Heart failure medical treatment in 2017: An update

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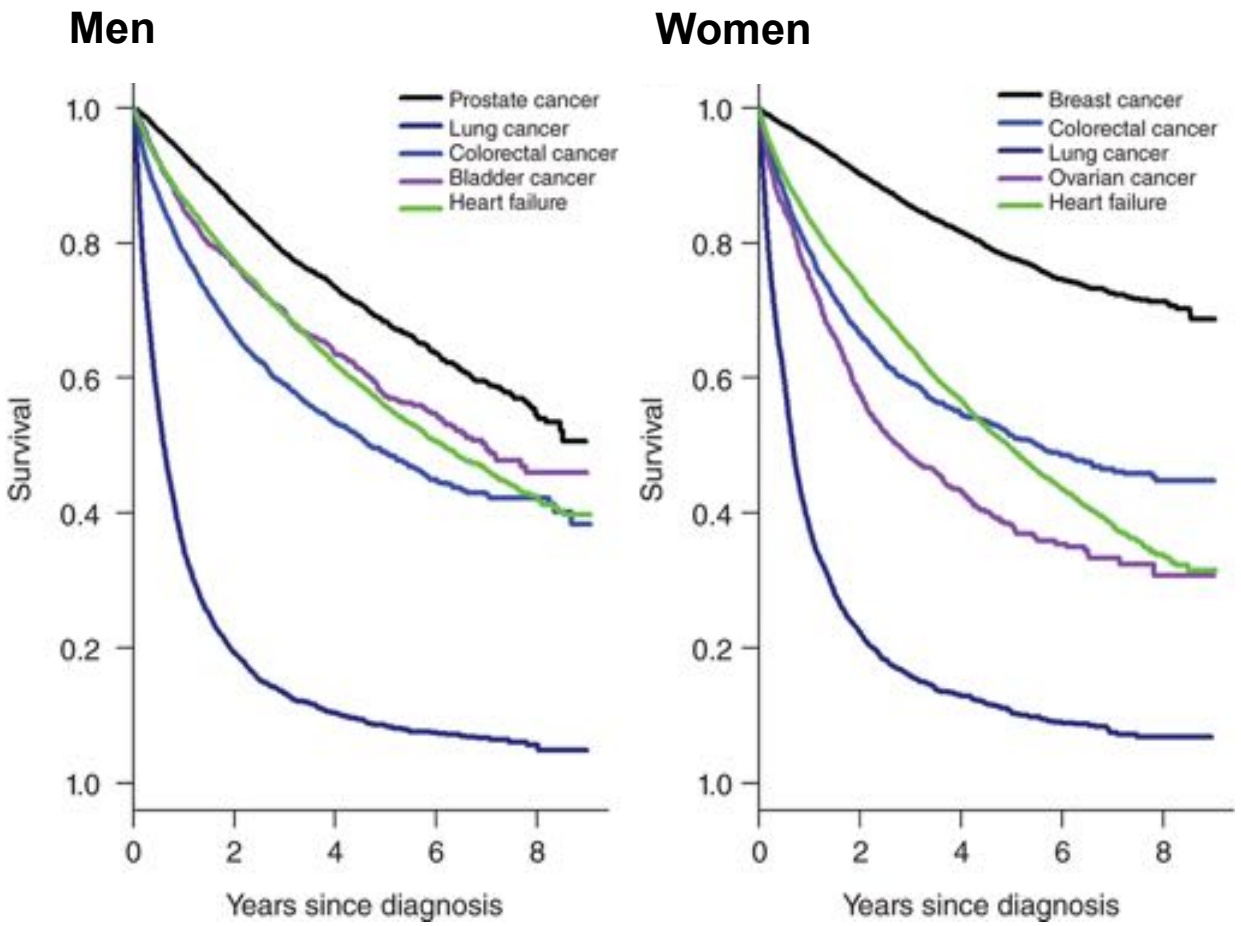
European Journal of Heart Failure (2017)
doi:10.1002/ejhf.803

