

# Lessons from clinical use of MIBG in Japan

## History and perspectives

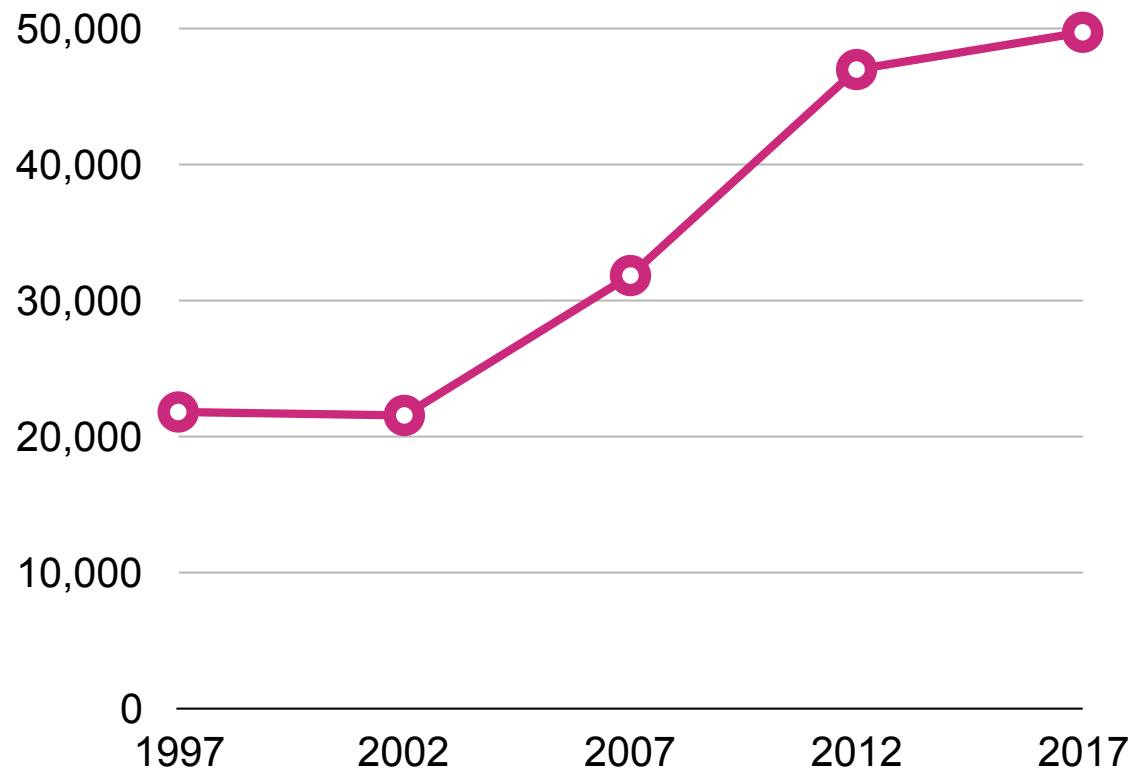
Kenichi Nakajima  
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Kanazawa University Hospital, Kanazawa  
Japan

# COI disclosure

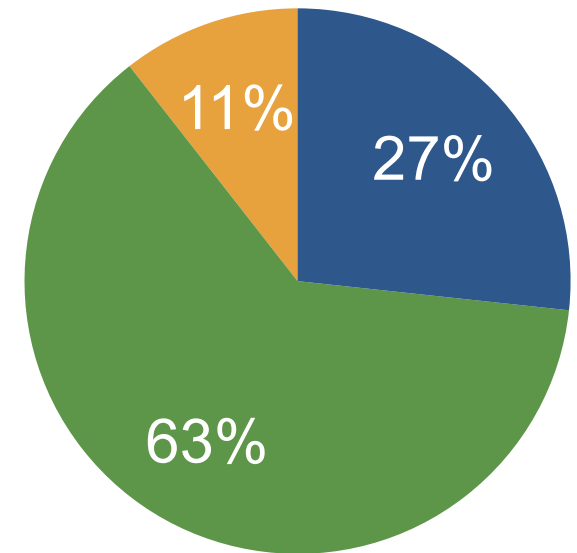
- Collaborative research work with FUJIFILM Toyama Chemical, Co. Ltd.

# $^{123}\text{I}$ -MIBG

- $^{123}\text{I}$ -MIBG approved for cardiac diseases in 1992
- Used for Lewy body disease
  - Parkinson disease 1994-
  - Dementia with Lewy bodies 2000-
- Need for standardization in multi-center study

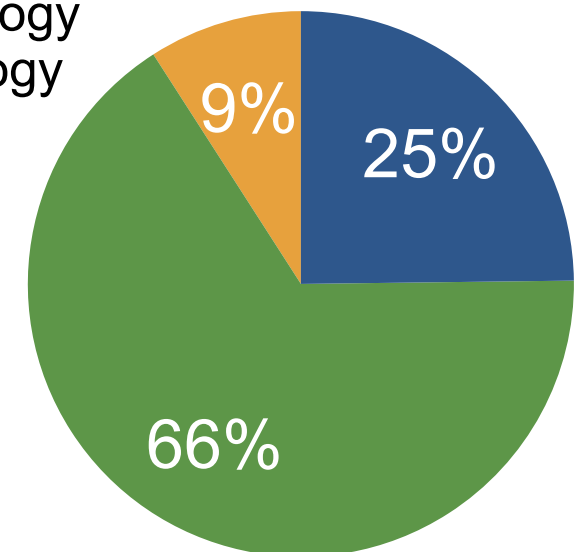


Year 2012



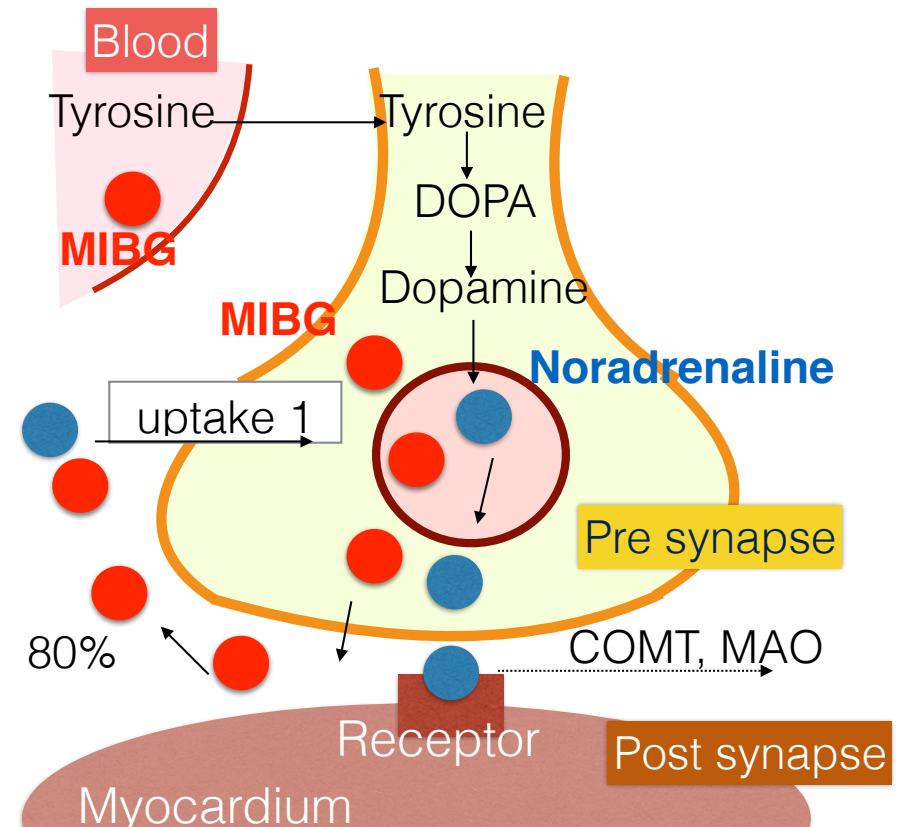
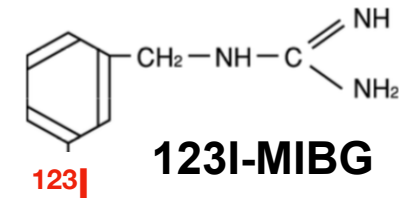
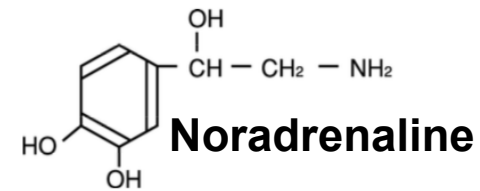
Year 2017

● Cardiology  
● Neurology  
● Oncology



# Sympathetic imaging: I-123 MIBG

- I-123 meta-iodobenzylguanidine
- Analogue of noradrenaline, guanethidine
- Shares storage and release in the sympathetic nerve terminal
- Uptake 1 mechanism
- Marker of sympathetic nerve activity and integrity





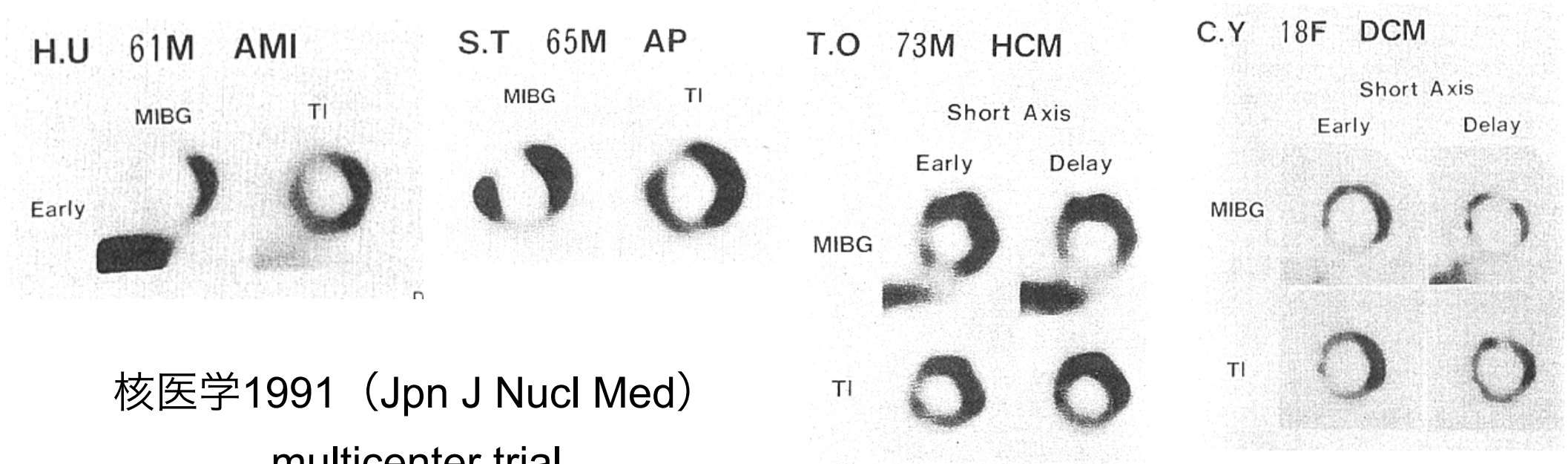
# MIBG: Approved indication in Japan (FUJIFILM Toyama Chemical Co, Ltd.)

- Cardiac scintigraphy
  - 15 min. after injection, 3-6 hours after injection
  - 111 MBq
- Tumor scintigraphy
  - Neuroblastoma
    - 400 MBq for children (200~400MBq/1.7m<sup>2</sup>)
    - 24 (-48h) after injection
  - Pheochromocytoma
    - 111 MBq (max. 222 MBq)
    - 24 h (6, 48 h)



# Initial experience of $^{123}\text{I}$ -MIBG

- 822 patients, Comparison with  $^{201}\text{Tl}$
- Effective findings in 95% of the patients
- Side effects in 0.4% (nausea, vascular pain during injection)
- Myocardial infarction: denervation in infarct region
- Angina pectoris and unstable angina: mismatch between MIBG and TI is frequently seen.
- Cardiomyopathy: high incidence of MIBG defect



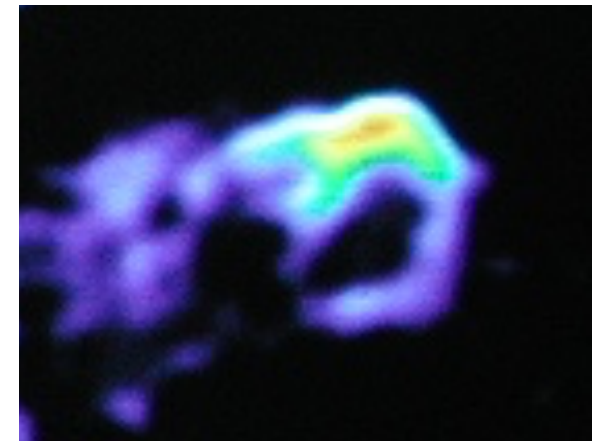
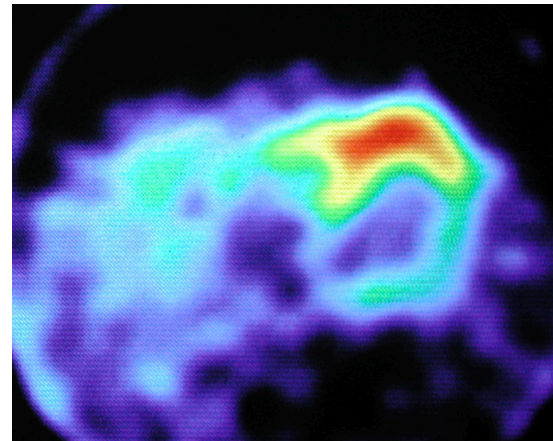
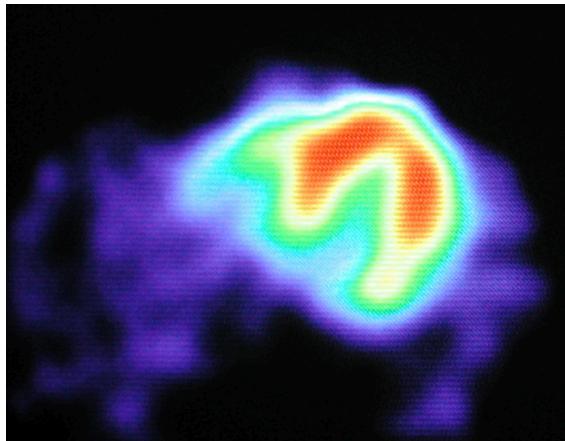
# TI-201 and I-123 MIBG in Japan during clinical trial, 1989 (Kanazawa University Hospital)

