mIBG Imaging Clinical Studies … 2010

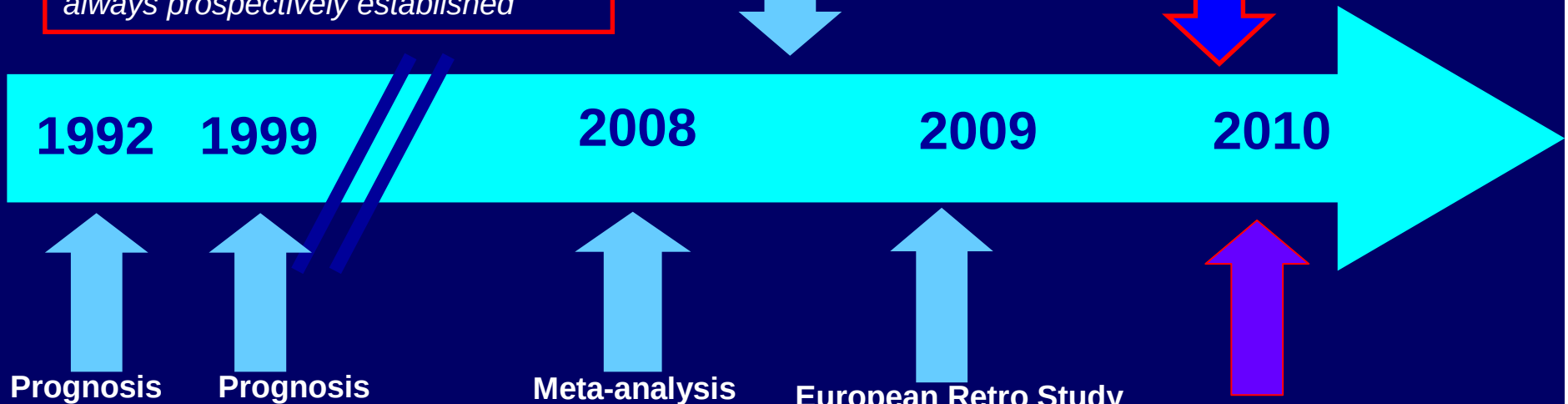
More than 250 publications…

But…

Single-centre, small number of patients

No standardised protocols

Diagnostic criteria and endpoints not always prospectively established



Prognosis Merlet et al J Nucl Med

Prognosis Merlet et al J Nucl Med

Meta-analysis Verberne et al European Heart

European Retro Study Agostini et al EJNMMI

Prognosis Manrique et al, EJNMMI

ADMIRE-HF, prognosis

JACC

Boogers, ICD

JACC

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

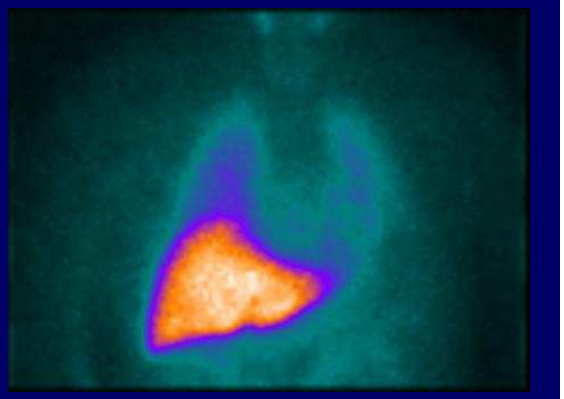
Arnold F. Jacobson, MD, PhD,* Roxy Senior, MD,† Manuel D. Cerqueira, MD,‡
Nathan D. Wong, PhD,§ Gregory S. Thomas, MD, MPH,§ Victor A. Lopez, BS,§
Denis Agostini, MD, PhD,‖ Fred Weiland, MD,¶ Harish Chandna, MD,# Jagat Narula, MD, PhD,§
on behalf of the ADMIRE-HF Investigators

Princeton, New Jersey; London, United Kingdom; Cleveland, Ohio; Irvine, California; Caen, France; Roseville, California; and Victoria, Texas

AdreView™ IOBENGUANE (^{123}I) INJECTION

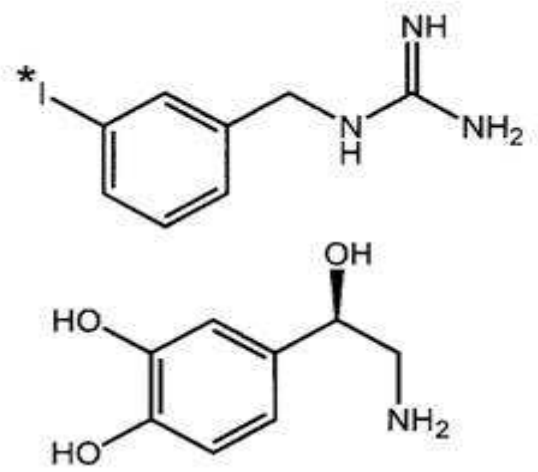
New Risk Stratification Evidence from the ADMIRE-HF Study

Pr Denis Agostini
MD - PhD
CAEN- FRANCE
- Bordeaux 2010 -

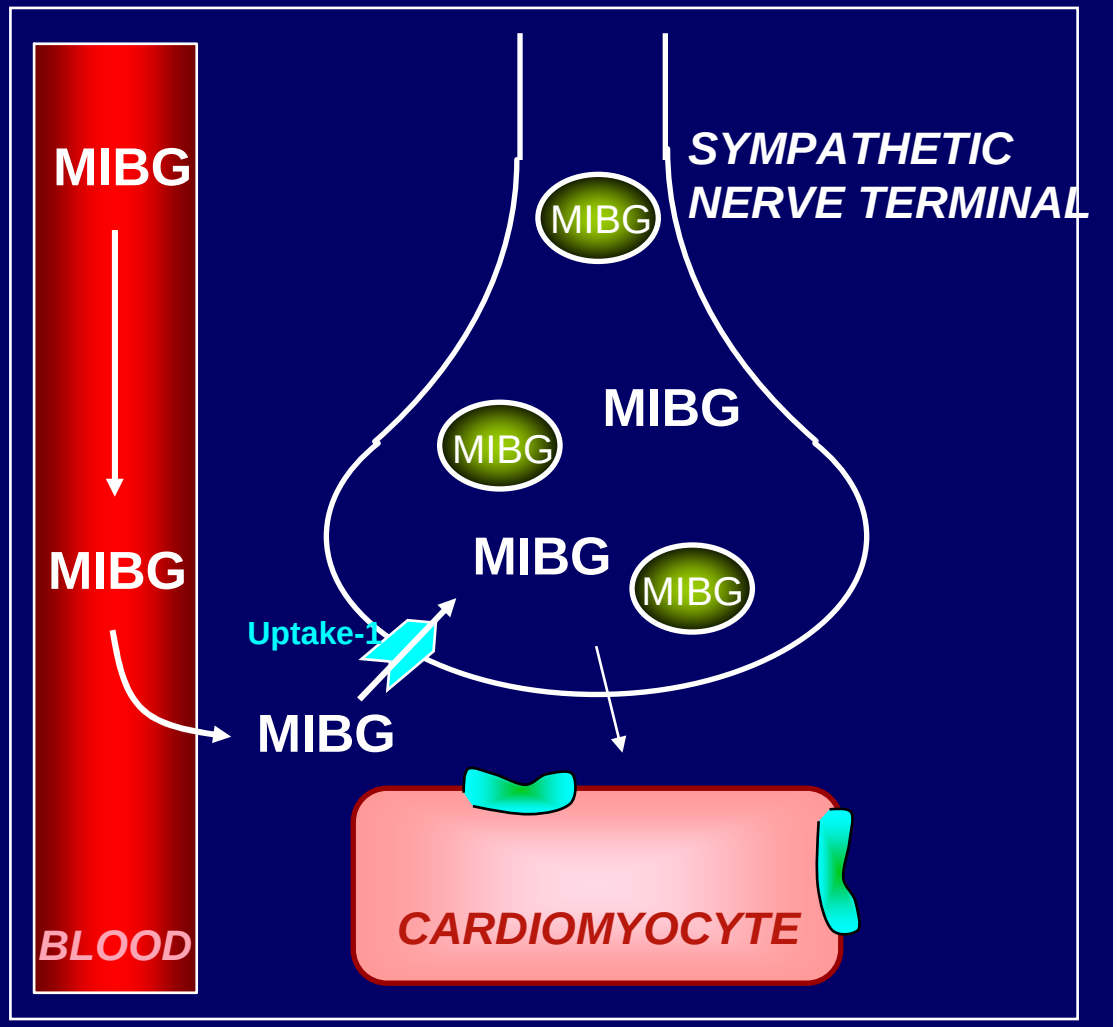


Tracing Presynaptic Sympathetic Innervation by MIBG Imaging

^{123}I-METAIODOBENZYL-GUANIDINE (MIBG)



