Pivotal Role of Beta Blocker in Heart Failure Management

Busan 16th of April 2010

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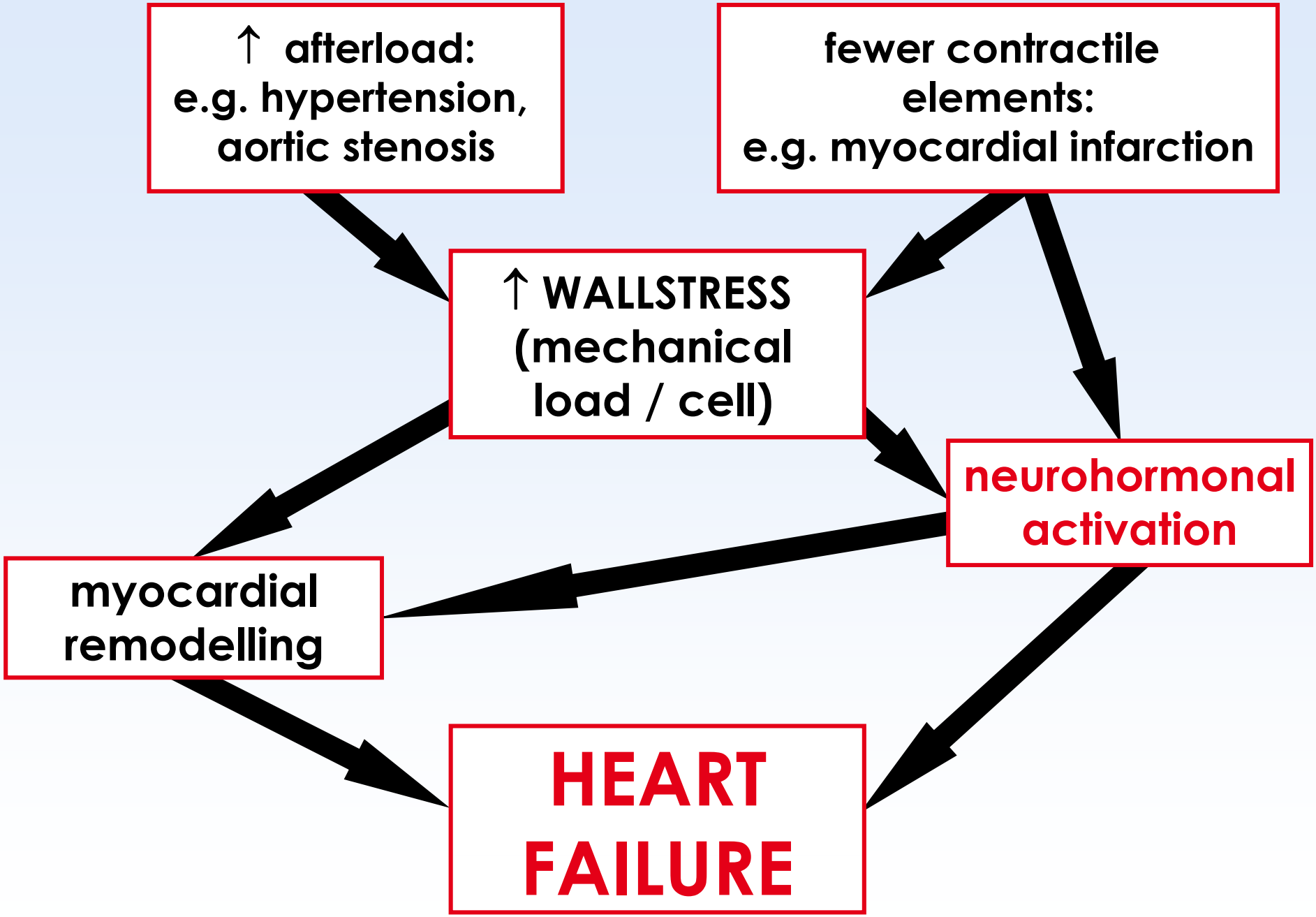

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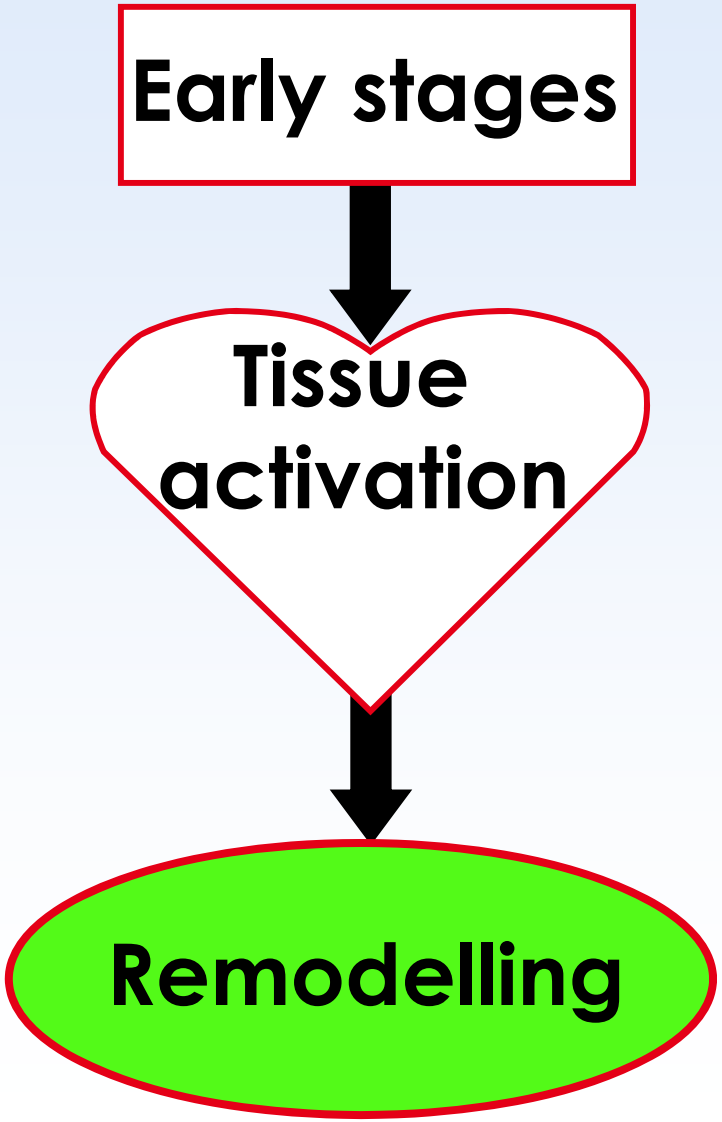
Neurohormonal activation



Heart
Vessels
Kidney
Brain

Neurohormonal activation

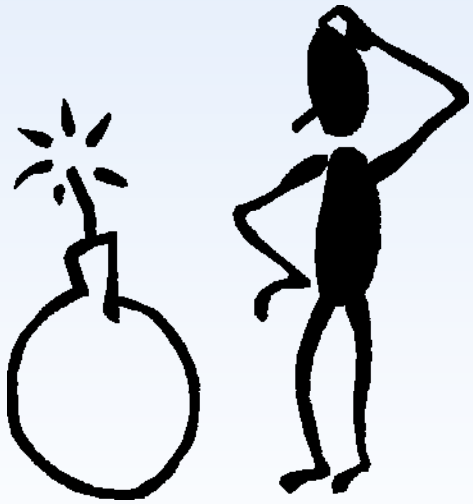
Early stages

Tissue activation

Remodelling

Late stages

Systemic activation



Remodelling

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Neurohormones

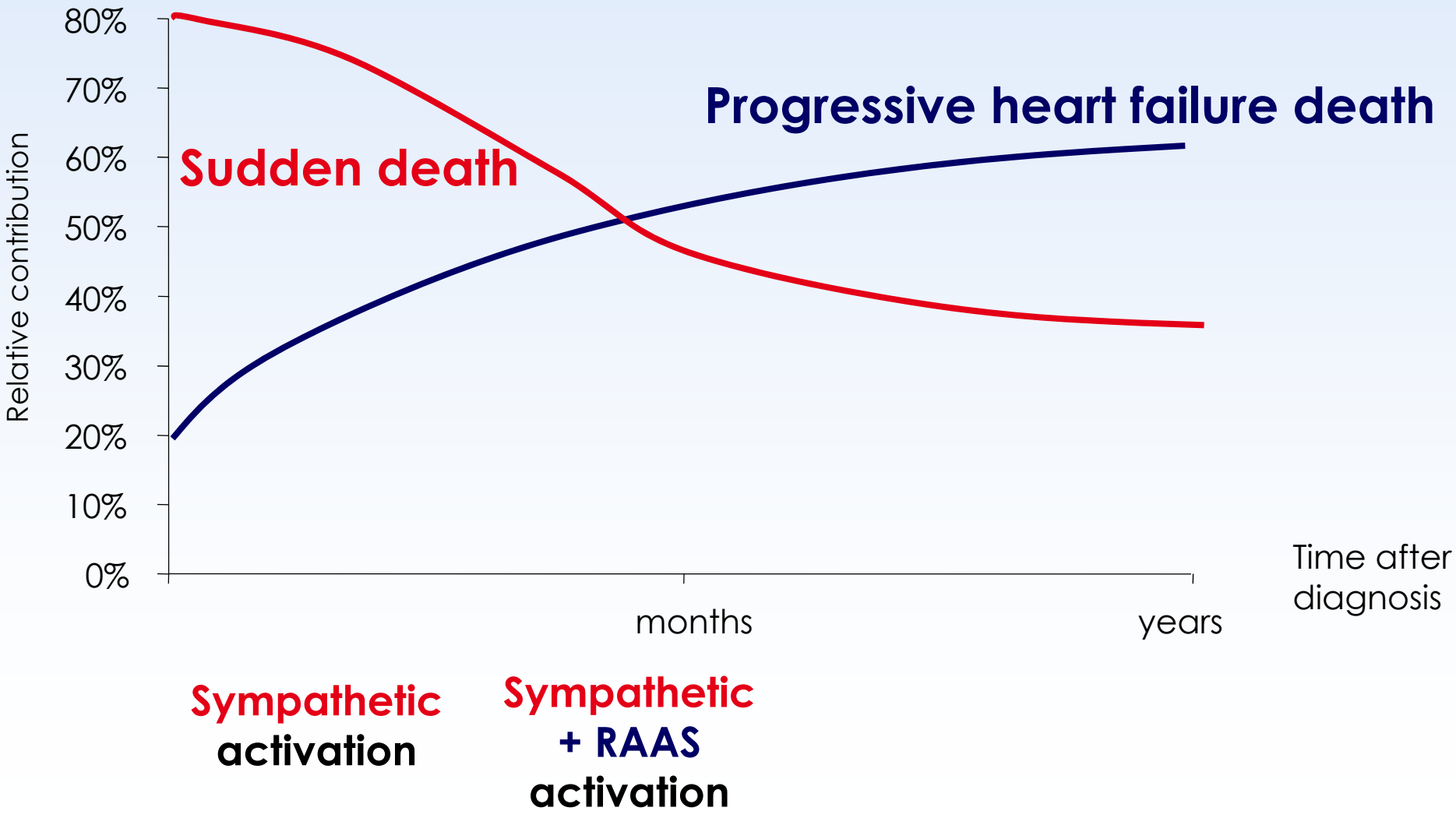
- norepinephrine
- angiotensin II
- aldosterone
- endothelin
- inflammatory cytokines
- peptide growth factors

Norepinephrine

- myocyte growth
- fetal gene reinduction
- downregulation of Ca^{2+} regulating genes
- tumor growth factor-ß expression
- apoptosis
- fibroblast DNA and protein synthesis

Mann. Circulation 1992;85:790-804 - Clark. Circ Res 1993;73:1163-76 - Takahashi. J Clin Invest 1994;94:1470-83 - Calderone. Circulation 1995;92:I-382 - Colucci. Am J Cardiol 1997;80:15-25L

The sympathetic system is the first system activated systemically



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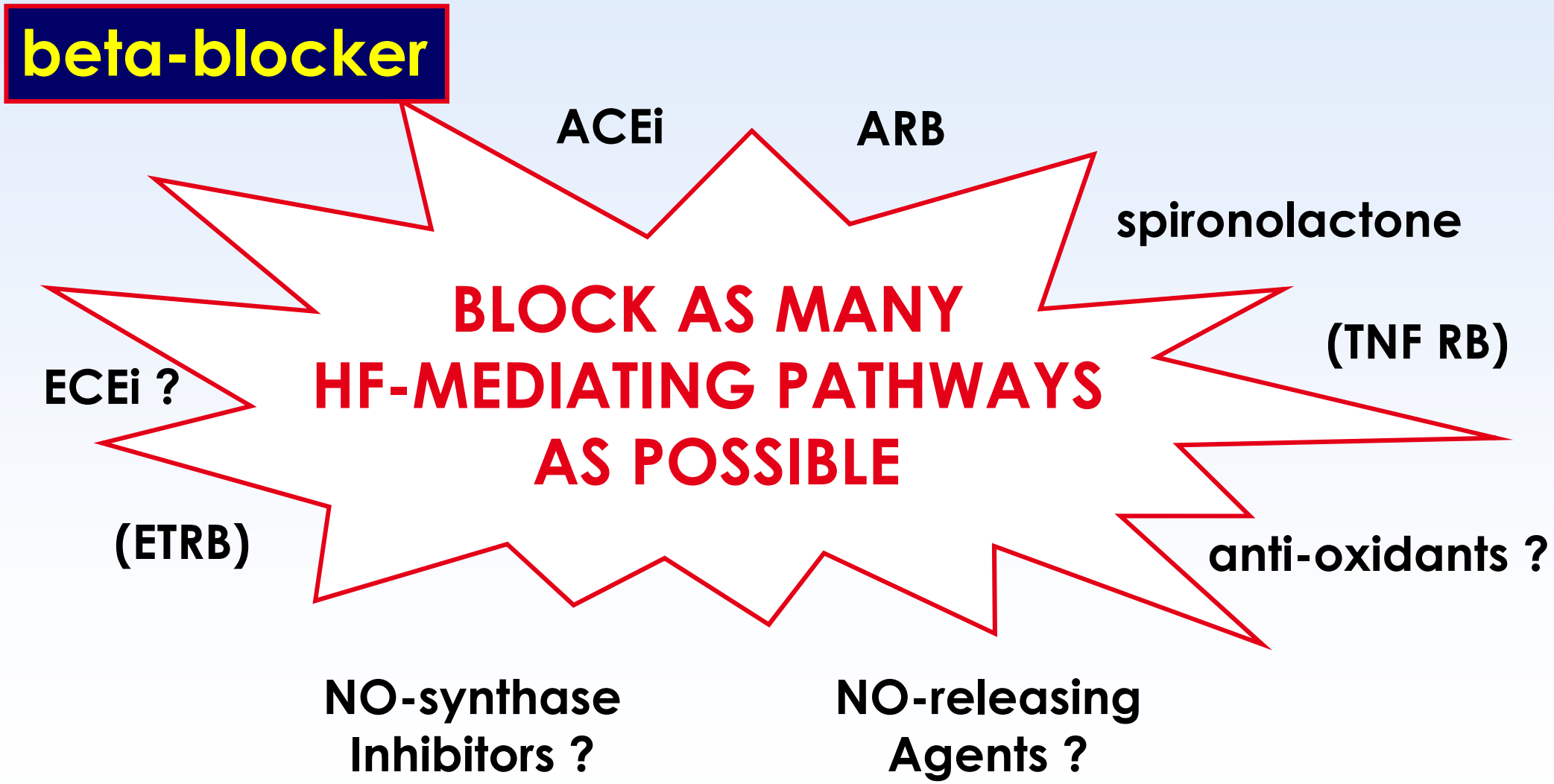
THERAPEUTIC STRATEGY



