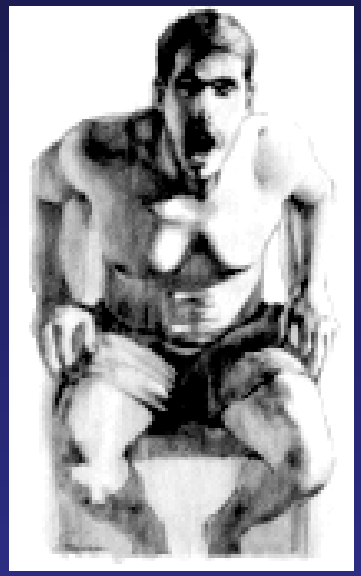
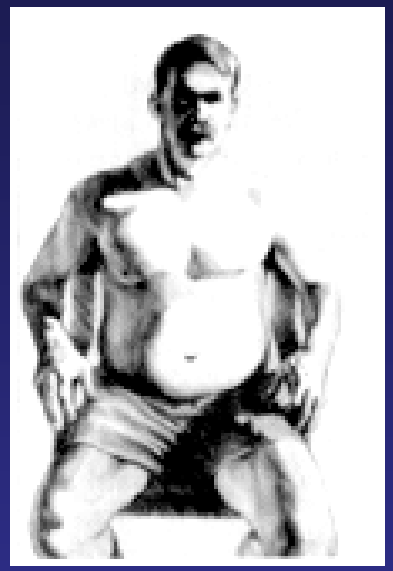
Heart Failure (II) Management

R. Zolty

Goal of HF Treatment





"I can't breathe"

"I can walk 30 minutes without stopping"

Case Study: JB

- 19 year old Caucasian man with known dilated CM and LVEF <20%
- MedicationS
  - Cozaar 50 mg BID
  - Aldactone 25mg QD
  - Lasix 40 mg QAM, 20mg QPM,
  - Digoxin 0.125 mg QD,
  - Isordil 20 mg TID
  - Hydralazine 25mg TID
- Subj: c/o nausea, vomiting, fatigue, abd pain and distension, no CP/↑ SOB

Case Study: JB

On exam:

- BP 78/-; HR 120 bpm
- JVP ↑↑↑, Chest Clear
- Labs: Cardiac enzymes wnl;
  Cr 2.8; K^+ 5.5

EKG: Tachycardia; P-R 0.18; LBBB

CXR: Cardiomegaly; vascular redistribution

Echocardiogram: EF 10%; Global HK; severe MR and TR

Q To ensure optimal therapy, the most important change would be to

- Increase diuretic dosage
- Decrease ARB/Hydralazine/Isordil
- Admit Patient
- Add a β-blocker

Q Next Step:

- Give patient N/S
- Give patient IV Lasix
- Send patient to ER
- Admit patient to the floor
- Admit patient to CCU

Goals Of Acute Therapy

- Reduce extracellular fluid volume excess
- Improve hemodynamics
  - Decrease left and right ventricular filling pressures
  - Increase cardiac output
- Maintain systemic perfusion pressure

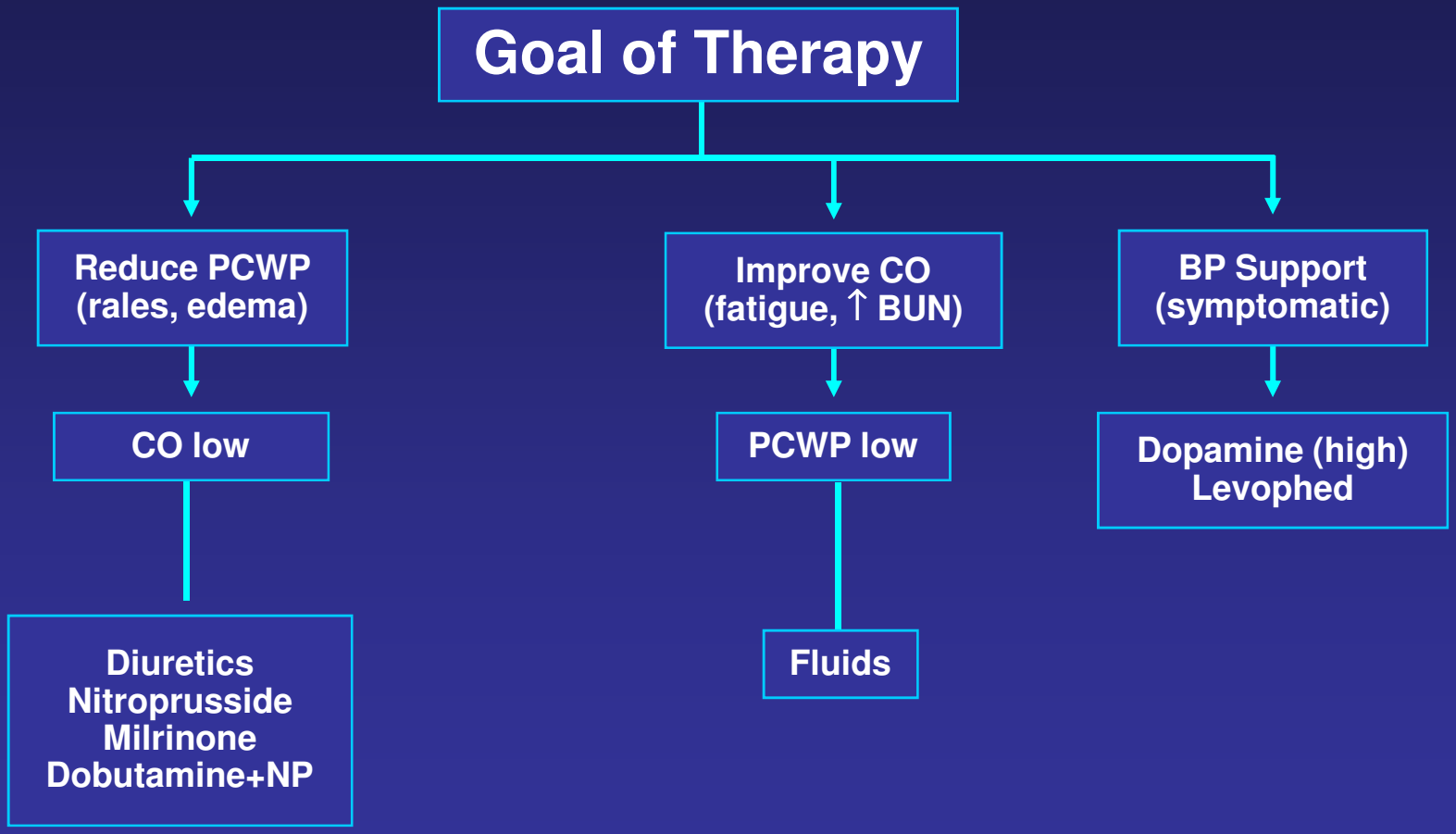
Clinical Profiles of HF

Low Perfusion at Rest	Congestion at Rest: NO	Congestion at Rest: YES
NO	**A** Warm & Dry	**B** Warm & Wet
YES	(Low Profile) **L** Cold & Dry	(Complex) **C** Cold & Wet

Signs/Symptoms of Congestion:
Orthopnea / PND
JV Distension
Hepatomegaly
Edema
Rates
Abd-Jugular Reflex

Possible Evidence of Low Perfusion:
Narrow pulse pressure
Sleepy / obtunded
Low serum sodium
Cool extremities
Hypotension with ACE inhibitor
Renal/hepatic dysfunction

Algorithm for Acute HF Treatment



Treatment Decisions in HF

Warm & Dry Optimize orally	**Warm & Wet** Diuretics Vasodilators
Cold & Dry IV inotropes	**Cold & Wet** IV inotropes and/or vasodilators

Common Used IV Medication For Acute Heart Failure

- Diuretics
- Nitrates
- Nipride
- Nesiritide
- Dobutamine
- Milrinone
- Dopamine

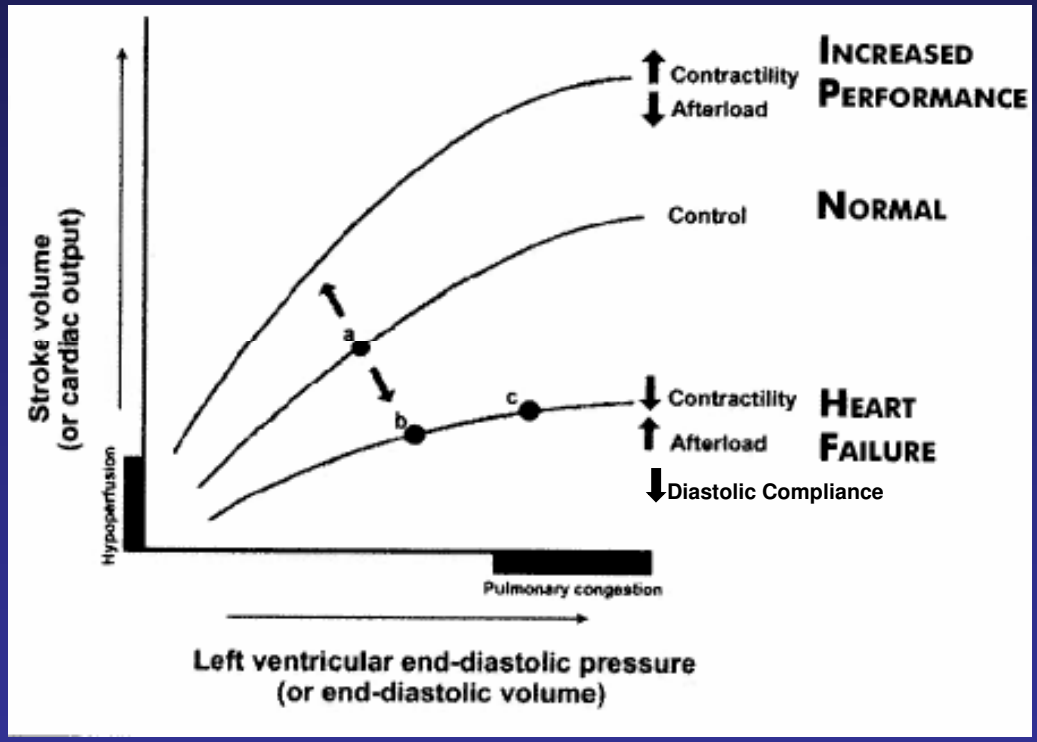
Case Study: JB

- The patient was admitted to the CCU I/V furosemide 40 mg given; resulted in 0.5 L diuresis
- BP 84/48 HR 110 bpm and patient felt slightly better

Q: To ensure optimal therapy, the most important change would be to

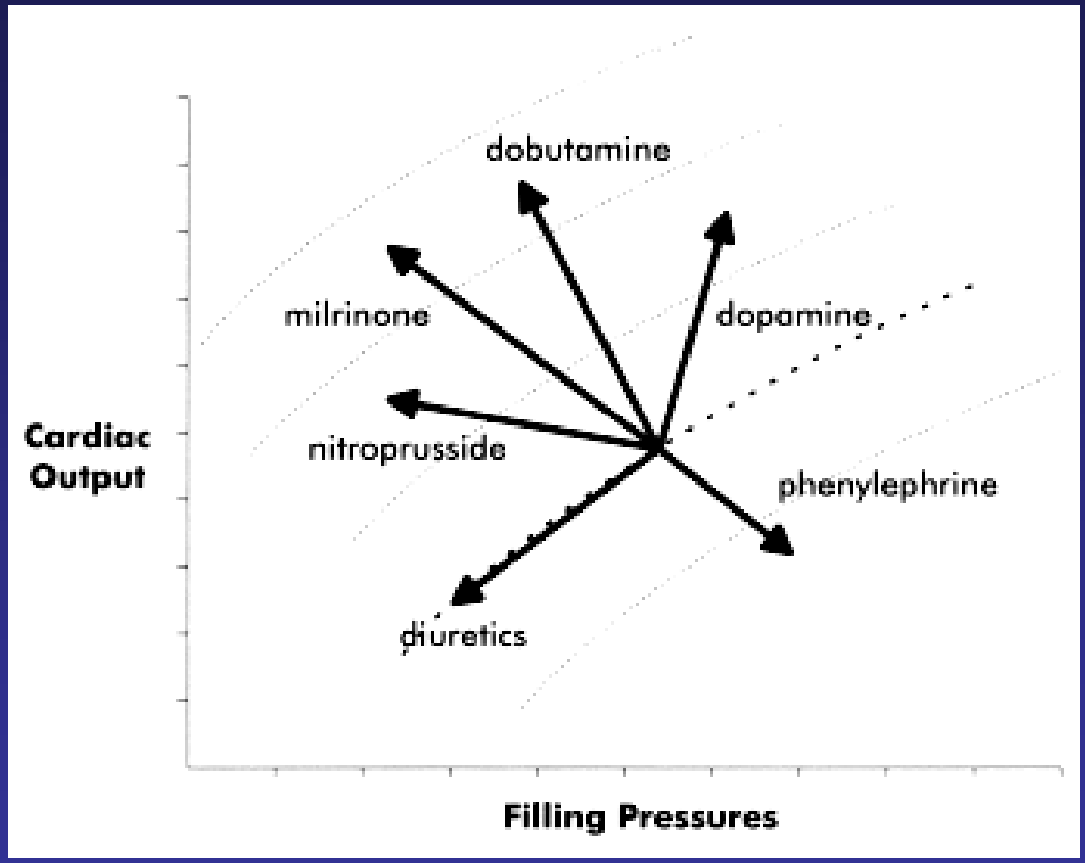
- Add Dopamine ?
- Add Dobutamine?
- Add a β-blocker ?
- I/V NTG or nitroprusside
- Other IV inotropic therapy
- Hemodynamic evaluation (right heart catheterization)

Frank-Starling Curve



Heart Failure results in a downard shift of the curve resulting in hypoperfusion (b), pulmonary congestion (c), or both

Comparative Effects of IV agents



Medical Therapy for AHF

Agent	PCW	CO	HR	SBP
Nitrates	↓↓↓	↑	↓	↓
Nitroprusside	↓↓	↑↑↑	↓↓	↓↓
Dobutamine	↓	↑↑↑↑	↑↑	↑
Levophed	↑↑	↑	↑↑	↑↑↑
Epinephrine	↑	↑↑	↑↑↑	↑↑
Isoproterenol	↓	↑↑↑	↑↑↑	↓
Dopamine (LD)	↑	↑	↑	↑↑
Dopamine (HD)	↑↑	↑↑	↑↑	↑↑↑
Milrinone	↓↓↓	↑↑↑↑	↑	↓

Mechanism of Action of IV Therapeutic Agents in HF

Agent	Mechanism		Response
Sympathomimetic Agents			
Dopamine			
Low dose	DA1-stimulation	++	↑Renal blood flow, vasodilatation, natriuresis
Higher dose	β1-stimulation	++	↑ positive inotropy
	α1-stimulation	++	Peripheral vasoconstriction
Dobutamine	β1-stimulation	+++	↑pos inotropy, ↑ HR
	β2-stimulation	+	Peripheral vasodilatation

Mechanism of Action of IV Therapeutic Agents in HF

Agent	Mechanism		Response
Sympathomimetic Agents			
Norepinephrine	β1-stimulation	+	↑cyclic AMP, ↑ positive inotropy
	α1-stimulation	+++	Peripheral vasoconstriction
Epinephrine	β1-stimulation	+++	↑ positive inotropy
	β2-stimulation	+	Peripheral vasodilatation
	α1-stimulation	+++	Peripheral vasoconstriction
Isoproterenol	β1-stimulation	+++	↑pos inotropy, ↑ HR
	β2-stimulation	+	Peripheral vasodilatation

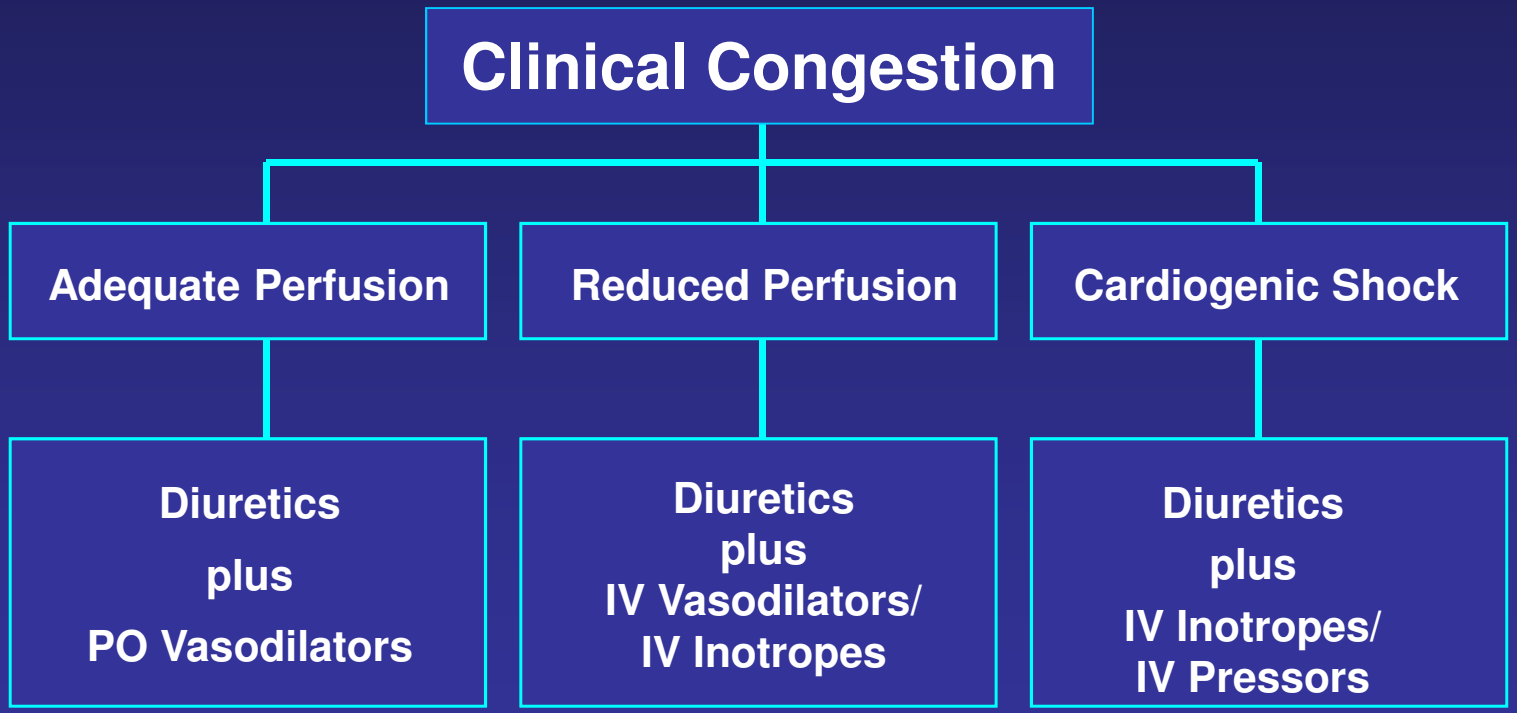
Mechanism of Action of IV Therapeutic Agents in HF

Agent	Mechanism		Response
Phosphodiesterase Inhibitors			
Milrinone	Phosphodiesterase-III inhibtion	++	↑cyclic AMP, ↑ positive inotropy, peripheral vasodilatation
Vasodilators			
Nitroglycerin	Nitric oxide donor	++	↑ cellular cGMP, venous and arterial vasodilatation
Nitroprusside			
Enalaprilat	ACE-Inhibitor	++	Venous and arterial vasodilatation
		+	natruresis

Current Pharmacologic Approach to Acute Therapy

- Diuretics to reduce ECF volume
  - IV loop diuretics ± metolazone/thiazide
- Intravenous vasodilators to optimize ventricular loading conditions
  - Nitroglycerin (preload + afterload)
  - Nitroprusside (+ afterload)
- Intravenous inotropic agents to improve cardiac performance
  - Sympathomimetic agents
  - Phosphodiesterase inhibitors

Rational Approach to Therapy in Volume Overloaded Patients



Diuretics
Few Principles of Diuretic Use in Management of Acute HF

- Higher doses are required to restore than to maintain optimal volume status
- Doses should be doubled when increased effect is desired
- Addition of metolazone or IV thiazides (Diuril®) frequently resolves apparent “diuretic resistance”.
- Relationship between dose of diuretic and mortality

Intravenous Vasodilators

- After diuretics, IV vasodilators are the most useful medications.
- They reduce filling pressures and symptoms.
- No direct effect on myocardial contractility
- Cardiac output increases
- Decrease mitral regurgitation
- Do not usually increase heart rate or exacerbate arrhythmias

Nitroprusside

- First vasodilator shown to improve cardiac output
- Rapidity of onset and offset
- Half-life of ~ 2 minutes
- Individual response varies markedly

Hemodynamic Effects of Vasodilators

	HR	CO	LVEDP	SVR
Nitroglycerin	↔	↑ ↓ ↔	↓ ↓	↓
Nitroprusside	↔	↑	↓	↓
ACE Inhibitors	↔	↑	↓	↓

CO = cardiac output; HR = heart rate; LVEDP = left ventricular filling pressure; SVR = systemic vascular resistance.

From McEvoy GK, ed. *American Hospital Formulary Service Drug Information 92*, 1992:670-673.

