TERAPIA DELLO SCOMPENSO CARDIACO:
certezze assodate e nuovi orizzonti

Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

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Direttore
UOC di Cardiologia

Disclosures

Novartis, Bayer, Vifor, Abbot, Astra-Zeneca, Merck

Terapia dello Scompenso Cardiaco

1. Certezze

2. Nuovi orizzonti

Terapia dello Scompenso Cardiaco

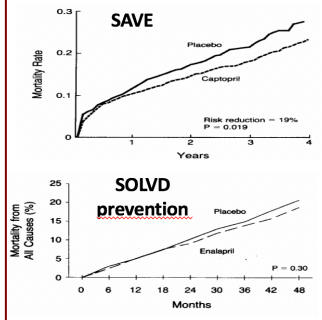
1. Certezze

2. Nuovi orizzonti

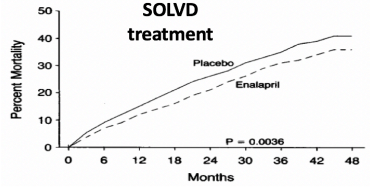
Certezze nella terapia medica dello Scompenso Cardiaco

ACE-inibitori

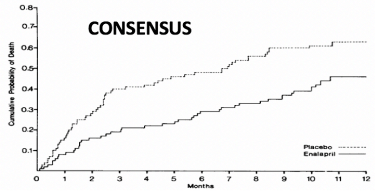
CLASS I



CLASS II-III



CLASS IV



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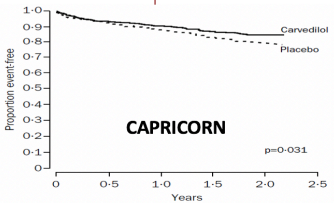
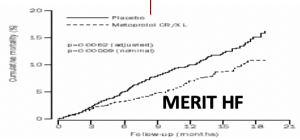
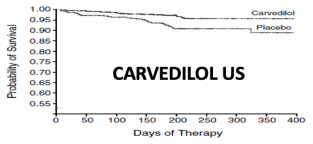
Beta-bloccanti

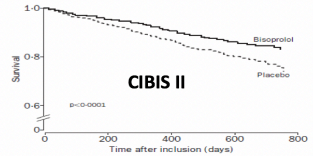
CLASS I



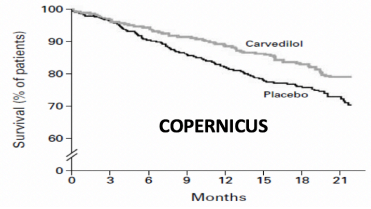
CLASS II-III







CLASS IV



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Antialdosteronici

CLASS I

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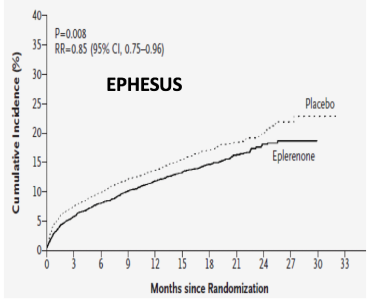
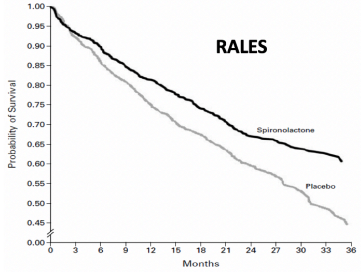
CLASS II



CLASS III-IV



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Ivabradina

CLASS I

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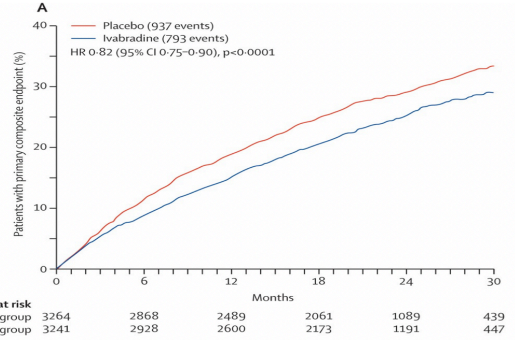
CLASS II-III

SHIFT trial



CLASS IV

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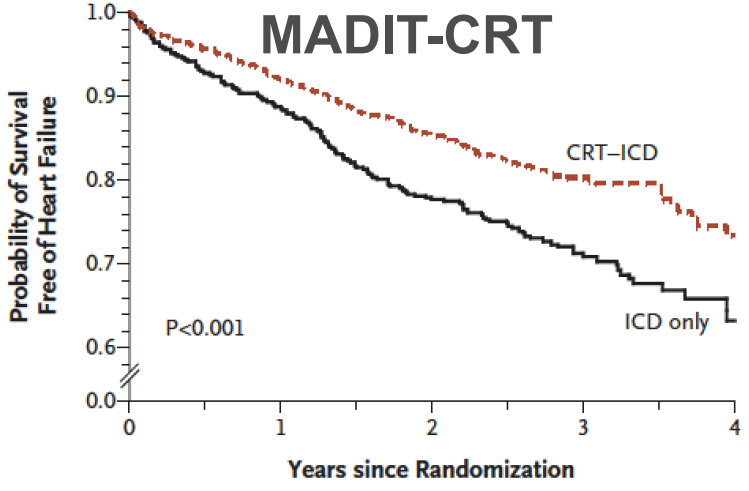
Terapia di resincronizzazione ventricolare

CLASS I-II

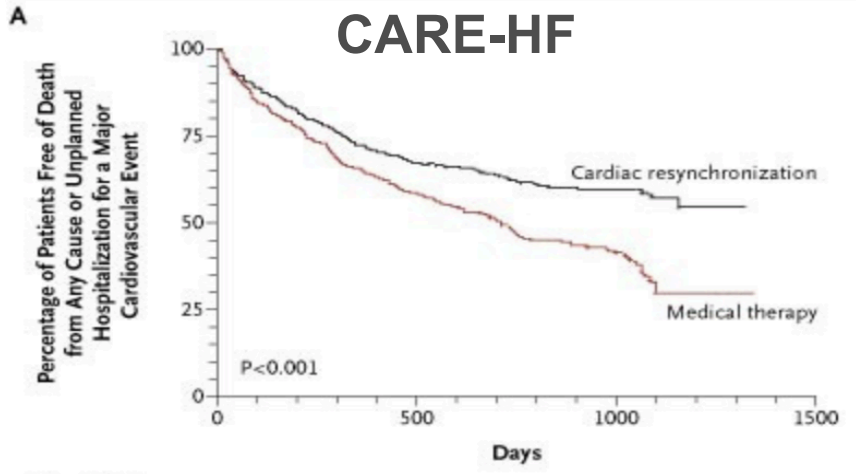
MADIT-CRT



No. at Risk (Probability of Survival)					
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

CLASS III-IV

CARE-HF



No. at Risk						
Cardiac resynchronization	409	323	273	166	68	7
Medical therapy	404	292	232	118	48	3

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Inibitori dell'angiotensina-neprilisina (ARNI)

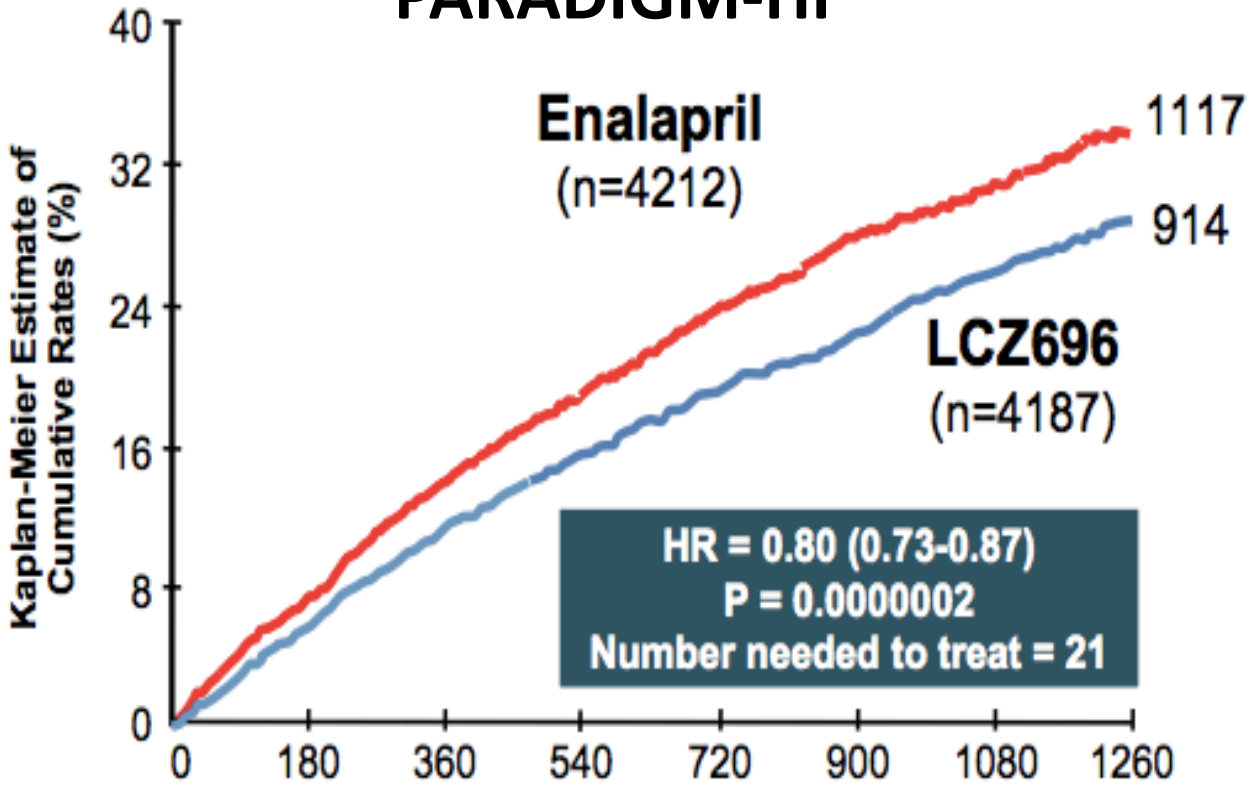
Sacubitril/valsartan: una nuova certezza!

CLASS I

?

CLASS II-III

PARADIGM-HF



CLASS IV

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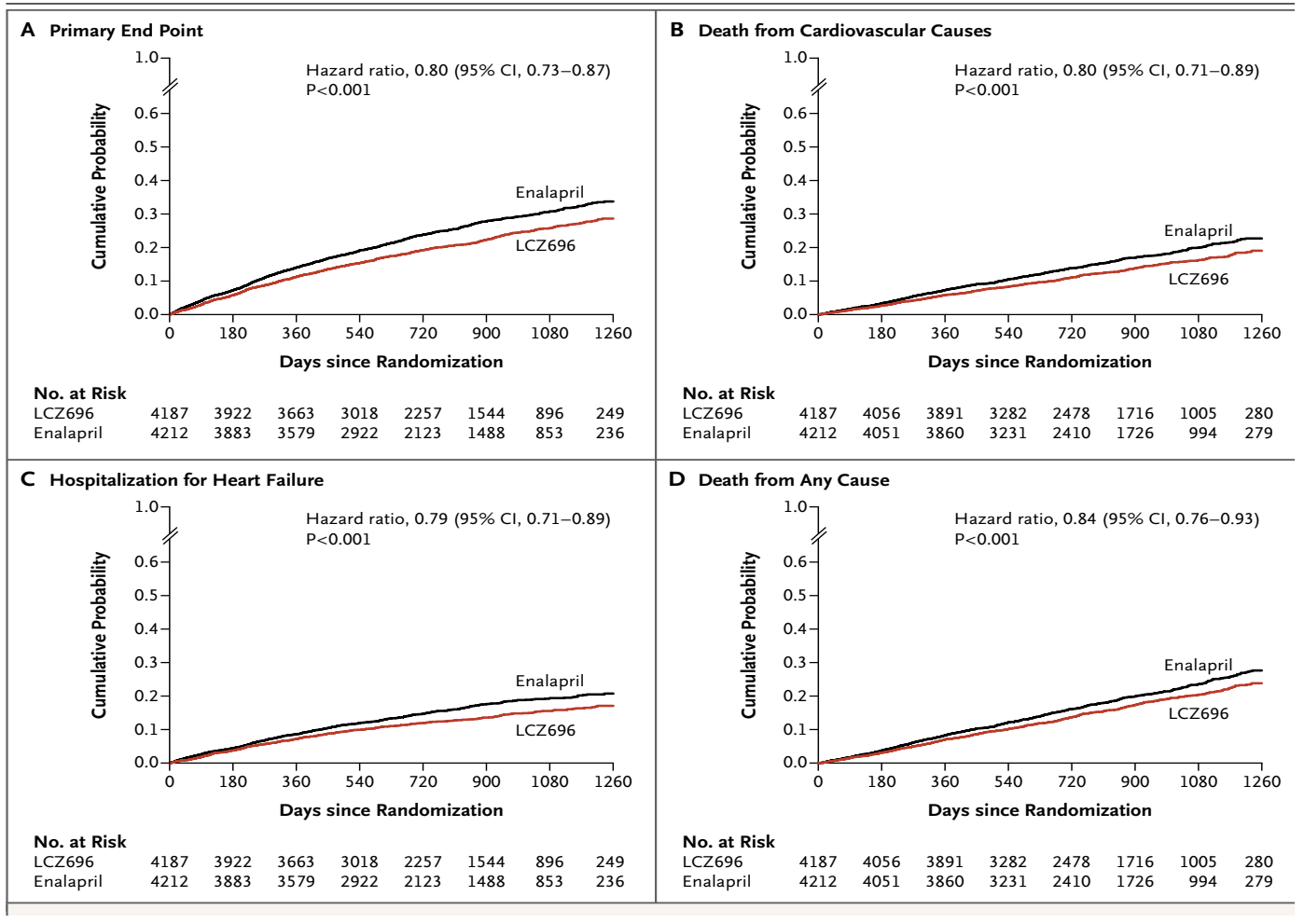
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure



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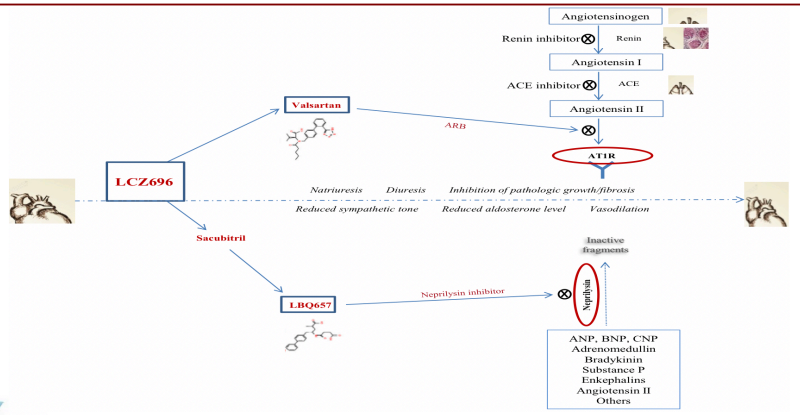
McMurray J et al. NEJM 2014

Sacubitril/valsartan

Sacubitril/Valsartan (LCZ696)
Meccanismo d'azione



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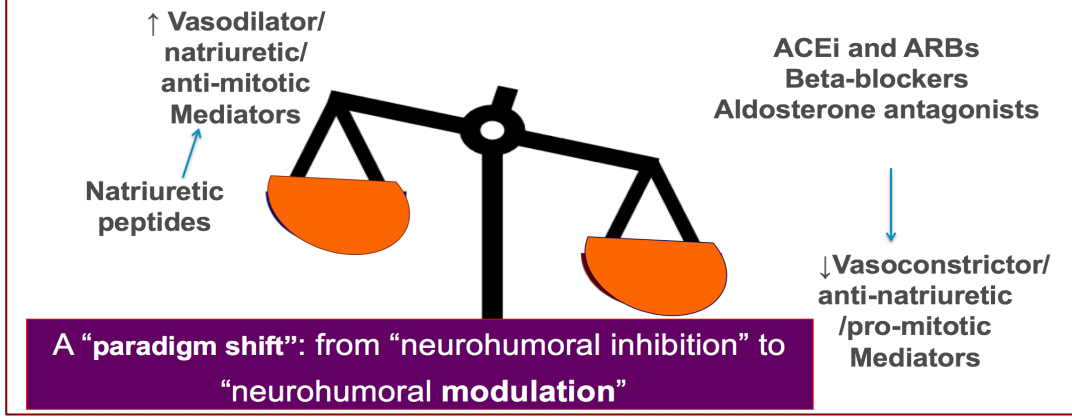
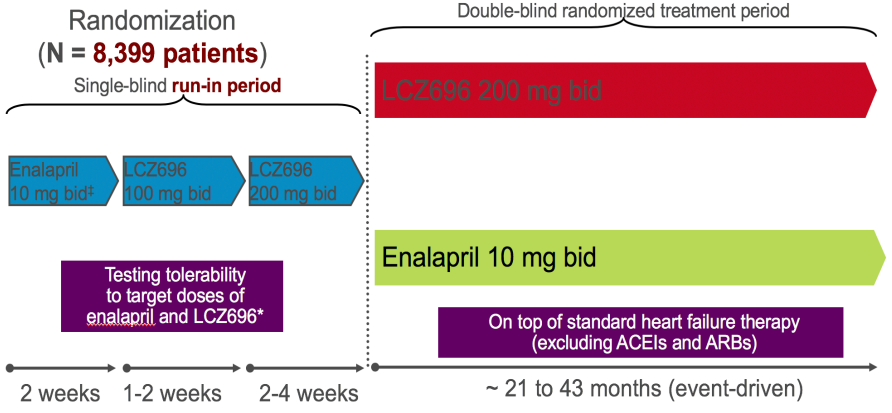
Gori M & Senni M, Exp Rev Cardiovasc Ther 2016

Scompenso cardiaco: "squilibrio neuro-umorale"



A "**paradigm shift**": from "neurohumoral inhibition" to "neurohumoral **modulation**"

PARADIGM-HF disegno dello studio



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McMurray J et al. N Engl J Med 2014

RANDOMIZED CLINICAL TRIALS in HFrEF (N=38) 1988-2014

VAS
ACE
AII R
Ca A
DIG
INOTROPES :

Drugs reducing mortality		
CONSENSUS	enalapril	1987
RALES	spironolactone	1999
CIBIS-2	bisoprolol	1999
PARADIGM	**LCZ696**	**2014**

PROMISE, VEST, PRIME II

PARADIGM first trial proposing a substitution rather than an "add-on" strategy in HFrEF patients.

