

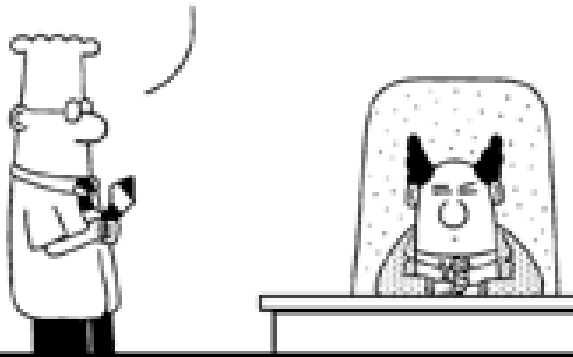
# Heart Failure Update

David Stultz, MD

August 16, 2006

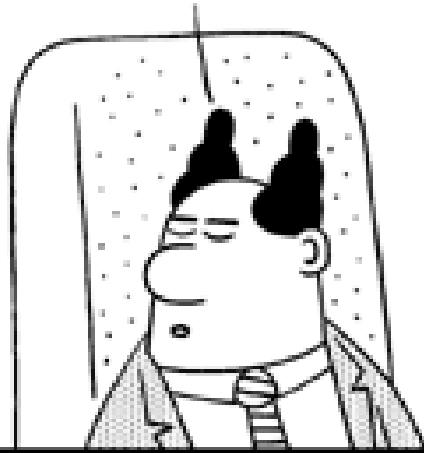


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IT'S FULL OF TECHNICAL JARGON AND IT'S WAY TOO LONG.



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DID YOU EVEN LOOK AT IT?



WHY WOULD I LOOK AT SOMETHING LIKE THAT?



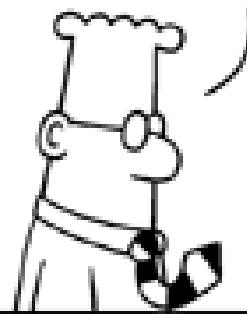
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OUR CEO ONLY HAS FIVE MINUTES. IS THAT ENOUGH TIME FOR YOUR POWERPOINT PRESENTATION?



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NO. AN INCOMPLETE EXPLANATION OF THE SITUATION WILL CAUSE MASSIVELY HARMFUL STRATEGIC CHOICES.



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WHAT CAN WE GET FOR FOUR-AND-A-HALF MINUTES?



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# Overview

- Background on Heart Failure
  - Established therapies for systolic heart failure
  - Recent investigational approaches to systolic heart failure
  - Quick summary of diastolic heart failure
  - Lots of Trial Data!
- ACC Heart Failure Guidelines will be cited where appropriate*

# What is Heart Failure?

- Heart failure is a complex *clinical* syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
- The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema.

# How to classify heart failure?

- Acute decompensated v Chronic
- Systolic v Diastolic dysfunction
- Low output v High output
- Ischemic v Nonischemic
- Medical v Device therapy
- Warm-Dry v Cold-Wet

# Classification of Recommendations

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  - Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
  - Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

## Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

# Classification Schemes

## New York Heart Association

- Class I - No symptom limitation with ordinary physical activity
- Class II - Ordinary physical activity somewhat limited by dyspnea (ie, long distance walking, climbing 2 flights of stairs)
- Class III - Exercise limited by dyspnea at mild work loads (ie, short distance walking, climbing one flight of stairs)
- Class IV - Dyspnea at rest or with very little exertion

# Classification Schemes

## ACC/AHA Stages

### A High risk for developing heart failure

- Hypertension, diabetes mellitus, CAD, family history of cardiomyopathy

### B Asymptomatic heart failure

- Previous MI, LV dysfunction, valvular heart disease

### C Symptomatic heart failure

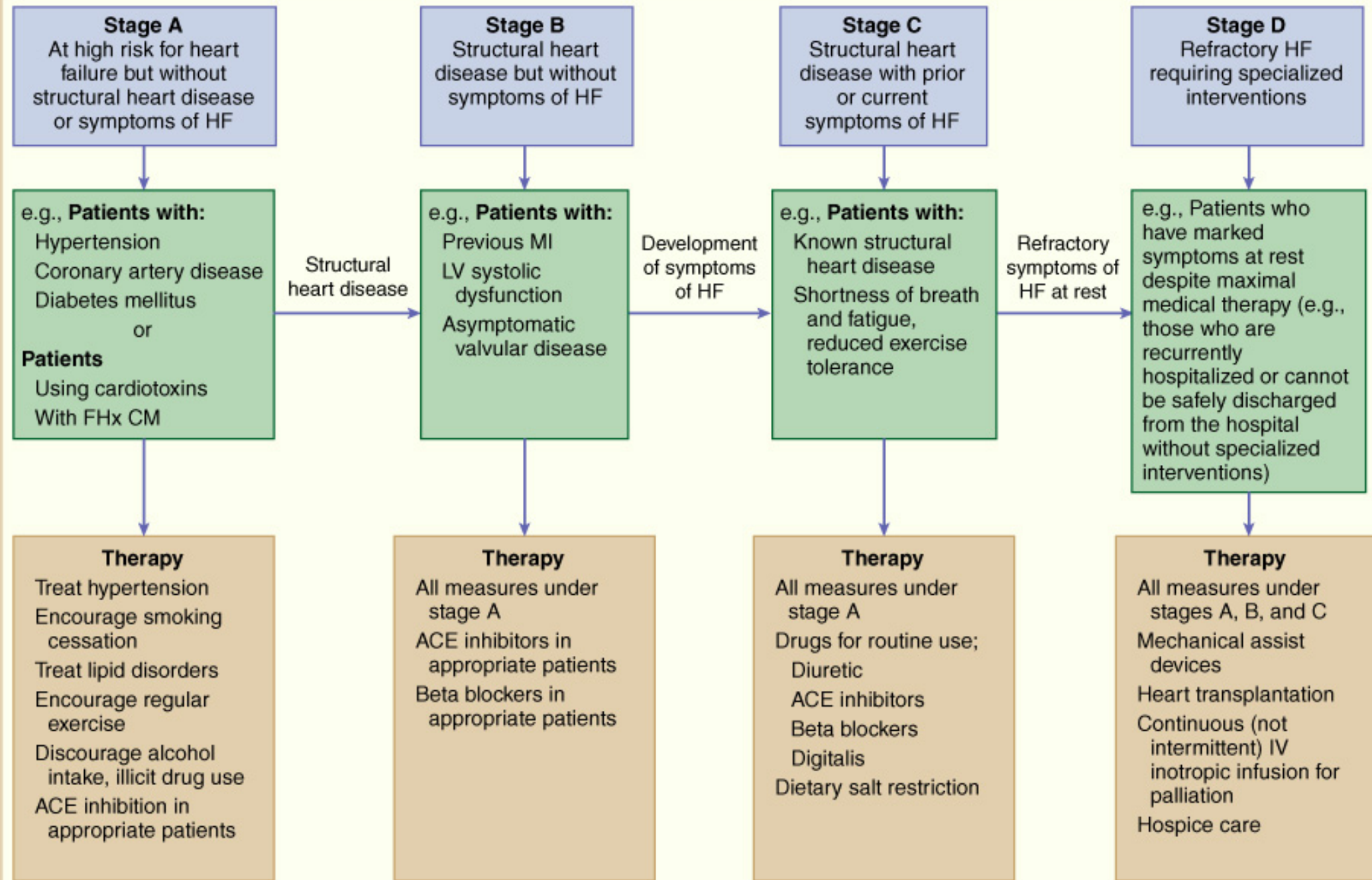
- Structural heart disease, dyspnea and fatigue, impaired exercise tolerance

### D Refractory end-stage heart failure

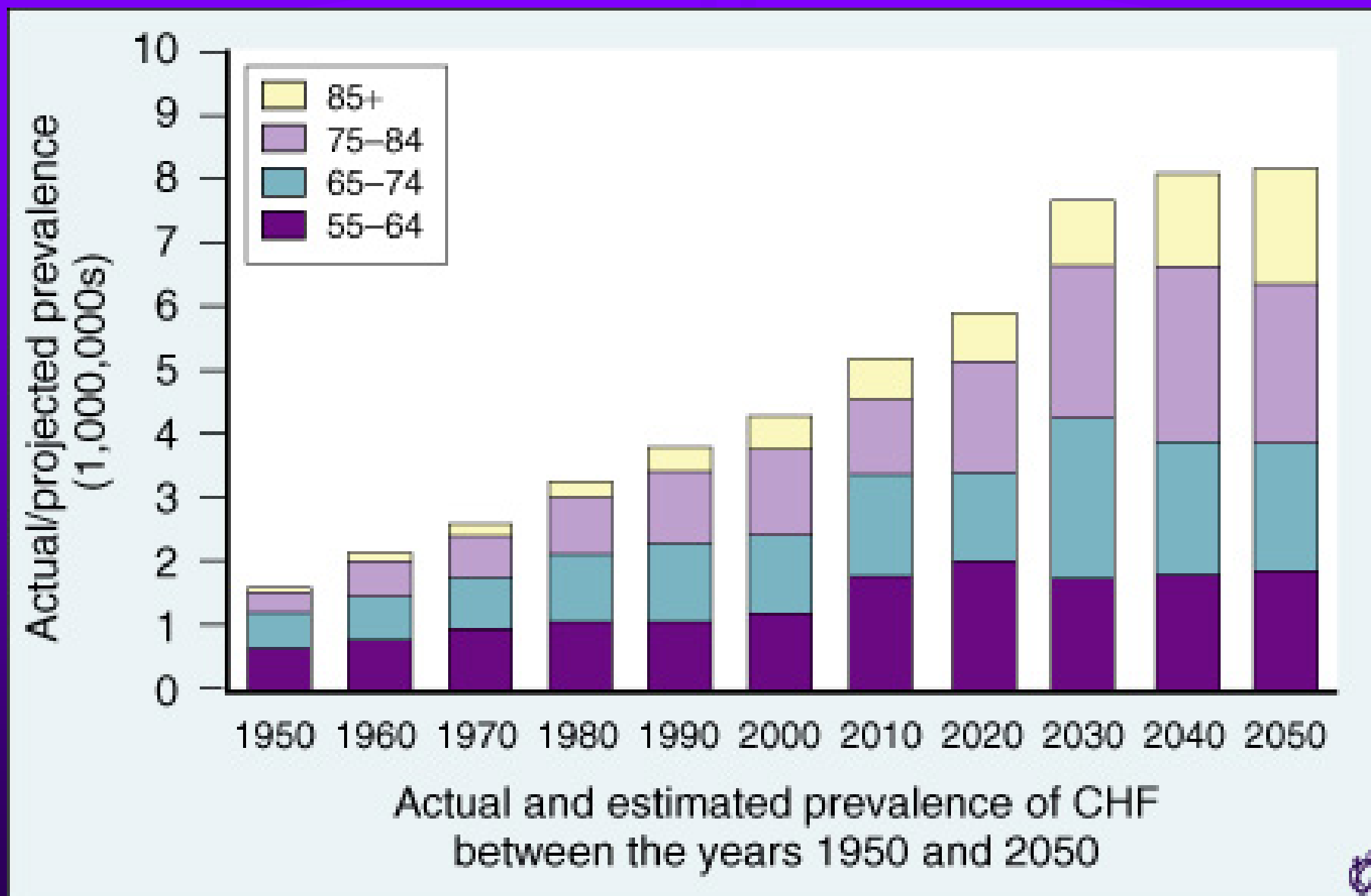
- Marked symptoms at rest despite maximal medical therapy



