New Strategies in Congestive Heart Failure Therapy

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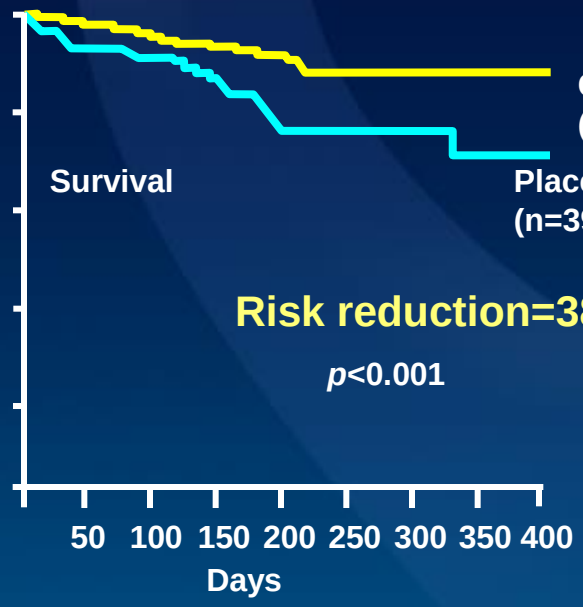
Heart Failure: A Disorder of the Elderly

- Heart failure incidence increases 10 fold from middle to old age
- 75% of all heart failure cases are 65 or older

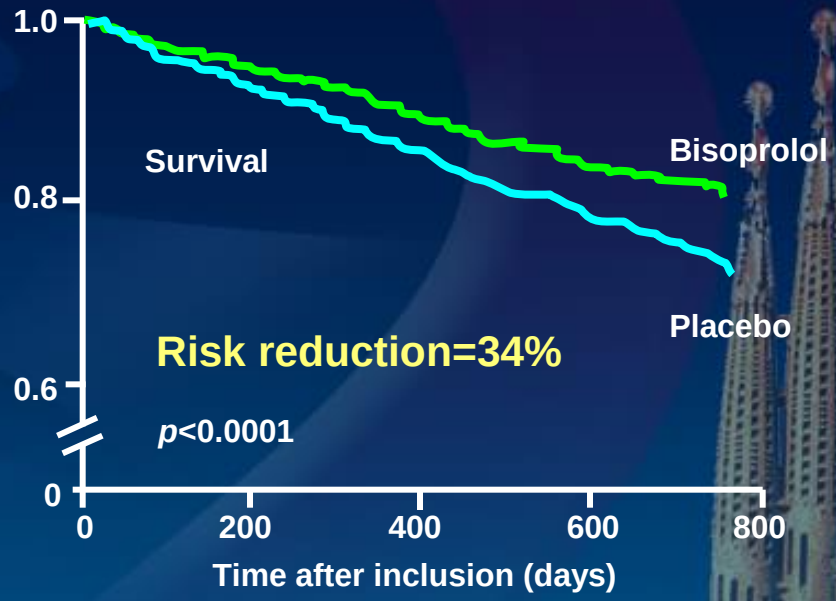
Beta Blockers in Heart Failure-All cause Mortality

US Carvedilol Programme



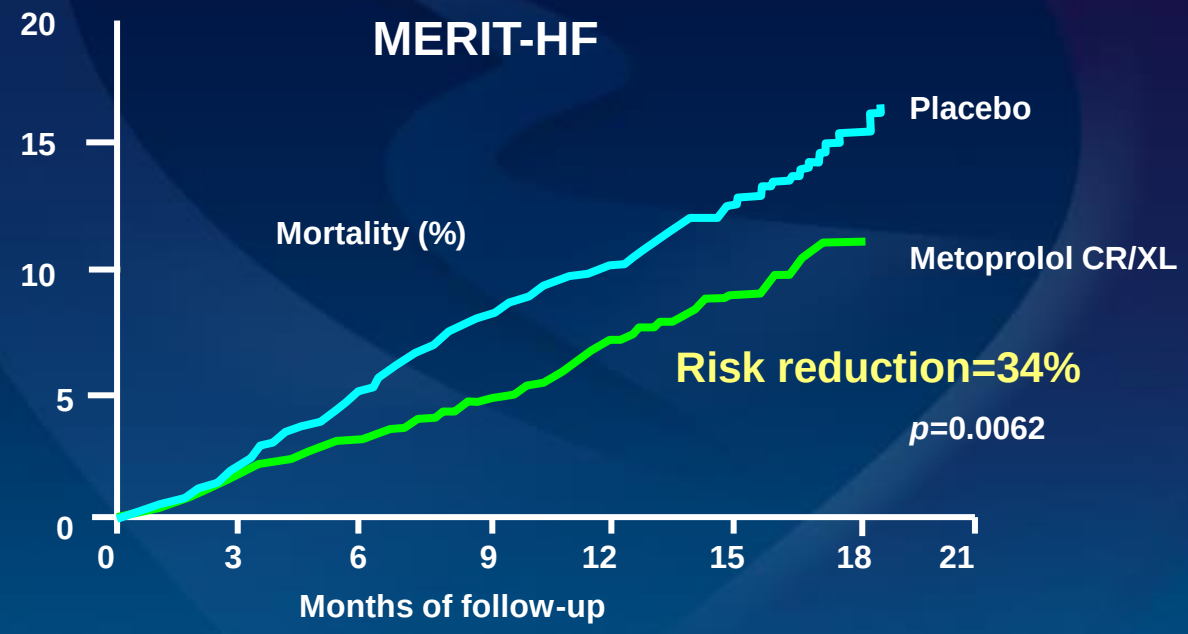
Packer et al (1996)

