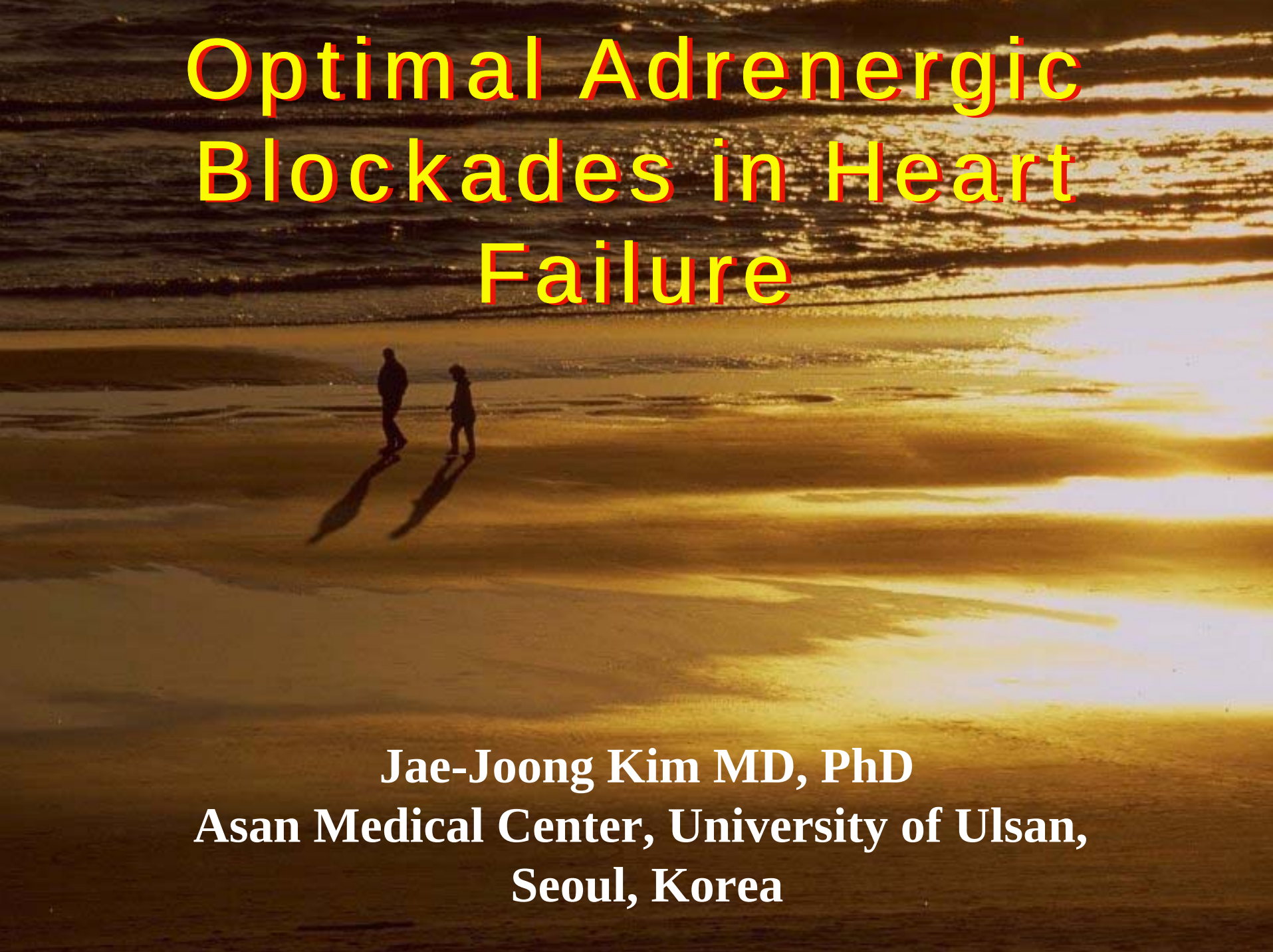
Optimal Adrenergic Blockades in Heart Failure

