

Heart Failure Update: *A Device Perspective*

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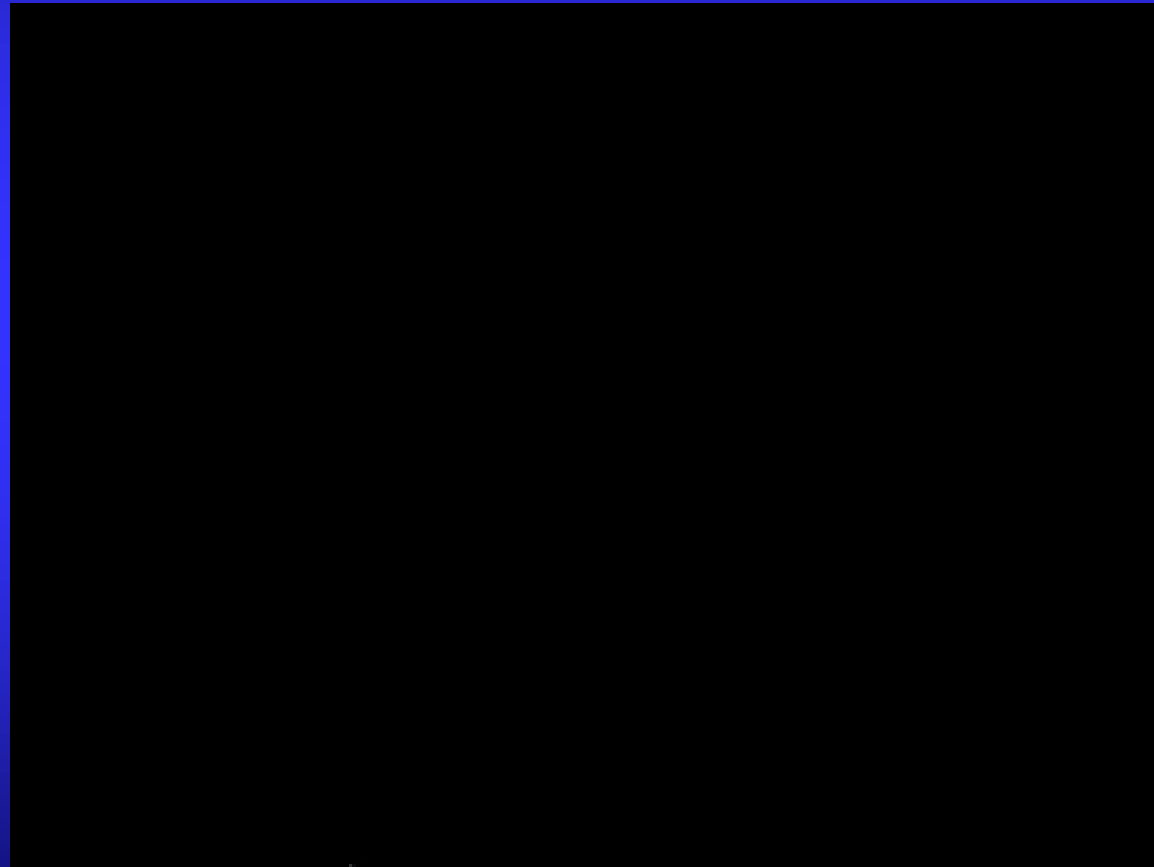
April 13th, 2013

What is Heart Failure?

Heart Failure: Defined

- A syndrome of inadequate tissue perfusion
(or the requirement for higher cardiac volumes or filling pressures to maintain perfusion)

Heart Failure: Abnormal Mechanics



Heart Failure:

□ **Cardinal Manifestations**

- Dyspnea and fatigue –often limiting exercise
- Fluid retention –leading to pulmonary and peripheral edema
- Impaired quality-of-life

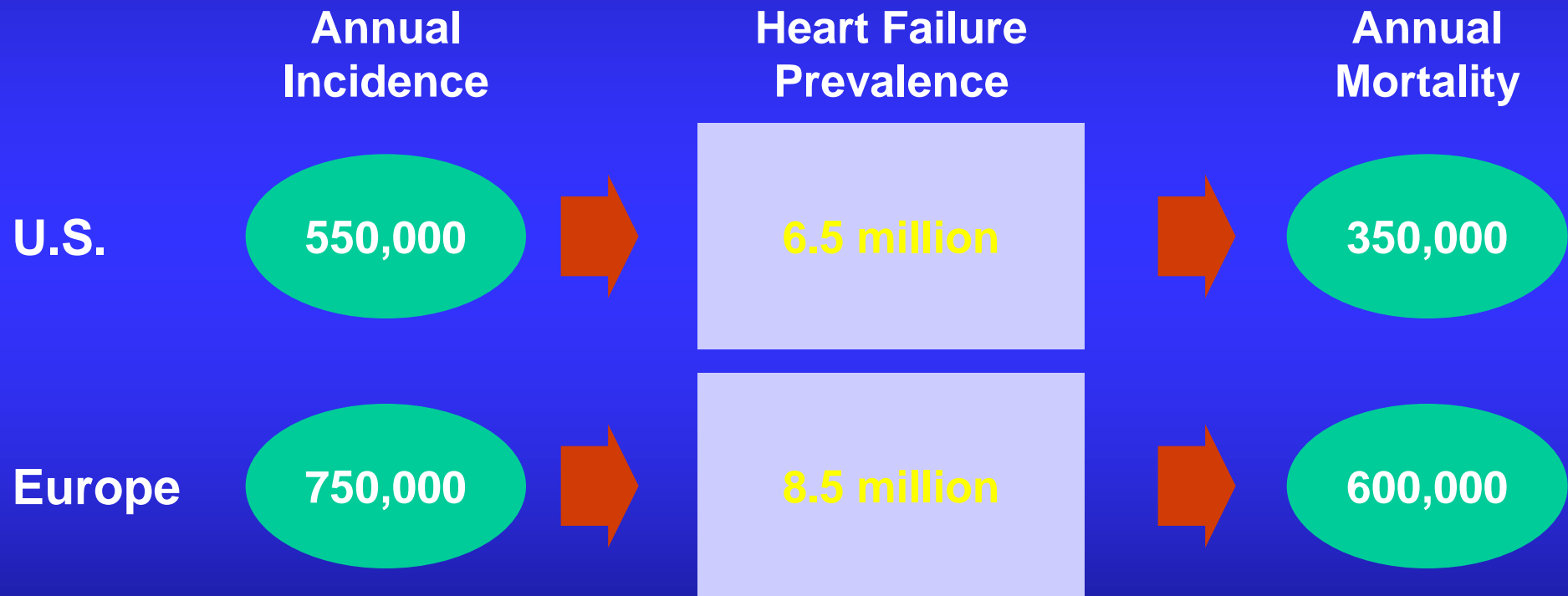
□ **Progressive disorder**

- Symptoms eventually at rest or with minimal exertion
- Deterioration of cardiac structure and function without recurrent injury, “silently”

The Epidemic of Heart Failure

A Growing Medical Challenge

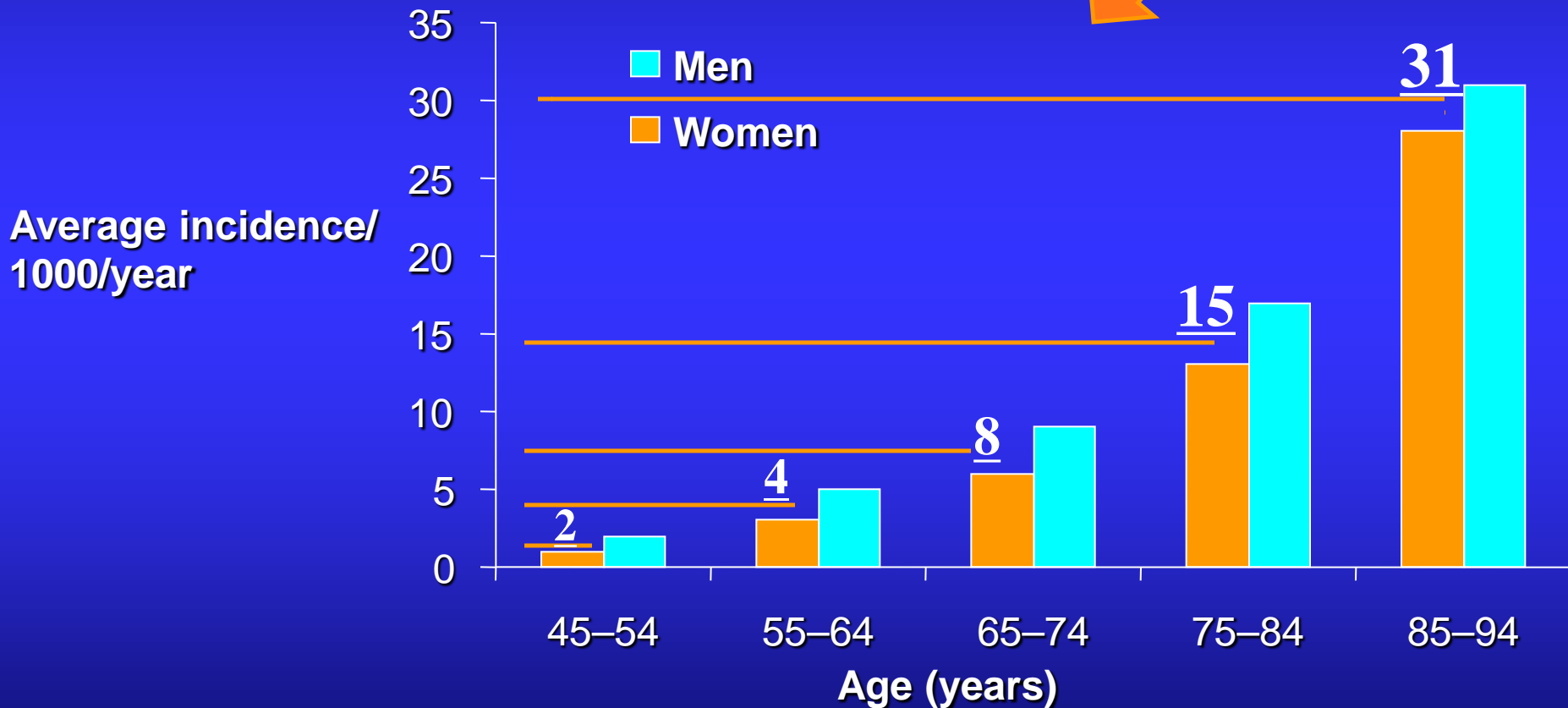
Heart failure management



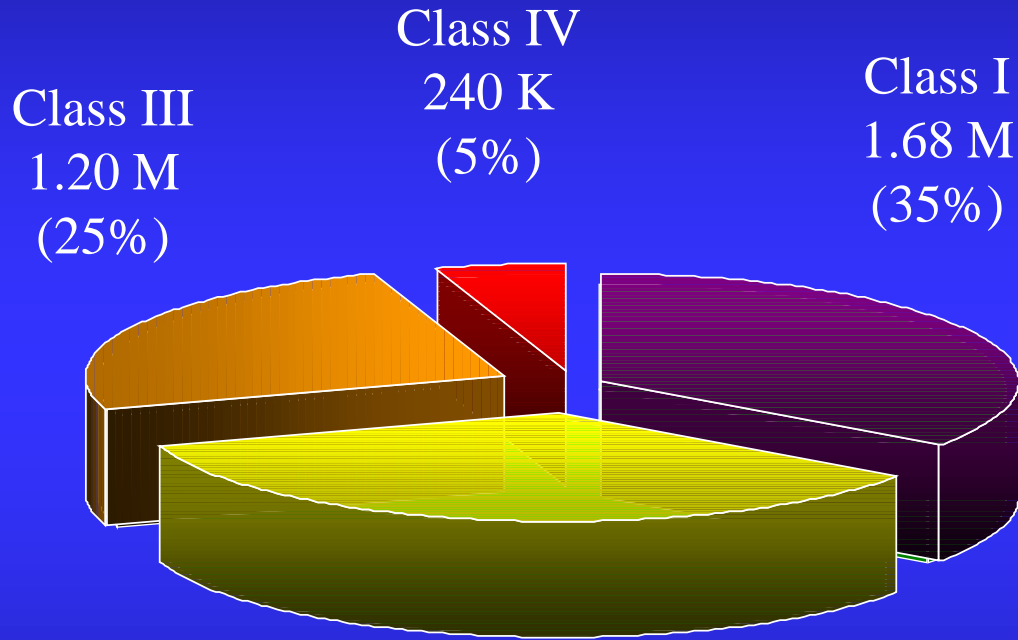
Incidence of Heart Failure by Age

Doubles every decade

Framingham Results



Prevalence by severity (NYHA Class)



Class I
No limitations of physical activity

Class II
Slight limitations

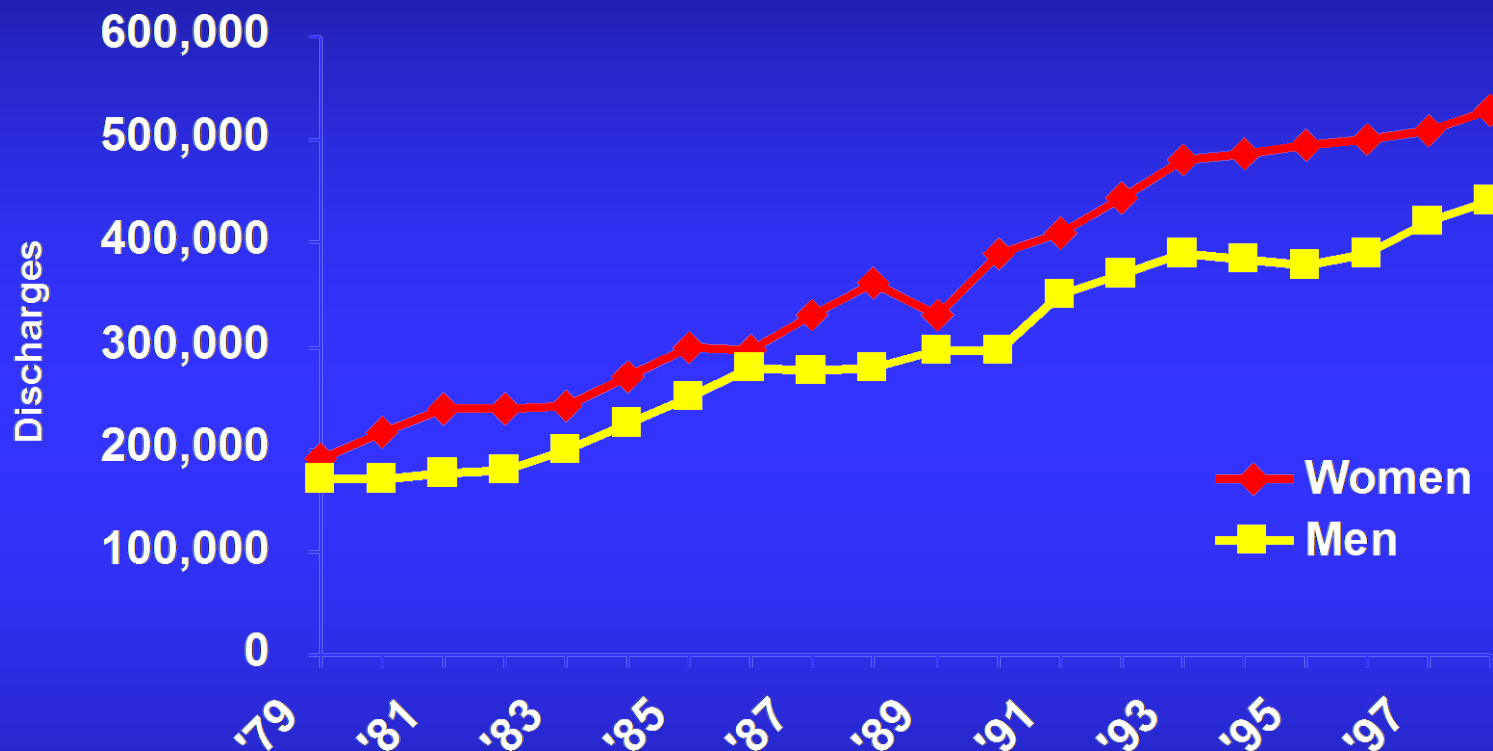
Class III
Marked limitations

Class IV
Symptoms at rest

70 % of patients have little or no symptoms

Class II
1.68 M
(35%)

Heart Failure Hospitalizations



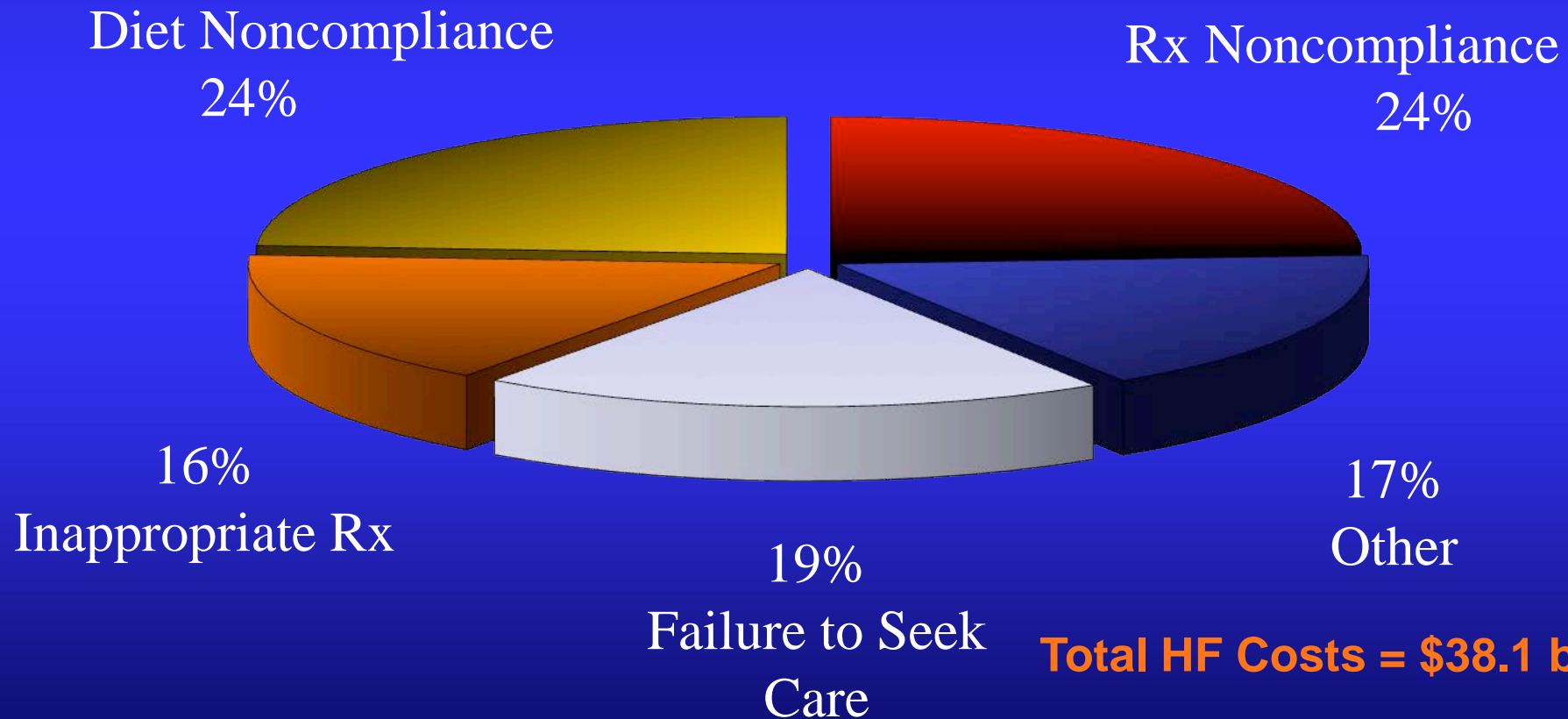
CDC/NCHS: Hospital discharges include living patients and in hospital deaths

AHA, 1998 Heart and Stroke Statistical Update

NCHS, National Center for Health Statistics

AHA Heart and Stroke Statistical Update 2001

Causes of Hospital Readmission for Congestive Heart Failure



**Total HF Costs = \$38.1 billion
(5.4% of total healthcare costs)**

Therapeutic Goals

Treatment Goals for Heart Failure Therapy

Goal: Improve the Quality and Quantity of Life

Objectives

- ❑ **Relieve symptoms and improve exercise tolerance**
- ❑ **Prevent sudden death, arrhythmias**
- ❑ **Slow progression of the underlying disease**
- ❑ **Decrease ER visits, hospitalizations, and costs**
- ❑ **Prevent complications, such as atrial fibrillation, stroke**

Historical Therapy For Heart Failure

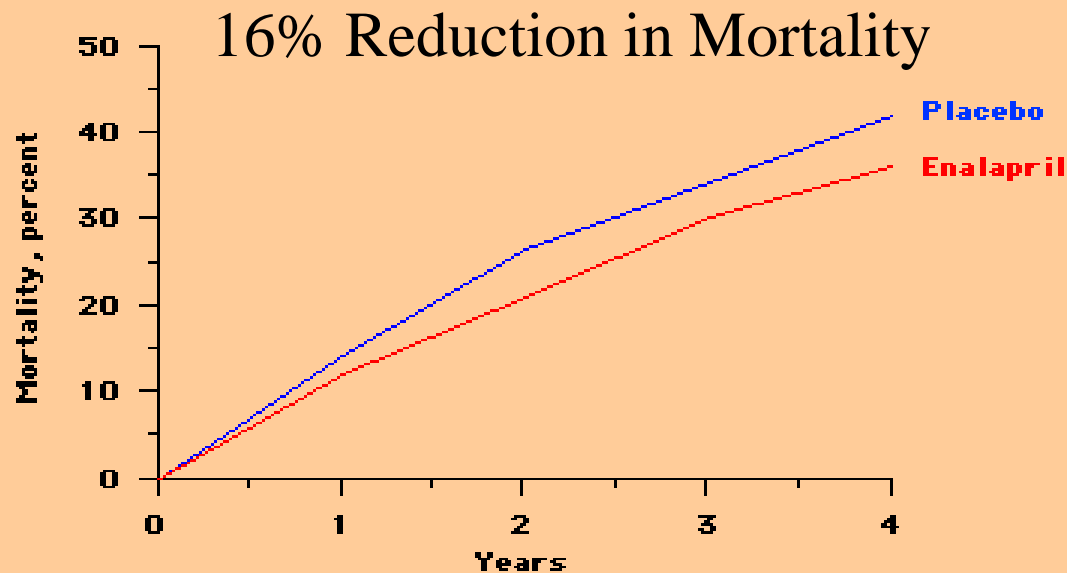




Drug Therapy

Enalapril Reduces Mortality in Heart Failure

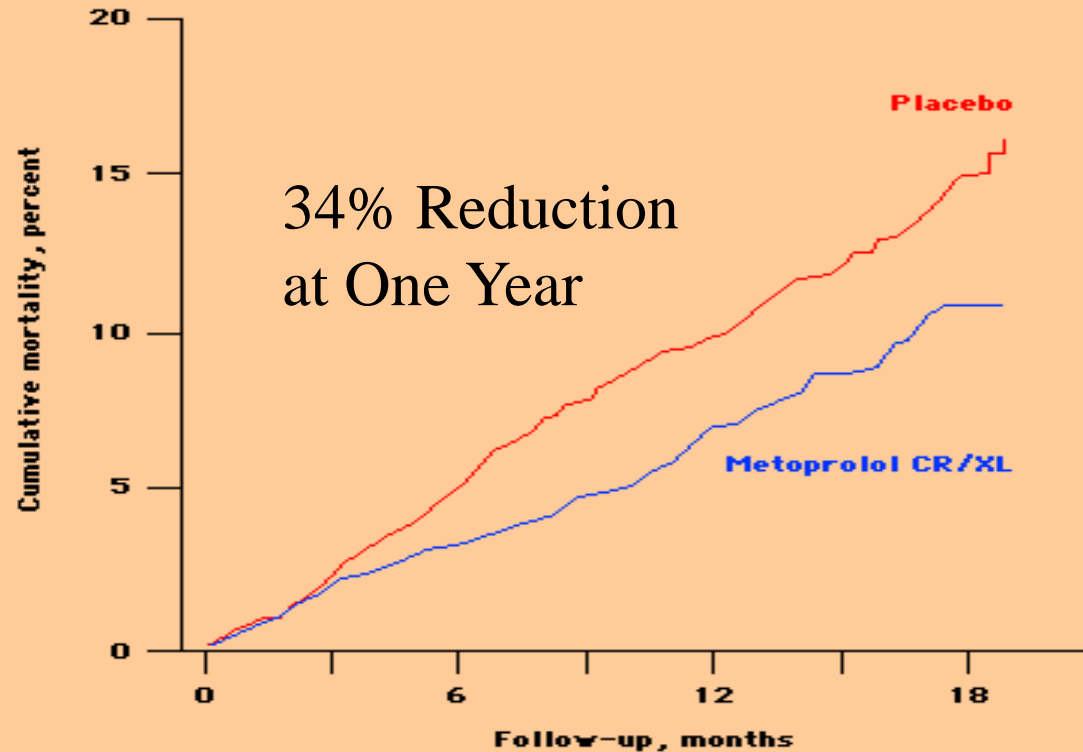
(SOLVD trial 1991)



ACE inhibitor improves survival in moderate CHF Enalapril, compared to placebo, decreases patient mortality in NYHA class II and III heart failure ($p = 0.0036$). (Data from The SOLVD Investigators, N Engl J Med 1991; 325:293.)

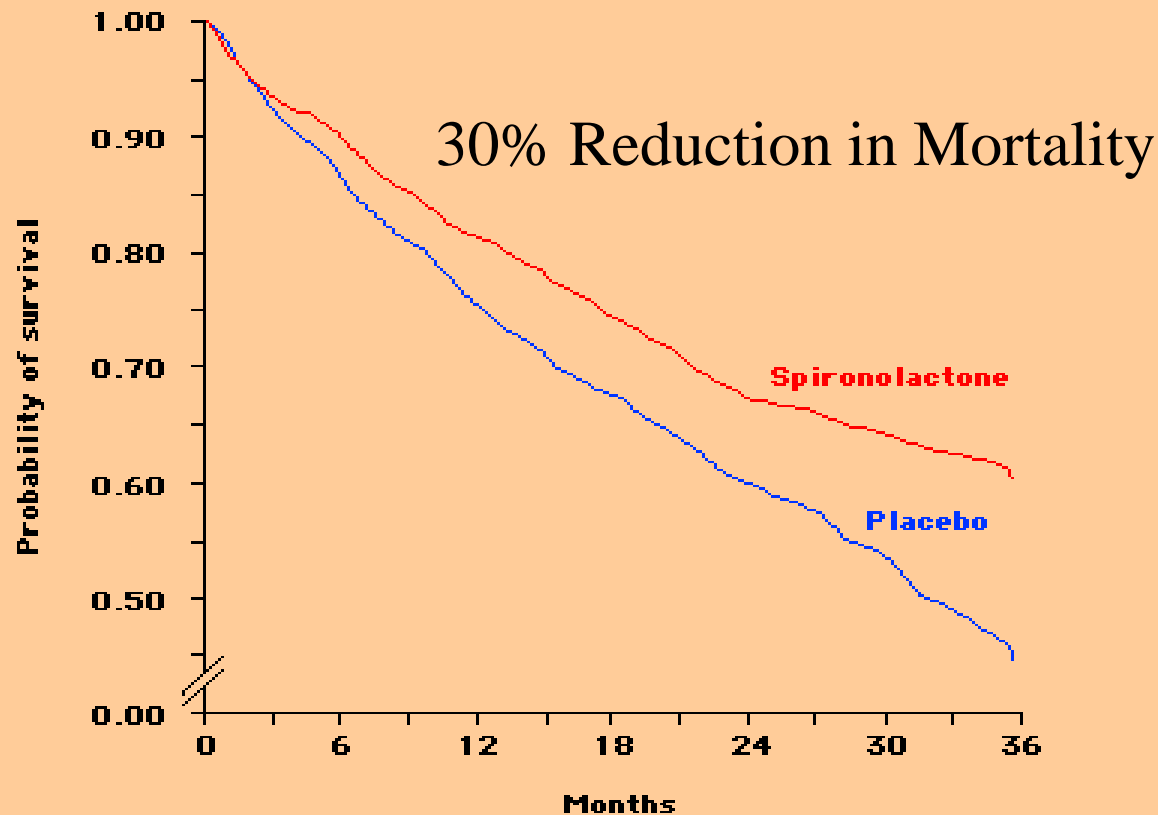
Metoprolol Reduces Mortality in Heart Failure

(MERIT-HF trial 1999)



Metoprolol reduces mortality in patients with heart failure The MERIT-HF trial randomized 3991 patients with NYHA class II to IV heart failure who were treated with digoxin, angiotensin converting enzyme inhibitors, and digoxin to metoprolol CR/XL or placebo. Kaplan-Meier curves show a significant reduction in total mortality at 12 months with metoprolol (7.2 versus 11 percent for placebo, $p = 0.006$). (Data from The MERIT-HF Study Group, *Lancet* 1999; 353:2001).

Spironolactone Reduces Mortality in Heart Failure (RALES trial 1999)



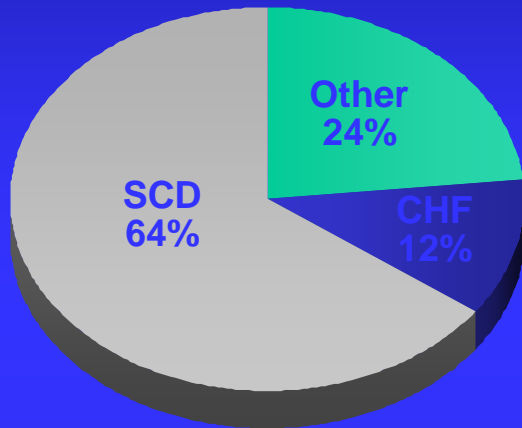
Spironolactone reduces mortality in heart failure Kaplan-Meier analysis of survival among 1663 patients with advanced heart failure in the RALES trial shows that spironolactone reduces mortality by 30 percent (35 versus 46 percent for placebo, $p < 0.001$). (Data from Pitt, B, Zannad, F, Remme, WJ, et al, N Engl J Med 1999; 341:709.)

