

**The Role of ICD Therapy
in
Cardiac Resynchronization**

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DISCLOSURE

Angel R. León consults for, and receives research grant support from, Medtronic and Guidant.

CRT CLINICAL TRIALS

MIRACLE

Contak-CD

InSync ICD

InSync III

MUSTIC

PATH-CHF II

COMPANION

6mo parallel comparison



3mo double crossover

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Prospective mortality study

SCD in the CRT Population

Mechanism of death at 2yrs in the non-ICD CRT Trials:

MIRACLE (n=591)	32*/91	(35%)
InSync III (n=422)	26*/65	(40%)

*deaths due to VT/VF

Progressive CHF and ventricular arrhythmia-SCD
contribute greatly to mortality in the CRT trials

CRT CLINICAL TRIALS (cont)

Endpoints included functional capacity, LV dimensions and performance, QoL and limited assessments of CHF hospitalization

Duration of follow-up designed to meet US-FDA requirement for device efficacy as CHF therapy

ICD THERAPY AND MORTALITY

VT/VF with previous MI

EPS in high risk pts

Prophylactic ICD

CRT-ICD

AVID

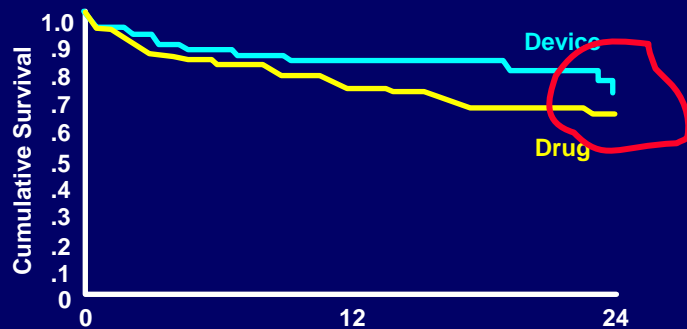
MUSTT, MADIT

MADIT-II, SCD-HeFT

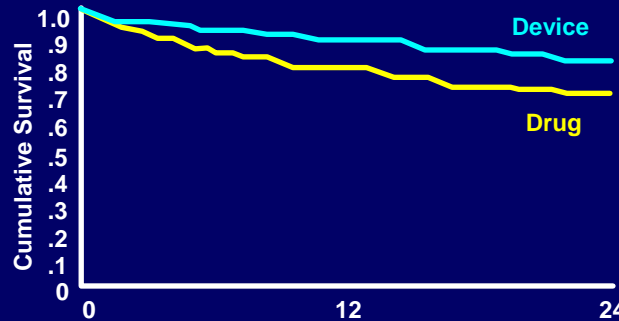
COMPANION

Survival with VT/VF and LV Dysfunction (AVID)

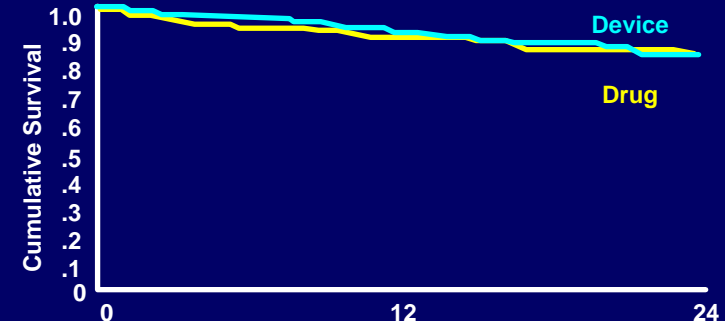
**LVEF <0.20
(Group 1)**



**LVEF 0.20 - 0.34
(Group 2)**



**LVEF > 0.34
(Group 3)**



NSVT in LV Dysfunction

LVD and CAD: ICD and inducible VT at EPS
(MUSTT) *Buxton, NEJM 2001*
(MADIT) *Moss, NEJM*

LVD without CAD: ICD provides no benefit over
amiodarone to pts with non-ischemic CMP and
NSVT (AMIOVERT) *Strickberger, JACC 2002*