CIBIS-II



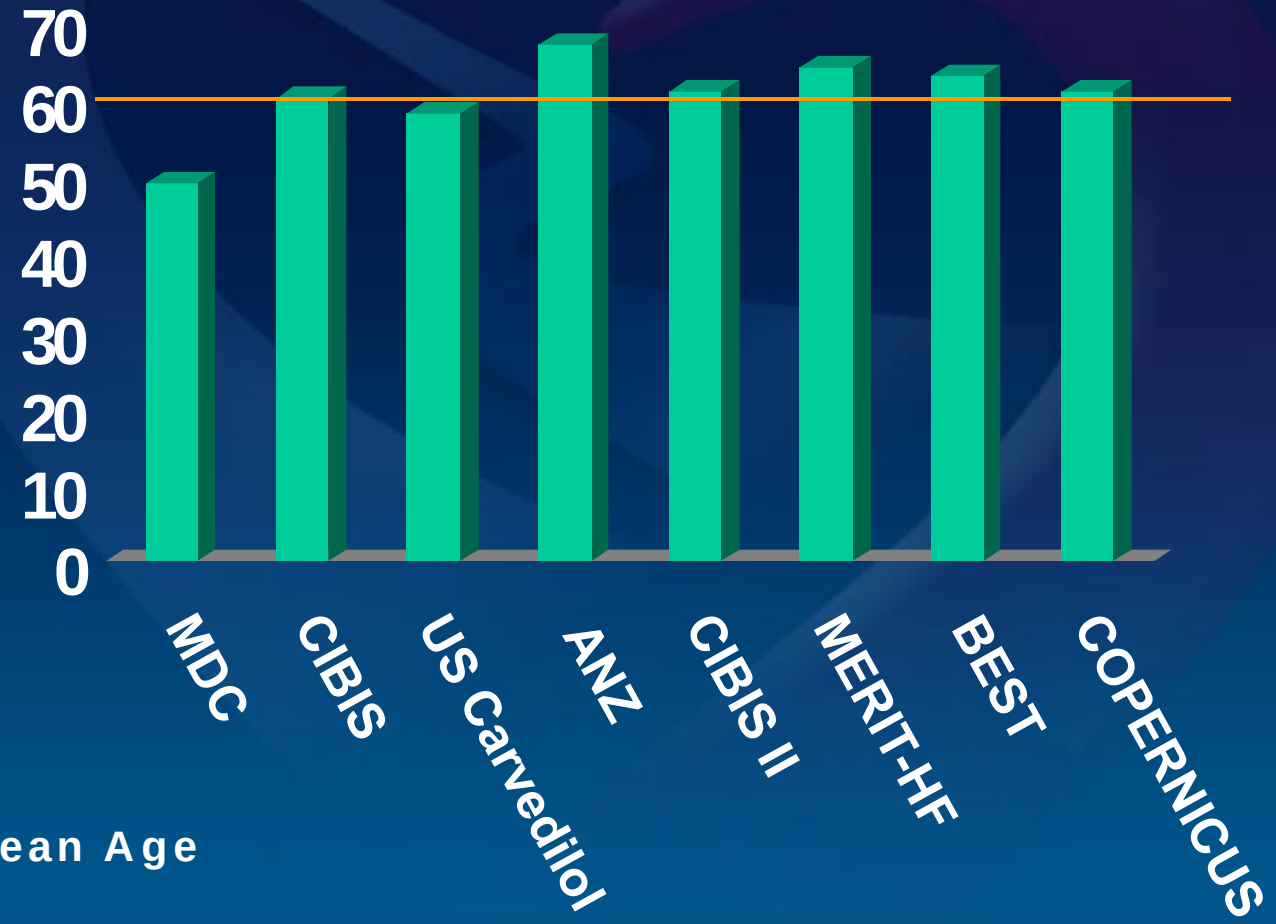
CIBIS-II Investigators (1999)

Beta Blockers in Heart Failure-All cause Mortality



The MERIT-HF Study Group (1999)

