Heart Failure Management Update

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Heart Failure - Definition

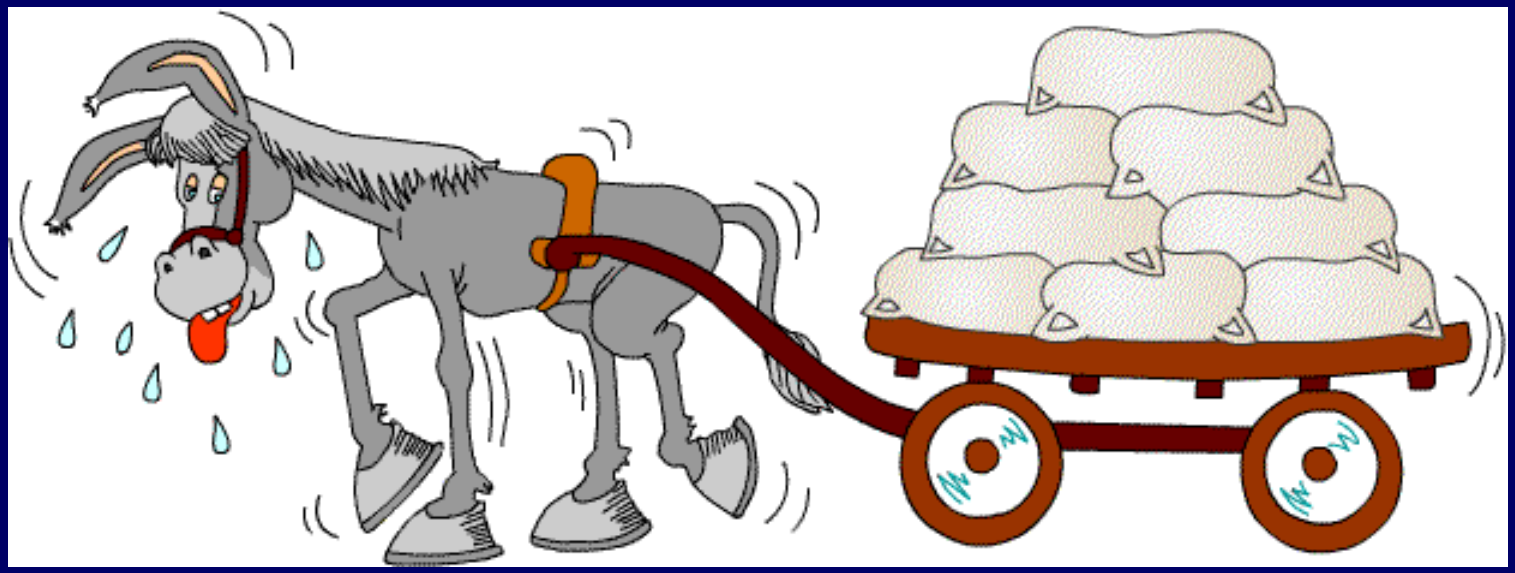
The situation when the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements of the body and venous return

Congestive Heart Failure - Definition

+ Volume overload

The Donkey Analogy

Heart dysfunction limits a patient's ability to perform the routine activities of daily living…



CHF: Epidemiology

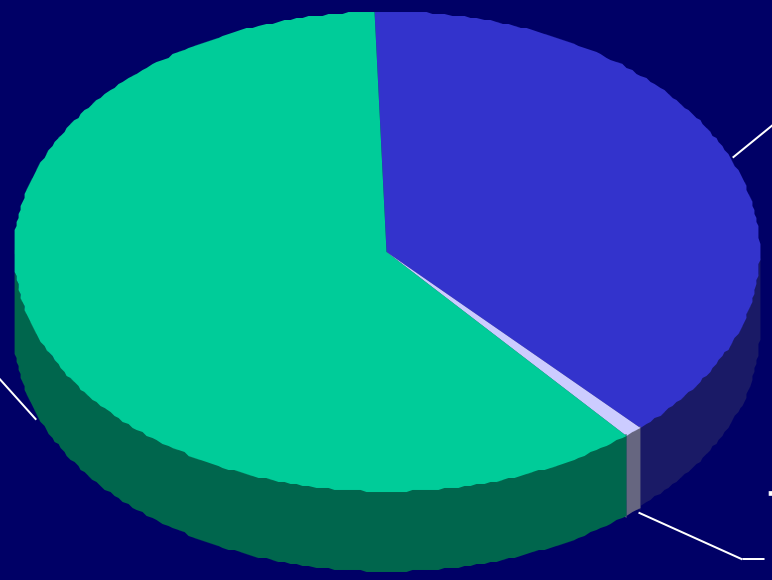
- 5 million Americans have heart failure
- 550,000 new cases diagnosed annually
- Over 250,000 deaths annually
- Over 850,000 hospitalizations annually
- Economic impact $40 billion dollars annually
- Incidence and prevalence increasing

Source:AHA,CDC

CHF:Epidemiology

- Significant increase in morbidity and mortality
- Prevalence 2-6%
- 150% increase over past 20 yrs.
  - Aging population
  - Improved outcome of ACS
  - AICD

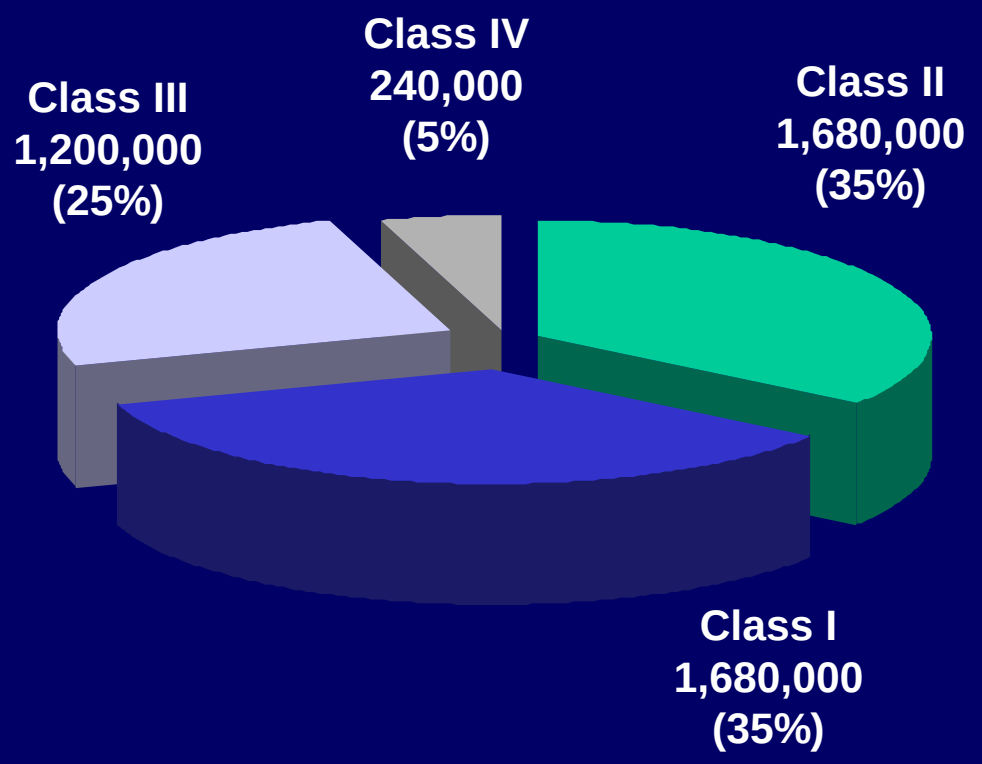
Hospitalization: The Predominant Contributor to CHF Costs



Total = $38.1 billion
(5.4% of total healthcare coats)

O'Connell JB et al. *J Heart Lung Transplant.* 1994;13:S107-S112

CHF Patient Population by NYHA Class



Class I
No limitations of physical activity
Class II
Slight limitations of physical activity
Class III
Marked limitations of physical activity
Class IV
Symptomatic at rest

Source: American Heart Association

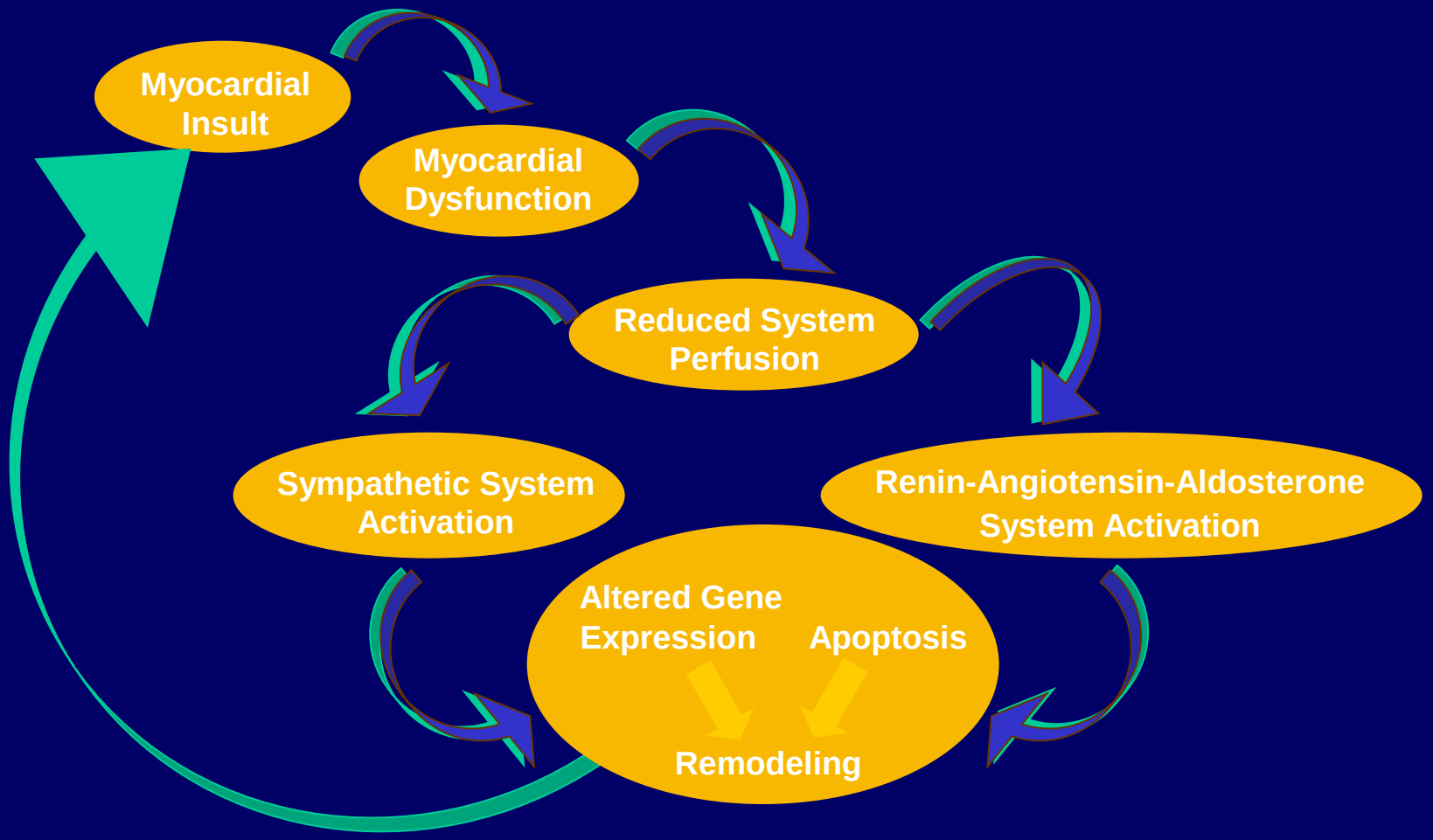
ACC-AHA Clinical Classification

ACC-AHA Stage	NYHA Functional Classification
A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)	None
B Structural heart disease but without symptoms of heart failure	I Asymptomatic
C Structural heart disease with prior or current symptoms of heart failure	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Refractory heart failure requiring specialized interventions	IV Symptomatic at rest

Farrell M et al, *JAMA* 2002

Pathogenesis of Heart Failure

Complex cascade



Etiology

- Systolic Failure
  - CAD
  - HTN
  - Dilated Cardiomyopathy
    - Idiopathic
    - Toxic
      - ETOH
      - Doxorubicin
    - Infection
      - Viral
      - Parasites
      - Other
    - Hemochromatosis

- Diastolic Failure
  - HTN
  - HCM
  - Restrictive Cardiomyopathy
    - Amyloidosis
    - Sarrcoidosis
  - Constrictve Pericarditis
  - High-output failure
    - Chronic anemia
    - AV shunts
    - Thyrotoxicosis

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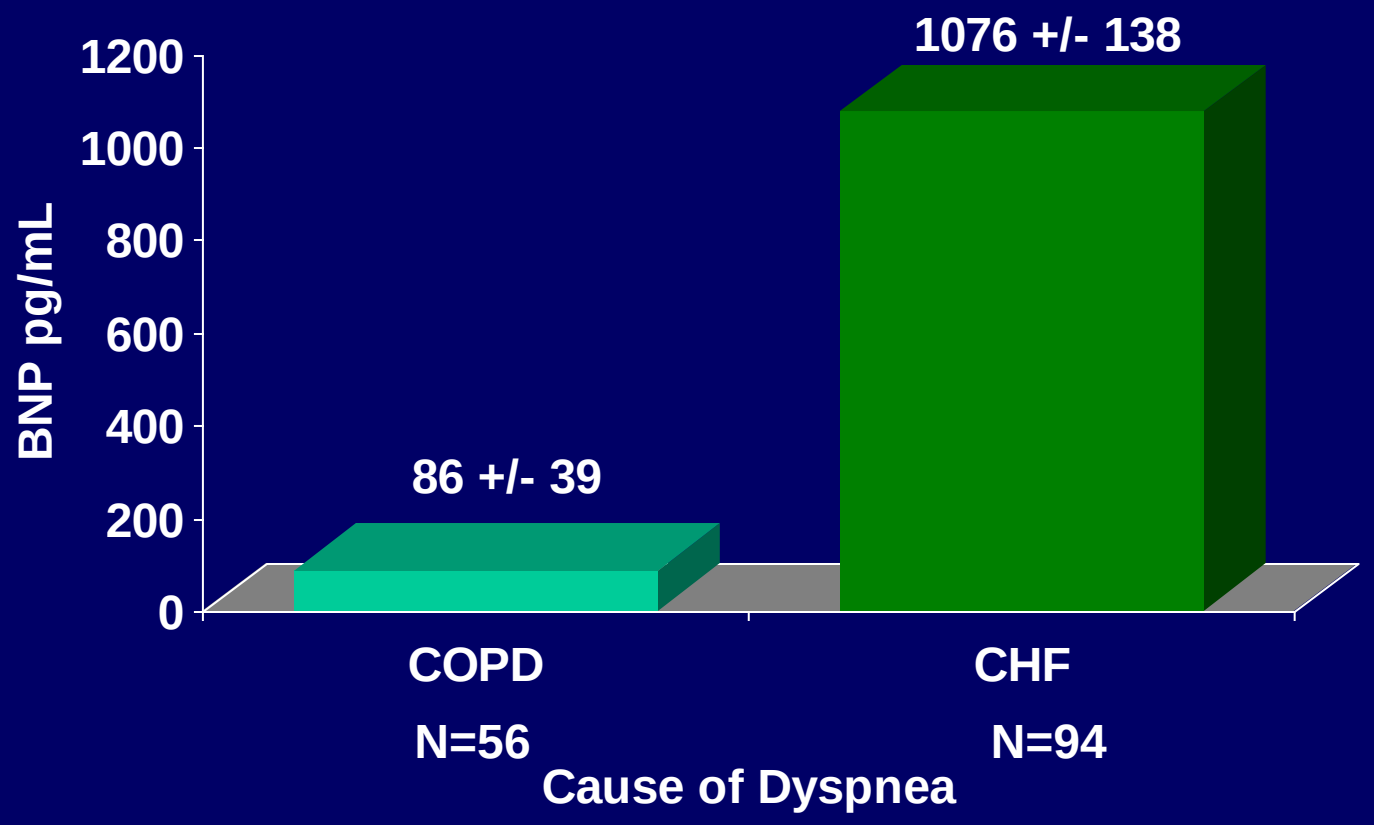
Diagnostic Work up