DEFINITE: NSVT in Non-Ischemic CMP

**ICD therapy vs. conventional medical therapy
in patients with NSVT and LV dysfunction not
due to CAD or previous MI**

ICD reduced overall mortality: $p=0.06$

Kadish, NEJM 2004

Prophylactic ICD Implantation

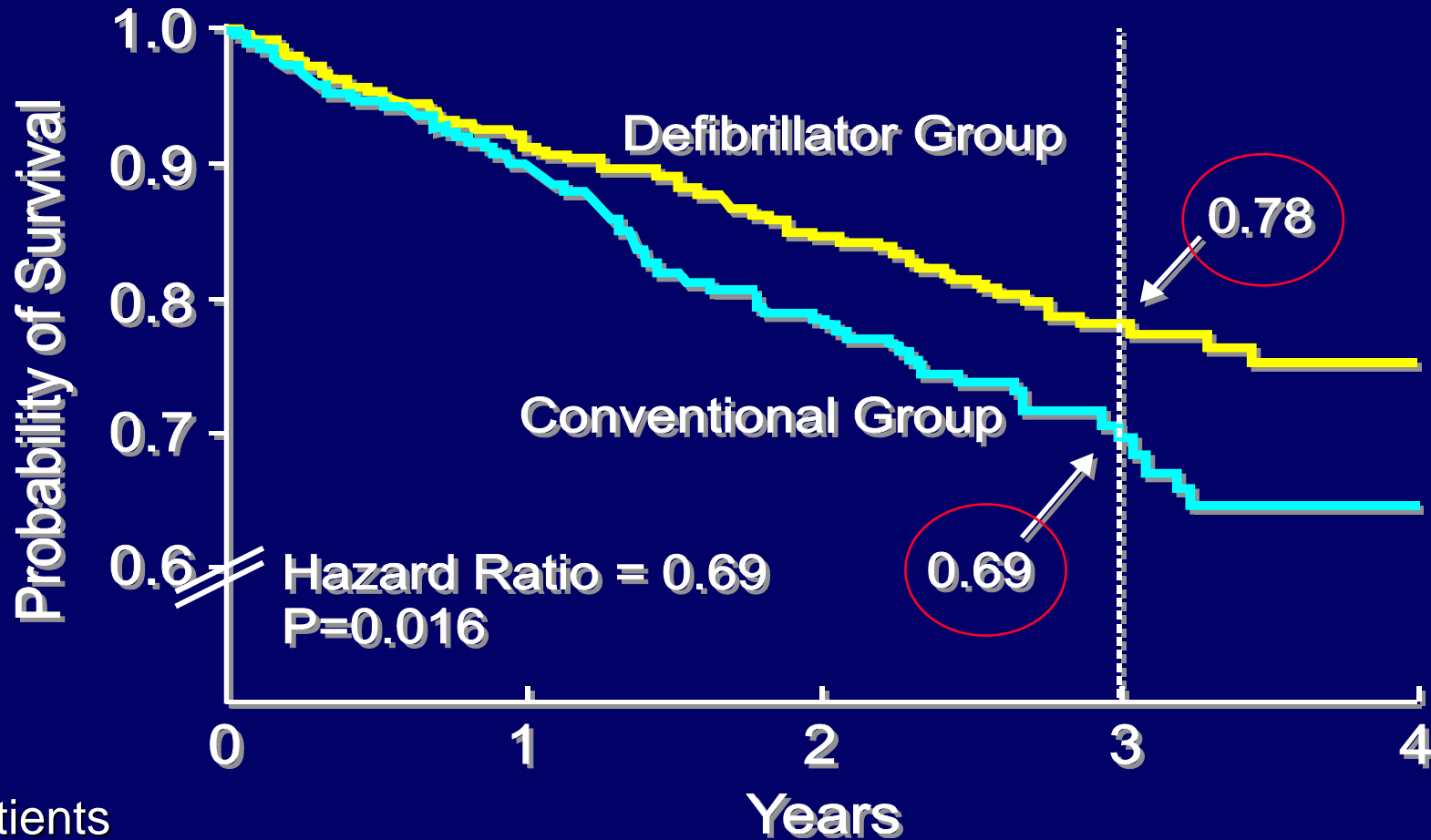
Will Implantation of an ICD in an individual with LV dysfunction (LVD) and CHF reduce all-cause mortality?