$^{201}\text{Tl}$

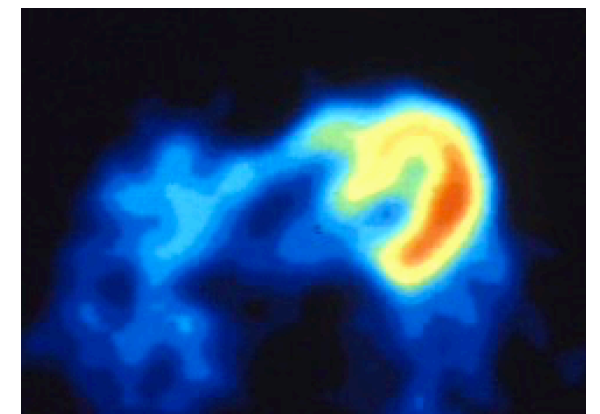
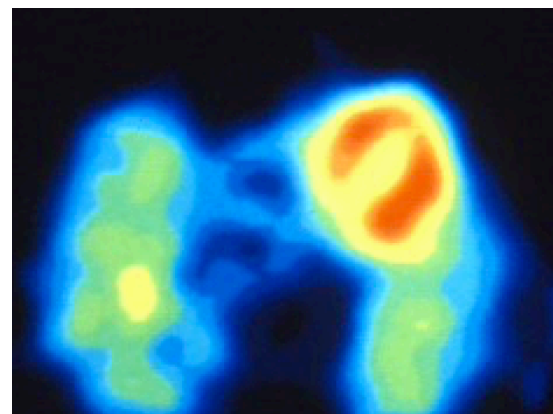
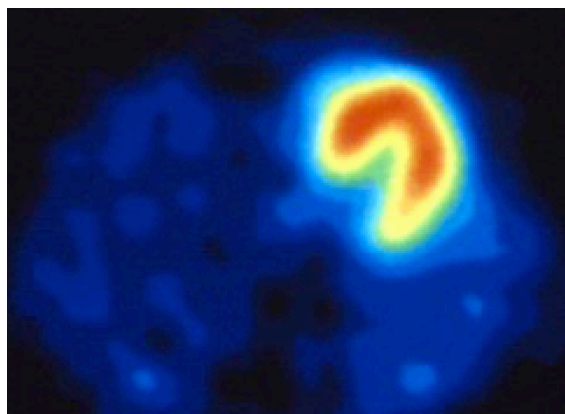
$^{123}\text{I}$ -mIBG 20 min

3 h

AMI after  
PCI



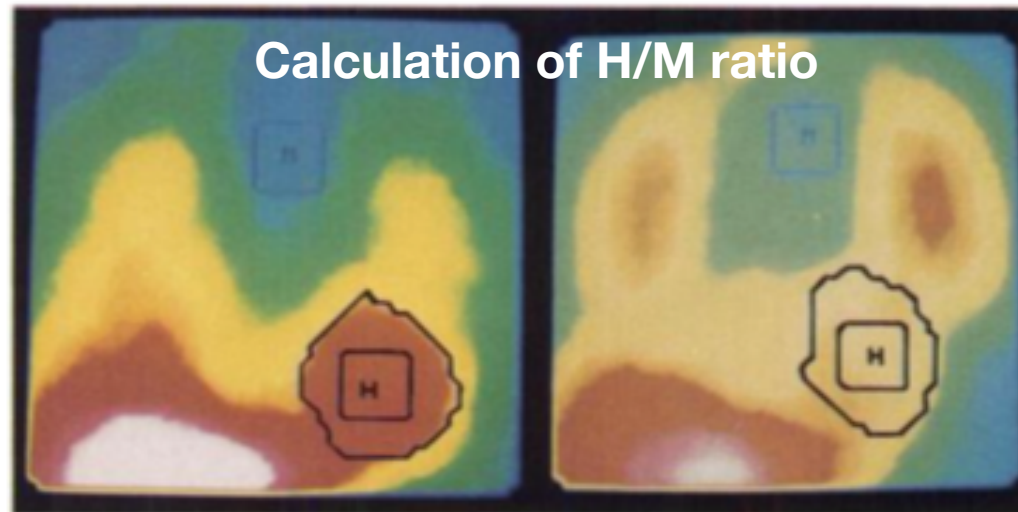
HCM



Shimazu: Dual-headed camera

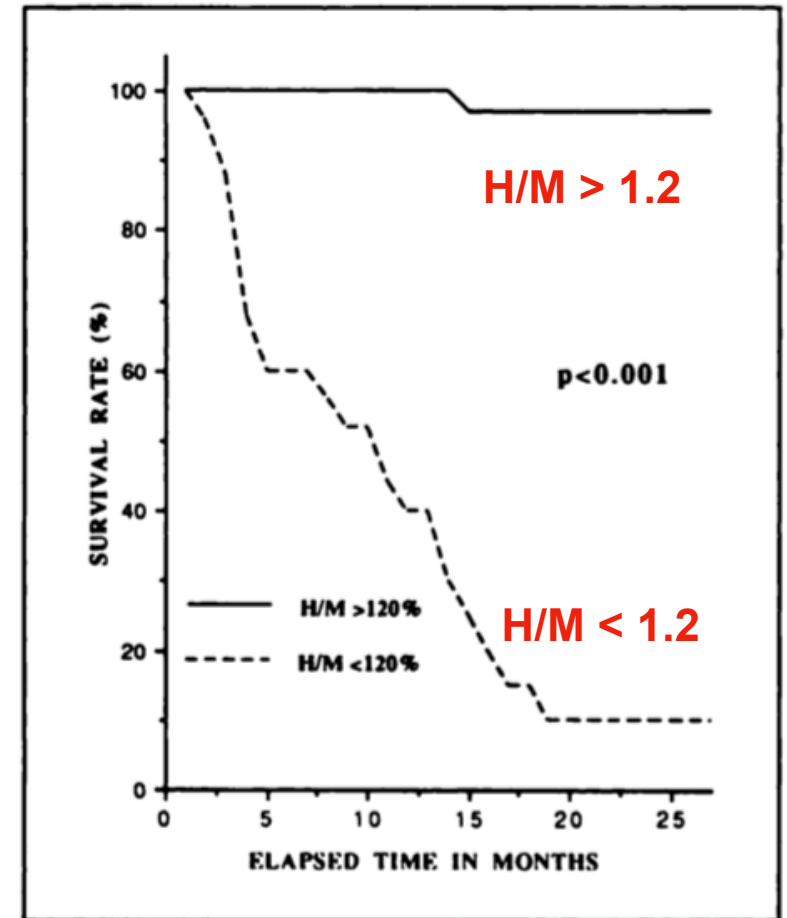
# Application to heart failure

- Merlet et al. JNM 1991 Prognostic value
- MIBG uptake was more potent to predict survival than other indices

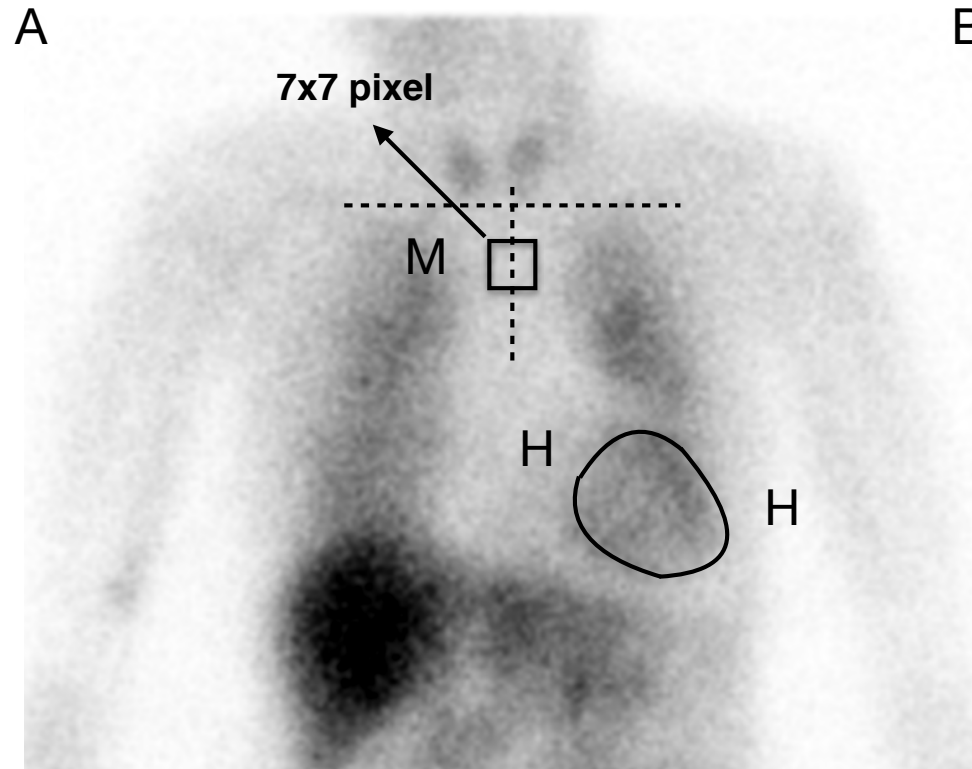


Predictor of life duration

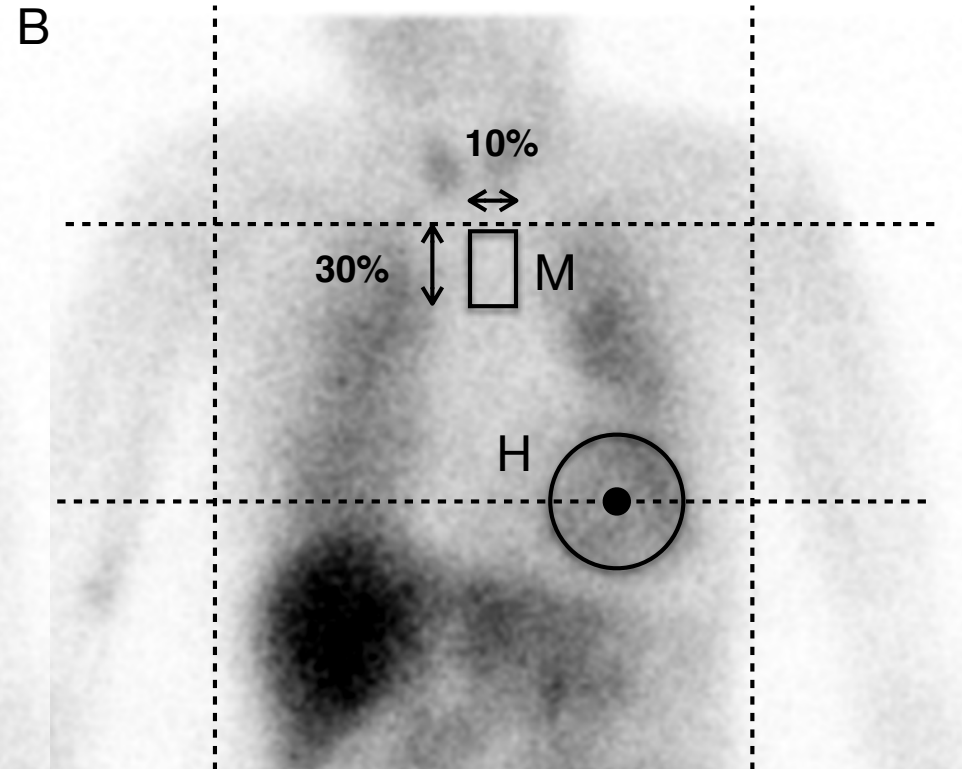
|           | Fisher | p       |
|-----------|--------|---------|
| MIBG HMR  | 37     | <0.0001 |
| LVEF      | 6      | 0.0098  |
| X-ray CTR | 6      | 0.0013  |