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

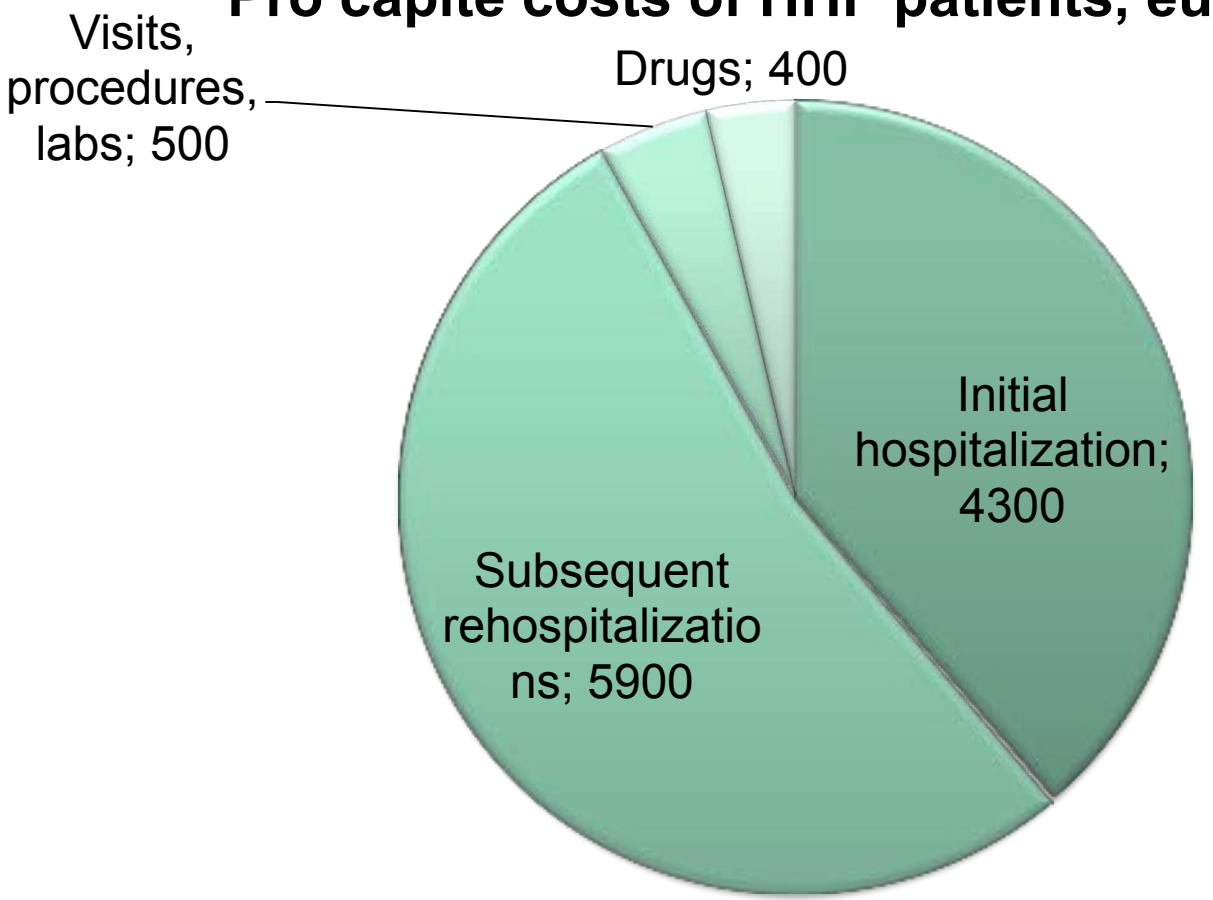


Mamas et al. Eur J Heart Fail 2017; 19: 1096-1105

Burden of new hospitalization for heart failure: a population-based investigation from Italy