- CBC, urine analysis, BMP, LFT, TSH, BNP
- ECG
- CXR
- Echocardiography
  - Systolic dysfunction
  - Diastolic dysfunction
  - Wall motion abnormality
  - Valvular dysfunction
- Cardiac Catheterization
- Noninvasive imaging to detect ischemia
- Endomyocardial biopsy (IIb)

BNP

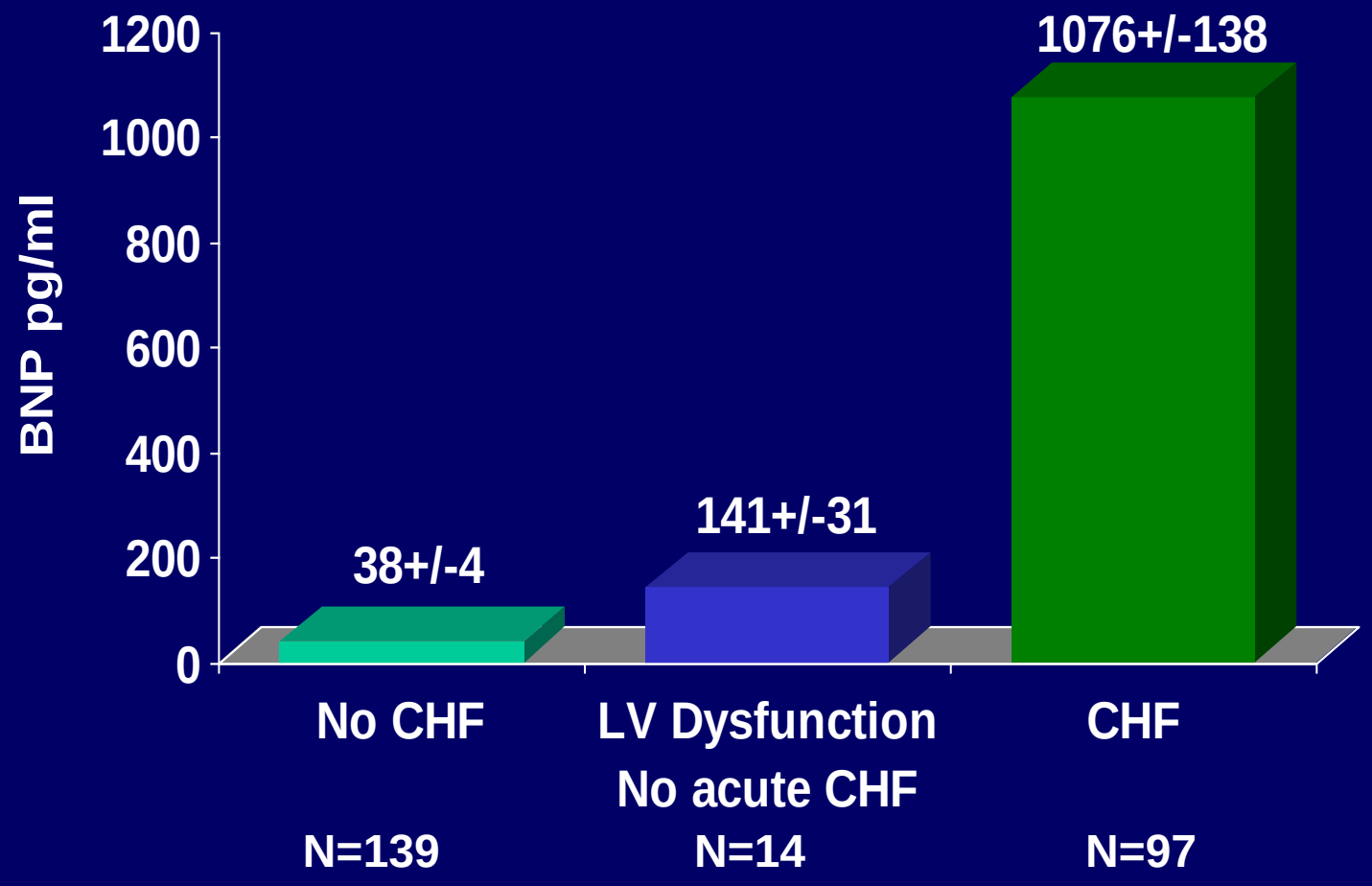
- B-type natriuretic peptide is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides
- Major source of plasma BNP is cardiac ventricles.
- BNP may be a more sensitive and specific indicator of ventricular disorders

BNP Levels in Patients With Dyspnea Secondary to CHF or COPD



Dao, Q., Maisel, A. et al. *J. American College of Cardiology*, Vol 37, No. 2, 2001

BNP Levels of Patients Diagnosed Without CHF, With Baseline Left Ventricular Dysfunction, and With CHF



Dao, Q., Maisel, A. et al. *J. American College of Cardiology*, Vol 37, No. 2, 2001

Treatment Goals in the Management of Heart Failure

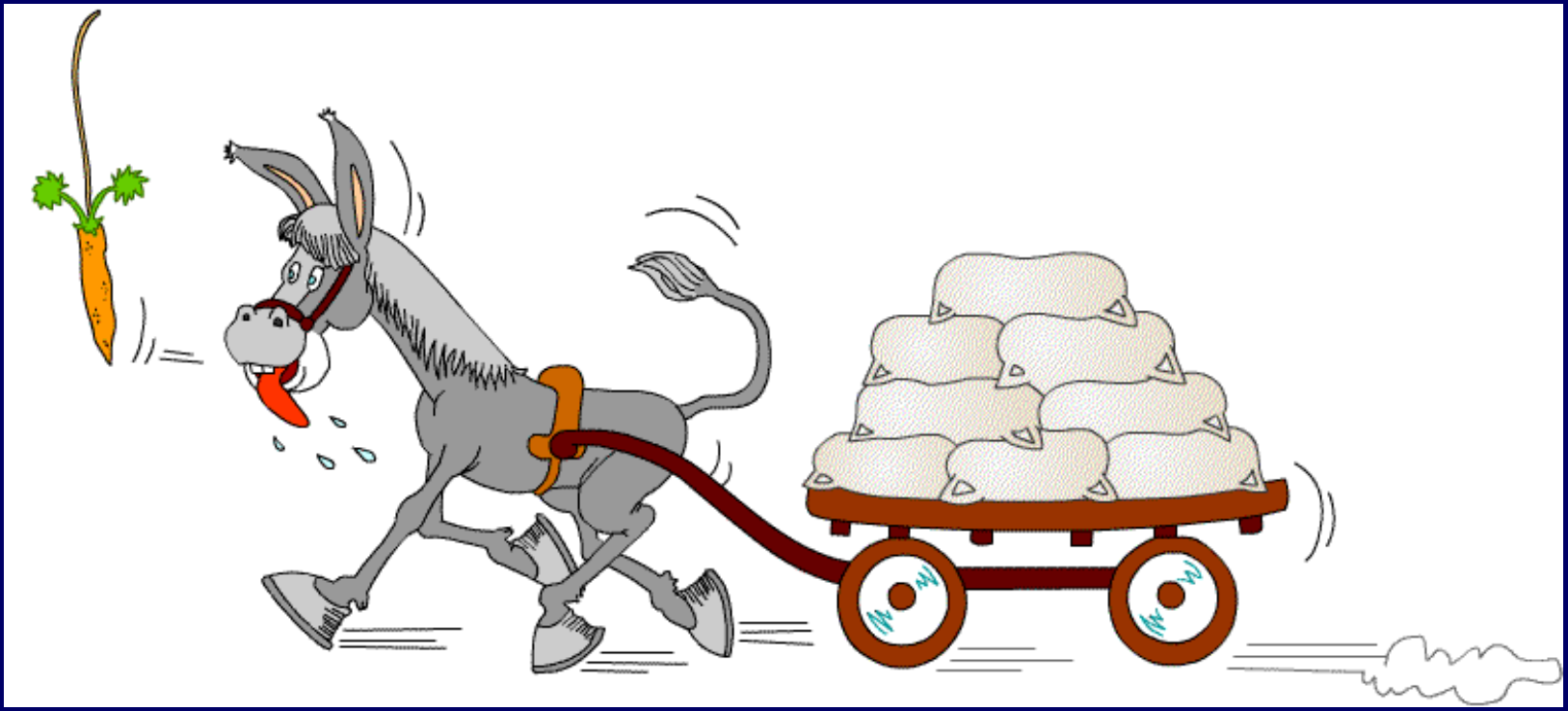
- **Relieve symptoms**
- **Reduce morbidity**
- **Improve survival**

Drug Therapy

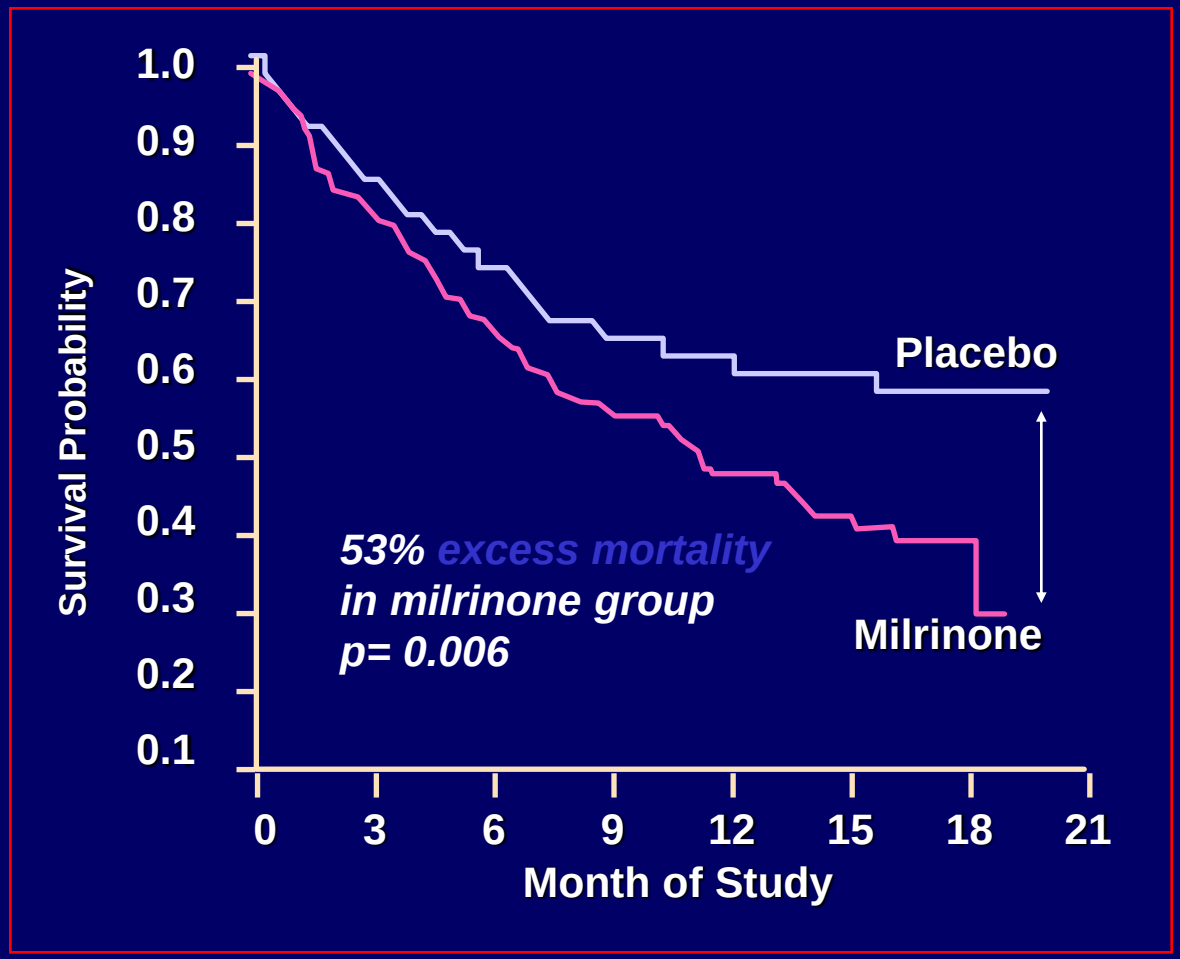
- **Diuretics**
- **Positive inotropes**
- **Vasodilators – ACEI, ARB**
- **β-blockers**
- **Spironolactone**

Digitalis Compounds

Like the carrot placed in front of the donkey



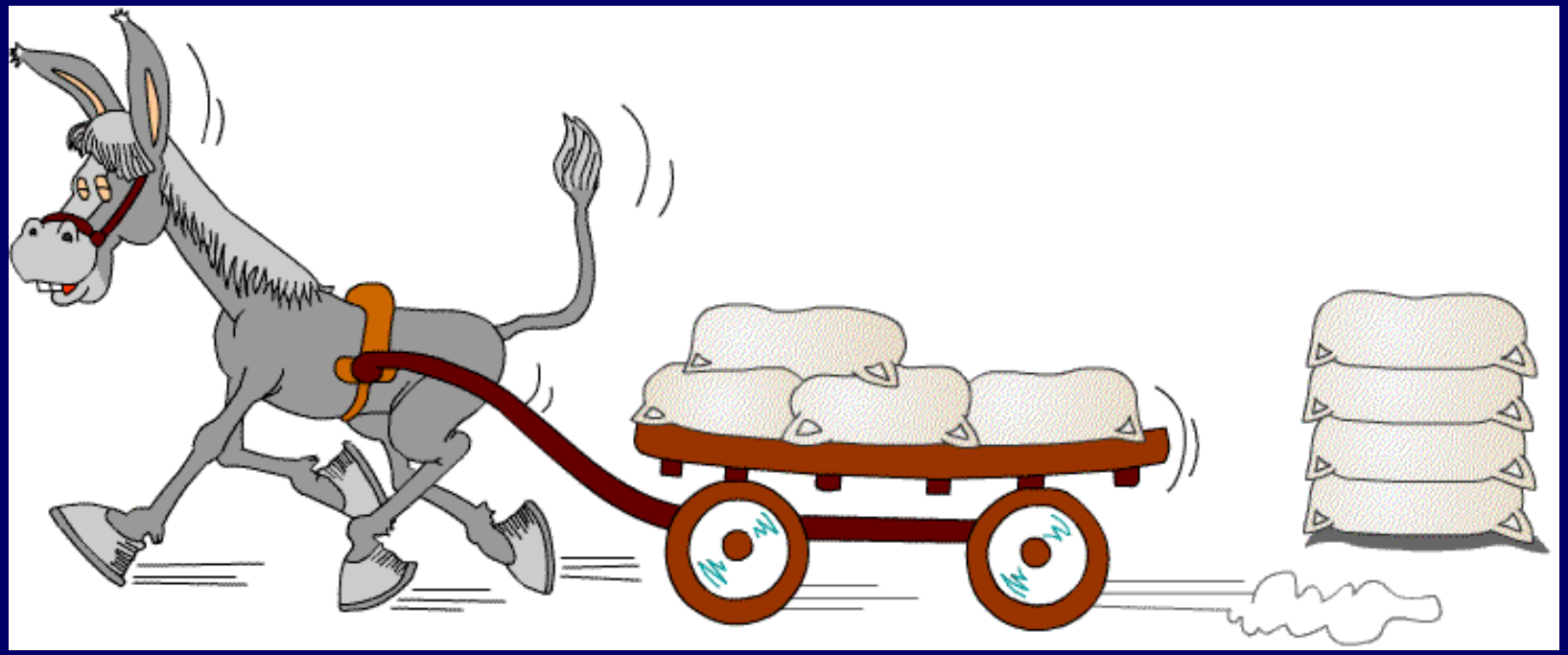
Milrinone Increases Mortality: "PROMISE"



