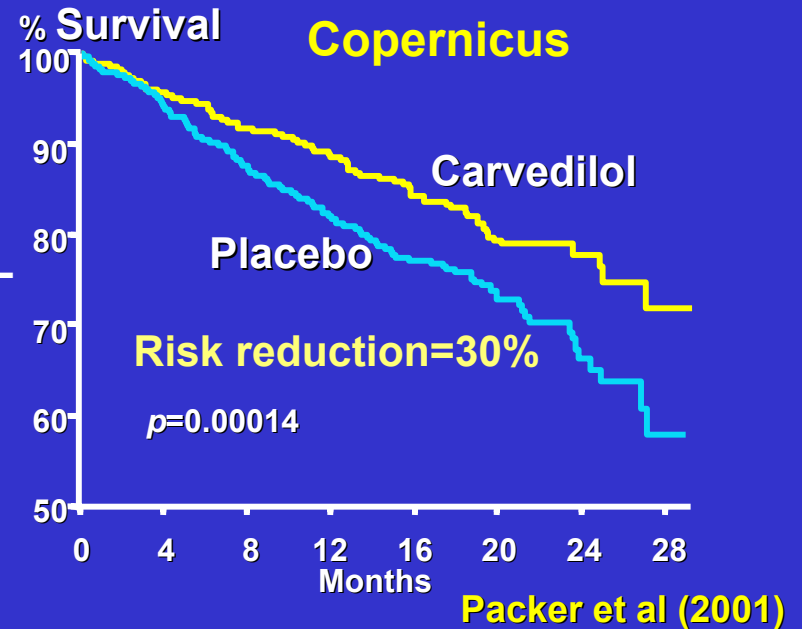
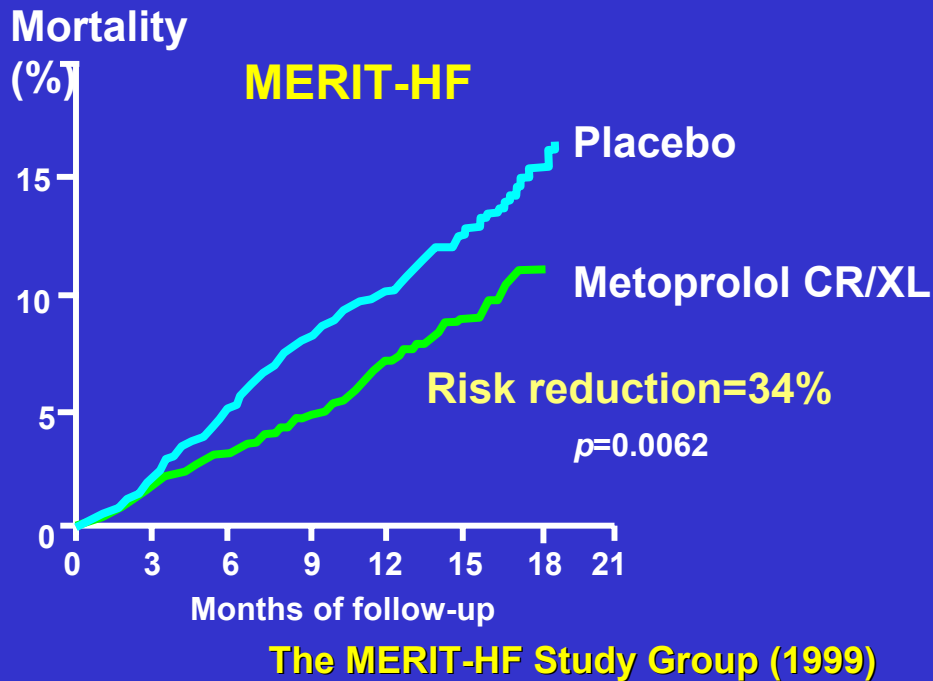
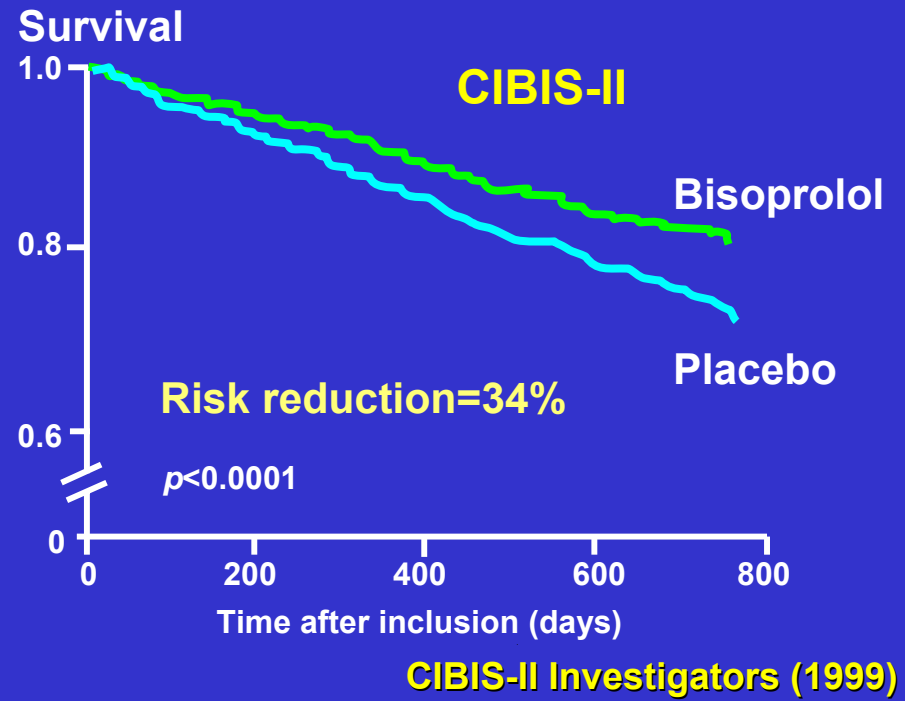
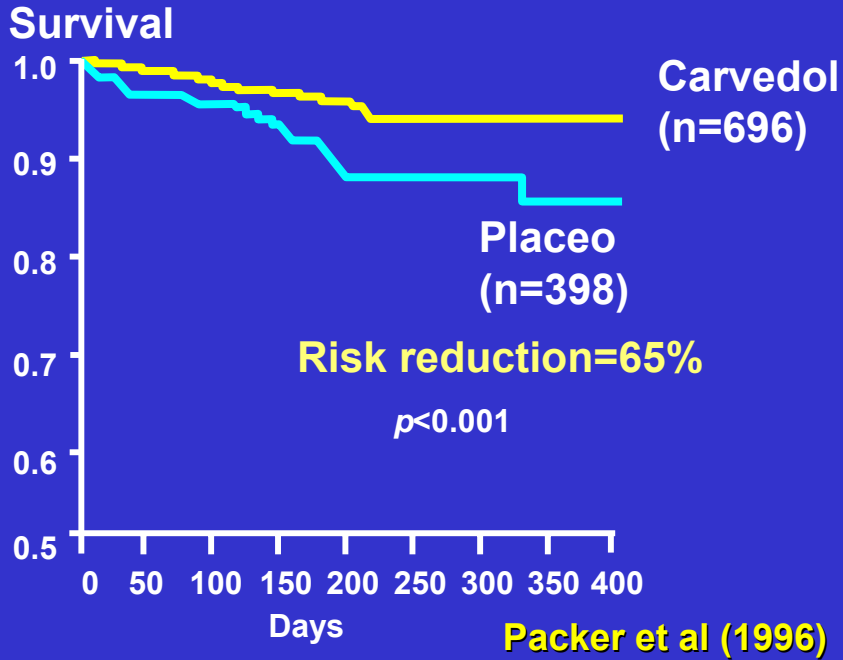


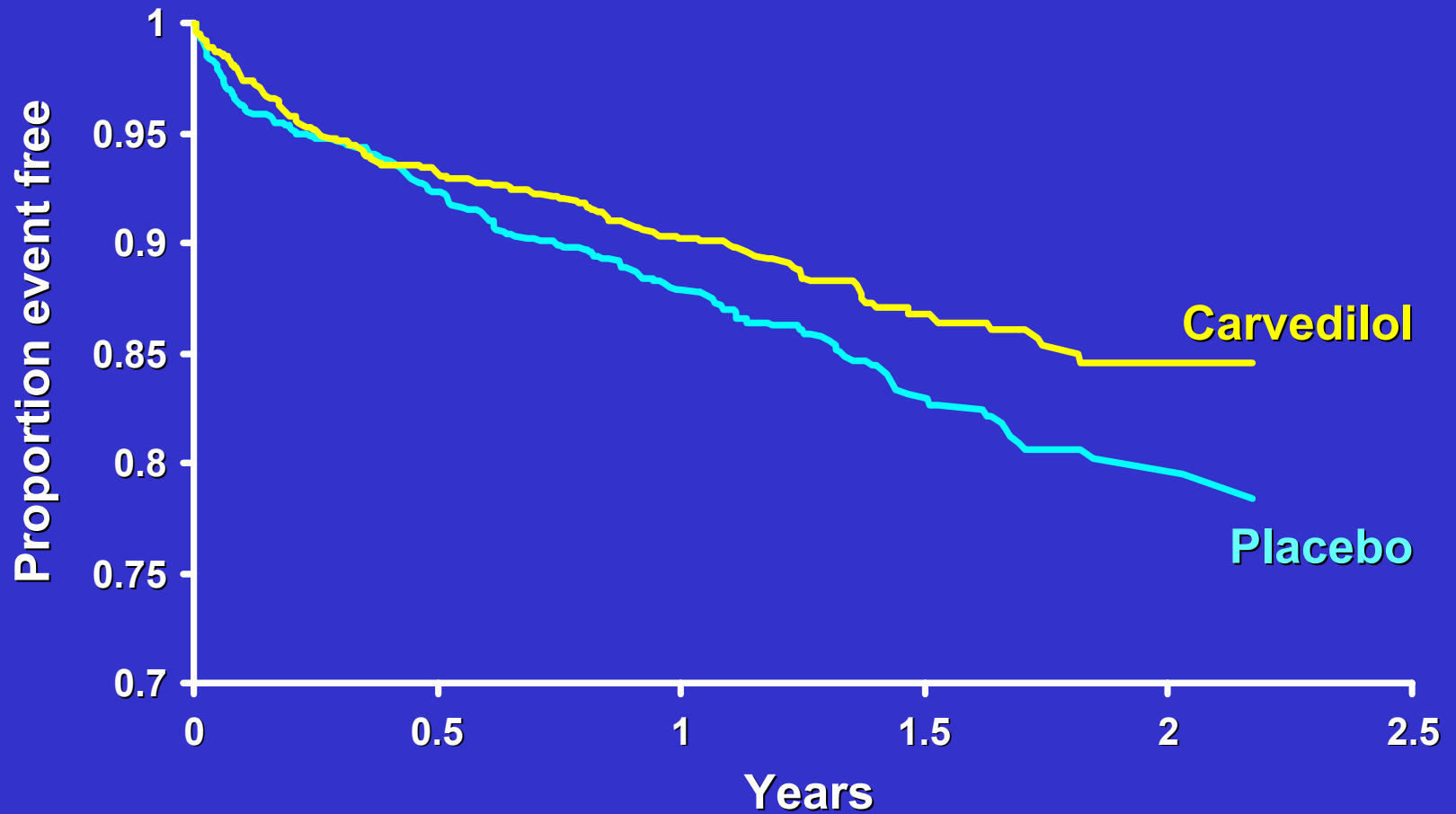
Beta-blockade in heart failure

- Beta-blocking agents are recommended for the treatment of **all** patients with stable mild, moderate and severe heart failure from ischemic and non-ischemic originon standard treatment including ACE inhibition and diuretics .. (level of evidence A, strength of recommendation 1)
- Beta-blocking agents are recommended in patients with LV dysfunction with/without heart failure post-MI for survival benefit (level B, recommendation 1)

US Carvedilol Programme

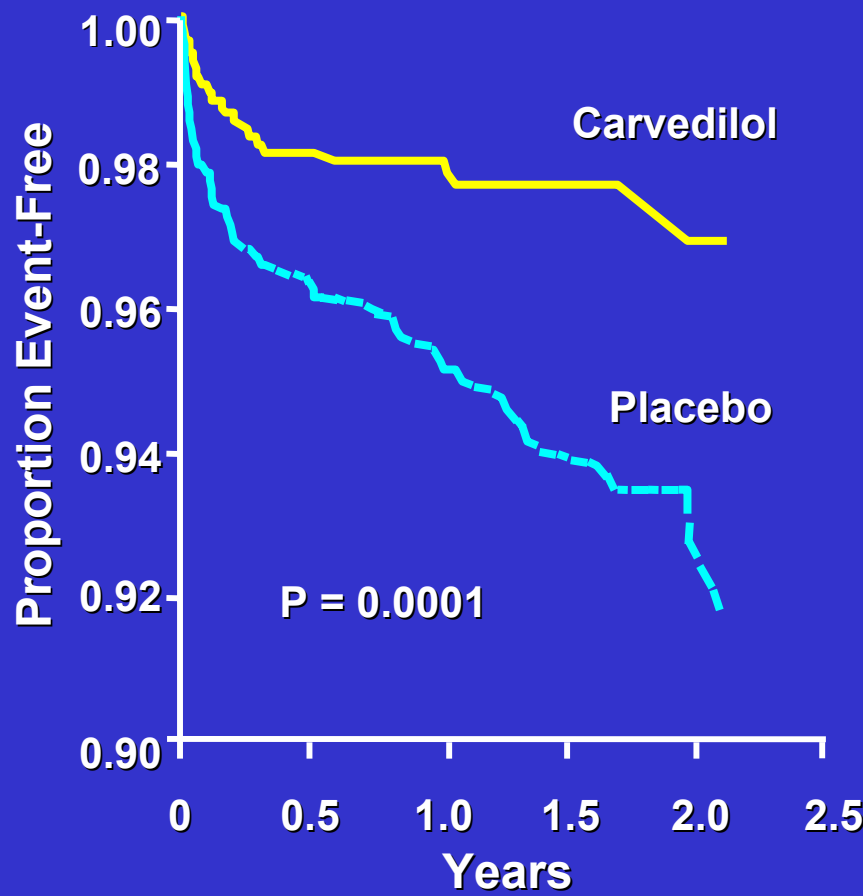


CAPRICORN - All Cause Mortality

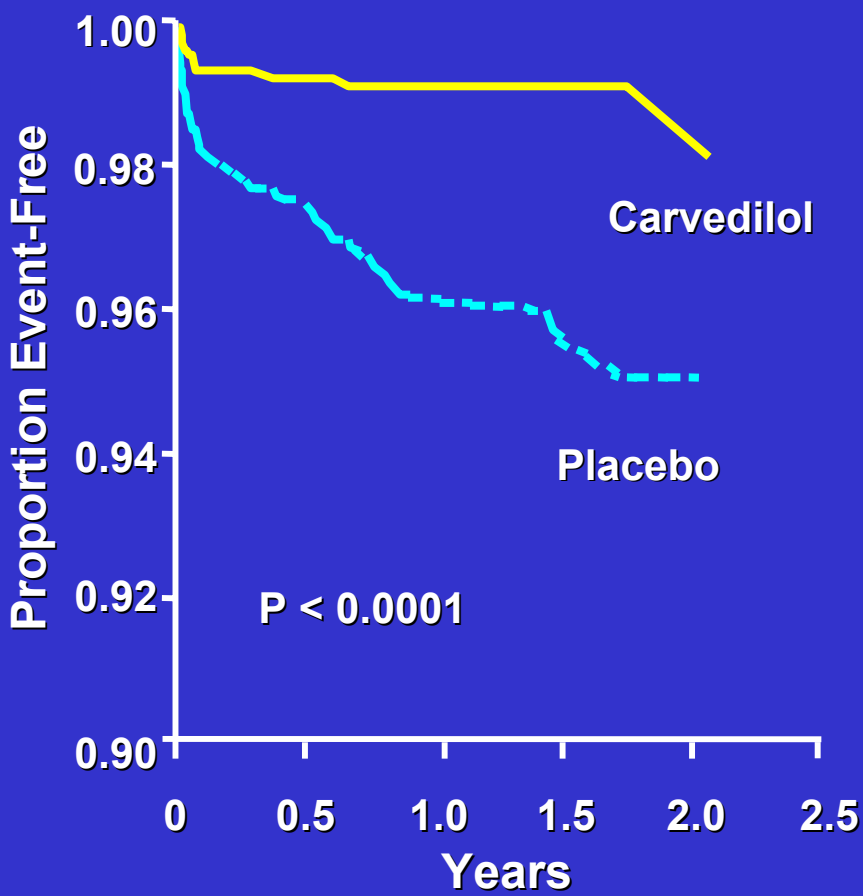


CAPRICORN Time to First Cardiac Arrhythmia

Atrial Flutter or Atrial Fibrillation

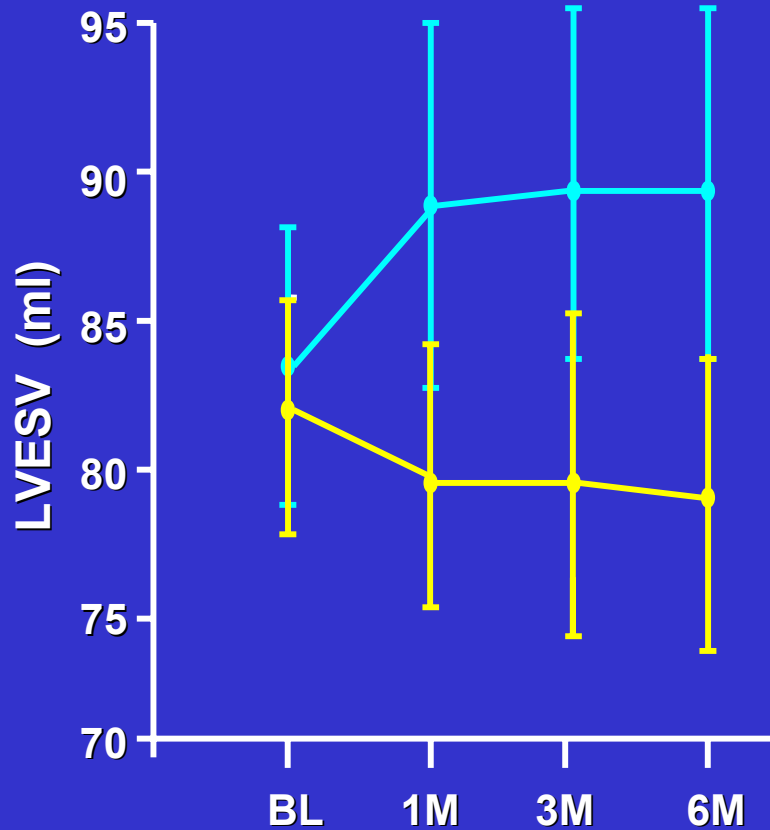


Ventricular Tachycardia or Ventricular Fibrillation

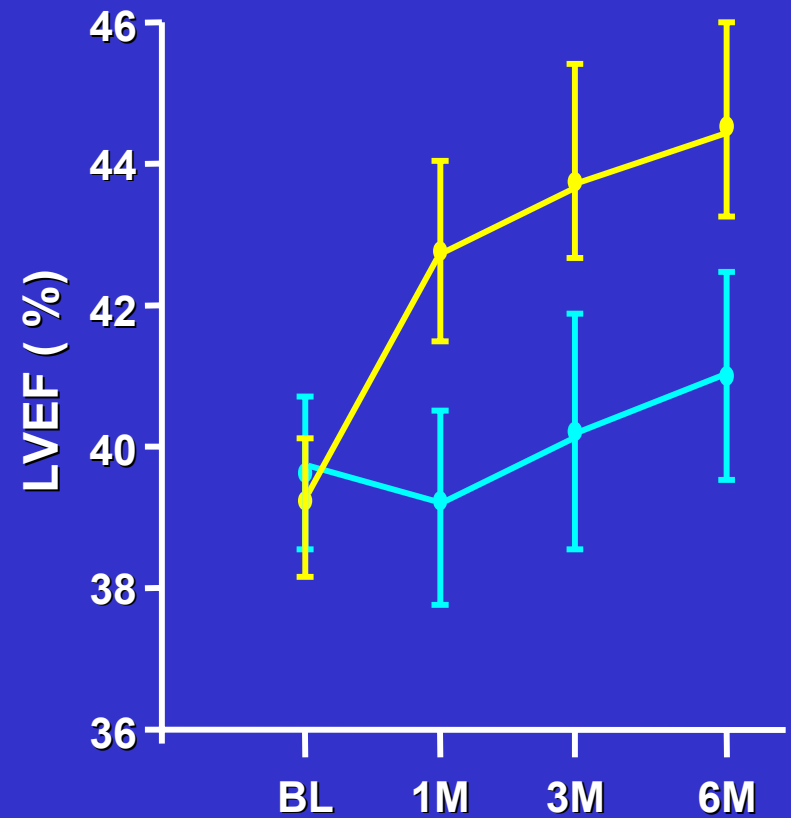


Remodelling in CAPRICORN

$\Delta = - 9.2 \text{ ml}$
 $P = 0.031$



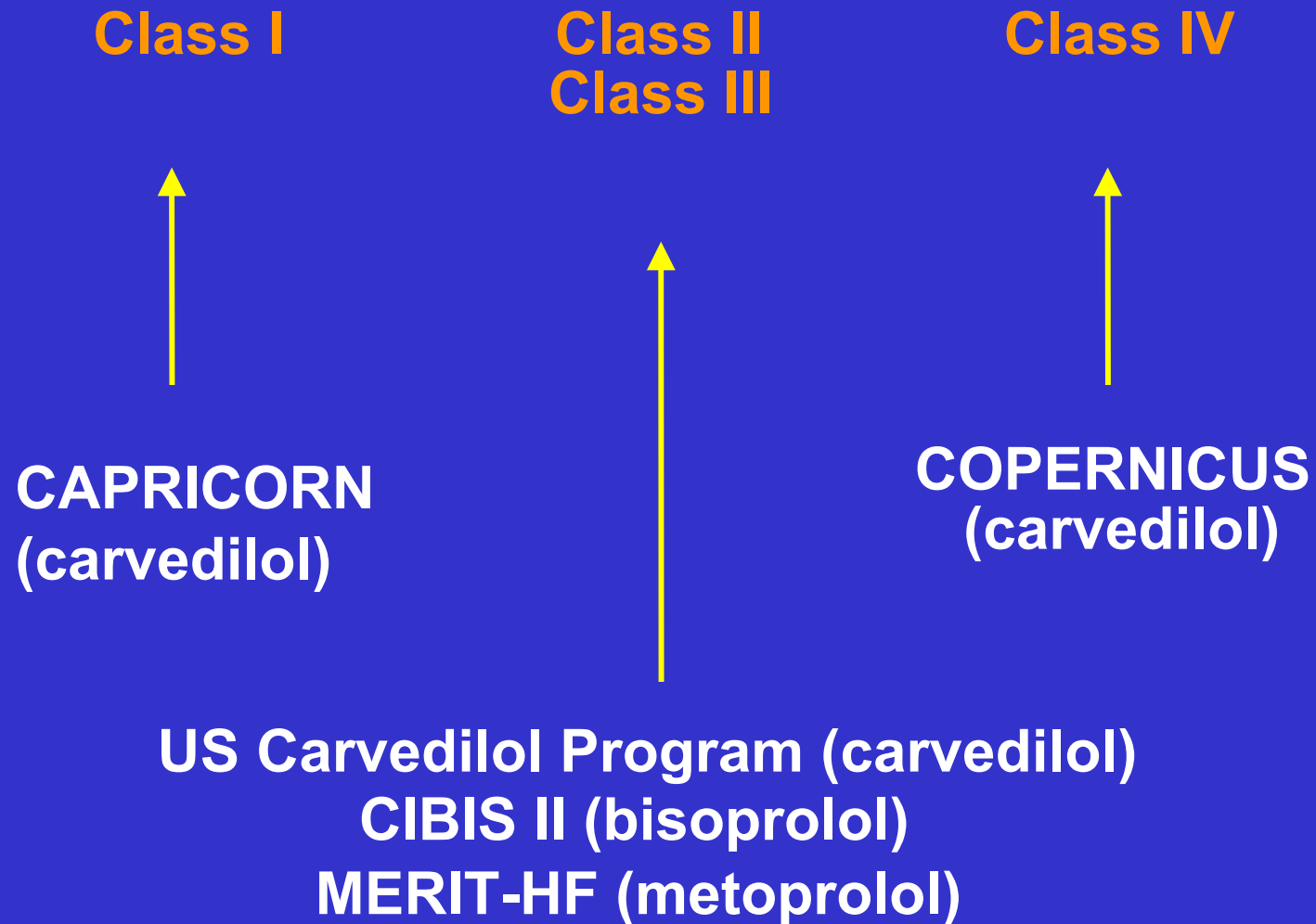
$\Delta = + 3.9\%$
 $P = 0.0037$



—●— Carvedilol —●— Placebo

Doughty R et al. In press

Beta-blockade –survival benefit in all class CHF

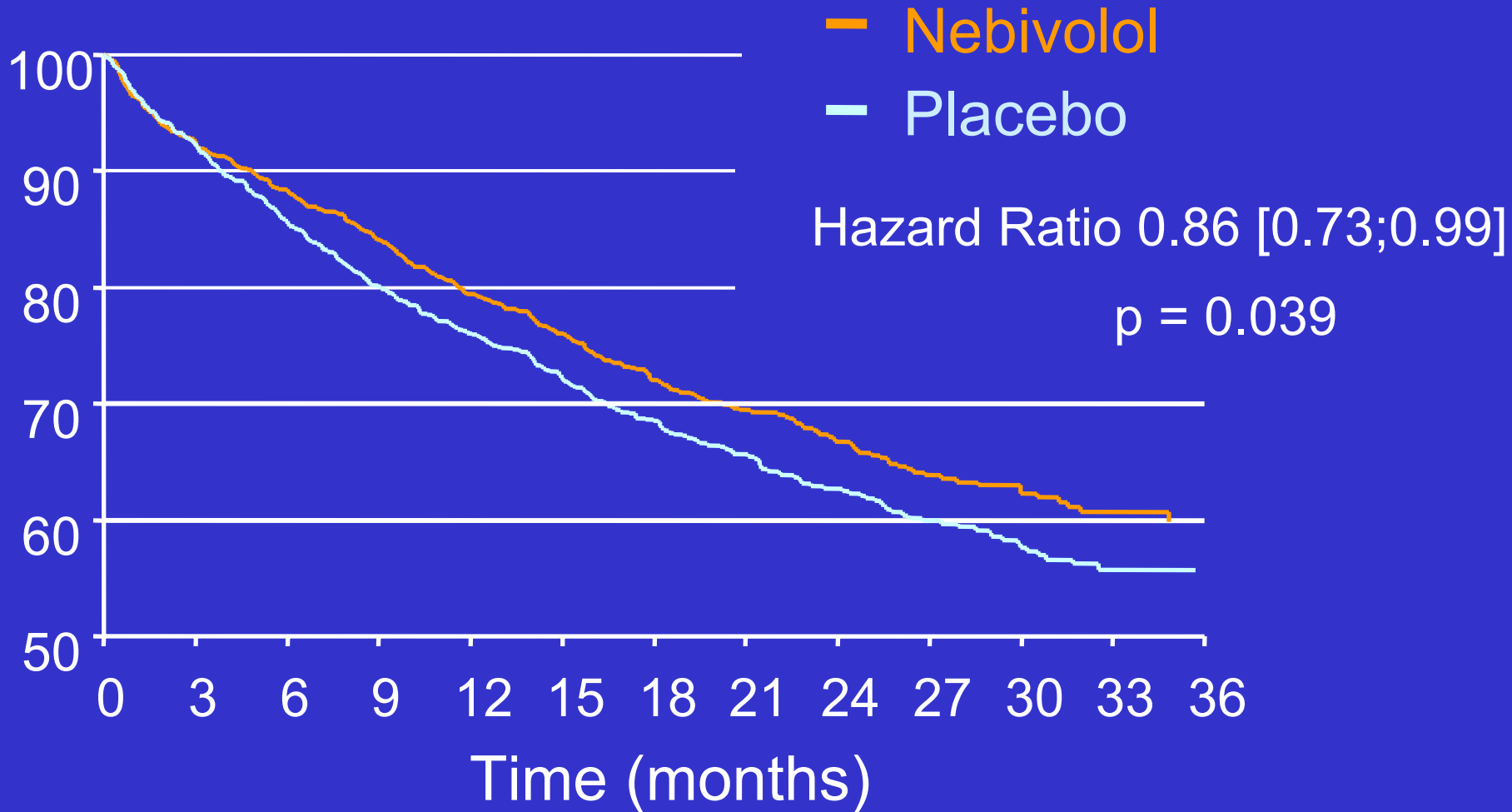


Remaining issues

- **Elderly**
- **Initiation of HF therapy : ACE inhibitor always first?**
- **Are all beta-blockers equally effective?**
- **Dose**

SENIORS trial : average age 76 yrs

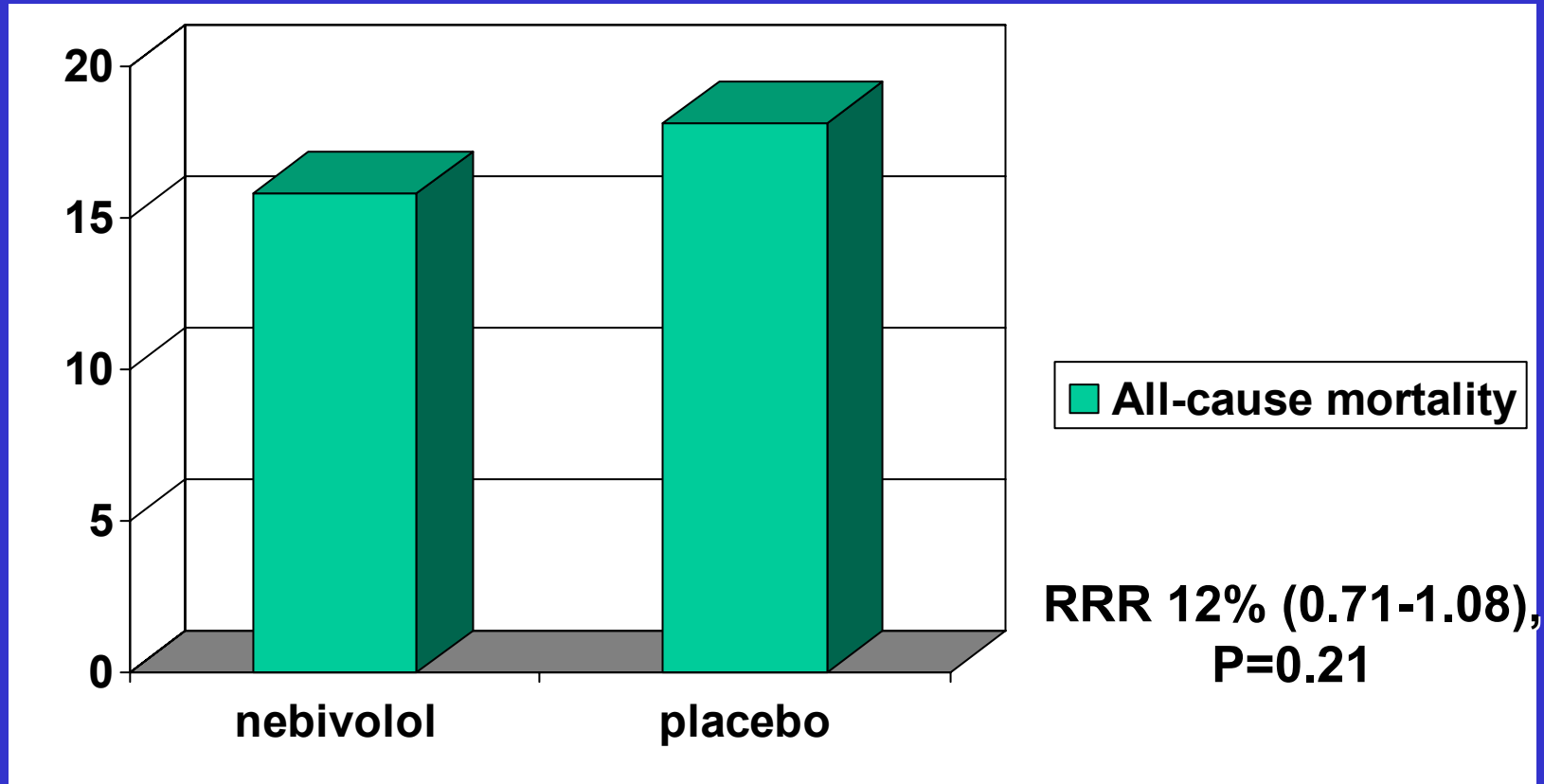
Time to all cause mortality or cardiovascular admission



Number of events: Nebivolol 332 (31.1%) Placebo 375 (35.3%)

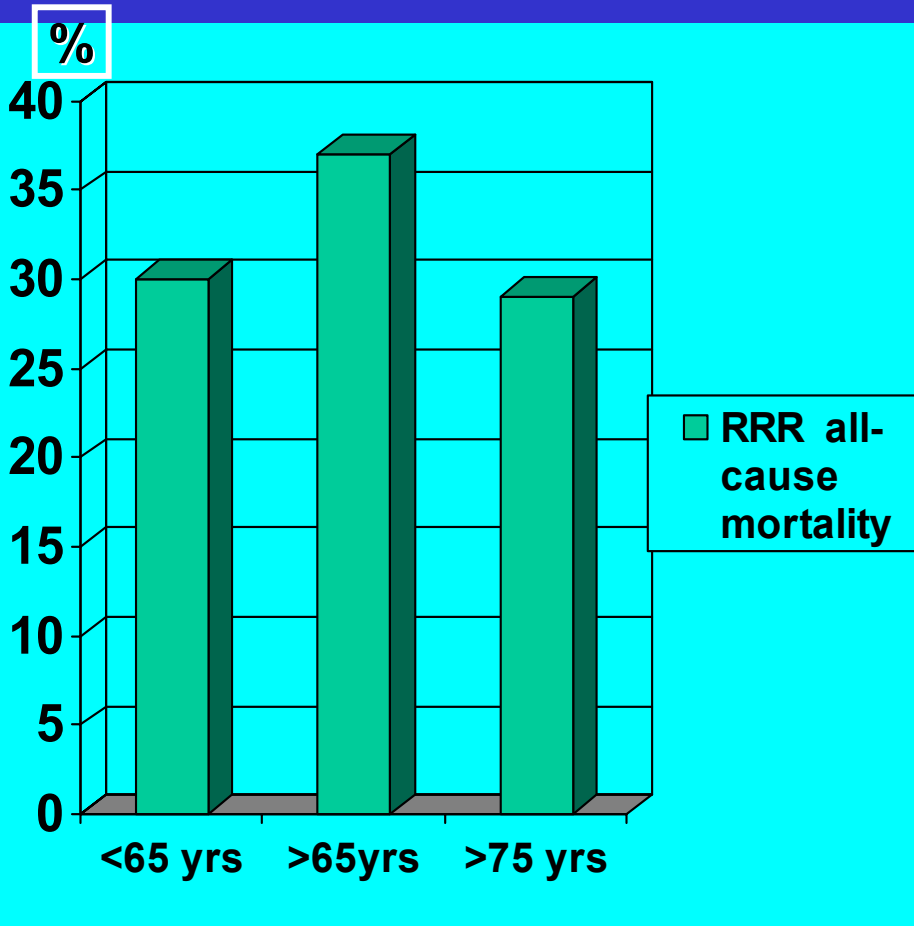
SENIORS- nebivolol does not reduce all- cause mortality or CV hospitalisation

% events

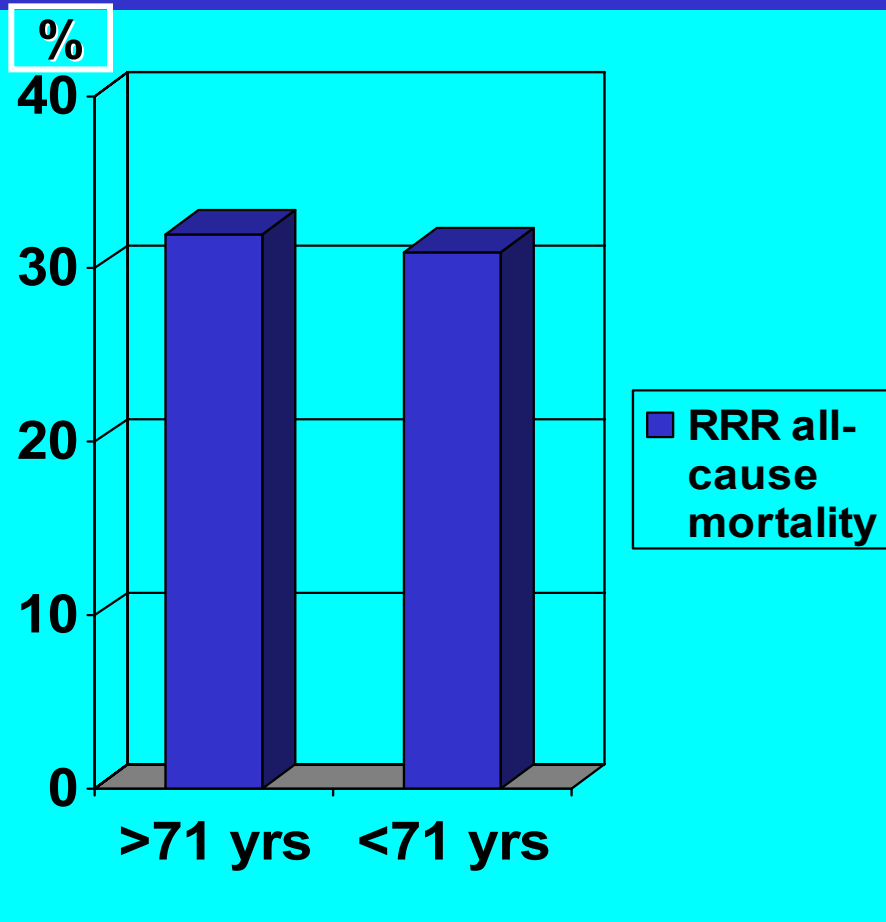


Flathers et al,2005

The effect of beta-blockade on mortality in HF does not depend on age



MERIT-HF

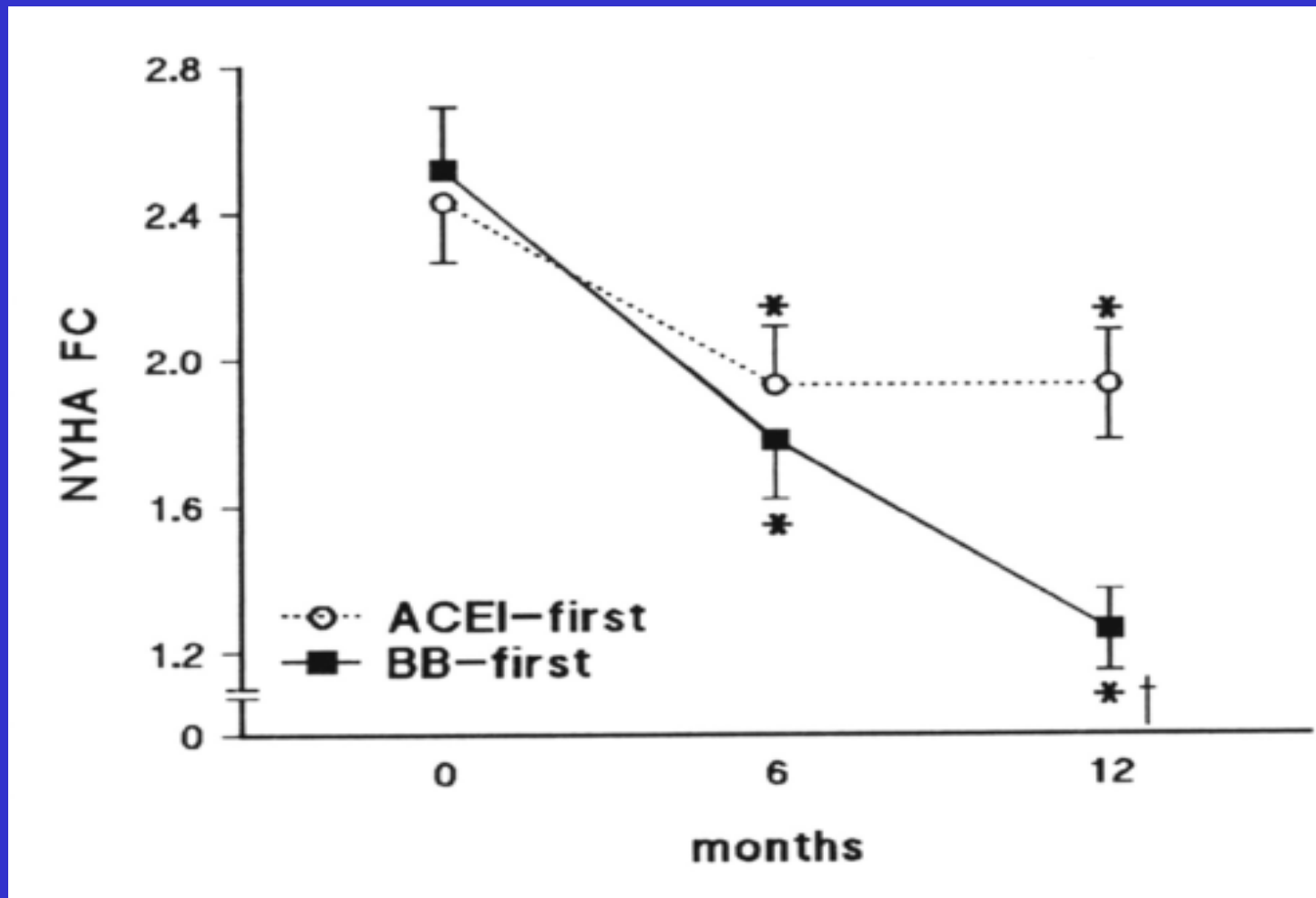


CIBIS 2

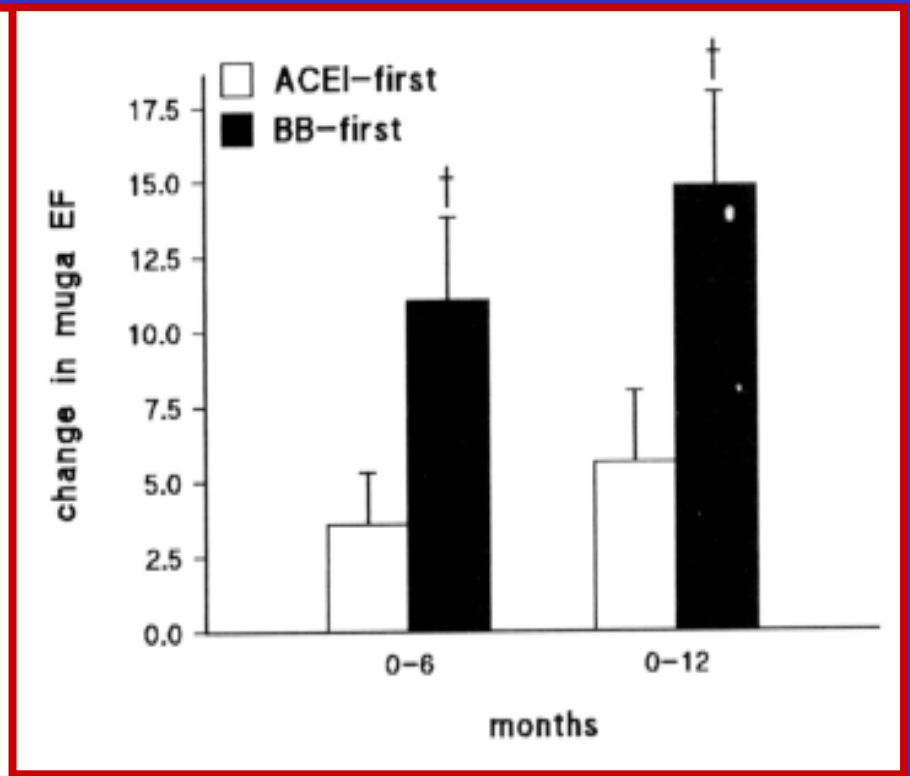
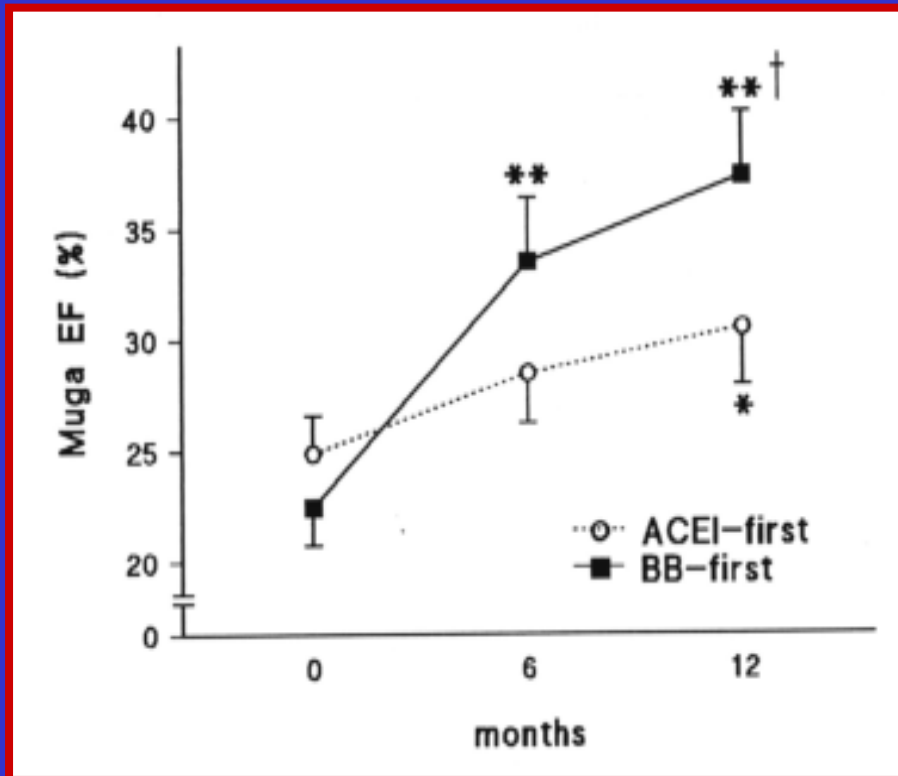
**Heart Failure Treatment –
Should ACE inhibition always be first-line
therapy?**

	For Survival/Morbidity	For Symptoms
	<i>Mandatory therapy</i>	<i>Supportive therapy</i>
NYHA I	continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI add beta-blocker if post-MI	reduce / stop diuretic
NYHA II	ACE inhibitor as first-line therapy ARB if ACE inhibitor intolerant. add beta-blocker add aldosterone antagonist if post-MI	+/- diuretic depending on fluid retention
NYHA III	continue ACE inhibitor add ARB or only ARB if ACE inhibitor intolerant continue beta-blocker add aldosterone antagonist	+ diuretics + digitalis If still symptomatic
NYHA IV	continue ACE inhibitor/ARB beta-blocker aldosterone antagonist	+diuretics + digitalis + consider temporary inotropic support

Effect of first-line (6 month) carvedilol or ACEi



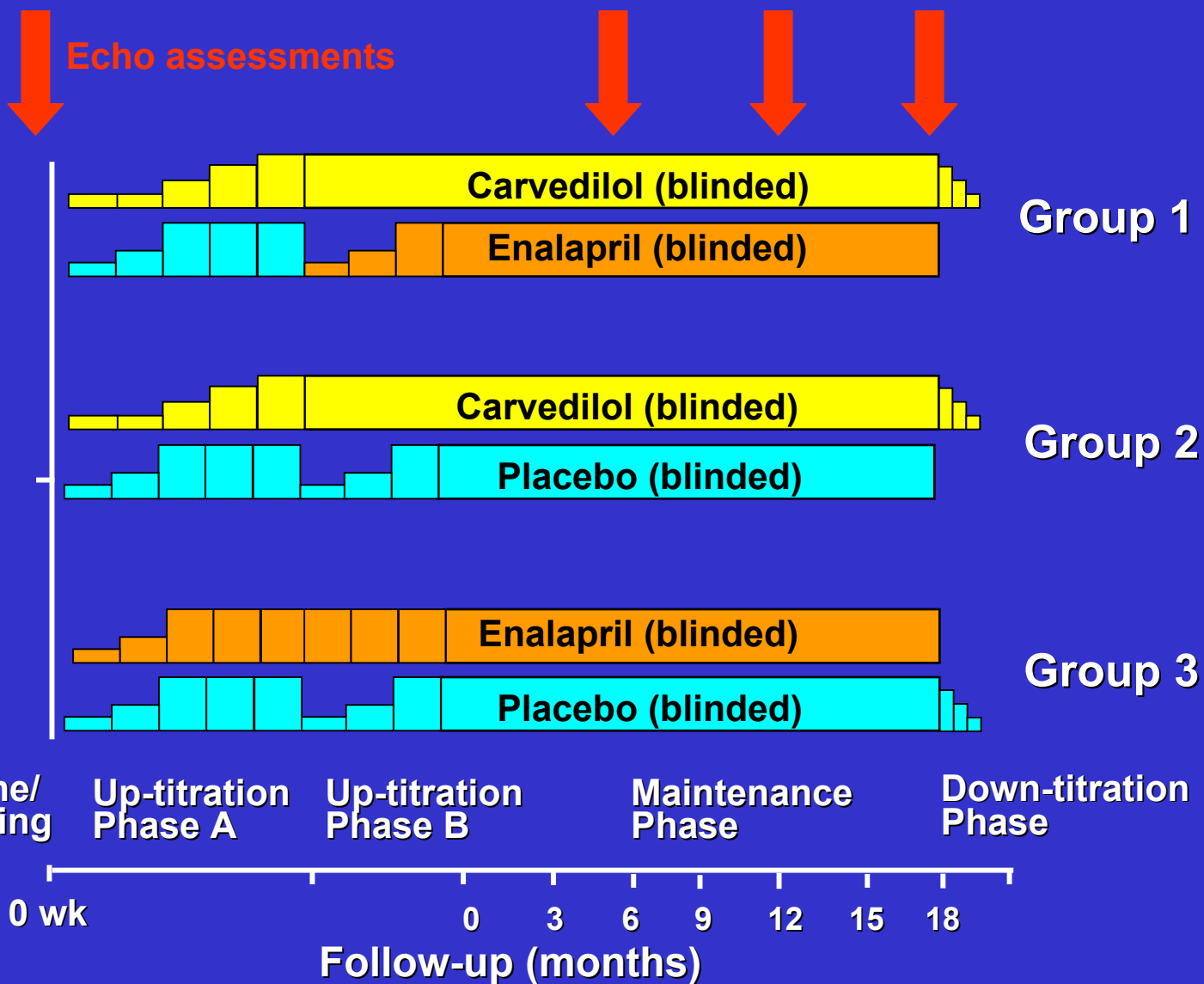
Effect of first-line (6 month) carvedilol or ACE



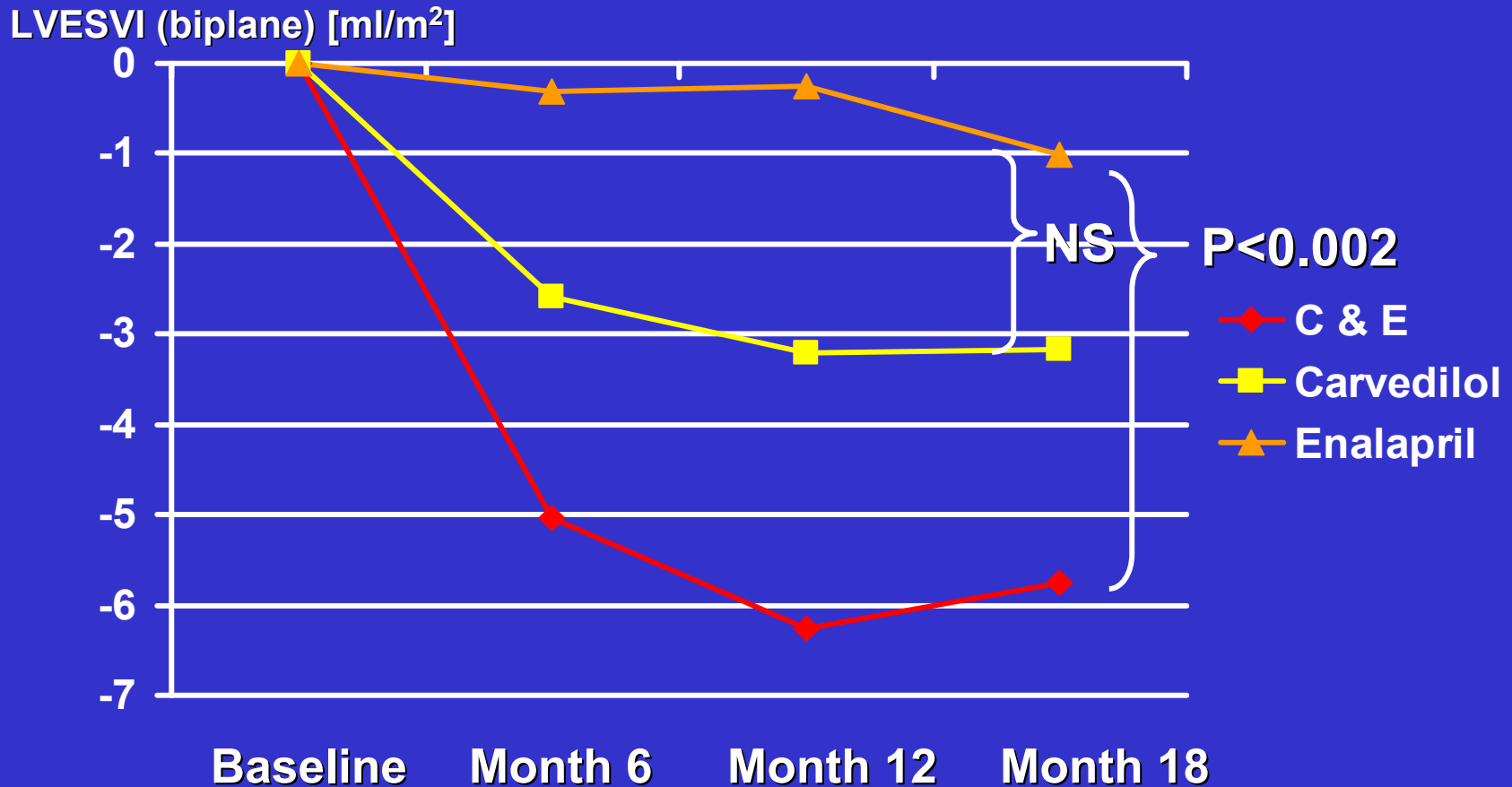
CIBIS III – presented at ESC 2005

- **Compared 6- month enalapril vs bisoprolol, followed by combined treatment for 6-18 months.**
- **Approximately 1000 patients with NYHA II-IV, average age 72 yrs**
- **Primary endpoint : non-inferiority bisoprolol first vs enalapril first**
- **Primary endpoint not reached in ITT population (in PP positive), no further superiority testing**

CARMEN Study Design

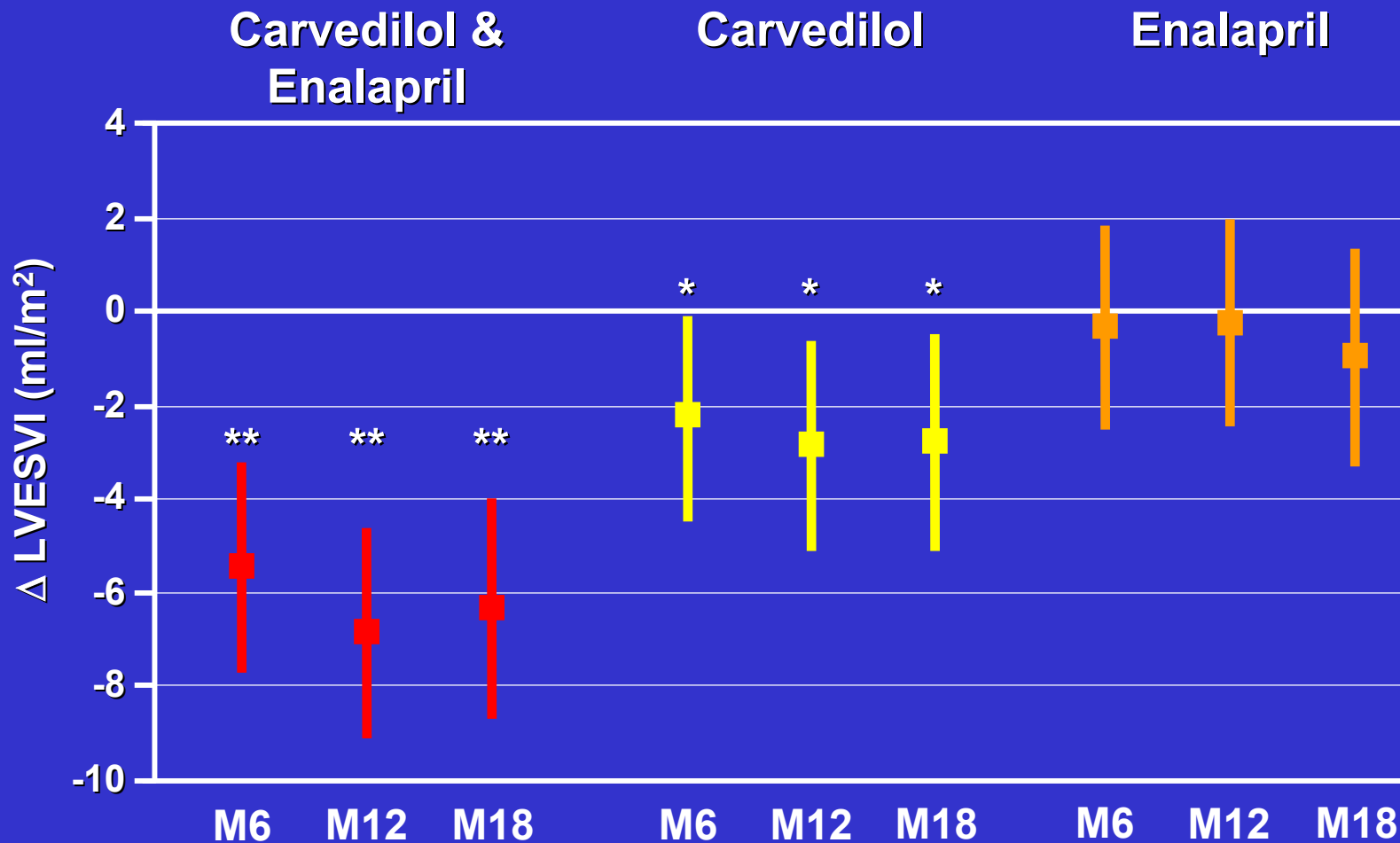


Primary Endpoint: Comparison of LVESVI Between Treatments



LVESVI = left ventricular endsystolic volume index

LVESVI: Change From Baseline Within Treatment-arm Comparison



* P < 0.05, ** P < 0.001

Conclusions

- **The combination of carvedilol and an ACE inhibitor therapy resulted in a highly significant improvement of LV remodelling and function**
- **Patients receiving carvedilol, either as monotherapy or in combination with enalapril, showed a reversal of LV remodelling - results not observed with enalapril monotherapy**

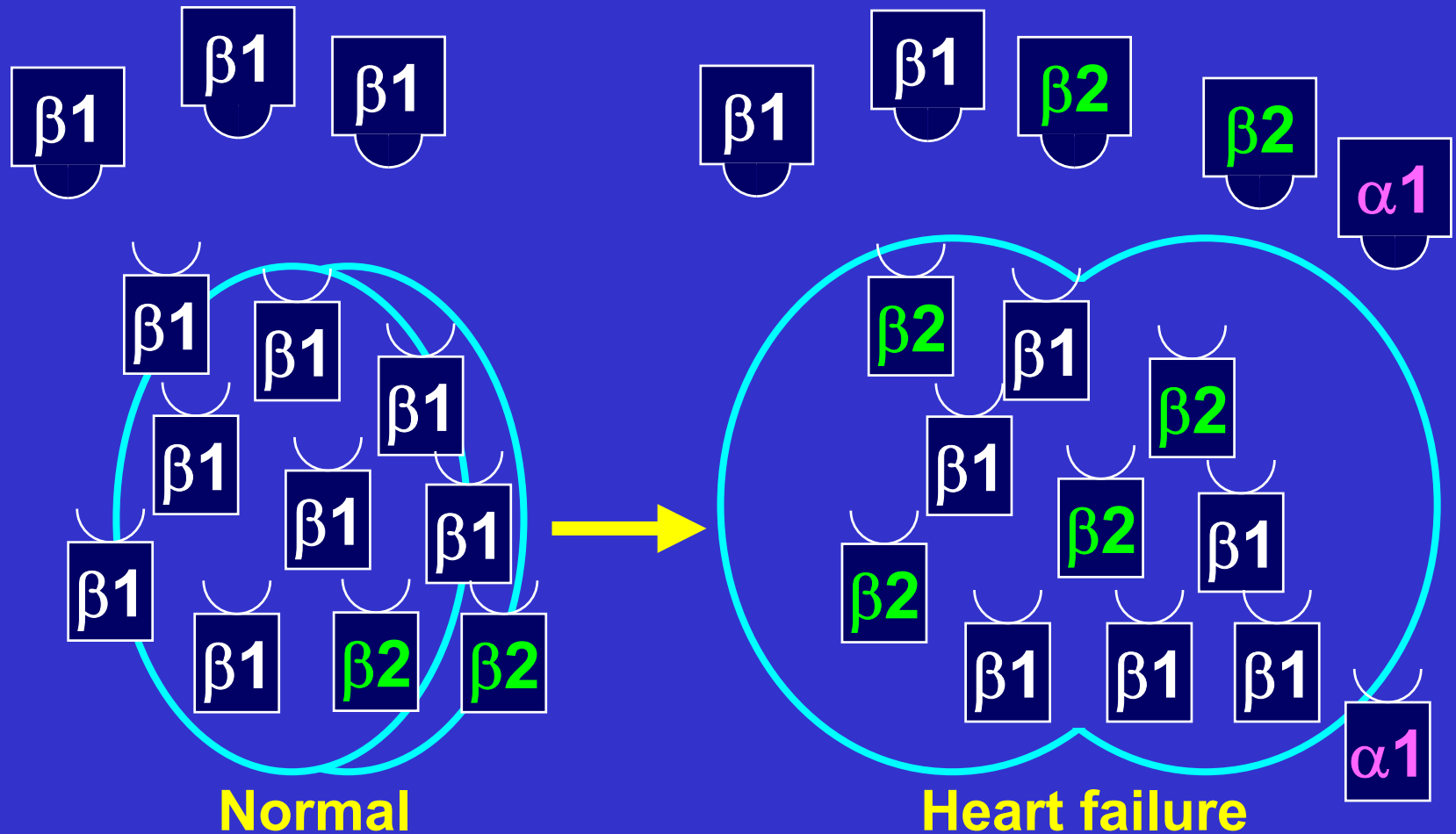
Clinical Implications

- Carvedilol was safely initiated before ACE inhibition and reversed LV remodelling in CHF. This might challenge the historical sequence of initiating ACE inhibition before β blockade
- The CARMEN results underscore the necessity for **not delaying prescription of combination therapy of an ACE inhibitor and carvedilol in mild-moderate heart failure.**

