

**RESYNCHRONIZATION THERAPY**  
**Where Do We Go From Here?**

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*April 2008*

# DISCLOSURE INFORMATION

Arthur J. Moss, MD

Company

Guidant Corporation

Relationship

Research Grant

Hold no stock or stock options in any device company. Not a member of any corporate advisory group or speakers' bureau.

# ELECTRICAL DEVICE THERAPY

**1954-1960: Zoll & Lown - Ext. Defibrillator**

**1960-1961: Chardack & Greatbatch - Pacer**

**1968-1971: Mirowski & Mower - ICD**

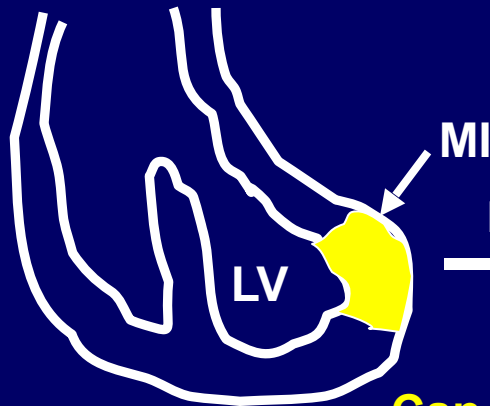
**1985-1990: Mirowski & Mower - CRT**

# **MADIT-III (MADIT-CRT)**

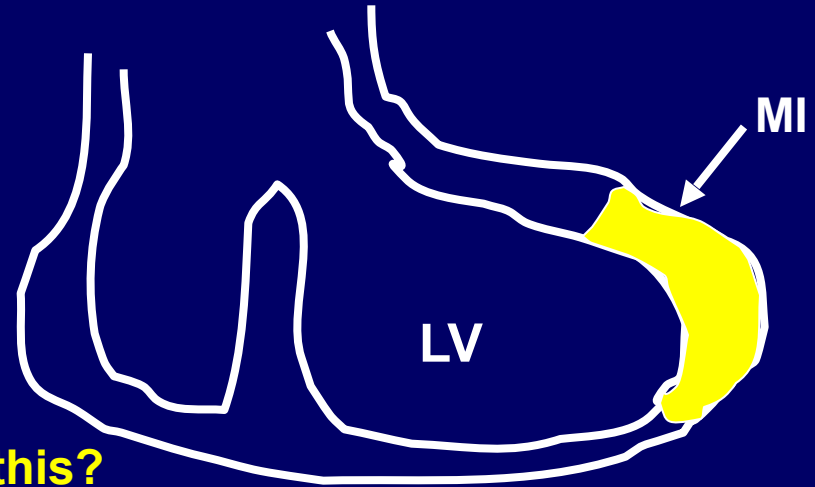
**A trial to determine if cardiac resynchronization therapy can inhibit or slow the development of heart failure in at-risk cardiac patients**

# DYSFUNCTIONAL REMODELING

Early



Late



Can CRT prevent this?

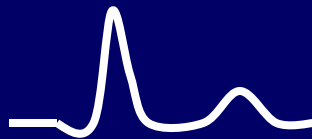
EF=0.30

EF=0.20

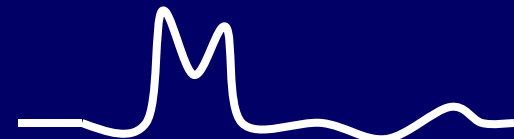
NYHA I-II

NYHA III-IV

ECG



QRS = 0.12s



QRS = 0.16s

# MADIT-III (MADIT-CRT)

- **Hypothesis:** in minimally symptomatic high-risk pts. with IHD (NYHA I or II) or NIHD (NYHA II), **wide QRS** ( $\geq 0.13s$ ), and low EF ( $\leq 0.30$ ), CRT will slow or prevent the development of heart failure
- **Randomized trial:** started December 2004
  - CRT-D vs. ICD-only
  - 1,800 pts: >90 enrolling cntrs. in US & Europe
  - duration of trial: 3-4 years
  - End point: Heart failure or death, which ever comes first

# MADIT-III (MADIT-CRT)

## Ongoing Substudies

- **Echocardiogram at baseline and 1 year (EF, EDV, ESV, mitral insuff.)**
- **Tissue doppler imaging**
- **12-lead ECG-QRS complexity analysis (PCA of QRS)**