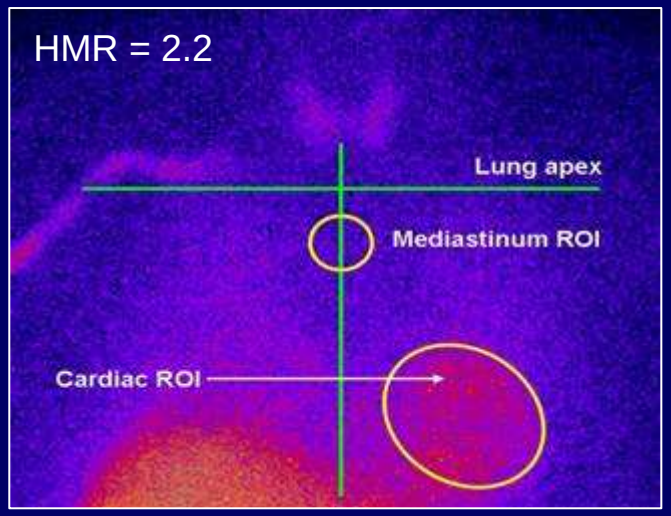
NOREPINEPHRINE



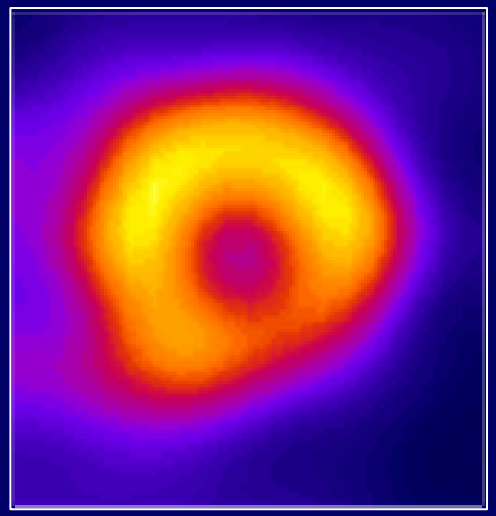
123-I Metaiodobenzylguanidine (123-I MIBG) Imaging

Normal MIBG uptake

PLANAR IMAGING

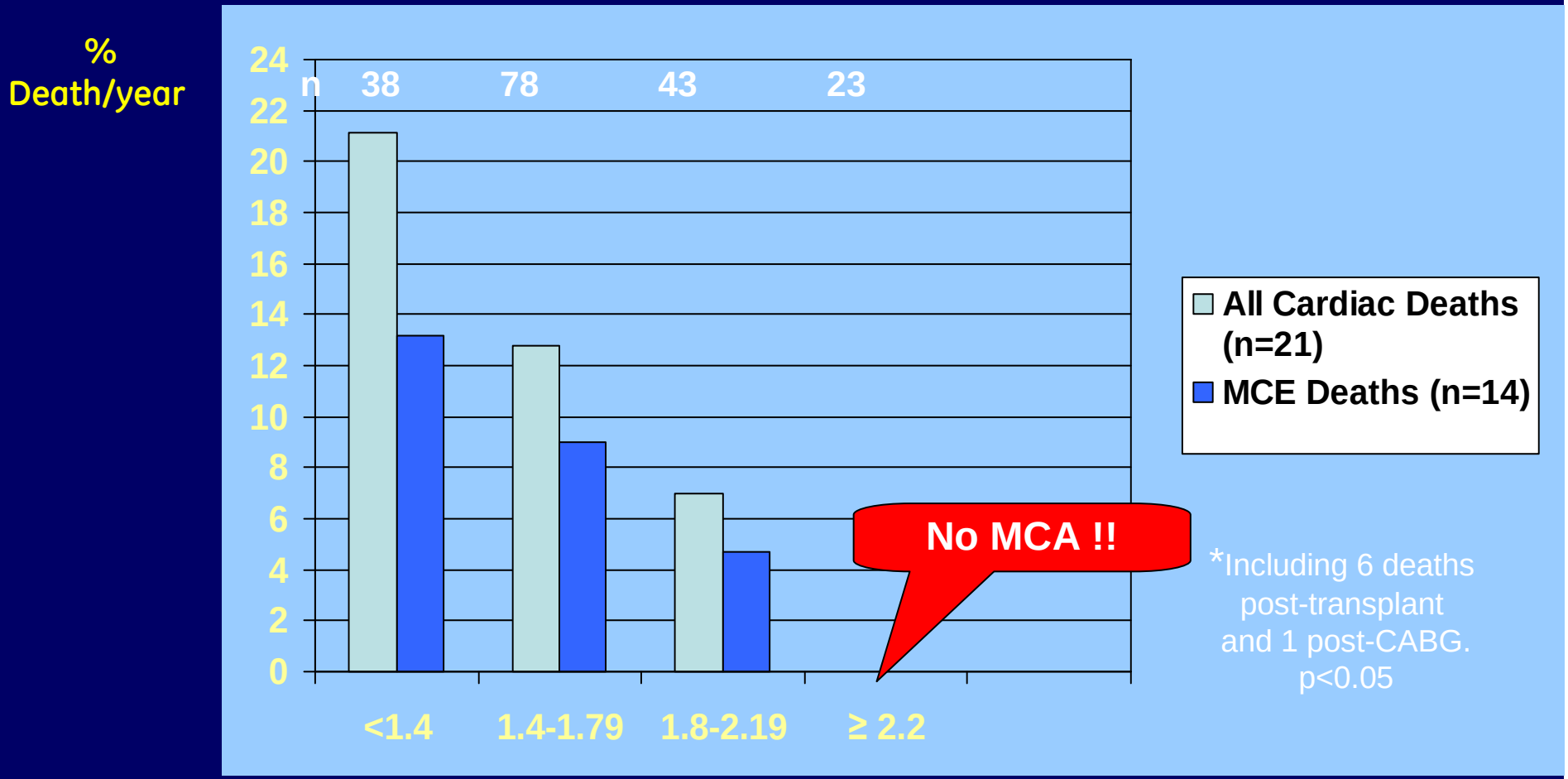


SPECT IMAGING



Agostini et al EJNMI 2009
Flotats et al EJNMI 2010

MIBG imaging and Patients NYHA II-III, LVEF ≤ 35% (n=182) : retrospective study



Agostini et al EJNMMI 2008

ADMIRE-HF patients Characteristics

NYHA II/III - 83% class II, 17% class III

Ischaemic and non-ischaemic heart failure - 66% ischaemic, 34% non-isch.