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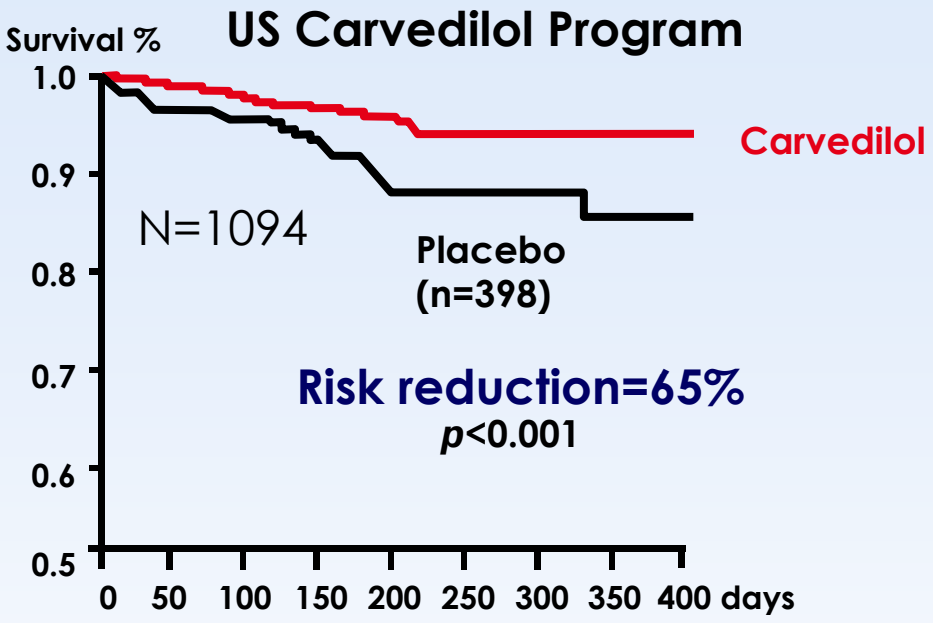
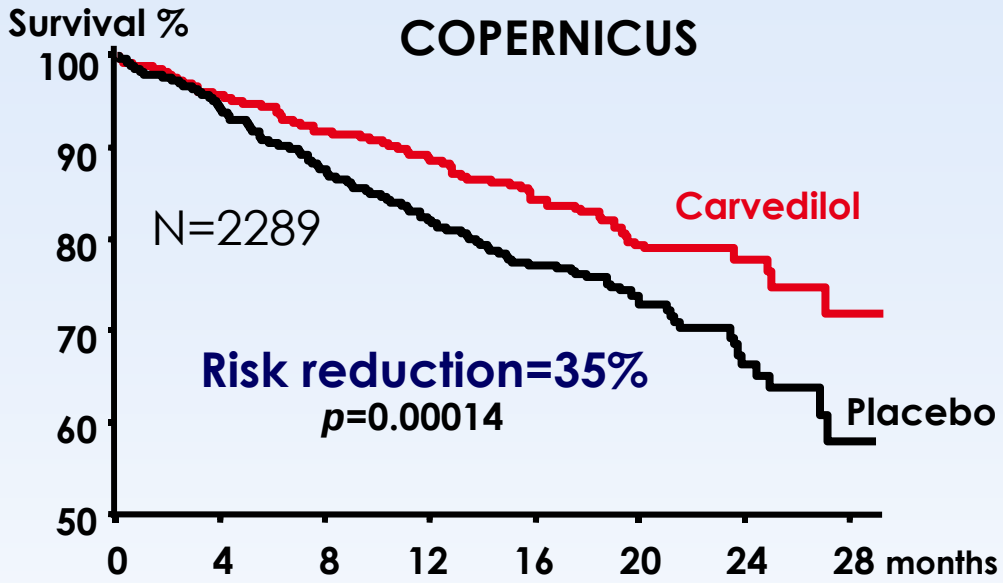
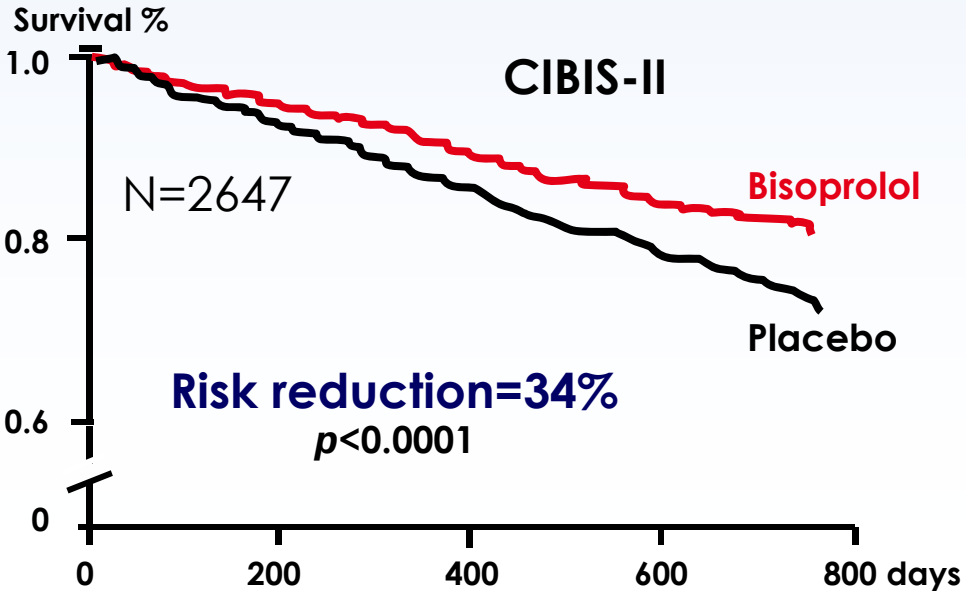
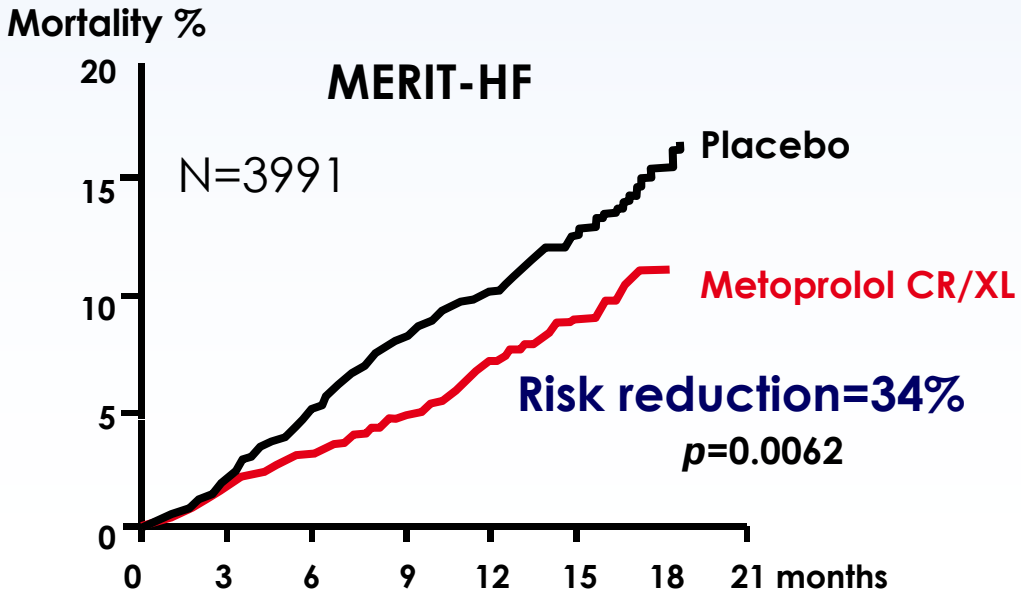
Betablockers in systolic CHF: mortality









CIBIS II
Main Results at a Glance

Bisoprolol vs. placebo reduced:

- All-cause mortality (independent of aetiology) by 34% (p<0.0001)
- Sudden death by 44% (p<0.0011)
- All-cause hospital admissions by 20% (p<0.0006)
- Hospital admissions due to worsening heart failure by 36% (p<0.0001)
- Permanent treatment withdrawals similar: 15% (p=0.98)

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

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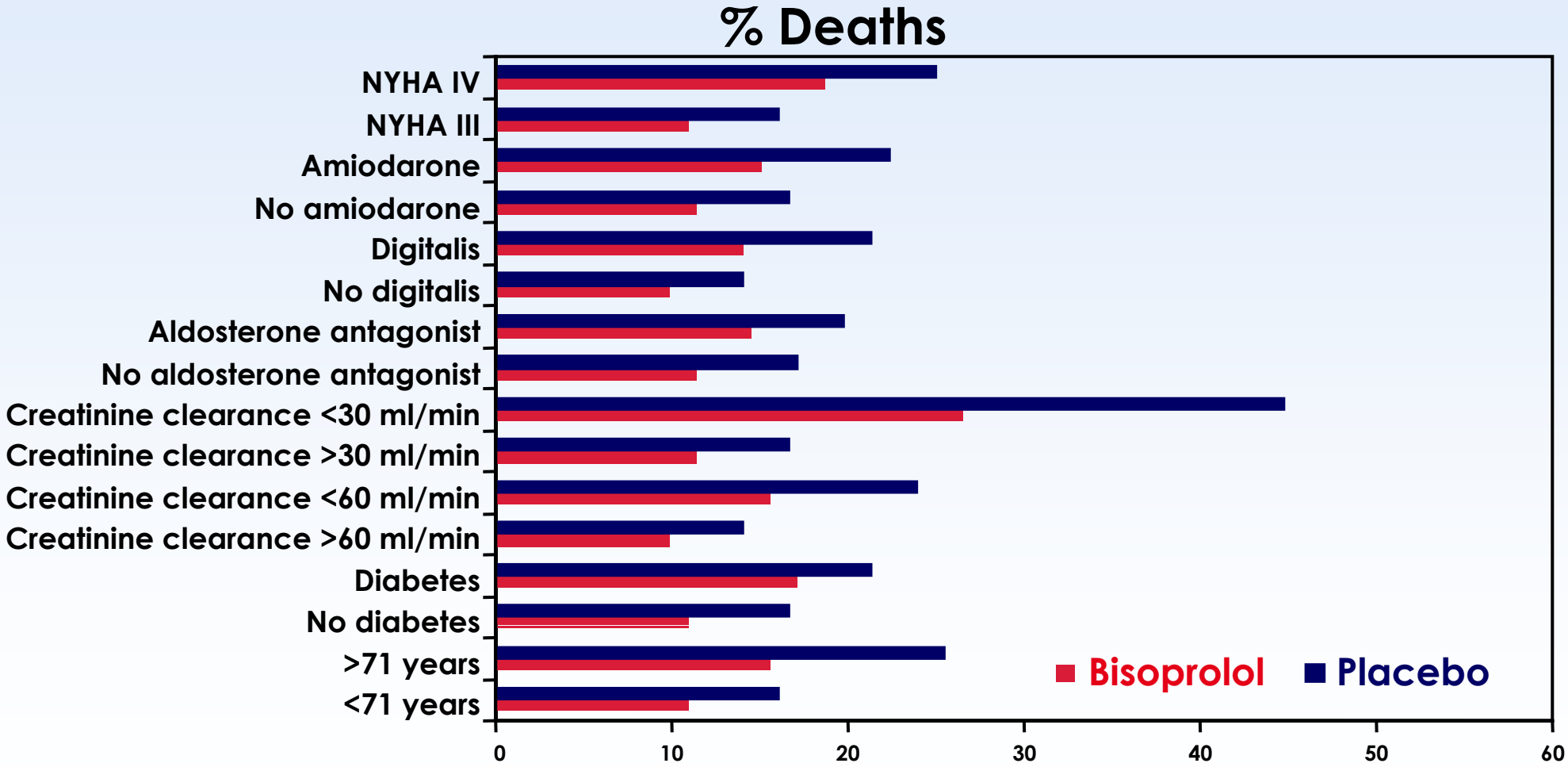
CIBIS II: Post Hoc Analyses
Effect of Bisoprolol on Mortality



→high-risk patients also benefit from β-blockade with bisoprolol

Erdmann E et al. Eur J Heart Fail 2001; 3:469-479

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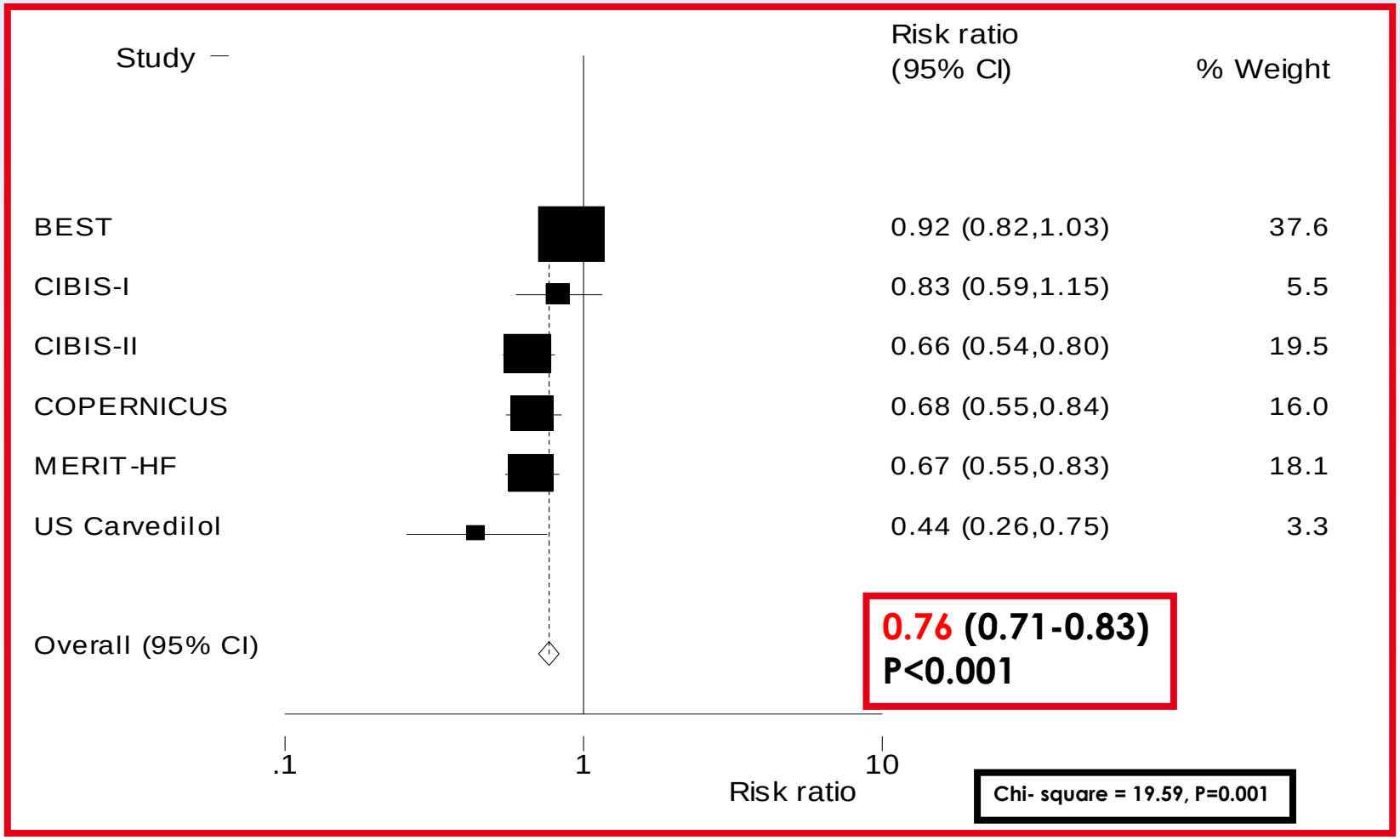
Mortality in Beta-Blocker Studies

Beta-Blockers on top of ACE Inhibitors



Krum H et al. Eur Heart J 2005

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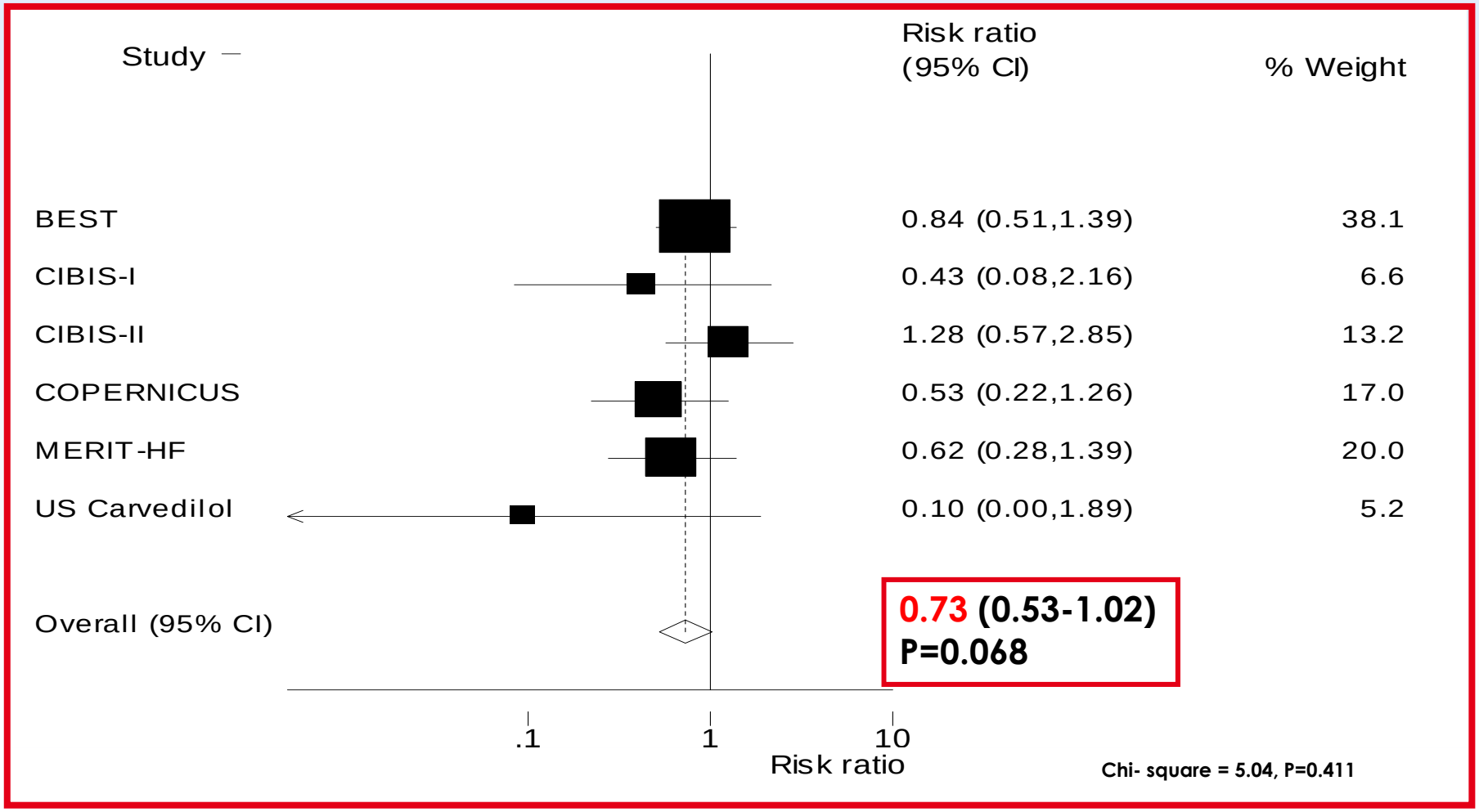
Mortality in Beta-Blocker Studies