Beta-blockade in heart failure

**Are all beta-blockers
equally effective in the
treatment of heart failure ?**

Heart Failure Converts the Circulation From a β_1 to a $\beta_1/\beta_2/\alpha_1$ -Environment



Effects of β_2 -Receptors

- **Direct chronotropic, inotropic, lusitropic (cAMP mediated)**
- **Hypertrophy, fibrosis, remodelling**
- **Anti-apoptotic**
- **Arrhythmogenic**
- **Facilitation of norepinephrine release (presynaptic)**

Effects of α_1 Receptors

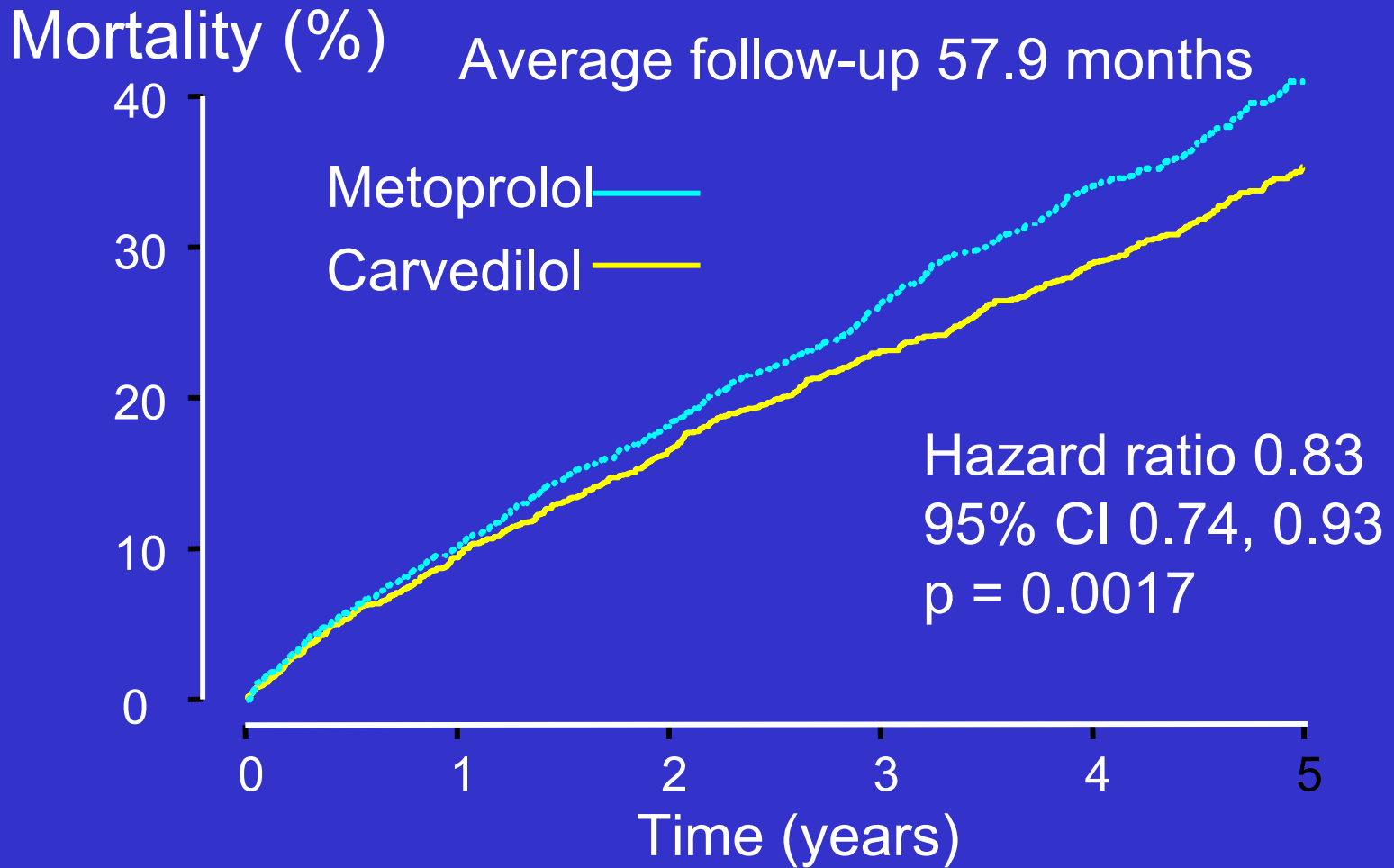
- Myocardial hypertrophy, fibrosis, remodeling
- Cardiotoxicity (with β receptors)
- Arrhythmogenic
- Peripheral vasoconstriction
- Renal hypoperfusion and sodium retention

Properties of selected beta-blockers

	β_1 blockade	β_2 blockade	α_1 blockade	ISA	Ancillary effects*
Carvedilol	+++	+++	+++	-	+++
Metoprolol	+++	-	-	-	-
Bisoprolol	+++	-	-	-	-
Bucindolol	+++	+++	-	++	-
Nebivolol	+++	-	-	-	++

*anti-oxidant, inhibit apoptosis, inhibit endothelin, NO generation

Primary endpoint of mortality



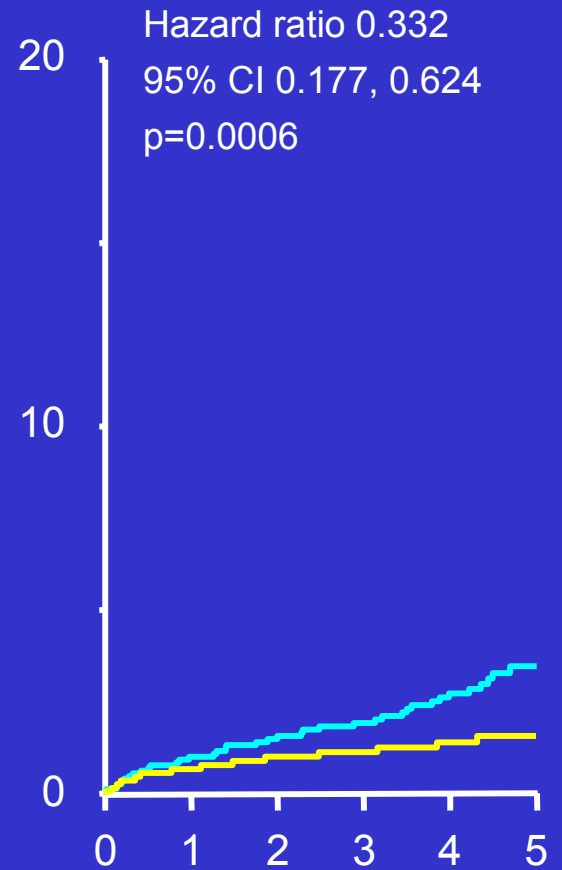
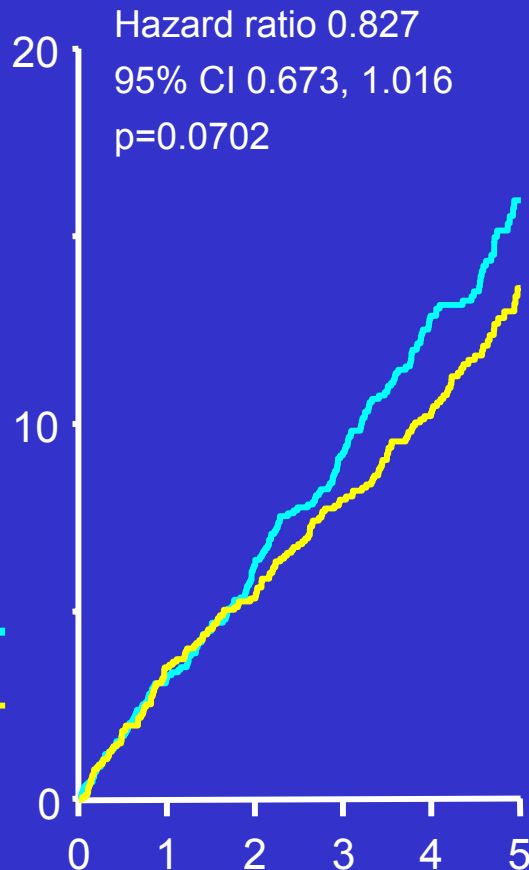
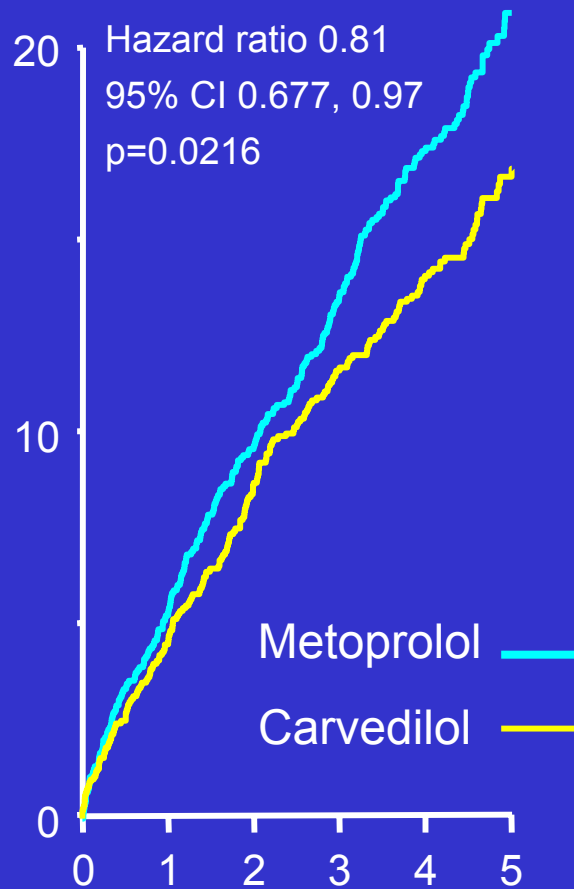
Mode of death

Sudden death

Circulatory failure

Death from stroke

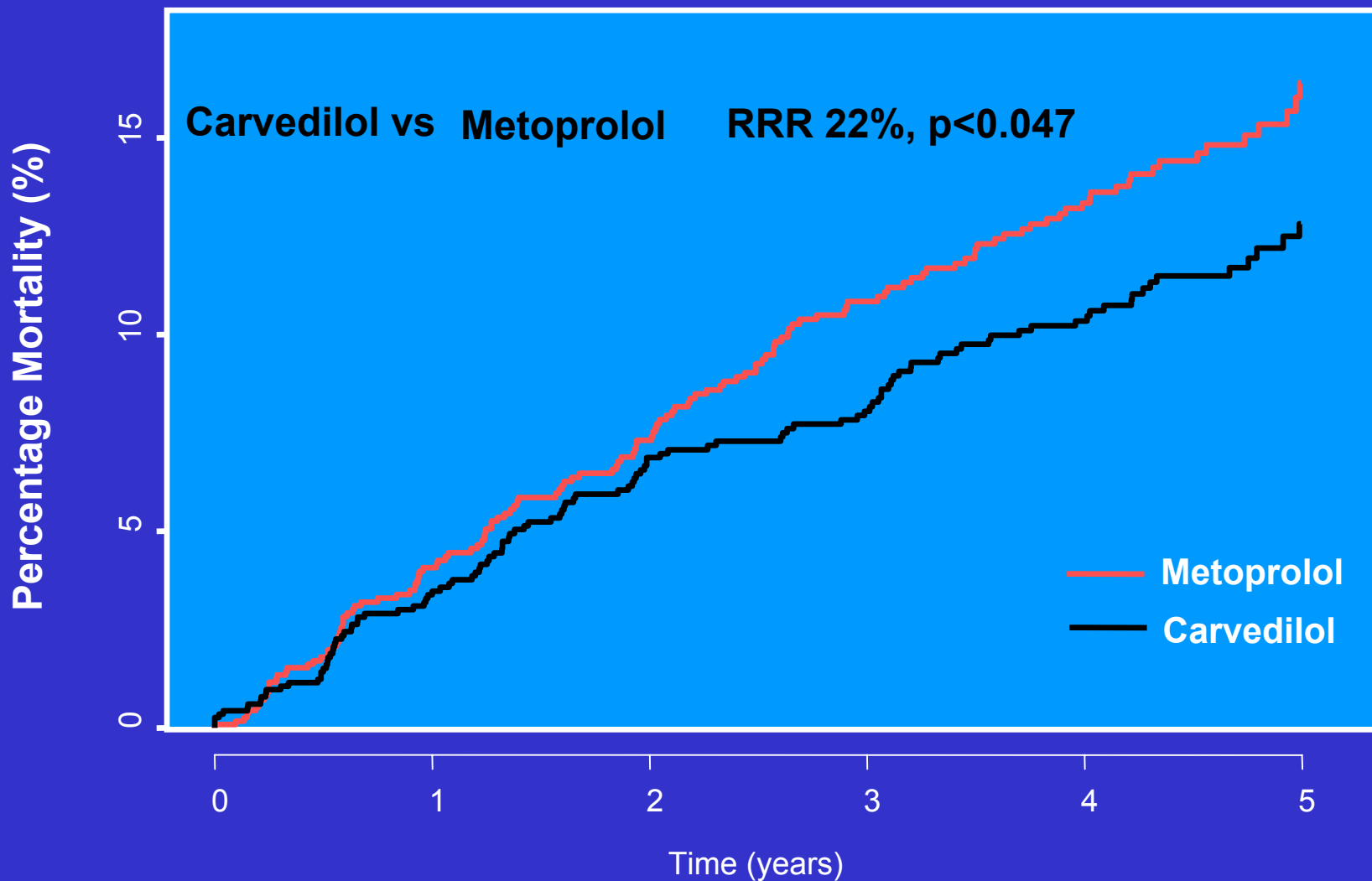
Mortality (%)



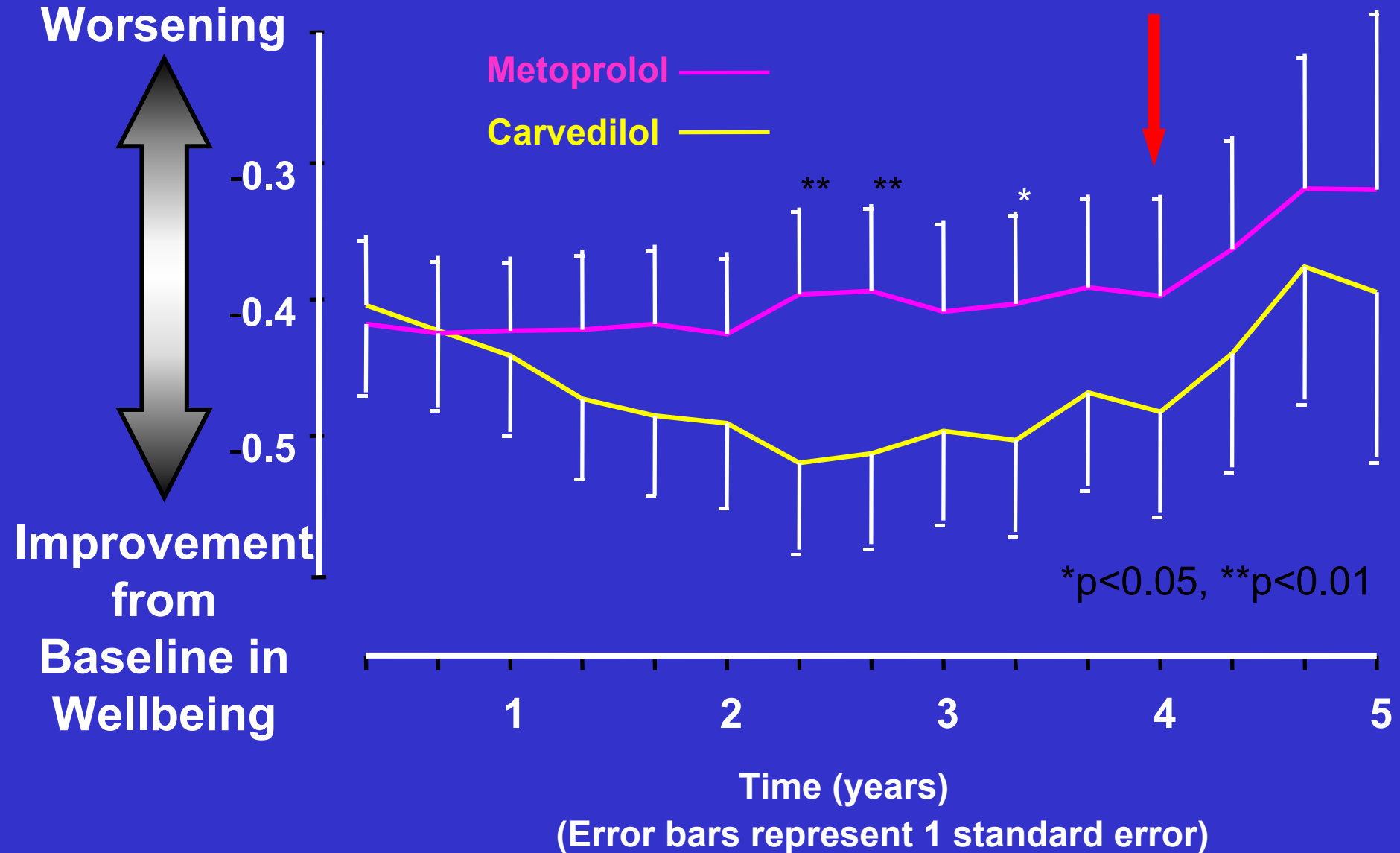
Time (years)

Poole-Wilson, HFSA 2003

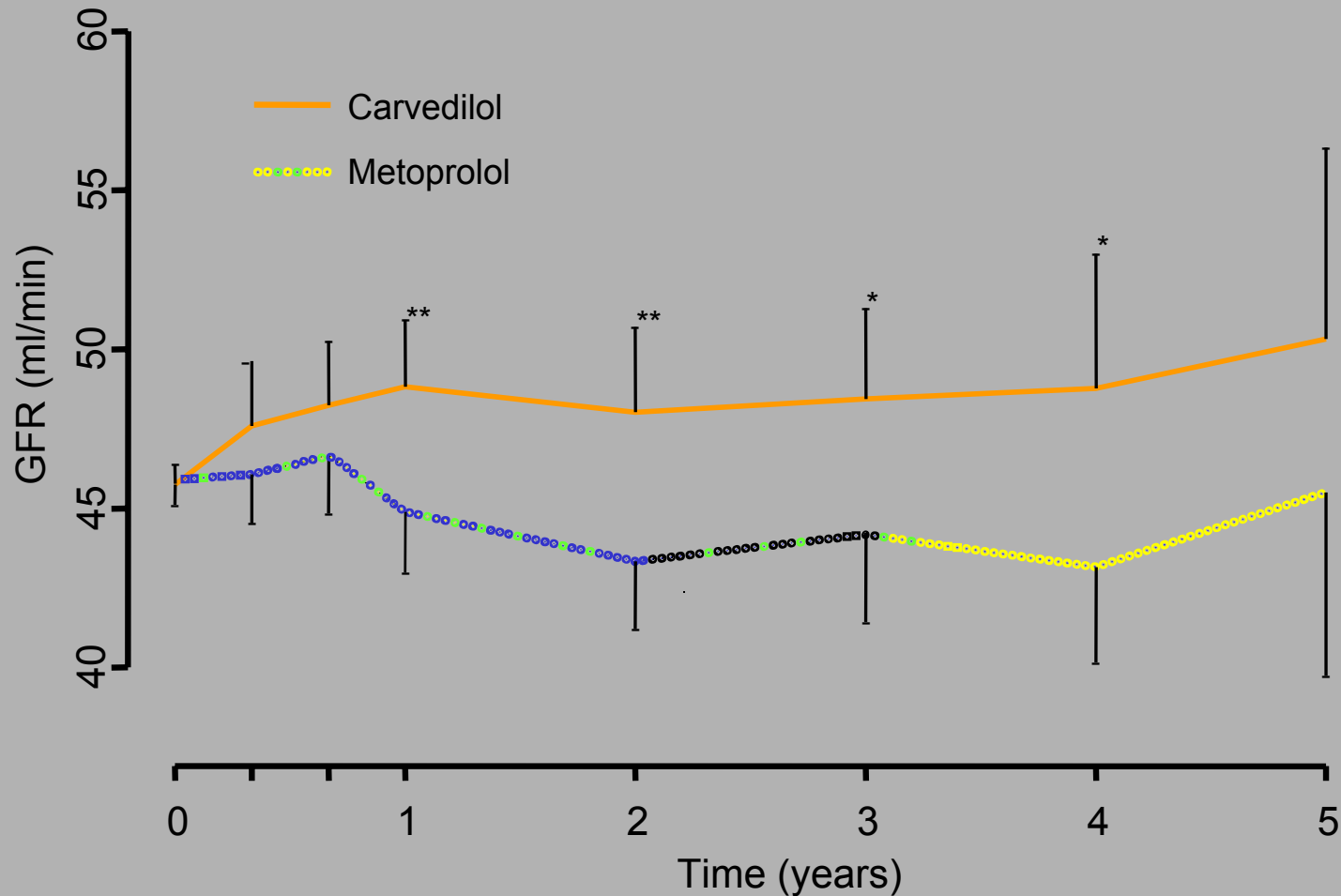
Less New Diabetes Endpoint with Carvedilol



Change in Wellbeing Score (ITT of survivors)



COMET - GFR by treatment group in patients with high creatinine levels at baseline

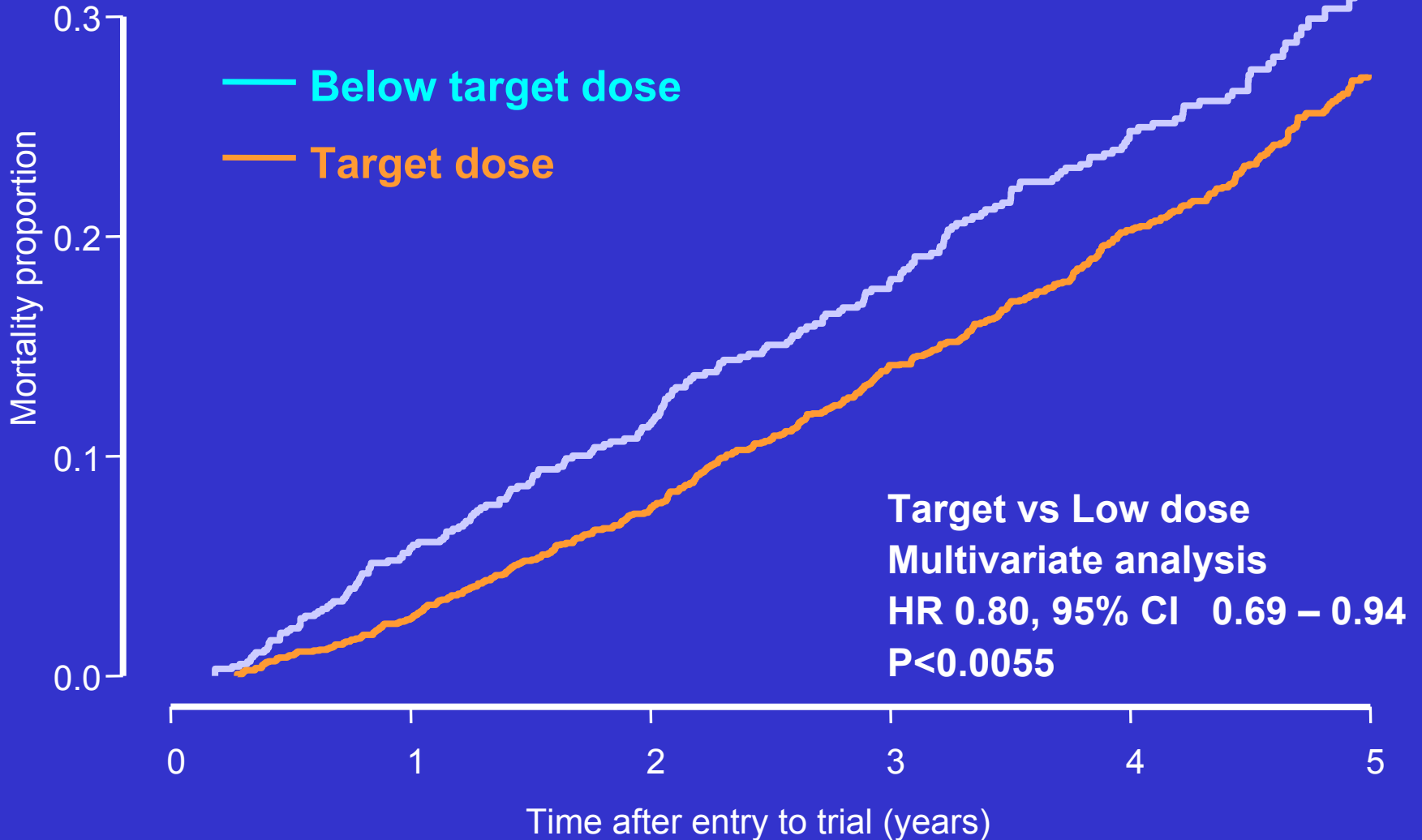


Error bars represent 1 standard error.

Dose

Are target dosages used in the large clinical trials really necessary?

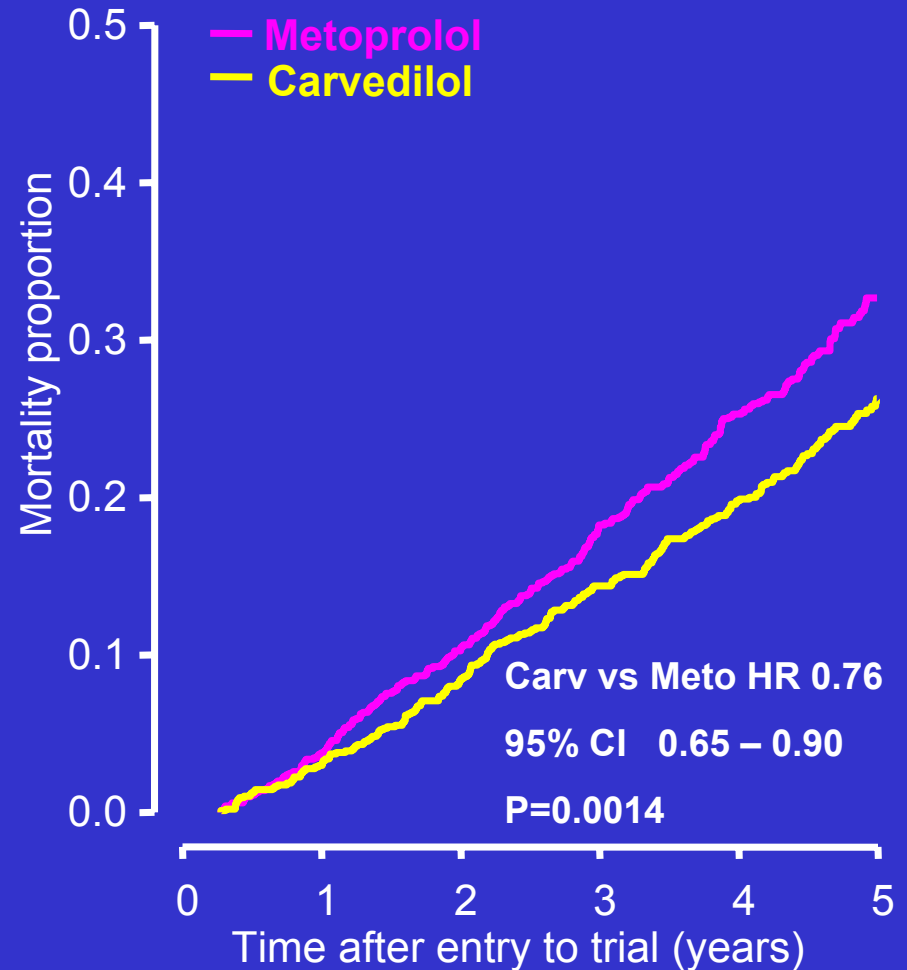
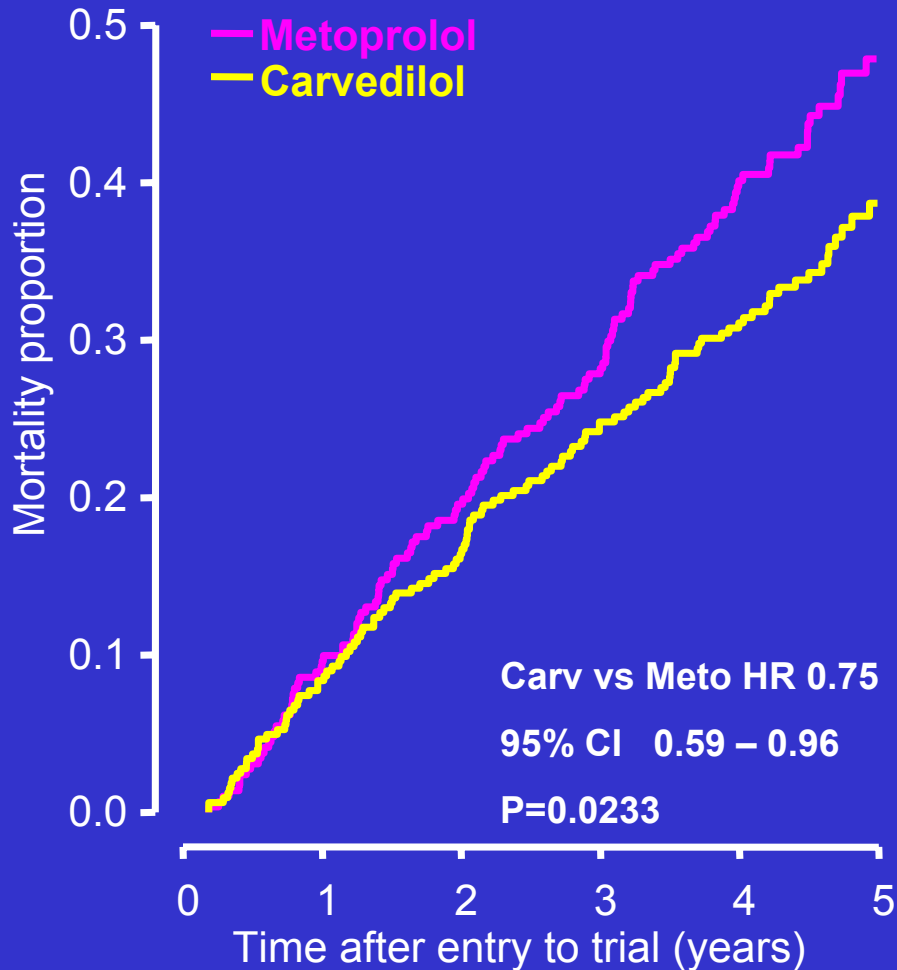
Mortality in Patients on Target and Lower BB Doses at 4 months (Adjusted for baseline and 4 months variables)



Mortality in Subgroups Split by Beta-blocker Dose

On Below Target
Beta-blocker dose

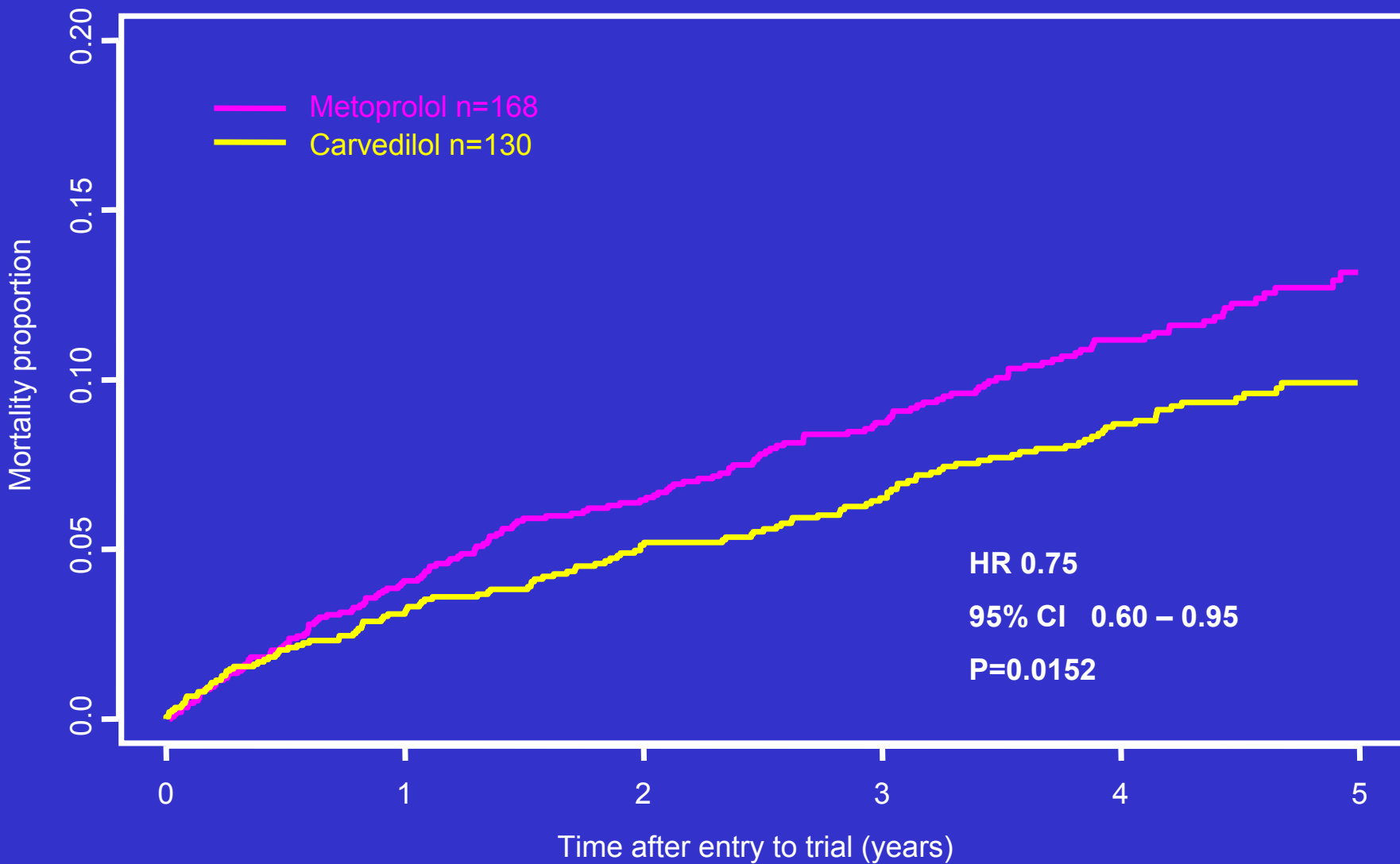
On Target
Beta-blocker Dose



Conclusion

- **Beta-blockade necessary element in HF therapy**
- **Effective in the elderly**
- **Early combination of ACEi and BB necessary, order of treatment to be decided by doctor**
- **Beta-blockers are not equally effective.**
Carvedilol better improves survival, clinical well-being and protect against new onset diabetes and renal dysfunction than metoprolol (tartrate).
- **Target dosages shown to be effective in large trials better protect against worsening HF than lower dosages.**

COMET Stroke or MI



Summary

Compared to metoprolol, carvedilol reduced:

- Sudden death by (19%)
- Worsening HF death by (17%)
- MI by 29%
- CV death or non-fatal MI by 19%
- Stroke by 21%
- Stroke death in 13 patients as compared to 38 on metoprolol
- Stroke or MI by 25 %

Differences were observed early and remained over time

COMET: Glomerular Filtration Rate

- Fewer patients showed a reduction of GFR on carvedilol at 12 months

CG formula (p=0.0036)	Carvedilol	Metoprolol tartrate
Unchanged or Increased	523 (50.8%)	439 (44.3%)
Decreased	506 (49.2%)	551 (55.7%)

MDRD formula (p=0.119)	Carvedilol	Metoprolol tartrate
Unchanged or Increased	401 (38.9%)	354 (35.6%)
Decreased	629 (61.1%)	641 (64.4%)

Mechanisms for benefit from carvedilol

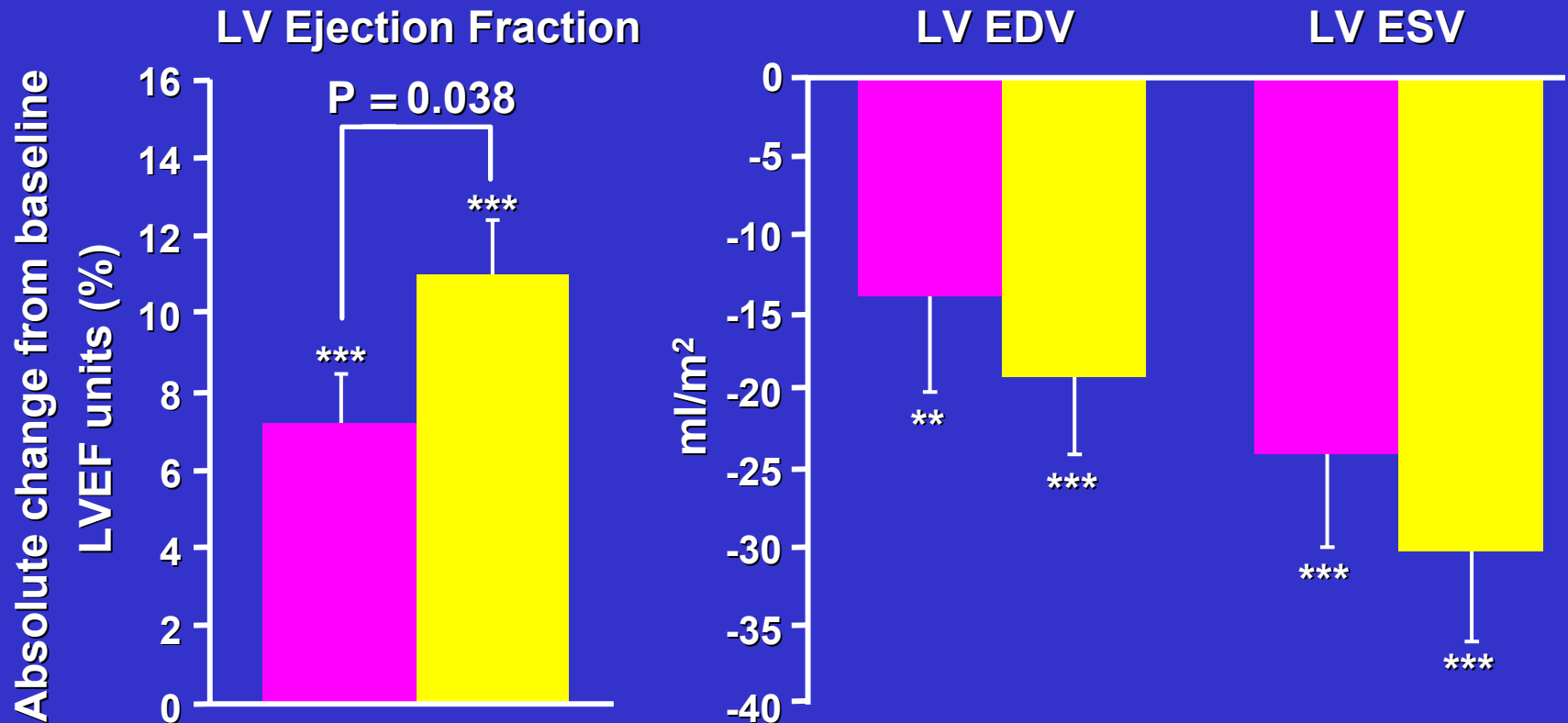
Biological mechanisms

1. Beta-2 blockade (complex)
2. Alpha-1 blockade
3. Beneficial effect on insulin sensitivity
4. Anti-oxidant properties
5. Anti-apoptotic activity
6. Electrophysiological actions, blockade of (HERG)
7. Reduction of hypokalaemia
8. No up-regulation of the beta1 receptor
9. High affinity of carvedilol for receptor

Technical mechanisms

1. Chance
2. Dose
3. Formulation

Carvedilol Reverses LV Remodelling to a Greater Extent than Metoprolol

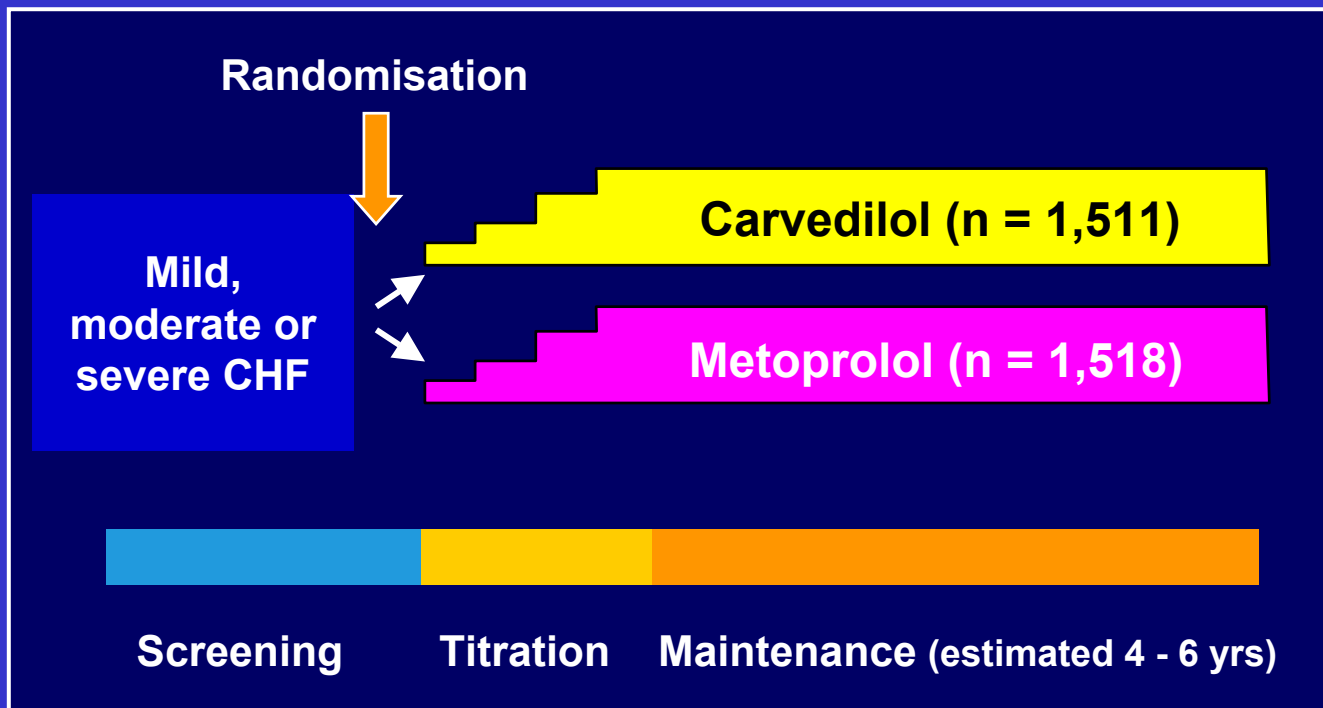


P < 0.01; *P < 0.001
vs baseline

Metoprolol Carvedilol

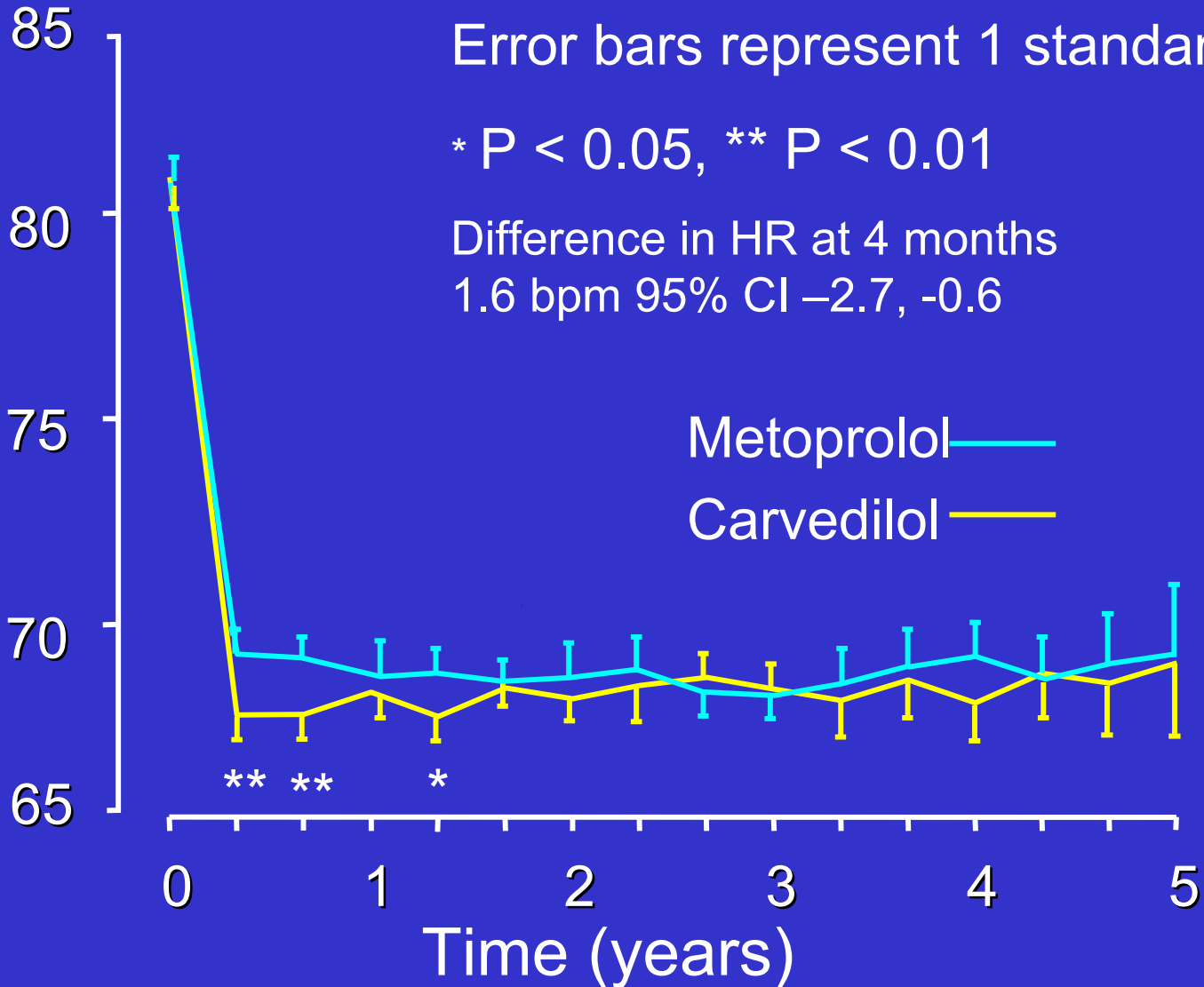
Objectives and Design

- To compare the effects of carvedilol with those of metoprolol on mortality and morbidity in patients with chronic heart failure
- No run-in period



Heart rate

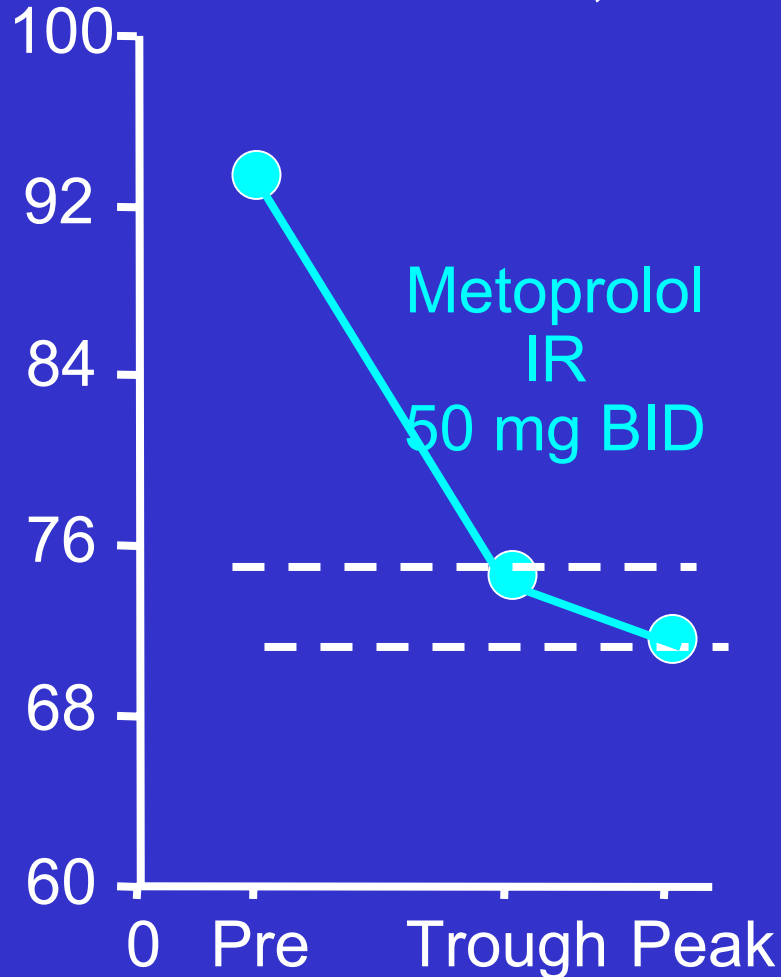
Heart rate (beats.min⁻¹)



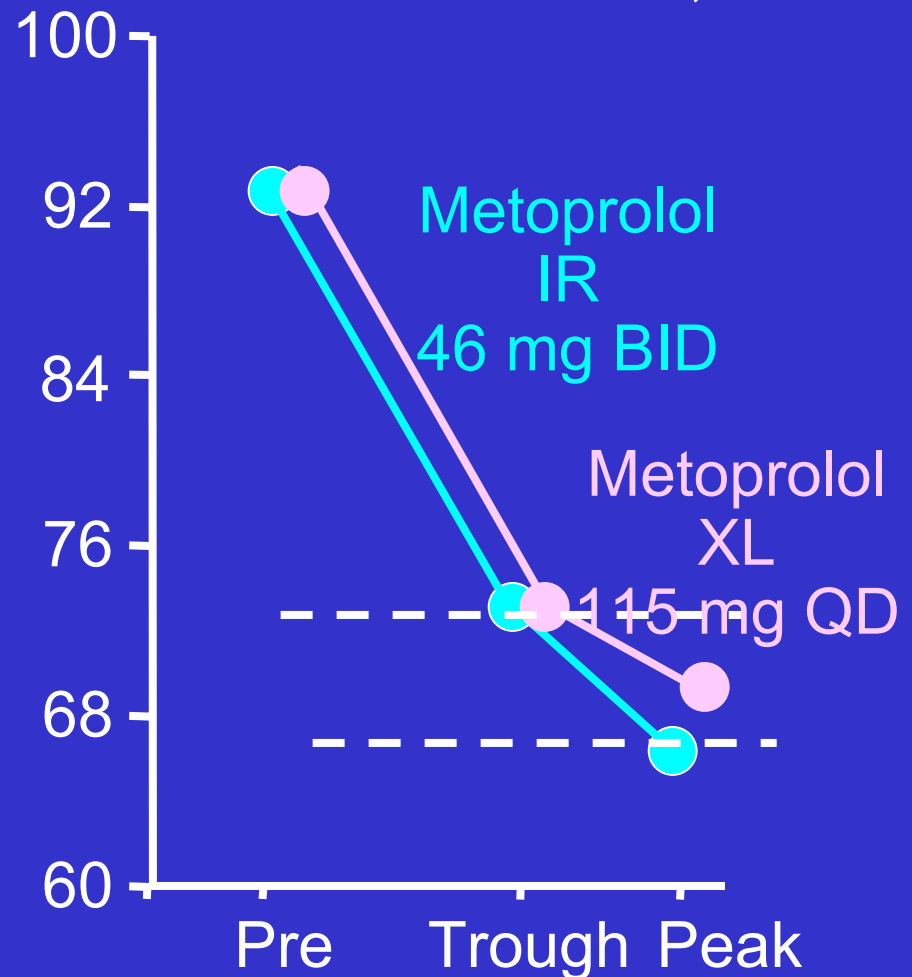
Peak and trough heart rate effects of long-term metoprolol IR and XL in heart failure

Heart rate

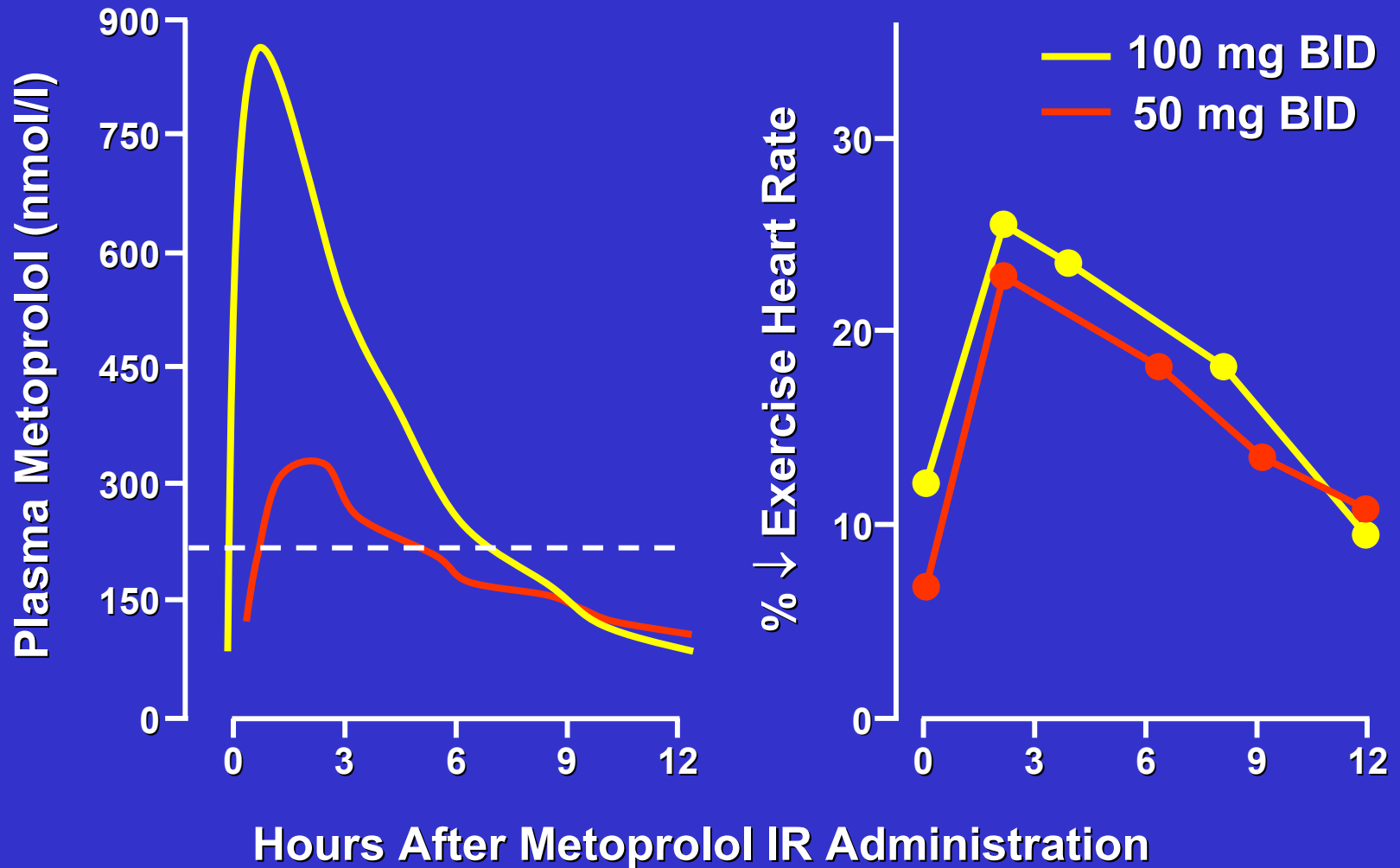
Kukin et al.
Heart 1997;78:444



Kukin et al.
JACC 2000;35:45

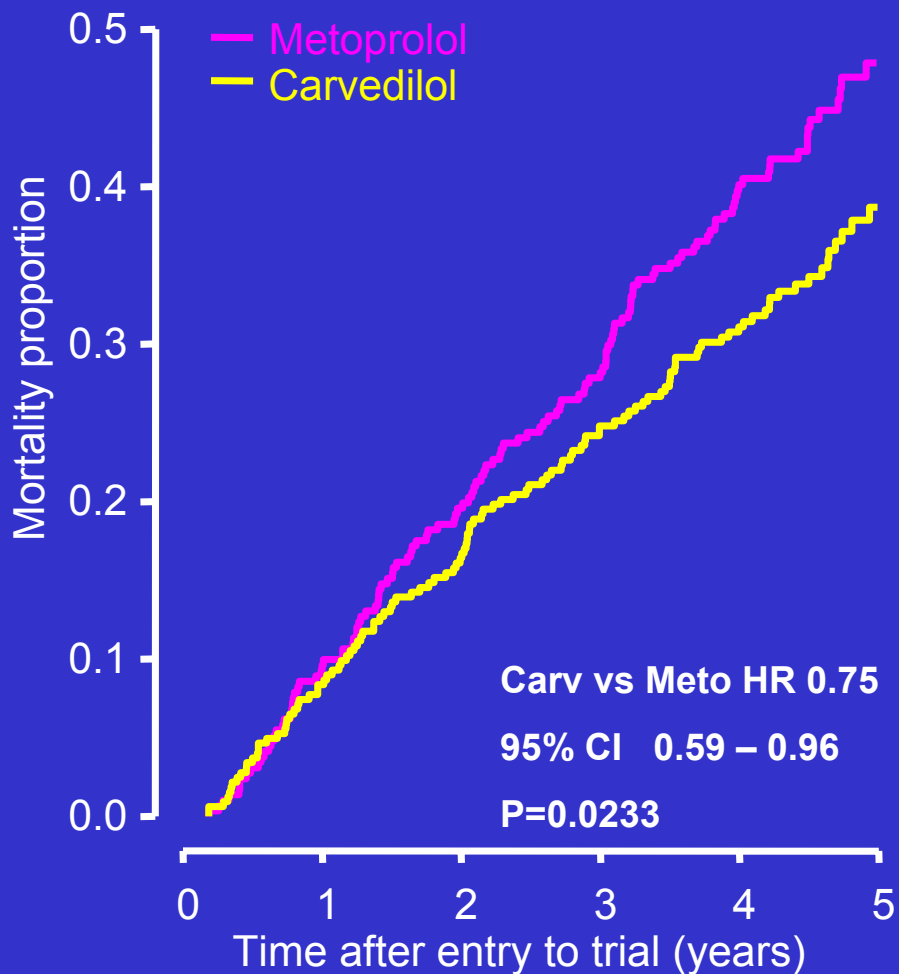


Pharmacokinetic and Pharmacodynamic Responses to Metoprolol IR 50/100 mg BID

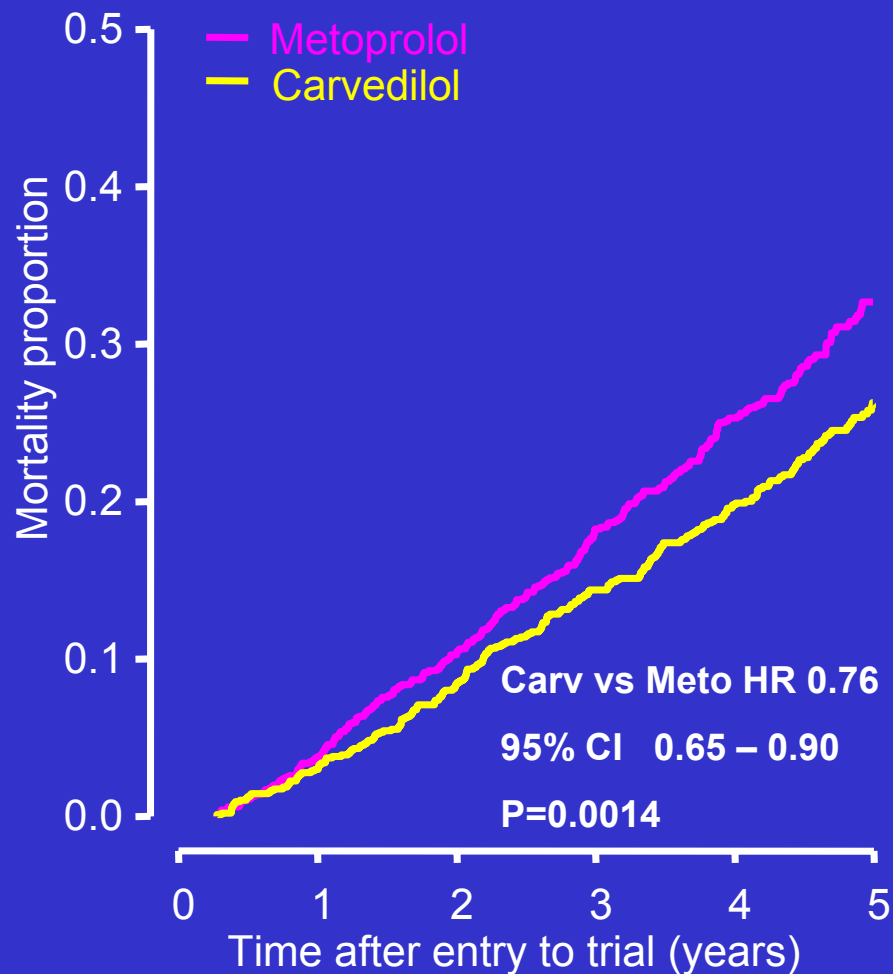


Mortality in Subgroups Split by Beta-blocker Dose

Below Target Beta-blocker dose



On Target Beta-blocker Dose



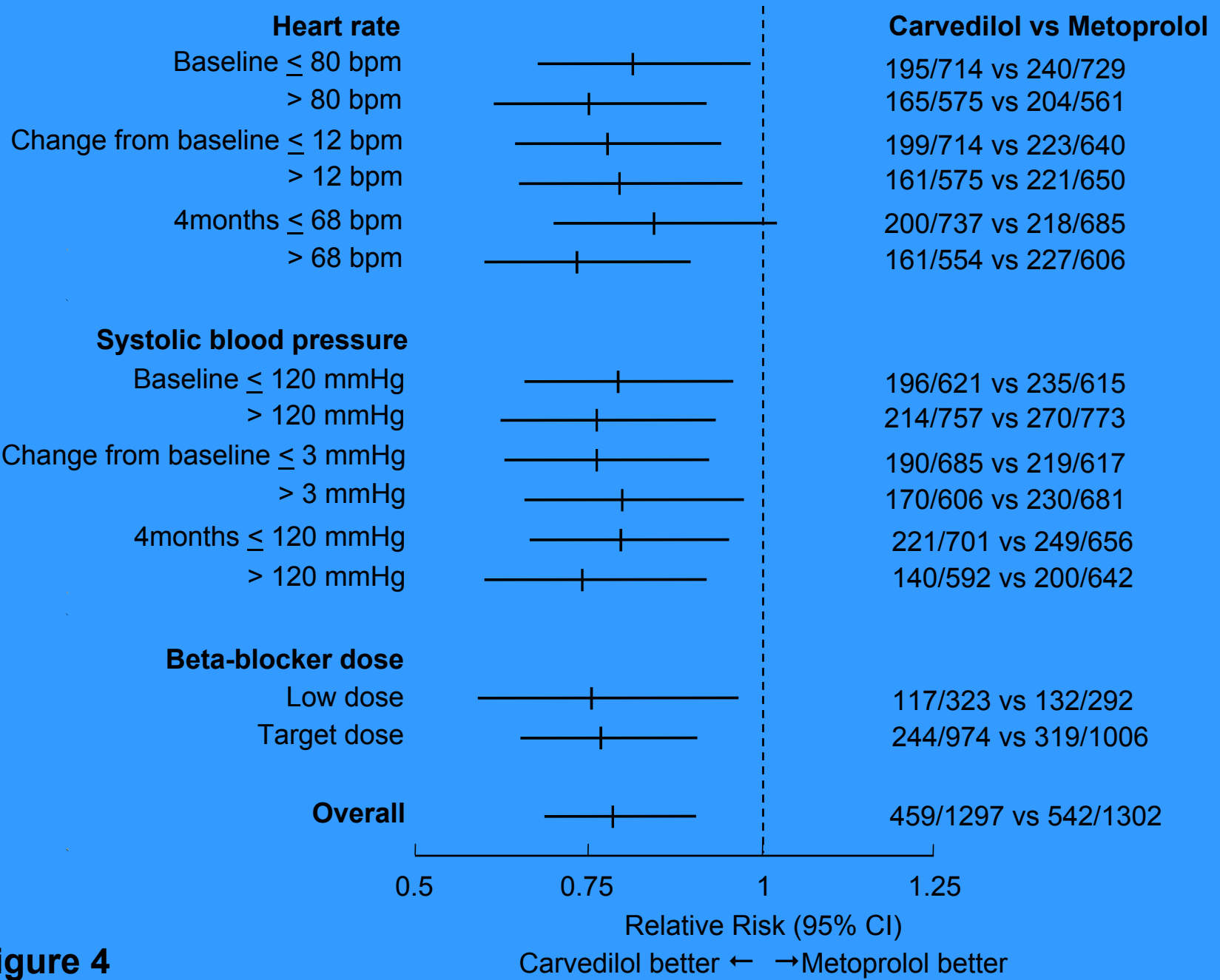


Figure 4

Conclusion

Result

COMET was clear and definitive

Mechanism

Unlikely to be due to doses or formulations of drugs

Most probable explanation is beta 2 and alpha-1 adrenoceptor blockade

Clinical

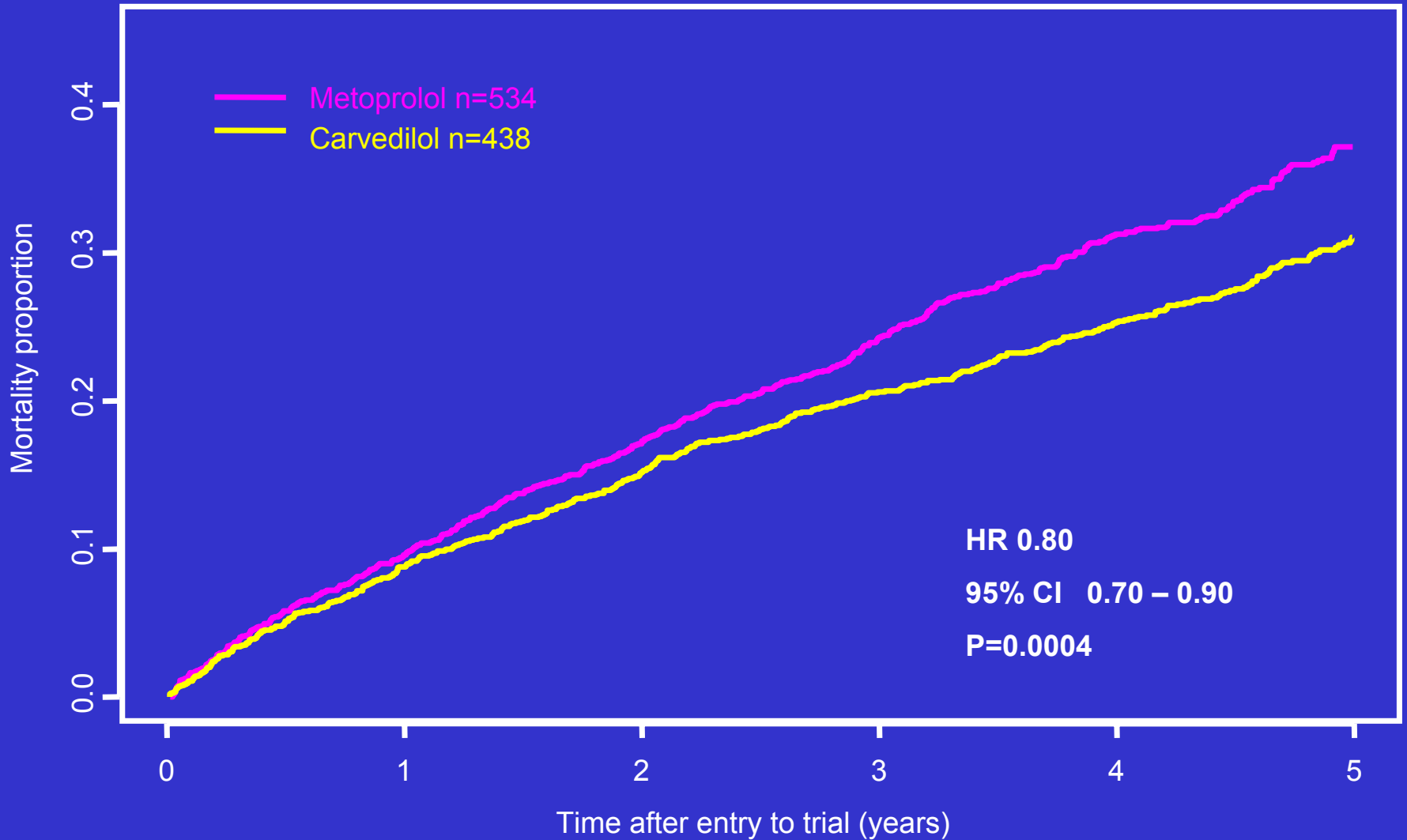
Implications

Beta-blockade is mandatory in all stages of heart failure . Should be given directly together with ACE inhibition (CARMEN)