LVEF ≤35%

Mean LVEF: 27% (range 5-35%)

Guidelines-based management including diuretic, statin (lipid reducer),

β -blockers, ACE inhibitors*, ARBs**, ARAs*** (Antihypertensive)

Mean age: 62.4 years

386 subjects had ICDs - 185 at baseline, 201 over course of study

*ACE inhibitors: Angiotensin Converting Enzyme Inhibitors
**ARB: Angiotensin Receptor Blockers
***ARA: Aldosterone Receptor Antagonist

ADMIRE-HF objective

Primary objective

- To demonstrate the prognostic value of the H/M ratio of AdreView for identifying subjects at higher risk of an adverse cardiac event

Secondary objectives

- To quantify the risks for adverse cardiac events due to heart failure and arrhythmias
- To assess myocardial sympathetic innervation H/M ratio as a continuous variable

ADMIRE-HF endpoints

Composite primary endpoint

- Occurrence of any of the following 3 categories of adverse cardiac events
- Heart failure progression, arrhythmia and cardiac death
- Defined by the time to first event in relation to the H/M ratio

Secondary endpoint

- Any secondary event following a first event of heart failure progression or arrhythmia
- Defined by the time to secondary event for all unique events in relation to H/M ratio

ADMIRE-HF finding

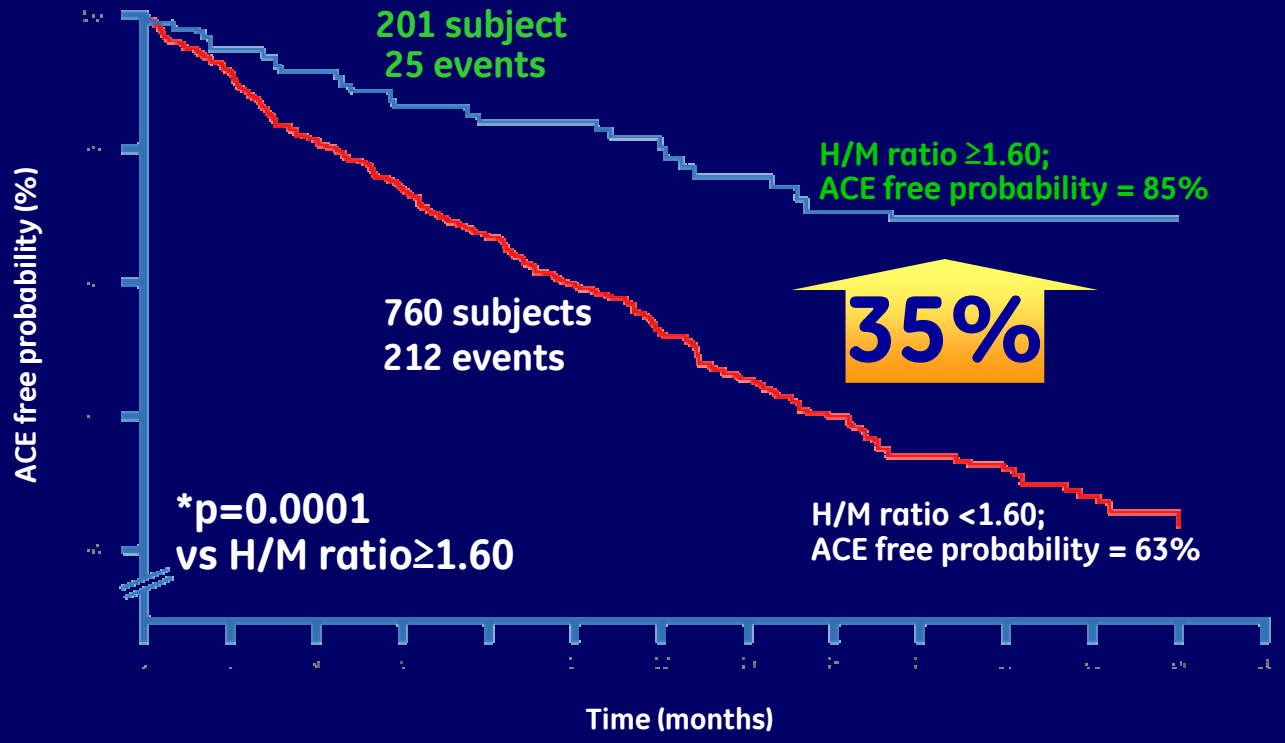
ADMIRE-HF supports a cut-off value for stratifying the risk of an adverse cardiac event

H/M ratio ≥1.6 – low risk

H/M ratio <1.6 – high risk

Kaplan-Meier estimates of *ACE* free probability H/M ratio

237 subjects had an adverse cardiac event on primary analysis



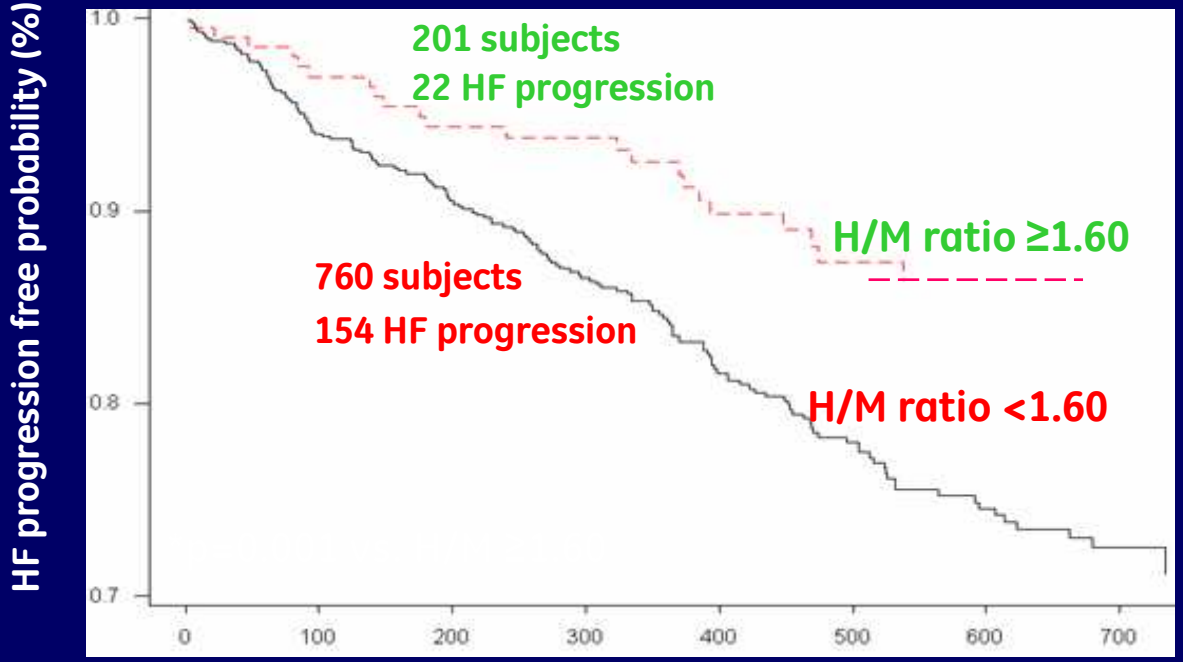
Separation from groups is evident within the first two months

35% greater probability of not experiencing an adverse cardiac event for patients with an H/M ratio ≥1.6 vs. those with H/M ratio <1.6