Beta-Blockers without ACE Inhibitors



Krum H et al. Eur Heart J 2005

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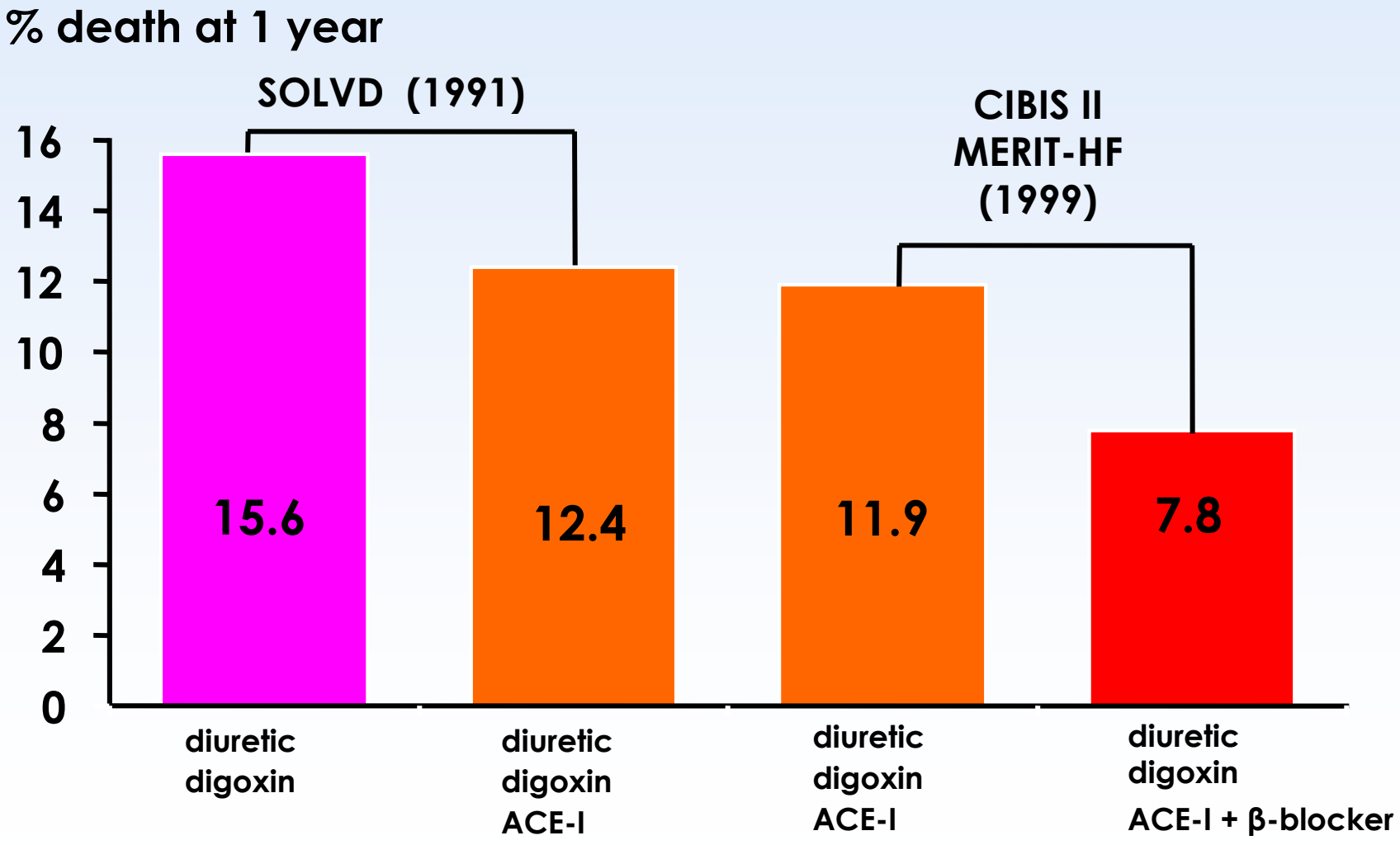
Mortality Benefit of Beta-blockers and ACE-inhibitors in CHF trials



McMurray Heart 1999

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ESC guidelines for HF 2008 - β-Blockers

Unless contraindicated or not tolerated, a β-blocker **should be used in all patients with symptomatic HF and an LVEF ≤40%**. β-blockade improves ventricular function and patient well-being, reduces hospital admission for worsening HF, and increases survival. Where possible, in hospitalized patients, treatment with a β-blocker should be initiated cautiously before discharge.

Class of recommendation I, level of evidence A

Betablockers

Proven mortality reduction for

- **bisoprolol**
- **metoprolol**
- **carvedilol**
- **(nebivolol)**

on top of ACE inhibitors

Beta-Blockers in Heart Failure

- Effective in mild-moderate stable CHF (CIBIS II, MERIT-HF)
- Effective in severe, stable CHF (COPERNICUS)
- Effective in post MI LV systolic dysfunction (CAPRICORN)
- Effective in systolic HF in the elderly (SENIORS)
- Effective irrespective of subgroup
- Choice of agents, dose interval may be clinically important (BEST, COMET)

Effect of carvedilol on risk of major clinical events in patients at highest risk: first 8 weeks vs. entire trial

End point	Placebo patients No./total	Carvedilol patients No./total	Hazard ratio
All-cause mortality			
-First 8 weeks	15/316	3/308	0.20
-Entire trial			0.61
Death or hospitalization			
-First 8 weeks	63/316	44/308	0.71
-Entire trial			0.71
Death, hospitalization, or permanent study drug withdrawal for any reason			
-First 8 weeks	76/316	51/308	0.67
-Entire trial			0.68

Krum H et al. *JAMA* 2003; 289:712-718.

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CIBIS III

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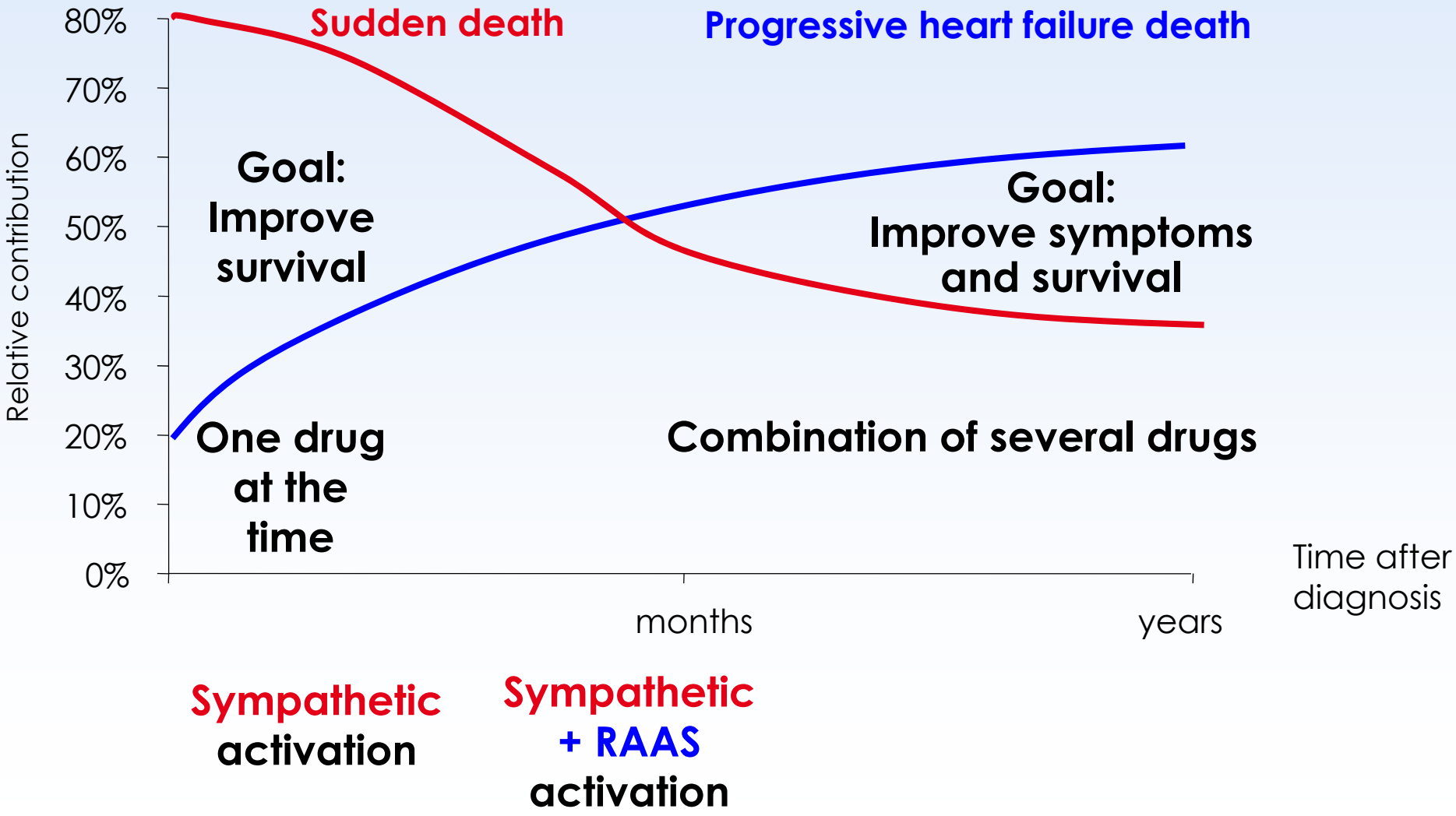
Rationale for CIBIS III

- In patients with newly diagnosed CHF, an ACE inhibitor is usually started first – especially in out-patients – and followed by a betablocker
- There is no evidence behind this tradition, although recommended by the ESC guidelines – but not by the US guidelines
- Is this the optimum way to initiate CHF treatment?

Why is early stage of CHF critically important?



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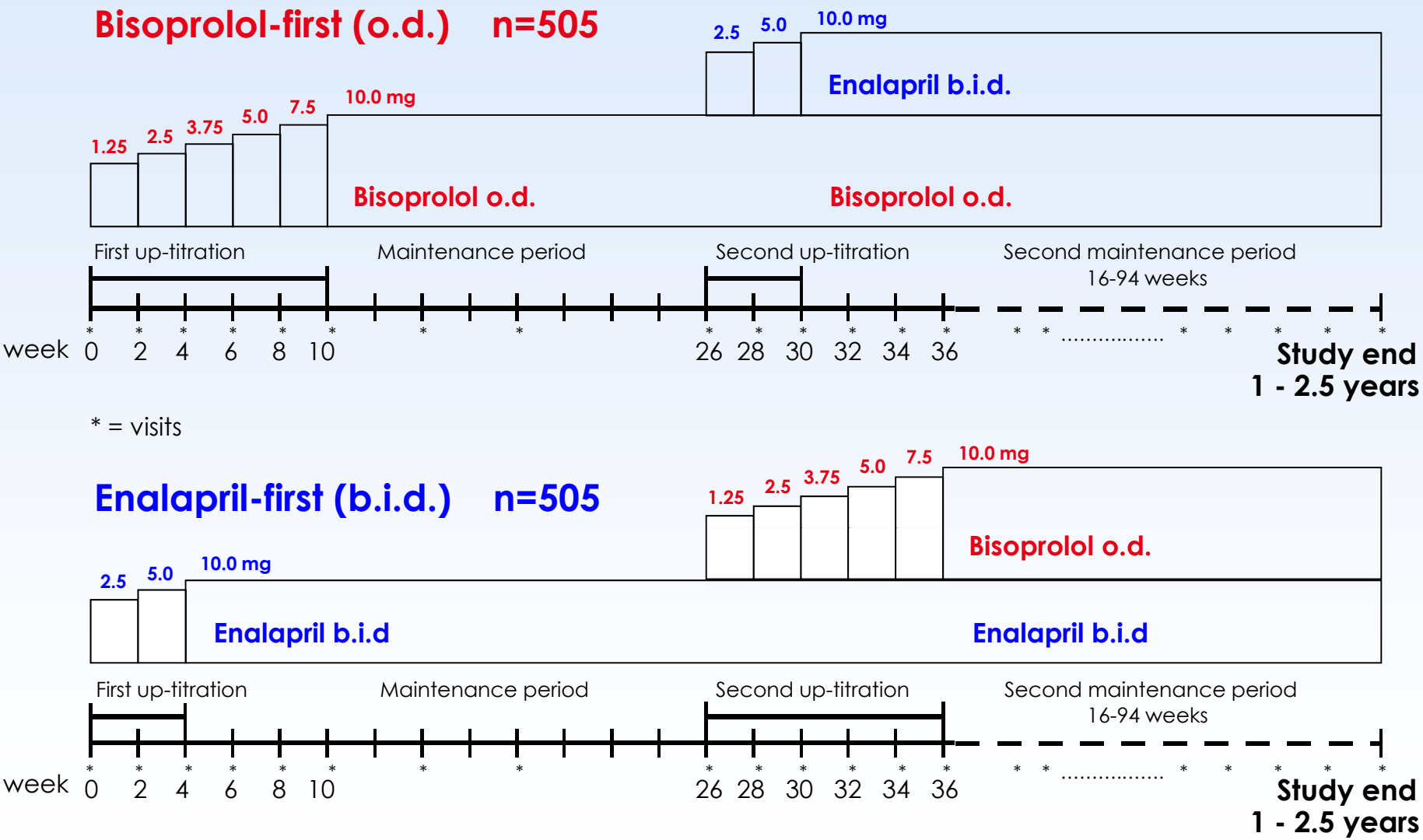
Study design



Willenheimer et al. Circulation. 2005;112:2426-2435.

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Prespecified time points of analysis

- End of monotherapy phase
  (157-230 days post randomization, mean 162 days)
- After the first year (minimum time of follow-up for all patients)
- Study end

Patients

- Age >= 65 years
- Mild to moderate CHF (NYHA class II or III)
- LVEF <= 35%
- Stable CHF since >= 7 days

  (without clinically relevant fluid retention/diuretic adjustment)
- No prior ACEI, betablocker or ARB

Willenheimer et al. Circulation. 2005;112:2426-2435.

Baseline data

	Bisoprolol-first (n=505) Mean / n	% / SD	Enalapril-first (n=505) Mean / n	% / SD
Age (years)	72.4	5.8	72.5	5.7
Males	333	65.9	356	70.5
NYHA Class II/III	245 / 260	48.5 / 51.5	250 / 255	49.5 / 50.5
LVEF (%)	28.8	4.8	28.8	5.2
Heart rate (bpm)	78.8	13.8	79.5	13.2
BP (mm Hg)	134 / 80	17 / 10	134 / 81	17 / 10
Etiology				
CAD	309	61.2	321	63.6
Hypertension	197	39.0	172	34.1
Diabetes	95	18.8	113	22.4
Diuretic treatment	430	85.1	421	83.4
Loop diuretics	361	71.5	338	66.9
Aldo rec blockers	72	14.3	62	12.3
Cardiac glycosides	166	32.9	155	30.7

Willenheimer et al. Circulation. 2005;112:2426-2435.

RESULTS

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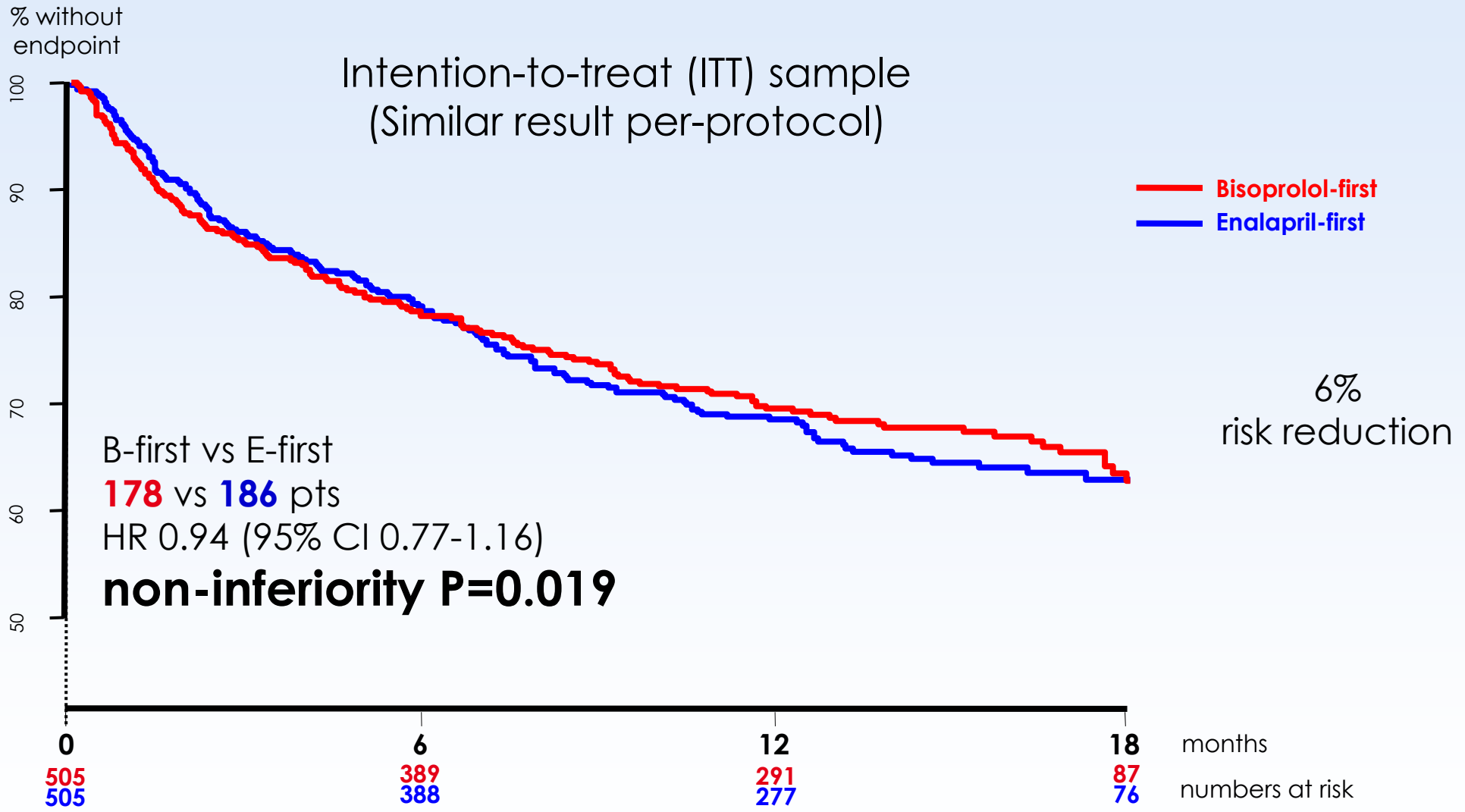
Primary endpoint – death / hospitalisation



Bisoprolol-first significantly non-inferior to enalapril-first if upper limit of 95% CI below hazard ratio (HR) 1.17, P<0.025. (=RR 1.125, AR +5%)

Willenheimer et al. Circulation. 2005;112:2426-2435.