# Regions of Interest: too simple but most widely used



Soman et al. J Nucl Cardiol 2015

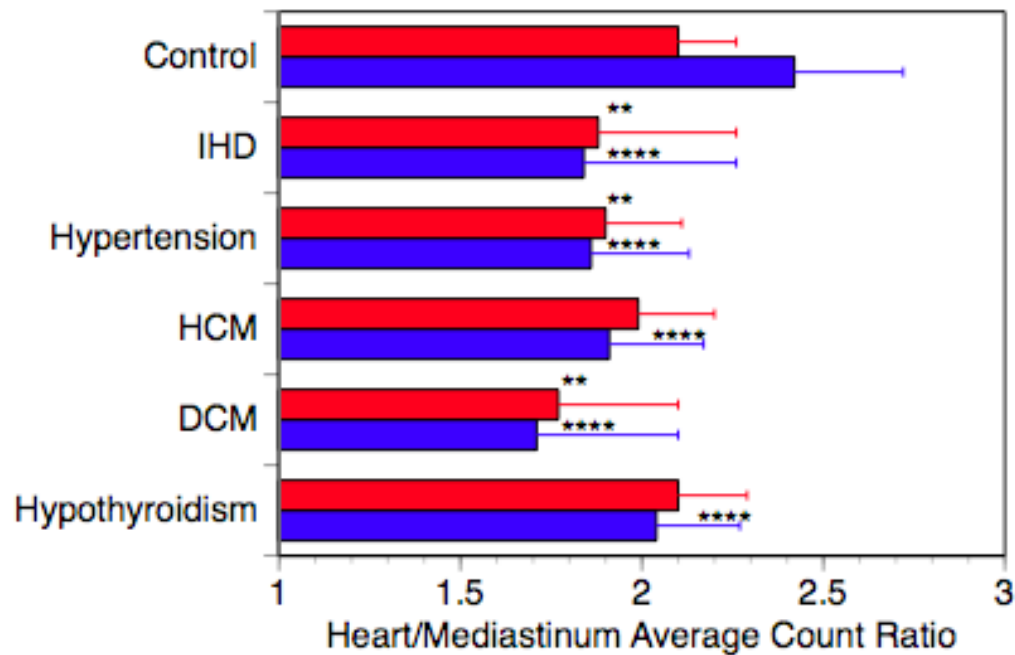


Okuda, Nakajima , et al. J  
Nucl Cardiol. 2011;18(1):82-9

semiautomatic, smartMIBG

# MIBG H/M ratios in various cardiac diseases

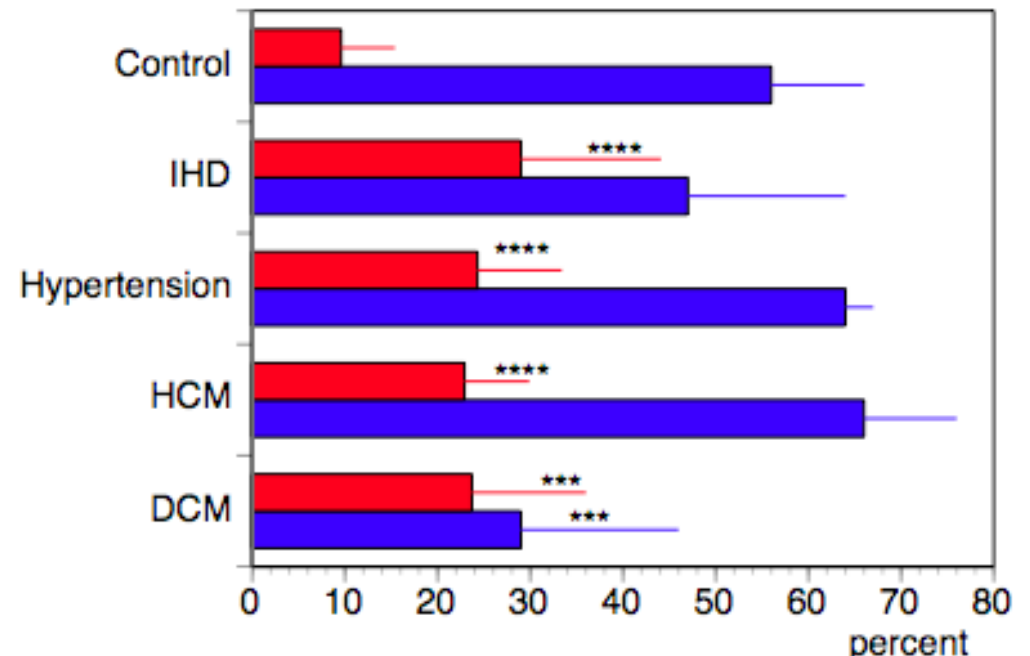
## Early and late HMRs



■ Early H/M ■ Delayed H/M

\*p<0.05, \*\*p<0.01, \*\*\*p<0.005, \*\*\*\*p<0.001, vs control

## Washout rate and LVEF



\*p<0.05, \*\*p<0.01, \*\*\*p<0.005, \*\*\*\*p<0.001, vs control

■ Washout Rate(%) ■ Ejection Fraction(%)



# MIBG H/M ratio in various cardiac diseases

Normal values (LEHR)

|                                 | Early                | Late                 |
|---------------------------------|----------------------|----------------------|
| H/M ratio                       | $2.10 \pm 0.16$      | $2.42 \pm 0.30$      |
| Total heart count/Injected dose | $1.48 \pm 0.30$<br>% | $1.39 \pm 0.35$<br>% |
| Washout rate                    | $9.6 \pm 5.8\%$      |                      |

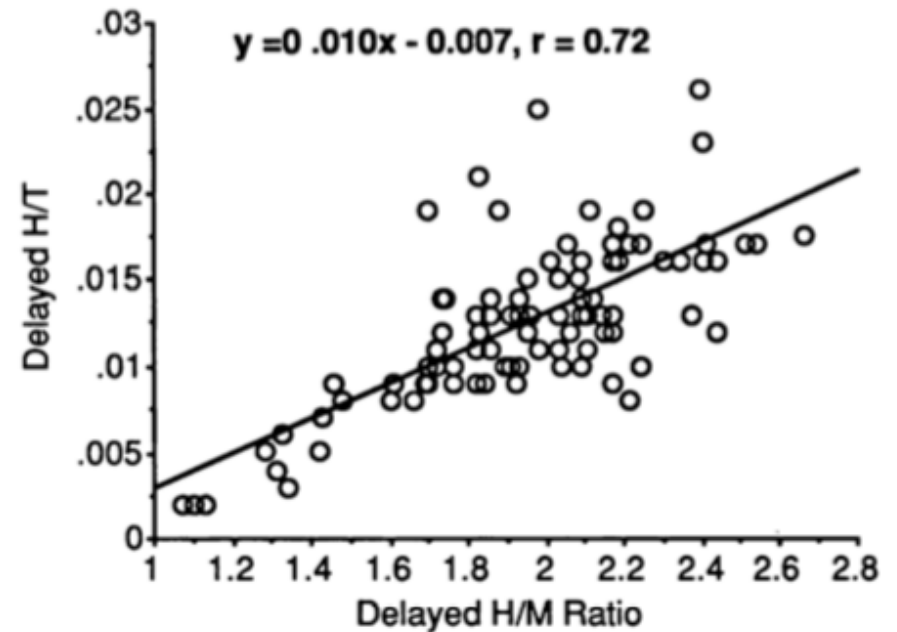


Fig. 2. Correlation between delayed heart-to-mediastinal average count ratio (H/M) and total heart count-to-total injected activity ratio (H/T).

**After standardization MEGP collimator condition, lower limit of H/M ratio is 2.2 for both early and late imaging**

# Clinical applications of 123I-mIBG imaging in various diseases reported by Japanese groups in Japanese Clinical Studies

| Clinical applications |                                       |                                                                                                   |
|-----------------------|---------------------------------------|---------------------------------------------------------------------------------------------------|
| Cardiac               | Atrial fibrillation                   | Contributions to clinical practice<br>Part of JCS guidelines<br>Included in diagnostic guidelines |
|                       | Athlete's heart                       |                                                                                                   |
|                       | Brugada syndrome                      |                                                                                                   |
|                       | Familial amyloidosis polyneuropathy   |                                                                                                   |
|                       | Hypertrophic cardiomyopathy           |                                                                                                   |
|                       | Takotsubo cardiomyopathy              |                                                                                                   |
|                       | Vasospastic angina                    |                                                                                                   |
| Non cardiac           | Chronic obstructive pulmonary disease | Movement society guidelines<br><br>JSNM draft guidelines for radiotherapy with 131I-mIBG          |
|                       | Diabetes mellitus                     |                                                                                                   |
|                       | Hypothyroidism                        |                                                                                                   |
|                       | Liver cirrhosis                       |                                                                                                   |
|                       | Renal failure                         |                                                                                                   |
|                       | Sleep apnea syndrome                  |                                                                                                   |
|                       | Systemic sclerosis                    |                                                                                                   |
|                       | Parkinson's disease                   |                                                                                                   |
|                       | Dementia with Lewy bodies             |                                                                                                   |
| USA                   | Heart failure: ICD                    | Potential to help determine ICD implantation indication                                           |

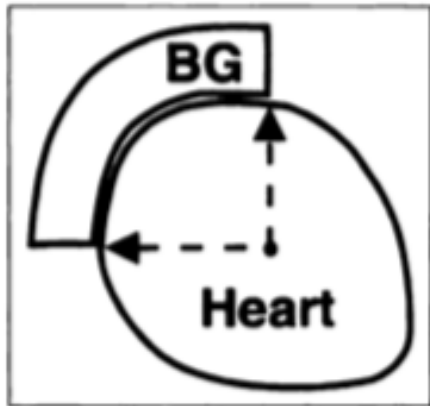


# Approval and reimbursement of <sup>123</sup>I-mIBG in Japan and USA

|                                                    | Japan                                                                                                                                                                                                                     | US                                                        |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Approval date                                      | November <b>1992</b><br>March 2012—additional indication                                                                                                                                                                  | March <b>2013</b>                                         |
| Approved diseases or conditions                    | Evaluation of cardiac function (November 1992)<br>Any cardiac disease<br>(additional approval—<br>March <b>2012</b> , reimbursement by social insurance for<br><b>Parkinson's disease and dementia with Lewy bodies</b> ) | NYHA Class II to III heart failure<br>with LVEF ≤ 35%     |
| Clinical role of <sup>123</sup> I mIBG by approval | JMHLW (Jp Ministry of Health, Labour and Welfare):<br>not specifically addressed                                                                                                                                          | FDA: lower 1- and 2-year mortality risks for HMR ≥1.6     |
| Suppliers                                          | FUJIFILM RI Pharma (FUJIFILM Toyama Chemical at present)                                                                                                                                                                  | GE healthcare                                             |
| Reimbursement Payment in 2018                      | \$612                                                                                                                                                                                                                     | \$1202.60                                                 |
| Tracer cost                                        | 3 mCi (111 MBq) \$398                                                                                                                                                                                                     | 10 mCi (370 MBq)<br>approximate range:<br>\$2,200–\$3,900 |

# MIBG clearance in patients with renal failure

- 21 patients with CRF vs. 11 controls



|                                     | Control         | Patients        |        |
|-------------------------------------|-----------------|-----------------|--------|
| Myocardial uptake 150 min (%/pixel) | 0.0053 ± 0.0016 | 0.0038 ± 0.0030 | 0.14   |
| <b>MIBG Clearance (%)</b>           | 7 ± 11          | 44 ± 23         | <0.001 |
| <b>Norepinephrine (pg/mL)</b>       | 324 ± 144       | 673 ± 620       | 0.02   |

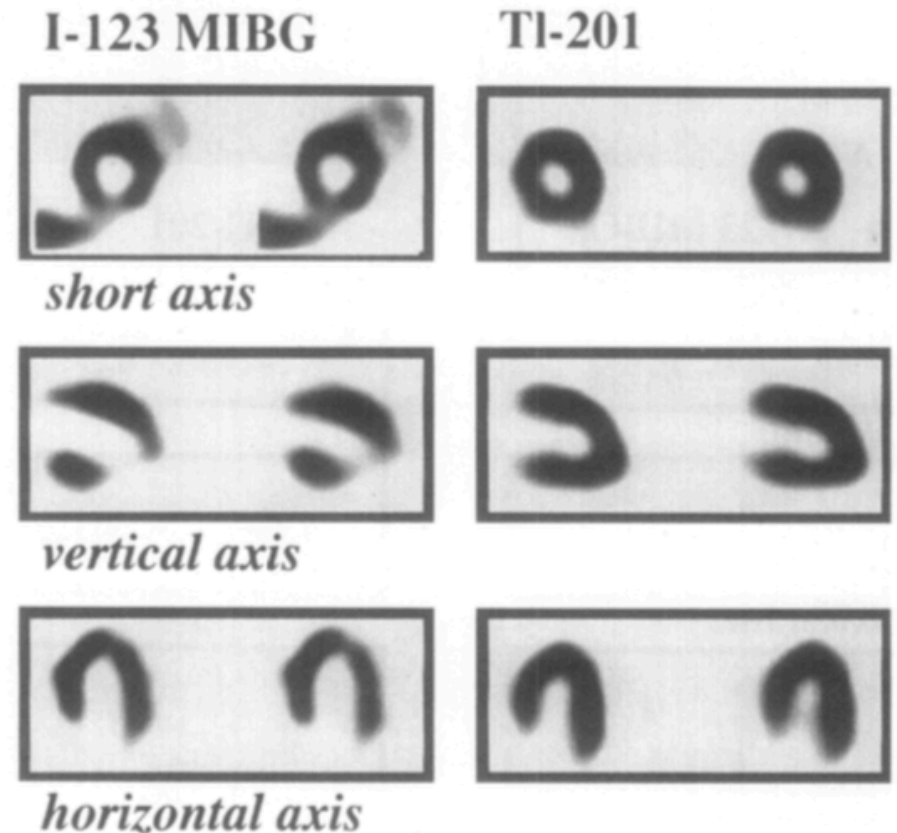
MU150/p myocardial uptake 150min after injection per pixel

**MIBG clearance** from the heart was rapid in patients with **chronic renal failure on dialysis** particularly those with LV dysfunction or hypertrophy, suggesting cardiac **sympathetic overactivity** in these patients

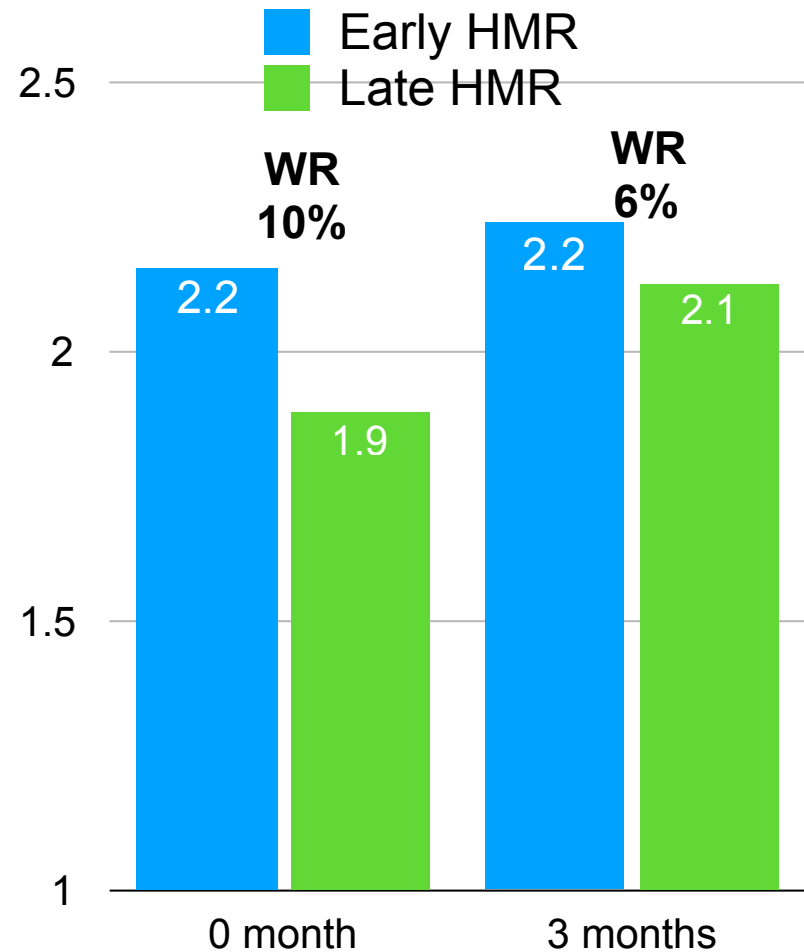
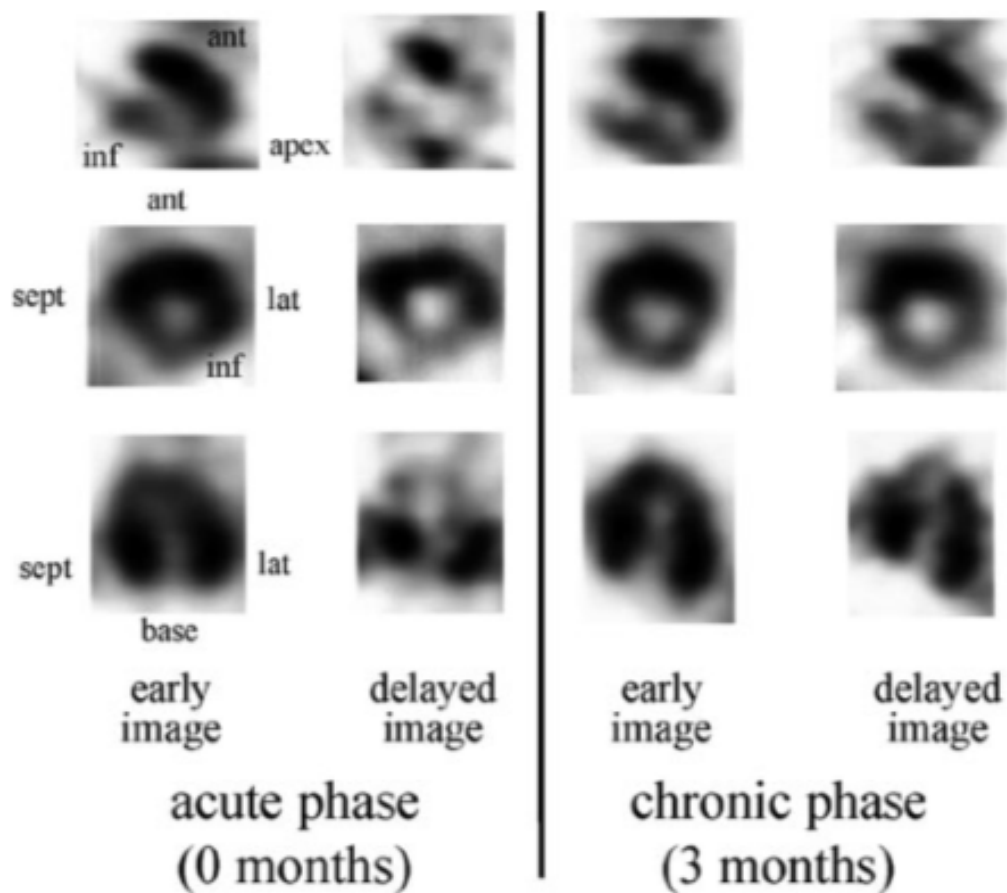
# Regional myocardial dysinnervation in patients with coronary vasospasm

