Sudden Cardiac Death in Patients with Left Ventricular Dysfunction: Focus on Primary Prevention with ICDs

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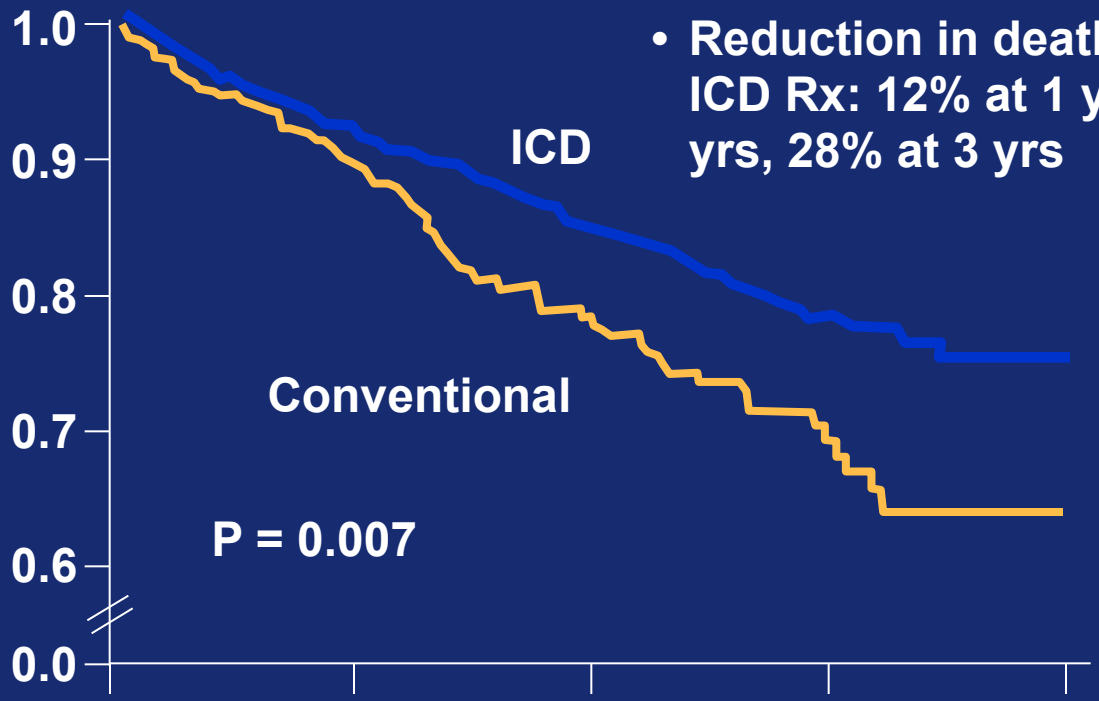
MADIT II: Probability of Survival in ICD vs Conventional Therapy Group

- Trial stopped at 20 months
- Reduction in death rate with ICD Rx: 12% at 1 yr, 28% at 2 yrs, 28% at 3 yrs



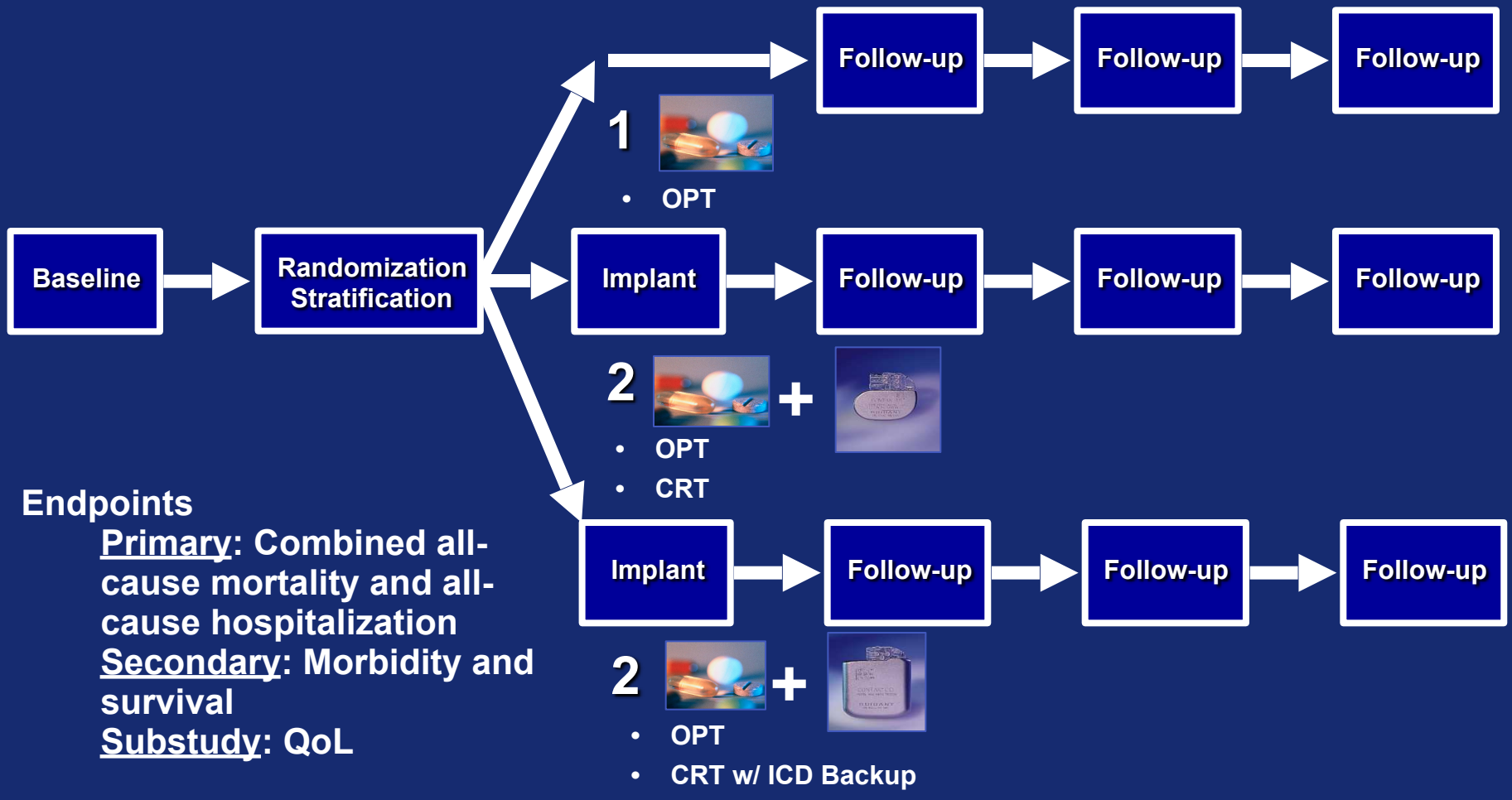
No. At Risk					
Defibrillator	742	502 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss et al. N Engl J Med 2002;346:877-83.

Comparison of Medical Therapy, Pacing and Defibrillation Therapies in Heart Failure (COMPANION) Trial

- NYHA Class III or IV
- NSR, QRS ≥120 ms, PR interval >150 ms
- LVEF ≤35%, LVEDD ≥60 mm
- Optimal pharmacological therapy (OPT)
  - β-blocker (for at least 3 months)
  - Diuretic, ACEI/ARB, spironolactone (1 month)
  - Digoxin
- HF hospitalization (or equivalent) in prior 12 months, >1 month prior to enrollment

COMPANION Design

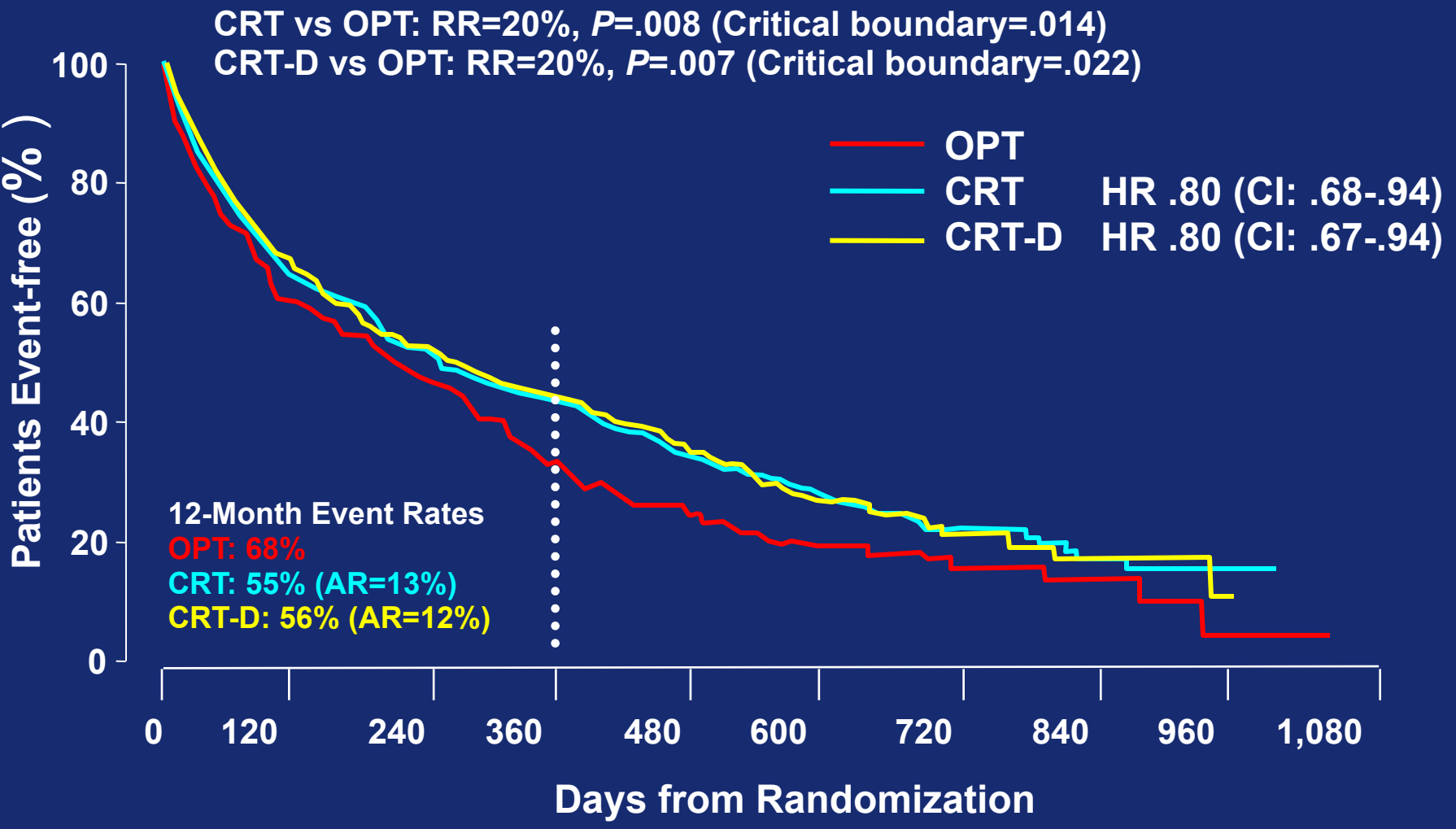


Endpoints

- **Primary**: Combined all-cause mortality and all-cause hospitalization
- **Secondary**: Morbidity and survival
- **Substudy**: QoL