Case Study: PG (cont'd)

- Dobutamine started at 5 mcg/kg/min with no improvement
- Another dose of IV Lasix 80mg was given with no response
- BP was 72/-; periphery was cool; JVD 16 cm; Cr 2.1; HR 120 bpm

Q: The patient is most likely to respond to

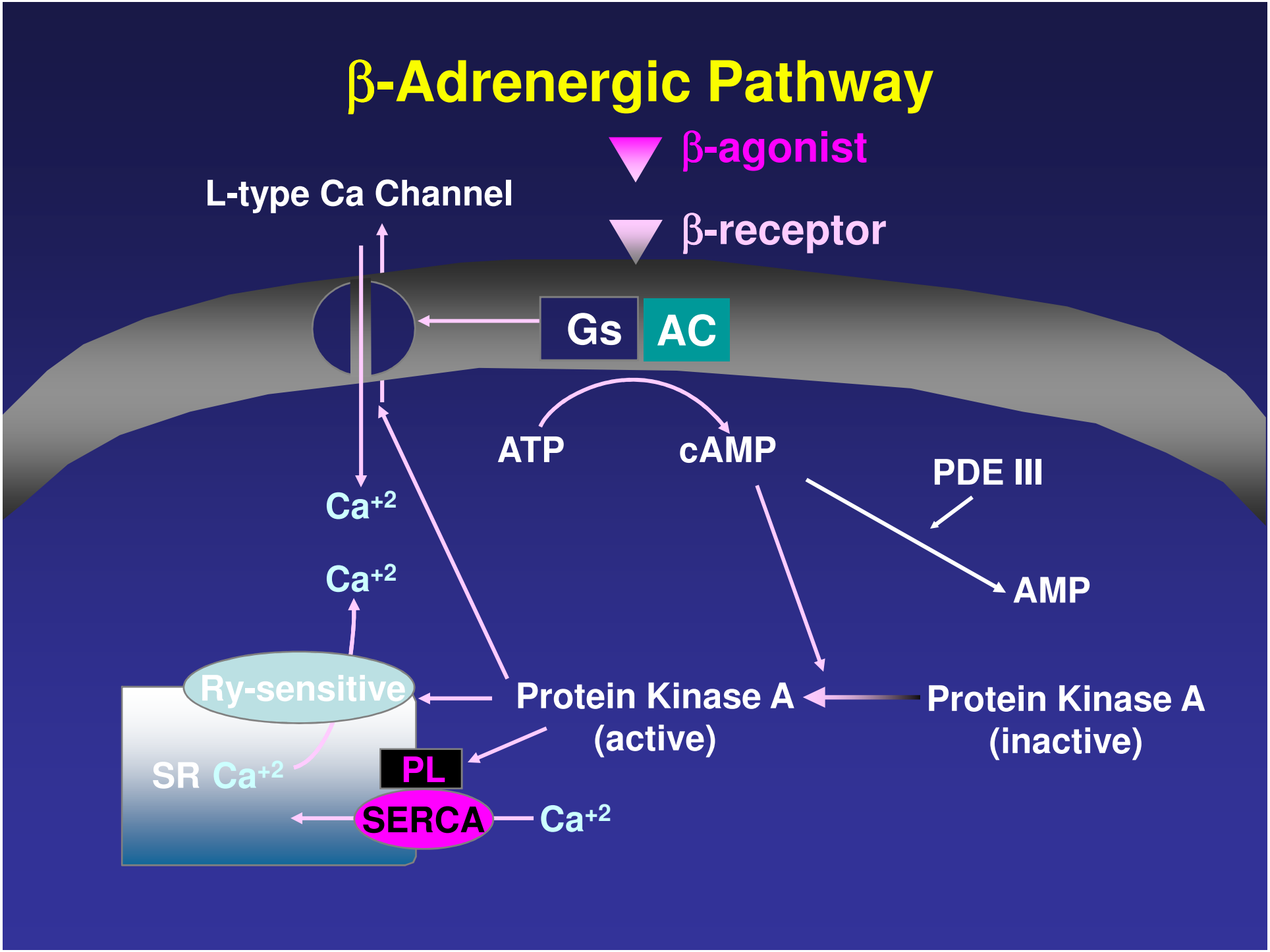
- An increase in the dose of Dobutamine
- Addition of or replacement with Milrinone
- Addition of Dopamine ?

IV Inotropic Agents

- Phosphodiesterase inhibitors
  - milrinone
  - amrinone
- Sympathomimetics
  - dopamine
  - dobutamine
  - isoproterenol
  - epinephrine
  - norepinephrine

Dobutamine (Inotrope)

- Dobutamine stimulates β- adrenergic receptors (AR) with little effect on α-AR → contractility is increased with peripheral vasodilatation.
- Does not affect dopaminergic receptor.
- Increases cardiac output and decreases filling pressures
- HR is consistently increased, particularly with AFib.

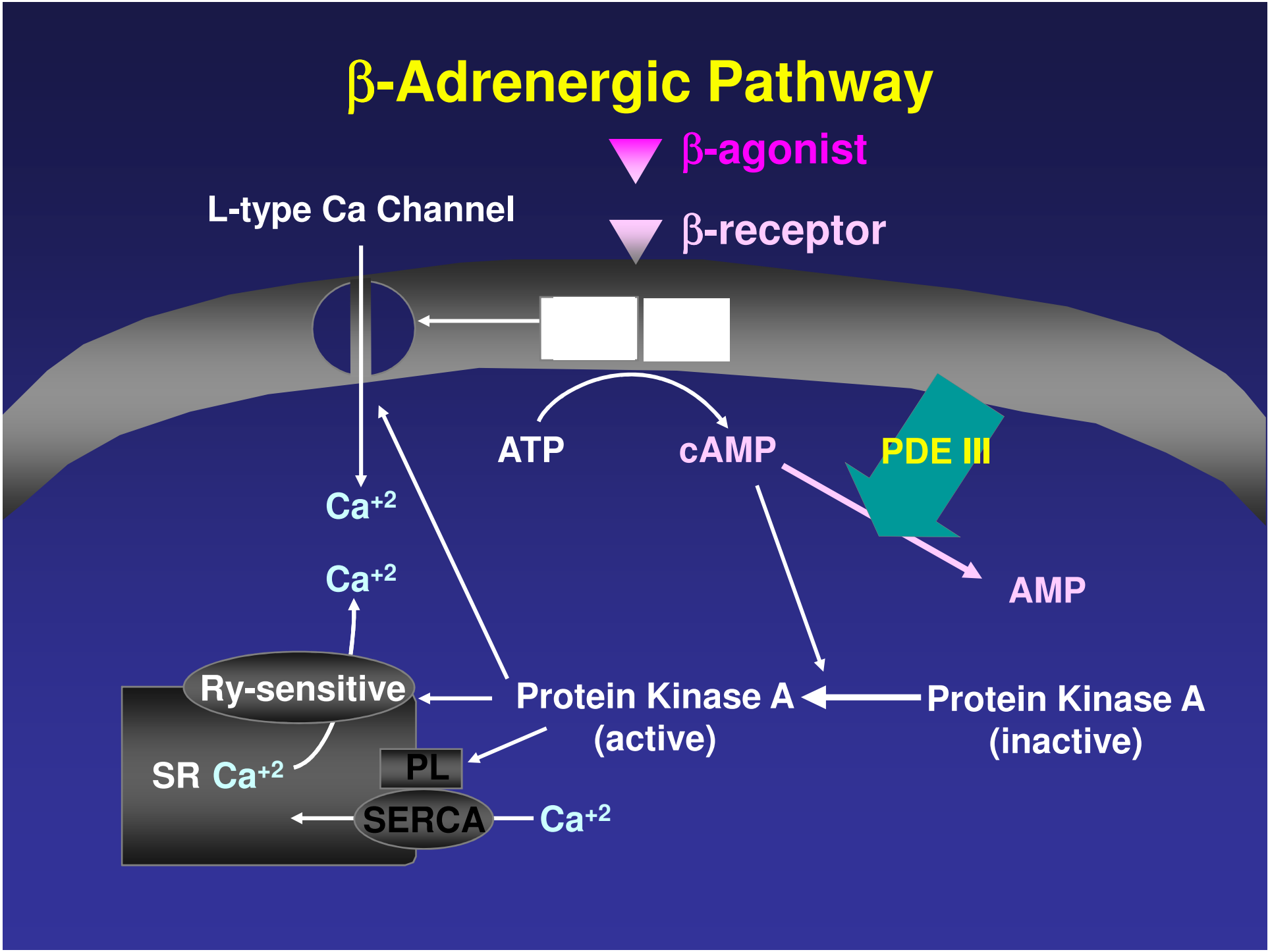

β-Adrenergic Pathway
β-agonist
β-receptor
L-type Ca Channel
Gs
AC
ATP
cAMP
PDE III
AMP
Ca+2
Ca+2
Ry-sensitive
SR Ca+2
PL
SERCA
Ca+2
Protein Kinase A
(active)
Protein Kinase A
(inactive)

Dobutamine

Dose range	Dobu	α_1	β_1	β_2	Heart rate	Cardiac output	SVR
2.5-20 mcg/kg /min	-	+	+++	++	↑	↑↑	↓

Milrinone (Inotrope/Vasodilator)

- Increases intracellular cyclic adenosine monophosphate (c-AMP) in both heart and vascular muscle cell by blocking its breakdown.
- Increases both contractility and causes marked vasodilatation.(10% of Pts with significant hypotension)
- Less elevation in HR compared to Dobutamine
- Prolonged physiologic half-time of 6 hours.
- When stopped, it persists for several hours within the circulation


β-Adrenergic Pathway
β-agonist
β-receptor
L-type Ca Channel
ATP
cAMP
PDE III
AMP
Ca+2
Ca+2
Ry-sensitive
SR Ca+2
PL
SERCA
Ca+2
Protein Kinase A
(active)
Protein Kinase A
(inactive)

Hemodynamic Effects of PDE Inhibitors

Cardiac Index (CI)	↑
SVR/MAP	↓
PCWP	↓
HR	↔ ↑
LVEDP	↓
Ventricular dP/dt	↑

J Clin Invest. 1985;75;643-649. *Circulation.* 1986;73(suppl III):168-174.
Circulation. 1984;70(6):1030-1037.

Distinguishing PDE Inhibitors From Dobutamine

- No dependence on β-receptors
- Vasodilator action
- Relaxation (lusitropic) action
- Minimal effect on heart rate
- Minimal effect on myocardial oxygen consumption

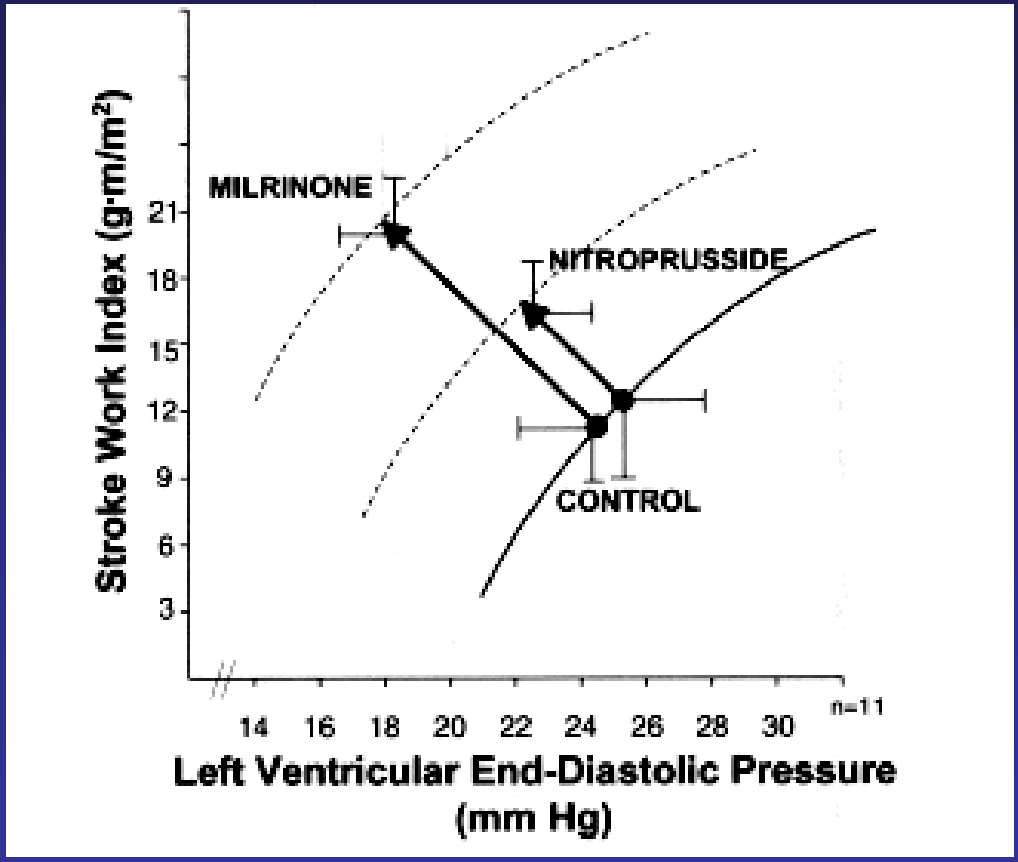
Adapted from *Heart Disease: A Textbook of Cardiovascular Medicine*. WB Saunders; 1984:503-559. *Circulation*. 1984;70(6):1030-1037. *Circulation*. 1986;73(suppl III):168-174.

Selection of an Inotropic Agent

	Dobutamine	Milrinone
SBP<80	1st choice	Usually in combination with pressor
Pulmonary HTN	Not a good pulmonary vasodilator	1st choice; lowers PVR
Myocardial ischemia	More taxing on myocardial O_2 demand	1st choice; least taxing on myocardial O_2 demand

Mehra M. *Heart/Lung.* 1997; 26:280-288.

Distinguishing between Nipride and Milrinone



Nesiritide (Natrecor®)

- Recombinant form of BNP
- IV vasodilator
- Like Nipride, increases c-GMP
- Lowers filling pressures
- Causes hypotension
- Also diuretic effect.
- Longer half life than NTG (18 min)
- Controversy if worsens renal function and increases mortality

Case Study: JB (cont'd)

- Dopamine was initiated at 10 mcg/kg/min and BP improved slightly 82/38 HR 130.
- Despite minimal improvement, no urine output and patient became lethargic and unresponsive.
- BP 73/32 HR 150, cyanotic, unresponsive.
- Intubation was performed
- BP 66/31 HR 152 post intubation
- Levophed was initiated at increased dose.

- Right heart catheterization revealed PAP 65/35; PCWP 36; CI 0.9 L/min/m^2

Q: The best long term treatment option is likely to be

- IABP
- LVAD
- Cardiac transplantation
- Mitral valvuloplasty and/or LV remodeling surgery
- Medical therapy alone

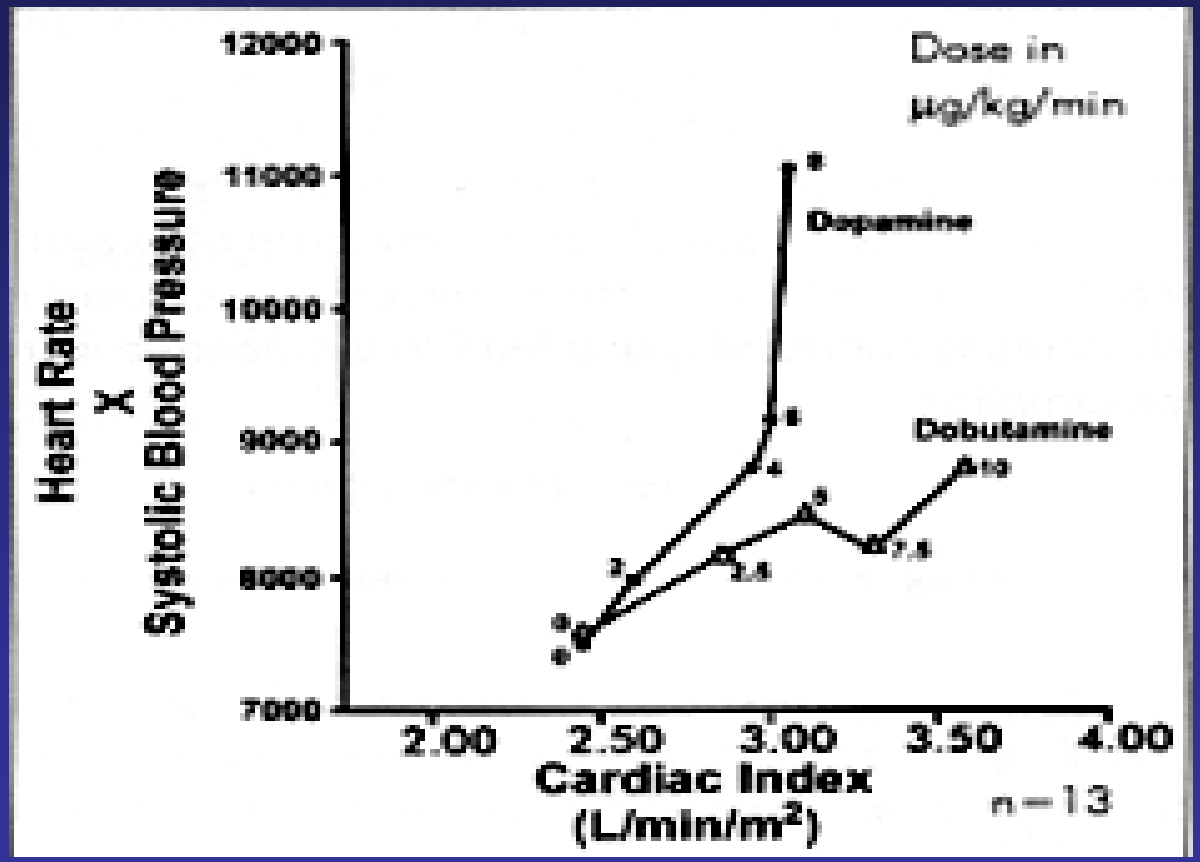
Dopamine (Inotrope/Vasoconstrictor)

- Dopamine (D) stimulates β-, α- and dopaminergic receptors.
- LD receptor stimulaton causes vasodilatation in the renal and peripheral vasculature.
- At ≤ 3 mcg/kg/min: D is predominantly vasodilatory.
- At 3-5 mcg/kg/min: D activates dopaminergic and β-adrenergic recpetors and so is also a positive inotrope.
- At ≥ 5 mcg/kg/min: D acts as an arterial and venous constrictor
- For BP support: D dose ≥ 5 mcg/kg/min.

Dopamine

Dose range	Dopa	α_1	β_1	β_2	Heart rate	Cardiac output	SVR
1-3 mcg/kg /min	+++	-	-	-	↔	↔	↔
3-5 mcg/kg /min	++	+	++	-	↑	↑↑	↔↑
5-20 mcg/kg /min	++	+++	++	-	↑↑	↔↑	↑↑

Distinguish between Dobutamine and Dopamine



Limitations of IV Agents

Class	Agent	Limitation
Nitrates	Nipride	Hypotension
	Nitroglycerin	Tolerance (NTG>NTP)
Phosphodiesterase Inhibitors	Milrinone	Slow onset of action
Catecholamines	Dobutamine	Tolerance (β-receptor down regulation)
	Dopamine	Tolerance, Central venous access used

Case Study: JB (cont'd)

- The patient underwent placement of IABP with no improvement of his hemodynamics.
- Underwent placement emergently of LVAD but patient bled profusely during surgery, received numerous blood units and RV failed.
- Patient died the next morning

New Agents (still investigational)

Levosimendan:

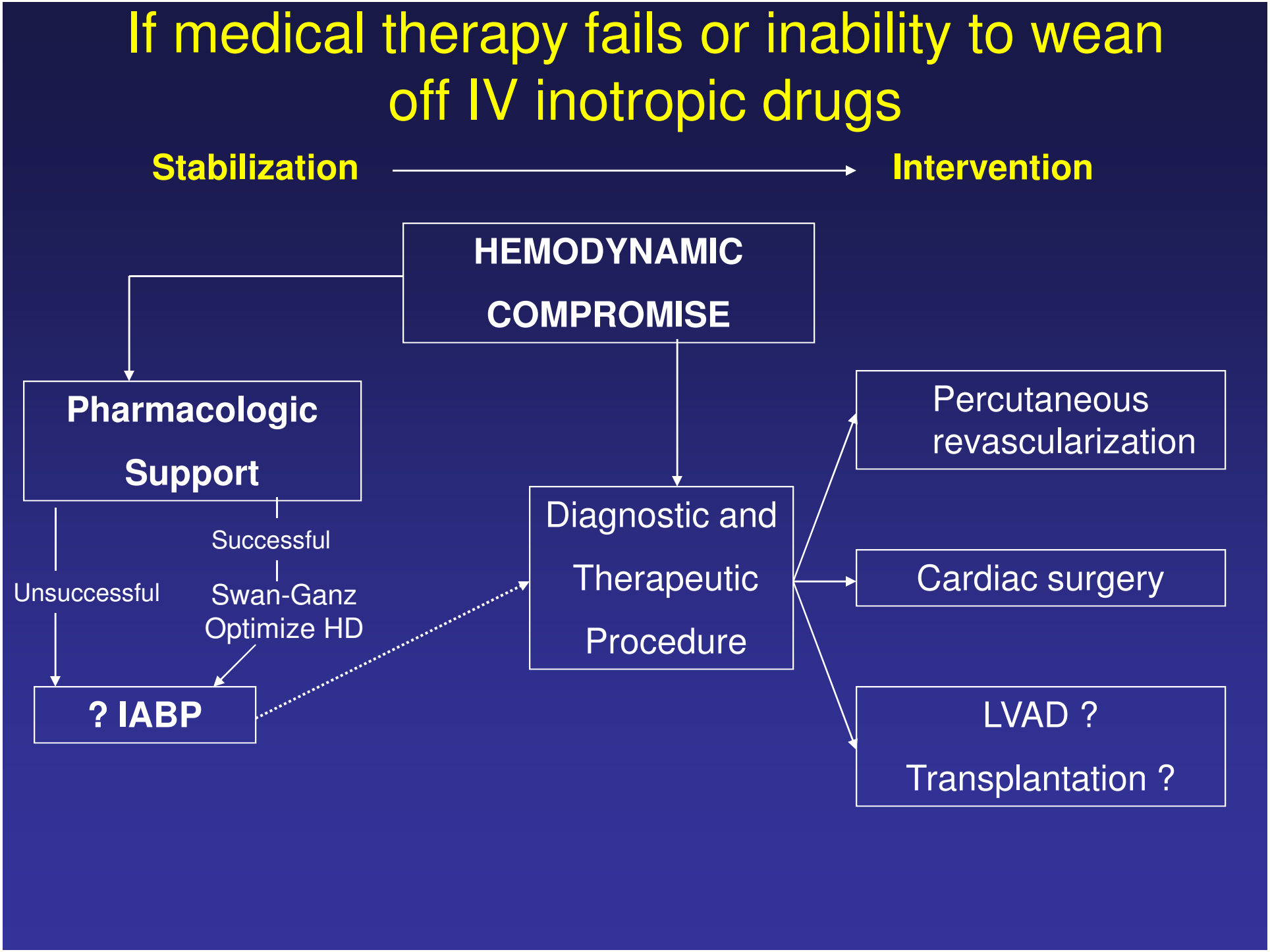
- Increases Ca sensitivity of Troponin C + has some phosphodiesterase III inhibitor properties. It is a positive inotrope and a vasodilator.
- Improves both systolic and diastolic dysfunction
- REVIVE Study

New Agents (still investigational)

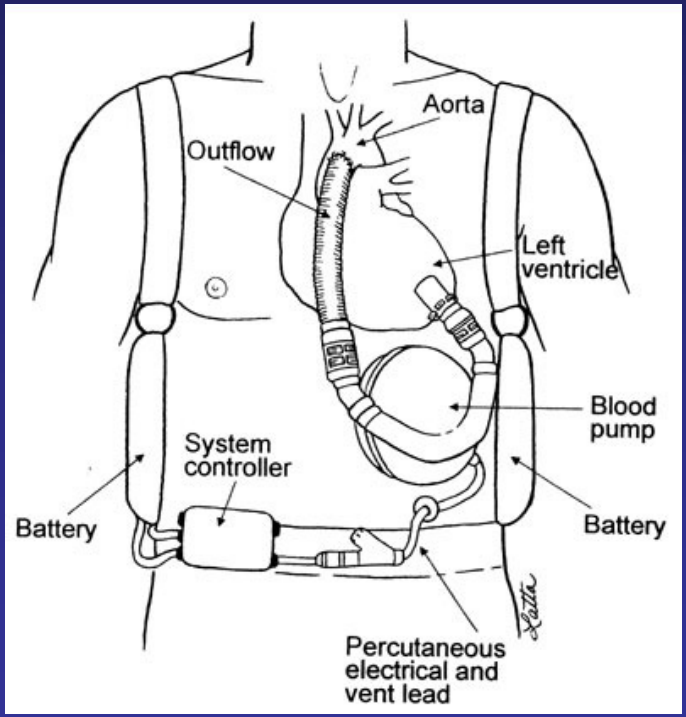
Adenosine A_1 Receptor Antagonists
BG9719

- Increases diuresis

If medical therapy fails or inability to wean off IV inotropic drugs



Left Ventricular Assist Device



If IV medical therapy: successful

- Taper the infusion gradually over 24-48 hours or even more
- Observe patient

Discharge Criteria for Hospitalization with HF

Clinical Status Goal

- Achievement of dry weight
- Definition of BP range
- Walking without dyspnea or dizziness

Stability Goals

- 24h without changes in oral HF regimen
- ≥48 h off IV inotropic agents, if used
- Fluid balance even on oral diuretics Z2
- Renal Function stable or improving

Home Plan

- Clinic appointment within 10 days
- Scheduled call to patient within 3 days

Slide 51

Z2 ZoltyR, 8/29/2004

Case Presentation

- 62 year AA old man
- PMH: -DM diag 3 years ago
  - BPH
  - ETOH quit 2/09
  - Tob (60 pyhx) quit 2/09
  - COPD??