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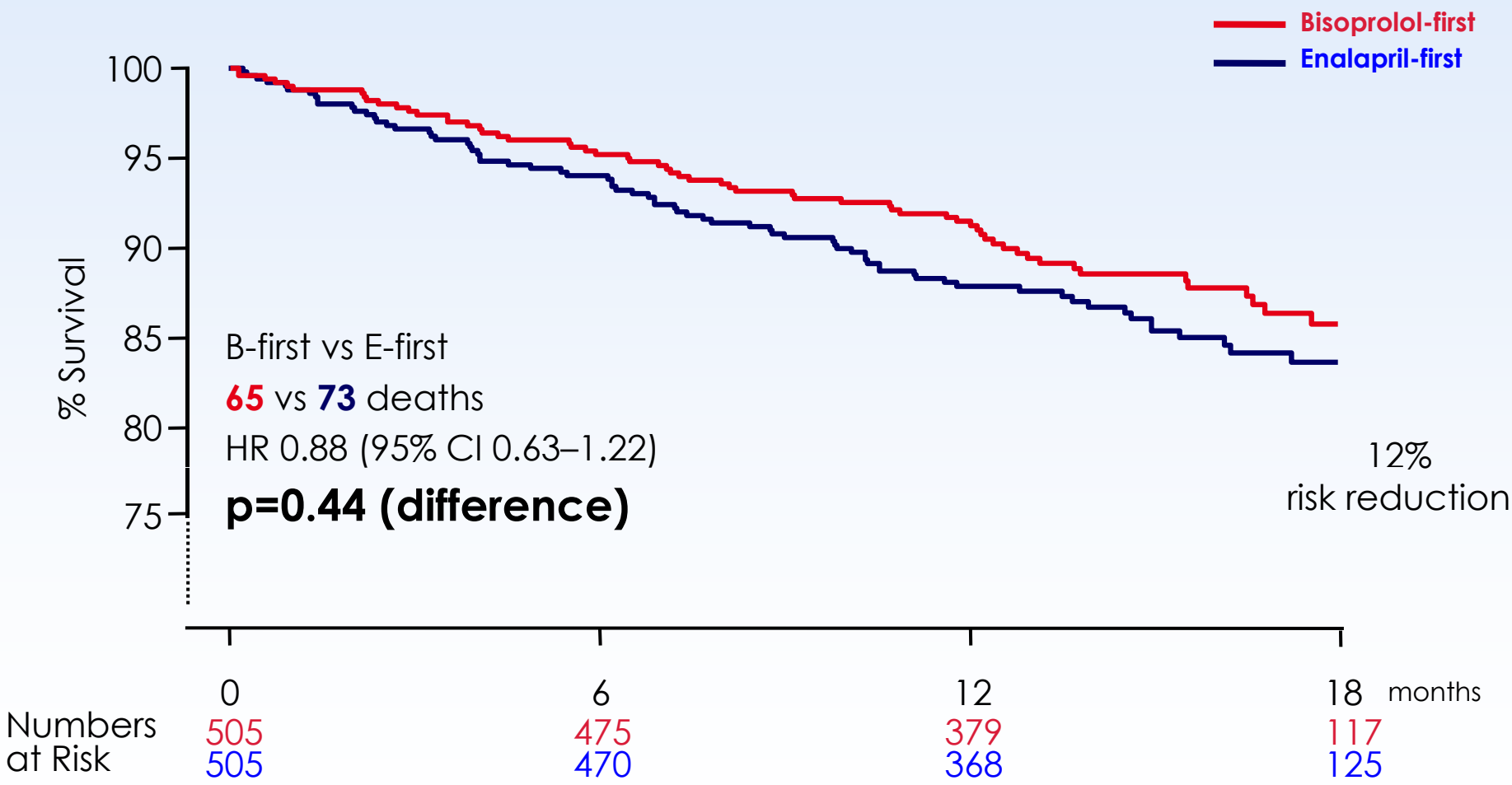
All cause mortality entire study (ITT)



Willenheimer et al. Circulation. 2005;112:2426-2435.

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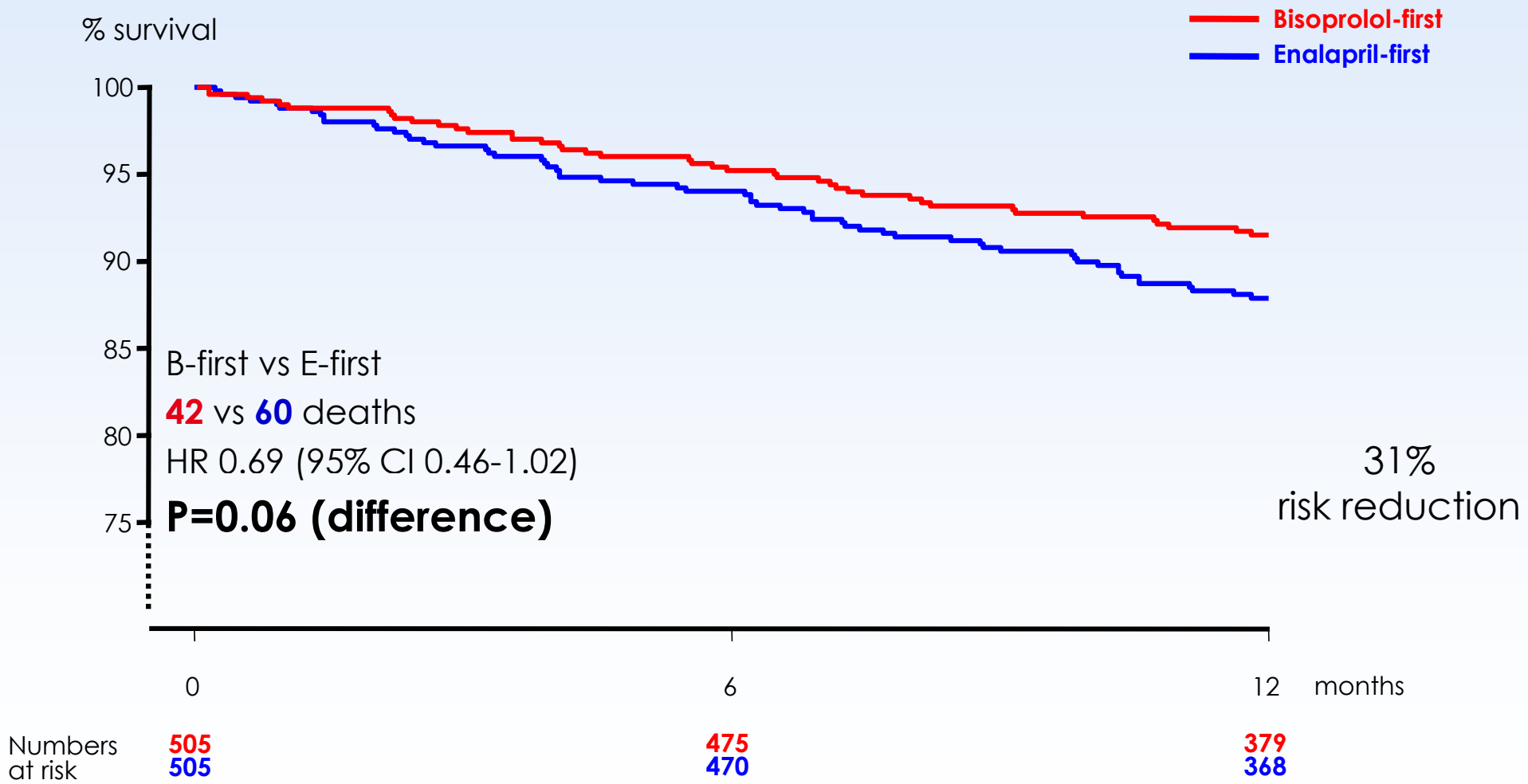
All cause mortality at 1 year (ITT)



Willenheimer et al. Circulation. 2005;112:2426-2435.

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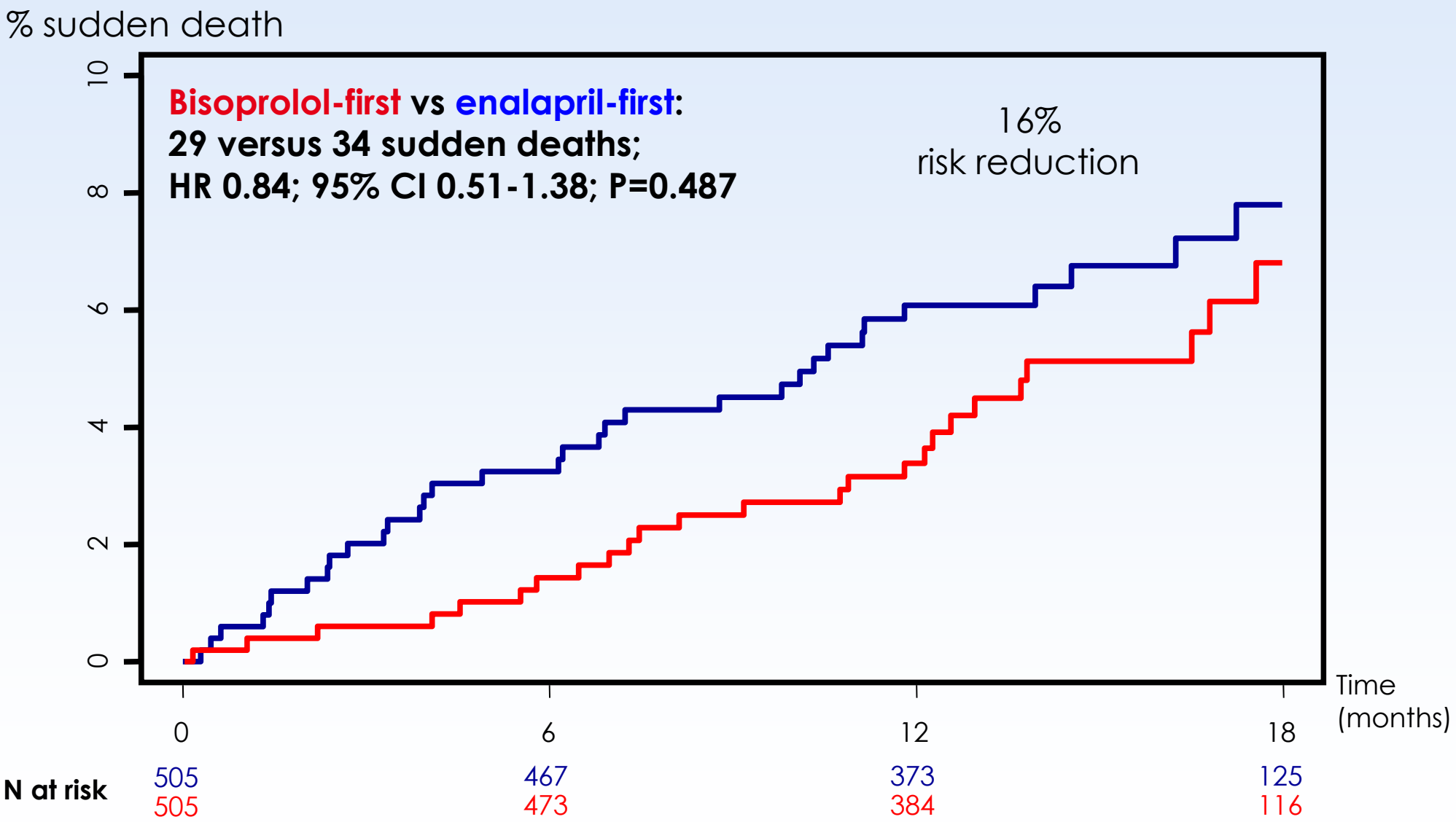
Sudden death – throughout study



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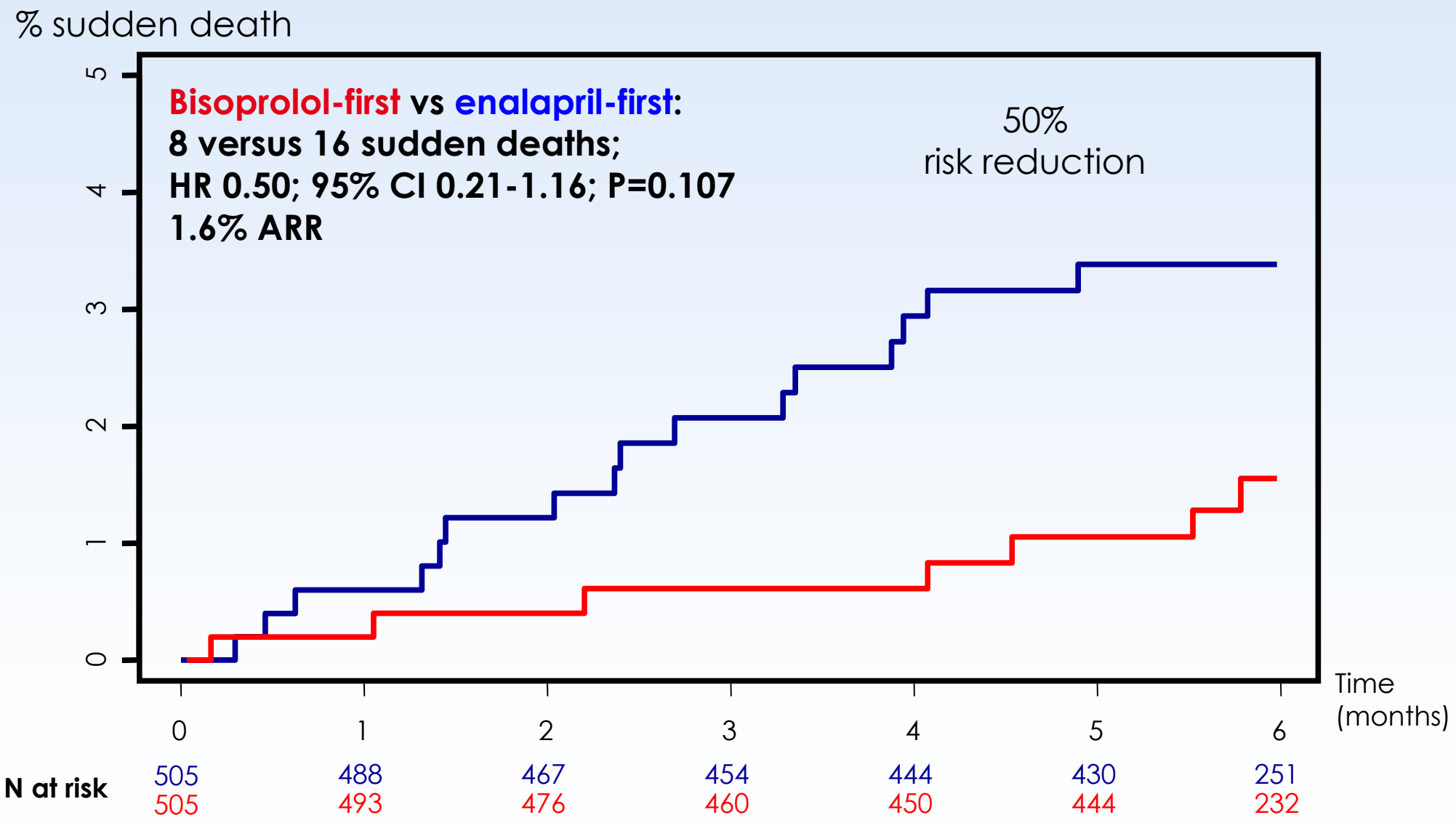
Sudden death - end of monotherapy



