



CIBIS III

Cardiac Insufficiency Bisoprolol Study III

**Effect on survival and hospitalization
of initiating treatment for chronic heart failure
with bisoprolol followed by enalapril,
as compared with the opposite sequence**

Results of the randomized
Cardiac Insufficiency Bisoprolol (CIBIS) III trial

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on behalf of the CIBIS III investigators



Background (1)

- Guidelines universally recommend that treatment of patients with chronic heart failure (CHF) should be initiated with an angiotensin-converting enzyme inhibitor (ACEi) to which a β -blocker should be added as second step therapy.
- These recommendations are not based on evidence.
- No study has examined the safety and efficacy of initiating CHF treatment with an ACEi versus a β -blocker.
- Several mechanistic reasons support choosing beta-blockade as first therapy in CHF.

Background (2)

- Sympathetic nervous system is activated prior to RAAS in CHF.
- In the early course of CHF, sudden death is the most prevalent mode of death.
- β -blockers in contrast to ACEi are proven highly effective in reducing sudden death.
- From the pathophysiological point of view it may be appropriate to start with a β -blocker first.

Hypothesis

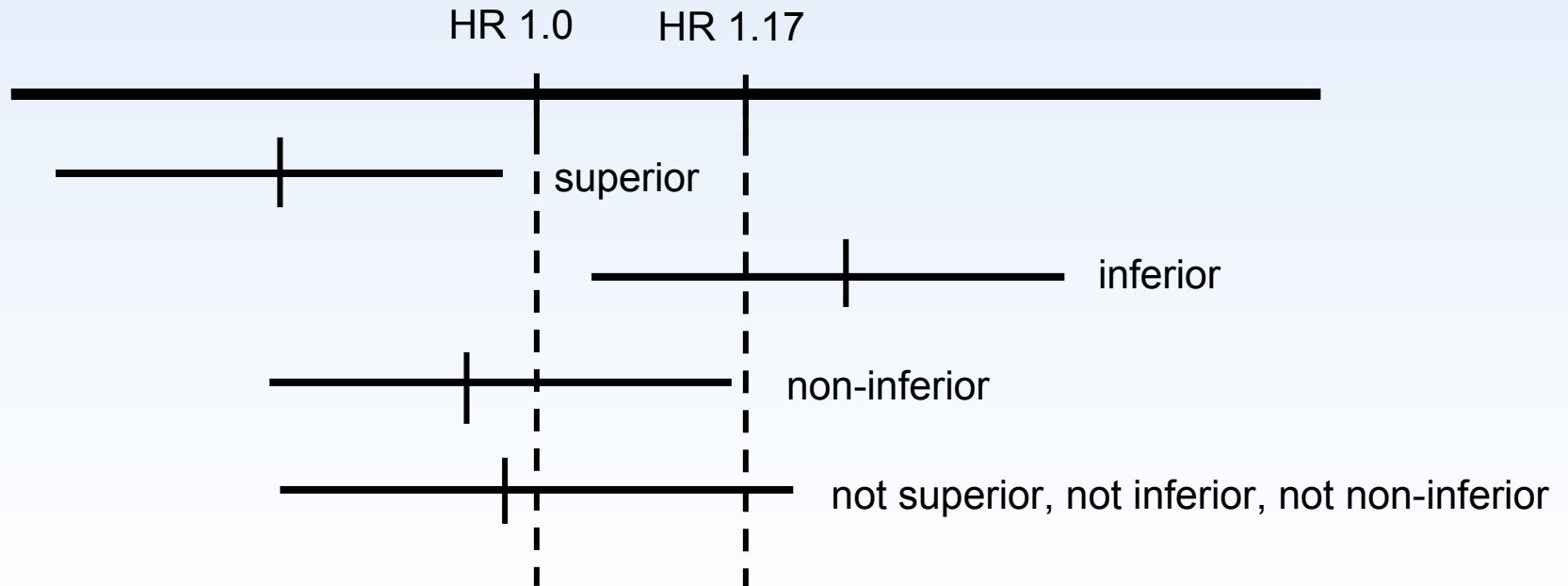
Initiation of treatment in patients with CHF with the β_1 -selective β -blocker bisoprolol (to which enalapril is subsequently added) is as effective and safe as a regimen beginning with the ACEi enalapril (to which bisoprolol is subsequently added).

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).

Statistical analysis

Bisoprolol-first
versus
Enalapril-first



HR=Hazard ratio

HR 1.17 = AR +5.0%

Secondary objectives

To compare the primary and secondary endpoints
in terms of superiority for bisoprolol-first.

Endpoints

Primary endpoint

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

Secondary endpoints

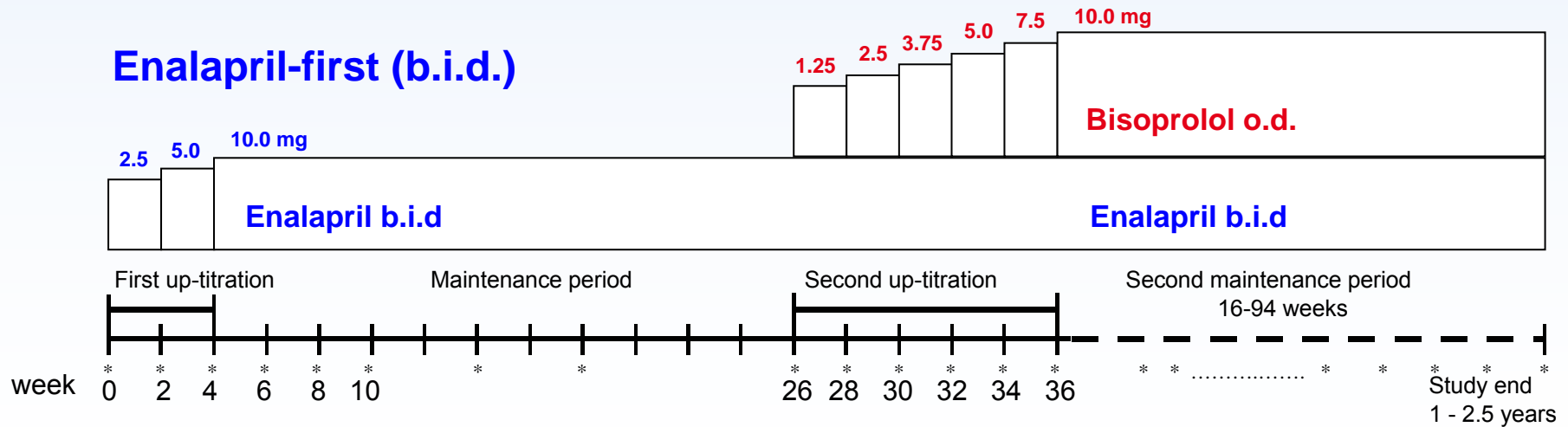
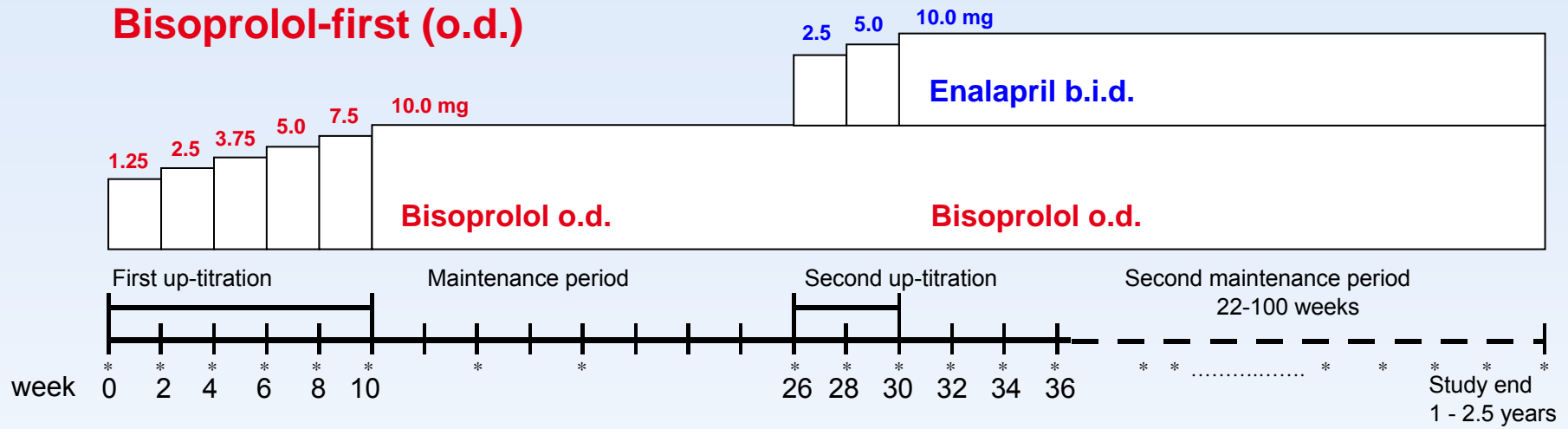
End of monotherapy phase