COPERNICUS, CAPRICORN

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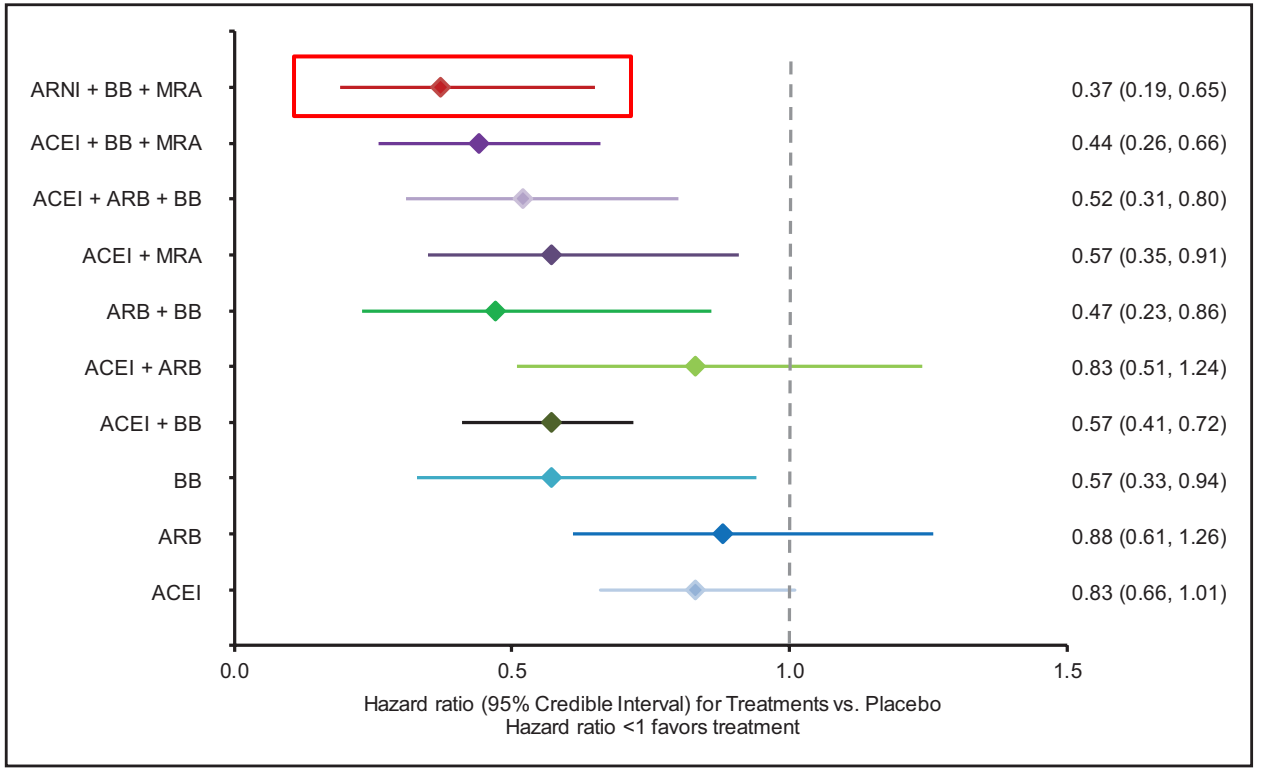
Sacubitril/valsartan

? Che cosa abbiamo imparato di importante negli ultimi quattro anni e mezzo

Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction

A Network Meta-Analysis

Heather Burnett, MSc; Amy Earley, BSc; Adriaan A. Voors, MD, PhD; Michele Senni, MD; John J.V. McMurray, MD; Celine Deschaseaux, MSc; Shannon Cope, MSc



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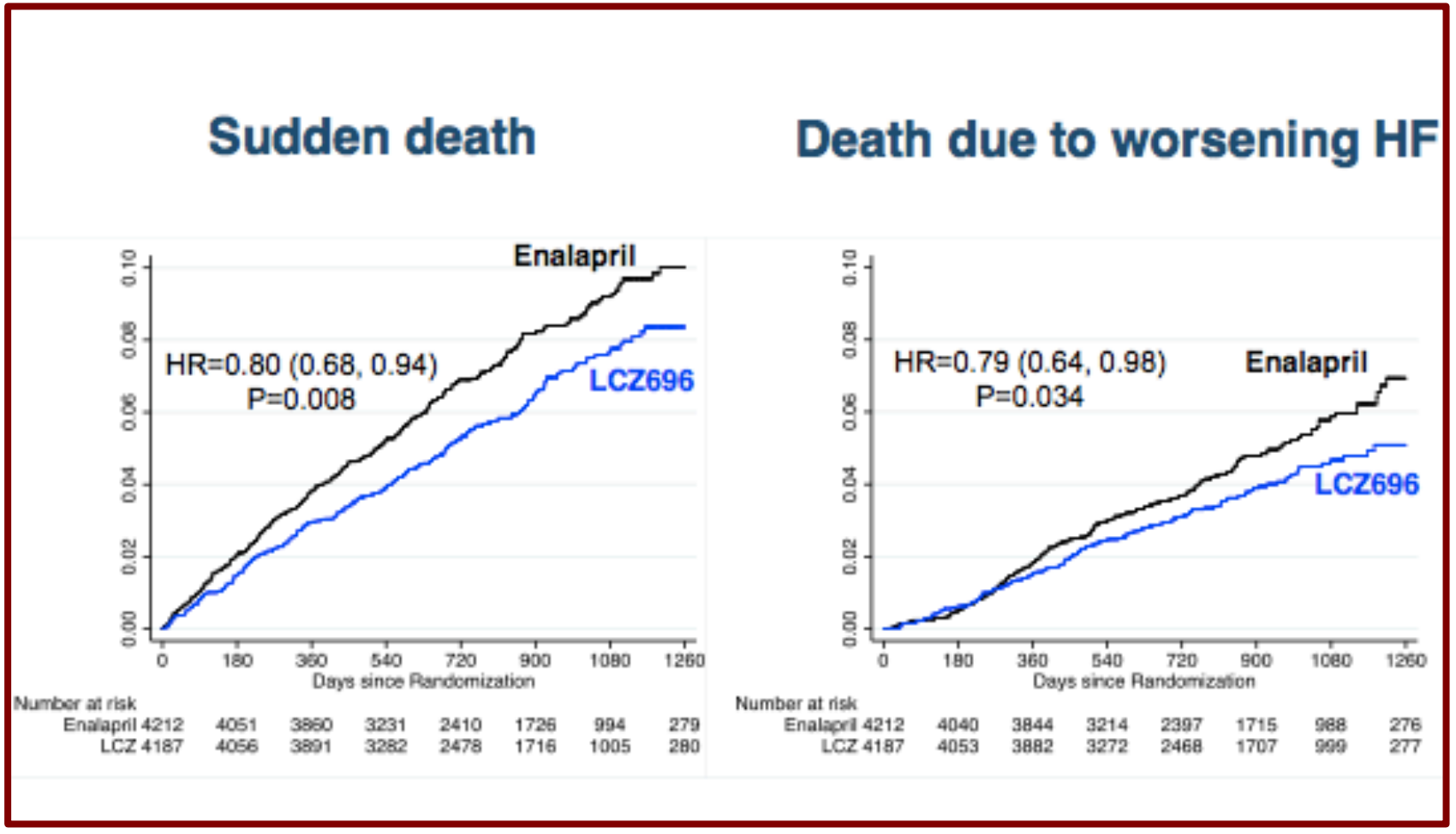
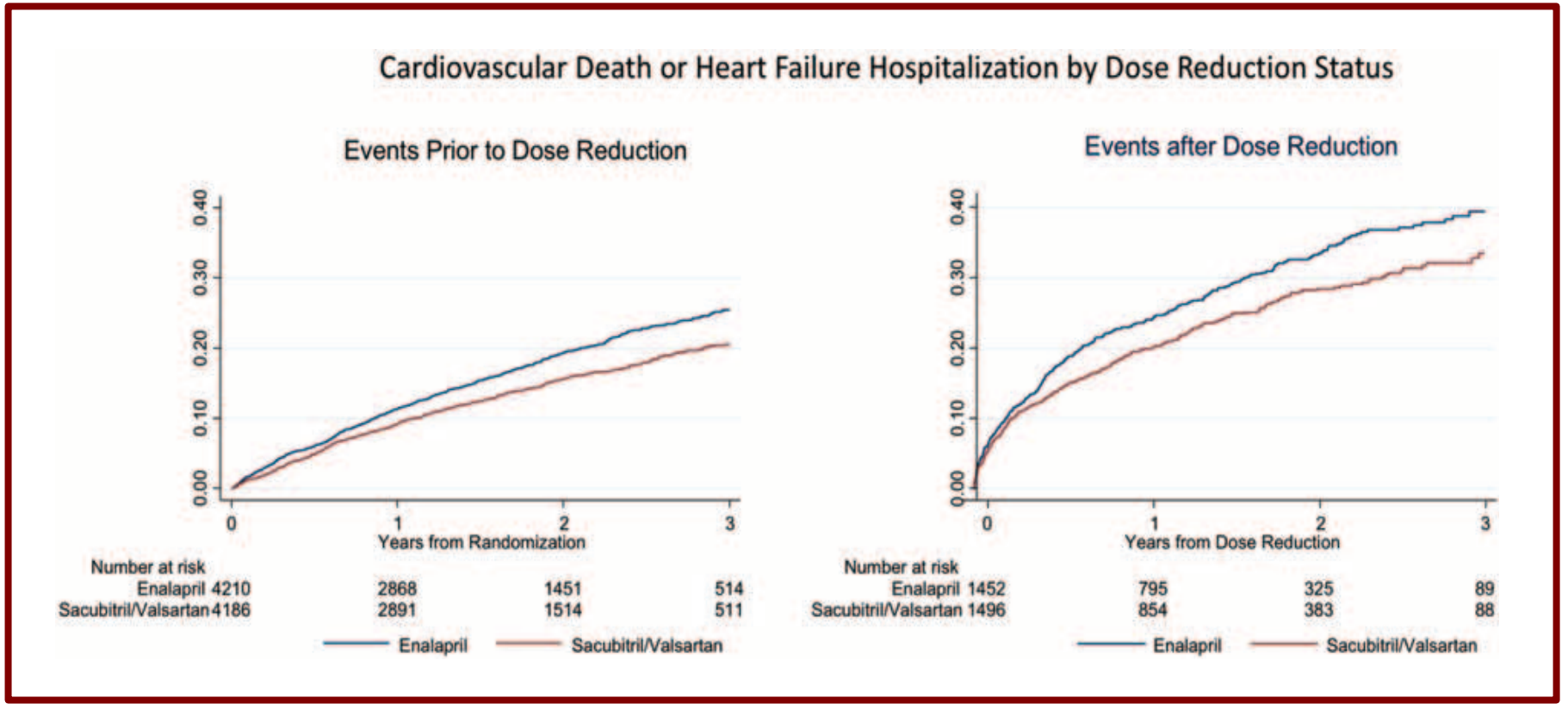
Circul HF 2017

Effetti sulla causa di morte



Desay AS et al. Eur Heart J 2015

E’ importante raggiungere e mantenere la dose target



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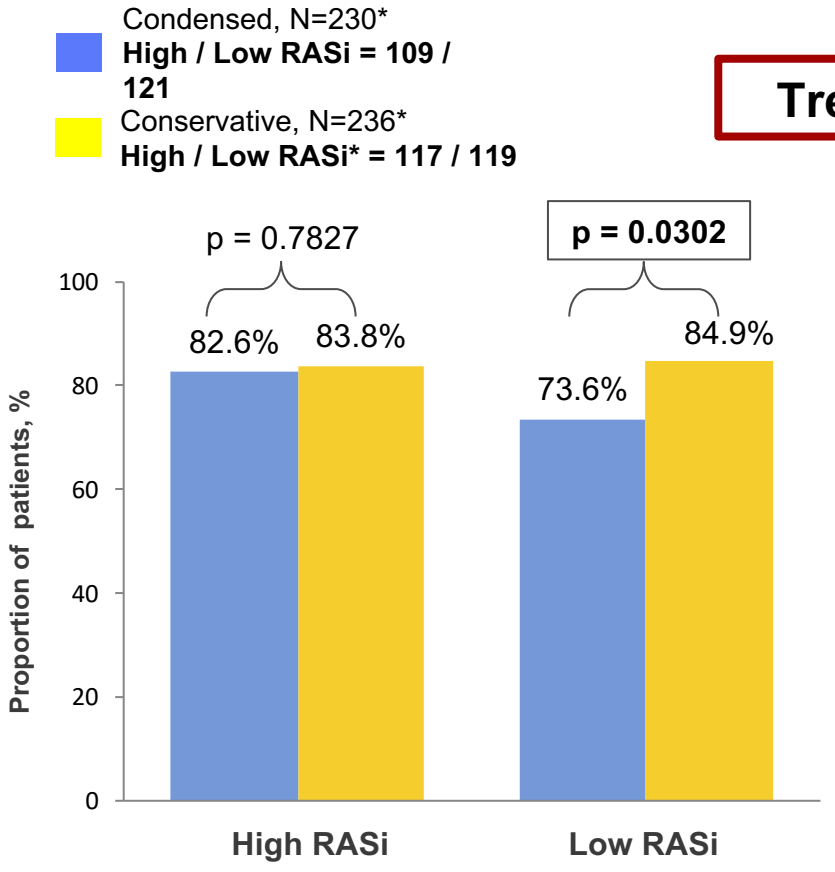
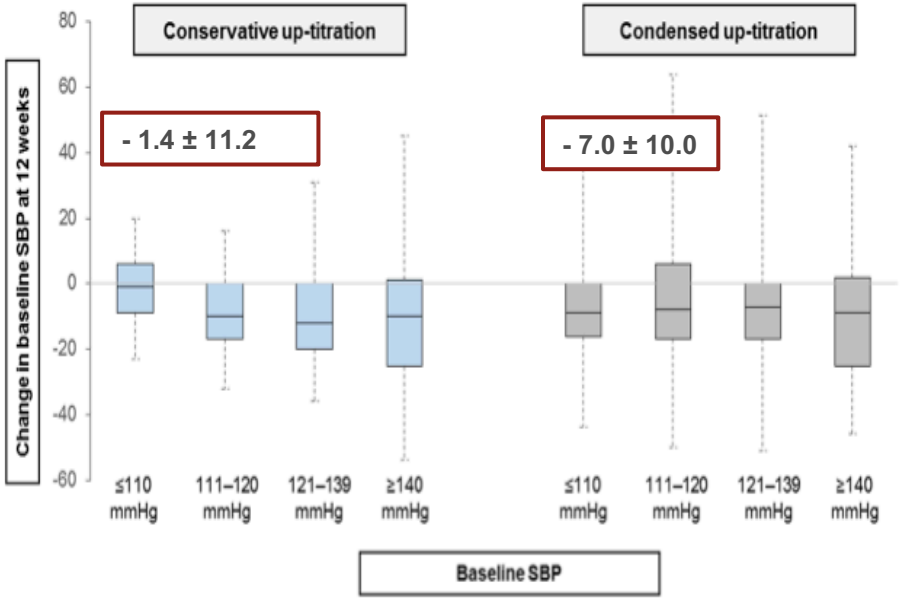
Vardeny O et al. Eur J Heart Fail 2016

Titration trial



Treatment success 80%



Senni M et al. Eur J Heart Fail 2016

Senni M et al. Eur J Heart Fail 2017

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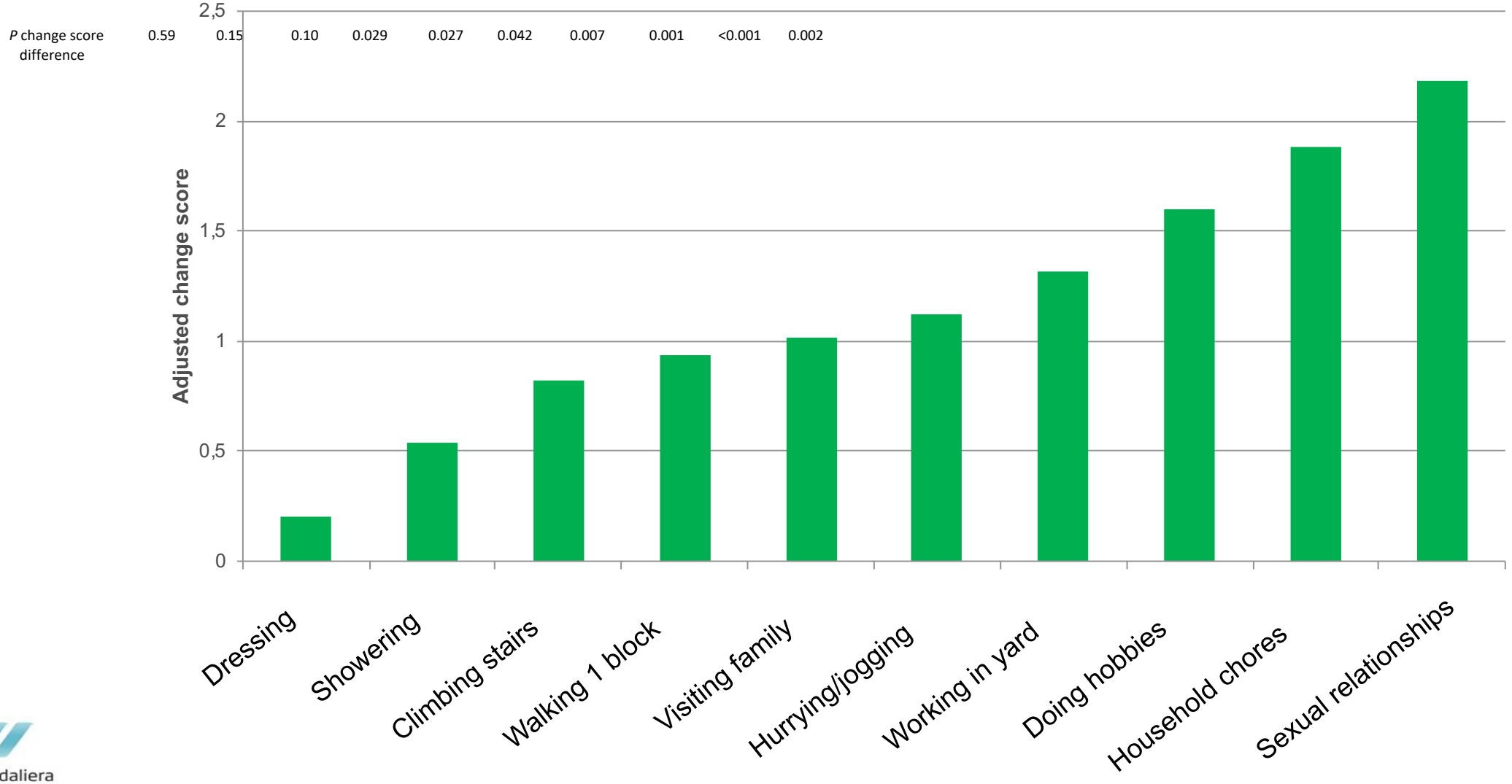
Cambiamenti della Qualita' della vita KCCQ

Differenze tra sacubitril/valsartan and enalapril



Chandra A et al. JAMA Cardiol 2018

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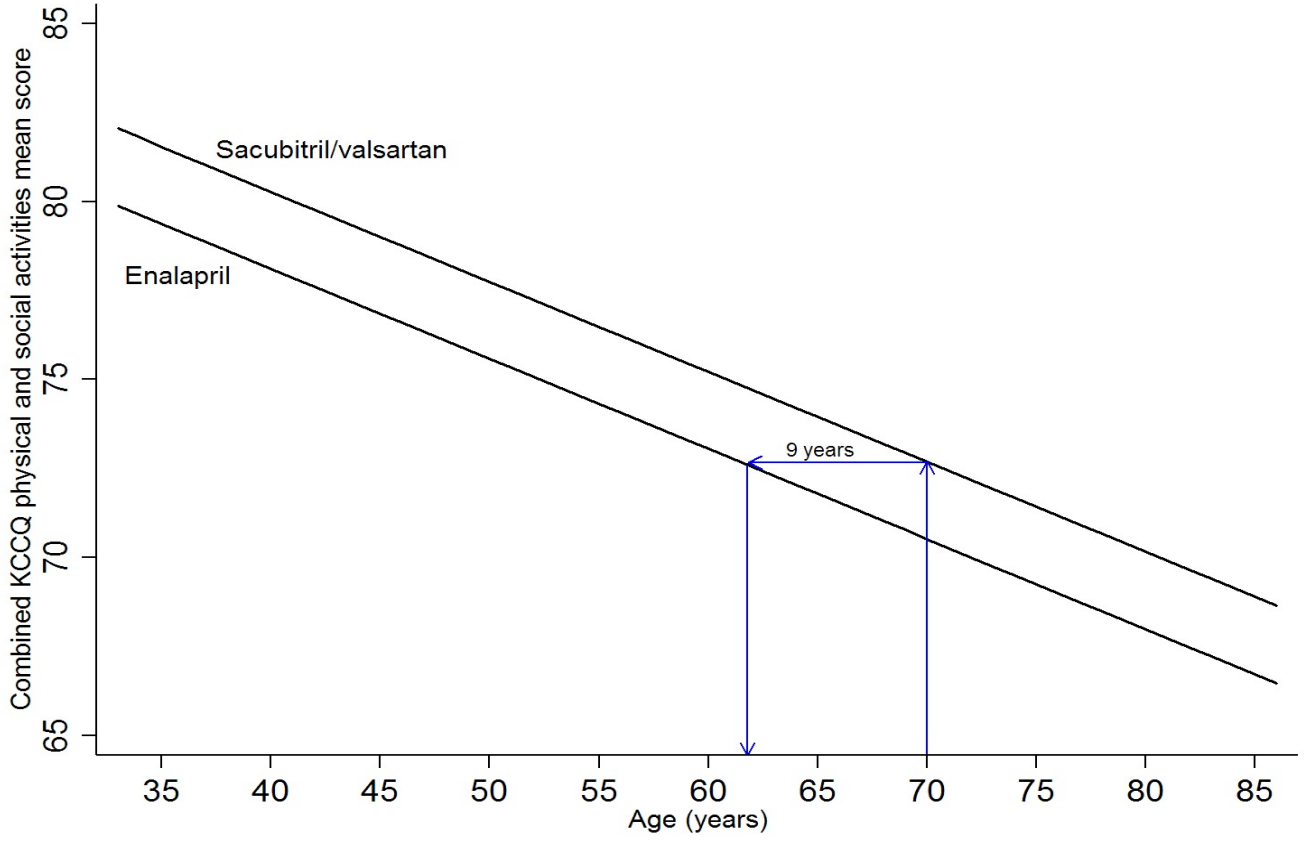
Relationship between Age and Physical and Social Activities and Effect of Sacubitril/Valsartan