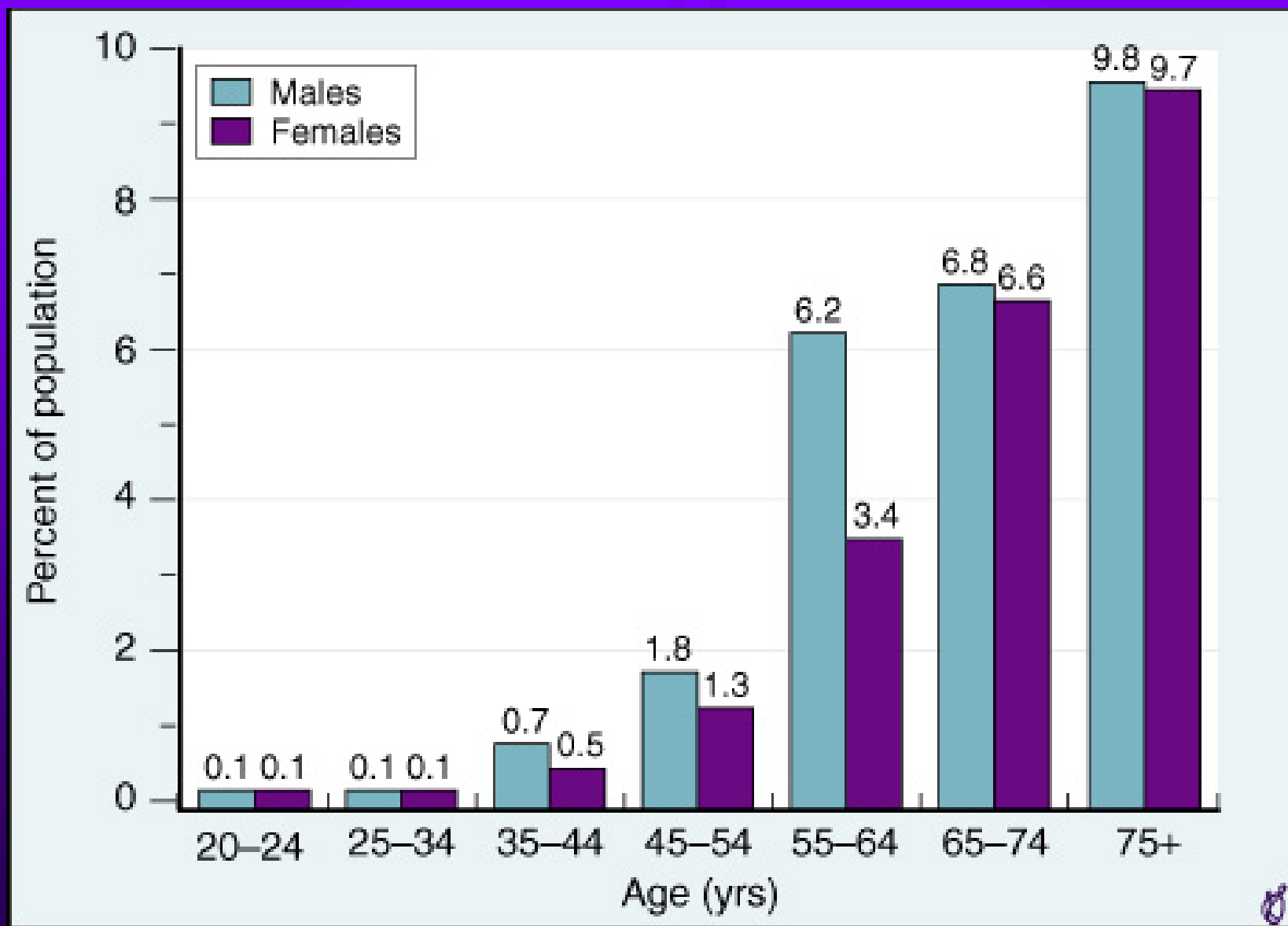
# ACC/AHA Heart Failure Stage



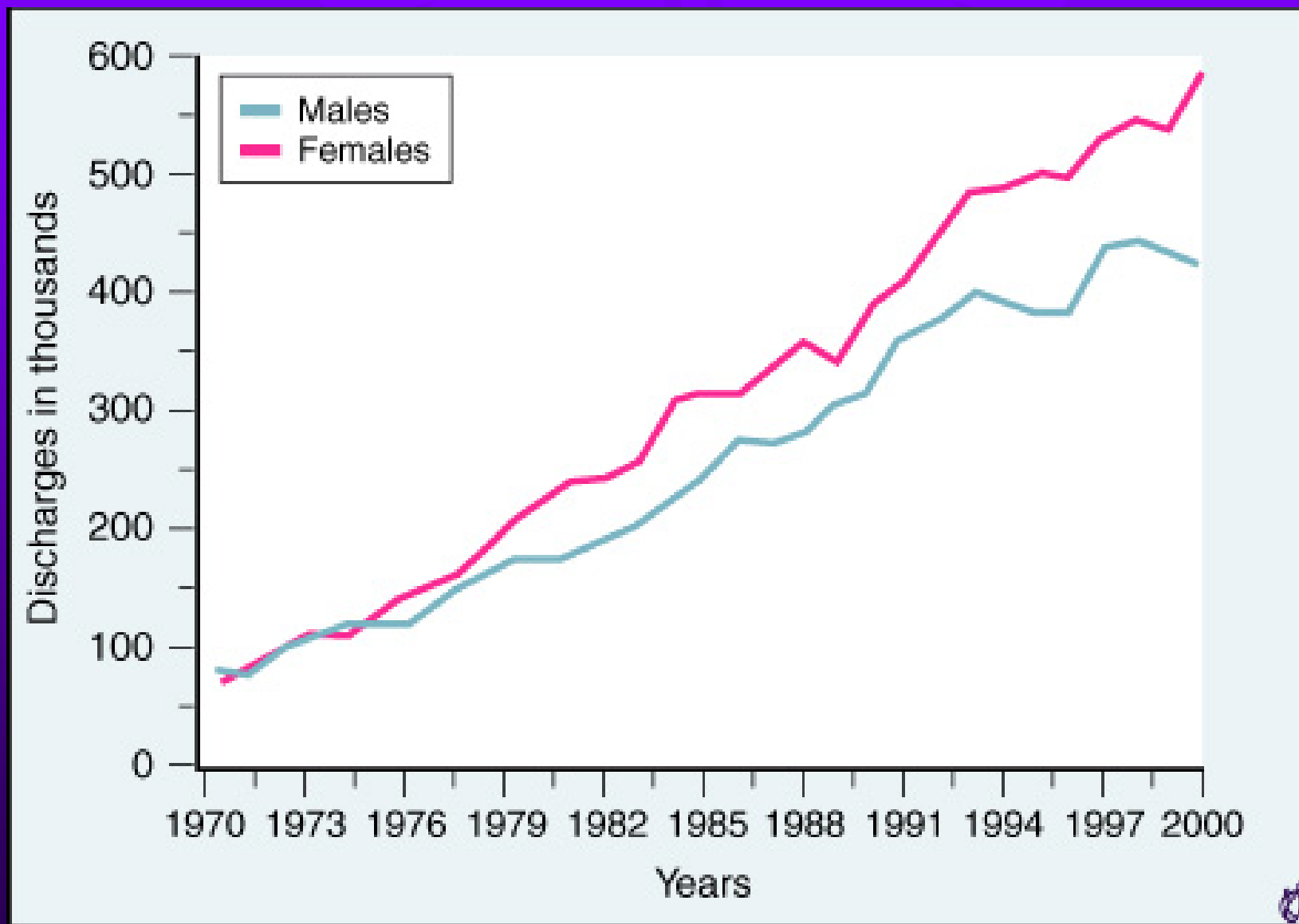
# Rising Prevalence of Heart Failure



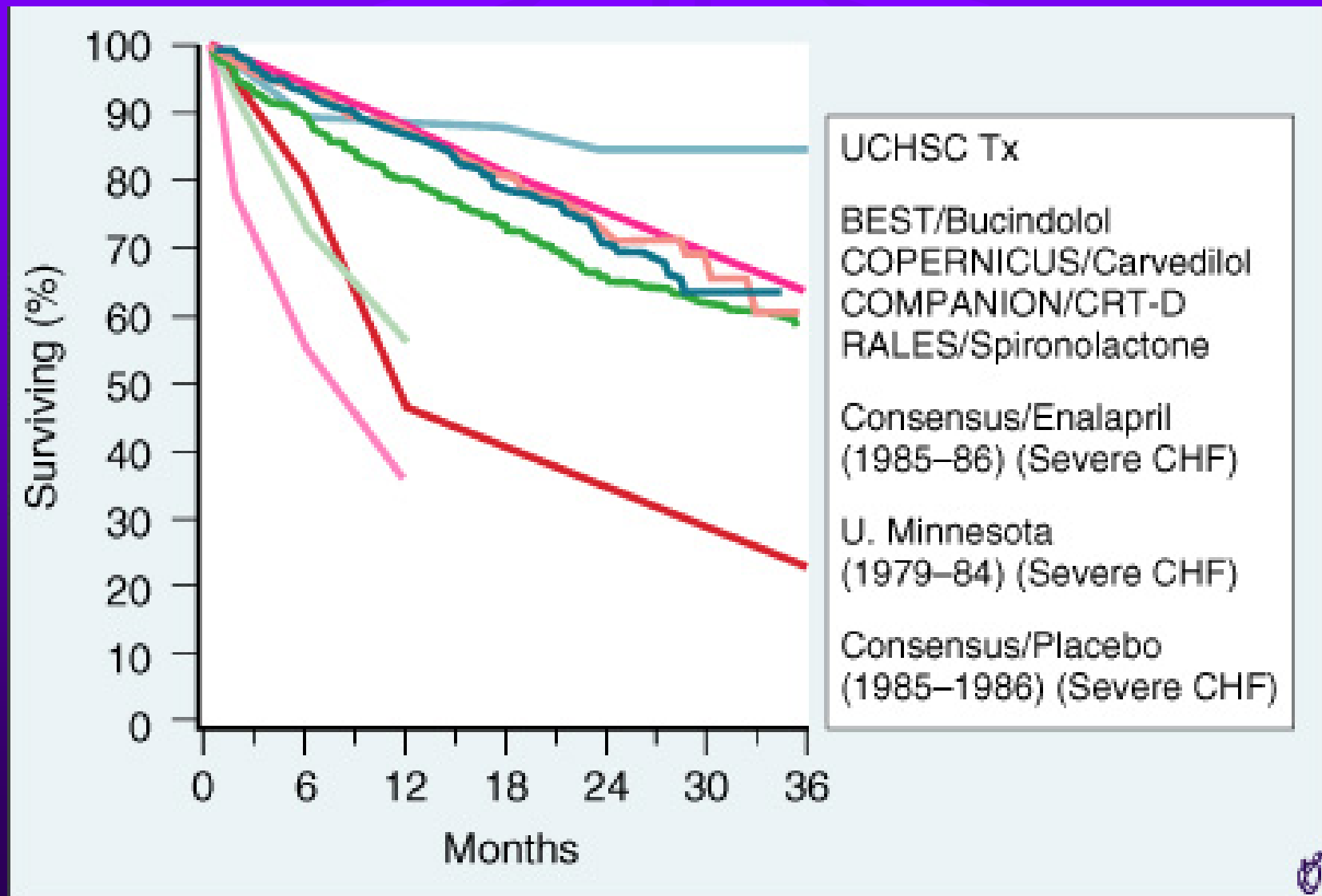
# Rising prevalence of Heart Failure with Aging



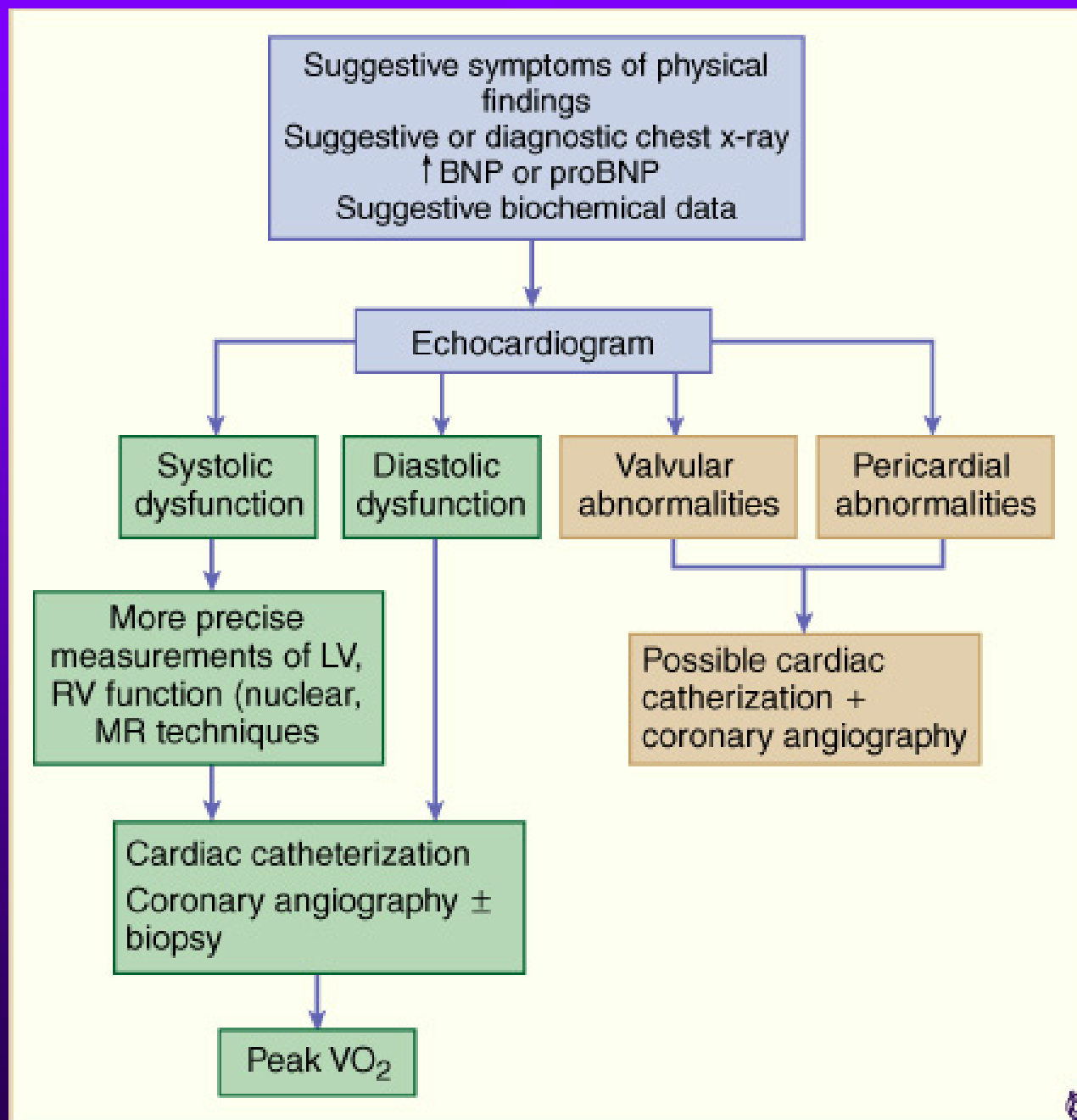
# Rising Discharges for Heart Failure



# Survival in Stage 3 or 4 Heart Failure vs Transplant



# Workup of Heart Failure



# High Output Heart Failure

**TABLE 22-7 High-Cardiac Output States**

Anemia

Acquired arteriovenous fistulas

    Traumatic

    Iatrogenic

    Infectious

    Surgical (hemodialysis)

    Atherosclerotic

    Malignancy

Congenital arteriovenous fistulas

    Hemangiomas

    Hereditary hemorrhagic telangiectasia

    Hepatic hemangioendothelioma

Thyrotoxicosis

Beriberi heart disease

Paget disease of bone

Fibrous dysplasia

Multiple myeloma

Polycythemia vera

Carcinoid syndrome

Acromegaly

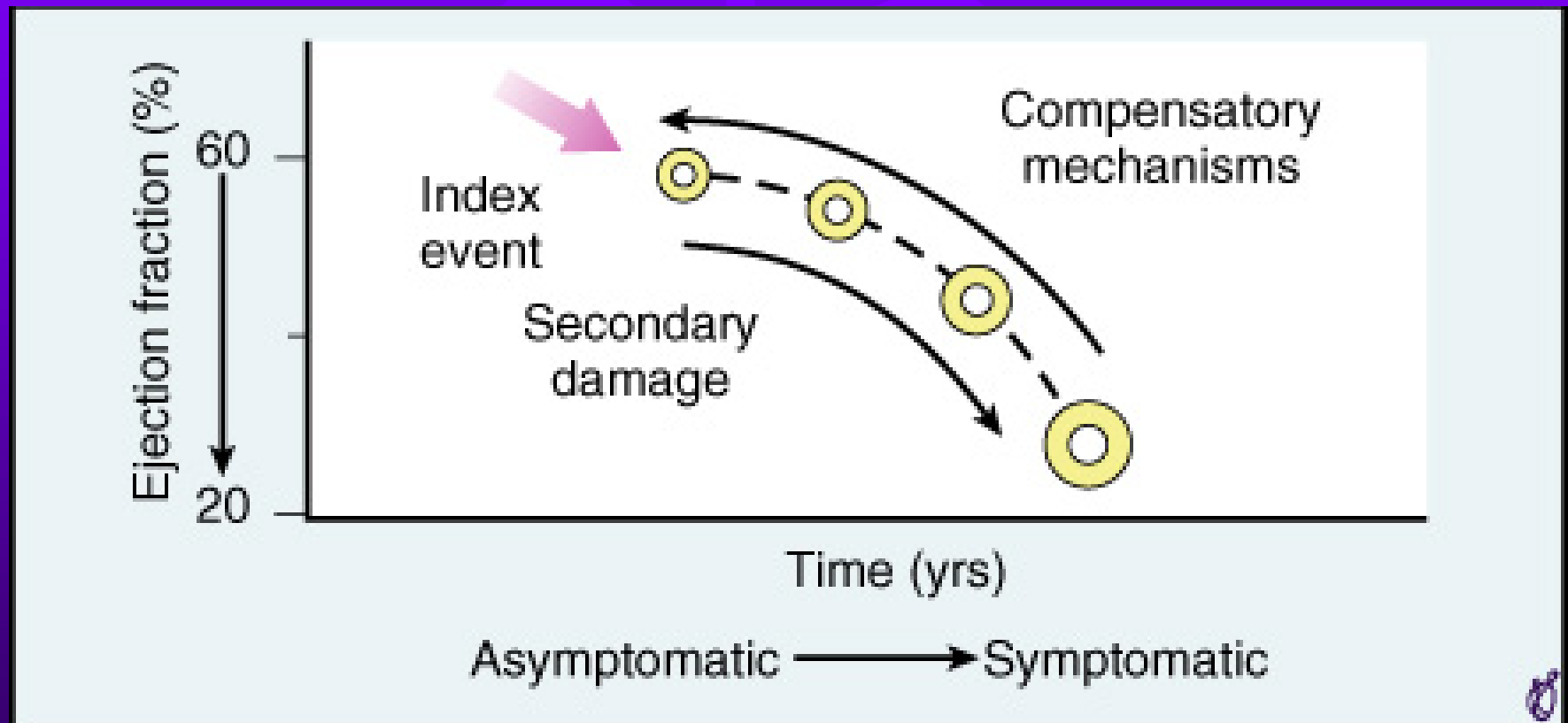
Pregnancy

# Systolic vs Diastolic Heart Failure

- Heart failure with low left ventricular ejection fraction vs normal ejection fraction
- Prevalence is approximately equal
- Etiologies are different
- Multiple clinical trials for systolic heart failure
- One randomized placebo controlled pharmaceutical trial for heart failure with preserved LVEF



# Development of Systolic Heart Failure



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# Etiologies of Heart Failure

**TABLE 24–1** General Etiologies of Cardiac Failure

General Cause	Specific Examples
Pericardial	Tamponade, pericardial constriction
Valvular	Aortic or mitral regurgitation
Myocardial	Idiopathic dilated cardiomyopathy, familial dilated cardiomyopathy, ischemic cardiomyopathy, valvular cardiomyopathy
Coronary vascular	Acute ischemic episodes
Rhythm disturbances	Tachycardia-induced heart failure

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# Framingham Criteria for Heart Failure

**TABLE 22-1 Framingham Criteria for Heart Failure\***

**Major Criteria**

Paroxysmal nocturnal dyspnea  
Neck vein distention  
Rales  
Radiographic cardiomegaly  
Acute pulmonary edema  
S<sub>3</sub> gallop  
Increased central venous pressure > 16 cm H<sub>2</sub>O  
Circulation time ≥ 25 sec  
Hepatojugular reflux  
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy  
Weight loss ≥ 4.5 kg in 5 days in response to treatment of heart failure

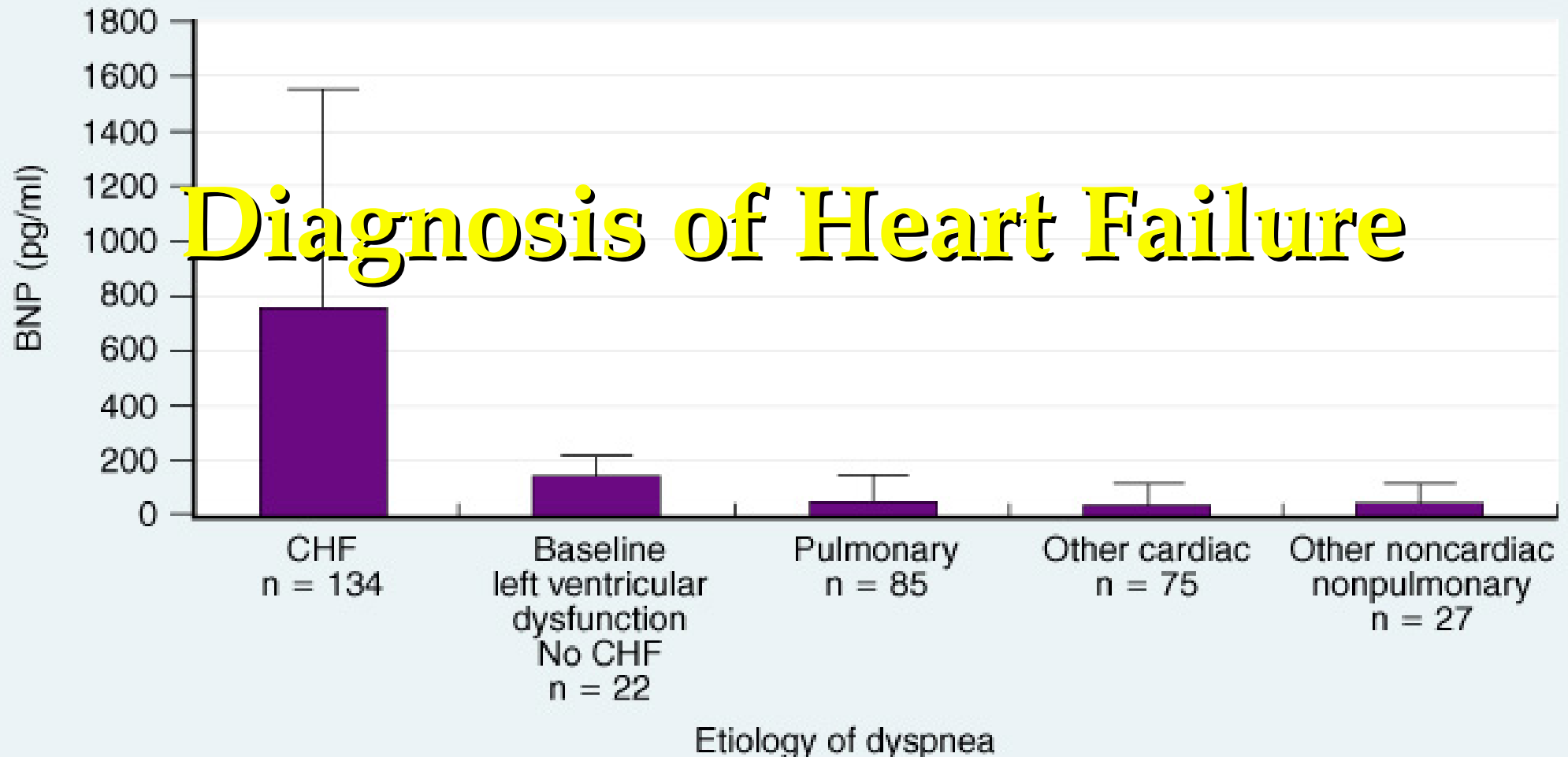
**Minor Criteria**

Bilateral ankle edema  
Nocturnal cough  
Dyspnea on ordinary exertion  
Hepatomegaly  
Pleural effusion  
Decrease in vital capacity by one third from maximal value recorded  
Tachycardia (rate ≥ 120 beats/min)

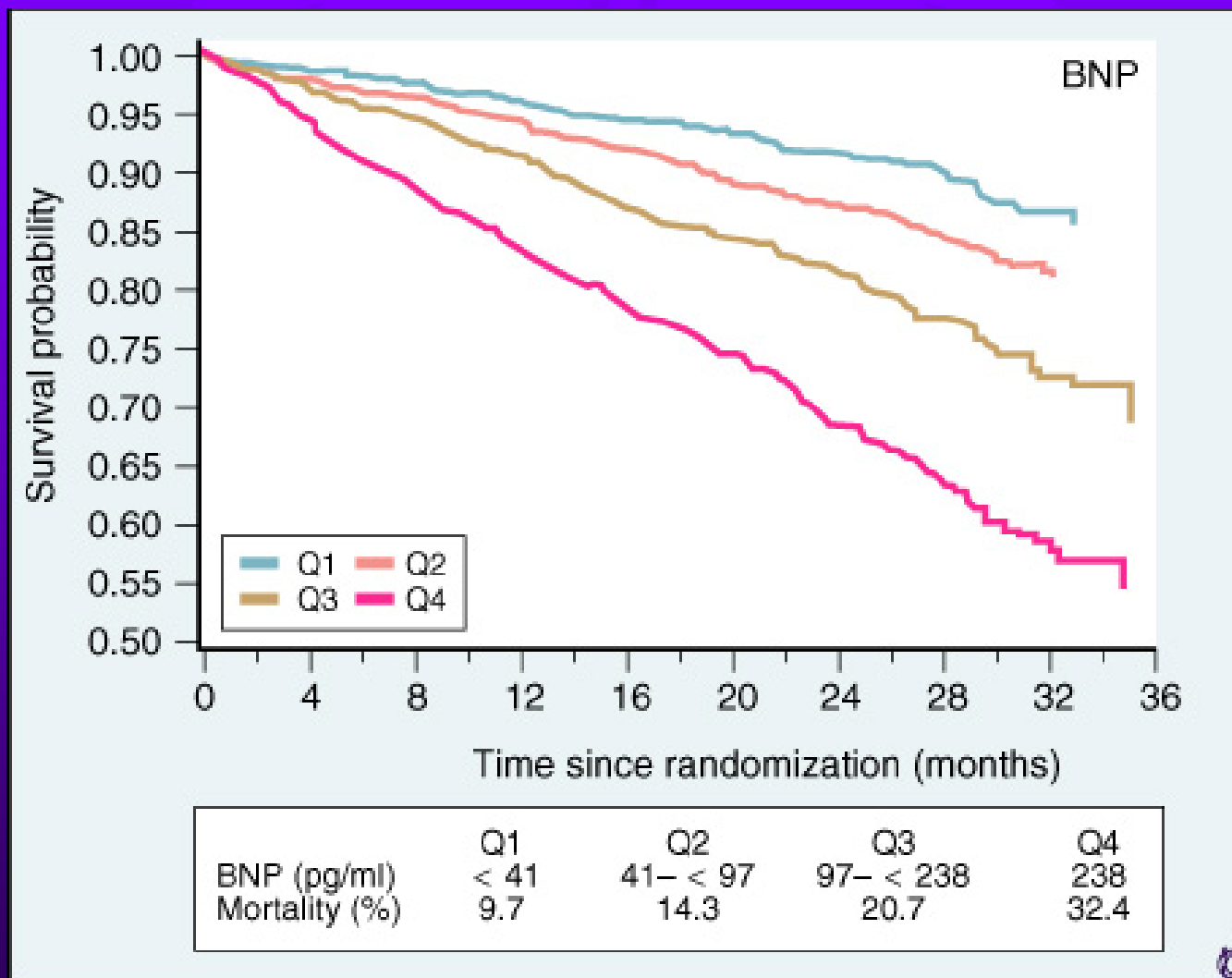
From Ho KL, Pinsky JL, Kannel WB, Levy D: The epidemiology of heart failure: The Framingham Study. *J Am Coll Cardiol* 22(Suppl A):6A, 1993.