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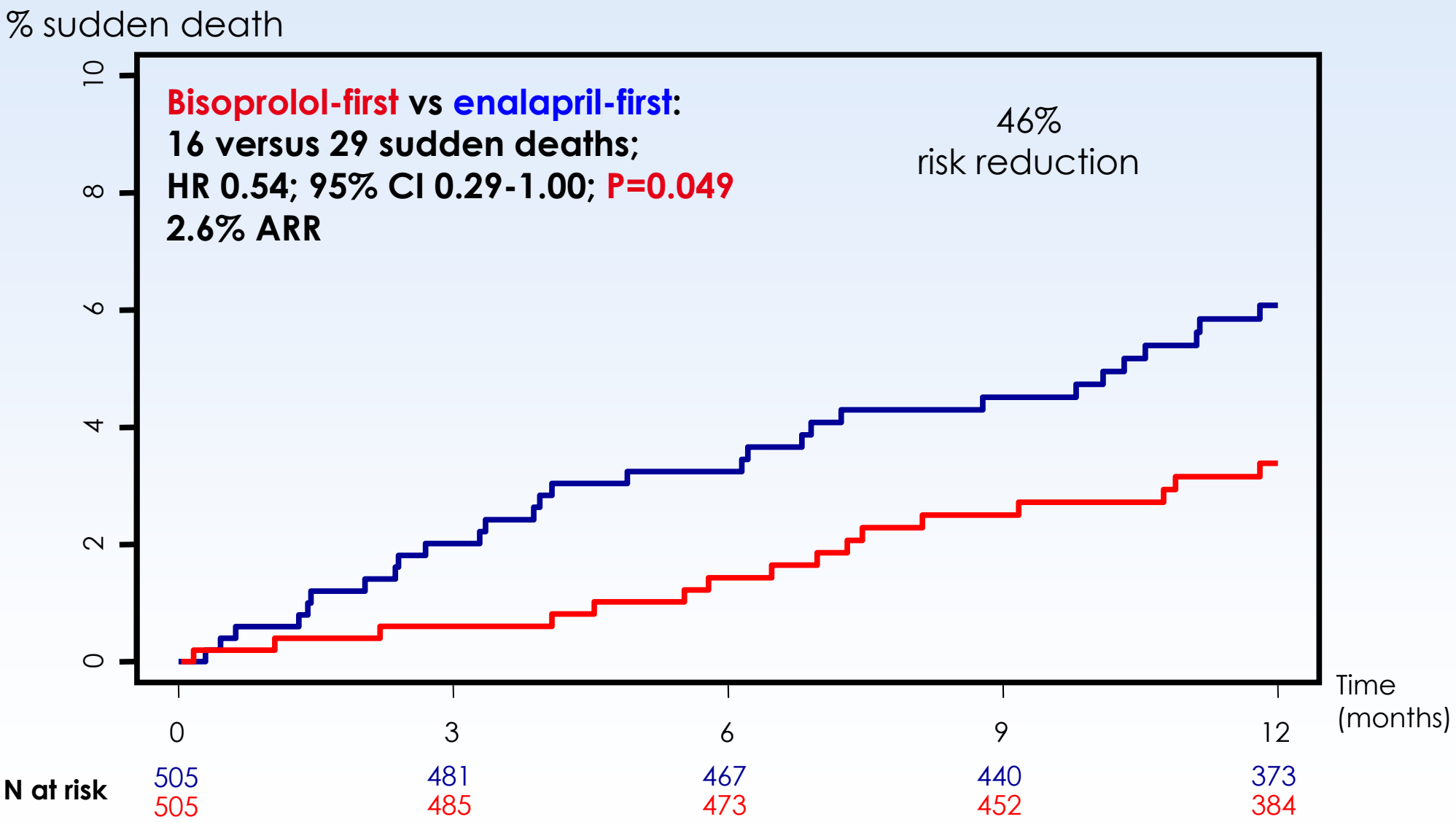
Sudden death – 1 year



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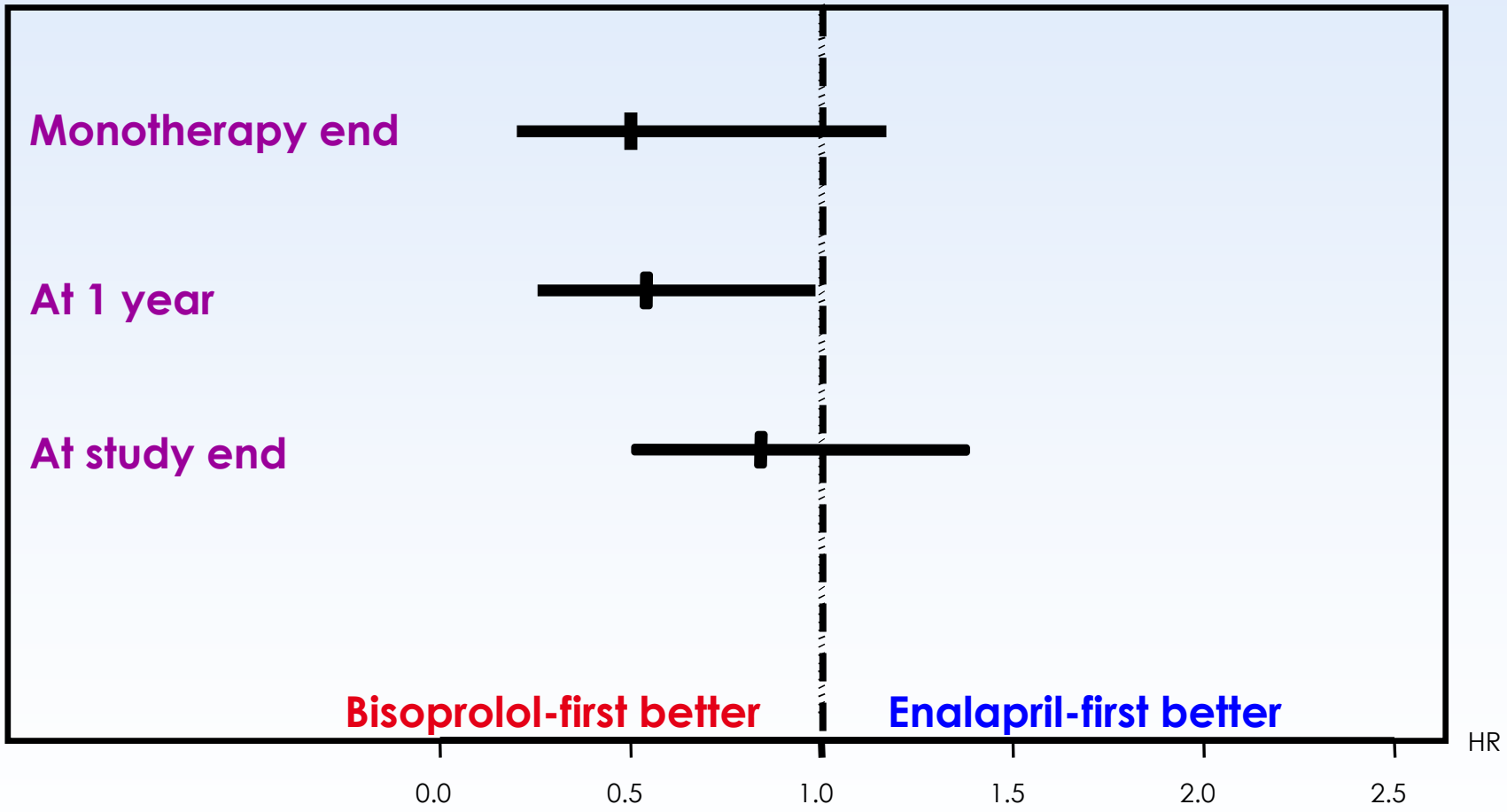
Sudden death – all three time points



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Worsening heart failure or all-cause mortality at all three time points

Bisoprolol-first vs Enalapril-first

at end of monotherapy phase	HR 1.12, 95% CI 0.77-1.64, P=0.54
at one year	HR 0.93, 95% CI 0.69-1.26, P=0.65
at study end	HR 0.98, 95% CI 0.74-1.29, P=0.89

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NYHA class and signs/symptoms of CHF

No difference between treatment strategies in
- change in NYHA class
- change in the 13 signs/symptoms of CHF assessed

In both treatment groups, general improvements were observed

Safety

	Bisoprolol-first (n=504)		Enalapril-first (n=502)	
	Number (%) of patients reporting	Number of reports	Number (%) of patients reporting	Number of reports
Monotherapy phase				
SAEs	113 (22.4)	192	111 (22.1)	163
AEs	316 (62.7)	813	319 (63.5)	861
Entire study period				
SAEs	184 (36.5)	360	187 (37.3)	354
AEs	396 (78.6)	1589	395 (78.7)	1769

All P=NS

Willenheimer et al. Circulation. 2005;112:2426-2435.

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% patients last prescribed at least half of study drug target dose

	Bisoprolol-first	Enalapril-first	
Bisoprolol >= 5 mg x 1	**86%**	**72%**	P<0.001
Enalapril >= 5 mg x 2	**82%**	**90%**	P<0.001

Dose and effect

Multivariable adjustment (19 variables)

Mortality or all-cause hospitalisation	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.53 (0.43 - 0.66)	47% RRR
Used ≥50% of enalapril target dose vs <50%	<0.003	0.59 (0.47 - 0.74)	

Mortality	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.34 (0.23 - 0.50)	66% RRR
Used ≥50% of enalapril target dose vs <50%	<0.012	0.61 (0.41 – 0.90)	

Mortality or CV hospitalisation	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.52 (0.40 - 0.67)	48% RRR
Used ≥50% of enalapril target dose vs <50%	0.003	0.61 (0.47 - 0.79)	

Time-dependent definition of target dose
On treatment rule

Conclusions (1)

Activation of the sympathetic system is vital to the pathophysiology of CHF, indicating that beta-blockade should be extremely valuable for the treatment of patients with CHF.

Conclusions (2)

Beta-blockade has a very well proven benefit on mortality and morbidity in patients with chronic systolic heart failure. It is a MUST in these patients, unless truly contraindicated (which is very rare).

Conclusions (3)

Beta-blockade and ACE inhibition should be combined in patients with chronic systolic heart failure.

Before CIBIS III, there was no evidence about which one (i.e. a beta-blocker or an ACE inhibitor) to initiate first.

Conclusions (4)

CIBIS III showed that initiating either bisoprolol or enalapril first - in patients with stable, chronic, systolic heart failure – were comparable in terms of combined mortality / hospitalisation.

In terms of safety, the two strategies were similar.

Conclusions (5)

CIBIS III showed that initiating bisoprolol first
- in patients with stable, chronic, systolic heart failure –
had some potential benefit in terms of survival,
especially with regards to sudden death.

Clinical implication

The CIBIS III result supports a free choice

of initial treatment for CHF - enalapril or bisoprolol -

based on the physician's individual judgment

in each patient with stable, systolic CHF

Willenheimer et al. Circulation. 2005;112:2426-2435.

Clinical implication

CIBIS III provides substantial support for starting bisoprolol as soon as possible, especially regarding sudden death

Clinical implication

β-blockers should be given early

and never be withheld

from any patient with CHF

unless contraindicated !!!

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Thank you!

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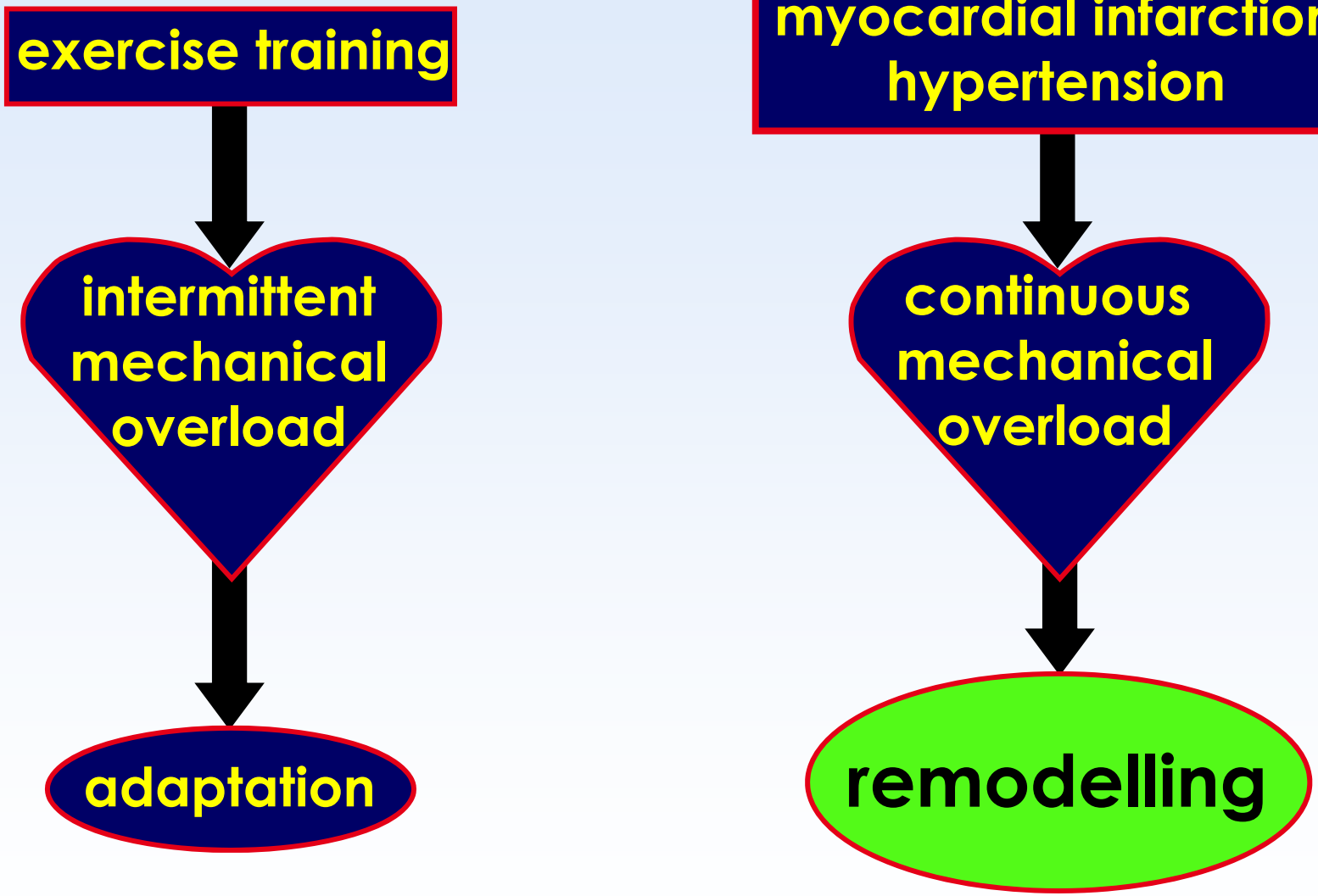
Back-up slides



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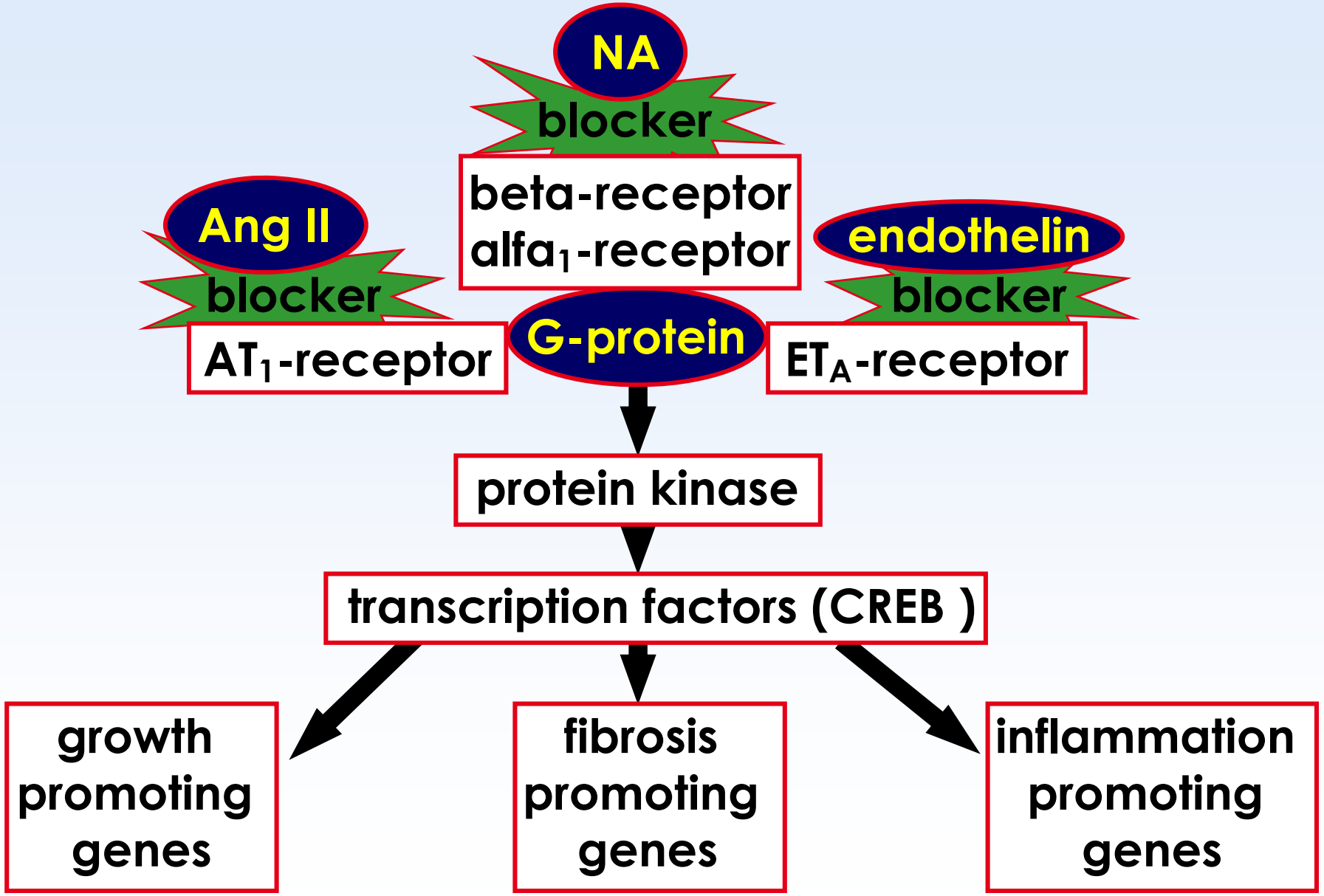

