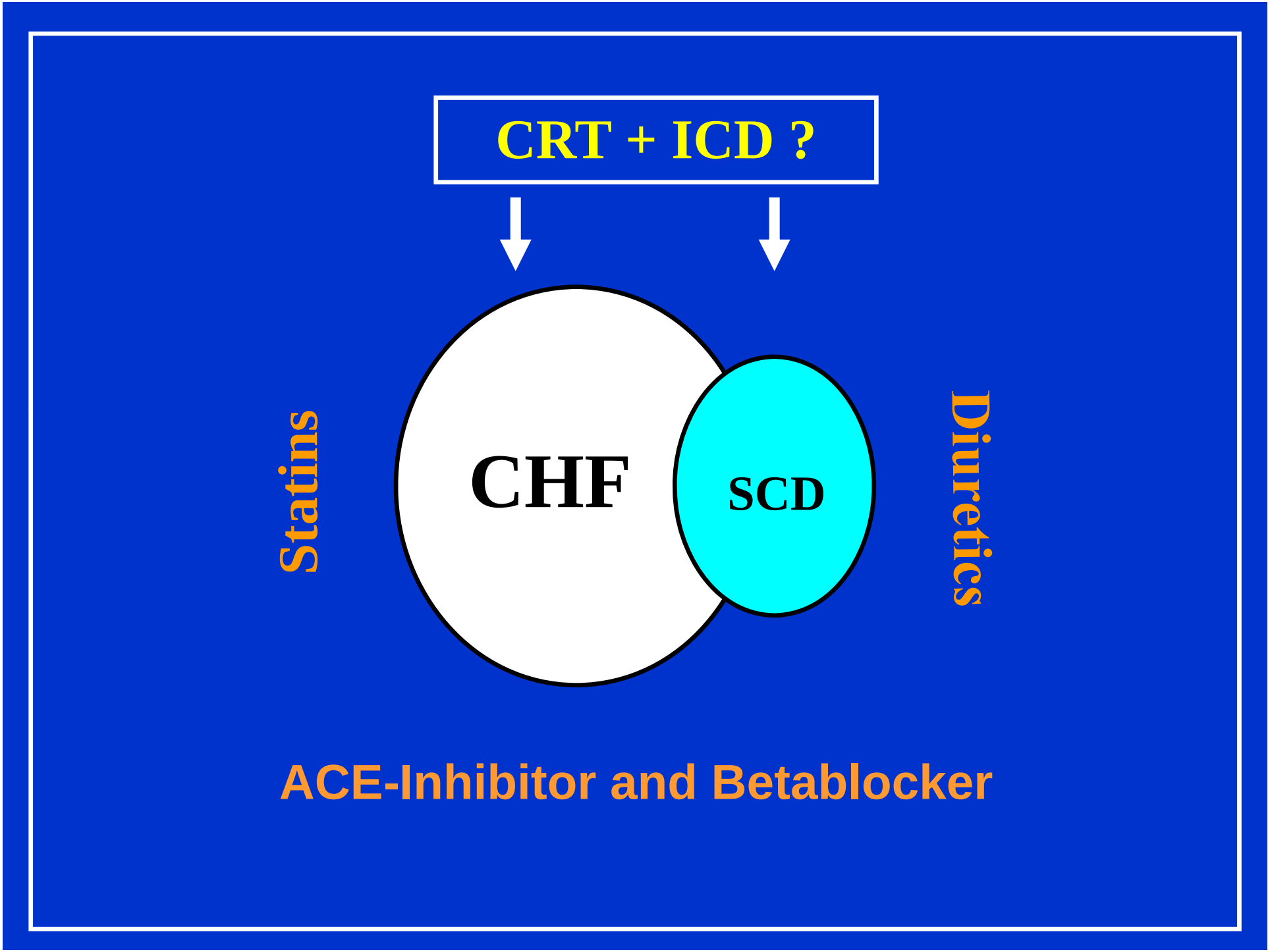
Heart failure and sudden death

What did we learn so far from important ICD- and CRT trials ?

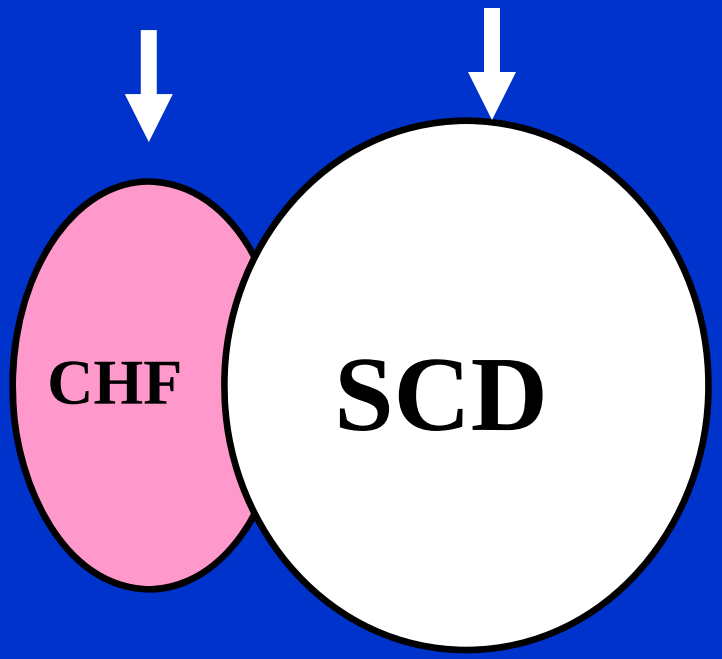
Helmut U. Klein M.D.
University of Rochester Medical Center
Heart Research Follow up Program

Arrhythmic substrate in pts. with depressed LV-function

- Dispersion of repolarization
- Altered neuro-humoral signaling
- Alteration of Ca^{++} homeostasis
- Altered conduction
- Myocardial ischemia
- Genetic disposition


CRT + ICD ?
CHF
SCD
Statins
Diuretics
ACE-Inhibitor and Betablocker

ICD + CRT ?



Statins

Diuretics

ACE-I and Betablocker

Sudden death and Heart failure

- The ICD is the most effective weapon against SCD (demonstrated by large trials)
- Heart failure and SCD are linked with each other
- It is difficult to predict at which moment in time the risk of death switches from CHF to SCD or vice versa

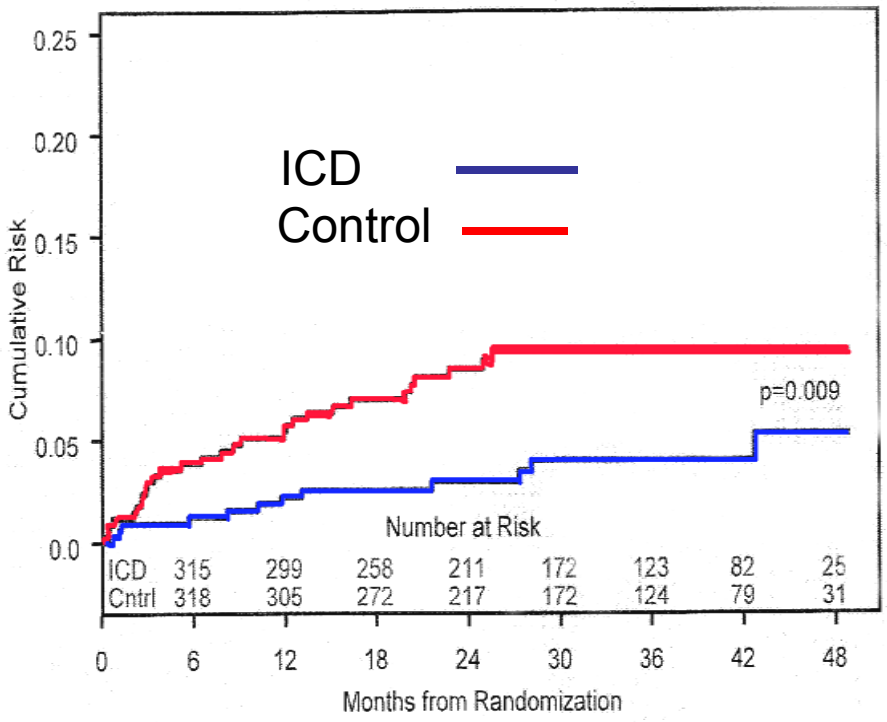
Primary Prevention Trials after Myocardial Infarction

Overall mortality / year

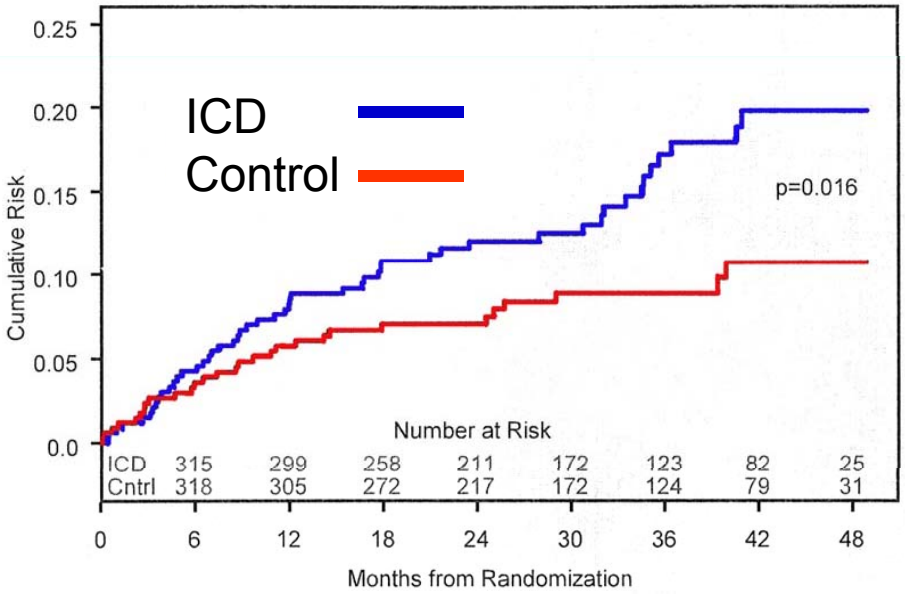
Trials	No ICD	ICD
MADIT	16%	7%
MUSTT	7.5%	5%
MADIT II	11%	8%
CABG- Patch	6%	7%
DINAMIT	6.9%	7.5%
SCD- Heft	7.2%	5.5%