\*The diagnosis of heart failure in this study required that two major or one major and two minor criteria be present concurrently. Minor criteria were acceptable only if they could not be attributed to another medical condition.

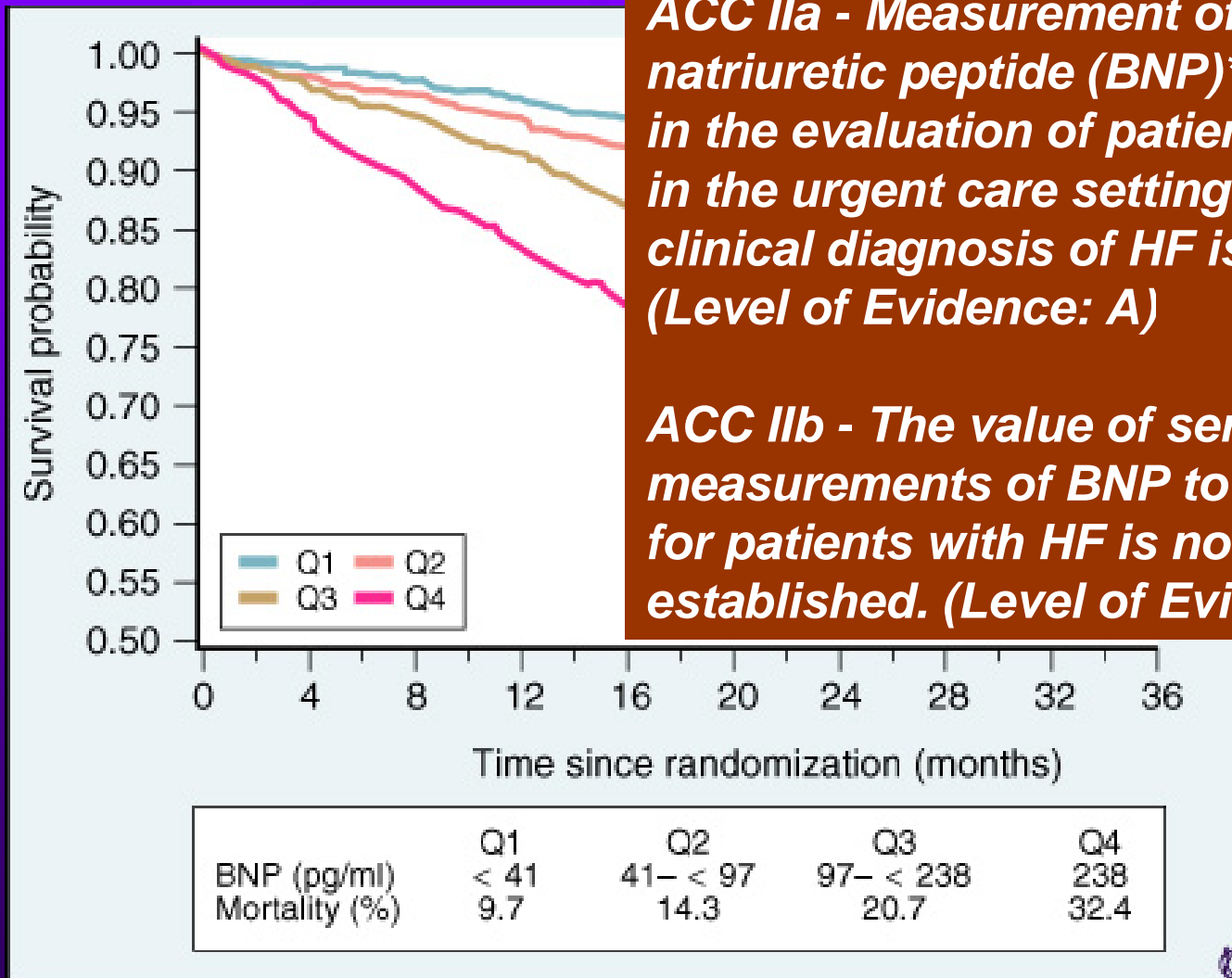
# BNP to differentiate etiology of acute dyspnea in ER setting



# Survival by BNP Quartile



# Survival by BNP Quartile




**ACC IIa - Measurement of B-type natriuretic peptide (BNP)\* can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of HF is uncertain. (Level of Evidence: A)**

**ACC IIb - The value of serial measurements of BNP to guide therapy for patients with HF is not well established. (Level of Evidence: C)**

# Treatment of Heart Failure

- Chronic Stable
  - Lifestyle
  - Risk Factor Modification
  - Pharmacological
  - Device/Nonpharmacologic
- Acute Decompensation
  - Pharmacological
  - Device/Nonpharmacologic



# Pharmacological Treatment of Heart Failure (Systolic Dysfunction)



# A Brief History of Digoxin

- 1785 - William Withering publishes *An Account of the Foxglove and some of its Medical Uses* which recounts an anecdote of treating a patient with Dropsy
- 1997 - DIG trial shows reduction in hospitalization but no mortality benefit of digoxin for heart failure
- Post Hoc DIG Analyses
  - 2002 - digoxin harmful to women (4% increase in mortality)
  - 2003 - target Digoxin level should be 0.5-0.8 ng/mL
  - 2006 - survival benefit with Digoxin Level 0.5-0.8



*Digitalis purpurea*

# Adjusted outcomes and hazard ratios by SDCs

Adjusted outcomes*	Placebo	HR** (95% CI) by SDC 0.5-0.8 ng/mL	HR (95% CI) by SDC 0.9- 1.1 ng/mL	HR (95% CI) by SDC 1.2 ng/mL or greater
All-cause mortality	Referent	0.80 (0.68-0.94)	0.89 (0.74-1.08)	1.16 (0.96-1.39)
Cardiovascular mortality	Referent	0.86 (0.72-1.02)	0.93 (0.76-1.14)	1.21 (0.99-1.47)
Worsening heart failure	Referent	0.66 (0.49-0.89)	0.86 (0.63-1.17)	0.95 (0.69-1.31)
All-cause hospitalization	Referent	0.83 (0.74-0.93)	1.02 (0.89-1.18)	0.90 (0.77-1.04)
Hospitalization for worsening heart failure	Referent	0.56 (0.46-0.67)	0.74 (0.60-0.92)	0.65 (0.52-0.82)

\*Adjusted for age; race; body mass index; LVEF; NYHA class; cardiothoracic ratio; number of HF signs and symptoms; systolic BP; heart rate; estimated glomerular filtration rate; duration of HF; primary cause of HF; history of MI, angina, diabetes, and hypertension; prior use of digoxin; and use of potassium-sparing diuretics, all other diuretics, ACE inhibitors, nitrates, hydralazine, and other vasodilators

\*\*HR-hazard ratio

# Post hoc DIG analysis

1687 Digoxin 3861 placebo	placebo	0.5-0.9 ng/mL	$\geq 1.0$ ng/mL
Mortality	33%	29% (p<0.01)	
All Cause Hospitalization	67%	64% (p $\approx$ 0.05)	
HF Hospitalization	33%	23% (p<0.01)	29% (p<0.01)

No interaction between EF>40% or gender

# Post hoc DIG analysis

1687 Digoxin 3861 placebo	placebo	0.5-0.9 ng/mL	$\geq 1.0$ ng/mL
Mortality	33%	29% (p<0.01)	
All Cause Hospitalization	67%	64% (p $\approx$ 0.05)	
HF Hospitalization	33%		

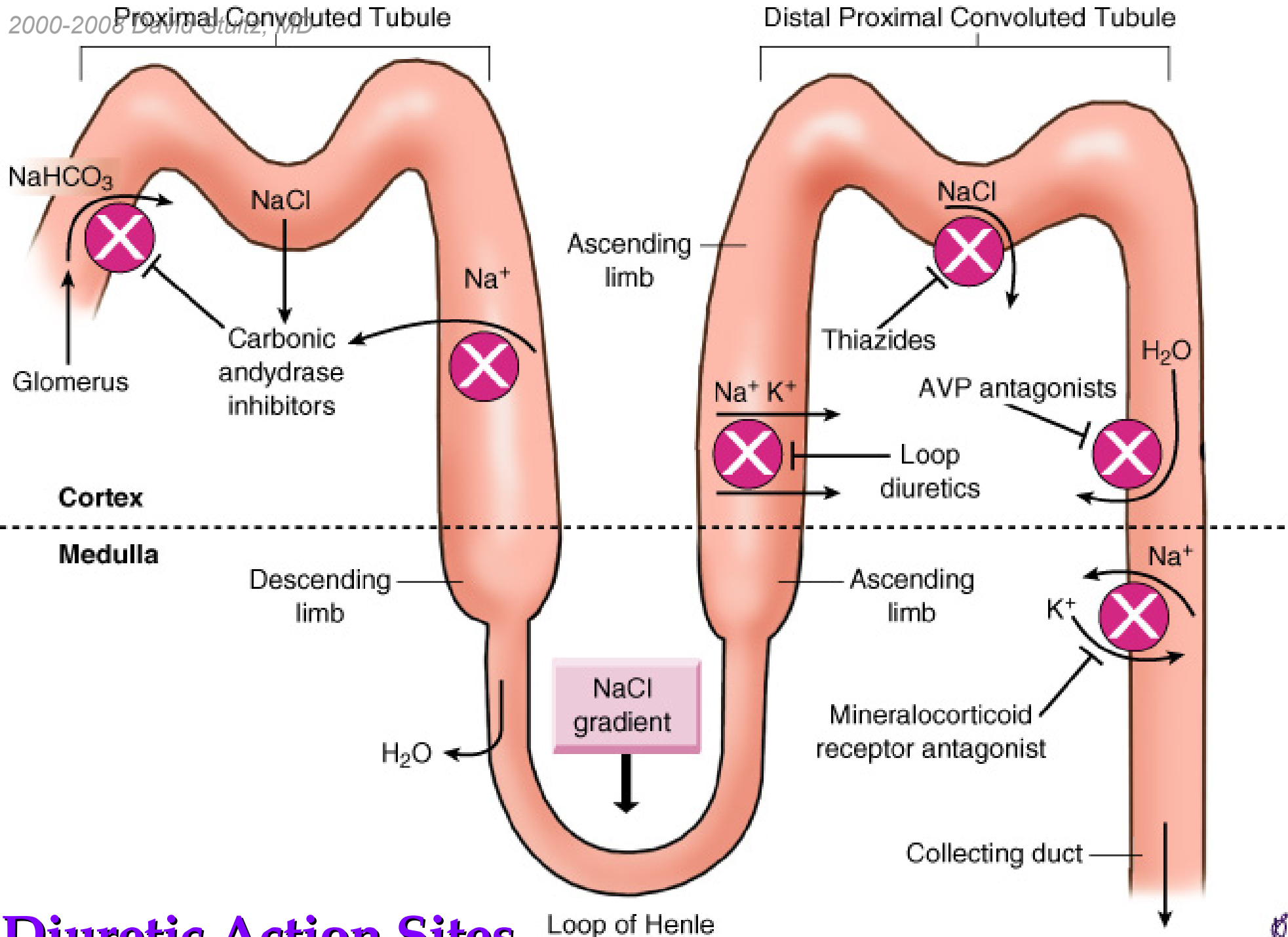
**ACC III - Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit. (Level of Evidence: C)**

No interaction between EF>40% or gender

# Diuretics in Heart Failure

- Loop diuretics used for volume control and relief of symptoms
- Thiazide diuretics may be added in conjunction
- No trial data!

*ACC I - Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention (see Table 4). (Level of Evidence: C)*



# Diuretic Action Sites

# Vasodilators in Heart Failure

- VHEFT 1 showed 27% relative reduction in mortality with vasodilators
  - Digoxin + diuretics
  - Placebo vs. isosorbide + hydralazine
- VHEFT 2 showed 7% absolute (25% vs 18%) mortality benefit of ACE over isordil/hydralazine
  - Enalapril 10mg bid vs isosorbide dinitrate 40mg qid + hydralazine 75mg qid

# ACE inhibitors in Heart Failure

- 1991 SOLVD – enalapril 10mg bid vs placebo for patients with chronic EF  $\leq 35\%$ 
  - 2569 patients, average 41 month followup

	Placebo	Enalapril
Death	39.7%	35.2% (p=0.004)
Hospitalization	74%	69% (p=0.006)



# ACE inhibitors in Heart Failure

- 1991 SOLVD – enalapril vs placebo for patients with EF  $\leq 35\%$

*ACC I - Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI. (Level of Evidence: A)*

- 2569 patients, average 41 month followup

	Placebo	Enalapril
Death	39.7%	35.2% (p=0.004)
Hospitalization	74%	69% (p=0.006)

# $\beta$ -Blockers in Heart Failure

- Improves survival in chronic heart failure

A. 1999 MERIT-HF (Toprol XL)

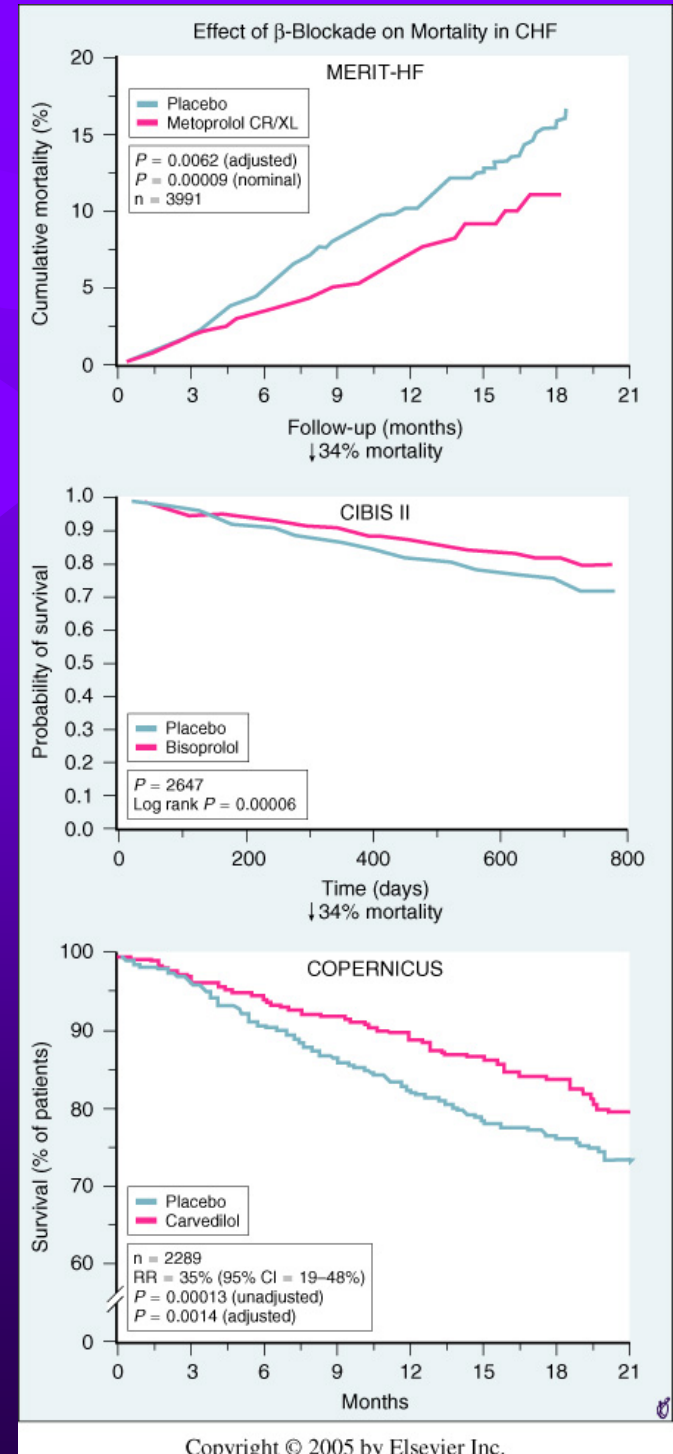
- EF  $\leq$ 40%, NYHA 2-4

B. 1999 CIBIS II (bisoprolol)

- EF  $\leq$ 35%, NYHA 3-4

C. 2001 COPERNICUS (Coreg)

- EF  $<$ 25%



# $\beta$ -Blockers in Heart Failure

- Improves survival in chronic heart failure

A. 1999 MERIT-HF (Toprol XL)

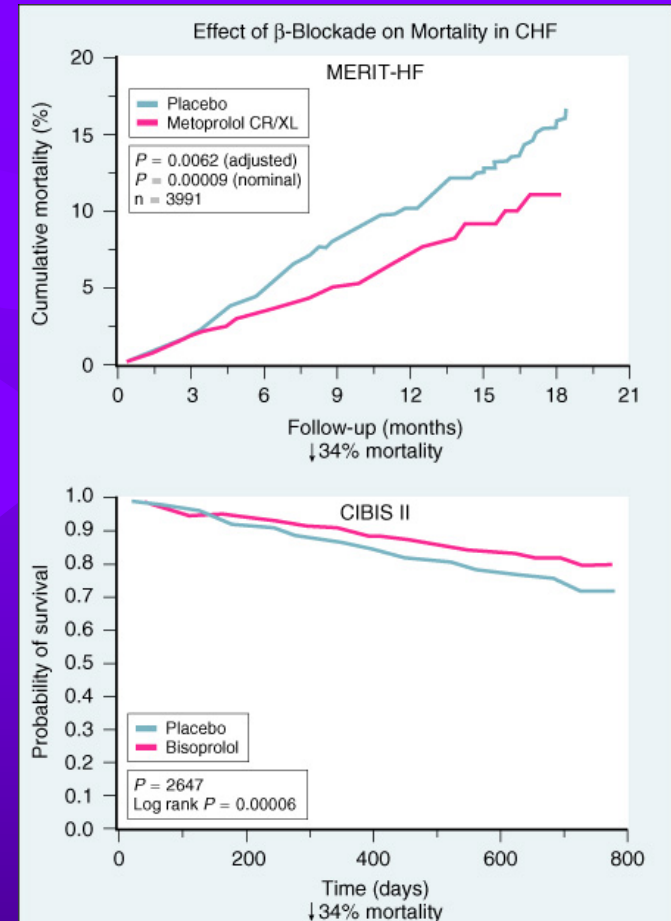
- EF  $\leq$  40%, NYHA 2-4

B. 1999 CIBIS II (bisoprolol)

- EF  $\leq$  35%, NYHA 3-4

C. 2001 COPERNICUS (Carvedilol)

- EF  $<$  25%



**ACC I - Beta-blockers and ACEIs should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF (see Table 3). (Level of Evidence: A)**