Results of Heart Failure Therapy

- More than one drug is needed and they work synergistically
- Optimal drug therapy in combination reduces mortality by about a third

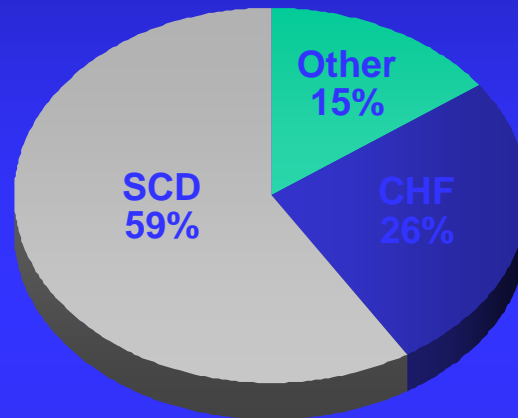
So How Could Device Therapy
Help?

Mechanism of Death in HF¹



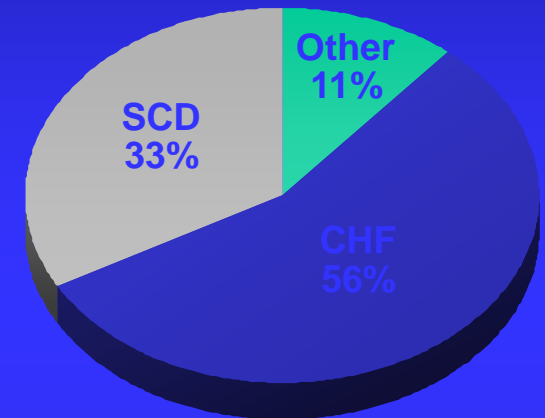
NYHA class II

**No. of deaths
n = 103**



NYHA class III

**No. of deaths
n = 232**

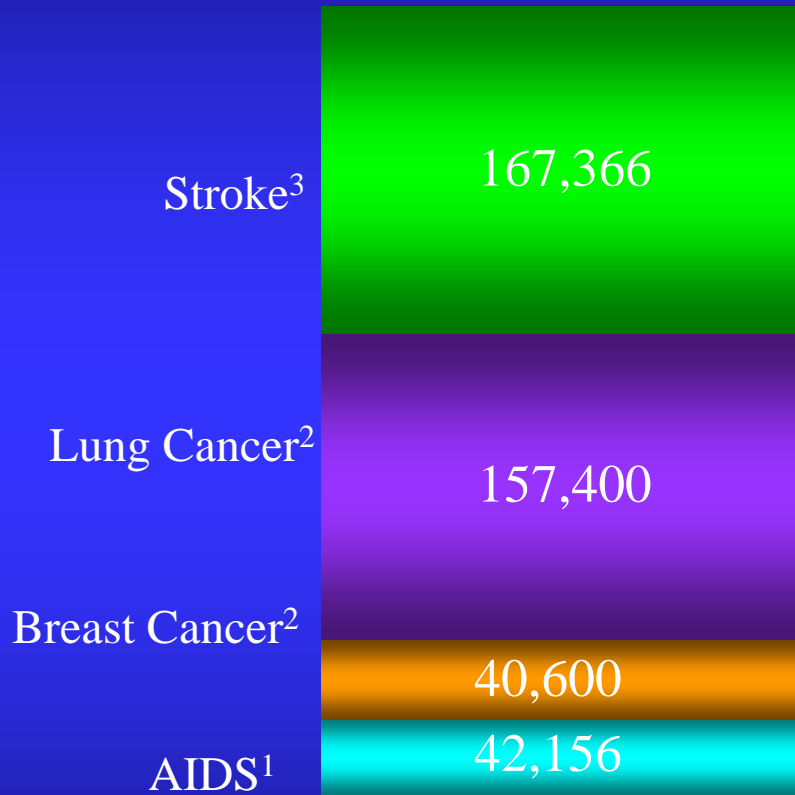


NYHA class IV

**No. of deaths
n = 27**

¹ MERIT-HF Study Group. *Lancet* 1999;353:2001-2007. (Permission for use requested)

Magnitude of SCA in the US



SCA claims more lives each year than these other diseases combined

450,000
SCA⁴

#1 the U.S.

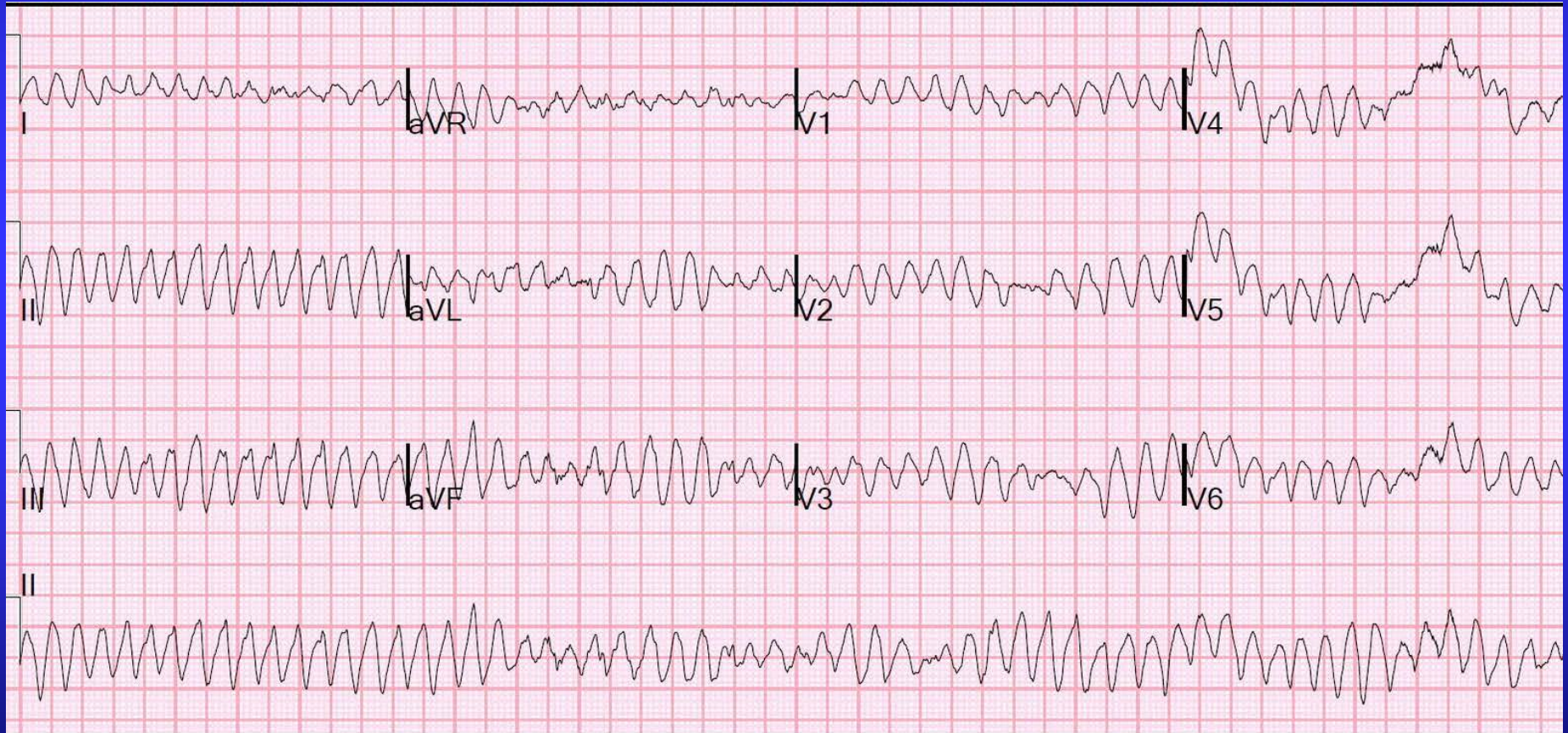
¹ U.S. Census Bureau, *Statistical Abstract of the United States: 2001*.

² American Cancer Society, Inc., *Surveillance Research, Cancer Facts and Figures 2001*.

³ *2002 Heart and Stroke Statistical Update*, American Heart Association.

⁴ *Circulation*. 2001;104:2158-2163.

SCD: Ventricular Fibrillation

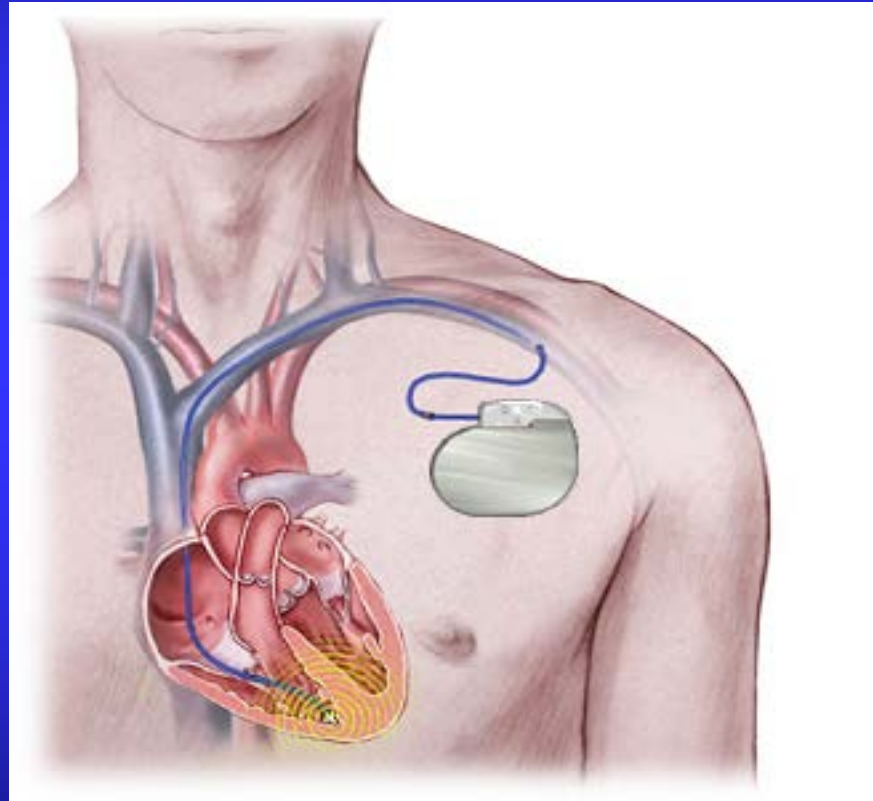


The Defibrillator



The Implantable Defibrillator Then

- Initially
Defibrillation only
- Surgical implant
during CABG
- Evolution to Sub-
clavicular



ICD Trials Summary

Relative Reduction in All-cause Mortality

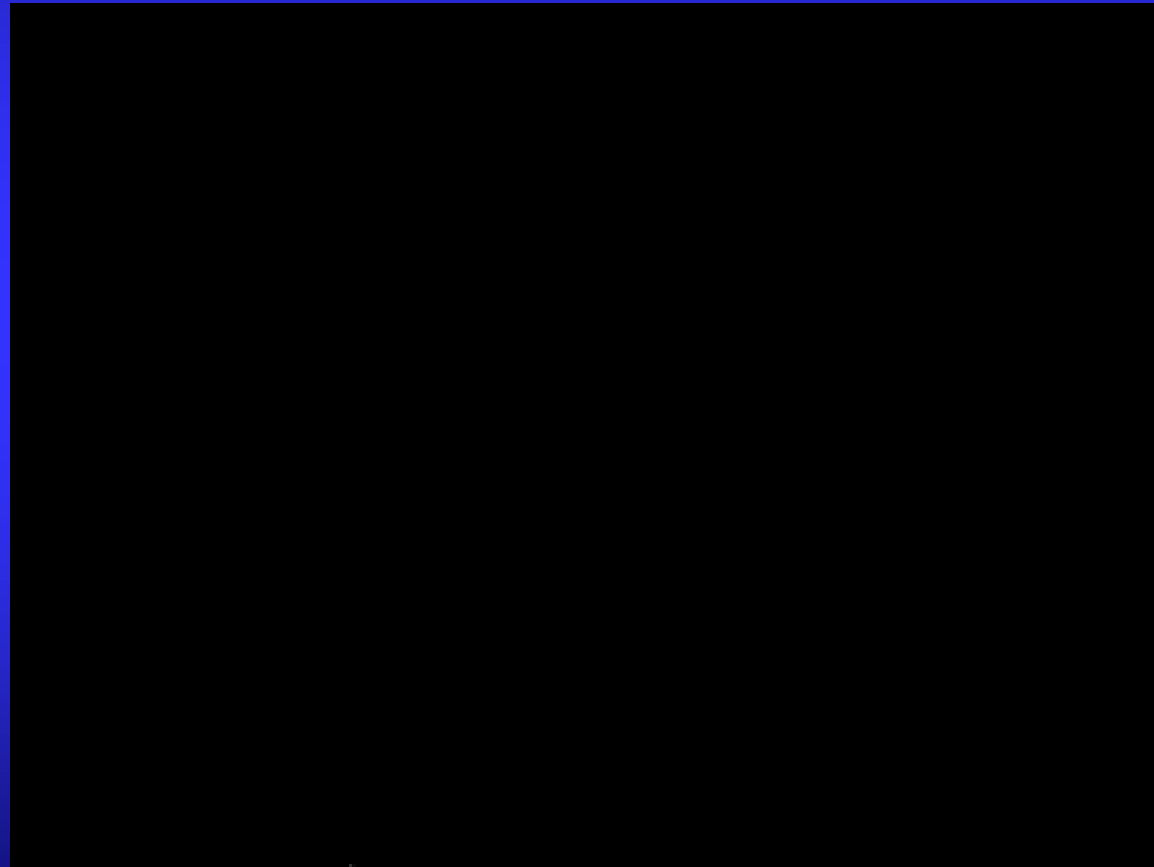


Results of Heart Failure Therapy

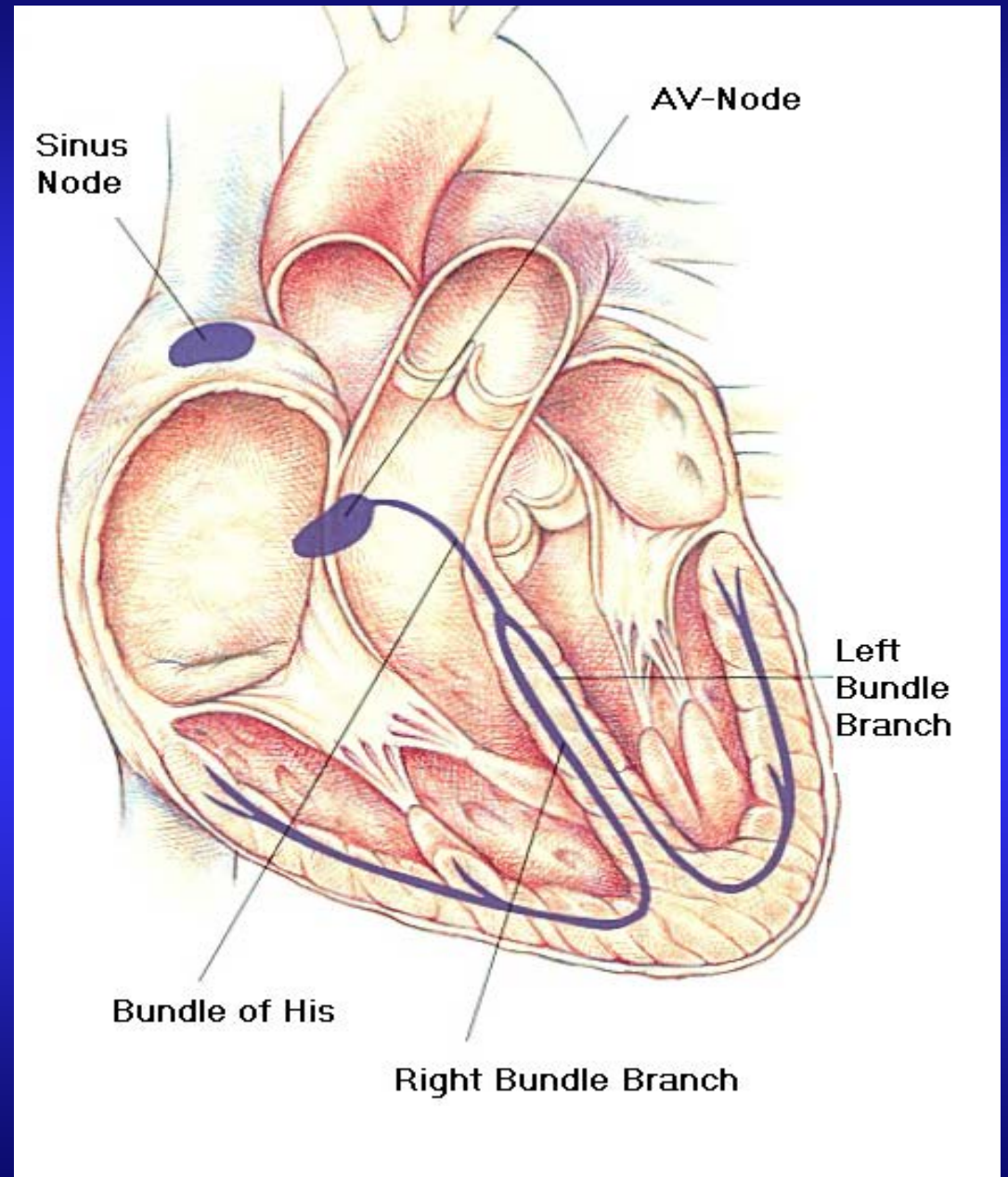
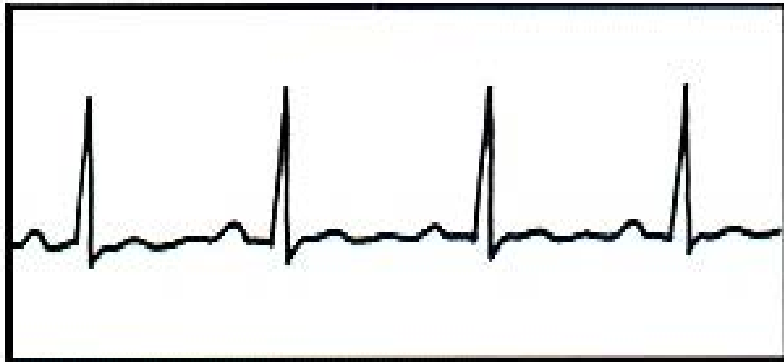
- Optimal drug therapy in combination reduces mortality by about a third
- Defibrillator therapy improves survival an additional 25 to 30%

An interesting Observation

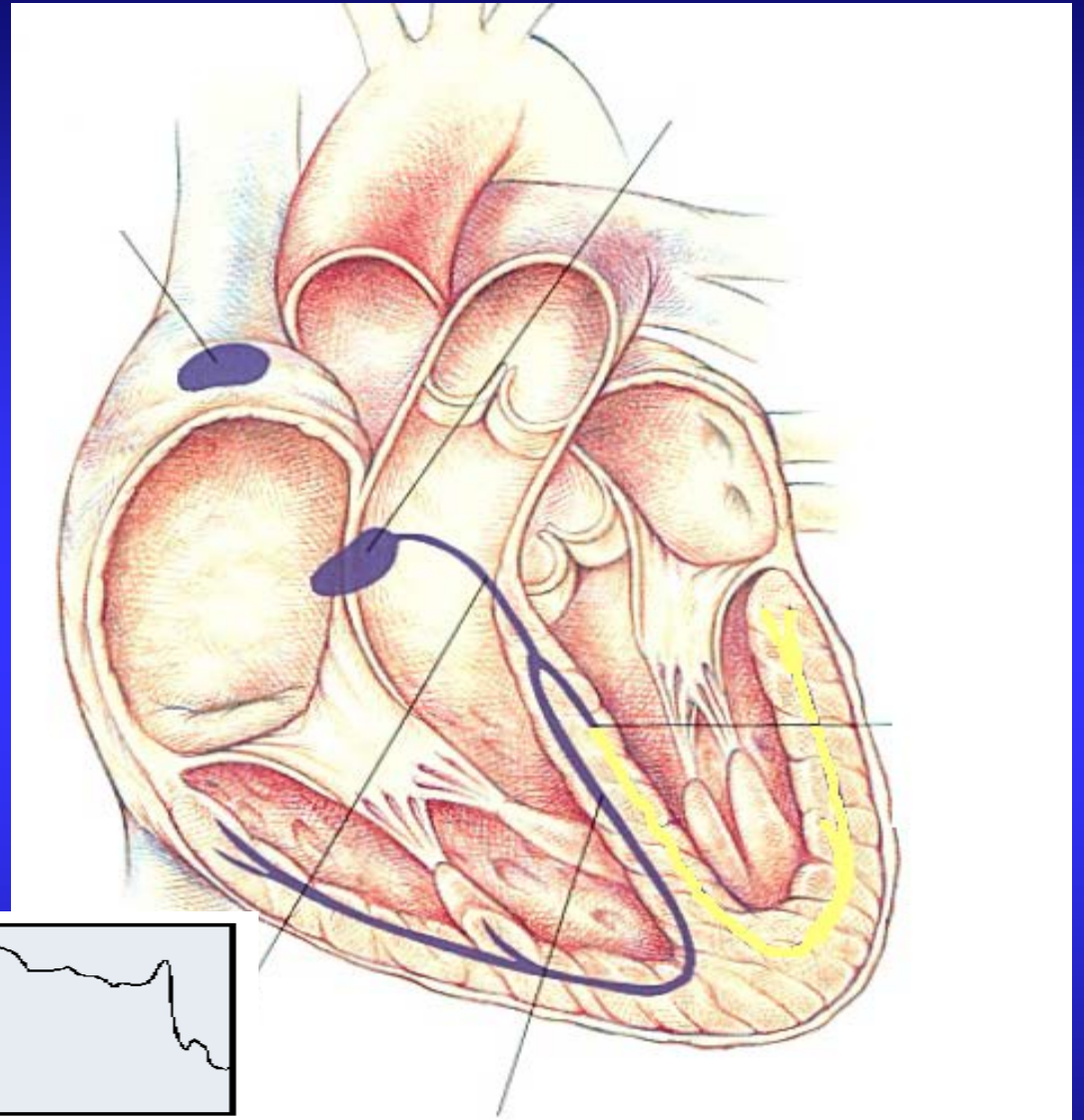
Heart Failure: Assynchronous Mechanics:



Normal Sinus Rhythm

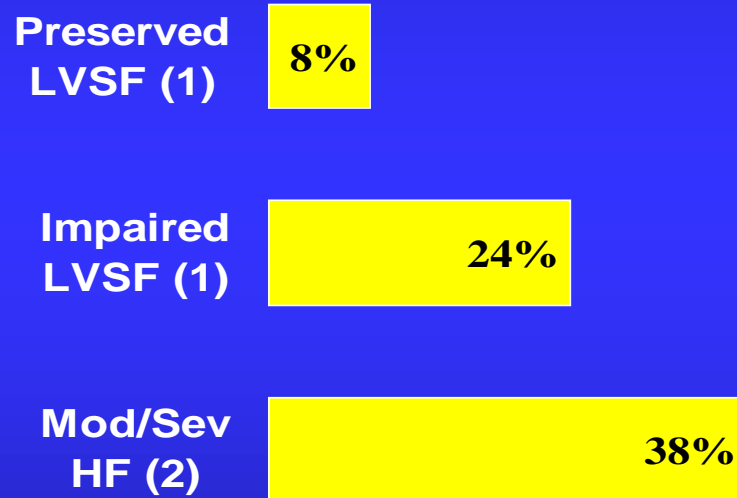


Left Bundle Branch Block



Prevalence and Prognosis of Ventricular Dysynchrony

LBBB More Prevalent with Impaired LV Systolic Function

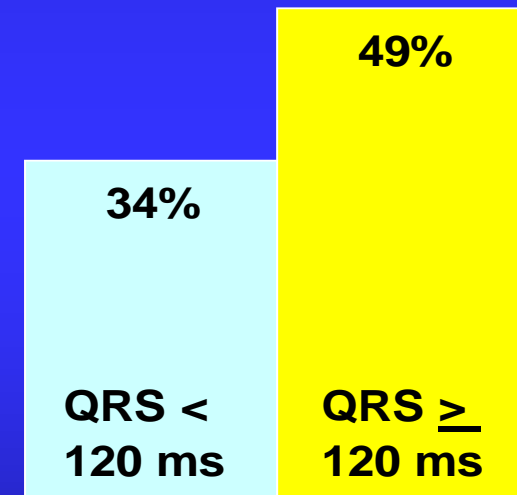


1. Masoudi, et al. JACC 2003;41:217-23

2. Aaronson, et al. Circ 1997;95:2660-7

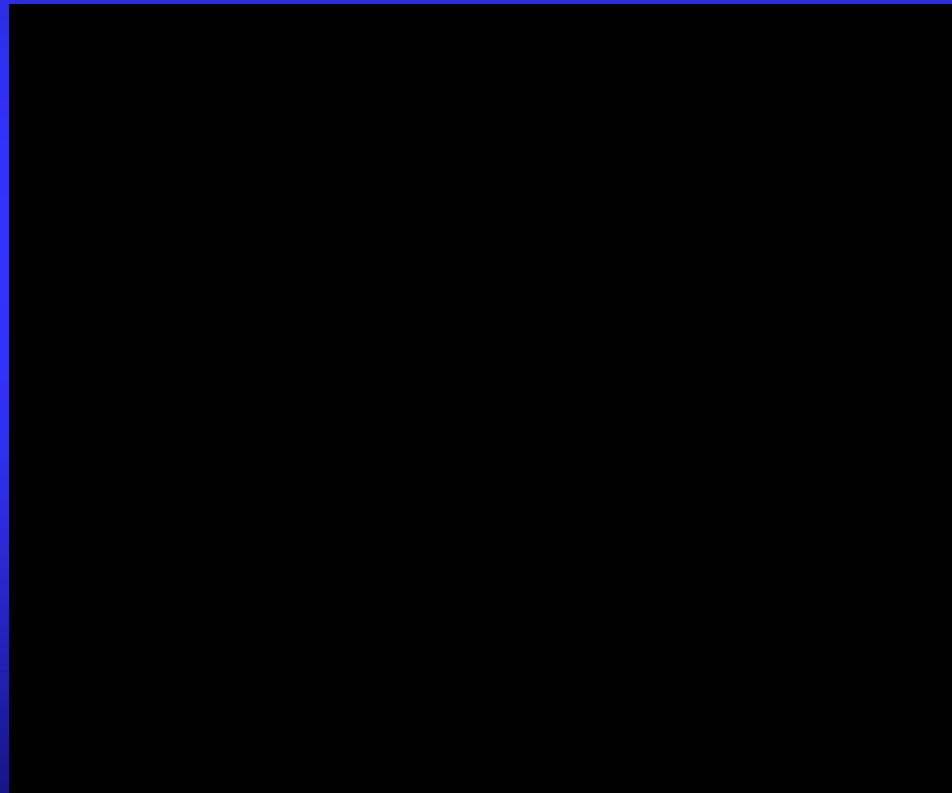
Increased All-Cause Mortality with Wide QRS at 45 Months (3)