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Clinical implication

A personal consideration

Imagine the opposite prevailing order:

There is nothing in the CIBIS III results supporting to start with enalapril rather than bisoprolol

MERIT-HF

Comparison of findings in subanalysis and entire MERIT-HF cohort

Endpoint	Reductions in entire MERIT-HF cohort	Reductions in class III and IV MERIT-HF subset
Total mortality	-34%	-39%
Sudden death	-41%	-45%
Death due to worsening HF	-49%	-55%

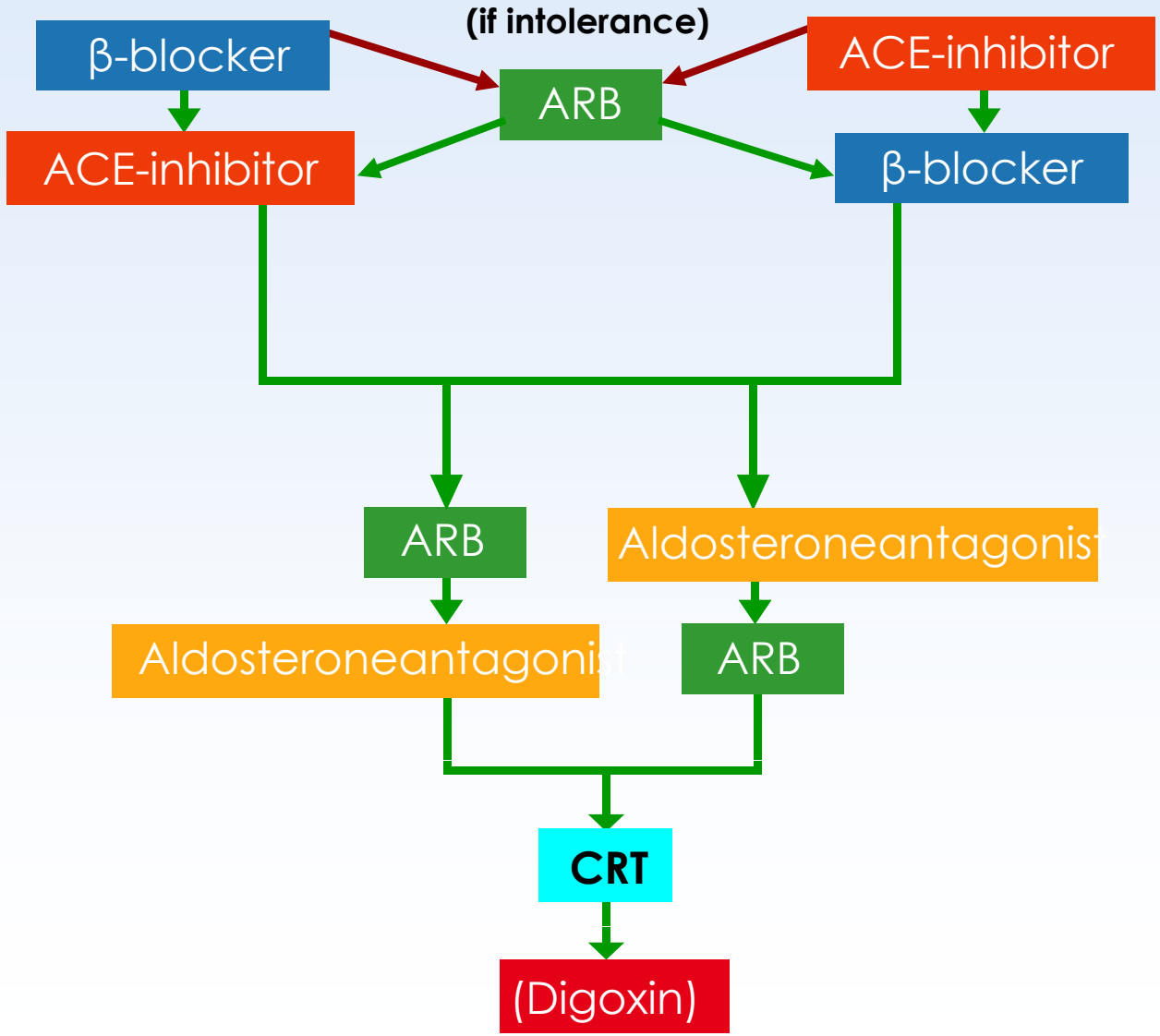
Goldstein S et al. *J Am Coll Cardiol* 2001; 38(4):932-8

Changes during ***monotherapy*** phase in signs/symptoms of CHF

Abs=absent Pres=present		Abs → abs unchanged	Abs → pres worsened	Pres → abs improved	Pres → pres unchanged
Peripheral edema					
Bisoprolol First	**499**	**331 (66.3%)**	**14 (2.8%)**	**83 (16.6%)**	**71 (14.2%)**
Enalapril First	**498**	**331 (66.5%)**	**22 (4.4%)**	**82 (16.5%)**	**63 (12.7%)**
Fatigue					
Bisoprolol First	**499**	**87 (17.4%)**	**17 (3.4%)**	**59 (11.8%)**	**336 (67.3%)**
Enalapril First	**498**	**100 (20.1%)**	**21 (4.2%)**	**54 (10.8%)**	**323 (64.9%)**
Dyspnoea at rest					
Bisoprolol First	**499**	**447 (89.6%)**	**20 (4.0%)**	**21 (4.2%)**	**11 (2.2%)**
Enalapril First	**498**	**449 (90.2%)**	**13 (2.6%)**	**21 (4.2%)**	**15 (3.0%)**
Dyspnoea on exertion					
Bisoprolol First	**499**	**13 (2.6%)**	**3 (0.6%)**	**54 (10.8%)**	**429 (86.0%)**
Enalapril First	**498**	**12 (2.4%)**	**6 (1.2%)**	**54 (10.8%)**	**426 (85.5%)**
Pulmonary crepitations					
Bisoprolol First	**498**	**347 (69.7%)**	**13 (2.6%)**	**89 (17.9%)**	**49 (9.8%)**
Enalapril First	**498**	**340 (68.3%)**	**21 (4.2%)**	**97 (19.5%)**	**40 (8.0%)**

All P=NS

Algorithm for CHF treatment

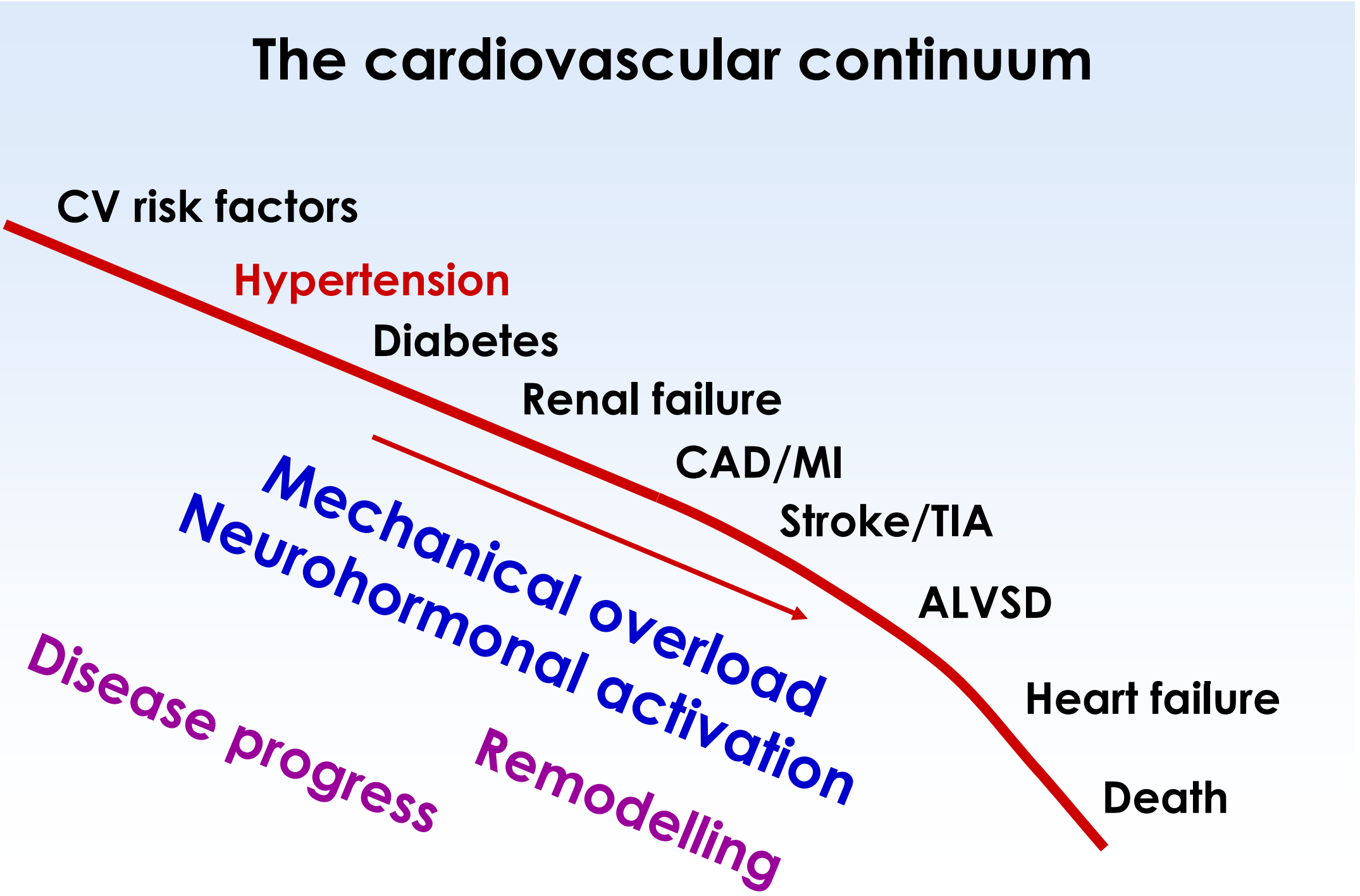


Basic treatment
(start with either in stable patients)

Add-on therapy if continued obvious symptoms

Final step

The cardiovascular continuum



Primary objective

To show that initial mono-therapy with bisoprolol followed by combination therapy with enalapril is *comparable* (non-inferior) to the reverse order in preventing death and hospitalization for all causes (combined endpoint).

Willenheimer et al. Circulation. 2005;112:2426-2435.

Secondary objectives

To compare the primary and secondary endpoints

in terms of superiority for bisoprolol-first.

Willenheimer et al. Circulation. 2005;112:2426-2435.

Endpoints

Primary endpoint

- Combined endpoint of mortality (all cause) and all cause hospitalization throughout the study period (time to event analysis)

Secondary endpoints

End of monotherapy phase

- Combined endpoint of all-cause mortality and hospitalization
- Early introduction of the second drug due to poor control of CHF

End of monotherapy phase + end of study

- Individual components of the primary endpoint
- Number of permanent treatment cessations
- Changes in NYHA class

Willenheimer et al. Circulation. 2005;112:2426-2435.

Exclusion criteria

- > 7 days ACEi, ARB or β-blocker within last 3 months
- PTCA or bypass surgery planned or performed within last 3 months
- Stroke within 1 month or with permanent neurological damage within last 6 months
- Resting heart rate < 60 beats per minute (without a pacemaker)
- Resting SBP < 100mm Hg
- Serum creatinine >= 220 µmol/l
- > 1st degree AV-block without a pacemaker
- Chronic obstructive lung disease, which would contraindicate bisoprolol at the discretion of the investigator

Willenheimer et al. Circulation. 2005;112:2426-2435.

Other secondary endpoints (ITT)

	Bisoprolol-first	Enalapril-first	P
Early introduction of second drug	39 (7.7%)	37 (7.3%)	0.81
Permanent treatment cessation			
Monotherapy phase	35 (6.9%)	49 (9.7%)	0.11
Total	82 (16.2%)	76 (15.0%)	0.60

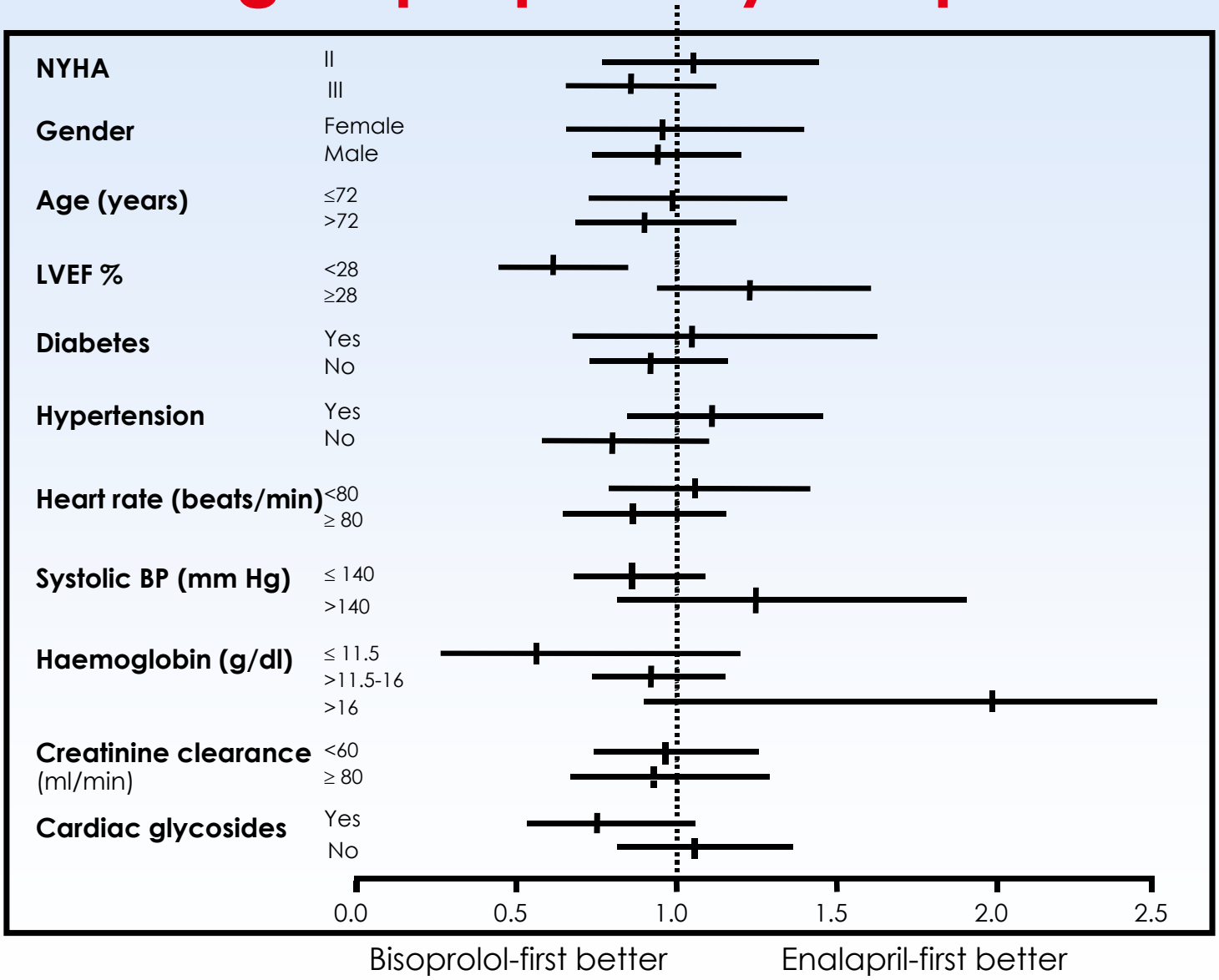
Willenheimer et al. Circulation. 2005;112:2426-2435.

Other secondary endpoints (ITT)

		Bisoprolol-first	Enalapril-first	P
Early introduction of second drug		39 (7.7%)	37 (7.3%)	0.81
Permanent treatment cessation				
Monotherapy phase		35 (6.9%)	49 (9.7%)	0.11
Combination phase	Bi(so)	19 (4.2%)	24 (5.5%)	0.37
	(Enal)	47 (10.4%)	16 (3.7%)	<0.0001
Total		82 (16.2%)	76 (15.0%)	0.60

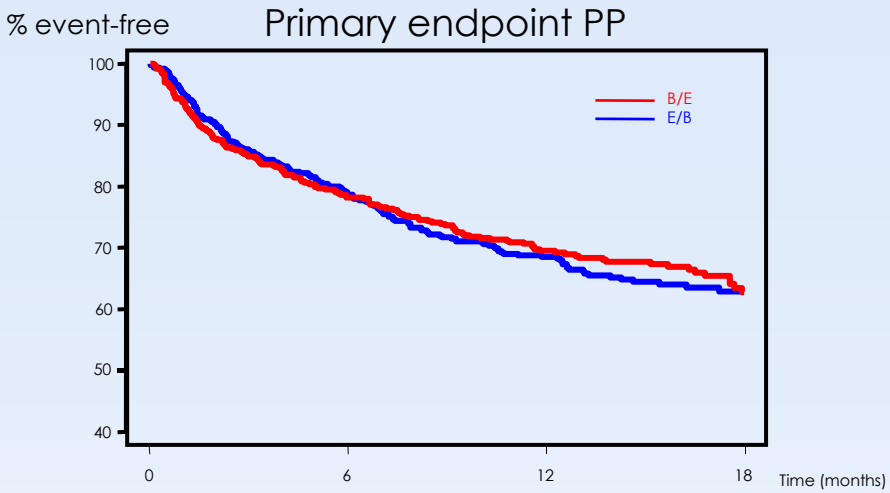
Willenheimer et al. Circulation. 2005;112:2426-2435.