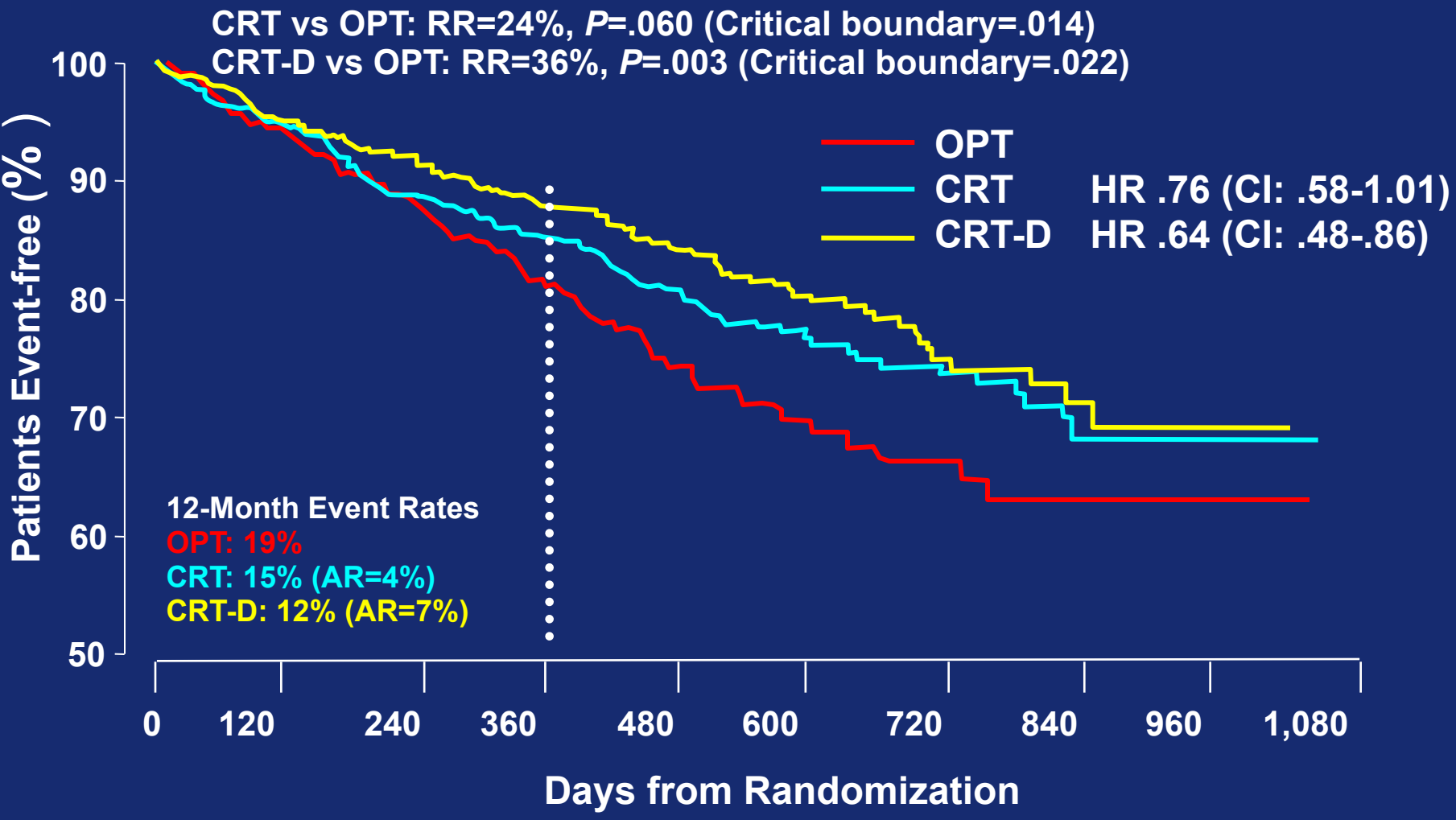
Time Post-Randomization

COMPANION:
Primary Endpoint: Mortality+Hospitalization



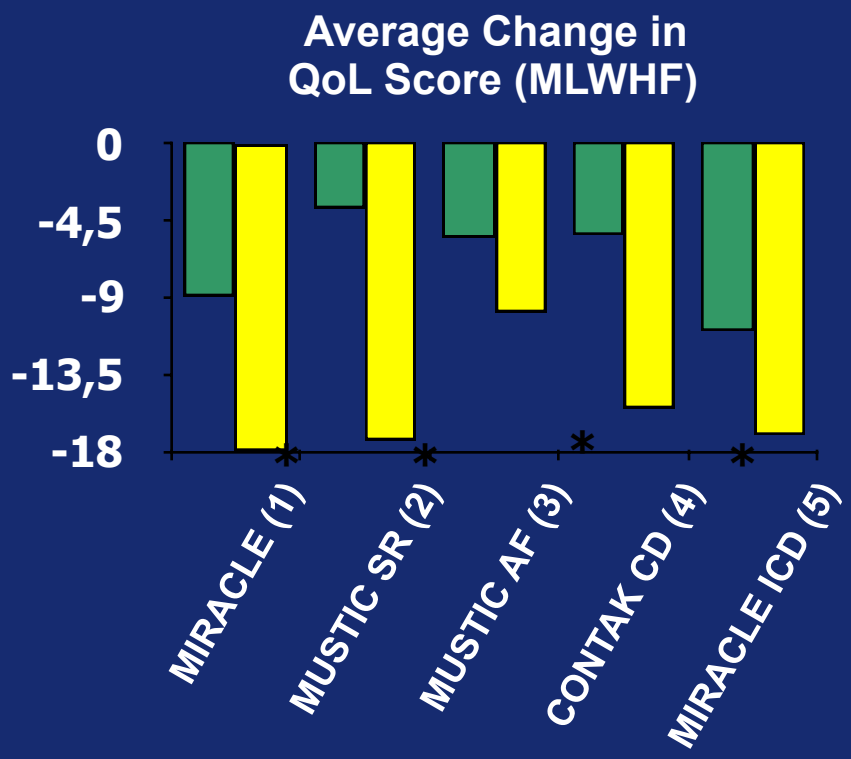
HFSA Late-Breaking Clinical Trials, September 24, 2003.
Bristow MR, et al. N Engl J Med 2004;350:2140-2150.

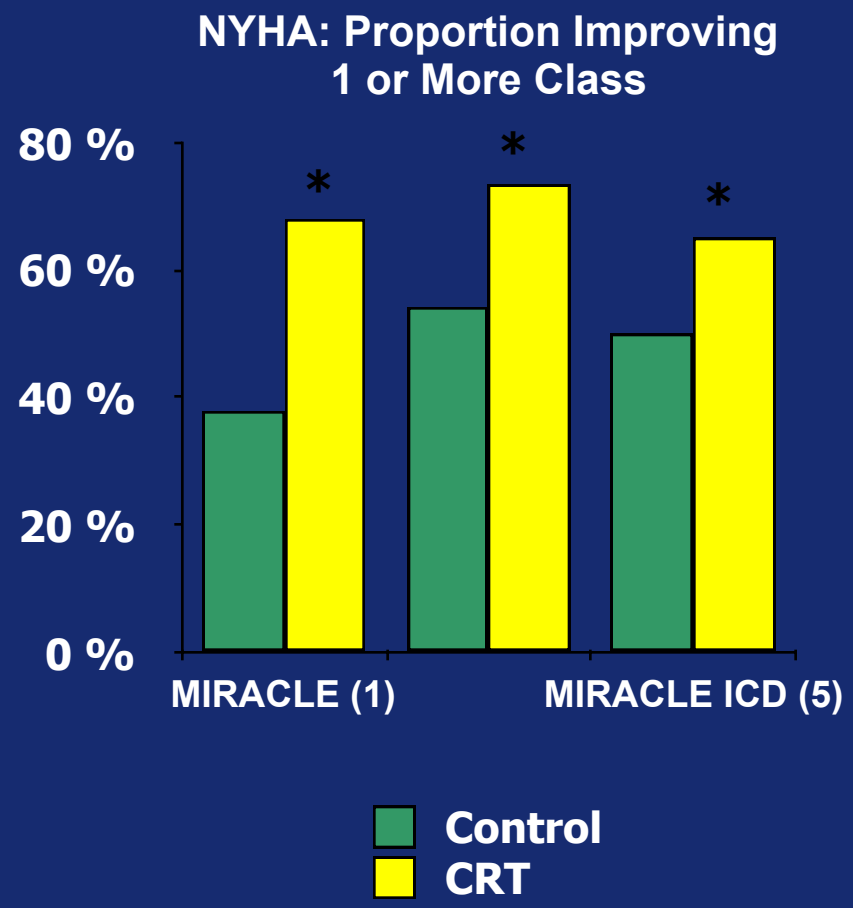
COMPANION:
Secondary Endpoint: All-Cause Mortality



HFSA Late-Breaking Clinical Trials, September 24, 2003.
Bristow MR, et al. N Engl J Med 2004;350:2140-2150.