P < 0.001

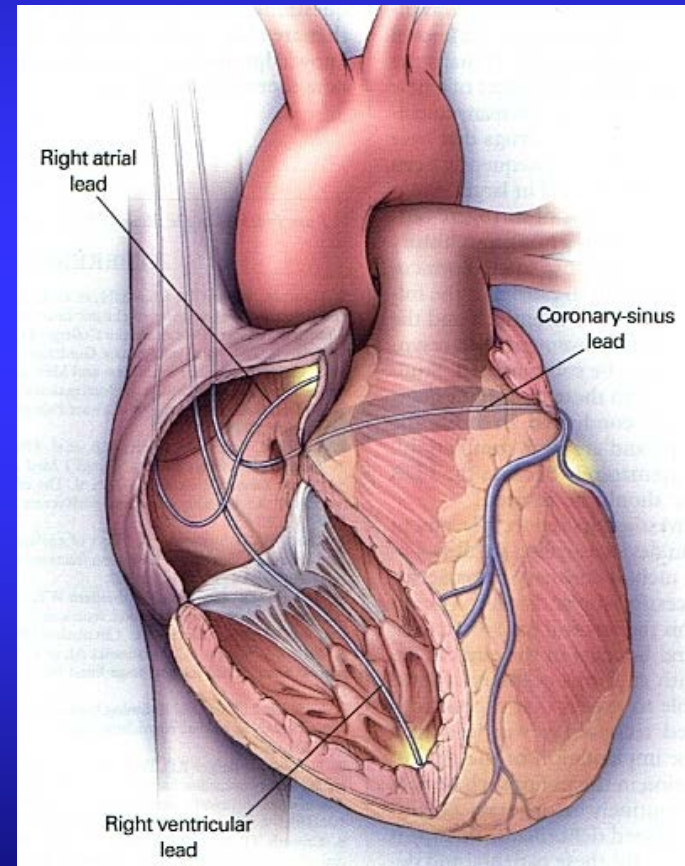


3. Iuliano et al. AHJ 2002;143:1085-91

Abnormal Ventricular Activation



CRT: Three-chamber Pacing



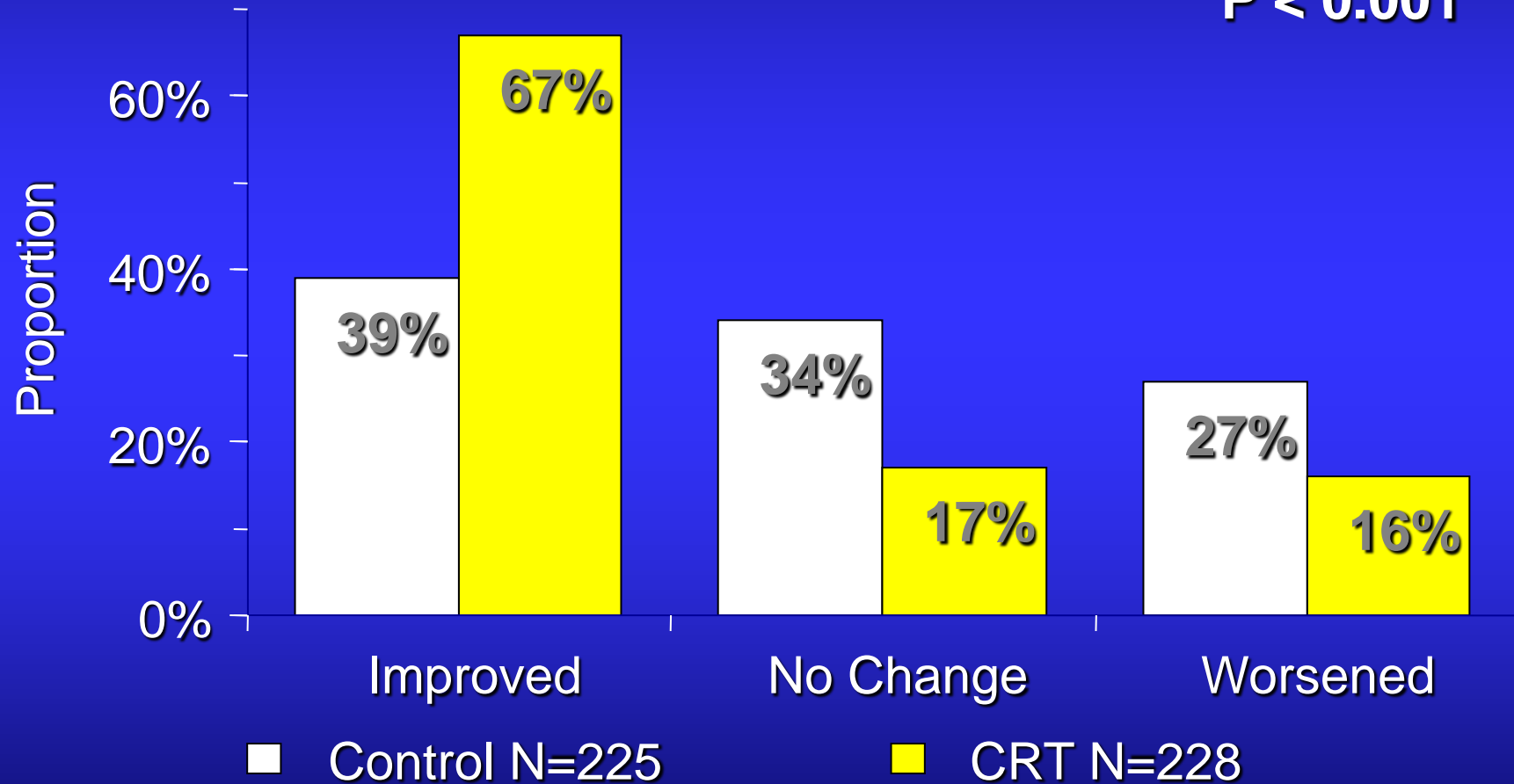
MIRACLE: 2002

Multi-center In Sync Randomized Clinical Evaluation Trial

- Double blinded RCT
- **First** US trial
- NYHA Class III or IV, on OPT, QRS >130 ms, EF<35%
- Enrollment of 453 patients

MIRACLE

P < 0.001

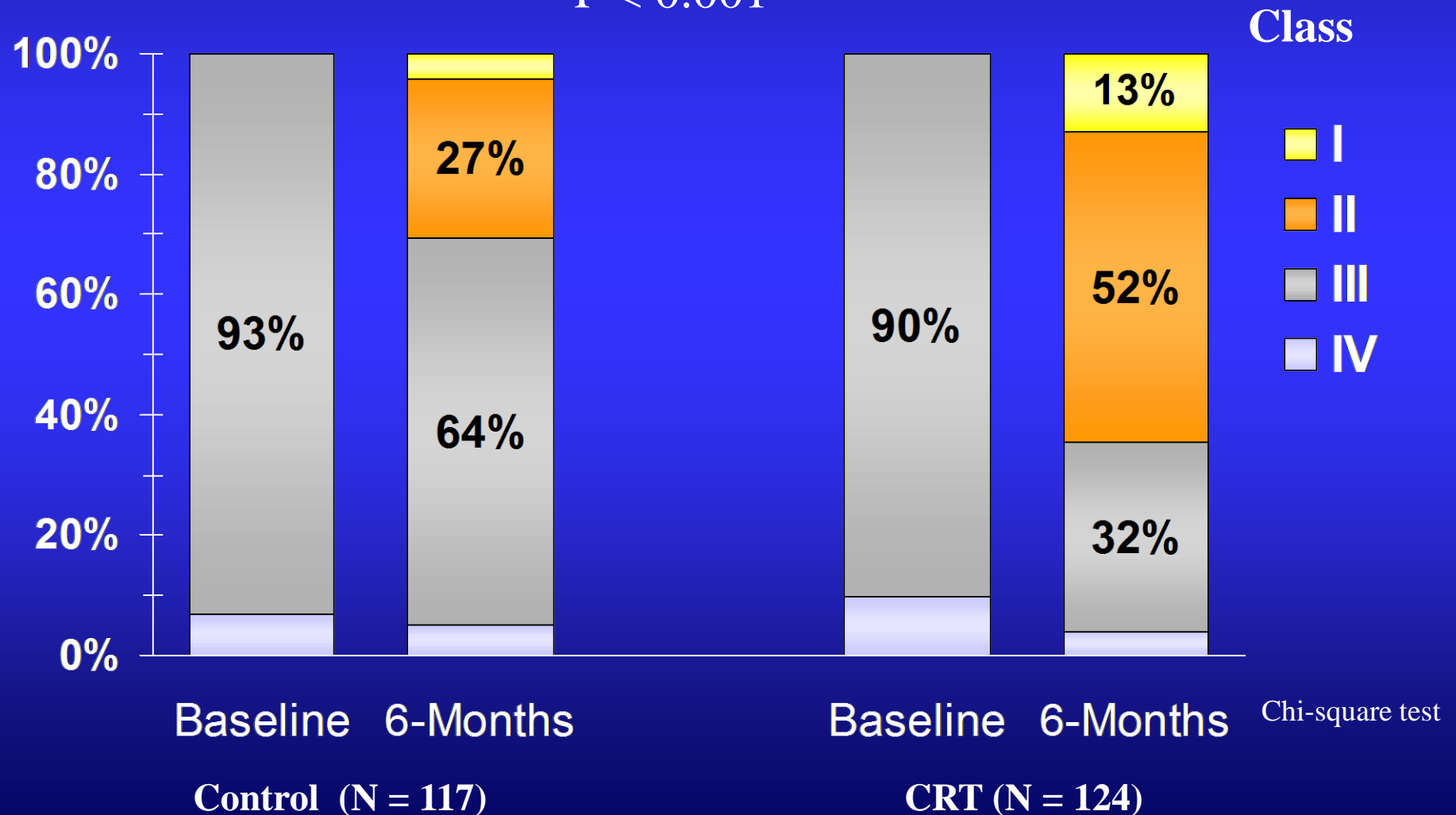


Nonresponders: older, ischemic CM, no MR, QRS<150
Responders: had shorter duration on CHF and longer QRS>155

Pivotal Study Phase

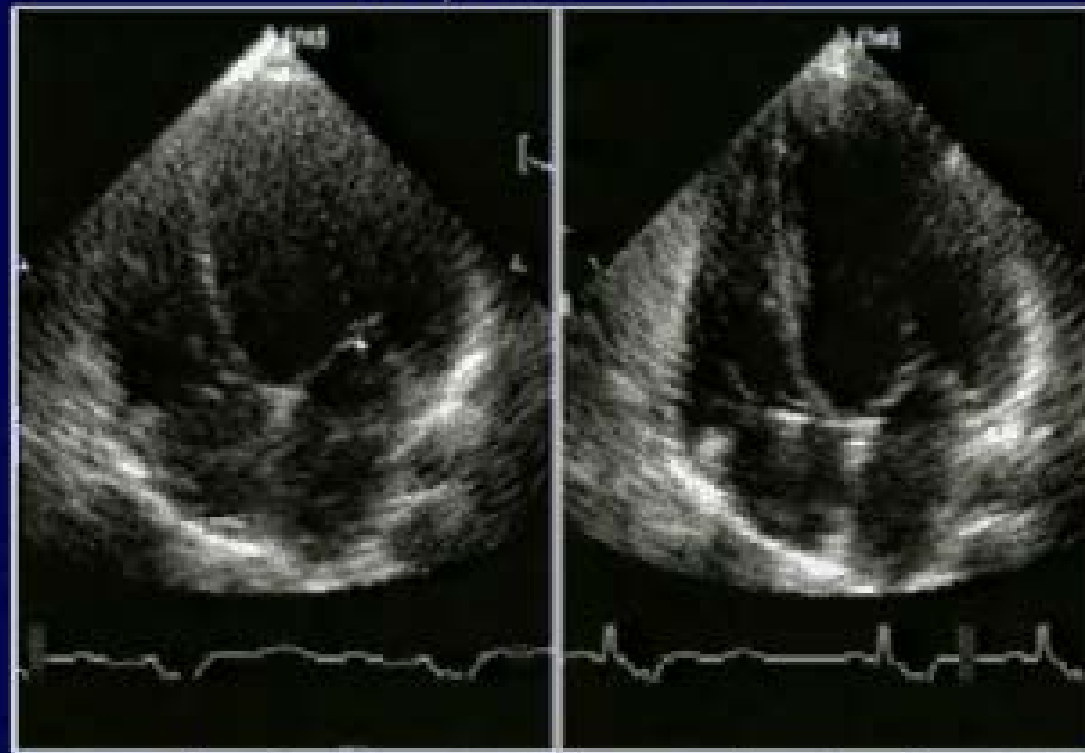
CRT Improves NYHA Class

P < 0.001



Improved Cardiac Mechanics with CRT

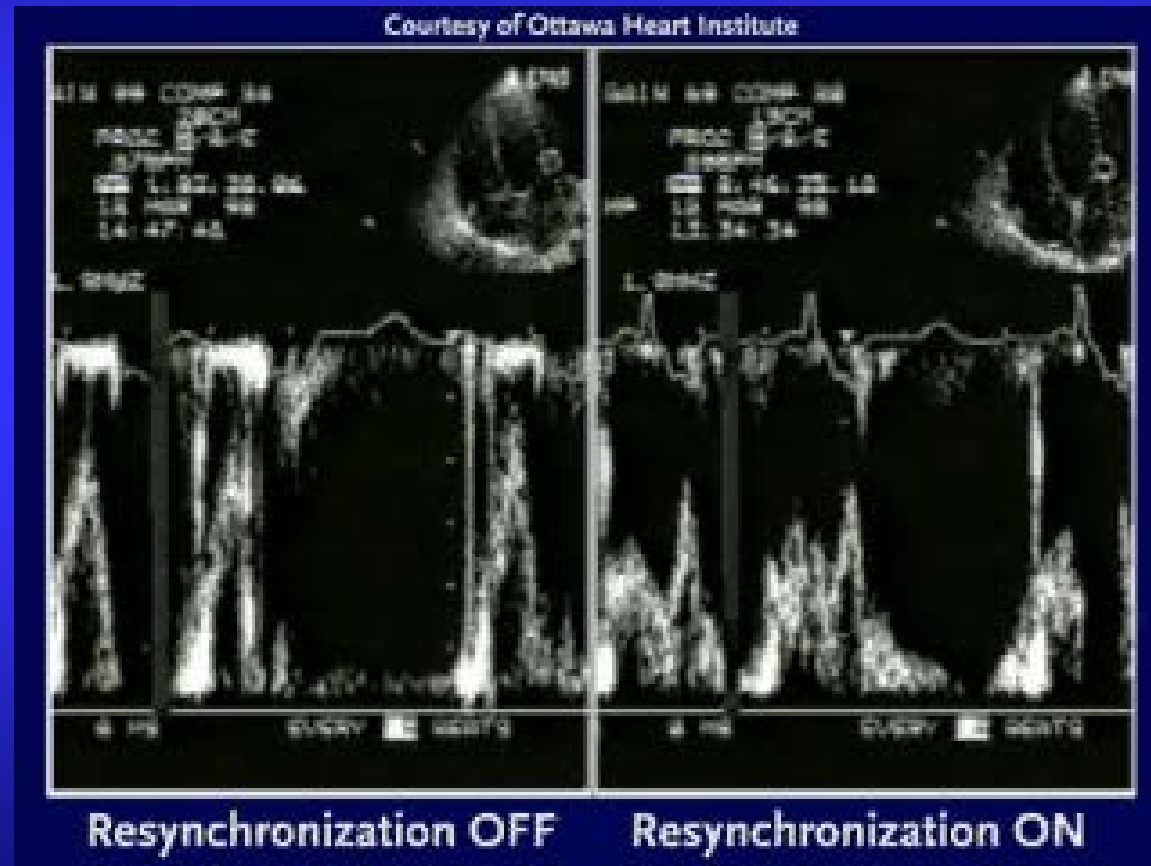
Courtesy of Ottawa Heart Institute



Resynchronization OFF

Resynchronization ON

Trans-mitral Flow



Could the addition of defibrillator
therapy to CRT therapy Help?

COMPANION Study

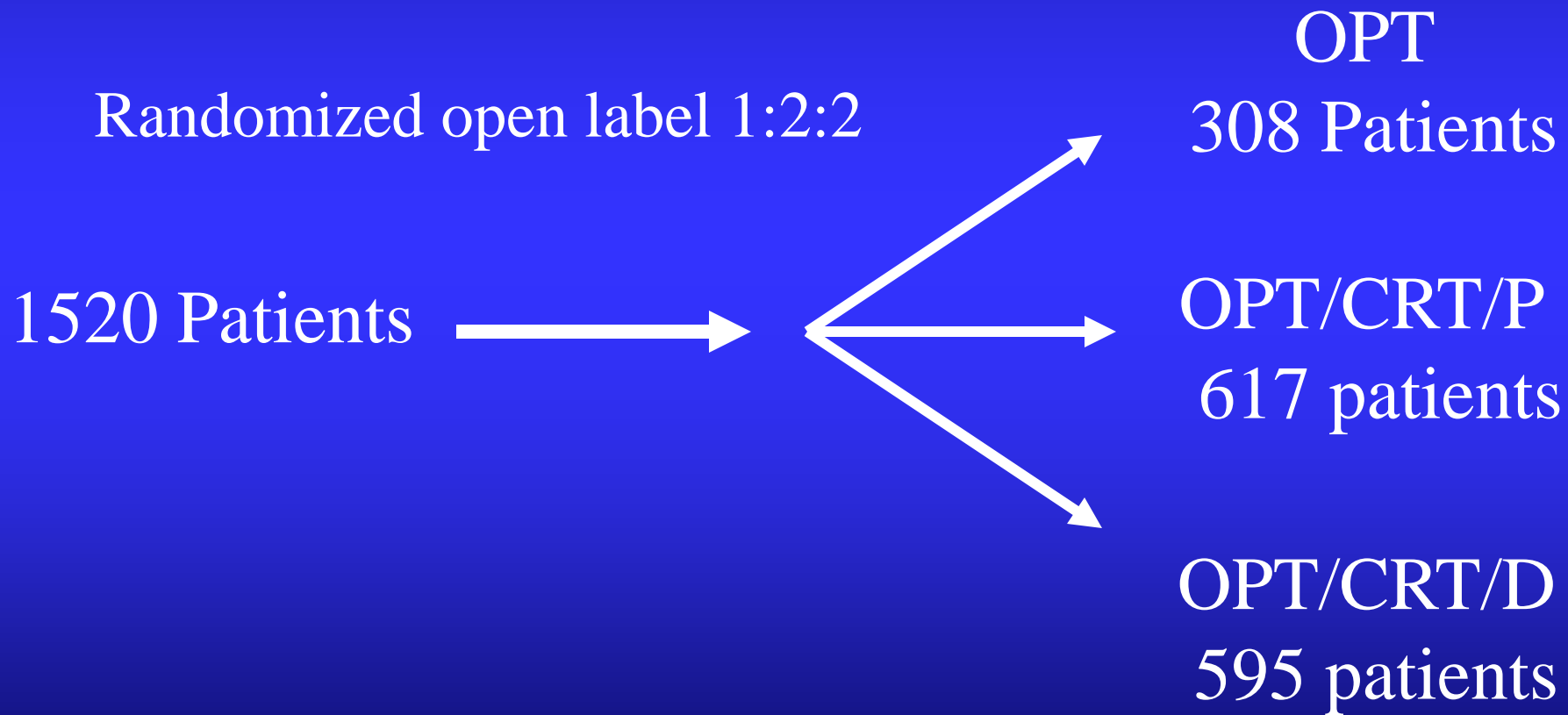
Comparison of Medical Therapy,
Pacing and Defibrillation In Heart
Failure

COMPANION: Primary Hypotheses

In Patients with advanced heart failure and QRS widening, when used in conjunction with optimal pharmacologic therapy:

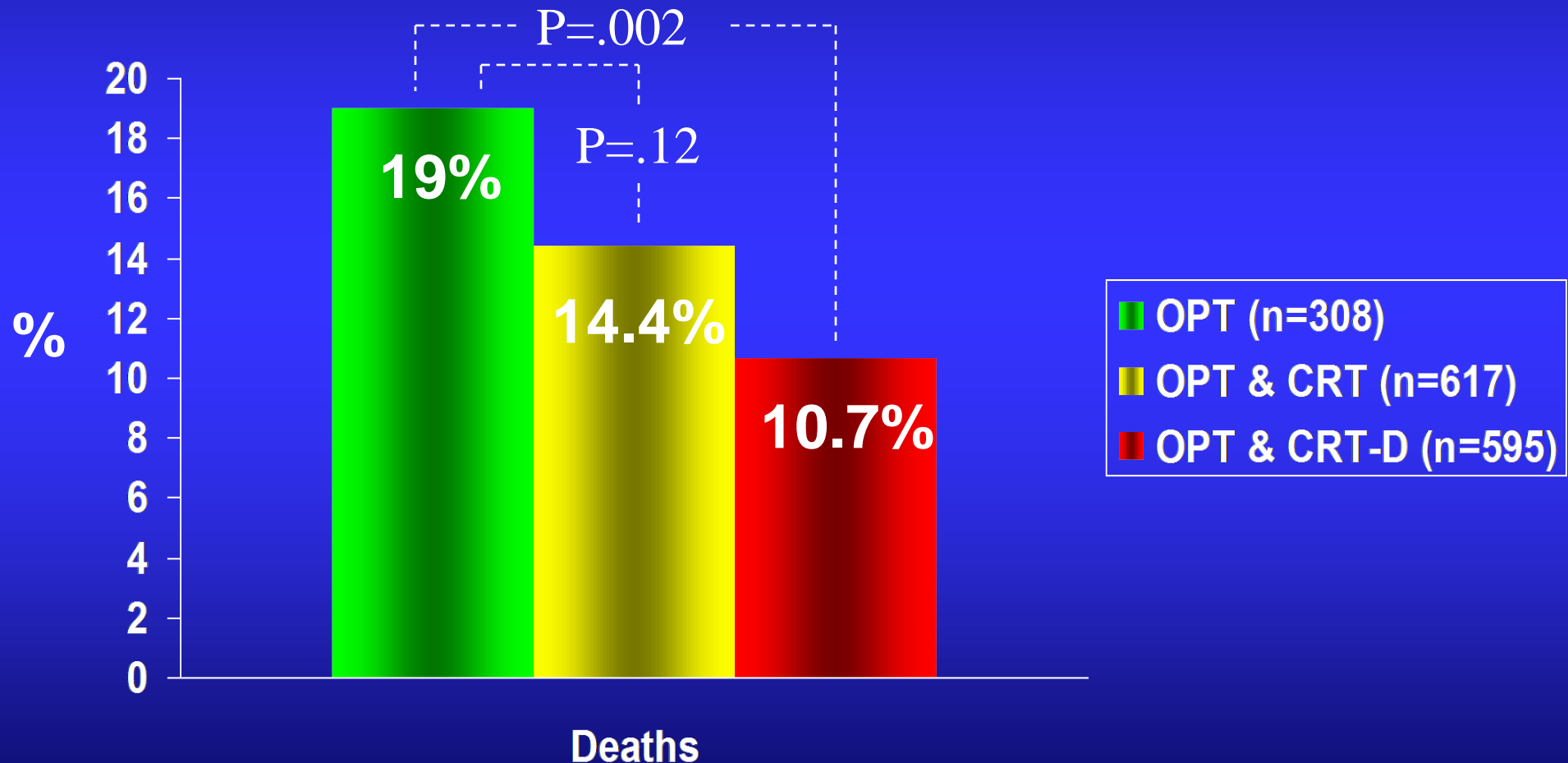
- Bi-ventricular cardiac resynchronization therapy (CRT) alone, or in combination with defibrillation (CRT-D) decreases all-cause mortality and all-cause hospitalization.

COMPANION: Results



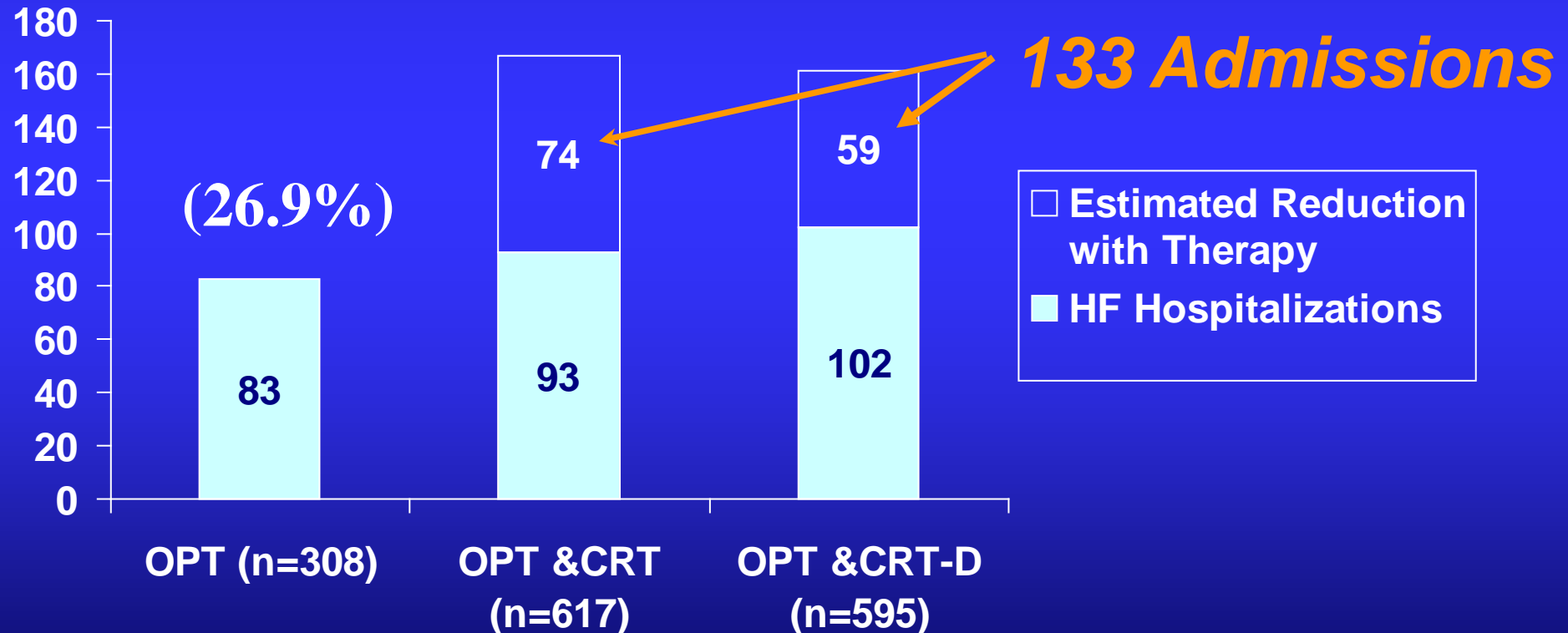
COMPANION: *All-Cause Deaths*

12 month Event-Rate



COMPANION: *Reduction in HF Hospitalization with Therapy*

Hospitalizations in the first 12 months

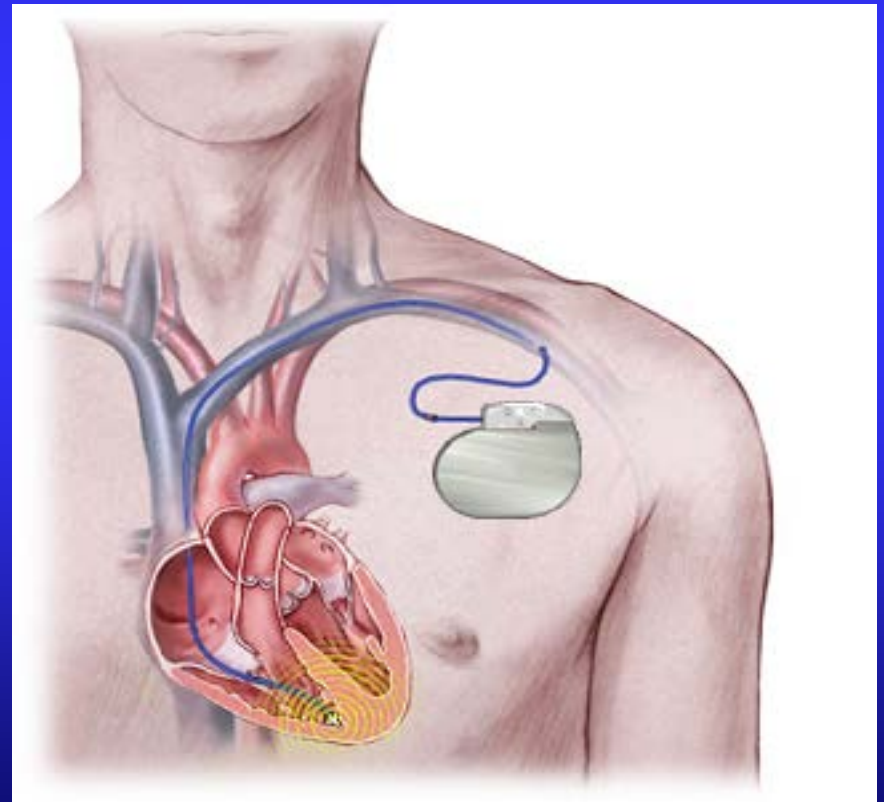


Results of Heart Failure Therapy

- Optimal drug therapy in combination reduces mortality by about a third
- Defibrillator therapy improves survival an additional 25 to 30%
- Cardiac resynchronization therapy in combination with above expands the survival benefit and reduces hospitalizations

The ICD Today: A Cardiac Performance Management System

- Advanced Pacing
- CRT
- Remote wireless Monitoring
- Defibrillation Therapy





Thank You

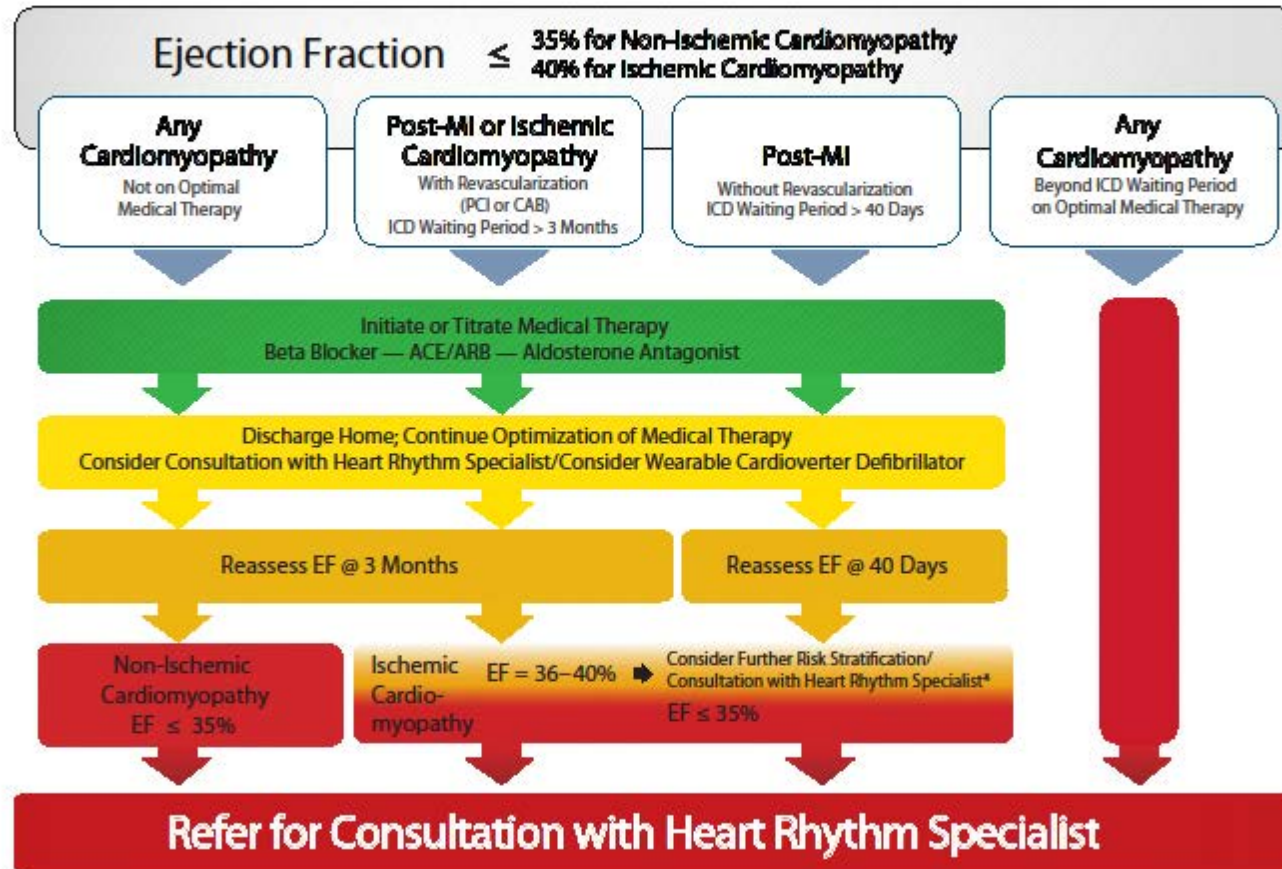
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Sudden Cardiac Death Primary Prevention Protocols

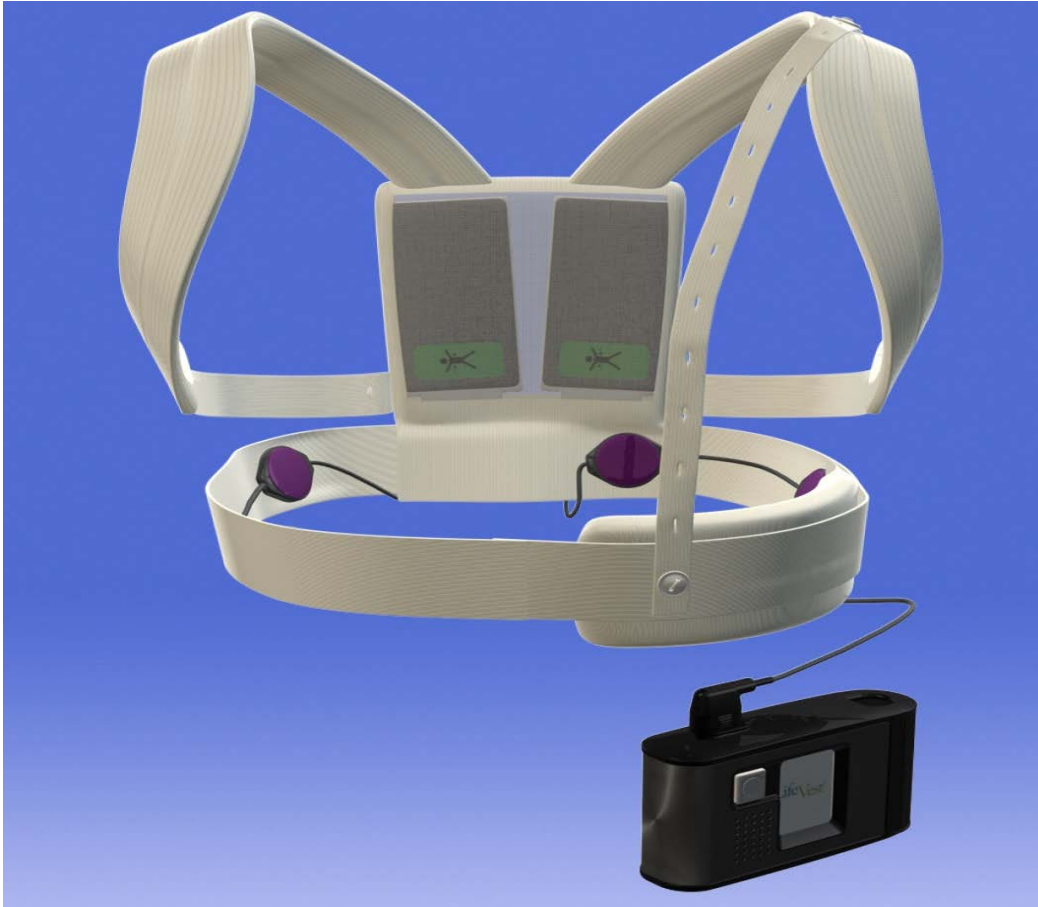
Learn more at
www.HRSonline.org



* Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. December 16, 1999;341(25):1882-1890.

