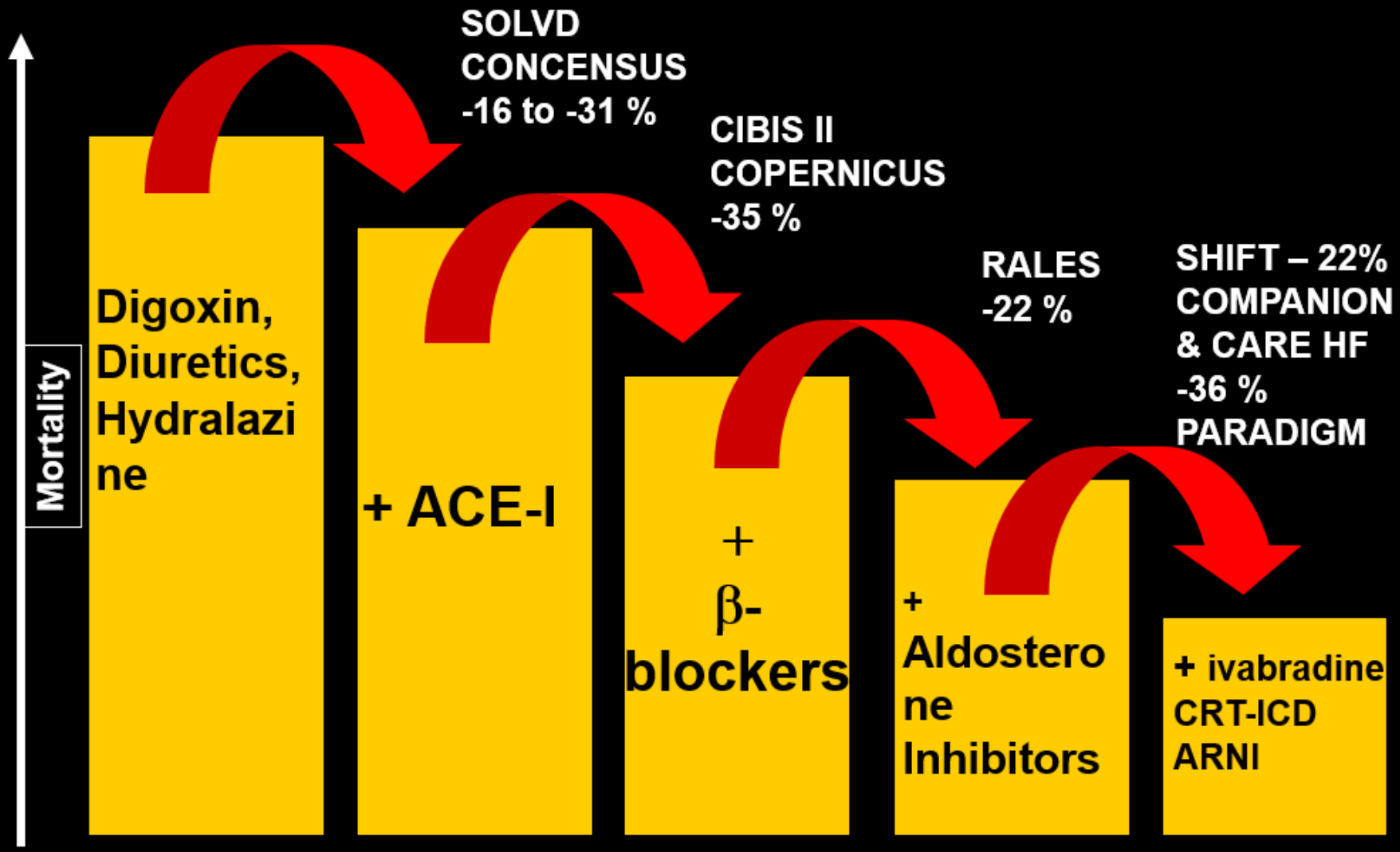
What is new in HF treatment?

Disclosures

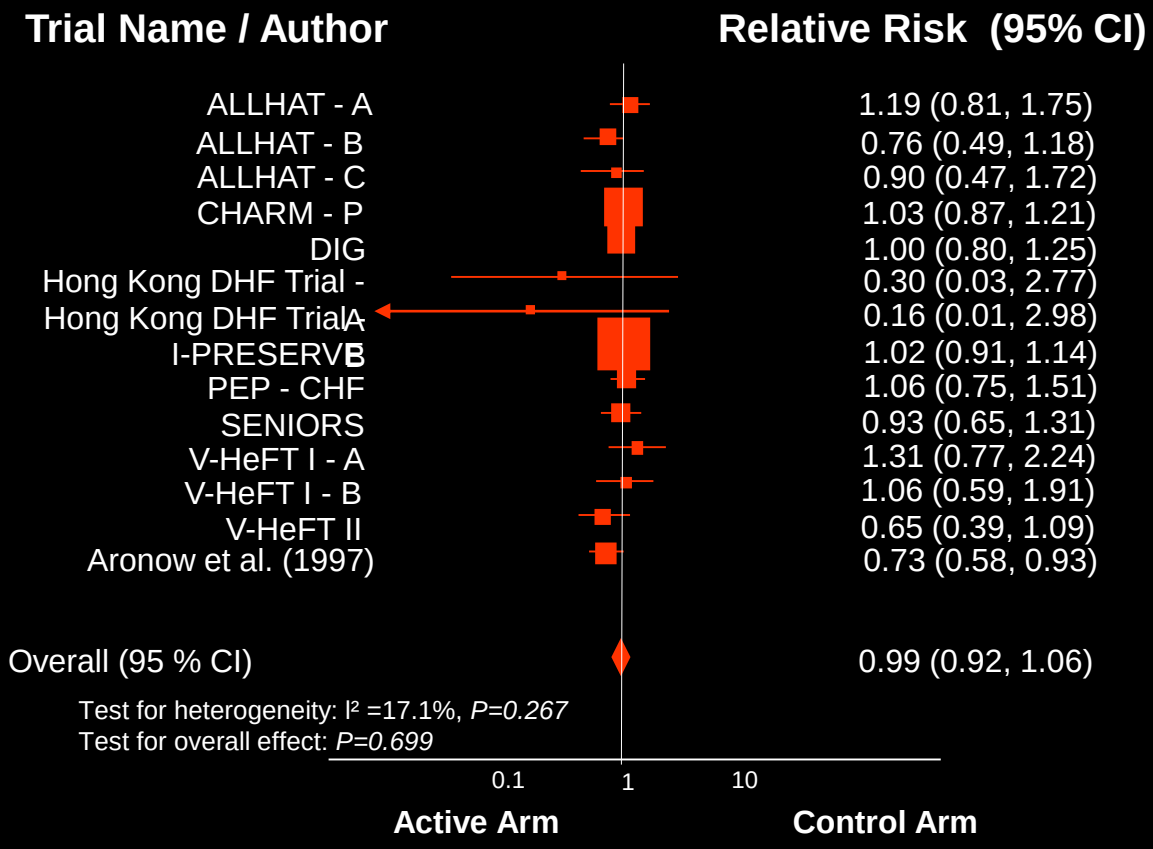
Speaker's bureau:	**Bayer, Merck Serono, Novartis, Amgen Servier International,**
Research grant:	**Boehringer Ingelheim, Novartis, Irbetch, Servier International**
Advisory Board:	**Boehringer Ingelheim, Novartis, Amgen, Abbott, Servier International**

HFrEF: Treatment: a success!



Ellenbogen KA, J Am Coll Cardiol 2005; 46: 2199-203

HFpEF Treatment: no improvement!

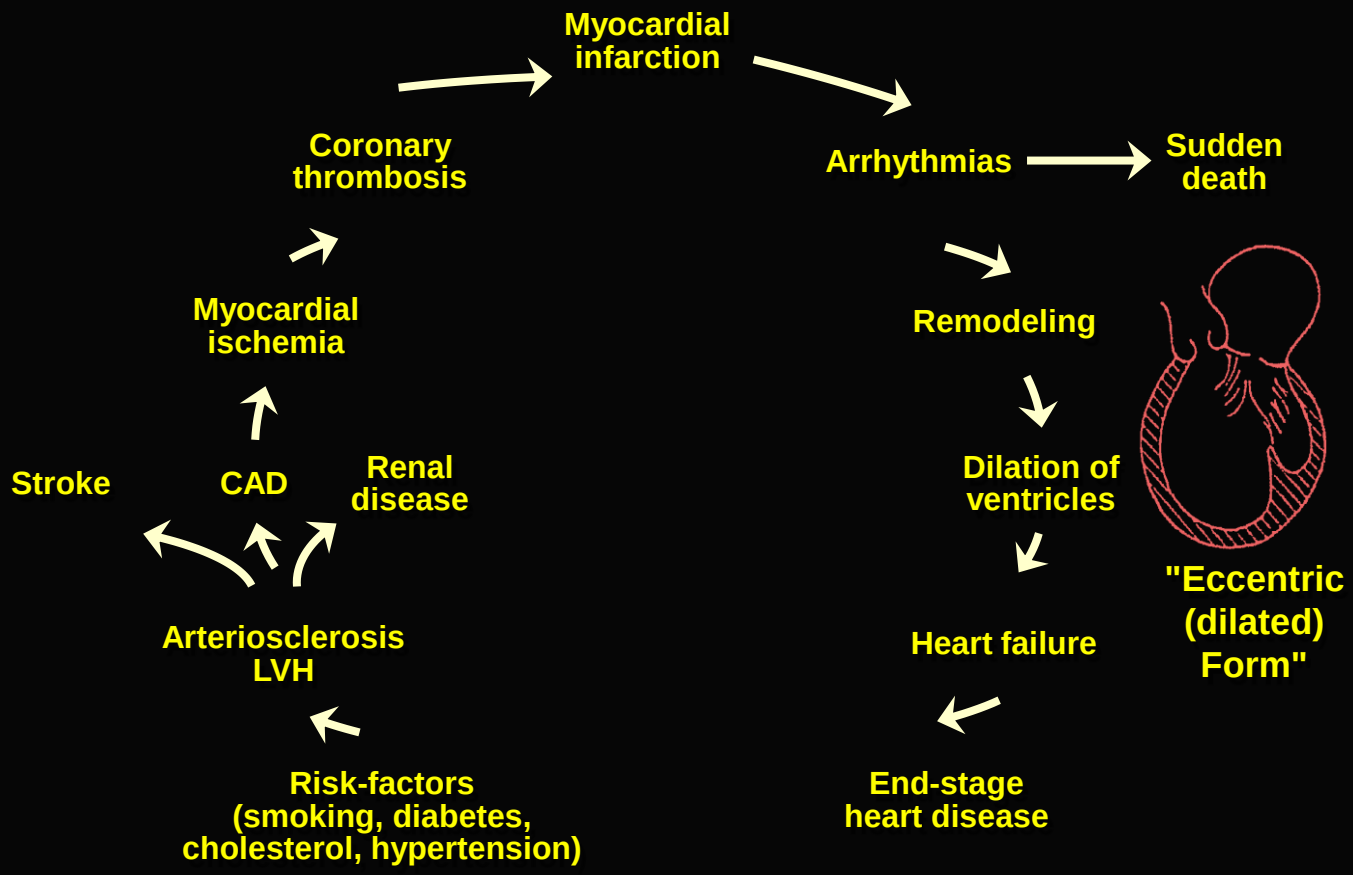


Holland et al., JACC, vol.57, 2011; 16:1676-86

HF with reduced or preserved EF are two distinct entities

- **HFrEF is a clinical syndrome, originated in the heart, driven by myocardial cell loss and fibrosis, with an important systemic component (*neuro-hormonal*) .**

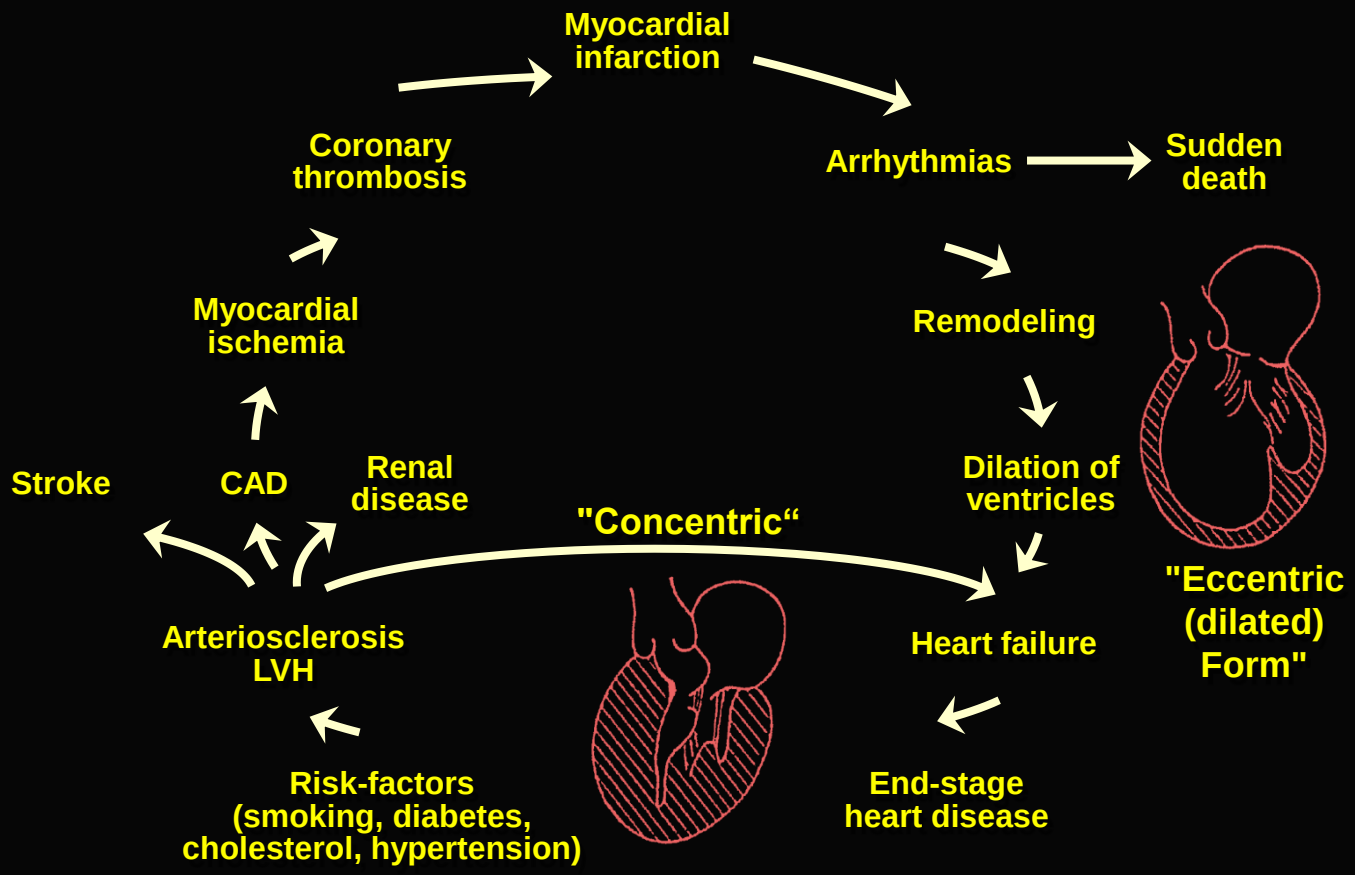
Pathways to Heart Failure with Reduced EF in the Cardiovascular Continuum



HF with reduced or preserved EF are two distinct entities

- **HFpEF is a systemic syndrome, driven by accumulated risk factors/comorbidities in vulnerable subjects, with an important cardiovascular component (*loss of compliance and adaptability*).**

Pathways to Heart Failure in the Cardiovascular Continuum



Success in treating HFrEF

- Depends on the capacity to reduce LV remodelling
- LV Remodelling: Several cellular, molecular and genetic alteration that determines the geometric alteration of ventricular volume

What determines remodelling?

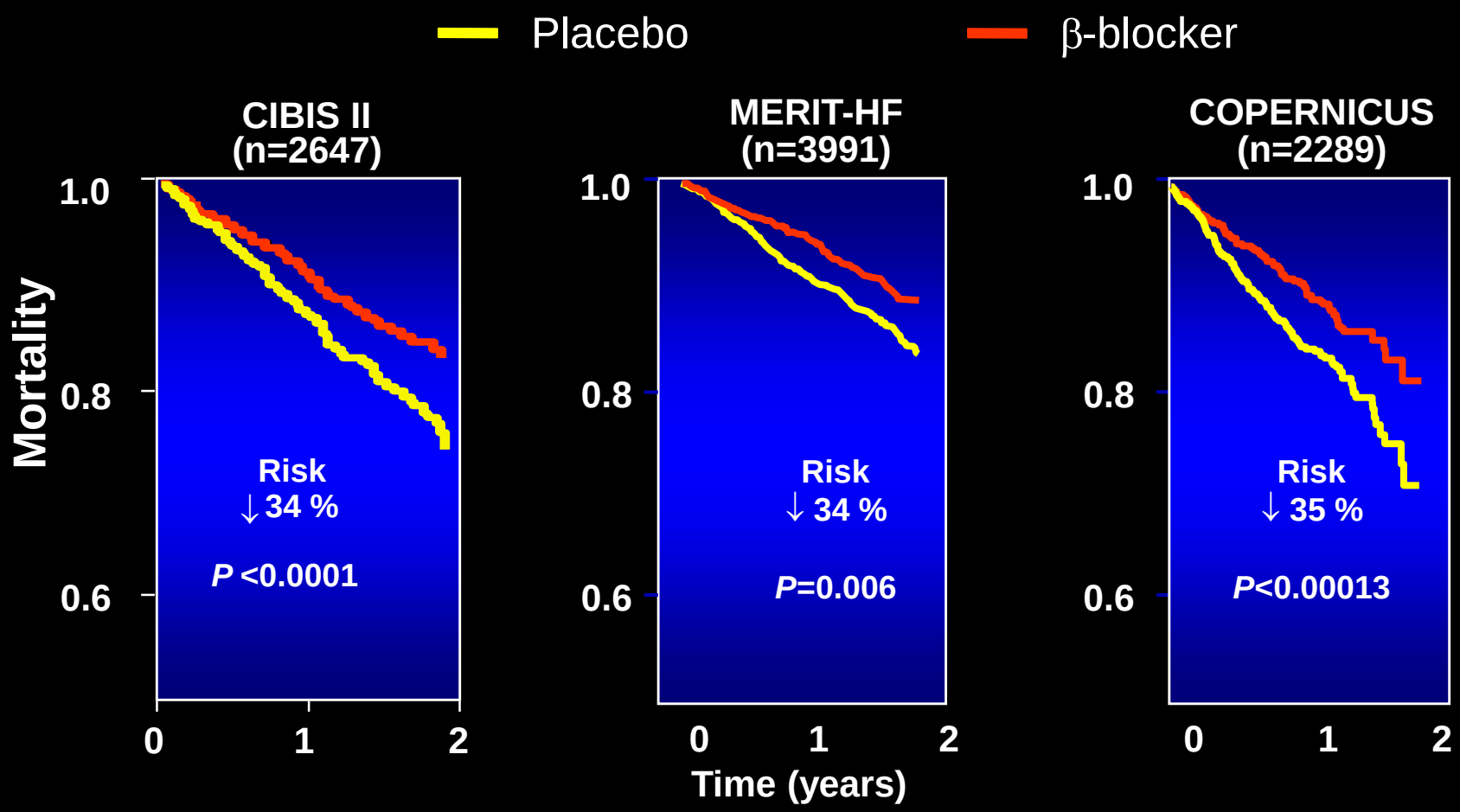
- Increased apoptosis (*death*) due to Re-enstatement of cell life/death cycle

- Return to embrionic genetic programme with expression of embrinonic myofilaments and SERCA

But clinically mainly because of

Increased of heart rate further deteriorated myocyte contractility

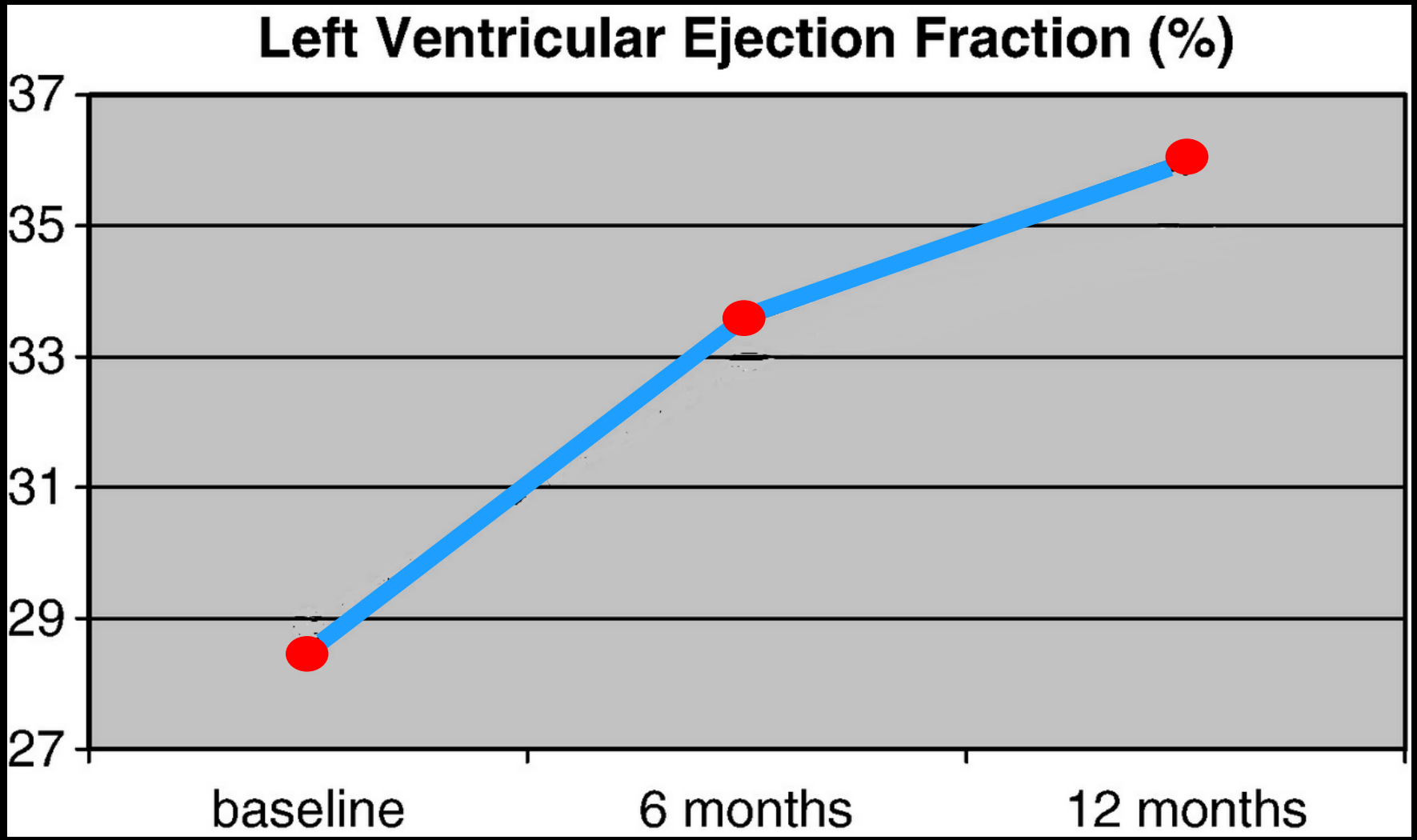
Prognostic effect of BBs in HF



All cause mortality	**34**	**34**	**35**
Sudden Death	**44**	**41**	**44**
HF Hospitalizations	**32**	**35**	**33**

CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial.

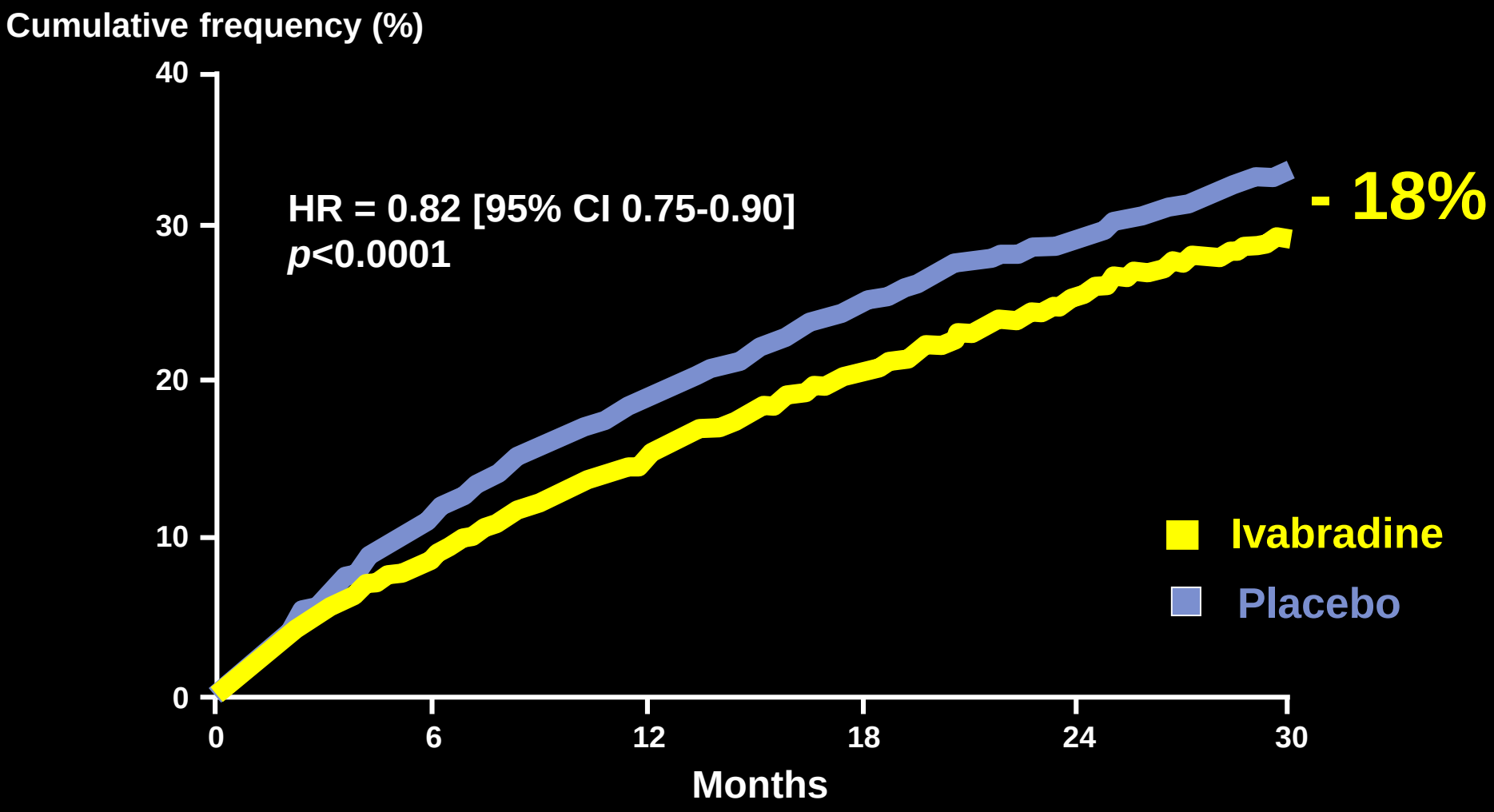
Changes in LV ejection fraction by bisoprolol (10mg qd) in CIBIS 3



LLM Van de Ven et al, International Journal of Cardiology 2010

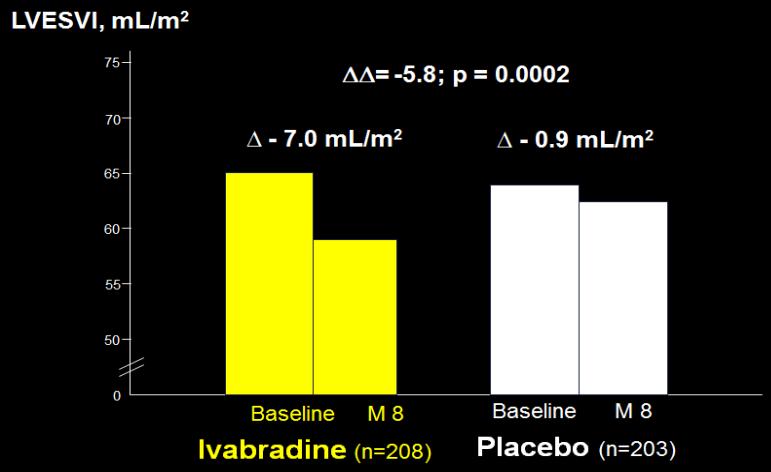
Primary composite endpoint

Ivabradine n=793 (14.5%PY) **Placebo n=937 (17.7%PY)**

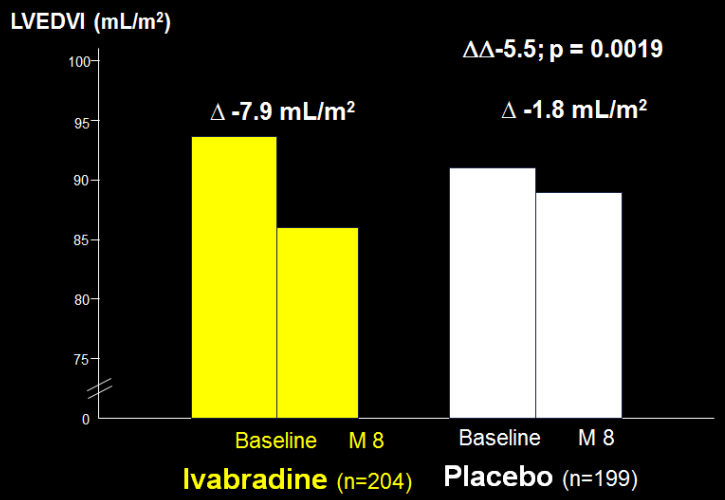


LV End Systolic Volume Index

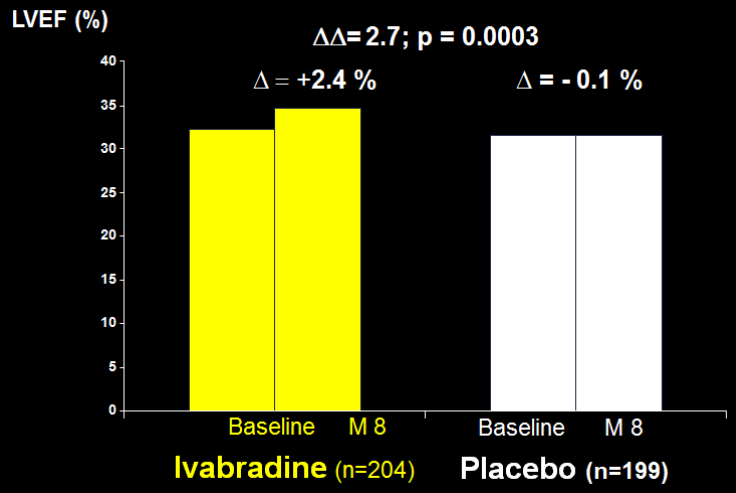
Primary endpoint



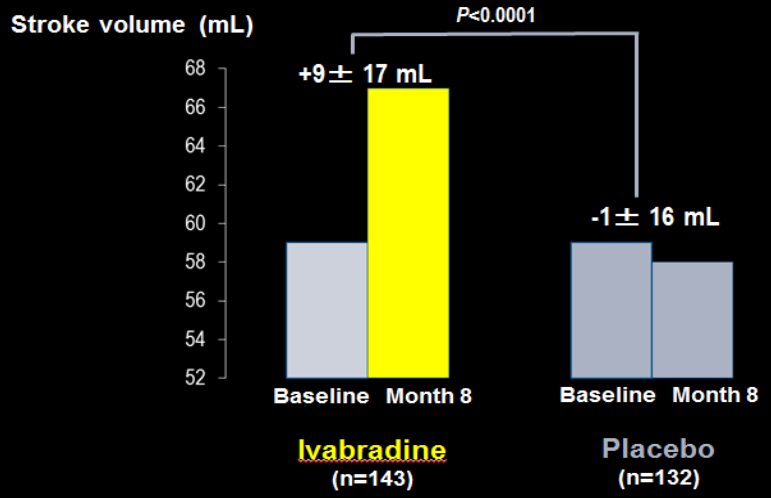
LV End Diastolic Volume Index



LV Ejection Fraction



Ivabradine increases stroke volume



The "*beta blocker and ivabradine paradox*"

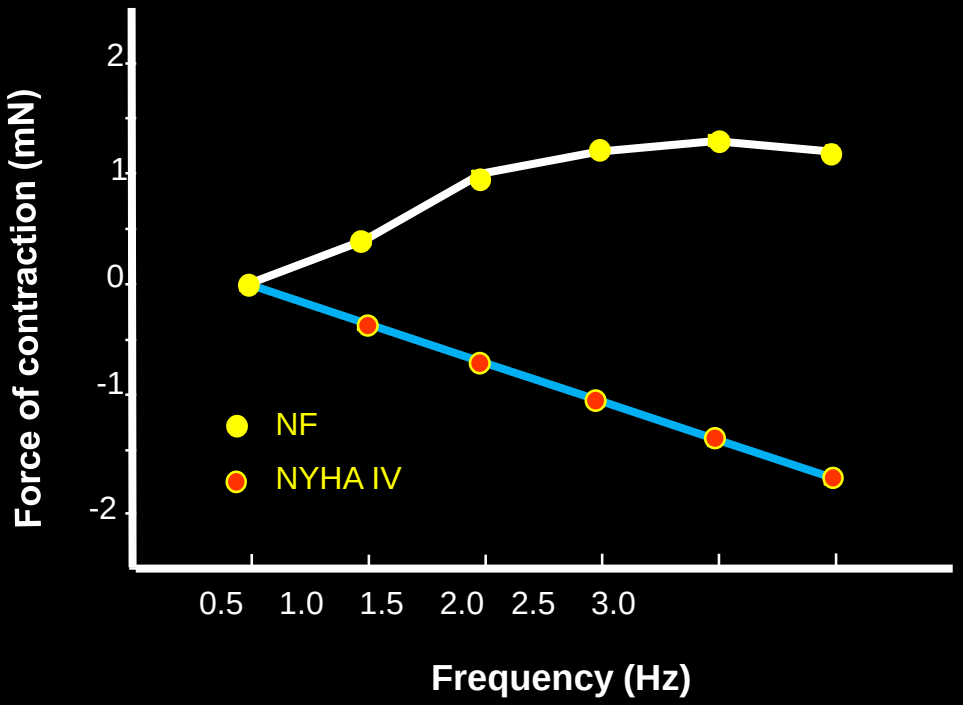
- **BBs and ivab in HF are the "*ideal*" inotropes**

Why?

- **By reducing HR, BBs and ivab improve EF without increasing O_2 consumption**

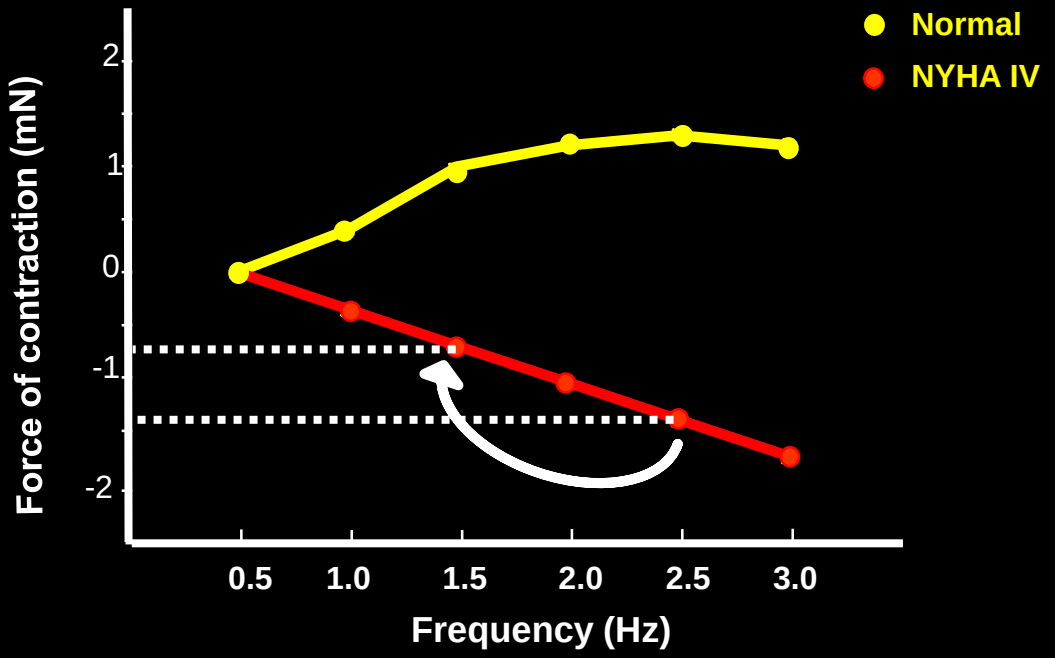
Inverse force- frequency relationship in HFrEF

Human Papillary Muscle Strips



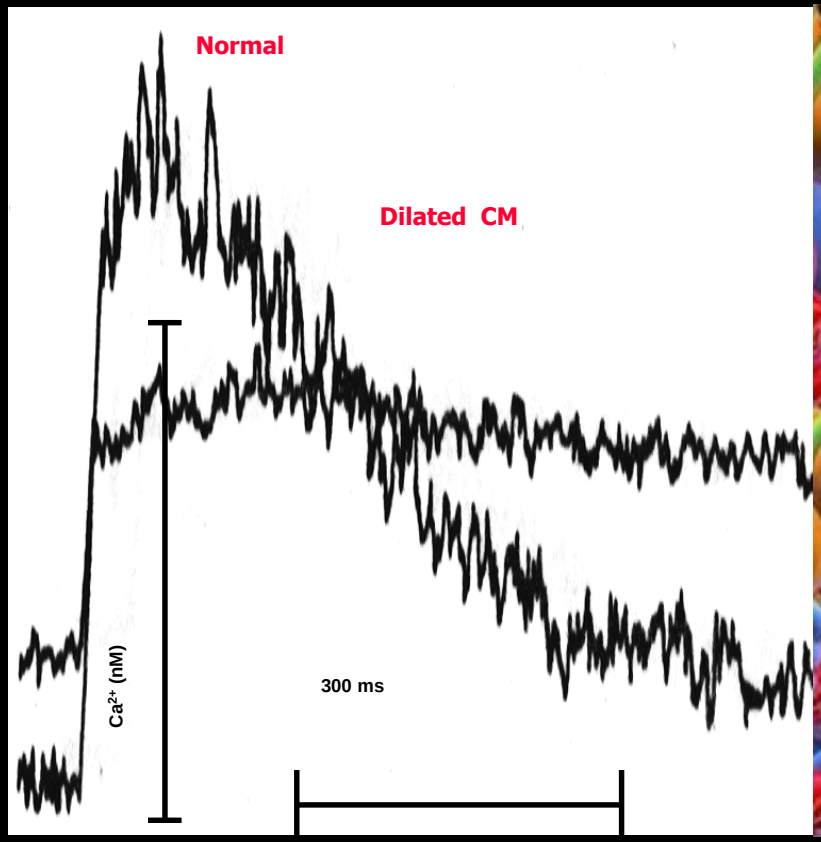
Böhm M, et al. *Clin Invest*. 1992;70:421-425.

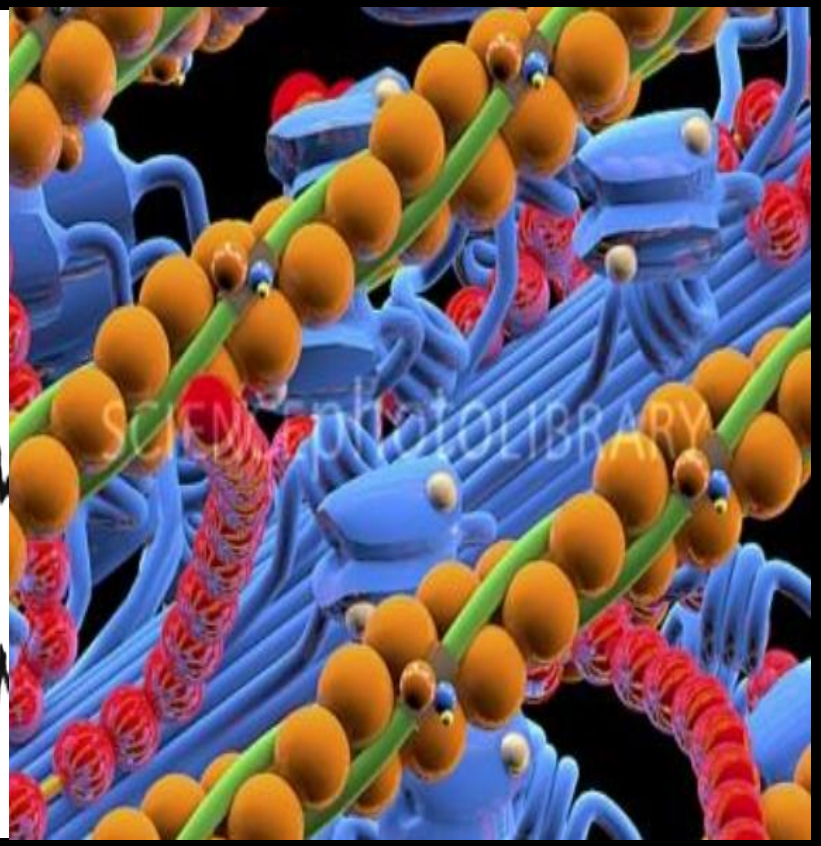
Force-frequency relationship Human papillary muscle strips



Böhm M, et al. *Clin Invest.* 1992;70:421-5.

Reducing heart rate in heart failure results in calcium sensitizing at the level of the myofilaments





No question that beta-blockers are useful in HF with reduced EF

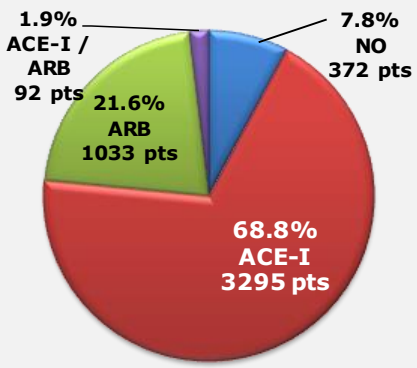
But…..

are we using them properly?

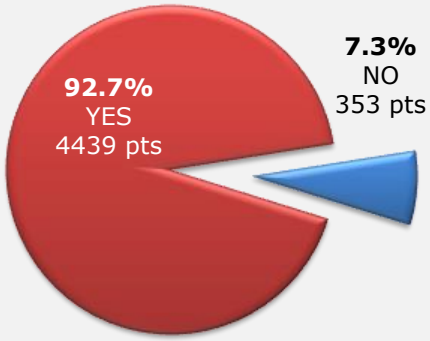
Are ambulatory patients with heart failure treated in accordance with ESC guidelines ?

Rate of use

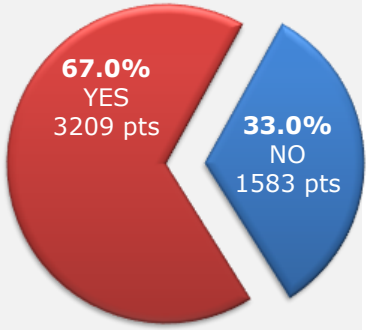
ACE-I/ARB



Betablockers



MRAs

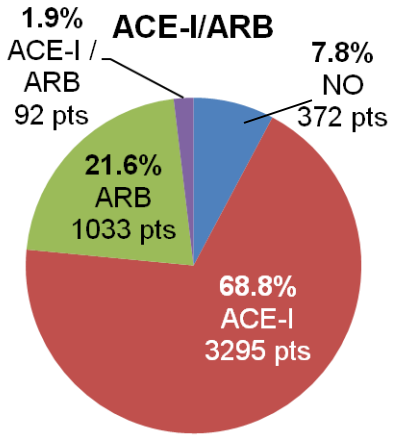


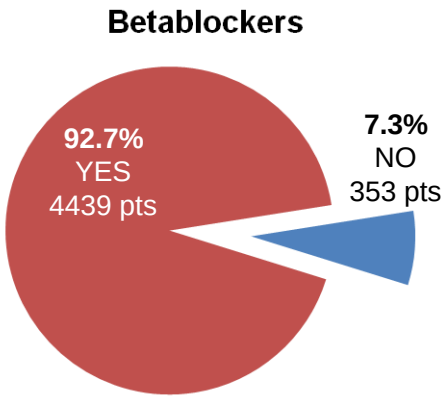
➔ **Rate of patients at target dosage of recommended pharmacological treatments**

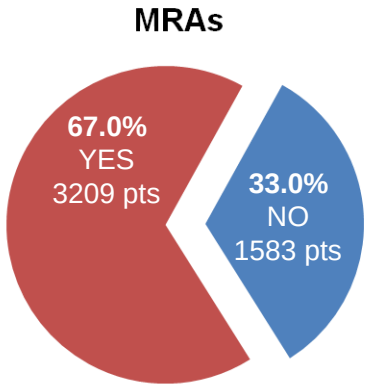
ACE-I (4710 pts)	**1380 (29.3)**	**B-blockers** (6468 pts)	**1130 (17.5)**	**MRAs** (4226 pts)	**1290 (30.5)**
ARBs (1500 pts)	**362 (24.1)**				

A. P. Maggioni, et al EJHF 2013 / IT / 5292

Rate of use and reasons for non use of recommended treatments in patients with reduced EF







Contraindicated	**n. 94 (2.0%)**
Severe renal dysfunction	*n. 61 (64.9%)*
Symptomatic hypotension	*n. 13 (13.8%)*
Hyperkalemia	*n. 8 (8.5%)*
Other	*n. 12 (12.8%)*
Not tolerated	**n. 123 (2.6%)**
Worsening renal function	*n. 22 (17.9%)*
Symptomatic hypotension	*n. 83 (67.5%)*
Hyperkalemia	*n. 6 (4.9%)*
Angioedema	*n. 2 (1.6%)*
Other	*n. 10 (8.1%)*
Real undertreatment	**n. 155 (3.2%)**

Contraindicated	**n. 78 (1.6%)**
Asthma/COPD	*n. 28 (35.9%)*
Bradyarrhythmia	*n. 11 (14.1%)*
Symptomatic hypotension	*n. 11 (14.1%)*
PAD	*n. 3 (3.8%)*
Other	*n. 25 (32.1%)*
Not tolerated	**n. 165 (3.4%)**
Bronchospasm	*n. 39 (23.6%)*
Symptomatic hypotension	*n. 46 (27.9%)*
Bradyarrhythmia	*n. 22 (13.3%)*
Worsening HF	*n. 36 (21.8%)*
Other	*n. 22 (13.3%)*
Real undertreatment	**n. 110 (2.3%)**

Contraindicated	**n. 268 (5.6%)**
Hyperkalemia	*n. 94 (35.1%)*
Renal dysfunction	*n. 153 (57.1%)*
Other	*n. 21 (7.8%)*
Not tolerated	**n. 147 (3.1%)**
Hyperkalemia	*n. 53 (36.1%)*
Worsening renal function	*n. 34 (23.1%)*
Gynecomastia	*n. 34 (23.1%)*
Other	*n. 26 (17.7%)*
Not indicated	**n. 908 (18.9%)**
Real undertreatment	**n. 260 (5.4%)**

Maggioni AP, et al. Eur J Heart Fail, online Aug 26, 2013

The BB dilemma in HF: target *dose* vs target *effect*

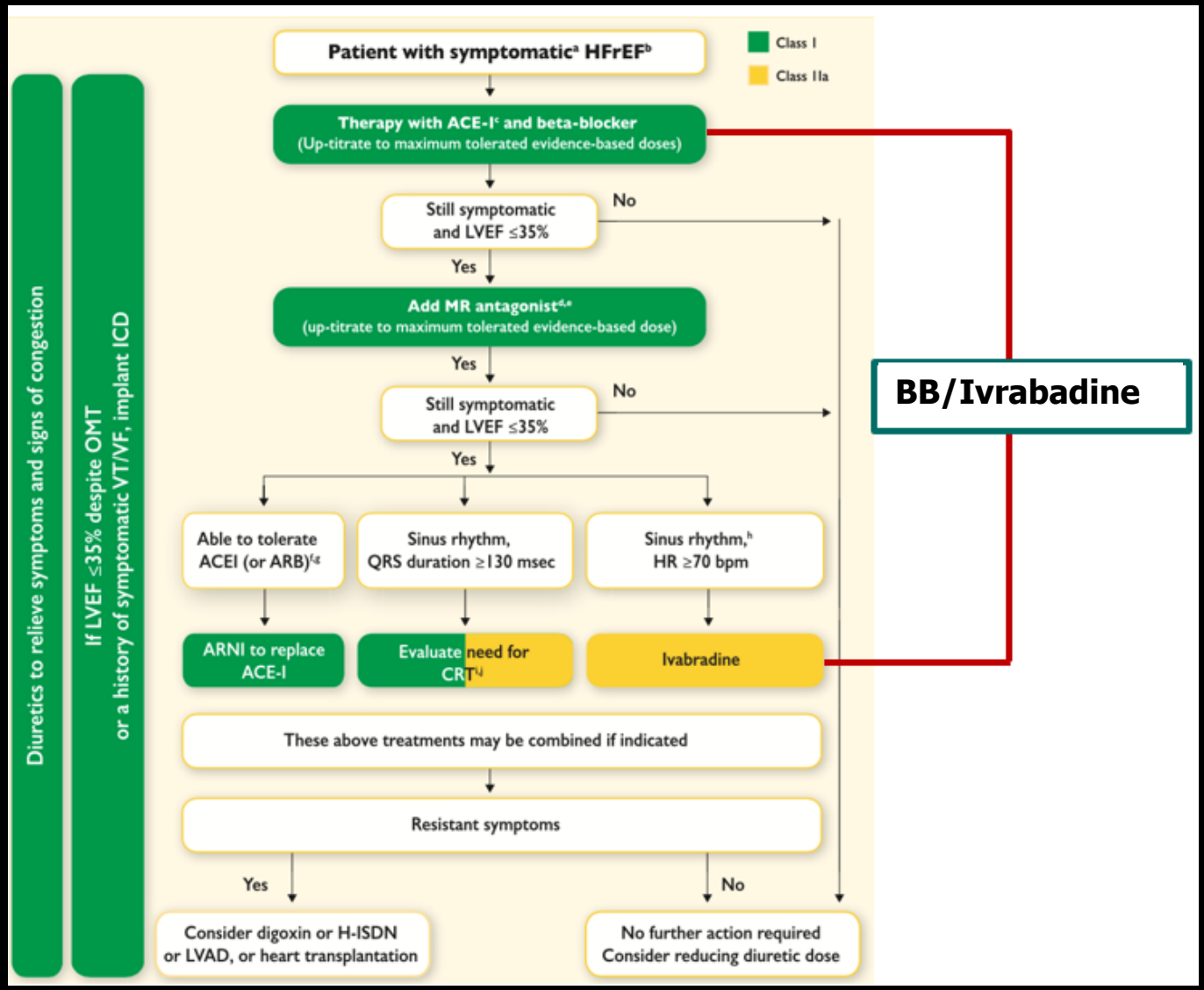
***Target dose*:**

- **defined in (*dated*) trials**
- **different background treatment**
- **by selected investigators**
- **other doses not tested**

***Target effect*:**

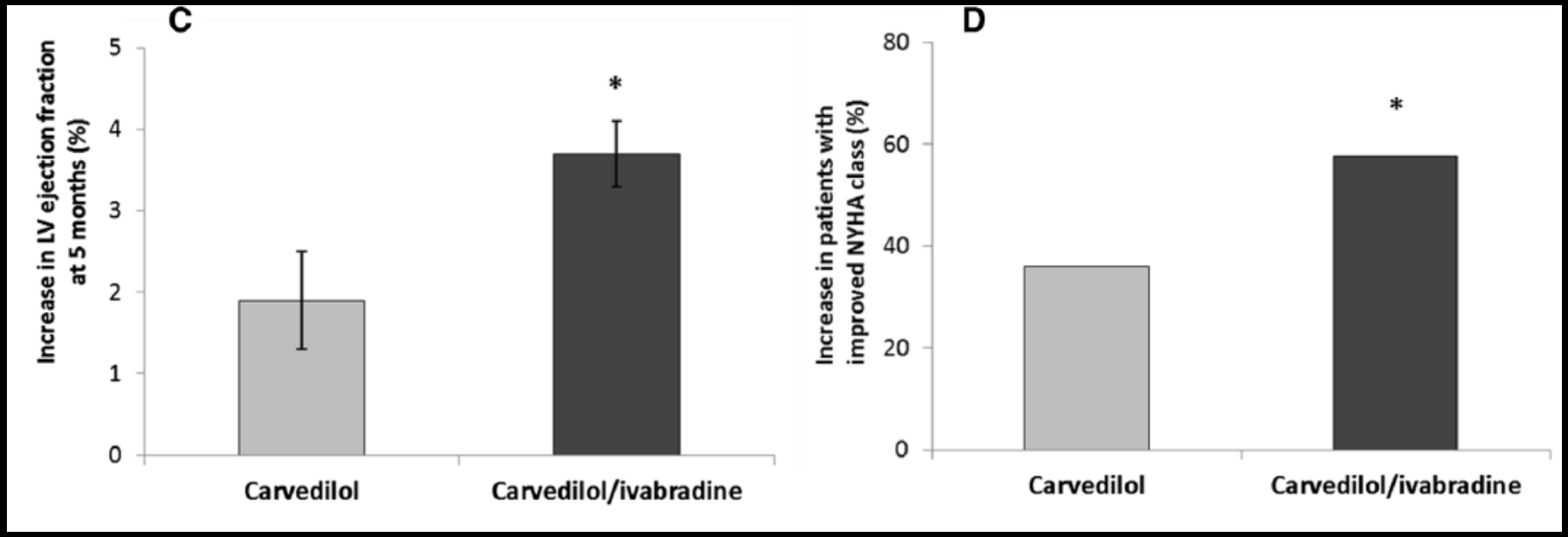
- **evaluated by a marker of *individual* efficacy and safety**
- **Often patients on bbs do not reach 60 bpm**

Fixed combination between BBS and ivabradine maybe a good idea



Early effects of Ivabradine with Carvediol

Ivabradine in combination improves LVEF in CHF



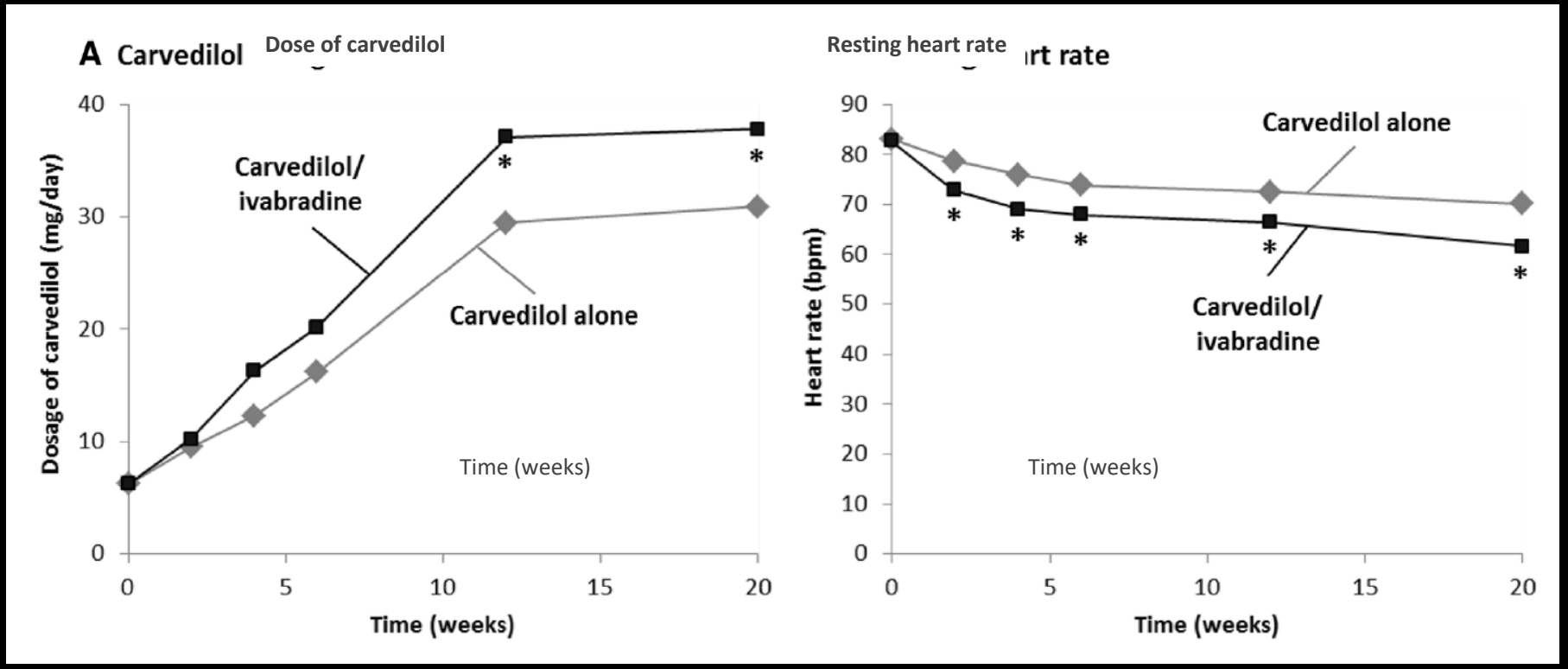
- n=69 pat. with CHF (n=36 carvedilol alone; n=33 carvedilol + ivabradine)

- Bagriy et al. *Adv Ther.* 2015;32:108-119.

Carvedilol / Ivabradine

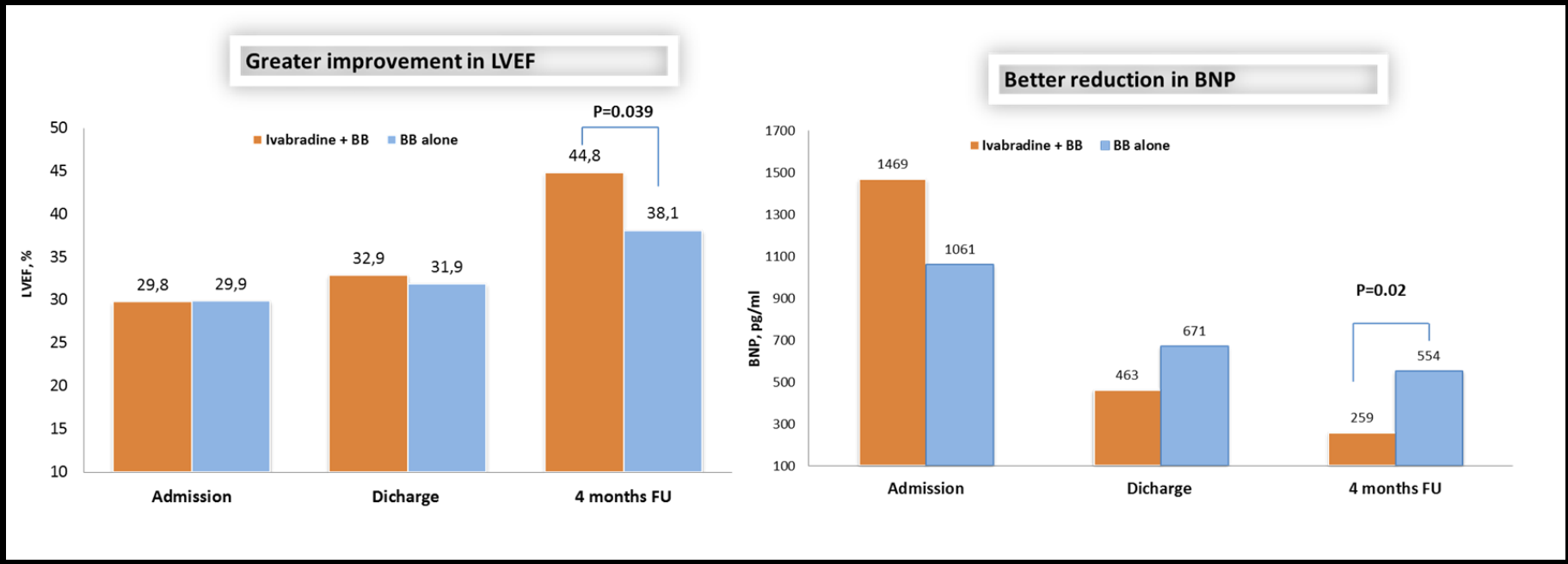
Better tolerance to up-titration of carvedilol

Improved HR control



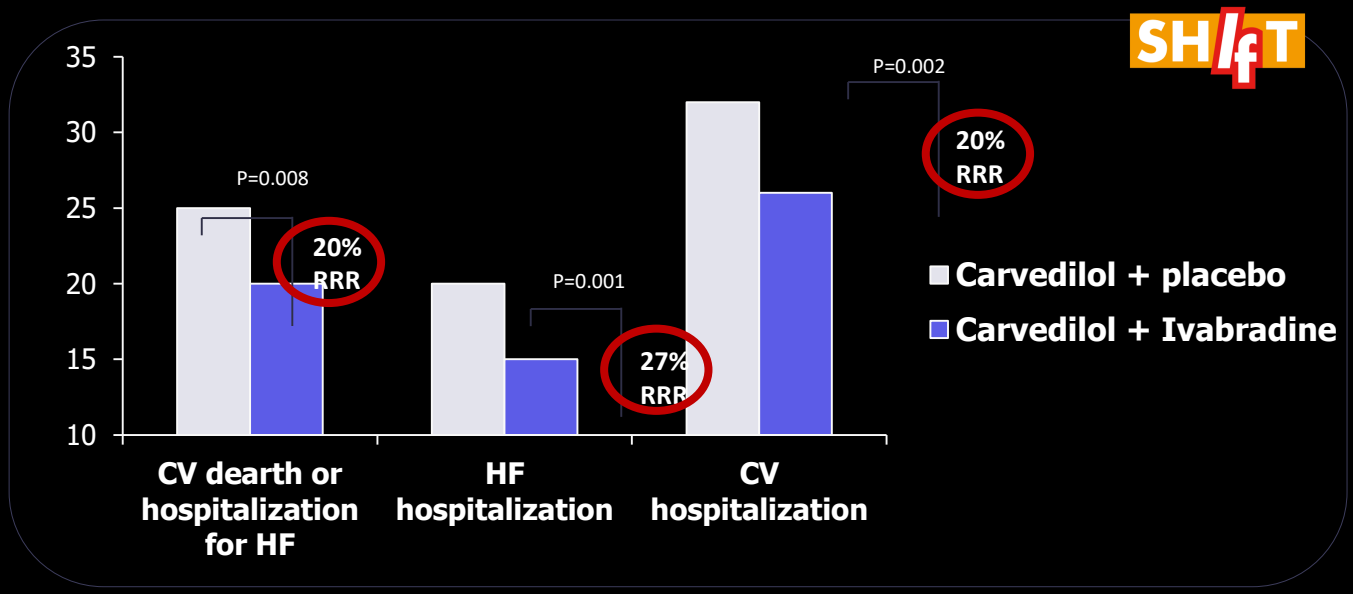
Bagriy AE et al. Adv Ther 2015;32:108

Effect of early treatment BBs+Ivabradine vs BB alone in patients hospitalized for WHF: randomized ETHIC-AHF study



Hidalgo FJ et al. Int J Cardiol. 2016;217:7-11

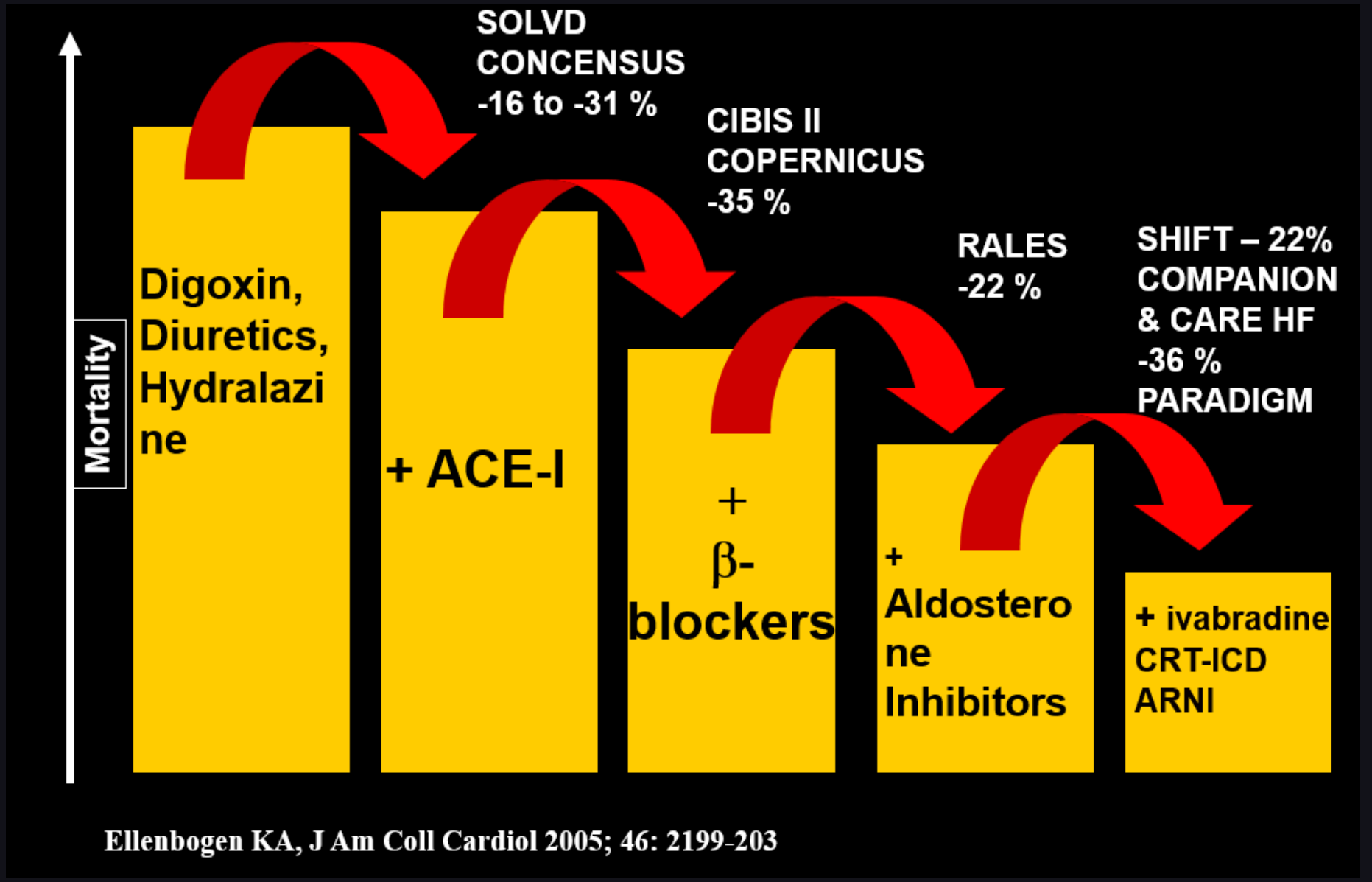
Complementary prognostic benefits of Carvedilol/Ivabradine



- Combination of ivabradine with carvedilol for a mean of 19 months was associated with an improvement in cardiovascular outcomes compared with carvedilol alone
- This combination was well tolerated

Bocchi EA et al. Cardiology 2015;131:218

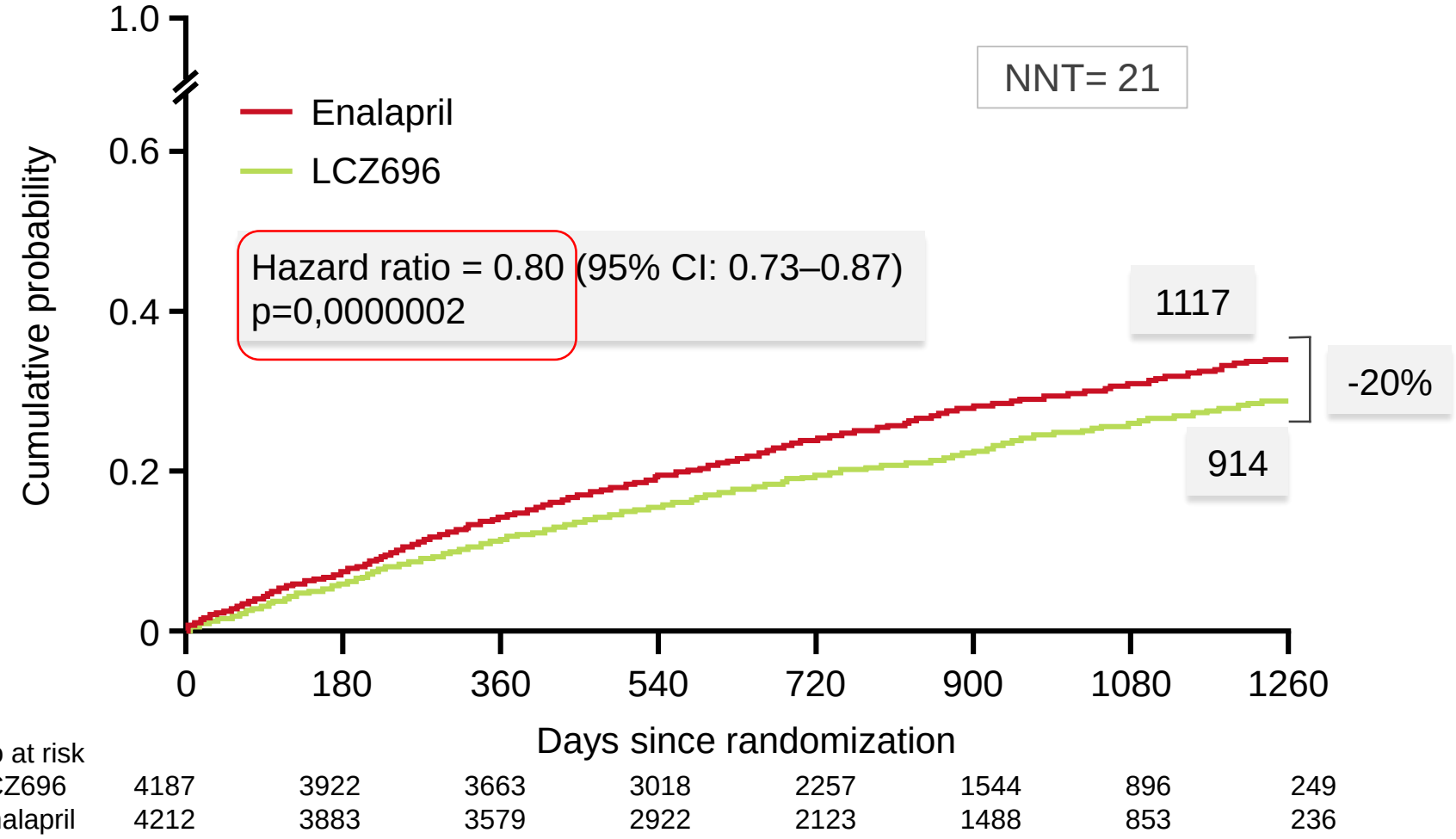
HFrEF: Treatment: a success!



Ellenbogen KA, J Am Coll Cardiol 2005; 46: 2199-203

PARADIGM-HF: RESULTS

Primary endpoint:
Death from CV causes or first hospitalization for HF



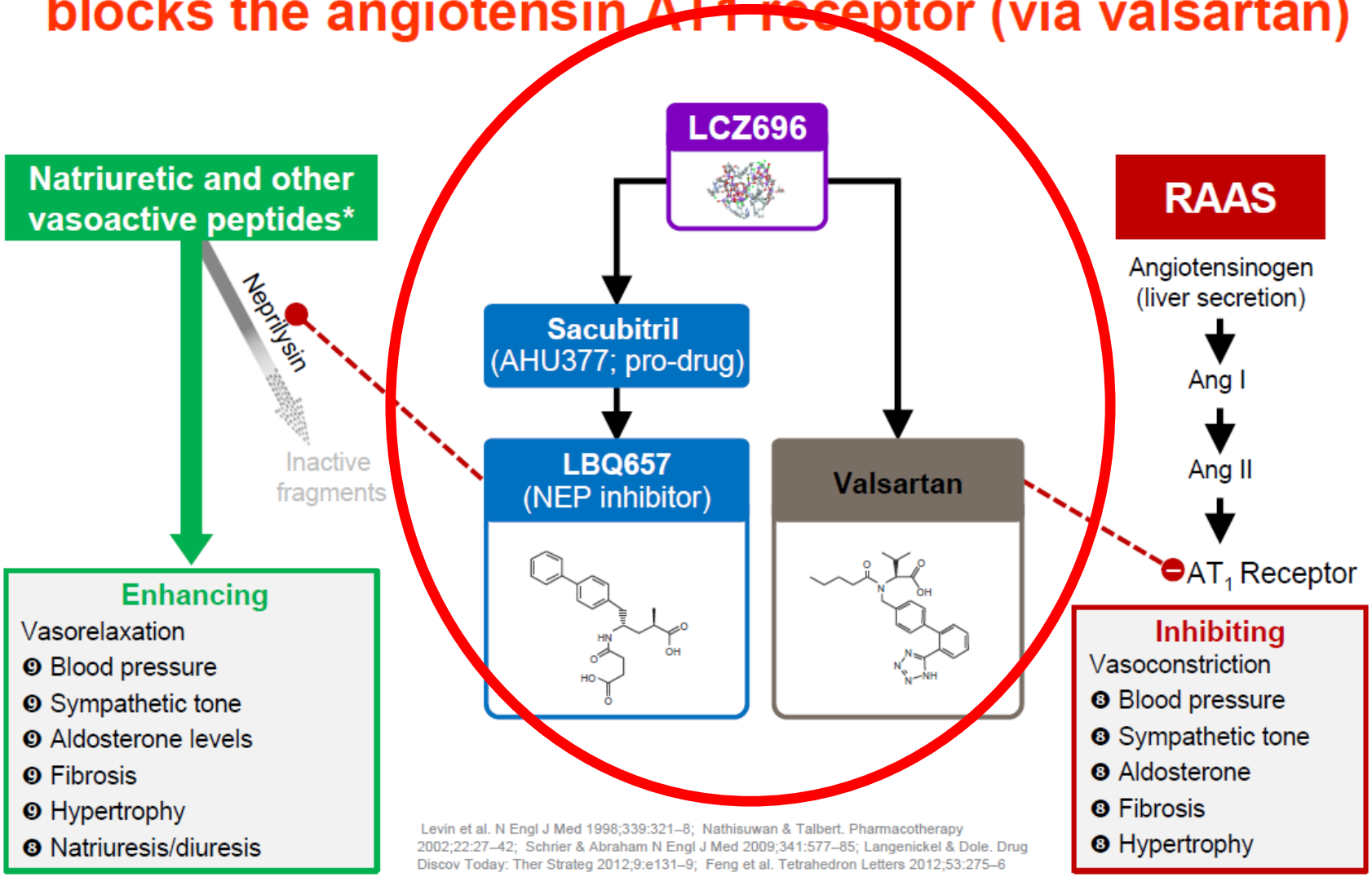
No at risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

29

McMurray, et al. N Engl J Med 2014;

Why?

LCZ696 simultaneously inhibits NEP (via LBQ657) and blocks the angiotensin AT1 receptor (via valsartan)

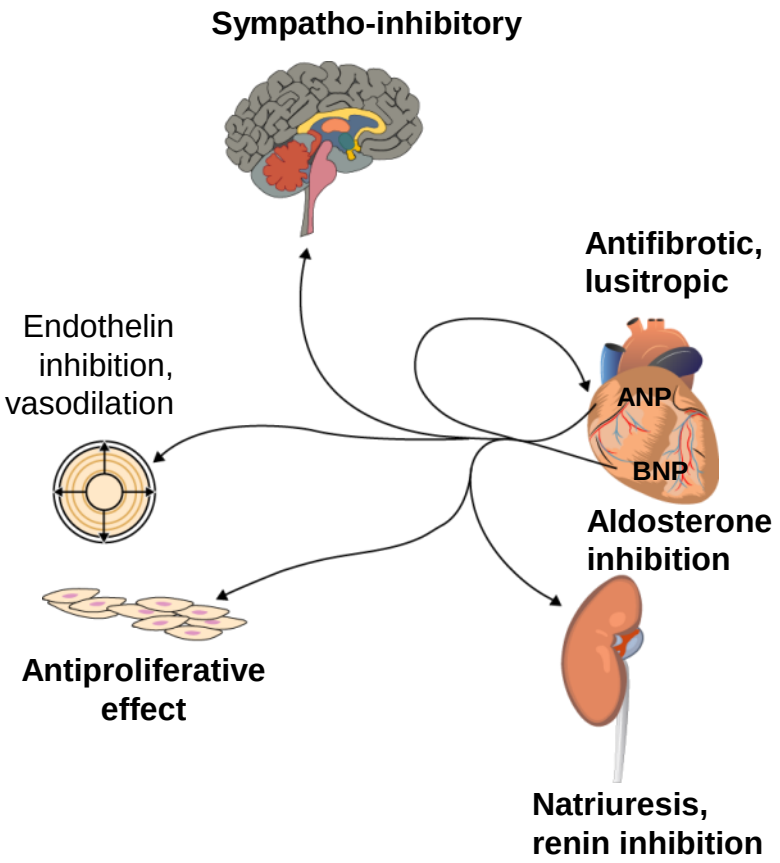


Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Schrier & Abraham N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9; Feng et al. Tetrahedron Letters 2012;53:275–6

- **New target: neprilysin (*NEP*) an ubiquitous enzyme which metabolizes low molecular weight peptides, potentially useful in HF such as natriuretic peptides**

- **Further antagonism of angiotensin II**

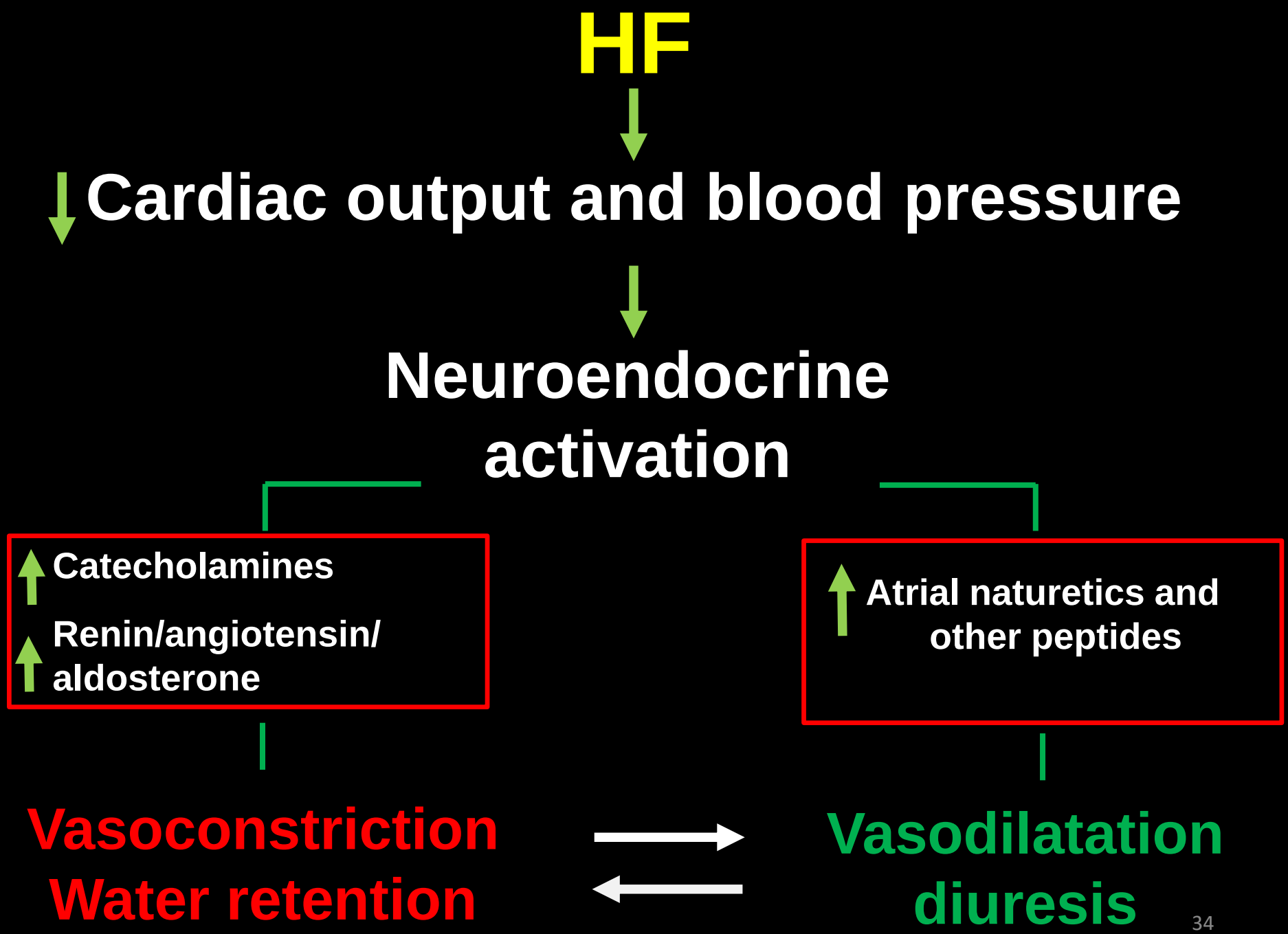
Natriuretic peptides have potential for protection of the heart, vessels and kidneys



- **NPs are released in response to cardiac wall stress and act in the brain, adrenal gland, kidney, vasculature and heart, leading to:**
  - **natriuresis and diuresis**
  - **vasodilation**
  - **inhibition of RAAS and sympathetic activity**
  - **attenuation of cardiac remodeling (LVH) and fibrosis**
  - **reverse vascular remodeling (arterial stiffness)**
  - **attenuation of renal fibrosis and improved renal hemodynamics**
  - **enhanced endothelial function**
  - **lipid mobilization**

ANP=atrial natriuretic peptide; LVH=left ventricular hypertrophy

Boerrigter & Burnett. Expert Opin Invest Drugs 2004;3:643–52; Rubattu et al. Am J Hypertens 2008;21:733–41


HF
Cardiac output and blood pressure
Neuroendocrine activation
Catecholamines
Renin/angiotensin/ aldosterone
Atrial naturetics and other peptides
Vasoconstriction
Water retention
Vasodilatation
diuresis

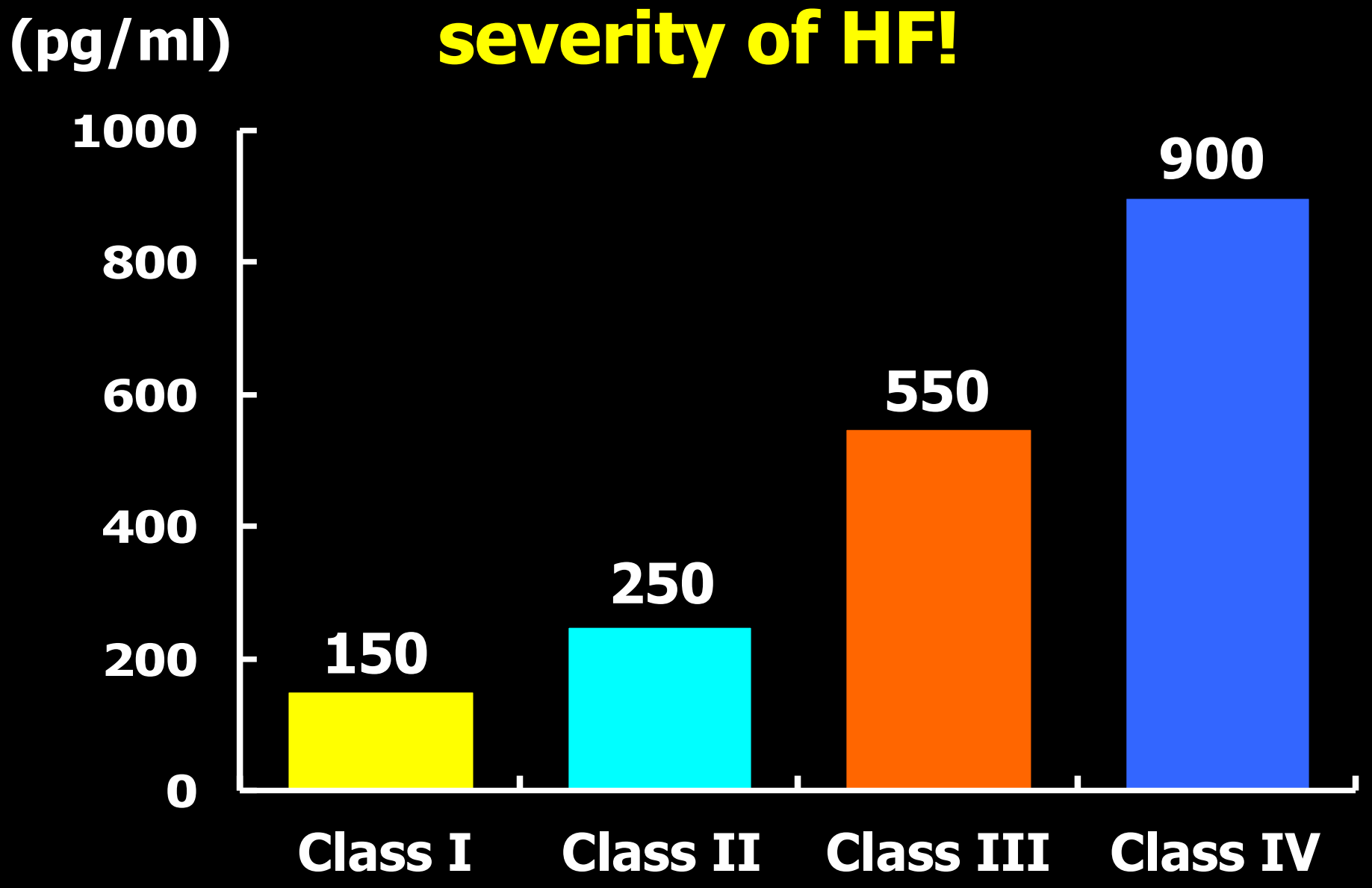
A new concept!

- From enhanced neuroendocrine activation
- to a deficit of useful neuroendocrine systems

A new concept!

- From neuroendocrine antagonization
- to integrative hormonal therapy

But…BNP Levels increase with the severity of HF!

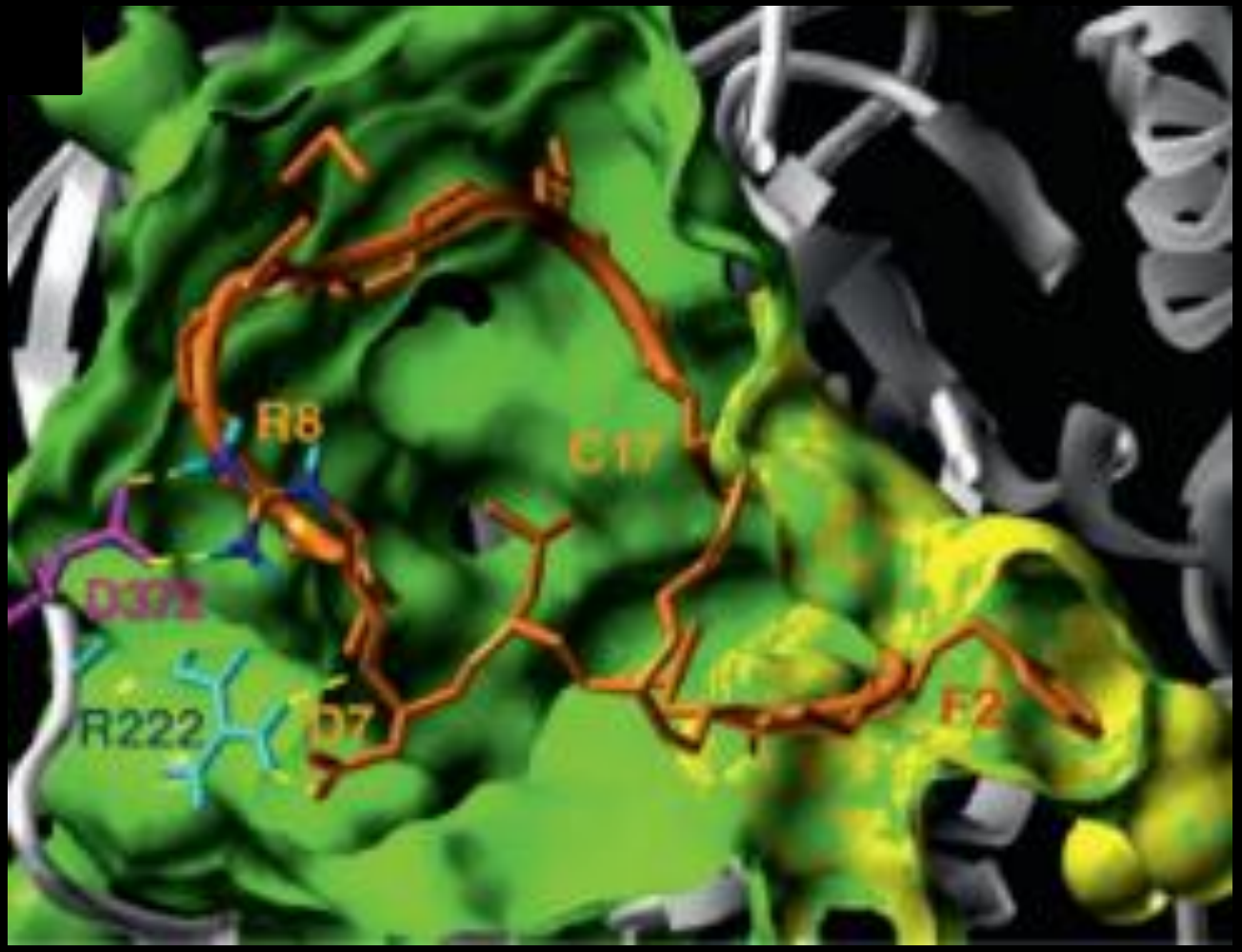


How to explain?

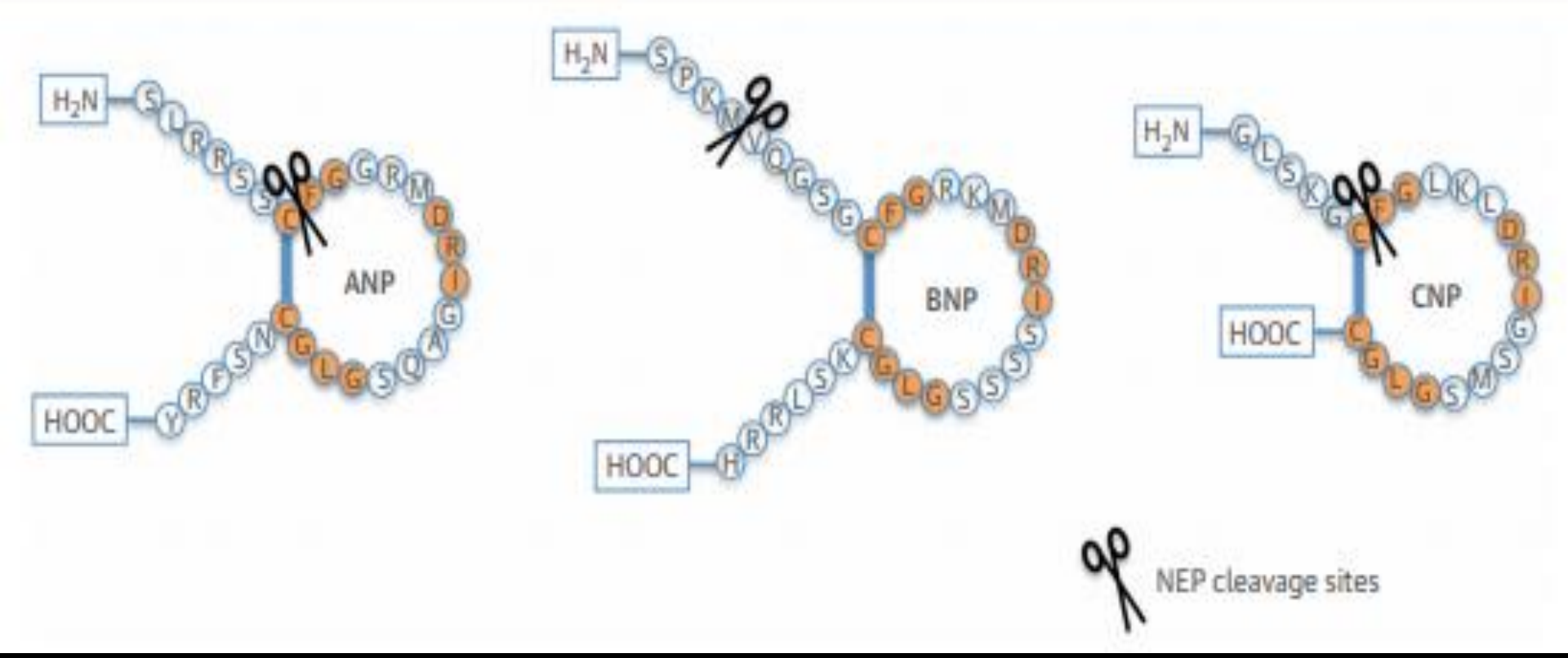
NEPRILYSIN (*NEP*) AND NATRIURETIC PEPTIDES

- **NEP Cleaves ANP (*Atrial Natriurietic Peptide*) and CNP (*C-type Natriurietic Peptide*) but not BNP**
- **The avidity of NEP for natriuretic peptides is CNP >ANP > BNP**

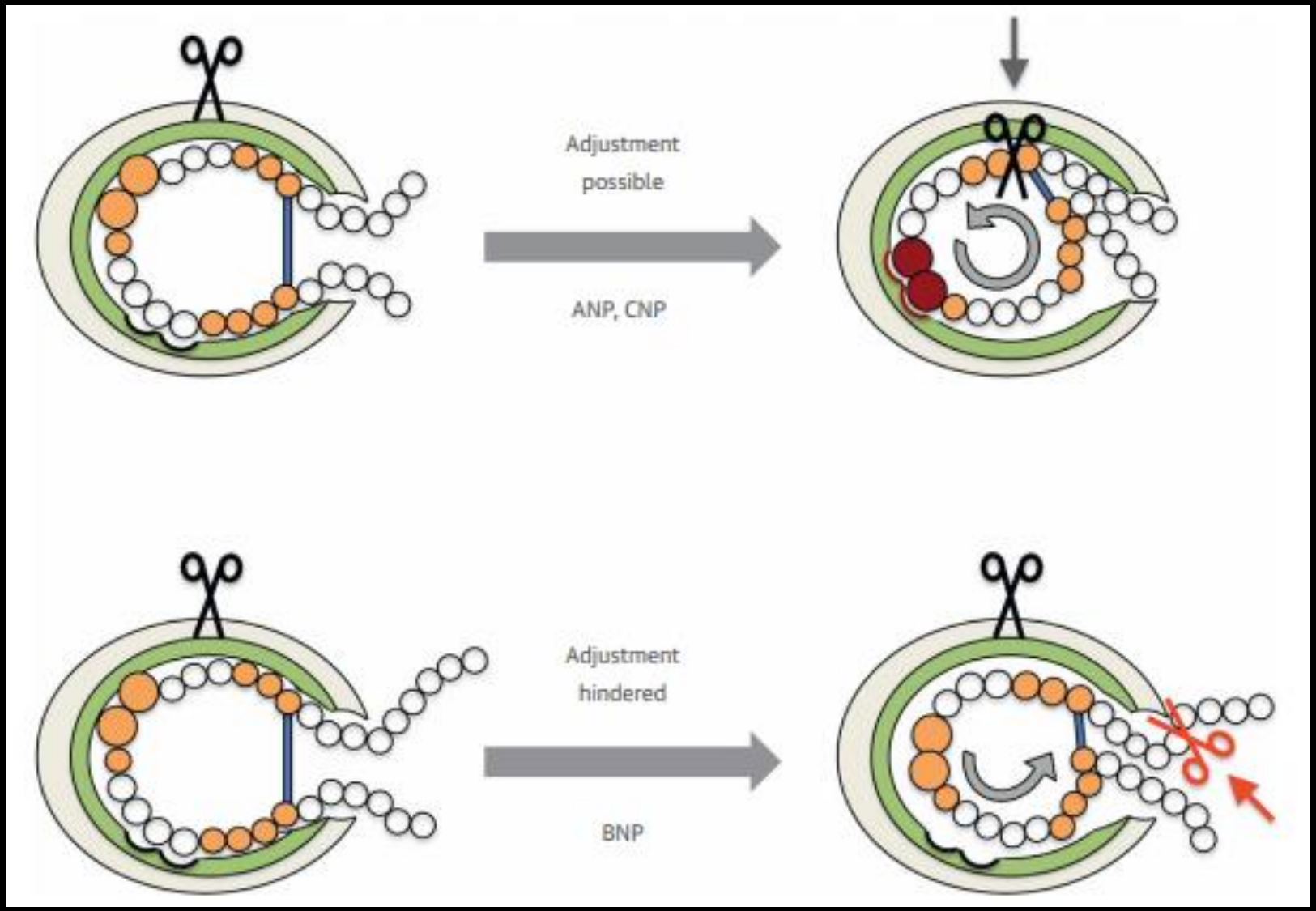
Interaction of Natriuretic peptide with Neprilysin



Primary NEP cleavage sites on human NPs



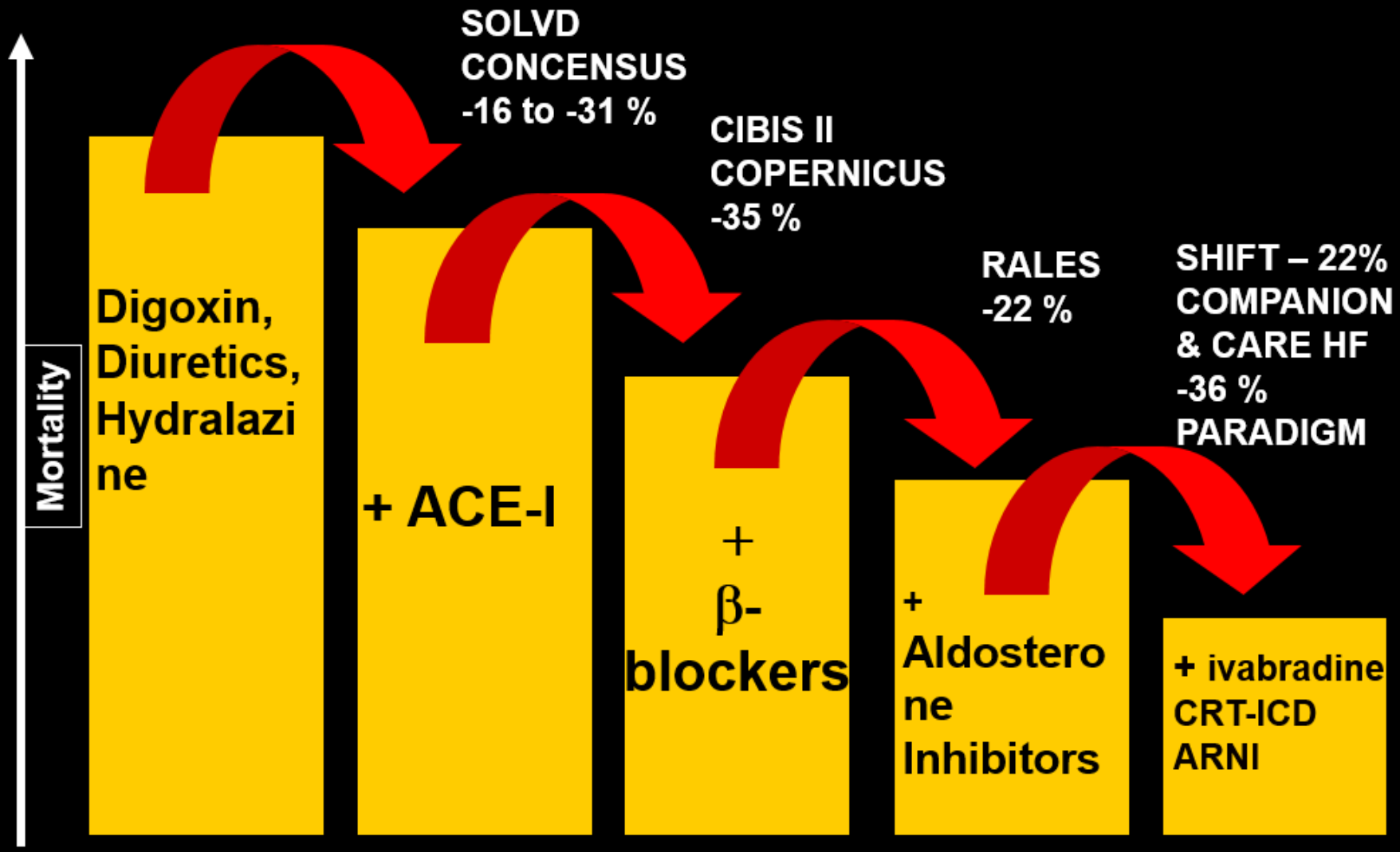
Interaction of individual NPs with Neprilysin



PARADIGM – HF three times first!

- **First time that a drug reduces CV mortality**
- **First time that a drug which increases a (*specific*) hormonal system is clinically effective**
- **First time that a trial does not "*add*" a new drug but substitutes an old one**

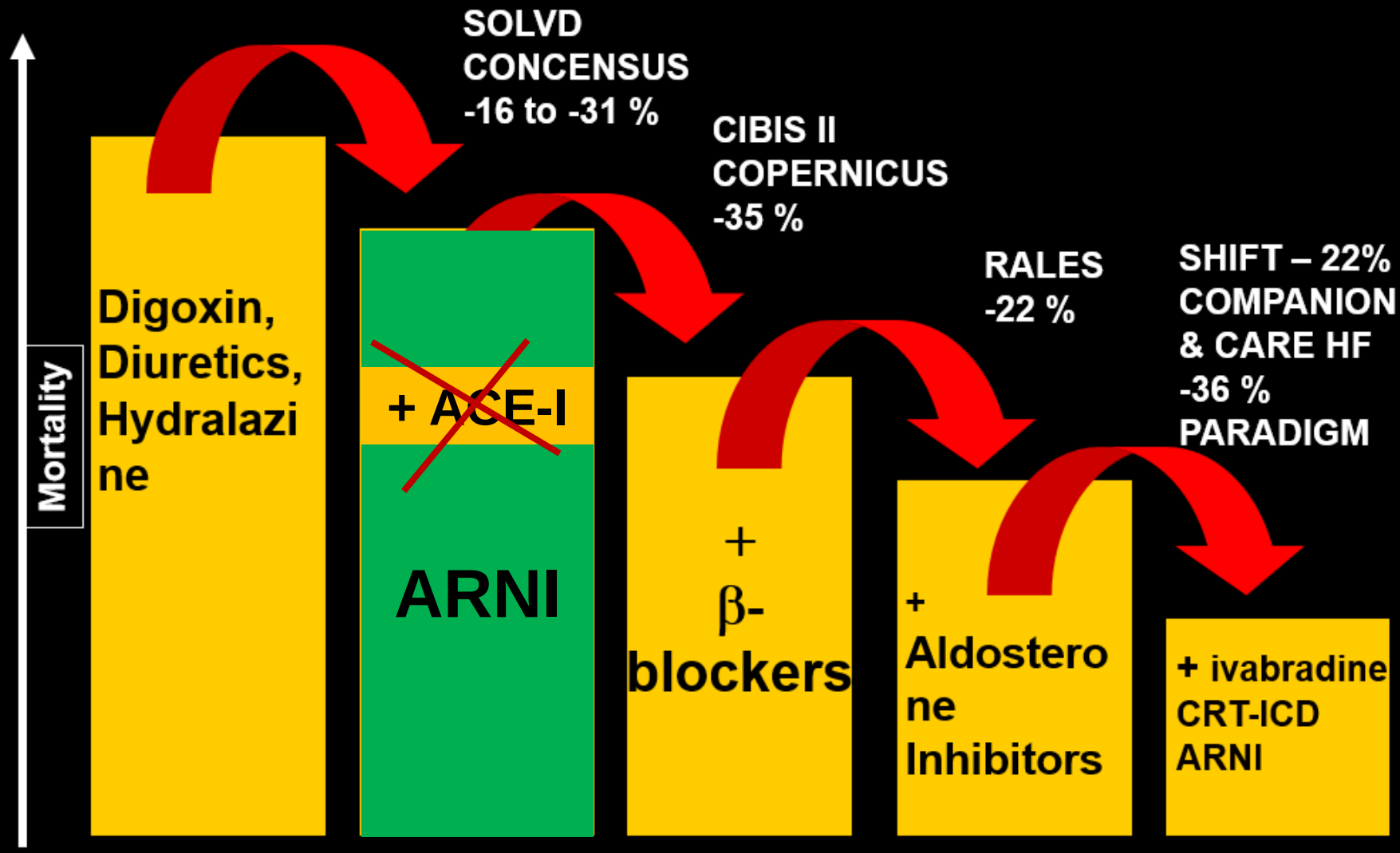
HFrEF: Treatment: a success!



Ellenbogen KA, J Am Coll Cardiol 2005; 46: 2199-203

HFrEF: Treatment: a success!

BUT …why to wait to prescribe ARNI?



PARADIGM-HF: Absolute benefits

Switching 1000 patients from an ACE inhibitor/ARB to LCZ696 avoided:

47	**primary endpoints**
31	**cardiovascular deaths**
28	**patients hospitalized for HF**
37	**patients hospitalized for any reason**
53	**admissions for HF**
111	**admissions for any reason**

over a median treatment period of 27 months

Adapted from Packer M. et al., Circulation 2015

Conclusive Message

- In patients with CHF and sinus rhythm heart rate reduction leads to prognostic benefits
- Increasing doses of beta-blockers can be associated with intolerance, side effects and high discontinuation rates.
- Ivabradine/carvedilol reduce the side effect of beta-blockers and increase tolerability, adherence, exercise performance and quality of life
- ARNI is a further possibility to improve prognosis of HF patients and the earlier the better