

Simposio
**MODULAZIONE DEI RECETTORI β -ADRENERGICI:
DAL LABORATORIO AL LETTO DEL MALATO**

**53° Congresso Nazionale SIGG
28 Novembre 2008**

**TERAPIA CON BETA BLOCCANTI NEL
CARDIOPATICO ANZIANO**

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“CARDIOVASCULAR CONTINUUM”

Structural abnormalities

Effort symptoms

Symptoms at rest

Stage A
Pts at high risk

- Pts with:
- Systemic Hypertension
 - CAD
 - Diabetes Mellitus
 - Alcohol abuse
 - Use of cardiotoxic drugs
- Absence of symptoms
- Absence of cardiac structural abnormalities

60 ML
of persons
in USA

Stage B
Asymptomatic
LV Dysfunction

- Pts with:
- LV hypertrophy or fibrosis
 - Ventricular dilatation
 - Asymptomatic VHD
 - Previous MI
- Absence of symptoms
- Presence of cardiac structural abnormalities

10 ML
of pts in USA
2 yrs mortality
8-12%

400-650,000
deaths/year

Stage C
Symptomatic
LV Dysfunction

- Pts with:
- Dyspnea
 - Decreased Exercise Tolerance
 - Pulmonary Oedema
- Presence of current symptoms of HF
- LV Structural Changes

5 ML
of pts in USA
2 yrs mortality
16-22%

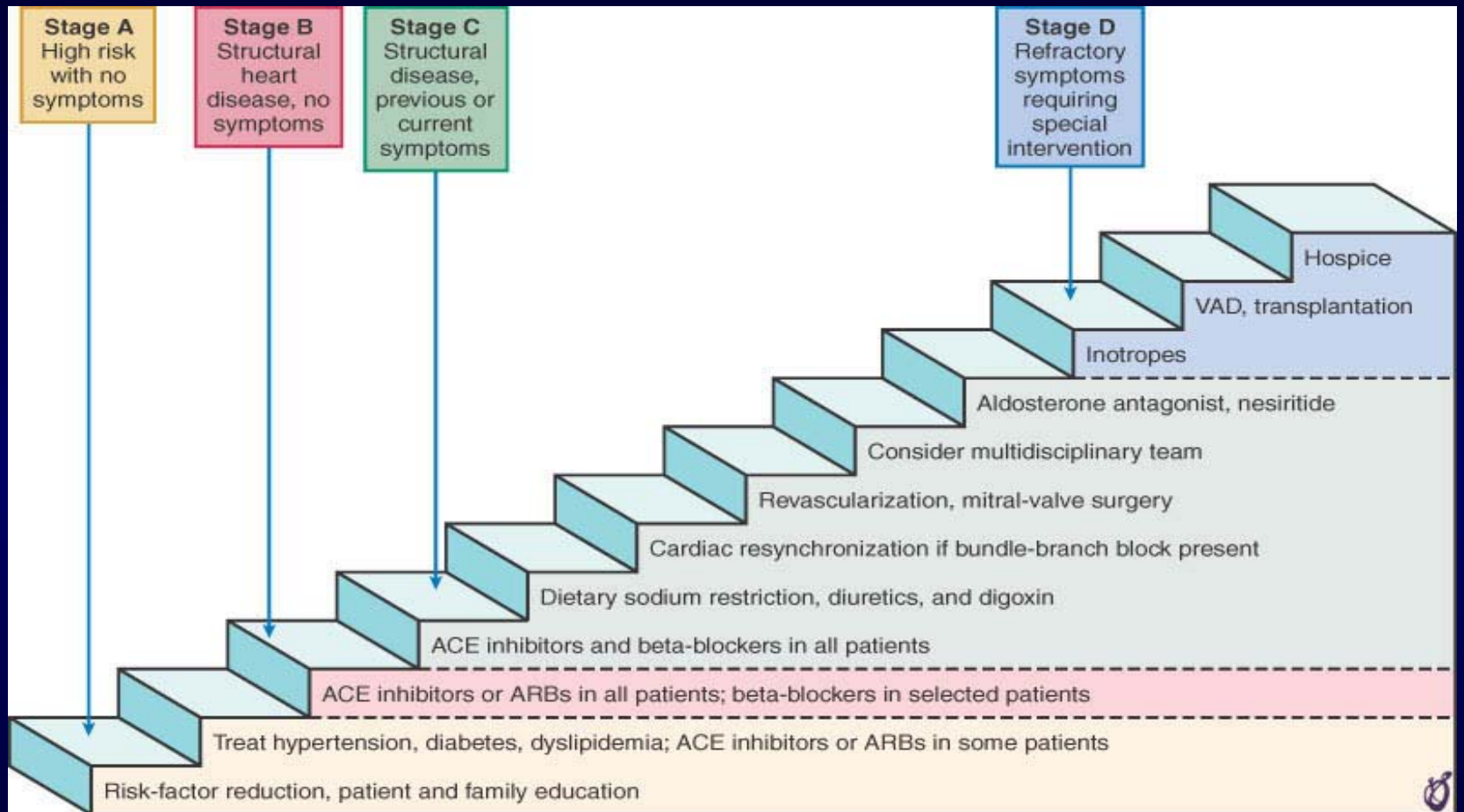
400-550,000
deaths/year

Stage D
Advanced Beat
Failure

- Pts with:
marked symptoms
at rest despite
maximal medical
therapy

200,000
pts in USA
1 year mortality
50%

100,000
deaths/year

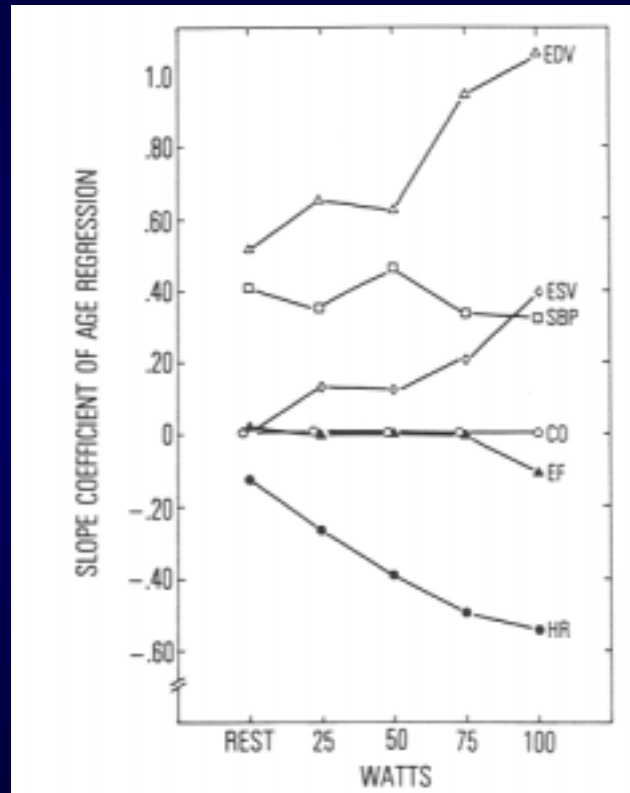


(Reprinted from Jessup M, Brozens S: Heart failure. N Eng J Med 348:2007-2018, 2003.)

CARDIOVASCULAR *FUNCTIONAL* MODIFICATIONS

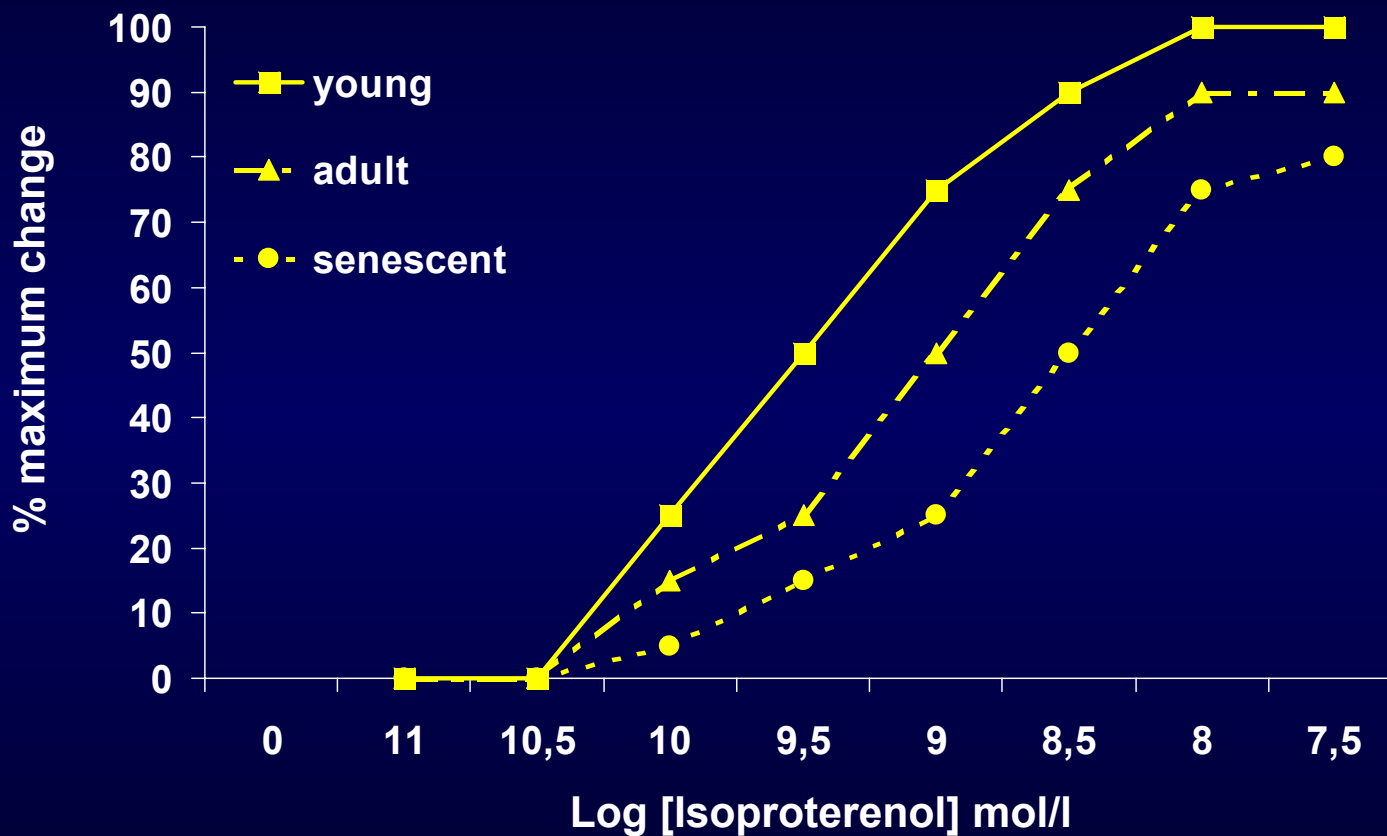
Age-related Changes	Plausible mechanisms	Implications to human disease
Altered regulation of vascular tone	NO production/effects	Vascular stiffness, hypertension Early atherosclerosis
↓ Threshold Ca ²⁺	Changes in gene expression of protein that regulate Ca ²⁺ handling	Lowered threshold for atrial and for overload ventricular arrhythmias, reduced diastolic and systolic function
↓ Cardiovascular reserve	↑ Vascular load ↓ Myocardial contractility ↑ Plasma levels of catecholamines ↓ of β-adrenergic modulation	
↓ Physical activity	Learned lifestyle	Negative impact on atherosclerotic vascular disease, hypertension and heart failure

