Saving Lives with Electrical Device Therapy

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DISCLOSURE INFORMATION
Arthur J. Moss, MD

Company	Relationship
Boston Scientific	Research Grant

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

ELECTRICAL THERAPEUTICS

Innovation and Patents (year)

Pacemaker: Greatbatch & Chardack (1959)

Implantable Defibrillator: Mirowski & Mower (1968)

Cardiac Resynchronization: Mower & Mirowski (1990)

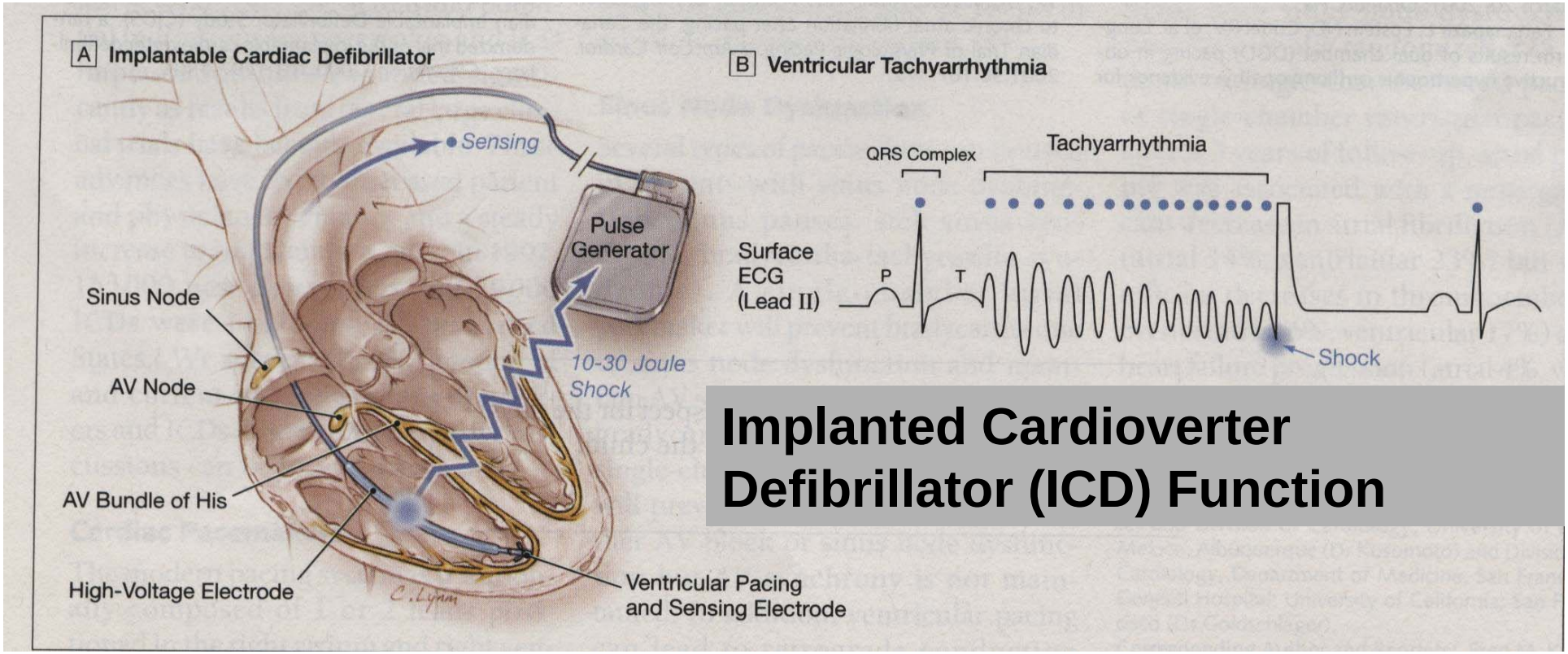
Mieczyslaw (Michel) Mirowski
Mordechai Frydman
1924-1990

Automatic Implantable Defibrillator (AID)

THERAPY AVAILABLE TO IMPROVE SURVIVAL IN HIGH-RISK CARDIAC PATIENTS

- Beta-blockers
- ACE-inhibitors
- Aldosterone blockers
- Revascularization
- Pacemakers
- ICD
- CRT

ICD



Implanted Cardioverter Defibrillator (ICD) Function

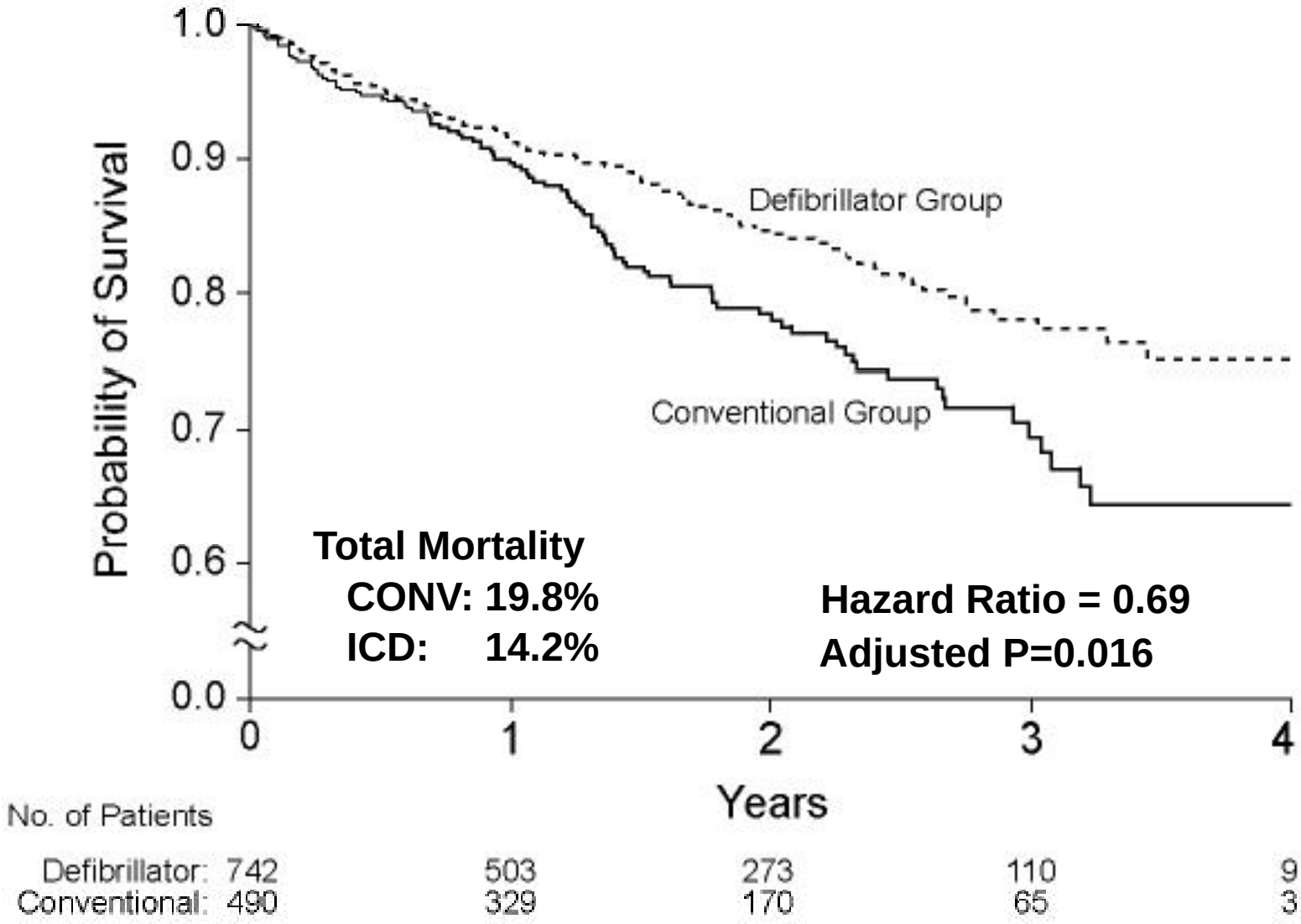
MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL-II (MADIT-II)