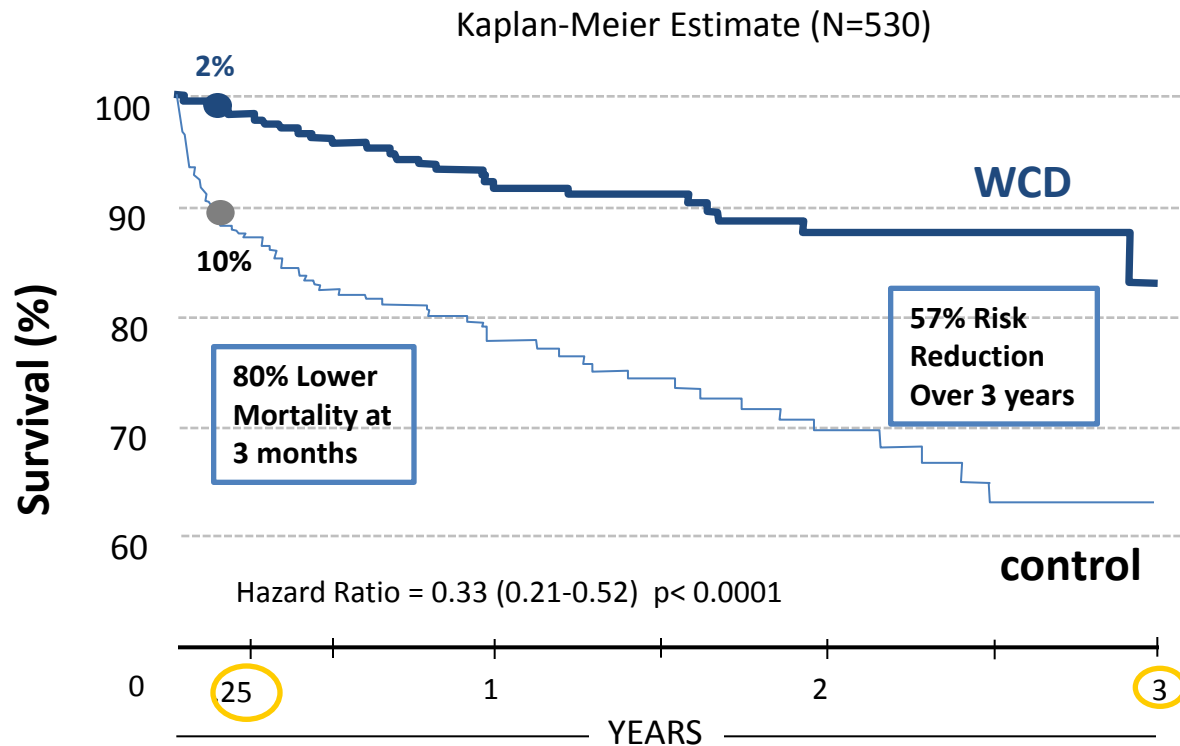
LifeVest

A Proven Treatment Option



Patients with Low EF Following PCI

WCD Reduces Total Mortality



- Post-PCI low EF ($\leq 35\%$) patients prescribed the WCD had an 80% lower 90-day mortality (2%) compared to a matched cohort of patients not prescribed the WCD (10%)¹
- Post-PCI patients prescribed the WCD had a 57% lower risk of death ($p < 0.0001$) over a mean follow-up of over 3 years¹
- Following the end of WCD use, a continued survival benefit was observed out to 3 years
 - WCD is commonly worn by patients for 90 days following PCI

WCD	265	210	172	82	19
control	265	186	134	65	36

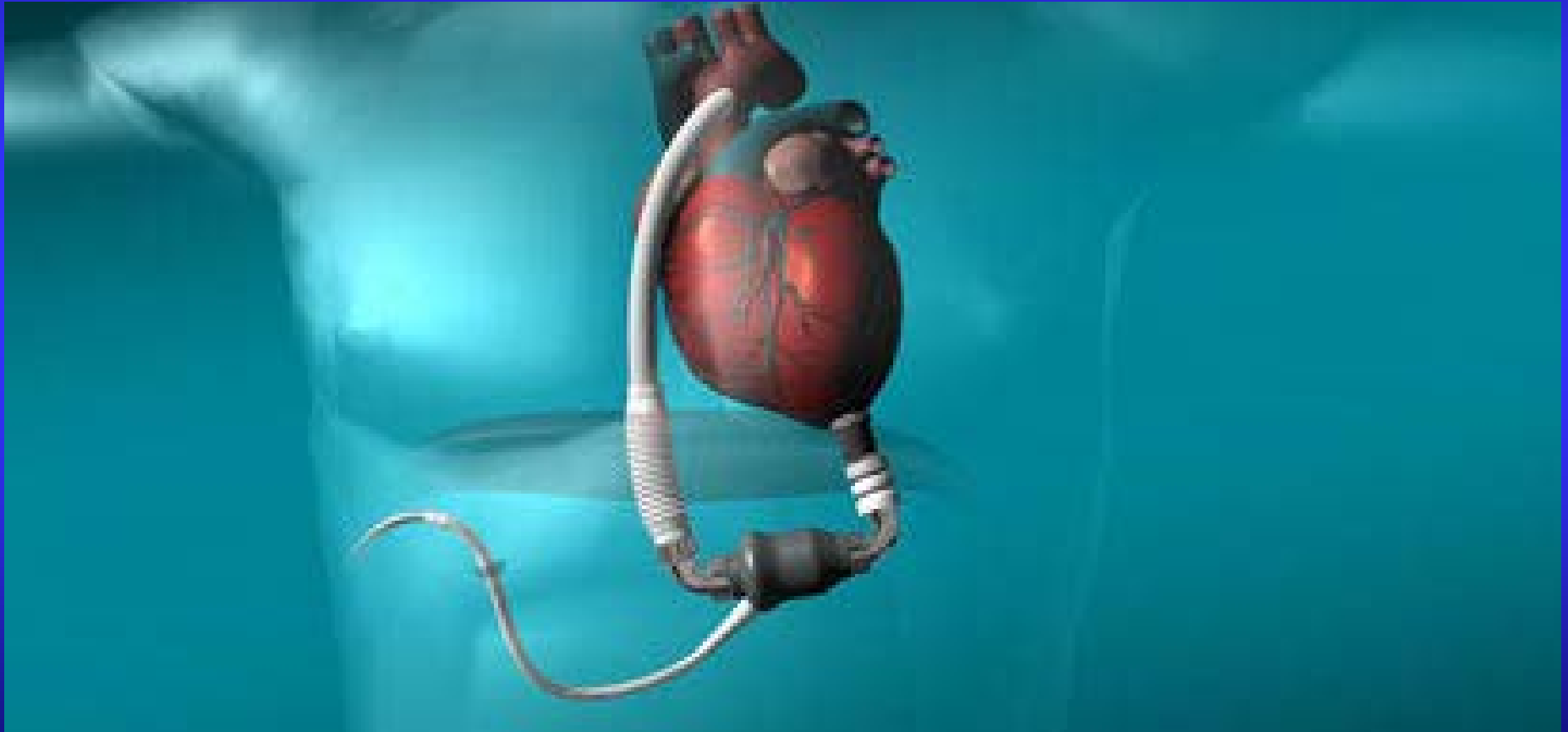
¹ Zishiri, E et al. Use of the Wearable Cardioverter Defibrillator and Survival After Revascularization in Patients with Left Ventricular Dysfunction. 2011;124:A9816.

Indications : Bridge to ICD

- Post Myocardial Infarction with low EF ($\leq 35\%$)
 - < 40 days after MI
 - < 90 post CABG
 - < 90 post PTCA
- Non-ischemic cardiomyopathy
 - < 3 months from diagnosis (90-270 days)
- ICD requires explantation
- Pre transplant, NYHA Class IV

Complications of Heart Failure

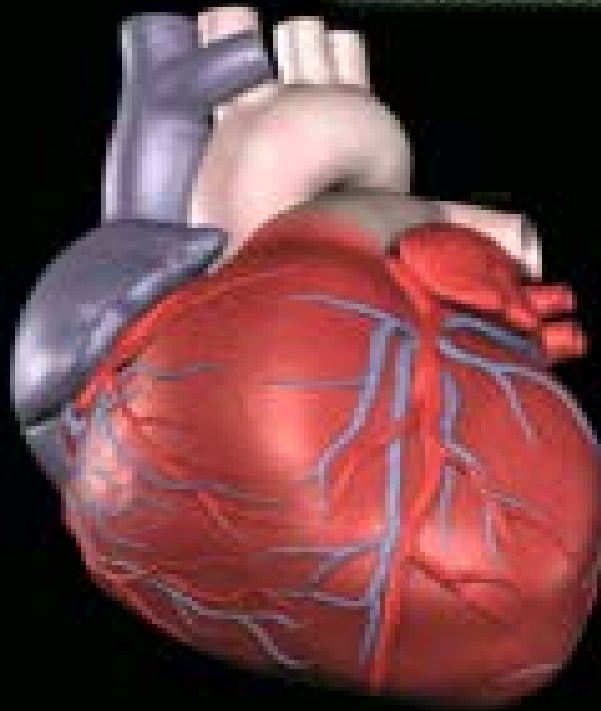
When All Else Fails ?



Results with LVAD Therapy

- 280 Patients
- 27% in-hospital mortality
- 56% one year survival

Normal Heartbeat

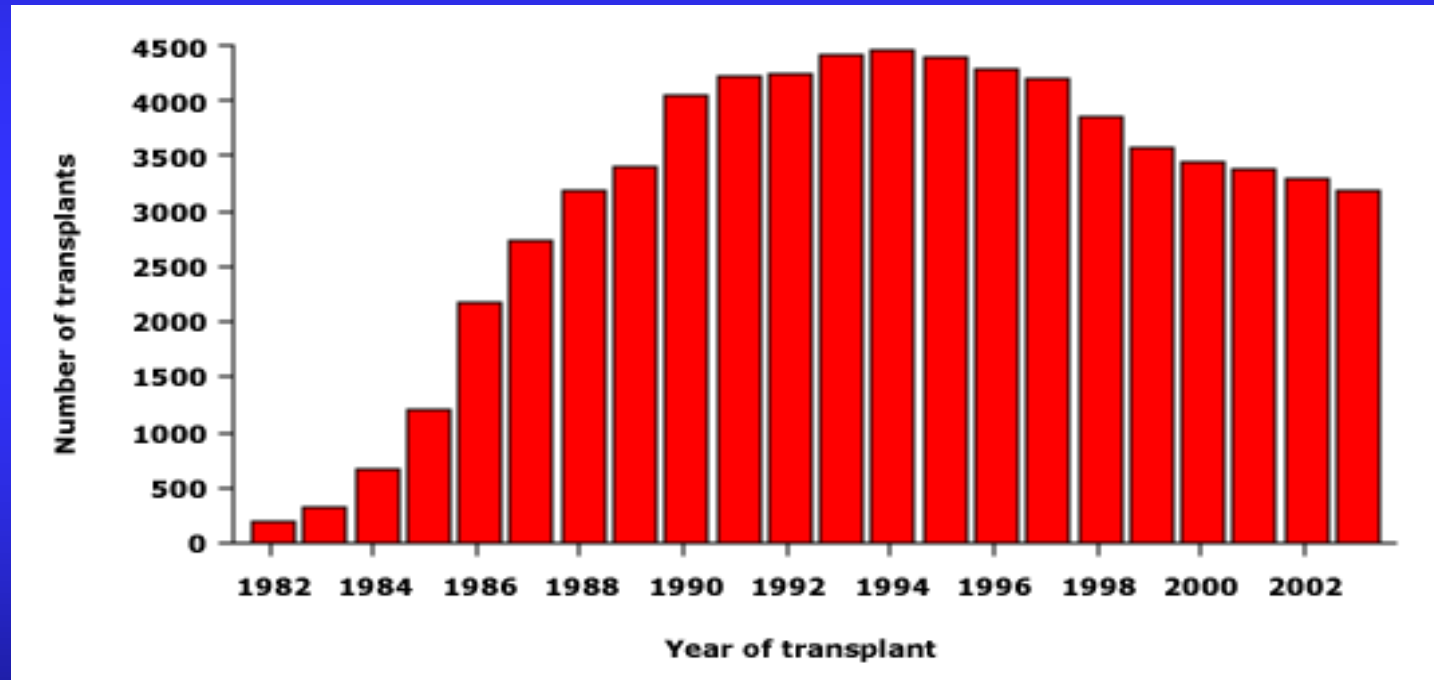


A normal heart pumps blood in a smooth and synchronized way.

Heart Transplantation

- A good solution to the failing heart– get a new heart
- Unfortunately we are limited by supply, not demand
- Approximately 2200 transplants are performed yearly in the US, and this number has been stable for the past 20 years.

Worldwide Heart Transplants



DECEMBER 10, 1984

\$1.95

TIME

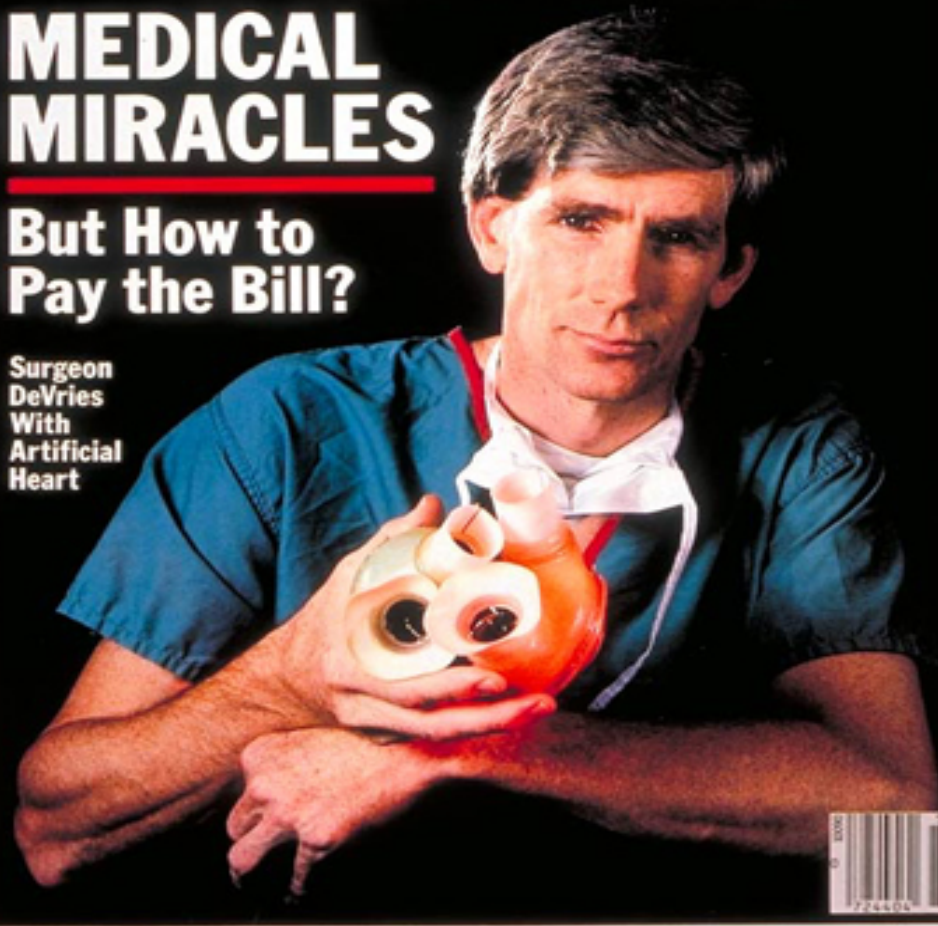
THE TAX WAR BEGINS
Reagan Weighs
A Sweeping
Reform



MEDICAL MIRACLES

**But How to
Pay the Bill?**

Surgeon
DeVries
With
Artificial
Heart

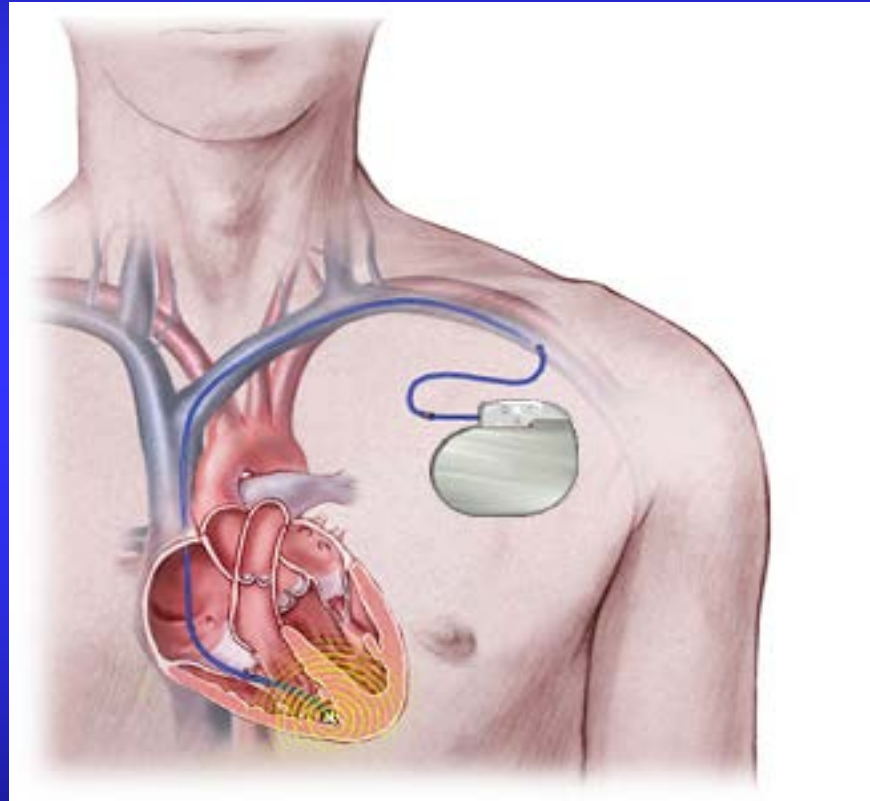


The Future of Device Therapy For Heart Failure

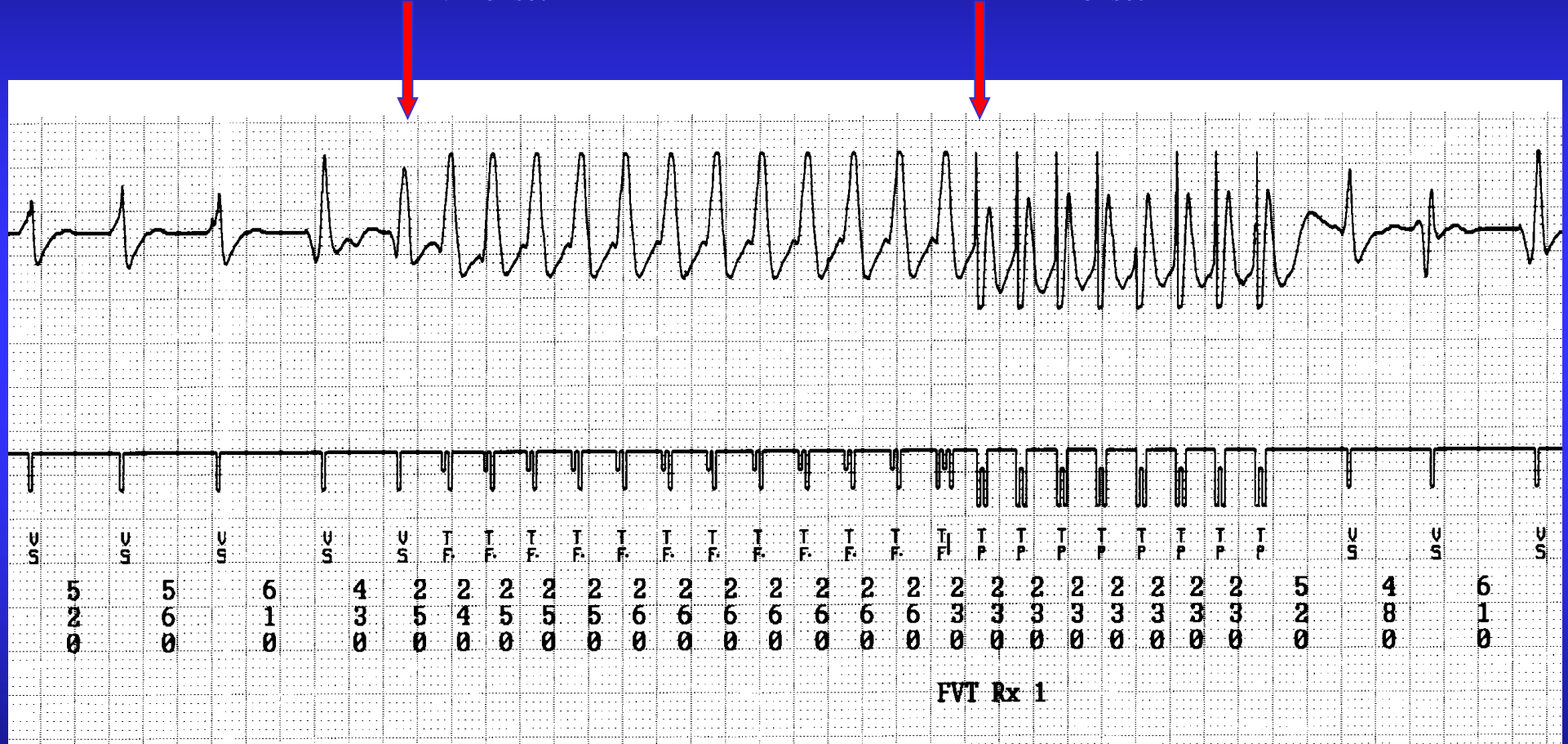
- Adaptive CRT
- Refinement of implanted systems from cardiac rhythm management (CRM) to that of cardiac performance management (CPM) systems

The ICD Today

- Defibrillation
- Synchronized Cardioversion
- Anti-tachycardia Pacing (ATP) Therapy



Anti-tachycardia Therapy: Success

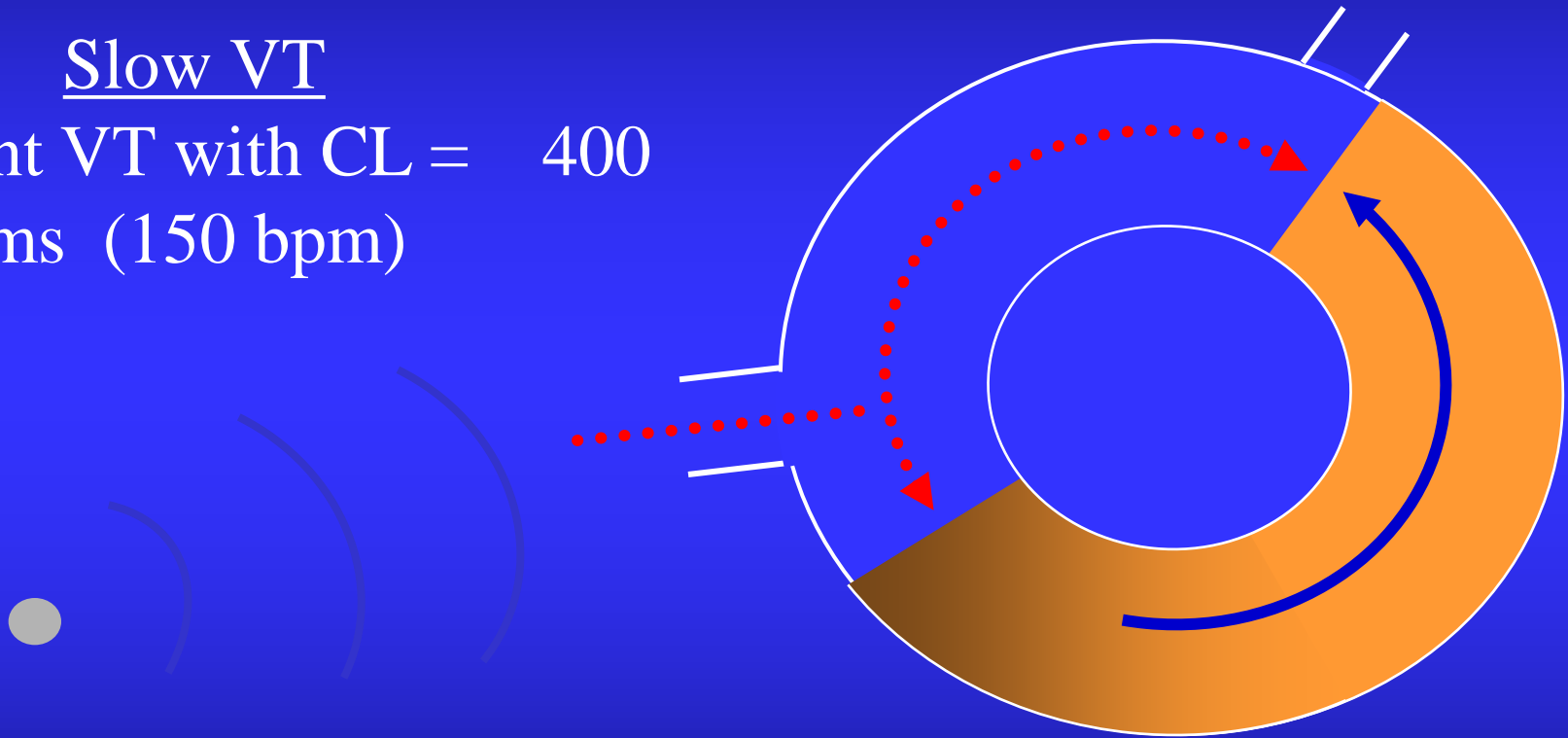


Episode duration = 5.3 s

Anti-tachycardia Therapy

Slow VT

Re-entrant VT with CL = 400
ms (150 bpm)



ATP Efficacy = 90-95%¹⁻³

¹Raitt MH, et al. *Circulation*. 1995; 91: 1996-2001

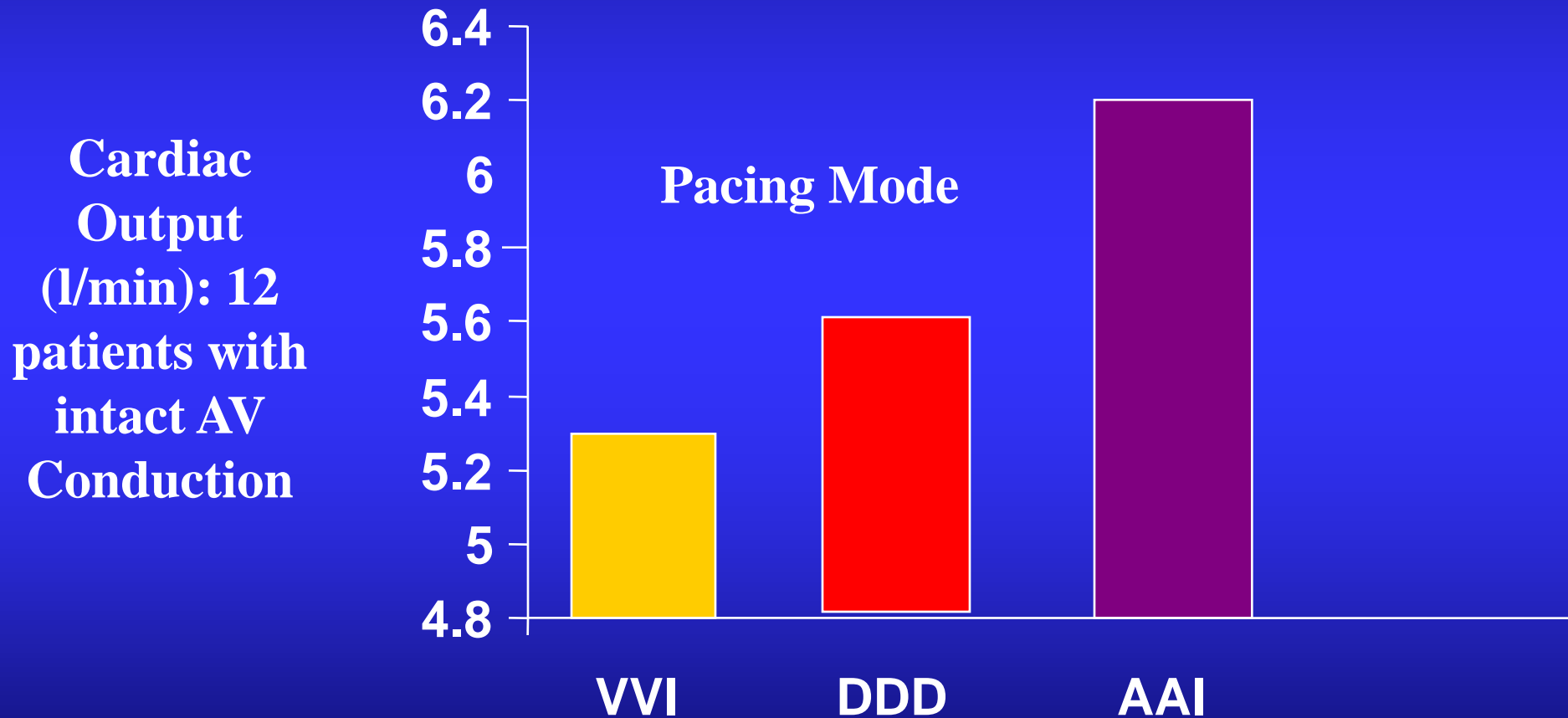
²Swerdlow CD, et al. *Circulation*. 1997; 95: 1497-1504

³Schaumann A, et al. *Circulation*. 1998; 97: 66-74.