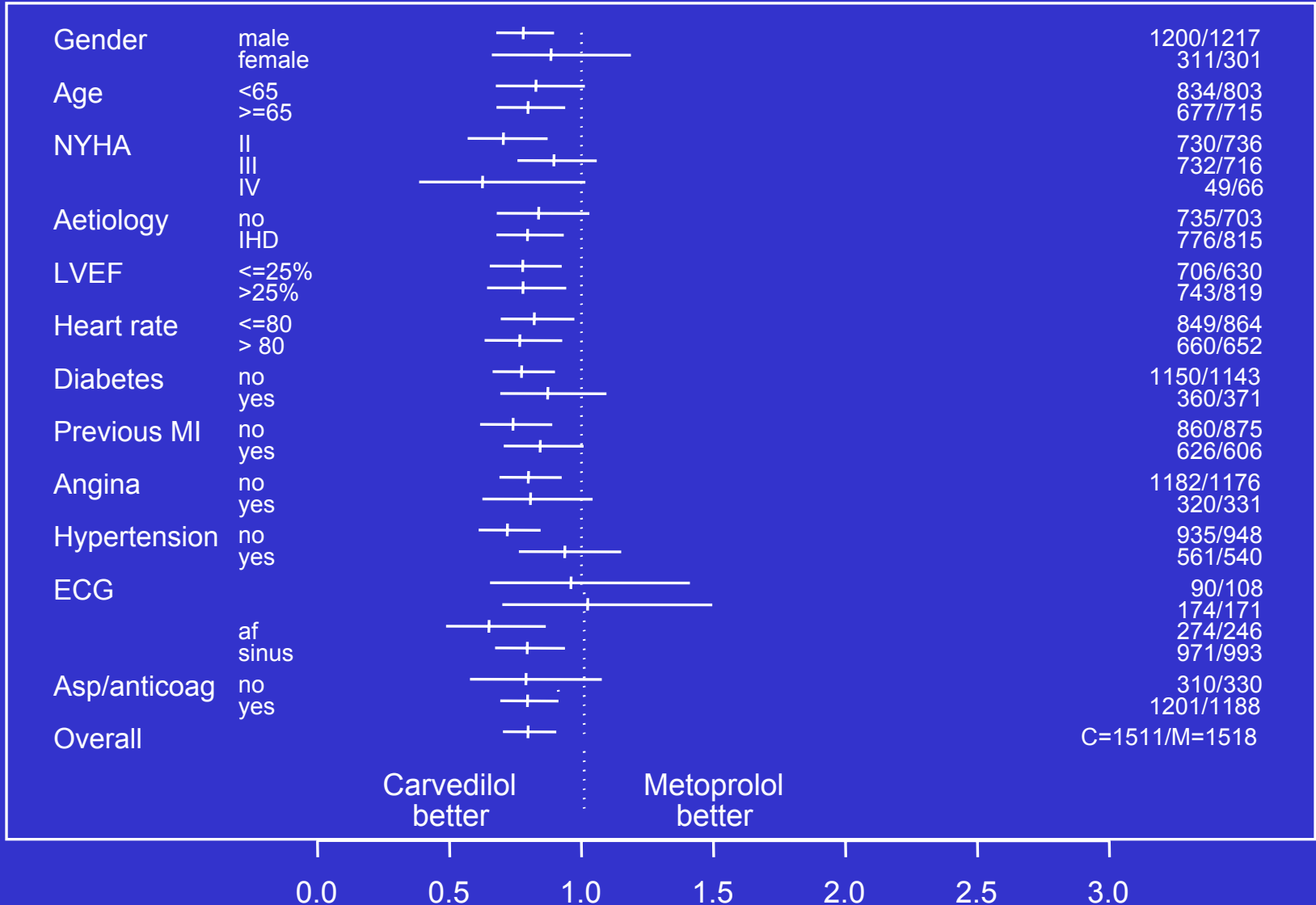
Beta-blockers differ in their effect on heart failure

The preferred beta blocker in the treatment of heart failure is carvedilol

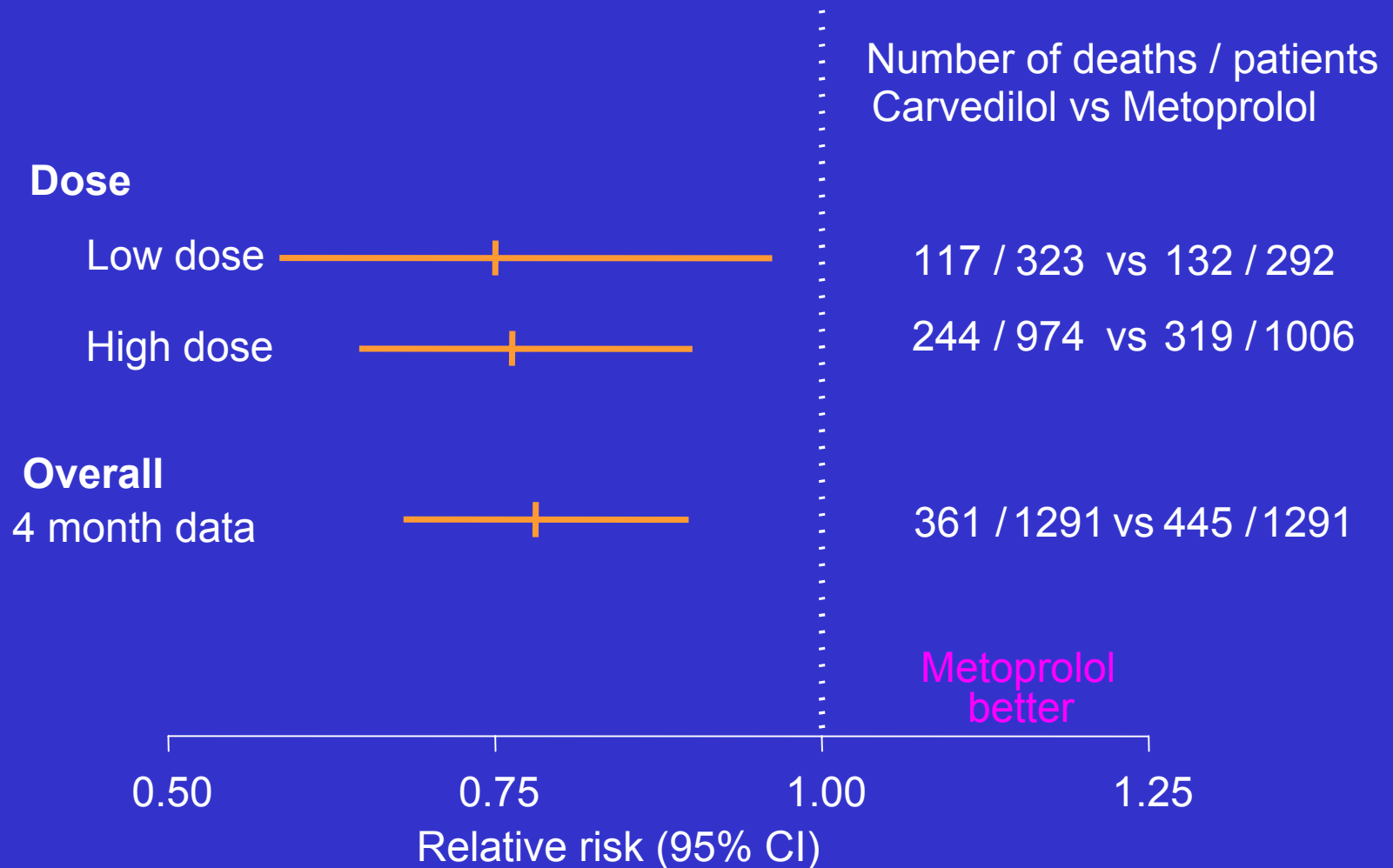
Cardiovascular Mortality



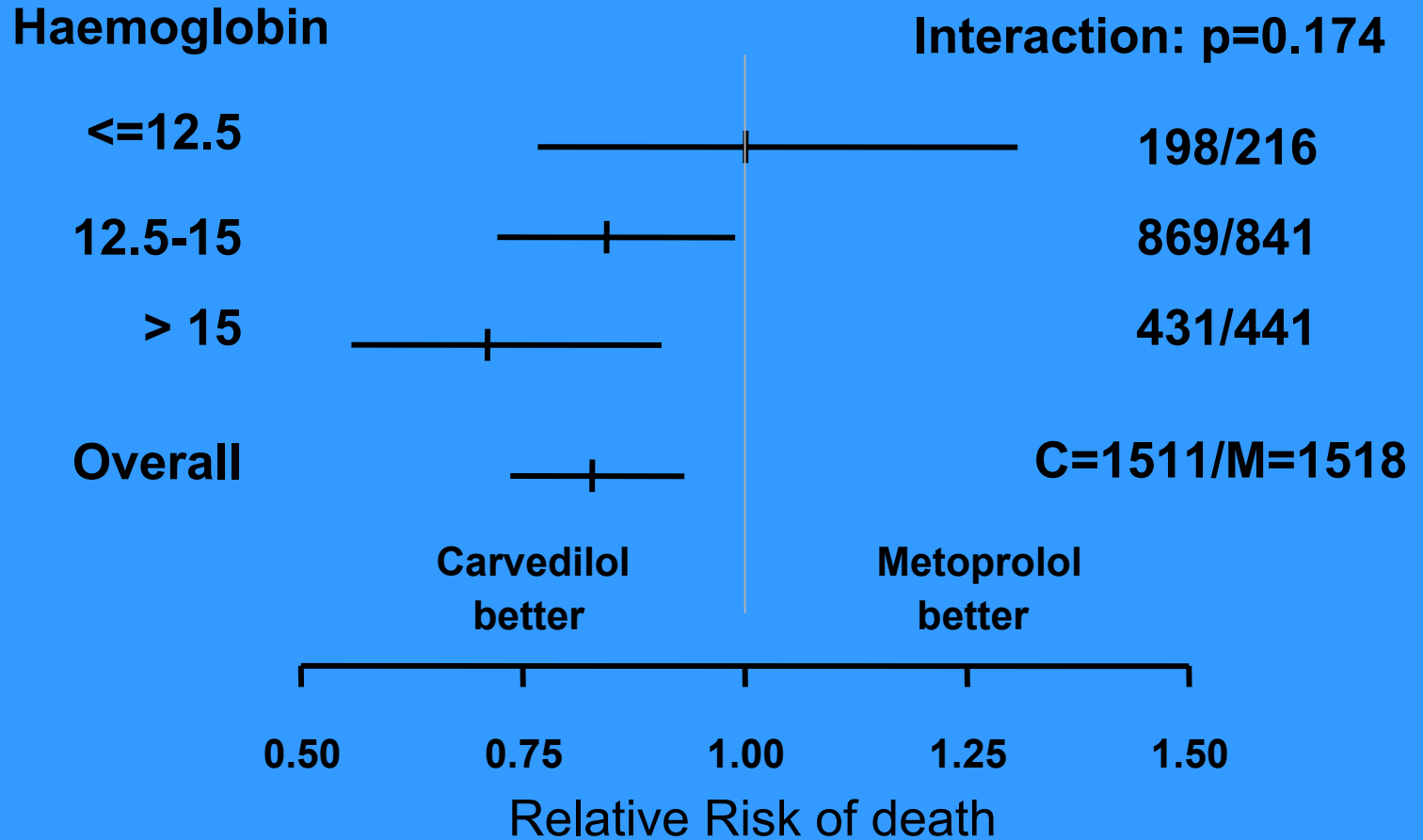
Cardiovascular Mortality by Subgroups



Mortality reduction by carvedilol vs metoprolol by dose subgroups



Treatment Effect on Mortality by Hb



Results

- **Decrease in GFR was independently related to subsequent mortality but did not explain the beneficial effects of carvedilol versus metoprolol tartrate, as seen from the adjusted relative risks***

	RR	95% CI	P Value
Carvedilol vs Metoprolol tartrate	0.804	0.676-0.957	0.0140
Inc Δ GFR at 12 months	0.990	0.984-0.996	0.0012

*Other variables included in the model and significantly related to subsequent mortality: age; gender; weight; NYHA Class II/III/IV; duration of HF; LVEF; previous MI; diabetes; digitalis; anti-arrhythmics; lipid-lowering drugs; S-sodium. Other variables included in the model and not significantly related to subsequent mortality: systolic BP; history of CAD; stroke; ECG rhythm; nitrates; hemoglobin.

Results

- Fewer patients showed an increase of creatinine on carvedilol at 12 months
p=0.0017

	Carvedilol	Metoprolol tartrate
Decreased (> 20 $\mu\text{mol/l}$)	87 (8.4%)	65 (6.5%)
Decreased (11-20 $\mu\text{mol/l}$)	105 (10.2%)	91 (9.1%)
Unchanged or Decreased (1-10 $\mu\text{mol/l}$)	330 (32%)	279 (28%)
Increased (1-10 $\mu\text{mol/l}$)	197 (19.1%)	268 (26.9%)
Increased (1-11 $\mu\text{mol/l}$)	151 (14.6%)	140 (14.1%)
Increased (> 20 $\mu\text{mol/l}$)	162 (15.7%)	153 (15.4%)

All-Cause Mortality Multivariate Analysis

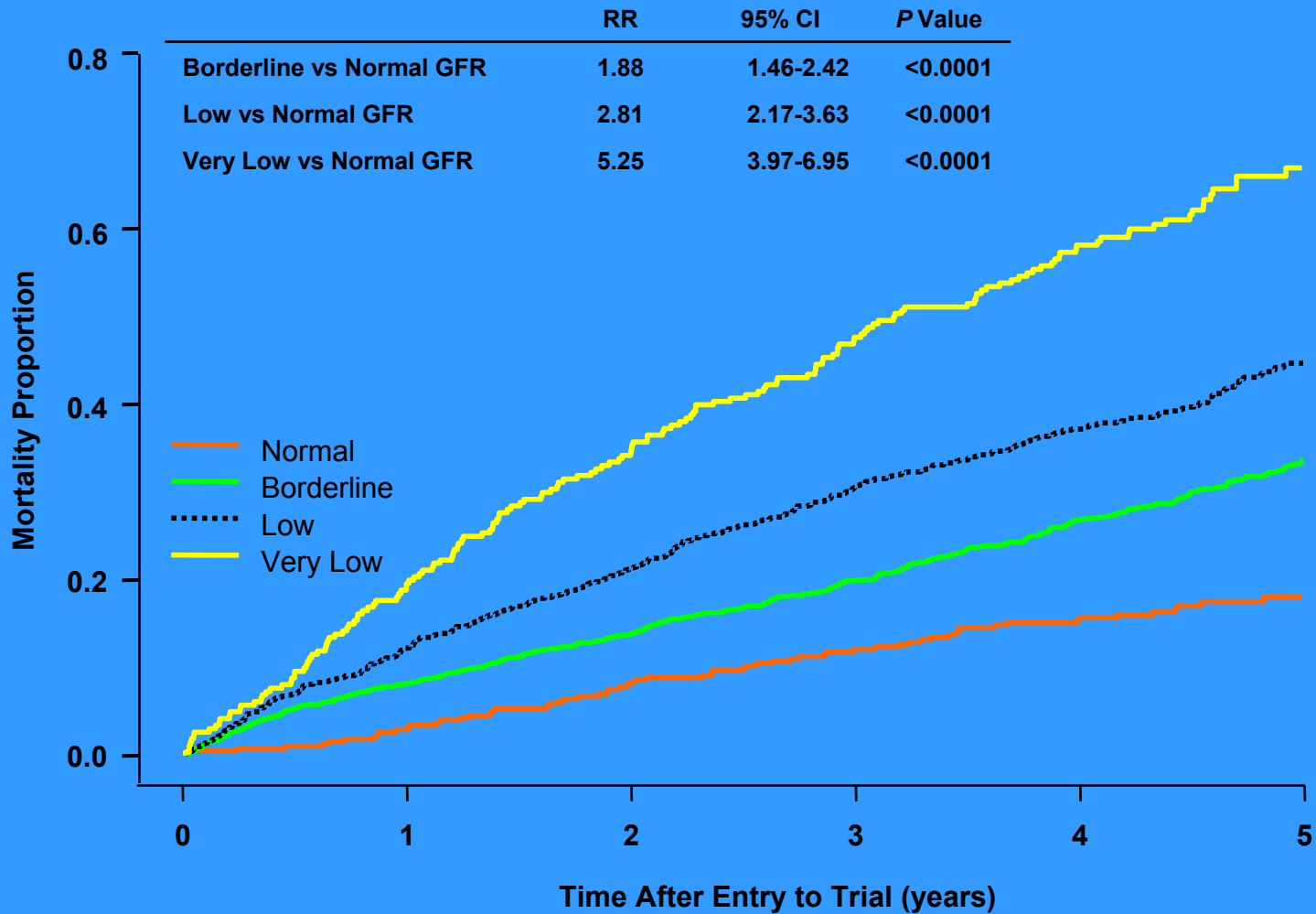
■ Adjusted hazard ratios*

	RR	95% CI	P Value
Borderline vs Normal GFR	1.68	1.27–2.22	0.0003
Low vs Normal GFR	1.67	1.25–2.25	0.0006
Very Low vs Normal GFR	2.59	1.87–3.58	<0.0001

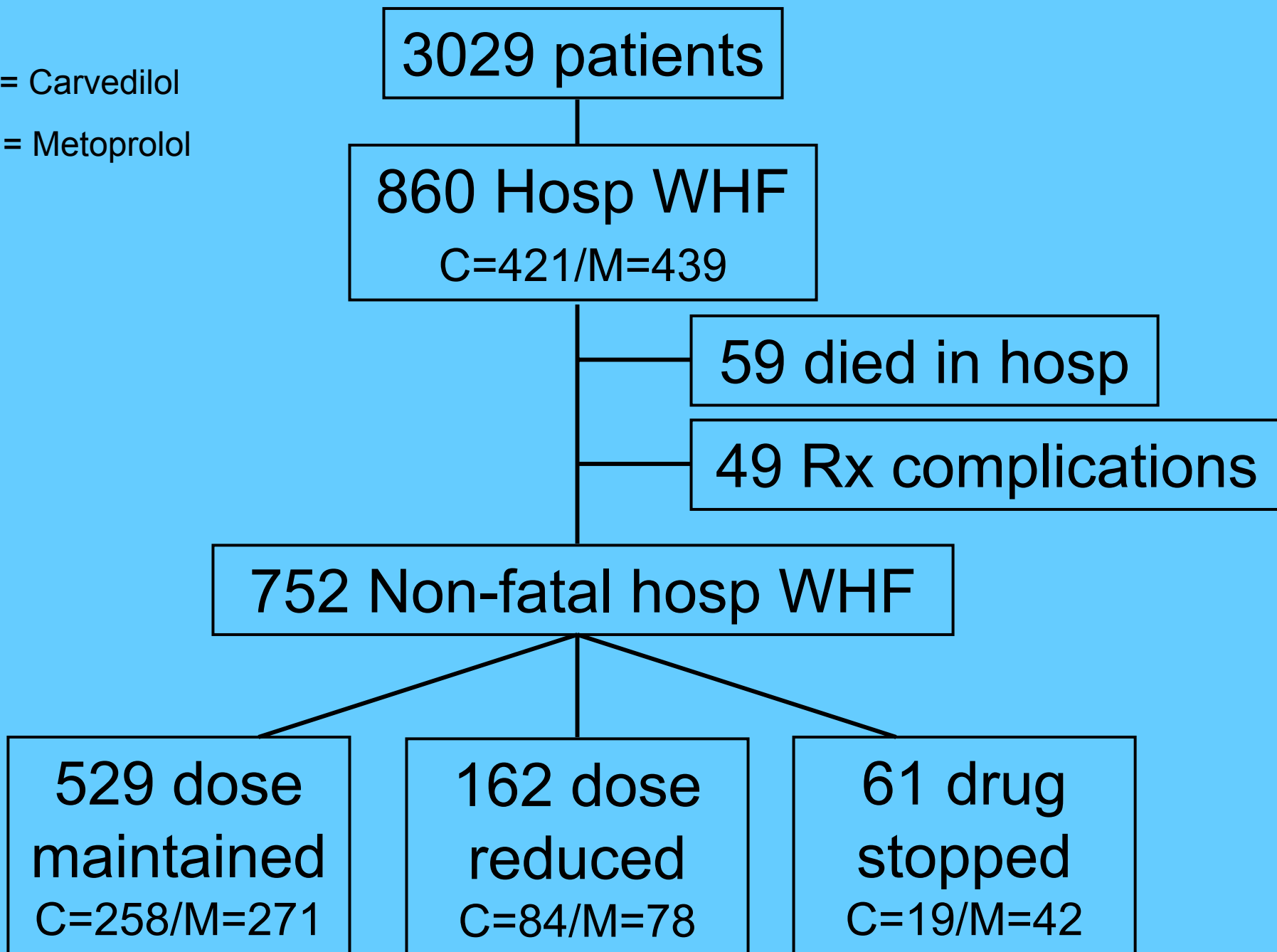
- No significant interaction was found with β -blocker treatment allocation

*Other variables included in the model: carvedilol vs metoprolol tartrate; age; gender; weight; systolic BP; NYHA Class II/III/IV; duration of HF; LVEF; previous MI; CAD yes/no/unknown; diabetes; stroke; ECG paced/AF/sinus rhythm/other; digitalis; anti-arrhythmics; nitrates; lipid-lowering drugs; hemoglobin; S-sodium

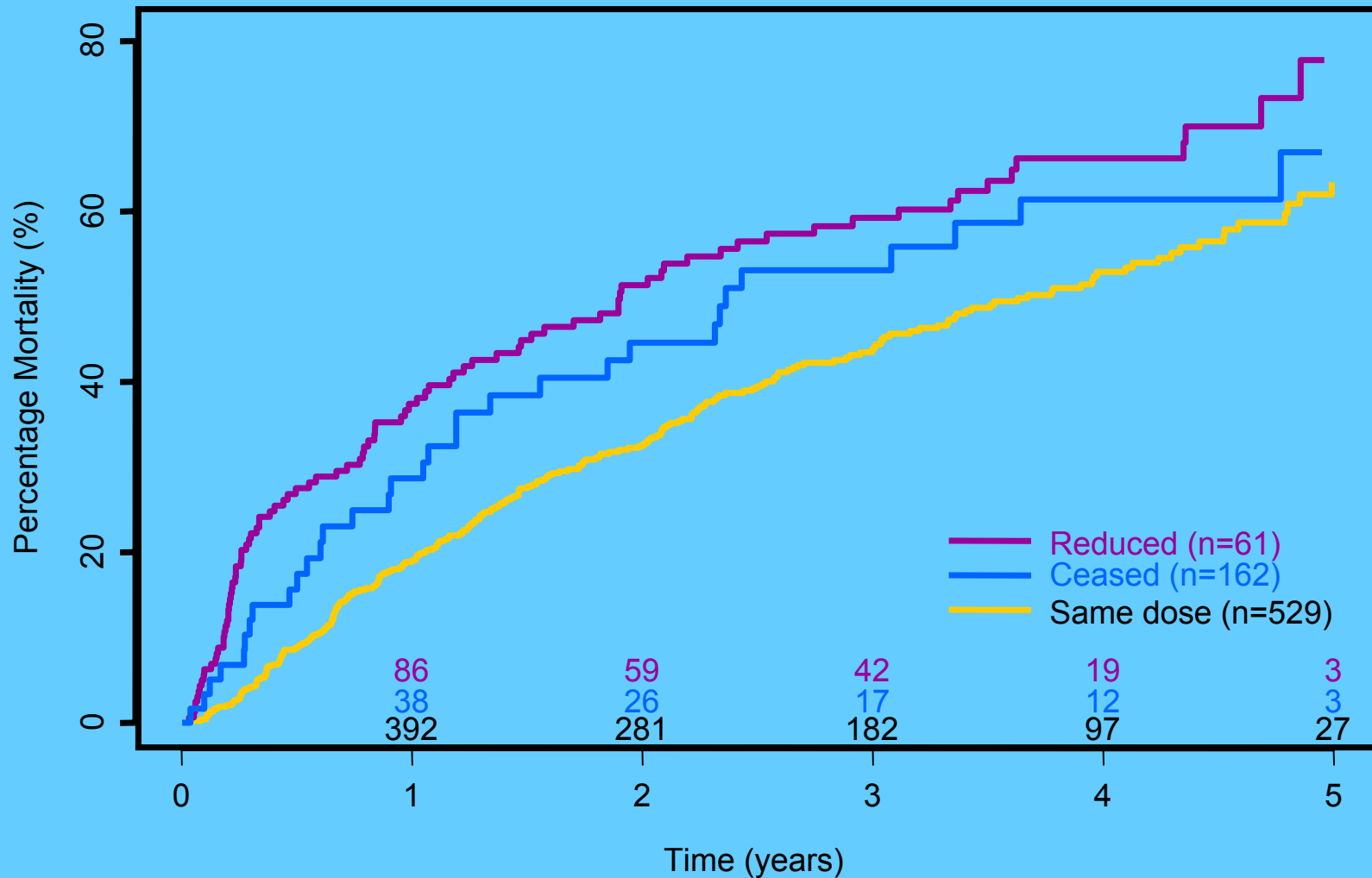
All-Cause Mortality



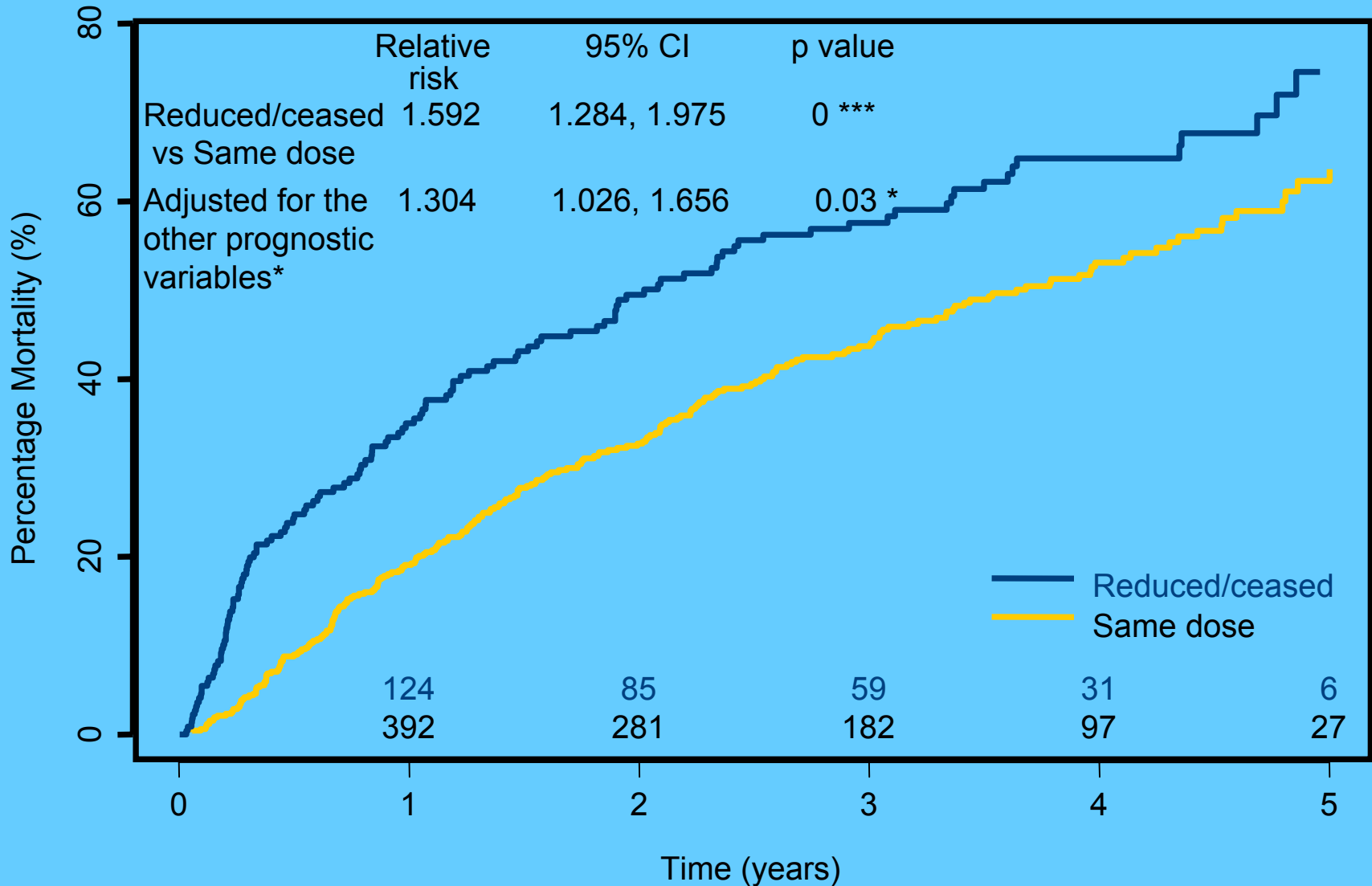
C = Carvedilol
M = Metoprolol



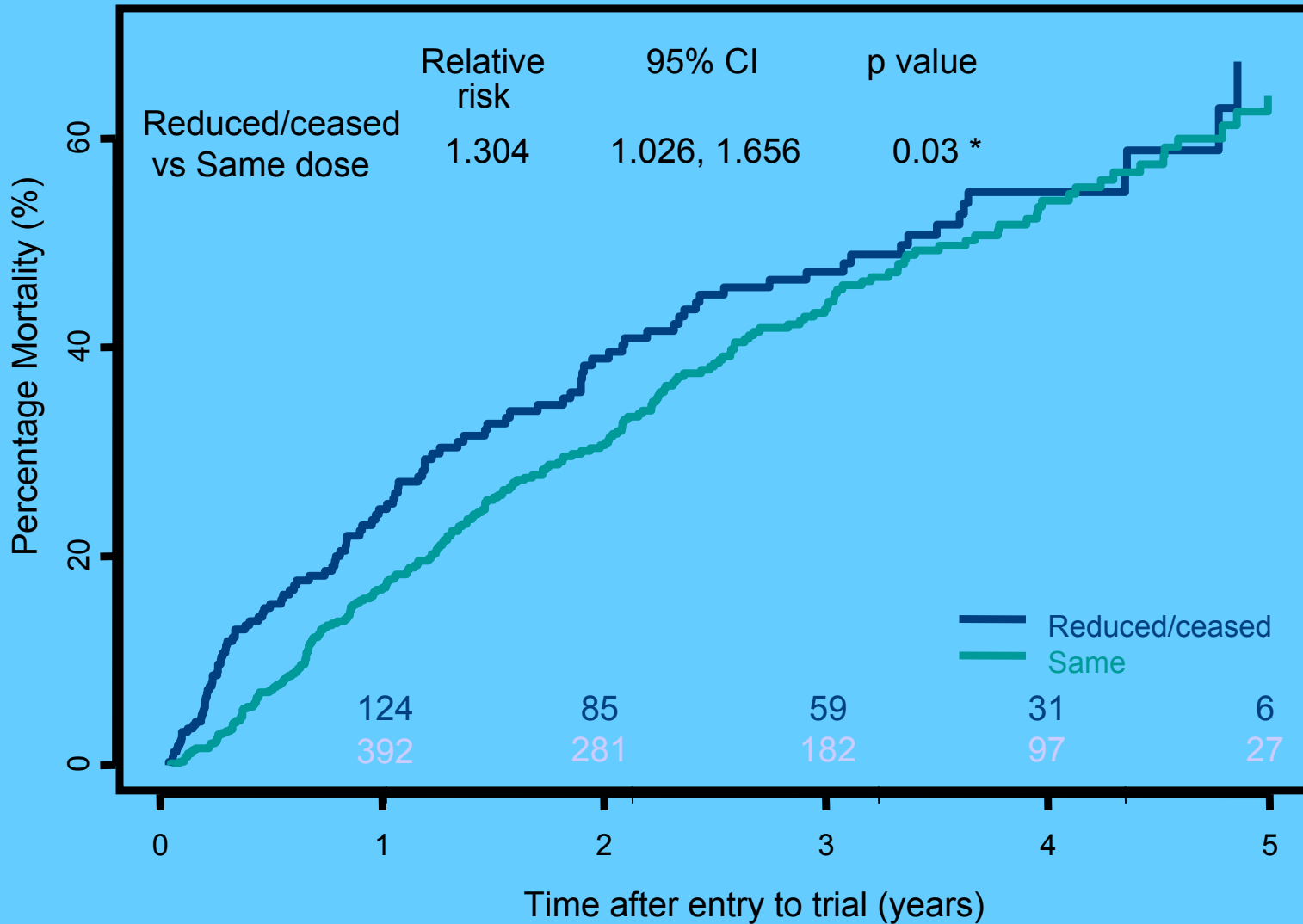
Mortality following Discharge



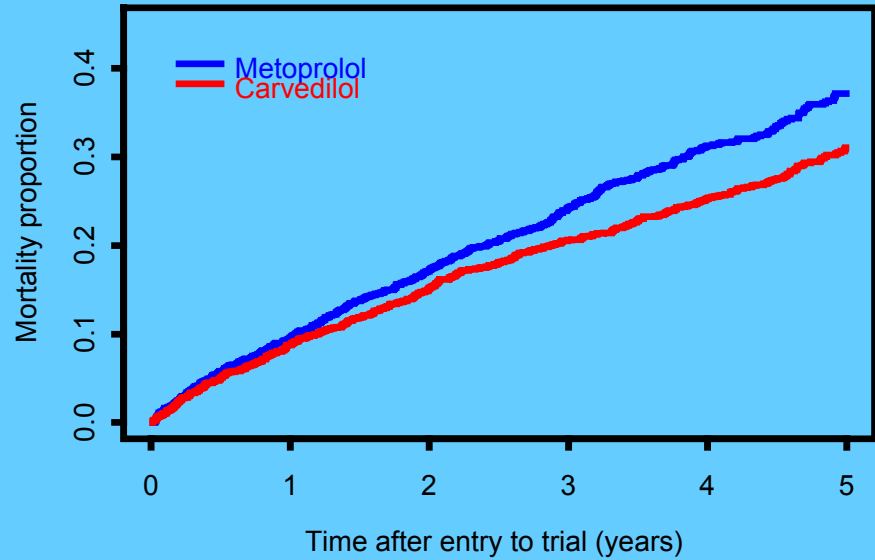
Mortality following discharge



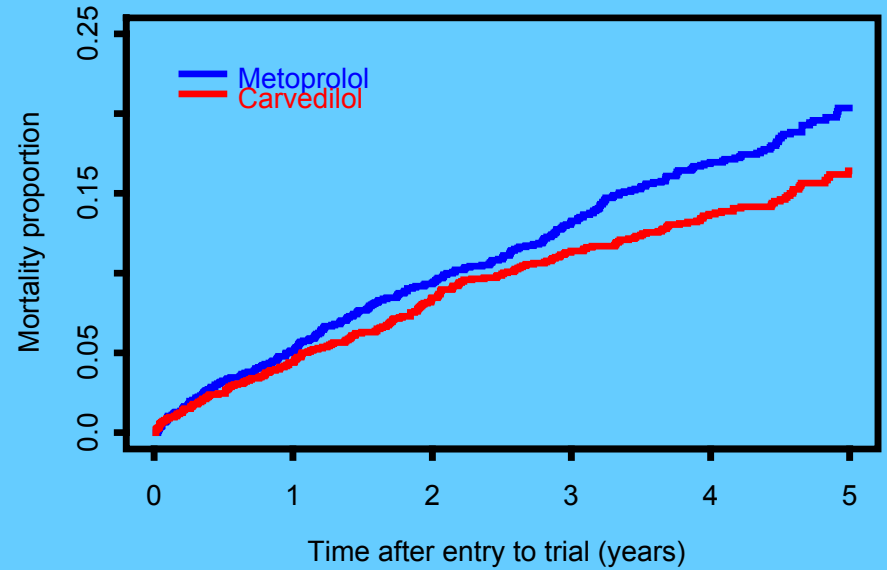
Mortality following discharge (adjusted for other prognostic variables)



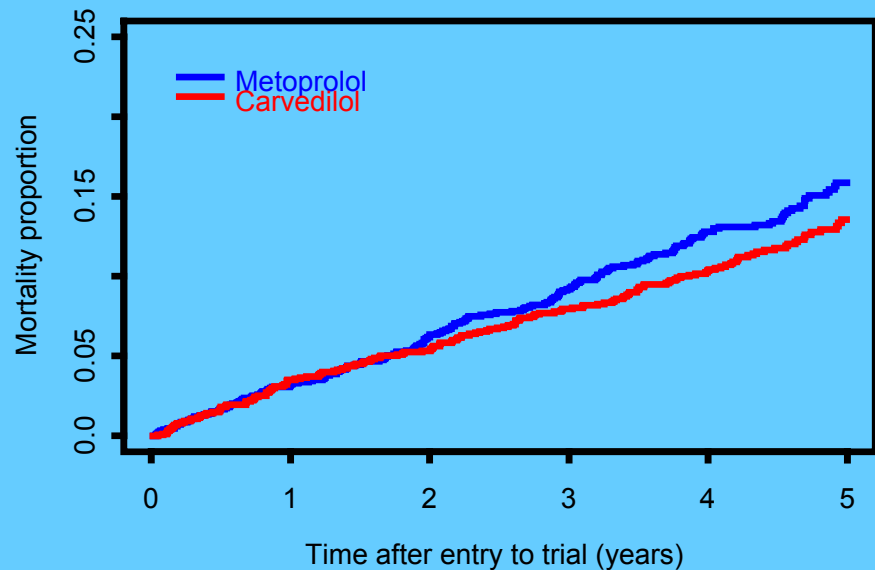
Cardiovascular mortality



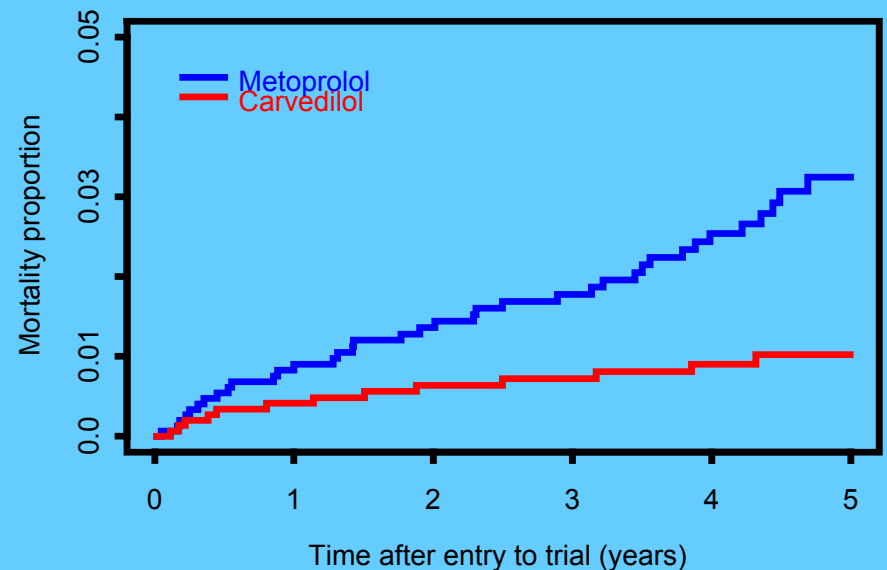
Sudden death



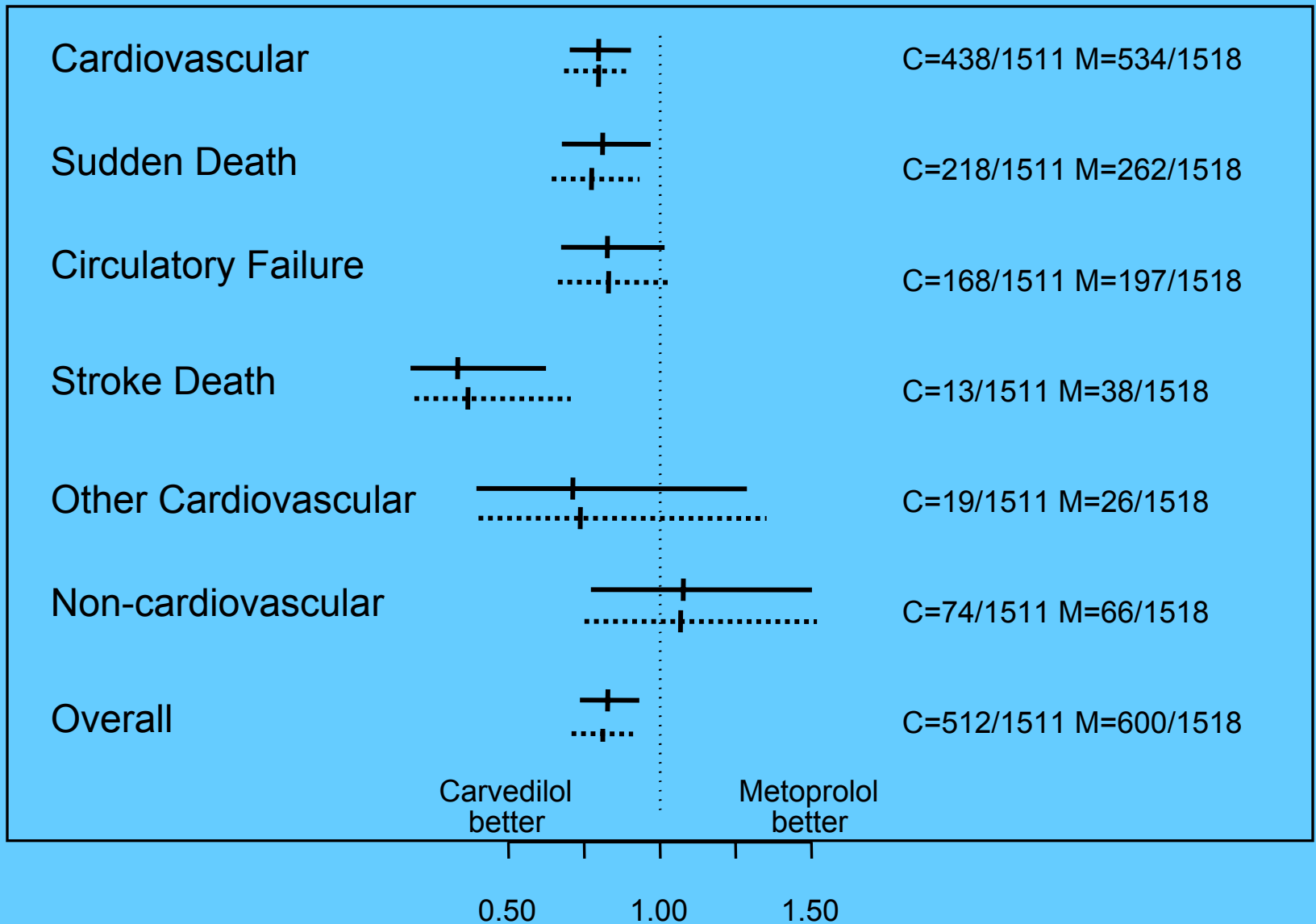
Circulatory failure



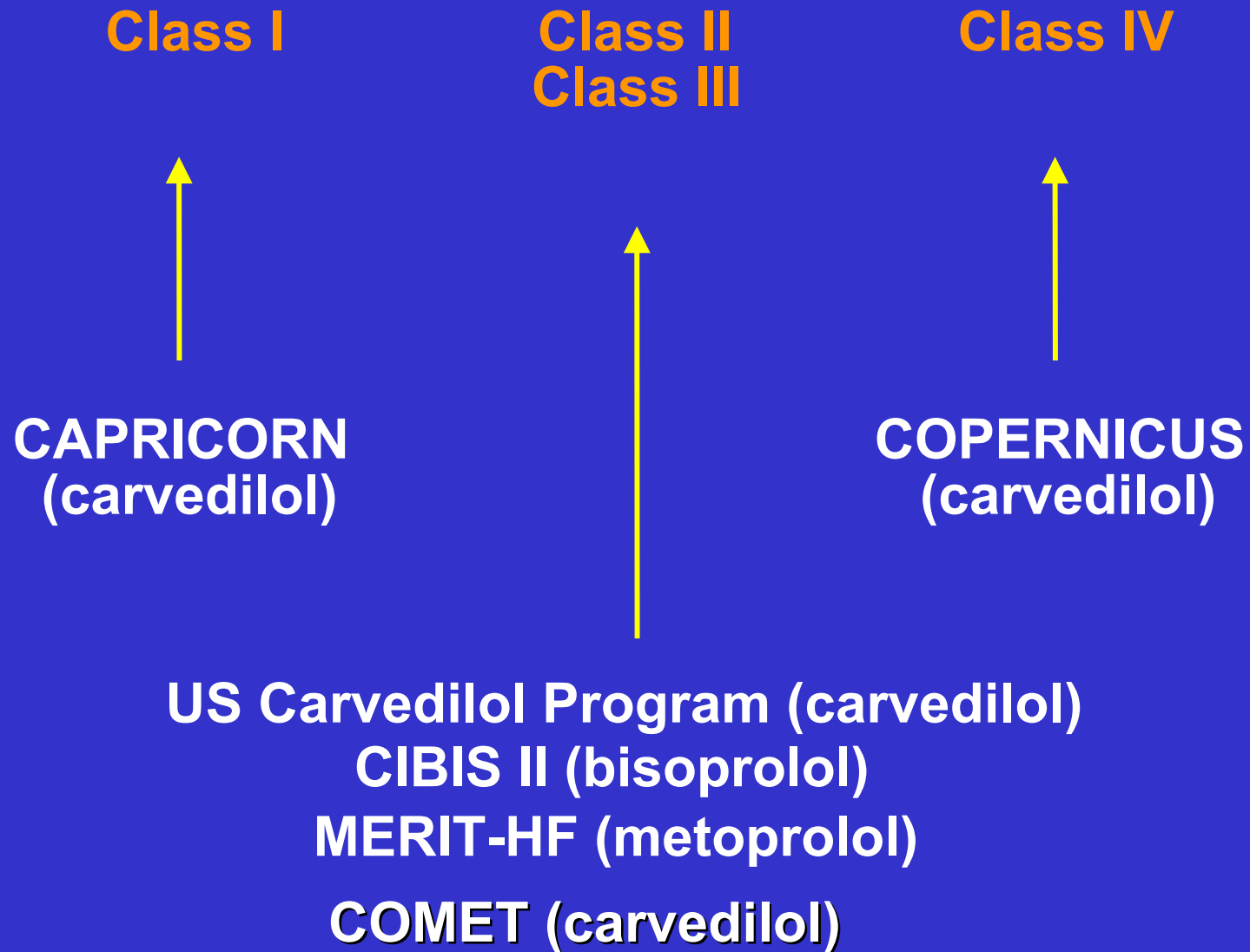
Stroke death



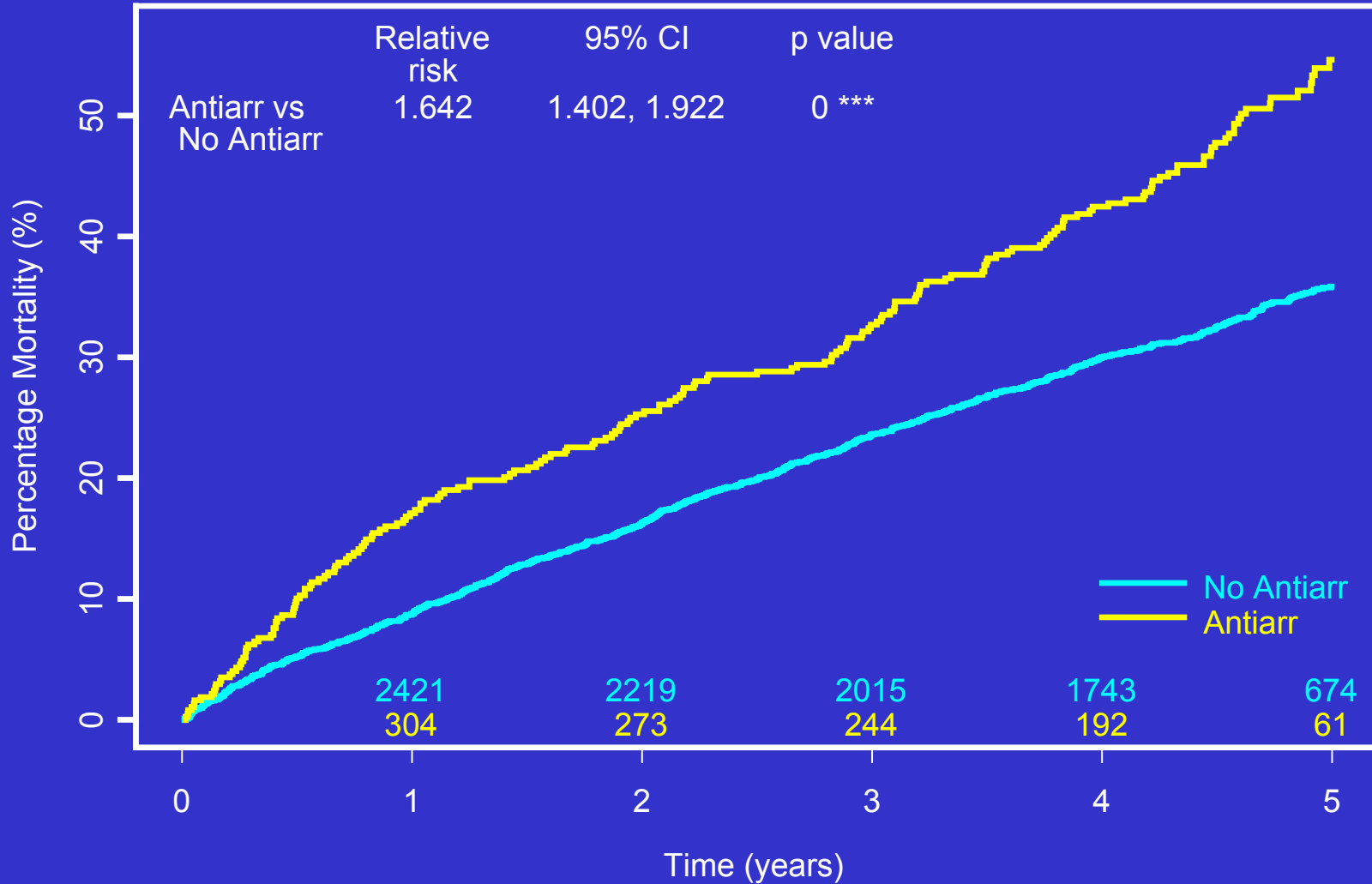
Relative risk of death



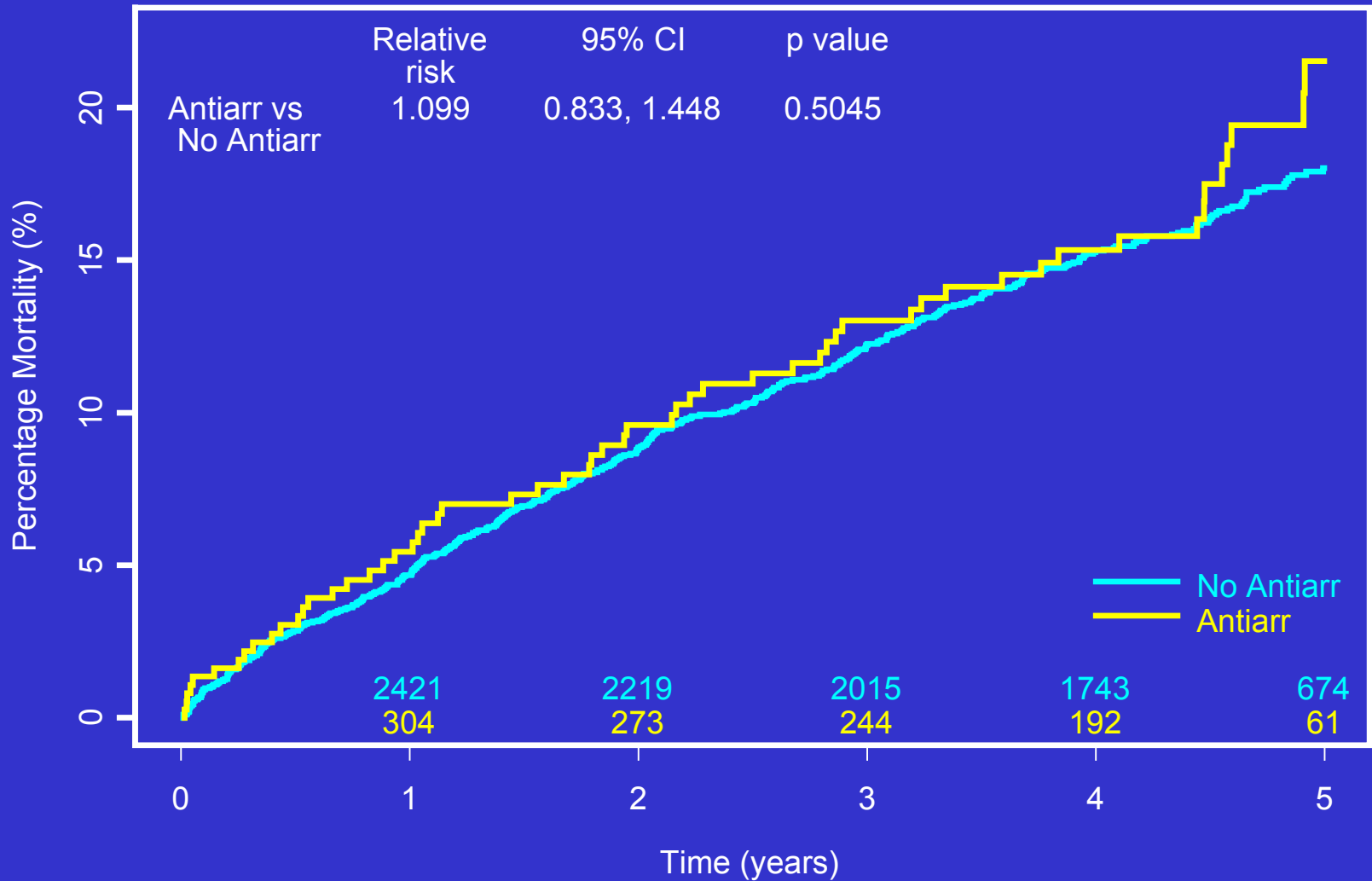
Beta-blockade –survival benefit in all class CHF