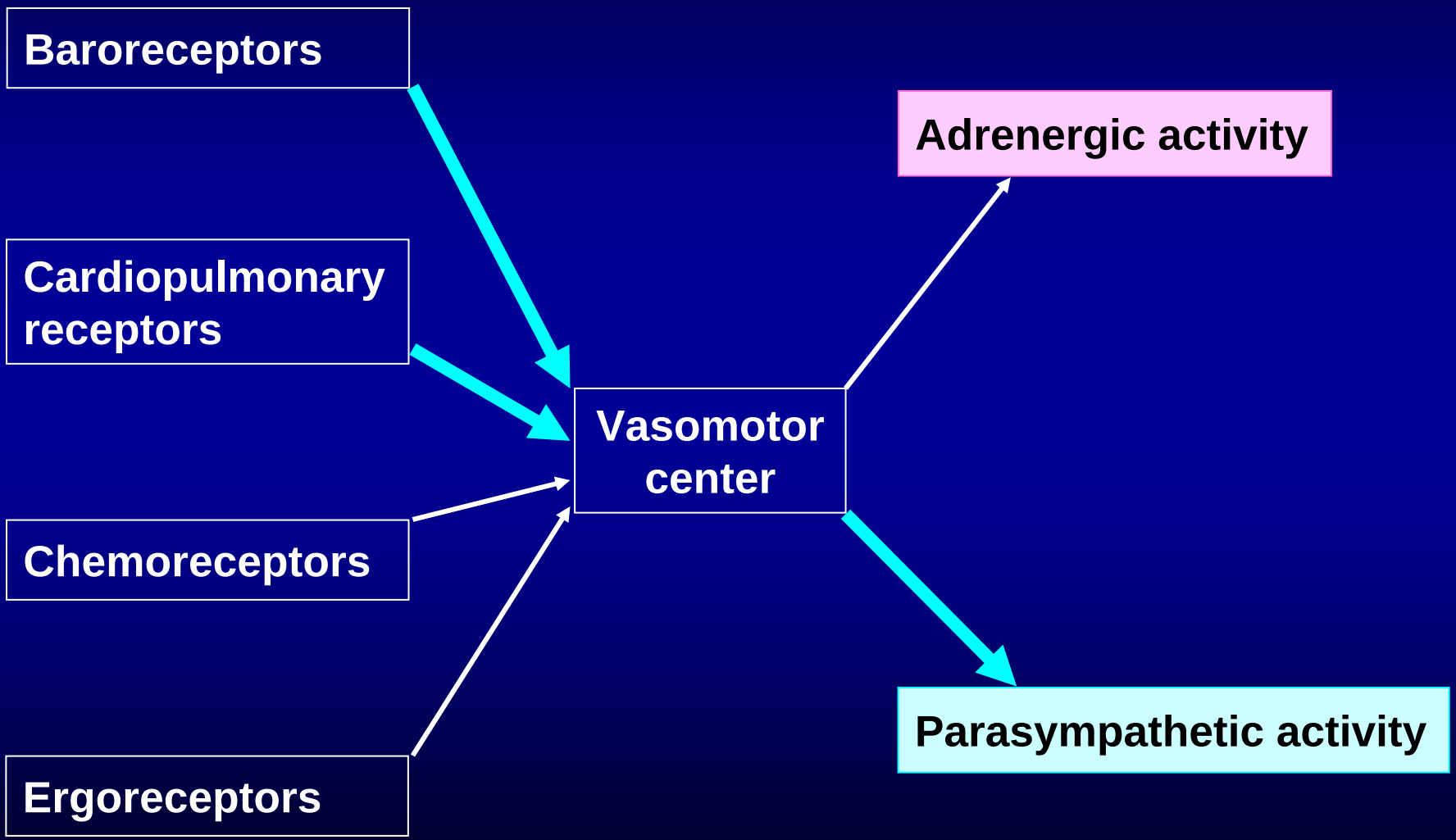


Jae-Joong Kim MD, PhD
Asan Medical Center, University of Ulsan, Seoul, Korea

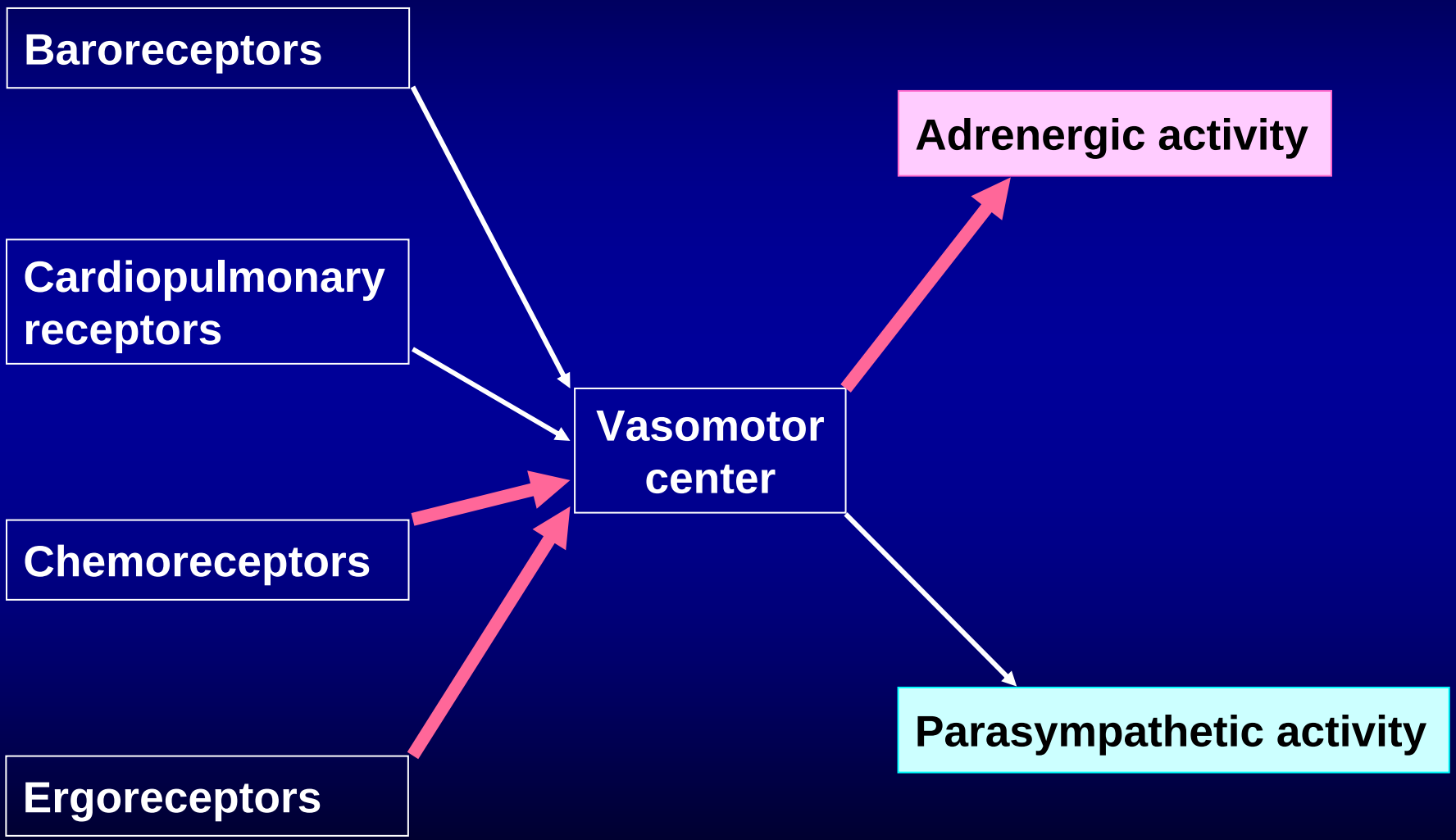
Contents

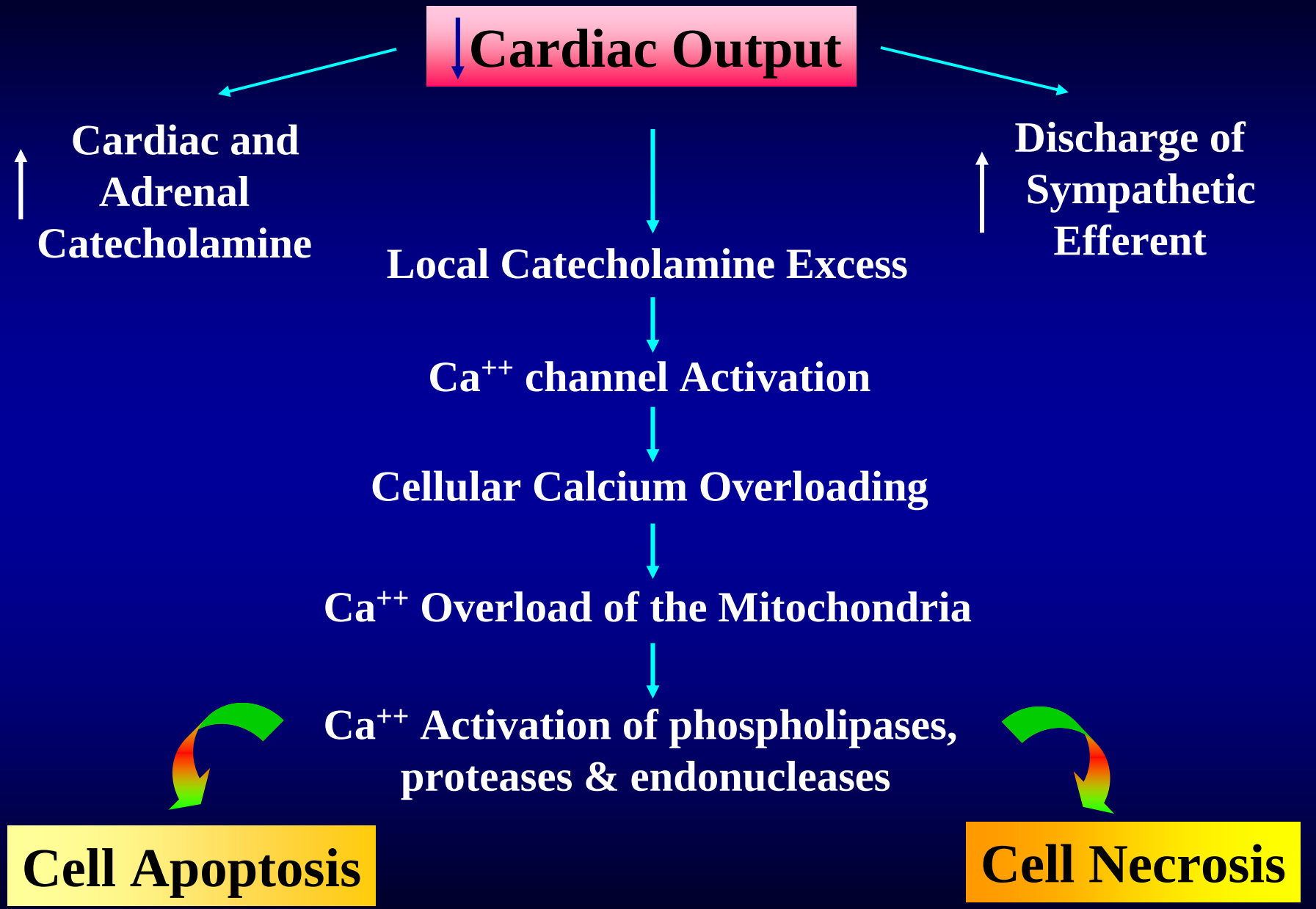
- Harmful effects of adrenergic system in heart failure
- Clinical studies of beta-blockers in CHF
- Questions in use of beta-blockers in CHF
- Recommendation of beta-blockers in CHF

Autonomic Control of the Circulation in Health

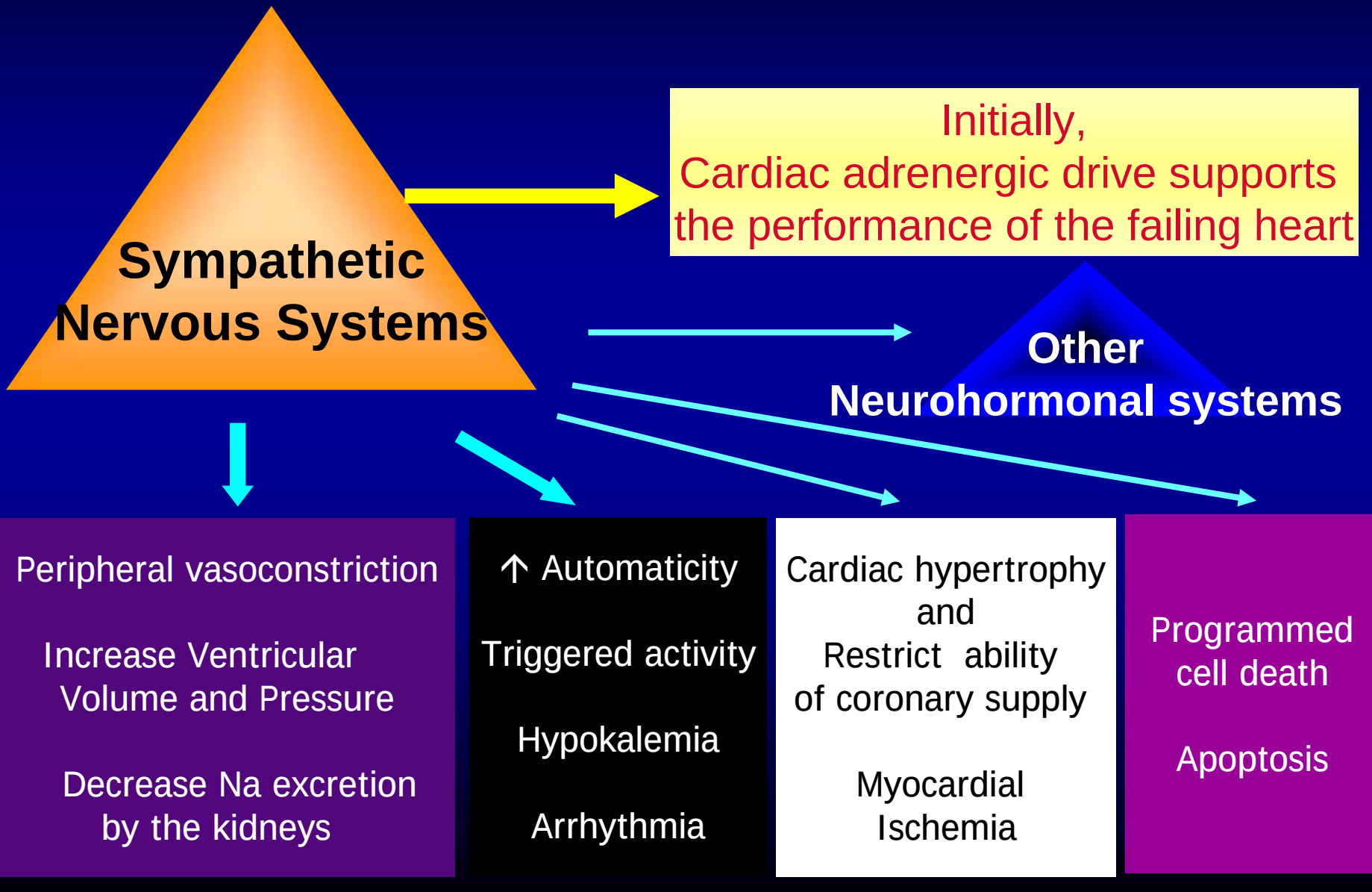


Autonomic Control of the Circulation in CHF




Cardiac Output
Cardiac and Adrenal Catecholamine
Discharge of Sympathetic Efferent
Local Catecholamine Excess
Ca++ channel Activation
Cellular Calcium Overloading
Ca++ Overload of the Mitochondria
Ca++ Activation of phospholipases, proteases & endonucleases
Cell Apoptosis
Cell Necrosis

Sympathetic NS in CHF



β-Blocker Effects in CHF

- Decrease energy demand
- Reduce activation of neuroendocrine activation
- Increase high energy phosphate
- Reverse pathologic remodeling
- Improve microcirculation
- Increase contractility (slowing heart rate)
- Long-term favorable effect on SERCA activity
- Modulation of adrenergic receptor or signal transduction

History of β-Blockers in CHF

- **1975**, Waagstein F ; effect of β-blocker in 7 pts with CHF
- **1979**, Swedberg K, Waagstein F ; prolongation of survival (historical comparison)
- **1985**, Anderson JL ; a long-term randomized trial of low dose metoprolol in 50 DCMP --- only a modest beneficial effect
- **1993**, ***MDC trial***, Waagstein F, Bristow MR ; the 1st major placebo controlled study in DCMP(metoprolol) using combined end point
- **1994**, ***CIBIS***; bisoprolol in CHF, the 1st trial using mortality as end point
- **1996**, Packer M, Bristow MR ; ***US Carvedilol Study, MOCHA***
- **1999**, ***CIBIS II*** (bisoprolol), ***MERIT-HF*** (metoprolol)
- **2001**, ***BEST*** (bucindolol), ***COPERNICUS*** (carvedilol)
- **2003**,***COMET*** (carvedilol vs metoprolol)

Metoprolol in Dilated CMP(MDC)

Waagstein F et al Lancet 1993;342:1441-1446

- Randomized, double blind, placebo-controlled, multicenter
- 383 pts (LVEF< 40%) were enrolled, follow-up for 12-18 months
- Target metoprolol dose ; 100 - 150mg/d (mean 108mg/day)

	Placebo	Metoprolol	P-value
Total mortality or need of heart transplantation	38	25	0.058
Need for transplantation	19	2	0.0001
Total mortality	19	23	NS
Progressive heart failure	5	5	NS
Sudden cardiac deaths	12	18	NS
Ejection fraction(% increase)	6	13	<0.005

Cardiac Insufficiency Bisoprolol Study (CIBIS)

CIBIS Investigators Circulation 1994;90:1765-1773

- Randomized, double blind, placebo controlled, multicenter
- the 1st trial using mortality as end point
- 641 pts with NYHA class III or IV and LVEF <40%, Mean F/U 1.9±0.1 years, target dose 5mg/d
- Premature withdrawal ; 25.5% in bisoprolol, 23.4% in placebo

	Bisoprolol	Placebo	P-value
Mortality	16.6%	20.9%	NS
Sudden death	4.7%	5.3%	NS
Death d/t VT,Vf	1.3%	2.2%	NS
Hospitalization	19.1%	28.0%	<0.01
1 NYHA ↑	21.3%	15.0%	<0.03

US Carvedilol Heart Failure Study

Packer M et al NEJM 1996;334:1349-1355

- Randomized, double blind, placebo-controlled, multicenter study
- Total 1197 pts with symptomatic CHF≥ 3 months and LVEF≤ 0.35, after open-label phase, 1094 (94.4%) pts were enrolled.
- Follow-up 6 months or more