**Beta-blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (see Table 3 and text). (Level of Evidence: C)**

# Spironolactone in Heart Failure

- 1999 RALES trial
  - 1663 patients with NYHA 3-4 and EF <35%
    - Excluded creatinine >2.5 mg/dL or K<sup>+</sup> >5 mmol/L
    - Mean 24 month followup
  - 25mg qd spironolactone vs placebo
    - No  $\beta$ -Blocker use
  - All cause mortality
    - 46% placebo
    - 35% spironolactone (p<0.001)

# Spironolactone in Heart Failure

- **ACC I - Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists. (Level of Evidence: B)**

- 25mg qd spironolactone vs placebo
  - No  $\beta$ -Blocker use
- All cause mortality
  - 46% placebo
  - 35% spironolactone ( $p < 0.001$ )

# Angiotensin Receptor Blockers

- 2001 Val-HeFT
  - 5010 patients with NYHA class 2-4, EF<40%
  - 2 year followup
  - Valsartan titrated to 160mg bid vs placebo
  - On top of ACE,  $\beta$ -blockers, diuretics, digoxin
  - No difference in all cause mortality (19.7% vs 19.4%)
  - Combined Death/CHF hospitalization favored valsartan (28.8% vs 32.1%,  $p=0.009$ )
- 2000 ELITE-2
  - No difference between captopril and losartan

# Angiotensin Receptor Blockers

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  - 5010 patients with NYHA
  - 2 year followup
  - Valsartan titrated to 160m
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  - No difference in all cause mortality (19.7% vs 19.4%)
  - Combined Death/CHF hospitalization favored valsartan (28.8% vs 32.1%,  $p=0.009$ )
- 2000 ELITE-2
  - No difference between captopril and losartan

*ACC IIa - Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. (Level of Evidence: A)*

# ARB's Revisited

- 2003 CHARM program
- CHARM-Added
  - 2548 patients, median followup 41 months
  - Candesartan 32mg daily added to ACE and other contemporary therapy
  - Reduction in death (23.7% v 27.3%,  $p=0.021$ )
  - Reduction in CHF hospitalization (24.2% v 28%,  $p=0.018$ )
- CHARM-Alternative
  - Patients intolerant of ACE benefited from ARB over placebo

McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003 Sep 6;362(9386):767-71.

Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003 Sep 6;362(9386):772-6.



# ARB's Revisited

- 2003 CHARM program *ACC IIb - The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (Level of Evidence: B)*
- CHARM-Added
  - 2548 patients, median follow-up 36 months
  - Candesartan 32mg daily vs contemporary therapy
  - Reduction in death (23.7% v 27.3%, p=0.021)
  - Reduction in CHF hospitalization (24.2% v 28%, p=0.018)
- CHARM-Alternative
  - Patients intolerant of ACE benefited from ARB over placebo

McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003 Sep 6;362(9386):767-71.

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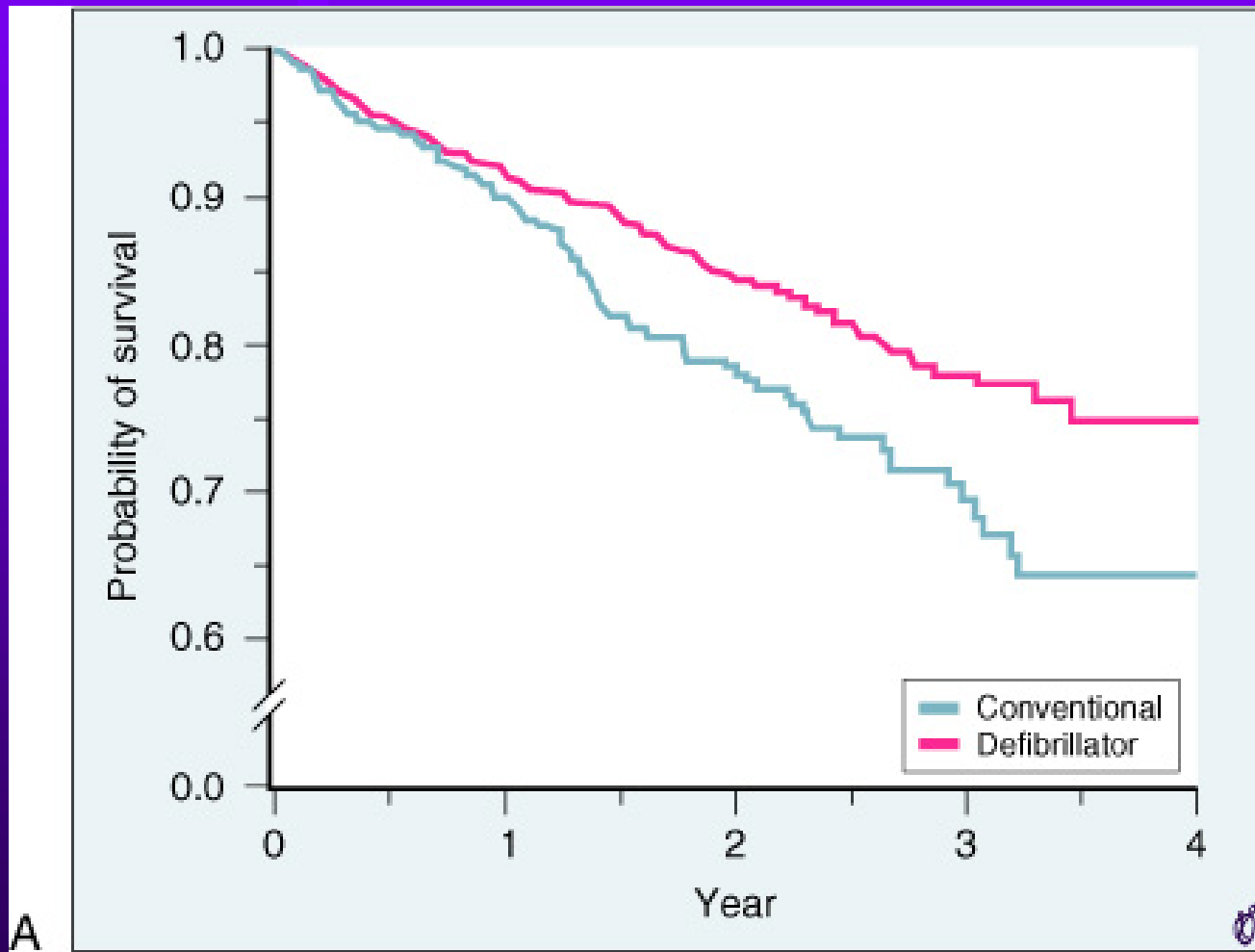
# Device Therapy in Heart Failure

## Device Therapy in Chronic Systolic Heart Failure



# ICD for primary prevention has mortality benefit for ischemic cardiomyopathy

- 2002 MADIT II
- Post MI
- LVEF <30%
- Conventional treatment vs. ICD



# ICD's beneficial in primary prevention for patients with Low EF regardless of etiology

- 2004 SCD-HEFT
- 2521 patients with NYHA 2-3, LVEF<35%
- ICD v amiodarone v placebo
- All cause mortality
  - 3 years: 17.1% v 24% v 22.3%
  - 5 years: 28.9% v 34.1% v 35.8%

# ICD's beneficial in primary prevention for patients with Low EF regardless of etiology

- 2004 SCD-HEFT
- 2521 patients with NYHA 2-3, LVEF<35%
- ICD v amiodarone v placebo
- All cause mortality

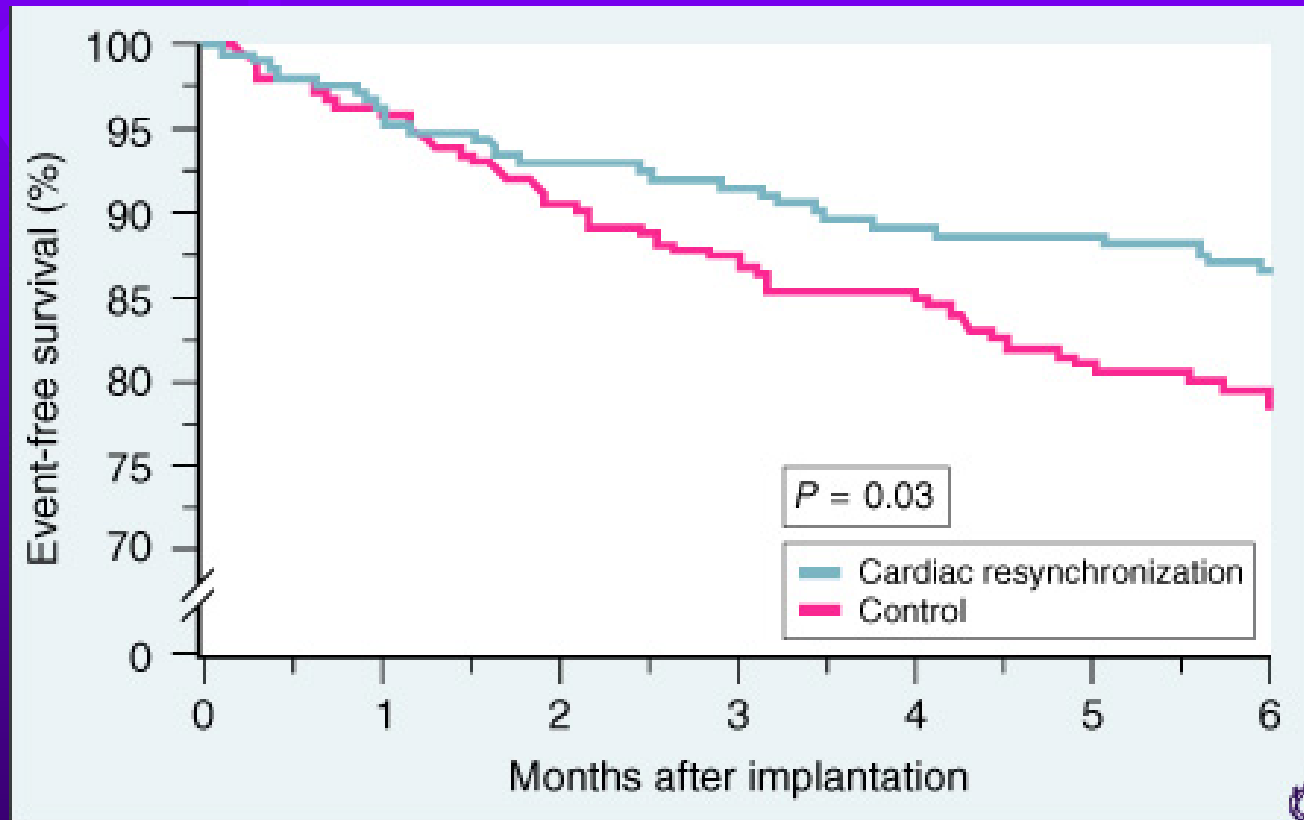
- 3 years: 17.1% v 24% v 22.3%

- 5 years

**ACC IIa - Placement of an implantable cardioverter-defibrillator is reasonable in patients with LVEF of 30% to 35% of any origin with NYHA functional class II or III symptoms who are taking chronic optimal medical therapy and who have reasonable expectation of survival with good functional status of more than 1 year. (Level of Evidence: B)**

# Cardiac Resynchronization improves combined HF worsening/Death in patients with low EF and wide QRS

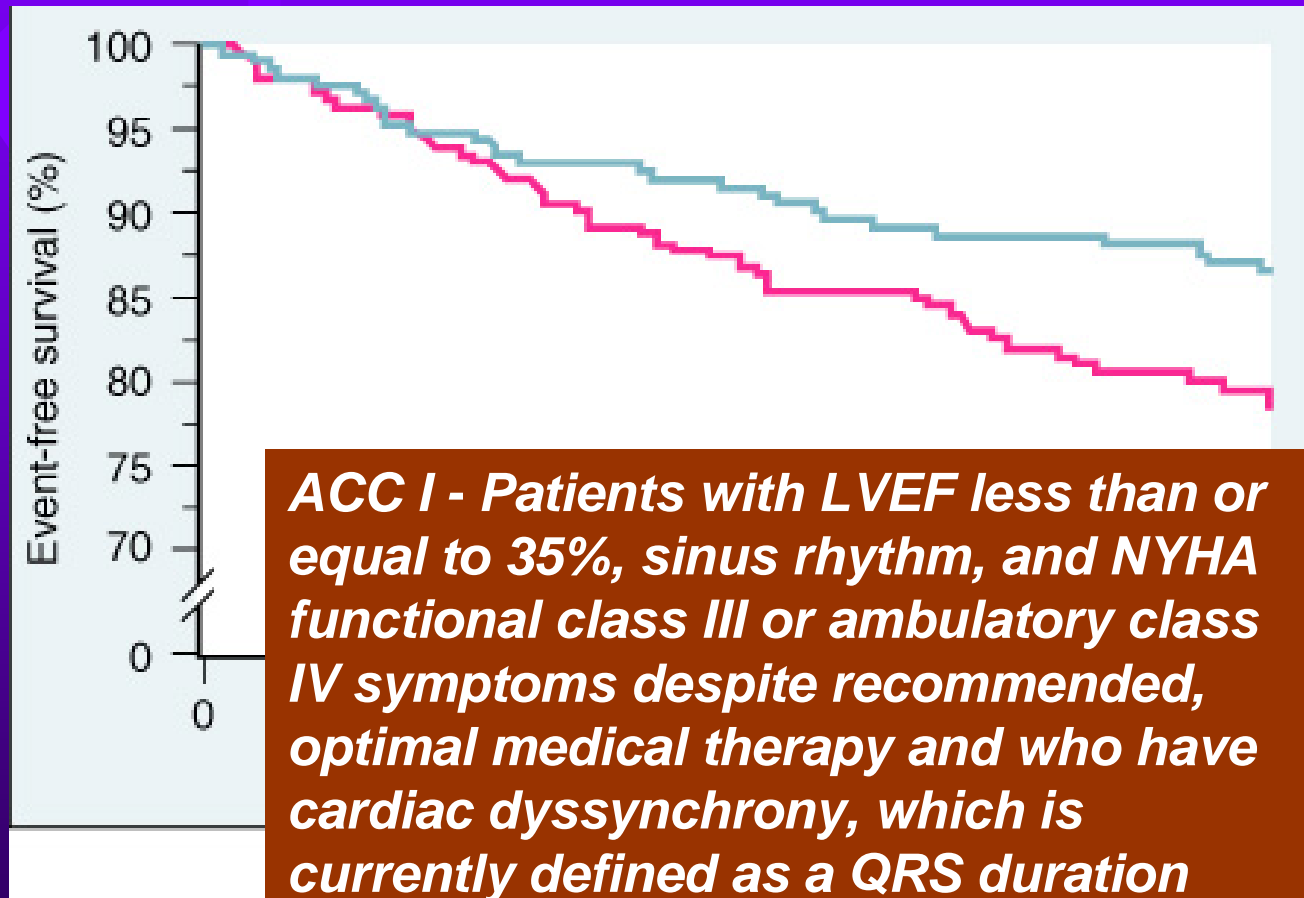
- 2002 MIRACLE
- 453 patients
- EF <35%
- QRS >130ms
- Cardiac Resynchronization vs placebo
- No mortality benefit demonstrated



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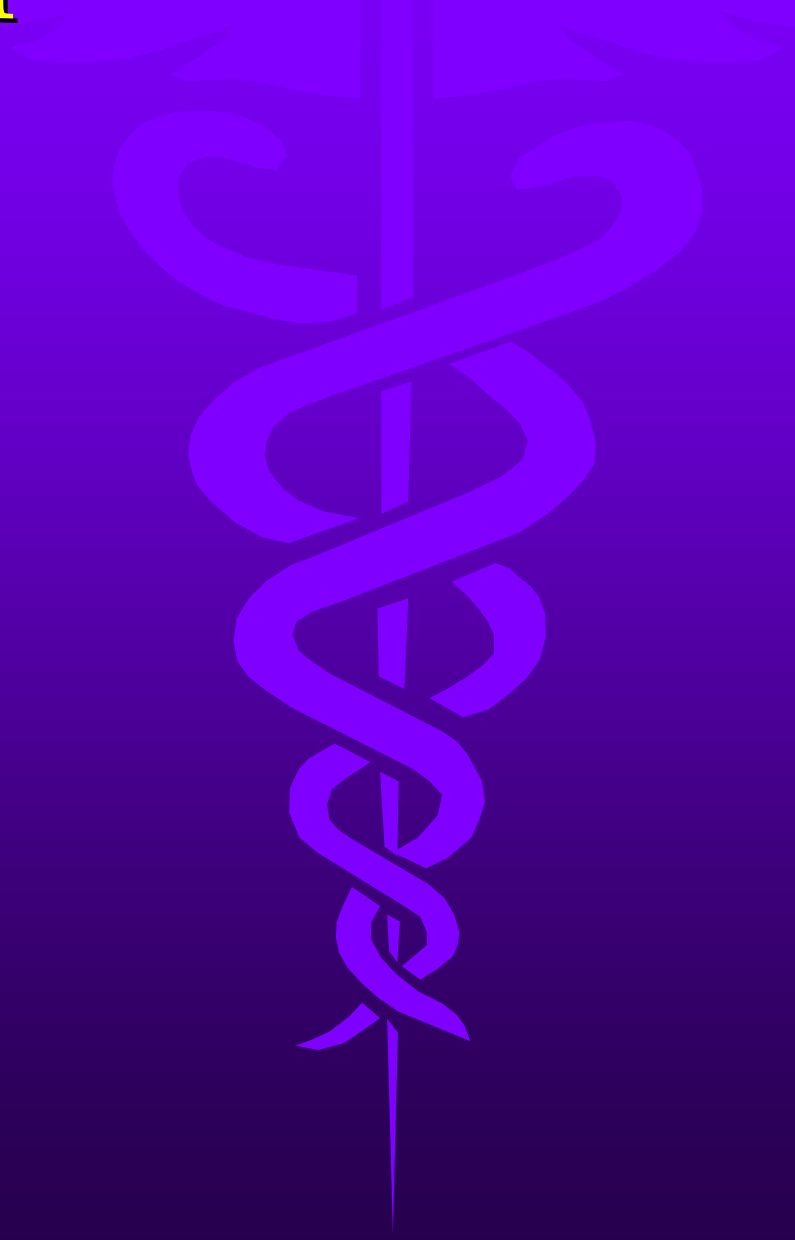
# Cardiac Resynchronization improves combined HF worsening/Death in patients with low EF and wide QRS