AdreView: additional prognostic value for adverse cardiac event risk

Kaplan-Meier estimates of *HF progression* free probability H/M ratio

176 patients had heart failure progression on secondary analysis



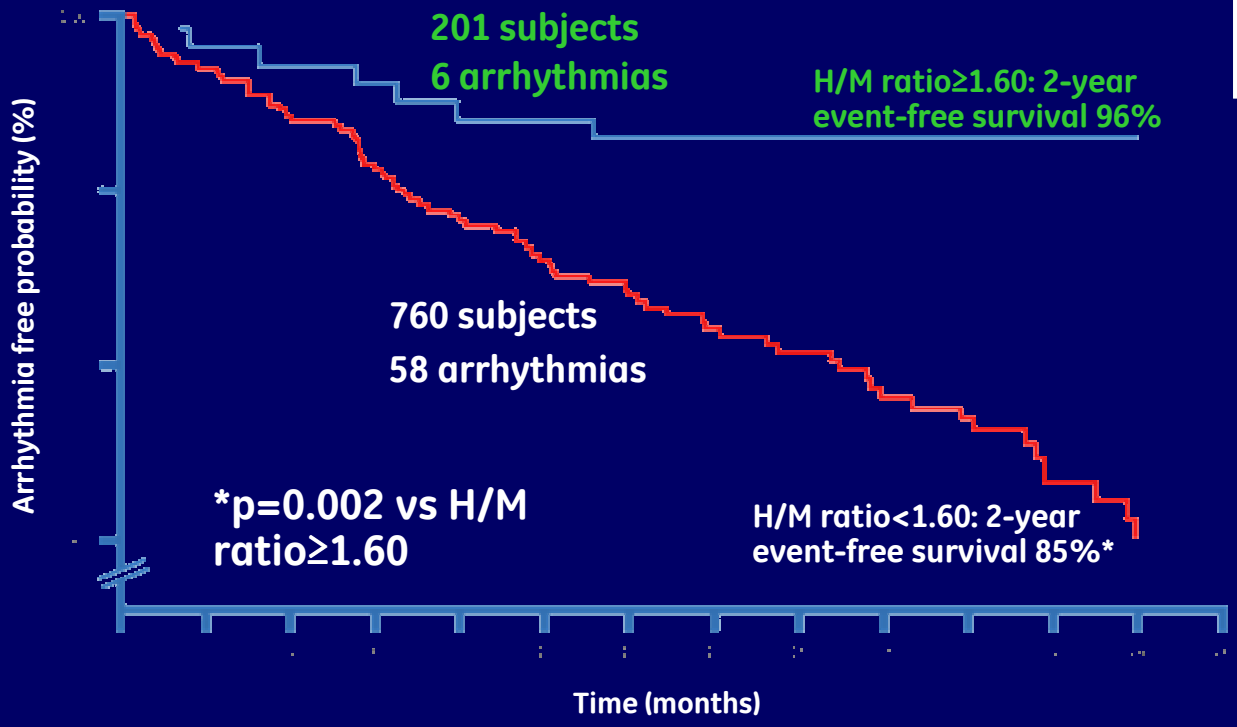
Greater probability of heart failure progression for patients with an H/M ratio <1.6 vs. those with H/M ratio ≥1.6[18]

AdreView: proven prognostic value for heart failure progression[18]

Jacobson AF et al JACC 2010

Kaplan-Meier estimates of *Arrhythmia* free probability H/M ratio

64 patients had an arrhythmia on secondary analysis



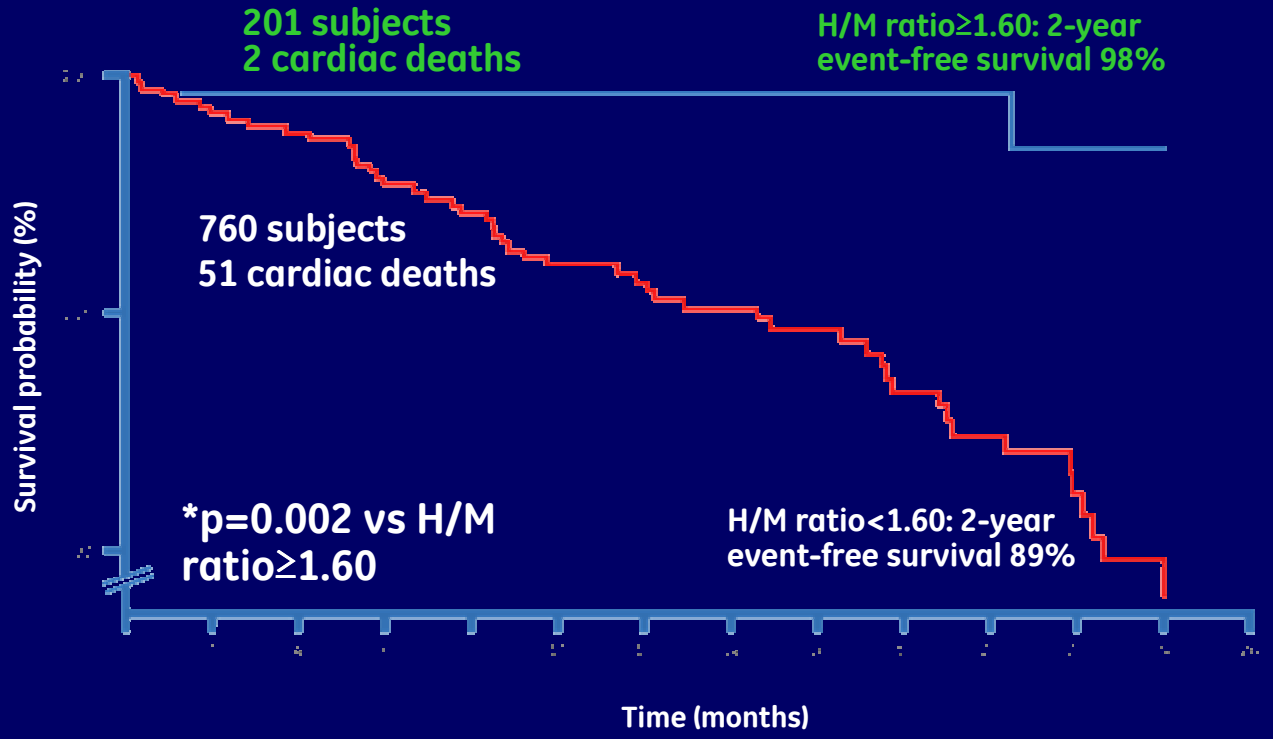
Negative Predictive Value of arrhythmia likelihood is 96%
NPV 96% for arrhythmias+++

Greater arrhythmia-free survival at 2 years for patients with H/M ratio ≥1.6 vs. those with H/M ratio of <1.6

AdreView: proven prognostic value for Arrhythmias

Kaplan-Meier estimates of *Survival* probability H/M ratio

53 patients died of cardiac death on secondary analysis



Negative Predictive Value of cardiac death likelihood is 98%

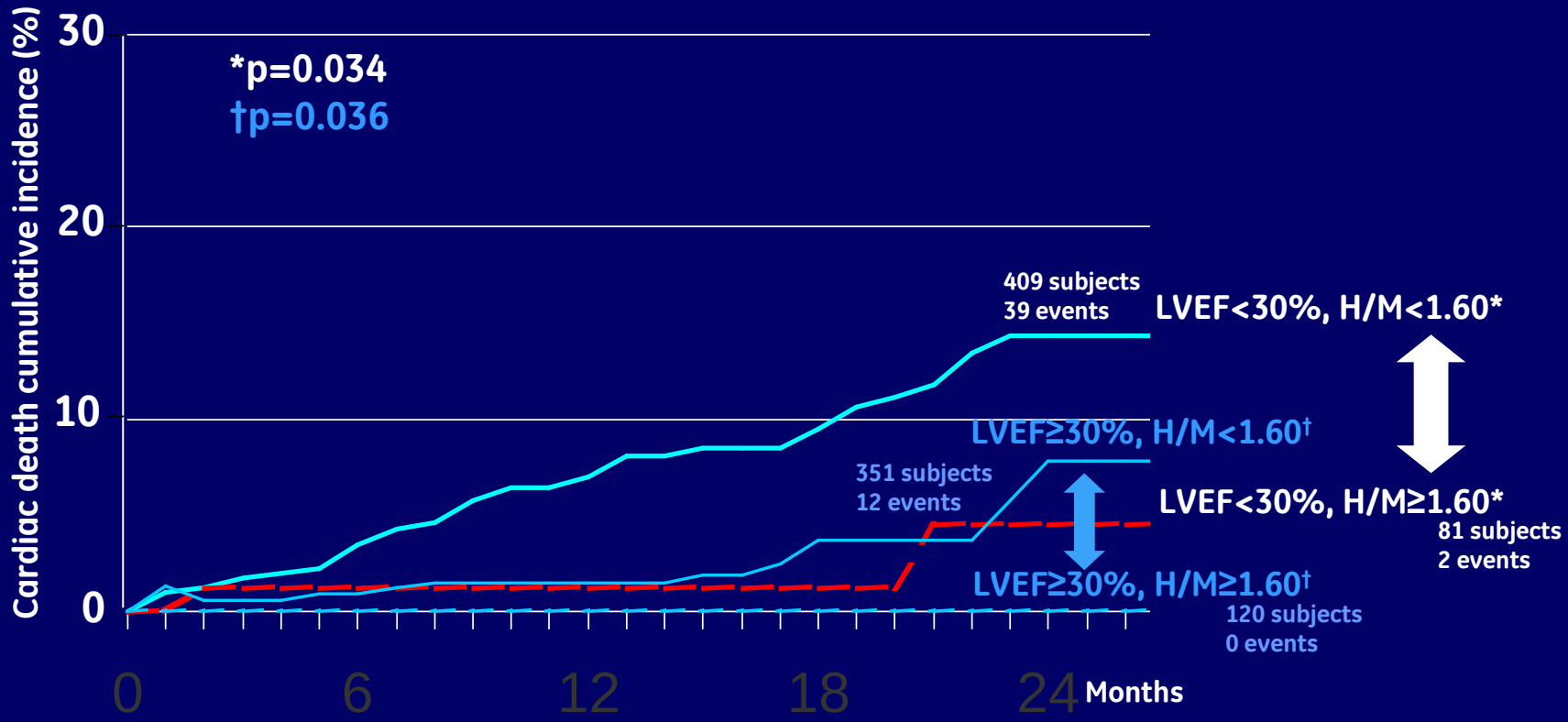
NPV 98% for cardiac death[21]