Population: prior MI; EF≤0.30

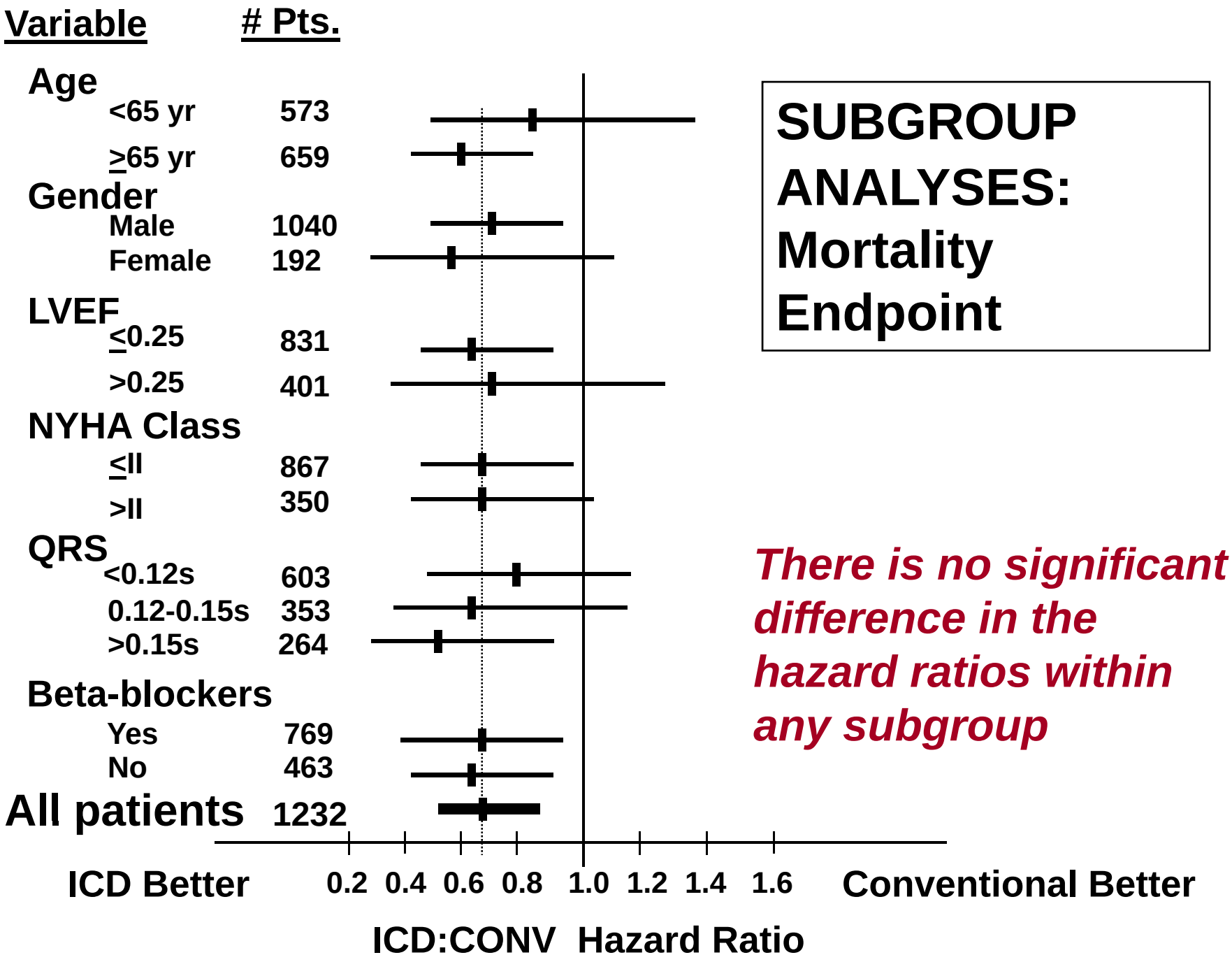
Primary Publication: 2002

Secondary Analyses: 2002-2007

MADIT-II: Kaplan-Meier Survival by Treatment Group



31% reduction in risk of all-cause mortality



SUBGROUP ANALYSES: Mortality Endpoint

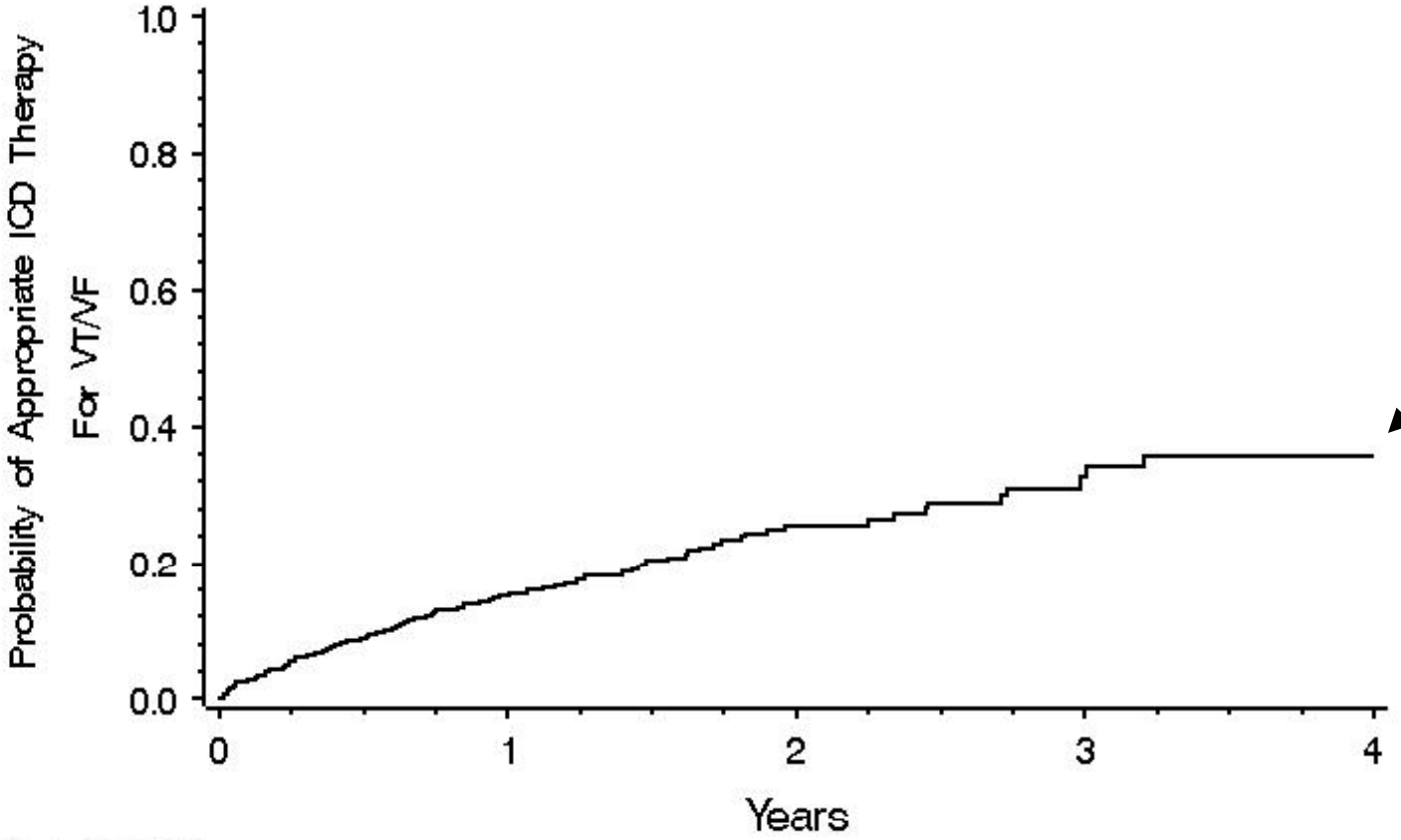
There is no significant difference in the hazard ratios within any subgroup

MADIT-II: Secondary Analyses (2002 – 2006)

1) Appropriate ICD Rx for VT/VF
2) Post-enrollment Heart Failure
3) Age
4) Time after index MI
5) Sudden cardiac death