DINAMIT

Arrhythmic Death



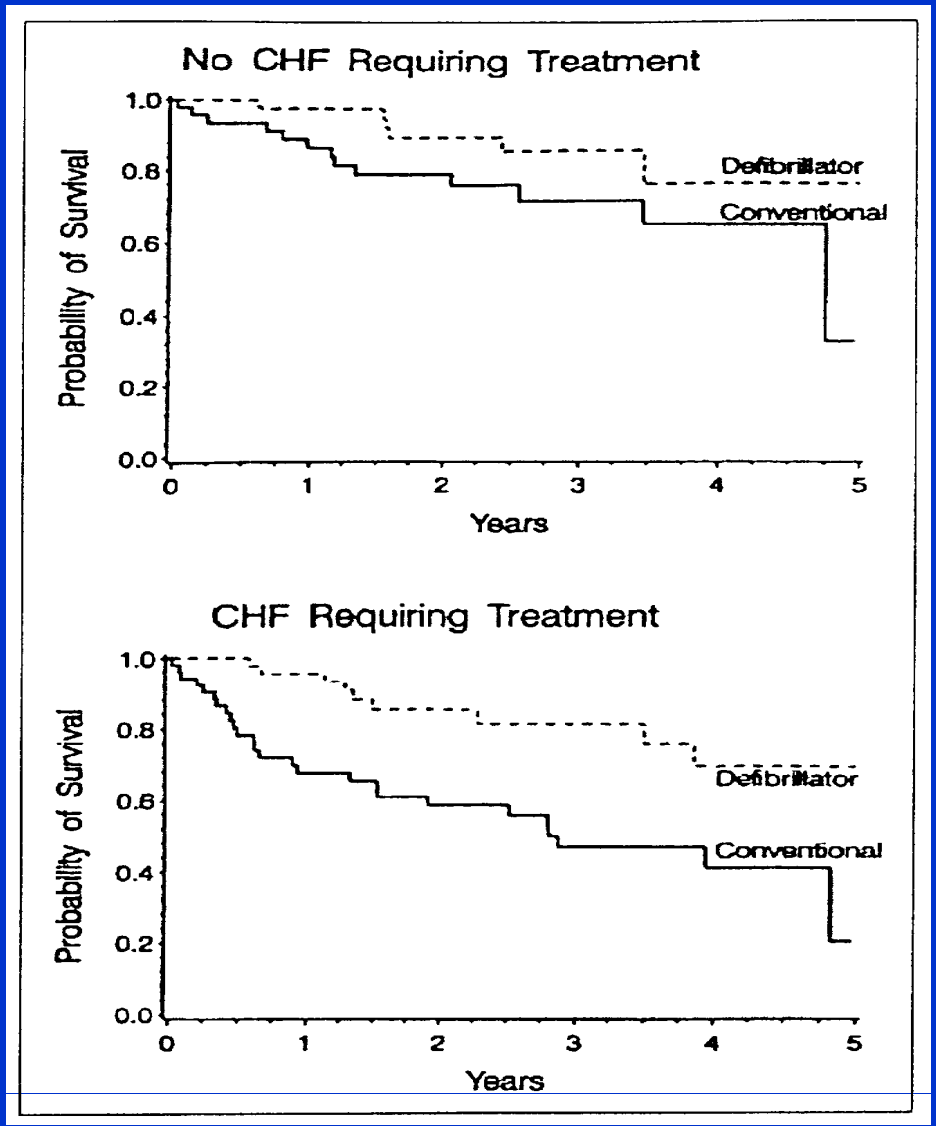
Non-Arrythmic Death



Hohnloser, NEJM 2004

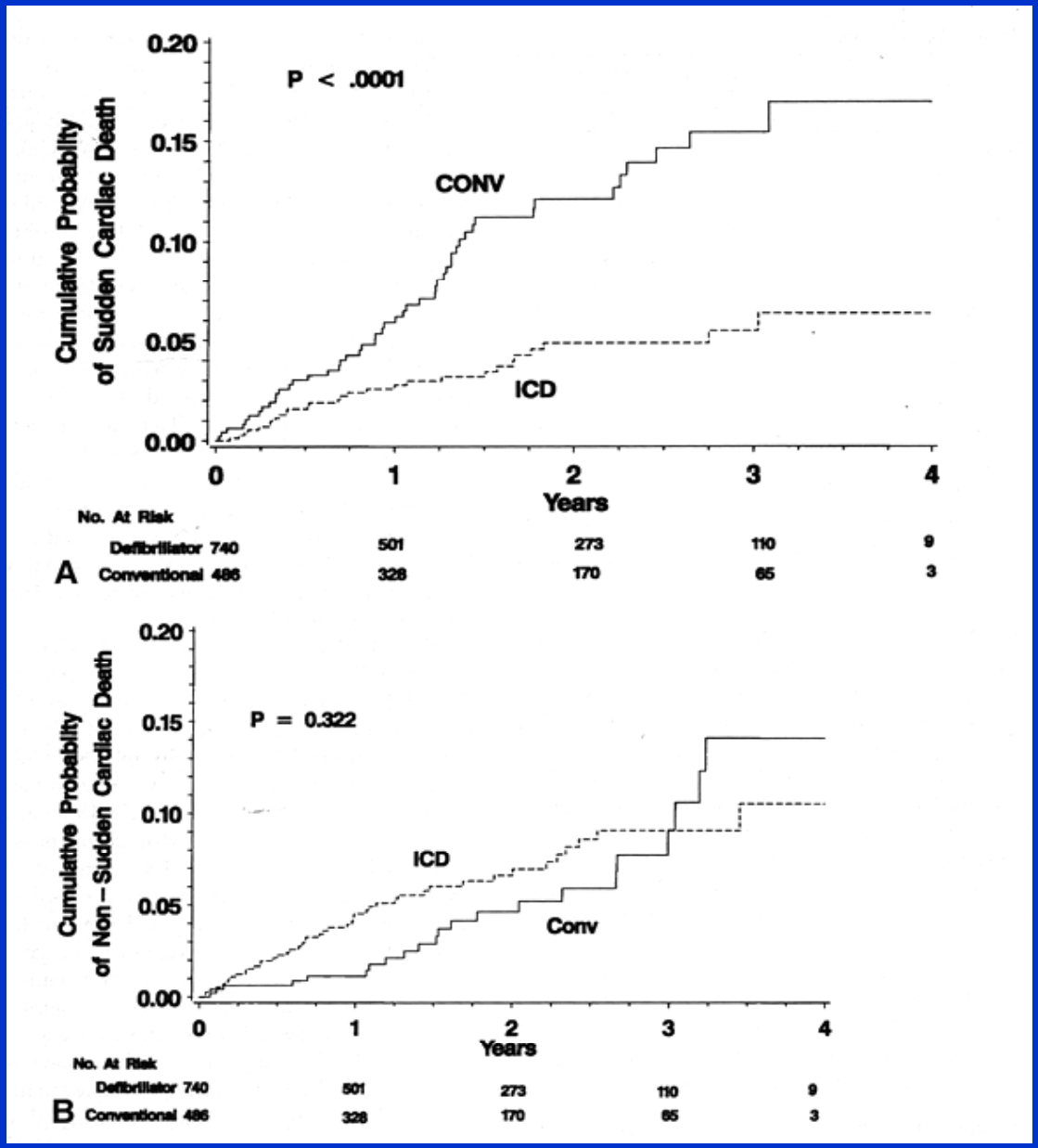
MADIT - Substudy

A. Moss et al. 1999



Heart Failure needs ICD treatment

MADIT II



SCD

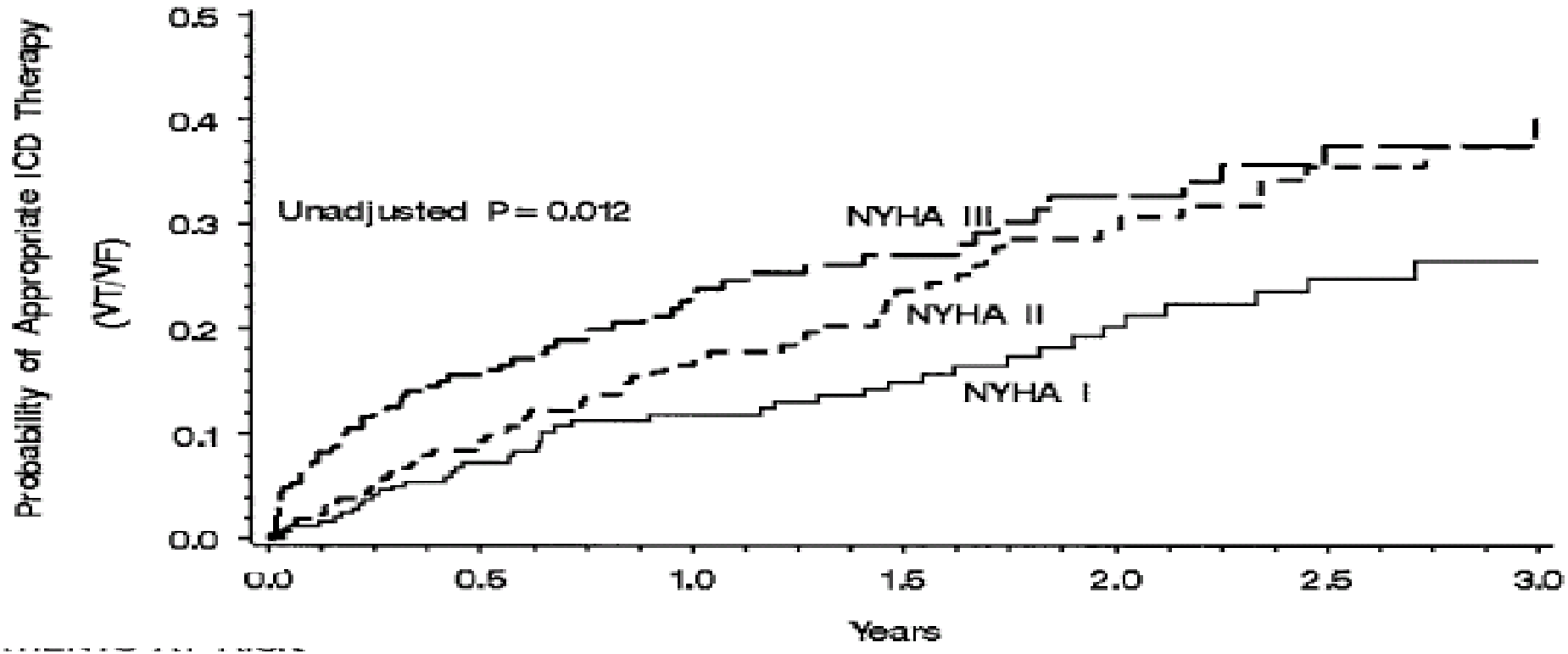
CHF-Death

A.Moss, H.Greenberg, 2004

ICD Intervention related to the degree of heart failure

(MADIT II)