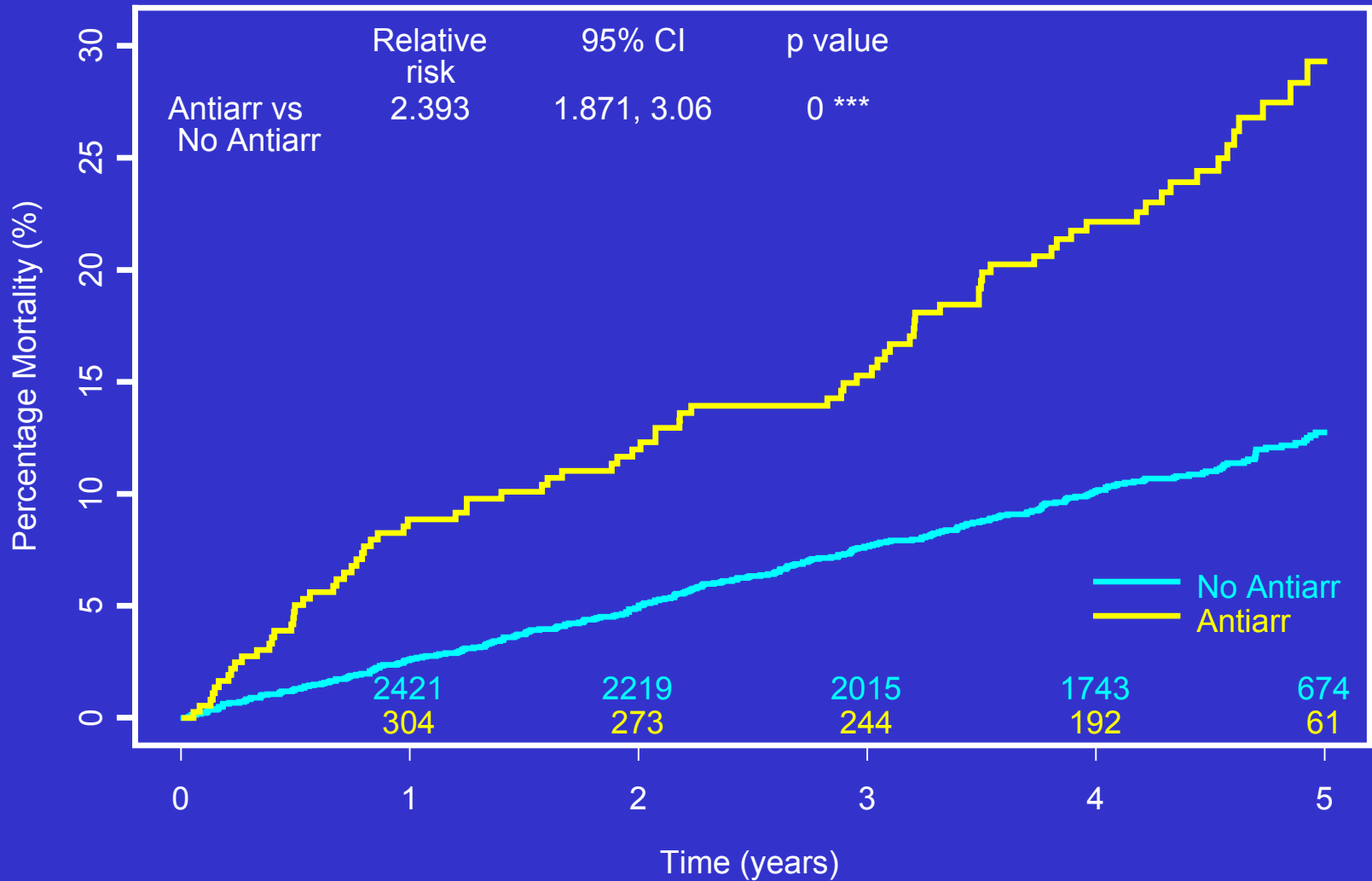
All cause mortality



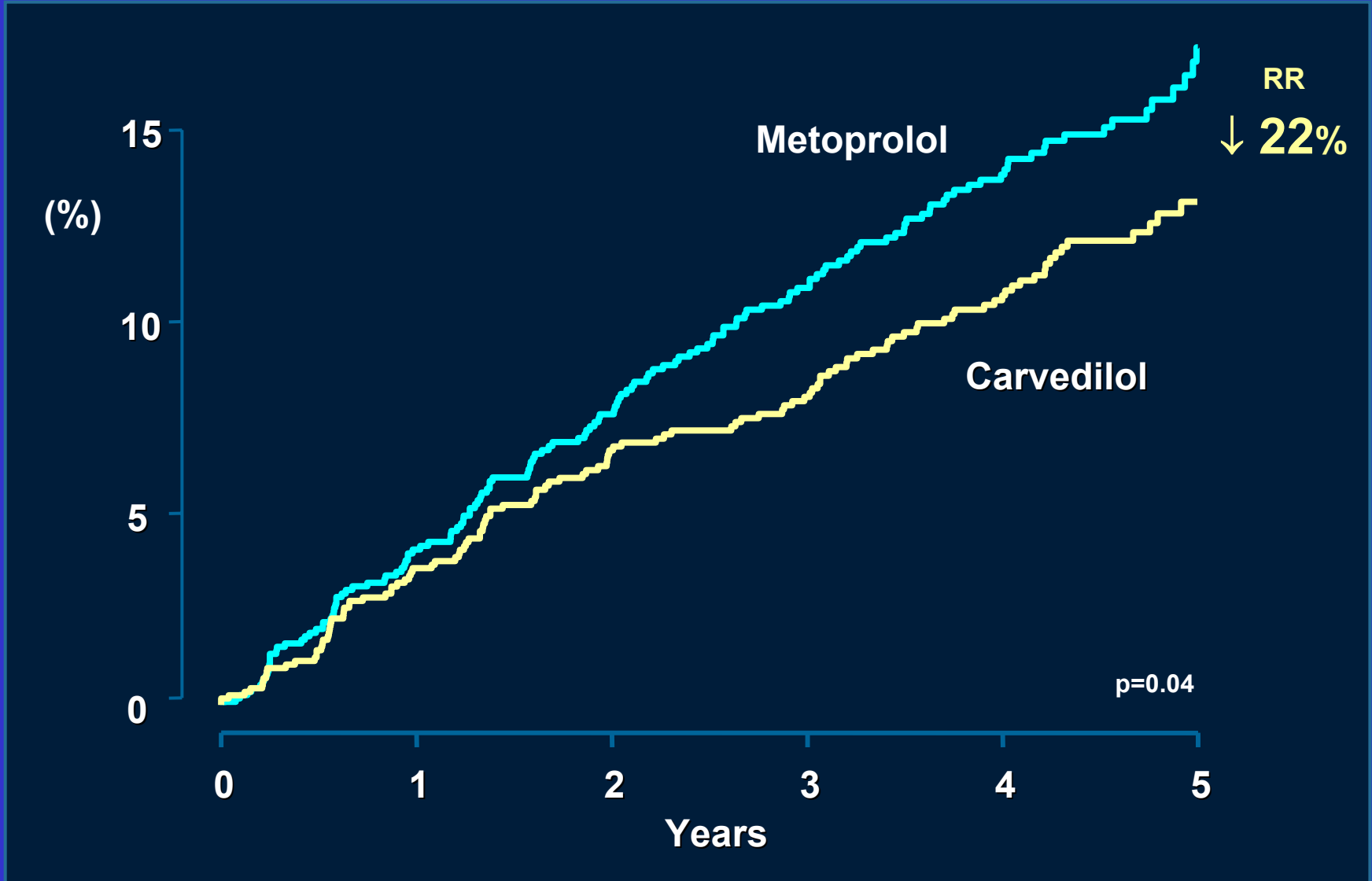
Sudden death



Death due to circulatory failure

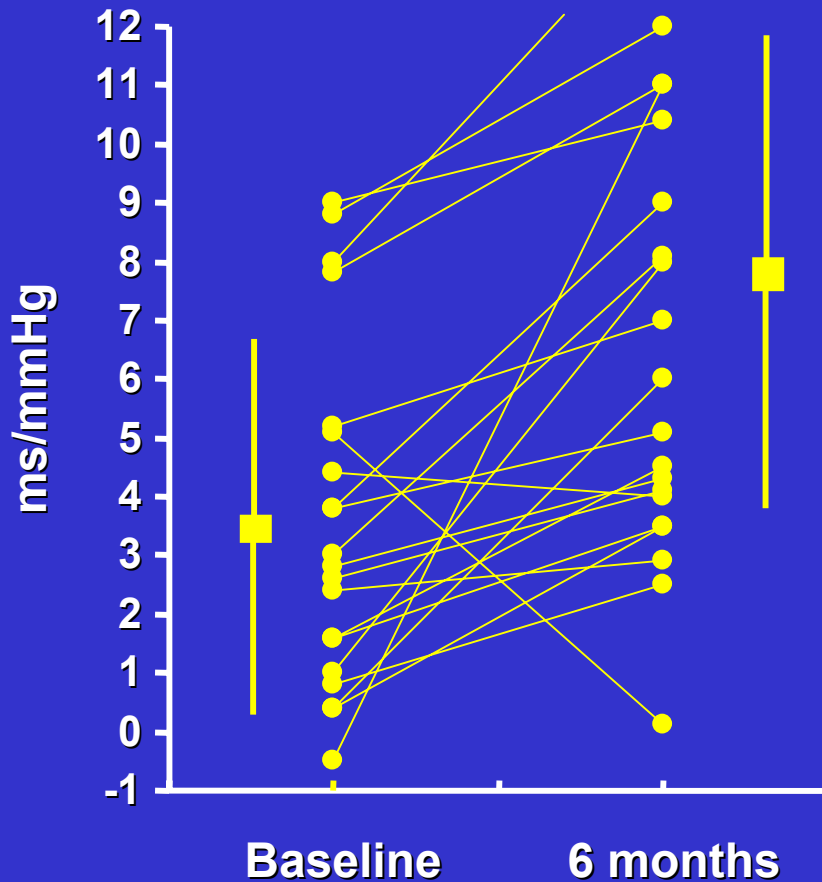


New Onset Diabetes Mellitus

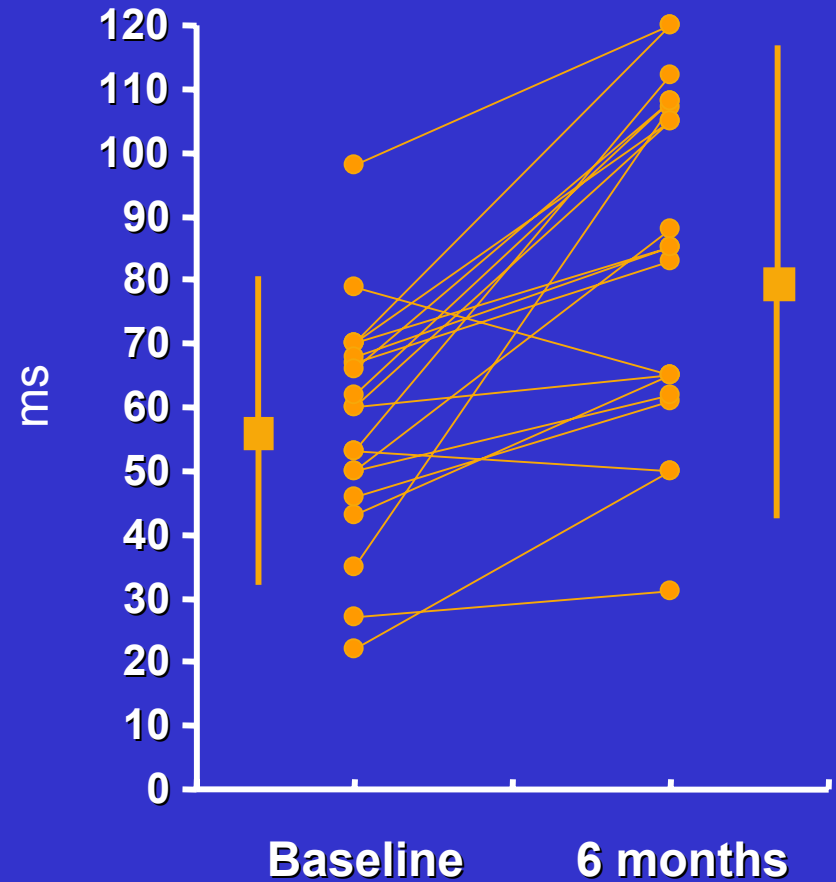


Carvedilol Improves Arterial Baroreflex Gain and Heart Rate Variability in CHF

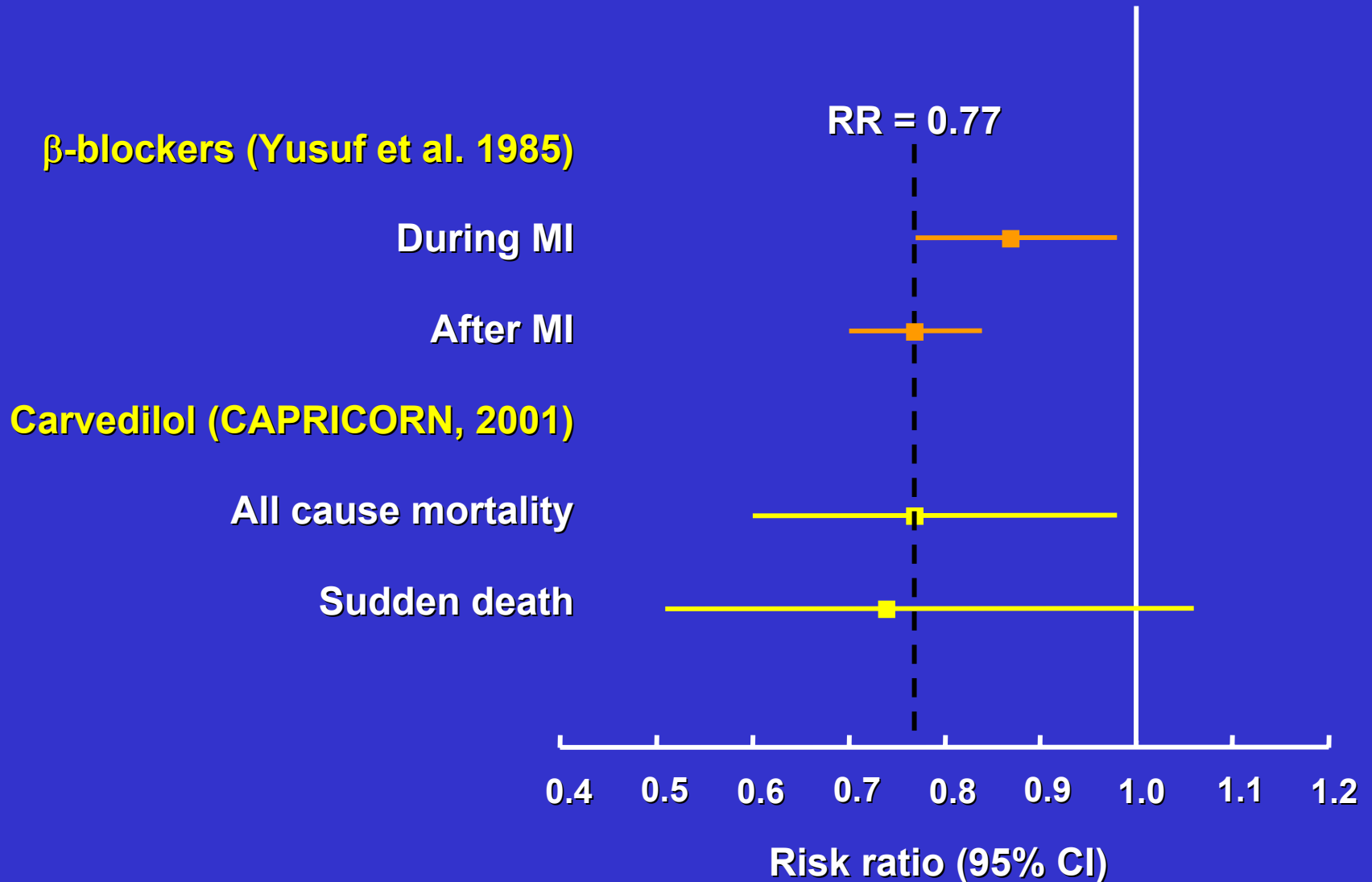
Baroreceptor Sensitivity



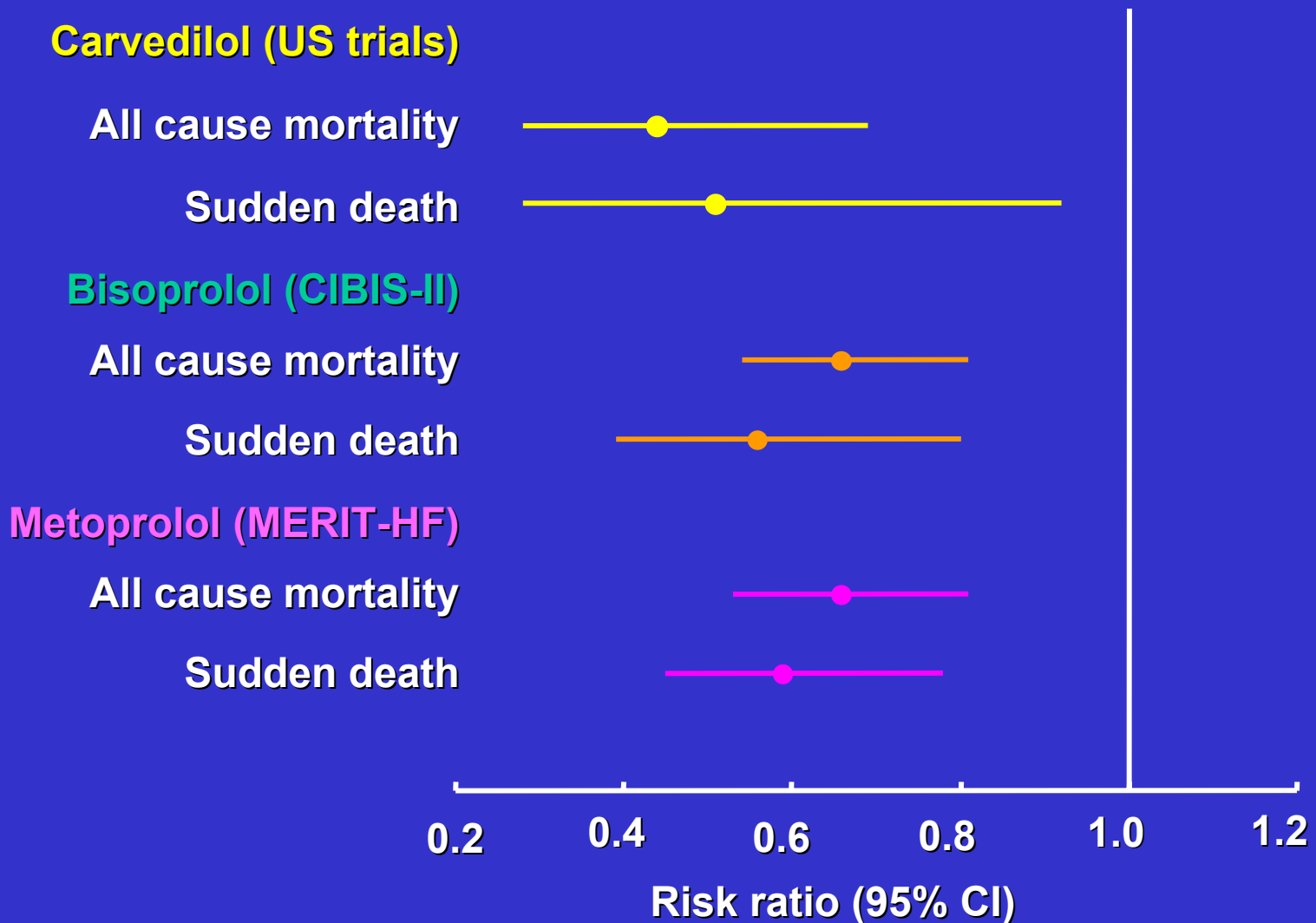
24-h R-R Interval Standard Deviation



Effects of β -blockers on Survival After AMI

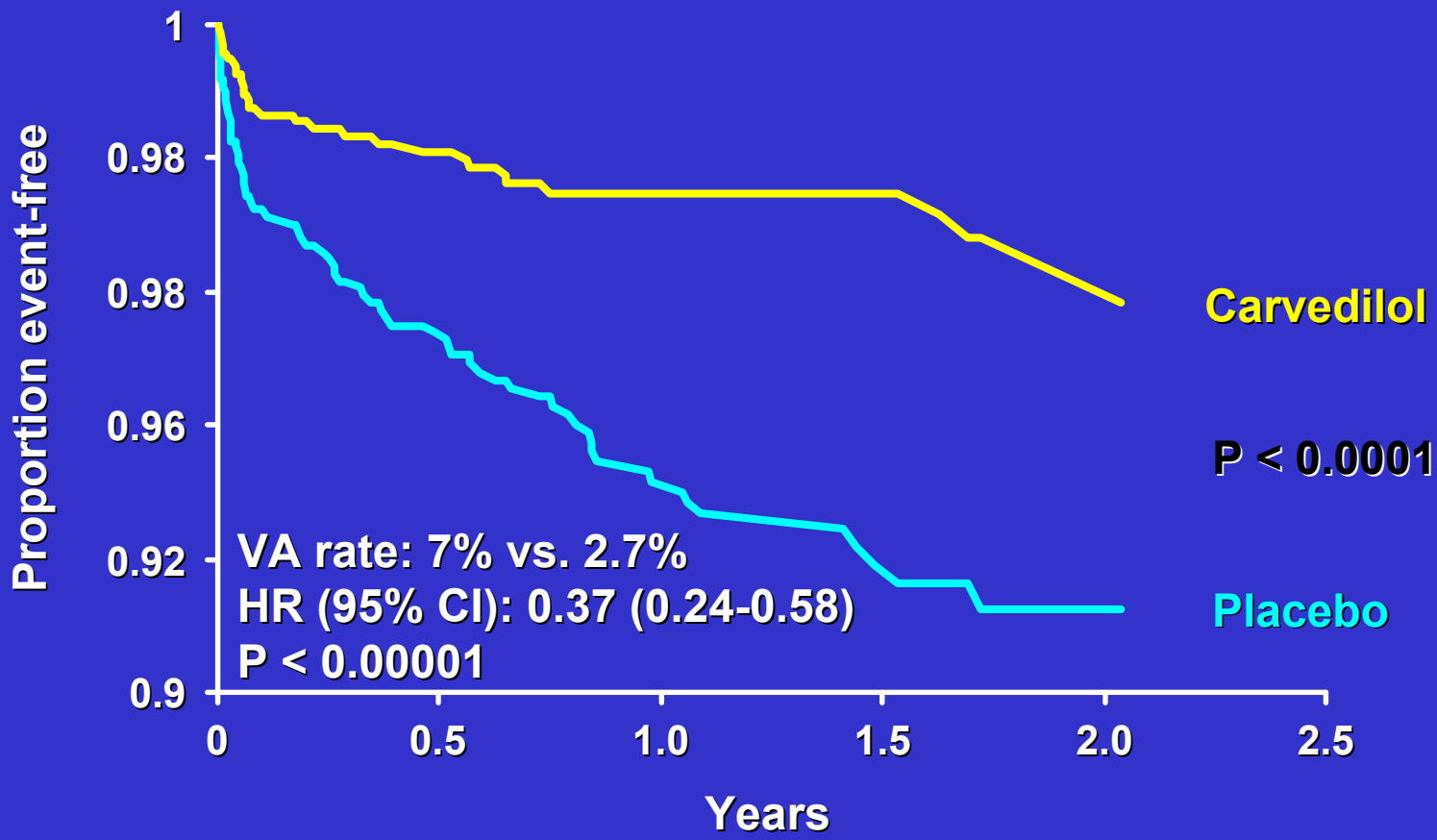


Effects of β -Blockers on Survival in Patients with CHF



CAPRICORN Trial: Incidence of Ventricular Arrhythmias

New events excluding index admission



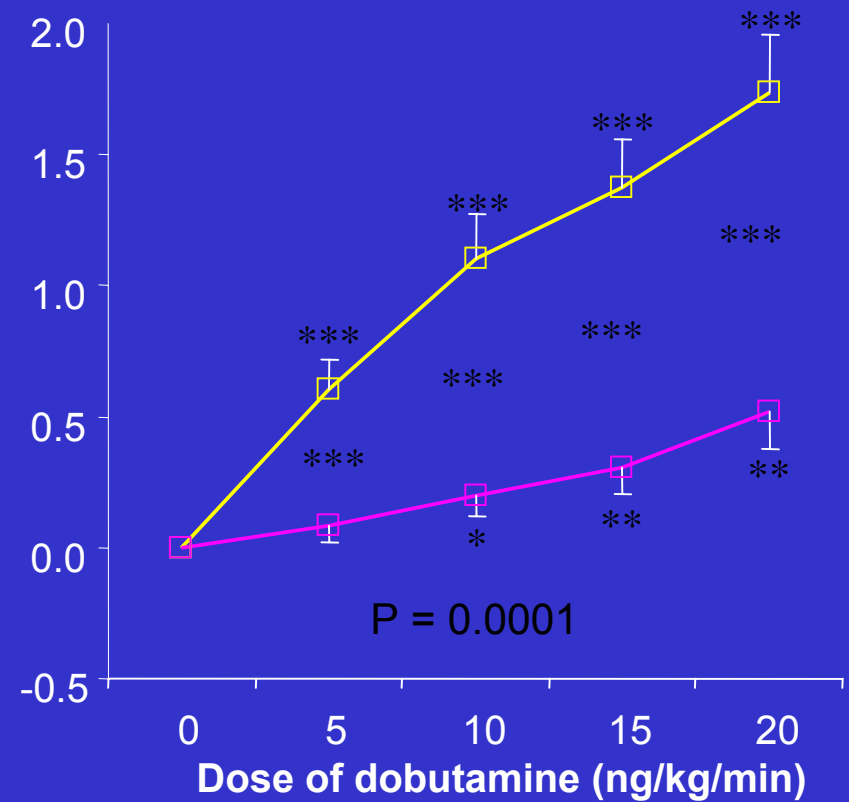
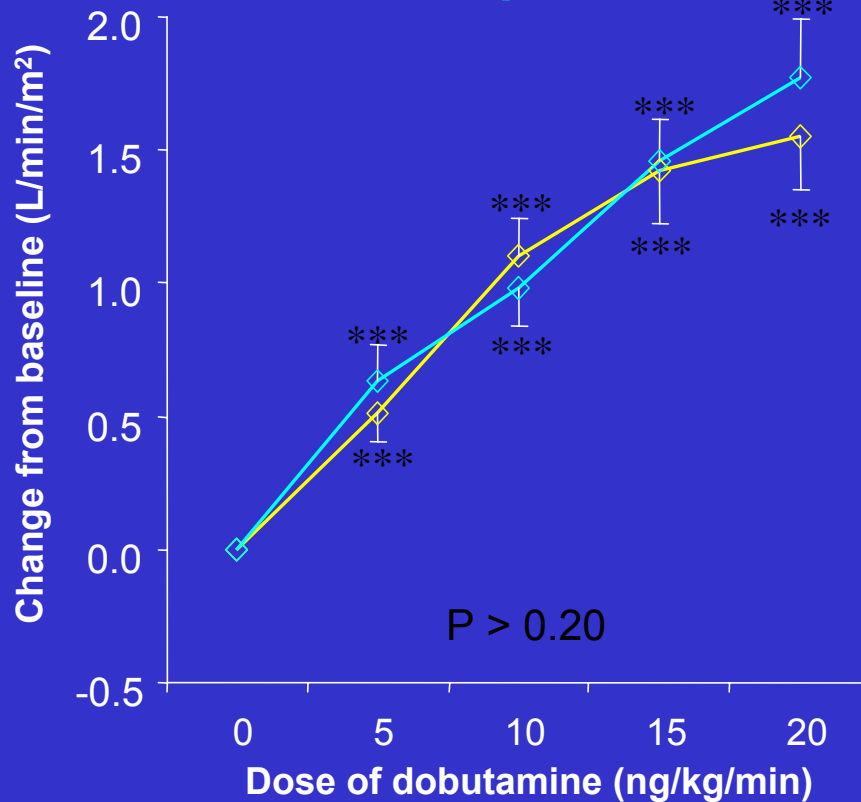
Carvedilol has "Tight Binding" to β -AR Receptors

(Asano et al., JCP 2001):

The Cardiac Index Response to Dobutamine

Metoprolol

Carvedilol

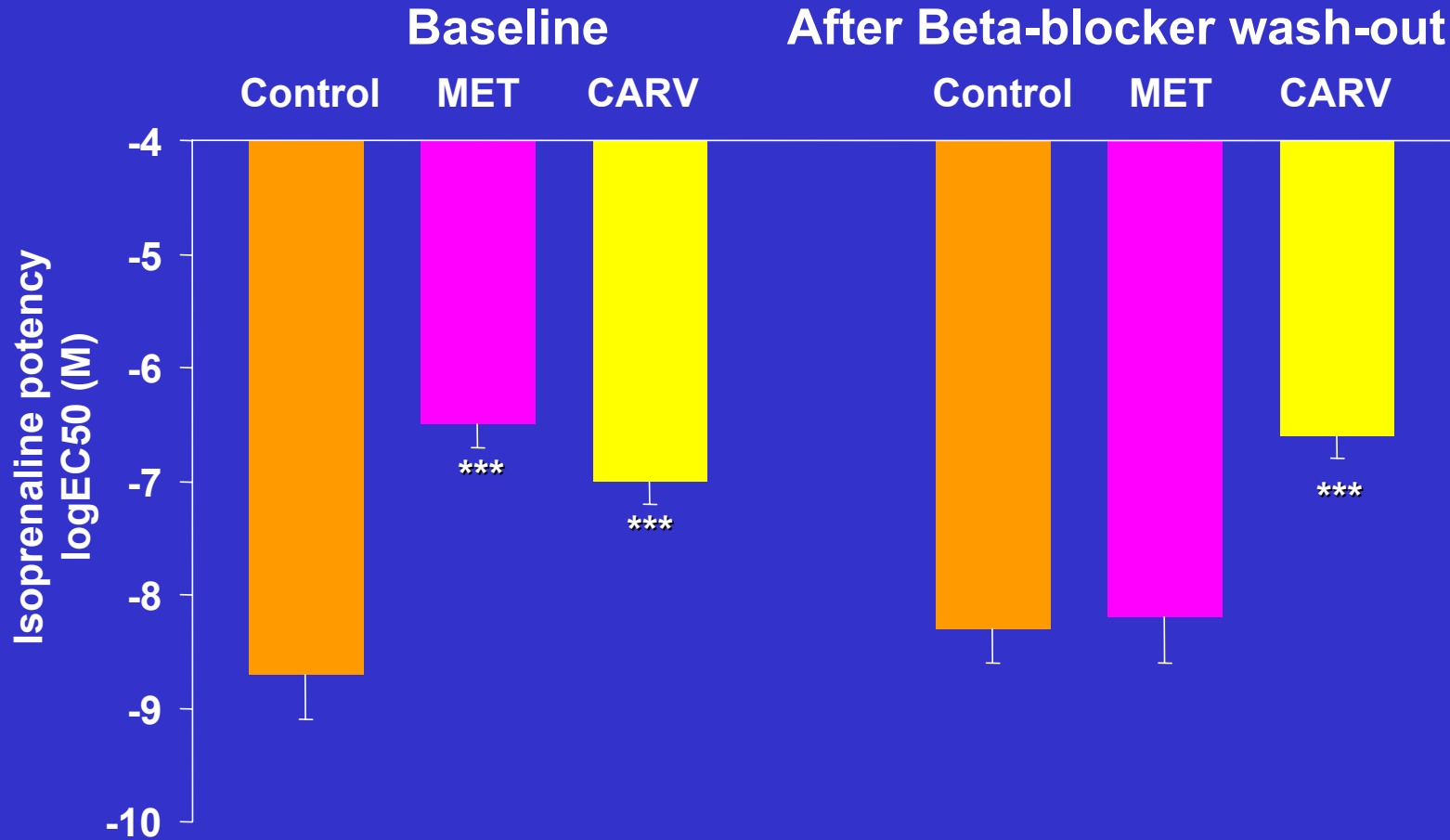


—□— —○— Control
—□— —○— During long-term metoprolol

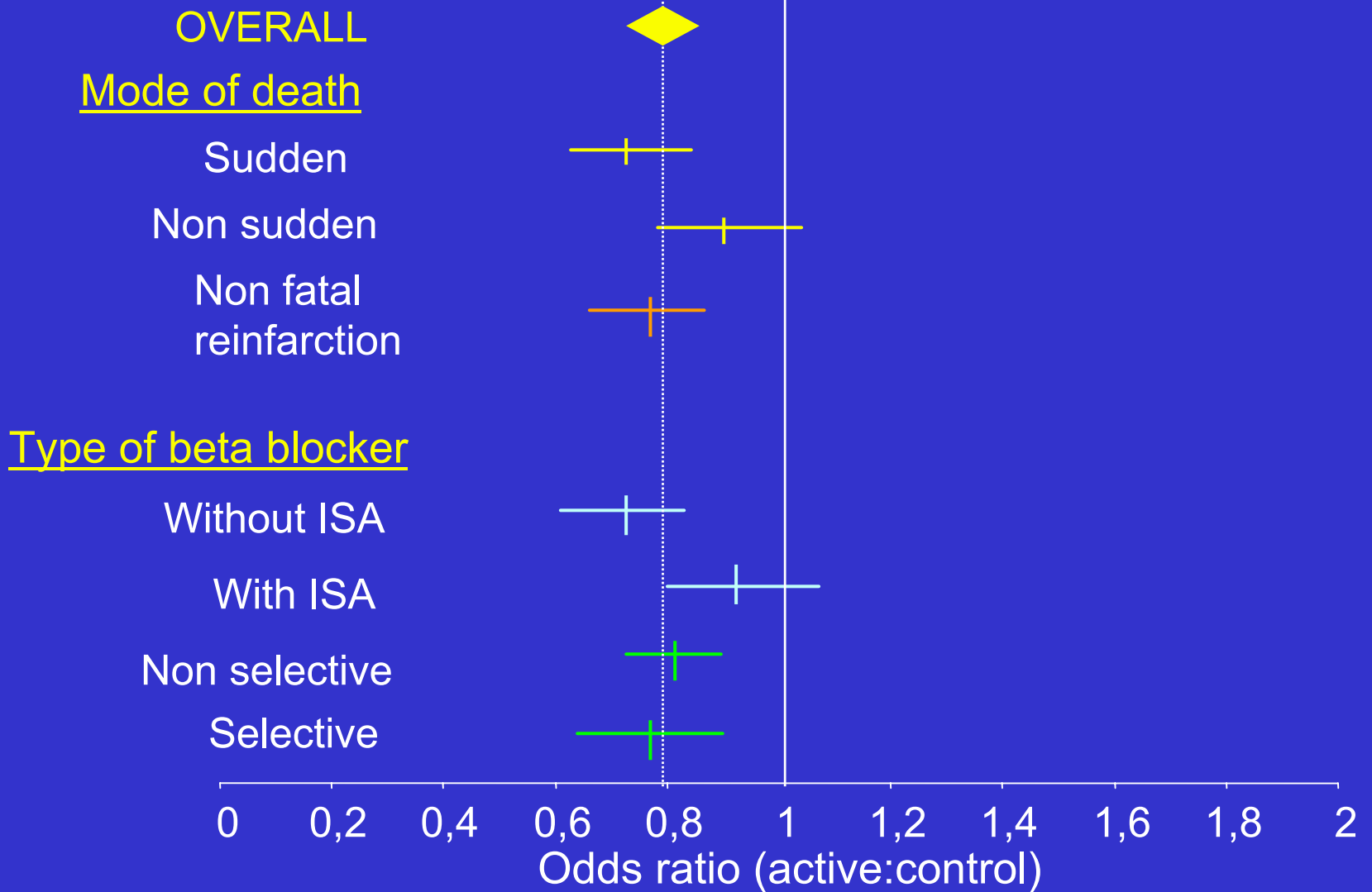
—□— —○— Control
—□— —○— During long-term carvedilol

Atypical Binding of Carvedilol to Beta-receptors

Prevents Rebound Phenomenon



Effects of Beta Blockers on the Mortality of Postinfarction Patients: Metanalysis of 27 Controlled Trials (>27,00 pts)



The Comparison Between β Blocker Effects Among Different Compounds

<i>Dosage</i>	<i>Carvedilol</i>	<i>Metoprolol IR</i>	<i>Metoprolol CR/XL</i>	<i>Bisoprolol</i>
<i>COMET Level 1</i>	<i>3.125 mg bid</i>	<i>6.25 mg bid</i>	<i>12.5 mg od</i>	<i>0.625 mg od</i>
<i>COMET Level 2</i>	<i>6.25 mg bid</i>	<i>12.5 mg bid</i>	<i>25 mg od</i>	<i>1.25 mg od</i>
<i>COMET Level 3</i>	<i>12.5 mg bid</i>	<i>25 mg bid</i>	<i>50 mg od</i>	<i>2.5 mg od</i>
<i>COMET Level 4</i>	<i>25 mg bid</i>	<i>50 mg bid</i>	<i>100 mg od</i>	<i>5 mg od</i>

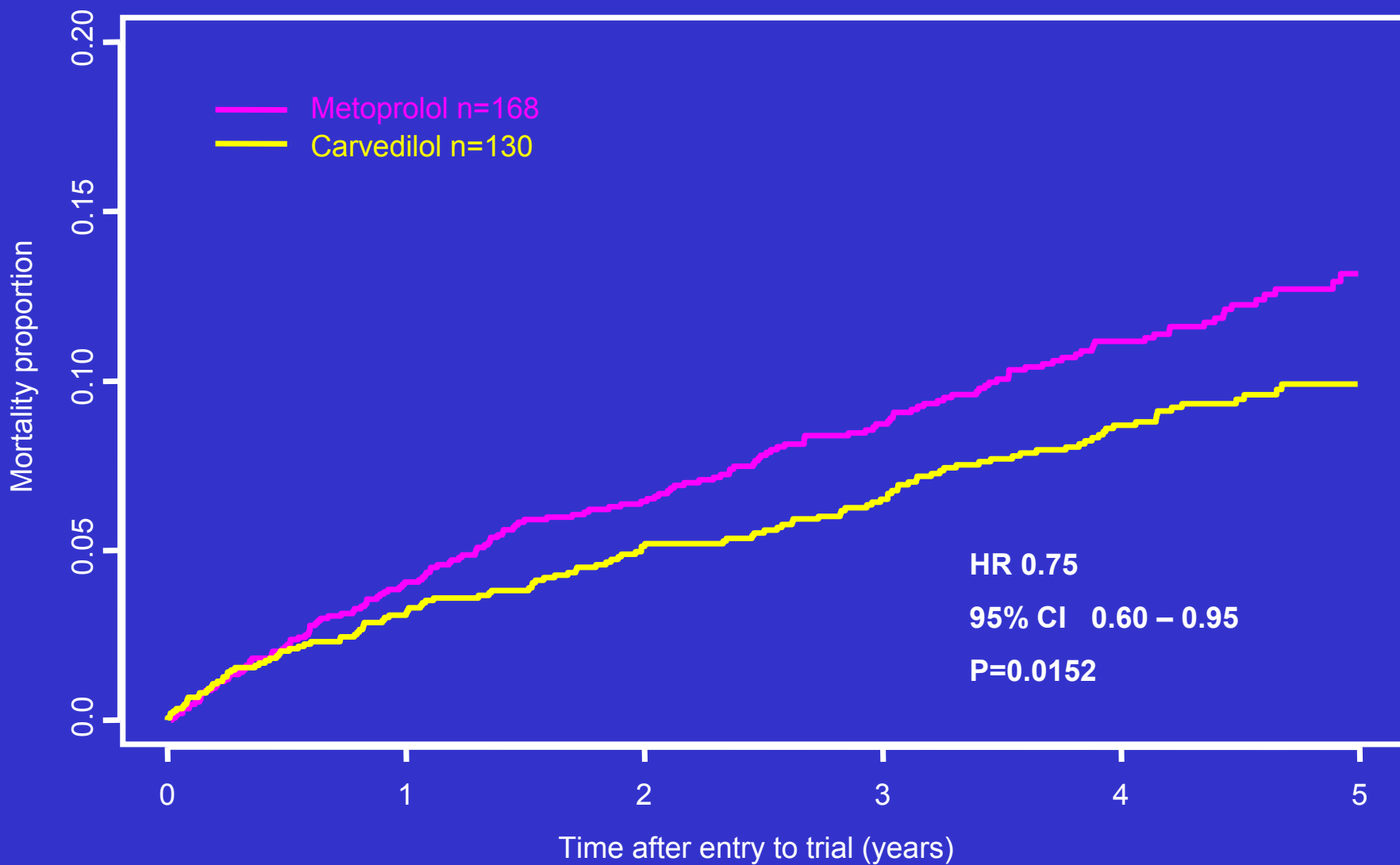
Further up-titration:

Max. dosage	50 mg bid	50 mg tid	200 mg od	10 mg od
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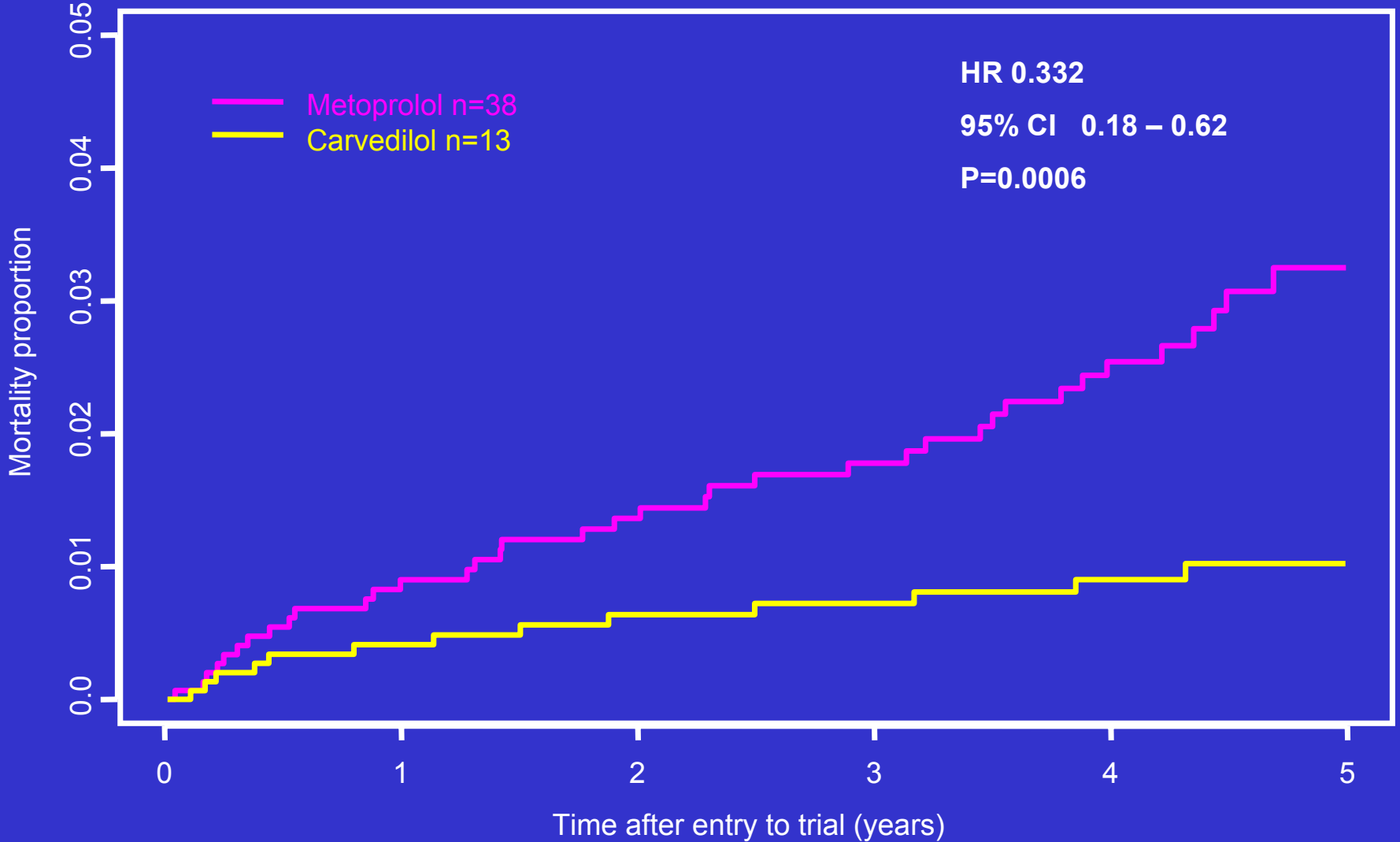
Suggested Procedures for the Closure of COMET after Cut-Off Date Nov. 15, 2002

- **As β blocker withdrawal may precipitate HF and arrhythmias, stable patients on blinded medication should be switched to open β -blockade**
- **The transition from one β blocker to another does not need down-titration of the initial agent**
- **The first dose of the new agent should be equivalent to one half of the last dosage of study medication**
- **Investigators free to choose the most appropriate blocker currently available**

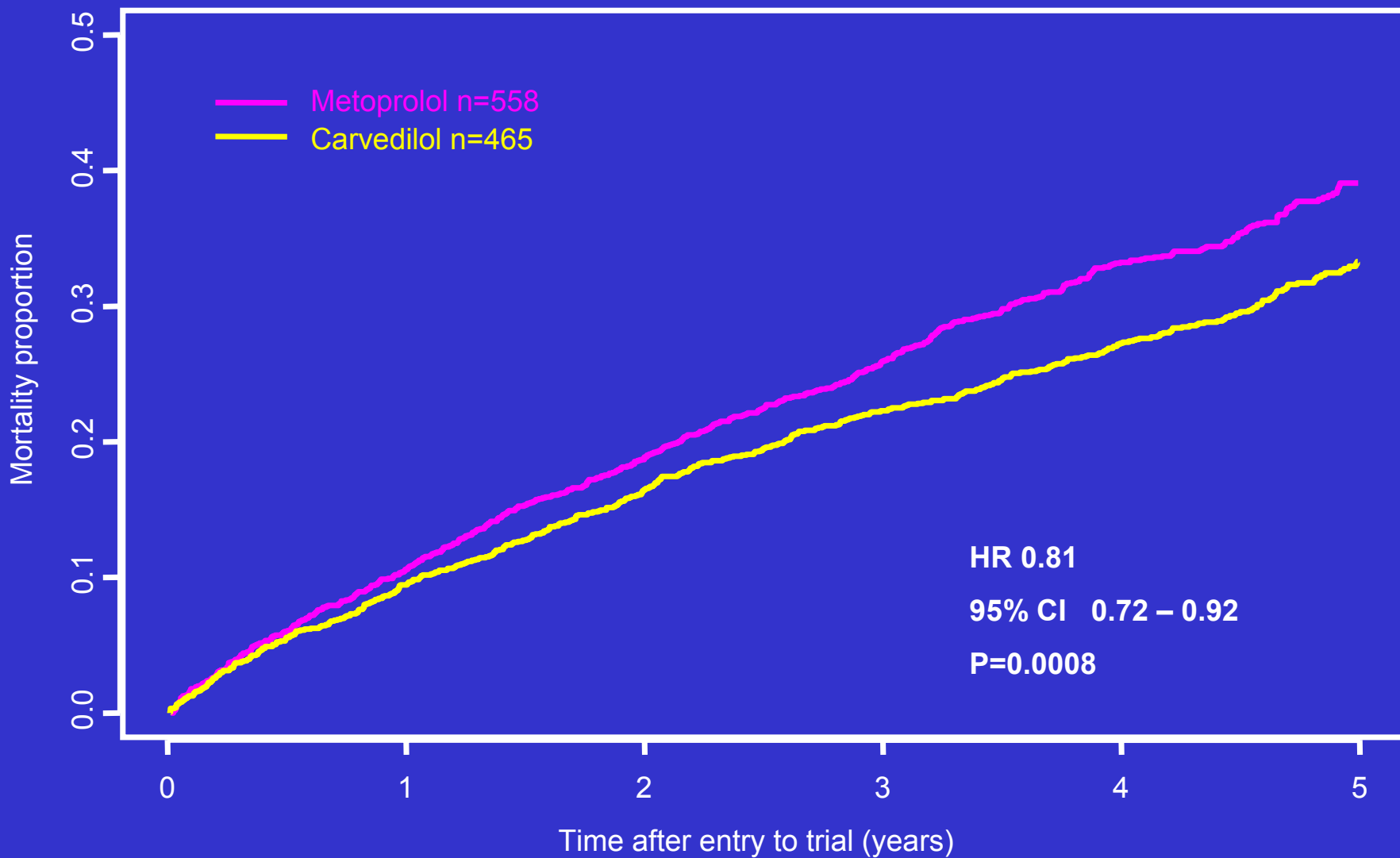
Stroke or MI



Stroke Death



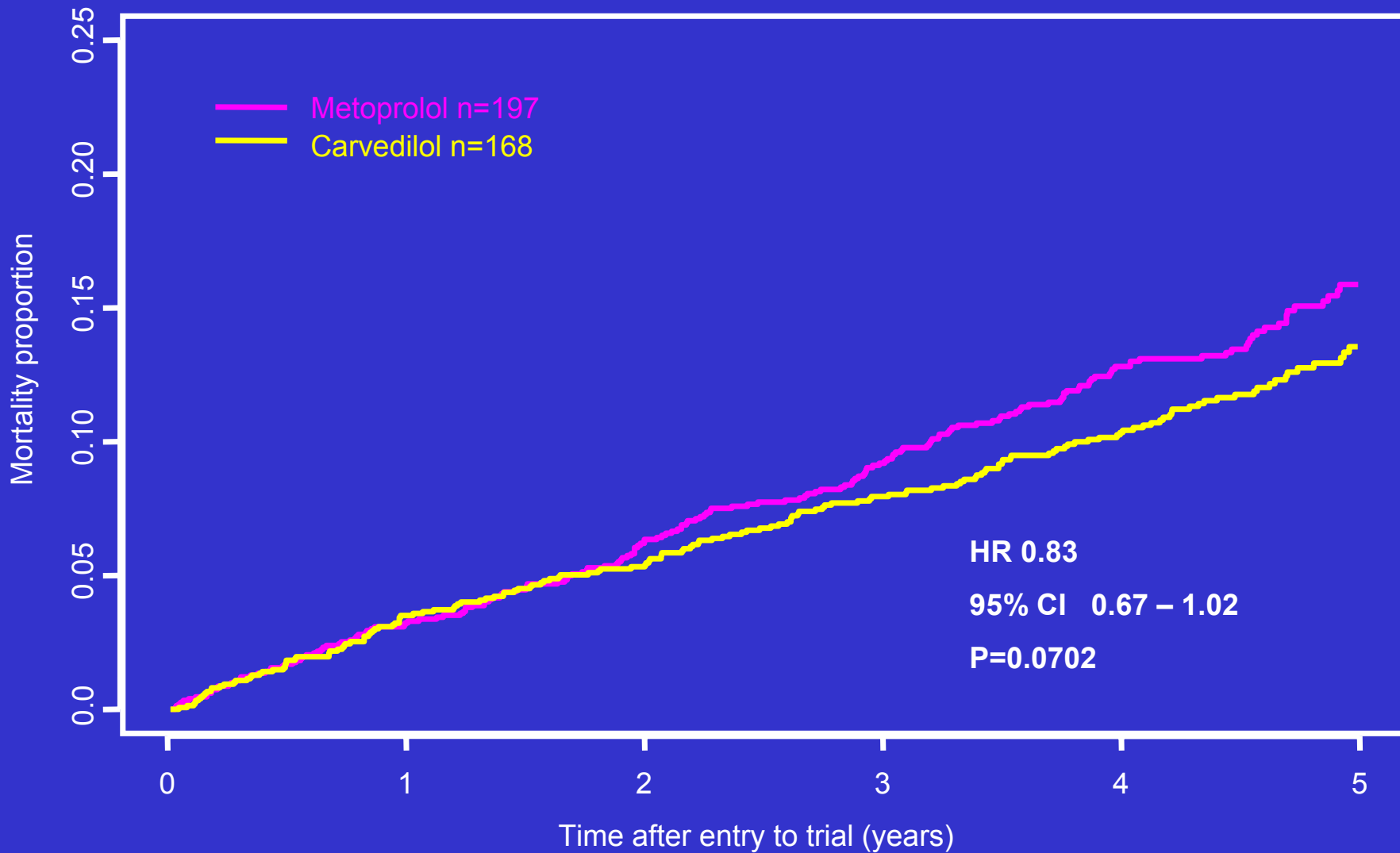
Cardiovascular Death or Non-Fatal MI



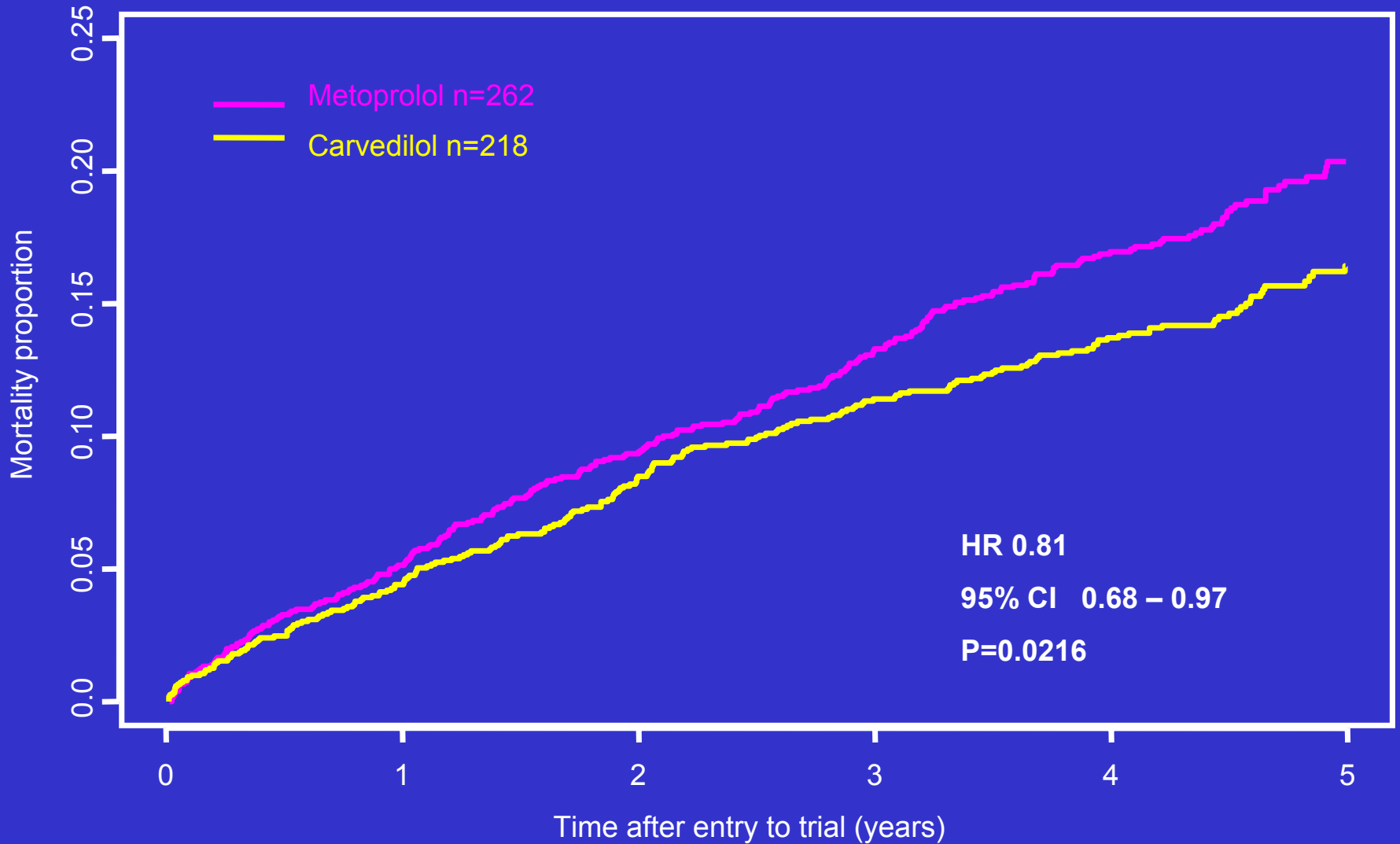
The Effect of Carvedilol and Metoprolol on Vascular Events

	Carvedilol	Metoprolol	RR	95% CI	p
Fatal or non-fatal MI	69	94	0.71	(0.52 – 0.97)	0.0333
Death or non-fatal MI	544	629	0.84	(0.75 – 0.94)	0.0025
CV death or non-fatal MI	465	558	0.81	(0.72 – 0.92)	0.0007
Stroke	65	80	0.79	(0.57 – 1.10)	0.1632
Stroke death	13	38	0.33	(0.18 – 0.62)	0.0006
Stroke or MI	130	168	0.75	(0.60 – 0.95)	0.02

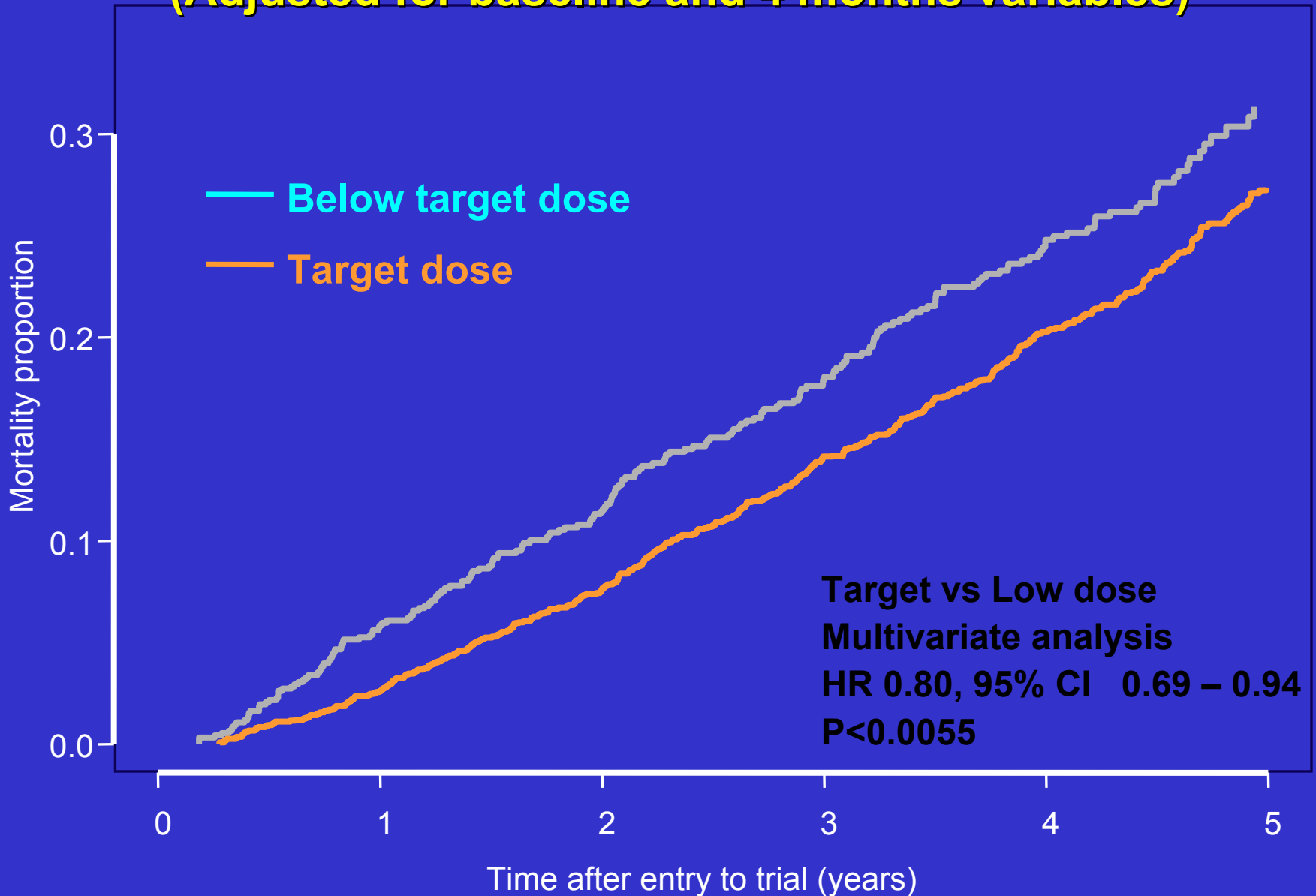
CHF Death



Sudden Death



Mortality in Patients on Target and Lower BB Doses (Adjusted for baseline and 4 months variables)



Predictors of death by multivariate analysis

	Relative risk	95% CI	P value
High versus low beta-blocker dose			
Unadjusted	0.61	0.52, 0.70	<0.0001
Adjusted for other variables	0.80	0.69, 0.94	0.0055
Study drug versus metoprolol)	(carvedilol 0.758	0.653, 0.88	0.0003

Variables also associated with increased mortality in the final model: increasing age, male sex, lower body weight, higher HR at 4 months, lower SBP at 4 months, NYHA class, CHF duration, lower LVEF, previous myocardial infarction, history of diabetes, lower serum hemoglobin, lower serum sodium, higher serum creatinine, digitalis therapy, anti-arrhythmic therapy, nitrate therapy, absence of lipid lowering therapy

β blockers in class IV heart failure

Proportion of patients
with class IV heart failure

US Carvedilol Program	3%
MERIT-HF	4%
CIBIS II	16%
BEST	8%

COPERNICUS

Primary endpoint

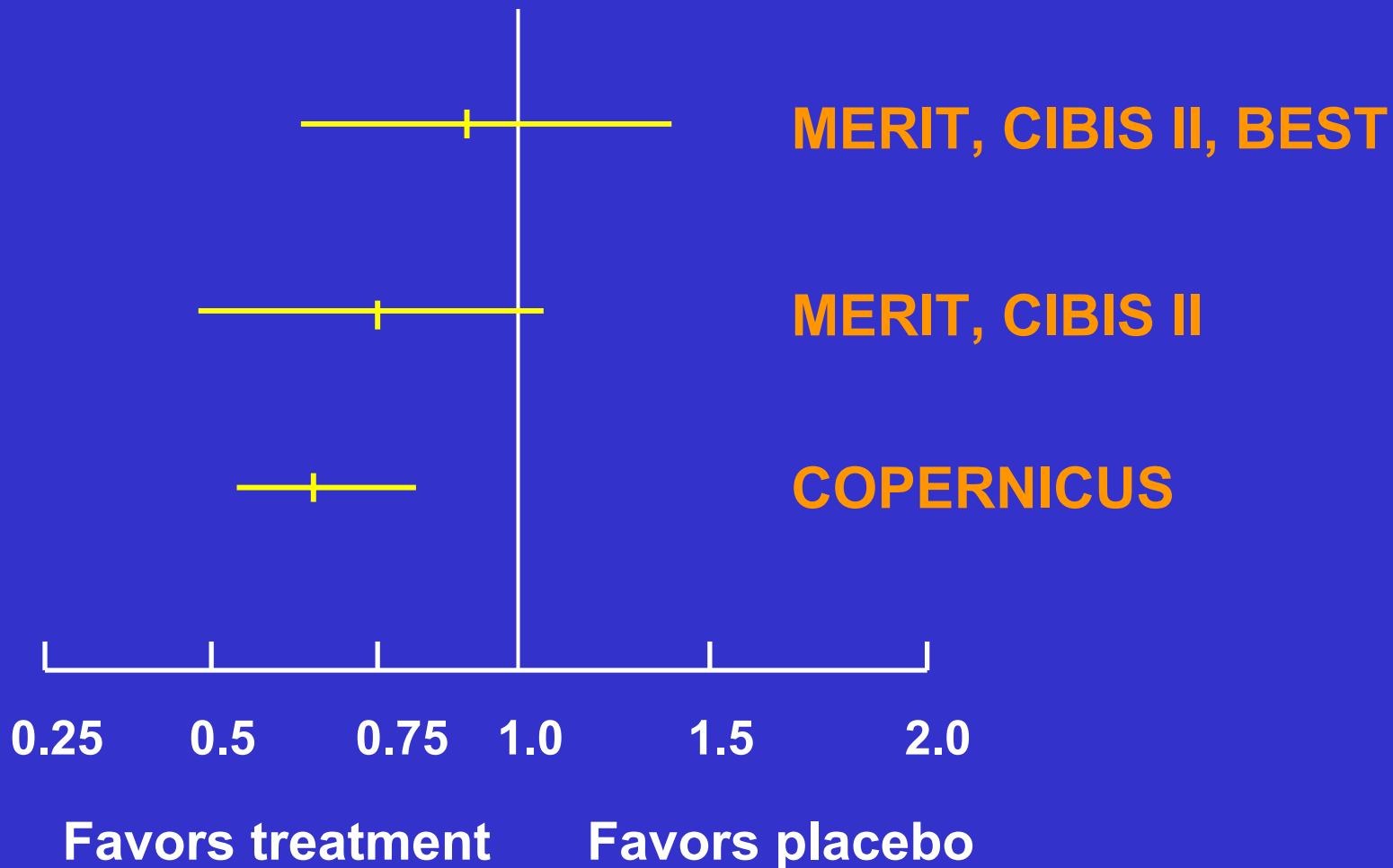
	Placebo	Carvedilol	Hazard ratio	Log-rank nominal <i>p</i> -value
All-cause mortality	190/1133 (18.5%)	130/1156 (11.4%)	0.65 (0.52,0.81)	0.00014

Adjusted $p=0.0014$

No patients lost to follow-up

β blockers in severe heart failure

Preliminary analyses

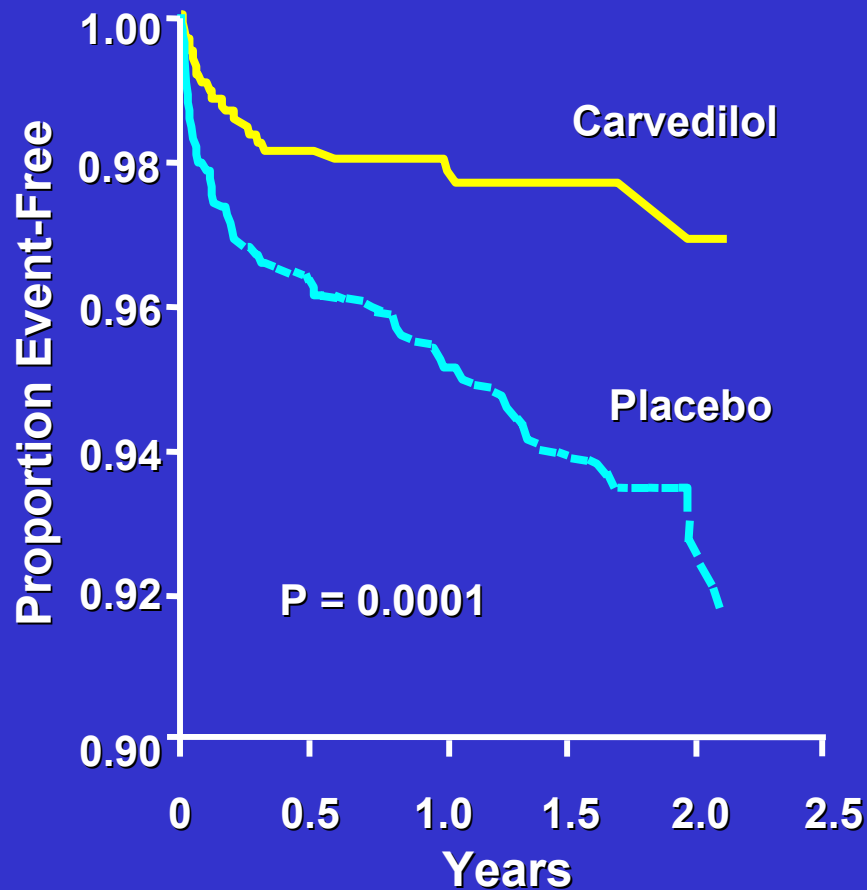


Effect on Cardiac Arrhythmia

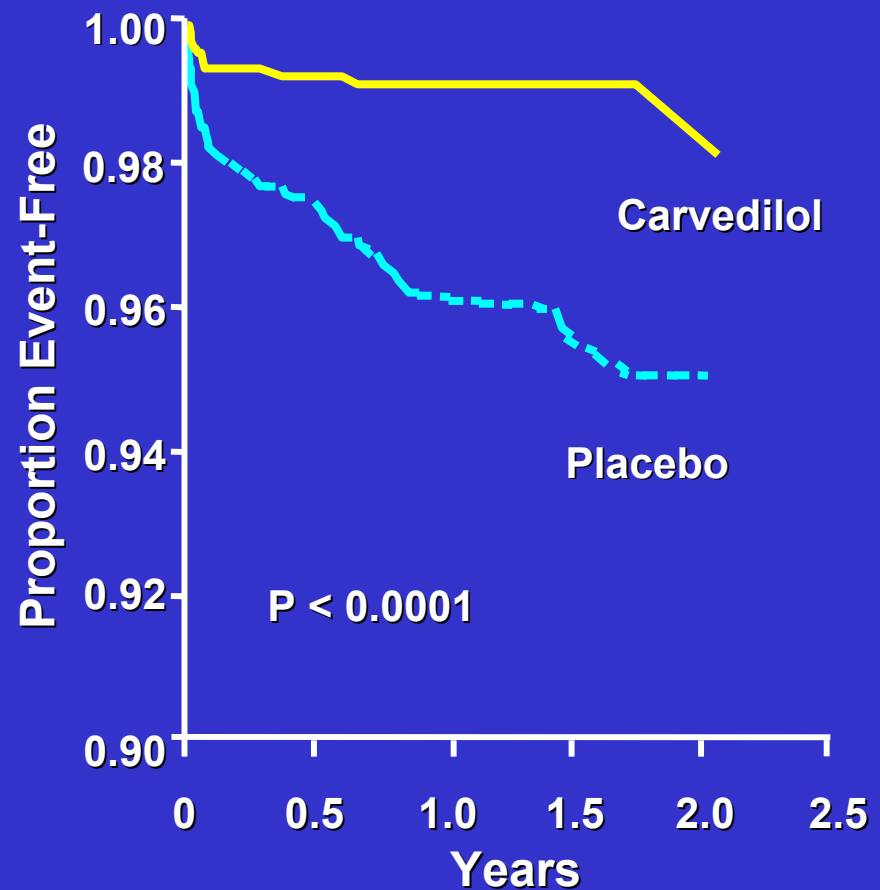
	Placebo	Carvedilol	Hazard ratio (95% CI)	P-Value
Any supraventricular arrhythmia	54	26	0.48 (0.30 - 0.76)	0.0015
Atrial flutter or atrial fibrillation	53	22	0.41 (0.25 - 0.68)	0.0003
Any ventricular arrhythmia	69	26	0.37 (0.24 - 0.58)	< 0.0001
Ventricular tachycardia or ventricular fibrillation	40	12	0.30 (0.16 - 0.57)	< 0.0001

Time to First Cardiac Arrhythmia

Atrial Flutter or Atrial Fibrillation



Ventricular Tachycardia or Ventricular Fibrillation



Beta-blockade in heart failure

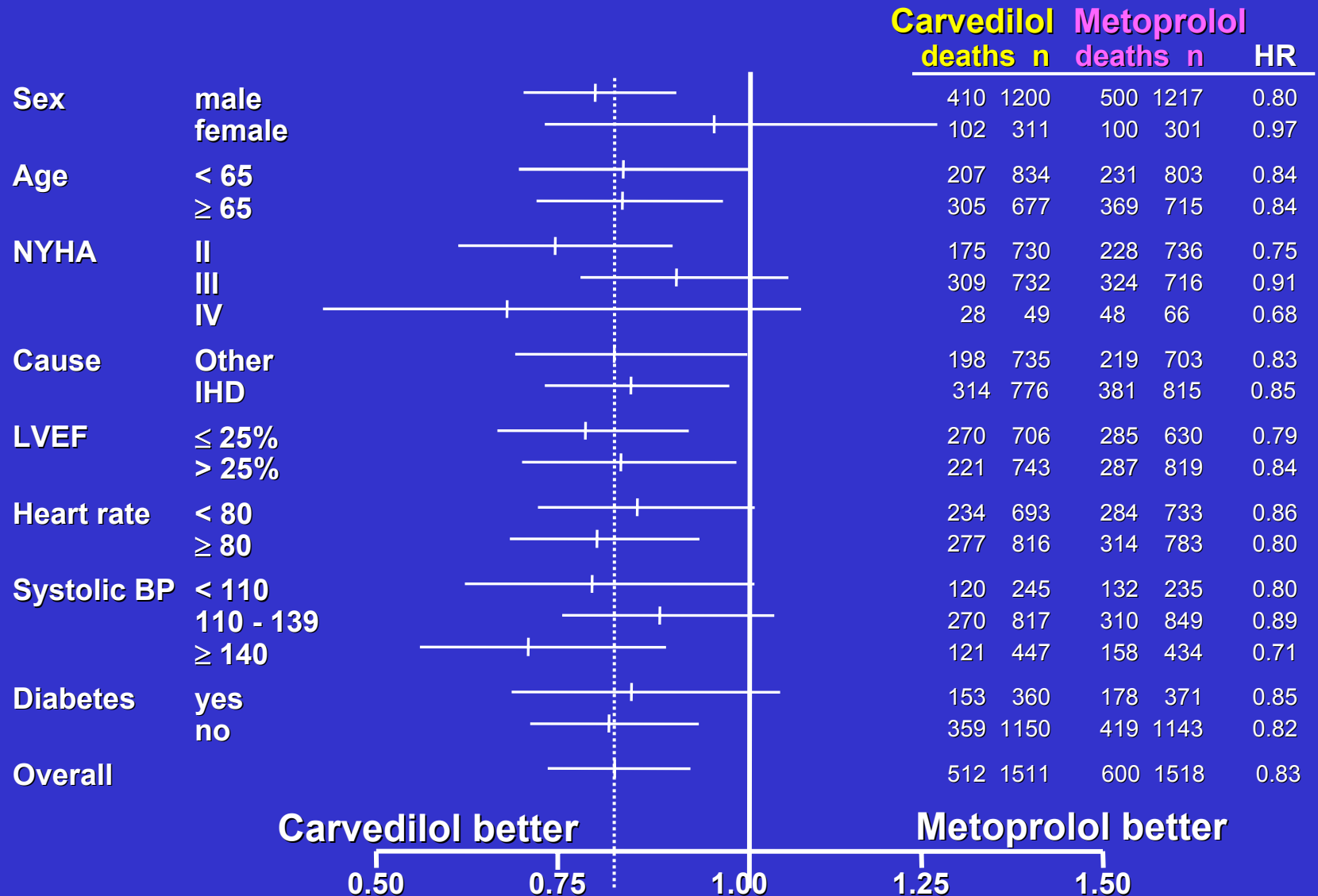
Is there anything new?