- 2002 MIRACLE
- 453 patients
- EF <35%
- QRS >130ms
- Cardiac Resynchronization vs placebo
- No mortality benefit demonstrated



**ACC I - Patients with LVEF less than or equal to 35%, sinus rhythm, and NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration greater than 0.12 ms, should receive cardiac resynchronization therapy unless contraindicated. (Level of Evidence: A)**

# Pharmacological Treatment of Acute Decompensated Heart Failure





# Pharmacological Treatment of Acute Decompensated Heart Failure

**TABLE 24-4** Pharmacological Therapy for Acute, Decompensated Heart Failure

Treatment Modality	Specific Examples
Intravenous diuretics	Furosemide, bumetamide, torsemide
Intravenous positive inotropic agents	Dobutamine, milrinone, enoximone
Intravenous vasodilators	Nitroprusside, nitroglycerine, nesiritide
Blood pressure, renal perfusion support	Intravenous dopamine, intravenous vasopressin

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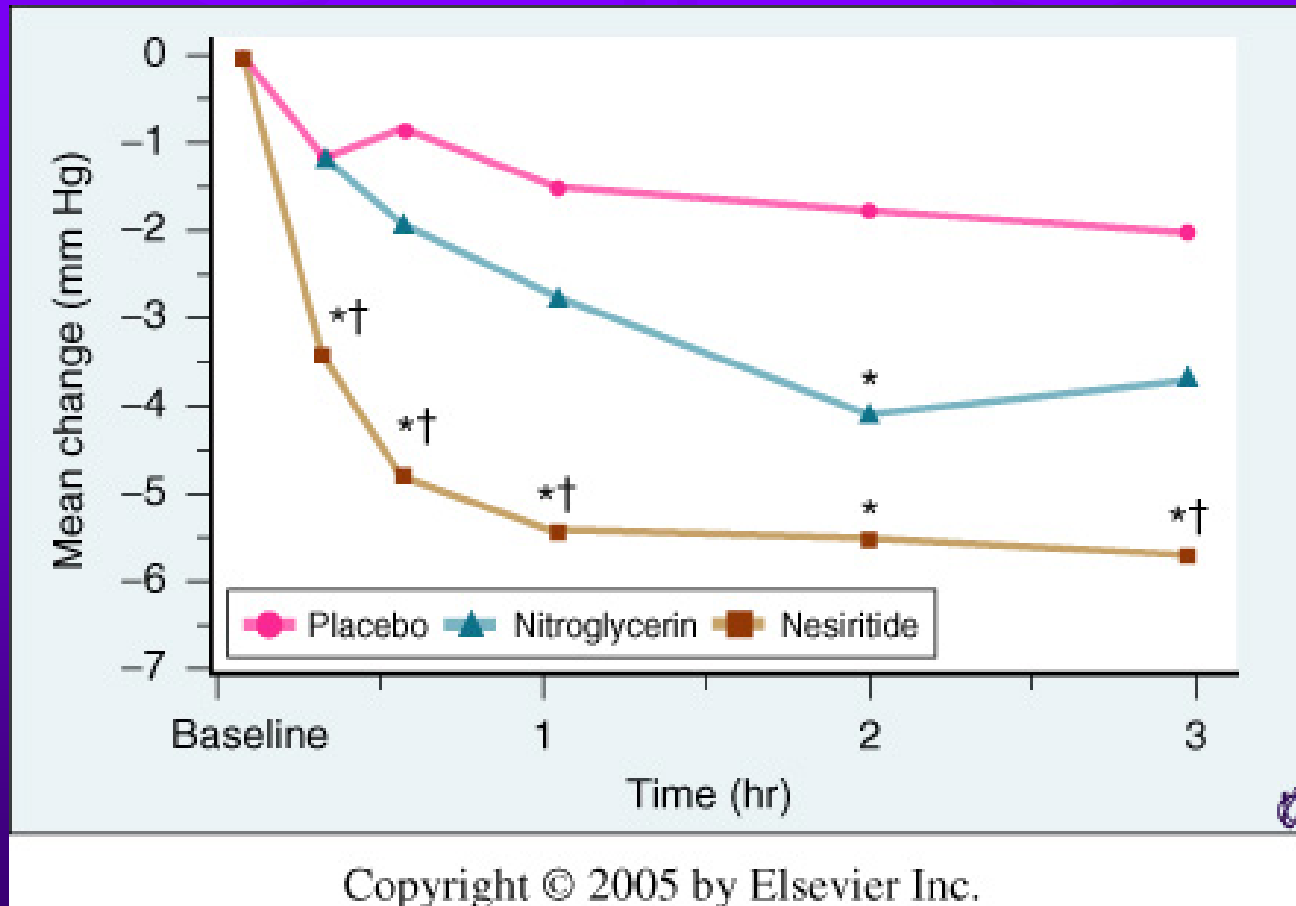
# Nonpharmacological/Device Therapy for Acute Decompensated Heart Failure

<b>TABLE 24-5 Nonpharmacological Therapy for Acute, Decompensated Heart Failure</b>	
<b>Treatment Modality</b>	<b>Specific Examples</b>
Oxygenation	Supplemental oxygen, mechanical ventilation
Balloon counterpulsation	Intraaortic balloon pump
VAD	Pulsatile-flow LVAD
Pacing	AV sequential pacemaker; biventricular pacing
Urgent cardiac catheterization	PTCA, mitral valvuloplasty, pericardiocentesis
Urgent cardiac surgery	CABG, AVR, MV repair or replacement, transplantation

AV = atrioventricular; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LVAD = left ventricular assist device; MV = mitral valve; PTCA = percutaneous transluminal coronary angioplasty; VAD = ventricular assist device.

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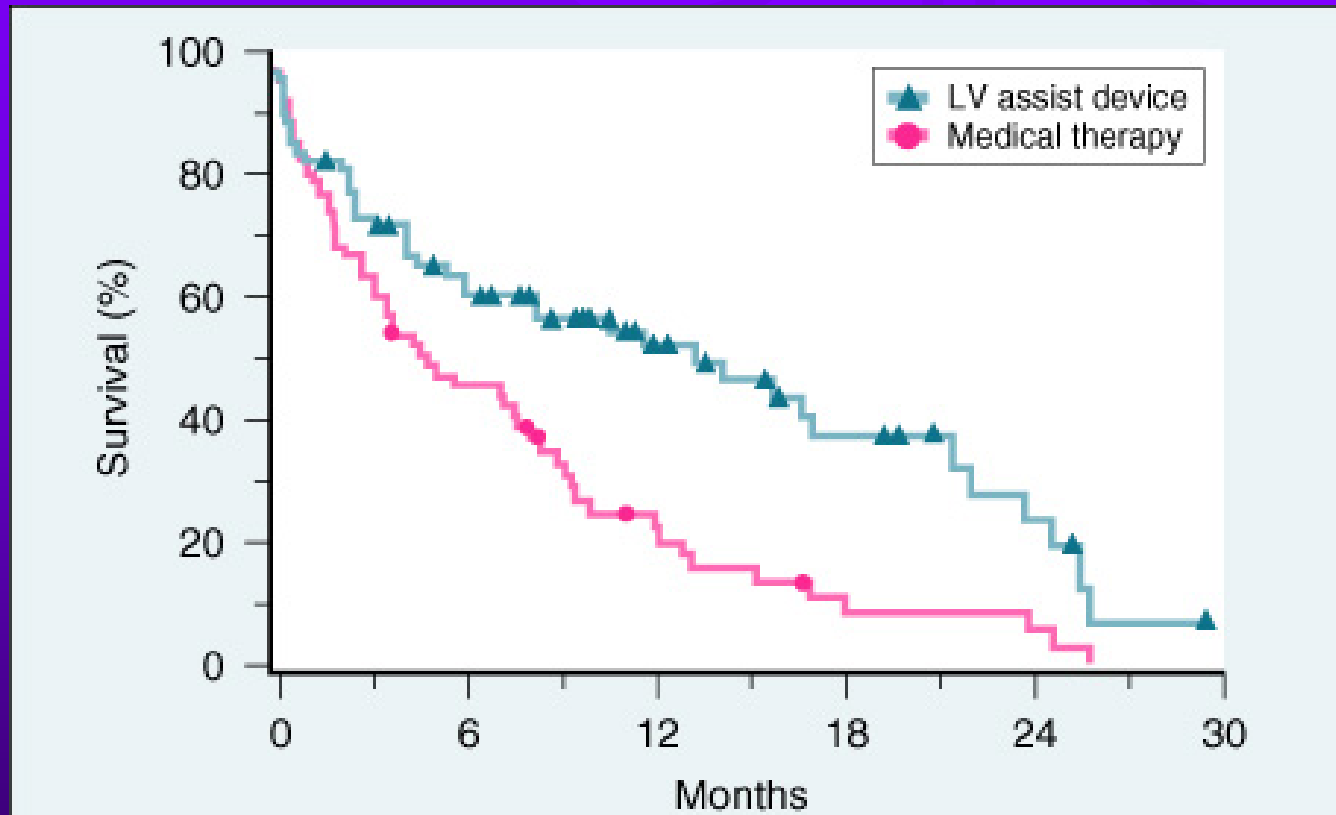
# Effect of Natrecor on PCWP



# Thoratec Heartmate

## 2004 REMATCH

### HF patients requiring inotropes



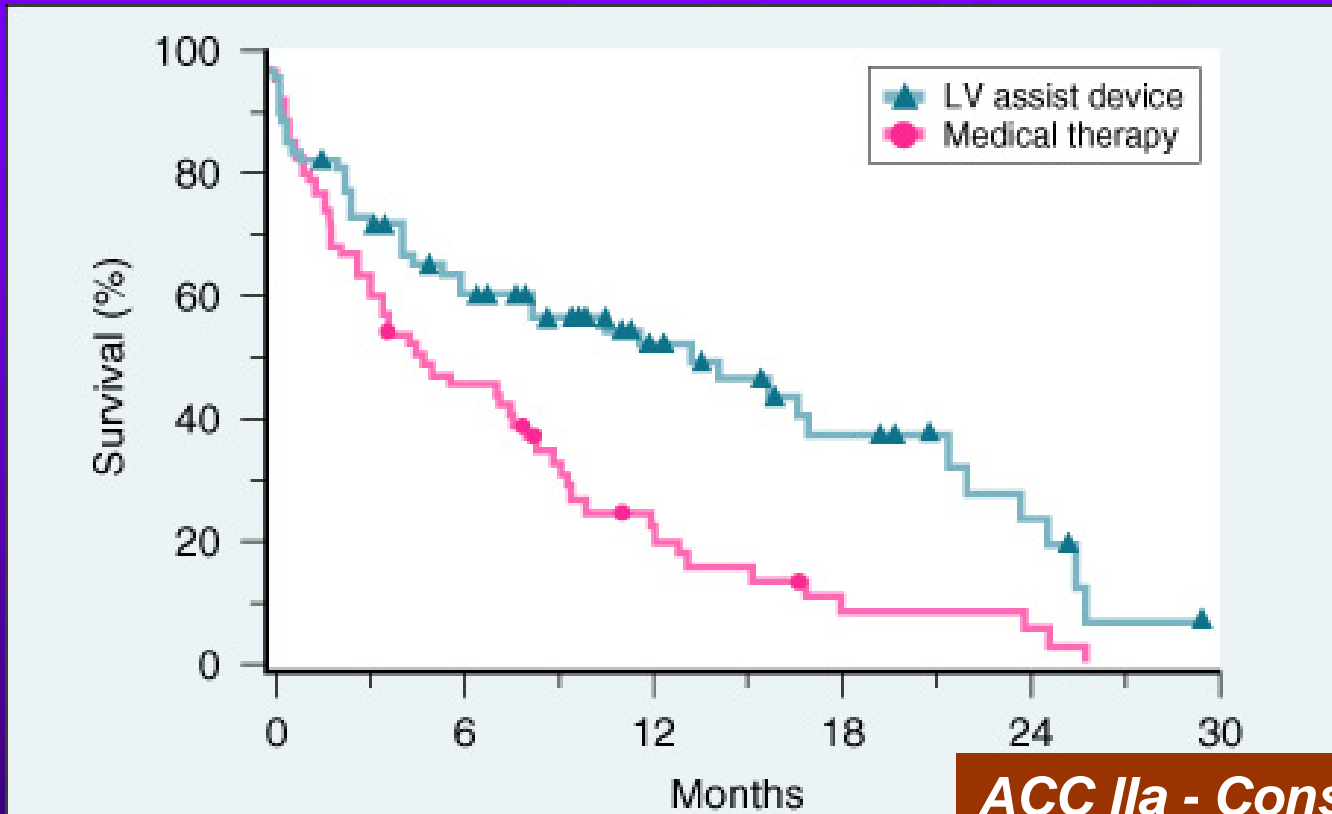
No. at risk							
LV assist device	68	38	22	11	5	1	
Medical therapy	61	27	11	4	3	0	



# Thoratec Heartmate

## 2004 REMATCH

### HF patients requiring inotropes



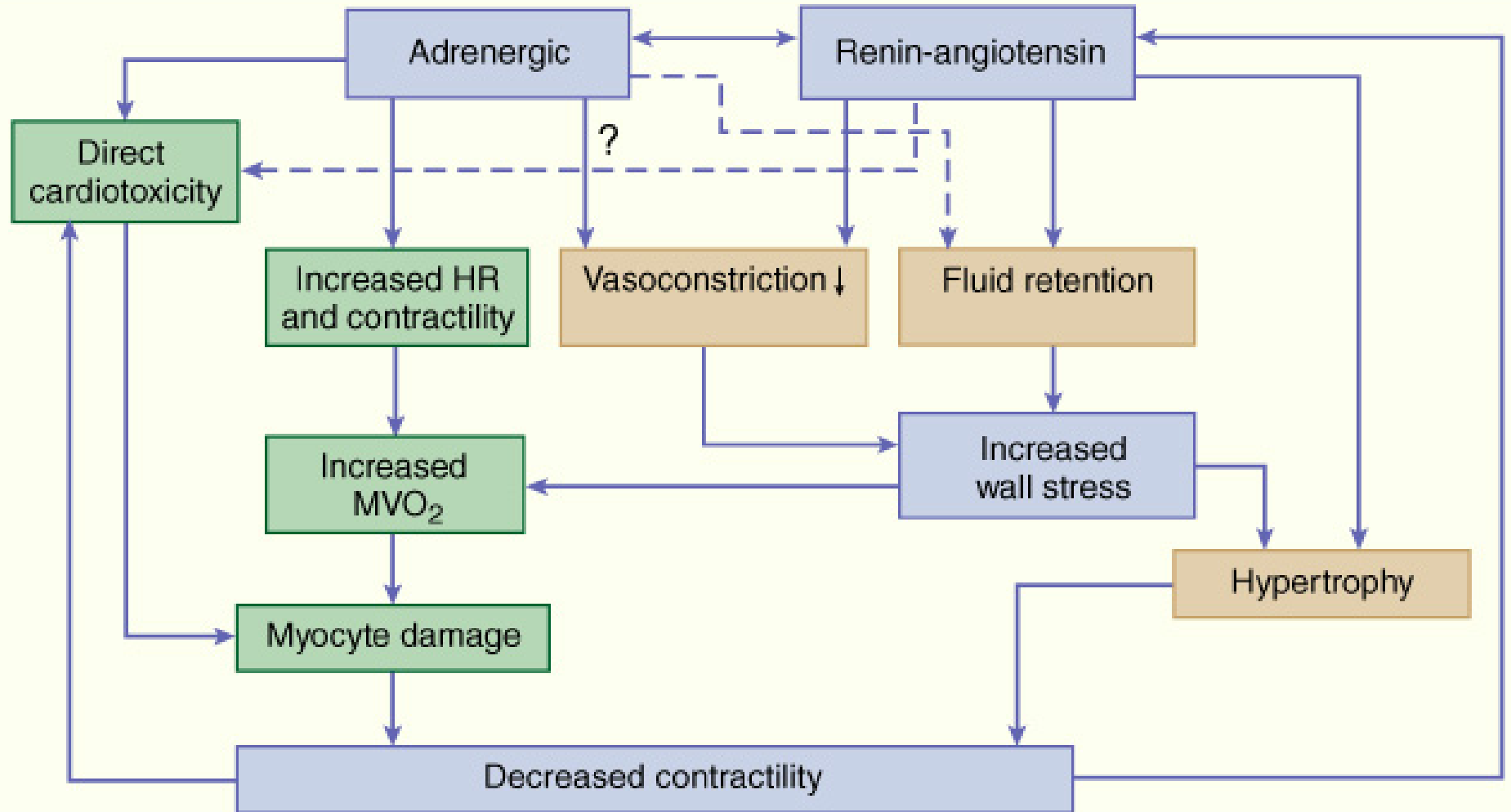
No. at risk					
LV assist device	68	38	22	11	
Medical therapy	61	27	11	4	

**ACC IIa - Consideration of an LV assist device as permanent or “destination” therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy. (Level of Evidence: B)**

# New Directions in Heart Failure

- Pathophysiologic implication of neurohormonal treatment
- New medications
- New devices
- Recognition of Comorbidities

# Renin-Angiotensin system



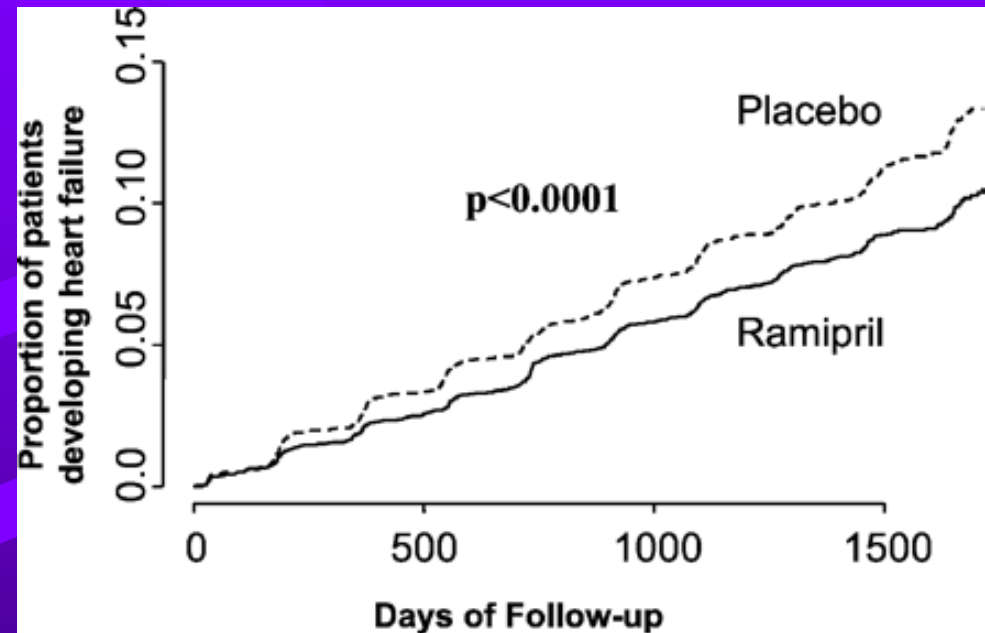
# Preventing Heart Failure

- 2003 HOPE trial
- $\geq 55$  years old with
  - CAD, CVA or PAD or
  - Diabetes + at least 1 risk factor
    - HTN, HLP, smoking, microalbuminuria
  - Excluded EF  $< 40\%$ , uncontrolled HTN, CVA or MI in past 4 weeks
- Ramipril 10mg daily vs placebo
- 9541 patients
- 4.5 year followup