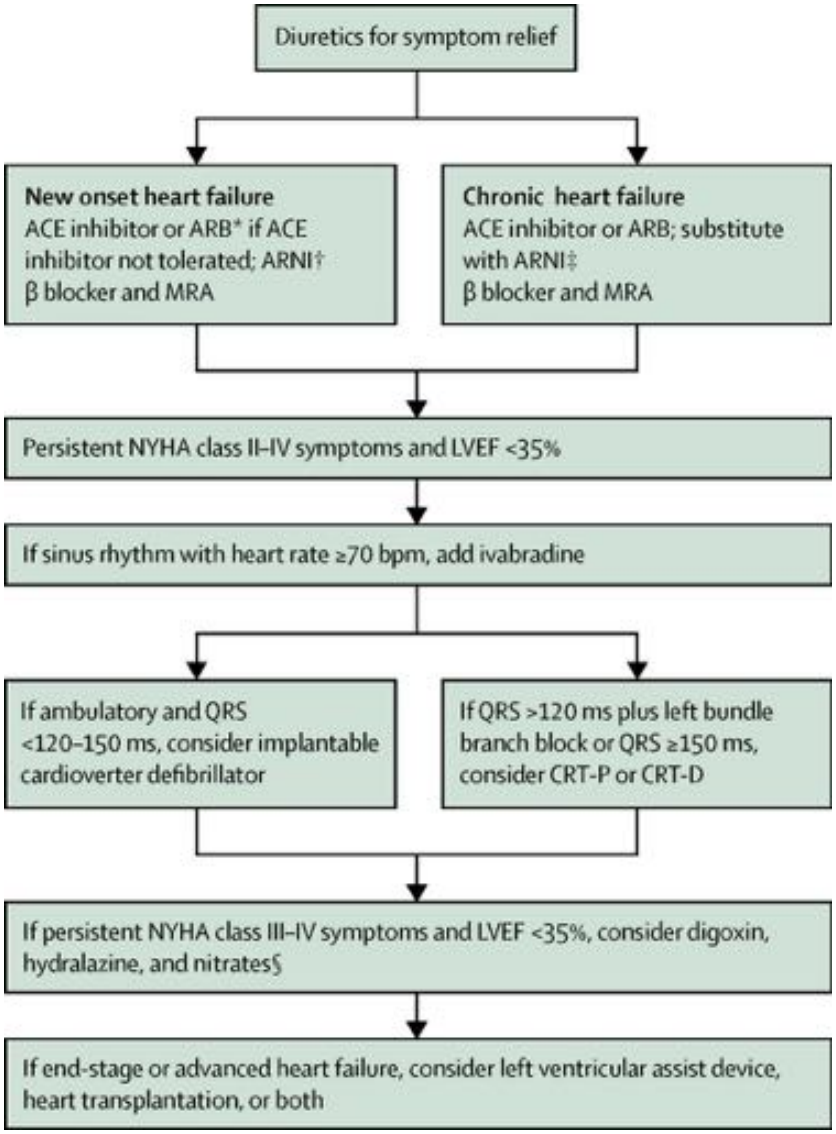
Giovanni Corrao[1]*, Arianna Ghirardi[1], Buthaina Ibrahim[1], Luca Merlino[2], and Aldo Pietro Maggioni[3]

