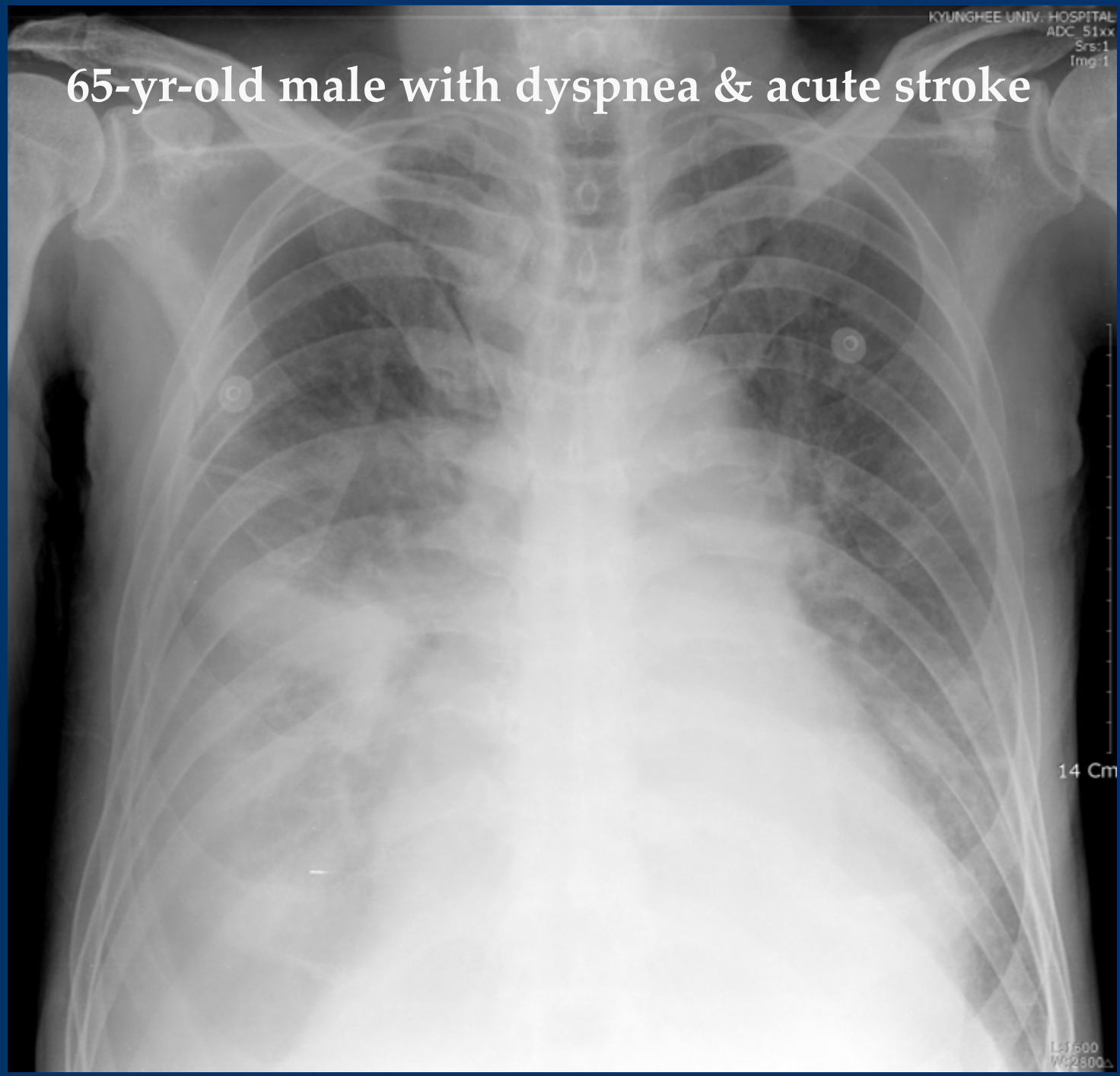
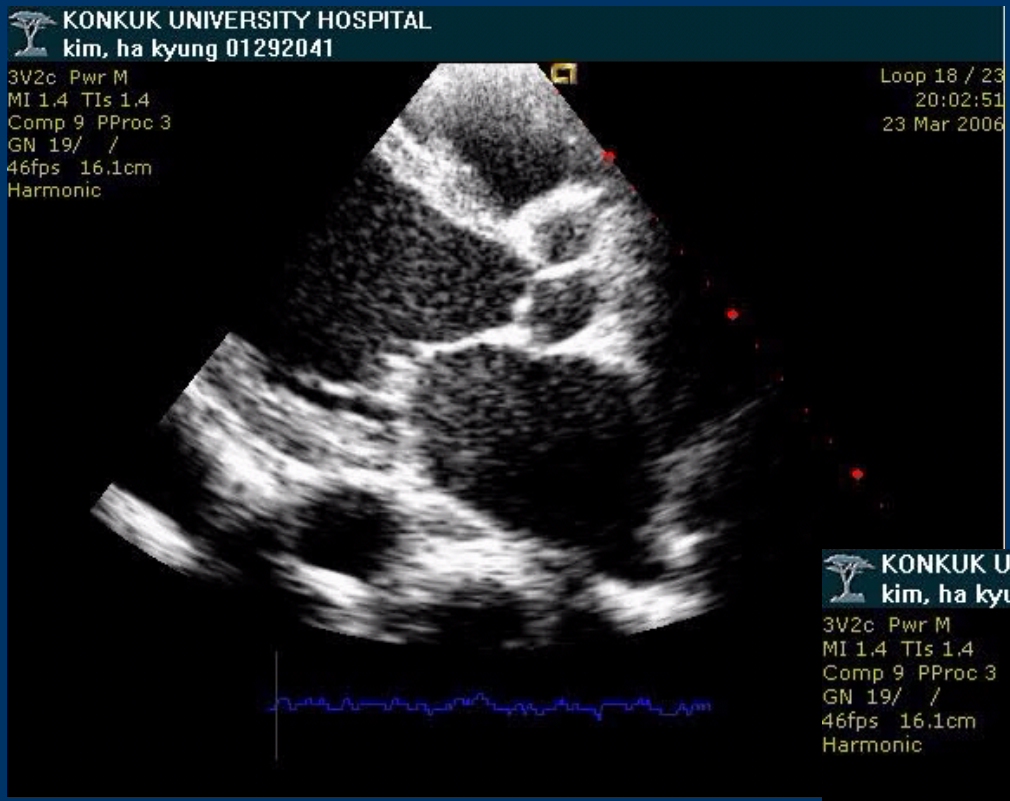
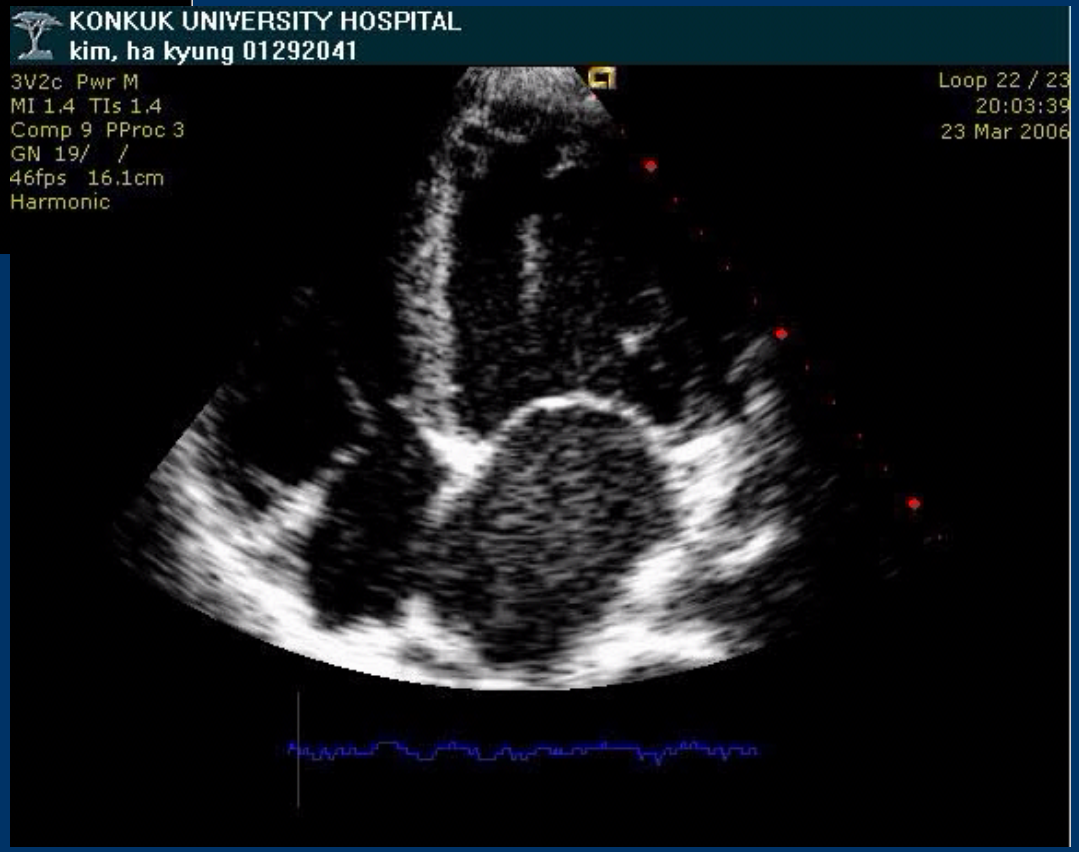
Beta-blocker in Heart Failure
The Best Way of Use

Konkuk University Hospital
Cardiovascular Center
Kyu Hyung Ryu, MD, PhD, FACC

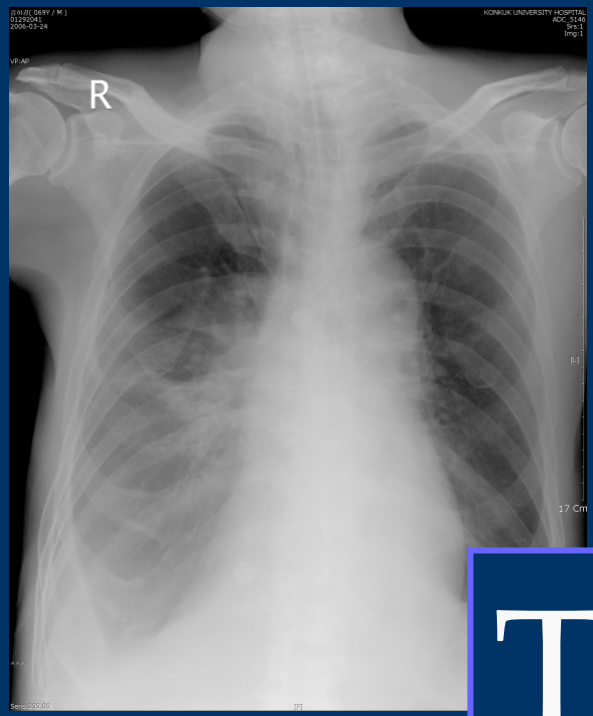

KYUNGHEE UNIV. HOSPITAL
ADC_51xx
Srs:1
Img:1
65-yr-old male with dyspnea & acute stroke
14 Cm

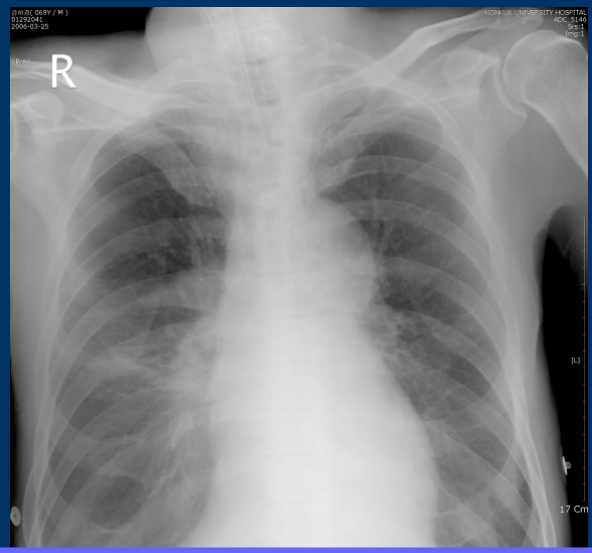


IV diuretics
Dobutamine
ACE inhibitor
Aldosterone antagonist
Digoxin

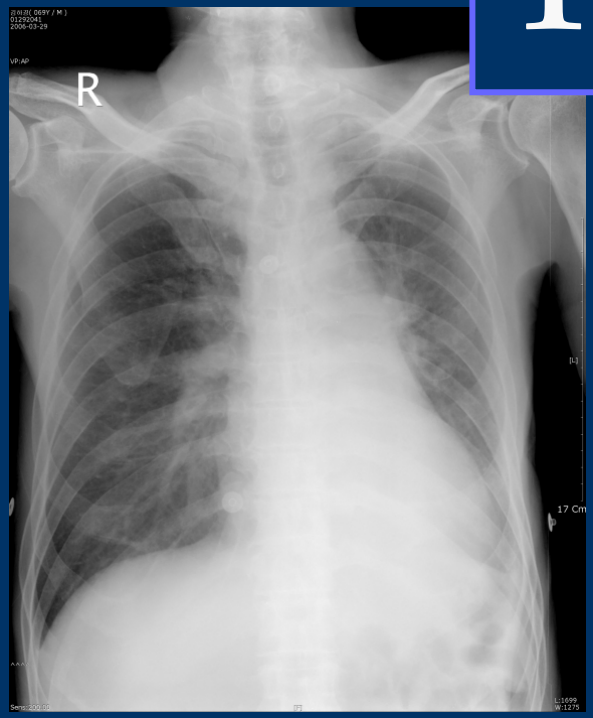


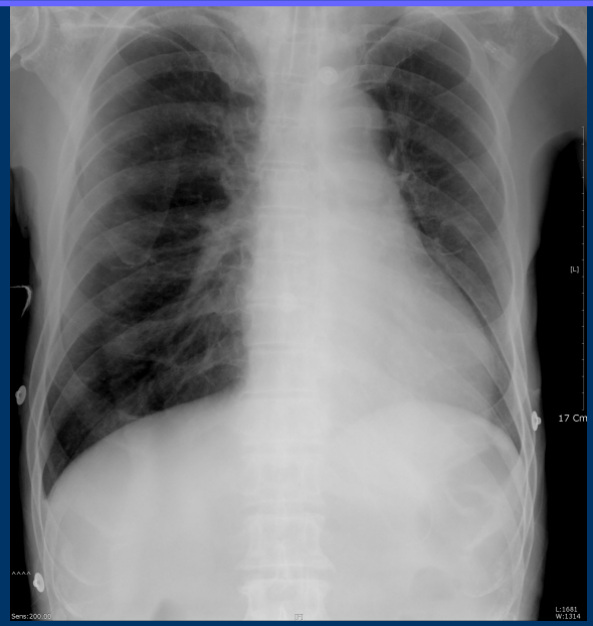
LVED dimension 62mm
LVEF 20%
Global hypokinesia

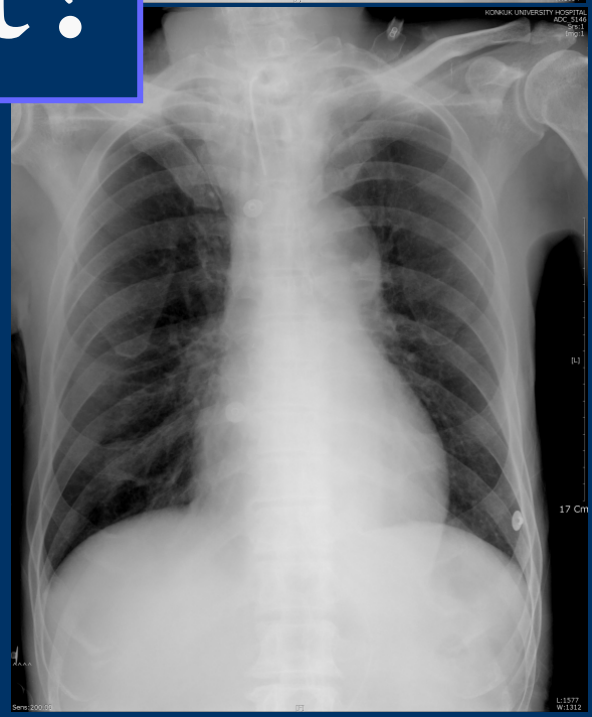




The Next?