Mean Age in Major Beta Blocker Trials



Beta Blockers in Elderly with CHF

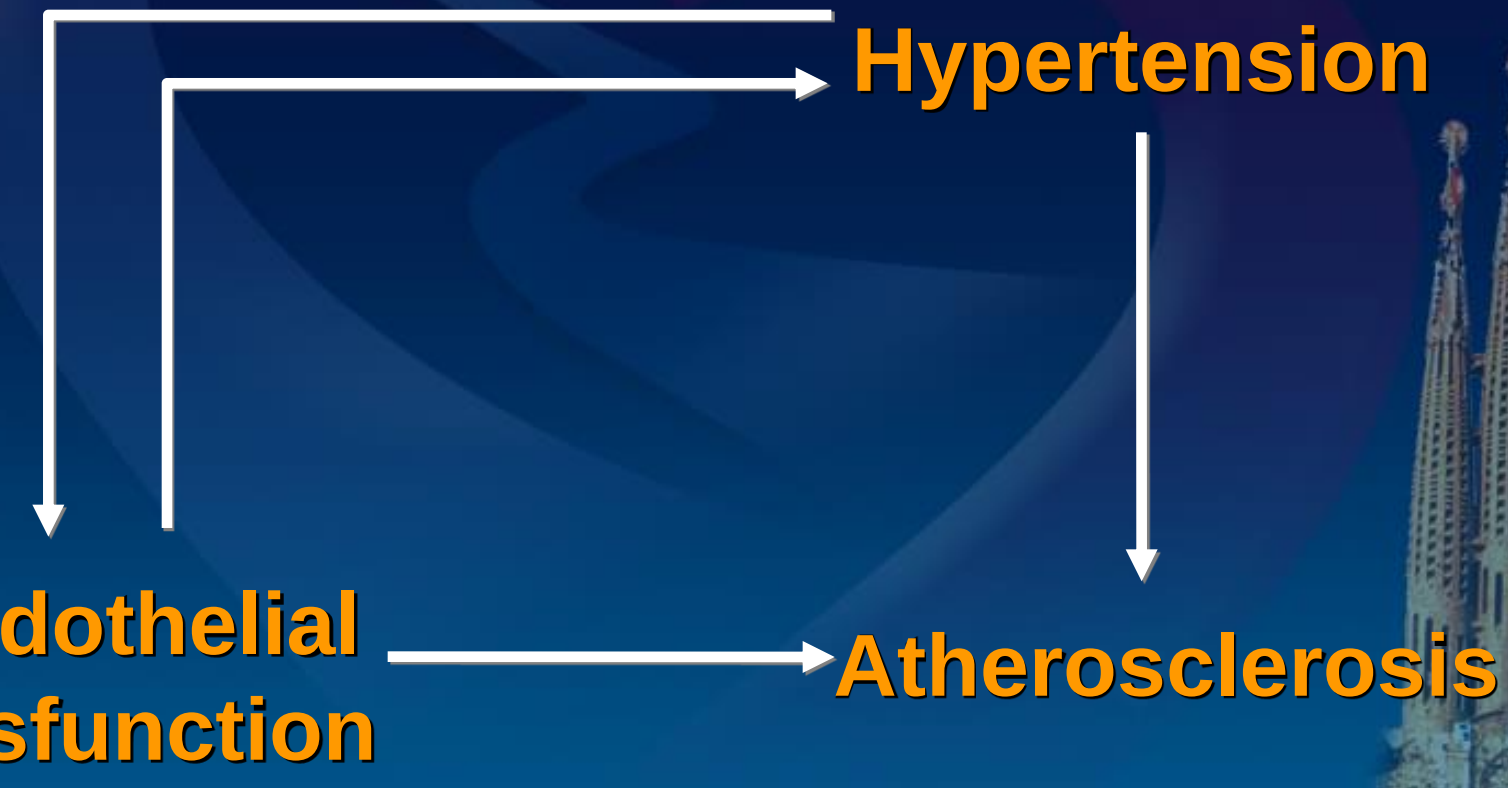
What are the issues?

- Proportion of patients age > 65 years in clinical trials is underrepresented
- Safety and tolerability of beta blockade in the elderly is not addressed
- More randomised information about the effects of beta blockers in elderly is needed

Elderly and Younger CHF Patients Differ

- Reduced cardiovascular reserve:
  - **increased vascular stiffness**
  - reduced peak contractility
  - reduced baroreflex sensitivity
- Multiple co-morbidities
- Multiple medications
- Altered pharmacokinetics

Central Role of Endothelial Dysfunction



Characteristics of Nebivolol

- a selective beta-1- blocker
- modulates the release of nitric oxide (NO)
- reduces vascular resistance
- reverses endothelial dysfunction
- reduces preload and afterload

Hemodynamic Effects of Nebivolol

- Preload ↓
- Afterload ↓
- Improved Diastolic Function
- Vessel Elasticity ↑
- LV Function ↑
- Antianginal effects
- Ejection Fraction ↑
- Cardiac Output ↑
- Heart Rate ↓

The ENECA Trial

Efficacy of **N**ebivolol in the Treatment of **E**lderly Patients with **C**hronic cardiac failure NYHA Class II-IV as an **A**dd-on therapy to ACE inhibitors or A-II Antagonists, Diuretics and/or Digitalis

A multicentre, double-blind, placebo-controlled phase III clinical trial

First Results

Conduct of ENECA - study protocol

Main Inclusion Criteria

- Out-patients aged ≥ 65 years
- Chronic heart failure stages NYHA II - IV
- Left ventricular ejection fraction (LVEF) ≤ 35 %
- Stable baseline medication:
  - ACE inhibitors or angiotensin-II-antagonists (RAAS Inhibitors)
  - Diuretics and/or digitalis

Primary and Secondary Study Objectives

Primary:

Efficacy of Nebivolol in elderly patients with chronic heart failure

Secondary:

Safety and tolerability of Nebivolol over 10 months treatment

Primary and Secondary Efficacy Variables

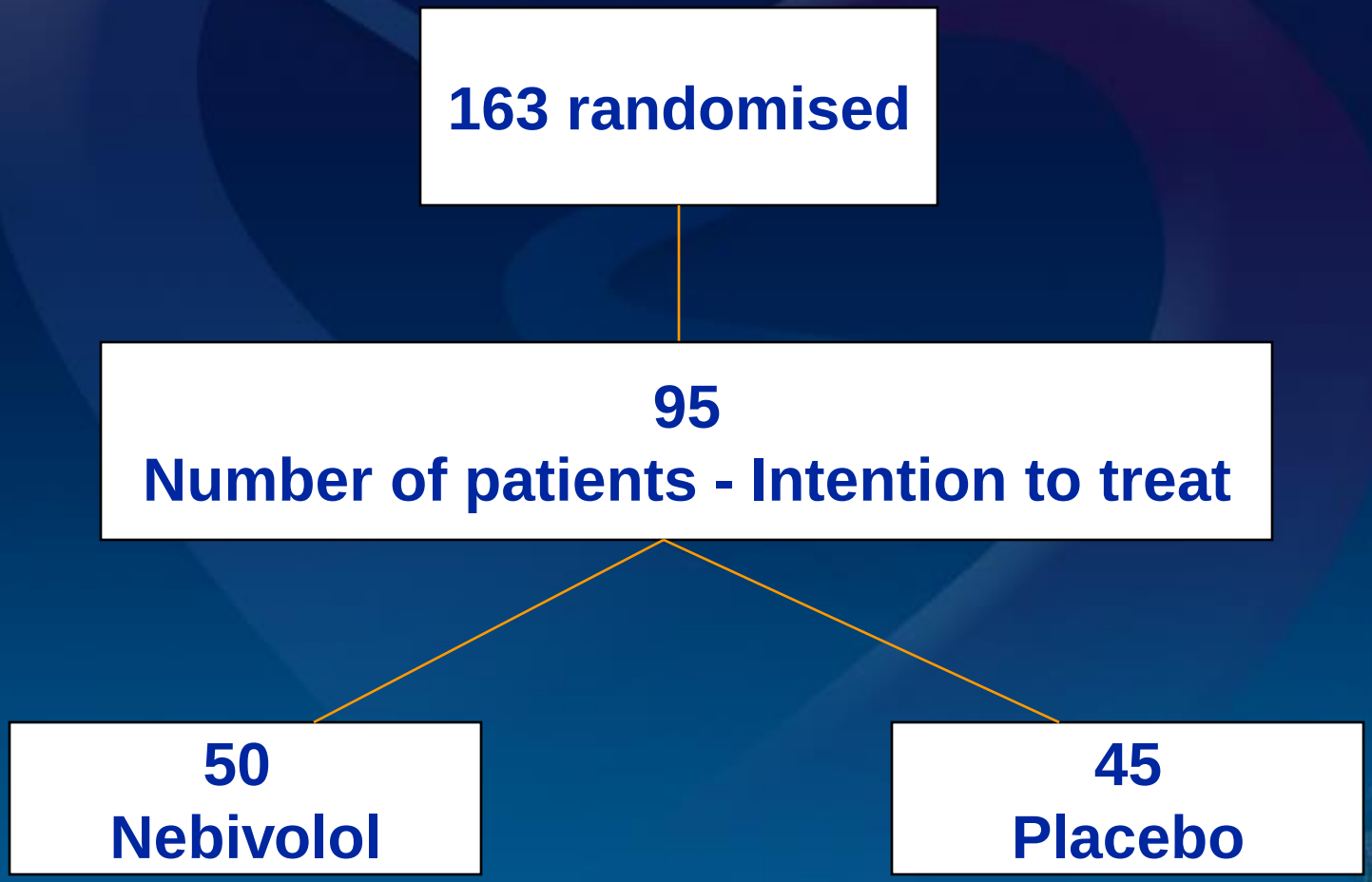
Primary:

Change in LVEF after 8 months treatment as compared to baseline

Secondary:

- ✓ Clinical Status (NYHA-Status)
- ✓ Hospitalisation
- ✓ Cardiac mortality
- ✓ Total mortality
- ✓ Combined endpoints
- ✓ Minnesota Living with Heart Failure Questionnaire

Patients included



Demographic Data

	Nebivolol N = 50	Placebo N = 45
Male	32 (64%)	32 (71%)
Female	18 (36%)	13 (29%)
Age	73,7	73,1
Weight	73,2	75,0
Height (cm)	167,1	170,5
BMI	26,1	25,8

Existing Therapy of Heart Failure before Inclusion

	Nebivolol N = 50	Placebo N = 45
RAAS Inhibitors	47 (94,0%)	44 (97,8%)
Diuretics	49 (98,0%)	43 (95.5%)
Digitalis	30 (60,0%)	25 (55,6%)

Concommitant Diseases

	Nebivolol n	%	Placebo n	%
Angina pectoris	1	(2.0%)	0	
Atrial Fibrillation	9	(18.0%)	7	(15.6%)
CAD	17	(34.0%)	13	(29.9%)
MI	1	(2.0%)	1	(2.2%)

Study Phases

Study- Phase	Visit	Week
Screening	1	0 - 2
Titration	2-6	2 - 10
Treatment	7-11	10 - 40
Follow up	12-13	40 - 48