1. Appropriate ICD Rx for VT/VF

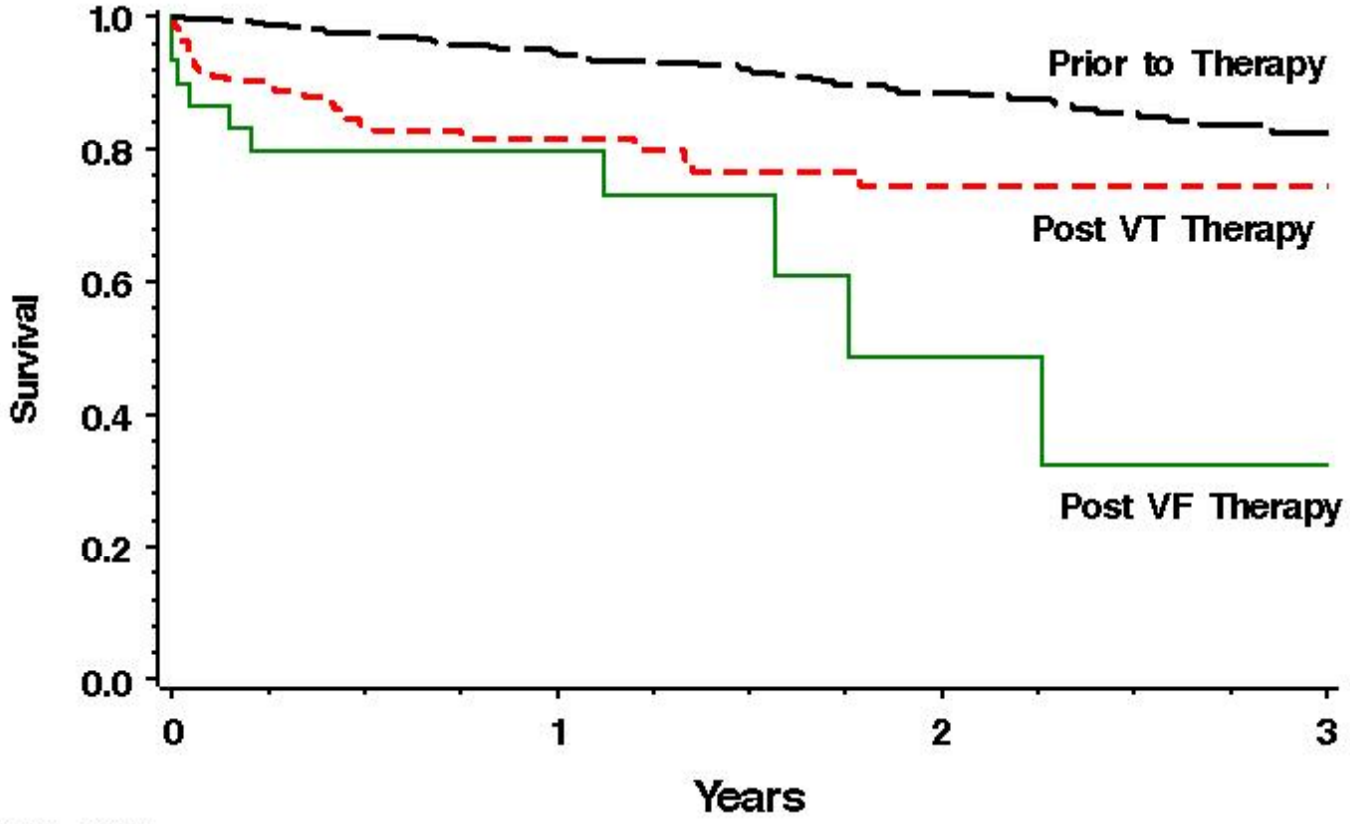
MADIT-II: ICD Therapy for VT/VF



PATIENTS AT RISK

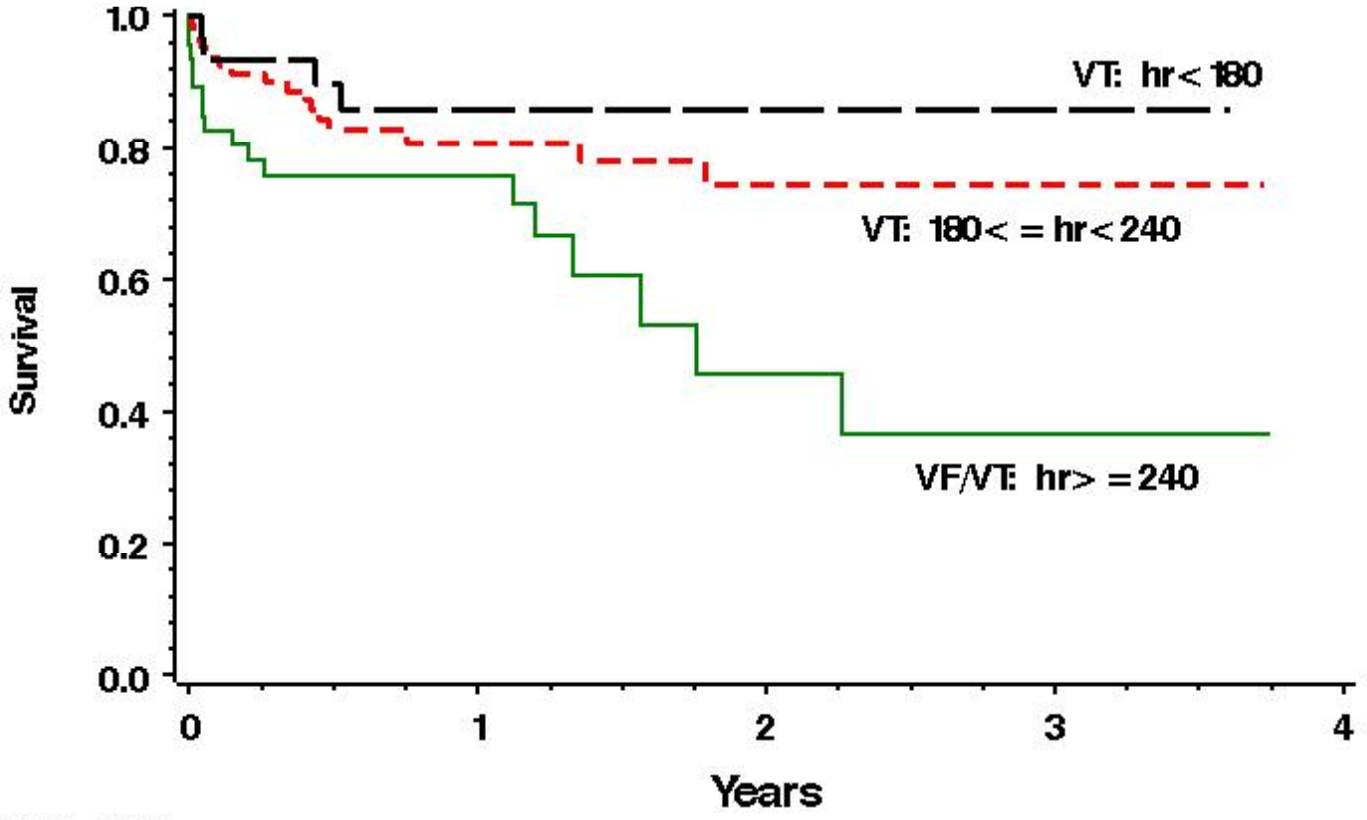
ICD	406	241 (0.15)	122 (0.26)	44 (0.33)	3 (0.36)

MADIT-II: Survival After First Device Therapy for VT or VF



PATIENTS AT RISK			
Prior to Therapy 720	420 (0.94)	207 (0.89)	75 (0.83)
Post VT Therapy 139	61 (0.82)	29 (0.74)	8 (0.74)
Post VF Therapy 30	15 (0.80)	3 (0.49)	1 (0.32)

MADIT-II: Survival After First Device Therapy by Rate of VT/VF



PATIENTS AT RISK					
VT: hr< 180	32	16 (0.86)	11 (0.86)	4 (0.86)	0 (0.86)
VT: 180< = hr< 240	84	35 (0.81)	16 (0.74)	3 (0.74)	0 (0.74)
VF/VT: hr> = 240	46	23 (0.76)	5 (0.46)	2 (0.36)	0 (0.36)

Cause of Death After Appropriate ICD Therapy

	First Terminated Arrhythmia		
	None	VT	VF
	(1-year mortality rate)*		
All cause	6	18	20
Cardiac	5	15	20
SCD	2	7	4
NSCD	3	8	16

*Adjusted for exposure time.