Exercise cardiac output is maintained with advancing age in healthy human subjects



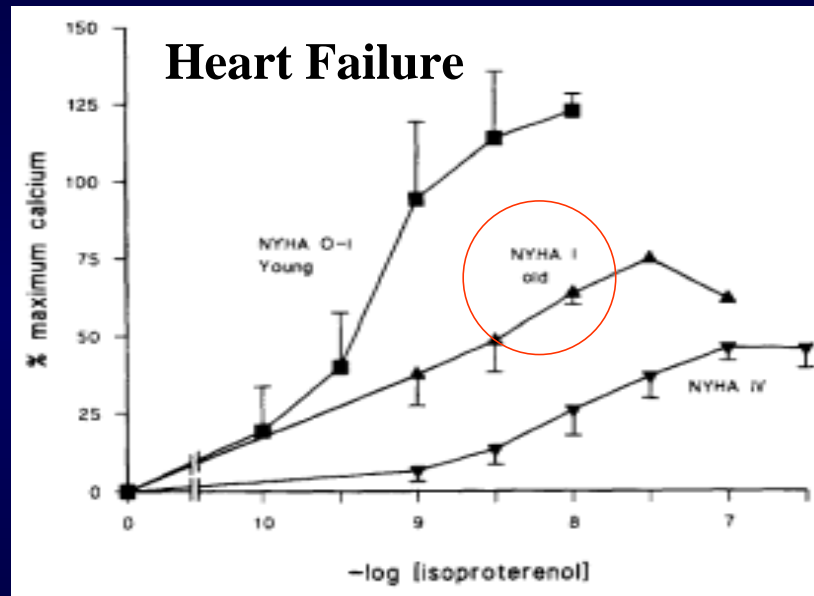
Rodeheffer RJ et al., Circulation 1984

Age-related decline to beta-adrenergic response

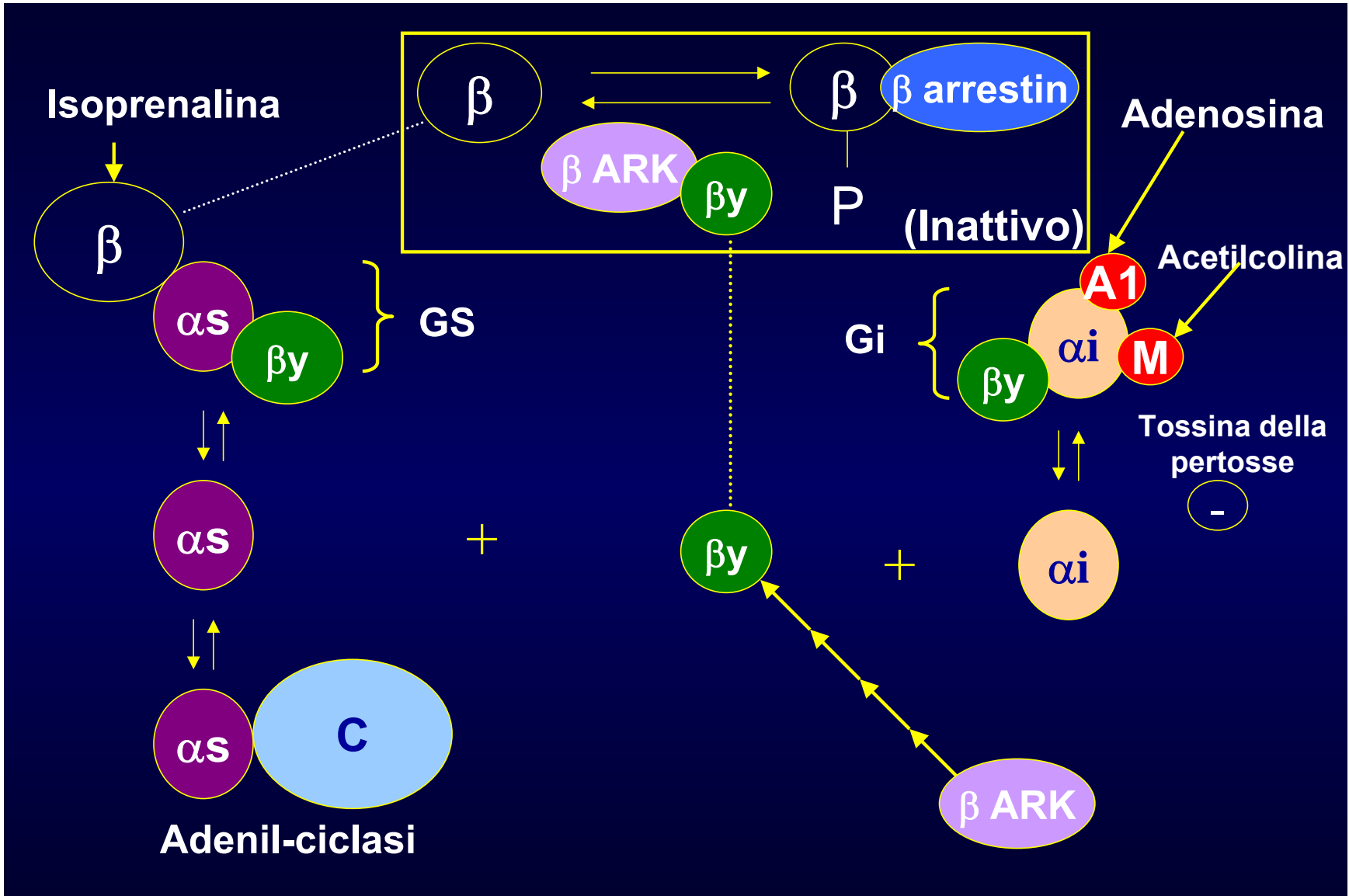


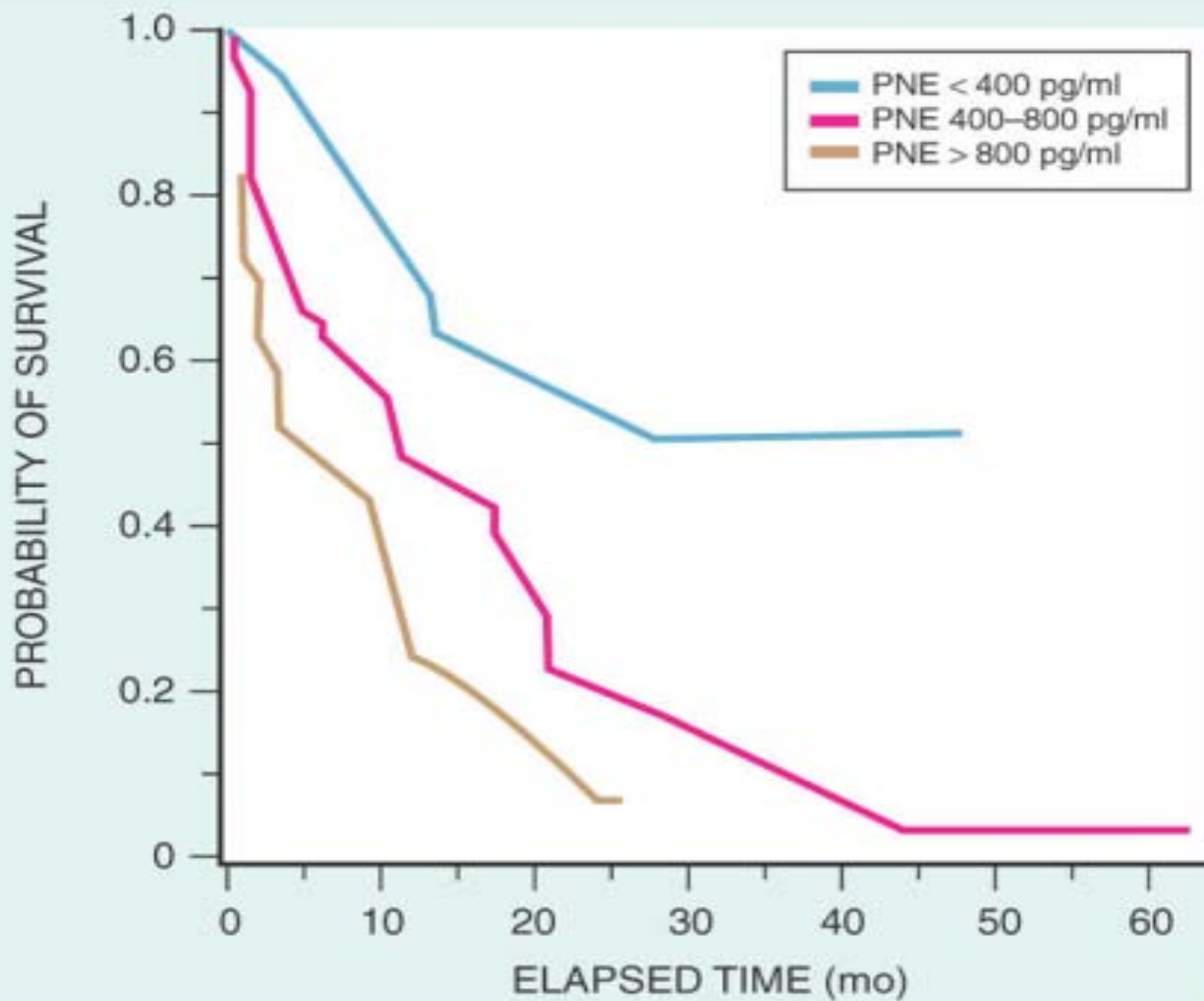
Ferrara N et al., J Mol Cell Cardiol 1996