Subgroups: primary endpoint

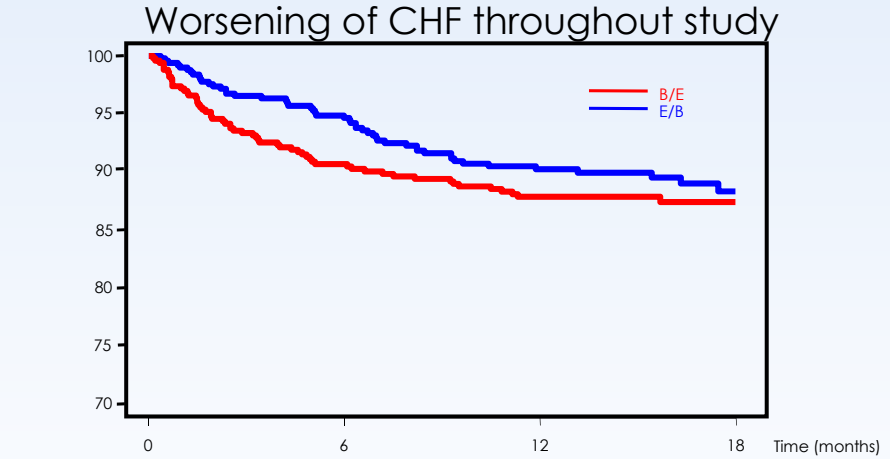


Willenheimer et al. Circulation. 2005;112:2426-2435.

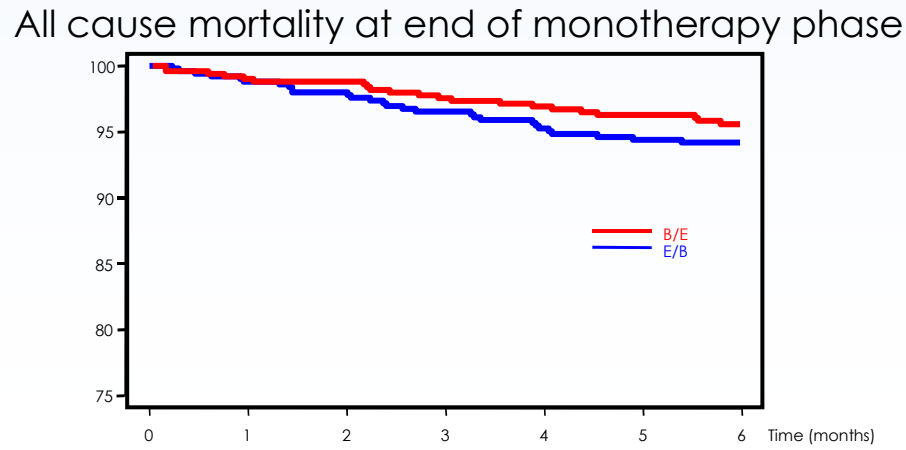
Thoughts for the future



Bisoprolol-first achieved clinically comparable survival and all-cause hospitalization compared with enalapril-first.



Bisoprolol-first was associated with a trend towards increased worsening of CHF in the early phase of treatment.



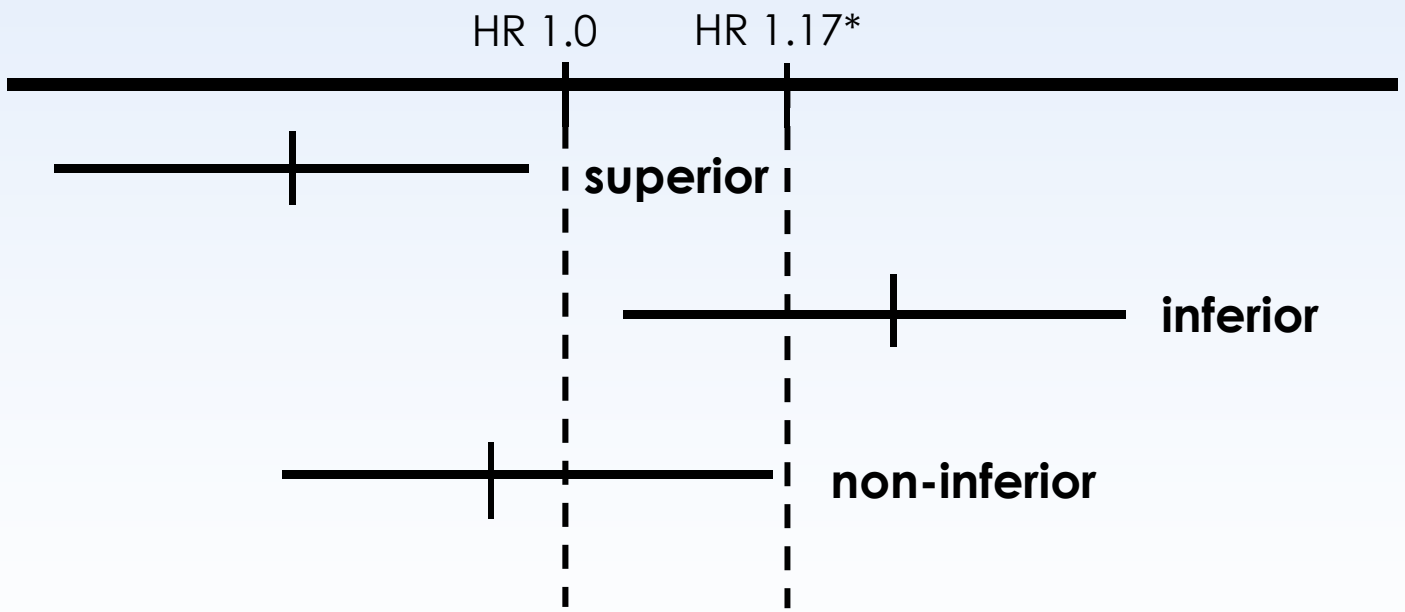
Bisoprolol-first showed a trend towards improved survival during the early study phase (which was maintained during combined therapy).

Thoughts for the future

- Bisoprolol-first might increase survival in the early phase of treatment, allowing a greater number of patients to subsequently benefit from combined β-blocker + ACEi.
- The bisoprolol-first strategy could be further improved with greater experience of up-titration of the β-blocker-first, leading to less worsening of CHF.
- This should be further examined.

Statistical analysis

Bisoprolol-first
versus
Enalapril-first



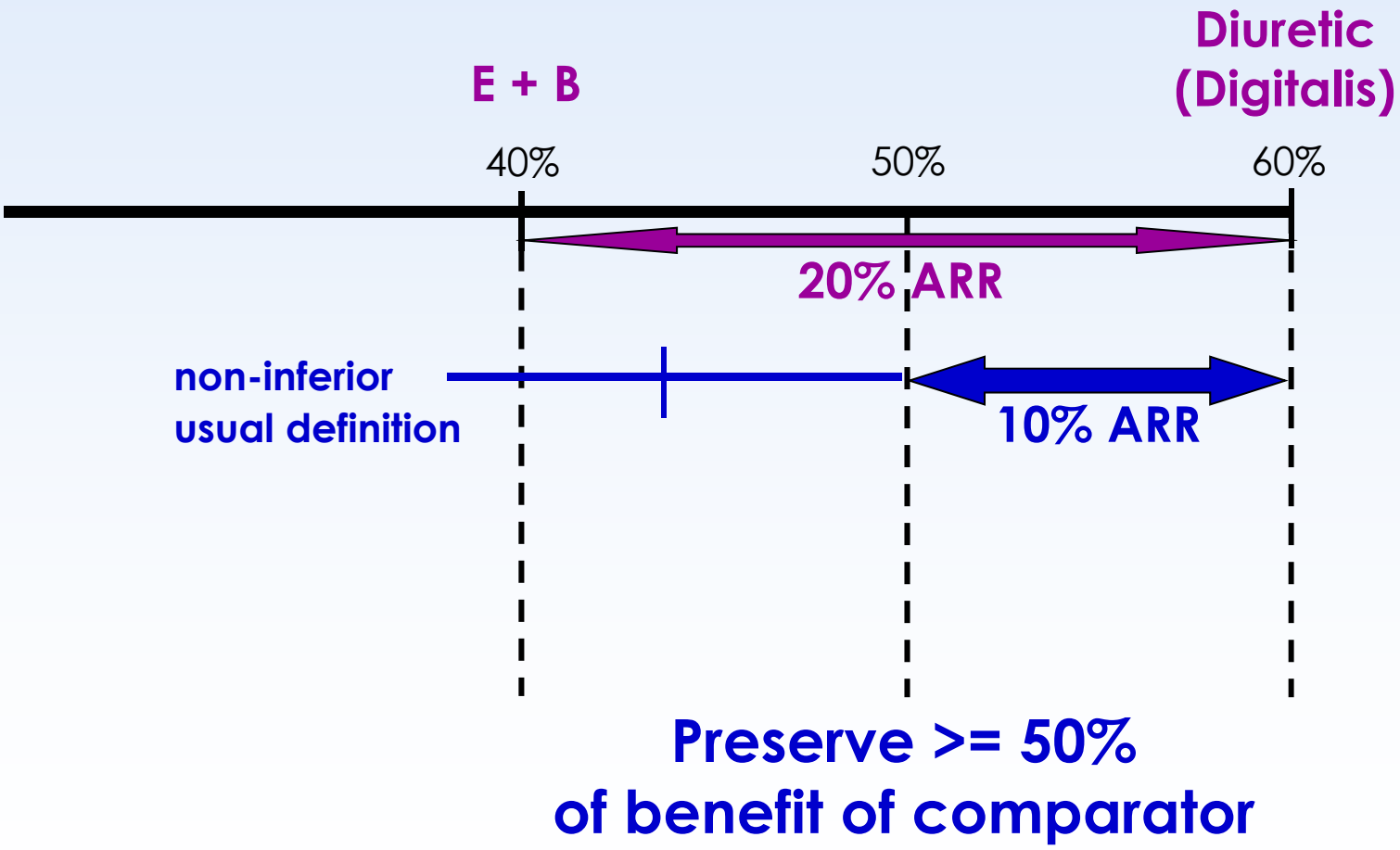
HR=Hazard ratio
(Risk by time-to-event analysis)

* RR 1.125
AR +5%

Willenheimer et al. Circulation. 2005;112:2426-2435.

Statistical analysis

Absolute risk of mortality / hospitalization



Statistical analysis

Absolute risk of mortality / hospitalization

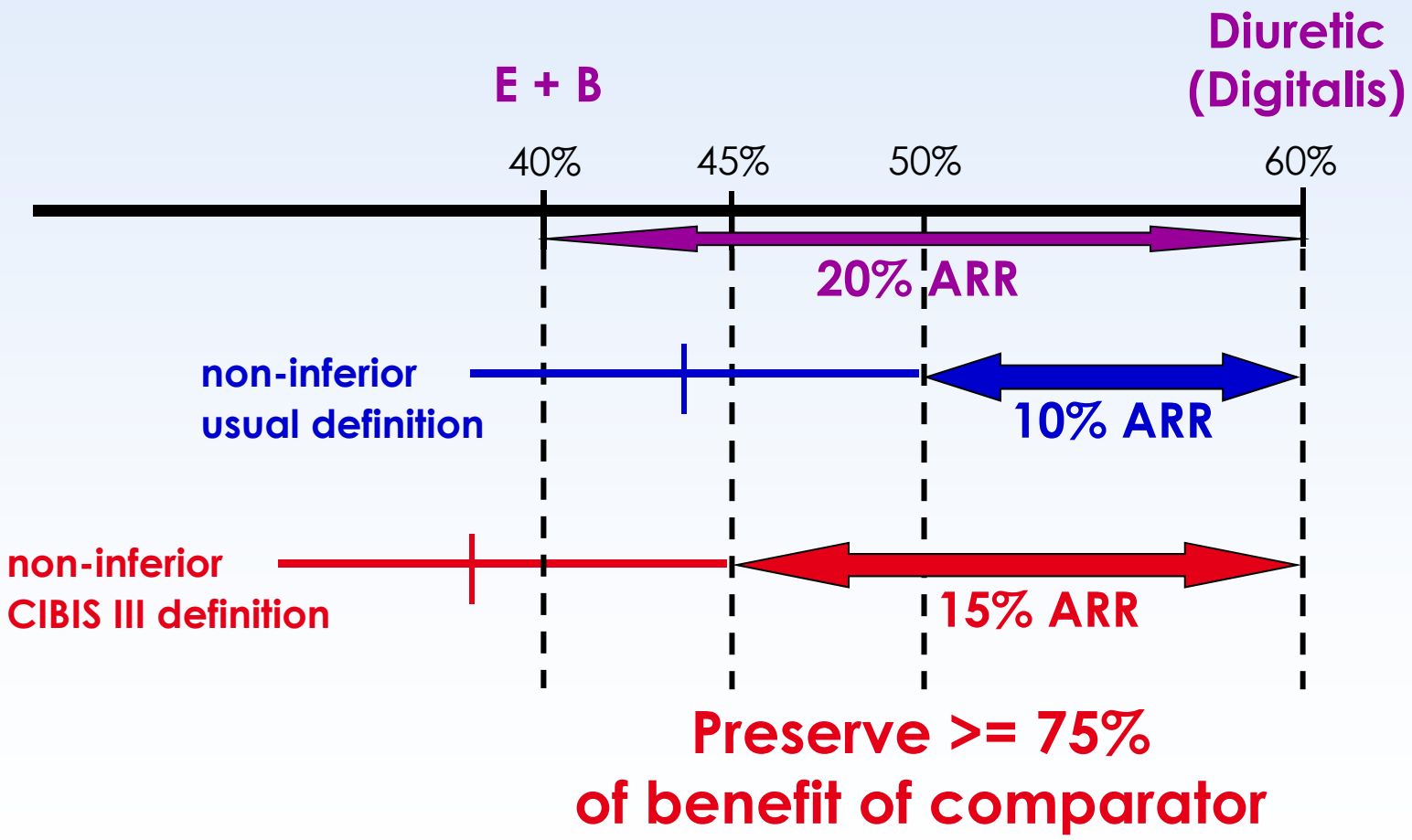


Table 1. Baseline data

		Bisoprolol-first (n=505)		Enalapril-first (n=505)	
		mean/n	%/SD	mean/n	%/SD
Age, years		72.4	5.8	72.5	5.7
Males		333	65.9	356	70.5
NYHA class II/III		245/260	48.5/51.5	250/255	49.5/50.5
Median duration of CHF, months		20		18	
Left ventricular ejection fraction, %		28.8	4.8	28.8	5.2
Serum creatinine, umol/l		99.6	26.1	101.9	26.9
Heart rate, beats per minute		78.8	13.8	79.5	13.2
Systolic BP, mm Hg		134.5	17.0	133.7	16.5
Etiology*	coronary artery disease	309	61.2	321	63.6
	hypertension	197	39.0	172	34.1
	valvular heart disease	11	2.2	15	3.0
	primary cardiomyopathy	49	9.7	51	10.1
	other	68	13.5	50	9.9
History of hypertension		354	70.1	314	62.2
History of myocardial infarction		254	50.3	243	48.1
History of angina pectoris		259	51.3	255	50.5
History of peripheral vascular disease		37	7.3	56	11.1
History of cerebrovascular disease		52	10.3	49	9.7
History of diabetes		95	18.8	113	22.4

History of renal disease	93	18.4	89	17.6
History of anemia	10	2.0	8	1.6
Prior PCI	22	4.4	18	3.6
Prior CABG	45	8.9	40	7.9
Pacemaker	38	7.5	33	6.5
Baseline diuretic treatment	430	85.1	421	83.4
Thiazide diuretics	97	19.2	115	22.8
Loop diuretics	361	71.5	338	66.9
Potassium sparing diuretics	52	10.3	53	10.5
Aldosterone-receptor blockers	72	14.3	62	12.3
Baseline antiplatelet medication	345	68.3	334	66.1
Baseline cardiac glycoside treatment	166	32.9	155	30.7
Baseline hypoglycemic medication	72	14.3	86	17.0

Table 2. Reasons* for permanent cessation of study medication during the entire study period.

	Bisoprolol-first	Enalapril-first	Total
Total number of patients	101	89	190
Partly or fully withdrawn consent	79	58	137
Met exclusion criterion	1	5	6
Needed non-permitted medication	3	8	11
Lost to follow-up	3	2	5
Non-specified	12	6	18
Adverse events	48	51	99
Cardiac disorders	14	17	31
Respiratory and thoracic disorders	10	16	26
Vascular disorders	13	12	25
Nervous system disorders	7	5	12
Gastrointestinal disorders	2	5	7
Various events	12	18	30

* Reasons are not mutually exclusive.

Table 4. Protocol violations.