COPERNICUS indicates that carvedilol leads to less withdrawals and better efficacy during the early phase of administration in severe CHF

Heart Failure Treatment – Should ACE inhibition always be first-line therapy?

- **Or could alternative forms of treatment , i.e. Beta-blockade be as useful or possibly better ?**
- **Target effective therapy in the individual**
- **If ACE inhibition is first-line therapy should beta-blockade only be added if patients remain symptomatic ? – introduces a delay in beta-blockade prescription**

Mortality in Sub-groups



Conclusions

- **The combination of carvedilol and an ACE inhibitor therapy resulted in a highly significant improvement of LV remodelling and function**
- **Patients receiving carvedilol, either as monotherapy or in combination with enalapril, showed a reversal of LV remodelling - results not observed with enalapril monotherapy**

Clinical Implications

- Carvedilol was safely initiated before ACE inhibition and reversed LV remodelling in CHF. This might challenge the historical sequence of initiating ACE inhibition before β blockade
- The CARMEN results confirm the current treatment guidelines and provide an additional mandate for **not delaying prescription of combination therapy of an ACE inhibitor and carvedilol in mild-moderate heart failure.**

Are There Differences Between β Blockers?

- β blockers are a heterogeneous class
 - More than 15 agents available
- Only three have shown significant survival benefits in mild to moderate CHF
 - Carvedilol
 - Metoprolol
 - Bisoprolol
- Only carvedilol has shown a mortality benefit in severe CHF in a large scale prospective randomised trial

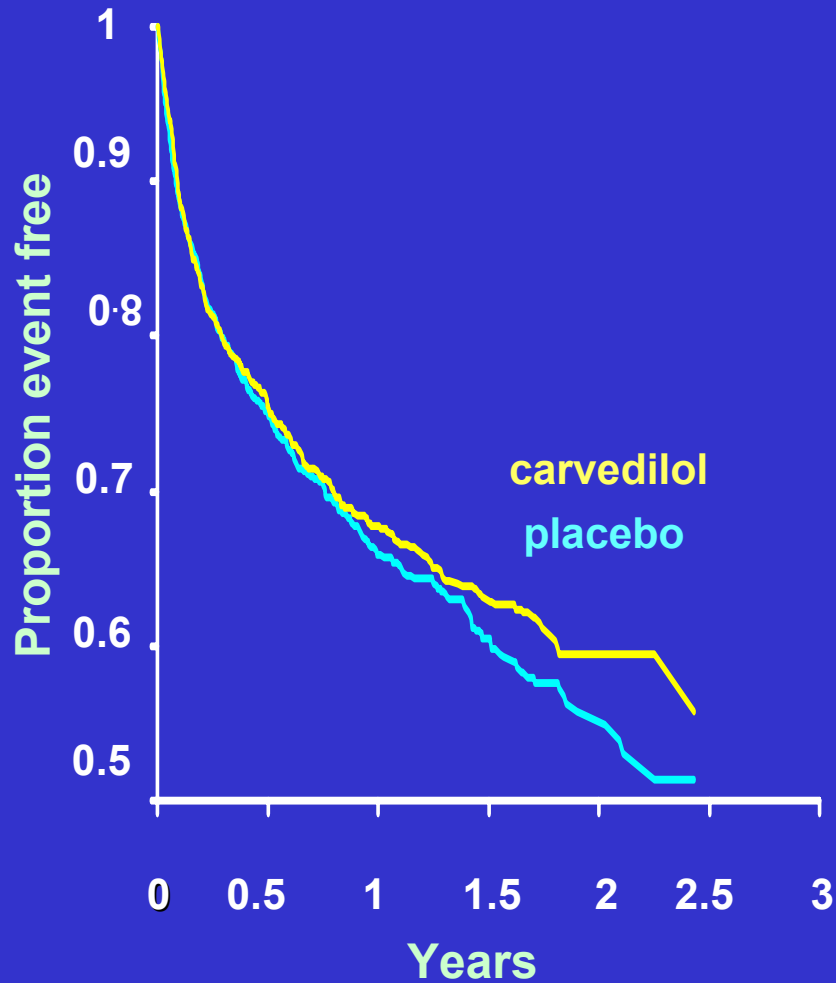
Objective / Design

- to evaluate the effect of carvedilol on clinical outcome in patients with LV dysfunction following an acute myocardial infarction (AMI) treated in the modern era
- multicentre, randomised, placebo-controlled, parallel-group trial in patients with LV ejection fraction $\leq 40\%$ with or without heart failure

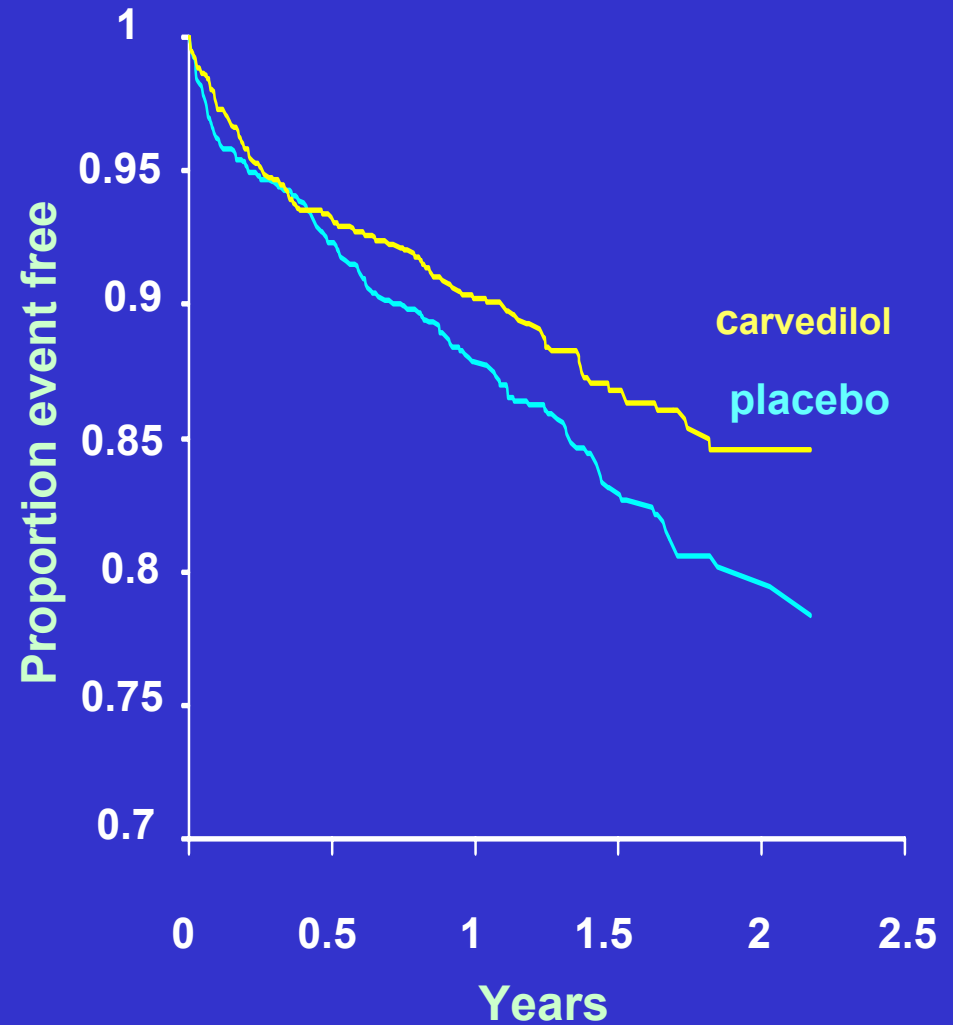
Inclusion Criteria

- confirmed acute myocardial infarction within 3 - 21 days (mean of 10 days)
- LV ejection fraction $\leq 40\%$
- all appropriate treatments for MI including aspirin, thrombolysis and percutaneous interventions
- receiving an ACE inhibitor for ≥ 48 hours
- patients were usually hospitalised, but may have been recently discharged

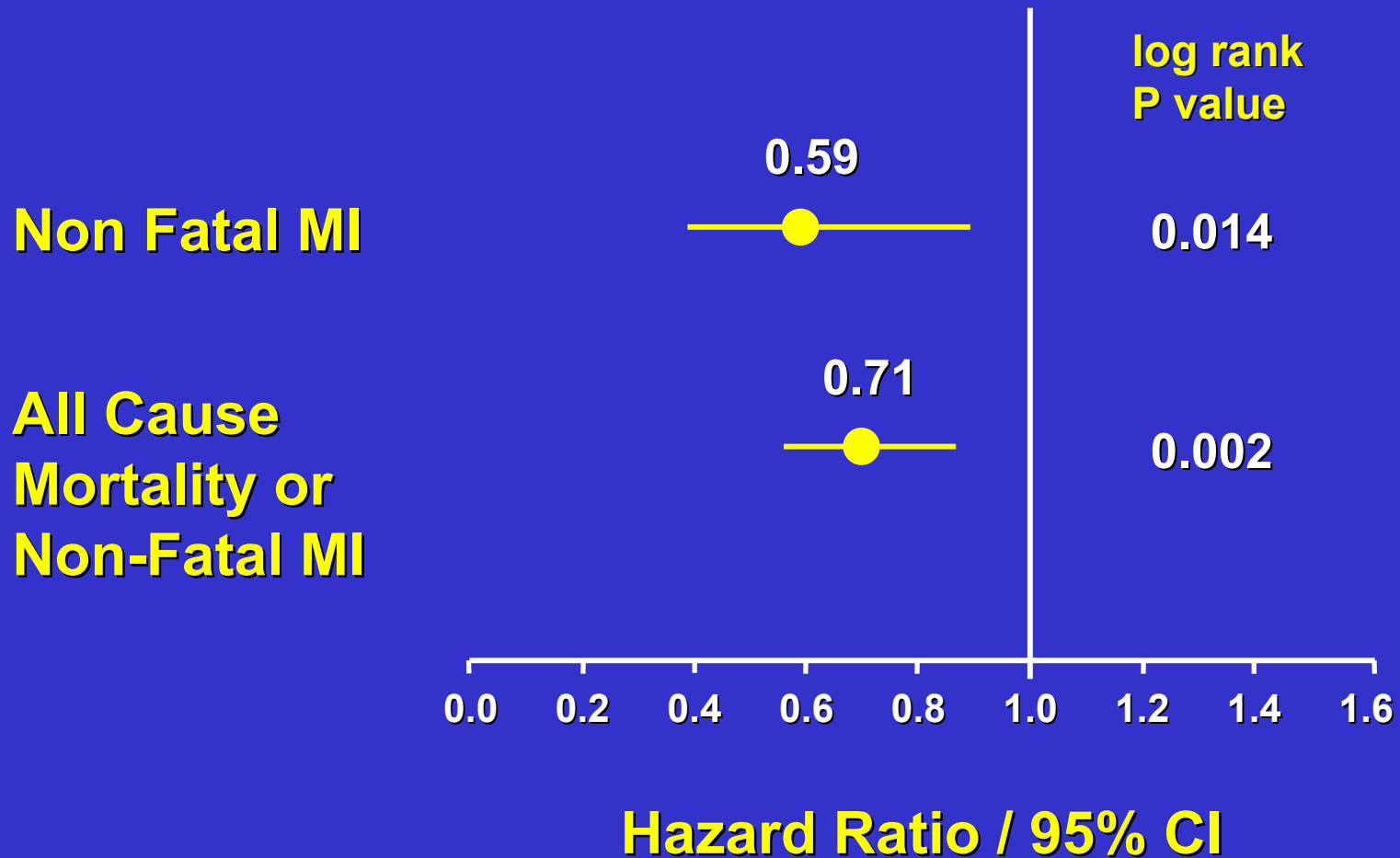
Death or CV hospitalisation



Survival



Major Coronary Events

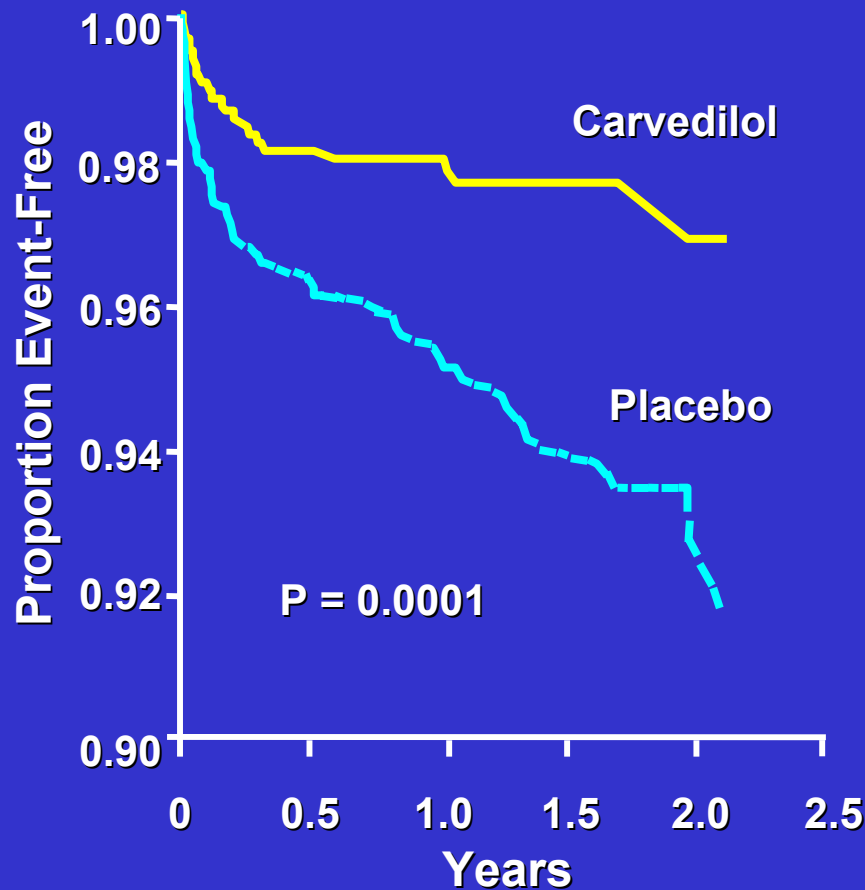


Effect on Cardiac Arrhythmia

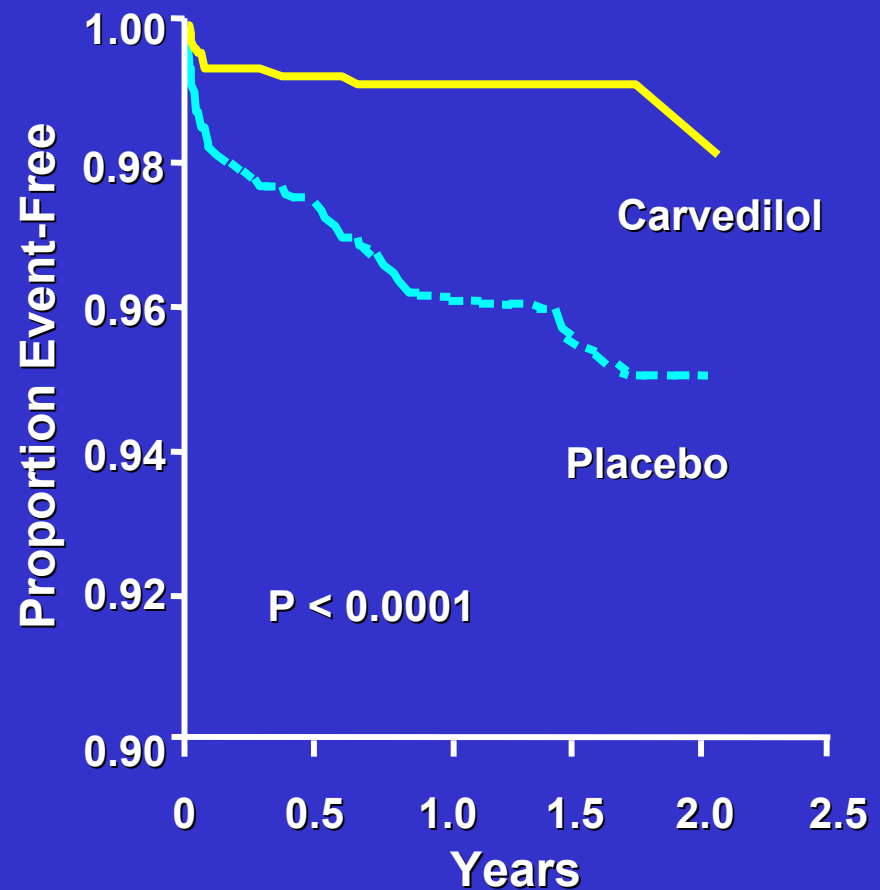
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Time to First Cardiac Arrhythmia

Atrial Flutter or Atrial Fibrillation



Ventricular Tachycardia or Ventricular Fibrillation



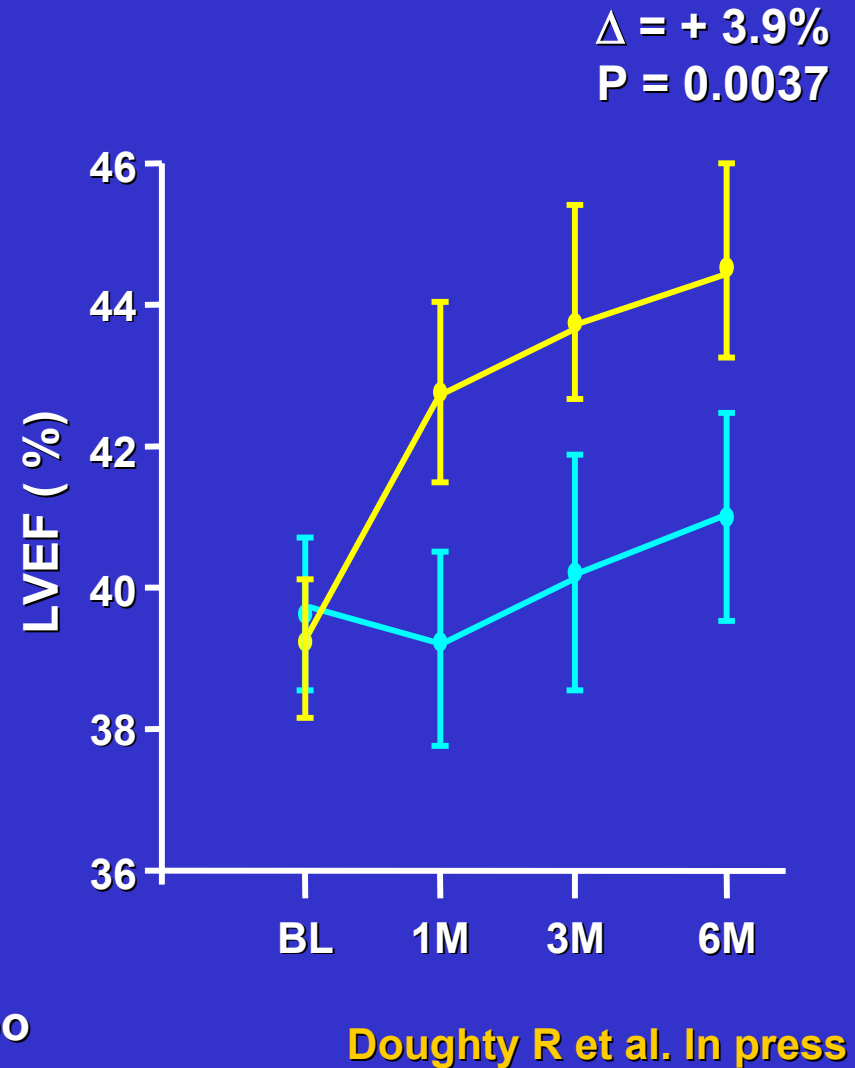
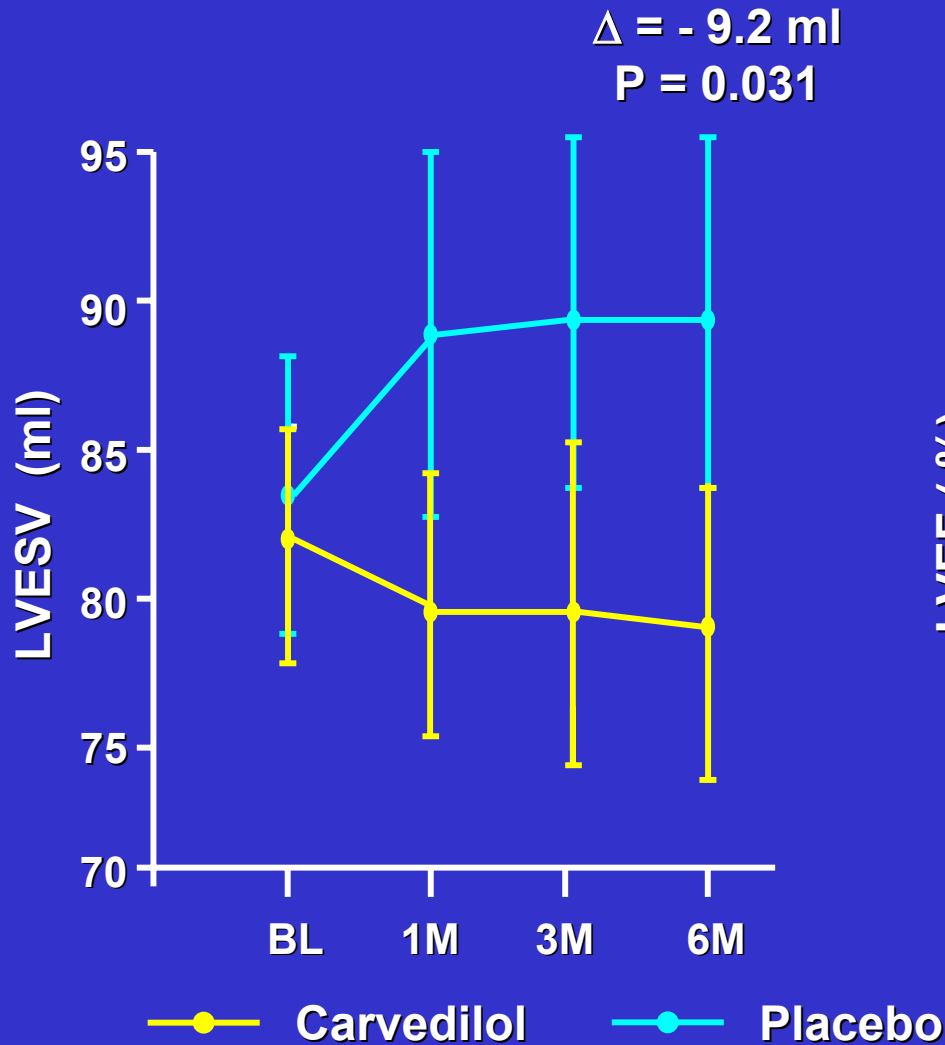
Xamoterol in severe heart failure

516 patients randomised to xamoterol (200 mg bd) or placebo
Symptoms and exercise capacity unchanged
Heart rate and systolic blood pressure reduced

	Xamoterol	Placebo	
n	352	164	
Total withdrawals (%)	67 (19%)	19 (12%)	
% of withdrawals with cardiovascular origins	73%	62%	
Total deaths (%)	32 (9.1%)	6 (3.7%)	p = 0.02

from Lancet 1990;336:1-6

Remodelling in CAPRICORN



CAPRICORN conclusion

- **In LV dysfunction and heart failure post-MI carvedilol significantly improved survival**
- **Reduces recurrent MI and combine endpoint all-cause mortality and non-fatal MI**
- **Prevents atrial flutter /fibrillation and serious ventricular arrhythmias (VT/VF)**
- **Leads to reversed LV remodelling**

Effects of metoprolol and carvedilol on beta receptors

Carvedilol

Non-selective β antagonist
Balanced β_1 agonist
 β_1 receptor not up-regulated
High affinity

Partial inverse β_2 agonist
Signal trafficking
Reduces β_2 stimulation of cAMP
 β_2 links to G_i , G_i inhibits β_1

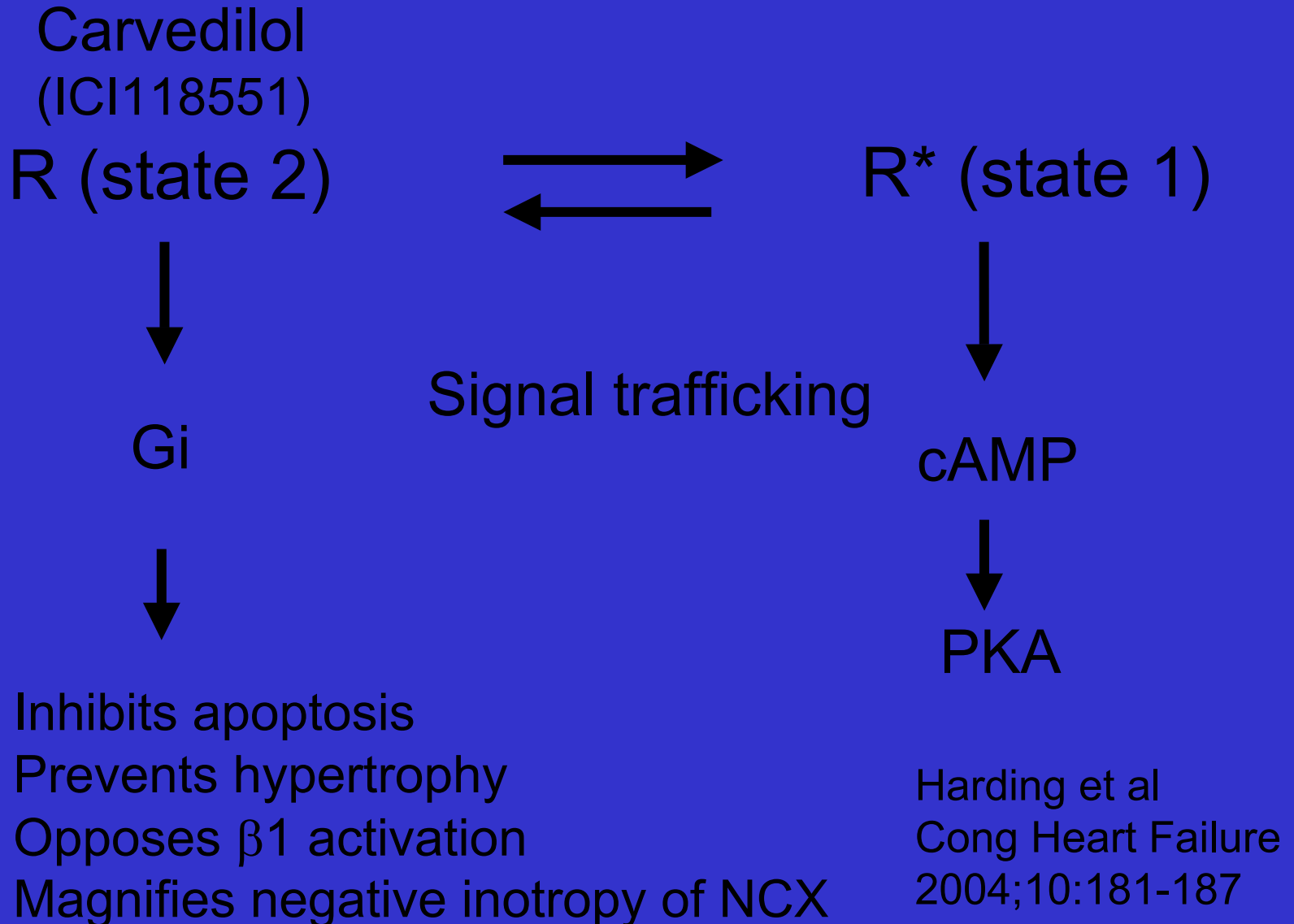
Metoprolol

Selective β_1 antagonist
Inverse β_1 agonist
 β_1 receptor up-regulated
Low affinity

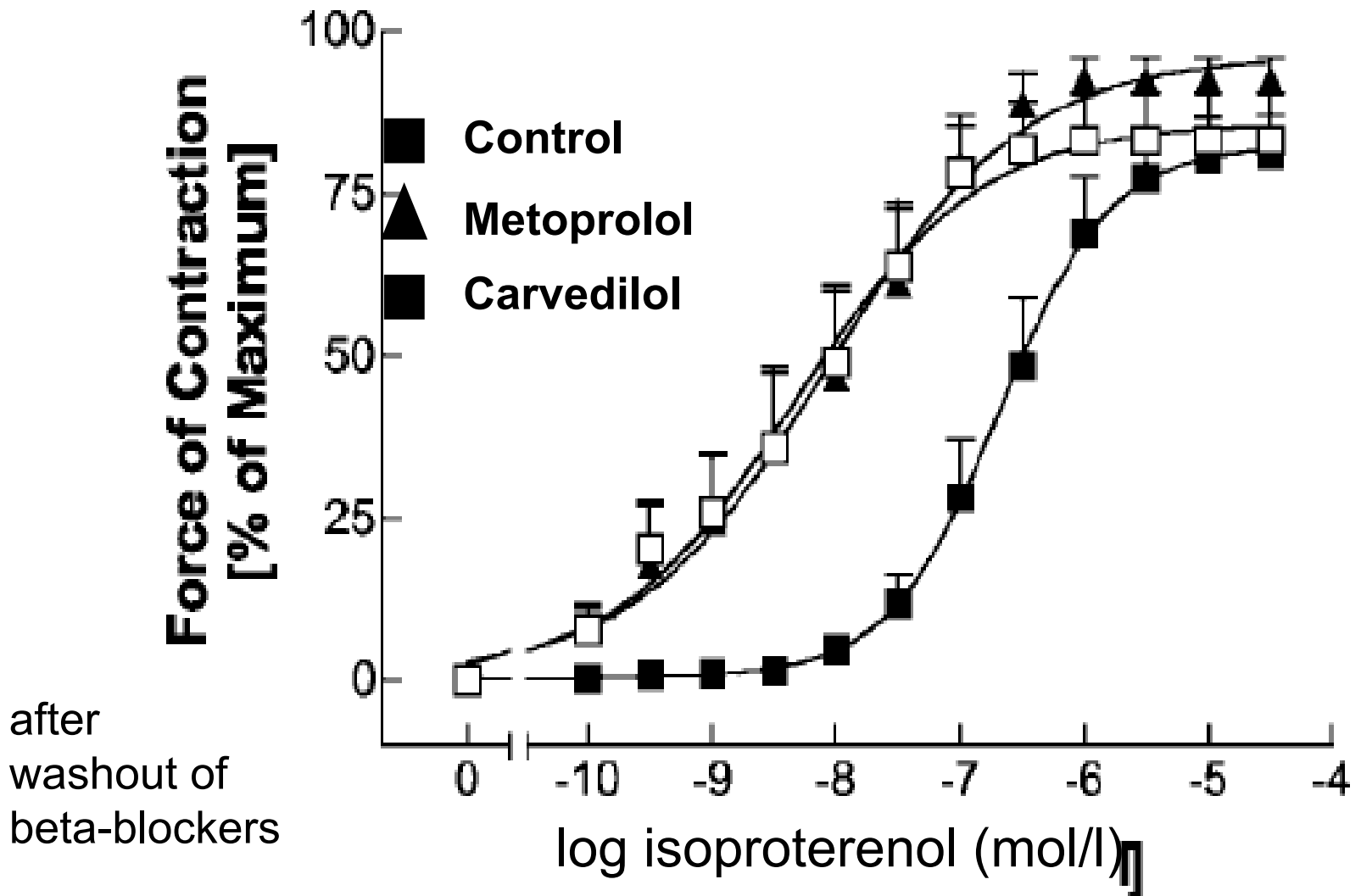
Issues arising from COMET

1. Validity of trial
2. Mechanisms for findings
3. Clinical implications

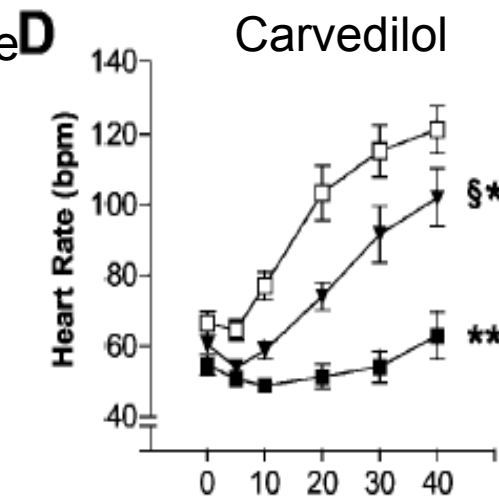
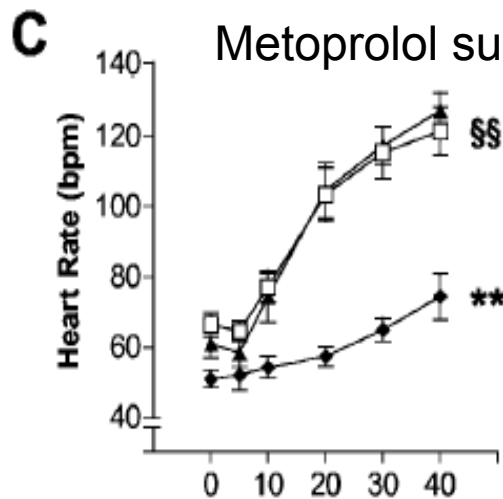
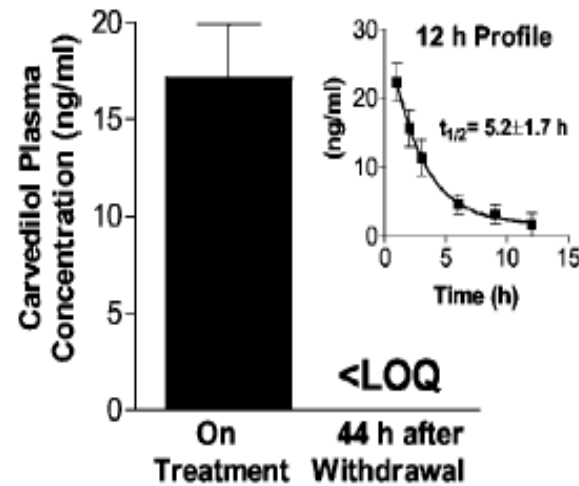
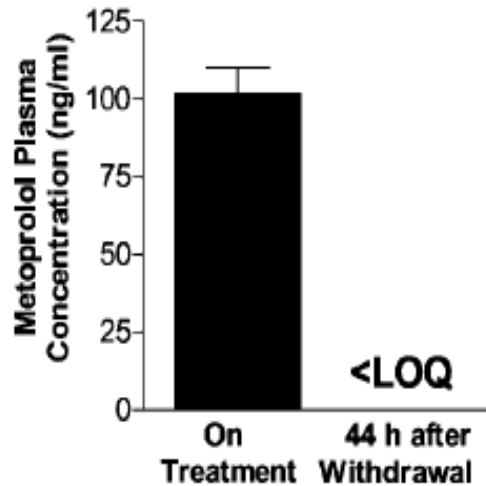
Effects of carvedilol on beta 2 receptors



Washout of beta-blockers from isolated human atrial muscle



Plasma concentration of metoprolol and carvedilol and heart rate response to dobutamine in human volunteers after 44 hours withdrawal



- Control
- ◆ Metoprolol
- ▲ Metoprolol>
- Carvedilol
- ▼ Carvedilol>
- * $p < 0.001$ vs Control
- ** $p < 0.0001$ vs Control
- § $p < 0.01$ vs on β -Blocker
- §§ $p < 0.0001$ vs on β -Blocker

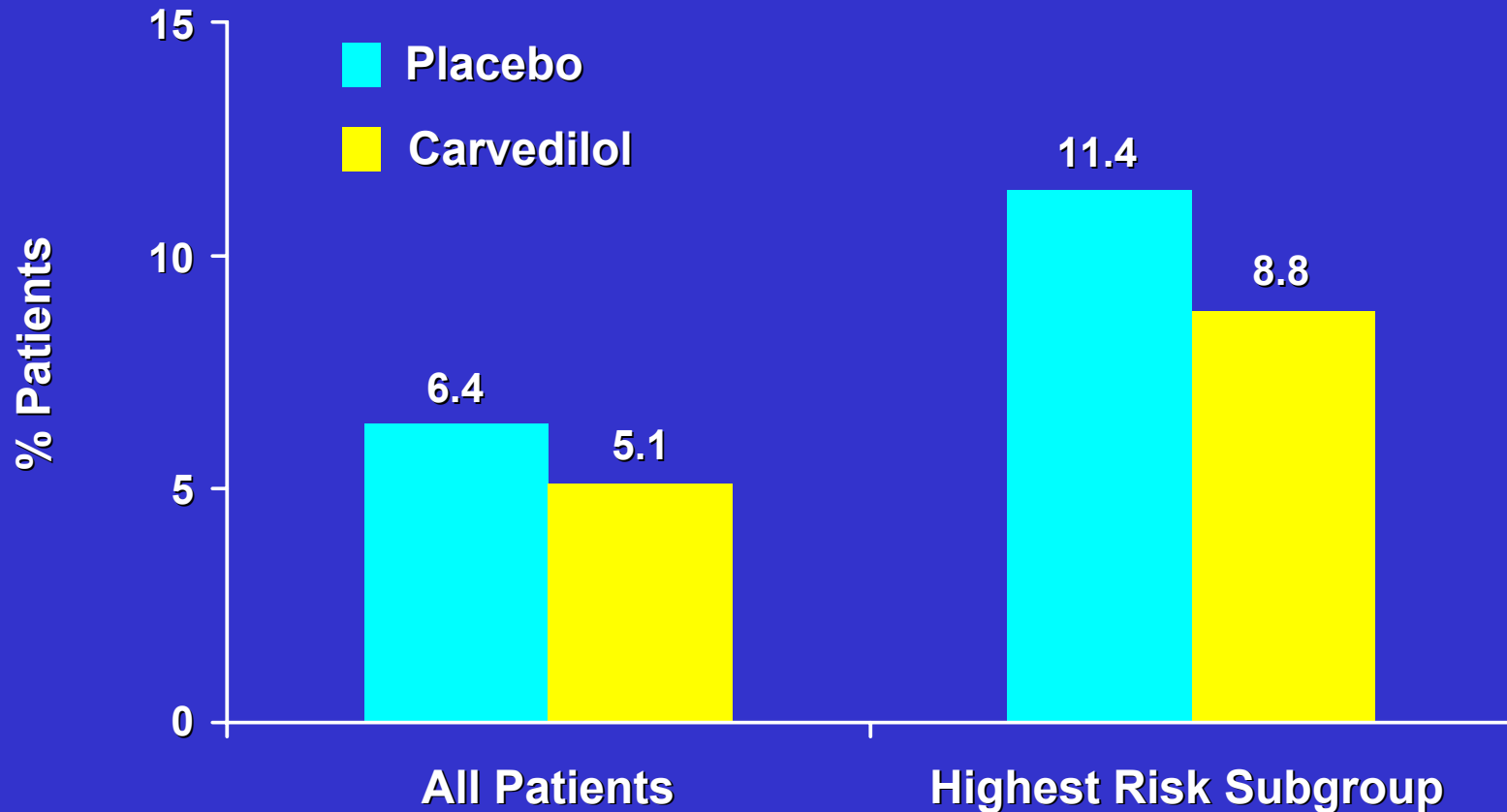
Dobutamine (ug/kg/min)

Beta 2 receptors in heart failure

1. 30% of adrenoreceptors are beta 2 in humans
In heart failure not down regulated; proportion increases
2. Cause tachycardia and positive inotropy on stimulation
3. Promote release of noradrenaline in neuronal synapse
(Negative inotropy if blocked by carvedilol
in isolated myocytes)
4. May promote/prevent cell growth and apoptosis
5. Can promote arrhythmias

COPERNICUS: Weeks 1 to 8

Worsening CHF



Reality

Regarding Tolerability of β Blockade in CHF





- Initiation and up-titration not as complex as perceived
- No increased risk of intolerance and / or worsening of CHF symptoms with initiation of carvedilol
- All of the above appears to hold true in patients with advanced disease



CArvedilol Remodeling in Mild heart failure Evaluation



Treatment of CHF: ESC Guidelines

	<i>For Symptoms</i>	<i>For Survival/Morbidity mandatory therapy</i>	<i>For Symptoms if Intolerance to ACE inhibition or β-blockade</i>
NYHA I	reduce / stop diuretic 	continue ACE inhibitor if asymptomatic, add β -blocker if post MI 	
NYHA II	+/- diuretic depending on fluid retention	ACE inhibitor as first-line treatment add β-blocker if still symptomatic 	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant
NYHA III	+ diuretics + digitalis if still symptomatic + nitrates / hydralazine if tolerated	ACE inhibitor and β -blockade add spironolactone 	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant
NYHA IV	diuretics + digitalis + nitrates / hydralazine if tolerated + temporary inotropic support	ACE inhibitor β -blockade spironolactone	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant

Heart Failure Treatment – Should ACE inhibition always be first-line therapy?

- **Or could alternative forms of treatment , i.e. Beta-blockade be as useful or possibly better ?**
- **Target effective therapy in the individual**
- **If ACE inhibition is first-line therapy should beta-blockade only be added if patients remain symptomatic ? – introduces a delay in beta-blockade prescription**

Beta-blockade in heart failure

**Are all beta-blockers
equally effective in the
treatment of heart failure ?**

**Results from
COMET**

Pharmacological Differences Within the β Blocker Class

	β_1 blockade	β_2 blockade	α_1 blockade	ISA	Ancillary effects*
Carvedilol	+++	+++	+++	-	+++
Metoprolol	+++	-	-	-	-
Bisoprolol	+++	-	-	-	-

*anti-oxidant, anti-endothelin, anti-proliferative

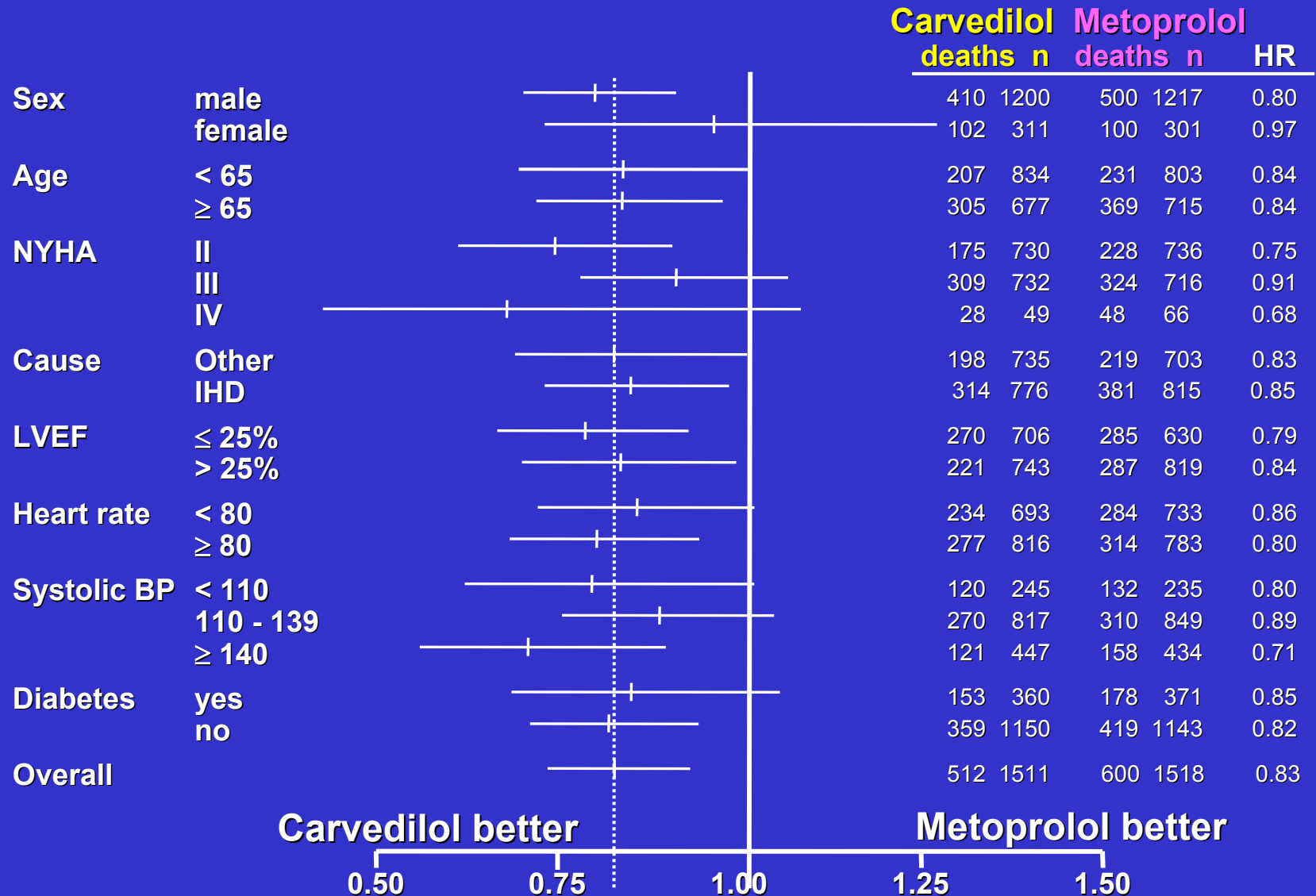
Effects of β_2 -Receptors

- **Direct chronotropic, inotropic, lusitropic (cAMP mediated)**
- **Hypertrophy, fibrosis, remodelling**
- **Anti-apoptotic**
- **Arrhythmogenic**
- **Facilitation of norepinephrine release (presynaptic)**

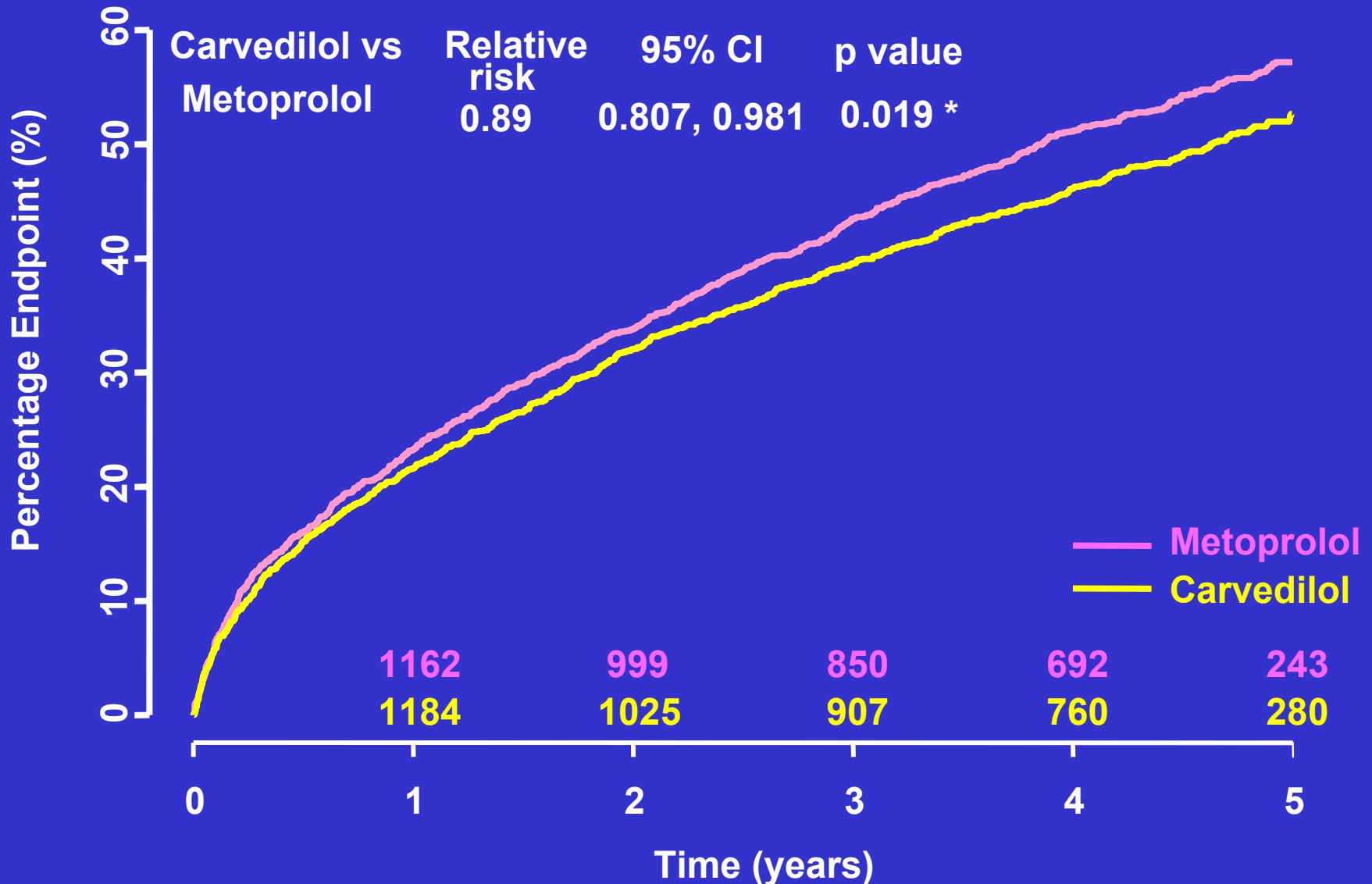
Effects of α_1 Receptors

- Myocardial hypertrophy, fibrosis, remodeling
- Cardiotoxicity (with β receptors)
- Arrhythmogenic
- Peripheral vasoconstriction
- Renal hypoperfusion and sodium retention

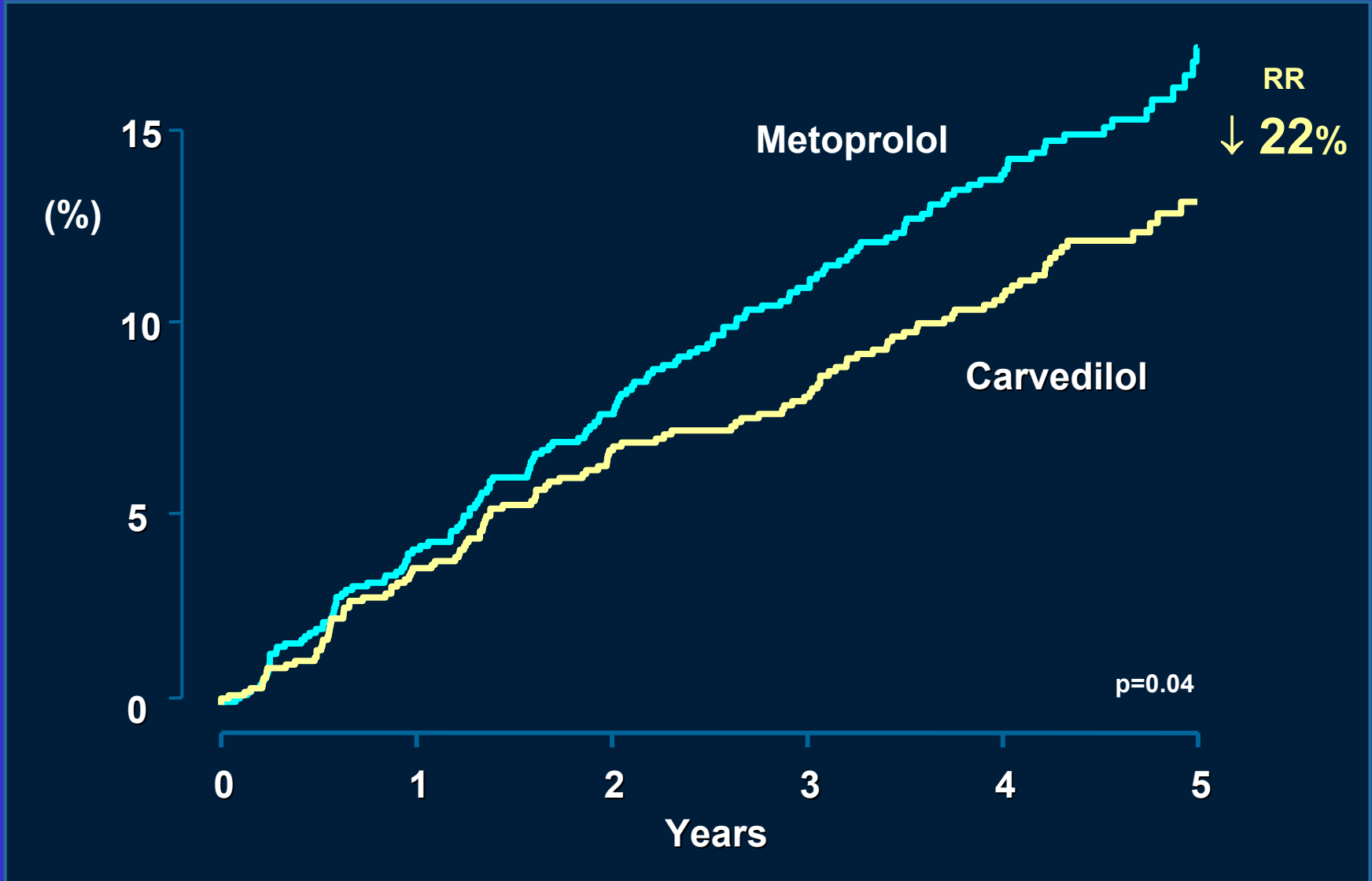
Mortality in Sub-groups



Death plus hospitalisation for worsening heart failure



New Onset Diabetes Mellitus

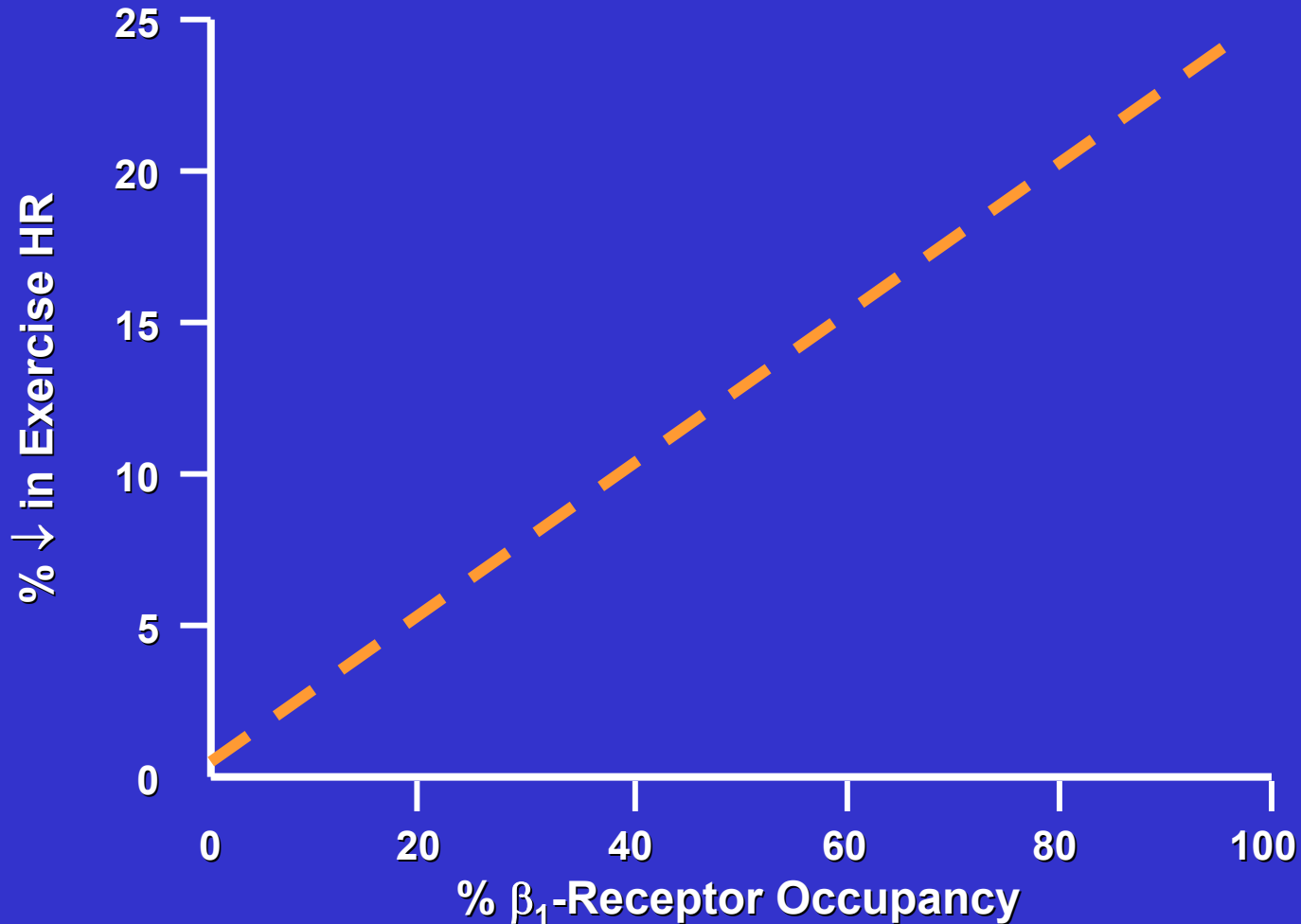


Were the Differences of the Effects of Carvedilol and Metoprolol on HR Clinically Meaningful ?

