ICD and CRT in Heart Failure

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DISCLOSURE INFORMATION
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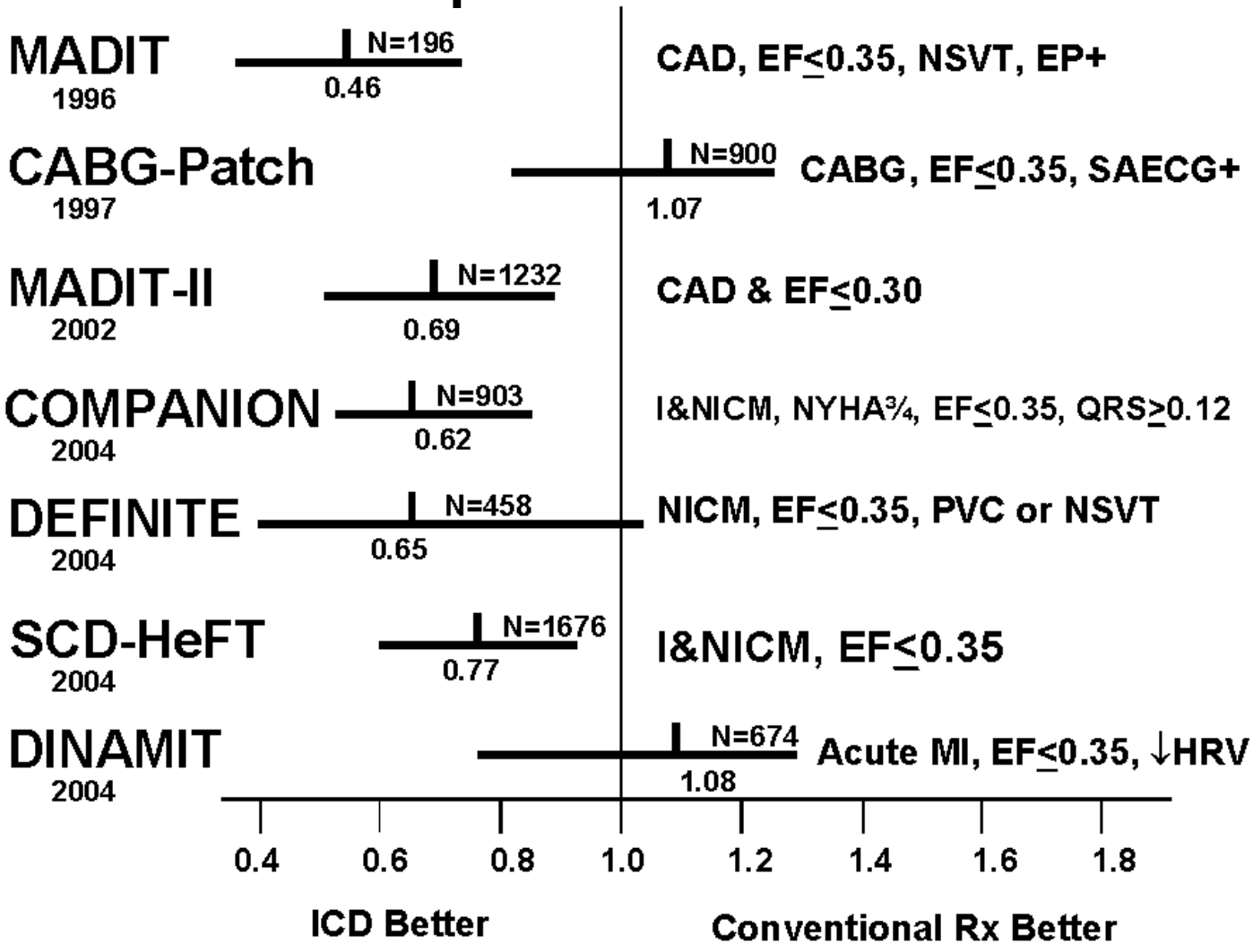
Company	Relationship
Guidant Corporation	Research Grant

