# ICD and CRT/CRTD in Preventing Sudden Cardiac Death

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# Treatments of Potential Utility to Reduce SCD

### Correcting Ischemia
- Revascularization
- Beta-blocker

### Preventing Plaque Rupture
- Statin
- ACE inhibitor
- Aspirin

### Stabilizing Autonomic Balance
- Beta-Blocker
- ACE inhibitor

### Improving Pump Function
- ACE inhibitor
- Beta-Blocker

### Prevention of Arrhythmias
- Beta-Blocker

### Terminating Arrhythmias
- ICDs, CRT-D
- AEDs

### Blocks Effects of Residual Aldosterone
- Aldosterone receptor blockade

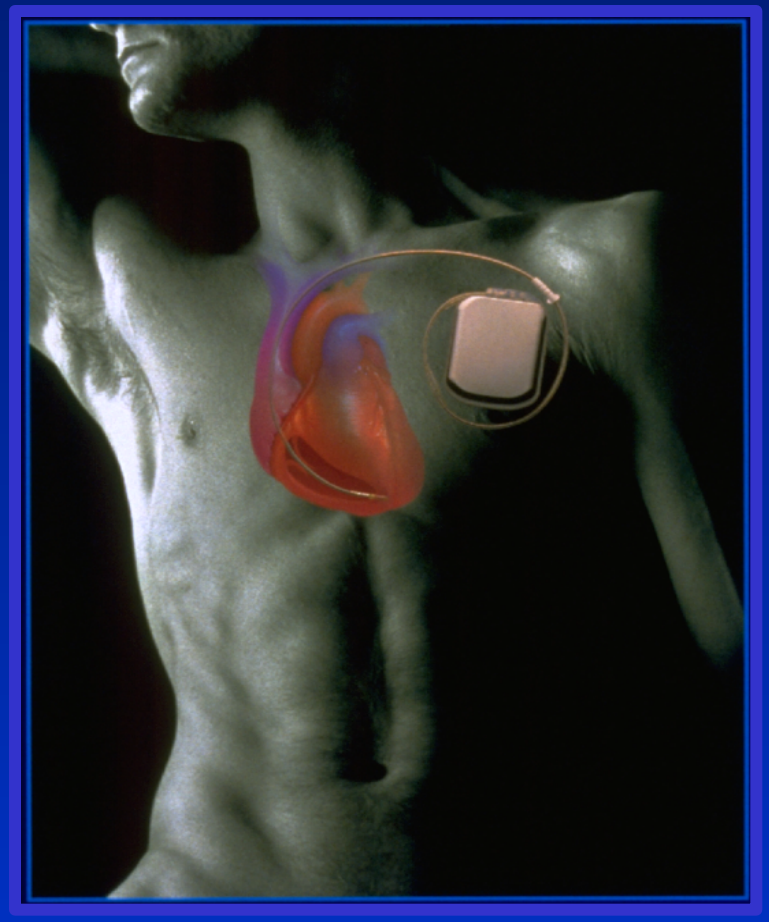
Zipes DP. *Circulation*. 1998;98:2334-2351.
Pitt B. *N Engl J Med*. 2003;348:1309-1321.

# Lifestyle / Risk Factor Modification in Post-MI Patients[1,2]

- Diet and Nutrition
- Weight Management
- Smoking Cessation
- Moderate Alcohol Consumption
- Exercise
- Stress Management

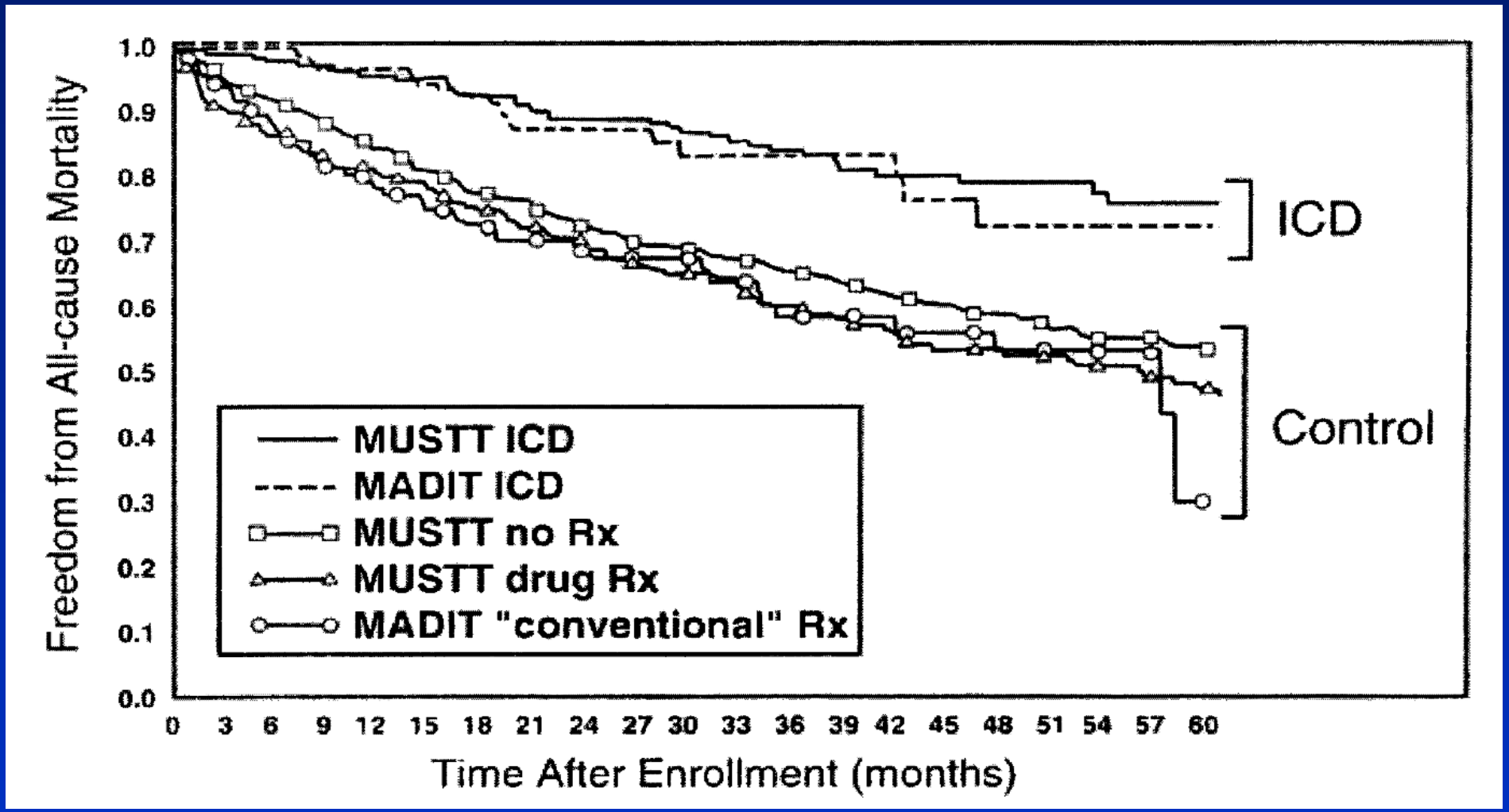

1. Castelli WP. Cardiovascular disease and multifactorial risk: challenge of the 1980s. Am Heart J 1983;109:1191.
2. Haskell WL et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: (SCRIP). Circulation. 1994;89:975.

# ICD Therapy

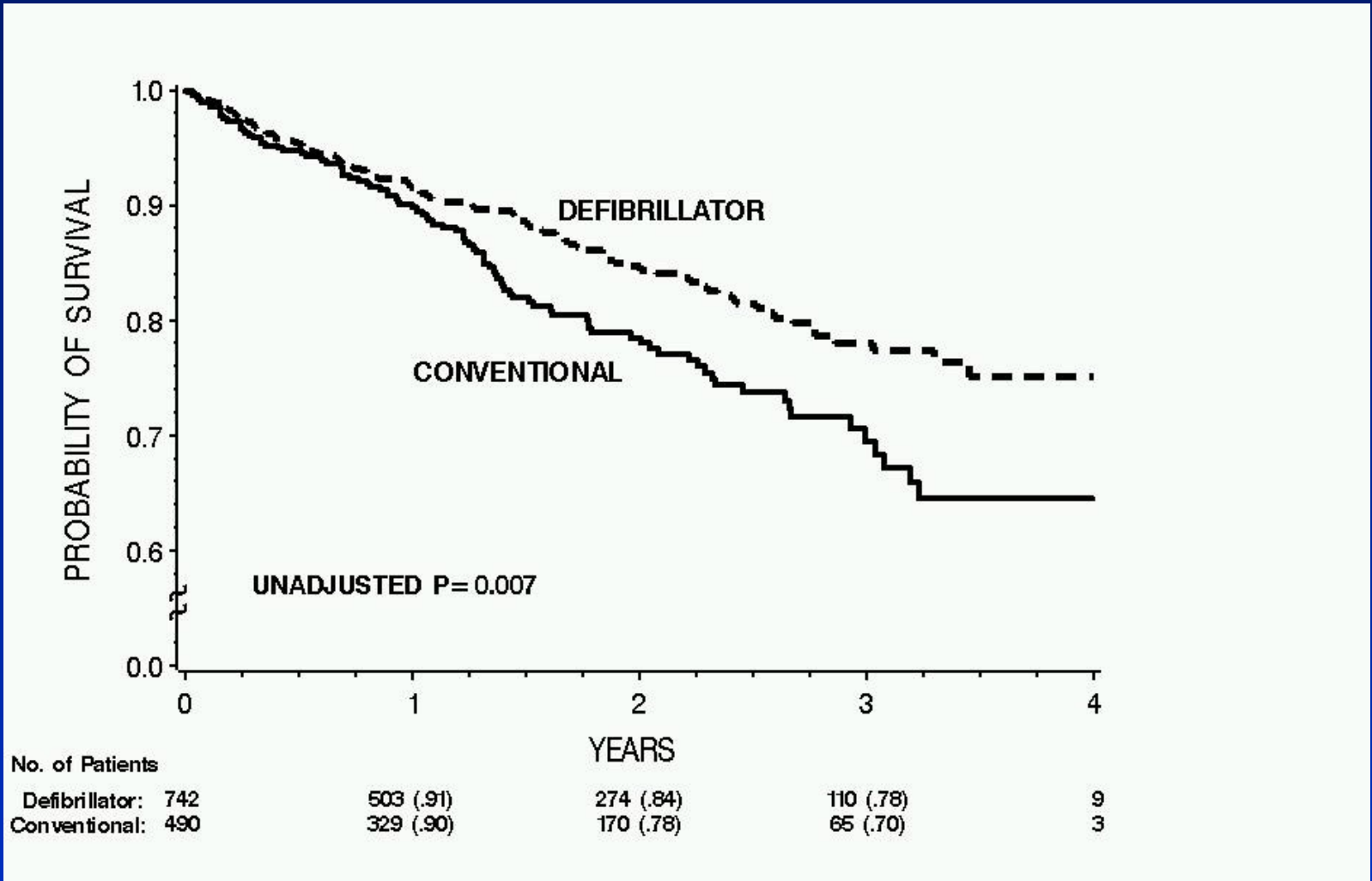


- ICD therapy consists of pacing, cardioversion, and defibrillation therapies to treat tachyarrhythmias. ICDs also have programmable diagnostic functions.
- An ICD system includes the device, and the pacing, sensing and defibrillation lead(s).