CRT Improves QoL and NYHA Functional Class

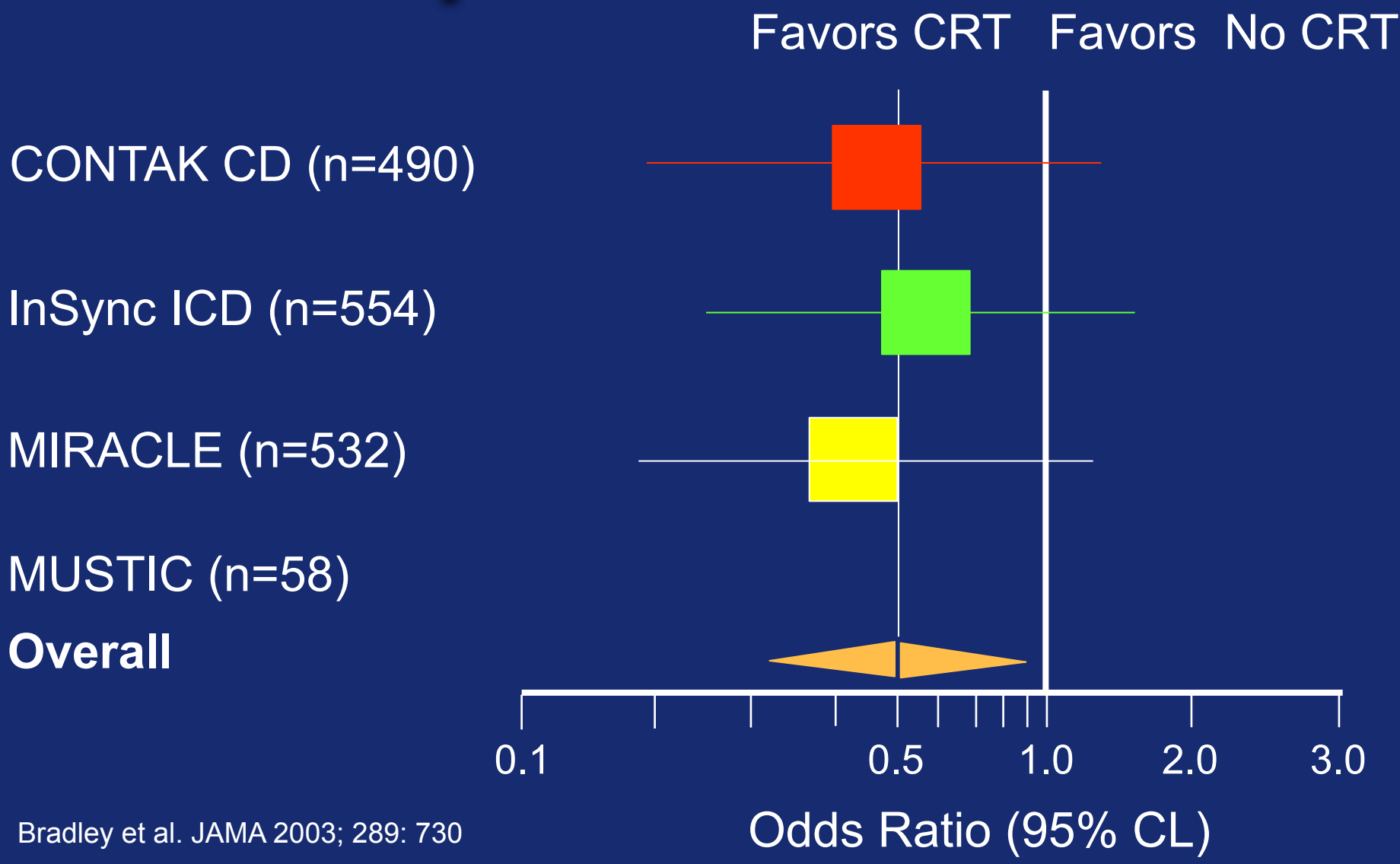




* *P*<0.05

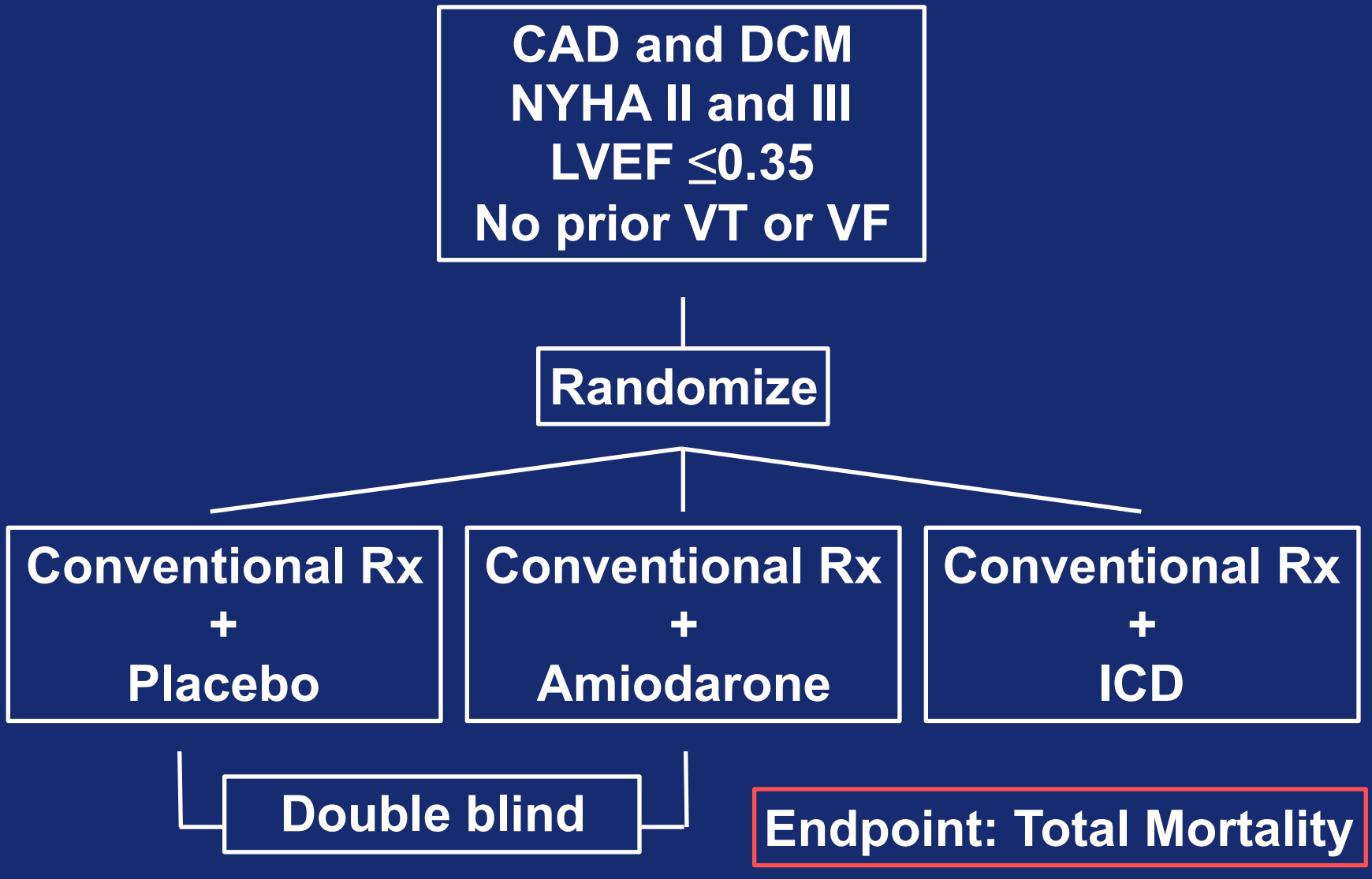
[1]Abraham WT et al. *N Engl J Med.* 2002;346:1845-1853. [2]Cazeau S. *N Engl J Med.* 2001;344:873-80.
[3]Leclercq C et al. *Eur Heart J.* 2002;23:1780-1787.[4]http://www.fda.gov/cdrh/pdf/P010012b.pdf. Accessed August 2, 2002.
[5]Young JB et al. *JAMA.* 2003;289:2685-2694.