- 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

Study design



Study design

- Investigator-initiated, multi-center, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) trial
- Independent
 - steering committee
 - data safety monitoring board
 - masked endpoint committee
 - clinical trial data center

Inclusion criteria

- Age \geq 65 years
- Mild to moderate CHF (NYHA class II or III)
- LVEF \leq 35%
- Stable CHF since \geq 7 days
(without clinically relevant fluid retention/diuretic adjustment)

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 \geq 220 $\mu\text{mol/l}$
- > 1st degree AV-block without a pacemaker
- Chronic obstructive lung disease, which would contraindicate bisoprolol at the discretion of the investigator

Participating Countries

128 centers in 20 countries

Austria
Belgium
Switzerland
Czech Republic
France
Germany
The Netherlands
Italy
Portugal

Poland
Sweden
Norway
Slovakia
UK/Ireland
Russia
Croatia
Hungary
Romania

Tunisia

Australia

1010 patients

5 pts LTFU
3 bisoprolol-first
2 enalapril-first

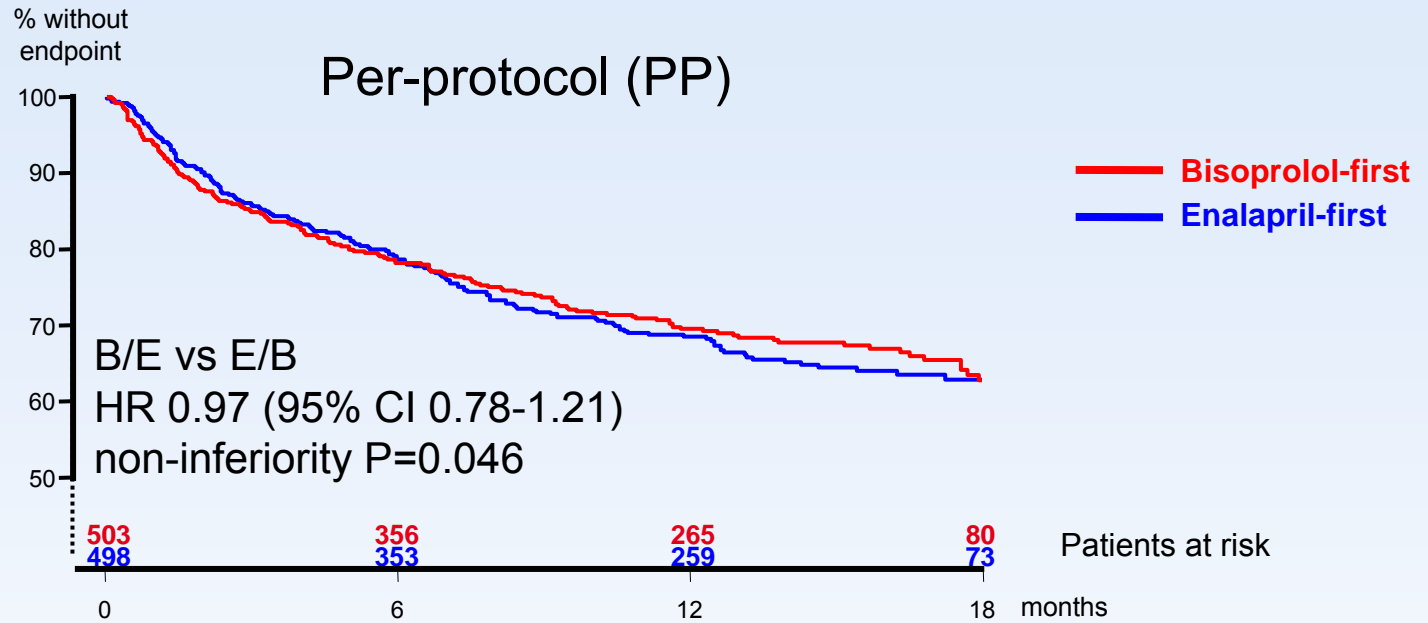
October 2002 - May 2005

Baseline data

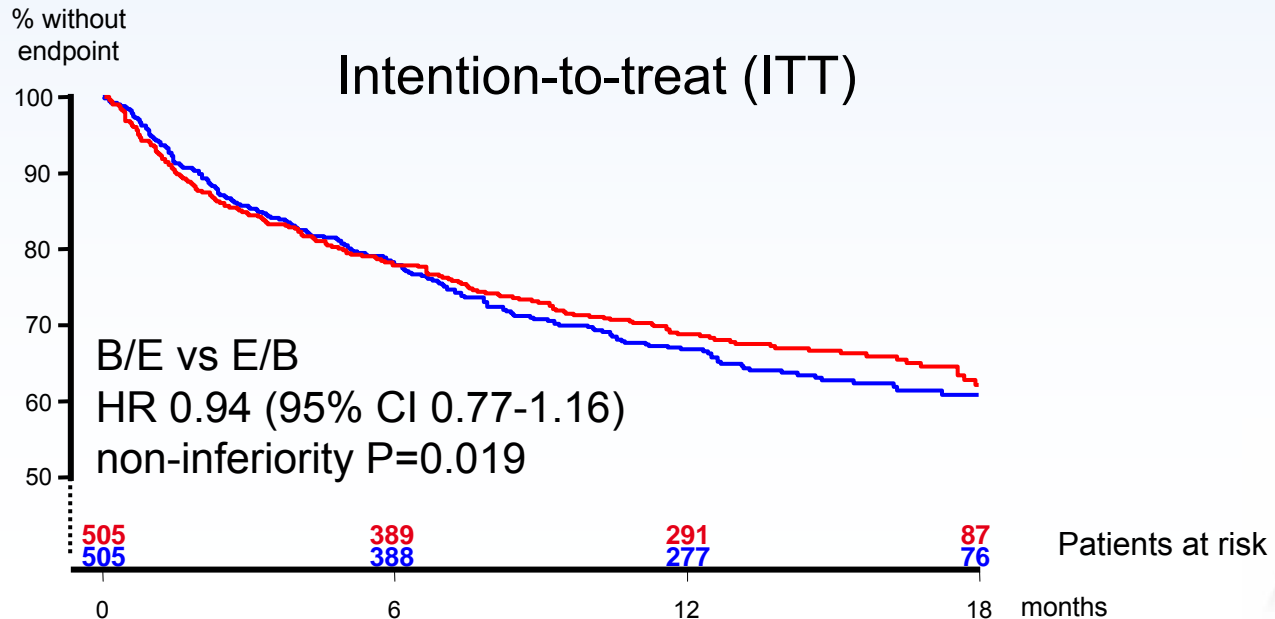
	Bisoprolol-first (n=505) Mean / n	% / SD	Enalapril-first (n=505) Mean / n	% / SD
Age (years)	72.4	5.8	72.5	5.7
Males	333	65.9	356	70.5
NYHA Class II/III	245 / 260	48.5 / 51.5	250 / 255	49.5 / 50.5
LVEF (%)	28.8	4.8	28.8	5.2
Heart rate (bpm)	78.8	13.8	79.5	13.2
BP (mm Hg)	134 / 80	17 / 10	134 / 81	17 / 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