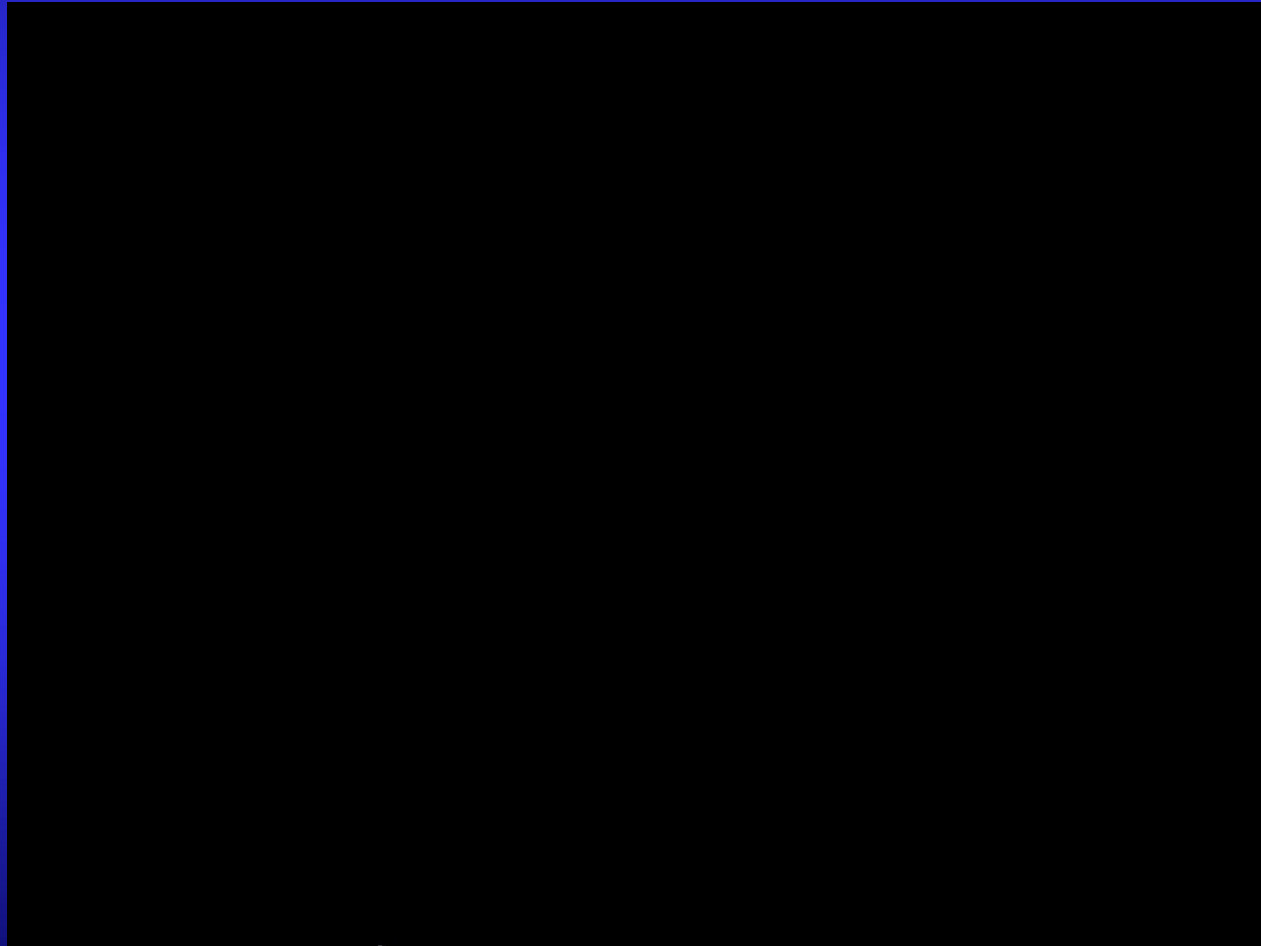
Heart Failure: Treatment Strategies

Clinical Goal	Treatments
Quality of Life (Symptom Relief)	Diuretics Inotropes (acute) Vasodilators
Prevent Progression	Ace Inhibitors B Blockade
Survival	Ace Inhibitors B Blockade ICDs
Reverse Remodeling	Heart Transplant

The Importance of the Sequence of Ventricular Activation



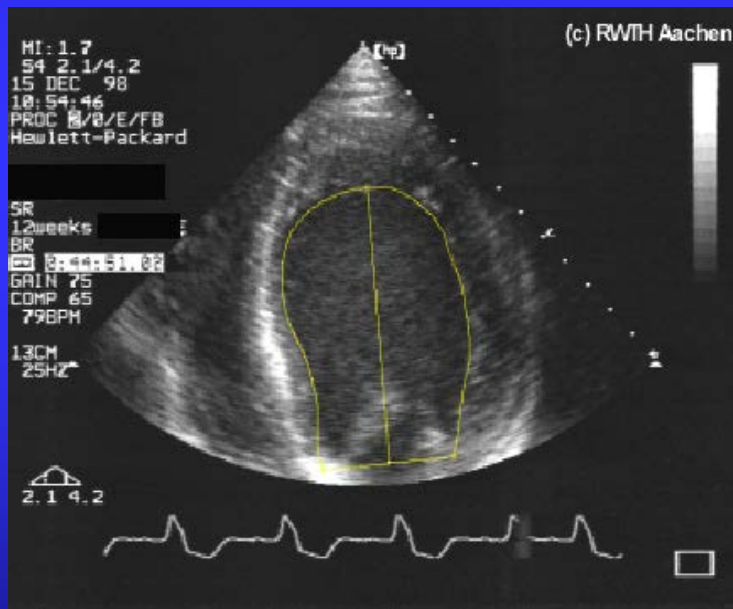
Contrasting Mechanics



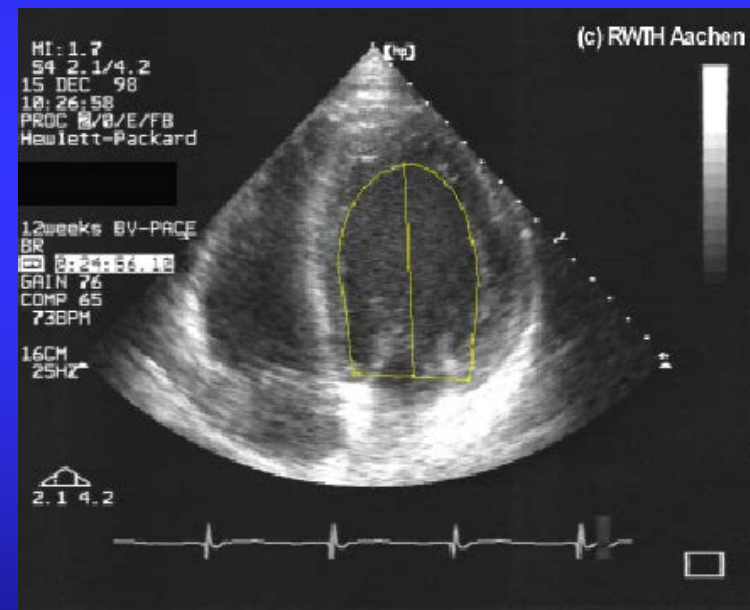
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Baseline



DCM - CRT



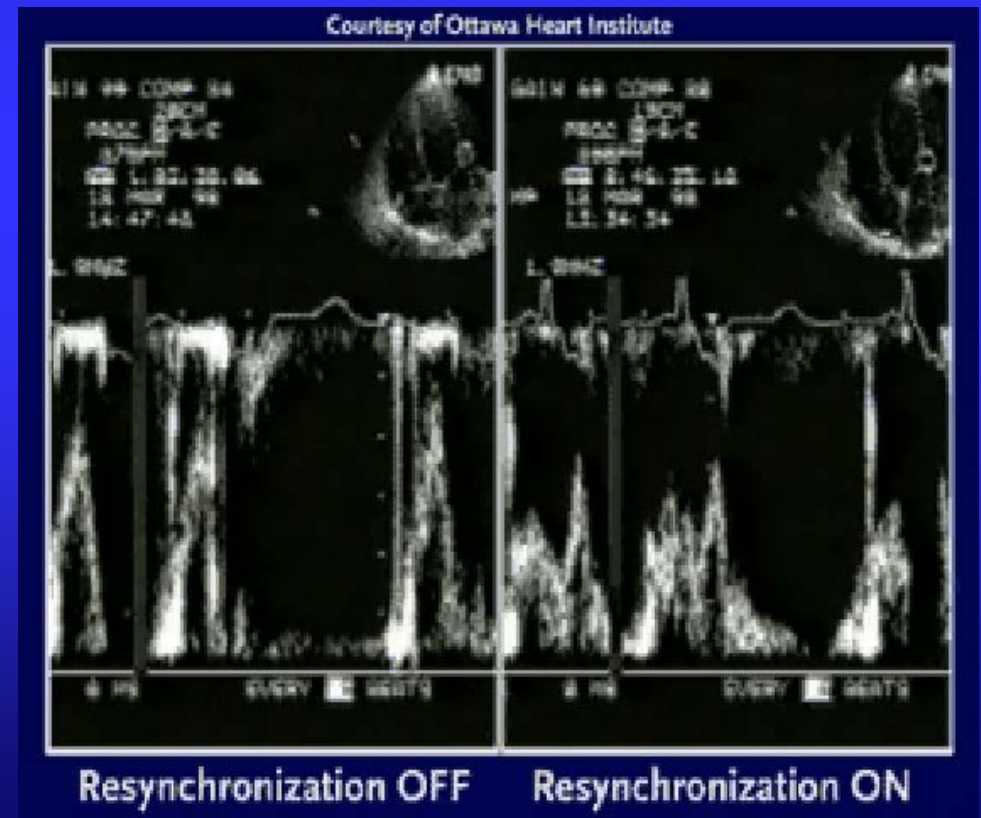
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Mitral Valve Function



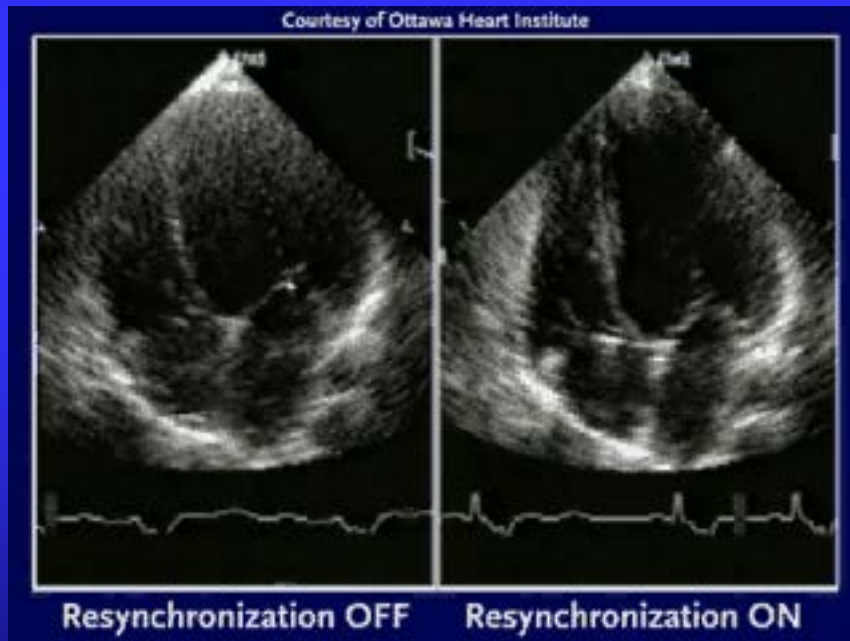
Diastolic Filling



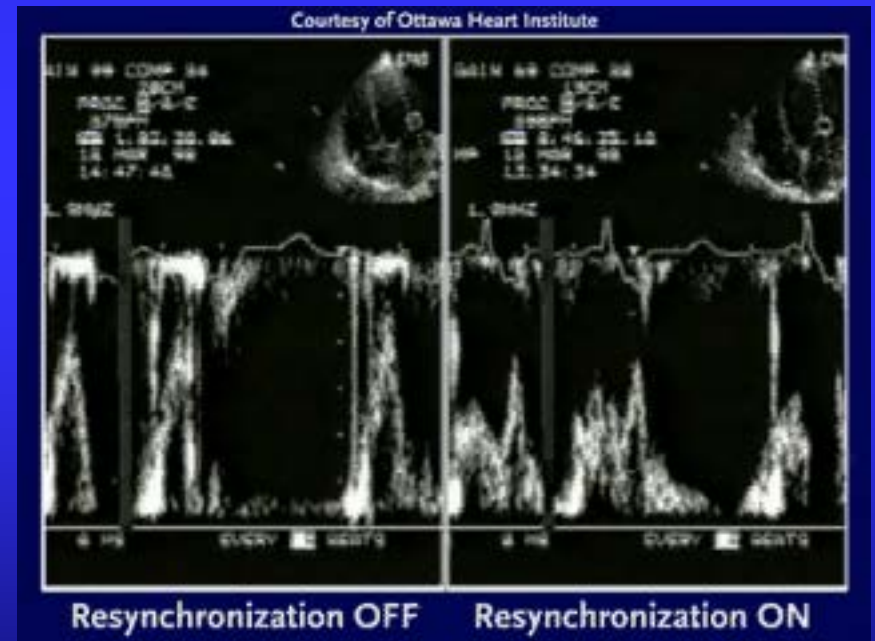
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Mitral Valve Function



Diastolic Filling

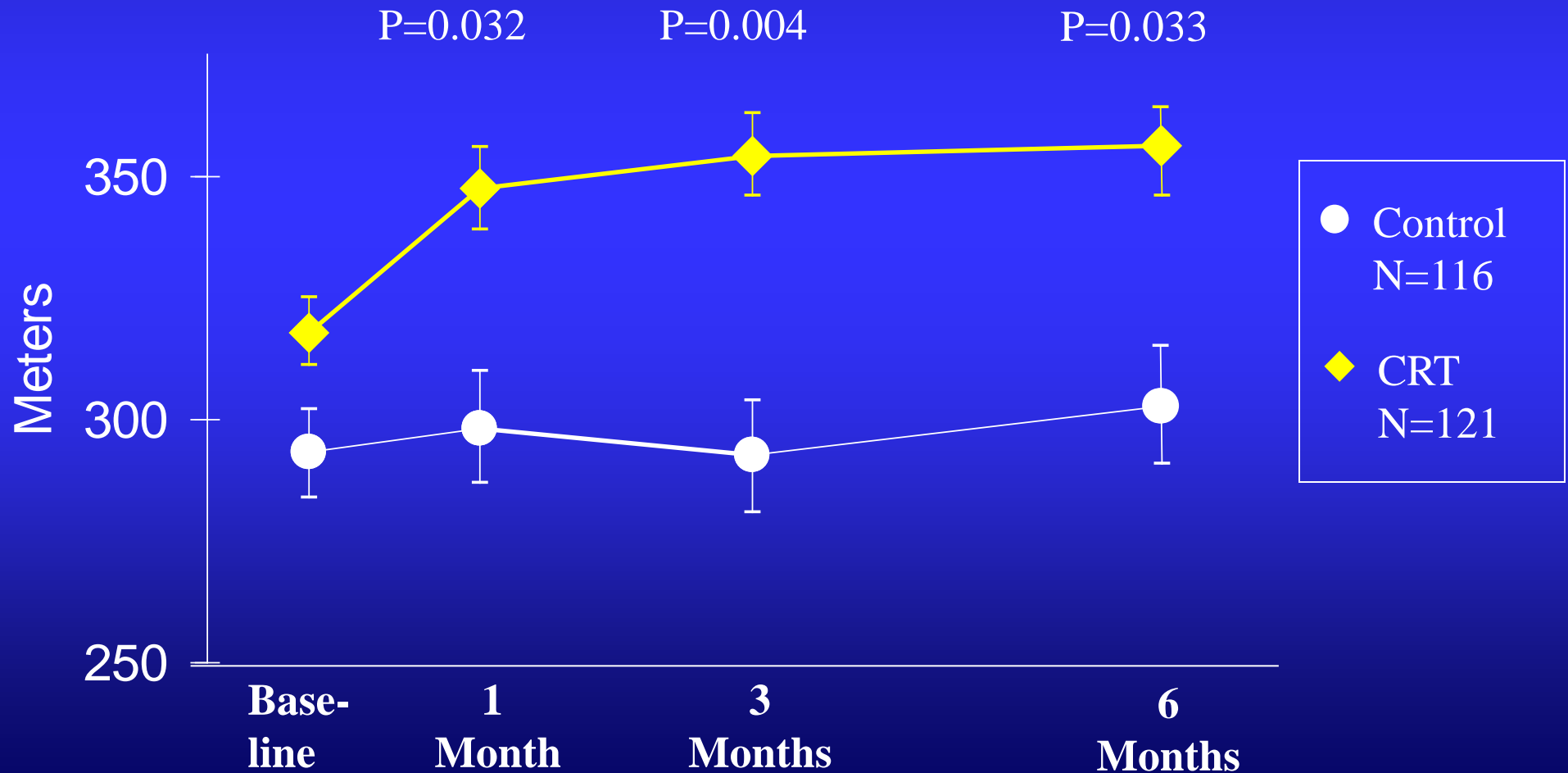


Cardiac Resynchronization Therapy

Early Results

MIRACLE Pivotal Phase

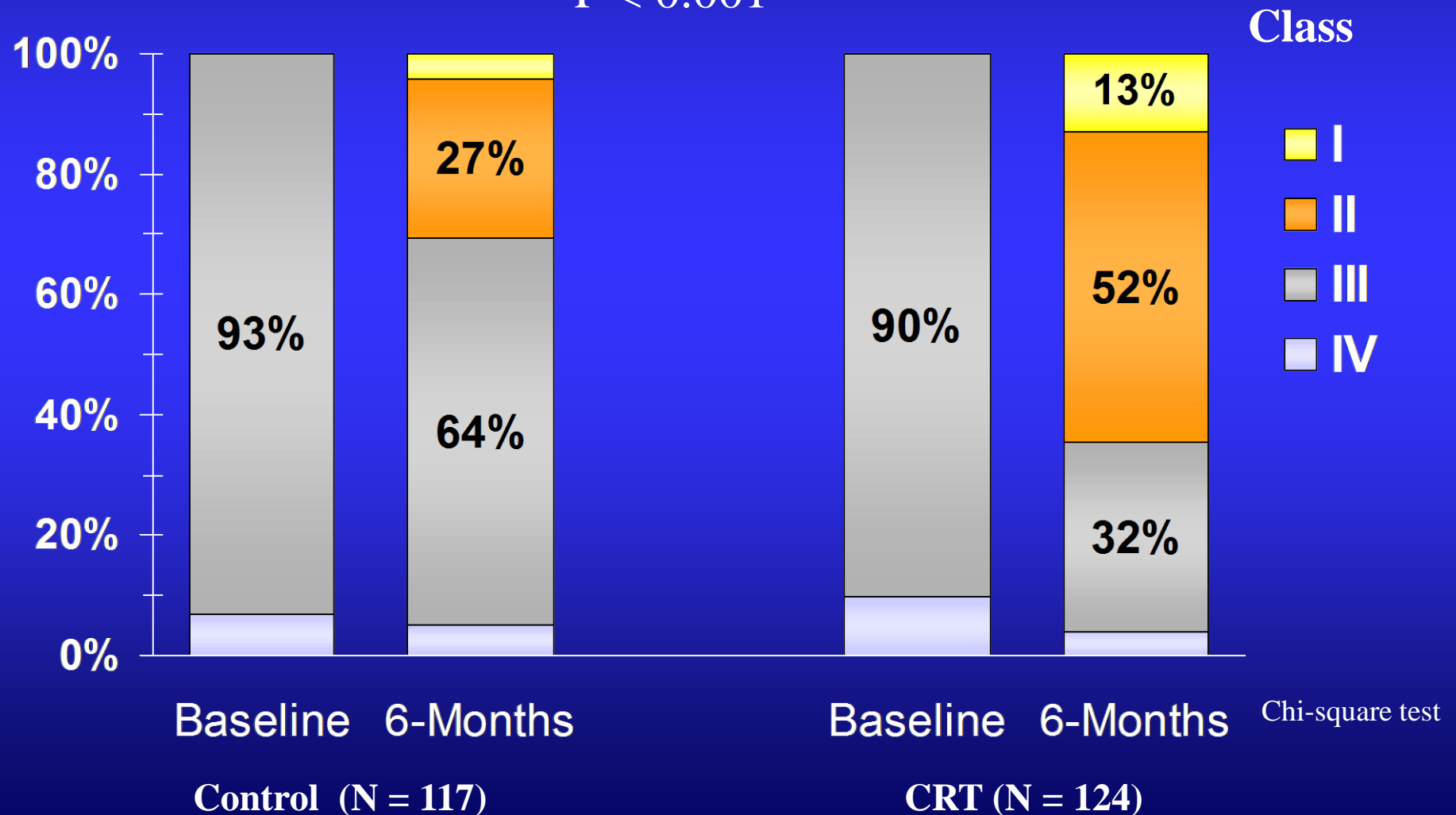
CRT Improves 6-Minute Hall Walk Distance



Pivotal Study Phase

CRT Improves NYHA Class

P < 0.001

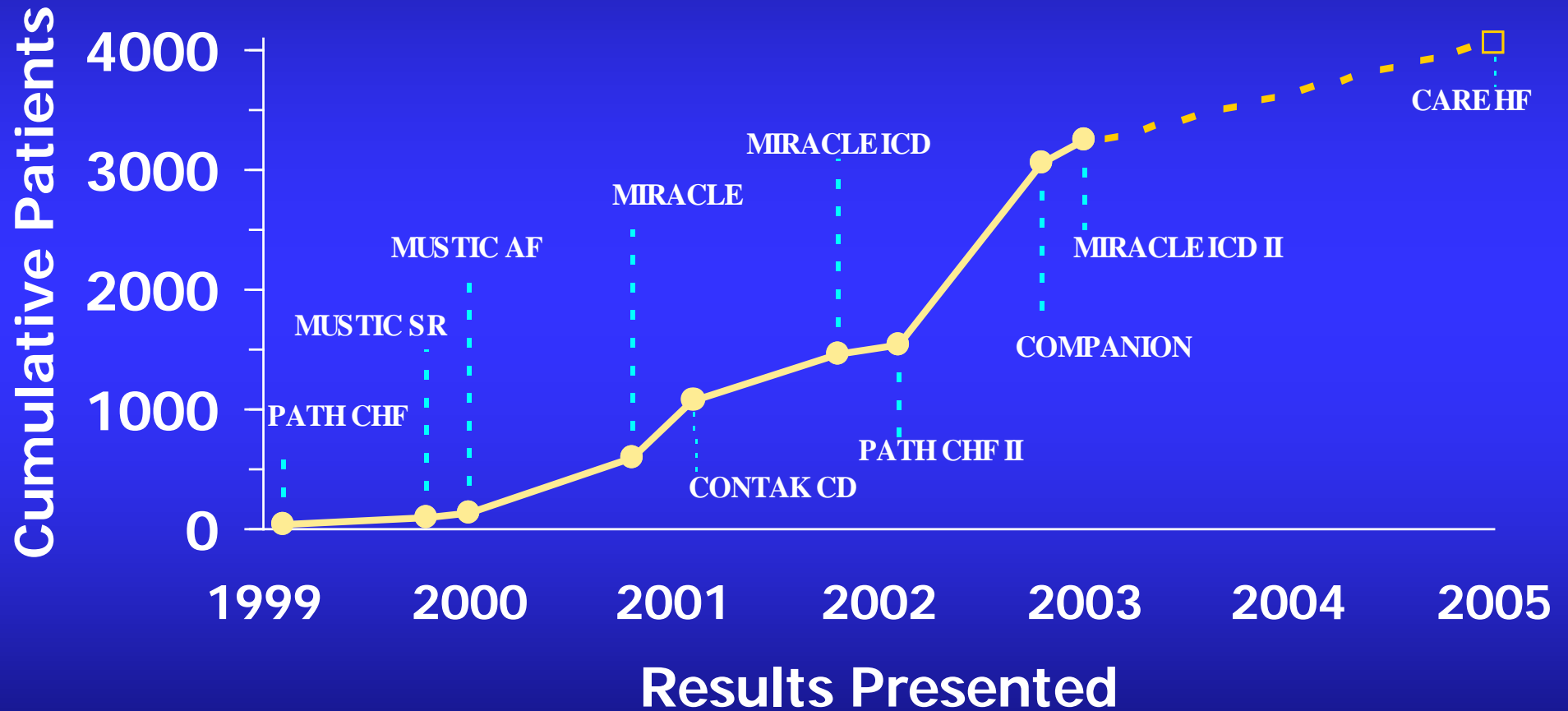


MIRACLE: Conclusions

In NYHA Class III and IV systolic heart failure patients with intraventricular conduction delays, CRT

- is safe and well tolerated
- improves Quality of Life, functional class, and exercise capacity
- improves cardiac structure and function
- improves heart failure composite response

Cumulative Enrollment in Cardiac Resynchronization Randomized Trials

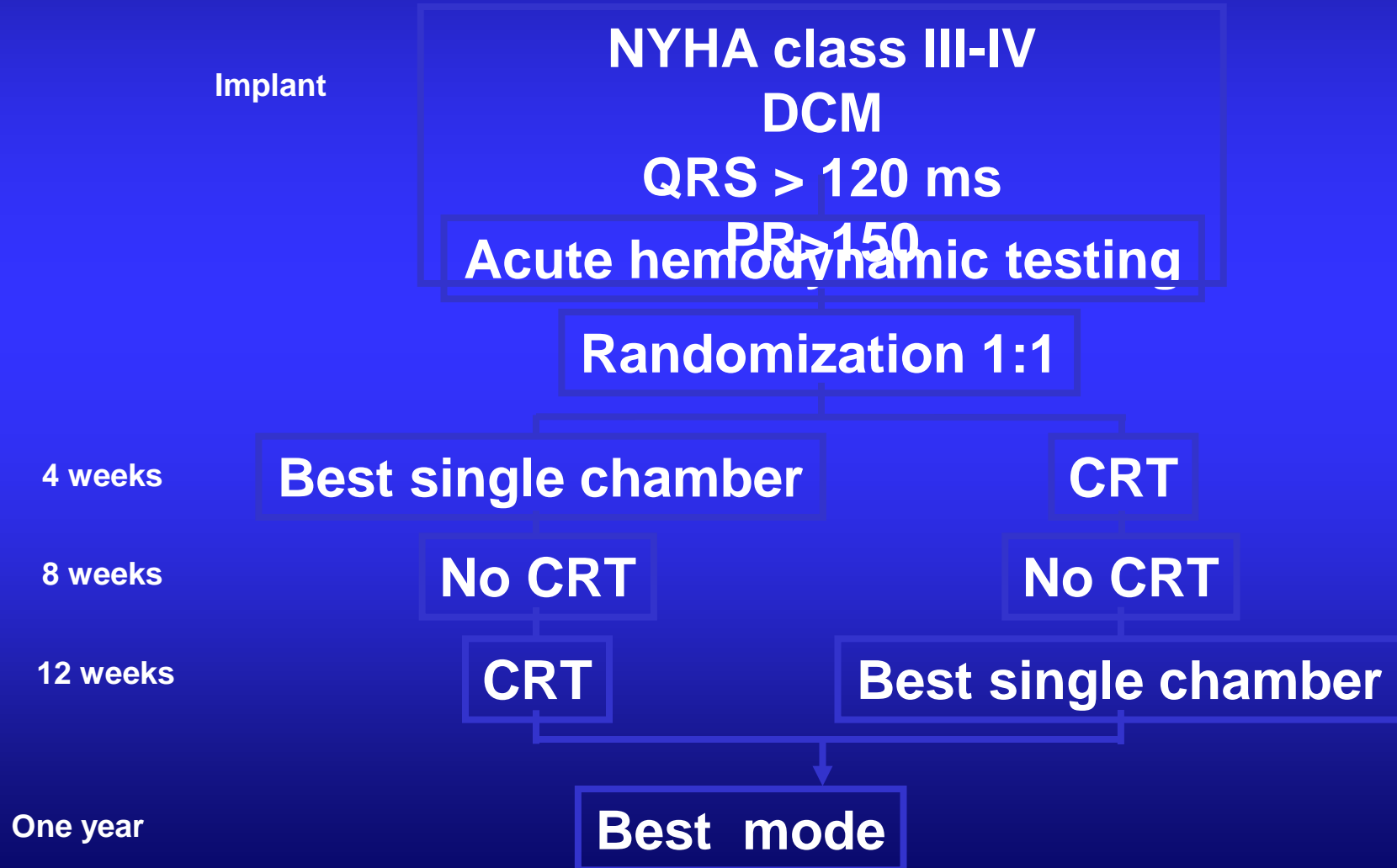


PATH-CHF: 1999

Pacing Therapy for Congestive Heart Failure

- This was the **first multicenter trial** and used the standard endocardial RV lead and an **epicardial** LV lead via thoracotomy or thorascope
- Single blinded RCT
- 53 centers in **Europe**
- **41** patients

PATH-CHF



PATH-CHF

□ Primary endpoints

- Peak VO₂
- Six-minute walk distance

□ Secondary endpoints

- Minnesota Living with Heart Failure score (QOL)
- NYHA class
- EF
- Trend towards decrease in Hospitalizations

□ Acute hemodynamic testing revealed that the lateral and posterolateral walls were the best target sites.