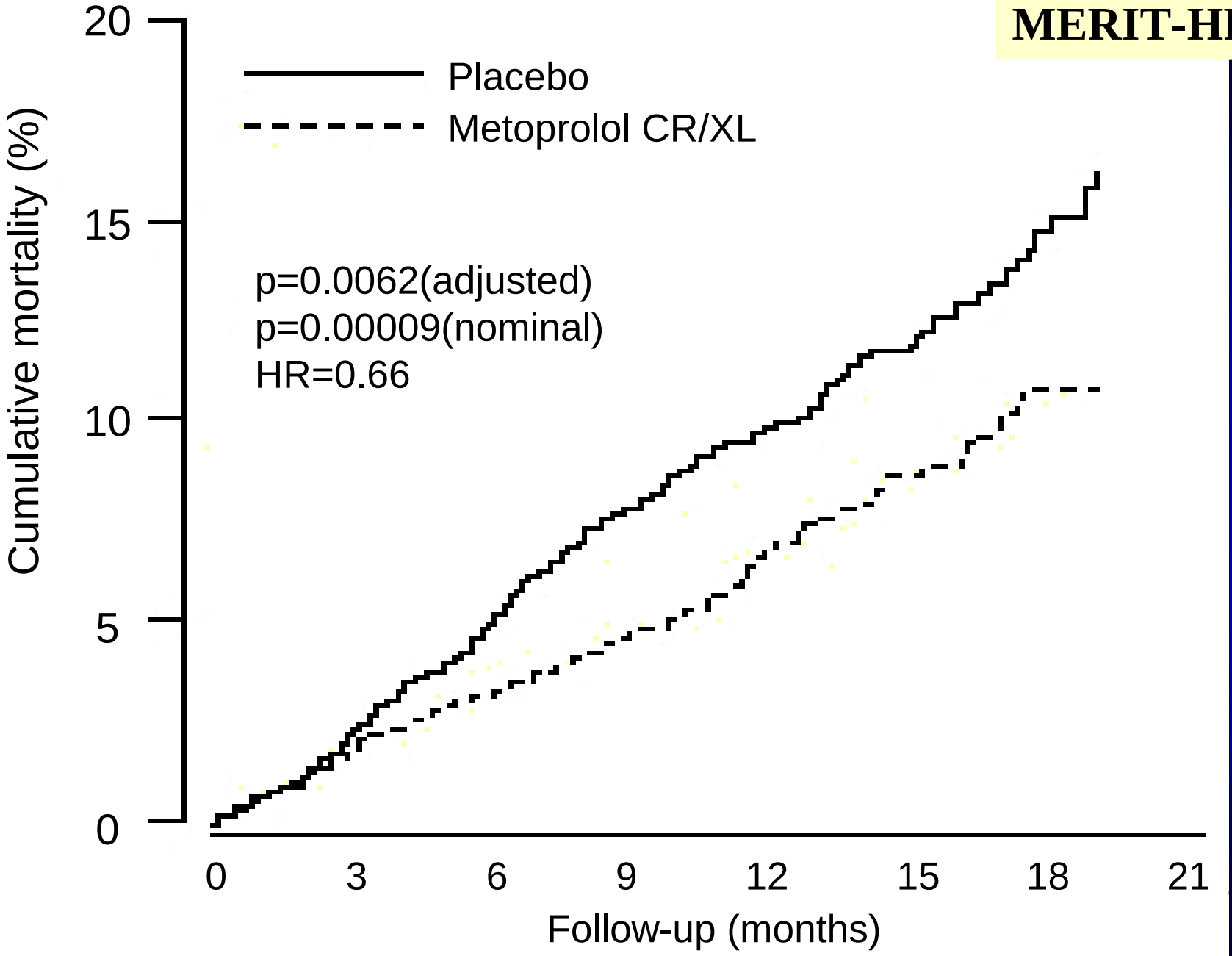
	Carvedilol	Placebo	Reduction
Total mortality	3.2%	7.8%	65%
Death d/t CHF	0.7%	3.3%	82%
Sudden death	1.7%	3.8%	55%
Hospitalization	14.1%	19.6%	27%
Combined	15.8%	24.6%	38%

MERIT-HF

MERIT-HF Study Group. Lancet 1999;353:2001-2007

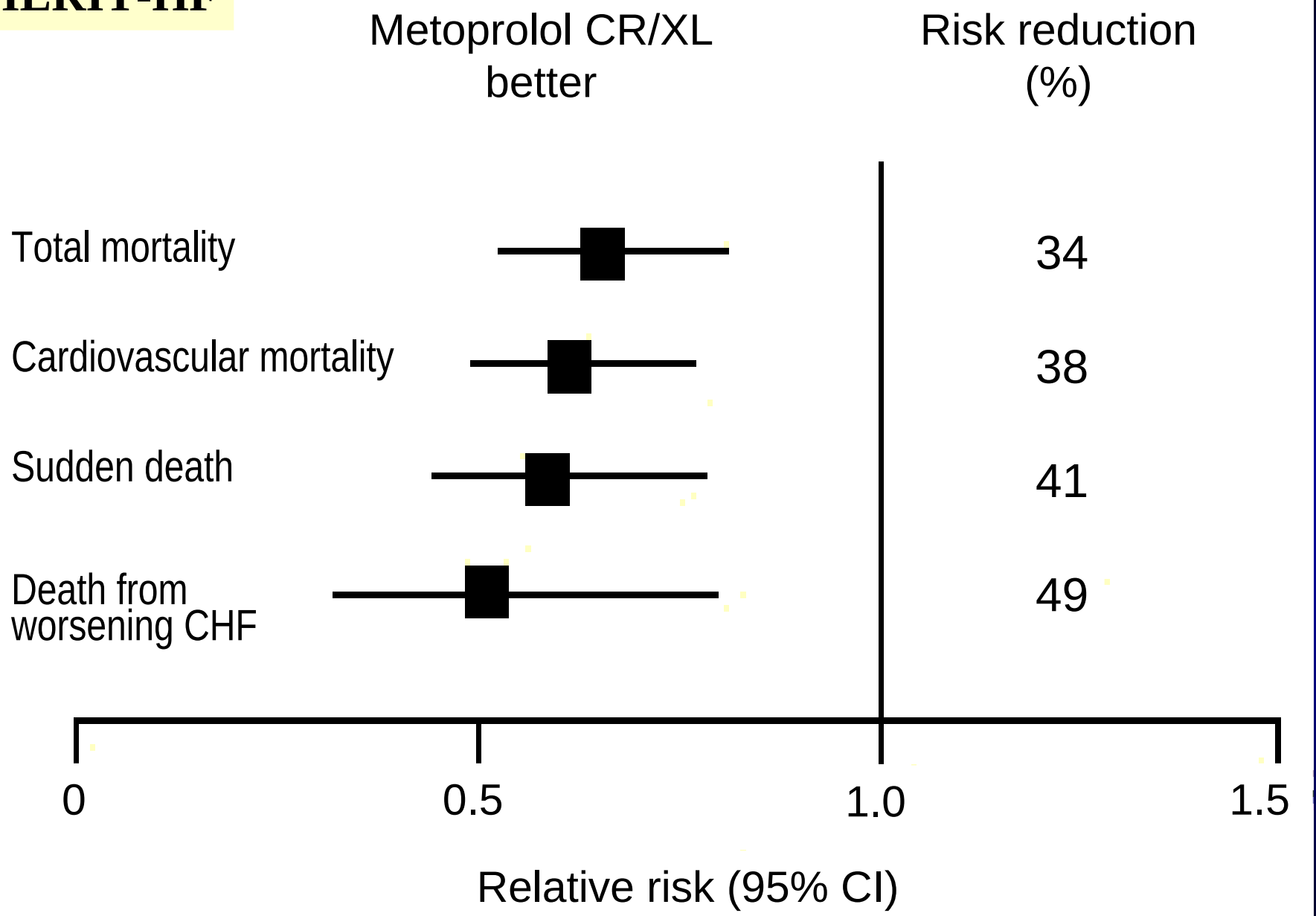
- Double-blind placebo controlled randomized study at 313 center in 13 European countries and US
- Metoprolol; lipophilic, β_1-selective blocker
- NYHA II(41%), III(55%) and IV(4%),
- Primary end points
  - → all cause mortality and combined all cause mortality and admission
- Total 2991 pts (metoprolol 1990, placebo 2001)
- Mean F/U; 1 year, mean 63 yrs old, ischemic in 65%
- Target dose; 200mg qd(64%), ≥100mg qd in 87%, mean 159mg/Day

MERIT-HF



MERIT-HF Study Group. Lancet 1999;353:2001-2007

MERIT-HF

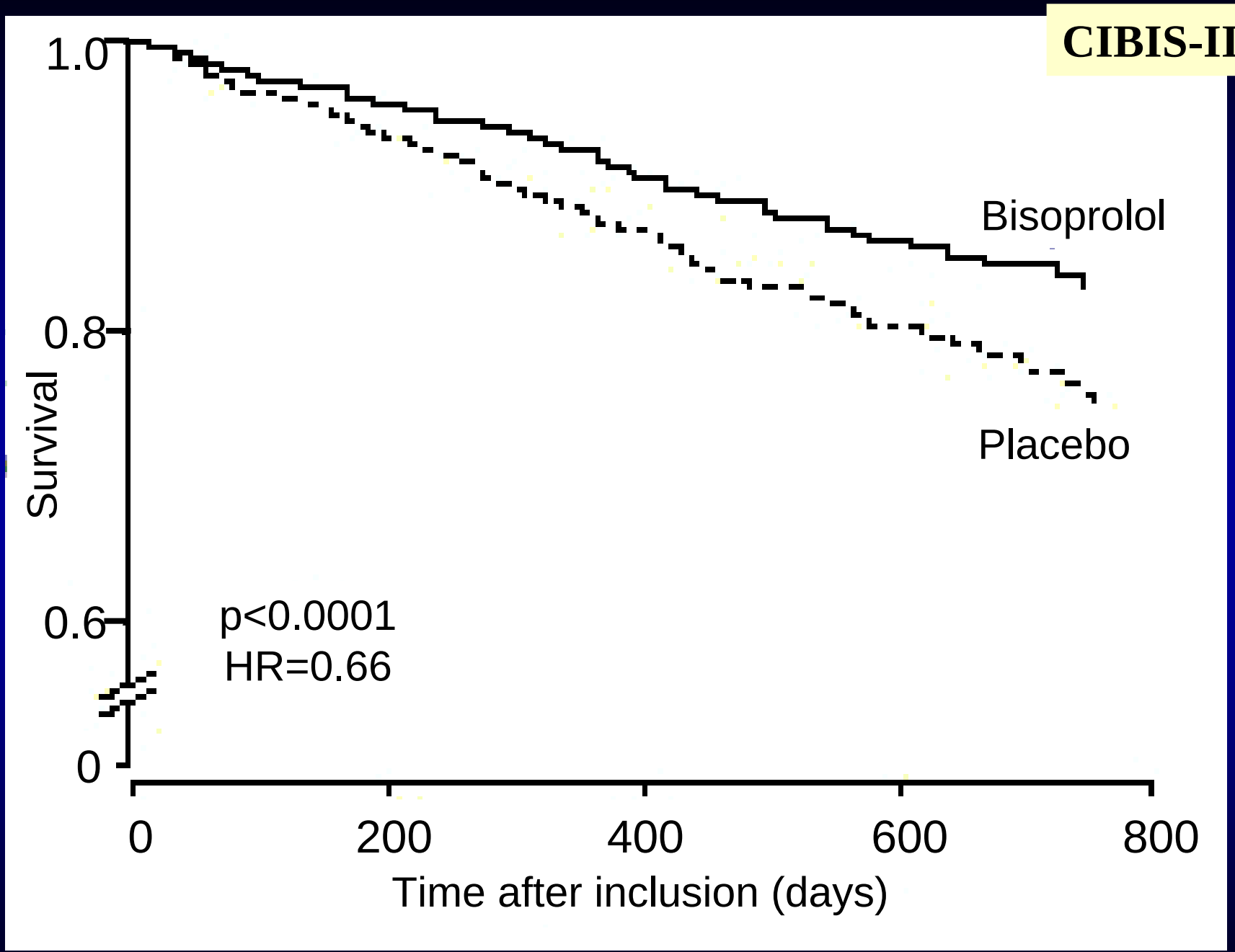


MERIT-HF Study Group. Lancet 1999;353:2001-2007

CIBIS-II

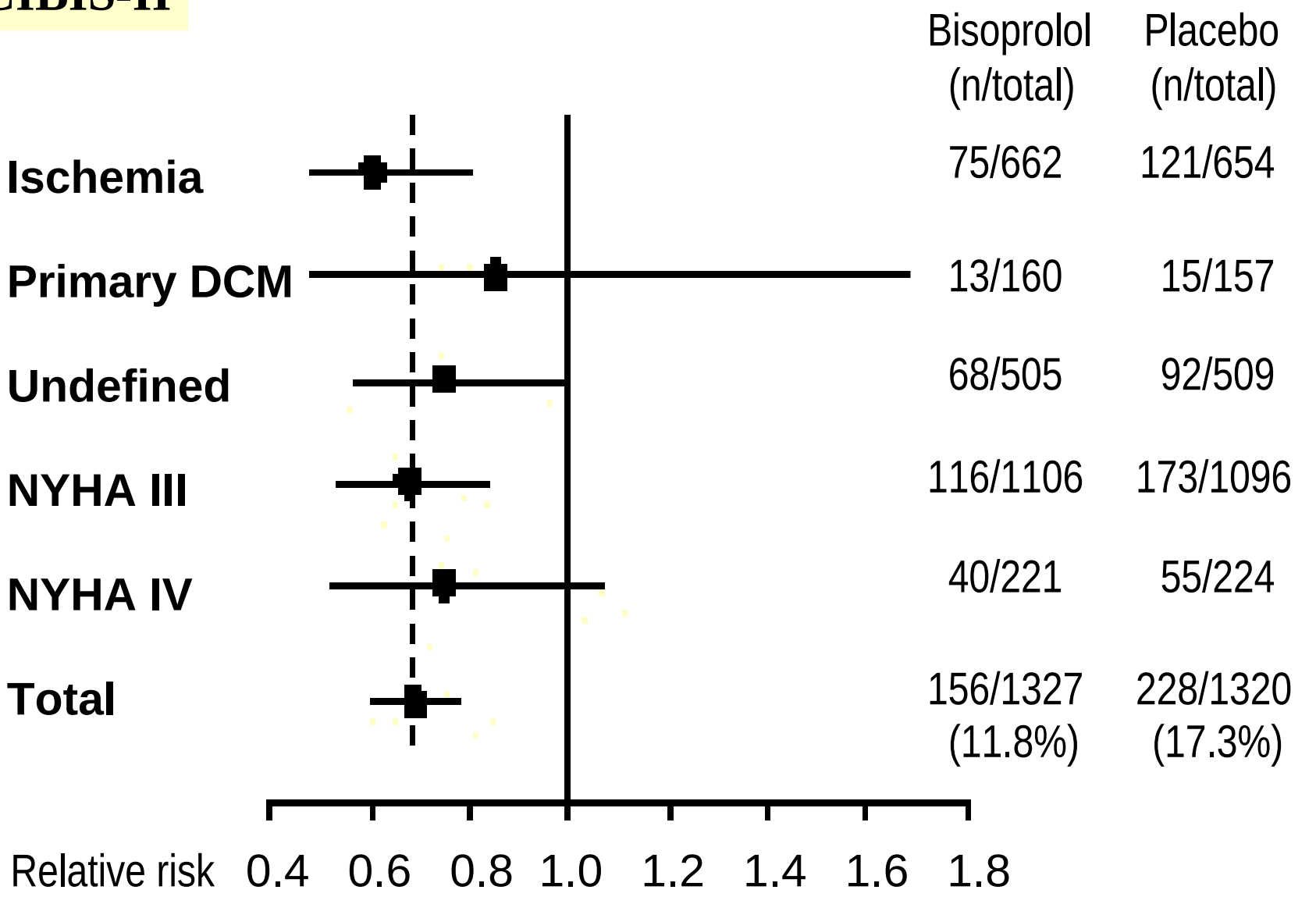
CIBIS-II Investigators and Committees Lancet 1999;353:9-13