	Mortality in Conventional Arm			Cardiac Events in ICD Arm			
		2-yr Mortality					
Subgroups	n	Total	SCD	n	Total Mortality	SCD	ICD Therapy
NYHA class							
I	187	16%	9%	243	11%	4%	20%
II	165	18%	11%	253	12%	5%	30%
III	130	34%	20%	216	24%	6%	33%
p Value		<0.001	0.033		<0.001	0.372	0.012



Zareba et al. Am J Card 2005

Risk markers of SCD

Electrophysiologic surrogates

- PVC, nsVT
- Conduction disorder
  - QRS duration
  - LP
  - EPS
- Dispersion of repolarization
  - QT dispersion; TWA
- Autonomic imbalance
  - Heart rate at rest
  - HRV; HRT; BRS

Functional – morphological surrogates

LV – EF
LV – diameter
NYHA – Class
Ischemia
LV – dyssynchrony
Peak VO_2
BNP
Renal function

Arrhythmic Risk stratification in heart failure

- No single risk stratification test is likely to be appropriate for every patient
- Combinations of various tests are necessary for accurate risk stratification
- Currently, there seems to be no better risk marker than LV-EF;
- All attempts to achieve high positive predictive accuracy with non-invasive risk parameters have been disappointing

Risk stratification

Risk factors and mechanisms of SCD do not remain constant, they evolve over the course of the disease

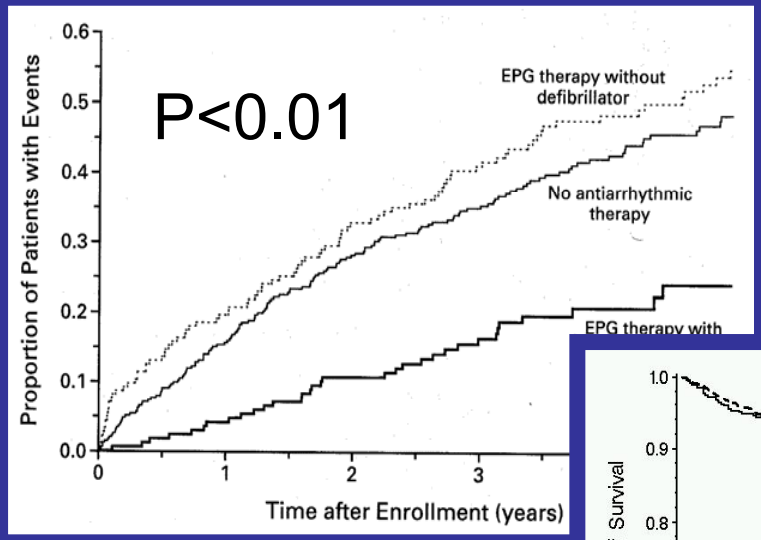
Important factors :

- **Type of the underlying disease**
- **Stage of the disease**
- **Role of ischemia**
- **Remodeling process**
- **Development of heart failure**

Two major problems have to be discussed

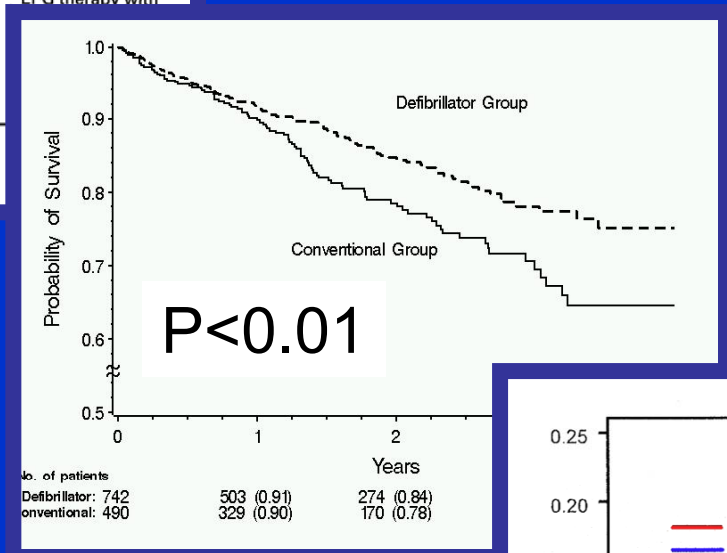
- What about the risk of SCD early (first month) after acute myocardial infarction, or when should the ICD be implanted after acute MI with low LV-EF ?
- The problem of NYHA Class IV, or what to do if the patient can’t get out of NYHA Class IV with medical therapy ? Will this patient still benefit from ICD therapy ?