Results

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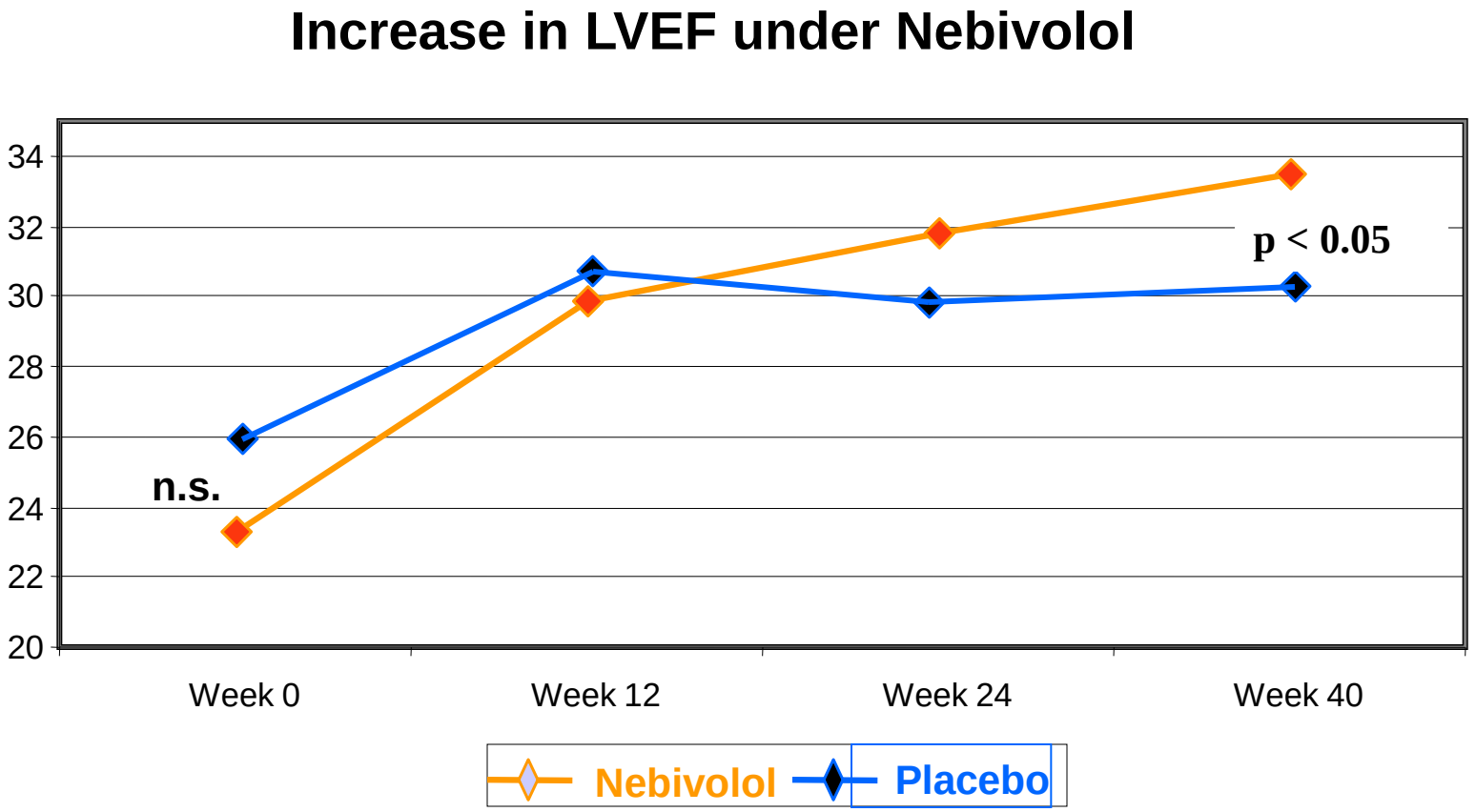
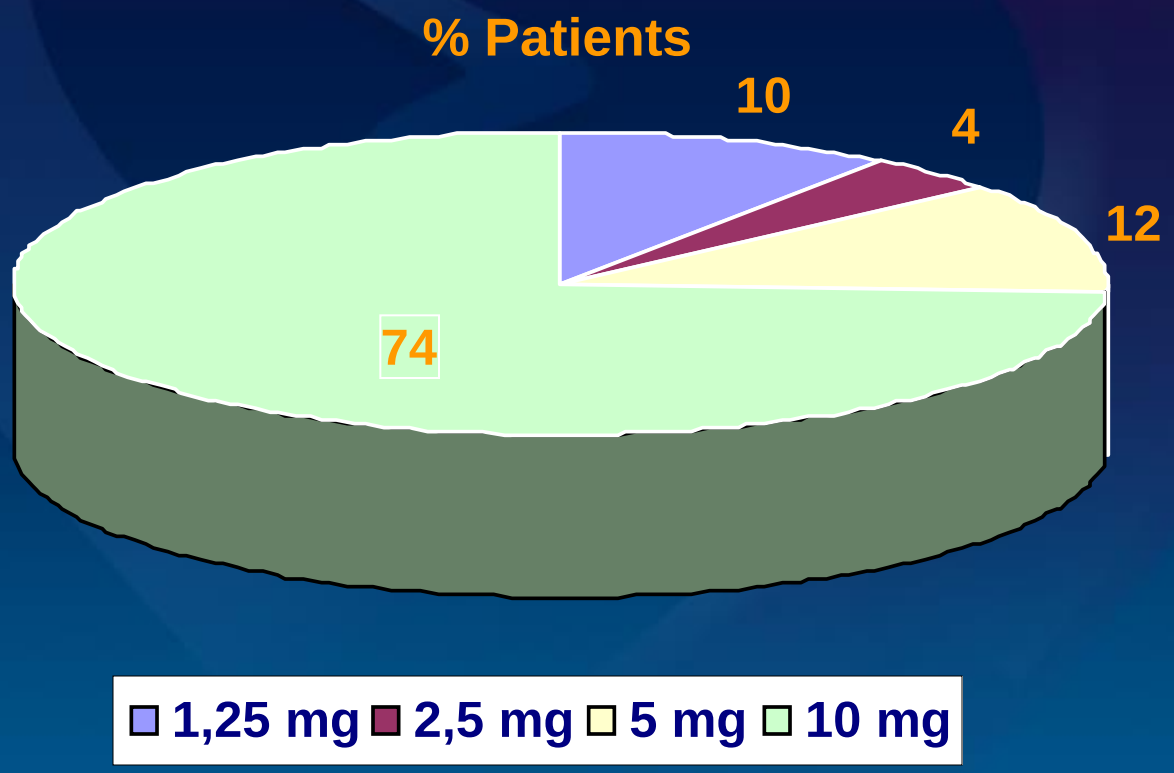
Comparison of LVEF