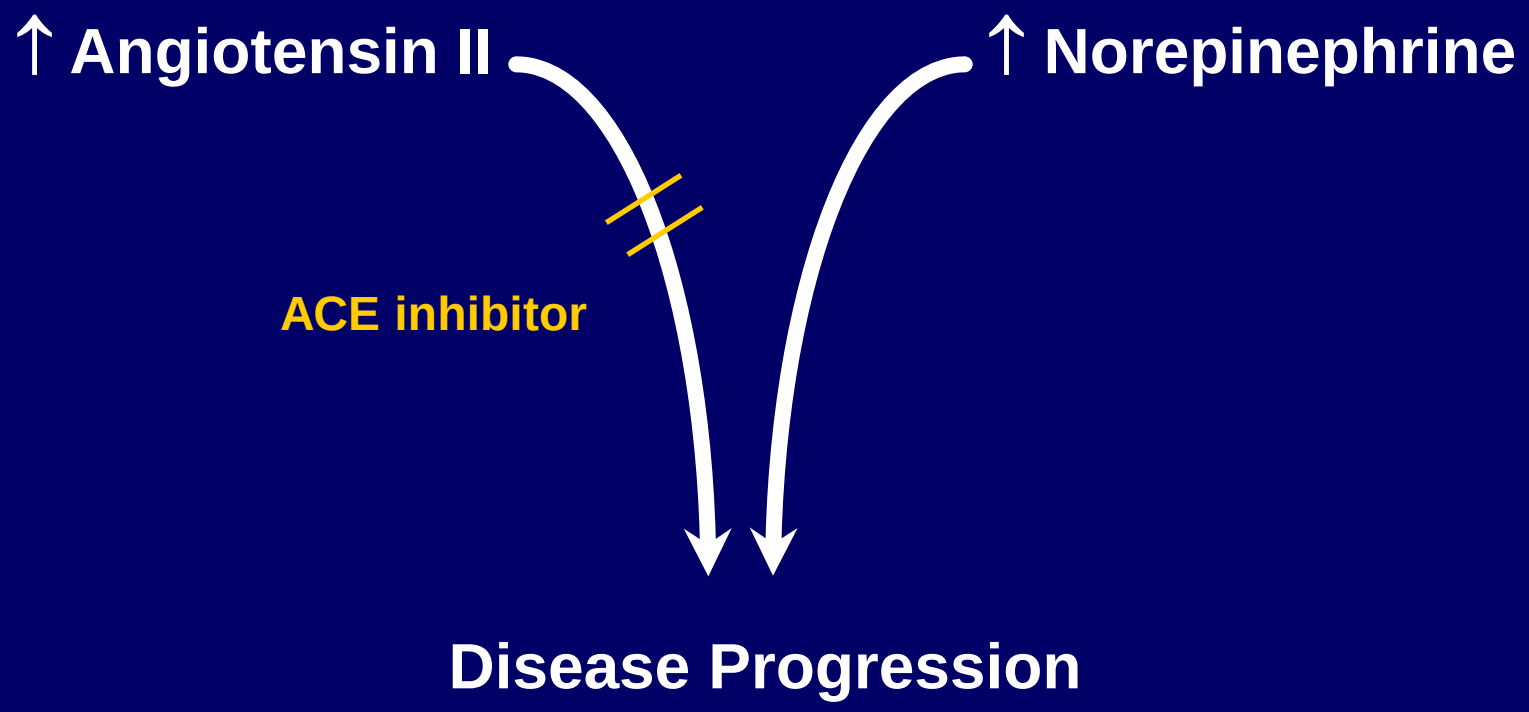
Packer M et al, *N Engl J Med* 1991

Diuretics, ACE Inhibitors, ARB

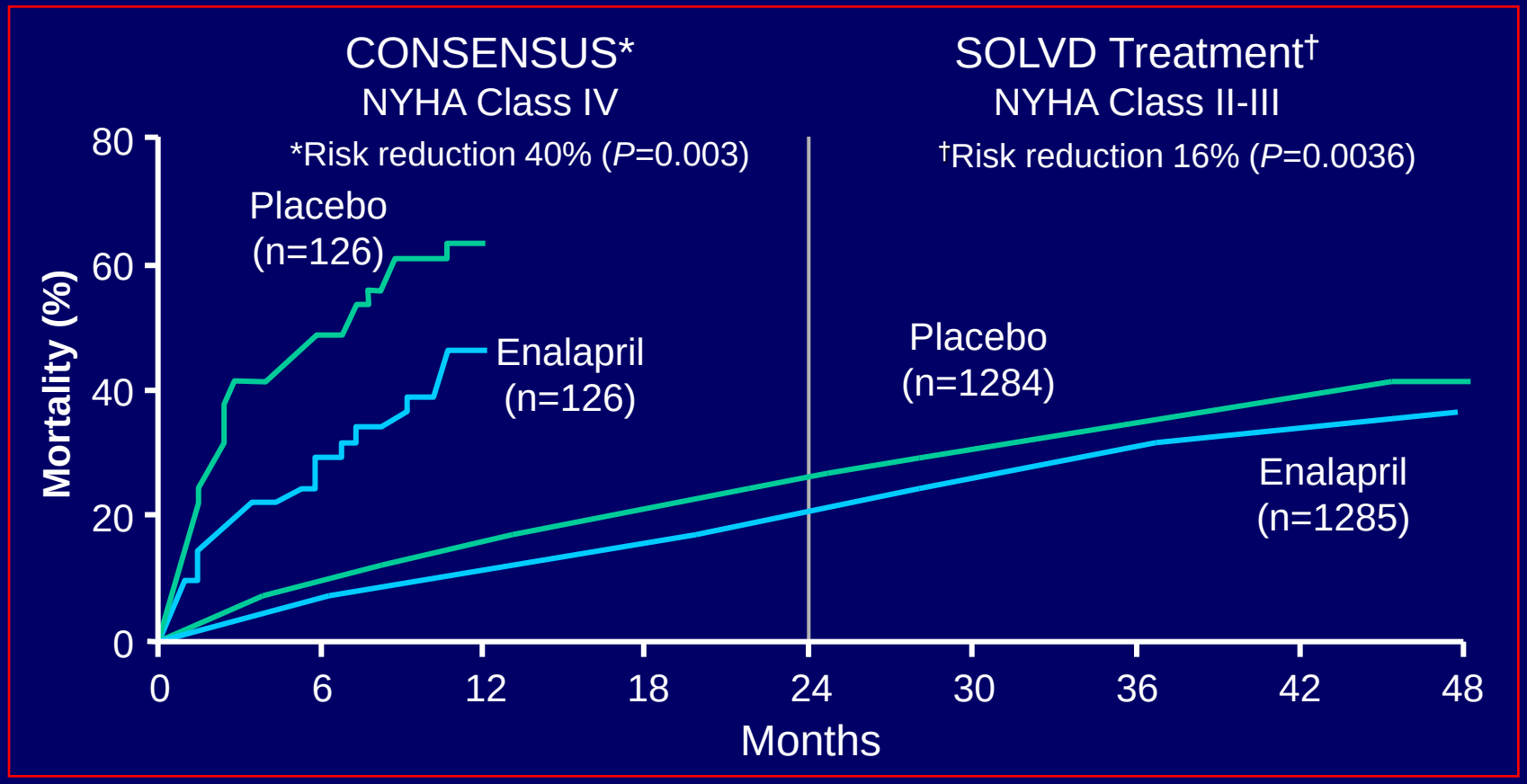
Reduce the number of sacks on the wagon



Effect of ACE Inhibition

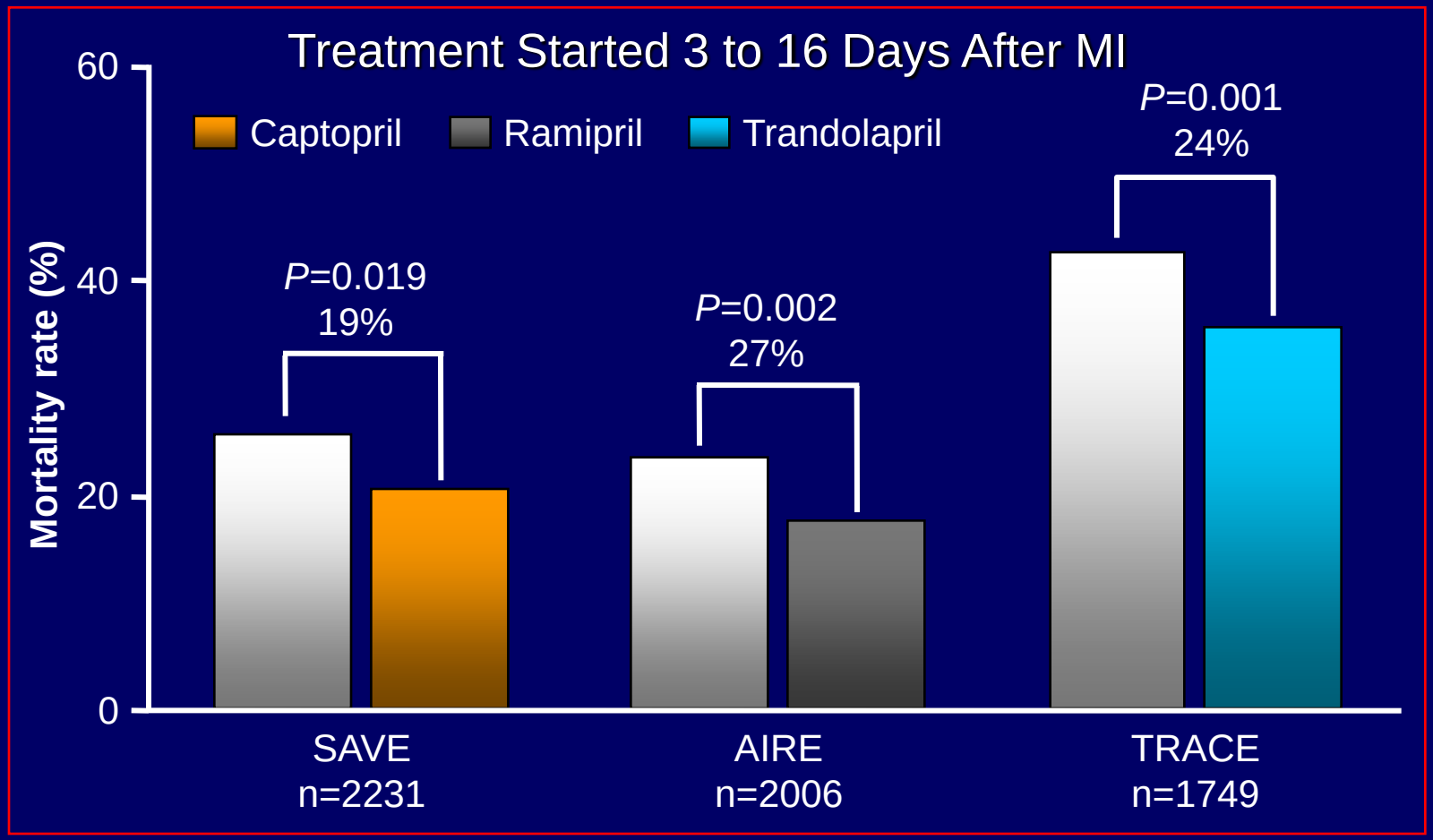


Effect of ACEIs in Patients with Symptomatic HF



Adapted from CONSENSUS Trial Study Group *N Engl J Med* 1987;
SOLVD Investigators *N Engl J Med* 1991

Effect of ACEIs in Post-MI Patients with LVSD



Adapted from Pfeffer M, et al *N Engl J Med* 1992; AIRE Study Investigators *Lancet* 1993;
Kober L, et al *N Engl J Med* 1995

Total Mortality Reduction with Spironolactone in HF: "RALES"

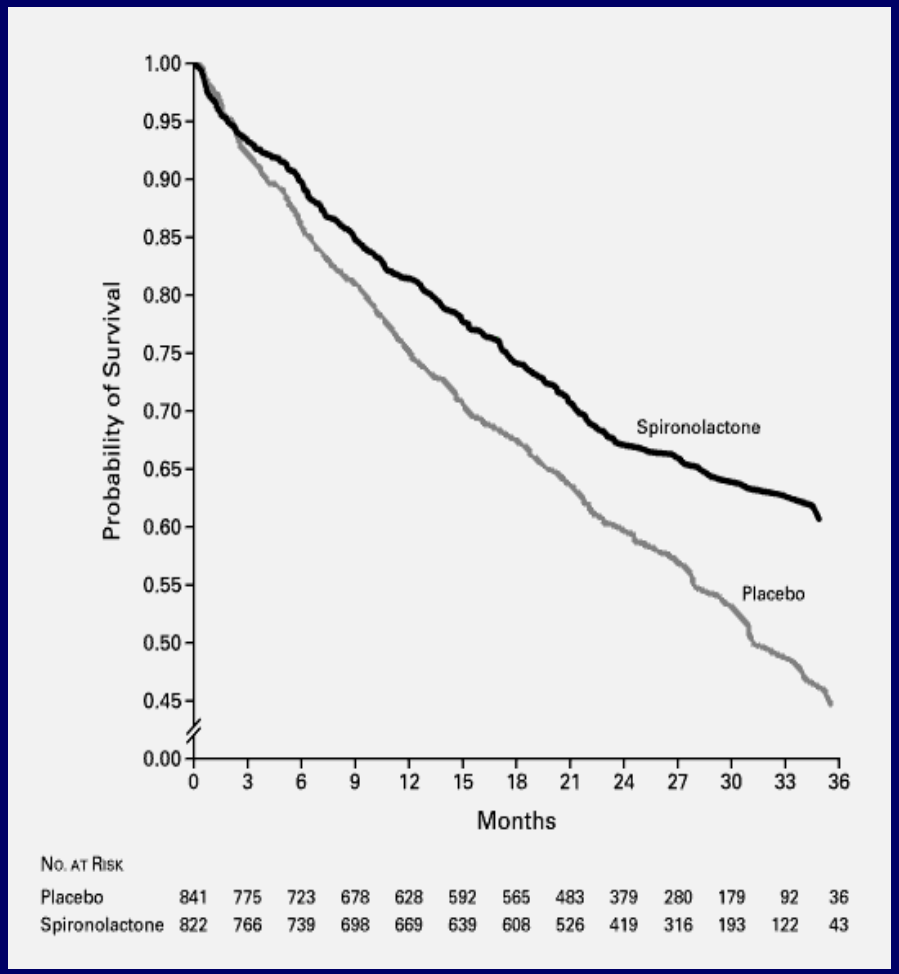
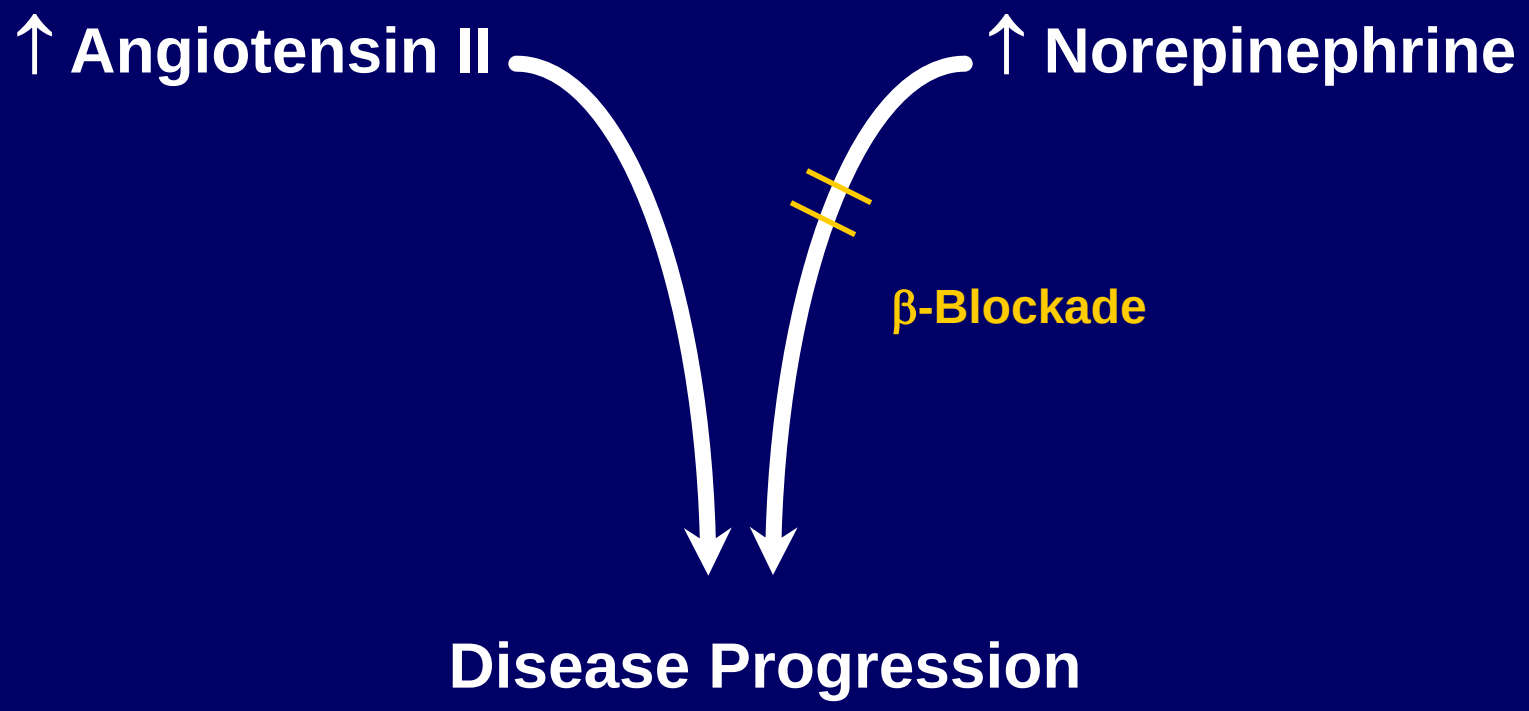


Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.