Pro capite costs of HHF patients, euros/year



Corrao et al. Eur J Heart Fail 2014; 16, 729–736

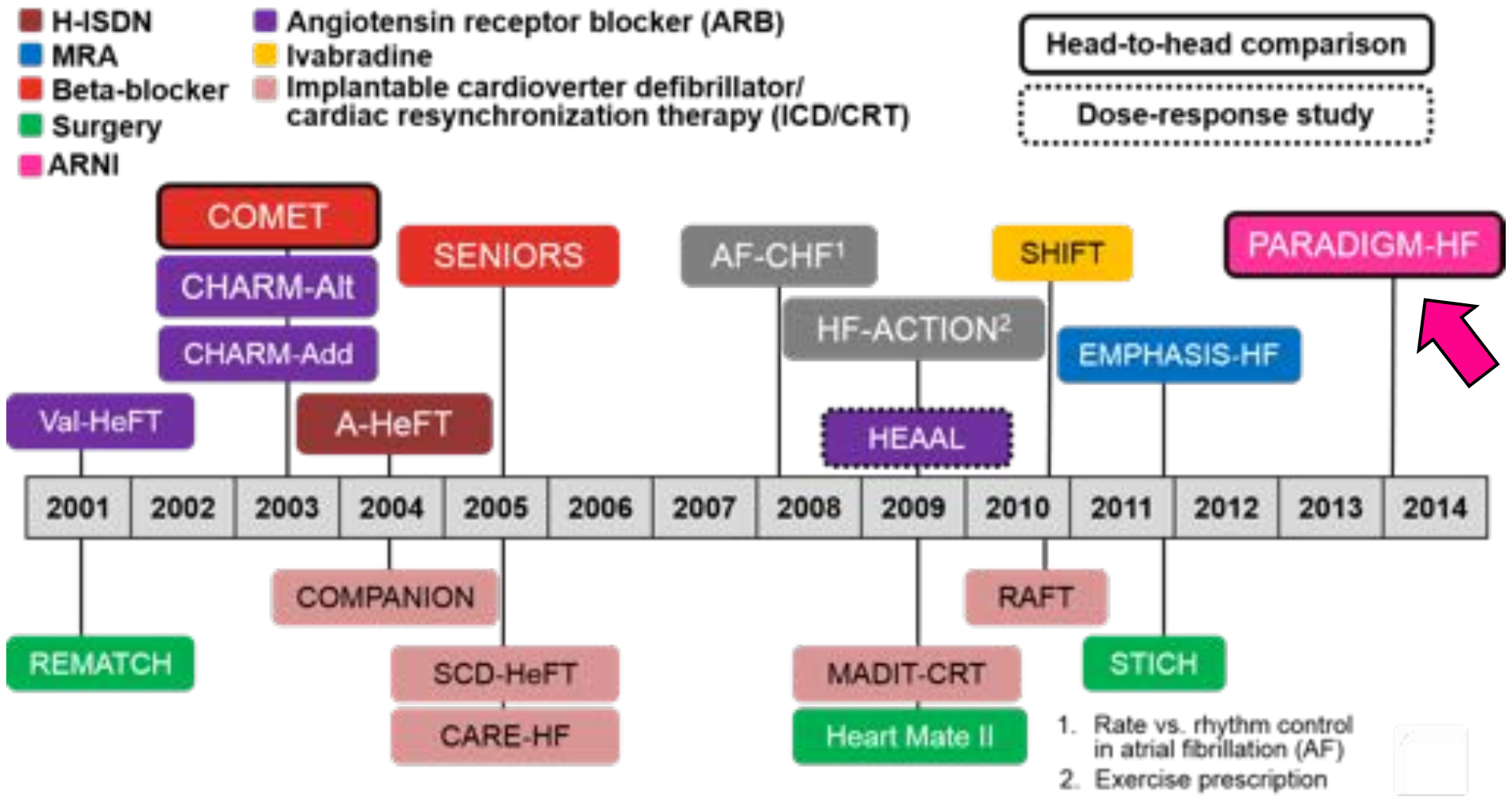