Effects of age on β -AR stimulated LV contractility in human LV myocytes



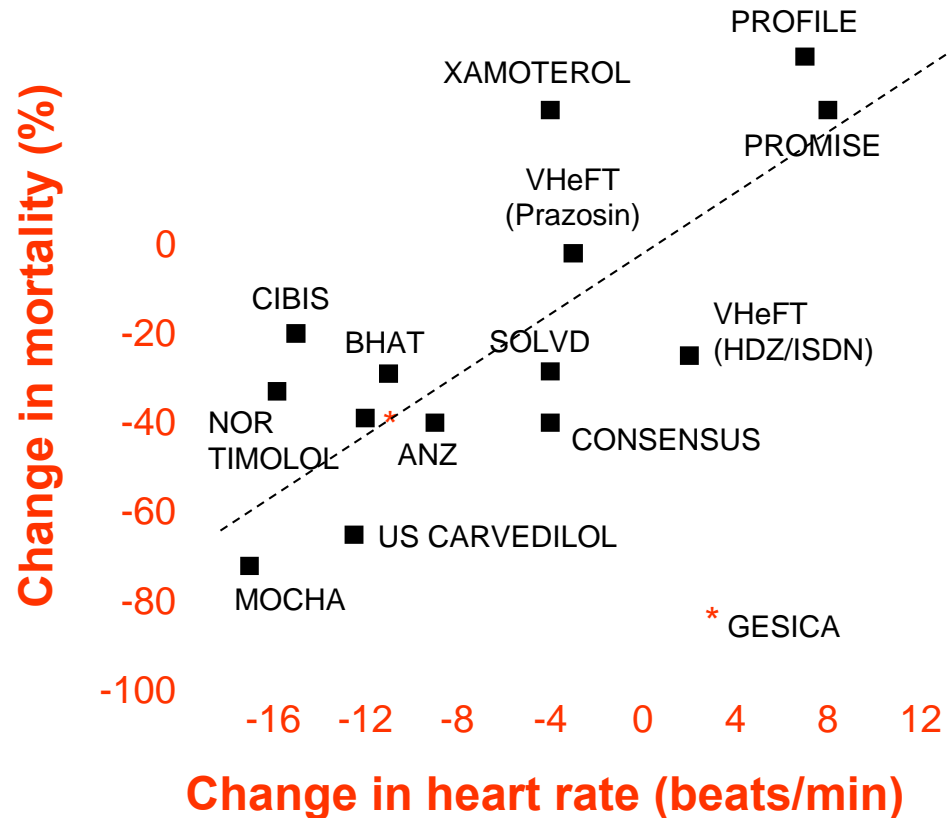
Davies, Ferrara, Harding. Cardiovasc Res, 1996





(From Colan JN, Levine TB, Olivari MT, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 311:918, 1984.)

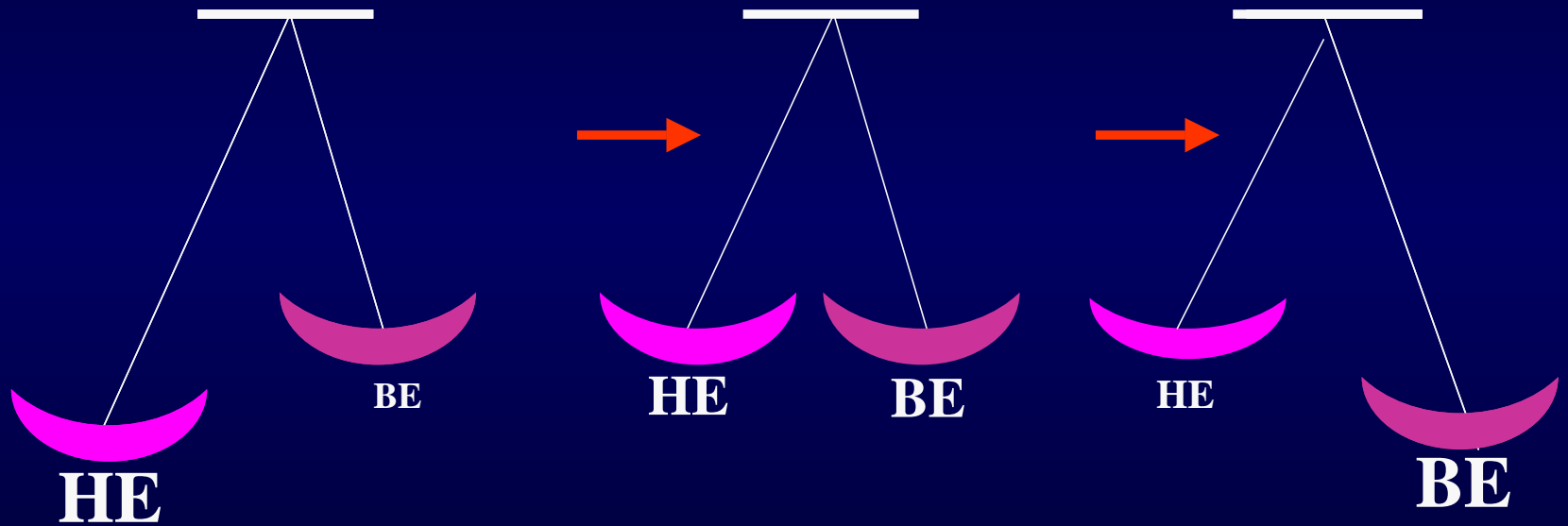
Heart rate and mortality



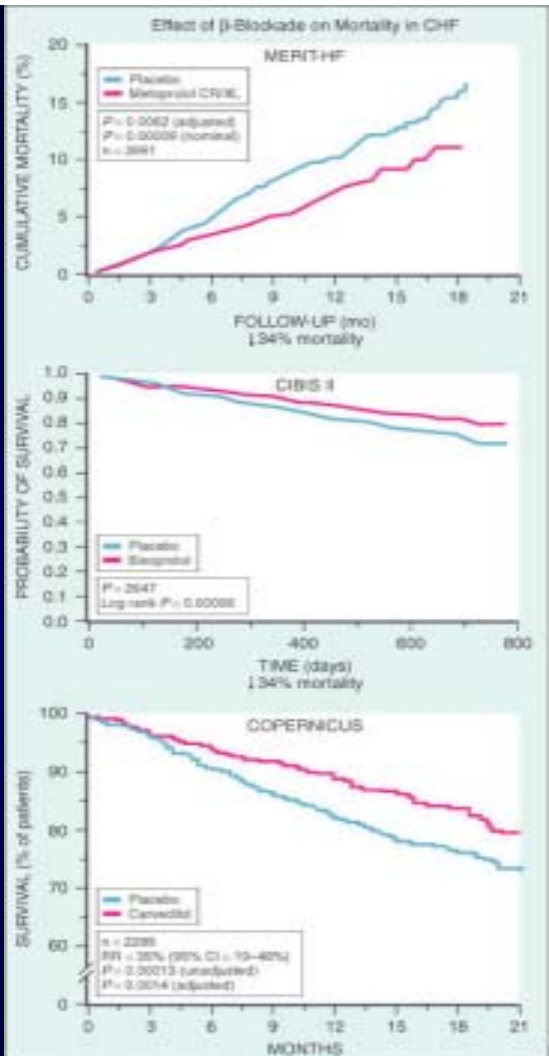
β -adrenergic blockers mechanism of action

- \uparrow Density of β_1 receptors
- Inhibit cardiotoxicity of catecholamines
- \downarrow Sympathetic activation
- \downarrow HR
- Antiischemic
- Antihypertensive
- Antiarrhythmic
- Antioxidant, Antiproliferative

Hemodynamic and Biological effects of Beta-blockers



HE= Hemodynamic Effect
BE= Biological Effect



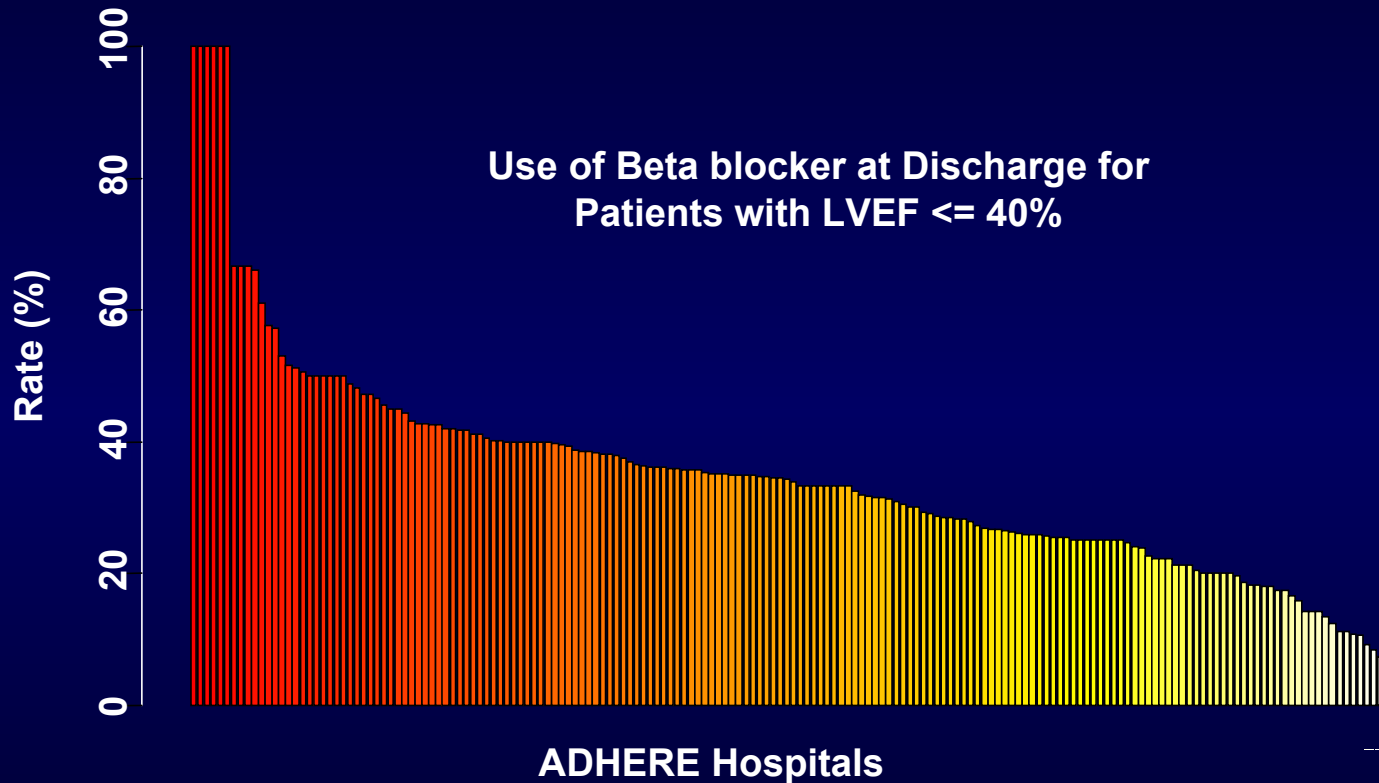
(Data from The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): A randomized trial. *Lancet* 353:6, 1999. Effect of metoprolol on chronic heart failure. Metoprolol CR/ER/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353:2001, 1999. and Packer M, Coats AJ, Fowler MB, et al: Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) Group: Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 344:1651, 2001.)