- A multicenter double-blind randomized placebo-controlled trial at 274 hospitals in 18 European countries
- Bisoprolol ; lipophilic, β_1-selective blocker
- NYHA III(83%) or IV(17%)
- Primary end-point
  - all cause mortality
- Total 2647 patients (1320 in placebo, 1327 in bisoprolol), mean F/U 1.3 years, *target dose 10mg(51%)*
- Results
  - Admission d/t VT or Vf(6 vs 20, p=0.006), hypotension (3 vs11, p=0.03) less in bisoprolol group
  - bradycardia(14 vs 2, p<0.004) more in bisoprolol group



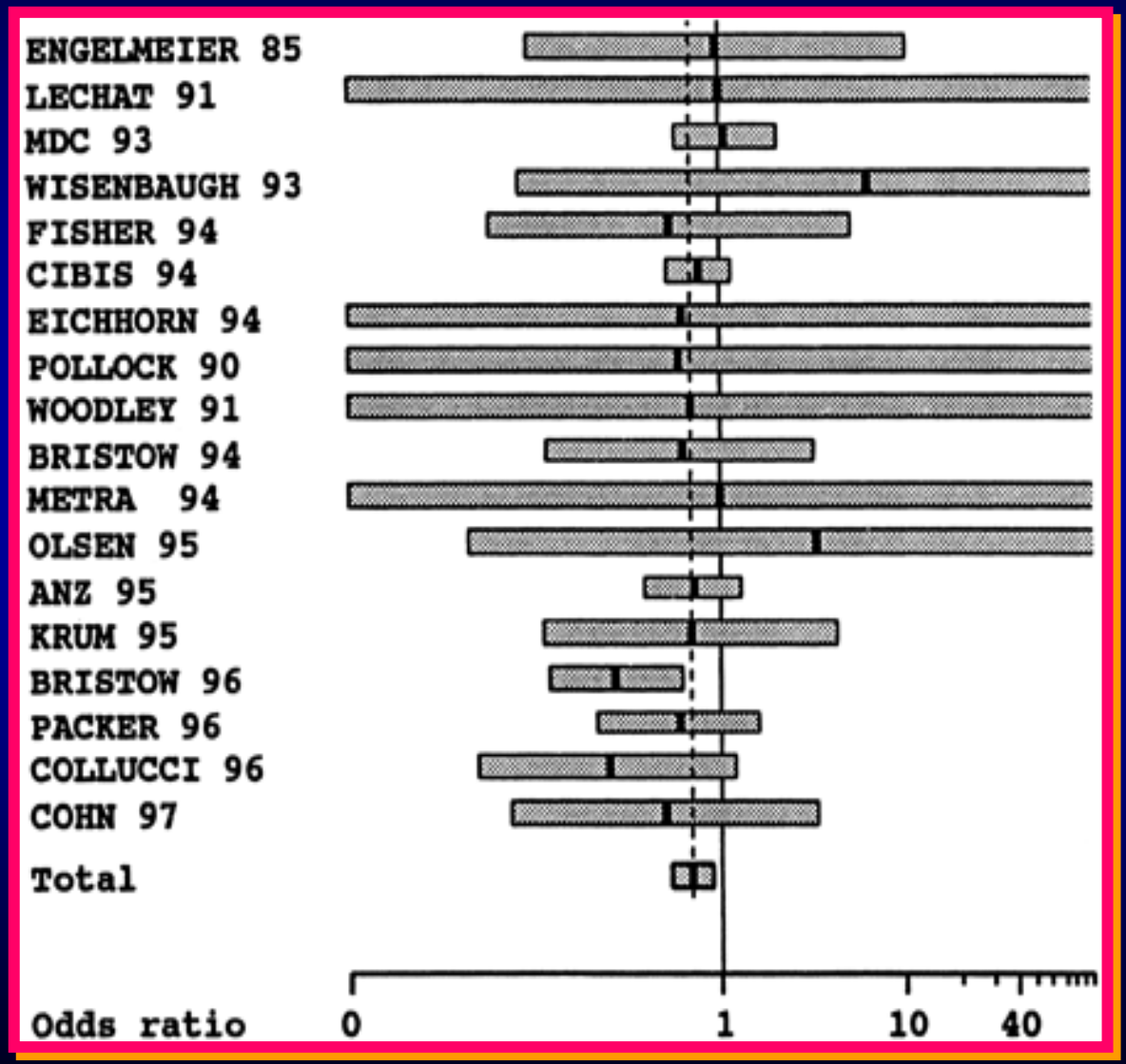
CIBIS-II Investigators and Committees Lancet 1999;353:9-13

CIBIS-II



CIBIS-II Investigators and Committees Lancet 1999;353:9-13

β-Blocker Effects on Mortality in CHF



Beta-blockers in CHF

Proven favorable effects on prognosis in controlled trials in patients with chronic heart failure

Carvedilol

Bisoprolol

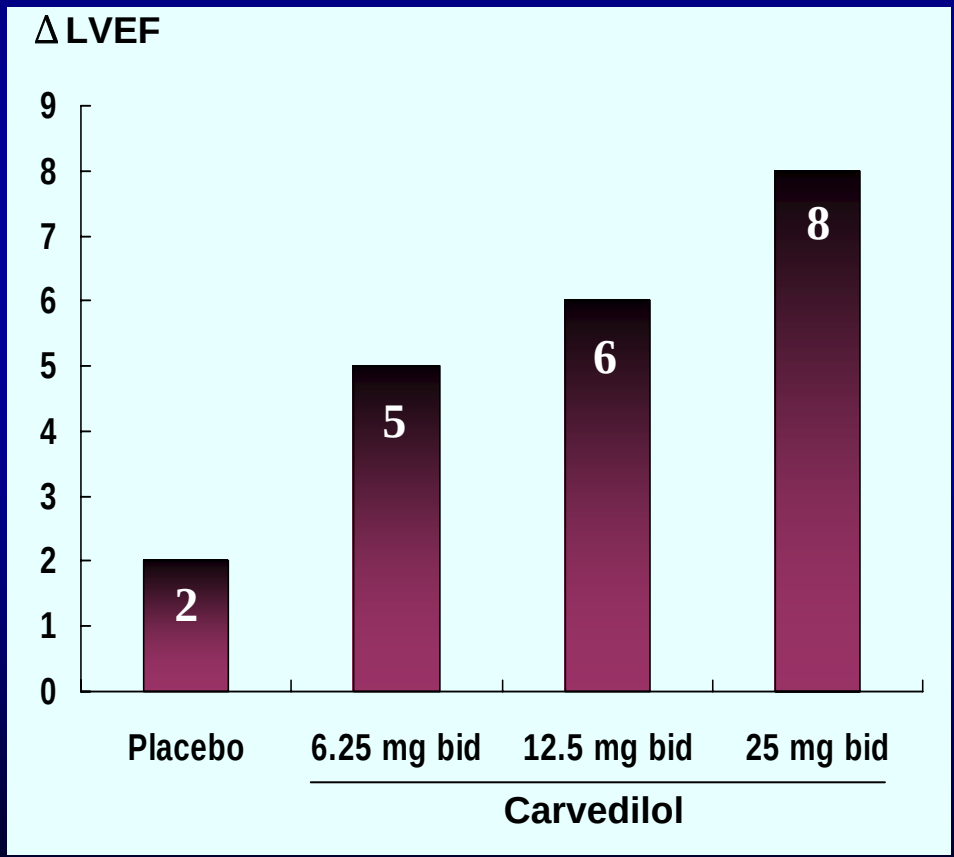
Metoprolol succinate

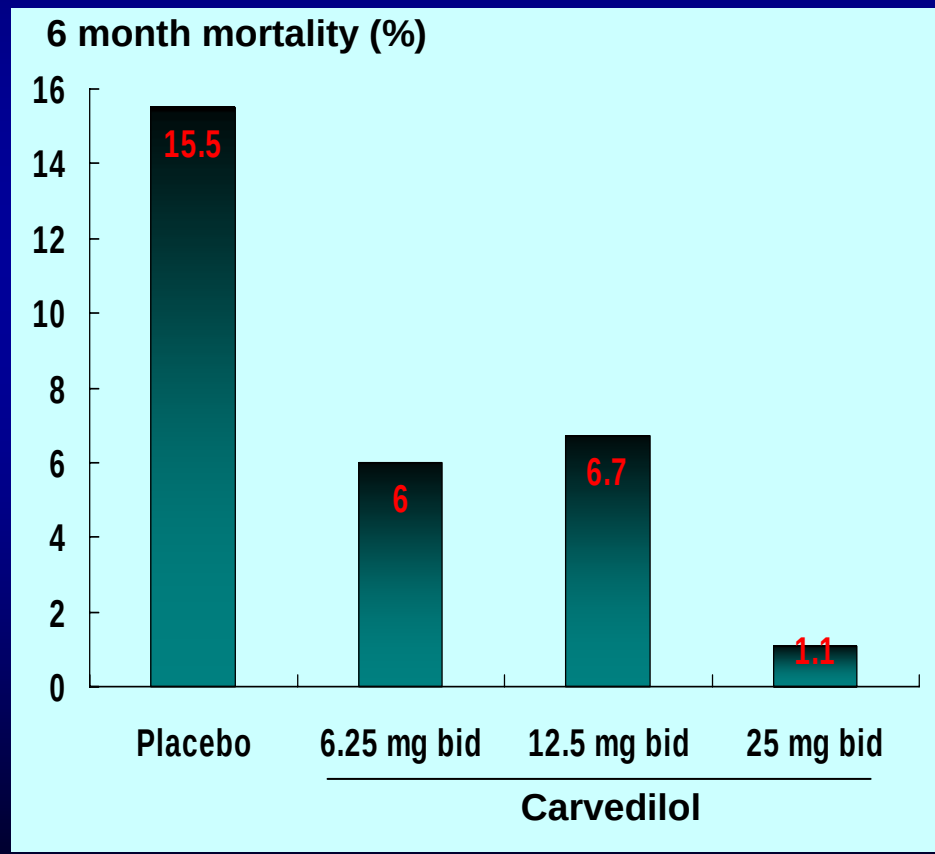
Questions about β–Blockers in Heart Failure

- Low dose vs high dose
  - MOCHA
- Effective in NYHA class IV patients ?
- Nonselective, selective, or with vasodilating
  - Are they same or which is more beneficial ?

Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)

n=345, mild- moderate CHF, EF ≤ 35%





Bristow MR, et al. MOCHA trial Circulation 1996;94:2807.