Randomization to Sacubitril/Valsartan Equivalent to Approximately 9 Years of age



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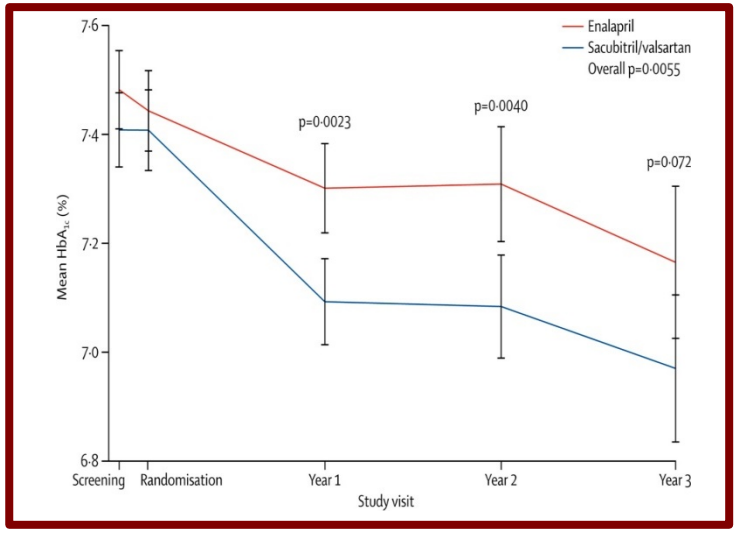
Chandra A et al. JAMA Cardiol 2018

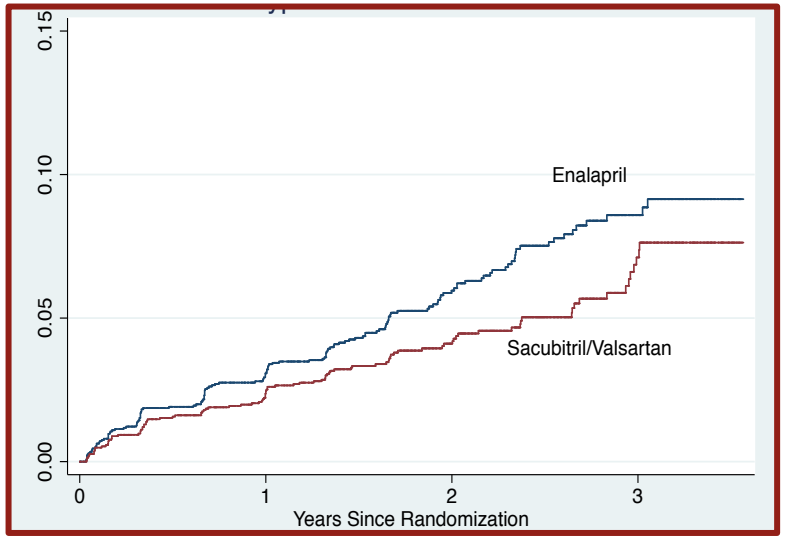
Sac/Vals e comorbilita’

Glycaemic control



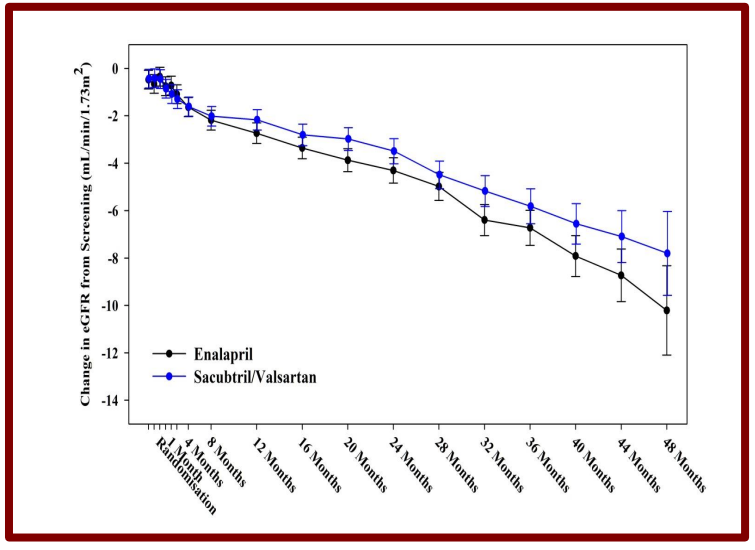
Seferovic JP et al. The Lancet Diabetes & Endocrinology 2017

Incidence of hyperkalaemia



Desai AS et al. JAMA Cardiol 2017

Change in eGFR



Damman K et al. JACC HF 2018

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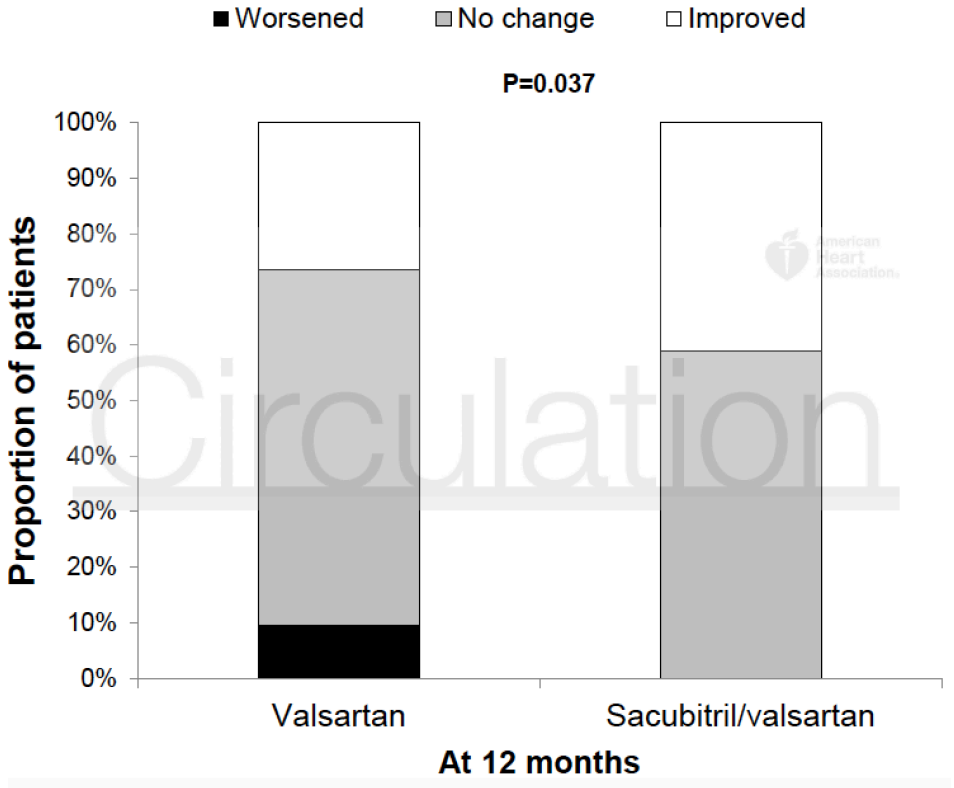
PRIME study:
Effetti del sacubitril/valsartan sull'insufficienza mitralica e sul ventricolo sx

Outcome	Change			
	Valsartan	Sacubitril/ valsartan	Difference (95%CI)	P value*
	n=53	n=51		
Primary endpoint				
EROA of MR – cm^2	-0.030±0.096	-0.077±0.080	-0.047 (-0.081 to -0.013)	0.008
Secondary endpoint				
Regurgitant volume – ml	-5.8±14.6	-14.1±13.0	-8.3 (-13.6 to -2.9)	0.003
End-systolic volume – ml	-12.9±29.9	-17.7±26.2	-4.7 (-15.5 to 6.1)	0.40
ESVI – ml/m^2	-7.0±16.5	-10.8±15.0	-3.7 (-9.9 to 2.4)	0.23
End-diastolic volume – ml	-11.7±35.1	-22.0±30.4	-10.3 (-22.9 to 2.2)	0.11
EDVI – ml/m^2	-6.3±19.6	-13.3±17.5	-7.07 (-14.30 to 0.16)	0.055
ILCA – cm^2	-0.20±0.41	-0.26±0.32	-0.06 (-0.20 to -0.09)	0.58



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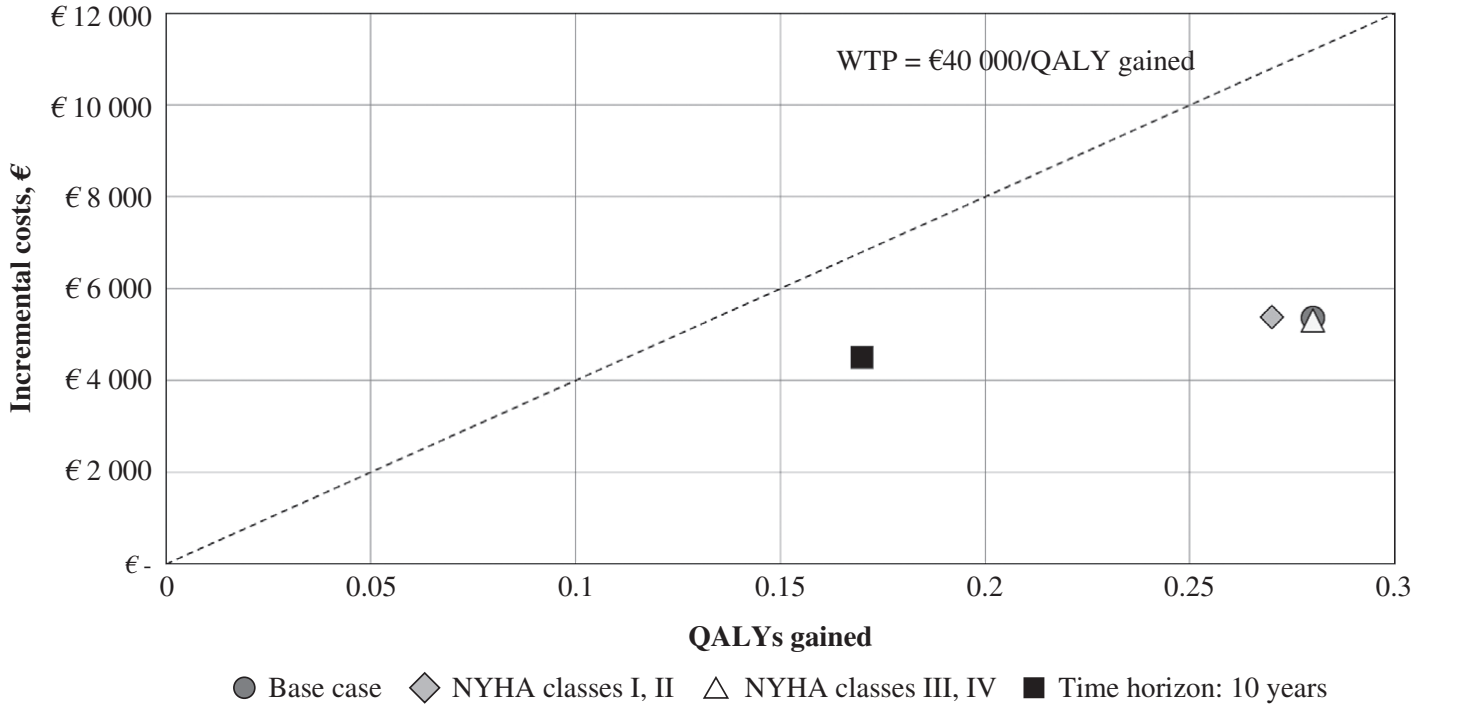
Kang D-H et al. Circulation 2019

Costo-efficacia del sac/val in Italia



Sac/vals had an Incremental Cost to Effectiveness Ratio (ICER) of € 19.487 per Quality- Adjusted Life Years (QUALY) gained, which is below the usually accepted willingness-pay (WTP) threshold of € 40.000 QUALY gained

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Angiolella LS … Senni M Eur J Heart Fail 2017

PARADIGM-HF trial fantastico ma …

- SC acuto
- Run-in
- De-novo

TRANSITION study design

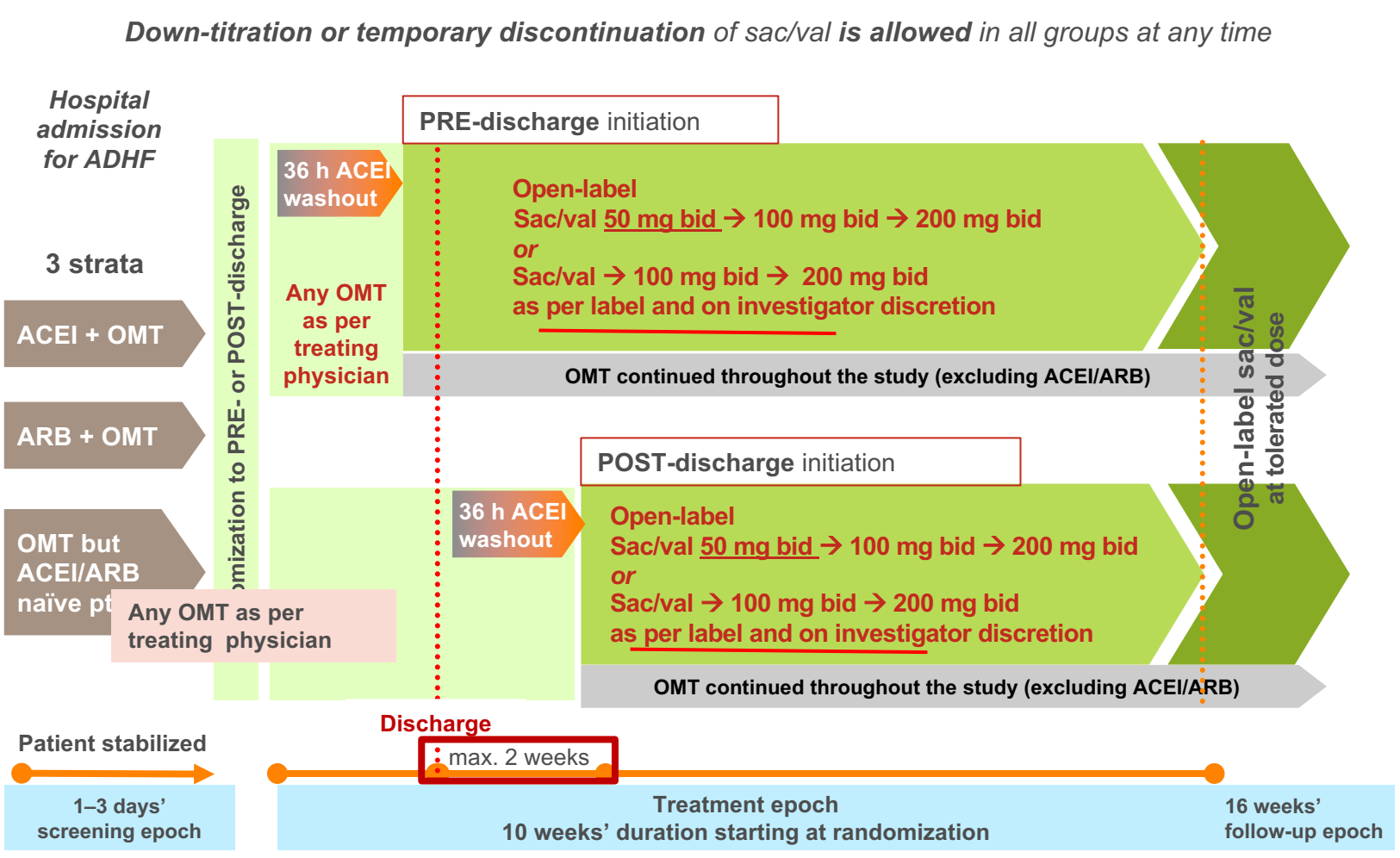
993 patients

EF≤40%

BP ≥110 mmHg

Stable therapy

(oral diuretics from 24h)



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Pascual-Figal et al. ESC Heart Fail 2018;5(2):327–368

TRANSITION:
Primary and secondary endpoints

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Wachter R, Senni M et al. Presented at ESC Congress 2018, Munich Germany

PIONEER-HF

Study design

881 patients

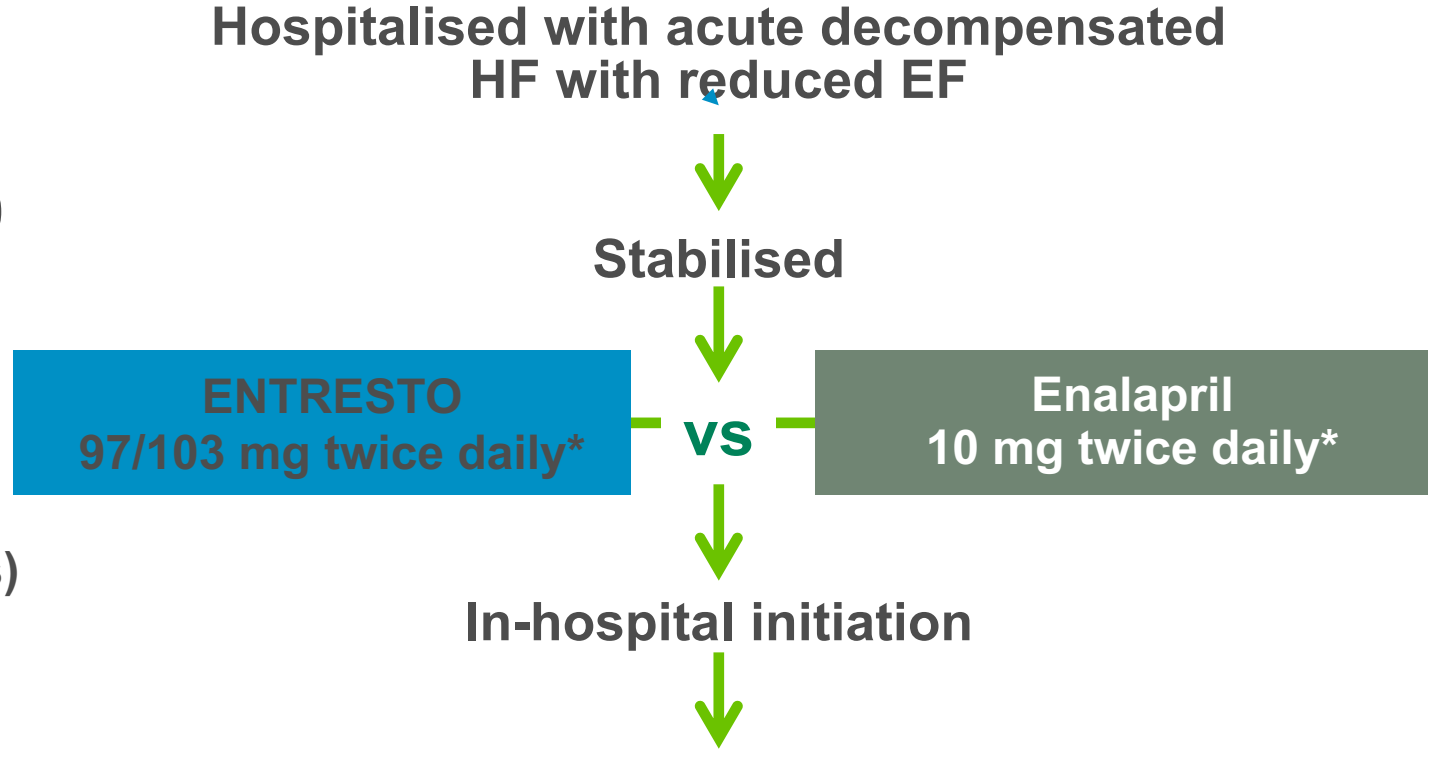
NTproBNP >1600

EF≤40%

BP ≥100 mmHg

Stable therapy

(including i.v. diuretics)