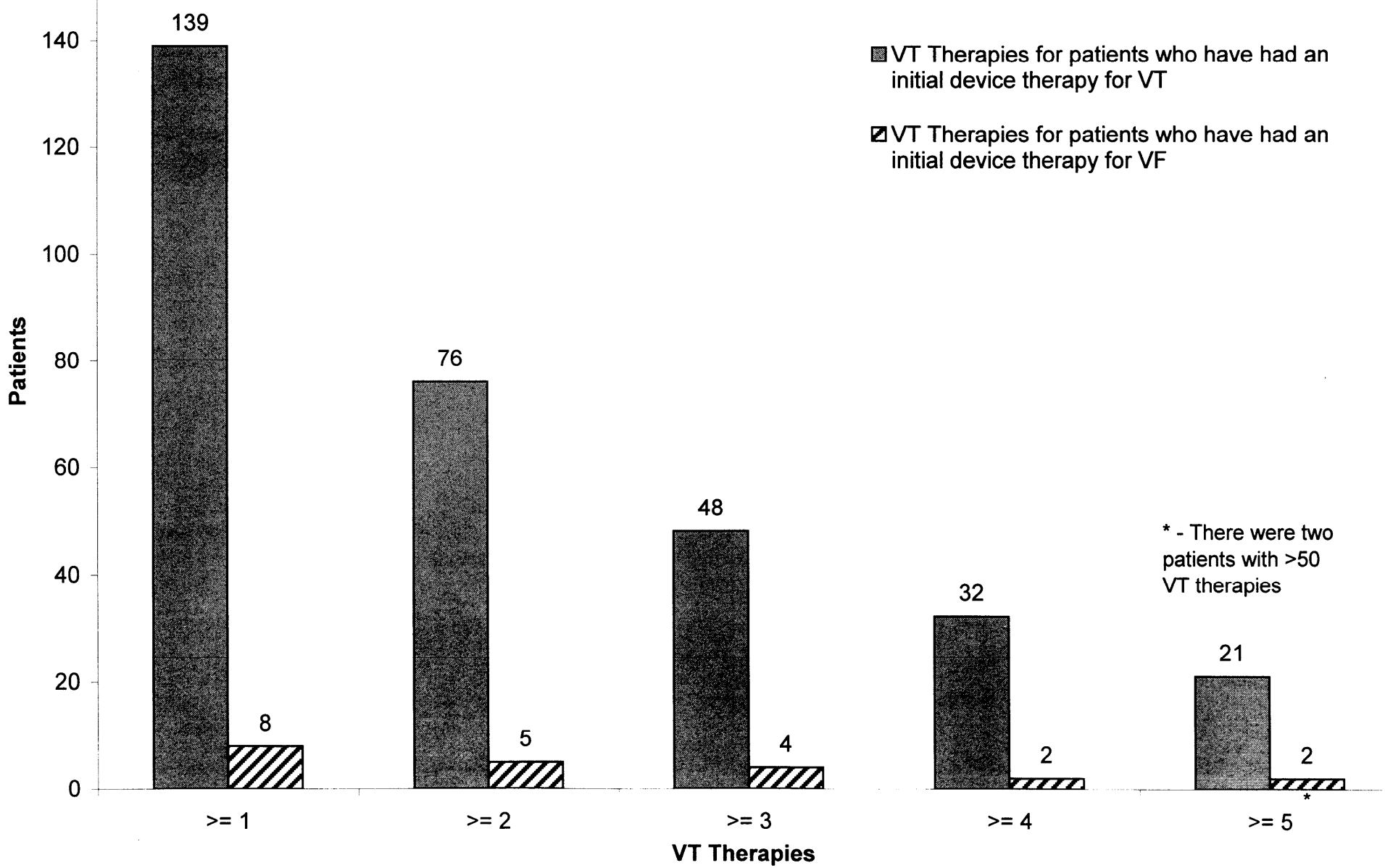
MADIT-II: Successful Device Therapies

720 patients received an ICD

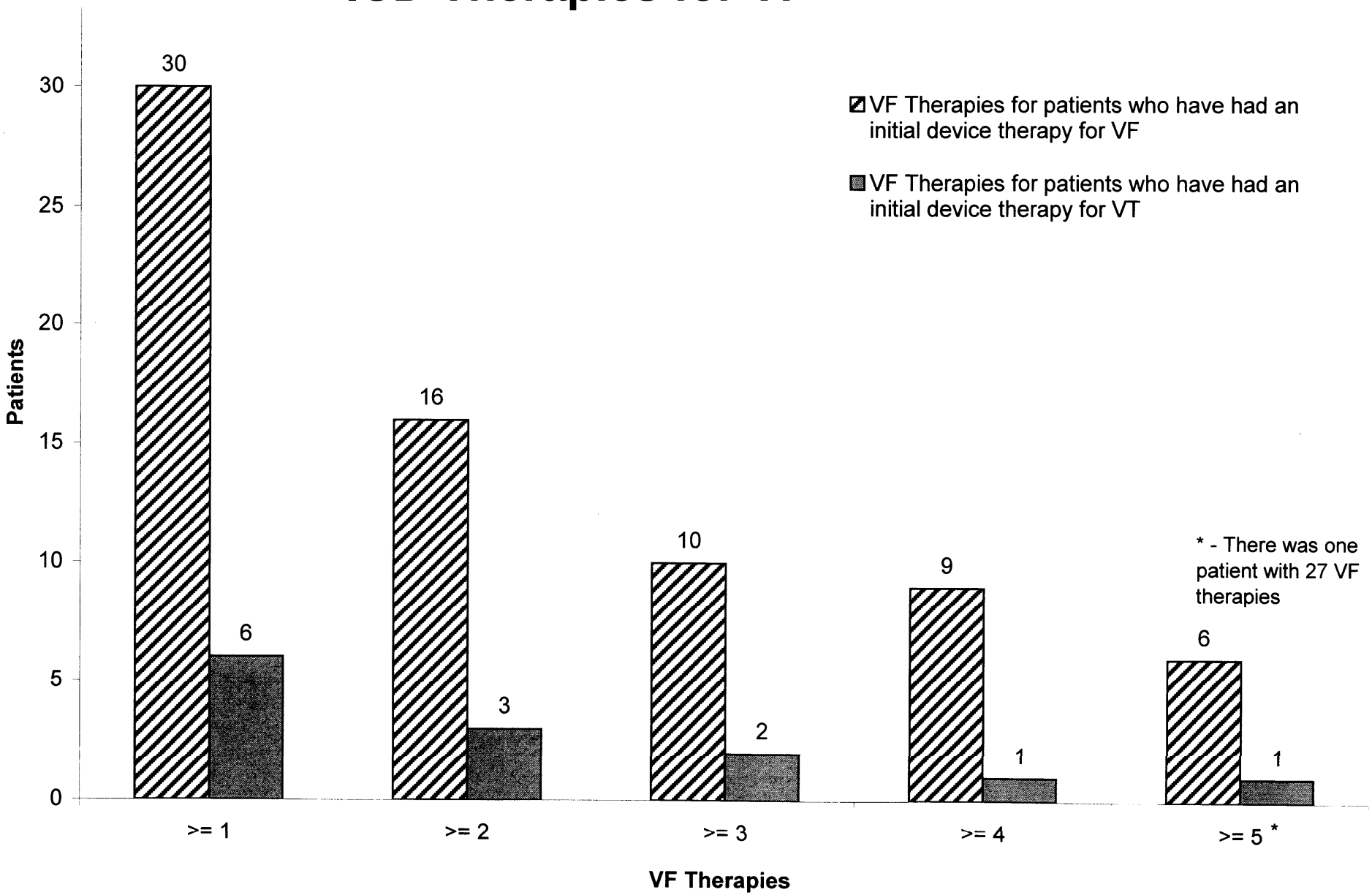
169 pts received 701 appropriate ICD therapies for VT or VF:

- 281 episodes of VT terminated by ATP
- 305 episodes of VT terminated by shock
- 115 episodes of VF terminated by shock

ICD Therapies for VT: 48% Terminated by ATP



ICD Therapies for VF



2. Post-enrollment Heart Failure

a) HF: As a risk factor for VT/VF

b) HF: After ICD Rx for VT/VF

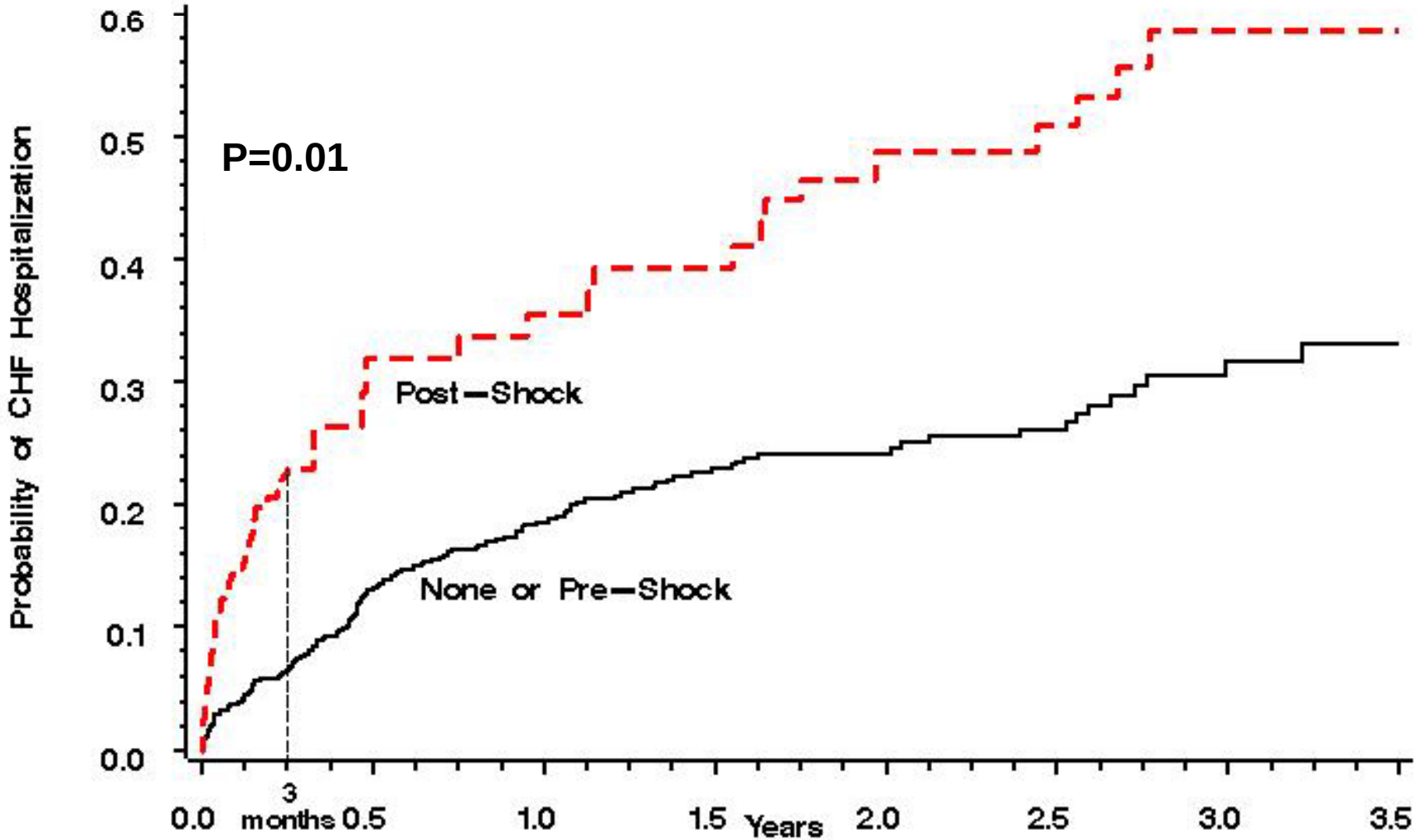
c) HF: As a risk factor for mortality

Risk Factors for 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.

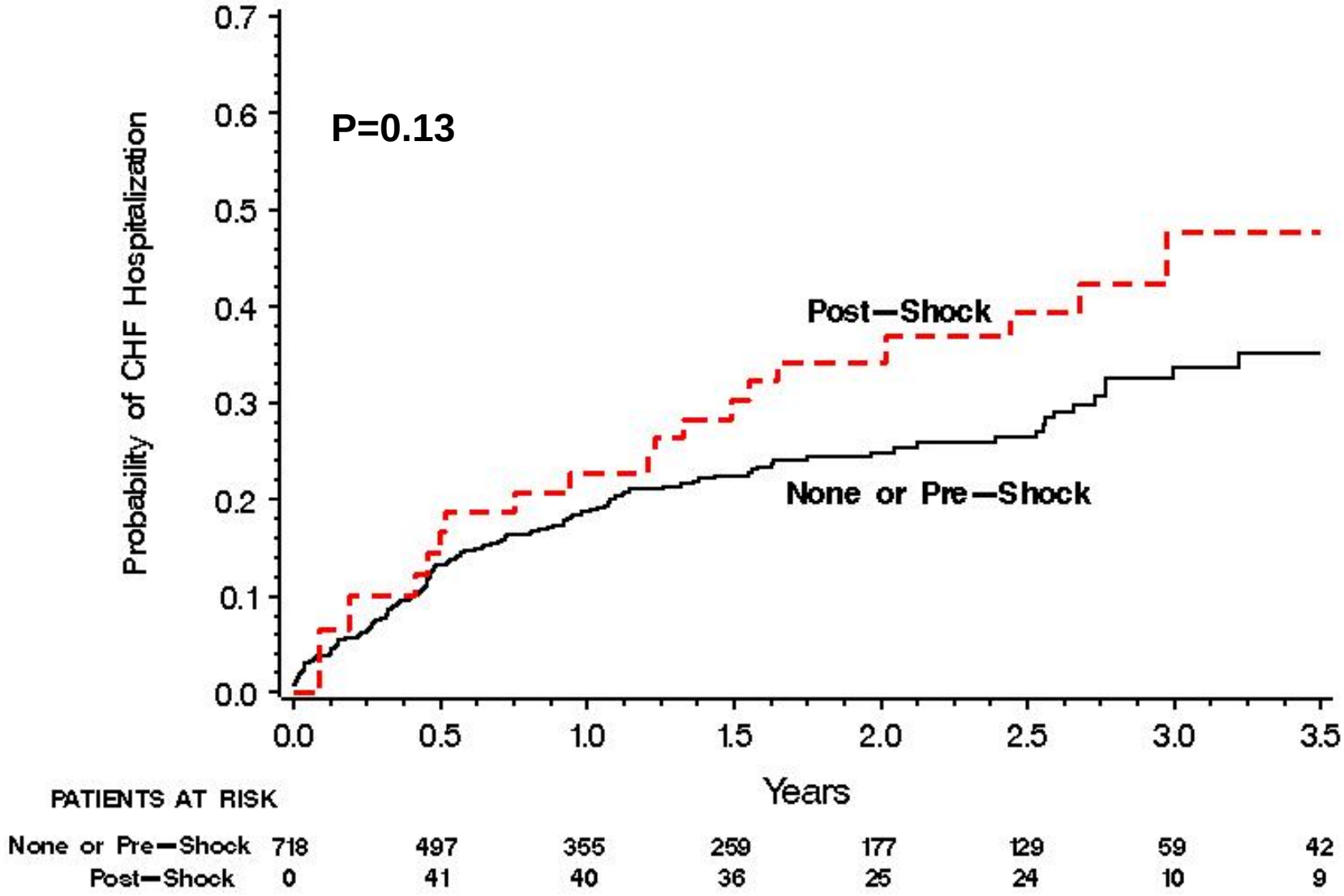
Heart Failure After Appropriate ICD Shock for VT/VF