- Diagnosed in Feb 09 with CHF

  Echocardiogram
  - LVEDD 6.6cm, LVEDS 5.6
  - Severe global hypokinesis, LVEF 25%
  - Moderate right ventricular hypokinesis
  - Severe MR, mod-severe TR
  - PASP 65mmHg

Case Presentation

- Coronary Angiogram: Clean cors
- LV Angiogram: LVEF 23%, MR3+
- PSH: None
- FMH: unremarkable
- Allergy: NKDA

Case Presentation

SUBJ:

- Chest pressure not related with exertion
- DOE after walking 2 blocks
- can claim 1 flight of stairs
- sleeps on 2-3 pillows
- since on Lasix no PND any more
- some lower extremities edema
- abdominal distension
- No palpitations, dizziness

Case Presentation

- MEDS:
  - Cozaar 100 mg QD
  - Metoprolol 50 mg BID
  - Bumex 4 mg BID
  - Proscar 5 mg QD
  - Amlodipine 5mg QD

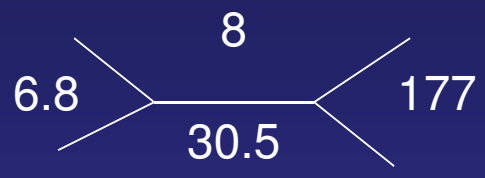
Case Presentation

PE

- BP 95/60 HR 88, RR 20, Anicteric, Afebrile Acyanotic
- JVP ~ 12cm
- Chest: Clear, no crackles, no rales, no wheezing
- CV: RRR, PMI displaced
- Abd: Soft, 0 tenderness, 0 HSM
- Legs: edema 1+

Case Presentation

LAB



LFTs: Normal

UA: WNL

EKG: Normal Sinus Regular Rhythm, RBBB QRS 150 msec

CXR: Cardiomegaly, no infiltrates

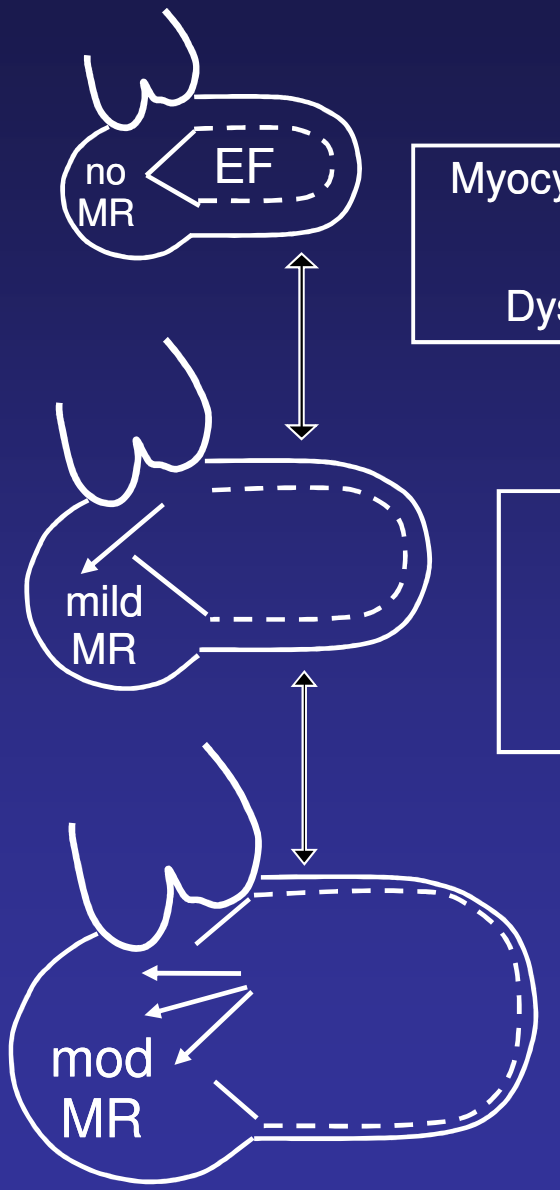
Case Presentation

- Right Beta-Blocker ?
- ACE-I *vs.* ARB ?
- Should we put Pts on both ACE-I and ARB ?
- Any other vasodilator ?
- Is patient a candidate for a device (AICD? BiV Pacer?)

Important Management Questions in Congestive Heart Failure

- What is remodeling?
- Can remodeling be reversed?
- Should ACE inhibitors be prescribed first?
- Does the dose matter?
- Should ACE inhibitor dose be decreased to allow uptitration of beta-blockers?
- Is the specific beta-blocker important?
- Are aldosterone antagonists valuable?
- When should an ARB be added?

MYOCARDIAL REMODELING IN HEART FAILURE



Myocyte Damage or Dysfunction

Cardiac Adrenergic Activation
Renin Angiotensin Activation
Cytokine Activation

Progressive Myocyte Dysfunction and/or Death

Systemic Adrenergic Activation
Systemic Renin Angiotensin Activation
Systemic Cytokine Activation

Progressive Myocyte Dysfunction and/or Death

Lindenfeld 2000

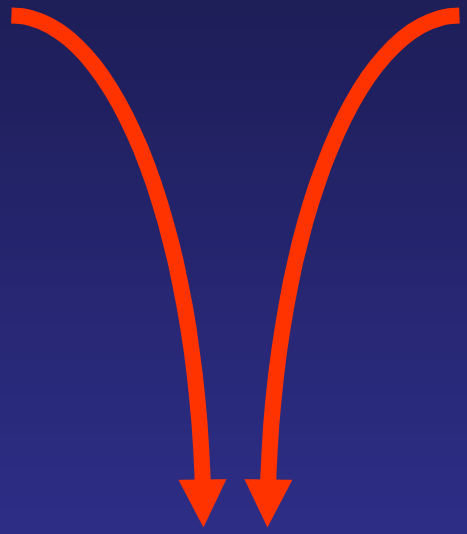

DANGER
1770

Pathophysiology of LV Systolic Dysfunction

Two Main Protagonists

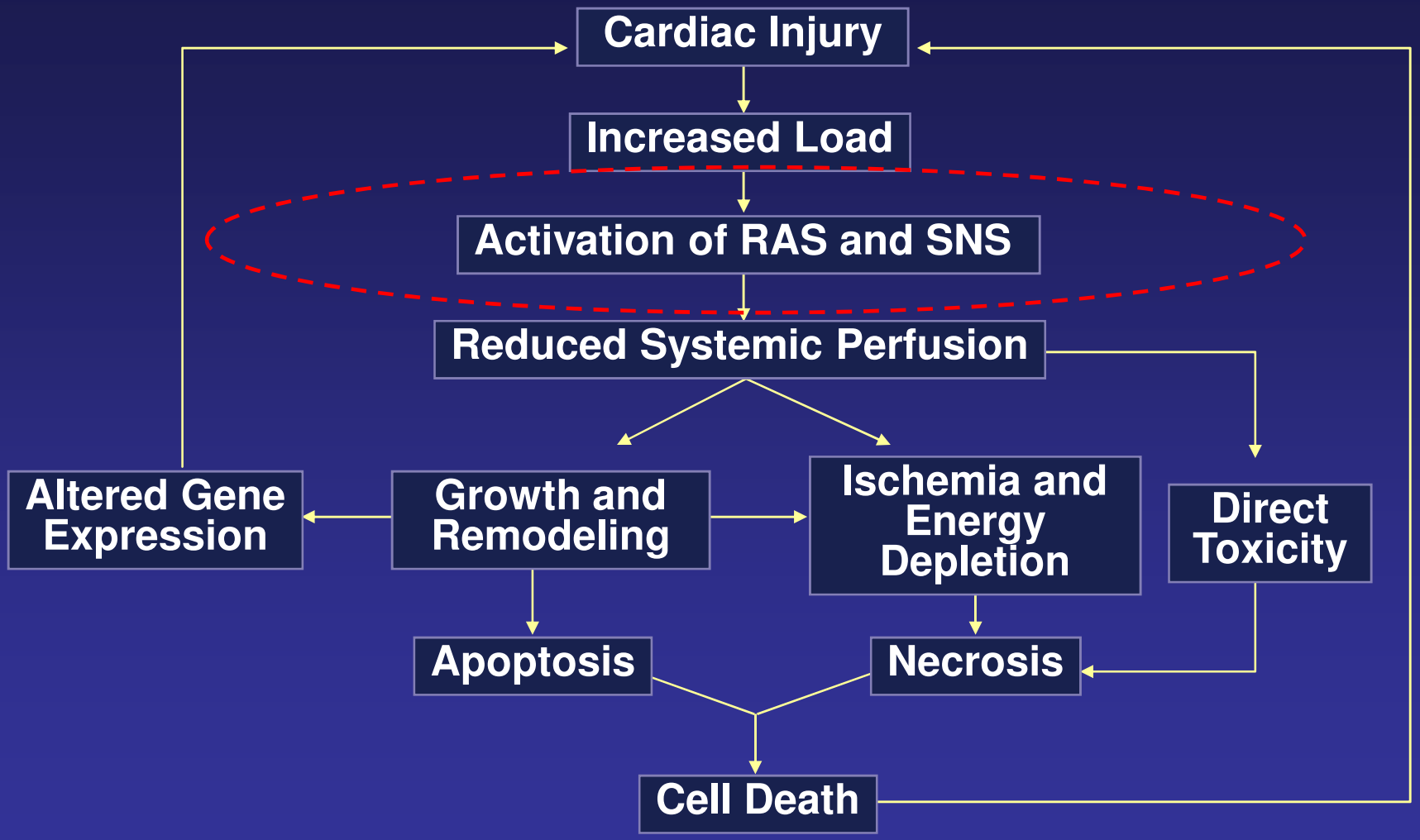
Renin-Angiotensin System (RAS)
Angiotensin II (A II)

Sympathetic Nervous System (SNS)
Norepinephrine (NE)



Hypertrophy, apoptosis, ischemia, arrhythmias, vasoconstriction, remodeling, fibrosis

Pathophysiology of LV Systolic Dysfunction



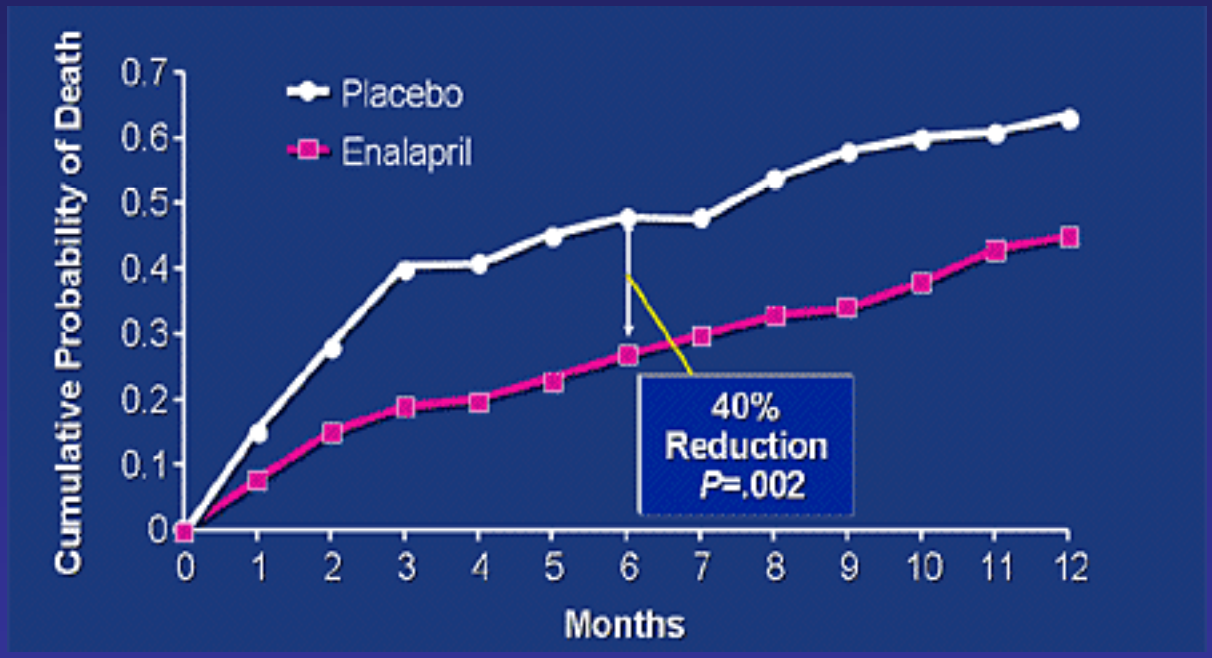
Eichhorn EJ, Bristow MR. *Circulation* 1996;94:2285-2296.

ACE Inhibitors in CHF

	Mortality		
Trial	**ACEI**	**Controls**	**RR (95% CI)**
Chronic CHF			
CONSENSUS I	39%	54%	0.56 (0.34–0.91)
SOLVD (Treatment)	35%	40%	0.82 (0.70–0.97)
SOLVD (Prevention)	15%	16%	0.92 (0.79–1.08)
Post MI			
SAVE	20%	25%	0.81 (0.68–0.97)
AIRE	17%	23%	0.73 (0.60–0.89)
TRACE	35%	42%	0.78 (0.67–0.91)
SMILE	5%	6.5%	0.75 (0.40–1.11)
Average	**21%**	**25%**	

Trials Examining ACE Inhibitors in HF patients

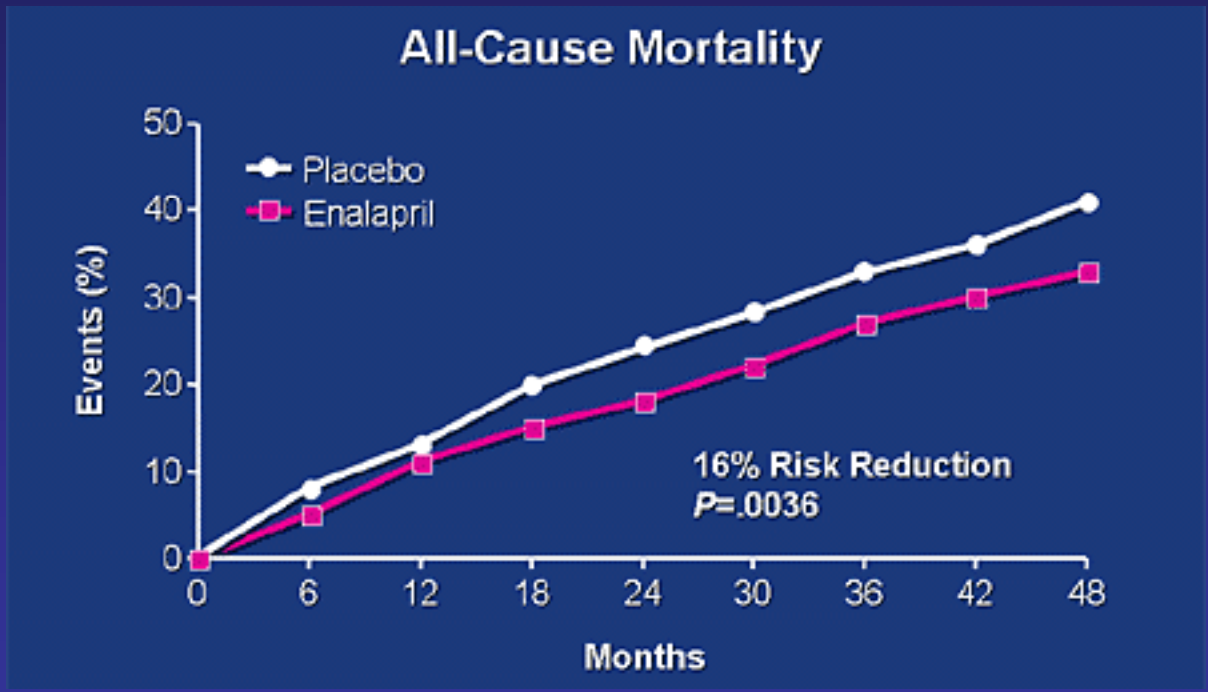
CONSENSUS Trial



Consensus Study Group, *NEJM* 1987; 316: 1420

Trials Examining ACE Inhibitors in HF patients

SOLVD Treatment Trial



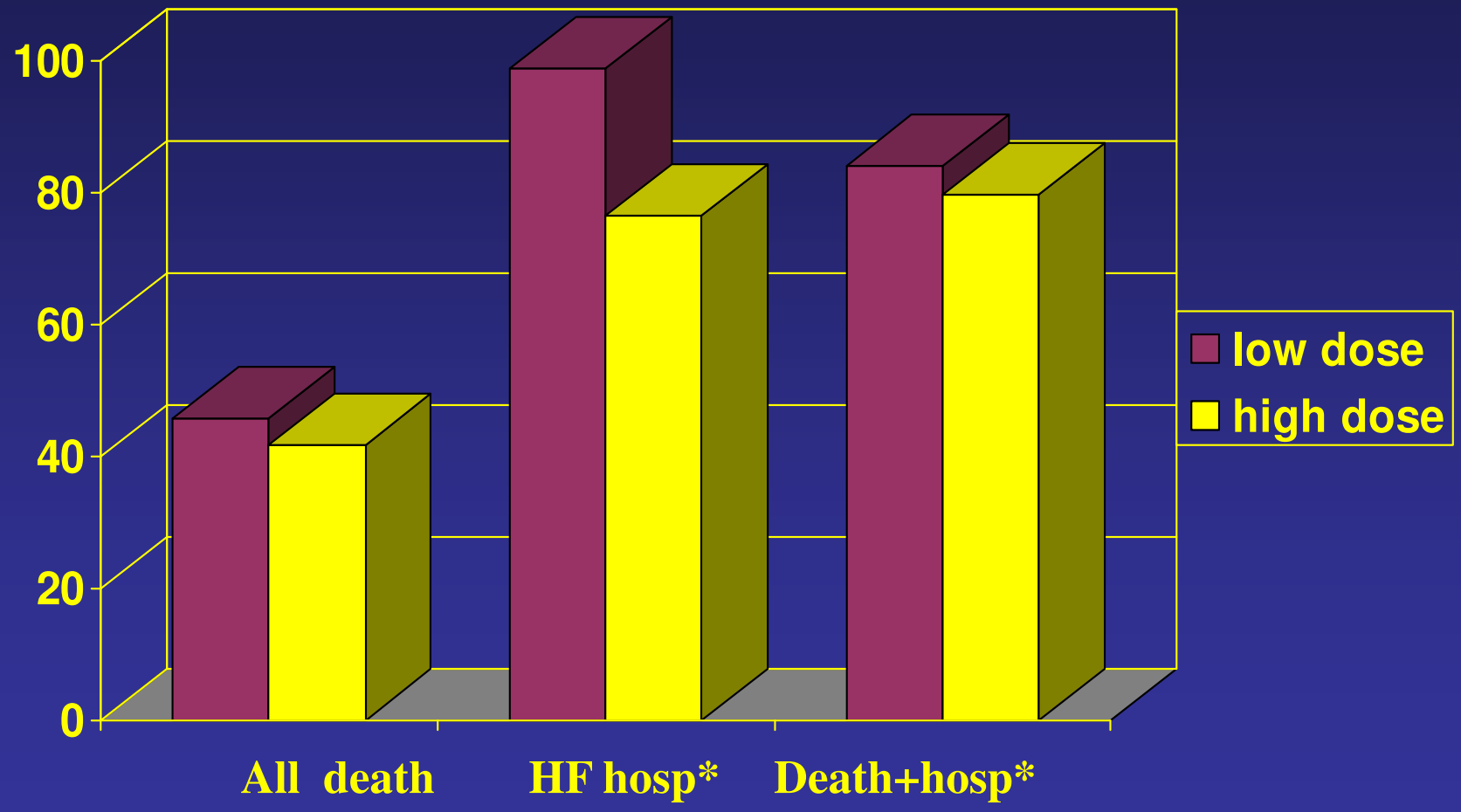
SOLVD Investigators NEJM 1991: 325:293

Low *vs.* High Dose ACE Inhibitors:ATLAS

- 3164 pts. f/u for a median of 45.7 months.
- NYHA class II-IV, mostly III (77 %).
- LVEF: 23 %.
- Lisinopril 2.5-5 mg vs 32.5-35 mg qd.
- 8 % reduction in mortality (p =0.128)
- 12 % reduction in death + all-cause hospitalization (p = 0.002).