# MADIT and MUSTT

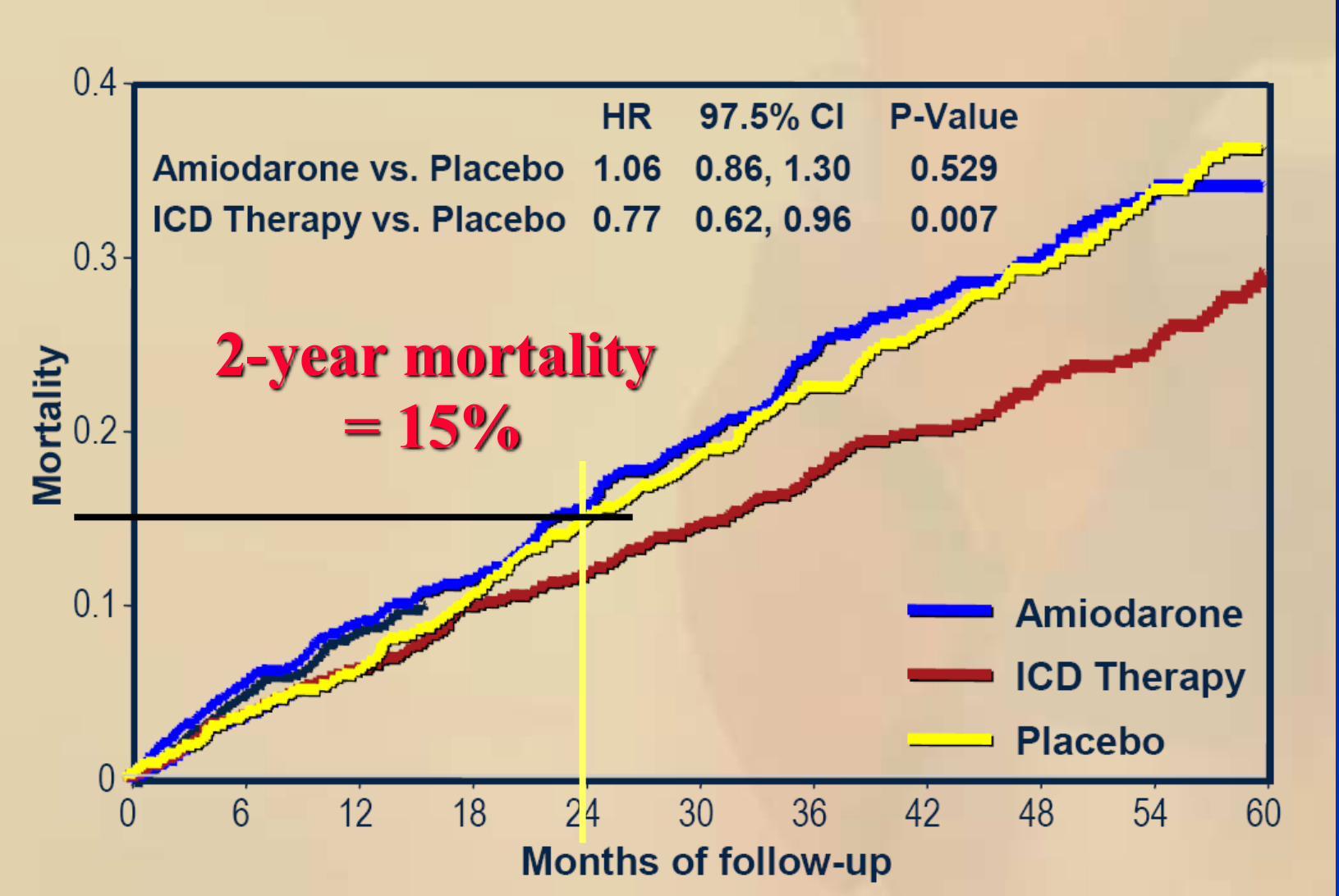


# MADIT-II

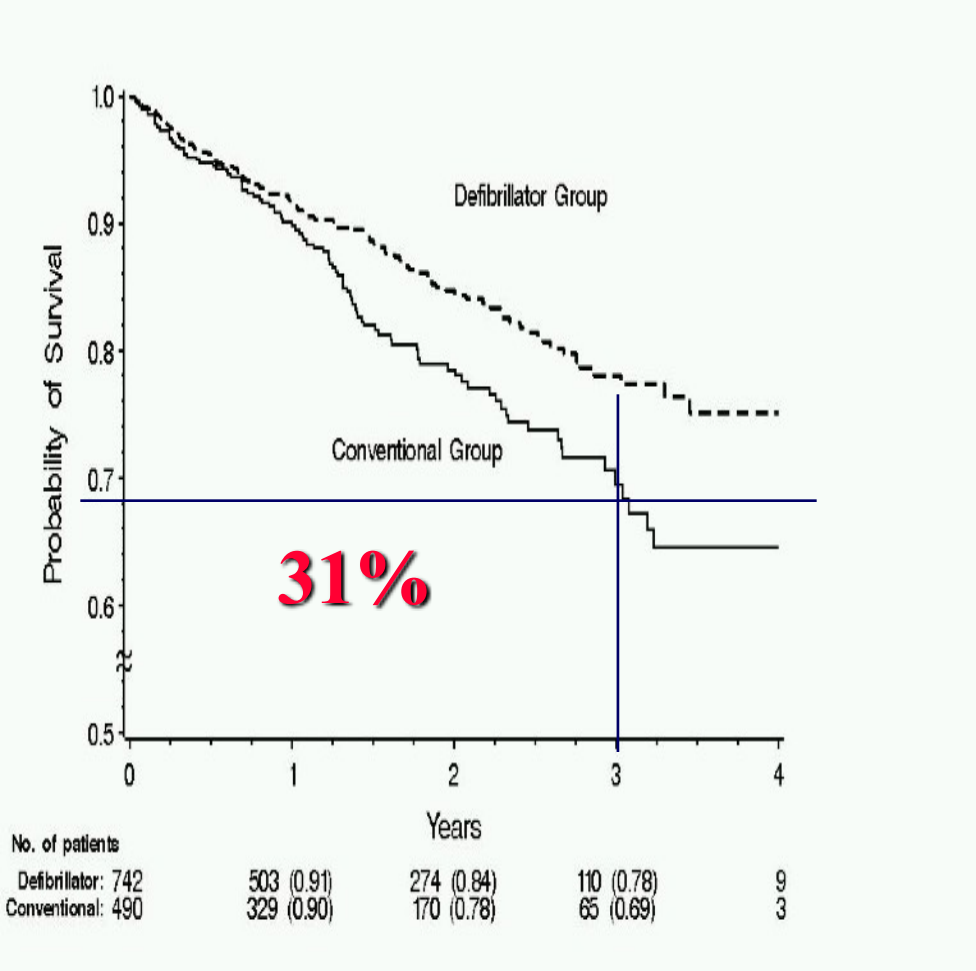



**HR=0.69 (p=0.016) ➞ 31% reduction in mortality**

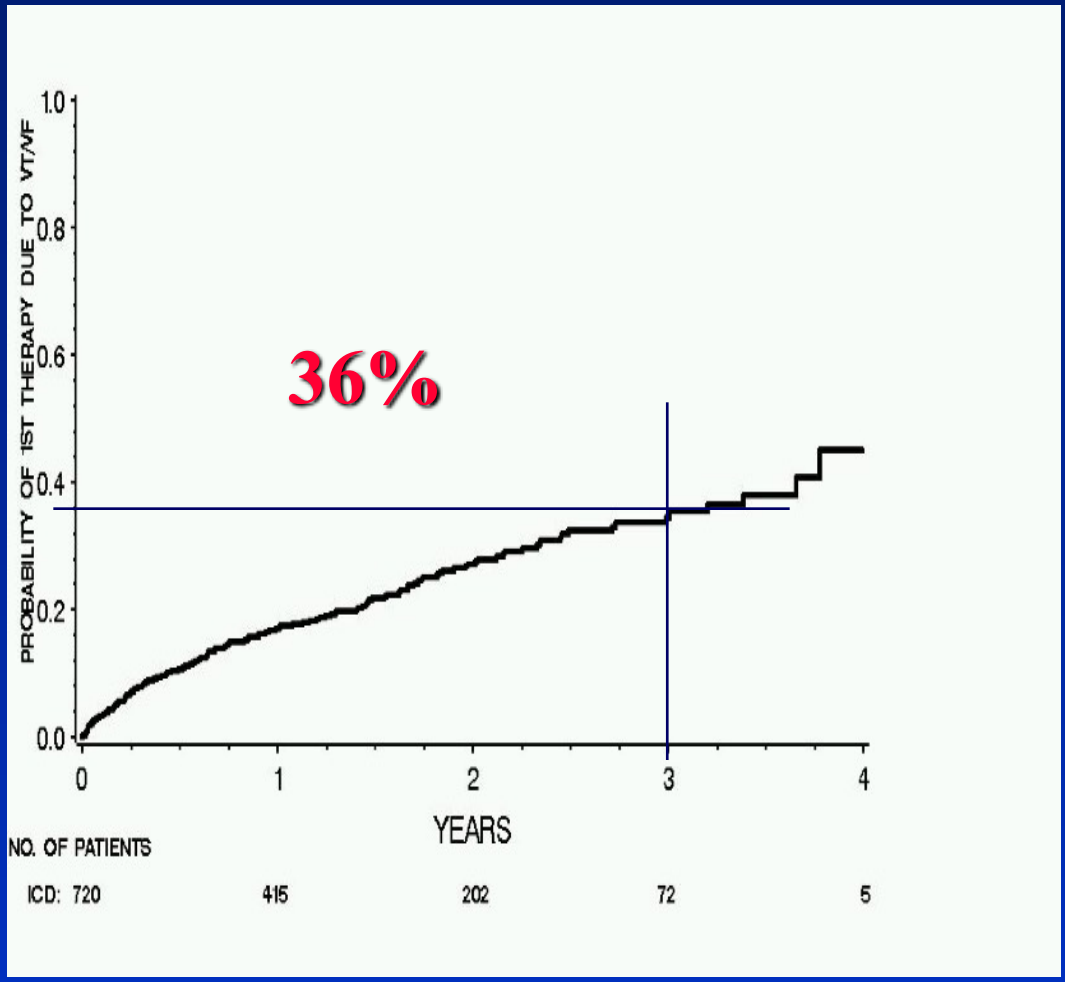
# SCD-HeFT


HR 97.5% CI P-Value
Amiodarone vs. Placebo 1.06 0.86, 1.30 0.529
ICD Therapy vs. Placebo 0.77 0.62, 0.96 0.007
2-year mortality = 15%
Mortality
0.4
0.3
0.2
0.1
0
0 6 12 18 24 30 36 42 48 54 60
Months of follow-up
Amiodarone
ICD Therapy
Placebo