	Bisoprolol-first (n=505, 100%)	Enalapril-first (n=505, 100%)	Total (n=1010, 100%)
Adjudicated reason	n (%)	n (%)	n (%)
Entirely excluded from PP analysis	2 (0.4)	7 (1.4)	9 (0.9)
Some data excluded from PP analysis*	83 (16.4)	78 (15.4)	161 (15.9)
Unstable CHF within 7 days prior to randomization	0 (0.0)	1 (0.2)	1 (0.1)
Non-permitted treatment prior to randomization	1 (0.2)	2 (0.4)	3 (0.3)
Failure to meet inclusion criteria	0 (0.0)	1 (0.2)	1 (0.1)
Never took any study medication	1 (0.2)	3 (0.6)	4 (0.4)
Never started second drug	4 (0.8)	7 (1.4)	11 (1.1)
Inadequate study medication compliance	3 (0.6)	2 (0.4)	5 (0.5)
Medically illegitimate early introduction of second drug	33 (6.5)	21 (4.2)	54 (5.3)
Medically illegitimate PTC	48 (9.5)	48 (9.5)	96 (9.5)

PP, per-protocol; PTC, permanent treatment cessation.

There were no statistically significant between-group differences.

* Data were included in the PP analysis until the time of the protocol violation.

Table 6. Effects on blood pressure and heart rate.

	n	Bisoprolol-first	n	Enalapril-first
Systolic BP, mm Hg (SD)				
Baseline	505	134.5 (17.0)	505	133.7 (16.5)
End of monotherapy	497	128,5 (16,9)	498	128,2 (17,9)
At 1 year	416	124,8 (17,2)	404	124,8 (17,2)
Diastolic BP, mm Hg (SD)				
Baseline	505	80.4 (10.0)	505	80.7 (9.5)
End of monotherapy	497	76.4 (9.8)	498	77.0 (10.2)
At 1 year	416	74,5 (10.0)	404	75,0 (9,5)
Heart rate, beats per minute (SD)				
Baseline	505	78.8 (13.8)	505	79.5 (13.2)
End of monotherapy	497	67.9 (13.7)*	498	78.6 (15.0)*
At 1 year	417	66,7 (11,8)	405	67,5 (12,7)

BP, blood pressure; SD, standard deviation

* Between-group difference P<0.001 (besides this there were no significant between-group differences).

Steering Committee

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Willenheimer et al. Circulation. 2005;112:2426-2435.

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US Carvedilol Heart Failure Trials Program

- 1094 patients, NYHA class II - IV, LVEF ≤ 35 %
- Mean age 58 years, 77 % men
- Standard treatment for CHF incl. ACEi
- DB, randomised, placebo vs carvedilol (1:2) 25-50 mg x 2
- Mean dose carvedilol 45 mg/d, placebo 60 mg/d
- 6.5 months median follow-up (premature interruption)
- Mortality 65 % lower on carvedilol: 3.2 vs 7.8 % (p<0.001)
- 27 % reduction of CV hospitalisation (p=0.036)

NEJM 1996; 334: 1349-55

Metoprolol MERIT-HF

- 3991 patients, NYHA class II-III(IV), LVEF < 40 %
- Mean age 64 years, 77 % men
- Standard treatment for heart failure incl ACEi
- DB, randomised, placebo vs metoprolol CR/XL 200 mg/d
- 64 % on target dose at 3 months
- Premature interruption
- Mortality 34 % lower on metoprolol (p=0,0062)
- Annual mortality 7.2 vs 11 %
- Sudden death 41 % less (p=0.0002)

Lancet 1999; 353: 2001-7

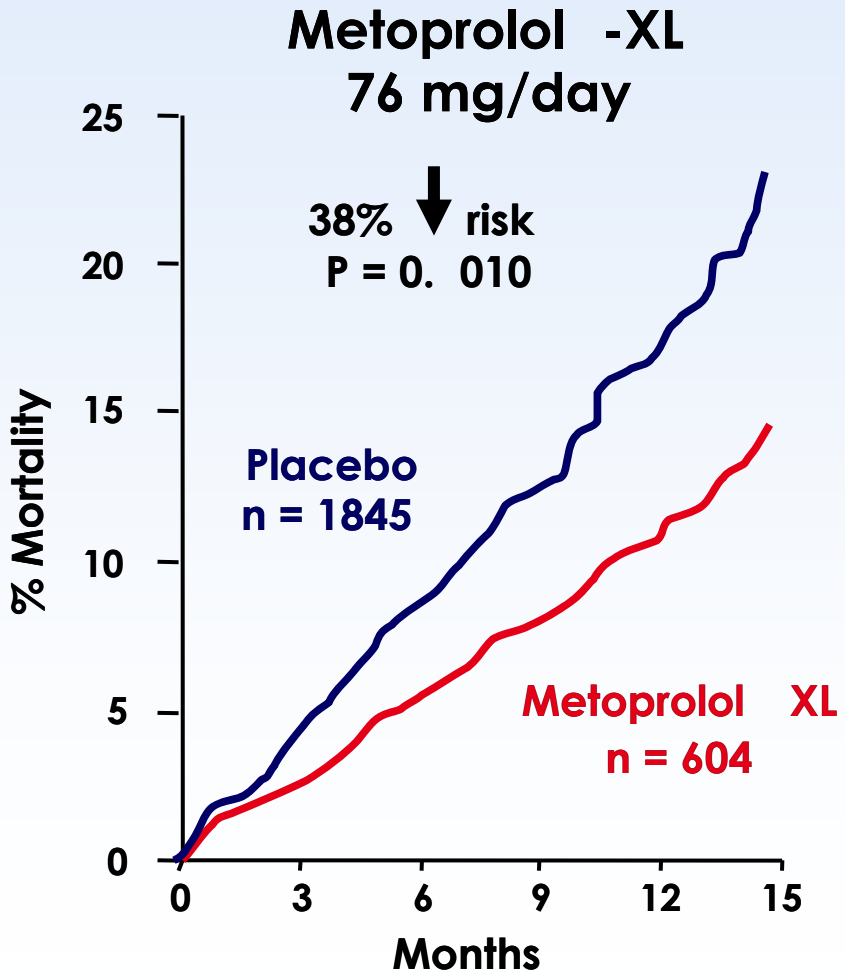
Carvedilol COPERNICUS

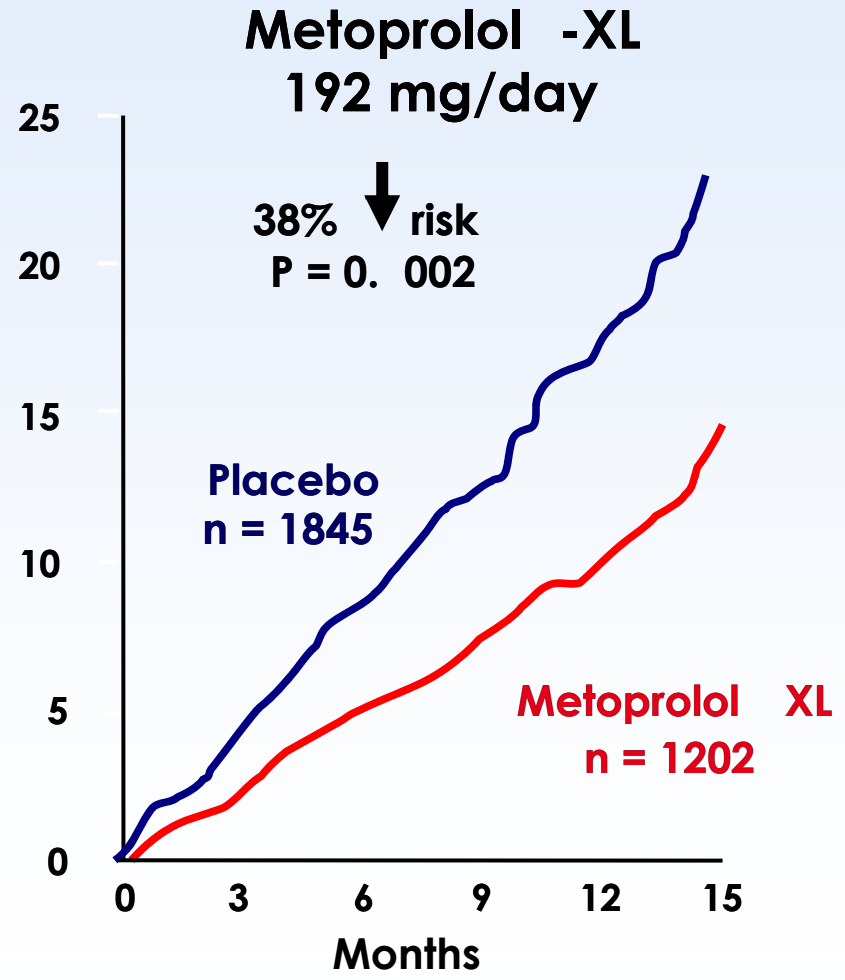
- 2289 patients, NYHA class IV, LVEF < 25 %, ”stabilised”
- Standard treatment for heart failure incl ACEi
- DB, randomised, placebo vs carvedilol 25 mg x 2 (target)
- Mean follow-up 10.4 months (premature interruption)
- Mortality 35 % lower on carvedilol (p=0,0014)
- 130 vs 190 deaths
- Annual mortality in placebo group 18.5 %
- 1000 treated for 3 years saved 200 lives
- Consistency across all subgroups

NEJM 2001; 344:1711-2

MERIT-HF Dosing Analysis

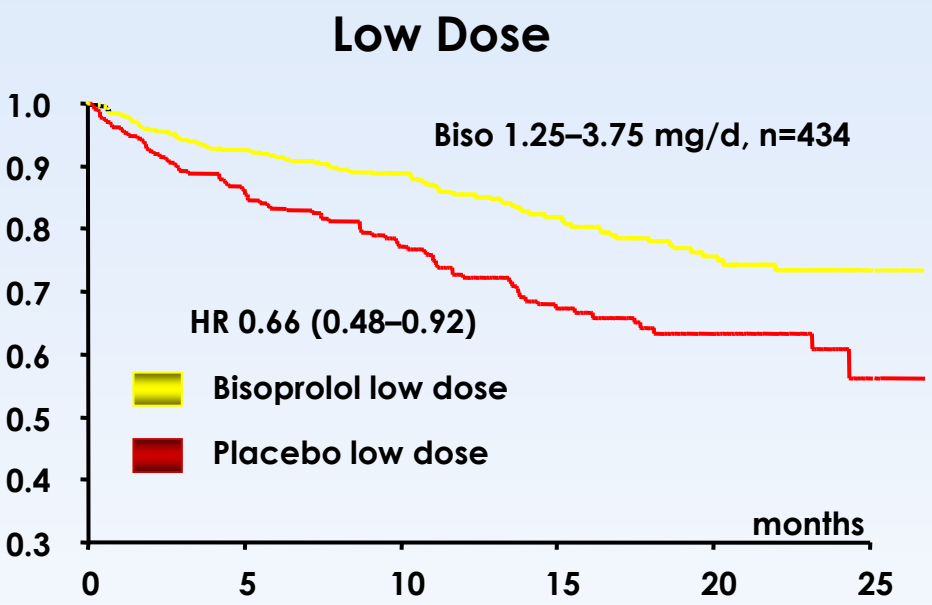
Effect of Dose on Survival Benefit

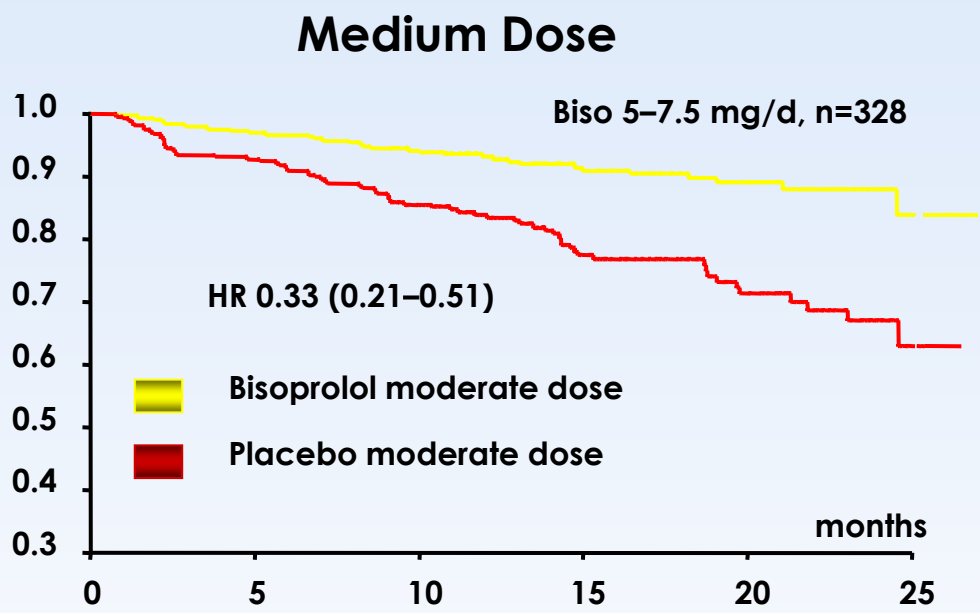


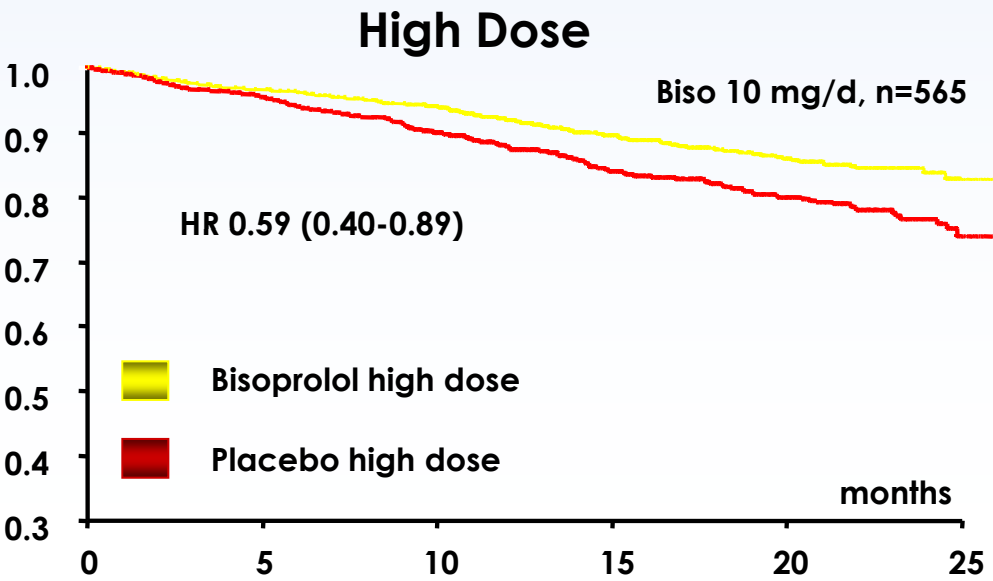


Wikstrand J et al. JACC 2002

CIBIS II Achieved Dose Analysis







Simon T et al.,
Eur Heart J 2003

Changes during ***monotherapy*** phase in signs/symptoms of CHF

Abs=absent Pres=present		Abs → abs unchanged	Abs → pres worsened	Pres → abs improved	Pres → pres unchanged
Peripheral edema					
Bisoprolol First	**499**	**331 (66.3%)**	**14 (2.8%)**	**83 (16.6%)**	**71 (14.2%)**
Enalapril First	**498**	**331 (66.5%)**	**22 (4.4%)**	**82 (16.5%)**	**63 (12.7%)**
Fatigue					
Bisoprolol First	**499**	**87 (17.4%)**	**17 (3.4%)**	**59 (11.8%)**	**336 (67.3%)**
Enalapril First	**498**	**100 (20.1%)**	**21 (4.2%)**	**54 (10.8%)**	**323 (64.9%)**
Dyspnoea at rest					
Bisoprolol First	**499**	**447 (89.6%)**	**20 (4.0%)**	**21 (4.2%)**	**11 (2.2%)**
Enalapril First	**498**	**449 (90.2%)**	**13 (2.6%)**	**21 (4.2%)**	**15 (3.0%)**
Dyspnoea on exertion					
Bisoprolol First	**499**	**13 (2.6%)**	**3 (0.6%)**	**54 (10.8%)**	**429 (86.0%)**
Enalapril First	**498**	**12 (2.4%)**	**6 (1.2%)**	**54 (10.8%)**	**426 (85.5%)**
Pulmonary crepitations					
Bisoprolol First	**498**	**347 (69.7%)**	**13 (2.6%)**	**89 (17.9%)**	**49 (9.8%)**
Enalapril First	**498**	**340 (68.3%)**	**21 (4.2%)**	**97 (19.5%)**	**40 (8.0%)**

All P=NS

% patients last prescribed at least half of study drug target dose

	Bisoprolol-first	Enalapril-first	
Bisoprolol >= 5 mg x 1	**86%**	**72%**	P<0.001
Enalapril >= 5 mg x 2	**82%**	**90%**	P<0.001

Dose and effect

Multivariable adjustment (19 variables)

Mortality or all-cause hospitalisation	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.53 (0.43 - 0.66)	47% RRR
Used ≥50% of enalapril target dose vs <50%	<0.003	0.59 (0.47 - 0.74)	

Mortality	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.34 (0.23 - 0.50)	66% RRR
Used ≥50% of enalapril target dose vs <50%	<0.012	0.61 (0.41 – 0.90)	

Mortality or CV hospitalisation	p	HR (95% CI)	
Used ≥50% of bisoprolol target dose vs <50%	<0.0001	0.52 (0.40 - 0.67)	48% RRR
Used ≥50% of enalapril target dose vs <50%	0.003	0.61 (0.47 - 0.79)	

Time-dependent definition of target dose
On treatment rule