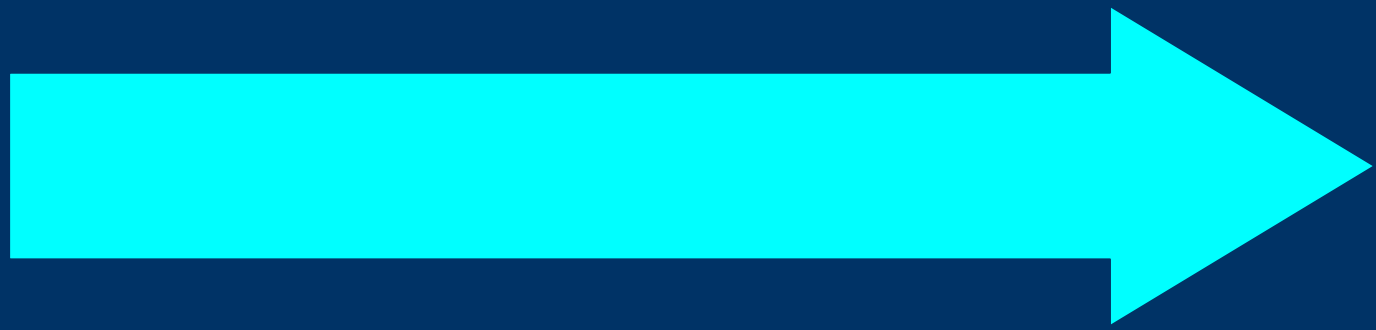






Evolving Models of Heart Failure

Cardiorenal	**Hemodynamic**	**Neurohormonal**
Digitalis and diuretic to perfuse kidneys	Vasodilators or positive inotropes to relieve ventricular wall stress	ACE inhibitors, beta blockers, and other agents to block neurohormonal activation



1940s 1960s 1970s 1990s–2000

Pepper, *Arch Intern Med* 1999.

What percentage of patients with CHF do you have on a beta-blocker?

1) less than 10%
2) 10%-30%
3) 31%-50%
4) 51%-75%
5) 76%-100%

Putting Evidence into Practice

It may take as long as 17 years for original research to be put into routine clinical practice

Balas EA, Boren SA. Managing Clinical Knowledge for Health Care Improvement. Yearbook of Medical Informatics. Schattauer, 2000: 65-70

Outcomes and Evidence-Based Clinical Practice

Translating Data Into Clinical Practice: Impediments

- Ignorance (education)
- Skepticism (doubt)
- Disbelief (trial flaws)
- Inconvenience (lazy)
- Disincentives (effort)

Outcomes and Evidence-Based Clinical Practice

Translating Data Into Clinical Practice: Solutions

- Education
- Practice guidelines
- Incentives
- Mandates
- "Jail"

Questions

- Why?
- For Whom?
- When?
- Where?
- What?
- How?

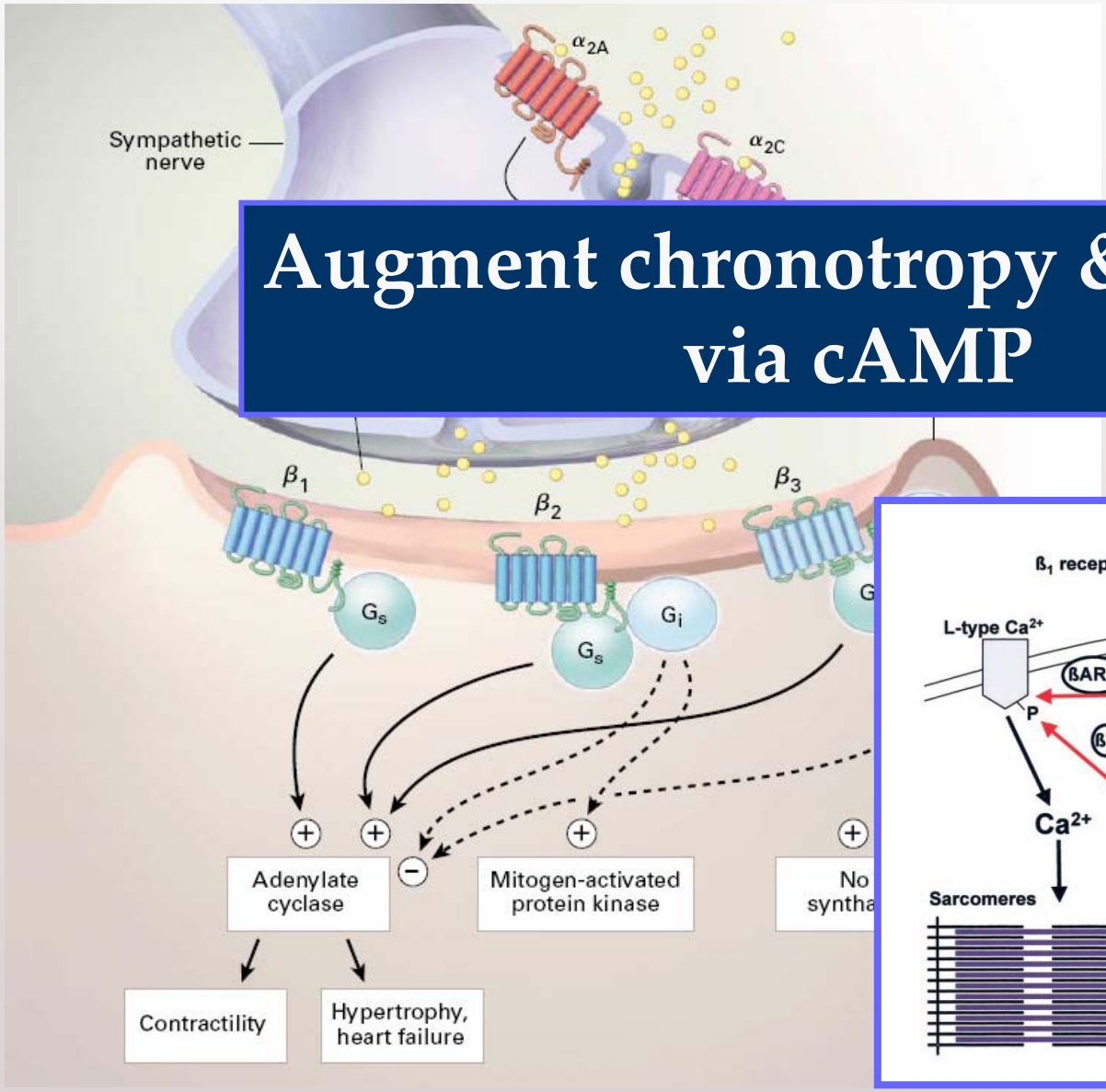
- Rationale, clinical data
- Indication
- Decompensated HF
- During hospitalization?
- Selective or non-selective
- Titration, monitoring, problem solving

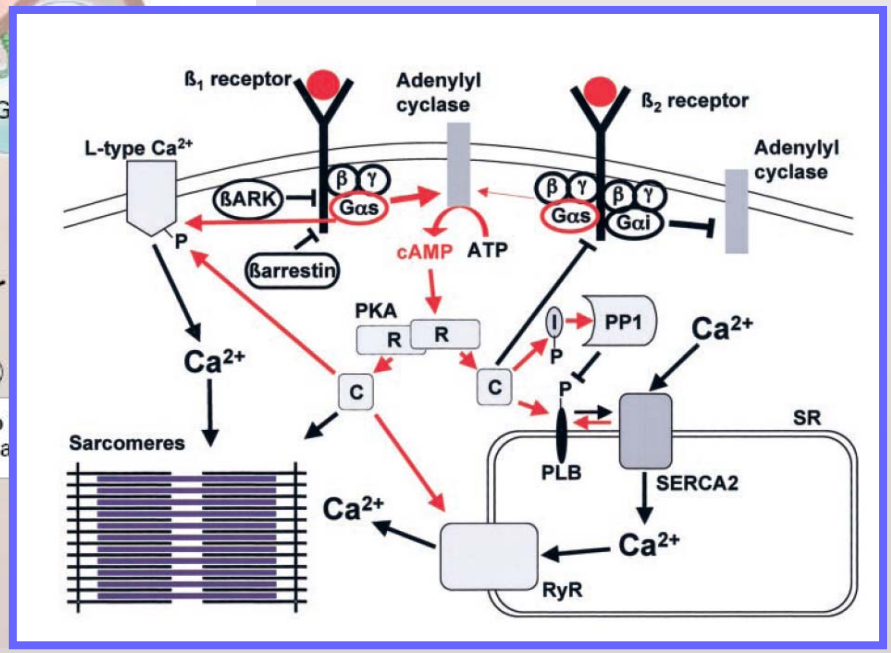
Background & Clinical Data

Experimental Data

Beta-adrenergic Receptor

Augment chronotropy & intotrpy via cAMP





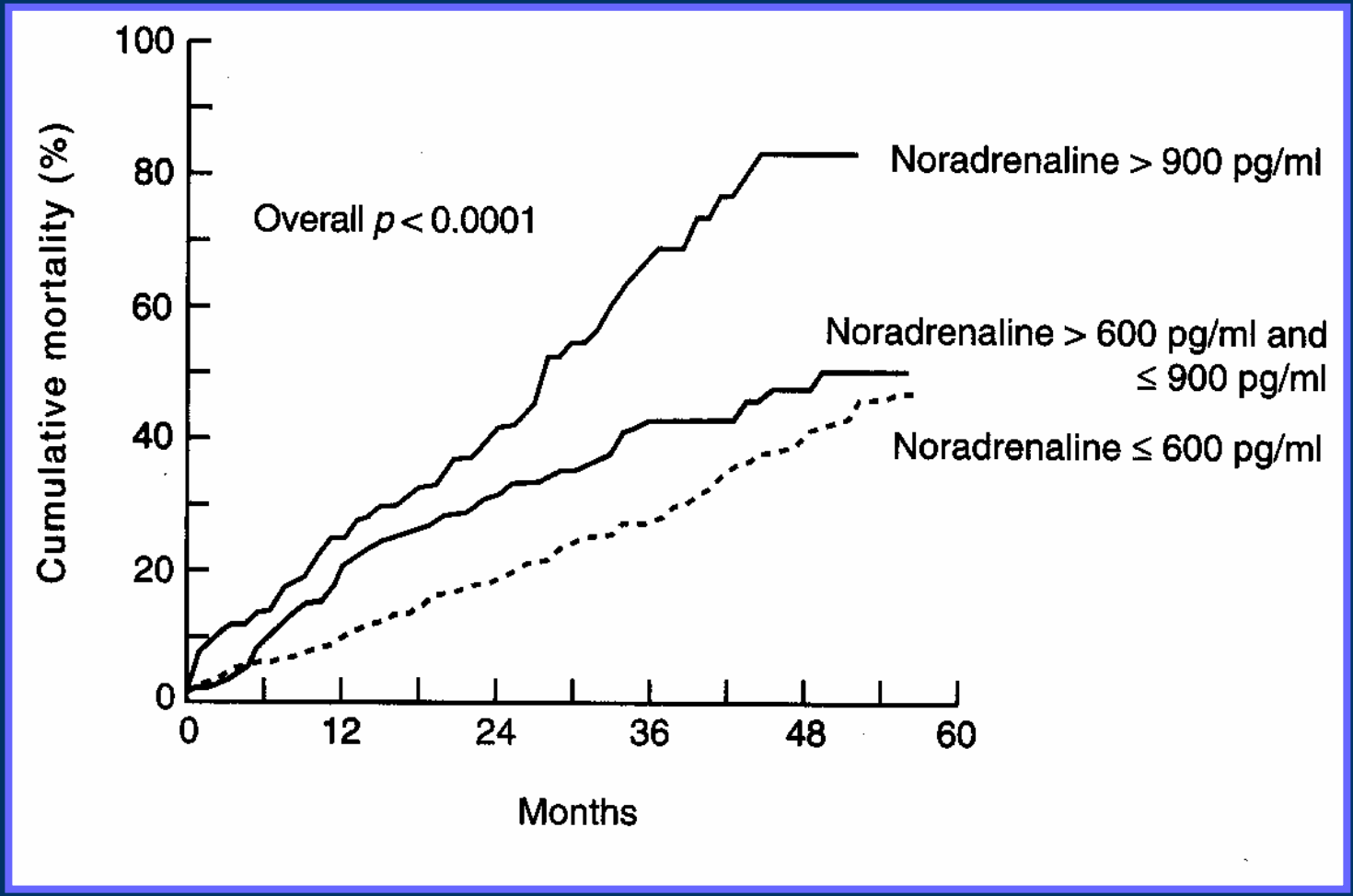
Effect of Stimulating α and β-adrenoreceptors

	Cardiac	Vascular	Neuroendocrine	Metabolic
α1	Minimal increase contractility	Venous and arterial constriction	Stimulation of renal renin release via arterial contriction	-
α2	Electrophysiological effect?	Venous and arterial constriction (less potent than α1)	Inhibition of norepinephrine release	Antagonises effect of β1-stimulation
β1	HR ↑ Contractility ↑ Excitability ↑ hypertrophy ↑	-	Stimulation of renin release	Lipolysis Platelet aggregation
β2	As β1, but less potent	Coronary and skeletal muscle arterial dilatation	-	Glycogenolysis