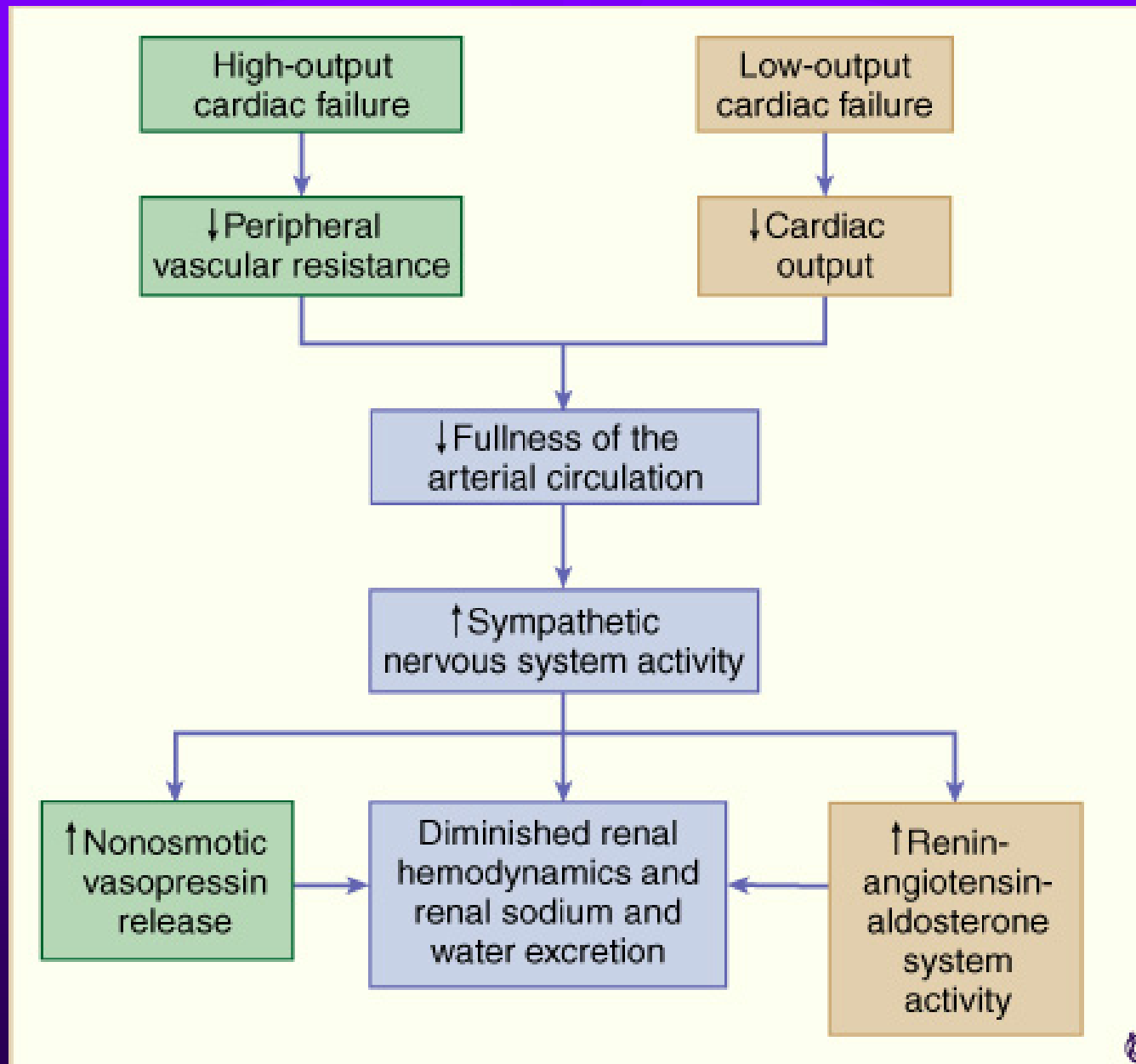
# HOPE results

- New onset heart failure
  - 9.0% with ramipril vs 11.5% placebo (p<0.0001)
- Reduced risk of HF whether or not there was an interim myocardial infarction
- Reduced risk for patients with SBP above median (139mmHg) and below median
- Conclusion – Ramipril reduces development of HF in at-risk patients

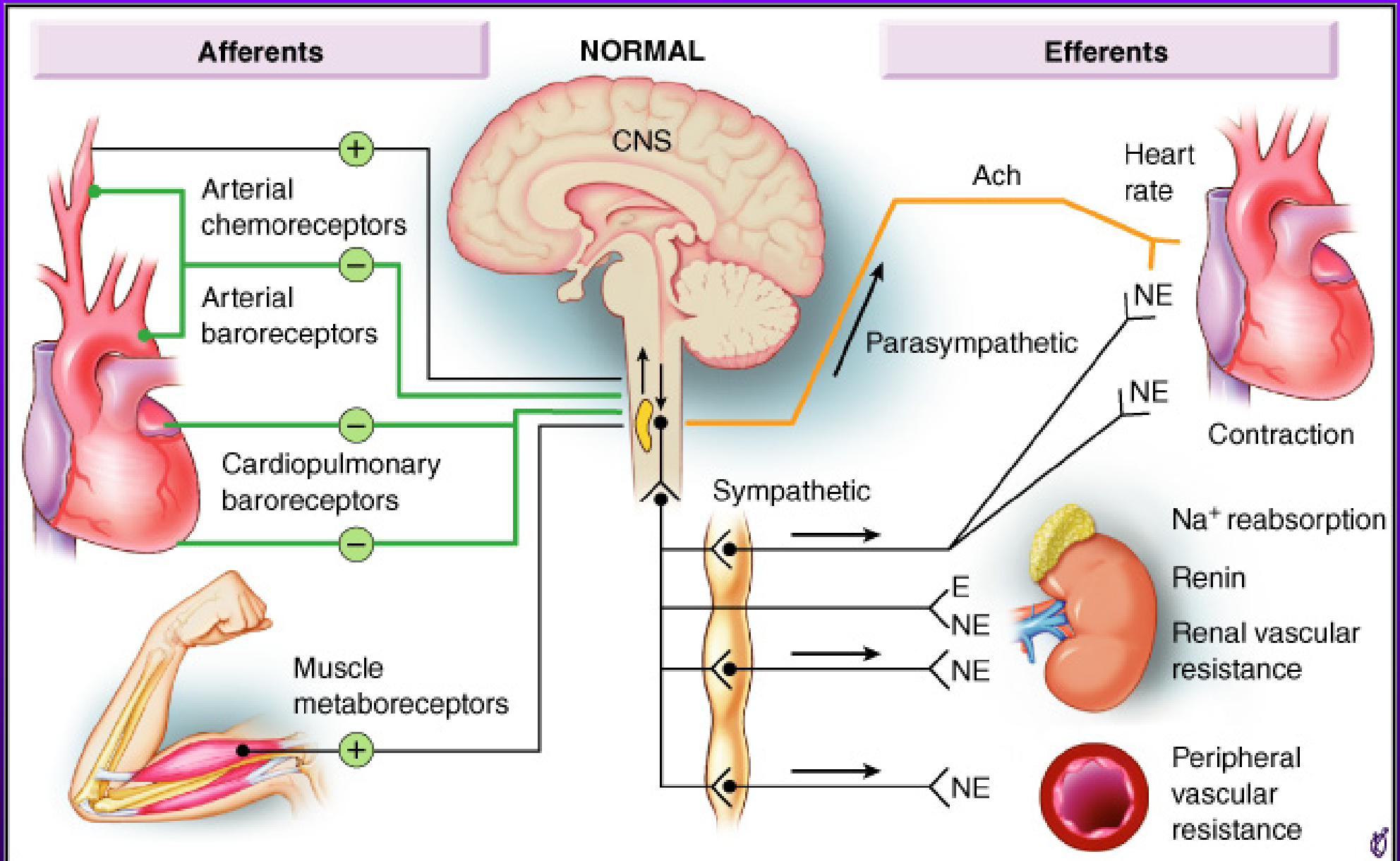


***ACC IIa - Angiotensin converting enzyme inhibitors can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (Level of Evidence: A)***

# Neurohumoral vasoconstriction leading to renal sodium and water retention

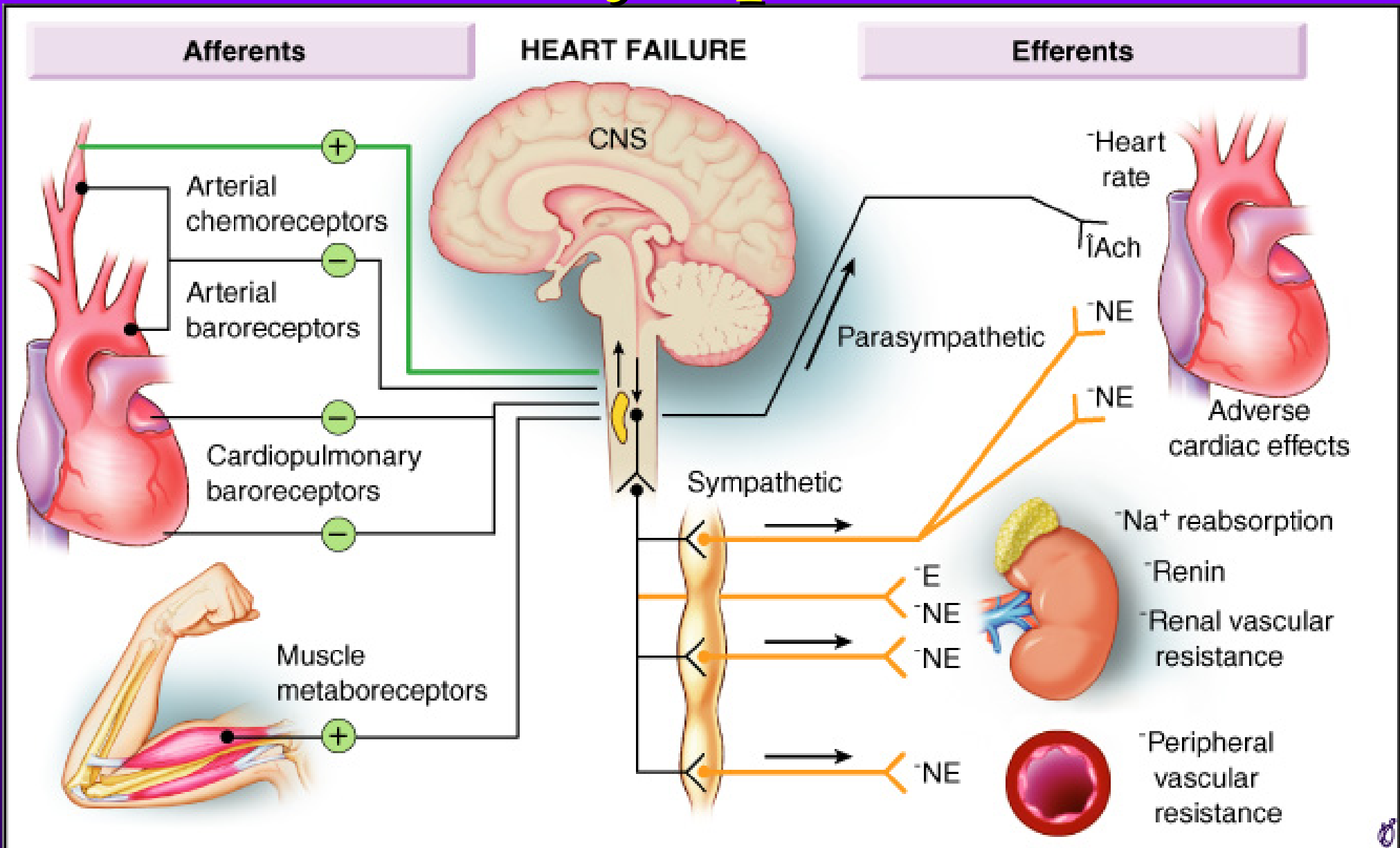


# Normal Parasympathetic tone



A

# Abnormal Sympathetic Tone



B

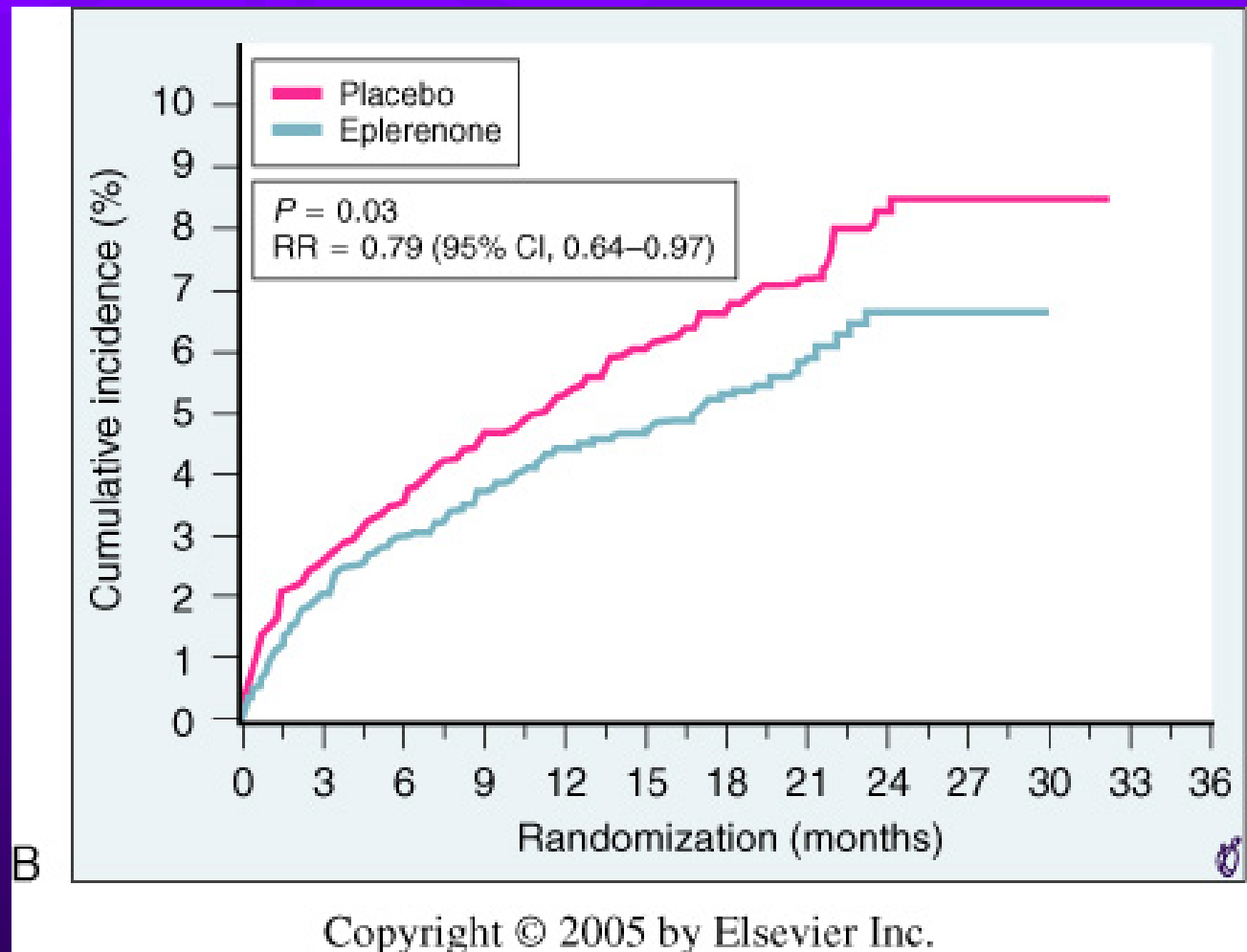


# **New Directions in Chronic Systolic Heart Failure**

# EPHESUS

## Rate of Cardiac Death

- 6632 patients
- Acute Myocardial Infarction
- EF <40% and
  - Heart Failure (Rales) or
  - Diabetes
- Eplerenone 25mg daily vs placebo



# EPHESUS

## Rate of Cardiac Death

- 6632 patients
- Acute Myocardial Infarction
- EF <40% and
  - Heart Failure (Rales) or
  - Diabetes
- Eplerenone 25mg daily vs placebo

***ACC I - Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF of less than or equal to 0.40, and have either symptomatic heart failure or diabetes. (Level of Evidence: A)***

Randomization (months)

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# Isosorbide/Hydralazine is beneficial in African Americans

- 2004 A-HeFT
- 1050 self-classified African-Americans
- NYHA class 3-4
  - LVEF  $\leq 35\%$  or
  - LVEF  $\leq 40\%$  with LV dilatation
- BiDil (20mg isordil + 37.5mg hydralazine) tid vs placebo
- On top of standard tx including ACE,  $\beta$ -blockers, diuretics



# A-HeFT results

- Mean 10 month followup
- BiDil improved mortality and 1<sup>st</sup> HF hospitalization

	placebo	BiDil
All-cause mortality	10.2%	6.2% (p=0.01)
1 <sup>st</sup> HF hospitalization	24.4%	16.4% (p=0.001)

# A-HeFT results

- Mean 10 month followup
- BiDil improved mortality and 1<sup>st</sup> HF hospitalization

**ACC IIa - The addition of isosorbide dinitrate and hydralazine to a standard medical regimen for HF, including ACEIs and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested. (Level of Evidence: A)**

All-cause  
mortality

**The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. (Level of Evidence: A)**

1<sup>st</sup> HF  
hospitalization



# **New Directions in Acute Decompensated Heart Failure**

# Arginine Vasopressin Receptor Antagonists

- New class of medications
- Blocks effect of antidiuretic hormone (ADH)
- Facilitates Aquaresis (net loss of water without electrolytes)
- Used in conjunction with other diuretics
- Receptors
  - V(1A) (vascular and myocardial effects)
  - V(2) receptors (renal effects)
- Conivaptan (IV) is a V(1A) + V(2) nonselective antagonist, approved for use in hyponatremia (SIADH)
- Tolvaptan (oral) is a V(2) selective antagonist

# In-hospital outcomes of oral tolvaptan and placebo in ACTIV in CHF

Outcome 319 patients	Tolvaptan 30 mg/day (n=78)	Tolvaptan 60 mg/day (n=84)	Tolvaptan 90 mg/day (n=77)	Placebo (n=80)
<b>Weight loss vs baseline, hospital day 1, median kg (p vs placebo)</b>	1.80 (0.002)	2.10 (0.002)	2.05 (0.009)	0.60
<b>Weight loss vs baseline, at discharge, median kg (p vs placebo)</b>	3.30 (0.006)	2.80 (0.002)	3.20 (0.06)	1.90
<b>Urine volume, hospital day 1, mean mL (p vs placebo)</b>	4056.2 (0.02)	4175.2 (<0.001)	4127.3 (<0.001)	2296.5

# Adenosine A1 receptor antagonists

- Elevated levels of plasma adenosine in heart failure
- Adenosine lowers renal cortical blood flow
- Small phase 2 trial completed
- Adenosine A1 receptor blockade can cause natriuresis and diuresis without impact on K<sup>+</sup> excretion or GFR

# Ultrafiltration

- Peripheral or central venous access options
- Catheter options include peripheral IVs, midlines or central
- Fluid removal adjustable from 10 to 500 ml/hour in 10 ml/hour increments
- Blood flow settable from 10 to 40 ml/min in 5 ml/min increments
- Total extracorporeal blood volume of 33 ml



# Primary and secondary end points, ultrafiltration vs standard diuresis in UNLOAD

End points	Ultrafiltration	Diuresis	p
48 hours			
• Weight loss, primary end point (mean kg)	5.0, n=83	3.1, n=84	0.001
• Dyspnea score, primary end point (mean)	6.4, n=80	6.1, n=83	0.35
• Net fluid loss (mean L)	4.6	3.3	0.001
• K<3.5 mEq/L (%)	1	12	0.018
• Need for vasoactive drugs (%)	3	13	0.015

**K=potassium**  
**ED=emergency department**



# Primary and secondary end points, ultrafiltration vs standard diuresis in UNLOAD

<u>End points</u>	<u>Ultrafiltration</u>	<u>Diuresis</u>	<u>p</u>
90 days			
• Rehospitalization (%)	18	32	0.022
• Rehospitalization days (mean)	1.4	3.8	0.022
• Unscheduled office/ED visits (%)	21	44	0.009
<hr/>			
<b>K=potassium</b>			
<b>ED=emergency department</b>			

# Calcium sensitization

## Levosimendan

- Novel agent which improves myocardial contractility without increasing intracellular calcium or c-AMP
- Improves myocardial sensitivity to calcium
- Vasodilator action by opening ATP sensitive K<sup>+</sup> channels

# Early Levosimendan Trials

- Advanced decompensated heart failure (IV)
  - 2003 LIDO (vs dobutamine)<sup>1</sup>
    - Improved PCWP and cardiac index
    - Improved 1 month (7.8% v 17%) and 6 month (26% v 38%) mortality
  - Improves BNP and inflammatory cytokines vs dobutamine<sup>2</sup>
  - Improves PCWP and Cardiac Index in sepsis-induced cardiac dysfunction vs dobutamine<sup>3</sup>
- Class 3-4 Heart Failure (oral)
  - Improves inotropic parameters and increases heart rate<sup>4</sup>

1 Follath F et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet*. 2002 Jul 20;360(9328):196-202.

2 Avgeropoulou C et al. The Ca<sup>2+</sup>-sensitizer levosimendan improves oxidative damage, BNP and pro-inflammatory cytokine levels in patients with advanced decompensated heart failure in comparison to dobutamine. *Eur J Heart Fail*. 2005 Aug;7(5):882-7.