- 15 patients with VSA, 14 patients with coronary stenosis >90%
- Sensitivity 92%, specificity 88% for vasospasm

|           | No. of patients | MIBG defect | TI defect | Mismatch |
|-----------|-----------------|-------------|-----------|----------|
| Vasospasm | 15              | <b>15</b>   | 0         | 15/15    |
| Stenosis  | 14              | <b>14</b>   | <b>14</b> | 0/14     |
| Control   | 8               | 0           | 0         | 0/8      |

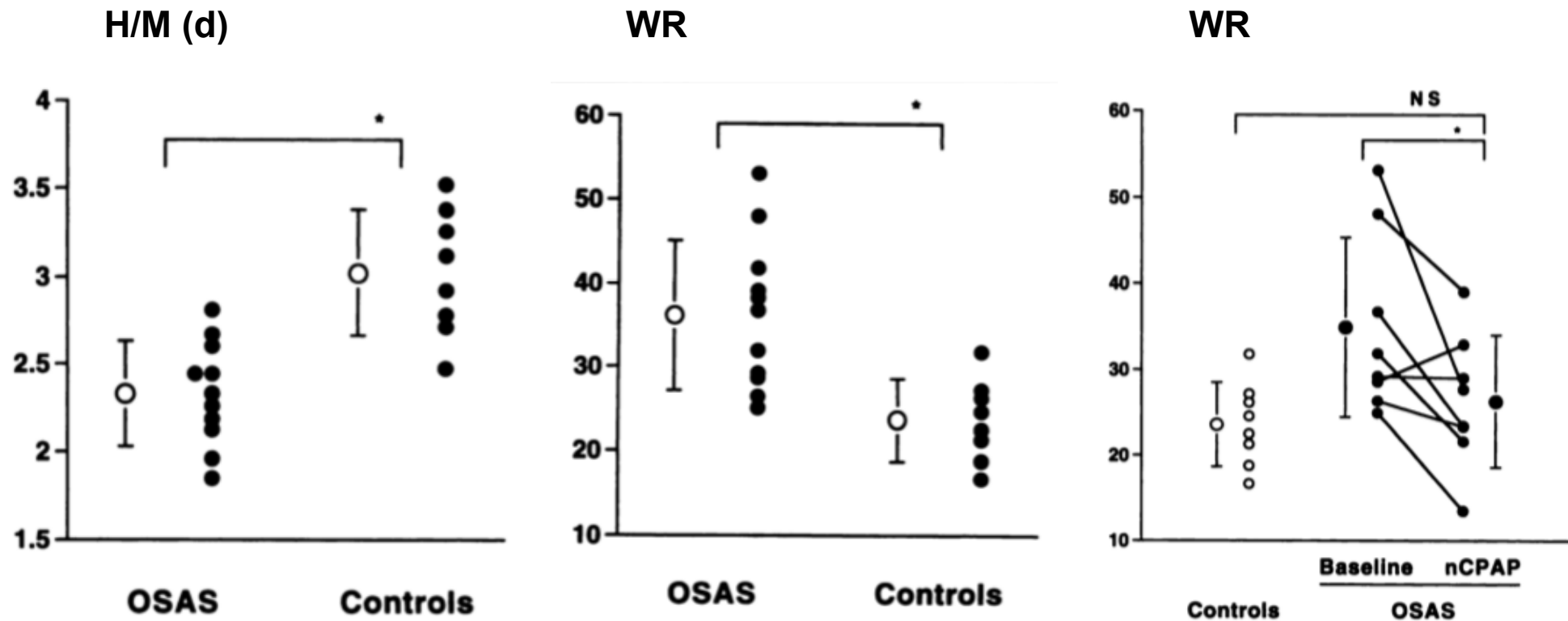


# Takotsubo syndrome



# MIBG in sleep apnea syndrome

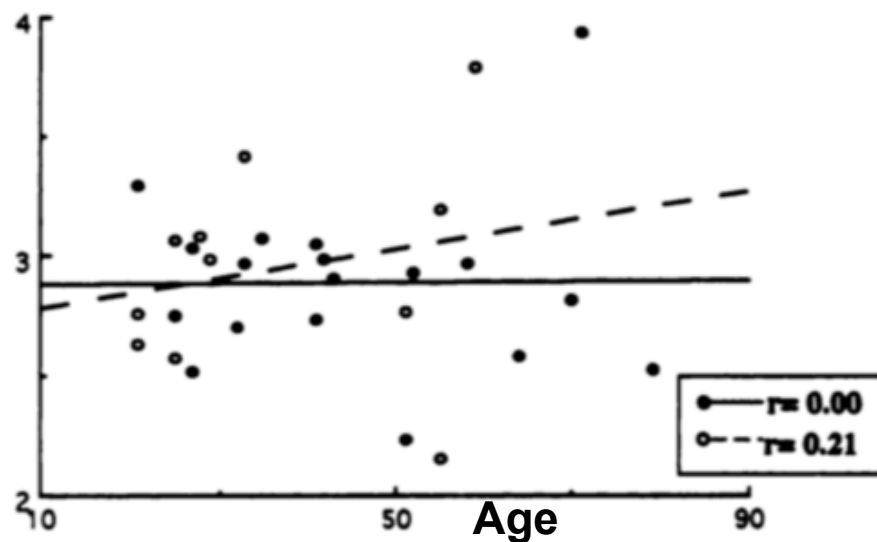
- 11 patients with sleep apnea syndrome and 8 age-matched controls
- H/M correlated to severity of SAS



# Age and gender difference

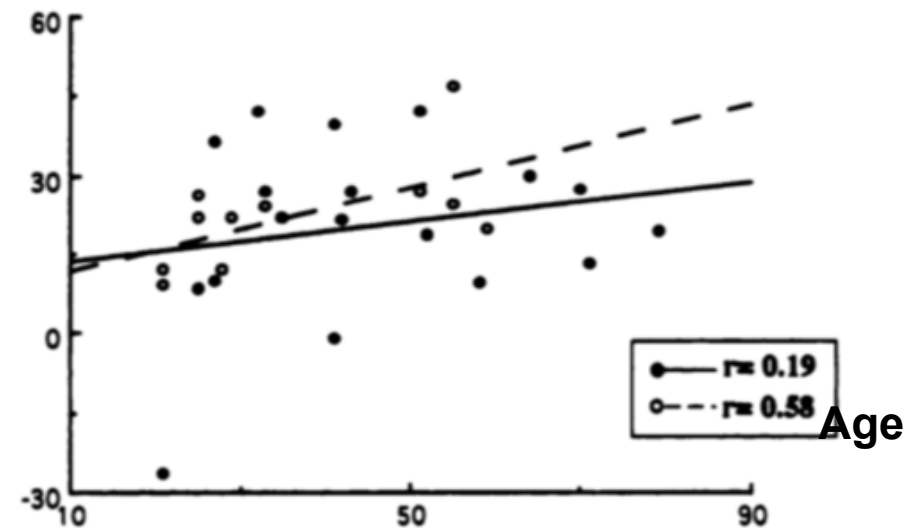
- 29 patients (21 to 79 years old), 13 normal volunteers, 16 patients with malignancy

H/M ratio



No difference between age >40 and <40 yrs.

Washout rate

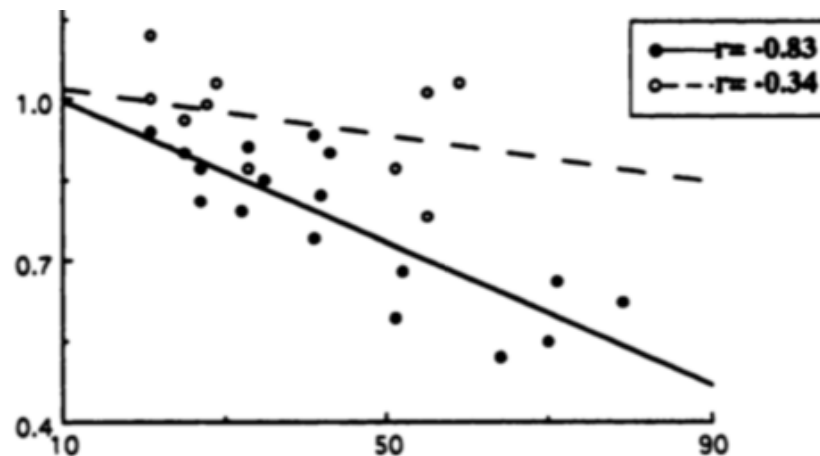


No difference between age >40 and <40 yrs.

# Age and gender difference

- 13 normal volunteers
- 16 patients with malignancy

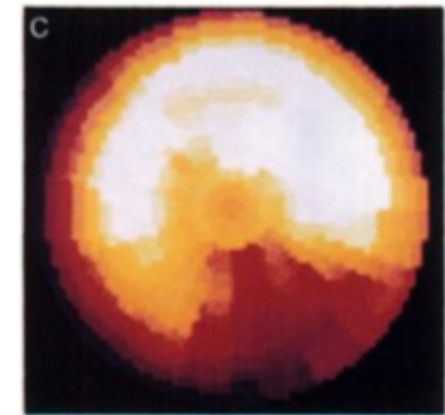
**Inferior/Anterior count ratio**



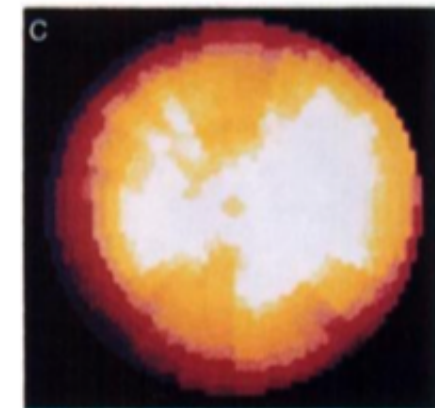
| Age   | I/A             | p     |
|-------|-----------------|-------|
| <40 y | $0.92 \pm 0.09$ | <0.05 |
| >40 y | $0.76 \pm 0.17$ |       |

| Sex    | I/A             | p      |
|--------|-----------------|--------|
| Male   | $0.96 \pm 0.10$ | <0.005 |
| Female | $0.77 \pm 0.14$ |        |