Algorithm for the treatment of HFrEF



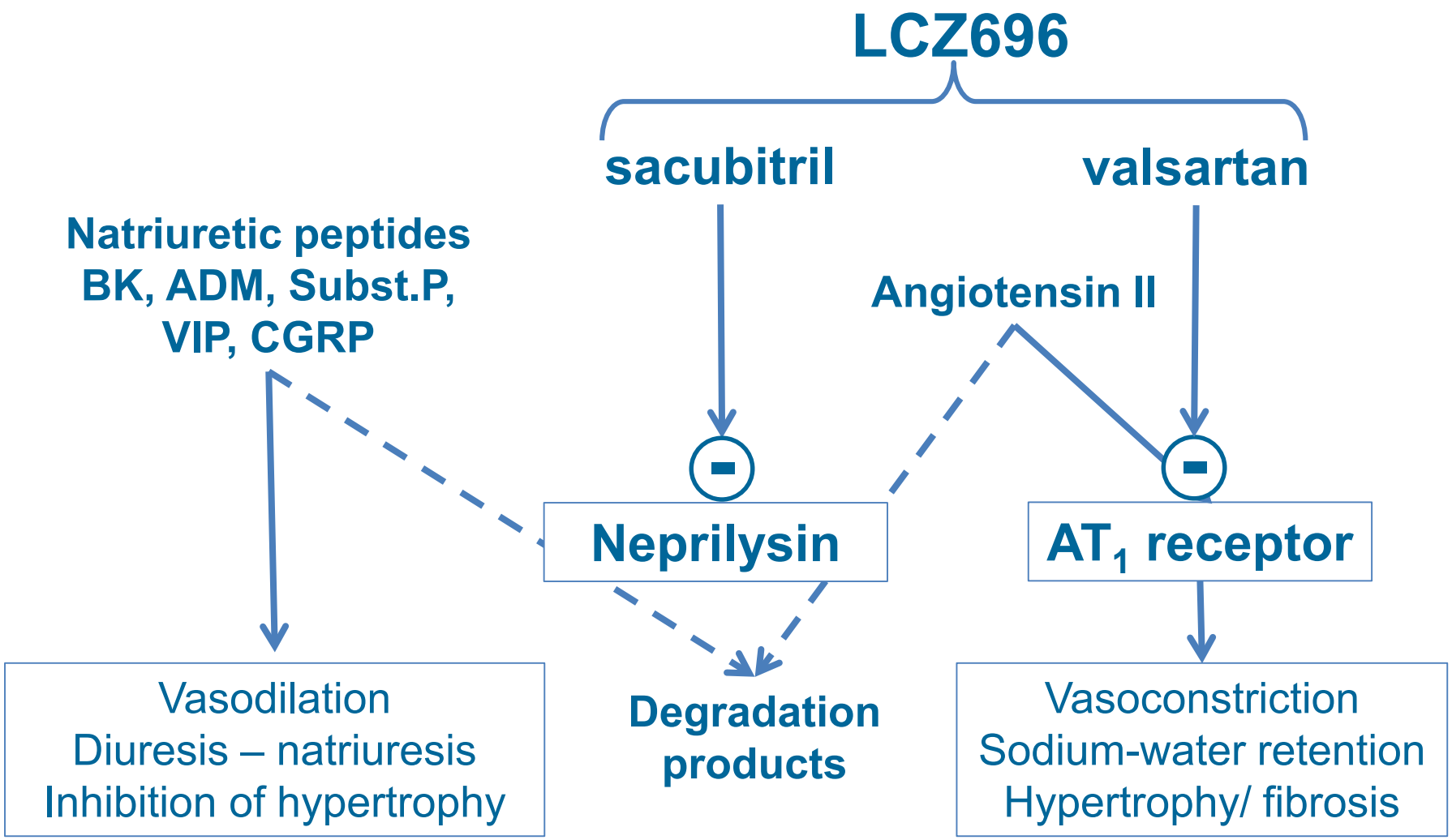
Metra, Teerlink. The Lancet DOI: (10.1016/S0140-6736(17)31071-1)