Questions about β–Blockers in Heart Failure

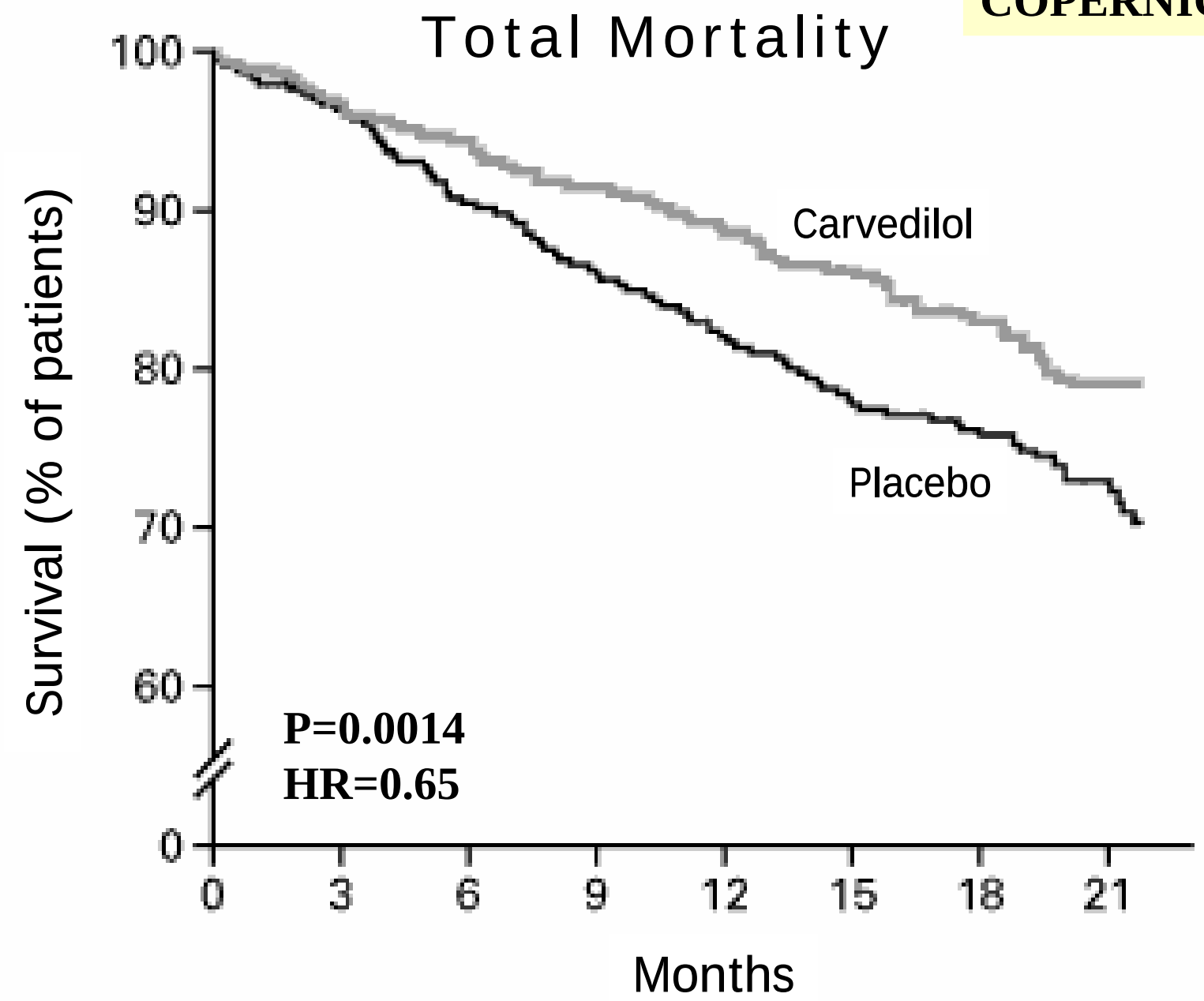
- Low dose vs high dose
- Effective in NYHA class IV patients ?
  - COPERNICUS
- Nonselective, selective, or with vasodilating
  - Are they same or which is more beneficial ?

COPERNICUS

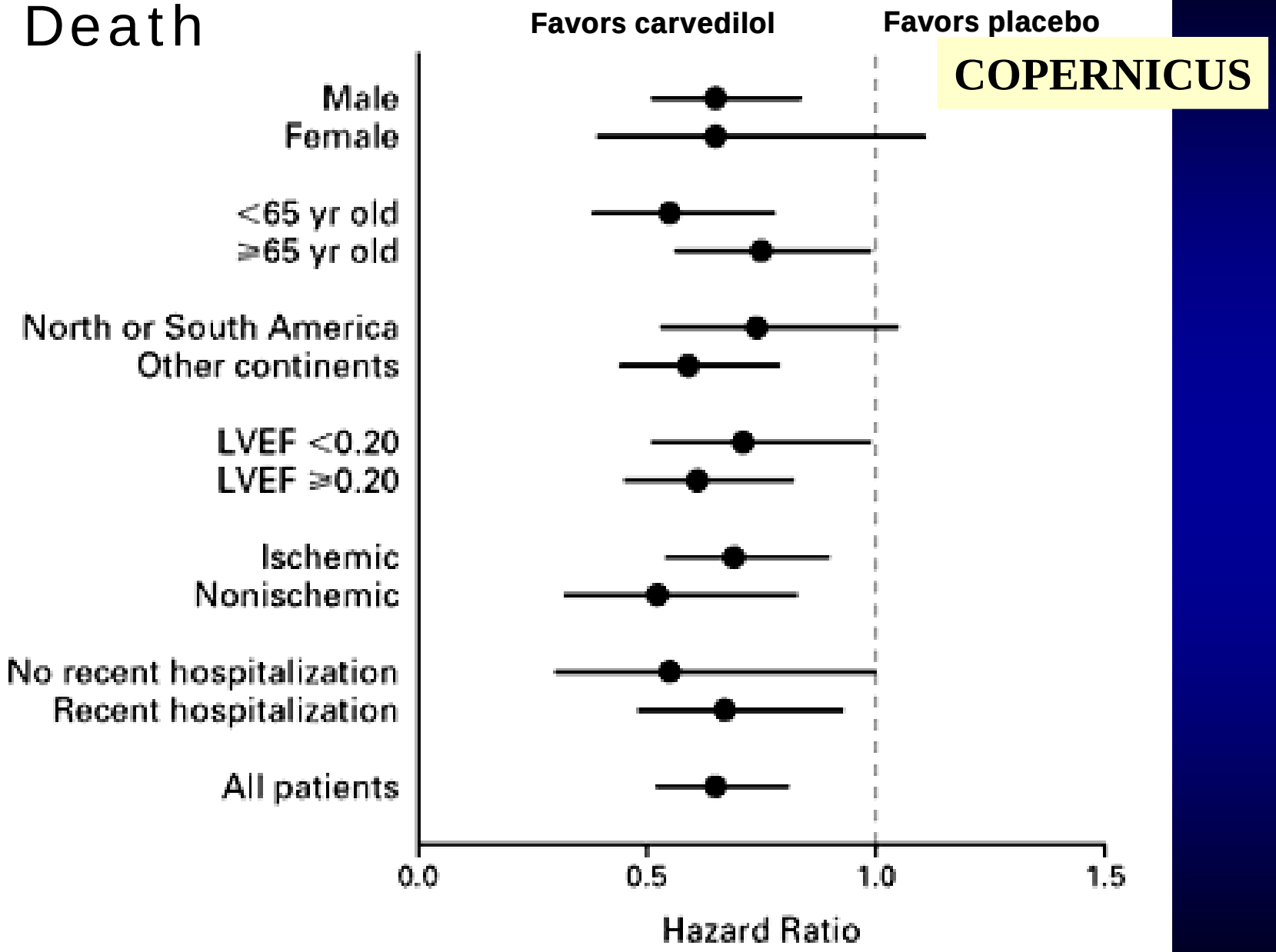
Packer M et al N Eng J Med 2001;344:1651-1658

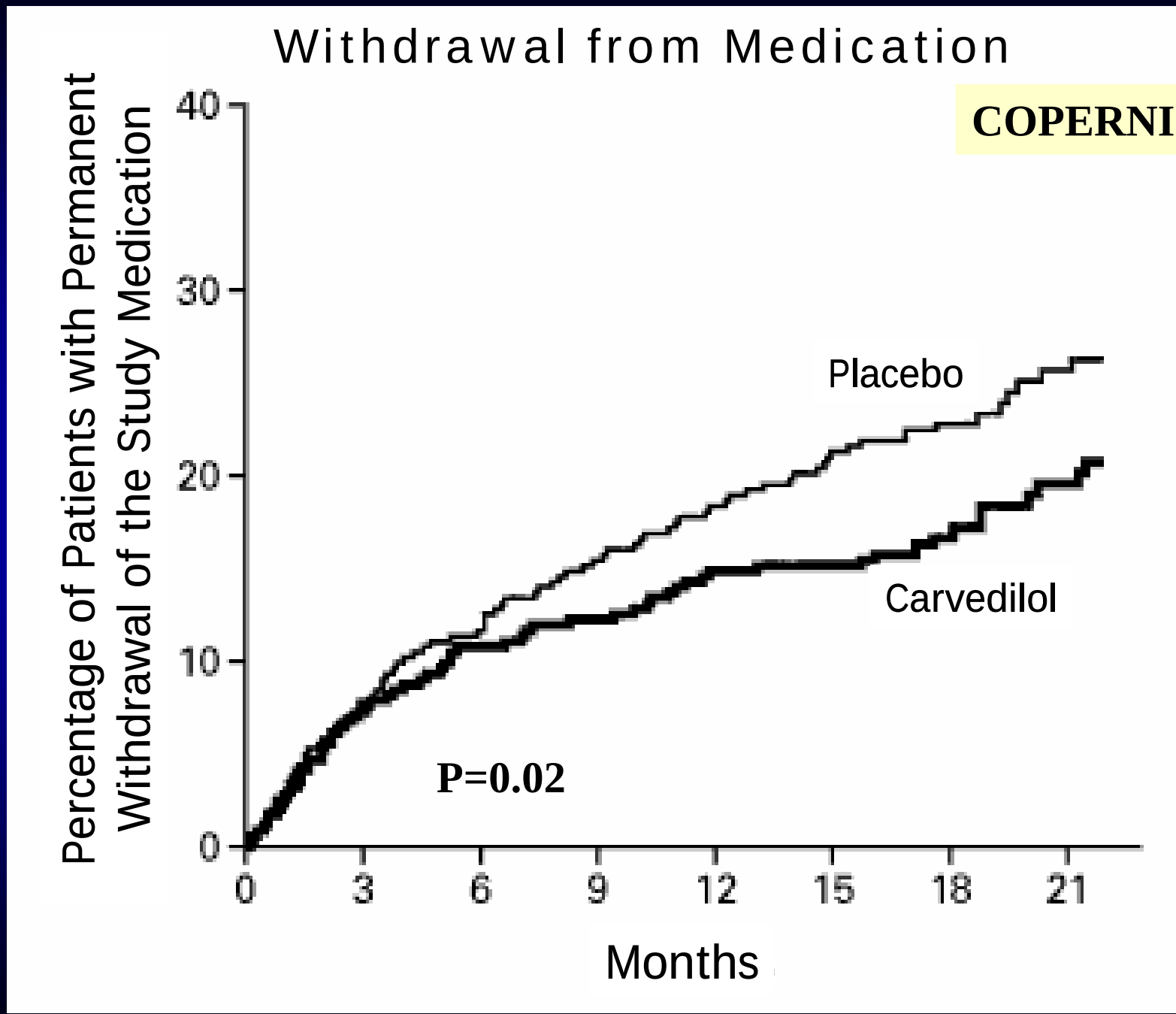
- Prospective, randomized, double-blinded, placebo-controlled trial at 334 centers in 21 countries
  - Dyspnea or fatigue at rest or on minimal exertion ≥ 2 mos and LVEF≤ 25% despite appropriate conventional therapy
  - Clinical euvolemia and not on iv inotropics nor vasodilator within 2 weeks
- Carvedilol (n=1156) vs placebo (n=1133)
- Primary end point; death of any reason
- Mean F/U; 10.4 months, 67% IHD, mean age 63 yrs
- No lost F/U and <5% protocol violence (open-label)

COPERNICUS


Total Mortality
Survival (% of patients)
100
90
80
70
60
0
0
3
6
9
12
15
18
21
Months
Carvedilol
Placebo
P=0.0014
HR=0.65