Choice of pharmacological therapy

	ACE-Inh.	β-blocker	Diuretics	Aldost.-Antag.
Asympt. LV dysfct.	indicated	post MI	not indicated	not indicated
Sympt. HF (NYHA II)	indicated	indicated	indicated if fluid retention	not indicated
Worsening HF (NYHA III)	indicated	indicated (under specialist care)	indicated	indicated
End-stage HF (NYHA IV)	indicated	indicated (under specialist care)	indicated	indicated

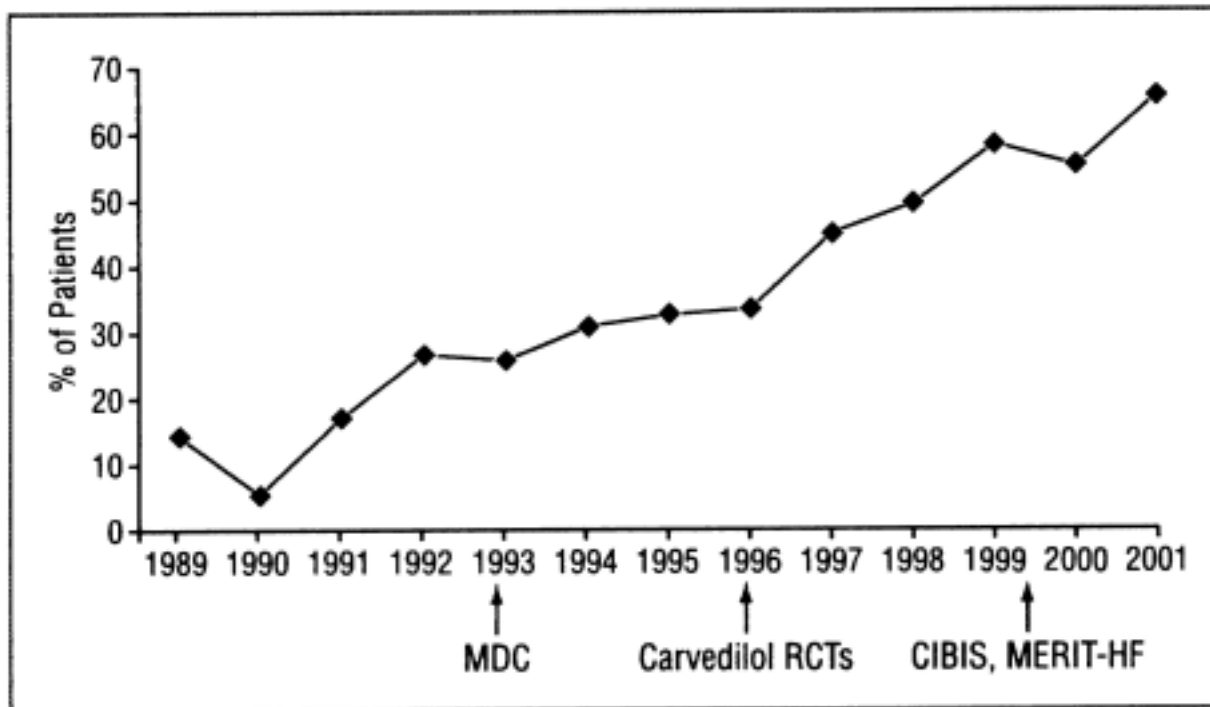
ESC HF guidelines

ADHERE: Variation in Beta Blocker Use



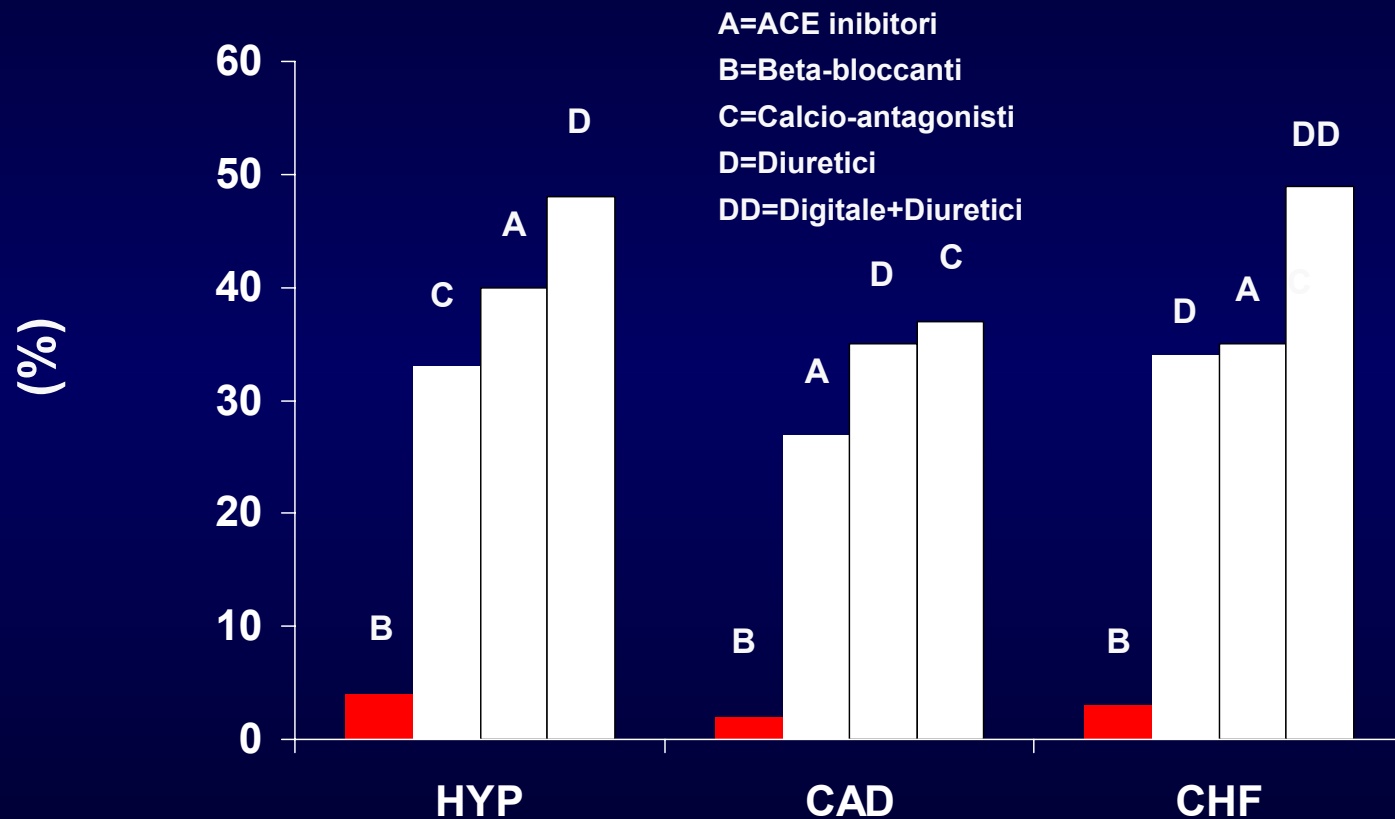
ADHERE: Dec 2002, 206 Hospitals (Subset with LVEF ≤ 0.40)
Fonarow J Card Fail 2003;9:S79

PRESCRIPTIONS OF β -BLOCKERS OVER TIME EXPRESSED AS THE PERCENTAGE OF NEW PATIENTS SEEN AT EACH PERIOD WHO STARTED β -BLOCKERS THERAPY



Tandon P. et al, Arch Intern Med 2004

Drug used in the treatment of Hypertension (HYP), coronary artery disease (CAD) and Congestive heart failure (CHF) in the elderly population of "Osservatorio Geriatrico Campano"



Cacciatore F et al., Arch Geront Geriatr, 1997

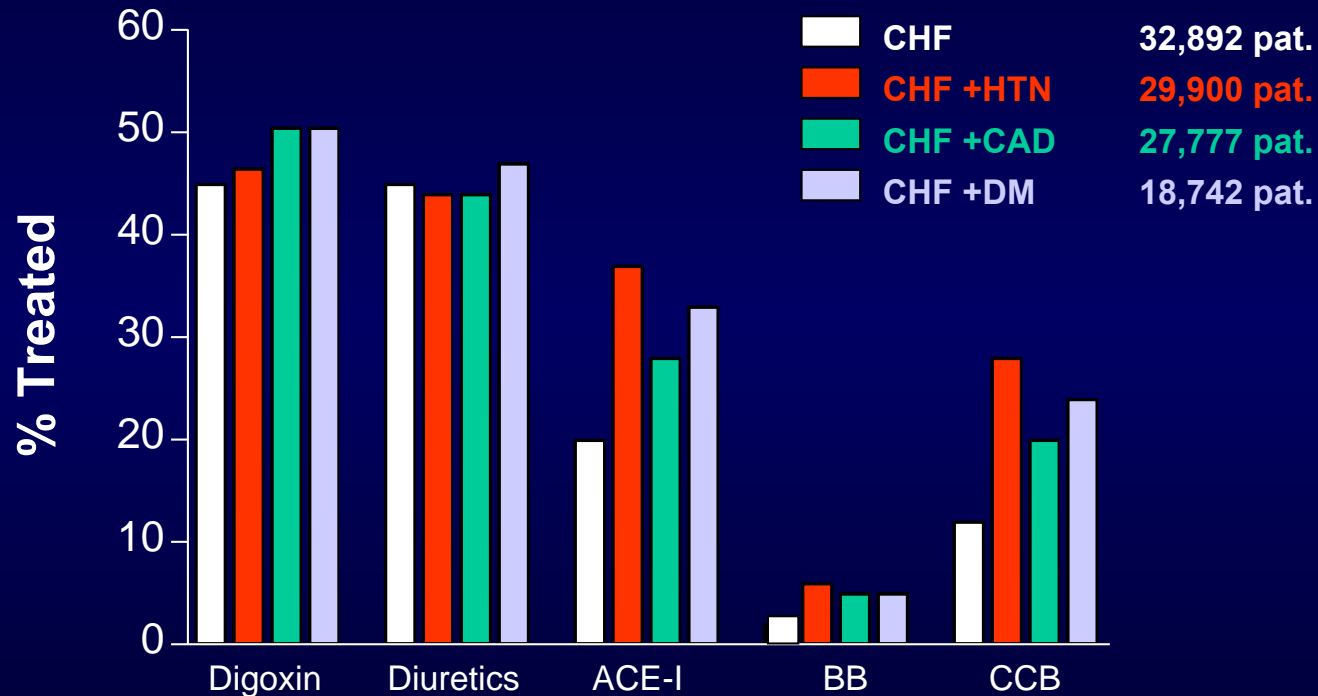
PHARMACOLOGIC TREATMENT OF HF IN ITALY

<i>Therapy</i>	<i>Age < 70 years (%)</i> <i>(n = 2294)</i>	<i>Age ≥ 70 years (%)</i> <i>(n = 1033)</i>	<i>p <</i>
Diuretics	85.3	90.2	0.001
ACE-inhibitors	84.7	74.9	0.001
Digitalis	69.3	68.9	NS
Beta-Blockers	13.1	6.9	0.001
Nitrate	37.2	52.0	0.001
Anti-platelets	32.8	37.4	0.001
Anticoagulants	29.1	20.5	0.001
Amiodarone	21.8	19.8	NS
Calcium-antagonists	12.4	17.2	0.001