MADIT II:	LVD due to CAD/MI
COMPANION:	CRT-ICD for QRS > 120ms
SCD-HFT:	CHF, systolic dysfunction

MADIT II: PREVALANCE OF CHF

- LV dysfunction EF \leq 0.30 due to MI at risk for SCD:
- EF 22%
- 60% >class II CHF
- 88% > 6mos post MI
- >70% on β -blockers and ACE-I
- Subgroup with prolong QRSd

MADIT-II: All Cause Mortality



No. of Patients

Defibrillator	742	503	273	110	9
Conventional	490	329	170	65	3

Absolute reduction in overall mortality = 9%

MADIT-II: Three Year Mortality

CONV
(n=490)

ICD
(n=742)

K-M survival 0.69

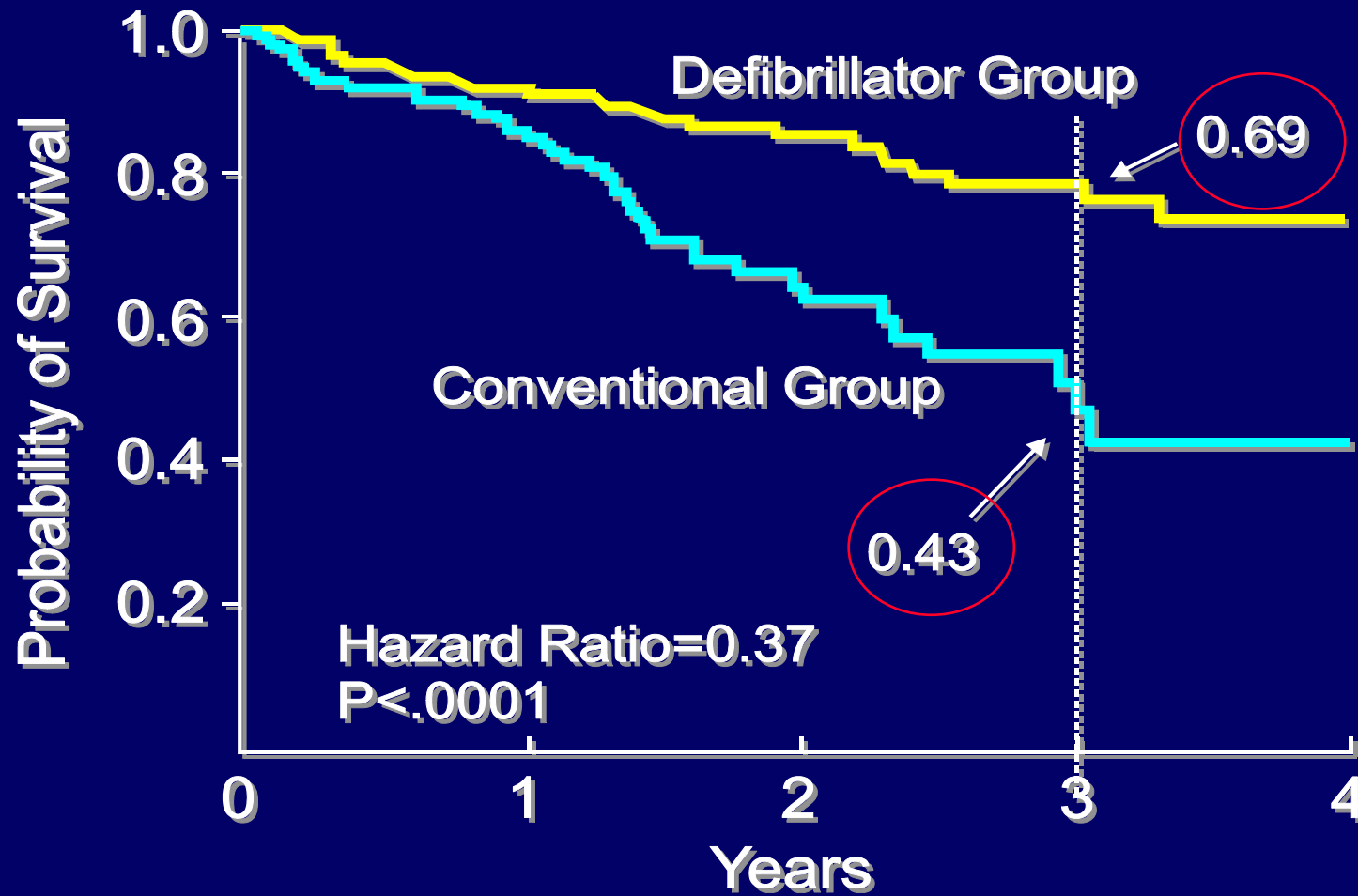
0.78

9% Absolute mortality reduction

Event curves begin to diverge after 1yr

Hazard Ratio (ICD:CONV) 0.69 (95% CI)
(0.51, 0.93) **p = 0.016**

MADIT-II: Subgroup QRSd > 150ms



Absolute overall mortality reduction 26%!!!