Thirty years of progress in HF-rEF

Positive drug, device and other trials 2001-2014

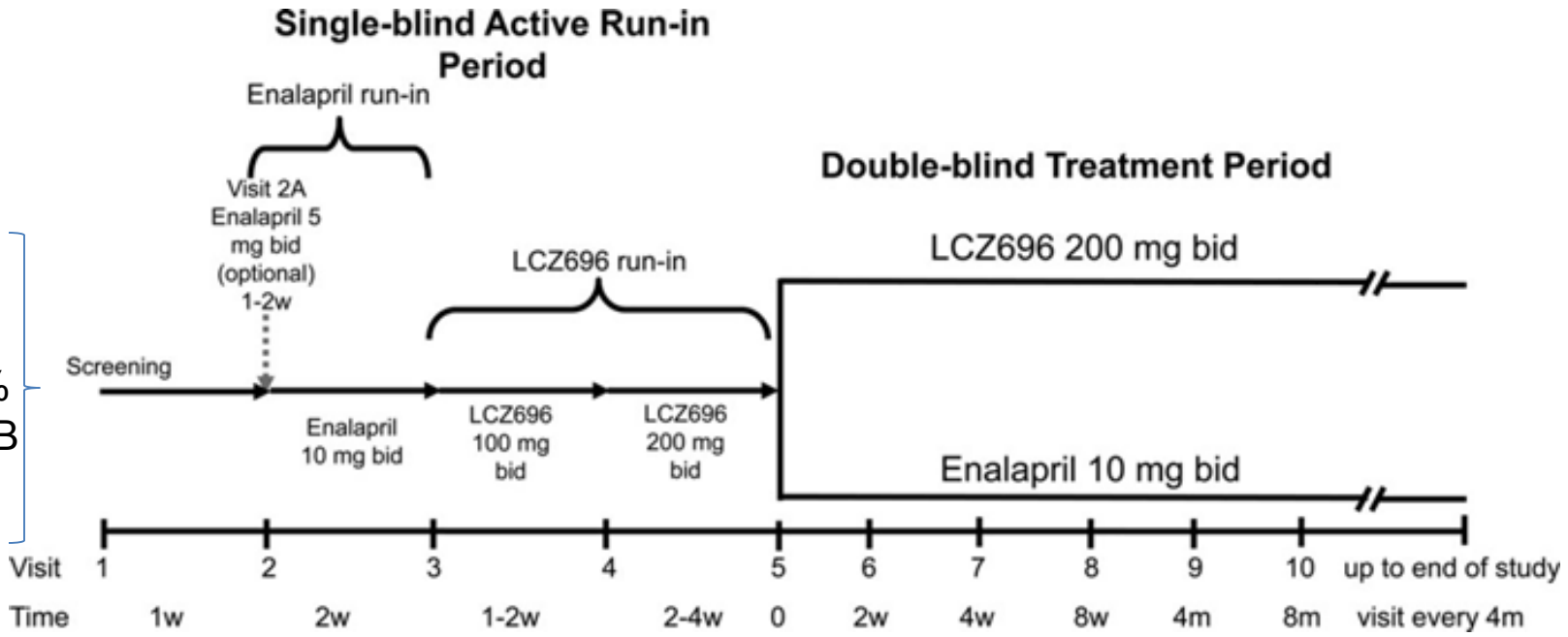


Combined AT_1 Receptor Neprilysin Inhibition (ARNI) for the treatment of Heart Failure



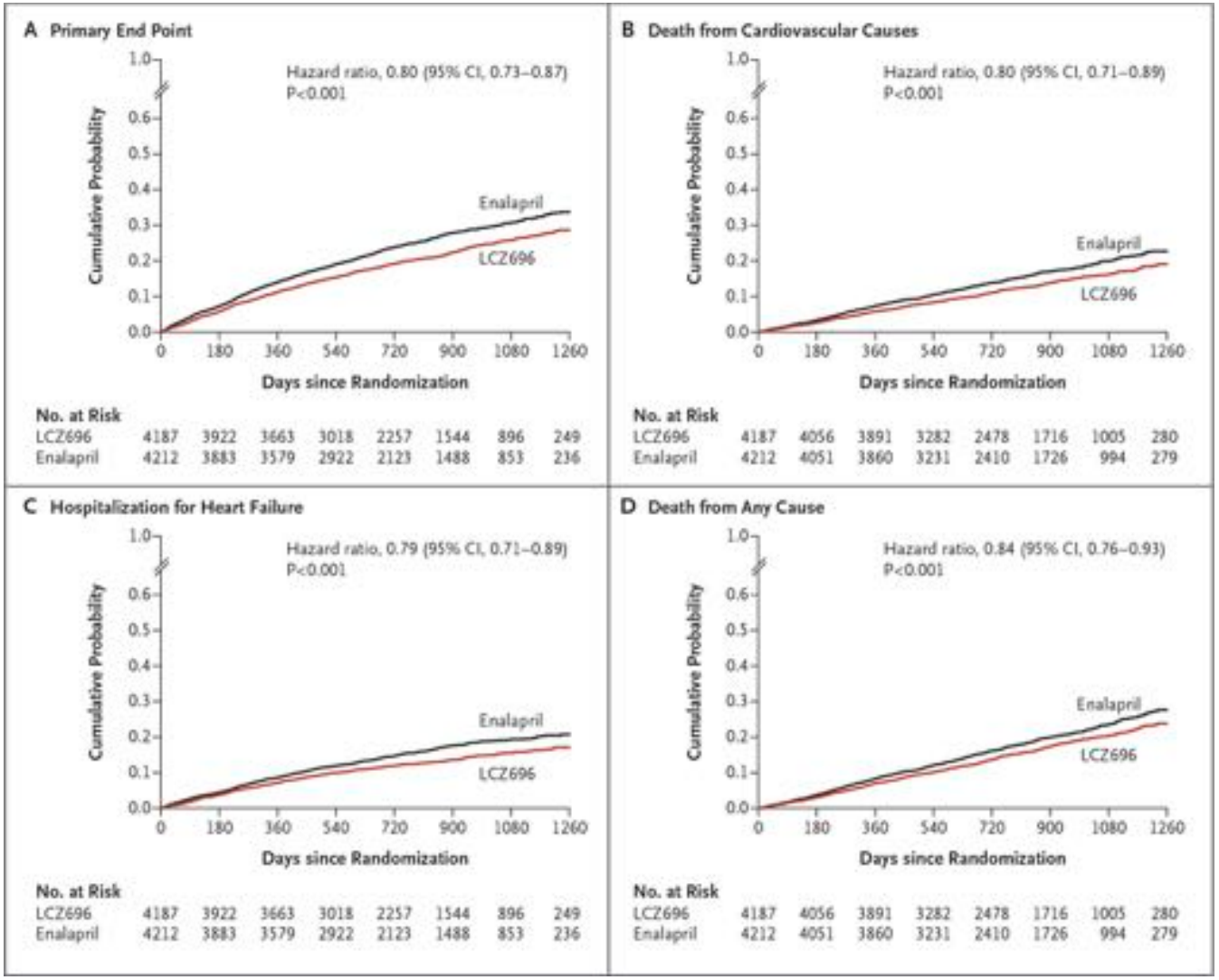
Dual Angiotensin Receptor and Neprilysin inhibition (ARNI) as an alternative to ACE inhibition in patients with chronic systolic HF. Design of the PARADIGM-HF Trial