Heart Failure Mortality in Meta Analysis of CRT Trials

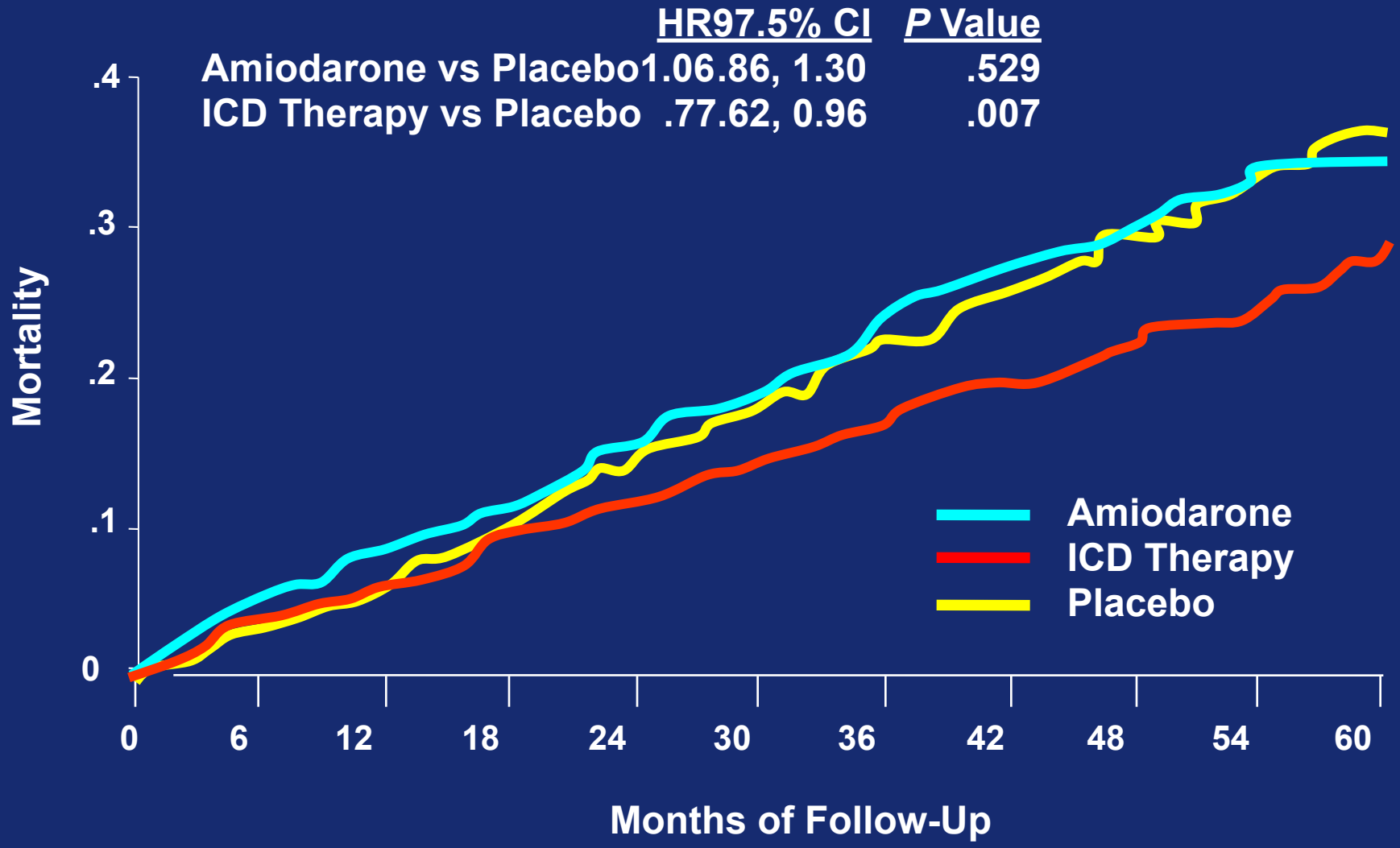


Bradley et al. JAMA 2003; 289: 730

Sudden Cardiac Death in Heart Failure Trial: SCD-HeFT



SCD-HeFT
Mortality by Intention-to-Treat



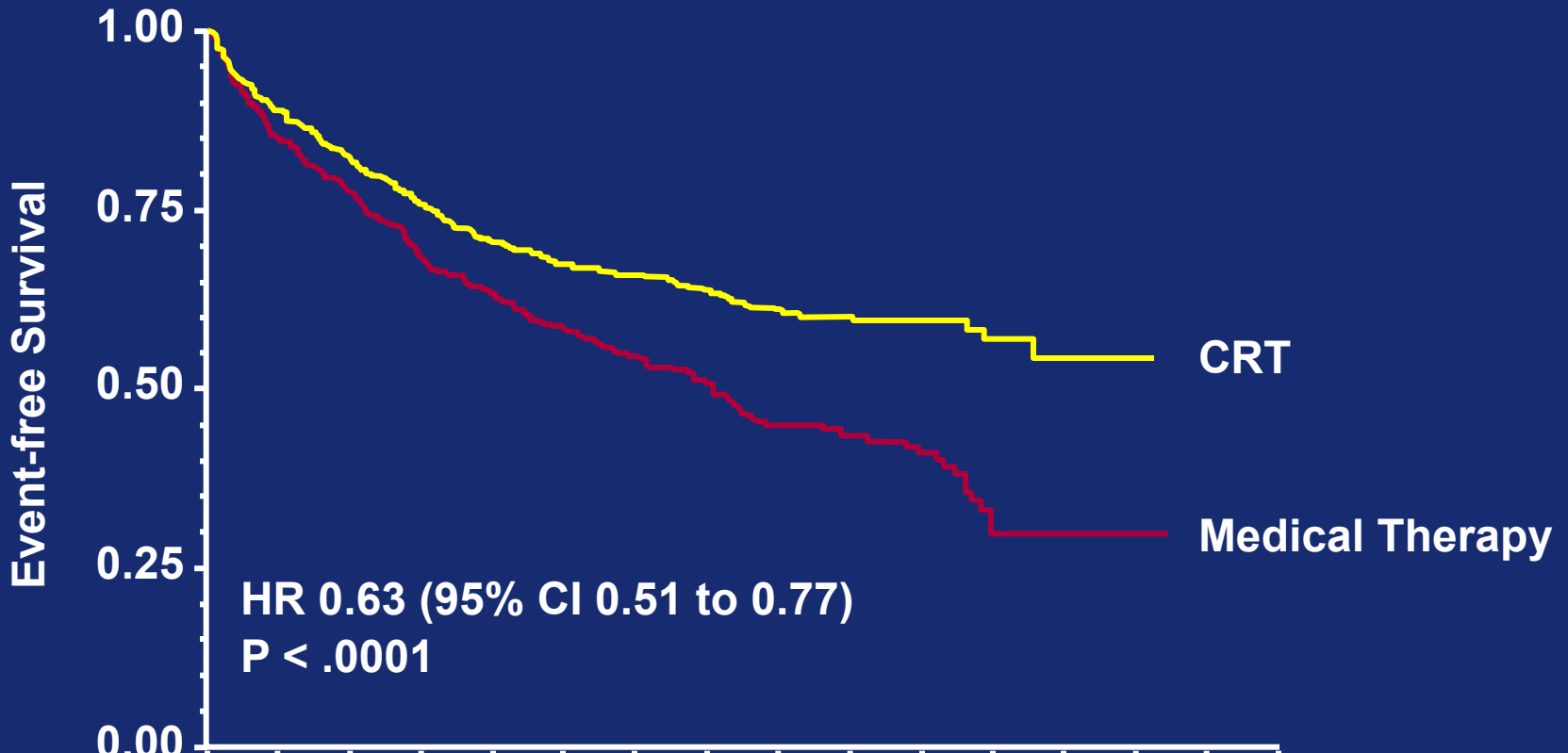
Bardy GH, et al. N Engl J Med 2005;352:225-237.

CARE-HF
Aims

- To assess the effect on morbidity and mortality of adding CRT to optimised pharmacological therapy in patients with moderate and severe HF due to LVSD complicated by cardiac dyssynchrony
- To investigate the mechanisms underlying the observed effect to identify markers predicting success or failure of CRT

Cleland JG, et al. N Engl J Med 2005;352:1539-1549.

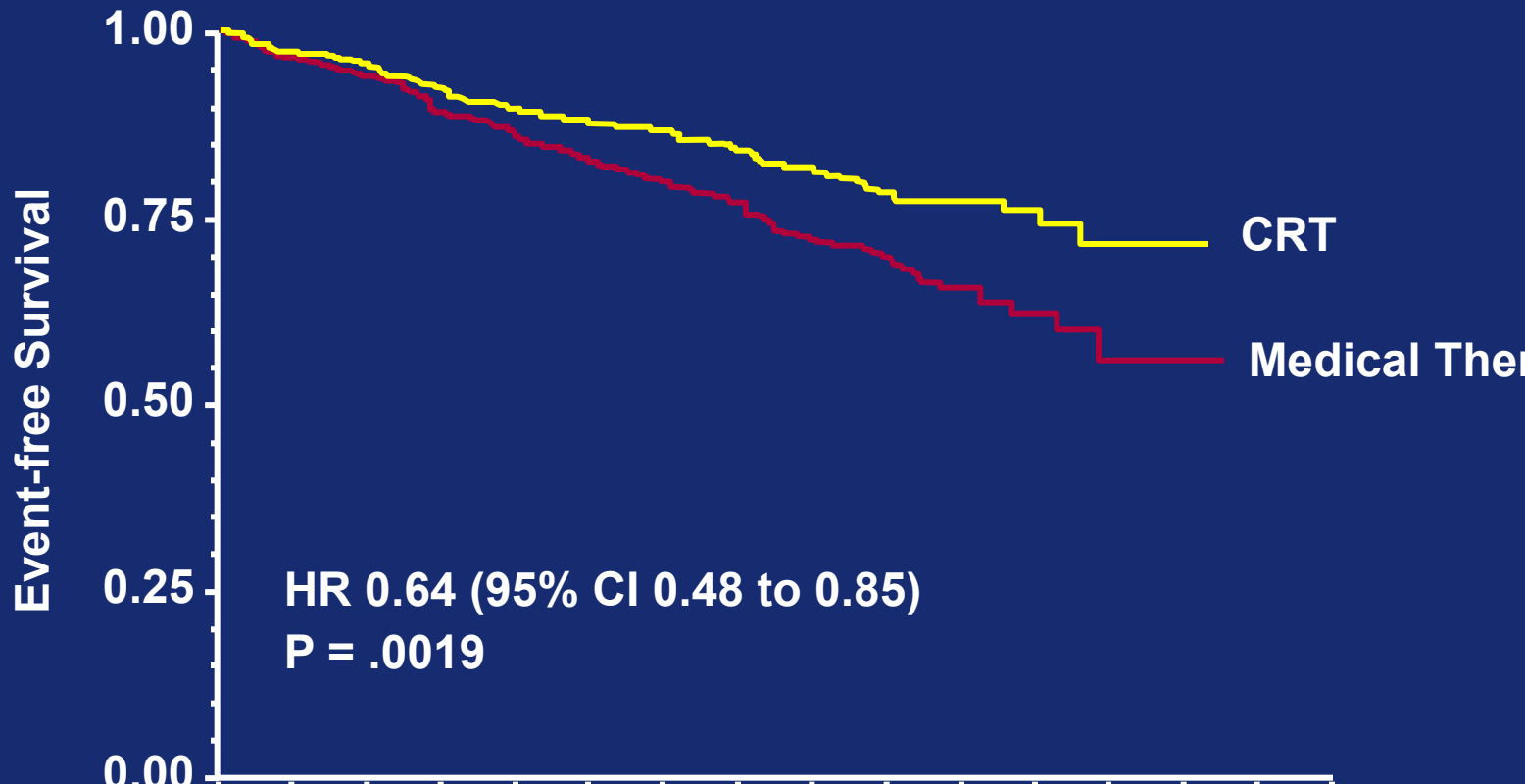
CARE-HF
Primary Endpoint
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)



Number at risk						
CRT	409	323	273	166	68	7
Medical Therapy	404	292	232	118	48	3

Cleland JG, et al. N Engl J Med 2005;352:1539-1549.

CARE-HF
All-Cause Mortality



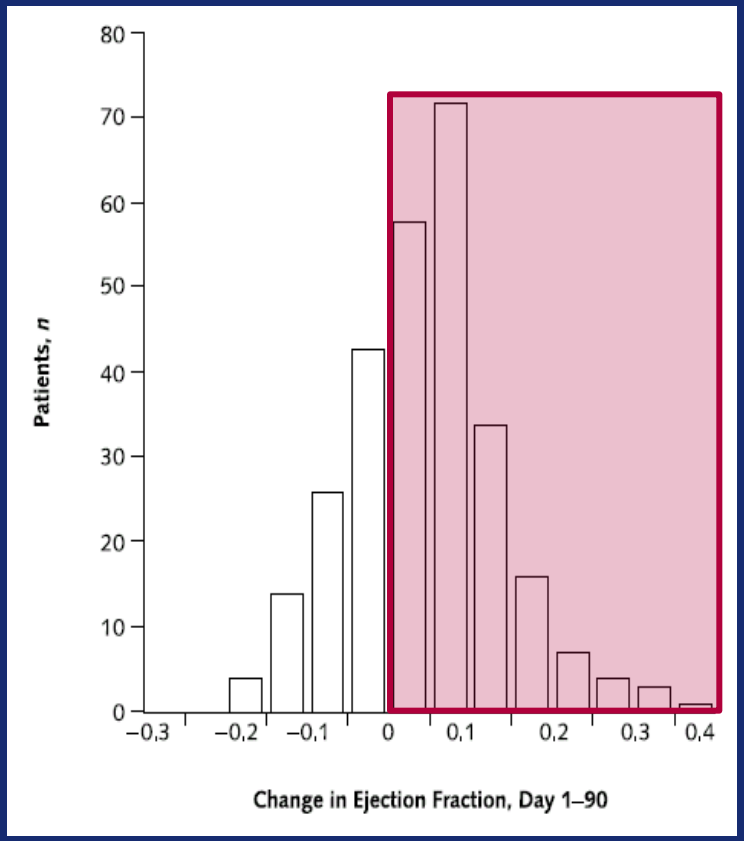
Number at risk						
CRT	409	376	351	213	89	8
Medical Therapy	404	365	321	192	71	5

Cleland JG, et al. N Engl J Med 2005;352:1539-1549.

