MIBG Imaging in Heart Failure Management

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All Disclosures/Conflicts
Manuel D. Cerqueira (4/2017)

Consultant/Advisory Board
– Astellas Pharma USA

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Which HF Patient Has Highest Risk?

Subject 11

76 y/o male

NYHA class II Ischemic

Meds: Carvedilol, Irbesartan, Lasix, Amlodipine, Atorvastatin, Digoxin

Core lab echo LVEF: 27%

BNP: 250

ICD: Yes

Subject 02

71 y/o male

NYHA class II Ischemic

Meds: Metoprolol, Lisinopril, Amlodipine, Atorvastatin

Core lab MPI LVEF: 33%

BNP: 484

ICD: Yes

Pathophysiology of HF With Reduced EF

MI

Virus, Toxin, HTN

Myocardial Injury

↓ CO   ↓ BP

Neurohumoral Activation
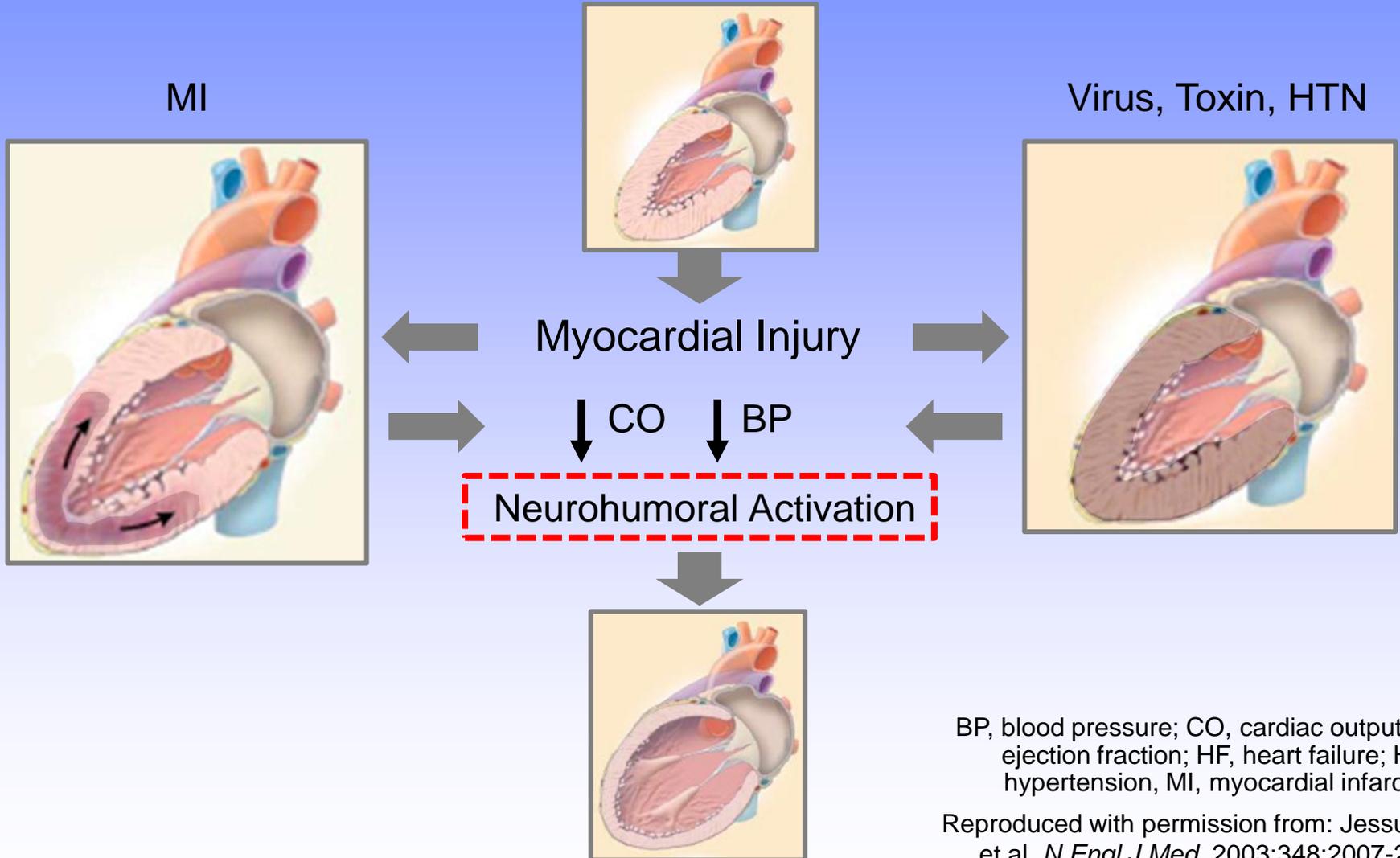
BP, blood pressure; CO, cardiac output; EF, ejection fraction; HF, heart failure; HTN, hypertension, MI, myocardial infarction.

Reproduced with permission from: Jessup M, et al. *N Engl J Med*. 2003;348:2007-2018.

Risk Stratification in HF

- LV ejection fraction (LVEF)

- Non-sustained VT (NSVT)

- NYHA class

- Microvolt T-wave alternans (MTWA)

- Measures of cardiac autonomic tone

- QT-interval duration and QT dispersion

- Signal averaged ECG (SAECG)

- Electrophysiology study (EPS)

- Biomarkers

- Imaging

Risk Stratification in HF-Imaging Options

- **Echocardiography-essential and basic to all HF**

- **SPECT and PET**

  - Exclusion of ischemia, scar size and hibernation

- **Cardiac MR**

  - Viability assessment, structure

- **Cardiac CT-Role to be defined**

- **Coronary angiography-definitive for revascularization**

Neurohormonal Activation in HF: SOLVD

Median Plasma Norepinephrine (pg/mL)
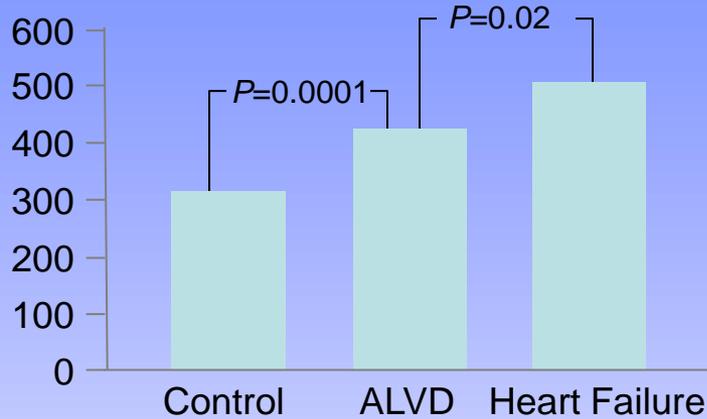
Median Plasma Renin Activity (pg/mL)
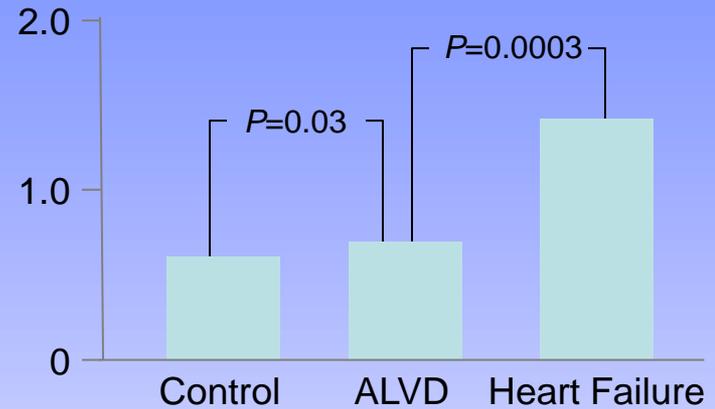
Median Plasma ANF (pg/mL)
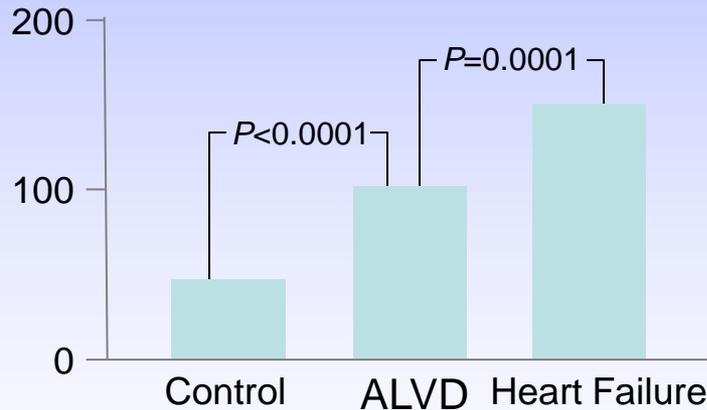
Median Plasma AVP (pg/mL)
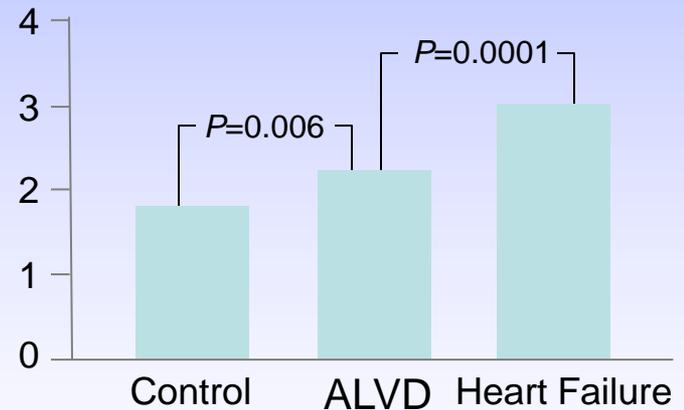
ALVD, asymptomatic left ventricular dysfunction; ANF, atrial natriuretic factor; AVP, plasma arginine vasopressin; SOLVD, Studies of Left Ventricular Dysfunction.
Francis GS, et al. *Circulation* 1990;82;1724-1729.

Prognostic Significance of Neurohormonal Activation

CONSENSUS Trial
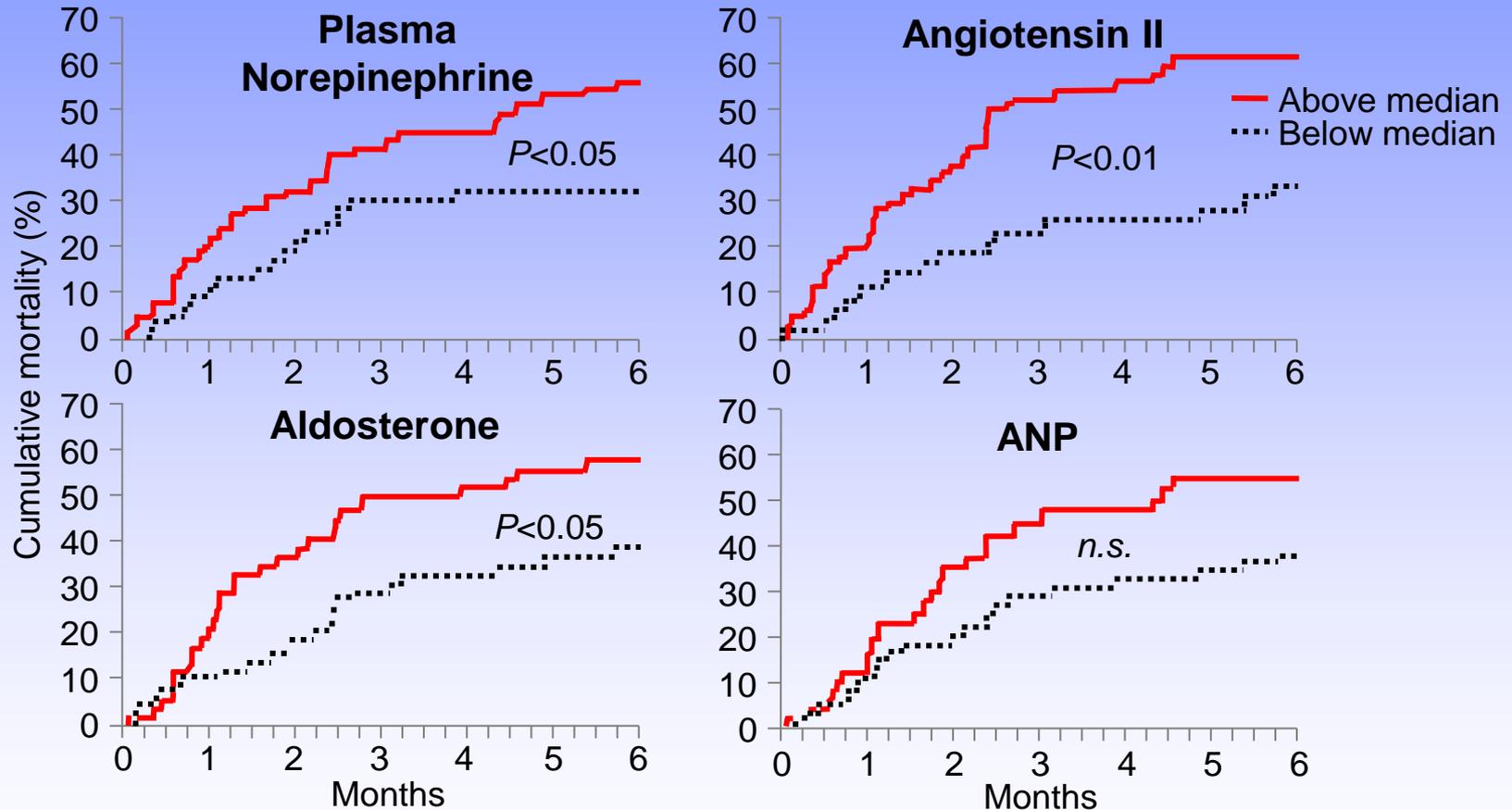
ANP, atrial natriuretic peptide.
Swedberg K, et al. *Am J Cardiol*. 1990;66:40D-44D.

