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Focused on You

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

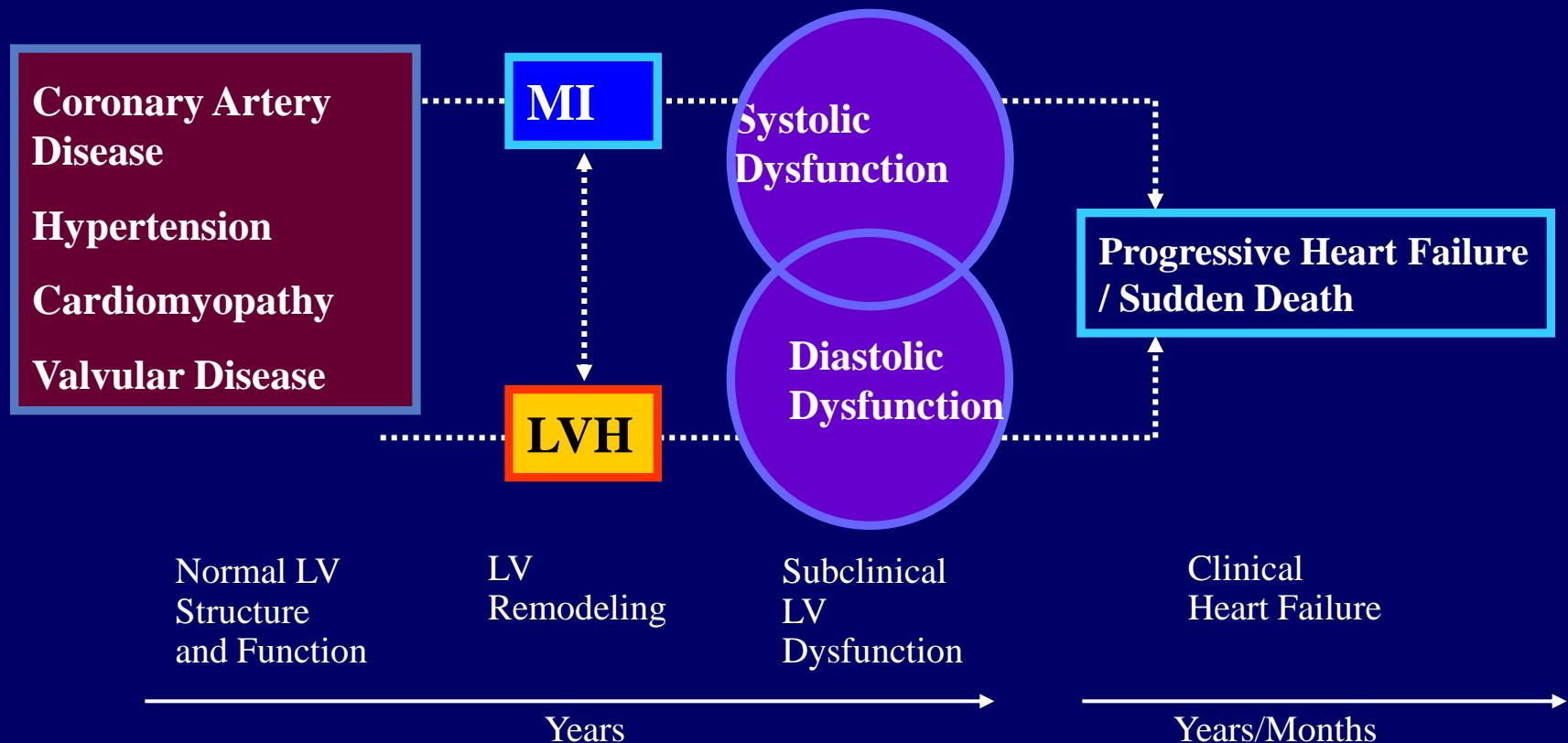
Heart Failure Classification

HFrEF: Heart failure with reduced Ejection fraction, LVEF <40%

HFmrEF: Heart failure with mid range EF, LVEF 40 – 49%

HFpEF: Heart failure with preserved EF, LVEF >50%

Progression of Cardiovascular Disease



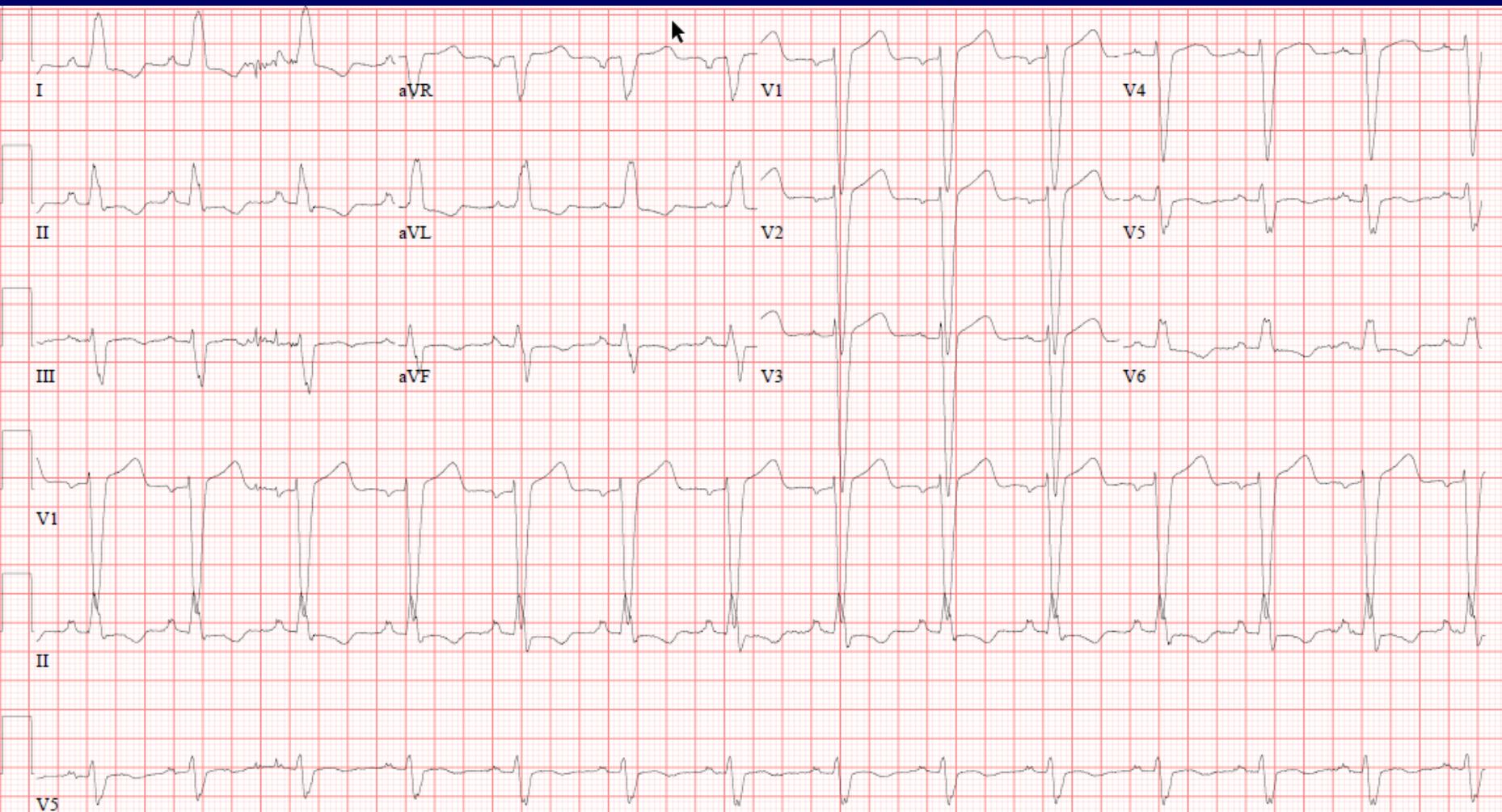
Adapted from: Levy et al. J Am Coll Cardiol. 1993;22(4):1111-1116.

→ = Possible pathway
of progression

NR 70M

- Presented to hospital July 12, 2017 with SOB with mild exertion
- Past Med Hx: HTN, DM on losartan 25 mg daily
- Physical Exam: Few basilar crackles
- Labs: K 5.4, otherwise normal
- ECG:

NR 70M



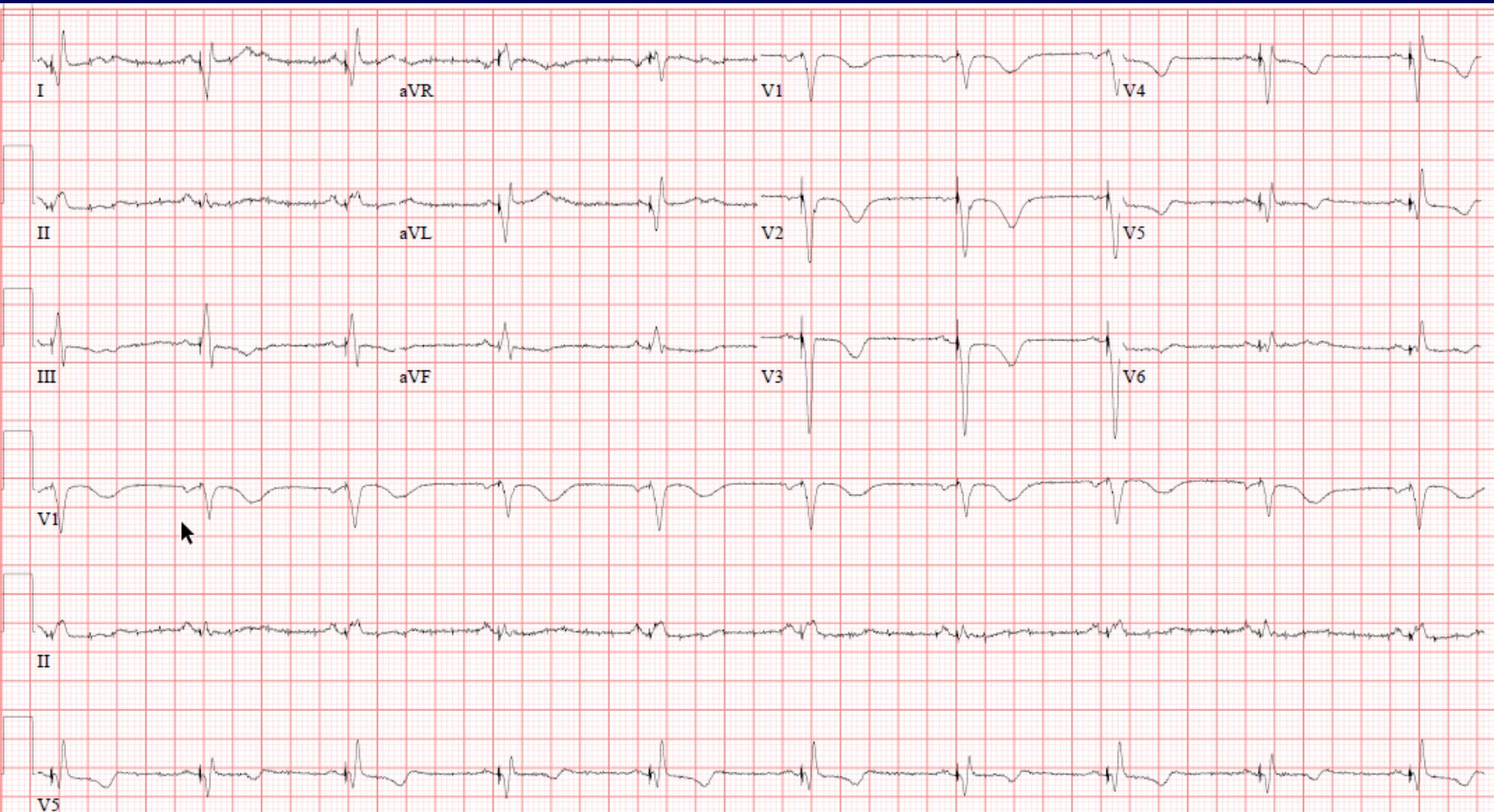
NR 70M

- Echocardiogram:
 - July 14, 2017: LVEF 20 – 25%
- Cardiac Catheterization: July 14, 2017
 - LVEF 25 – 30%, LCX 40-50% stenosis, other arteries showed minimal disease
- Started Metoprolol succinate 25 mg daily, lisinopril 5 mg daily, spironolactone 25 mg daily
- Metoprolol gradually increased to 100 mg daily

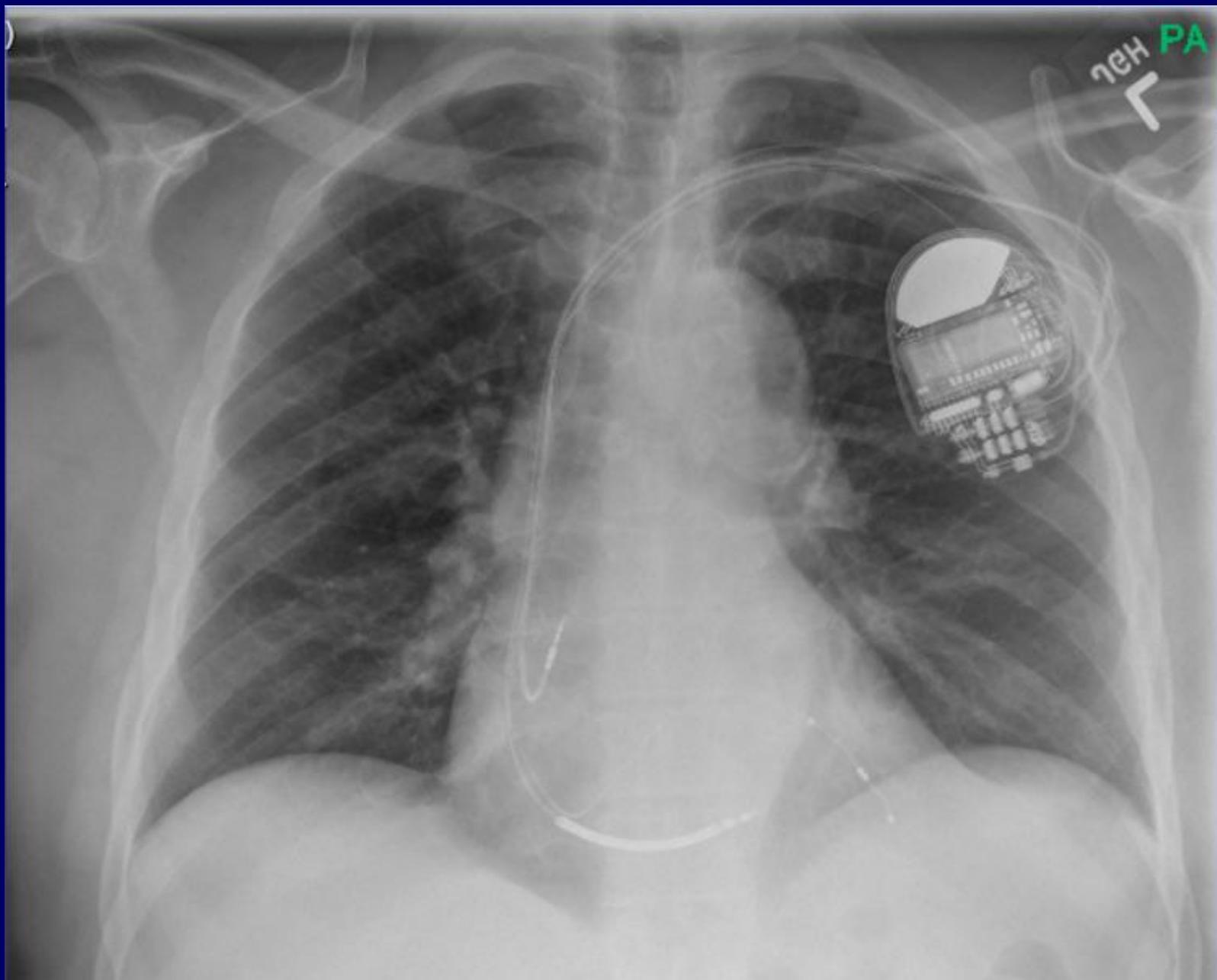
NR 70M

- Echocardiogram: October 10, 2017:
 - LVEF 25%
- Nov 11, 2017: Still SOB 1 flight of stairs
- Nov 28, 2017: Biventricular defibrillator implantation
- ECG:

NR 70M

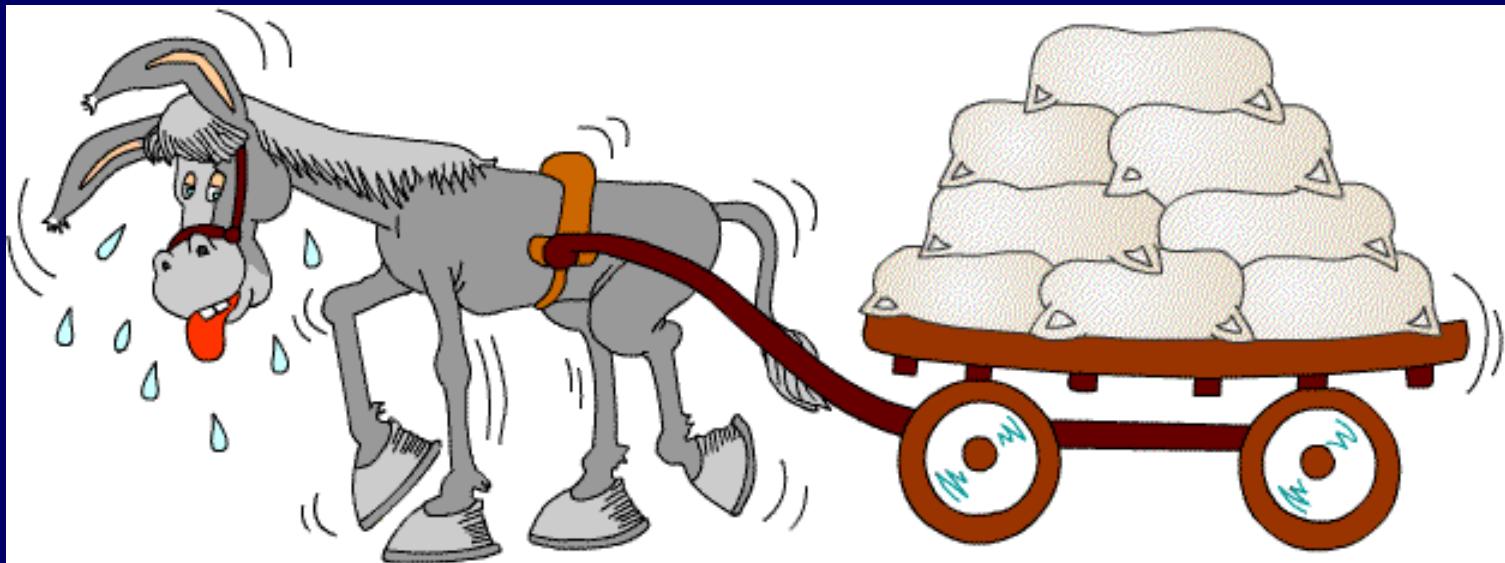


NR 70M



The Donkey Analogy

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



CHF: Epidemiology

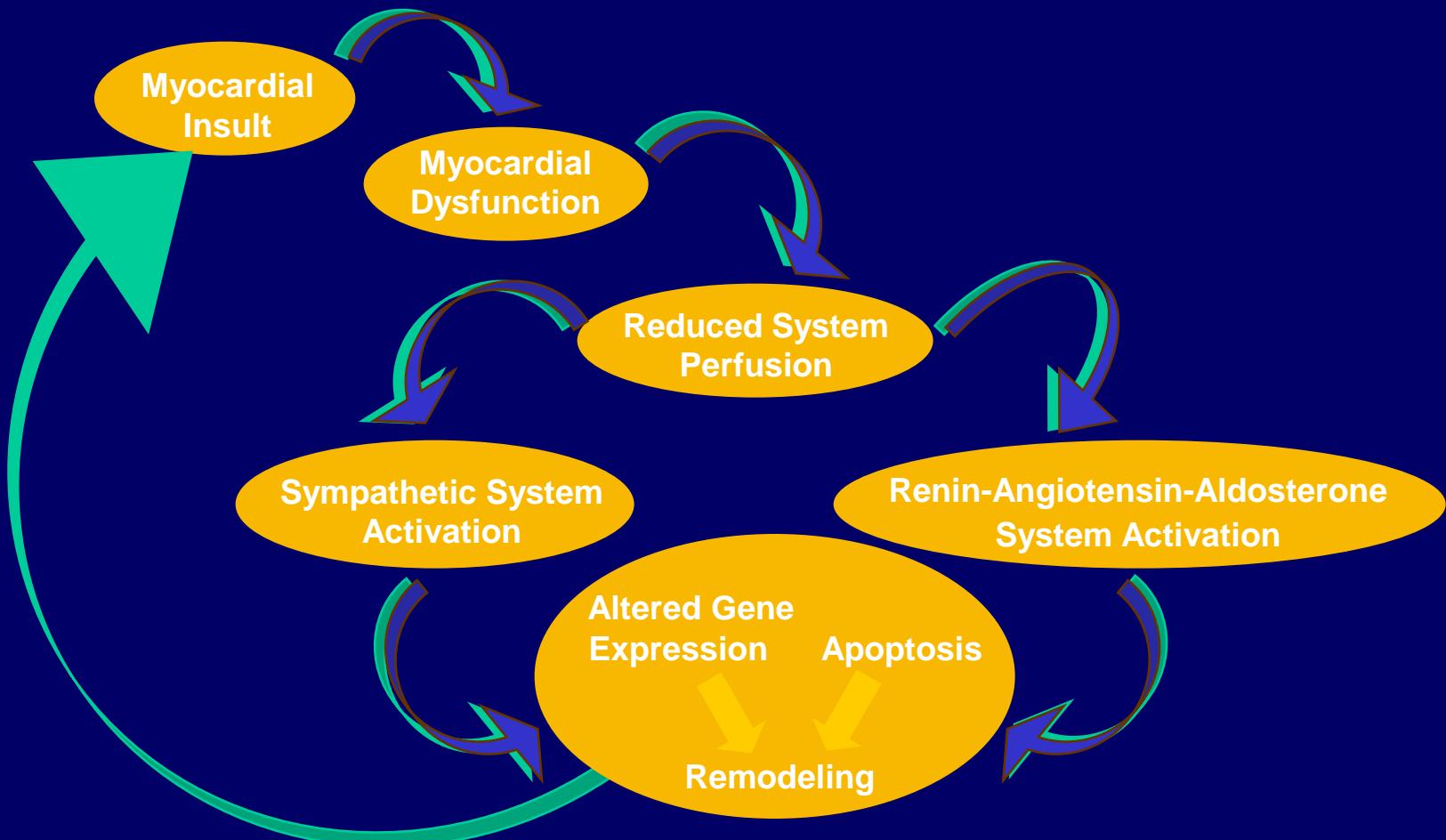
- 5 million Americans have heart failure
 - 550,000 new cases diagnosed annually
 - Over 250,000 deaths annually
 - Over 850,000 hospitalizations annually
 - Economic impact \$40 billion dollars annually
 - Incidence and prevalence increasing
- Source:AHA,CDC

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

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
 - Sarcoidosis
 - Constrictive Pericarditis
 - High-output failure
 - Chronic anemia
 - AV shunts
 - Thyrotoxicosis

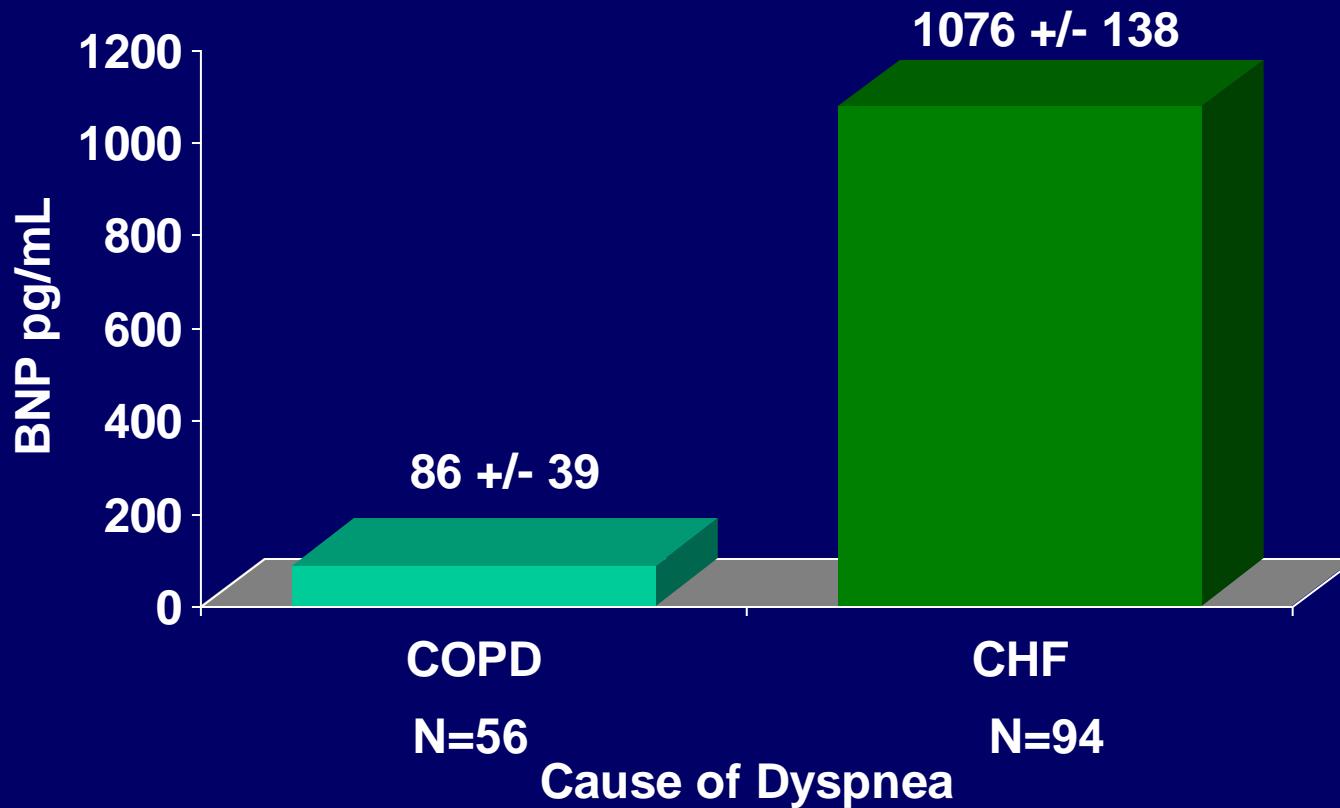
History, Physical Exam & Rx Plan

- Detail history including level of activity that causes shortness of breath
- Any symptom to suggest CAD
- Any recent viral infection
- Plan of care:
 - short, but frequent visits to physician.
 - At each visit patient's symptom should be compared with baseline presentation

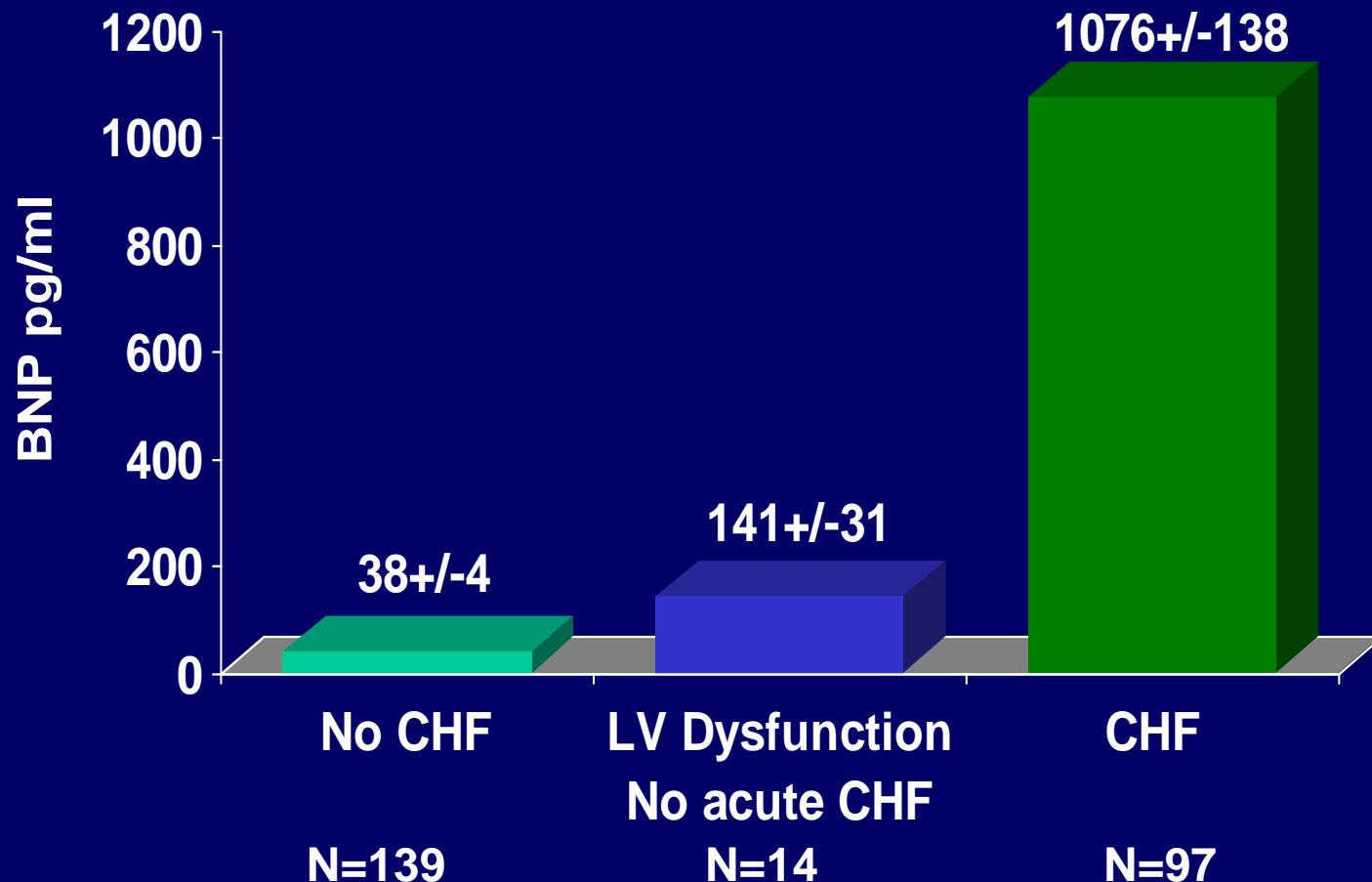
Diagnostic Work up

- 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 Levels in Patients With Dyspnea Secondary to CHF or COPD



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



Treatment Goals in the Management of Heart Failure

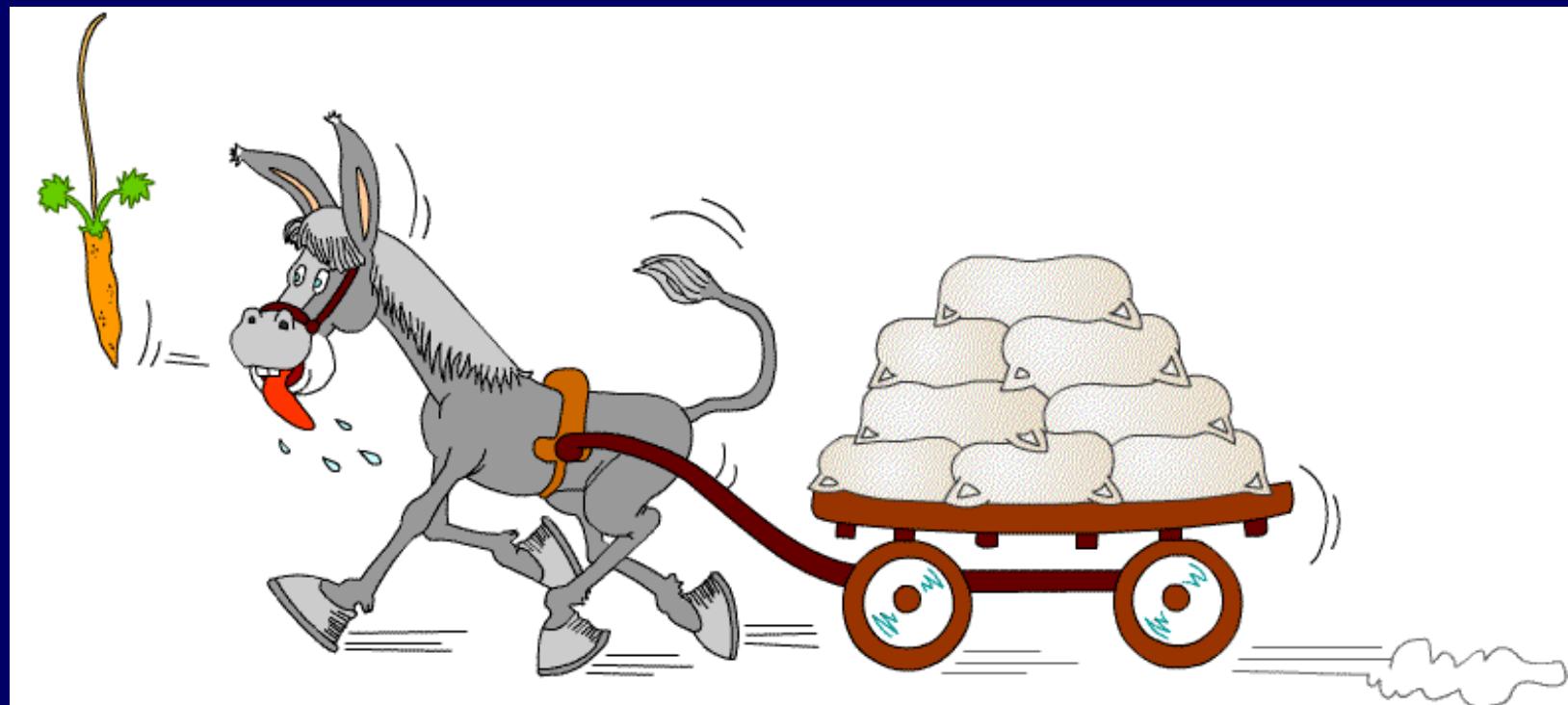
- Relieve symptoms
- Reduce morbidity
- Improve survival