PRIMARY PREVENTION

Absolute mortality difference demonstrates the incremental benefit of the ICD over conventional therapy

The number of implants needed to save one patient:

$$\frac{1}{\text{absolute mortality difference}}$$

MADIT-II: Results

**ICD as primary prevention in long QRS:
26% Absolute mortality reduction**

Overall MADIT-II (0.09): 11 implants to save 1 life

In pts with QRS >150 (0.26): 4 implants to save 1 life

SCD-HeFT Patient Flow

LVEF \leq 35%,
NYHA Class II or III CHF
N = 2,500 (expected enrollment)

Randomization

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graph TD; A["LVEF ≤ 35%,  
NYHA Class II or III CHF  
N = 2,500 (expected enrollment)"] -- Randomization --> B["Conventional CHF Rx  
& placebo  
(n = 833)*"]; A -- Randomization --> C["Conventional CHF Rx  
& amiodarone  
(double blind)  
(n = 833)*"]; A -- Randomization --> D["Conventional CHF Rx  
& ICD  
(n = 833)*"];
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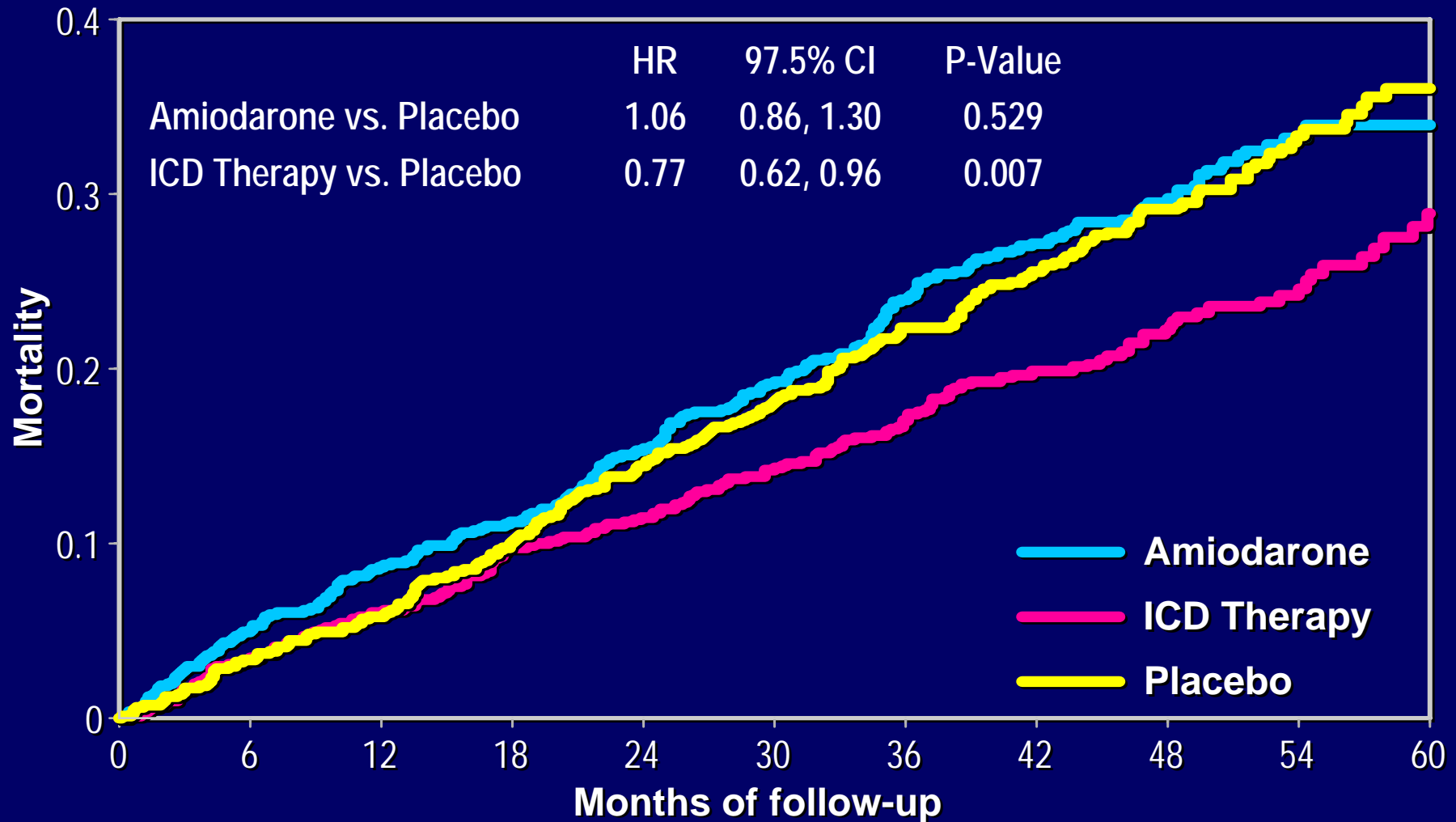
**Conventional CHF Rx
& placebo
(n = 833)***