Norepinephrine Levels and Mortality

V-HeFT II
Baseline Plasma Norepinephrine (pg/mL)
### (Cumulative Mortality by Risk Category)

PNE > 900 pg/mL

PNE > 600 and ≤ 900 pg/mL

PNE ≤ 600 pg/mL

Two Year
$P<0.0001$

Overall
$P<0.0001$

Cumulative Mortality (%)

Months
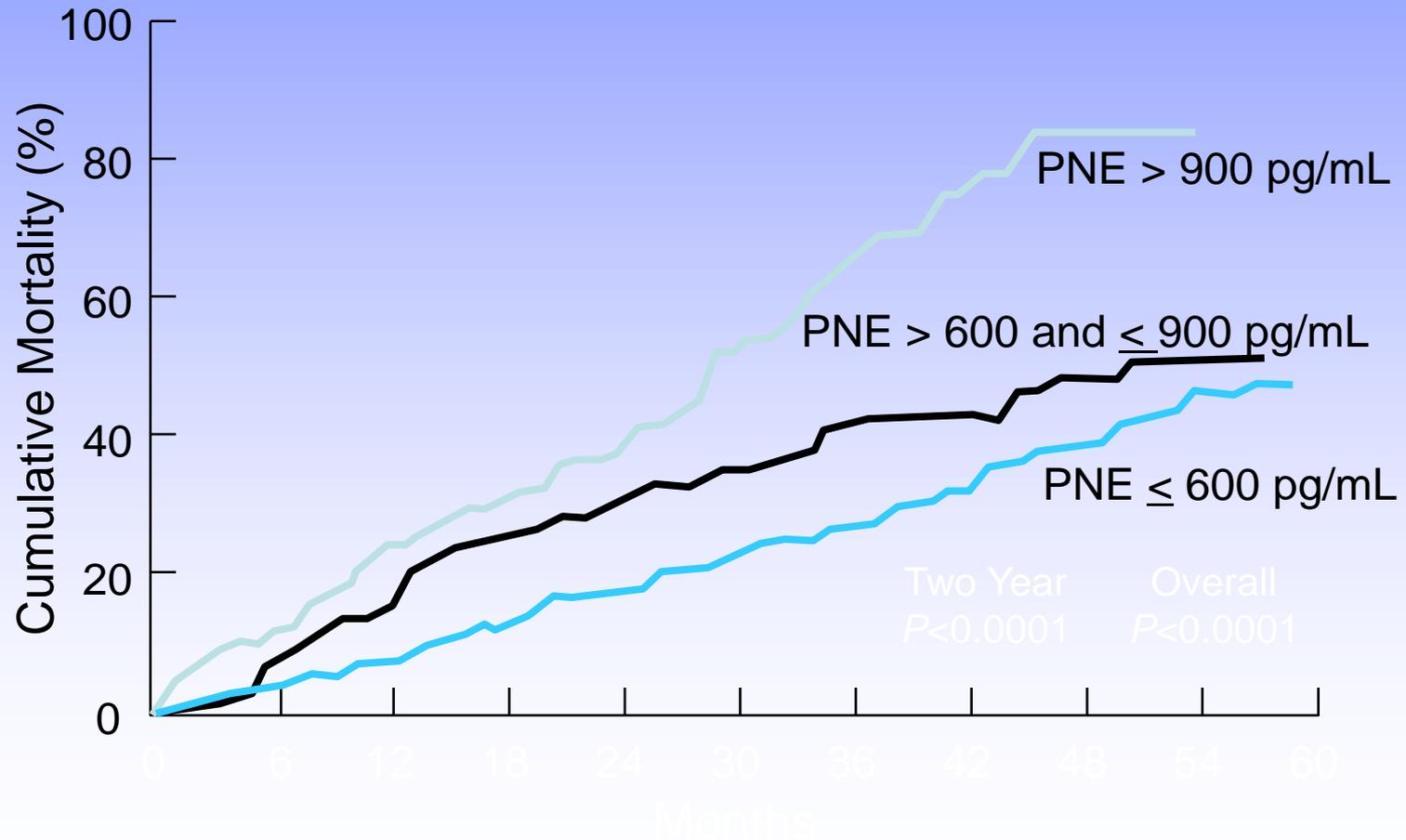
b-adrenergic Neuroeffector Abnormalities in the Failing Human Heart

| Group		β receptor density			ICYP K_D	% $β_1$	% $β_2$	$α_1$ receptor density	IBE-2254 K_D
		Total β	$β_1$	$β_2$					
		fmol/mg			pM			fmol/mg	pM
A (Nonfailing $n = 12$),	LV	87.7±7.4	68.0±6.4	19.6±2.3	11.9±2.7	77.0±2.3	22.9±2.2	8.8±1.2	39.5±12.1
	RV	102.1±9.2§	81.2±10.0§	18.0±2.7	12.3±3.0	80.0±3.0	19.9±2.9	6.8±4.0	27.4±20.0
B (Biventricular failure, $n = 54$)	LV	51.1±1.9*	32.8±1.6*	18.2±0.9	15.3±1.8	63.4±1.5*	36.1±1.4*	17.6±3.3	41.9±5.3
	RV	47.8±2.6*	33.9±2.5*	17.1±1.1	15.2±2.2	65.6±2.2*	34.4±2.0*	15.9±3.2	38.9±7.3
C (PPH, isolated RVF, $n = 12$)	LV	85.4±6.1‡	62.1±4.2‡	24.9±3.4‡	9.4±1.6	72.0±2.5‡	28.2±2.2‡	16.4±2.7	39.3±11.7
	RV	41.9±4.0*§	23.2±2.6*§	19.6±3.7	10.2±2.5	56.0±5.6*§	41.5±4.6*§	14.6±2.8	34.0±10.7

Values are given as mean±SEM. Abbreviations: LV, left ventricle; RV, right ventricle. * $P < 0.05$ vs. respective chamber in A. ‡ $P < 0.05$ vs. respective chamber in B. § $P < 0.05$ vs. LV.

Bristow J. Clin. Invest. 1992.89:803

Mechanisms of Receptor Downregulation
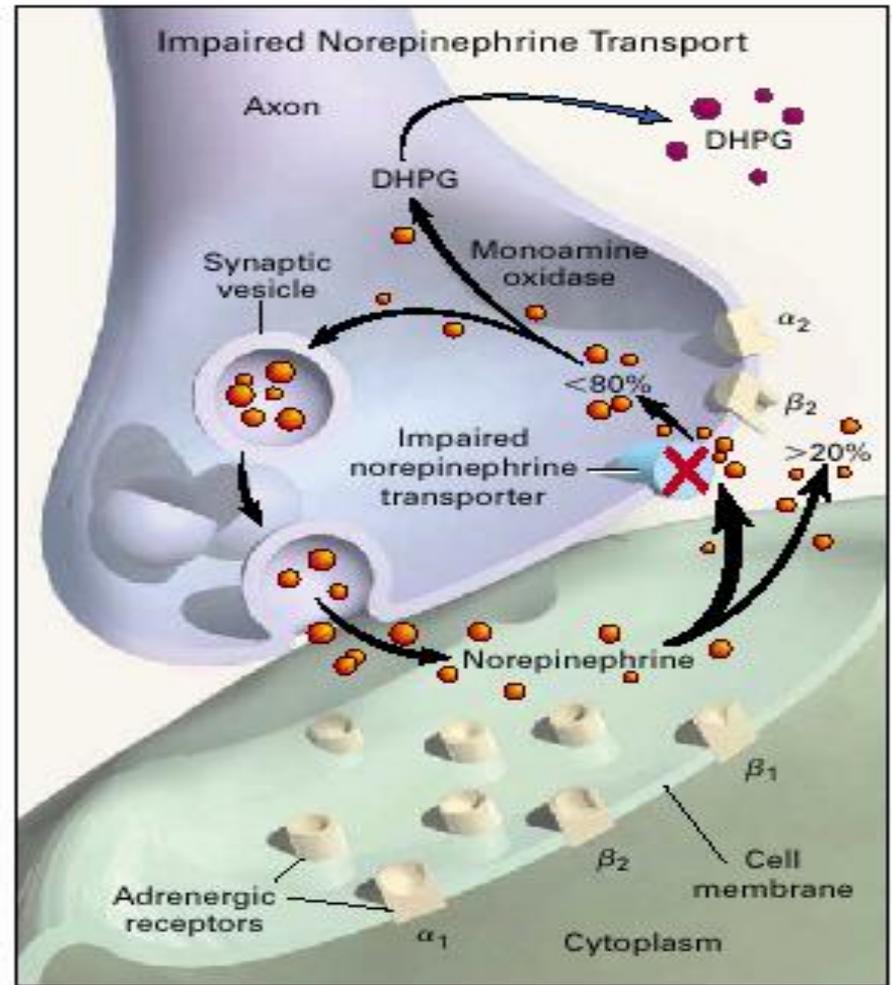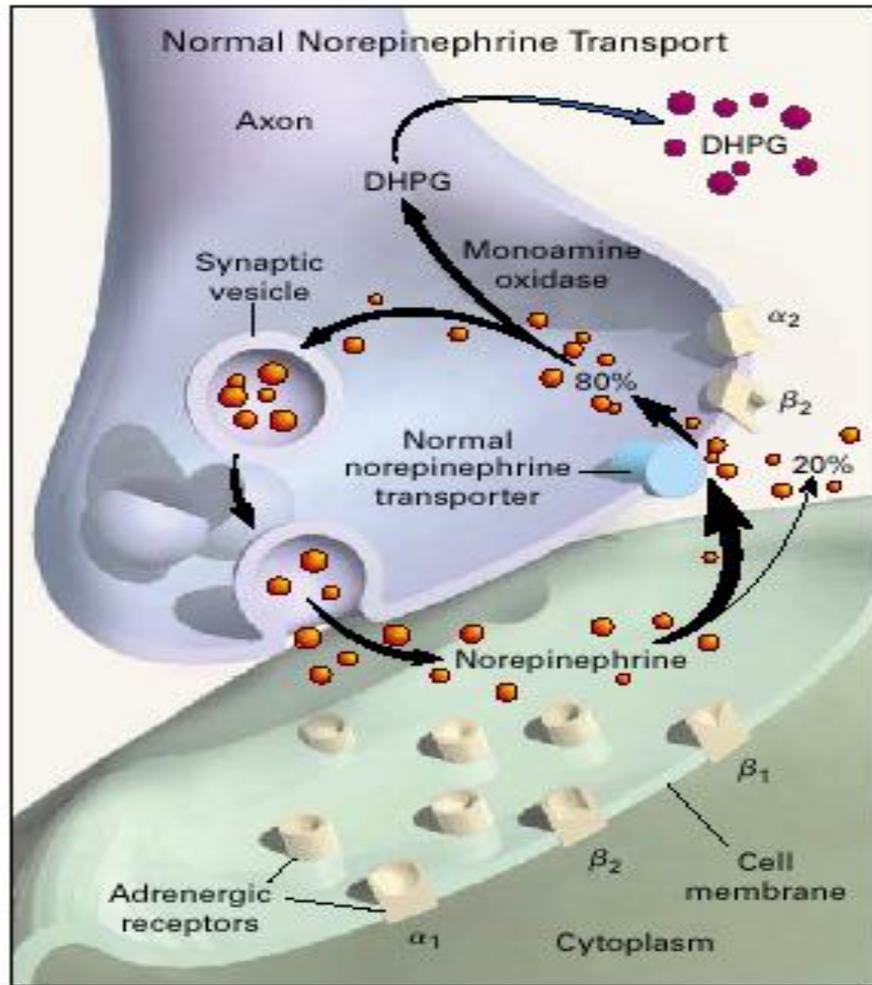
Iobenguane I 123: Chemical Structure