Recovery of LV Function Post MI

- 261 patients in HEART (ramipril) trial, all with reperfusion therapy
- Day 1, 9/261 had normal LV function (EF ≥0.55, 3.4%)
- 171/261 (66%) had improvement in EF (0.05 ± 0.10). Final EF 0.57 ± 0.96
- Of 252 patients with EF <0.55:
  - 13% complete recovery by day 14
  - 22% complete recovery by day 90
  - Additional 36% had partial recovery by day 90

➔ Early dysfunction often improves

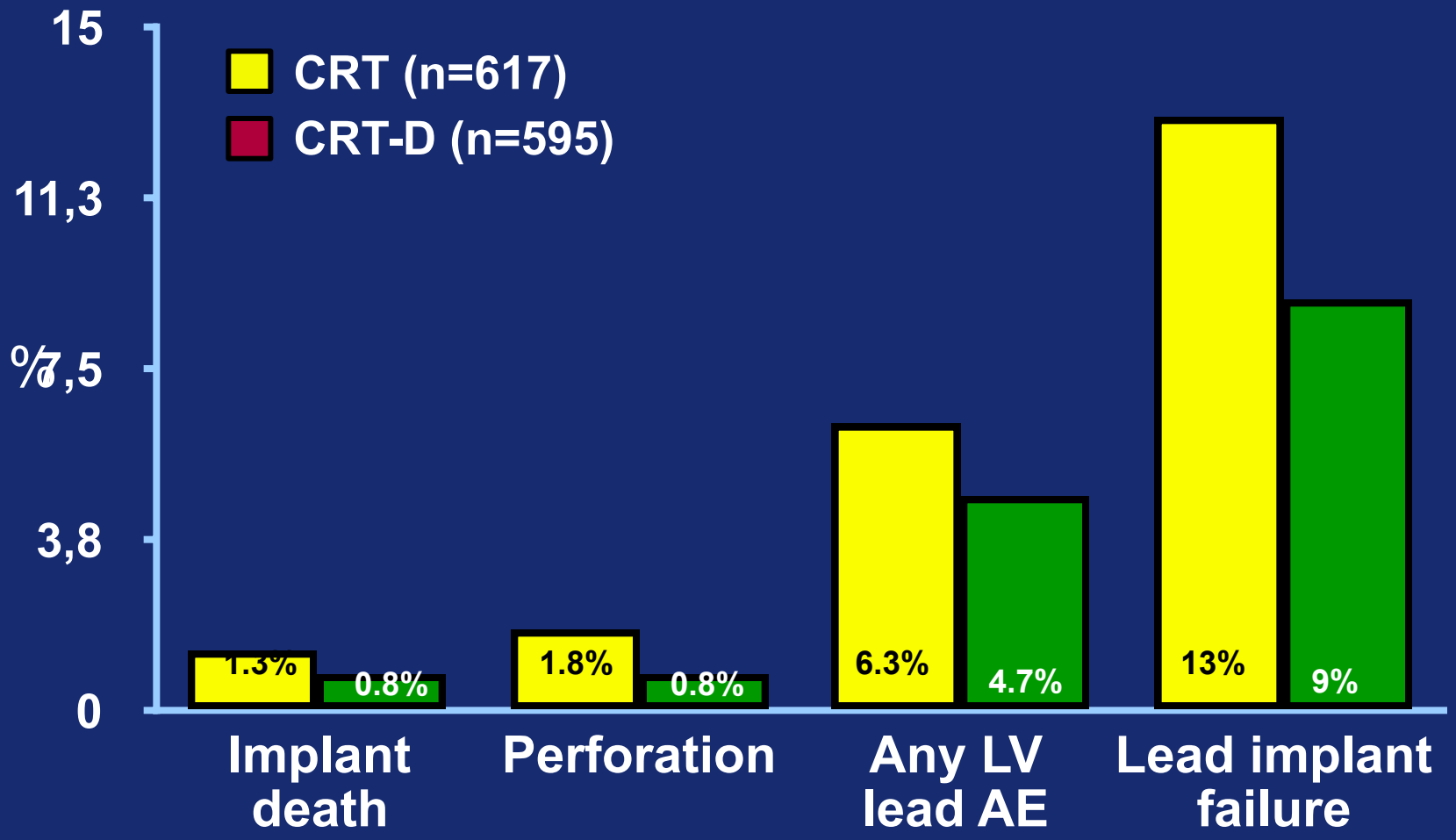


Solomon et al.
Ann Intern Med 2001;134:451-8

Reasons for Nonresponse

- Inappropriate patient selection
  - End stage
  - No dyssynchrony
  - No correctable dyssynchrony
- Too strict definition of response
  - Is prevention of disease progression “response”?
- More attention needs to paid to VV timing and AV delays

Procedural Outcomes and Complications in COMPANION Trial



Saxon et al. Circulation 2004:110:111.

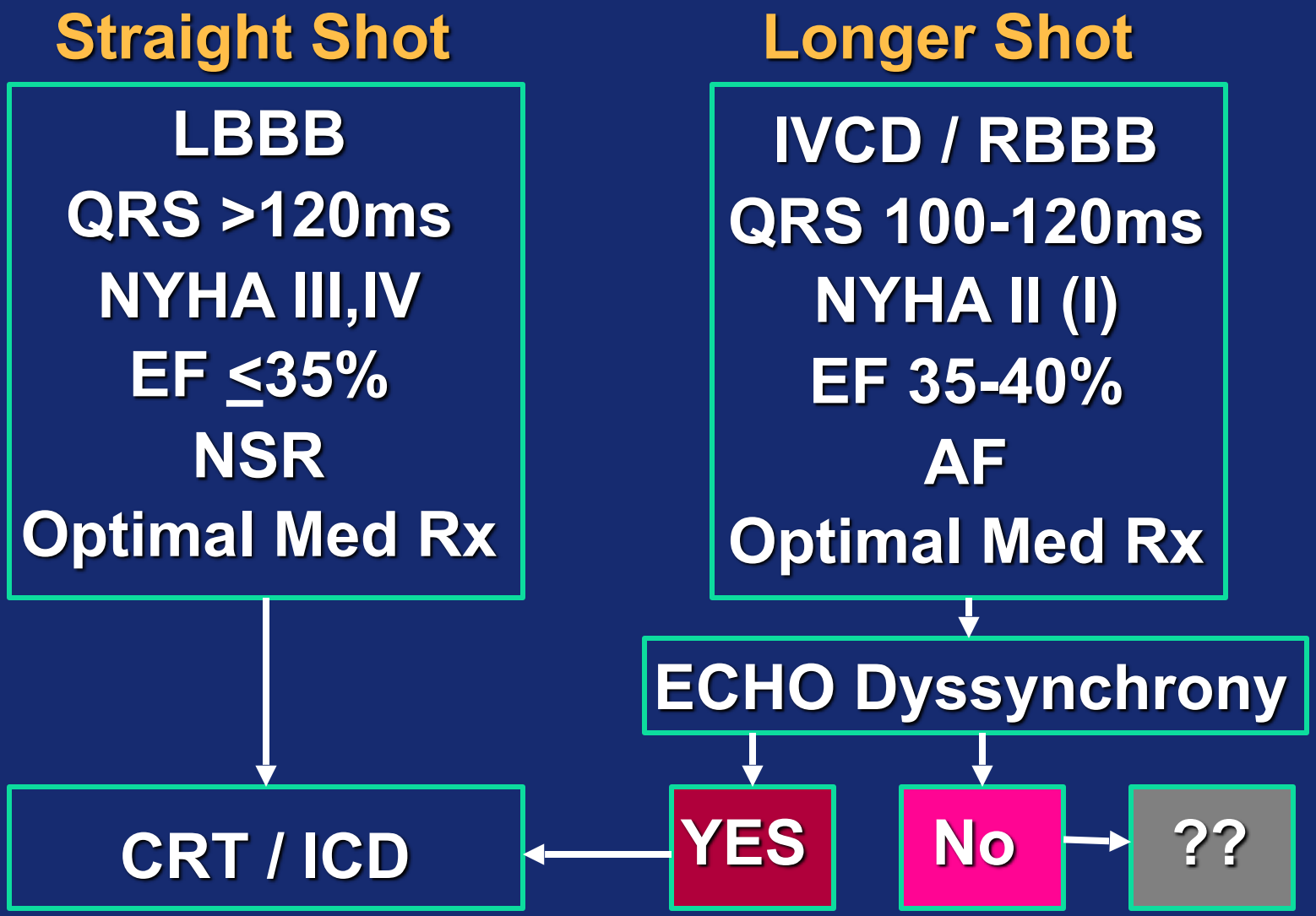
Cardiac Resynchronization Therapy Entry Criteria Randomized Trials

Study *(n)*	NYHA	QRS	EF	Status
MIRACLE *(524#)*	III, IV	≥130	≤ 35%	Published
MUSTIC SR *(58)*	III	>150	≤ 35%	Published
MUSTIC AF *(43)*	III	>200*	≤ 35%	Published
PAT				
COI				
MIR				
PAT				
COI				
CAR				
MIRACLE ICD II *(186)*	II	≥130	≤ 35%	Presented
PACMAN *(328)*	III	≥150	≤ 35%	Enrolled
VecToR *(420)*	II-IV	≥140	≤ 35%	Enrolling

No Randomized Trials Used an Imaging Dyssynchrony Study

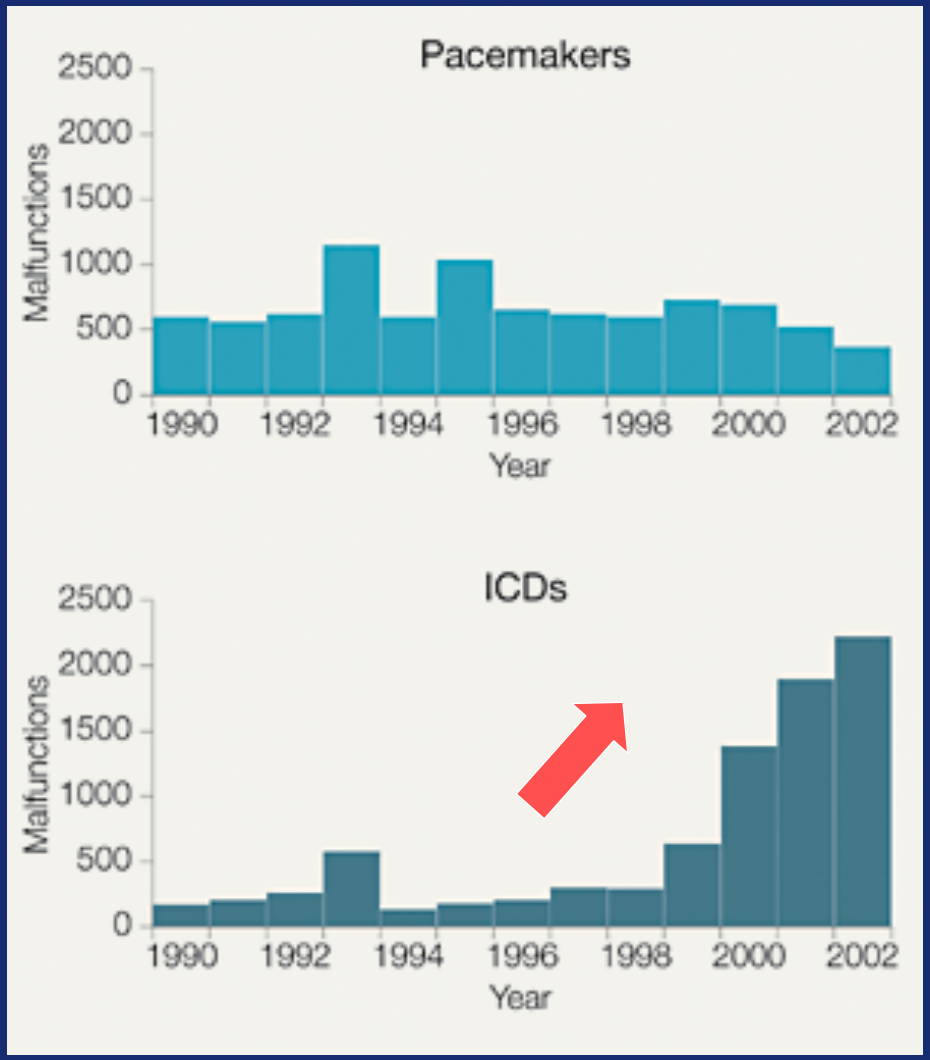
From WT Abraham

Should all Patients with CHF get a CRT Device?