Packer et al. Circulation 1999;100:2312-2318

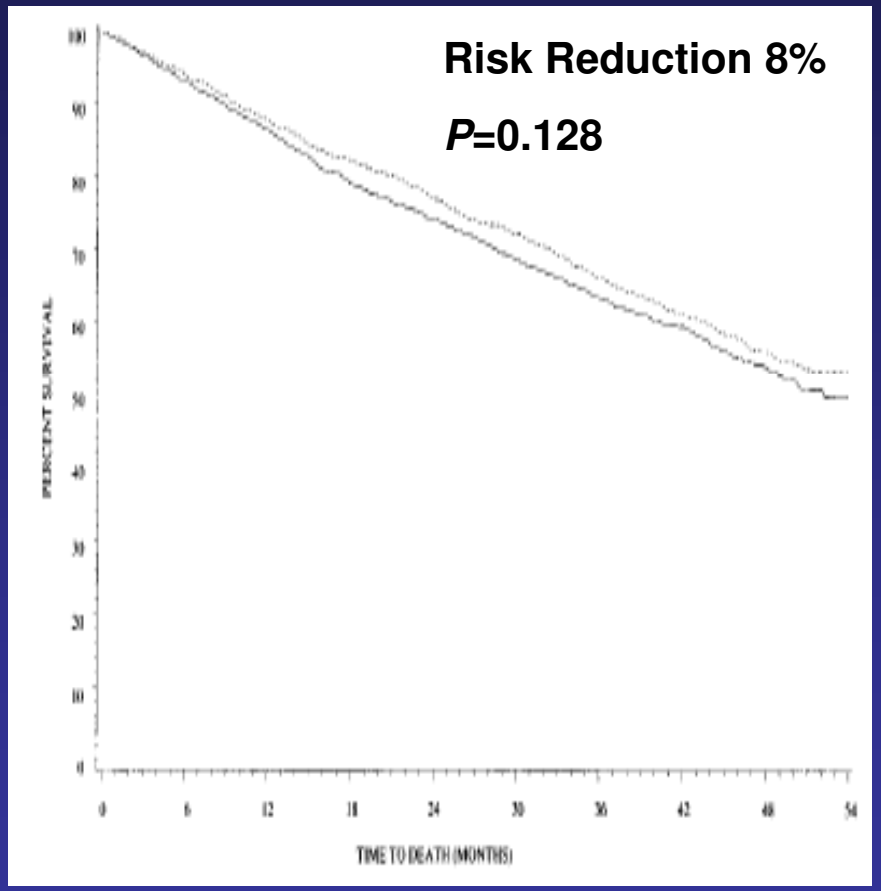
ATLAS Assessment of Treatment with Lisinopril And Survival



* p = significant

Packer et al. Circulation 1999; 100: 2312- 2318.

ACE-I: High-Dose versus Low-Dose



ATLAS Study Group. *Circulation* 1999;100:2312-2318.

Low vs High Dose ACE-I
ATLAS Trial

	Low-Dose	High-Dose	Hazard Ratio	*P*
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
All-cause mortality+hospitalization for cardiovascular reason	1182 (74.1)	1115 (71.1)	0.92 (0.84–0.99)	0.036
All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Values in parentheses indicate percentage or range. *P* values determined by log-rank test. Hazard ratios represent 95% CI, except for all-cause mortality, shown as 96.1% CI.

*Analysis not specified in protocol before breaking the blind.

Circulation 1999; 100: 2312-18.

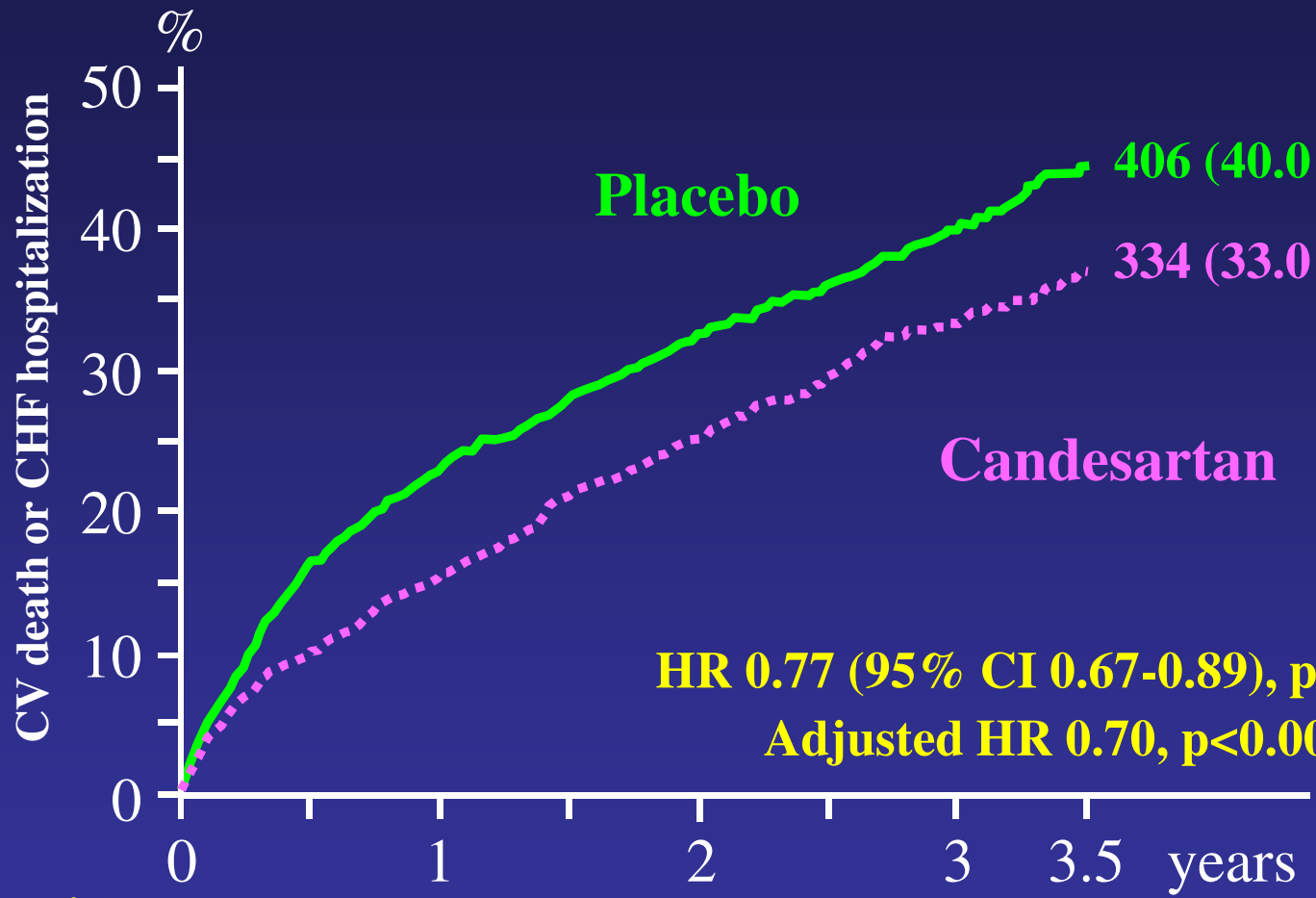
What is an adequate dose of an ACE inhibitor?

	Network (enalapril)			Atlas (lisinopril)		
	2.5 bid	5 bid	10 bid	5 qd	35 qd	
n	506	510	516	1596	1568	
Death	4.2%	3.3%	2.9%	45%	42%	
Death + HF Hosp	6.8%	6.9%	8.9%	60%	55%	*

Cleland, Eur Ht J, 1998, Packer Circ, 1999

ACE-I or ARB ?

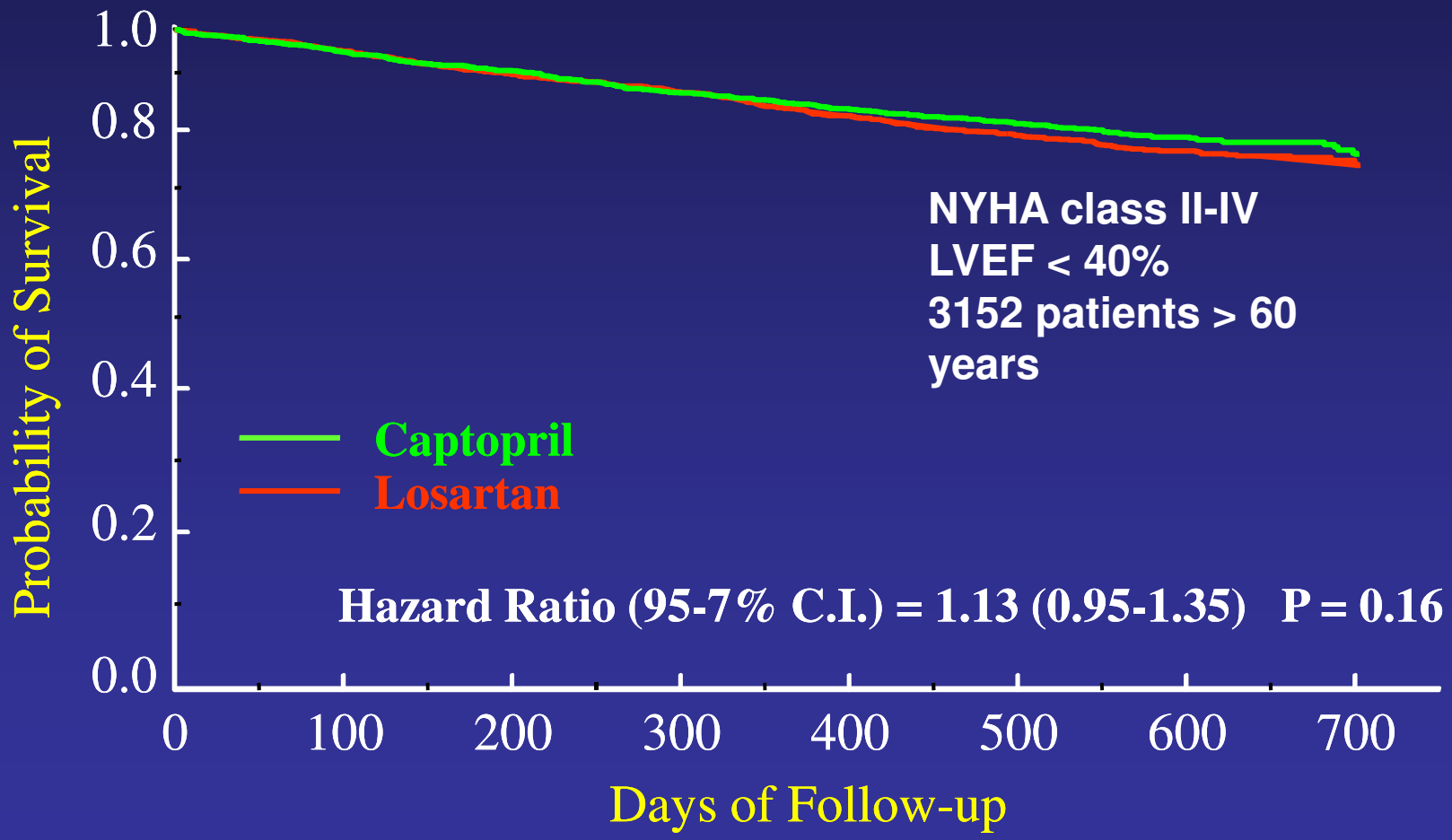
ARB's: CHARM-Alternative



Number at risk					
Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

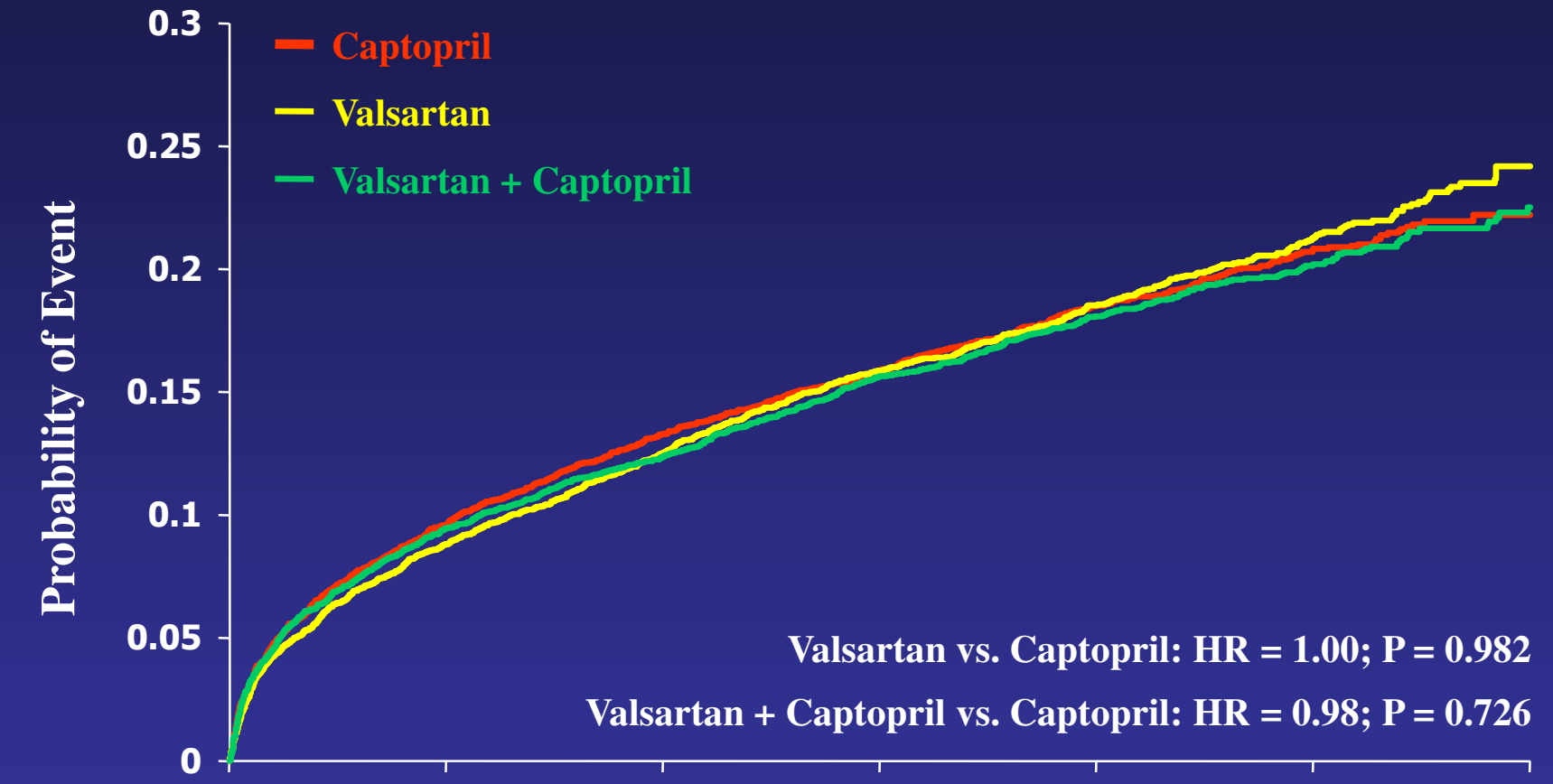
Granger CB et al. Lancet 2003;362:772-776

ELITE-II: All-Cause Mortality



Pitt B et al. Lancet 2000;355:1582-87

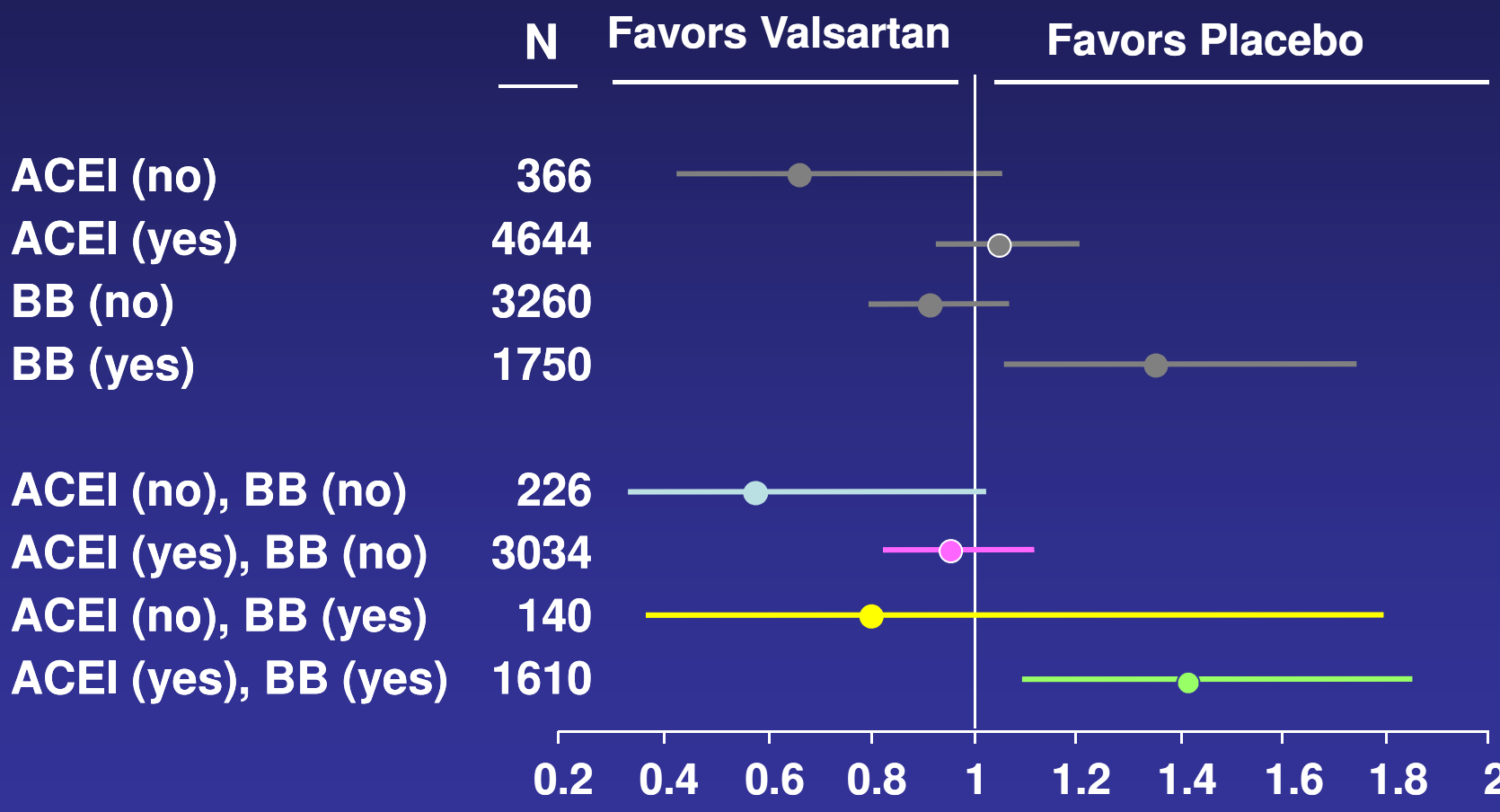
VALIANT: All-Cause Mortality



Months	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Val + Cap	4885	4414	4265	3994	2648	1435	382

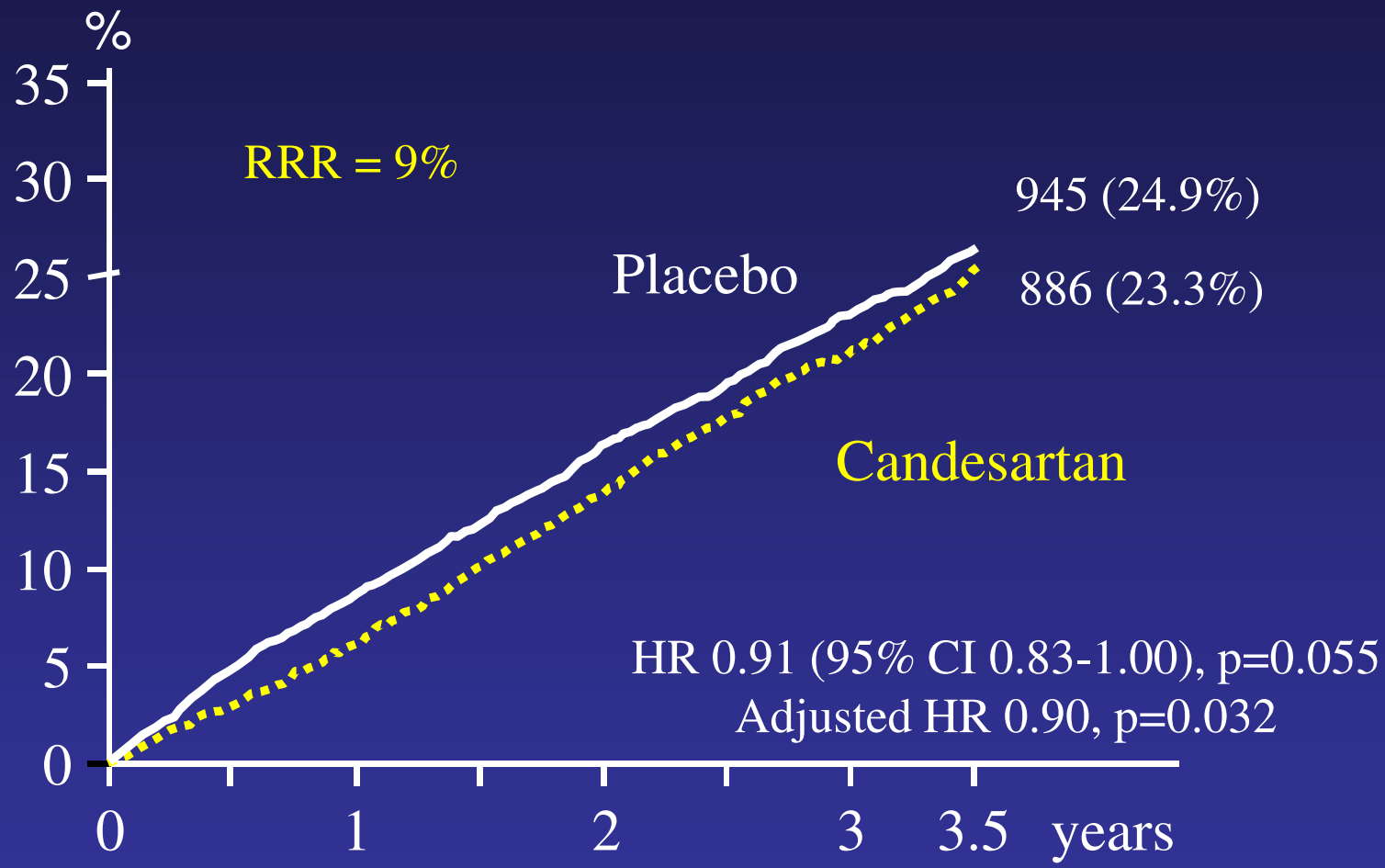
Pfeffer MA et al. NEJM 2003;349:1893-1905