Significantly greater probability of survival at 2 years for patients with H/M ratio ≥1.6 vs. those with H/M ratio <1.6[18]

AdreView: additional prognostic value for cardiac mortality

Kaplan-Meier estimates of *Cardiac Death* incidence
MIBG vs. LVEF

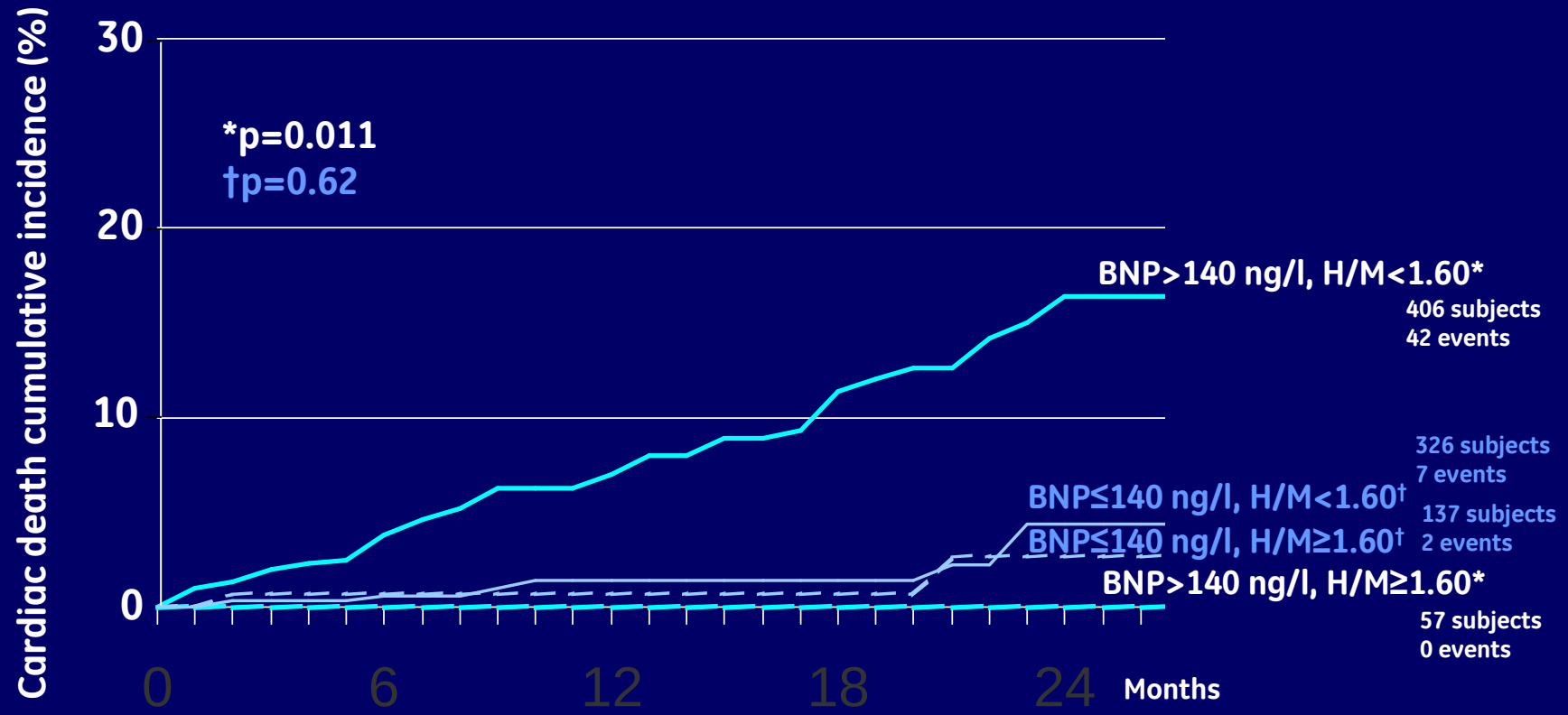
H/M ratio 1.6 ADMIRE-HF threshold vs. LVEF 30% MADIT II threshold on cardiac death



H/M ratio 1.6 threshold provides additional prognostic information over EF 30% threshold[21]

Kaplan-Meier estimates of *cardiac death* incidence
MIBG vs. BNP

H/M ratio 1.6 ADMIRE-HF threshold vs. BNP 140 ng/l threshold on cardiac death



H/M ratio 1.6 threshold provides additional prognostic information over BNP 140 ng/l t'hold

Learning from these comparisons **Adreview** vs LVEF and BNP

- **H/M ratio 1.6 threshold** provides additional prognostic information **over the MADIT II LVEF 30% threshold**

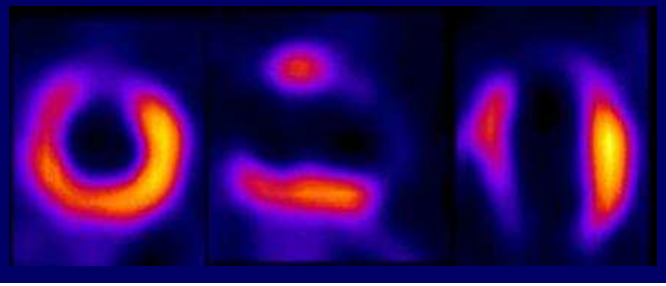
- **H/M ratio 1.6 threshold** provides additional prognostic information **over the BNP 140 ng/l threshold**

Cardiac Sympathetic Denervation Assessed With 123-Iodine Metaiodobenzylguanidine Imaging Predicts Ventricular Arrhythmias in Implantable Cardioverter-Defibrillator Patients

Mark J. Boogers, MD,*‡ C. Jan Willem Borleffs, MD,* Maureen M. Henneman, MD,*
Rutger J. van Bommel, MD,* Jan van Ramshorst, MD,* Eric Boersma, PHD,§
Petra Dibbets-Schneider, MSC,† Marcel P. Stokkel, MD, PHD,† Ernst E. van der Wall, MD, PHD,*
Martin J. Schalij, MD, PHD,* Jeroen J. Bax, MD, PHD*