3 Morelli A, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med*. 2005 May;31(5):638-44. Epub 2005 Apr 6.

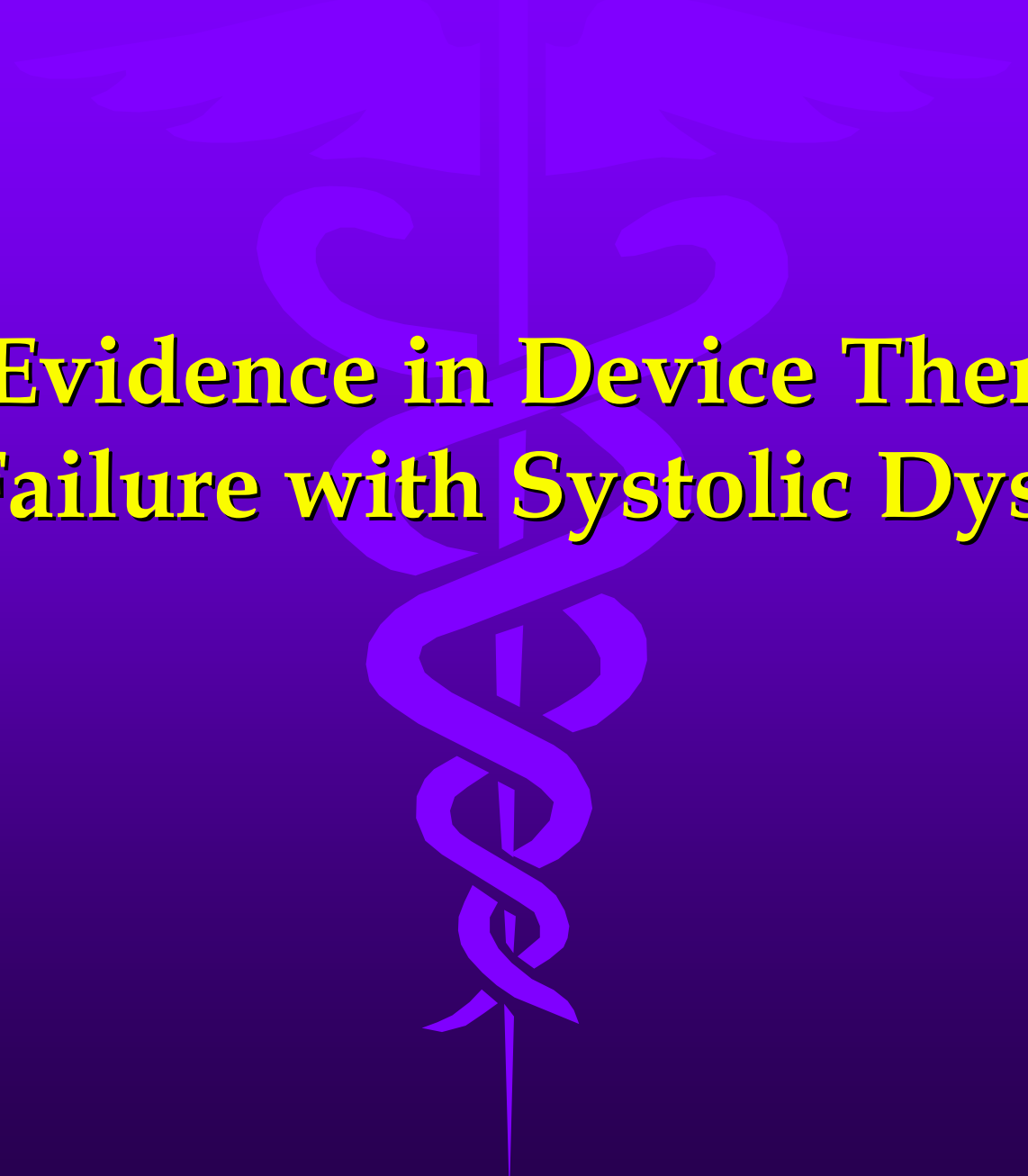
4 Poder P, Eha et al. Pharmacodynamics and pharmacokinetics of oral levosimendan and its metabolites in patients with severe congestive heart failure: a dosing interval study. *J Clin Pharmacol*. 2004 Oct;44(10):1143-50.

# Later Levosimenden Trials

- 2005 REVIVE-2
  - Acute decompensated HF (EF $\leq$ 35%), vs placebo; 600 patients
  - “Clinical Improvement” better at 24h and 5d with levosimenden
  - 90 day mortality rate favored placebo (11% v 15%, p=NS)
- 2005 SURVIVE
  - Acute decompensated HF (EF $\leq$ 30%), vs dobutamine; 1327 patients
  - No significant survival advantage up to 6 months
- 2006 PERSIST (phase 2), Orion company sponsored
  - Severe Heart failure patients (outpatient, oral)
  - No benefit vs placebo
  - No plans for phase 3 trial
- Subsequent trials have identified higher rates of atrial fibrillation, ventricular tachycardia, and hypotension with levosimenden

# Endothelin Antagonists in Acute Decompensated Heart Failure

- 2005 VERITAS
  - Tezosentan – IV dual endothelin receptor antagonist v placebo on top of usual care
  - Largest study in acute decompensated HF – 1400 patients
  - No difference in dyspnea at 24h
  - No difference in worsening heart failure or mortality at 7 days (26% v 26%)
  - No mortality benefit at 6 months



# **New Evidence in Device Therapy for Heart Failure with Systolic Dysfunction**

# Cardiac Resynchronization improves mortality with EF<35% and wide QRS

- 2005 CARE-HF
- 813 patients with NYHA 3-4, LVEF  $\leq 35\%$ , QRS  $\geq 120\text{ms}$
- 29.4 month followup
- Cardiac resynchronization (Bi-V pacing) vs standard medical therapy
- All cause mortality 20% v 30% ( $p < 0.002$ )

# Cardiac Resynchronization for NYHA class 2 patients?

- 50 patients Class 2 v 50 patients Class 3-4
- NYHA class 2, LVEF  $\leq 35\%$
- QRS  $>120\text{ms}$
- Class 2 patients
  - EF improved from 25% to 33%
  - Only 8% had worsening HF symptoms
  - Results comparable to Class 3-4 patients

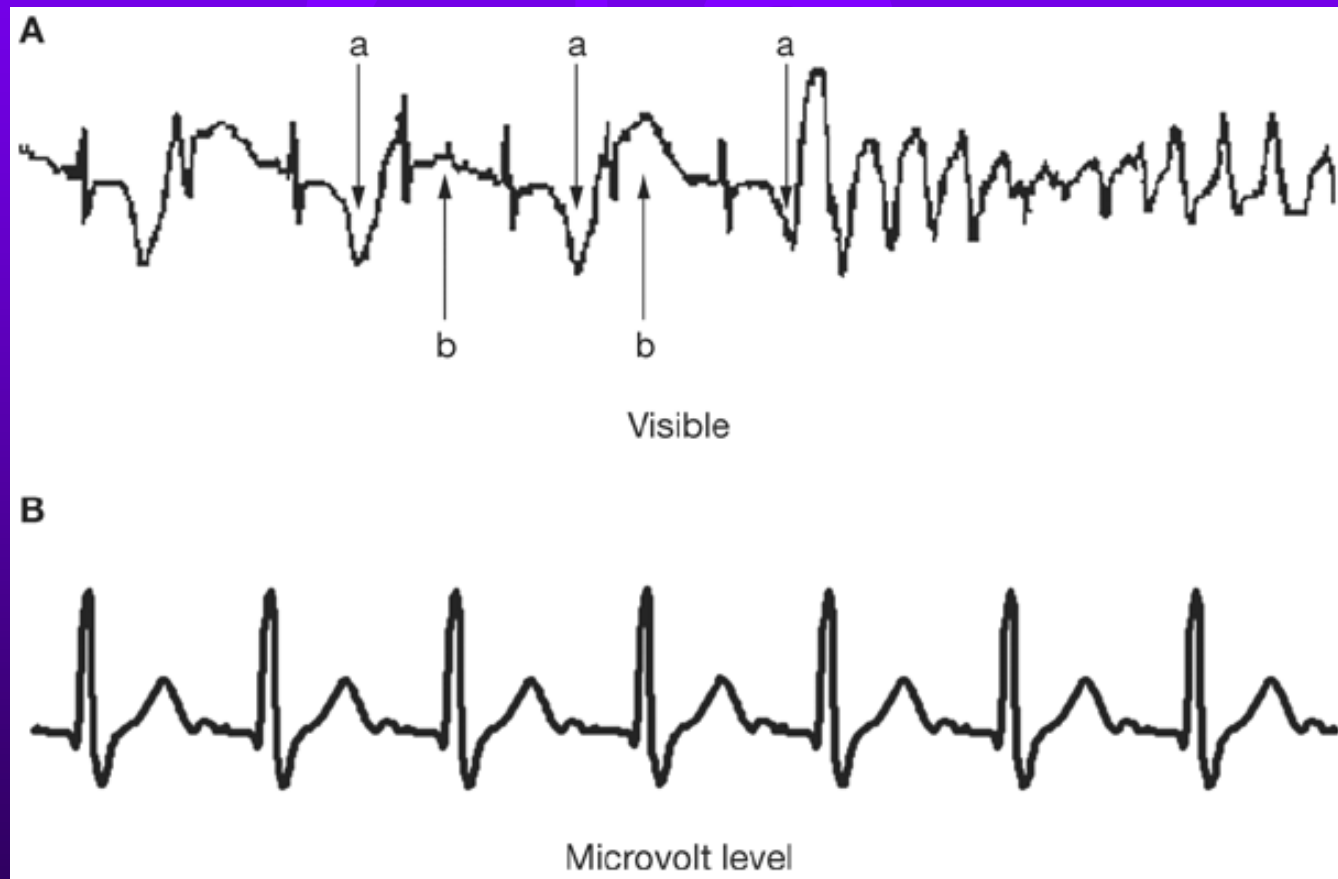


# Predicting Responders to CRT

- Currently a QRS width of  $>120$ ms is used as a marker of LV dyssynchrony
- Echocardiographic parameters are useful to determine dyssynchrony
  - Paradoxical septal motion
  - Tissue doppler imaging
  - Speckle
  - Strain

# Risk Stratification for ICDs

## Microvolt T Wave Alternans



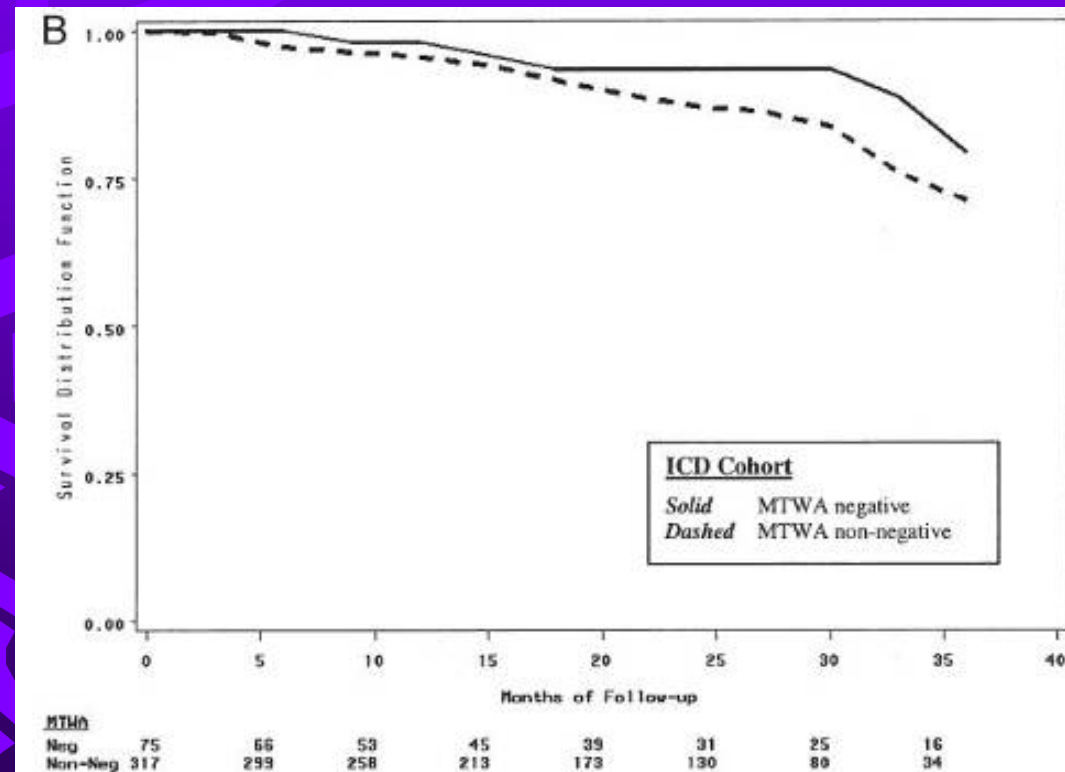
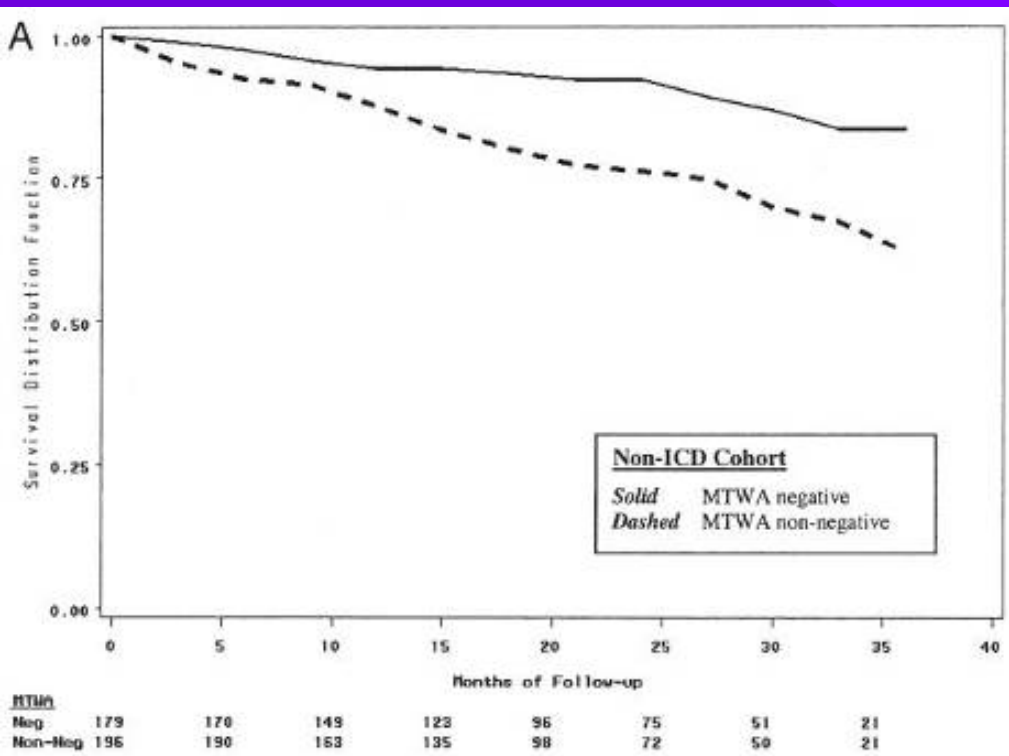
Chow T, Kereiakes DJ, Bartone C, Booth T, Schloss EJ, Waller T, Chung ES, Menon S, Nallamothu BK, Chan PS. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol.* 2006 May 2;47(9):1820-7. Epub 2006 Apr 19.