**Some Relevant Findings  
from  
Recent MADIT-II  
Secondary Analyses**

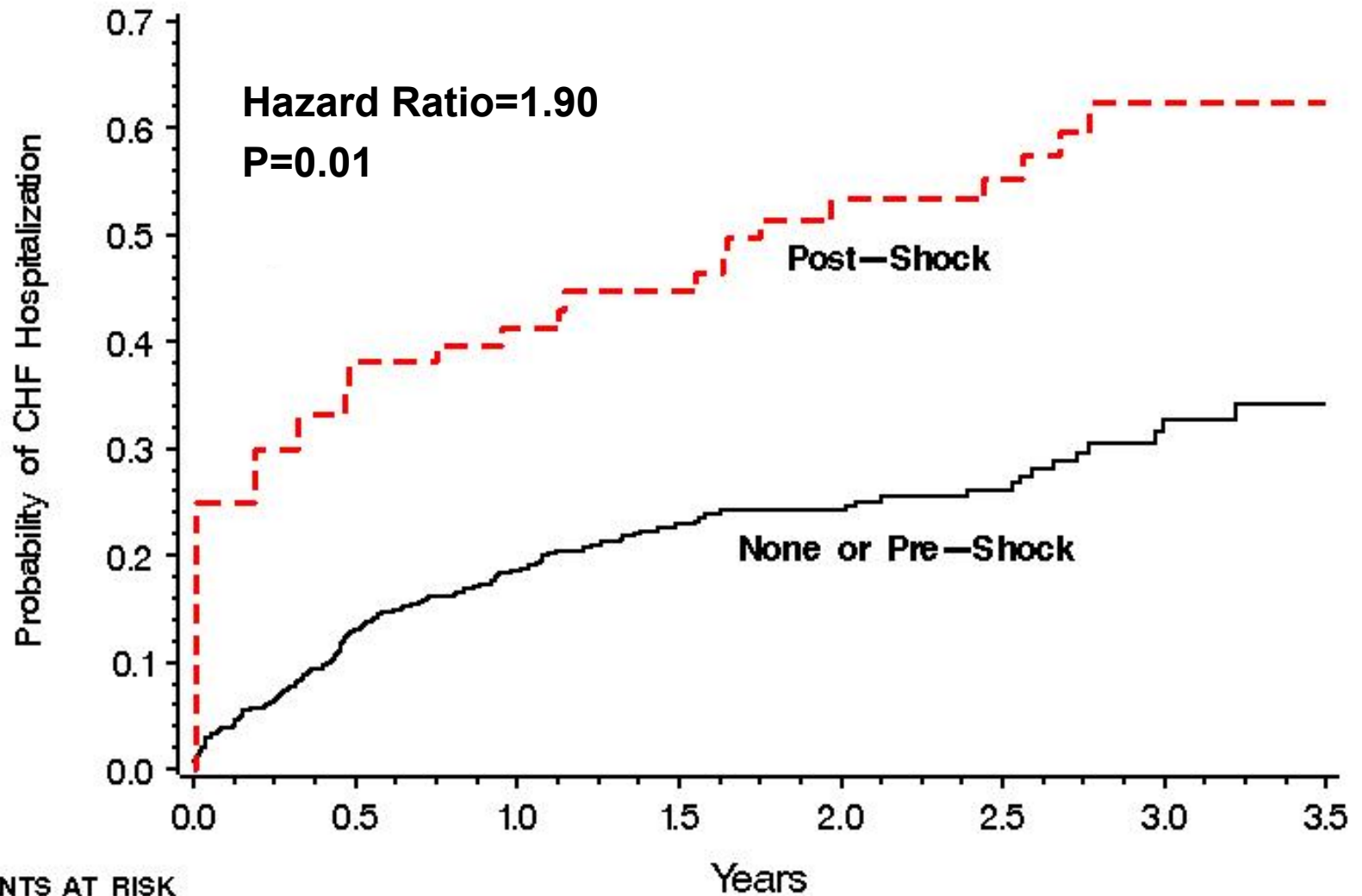


# Factors Affecting Appropriate Device Therapy for VT/VF

| <u>Variable</u> | <u>Hazard Ratio</u> | <u>P-value</u> |
|-----------------|---------------------|----------------|
| HF event*       | 2.5                 | 0.001          |
| MI/UA*          | 1.4                 | 0.19           |