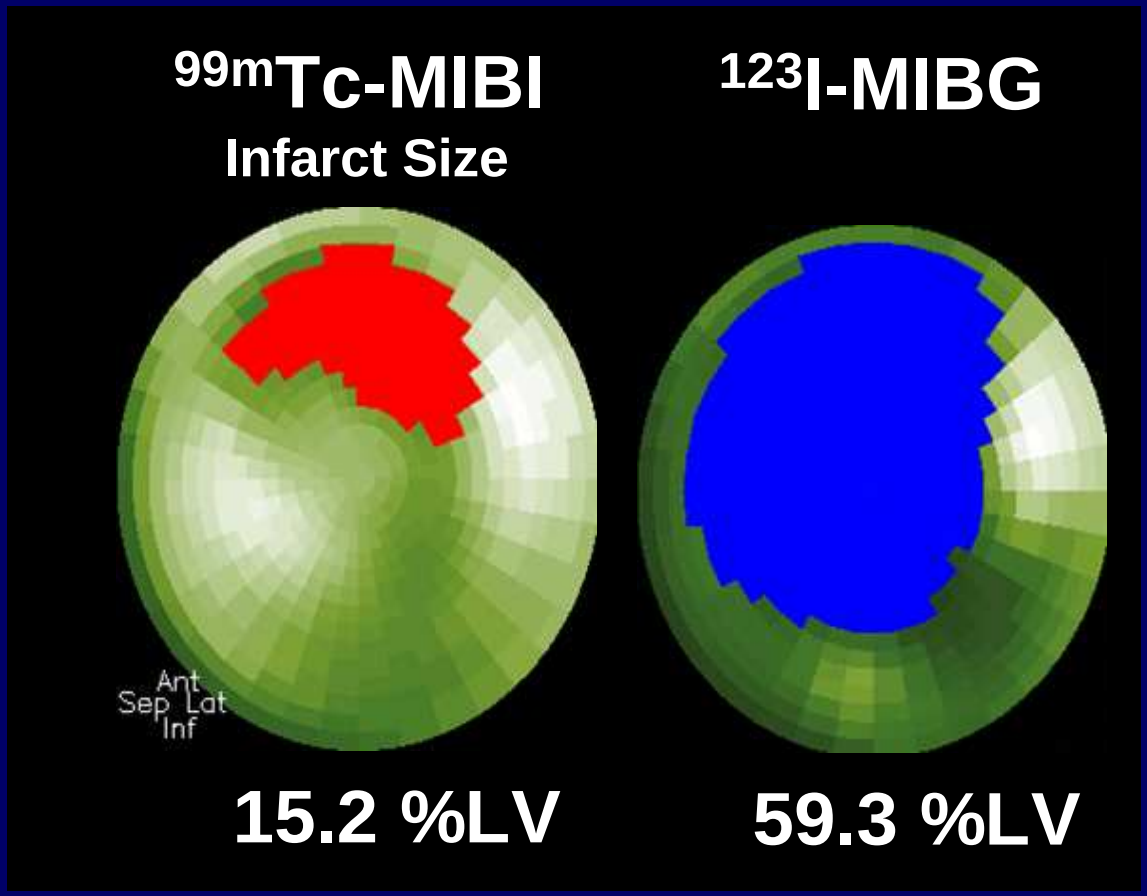
Leiden, Utrecht, and Rotterdam, the Netherlands

Could AdreView™ IOBENGUANE (123I) INJECTION be the gatekeeper for ICD implantation in primary prevention of sudden death?



Boogers et al. JACC 2010

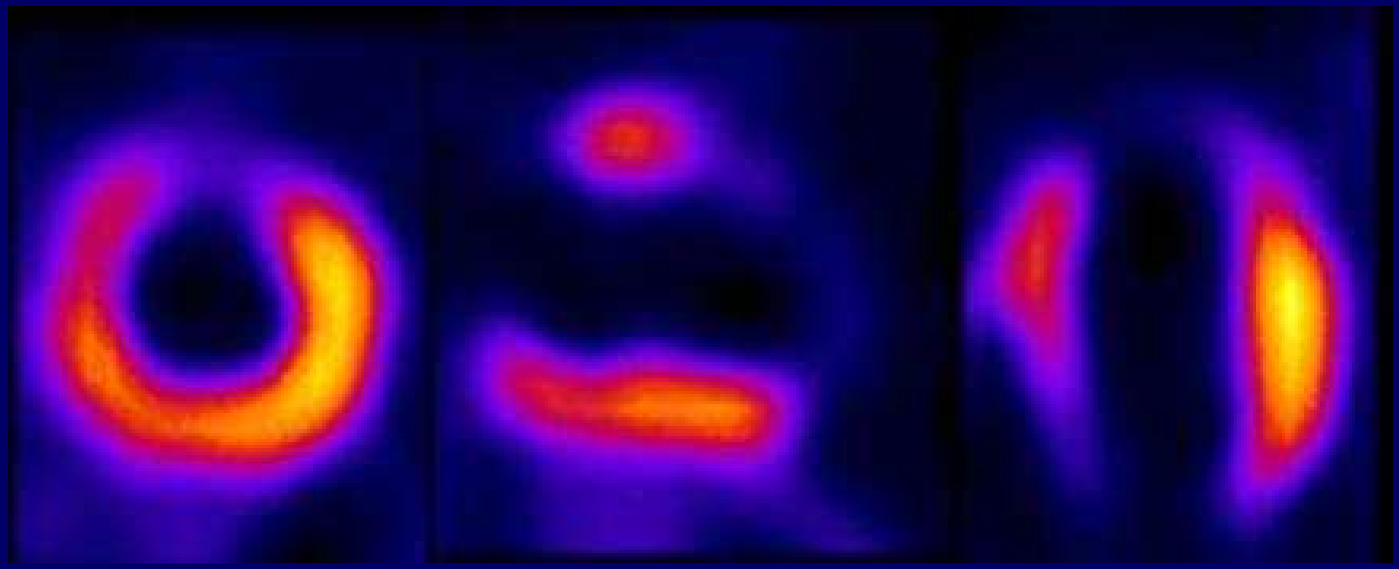
Extent of Cardiac Sympathetic Denervation is far more EXTENSIVE than the infarct size



(perfusion – MIBG mismatch)

Matsunari et al. Circ 2000

Since ventricular arrhythmias (underlying SCD) come from a localized focus in the LV, a SPECT study may be preferred since it detects regional abnormalities



Study Population (n = 116)

116 consecutive patients referred for ICD implantation based on guidelines for primary prevention

Baseline characteristics of the study population (n = 116)

Characteristics	Values
Age (yrs)	65 ± 9
Male	80 (69)
Ischemic cardiomyopathy	86 (74)
NYHA functional class	3.0 ± 0.5
LVEF (%)	27 ± 8

Endpoints

Clinical Follow-up
From ICD implantation to first documented:

Appropriate ICD therapy (prim endpoint)
ATP or ICD shock induced by ventricular tachyarrhythmia

ICD therapy + Cardiac mortality (sec endpoint)

Results at 3 yr follow-up

Primary endpoint (n = 24)

86 episodes of appropriate ICD therapy in 24 pts (21%)

Secundary endpoint (n = 32)

Composite of appropriate ICD therapy or cardiac death in 32 pts (28%)

Predictors for ICD therapy (prim endpoint) - Imaging variables

Univariable and multivariable analyses of baseline imaging variables

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
123-I MIBG imaging				
Early H/M ratio	0.43 (0.05 - 4.11)	0.5		
Late H/M ratio	0.32 (0.04 - 2.81)	0.3		
Cardiac washout rate (%)	1.03 (0.96 - 1.10)	0.5		
Early summed score	1.08 (1.03 - 1.12)	<0.01*		
Late summed score	1.15 (1.09 - 1.22)	<0.01*	1.15 (1.07 - 1.23)	<0.01*
^{99m}Tc-tetrofosmin GMPS imaging				
Summed rest score	1.02 (0.98 - 1.06)	0.4		
Summed stress score	1.03 (0.99 - 1.07)	0.2		
Summed difference score	1.07 (0.98 - 1.16)	0.13*	0.98 (0.87 - 1.11)	0.7
123-I MIBG/GMPS mismatch score	1.06 (1.02 - 1.09)	<0.01*	1.01 (0.98 - 1.04)	0.5

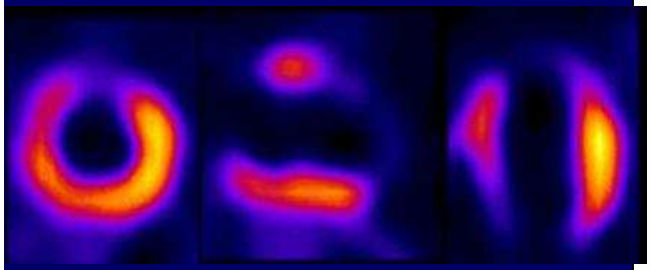
Predictors for ICD therapy or cardiac death (sec endpoint) – imaging variables

