Managing Heart Failure in Elderly:

The Role of New Beta-blocker

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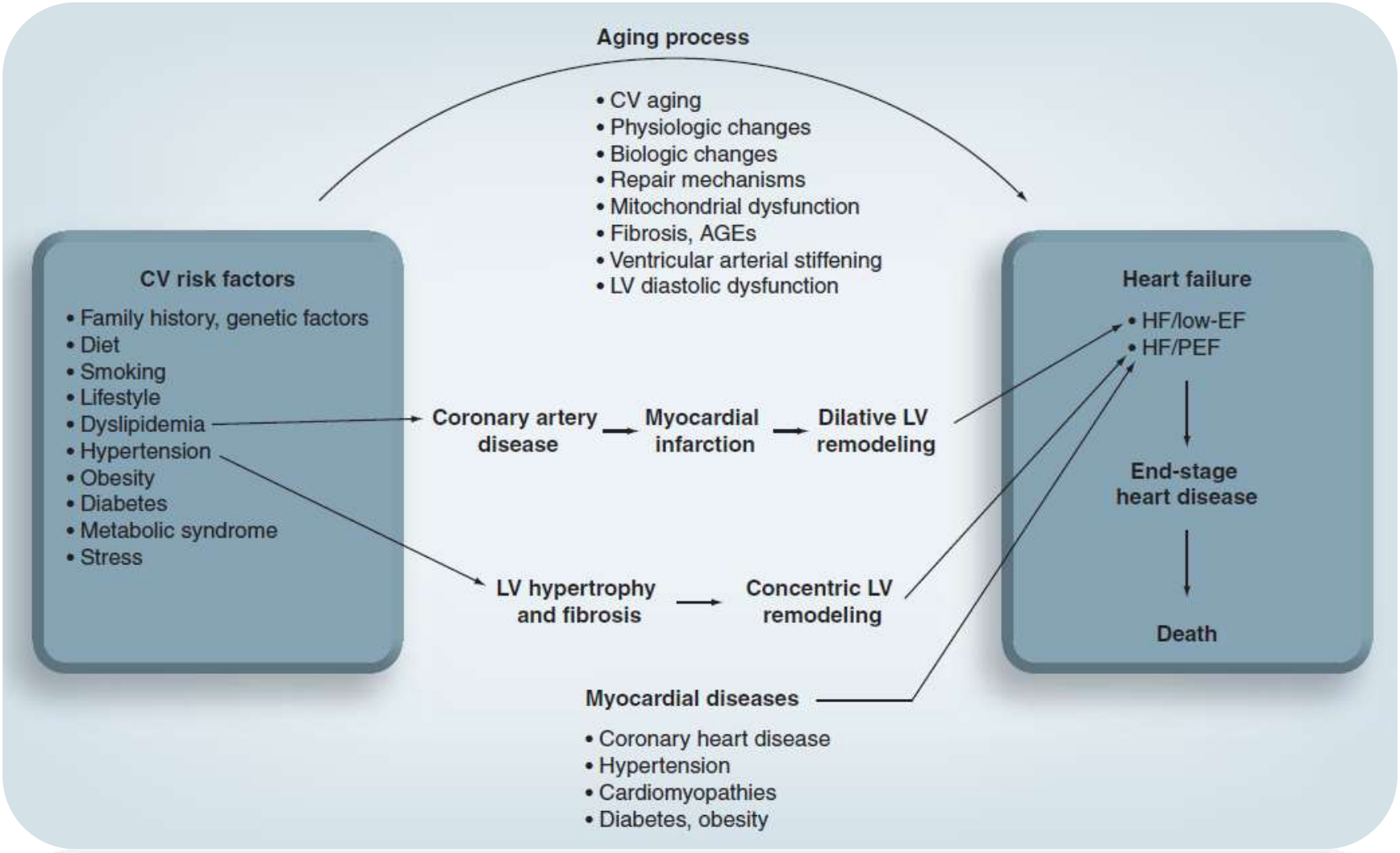
ELDERLY = more than 65 yo

Five reasons why heart failure is important in elderly

1. **Most of HF patients are elderly** (80%) and acute HF is the leading cause of hospitalization in patients > 65 yo
2. Elderly patients with HF often present with **complex comorbidities** and **polypharmacy**
3. The **clinical decision-making** process required in these patients may be very **challenging**
4. Improved CVD therapies, have increased the number of younger patients who **survive into old age**
5. **MI and hypertension are more common in the elderly** and it leads to more severe left ventricular dysfunction, adverse remodeling and HF in elderly

Pablo Díez-Villanueva. Geriatr Cardiol 2016; 13: 115-117

Heart Failure, Aging, and CV Continuum



Expert Review of Cardiovascular Therapy, 8:5, 695-715

Diastolic Heart Failure in Elderly

Dia is

Definition of heart fa on fraction (HFrEF)

Type of HF		HFrEF
CRITERIA	1	Symptor
	2	LVEF <4
	3	–

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

ides[b];

e (LVH and/or LAE),
s see Section 4.3.2).

(Ponikowski P. et al, EHJ 2016)

Common problems with medical therapy of HF in the elderly

- Underuse and under-dosage of recommended pharmacotherapies with known mortality benefit
- Comorbidities are common, aggravate HF, complicate therapy and increase the total HF burden
- Response to diuretics, ACE inhibitors, b-blockers and/or positive inotropes may be diminished
- Frailty and cognitive impairment are common and lead to reduced compliance

European Journal of Heart Failure (2013) 15, 717–723

Heart Failure Drugs in Elderly

Diuretics

- Controlled studies on the effects of prolonged diuretic therapy in elderly patients with CHF are lacking
- Elderly patients are more susceptible to diuretic-induced hypovolemia and orthostatic hypotension
- Diuretic therapy should be started immediately in elderly patients with CHF and signs of significant volume overload
- Continued diuretic therapy is of questionable value in the management of CHF when congestion is not present

Heart Failure Clin 13 (2017) 503–512

Clinical evaluation of the necessity for diuretic use for heart failure in elderly patients

Current and past indications for diuretic therapy

Symptoms or signs of congestive heart failure

Blood pressure levels (pretreatment and treated)

Peripheral oedema (when disabling or complicated by ulcera crurae

Glaucoma
Renal disease
Hypercalciuria

Relevant factors

Cardiac function

systolic and diastolic function, cardiac arrhythmias, valvular disease

Cardiac events

recent myocardial infarction, acute congestive heart failure

Hypertensive organ damage

stroke, renal disease, left ventricular hypertrophy

Duration of diuretic therapy

Comorbidity

Presence or anticipation of adverse effects

Presence of drug-drug interactions

Possible alternatives

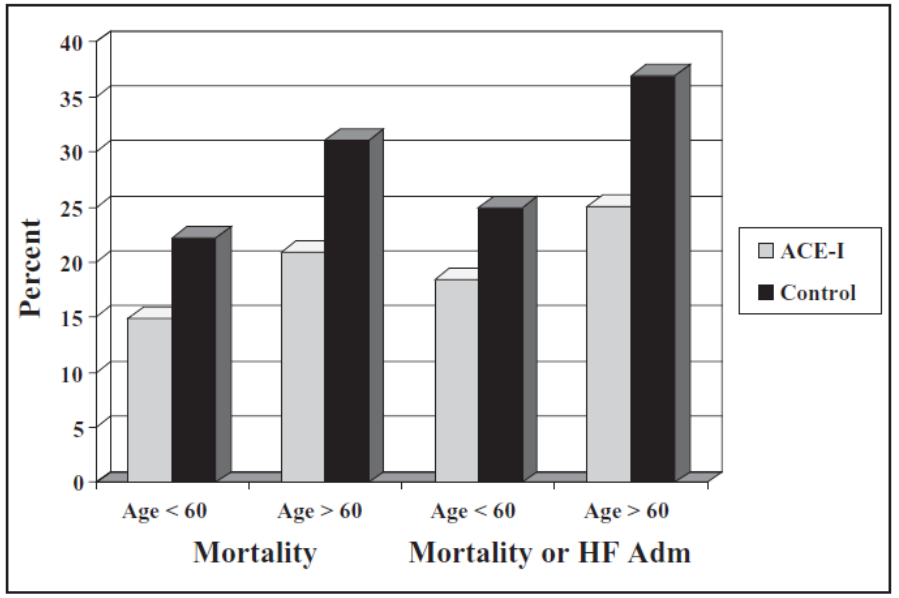
salt restricted diet, other medications, elastic stockings

Withdrawal of diuretic therapy should be gradual, with careful follow-up including blood pressure measurement and evaluation of signs and symptoms of fluid retention

Drugs & Aging 2000 Apr; 16 (4): 289-300

What is the evidence for treatment in the elderly?

- **ACEi / ARBs**
  - Available data suggest that the effects of angiotensin receptor blockers (ARBs) and Angiotensin-Converting Enzyme Inhibitors (ACEI) are **<u>similar</u>** in the younger and in the elderly



Effects of angiotensin-converting enzyme inhibitors (ACE-I) on mortality and heart failure admissions in older compared with younger patients

Garg R. JAMA. 1995;273:1450–1456.

What is the evidence for treatment in the elderly?

- **MRA**
  - Limited information concerning aldosterone antagonists in elderly patients, although a subgroup analysis of the Randomized Aldactone Evaluation Study (**RALES**) trial showed a **similar effect** on outcome in patients aged <67 and >67 years
  - Older age is associated with an increased incidence of side effects, particularly **hyperkalaemia**

N Engl J Med 1999; 341:709-717

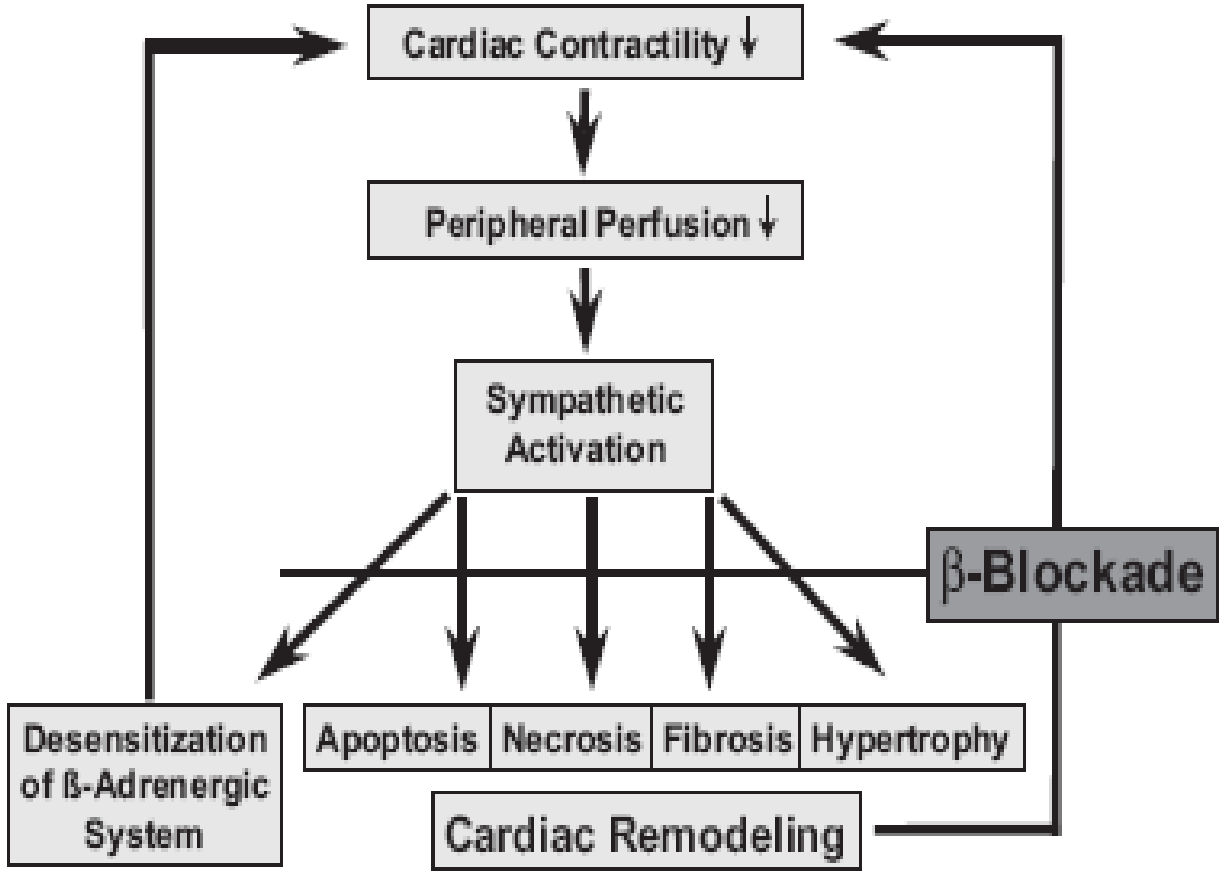
What is the evidence for treatment in the elderly?

- Beta Blocker
  - Meta-analyses of beta-blocker trials have shown the possibility of this class of drugs to reduce mortality and morbidity rates by 30%. [1]
  - The **largest** trial evaluating the efficacy of beta-blocker therapy in the elderly was the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (**SENIORS**) study. [2]

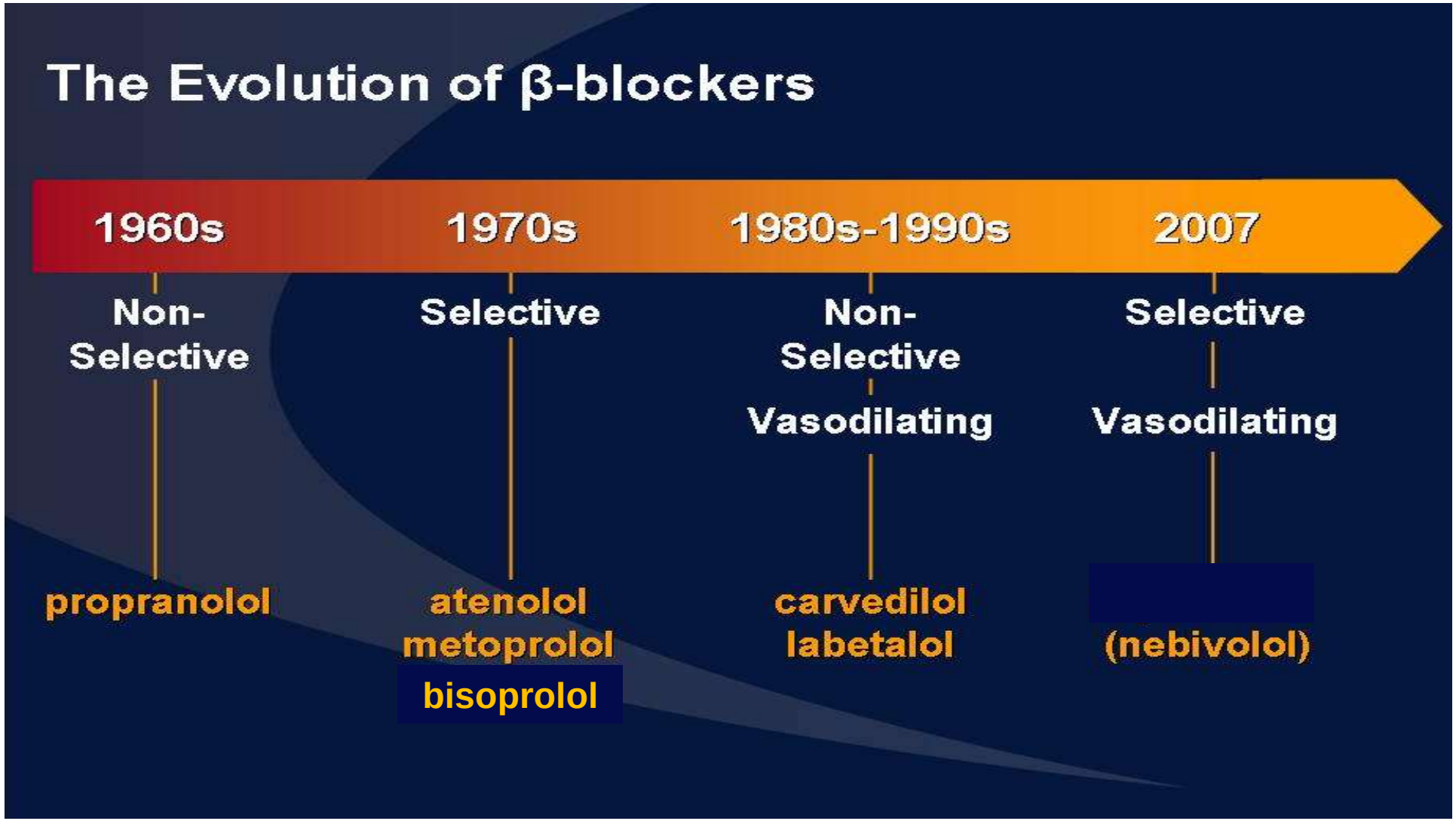
1. Brophy JM. Ann Intern Med. 2001;134:550–560
2. Flather MD,Eur Heart J. 2005;26:215–225.

How well do β-blockers work in HF ?

- ± 34 % reduction in mortality
- Suggested mechanisms also include reduce remodeling
- β-Blockers may be beneficial through re-sensitization of the down-regulated receptor, improving myocardial contractility.
- Acts primarily by inhibiting the sympathetic nervous system.
- Increases beta receptor sensitivity (up regulation).
- Anti-arrhythmic properties.
- Anti-oxidant properties



Kumar S, 2009. CHF – Le Jacq Comm, 2003

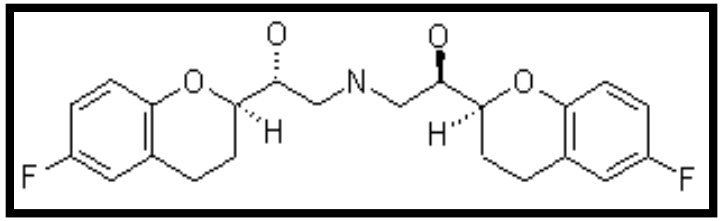

The Evolution of β-blockers
1960s
1970s
1980s-1990s
2007
Non-Selective
Selective
Non-Selective
Vasodilating
Selective
Vasodilating
propranolol
atenolol
metoprolol
bisoprolol
carvedilol
labetalol
(nebivolol)

Trials with significant positive results

- CIBIS II - bisoprolol
- COPERNICUS - carvedilol
- MERIT-HF - metoprolol
- CAPRICORN - carvedilol (*post-AMI)*
- COMET - carvedilol/metoprolol
- SENIORS - nebivolol

Flather MD, et al. Eur Heart J 2005; 26:215-25; Cibis II Investigators. Lancet 1999; 335:9-13; Packer N, et al. N Eng J Med 1996; 334:1349-55; Packer N, et al. N Eng J Med 2001; 344(22): 1651-8; MERIT-HF. Study group. Lancet 1999; 353:2001-7; Mc Murray J, et al. J Am Coll Cardiol 2005; 45(4):525-30; Poole-Wilson PA, et al. Lancet 2003; 362 (9377): 7-13.

Nebivolol:
Ultraselective, Vasodilating β_1-blocker



A Nitric-oxide-donating, vasodilating, lipophilic 3rd generation highly selective Beta-1- adrenoceptor Blocker

Racemic mixture of 2 enantiomers d & l-Nebivolol

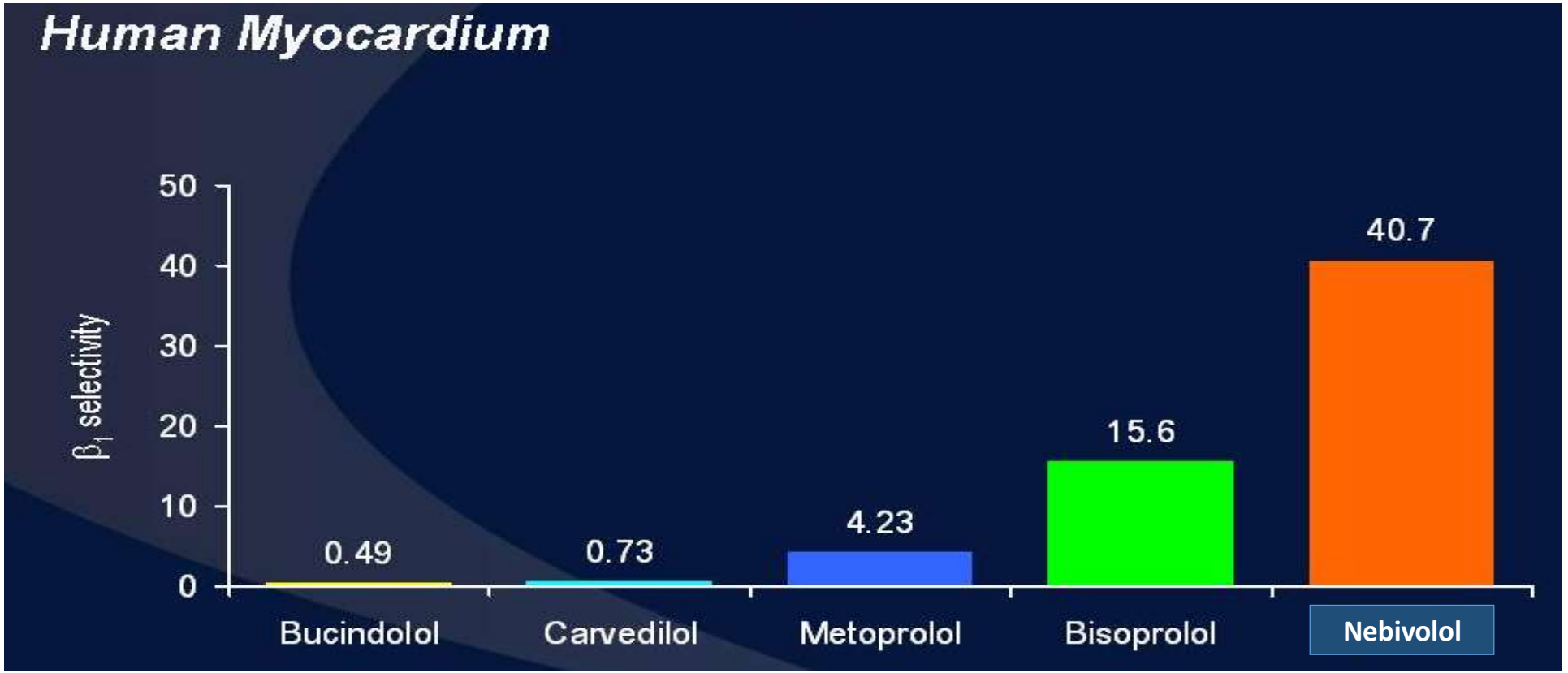
d- Nebivolol

- responsible for selective β-1-antagonism
- highly selective β1-receptor antagonist and a β3-receptor agonist.

l- Nebivolol

- involved in the nitric oxide (NO)-mediated endothelium-dependent dilatation, through L-arginine / NO pathway †
- responsible for the vasodilatory, antioxidant, antiproliferative and anti-platelet actions of the

Nebivolol : ß$_1$ Receptor Selectivity



β_1 Selectivity = K_i (β_2) / K_i (β_1).
In extensive metabolizers and at doses less than or equal to 10 mg,
Brixius K et al. *Br J Pharmacol*. 2001;133:1330-1338.

ß$_1$ Selectivity = K_1 (ß$_2$)/K_1(ß$_1$).; In extensive metabolizers and at doses less than or equal to 10 mg, nebivolol is preferentially ß$_1$ selective.; Brixius K et al. *Br J Pharmacol*. 2001;133:1330-1338

Nebivolol Safety and Tolerability Profile

Ancillary effects of Nebivolol	Peripheral vasodilatory effects(4)
	Low risk of bronchocostriction(34)
	No interference with sexual activity(29)
	No interfence with lipids and glycemic control(30)
Adverse effects of traditional β-blockers	Cold extremities(A,B)
	Reynaud Phenomenon(A,M)
	Bronchospasm(A,M,B)
	Impotence(A,M,B)
	Alteration of glucose(A)
	Alteration of lipid metabolism (A,M,B)

A = Atenolol SmPC; B = Bisoprolol SmPC; M = Metoprolol SmPC

SENIORS

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

A randomised, double-blind, placebo-controlled phase III study

Background

BRING UP
Reasons for not commencing β-blockade

	OR	95% CI	P value
Age	0.97	0.96 - 0.97	0.0001
NYHA class (III-IV v I-II)	0.62	0.51 - 0.75	0.0001
Systolic blood pressure	1.02	1.01 - 1.02	0.0001
Heart rate	1.01	1.01 - 1.02	0.0001
Ejection fraction (not available vs. available)	0.46	0.28 - 0.76	0.0022

Maggioni A et al. Heart 2003

Study objective

- To evaluate the effect of Nebivolol compared to placebo on mortality and morbidity in elderly CHF patients

Inclusion criteria

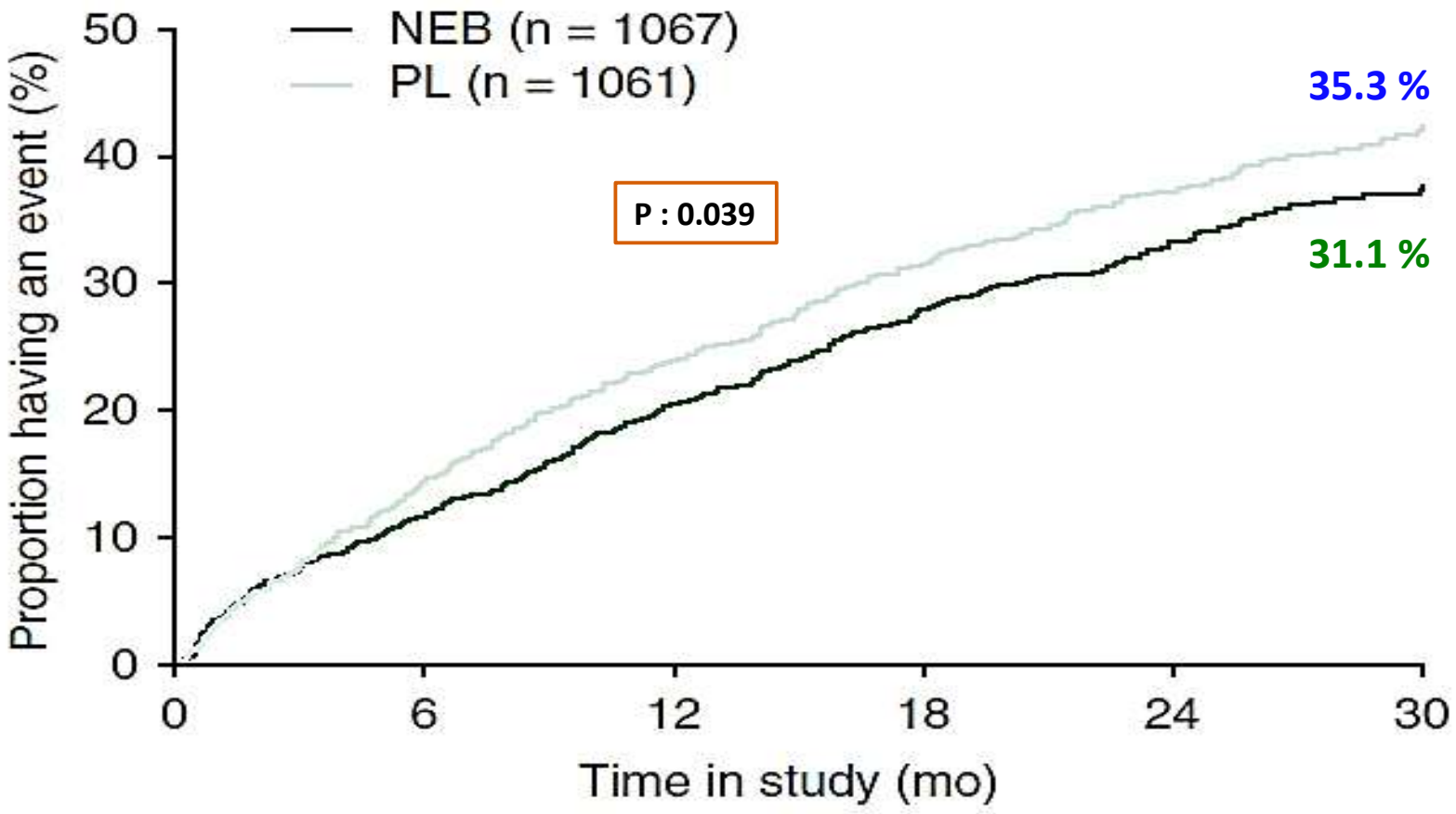
- Age ≥ 70 years
- A clinical diagnosis of chronic heart failure (HF) and either of:
  a) documented LVEF ≤ 35% within previous 6 months

  or

  a) hospital admission within previous 1 year for congestive HF
- Written consent prior to enrolment into the study

SENIORS:

EFFECT OF NEBIVOLOL ON TIME TO ALL CAUSE MORTALITY OR CV HOSPITALIZATION



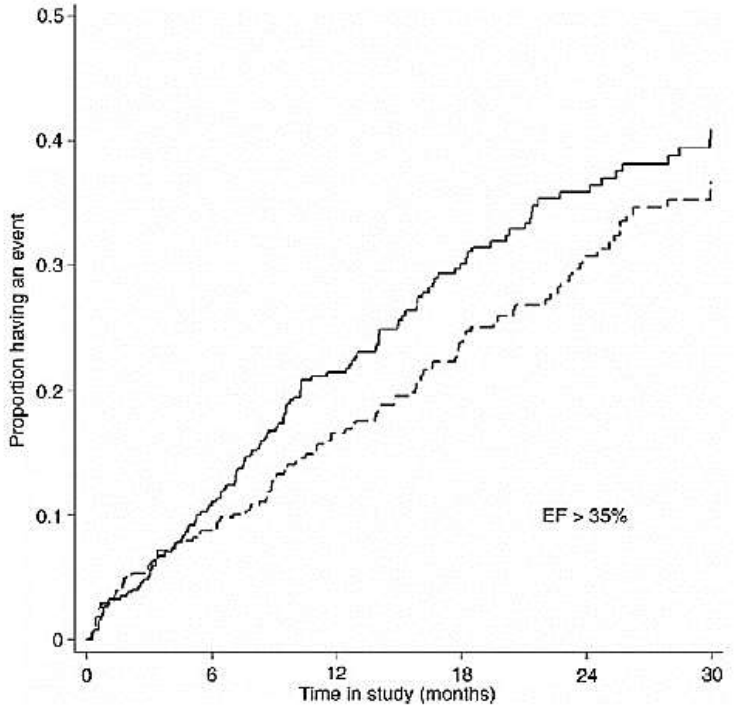
Flather MD, Shibata MC. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). European Heart Journal (2005) 26, 215–225

SENIORS on HFpEF

Primary and main secondary outcomes in LVEF ≥ 40%

Outcome	LVEF ≥40%		
	Nebivolol (n = 320)	Placebo (n = 323)	HR (95% CI)
Primary outcome (all-cause mortality or CV hospitalization)	92 (28.8)	108 (33.4)	0.82 (0.62–1.08)
All-cause mortality	44 (13.8)	48 (14.9)	0.92 (0.61–1.36)
All-cause mortality or HF hospitalization	67 (20.9)	75 (23.2)	0.88 (0.63–1.23)
CV mortality	28 (8.8)	35 (10.8)	0.80 (0.49–1.32)

- Ischemia plays an important role in the pathophysiology of HF, which may be even more prominent in patients with HFpEF
- Nitric oxide release, specifically induced by nebivolol, may cause an additional improvement of early relaxation



Kaplan-Meier curve of primary outcome for preserved (35%) EF group for nebivolol (dotted line) vs placebo (solid line).

van Veldhuisen et al. J Am Coll Cardiol 2009;53:2150–8

SENIORS CONCLUSION

- Nebivolol significantly reduced death or hospitalization in elderly patients with heart failure
- The effect was similar regardless of ejection fraction, age or gender
- SENIORS further expands our understanding of the use of *cardioselective* blockers among elderly patients and patients with diastolic dysfunction

Clinical implications

- Advanced age should not be considered a contraindication to beta blockade in chronic heart failure
- The SENIORS study indicates that beta blockade can be recommended for heart failure regardless of ejection fraction
- Nebivolol is an effective agent for elderly heart failure patients

Conclusion

- Heart failure in the elderly will continue to be an increasing health burden
- Elderly patients with HF commonly have a complex profile characterized by multiple co-morbidities, polypharmacy, and social problem
- Nebivolol significantly reduced death or hospitalization in elderly patients with heart failure
- The effect of betablockade (with nebivolol) is similar in HF patients with preserved and impaired EF in elderly

Thank You