Time after AMI



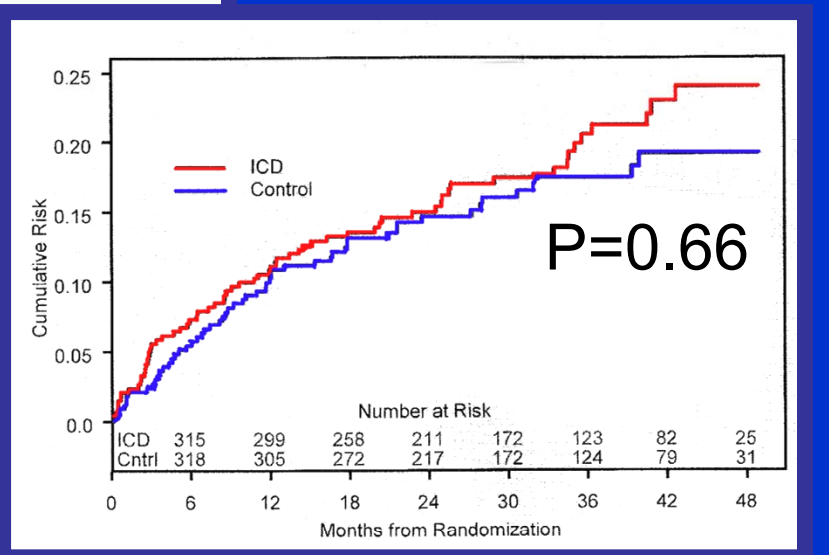
MUSTT

≈ 39 Months



MADITT II

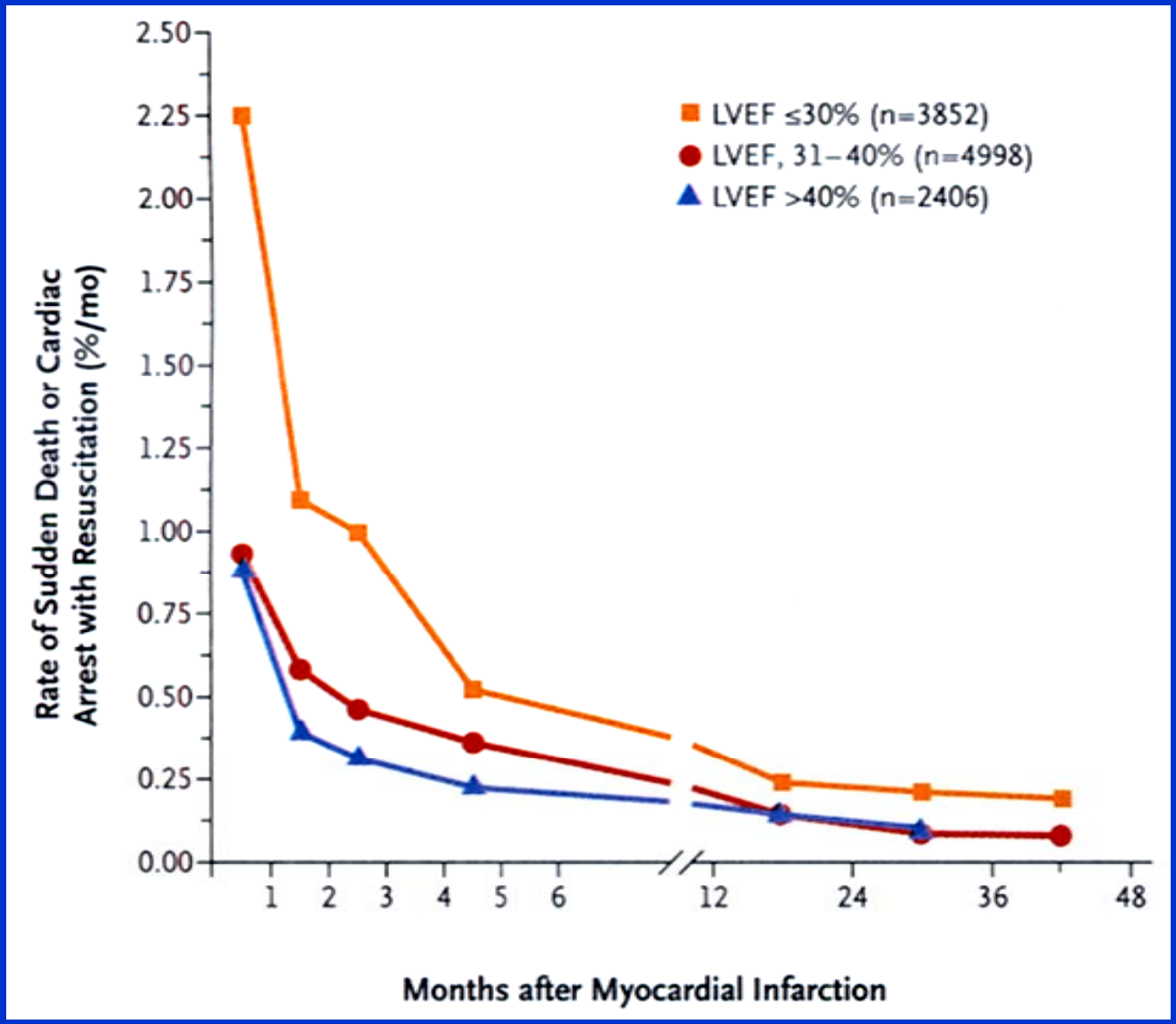
≈ 81 Months



DINAMIT

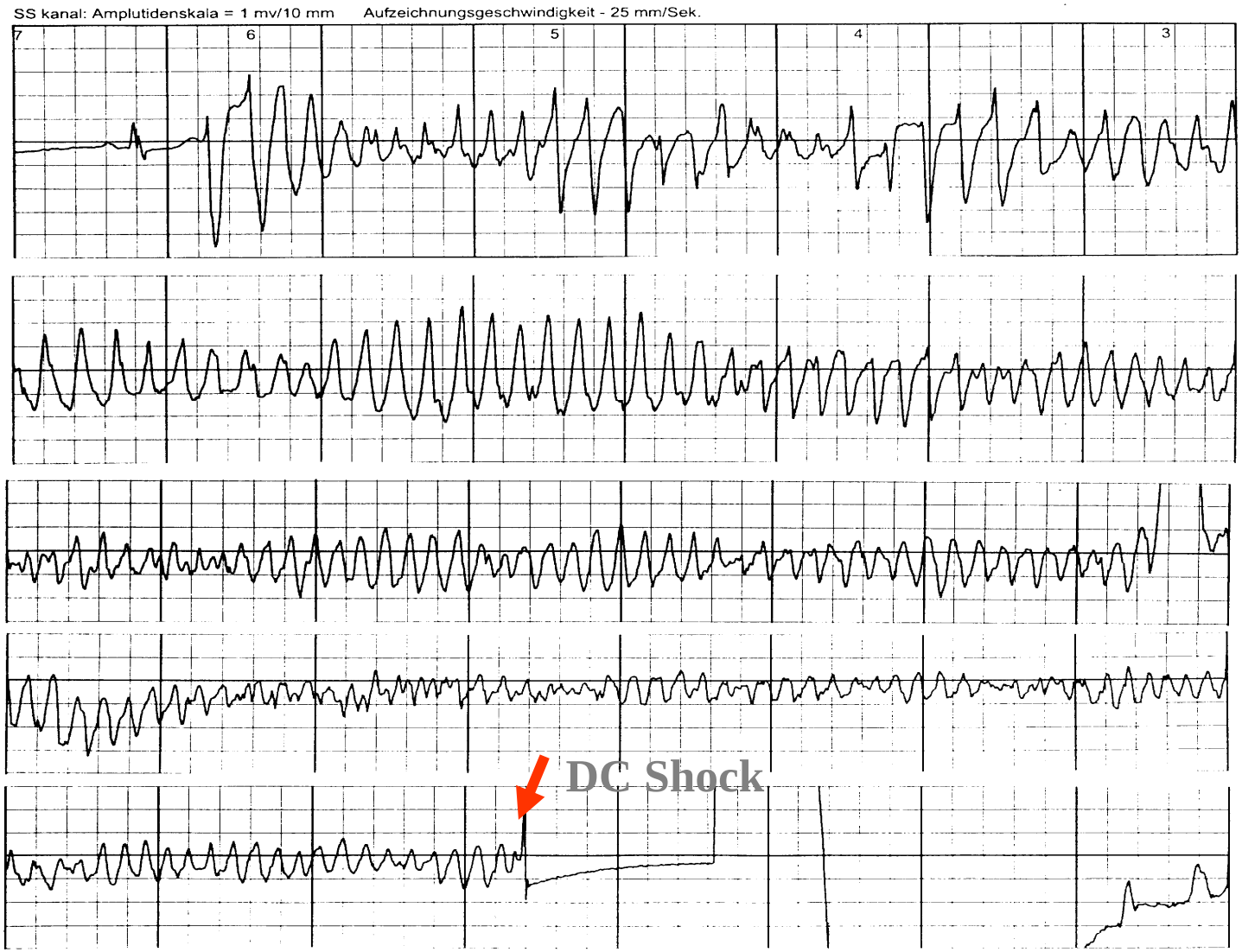
≈ 18 days

Rate of SCD / CA with Resuscitation versus LV-EF



S.Solomon; NEJM 2005;352:2581

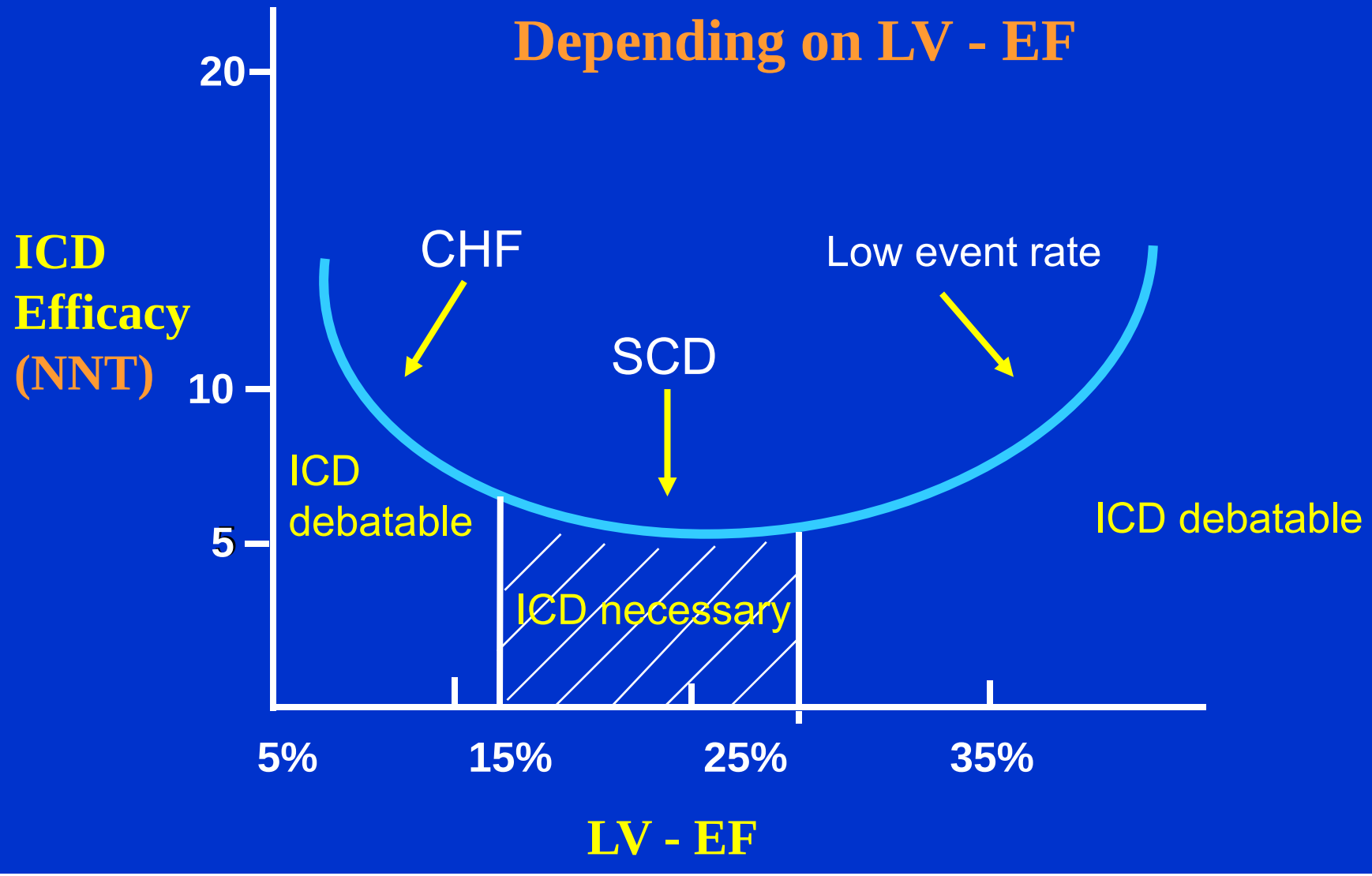
Role of the Wearable Defibrillator (WCD)



E. R. 47 y, 3 weeks after AMI, LV-EF: 20%

Cost/Effectiveness of ICD

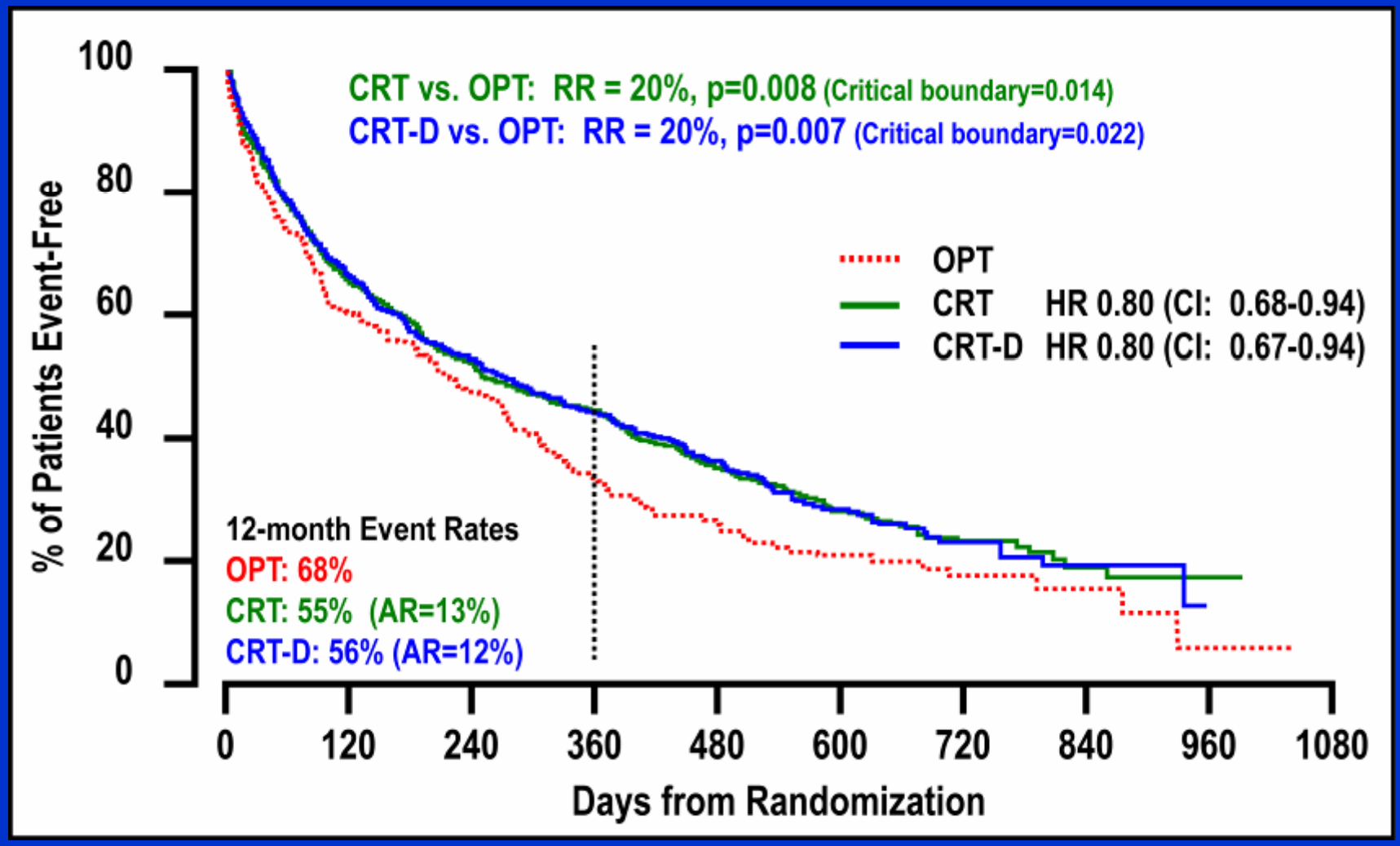
Depending on LV - EF



Until 2003 there was no proof that CRT can significantly reduce:

1. overall mortality
2. sudden arrhythmic death

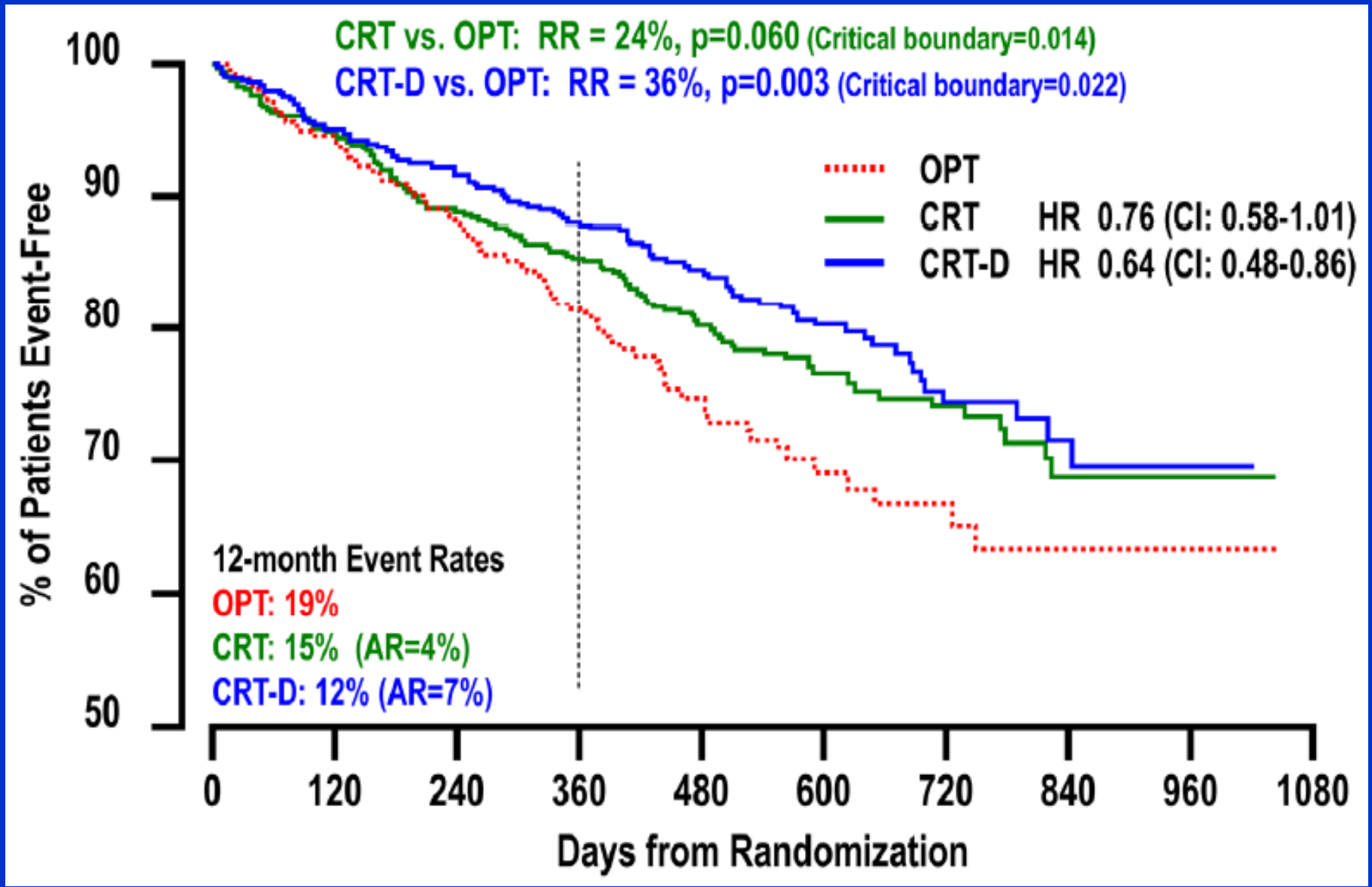
COMPANION: Primary Endpoint



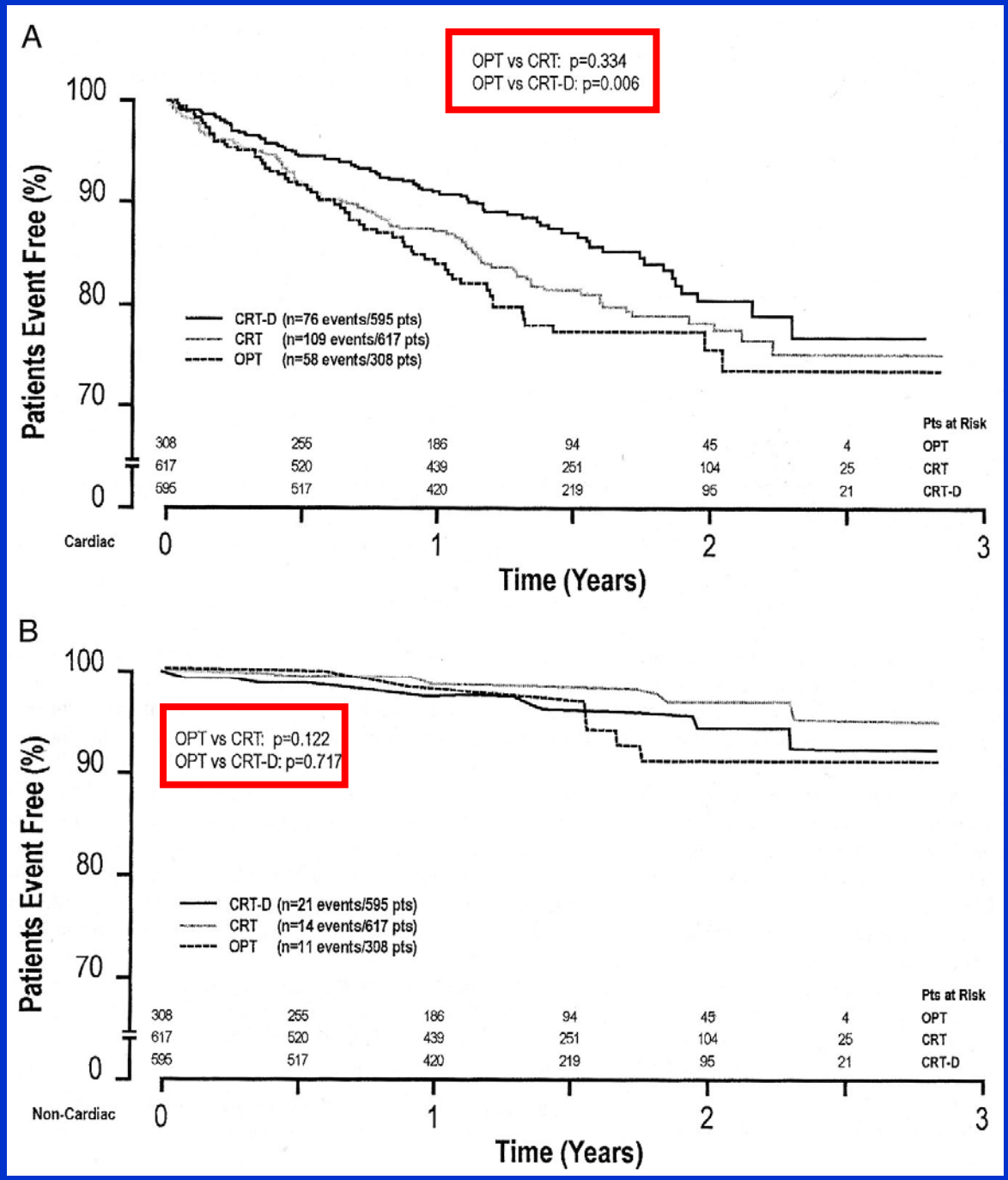
Bristow et al. *NEJM.* 2004; 350: 2140-50