- The best responders were those with QRS>150 , long PR and dP/dt < 700 mm Hg/s

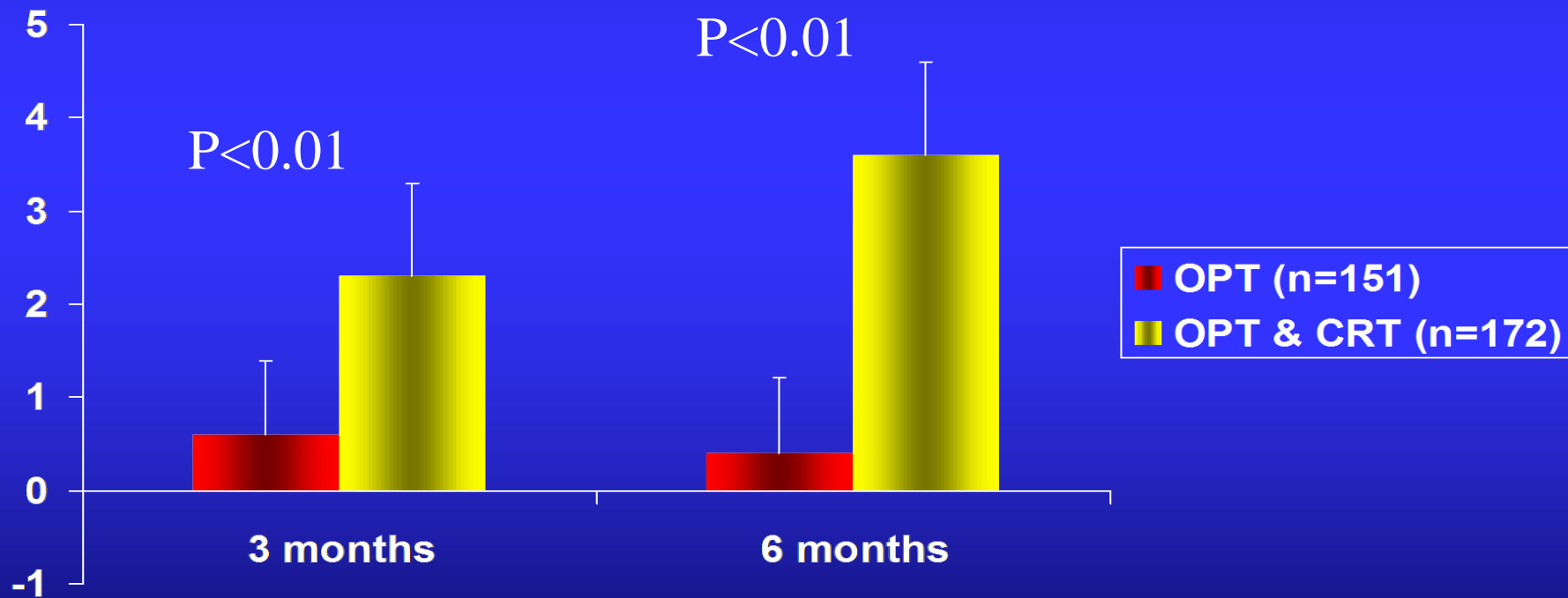
MUSTIC: 2001

Multicenter Stimulation in CM

- European study with 67 patients
- QRS>150, CHF, EF <35%
- BiVP versus backup VVI pacing at 40 BPM
- Increase in 6 minute walk time , QOL and Peak VO2 with BiVP and persisted for up to 12 months
- 60% decrease in CHF hospitalizations
- **First to use endocardial LV leads** via the CS
- No significant change in mortality, but a trend towards an improvement.
- Acute hemodynamic studies showed the **mid lateral wall** to be the best site

Reverse Remodeling with CRT

Changes in LVEF, (%) median +/- 95% CI

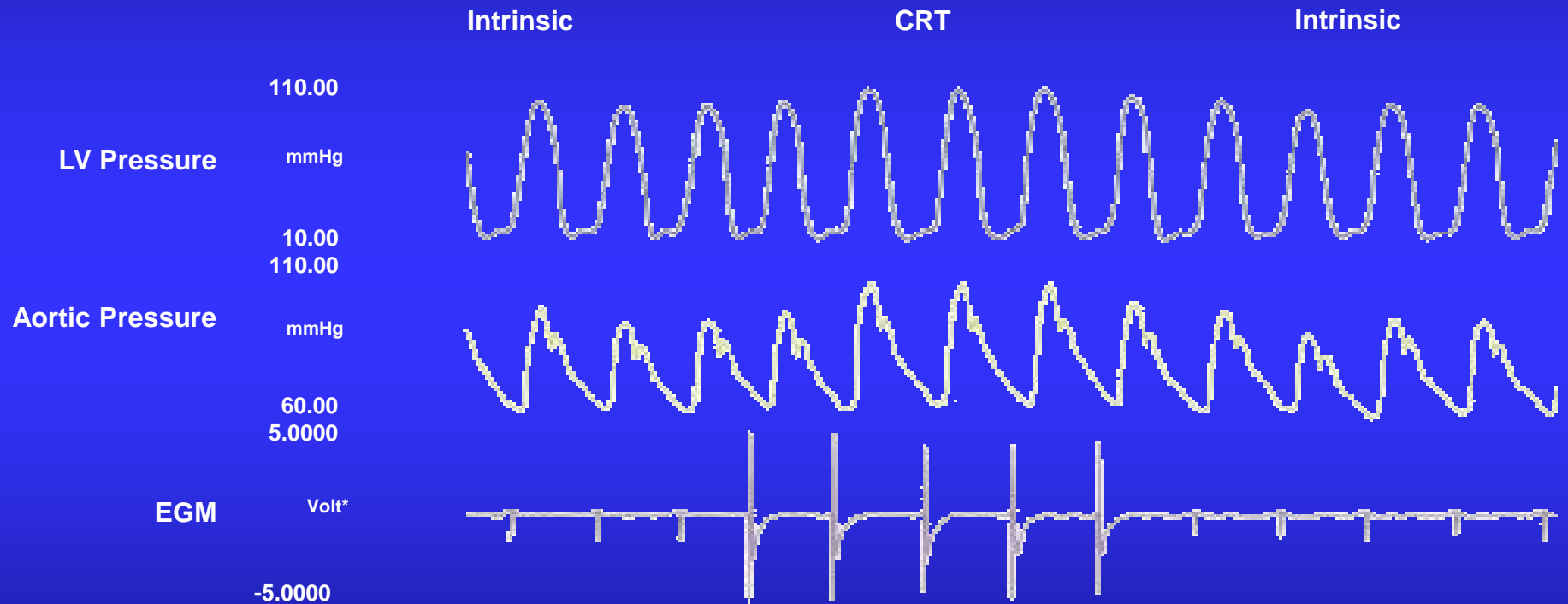


Cardiac Resynchronization Therapy

Myocardial Energetics

Acute Results With CRT

An immediate hemodynamic response



*Voltage scale amplified.

Reprinted with permission.

Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation*. 1999;99:2995.

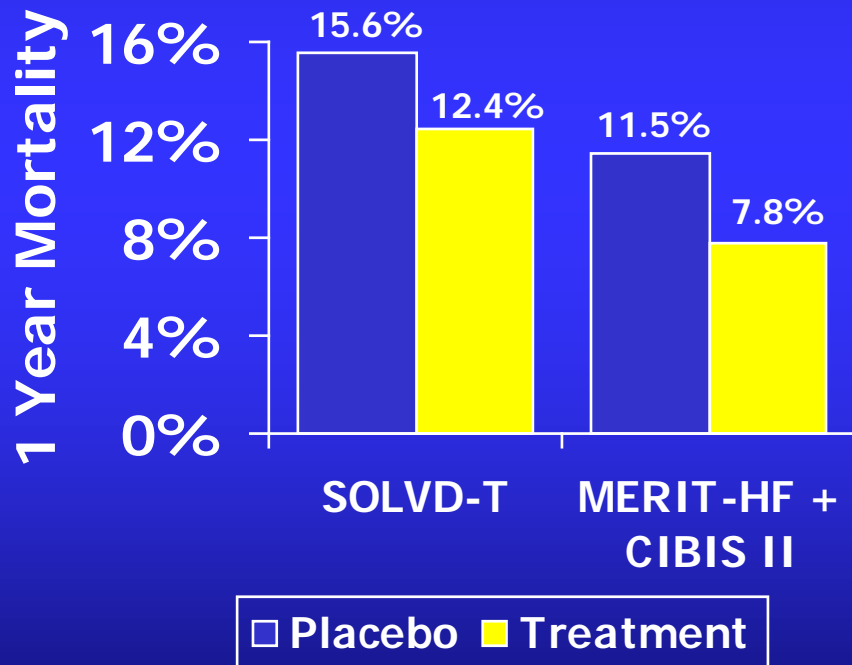
Cardiac Resynchronization Therapy

- A reduction in heart failure symptoms
- Improvement in cardiac performance

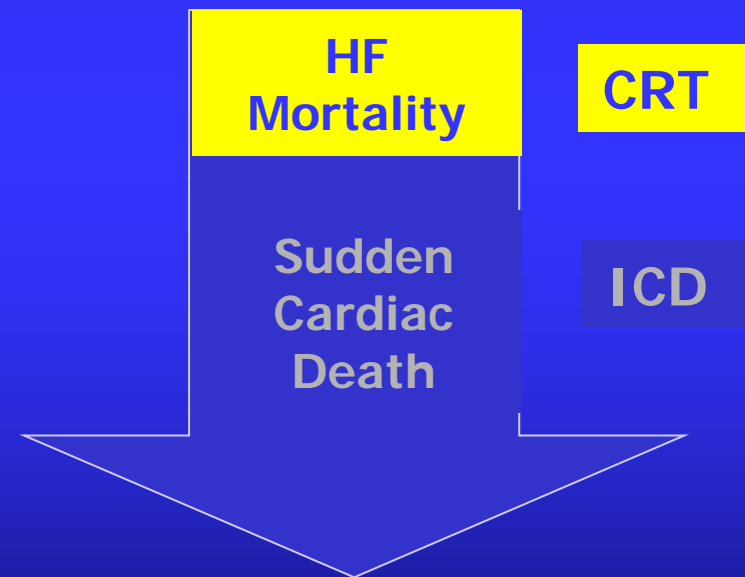
- *Can such therapy reduce hospitalization and improve survival?*

Reduced Mortality in Heart Failure

ACE-I & Beta Blockade
Reduce Mortality

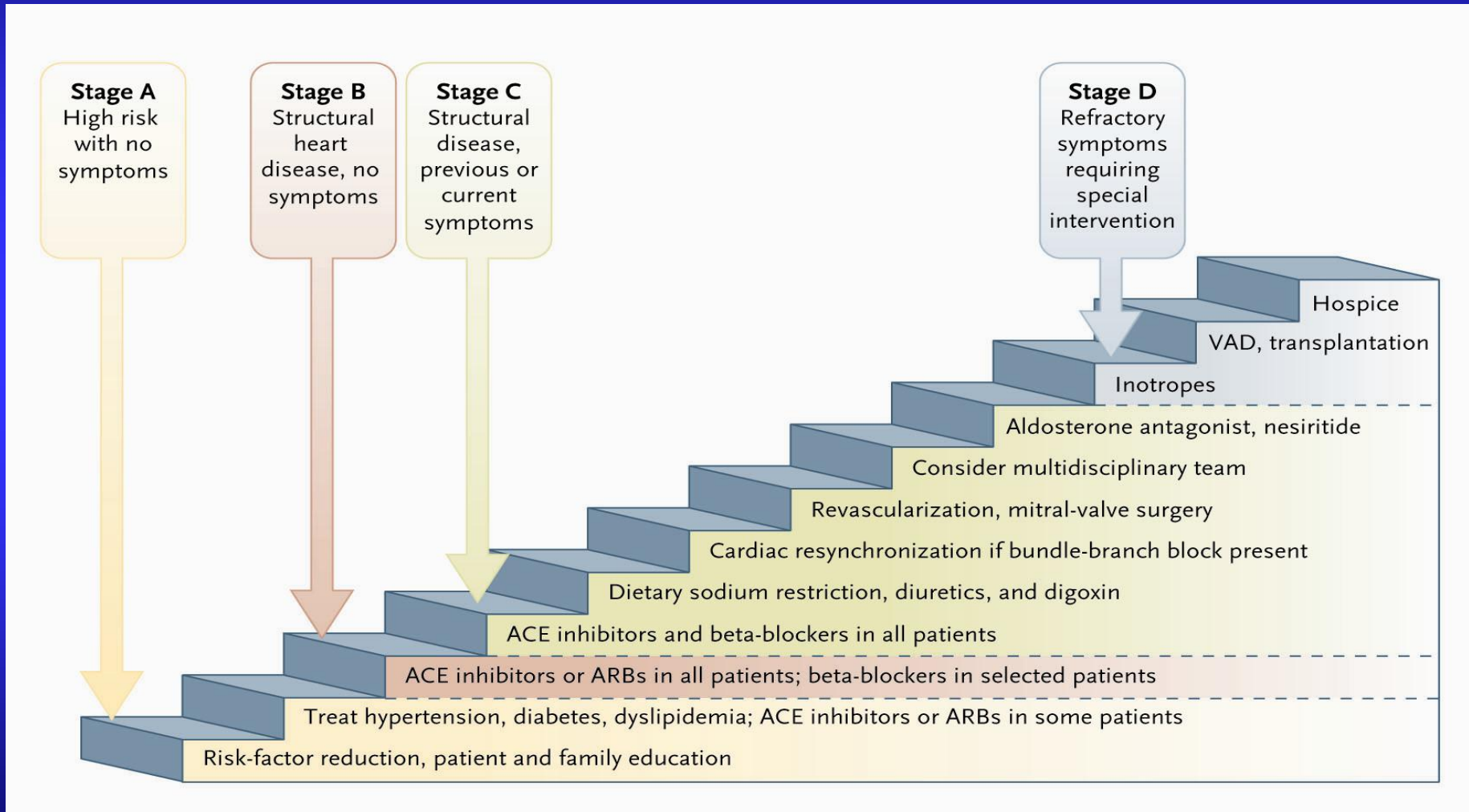


Further Reduction with CRT + ICD
for Higher Risk Patients



Adapted from McMurray JJV; Heart 1999;
82(Suppl IV):IV14-IV22

CRT: Moderate to severe systolic heart failure with wide QRS

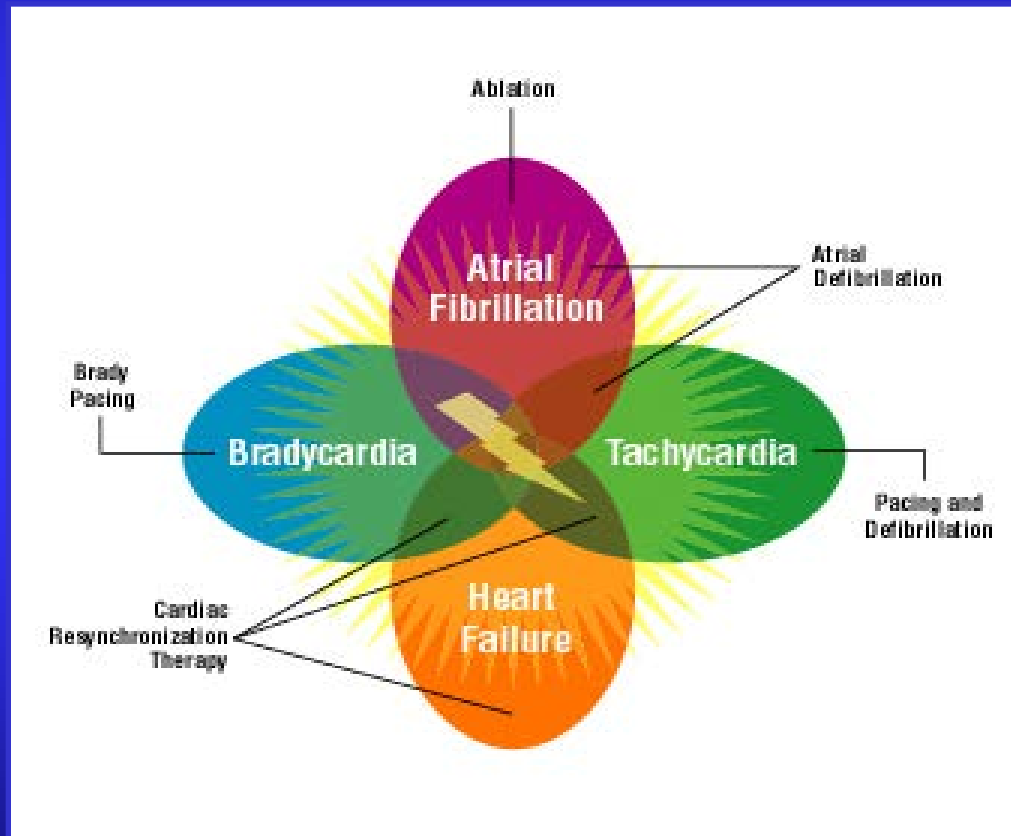


Conclusions

- Large number of patients studied in RCTs
- Concordant proof that CRT improves quality of life, exercise capacity, functional capacity
 - Improvements persist through 1 year
- CRT reduces the risk of mortality and heart failure due to worsening HF
- CRT + ICD reduces risk of mortality
- CRT improves cardiac function and structure

Heart Failure Device Therapy

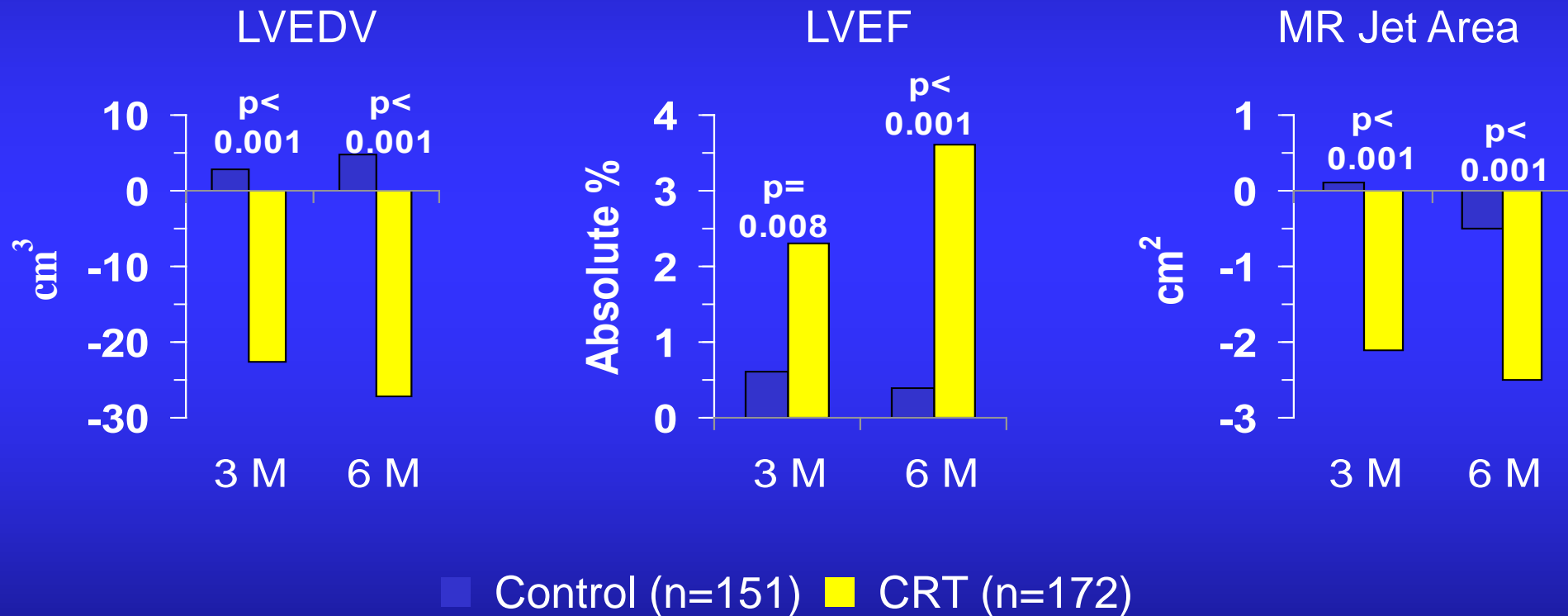
Cardiac rhythm management technology



Cardiac Resynchronization Therapy Overview

Cardiac Resynchronization Therapy Effect on LV Size and Function (MIRACLE)

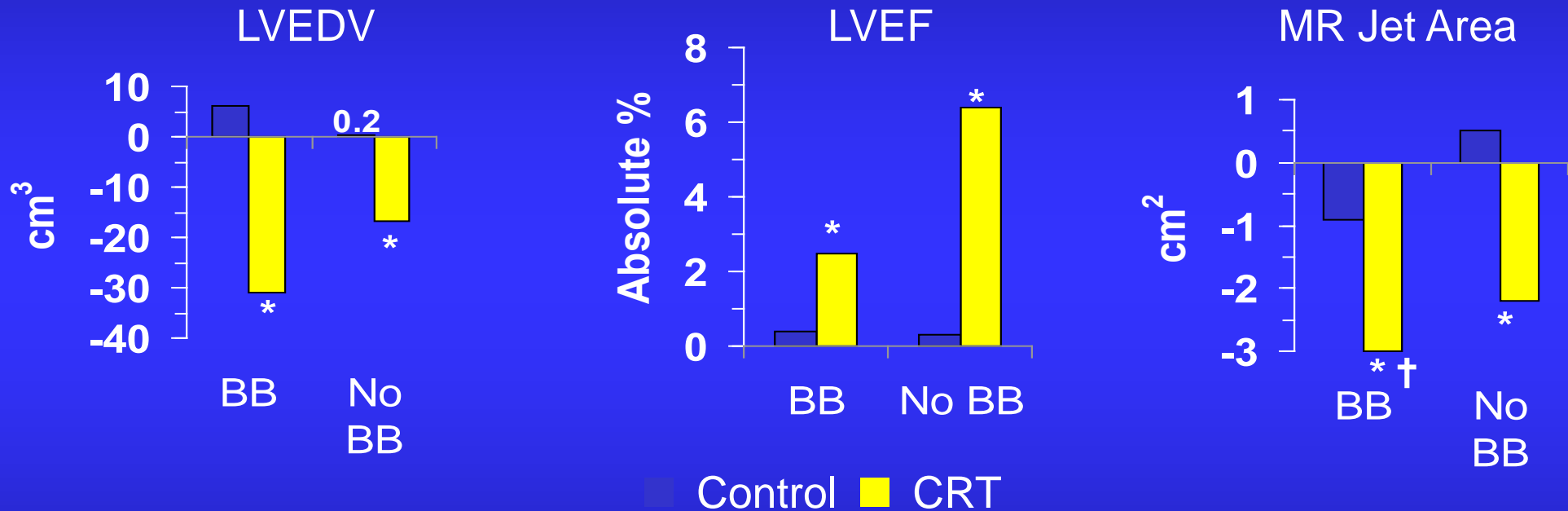
Paired, Median Changes from Baseline



St. John Sutton M, et al. *Circulation* 2003;107:1985-1990

Effect of β -blocker Therapy

Paired, Median Changes from Baseline at 6 Months

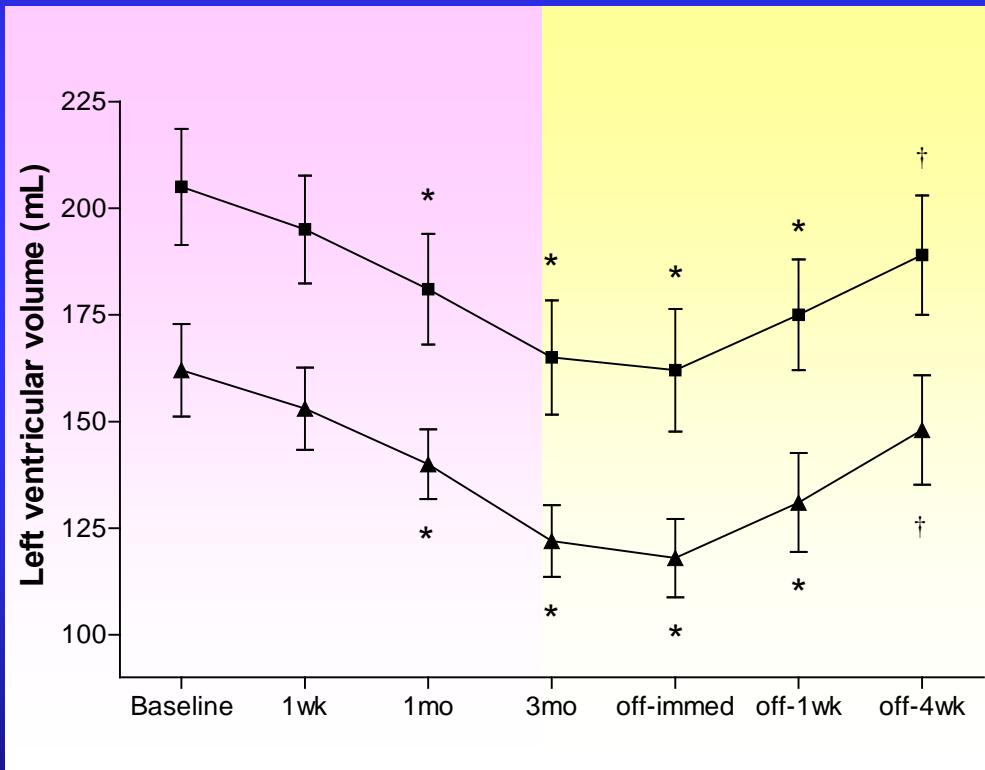


* p < 0.05, CRT vs. Control within subgroups
† p < 0.05, CRT vs. CRT between subgroups