Patients at risk:

Pre—Shock	718	512	360	262	178 (0.24)	129	62	46
Post—Shock	0	26	35	33	24 (0.49)	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

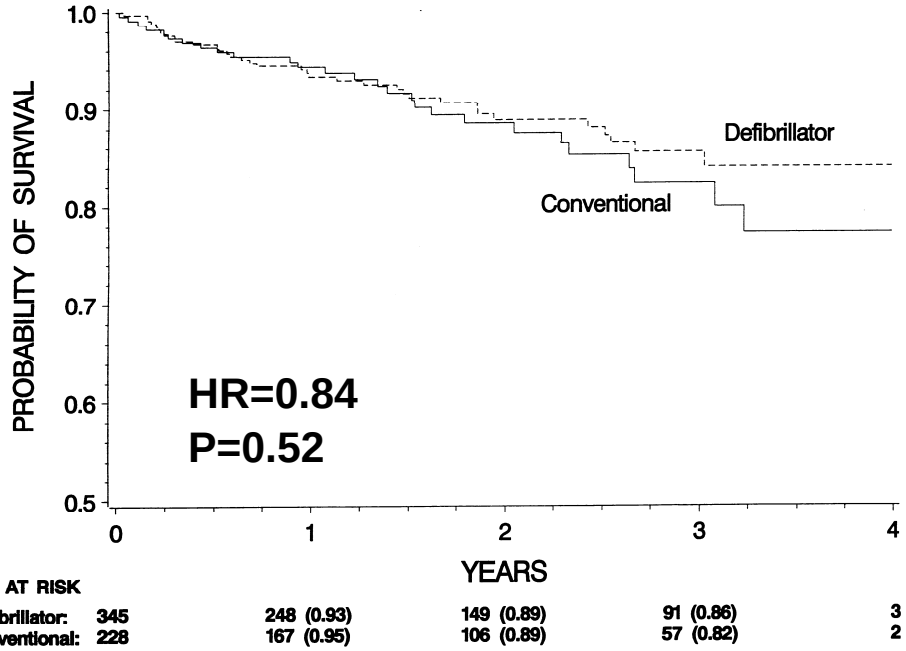
Interpretation

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

3. Age

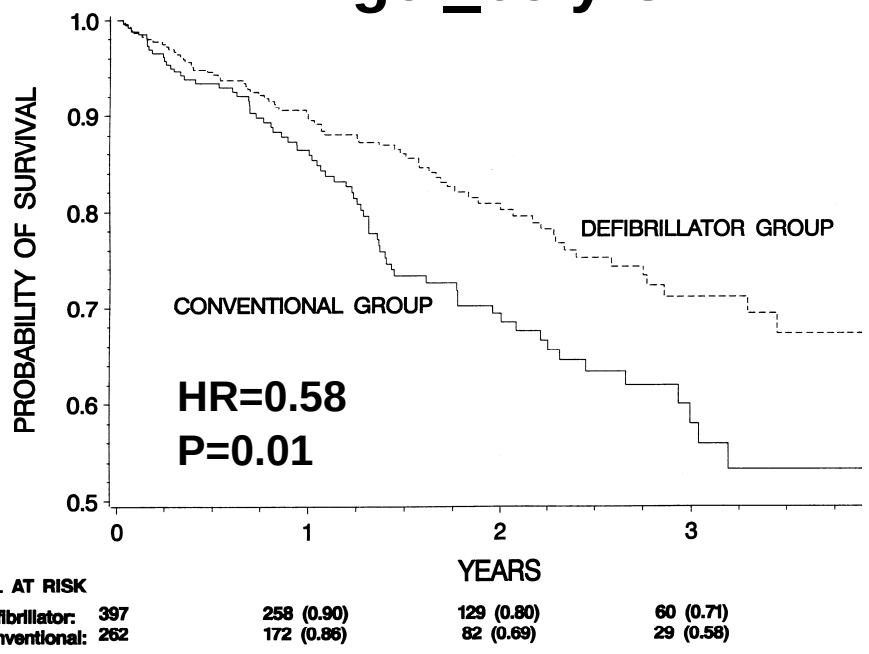
MADIT-II and Age

Age <65 yrs



NO. AT RISK					
Defibrillator:	345	248 (0.93)	149 (0.89)	91 (0.86)	3
Conventional:	228	167 (0.95)	106 (0.89)	57 (0.82)	2

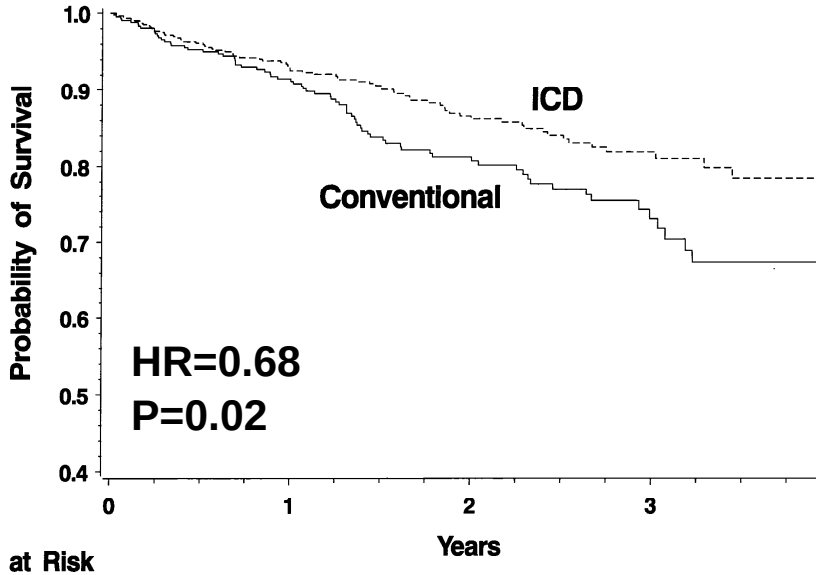
Age ≥65 yrs



NO. AT RISK				
Defibrillator:	397	258 (0.90)	129 (0.80)	60 (0.71)
Conventional:	262	172 (0.86)	82 (0.69)	29 (0.58)

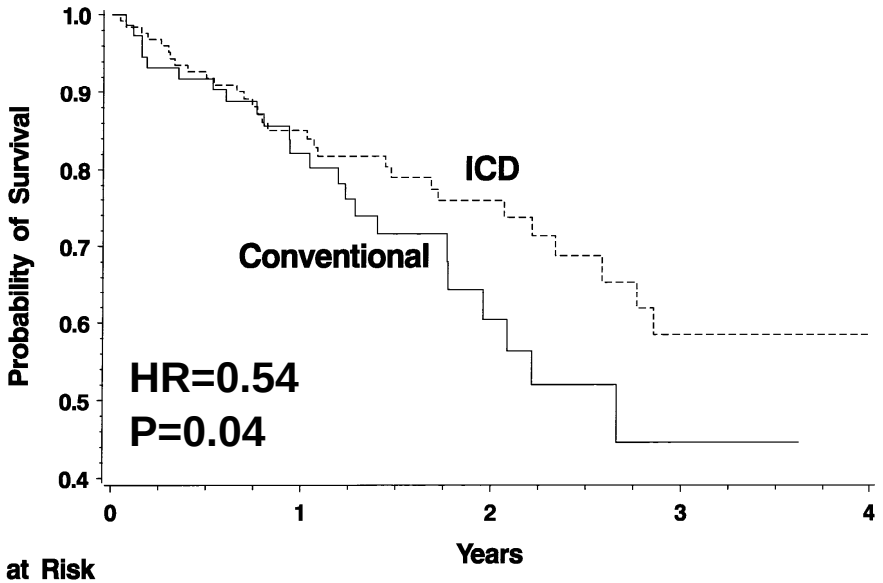
MADIT-II and Age

Age <75 yrs



No. at Risk				
ICD: 614	425 (0.93)	237 (0.86)	96 (0.82)	
Conv: 414	283 (0.91)	155 (0.81)	61 (0.73)	

Age ≥75 yrs



No. at Risk				
ICD: 128	78 (0.85)	37 (0.76)	14 (0.58)	1
Conv: 76	46 (0.86)	15 (0.60)	4 (0.45)	0