The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group ($P<0.001$).

Pitt B et al, *N Engl J Med* 1999

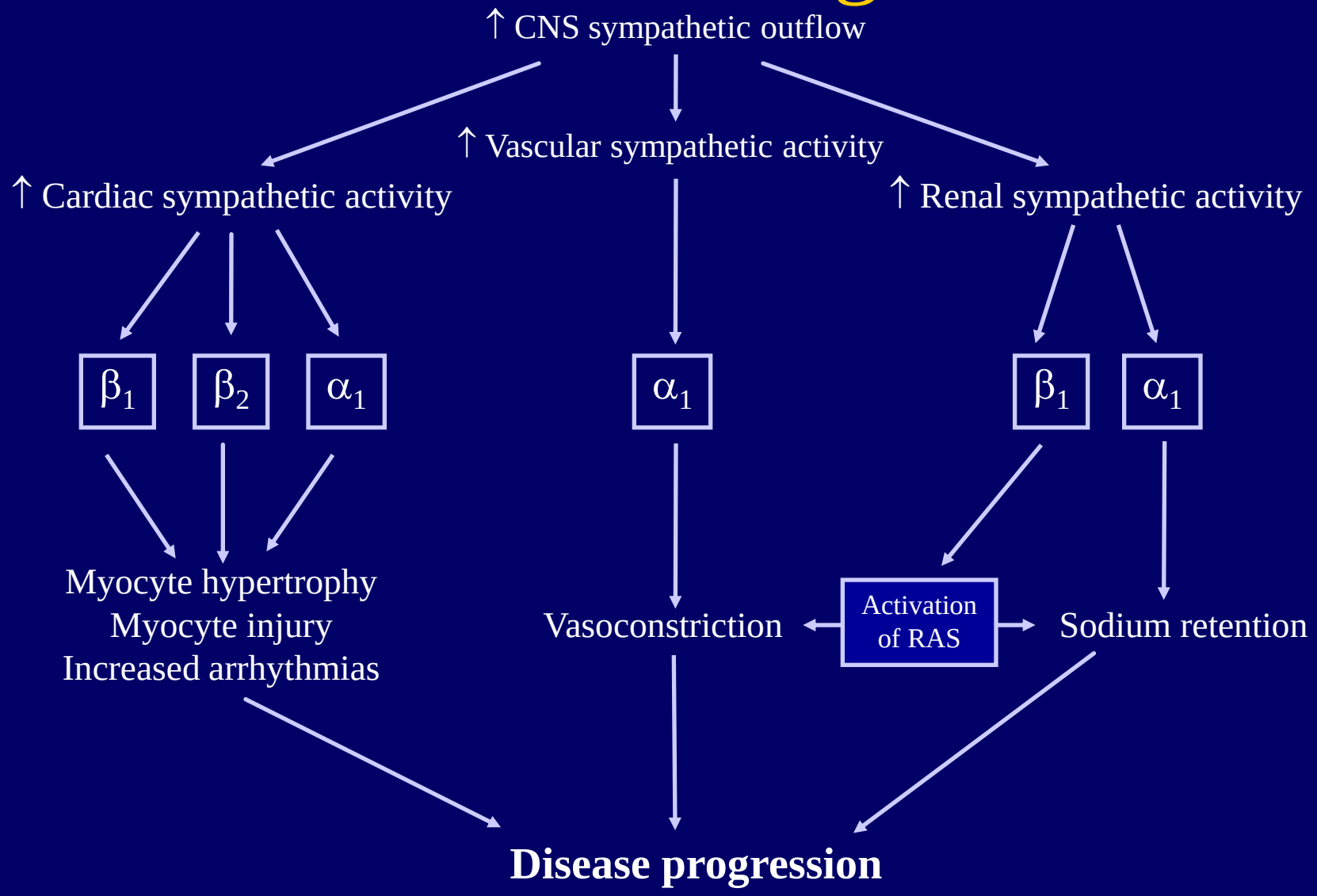
Effect of β-Blockade



Are There Differences in Beta Blockers in Heart Failure?

- Different pharmacologic properties
- Different mechanisms to explain improved LV function
- ? Differences in sub-groups
- ? Dose response

Adrenergic Pathway in Heart Failure Progression



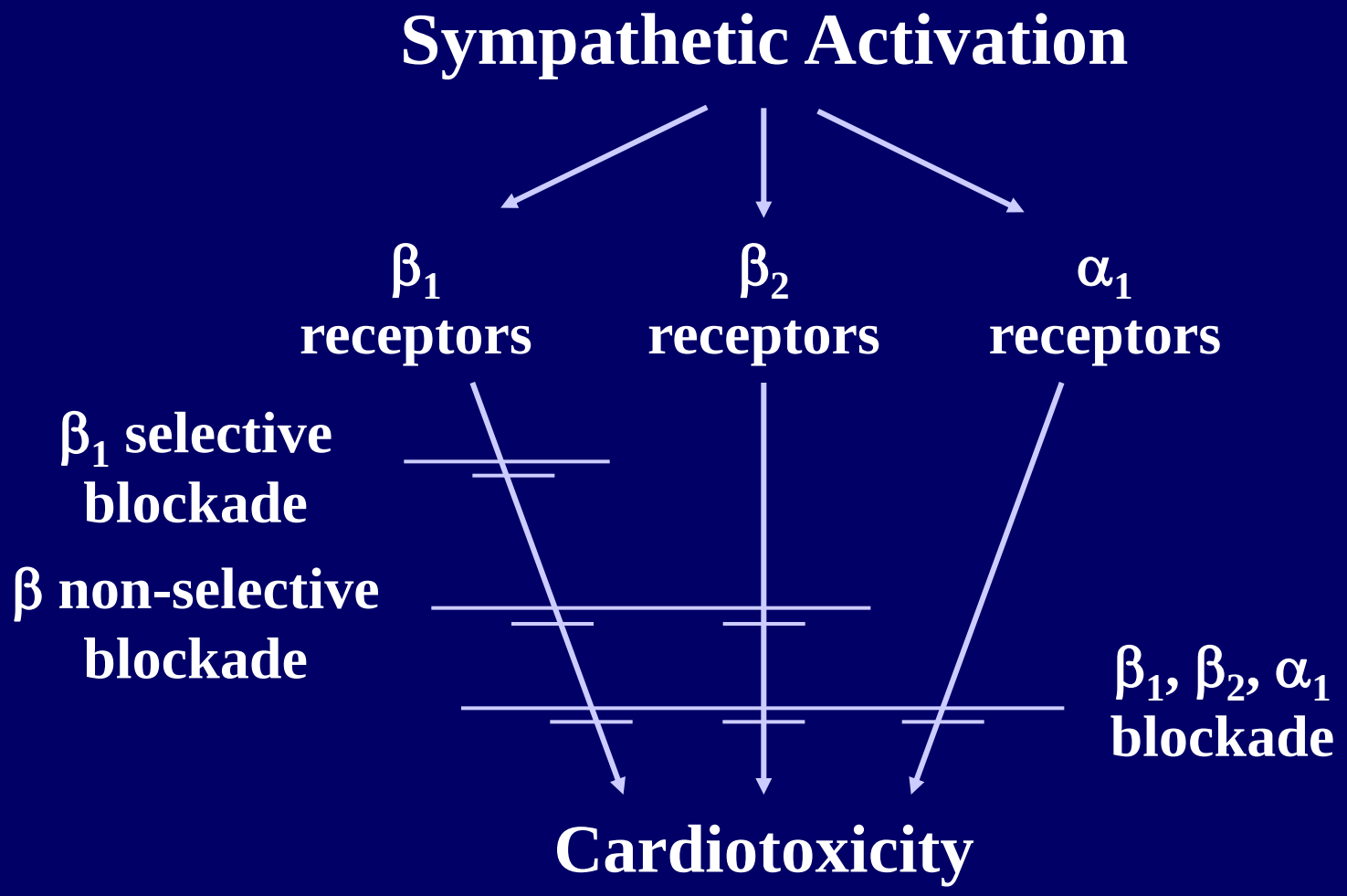
Ratio of Adrenergic Receptors in the Heart

In the failing heart, the ratio of receptors shifts, increasing the relative proportion of β_2 and α_1 receptors

	β_1	β_2	α_1
Normal Heart	**70**	**20**	**10**
Failing Heart	**50**	**25**	**25**

Adapted from Bristow MR. *J Am Coll Cardiol.* 1993;22(4 Suppl A):61A–71A.

Selectivity of β-Blocking Agents



Major Placebo Controlled Trials of Beta-Blockade in Heart Failure

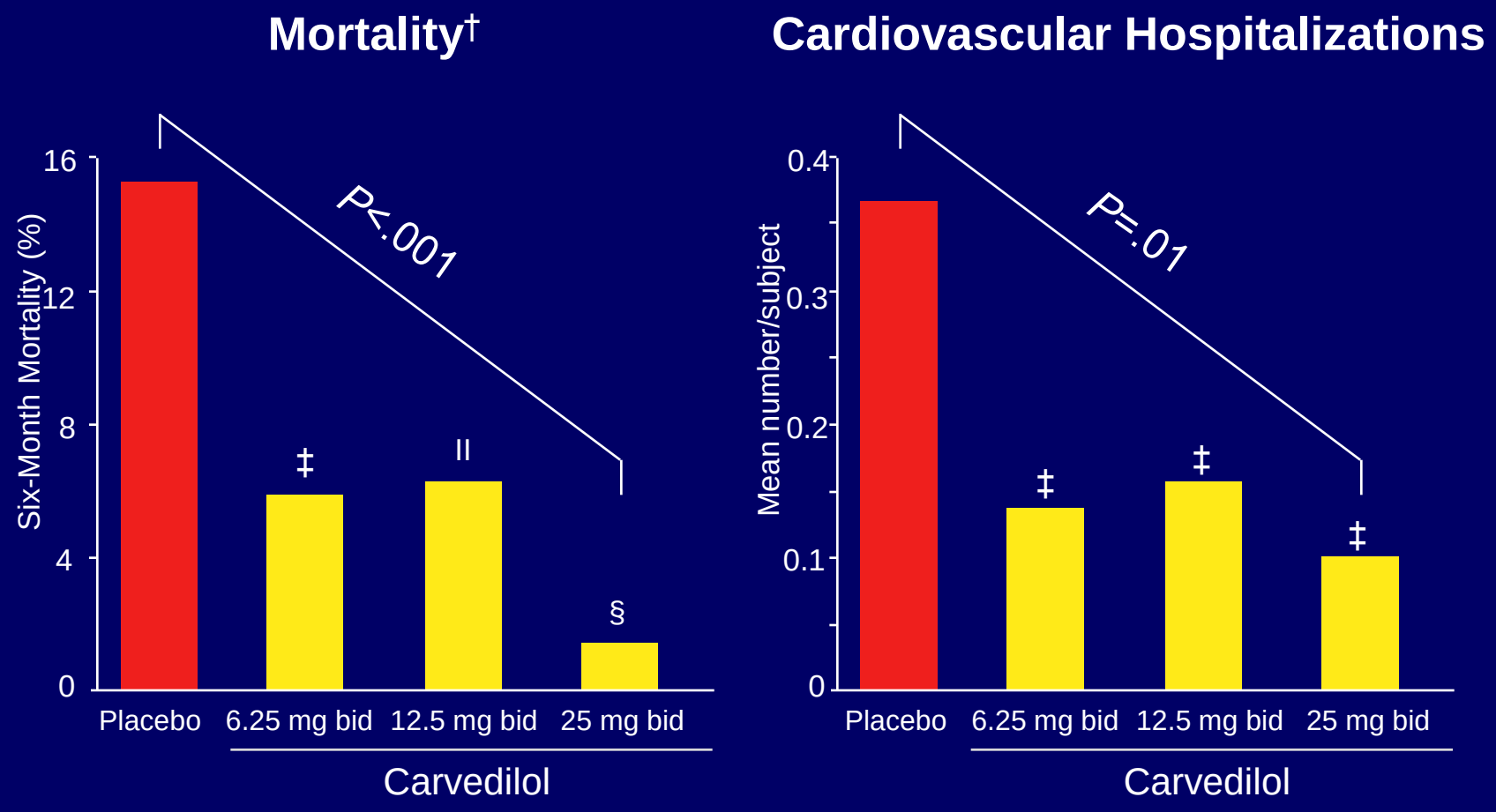
Study	Drug	HF Severity	Patients (n)	Follow-up (yrs)	Target Dosage (mg)	Mean Dosage Achieved (mg/day)	Effects on Outcomes
CIBIS *Circ.* 1994	bisoprolol*	moderate/ severe	641	1.9	5 qd	3.8	All-cause mortality NS
CIBIS-II[3] *Lancet* 1999	bisoprolol*	moderate/ severe	2647	1.3	10 qd	7.5	All-cause mortality ↓34% (*P*<.0001)
MDC *Lancet* 1993	metoprolol tartrate*	mild/ moderate	383	1	200 qd	108	Death or need for transplant (primary endpoint) NS
MERIT-HF[1] *Lancet* 1999	metoprolol succinate	mild/ moderate	3991	1	200 qd	159	All-cause mortality ↓34% (*P*=.0062)
BEST[4] *NEJM* 2001	bucindolol*	moderate/ severe	2708	2	50-100 bid	152	All-cause mortality NS
US Carvedilol[2] *NEJM* 1996	carvedilol	mild/ moderate	1094	6.5 months	6.25 to 50 bid	45	All-cause mortality† ↓65% (*P*=.0001)
COPERNICUS[5] *NEJM* 2001	carvedilol*	severe	2289	10.4 months	25 bid	37	All-cause mortality ↓35% (*P*=.0014)

†Not a planned end point.

Coreg and Toprol-XL are indicated for the reduction of the combined endpoint of morbidity and mortality.