Drug Therapy

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

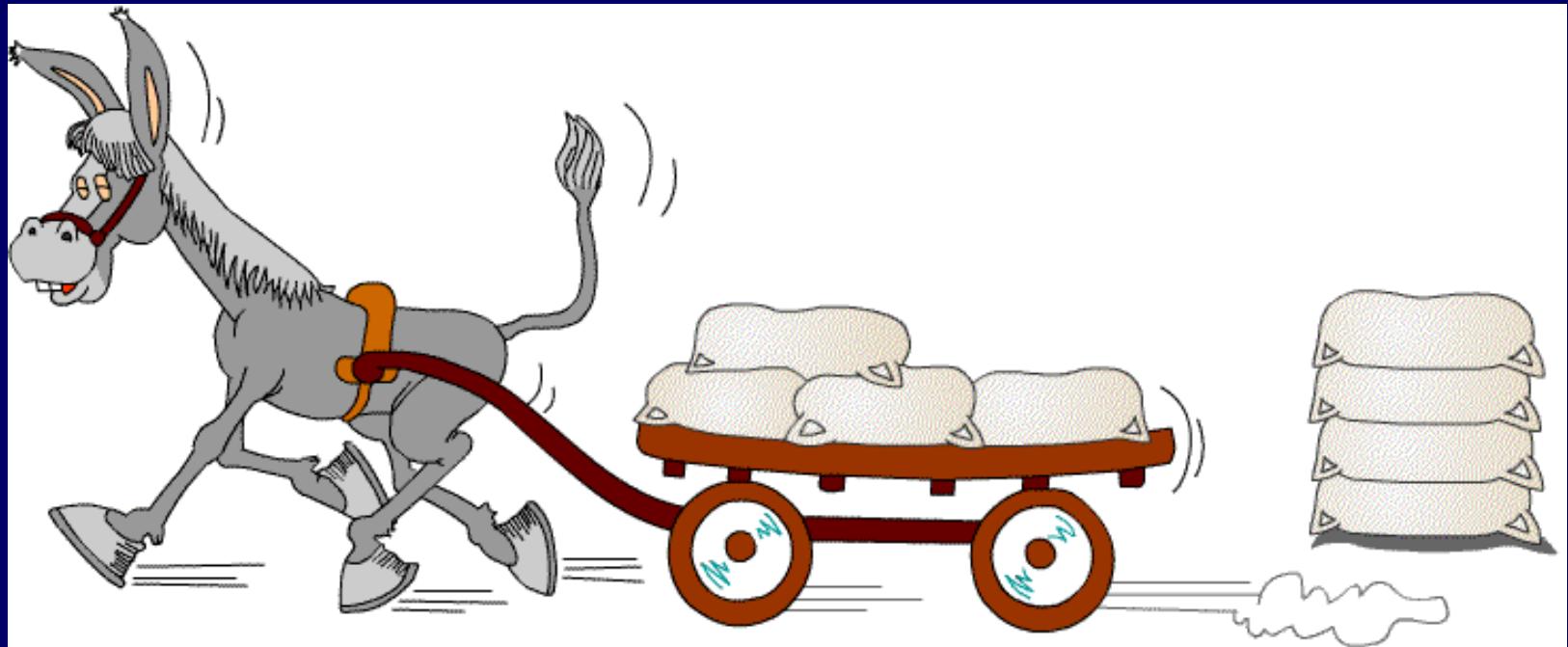
Digitalis Compounds

Like the carrot placed in front of the donkey

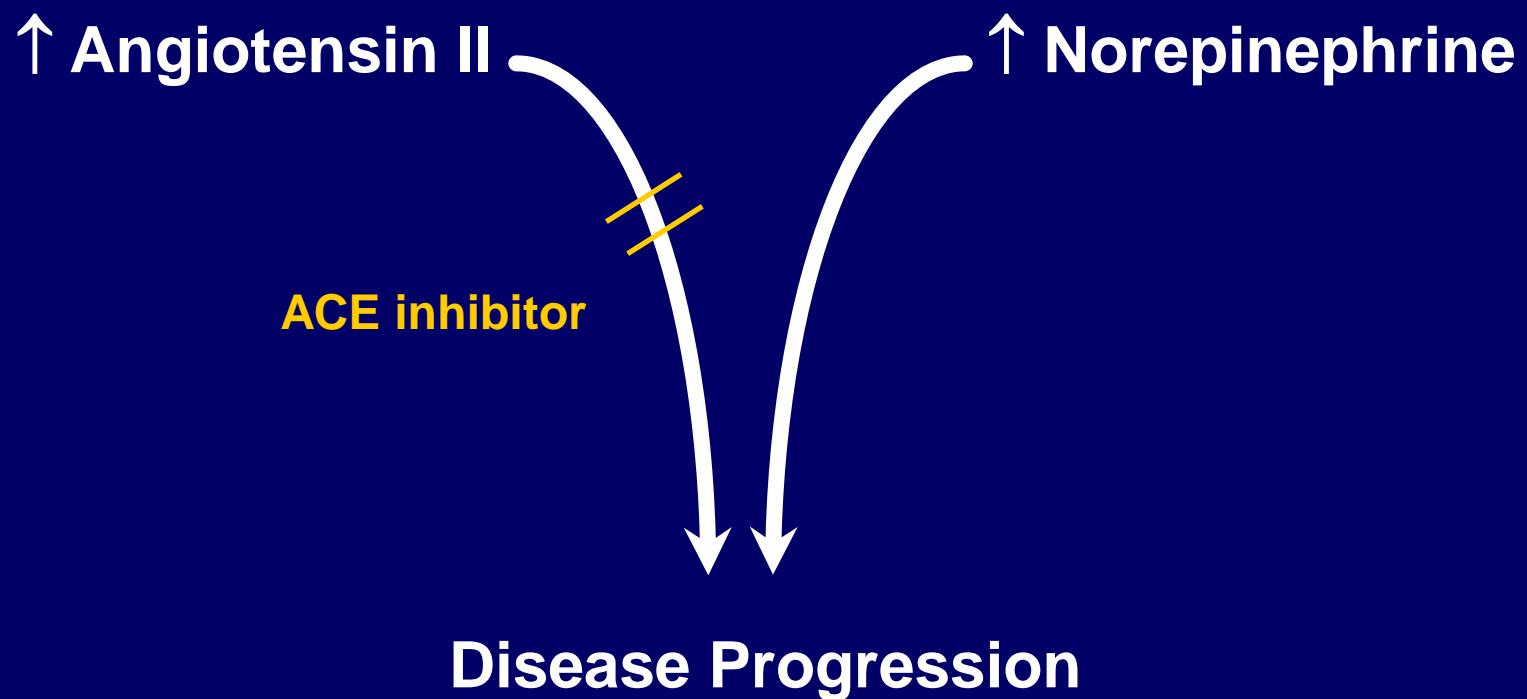


Diuretics, ACE Inhibitors, ARB

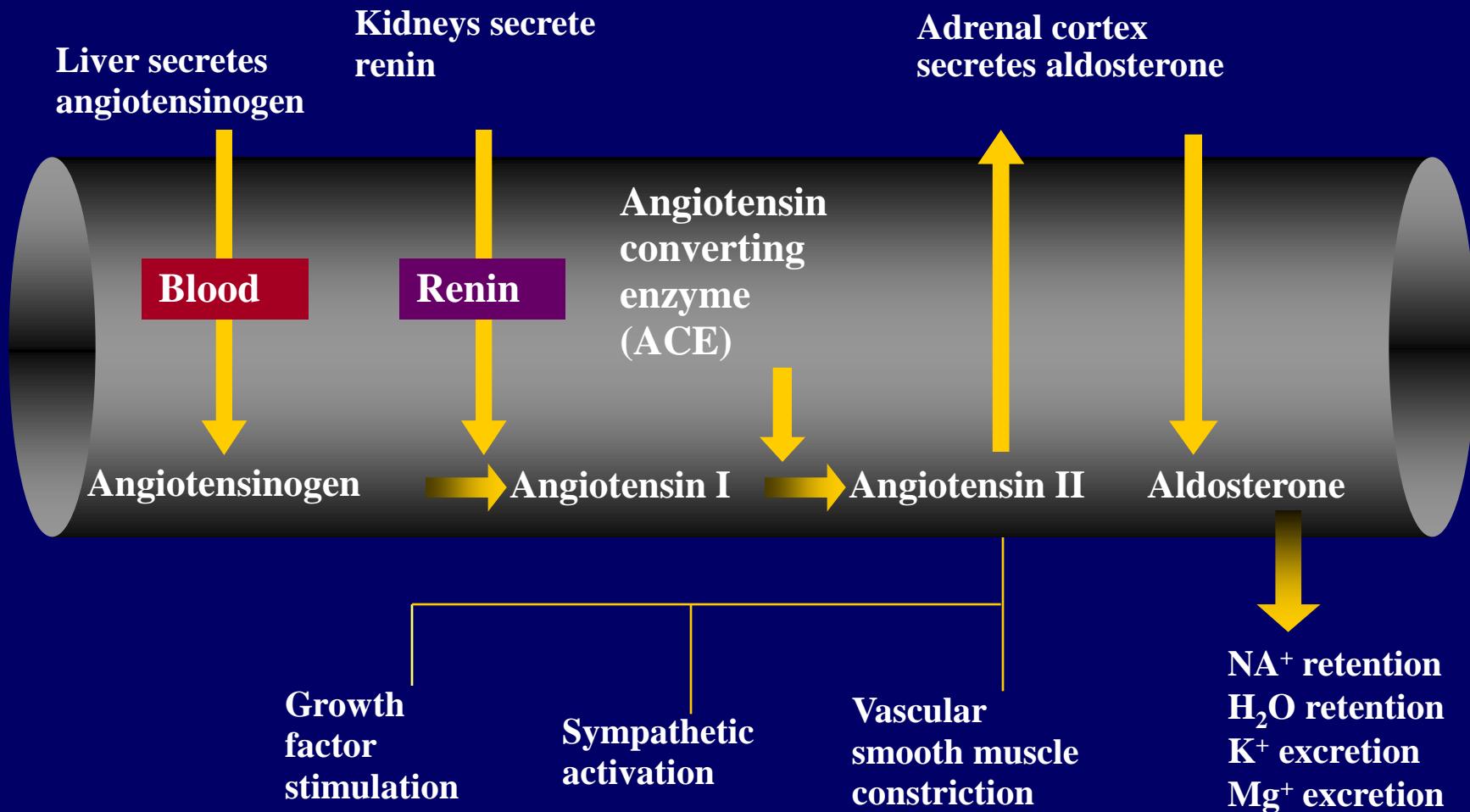
Reduce the number of sacks on the wagon



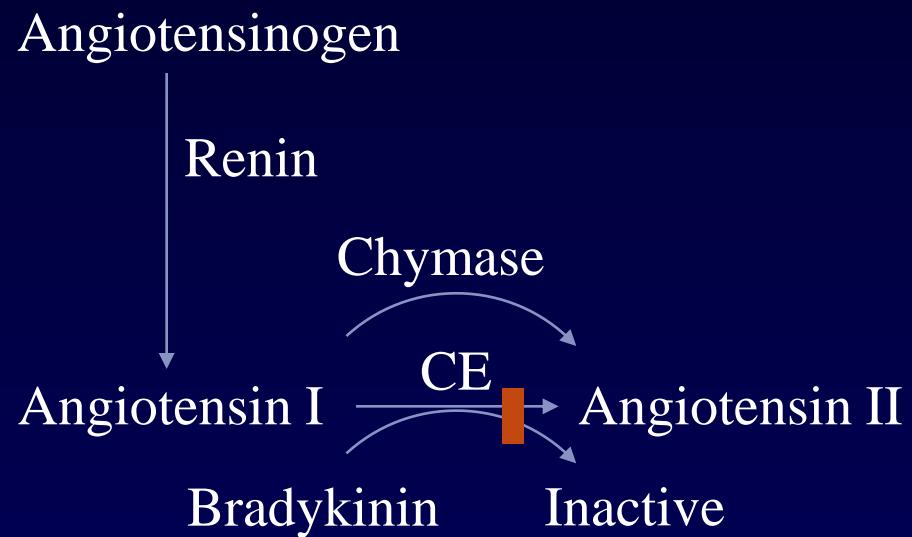
Effect of ACE Inhibition



The Renin-Angiotensin-Aldosterone (RAA) System

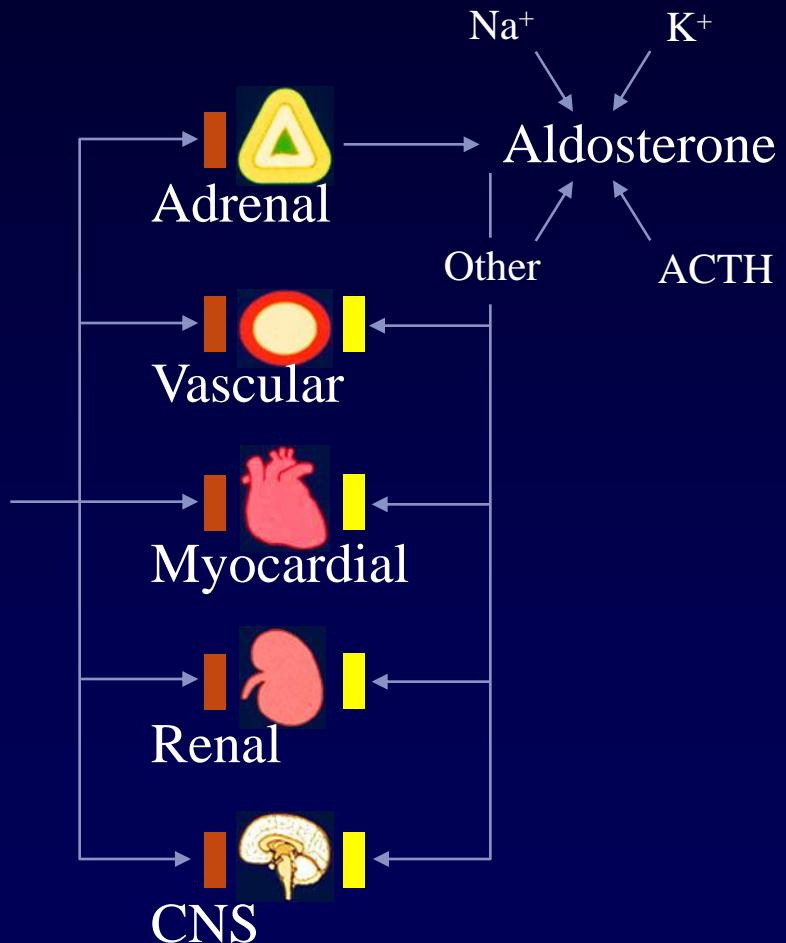


Dual Intervention in RAA System Pathways to Target Receptor Sites

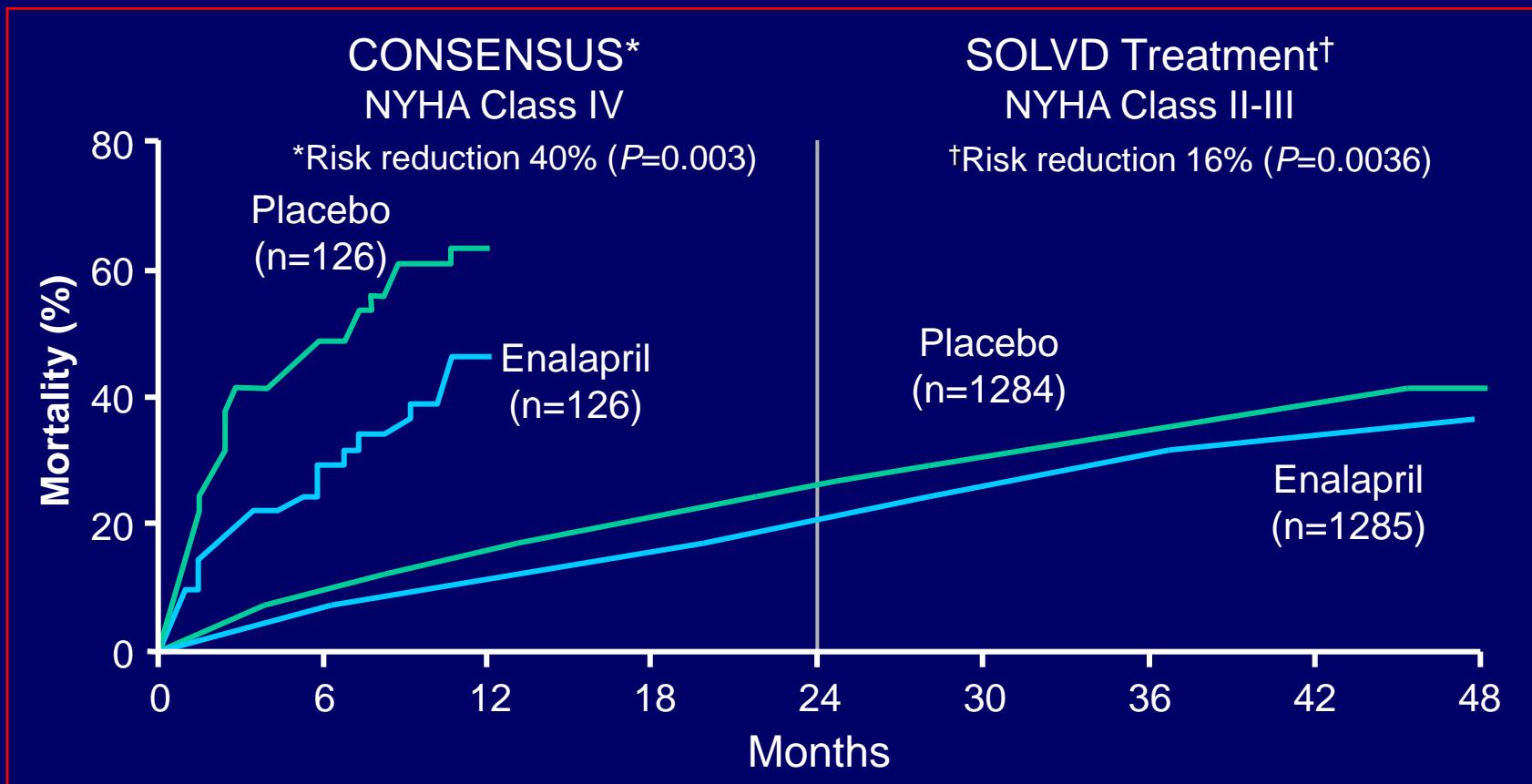


■ = Angiotensin II receptor blockade

■ = Aldosterone receptor blockade

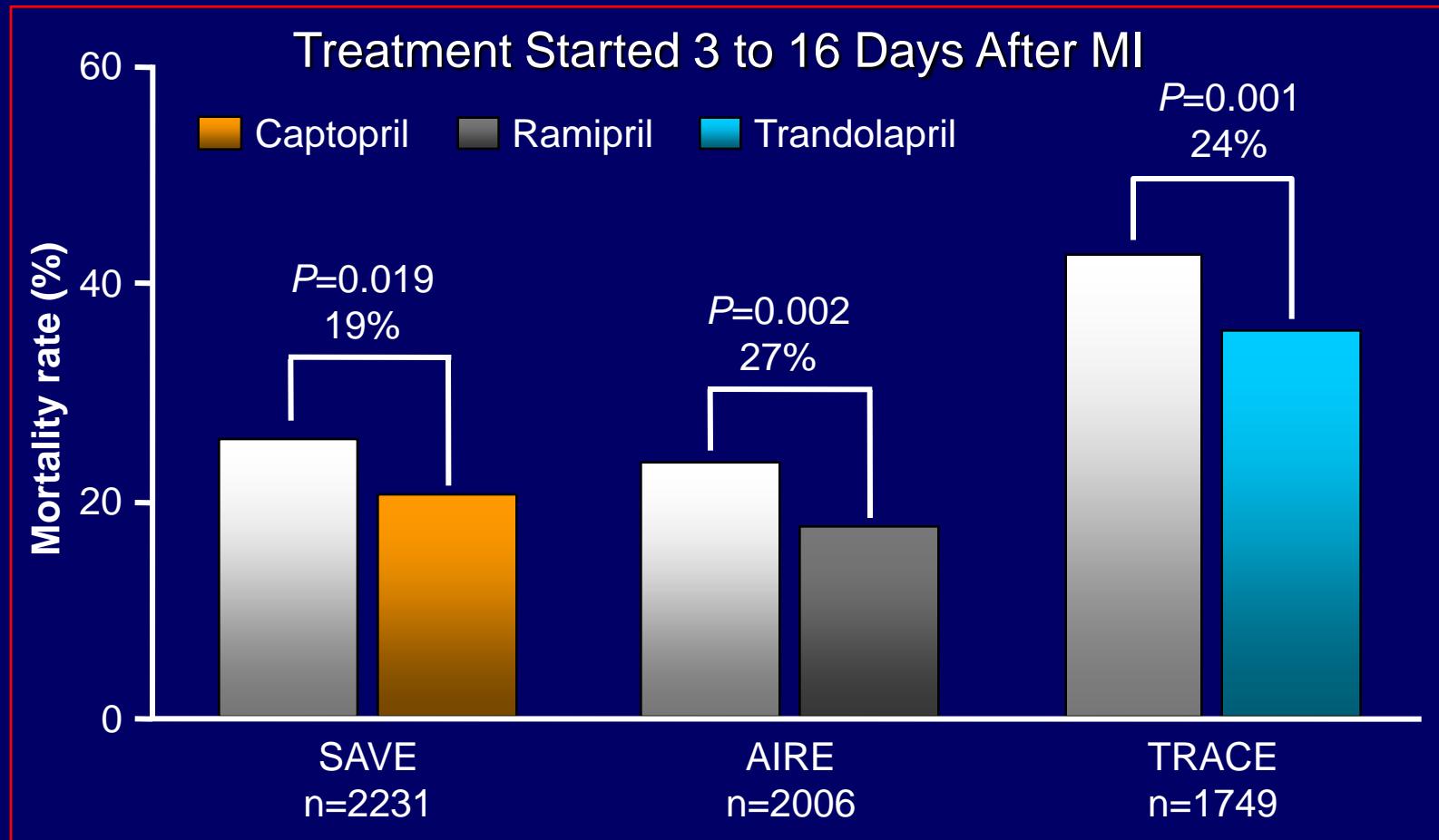


Effect of ACEIs in Patients with Symptomatic HF



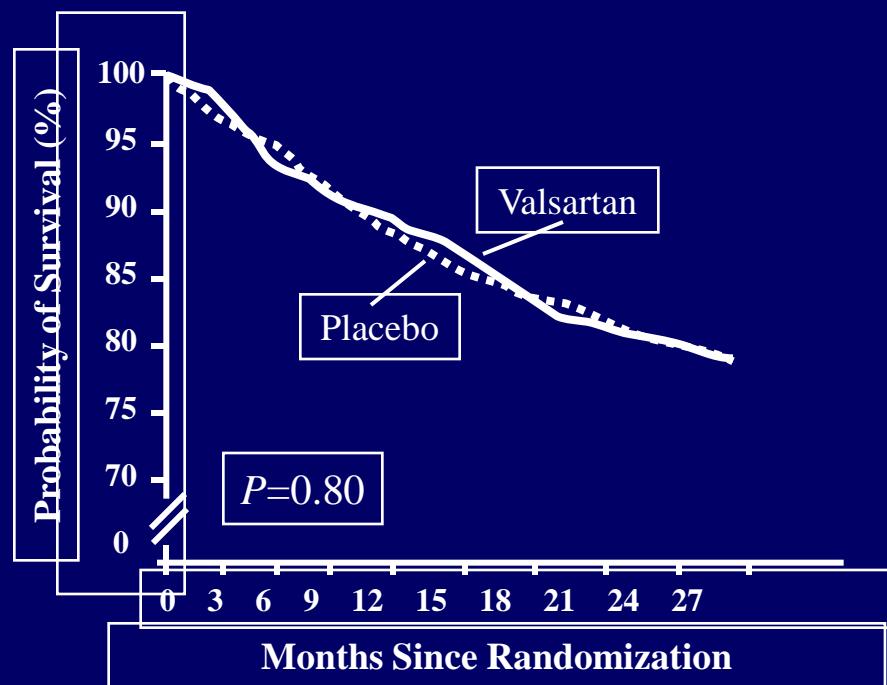
Adapted from CONSENSUS Trial Study Group *N Engl J Med* 1987;
SOLVD Investigators *N Engl J Med* 1991