Age



71 years

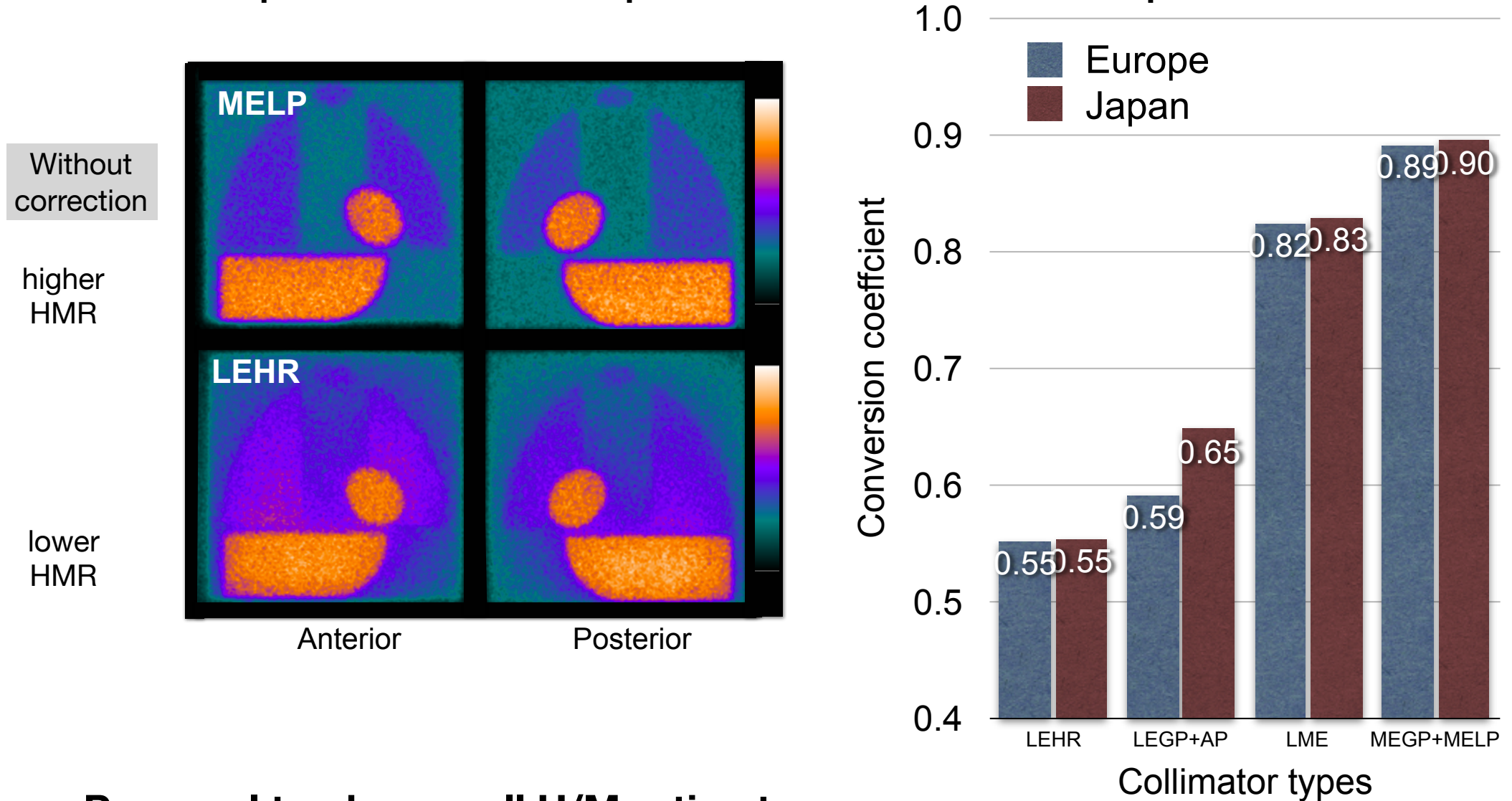


21 years



# Standardization of camera-collimator difference

Phantom experiments > 1000 in Japan and >200 conditions in Europe



Proposal to change all H/M ratios to  
**MEGP**-collimator conditions

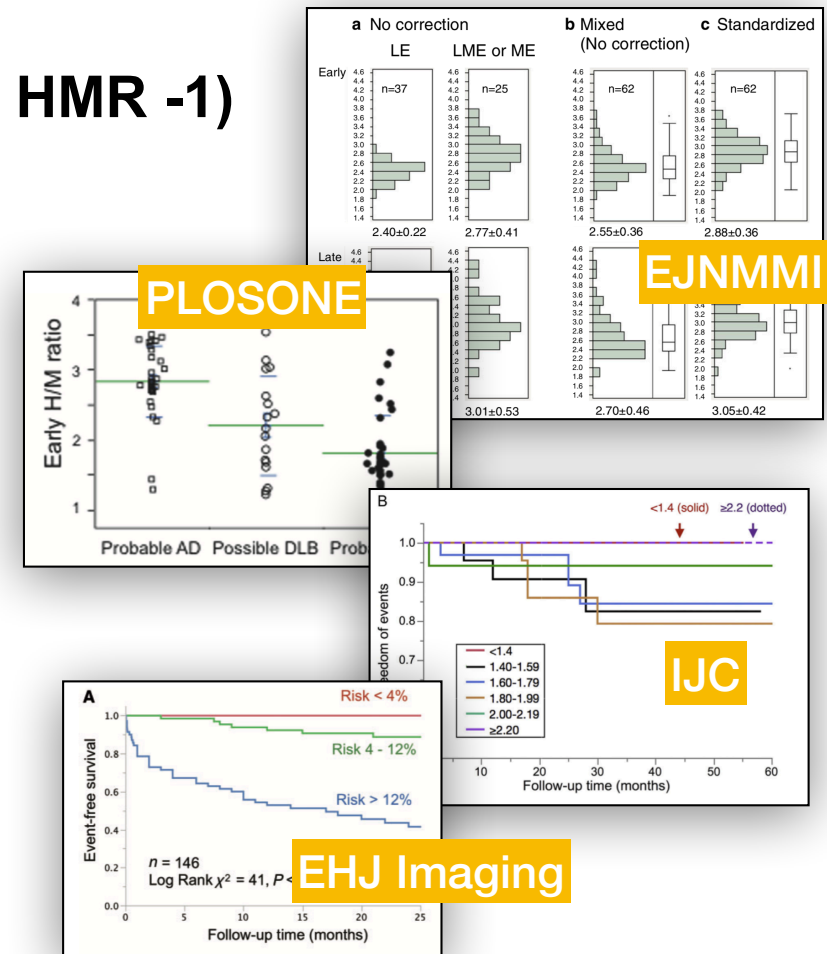


# Application of standardized HMR

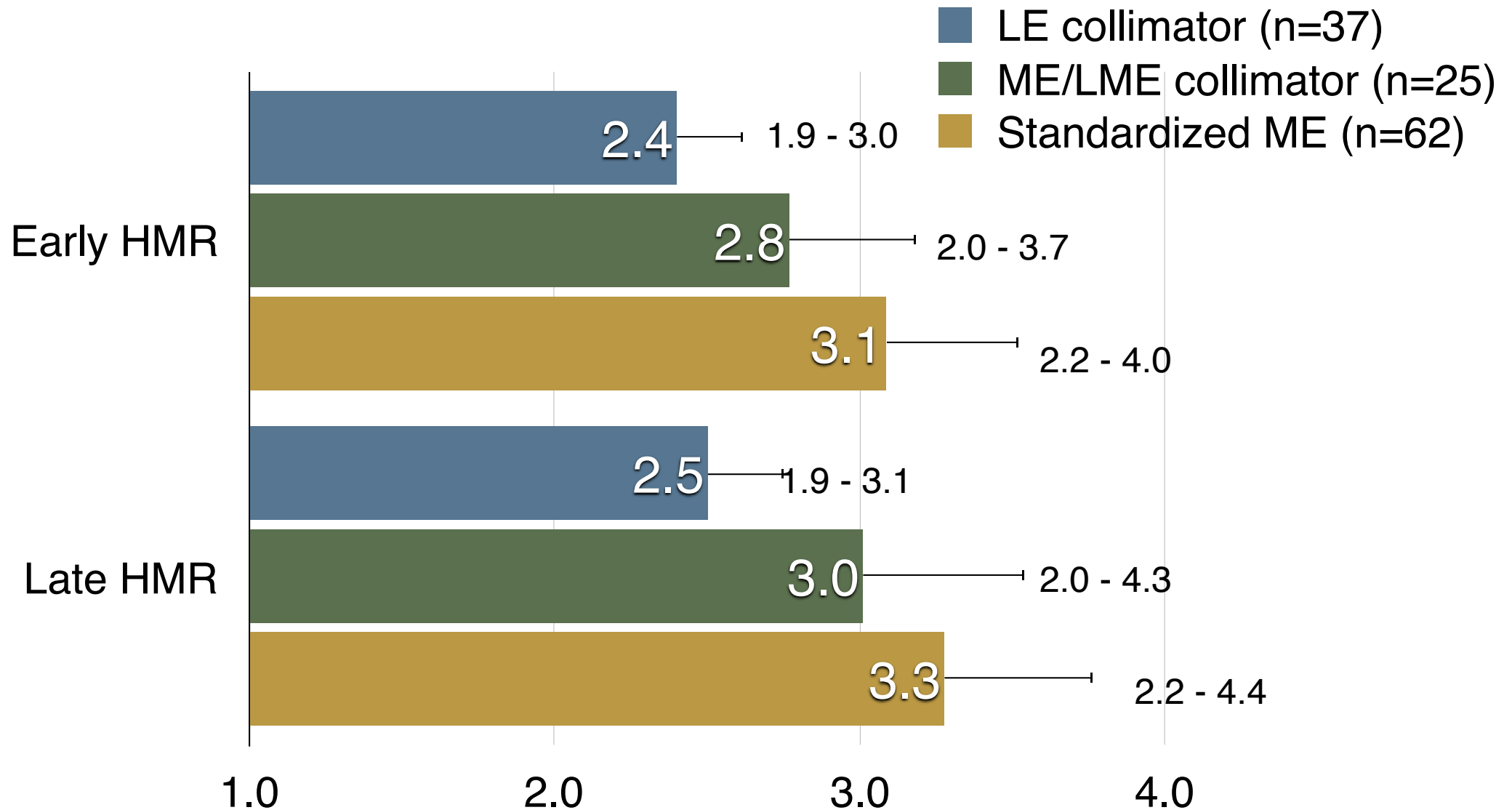
## Standardized HMR -1

$$= \frac{0.88}{\text{conversion coefficient}} * (\text{measured HMR} - 1)$$

- Neurology
  - EJNMMI 2012: AD and DLB
  - PLOSONE 2015: AD and DLB, multicenter
- Heart
  - Int J Cardiol 2017 ... appropriate ICD therapy
  - EHJ Cardiovasc Imaging 2018 ... risk model