**Conventional CHF Rx
& amiodarone
(double blind)
(n = 833)***

**Conventional CHF Rx
& ICD
(n = 833)***

SCD-HeFT Treatment Group Mortality

Intention-to-Treat



Adapted from Bardy, et. al. NEJM 2005

SCD-HeFT: RESULTS

Primary therapy with the ICD provided a 7.5% absolute decrease in mortality at 5 years

Event curves do not diverge until 18mo after ICD

Amiodarone did not improve survival in heart failure pts

ICD THERAPY FOR SCD

ICD: The most effective therapy to reduce SCD in the overall LV dysfunction and CHF population

The impact of ICD therapy appears greatest in the prolonged QRS population

Annual mortality in overall CHF population at 7.2%

MADIT and SCD-HeFT RESULTS

ICD as primary prevention for SCD:

MADIT-II (0.09): 11 implants to save 1 life

MADIT-II QRS >150 (0.26): 4 implants to save 1 life

SCD-HeFT: 14 implants to save 1 life

MORTALITY AND DYSSYNCHRONY

LV dysfunction, CHF, and prolonged QRSd each individually increase the risk of death

The CRT population differs from the general LV dysfunction population due to prolonged QRS

SCD in the CRT Population

Mechanism of death at 2yrs in the non-ICD CRT Trials:

MIRACLE (n=591)	32*/91	(35%)
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InSync III (n=422)	26*/65	(40%)
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*deaths due to VT/VF

Meta-analysis of CRT trials shows that CRT significantly reduces CHF mortality, but only a trend in reducing all-cause mortality.

