A reappraisal of the benefits and potential hazards of ICD therapy will enable physicians to have a more mutually informed and balanced dialogue with their patients. *(J Am Coll Cardiol 2008;52:1111–21) © 2008 by the American College of Cardiology Foundation*
USE OF MIBG AND HRV TO PREDICT SUDDEN DEATH

- From 7/99, 17 pts with ICD were recruited from Montefiore Medical Center outpatient arrhythmia clinic
  - Pts deliberately selected to include both pts with prior discharge and pts without.
  - Controls: 4 with CHF/LV dysfunction but no ICD, 2 pts without known heart disease.

- Patients injected with 3-4 mCi MIBG (DRL, Syncor, Nordion). Imaged at 15’ (early) and 4 hrs (late), planar and SPECT.

- Holter recorded for HRV analysis (overlapping MIBG imaging).

- MIBG images and HRV data were correlated with the occurrence of ICD discharge(s)

RELATIONSHIP OF MIBG AND HRV VARIABLES TO ICD DISCHARGES

ICD Discharge

NO ICD Discharge

HMR = 1.54

EARLY HMR

Group I

* p = 0.03 compared with Group IV

EARLY HMR

Predicting the Need for ICD with MIBG, BNP and LVEF

54 patients with ICD

Predicting the Need for ICD with MIBG, BNP and LVEF

54 patients with ICD


![Graph showing ROC curve values for LVEF, BNP, and L-HMR](image)

**FIGURE 1.** Receiver operating characteristic curves of cardiac late MIBG activity (HMR), LVEF, and BNP, indicating that optimal cutoffs for identifying lethal arrhythmic events are 1.95 for HMR, 50% for LVEF, and 187 pg/mL for BNP. Dotted arrows show suboptimal values (*) of LVEF (35%) and BNP (110 pg/mL) that were used for subgroup analysis, for which results are shown in Figure 4. EF = ejection fraction.

**TABLE 5** Multivariate Analysis Using Cox Hazard Proportional Model in All Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald χ²</th>
<th>Hazard ratio</th>
<th>95% CI of hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late HMR</td>
<td>6.989</td>
<td>0.141</td>
<td>0.033 0.603</td>
<td>0.008</td>
</tr>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td>0.140</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.
Prediction of SCD with Mild-Moderate CHF Using $^{123}$I-MIBG

97 outpatients with CHF and LVEF <40% (mean 29%± 7.5%)

16% NYHA I  59% NYHA II  25% NYHA III

Followed 65 ± 29 months.

SCD: witnessed cardiac arrest or death within an hour of the onset of acute symptoms or unexpected, or unwitnessed death in a patient known to have been well in the previous 24 hours.

106 consecutive stable CHF pts with LVEF <40%.

(WO threshold = 27%)

SCD = witnessed cardiac arrest or death within 1 h after onset of acute symptoms, or unexpected, unwitnessed death in a patient known to have been well within previous 24 h.

Arrhythmic Events

H/M ≥ 1.60: 2-year event-free survival 96%

H/M < 1.60: 2-year event-free survival 85%*

*p = 0.002 vs H/M ≥ 1.60

2-Year HF and Arrhythmic Event Probability vs H/M Ratio

- H/M Ratio
  - <1.20
  - 1.20-1.59
  - ≥1.60

2-Year Event Probability (%)

- HF Prog
- Arr

*p=0.0003 and 0.002 vs H/M<1.20 & 1.20-1.59 respectively.

**p=0.057 and 0.002 vs H/M<1.20 & 1.20-1.59 respectively.

Jacobson AF. Presented at American College of Cardiology
Scintigraphic and Electrophysiological Evidence of Canine Myocardial Sympathetic Denervation and Reinnervation Produced by Myocardial Infarction or Phenol Application

Joseph D. Minardo, MD, Mahmoud M. Tuli, MD, Bruce H. Mock, PhD,
Ronald E. Weiner, PhD, Harald P. Pride, BS,
Henry N. Wellman, MD, and Douglas P. Zipes, MD