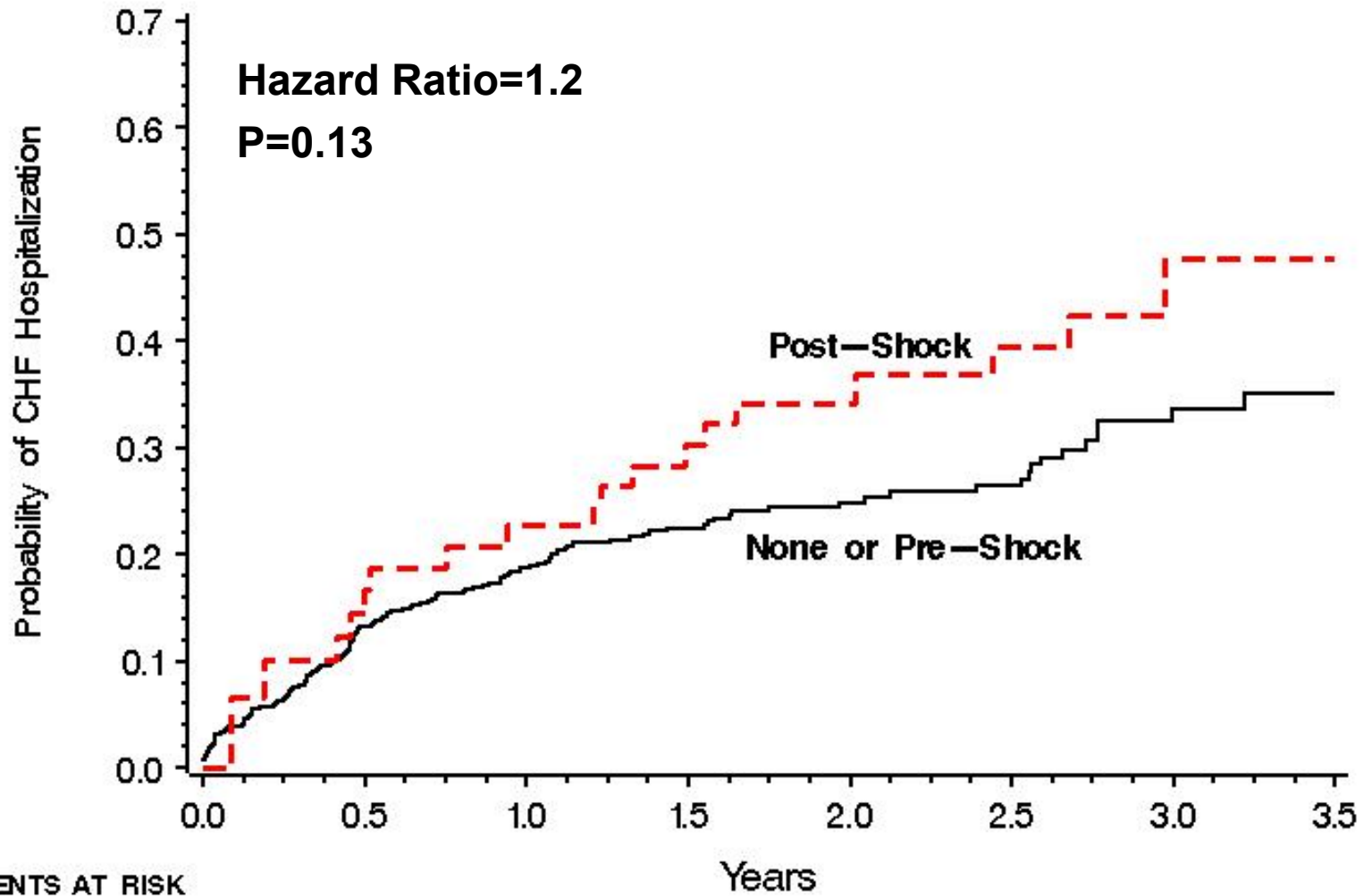
\*Time-dependent post-enrollment hospitalization for heart failure (HF) or myocardial infarction/unstable angina (MI/UA) after adjustment for relevant baseline covariates.