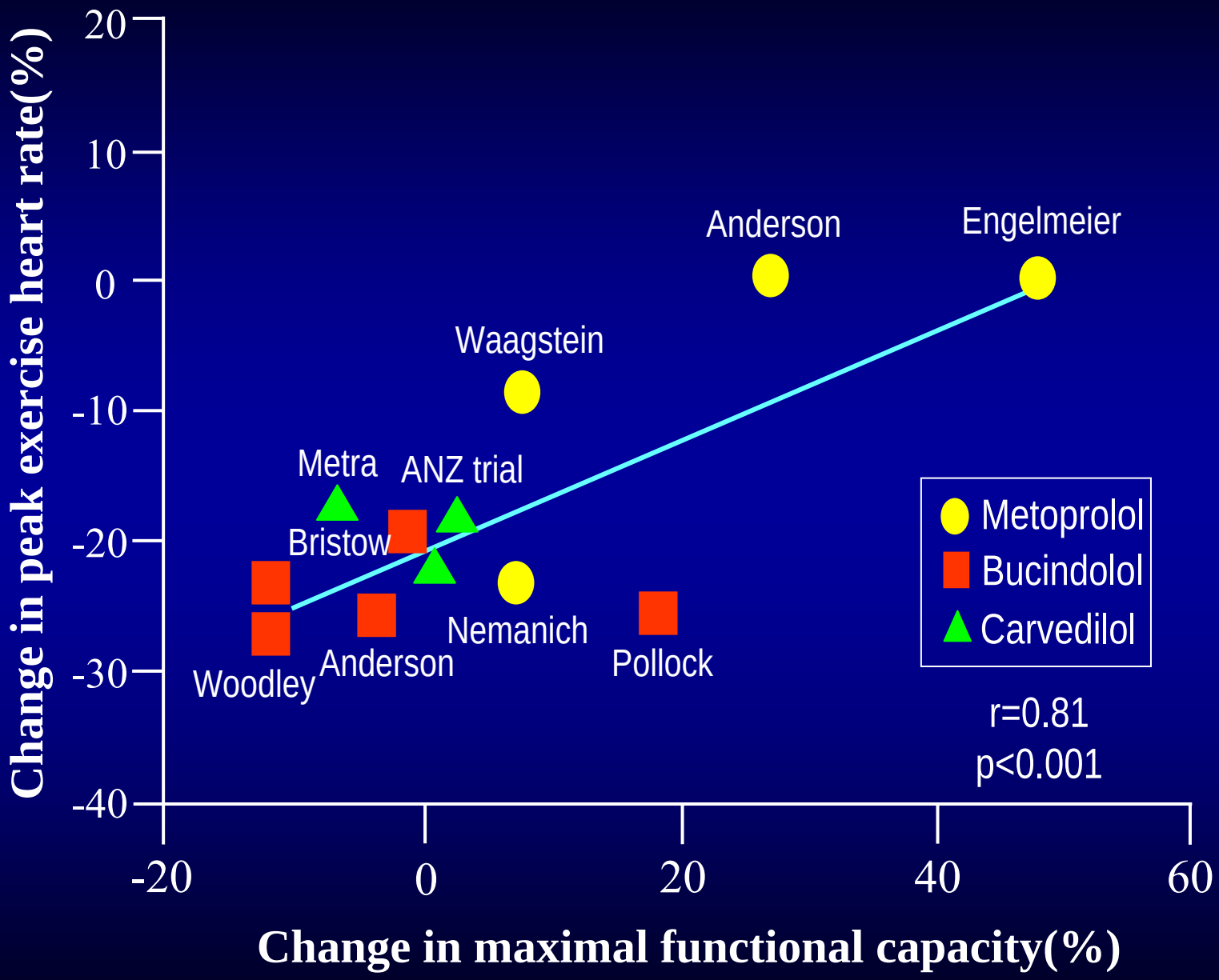
Death

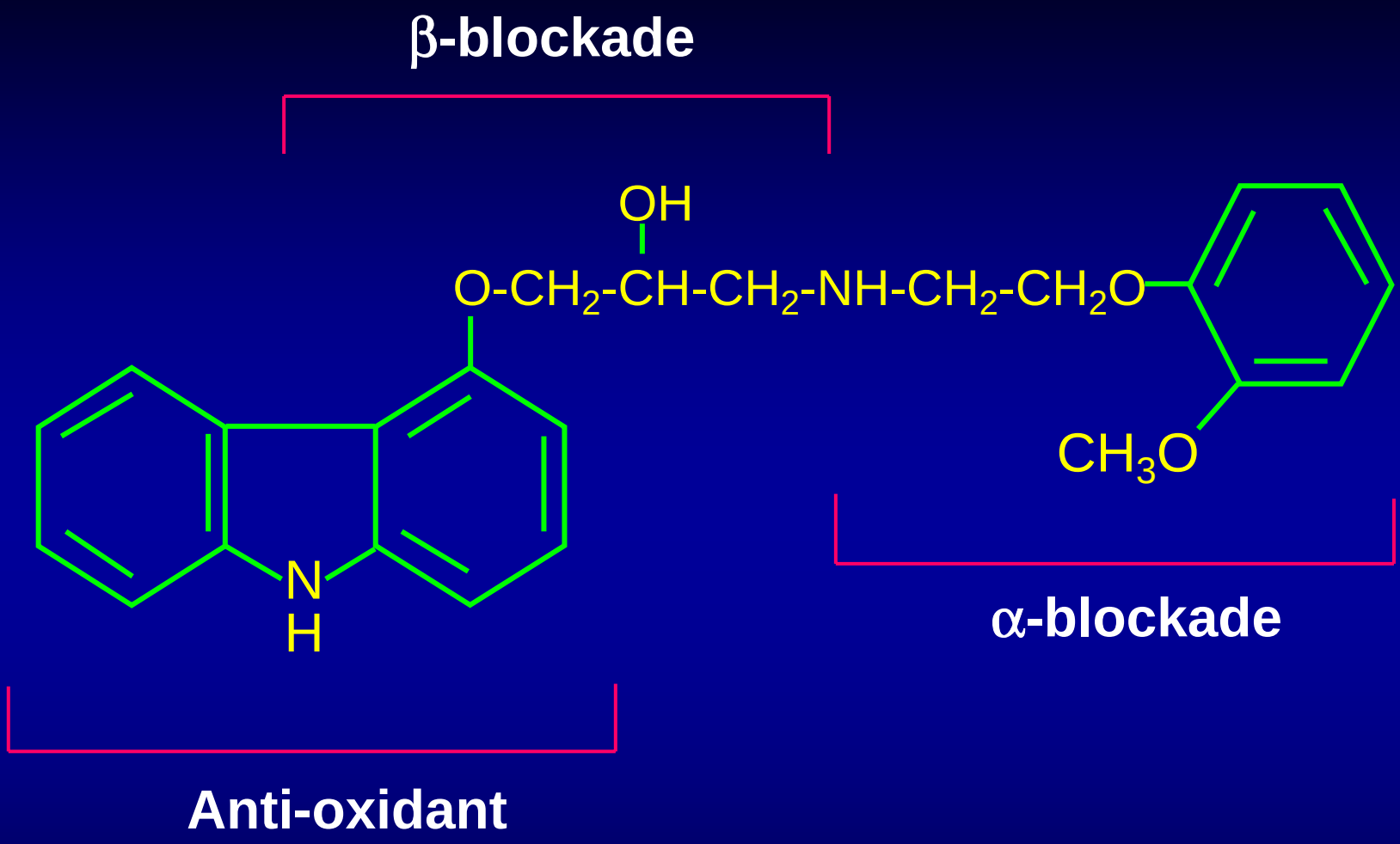

Favors carvedilol
Favors placebo
COPERNICUS
Male
Female
<65 yr old
≥65 yr old
North or South America
Other continents
LVEF <0.20
LVEF ≥0.20
Ischemic
Nonischemic
No recent hospitalization
Recent hospitalization
All patients
0.0
0.5
1.0
1.5
Hazard Ratio


Withdrawal from Medication
COPERNICUS
Percentage of Patients with Permanent Withdrawal of the Study Medication
40
30
20
10
0
Placebo
Carvedilol
P=0.02
0
3
6
9
12
15
18
21
Months

Questions about β–Blockers in Heart Failure

- Low dose vs high dose
- Effective in NYHA class IV patients ?
- Nonselective, selective, or with vasodilating
  - Are they same or which is more beneficial ?
    - → COMET


Change in peak exercise heart rate(%)
20
10
0
-10
-20
-30
-40
-20
0
20
40
60
Change in maximal functional capacity(%)
Anderson
Engelmeier
Waagstein
Metra
ANZ trial
Bristow
Nemanich
Woodley
Anderson
Pollock
Metoprolol
Bucindolol
Carvedilol
r=0.81
p<0.001



Carvedilol = 1-(9H-Carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}-2-propanol

Carvedilol

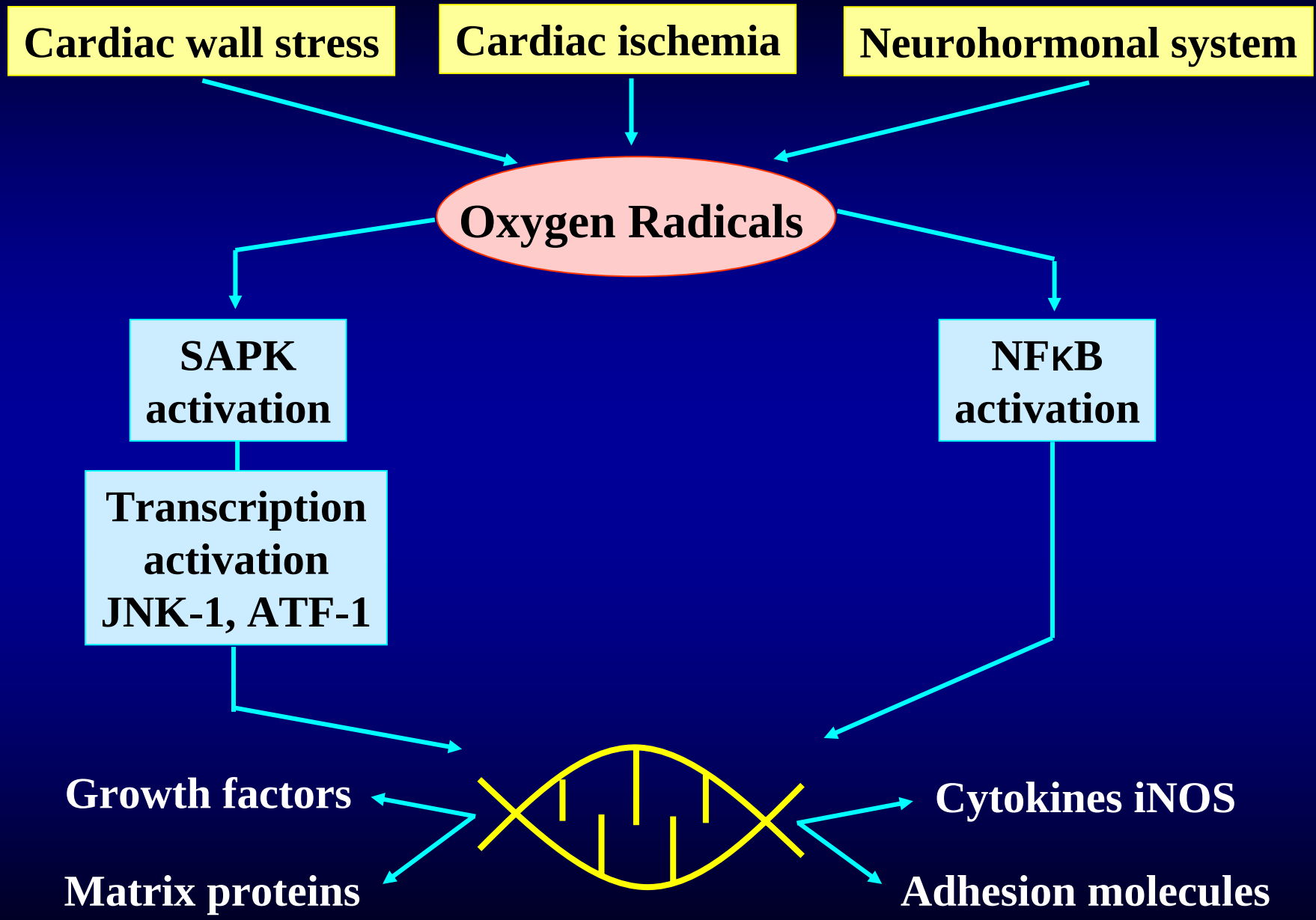
- β-and α_1-adrenergic receptor blocker
- Receptor affinity ; $\beta_1 : \alpha_1 = 3 : 1$