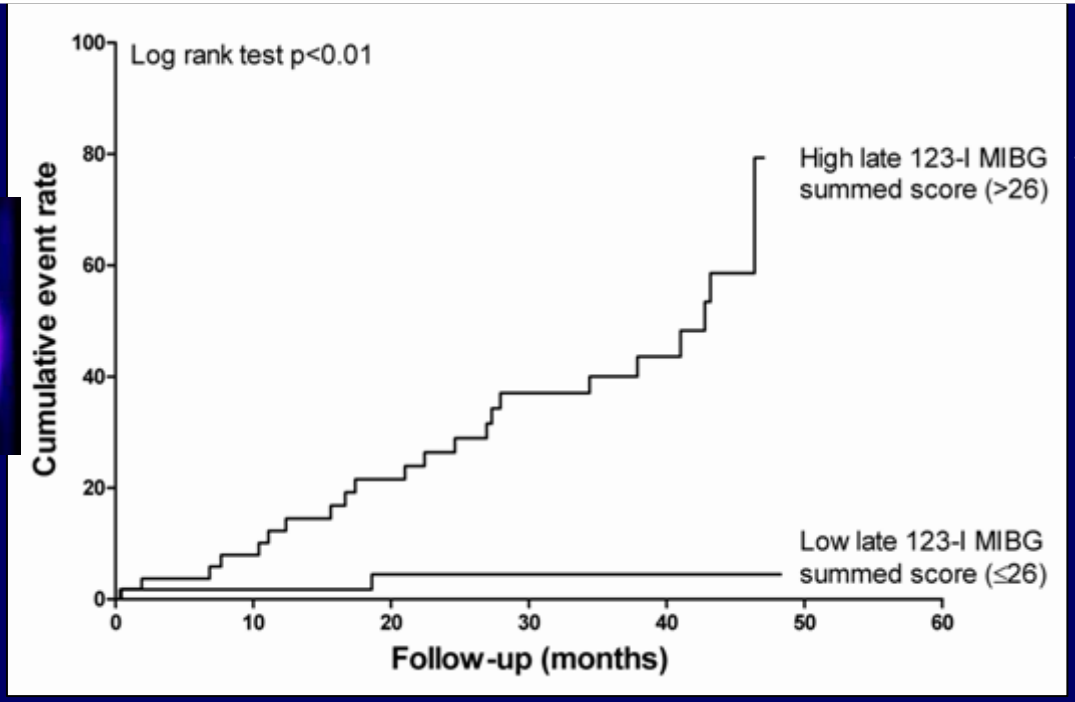
Univariable and multivariable analyses of baseline imaging variables

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
123-I MIBG imaging				
Early H/M ratio	0.30 (0.04 - 2.19)	0.2		
Late H/M ratio	0.21 (0.03 - 1.36)	0.10*	0.36 (0.03 - 4.02)	0.4
Cardiac washout rate (%)	1.04 (0.98 - 1.10)	0.2		
Early summed score	1.08 (1.04 - 1.12)	<0.01*		
Late summed score	1.13 (1.09 - 1.19)	<0.01*	1.12 (1.06 - 1.18)	<0.01**
^{99m}Tc-tetrofosmin GMPS imaging				
Summed rest score	1.02 (0.99 - 1.06)	0.3		
Summed stress score	1.02 (0.99 - 1.06)	0.2		
Summed difference score	1.03 (0.95 - 1.13)	0.5		
123-I MIBG/GMPS mismatch score	1.05 (1.02 - 1.08)	<0.01*	1.01 (0.98 - 1.04)	0.5

Cumulative event rate for ICD therapy (MIBG-SPECT)

Population divided according to median MIBG summed defect score (26)





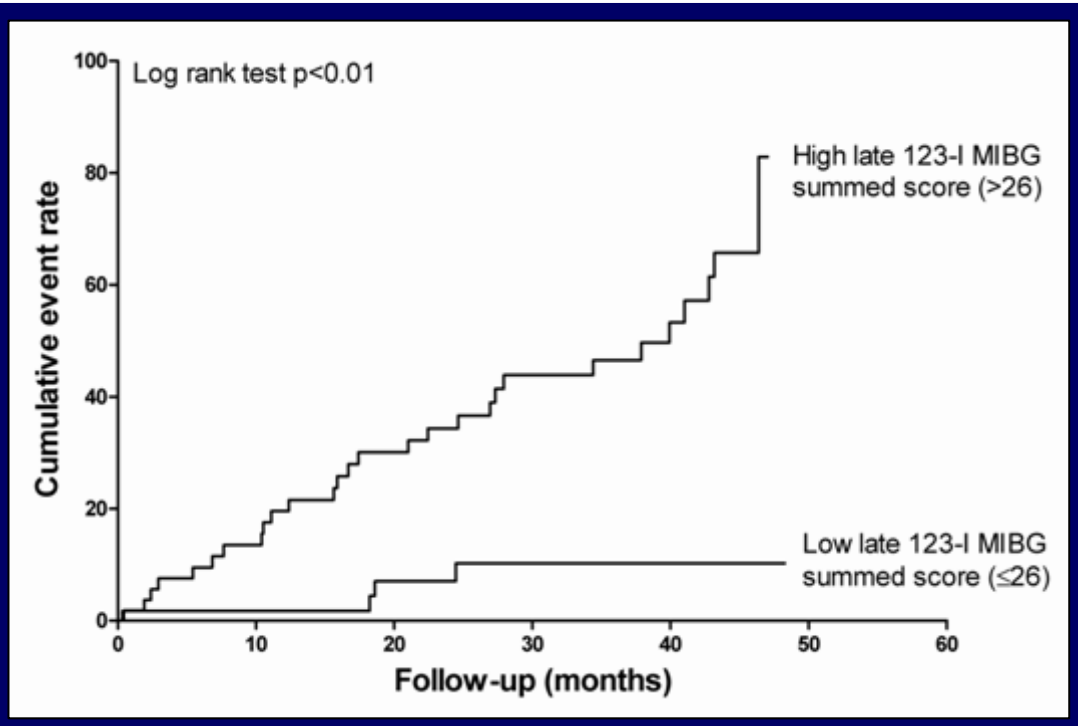
52%

5%

Cumulative event rate 52% vs. 5%
3-year follow-up data

Cumulative event rate for ICD therapy or cardiac death

Population divided according to mean MIBG summed defect score (26)



57%

10%

Cumulative event rate 57% vs. 10%
3-year follow-up data

Conclusions from the Leiden MIBG – ICD study

- Cardiac innervation with AdreView™ IOBENGUANE (^{123}I) INJECTION can be used for ICD selection in patients meeting MADIT II criteria

- A cut-off value of **26** for MIBG- SPECT (summed defect score) resulted in **95% certainty of no ICD shocks**

Case 1

Male, aged 54 years, is considered for a CRT-ICD implantation but *he does not fulfill the general criteria according to the international guidelines (LVEF <35%)*

Clinical Characteristics

Medical history: Anteroseptal myocardial infarction, LVEF 38%, heart failure NYHA II-III