Biological Responses Mediated by Adrenergic Receptors in the Human Heart

Biological Response	**Adrenergic Receptor Mediation**
Cardiac myocyte growth	β_1, β_2, α_1
Positive inotrophic response	β_1, β_2, α_1(minimal)
Positive chronotropic response	β_1, β_2
Myocyte toxicity	**β_1, β_2(?<β_1)**
Myocyte apoptosis	**β_1**

Plasma Norepinephrine and Mortality in CHF

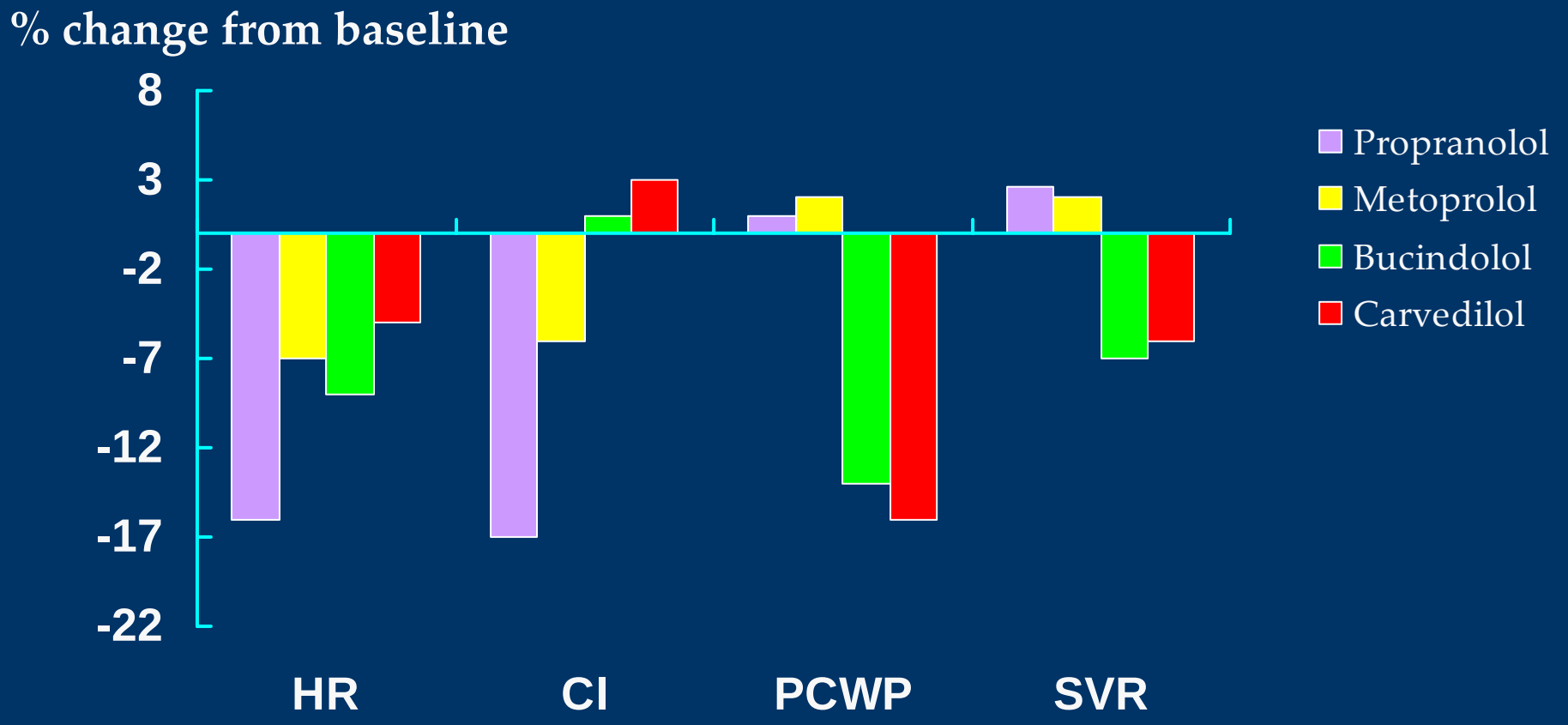


Francis et al *Circulation* 1993

Beta-blocker,
Effects on the myocardium

- Prevention of catecholamine toxicity
- Reduction of myocardial ischemia
- Prevention of coronary thrombosis
- Cardiac volumes
- Reduction of arrhythmias

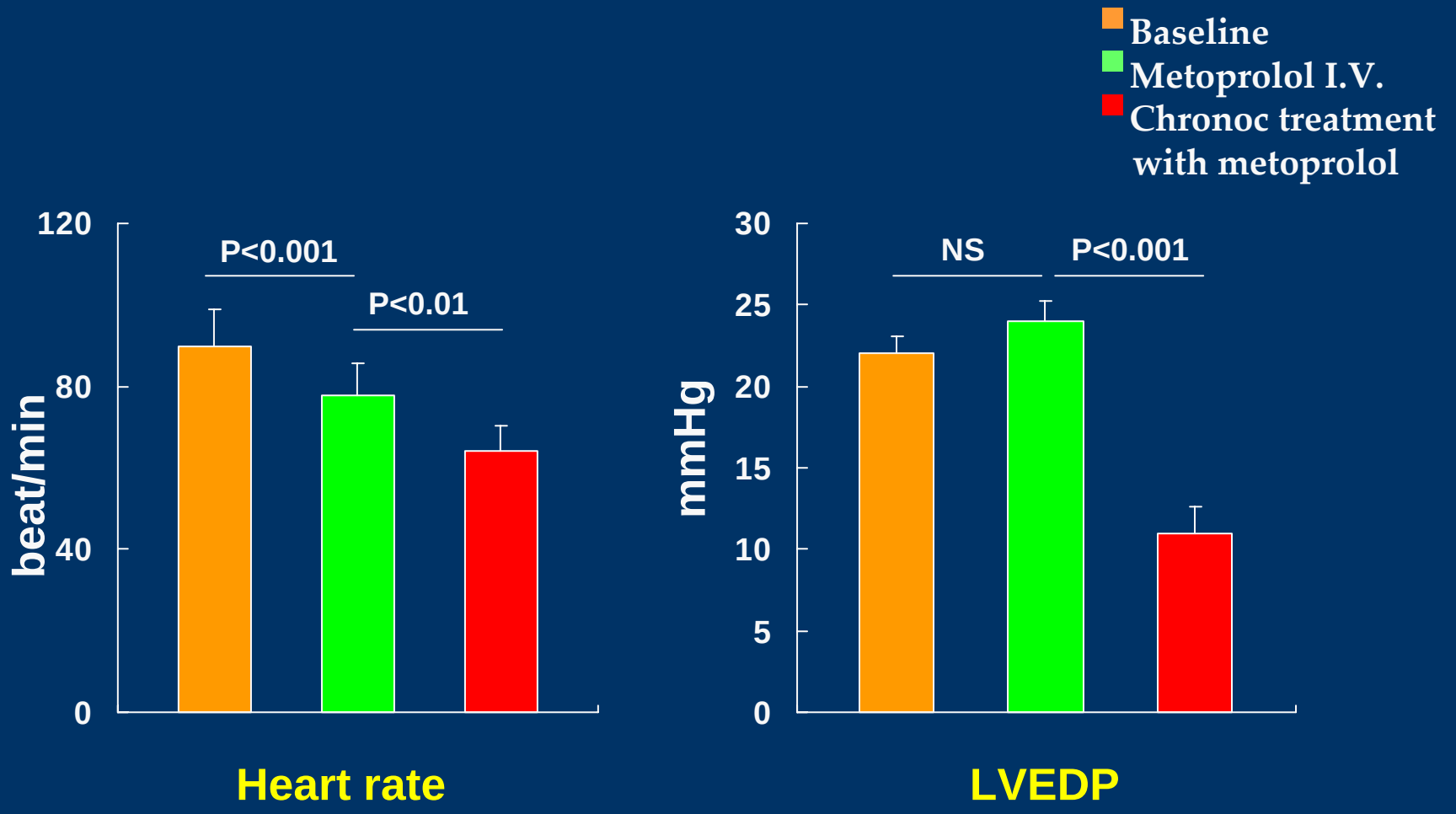
Acute hemodynamic effect of various β-blocking drugs



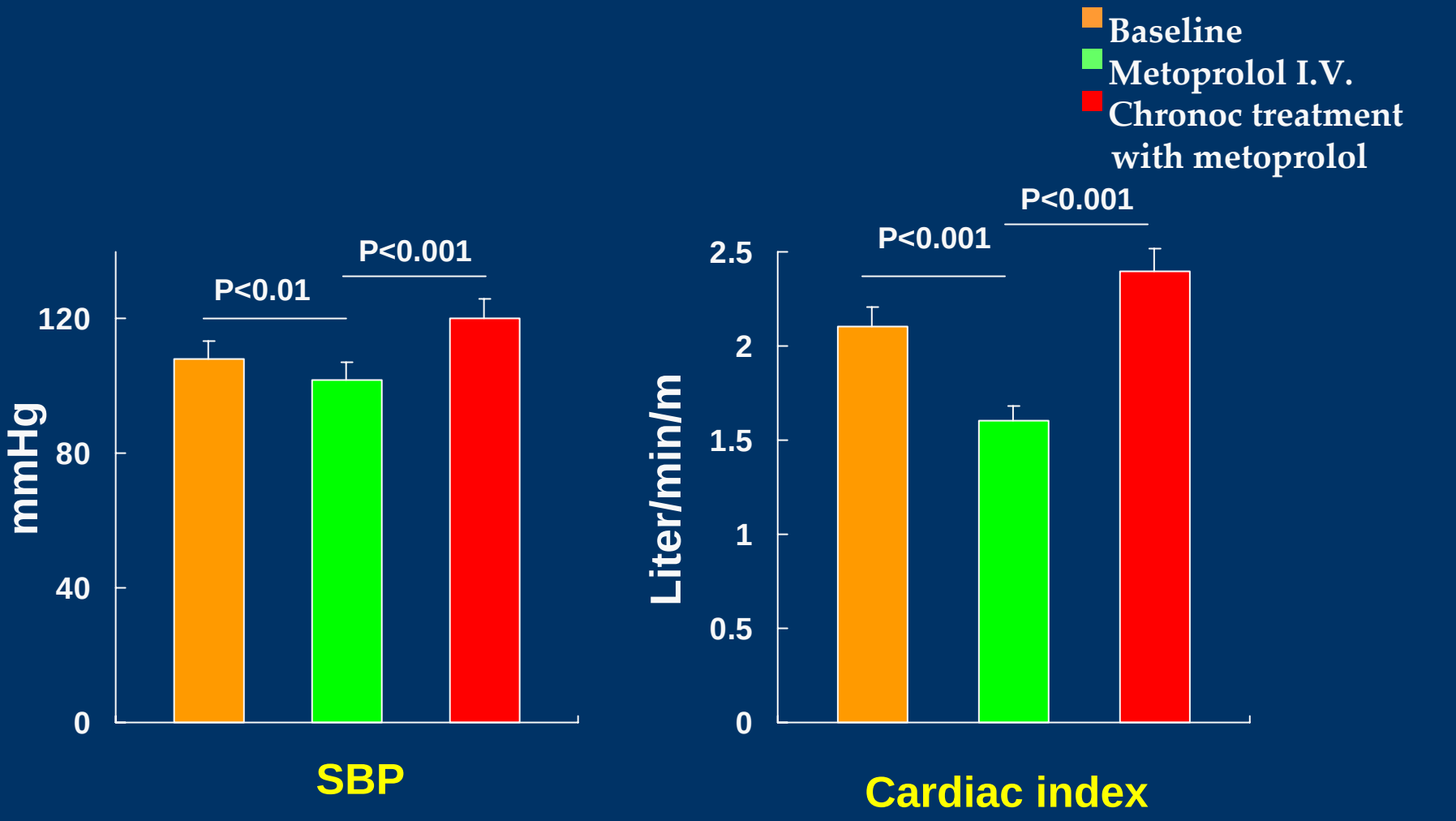
Measurements taken from peak effect data obtained up to 4 hours post dose

Bristow (1997)

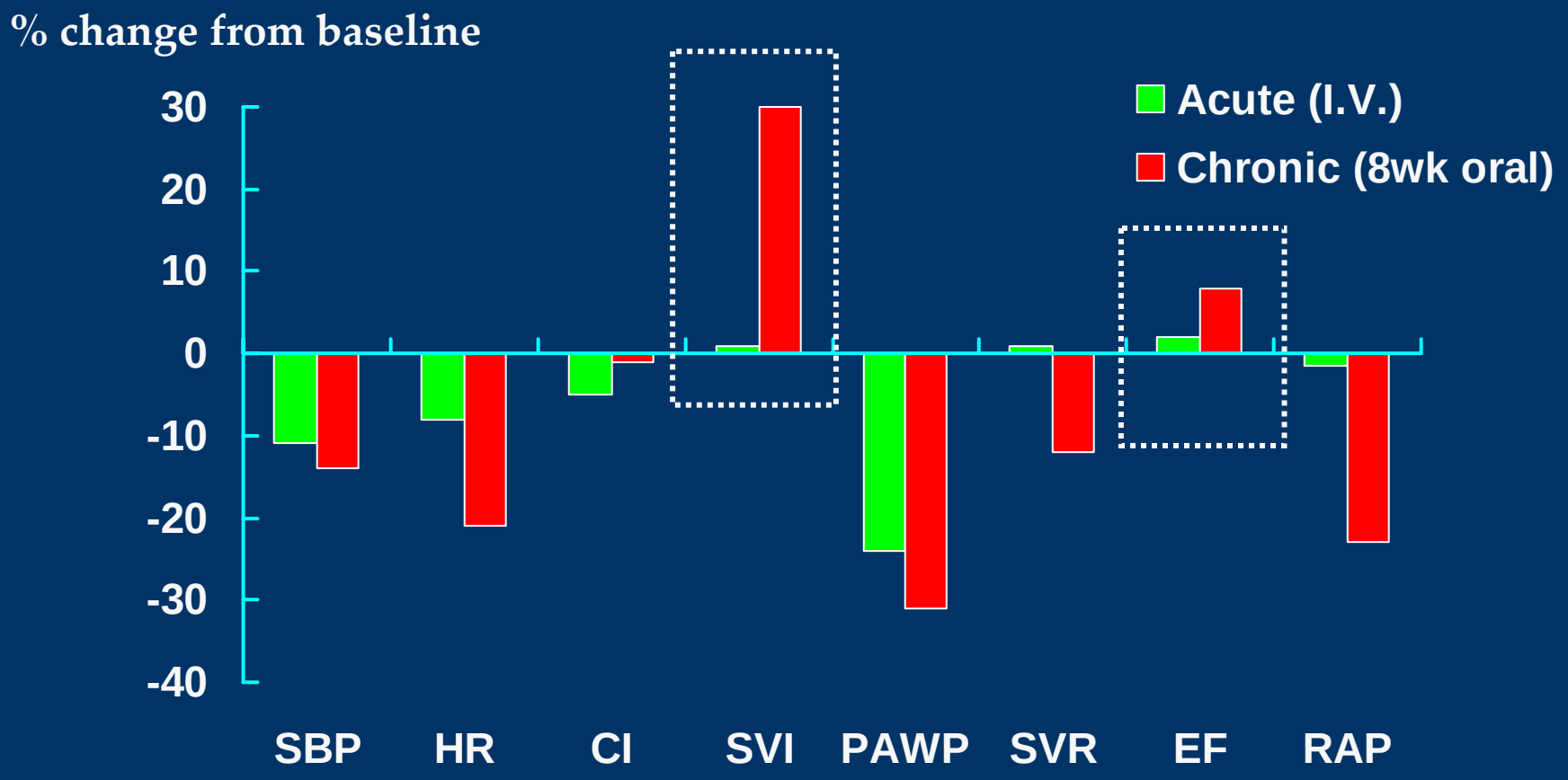
Acute and chronic hemodynamic effect of metoprolol in patient with DCM(1)