Primary endpoint

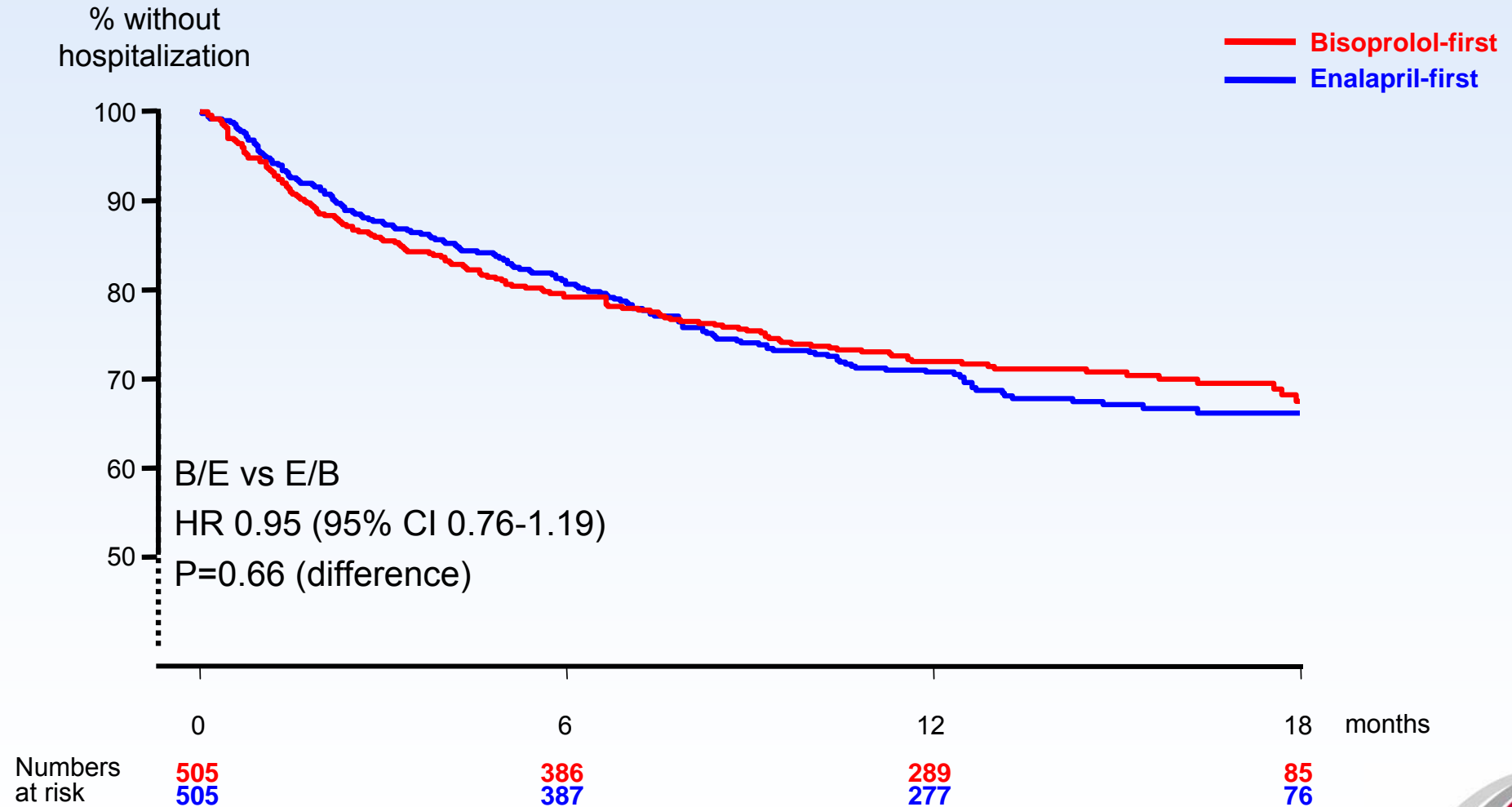
Mean follow-up
1.25 years



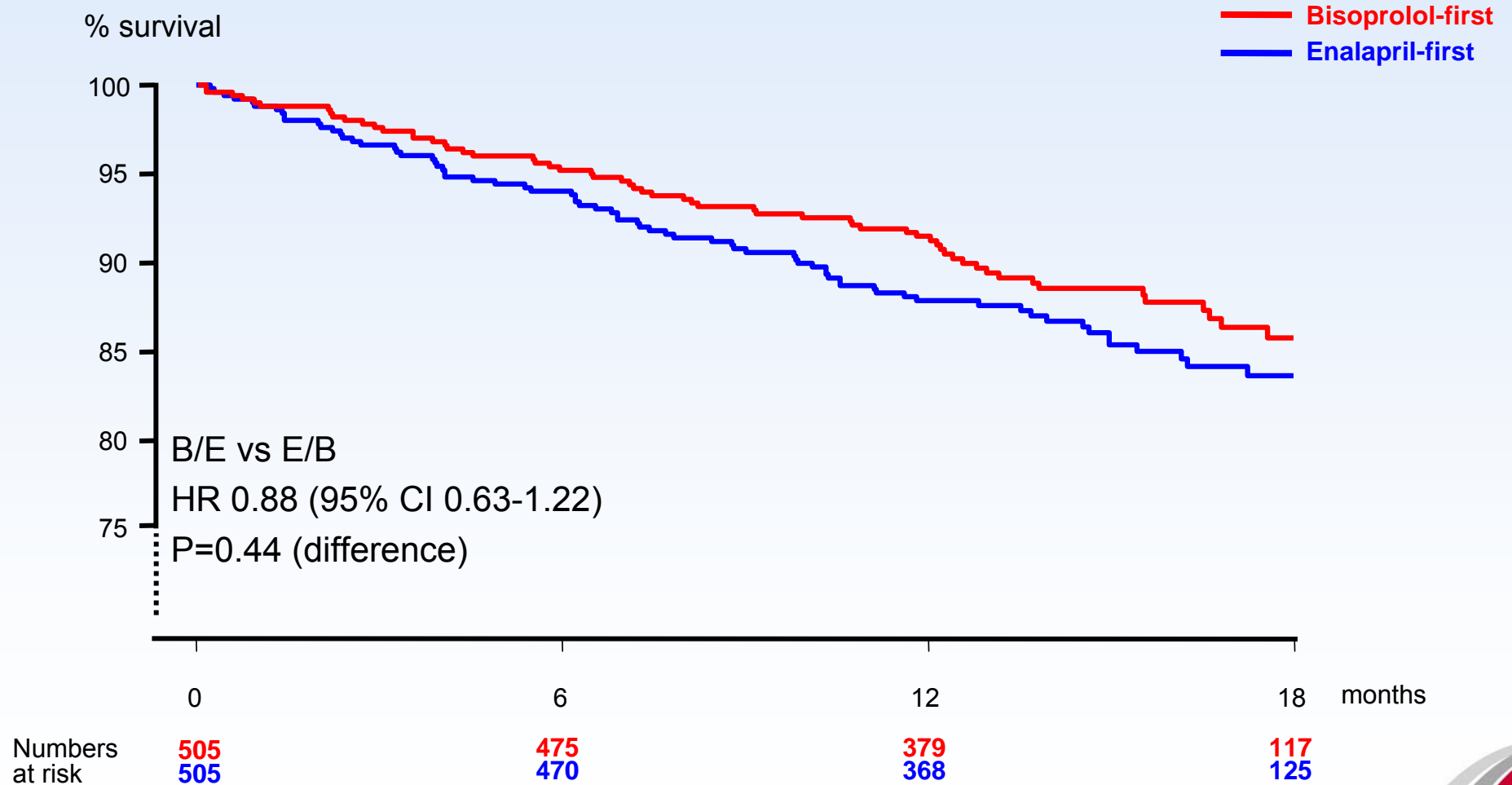
For non-inferiority
P<0.025 denotes
statistical significance
(unilateral test)



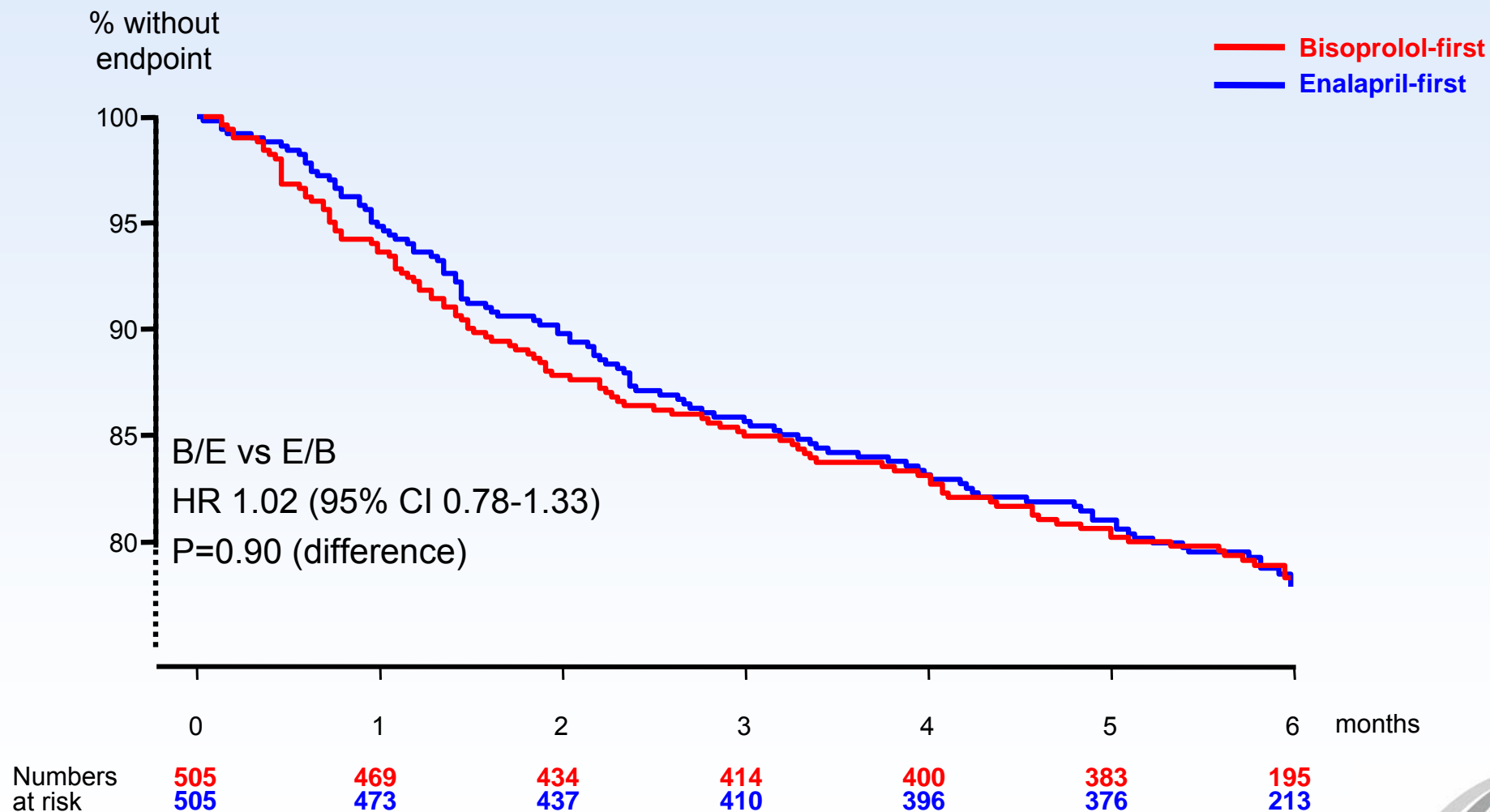
All-cause hospitalization throughout study (ITT)



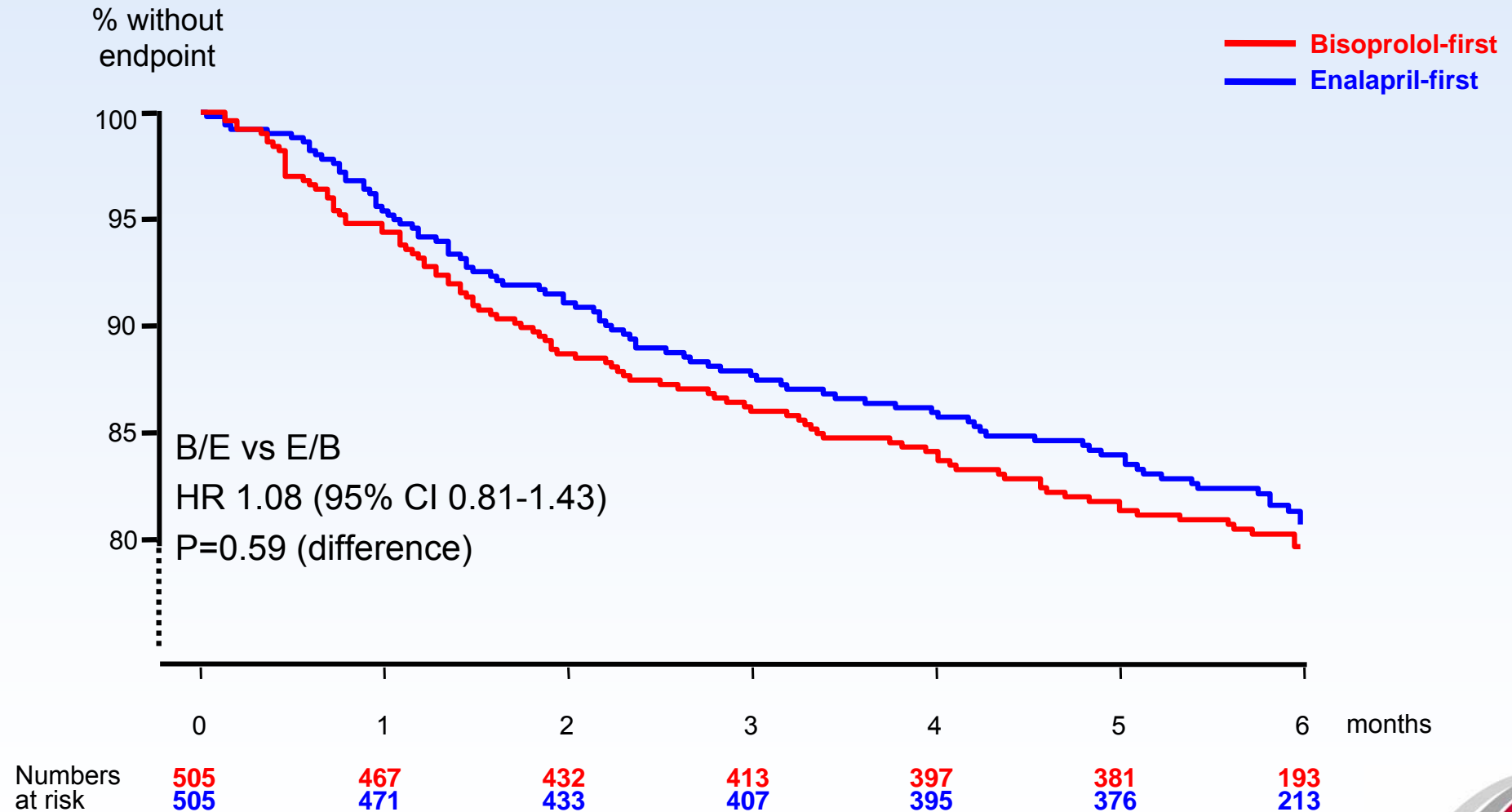
All cause mortality throughout study (ITT)



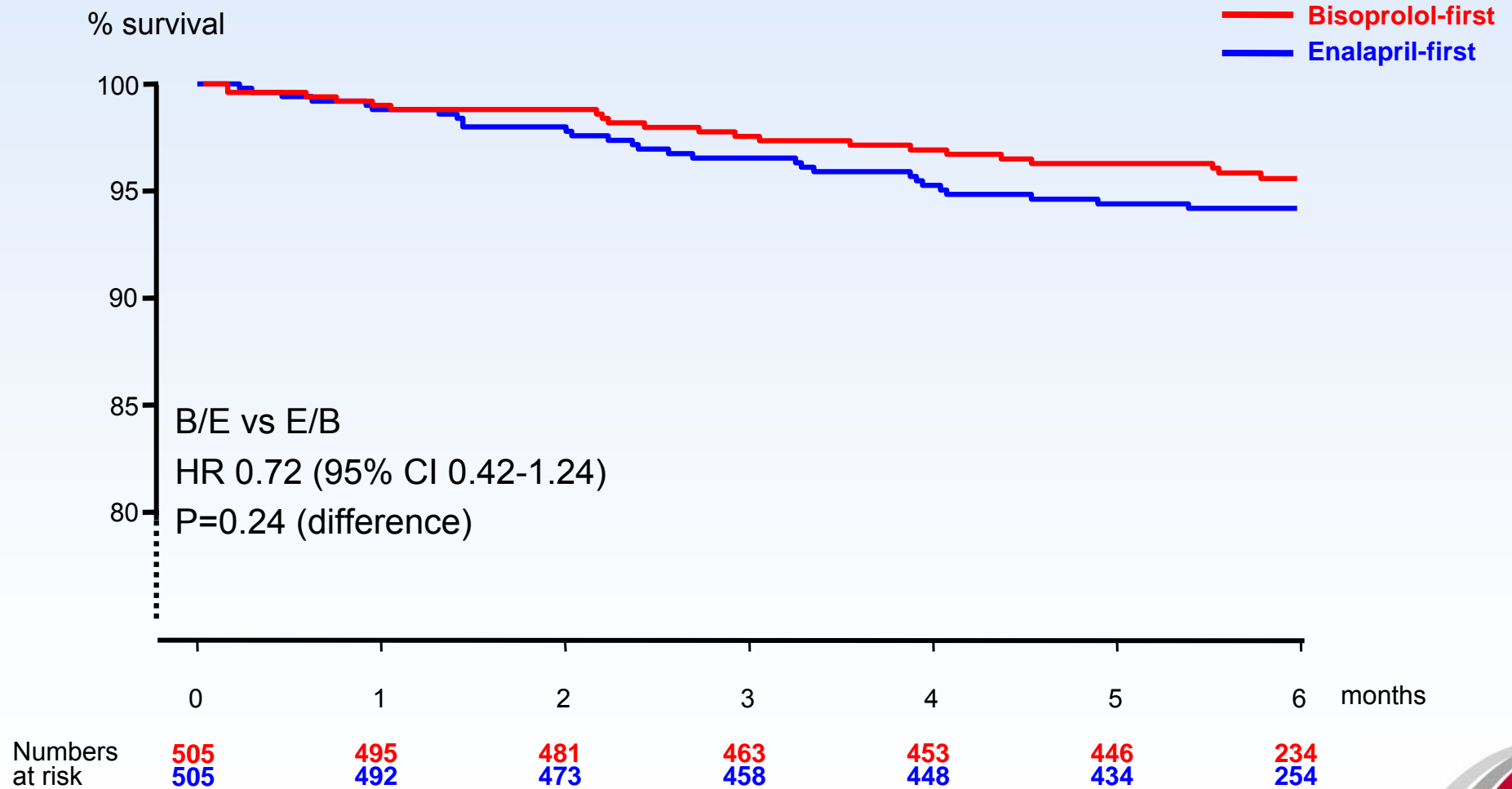
Primary endpoint at end of monotherapy (ITT) (all cause mortality and all cause hospitalization)



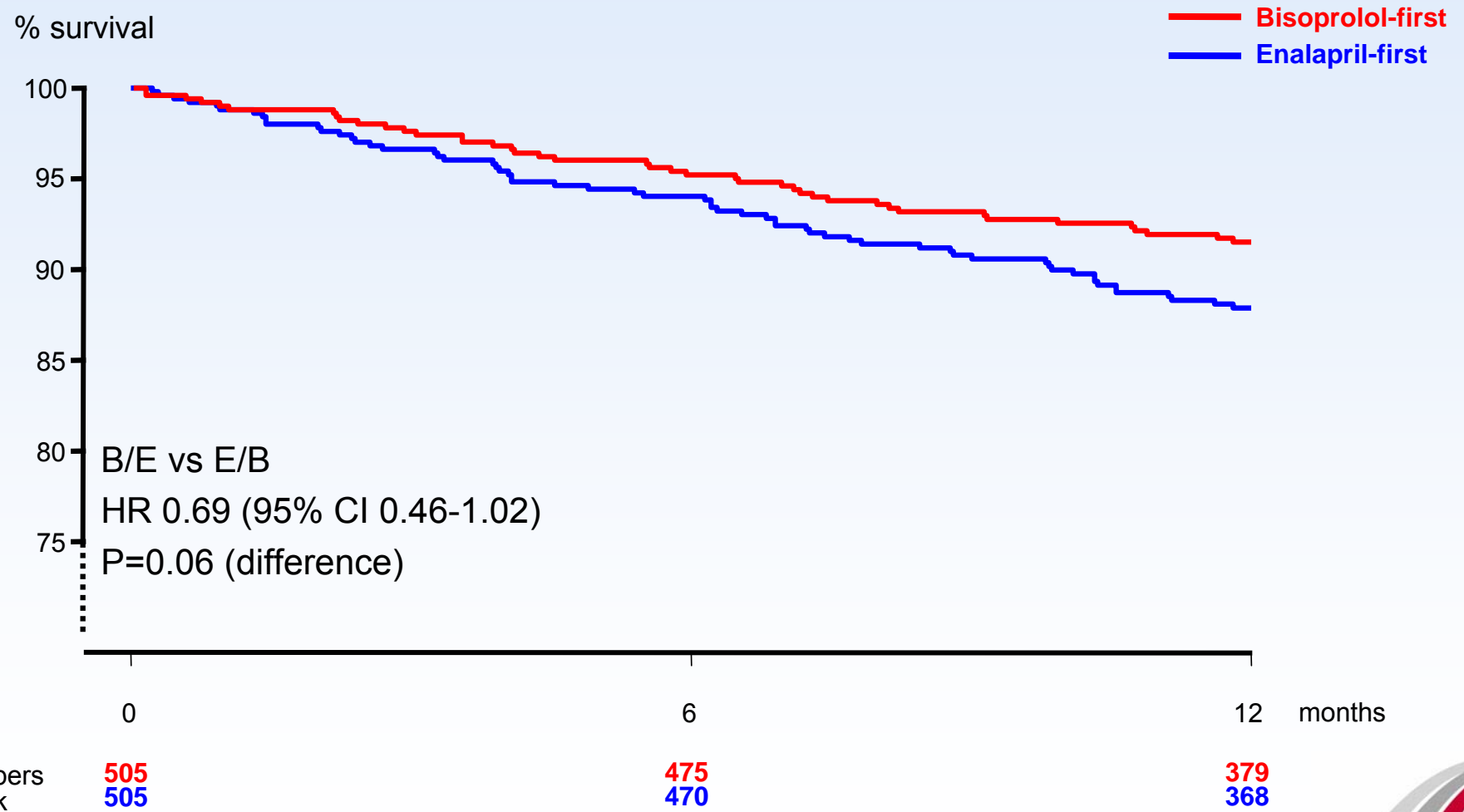
Hospitalization (all cause) at end of monotherapy (ITT)



All cause mortality at end of monotherapy (ITT)

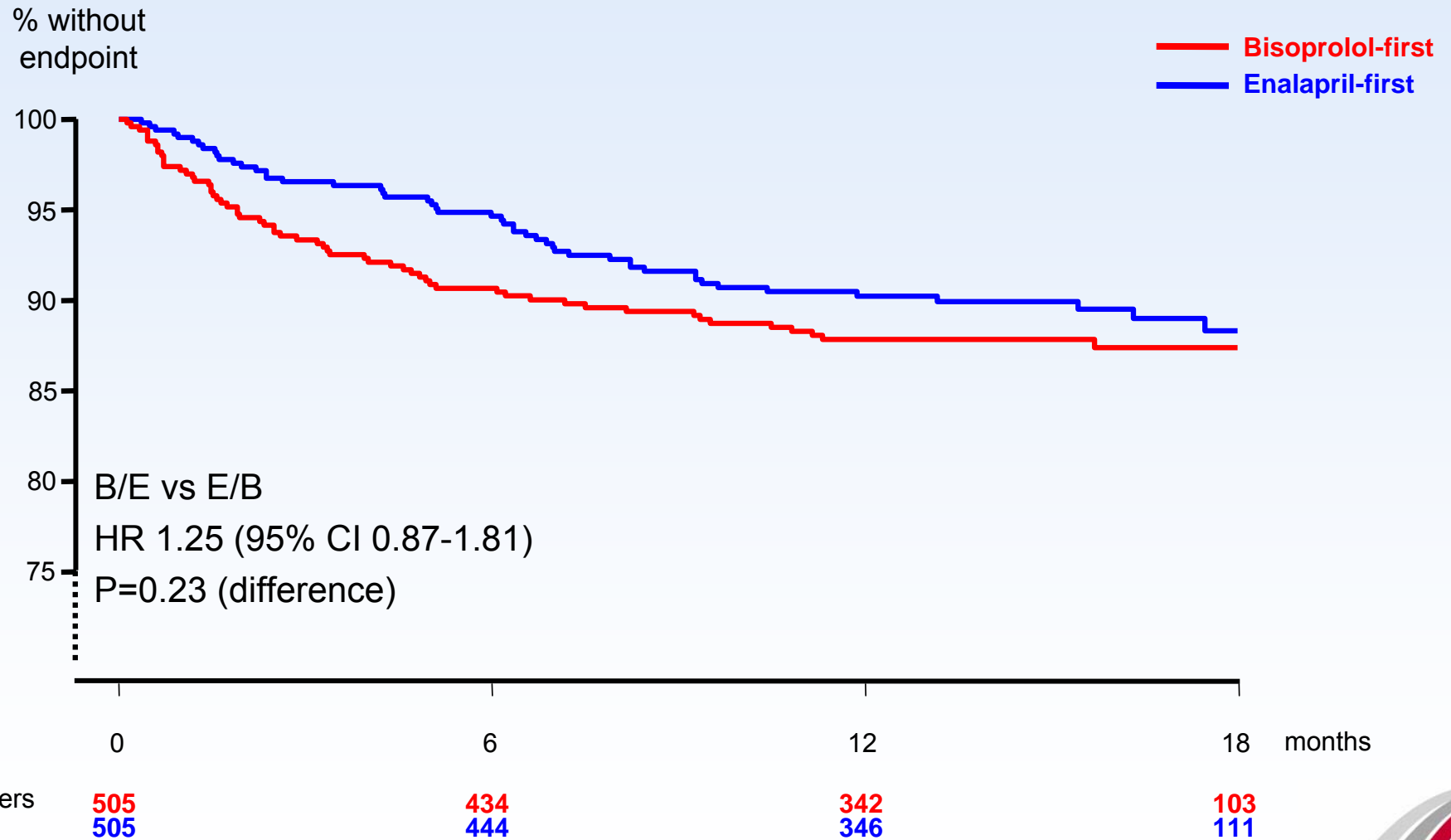


All cause mortality up to 1 year (ITT)



Worsening heart failure (ITT)

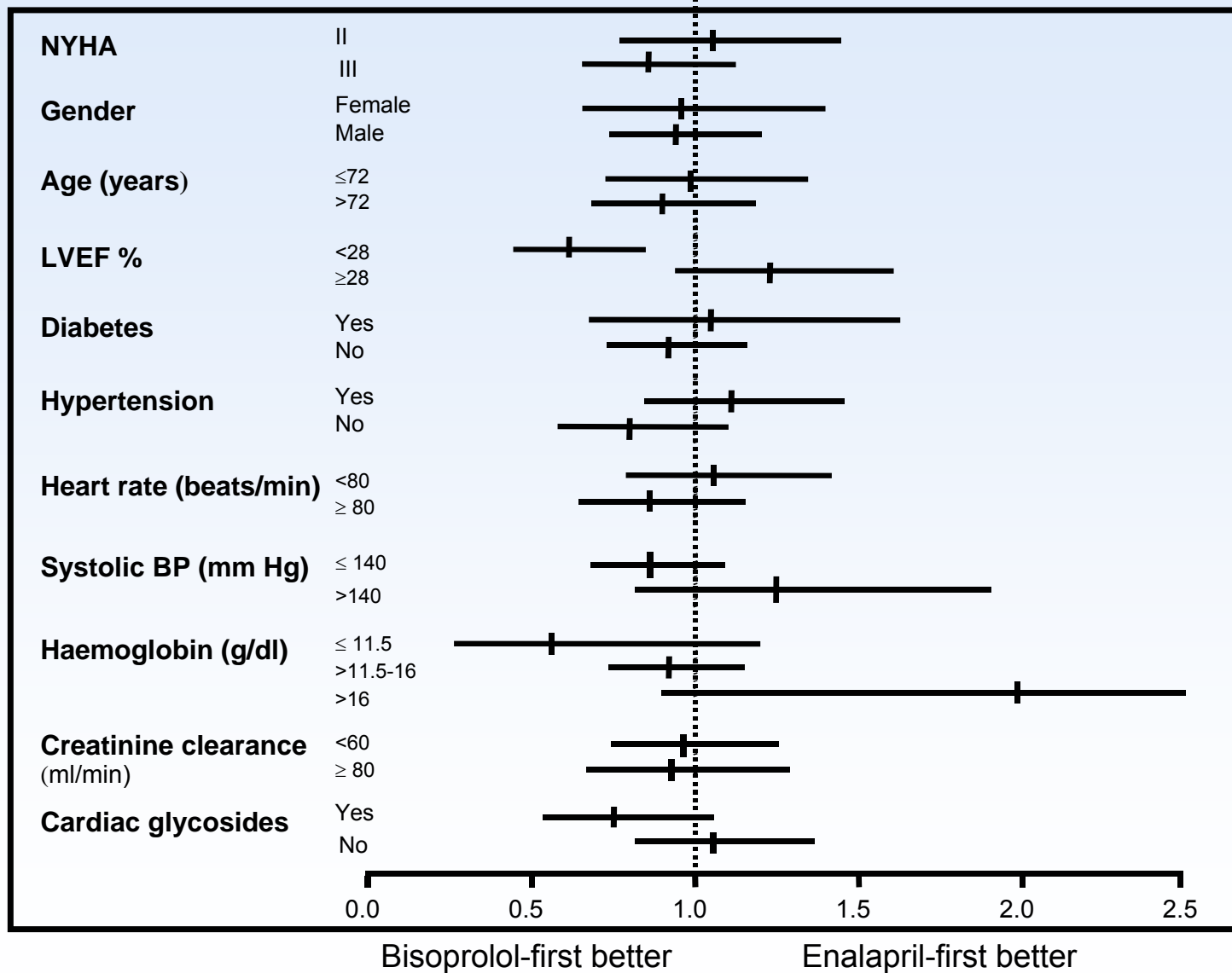
Requiring hospitalization or occurring in hospital



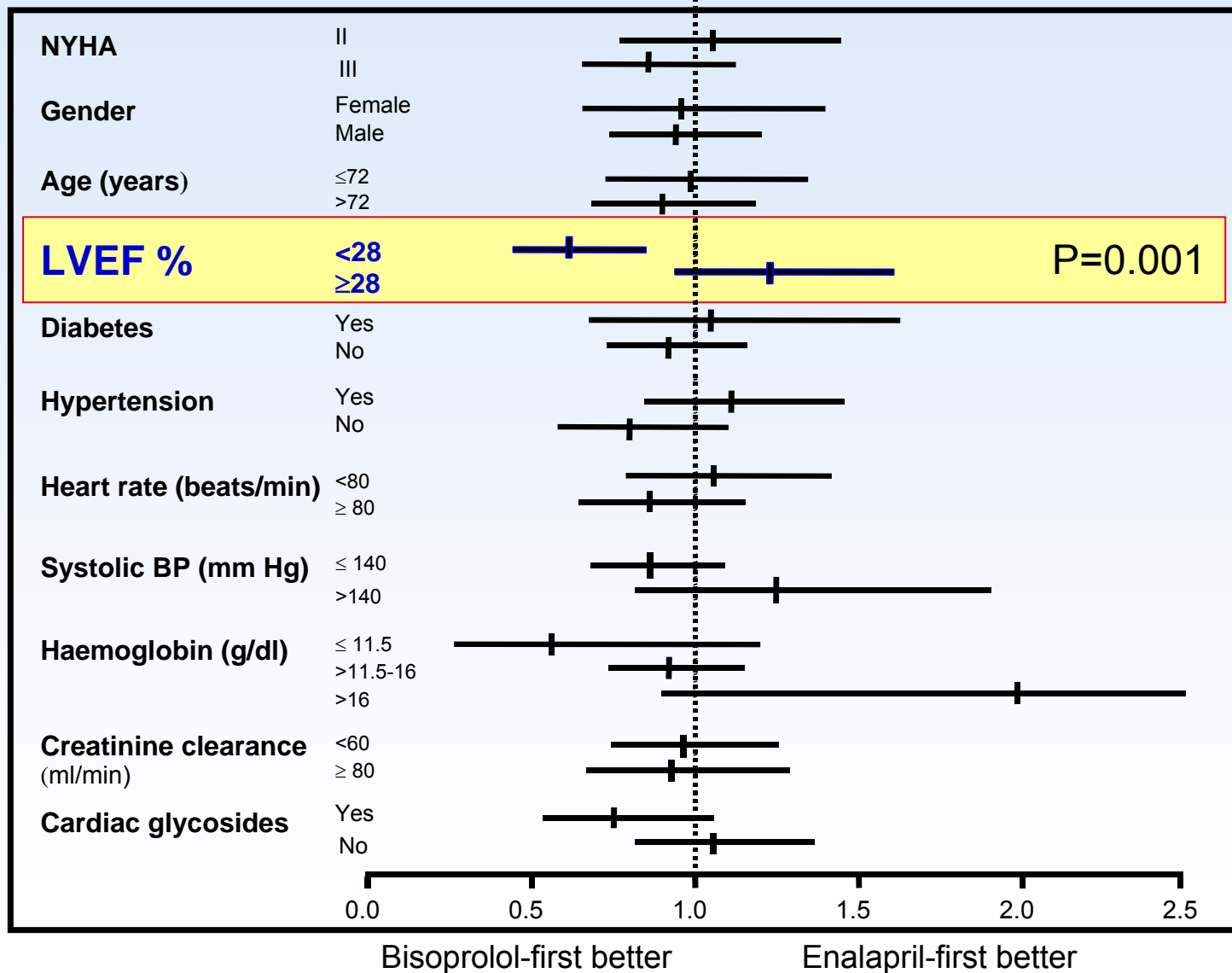
Other secondary endpoints (ITT)

	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 (Biso)	19 (3.8%)	24 (4.7%)	0.37
Combination phase (Enal)	47 (9.3%)	16 (3.2%)	<0.001
Total	101 (20.0%)	89 (17.6%)	0.33

Subgroups: primary endpoint



Subgroups: primary endpoint



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

Last prescribed study drug dose ≥ 50% of 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

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

Conclusions (1)

In terms of combined mortality / hospitalization

Bisoprolol-first was non-inferior to enalapril-first
in the ITT sample

Bisoprolol-first was close to non-inferior to enalapril-first
in the PP sample

Conclusions (2)

There was no difference in safety between the two strategies, showing that a bisoprolol-first strategy does not cause concerns

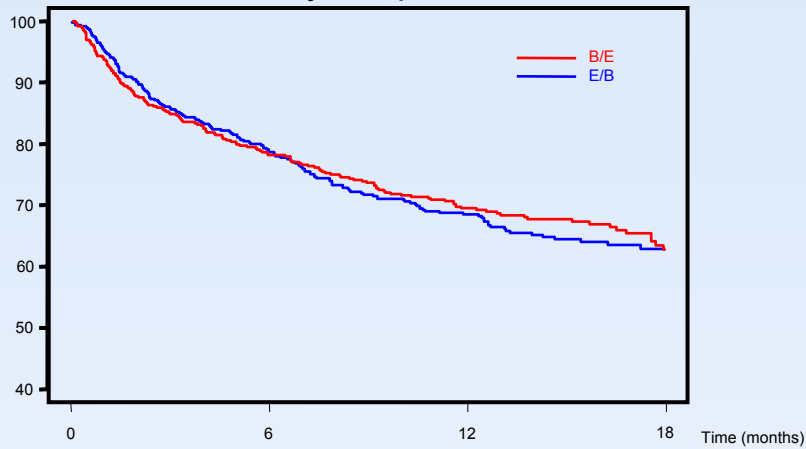
Thoughts for the future

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

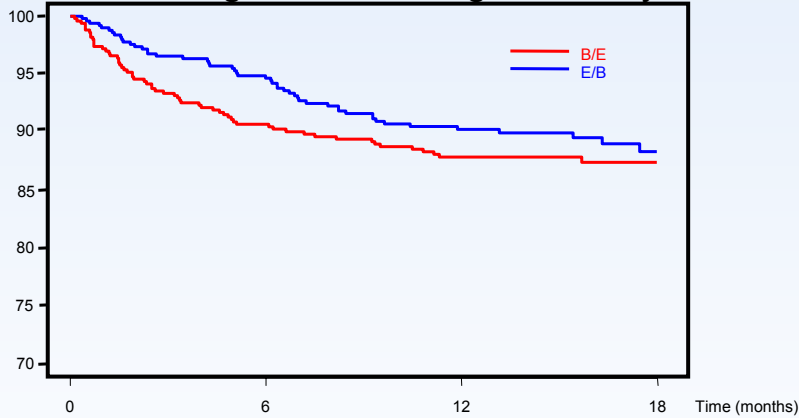
Bisoprolol-first was associated with a trend towards increased worsening of CHF in the early phase of treatment.

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

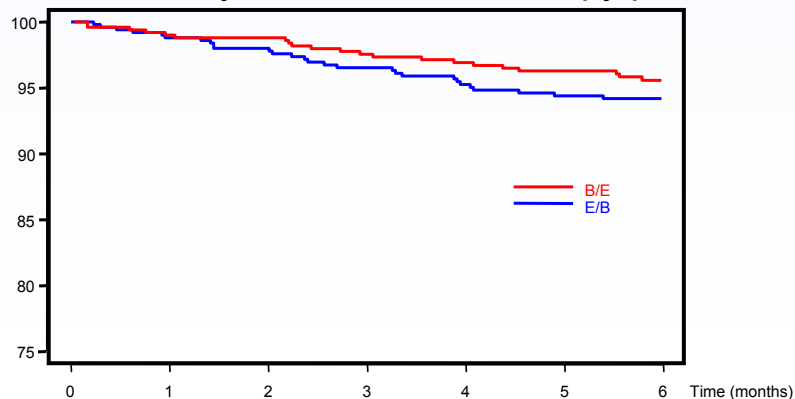
% event-free Primary endpoint PP



Worsening of CHF throughout study



All cause mortality at end of monotherapy phase



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.

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

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Endpoint Committee

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- S. Hansen, Eksjö, Sweden
- E. Vanoli, Pavia, Italy



THANK YOU!

- All participating patients
- The Merck medical team
- Monitors
- Nurses and other study personnel
- Investigators

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