# Heart Failure After Appropriate ICD Shock for VT/VF



| PATIENTS AT RISK  |     |     |     |     |     |     |    |    |  |
|-------------------|-----|-----|-----|-----|-----|-----|----|----|--|
| None or Pre-Shock | 718 | 512 | 360 | 262 | 178 | 129 | 61 | 45 |  |
| Post-Shock        | 0   | 26  | 35  | 33  | 24  | 24  | 8  | 6  |  |

# Heart Failure After Inappropriate Shocks



| PATIENTS AT RISK  |     | 0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 |
|-------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| None or Pre-Shock | 718 | 497 | 355 | 259 | 177 | 129 | 59  | 42  |     |
| Post-Shock        | 0   | 41  | 40  | 36  | 25  | 24  | 10  | 9   |     |

# MADIT-II: Risk of Death

| <u>Risk factor</u>  | Hazard<br><u>Ratio</u> | <u>P-value</u> |
|---------------------|------------------------|----------------|
| ICD vs. Conv        | 0.60                   | <0.001         |
| Post-enrollment HF* | 3.80                   | <0.001         |

\* Time-dependent risk factor

# ICD Survival Benefit

|           | <b>ICD:CONV</b>            |
|-----------|----------------------------|
|           | <b><u>Hazard Ratio</u></b> |
| Entire FU | 0.60 (0.45-0.81)           |
| Before HF | 0.55                       |
| After HF  | 0.70                       |

p=0.158\*

\*Indicates no significant interaction of ICD with post-enrollment heart failure on outcome after adjustment for relevant covariates

# Interpretation

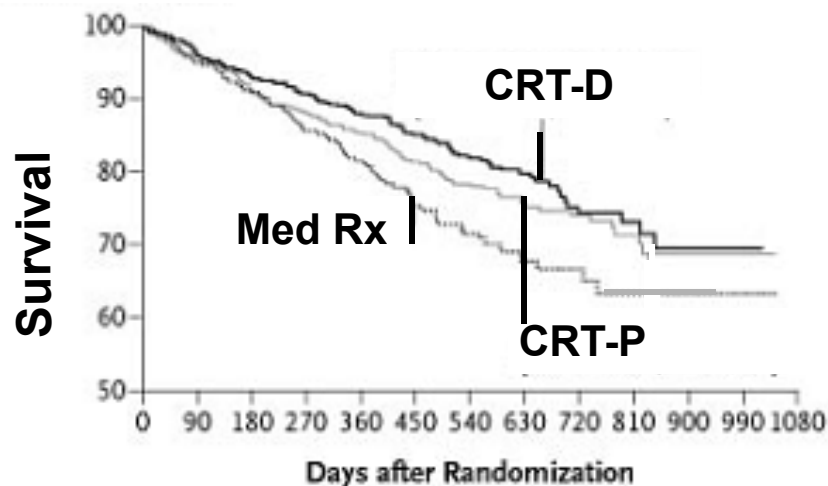
**Life-prolonging ICD  
therapy appears to transform  
a sudden death risk to a heart  
failure risk**

**CRT-P vs. CRP-D**

# COMPANION: 2004

## CRT-D vs. CRT vs. Med Rx

(EF=22%)

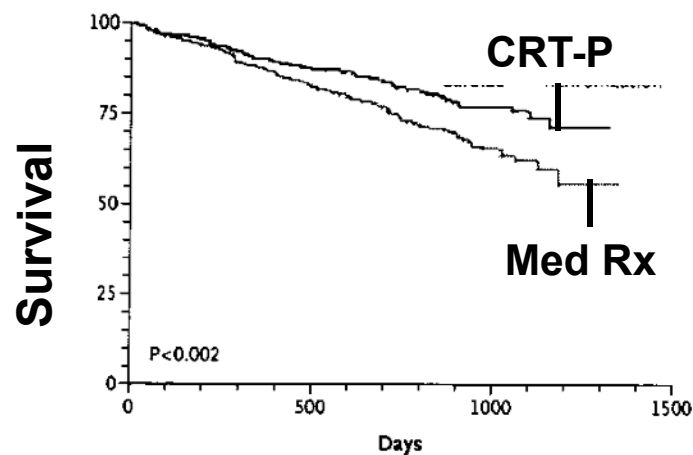


| No. at Risk             | 0   | 90  | 180 | 270 | 360 | 450 | 540 | 630 | 720 | 810 | 900 | 990 | 1080 |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Pharmacologic therapy   | 308 | 284 | 255 | 217 | 186 | 141 | 94  | 57  | 45  | 25  | 4   | 2   |      |
| Pacemaker               | 617 | 579 | 520 | 488 | 439 | 355 | 251 | 164 | 104 | 60  | 25  | 5   |      |
| Pacemaker-defibrillator | 595 | 555 | 517 | 470 | 420 | 331 | 219 | 148 | 95  | 47  | 21  | 1   |      |