HR was reduced to a greater extent with carvedilol compared to metoprolol

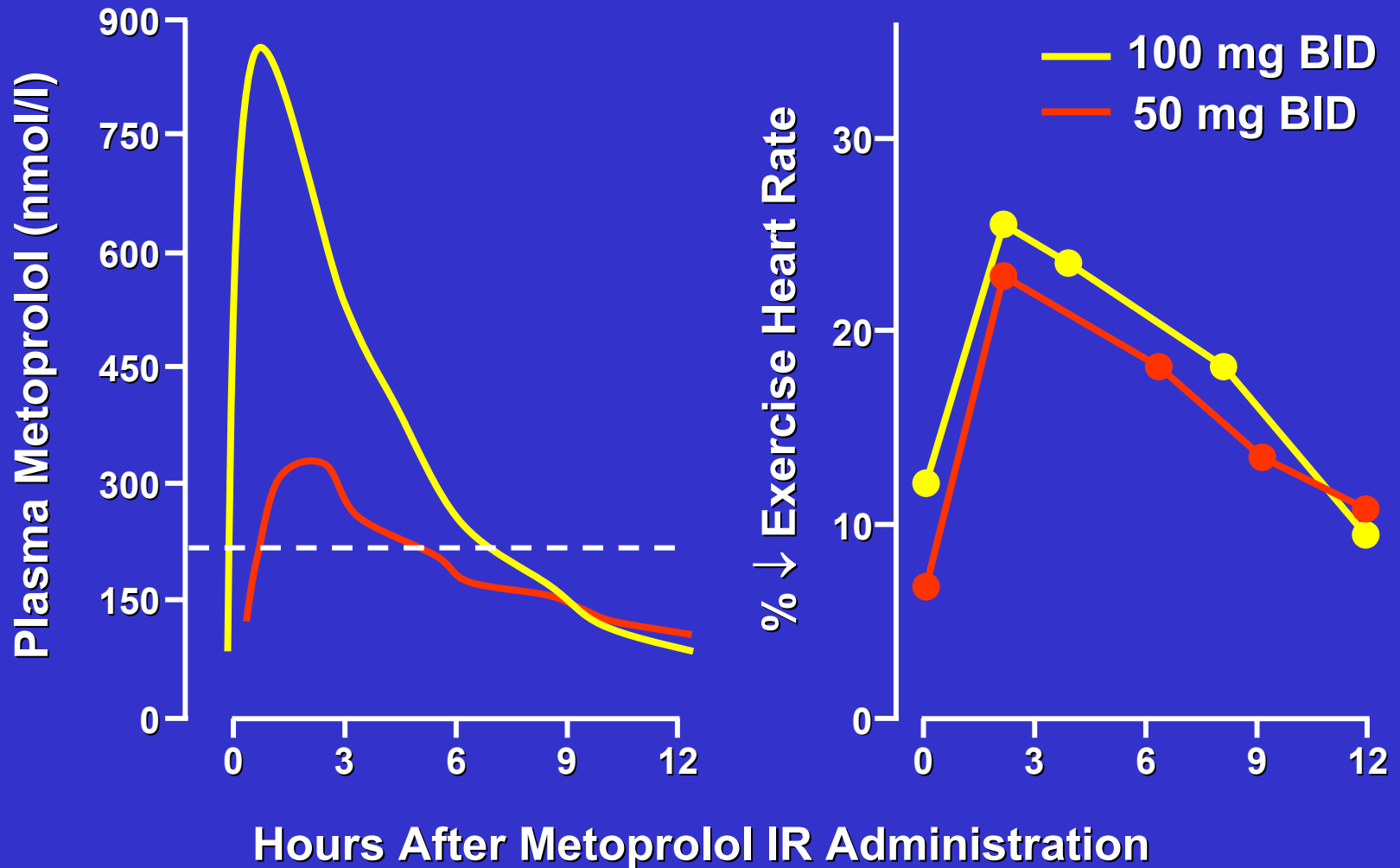
- The difference was slight (1.6 bpm) and transient (4, 8 and 16 months only)
- The effects of beta-blockade on absolute mortality was independent from the HR changes in CIBIS-II

Degree of β_1 -Blockade Can Be Assessed by Inhibition of Exercise-Induced Tachycardia

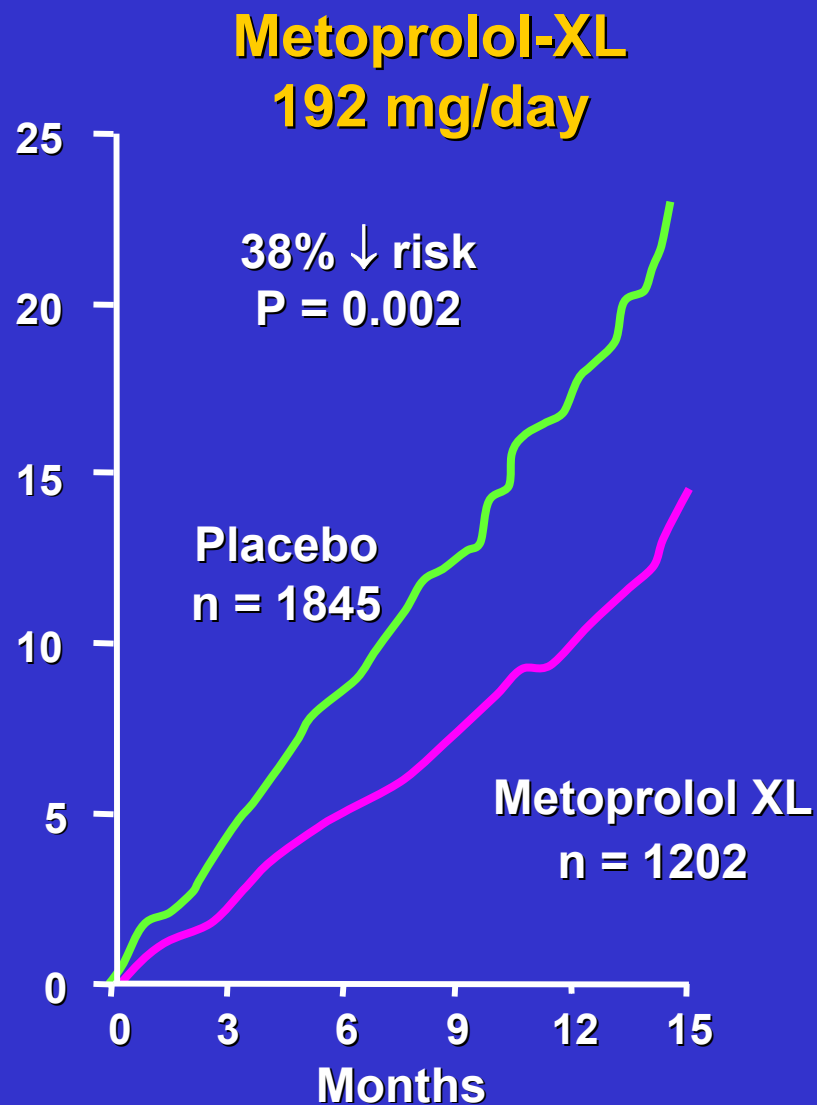
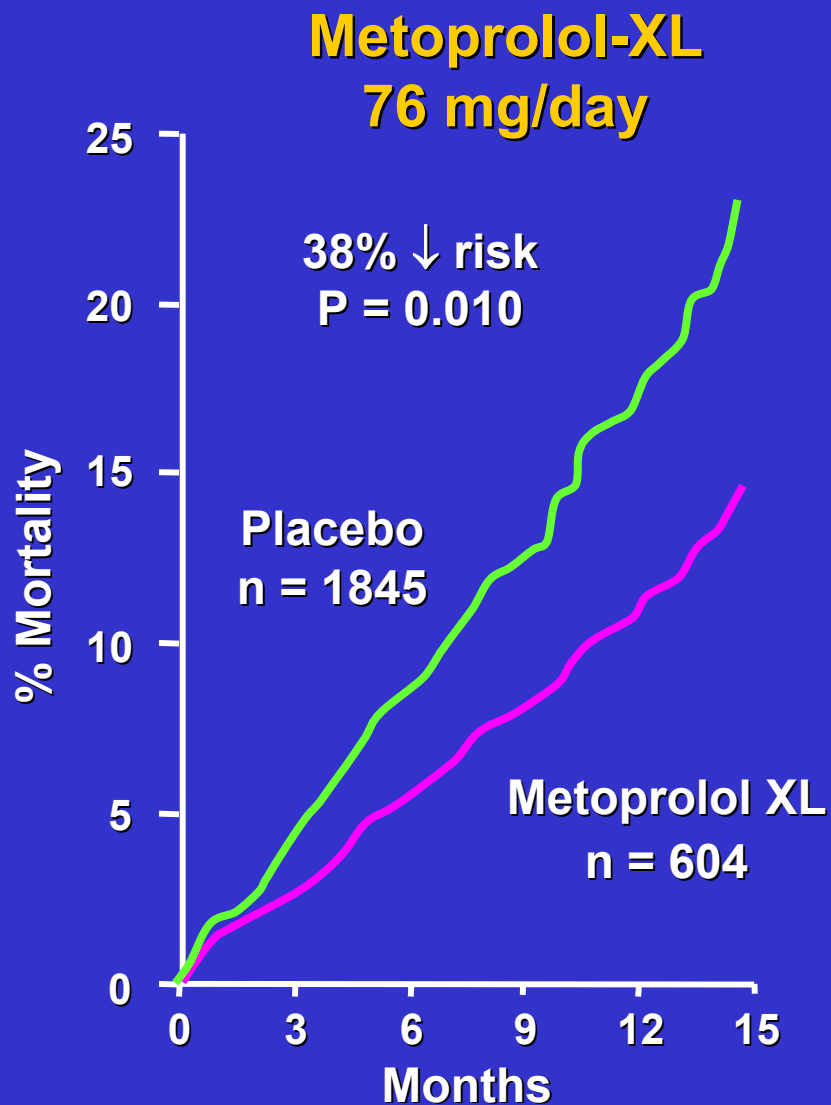


Modified from deMey et al. Br J Clin Pharmacol 1994

Pharmacokinetic and Pharmacodynamic Responses to Metoprolol IR 50/100 mg BID



MERIT-HF: Effect of Dose on Survival Benefit



Summary and Conclusion

- First head-to-head mortality study comparing two beta-blocking agents in CHF
- Carvedilol saved significantly more lives than metoprolol (by 17%, $P = 0.0017$)
- Carvedilol compared to metoprolol reduced annual mortality from 10.0% to 8.3% and prolonged median survival by 1.4 years
- Carvedilol significantly reduced all MI, stroke death and new onset diabetes as compared to metoprolol

COMET

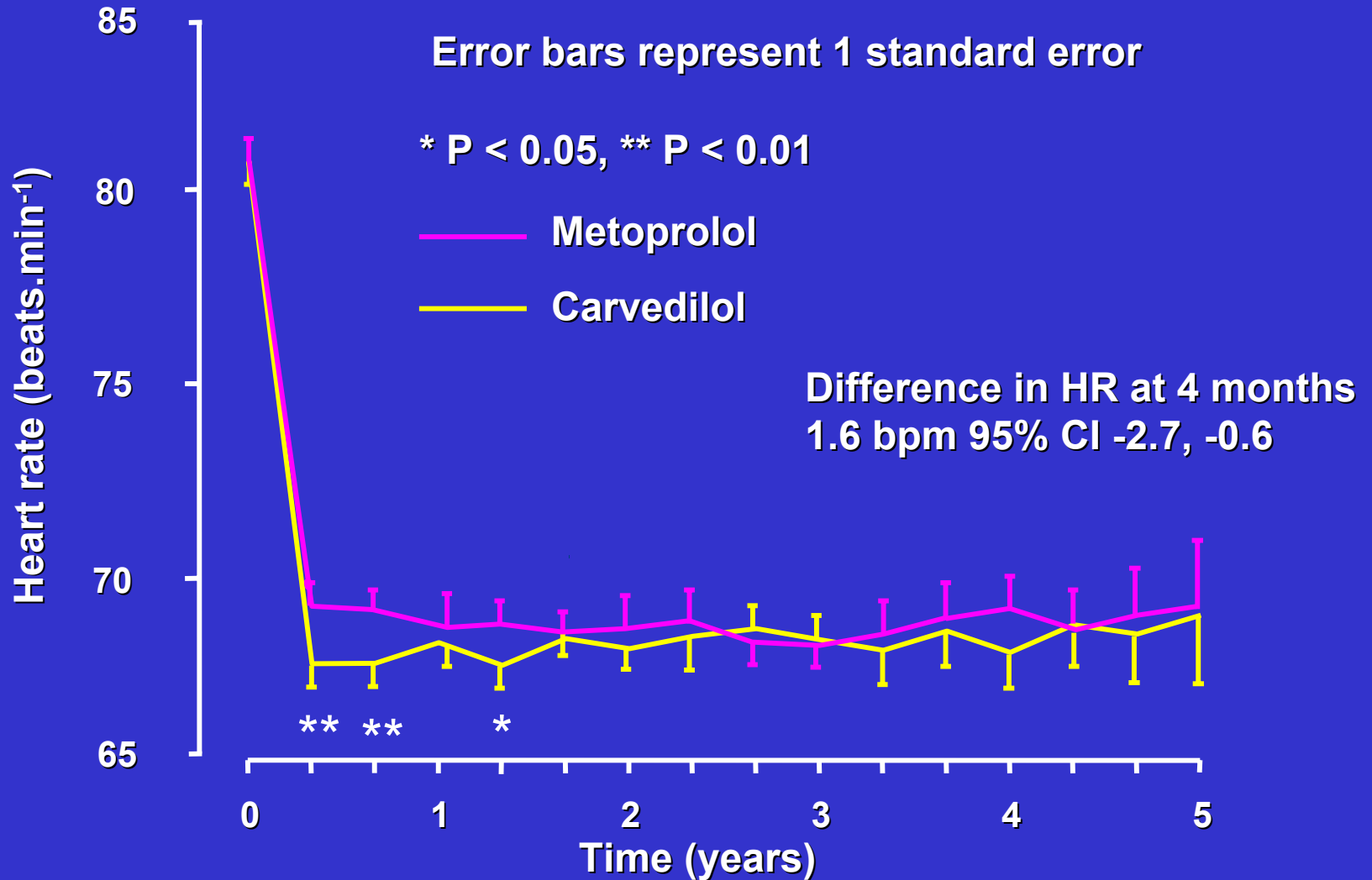
Results Clear and definitive

Mechanism Unlikely to be due to doses or formulations of drugs.

Most probable explanation is beta-2 and alpha-1 adrenoceptor blockade

Clinical implications The preferred beta blocker in the treatment of heart failure is carvedilol

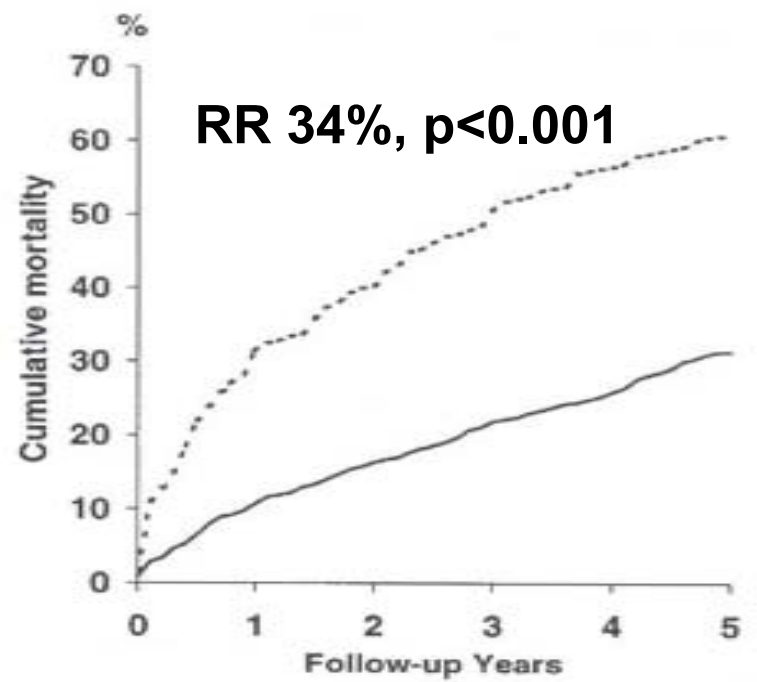
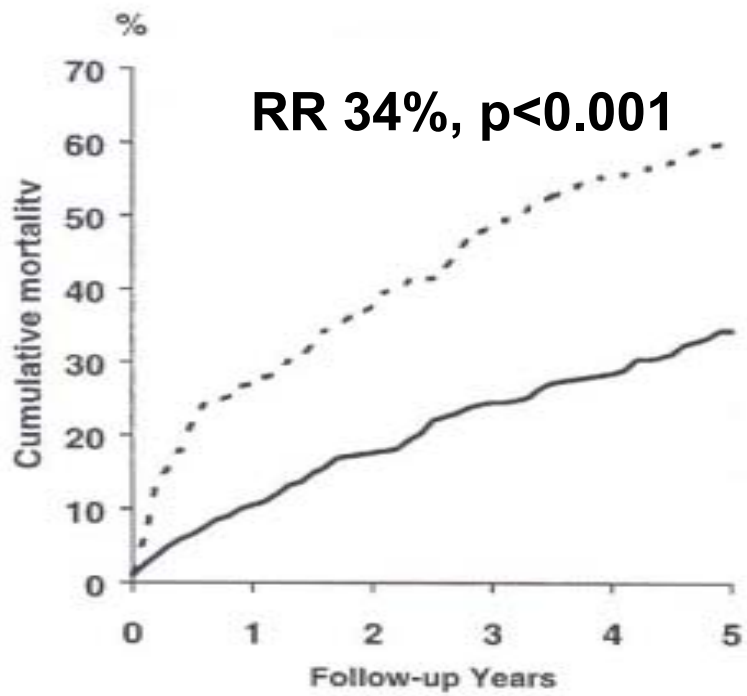
Heart Rate



Metoprolol IR and XL/CR show both 34% RR over 5 years post MI

Metoprolol IR (N=413)
12.5, 25, 50 or 100 mg bid
vs No β -blocker (N=246)
Period 1986-87

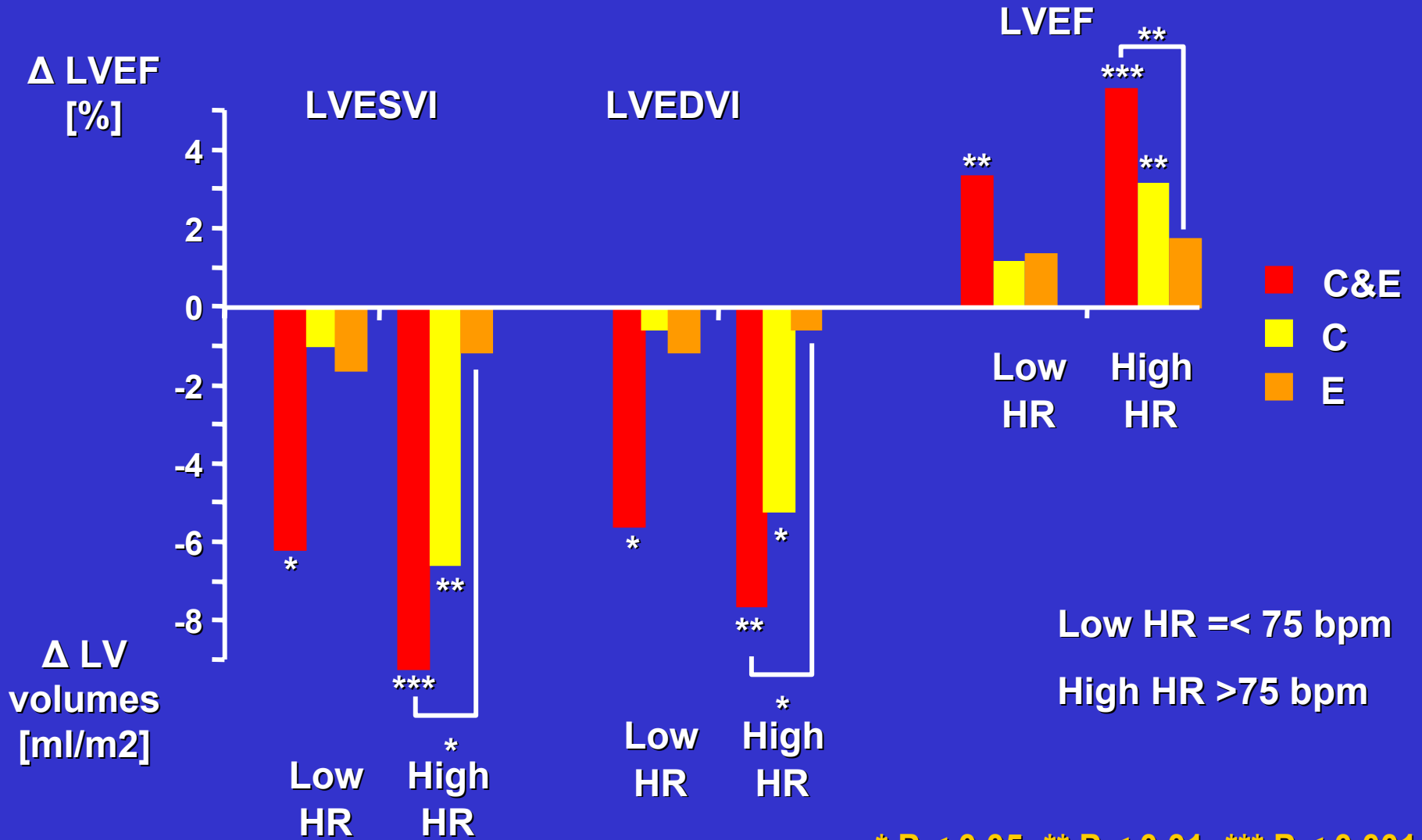
Metoprolol XL/CR (N=876)
25, 50, 100 or 200 mg od
Vs. No β -blocker (N=339)
Period 1990-91



- - - No β -blocker, — Metoprolol

LV function [PP population]

Mean Change Baseline to 18 months



* P < 0.05; ** P < 0.01; *** P < 0.001

Conclusions Subgroup Results

- In CARMEN baseline HR was an important predictor of the magnitude of the benefit of carvedilol on remodeling.
- The largest effects of carvedilol on remodeling were seen in patients with higher heart rates (>75bpm).
- Carvedilol may be considered first-line treatment in mild-moderate heart failure when heart rates are high.

Could the small difference in HR reduction explains greater benefits of carvedilol?

- No interaction between effect on mortality and Δ HR
- By multivariate analysis neither baseline HR nor Δ HR associated with mortality

COMET: Median Survival

Carvedilol 8.0 years

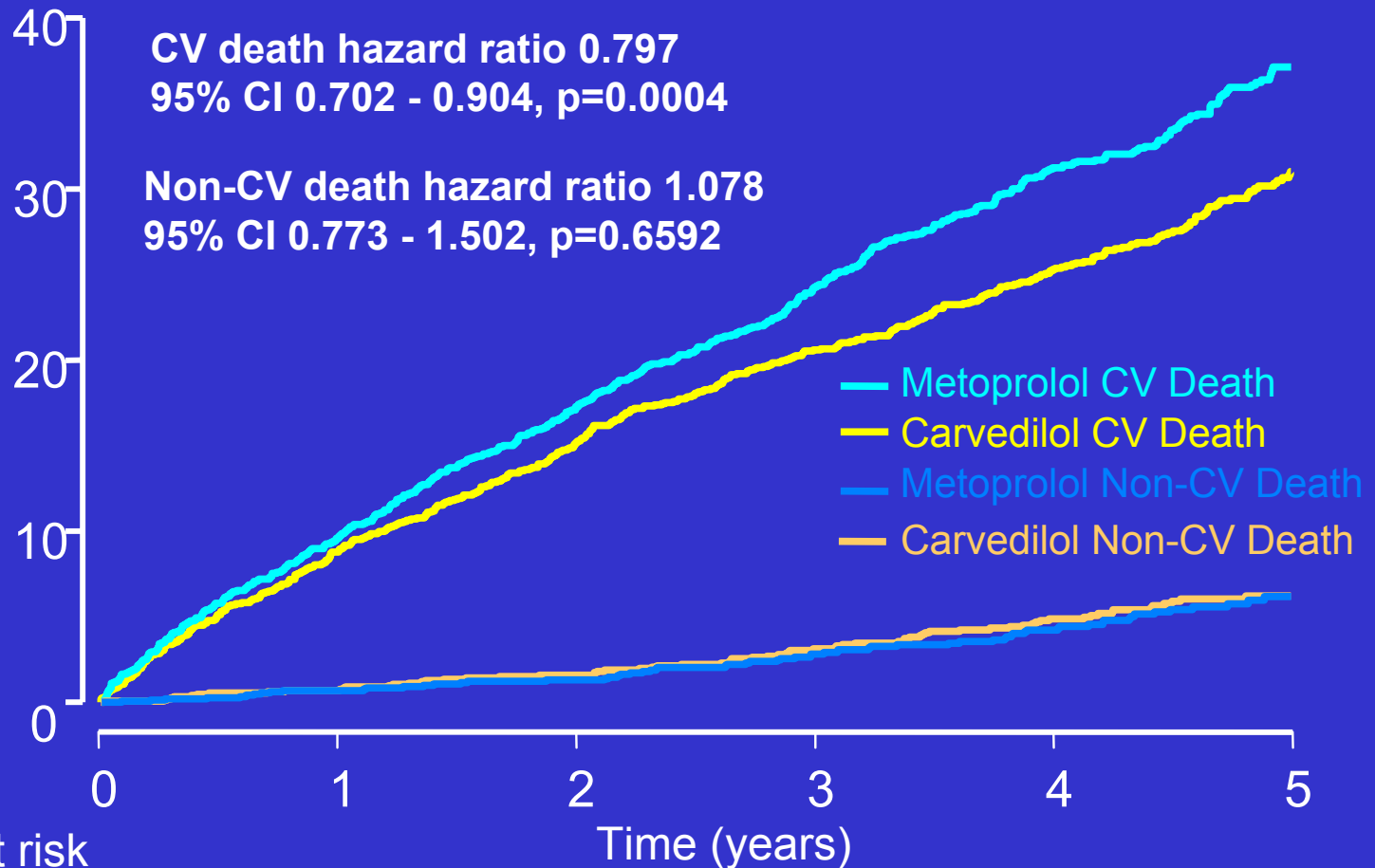
Metoprolol 6.6 years

Carvedilol prolonged median survival by 1.4 years beyond that achieved with metoprolol

Assuming constant hazard

Cardiovascular and Non-Cardiovascular Death

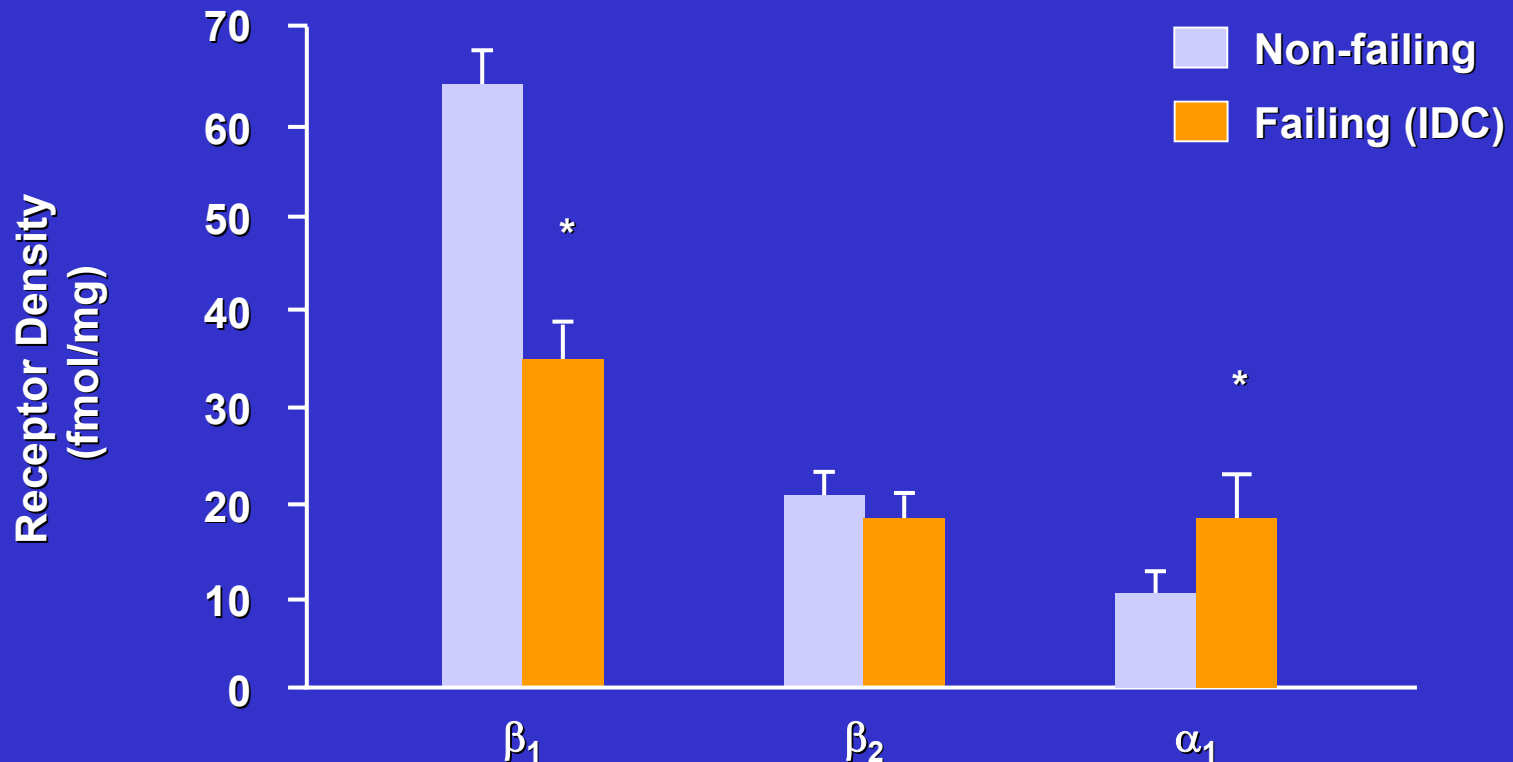
Mortality %



Number at risk

	0	1	2	3	4	5
Metoprolol	1518	1359	1234	1105	933	352
Carvedilol	1511	1366	1258	1154	1002	383

Adrenergic Receptor Densities in Human LV Myocardium

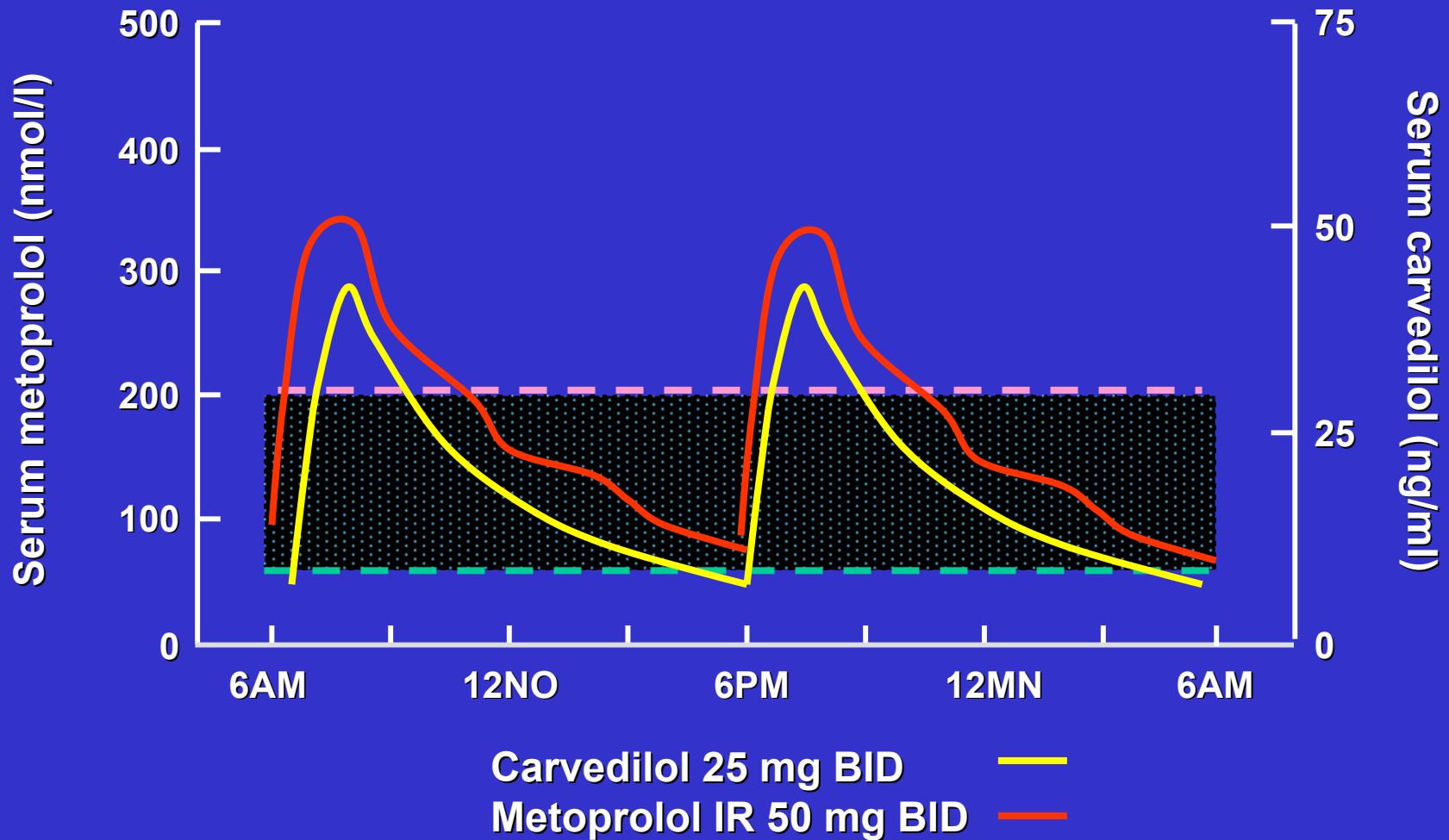


* P < 0.05 vs. non-failing

IDC = Idiopathic Dilated Cardiomyopathy

Bristow MR et al. Clin Drug Ther 1989

Time Course of Plasma Levels of Metoprolol and Carvedilol During 24-Hour Period



Sandberg A et al. Eur J Clin Pharmacol 1988. de Mey C et al. Clin Pharmacol Ther 1994
Abrahamson et al. J Clin Pharmacol 1990

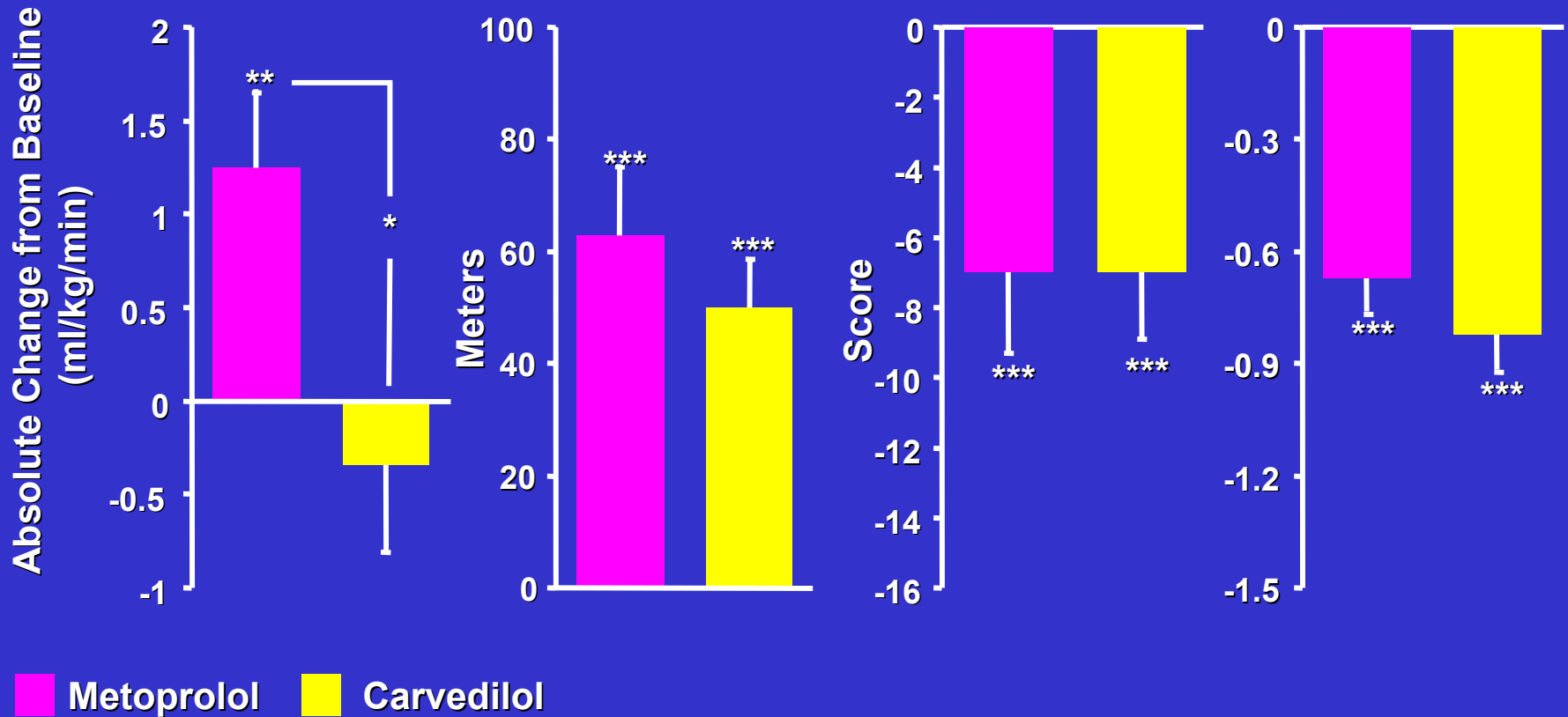
Absolute Changes in Exercise Tolerance and Symptoms After Long-term Treatment with Metoprolol or Carvedilol

Peak VO₂

Six min walk

MLHF

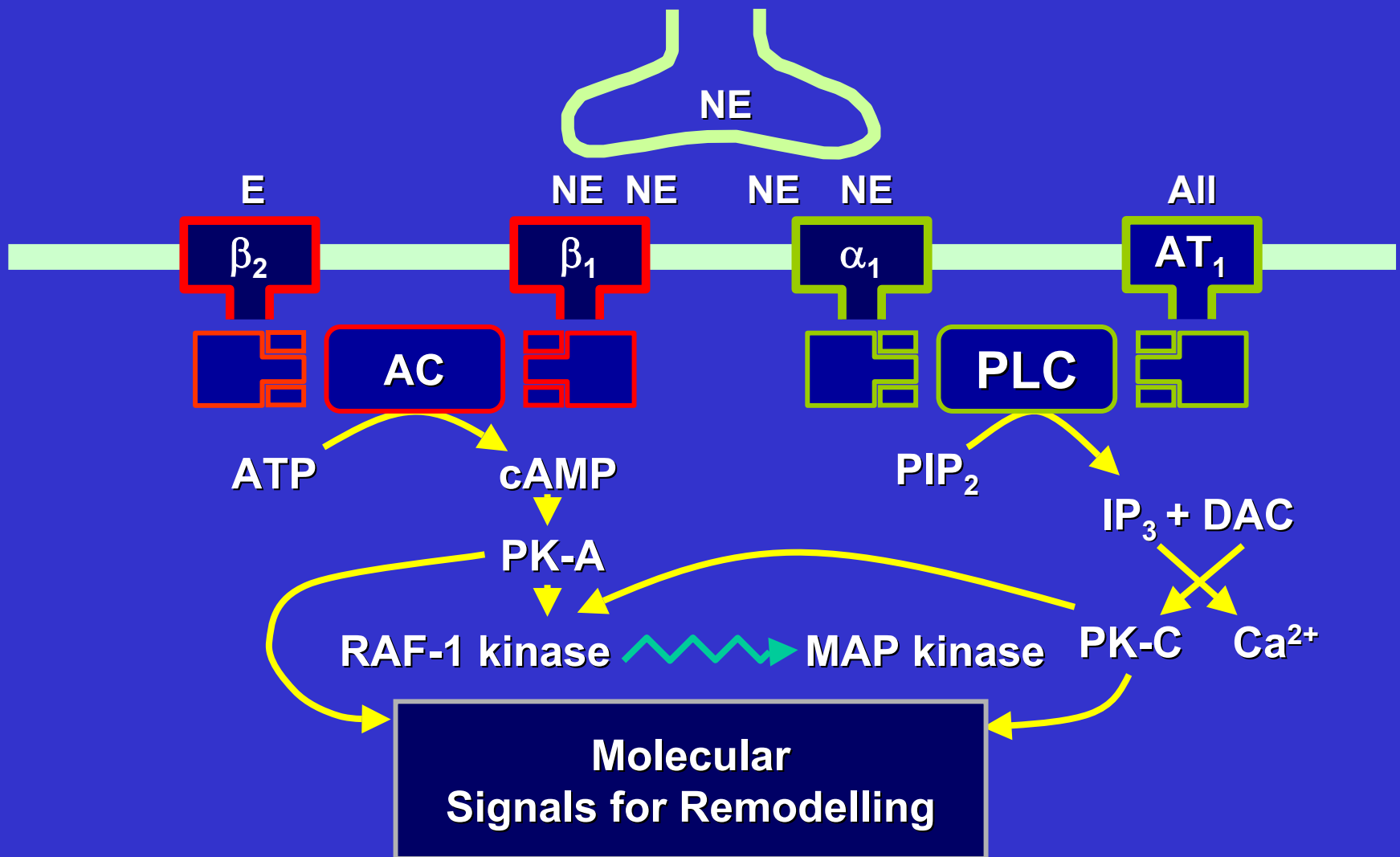
NYHA class



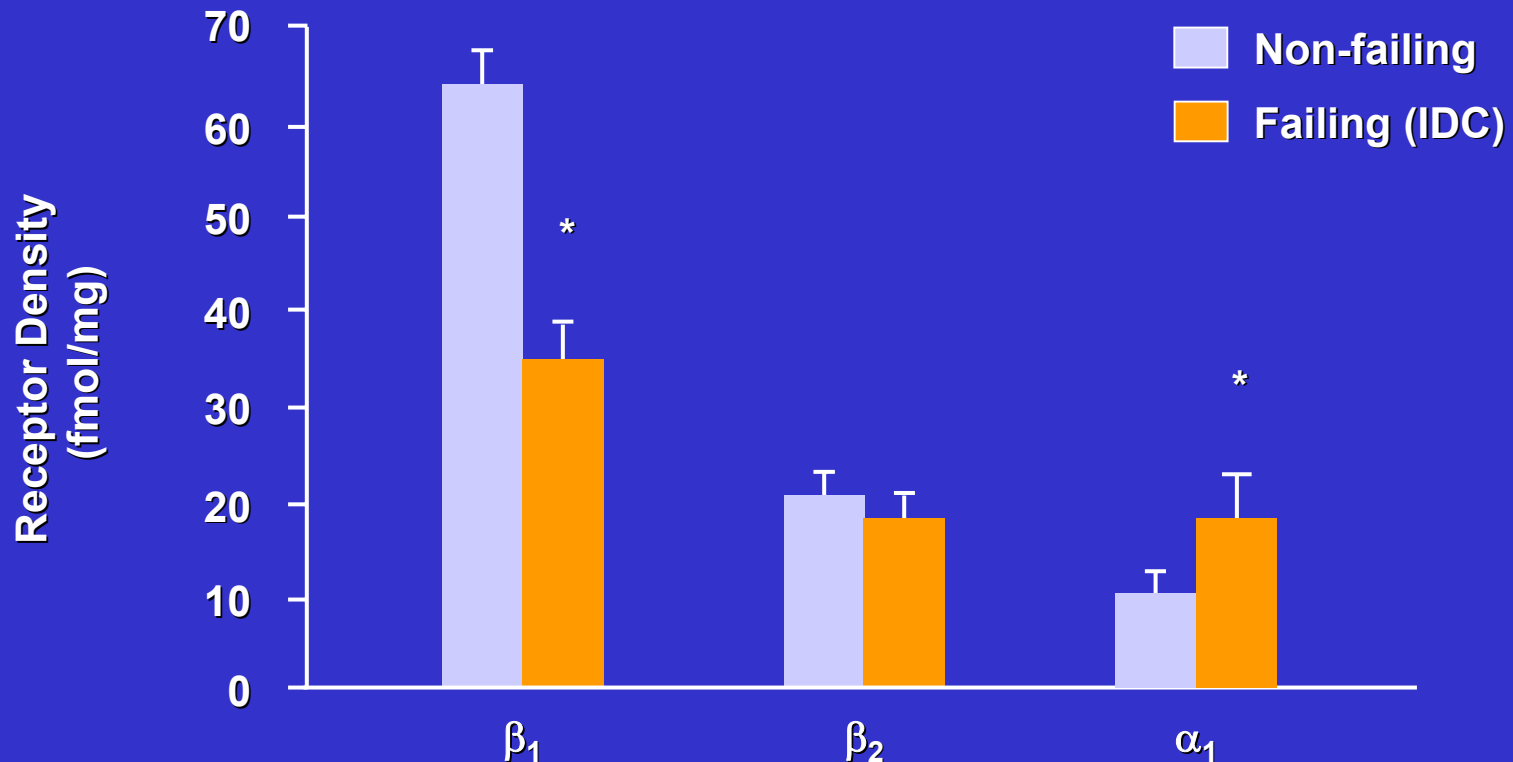
MLHF = Minnesota Living with Heart Failure

Metra M et al. Circulation 2000

Adrenergic Activation Leads to Remodelling Through Both α and β Receptors



Adrenergic Receptor Densities in Human LV Myocardium



* P < 0.05 vs. non-failing

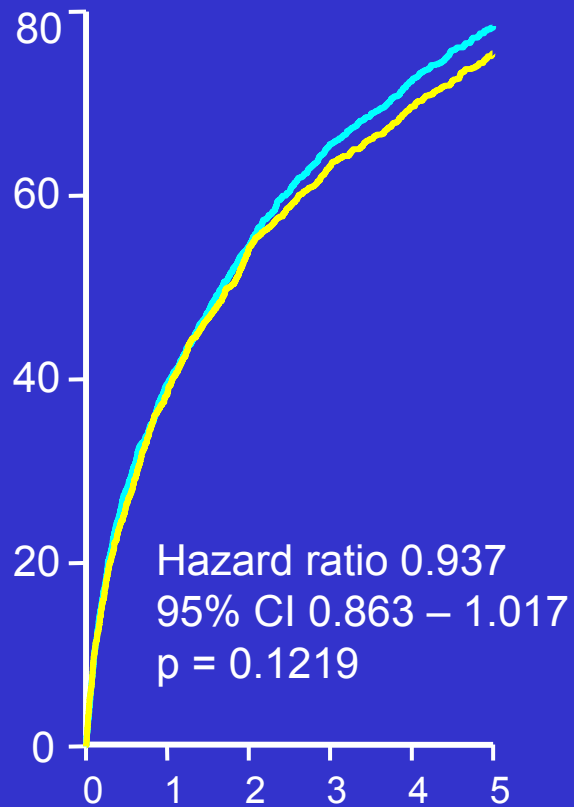
IDC = Idiopathic Dilated Cardiomyopathy

Bristow MR et al. Clin Drug Ther 1989

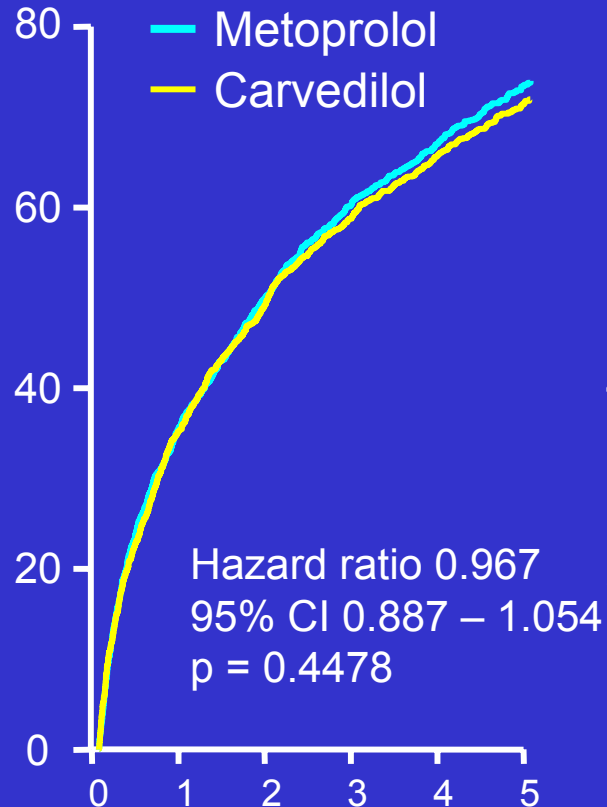
Endpoint of hospitalisation

Death or all cause hospitalisation

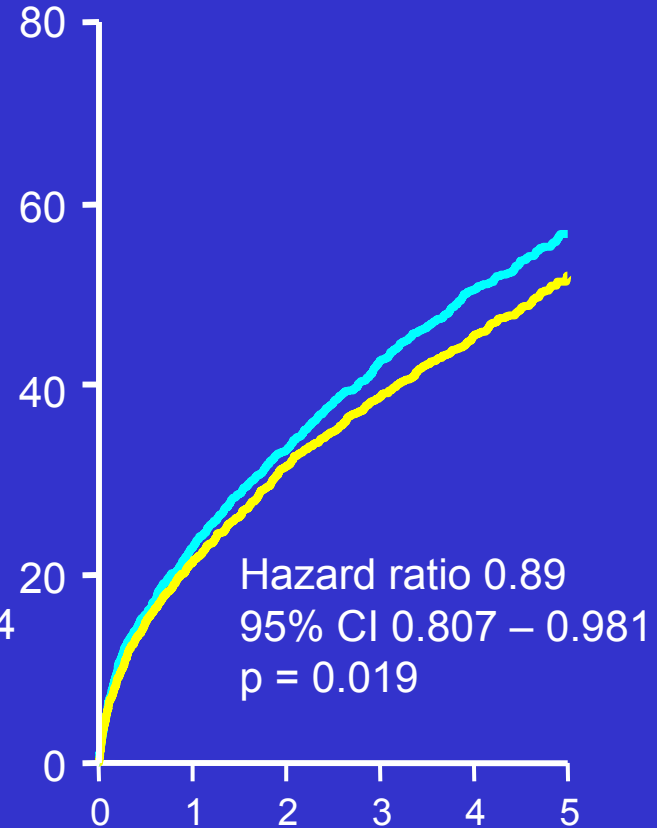
Endpoint (%)



All cause hospitalization



Death or hospitalization for worsening heart failure

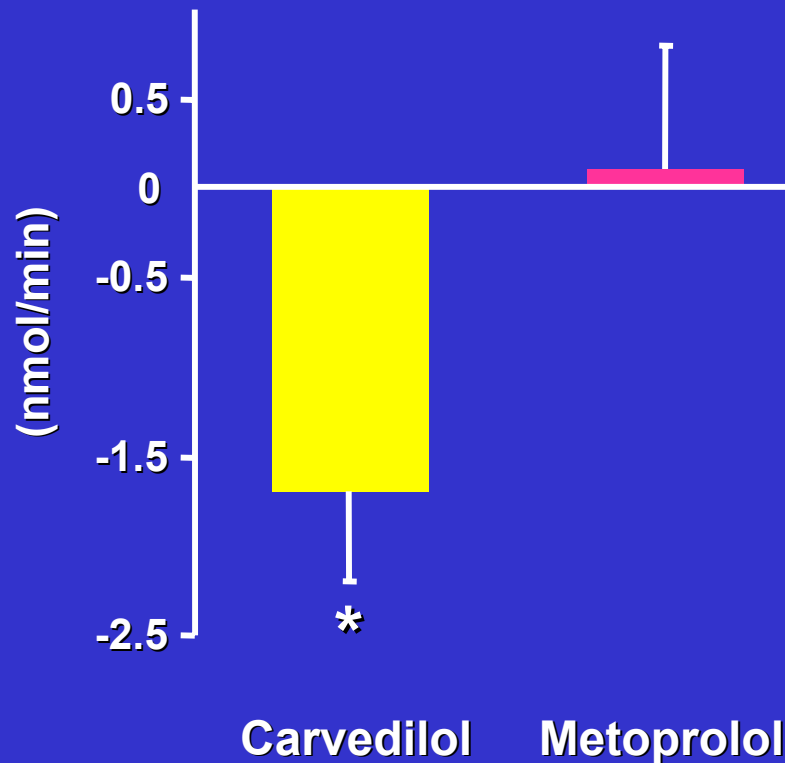


Time (years)

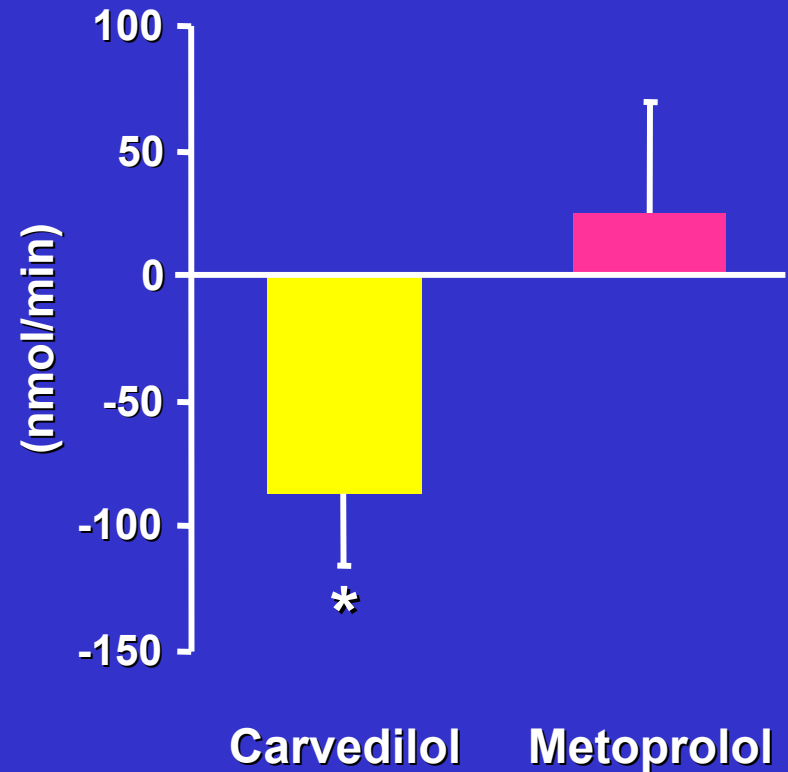
Poole-Wilson, HFSA 2003

Carvedilol, But Not Metoprolol, Reduces Total Body and Cardiac Sympathetic Drive

**Total Body
Norepinephrine Spillover**



**Cardiac
Norepinephrine Spillover**



* P < 0.05 vs. baseline and vs. metoprolol

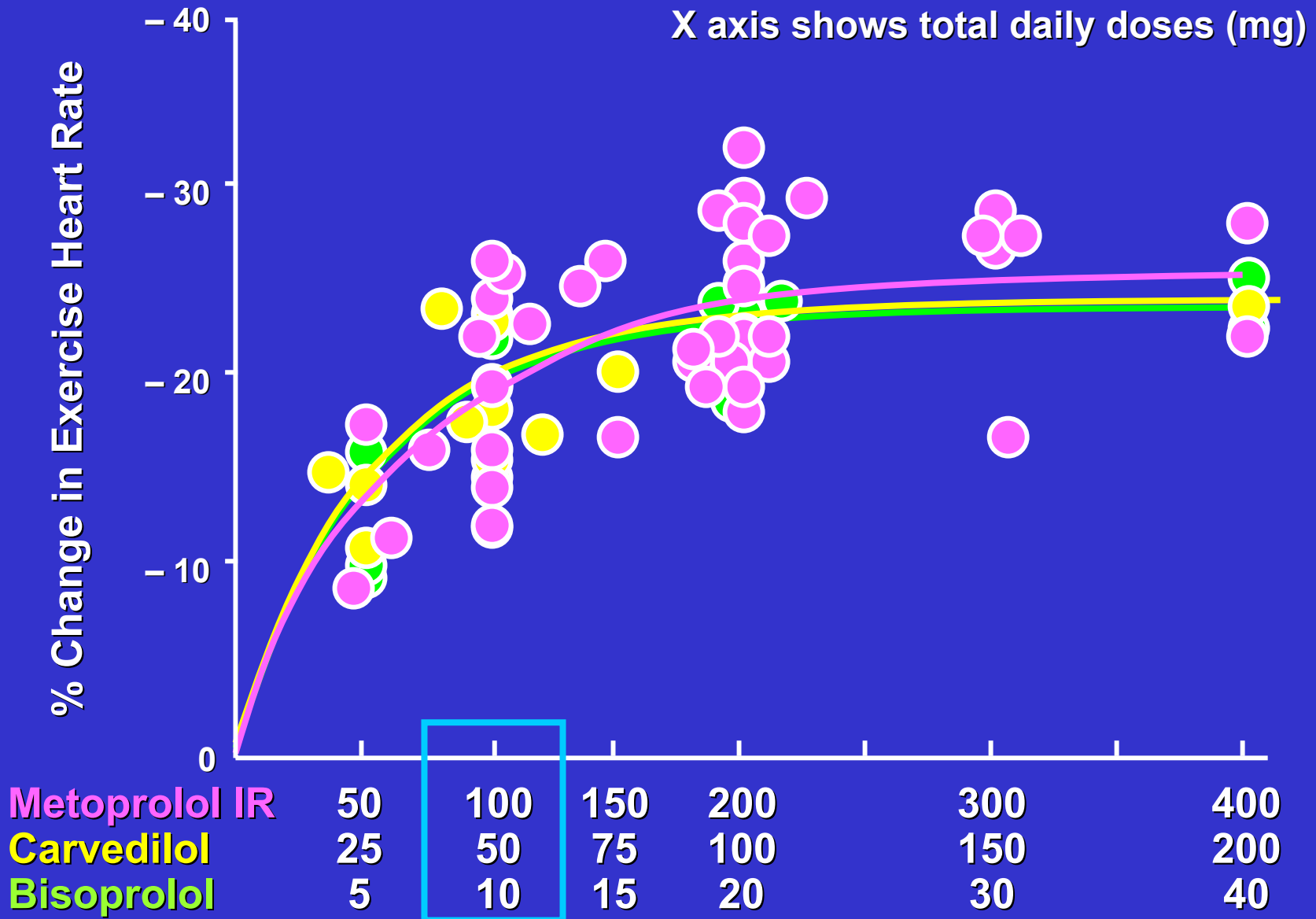
Azevedo et al. *Circulation* 2001

Baseline echocardiographic characteristics

	Carvedilol & Enalapril	Carvedilol	Enalapril
Low Heart rate	N=66	N=75	N=67
LVESVI (ml/m ²)	54.9 ± 2.1	61.5 ± 3.2	61.5 ± 3.1
LVEDVI (ml/m ²)	79.6 ± 2.4	86.9 ± 3.7	87.3 ± 3.4
LVEF (%)	31.8 ± 0.7	30.7 ± 0.7	30.8 ± 0.8
High Heart Rate	N=92	N=86	N=93
LVESVI (ml/m ²)	62.2 ± 2.4	65.7 ± 2.5	63.6 ± 2.2
LVEDVI (ml/m ²)	86.0 ± 2.6	89.5 ± 2.8	87.7 ± 2.4
LVEF (%)	28.9 ± 0.7	28.0 ± 0.7	28.6 ± 0.7

Means ± SD

Dose Response Characteristics for β Blockers



Beta-blockade in heart failure

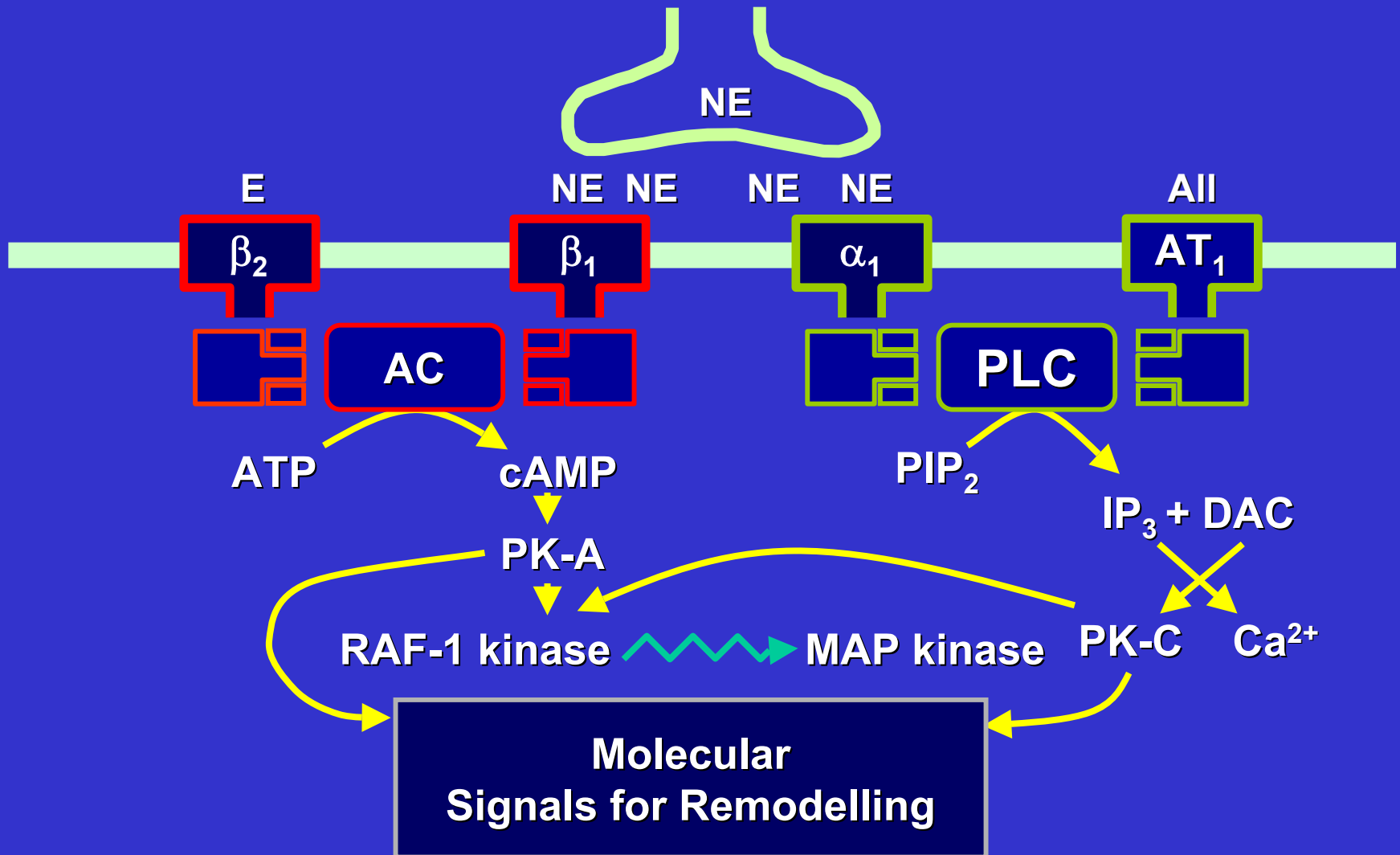
Is there anything new?