# MADIT-II



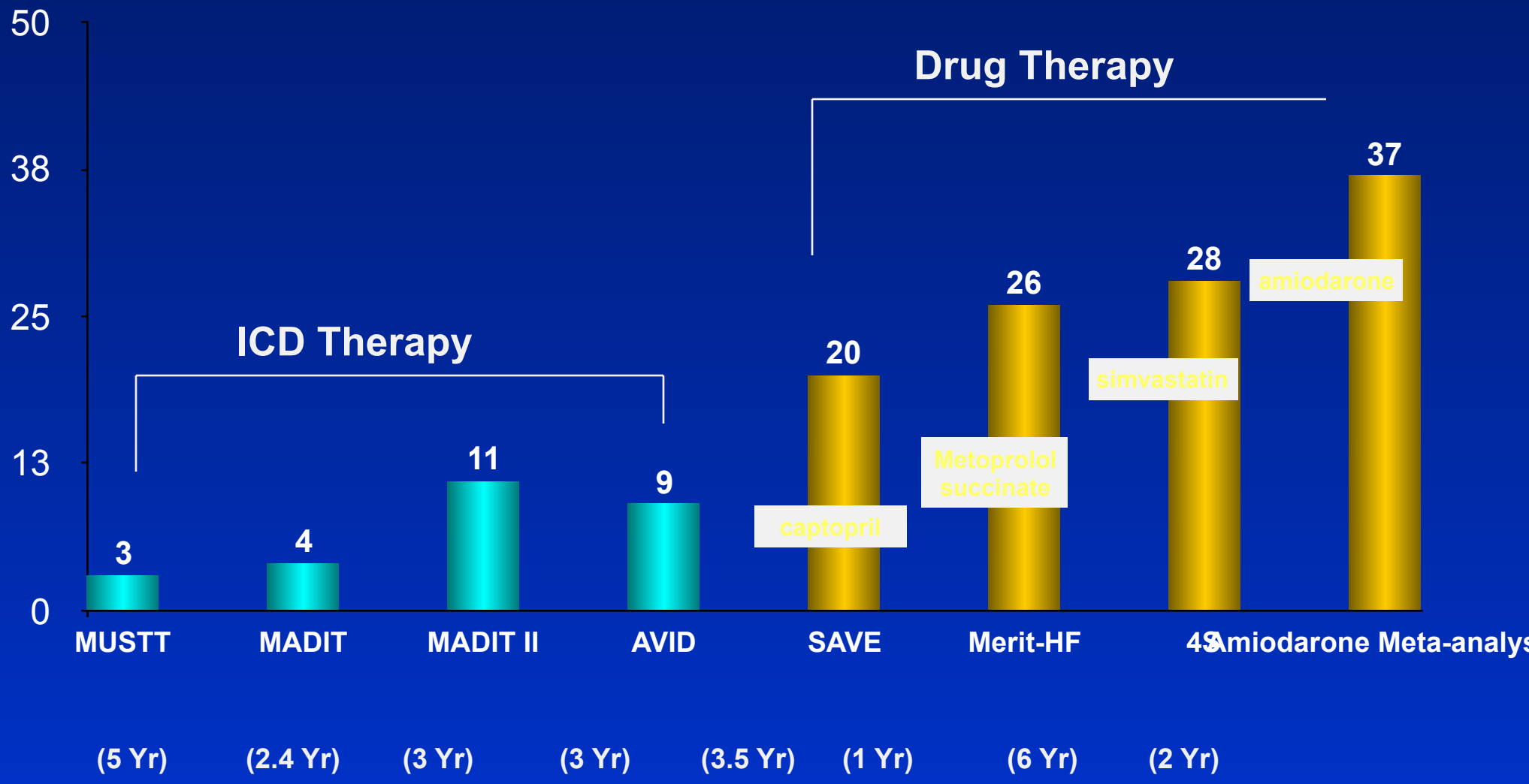

31% cumulative probability of mortality in the conventional arm at 3 years



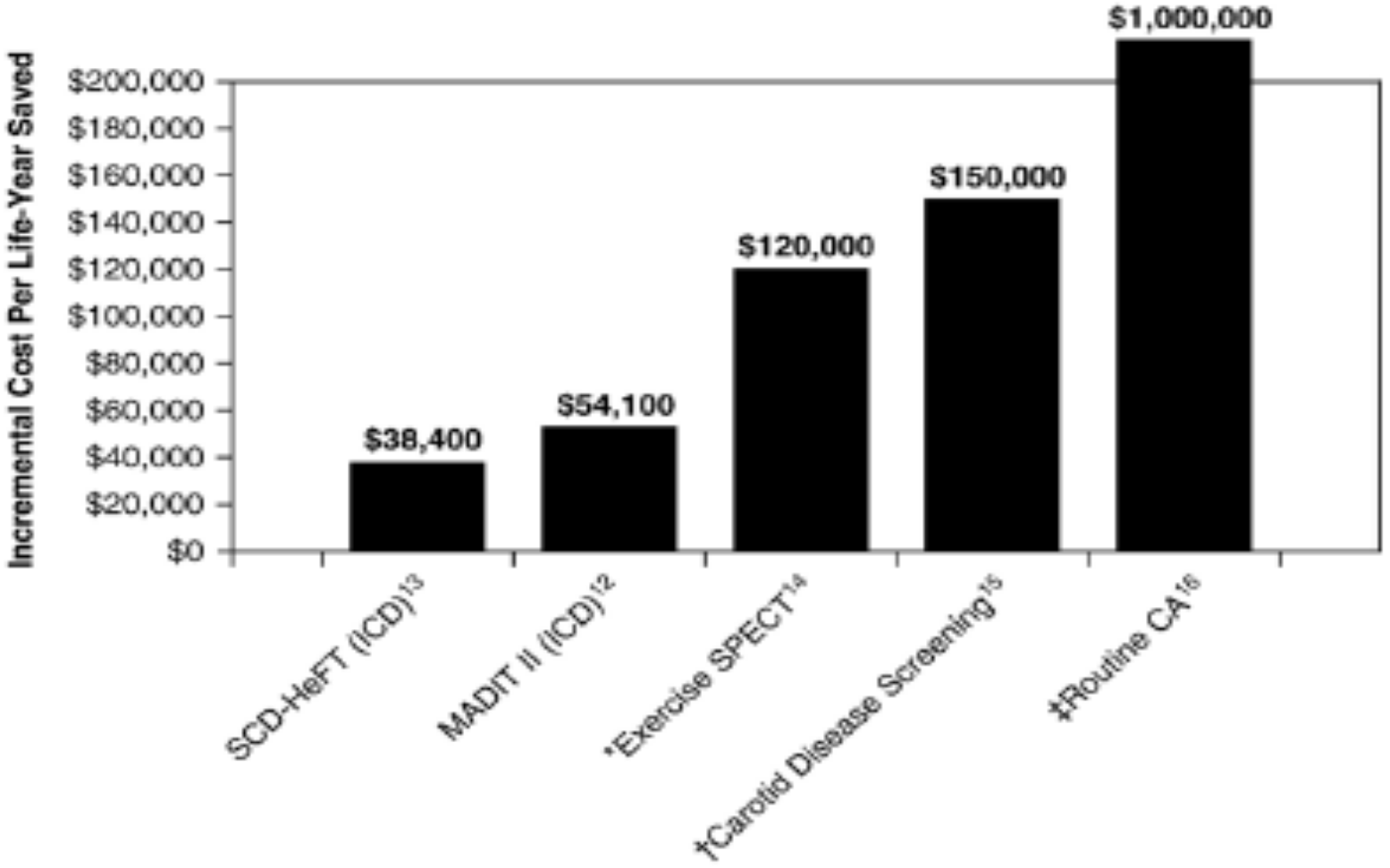

36% cumulative probability of appropriate ICD therapy at 3 years

# Number Needed to Treat To Save A Life

$NNT_{x\ years}$ = 100 / (% Mortality in Control Group – % Mortality in Treatment Group)

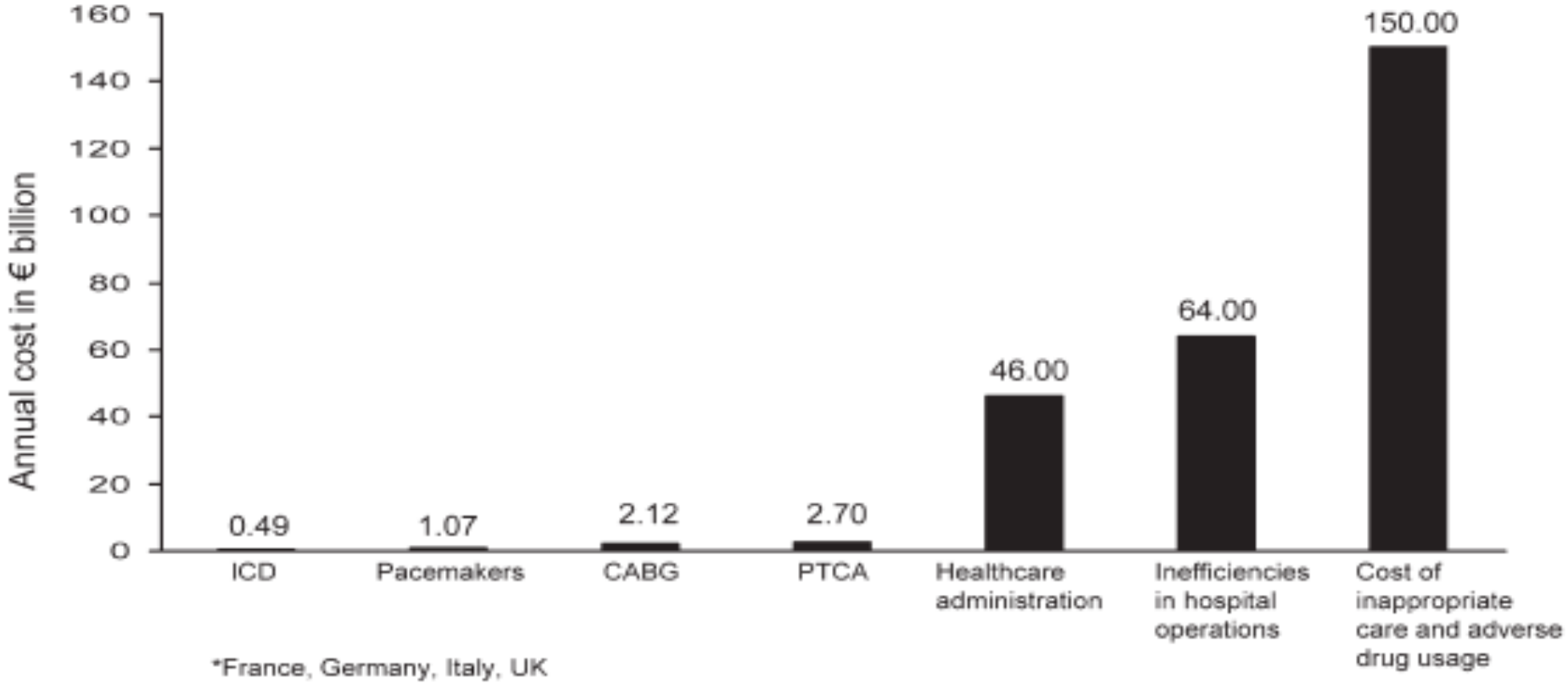


# ICD Therapy:
# Is It Really Expensive?




Cost effectiveness of Device therapy in the Heart Failure population 2003

# ICD Therapy:
# Is It Really Expensive?
# Annual Cost




Camm A et al.. Eur Heart J 2007;28:392

# Number of Potential ICD Therapy Candidates in the US

| Indication/ Patient Groups | Estimated Net Prevalence | Estimated % Penetration of Net Prevalence |
|---|---|---|
| Class I (AVID, MADIT, MUSTT) | 390,000 | ~34% [1] |
| Class IIa (MADIT II) | 280,000 | ≤10% [2] |
| Total | 670,000 | ~20%* |