Study drug for 8 weeks

Evaluate biomarker surrogates of efficacy

Evaluate safety and tolerability

Explore clinical outcomes

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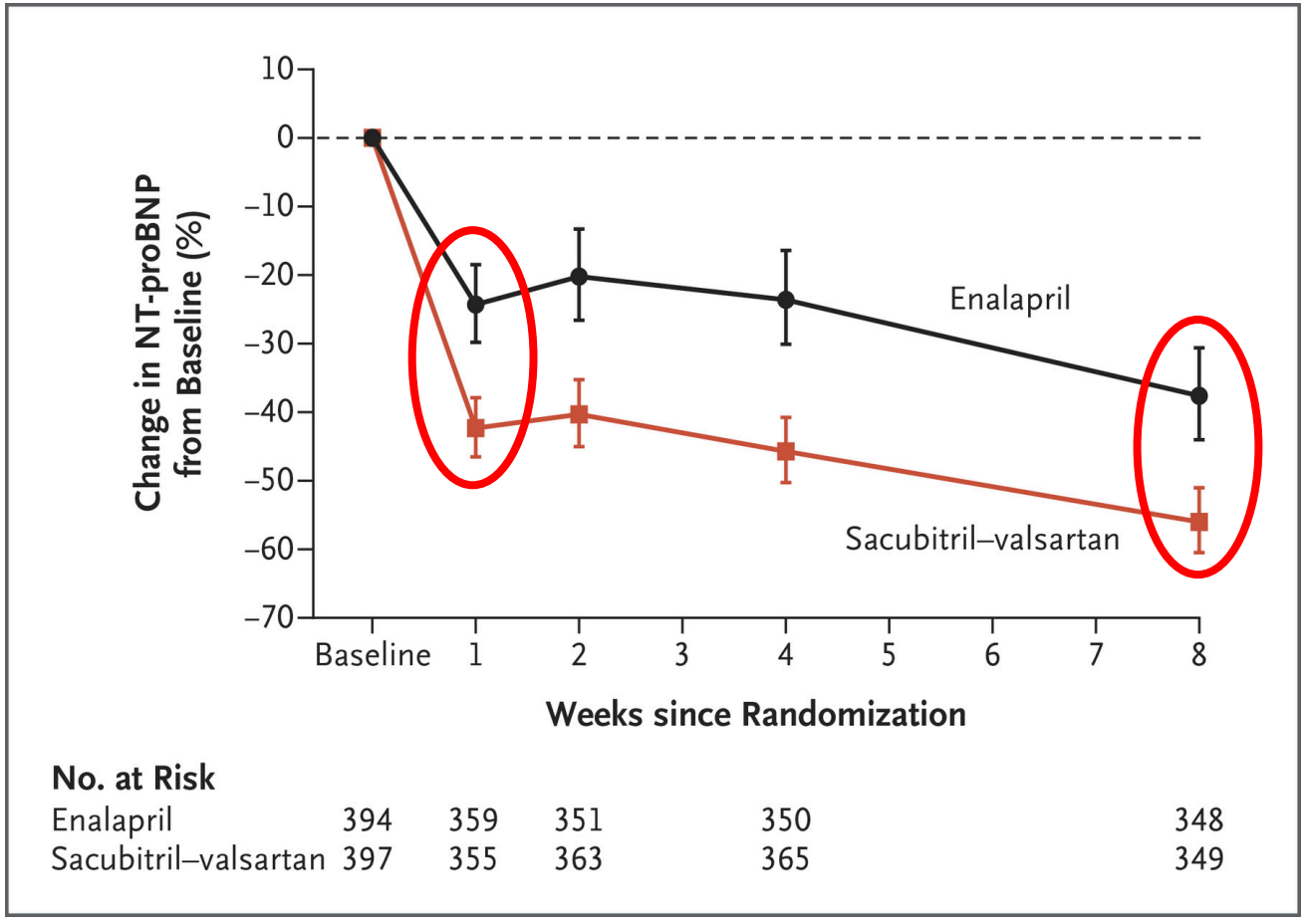
Valazquez EJ et al. NEJM 2018

PIONEER-HF

Primary endpoint: Changes in NTproBNP concentration



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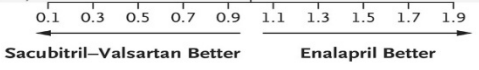
Valazquez EJ et al. NEJM 2018

PIONEER-HF
Subgroup analysis of changes in NTproBNP level

Subgroup	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Ratio of Change in NT-proBNP with Sacubitril–Valsartan vs. Enalapril (95% CI)	P Value for Interaction
	no. of patients (ratio of NT-proBNP at weeks 4 and 8 vs. baseline)			
All patients	379 (0.53)	374 (0.75)	0.71 (0.63–0.81)	
Age				0.76
<65 yr	229 (0.50)	202 (0.68)	0.73 (0.61–0.87)	
≥65 yr	150 (0.61)	172 (0.82)	0.74 (0.63–0.87)	
Sex				0.61
Male	289 (0.55)	265 (0.78)	0.70 (0.60–0.80)	
Female	90 (0.50)	109 (0.66)	0.75 (0.59–0.95)	
Race				0.13
White	226 (0.50)	219 (0.74)	0.68 (0.58–0.80)	
Black	133 (0.56)	129 (0.78)	0.72 (0.57–0.89)	
Other	20 (0.82)	26 (0.70)	1.17 (0.72–1.91)	
Previous heart failure				0.40
No	130 (0.37)	148 (0.56)	0.65 (0.53–0.81)	
Yes	249 (0.65)	225 (0.90)	0.72 (0.63–0.83)	
Previous hypertension				0.62
No	50 (0.42)	64 (0.63)	0.66 (0.49–0.90)	
Yes	329 (0.55)	309 (0.77)	0.72 (0.63–0.82)	
Previous atrial fibrillation				0.32
No	251 (0.49)	230 (0.71)	0.70 (0.60–0.81)	
Yes	127 (0.62)	140 (0.79)	0.79 (0.64–0.96)	
Previous use of ACE inhibitor or ARB				0.98
No	209 (0.48)	196 (0.66)	0.72 (0.60–0.86)	
Yes	170 (0.61)	178 (0.85)	0.72 (0.61–0.85)	
Systolic blood pressure at randomization				0.93
≤118 mm Hg	188 (0.60)	185 (0.84)	0.71 (0.60–0.84)	
>118 mm Hg	191 (0.48)	189 (0.67)	0.72 (0.60–0.86)	
Left ventricular ejection fraction at screening				0.37
≤25%	246 (0.51)	243 (0.74)	0.69 (0.59–0.80)	
>25%	132 (0.59)	131 (0.76)	0.77 (0.63–0.95)	
Estimated GFR at randomization				0.81
<60 ml/min/1.73 m^2	194 (0.55)	192 (0.76)	0.73 (0.61–0.87)	
≥60 ml/min/1.73 m^2	181 (0.51)	177 (0.72)	0.70 (0.59–0.84)	
NT-proBNP concentration at randomization				0.30
≤2701 pg/ml	180 (0.63)	200 (0.93)	0.67 (0.57–0.80)	
>2701 pg/ml	199 (0.45)	174 (0.60)	0.76 (0.63–0.90)	
NYHA class at randomization				0.48
I or II	90 (0.52)	112 (0.78)	0.67 (0.53–0.84)	
III or IV	278 (0.54)	258 (0.73)	0.73 (0.63–0.85)	
Time from presentation to randomization				0.66
≤67.7 hr	192 (0.52)	186 (0.71)	0.74 (0.62–0.87)	
>67.7 hr	186 (0.54)	188 (0.79)	0.69 (0.58–0.83)	



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Bergamo

Valazquez EJ et al. NEJM 2018

PIONEER-HF

Secondary endpoints: efficacy

Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

Valazquez EJ et al. NEJM 2018

PIONEER-HF

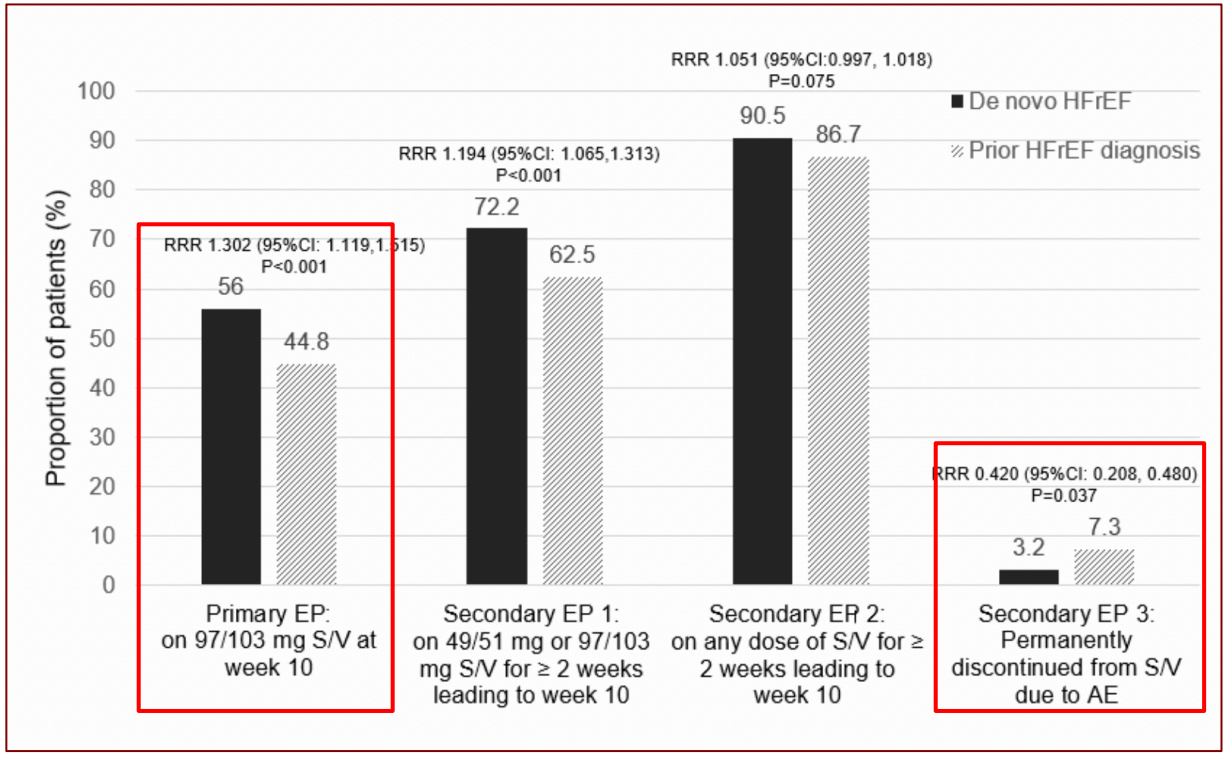
Secondary endpoints: safety

Permanent discontinuations	Sacubitril/Valsartan	Enalapril
	51 (11.5%)	45 (10.1%)

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)

Valazquez EJ et al. NEJM 2018

Pazienti De-novo nel TRANSITION trial



Event	*De novo* HFrEF (N=286) n (%)	Previous diagnosis of HFrEF (N=705) n (%)	P-value
At least one AE	178 (62.2)	478 (67.8)	0.103
Selected AEs of interest			
Hyperkalemia	24 (8.4)	85 (12.1)	0.116
Hypotension	26 (9.1)	108 (10.9)	0.263
Cardiac failure	13 (4.5)	58 (8.2)	0.042
Renal failure	3 (1.0)	16 (2.3)	0.306
Blood creatinine increased	3 (1.0)	26 (3.7)	0.023
Renal impairment	8 (2.8)	32 (4.5)	0.284
At least one serious AE	33 (11.5)	130 (18.4)	0.008
Death	1 (0.3)	5 (0.7)	0.679
Temporary treatment interruption due to AE	22 (7.7)	87 (12.3)	0.034

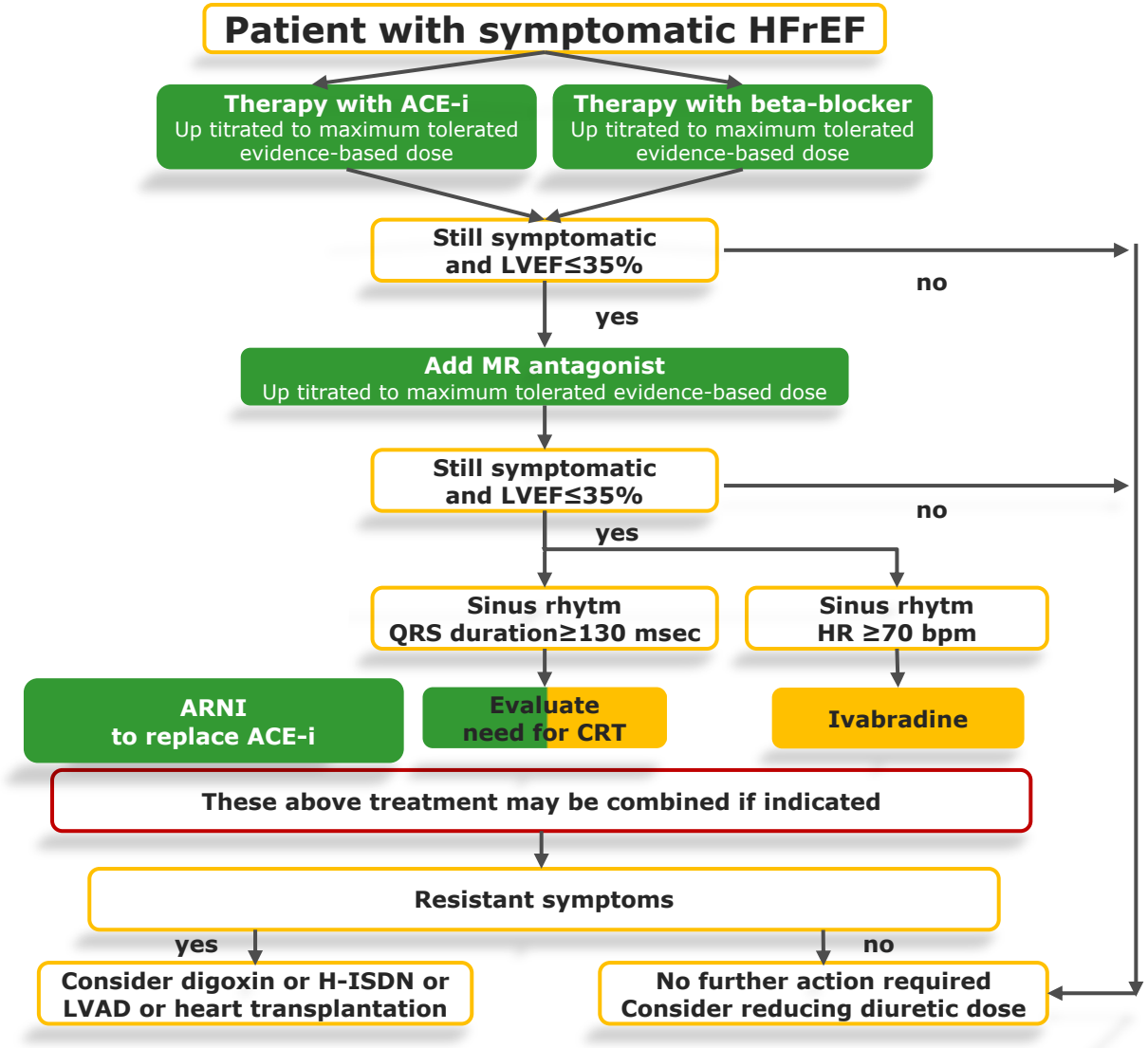
Senni M et al. (submitted)

ESC Guidelines

Therapeutic algorithm for a patient with symptomatic HFrEF

Diuretics to relieve symptoms and sign of congestion

If LVEF≤35% or a history of VT/VF, implant ICD



CLASS I

CLASS IIa

Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Ponikowski et al. Eur J Heart Fail 2016

Prima linea di trattamento dello SC: Caratteristiche

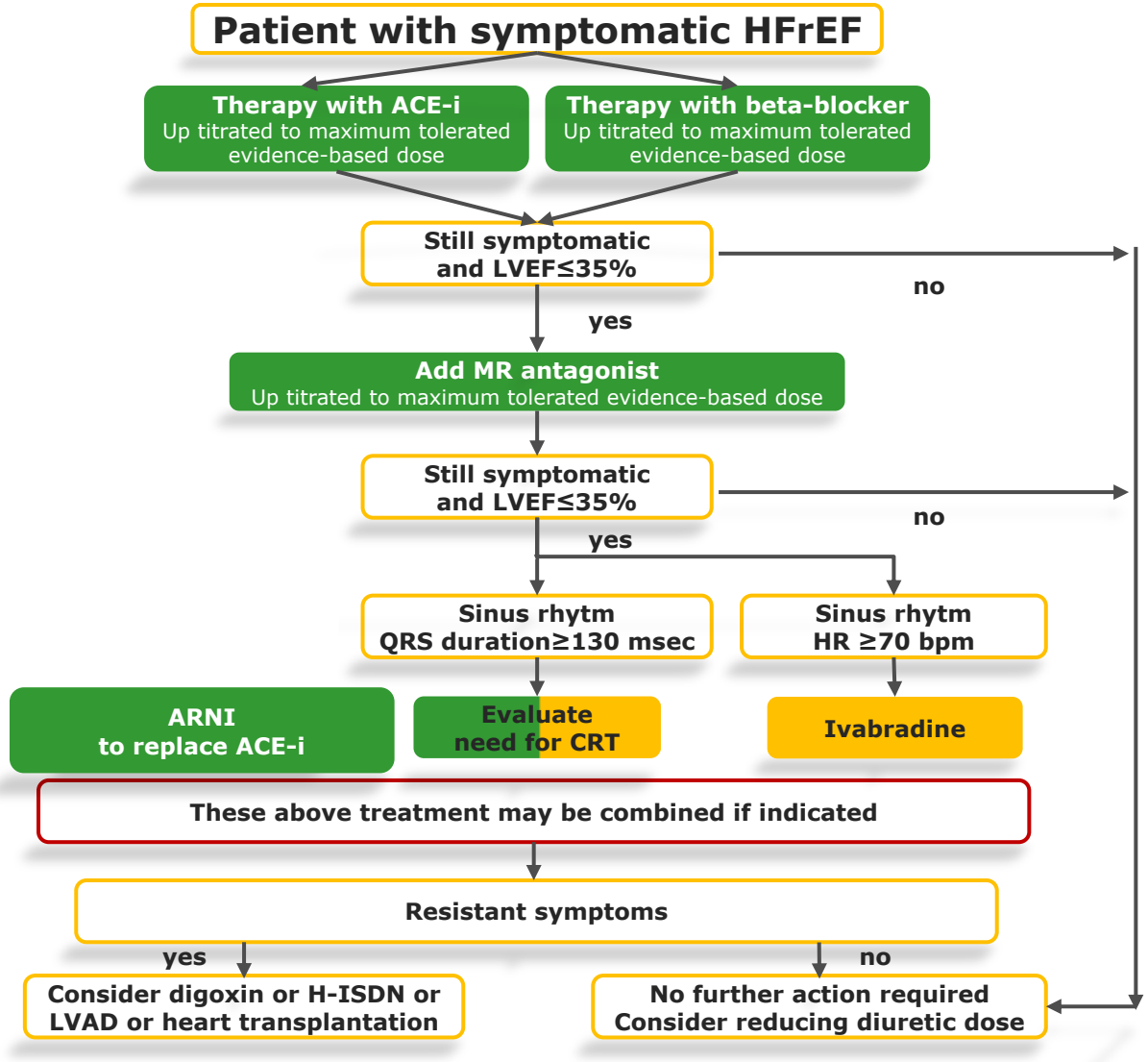
- Requisiti Classe I and livello di evidenza A
- Corretto comparatore
- Miglioramento della Qualita' della vita
- Ridotti eventi avversi seri
- Facilitare l'uso di terapia «certe»
- Utilizzo nei pazienti de-novo