Effect of ACEIs in Post-MI Patients with LVSD

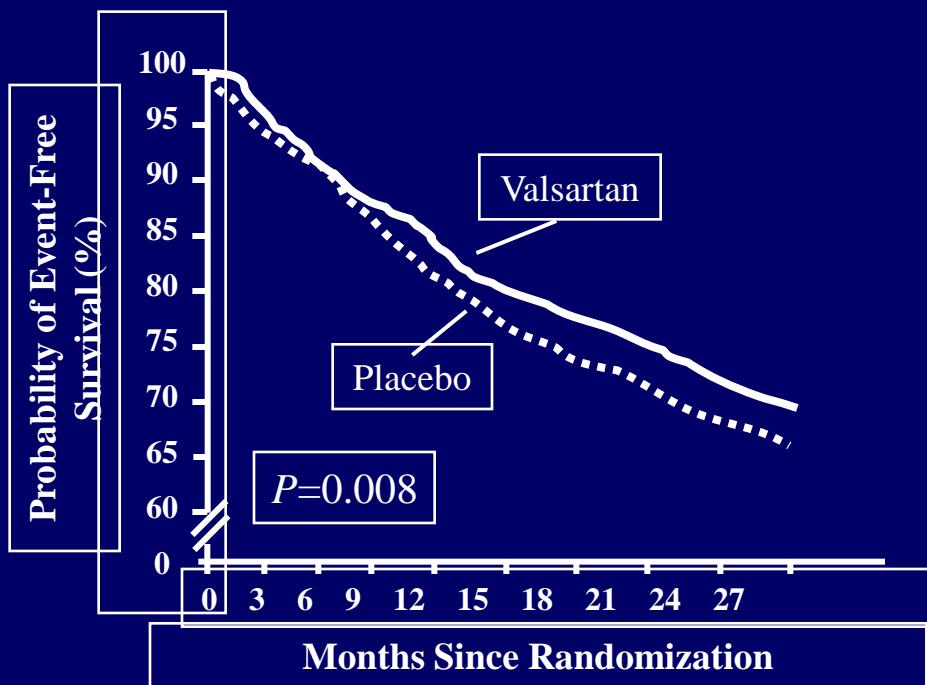


Adapted from Pfeffer M, et al *N Engl J Med* 1992; AIRE Study Investigators *Lancet* 1993;
Kober L, et al *N Engl J Med* 1995

Val-HeFT ARB vs Placebo

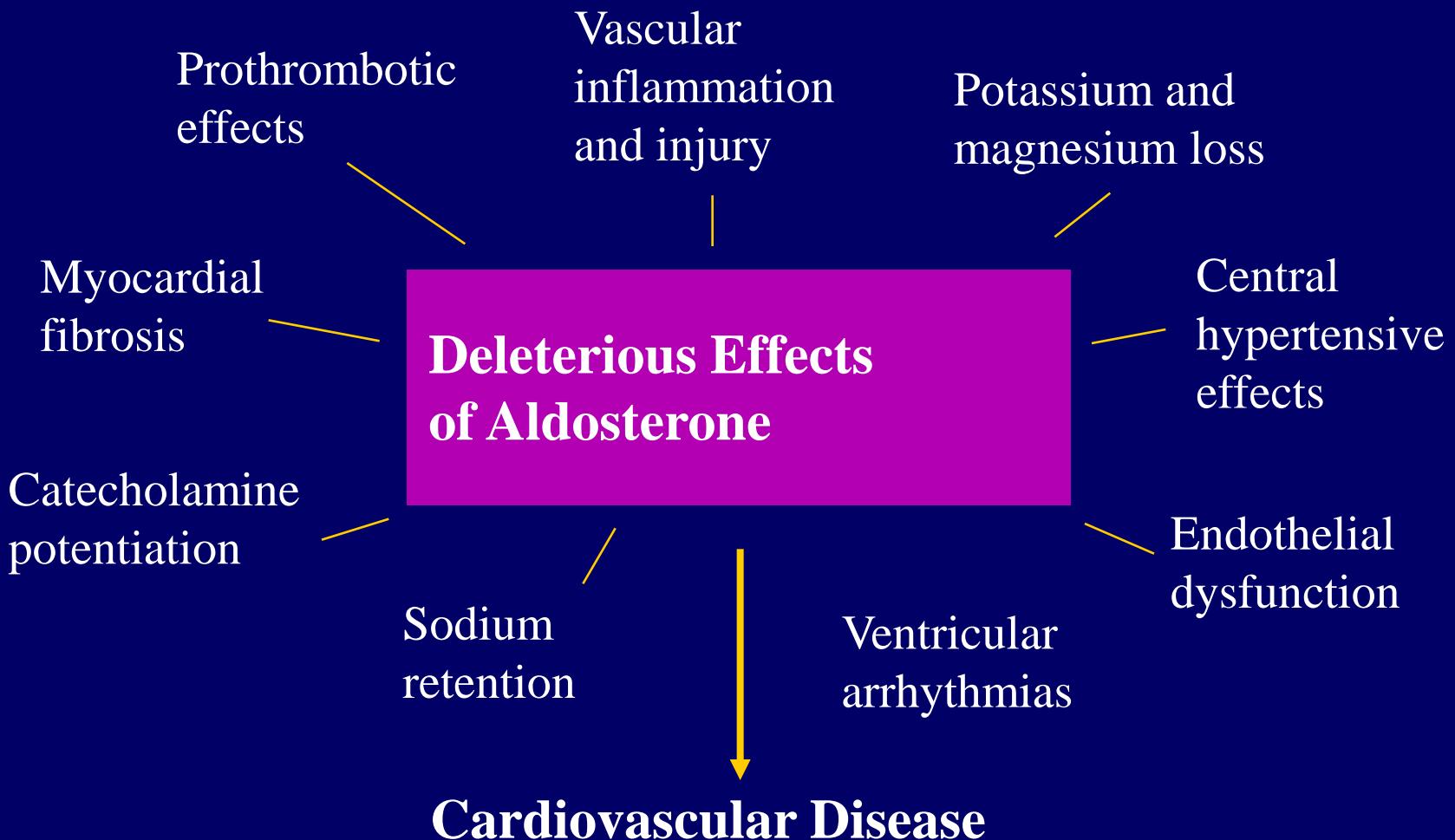


All-Cause Mortality



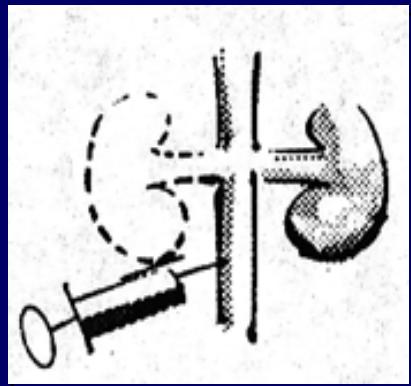
All-Cause Mortality/Morbidity

Aldosterone's Role in Cardiovascular Disease

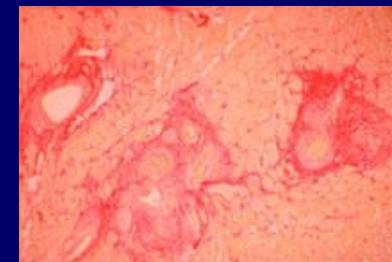


Spironolactone Prevents Myocardial Fibrosis

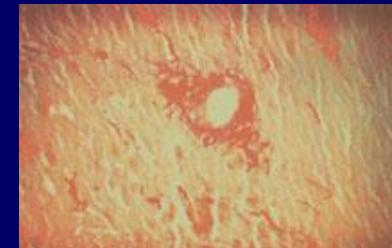
Aldosterone Infusion in Uninephric Rat



Treatment	HBP	LVH	Fibrosis
Control (aldosterone active)	Yes	Yes	Yes
Low-dose spironolactone	Yes	Yes	No
High-dose spironolactone	No	No	No



Fibrosis

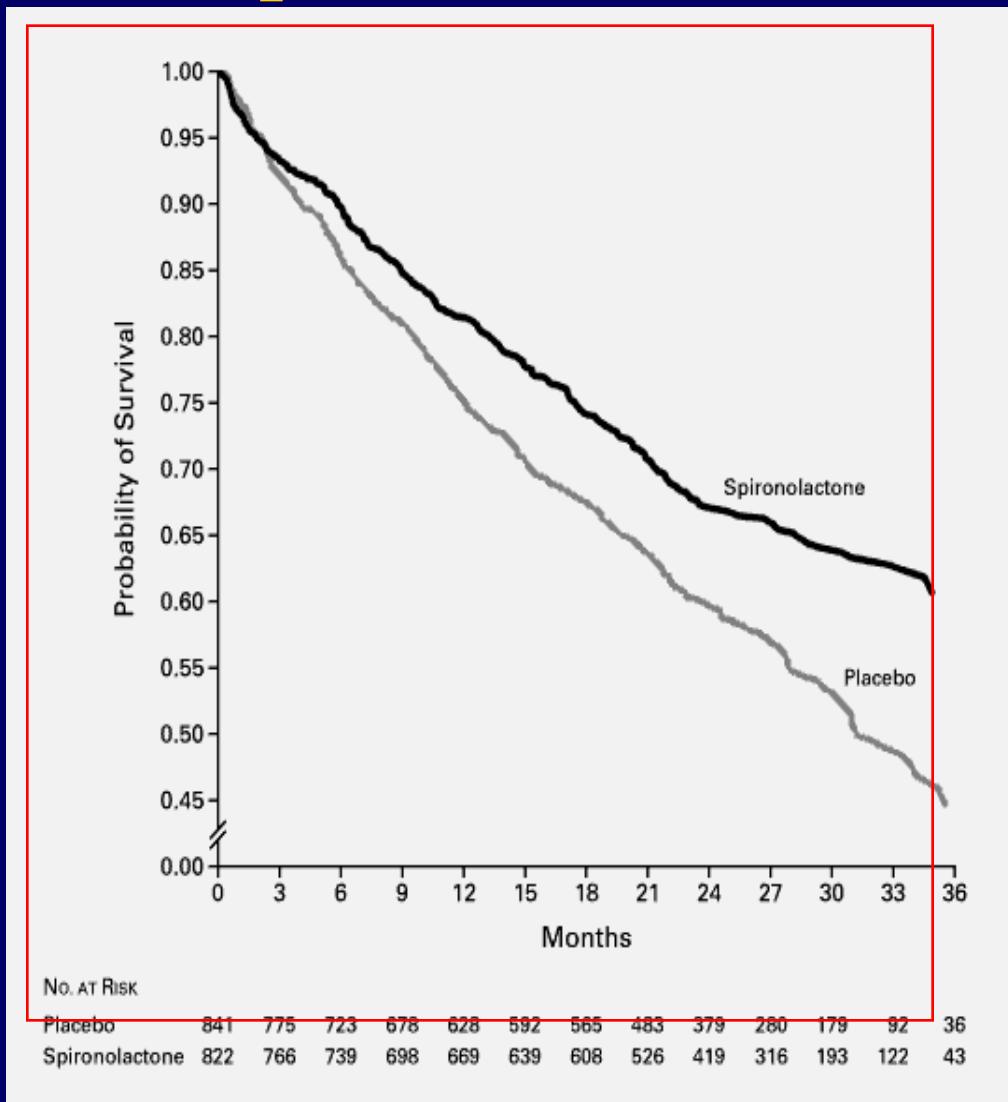


No fibrosis

HBP = high blood pressure; LVH = left ventricular hypertrophy

Adapted from Weber KT, Brilla CG. *Circulation*. 1991;83:1849-1865.