Acute and chronic hemodynamic effect of metoprolol in patient with DCM(2)



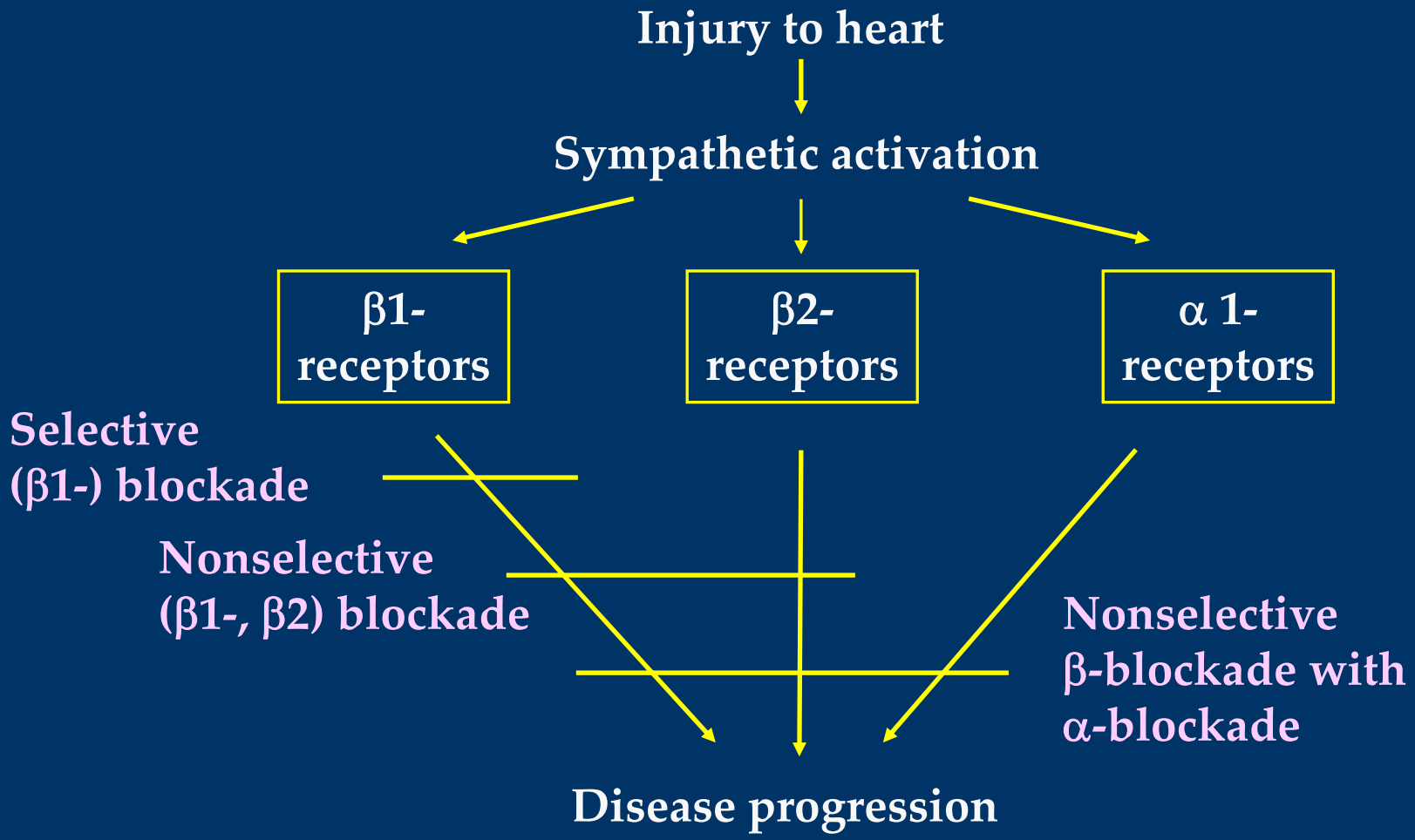
Acute and chronic hemodynamic effect of carvedilol in patient with CHF



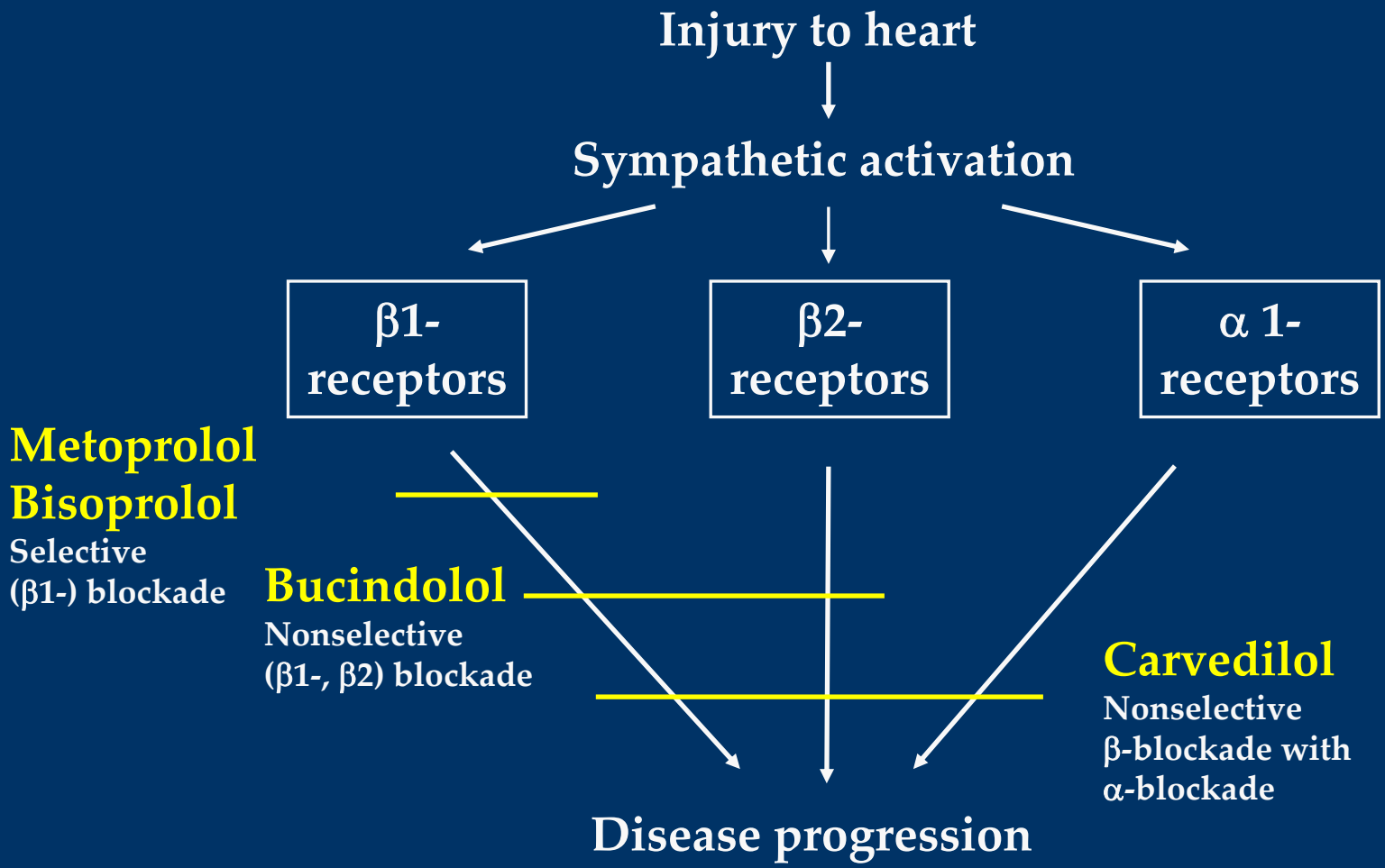
SVI: stroke volume index

Das Gupta (1990)

Sympathetic nervous system activation in heart failure



Blockade of sympathetic nervous system



Benefits of Beta-blocker in Heart Failure

Clinical Data

Beta-blocker, Historical Report

- **Waagstein et al (1975) :**

  59-yr-old women with dilated CMP

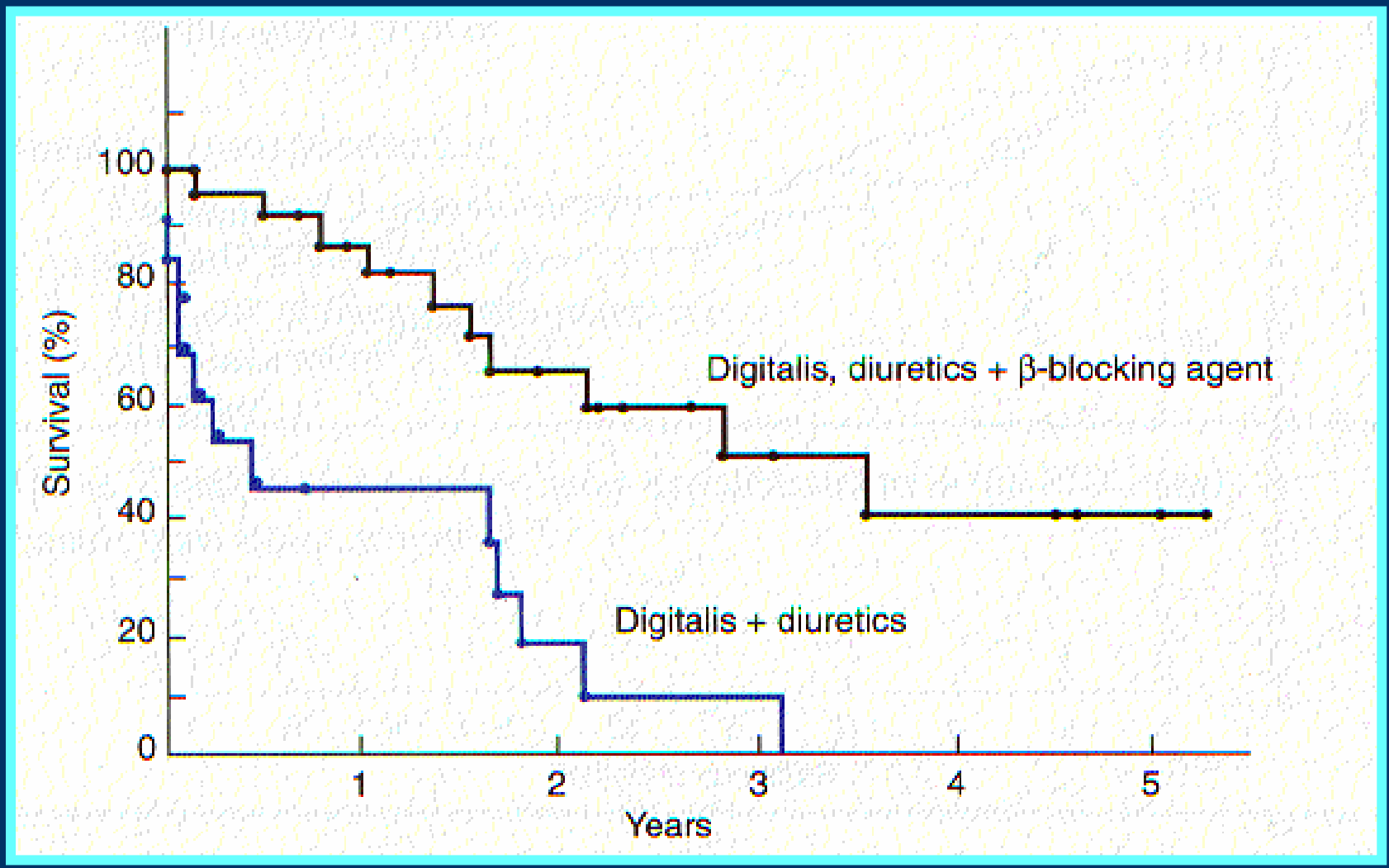
  tachycardia & acute pulmonary edema

  single bolus injection of practolol

  markedly improved heart failure

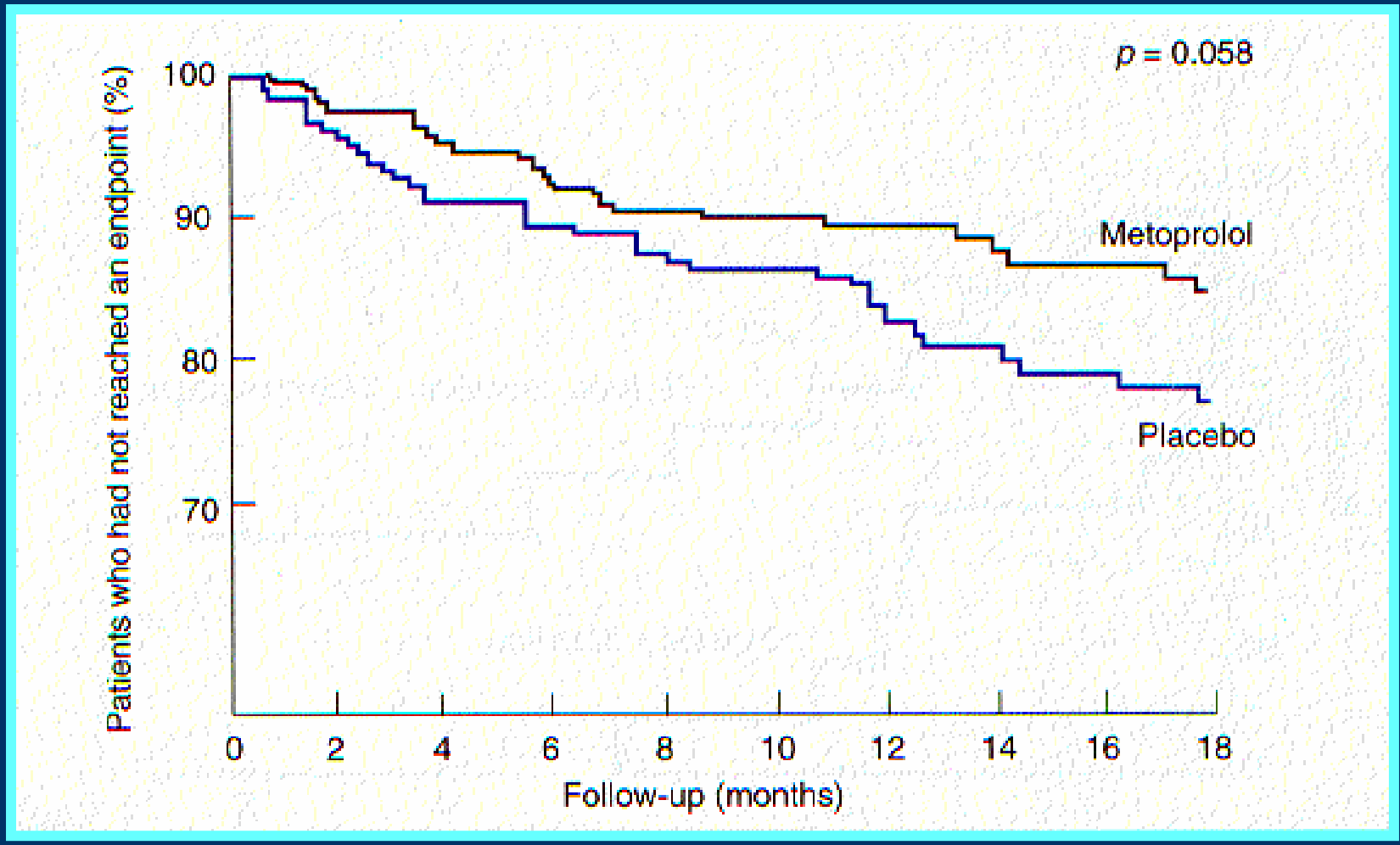
  at 82 yrs old, remained stable condition