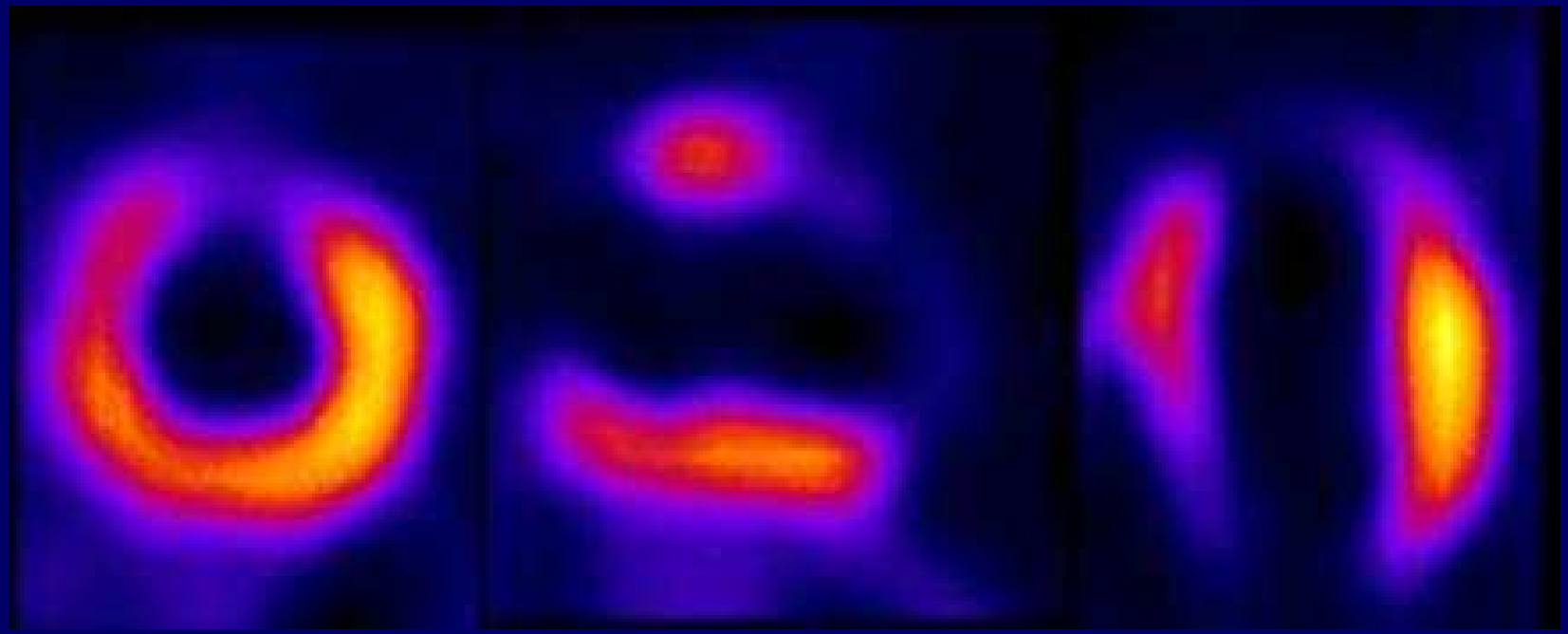
Risk profile: Ex-smoker

Perfusion SPECT: Antero-apical perfusion defect

Data and Images courtesy of Prof. Jeroen Bax – Leiden University Medical Center – The Nederlands

MIBG SPECT imaging

Short axis Vertical long axis Horizontal long axis

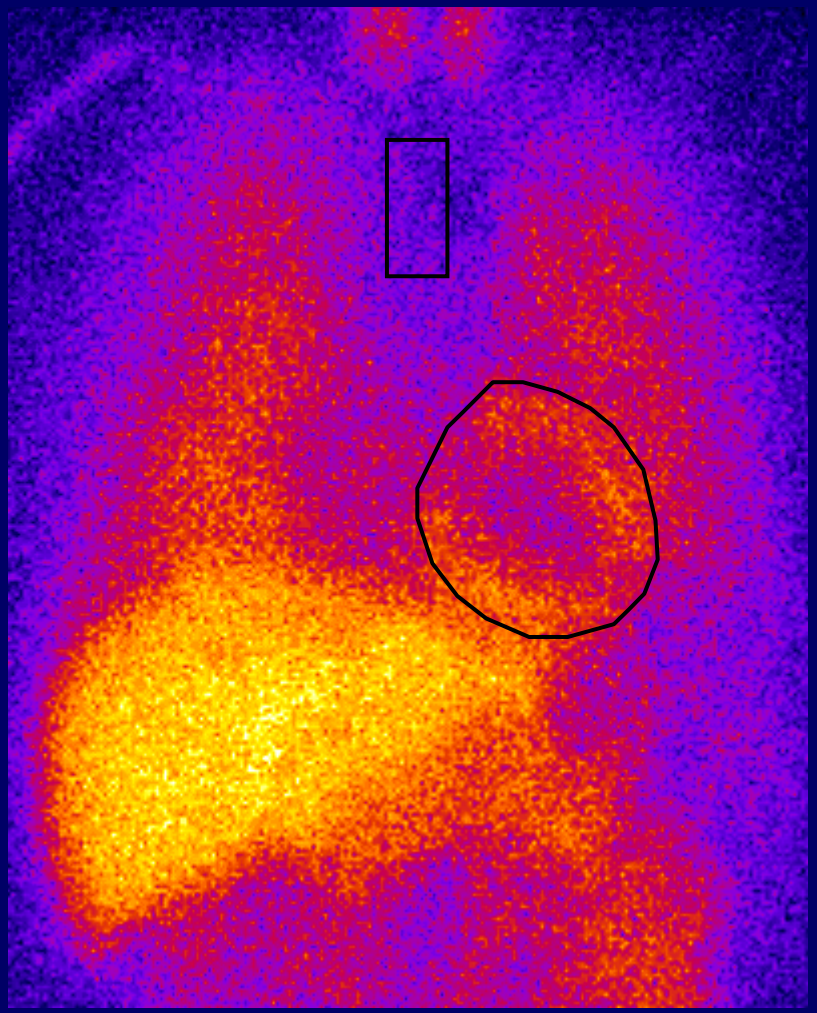


Data and Images courtesy of Prof. Jeroen Bax – Leiden University Medical Center – The Nederlands

Data and Images courtesy of Prof. Jeroen Bax – Leiden University Medical Center – The Nederlands

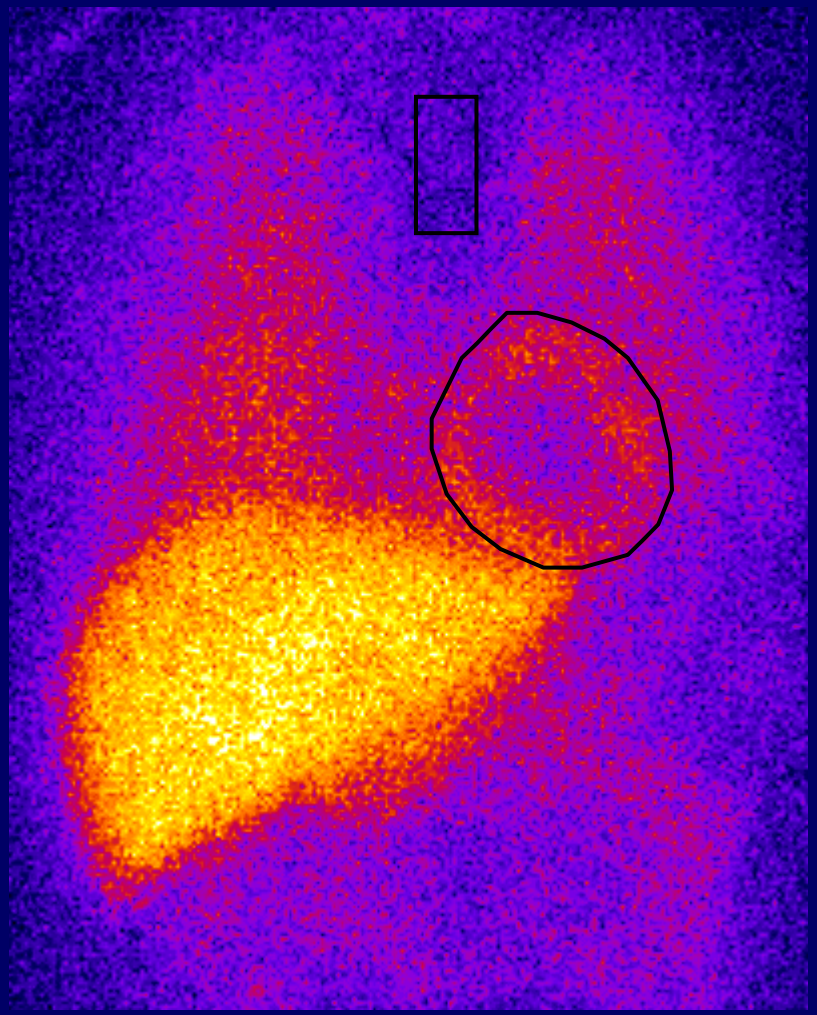
mIBG planar imaging

Early image



H/M Ratio 2.06

Late Image: 4 hours



H/M Ratio 2.07

Conclusion

The H/M ratio, wich indicates the degree of heart's denervation measured by MIBGscan ,showed that the cardiac innervation in this subject was preserved (>1.6), and helped the cardiologist to decide not to implant any CRT-ICD device

Data and Images courtesy of Prof. Jeroen Bax – Leiden University Medical Center – The Nederlands

CONCLUSION

THE GOAL IS TO.....IN 201....