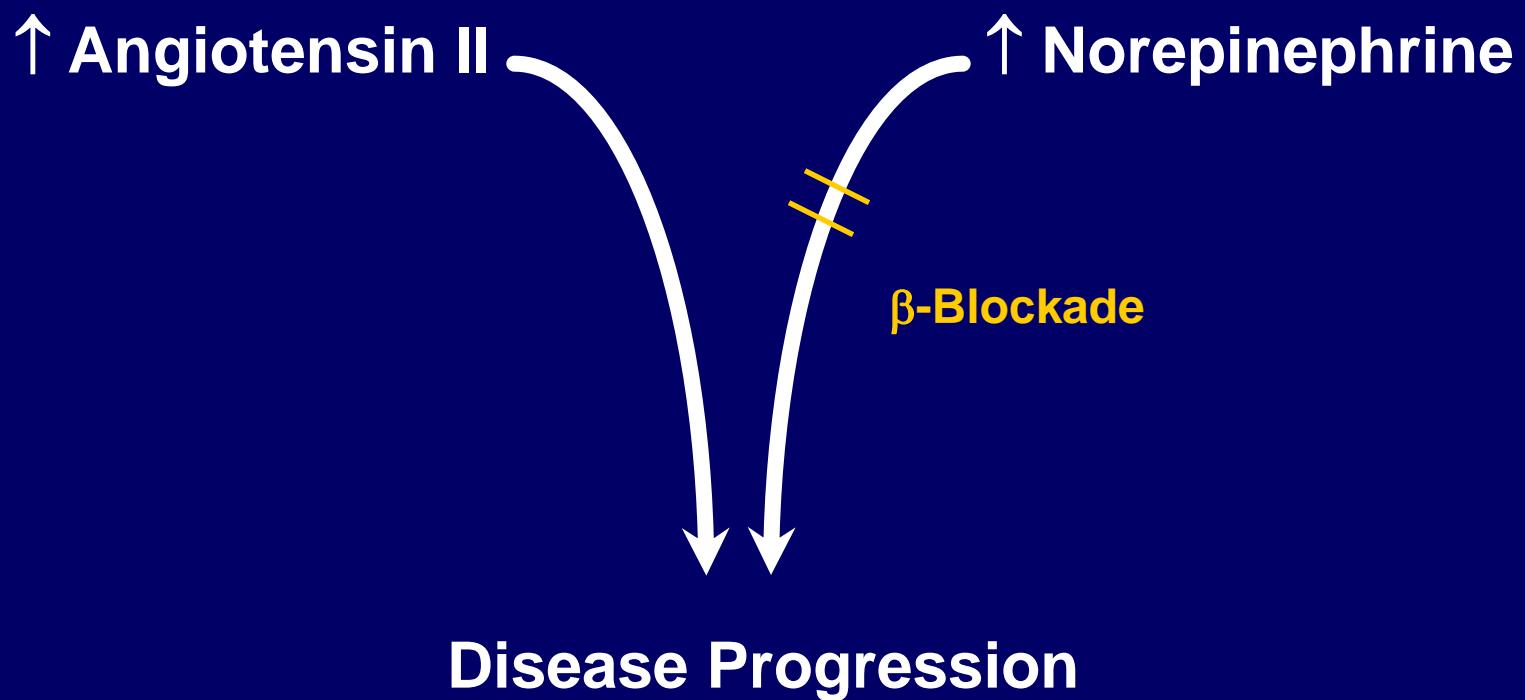
Mortality Reduction with Spironolactone in HF: “RALES”



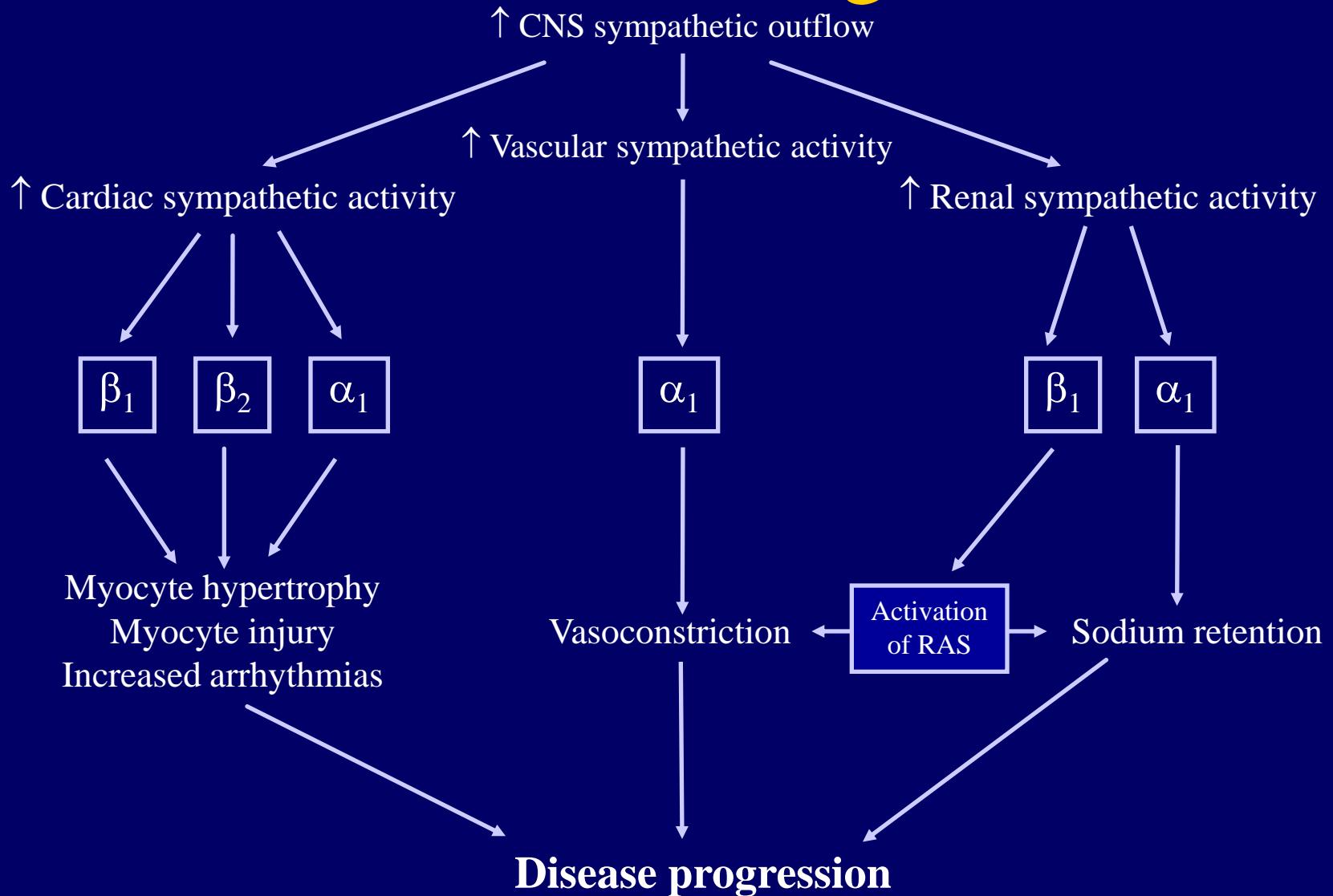
Kaplan–Meier Analysis: risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group ($P<0.001$).

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

Effect of β -Blockade



Adrenergic Pathway in Heart Failure Progression

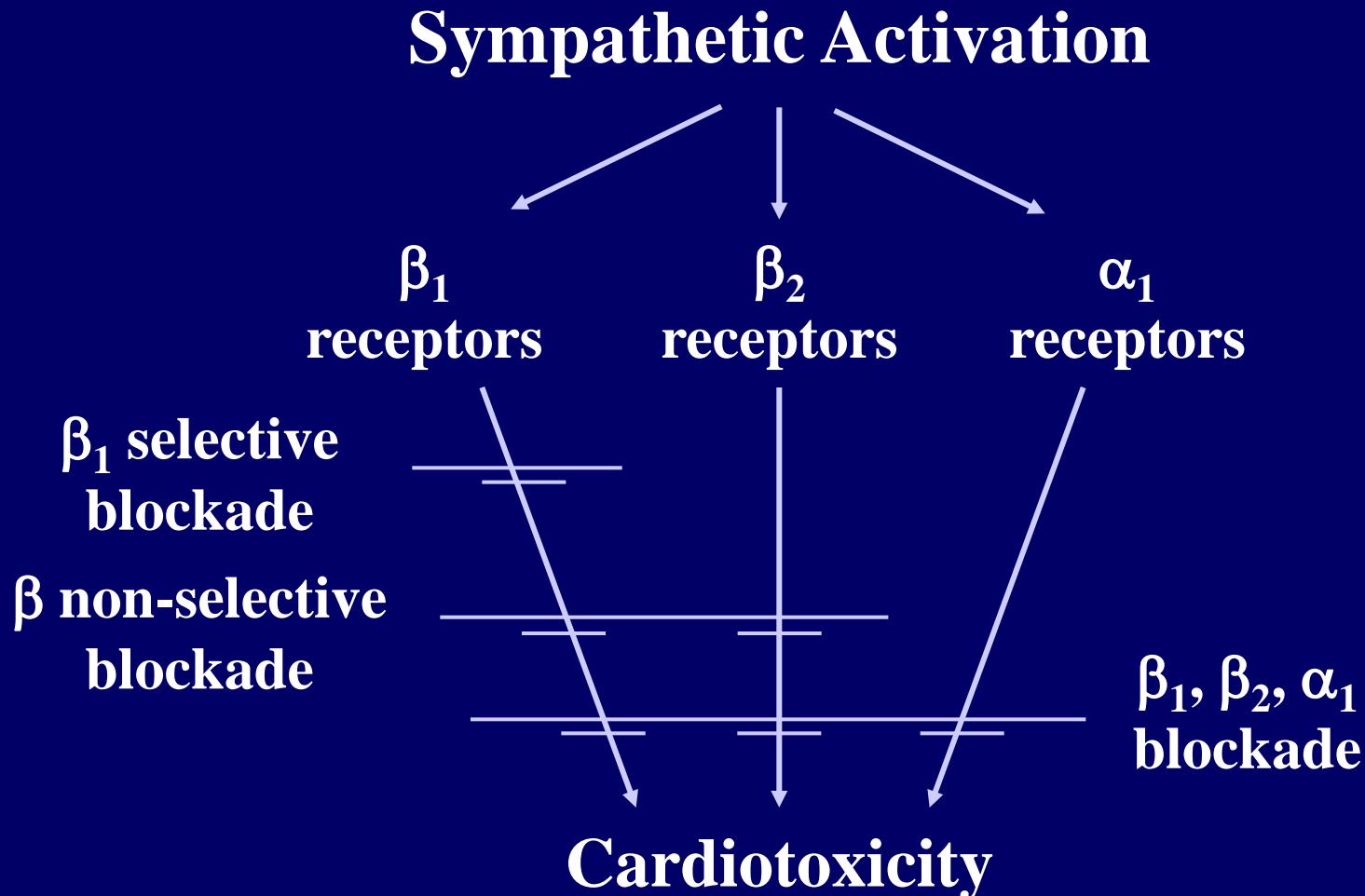


Ratio of Adrenergic Receptors in the Heart

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

Selectivity of β -Blocking Agents



Major Placebo Controlled Trials of Beta-Blockade in Heart Failure

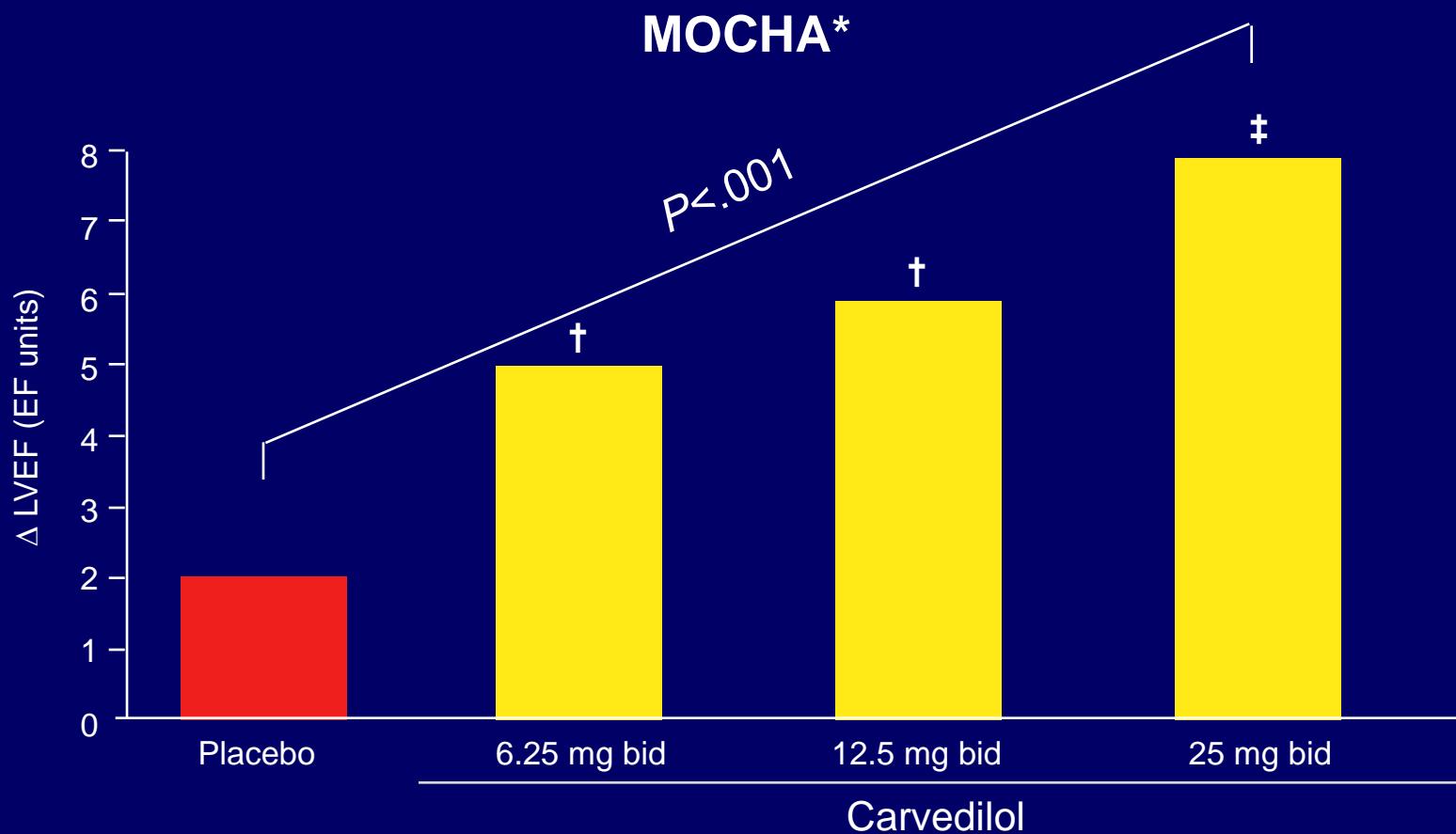
Study	Drug	HF Severity	Patients (n)	Follow-up (yrs)	Target Dosage (mg)	Mean Dosage Achieved (mg/day)	Effects on Outcomes
CIBIS <i>Circ. 1994</i>	bisoprolol*	moderate/severe	641	1.9	5 qd	3.8	All-cause mortality NS
CIBIS-II ³ <i>Lancet 1999</i>	bisoprolol*	moderate/severe	2647	1.3	10 qd	7.5	All-cause mortality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

Effect of Carvedilol Dose on Left Ventricular Ejection Fraction



Patients receiving diuretics, ACE inhibitors, \pm 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.