Maintenance Dose - Nebivolol Group



Increase in LVEF - Maximum Dose Nebivolol

Nebivolol-Dose	Number of Patients	Week 40 vs. baseline LVEF (%)
1.25mg	**5** (10%)	**6.0**
2.5mg	**2** (4%)	**8.0**
5.0mg	**6** (12%)	**8.7**
10.0mg	**37** (74%)	**11.1***

Change in systolic and diastolic Bloodpressure[1]

vs baseline	Nebivolol		Placebo	
	syst.	diast.	syst.	diast.
Week 12	- 3.7	- 4.0	- 0.6	- 3.3
Week 24	- 0.7	- 2.8	- 1.3	- 1.1
Week 40	2.7	- 1.5	1.6	- 2.7

[1] Value after 5 minutes in supine position, two measurements

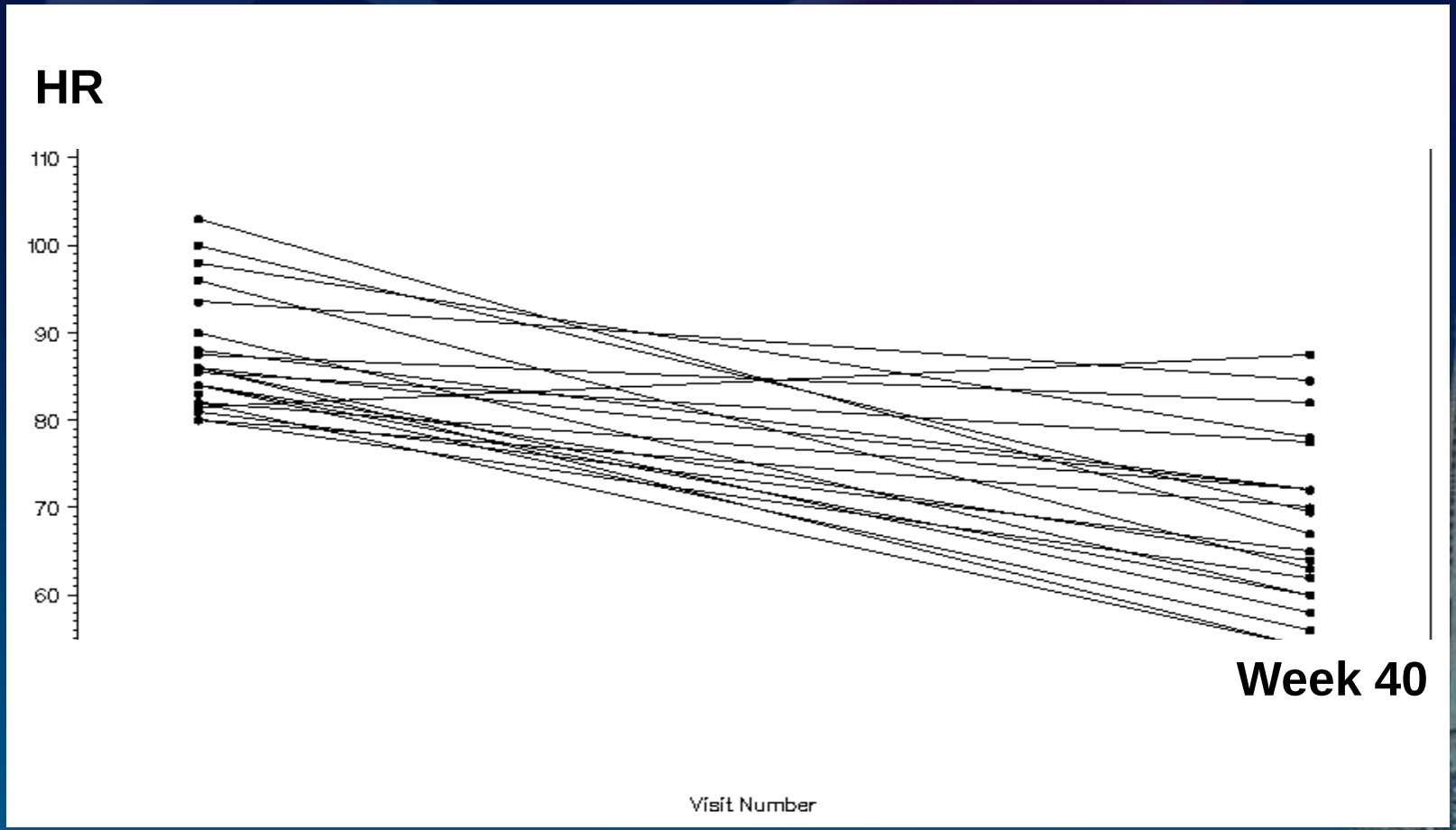
Decrease in Heart Rate

vs baseline	Nebivolol	Placebo
Week 12	- 14.8*	3.1
Week 24	- 11.9*	0.5
Week 40	- 11.7*	-1.3

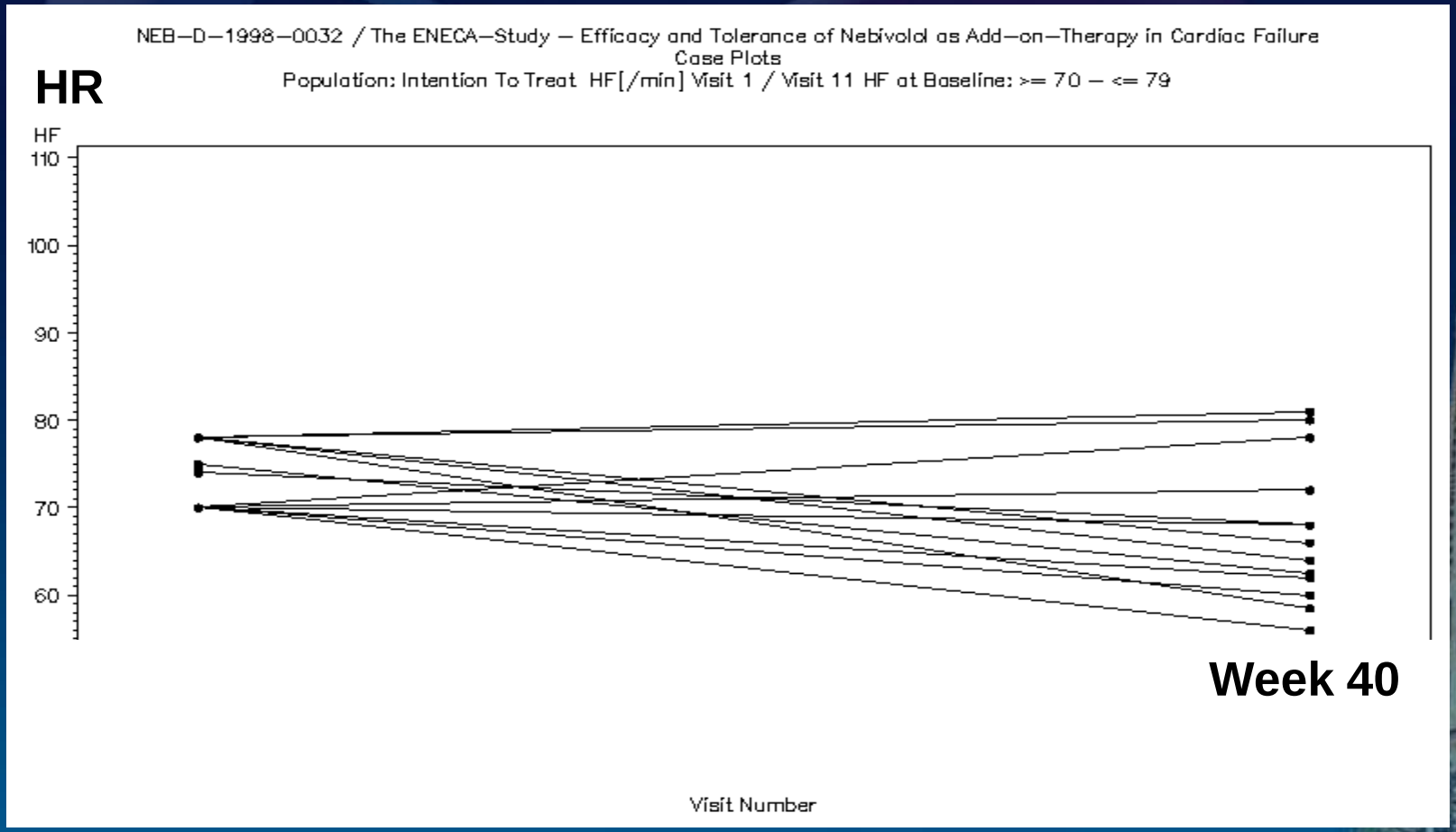
* p < 0.05

Baseline Heart Rate (>80/min)