Early reported clinical trial
-Swedberg et al 1979-

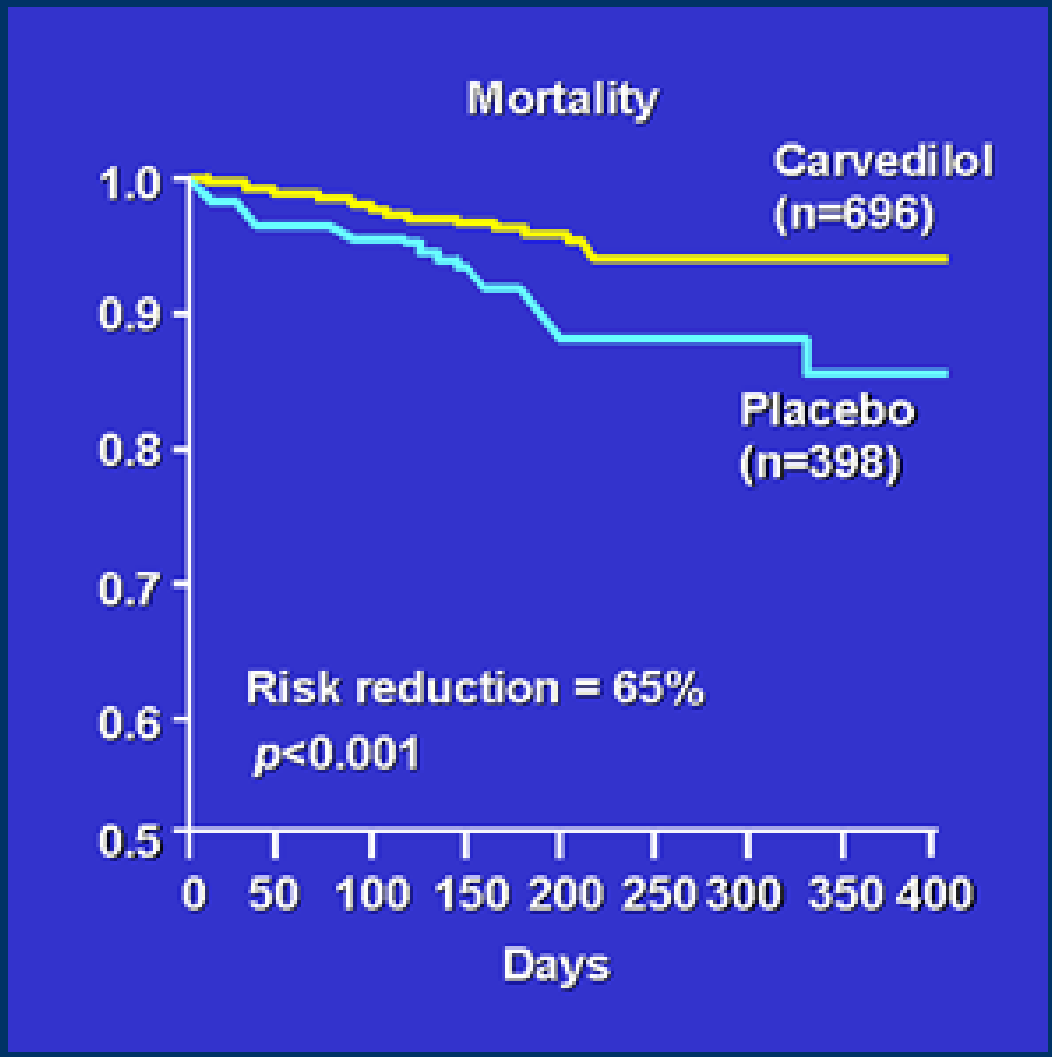


Metoprolol Dilated Cardiomyopathy (MDC) trial

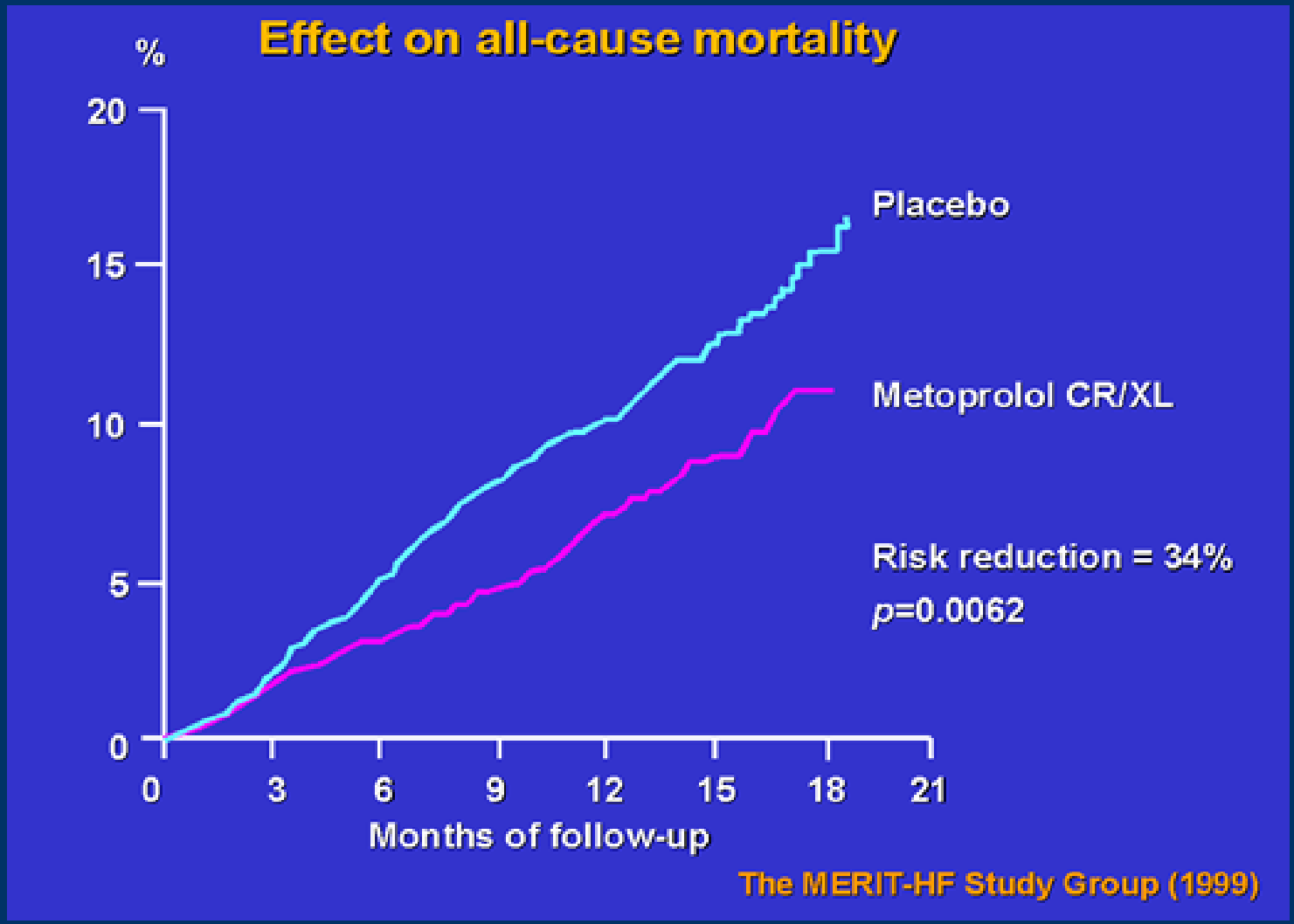
- Waagstein et al 1993-



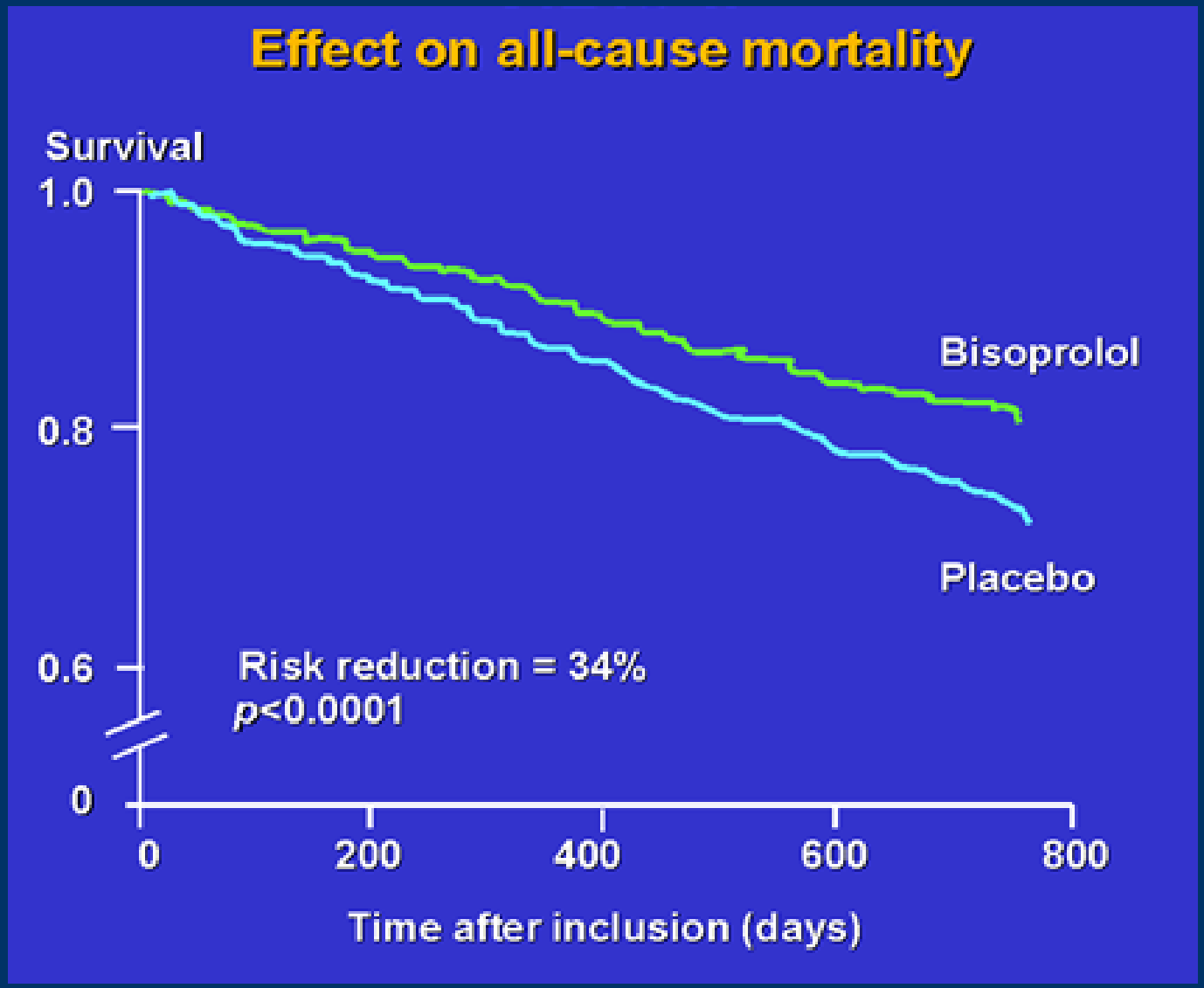
US Carvedilol Heart Failure Program



Metoprolol in CHF (MERIT-HF)



Bisoprolol in Heart Failure (CIBIS-2)