NOT AN APPROVED INDICATION

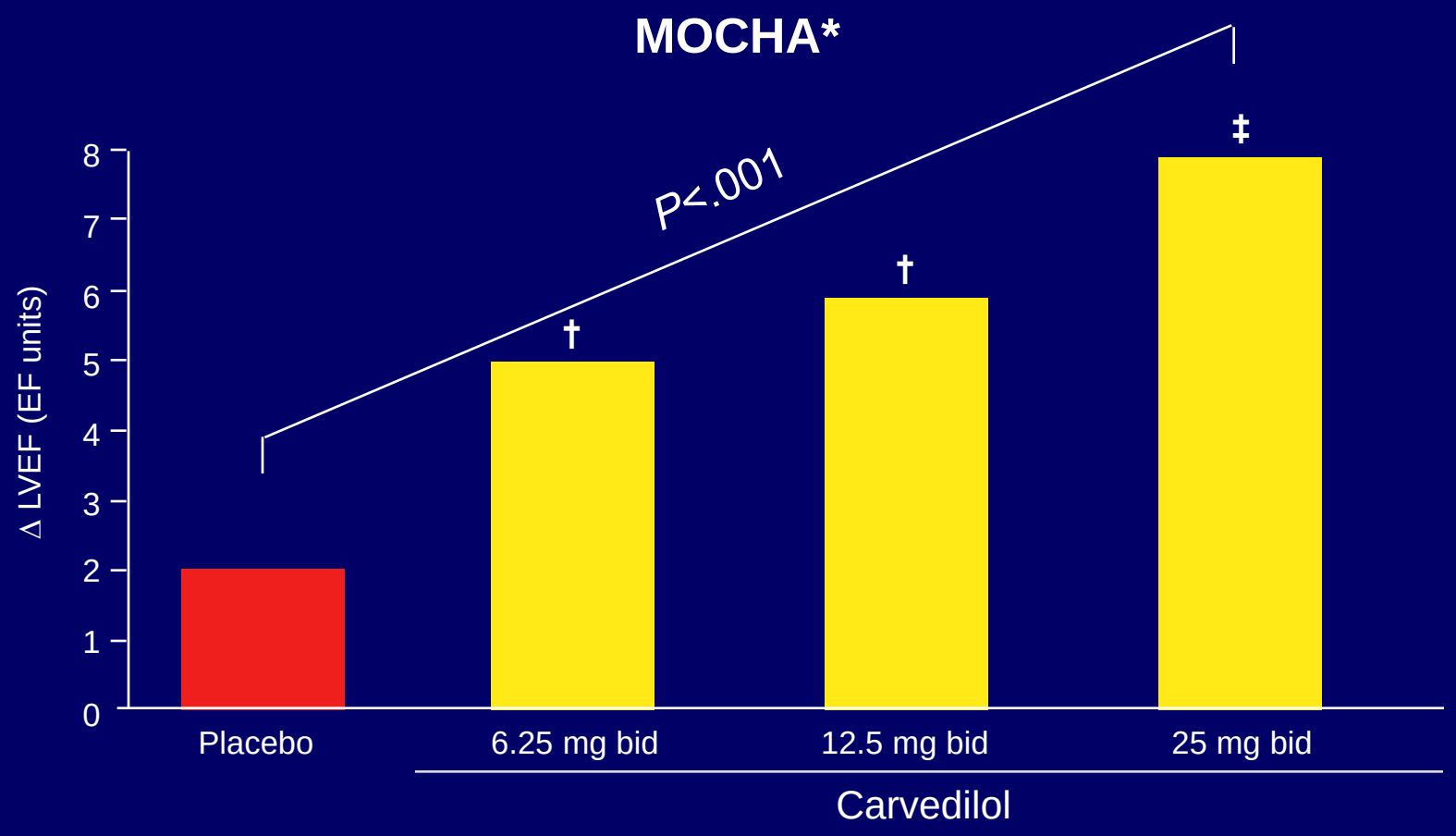
Carvedilol Dose-Response Trial (MOCHA*): Effect on Mortality and Morbidity



‡*P*<.05 vs placebo.
§*P*<.001 vs placebo.
II*P*=.07 vs placebo.

Adapted from Bristow MR et al. *Circulation*. 1996;94:2807–2816.

Effect of Carvedilol Dose on Left Ventricular Ejection Fraction

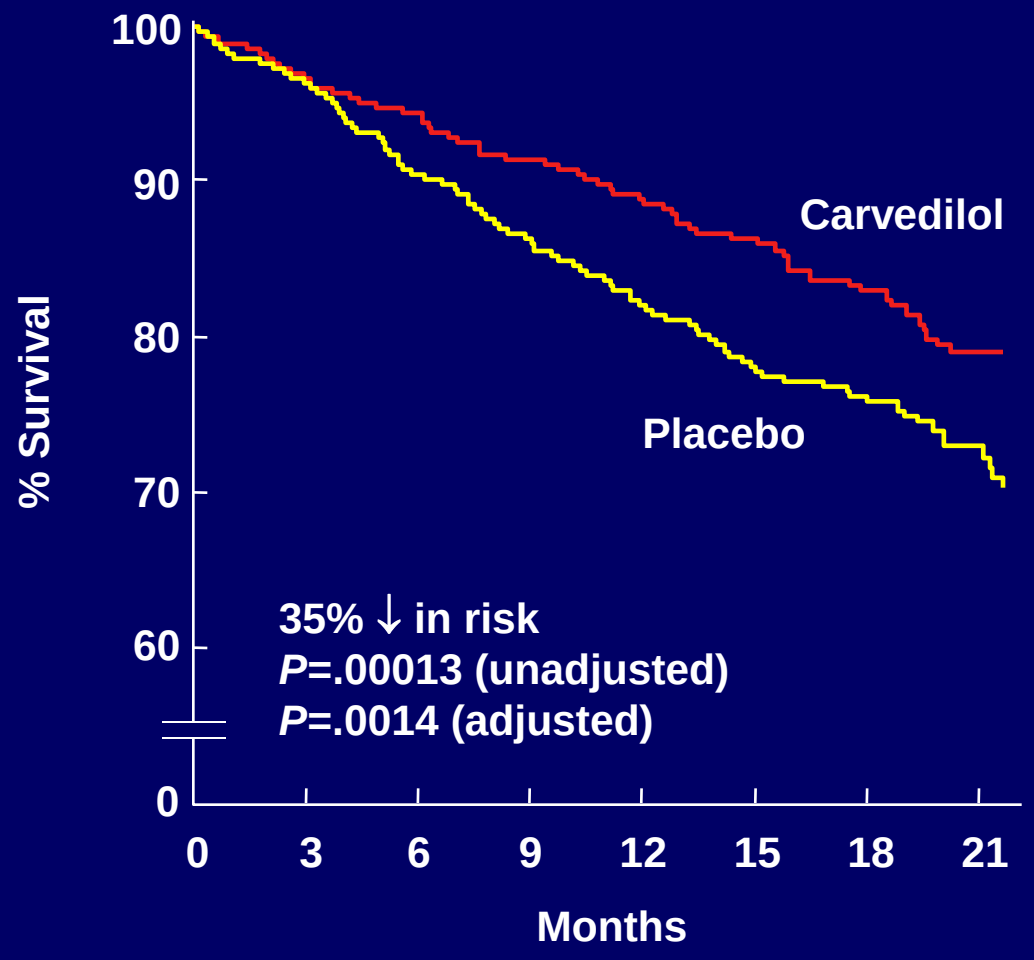


Patients receiving diuretics, ACE inhibitors, ± digoxin; follow-up 6 months; placebo (n=84), carvedilol (n=261).
*Multicenter Oral Carvedilol Heart Failure Assessment.
Adapted from Bristow MR et al. *Circulation*. 1996;94:2807–2816.

†*P*<.005 vs placebo.
‡*P*<.0001 vs placebo.

COPERNICUS

All-Cause Mortality



Packer M et al. *N Engl J Med.* 2001;344:1651–1658.

Beta blockers are not used routinely in HF

- 25-30% of HF patients get beta blockers
- Physician perception regarding beta blockers
  - Combining ACEI and BBs Rx is a hassle
  - Initiation only when stable
  - Initiation often leads to deterioration
  - Benefits are not seen for months
  - Rx can be expensive

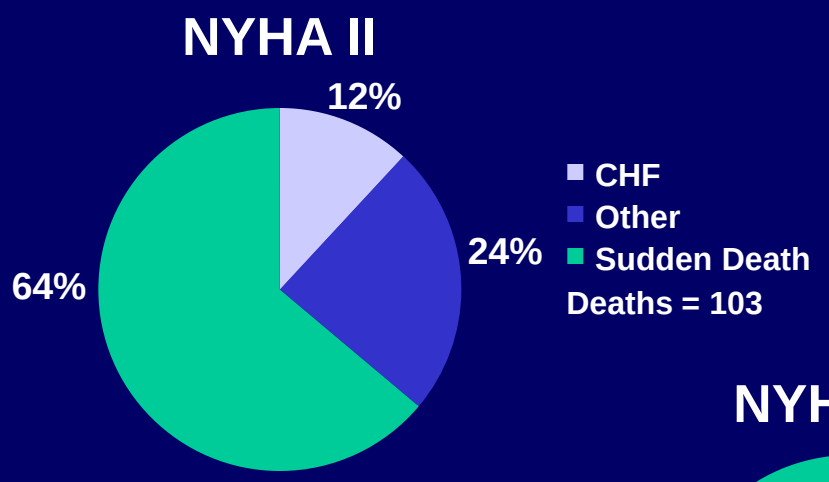
Should Physicians Increase the Dose of ACE Inhibitor or Add β-Blockade?

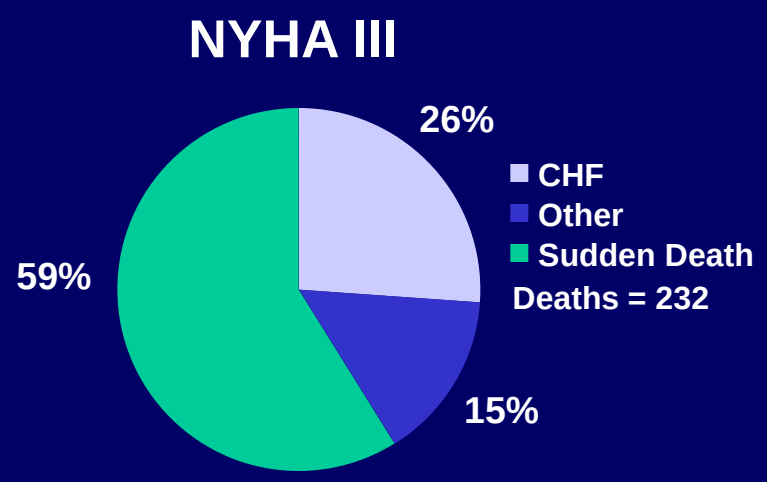
	"Low" dose ACEI → "High" dose ACEI*	**"Average" dose ACEI → + β-blockade†**
Symptoms	Unchanged	Improved
Morbidity/ mortality	↓ 12%	↓ 35%-40%
Mortality	↓ 8%	↓ 30%-35%

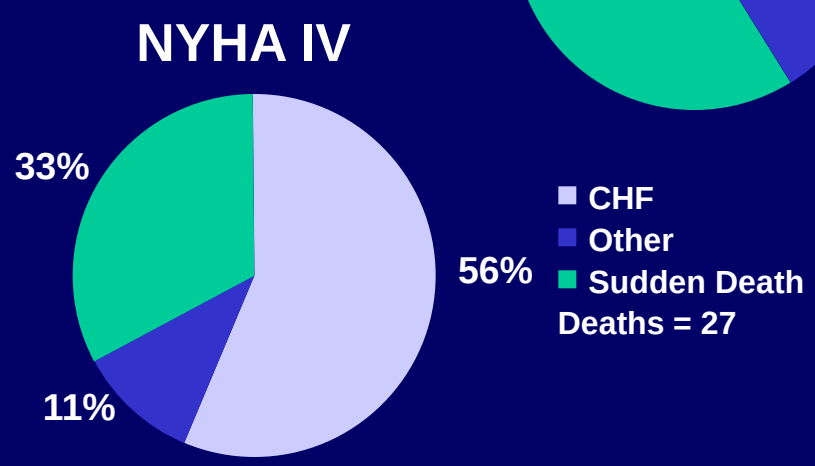
*Adapted from Packer et al. Eur Heart J. 1998;19(suppl):142.
†Adapted from Lechat et al. Circulation. 1998;98:1184-1191.

Sudden Cardiac Death in Heart Failure

SCD–a prominent mode of death

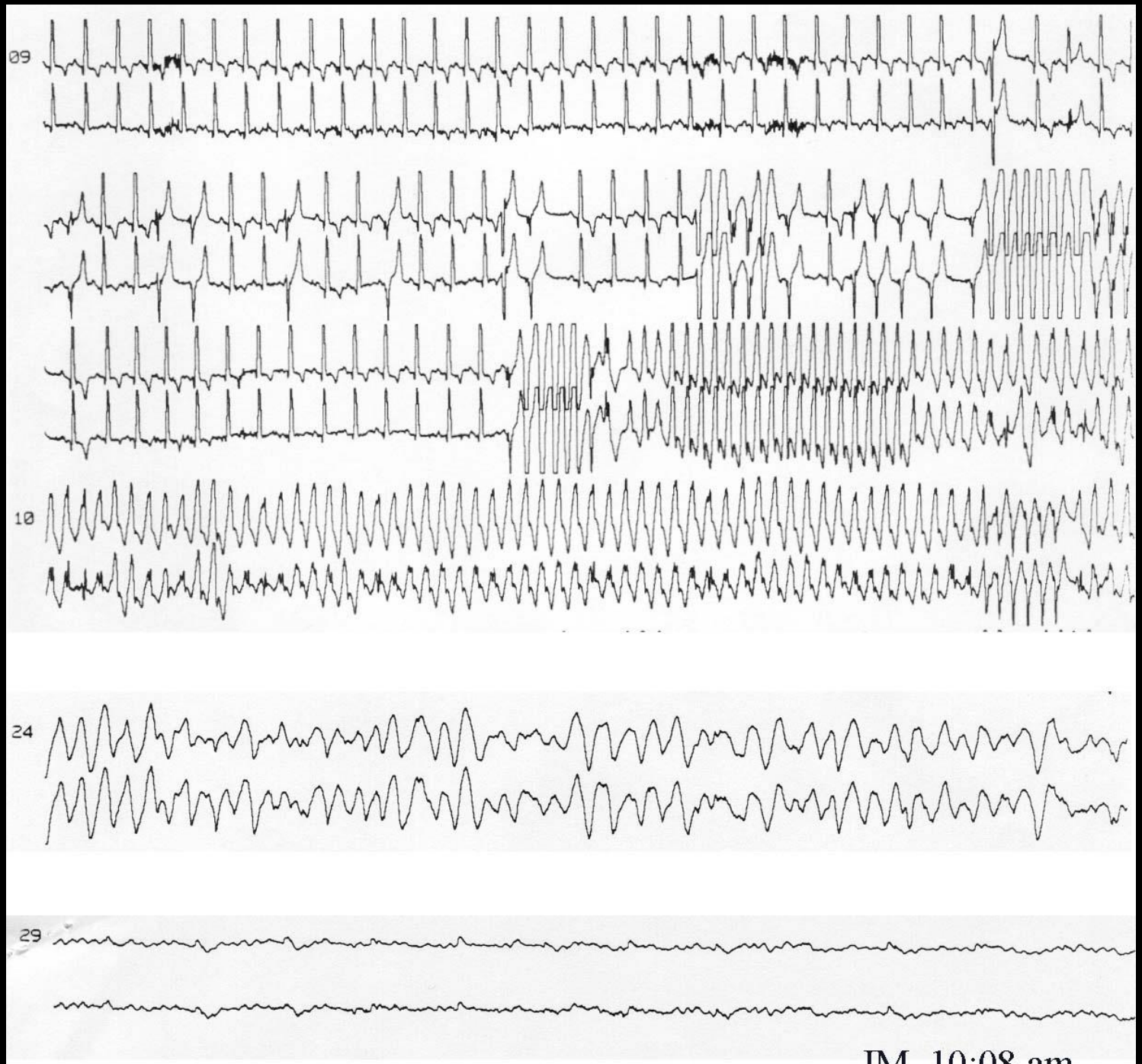






Reprinted with permission from Elsevier Science (*The Lancet*, 1999;353:2001-2007).