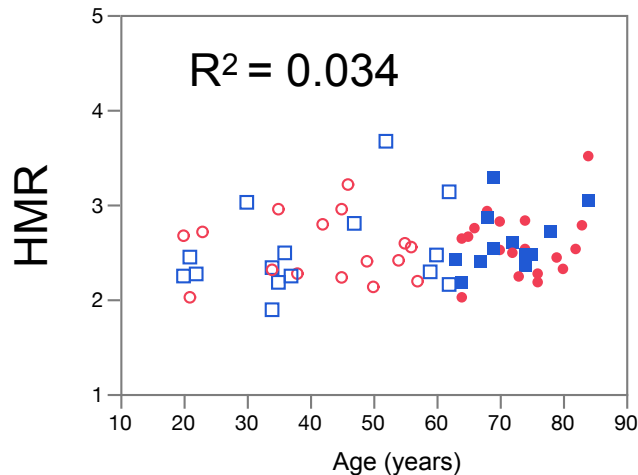


# Normal values using standardized H/M ratio

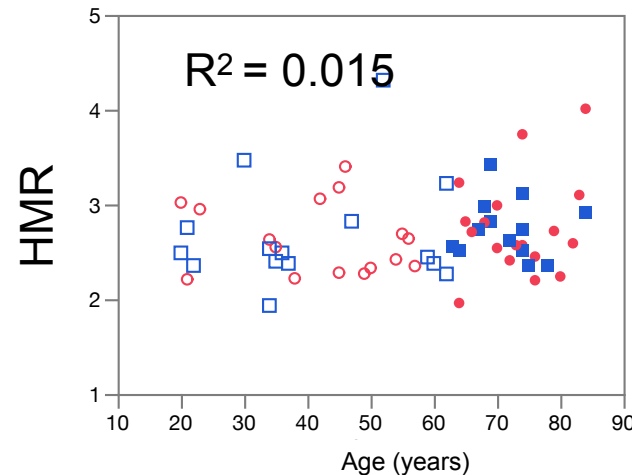


# Age and sex difference in JSNM WG normal databases

**A. Early HMR (no correction)**

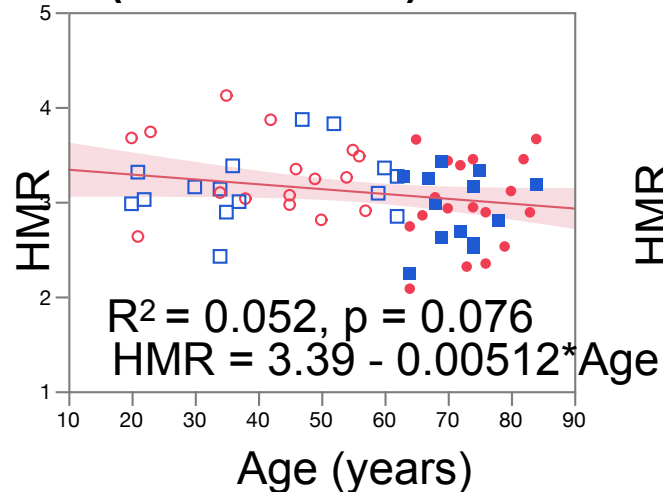


**B. Late HMR (no correction)**

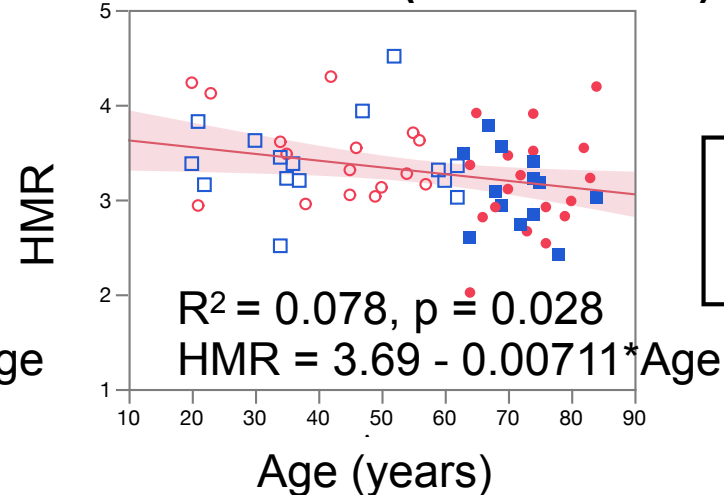


**C. Early HMR (standardized)**

**MEGP  
condition**



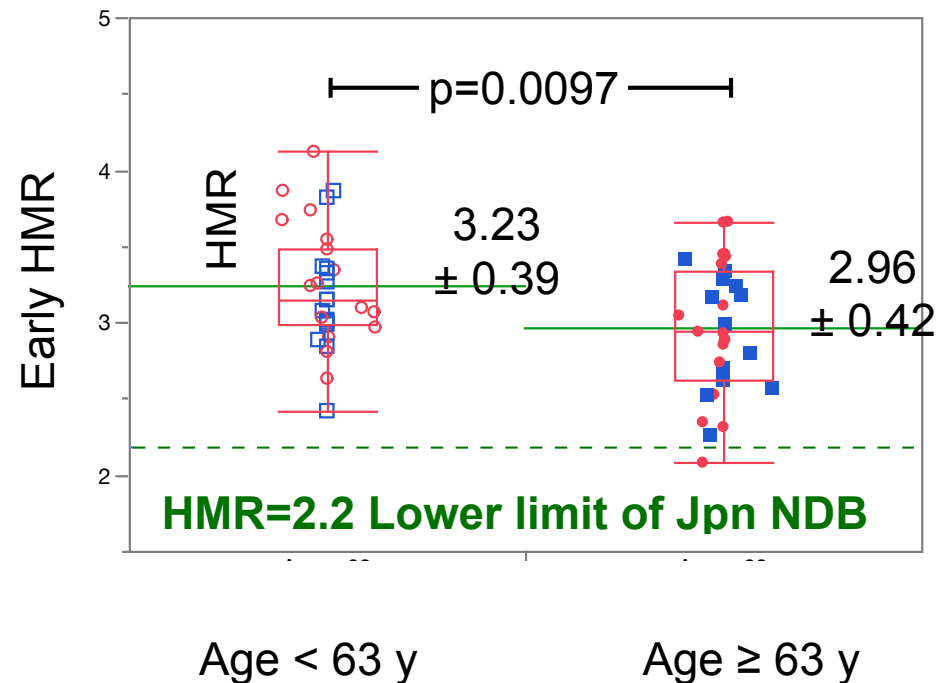
**D. Late HMR (standardized)**



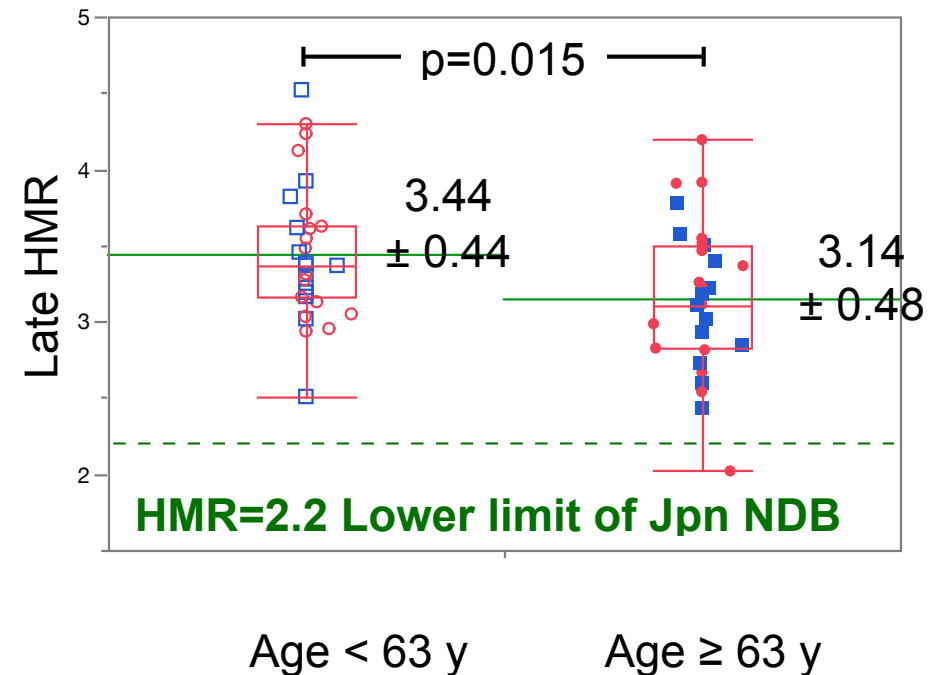
**30 years older  
= lower HMR by  
0.2**

# Age vs. early and late HMR

A. Early HMR (standardized)

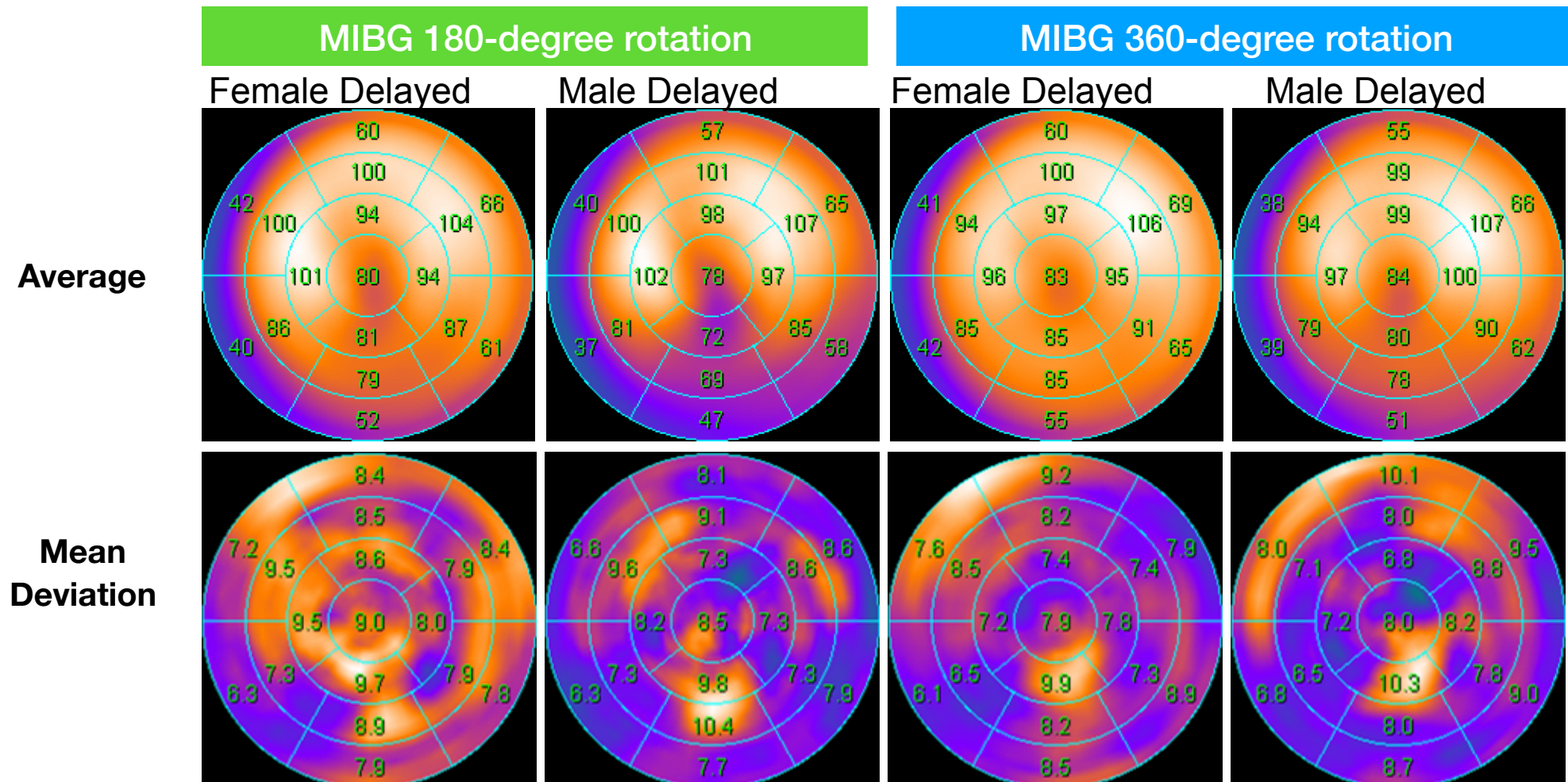


B. Late HMR (standardized)



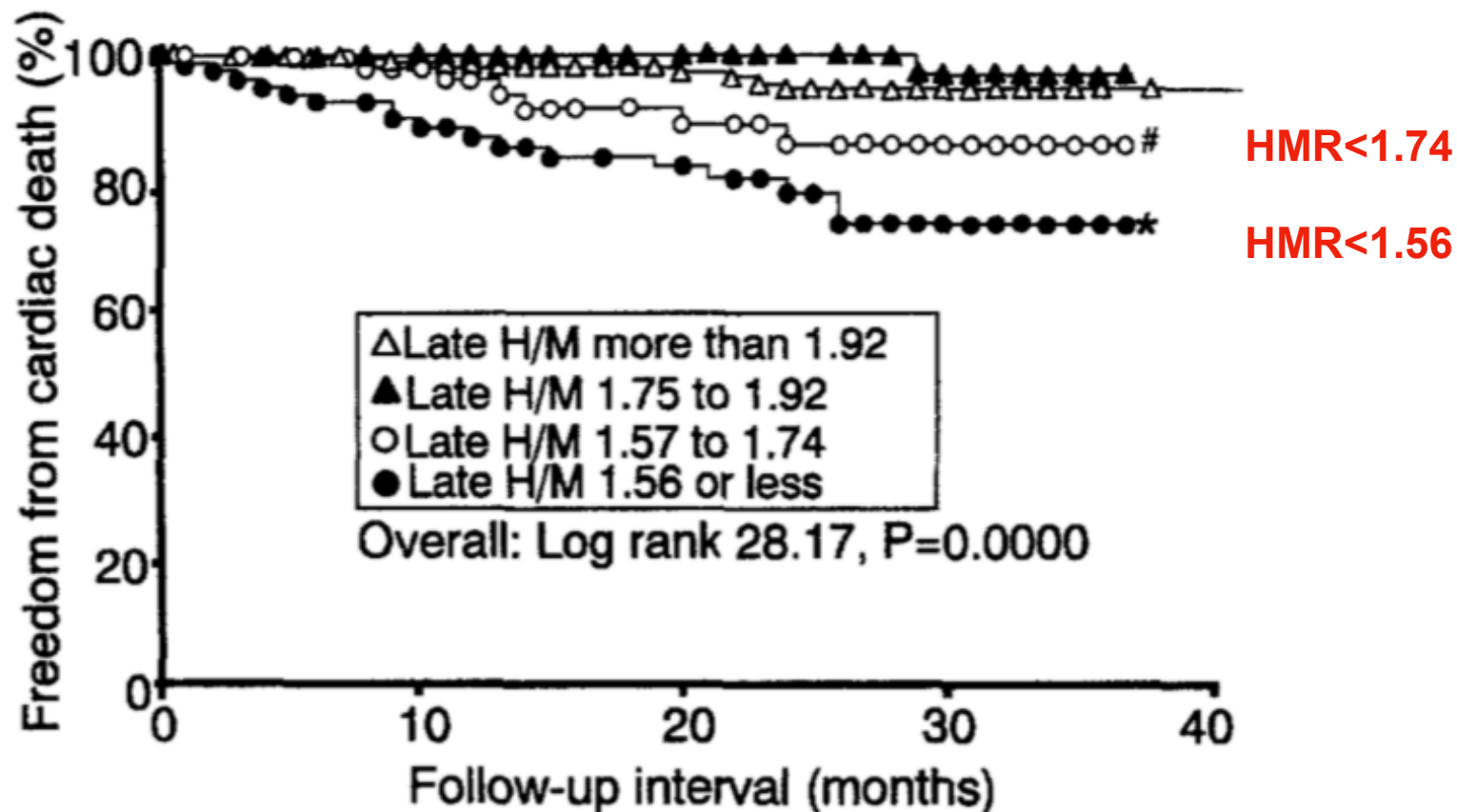
**Notes: patients with aged patients with dementia, lower limit of HMR = 2.2 can be used anyway.**

# JSNM WG database for MIBG SPECT



# MIBG in failing and non-failing heart

- 414 consecutive patients (173 with symptomatic HF)
- Follow-up 22 months, 37 cardiac death (23 HFD, 9 SCD, 5 AMI)





# 123I-MIBG for heart failure and Lewy body diseases

## JCS guidelines



Circulation Journal  
Official Journal of the Japanese Circulation Society  
<http://www.j-circ.or.jp>