St. John Sutton M, et al. *Circulation* 2003;107:1985-1990

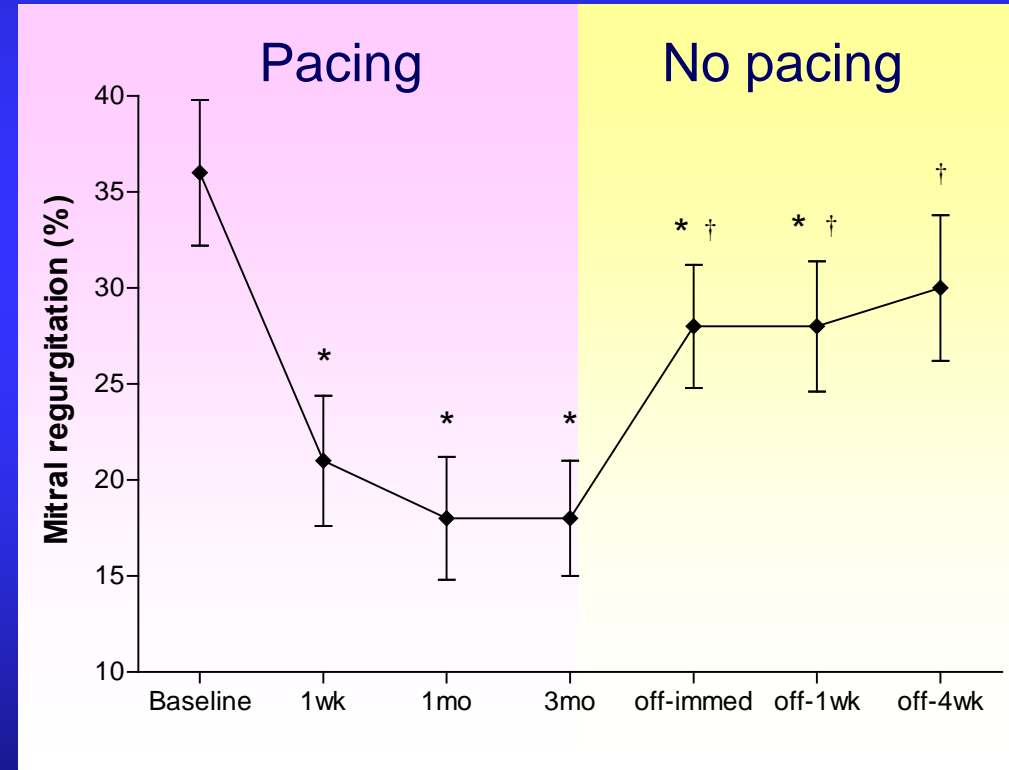
LV Reverse Remodeling after CRT

LV End Systolic and Diastolic Volumes



N = 25

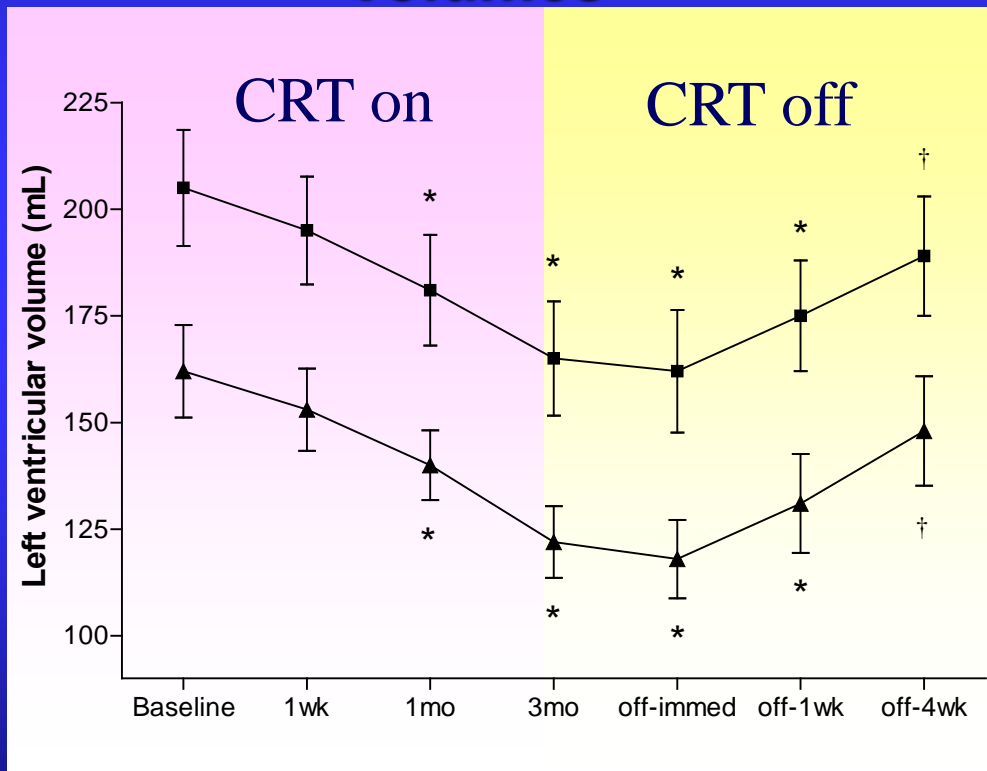
MR area



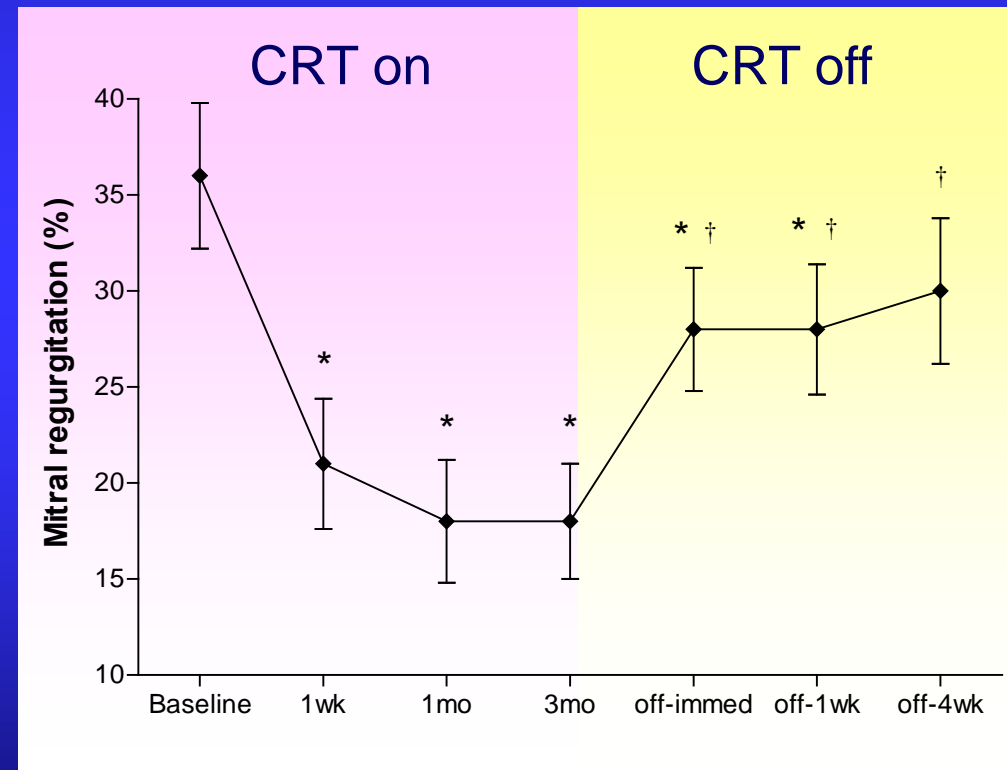
Yu CM, et al, Circulation 2002;105:438-445

LV Reverse Remodeling after CRT

LV End Systolic and Diastolic Volumes



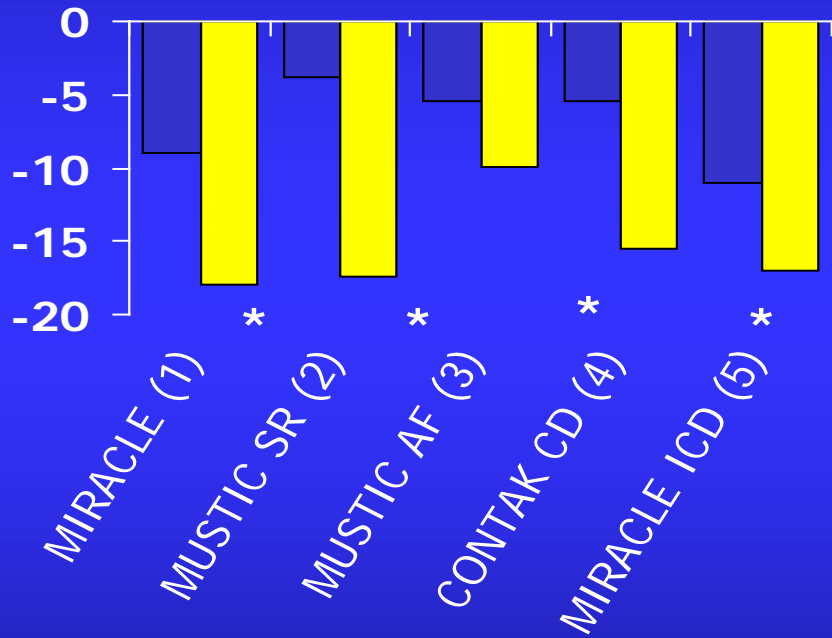
MR area



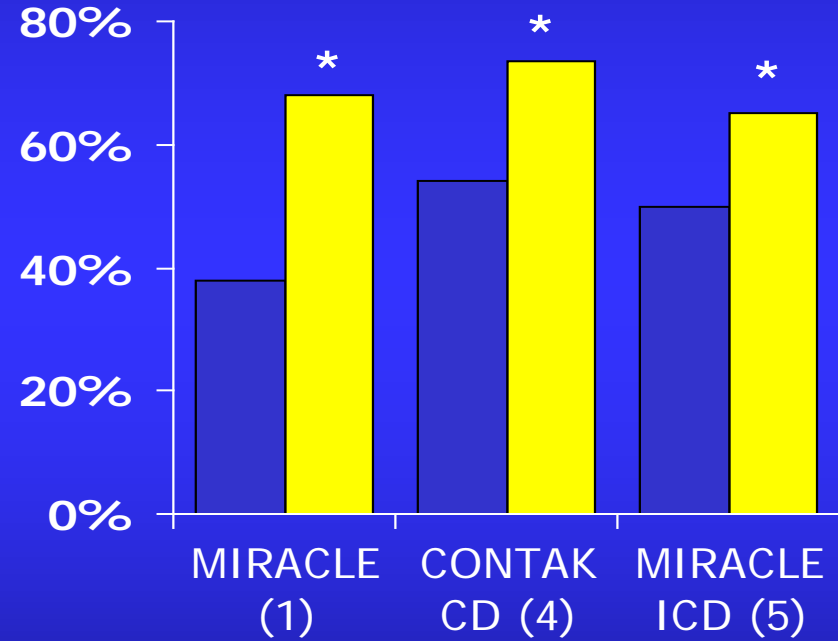
N = 25

Cardiac Resynchronization Therapy Improves Quality of Life and NYHA Functional Class

Average Change in QoL Score (MLWHF)



NYHA: Proportion Improving 1 or More Class



Control CRT

* P < 0.05

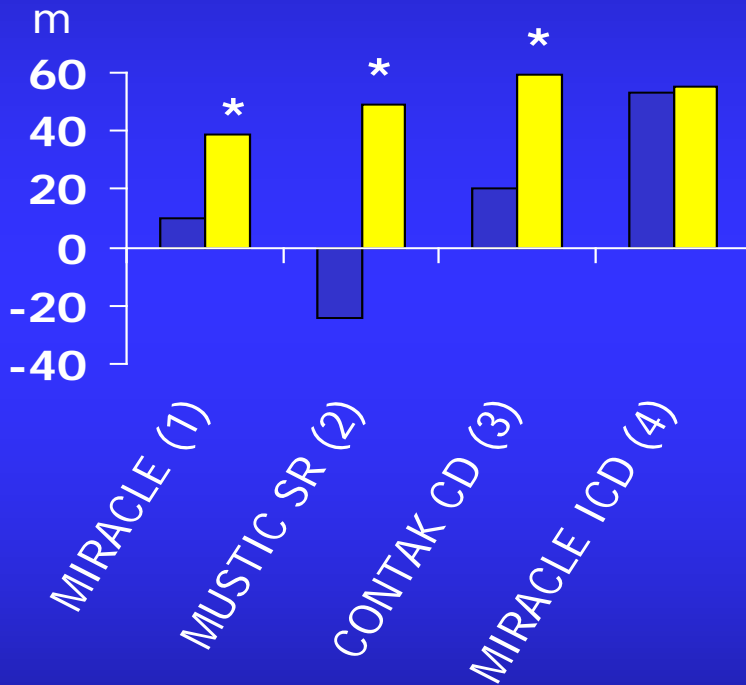
Control CRT

1. *NEJM* 2002;346:1845-53
2. *NEJM* 2001;344:873-80
3. *Eur Heart J* 2002;23:1780-1787
4. <http://www.fda.gov/cdrh/pdf/P010012b.pdf>. Accessed August 2, 2002

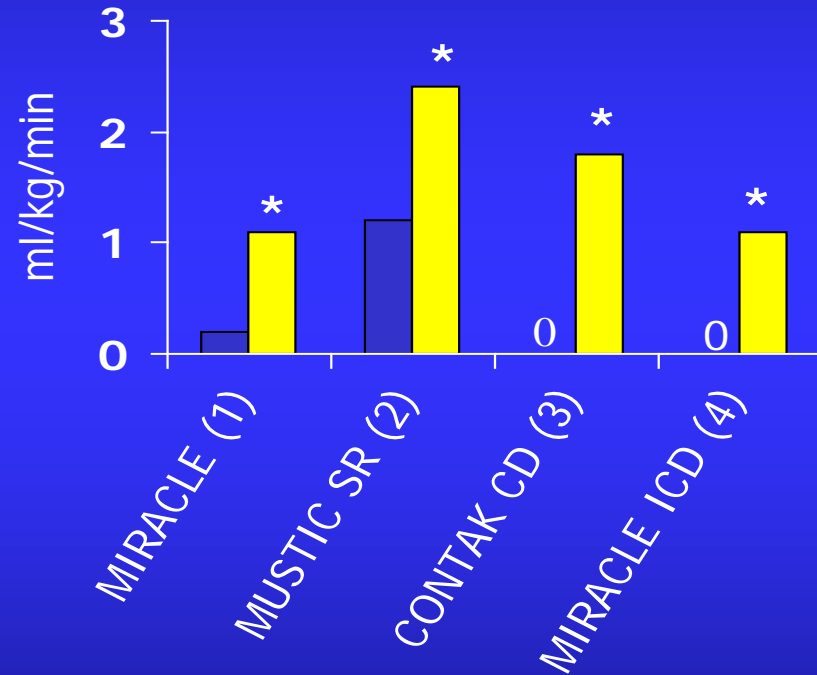
Cardiac Resynchronization Therapy

Improves Exercise Capacity

Average Change in 6 Minute Walk Distance



Average Change in Peak VO₂



■ Control ■ CRT

* P < 0.05

■ Control ■ CRT

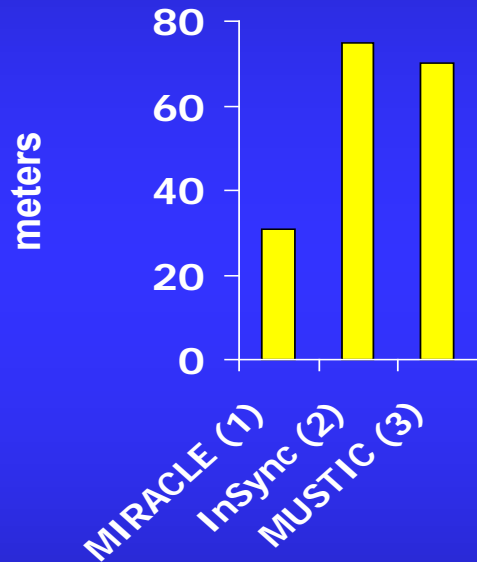
1. *NEJM* 2002;346:1845-53

2. *NEJM* 2001;344:873-80

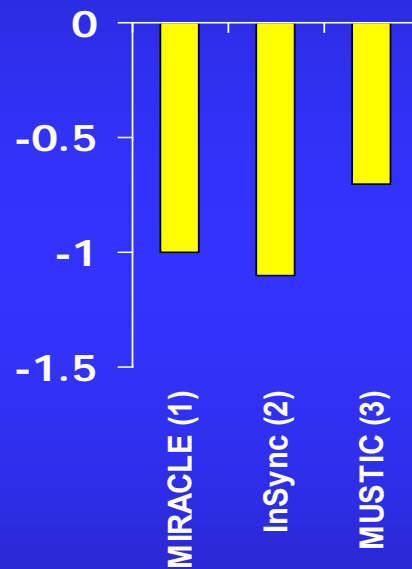
3. <http://www.fda.gov/cdrh/pdf/P010012b.pdf>. Accessed August 2, 2002

Benefits Sustained Through 1 Year

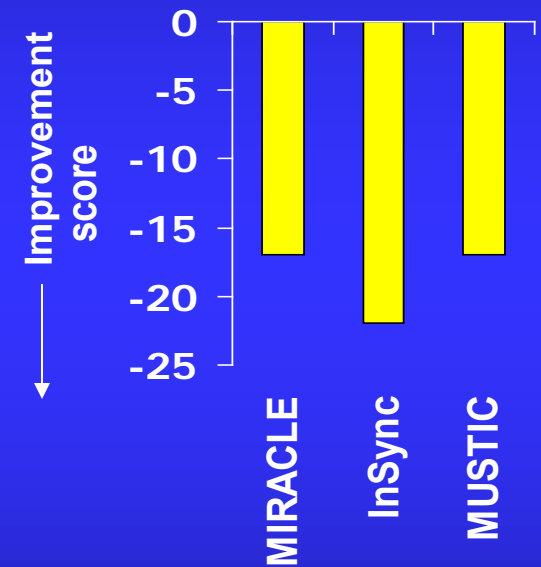
Change from baseline in 6 minute walk distance



Change from baseline in NYHA Class



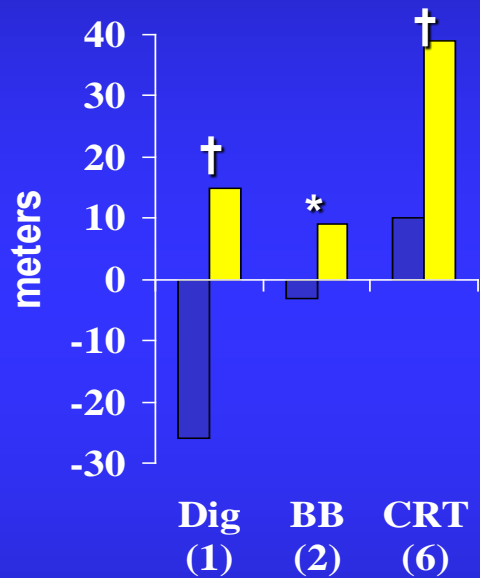
Change from baseline in QoL (MLWHF) Score



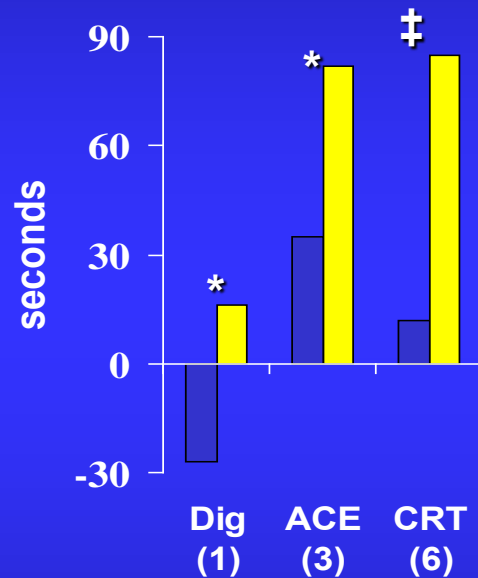
1. *World Congress of Cardiology 2002* (MIRACLE)
2. *Eur J Heart Fail* 2002;4:311-20 (InSync Europe & Canada)
3. *JACC* 2002;4:111-8 (MUSTIC)

Cardiac Resynchronization Therapy: An Adjunct to Optimal Medical Therapy

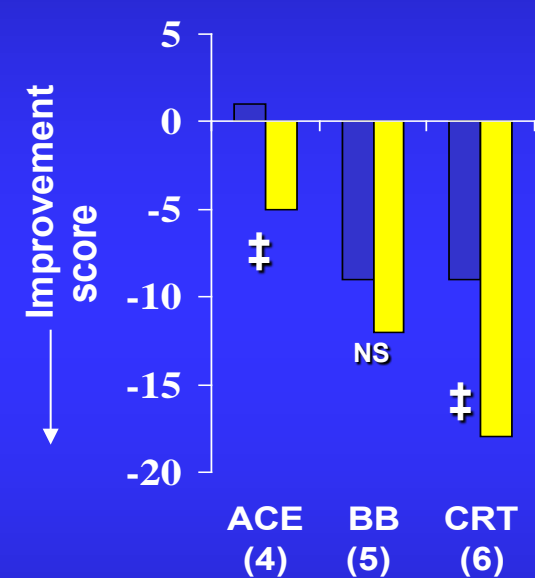
Change from baseline in 6 minute walk distance



Change from baseline in CPX Duration



Change from baseline in QoL (MLWHF) Score



■ Control ■ Treatment

- 1 *NEJM* 1993;329:1-7 (RADIANCE)
- 2 *Circulation* 1996;94:2793-2799 (PRECISE)
- 3 *JAMA* 1988;259:539-544
- 4 *Am J Cardiol* 1993;71:1106-1107 (SOLVD Treatment)
- 5 *J Cardiac Failure* 1997;3:173-179
- 6 *NEJM* 2002;346:1845-53 (MIRACLE)

* P ≤ .05

† P ≤ .01

‡ P ≤ .001

Who Responds to Cardiac Resynchronization?

Responder Parameter(s)	Finding	Limitation(s)
NYHA III/IV, QRS \geq 130 ms, EF \leq 35%, LVEDD \geq 55 mm	Confirmed in RCTs of over 2,500 patients	<input type="checkbox"/> ~ 70% respond favorably
QRS \geq 150/155 and/or dP/dt \leq 700 mm Hg/s	Correlated with improved dP/dt ^{1,2}	<input type="checkbox"/> Small studies, < 30 pts; <input type="checkbox"/> No clinical endpoint <input type="checkbox"/> not confirmed by MIRACLE
Difference in time to peak systolic contraction	Correlated with \downarrow volumes ^{3,4,5}	<input type="checkbox"/> Small studies, \leq 30 pts; <input type="checkbox"/> Varying techniques <input type="checkbox"/> No clinical endpoint
No MI, significant mitral regurgitation	Correlated with improved NYHA ⁶	<input type="checkbox"/> Observational study; <input type="checkbox"/> not confirmed by MIRACLE

1. *Circulation*. 2000;101:2703-2709

2. *Circulation* 1999;99:2993-3001

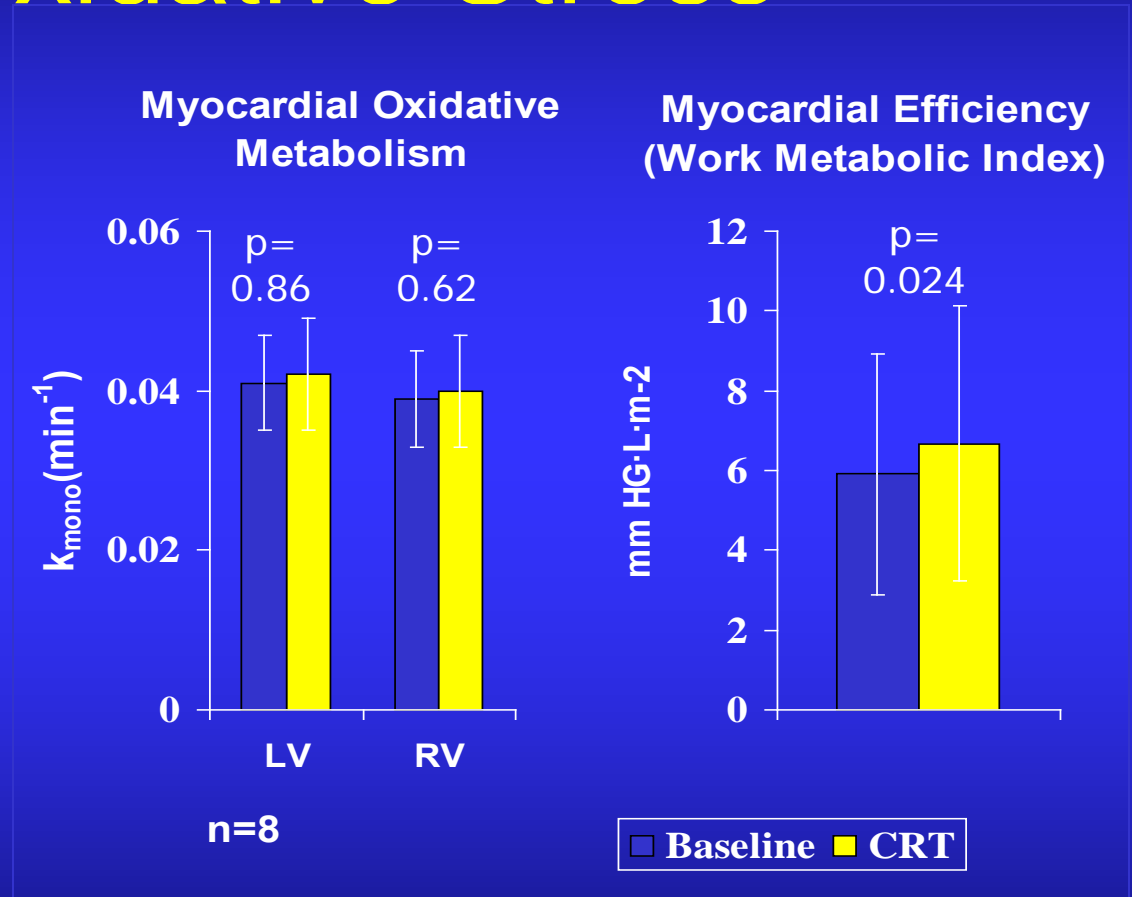
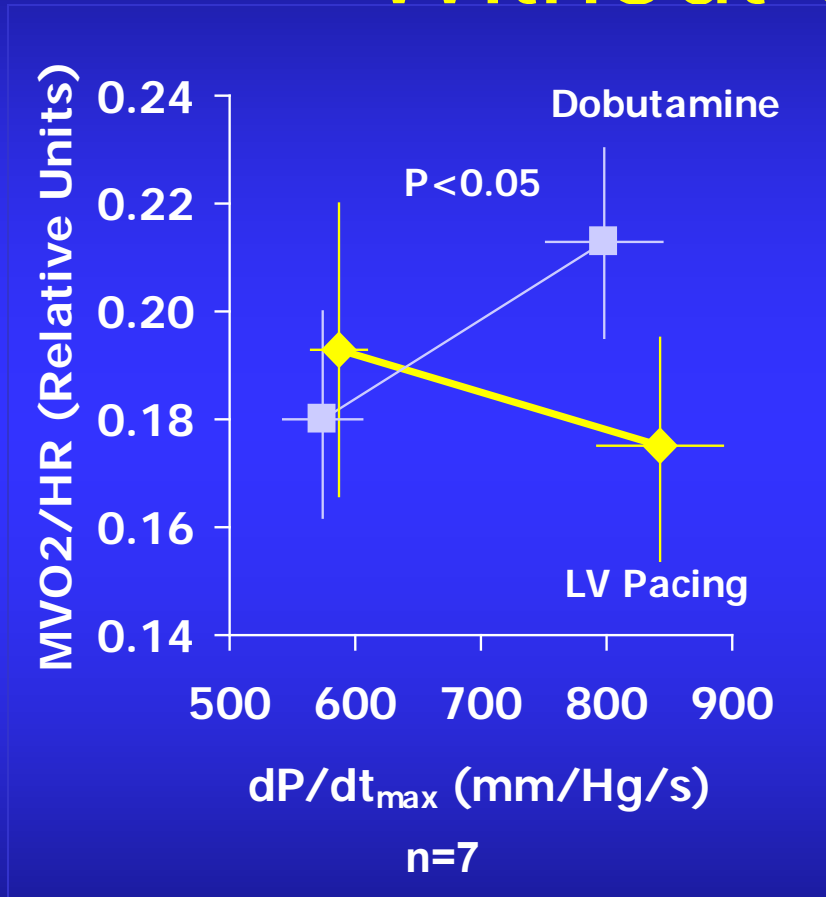
3. *Am J Cardiol* 2002;91:684-688

4. *J Am Coll Cardiol* 2002;40:1615-1622

5. *J Am Coll Cardiol* 2002;40:723-730

6. *Am J Cardiol* 2002;89:346-350

Improved Cardiac Function Without Oxidative Stress



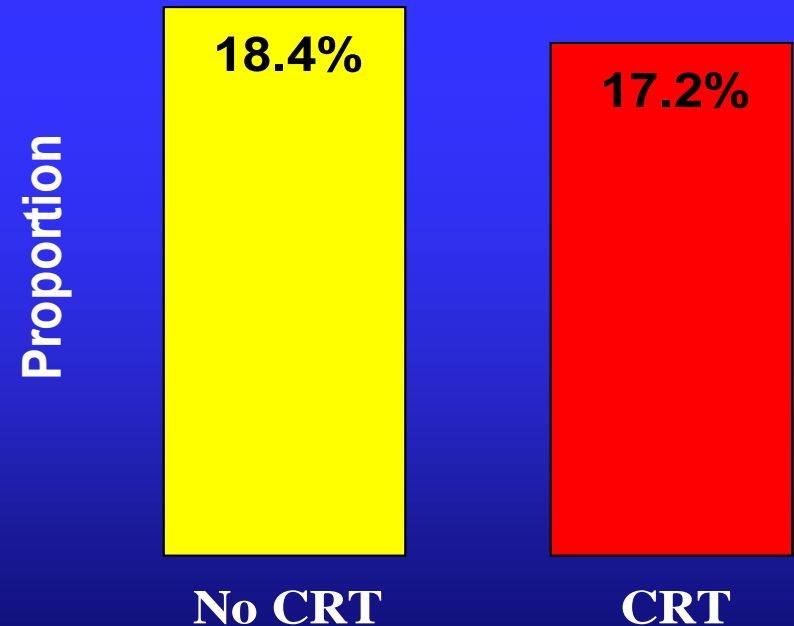
Nelson et al. *Circulation* 2000;102:3053-3059

Ukkonen et al. *Circulation* 2003;107:28-31

Cardiac Resynchronization Therapy Does Not Promote Ventricular Arrhythmias

- Analyzed 1,044 patients with ICDs from 2 trials:
 - CONTAK CD
 - MIRACLE ICD
- Odds ratio (CI):
0.92 (0.67 – 1.27)