MERIT-HF study group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *LANCET.* 1999;353:2005.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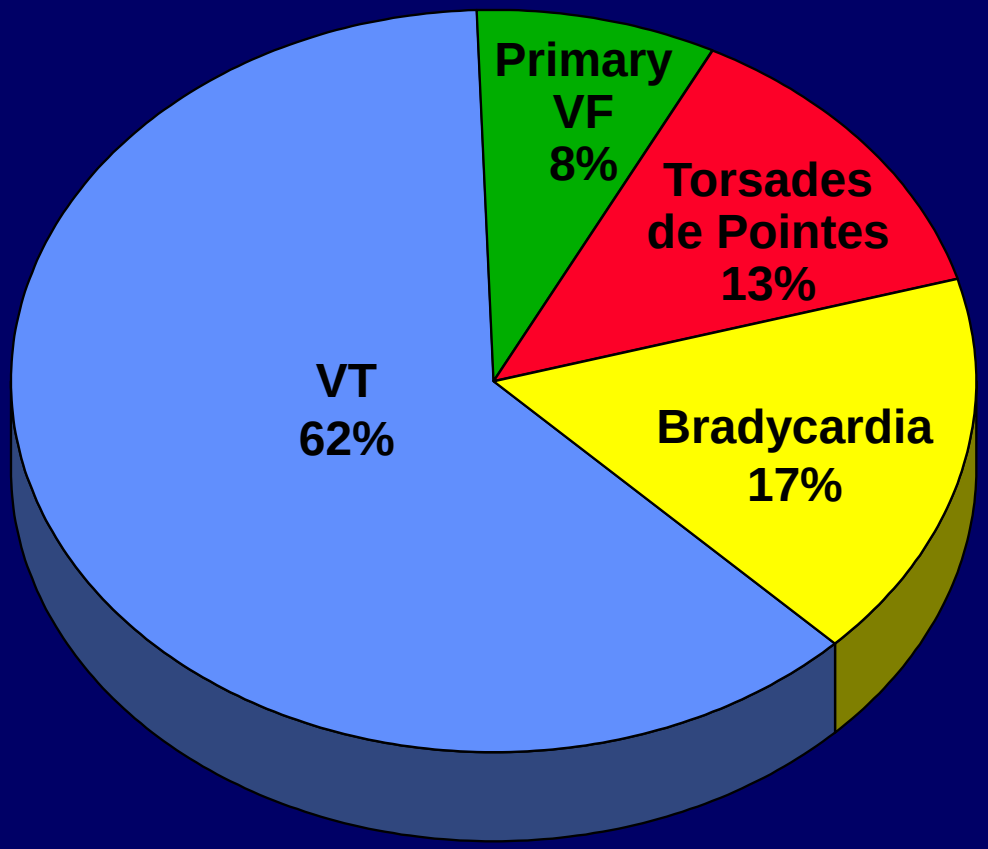
Underlying Arrhythmia of Sudden Death



Adapted from Bayés de Luna A. Am Heart J. 1989;117:151-159.

Risk Factors for Sudden Death in Post-MI Patients

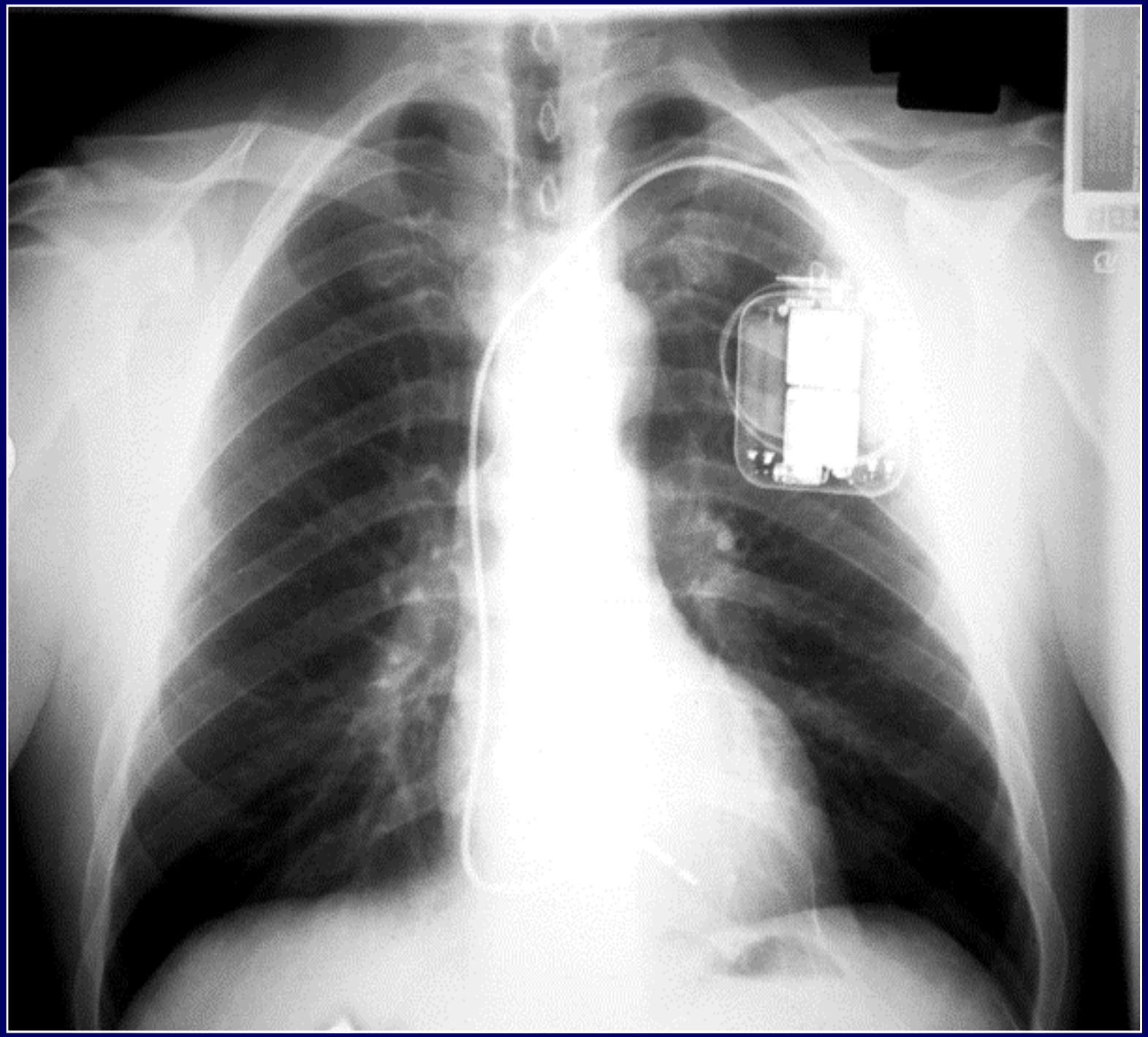
- LVEF < 40%
- Frequent ventricular ectopy

Pharmacologic Management of VT/VF

- Empiric
- Holter-guided
- EPS-guided
- Combination

Non-Pharmacologic Management of VT/VF

- Catheter ablation
- ICD
- Transplant



Sudden Cardiac Death

- Primary Prevention: Can we reduce sudden death by prophylactic treatment of high risk patients?

- Secondary prevention: Can we improve survival after resuscitation from sudden death?

Clinical Trials in Ventricular Arrhythmias or Sudden Death

	VT/VF	Post-MI	Heart Failure
AA drugs vs. placebo		CAST, EMIAT, CAMIAT, SWORD	GESICA, CHF-STAT, SCD-HeFT*
Conventional AA drugs vs. amiodarone or sotalol	**ESVEM** **CASCADE**		SCD-HeFT*
ICD vs. AA drugs	CIDS, CASH, AVID, MUSTT	MADIT MADIT II	SCD-HeFT*
ICD vs. placebo		CABG Patch	SCD-HeFT*

*** Ongoing**

CAST

Cardiac

Arrhythmia

Suppression

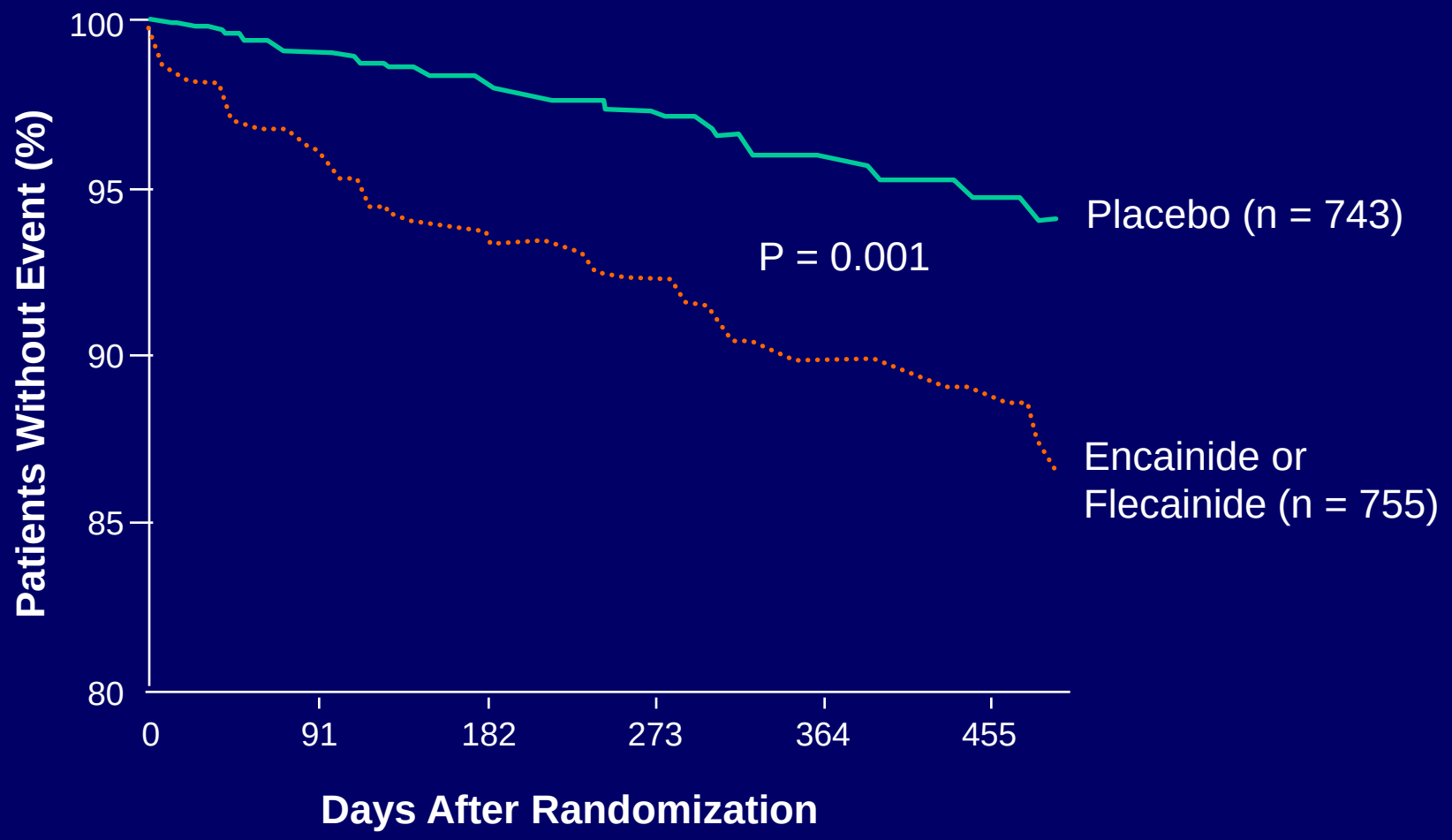
Trial

CAST

- NHLBI trial initiated in June 1987
- Hypothesis: whether suppression of asymptomatic or mildly symptomatic ventricular arrhythmias with antiarrhythmics in post-MI patients would reduce arrhythmic death

CAST-I

Prognosis of Post-MI Patients Treated with Placebo vs. Encainide/Flecainide



Echt DS. N. Engl J Med. 1991;324:781-788.

CHF-STAT: Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy

- Hypothesis: Amiodarone will reduce mortality in patients with CHF and ventricular arrhythmias

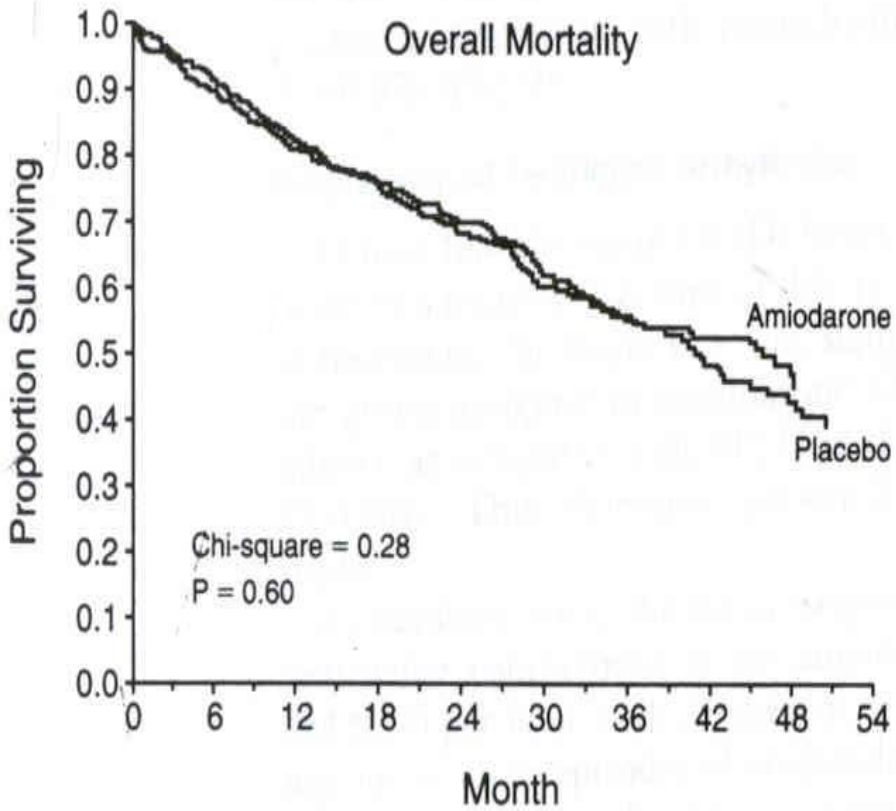
CHF-STAT

Inclusion Criteria:

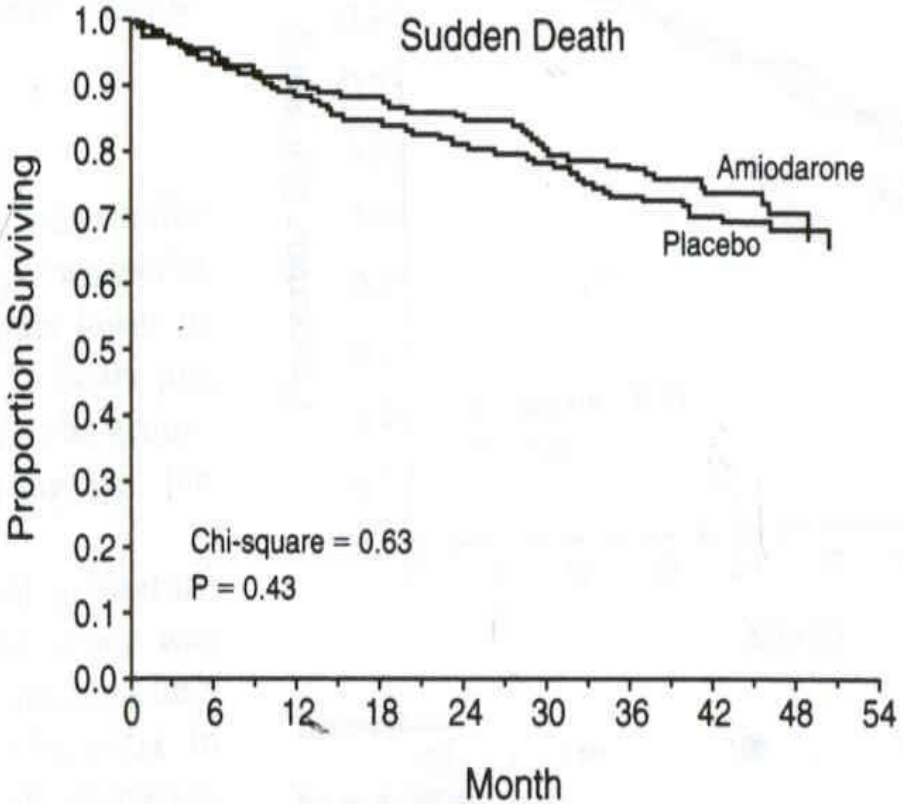
- CHF
- LVEF <40%
- > 10 VPC/ hour by Holter

Excluded: Symptomatic VT, Aborted cardiac arrest.