ESC Guidelines

Therapeutic algorithm for a patient with symptomatic HFrEF

Diuretics to relieve symptoms and sign of congestion

If LVEF≤35% or a history of VT/VF, implant ICD



CLASS I

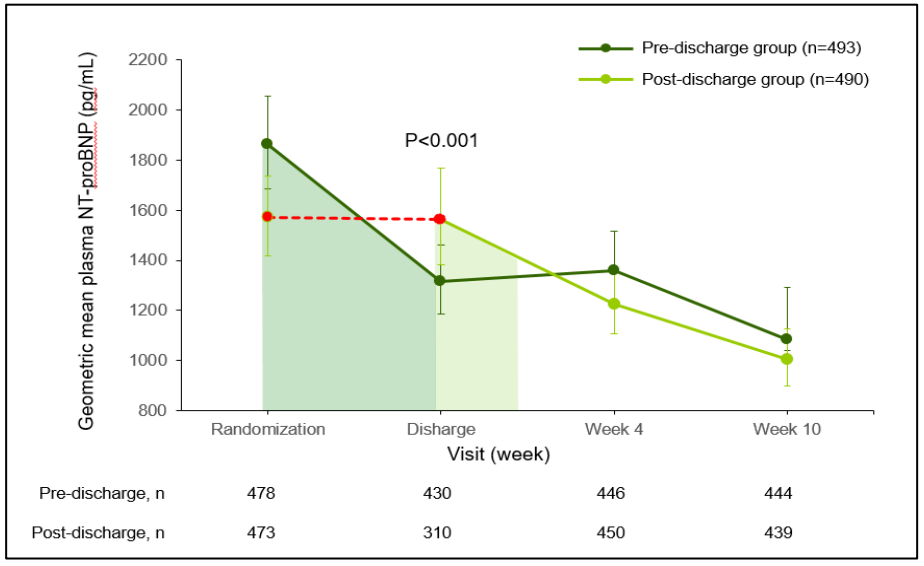
CLASS IIa

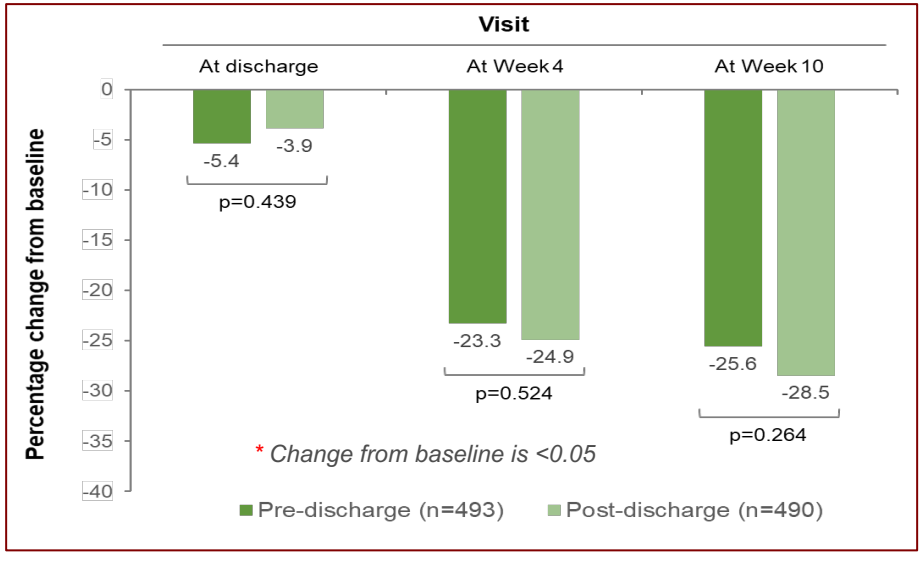
Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Ponikowski et al. Eur J Heart Fail 2016

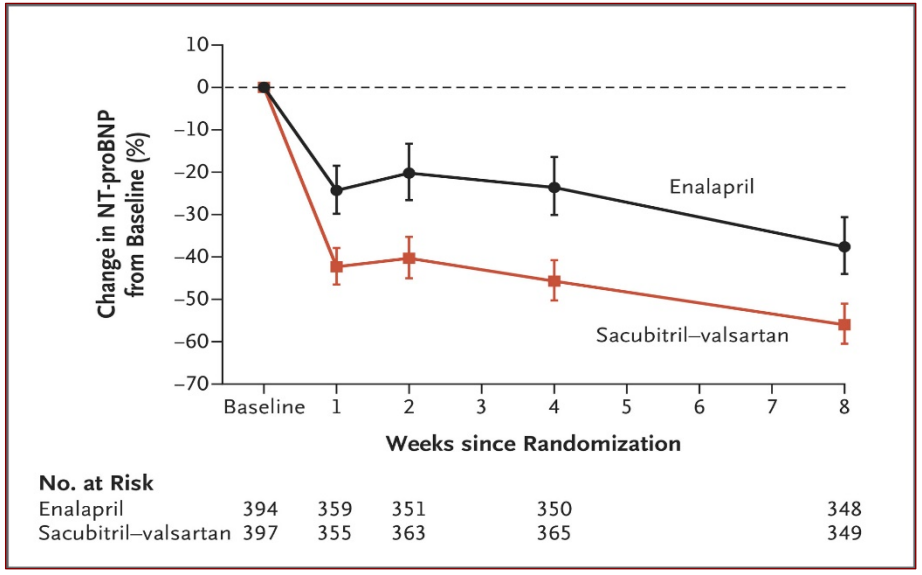
Effetti su NT-proBNP e hs-troponin

TRANSITION Trial





PIONEER Trial



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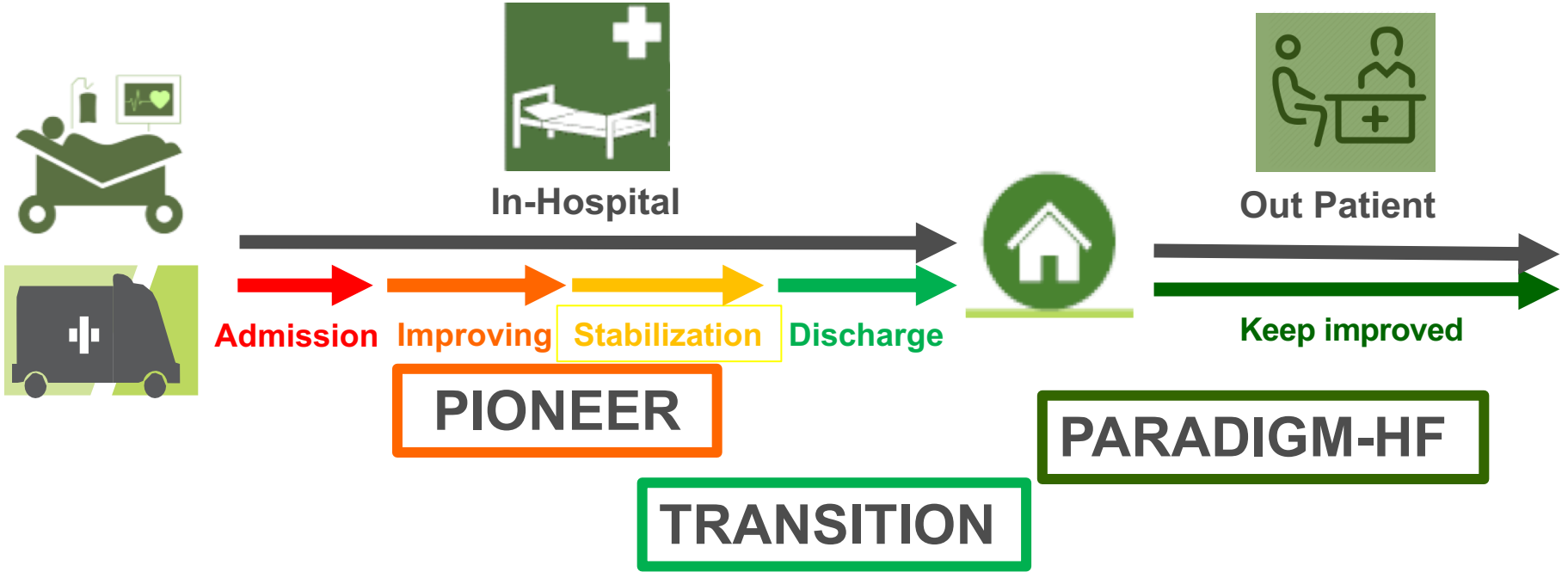
ascual Figal D, Senni M et al. Presented at AHA Congress 2018, Chicago

Storia naturale del paziente con SC

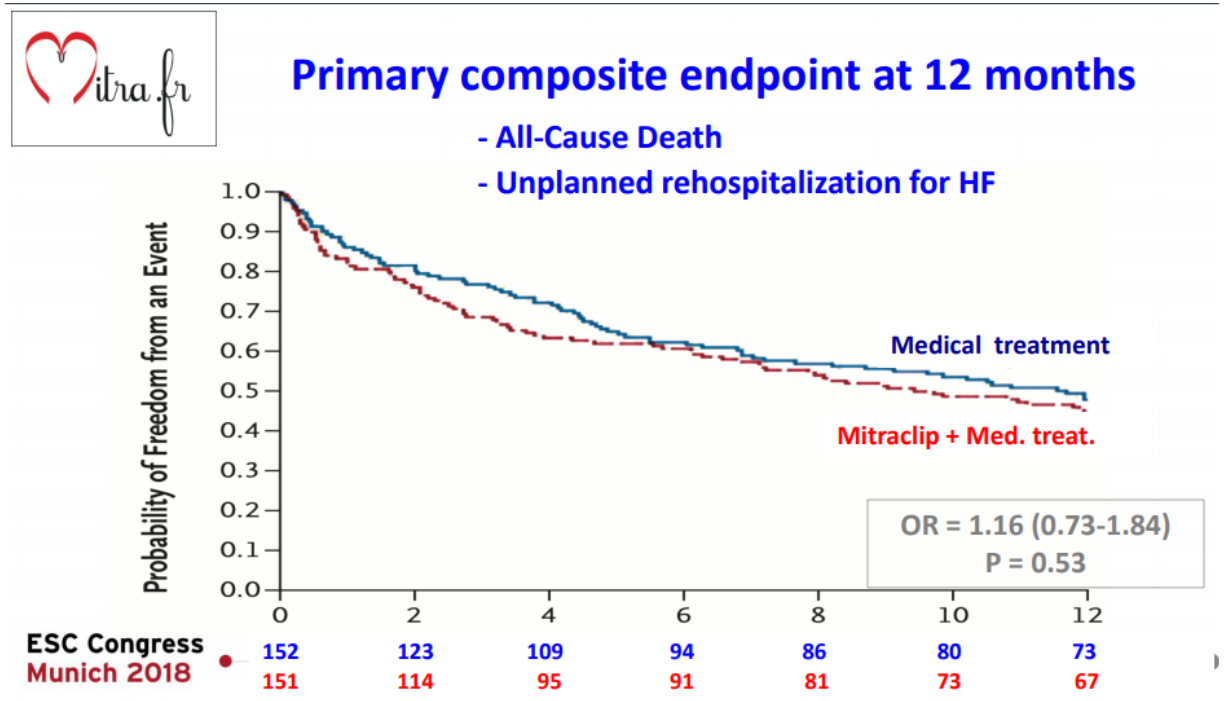


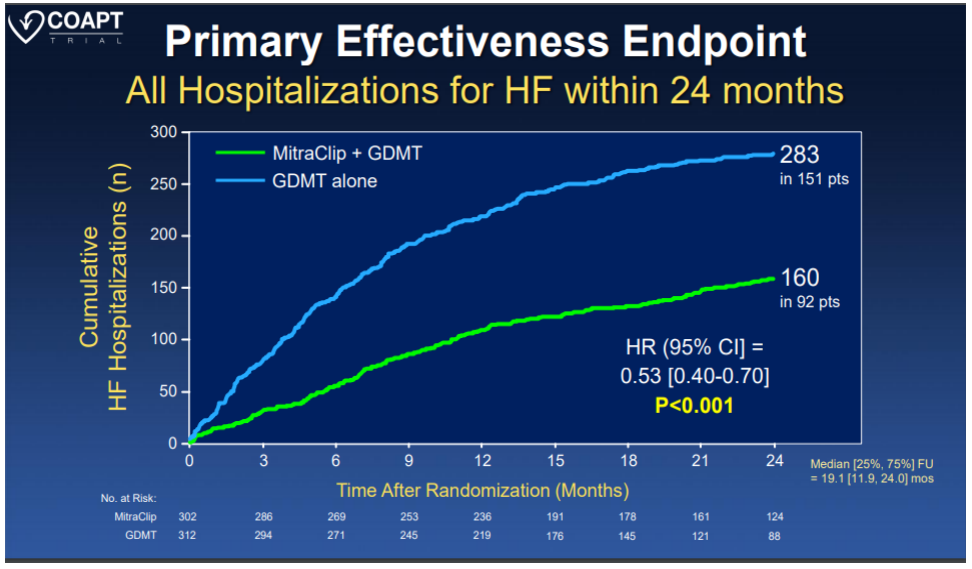
Terapia dello Scompenso Cardiaco

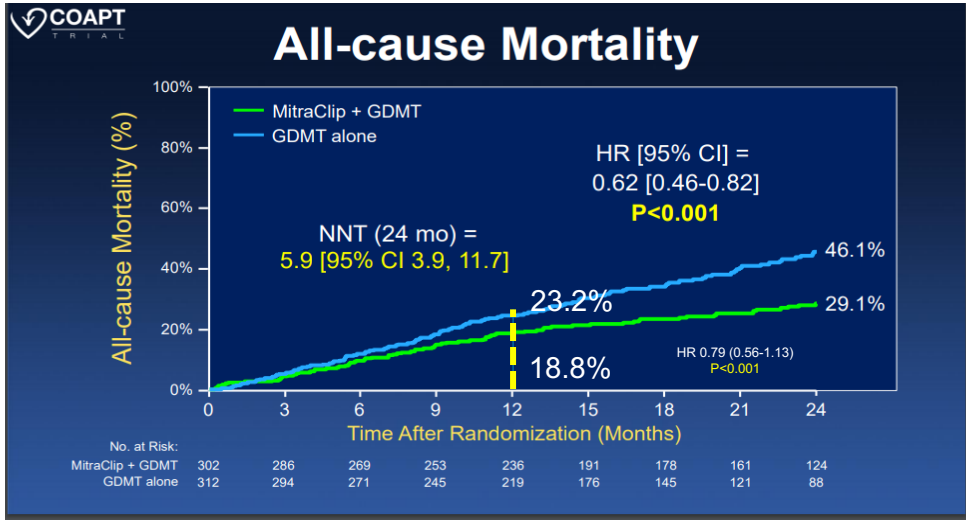
Altre recenti certezze ?

MitraFR e COAPT trials nell'insufficienza mitralica funzionale

Contraddittori o Complementari ?







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Differenze tra COAPT trial e MITRA FR: Criteri di inclusione

VARIABLE	COAPT (N=614)	MITRA FR (N=304)
Etiology	Ischemic and non ischemic cardiomyopathy	Ischemic and non ischemic cardiomyopathy
NHYA	II-IV despite a stable OMT	II-IV despite a stable OMT
LVEF (%)	**20-50**	15-40
LVESD (mm)	**< 70**	NA
Severity of MR	Moderate to severe (3+) or severe (4+)	**ERO > 20 mm²** or RV > 30 ml
Previous HF hospitalization and/or BNP values	At least one HHF within 12 months and/or BNP > 300 pg/ml or NT-proBNP > 1500 pg/ml	At least one HHF within 12 months, **BNP not required**

Differenze tra COAPT e MITRA FR: Ragioni

- **Heart Team:** COAPT comitato centrale di elegibilita'
- **Selezione della popolazione:** COAPT maggiore (annual rate 1,66)
- **Potenza statistica del trial:** COAPT 614 - MitraFR 304 (sottogruppi pre-specificati)
- **"Qualita' di conduzione" del trial**
  - **echo missing** (MitraFR: 19% alla dimissione, 25% a 1 anno f-up)
  - **cambiamenti nella terapia dello SC:** (solo riportati nel COAPT)
- **Grado dell'IM:** COAPT ERO 41±15 – MitraFR ERO 31±10
- **Volumi VSx:** COAPT VTD 101±34 – MitraFR VTD 135±35
- **MitraClip risultati:**
  - IM 3+ periop COAPT 5%, MitraFR 9%
  - Complicazioni periop COAPT 8.5%, MitraFR 14.6%
  - IM 3+ 1 anno COAPT 5%, MitraFR 17%

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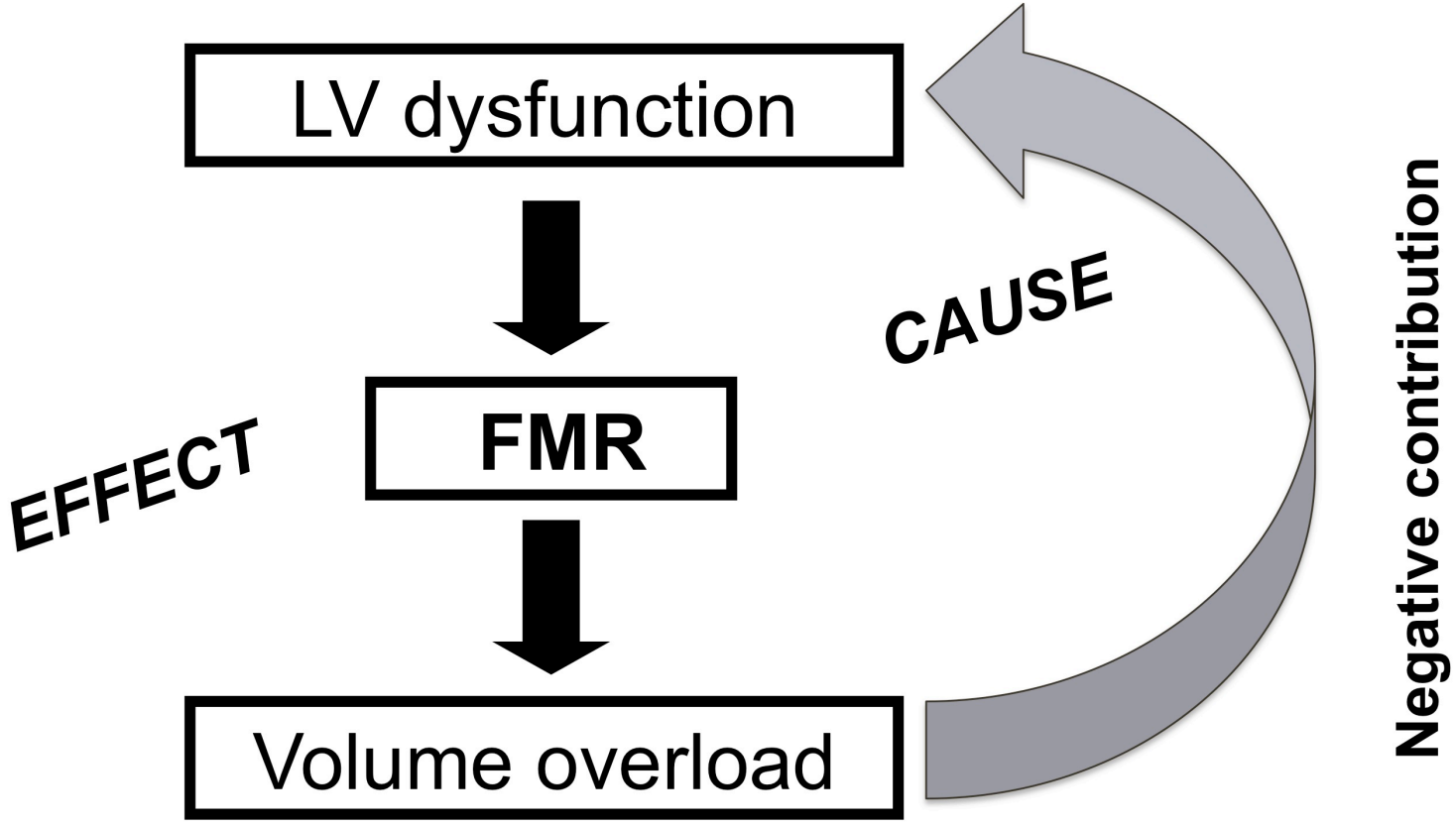
“Treatment of functional mitral regurgitation in chronic heart failure: Can we get a “proof of concept” from the MITRA-FR and COAPT trials?”