# CARE-HF: 2005

## CRT vs. Med Rx

(EF=25%)



| No. at Risk               | 0   | 500 | 1000 | 1500 |    |   |
|---------------------------|-----|-----|------|------|----|---|
| Cardiac resynchronization | 409 | 376 | 351  | 213  | 89 | 8 |
| Medical therapy           | 404 | 365 | 321  | 192  | 71 | 5 |

Note: No CRT-D Rx in CARE-HF

COMPANION Pts. Have More Severe Heart Disease than CARE-HF Pts.



# **Indications for Resynchronization Therapy (2006)**

- Treat advanced heart failure**
- Prevent SCD**
- ? Inhibit development of HF**

**WHERE DO WE GO FROM HERE?**

# **THE KEY QUESTION**

**How can we better identify those who will benefit from resynchronization therapy?**

# FOUR QUESTIONS?

1. Can MRI enhance echo/TDI-TSI assessment for optimizing lead placement site ?
2. Can ECG electrical parameter other than QRS duration improve identification of patients who will benefit from CRT?
3. Is AV ablation always indicated when treating HF-chronic AF with CRT?
4. Will epicardial electrode placement replace CS leads for optimizing resynchronization?

# Cardiac Magnetic Resonance Imaging

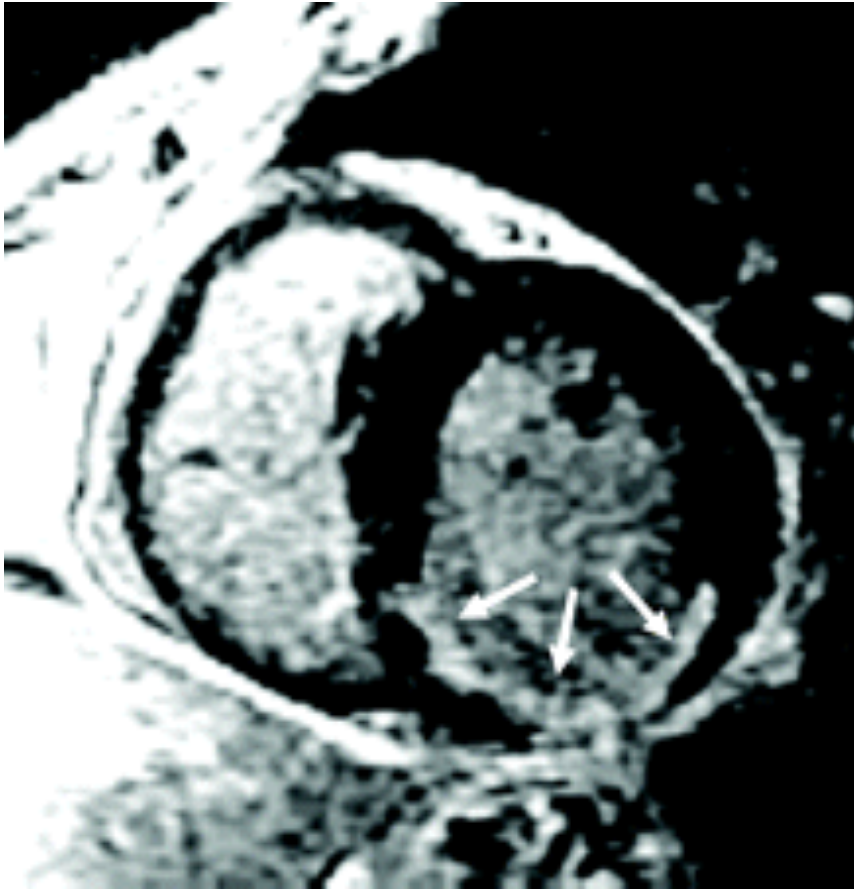
## Myocardial Delayed Enhancement: MDE

$$\%MDE_{\text{periphery}} = (MDE_{\text{periphery}} / MDE_{\text{total}}) \times 100$$