Courtesy of Kenneth A. Ellenbogen, MD

Pacemaker and ICD Malfunctions



Pacemakers n=8834
ICDs n=8489
Devices explanted and malfunction confirmed

Maisel WH, et al.
JAMA 2006; 295:1901-1906.

Multicenter Experience With 1,355 Failed and Recalled Implantable Cardioverter Defibrillators

- Over 200,000 ICDs are implanted or replaced annually in patients who are at risk for SD.
- In 2005 over 150,000 ICDs were the subject of recalls or safety alerts by their manufacturers.
- A recent Food and Drug Administration study suggested that ICD malfunctions are increasing.
- The Multicenter Registry is funded entirely by a grant from the Minneapolis Heart Institute Foundation, and is supported by the voluntary efforts of its participants.

The Multicenter Registry Investigators
American College of Cardiology, 2006

Objective

- The aim of the present study was to examine the failure modes and implant times of contemporary ICD pulse generators in that had failed, or were replaced due to manufacturers recalls.
- We also evaluated the causes and major adverse clinical events associated with ICD failure and replacement.

Methods

- 9 centers in the U. S. and Canada.
- Failure reports entered via Internet since 4/99:
  - Manufacturer and model
  - Dates of implant and failure
  - Signs of failure and clinical consequence
  - Cause of failure
- A pulse generator failed if it was not performing according to its intended use, or as described in the manufacturer's published specifications. *A normally functioning device that was replaced, removed, or abandoned as the result of a manufacturer's recall was a failure.*

PACE 2001; 24:82-87.

Methods (2)

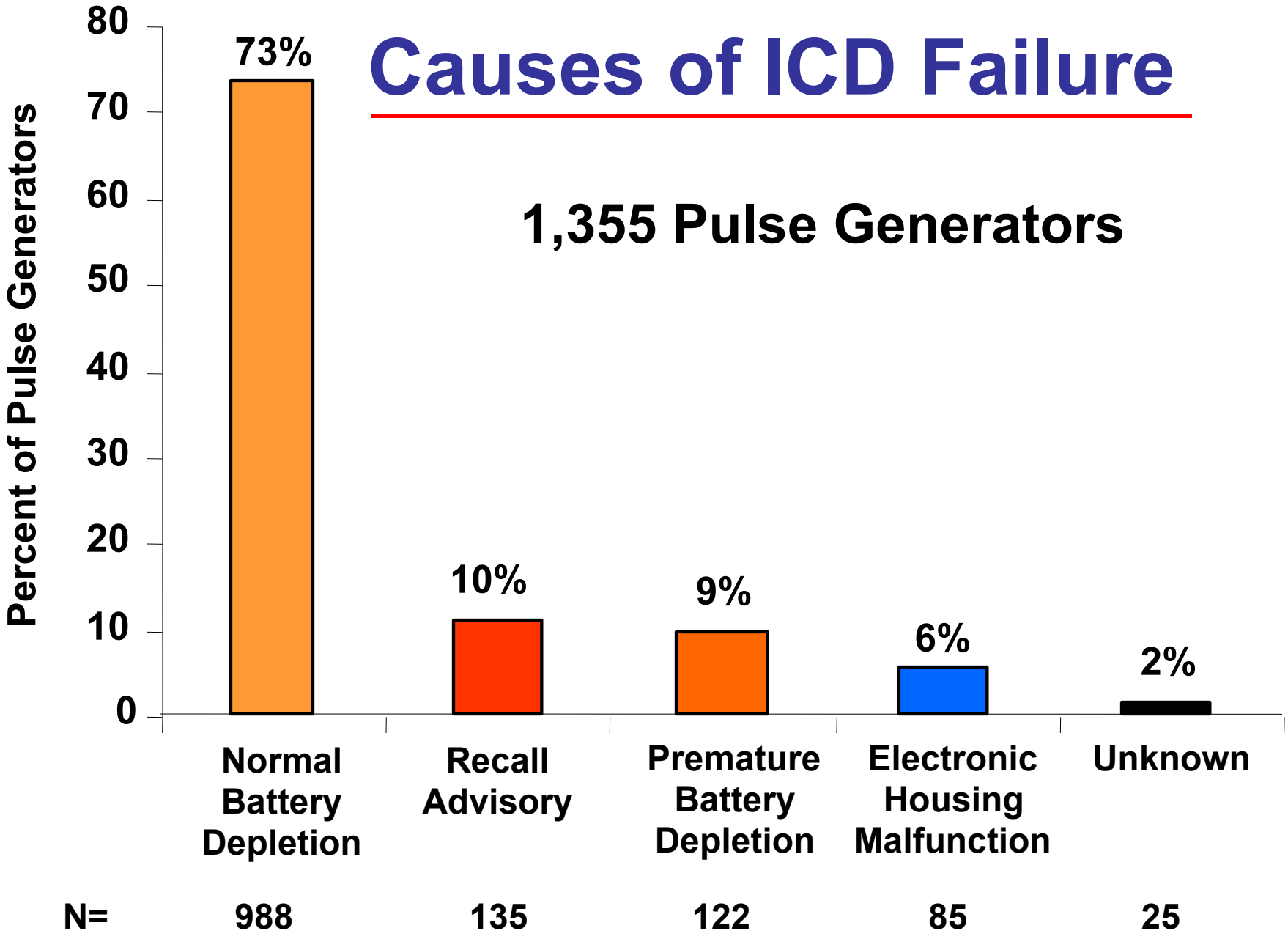
- Categories of ICD pulse generator failure included:

  Normal battery depletion (ERI)
  Premature battery depletion (ERI ≤ 3 yrs)
  Electronic or housing malfunction
  Replacement for Recall-Advisory Unknown

- Cause of failure was determined by the reporting center based on clinical and technical evaluations and manufacturers reports.

PACE 2001; 24:82-87.

Causes of ICD Failure



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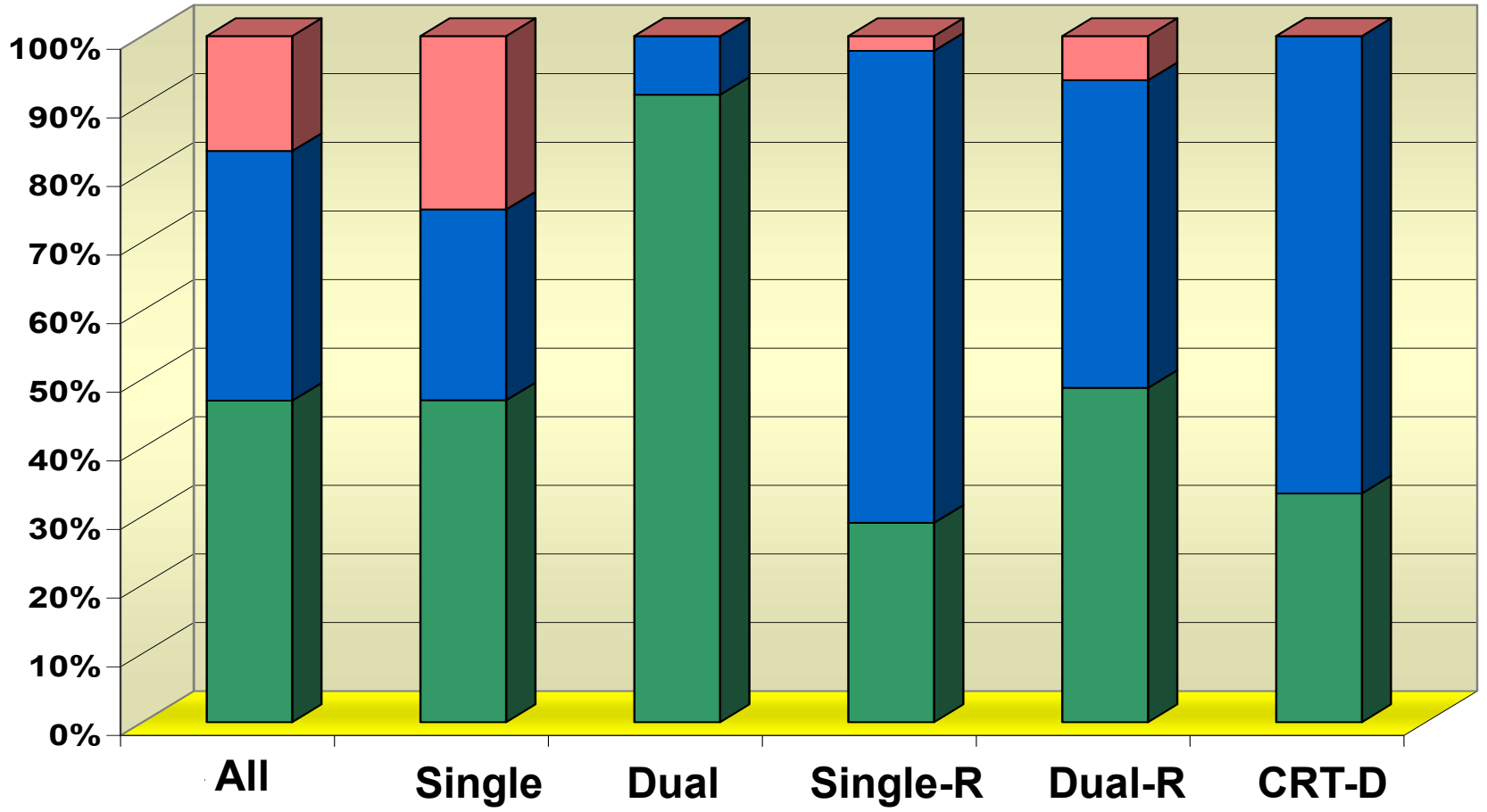
ICD Types and Manufacturers

	All	Single	Dual	Single-R	Dual-R	CRT-D
N=	1,355	791	35	93	388	48
% =	100%	58%	3%	7%	29%	4%