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

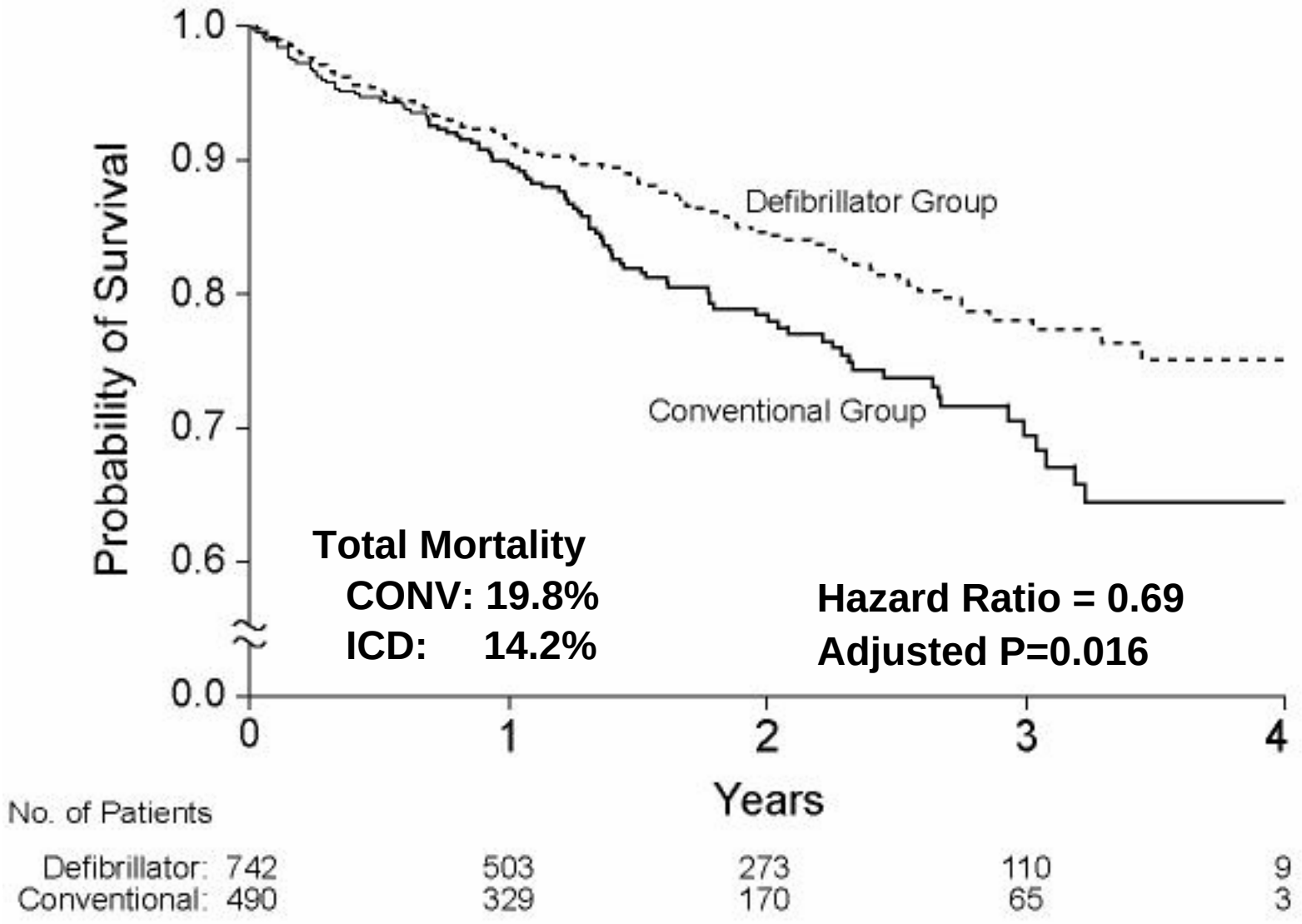
Hazard Ratios in 7 Primary Prevention ICD Trials to Improve Survival



(N=6,039; Hazard Ratio=0.71; P<0.001)