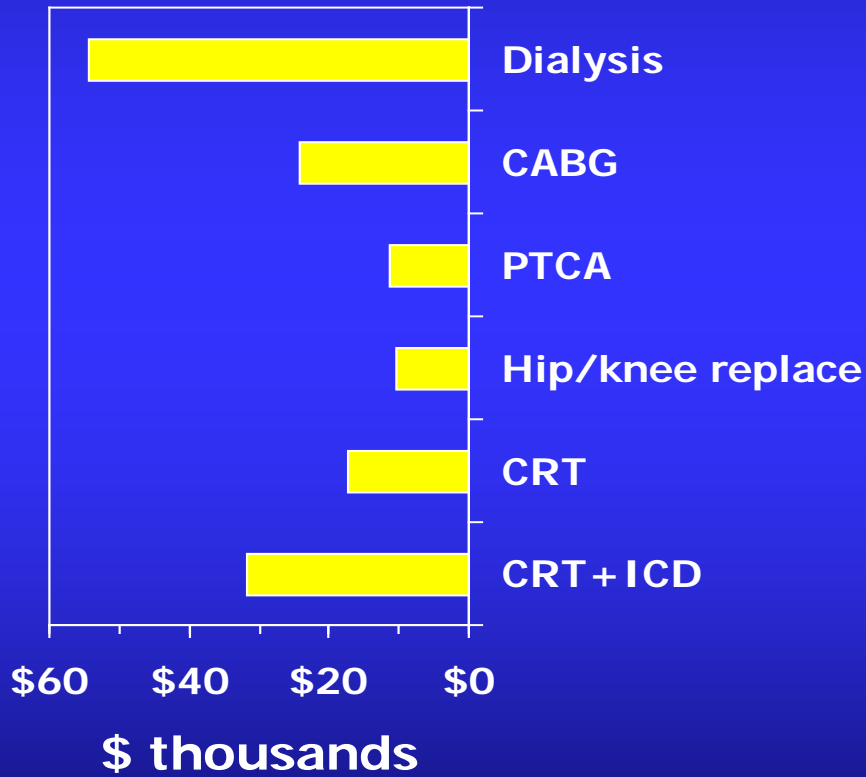
Patients with VT or VF during Follow-up



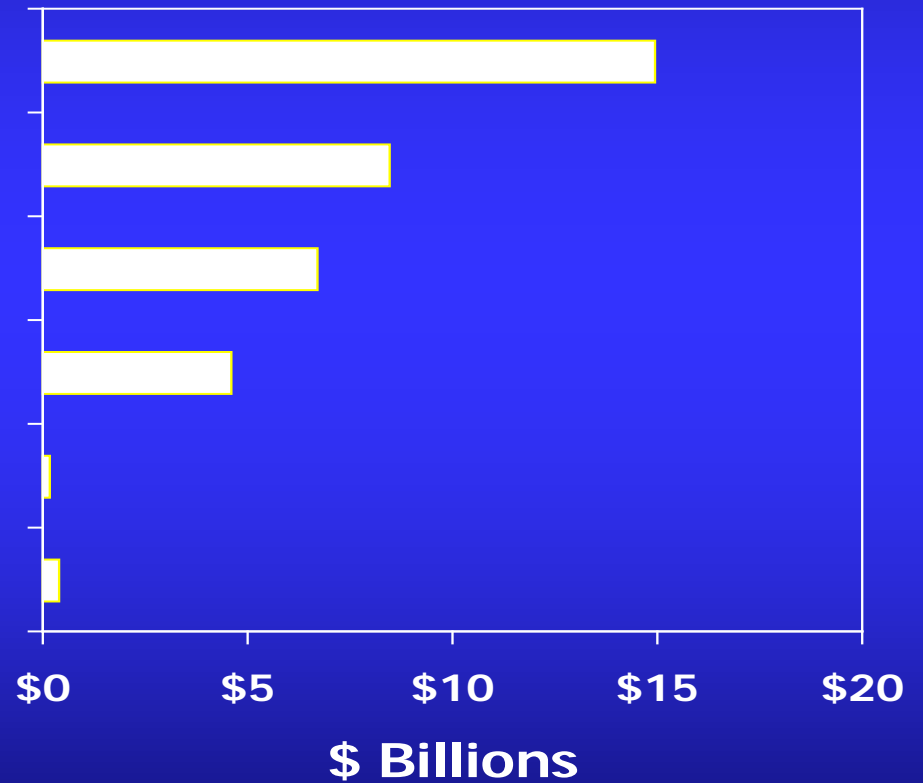
Bradley DJ, et al. JAMA 2003;289:730-740

Relative Cost of CRT

Cost per patient



Total Annual Expenditures



MADIT-II

Multicenter Automatic Defibrillator Implantation Trial - II

MADIT-II Hypothesis

ICD therapy is able to reduce overall mortality
assuming:

- Mortality in control = 19%
- Mortality in ICD = 11.8%
- 38% reduction in mortality at 2 years

MADIT-II Inclusion Criteria

- Q-wave MI \geq 4 weeks
- LVEF \leq 0.30
- \geq 21 years of age; no upper age limitation
- No requirement for NSVT or EPS

MADIT-II Exclusion Criteria

- Indication for ICD approved by FDA
- NYHA Class IV at enrollment
- CABG < 3 months
- Q-wave MI < 4 weeks
- Advanced cerebrovascular disease
- High likelihood of death during trial

MADIT-II Endpoints

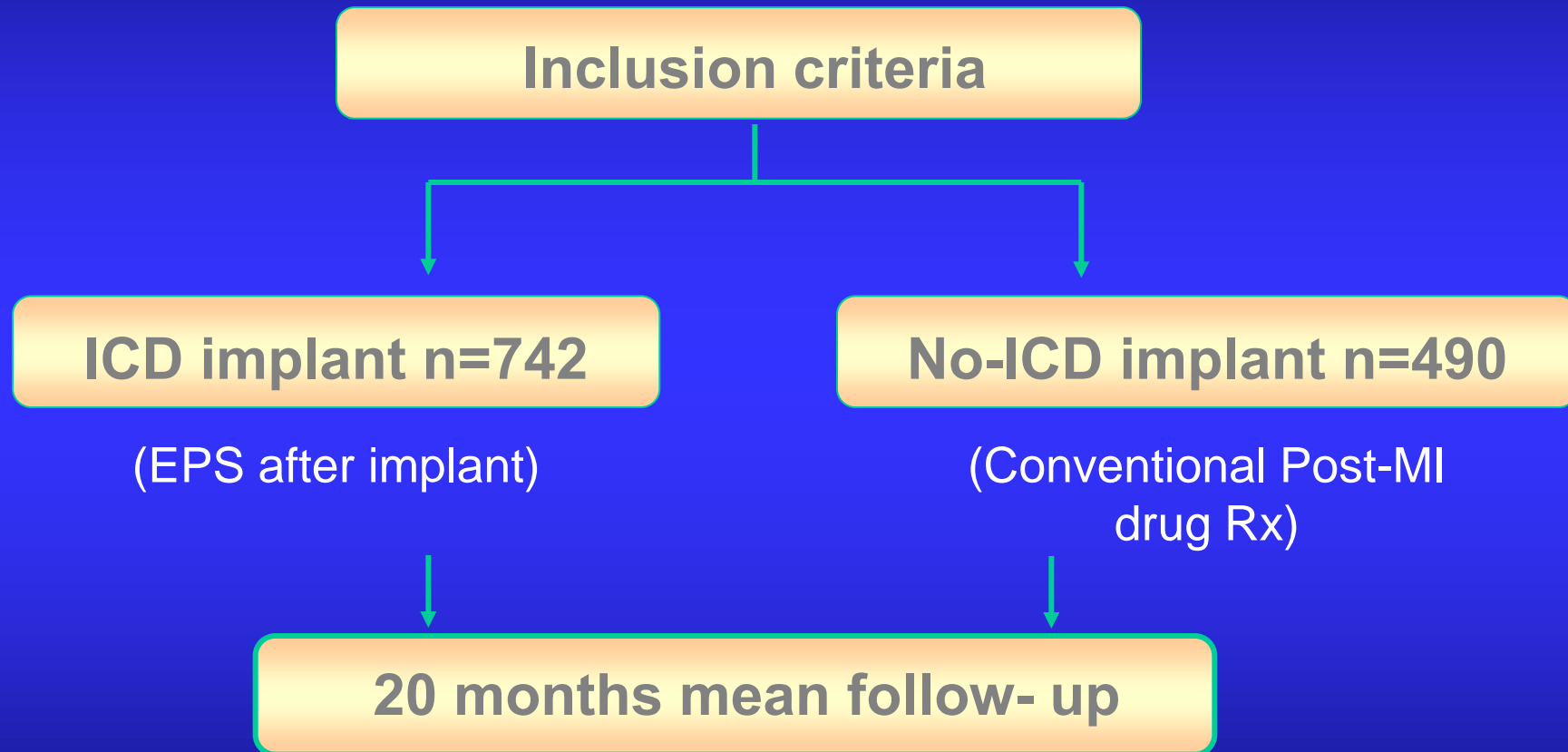
Primary:

- All cause mortality
(intention-to-treat analysis)

Secondary:

- Predictability of ICD discharge based on VT inducibility at EPS
- Usefulness of SAECG, HRV, TWA in predicting mortality or ICD discharge
- Cost-effectiveness
- Quality of life

MADIT-II Protocol



- **Avoid AAD**
- **Optimize: BB, ACE-I, Diuretics**

MADIT-II

Patient Characteristics

	Conventional Rx n =490	ICD Rx n=742
LVEF (mean)	23%	23%
AMI > 6 mos	87%	88%
AGE (mean)	64 yr	65 yr
Prior CABG	56%	58%
Prior PTCA	42%	45%

MADIT-II

Patient Characteristics

	Conventional Rx n =490	ICD Rx n=742
NYHA Class I	39%	35%
II	34%	35%
III	23%	25%
IV	4%	5%
QRS interval \geq 0.12 sec	50%	51%

MADIT-II

Patient Characteristics

Medications at Last Contact	Conventional Rx n =490	ICD Rx n=742
ACE I	72%	68%
Beta Blockers	70%	70%
Lipid Lowering Statins	64%	67%
Digitalis	57%	57%
Amiodarone	10%	13%
Class I AA	2%	3%

MADIT-II Results

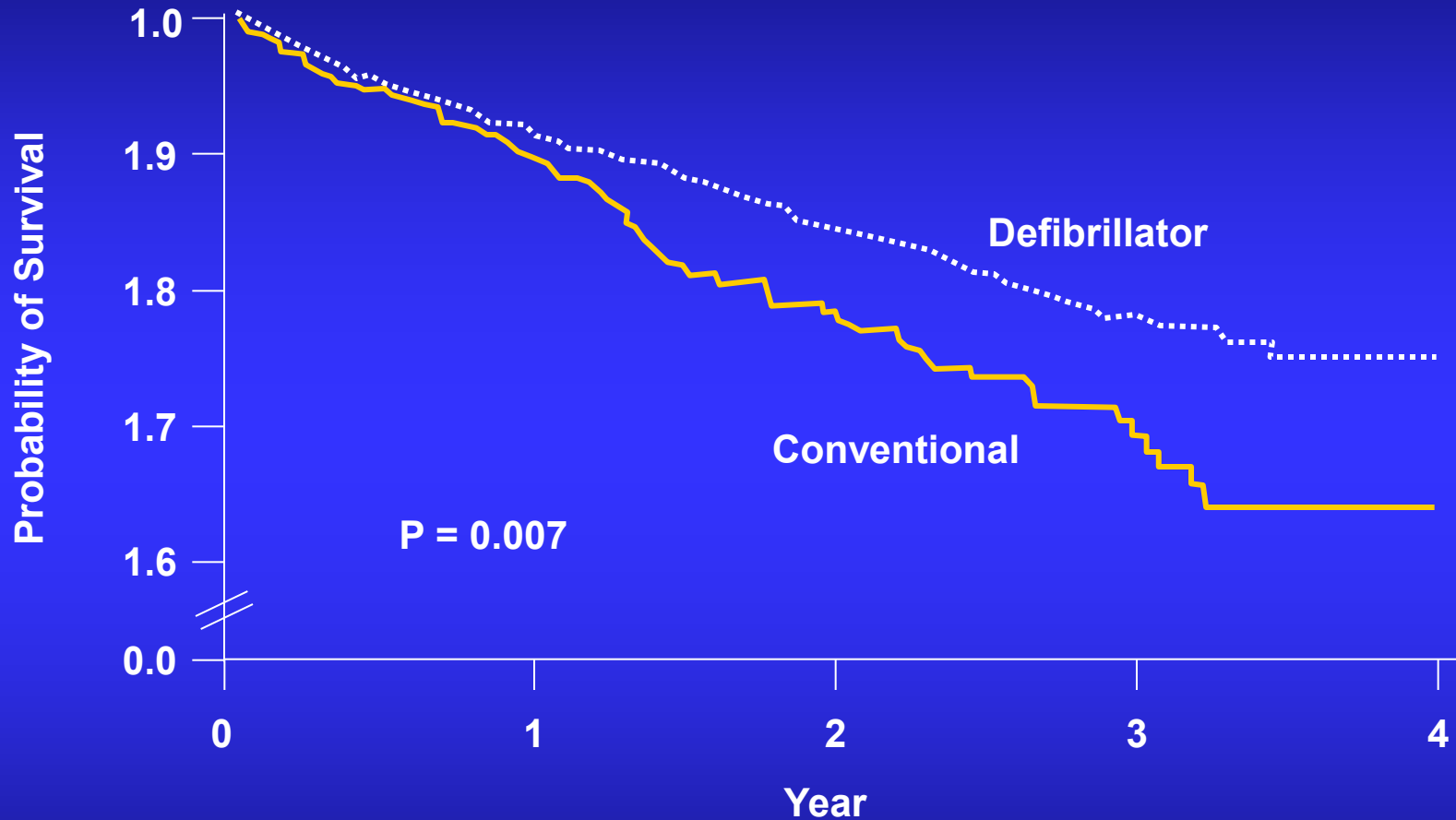
	Conventional Rx n =490	ICD Rx n=742
Lead Problems	-	1.8%
Non-fatal Infections	-	0.7%
Heart Failure Hospitalization	14.9%	19.9%

MADIT-II Conclusions

For post-MI patients with LVEF \leq 30%:

- ICD therapy significantly reduced the incidence of overall mortality by 31%
- ICD therapy provided significant benefit among patients who were on optimal drug therapies.

MADIT-II Survival Results

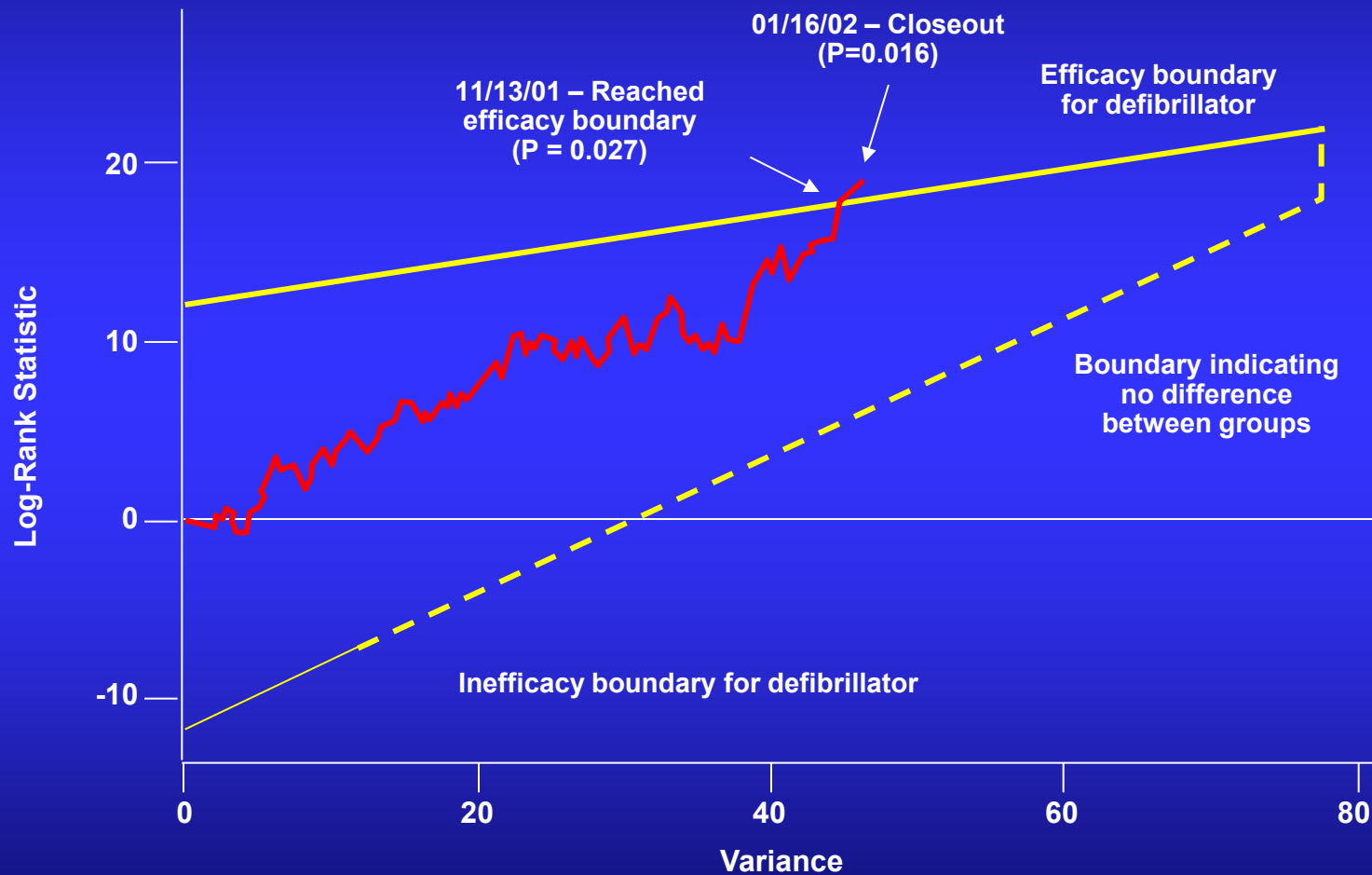


No. At Risk

Defibrillator	742	502 (0.91)	274 (0.94)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

MADIT-II Statistical Analysis

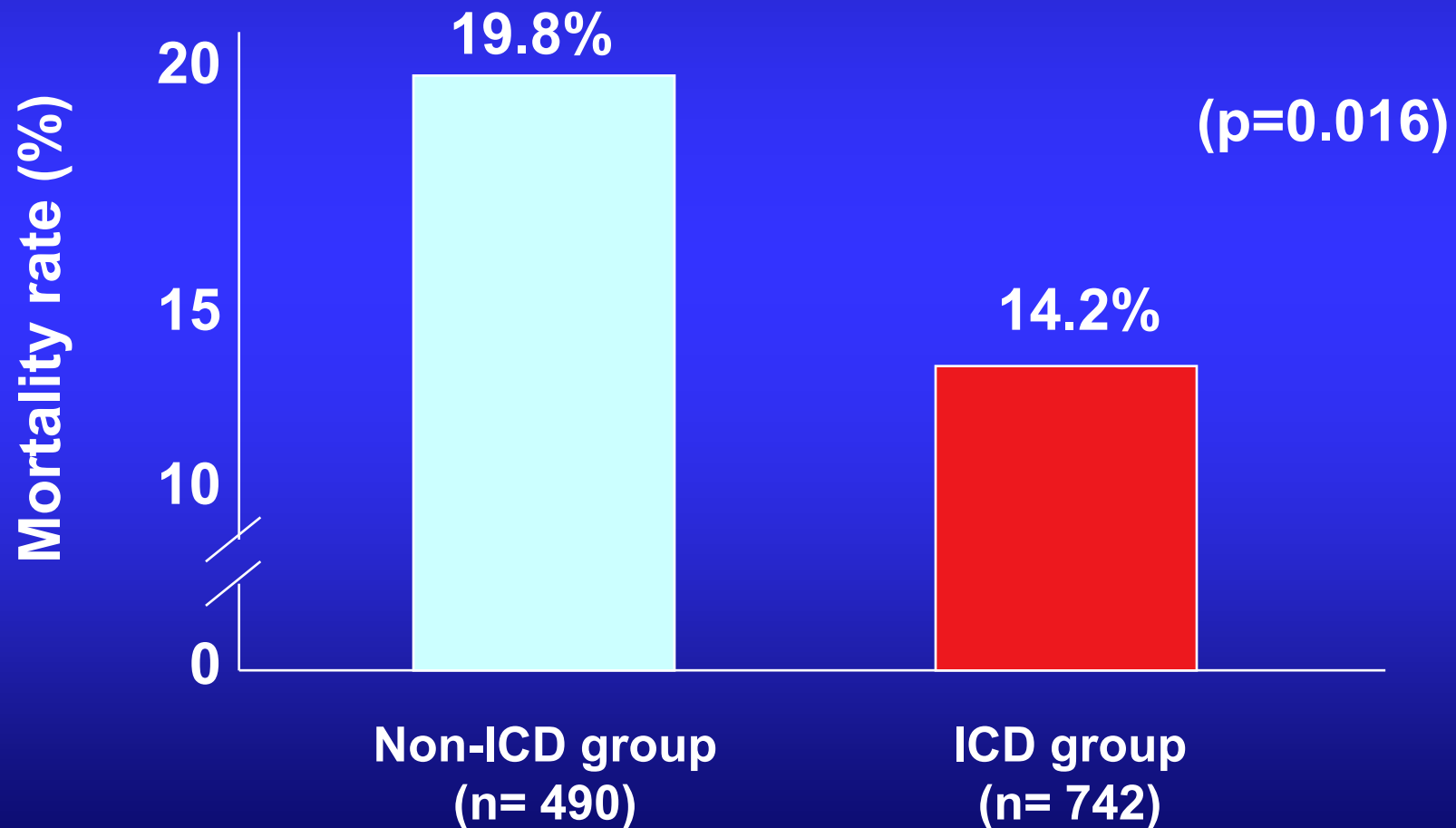
Triangular Sequential Design



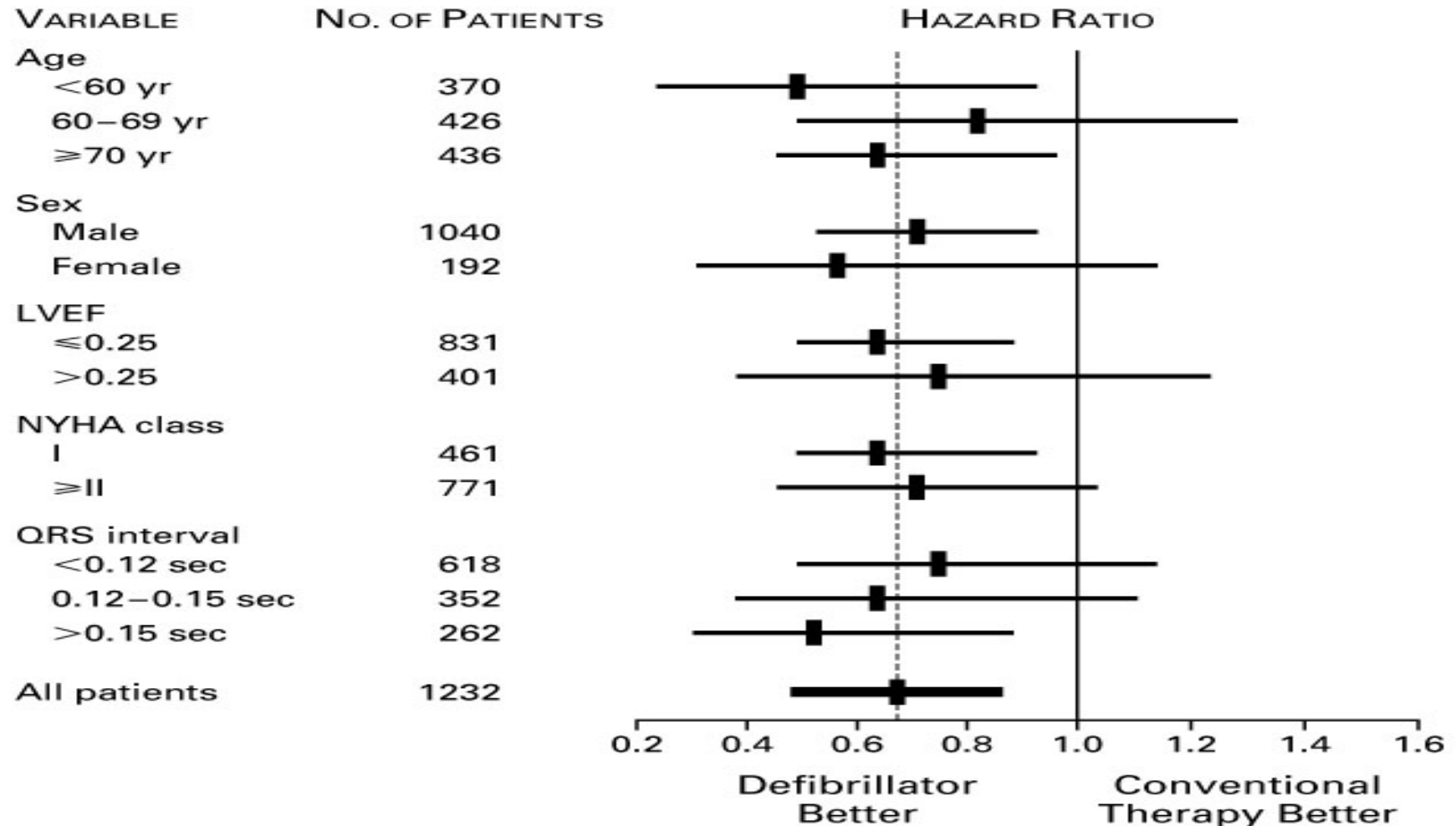
Sequential Monitoring in the Triangular Design

Mortality rate by type of therapy

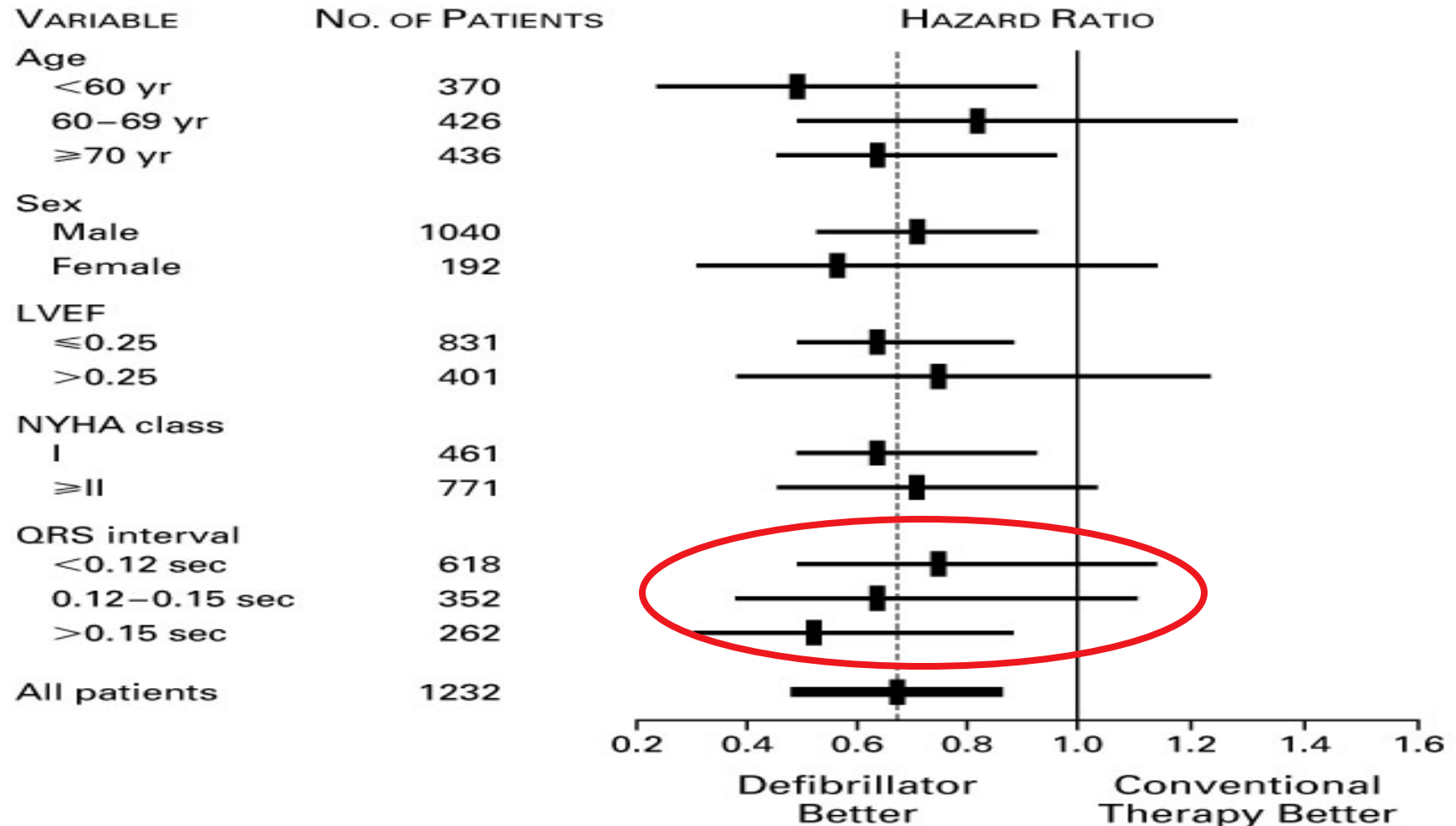
MADITT-II, mean follow-up 20 months



MADIT-II: Survival Results



MADIT-II: Survival Results



Hospitalizations for heart failure by type of therapy

MADITT-II, mean follow-up 20 months