Epicardial phenol application or transmural myocardial infarction in dogs produces sympathetic denervation of myocardium apical to the site of the intervention. Because efferent denervation is probably postganglionic, reinnervation most likely occurs but has not been shown. We investigated whether \(^{123}\)-labeled metaiodobenzylguanidine (MIBG), a norepinephrine analogue taken up by sympathetic nerve terminals, could provide a scintigraphic image that would detect apical sympathetic denervation and possible reinnervation. Dogs underwent MIBG scintigraphic imaging at various times after phenol application or transmural myocardial infarction. The results of MIBG scintigraphy were correlated with electrophysiological responses obtained during ansae subclaviae and norepinephrine stimulation to establish the presence of neural denervation and reinnervation. Apical defects in the MIBG scan, which were associated with either normal perfusion by thallium or a smaller-sized defect, were found consistently in dogs that had apical sympathetic innervation. MIBG scintigraphic images returned to normal after 14 weeks (mean) at a time when reinnervation was shown to have occurred. Thus, the results of MIBG scintigraphy correlated accurately with the presence of denervation and reinnervation established by neuroelectrophysiological testing. Supersensitive refractory period shortening in response to norepinephrine infusion was present after denervation and persisted for more than 3 weeks after scintigraphic and electrophysiological evidence of reinnervation. Conclusions are that 1) MIBG can be used noninvasively to determine the presence of regional myocardial efferent sympathetic denervation and subsequent reinnervation, 2) reinnervation occurs after phenol application or transmural myocardial infarction, and 3) denervation supersensitivity persists even after reinnervation occurs. (Circulation 1988;78:1008–1019)
MIBG Image Findings in Relation to Occurrence of ICD Discharges

ICD PATIENT: NO SHOCK
LATE MIBG AND REST SESTAMIBI SPECT IMAGES
ICD PATIENT: SHOCK
LATE MIBG AND REST SESTAMIBI SPECT IMAGES
**123I-MIBG Scintigraphy to Predicts Inducibility of Ventricular Arrhythmias on Cardiac Electrophysiology Testing**

(European/USA Multicenter Study)

50 pts. with MI and LVEF ≤ 40% referred for EP study for syncope or NSVT.

Multivariate analysis: 4 hr MIBG SPECT score correlated with EP inducibility. MIBG/tetrofosmin mismatch and H/M did not.

Pre-synaptic PET Tracers

**Table 1.** Radiotracers for PET imaging of presynaptic sympathetic innervation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type of neurotransmitter</th>
<th>Intraneuronal metabolism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-11 meta-hydroxyephedrine</td>
<td>Analog</td>
<td>No</td>
<td>Extensive clinical application, high uptake-1 selectivity</td>
</tr>
<tr>
<td>F-18 6-fluorodopamine</td>
<td>True</td>
<td>Yes</td>
<td>Clinical tracer, rapid systemic degradation, assessment of uptake and washout</td>
</tr>
<tr>
<td>C-11 epinephrine</td>
<td>True</td>
<td>Yes</td>
<td>Few clinical studies, marker of uptake and vesicular storage</td>
</tr>
<tr>
<td>C-11 phenylephrine</td>
<td>Analog</td>
<td>Yes</td>
<td>Few clinical studies, marker of uptake and intraneuronal metabolism</td>
</tr>
<tr>
<td>F-18 6-fluorometaraminol</td>
<td>Analog</td>
<td>No</td>
<td>Experimental, low specific activity, potential pharmacologic effects</td>
</tr>
<tr>
<td>F-18 (-)-6-fluoronorepinephrine</td>
<td>True</td>
<td>Yes</td>
<td>Experimental</td>
</tr>
<tr>
<td>F-18 para-fluorobenzylguanidine</td>
<td>Analog</td>
<td>No</td>
<td>Experimental</td>
</tr>
<tr>
<td>F-18 fluoroiodobenzylguanidine</td>
<td>Analog</td>
<td>No</td>
<td>Experimental, low uptake-1 selectivity</td>
</tr>
<tr>
<td>Br-76 metabolobenzylguanidine</td>
<td>Analog</td>
<td>No</td>
<td>Experimental, low uptake-1 selectivity</td>
</tr>
</tbody>
</table>

Healthy Volunteer

Idiopathic DCM, EF = 22%.
Perfusion/autonomic mismatch

Figure 3. Polar map display of left ventricular (LV) tracer distribution in healthy individuals for the SPECT tracer I-123 MIBG and the PET tracers C-11 hydroxyephedrine (HED) and C-11 epinephrine.

Sympathetic Neuron Synapse

PRESYNAPSE

Axon → Tyrosine → Dopa → Dopamine → Norepinephrine

Vesicles → NE release into synaptic space

Uptake 1

SYNAPTIC CLEFT

 Postsynaptic receptors

α₁ β₁ β₂

Myocyte → NE

NE

Uptake 2

AMP → cAMP

Myocyte → G → AC → cAMP
Cardiac Postsynaptic Sympathetic Imaging

- Postsynaptic receptors transmit sympathetic signal to target tissues.
- Only a small number of tracers have been established.
- Problem: difficult to find a tracer with high specificity but low nonspecific binding.

# Post-synaptic PET Tracers

## Table 2. Radiotracers for PET imaging of postsynaptic adrenergic receptors

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Receptor type</th>
<th>Subtype</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-11 CGP12177</td>
<td>β</td>
<td>Nonselective</td>
<td>Clinical tracer, no broad application because of difficult synthesis</td>
</tr>
<tr>
<td>C-11 CGP12388</td>
<td>β</td>
<td>Nonselective</td>
<td>Applied in human beings, not yet clinically established, easier synthesis</td>
</tr>
<tr>
<td>F-18 fluorocarazolol</td>
<td>β</td>
<td>Nonselective</td>
<td>Experimental, lipophilic (binding to internalized receptors), poor heart-to-lung contrast</td>
</tr>
<tr>
<td>C-11 CGP26505</td>
<td>β</td>
<td>1</td>
<td>Experimental, low specific binding</td>
</tr>
<tr>
<td>C-11 bisoprolol</td>
<td>β</td>
<td>1</td>
<td>Experimental, low specific binding</td>
</tr>
<tr>
<td>C-11 formoterol</td>
<td>β</td>
<td>2</td>
<td>Experimental, promising, binds specifically in lungs and heart</td>
</tr>
<tr>
<td>C-11 procaterol</td>
<td>β</td>
<td>2</td>
<td>Experimental, low specific binding</td>
</tr>
<tr>
<td>C-11 prazosin</td>
<td>α</td>
<td>1</td>
<td>Experimental, low specific binding</td>
</tr>
<tr>
<td>C-11 GB67</td>
<td>α</td>
<td>1</td>
<td>Initial application in human beings reported</td>
</tr>
</tbody>
</table>

Evidence for Pre- to Postsynaptic Mismatch of the Cardiac Sympathetic Nervous System in Ischemic Congestive Heart Failure

James H. Caldwell\textsuperscript{1,2}, Jeanne M. Link\textsuperscript{2}, Wayne C. Levy\textsuperscript{1}, Jeanne E. Poole\textsuperscript{1}, and John R. Stratton\textsuperscript{3}

\textsuperscript{1}Division of Cardiology, Department of Medicine, University of Washington, Seattle, Washington; \textsuperscript{2}Department of Radiology, University of Washington, Seattle, Washington; and \textsuperscript{3}Division of Cardiology, Department of Medicine, VA Medical Center and University of Washington, Seattle, Washington \textit{J Nucl Med} 2008; 49:234-241.

13 patients with CHF compared with 25 controls. CHF pts had more mismatch, and worse outcomes.

\textbf{FIGURE 4.} Short-axis PET images of \textsuperscript{11}C-mHED (35- to 45-min sum) and \textsuperscript{11}C-CGP (10- to 20-min sum from injection 1) in CHF patient. Apical slices are at upper left and basal slices are at lower right of each panel. Arrows indicate extensive mismatch between \textsuperscript{11}C-mHED and \textsuperscript{11}C-CGP.
- At this time is problematic. Very few studies.
  - Low density of cholinergic neurons in heart
  - Tracer design is difficult
    » Rapid degradation of acetylcholine by esterase
    » High specificity of presynaptic receptor system for acetylcholine
- Vesamicol: base structure for tracer design
  - $^{18}$F-FEOBV used in rats, but low myocardial specificity
- $^{11}$C-MQNB: postsynaptic muscarinic receptor agonist – some work in humans
- $^{18}$F-D-glucose-A85380 used in humans with neurogenerative disorders (nicotinic acetylcholine receptors)

Disruption of the cardiac neuronal system may occur as a result of cardiac disease and/or itself may be the cause of cardiac problems.

Cardiac neuronal abnormalities occur in a variety of cardiac disease states.

Patients with cardiac neuronal abnormalities are at increased risk, including a higher potential for sudden, arrhythmic death.

Imaging with radionuclide tracers is an effective way of assessing the state of cardiac neuronal function.

Cardiac neuronal imaging can both help guide and follow therapy.
Slides are not to be reproduced without permission of author.
BACK-UP SLIDES
CONCLUSIONS (1)

- CHF is a major problem in USA: prevalence, morbidity and mortality, cost.

- Pathophysiology is more than low EF and pulmonary edema.
  - Is largely a neurohormonal condition.

- Radionuclide tracer imaging can play an important role in characterizing CHF, and in guiding and following therapies.
Disruption of the cardiac neuronal system plays a key role in the pathophysiology of CHF.

Imaging of the cardiac neuronal system with a radiotracer, such as $^{123}$I-mIBG, has been consistently shown to have high prognostic utility, better than other parameters (LVEF, BNP).

Cardiac neuronal imaging may help follow and possibly direct medical therapy.

Cardiac neuronal imaging can help determine if medical therapy is not working, and whether other therapies (CRT, transplant) should be considered.

Cardiac neuronal imaging can identify patients at increased risk for arrhythmic death, and may help decide who would benefit from ICD therapy.
Radioligands Used for Assessment of Cardiac Pre- and Postsynaptic Processes

ATP = adenosine triphosphate; DOPA = dihydroxyphenylalanine; NE = norepinephrine

## Properties of Cardiac Autonomic System

<table>
<thead>
<tr>
<th></th>
<th>Sympathetic System</th>
<th>Parasympathetic System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Intermediate horn of T3-T6</td>
<td>Brain stem via Vagus nerve</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Atria and ventricles</td>
<td>Predominantly in atria</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>Adrenoceptors: $\beta_1$, $\beta_2$, $\alpha_1$, $\alpha_2$</td>
<td>Muscarinic receptors</td>
</tr>
<tr>
<td><strong>Neurotransmitters</strong></td>
<td>Norepinephrine (major)</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td><strong>Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>↑: Mainly $\beta_1$, also some $\beta_2$</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>↑: Mainly $\beta_1$, also some $\beta_2$</td>
<td>↓ (atria also)</td>
</tr>
<tr>
<td><strong>Conduction</strong></td>
<td>↑: $\beta_1$</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Coronaries</strong></td>
<td>Dilation ($\beta_2$); constriction ($\alpha$)</td>
<td>Dilation</td>
</tr>
</tbody>
</table>

Kline et al. first reported on use of norepinephrine (NE) analog, meta\textsuperscript{123}Iiodobenzylguanidine, to image cardiac adrenergic innervation.

**UPTAKE MECHANISM** is incompletely understood.

- **Uptake-1 system (NET-1):**
  Pre-synaptic terminal. Sodium and energy dependent. Serves normally to conserve NE and bring cessation to neurotransmission. Predominant mechanism for doses used for imaging.

- **Uptake-2 system:**
  Non-neuronal, sodium independent. Dominates at higher concentrations. Probably result of passive diffusion. Some studies suggest uptake-2 may be minimal-absent in humans.

**MIBG** is not metabolized by local enzymes (unlike NE). Localizes in sympathetic nerve endings, allowing effective visualization.

\textsuperscript{123}I-MIBG can assess **global & regional cardiac sympathetic innervation**.

MIBG Prediction of Cardiac Death in CHF

414 pts. with CHF

Freedom from Cardiac Death (%)

Follow-up interval (months)

H/M > 1.92
H/M 1.75 - 1.92
H/M 1.57 - 1.74
H/M <=1.56

Overall: Log rank 28.17
p = 0.0000

Cardiac autonomic abnormalities are seen in patients with:

- Congestive heart failure and cardiomyopathies
- Arrhythmias: Secondary and primary
- Post cardiac transplant
- Coronary artery disease
- Diabetic neuropathy

Nuclear imaging is unique in its ability to visualize the cardiac neuronal condition.
Patients with relatively advanced impairment of MIBG uptake were more likely to show improved cardiac sympathetic function in response to carvedilol therapy.


Figure 4. Change in I-123 MIBG 4-hour heart-mediastinum ratio with carvedilol treatment as a function of the baseline I-123 MIBG ratio. Patients with a low baseline ratio (<1.40) showed a more consistent improvement in cardiac neuronal function than did those with relatively mild baseline impairment (ratio ≥1.40). Overall, there was no significant relationship between baseline I-123 MIBG ratio and subsequent change in MIBG ratio with carvedilol treatment ($r = -0.316, P > .05$).
Idiopathic RV Outflow Tachycardia

Myocardial catecholamine reuptake and beta adrenoceptor density were reduced in patients with idiopathic RVO-VT.

Leads to increased local catecholamine levels at synapse.

Fig. 2. Scatterplot of the myocardial WR of MIBG and the increase in LVEF between baseline and 1 year follow-up in the carvedilol group. WR showed a significant inverse correlation with the increase in EF (p= –0.74, P= .02).

MIBG Scintigraphy for Prediction of Response to β-Blocker Therapy in Dilated CM

Fig. 1. H/M activity ratios on initial and delayed images of iodine-123 MIBG myocardial scintigraphy before β-blocker therapy in patients with dilated cardiomyopathy. H/M ratio on initial images (30 min after injection of iodine-123 MIBG, left) showed an overlap in two groups of patients who did and did not respond to bisoprolol. By contrast, H/M ratio on delayed images (4 hr after injection, right) separated two groups at threshold value of 1.7. In nine normal controls, H/M ratios on initial and delayed images were 2.3 ± 0.2 and 2.6 ± 0.2, respectively.

Response to bisoprolol: LVEF increase by 20% with reduction in LV dimension and sx improved by one NYHA class.

ICD Discharge Related to SPECT Mismatch Defects

<table>
<thead>
<tr>
<th></th>
<th>ICD Discharge (n = 10)</th>
<th>No ICD Discharge (n = 7)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early MIBG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defect Scores</td>
<td>34.6 ± 15.5</td>
<td>17.3 ± 15.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Mismatches (#)</td>
<td>5.7 ± 3.1</td>
<td>2.9 ± 2.6</td>
<td>NS (0.11)</td>
</tr>
<tr>
<td><strong>Late MIBG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defect Scores</td>
<td>41.3 ± 18.1</td>
<td>18.0 ± 17.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Mismatches (#)</td>
<td>8.6 ± 4.0</td>
<td>3.4 ± 3.6</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>99mTc-sestamibi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defect Scores</td>
<td>16.8 ± 11.1</td>
<td>7.3 ± 9.3</td>
<td>NS (0.12)</td>
</tr>
</tbody>
</table>

(17 segments scored 0-4)

Predictive Value of MIBG in Ischemic and Non-ischemic Cardiomyopathies

Prognostic Value of SERIAL Cardiac $^{123}$I-MIBG Imaging in Patients with Stabilized Chronic CHF and Reduced LVEF

208 patients with CHF Followed 4.5 ± 1.8 years.

56 had fatal cardiac events.

$\Delta$WR was the only independent incremental predictor of SCD.

Univariate CD predictors
Baseline: H/M, WR, EF
FU: % denervation, H/M, WR, EDV, ESV, EF
$\Delta$: %denervation, H/R, WR, EDV, ESV, EF

CARDIAC TRANSPLANT
Autonomic imaging can be used to follow cardiac innervation following cardiac transplant

- HMR correlates positively with time after transplant.
- Pts 2-12 yrs post-transplant have higher HMR than those before 2 yrs
- Delays in sympathetic reinnervation may indicate vasculopathy.

Restoration of sympathetic innervation is associated with improved response of heart rate and contractile function to exercise.

Effect of Sympathetic Reinnervation on Cardiac Performance after Heart Transplant

29 cardiac transplant recipients imaged with C-11 HED

Contractile response to exercise significantly enhanced in pts. with reinnervation. HED was only independent determinant of exercise induced increase in EF.

10 pts. with IDC (EF < 45%). Measured change in EF (by echo) before and after 20 mos. of carvedilol rx.

Conclusion: patients with advanced downregulation of post-synaptic receptors, indicating higher adrenergic drive, may receive greater benefit from carvedilol.

METHODS (1)

Patient Recruitment, Imaging, Interpretation

- RECRUITED: Patients with NYHA II/III CHF and LVEF $\leq$ 35% who were treated with guideline-based management (ACE-I, $\beta$-blockers).

- Underwent rest and 4-hour delayed imaging.

- Quantitation of H/M judged by 3 blinded readers at an independent core laboratory.
  - Derived consensus H/M for each subject from 4-hour planar images.
Methods (2)

Outcome Events

- Clinical care provided by subject’s cardiologist and other providers.

- Follow-up data collected every 6 weeks for up to 2 years.

- Adverse cardiac event determined by independent adjudication of 5 cardiologists.
  - All potential events were adjudicated (Jacobson et al. JNC 2009; 16:113-21.)

- Median follow-up: 17 months (2 days - 27 months)
Molecular Structures of Norepinephrine (NE), Guanethidine, and $^{123}$I-MIBG
ANALYSIS OF MIBG PLANAR IMAGES

**HM Ratio**
ROI’s drawn around heart and mediastinum, counts per pixel determined for each, and ratio calculated.

All-cause Mortality vs BNP (Median 140) & H/M

Two-year Survival Probabilities

<table>
<thead>
<tr>
<th></th>
<th>BNP&lt;140 pg/l</th>
<th>BNP&gt;140 pg/l</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M&lt;1.60</td>
<td>91.3%</td>
<td>79.9%</td>
<td>85.2%</td>
</tr>
<tr>
<td>H/M≥1.60</td>
<td>98.2%</td>
<td>96.2%</td>
<td>97.6%</td>
</tr>
<tr>
<td>Total</td>
<td>93.4%</td>
<td>82.2%</td>
<td>87.2%</td>
</tr>
</tbody>
</table>

* p=0.024 vs BNP>140 & H/M ≥1.60

Jacobson AF. Presented at American College of Cardiology
RESULTS
Patient Cohort

- 961 ADMIRE-HF CHF subjects available for primary efficacy analyses
  - 985 dosed, but 21 withdrawn for protocol violations, AE, or subject request. 3 removed from follow-up because of blinded reader interpretation issues.

- Multivariate analyses included 905 subjects
  - 56 subjects in primary efficacy population had incomplete data for BNP and/or NE.
### Patient Characteristics (n = 961)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>62.4</td>
</tr>
<tr>
<td>Gender (Male, %)</td>
<td>80.1</td>
</tr>
<tr>
<td>Race (White, %)</td>
<td>74.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.2 ± 6.1</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
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<tr>
<td>Diabetes (%)</td>
<td>36.0</td>
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<tr>
<td>Hypertension (%)</td>
<td>64.5</td>
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<tr>
<td>Smoker, current or past (%)</td>
<td>73.9</td>
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<tr>
<td>Dyslipidemia (%)</td>
<td>72.4</td>
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<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>92.0</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>94.0</td>
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<tr>
<td>Lipid lowering agents (%)</td>
<td>73.7</td>
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<tr>
<td>Aldosterone inhibitors (%)</td>
<td>34.3</td>
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<tr>
<td><strong>CHF parameters</strong></td>
<td></td>
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<tr>
<td>NYHA II/III (%)</td>
<td>82.7/17.3</td>
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<tr>
<td>Ischemic/non-ischemic (%)</td>
<td>66.0/34.0</td>
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<tr>
<td>LVEF (%)</td>
<td>27.1 ± 6.2</td>
</tr>
</tbody>
</table>
RESULTS

Patient Outcome (n=905)

Total deaths: 75 (8.3%)

- Cardiac deaths: 51
- Non-cardiac deaths: 24

  » Cancer = 5, Pneumonia = 4, COPD = 3, CVA = 3, Accidents = 3, Renal failure = 2, Seizure = 1, subarachnoid hemorrhage = 1, sepsis = 1, ? = 1.
A Study in Contrasts