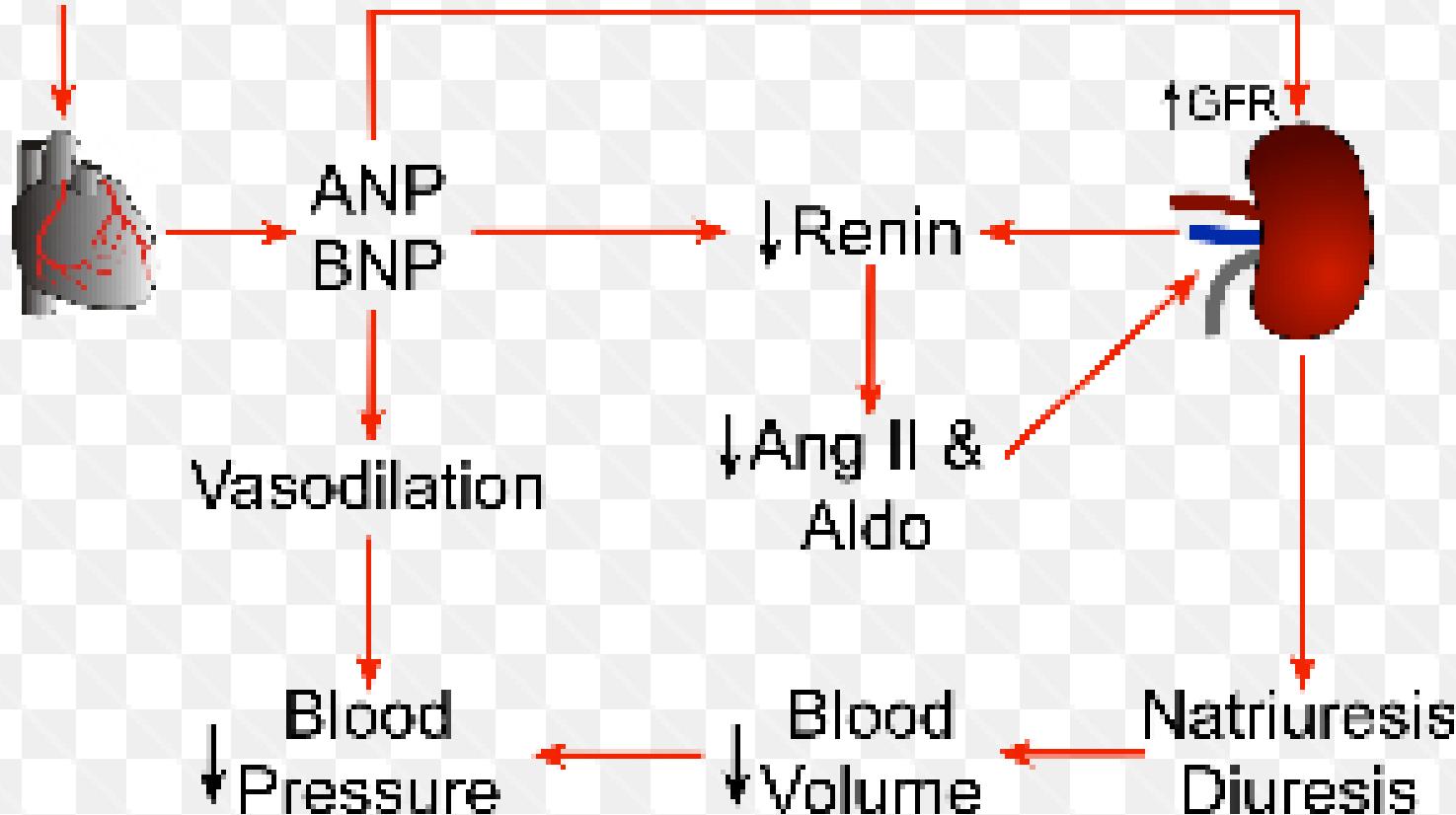
‡P<.0001 vs placebo.

Beta blockers are not used routinely in HF

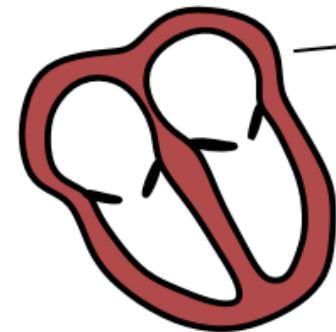
- 25-30% of HF patients get beta blockers
- Physician perception regarding beta blockers
 - Combining ACEI and BBs Rx is a hassle
 - Initiation only when stable
 - Initiation often leads to deterioration
 - Benefits are not seen for months
 - Rx can be expensive

Natriuretic Peptides

Cardiac distension
Sympathetic stimulation
Angiotensin II



Natriuretic Peptide Physiology



Atrial Natriuretic Peptide (ANP)

secreted by the atria in response to atrial distension

B-type Natriuretic Peptide (BNP)

secreted by the ventricles in response to distension from volume overload

C-type Natriuretic Peptide (CNP)

secreted by vascular endothelial cells in response to inflammatory mediators

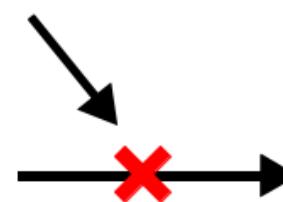


Sacubitril (Entresto®)

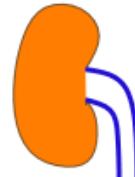
inhibits neprilysin and blocks ANP, BNP, and CNP metabolism

Neprilysin

metabolizes ANP, BNP and CNP



ANP
BNP
CNP



ANP and BNP stimulate sodium and fluid excretion



ANP and BNP promote myocardial relaxation and



ANP and BNP suppress sympathetic outflow



ANP, BNP, and CNP stimulate vasodilation

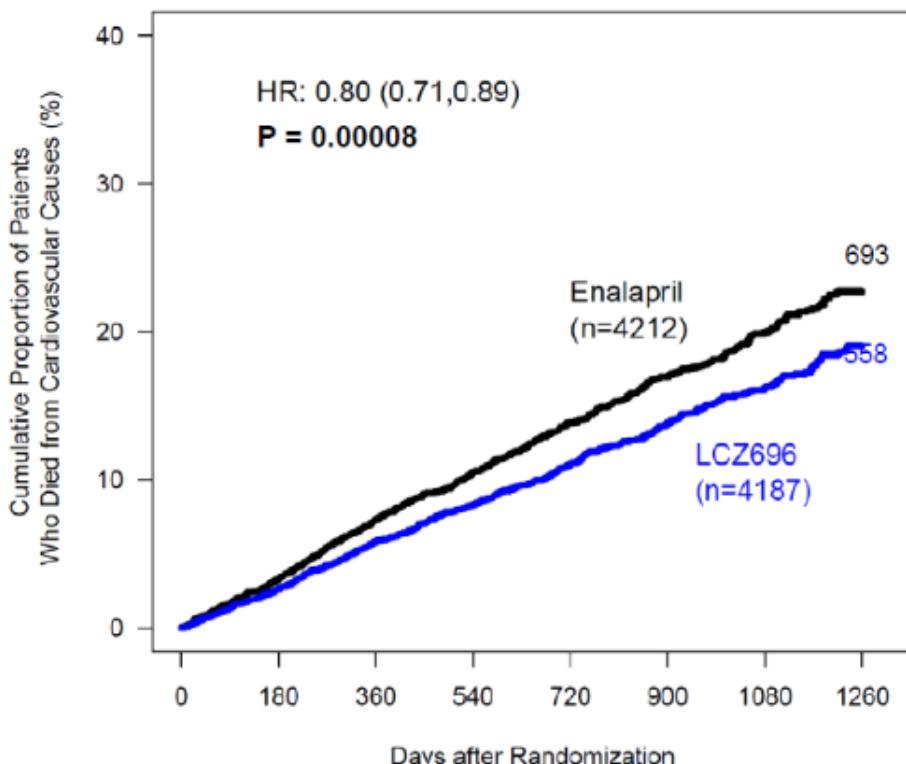
PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

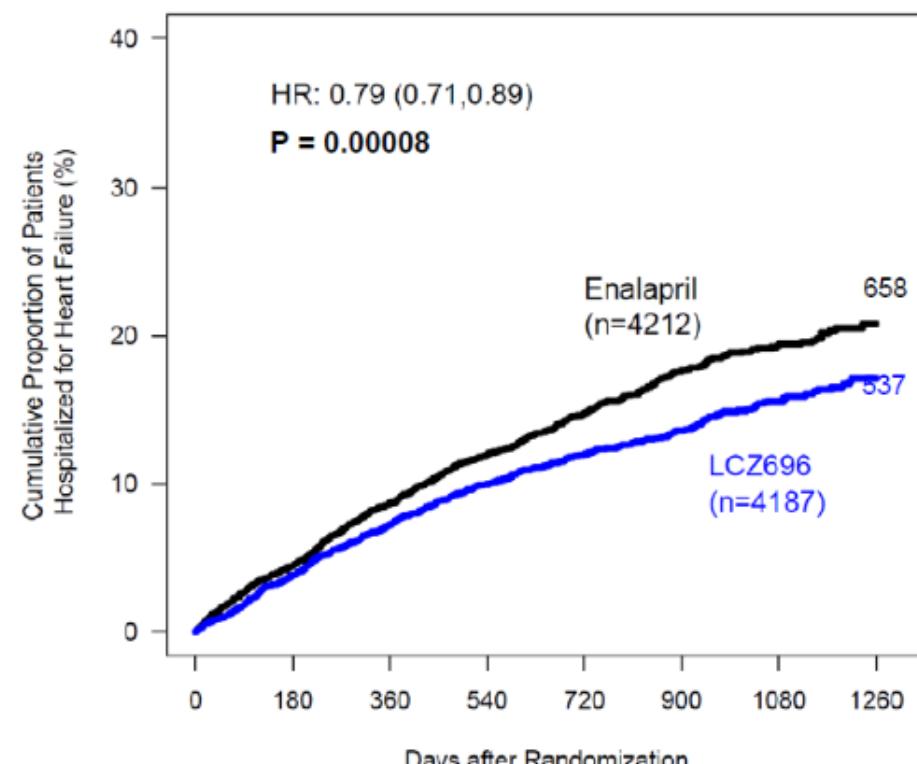
Primary composite outcome

HR: 0.80 (0.73, 0.87) p = 0.0000004

Death from CV causes
20% risk reduction



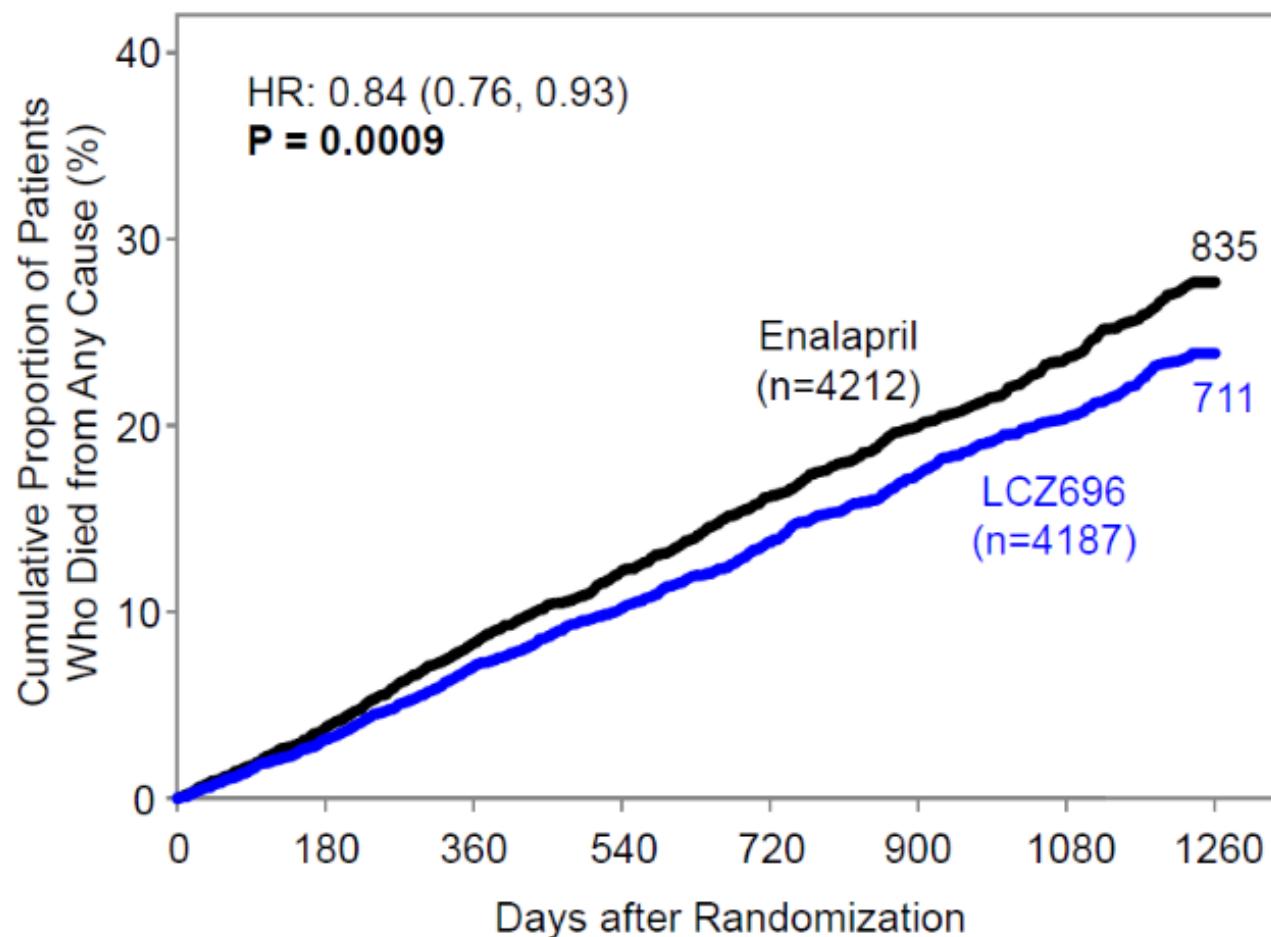
HF hospitalization
21% risk reduction



PARADIGM-HF

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause 16% risk reduction

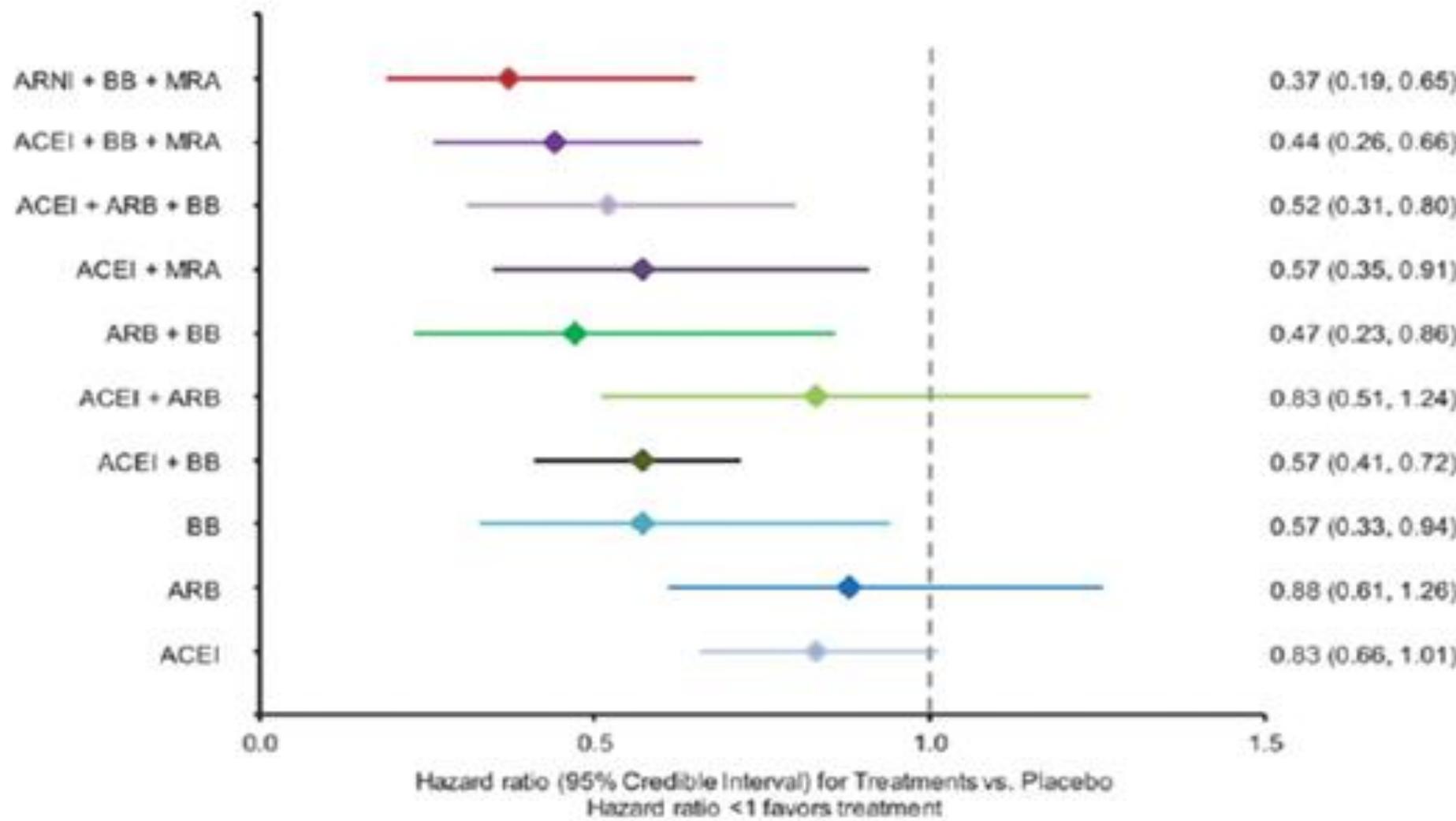


Sacubitril/ Valsartam

- Starting dose 24/26 mg BID
- Titrate to 49/51 mg BID
- Max dose 97/103 mg BID

Pooled Data from 78 studies (57 RCT)