JCS GUIDELINES

### Guidelines for Clinical Use of Cardiac Nuclear Medicine (JCS 2010)

– Digest Version –

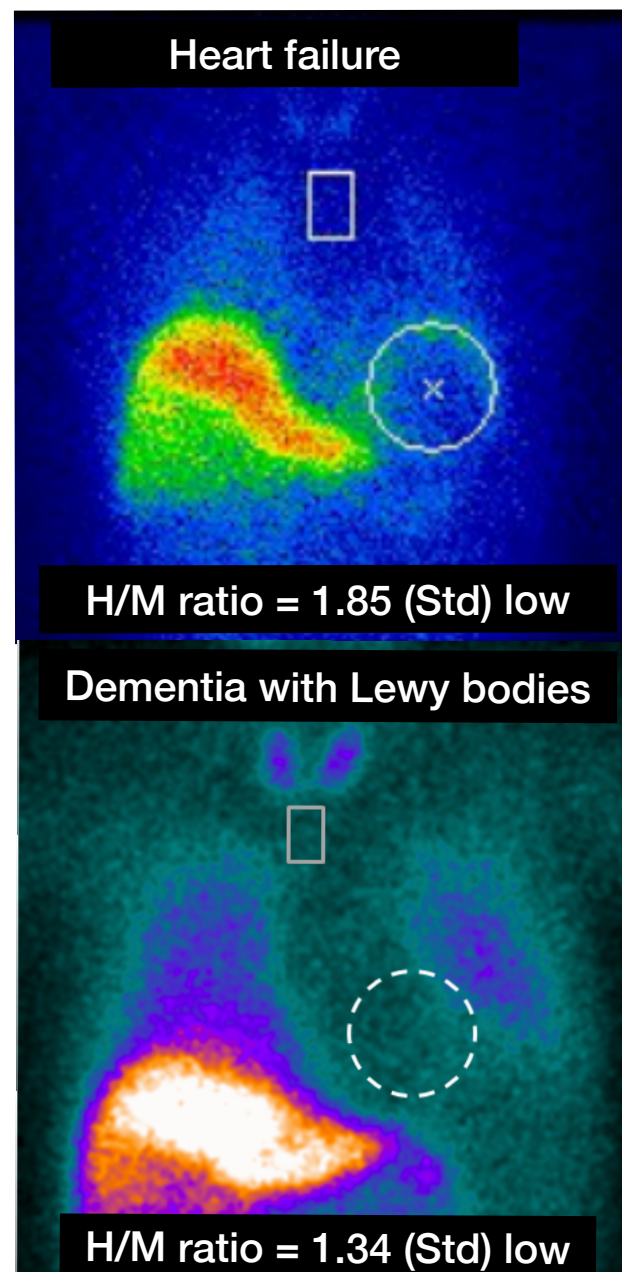
JCS Joint Working Group

**Table 3. Recommendations for Myocardial Sympathetic Nerve Imaging Using I-123 MIBG**

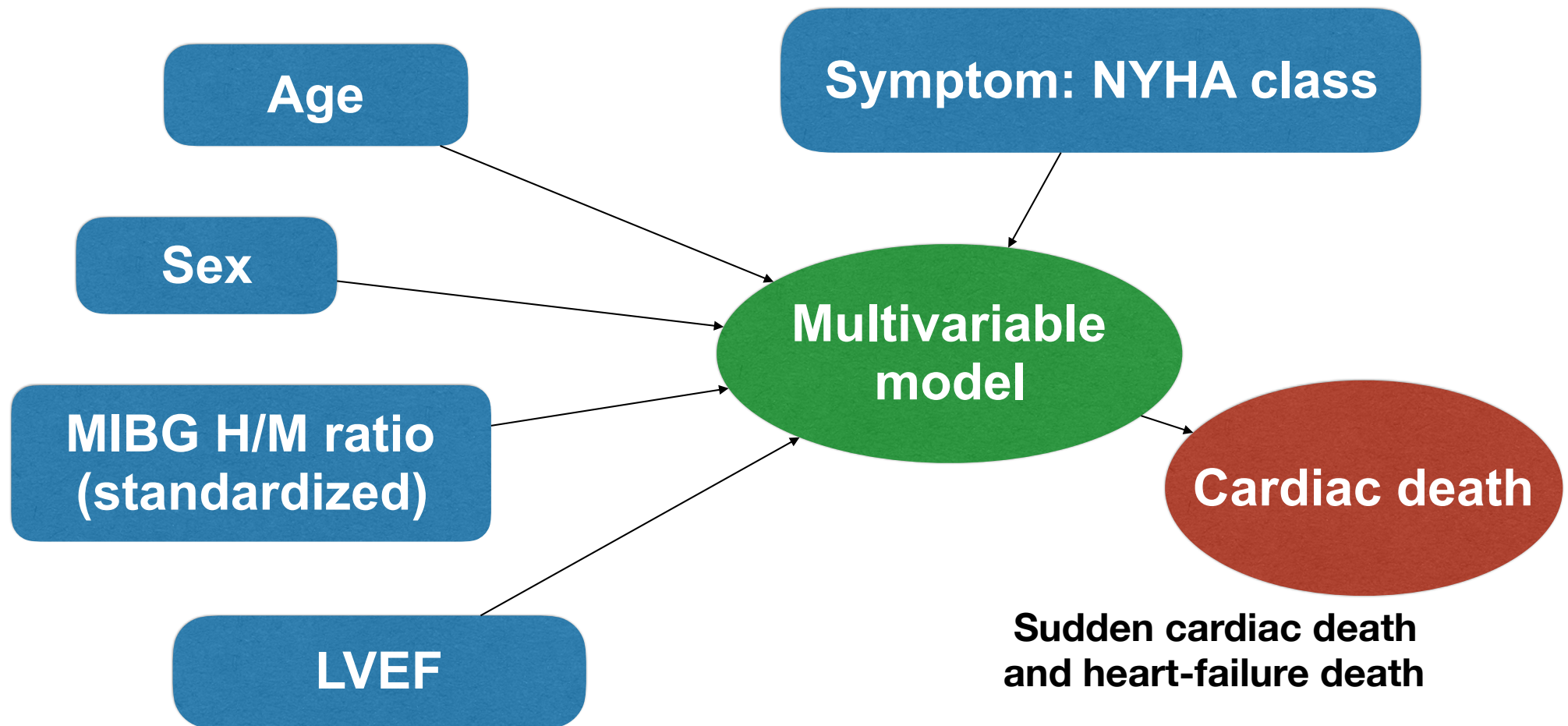
| Indications                                           | (1) | (2) |
|-------------------------------------------------------|-----|-----|
| Assessment of severity and prognosis of heart failure | I   | B   |
| Assessment of treatment effects of heart failure      | IIa | C   |
| Arrhythmogenic disease                                | IIb | C   |

(1): classification of recommendations, (2): level of evidence.  
I-123 MIBG, I-123-metaiodobenzylguanidine.

Under revision by JCS: guidelines for ischemic heart disease



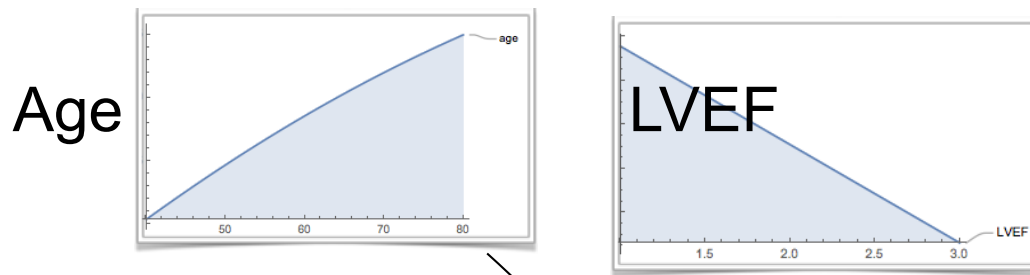
# Multivariate model to estimate cardiac mortality



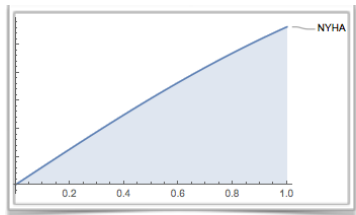


# 5 or 2-year cardiac mortality risk model

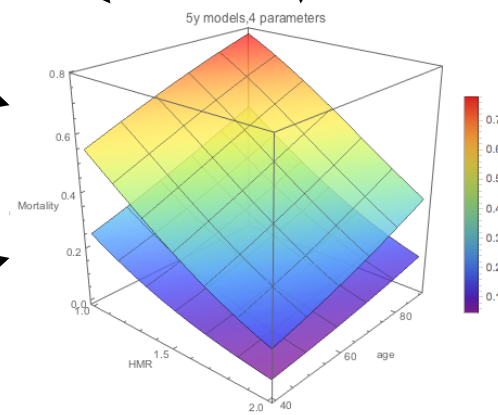
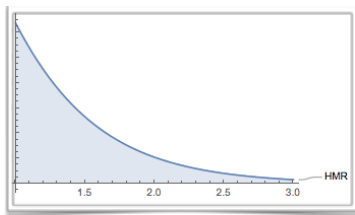
4 or 5 variable model



NYHA class



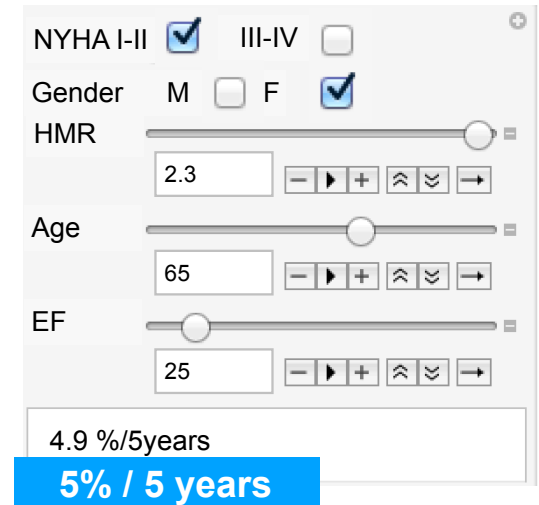
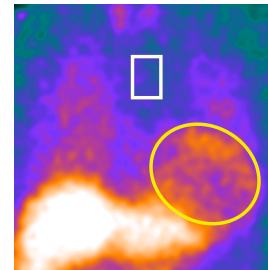
$^{123}\text{I}$ -MIBG H/M ratio



65-year-old women

NYHA Class II

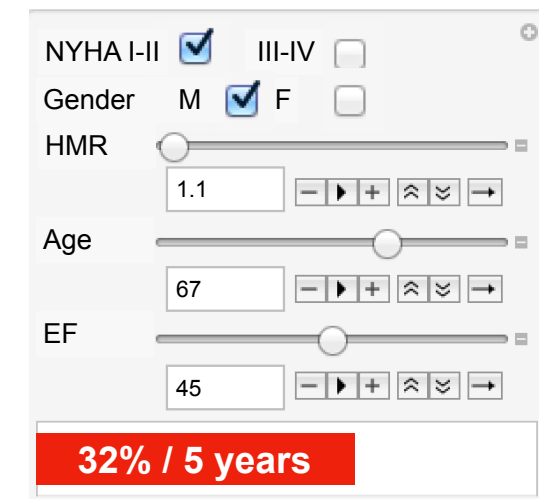
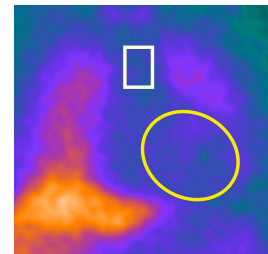
LVEF=25%



67-year-old man

NYHA Class I

LVEF=45%

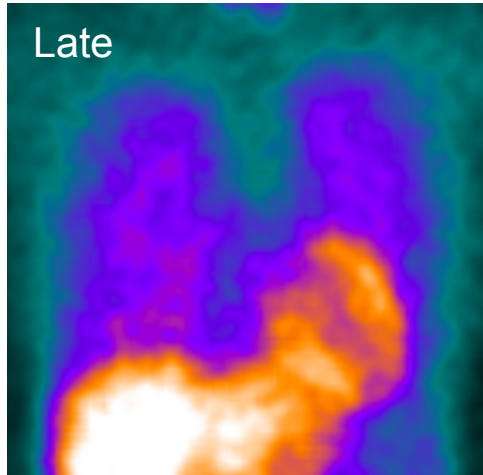


Nakajima K, et al. Eur J Nucl Med Mol Imaging. 2014; 41: 1673–1682

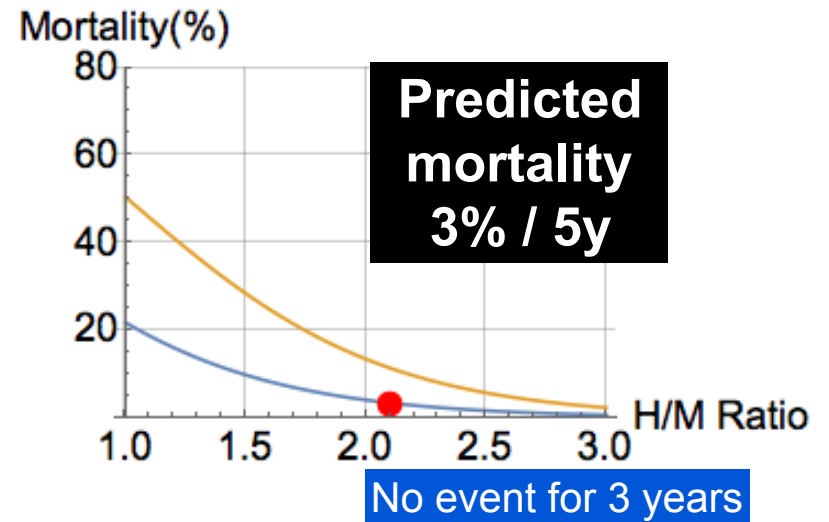
Nakajima K, et al. EHJ Cardiovascular Imaging 2016; 17, 1138–45

# Two patients with DCM

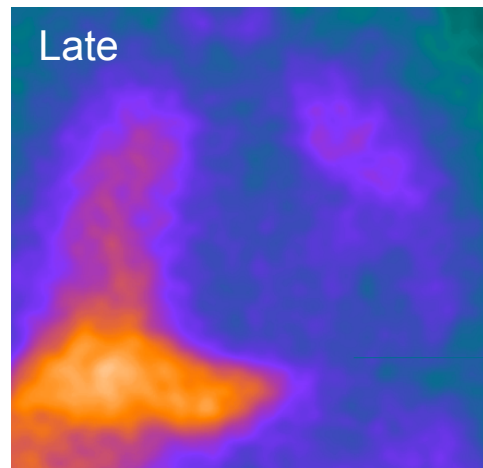
Case 1.  
33-year  
old  
female



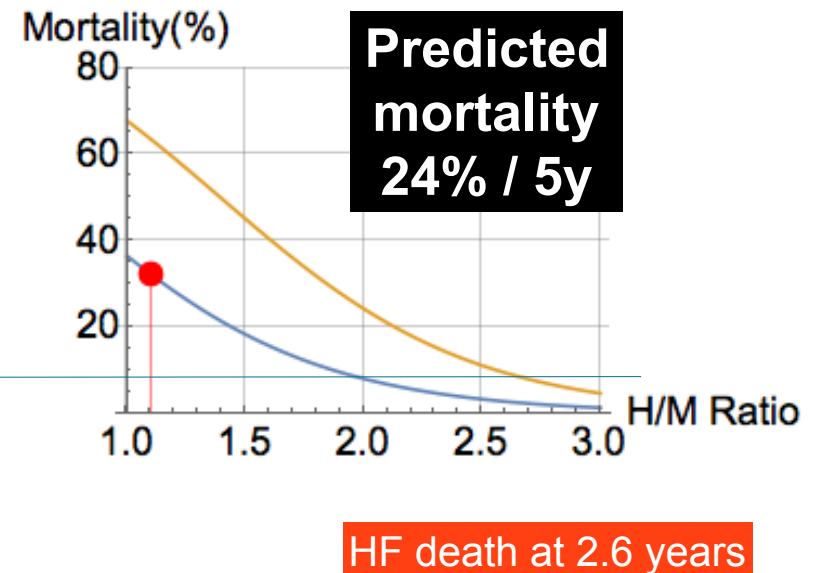
Idiopathic DCM  
NYHA Class II  
EF=23%  
MIBG  
Early H/M=2.9  
Late H/M=2.7  
Washout  
rate=28%