Michele Senni MD, Marianna Adamo MD, Ottavio Alfieri MD, Alec Vahanian MD



(Eur J Heart Fail, in press)

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Criteri per la selezione del paziente

1. Accurata valutazione della OMT, prima e dopo l'intervento
2. Presenza di una severa IM (EROA >30 mm^2 e RV >45 mL)
3. Assenza di:

- cardiopatia avanzata, (severa dilatazione e riduzione della FE)
- NYHA class IV
- disfunzione ventricolare dx
- severa insufficienza tricuspidale

Importanza dell'Heart Team

Scelta del Timing per la correzione dell'IM

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Terapia dello Scompenso Cardiaco

1. Certezze

2. Nuovi orizzonti

Terapie promettenti nel trattamento dello scompenso cardiaco

Sacubitril/valsartan nello SC a frazione di eiezione preservata

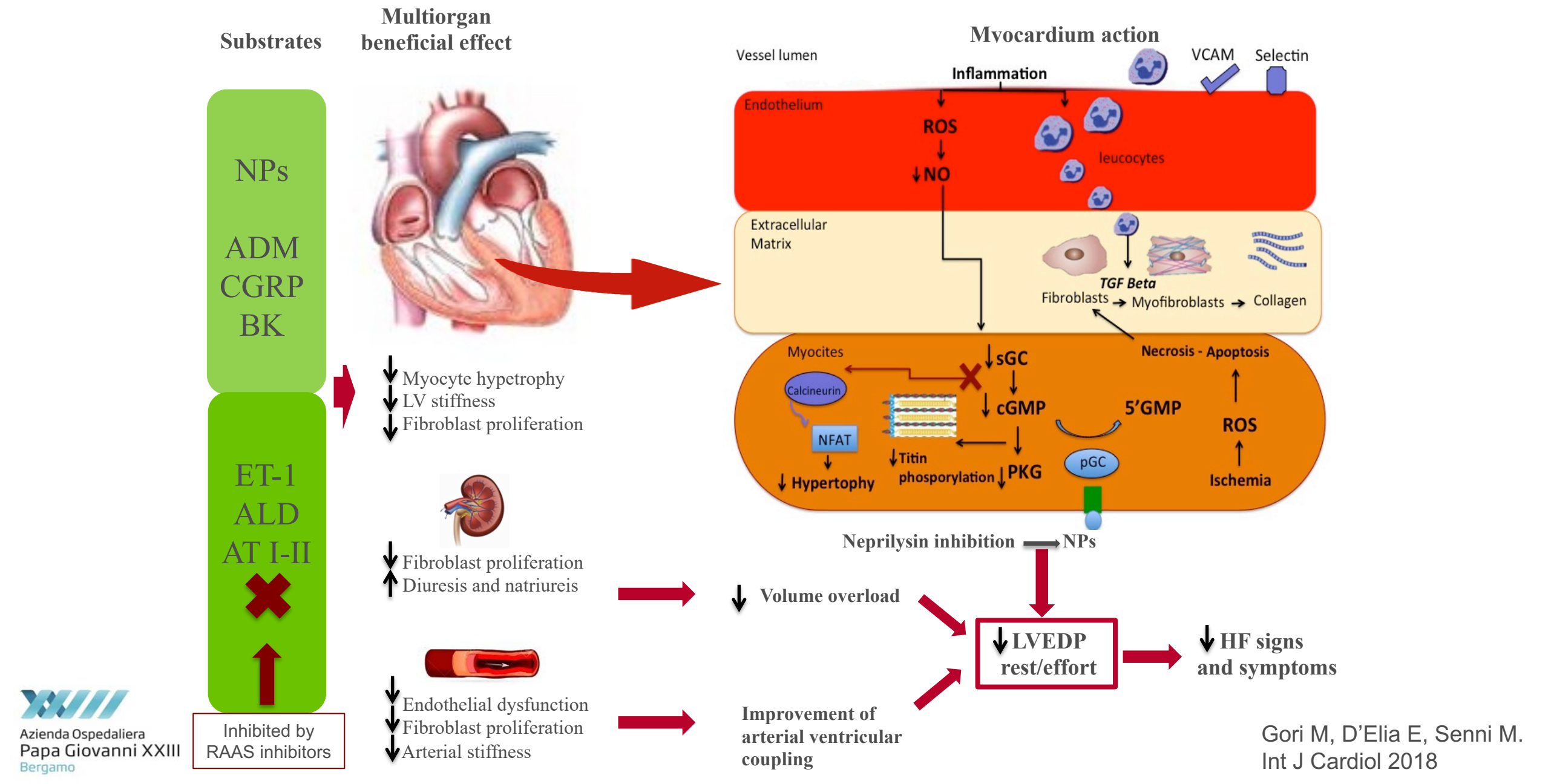
Attivatori della Guanilato ciclasi (vericiguat)

SGLT-2 inibitori (empaglifozin, dapaglifozin)

Ferro carbossimaltosio

Agenti inotropi

Sac/vals meccanismi di azione nel HFpEF



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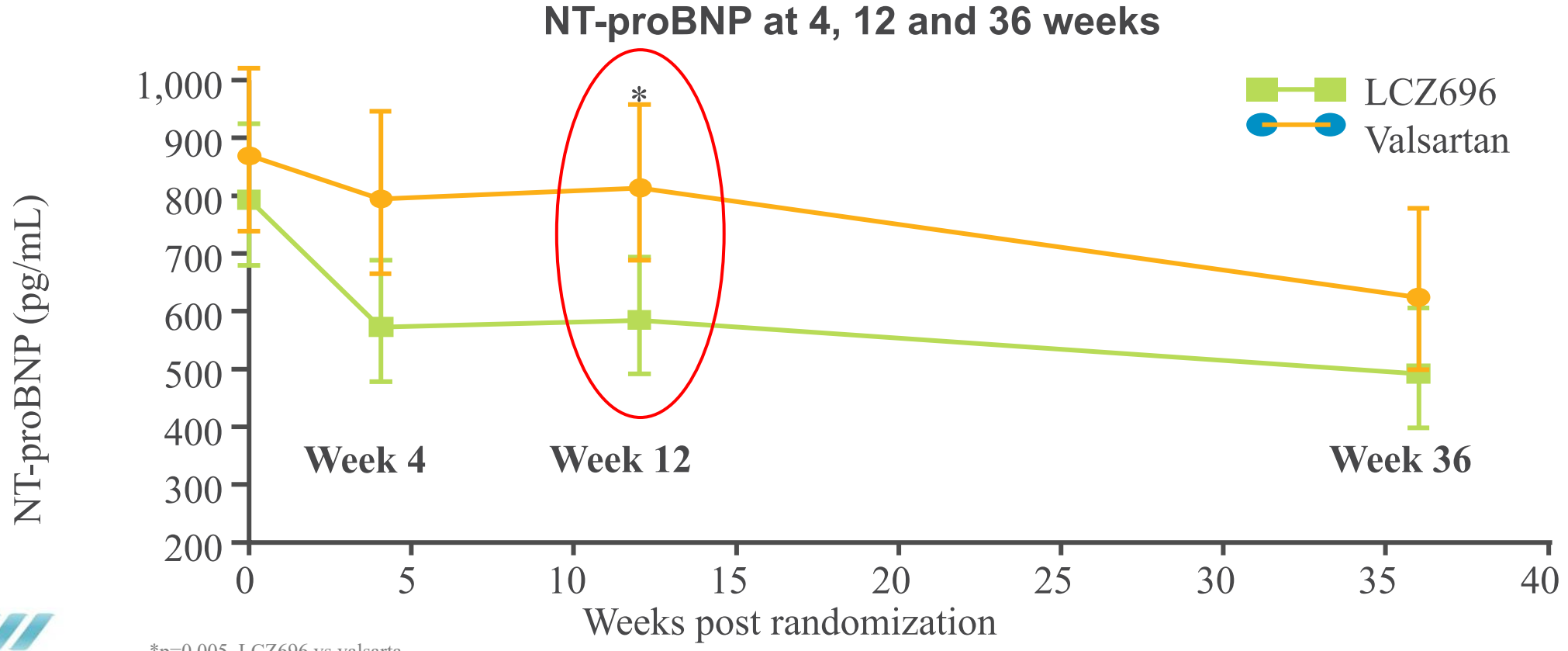
Gori M, D'Elia E, Senni M. Int J Cardiol 2018

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

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Solomon S et al. Lancet 2012

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/m²)	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/m²)	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

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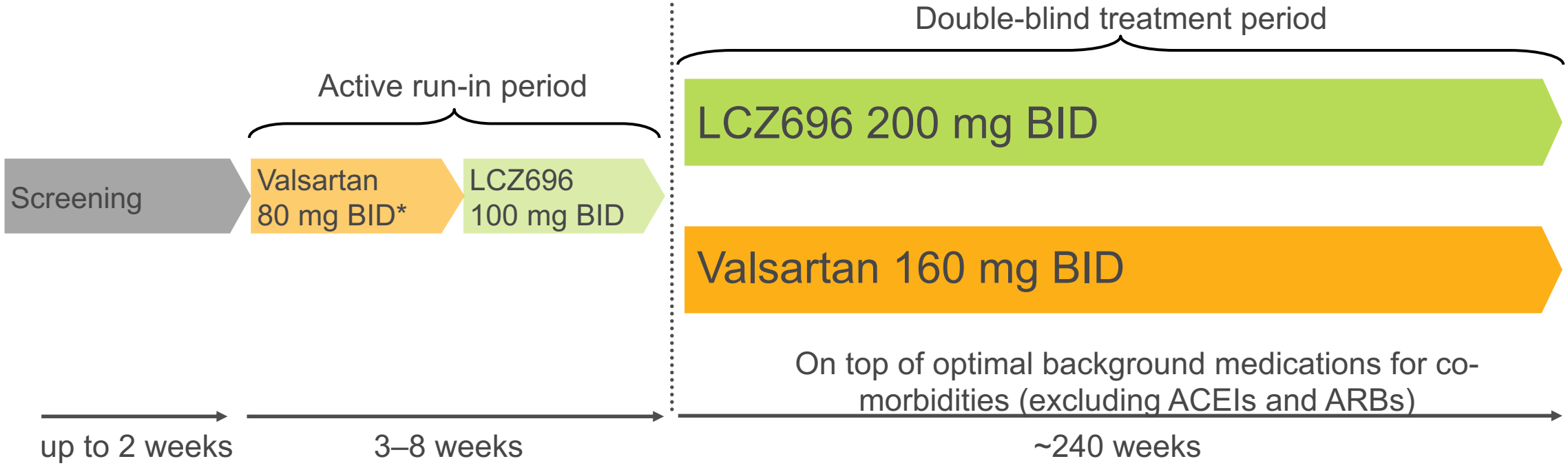
Solomon S et al. Lancet 2012

PARAGON-HF

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

Randomization 1:1



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

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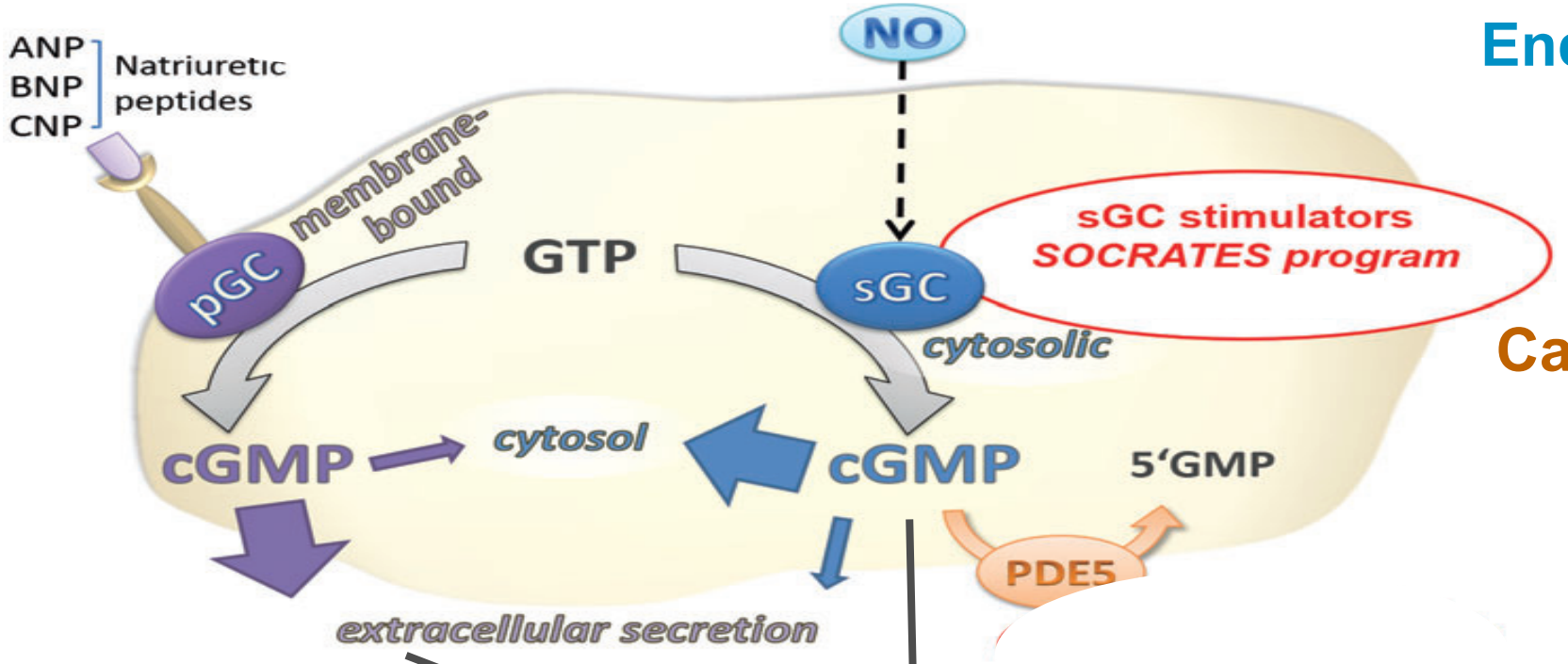
Via NO/cGMP



Endothelium

Cardiomyocytes

Hipertrophy

↑Stifness

Myocardial function

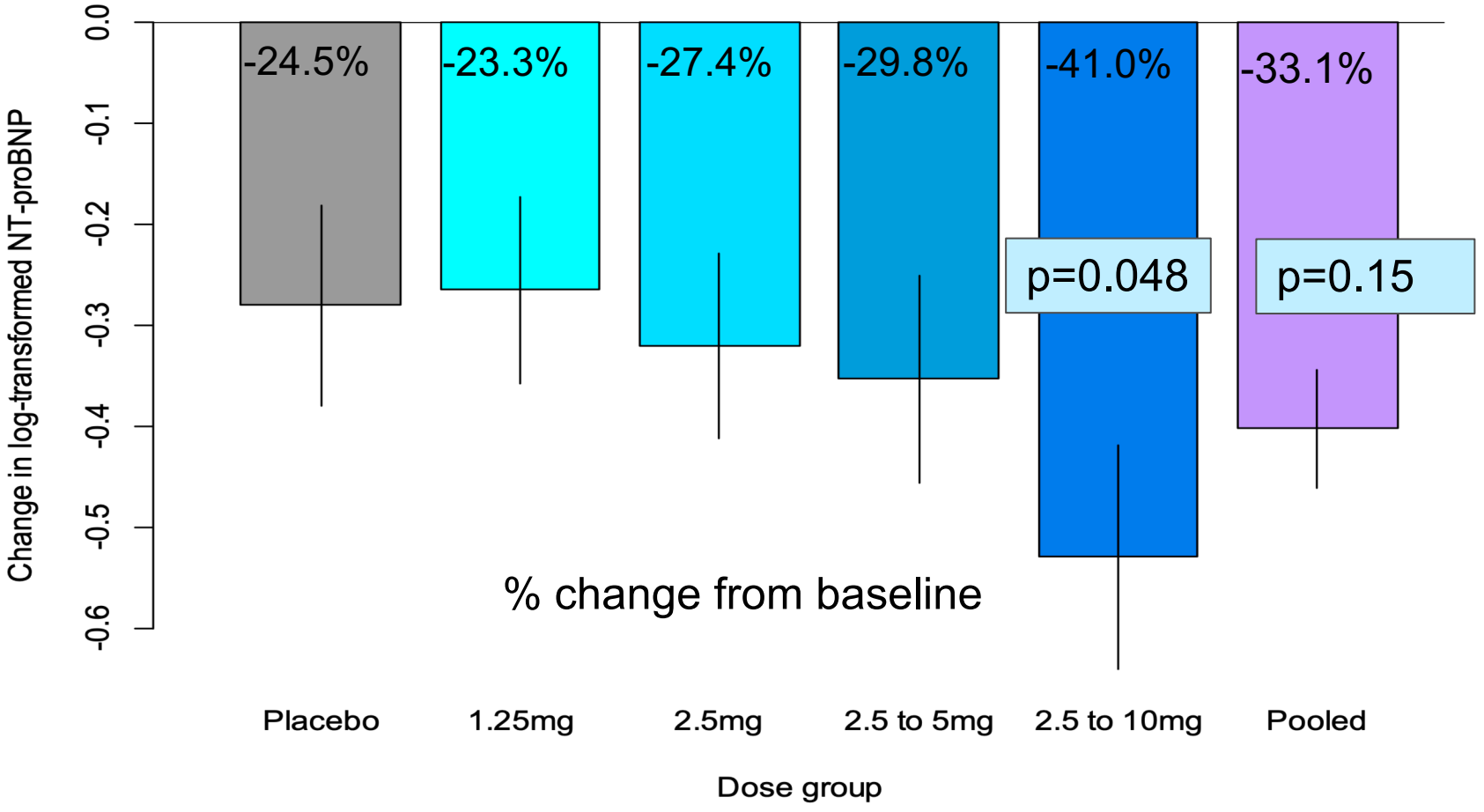
PKG

Vascular function

Senni M et al. EHJ 2014

SOCRATES-REDUCED: vericiguat

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)

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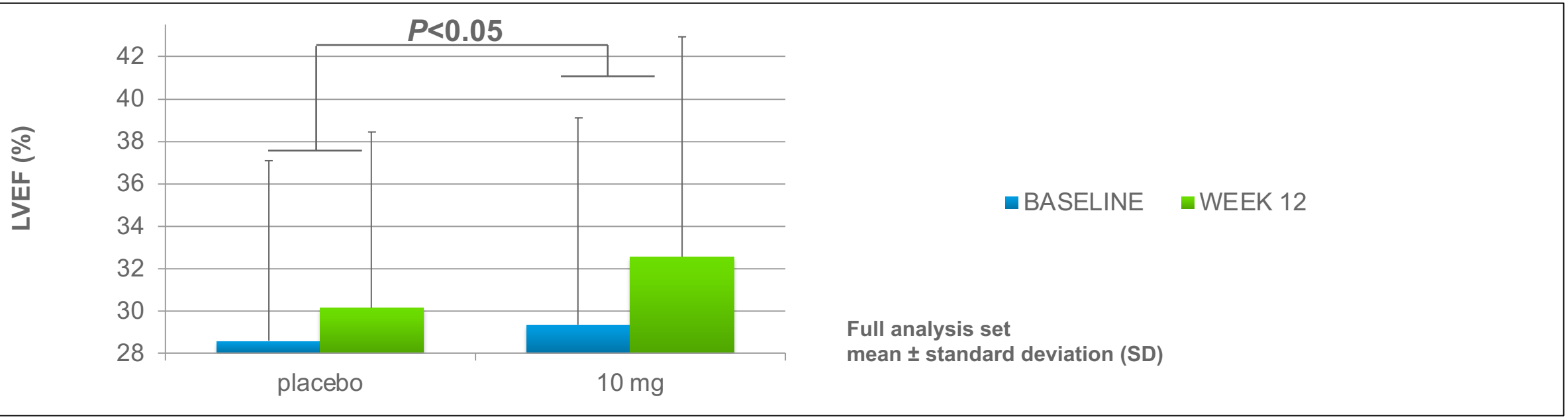
SOCRATES-REDUCED: funzione sistolica