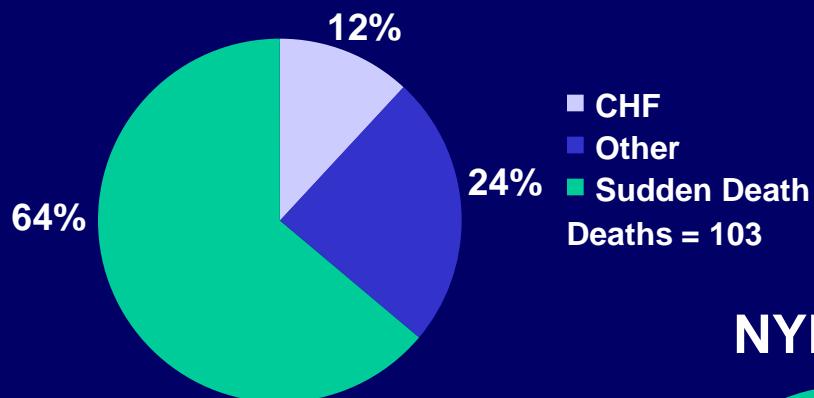
Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals.



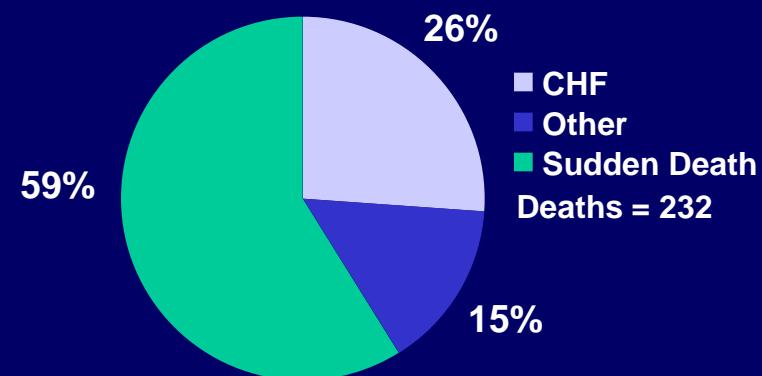
Sudden Cardiac Death in Heart Failure

SCD—a prominent mode of death

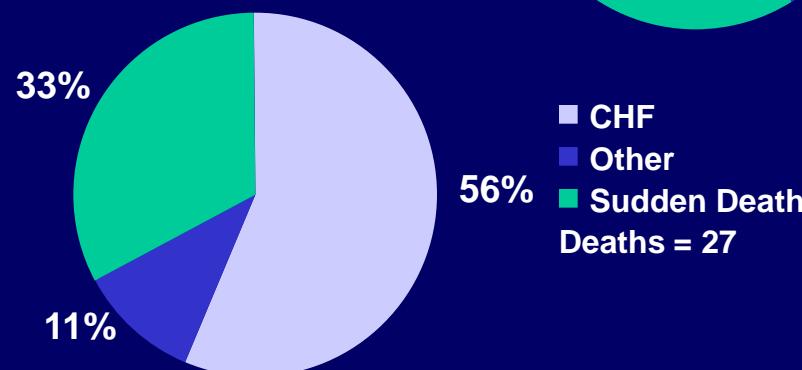
NYHA II



NYHA III

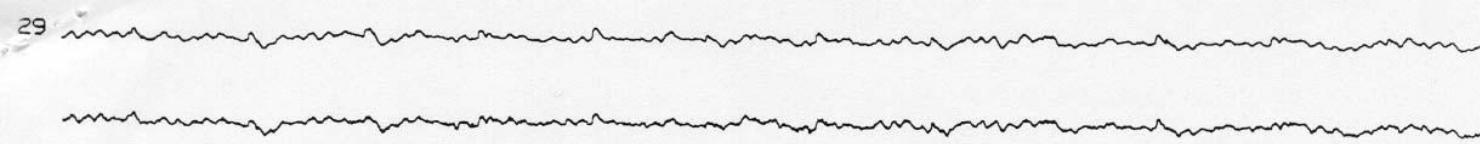
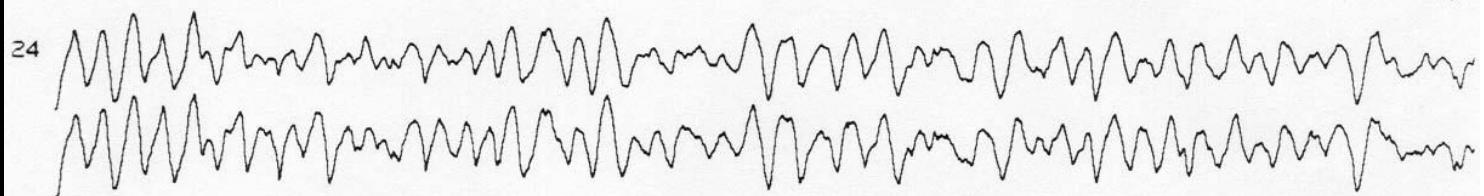
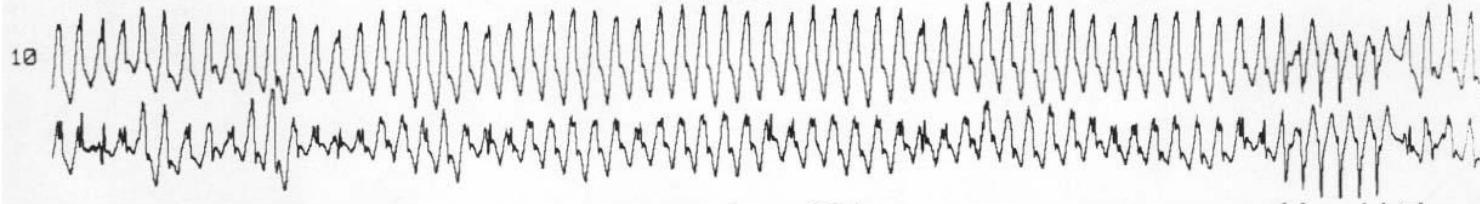
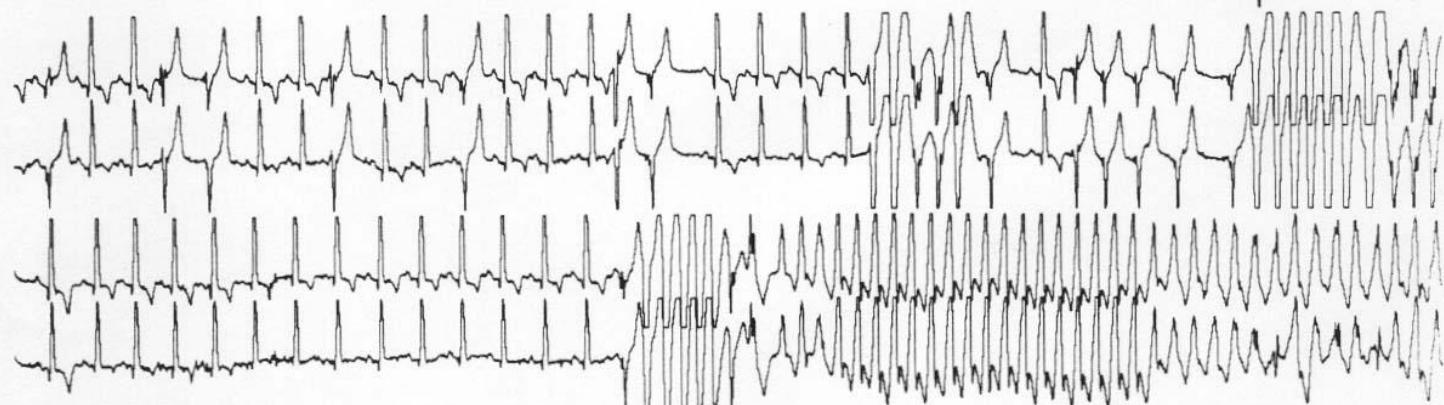
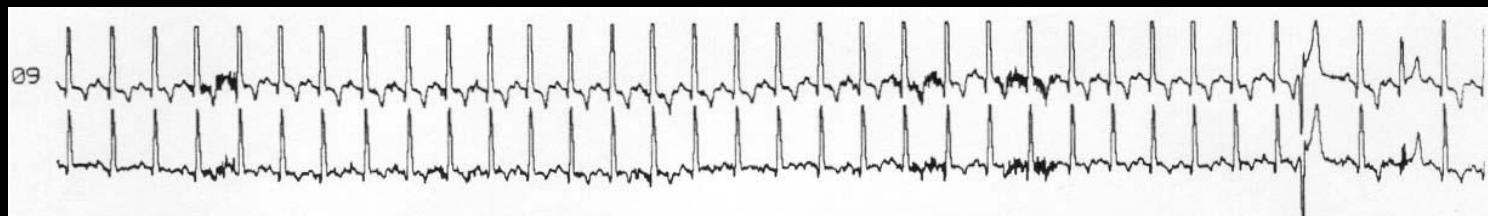


NYHA IV



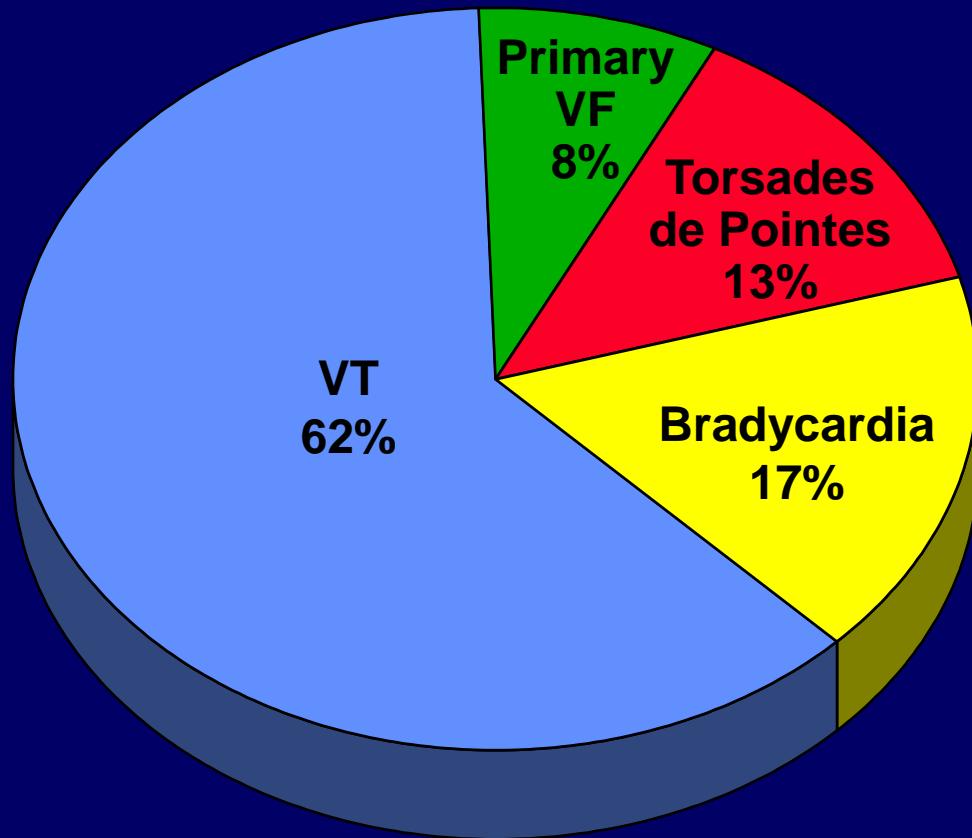
Reprinted with permission from Elsevier Science (*The Lancet*, 1999;353:2001-2007).

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.

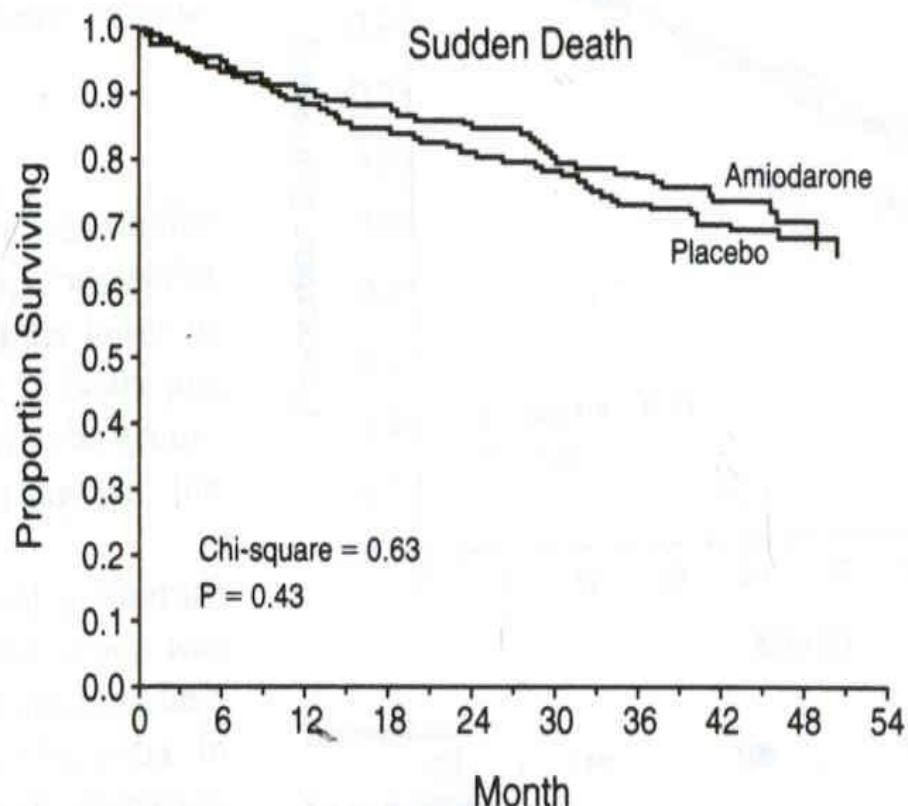
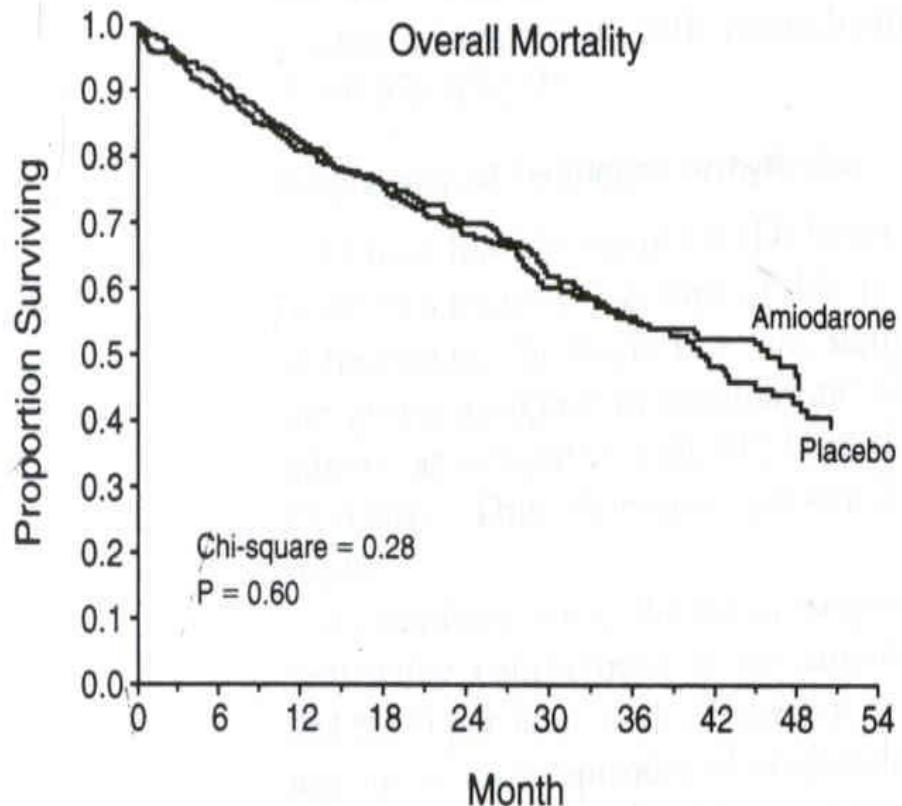