CHF-STAT - Results



Amiodarone	336	260	175	101	33
Placebo	338	263	178	95	39



Amiodarone	336	260	175	101	33
Placebo	338	263	178	95	39

Singh SN, et al:NEJM 1995:333;77-82

Unanswered Question

- Can we reduce mortality in patients with depressed LV function?

SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

SCD-HeFT Patient Flow

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

Randomization

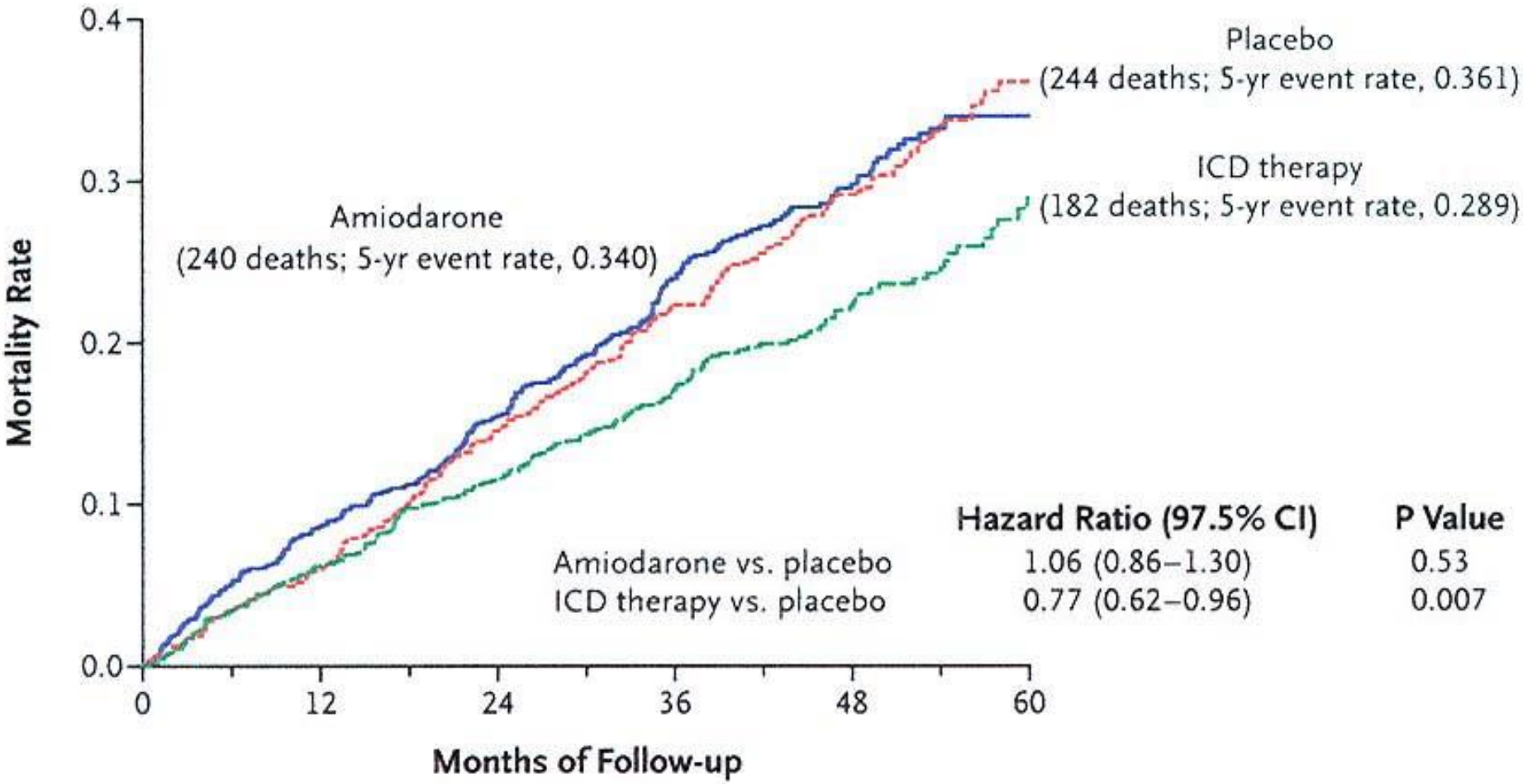
Conventional CHF Rx & placebo (n = 833)*

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

Conventional CHF Rx & ICD (n = 833)*

Bardy GH. *PACE* 1997;20(4, part II):1148.

SCD-HeFT MORTALITY



No. at Risk						
Amiodarone	845	772	715	484	280	97
Placebo	847	797	724	505	304	89
ICD therapy	829	778	733	501	304	103

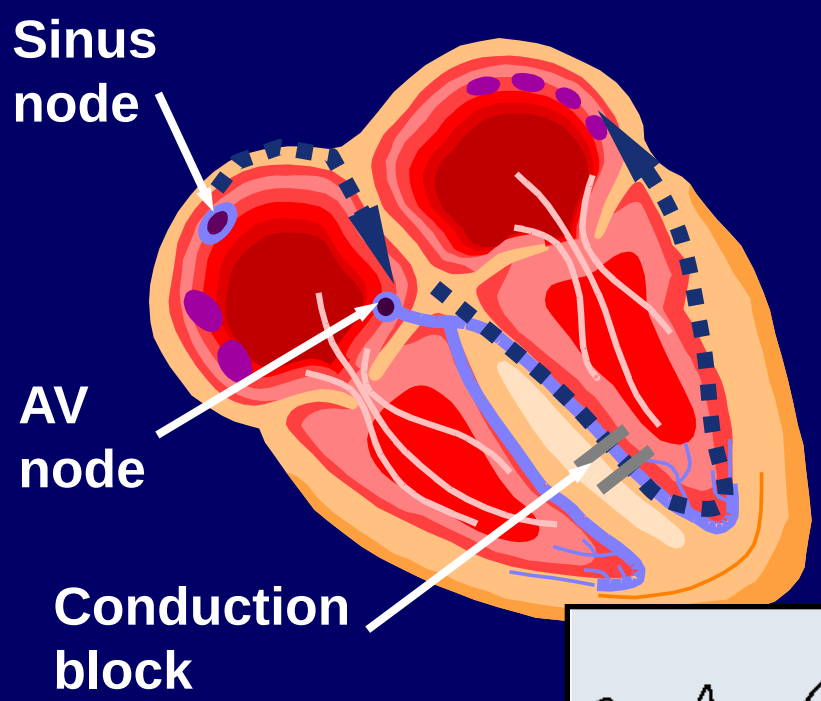
Bardy GH. *N Engl J Med 2005;352:225-37*

Question

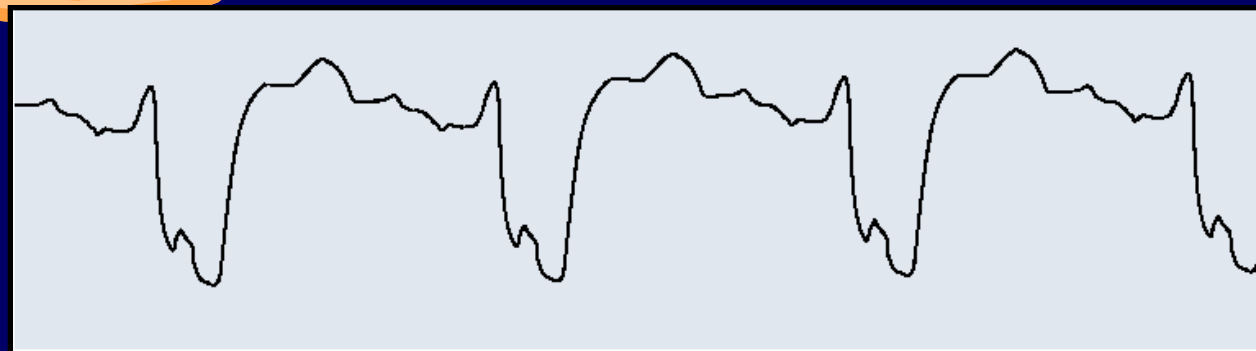
- Can we improve the quality of life in class III & IV heart failure in patients who are symptomatic despite optimal medical management?

Issues Associated with Heart Failure

Ventricular Dysynchrony with LBBB



- Delayed lateral wall contraction
- Disorganized ventricular contraction
- Decreased pumping efficiency



Issues Associated with Heart Failure

Abnormal local wall strain

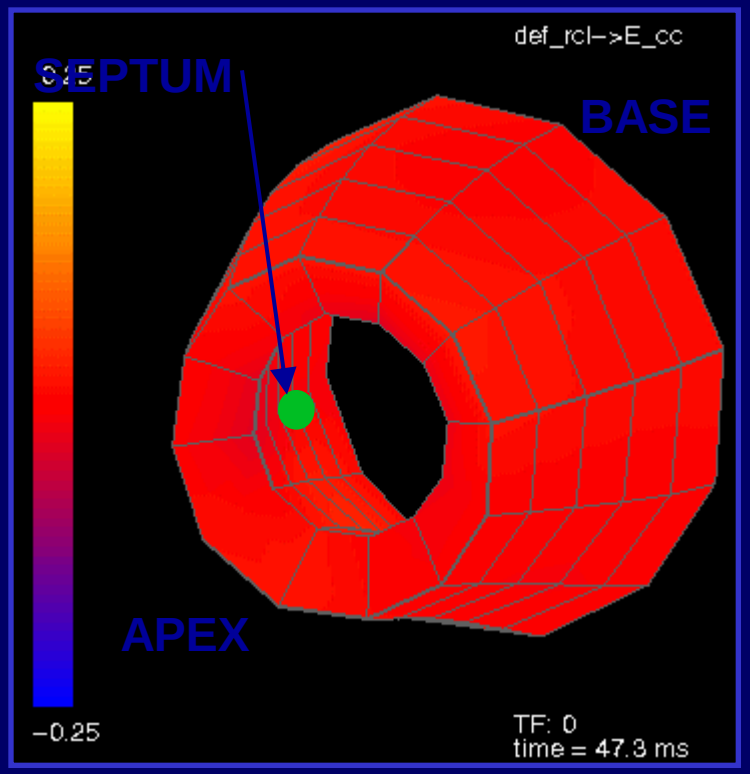
Healthy

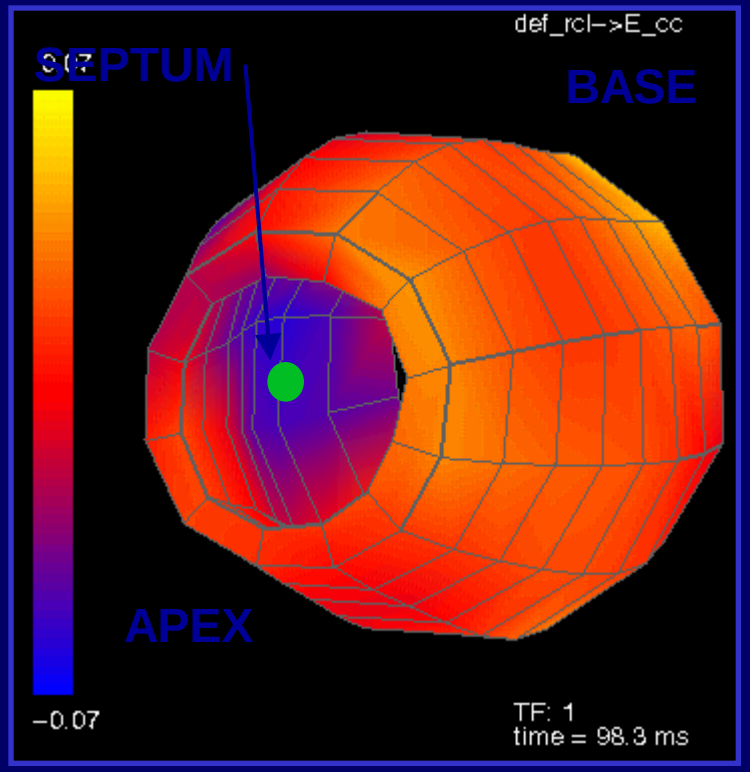
Dilated Cardiomyopathy (DCM)