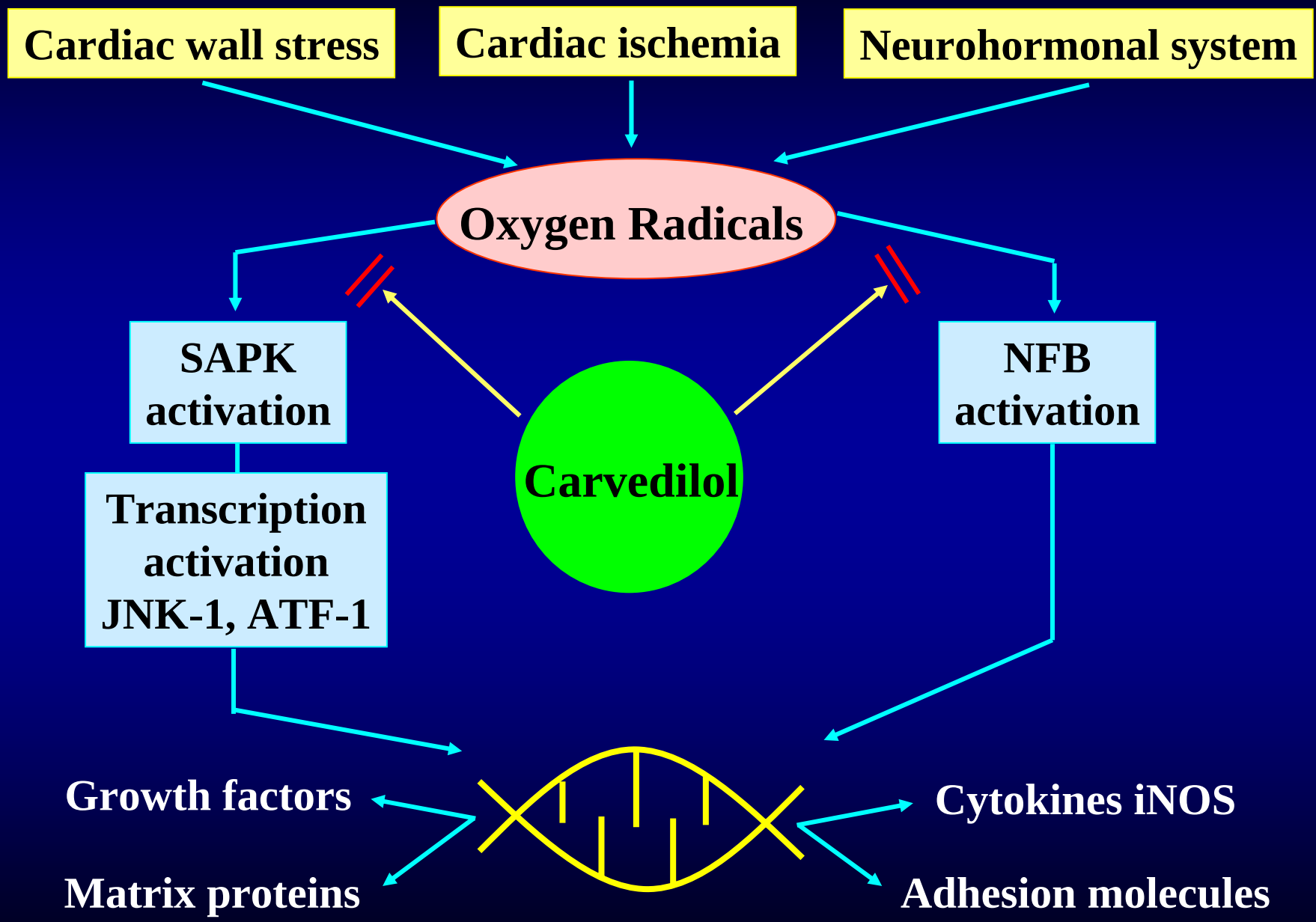
  cf) expression of adrenergic receptor in failing heart

  ; $\beta_1 : \beta_2 : \alpha_1 = 2:1:1$
- Potent antioxidant effect ;10-fold more potent than Vit E
  - Hydroxylated derivatives

    50 to 80-fold more potent than carvedilol,

    1000-fold more potent than vitamin-E
- Blocks the production of angiotensin II
- Suppresses the synthesis of endothelin
- Antiproliferative activity


Cardiac wall stress
Cardiac ischemia
Neurohormonal system
Oxygen Radicals
SAPK activation
NFκB activation
Transcription activation JNK-1, ATF-1
Growth factors
Matrix proteins
Cytokines iNOS
Adhesion molecules


Cardiac wall stress
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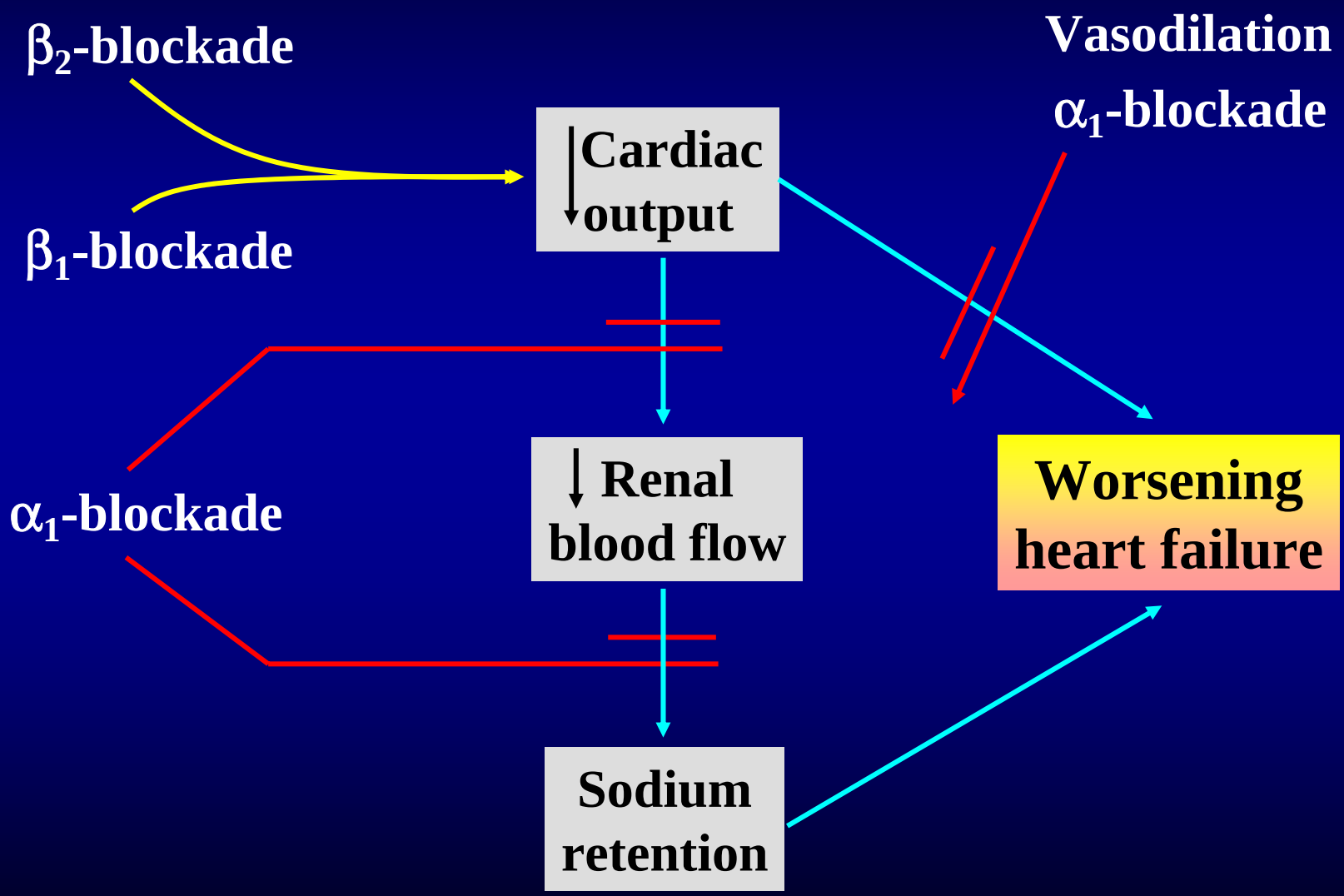
SAPK activation
NFB activation
Carvedilol
Transcription activation JNK-1, ATF-1
Growth factors
Matrix proteins
Cytokines iNOS
Adhesion molecules

Effects on Heart Failure Progression and Remodeling

	Beta 1	Beta 2	Alpha 1
Positive inotropic	+++	++	+
Positive chronotropic	+++	++	0
Myocyte hypertrophy	+++	+	++
Fibroblast hyperplasia	+++	+	NA
Myocyte toxicity	+++	+	+
Myocyte apoptosis	++	-	-
Tachyarrhythmias	++	++	+
Vasoconstriction	0	-	++
Sodium retention	0	0	++
Renin secretion	+	0	0

Worsening CHF after β-Blockade

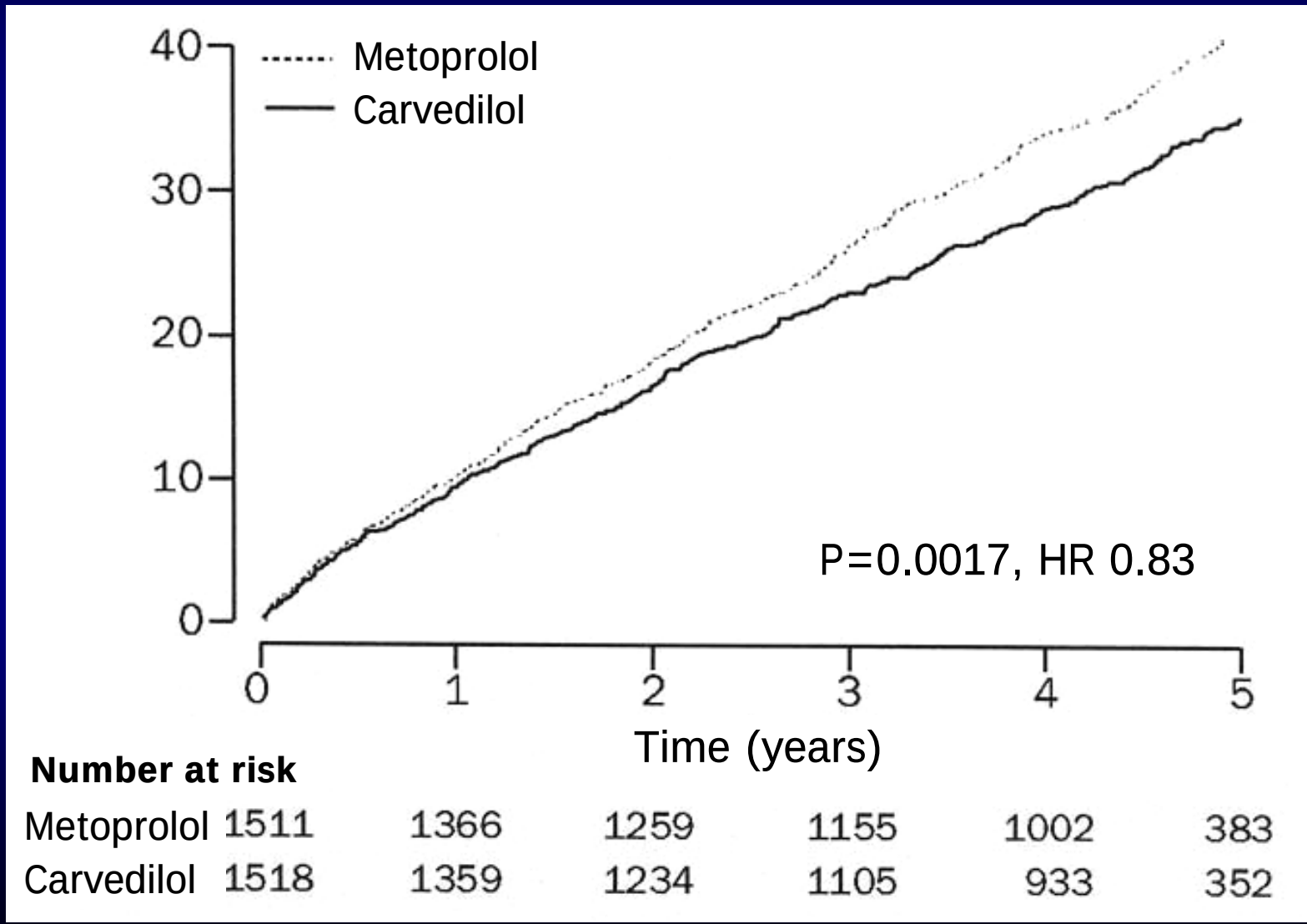


COMET

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

- Multicenter, double-blind, randomized parallel study
- Chronic heart failure, LVEF<0.35 with optimal treatment
- 1511 pts with carvedilol vs 1518 pts with metoprolol tartrate
- Primary endpoint; all cause mortality
- Composite endpoint; all cause mortality or all admission
- Results (carvedilol vs metoprolol tartrate)
  - Mean study duration; 58 months
  - All cause mortality; 34 vs 40%(HR 0.83, p=0.0017)
  - Composite endpoint; 74 vs 76%(HR 0.94, p=0.122)
  - Drug withdrawal and side effects; no difference