Bradley JAMA 2003

ICD in CRT: COMPANION

Comparison of CRT-P, CRT-D, and no device

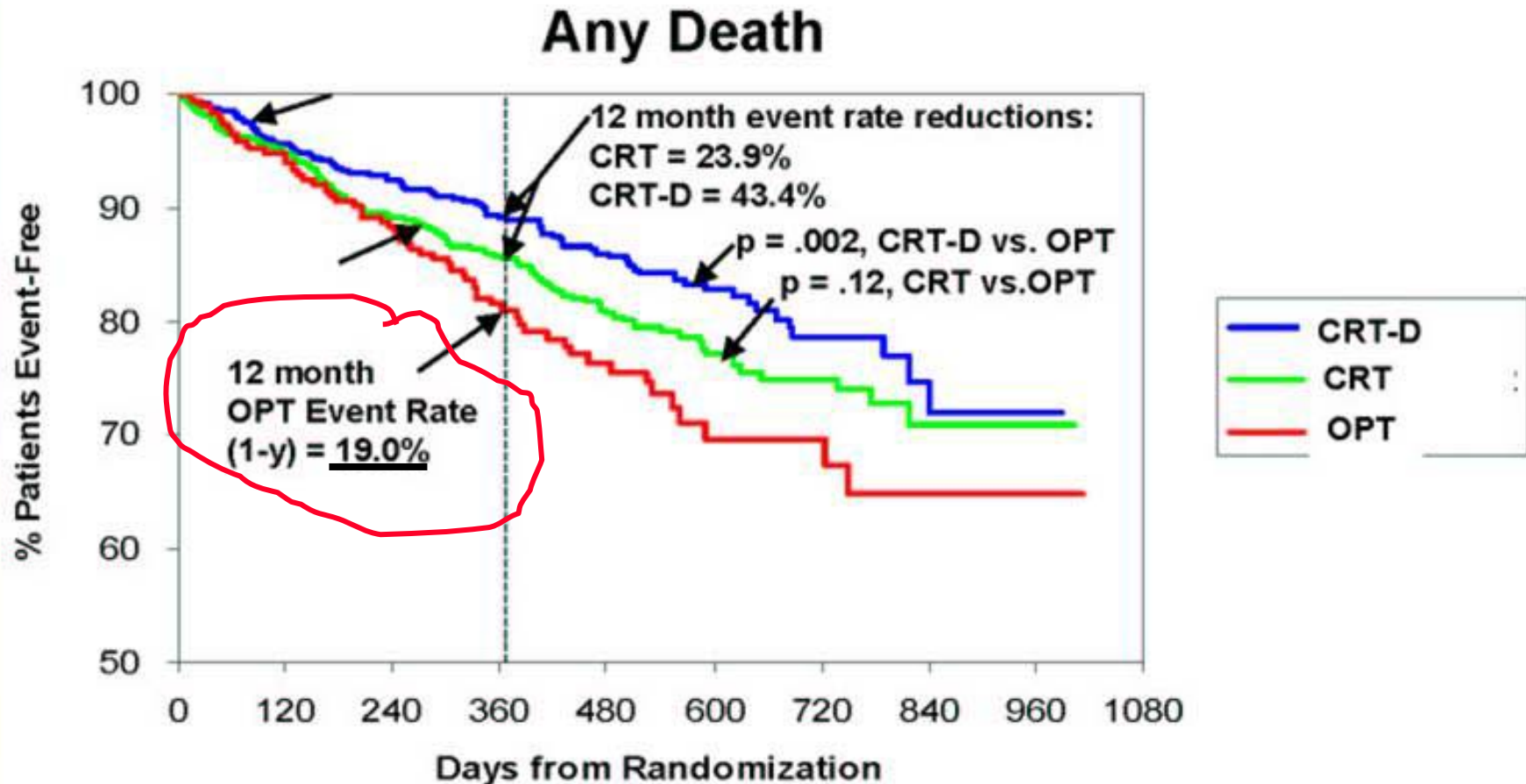
EF < 0.35, NYHA Class III-IV, QRSd > 120ms:

Endpoints: Overall mortality and hospitalization
Overall mortality

Statistical power: CRT-D vs. optimal med. Rx
CRT-P vs. optimal med. Rx

COMPANION: Secondary Endpoint of All-Cause Mortality

Bristow NEJM 2003



COMPANION: Mortality

Population enrolled similar to other CRT trials and to CHF trials except for prolonged QRSd:

19% 1yr mortality in COMPANION control group

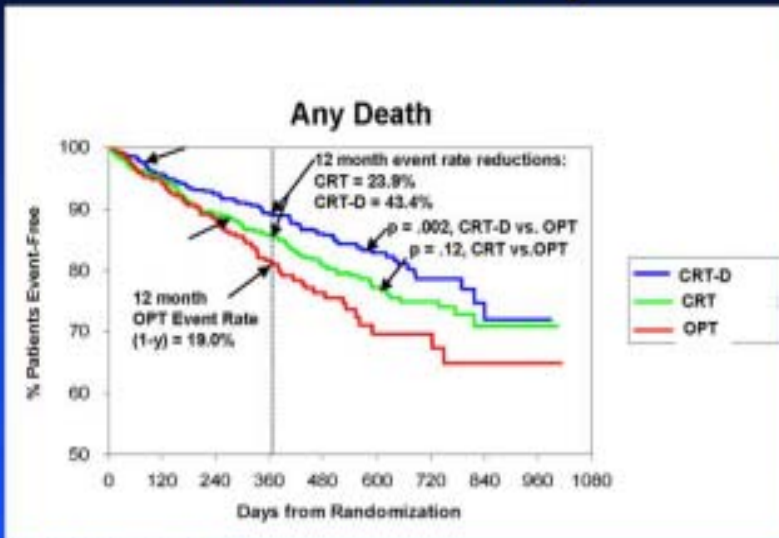
7.2% annual mortality in SCD-HeFT control group