# Clinical Implementation of ICD Guidelines – The Netherlands Experience

- 1886 patients in- and out-patients in November 2005
- 135 had indications for ICD
- 19 had/received ICD (14%)
- 9/124 (7%) with primary and 10/11 (91%) with secondary prevention
- 116 patients included 14 new patients
- 102 “old” patients had 466 cardiologist contacts over prior year (4.57/pt)

Botleffs et al. Neth Heart J 2007

# Risk Stratifiers

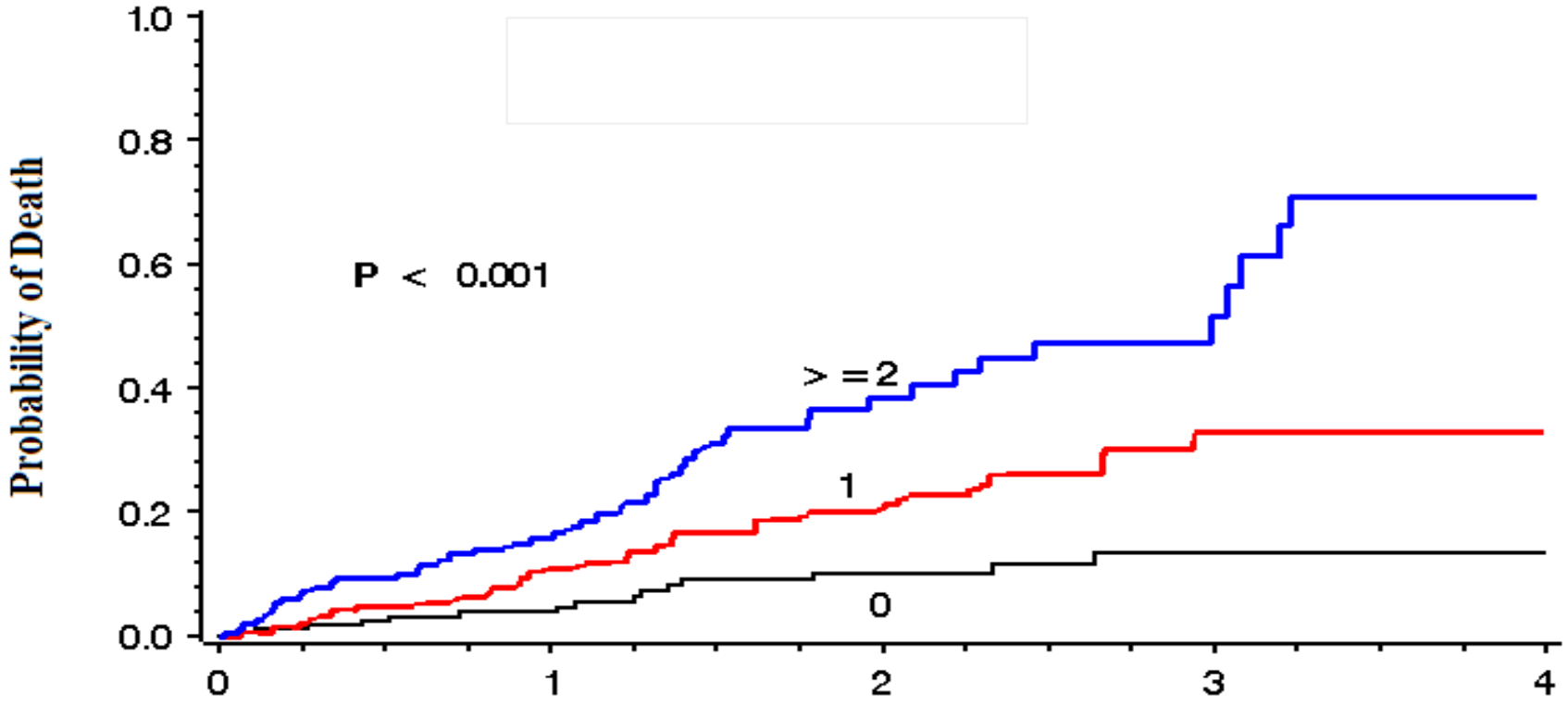
- Cardiac Arrest
- Syncope
- EF
- NSVT, VPBs
- EP Inducibility
- SAECG
- HRV
- CHF
- QTc
- QTd
- TWA
- HRT
- QTV
- T wave morphology
- Other:
  - CRP, BNP, genetics, …

# Bedside Risk Scoring in MADIT II

# Bedside Risk Stratification for Risk of Mortality in MADIT II Patients

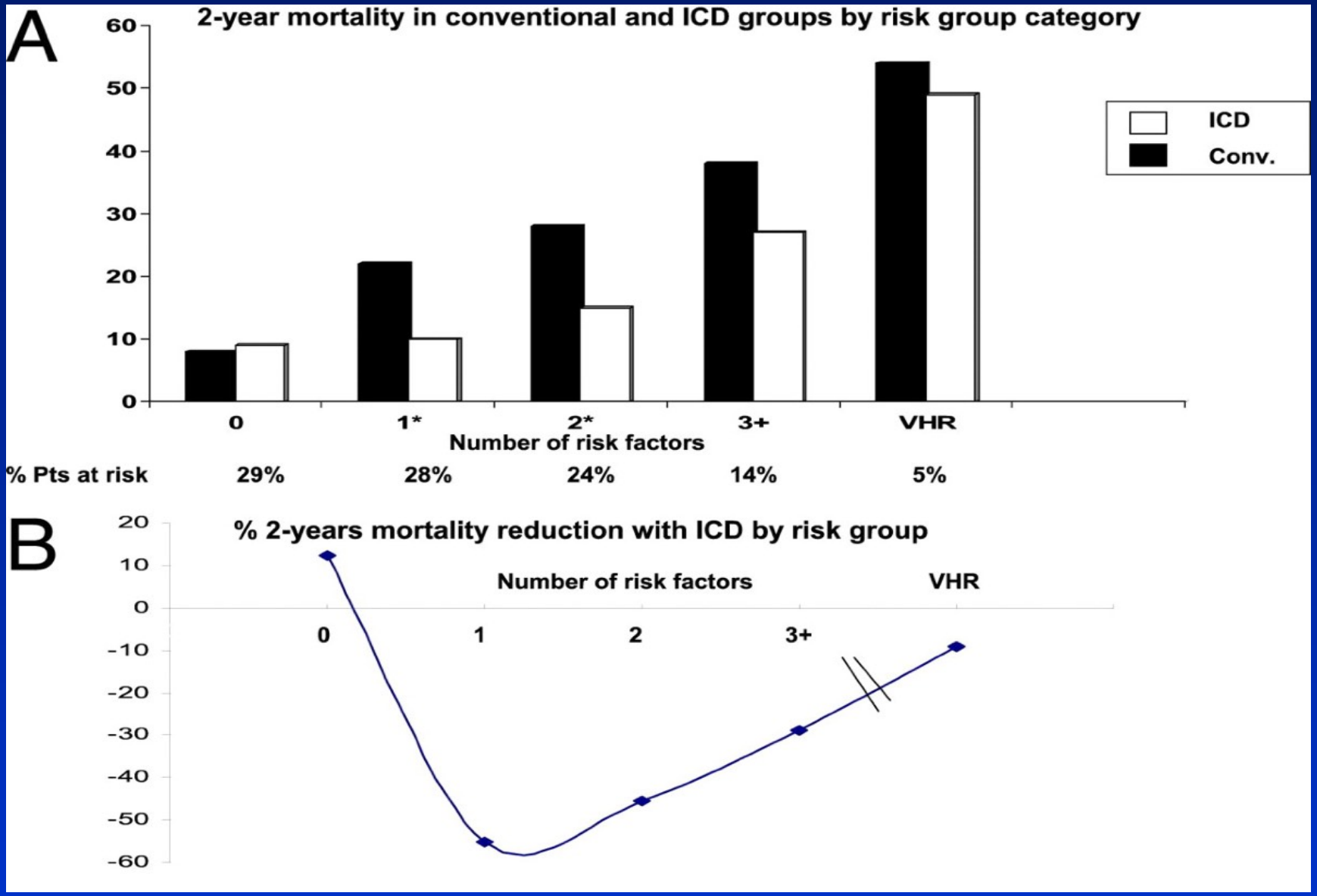
| Risk Factor | HR | CI | P |
|---|---|---|---|
| NYHA functional class >II | 1.87 | 1.23–2.86 | 0.004 |
| Atrial fibrillation | 1.87 | 1.05–3.22 | 0.034 |
| QRS >120 ms | 1.65 | 1.08–2.51 | 0.020 |
| Age >70 yrs | 1.57 | 1.02–2.41 | 0.042 |
| BUN >26 and <50 mg/dl | 1.56 | 1.00–2.42 | 0.048 |