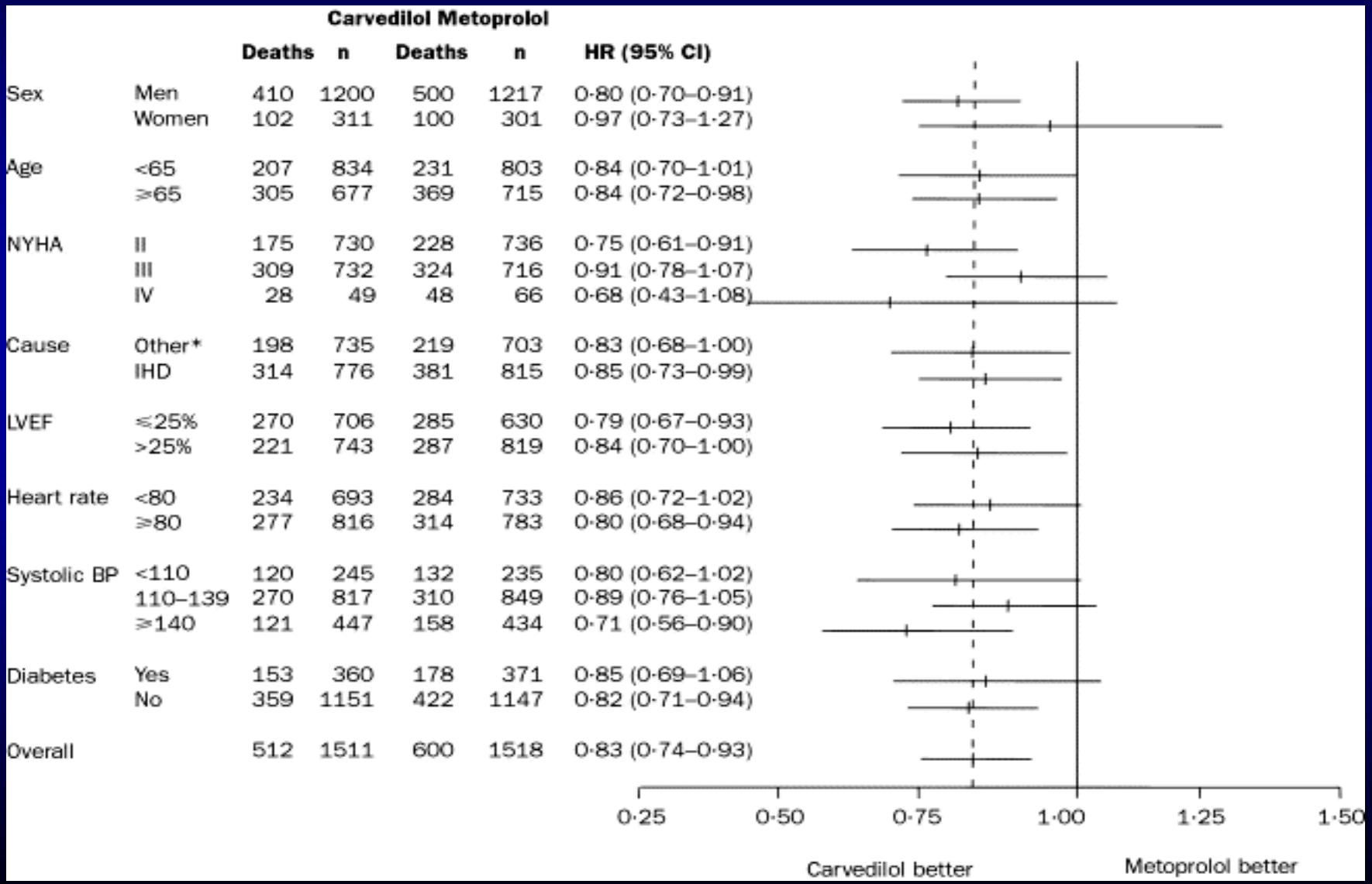
COMET-all cause mortality



Number at risk

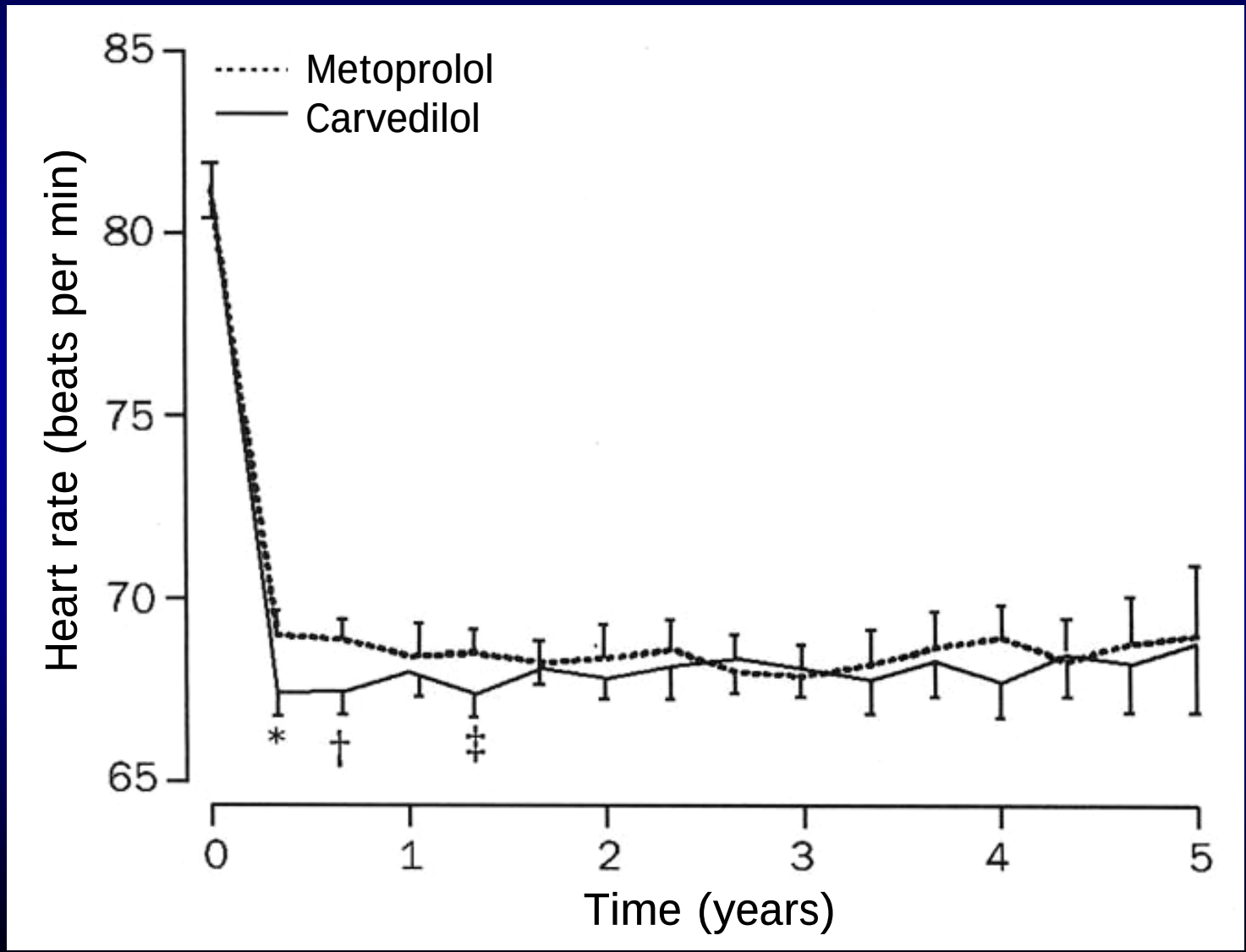
Metoprolol	1511	1366	1259	1155	1002	383
Carvedilol	1518	1359	1234	1105	933	352

COMET-predefined subgroup



		Carvedilol		Metoprolol		
		Deaths	n	Deaths	n	HR (95% CI)
Sex	Men	410	1200	500	1217	0·80 (0·70–0·91)
	Women	102	311	100	301	0·97 (0·73–1·27)
Age	<65	207	834	231	803	0·84 (0·70–1·01)
	⩾65	305	677	369	715	0·84 (0·72–0·98)
NYHA	II	175	730	228	736	0·75 (0·61–0·91)
	III	309	732	324	716	0·91 (0·78–1·07)
	IV	28	49	48	66	0·68 (0·43–1·08)
Cause	Other*	198	735	219	703	0·83 (0·68–1·00)
	IHD	314	776	381	815	0·85 (0·73–0·99)
LVEF	⩽25%	270	706	285	630	0·79 (0·67–0·93)
	>25%	221	743	287	819	0·84 (0·70–1·00)
Heart rate	<80	234	693	284	733	0·86 (0·72–1·02)
	⩾80	277	816	314	783	0·80 (0·68–0·94)
Systolic BP	<110	120	245	132	235	0·80 (0·62–1·02)
	110–139	270	817	310	849	0·89 (0·76–1·05)
	⩾140	121	447	158	434	0·71 (0·56–0·90)
Diabetes	Yes	153	360	178	371	0·85 (0·69–1·06)
	No	359	1151	422	1147	0·82 (0·71–0·94)
Overall		512	1511	600	1518	0·83 (0·74–0·93)

COMET-heart rate



β-Adrenergic Receptor Blockers

Recommendation 1

- Recommended for the treatment of all patients with *stable,* mild, moderate and severe heart failure from ischemic and nonischemic cardiomyopathies and reduced LV ejection fraction, in *NYHA class II to IV*, *on standard treatment*, including diuretics and ACE inhibitors, unless there is contraindications for β-blockers

β-Adrenergic Receptor Blockers

Recommendation 2

- Recommended in patients with LV systolic dysfunction, with or *without symptomatic heart failure*, following an *acute myocardial infarction* in addition to ACE inhibition to reduce mortality

β-Adrenergic Receptor Blockers

How to use

- β-blocker therapy should be initiated *at low doses and up-titrated slowly*, generally no sooner than at 2-week intervals
- Patient education regarding early recognition of symptom exacerbation and side effects is considered important

Titration Scheme of β-blockers in Recent Large, Controlled Trials

β-blocker	First dose (mg)	Increments (mg. Day^{-1})	Target dose (mg. Day^{-1})	Titration period
Bisoprolol	1·25	2·5, 3·75, 5, 7·5, 10	10	Weeks-month
Metoprolol tartrate	5	10, 15, 30, 50, 75, 100	150	Weeks-month
Metoprolol succinate CR	12·5/25	25, 50, 100, 200	200	Weeks-month
Carvedilol	3·125	6·25, 12·5, 25, 50	50	Weeks-month

β-Adrenergic Receptor Blockers

Worsening heart failure symptoms/signs

- After drug initiation or during titration
  - → adjustment of concomitant medication or reduction of β-blocker dose

β-Adrenergic Receptor Blockers

Worsening heart failure symptoms/signs

- During chronic maintenance treatment
  - ➔less likely caused by chronic β-blocker therapy than other precipitating factors
  - ➔should be continued on β-blocker therapy

Rationale for β–Blocker + PDEI

- Type III PDEI, different site of action beyond the β–adrenergic receptor, retain their hemodynamic action in the face of β-blocker.
  - ➔Type III PDEI inhibit the phosphorylation of the phospholamban on the SR
- β-blocker can reduce the adverse event profile of the type III PDEIs by lowering HR and decreasing proarrhythmic potential.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