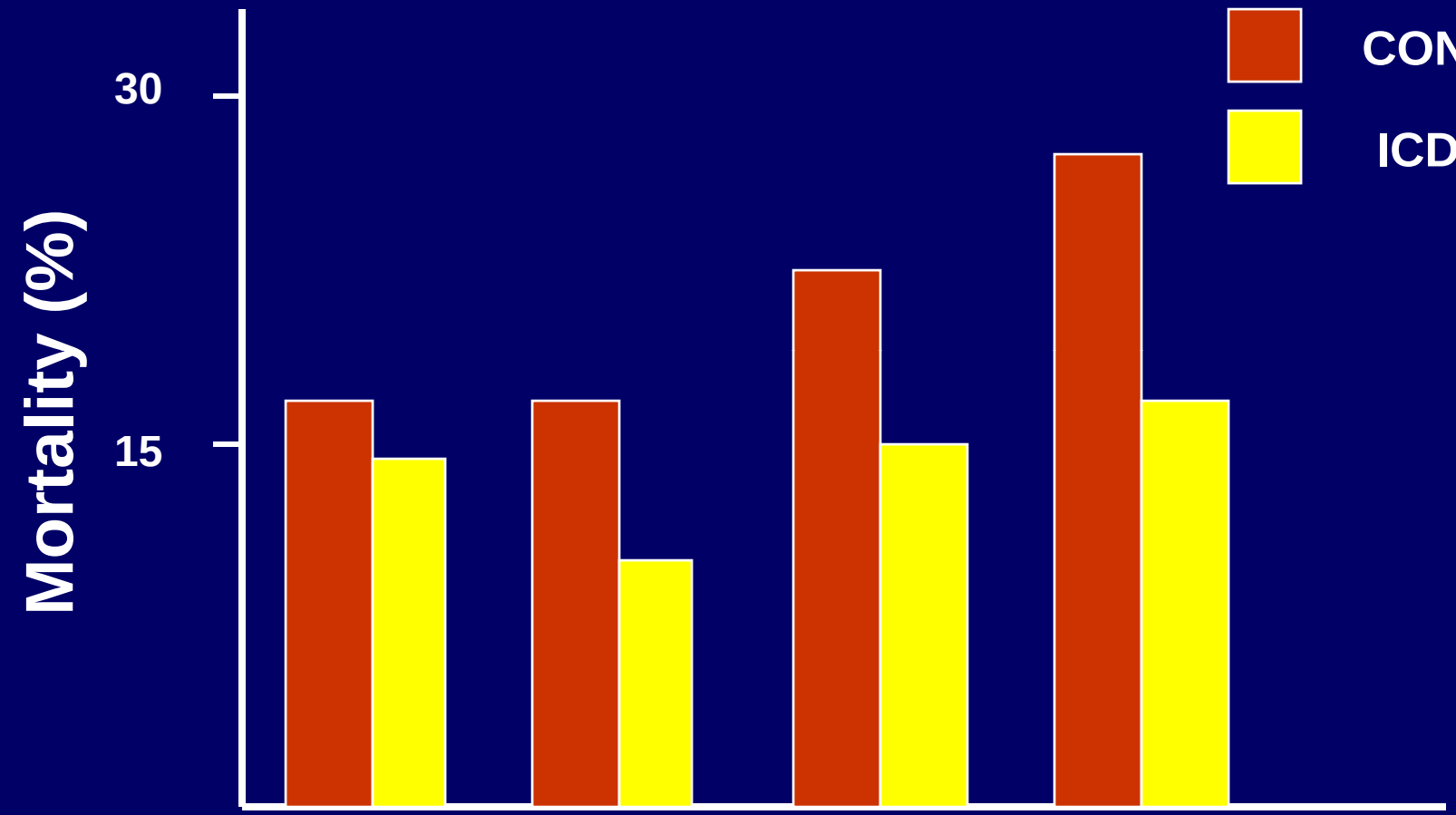
MADIT-II: Risk by Age Group

	$Mortality_{ICD:CONV}$ Hazard Ratio	P-value
Medicare Age (yrs)		
<65	**0.84**	**0.52**
≥65	**0.58**	**0.01**
Geriatric Age (yrs)		
<75	**0.68**	**0.02**
≥75	**0.54**	**0.04**

Note: the lower the hazard ratio below 1.0, the greater the survival benefit from the ICD.

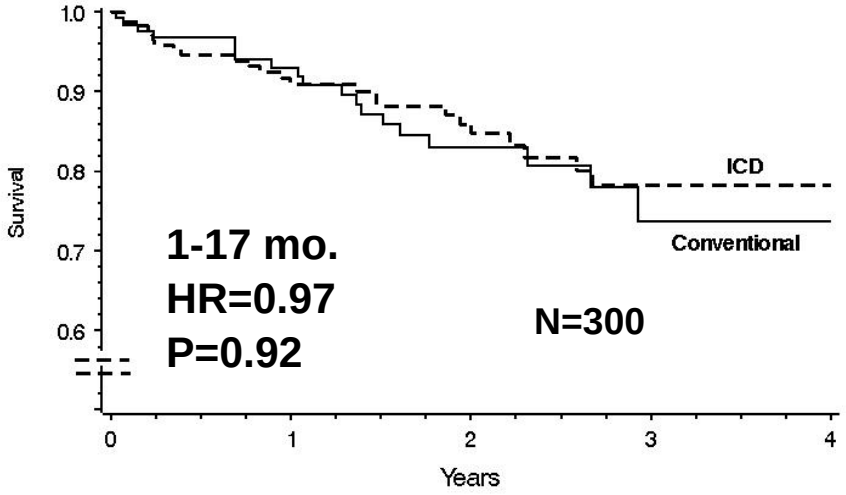
4. Time After MI

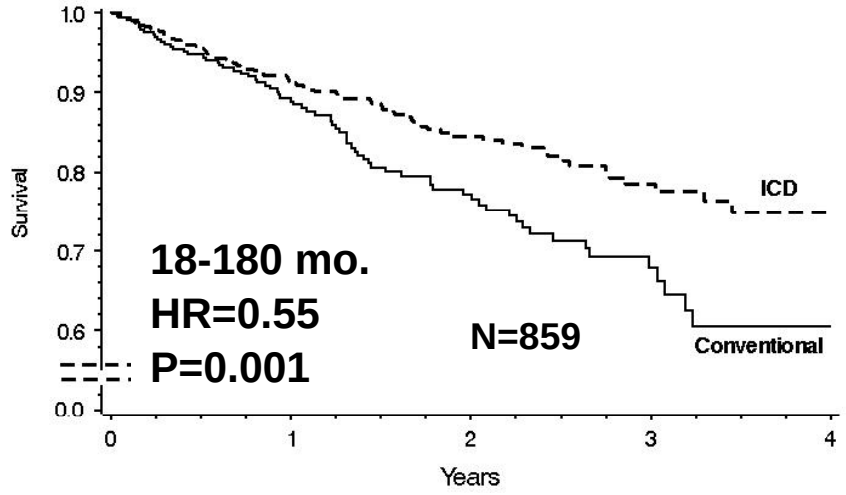
Mortality Risk & ICD Efficacy: Time After MI