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

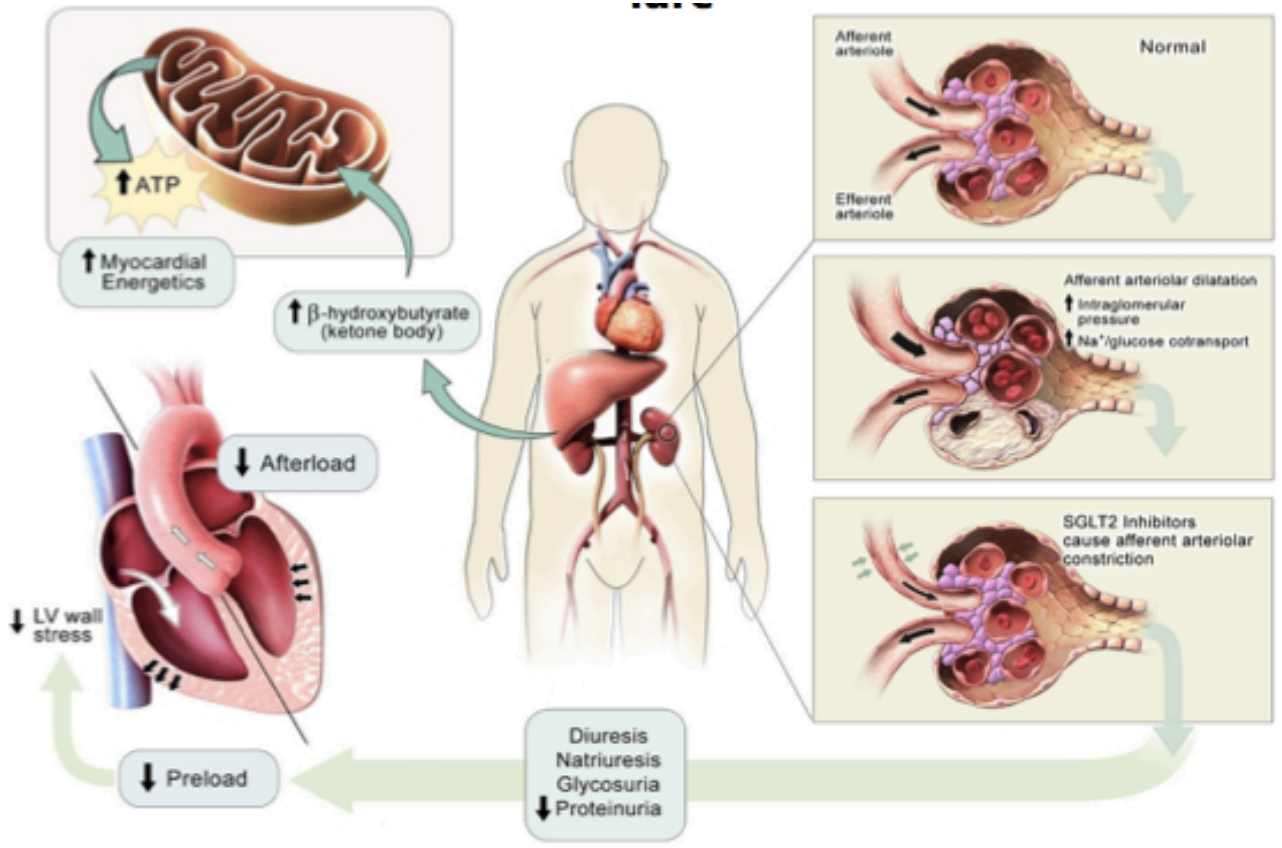
LVEF, left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume

mean values

VICTORIA Trial
Studio di fase III - NYHA II-IV - HFrEF

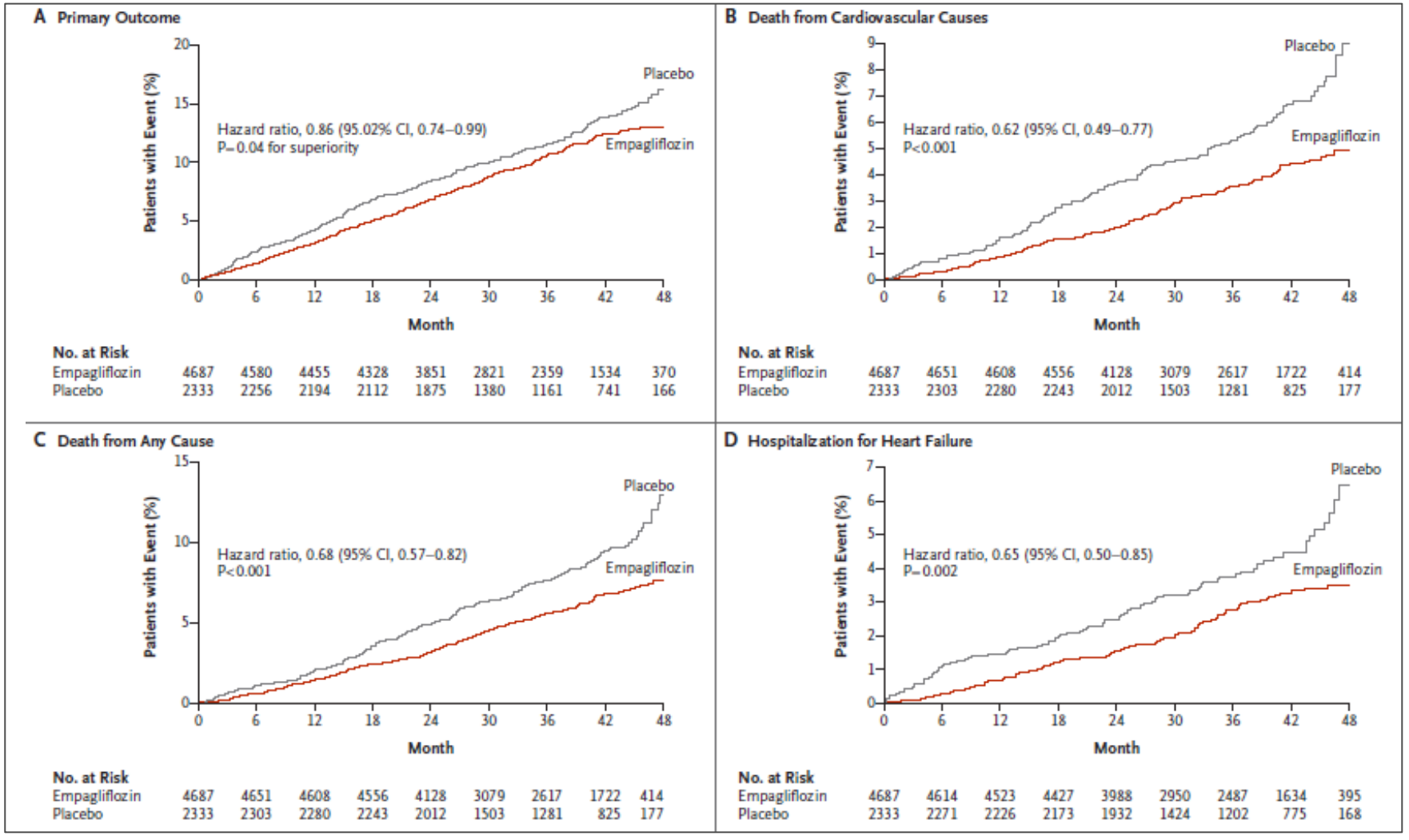
- **Primary objective:** To study the efficacy and safety of vericiguat vs. placebo on a background of usual care in HFrEF patients
- Target enrollment of approximately 4800 patients with the following:
  - HFrEF (EF < 45%)
  - NYHA II-IV on standard therapy
  - Prior HF hospitalization (6 months) or 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

I possibili meccanismi di azione dei SGLT2 inibitori



Verma, McMurray & Cherney JAMA Cardiol 2017

EMPA-REG Outcome trial



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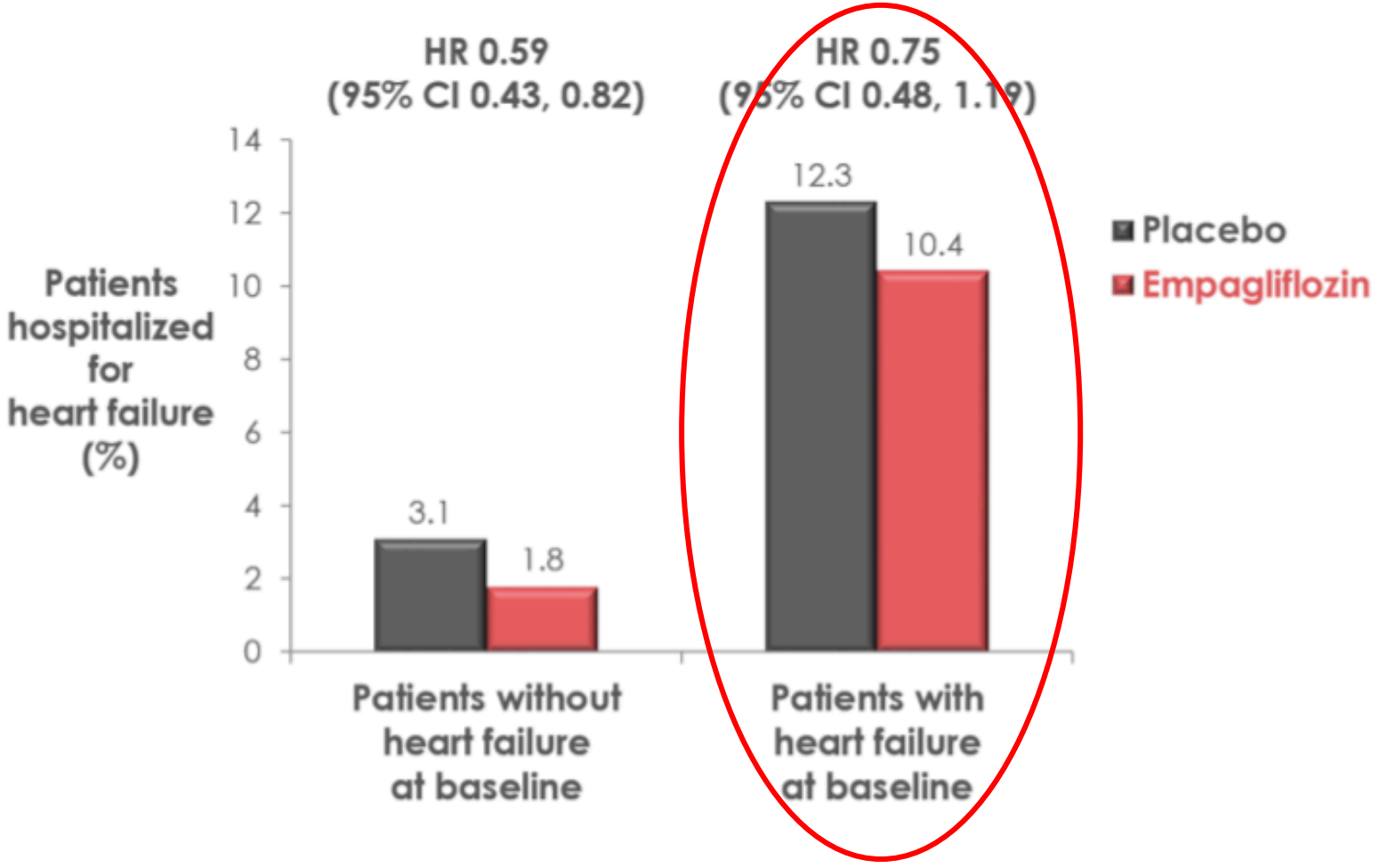
EMPEROR trial

HF Hospitalizations in patients with or without HF



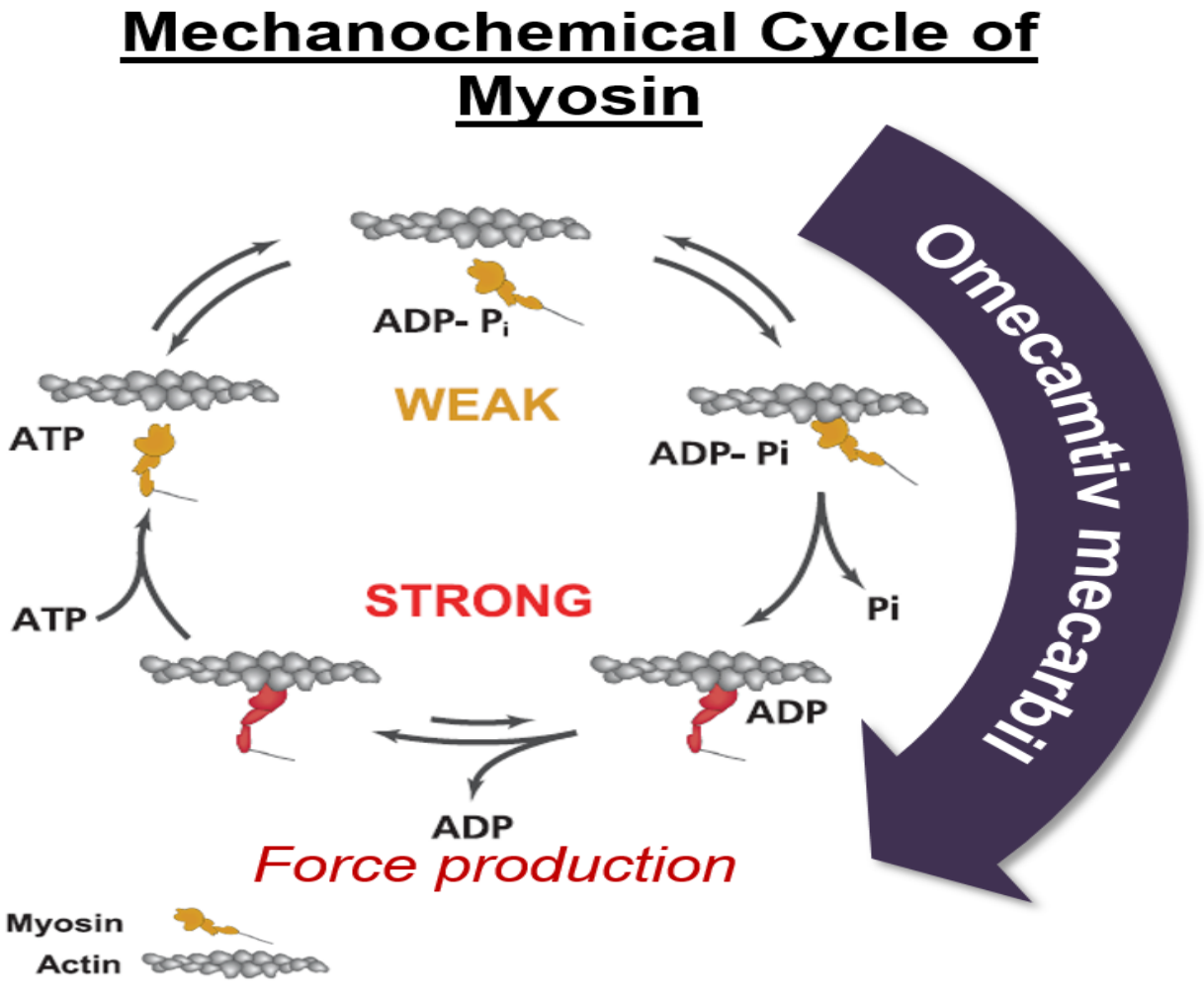
Fitchett et al. Eur Heart J 2016

SGLT2 inibitori
Trials fase III in corso

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

Butler J et al. Eur J Heart Fail 2017

Omecamtiv mecarbil: attivatore selettivo della miosina



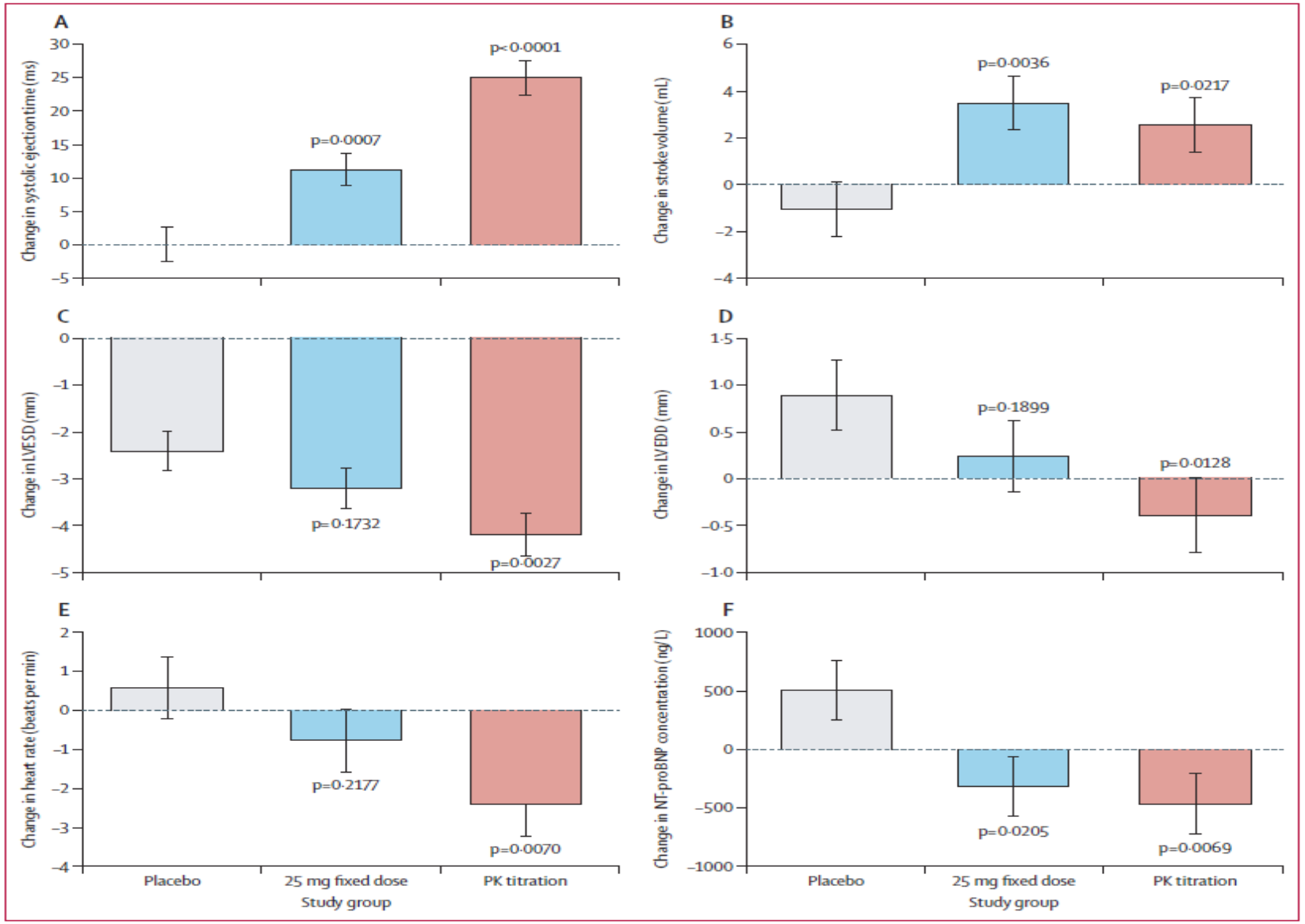
OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

"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

Malik FI, *et al. Science* 2011; 331:1439-43

Omecamtiv mecarbil in HFrEF: COSMIC-HF



Teerlink JR et al. Lancet 2016

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

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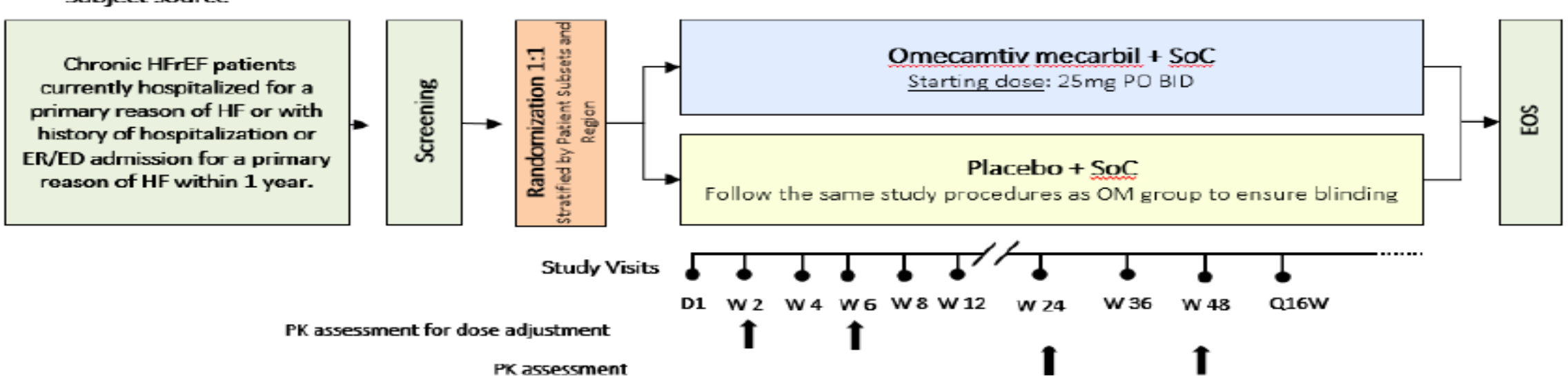
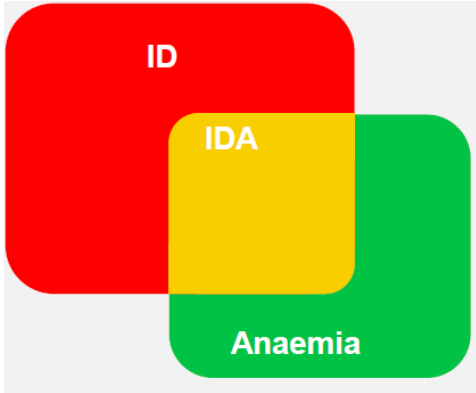
Study Design and Treatment Schema