Beta-Blockers in CHF Trials

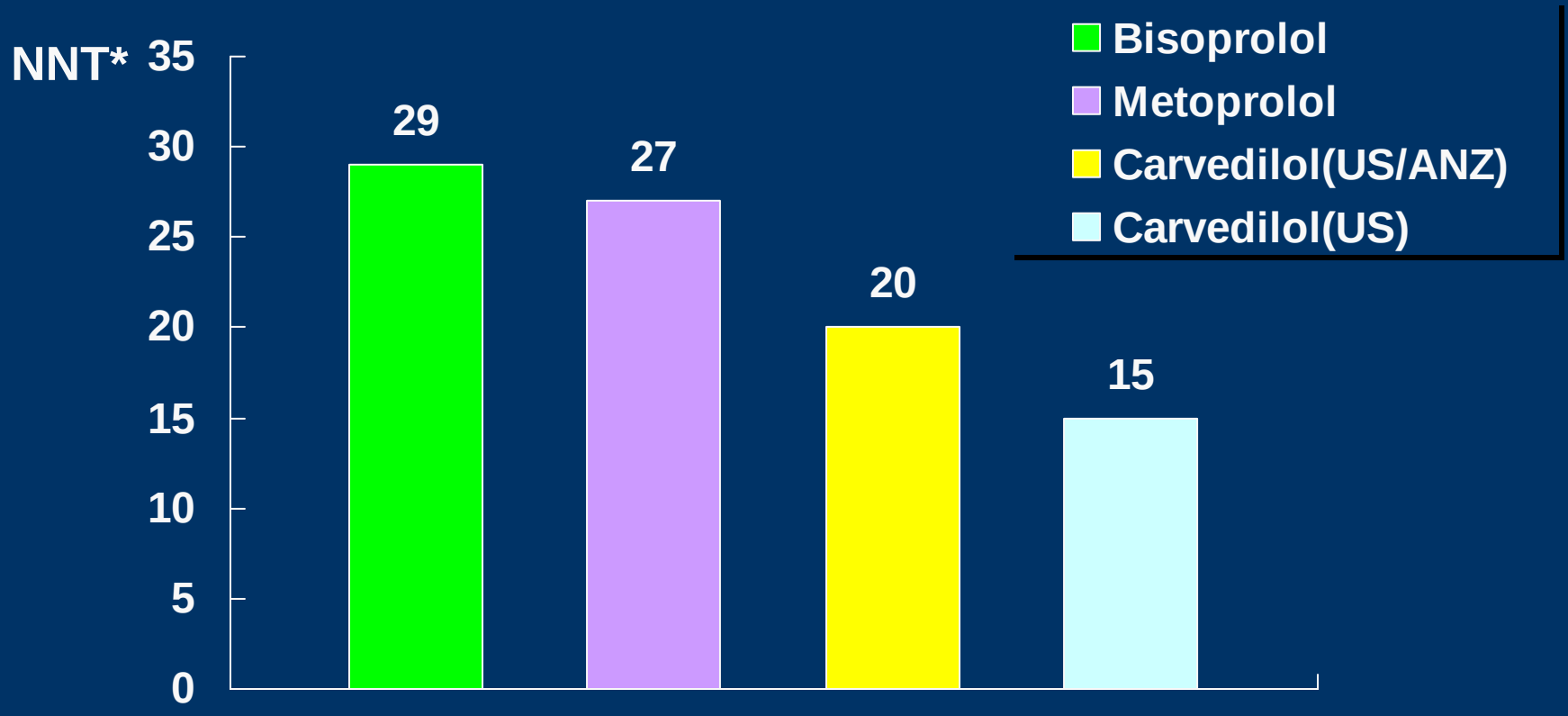
	Placebo mortality rate (annualized %)	β-blocker mortality rate (annualized %)	Risk reduction
US carvedilol	15.0*	6.0*	65%
CIBIS-2	13.2	8.8	34%
MERIT-HF	11.0	7.2	34%

All were double-blind, randomized, placebo controlled trials

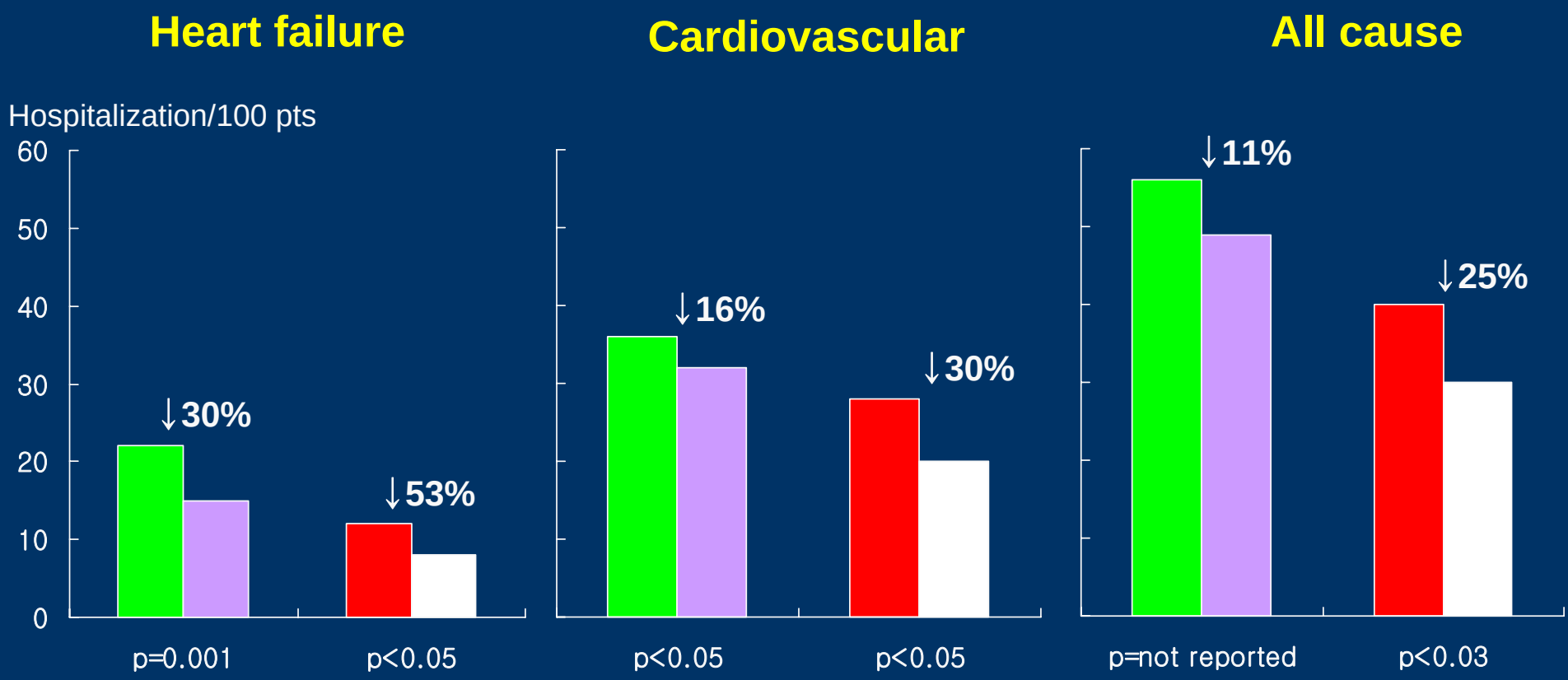
1 MERIT-HF Study Group. *Lancet.* 1999;353:2001–2007.
2 Packer M. *N Engl J Med.* 1996;334:1349–1355.
3 CIBIS-II Investigators. *Lancet.* 1999;353:9–13.

Beta-blocker in heart failure

Number needed to treat for one year to save one life*



Effect of β-blocker on hospitalization in heart failure



Placebo (n=2001)
Metop CR/XL (n=1990)
MERIT-HF (Goldstein, 1999)

Placebo (n=398)
Carvedilol (n=696)
US carvedilol (Fowler, 1996)

Tolerability

Tolerability of Beta blockade in HF: perception and reality

Perception to beta-blocker

- Difficult to initiate and uptitrate
- Multiple contraindications mean that very few eligible patients can be considered for the drug
- Only highly selected patients will be tolerate beta-blocker

Tolerability of Beta blockade in HF: perception and reality

Reality with beta-blocker

- Good tolerability in placebo-controlled randomized clinical trials (RCTs)
- Fewer patients discontinued beta blocker than placebo in RCTs
- RCT data supported by recent open-label evaluations in everyday clinical practice

Tolerability in Clinical Trials
% drug discontinuation c.f. ACE inihibitor

	Placebo	Active drug
US carvedilol	7.8	5.7
SOLVD	-	12.0

Tolerability in Clinical Trials
% drug discontinuation

		Av. Duration	Discontinuation rate		
	n	(months)	Placebo	β-blocker	RR
US carvedilol	1094	6	7.8	5.7	0.73
CIBIS-2	2647	15	15.0	15.0	1.00
MERIT-HF	3991	12	15.3	13.9	0.90

Tolerability in Clinical Trials
Major adverse events leading to discontinuation (%)

	Dizziness Worsened		Bradycardia		Worsened Heart failure	
	BB	Pla	BB	Pla	BB	Pla
US carvedilol	0.4	0	0.9	0	1.6	2.3
MERIT-HF	0.7	0.3	0.8	0.2	4.1	6.0

BB: beta-blocker group
Pla: placebo group

How?
Practical guideline

Checklist before initiation of β blockade in heart failure

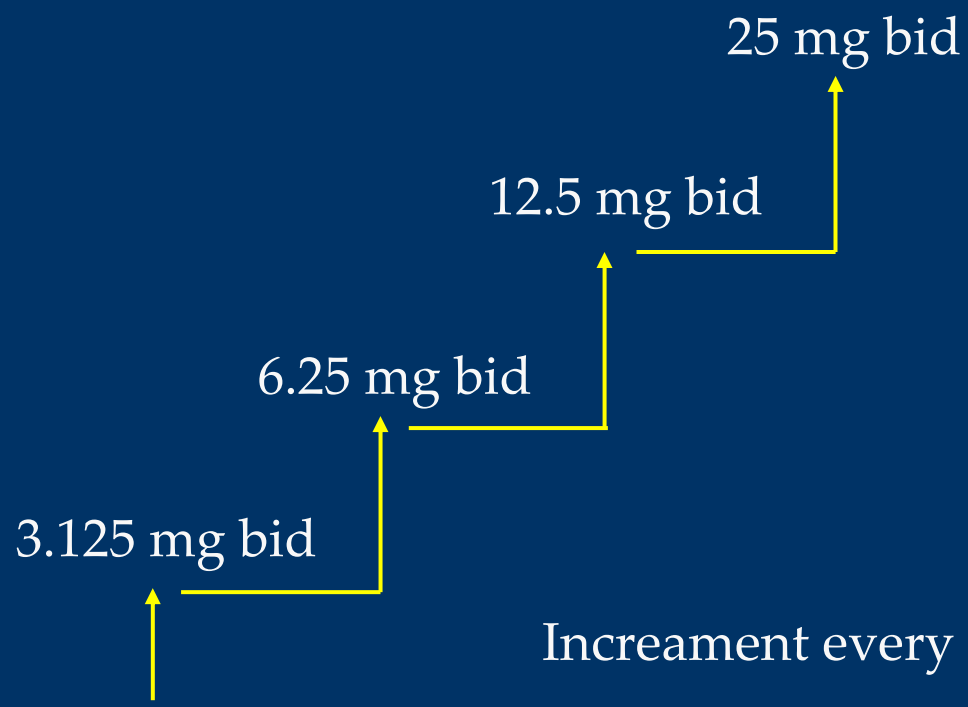
- NYHA class II-III symptoms
- Stabilized class IV symptoms (4 days)
- On diuretics+ACE inhibitor
- No contraindications
- No acute medical illness
- No physical evidence of fluid retention

Patients are ideal candidate for treatment with β blocker

- Edema free (Should be)
- Not receiving intravenous medications for heart failure (>4days)

Initiation and maintenance

Titration regimen for carvedilol



Increament every 2-4 weeks or more

Initiation and maintenance

Titration regimen for metoprolol CR/XL

Up to 200mg qd

Increament every 2 weeks or more*
* bradycardia: delayed titration

Class II 25mg
Class III 12.5mg early in the morning

Recommended monitoring during first 2-6 weeks of β blocker therapy

- Blood pressure
- Heart rate and heart rhythm
- Body weight

Remember

- Get the patient to dry weight *before* treatment
- Keep the patient at dry weight *during* treatment

Beta-blocker in practice guidelines

Asymptomatic LV dysfunction

Highly recommended with evidence in post MI pts
expert consensus in non-post MI pts

Post MI

BB

	HFSA	ACC/AHA	ESC
Recommendation	Recommended	I	I
Level of Evidence	B	B	B

BB

	HFSA	ACC/AHA	ESC
Recommendation	Recommended	I	
Level of Evidence	C	C	

Symptomatic LV dysfunction (LVEF<40%)

Highly recommended with strong evidence
add on ACE inhibitors

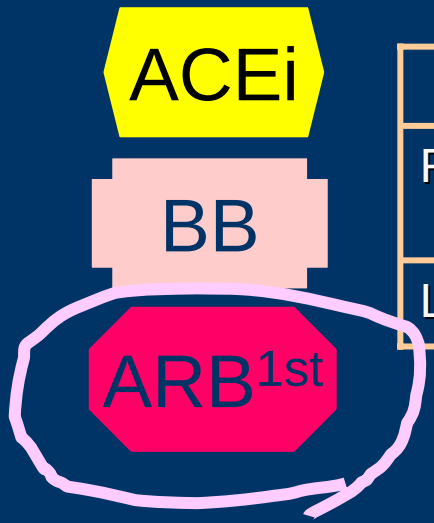
ACEi

BB

	HFSA	ACC/AHA	ESC
Recommendation	Recommended	I	I
Level of Evidence	A	A	A

Symptomatic LV dysfunction (LVEF<40%)

Not recommended triple blocking therapy



	HFSA	ACC/AHA	ESC
Recommendation	Not Recommended	IIb	NA
Level of Evidence	A	B	

Val-HEFT trial

Indications

- Nonsymptomatic LV dysfunction
- Post MI state
- Symptomatic LV systolic dysfunction
- Severe (NYHA class IV) HF…

- Etiology : ischemic CMP, dilated CMP, HT with LV systolic dysfunction
- cf. primary valvular heart disease: not indicated or cautionary

Beta-blocker in Severe HF

	Placebo mortality rate	Reduced mortality benefits	Proportion of patients with class IV heart failure
U.S. Carvedilol Program	11.1%	65%	3%
MERIT-HF	11.0%	34%	4%
CIBIS-II	13.2%	34%	16%
BEST	17.0%	10%	8%

Beta-blockers in severe HF

COPERNICUS trial

VOLUME 344 MAY 31, 2001 NUMBER 22

EFFECT OF CARVEDILOL ON SURVIVAL IN SEVERE CHRONIC HEART FAILURE

MILTON PACKER, M.D., ANDREW J.S. COATS, M.D., MICHAEL B. FOWLER, M.D., HUGO A. KATUS, M.D., HENRY KRUM, M.B., B.S., PH.D., PAUL MOHACSI, M.D., JEAN L. ROULEAU, M.D., MICHAL TENDERA, M.D., ALAIN CASTAIGNE, M.D., ELLEN B. ROECKER, PH.D., MELISSA K. SCHULTZ, M.S., AND DAVID L. DEMETS, PH.D., FOR THE CARVEDILOL PROSPECTIVE RANDOMIZED CUMULATIVE SURVIVAL STUDY GROUP*

