

**Effect on sudden death
of heart failure treatment
started with bisoprolol followed by enalapril,
compared to the opposite order:
Results of the randomized CIBIS III trial**

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For the CIBIS III committees and investigators



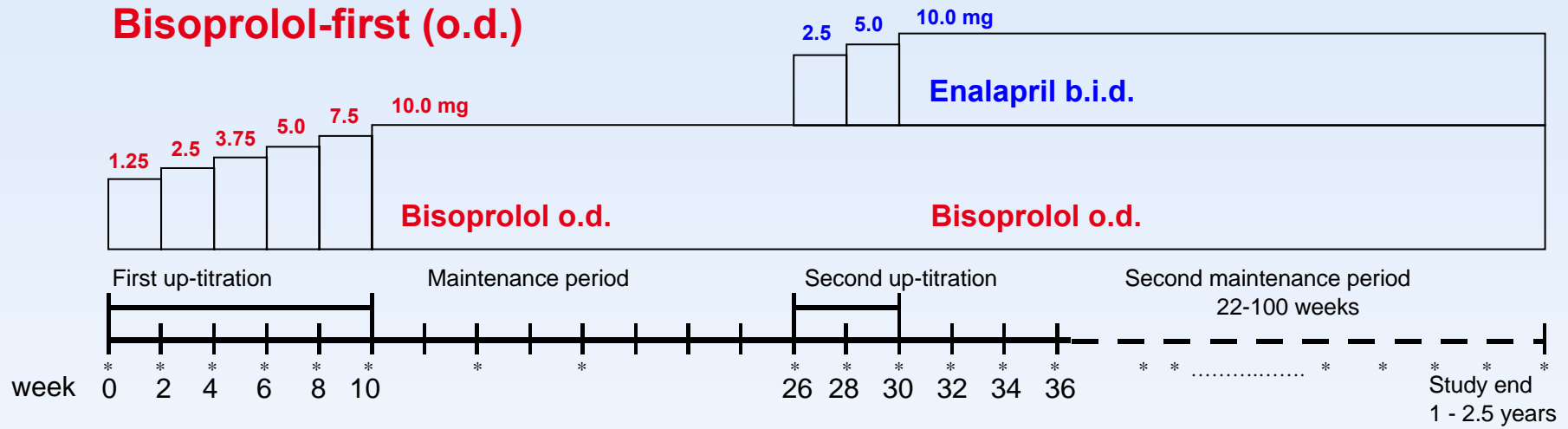
CIBIS III – Rationale

- In patients with newly diagnosed CHF, mortality high during the early phase
- Mainly due to sudden death
- β -blockers reduce sudden death more effectively than ACEi

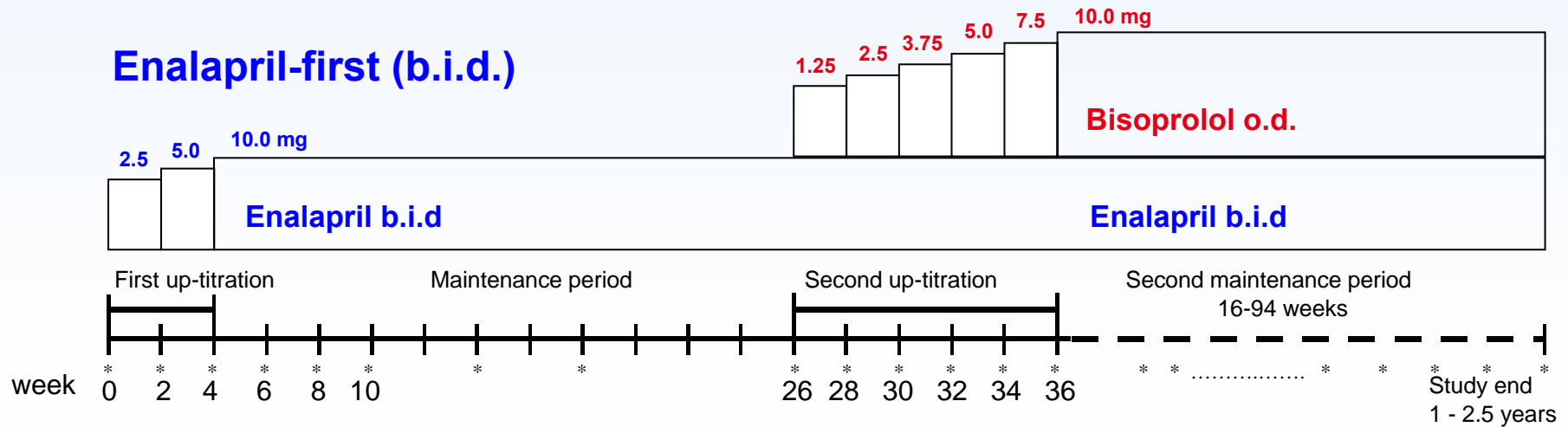
CIBIS III – Rationale

- **The sympathetic system activated early in the disease**
- **The RAAS triggered at a later stage**
- **From the pathophysiological point of view reasonable to start treatment with a betablocker**
- **Important to investigate if β -blockade or ACEi should be initiated first in CHF**

CIBIS III - Study design



* = visits



CIBIS III – Patients

- **Age ≥ 65 years**
- **Mild to moderate CHF (NYHA class II-III)**
- **LVEF $\leq 35\%$**
- **Stable CHF since ≥ 7 days**
- **Essentially without prior treatment with β -blockers, ACE inhibitors and angiotensin-receptor blockers**

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



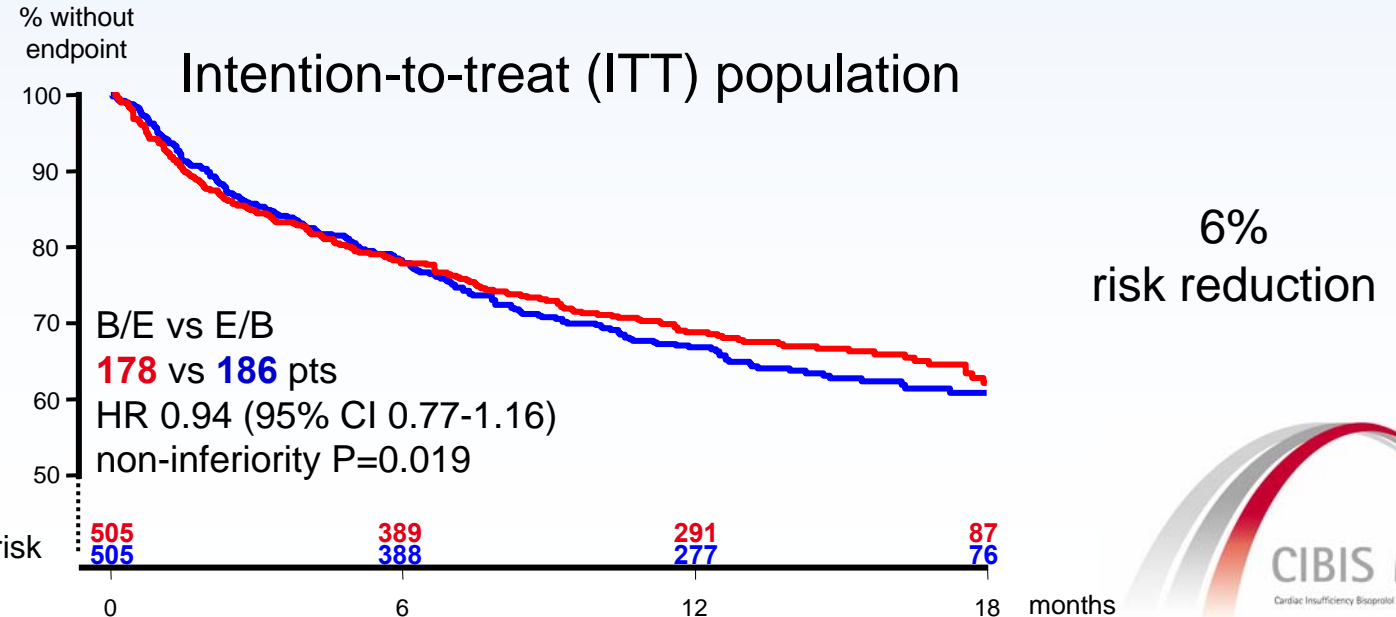
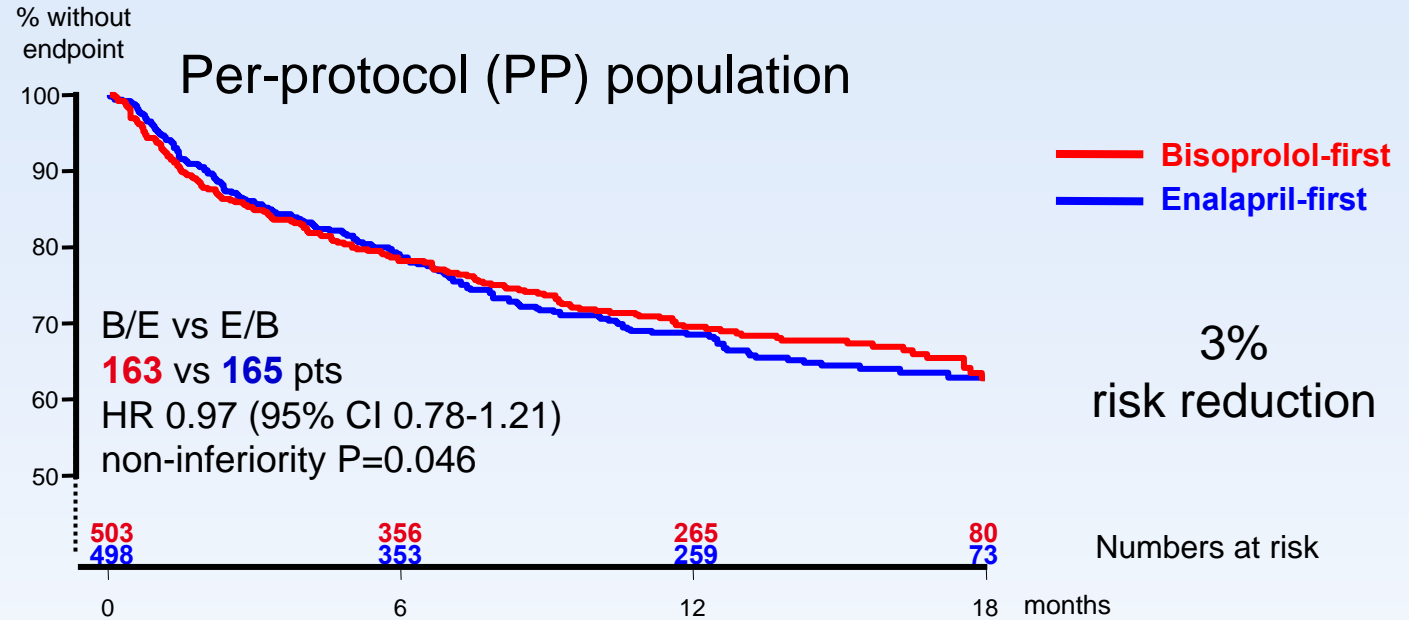
Combined primary endpoint

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%)

In the PP population, bisoprolol-first was not significantly non-inferior to enalapril-first

Mean follow-up 1.22 years

In the ITT population, bisoprolol-first was significantly non-inferior to enalapril-first



CIBIS III – sudden death

Study objective:

**To compare initiation of treatment in patients with CHF
with the β_1 -selective β -blocker bisoprolol
(to which enalapril was subsequently added)
to a regimen beginning with enalapril
(to which bisoprolol was subsequently added)
in terms of the effect on sudden death**

CIBIS III – sudden death

A sudden death was a cardiovascular death:

- **Occurring within 1 hour of the occurrence of new symptoms or without symptoms.**
- **Occurring at night during sleep without other cause.**
- **Occurring in odd places without other cause.**
- **Occurring within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death.**
- **Which was unwitnessed, in the absence of pre-existing progressive circulatory failure or other causes of death.**

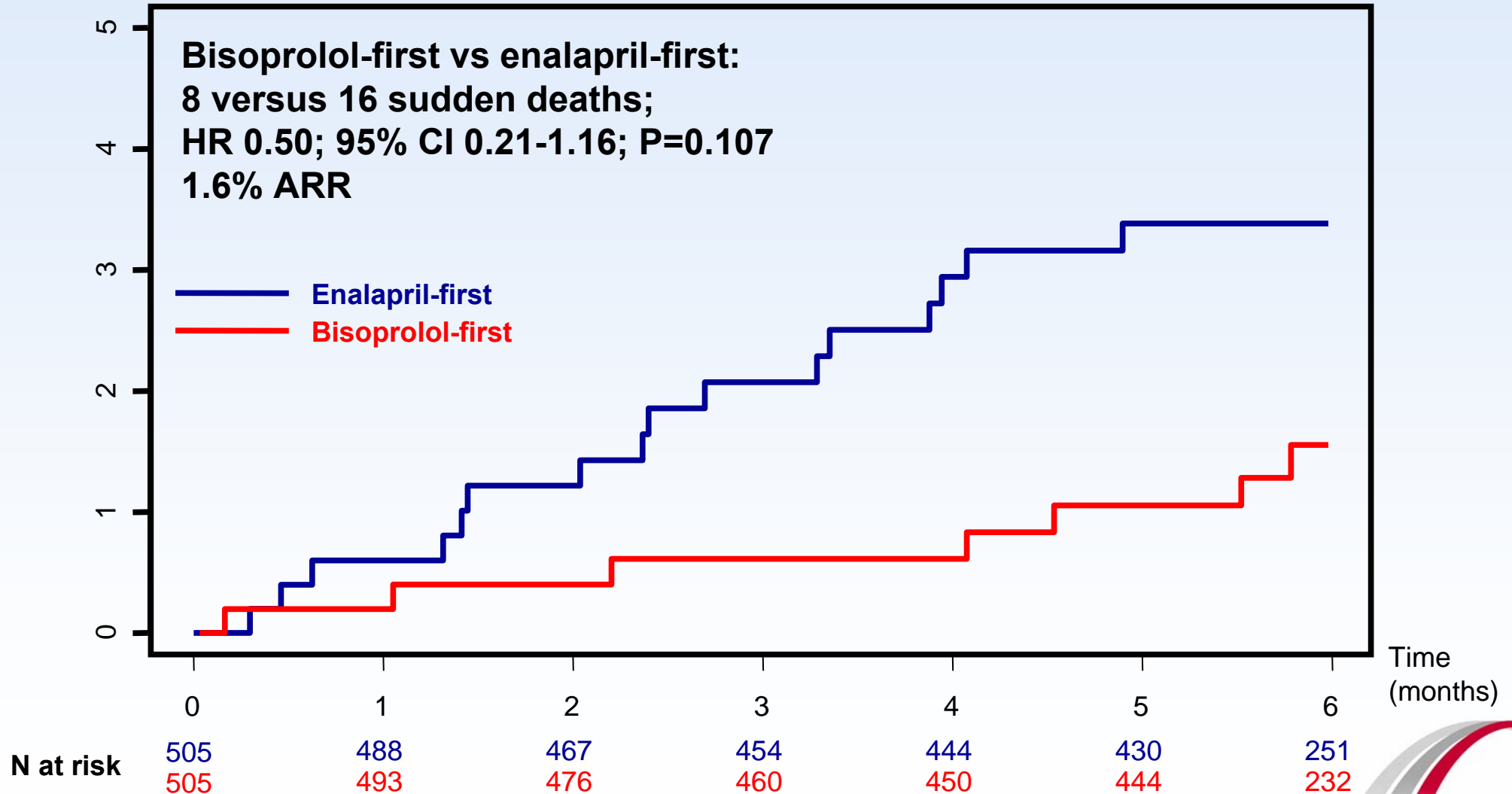
CIBIS III – sudden death

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

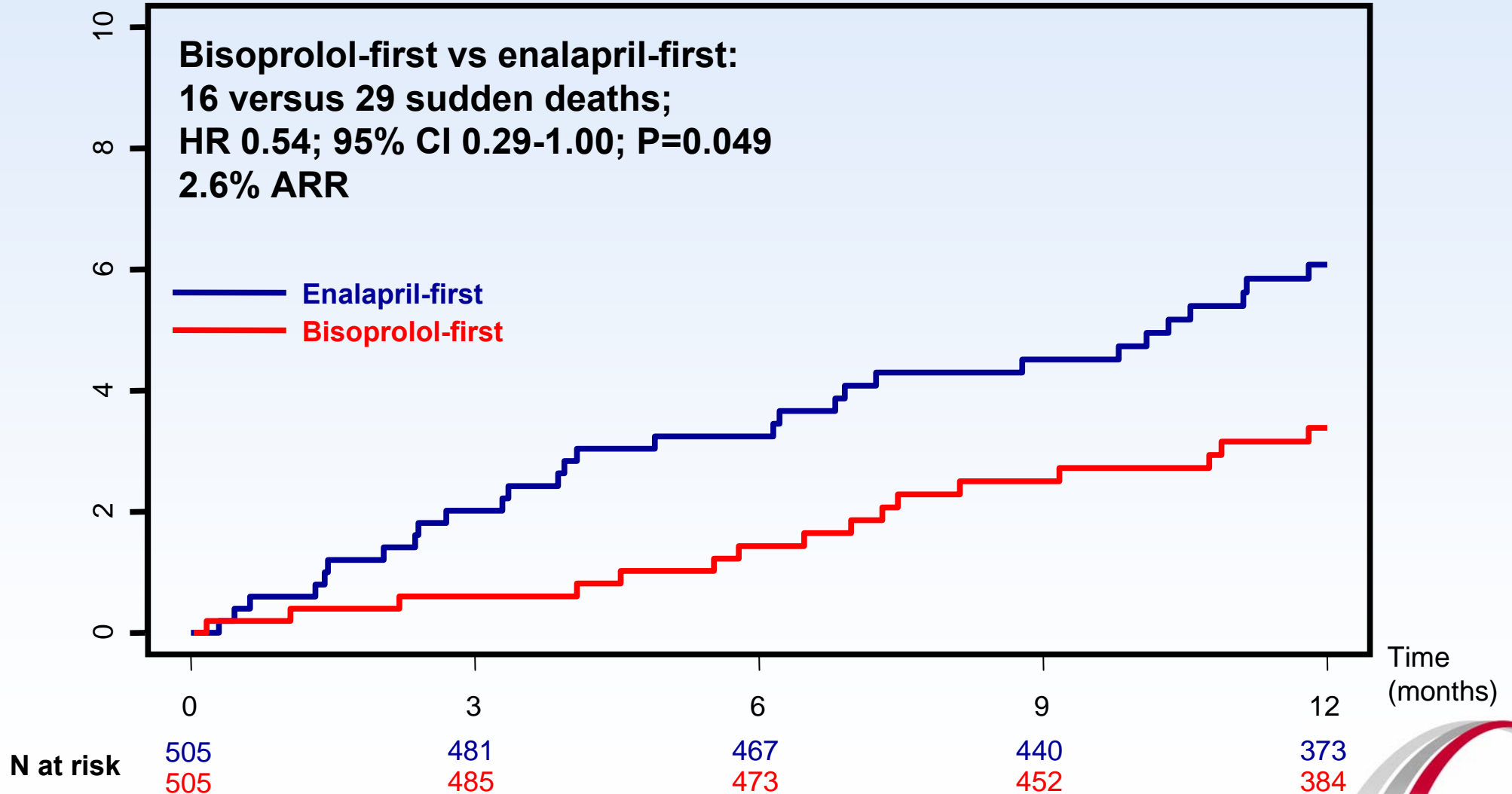
Sudden death - monotherapy phase

% sudden death



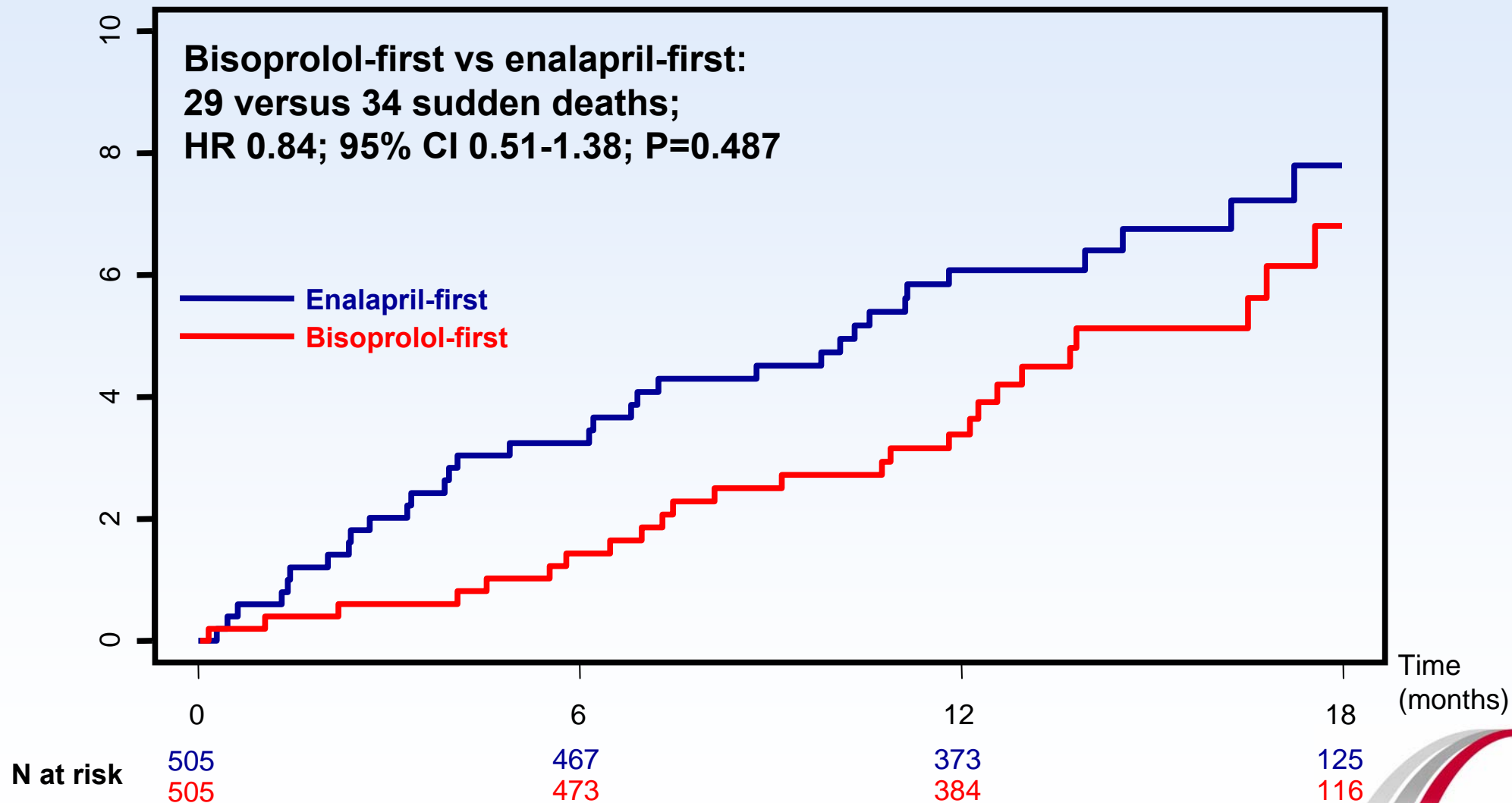
Sudden death – first year

% sudden death



Sudden death – entire study

% sudden death

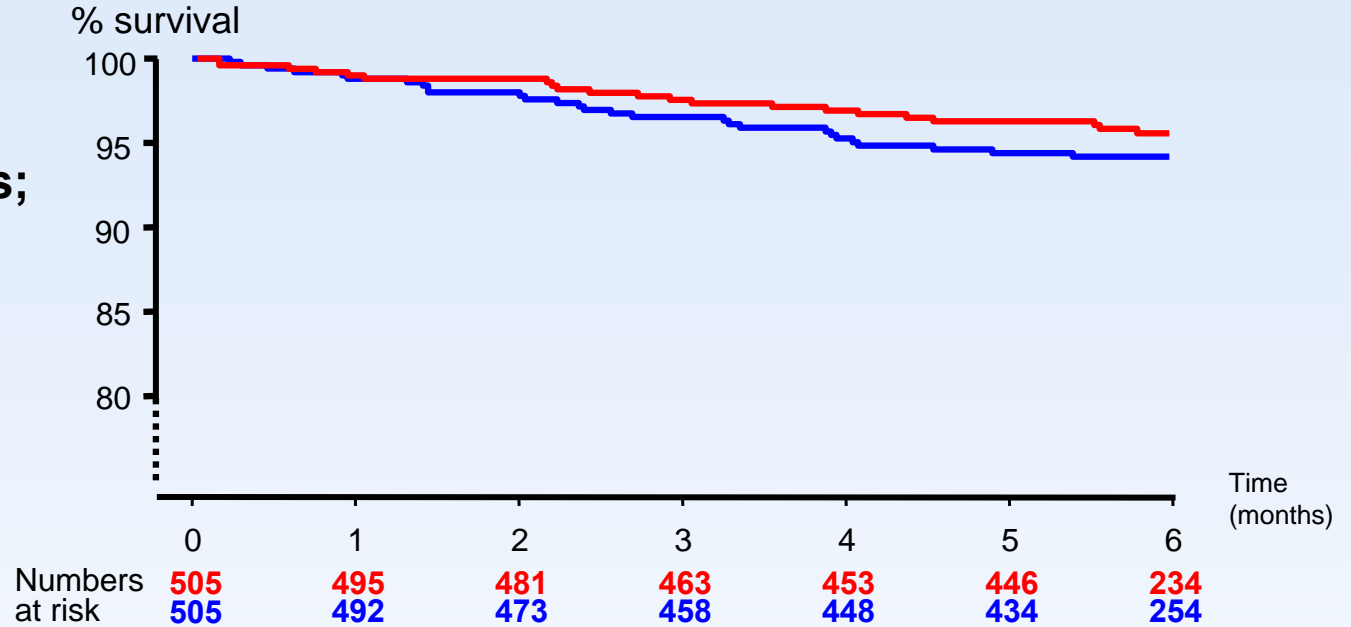


All cause mortality

Monotherapy

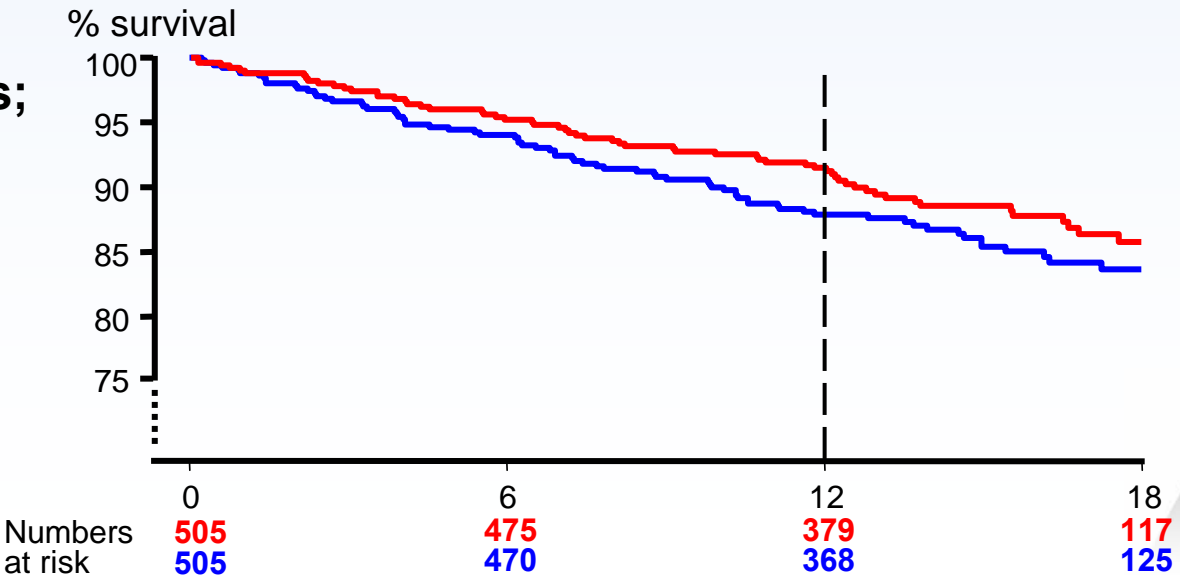
B-first vs E-first: 23 vs 32 pts;
 HR 0.72; 95% CI 0.42-1.24;
 P=0.24

— Enalapril-first
 — Bisoprolol-first



First year

B-first vs E-first: 42 vs 60 pts;
 HR 0.69; 95% CI 0.46-1.02;
 P=0.06



Entire study

65 vs 73 pts; HR 0.88;
 95% CI 0.63-1.22; P=0.44



Patients with event-related hospitalizations

	Bisoprolol-first n=505		Enalapril-first n=505	
	n	%	n	%
MONOTHERAPY PHASE				
All hospitalizations	84	16.6	73	14.5
CV hospitalizations	58	11.5	48	9.5
Worsening of CHF hospitalizations	39	7.7	25	5.0
Non-CV hospitalizations	26	5.1	25	5.0
FIRST YEAR				
All hospitalizations	117	23.1	120	23.8
CV hospitalizations	82	16.2	76	15.1
Worsening of CHF hospitalizations	49	9.7	40	7.9
Non-CV hospitalizations	35	6.9	44	8.7
ENTIRE STUDY DURATION				
All hospitalizations	131	25.9	136	26.9
CV hospitalizations	91	18.0	85	16.8
Worsening of CHF hospitalizations	53	10.5	44	8.7
Non-CV hospitalizations	40	7.9	51	10.1

CV, cardiovascular; CHF, chronic heart failure. All between-group differences were non-significant.



Mean study drug dose at 1 year

	Bisoprolol-first	Enalapril-first	
Bisoprolol mg/day	8.4 (2.7)	7.4 (3.3)	P<0.0001
Enalapril mg/day	17.1 (5.4)	18.6 (5.0)	P=0.14

At study end, for both study drugs the dose was significantly higher if it was the first initiated drug, compared to if it was the second drug.

Limitations

- **The study was not designed to primarily assess sudden death. Consequently it was not adequately powered in this respect.**
- **The length of the monotherapy phase may be questioned from a clinical point of view. It does not constitute a recommendation.**

Summary

- **In patients ≥ 65 years of age with mildly or moderately symptomatic, stable CHF and LVEF $\leq 35\%$, initiating CHF therapy with bisoprolol was significantly superior to initiating therapy with enalapril in reducing sudden death during the first year.**
- **The hazard reduction was similar at the end of the monotherapy phase, although not statistically significant.**
- **The difference between the two treatment strategies leveled out after more than six months of combined treatment.**

Summary

- **The early reduction in sudden death for bisoprolol-first was accompanied by a non-significant reduction in early all-cause death of similar magnitude, indicating that this strategy does not simply alter the mode of death to death of progressive CHF or other non-sudden death.**
- **The early reduction of sudden death was balanced by a non significant increase in hospitalizations for worsening of CHF.**

Conclusions

- **These results indicate the need for early treatment with a betablocker in patients with CHF, especially to reduce early sudden death.**
- **A possible increased risk of early hospitalization for worsening of CHF has to be considered in this regard.**

Thank you!