# Risk Scoring and Risk of Mortality in MADIT II



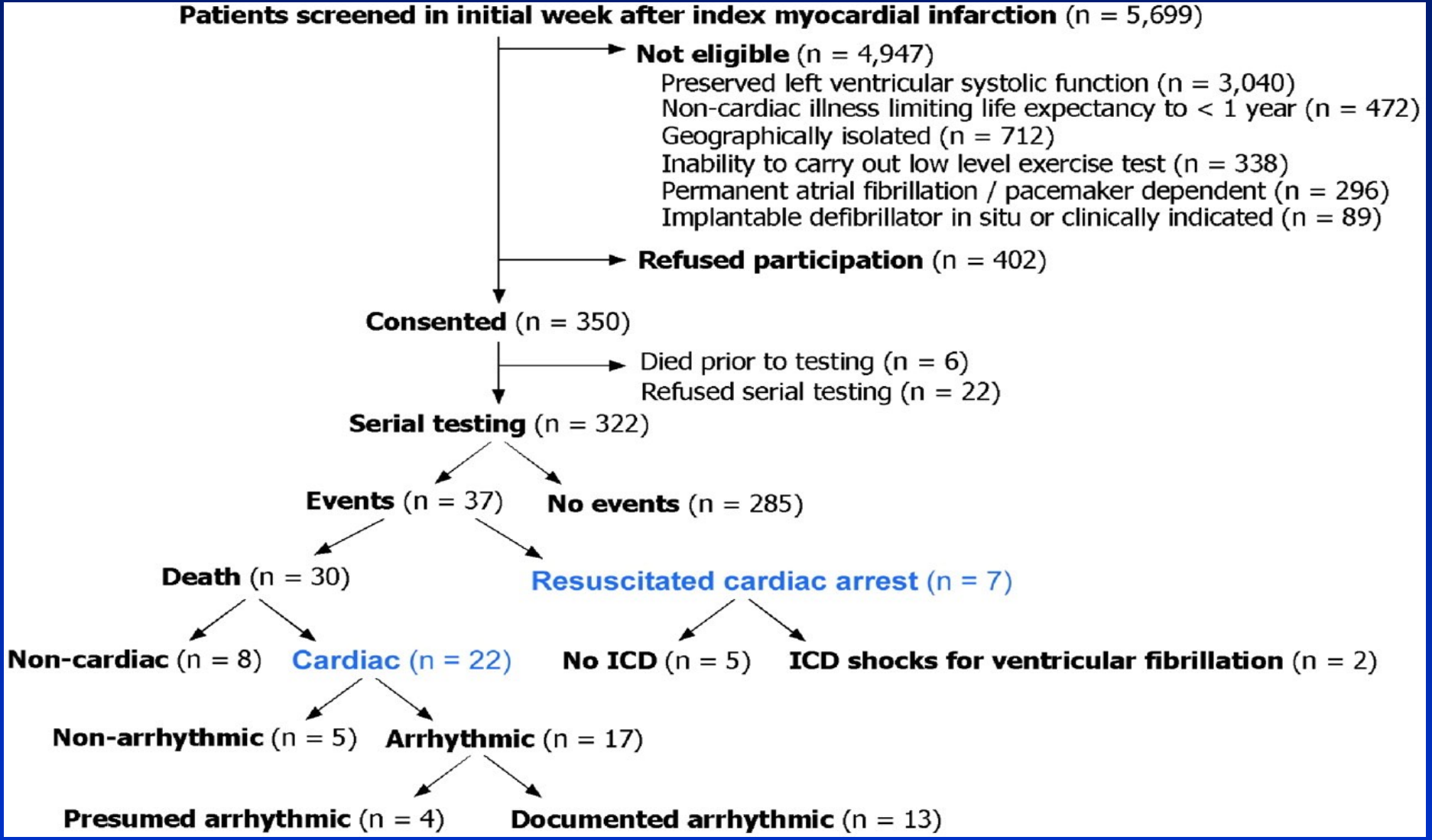

| # Risk Factors | | | | | |
|---|---|---|---|---|---|
| > = 2 | 152 | 93 | 32 | 11 | 1 |
| 1 | 148 | 108 | 57 | 23 | 0 |
| 0 | 168 | 120 | 77 | 30 | 2 |

# U-Shaped Curve for ICD Efficacy




Goldenberg, I. et al. J Am Coll Cardiol 2008;51:288-296

# Postinfarction Risk Stratification: Patient Selection and Outcomes

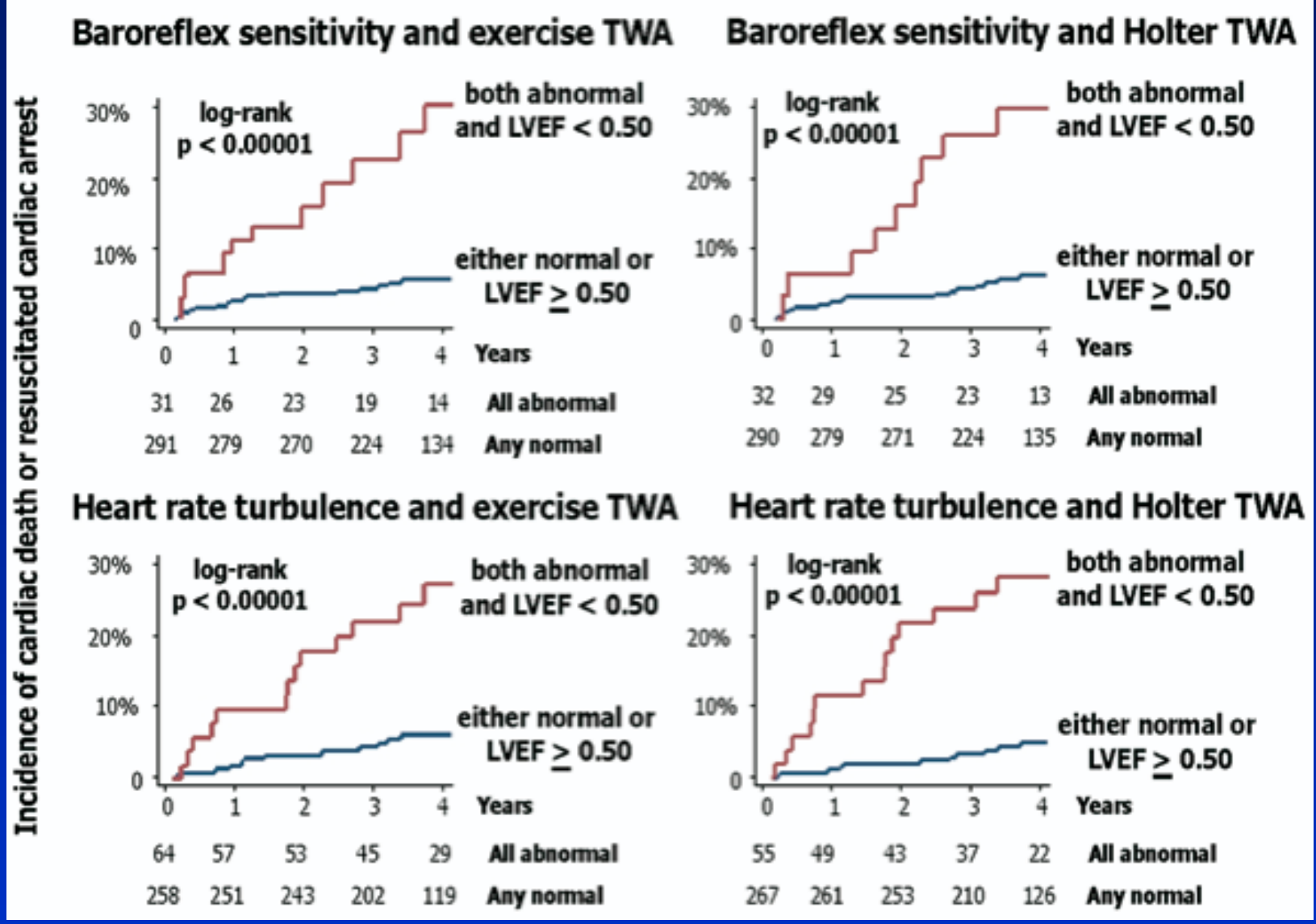



Exner, D. V. et al. J Am Coll Cardiol 2007;50:2275-2284

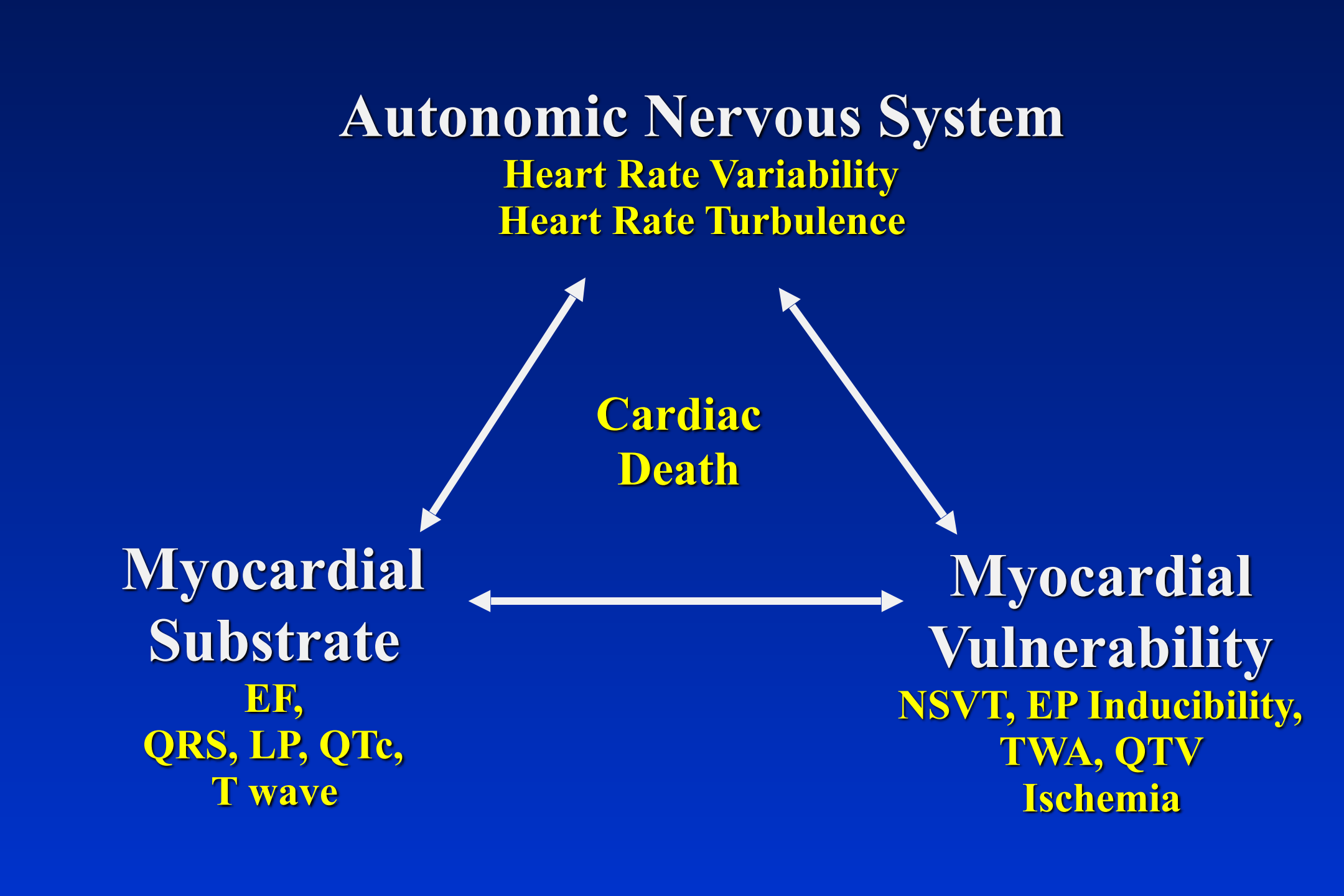
| Impairment | 2 to 4 Weeks After Index MI | 10 to 14 Weeks After Index MI |
|---|---|---|
| Heart rate variability (SDNN <105 ms) | 1.24 (0.50–3.27) | 2.15 (0.95–4.87) |
| | 0.65 | 0.066 |
| Heart rate turbulence (HRT1 or HRT2) | 1.42 (0.54–3.75) | 2.91 (1.13–7.48) |
| | 0.47 | 0.026 |
| Exercise repolarization alternans (non-negative vs. negative) | 2.42 (0.96–7.71) | 2.75 (1.08–7.02) |
| | 0.060 | 0.034 |
| Holter repolarization alternans (5 μV) | 2.09 (0.95–4.60) | 2.94 (1.10–7.87) |
| | 0.067 | 0.031 |
| QRS width ( 114 vs. <114 ms) | 1.35 (0.54–3.36) | 1.75 (0.76–3.99) |
| | 0.53 | 0.19 |
| History of diabetes | 2.68 (1.21–5.92) | 2.72 (1.23–5.99) |
| | 0.014 | 0.013 |
| Left ventricular EF ( 0.30 vs. >0.30) | 3.06 (1.39–6.74) | 3.30 (1.43–7.63) |
| | 0.005 | 0.005 |