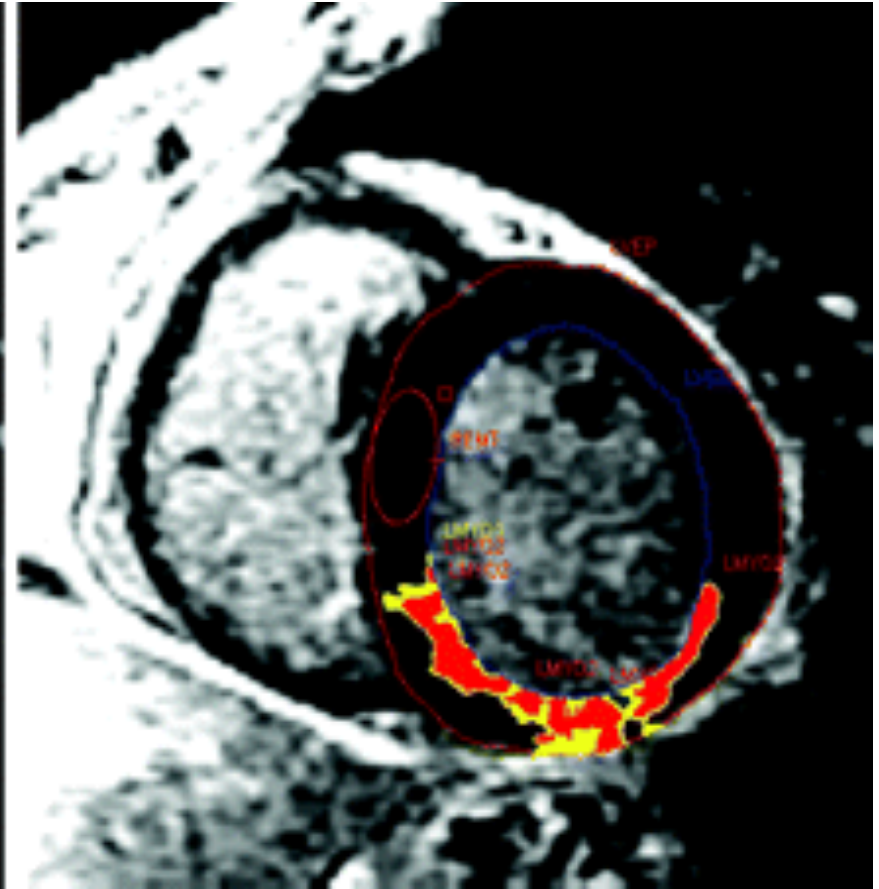
**MDE<sub>periphery</sub>: Potentially arrhythmic heterogeneous zone of viable and nonviable peri-infarct myocardium**