Primary prevention trials

MADIT-II: Kaplan-Meier Survival by Treatment Group



31% reduction in risk of all-cause mortality

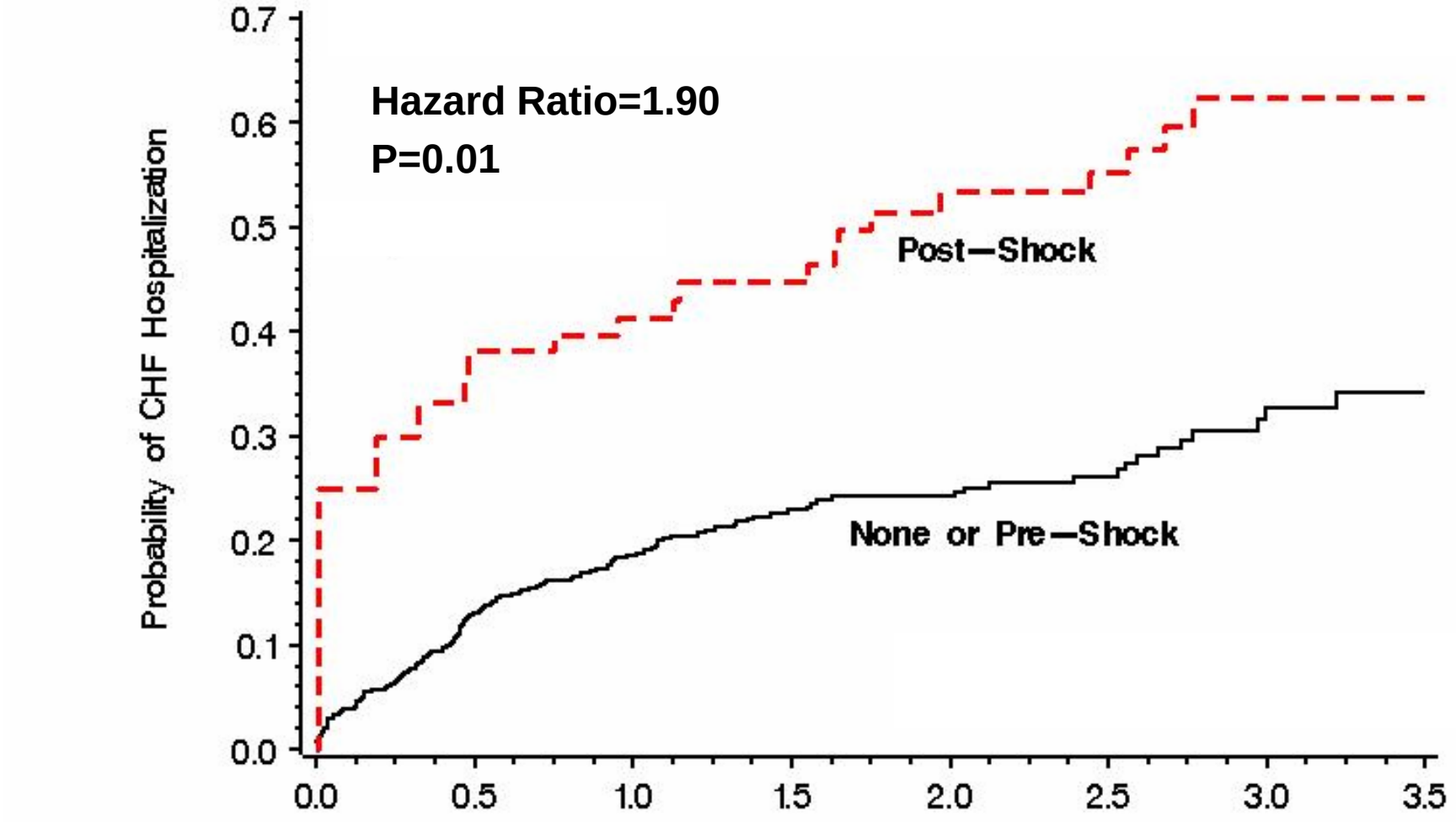
Post-enrollment Heart Failure

Factors Affecting Appropriate Device Therapy for VT/VF

Variable	Hazard Ratio	P-value
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.

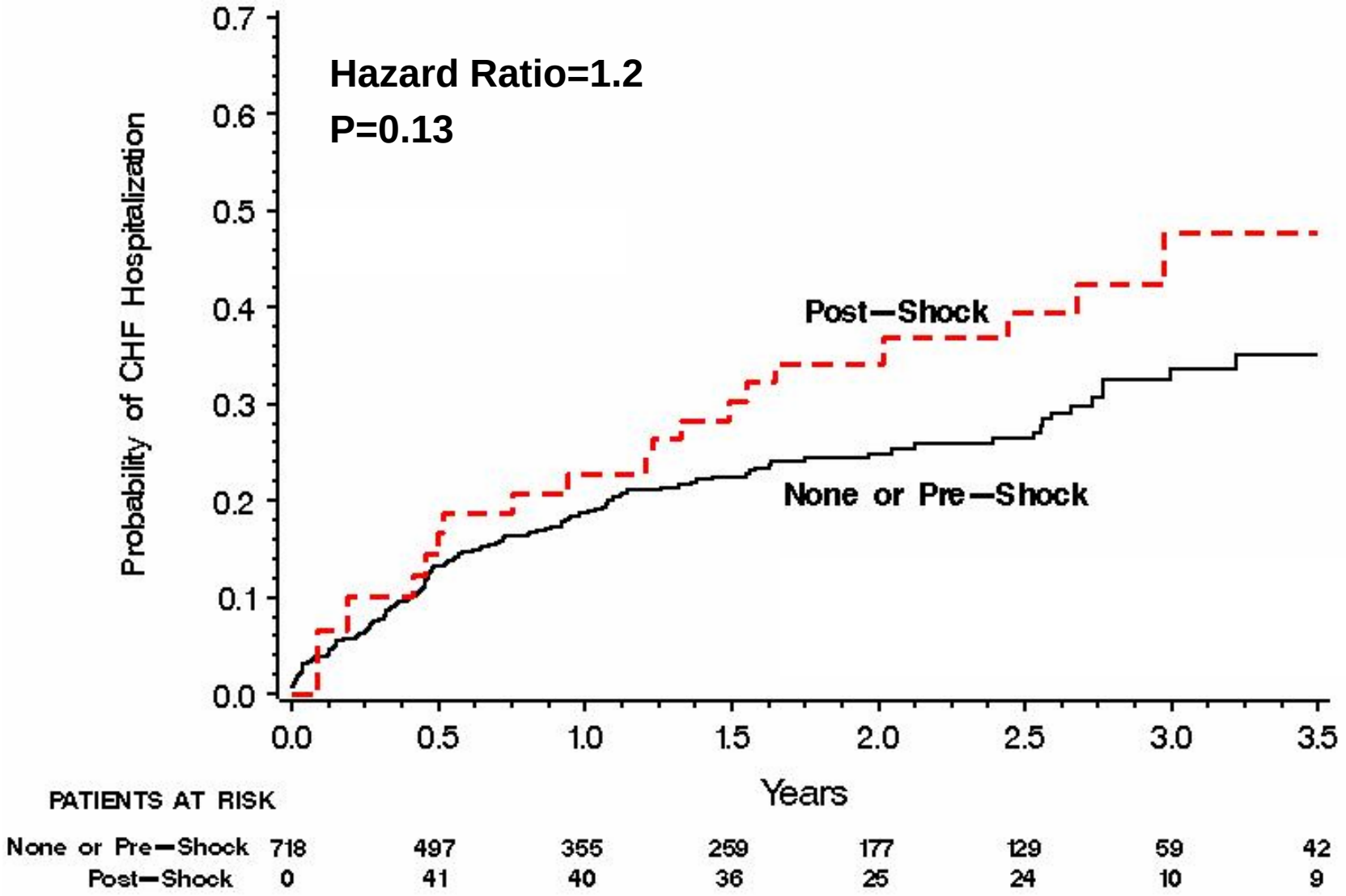
Heart Failure After Appropriate ICD Shock for VT/VF



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



MADIT-II: Risk of Death

Risk factor	Hazard Ratio	P-value
ICD vs. Conv	0.60	<0.001
Post-enrollment HF*	3.80	<0.001

* Time-dependent risk factor

ICD Survival Benefit

	ICD:CONV Hazard Ratio	
Entire FU	0.60 (0.45-0.81)	
Before HF	0.55	p=0.58*
After HF	0.70	

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

Interpretation

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

HEART FAILURE

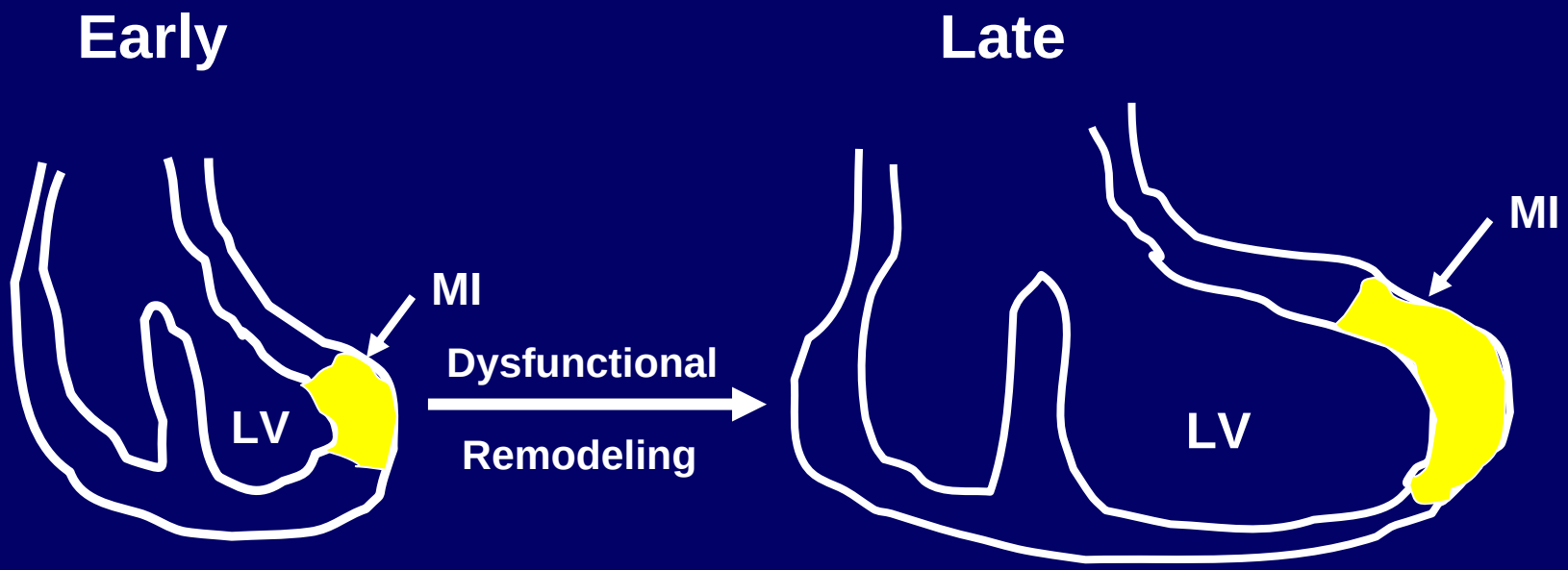
- **Major unresolved public health problem**
- **Vulnerable cardiac substrate: low EF**
- **Heart failure results from dysfunctional remodeling of the LV that occurs over time after MI**

DYSFUNCTIONAL REMODELING

a) Role of asynchronous LV contraction in the development of heart failure

b) Cardiac resynchronization therapy (CRT)

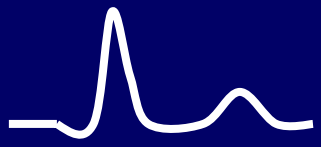
DYSFUNCTIONAL REMODELING AFTER MI



EF=0.30

NYHA I-II

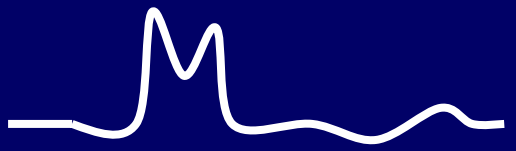
ECG



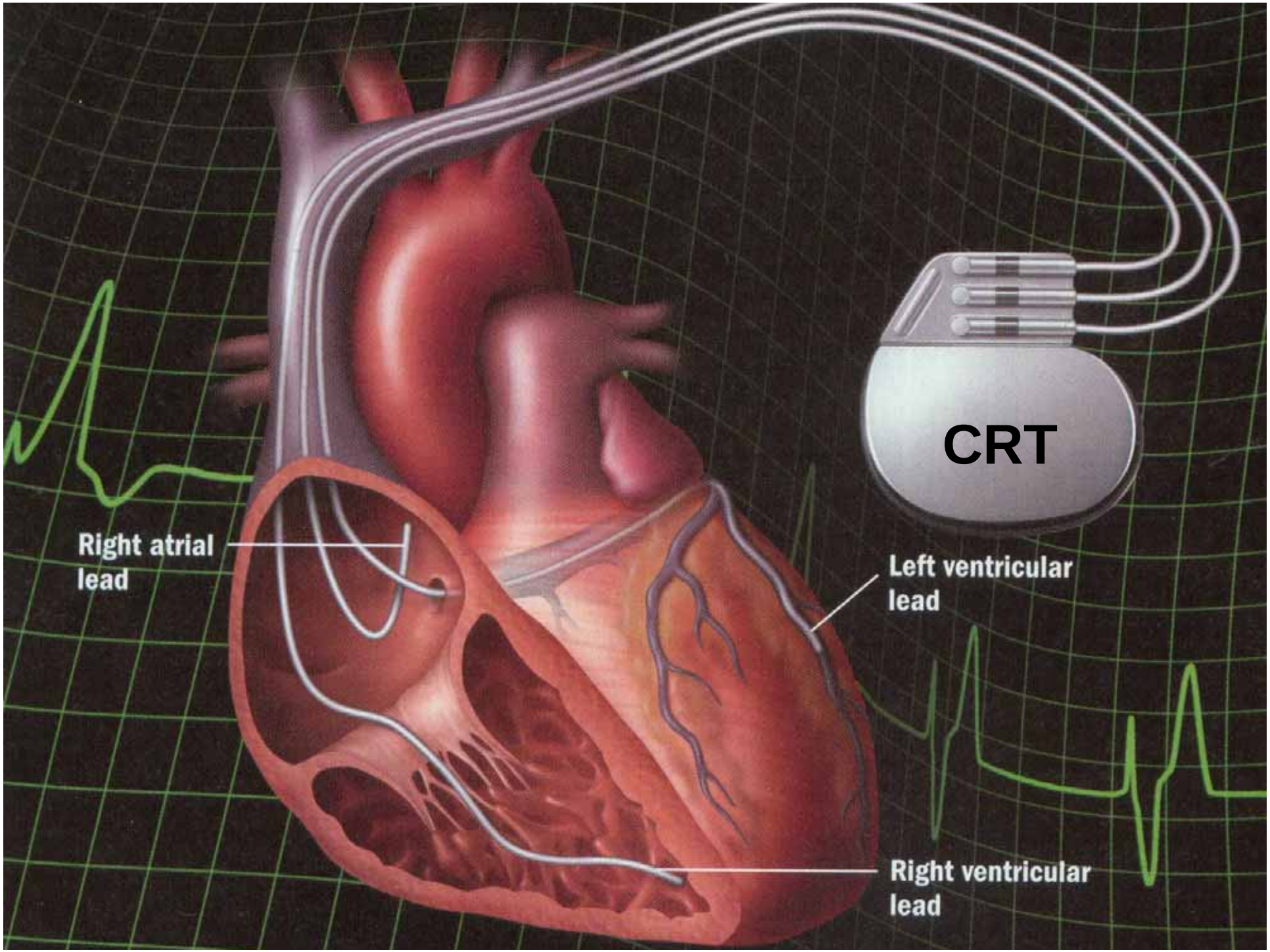
QRS = 0.12s

EF=0.20

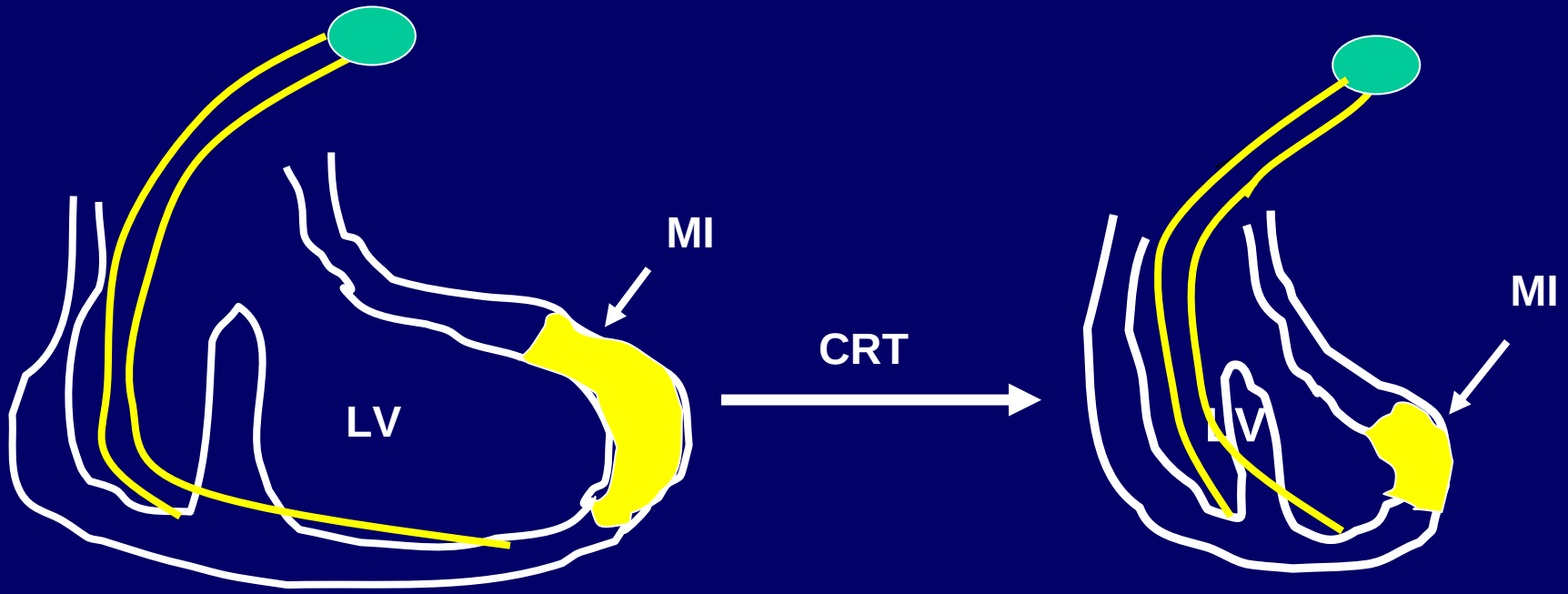
NYHA III-IV



QRS = 0.16s


CRT
Right atrial lead
Left ventricular lead
Right ventricular lead

REVERSE REMODELING WITH CRT (BIV)



EF=0.20

NYHA III-IV

ECG

QRS = 0.15s

EF=0.30

NYHA II-III

QRS = 0.14s

CRT TRIALS IN CHF

(2001-2005: all showed CRT efficacy)

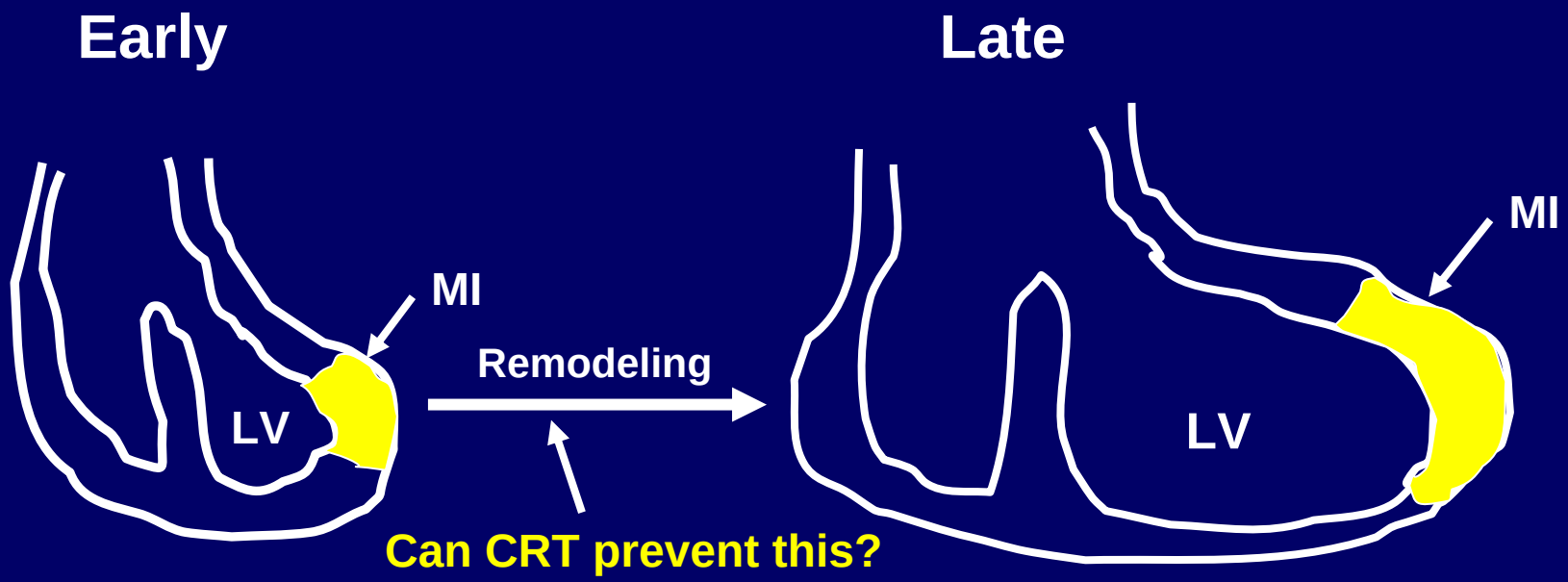
1. PATH-CHF (JACC; 2001) n=25
2. MUSTIC (NEJM; 2001) n=67
3. VIGOR-CHF (JACC; 2002) n=35
4. MIRACLE (NEJM; 2002) n=453
5. CONTAK-CD (JACC; 2003) n=490
6. COMPANION (NEJM; 2004) n=1520
7. CARE-HF (NEJM; 2005) n=813

EF≤0.35; QRS≥0.12; NYHA III-IV

MADIT-III (MADIT-CRT)

A trial started in Dec. 2004 to determine if cardiac resynchronization therapy can inhibit or slow the development of heart failure in at-risk cardiac patients in NYHA class I-II.

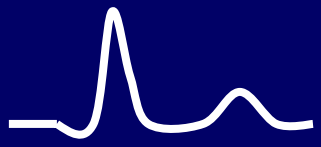
DYSFUNCTIONAL REMODELING



EF=0.30

NYHA I-II

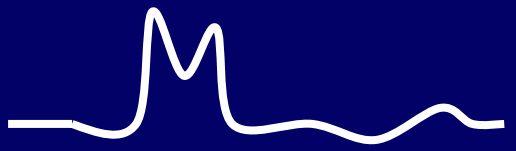
ECG



QRS = 0.12s

EF=0.20

NYHA III-IV



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 (>0.12s), and low EF (≤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

CRT in Heart Failure

- **CRT is clearly indicated in patients with moderate to severe heart failure**
- **CRT is not currently approved for the treatment mild heart failure**
- **MADIT-CRT is designed answer the question of the safety and efficacy of CRT for the prevention of heart failure**