Mortality by ACEI/BB Subgroups (Val-HeFT)



(Adapted from Cohn JN, et al. [abstract]. *Circulation*, 2001)

CHARM-Overall: All-cause death



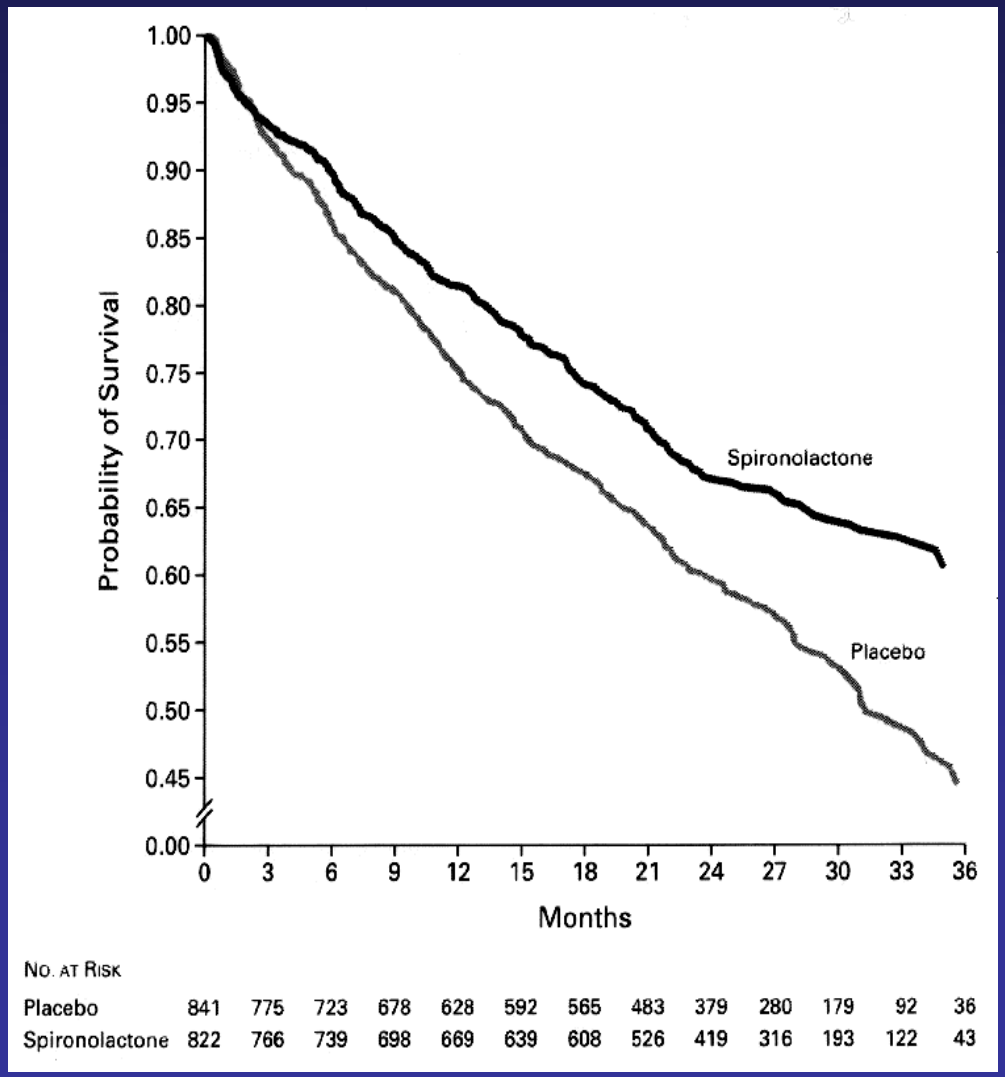
Number at risk					
Candesartan	3803	3563	3271	2215	761
Placebo	3796	3464	3170	2157	743

Pfeffer MA et al. Lancet 2003;362:759-66

ACE-I, ARB Rx

- Per AHA/ACC Guidelines:
  - ARB's only if proven intolerant to ACE-I
- No evidence of ARB superior to ACE-I

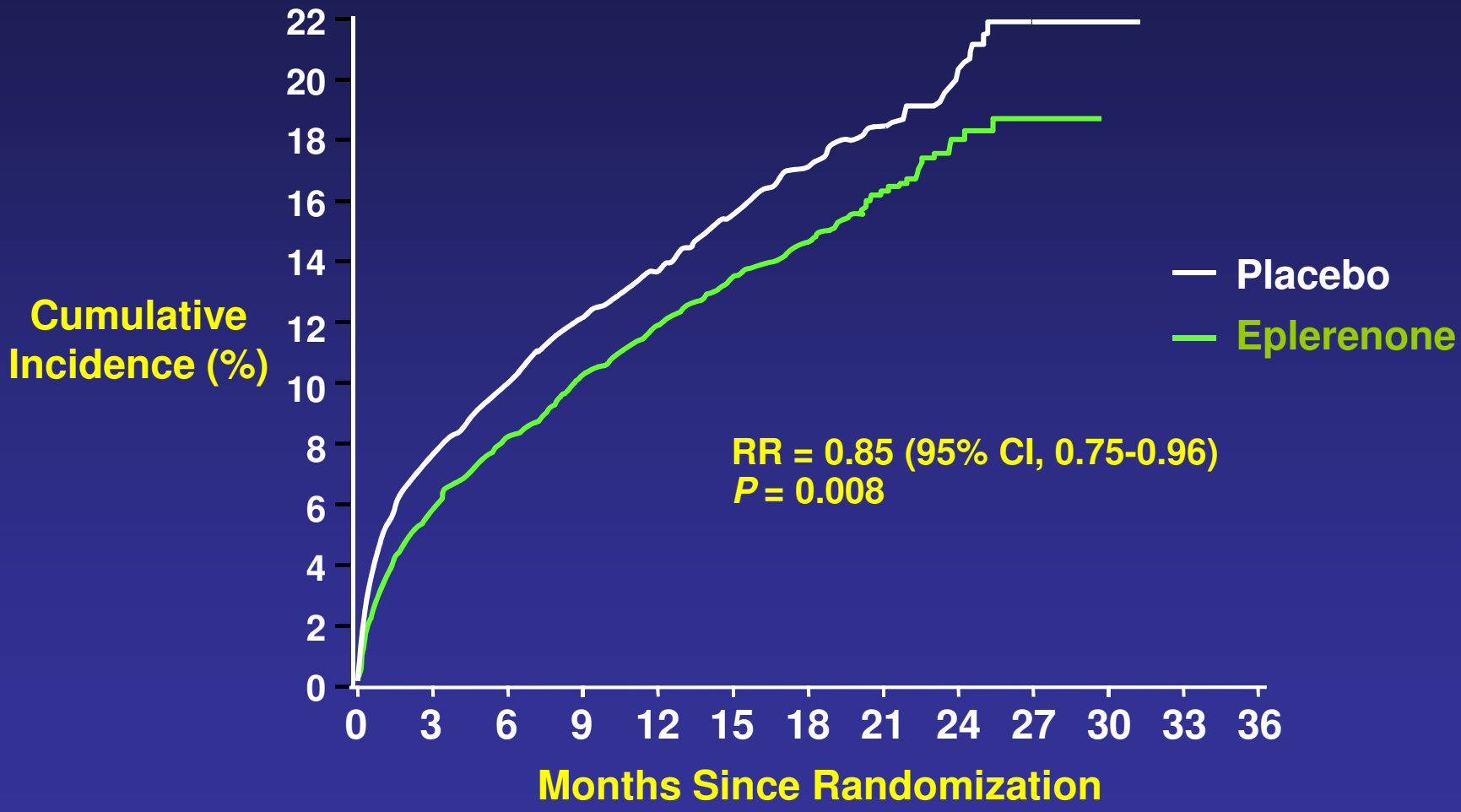
Spironolactone Improves Survival in Advanced Heart Failure (RALES)



p < .001
30% risk reduction

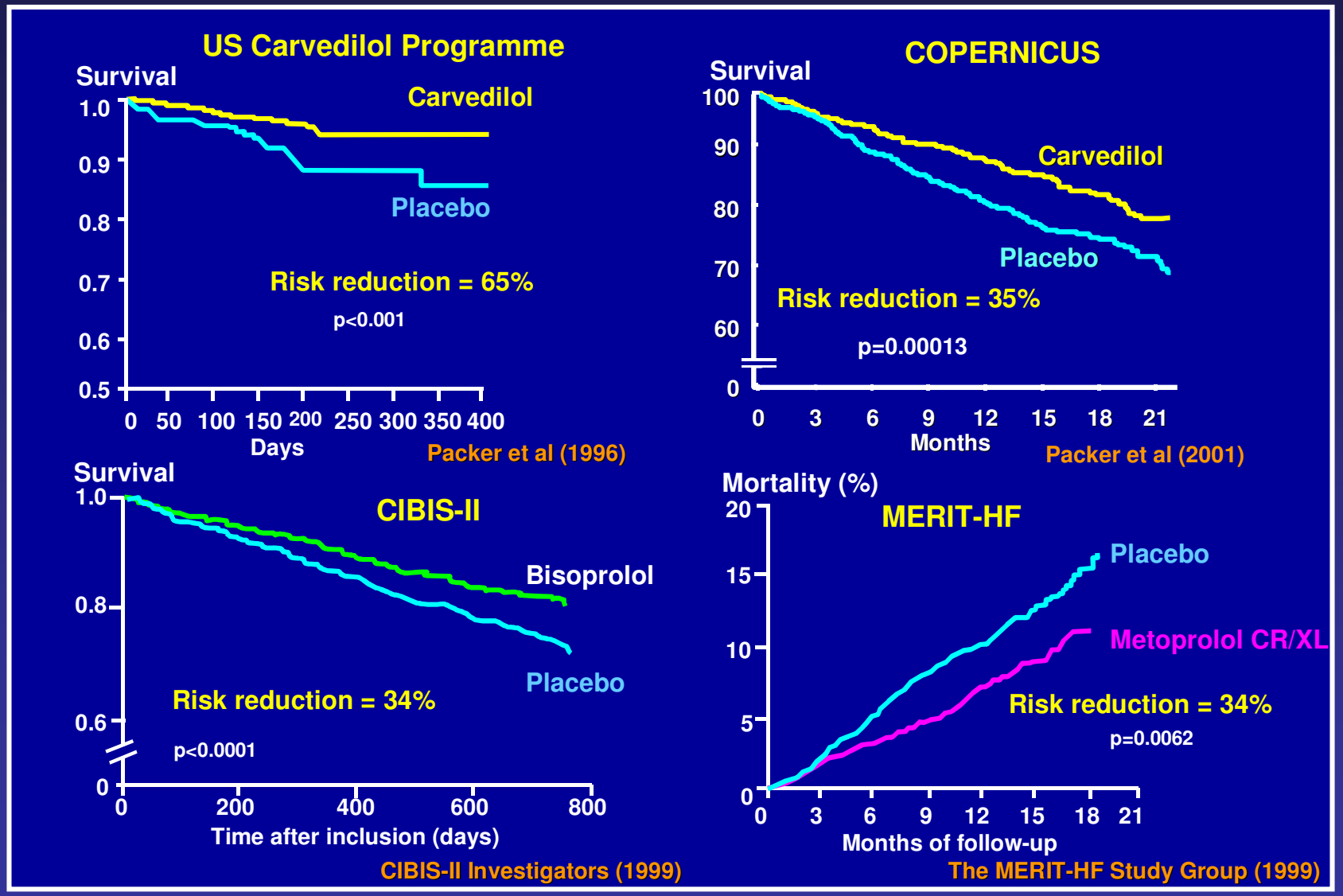
Pitt et *al NEJM* 1999

Eplerenone: EPHESUS
Relative Risk of Total Mortality



Pitt B. et al. NEJM 348;14:1309-21.

Historical Prospective:



Major Trials of β-Blockade in Heart Failure

	Patients (n)	Follow-up (yrs)	Target Dosage (mg)	Mean Dosage Achieved (mg/day)	Effects on Outcomes
CIBIS	641	1.9	bisoprolol 5 mg qd	3.8	All-cause mortality: NS
CIBIS-II	2647	1.3	bisoprolol 10 mg qd	7.5	All-cause mortality: ↓ **34%** (*P*<.0001)
MDC	383	1	metoprolol 50-75 mg bid	108	Death or need for transplant (primary end point): NS
MERIT-HF†	3991	1	metoprolol CR/XL 200 mg qd	159	All-cause mortality: ↓**34%** (*P*=.0062)
US Carvedilol Trials†	1094	7.5 months	carvedilol 6.25-50 mg bid	45	All-cause mortality*: ↓**65%** (*P*=.0001)
COPERNICUS	2289	10.5 months	carvedilol 25 mg bid	37	All-cause mortality: ↓**35%** (*P*=.00013)

*Not a planned end point.

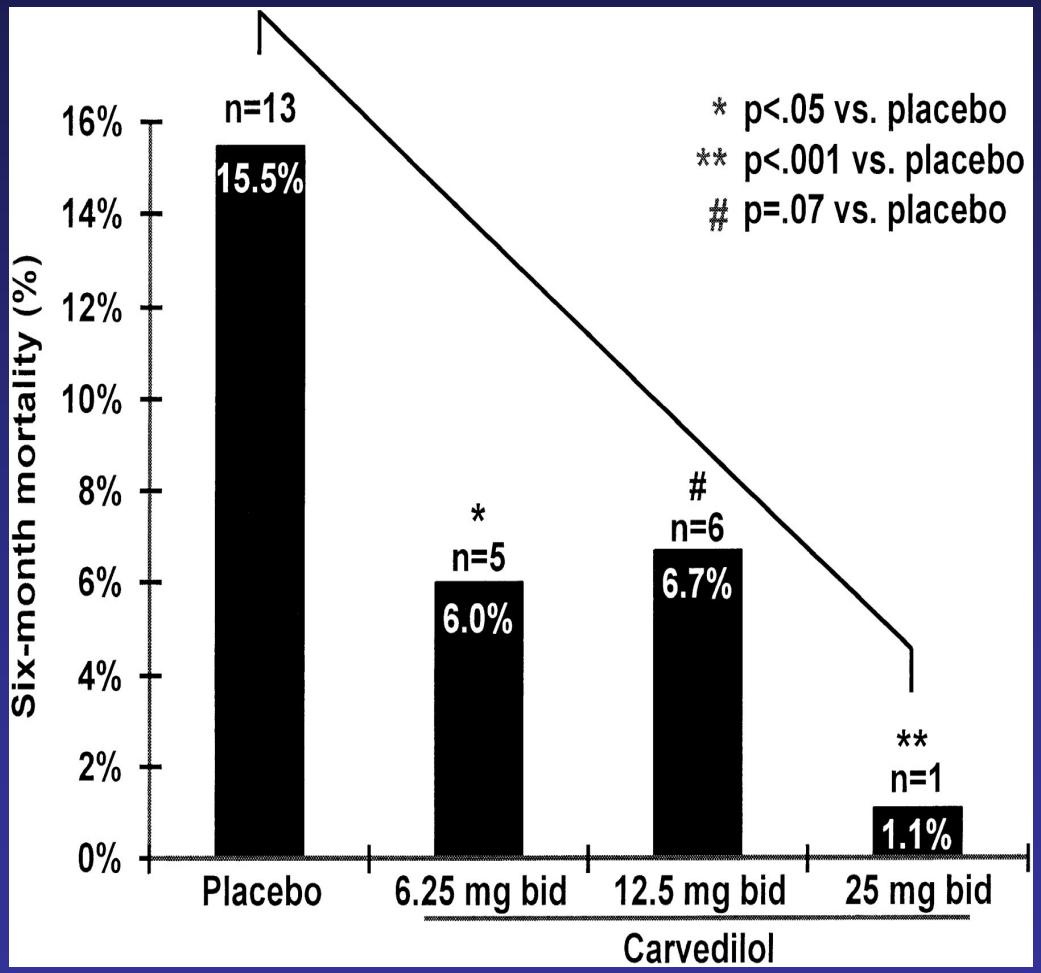
†Carvedilol and metoprolol CR/XL are the only agents with β-blockade approved by the FDA for the treatment of mild to moderate heart failure.

Beta-Blockers: Recent Trials in HF

	Annual Placebo Mortality Rate	RRR
US Carvedilol[1]	11.1%	65%
MERIT-HF[2]	11.0%	34%
CIBIS II[3]	13.2%	34%
BEST[4]	17%	10%
COPERNICUS[5]	18.5%	35%

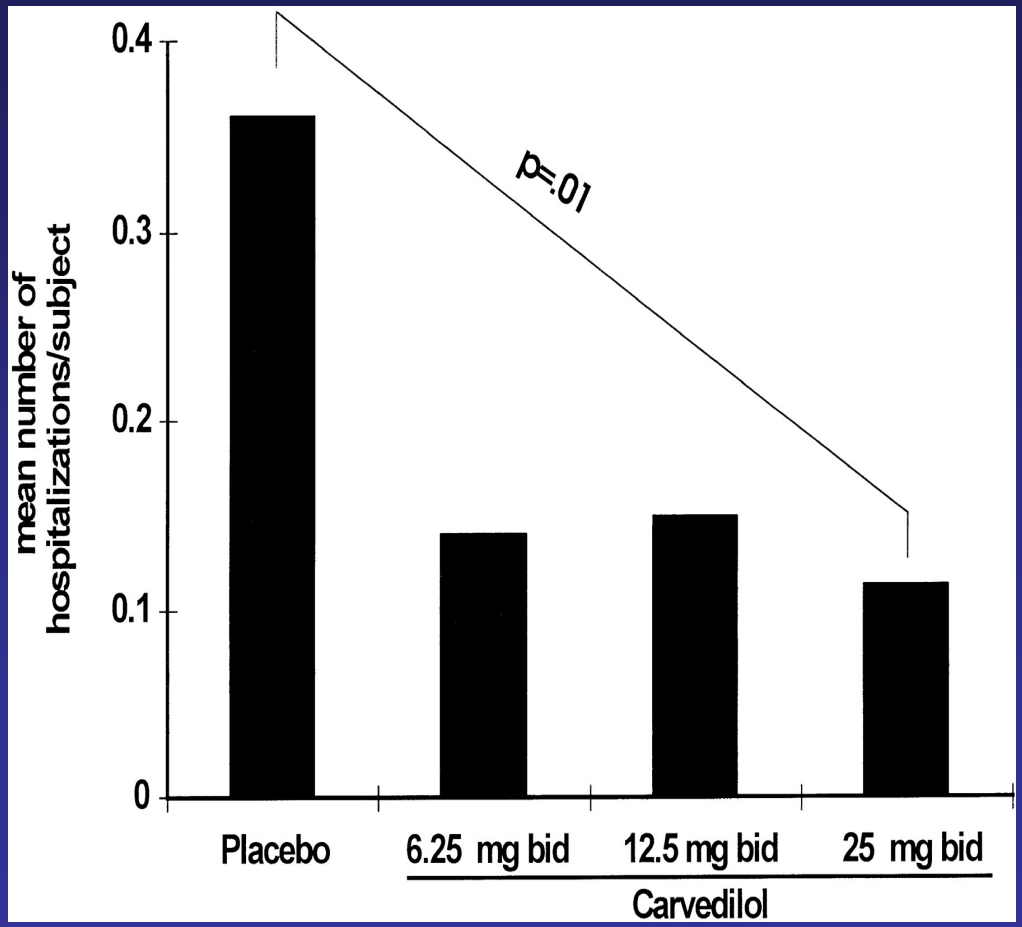
[1]Packer et al. *N EJM.*. 1996. [2]MERIT-HF Study Group. *Lancet*. 1999. [3]CIBIS-II Investigators. *Lancet*. 1999. [4]The Beta-Blocker Evaluation of Survival Trial Investigators. NEJM. 2001. [5]Packer et al. for the COPERNICUS study group. NEJM. 2001.

β-blockade — Dose Effect?



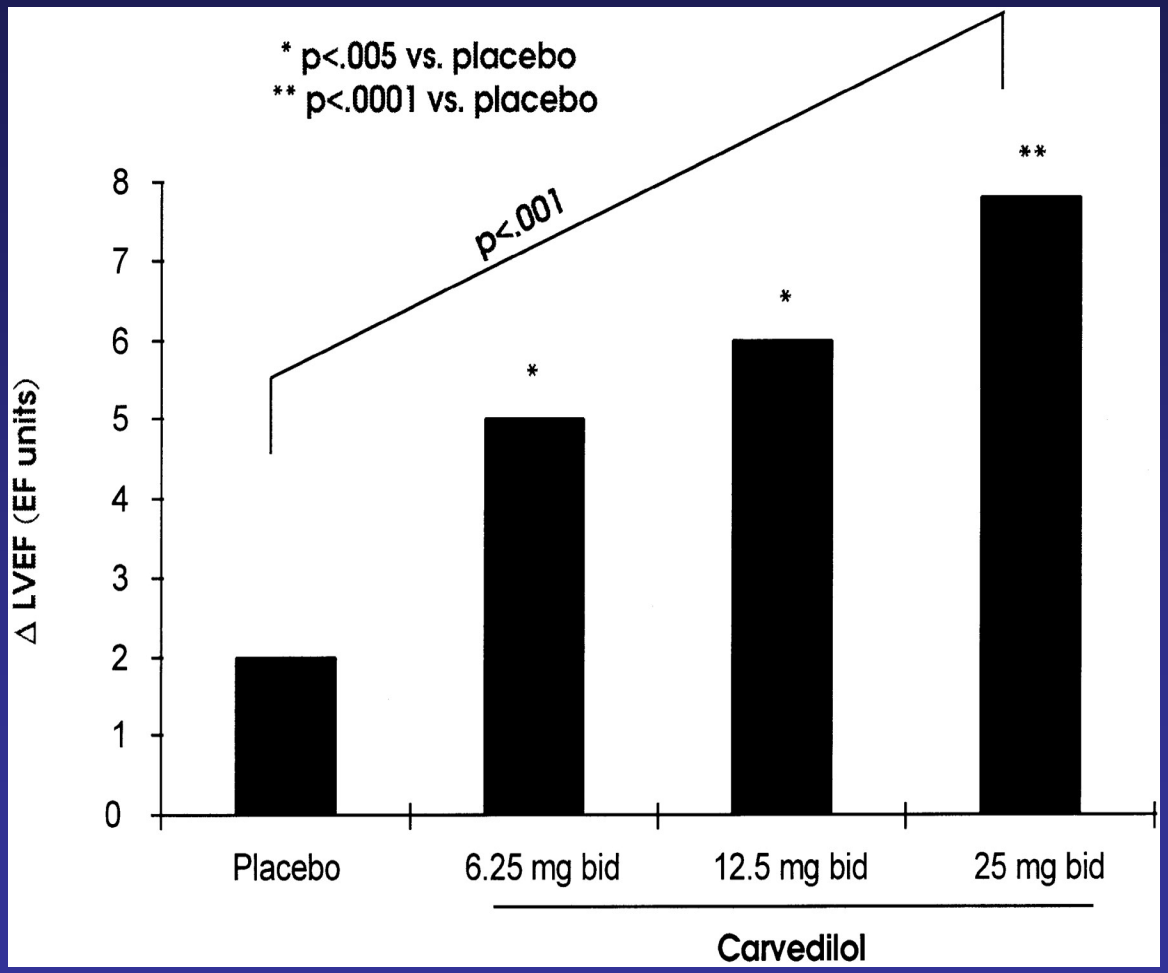
Bristow MR et al. MOCHA Investigators. *Circulation*1996;94:2807-2816.