JM 10:08 am

Underlying Arrhythmia of Sudden Death



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

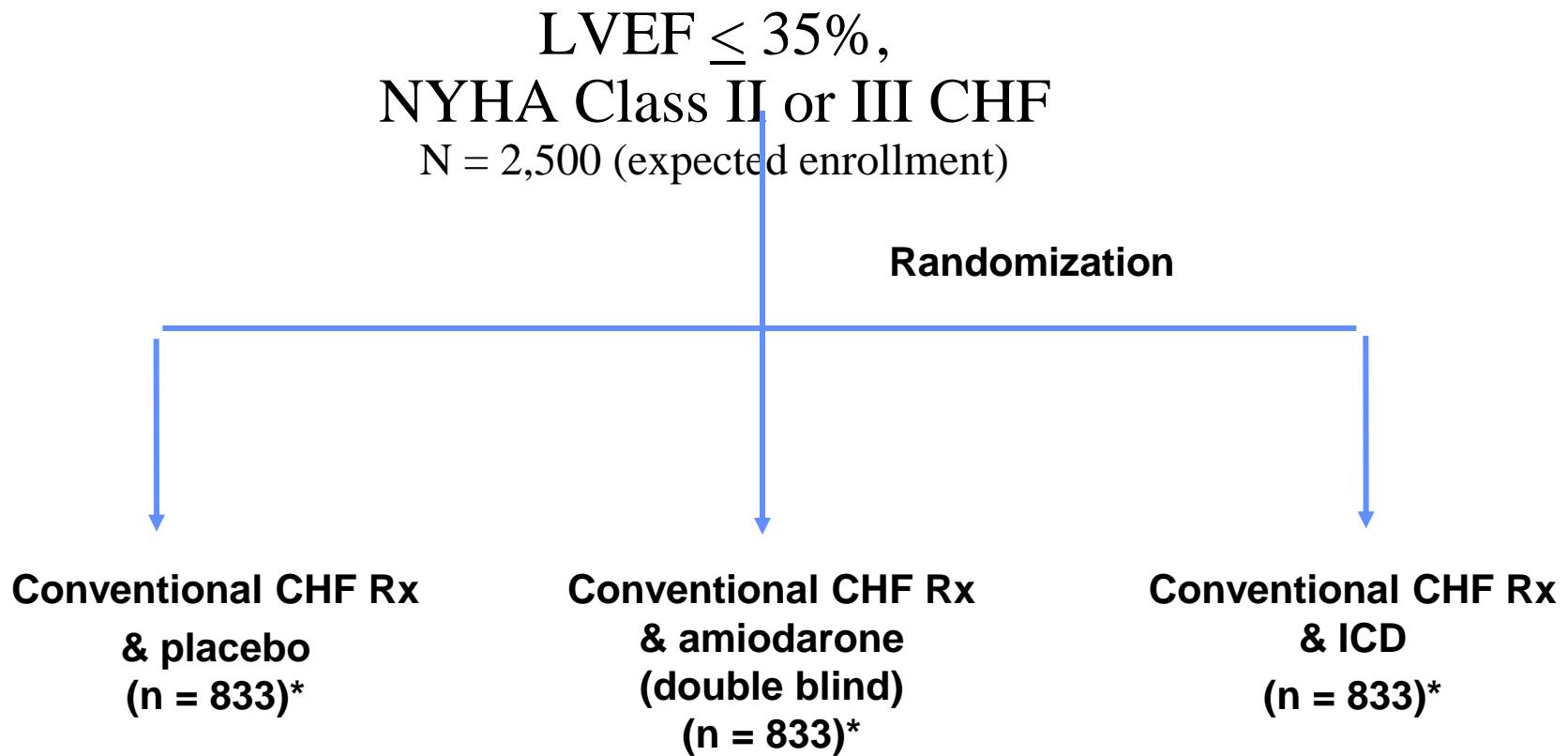
Unanswered Question

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

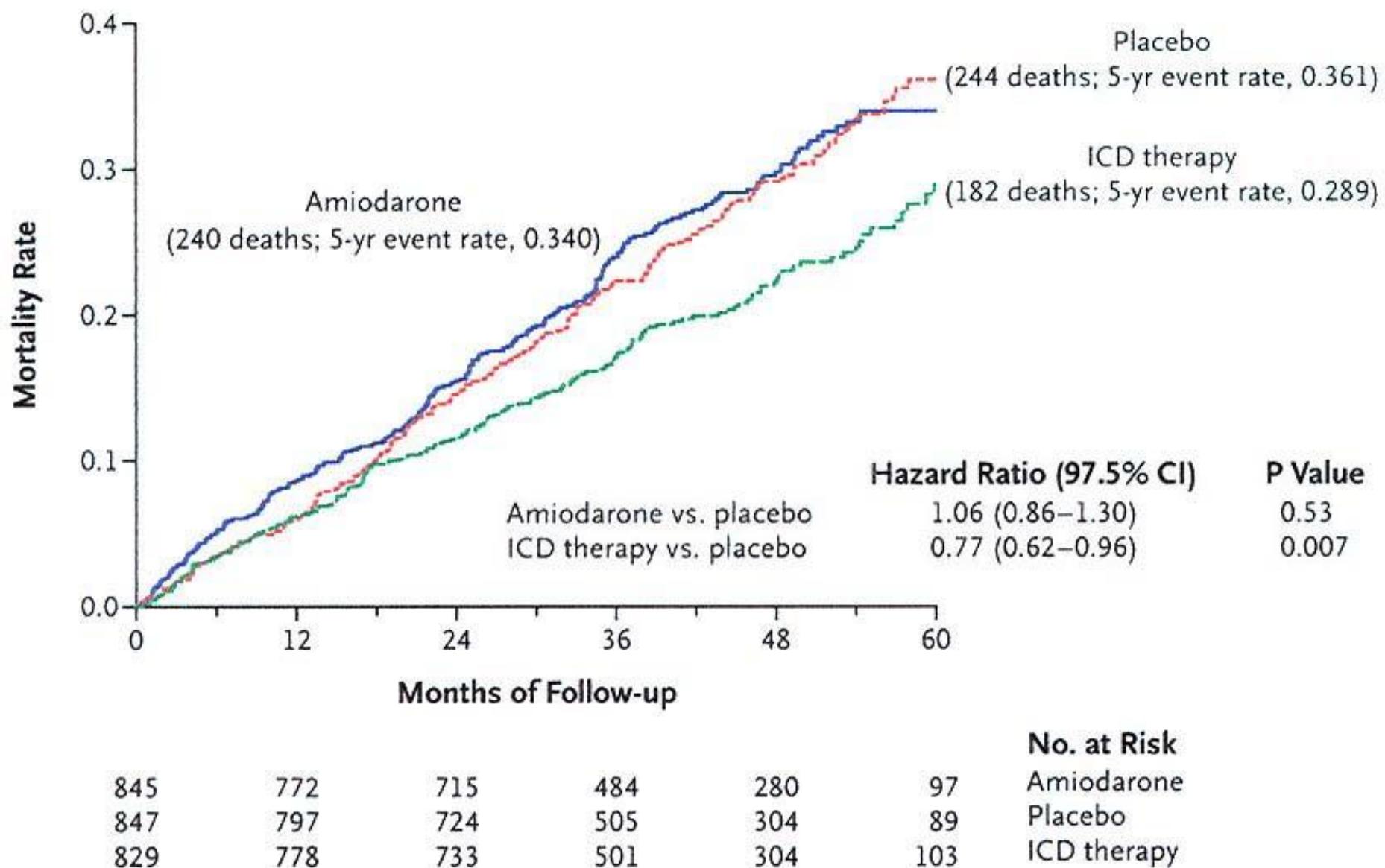
SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

SCD-HeFT Patient Flow



SCD-HeFT MORTALITY

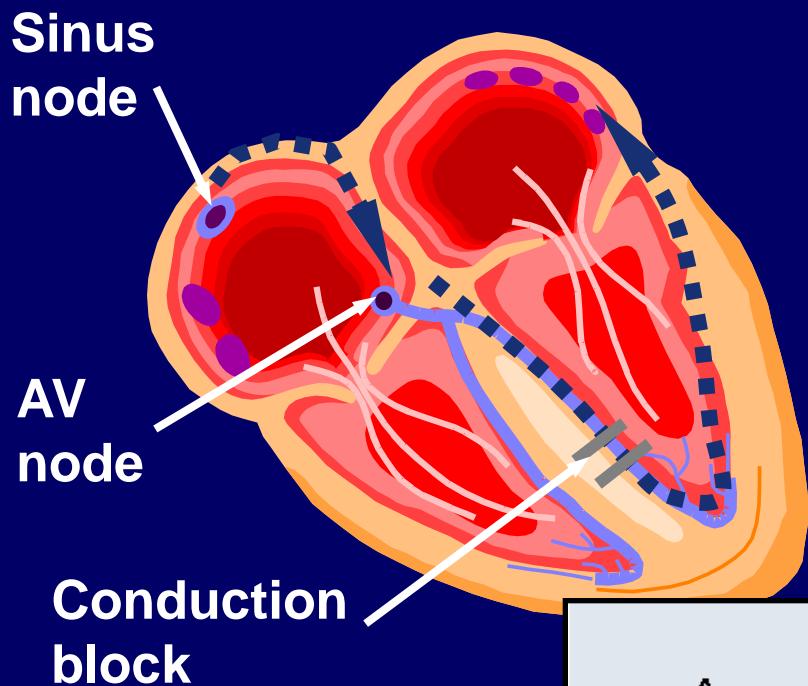


Question

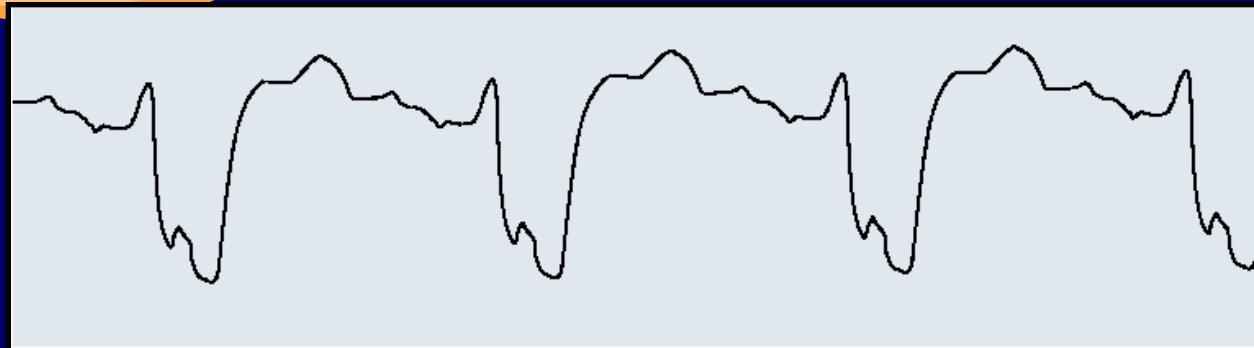
- Can we improve the quality of life in class III & IV heart failure in patients who are symptomatic despite optimal medical management?

Issues Associated with Heart Failure

Ventricular Dysynchrony with LBBB

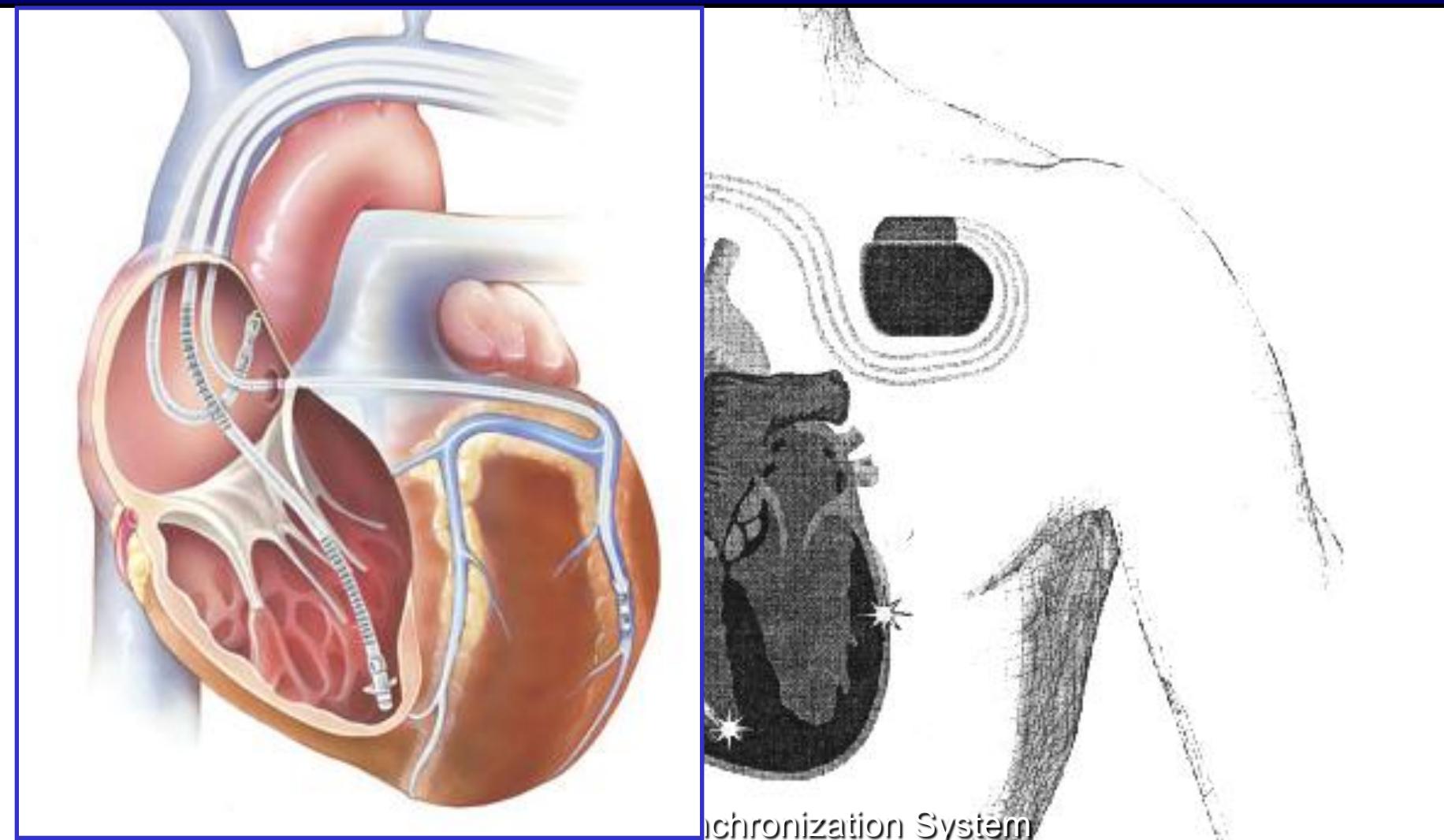


- Delayed lateral wall contraction
- Disorganized ventricular contraction
- Decreased pumping efficiency



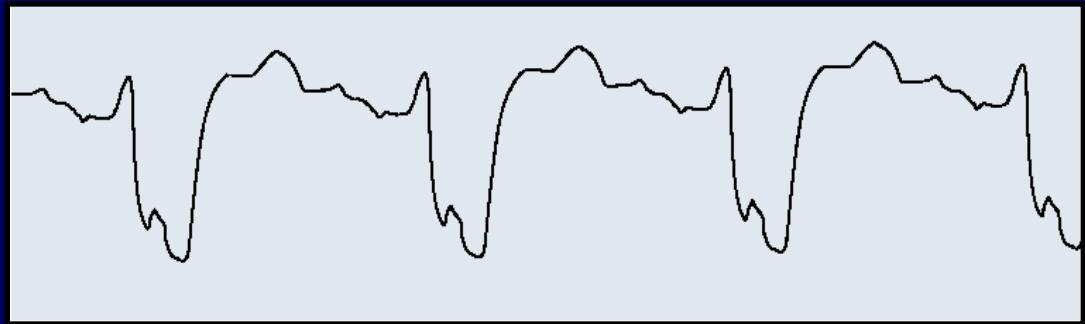
Achieving Cardiac Resynchronization

Mechanical Goal: Pace Right and Left Ventricle



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

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.