COMPANION

2. Endpoint: All-Cause Mortality



COMPANION

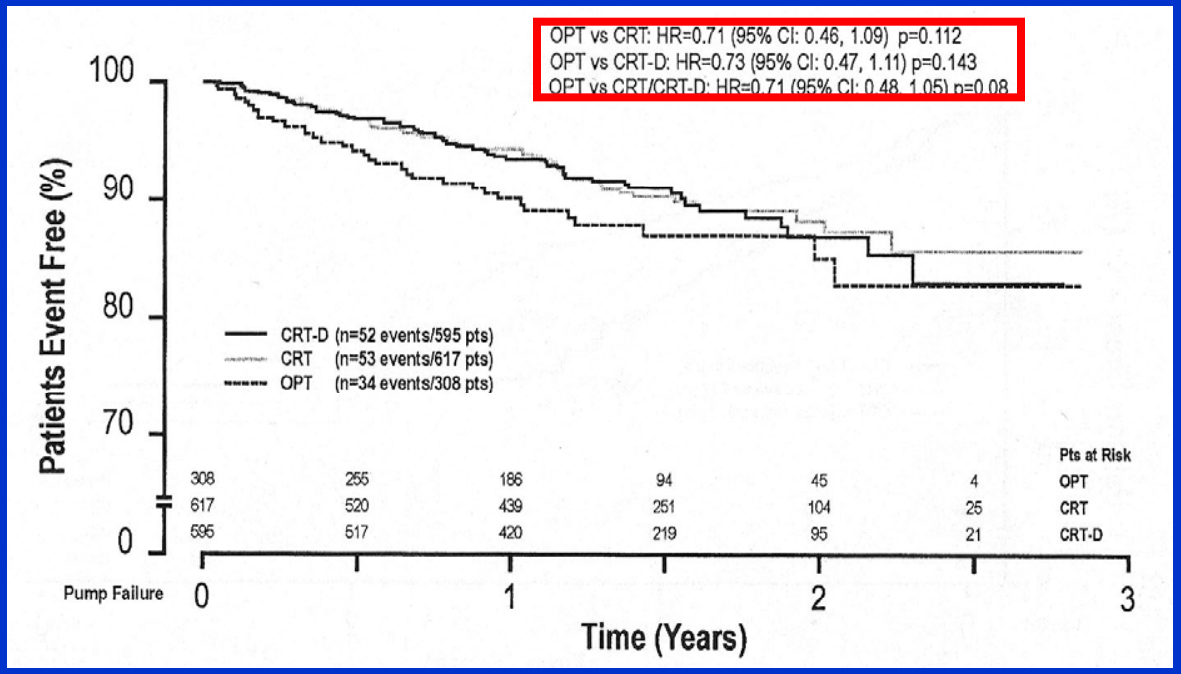


Cardiac Death

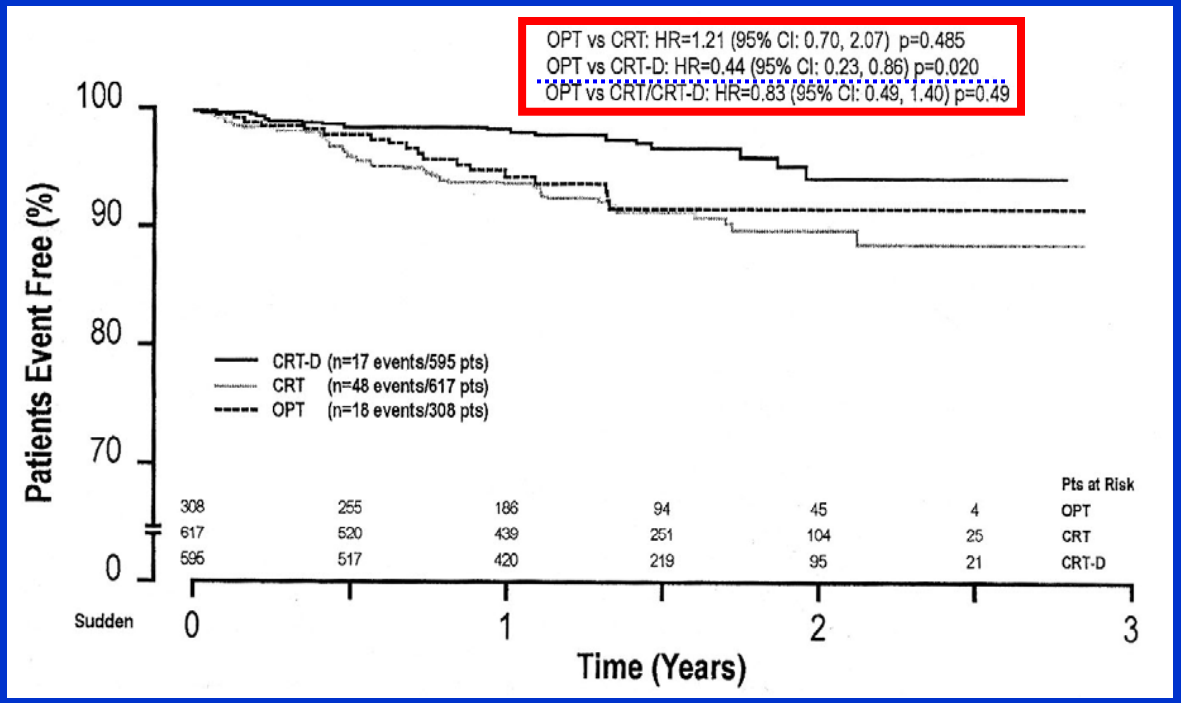
Non Cardiac Death

Carson et al. 2005

COMPANION



Pump Failure
Death



Sudden
Death

Carson et al.
2005

CARE - HF

Study Design

NYHA III, IV > 6 weeks

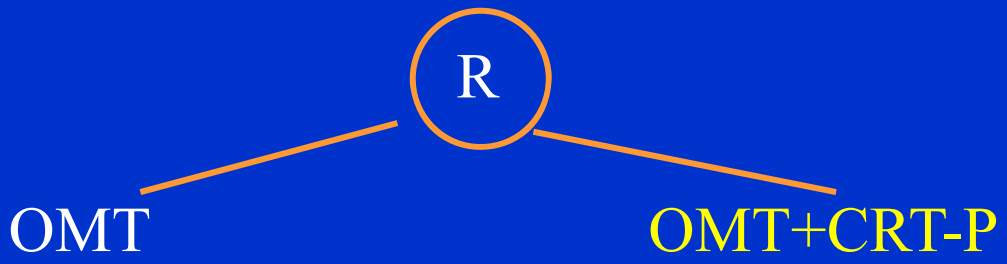
LV- EF ≤ 35%

QRS ≥ 120 ms

Demonstration of LV- Dys-synchrony

Optimal Medical Therapy (OMT)

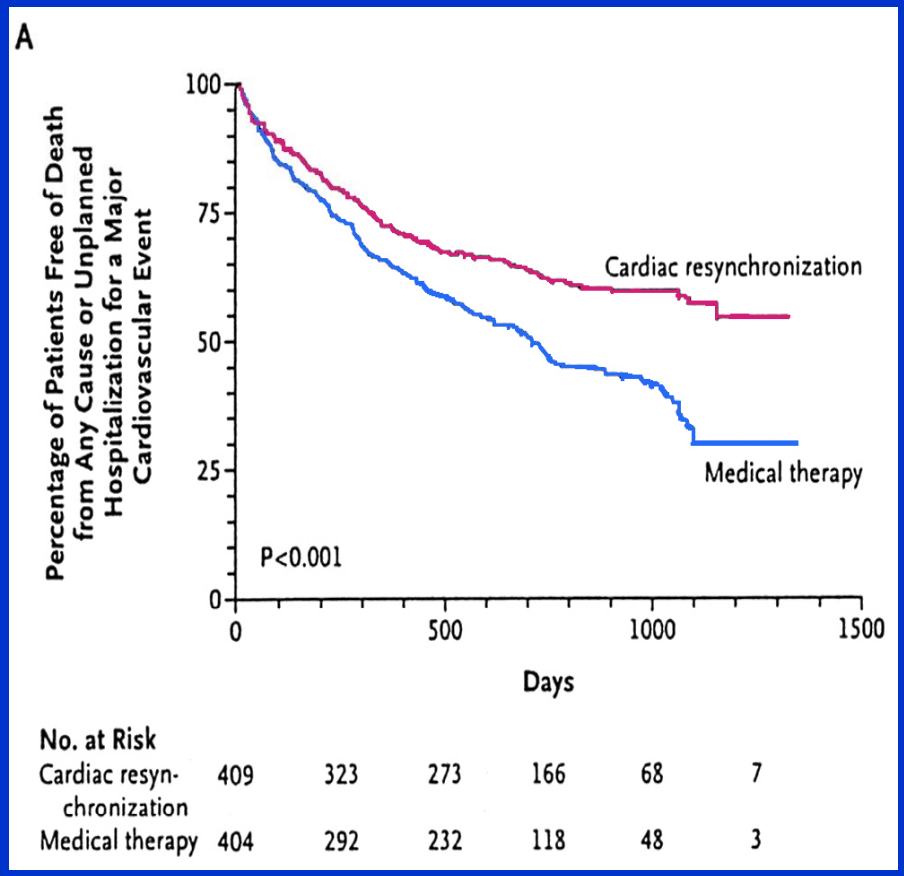
813 pts. (82 European Centers)