# CMR Imaging in 64-y/o male

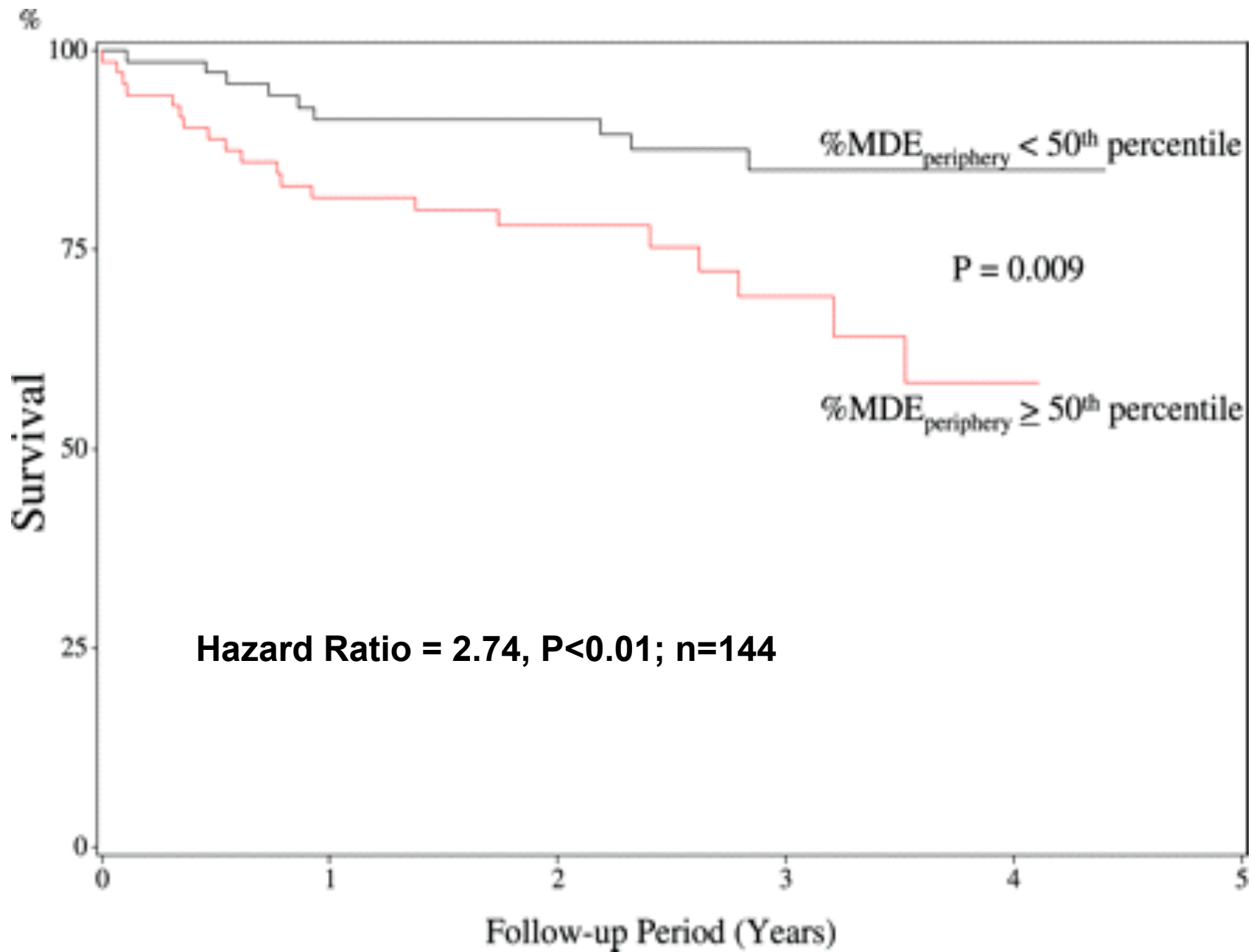
## Inferior MI; EF 61%



Inferior MI (white arrows)