β-blockade — Dose Effect?



Bristow MR et al. MOCHA Investigators. *Circulation* 1996;94:2807-2816

β-blockade — Dose Effect?



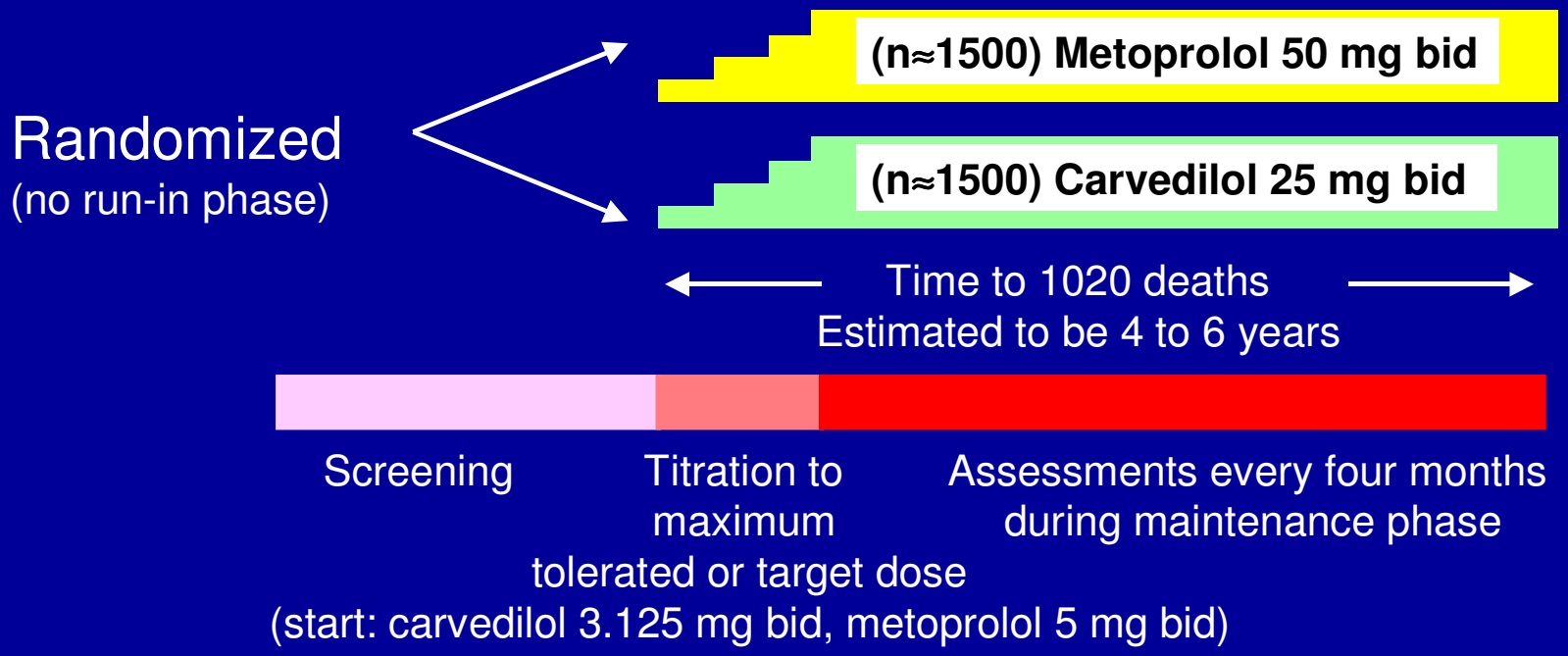
Bristow MR et al. MOCHA Investigators. *Circulation* 1996;94:2807-2816.

Does it Really Matter?

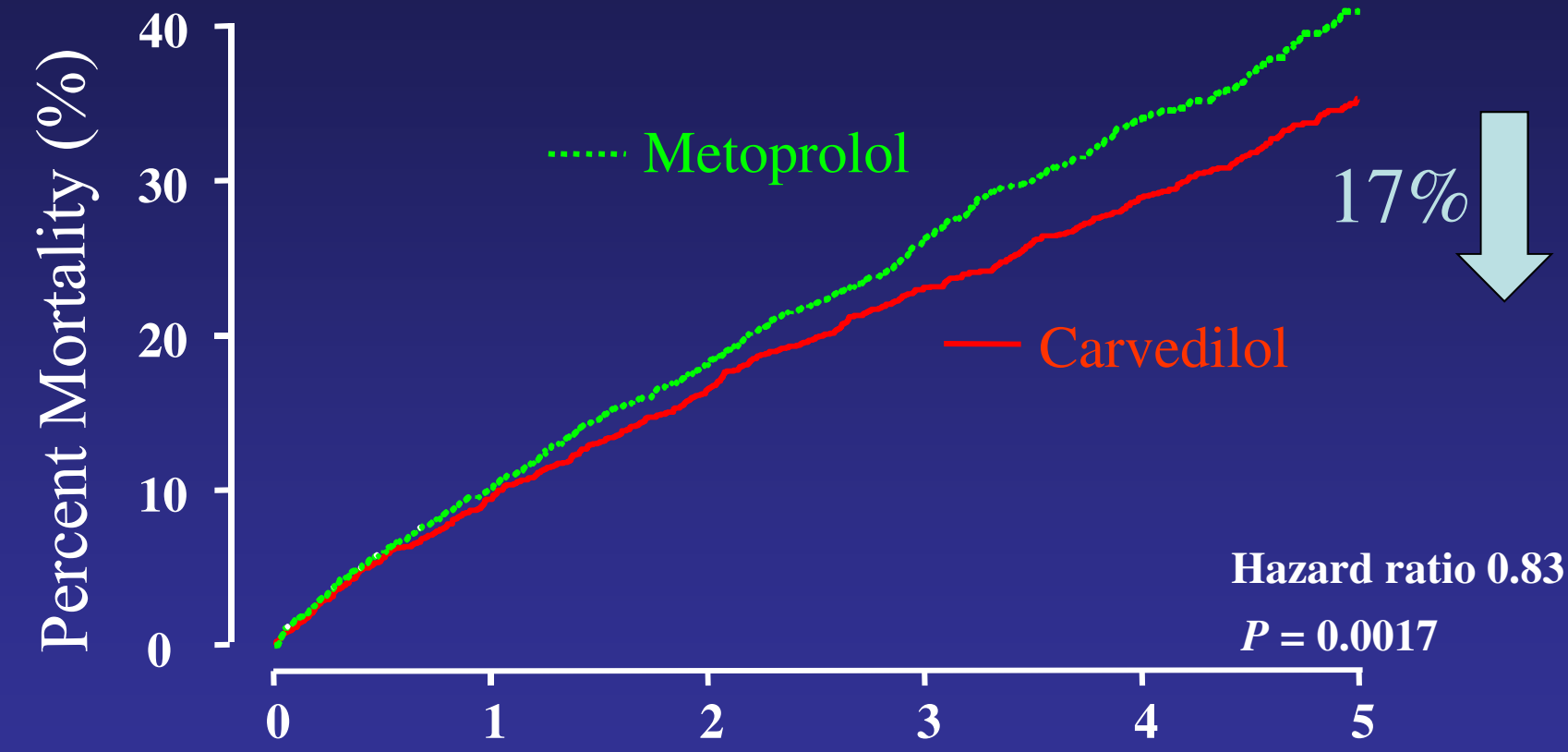
- Which β-blocker?

COMET Study

3000 patients with stable heart failure, NYHA II-IV, receiving standard treatment including ACE inhibitors



COMET: All-cause Mortality

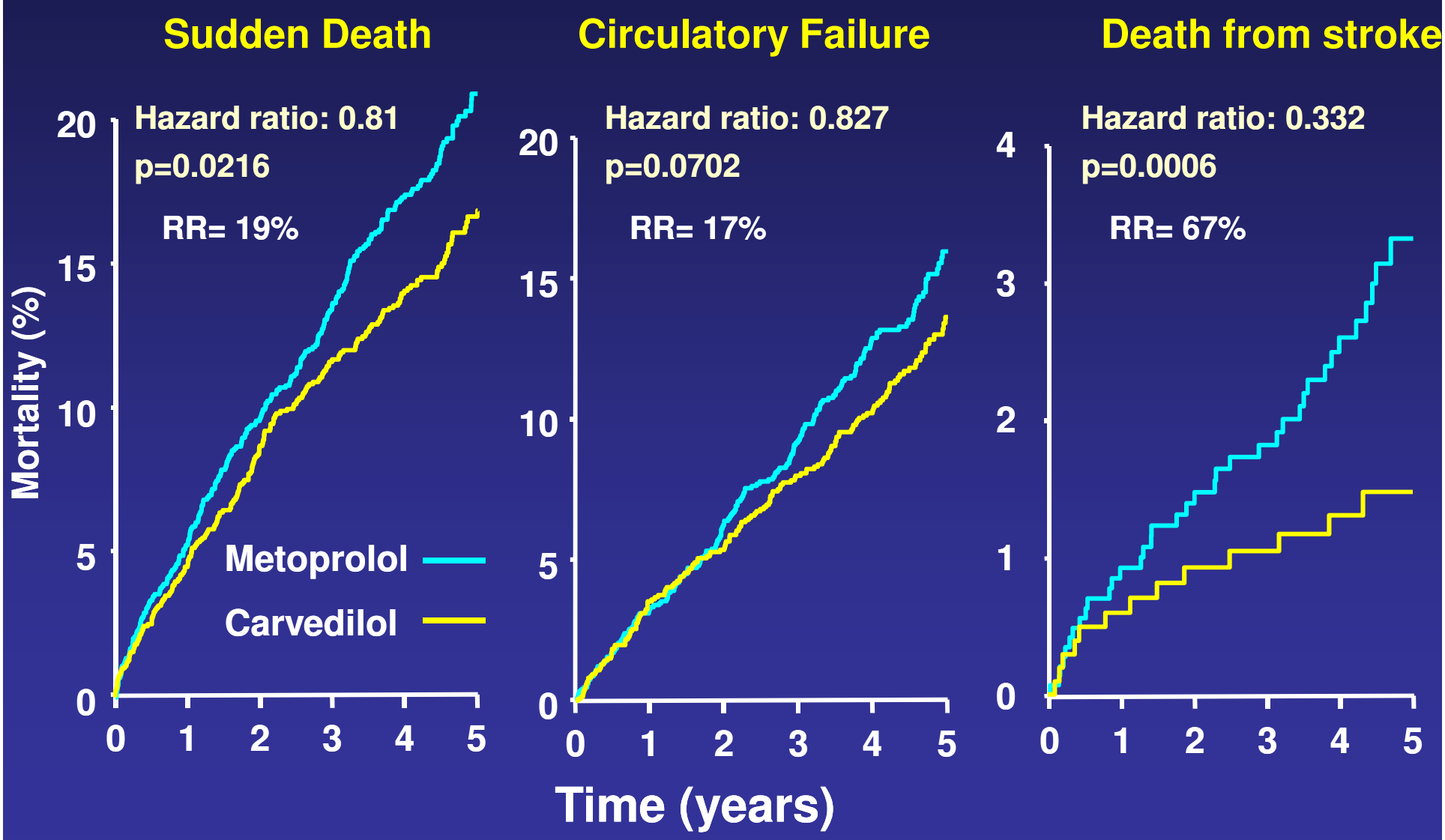


Number at risk

Carvedilol	**1511**	**1367**	**1259**	**1155**	**1002**	**383**
Metoprolol	**1518**	**1359**	**1234**	**1105**	**933**	**352**

Poole-Wilson PA et al. Lancet 2003;362:7-13

Primary Endpoint:
All Cause Mortality

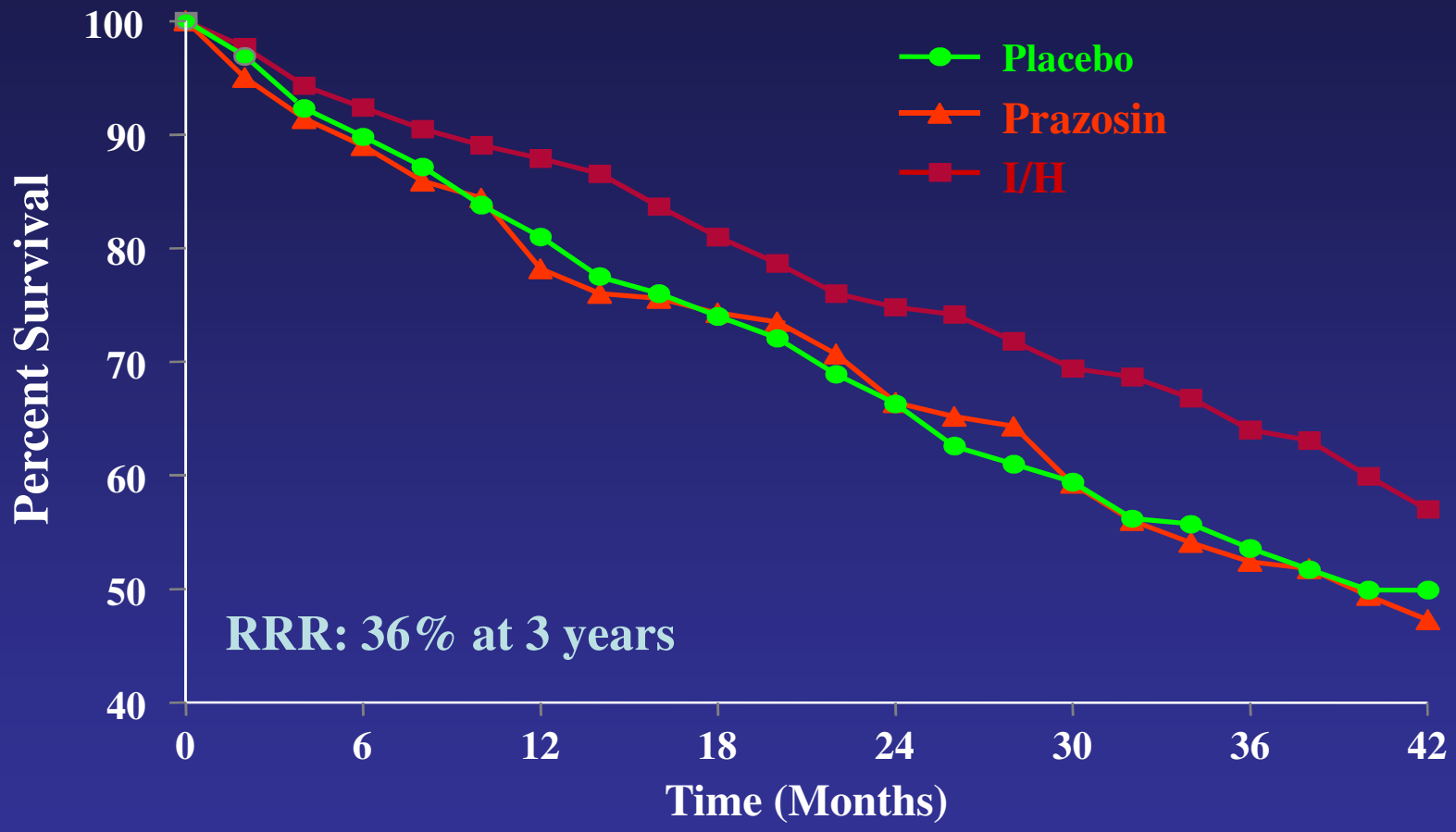


Beta-Blockers: How to use them?

- Start low and only in ***compensated*** patients
- Carvedilol 3.125 bid (goal 25- 50 mg bid) Metoprolol XL 12.5 mg qd (goal 200 mg qd)

  Bisoprolol 1.25 mg qd (goal 10 mg qd) Metoprolol Tartrate 6.25 mg bid, goal 100 mg bid.
- Double the dose every 1 to 2 weeks or as tolerated.
- Increase diuretic dose if dyspnea without hemodynamic compromise

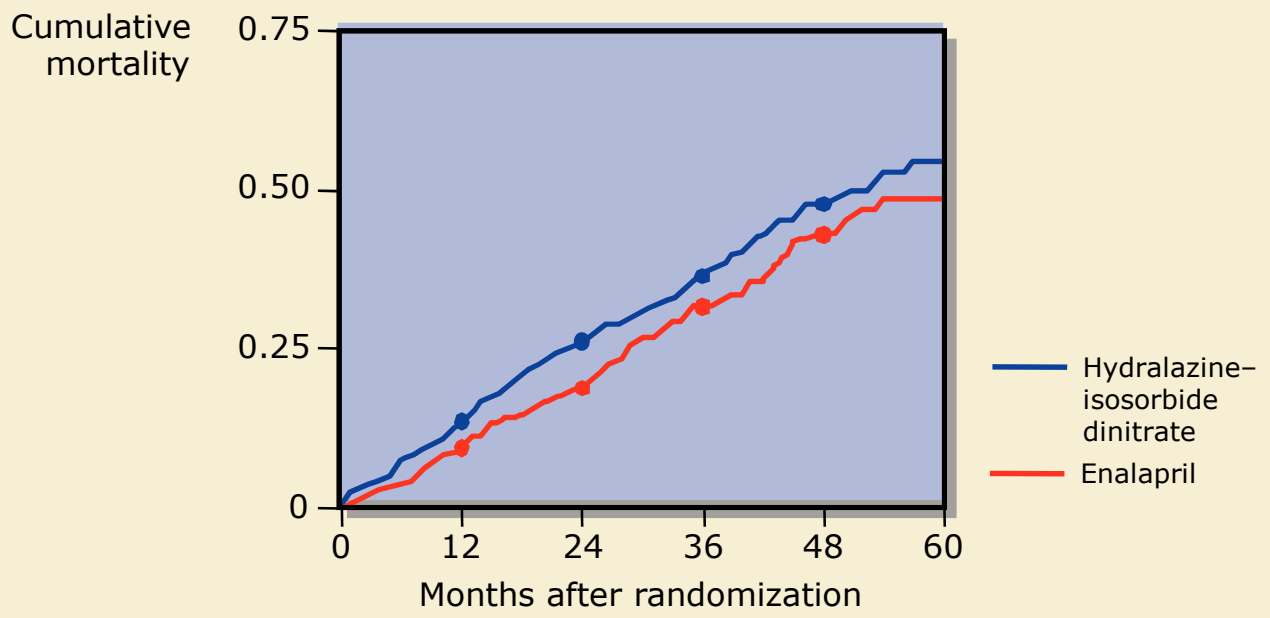
V-HeFT I: ISDN/HDZN



Placebo: N (cumulative death)	273	201 (53)	132 (94)	82 (128)
I/H: N (cumulative death)	186	147 (23)	108 (48)	70 (67)

Cohn JN et al. NEJM. 1986;314:1547-52

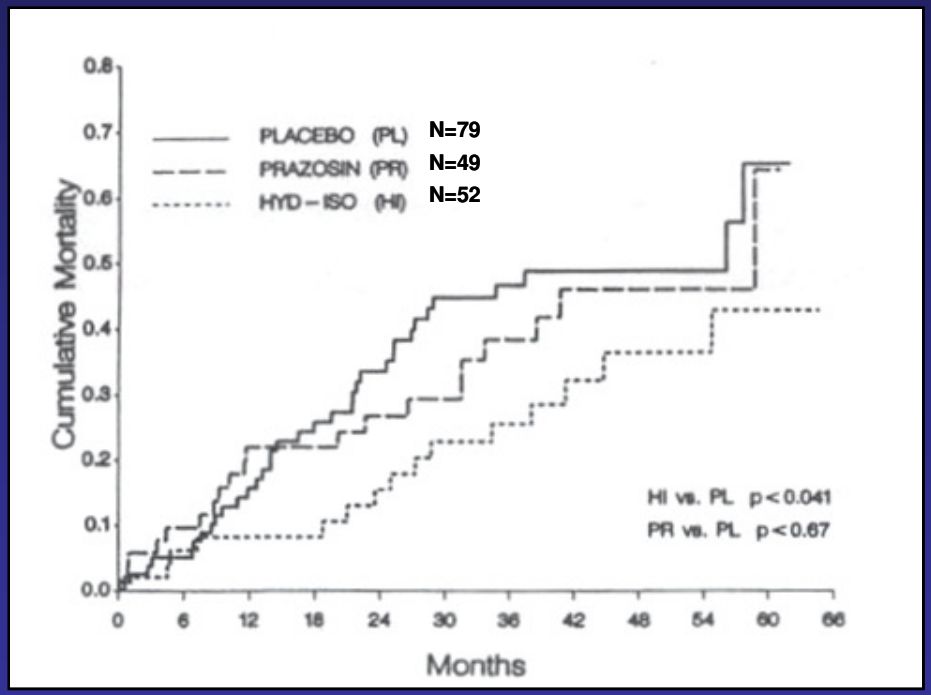
V-HeFT II: Vasodilator–Heart Failure Trial



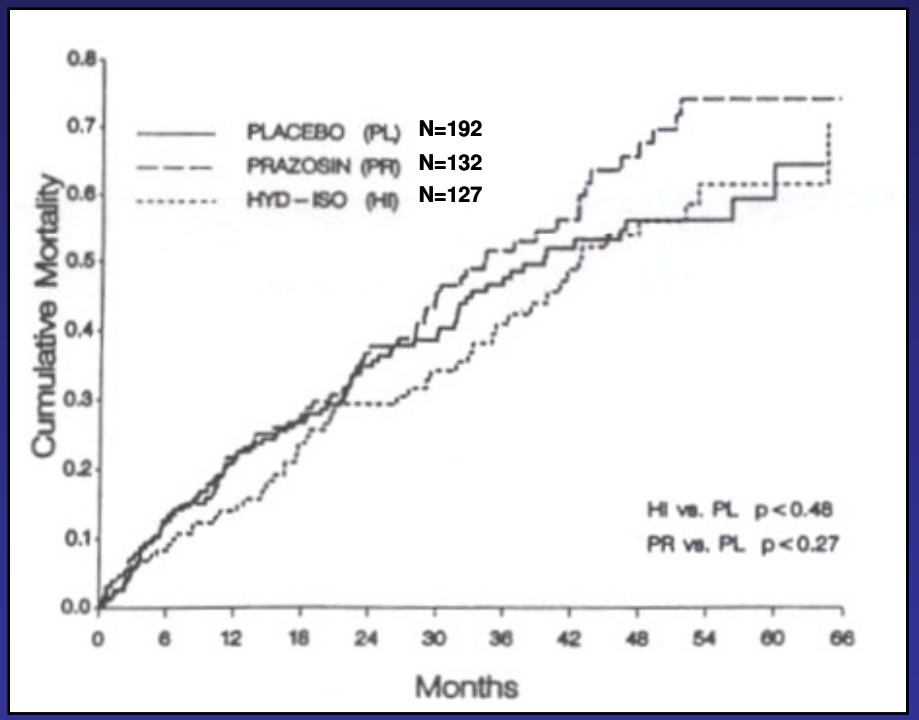
Cohn et al. *N Engl J Med* 1991; **325**:303–10.