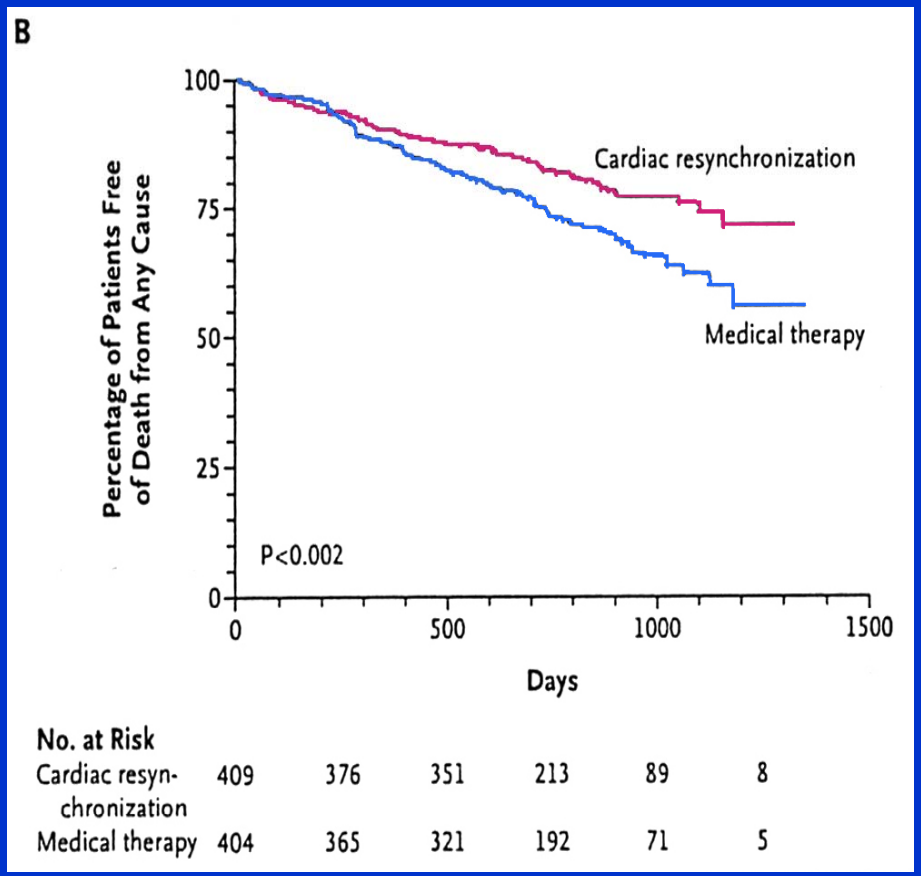
Follow-up 18 months

Enrollment: 1/2001- 3/2004

CARE-HF



Mortality or Hospitalization for CV-Event



Total Mortality

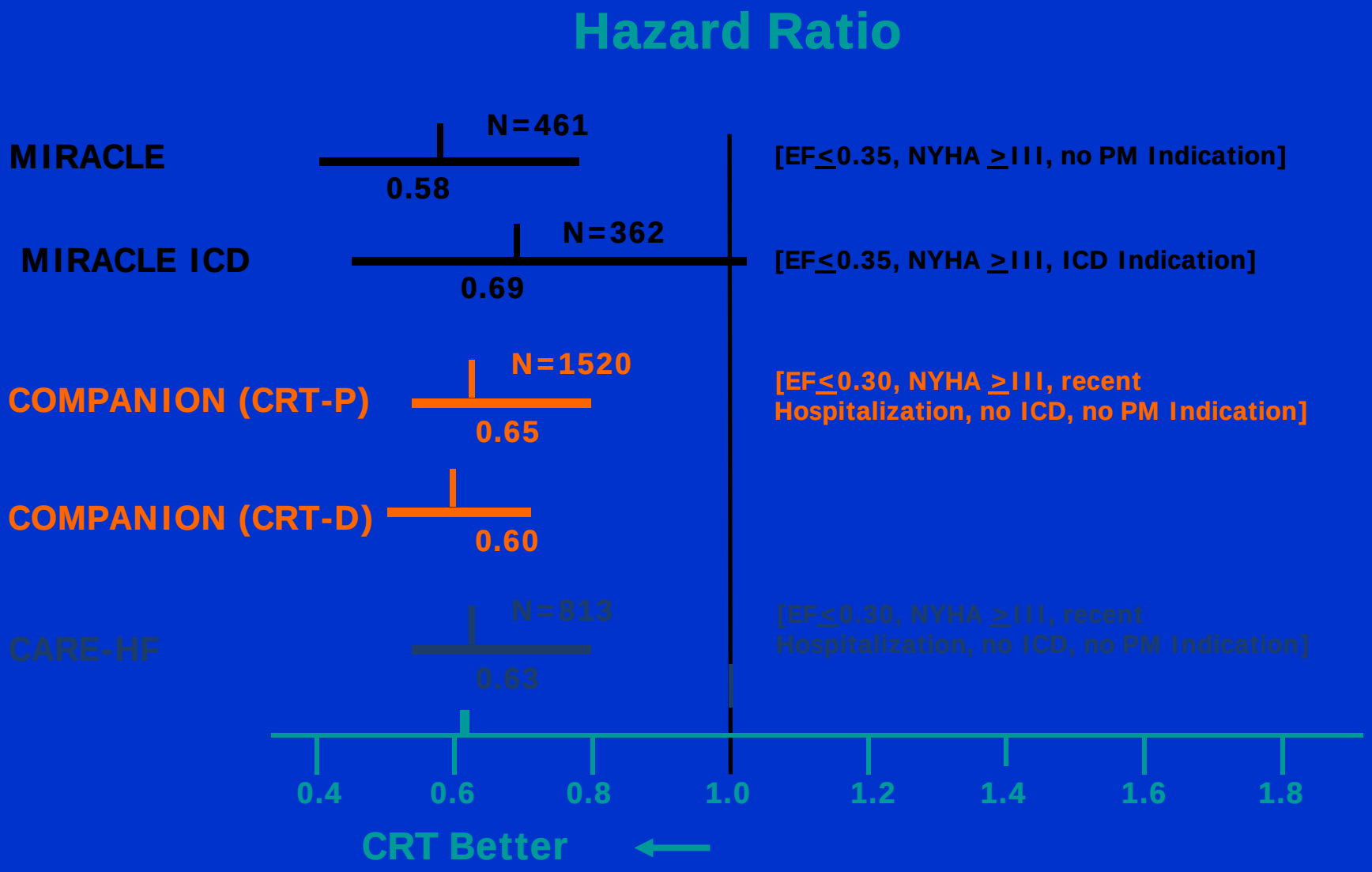
CARE-HF with extension phase

Follow up 29.4 mon. → 37.4 mon.

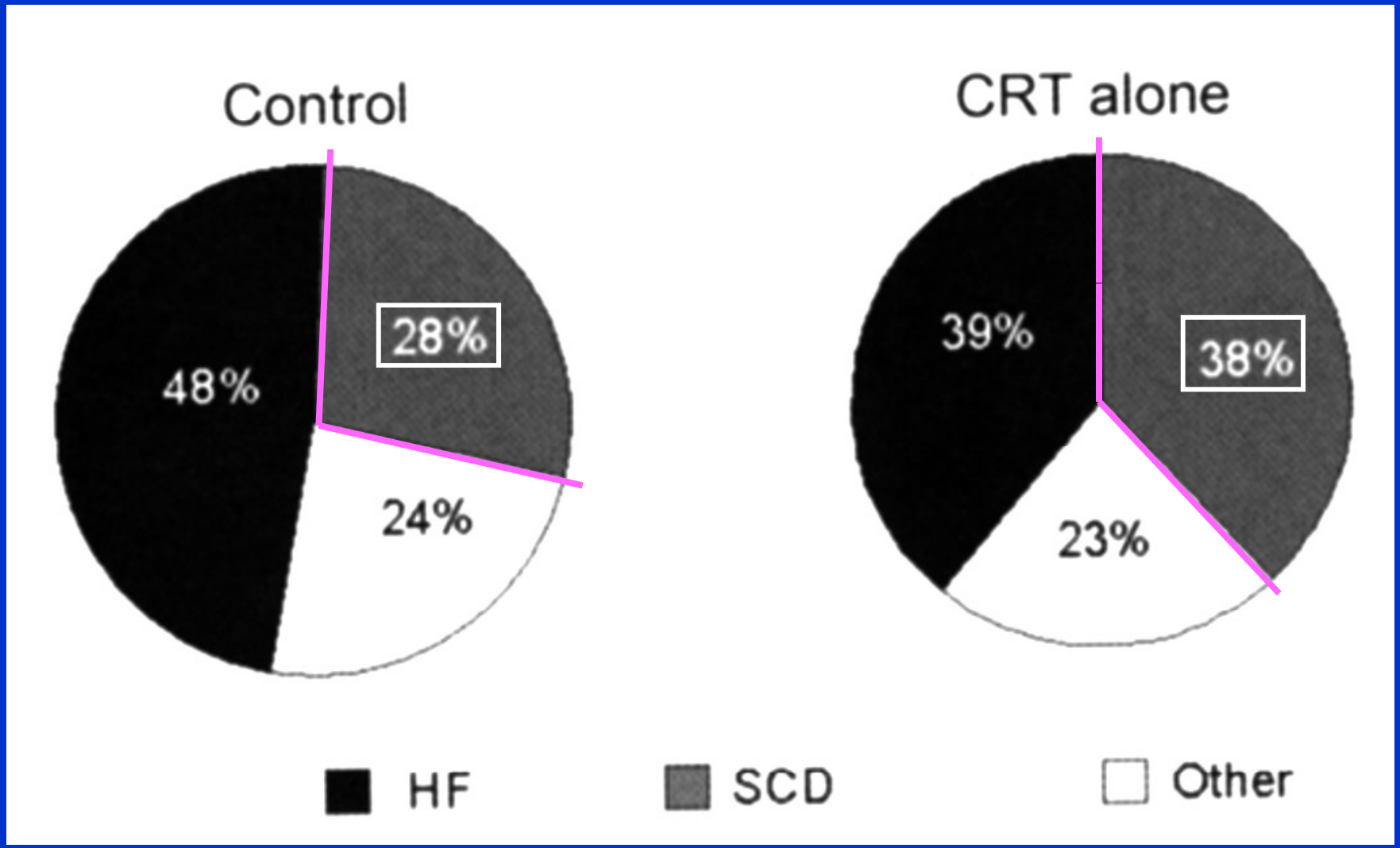
	OMT (n = 404)	CRT (n = 409)
Total mortalität	154 (38.1%)	101 (24.7%)
- extension	34	19
mort./year	12.2 %	7,9 %
CHF death	64	38
mort./year	5.1 %	3.0 %
SCD	54	32
- extension	16	3
mort./year	4.3 %	2.5 %

(Cleland, NEJM 2006)

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



Relative contribution of mode of death to overall mortality in pts with CRT alone



Rivero-Ayerza et al. EHJ 2006, 27:2682-88

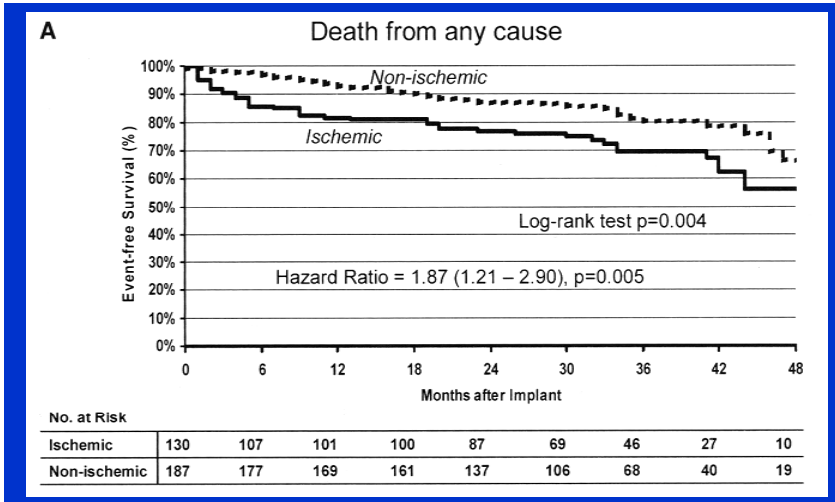
Is CRT in

Ischemic Cardiomyopathy (CAD) as beneficial as it is in

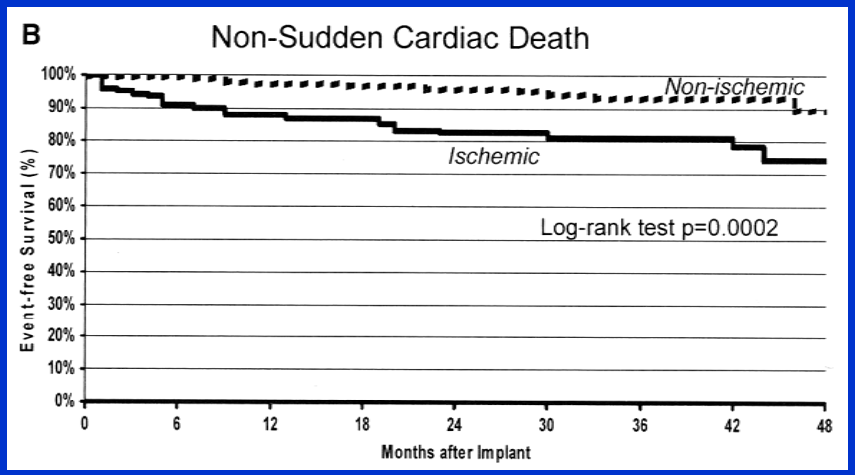
Non-ischemic cardiomyopathy (DCM) ?