^{123}I-meta-iodobenzylguanidine (^{123}I-mIBG)
Iobenguane I-123

Norepinephrine
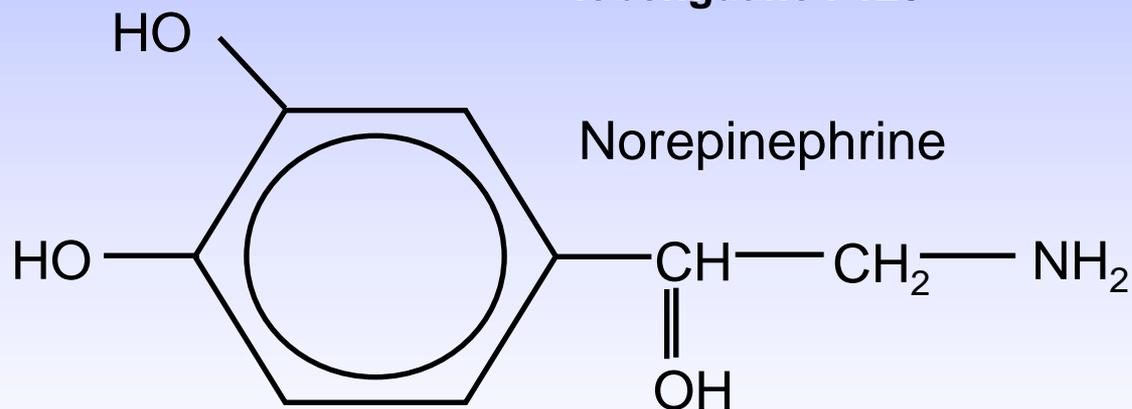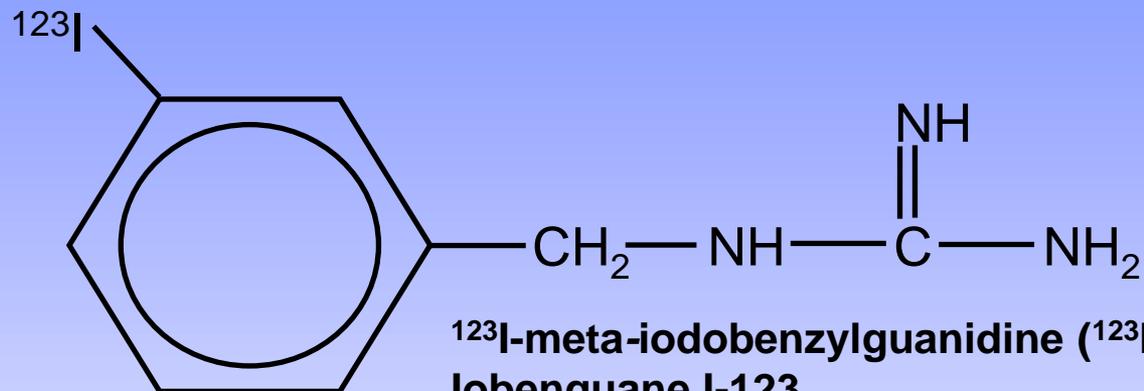
Imaging of Innervation at Cardiac Sympathetic Synapse

Evidence suggests that mIBG employs the same uptake and storage mechanisms as NE but it is not metabolized by MAO or COMT which results in it being localized in a high concentration in the presynaptic neuron

Axon →

NE

mIBG

mIBG

NE

NET 1

NET 1

Uptake 1

mIBG

NE

NE

mIBG

mIBG

NE

Uptake 2

SYNAPTIC CLEFT

| α1 | α1 | β1 | β1 | β2 | β2 |

Post-synaptic receptors

Myocyte

To plasma ←

COMT, catechol-O-methyl transferase;
MAO, monoamine oxidase;
NE, norepinephrine;
NET, norepinephrine transporter
Travin MI. *Cardiol Clin.* 2009;27:311-327.

Imaging Considerations

I-123:
- $T_{1/2}$: 13.2 hours
- Gamma emission (principal emission): -159 keV

Dosage: 10 mCi (370 MBq)

Absorbed radiation dose: ~5 mSv

Collimator: low energy, high-resolution

Matrix: 128 x 128 for planar image

Camera
- Image must include mediastinum and heart

Iobenguane I 123 Imaging Protocol

Energy window: 159 ± 20%

Camera positioning: include the entire heart and as much of the upper chest as possible within the field of view

Imaging: Anterior planar view of the chest at 4 hours following administration of AdreView

- Optional:
  - SPECT imaging should be done after the planar imaging at 4 hours

Estimation of the H/M Ratio

Step 1: Visual examination of the location, pattern and intensity of cardiac radioactivity uptake to guide quantitative assessment

Step 2: Quantitative assessment of radioactivity uptake using H/M ratio on anterior planar images of the chest

Step 1: Visual Assessment of Anterior Planar Image

Normal

Distinct visualization of the left ventricular myocardium in the left lower chest, with greater uptake in the heart than in the adjacent lungs and mediastinum
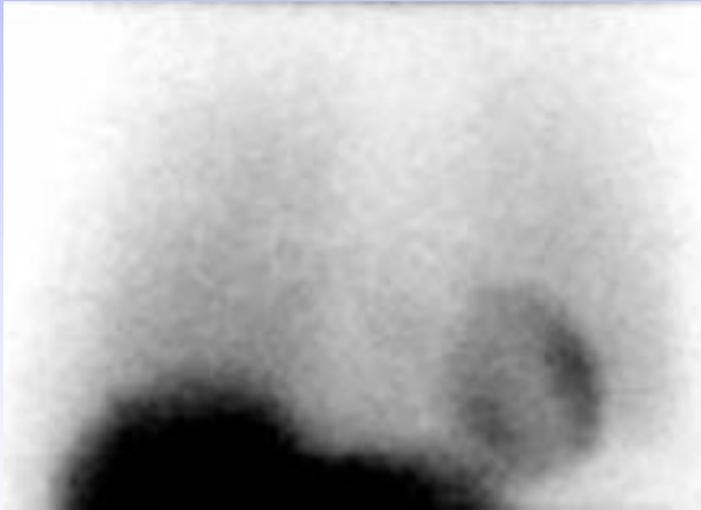
Abnormal

Decreased cardiac uptake (homo- or heterogeneous) with indistinct/absent LV visualization

**A: Cardiac activity: usually less than that of adjacent left lung**

B: In extreme cases, little or no cardiac AdreView uptake seen


LV, left ventricle.
AdreView PI.

Quantitating I-123 Cardiac Uptake
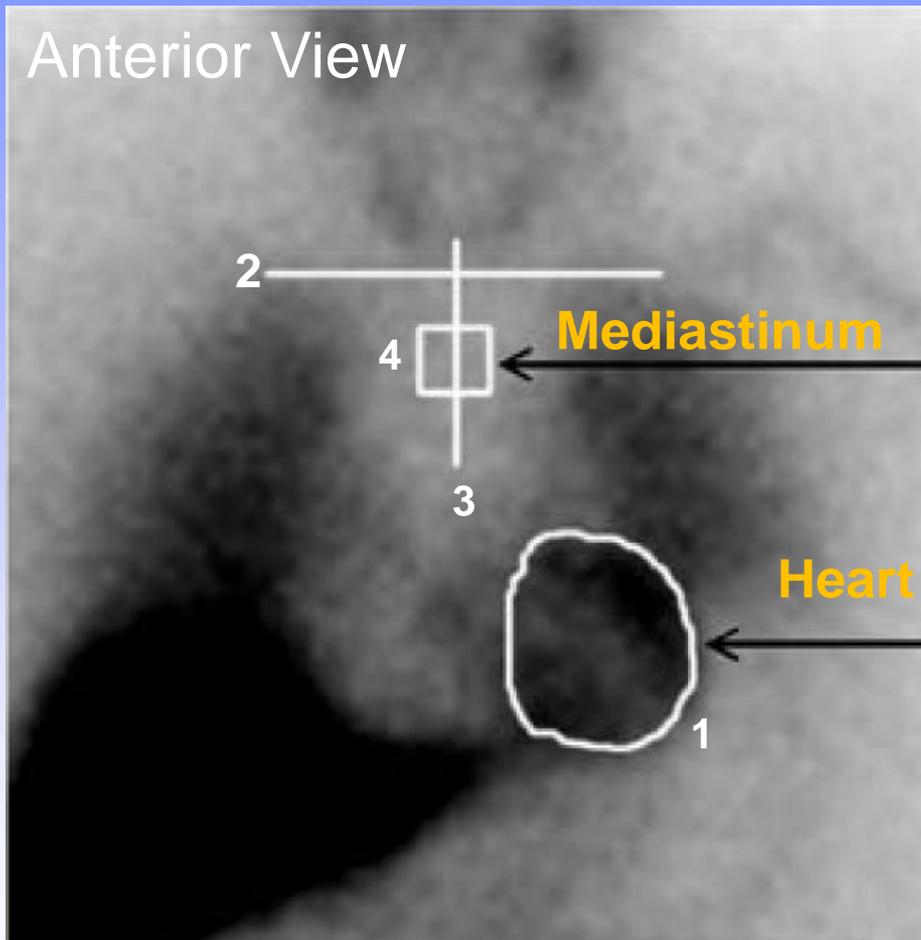
Steps

1. **Draw ROI defining epicardial LV border**

2. **Draw horizontal line to mark estimated location of lung apices**

3. **Draw vertical line ~equidistant from medial aspects of right and left lung**