A

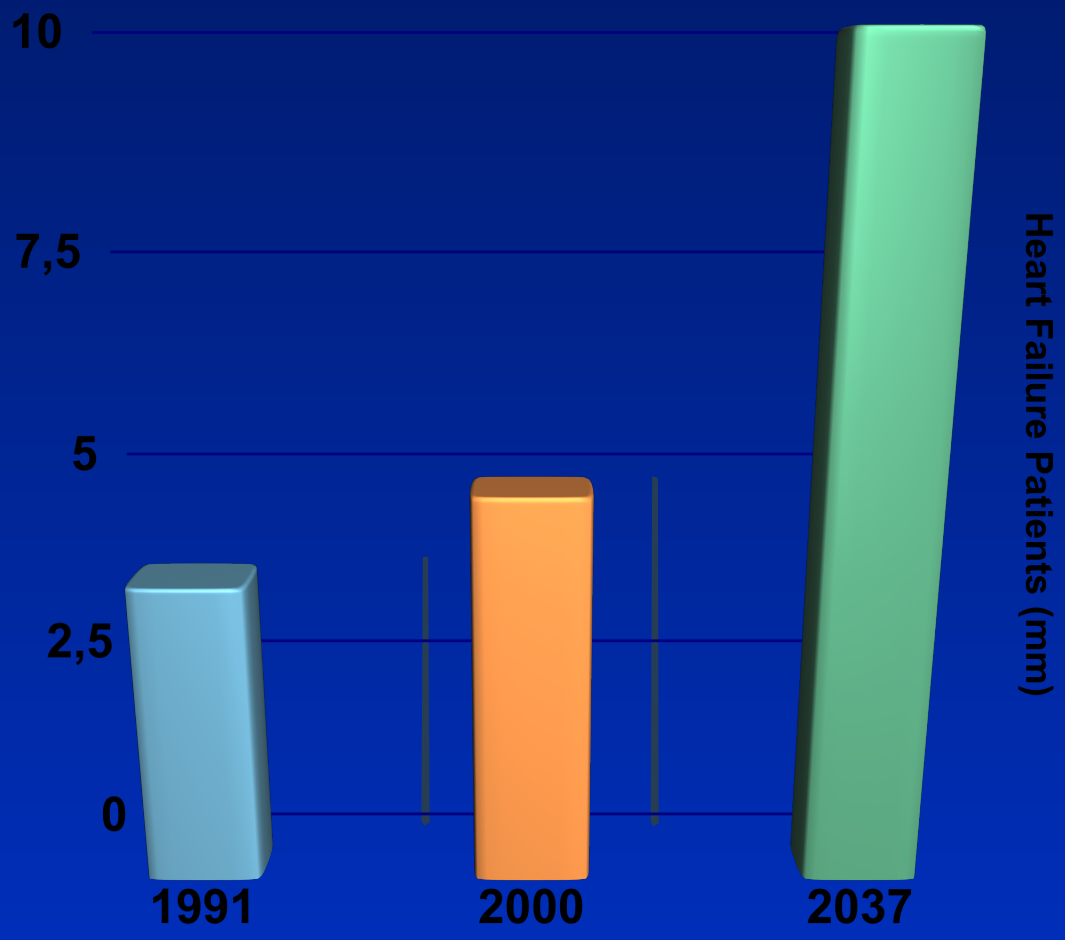
## Primary outcome: cardiac death or resuscitated cardiac arrest




Exner, D. V. et al. J Am Coll Cardiol 2007;50:2275-2284


Autonomic Nervous System
Heart Rate Variability
Heart Rate Turbulence
Cardiac
Death
Myocardial
Substrate
EF,
QRS, LP, QTc,
T wave
Myocardial
Vulnerability
NSVT, EP Inducibility,
TWA, QTV
Ischemia

# The Heart Failure Epidemic




- 5 million patients with heart failure in the United States[1]
- 550,000 new cases/year[1]
- 6.6% – 9.8% aged > 65 years have heart failure[1]
- Five-year mortality: men 59%; women 45%[2]
- 285,000 deaths annually (50,000 as primary cause)[3]


[1] AHA. *Heart and Stroke Statistics – 2004 Update.* Dallas, TX: American Heart Association; 2003.
[2] Levy D et al. *N Engl J Med* 2002;347:1397-1402.
[3] Rich MW et al. *J Am Coll Cardiol.* 2001;38(3):806-13.

# Indications for CRT

- Moderate to severe HF (NYHA class III/IV)
- EF ≤ 35%
- QRS duration ≥ 120 ms
- Remains symptomatic despite stable, optimal heart failure drug therapy

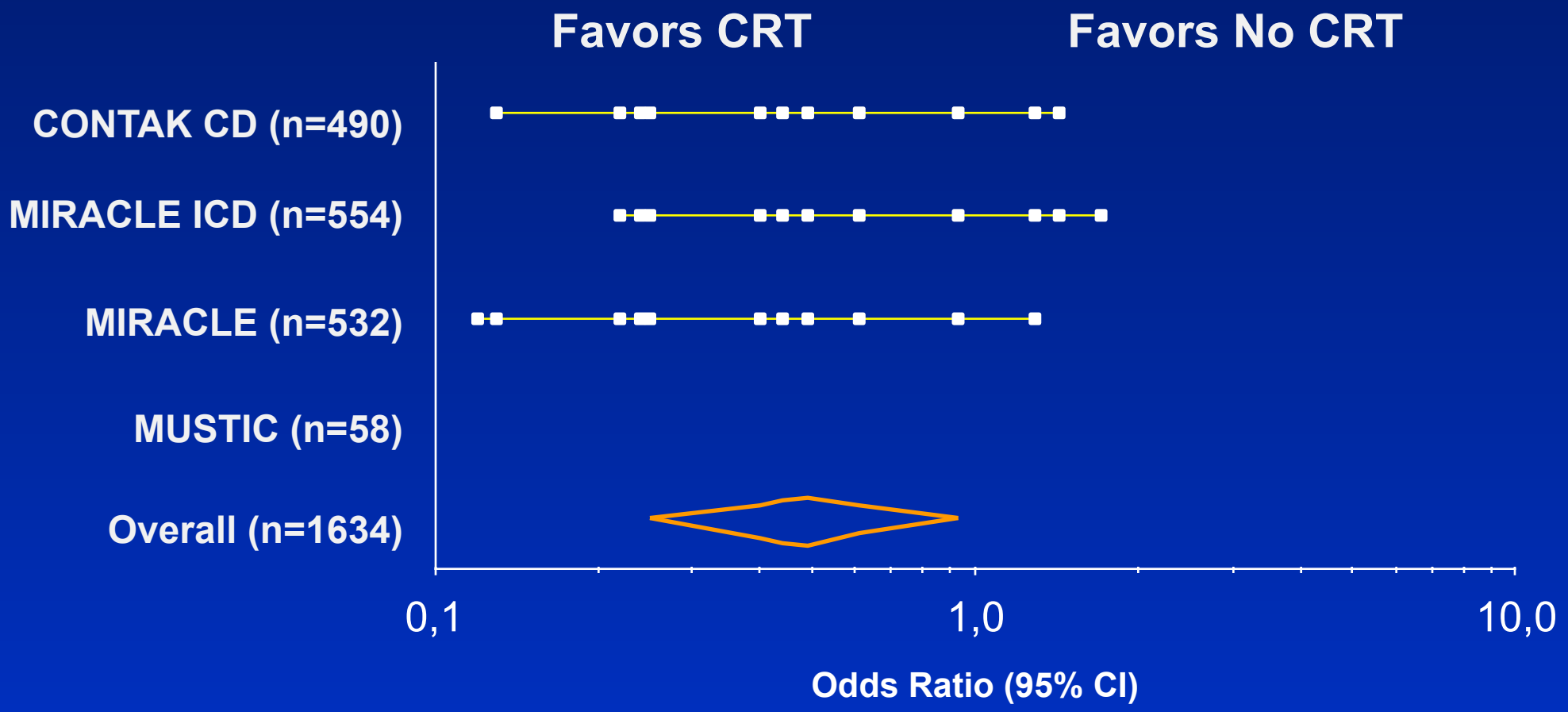
# Parameters Used in Predicting Response to CRT

- Presence of dyssynchrony at baseline
- Acute recovery of LV dyssynchrony
- Size of myocardial scar
- LV volume/function improvement
- QRS shortening