Italian InSync Registry

(Gasparini, PACE 2006)



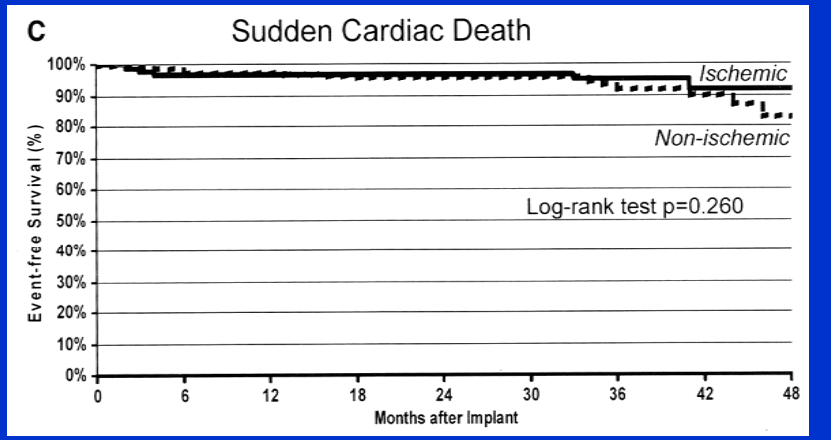
Total mortality



Pump failure

CAD versus DCM

SCD



Unanswered questions in CRT

Is CRT useful in pts with CHF but with normal (narrrow) QRS ?

(about 25% of CHF pts with normal QRS exhibit mechanical dyssynchrony)

RethinQ study

J.F Beshai et al. NEJM 2007

Aim:

Assess efficacy of CRT-D in pts with ICD indication,

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.HWT

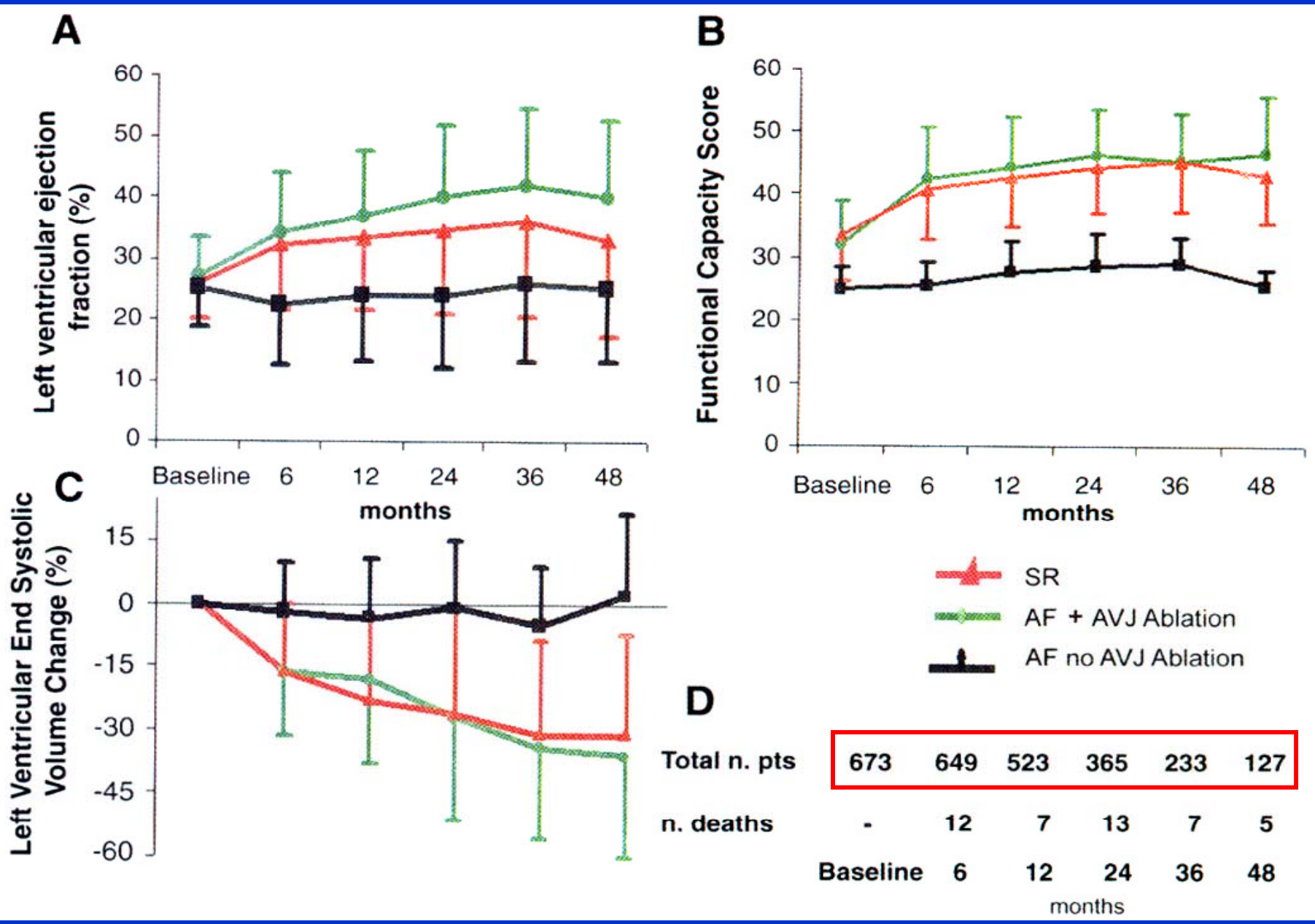
Conclusion

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

Unanswered questions in CRT

CRT response in pts with atrial fibrillation ?

CRT during Sinusrhythm and Atrial Fibrillation



Gasparini et al. JACC 2006 The Milan and Magdeburg experience

Unanswered questions in CRT

4. Effect of CRT in standard RV pacing ?

PAVE study

R.Doshi et al. JCE 2005

184 pts with AVN-Ablation for rapid AFib.

103 pts with BiV-P versus 81 pts with RV-P

Follow up: 6 months

Results

- Outcome of 6 min HWT and LV-EF sign. better with BiV-P than with RV-P
- Best results with BiV-P in pts with LV-EF≤45%

Commentary:

It was more a deterioration of LV function with RV-P than a benefit of BiV-P

- Is CRT in NYHA I/II as beneficial as it is in NYHA III/IV ?

  or

- Can CRT prevent the development of severe heart failure in pts. with no / mild heart failure ?

REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction

REVERSE

Principal Investigators:
Cecilia Linde; MD
Michael Gold, MD
William T. Abraham, MD

REVERSE

Aim: establish whether CRT with OMT can attenuate HF disease progression in pts. with NYHA I / II

PE: HF clinical composite response end point (Packer)

worse: death or hospitalized for worsening CHF; worsened NYHA

improved: NYHA-class / patient global assessment score

no change: neither improved or worsened

► improved and unchanged considered as: positive response to treatment

SE: LVESV index; NYHA; QoL; VAR in ICD pts. Healthcare utilization

REVERSE

Study Design:

double-blind (patient + investigator), parallel

Randomization: 1 : 2

CRT-OFF (OMT or OMT + ICD)

CRT-ON (OMT + CRT or OMT + CRT-D)

Follow-up: 12 months

After 1 year all pts: CRT on with another follow-up of 1 year

(European pts. (43%) remain 24 months in randomized assignment)

All pts. will be followed for a total of 5 years (FDA)

REVERSE

Study Patients (on optimal medical treatment)

NYHA I, II (I = previously symptomatic)

QRS ≥ 120 ms

LV-EF ≤ 40 %

LVEDD ≥ 55 mm

planned: 683 pts enrolled; Start: 9/2004

(expected: improved /12 month: 78% CRT on
66% CRT off)

REVERSE Characteristics

(n=610)

Age (years)	62.5 ± 11.0
Female	21.5%
Ischemic etiology	54.6%
BMI kg/m^2	28.5 ± 5.2
Systolic BP mmHg	125 ± 18.8
Diastolic BP mmHg	72.1 ± 11.2
Diabetes	22.5%
NYHA Class I / II	17.7% / 82.3%
CRT-D / CRT	83.4% / 16.6%
LV-EF	26.7%
QRS	153 ms

Courtesy C.Linde

MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL – CARDIAC RESYNCHRONIZATION THERAPY (MADIT-CRT)

Start: 12/2004, 1/2005

Supported by a Research Grant from Boston Scientific to the

University of Rochester, NY

Principal Investigator: Arthur J. Moss, MD

MADIT- CRT

Purpose of the Trial

To determine if prophylactic CRT in asymptomatic high-risk patients

- Reduces the risk of all-cause mortality and HF events by ~25% (i.e. 2-year cumulative event rates from 30% to 22.6%) when compared to ICD therapy alone

  (Previous studies of CRT-D indicate that the combined 2 year event rate may be reduced by 25% or more)

- Can prevent heart failure by delaying the progression or even reverse remodeling

MADIT-CRT PROTOCOL: Primary Objective

- When compared to ICD-only therapy, prophylactic CRT-D will significantly reduce the combined rate of mortality or HF event, whichever comes first, in asymptomatic high-risk cardiac patients (EF ≤0.30) with ischemic (NY Class I/II) or non-ischemic (NY Class II) cardiomyopathy and QRS >0.12 sec.

MADIT-CRT
End Points

- All-cause Mortality
- Heart-failure Event

  Signs & symptoms of HF and:

- 1) iv decongestive therapy in an “out-patient” setting; or
- 2) augmented iv or oral decongestive therapy during in-hospital stay

MADIT-CRT
Baseline Characteristics (12/31/07)

N=1654

	%
• Age ≥ 65 yrs	49
• Male	75
• IHD	55
• Ejection fraction <0.25	41
• QRS >150ms	60
• NYHA CHF Class II	86
• BUN >30mg/dl	16

MADIT-CRT
Conclusions

- MADIT-CRT is currently the largest ongoing CRT trial
- Enrollment will be completed shortly
- The trial is on-target to determine if CRT can inhibit or slow the development of CHF in at-risk cardiac patients
- Final results will be available spring 2009