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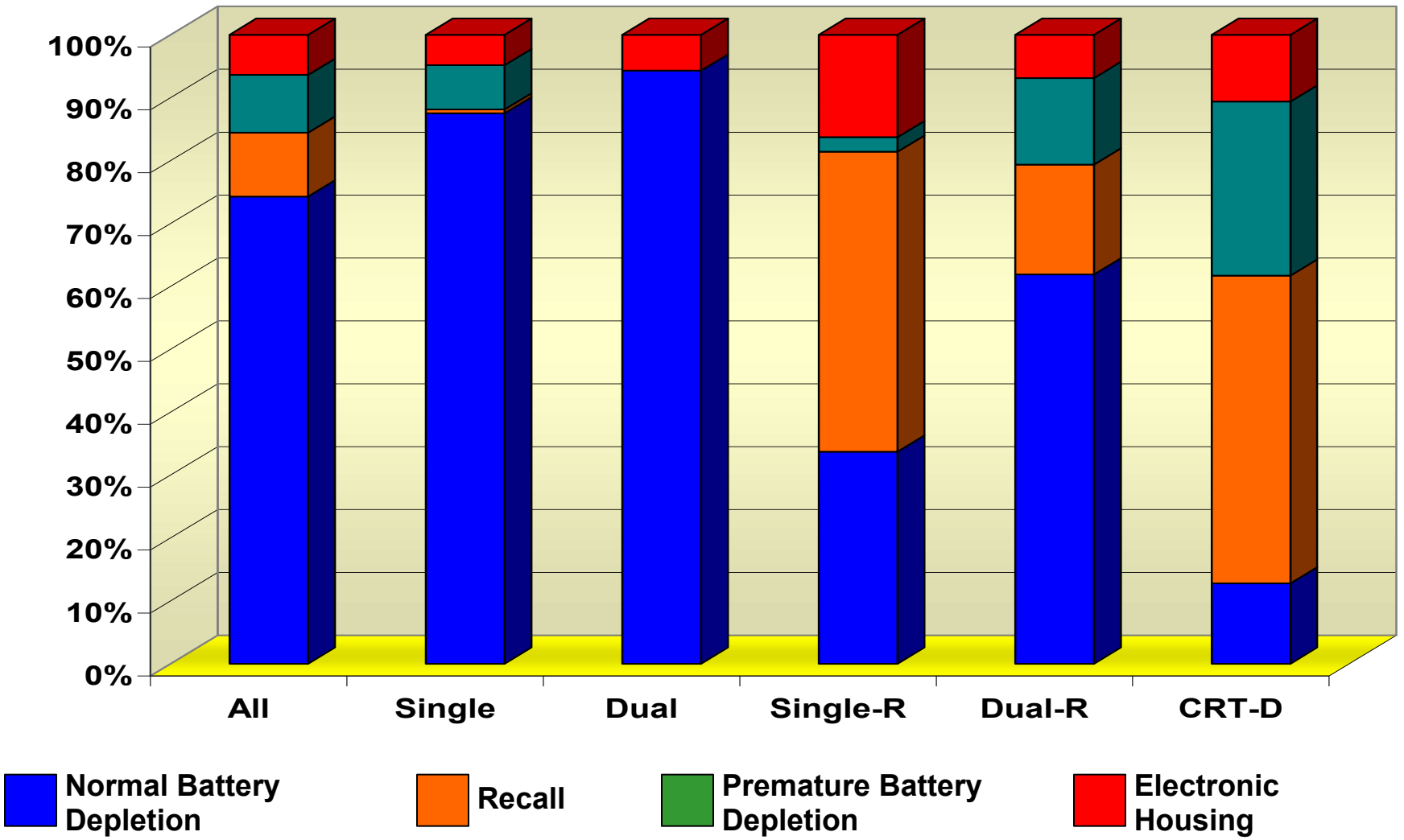
Causes of Failure for Each ICD Type



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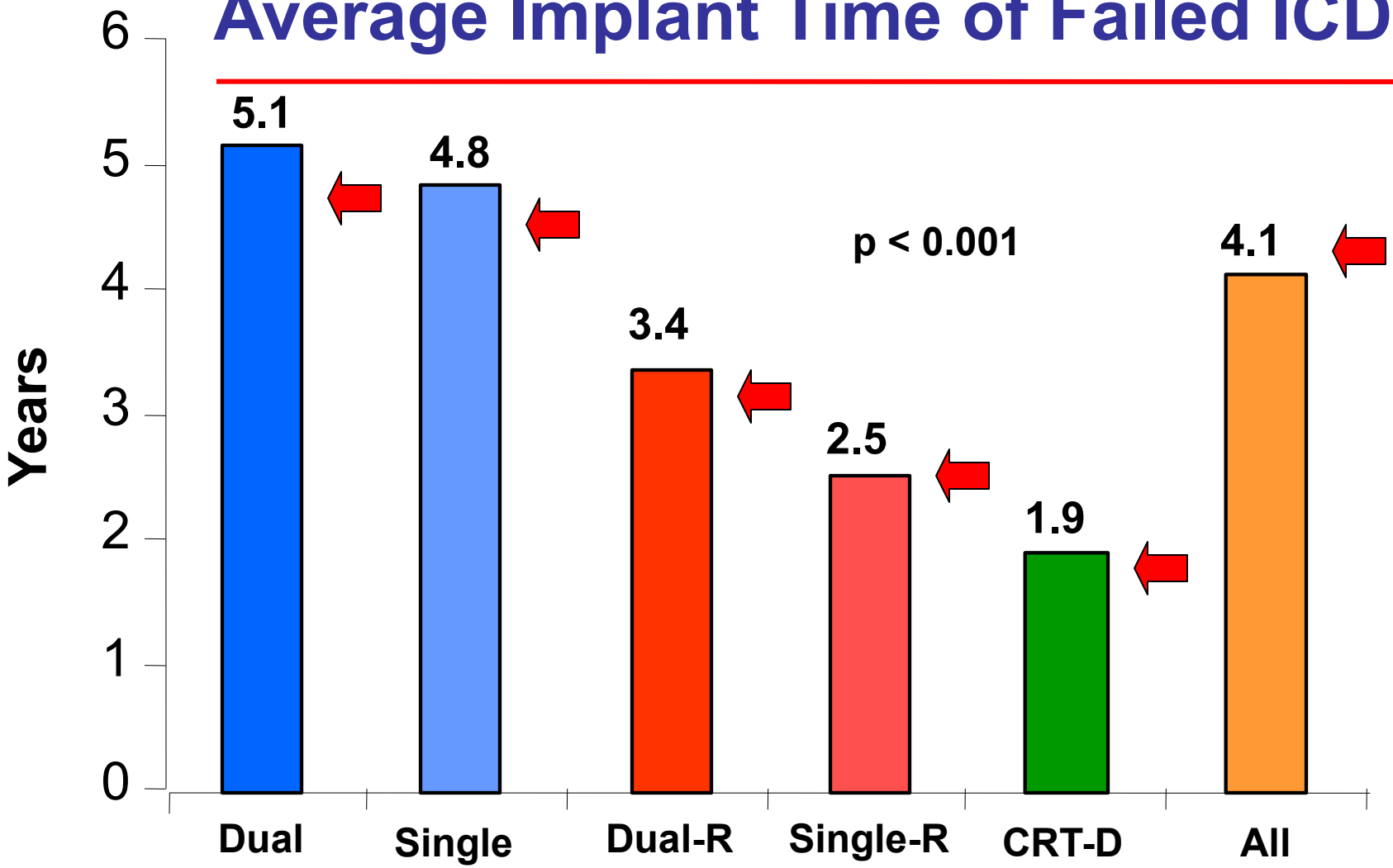
Average Implant Time of Failed ICDs



	Dual	Single	Dual-R	Single-R	CRT-D	All
N =	35	791	388	93	48	1,355
% =	3%	58%	29%	7%	4%	100%

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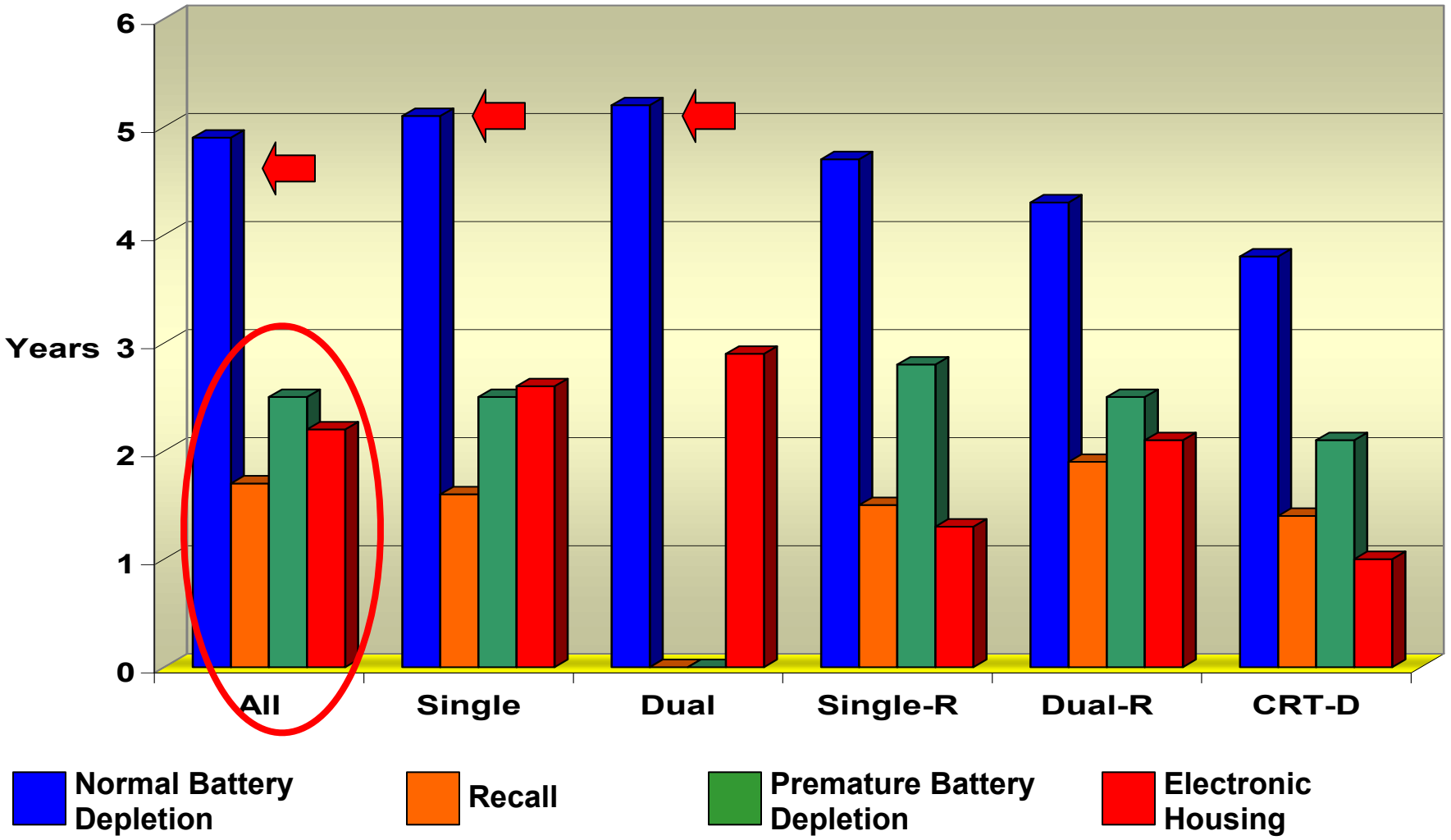
Average Implant Time of Failed ICDs According to Cause of Failure