CRT-D & control event curves separate immediately

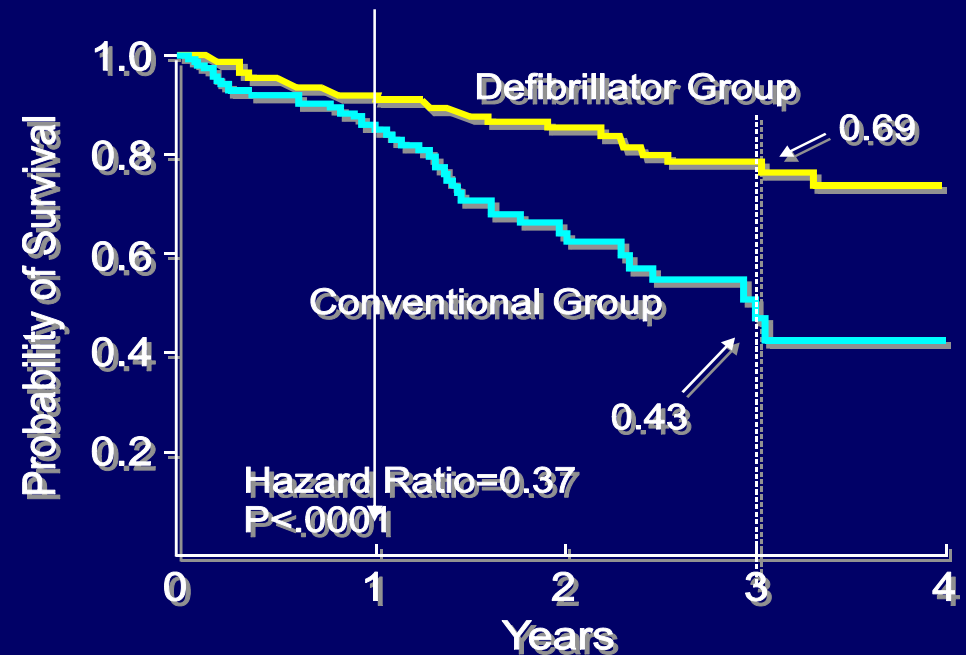
CRT-ICD reduced mortality by 8% at 1yr

COMPANION & MADIT II

COMPANION: Secondary Endpoint of All-Cause Mortality



MADIT II QRS > 150



The effect of ICD therapy in the MADIT-II prolonged QRS group closely resembles the impact of CRT-D in COMPANION

COMPANION MORTALITY BENEFIT

What was the relative contribution of CRT vs ICD to the mortality reduction in COMPANION?

CRT-P produced no statistically significant impact on mortality (over the 1yr follow-up period)

CRT-D impact much earlier than ICD alone in the other trials

MORTALITY: CRT-D vs ICD

MADIT-II:

9% reduction at 3 yrs

MADIT-II QRS >150 (0.26):

26% reduction at 3yrs

SCD-HeFT:

7.5% reduction at 5 yrs

COMPANION:

8% reduction at 1yr

US CRT TRIALS: LIMITATIONS

Relatively short follow-up period to assess the potential effects on remodeling and mortality

No direct comparison of CRT-P and CRT-D

No US clinical trial assessed the isolated impact of CRT on mortality. CRT vs. ICD benefit unknown

CARE-HF: CRT-P

What is the isolated effect of CRT on mortality, LV function and hospitalization?

NYHA Class III-IV, QRSd > 120ms, EF < 0.35

CRT-P vs optimal medical therapy, NO ICD

Cleland, NEJM, 2005

CARE HF: Patient Flow

Enrolled n=813, mean follow up 29mo

OPT

CRT

<u>Death or Hosp</u>	n = 224 (0.55)	n = 159 (0.39)	HR 0.63 [.51-.77] p < 0.001
<u>Death</u>	n = 120 (0.30)	n = 82 (0.20)	HR 0.64 [.48-.85] p < 0.002

Echocardiographic endpoints: MR, IVMD, LVESI p < 0.01

Symptom and Quality of Life score p < 0.01

Cleland, NEJM 2005(352)

CONCLUSIONS

1. CRT Improves functional status, LV performance and decreases hospitalization
2. CRT-D improves overall mortality over control
3. CRT-P improves overall mortality over control
4. The incremental benefit of CRT-D over CRT-P has not been tested