Case 2.  
67-year  
old male

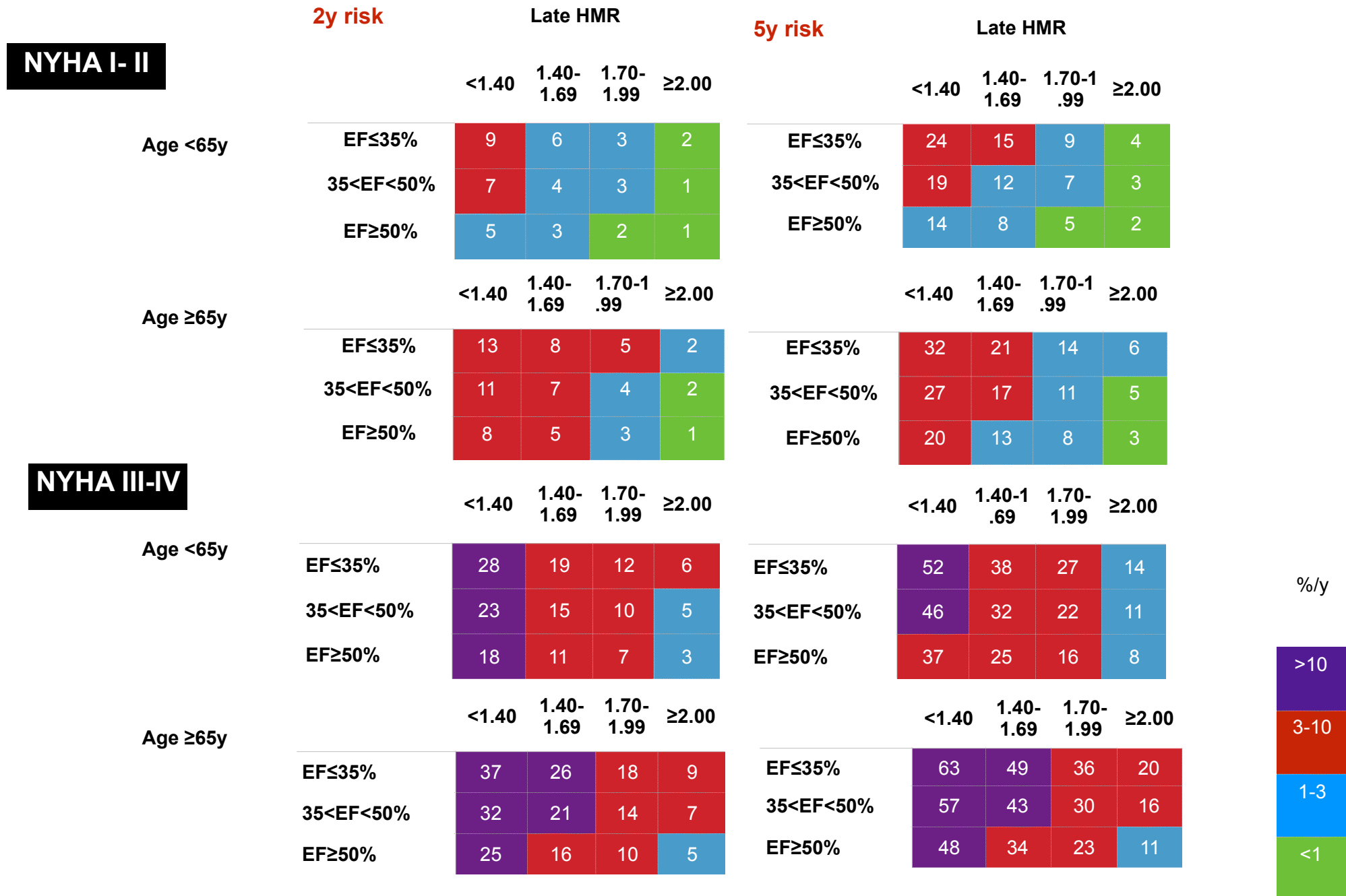


Idiopathic DCM  
NYHA Class I  
EF=45%  
MIBG  
Early H/M=1.3  
Late H/M=1.1  
Washout  
rate=29%



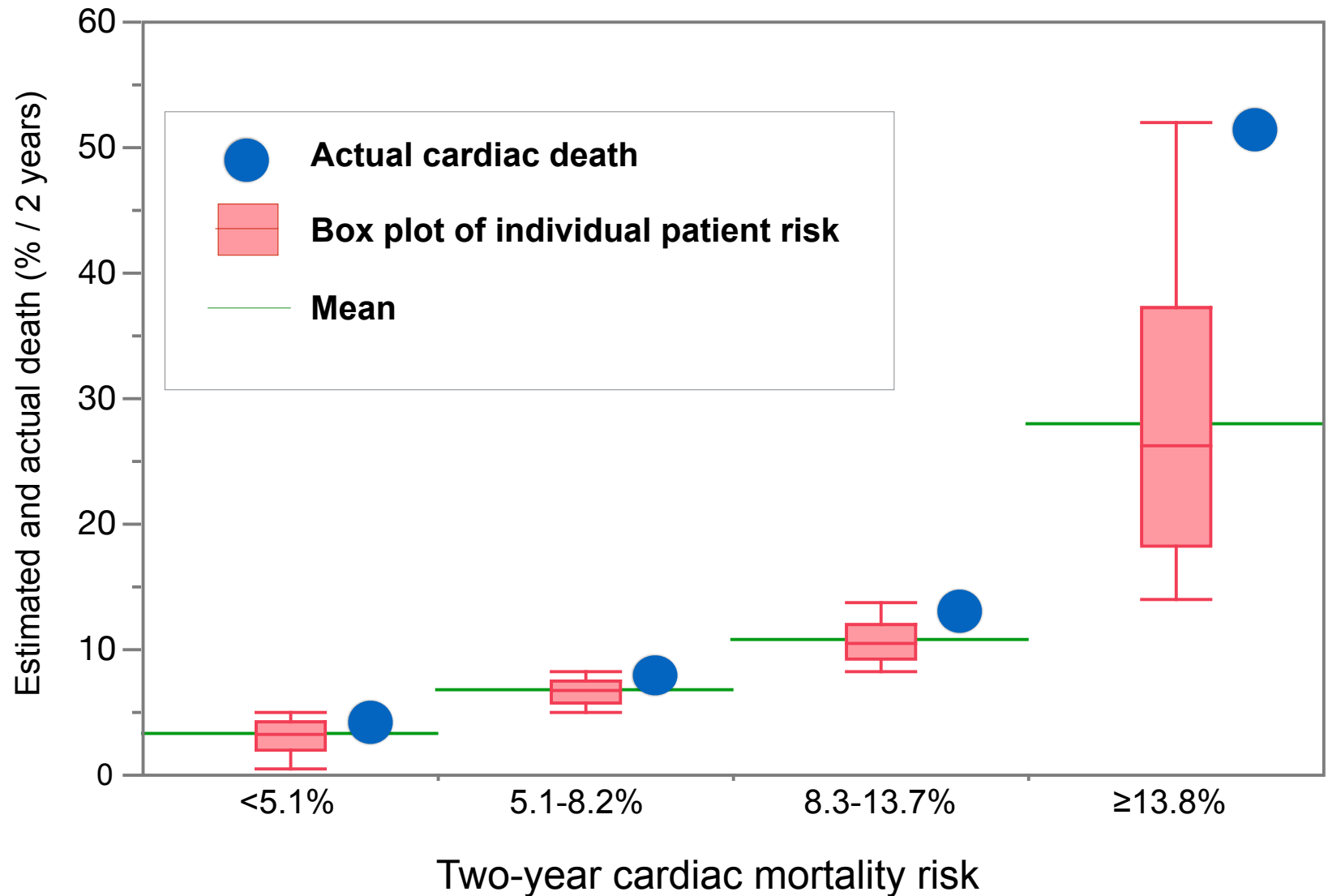
Case 1 from Kanazawa University, Case 2 from Sapporo Medical University  
I-123 mIBG 111 MBq, Early at 20-30 minutes, late at 3.5-4 hours

# Mortality Risk Chart using I-123 MIBG (4-variable model)

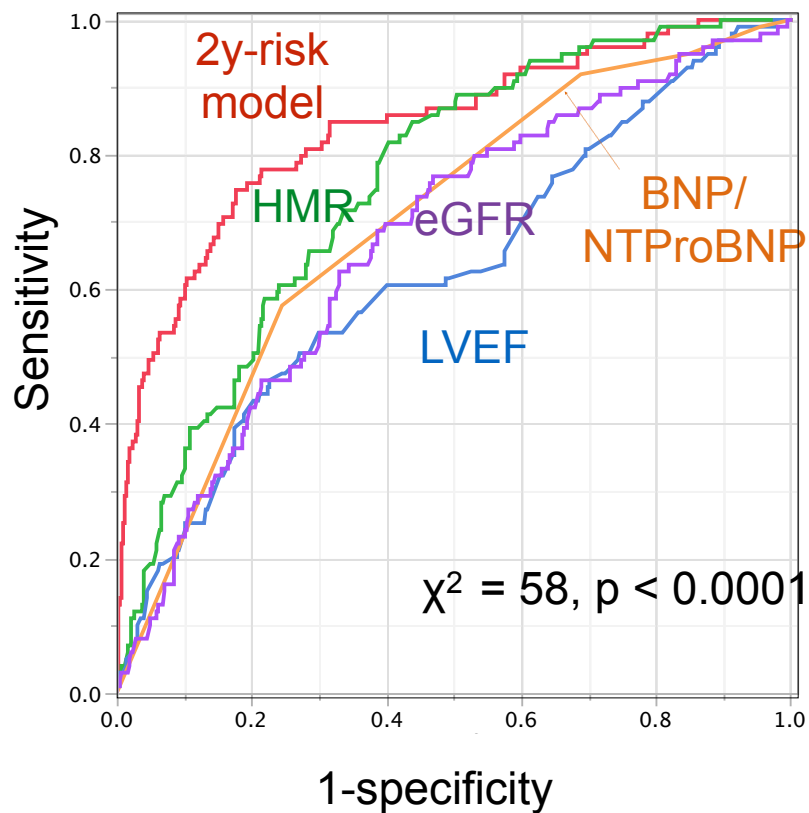


# Risk model can predict actual outcome of cardiac death

Validation  
study in 546  
patients



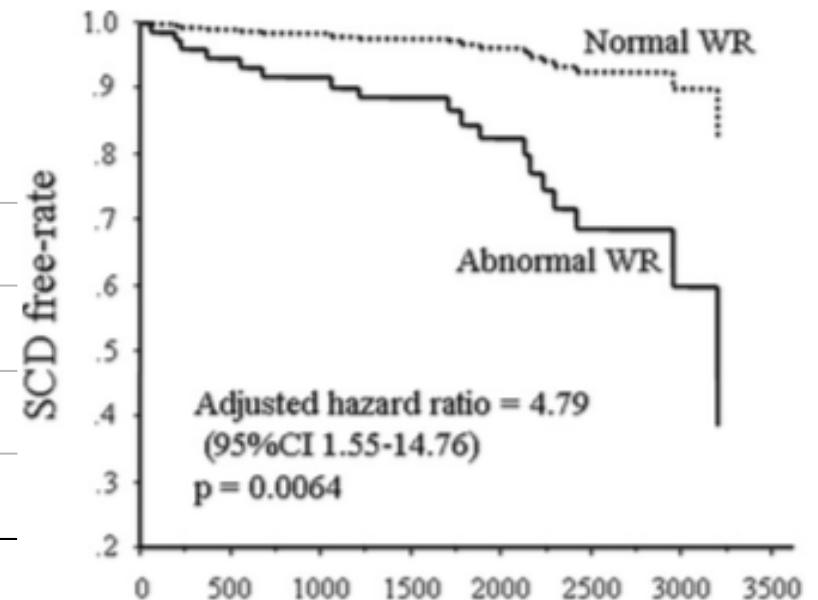
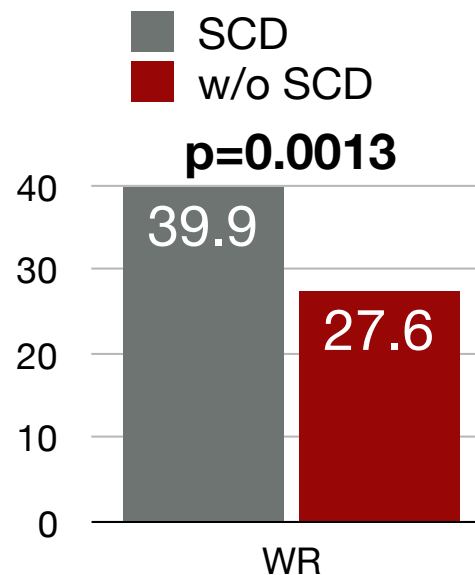
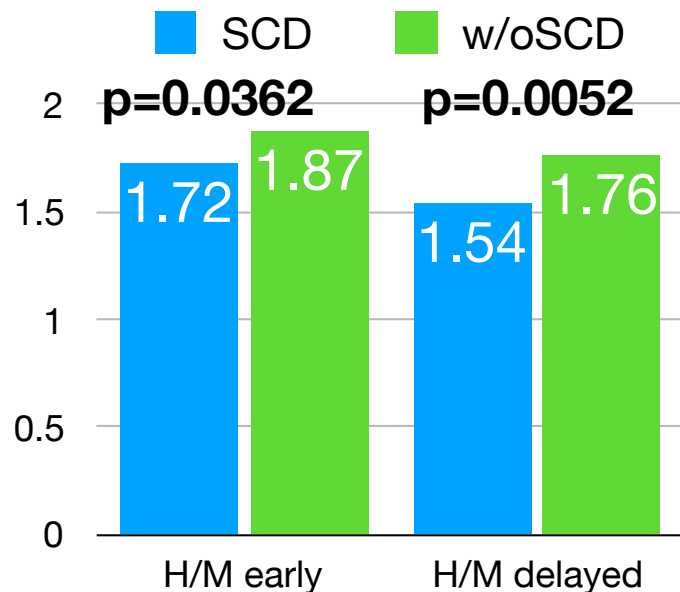
# 2-year risk model better than BNP, LVEF and MIBG H/M alone to predict cardiac death



|                      | AUC  | SE   | Lower 95% | Upper 95% | p vs. 2y-risk model |
|----------------------|------|------|-----------|-----------|---------------------|
| <b>2y-risk model</b> | 0.84 | 0.02 | 0.79      | 0.88      | -                   |
| <b>Late HMR</b>      | 0.76 | 0.02 | 0.71      | 0.80      | 0.0004              |
| <b>BNP/NT-ProBNP</b> | 0.70 | 0.03 | 0.65      | 0.75      | < 0.0001            |
| <b>eGFR</b>          | 0.67 | 0.03 | 0.61      | 0.73      | < 0.0001            |
| <b>LVEF</b>          | 0.63 | 0.03 | 0.56      | 0.69      | < 0.0001            |

# Cardiac Iodine-123 MIBG Imaging Predicts Sudden Cardiac Death Independently of Left Ventricular Ejection Fraction in Patients With CHF

- 106 patients with LVEF <40%
- MIBG, signal-averaged electrocardiogram (SAECG), Holter ECG, ECG
- F/U 65 months, 18 died
- Patients with an abnormal WR (>27%) had a significantly higher risk of SCD (adjusted Haz Ratio: 4.79)



# MIBG in CHF

*Risk stratification and clinical decision making*

***I-123 MIBG***



**Standardized  
MIBG HMR  
+ Risk model**

**Low risk**

**Intermedi  
ate risk**

**High risk**

**Observation**

**Optimal medications**

**Cardiac device  
treatment**

**Cardiac transplantation  
Artificial heart  
implantation  
Palliative care**



# I-123 MIBG: History and perspectives

- In Japan, I-123 MIBG has been examined in various cardiac diseases, showing **wide range of applicability**.
- However, the number of patients are **relatively limited and single-center experience in Japan**
- Effective use of MIBG is confirmed in patients **chronic heart failure**, and included in Japanese Circulation Society's guidelines.
- Large number of databases could be compiled using **standardized approaches** using a phantom-based correction method.
- International collaboration is expected in cardiology and neurology.

# Thanks

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