Mo. after MI	1-17	18-59	60-121	>121
Odds Ratio	0.88	0.63	0.68	0.63

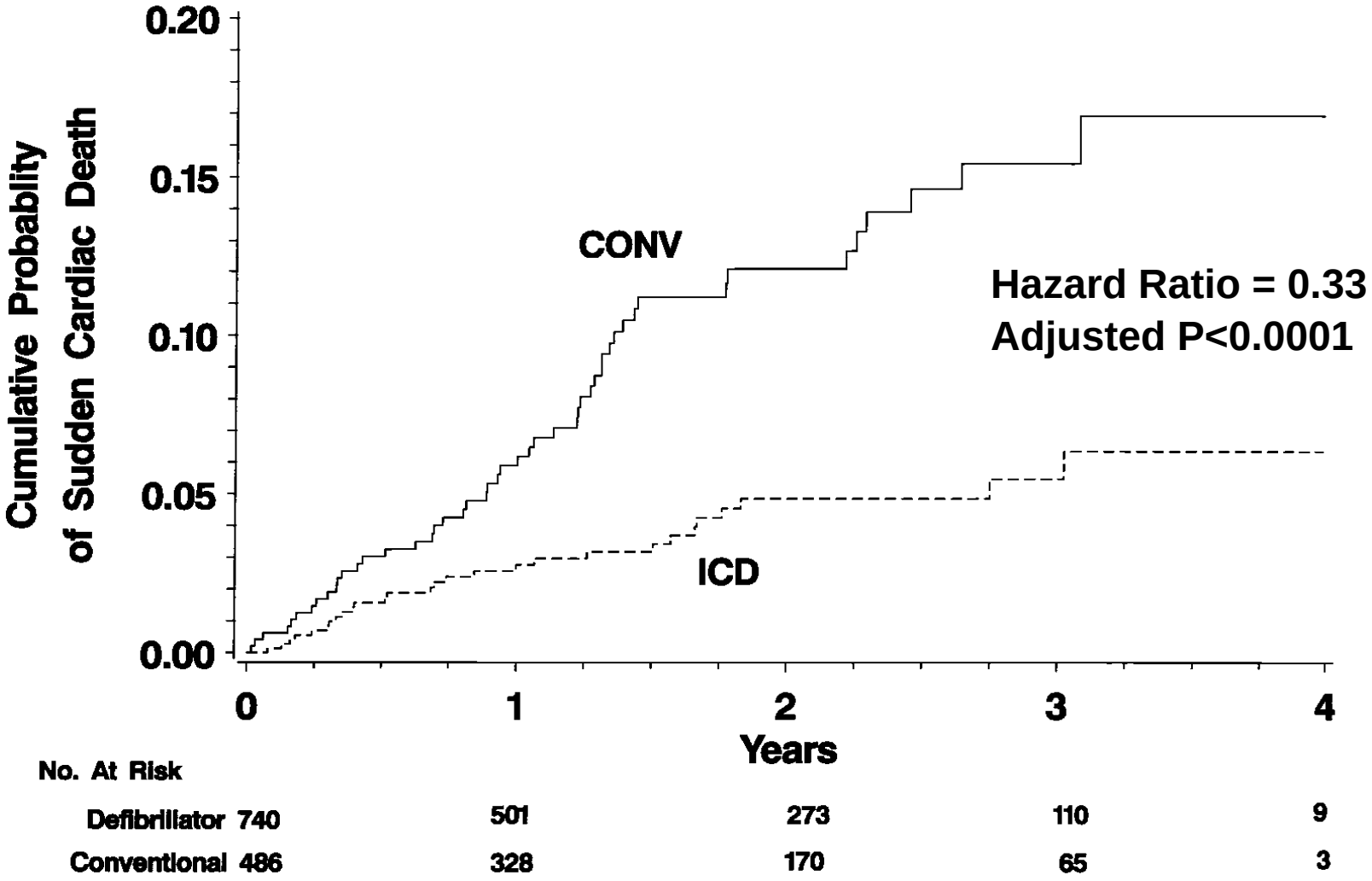
Time from Most Recent MI





5. Sudden Cardiac Death

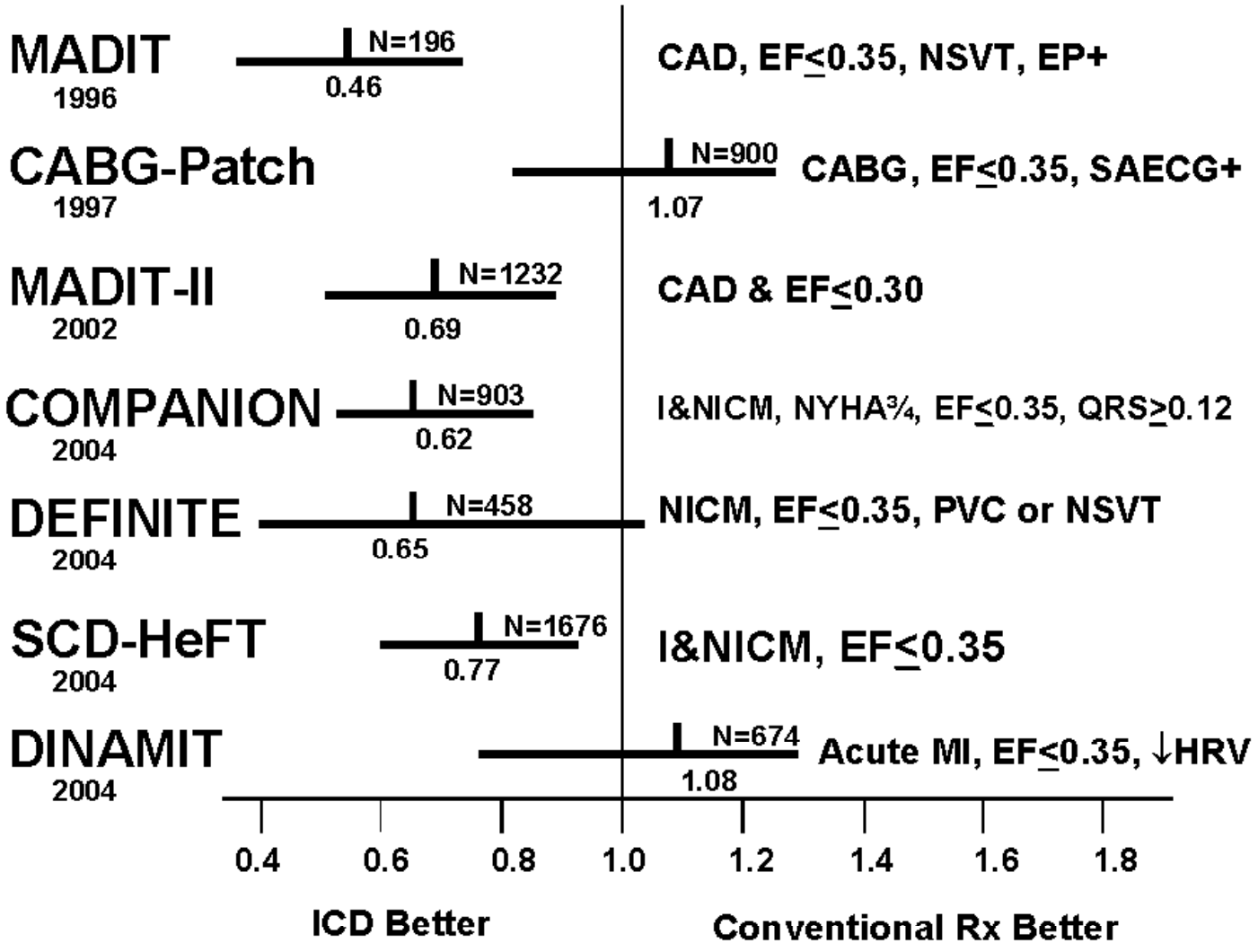
MADIT-II: SCD


Cumulative Probability of Sudden Cardiac Death
0.20
0.15
0.10
0.05
0.00
CONV
ICD
Hazard Ratio = 0.33
Adjusted P<0.0001
0
1
2
3
4
Years
No. At Risk
Defibrillator 740 501 273 110 9
Conventional 486 328 170 65 3

MADIT-II: CONCLUSIONS

1. ICD saves lives by reducing SCD in high-risk coronary patients with LVD
2. ICD consistently effective in all MADIT-II subgroups, with greater efficacy in pts. at higher risk
3. Post-enrollment HF plays an important role in the clinical course of ICD-treated patients
4. Life-prolonging ICD therapy appears to transform a SCD risk into a HF risk

Hazard Ratios in 7 Primary Prevention ICD Trials



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

HEART FAILURE

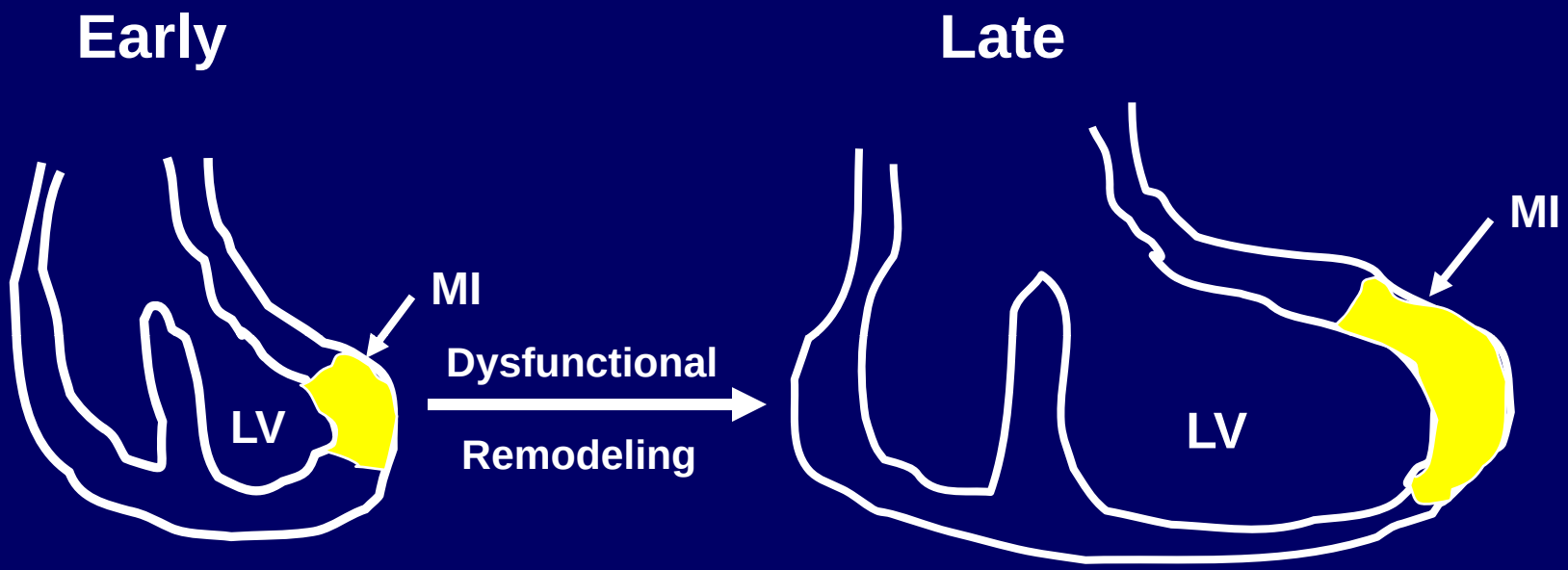
- **Major unresolved public health problem**
- **Vulnerable cardiac substrate: low EF**
- **Heart failure results from dysfunctional remodeling of the LV that occurs over time after MI**