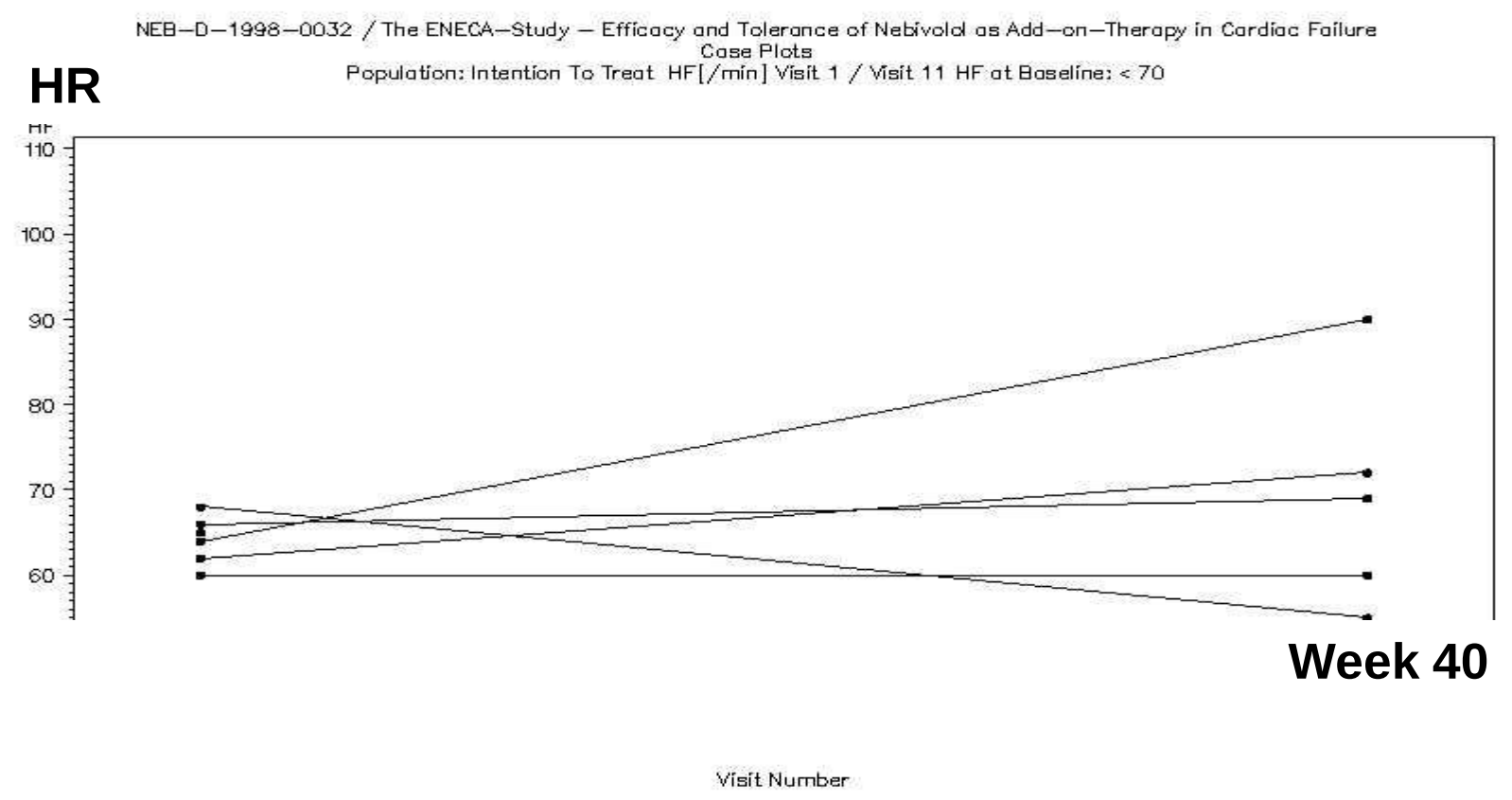
Nebivolol-Group



Baseline Heart Rate (70-79/min)
Nebivolol-Group



Baseline Heart Rate (< 70/min)
Nebivolol-Group



Secondary Variables

	Nebivolol		Placebo	
Hospitalisation*	**6**	**(12.0%)**	**10**	**(22.0%)**
Death	**1**	**(2.0%)**	**2**	**(4.4%)**
Adverse Events (total)	**47**	**(56.6%)**	**51**	**(63.8%)**
Adverse Events (cardiac)	**16**	**(19.3%)**	**15**	**(18.8%)**

*** p < 0.05**

Conclusions from ENECA:

Nebivolol

- **is effective in elderly patients with CHF**
- **shows a significant improvement in LVEF**
- **is superior to placebo**
- **reduces hospitalisation rate significantly**
- **has an excellent safety and tolerability profile**
- **maximum dose can be reached within 8 weeks**

Take Home Message

The unique profile of Nebivolol leads to

- pronounced efficacy

- excellent safety and tolerability

- easy handling for physicians and patients

“I feel good as long
as my doctor feels good”

George Berhard Shaw