CARMEN indicates that beta-blockade (carvedilol) should not be delayed in early CHF

and

can be first-choice treatment

Adrenergic Activation Leads to Remodelling Through Both α and β Receptors



Background on Remodelling

**Acute infarction
(hours)**



**Infarct expansion
(hours to days)**



**Global remodelling
(days to months)**



Improvement of LV remodelling has been associated with improvement in mortality and morbidity outcomes in CHF

Inclusion Criteria

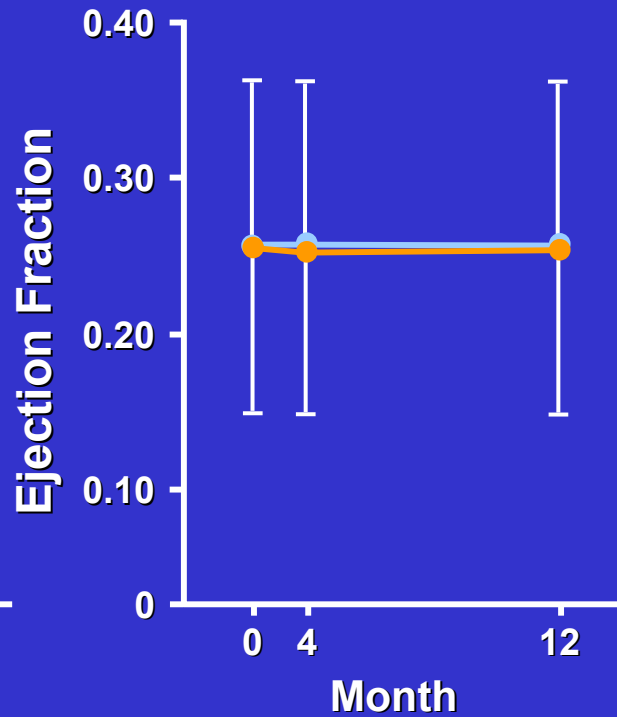
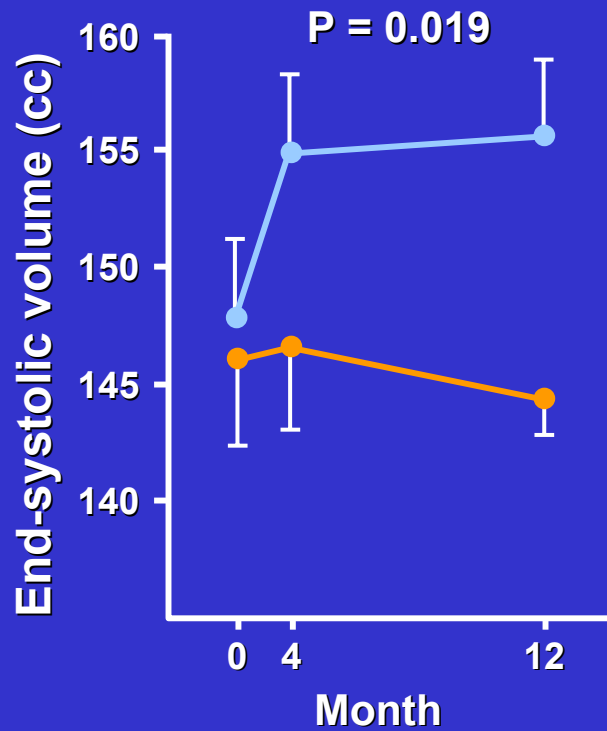
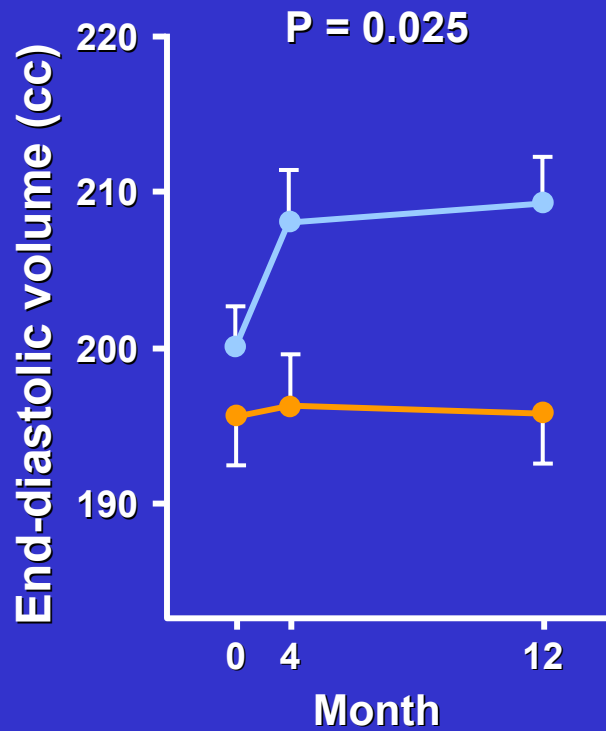
- Male or female patients ≥ 18 years of age with stable mild heart failure ($>$ two-month history of symptoms)
- Ejection fraction of ≤ 0.39 at baseline
- Echocardiographic recordings of sufficient quality
- Unmodified heart failure medication (2 weeks)
- No acute cardiovascular hospitalisations (2 weeks)
- Written informed consent

Beta-blockade in heart failure

Is there anything new?

COPERNICUS indicates that carvedilol leads to less withdrawals and better efficacy during the early phase of administration in severe CHF

ACE Inhibition Prevents Remodelling: SOLVD – Echocardiographic Substudy

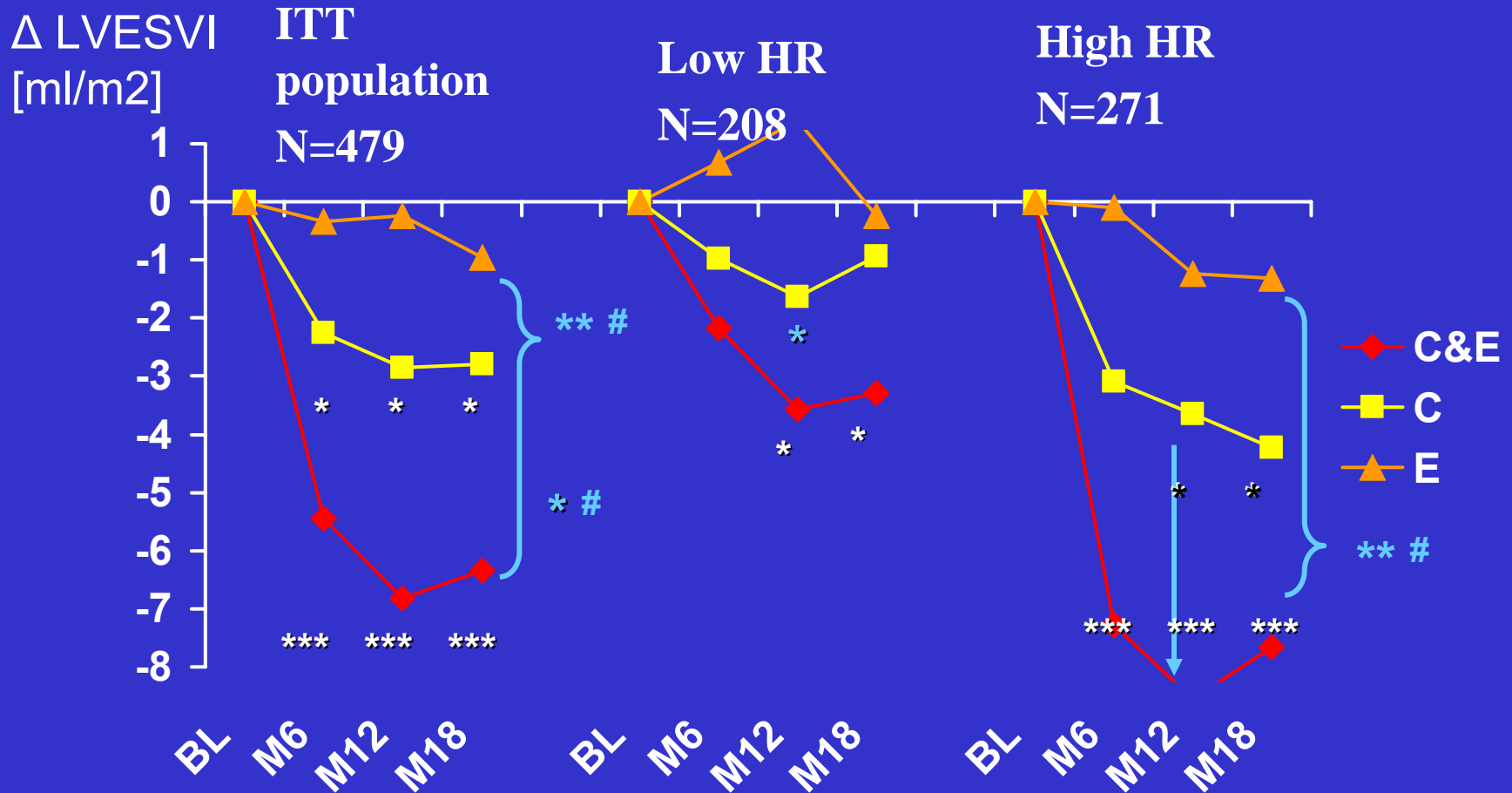


■ Placebo n = 130
■ Enalapril n = 128

130
127

142
137

Mean Change in LVESVI from baseline



* P < 0.05; ** P < 0.01; *** P < 0.001

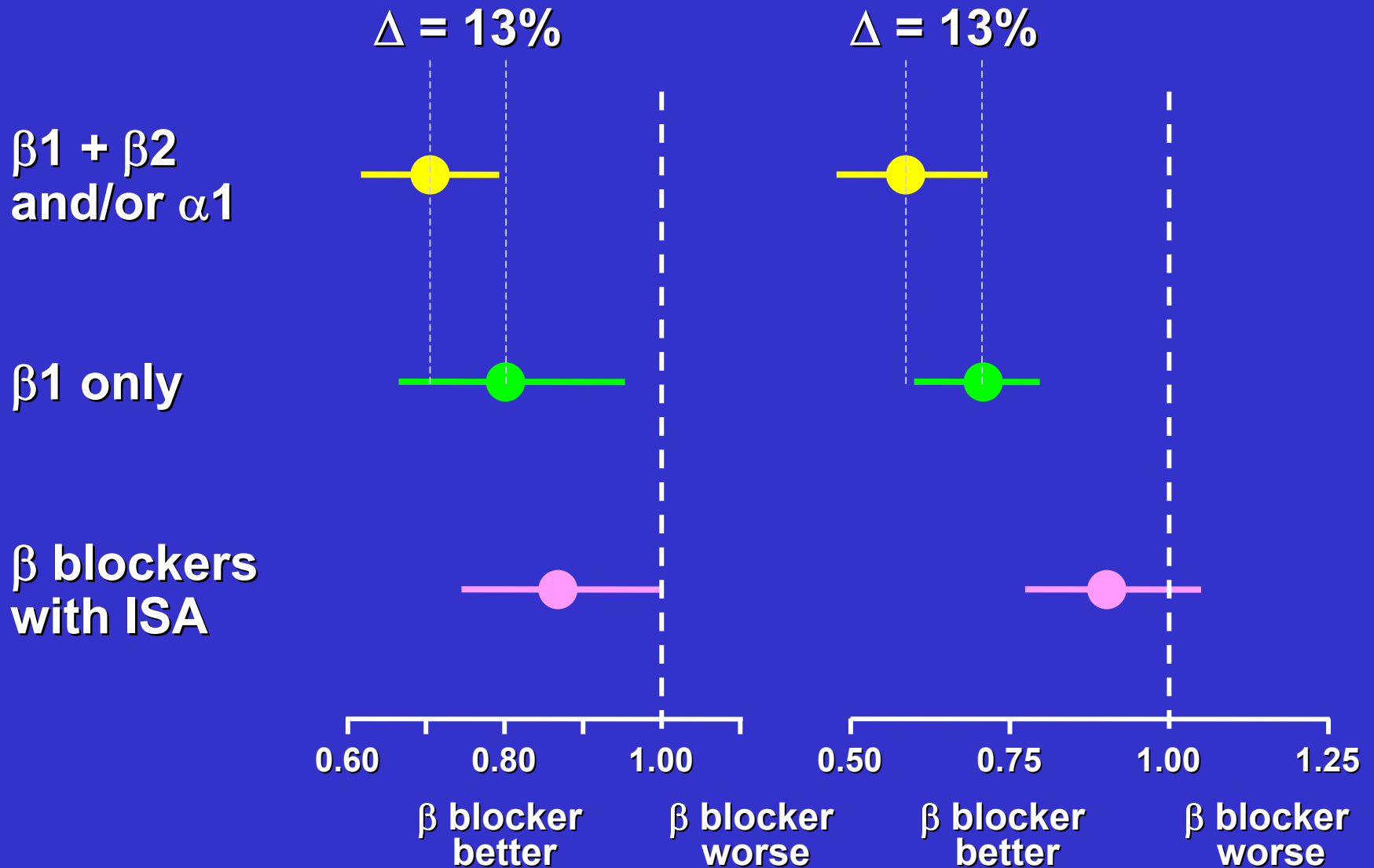
White asteriks: Significant changes from baseline (within group comparison)

P values for Δ BL to M6, M12, M18 between group comparisons

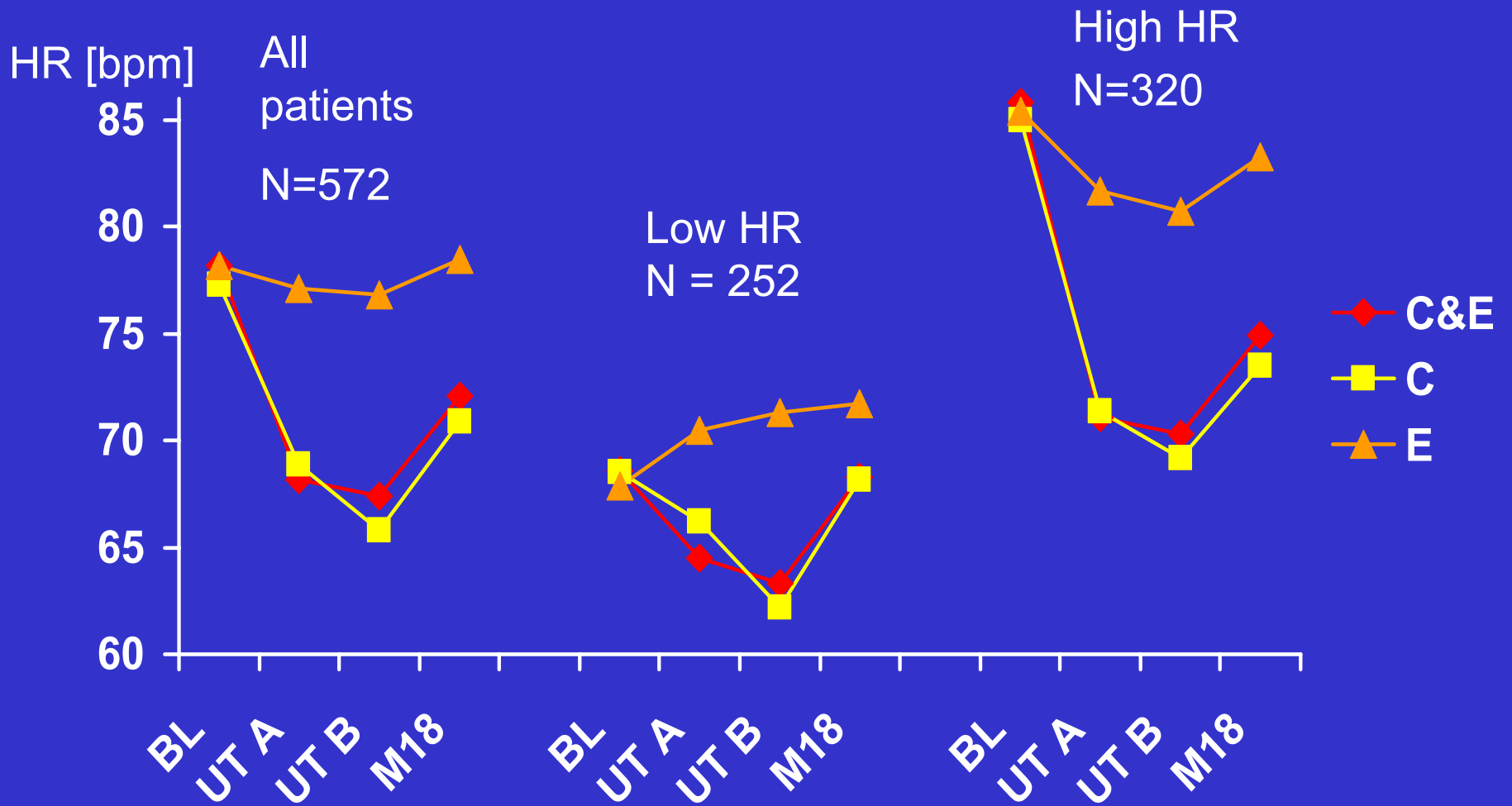
Blue asteriks: Significant differences between group comparisons

32 Post-Infarction Trials (n = 26,580)

27 Heart Failure Trials (n = 15,851)



Mean Heart Rate

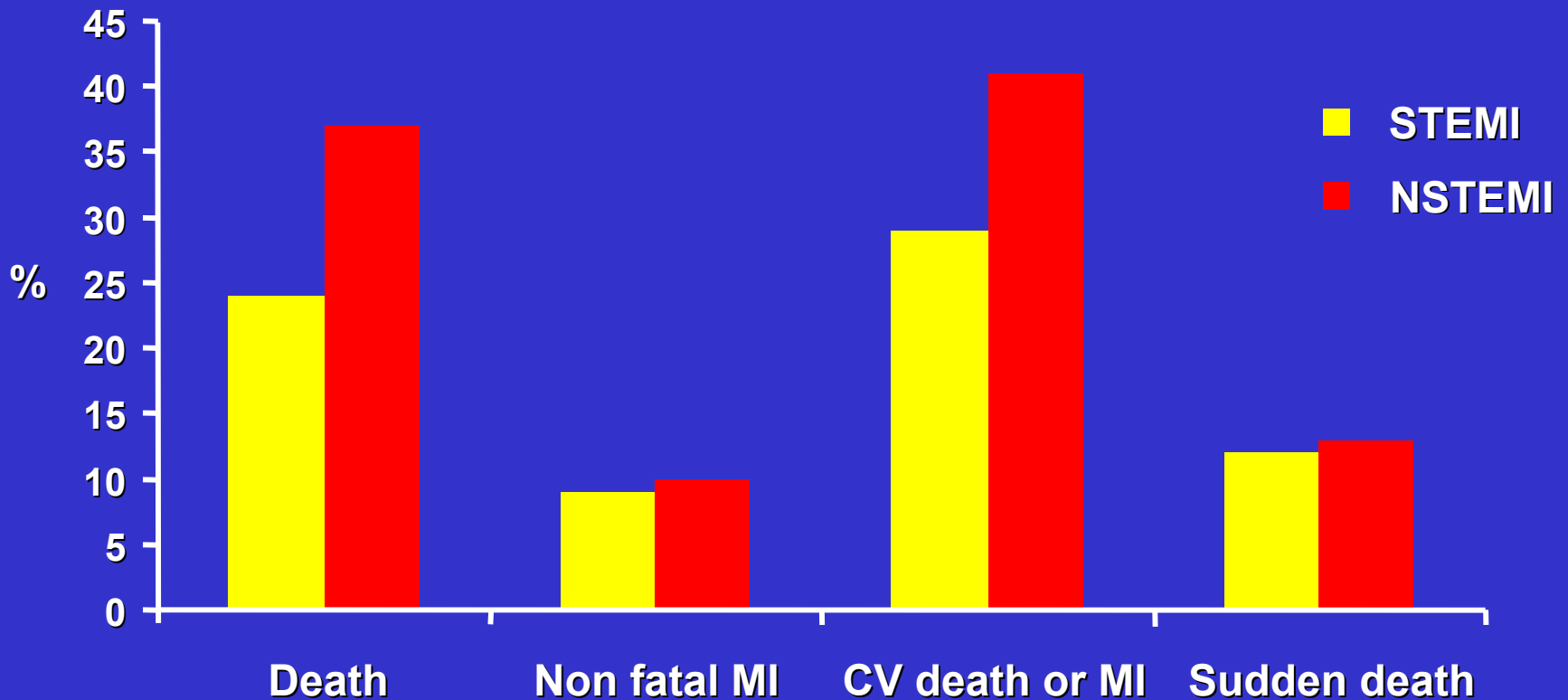


UT A: Up-titration A, UT B: Up-titration B

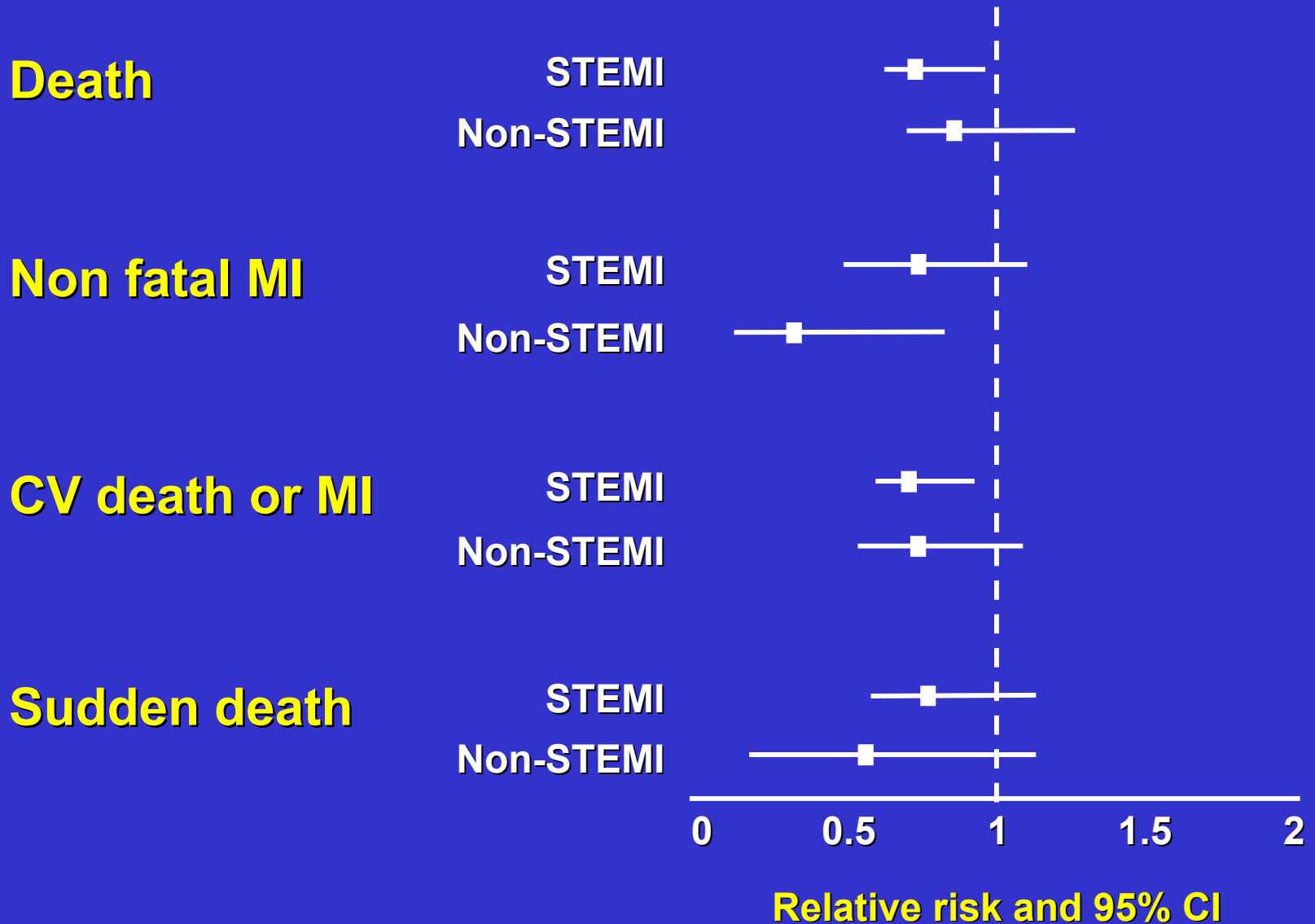
'Pan CV Endpoint' (CV Death, MI or CHF)

Placebo (n = 984)	Carvedilol (n = 975)	Hazard Ratio (95% CI)	Log rank P value
258 (26%)	211 (22%)	0.81 (0.68 - 0.97)	0.023

Event Rate (%) in STEMI and NSTEMI



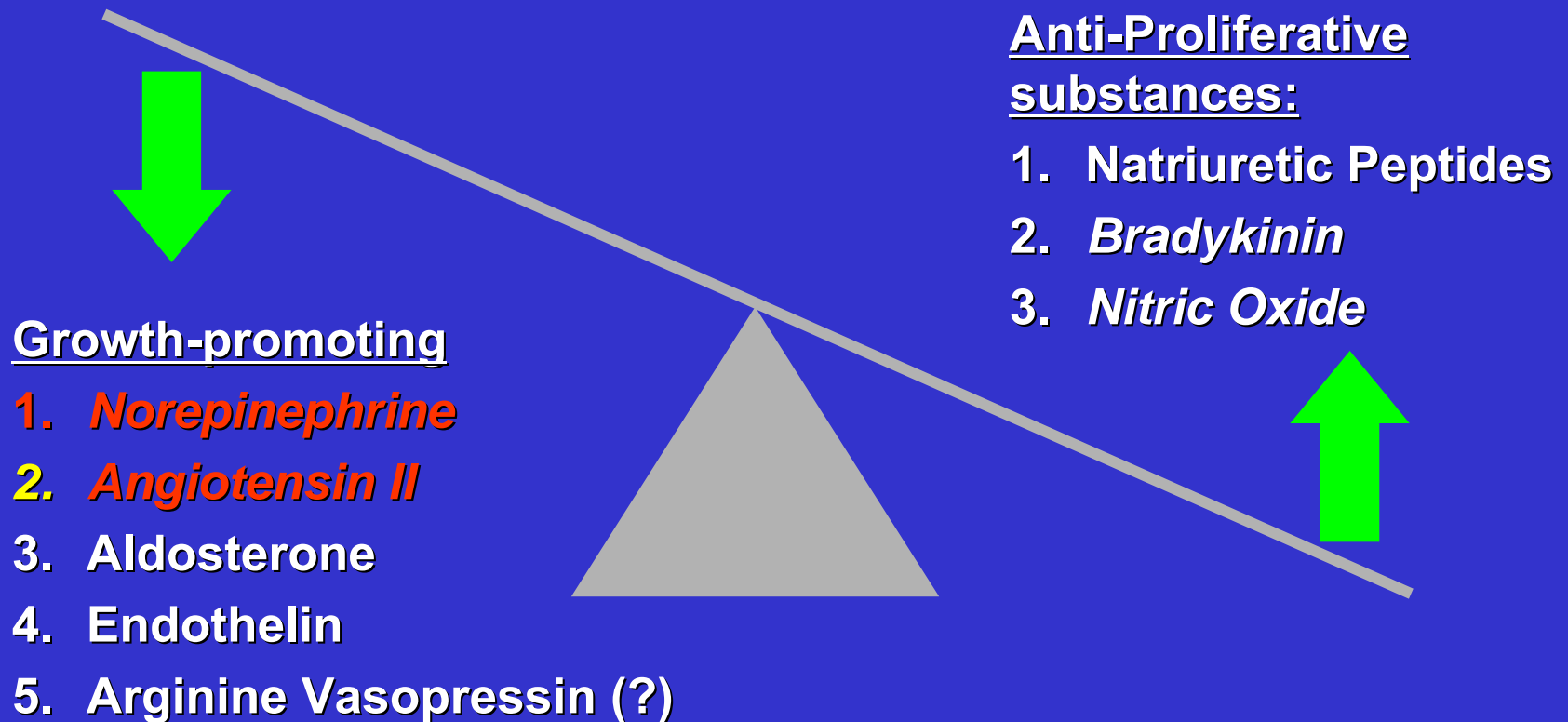
Results



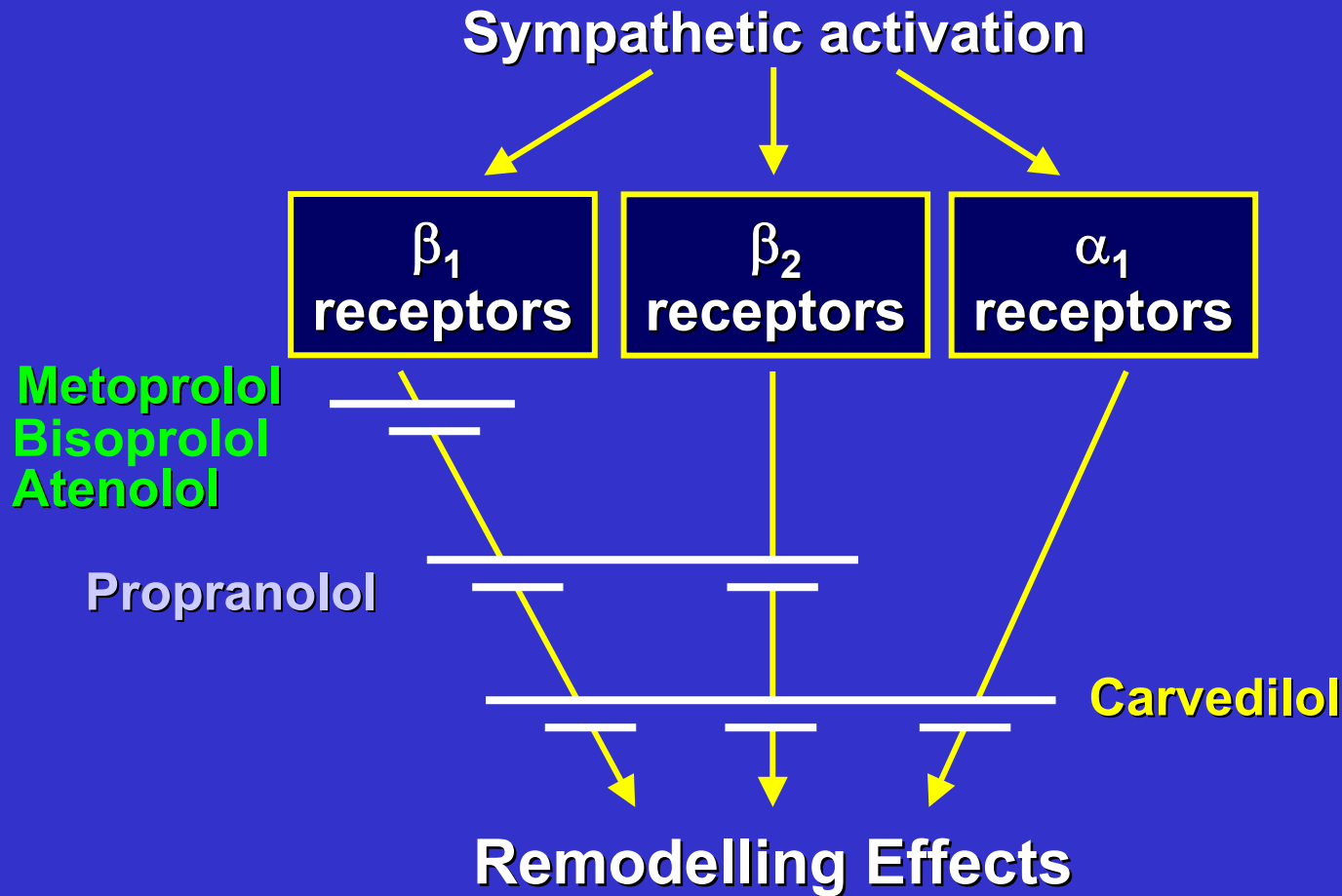
Neurohormonal Blockade Post MI: Number Needed-To-Treat

Treatment	NNT to prevent one death / year
Beta-blockers	
All patients (overview)	96
ACE inhibition	
LV dysfunction (SAVE)	60
CHF (AIRE)	21
Carvedilol	
LV dysfunction (ACE inhibition established)	43

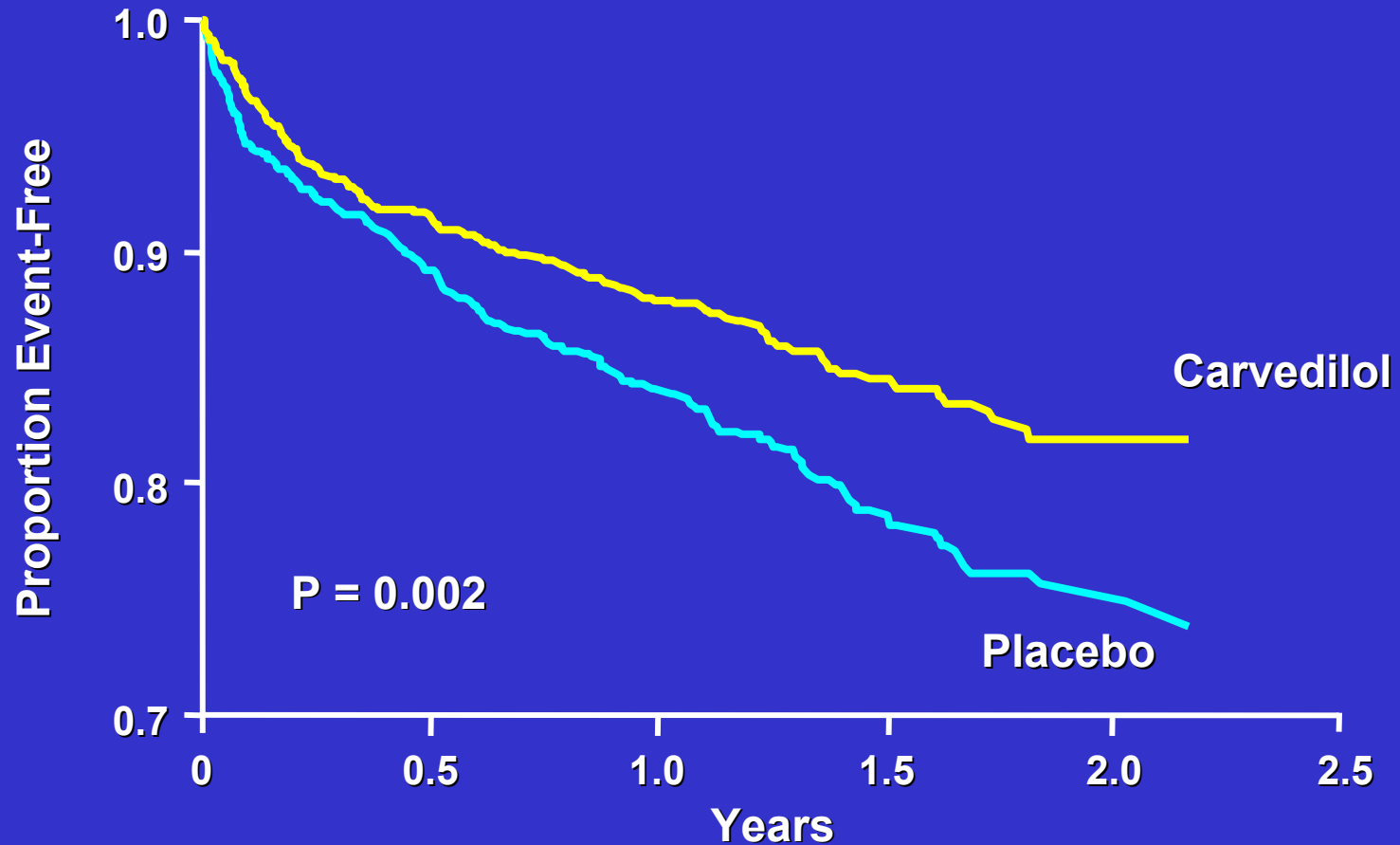
Neuroendocrine Imbalance in HF- Pivotal in Cardiac Remodelling



Antiadrenergic Therapy by β Blockade

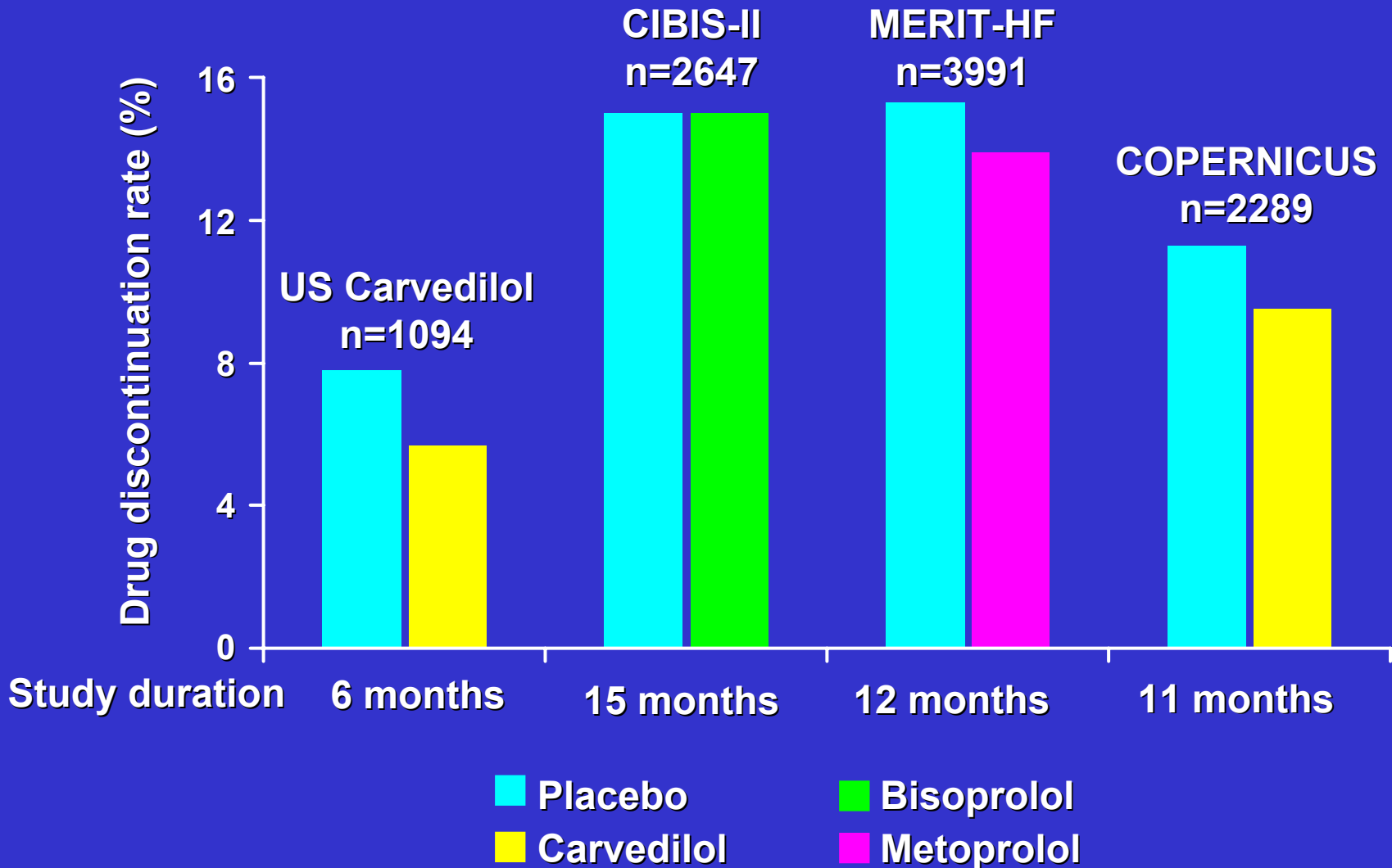


All-Cause Mortality or Recurrent Myocardial Infarction

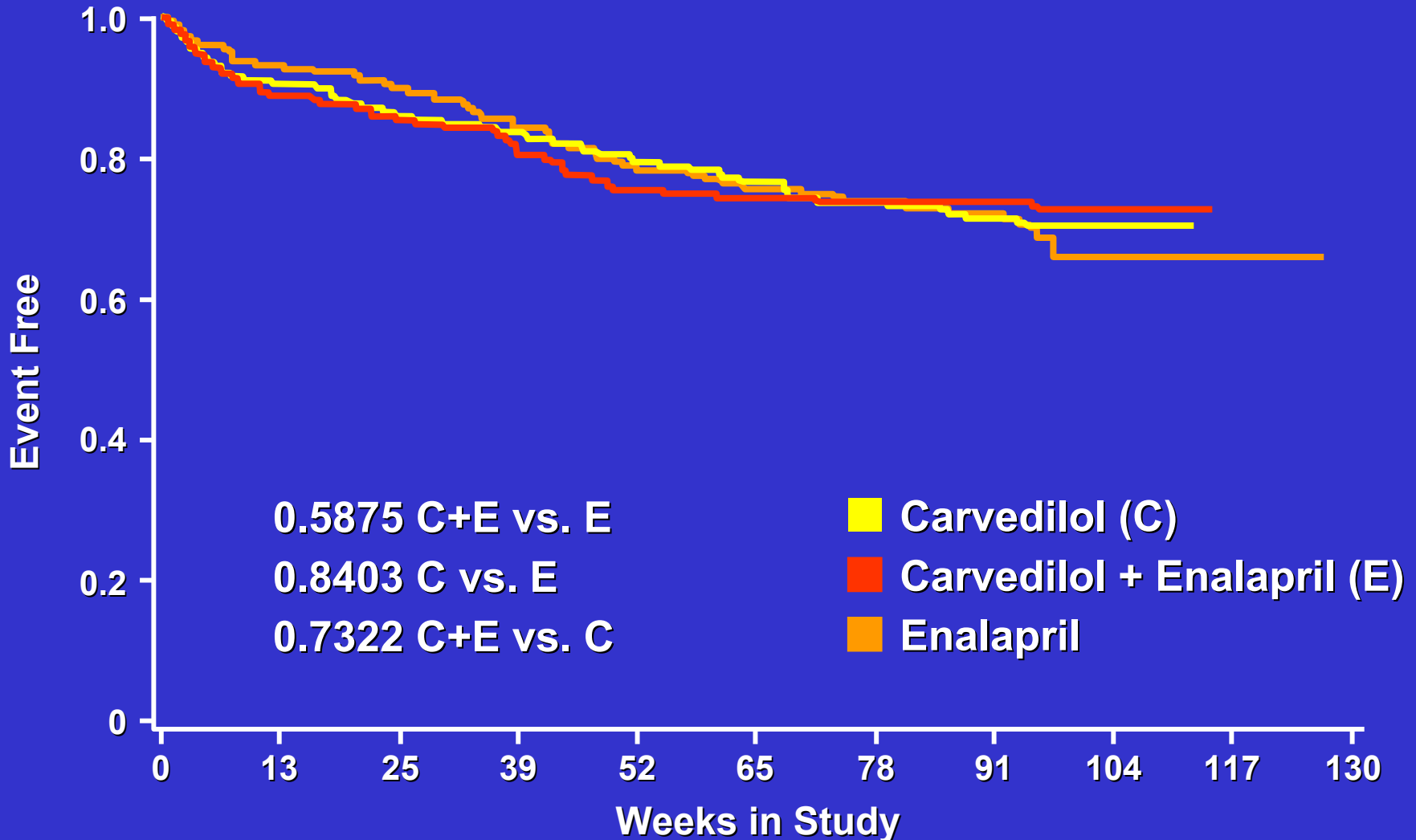


The CAPRICORN Investigators. Lancet 2001

Discontinuation Rates in Mild-Moderate and Severe CHF



All-cause Mortality or Hospitalisation



AIMS

Evaluate efficacy in terms of LV remodelling and function, tolerability and safety of carvedilol alone or the combination carvedilol/ACE inhibition versus ACE inhibition alone in patients with mild- moderate heart failure

Endpoints

■ Primary endpoint

- Change from baseline to month 18 in LVESVI assessed by echocardiography between
 - Carvedilol & Enalapril versus Enalapril
 - Carvedilol versus Enalapril

■ Major secondary endpoints

- changes from baseline in LVESVI within treatment group
- changes from baseline in LVEDVI, LVEF

LVESVI = left ventricular endsystolic volume index

LVEDVI = left ventricular enddiastolic volume index

Baseline NYHA & LV Assessments

	C & E N = 158	C N = 161	E N = 160
Class I (%)	7	9	7
Class II (%)	68	65	62
Class III (%)	25	26	31
LVESVI (ml/m²)	59.2	63.7	62.7
LVEDVI (ml/m²)	83.3	88.3	87.6
LVEF (%)	30.1	29.3	29.5

Does Baseline Heart Rate Determine the Effect of Carvedilol on Ventricular Remodeling in Heart Failure? –

Results of a CARMEN sub-study

Are There Differences Between β Blockers?

- β blockers are a heterogeneous class
 - More than 15 agents available
- Only three have shown significant survival benefits in mild to moderate CHF
 - Carvedilol
 - Metoprolol
 - Bisoprolol
- Only carvedilol has shown a mortality benefit in severe CHF in a large scale prospective randomised trial

Flow Chart of Patients

Randomised
3029

Carvedilol
1511

Assigned to drug
and received at least one tablet

Metoprolol
1518

Withdrew consent 10
Lost to follow-up 3

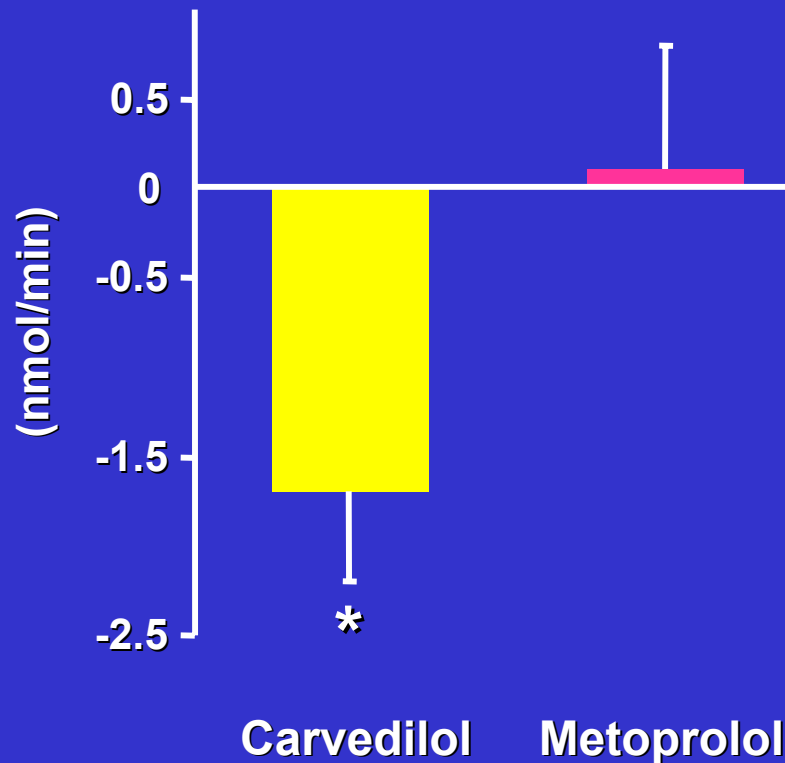
Withdrew consent 18
Lost to follow-up 2

Baseline Characteristics

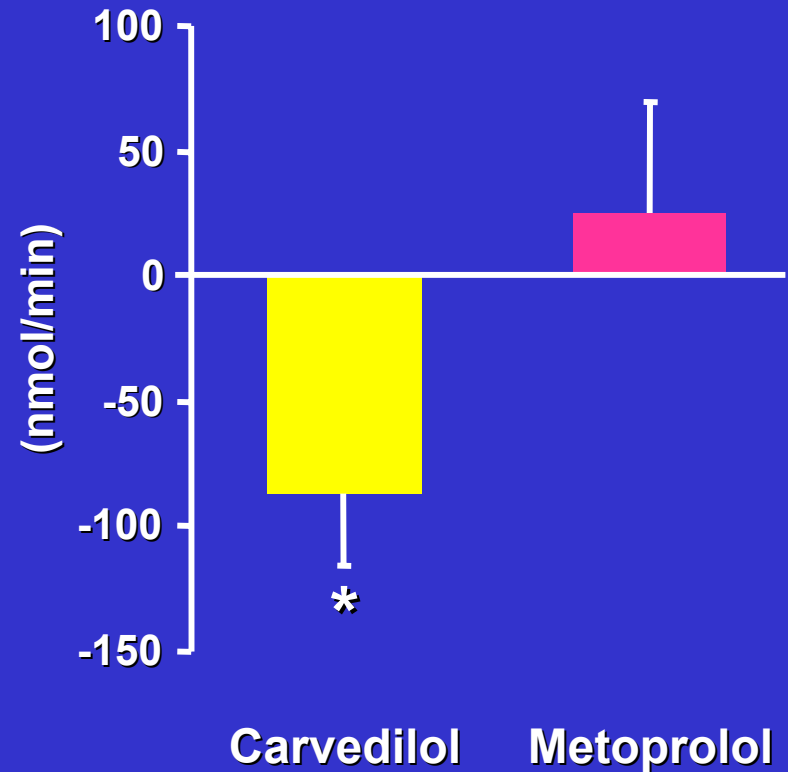
	Carvedilol (n=1511)	Metoprolol (n=1518)
Age (y, mean/sd)	62 (11.3)	62 (11.4)
Male (%)	79	80
Aetiology (IHD %)	52	54
Months of HF (mean/median)	42.6/22	42.2/20
Heart rate (beats/min)	81	81
Systolic BP (mm Hg)	126	126
Diastolic BP (mm Hg)	77	77
NYHA class (%) II/III/IV	48/48/3	49/47/4
AF/flutter (%)	20	19
Diabetes	24	24

Carvedilol, But Not Metoprolol, Reduces Total Body and Cardiac Sympathetic Drive

**Total Body
Norepinephrine Spillover**



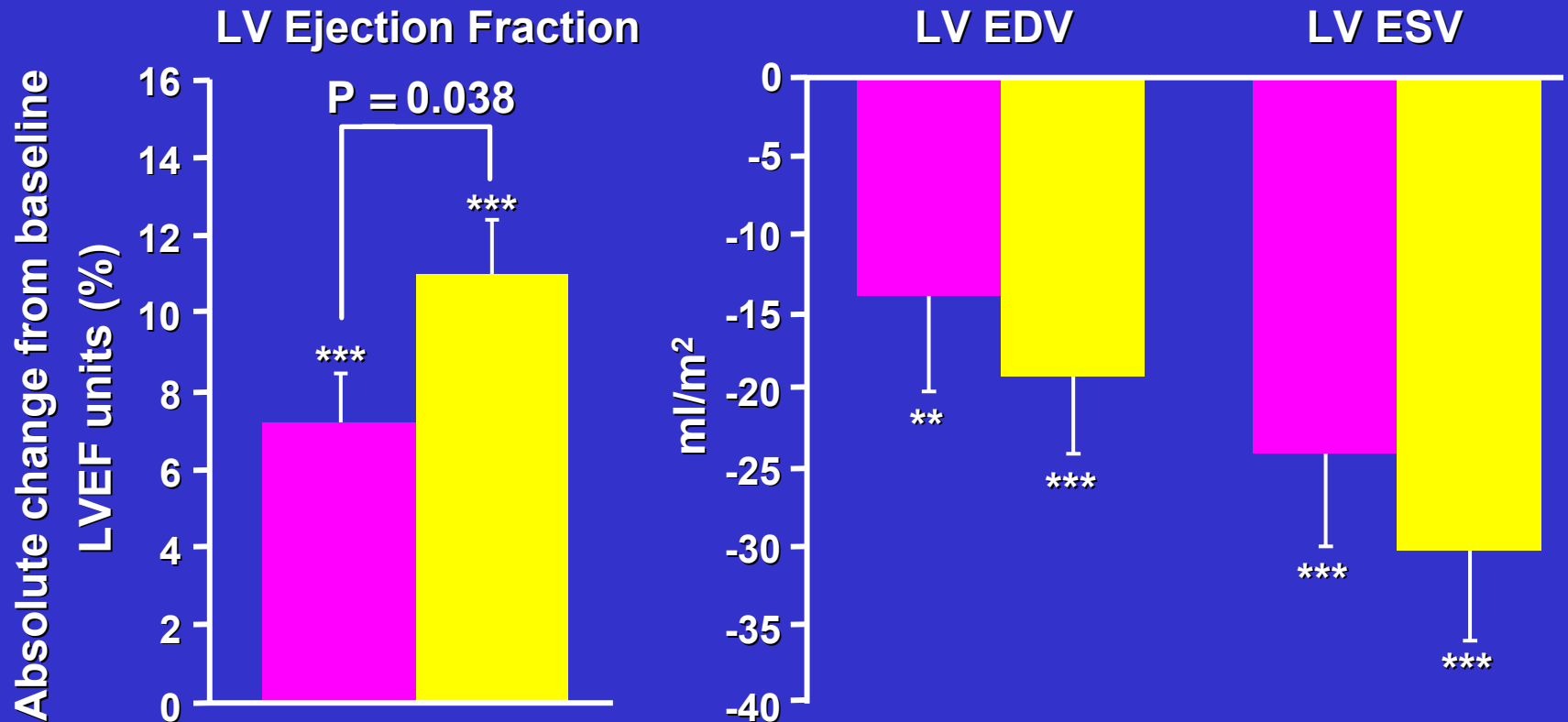
**Cardiac
Norepinephrine Spillover**



* P < 0.05 vs. baseline and vs. metoprolol

Azevedo et al. *Circulation* 2001

Carvedilol Reverses LV Remodelling to a Greater Extent than Metoprolol



P < 0.01; *P < 0.001
vs baseline

Metoprolol Carvedilol

β blockers in NYHA class IV heart failure

Proportion of patients with class IV heart failure

US Carvedilol Programme

3%

MERIT-HF

4%

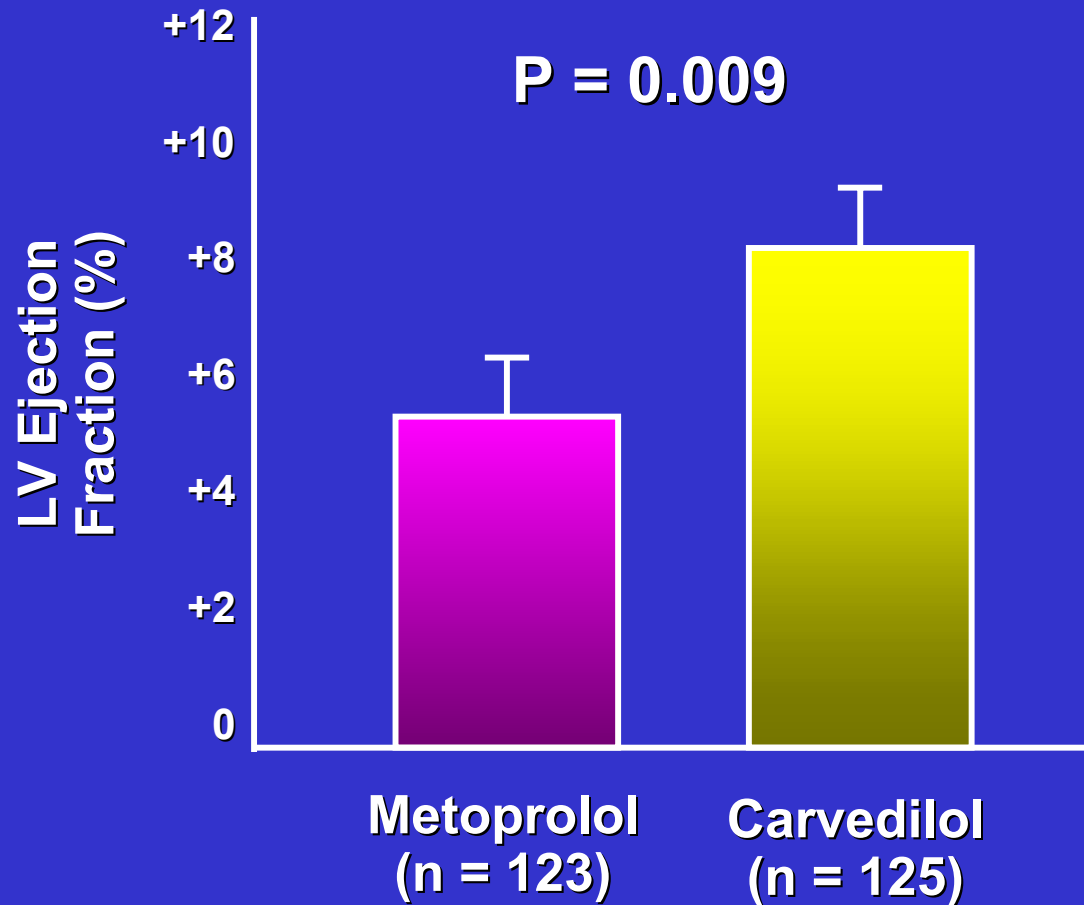
CIBIS-II

17%

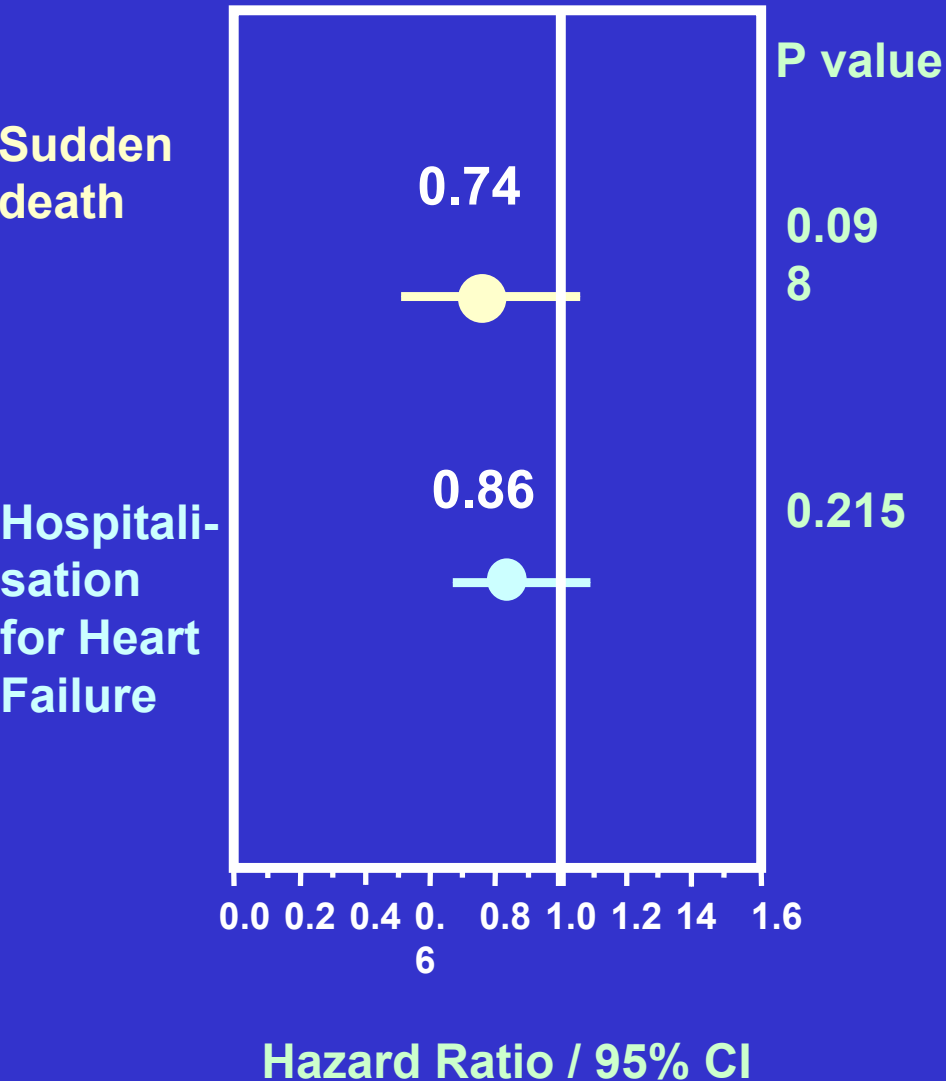
BEST

8%

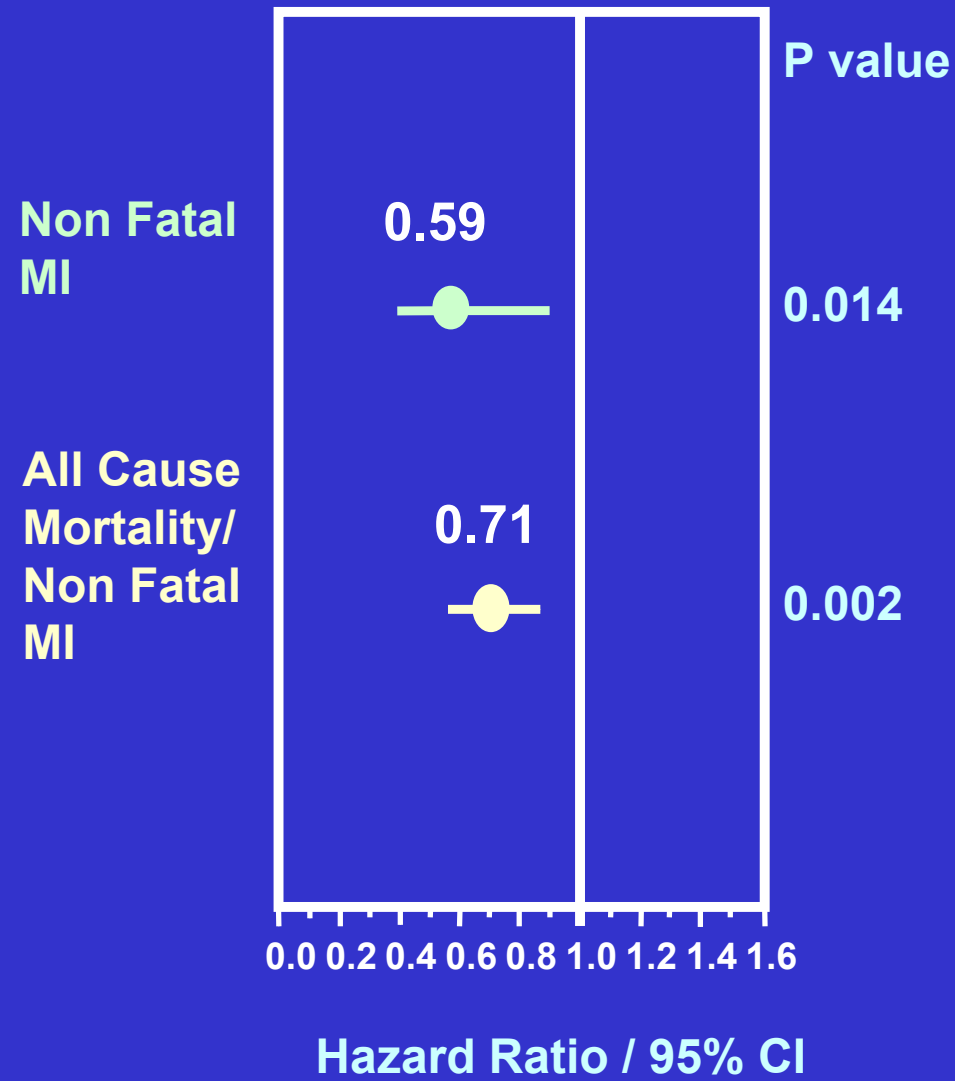
Results of Direct Comparison Trials with Metoprolol and Carvedilol in CHF Patients