# Progressive Heart Failure Mortality

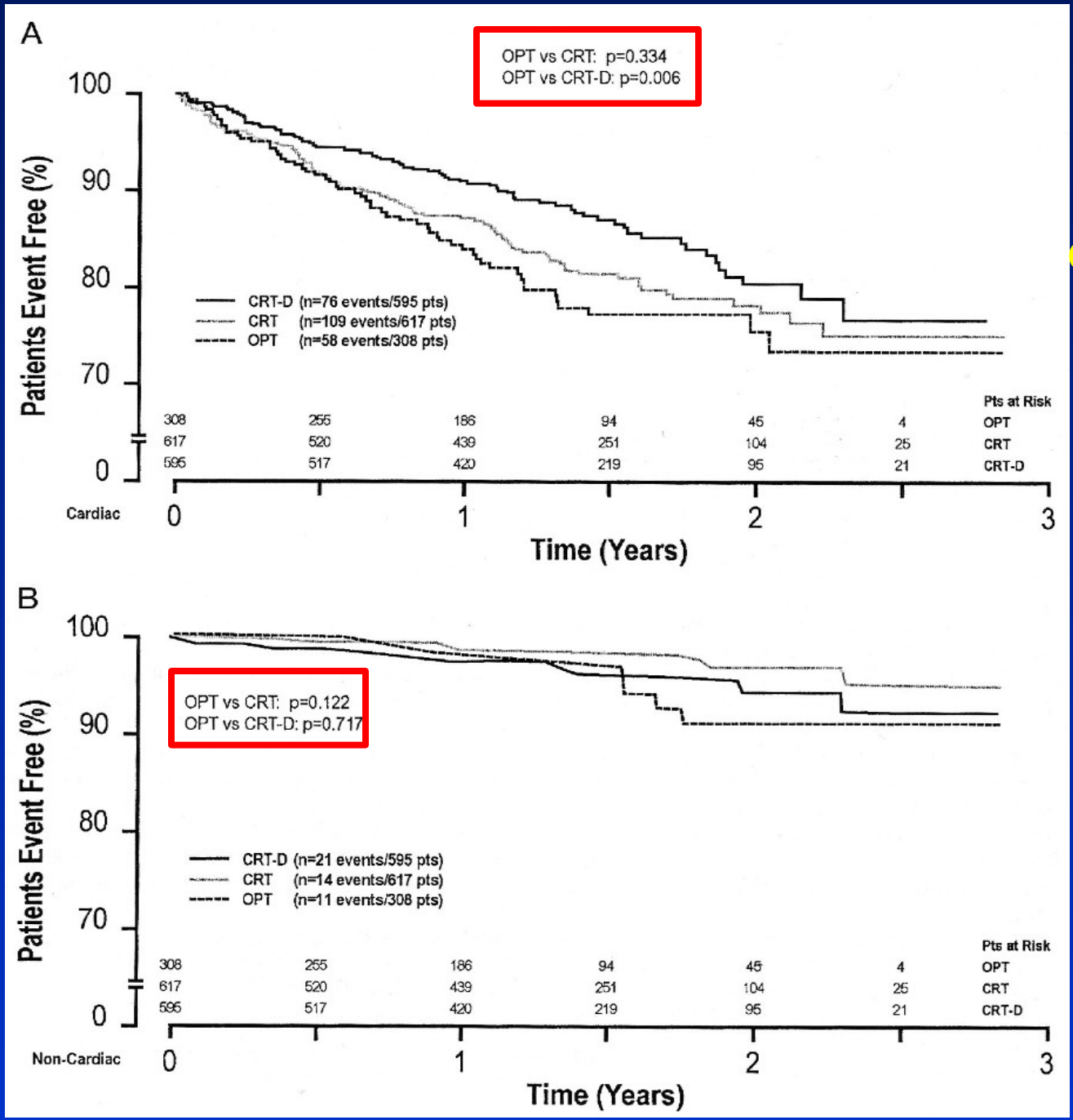
## 51% Relative Reduction with CRT

Overall odds ratio (95% CI) of 0.49 (0.25 - 0.93)




Bradley DJ, et al. *JAMA* 2003;289:730-740

**COMPANION**




**Cardiac Death**

**Non Cardiac Death**

**Carson et al. 2005**

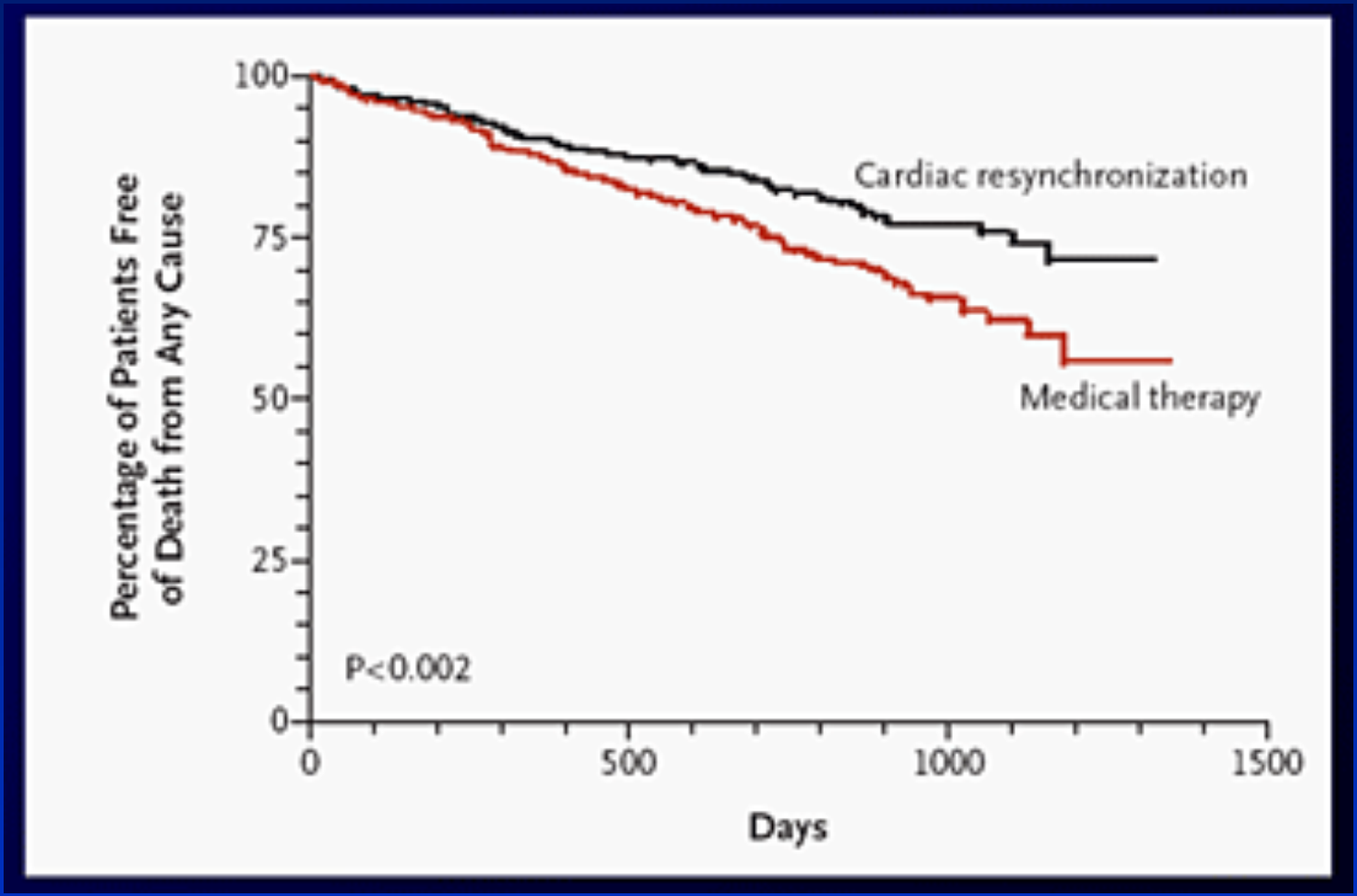
# CARE - HF

## Study Design

NYHA III, IV > 6 weeks
LV- EF ≤ 35%
QRS ≥ 120 ms
Demonstration of LV- Dys-synchrony
Optimal Medical Therapy (OMT)
813 pts. (82 European Centers)

