Beta-blocker therapy in heart failure

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Betablokátory a Ca antagonisté moderním pohledem
Sympozium Herbacos Recordati, s.r.o
XXVII. Výroční sjezd České kardiologické společnosti
13. Května 2019, Brno

Within the last 40 years beta-blocker therapy status in chronic heart failure has changed from being the most hazardous drug to the most effective therapy.

Guillaume Jondeau and Olivier Milleron

Short history of beta blockers

1900 - 1948

- idea that catecholamines were binding selectively to receptor-like structures and that this was the cause of their pharmacological actions
- Ehrlich and Langley – formulation of the receptor theory

1948

- Raymond P. Ahlquist - „A study of the adrenotropic receptors“ – 1st description of two types of adrenergic receptors (α and β) – the study was ingnored

1958

- 1st description of the pharmacological properties of dichloroisoproterenol (isoprenaline analogue by E. Powell and I.H. Slater's (study of bronchoconstriction)

James W. Black

- 1962 - first beta blocker (pronethalol) to treat anginal symptoms, toxic
- 1964 - propranolol (Inderal®) – ready for clinical use
- 1988 - Nobel Prize

Quirke V. Med Hist. 2006 Jan 1; 50(1): 69–92.

Beta-blockade in chronic heart failure

British Heart Journal, 1975, 37, 1022–1036.

Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy

F. Waagstein, Å. Hjalmarson, E. Varnauskas, and I. Wallentin

From the Department of Medicine I, Division of Cardiology and Department of Clinical Physiology, Sahlgren's Hospital, University of Göteborg, Sweden

- 7 pts with advanced congestive cardiomyopathy
- beta-adrenergic receptor blockade (alprenolol, practolol) for 2 to 12 months
- improvement in clinical condition, in increase in physical working capacity and a reduction of heart size
- improved ventricular function (phonocardiogram, carotid pulse curve, apex cardiogram, and echocardiogram)

Waagstein Fet al. (1975) Br Heart J 37:1022–1036.

Beta-blockade in chronic heart failure

2nd publication:

Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. Beta-adrenergic receptor blockade (alprenolol, practolol) for 2 to 12 months

- 28 pts, treatment: metoprolol, practolol, alprenolol, follow-up: 62 months

Results:

- increase of LVEF: 0.32 +/- 0.02 to 0.42 +/- 0.04
- increase of exercise capacity
- improved survival

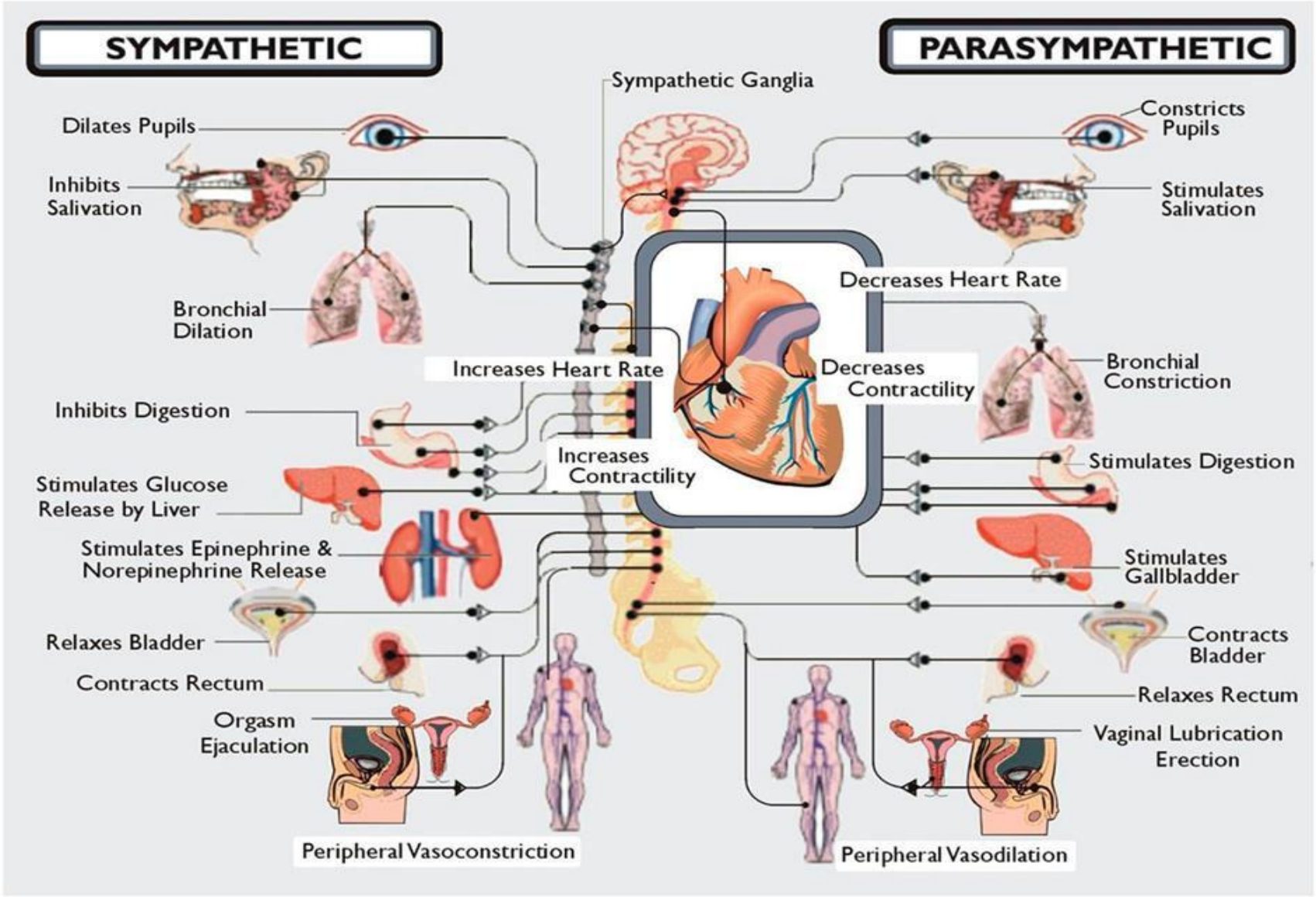
Br Heart J 1980; **44**: 117–33

Beneficial effects of long-term beta-blockade in congestive cardiomyopathy

KARL SWEDBERG, ÅKE HJALMARSON, FINN WAAGSTEIN, INGEMAR WALLENTIN

From the Departments of Medicine I and Clinical Physiology, Sahlgren's Hospital, University of Göteborg, Göteborg, Sweden

Autonomic nervous system



Effects of autonomic nervous system on the heart

Organ	Sympathicus		Parasympathicus	
	Response	Receptor	Response	Receptor
SA node	acceleration	β_1	slowing	M_2
Atrial myocardium	↑ contraction	β_1	↓ contraction	M_2
AV node	↑ automaticity	β_1	↓ conduction	M_2
Ventricle myocardium	↑ automaticity ↑ contraction	β_1	↓ automaticity ↓contraction	M_2

In summary: <u>cardiovascular actions of SNS in normal heart:</u>

- **heart rate acceleration**
- **↑ in cardiac contractility**
- **↓ of venous capacitance**
- **constriction of resistance vessels**

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Results of chronically increased SNS activity in HF

HF → neurohormonal changes (up-regulation of the angiotensin II type 1 receptor, nitric oxide inhibition, and increased production of superoxide anion) → ↑ SNS activity

Prolonged ↑ SNS activity:

- affects excitation-contraction coupling (β1)
- ↑apoptotic pathways
- ↓ density of β1 and desensitization of β1 (protective mechanism: keeps low intracellular CAMP level) = **downregulation**

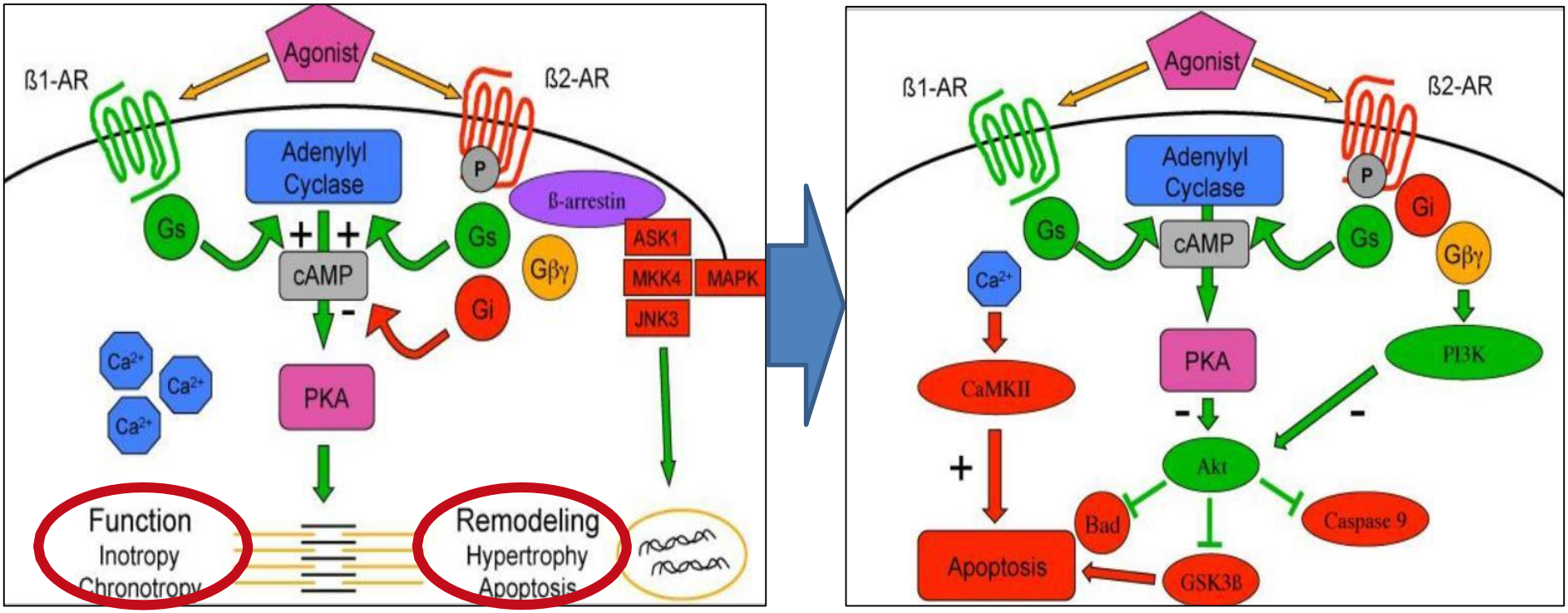
→ progression of heart failure (initial hypertrophy → chronic dilatation)

Cardiac reflexes are changed:

- suppression of sympathoinhibitory reflexes (e.g. arterial baroreceptor reflex)
- augmentation of sympathoexcitatory reflexes (cardiac sympathetic afferent and chemoreceptor reflex)
- destabilization of efferent neuronal cardiac control

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Shift of the AR paradigm



Hypothesis:

- **β1-receptors are cardiotoxic and β2-receptors are cardioprotective**

→ selective β1-blockade combined with subtype selective β2-stimulation might be beneficial

Catecholamine cardiotoxicity

Iv. infusion of isoproterenol or NE results in:

- acute contraction band lesions
  - local hypoxia, ↑ sarcolemmal permeability, calcium overload, ↑ of cAMP, activation of alpha-ARs, activation of beta-ARs, formation of oxidative catecholamine metabolites
- role in tako-tsubo CMP (↑ circulating EPI trigger a negative inotropic switch in intracellular signal trafficking in ventricular cardiomyocyte - at the apex - beta-AR density is greatest)

Chronic catecholamine administration:

- interstitial fibrosis, reduced beta-AR–mediated inotropic responses
- myocyte apoptosis
- heart failure

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Beta-blockade in chronic heart failure

Generation	Receptor selectivity, effect	Molecules
1st	nonselective competitively block both the β_1 and β_2	propranolol, nadolol, timolol
2nd	selective ($\beta_1 >> \beta_2$)	metoprolol, atenolol, bisoprolol
3rd	selective nonselective peripheral vasodilation mediated by: $\alpha_1$blockade (bucindolol, carvedilol, labetalol), $\beta_2$agonism (celiprolol), or nitric oxide synthesis (nebivolol)	celiprolol, nebivolol bucindolol, carvedilol, labetalol

- Cardioselectivity of BB is dose-dependent and ↓ with larger doses
- Nonconventional partial agonists (with ISA, pindolol, alprenolol, oxprenolol) - considered potentially arrhythmogenic and should not be used for heart failure treatment

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Beta-blockade in chronic heart failure

Benefits of chronic beta-blocker in heart failure patients

- left ventricular remodeling, reduces risk of hospitalization, improves survival

Protective mechanisms:

- inhibition of catecholamine cardiotoxic effects
- beta1-AR up-regulation (carvedilol is an exception)
- attenuation of neurohumoral vasoconstrictive, growth-promoting, and pro- apoptotic systems
- subendocardial coronary flow enhancement (as a result of diastolic prolongation)
- restoration of the reflex control on the heart and circulation
- improved myocardial performance (by reducing heart rate and oxygen demand)

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Beta-blockade in CHF randomized trials

Beta-Blocker	Trial(s)	Year	n	Benefit
Metoprolol	MDC (104)	1993	383	All-cause mortality or morbidity was 34% lower in the metoprolol than in the placebo group (HR: 0.66; 95% CI: 0.62 to 1.06; p = 0.058). The change in LVEF from baseline to 12 months was significantly greater with metoprolol than with placebo (0.13 vs. 0.06; p < 0.0001)
Metoprolol CR/XL	MERIT-HF (105)	1999	3,991	All-cause mortality was 34% lower in the metoprolol CR/XL group than in the placebo group (7.2% vs. 11.0%; HR: 0.66; 95% CI: 0.53 to 0.81; p = 0.00009)
Carvedilol	U.S. Carvedilol HF Study Group (106)	1996	1,094	All-cause mortality was 65% lower in the carvedilol than in the placebo group (3.2 vs. 7.8%; HR: 0.65; 95% CI: 0.39 to 0.80; p < 0.001)
	Australia/New Zealand HF Research Collaborative Group (107)	1997	415	All-cause mortality or morbidity was 26% lower in the carvedilol than in the placebo group (104 vs. 131; HR: 0.74; 95% CI: 0.57 to 0.95)
	CAPRICORN (108)	2001	1,959	All-cause mortality was lower in the carvedilol than in the placebo group (12% vs. 15%; HR: 0.77; 95% CI: 0.60 to 0.98; p = 0.03)
	COPERNICUS (109)	2001	2,289	Carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% (p = 0.00002) and the combined risk of death or HF hospitalization by 31% (p = 0.000004)
	COMET (110)	2003	3,029	All-cause mortality was lower in the carvedilol than in the metoprolol group (34% vs. 40%; HR: 0.83; 95% CI: 0.74 to 0.93; p = 0.0017)

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Beta-blockade in CHF randomized trials

Beta-Blocker	Trial(s)	Year	n	Benefit
Bisoprolol	CIBIS (111)	1994	641	All-cause mortality did not reach statistical significance: 67 patients died on placebo, 53 on bisoprolol (HR: 0.80; 95% CI: 0.56 to 1.15; p = 0.22). Bisoprolol reduced HF hospitalization (p < 0.01) and improved the functional status
	CIBIS II (112)	1999	2,647	All-cause mortality was 34% lower with bisoprolol than on placebo (11.8% vs. 17.3%; HR: 0.66; 95% CI: 0.54 to 0.81; p < 0.0001)
	CIBIS III (113)	2005	1,010	This study demonstrated that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril
Nebivolol*	SENIORS (114)	2005	2,128	All-cause mortality or cardiovascular hospital admission occurred in 332 patients (31.1%) on nebivolol compared with 375 (35.3%) on placebo (HR: 0.86; 95% CI: 0.74 to 0.99; p = 0.039)

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Metoprolol in Dilated Cardiomyopathy (MDC) Trial

Study population

- 383 HF pts with (idiopathic dilated cardiomyopathy, LVEF < 0.40)
- NYHA II a III: 94%

Treatment

- placebo vs. metoprolol (up to 100-150mg/day)

Results:

- metoprolol group: ↓ 34% (95% CI -6 to 62%, p = 0.058) fewer primary endpoints
- Δ LVEF greater with metoprolol (0.13 vs 0.06, p < 0.0001)
- pcw pressure significantly decreased (5 vs 2 mm Hg, p = 0.06)
- exercise time at 12 months was significantlyincreased in metoprolol group

Waagsterin F et al.: Lancet. 1993 Dec 11;342(8885):1441-6.

Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)

- 3991 pts (40–80 yrs, NYHA II–IV)

Primary objectives:

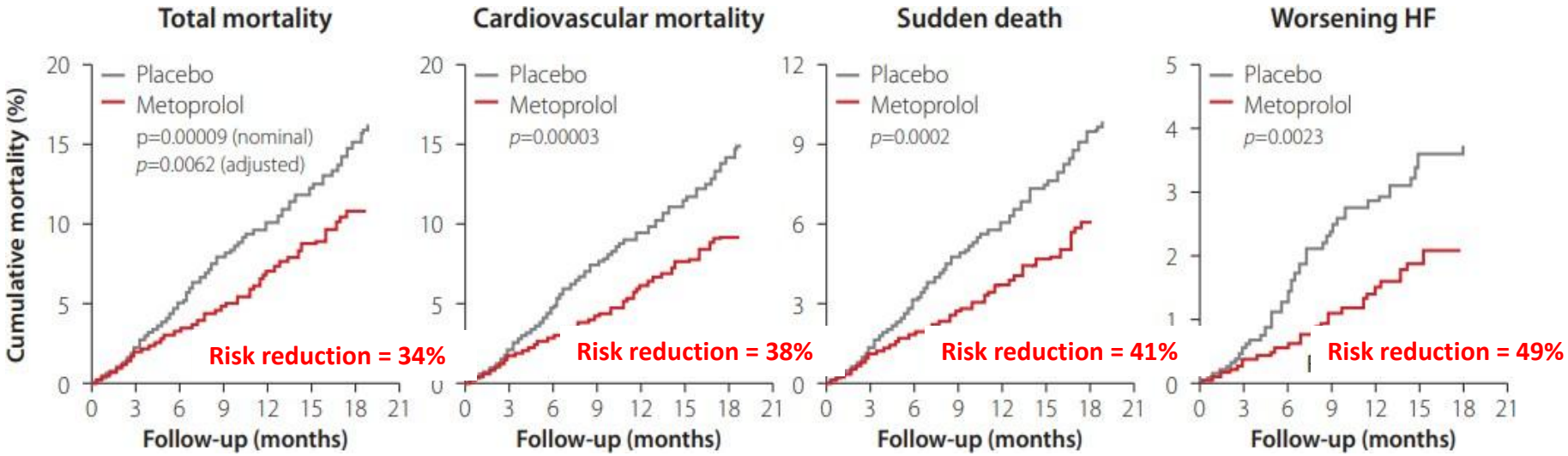
- **total mortality**
- **the combined endpoint of all-cause mortality and all-cause hospitalization**

Secondary objectives:

- combined endpoint of all-cause mortality and hospital. HF
- combined endpoint of death and heart transplantation
- death due to cardiovascular causes with cause-specific mortality for HF and sudden death
- the pooled incidence of cardiac death and nonfatal acute myocardial infarction hospitalizations due to HF

Lancet 1999; 353: 2001–07.

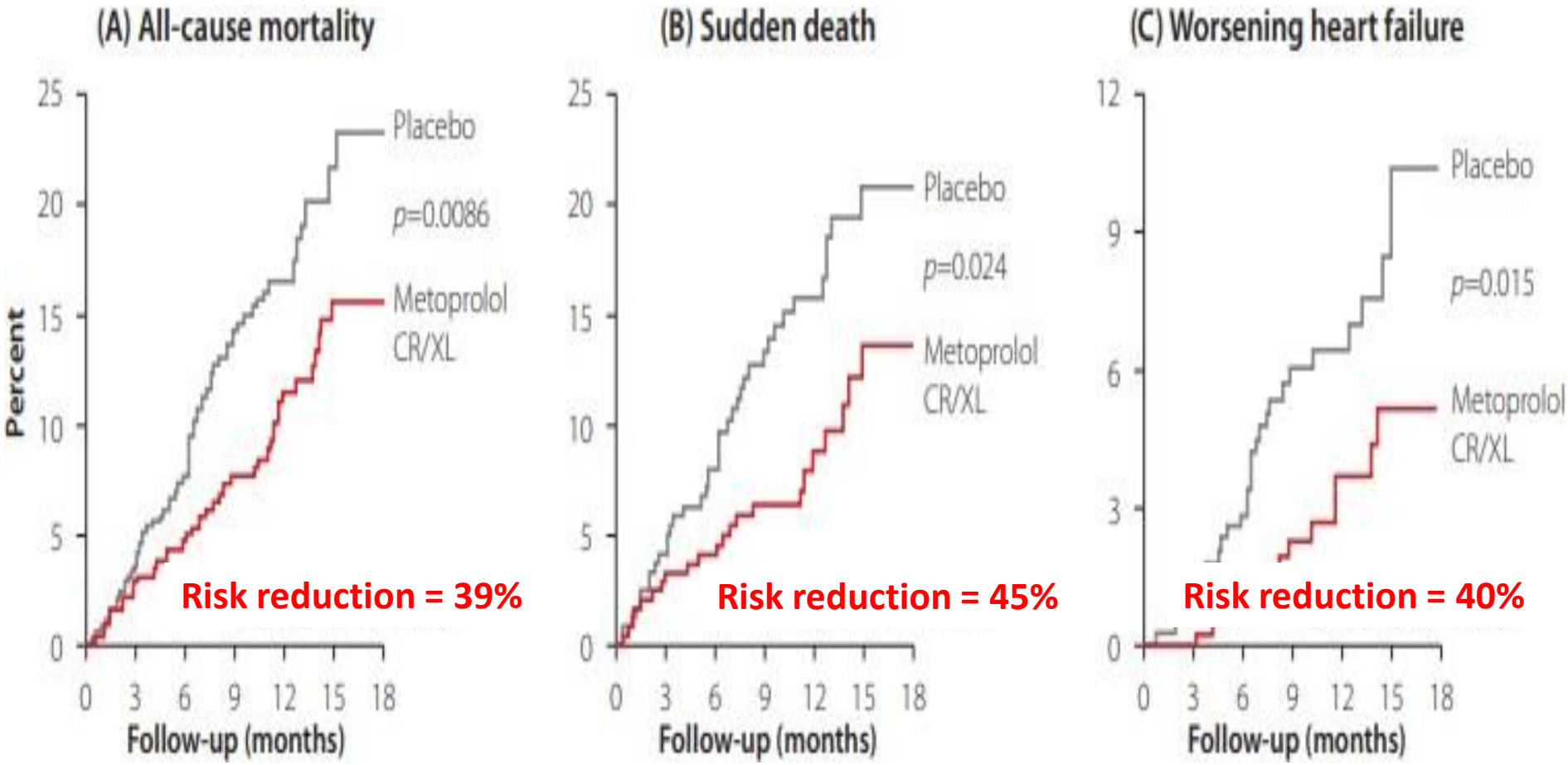
Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)



Combined Endpoints	Metoprolol CR/XL Group, No. of Patients (n = 1990)	Placebo Group, No. of Patients (n = 2001)	Total	Risk Reduction, % (95% Confidence Interval)
Total mortality or all-cause hospitalization	641	767	**1408**	19 (10-27)
Total mortality or hospitalization due to worsening heart failure	311	439	**750**	31 (20-40)
Death or heart transplantation	150	218	**368**	32 (16-45)
Cardiac death or nonfatal acute myocardial infarction	139	225	**364**	39 (25-51)
Total mortality or hospitalization or emergency department visit due to worsening heart failure	318	455	**773**	32 (21-41)

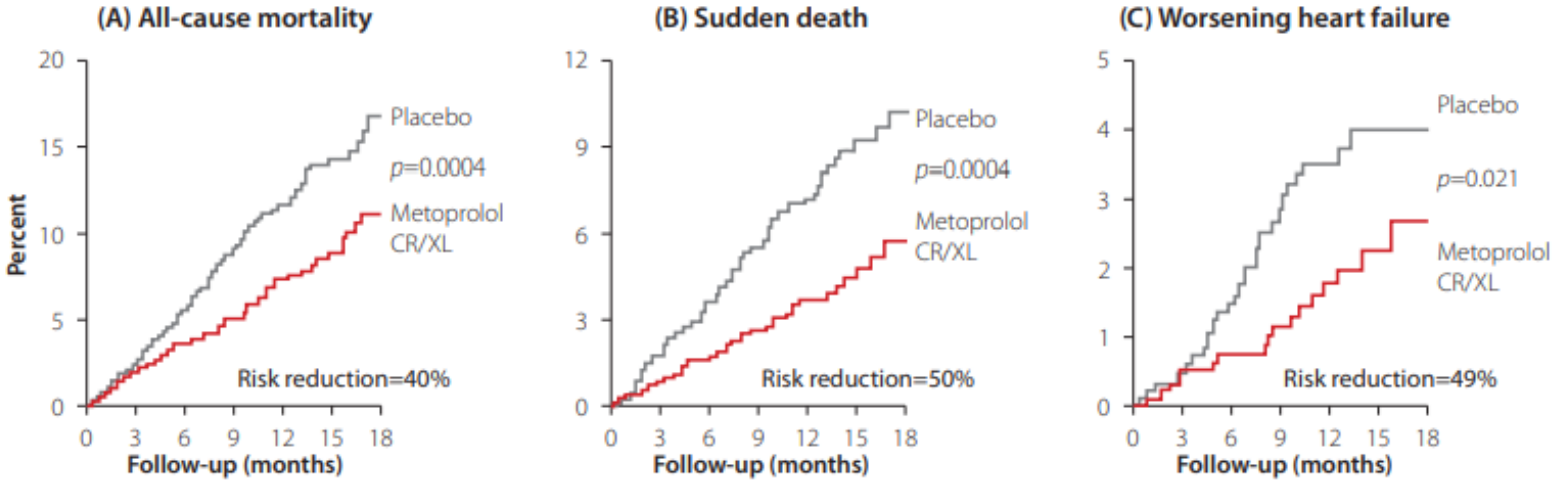
Lancet 1999; 353: 2001–07.

Metoprolol in patients with low LVEF (< 0.25)
(subanalysis of MERIT-HF)



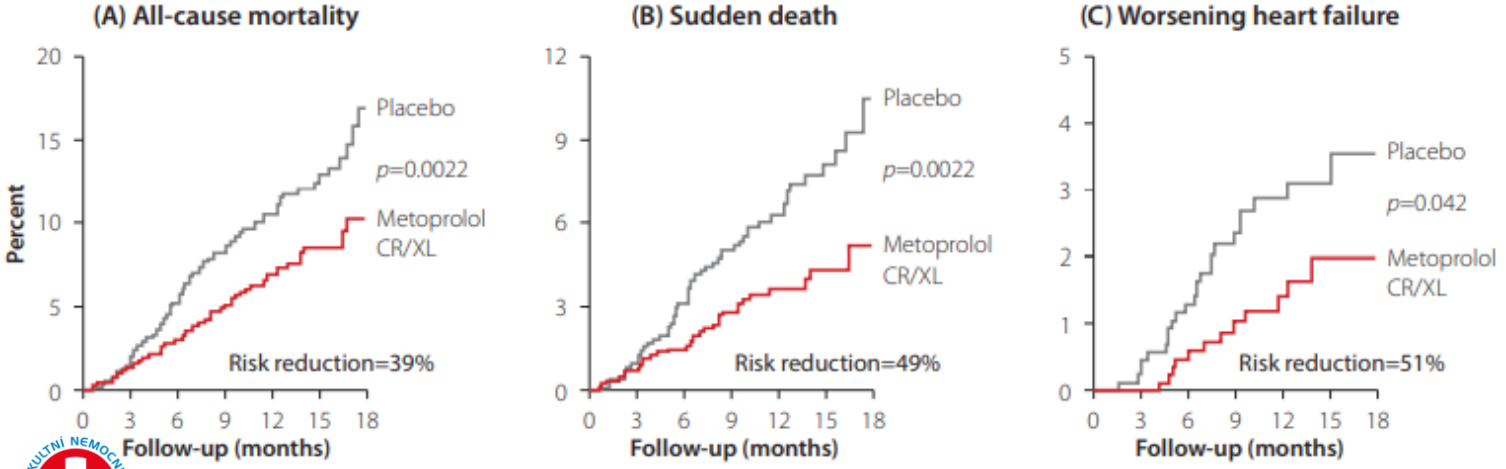
Goldstein S et al. J Am Coll Cardiol. 2001;38(4):932-8

Metoprolol in patients in post MI patients
(subanalysis of MERIT-HF)



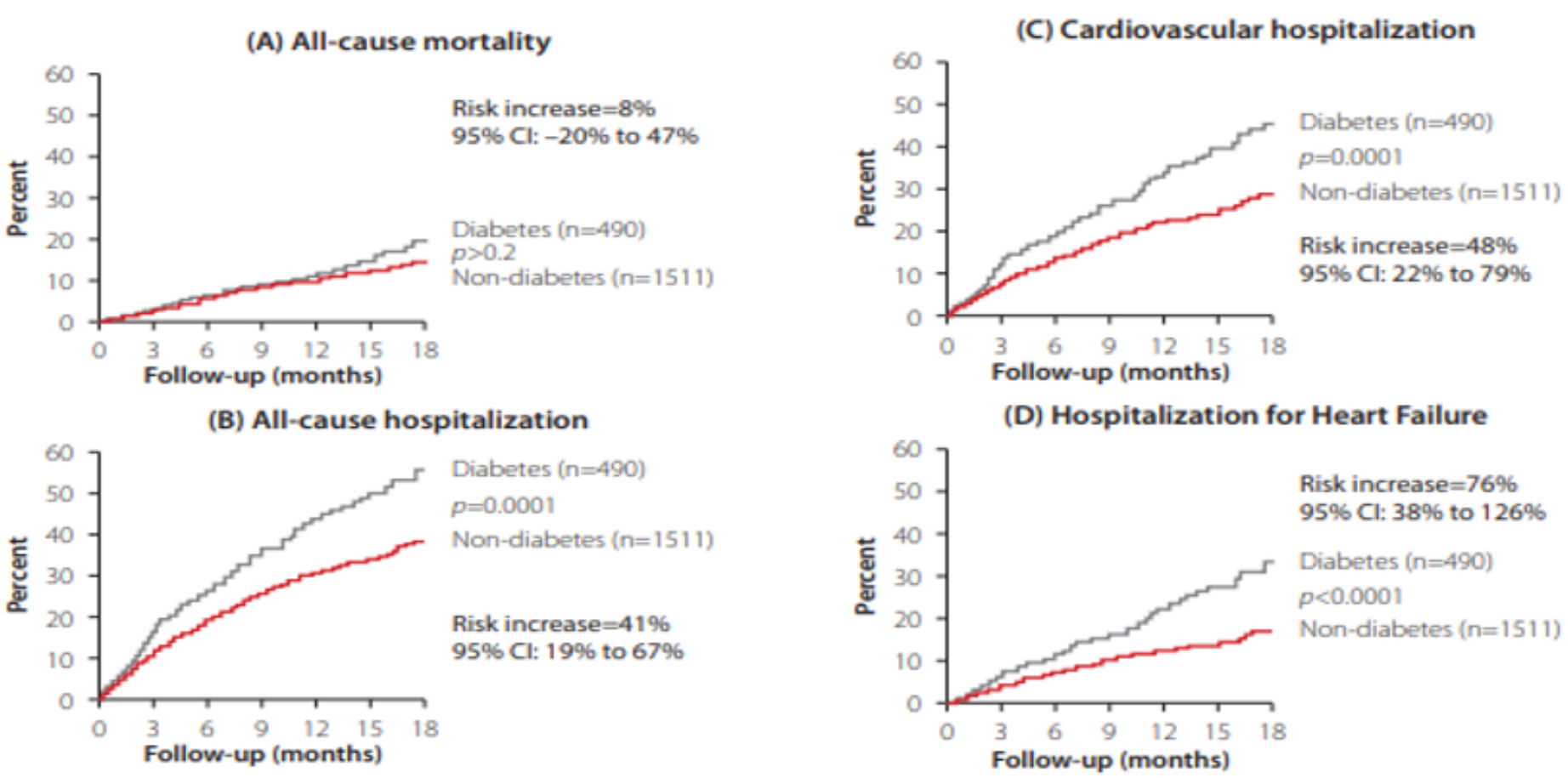
Jánosi A et al. Am Heart J. 2003;146(4):721-8

Metoprolol in patients in hypertensive patients
(subanalysis of MERIT-HF)



Herlitz J et al. J Card Fail. 2002;8(1):8-14

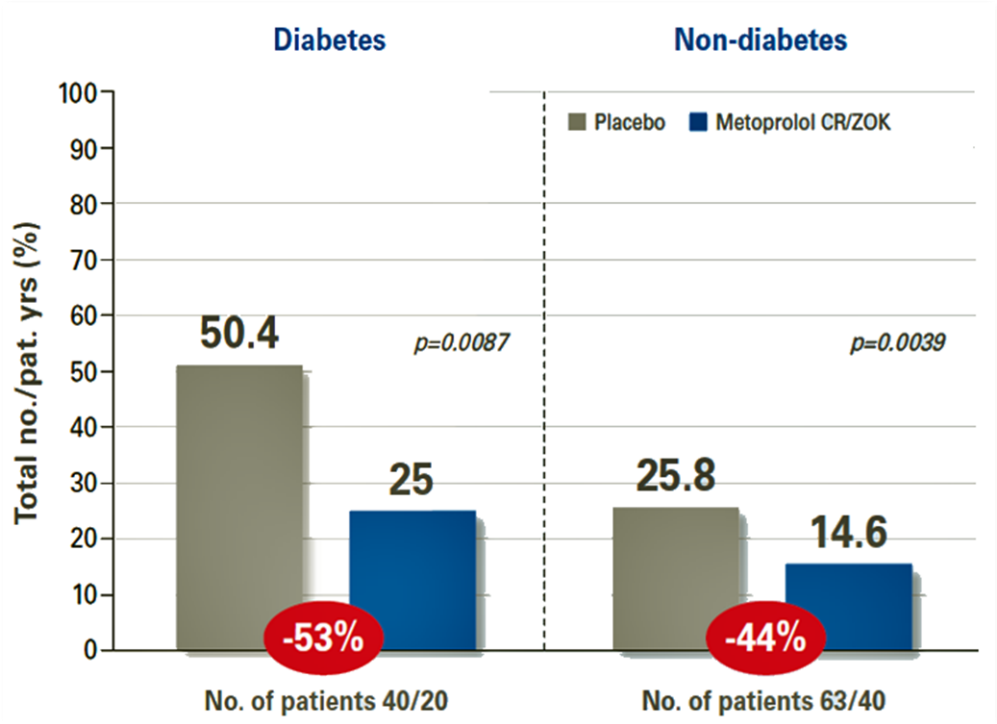
Metoprolol in patients in diabetic patients
(subanalysis of MERIT-HF)



Deedwania PC et al. Am Heart J. 2005;149(1):159-67

MERIT-HF: patients with diabetes and CHF *

Relative risk reduction for number of patients hospitalised for worsening heart failure



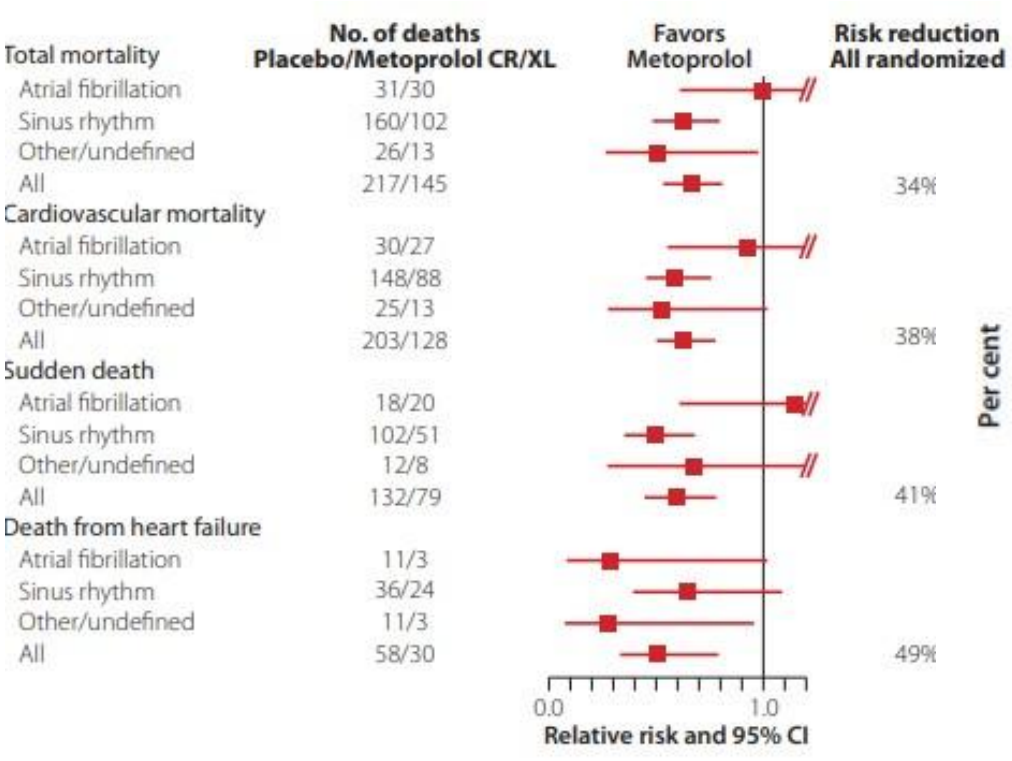
Relative risk reduction for number of patients (with and without diabetes) with severe heart failure from MERIT-HF (NYHA III/IV and EF of <0.25) hospitalized for worsening heart failure

Significant reduction in hospitalisations for heart failure with metoprolol CR/XL regardless of diabetic status and severity of heart failure

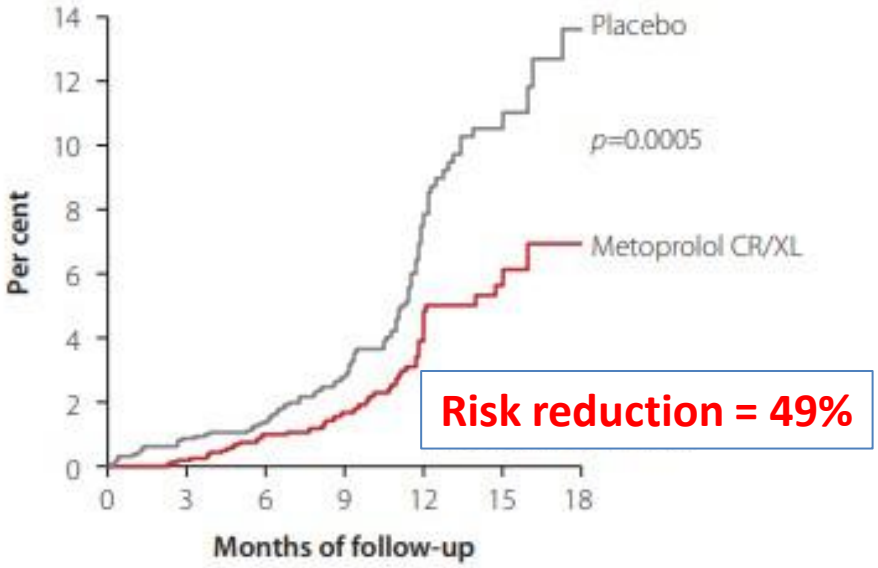
** Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure*

Deedwania PC, et al. Am Heart J. 2005;149:159-167.

Metoprolol in patients in atrial fibrillation pts
(subanalysis of MERIT-HF)



Newly diagnosed AF

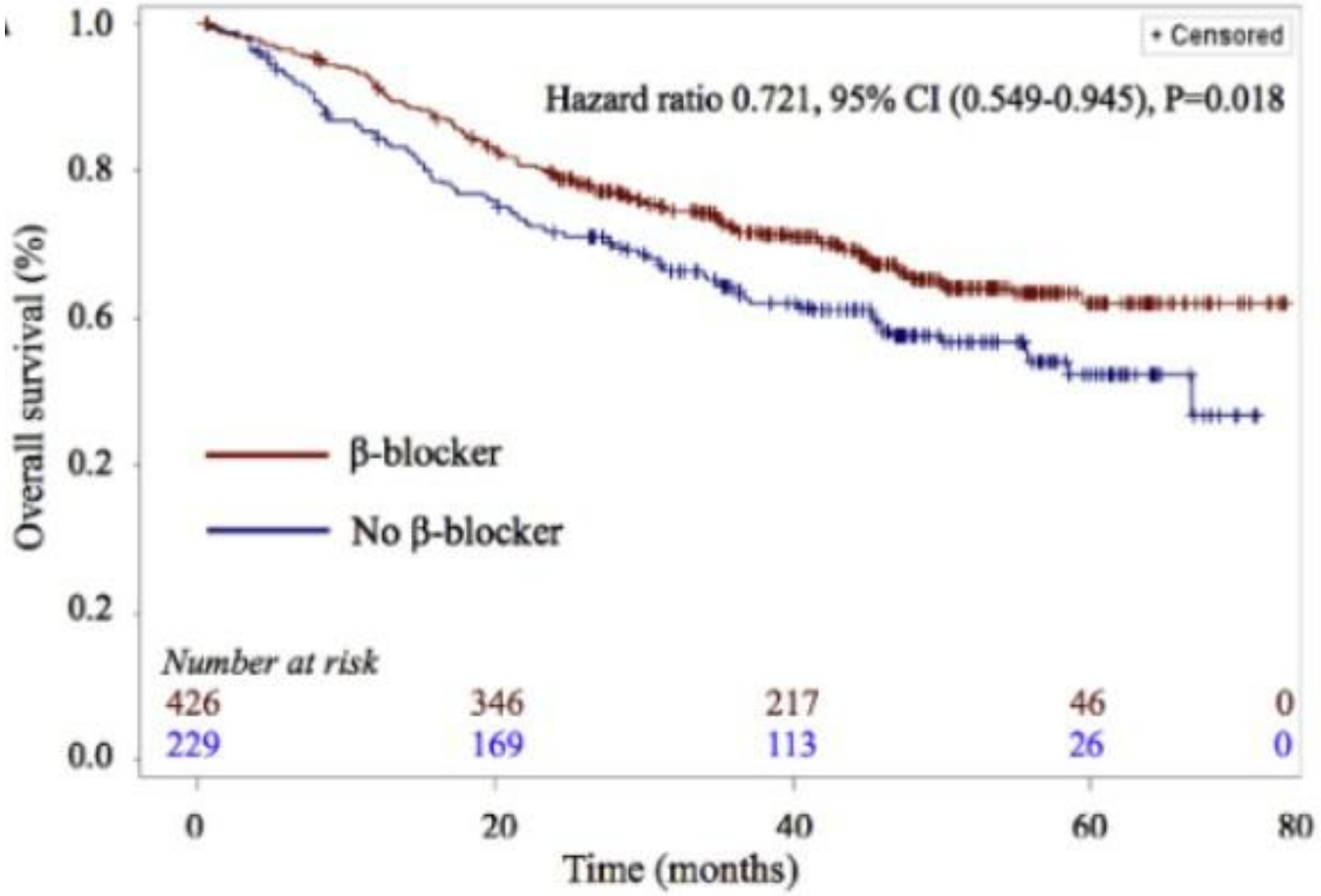


Risk reduction = 49%

van Veldhuisen DJ et al. Eur J Heart Fail. 2006;8(5):539-46

Beta-blockers in CHF patients with atrial fibrillation

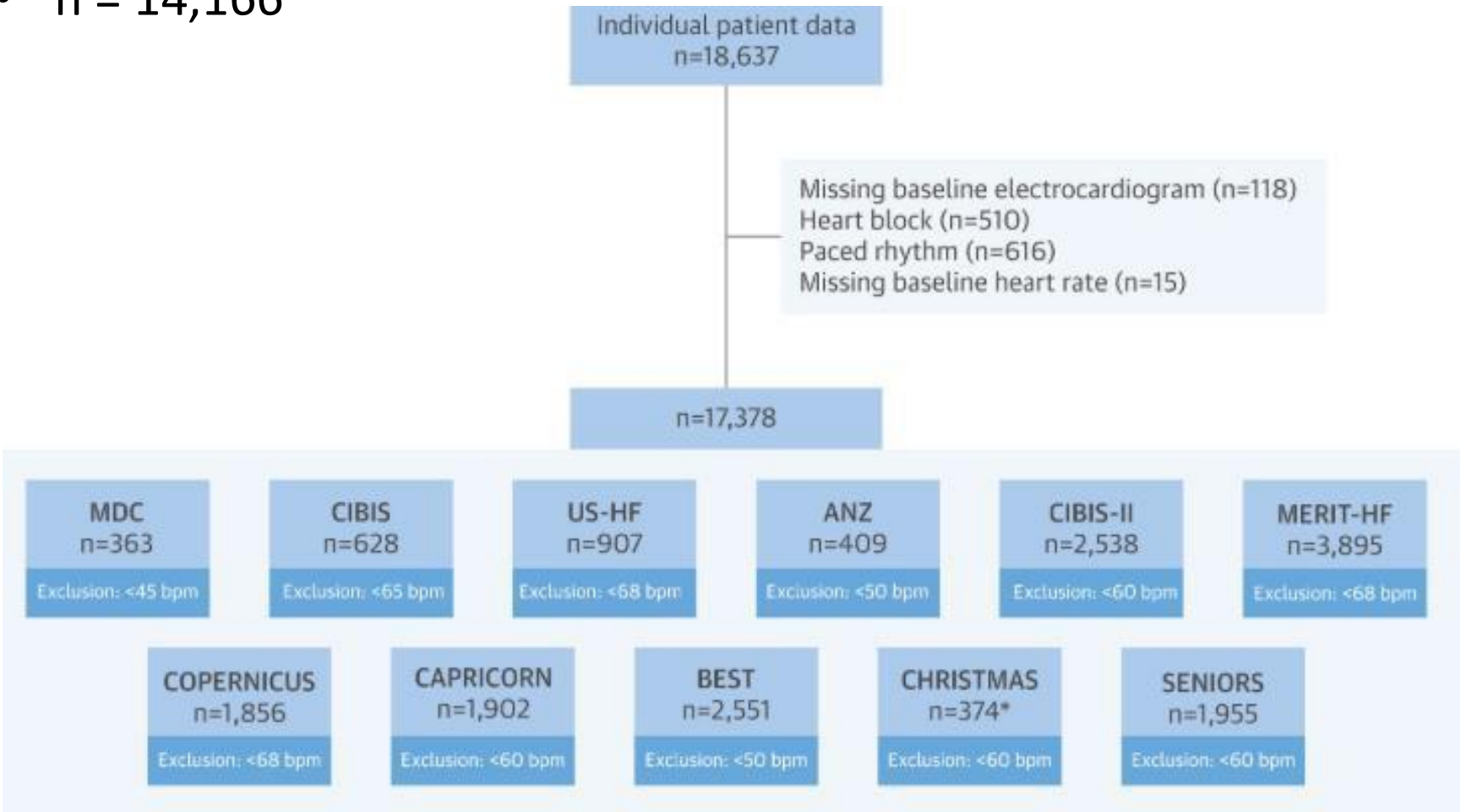
- 1,376 subjects randomized in the AF-CHF trial
- beta-blockers were associated with significantly lower mortality but not hospitalizations in patients with HFrEF and AF



Cadrin-Tourigny J et al. JACC Heart Fail. 2017 Feb;5(2):99-106. doi: 10.1016/j.jchf.2016.10.015. Epub 2017 Jan 11.

Beta-blockers in CHF: effect of HR on mortality

- meta-analysis of 11 double-blind randomized controlled trials
- n = 14,166

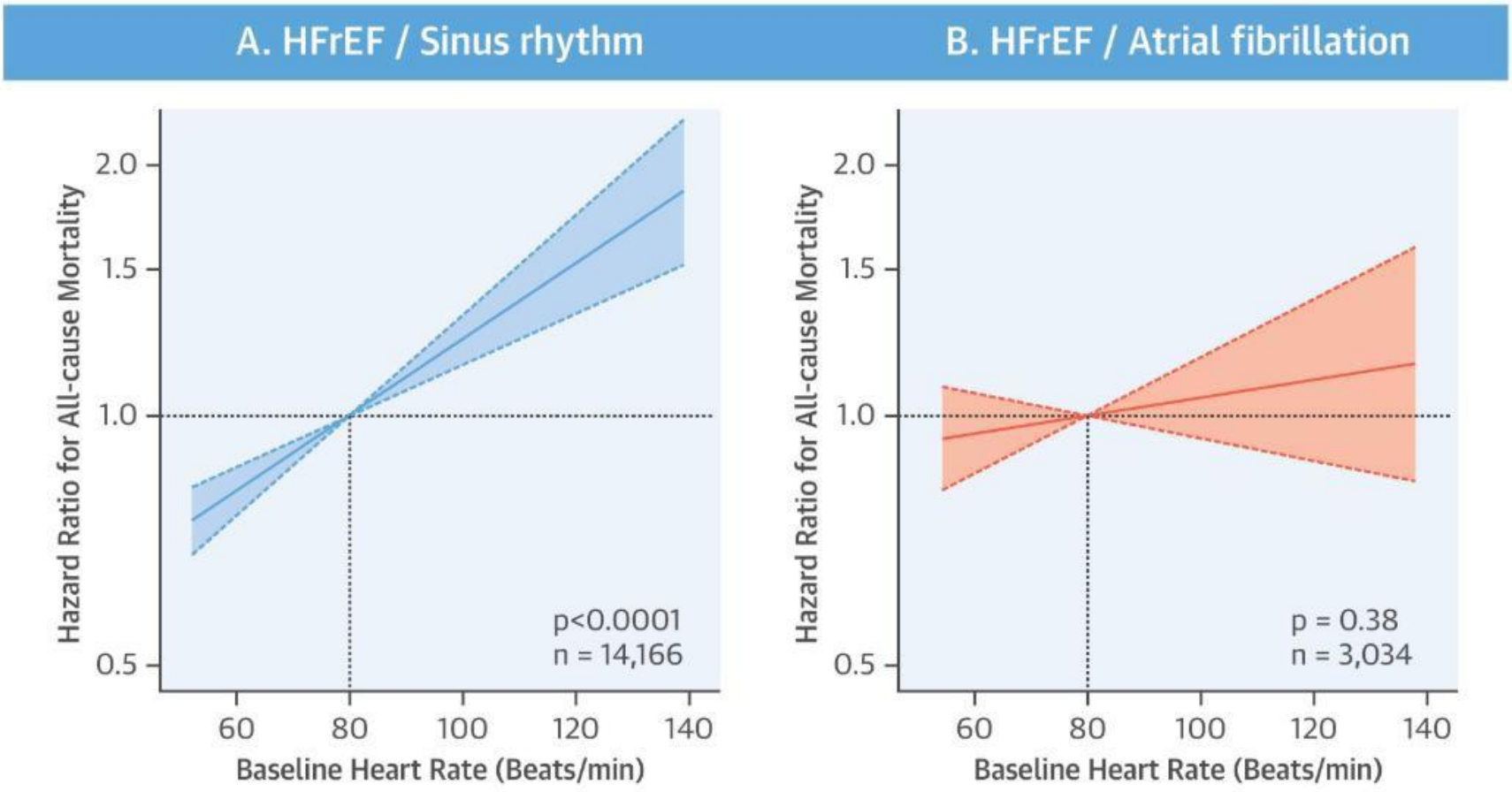


Kotecha D. et al. J Am Coll Cardiol. 2017 Jun 20;69(24):2885-2896.

Beta-blockers in CHF: effect of HR on mortality

Results:

- **beta-blockers ↓ mortality in HFrEF patients in sinus rhythm**
- **a lower heart rate is associated with better prognosis, but only for those in sinus rhythm**



Kotecha D. et al. J Am Coll Cardiol. 2017 Jun 20;69(24):2885-2896.

Beta-blockers in CHF: effect in AFib patients

TABLE 1 Main Studies Assessing the Effect of BB Therapy on Mortality in HFrEF Patients

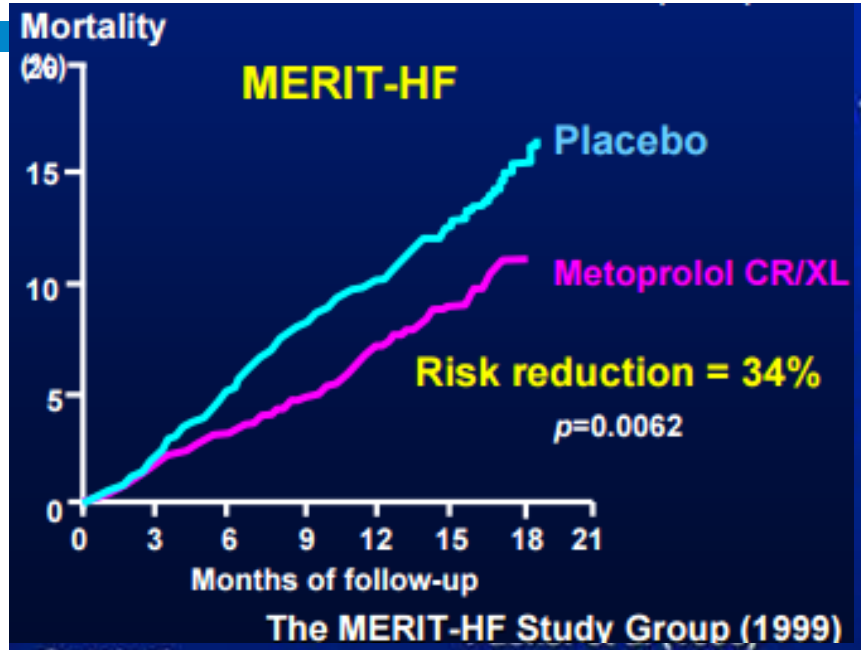
First Author, Year (Ref. #)	Study Type	No. of Patients	AF	Beta-Blocker Effect in SR	Beta-Blocker Effect in AF	Interaction p Value
Rienstra et al., 2013 (9)	Meta-analysis	8,680	1,677 (19)	**0.63 (0.54-0.73)**	0.86 (0.66-1.13)	0.048
Kotecha et al., 2014 (3)	Meta-analysis	18,254	3,066 (17)	**0.73 (0.67-0.80)**	0.97 (0.83-1.14)	0.002
Li et al., 2015 (10)	HF registry	18,858	7,392 (39)	**0.77 (0.63-0.94)**	**0.71 (0.61-0.84)**	0.637
Nielsen et al., 2016 (12)	AF registry, PS matching	39,741	39,741 (100)	–	**0.75 (0.71-0.79)**	–
Cadrin-Tourigny et al., 2017 (11)	RCT subanalysis, PS matching	1,376	1,376 (100)	–	**0.72 (0.55-0.95)**	–

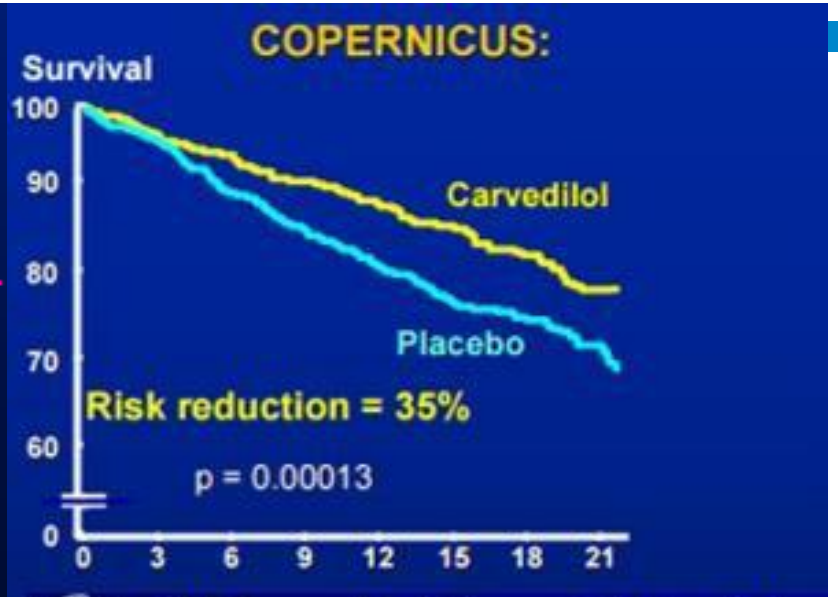
Summary:

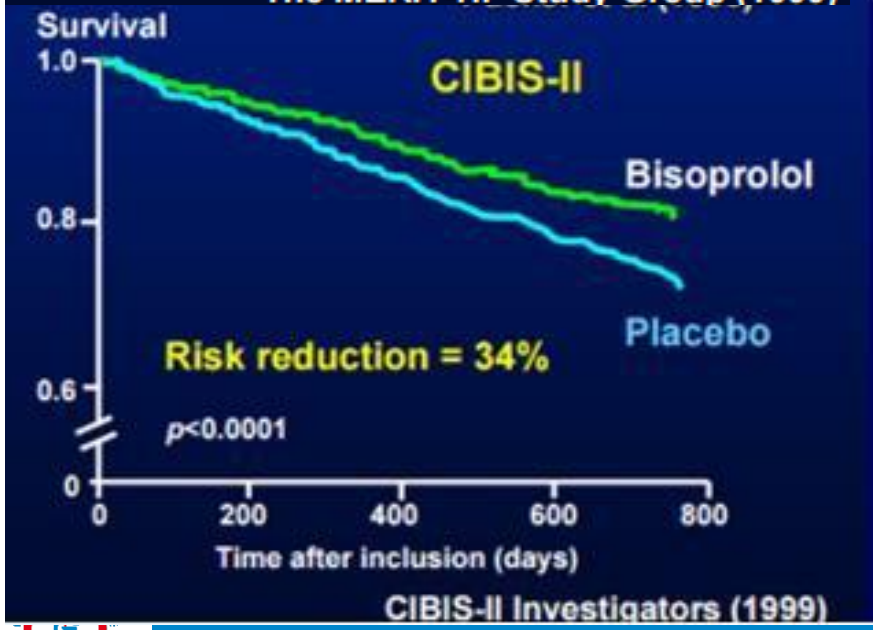
- Until more solid evidence is available, BB remain a cornerstone of HFrEF treatment, but in patients with AF, they should be titrated based on individual patients' profiles, HR, clinical responses, and general tolerability.

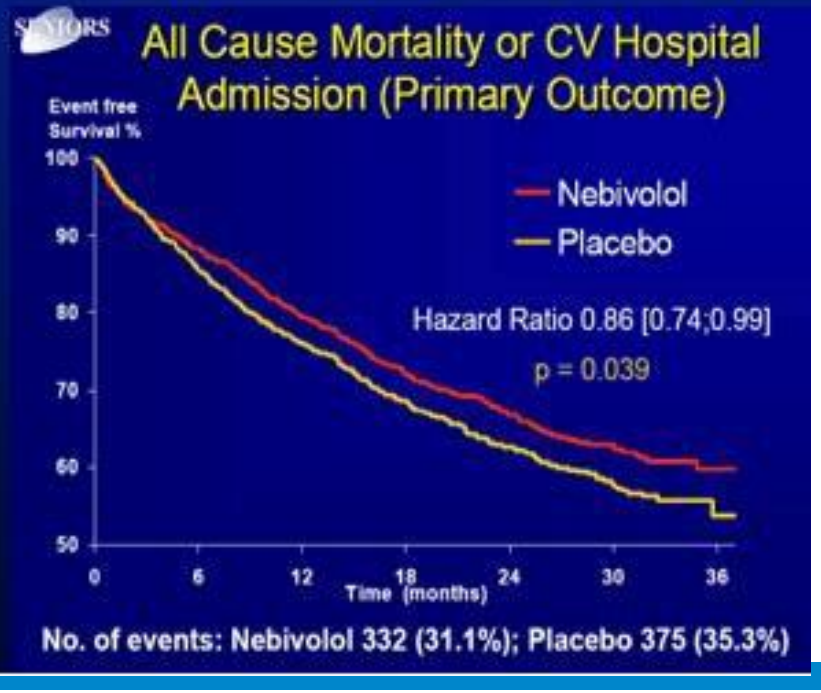
Gerasimos Filippatos, Dimitrios Farmakis
How to Use Beta-Blockers in Heart Failure With Reduced Ejection Fraction and Atrial Fibrillation
Journal of the American College of Cardiology, Volume 69, Issue 24, 20 June 2017, Pages 2897-2900

Main betablocker studies









beta-adrenergic receptor polymorphisms

functional polymorphisms in AR genes are associated with heart failure phenotypes and interaction with beta-blockers

beta1-ARs common polymorphisms:

1) arginine to glycine switch at codon 389 (Arg389Gly)
2) serine to glycine switch at codon 49 (Ser49Gly)

beta2-ARs common polymorphisms:

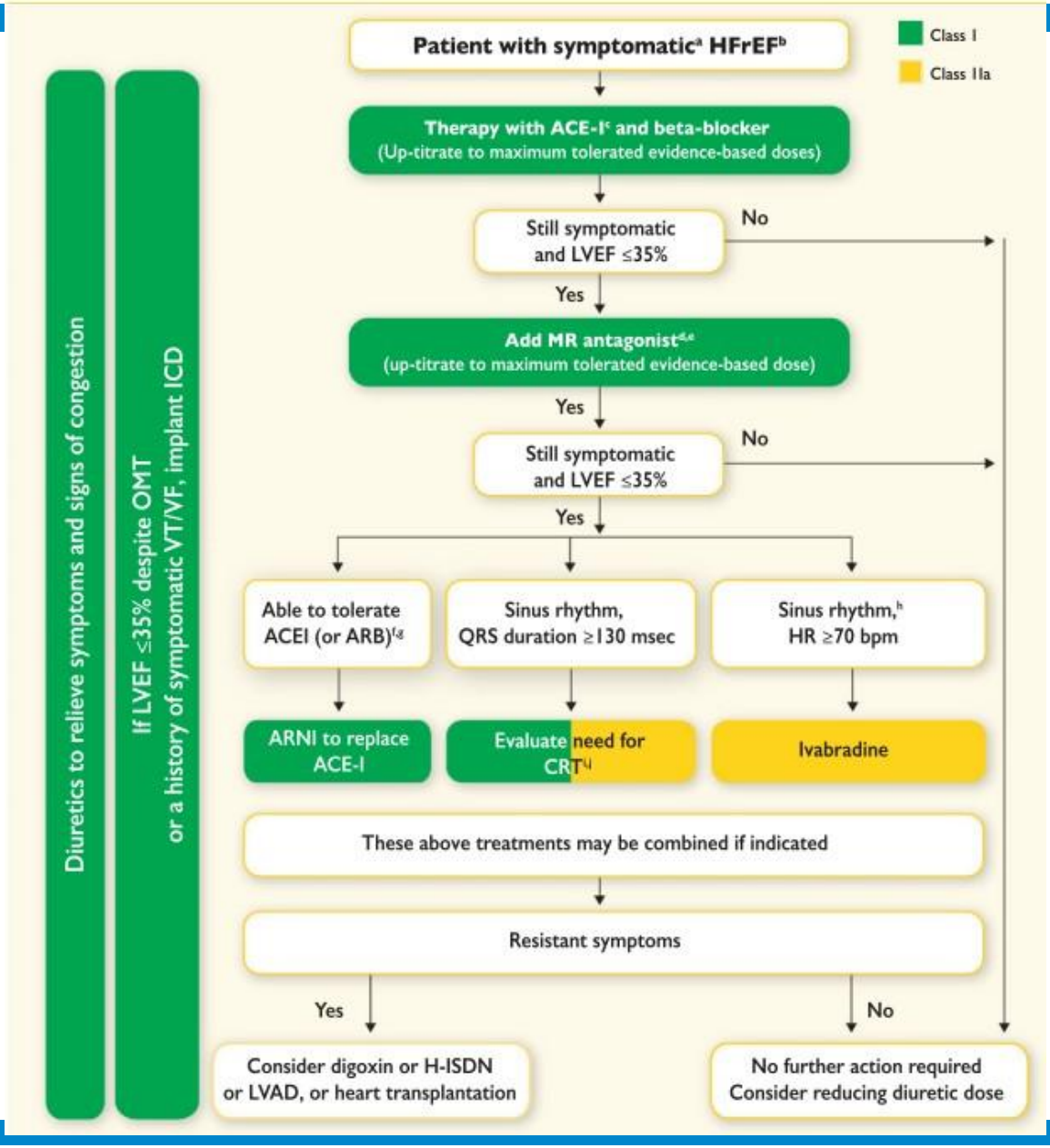
1) glycine to arginine switch at codon 16 (Gly16Arg)
2) glutamine to glutamic acid switch at codon 27 (Gln27Glu)
3) threonine to isoleucine switch at codon 164 (Thr164Ile)

Clinical significance:

1) lower prevalence of ventricular arrhythmias has been attributed to the Gly389 allele

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Betablockers in guidelines



Ponikovski P, Voors A, Anker S et al. Eur Heart J 2016;37: 2129–2200

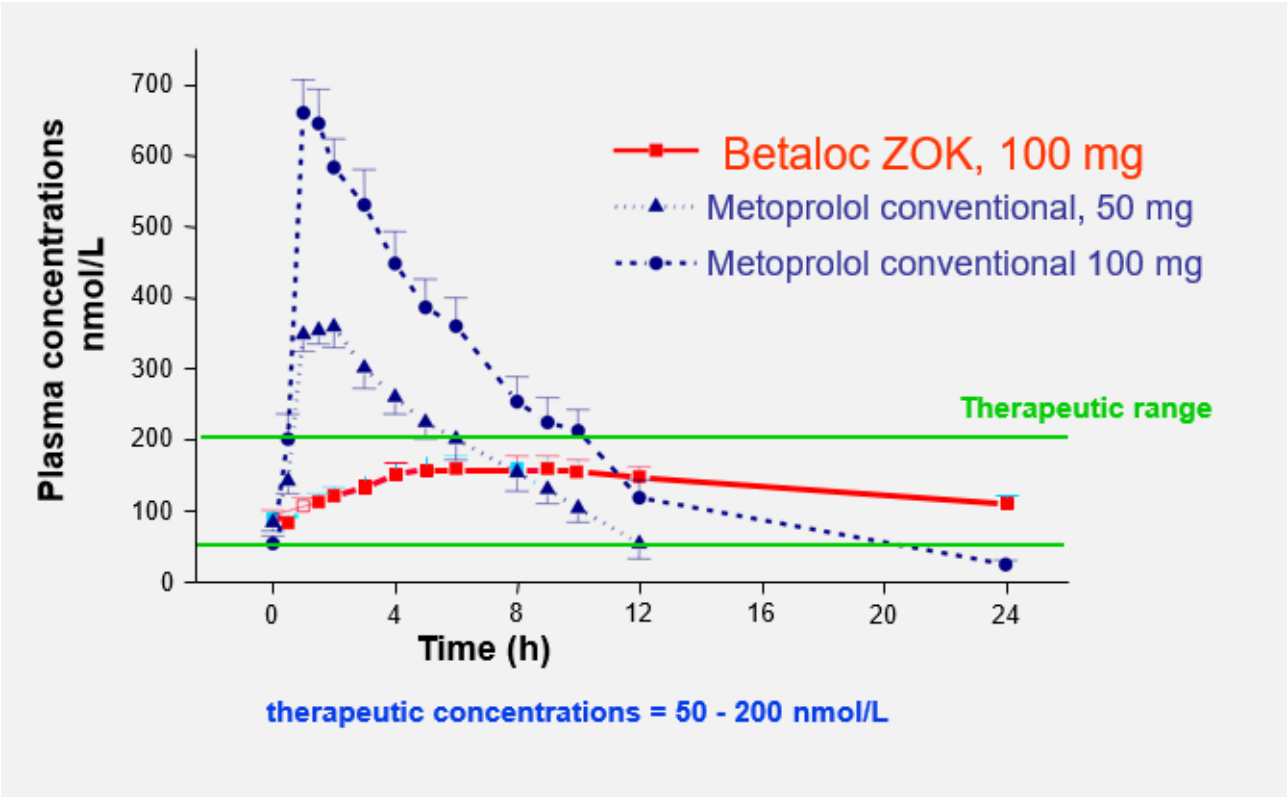
Betablockers in guidelines

	Starting dose (mg)	Target dose (mg)
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*

Ponikovski P, Voors A, Anker S et al. Eur Heart J 2016;37: 2129–2200

Which metoprolol is approved?

- only Metoprolol succinate ZOK is approved for HF treatment
- tablets: consists of microcapsules with pelets – zero order kinetics



- Indication: HF in pts with: hypertension, CAD/MI, migraine, palpitations, arrhythmias,

Ponikovski P, Voors A, Anker S et al. Eur Heart J 2016;37: 2129–2200

Take home messages

- Beta-blockers are cornerstones of the therapy HFrEF
  - reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI, and a diuretics

….thank you for attention

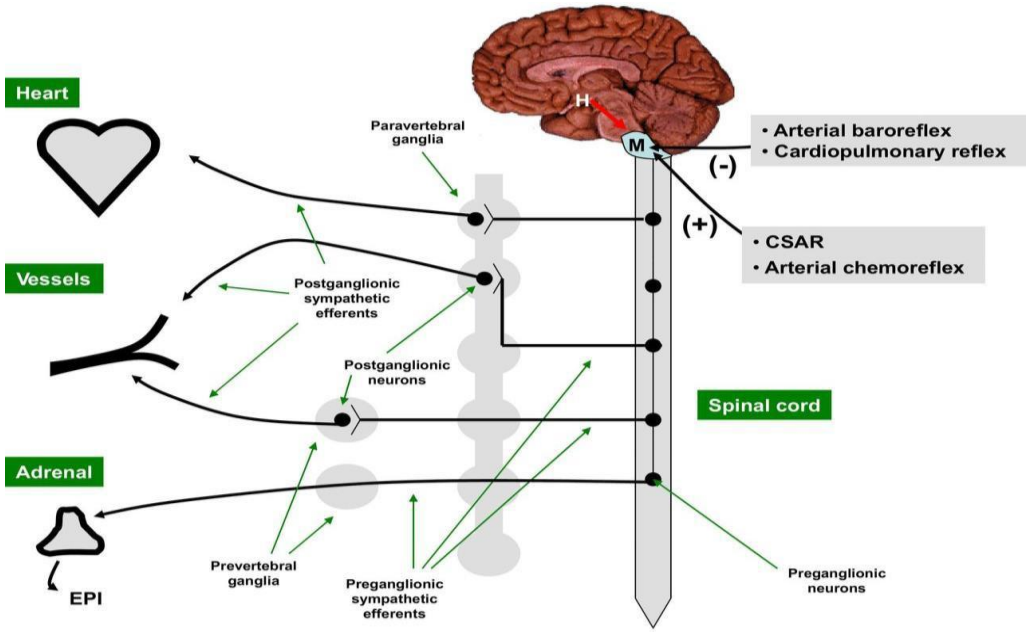
Afferent impulses for SNS

- **proprioreceptors** (muscles, tendons, and joints) mechanically-sensitive → ↑SNS activity
- **baroreceptors** (aortic arch and carotic arteries) ↓ pressure → ↑SNS activity
- **chemoreceptors** (change pH, lactate, O2, CO2)
- **limbic system stimuli** (panic attack) → ↑SNS activity
- **Bainbridge reflex -** ↑ of HR as a result of ↑blood volume (atrial baroreceptors)
- **Bezold-Jarisch reflex -** ↓SNS activity (hypotension, bradycardia, and dilation of the coronary arteries as a paradoxical result of activation of ventricle baroreceptors – anaesthesia…)

Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Mediation of SNS activity

- norepinephrine released by **right stellate ganglion** (SA and AV node) and by **left stellate ganglion** (↑contractile strength and and blood pressure)
- epinephrine released in circulation by the **adrenal cortex** (effect on myocardium and peripheral vessels)
- **local release** of EPI and NE (direct effect on peripheral vessels)
- **circulating NE** (increase in heart rate during exercise of heart transplant recipients)



Floras J. JACC 2009, 54 (5().DOI: 10.1016/j.jacc.2009.03.061

Cardiovascular Adrenergic Receptors (ARs)

AR subtypes

- 3 types of alpha 1 ($\alpha_{1A,}$ $\alpha_{1B,}$ α_{1D})
- 3 types of alpha 2 ($\alpha_{2A,}$ $\alpha_{2B,}$ α_{1C})
- 3 types of beta ($\beta_{1,}$ $\beta_{2,}$ β_{3})

Human heart

- contains $\beta_{1,}$ $\beta_{2,}$ β_{3} receptors
- expression $\beta_1 : \beta_2 = 70 : 30$
- stimulation of β_1 and $\beta_2 \rightarrow \uparrow$ contractility, frequency and rate of relaxation
- β_3 receptors:
  - predominantly inactive during normal conditions
  - stimulation: negative inotropic effect opposite to that induced by excessive adrenergic stimulation ("safety valve")
- expression of alpha 1 receptors is low ($\alpha_{1A\,,}$ α_{1B}) ~ 20% of beta receptors

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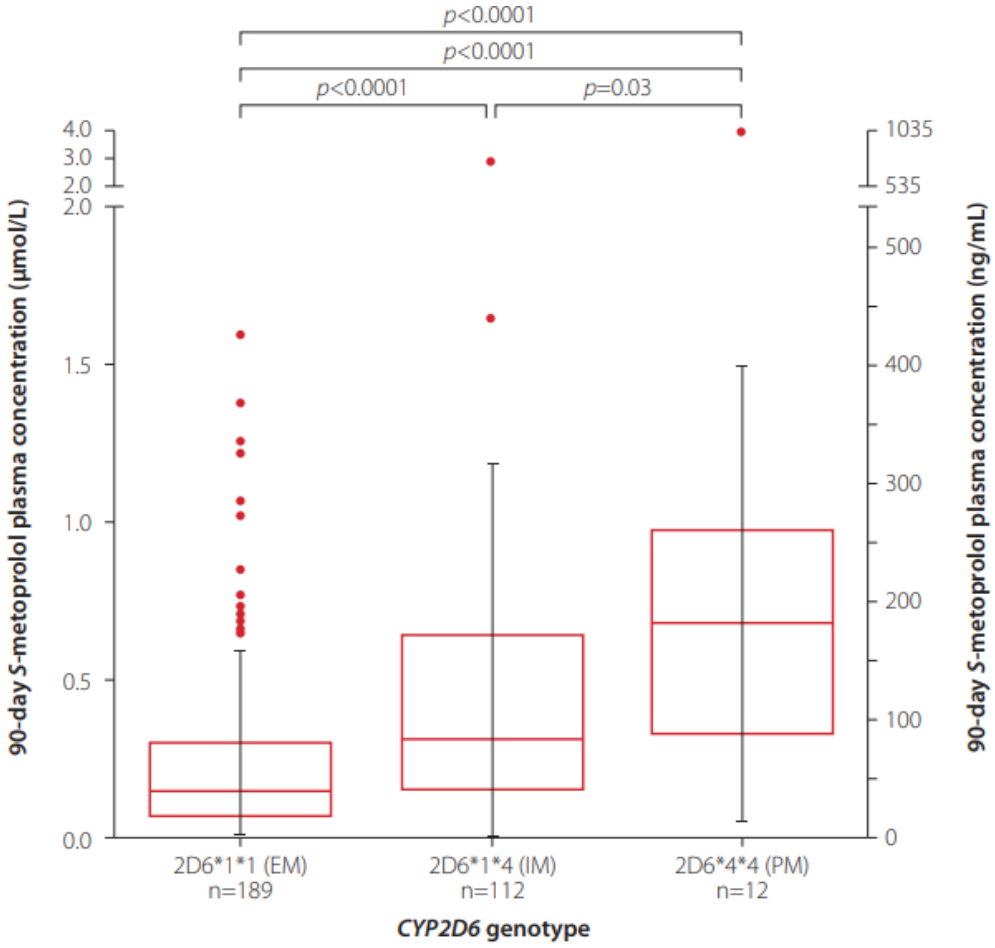
CYP2D6 genotype and the clinical pharmacology of metoprolol *(subanalysis of MERIT-HF)*

metoprolol - extensive hepatic inactivation:

- primarily oxidized (polymorphic CYP2D6 gene) metabolizes to non effective product
- important null allele - CYP2D6*4 (≈20% of Caucasian people)
- >75% of poor metabolizers (PMs) are carriers of this polymorphism



Batty JA et al. Clin Pharmacol Ther. 2014;95(3):321-30