DYSFUNCTIONAL REMODELING

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

b) Electrical resynchronization therapy

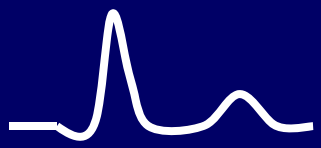
DYSFUNCTIONAL REMODELING AFTER MI



EF=0.30

NYHA I-II

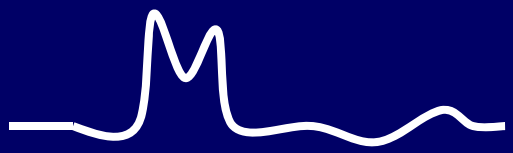
ECG



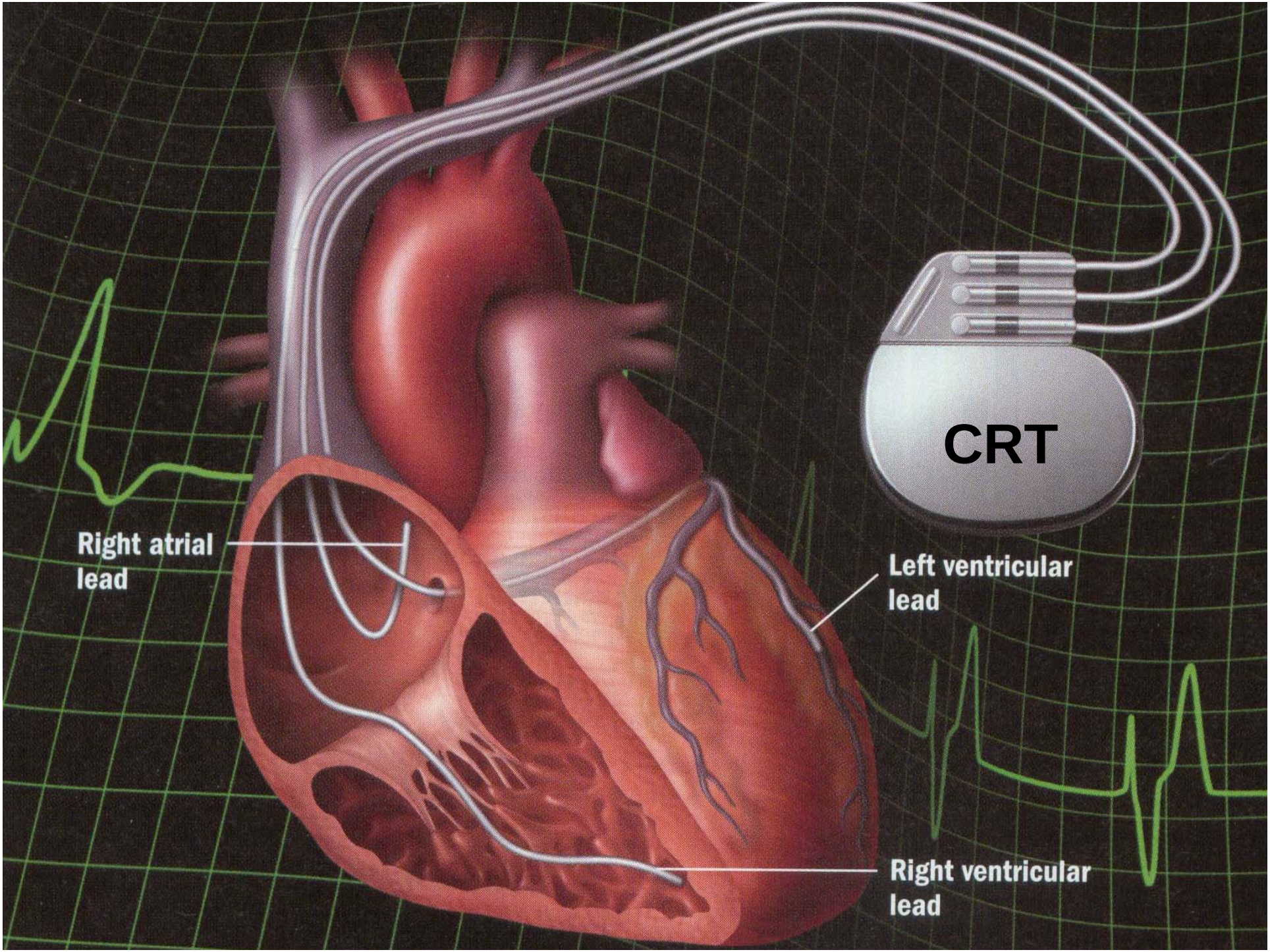
QRS = 0.12s

EF=0.20

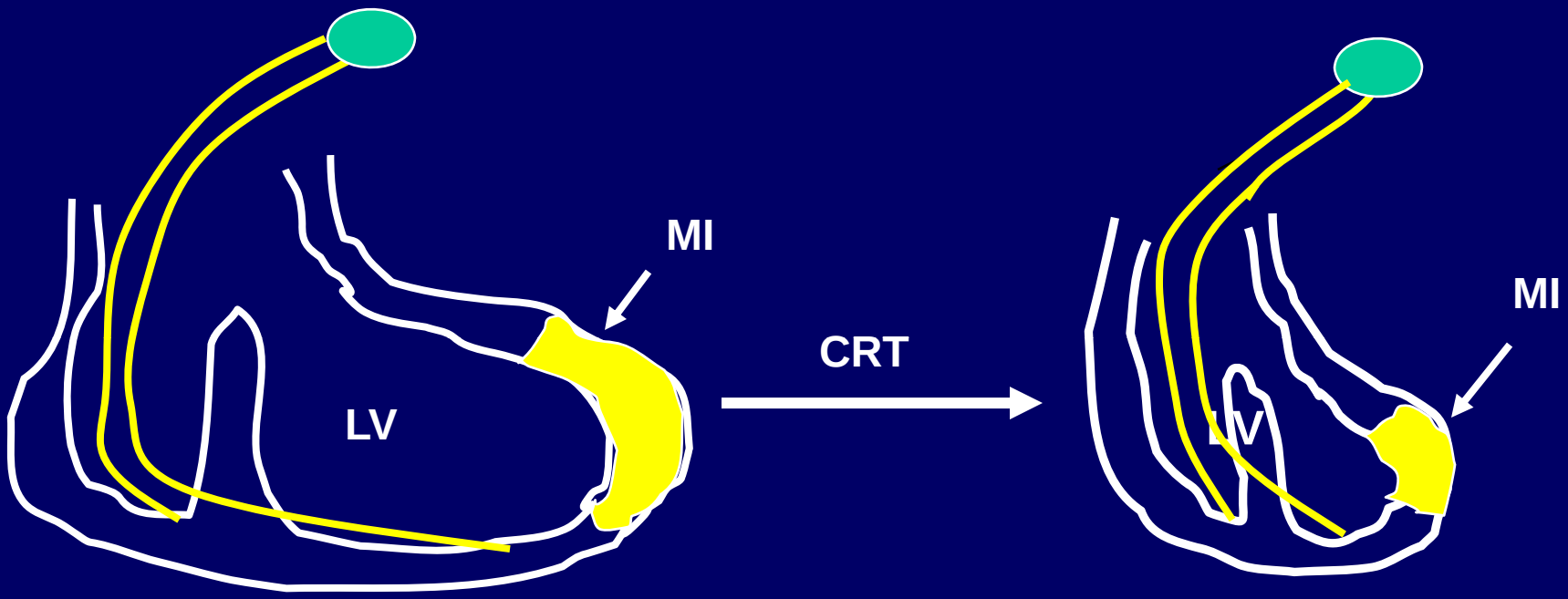
NYHA III-IV



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 (2001-2006)

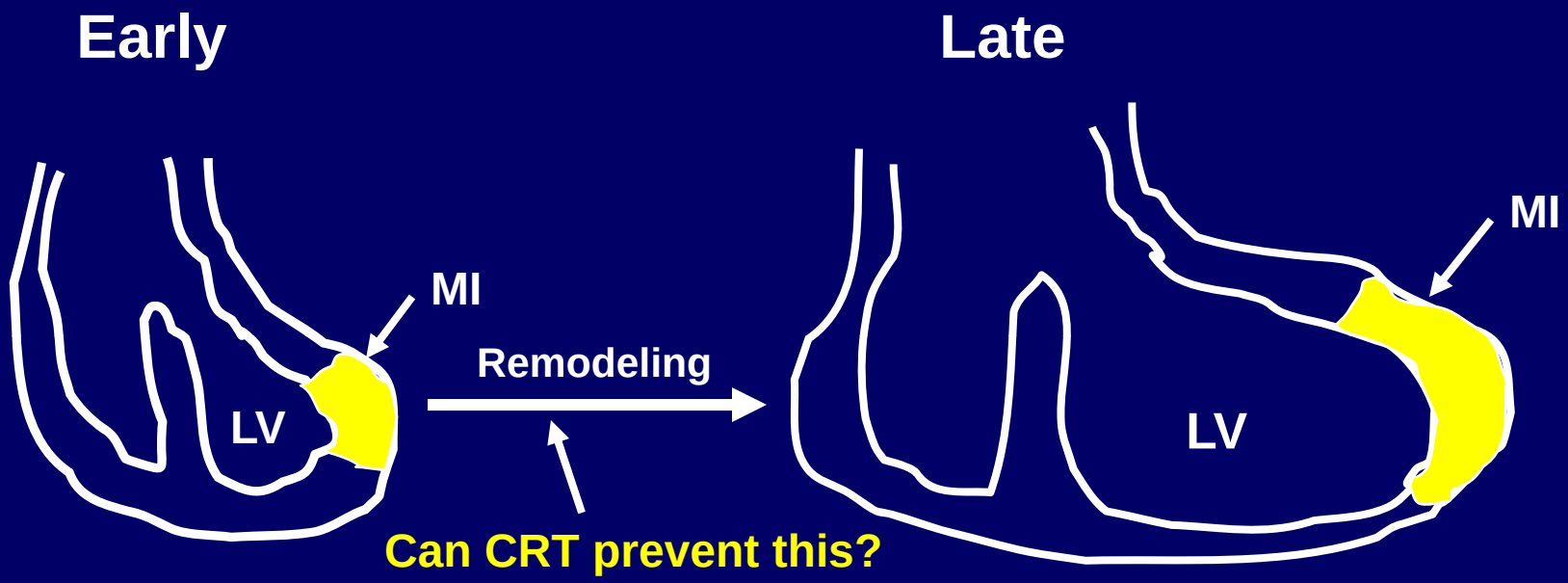
1. PATH-CHF (JACC; 2001) n=25
2. MUSTIC (NEJM; 2001) n=67
3. VIGOR-CHF (JACC; 2002) n=35
4. MIRACLE (NEJM; 2002) n=453
5. CONTAK-CD (JACC; 2003) n=490
6. COMPANION (NEJM; 2004) n=1520
7. CARE-HF (NEJM; 2005) n=813
8. CARE-HF LTFU (EU HT J, 2006)

EF≤0.35; QRS≥0.12; NYHA III-IV

MADIT-III (MADIT-CRT)

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

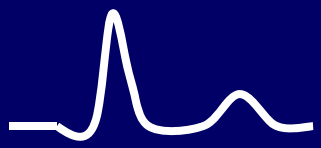
DYSFUNCTIONAL REMODELING



EF=0.30

NYHA I-II

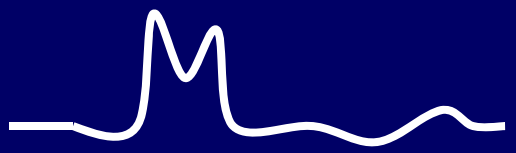
ECG



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 (≥0.13s), 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: 100 enrolling cntrs. in US & Europe
  - duration of trial: 3-4 years
  - End point: heart failure or death, which ever comes first

CONCLUSION

- **Past and Present:** development and application of electrical devices for: 1) prevention of sudden death (pacemakers & ICDs), and 2) treatment of heart failure (CRT)
- **Future:** 1) refinement of electrical devices to prevent and/or slow development of heart failure; 2) electric fields to locally inhibit intravascular coagulation