Racial Differences in Mortality:
V-HeFT I

African American



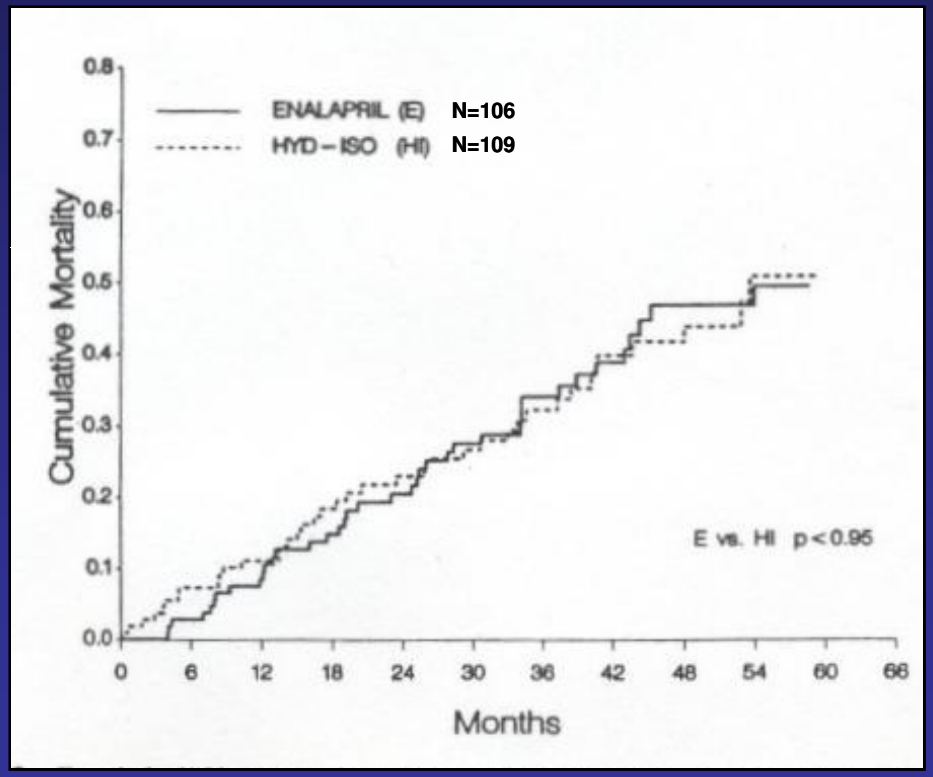
White



J Cardiac Failure 1999; 5(3): 178-87

Racial Differences in Mortality:
V-HeFT II

African American



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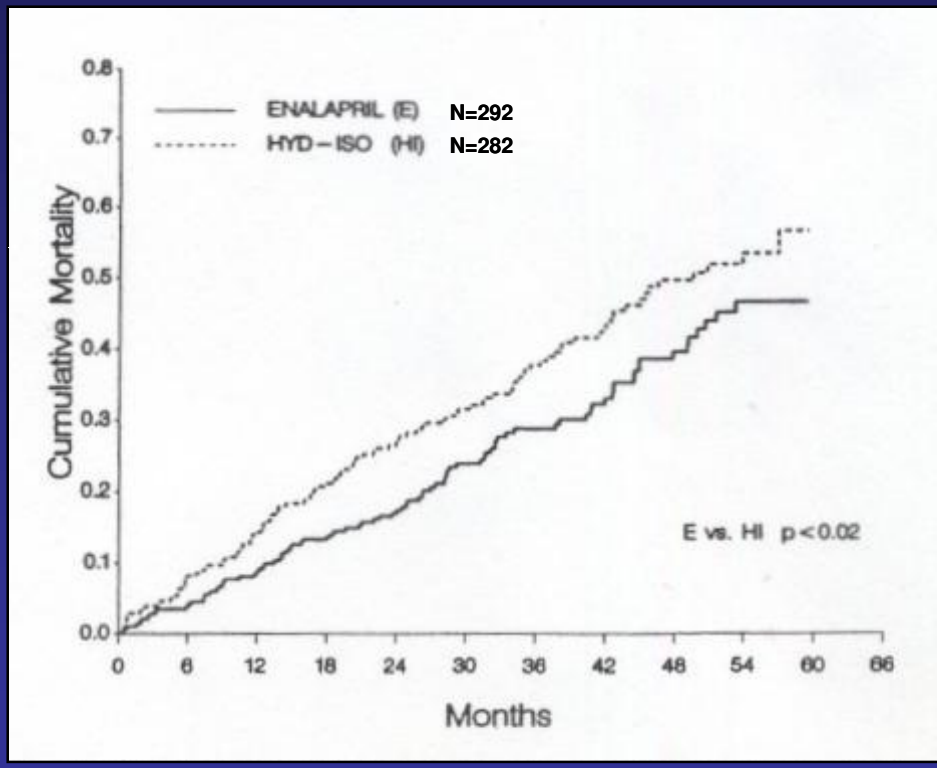


J Cardiac Failure 1999; 5(3): 178-87

African American Heart Failure Trial:
A-HeFT

AA, LVEF < 35%, NYHA III-IV
1 prior hospital for HF
Maintained on standard therapy

BiDil	6 months	Placebo
1-2 po TID N=300		N=300

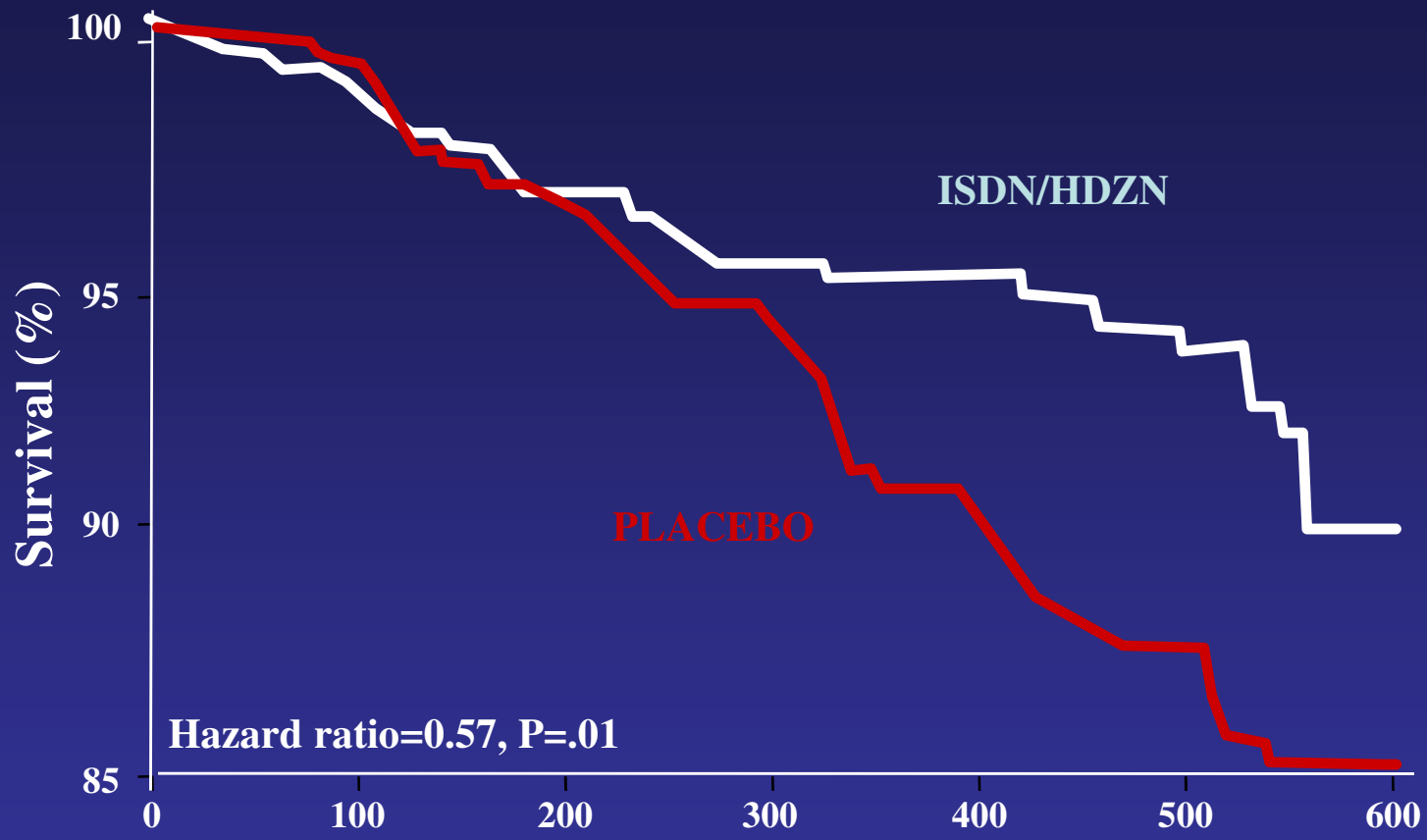
Primary endpoints: All cause mortality
Death + 1st Hospitalization + QOL

BiDil: 37.5mg Hydralizine + 20mg ISDN

N Engl J Med 2003; 348: 1309-1321.

J Cardiac Failure 2002; 8(3): 128-135.

A-HeFT: ISDN/HDZN



Fixed-dose I/H	518	463	407	359	313	251	13
Placebo	532	466	401	340	285	232	24

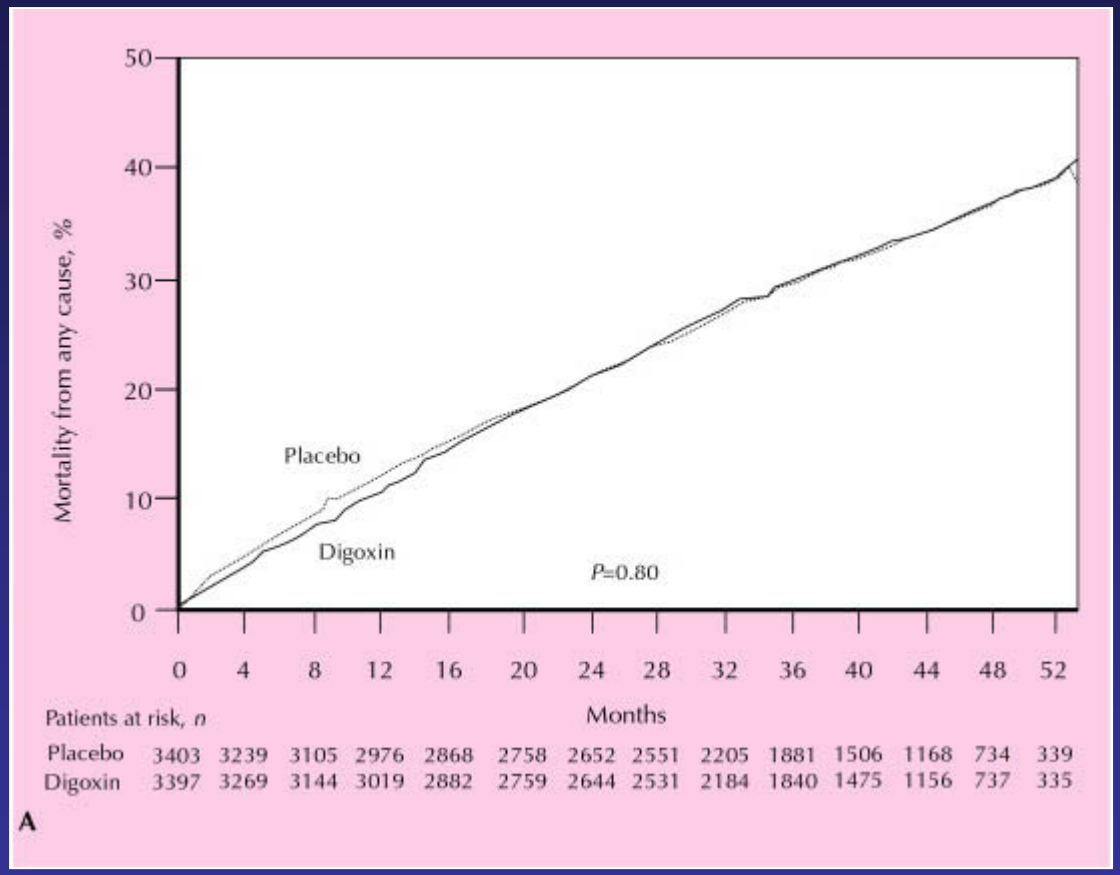
Taylor AL et al. NEJM,2004;351:2049-57

PRAISE 1 & 2: MORTALITY

	Placebo (n = 1408)	Amlodipine (n = 1397)
Number of deaths	479	466
% mortality	34.0%	33.4%
Odds ratio		0.98

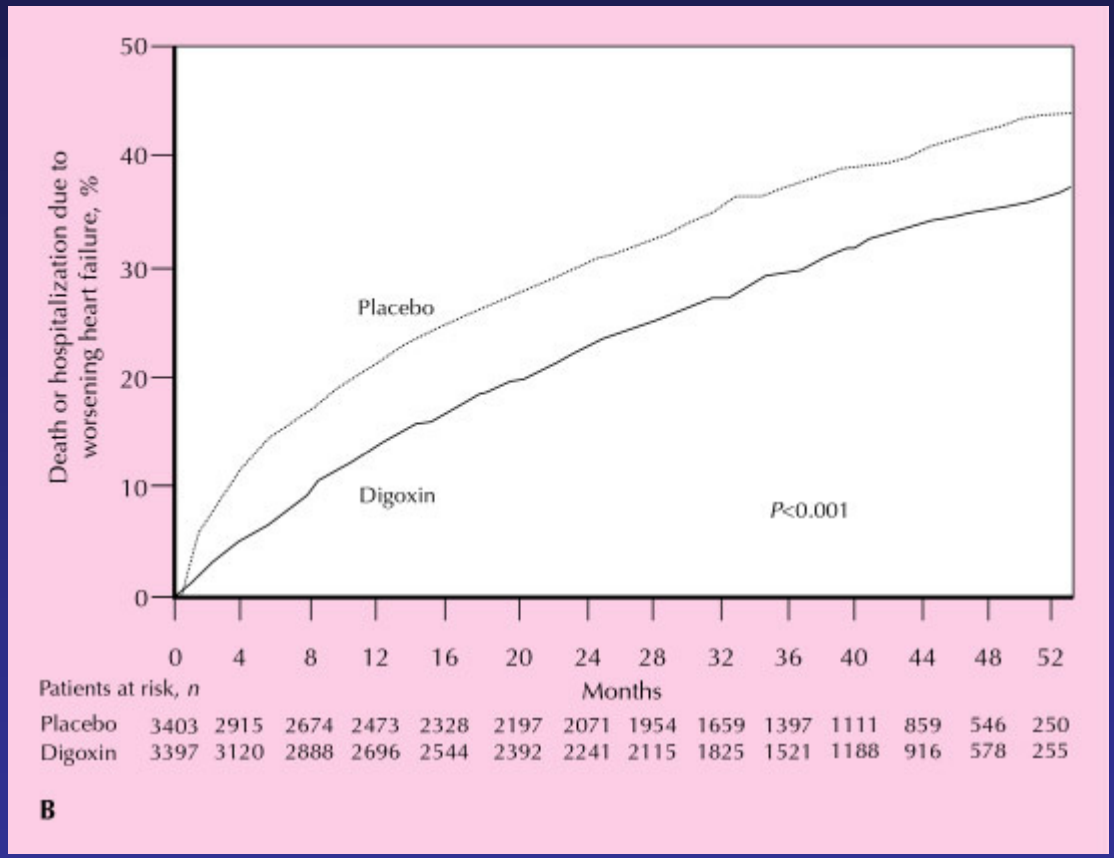
Packer M. ACC 49th annual scientific session. March, 2000

Digoxin



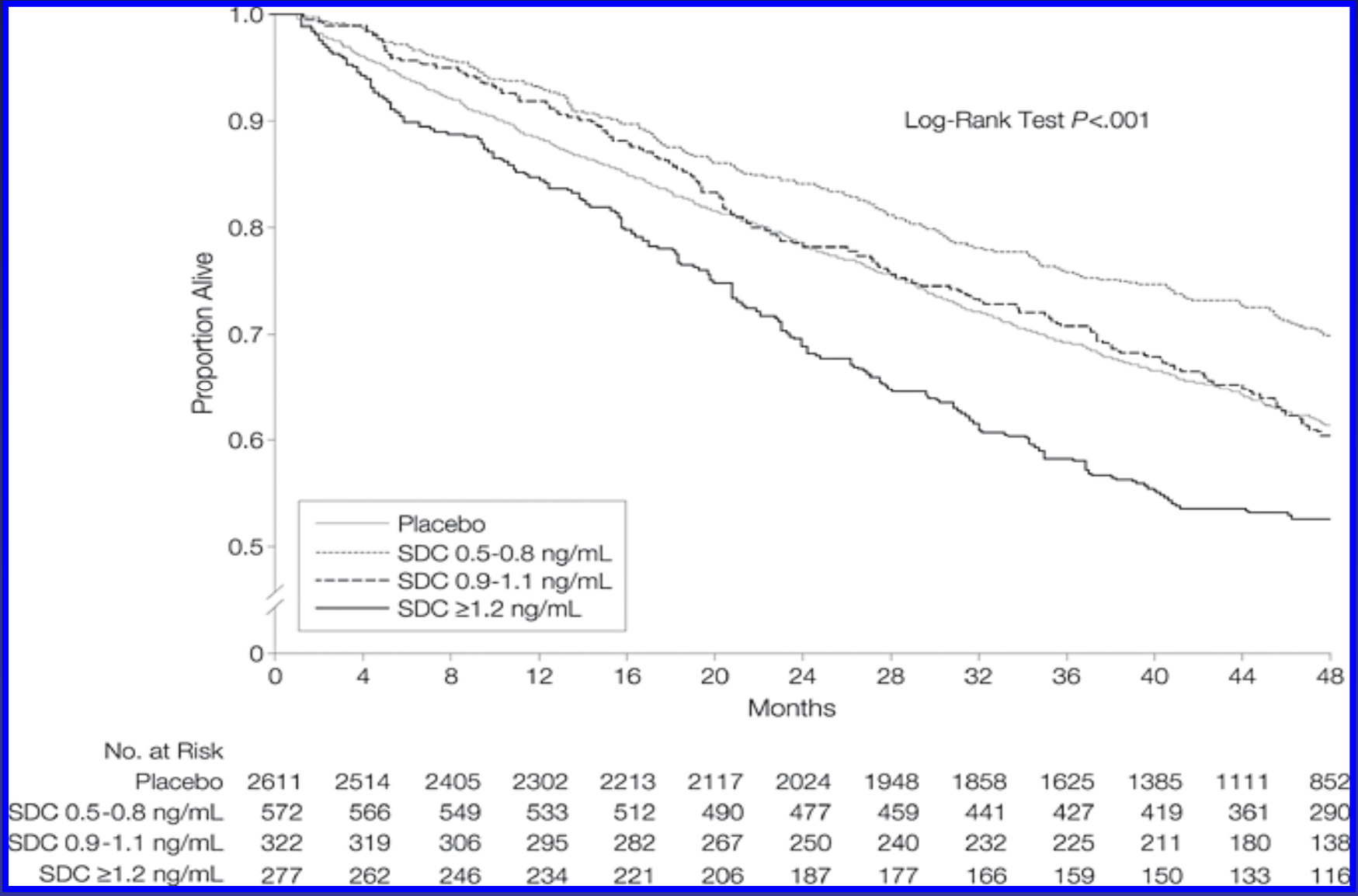
The Digitalis Investigation Group (DIG) trial evaluated the effects of digoxin on survival in 6800 patients. The average follow-up was 37 months. Digoxin did not increase or decrease overall mortality

Digoxin: DIG Trial



Digoxin-treated patients had a reduction in the overall rate of hospitalization and also the rate of hospitalization for worsening heart failure

Digoxin: Level and Survival



No. at Risk													
Placebo	2611	2514	2405	2302	2213	2117	2024	1948	1858	1625	1385	1111	852
SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
SDC ≥1.2 ng/mL	277	262	246	234	221	206	187	177	166	159	150	133	116

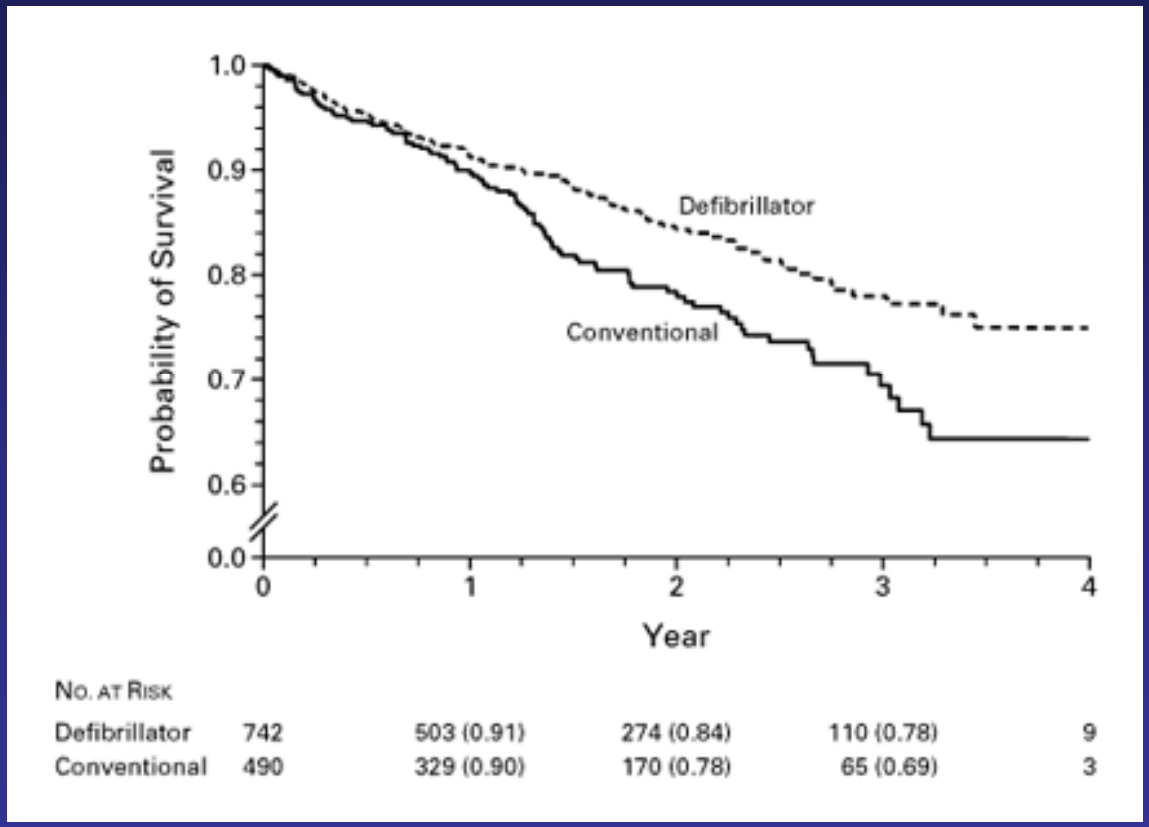
Rathore S. et al. JAMA. 2003;289:871-78

The PROMISE of Milrinone

- 1088 pts. With class III or IV heart failure.
- Median duration of f/u was 6.1 months.
- LV EF: 21 %. Digoxin level 1.5 mmol/l.
- Milrinone po vs placebo.
- All-cause mortality was increased by 28 %.
- It increased by 53 % in class IV patients.
- Similar tendencies with vesnarinone, ibopamine and pimobendan.