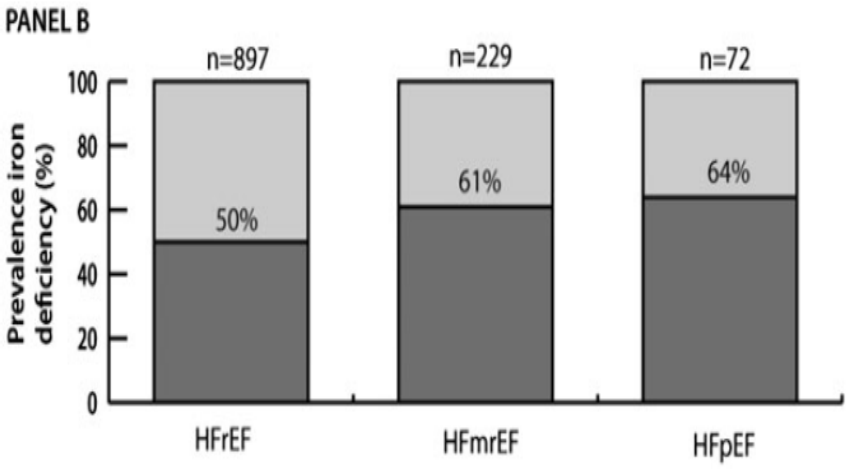
2 years enrollment, approx. 4 years total follow-up/study period



DEFICIT DI FERRO NELLO SCOMPENSO CARDIACO

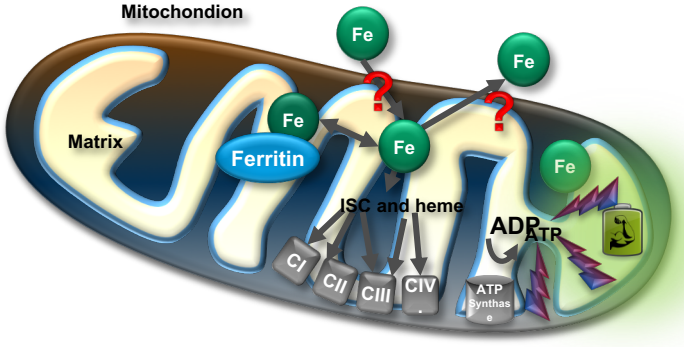
ID and Anemia relationship

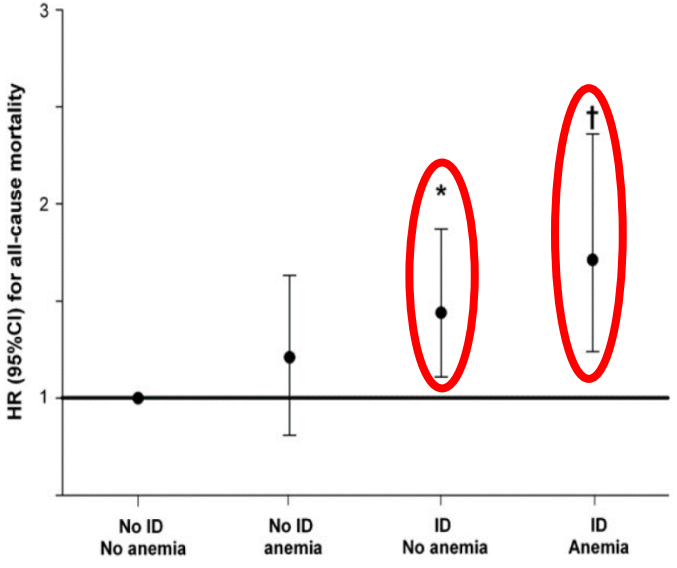




Martens P et al. Acta Cardiol 2017

ID and ATPasi sintetasi





Jankowska EA et al. Eur Heart J 2010

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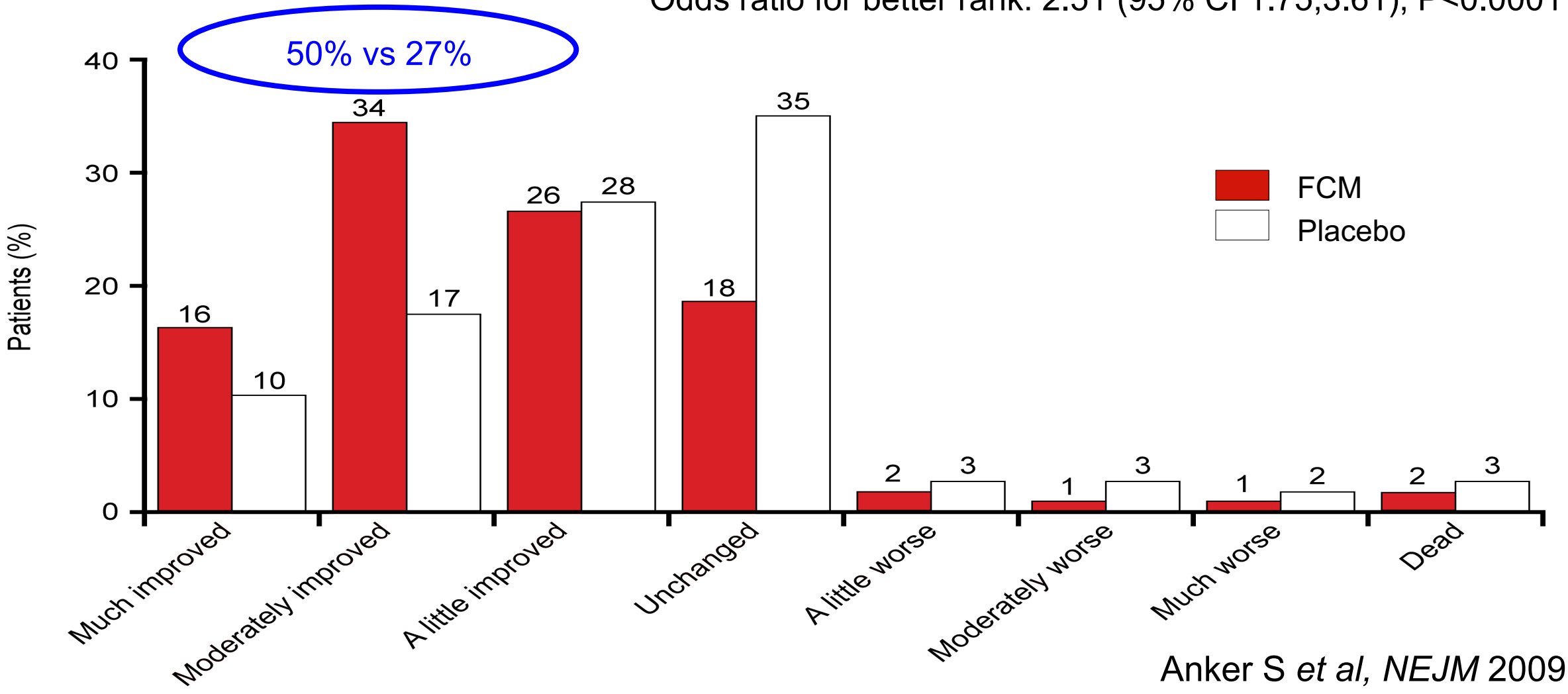
Bergamo

Endpoint primario 1:
Patient Global Assessment a 24 settimane

459 HFrEF patients, LVEF≤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

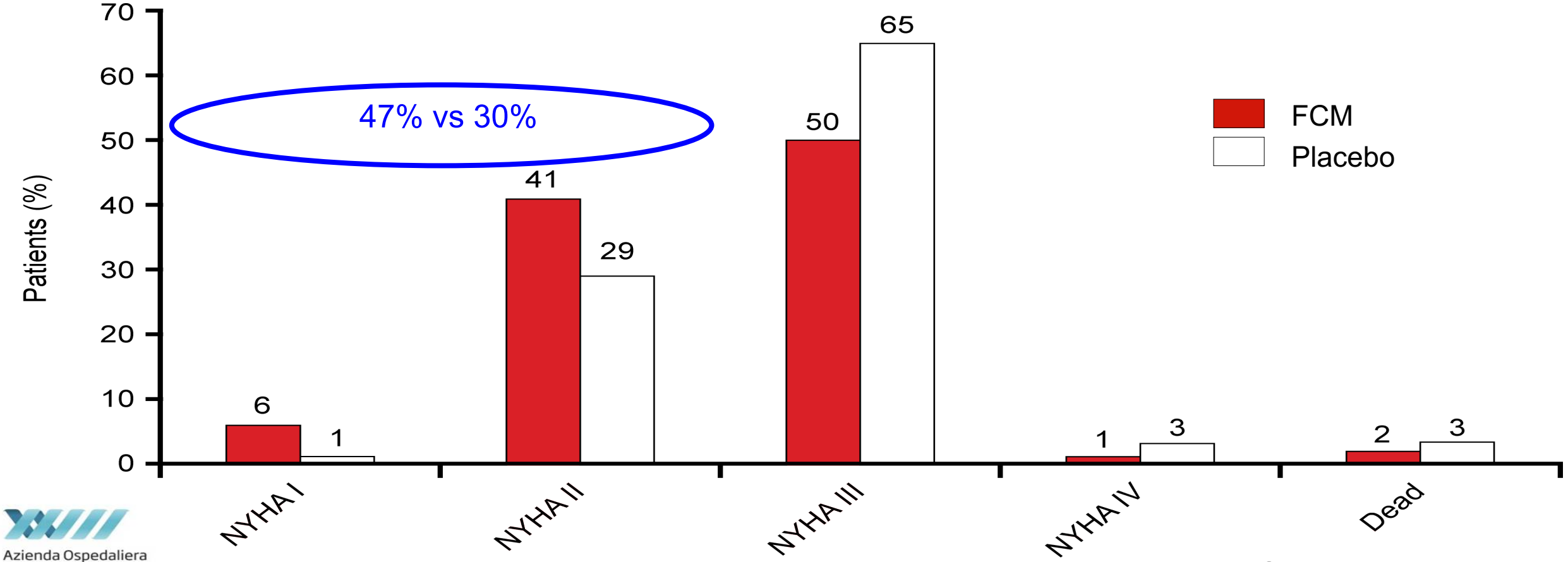


Anker S *et al, NEJM* 2009

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*



Anker S *et al, NEJM* 2009

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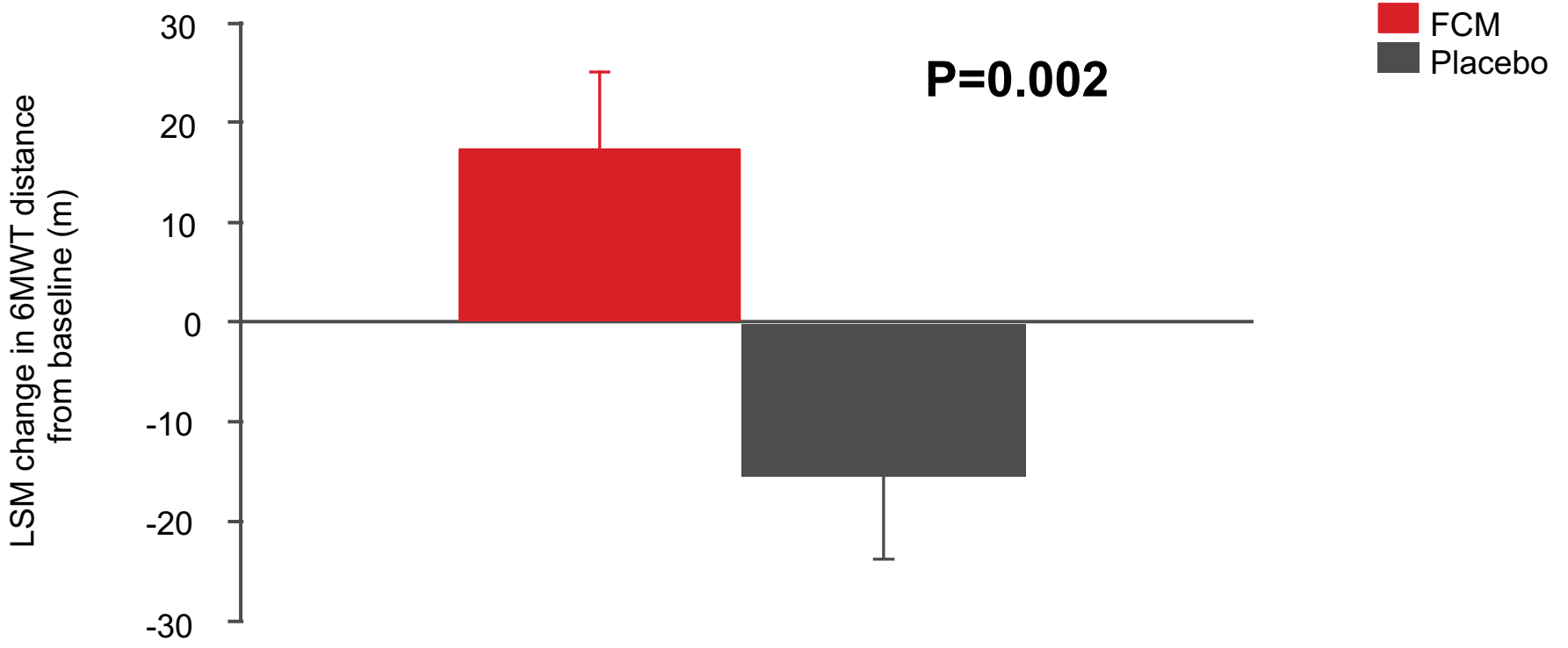
CONFIRM-HF: endpoint primario
6-minutes walking distance a 24 settimane

CONFIRM-HF

300 HFrEF patients, LVEF≤45%

FCM improved 6MWT at week 24

FCM vs placebo: 33 ± 11 m *(least squares mean ± SE)*



Ponikowski P et al. *Eur Heart J*. 2015

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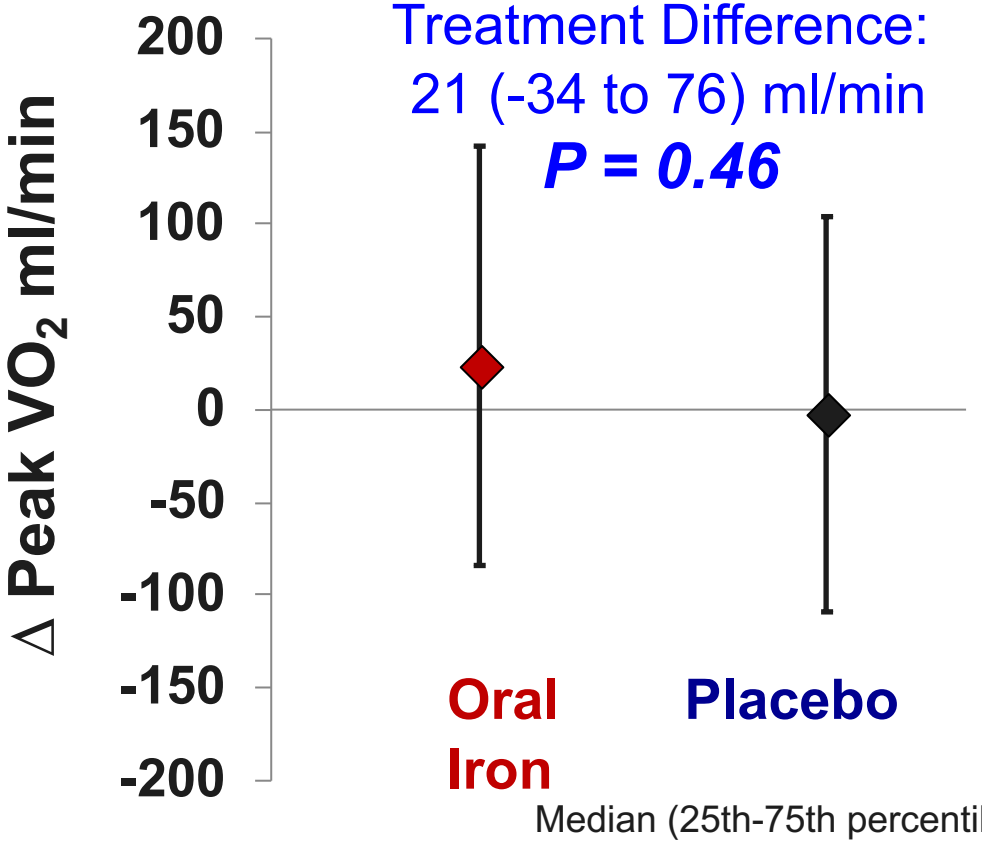
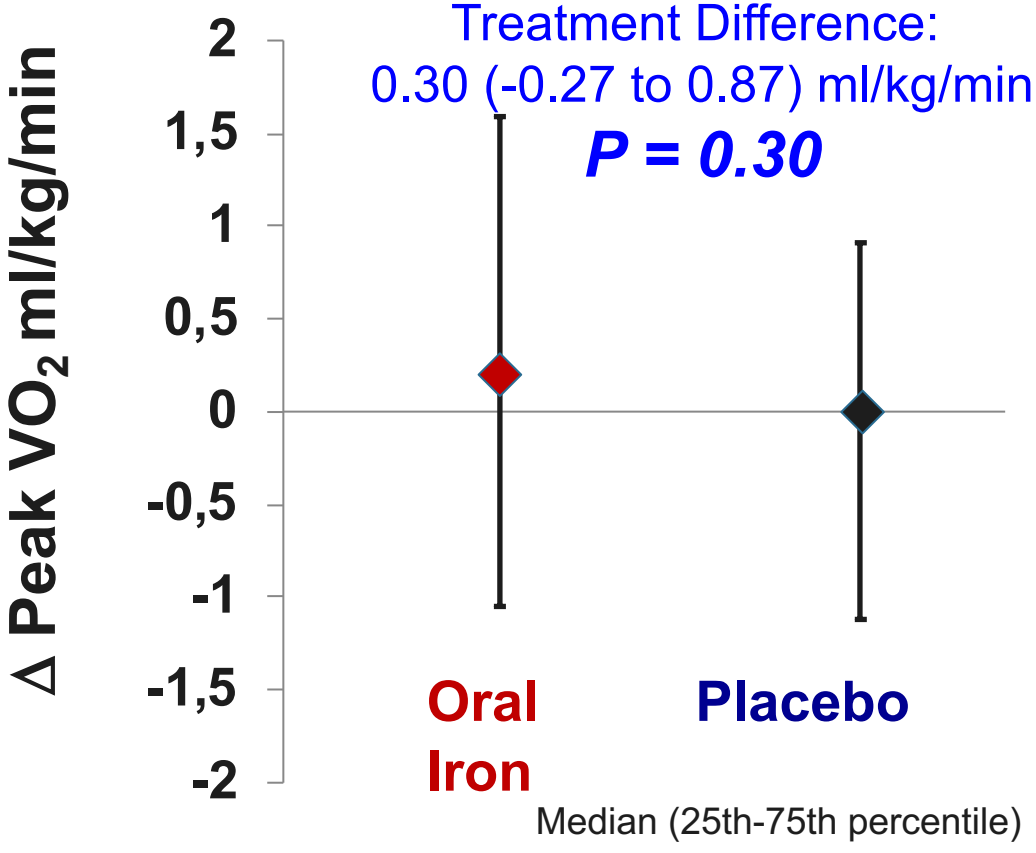
Bergamo

Ironout-HF

300 patients, LVEF<40%





Baseline peak VO_2 (IQR) 13.3 (11.4–15.8) 12.9 (10.5–15.6)

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

Study	AFFIRM AHF[1]	FAIR HF2[2]	HEART FID[3]	IRONMAN[4]
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

Conclusione

Sebbene siano stati ottenuti grandi risultati nel trattamento dello scompenso cardiaco, la strada d'avanti a noi e' ancora lunga.

Farmaci promettenti e nuovi approcci alla terapia (personalizzazione) potranno migliorare i risultati anche in aree dove non abbiamo ad oggi nessuna terapia basata sull'evidenza (HFpEF).

“Now, this is not the end.

It is not even the beginning of the end.

But it is, perhaps, the end of the beginning.”

Sir Winston Churchill, 1942