Data from Italian Network on Congestive Heart Failure from ANMCO

Heart Failure treatment in the very old

SAGE-Program (Systematic Assessment of Geriatric Drug Use via Epidemiology)



Gambassi et al., Am Heart J 2000

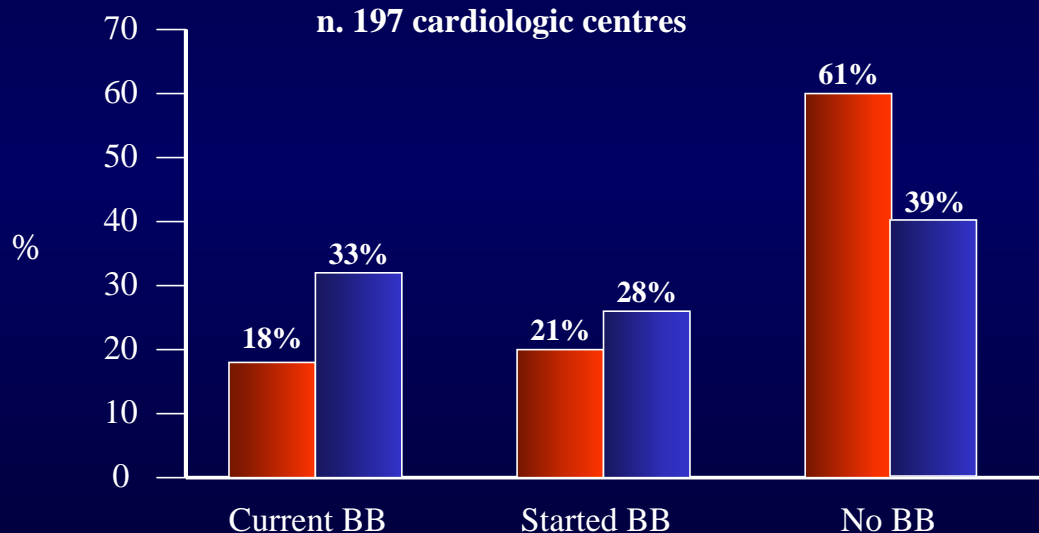
CHARACTERISTICS OF PATIENTS NOT RECEIVING β -BLOCKERS *(Cooperative Cardiovascular Project Survey)*

- **advanced age**
- **low ejection fraction**
- **black race**
- **heart failure**
- **obstructive pulmonary disease**
- **elevated serum creatinine**
- **diabetes mellitus type I**

USE OF β -BLOCKERS IN PATIENT >70 YEARS

(Bring-up Study 1 and 2)

- BRING-UP 1: age \geq 70 years
- BRING-UP 2: age \geq 70 years



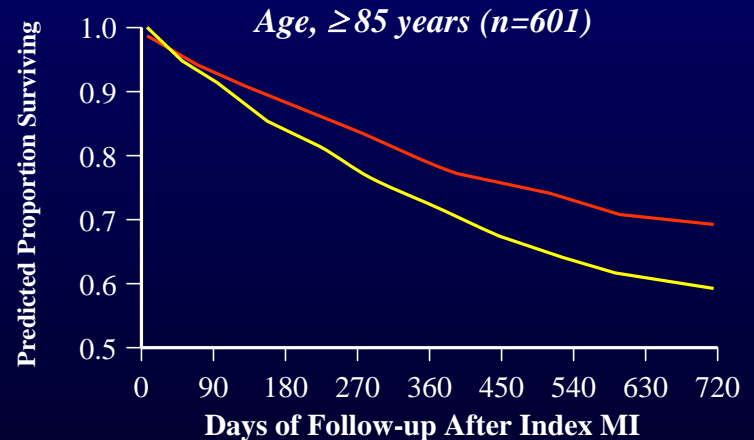
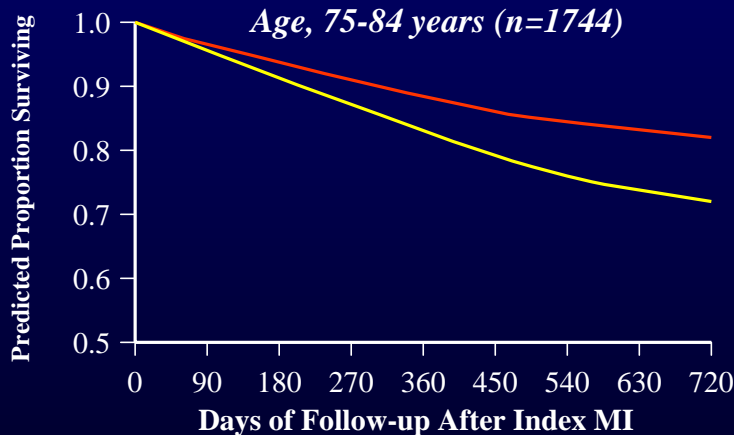
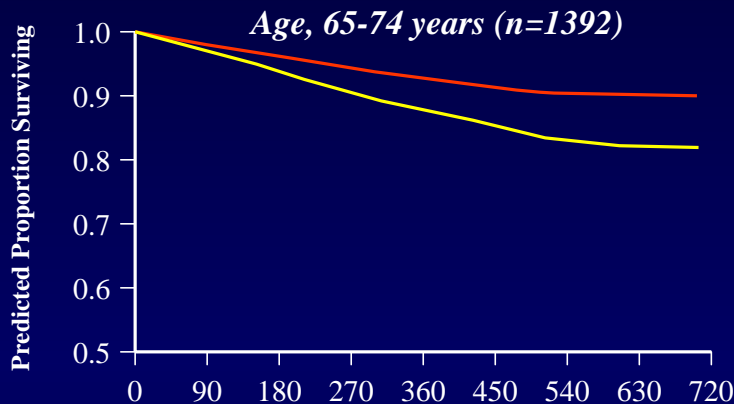
OBJECTIVES:

- 1) To accelerate the adoption of beta-blockade in clinical practice
- 2) to provide an epidemiology estimate of the proportion of patients with heart failure suitable for this treatment in general cardiology care;
- 3) to assess effectiveness of these drugs outside the setting of clinical trials.

PREDICTED SURVIVAL FOR β -BLOCKERS RECIPIENTS AND NON-RECIPIENTS STRATIFIED BY AGE

Soumerai et al., JAMA 1997

GLOBAL MORTALITY REDUCTION 43%



The Use of β -Blockers in a Tertiary Care Heart Failure Clinic

Dosing, Tolerance, and Outcomes

Puneeta Tandon, MD; Finlay A. McAlister, MD, MSc; Ross T. Tsuyuki, PharmD, MSc; Marilou Hervas-Malo, MSc; Ruth Dupuit, BSc; Justin Ezekowitz, MD; Bibiana Cujec, MD; Paul W. Armstrong, MD

Background: Little is known about the dosing, tolerability, and impact of β -blockers in nontrial participants. This study was conducted to evaluate the use and outcomes of β -blockers in a tertiary care heart failure clinic.

Methods: Analysis of prospectively collected data from a cohort of 1041 patients with heart failure seen at the University of Alberta Heart Function Clinic, Edmonton, from September 1, 1989, through July 1, 2001, with objective measurement of ejection fraction at baseline and prospective collection of data at all subsequent clinic visits.

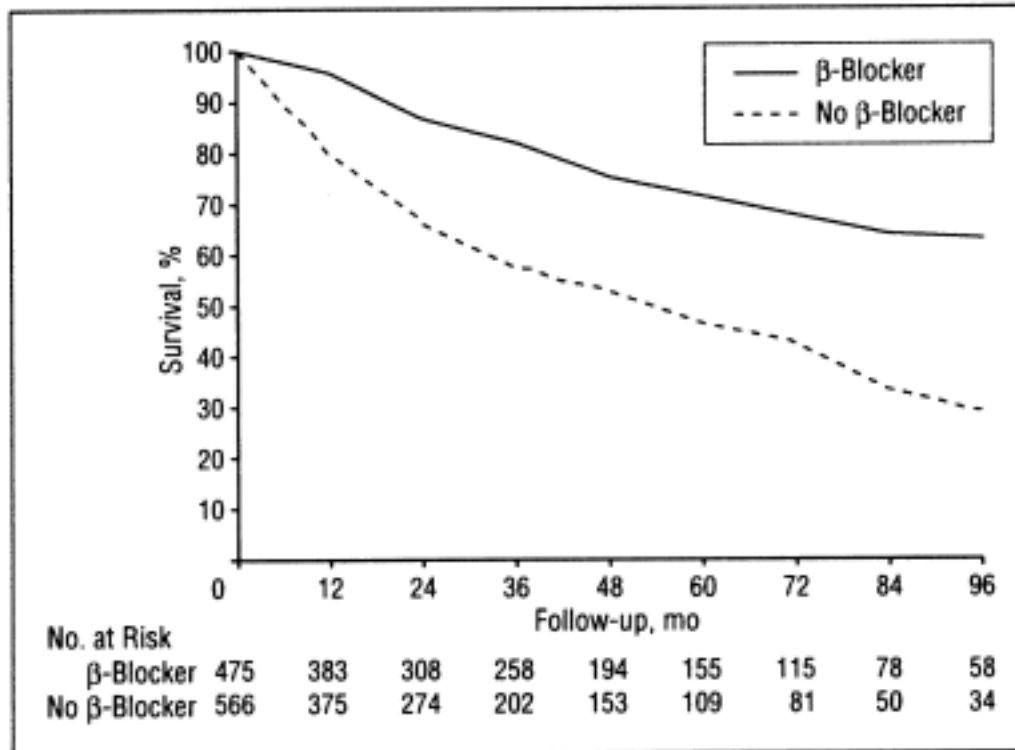
Results: Median age at baseline was 69 years; 65% were male; 75% had systolic dysfunction; mean ejection fraction was 33%; and 51% had New York Heart Association class III or IV symptoms. Median duration of follow-up was 32 months (interquartile range, 13-62 months). Overall, 46% of patients received β -blockers, but only 18% of these were ultimately prescribed the dosages achieved in the trials (mean maximum dosages

achieved, 27 mg/d for carvedilol and 81 mg/d for metoprolol tartrate). Of those patients prescribed β -blockers, 74% continued to receive them during follow-up. Blood pressure, heart rate, and failure symptomatology did not change appreciably before and after β -blockers were prescribed, or during the upward titration of the dosage. Although our patients were prescribed lower dosages than those used in trials, Cox multivariate regression revealed that β -blockers were associated with improved survival, even after adjusting for potential confounders including New York Heart Association class, year of prescription, and concomitant medication use (relative risk, 0.63; 95% confidence interval, 0.50-0.81).

Conclusions: The benefits of β -blockers seen in randomized trials extend to nontrial participants treated in a tertiary care clinic specializing in heart failure. In our cohort of elderly patients with multiple comorbidities, β -blockers were well tolerated.

Arch Intern Med. 2004;164:769-774

SURVIVAL OF PATIENTS WITH HEART FAILURE RECEIVING OR NOT RECEIVING β -BLOCKERS



Tandon P. et al, Arch Intern Med 2004

Age-Subgroups Analysis in the Major Clinical Trials on β -blockers Therapy in HF

Total Mortality

>59 yrs

<59 yrs

Total Mortality

>70 yrs

<70 yrs

Total Mortality and Hospital Admission

>70 yrs

<70 yrs

Total Mortality

>70 yrs

<70 yrs

Total Mortality

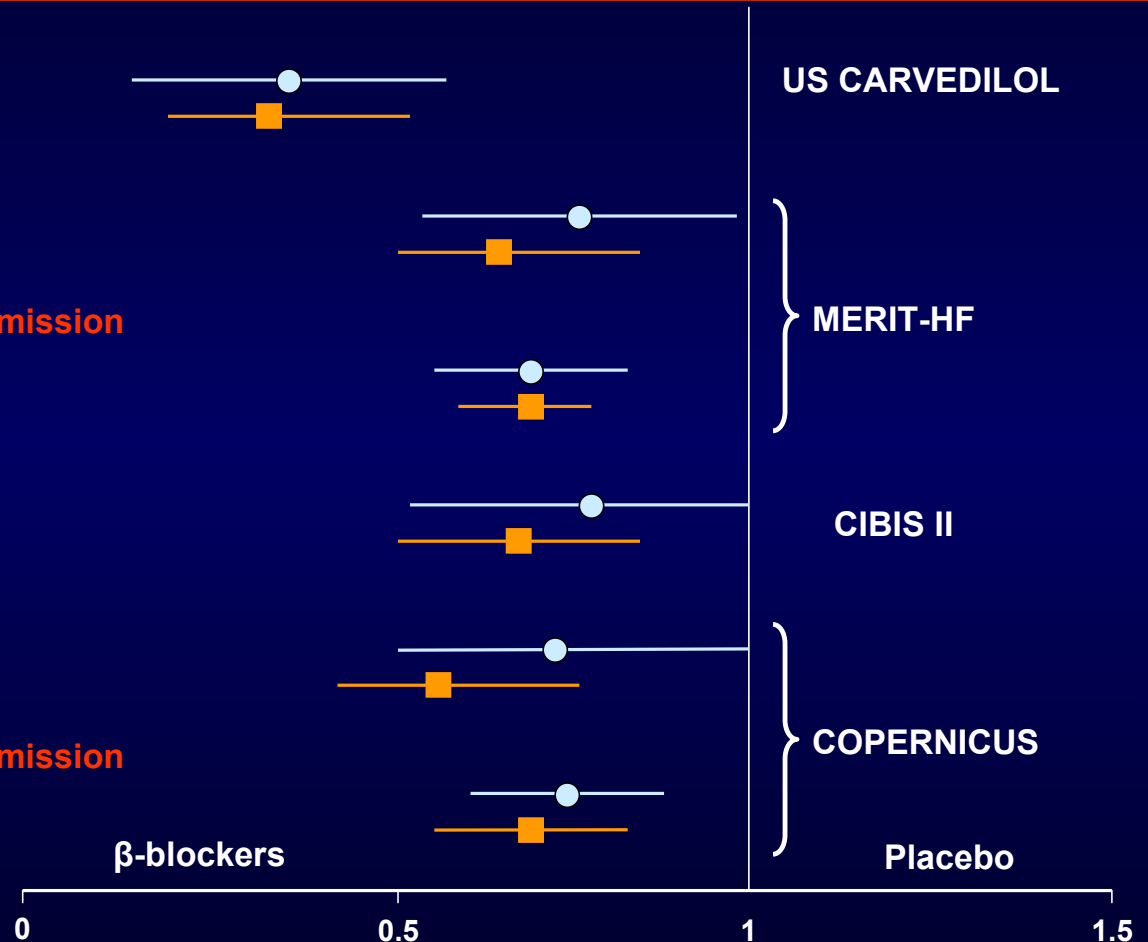
>65 yrs

<65 yrs

Total Mortality and Hospital Admission

>65 yrs

<65 yrs



DO THESE TRIALS LOOK AT THE ELDERLY ?



Do These Trials Look at the Elderly ?

Study

Drug

US Carvedilol

Carvedilol

CIBIS-II

Bisoprolol

Merit-HF

Metoprolol

BEST

Bucindolol

COPERNICUS

Carvedilol

CIBIS III

Bis vs Enal

Do These Trials Look at the Elderly ?

Study	Drug	Age
US Carvedilol	Carvedilol	58± 12
CIBIS-II	Bisoprolol	61±13
Merit-HF	Metoprolol	>70 y 32%
BEST	Bucindolol	60±12
COPERNICUS	Carvedilol	63±4
CIBIS III	Bis vs Enal	72±6

Do These Trials Look at the Elderly ?

Study	Drug	Age	Male
US Carvedilol	Carvedilol	58± 12	68%
CIBIS-II	Bisoprolol	61±13	81%
Merit-HF	Metoprolol	>70 y 32%	72%
BEST	Bucindolol	60±12	78%
COPERNICUS	Carvedilol	63±4	80%
CIBIS III	Bis vs Enal	72±6	70%

Do These Trials Look at the Elderly ?

Study	Drug	Age	Male	Comorbidity
US Carvedilol	Carvedilol	58± 12	68%	No
CIBIS-II	Bisoprolol	61±13	81%	No
Merit-HF	Metoprolol	>70 y 32%	72%	No
BEST	Bucindolol	60±12	78%	No
COPERNICUS	Carvedilol	63±4	80%	No
CIBIS III	Bis vs Enal	72±6	70%	No

Do These Trials Look at the Elderly ?

Study	Drug	Age	Male	Comorbidity	Disability
US Carvedilol	Carvedilol	58± 12	68%	No	No
CIBIS-II	Bisoprolol	61±13	81%	No	No
Merit-HF	Metoprolol	>70 y 32%	72%	No	No
BEST	Bucindolol	60±12	78%	No	No
COPERNICUS	Carvedilol	63±4	80%	No	No
CIBIS III	Bis vs Enal	72±6	70%	No	No

Target HF population in randomized clinical trial vs clinical “real world”

	RCTs	Real World
Age (years)	50-65	≥75
Gender	M>F	F>M
Diagnosis	HF main diagnosis	Comorbidity
Therapy	Focused on HF	Multi drugs therapy
Compliance	Optimal	Variable, often low

**TREAT ALL ELDERLY PATIENTS AND NOT ONLY
THE ATHLETES !**



The logo for the SENIORS study, featuring the word "SENIORS" in a serif font with a blue brushstroke behind the letters "I" and "O".

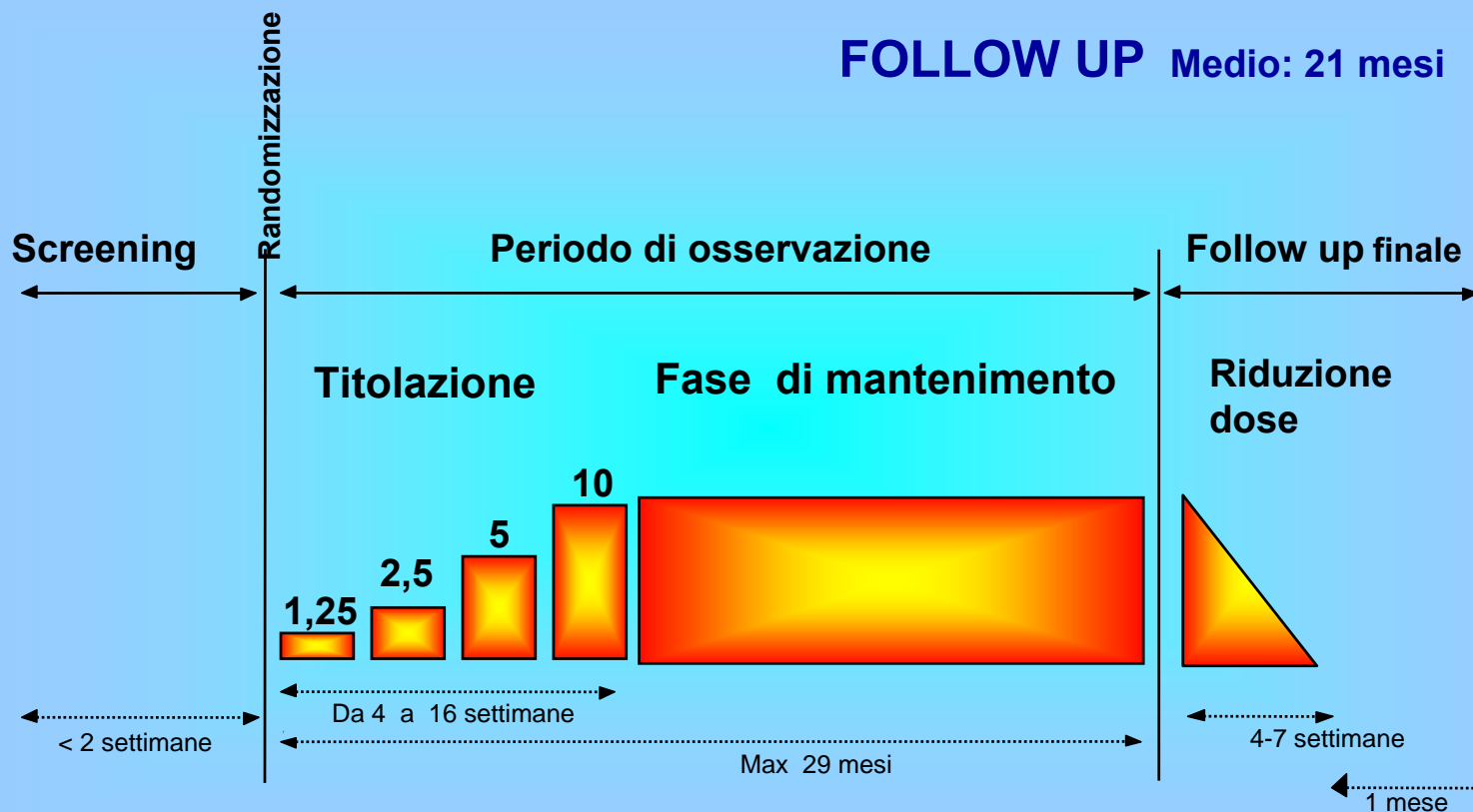
SENIORS

**Study of Effects of Nebivolol Intervention
on Outcomes and
Rehospitalisation
in Seniors with Heart Failure**

Flather MD. EHJ 2005;26:215-25

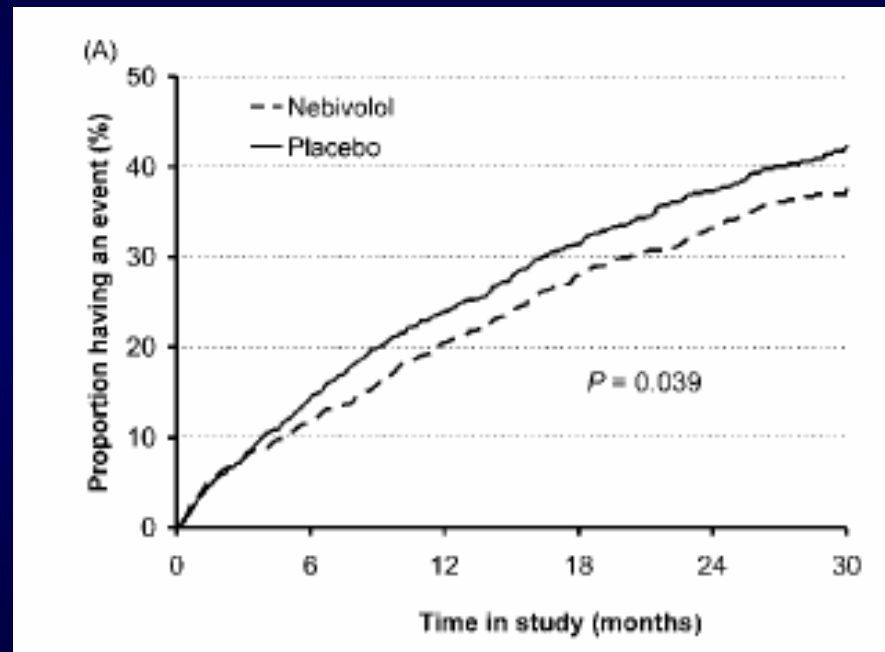
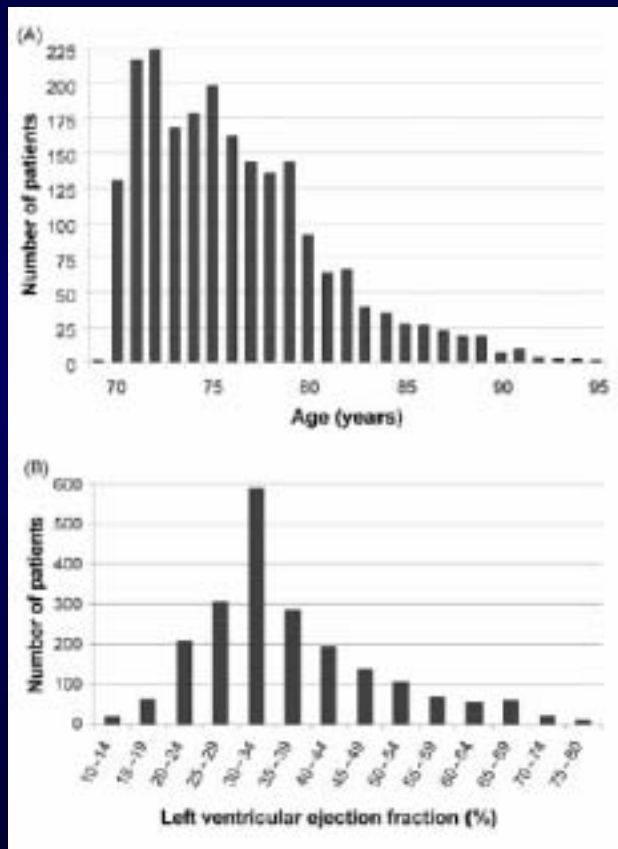
DISEGNO DELLO STUDIO

FOLLOW UP Medio: 21 mesi



Elaborato da: Flather MD. EHJ 2005;26:215-25 / Shibata MC. Int J Cardiol 2002;86:77-8.

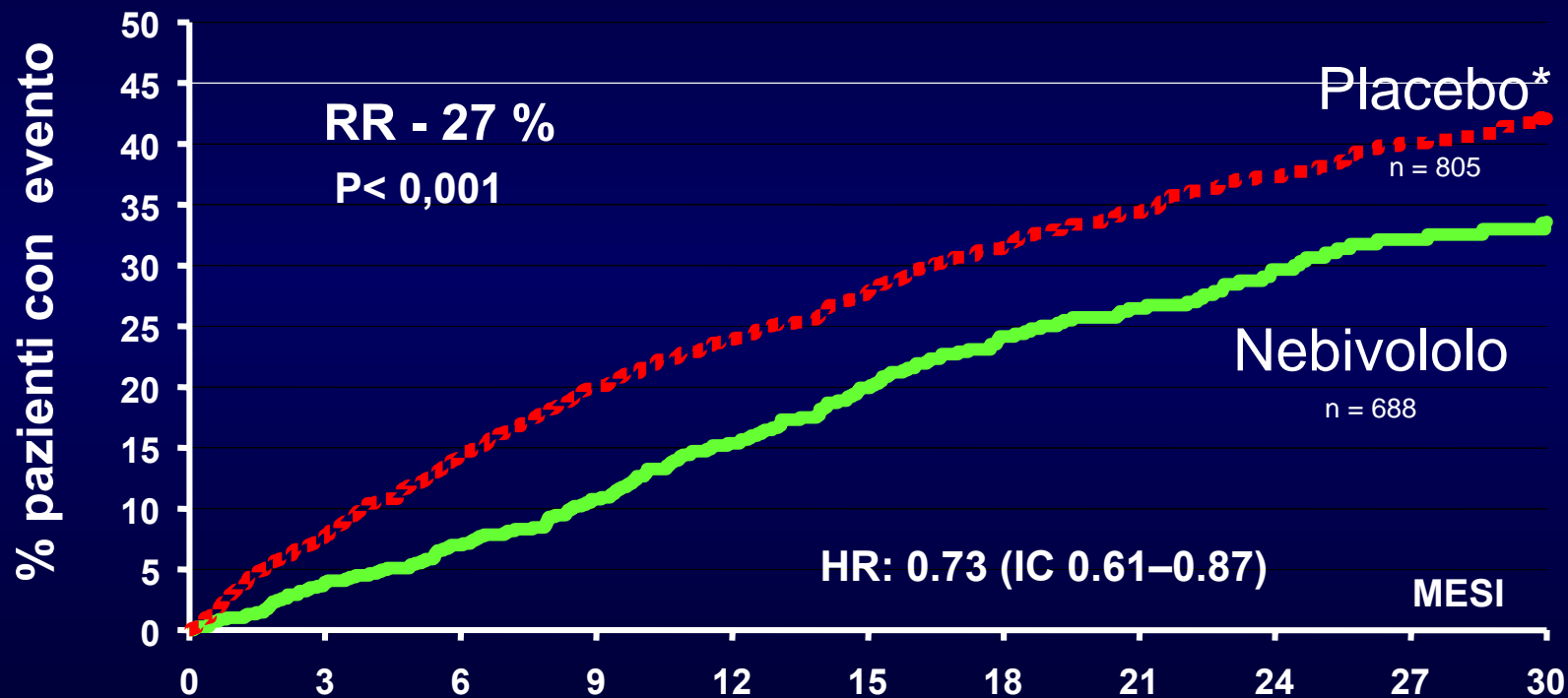
Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)



Endpoint PRIMARIO:

Mortalità totale - Ospedalizzazioni cause Cardiovascolari

Nebivololo dose target 10 mg vs. placebo



* Placebo: ACE-I e/o diuretici e/o digitale

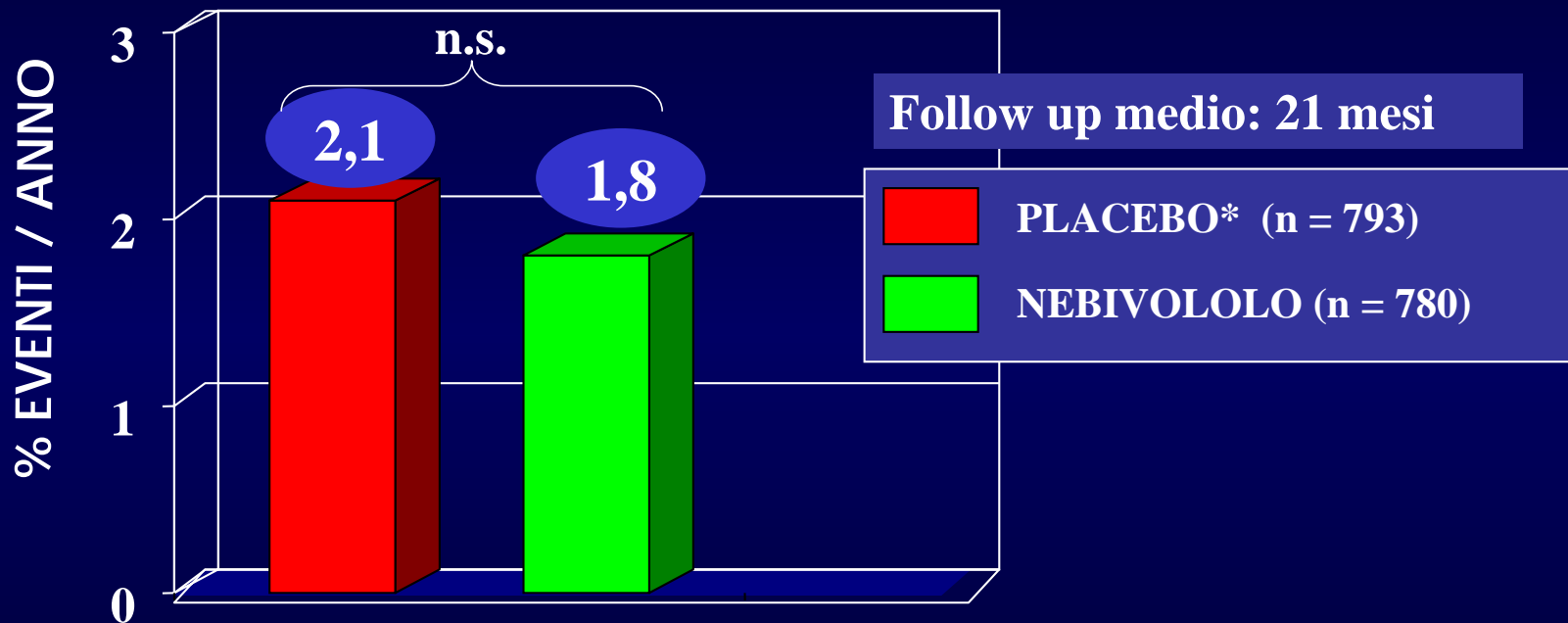
Da: Moen MD. Drugs 2006
Elaborata da data on file.

Variazioni dei valori medi di glicemia (mmol/l) nei pazienti diabetici e non-diabetici

	Non-diabetici		Diabetici	
	Nebivololo	Placebo*	Nebivololo	Placebo*
Basale	5.50	5.61	9.02	8.82
Δ fine studio	+ 0.03	+ 0.05	- 0.32	- 0.11

* Placebo = ACE-I e/o diuretici e/o digitale

NUOVI CASI di DIABETE MELLITO:
pazienti non diabetici al basale,
che hanno sviluppato diabete mellito durante lo studio

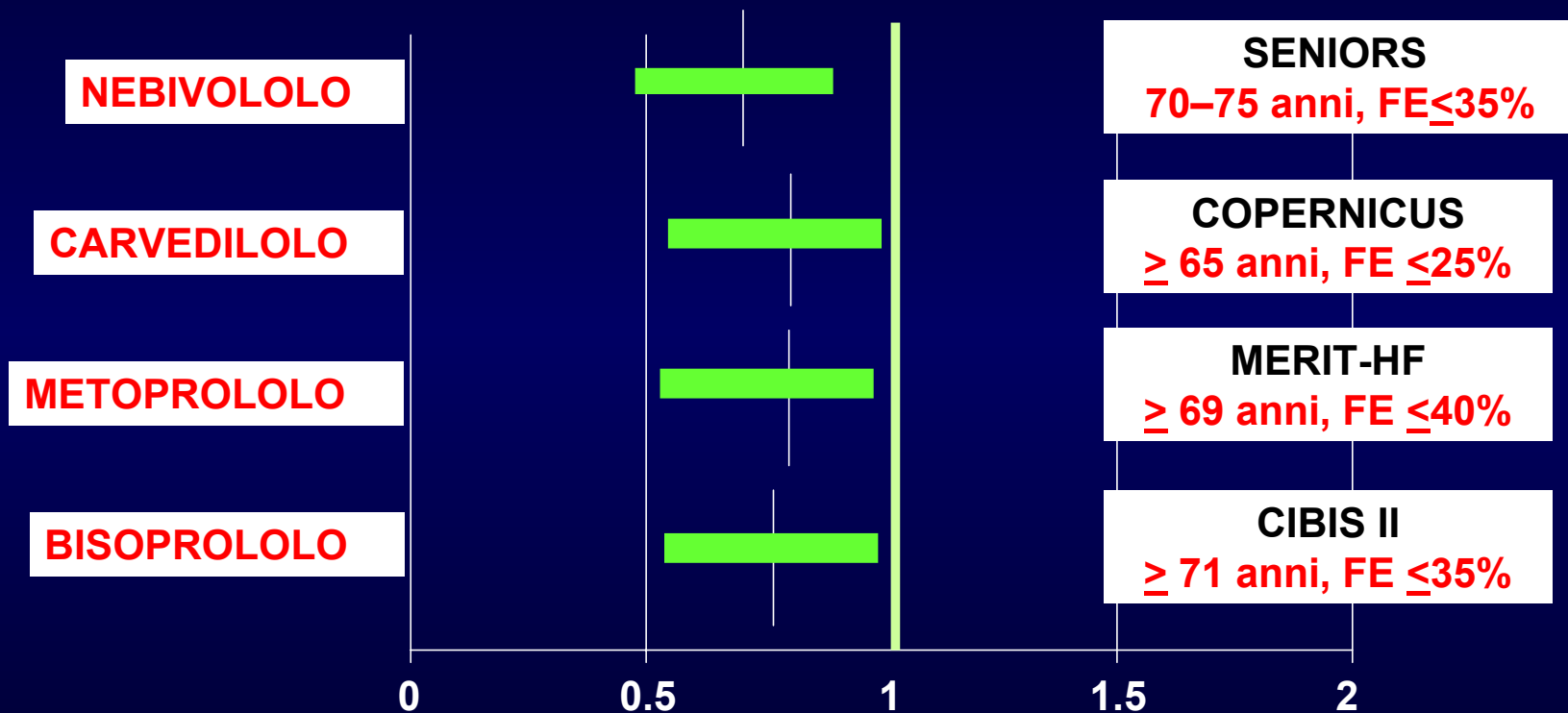


**Il trattamento con nebivololo non si associa
all'aumento di nuovi casi di diabete**

* Placebo = ACE-I e/o diuretici e/o digitale

Mortalità totale (Hazard Ratio)

Sottogruppi di pazienti confrontabili per caratteristiche clinico-epidemiologiche, studiati nei 4 principali studi condotti con β -antagonisti vs placebo, nello scompenso cardiaco



* Placebo: ACE-I e/o diuretici e/o digitale

Moen MD. Drugs 2006;66(10):1389-1409

Interruzione anticipata del trattamento*:

* Cause diverse dalla "morte"

	Nebivololo	Placebo
• Interruz. anticipate	27%	25%

Long-Term Cost-Effectiveness Analysis of Nebivolol Compared with Standard Care in Elderly Patients with Heart Failure

An Individual Patient-Based Simulation Model

*Guiqing Yao,¹ Nick Freemantle,¹ Marcus Flather,^{2,3} Puvan Tharmanathan,¹
Andrew Coats⁴ and Philip A. Poole-Wilson³ on behalf of the SENIORS Investigators.*

Long-Term Cost-Effectiveness Analysis of Nebivolol Compared with Standard Care in Elderly Patients with Heart Failure

An Individual Patient-Based Simulation Model

Guiqing Yao,¹ Nick Freemantle,¹ Marcus Flather,^{2,3} Puzan Tharmanathan,³ Andrew Coats⁴ and Philip A. Poole-Wilson³ on behalf of the SENIORS Investigators.

Abstract

Background and objective: The SENIORS trial demonstrated that nebivolol is effective in the treatment of heart failure in elderly patients (e.g. ≥ 70 years). This analysis evaluates the cost effectiveness of nebivolol compared with standard treatment.

Methods: An individual patient-simulation model based on a Markov modelling framework was developed to compare costs and outcomes for nebivolol and standard care in patients with heart failure starting treatment at the age of 70 years. Health states were defined by New York Heart Association (NYHA) class and death. At a given NYHA class and a given cycle, patients could die, be hospitalized for cardiovascular disease or remain stable. Risks for these events were derived from individual patient data from the SENIORS trial. The risk of each event in a given cycle was based on the subject's baseline characteristics and time in the current health state.

The economic analysis was conducted from the UK NHS perspective with a lifetime horizon. The costs (€; year 2006 values) considered were drug costs for nebivolol and other cardiac drugs, costs of GP visits, outpatient specialist visits and cardiovascular-related hospitalizations. Univariate and probabilistic sensitivity analysis was conducted.

Results: In the baseline analysis, the total cost per patient was €6740 and €9288, and QALYs were 5.194 and 5.843 for patients aged 70 years at the start of treatment for the standard treatment and nebivolol groups, respectively. The probabilistic sensitivity analysis provided an incremental cost-effectiveness ratio of €3926 (95% CI 3731, 4159) per QALY.

Conclusions: This analysis indicates that nebivolol appears to be a cost-effective treatment for elderly patients with heart failure compared with standard care.

Gli autori utilizzando il parametro "QALY" (acronimo di Quality Adjusted Life Years), un'unità di misura impiegata nell'analisi costi/benefici che combina insieme la durata della vita con la qualità della stessa, hanno osservato che il Nebivolo appare essere un trattamento con un favorevole rapporto (rispetto alle terapie convenzionali) nella cura dei pazienti anziani con scompenso cardiaco.

Pharmacoeconomics. 2008;26(10):879-89

HOW TO TREAT THE ELDERLY ?

... The therapeutic approach to systolic dysfunction in the elderly should principally be identical to that in younger heart failure patients with respect to the choice of drug treatment.

Due to altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in the elderly, therapy should be applied more cautiously. Sometimes reduced dosages are necessary.

... **Beta-blockade should not be withheld because of increasing age alone.**

β -Adrenergic Blockers - Initiation and titration

- **Patient stable**
 - **no physical evidence of fluid retention**
 - **no need for i.v. inotropic drugs**
- **Start ACE-Inh. / diuretic first**
- **Patients may initially worsen or experience adverse effects (hypotension) – monitor and adapt other therapy first before changing β -blocker dose**
- **Start low, increase slowly (increase the dose every 2 - 4 weeks)**

CONCLUSIONS

The recent large registries conducted in Europe and in U.S. (200.000 pts) indicate that the mean age of HF at the time of diagnosis is 75 yrs and more than 50% of pts are more than 80 yrs of age.

Beta-blocker therapy appears to be beneficial in elderly pts with cardiovascular disease, and in particular in those with HF. Those beneficial results are associated with a significant reduction in mortality and morbidity.