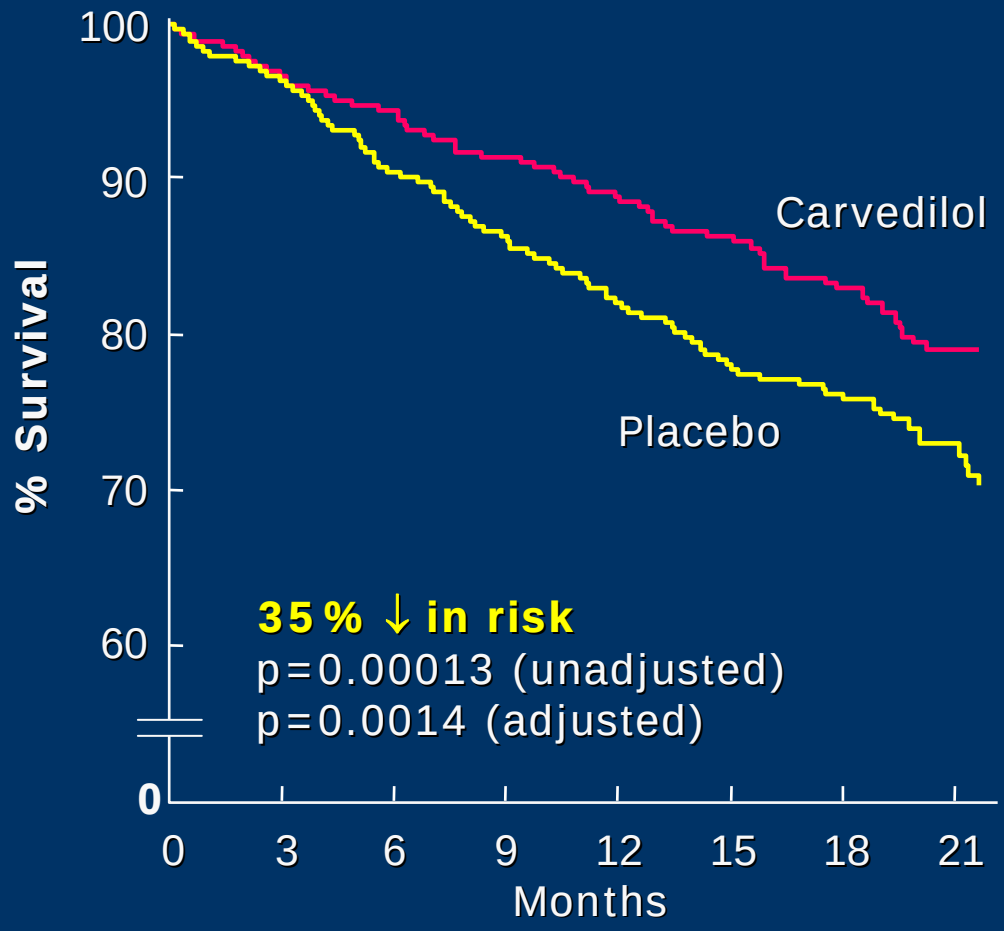
N Engl J Med 2001

COPERNICUS
Inclusion Criteria

- 2,289 patients with symptoms of heart failure at rest or minimal exertion with a LV ejection fraction < 25%, despite diuretics and an ACE inhibitor (± digitalis)
- Diuretics were optimized to achieve euvolemia
- No need for intensive care and no treatment with IV inotropic or IV vasodilator therapy within 4 days
- Patients were randomized to placebo or carvedilol (1:1) [target dose 25 mg b.i.d.] to up to 29 months

Beta-blockers in severe HF
COPERNICUS trial

All-Cause Mortality



The Sequence, Beta-blocker before ACEi

Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence

Results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III

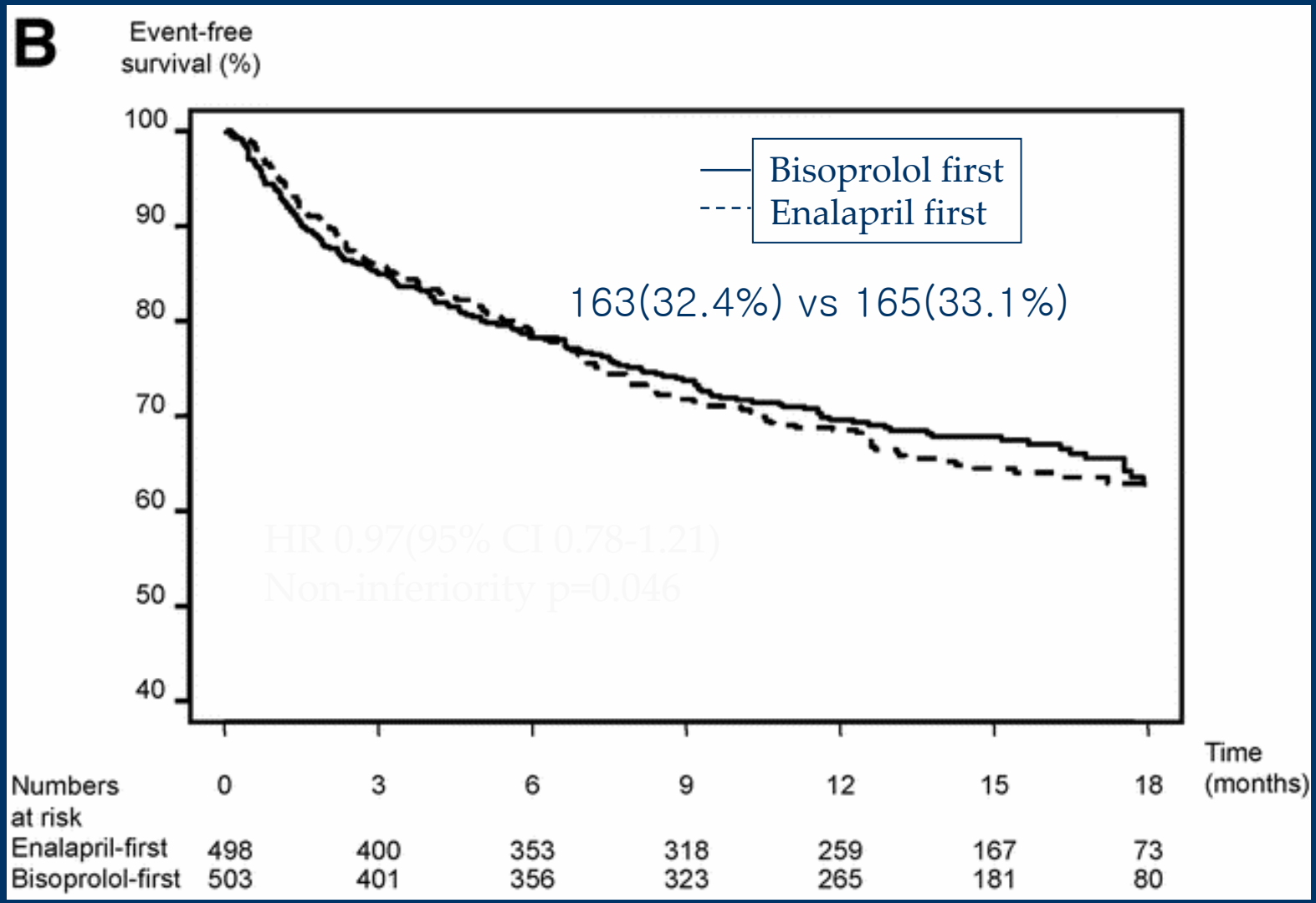
Hypothesis

Initiation of treatment in patients with CHF with the $Beta_1$-selective blocker bisoprolol (to which enalapril is subsequently added) is as effective and safe as a regimen beginning with the ACEi enalapril (to which bisoprolol subsequently added)

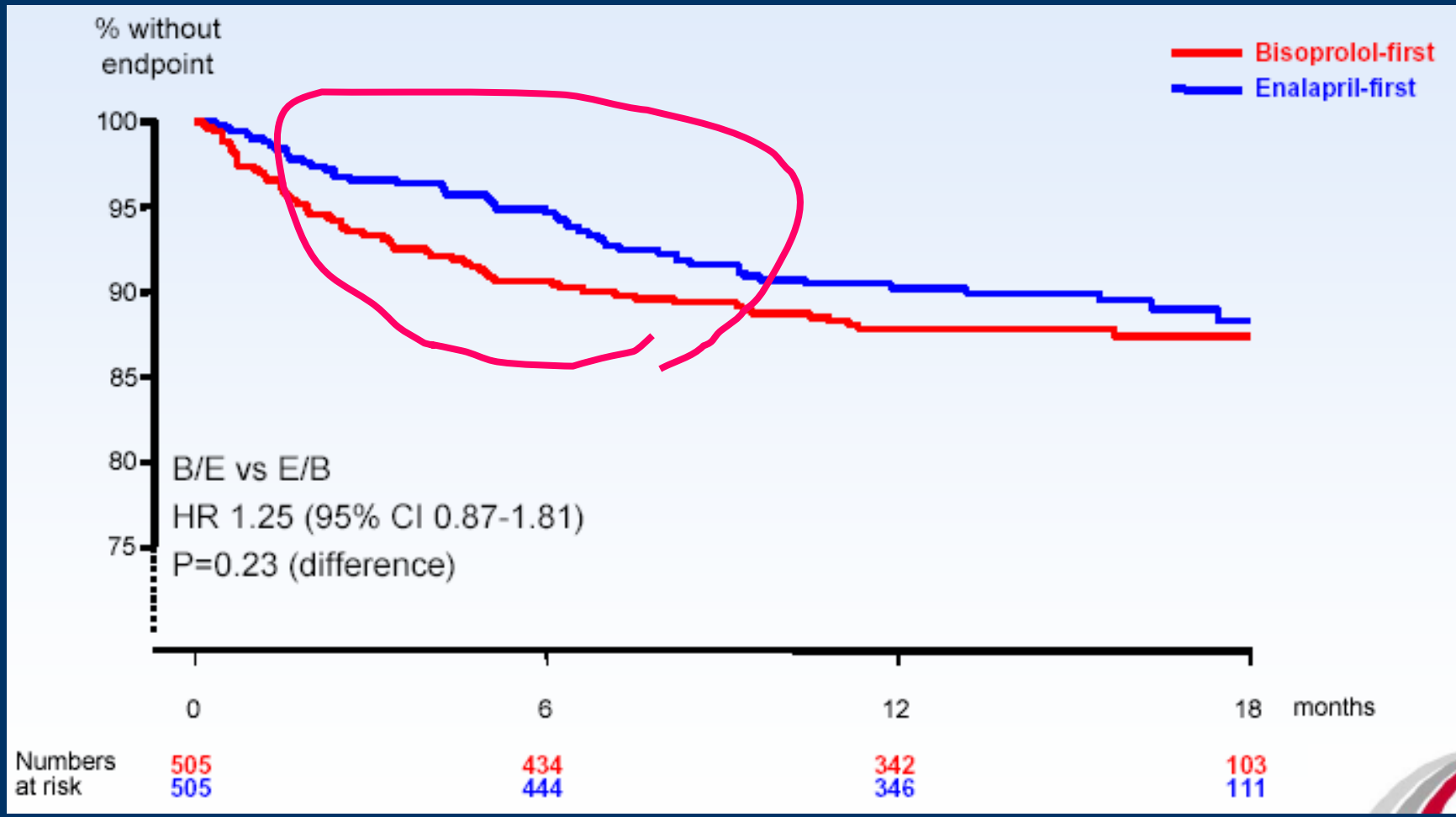
First null hypothesis

Initiation of therapy with bisoprolol is inferior in efficacy
to initiation of therapy with enalapril

Primary endpoint (per protocol)



But, Is it safe?
Aggravating Heart Failure



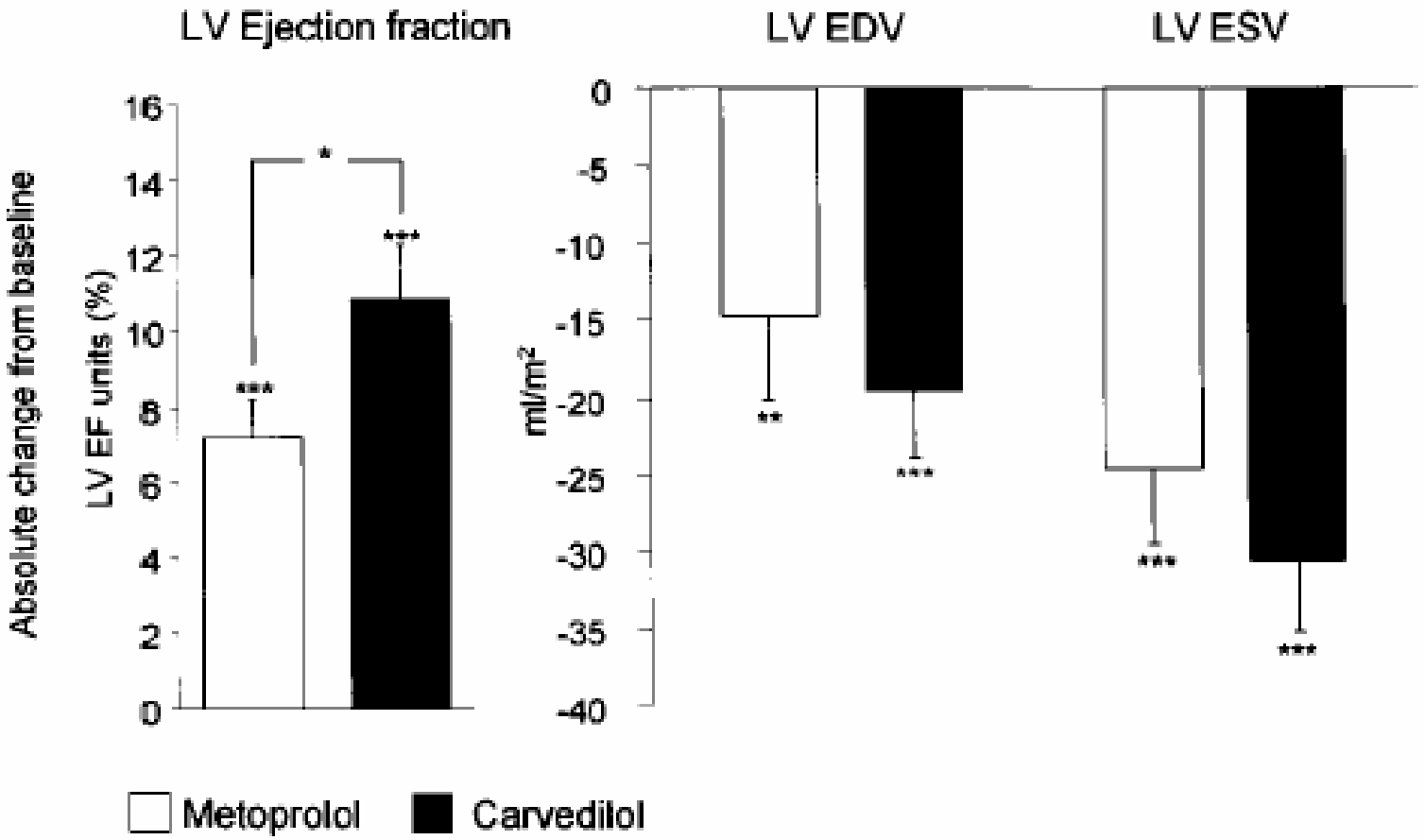
What?