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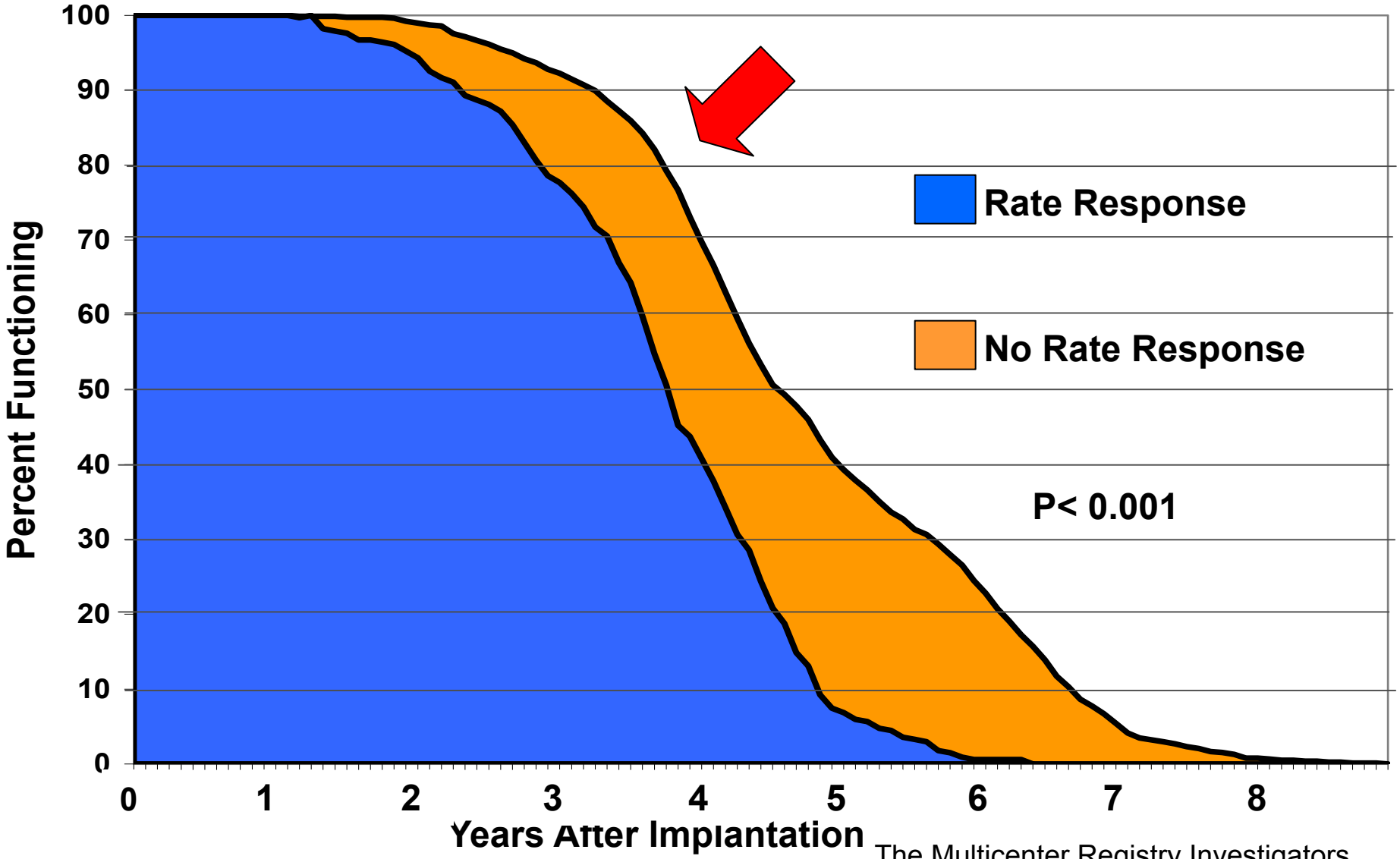
ICDs with and w/o Rate Response



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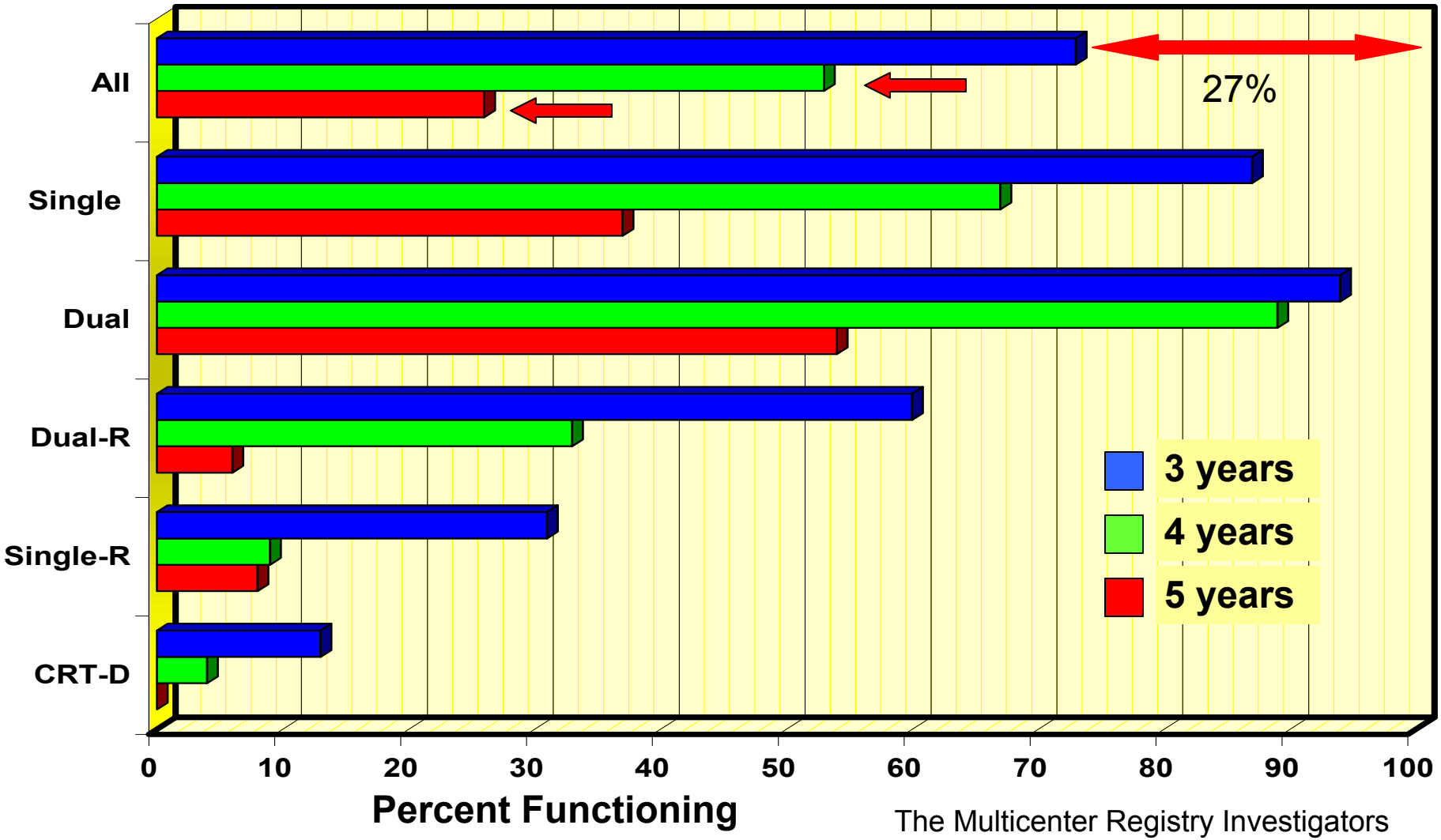
Proportion of Failed ICDs That Were Functioning 3, 4, & 5 Years After Implant



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Major Adverse Clinical Events

- 20 patients had a major adverse clinical event.
- 1 patient died due to short-circuiting during shock delivery.
- 1 patient died of a stroke following replacement of a normally functioning recalled device.
- 4 patients were rescued when their devices failed to treat VT/VF during device testing.
- 3 patients experienced syncope due to battery depletion (2) and electronic component failure.
- 11 patients received inappropriate shocks caused by electronic and housing defects.

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Limitations

- Average implant time may significantly underestimate device longevity when compared to actuarial survival data.
- The longevity of an ICD pulse generator is the result of a complex interplay between multiple hardware components, the ICD lead, and the individual patient's needs for therapy, energy requirements for pacing and defibrillation, and diagnostic information including electrograms. We did not evaluate all these variables.

Conclusions

- Based on this analysis of failed ICDs, the performance of ICDs, particularly those offering advanced pacing capabilities, has been adversely affected by early battery depletion, electronic or housing failure and recalls.
- A comprehensive, independent national registry is needed to accurately estimate ICD longevity and determine the incidence of unexpected failure modes and adverse clinical events.

Complications Associated with ICD Replacement in Response to Advisories:
Canadian Heart Rhythm Society Working Group on Device Advisories

- **17 Centers, 2915 recalled devices**
  - **533 (18.3%) replaced**
    - **66% primary prevention**
- **Complications in 43 pts (8.1%)**
  - **Major requiring reoperation: 31 pts (5.8%)**
  - **Death: 2 pts**
  - **Minor complications: 12 pts (2.3%)**
  - **Of explanted devices, 3 (0.1%) had malfunction (early battery depletion), none with clinical consequence.**

Gould et al.
JAMA 2006; 295:1907-1911.

Indications for ICD Therapy

Class I

- Cardiac arrest due to VF or VT not due to a transient or reversible cause
- Spontaneous sustained VT in association with structural heart disease
- Syncope of undetermined origin with clinically relevant, hemodynamically significant, sustained VT or VF induced at EP study when drug therapy is ineffective, not tolerated, or not preferred
- Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at EP study that is not suppressible by a Class I antiarrhythmic drug.

Class II

- Patients with LVEF ≤.30, at least 1 month post MI and at least 3 months post coronary revascularization surgery

Gregoratos G, et al. *Circulation*. 2002;106:2145-2161.

Indications for Resynchronization Therapy

Class II

- Medically refractory, NYHA Class III or IV heart failure despite optimal medical therapy
- Ischemic or nonischemic cardiomyopathy with
  - QRS ≥130 ms
  - LVEF ≤0.35

Gregoratos G, et al. *Circulation*. 2002;106:2145-2161.

Summary

- **Multiple RCTs have shown that CRT:**
  - **Is safe and well tolerated improves quality of life, functional status, and exercise capacity.**
  - **Improves cardiac structure and function.**
  - **Reduces hospitalization and mortality with or without ICD backup.**
- **Studies needed to risk stratify, identify likely responders, and new groups who may benefit from CRT.**
- **Reliability/advisory issues recognized and need guidelines for management.**