<http://www.nature.com/ncpcardio/journal/v2/n10/images/ncpcardio0323-F1.gif>

# Risk Stratification for ICDs

## Microvolt T Wave Alternans

- Ischemic Cardiomyopathy, EF  $\leq$  35%
- Observational Cohort Study



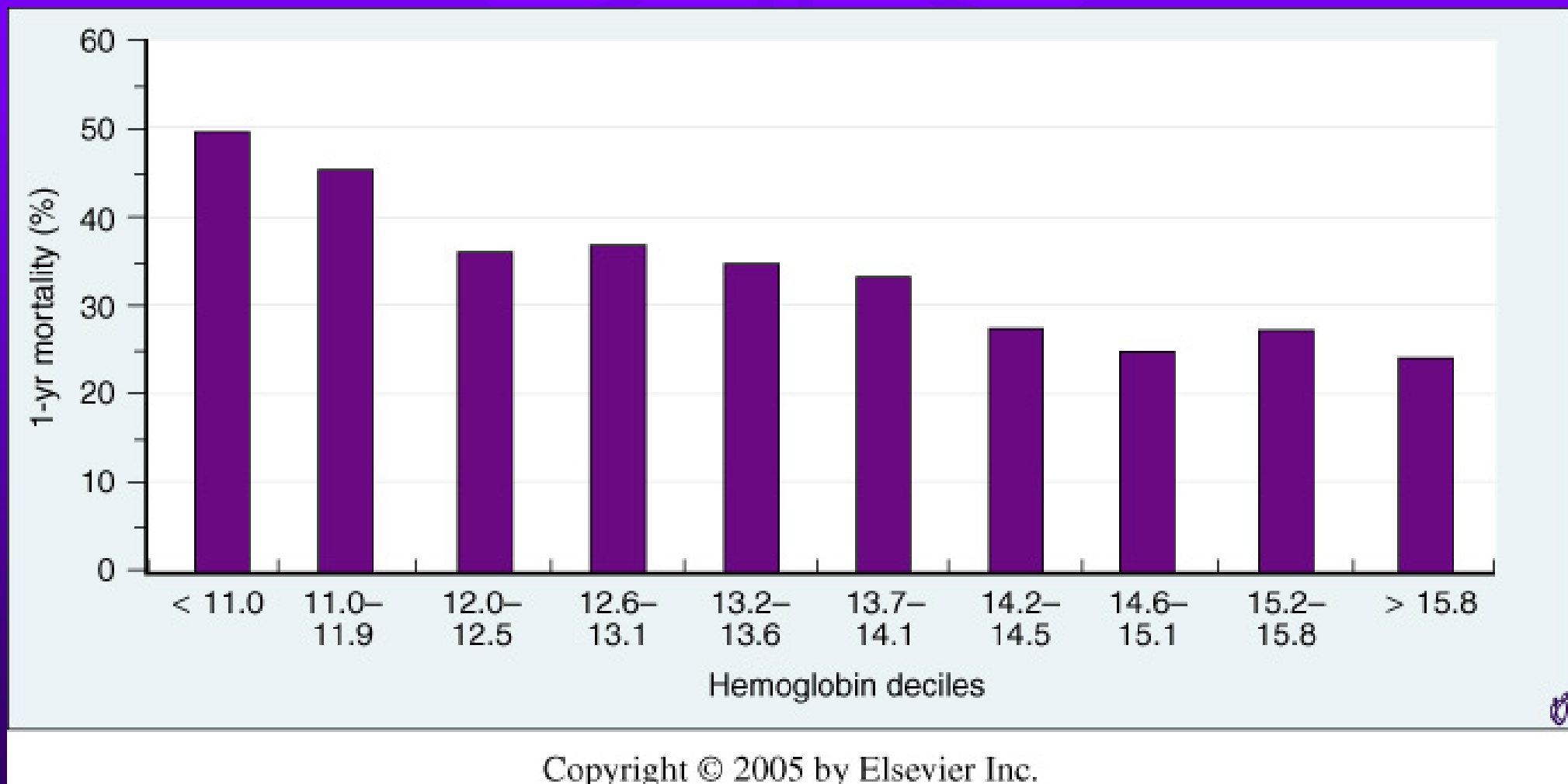
Chow T, Kereiakes DJ, Bartone C, Booth T, Schloss EJ, Waller T, Chung ES, Menon S, Nallamothu BK, Chan PS. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2006 May 2;47(9):1820-7. Epub 2006 Apr 19.

<http://www.nature.com/ncpcardio/journal/v2/n10/images/ncpcardio0323-F1.gif>

# Comorbidities in Heart Failure



# Anemia is associated with increased mortality in Heart Failure



# Treating anemia improves function in heart failure

- Treatment with erythropoietin 15,000-30,000 IU/week over 3 months improved anemia and function in small study of 26 patients
- Patients with LVEF $\leq$ 40%, NYHA 3-4, Hgb 10-11.5g% treated with epogen and IV iron over 8 months have improved EF, improved function, decreased need for diuretics, and decreased hospitalizations (n=32)

Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003 Jan 21;107(2):294-9.

Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A.. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001 Jun 1;37(7):1775-80.

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**ACC IIb - The benefit of enhancing erythropoiesis in patients with HF and anemia is not established. (Level of Evidence: C)**

Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003 Jan 21;107(2):294-9.

Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A.. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001 Jun 1;37(7):1775-80.

# Cardiorenal Syndrome

- Concomitant Cardiac and Renal dysfunction leading to diuretic resistance and volume overload
- No formal standard definition
  - Rise in creatinine of 0.3 mg/dL
- 1/3-1/2 of heart failure patients develop renal insufficiency (GFR <60mL/min/1.73m<sup>2</sup>) in clinical trials
- Worse renal function = worse prognosis



# Risk Factors for Worsening Renal Function in the SOLVD trials

- Old age
- Low EF
- Baseline Renal dysfunction
- Low systolic blood pressure
- Diabetes Mellitus
- Hypertension
- Use of antiplatelet tx, diuretics, or  $\beta$ -Blockers

# Treatment of Cardiorenal Syndrome

- ACE inhibitors
  - Start when patient is not dehydrated, cautious use with creatinine  $>2.0$
- Diuretics
  - May lead to higher mortality, pump failure
  - Diuretic resistance is a marker for advanced disease



# **New Horizons in Surgical Treatment for Heart Failure**

# Stem Cell Therapy

- EF <35%, scheduled primary off-pump CABG
- Epicardial autologous stem cell transplantation (CD34+); injection sites determined by pre-operative echocardiogram, catheterization, and nuclear stress imaging.
- 20 patients randomized (placebo v stem cell)
- Average baseline EF 30%, median 1 bypass graft
- 6 month FU
  - Mean EF improved in stem cell group (46% v 37%, p<0.001)



# Update on Anticoagulation Trials

# Anticoagulation Does Not Reduce Thromboembolic Risk in HF

- 2004 WATCH<sup>1</sup>
  - 1587 patients with HF and LVEF <35%; 23 months FU
  - ASA (162mg/d) v clopidogrel v Warfarin (INR 2.5-3)
  - Similar rates of death, MI and stroke
- 2004 WASH<sup>2</sup>
  - 279 patients with HF; 27 months FU
  - Placebo v ASA v Warfarin
  - No differences in primary endpoint of death, nonfatal MI, or nonfatal stroke
- 2006 HELAS<sup>3</sup>
  - Ischemic/nonischemic cardiomyopathy
  - 115 patients, ASA v Warfarin; 2.5 years FU
  - No differences in the primary composite end point of death, MI, hospitalization, HF exacerbation, or hemorrhage

1 Massie BM et al. Warfarin and Antiplatelet Therapy in Heart Failure Trial (WATCH). Presented at ACC Scientific Sessions 2004, New Orleans, LA.

2 Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart Failure (WASH): A randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004; 148:157-64.

3 Cokkinos DV, Haralabopoulos GC, Kostis JB, et al. Efficacy of antithrombotic therapy in chronic heart failure: The HELAS study. *Eur J Heart Fail* 2006; 8:428-432.

# Anticoagulation Does Not Reduce Thromboembolic Risk

## ACC IIb

**ACC IIb - The usefulness of anticoagulation is not well established in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (Level of Evidence: B)**

- 2004 WATCH<sup>1</sup>
  - 1587 patients
  - ASA (162)
  - Similar rates
- 2004 WASH<sup>2</sup>
  - 279 patients with HF; 27 months FU
  - Placebo v ASA v Warfarin
  - No differences in primary composite end point of death, MI, or nonfatal stroke
- 2006 HELAS<sup>3</sup>
  - Ischemic/nonischemic cardiomyopathy
  - 115 patients, ASA v Warfarin; 2.5 years FU
  - No differences in the primary composite end point of death, MI, hospitalization, HF exacerbation, or hemorrhage

## Update on Anticoagulation Trials

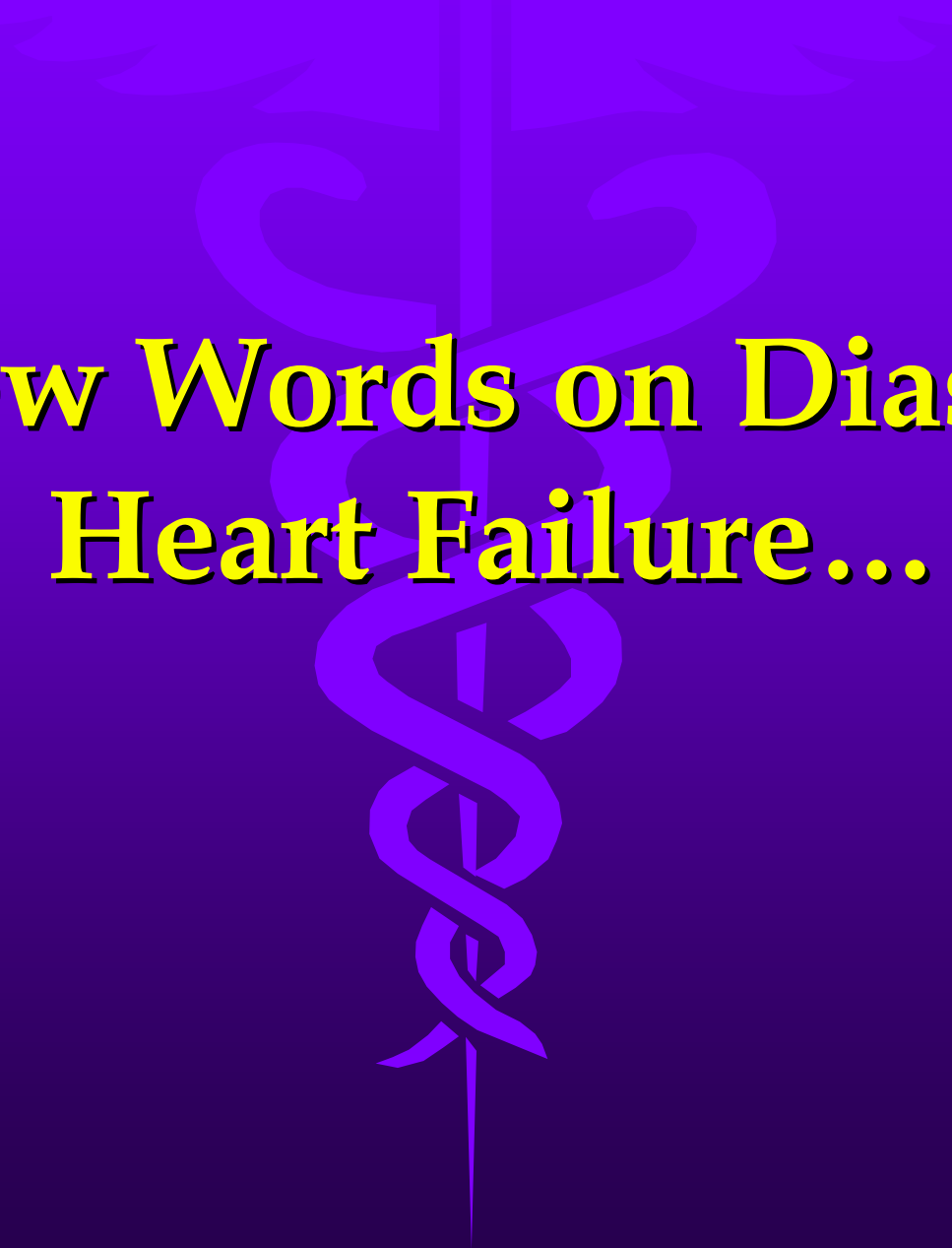
1 Massie BM et al. Warfarin and Antiplatelet Therapy in Heart Failure Trial (WATCH). Presented at ACC Scientific Sessions 2004, New Orleans, LA.

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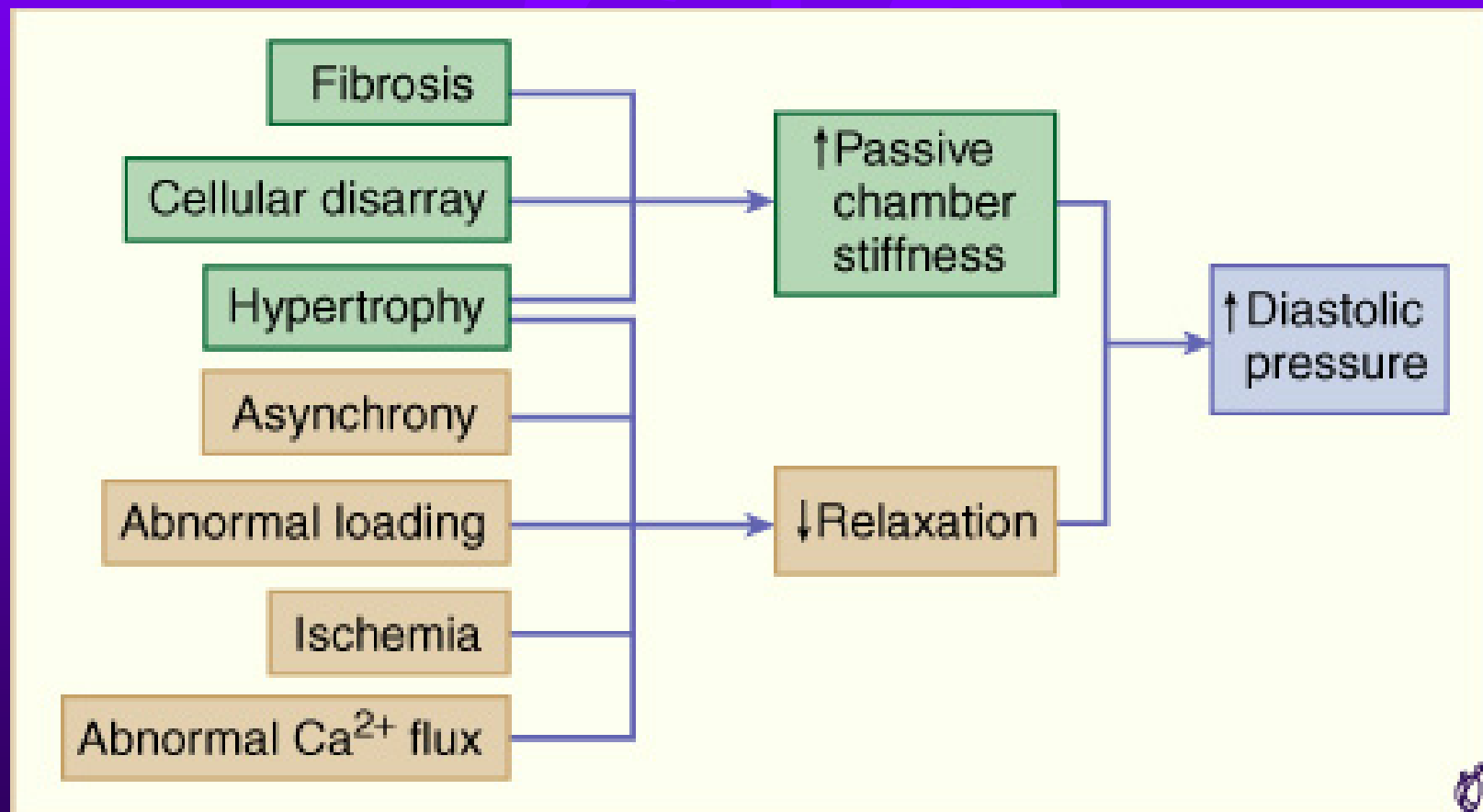
# **Diastolic Heart Failure**

**A Few Words on Diastolic  
Heart Failure...**





# Development of Diastolic Heart Failure



# Diagnostic Criteria for Diastolic Heart Failure

**TABLE 22-4** Diagnostic Criteria for Diastolic Heart Failure

Criterion	Possible Diastolic Heart Failure
Definitive evidence of HF	Signs and symptoms of HF, supporting laboratory tests,* and response to diuretics
Objective evidence of normal LV systolic function	LVEF $\geq$ 50% but not at the time of HF event
Objective evidence of LV diastolic dysfunction	No conclusive information

\*Chest radiograph, B-type natriuretic peptide level.

HF = heart failure; LV = left ventricular; LVEF = LV ejection fraction.

Adapted from Vasan RS, Levy D: Defining diastolic heart failure: A call for standardization. *Circulation* 2003;108:2754-2763.

# Diagnostic Criteria for Diastolic Heart Failure

Criteria	
Probable Diastolic Heart Failure	Definite Diastolic Heart Failure
Signs and symptoms of HF, supporting laboratory tests,* and response to diuretics	Signs and symptoms of HF, supporting laboratory tests,* and response to diuretics
LVEF $\geq$ 50% within 72 hr of HF event	LVEF $\geq$ 50% within 72 hr of HF event
No conclusive information	Abnormal LV relaxation, filling and/or distensibility at cardiac catheterization

Standardized diagnostic criteria. Circulation 101:2118, 2000.

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**Table 8.** Recommendations for Treatment of Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

<b>Recommendation</b>	<b>Class</b>	<b>Level of Evidence</b>
Physicians should control systolic and diastolic hypertension, in accordance with published guidelines.	I	A
Physicians should control ventricular rate in patients with atrial fibrillation.	I	C
Physicians should use diuretics to control pulmonary congestion and peripheral edema.	I	C
Coronary revascularization is reasonable in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to be having an adverse effect on cardiac function.	IIa	C
Restoration and maintenance of sinus rhythm in patients with atrial fibrillation might be useful to improve symptoms.	IIb	C
The use of beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists in patients with controlled hypertension might be effective to minimize symptoms of heart failure.	IIb	C
The use of digitalis to minimize symptoms of heart failure is not well established.	IIb	C

# CHARM-preserved trial

- 3025 patients, median followup 36 months
- Candesartan titrated to 32mg daily vs placebo

	placebo	candesartan
CV Death	11.3	11.2
CHF Hospitalization	18.3	15.9 (p=0.047)

# Prognosis of Diastolic v Systolic Heart Failure

- Canadian 1 year study
  - 2802 patients with new HF and documented EF
  - Compared 1570 pts with EF<40% with 880 pts with EF>50%
  - Groups clinically not distinguishable at admission
  - 1 year mortality 22% (diastolic) v 25% (systolic)
- American 15 year study
  - 4596 patients discharged with HF
  - 2429 pts with EF <50%, 2167 pts with EF ≥50%
  - At 5 years, mortality hazard ratio for diastolic HF was 0.96 (CI 0.92-1.00); better for <65 yrs age (0.87)

Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; 355:260-269.

Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; 355:251-259.

# In Summary: The Old

- Digoxin
  - For relief of symptoms
- Diuretics
  - As needed for volume control and symptoms
- ACE Inhibitors
  - All patients with systolic dysfunction
  - To prevent HF in high risk population
  - ARB ok if ACE intolerance
- $\beta$ -Blockers
  - For all patients with systolic dysfunction
- Aldactone
  - For class NYHA 3-4 patients

# The Recent New

- Isordil/Hydralazine
  - African Americans, on top of other therapy
- ARB's in addition to ACE
- ARB's for diastolic heart failure
- ACE may prevent heart failure
- ICD for EF <35%
- BiVentricular pacing
  - EF<35%, QRS 120ms, NYHA 3-4



# The New

- Ultrafiltration for decompensated heart failure
- LVAD as a destination therapy for refractory heart failure
- AVP receptor antagonists
- Adenosine A<sub>1</sub> antagonists
- Stem cell therapy
- Predicting risk of sudden cardiac death by microvolt t-wave alternans
- Recognition that diastolic and systolic heart failure have similar (bad) prognosis

# References

- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology