

Clinical Trial Update

**Effect on mode and cause of death of initiation of treatment
for chronic heart failure with bisoprolol followed by
additional enalapril compared to the opposite sequence:
results of the randomized CIBIS III-trial**

DISCUSSANT

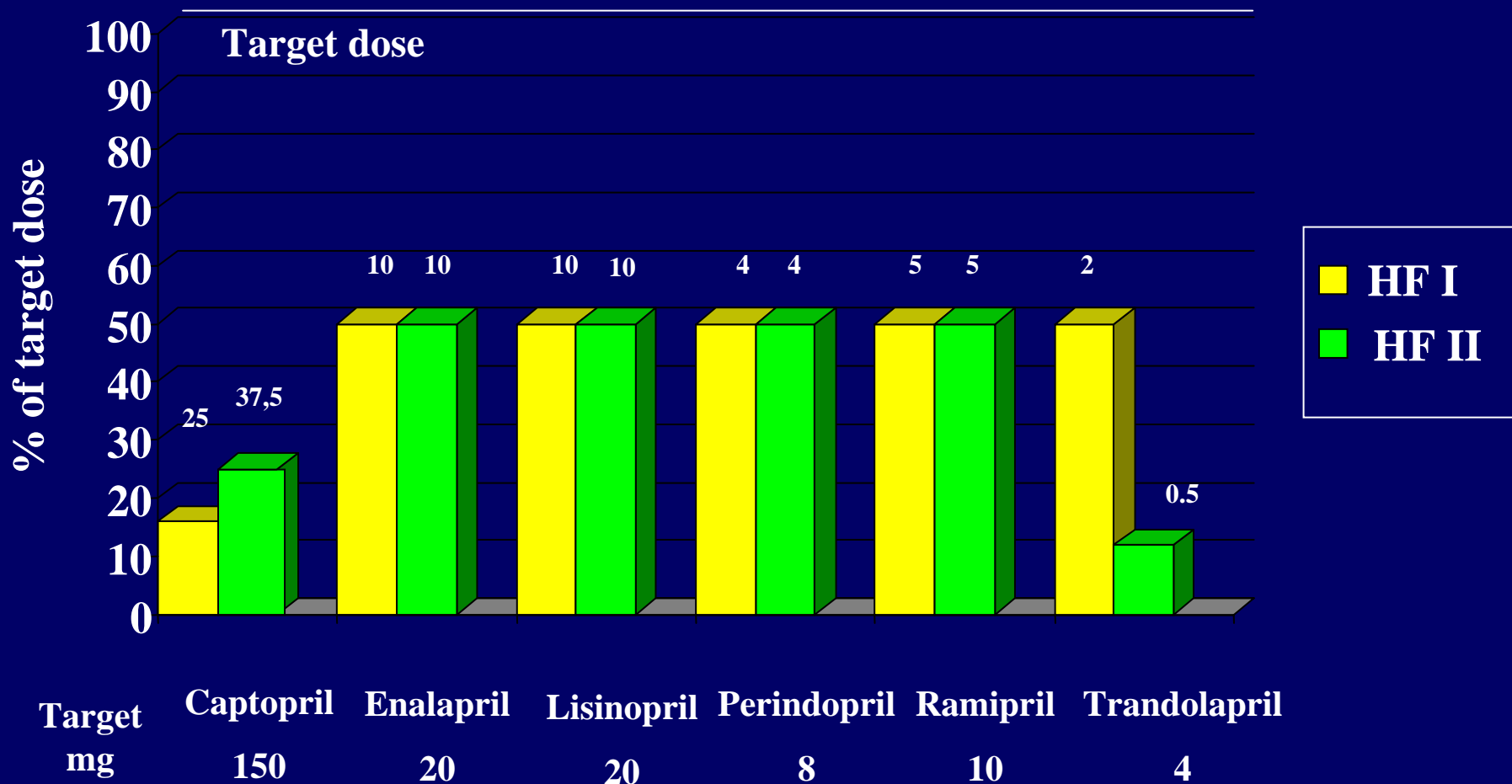
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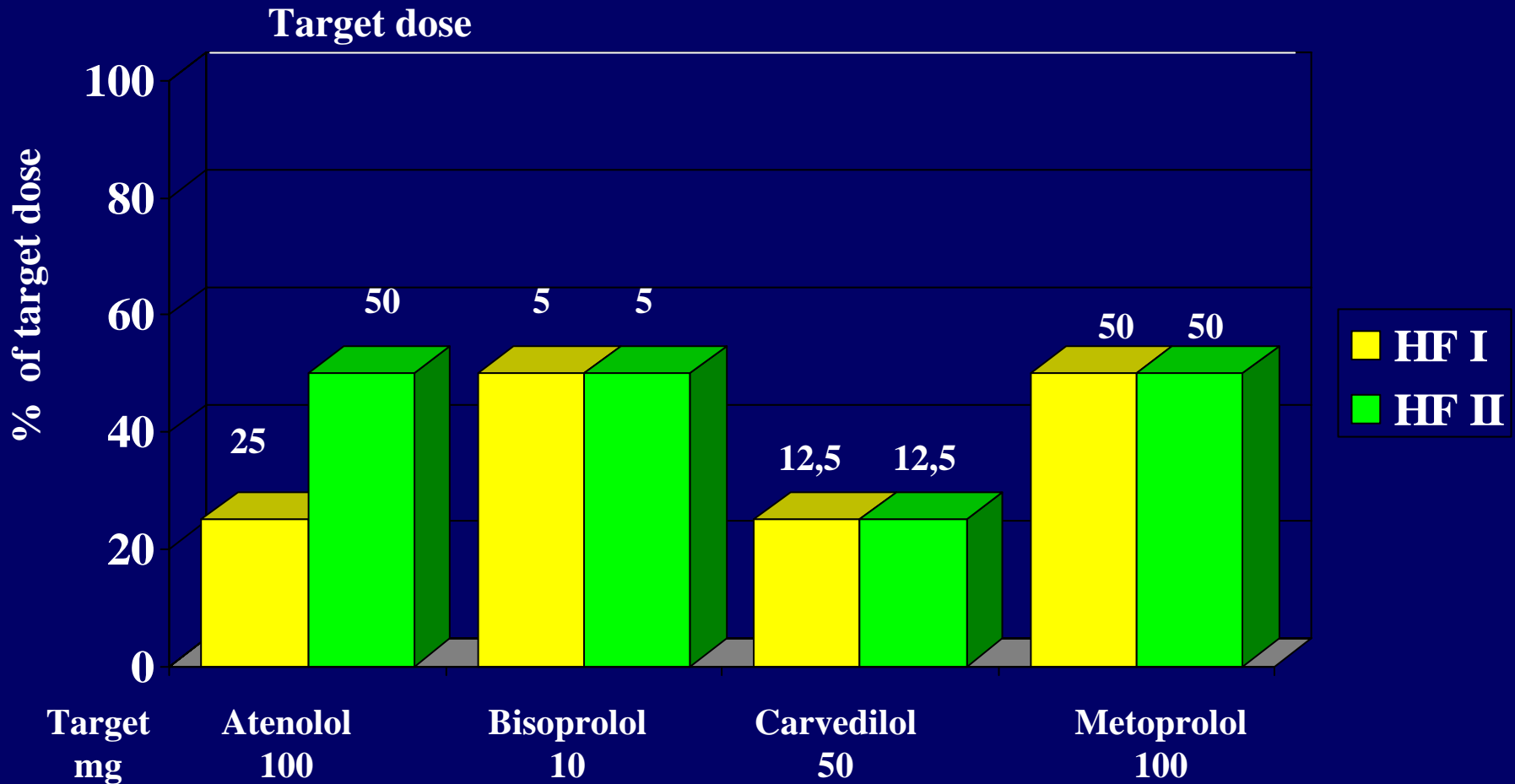
Heart Failure Survey I and II

ACE-I doses at discharge in % of target doses



Heart Failure Survey I and II

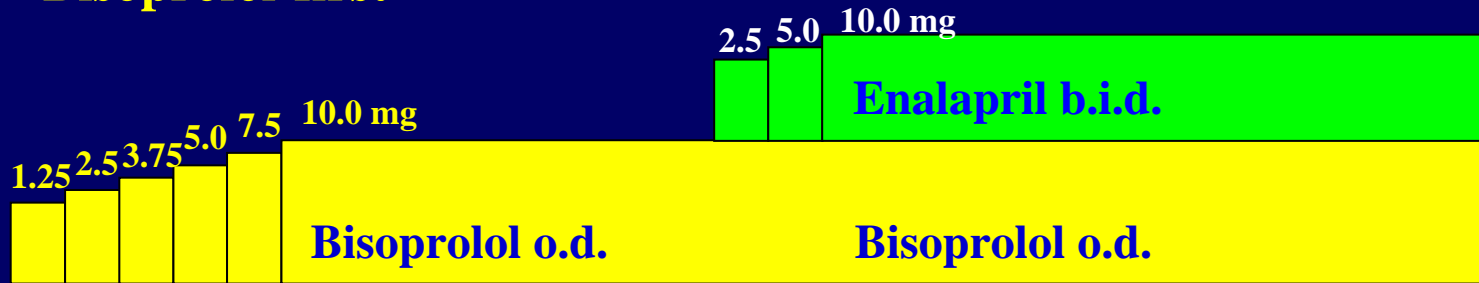
Beta-blocker doses at discharge in % of target doses



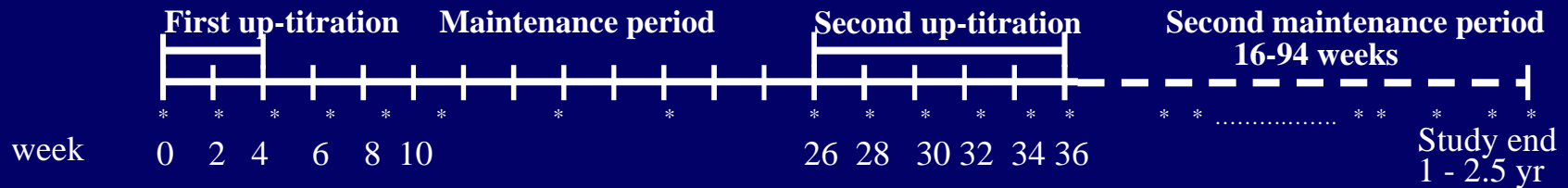
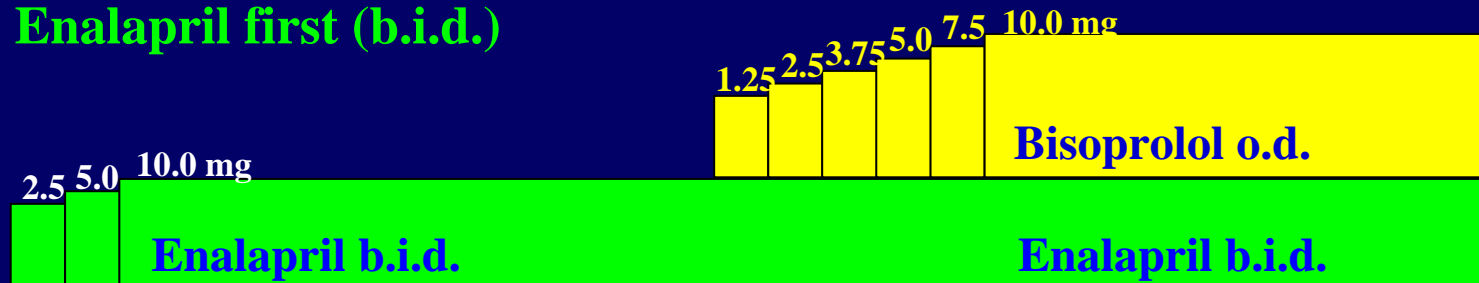
CIBIS III

Study Design

Bisoprolol-first



Enalapril first (b.i.d.)



A therapeutic strategy based on 9 up-titration steps in 8 months will not be incorporated in clinical practice

CIBIS III

Primary Endpoint

Combined endpoint of mortality (death from any cause) and first all-cause hospitalisation at study end.

CIBIS III

Secondary End-points

End of monotherapy phase

- **Primary endpoint**
- **Early introduction of the second drug due to poor control of CGF**

End of the monotherapy phase and study end

comparison of the individual components of the primary endpoint

- **Cardiovascular death (including sudden death)**
- **Cardiovascular hospitalisation**
- **Comparison of safety and tolerability of both regimens (PTC, incidence and type of AEs, BP, Biochemistry)**

Sudden death at one year follow-up was not a predefined end-point

CIBIS III - Mortality

	Bisoprolol-first N=505		Enalapril-first N=505
• <i>End of monotherapy phase</i>			
All deaths	23		32
Sudden deaths	8		16
Non-sudden CV deaths	12		6
Non CV deaths	2		9
• <i>At one year</i>			
All deaths	42		60
Sudden deaths	16	*	29
Non-sudden CV deaths	19		16
Non CV deaths	5		13
• <i>At study end</i>			
All deaths	65		73
Sudden deaths	29		34
Non-sudden CV deaths	26		19
Non CV deaths	8		18

* HR 0.54, 95% CI 0.29-1.00, P= 0.049

CIBIS III

Assessment of sudden death was done

- during the monotherapy phase
 - by intention to treat
 - censoring patients given combined therapy
- during actual monotherapy, including patients not starting or starting late the second drug
- after one year of treatment
- at the end of study

Many “subgroup-subtime” analyses expose to overinterpretation of the results (statistically significant differences by chance) if stricter criteria of significance are not applied

None of the 1010 patients with symptomatic HF, mean LVEF 29% (62% with CAD) enrolled in CIBIS III and followed-up for 1-2.1 years received an implantable defibrillator.

Final comment

I feel that beta-blocker therapy can be initiated first in selected HF patients but the CIBIS III trial results do not allow to recommend this strategy in the clinical practice.

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.