Packer M et al. NEJM 1991;325:1468-1475

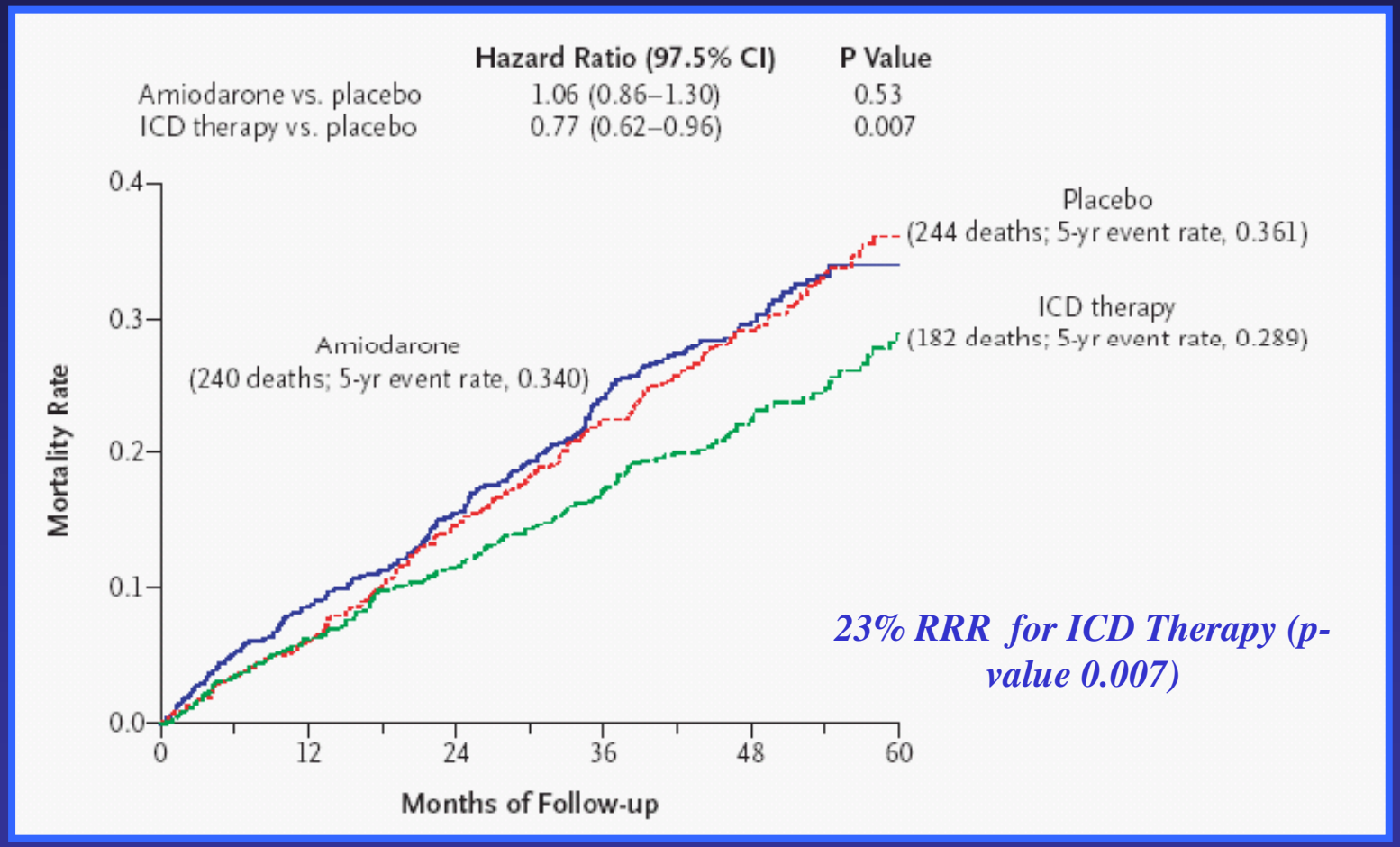
MADIT II Trial



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

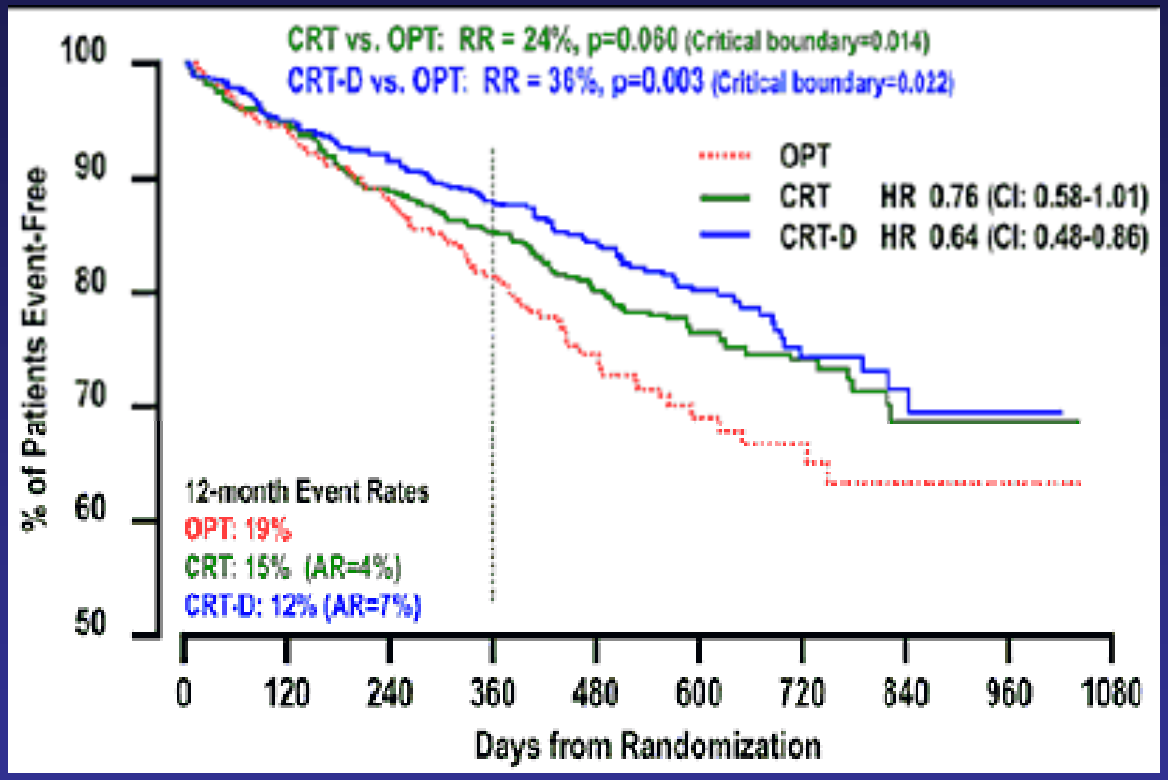
Moss et al. *NEJM* 346 (12): 877,2002

SCD-HeFT: All Cause Mortality



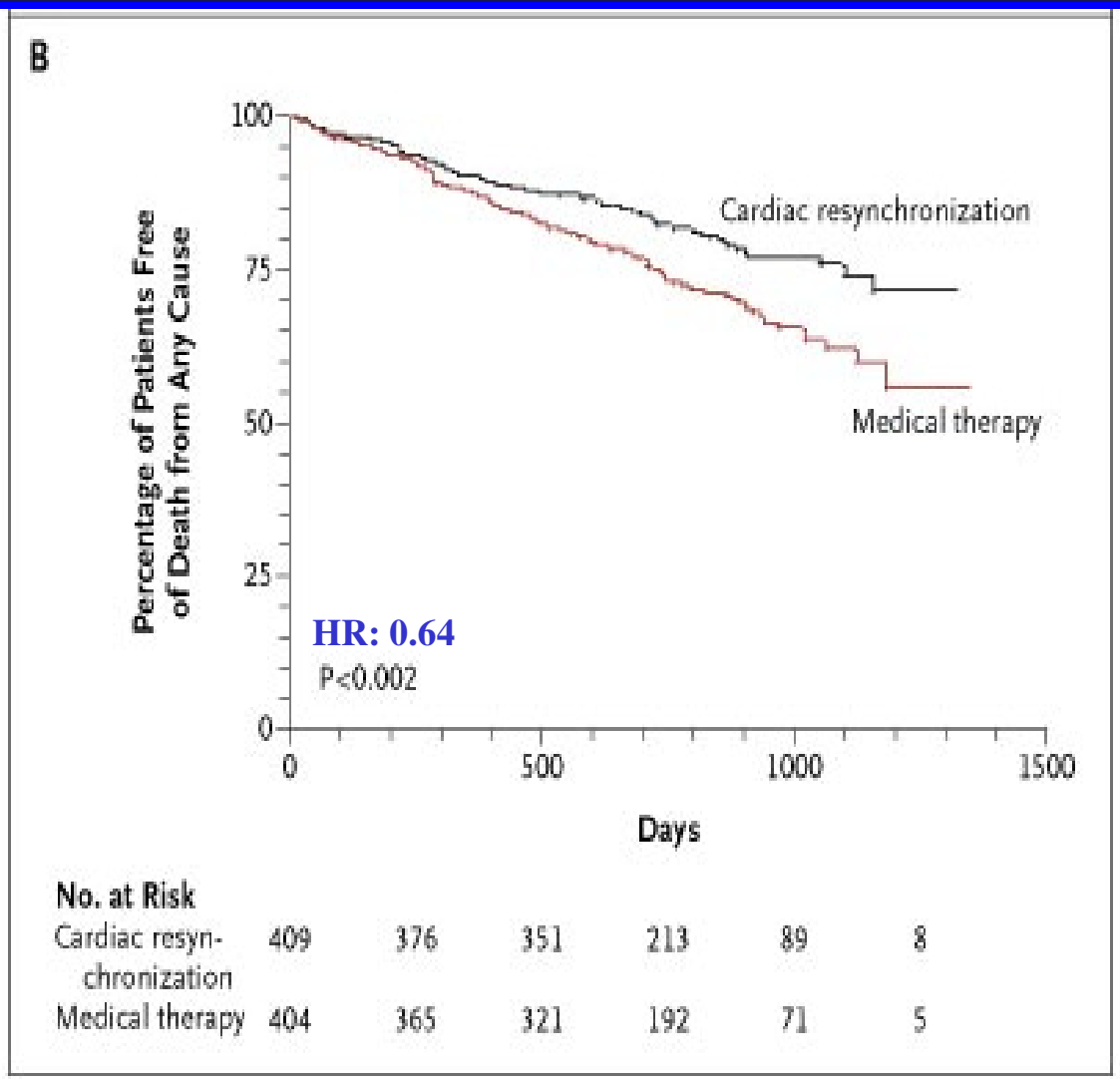
Bardy GH, Lee KL, Mark DB, et al. for the SCD-HeFT investigators. *N Engl. J Med.* 2005; 352:225-237.

COMPANION: All-Cause Mortality



The group that did best was the CRT plus ICD (CRT-D) group, the group that had a device with a defibrillator; there was a 36% reduction in mortality. Interestingly, the group with the CRT pacemaker also had an improvement in mortality, although it did not quite reach statistical significance.

CARE-HF: All-Cause Mortality



Cleland JGF et al. for the CARE-HF study investigators. NEJM. 2005;352:1539-49

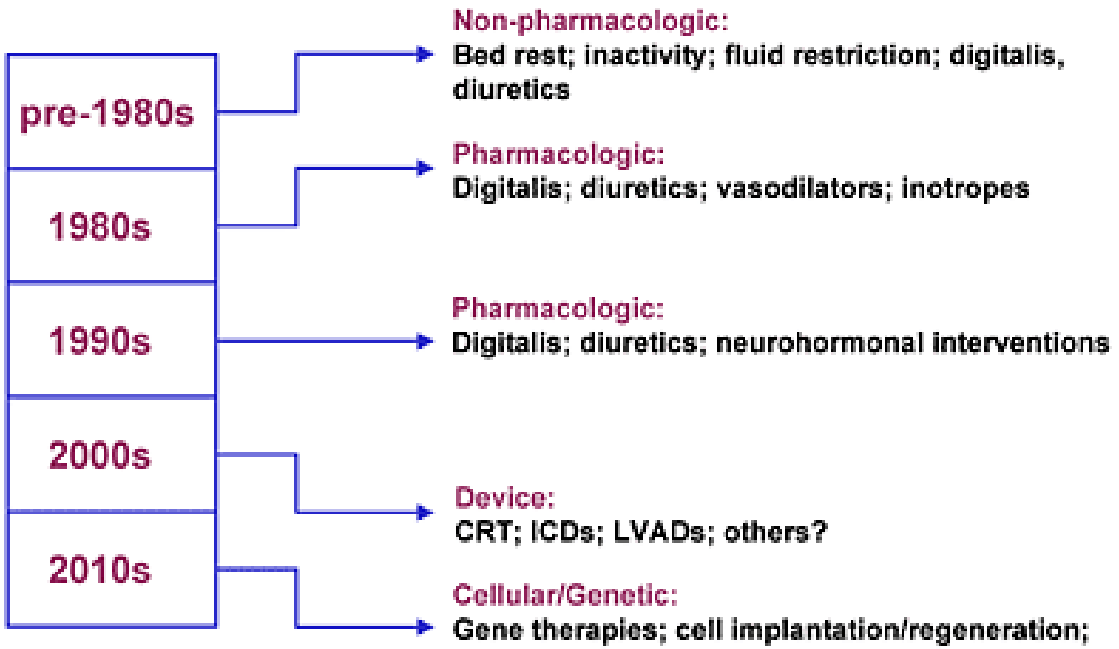
Combination therapy in CHF

	Symptoms	Morbidity	Mortality
High dose ACEI	Same	↓ 10-15%	NS
Add an ARB	↓	↓ 10-15%	↔↓
Add Aldosterone Inhibitor	↓	↓ 8-35%	↓15-30%
Add β-blockade	↓	↓ 36%	↓ 35%
AICD	Same		↓30%

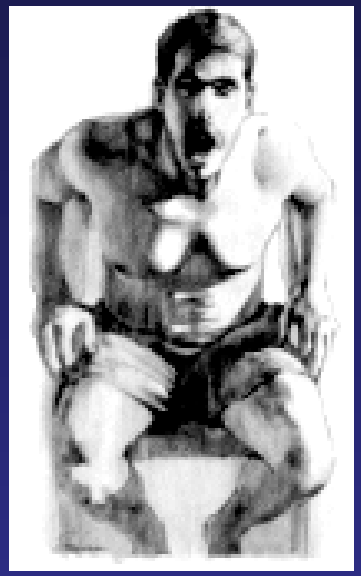
Case Presentation

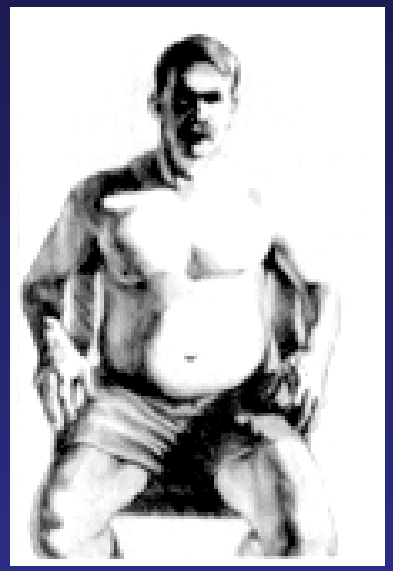
- In this Patient:
  - Coreg (to max dose)
  - Lisinopril (at least 5mg QD)
  - Spironolactone (low dose)
  - Hydralazine + Isosorbide ?
  - Digoxin
  - Repeat echocardiogram: if LVEF still <35% → BiV Pacer/AICD
  - V02 exercise test to assess his functional capacity

Heart Failure Therapy Timeline



Conclusion

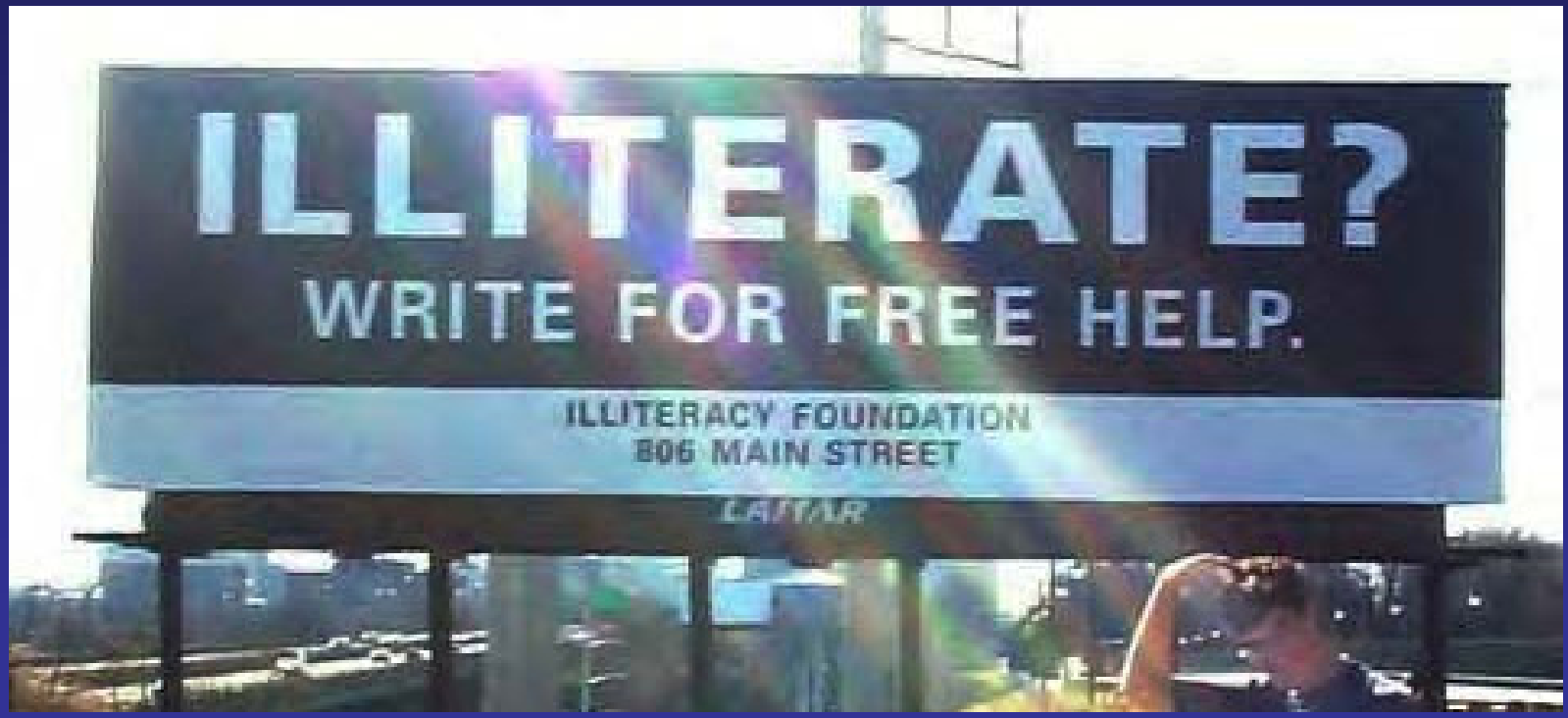




"I can't breathe"

"I can walk 30 minutes without stopping"

Questions


ILLITERATE?
WRITE FOR FREE HELP.
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