Quantitating I-123 Cardiac Uptake

Anterior View

2 —

4

Mediastinum

3

Heart

1
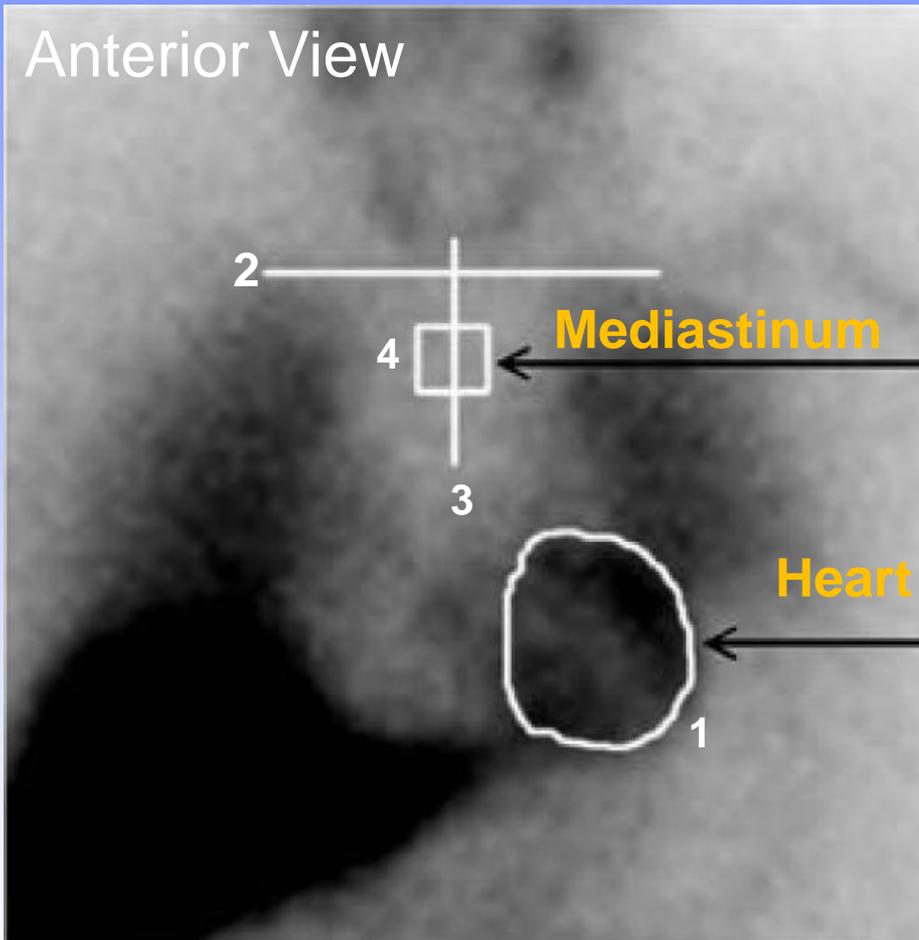
Steps

1. **Examine the counts for the 12 pixels along the vertical line starting 4 pixels below the intersection point with the horizontal line determined in *Step 2*, and identify the pixels with the lowest counts. If more than one pixel has this same number of counts, choose the most superiorly located pixel and then draw 7x7 pixel ROI around pixel on line 3 with lowest counts**

2. **H/M ratio = counts/pixel in the total myocardium. ROI determined in *Step 1* divided by counts/pixel in the 7x7 pixel mediastinal ROI determined in *Step 4*.**

I-123 MIBG Imaging:
Specific Patient Considerations

Patients at risk for thyroid accumulation:

– Administer Potassium Iodide Oral Solution or Lugol's Solution at least 1 hour before administration of AdreView

Patients with prior reactions to iodine

– Consider expected benefits vs risk of potential hypersensitivity

Patients with conditions affecting the sympathetic nervous system, eg, Parkinson's disease

– May show decreased cardiac uptake of AdreView independent of heart disease

I-123 MIBG:
Use of Concomitant Medications

Medications with potential to interfere with MIBG Imaging

– Risk of unreliable imaging results

If MIBG imaging is essential, physicians must consider if they can safely withdraw the following categories of medications

Category of medication	Examples
Antihypertensives that deplete NE stores or inhibit reuptake	Reserpine, labetalol
Antidepressants that inhibit NE transporter function	Amitriptyline and derivatives, imipramine and derivatives, SSRIs
Sympathomimetic amines	Phenylephrine, phenylpropanolamine, pseudoephedrine, ephedrine
	Cocaine

NE, norepinephrine; SSRIs, selective serotonin reuptake inhibitors.

I-123 MIBG:
Use of Concomitant Medications

**Period of time necessary to discontinue any specific medication prior to AdreView dosing has not been established**

Clinical studies have not determined:

– Which specific drugs may cause false-negative imaging results

– Whether all drugs in any specific pharmacologic class have the same potential to produce the negative imaging results

Increasing AdreView dose will not overcome any potential uptake limiting effect of these drugs

Before AdreView administration, discontinue (for ≥5 biological half-lives) drugs known or expected to reduce NE uptake, as clinically tolerated

Calculation of late H/M ratio
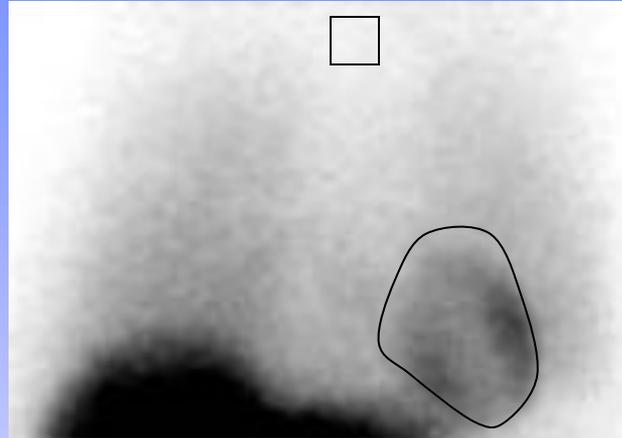

Healthy individual without heart disease (H/M = 2.40)
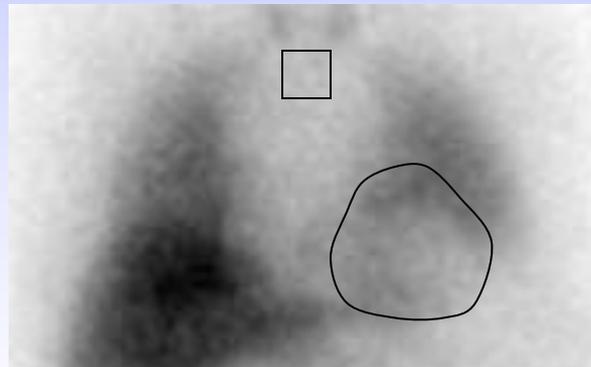
Heart failure patient with moderately reduced cardiac uptake (H/M = 1.34)

Prediction of HF vs Arrhythmic Death

Representative ADMIRE-HF Patients

On the basis of the H/M ratios, 2-year cardiac mortality risk for patient 1 is 10 times that of patient 3.

1	2	3

65 y/o M	**51 y/o M**	**64 y/o M**
NYHA 2	**NYHA 2**	**NYHA 2**
LVEF = 25%	**LVEF = 33%**	**LVEF = 30%**
H/M = 0.96	**H/M = 1.38**	**H/M =1.67**
Died at 8 mo HF progression	**Died at 8 mo, SCD (No ICD)**	**No event**
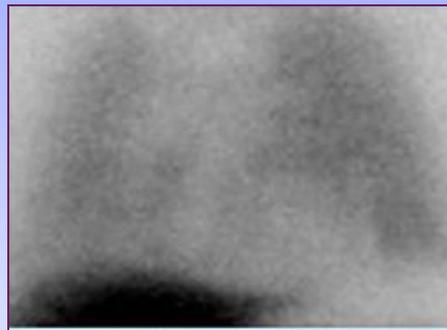
Jacobson A. Late-Breaking Clinical Trials. ACC 2009.

Iobenguane I 123:
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Feasibility for SPECT Imaging

Normal

Abnormal

4-hour delayed images in patient with planar H/M = 2.4
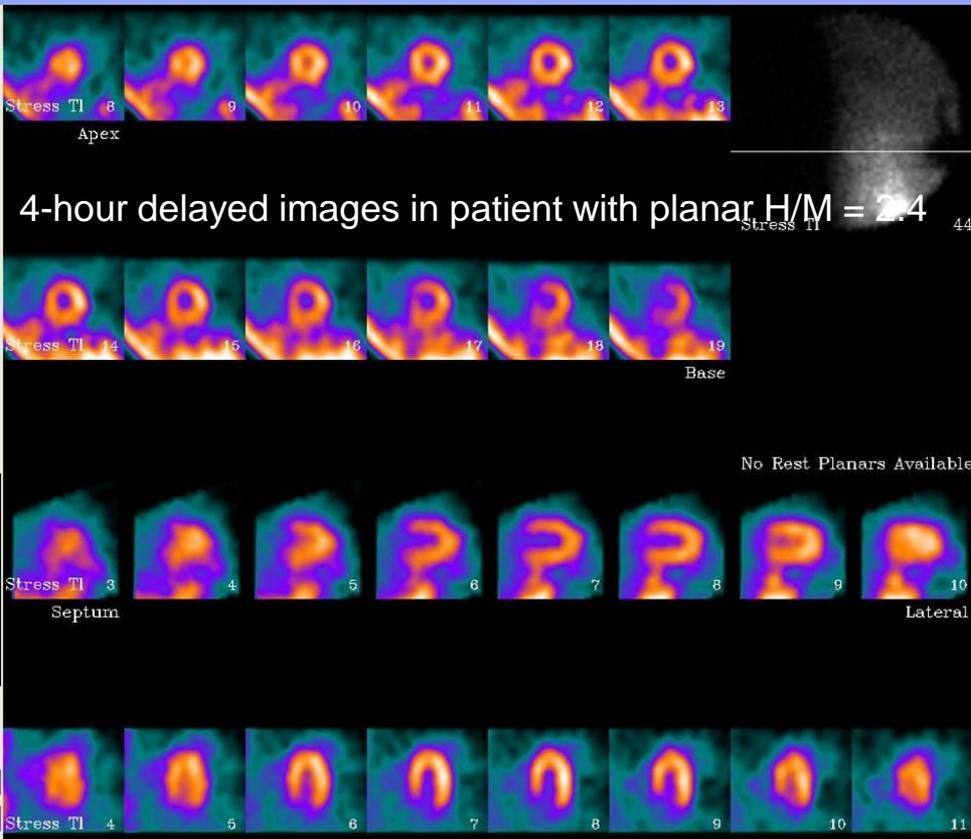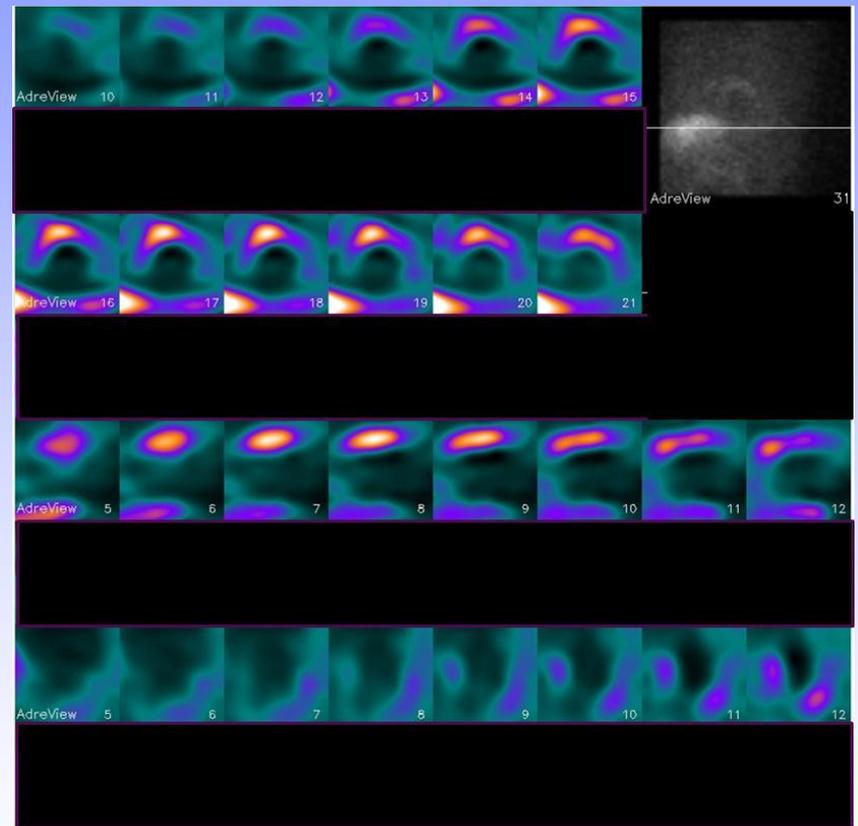
¹²³I-*m*IBG: Normal SPECT Imaging
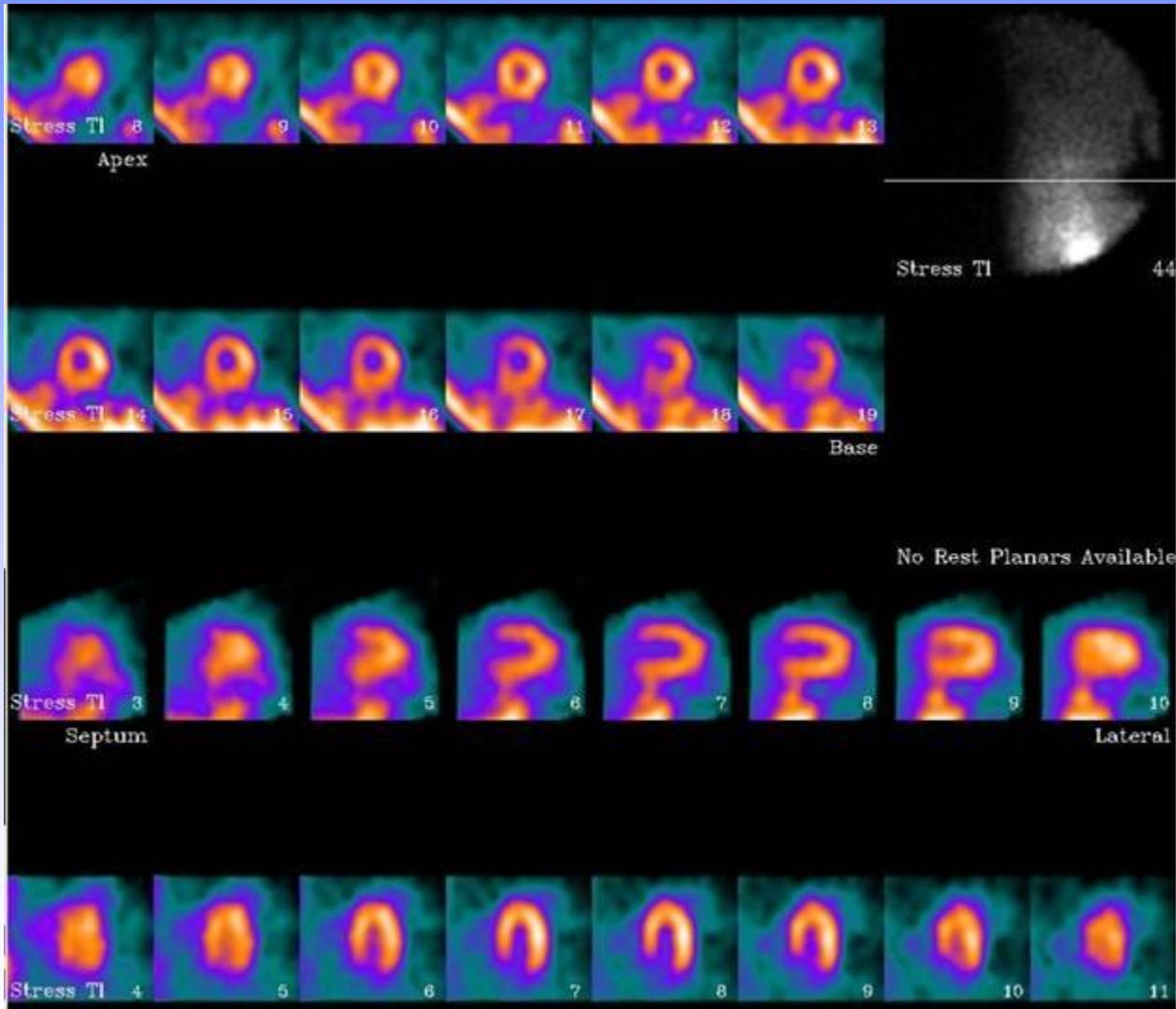
Images provided by A. Jacobson, MD of GE Healthcare

# Abnormal ^{123}I-*m*IBG SPECT
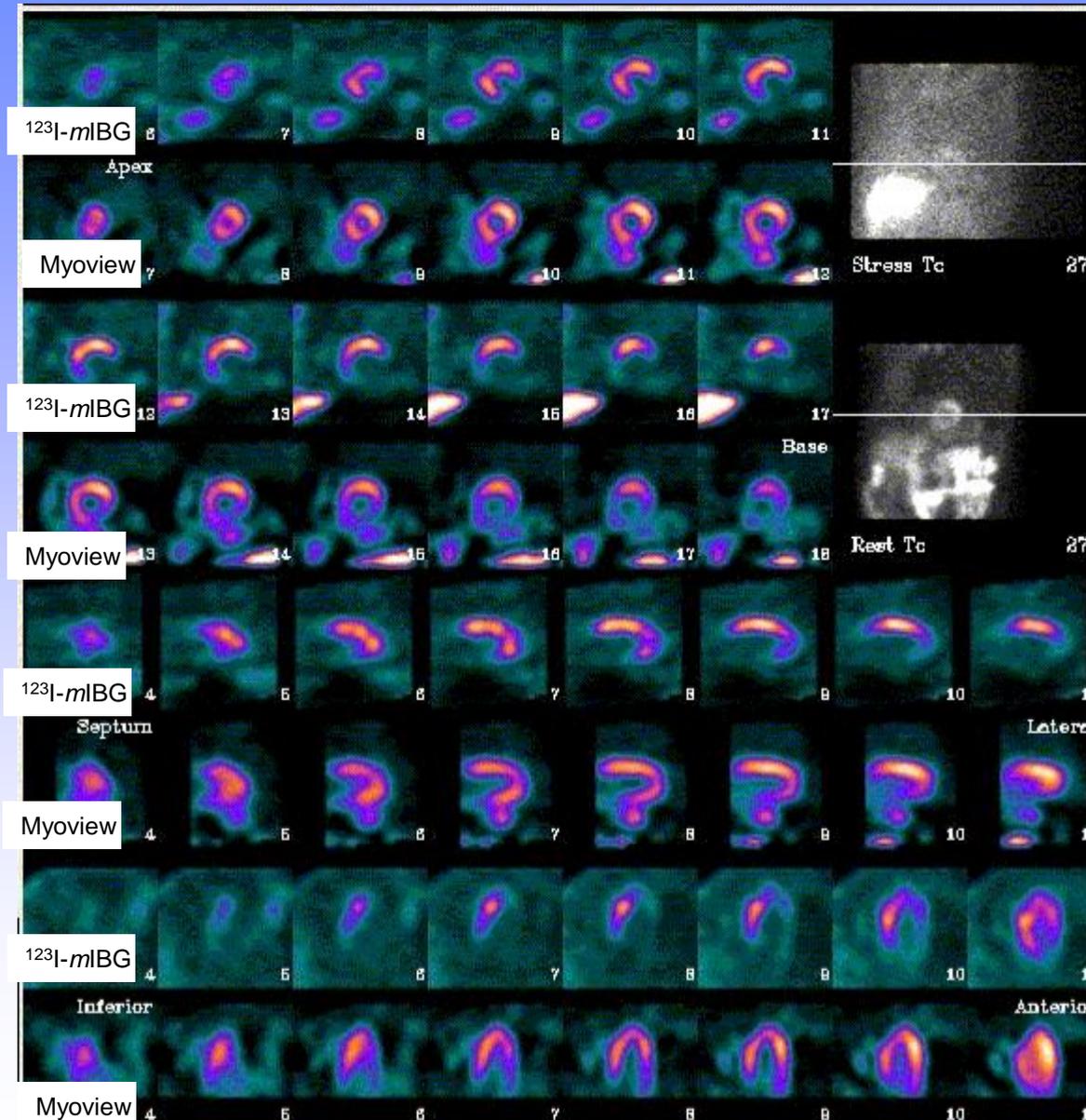
Quantitative Analysis
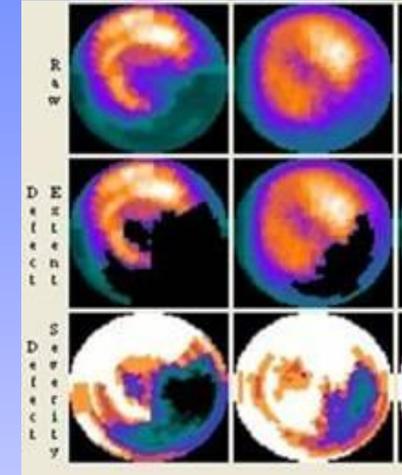
^{123}I-*m*IBG   Myoview

^{123}I-*m*IBG/rest Myoview with matched basal Inferolateral infarct and a larger peri-nfarct area of dennervation on ^{123}I-*m*IBG.

Images provided by A. Jacobson, MD of GE Healthcare

Abnormal ¹²³I-*m*IBG SPECT
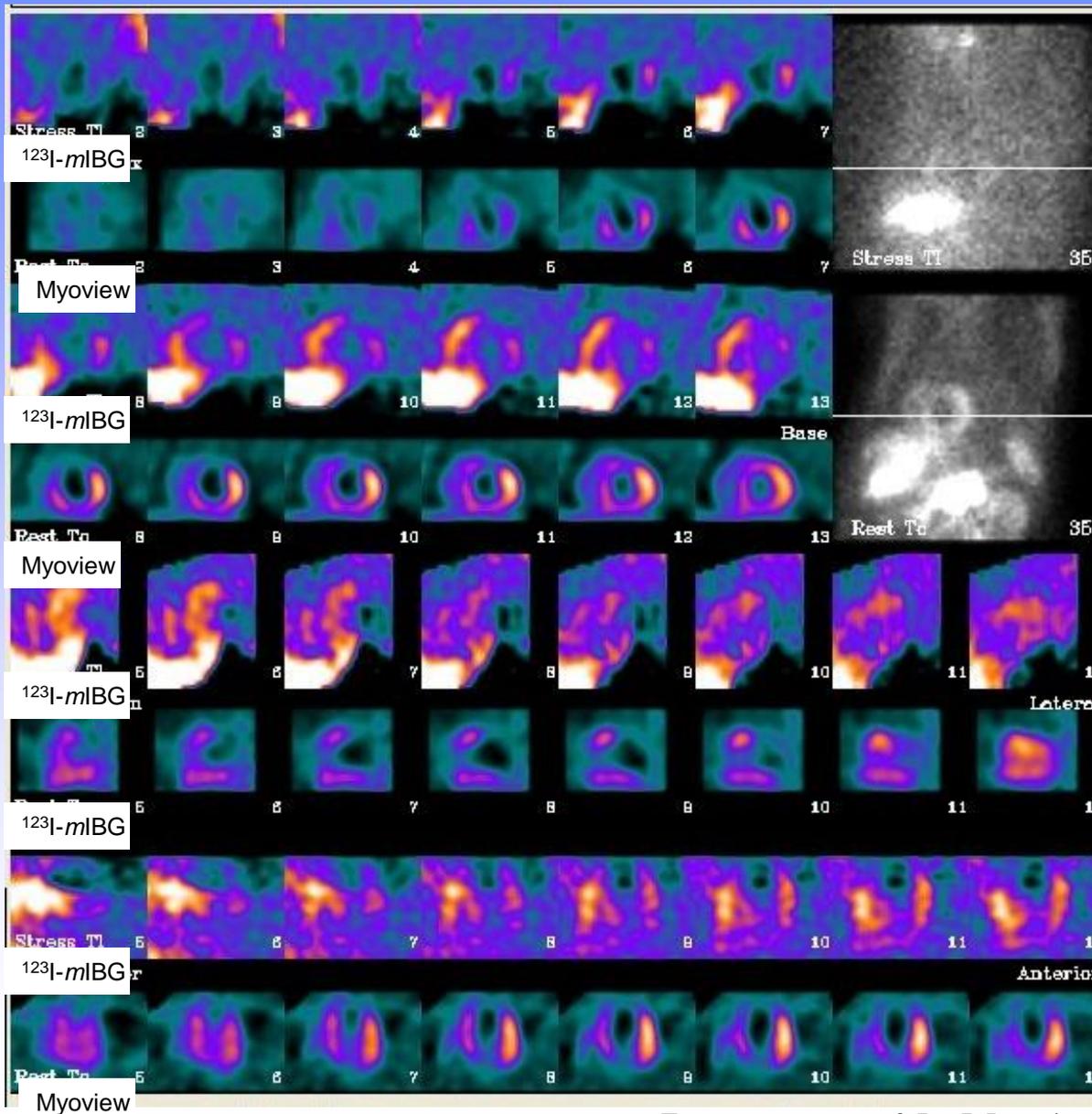
Quantitative Analysis
¹²³I-*m*IBG Myoview
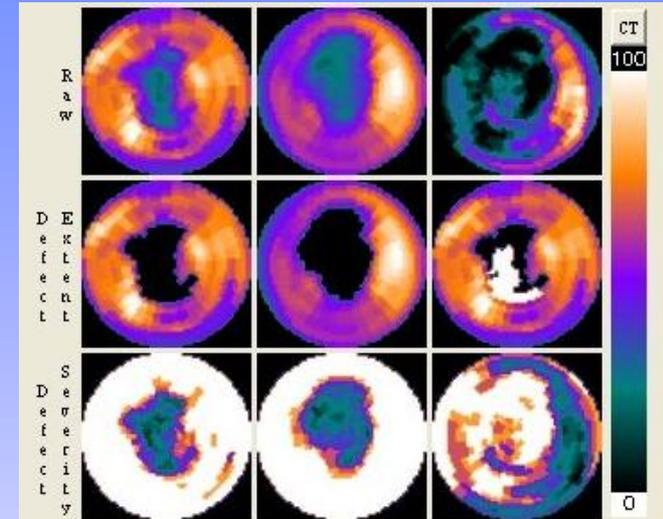

Anterior and apical infarct. Global reduction of *m*IBG uptake results in poor quality SPECT and underestimation of disease severity on bullseye plot.

Impact of Effective HF Therapy on ^{123}I-*m*IBG Imaging
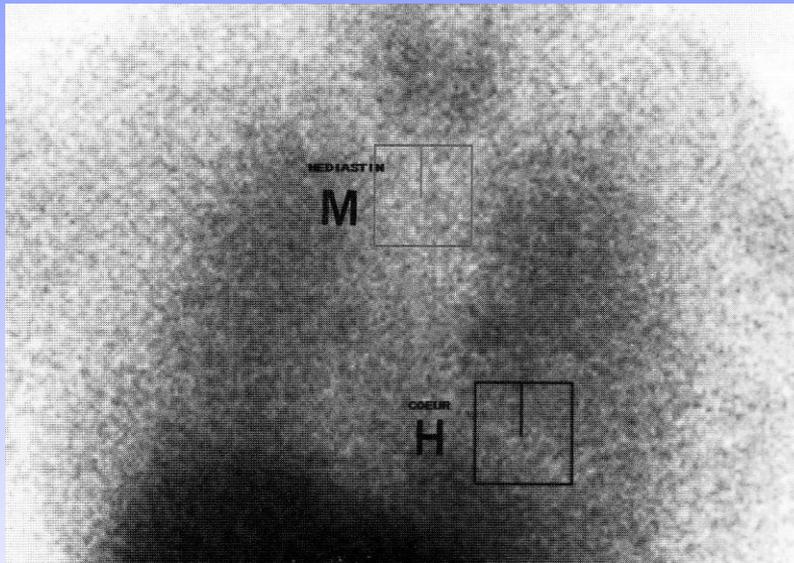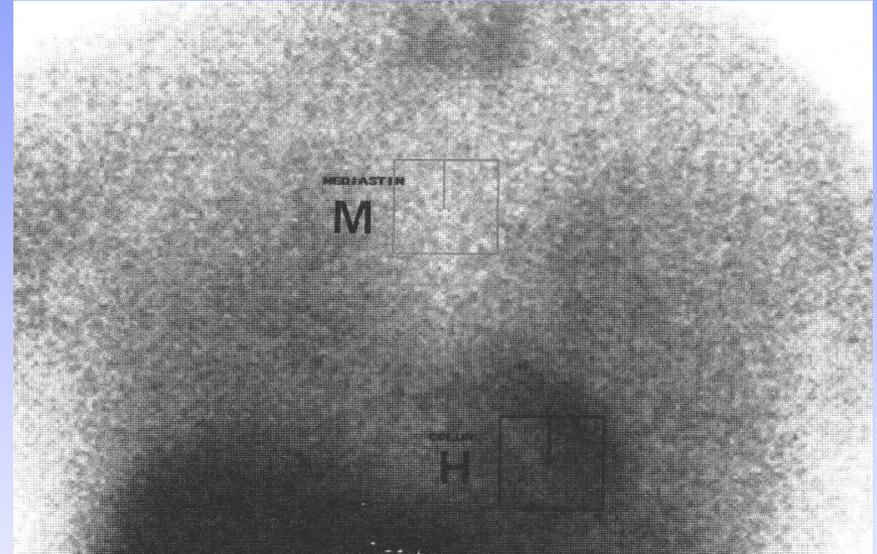
Pre-therapy: H/M=1.11　　　**Post-therapy: H/M=1.62**

Agostini D J Nucl Med 2000;41:845

Sudden Cardiac Death (SCD)

Most common cause of death in the United States

More than 350,000 deaths per year

Claims more lives than stroke, lung cancer, breast cancer, and AIDS combined

Relationship of SCD to NYHA Class

NYHA Class	Annual Mortality (%)	Sudden Death (%)
II	5-15	50-80
III	20-50	30-50
IV	30-70	5-30

MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007.

Goals of SCD Risk Stratification

Identify low-risk patients in high-risk populations

Identify high-risk patients in low-risk populations

Limitations of Current Risk Stratification for ICD Implantation

Low Incidence of Appropriate Shocks

SCD-HeFT

21% appropriate shocks at approx 4 years

MADIT-II

10 million in US qualify for prophylactic ICD

$200 billion to healthcare costs
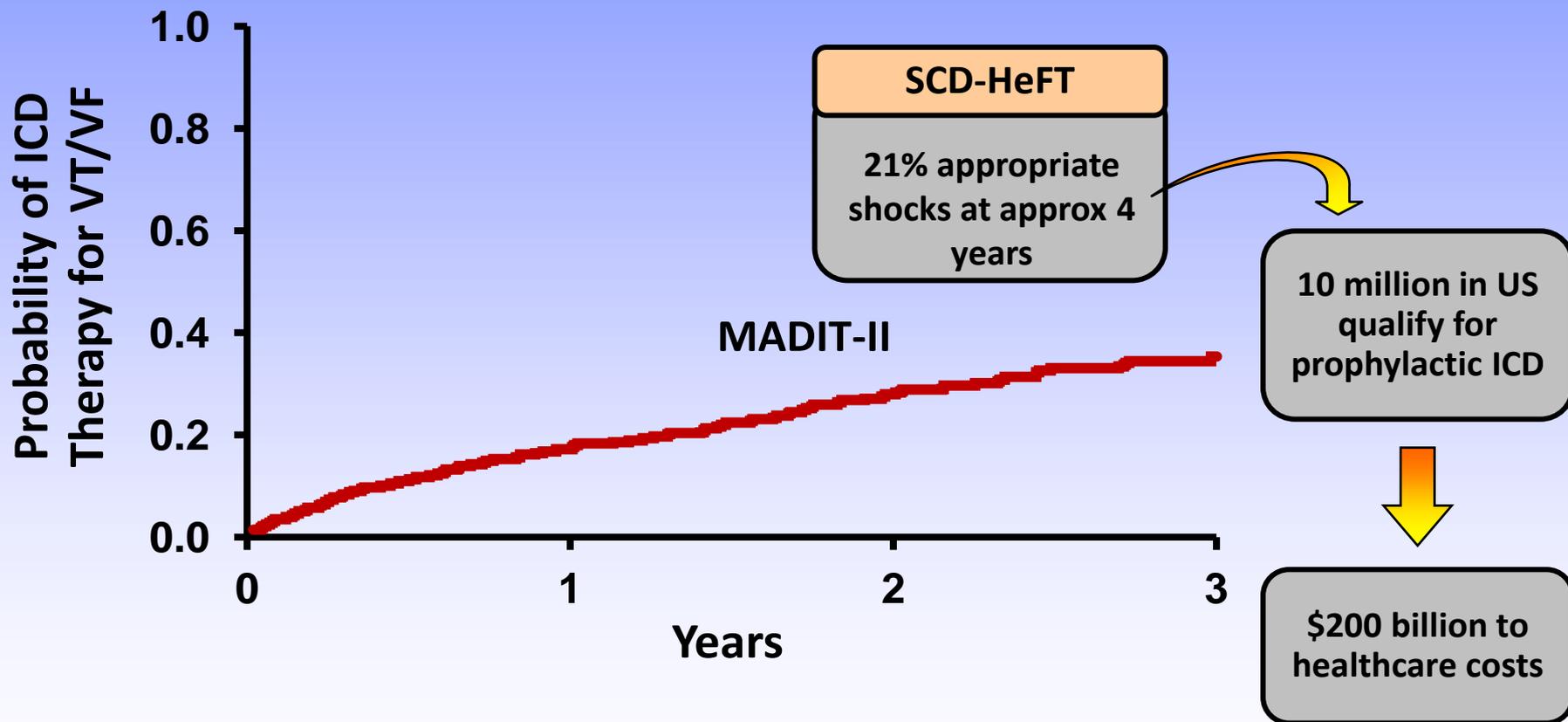
Moss AJ, et al. *Circulation.* 2004;110:3760-3765.
Poole JE, et al. *N Engl J Med*. 2008;359:1009-1017.

LVEF

- **LVEF is the most consistent and one of the strongest predictors of all-cause mortality in patients with ischemic and nonischemic cardiomyopathy**

- **LVEF lacks specificity as a predictor of arrhythmic events**

- **LVEF alone is not enough!**

Predicting ICD Discharge With MIBG and HRV

17 patients w ICDs

10 with history of ICD discharge, 7 without

MIBG + HRV analysis

Those with ICD discharge: Lower H/M ratio, greater MIBG defect, multiple decreased HRV variables

Combined MIBG and HRV analysis identified patients with appropriate shocks and those with no shocks/no arrhythmia

Arora R, et al. *J Nucl Cardiol*. 2003;10:121-131.

Prognosis in HF and Sympathetic Innervation by MIBG: ADMIRE-HF

N = 961 patients with HF and LVD

EVENT = HF prog, arrhythmic event, or cardiac death

H/M ≥ 1.6: 2-year event-free survival 85%

H/M < 1.6: 2-year event-free survival 63%*

*P < .0001 vs H/M ≥ 1.6

Event-Free Survival Probability

Time (Days)

Jacobson AF, et al. *J Am Coll Cardiol*. 2010;55:2212-2221.
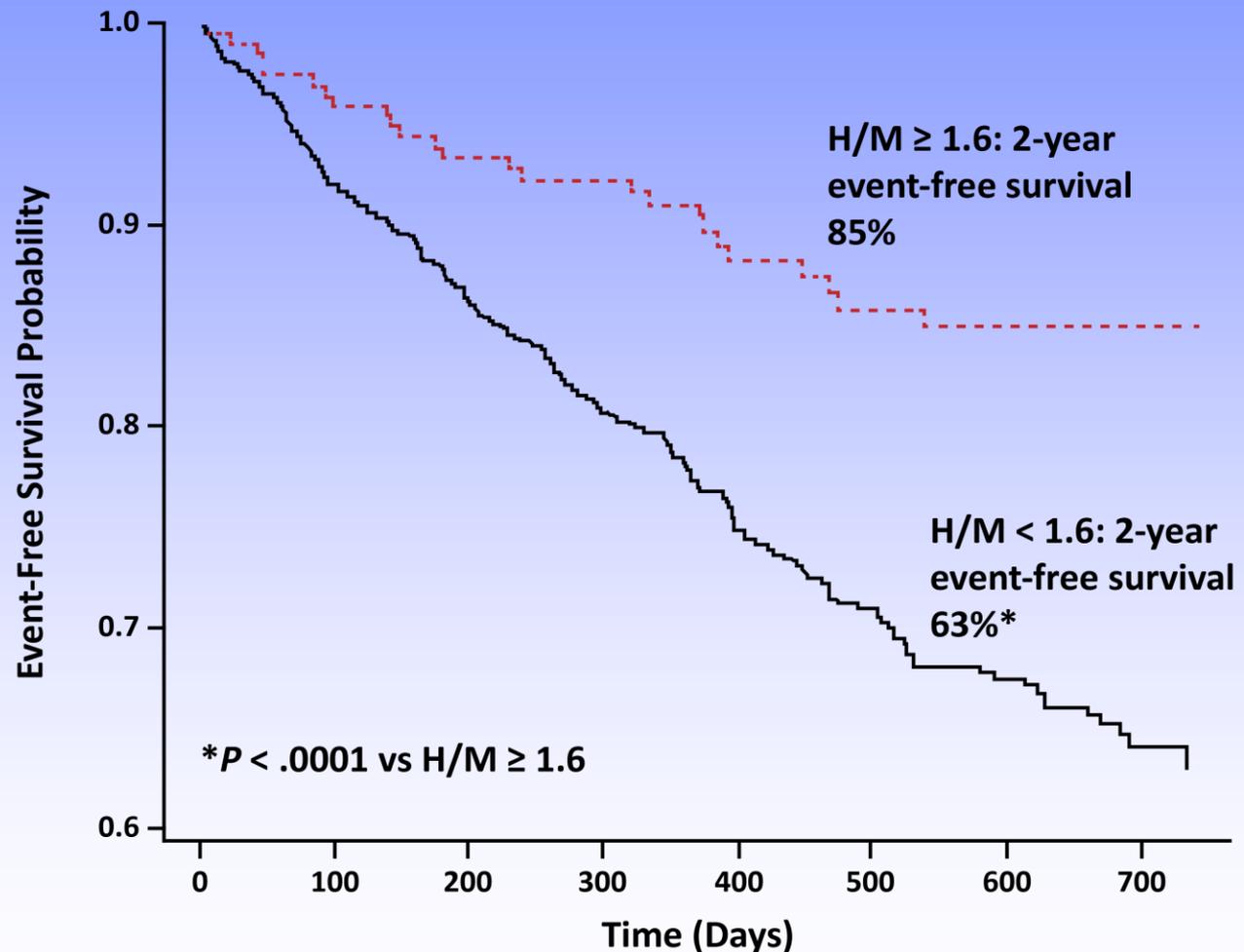
ADMIRE-HF: Composite Primary Endpoint

Jacobson AF, et al. *J Am Coll Cardiol*. 2010;55:2212-2221.
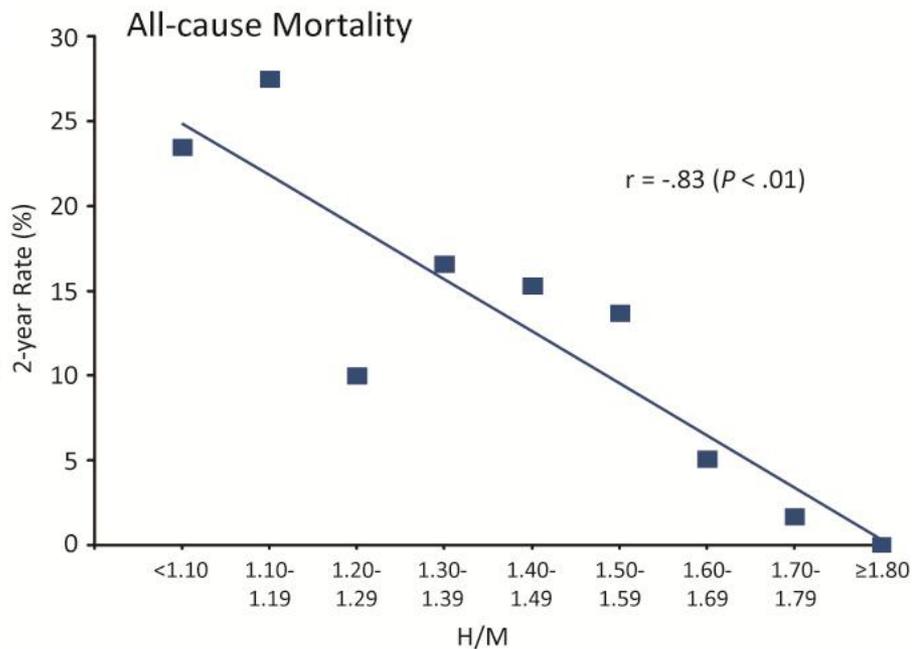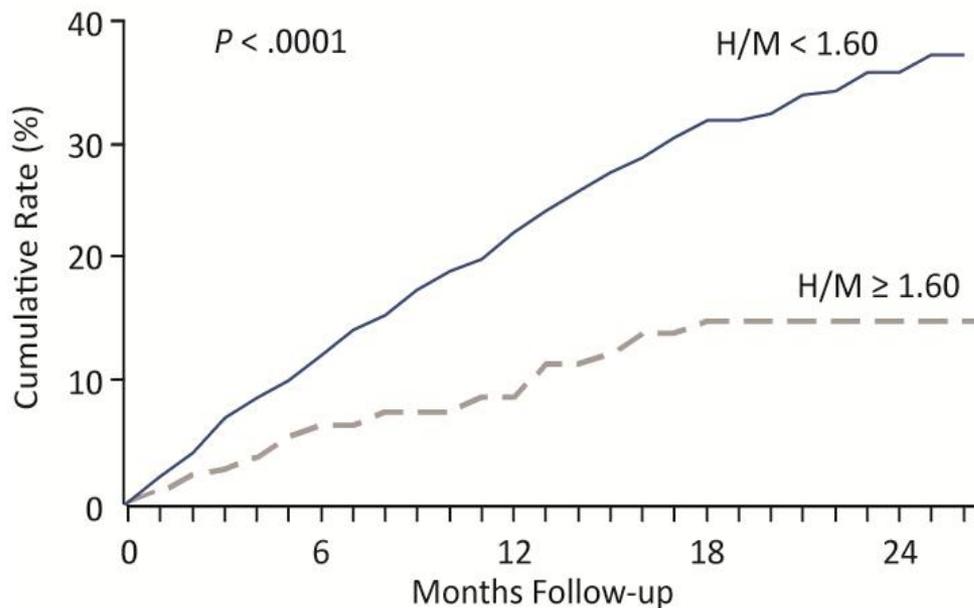
ADMIRE-HF: Secondary Endpoints

Jacobson AF, et al. *J Am Coll Cardiol*. 2010;55:2212-2221.
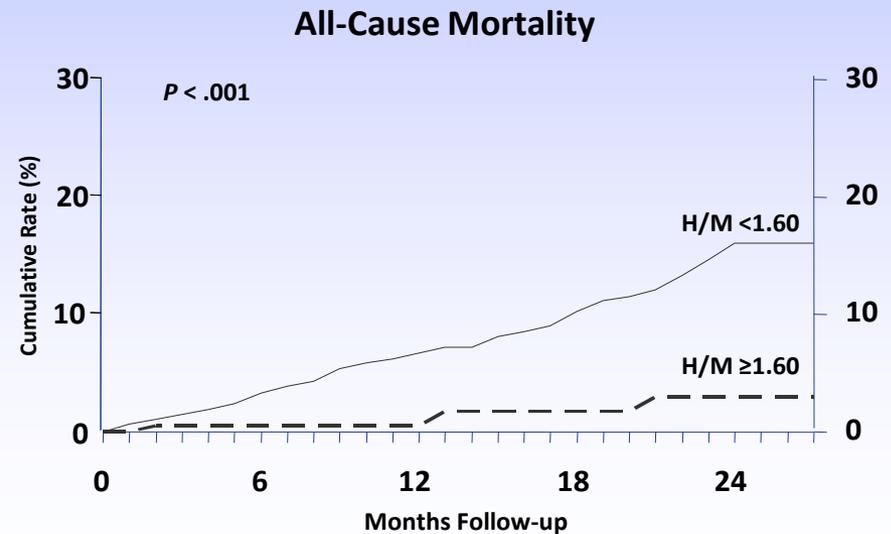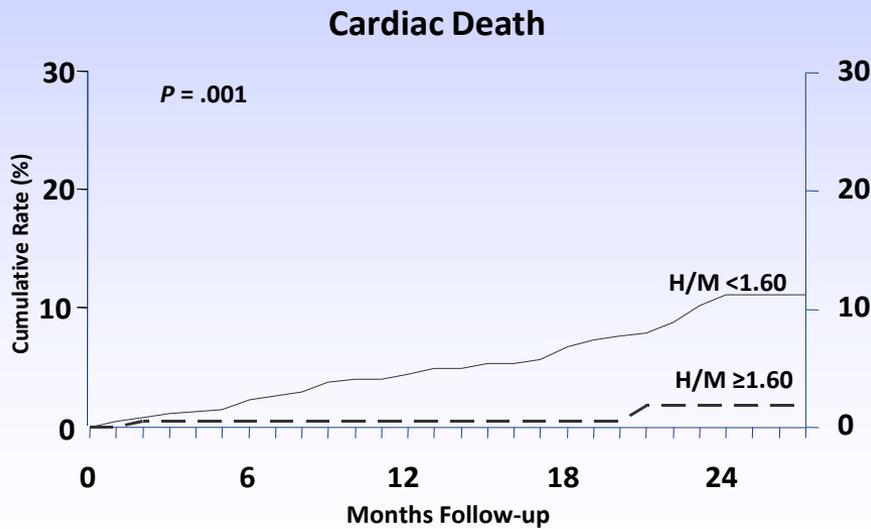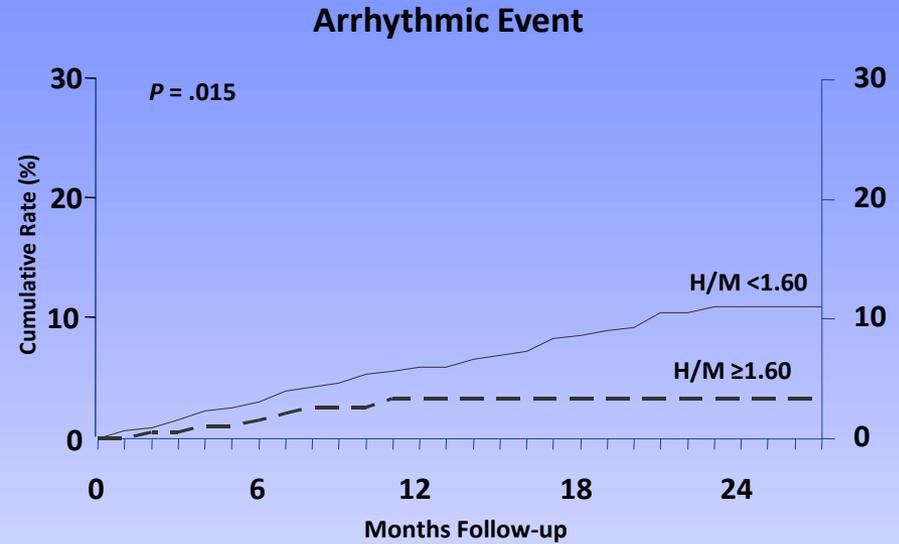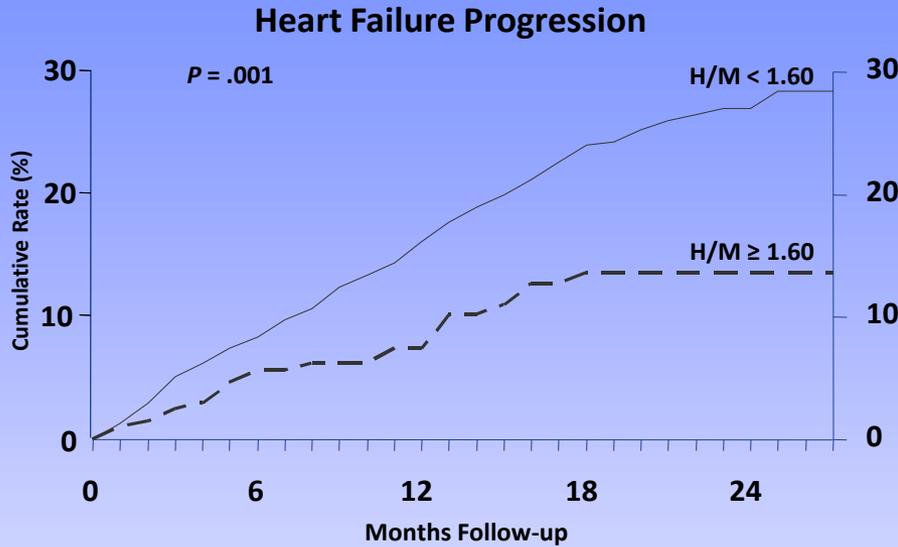
Patient Selection for ICD Placement

Extent of myocardial scar/fibrosis

– May be more predictive of mortality than LVEF resting perfusion defect size—Elhendy A, et al. *Am J Cardiol*. 2003:1165; gadolinium enhancement on MRI–Assomull RG, et al. *J Am Coll Cardiol*. 2006;48:1977-1985

– Rest perfusion defect size not predictive of cardiac events in the ADMIRE-HF study

Can assessment of sympathetic nervous system activity by ^{123}I-MIBG predict which patients will have appropriate therapy from an ICD?

ADMIRE-HF Study Arrhythmic Events

86 of 961 (9%) patients had arrhythmic events
- 63 nonfatal events (sustained VT, aborted cardiac arrest, ICD firing)
- 23 SCDs

Multivariable predictors:
1) LVEF ($P < .001$)
2) H/M ratio < 1.60 ($P = .017$)

Senior R, et al. *Circulation*. 2009;120:S349. Abstract 516.

SCD Stratified by H/M Ratio

ADMIRE-HF study, data courtesy of Arnold Jacobson, MD, PhD
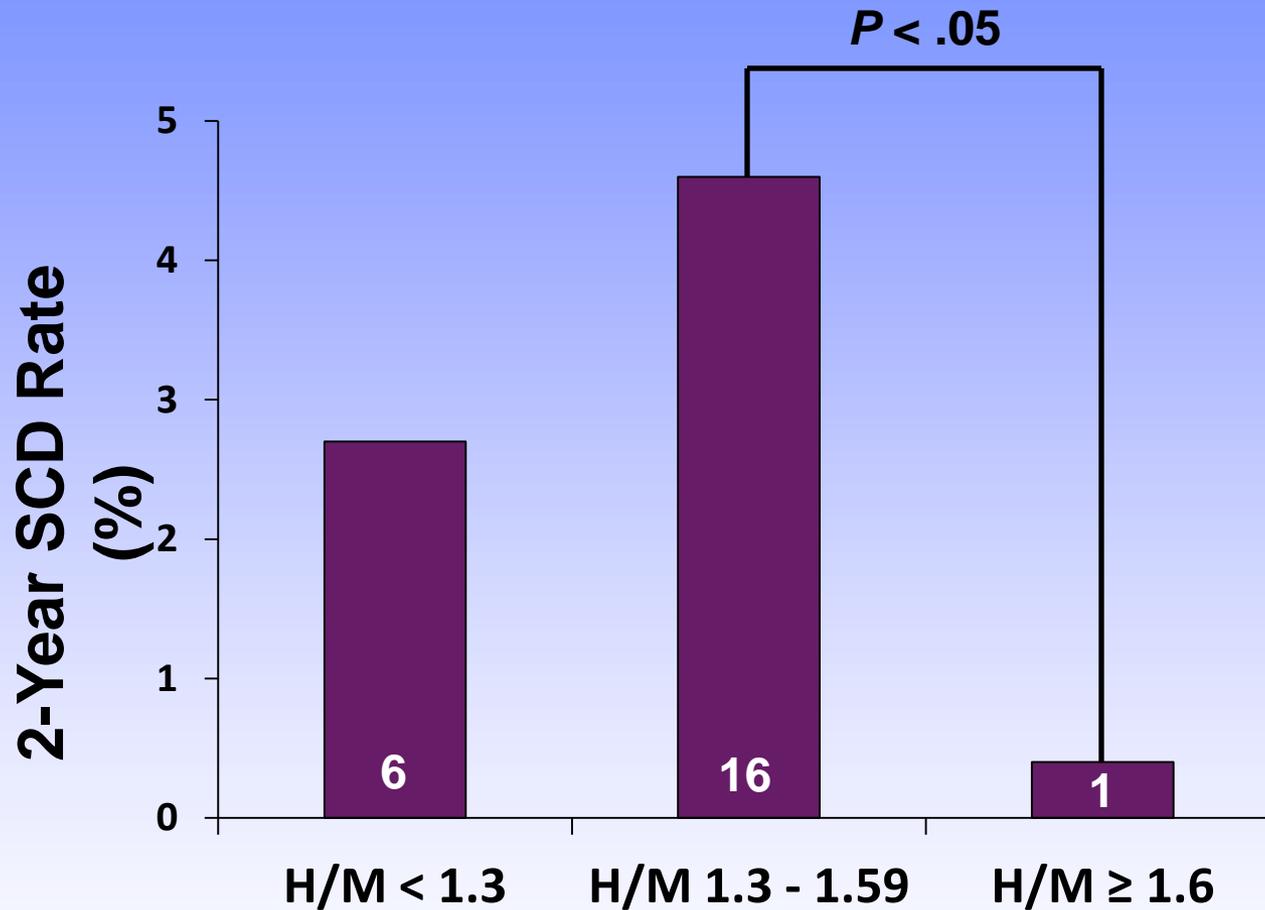
Seattle Heart Failure Model (SHFM)

- **Multivariate predictor of survival from 1 to 5 years and life expectancy**
- **SHFM includes:** (Circulation 2009;120:835)
  - Demographic (age, gender, ischemic etiology)
  - Clinical markers (SBP, EF, NYHA)
  - Lab variables - Na, Cr, Hgb, % Lymphs
  - Medications - ACEI/ARB, Beta-blocker, Dig, Statin, Diuretic
  - Devices - ICD, CRT, CRT-D
- **Widely validated in tens of thousands of subjects**

Addition of Late H/M Ratio to SHFM and Predicted Annual Mortality
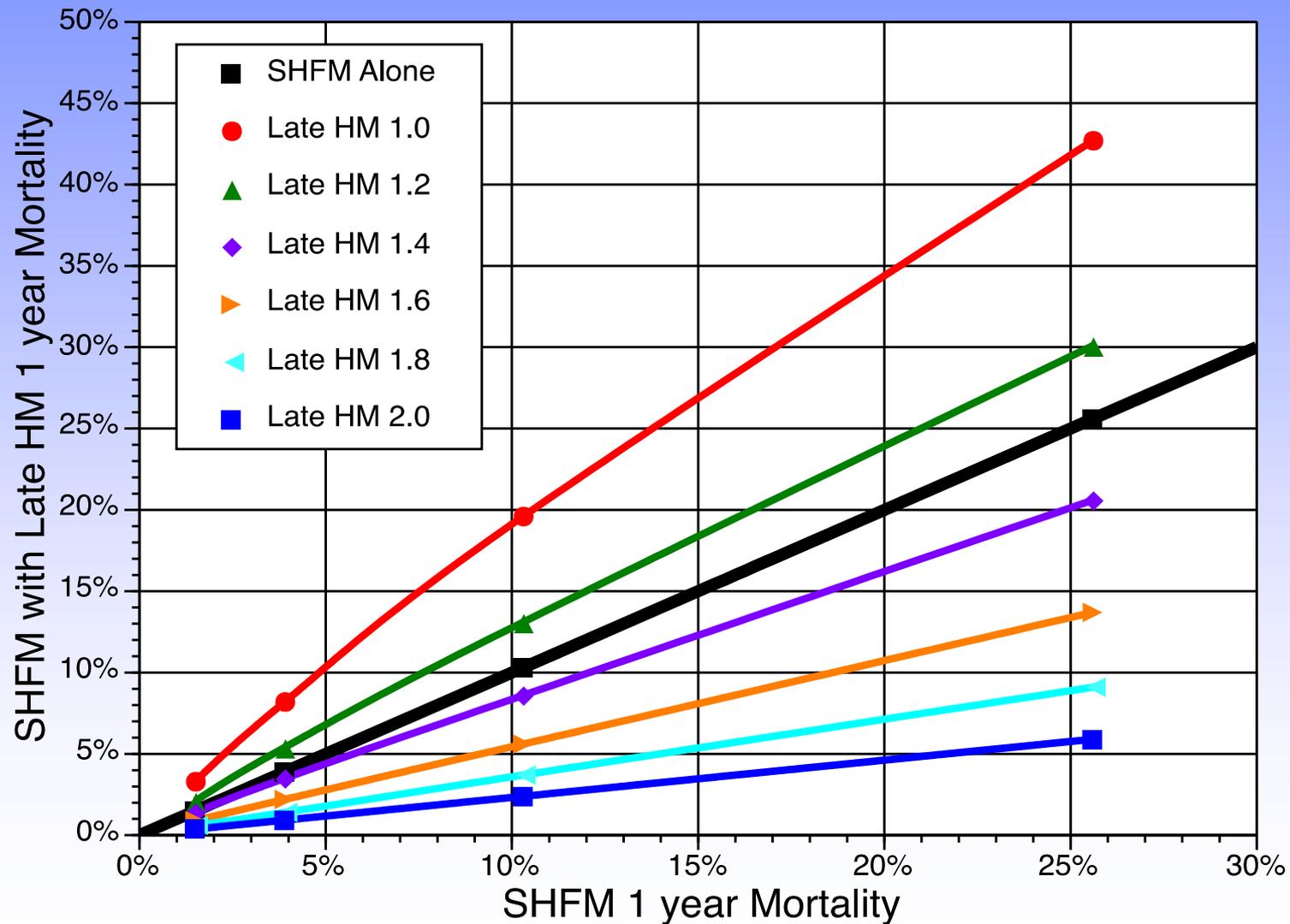
Which Patient Has Highest Risk?

Subject 11

76 y/o male, NYHA class II Ischemic

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Core lab echo LVEF: 27%

BNP: 250

ICD: Yes

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71 y/o male, NYHA class II Ischemic

Meds: Metoprolol, Lisinopril, Amlodipine, Atorvastatin

Core lab MPI LVEF: 33%

BNP: 484

ICD: Yes

MIBG Ratios

Subject 11

H/M=1.29

Event: Resuscitated cardiac arrest day 484

Subject 02

H/M=1.70
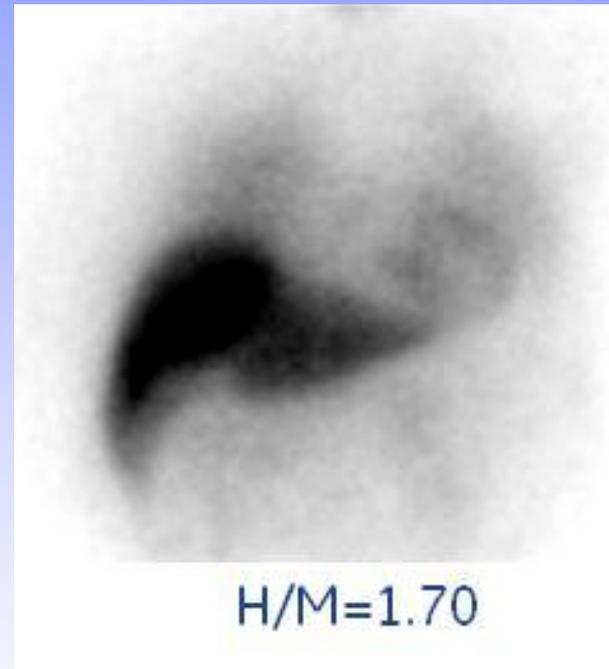
Event: None

Can Sympathetic Innervation Imaging Help in Patient Selection for ICD?

PATIENTS AT RISK

LVEF > 35%

High Clinical Risk: NSVT, Symptoms, Large Perfusion Defect

H/M < 1.6

H/M ≥ 1.6

?

ICD

NO ICD

LVEF ≤ 35%

H/M < 1.6

H/M ≥ 1.6, < 2% arrh. events/yr

ICD

Is ICD cost-effective?