Longer

Relaxed

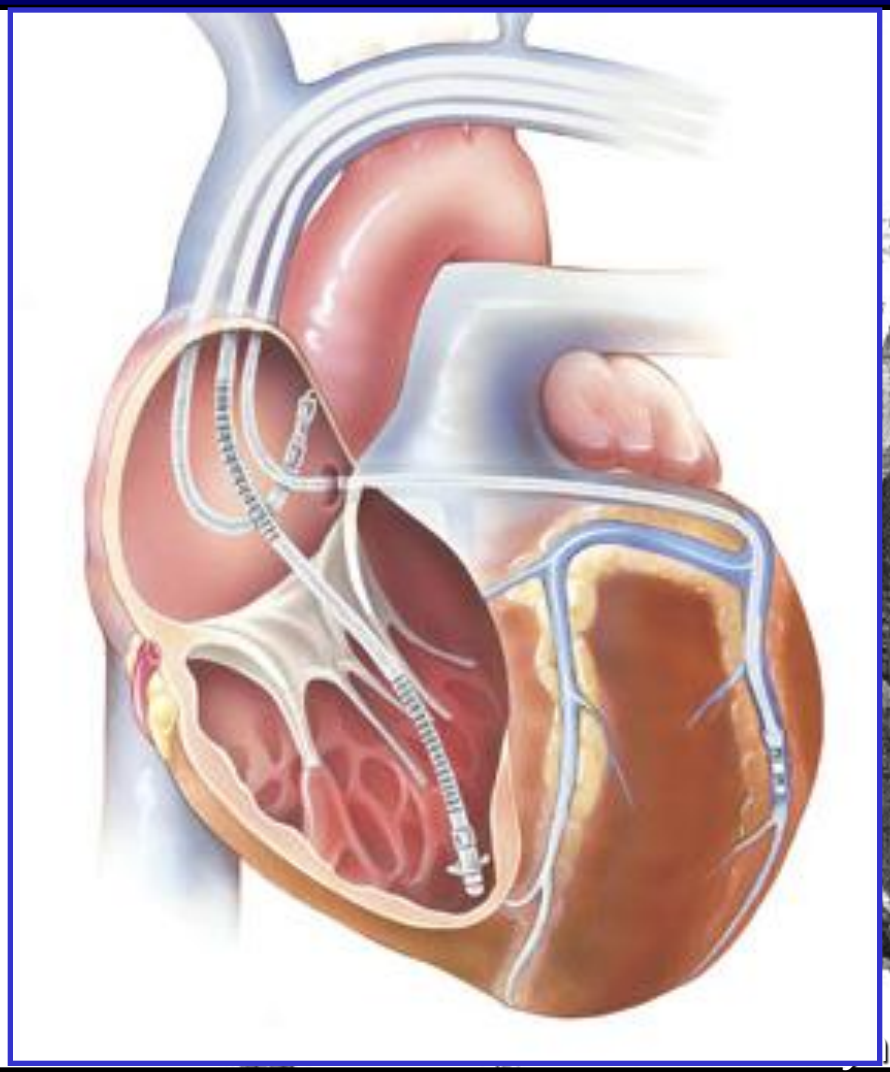
Shorter

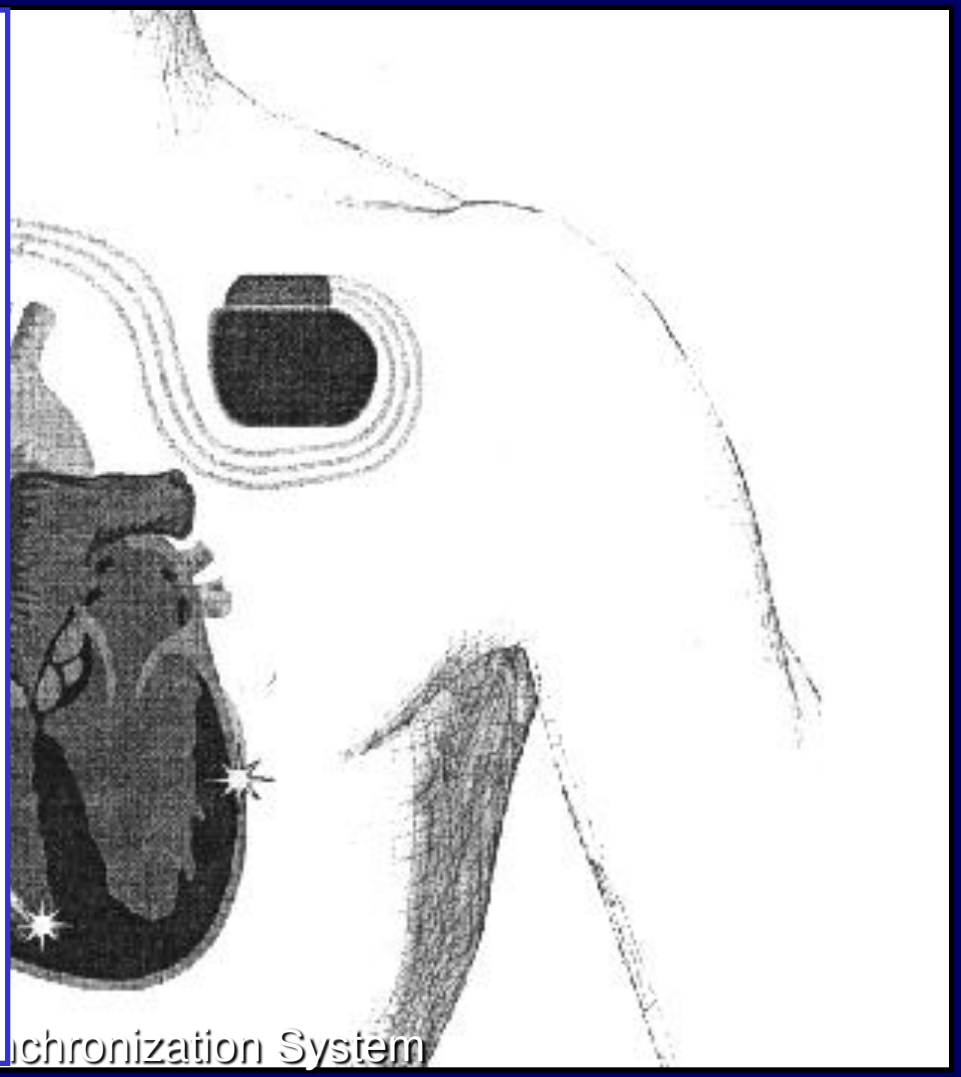




Courtesy of D. Kass, MD, Johns Hopkins University, Maryland.

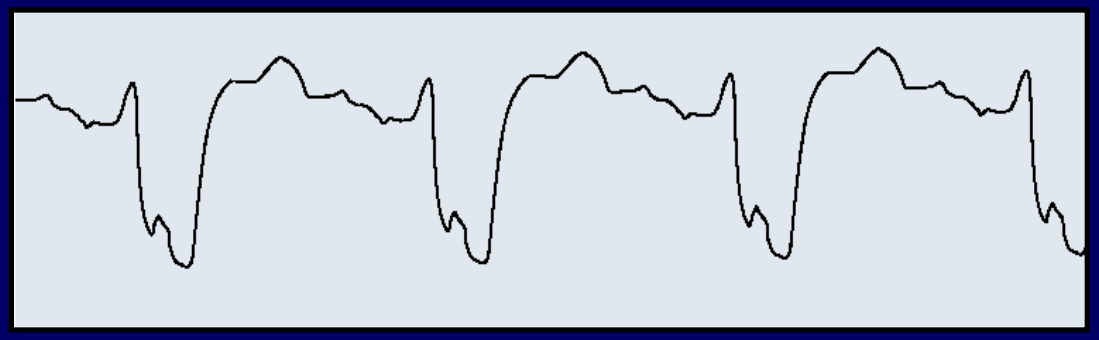
Achieving Cardiac Resynchronization
Mechanical Goal: Pace Right and Left Ventricles



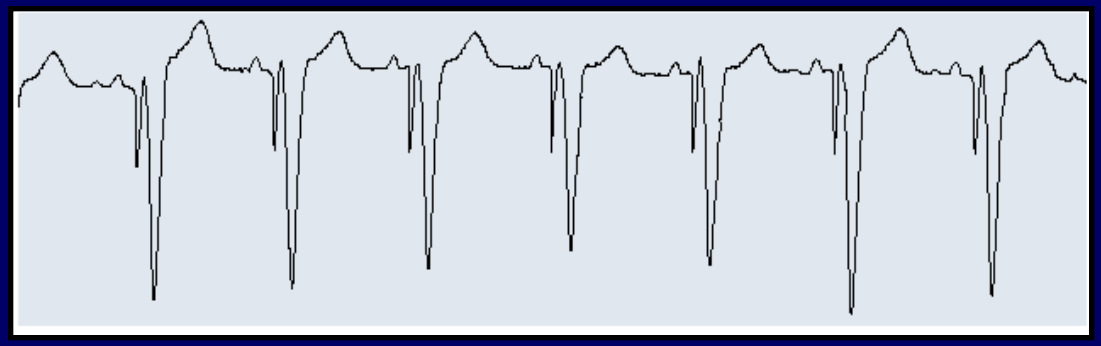


Cardiac Resynchronization Therapy

- Cardiac resynchronization, in association with an optimized AV delay, improves hemodynamic performance by forcing the left ventricle to complete contraction and begin relaxation earlier, allowing an increase in ventricular filling time.
- Coordinate activation of the ventricles and septum.

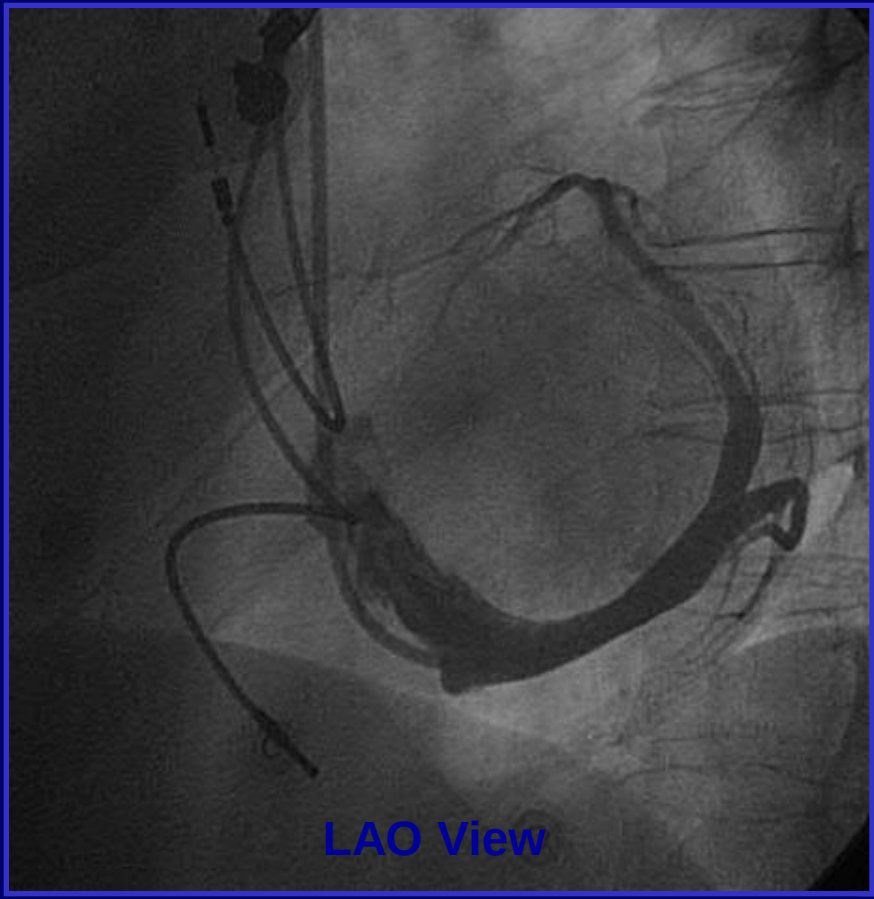


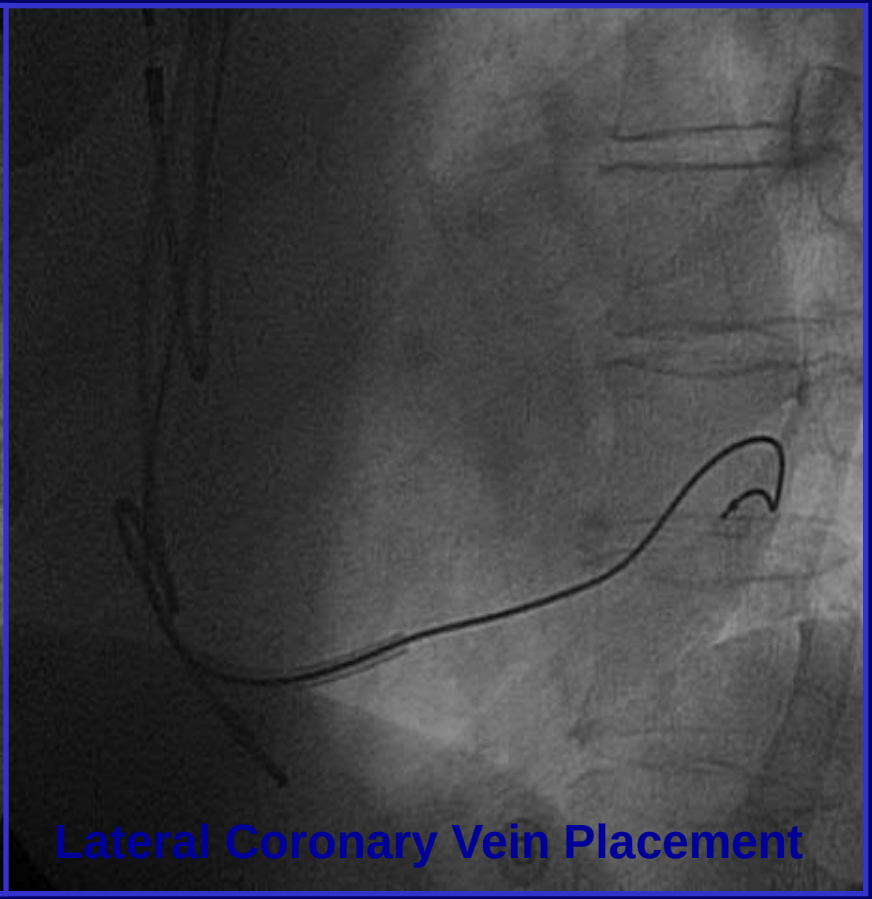
ECG depicting IVCD



ECG depicting cardiac resynchronization

LV Lead System





Courtesy of A. Auricchio, MD, University of Magdeburg, Germany.

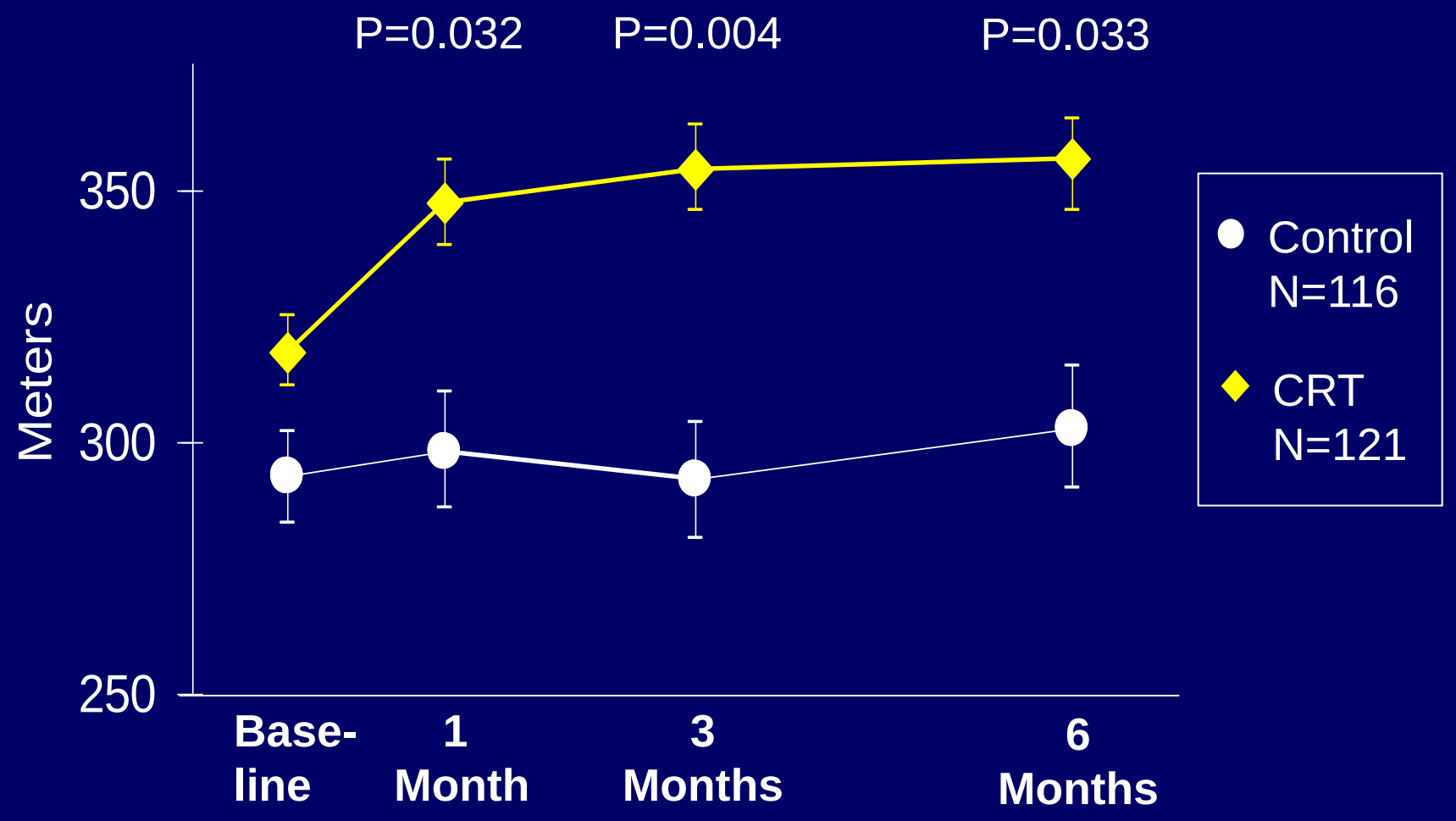
MIRACLE Trial

(Multicenter InSync Randomized Clinical Evaluation)

Pivotal Phase Results

Adapted from presentation by
William T. Abraham, MD
For the MIRACLE Investigators at the
Late Breaking Clinical Trials II Session,
American College of Cardiology
Orlando, FL; March 20, 2001

MIRACLE: 6-Minute Hall Walk Distance



Summary

- Pharmacological treatment is the mainstay in the management of patients with heart failure
- Cardiomyopathy patients with EF <35 should be considered for defibrillator implantation
- Class III/IV CHF patients with LBBB should be considerd for biventricular pacer.

Summary

- Primary etiology of heart failure should be identified and treated.
- Prevention: is the best treatment for CHF and patients at risk of HF should be treated aggressively.