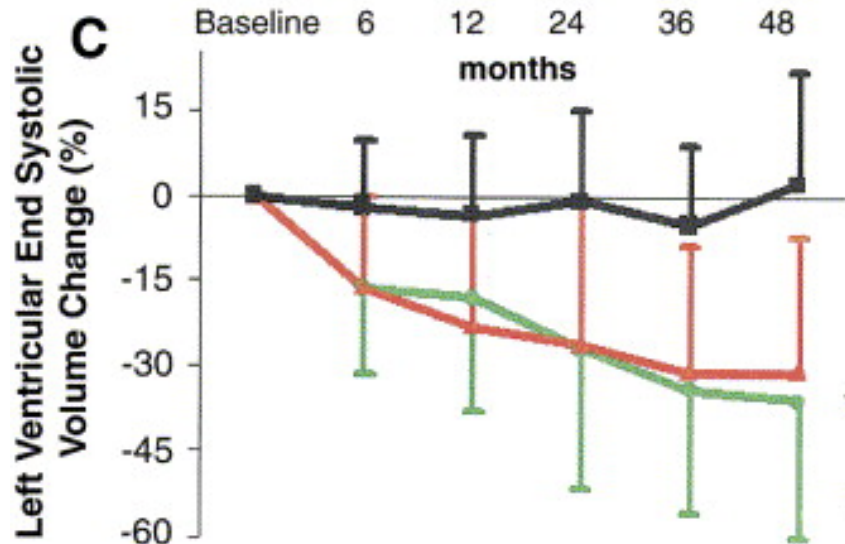
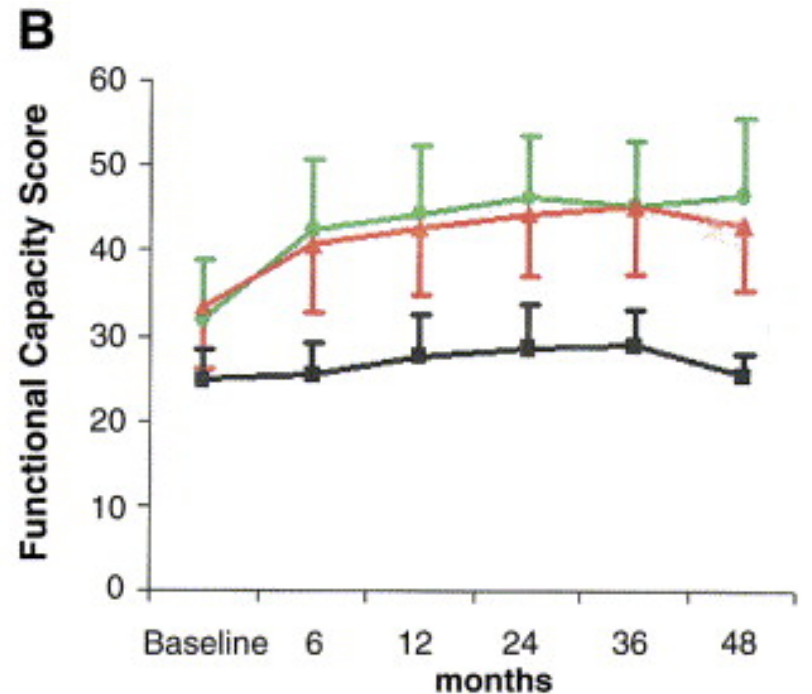
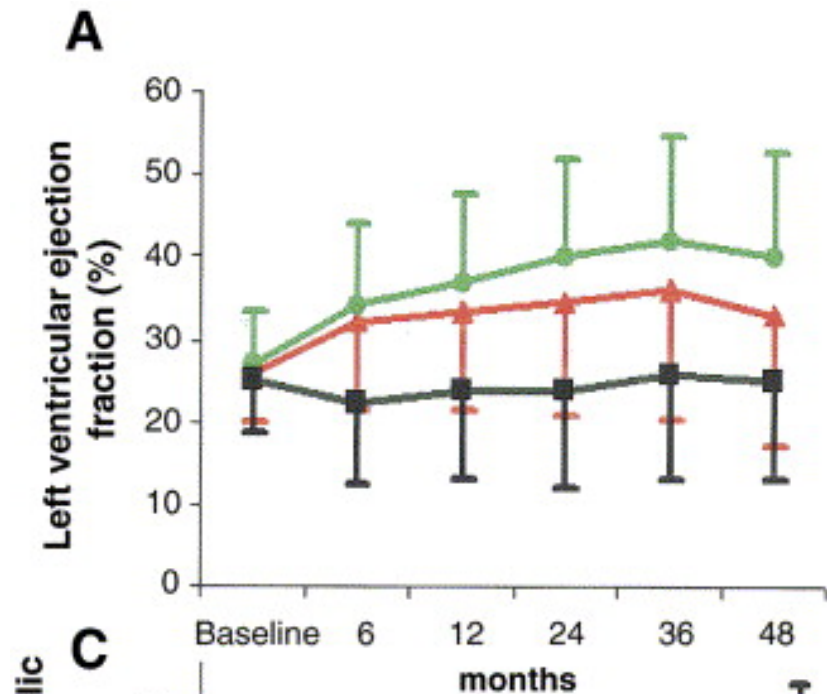


Infarct core (red); Peri-infarct (yellow);  
 $\%MDE_{\text{periphery}}=27\%$



**? AV ABLATION BEFORE  
CRT IN AF**





**D**

|              | Baseline | 6   | 12  | 24  | 36  | 48  |
|--------------|----------|-----|-----|-----|-----|-----|
| Total n. pts | 673      | 649 | 523 | 365 | 233 | 127 |
| n. deaths    | -        | 12  | 7   | 13  | 7   | 5   |

months

# LEAD PLACEMENT

- **Site of latest activation where viable issue and minimal scar exists**
- **Echo/Doppler/MRI/Nuclear imaging – how much is enough?**
- **Limitations related to coronary vein anatomy**

# **WHAT THE FUTURE HOLDS: Lessons Learned from ICD Rx**

- **Advances in diagnostic and therapeutic technology**
- **Improved pt. selection**
- **Cost-effectiveness**
- **Safety issues and recalls**