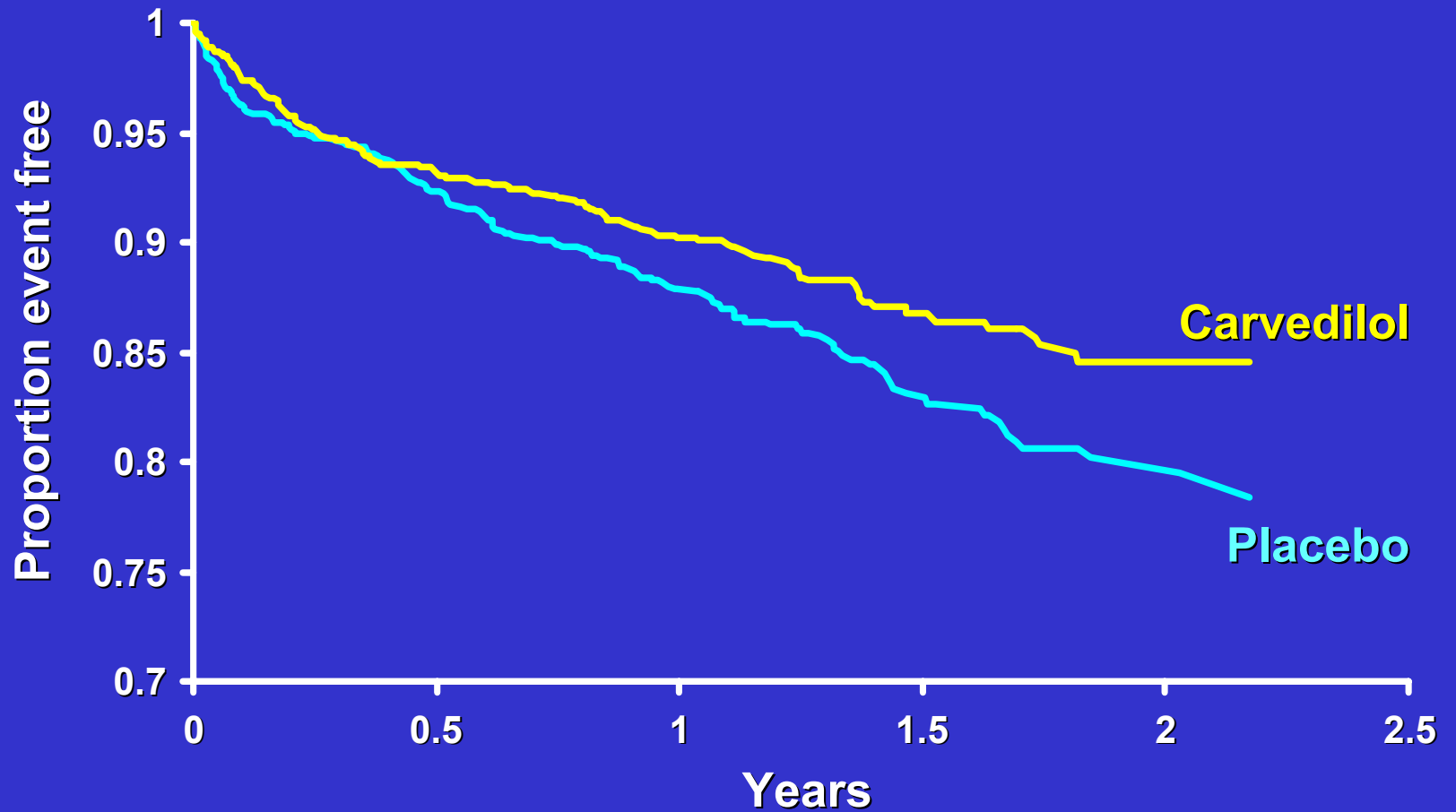
Secondary Endpoints



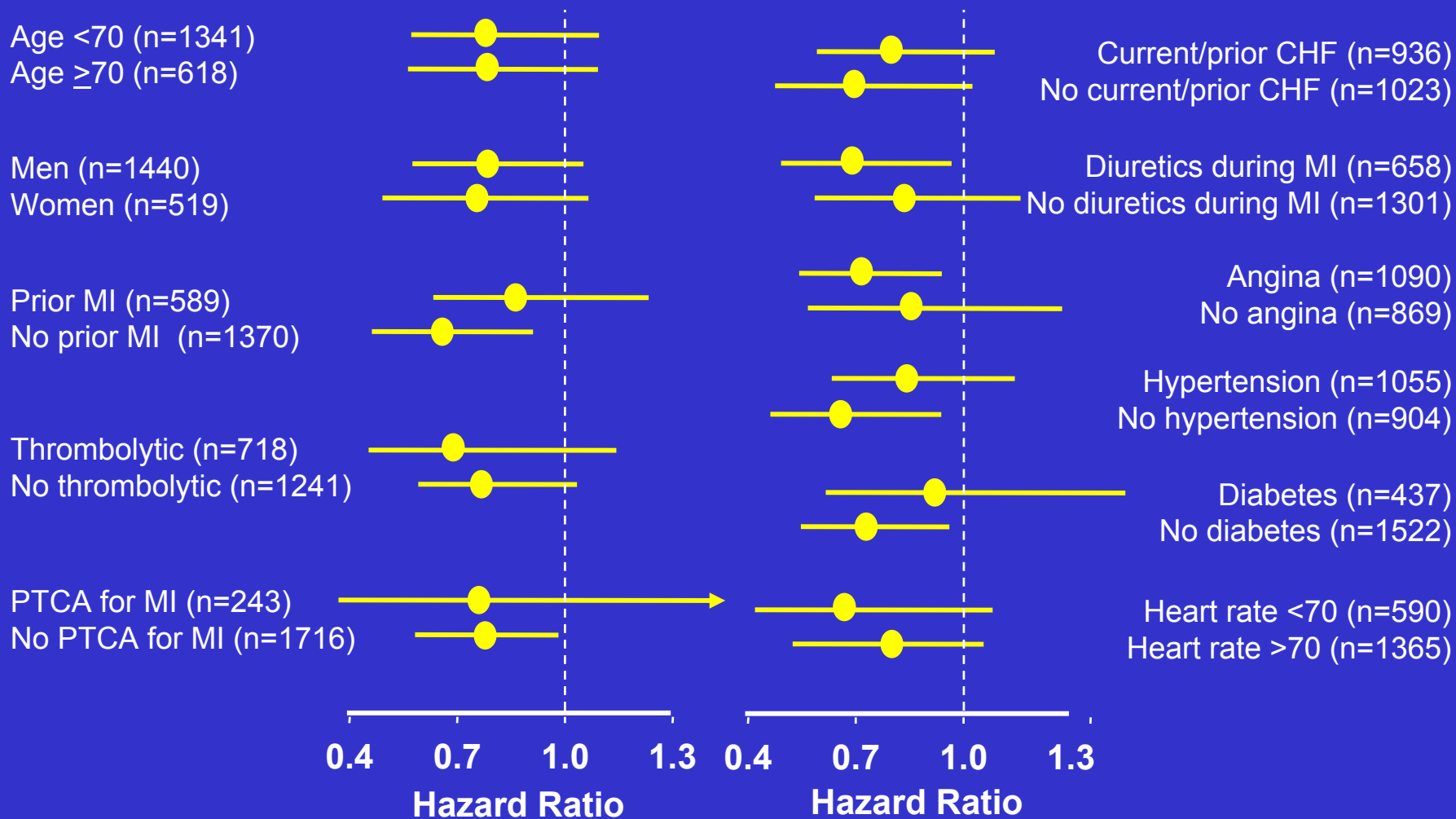
Major Coronary Events



All Cause Mortality



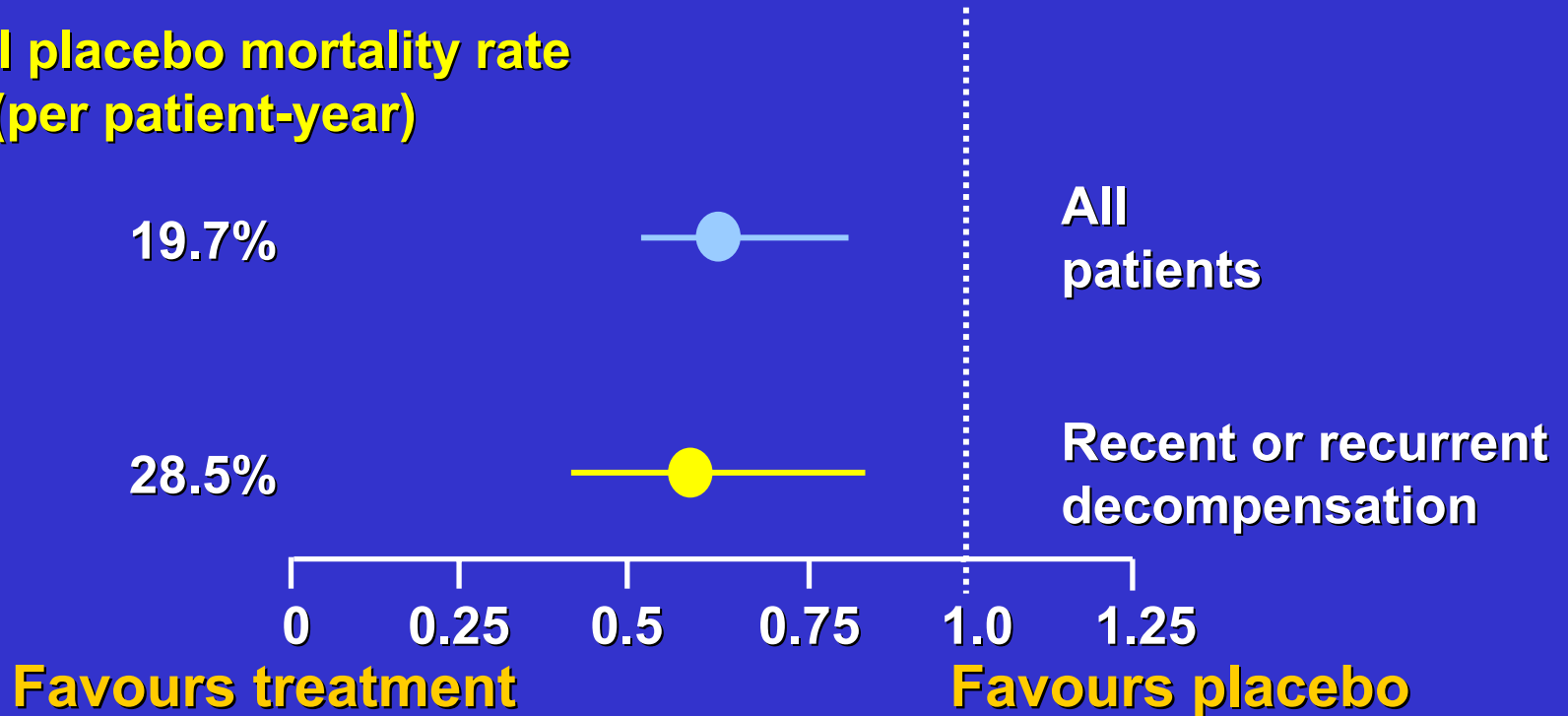
CAPRICORN: All-Cause Mortality Subgroups



COPERNICUS

Effect of carvedilol on mortality

Annual placebo mortality rate
(per patient-year)







Adverse Events

	C & E	C	E
	N = 191	N = 191	N = 190
% pts. Any AE	79	77	75
Total No. of AE	497	426	461
% pts. Serious AE	28	29	34
Total No. of SAE	81	101	94
% pts. AE leading to withdrawal	18	18	21
Total No. of AE leading to withdrawal	45	43	48

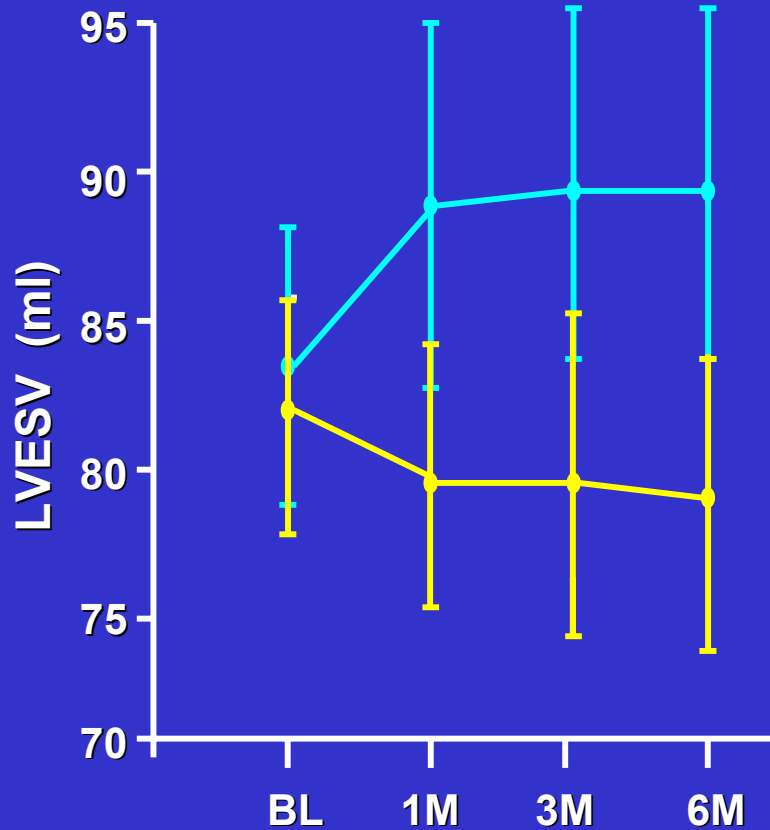


Treatment of CHF: ESC Guidelines

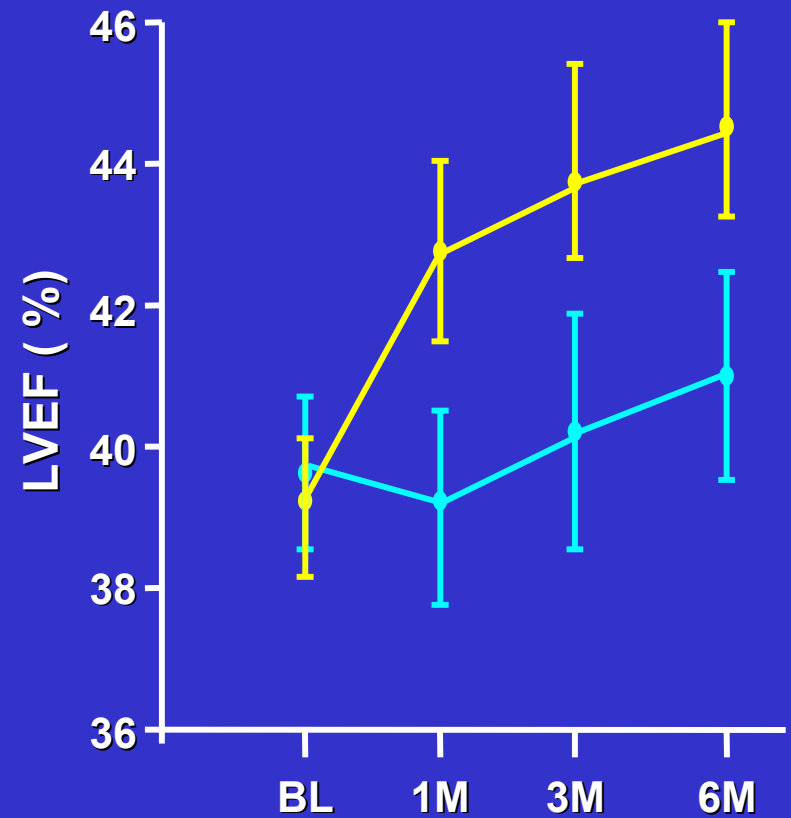
	<i>For Symptoms</i>	<i>For Survival/Morbidity mandatory therapy</i>	<i>For Symptoms if Intolerance to ACE inhibition or β-blockade</i>
NYHA I	reduce / stop diuretic 	continue ACE inhibitor if asymptomatic, add β -blocker if post MI 	
NYHA II	+/- diuretic depending on fluid retention	ACE inhibitor as first-line treatment add β-blocker if still symptomatic 	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant
NYHA III	+ diuretics + digitalis if still symptomatic + nitrates / hydralazine if tolerated	ACE inhibitor and β -blockade add spironolactone 	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant
NYHA IV	diuretics + digitalis + nitrates / hydralazine if tolerated + temporary inotropic support	ACE inhibitor β -blockade spironolactone	ARB if ACE inhibitor intolerant or ACE inhibitor + ARB if β -blocker intolerant

Remodelling in CAPRICORN

$\Delta = -9.2$ ml
 $P = 0.031$



$\Delta = +3.9\%$
 $P = 0.0037$



—●— Carvedilol —●— Placebo

Doughty R et al. In press

Effect on Cardiac Arrhythmia

	Placebo	Carvedilol	Hazard ratio (95% CI)	P-Value
Any supraventricular arrhythmia	54	26	0.48 (0.30 - 0.76)	0.0015
Atrial flutter or atrial fibrillation	53	22	0.41 (0.25 - 0.68)	0.0003
Any ventricular arrhythmia	69	26	0.37 (0.24 - 0.58)	< 0.0001
Ventricular tachycardia or ventricular fibrillation	40	12	0.30 (0.16 - 0.57)	< 0.0001

COPERNICUS

Carvedilol Prospective Randomized Cumulative Survival Trial

Objectives and design

- To determine the effect of carvedilol compared with placebo on all-cause mortality in patients with severe chronic heart failure
- Randomised, placebo-controlled, parallel-group multicenter study in patients with ischaemic or non-ischaemic cardiomyopathy

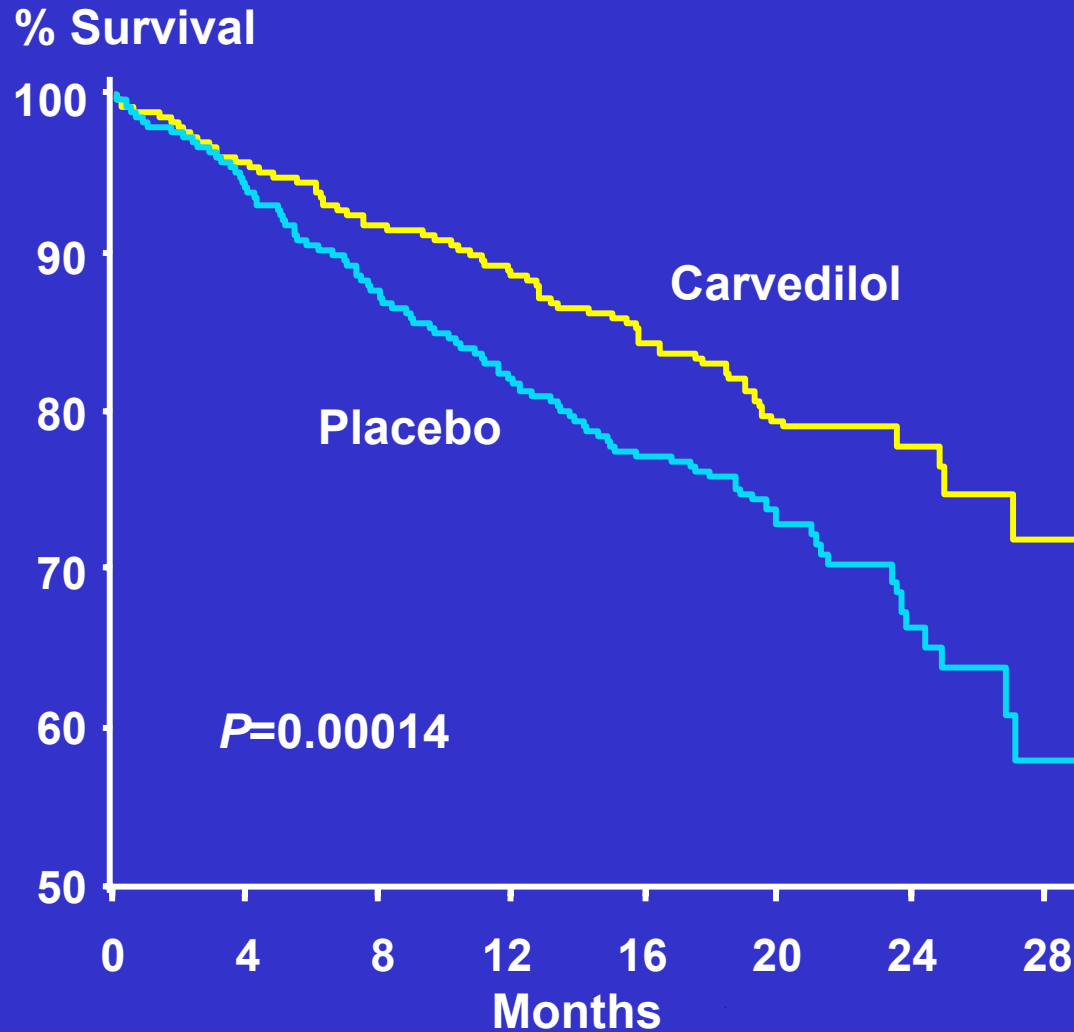
COPERNICUS

Patient Characteristics

- Symptoms of heart failure at rest or minimal exertion for at least 2 months
- LV ejection fraction $<25\%$
- Receiving diuretics and an ACE inhibitor (+ digitalis) ≥ 2 months. Diuretics optimised to achieve euvolaemia
- No need for intensive care and no treatment with IV inotropic or IV vasodilator therapy within 4 days of screening

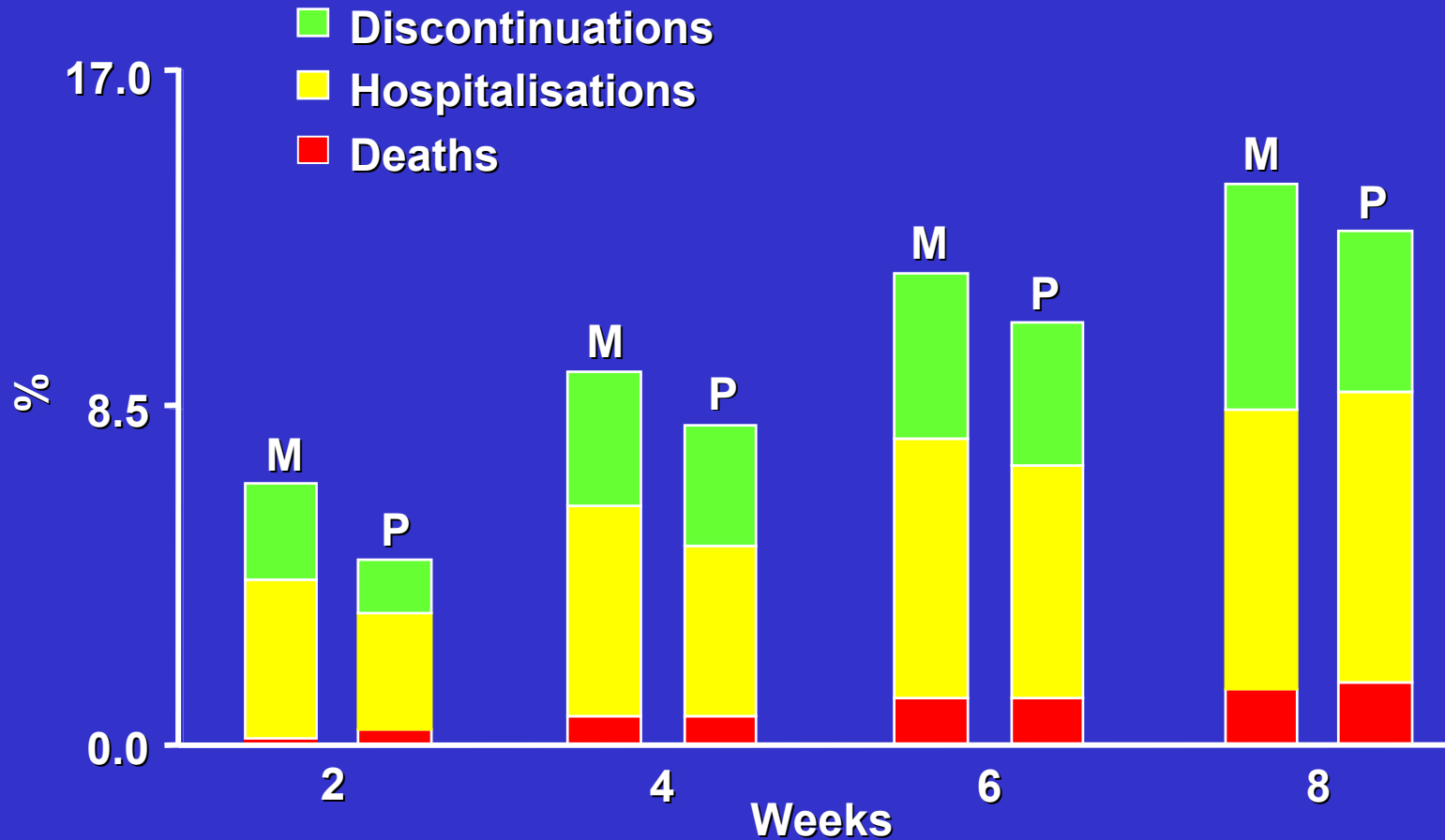
COPERNICUS

All-cause mortality



MERIT-HF: Weeks 1 to 8 of Therapy

NYHA Class III - IV Patients

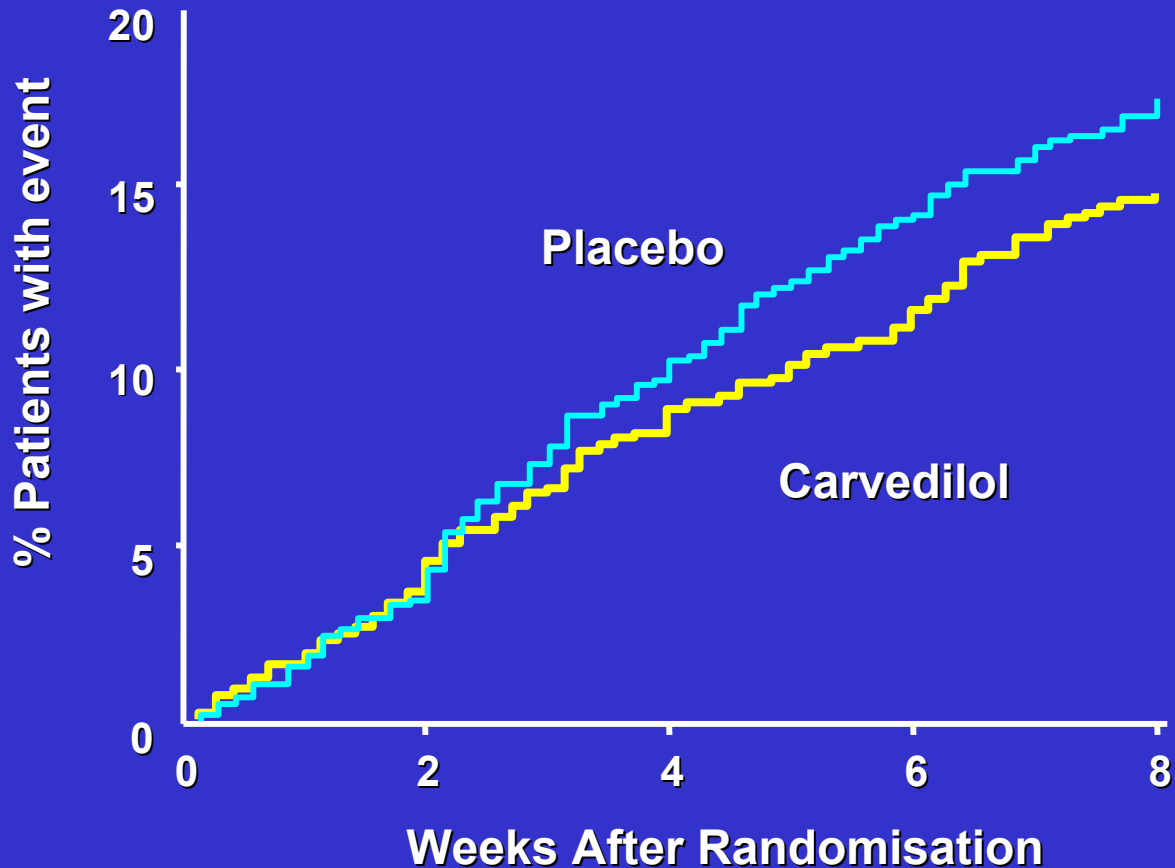


M = Metoprolol
P = Placebo

Gottlieb S et al. Circulation 2000

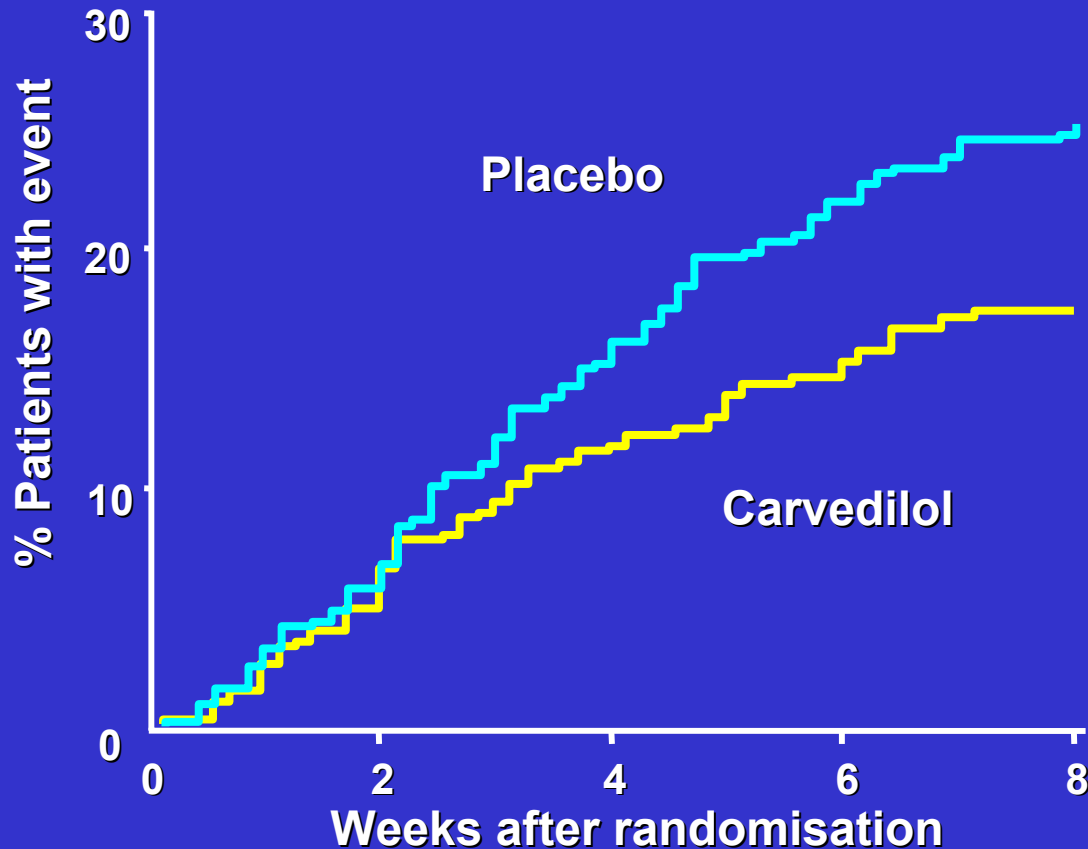
COPERNICUS: Weeks 1 to 8

Death, hospitalisation and withdrawal: all patients

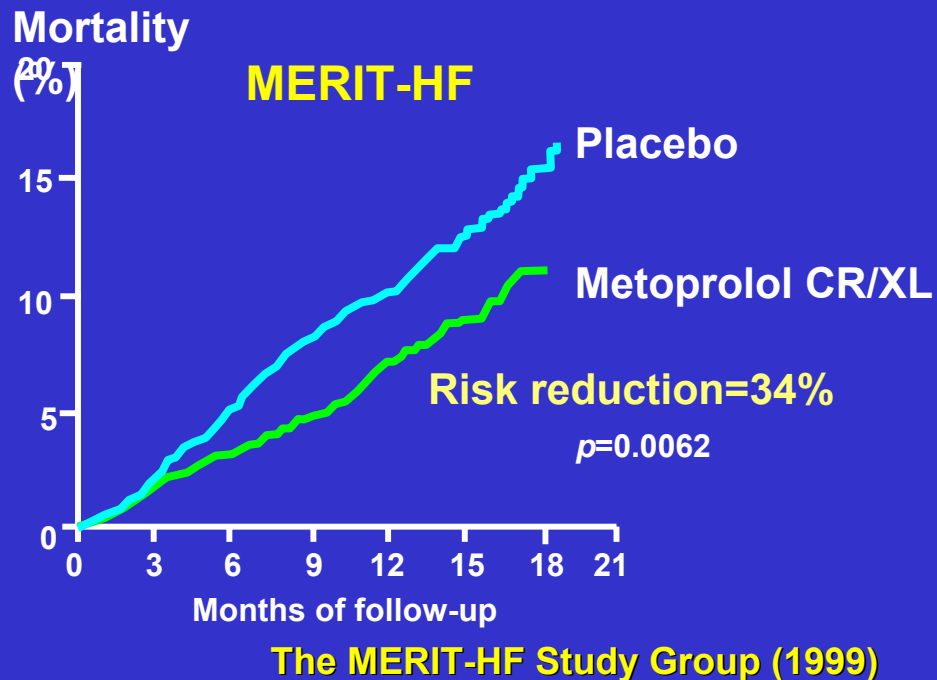
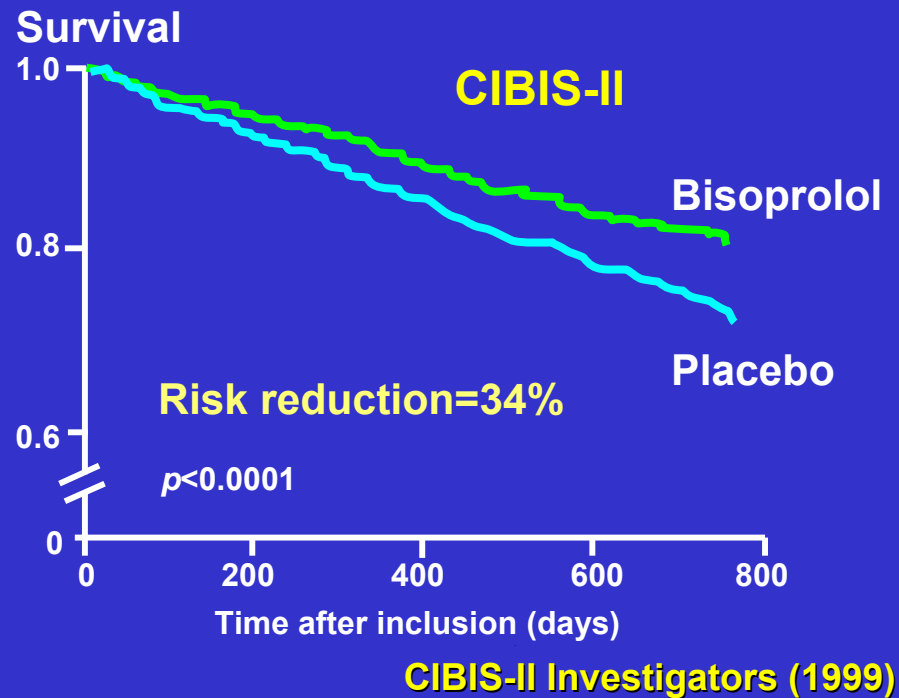
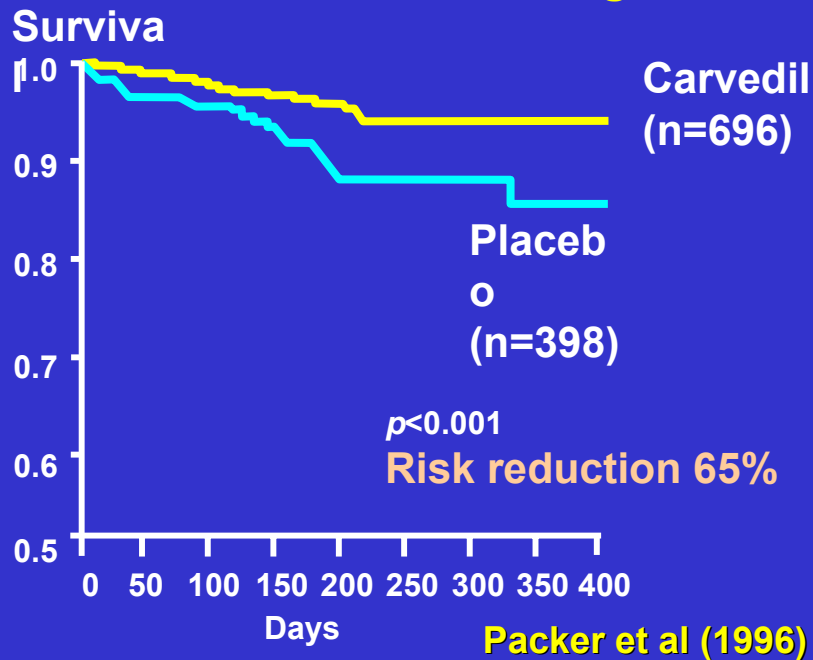


COPERNICUS: Weeks 1 to 8

Death, hospitalisation and withdrawal: highest risk patients

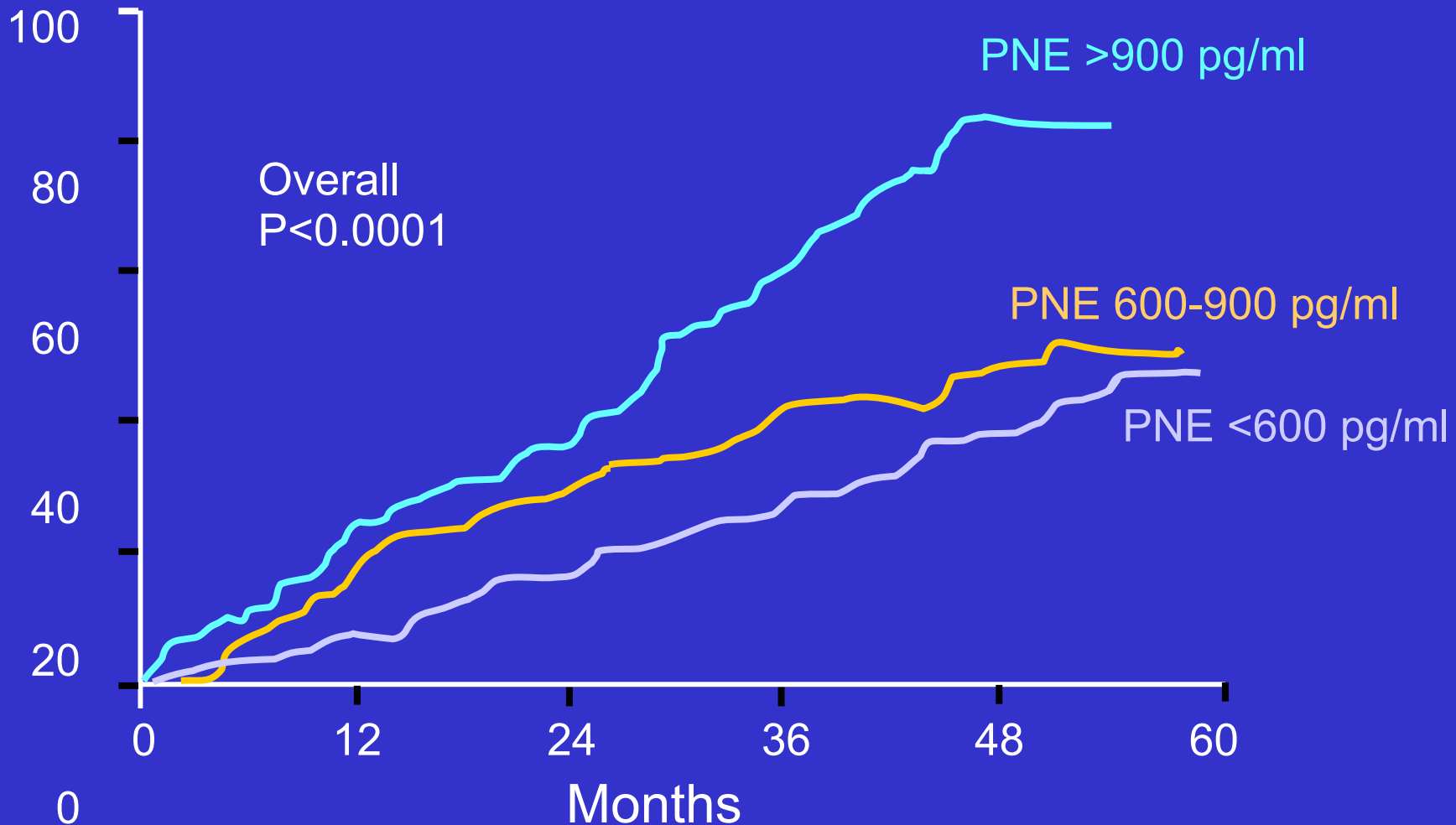


US Carvedilol Programme

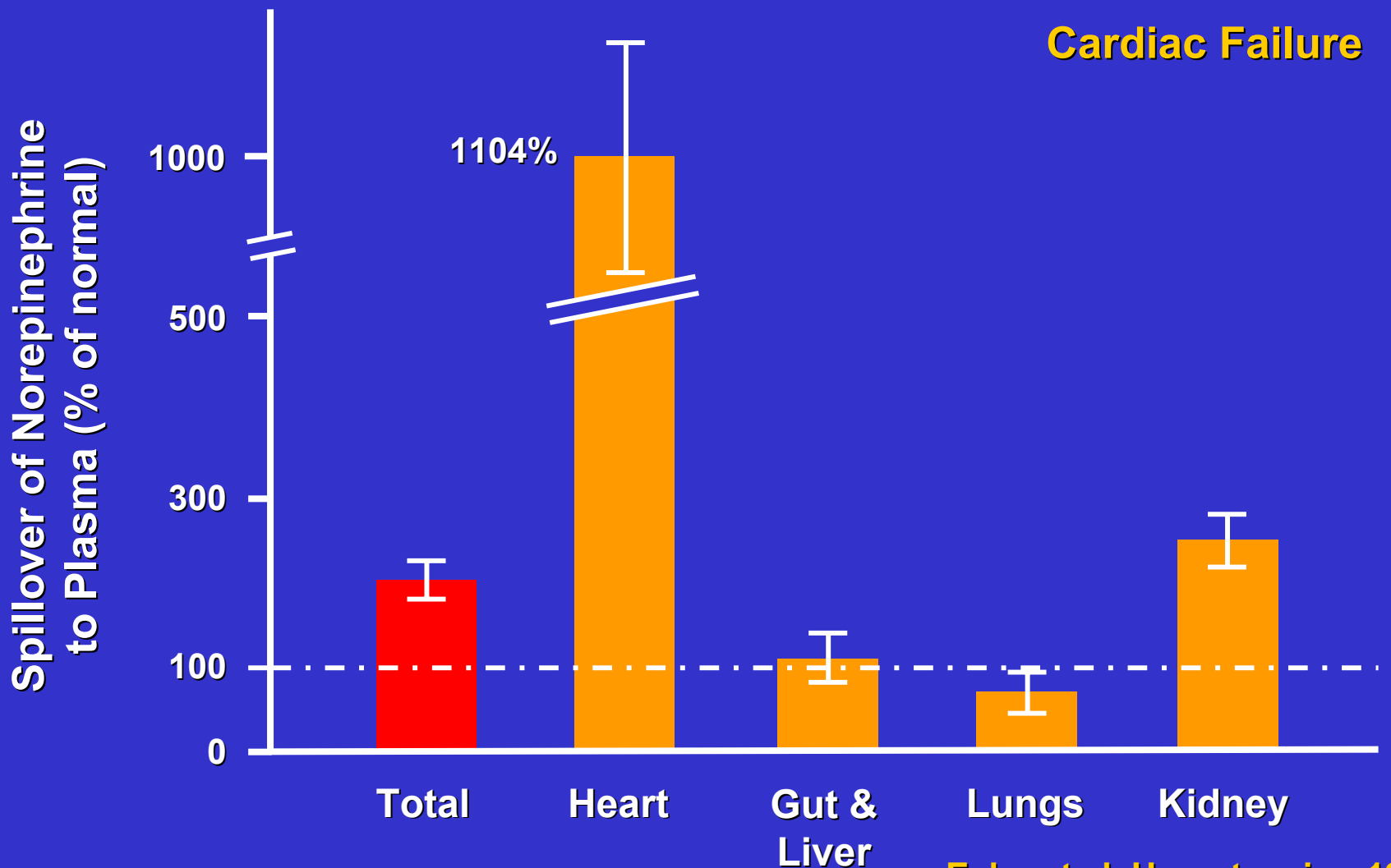


Relationship between plasma norepinephrine and mortality in heart failure

Cumulative mortality (%)



Norepinephrine Spillover in Heart Failure



Esler et al. Hypertension 1988

CARMEN - Rationale & Background

- **Carvedilol may have a similar or better profile than ACE inhibition in reversing remodelling and preventing progression of CHF**
- **This could challenge the paradigm of ACE inhibition as mandatory first line treatment in CHF**
- **Would allow for a more individualised approach in selected patients**

ACE Inhibition vs Carvedilol: Comparative Pharmacology

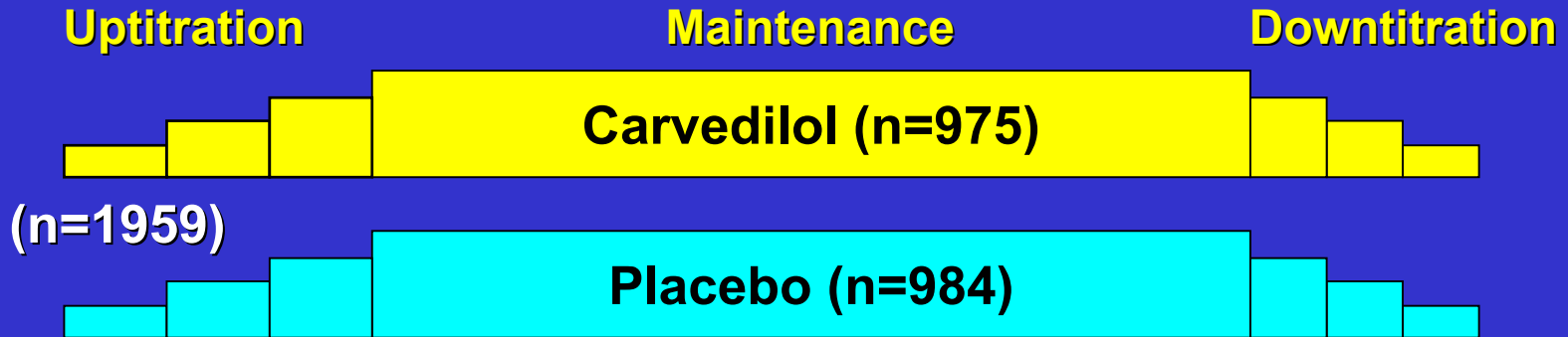
	Carvedilol (β + α blockade)	ACE inhibition
Neurohormonal modulation	SNS >> RAS	RAS > SNS
Cardiac antiadrenergic	+	\pm
β_2 -Blockade	+	-
α_1 -Blockade	+	-
Bradykinin/NO	-	++
Antioxidant	++	+
Apoptosis	+	+?
Anti-ischaemic	++	+?
Heart rate reduction	+	-

Carvedilol better remodelling effects than ACEi?



CArvedilol **P**ost-infa**R**ct survival
COnt**R**ol in LV dysfunction**N**

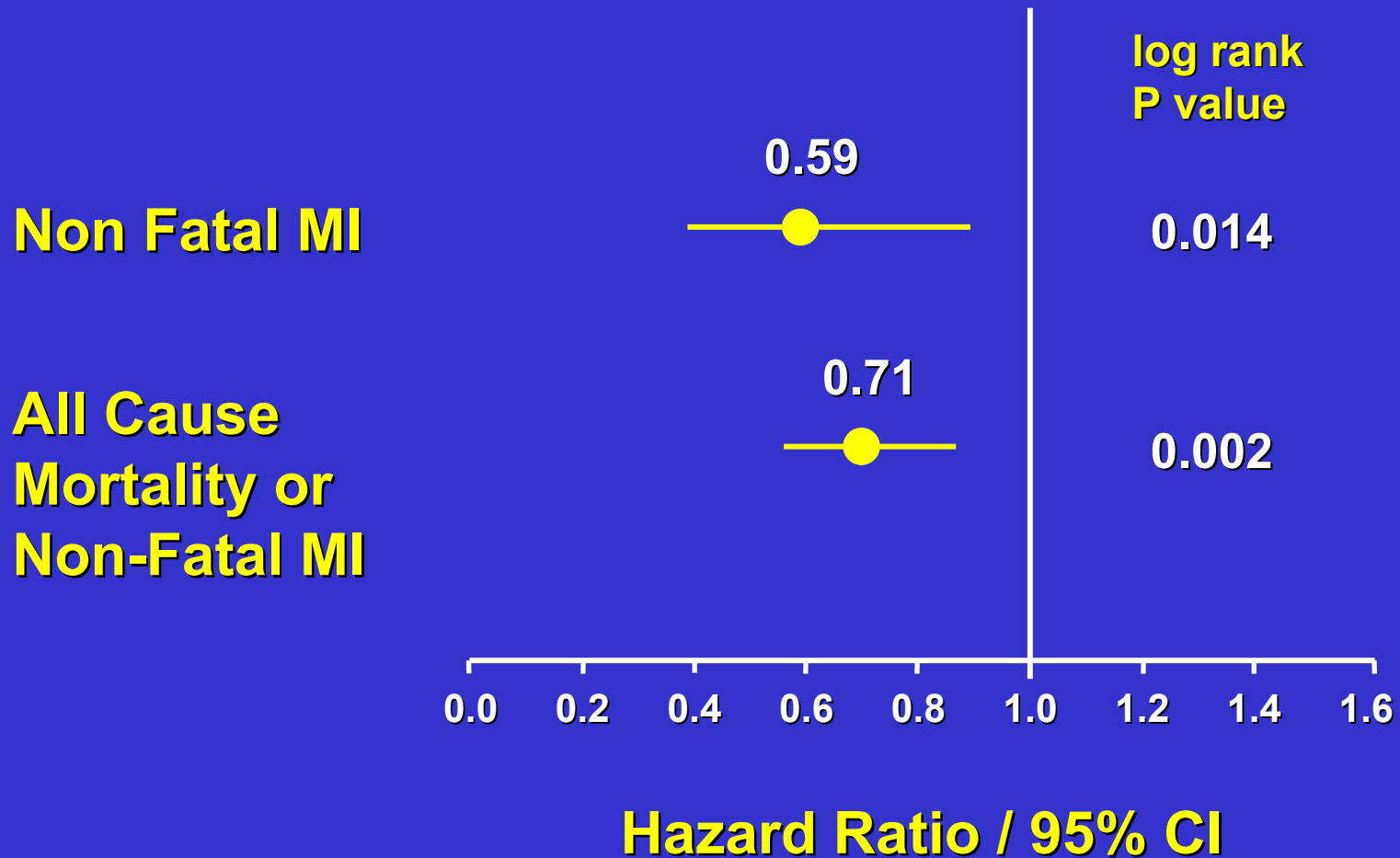
Study Plan



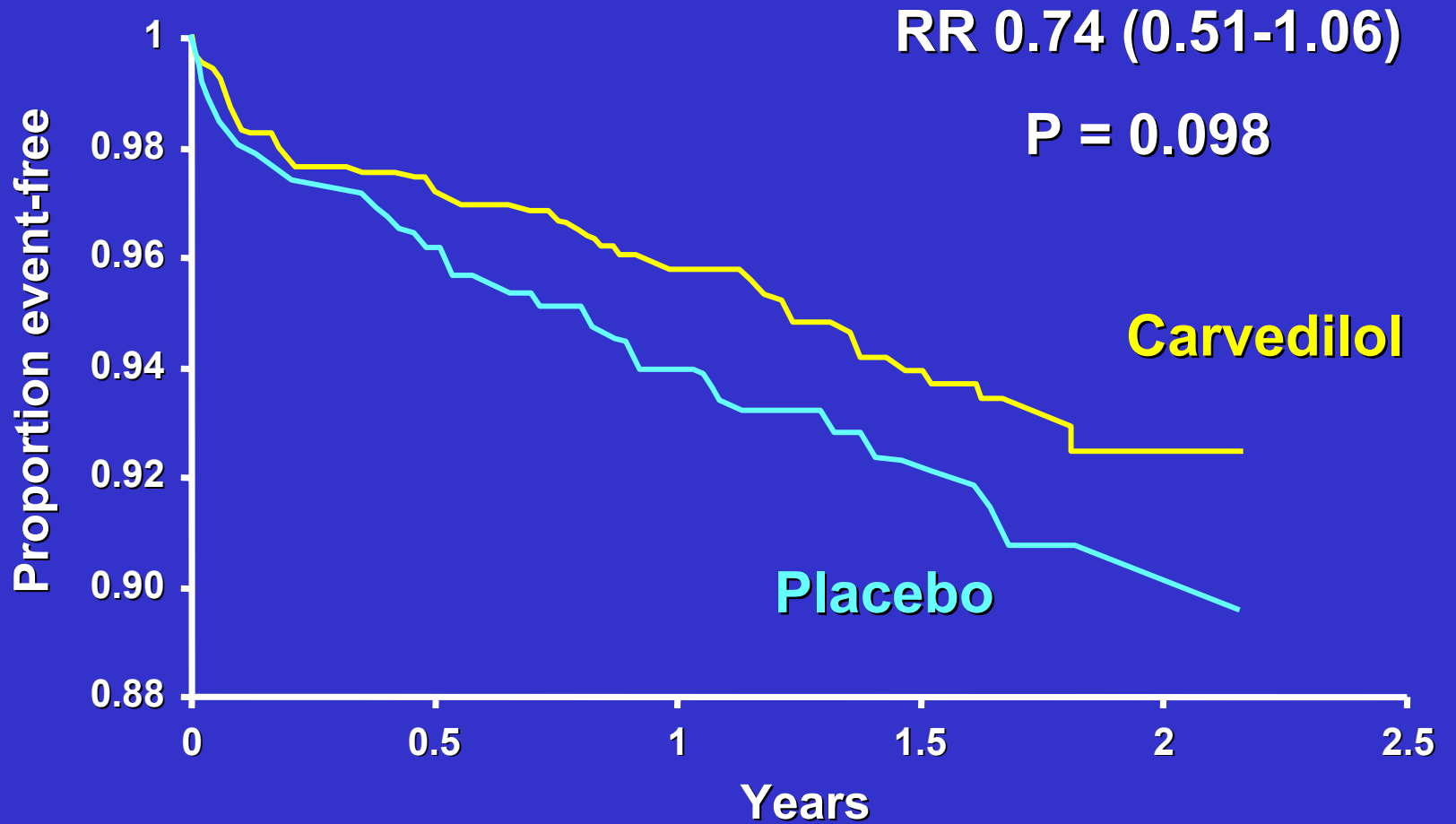
Initiation with 6.25 mg or 3.125 mg bid
Uptitration to maximum tolerated dose
over 2 – 4 weeks. Target 25 mg bid



Major Coronary Events



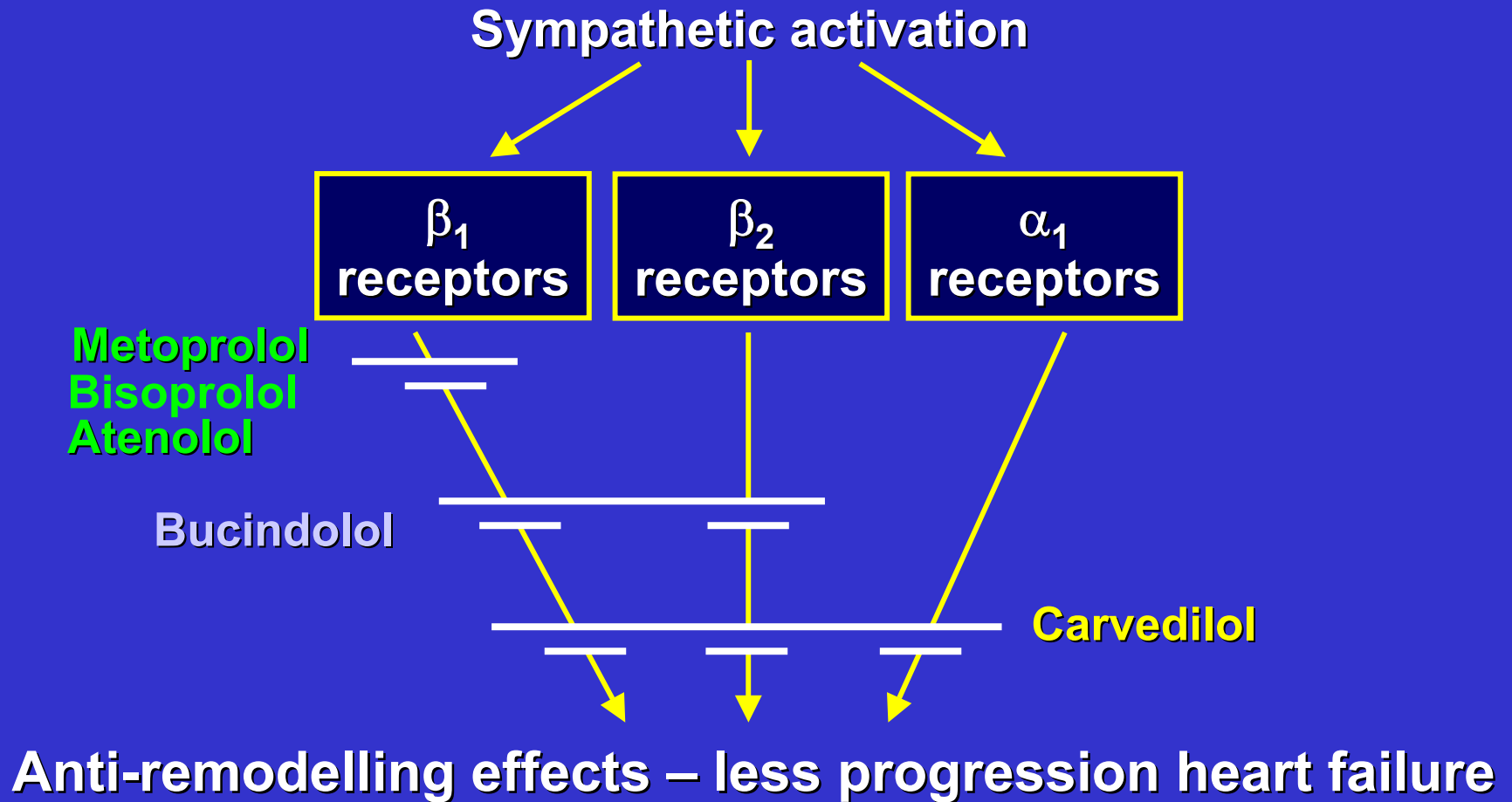
Sudden Death





CArvedilol Remodeling in Mild heart failure Evaluation

Antiadrenergic Therapy by β Blockade



Effects of β_1 receptors

- **Positive chronotropic , inotropic and lusiptropic effects**
- **Cardiac hypertrophy, fibrosis , remodelling**
- **Arrhythmogenic**
- **Renin stimulation – angiotensin II production**
- **Cardiac toxicity**

Beta-blockers for heart failure early open or unblinded studies

Author	Date	Design	n	Duration (months)	Symptom	Haemod.	Ejection fraction
Waagstein	1975	O,U	7	5	benefit	benefit	
Swedberg	1980	O,U	28	23	benefit	benefit	increased
Heilbrunn	1989	O,U	14	6	benefit		increased
Nemanich	1990	O,U	10	2			increased
Andersson	1991	O,U	21	14	benefit	benefit	increased
Gilbert	1987	R	15	2	benefit		increased

O=open, U=uncontrolled, R=randomised