Selective vs Non-selective Beta-blocker

Differential Effects of β-Blockers in Patients With Heart Failure

A Prospective, Randomized, Double-Blind Comparison of the Long-Term Effects of Metoprolol Versus Carvedilol

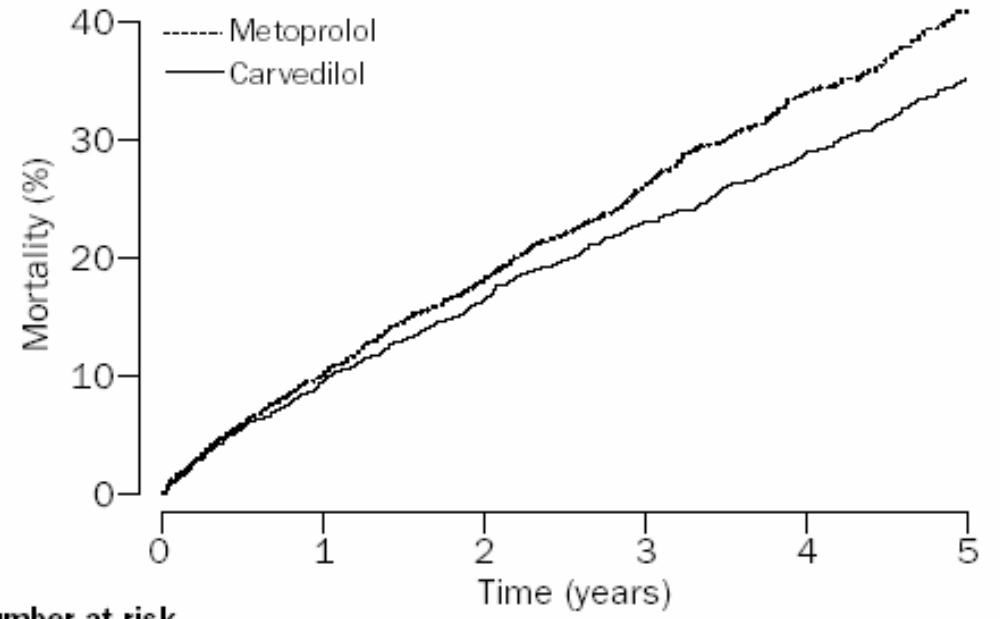
Metra M *Circulation 2000*



Articles

Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial

*Philip A Poole-Wilson, Karl Swedberg, John G F Cleland, Andrea Di Lenarda, Peter Hanrath, Michel Komajda, Jacobus Lubsen, Beatrix Lutiger, Marco Metra, Willem J Remme, Christian Torp-Pedersen, Armin Scherhag, Allan Skene, for the COMET investigators**



Number at risk

Carvedilol	1511	1366	1259	1155	1002	383
Metoprolol	1518	1359	1234	1105	933	352

Figure 2: **All-cause mortality**

Carvedilol 25mg bid vs
Metoprolol tartarate 50mg bid

34% vs 40% RR 17%

Heart rate in COMET

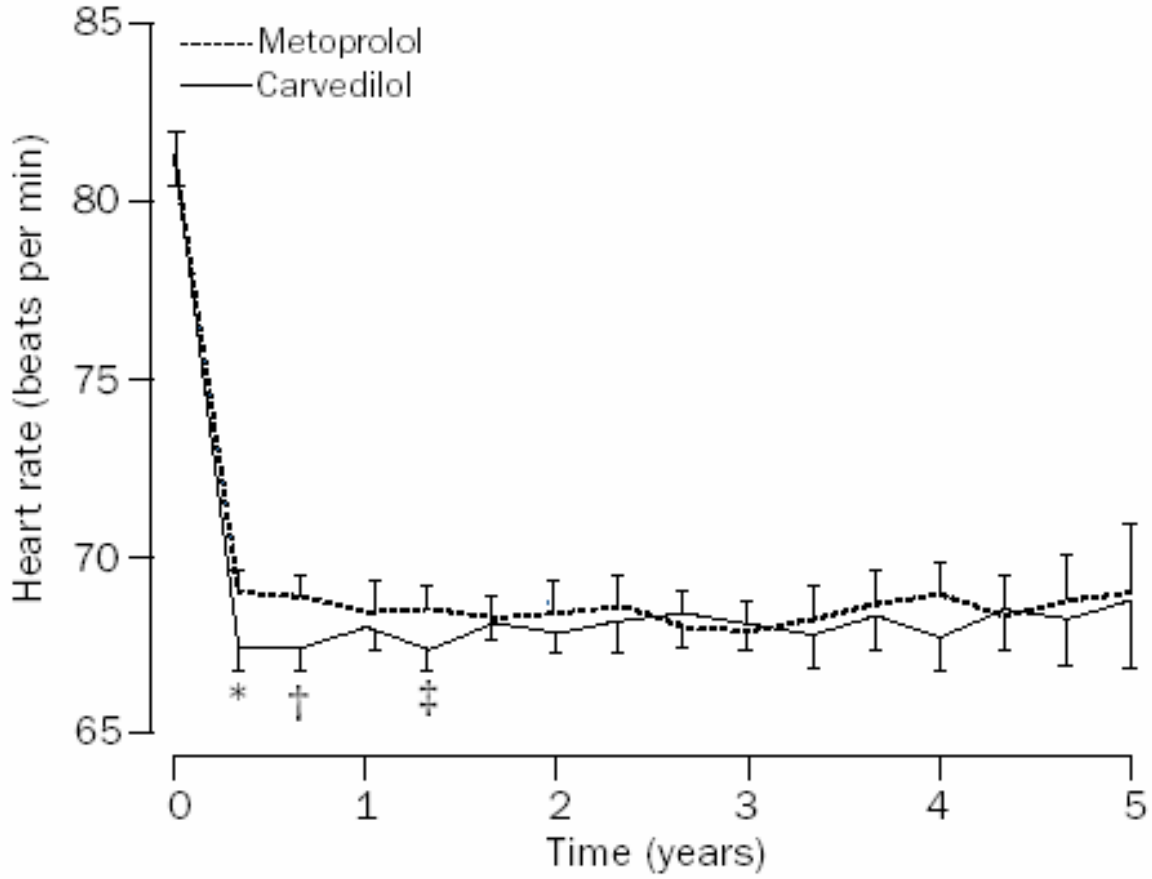
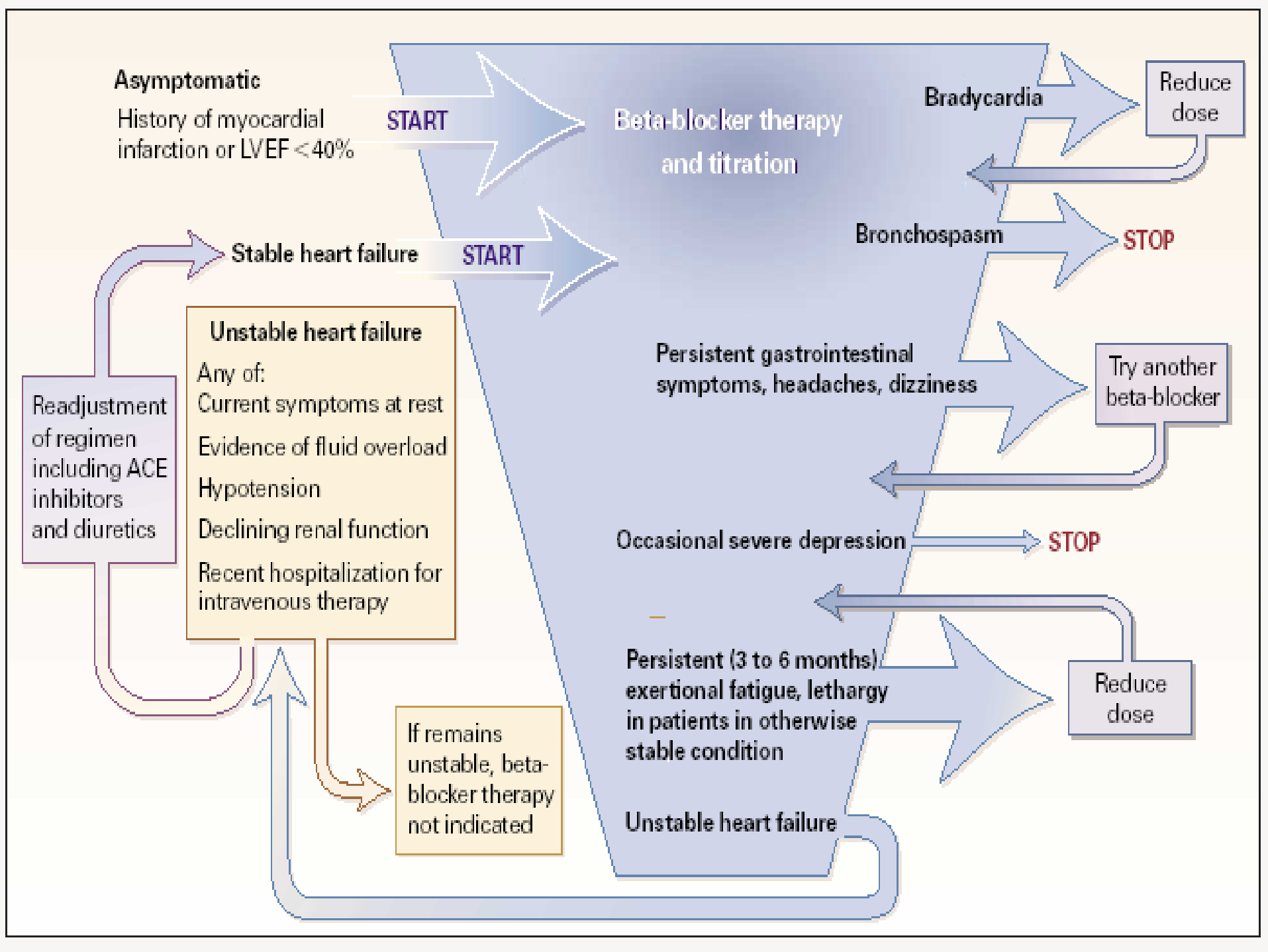


Figure 4: **Heart rate at each visit on treatment**

Error bars are 1 SE. *p=0·0022. †p=0·0034. ‡p=0·0040.


Asymptomatic
History of myocardial infarction or LVEF < 40%
START
Beta-blocker therapy and titration
Bradycardia
Reduce dose
Bronchospasm
STOP
Stable heart failure
START
Unstable heart failure
Any of:
Current symptoms at rest
Evidence of fluid overload
Hypotension
Declining renal function
Recent hospitalization for intravenous therapy
Readjustment of regimen including ACE inhibitors and diuretics
Persistent gastrointestinal symptoms, headaches, dizziness
Try another beta-blocker
Occasional severe depression
STOP
Persistent (3 to 6 months) exertional fatigue, lethargy in patients in otherwise stable condition
Reduce dose
If remains unstable, beta-blocker therapy not indicated
Unstable heart failure

Problem soliving
symptomatic hypotension

- Reconsider need for nitrate, CCB and other vasodiltors
- If no sign of congestion – reduce diuretics dose

Problem soliving
worsening symptom & sign

- Double dose of diuretics or/and ACEi
- Temporarily reduce beta-blocker dose if increasing diuretics dose not work
- Rewiew patient in 1-2 weeks: if no improvement, consult to specialist
- If serious deterioration,halve dose of beta-blocker
- Stop beta-blocker, rarely indicated

Problem soliving
Bradycardia

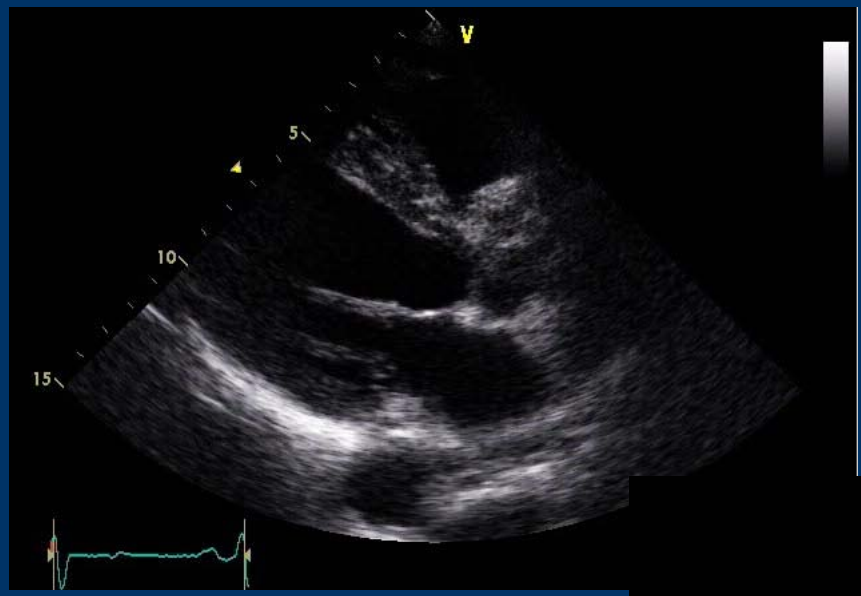
- ECG to exclude heart block
- Consider pacemaker back up if severe bradycardia or AV block, Sick sinus node
- Review need, reduce or stop of digoxin, amiodarone..
- Reduce beta-blocker, discontinuation rarely needed

Problem soliving
severe decompensated HF

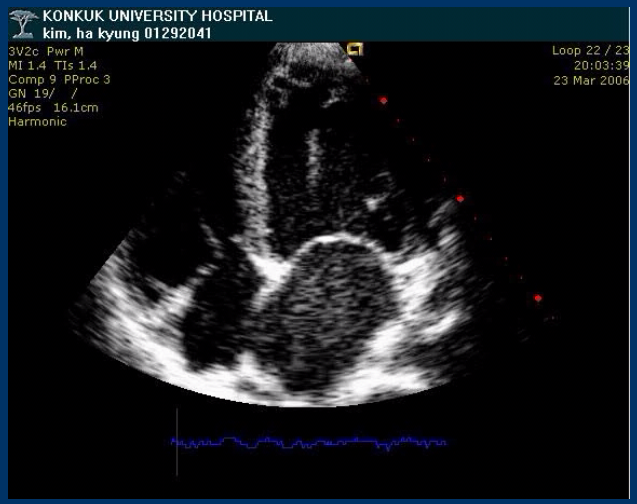
- Admission
- Discontinue beta-blocker, inotropic support
- Levosimendan, mirlinone

Summary

- Over 10,000 patients evaluated in long-term placebo-controlled clinical trials
- Improvement in cardiac function and symptoms: equivocal effects on exercise tolerance
- Decrease in all-cause mortality by 30-35%($p<0.0001$);effect shown in 3 indivisual trials- US carvedilol, CIBIS-2, MERIT-HF
- Decrease in combined risk of death and hospitalization by 35-40%($p<0.001$); effect shown in 6 indivisual trials
- Effect shown in patients arleady receiving ACE inhibitors



4 months after carvedilol treatment



At admission