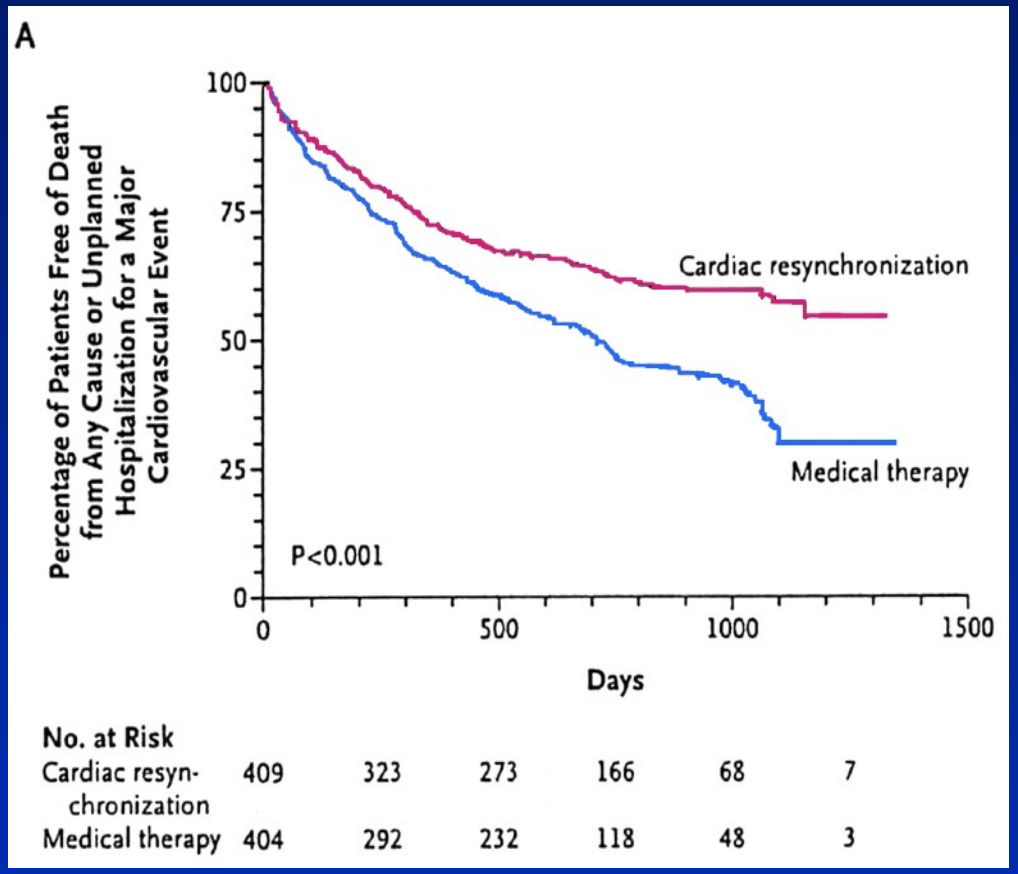

Follow-up 18 months
Enrollment: 1/2001- 3/2004

# CARE-HF Mortality Reduction

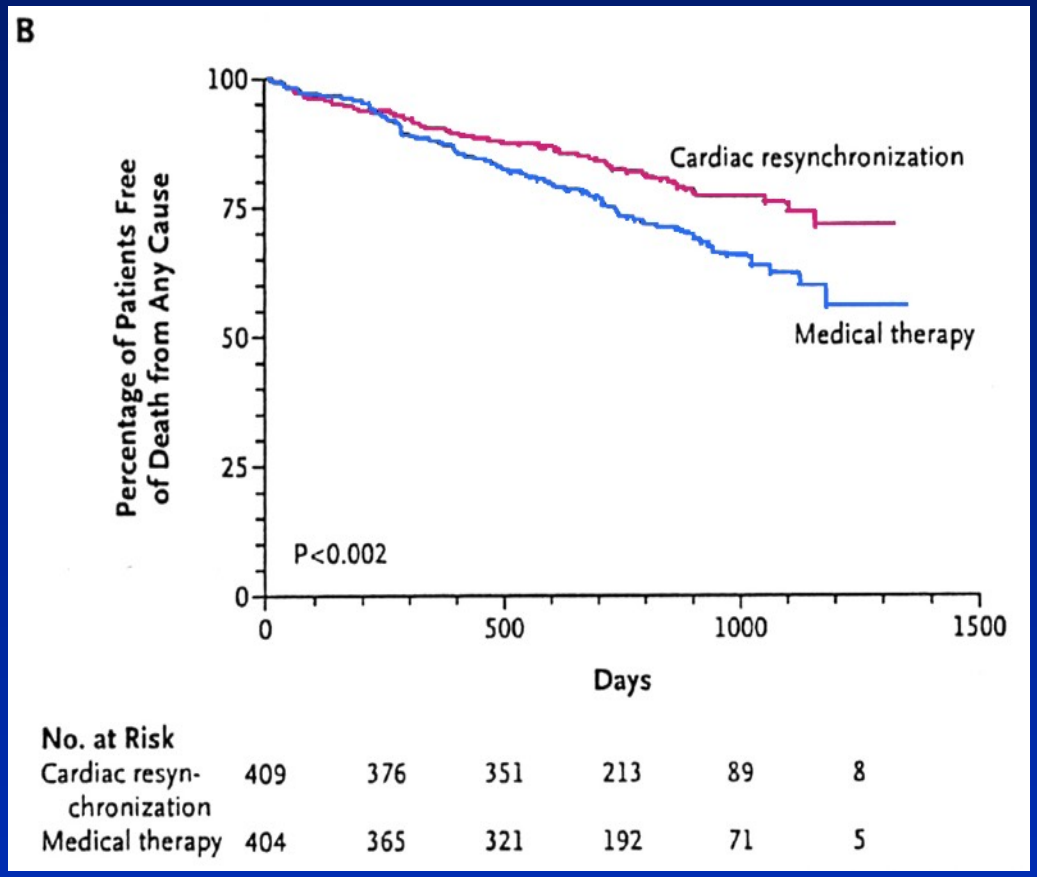



Cleland et al. NEJM; 2005:352

# CARE-HF




Mortality or Hospitalization for CV-Event




Total Mortality

# CARE-HF

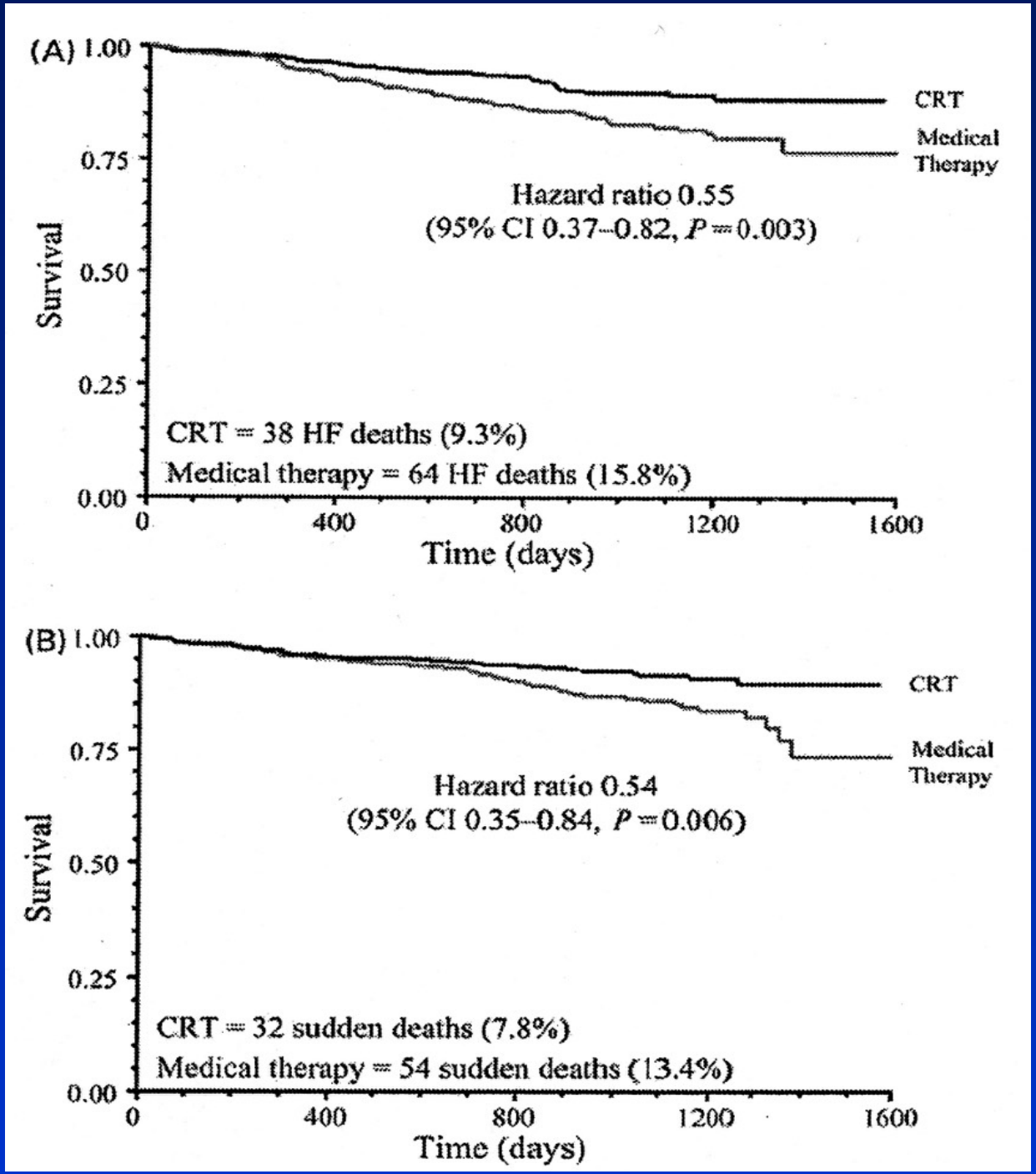
## (Follow up extended from 29 to 37 months)

| | OMT (n = 404) | CRT (n = 409) |
|---|---|---|
| Total mortality | 154 (38.1%) | 101 (24.7%) |
| - extension | 34 | 19 |
| mort./year | 12.2 % | 7.9 % |
| CHF death | 64 | 38 |
| mort./year | 5.1 % | 3.0 % |
| SCD | 54 | 32 |
| - extension | 16 | 3 |
| mort./year | 4.3 % | 2.5 % |

(Cleland, NEJM 2006)

CARE-HF

Extension phase



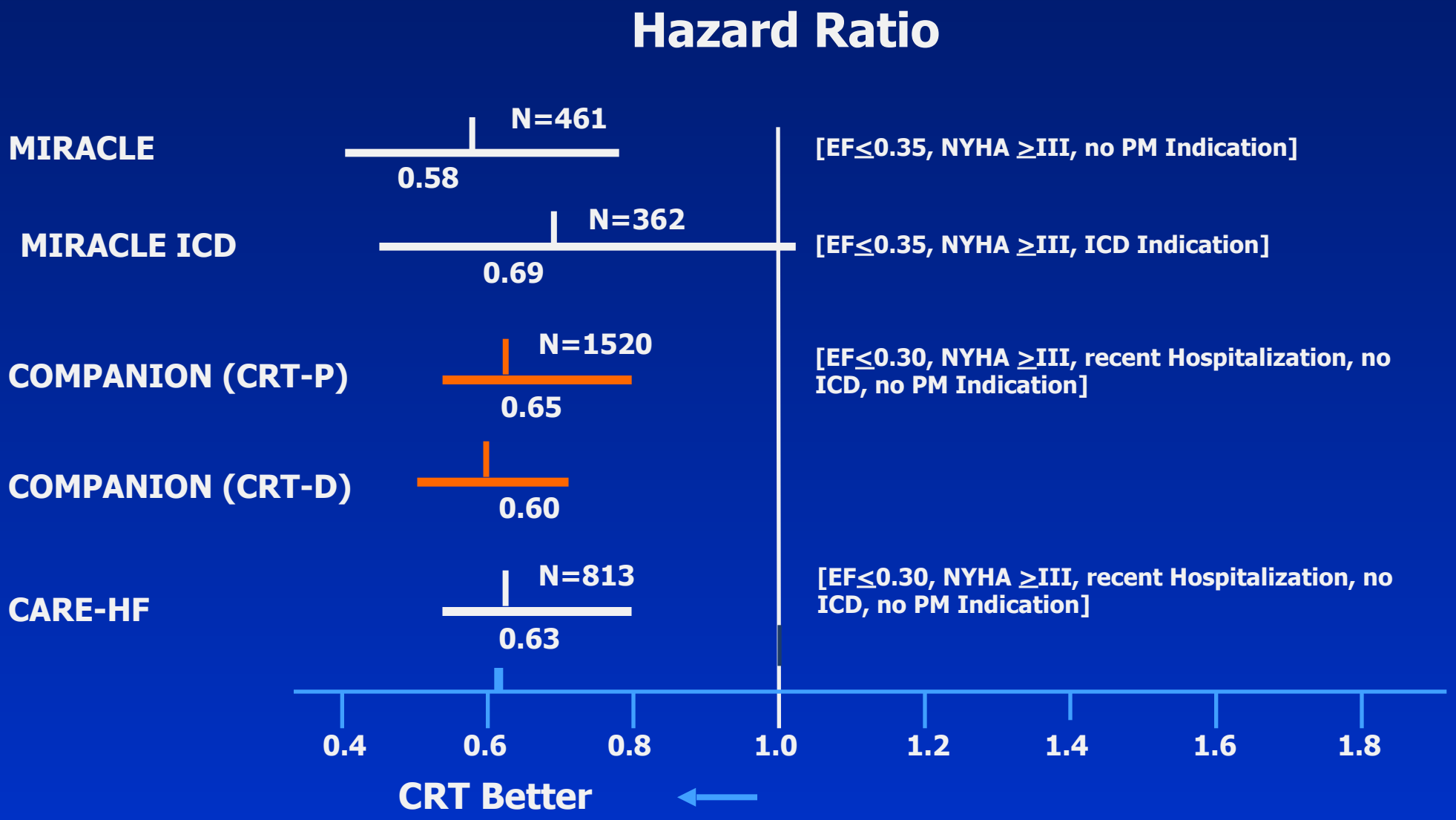

CHF death

SCD

Cleland et al.

EHJ 2006

# Effect of CRT on Death, Hospitalization, and iv. Medications



# RethinQ study

J.F Beshai et al. NEJM 2007

- LV-EF<35%, NYHA III, and QRS<130ms but mechanical dyssynchrony (TDI) >65ms; 6 months follow up
- Primary endpoint: Improvement of exercise capacity (peak $VO_2$) with CPET (≥1ml/kg/min)
- Secondary endpoint: NYHA; QoL; 6 minHWT
- Patient population: 172 pts; LV-EF 26%; QRS 106 ms (71% <120ms; 29% 120-130ms), all NYHA III; (1:1 randomization)
- Sponsor: SJM

# RethinQ study

J.F Beshai et al. NEJM 2007

## Results

- After 6 months: no sign.difference between CRT-D and ICD alone group

  (only in the prespecified subgroup of QRS 120-130ms a sign.difference was found)
- NYHA class improved (??), but not QoL or 6 min WT

## Conclusion

Pts. with heart failure, low LV-EF, but narrow QRS do not benefit from CRT

# Indications for CRT

- Moderate to severe HF (NYHA class III/IV)
- EF ≤ 35%
- QRS duration ≥ 120 ms
- Remains symptomatic despite stable, optimal heart failure drug therapy

# Summary

- ICD therapy for primary prevention of sudden death is heavily underutilized.
- More aggressive approach by physicians further supported by exercising risk stratification strategies is expected to decrease overall burden of SCD.
- Resynchronization therapy should be used in patients with currently approved indication based on wide QRS complex.