



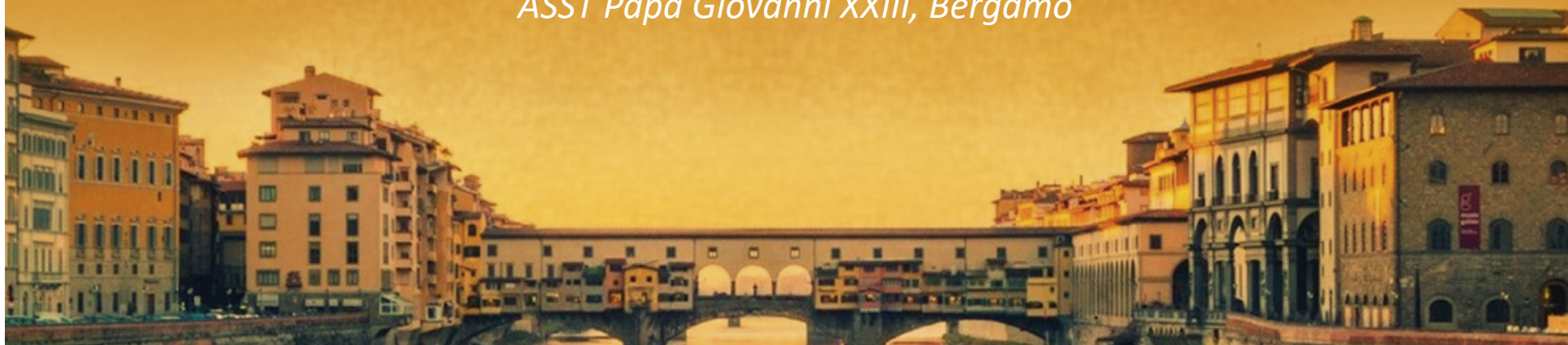
Conoscere **8**  
e Curare  
il Cuore **2018**

VENERDI' 16 MARZO

## TERAPIA MEDICA DELLO SCOMPENSO: PASSATO, PRESENTE E FUTURO

Michele Senni

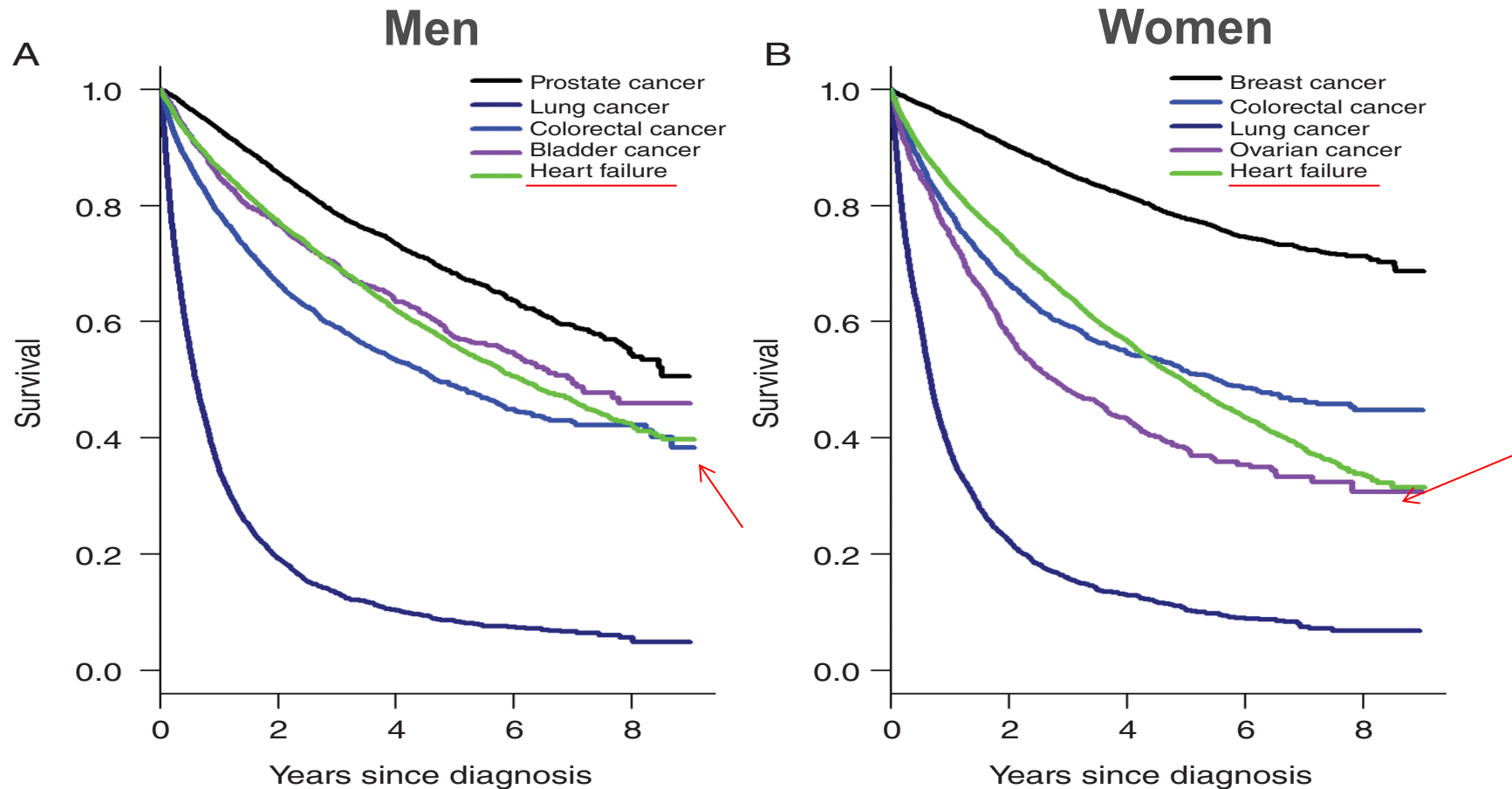
*U.S.C. di Cardiologia 1  
ASST Papa Giovanni XXIII, Bergamo*



# Disclosures

Received consultancy honoraria from Novartis, Bayer, Merck-SD, Abbot Vascular, Boehringer

# Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland





# The war against heart failure: the *Lancet* lecture

*Eugene Braunwald*

*Lancet* 2015; 385: 812-24



# Emodinamica cardiaca

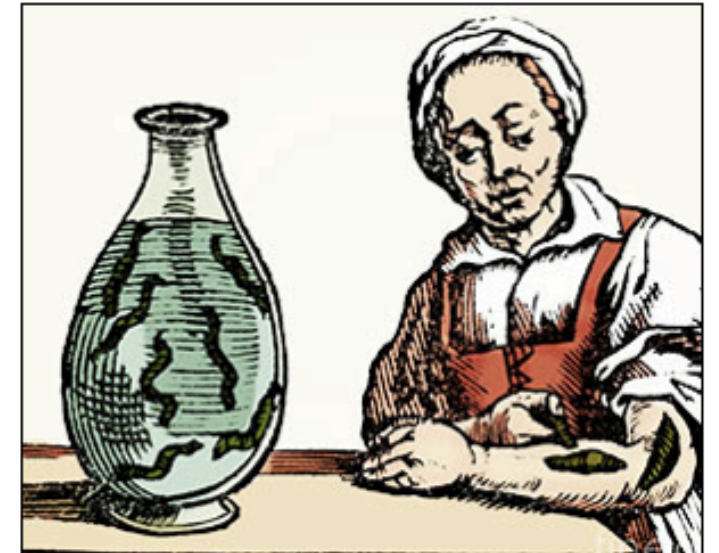
(dal '600 al '700)

## Non farmacologiche

Riposo al letto

Restrizione idrica

Salassi



# Emodinamica cardiaca

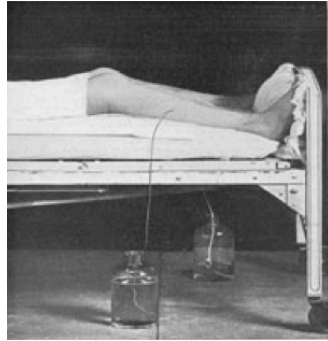
(200 anni di storia: 1785 – 1988)

## Non farmacologica

Riposo al letto

Restrizione idrica

Salassi – Southey tubes



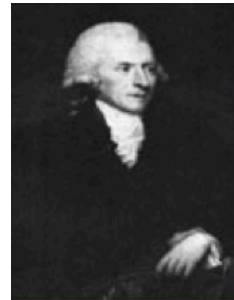
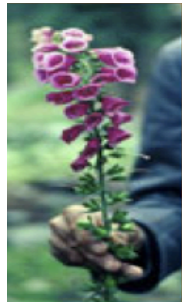
Paul Wood, 1957  
Southey tubes

## Farmacologica

Inotropi: Digitale

Diuretici: Mercurio – Sulfaniramide

Vasodilatatori: Nitroglicerina



William Withering, 1785  
Digitalis



William Stokes, 1854  
Mercury



John B Johnson, 1957  
Nitroglycerin



Gerhard Domagk, 1949  
Sulfaniramide

# Emodinamica cardiaca

(200 anni di storia: 1785 – 1988)

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## Non farmacologica

Riposo al letto

Restrizione idrica

Salassi – Southey tubes

## Farmacologica

Inotropi: Digitale- Dobutamina – Dopamina – Adrenalina

Diuretici: Mercurio– Sulfaniramide - Furosemide

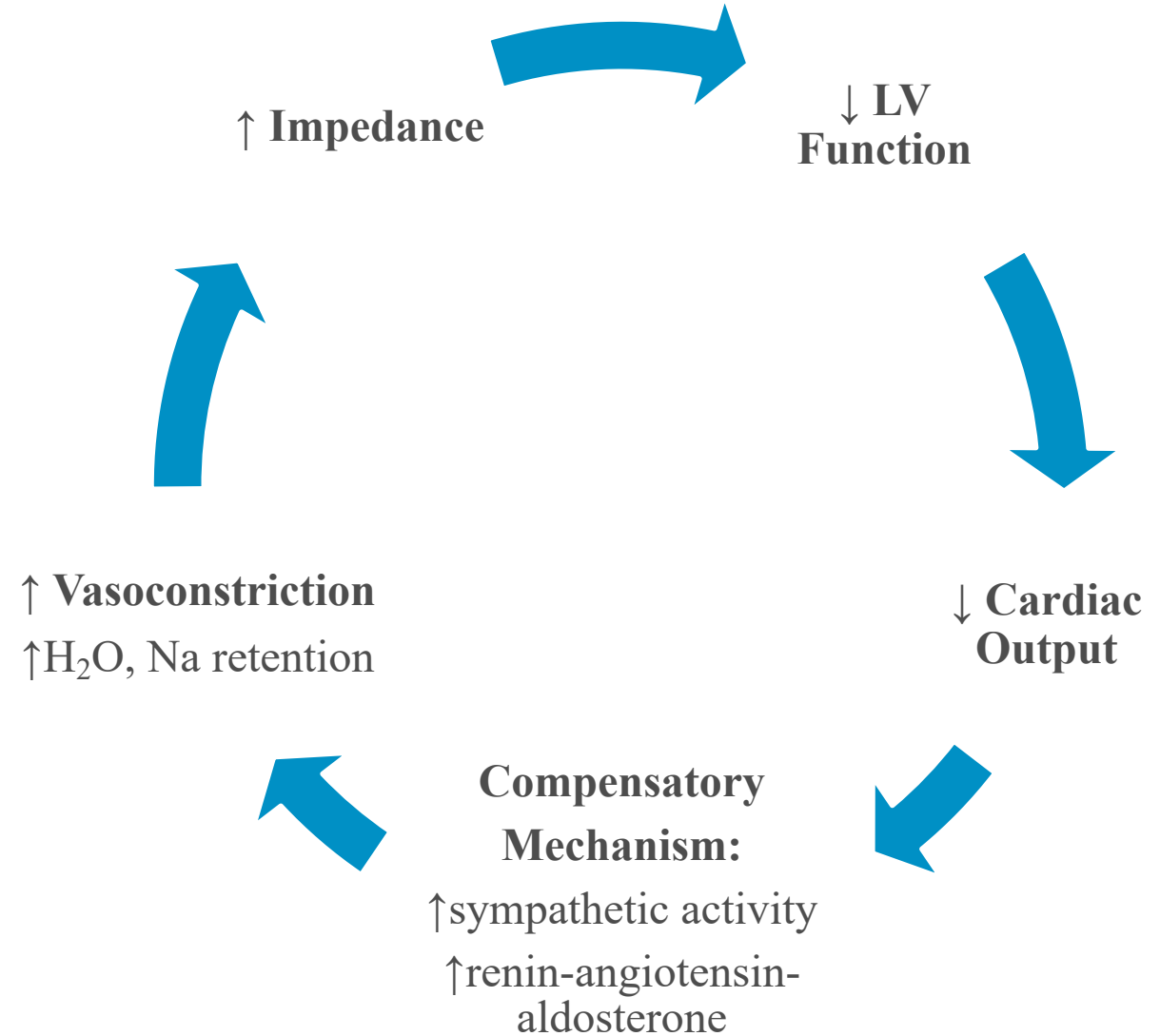
Vasodilatatori: Nitroglicerina– Nitroprussiato

Inodilatatori: Enoximone - Amrinone

# Il circolo vizioso dello scompenso cardiaco



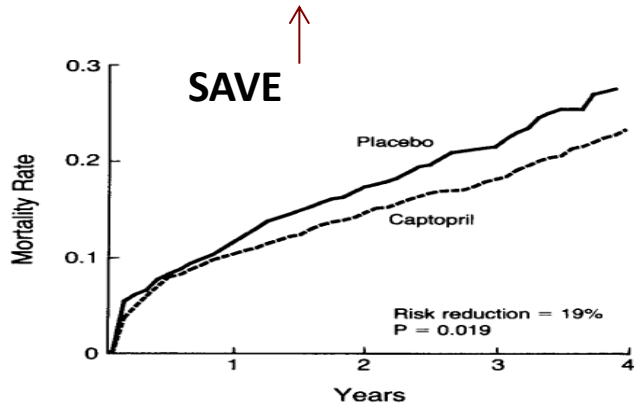
Jay H Cohn



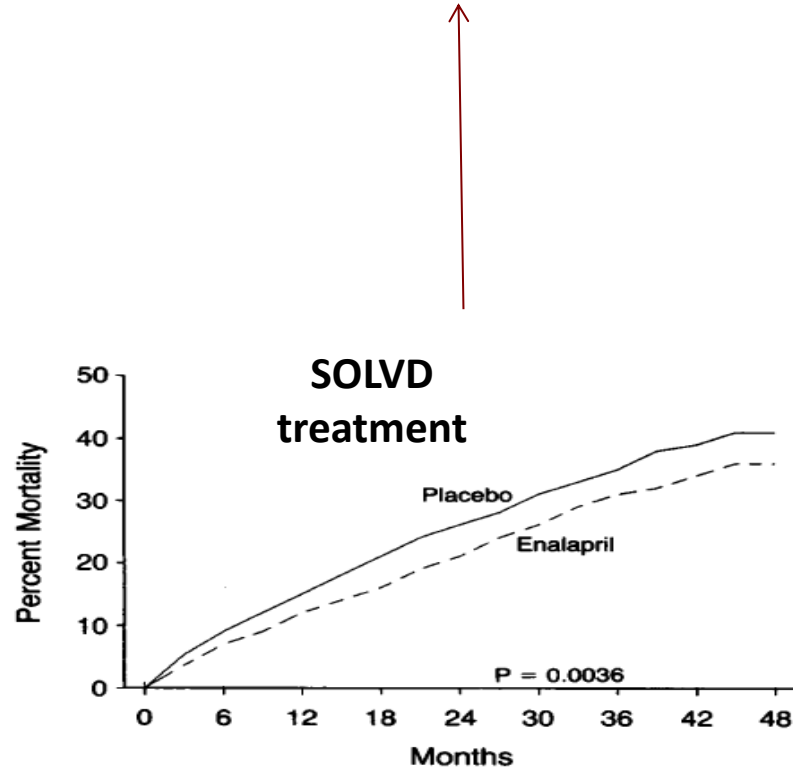


# ACE-inibitori

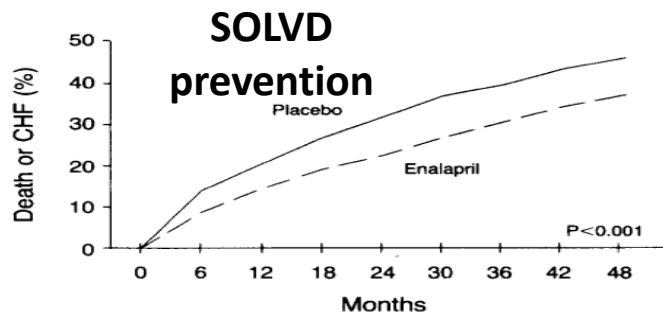
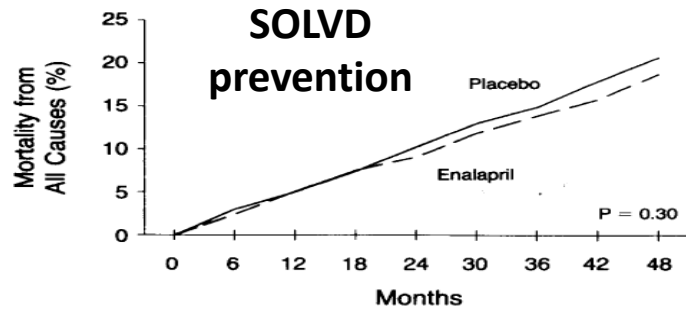
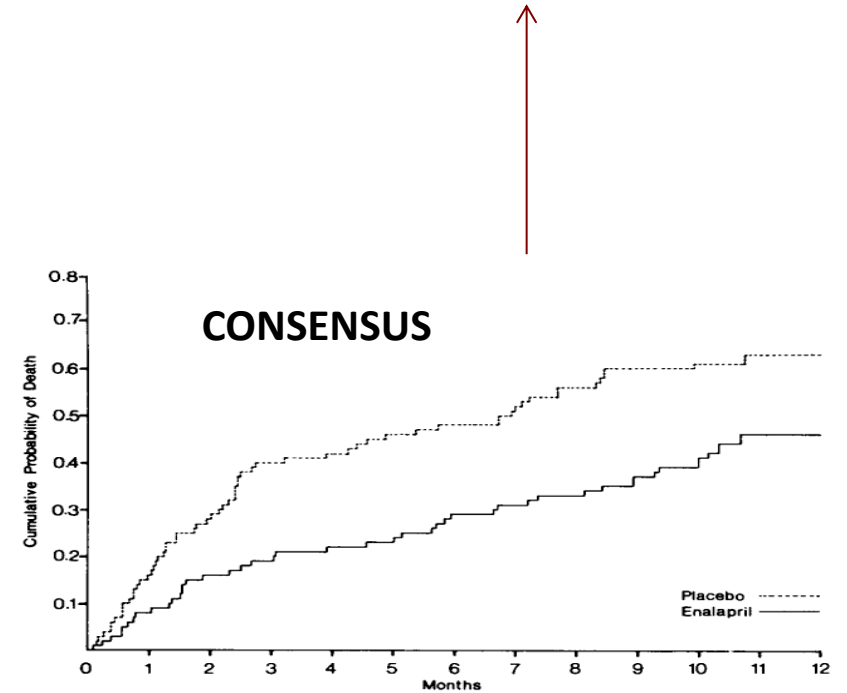
CLASS I



CLASS II-III

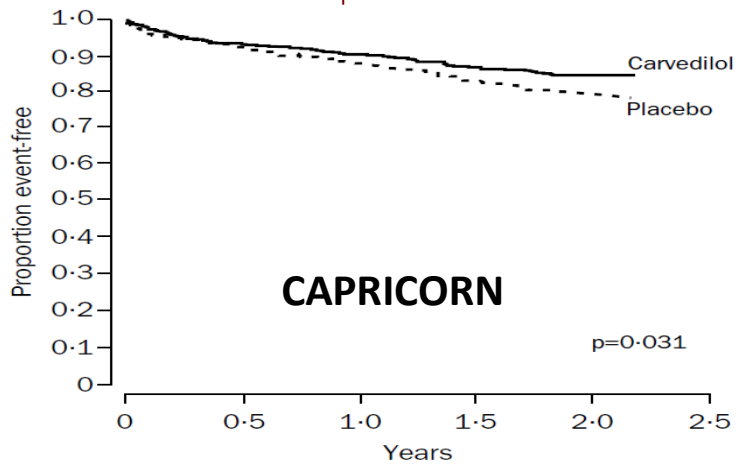


CLASS IV

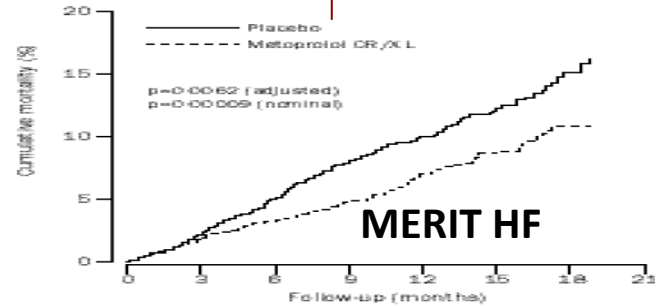


# Beta-bloccanti

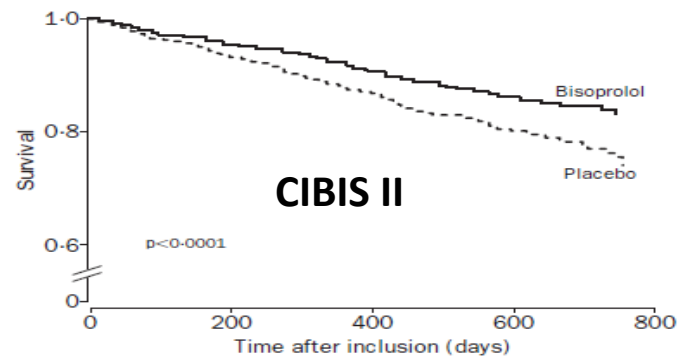
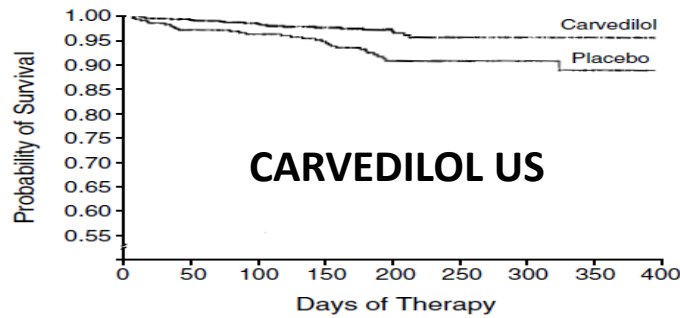
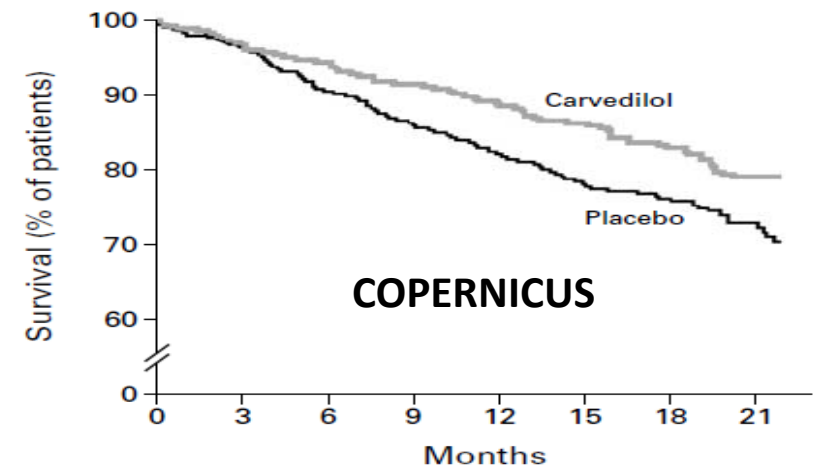
CLASS I



CLASS II-III



CLASS IV



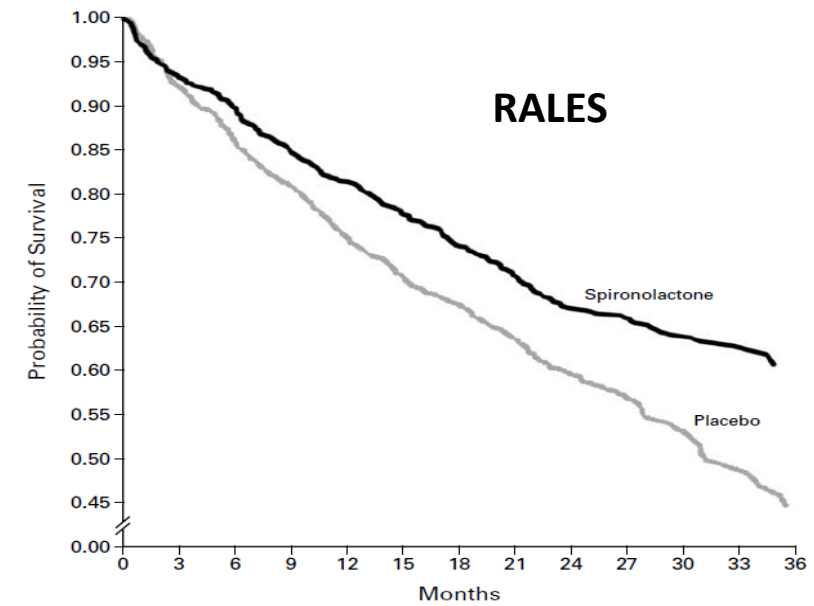
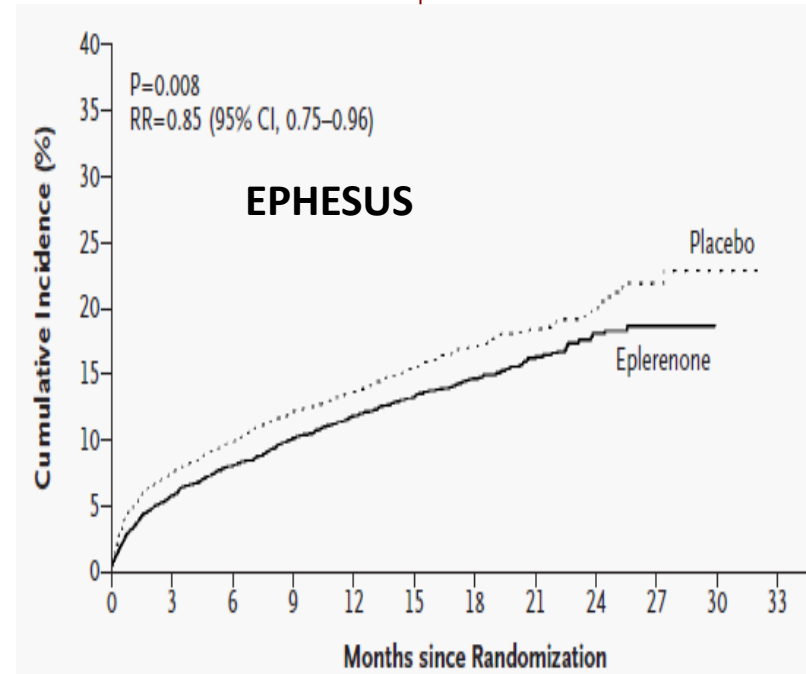
# Antialdosteronici

CLASS I

CLASS II

CLASS III-IV

?



# Inibitori dell'angiotensina-neprilisina (ARNI)

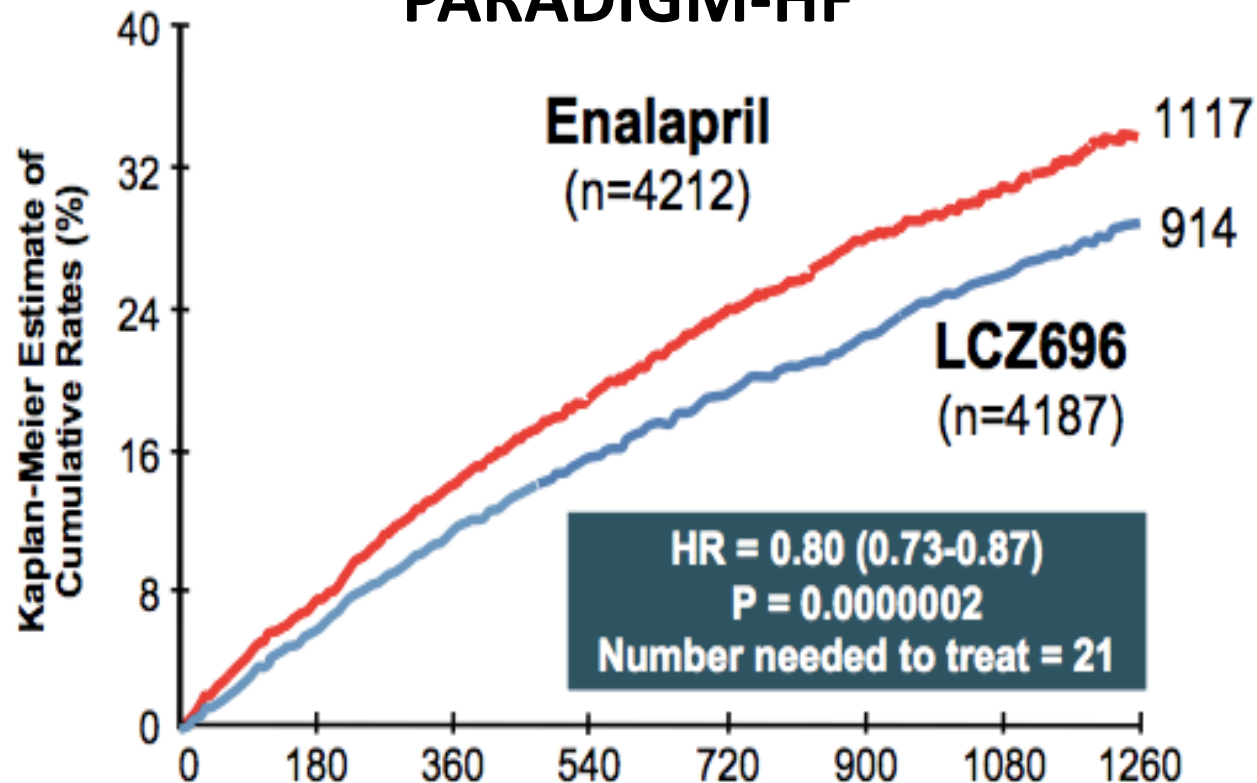
CLASS I

CLASS II-III

CLASS IV

?

PARADIGM-HF



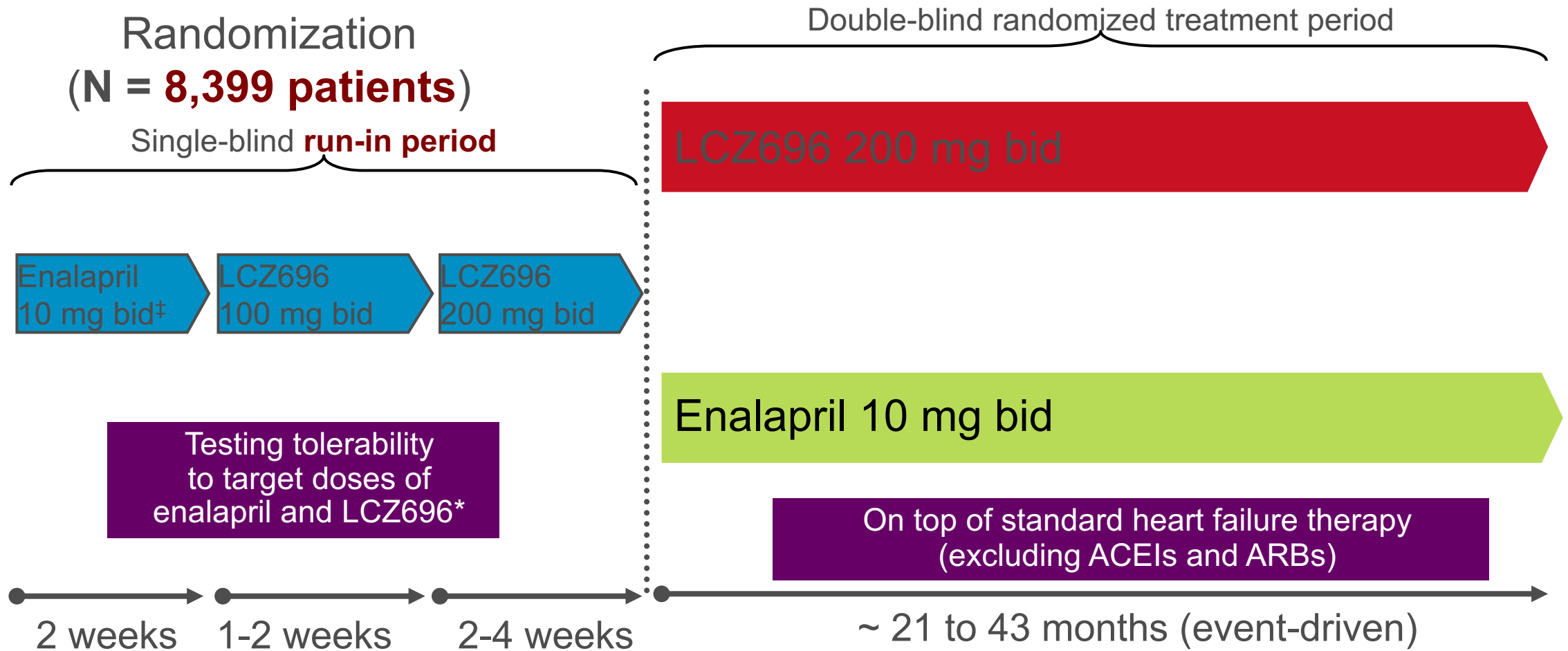
?

# PARADIGM-HF

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- ? Quali sono gli aspetti piu' significativi
- ? Che cosa abbiamo imparato di piu' importante negli ultimi tre anni e mezzo

# PARADIGM-HF disegno dello studio



# Scompenso cardiaco: “squilibrio neuro-umorale”

↑ Vasodilator/  
natriuretic/  
anti-mitotic  
Mediators

ACEi and ARBs  
Beta-blockers  
Aldosterone antagonists

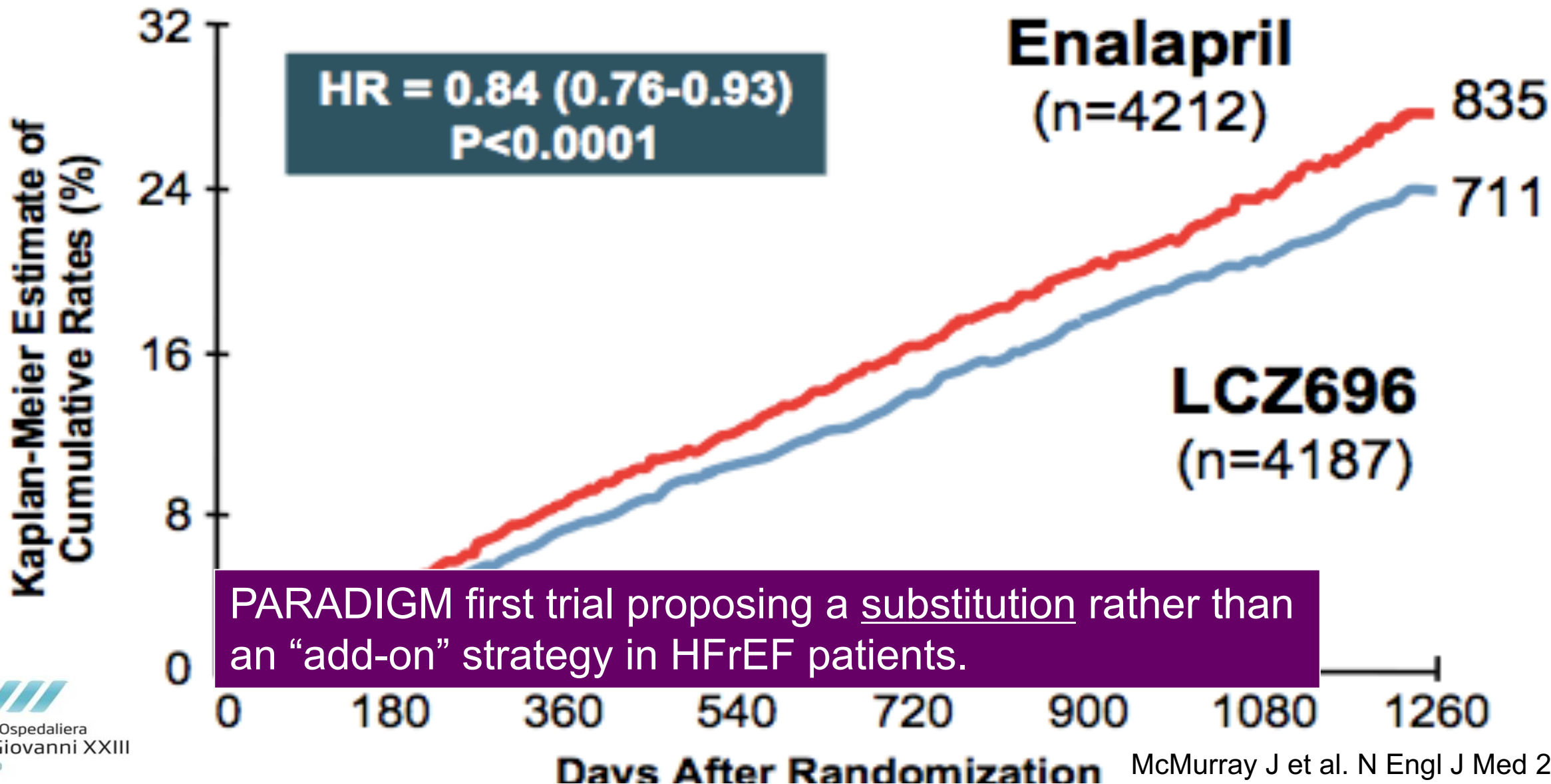
Natriuretic

↑ pro-mitotic  
Mediators

A “paradigm shift”: from “neurohumoral inhibition” to  
“neurohumoral modulation”



# PARADIGM-HF: mortalità per tutte le cause





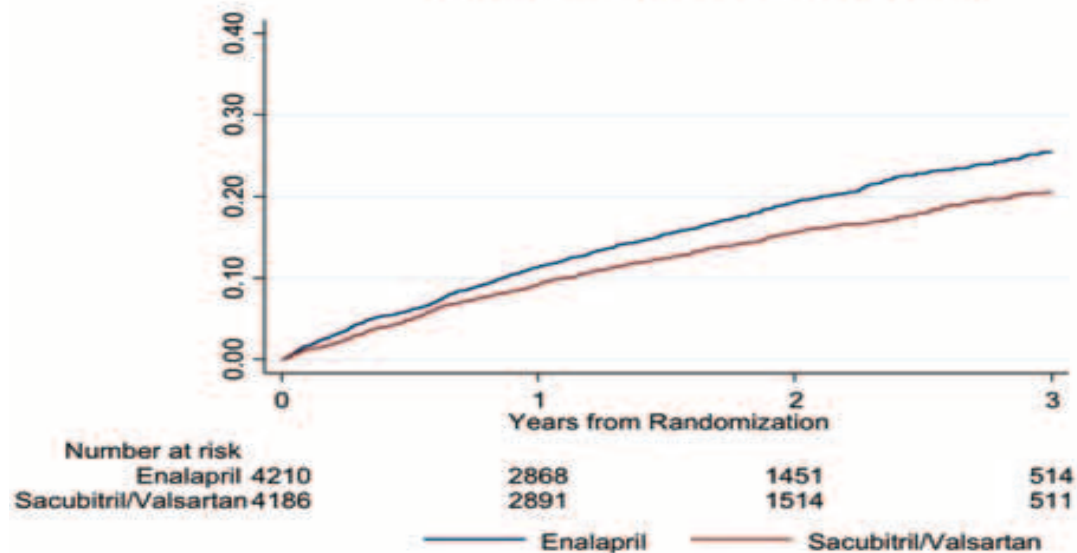
# PARADIGM-HF: Adverse Events

Prospectively identified adverse events	LCZ696	Enalapril	
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine $\geq$ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
<b>Discontinuation for adverse event</b>	<b>449</b>	<b>516</b>	<b>0.02</b>
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
<b>Angioedema (adjudicated)</b>			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS

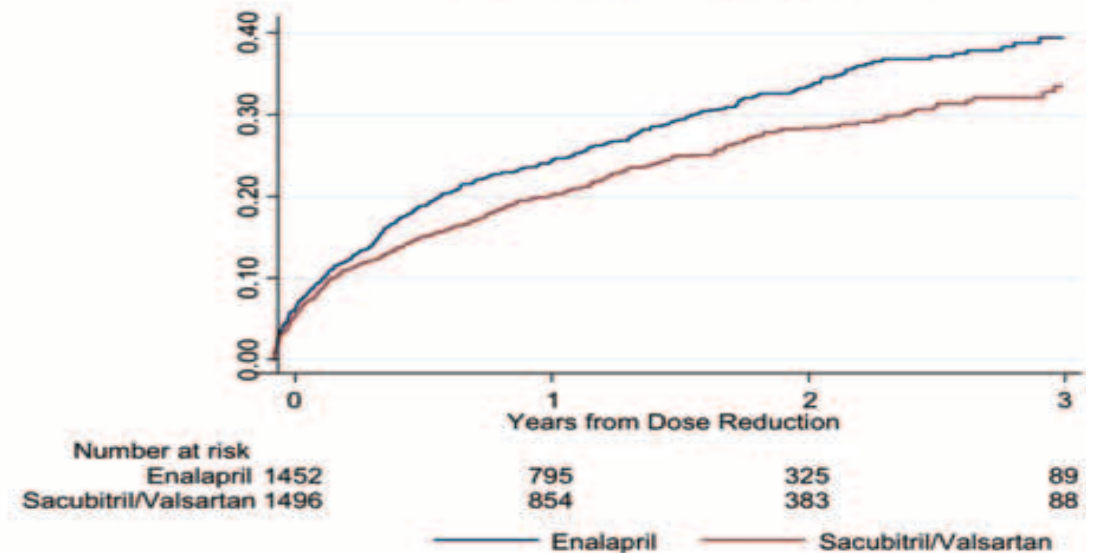
# L'importanza di raggiungere e mantenere la dose target

Cardiovascular Death or Heart Failure Hospitalization by Dose Reduction Status

Events Prior to Dose Reduction

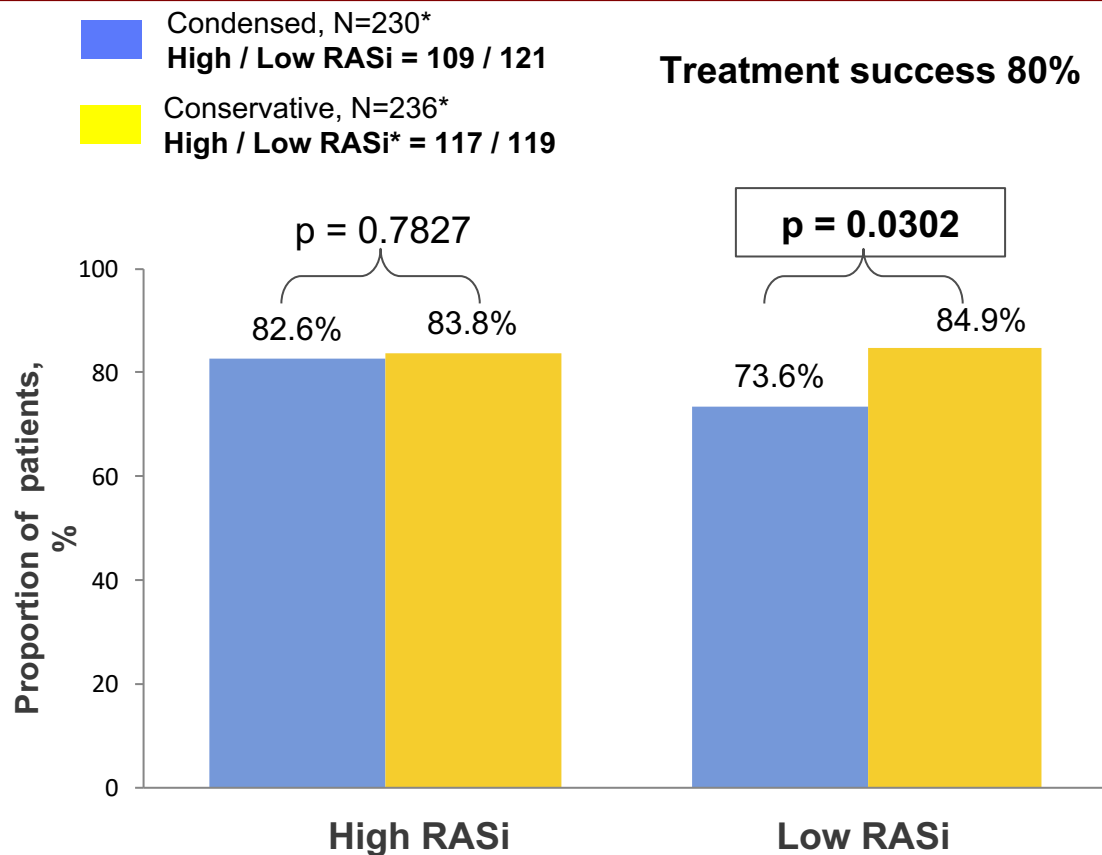


Events after Dose Reduction

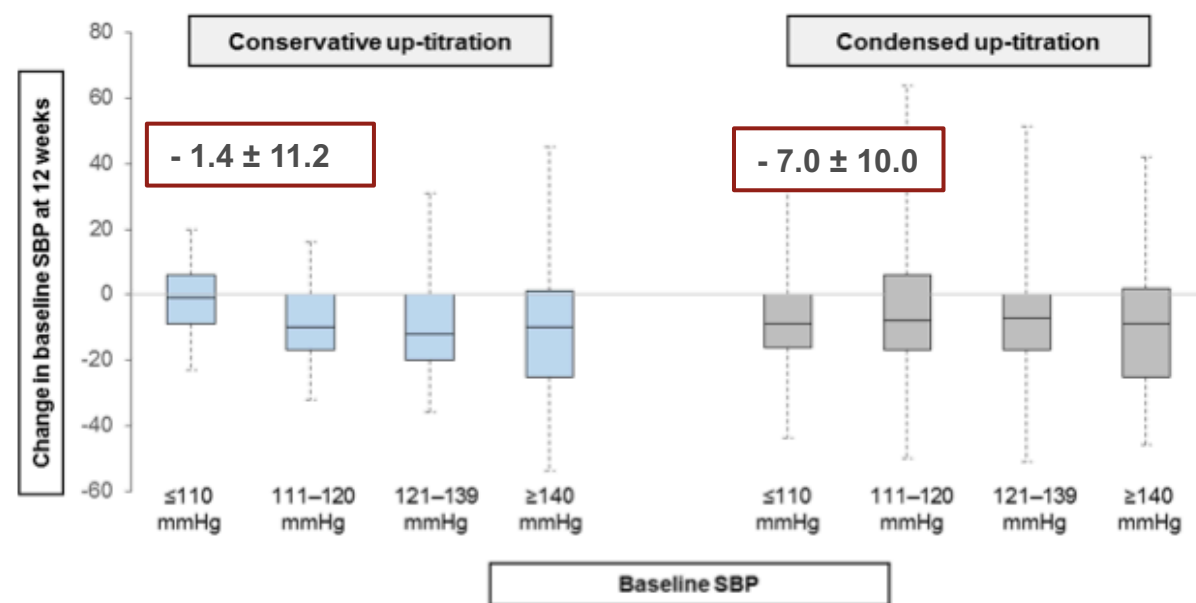


# Titration trial

Quale la miglior strategia di titolazione?



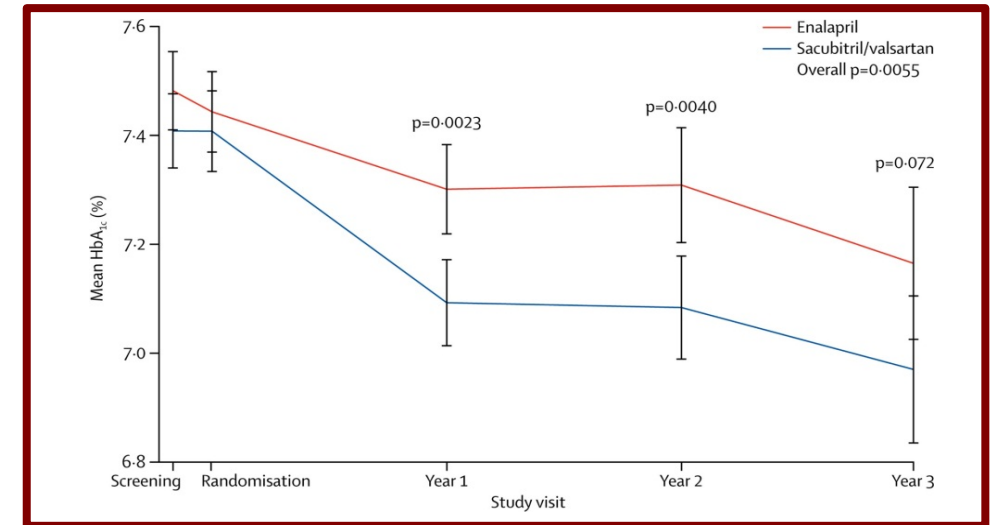
Senni M et al. Eur J Heart Fail 2016



Senni M et al. Eur J Heart Fail 2017

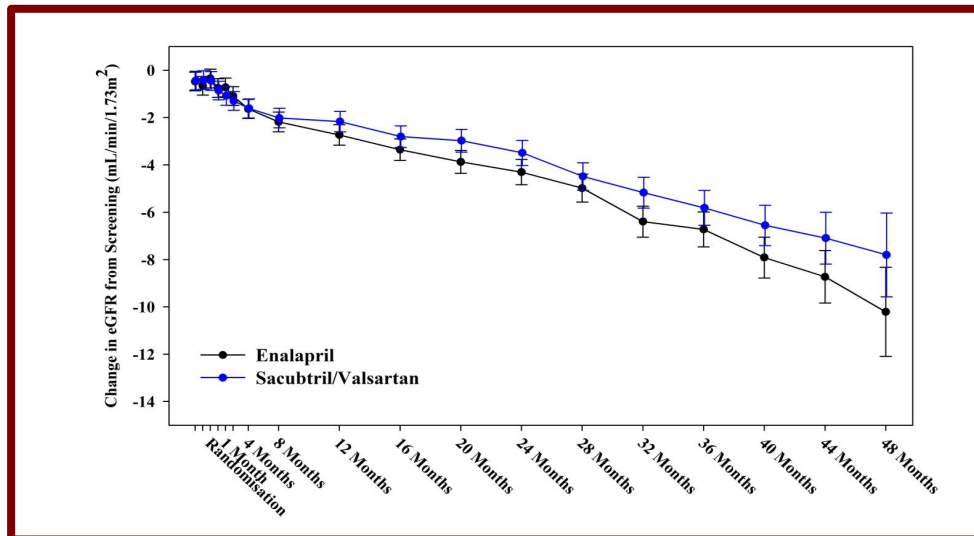
# LCZ696 (Sac/Vals) e comorbidità

## Glycaemic control



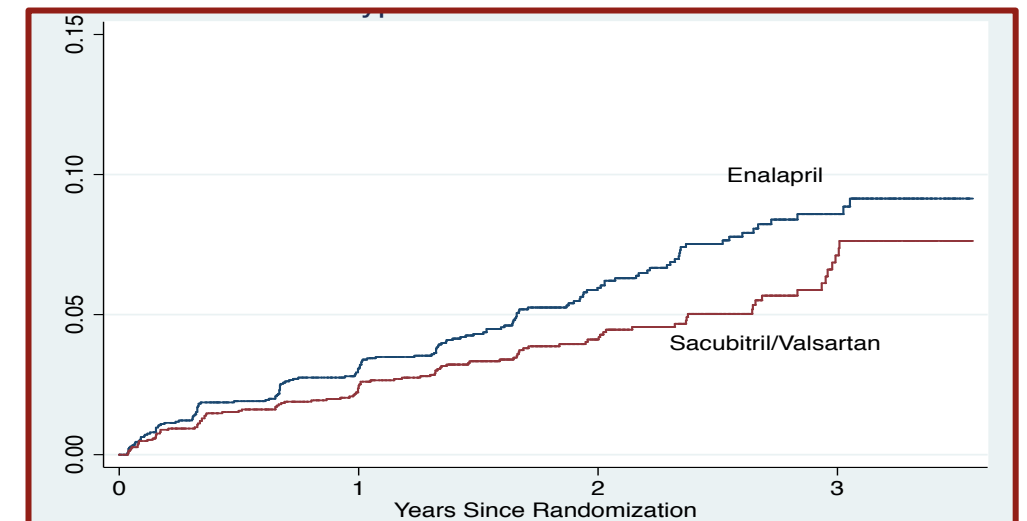
Seferovic JP et al. The Lancet Diabetes & Endocrinology 2017

## Change in eGFR



Damman K et al. JACC HF (in press)

## Incidence of hyperkalaemia



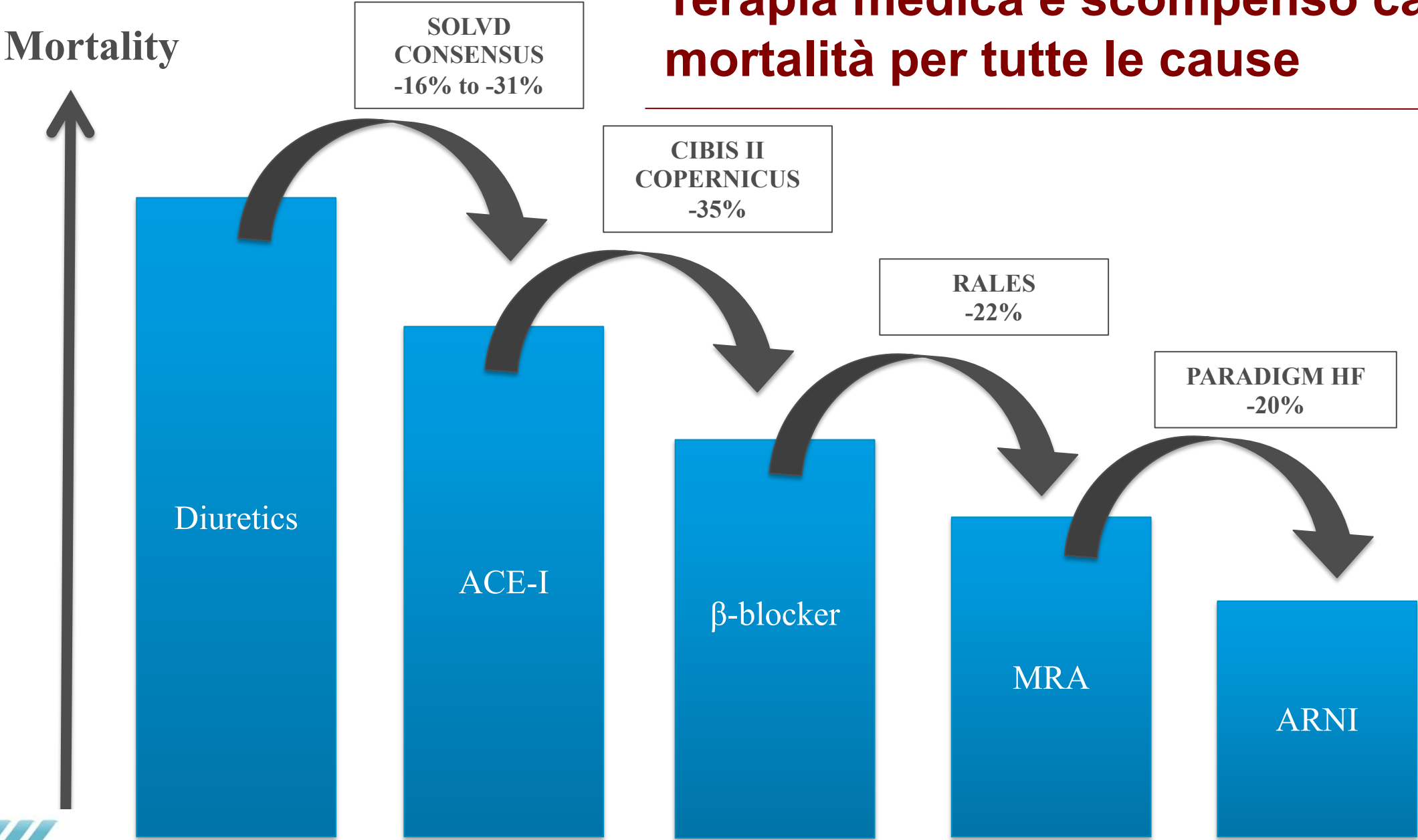
Desai AS et al. JAMA Cardiol 2017

# PARADIGM-HF

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**!** Da qualunque parte vengano analizzati i dati sono sempre a favore del LCZ696 rispetto all'enalapril

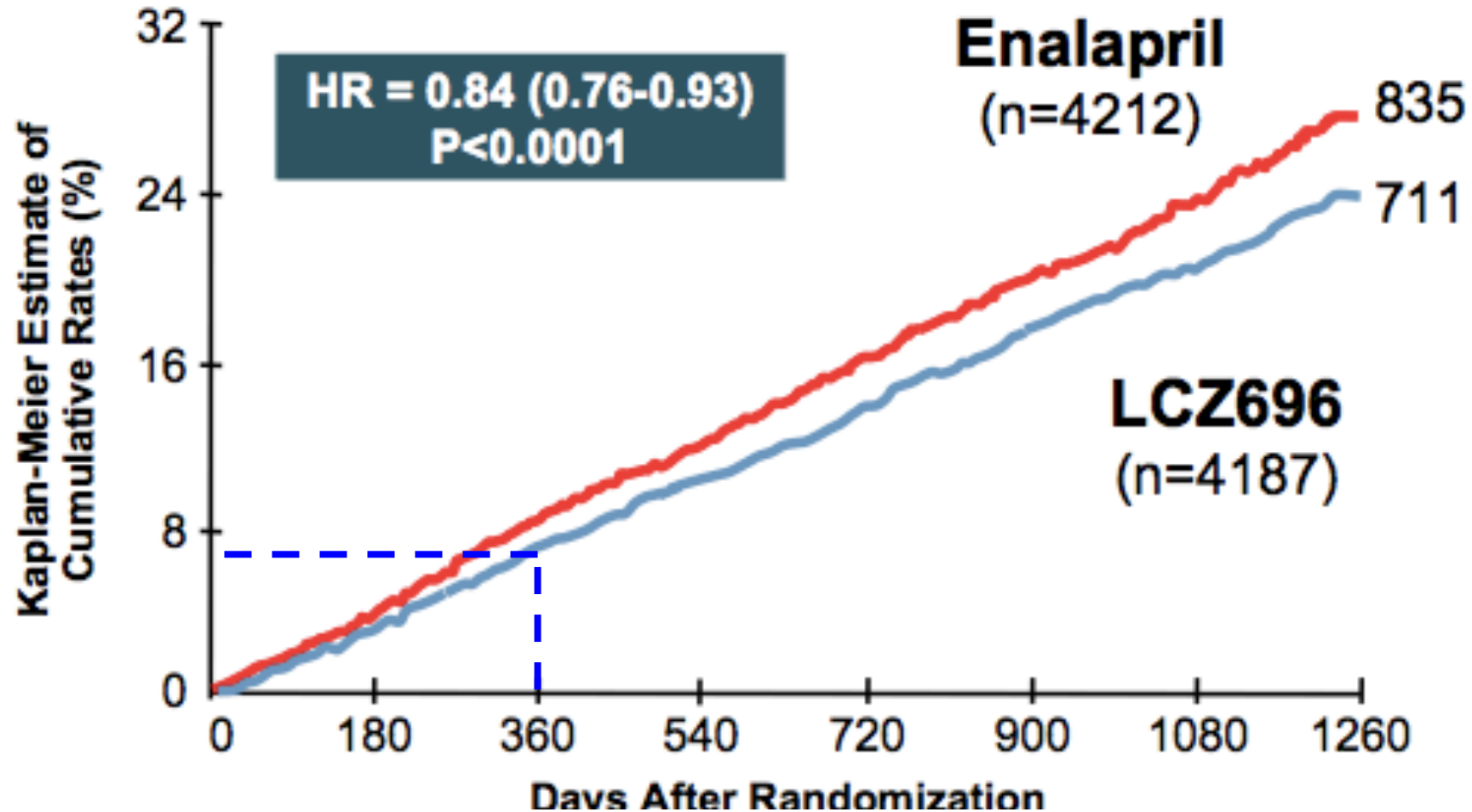
# Terapia medica e scompenso cardiaco: mortalità per tutte le cause





# Ipotesi neuroormonale

# PARADIGM-HF: mortalità per tutte le cause

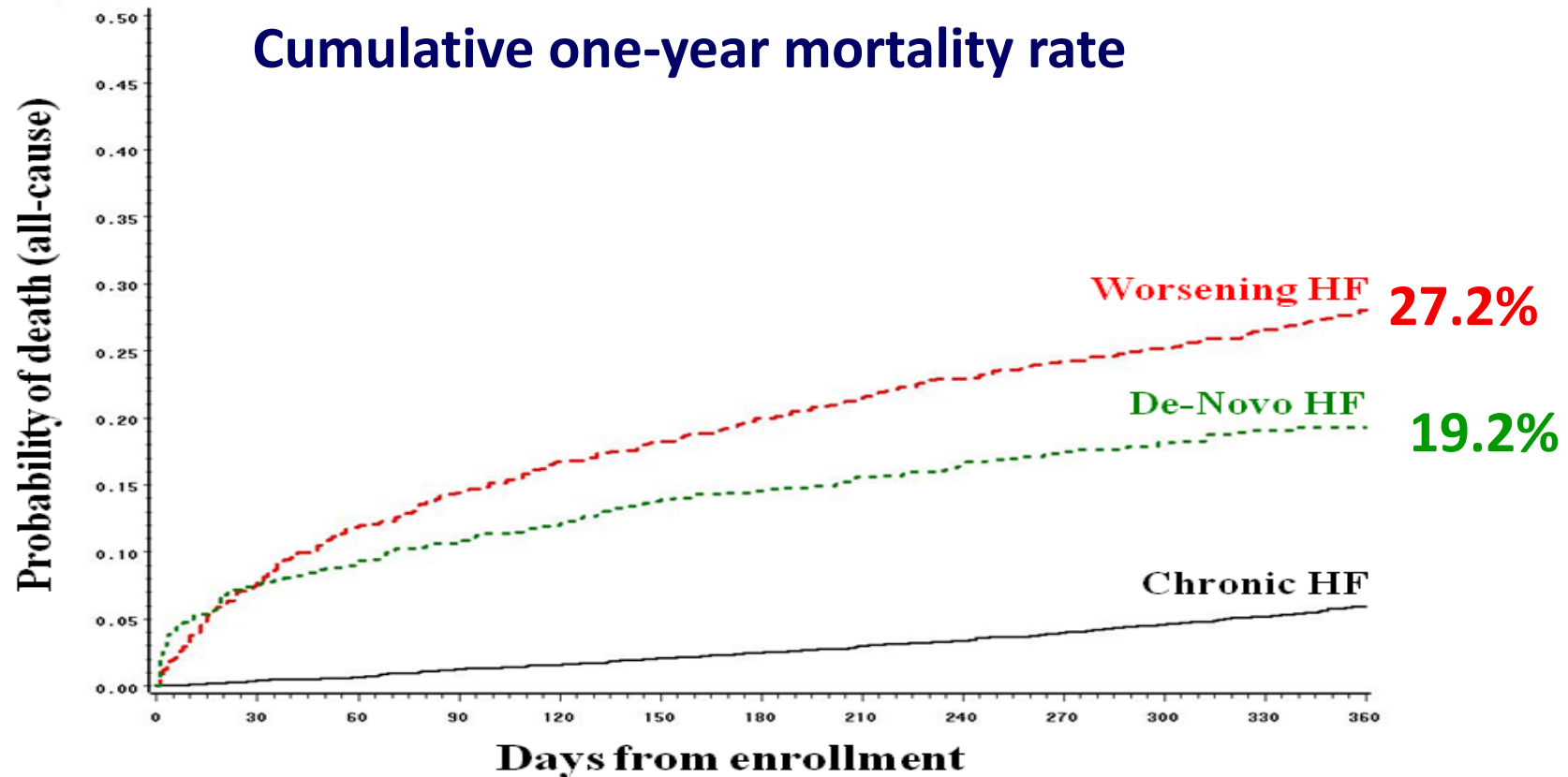




# Multicenter Prospective Observational Study on Acute and Chronic Heart Failure: The One-Year Follow-Up Results of IN-HF Outcome Registry

Luigi Tavazzi, Michele Senni, Marco Metra, Marco Gorini, Giuseppe Cacciatore, Alessandra Chinaglia, Andrea Di Lenarda, Andrea Mortara, Fabrizio Oliva and Aldo P. Maggioni

*Circ Heart Fail* published online March 8, 2013;

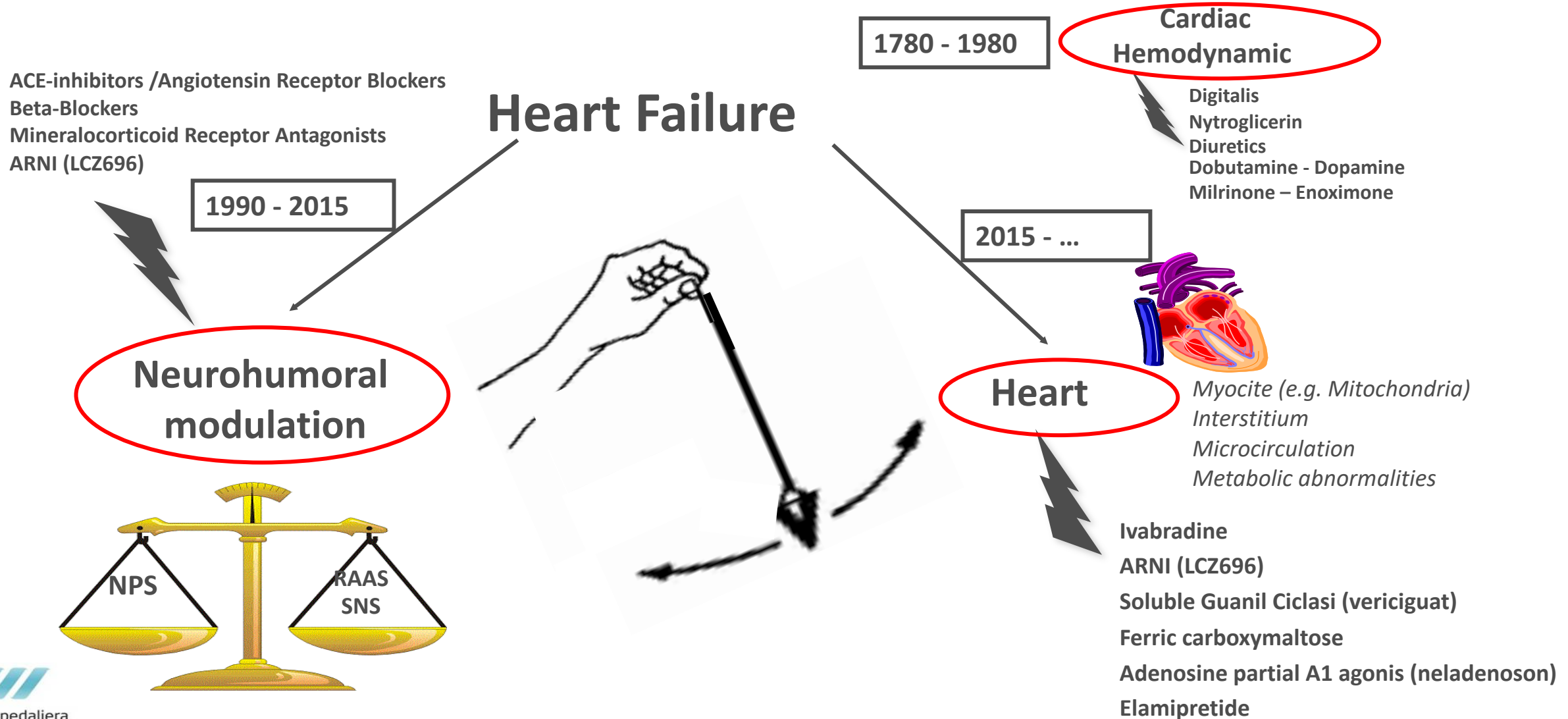


# TARGETS FOR HEART FAILURE THERAPY

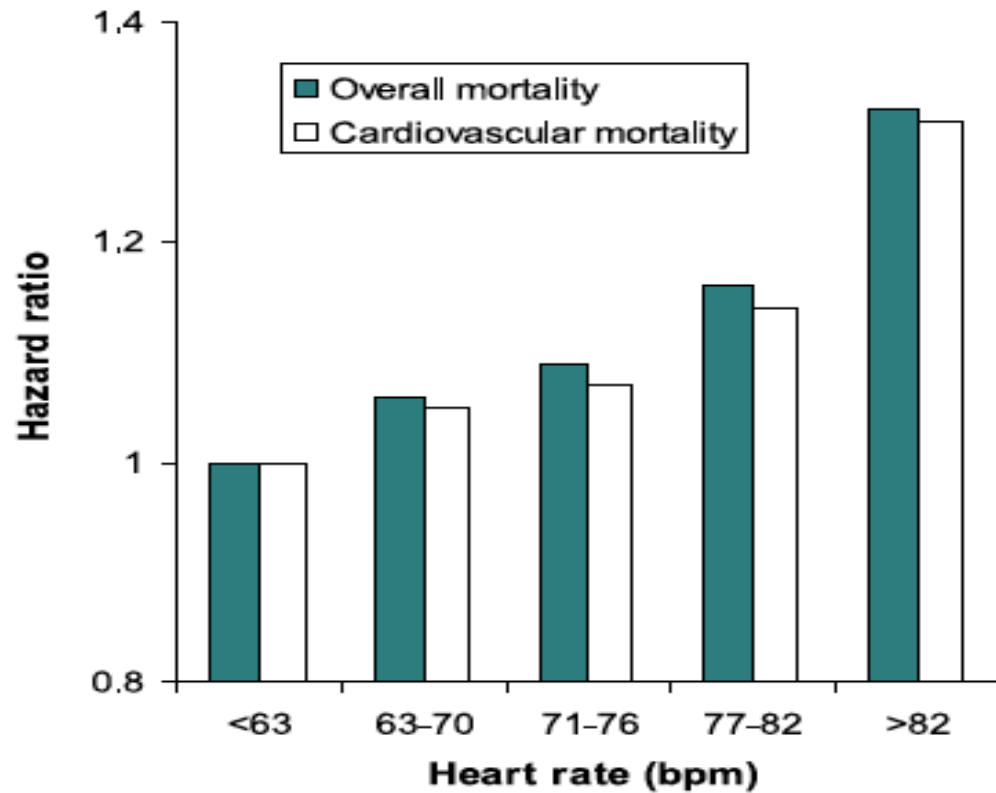
## “The Swinging Pendulum”

Modified from:

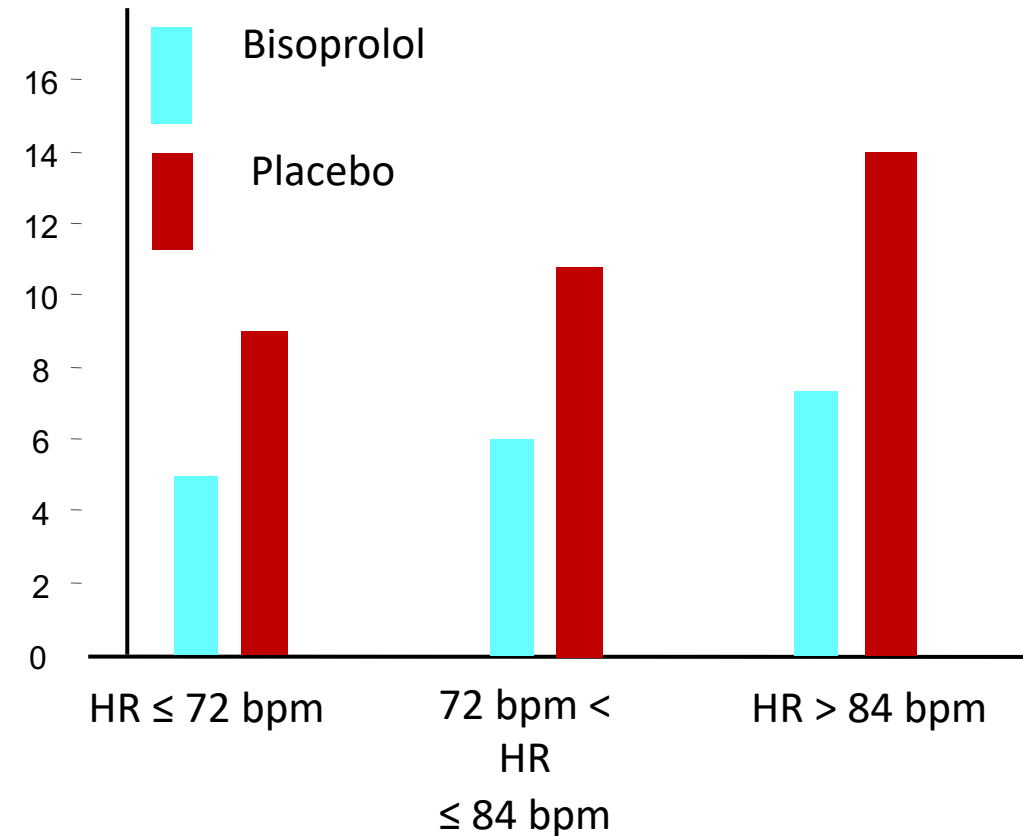
Senni M et al. Eur J Heart Fail 2015



# Frequenza cardiaca e scompenso



## CIBIS II: all-cause mortality

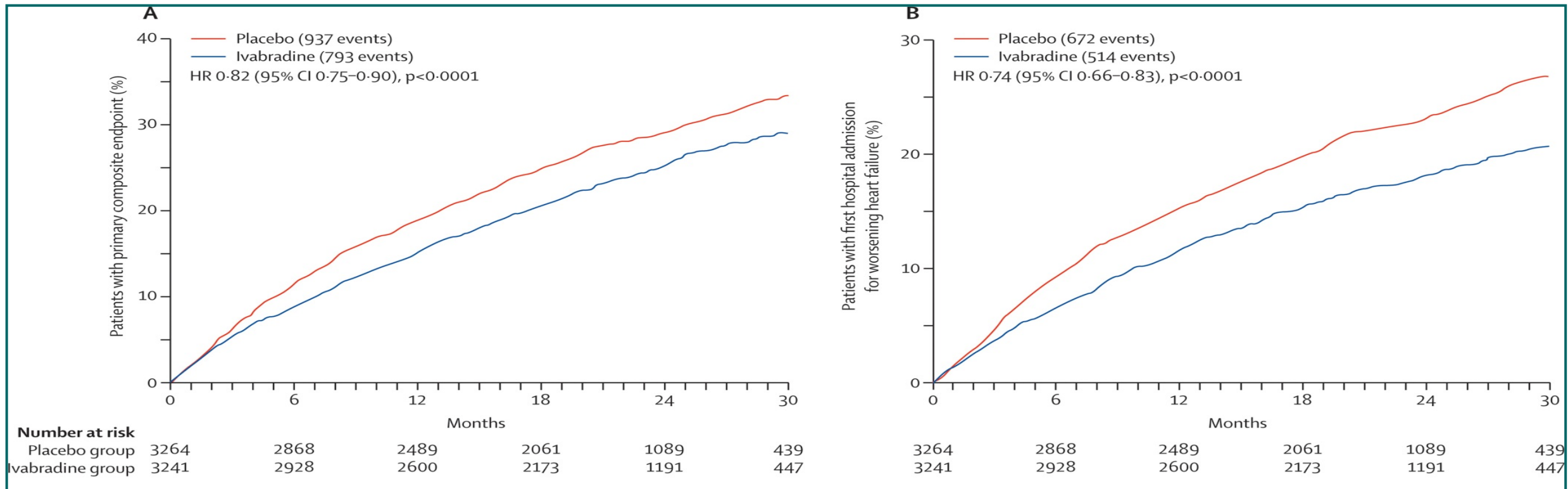


**Increase in mortality risk by 3% per 1 bpm ↑, 16% per 5 bpm ↑**

# SHIFT trial

## CV death or HF hospitalization (primary end-point)

## HF hospitalization (secondary end-point)



# **Cuore al centro ...**

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**1. Via NO-cGMP**

**2. Nuovi inotropi**

**3. Energetica (produzione di ATP)**



# Cuore al centro ...

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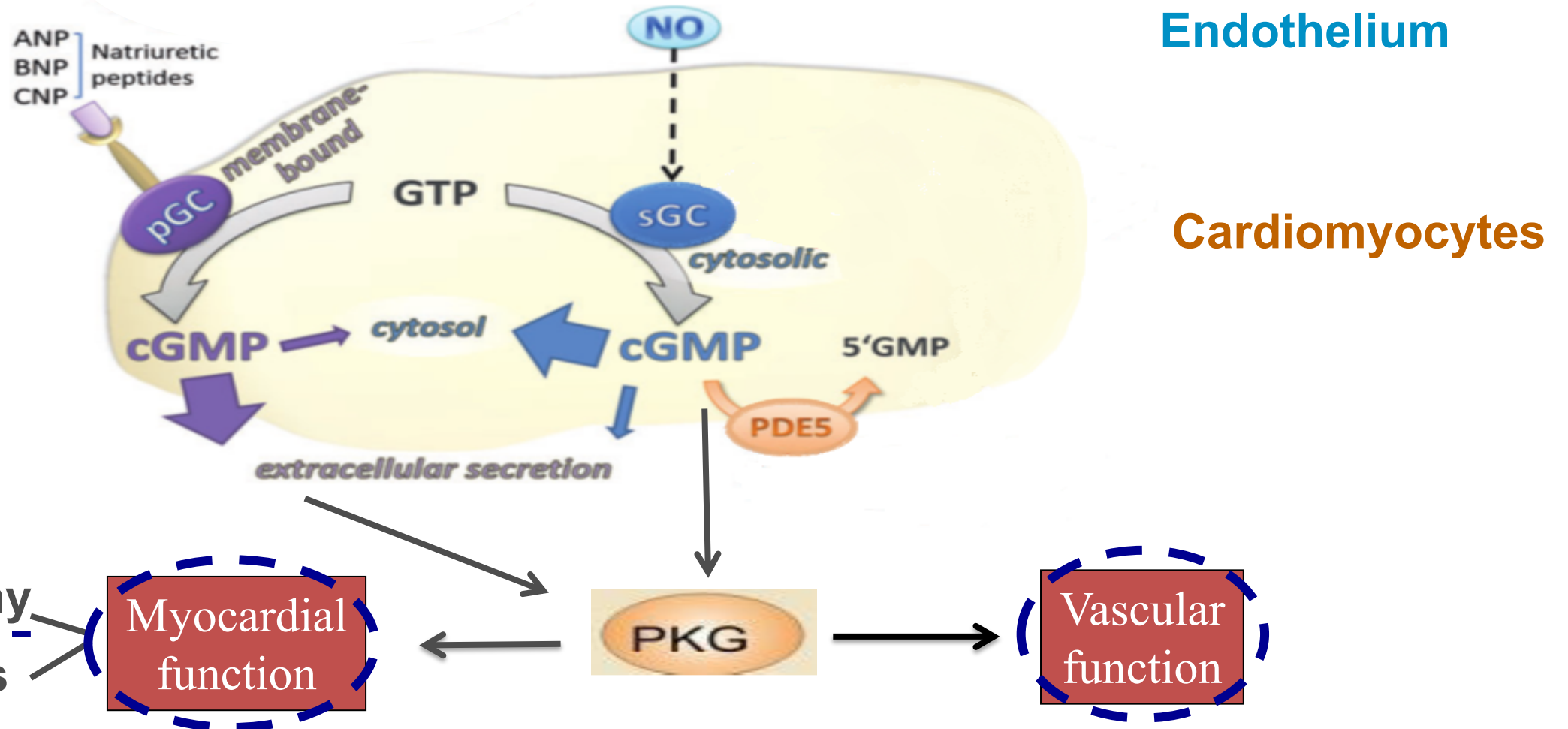
**1. Via NO-cGMP**

2. Nuovi inotropi

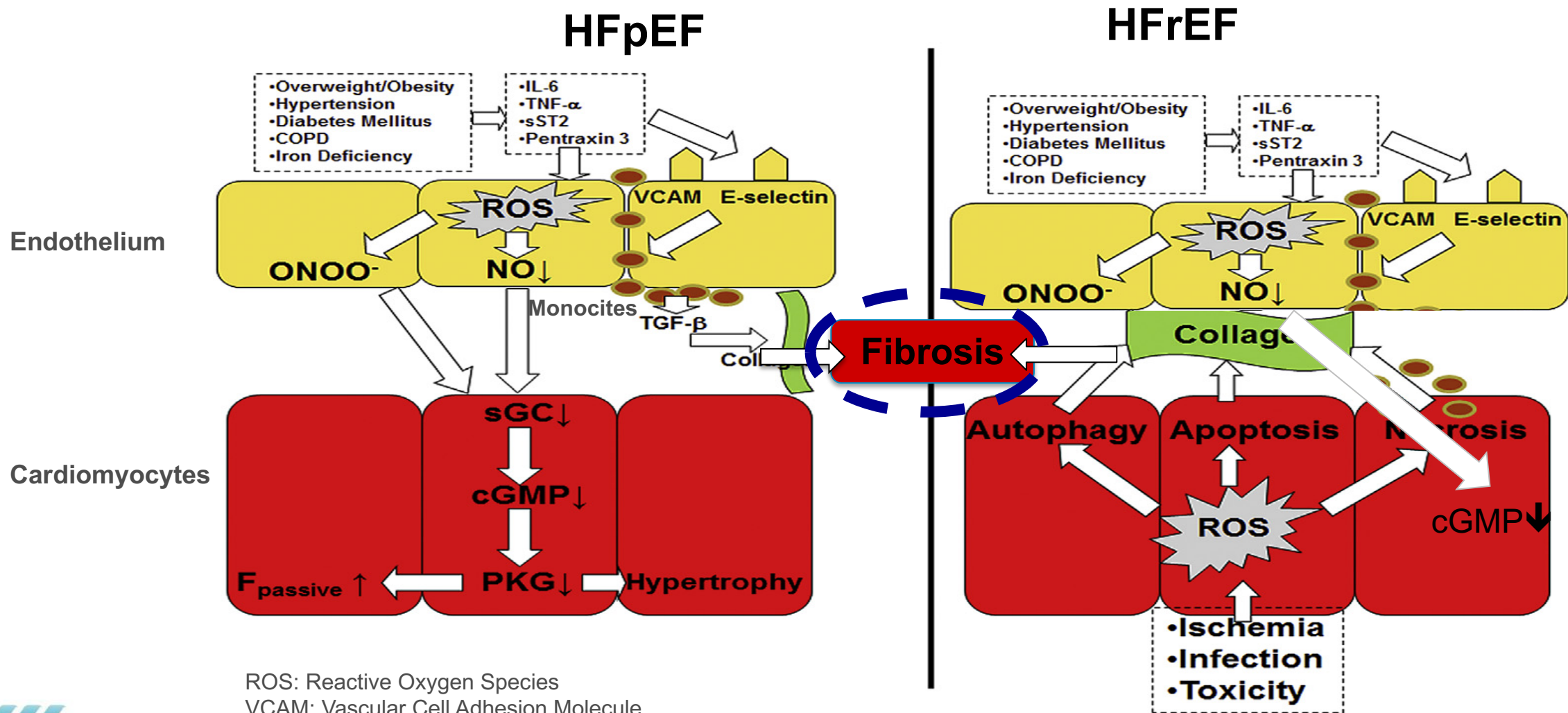
3. Energetica (produzione di ATP)



# Via NO/cGMP



# Disfunzione e rimodellamento cardiaco

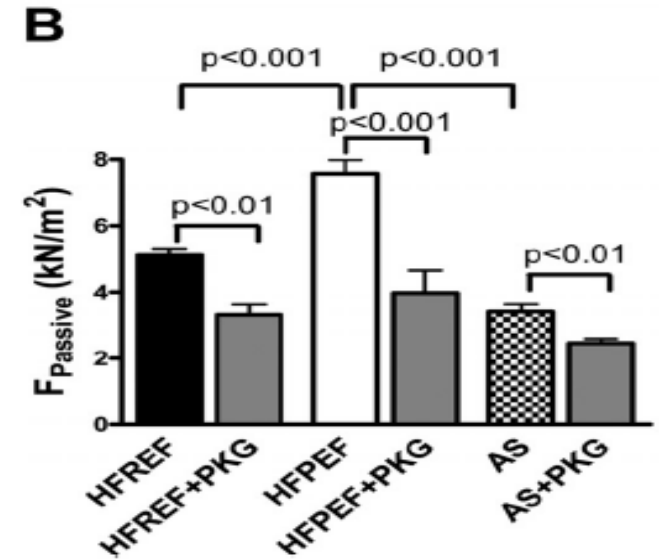
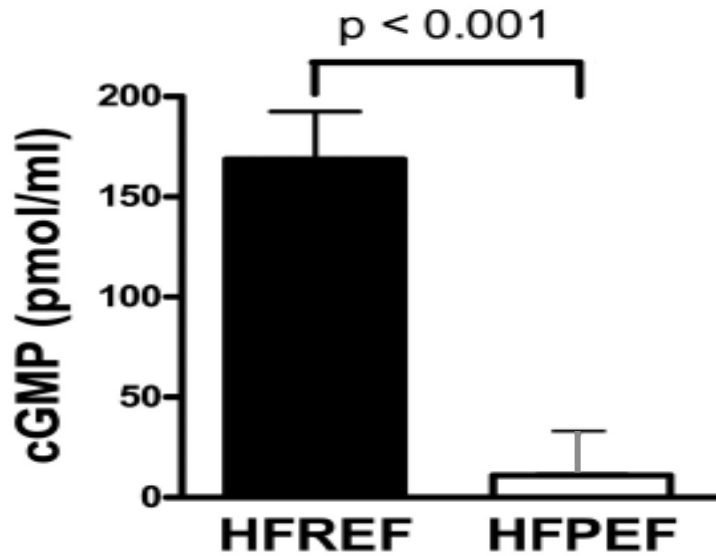


ROS: Reactive Oxygen Species  
 VCAM: Vascular Cell Adhesion Molecule  
 ONOO<sup>-</sup>: Peroxynitrite  
 TGF- $\beta$ : Transforming Growth Factor  $\beta$

*Modified from:  
 Paulus and Tschoepe, JACC 2013*



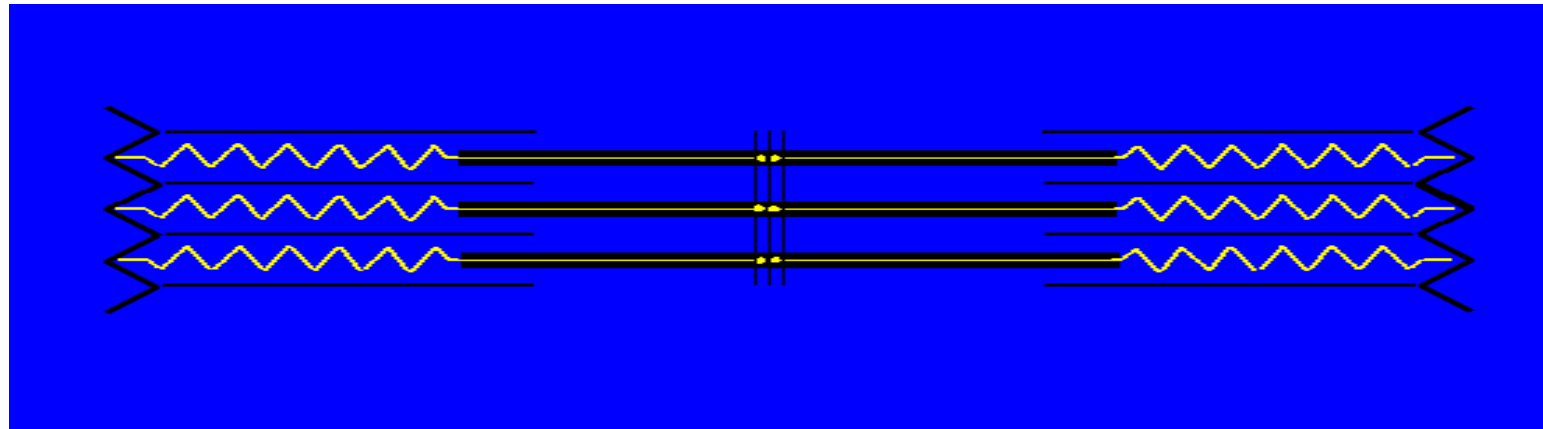
# “Stiffness” miocardico



PKG is activated by cyclic guanosine monophosphate (cGMP). Phosphorylation of the N2B isoform by protein kinase A (PKA) or G (PKG) decreases cardiomyocyte resting stiffness.

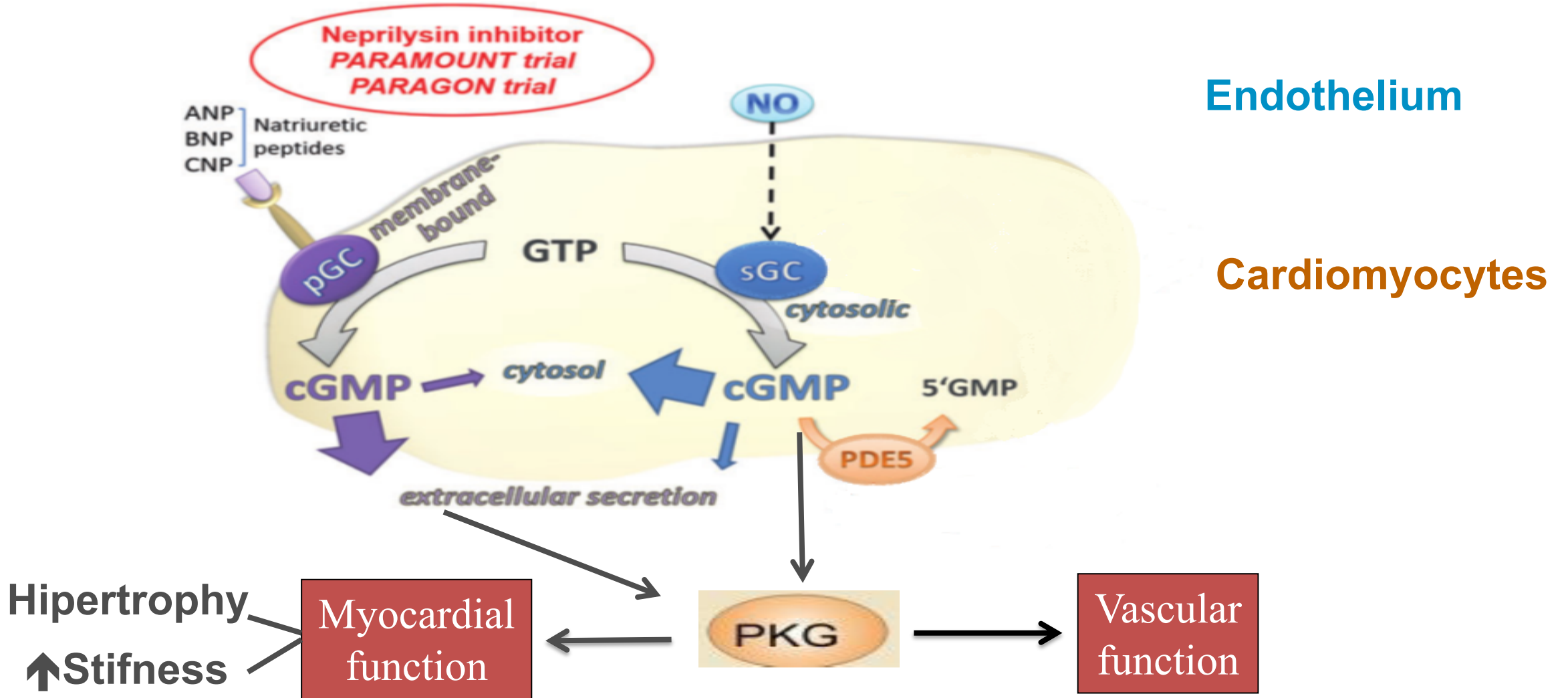
# TITINA

(1976)



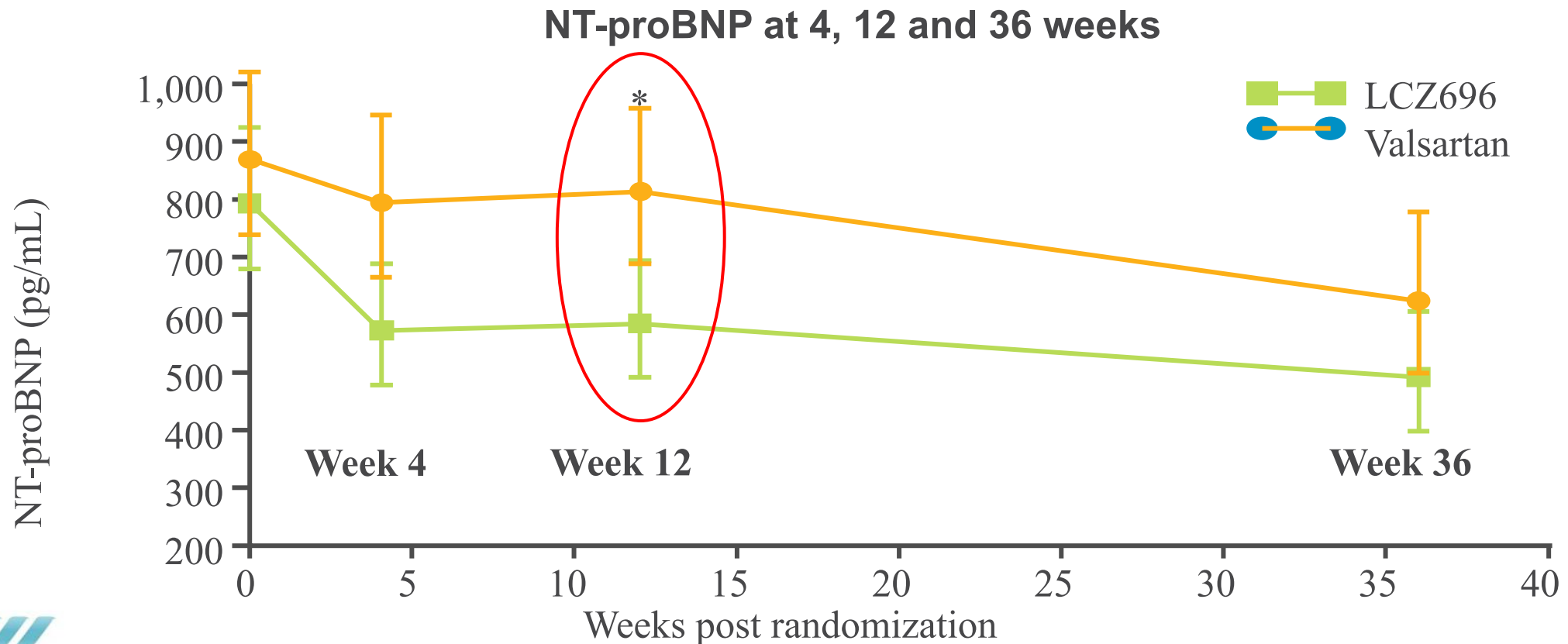
- **The giant protein titin functions as a molecular spring is extended during diastolic stretch**
- **Recoils elastically during systole**
- **Two isoforms: N2B (>stiff) and N2BA (>elastic)**
- **Is responsible for most of the passive tension of myocardium**

# Via NO/cGMP



# PARAMOUNT: NT-proBNP con LCZ696 a 12 settimane

- Reduction in NT-proBNP from baseline was sustained to Week 36 with LCZ696, although the difference between treatment groups was no longer significant ( $p=0.20$ ) due to further reduction in NT-proBNP with valsartan



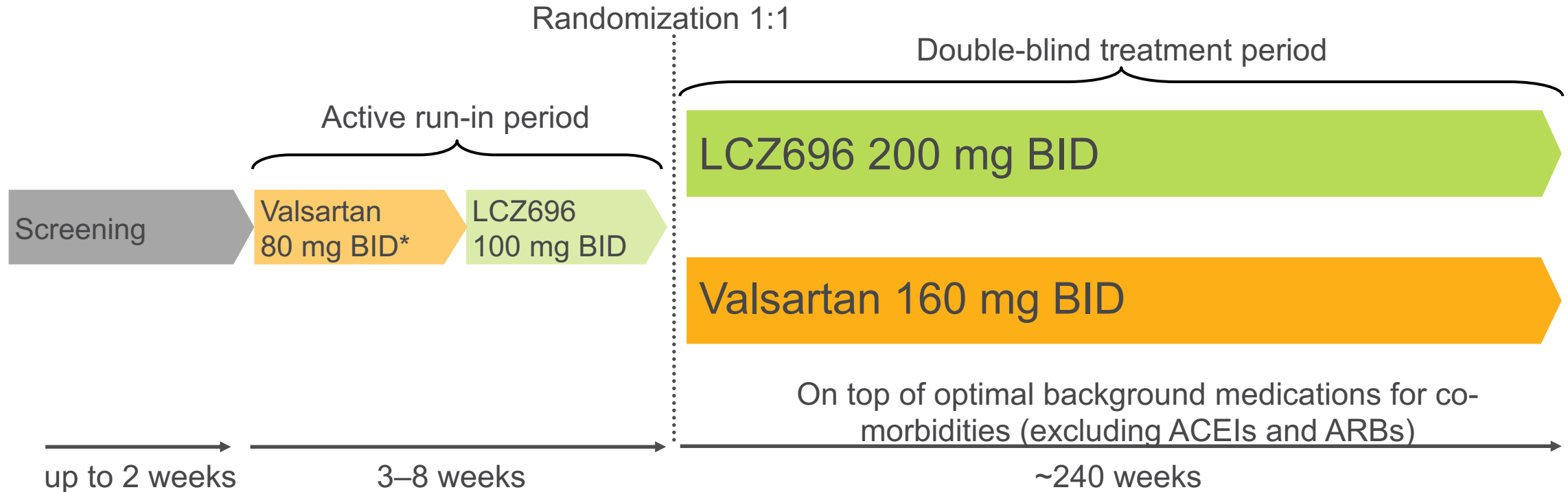
\* $p=0.005$ , LCZ696 vs valsarta

# PARAMOUNT: variazione dei parametri ecocardiografici

	12 weeks							36 weeks						
	LCZ696			Valsartan			p value	LCZ696			Valsartan			p value
	n	Baseline	Δ from baseline	n	Baseline	Δ from baseline		n	Baseline	Δ from baseline	n	Baseline	Δ from baseline	
Ejection fraction	114	58.2% (7.6)	1.06% (5.0)	118	58.0% (8.0)	1.04% (4.9)	0.85	94	58.3% (7.7)	2.7% (6.5)	111	58.1% (8.0)	3.07% (5.9)	0.69
Lateral mitral annular relaxation velocity (e'; cm/s)	97	7.7 (2.7)	0.57 (1.7)	106	7.2 (2.9)	0.55 (1.5)	0.56	84	7.6 (2.7)	0.55 (2.3)	96	7.3 (2.8)	0.92 (2.0)	0.40
Mitral inflow velocity to mitral annular relaxation velocity ratio (E/e')	96	12.6 (8.4)	-1.3 (3.4)	106	13.0 (7.3)	-1.3 (4.3)	0.71	83	12.3 (5.5)	-1.3 (3.1)	95	12.7 (6.2)	-1.0 (4.7)	0.42
Early to late mitral inflow velocity ratio (E/A)	72	1.1 (0.56)	-0.09 (0.36)	78	1.1 (0.66)	-0.08 (0.67)	0.90	60	1.1 (0.51)	-0.05 (0.39)	68	1.1 (0.65)	-0.03 (0.61)	0.43
Left atrial width (cm)	116	3.7 (0.42)	-0.07 (0.25)	114	3.7 (0.53)	-0.02 (0.22)	0.07	99	3.7 (0.43)	-0.15 (0.31)	108	3.7 (0.53)	-0.08 (0.30)	0.03
Left atrial volume (mL)	113	67.0 (23.2)	-3.2 (12.2)	119	68.1 (28.1)	-1.3 (12.5)	0.18	96	65.3 (22.5)	-4.6 (13.7)	112	68.3 (29.3)	0.37 (15.9)	0.003
Left atrial volume index (mL/m <sup>2</sup> )	110	35.9 (12.5)	-0.98 (7.6)	118	36.5 (14.4)	-0.41 (6.8)	0.45	90	35.0 (11.7)	-2.6 (7.3)	106	36.8 (14.8)	0.31 (9.3)	0.007
Left ventricular end-diastolic volume (mL)	114	110.3 (26.4)	-2.90 (10.5)	118	113.1 (31.3)	-3.27 (12.3)	0.99	94	111.8 (26.3)	-10.4 (14.4)	111	114.3 (31.5)	-12.7 (17.3)	0.39
Left ventricular end-systolic volume (mL)	114	46.5 (15.7)	-3.3 (6.5)	118	48.5 (20.9)	-2.7 (8.9)	0.97	95	46.9 (15.8)	-6.9 (9.1)	111	48.8 (20.6)	-8.70 (11.0)	0.31
Left ventricular mass index (kg/m <sup>2</sup> )	112	77.4 (20.7)	-1.2 (13.0)	112	78.8 (21.5)	-4.2 (11.8)	0.10	91	76.6 (19.8)	-2.8 (14.0)	100	79.5 (22.7)	-1.9 (19.2)	0.35
Relative wall thickness	116	0.38% (0.09)	-0.002% (0.045)	114	0.37% (0.07)	0.001% (0.033)	0.76	98	0.37% (0.07)	0.01% (0.06)	107	0.37% (0.07)	0.01% (0.06)	0.96
Tricuspid regurgitant velocity (m/s)	45	2.5 (0.36)	0.008 (0.25)	42	2.5 (0.33)	0.09 (0.33)	0.19	35	2.6 (0.44)	-0.01 (0.24)	42	2.52 (0.34)	0.06 (0.35)	0.38

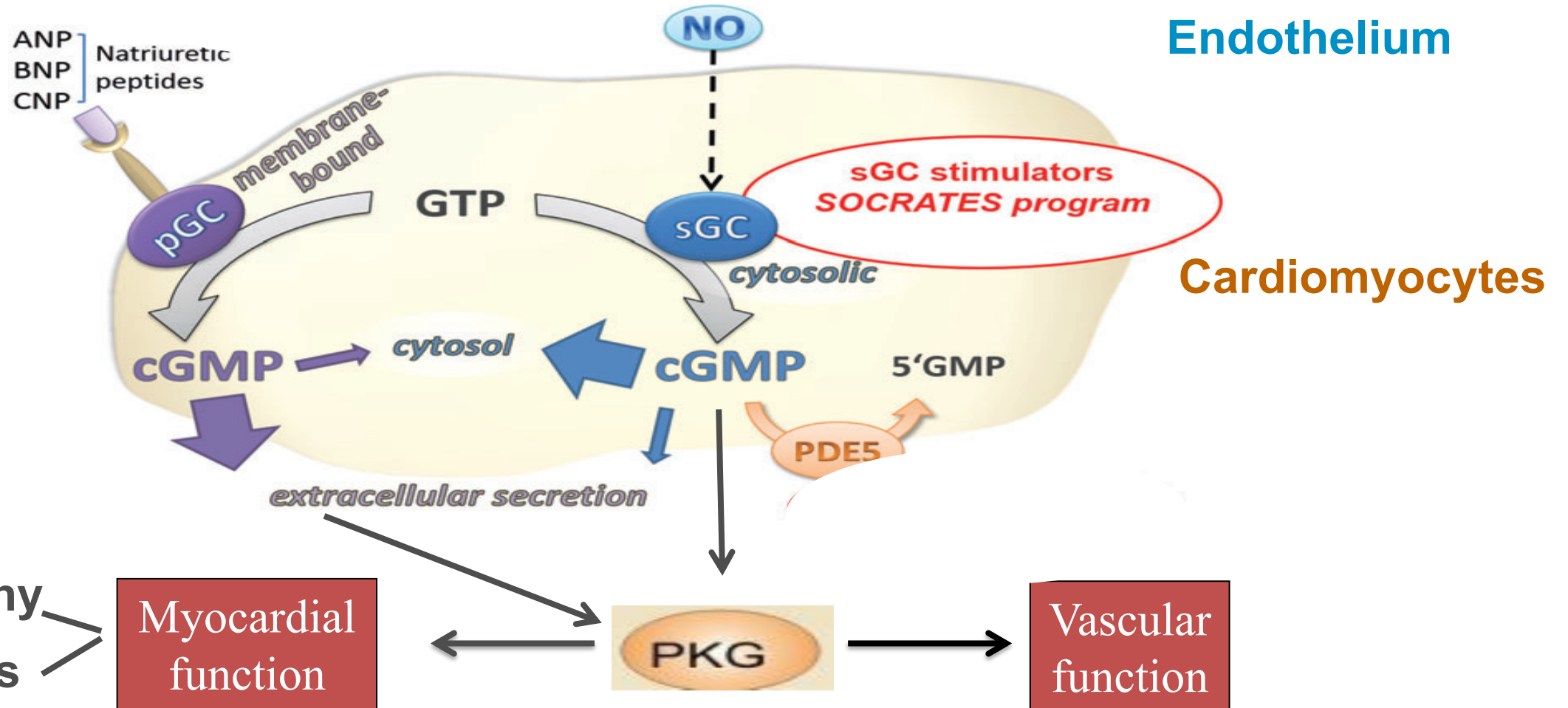
# PARAGON-HF

Target patient population: ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF  $\geq$ 45%



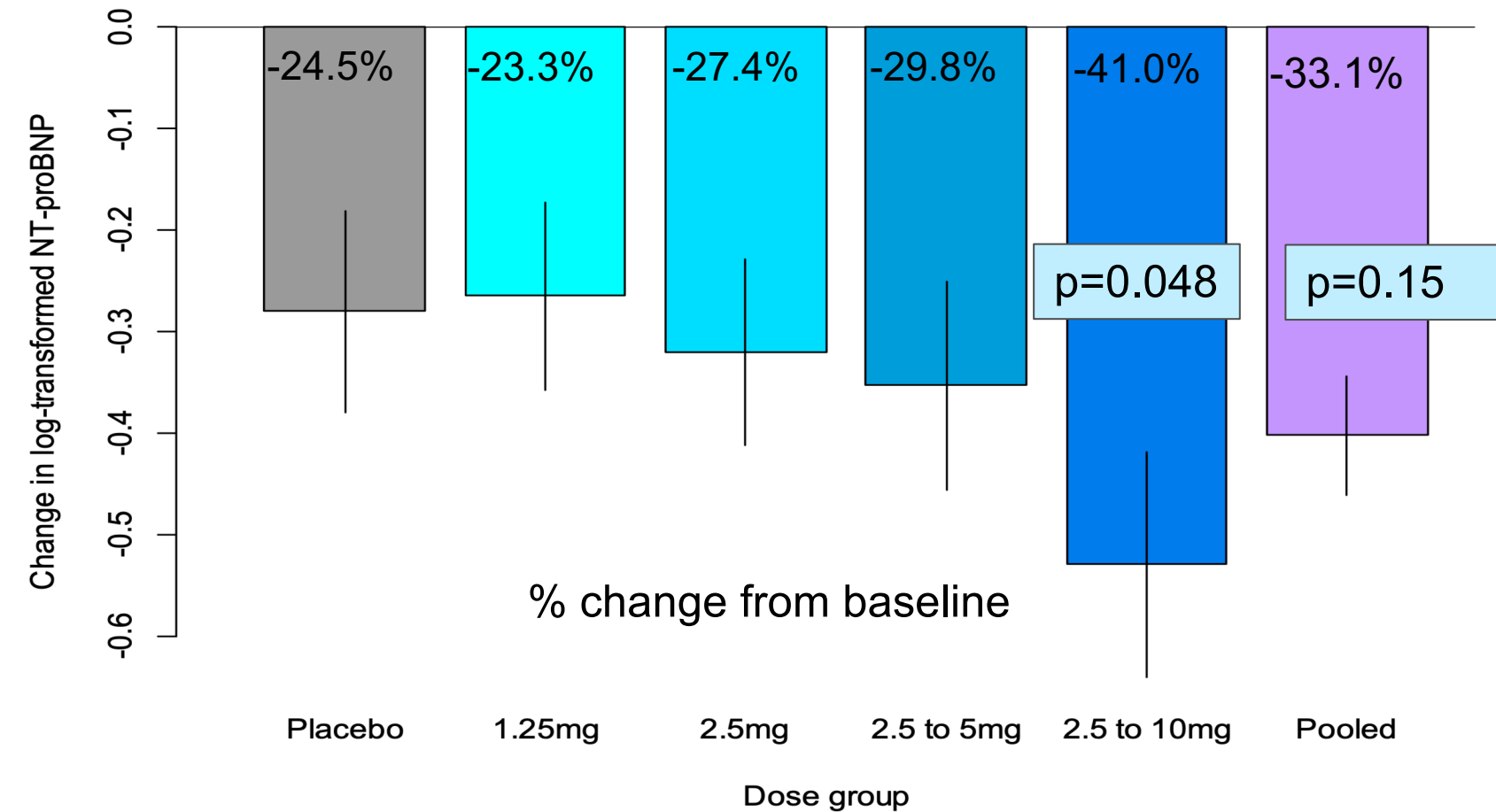
**Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)**

# Via NO/cGMP



# SOCRATES-REDUCED: endpoints

## Change in NT-proBNP at 12 weeks (per protocol analysis)



### **Primary endpoint**

#### ▶ **Primary analysis:**

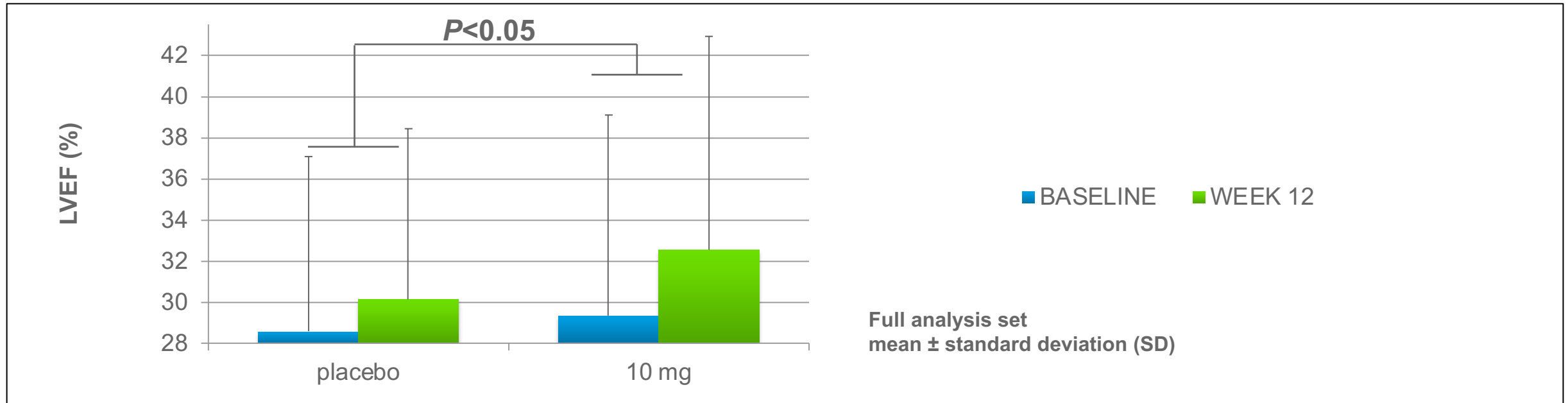
NTproBNP reduction in pooled 2.5/5/10 mg dose groups > reduction in placebo (NS, p=0.1506)

#### ▶ **Secondary analyses:**

NT-proBNP reduction in 10 mg group > placebo (p=0.0483; pre-specified pairwise comparison, exploratory only)



# SOCRATES-REDUCED: funzione sistolica



Parameter	Placebo		1.25 mg		2.5 mg		2.5 to 5 mg		2.5 to 10 mg	
	Baseline	Change at wk 12	Baseline	Change at wk 12	Baseline	Change at wk 12	Baseline	Change at wk 12	Baseline	Change at wk 12
LVEF (%)	28.6	+ 1.5	29.5	+ 2.8	29.2	+ 2.7	31.5	+ 2.1	29.3	+ 3.7
LVEDV (mL)	174	- 7	173	-6	174	-10	177	-17	161	-7
LVESV,(mL)	127	- 7	125	-9	126	-11	125	-15	120	-11

LVEF, left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume

mean values

# VICTORIA Trial

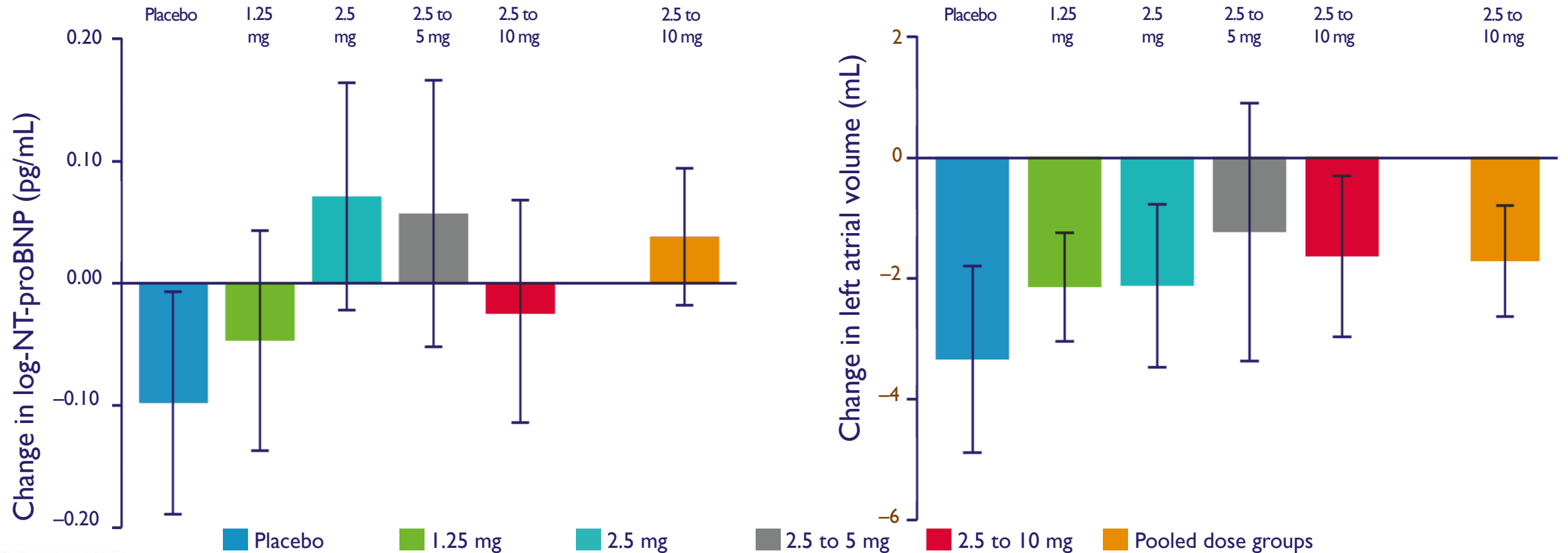
## Studio di fase III - NYHA II-IV - HFrEF

- **Primary objective:** To study the efficacy and safety of vericiguat vs. placebo on a background of usual care in HFrEF patients
- Target enrollment of approximately 4800 patients with the following:
  - HFrEF (EF < 45%)
  - NYHA II-IV on standard therapy
  - Prior HF hospitalization (6 months) or IV diuretic (3 months)
  - Elevated natriuretic peptides
  - Not taking long-acting nitrates
- Primary outcome: composite endpoint of cardiovascular (CV) mortality or HF hospitalization
- Secondary outcomes include:
  - Time to the First Occurrence of CV Death
  - Time to the First Occurrence of HF Hospitalization
  - Time to Total HF Hospitalizations (including first and recurrent events)
  - Time to First Occurrence of Composite Endpoint of All-cause Mortality or HF Hospitalization
  - Time to All-cause Mortality

# SOCRATES-PRESERVED

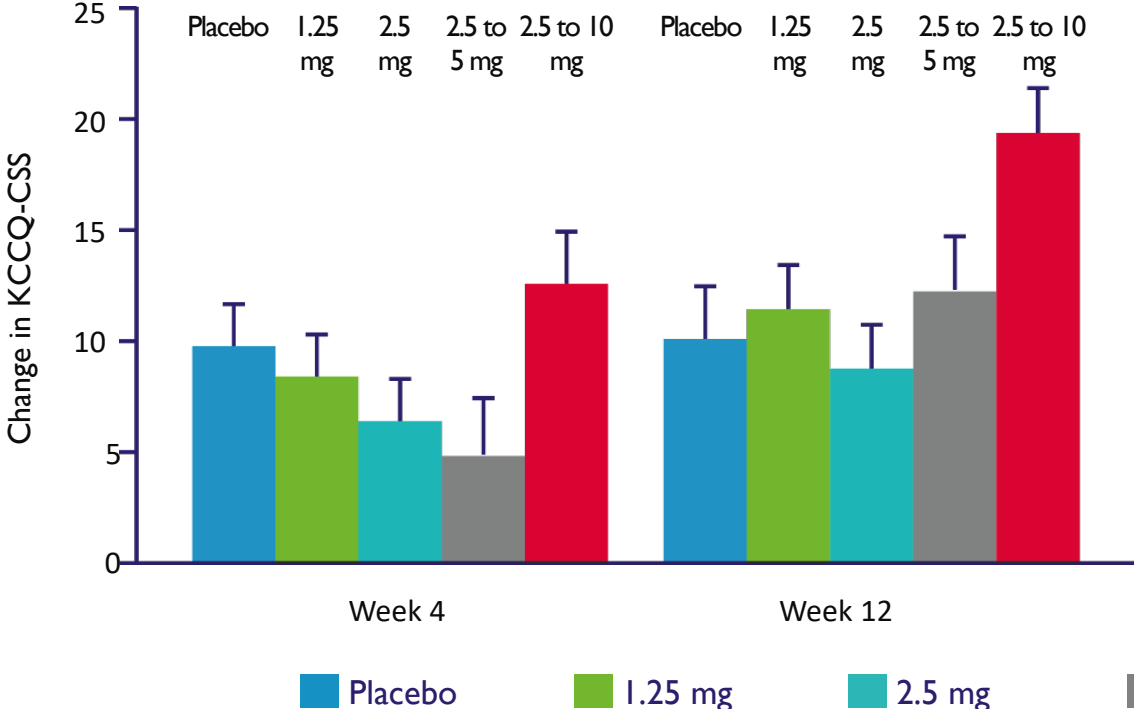
## Endpoint primari: log-NT-proBNP e LAV

477 HFpEF patients, EF  $\geq$  45%

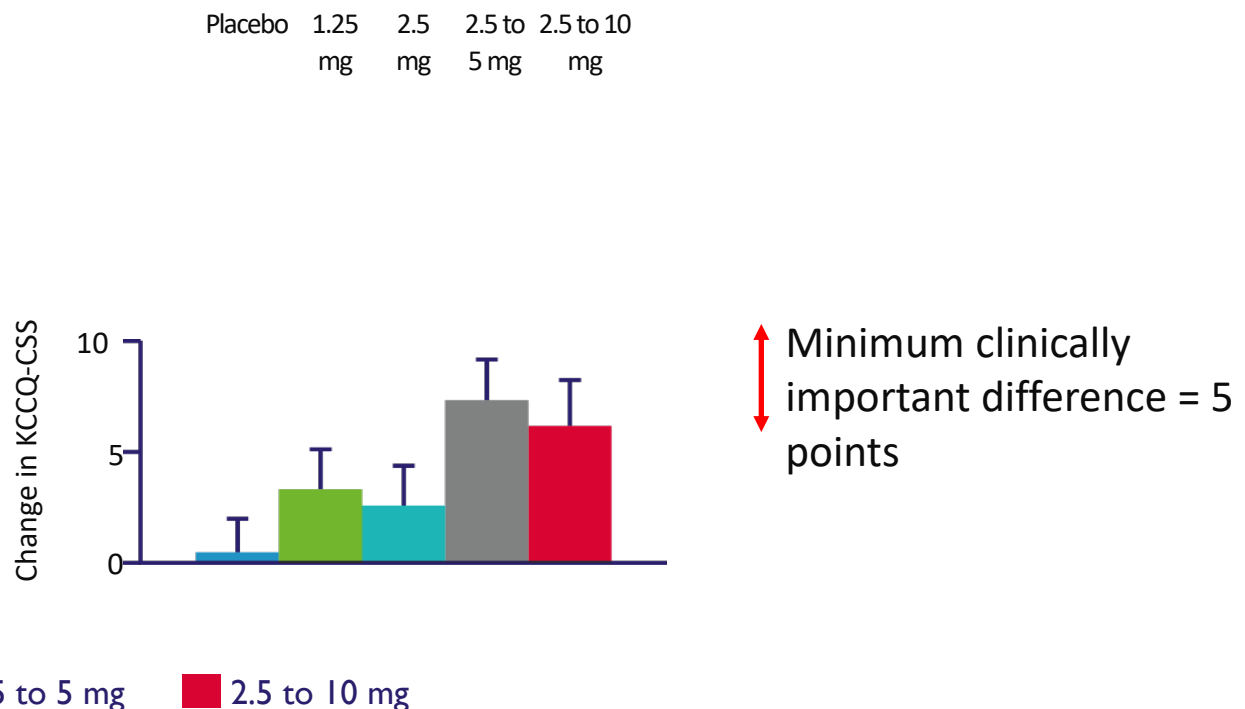


# SOCRATES-PRESERVED: qualita' della vita (KCCQ score)

Change from baseline in KCCQ clinical summary score



Change from week 4 in KCCQ clinical summary score at week 12



# Cuore al centro ...

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**1. Via NO-cGMP**

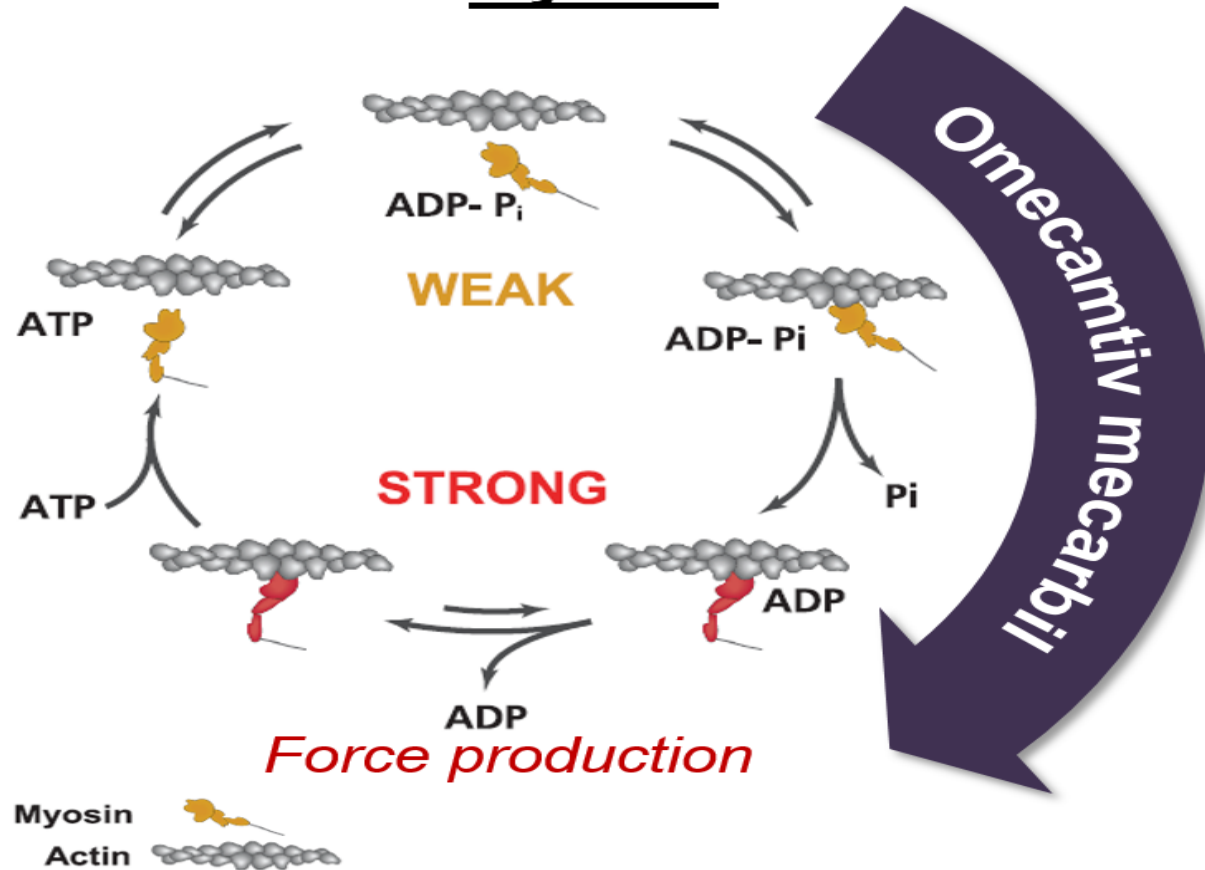
**2. Nuovi inotropi**

**3. Energetica (produzione di ATP)**



# Omecamtiv mecarbii: attivatore selettivo della miosina

## Mechanochemical Cycle of Myosin



**OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin**

**“More hands pulling on the rope”**

Increases duration of systole

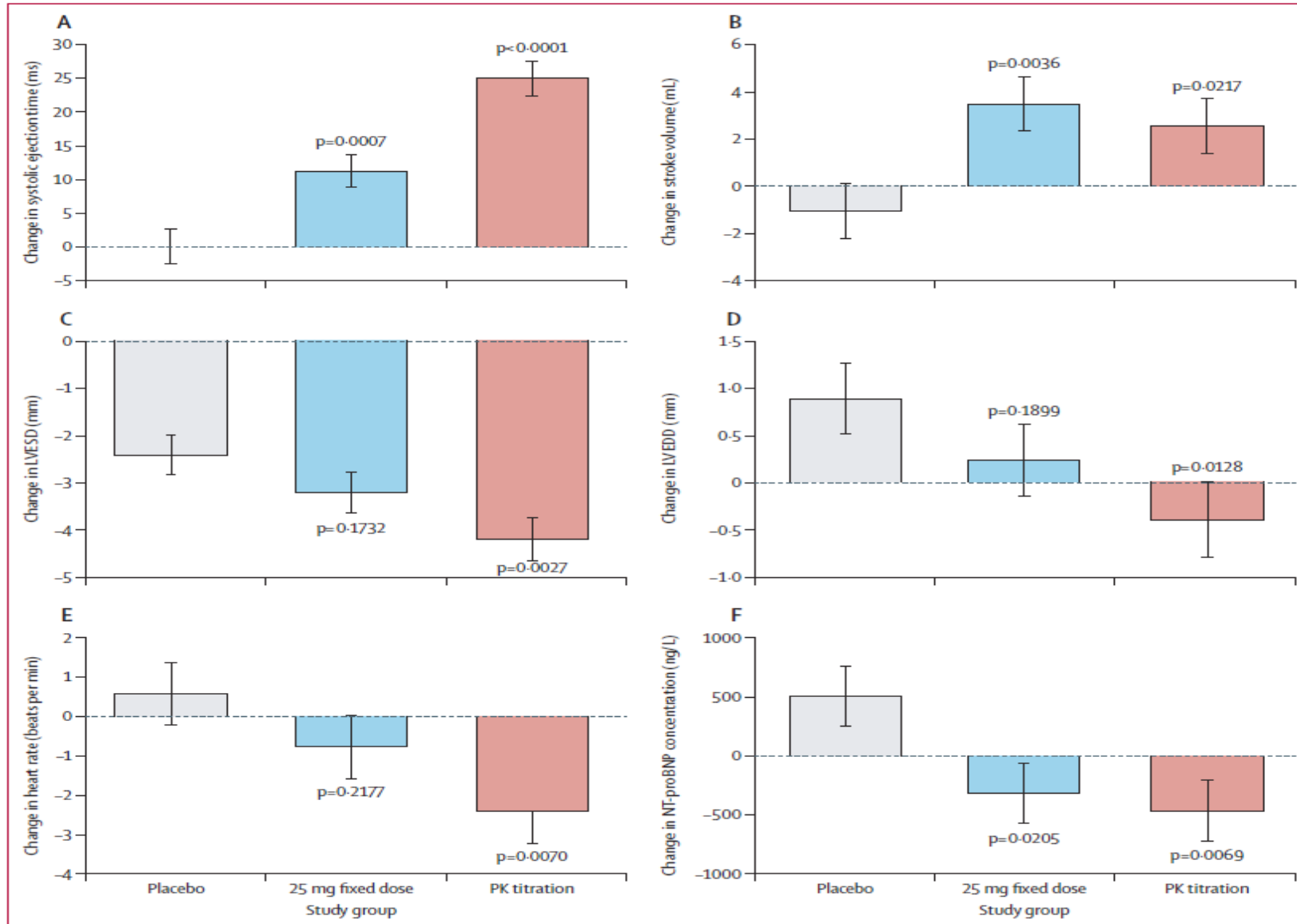
Increases stroke volume

No increase in myocyte calcium

No change in  $dP/dt_{\max}$

No increase in  $MVO_2$

# Omecamtiv mecarbil in HFrEF: COSMIC-HF



# Title: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction

Amgen Protocol Number (Omecamtiv Mecarbil [AMG 423]) 20110203

EudraCT number 2016-002299-28

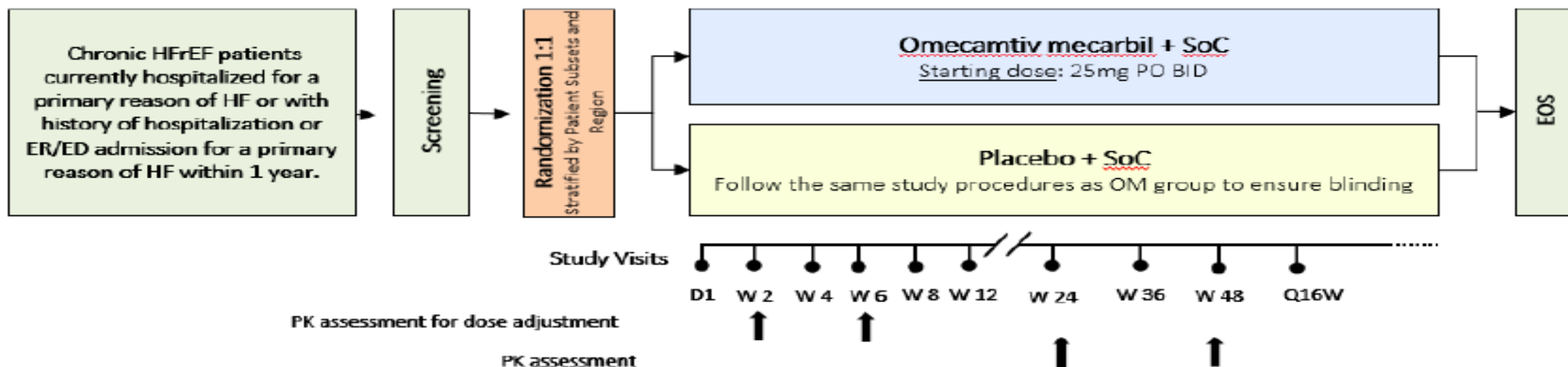
GALACTIC-HF

Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure

## Study Design and Treatment Schema

2 years enrollment, approx. 4 years total follow-up/study period

Subject source





# Cuore al centro ...

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**1. Via NO-cGMP**

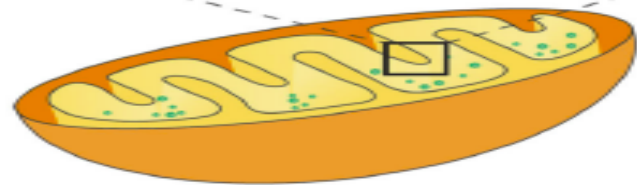
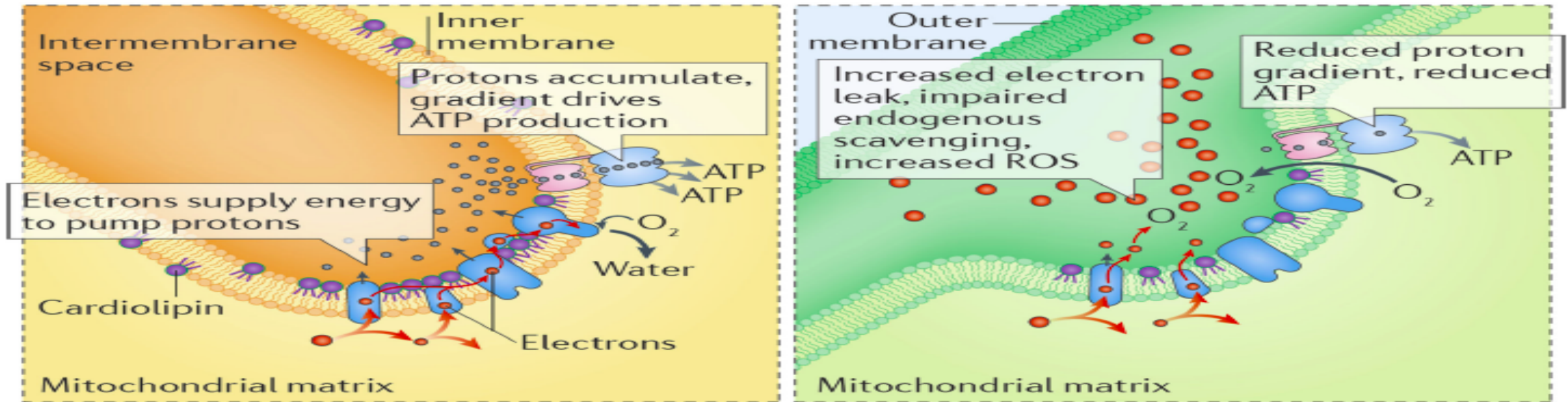
**2. Nuovi inotropi**

**3. Energetica (produzione di ATP)**



# Inadeguata produzione di energia a livello della membrana mitocondriale interna

Progression to heart failure



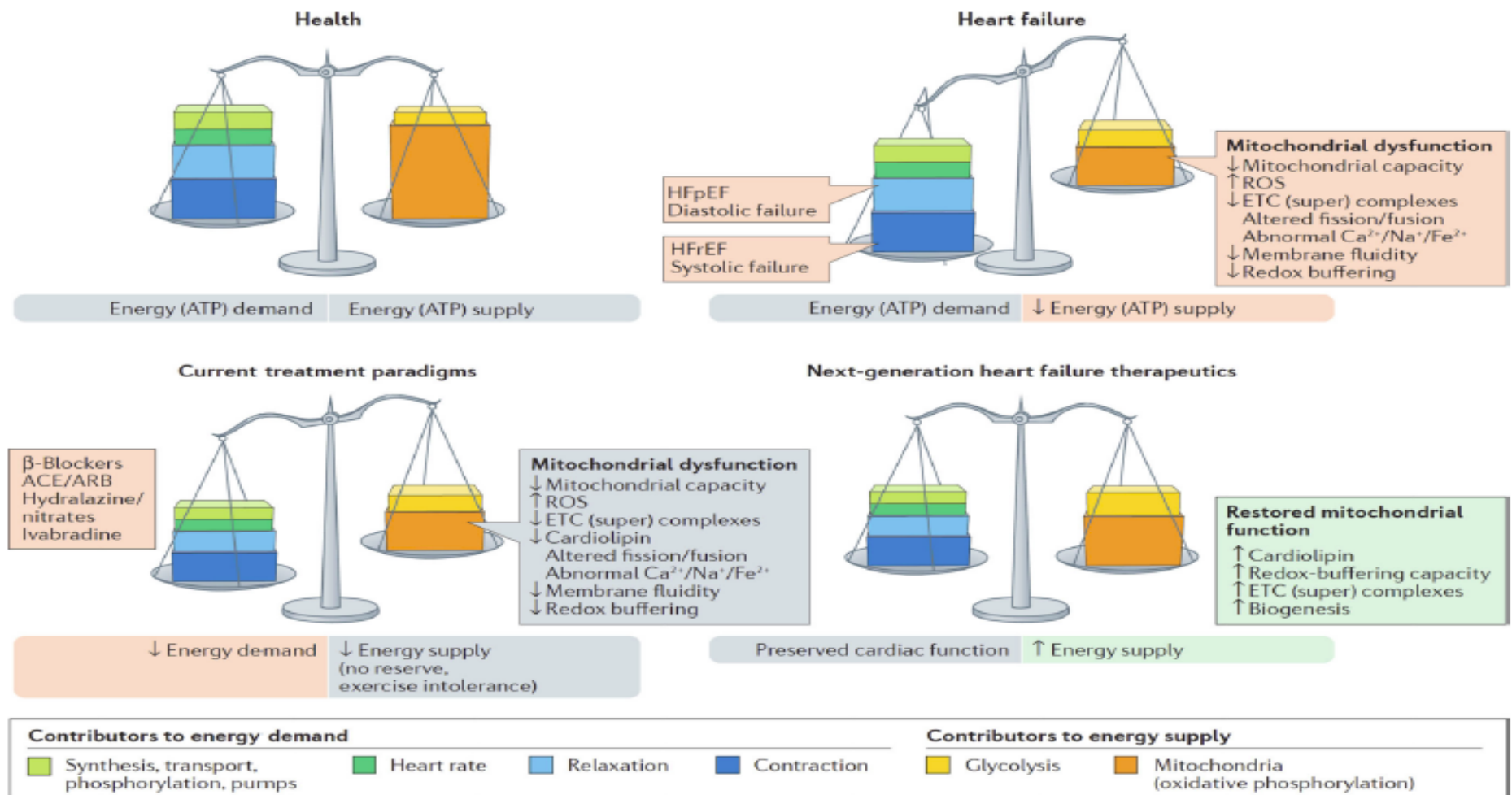
Healthy mitochondrion

↓ ATP  
↑ ROS



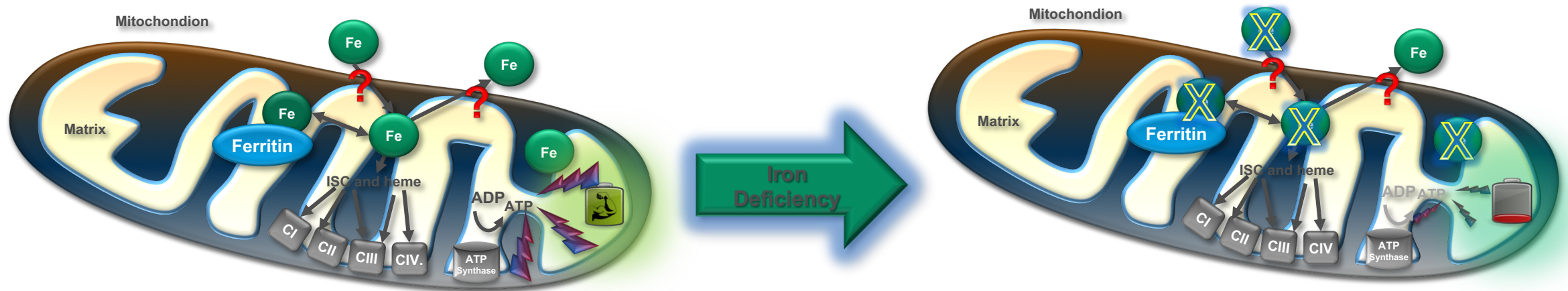
Dysfunctional mitochondrion

# Produzione di energia come target terapeutico nello scompenso cardiaco

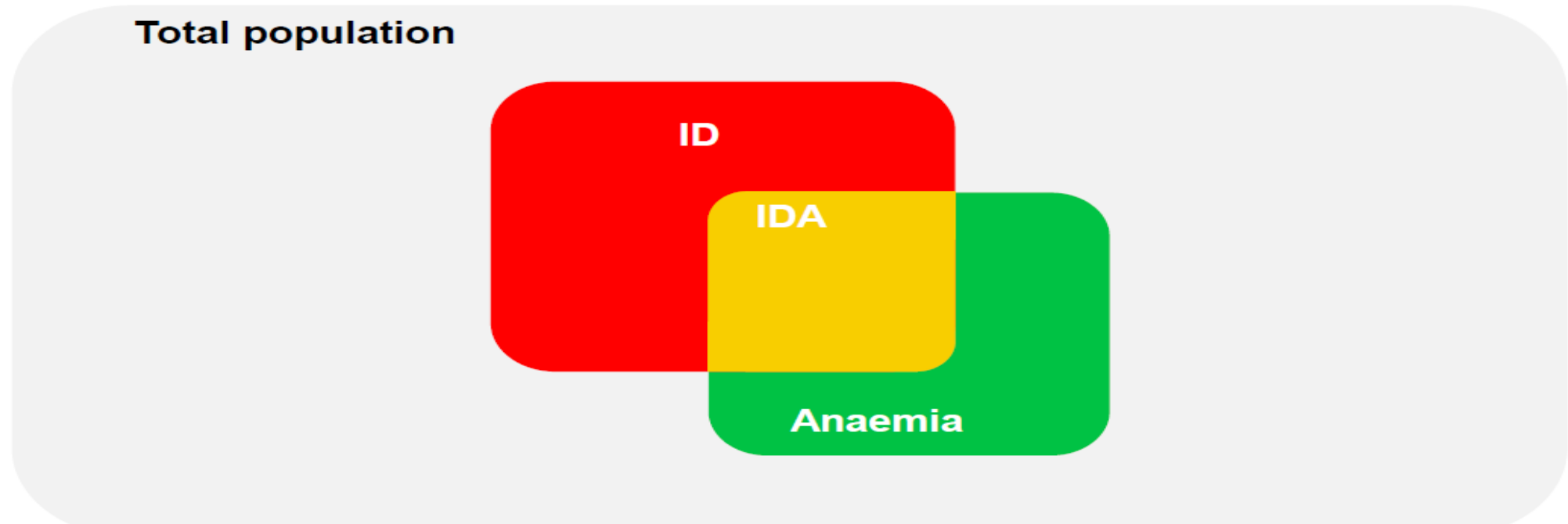


# Conseguenze della carenza di ferro in CHF: alterazione del metabolismo energetico cellulare

Il ferro è necessario poiché è un componente dei cluster Fe/S proteici e dei gruppi Fe-eme dei citocromi dei complessi I-IV responsabili del trasporto degli elettroni, che sostiene l'attività dell'ATP sintetasi all'interno dei mitocondri<sup>1</sup>



# Carenza di ferro: relazioni con l'anemia



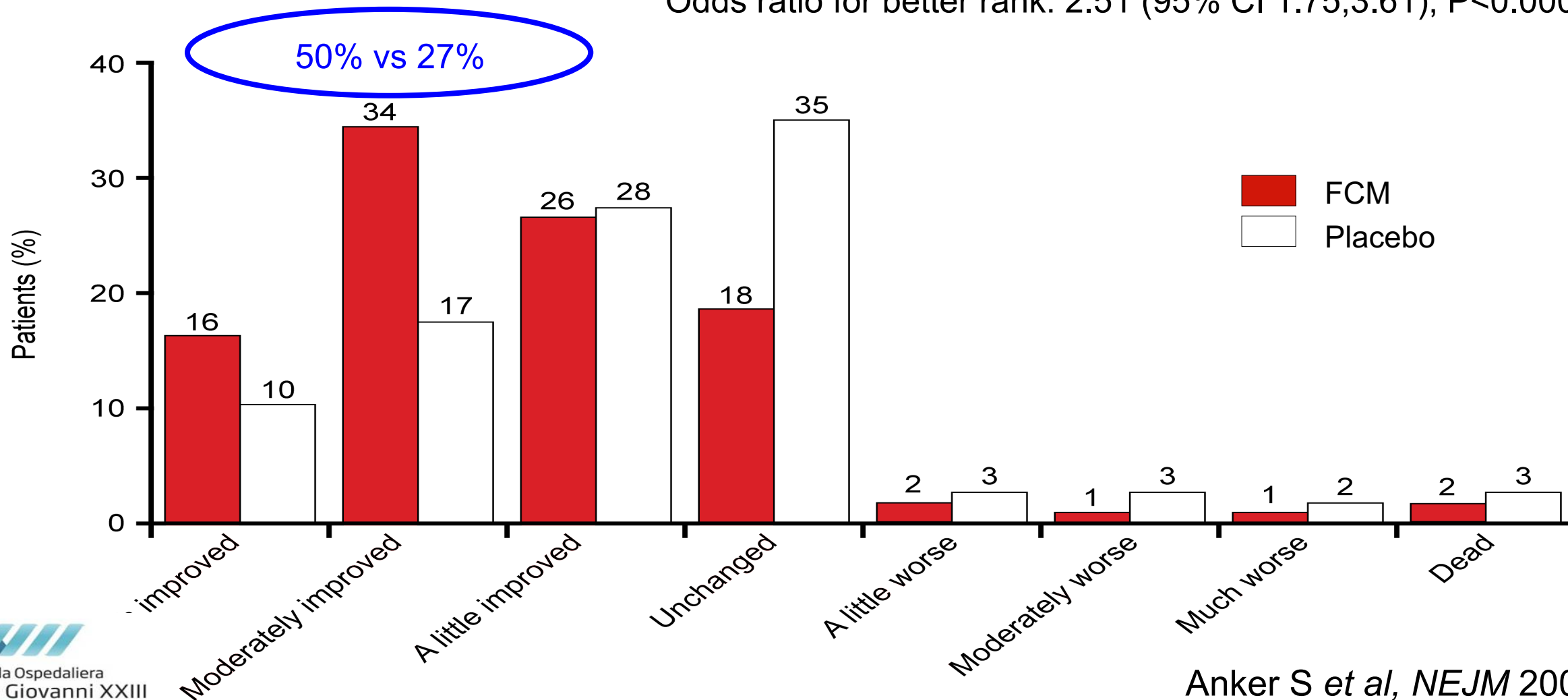
**Definition of Iron deficiency:  
serum ferritin  $<100 \mu\text{g/L}$  or  $<300 \mu\text{g/L}$ , if TSAT  $<20\%$**

# Endpoint primario 1: Patient Global Assessment a 24 settimane



459 HFrEF patients, LVEF<sub>≤</sub>45%

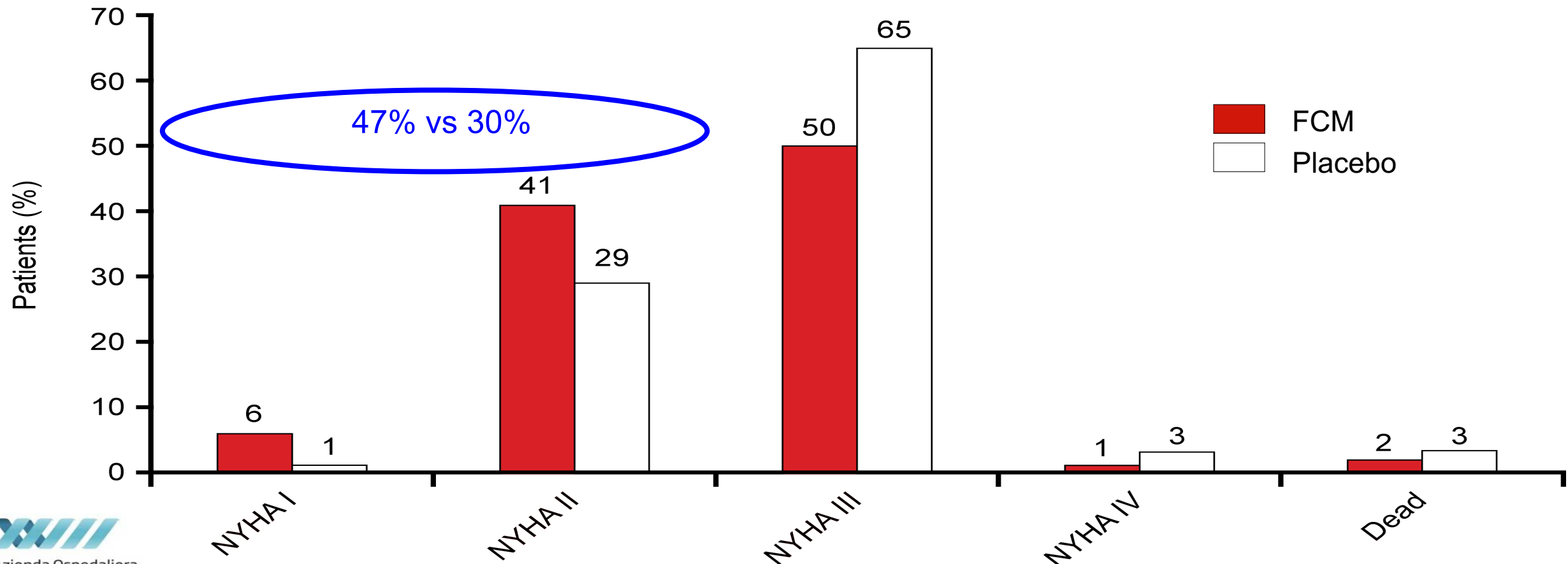
FCM improved self-reported PGA scores at week 24  
Odds ratio for better rank: 2.51 (95% CI 1.75,3.61), P<0.0001



# Endpoint primario 2: classe NYHA a 24 settimane

FCM improved NYHA functional class at week 24

Odds ratio for improvement by 1 class: 2.40 (95% CI 1.55,3.71),  $P < 0.0001^*$



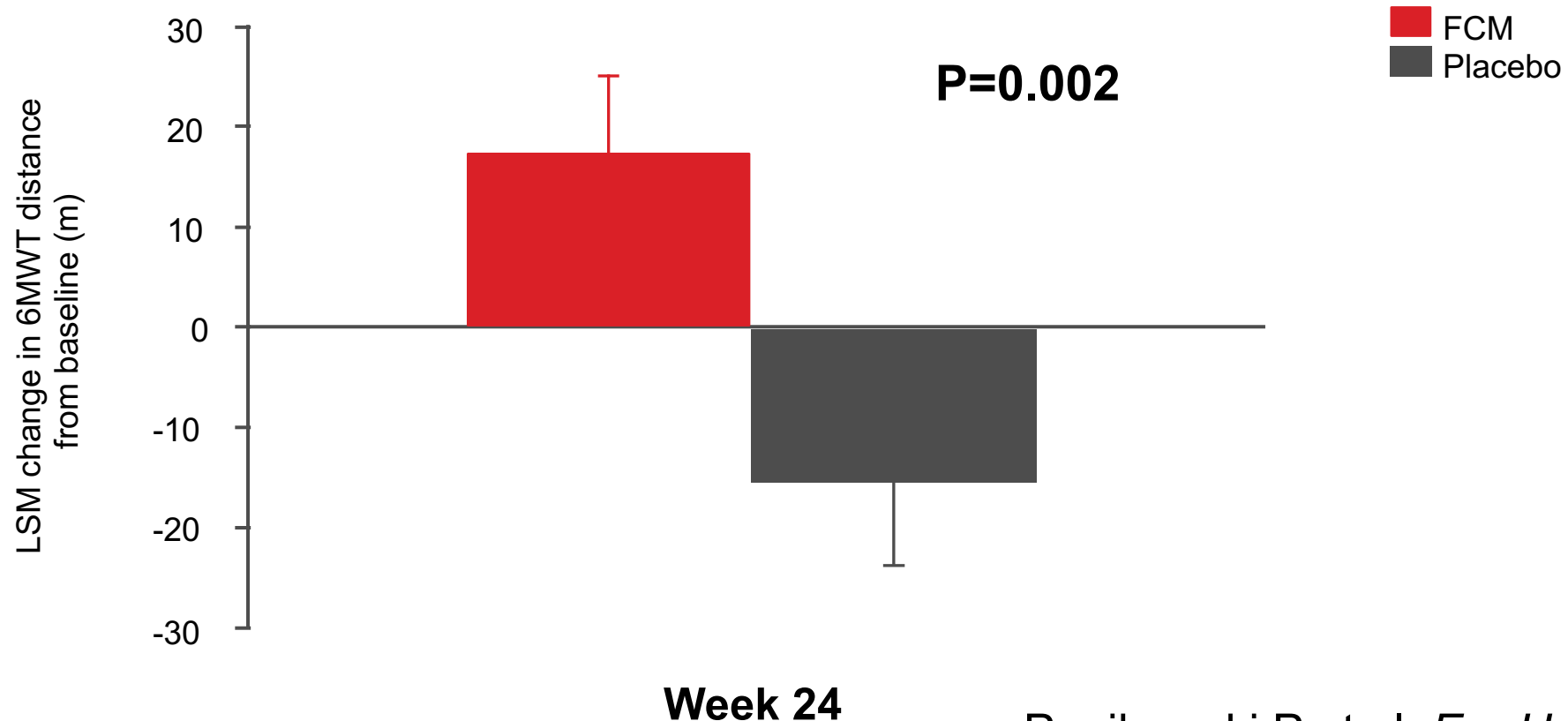


# CONFIRM-HF: endpoint primario

## 6-minutes walking distance a 24 settimane

300 HFrEF patients, LVEF $\leq$ 45% FCM improved 6MWT at week 24

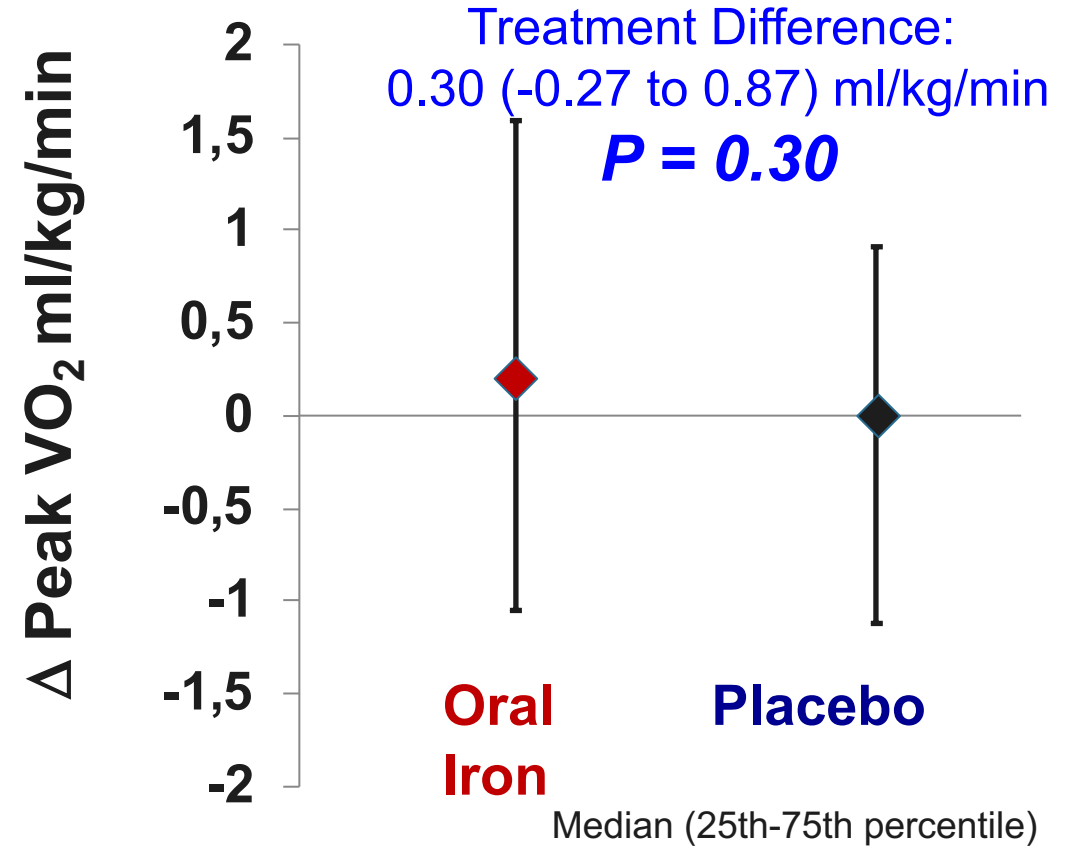
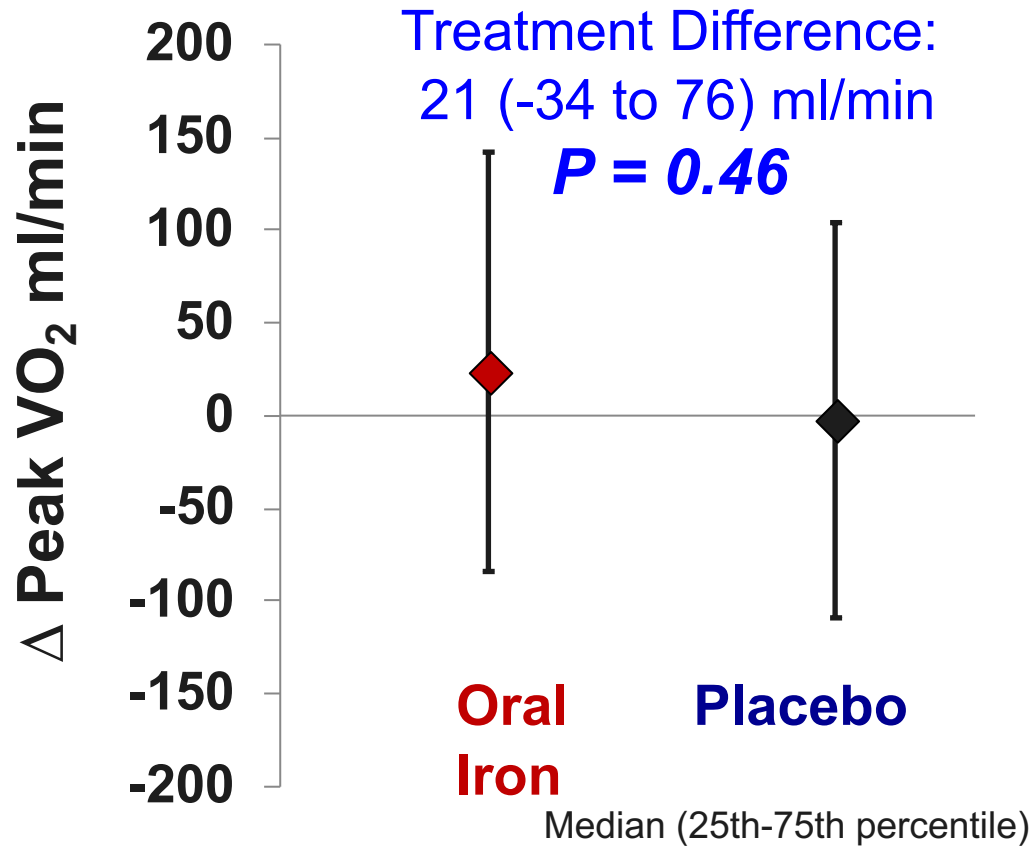
FCM vs placebo:  $33 \pm 11$  m (*least squares mean  $\pm$  SE*)





# Ironout-HF

300 patients, LVEF < 40%



Baseline peak VO<sub>2</sub> (IQR) 13.3 12.9  
(11.4–15.8) (10.5–15.6)

# Studi in corso di Mortalita' e Morbidita' con terapia marziale e.v.

Study	AFFIRM AHF <sup>1</sup>	FAIR HF2 <sup>2</sup>	HEART FID <sup>3</sup>	IRONMAN <sup>4</sup>
Design	Prospective, double-blind, randomised, parallel-group, placebo controlled	Prospective, double-blind, randomised, parallel-group, placebo controlled	Prospective, double-blind, randomised, parallel-group, placebo controlled	Prospective, single-blind, parallel group, randomized, open-label, multicentre
Population	Patients (N=1100) admitted with acute HF and stabilized, and iron deficiency	Patients (N=1200) with CHF (or acute HF) and iron deficiency	Patients (N=3014) with CHF and iron deficiency	Patients (N=1300) with HFrEF and iron deficiency
i.v. iron	Ferric carboxymaltose	Ferric carboxymaltose	Ferric carboxymaltose	Iron (III) isomaltoside
Primary endpoint	Effect on the composite of recurrent HF hospitalizations for worsening HF and CV death up to 52 weeks after randomization	Combined rate of recurrent hospitalizations for HF and of CV death after at least 12 months of follow-up	Treatment response over 12 months for incidence of death, incidence of hospitalization for heart failure and change in 6 MWT	CV mortality or hospitalization for worsening HF (analysis will include first and recurrent hospitalisations). Minimum 2.5 years follow-up from last patient recruited

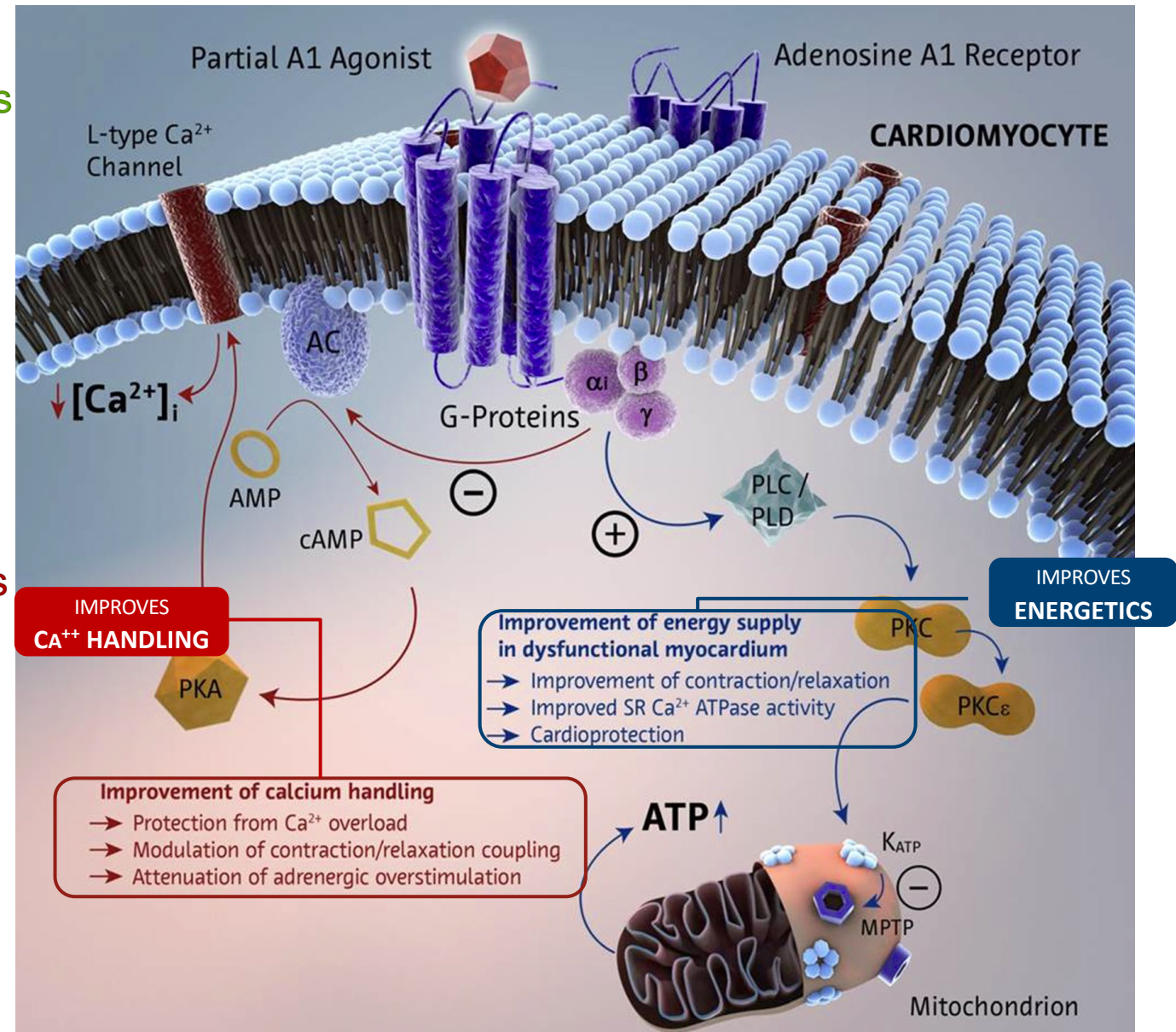
# Agonista parziale dell'adenosina (Neladenoson): un nuovo meccanismo

## Partial A<sub>1</sub>R Agonists → desired physiological effects

- Improvement of cardiac function and myocyte energetics
- Prevention of progressive remodeling
- No effects on BP and AV conduction
- Reduction of Free Fatty Acid (FFA)
- No CNS effects
- Protection of renal function

## Full A<sub>1</sub>R Agonists → undesired physiological effects

- Bradycardia
- Higher degree AV block
- Negative inotropy
- CNS effects: sedation
- Antidiuretic effects



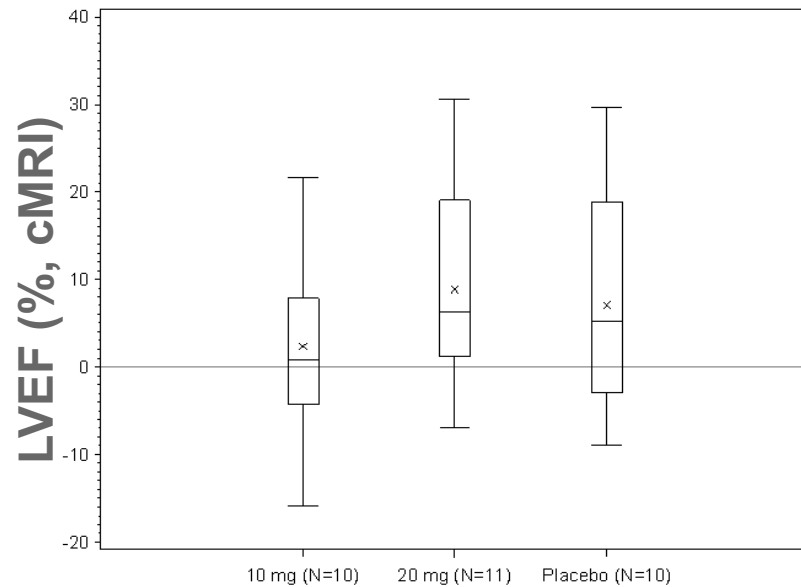
# PARSIFAL PILOT STUDY

## Safety

No effects on BP

No effects on PR conduction/no higher degree AV-blocks or syncope – transient mild decrease in HR (2-5 bpm) – no increase of cardiac markers (hsTnT)

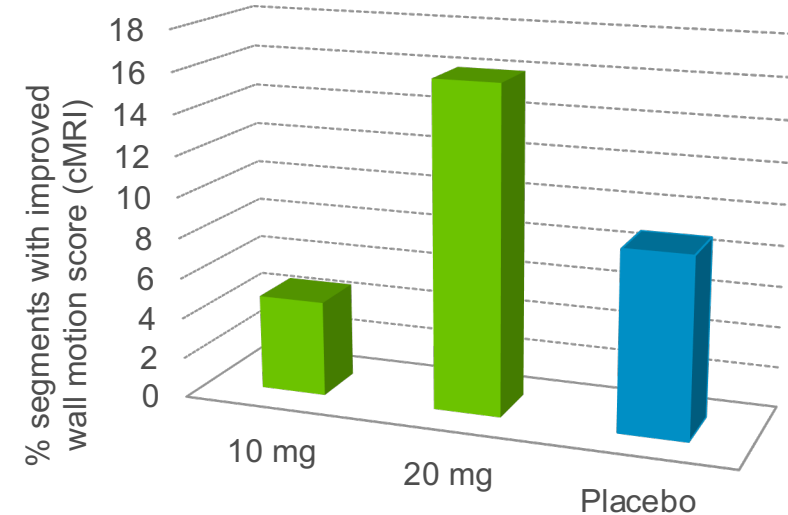
### EF change vs baseline



20 MG IMPROVED (AND PLACEBO, DUE TO BASELINE DIFFERENCES)

### Wall Motion Score

% of segments improved



TREND TOWARDS AN IMPROVED SEGMENTAL FUNCTION WITH 20 MG: RECOVERY OF VIABLE DYSFUNCTIONAL MYOCARDIUM



# Agonista parziale dell'adenosina nello scompenso cardiaco: trials di fase II

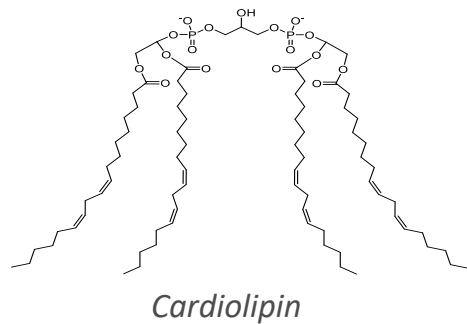
	PANTHEON	PANACHE
Design	2 multicenter, randomized, parallel-group, placebo-controlled, double-blind, dose finding phase II studies of 5 dose regimens of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks	
Inclusion Criteria	≥18 years old	≥45 years old
	CHF diagnosis, NYHA II-IV (≤6 m)	CHF diagnosis, NYHA II-IV (≤6 m)
	LVEF ≤35% (≤6 m)	LVEF ≥45% (≤6 m)
	worsening CHF requiring hospitalization or unscheduled visit (≤3 m), both requiring initiation/intensification of HF therapy <b>AND</b> NT-proBNP ≥400/1200 (SR/AF) ≤3 m <b>AND/OR</b> NT-proBNP ≥1200/2400 (SR/AF) ≤1 m	diuretic (≤6 m) <b>AND</b> NT-proBNP ≥300/900 (SR/AF) (≤6 m) <b>AND</b> LA enlargement / LV hypertrophy / elevated filling pressure (≤6 m)
		6MWD 100-550 m
Primary Outcome	LVEF change at 20 weeks	6MWD change at 20 weeks
Sample size	384 patients in 6 arms (allocation 5/10/20/30/40/placebo=1:2:2:2:2:3)	288 patients in 6 arms (allocation 5/10/20/30/40/placebo=1:2:2:2:2:3)

ClinicalTrials.gov Identifier: NCT02992288

# Elamipretide (Bendavia)



Cardiolipin in the Inner Mitochondrial Membrane (IMM)  
Establishes Structure, Enables Function



Szeto, Birk, Am J Physiol 2014

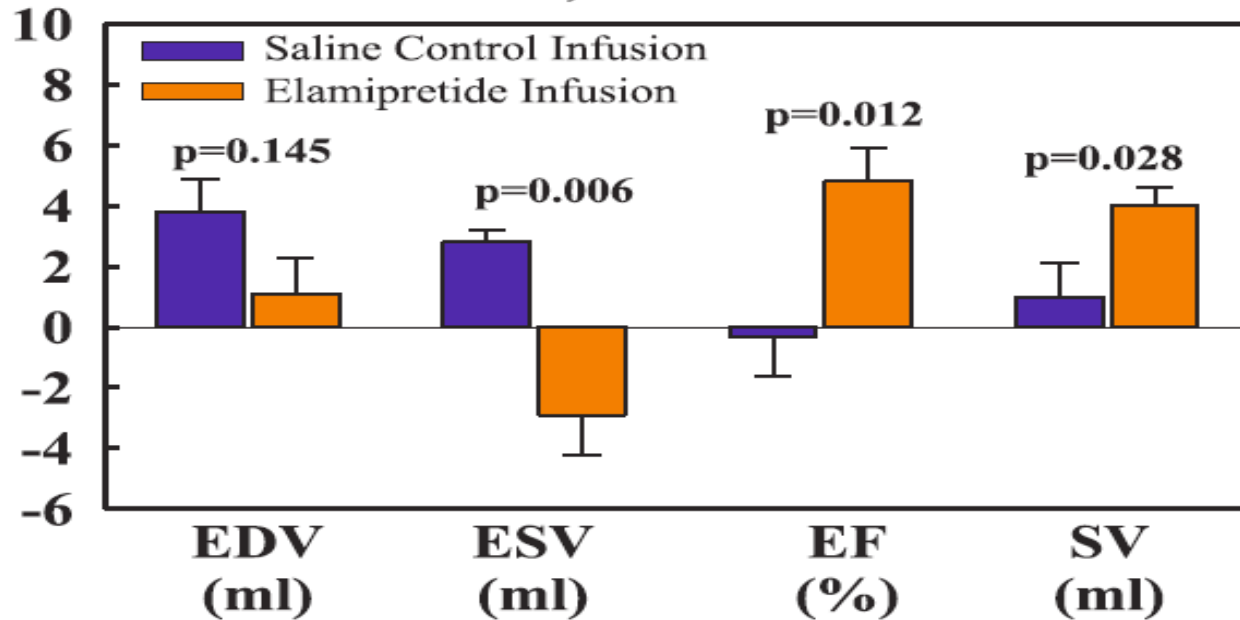
Szeto, Birk, Am J Physiol 2014

Szeto HH, Birk AV. Clin Pharmacol Ther. 2014

# Elamipretide e sistema neuro-ormonale

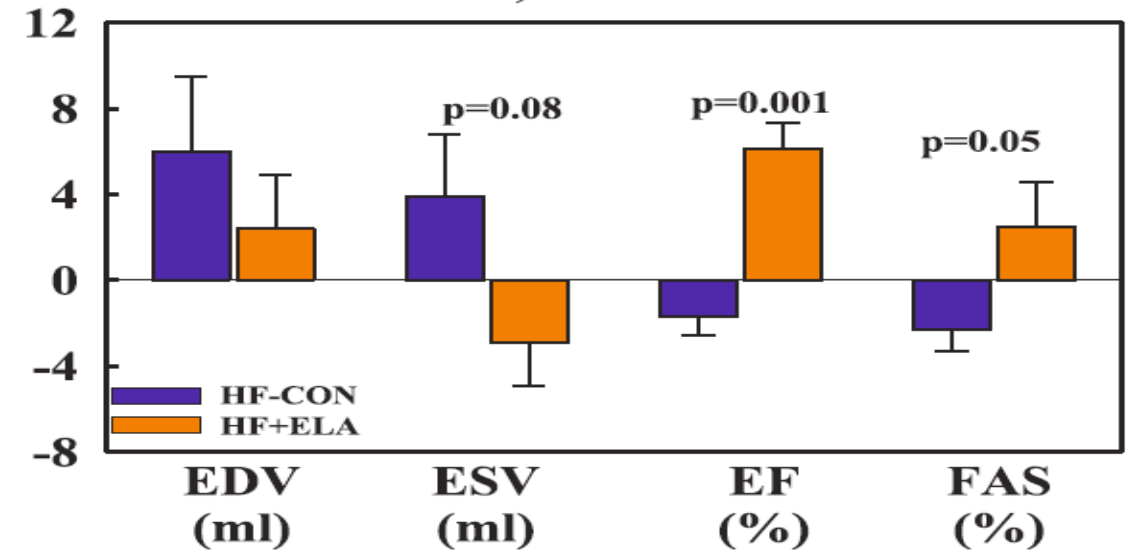
## 2 Hours Intravenous Infusion

Treatment Effect,  $\Delta$

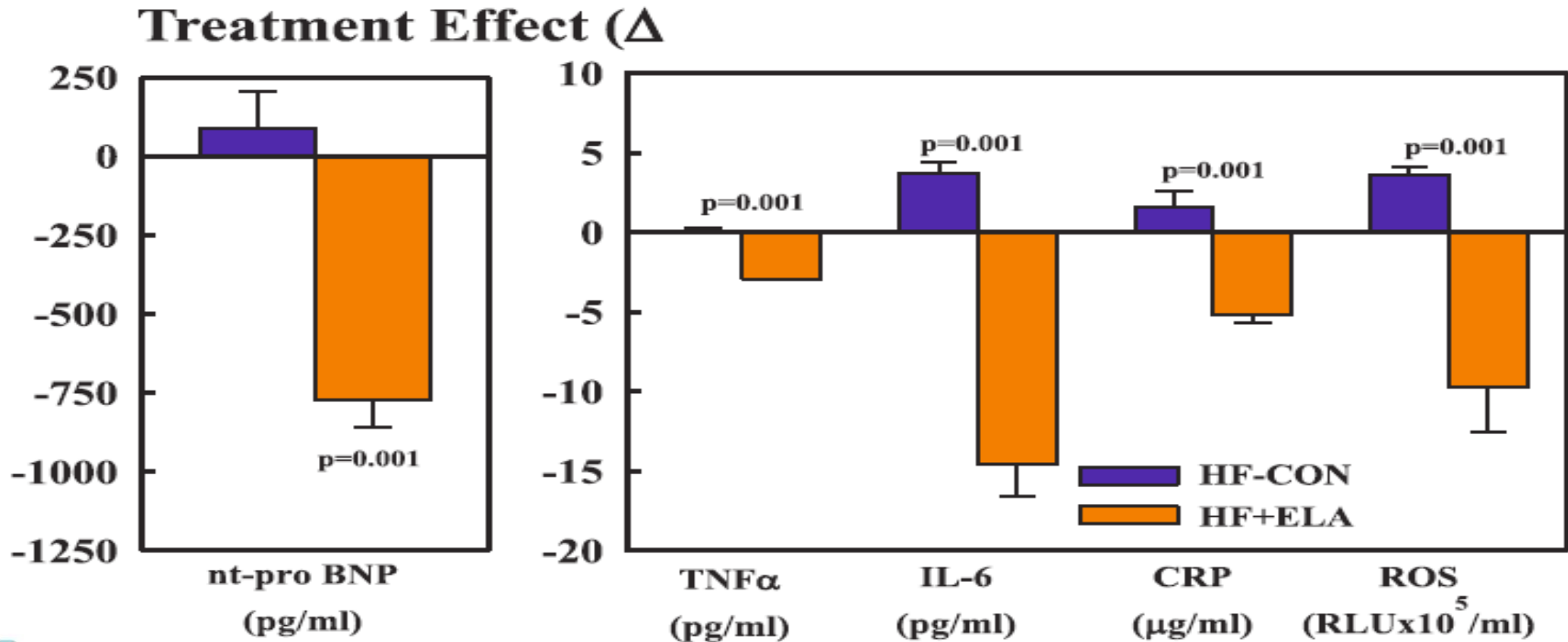


## 3 Months Subcutaneous Treatment

Treatment Effect,  $\Delta$



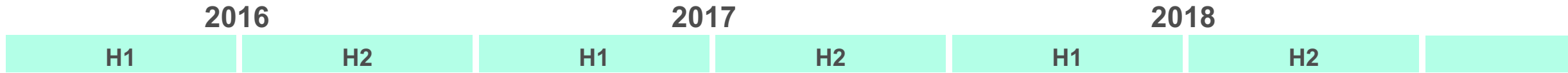
# Elamipretide e sistema neuro-ormonale





# Heart Failure Program

## Elamipretide Unique MOA Supports Addressing Large HF Unmet Need



### HFpEF Trial Phase 2 Study SPIHF-203



**46 patients**  
2 arms  
• 1 active  
• 1 placebo

- Double-blind placebo control
- 1 month duration of therapy
- Primary efficacy endpoints assessment of E/e' at rest and during submaximal stress

### HFrEF Trial Phase 2 Study SPIHF-201



**45 patients**  
3 arms  
• 2 active  
• 1 placebo

- Double-blind placebo control
- 1 month duration of therapy
- Primary efficacy endpoints assessment of heart function by MRI and Echo, 6 MWT, biomarkers

### IDDEA-HF Phase 2 Study SPIHF-204



**300 patients**  
2 arms  
• 1 active  
• 1 placebo

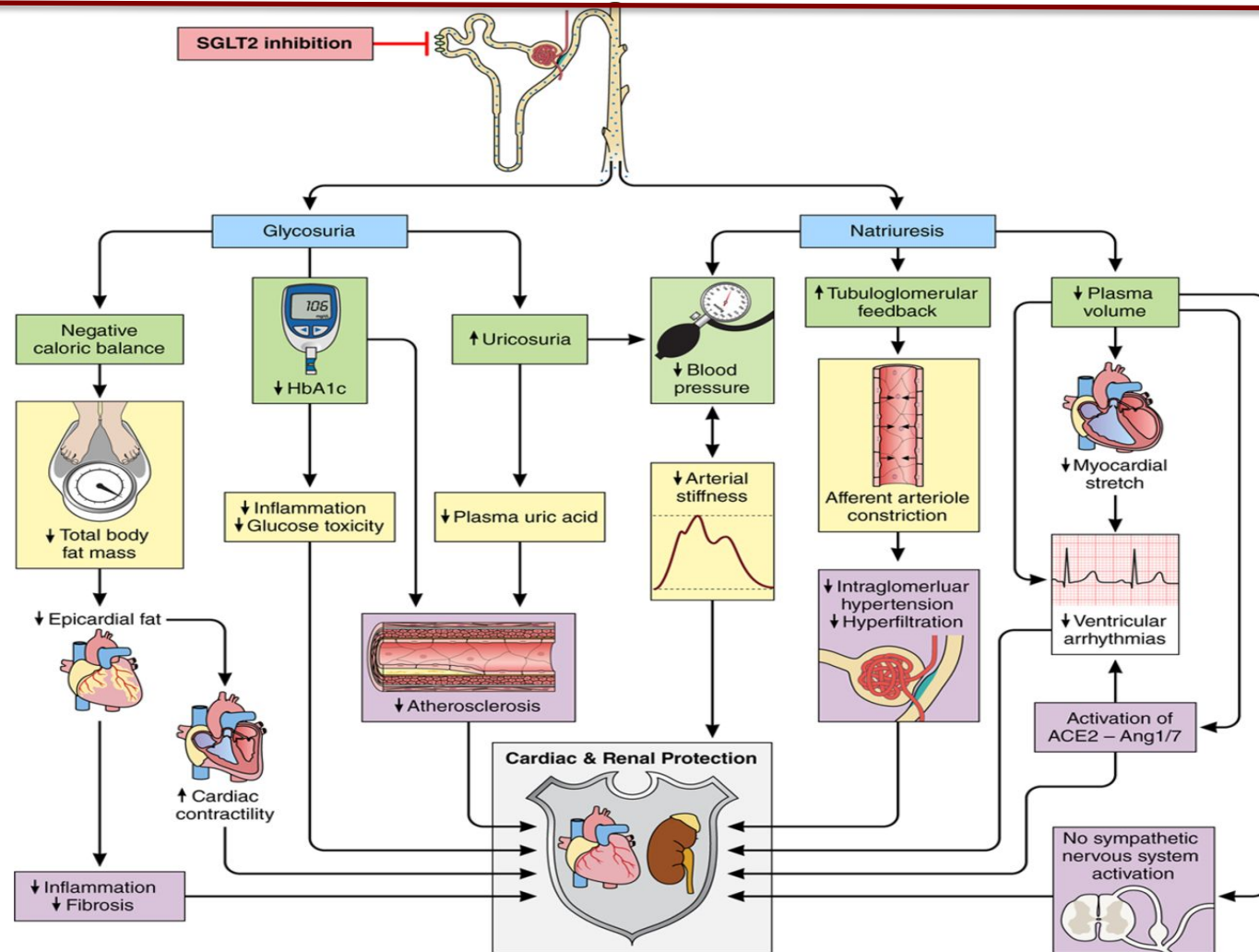
- Double-blind placebo control
- 7 day duration of therapy
- Primary efficacy endpoints assessment of NT pro-BNP, weight, biomarkers

### Acute HF Trial Phase 3 Study

- Patients hospitalized with acute heart failure
- Administer in hospital and discharge home on elamipretide
- Opportunity for acute and chronic indications



# Possibili meccanismi nefro/cardioprotettivi degli inibitori di SGLT2.



## Ongoing trials

Drug	Cohort	Primary endpoint
Canagliflozin <sup>a</sup>	Chronic HF	Change from baseline aerobic exercise capacity at 12 weeks Change from baseline ventilator efficiency at 12 weeks
Dapagliflozin <sup>a</sup>	Chronic HF	Time to first occurrence of CV death or hospitalization for HF or urgent HF visit
Empagliflozin <sup>a</sup>	CKD	Time to first occurrence of ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death
	HFpEF	Time to first adjudicated CV death or adjudicated hospitalization for HF
Luseogliflozin	HFrEF CKD	Composite CV death and renal disease progression
Ertugliflozin	N/A	N/A
Sotagliflozin	N/A	N/A

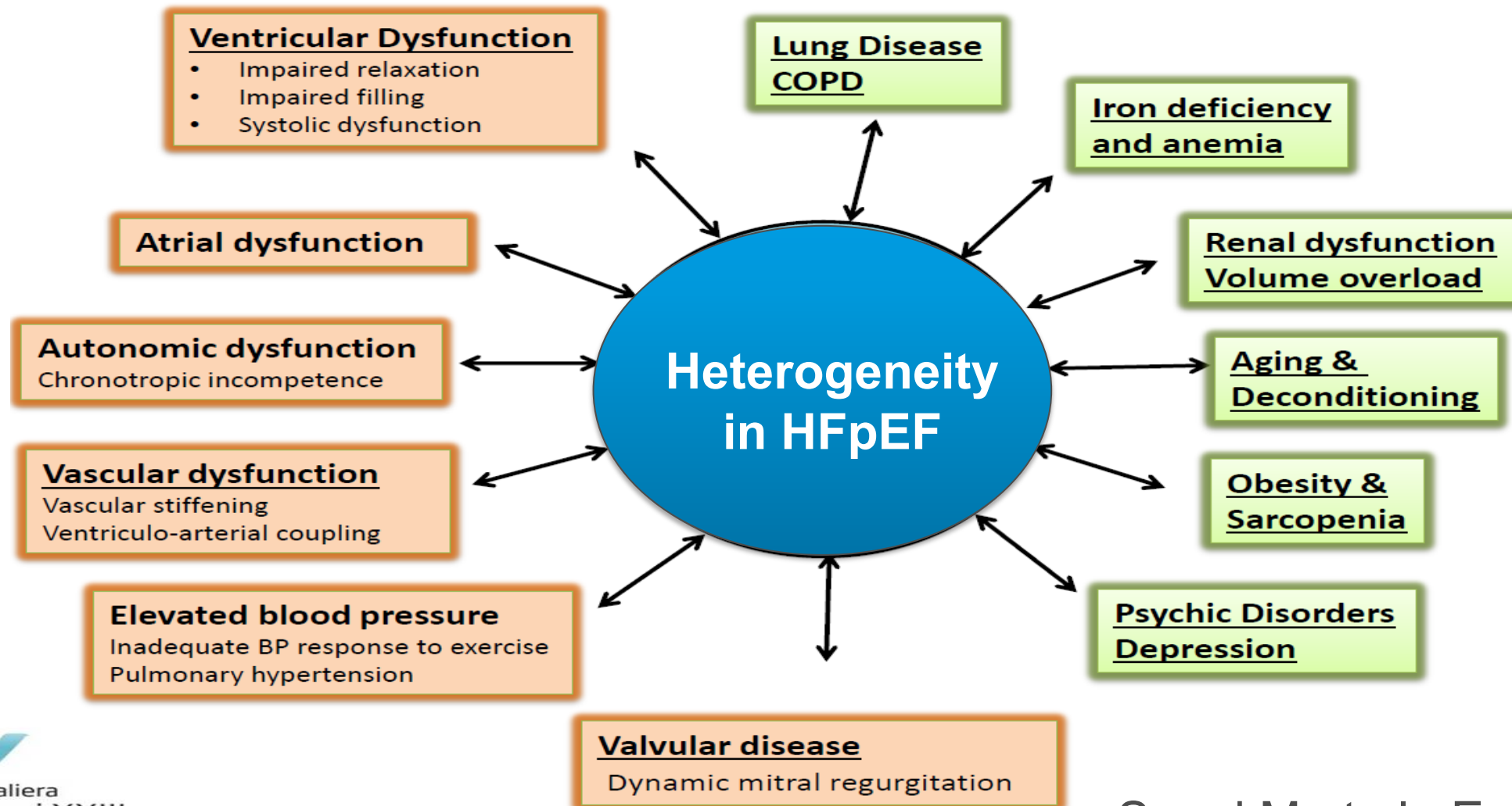
Hiddo J.L. Heerspink et al. Circulation. 2016

Butler J et al. Eur J Heart Fail 2017

# ? Quali sono oggi gli “Unmet clinical needs” piu' importanti in Cardiologia

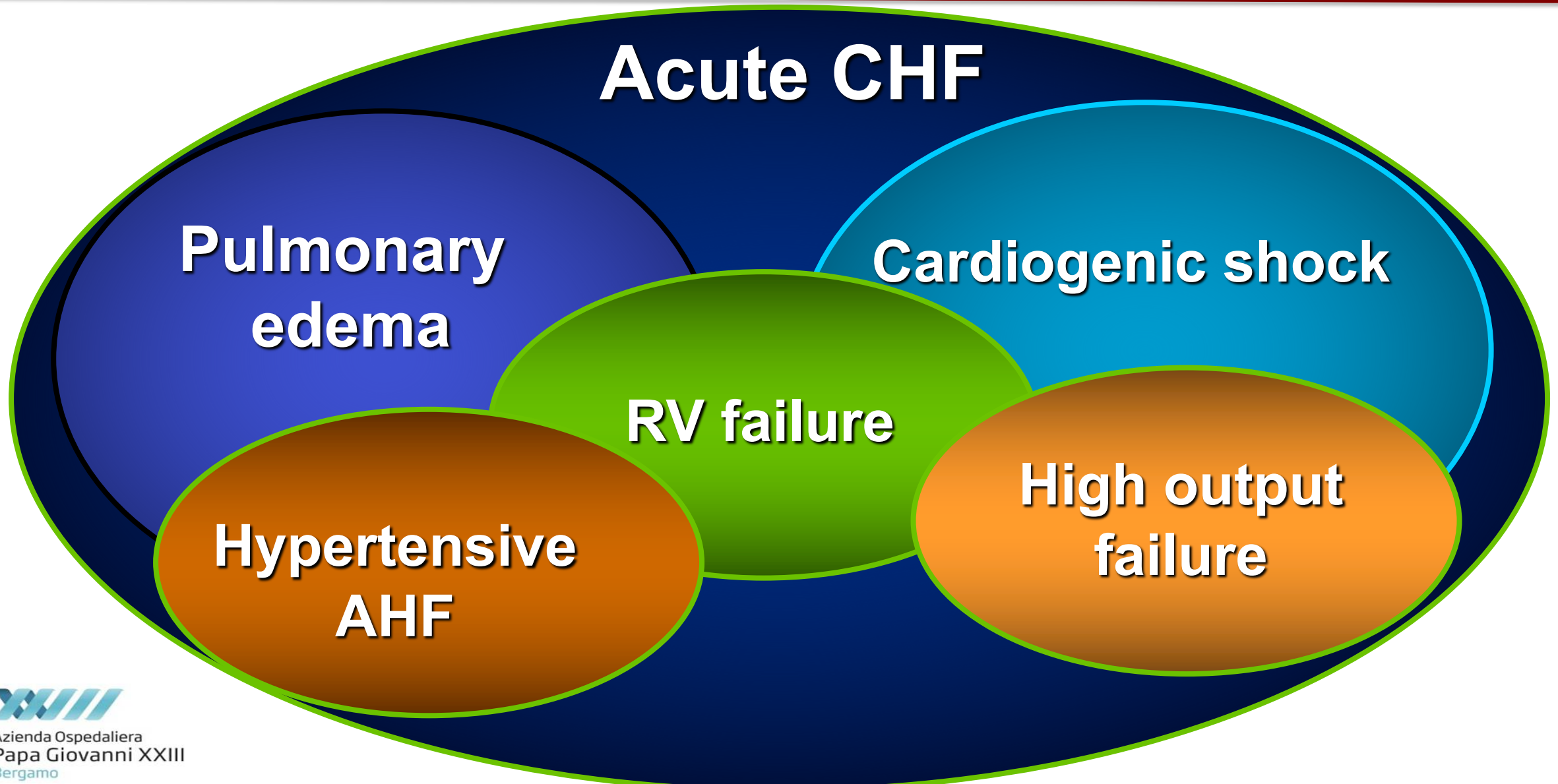
- a. Scompenso Cardiaco a Funzione Sistolica Preservata
- b. Scompenso Cardiaco Acuto

# HFpEF: Fisiopatologia



# Acute CHF

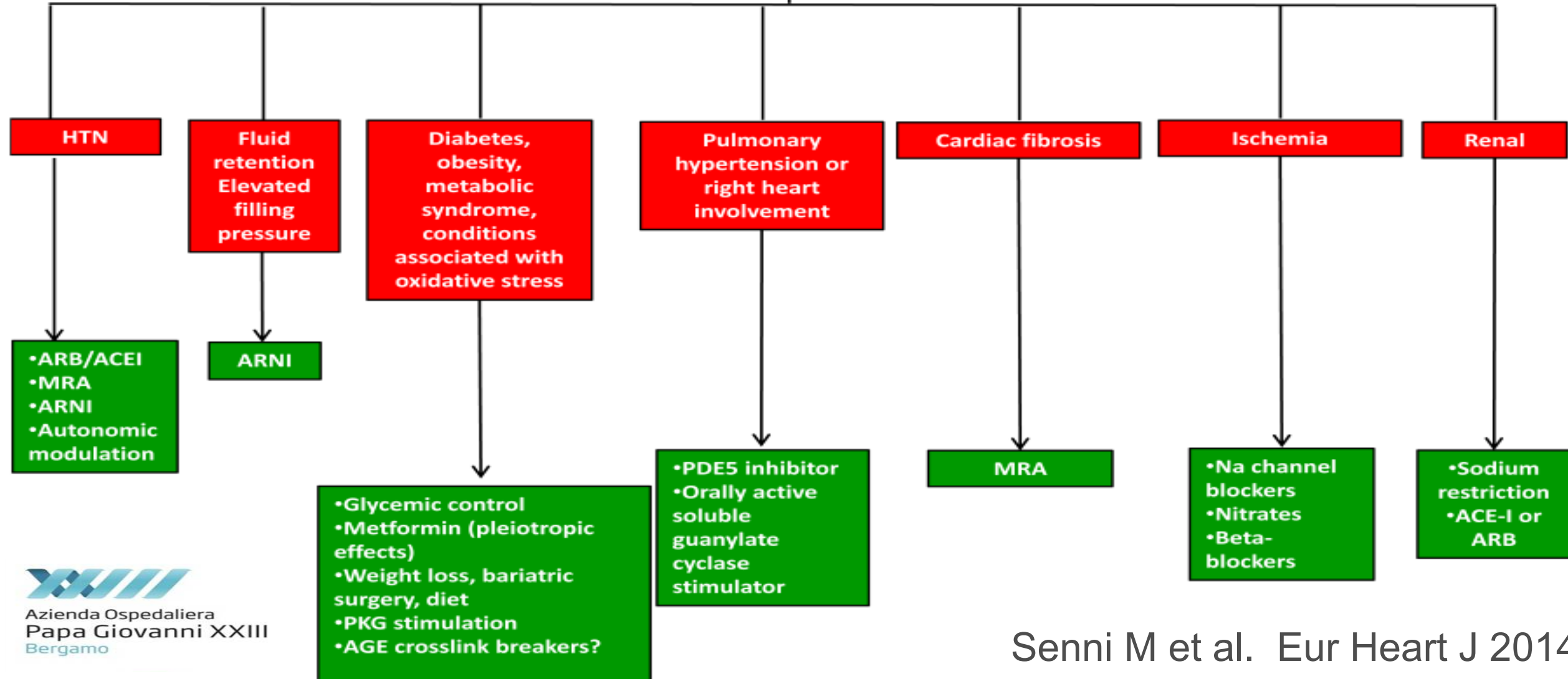
## *Differenti quadri fisiopatologici*



# HFpEF: approccio per fenotipi clinici

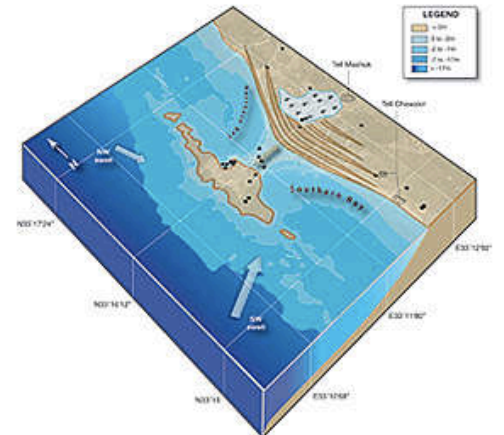
HF signs and symptoms  
Preserved LVEF

Plus Primary Comorbidity(ies)



# Come Alessandro Magno ...

1. Conoscere la natura del posto e le proprie forze
2. “Personalizzare” ogni conquista di città’



# HFpEF e scompenso acuto: quale futuro a medio e lungo termine della terapia medica

Terapia personalizzata sulla base dei fenotipi, conoscendo la fisiopatologia e il meccanismo d'azione dei farmaci, invece dell'approccio "one-pill-fits-all".