- Aged ≥ 18 years
- NYHA II-IV LVEF ≤ 40%
- BNP/NTproBNP ≥ 150 / 600 pg/mL



McMurray et al. European Journal of Heart Failure; 15: 1062-73

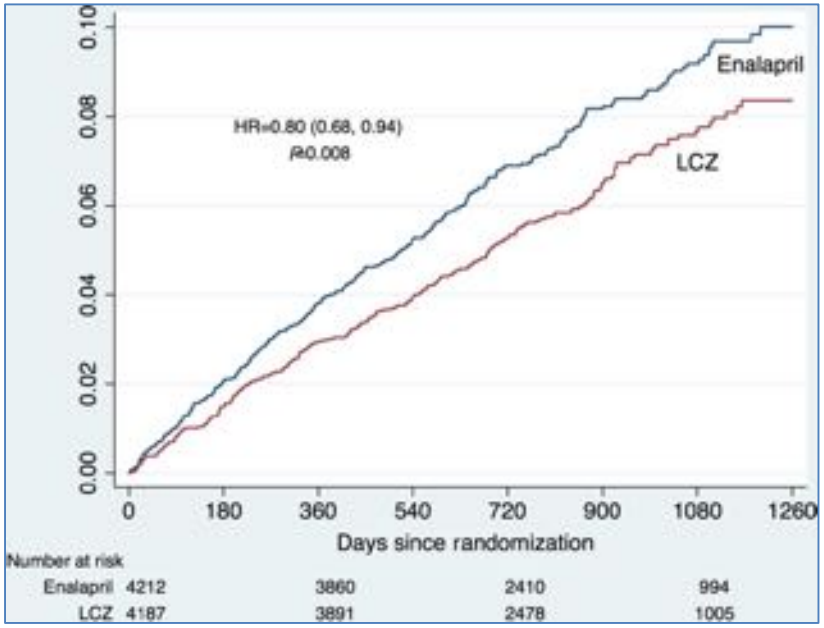
Kaplan–Meier Curves for Key Study Outcomes, According to Study Group



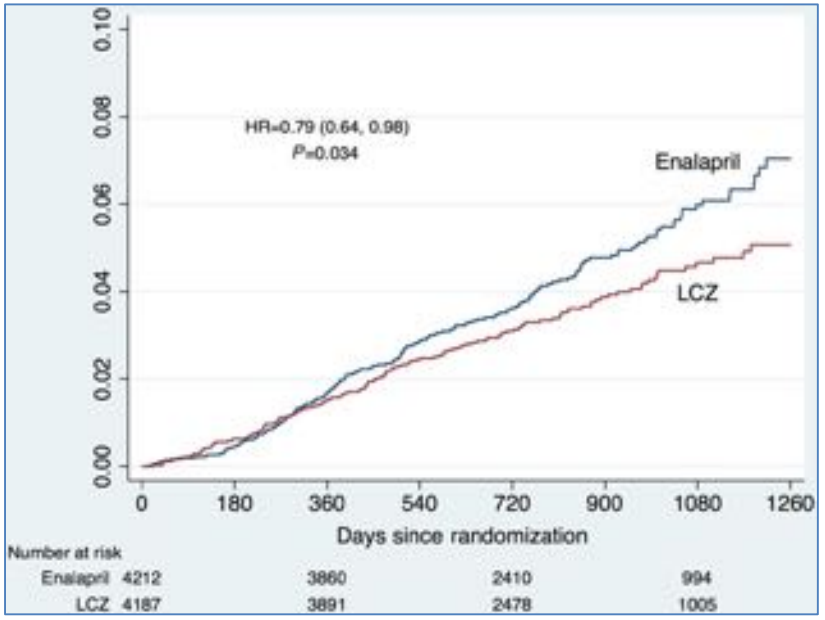
McMurray JJV et al. N Engl J Med 2014;371:993-1004

Effect of LCZ696 compared with enalapril on mode of death in heart failure patients

Sudden cardiac death

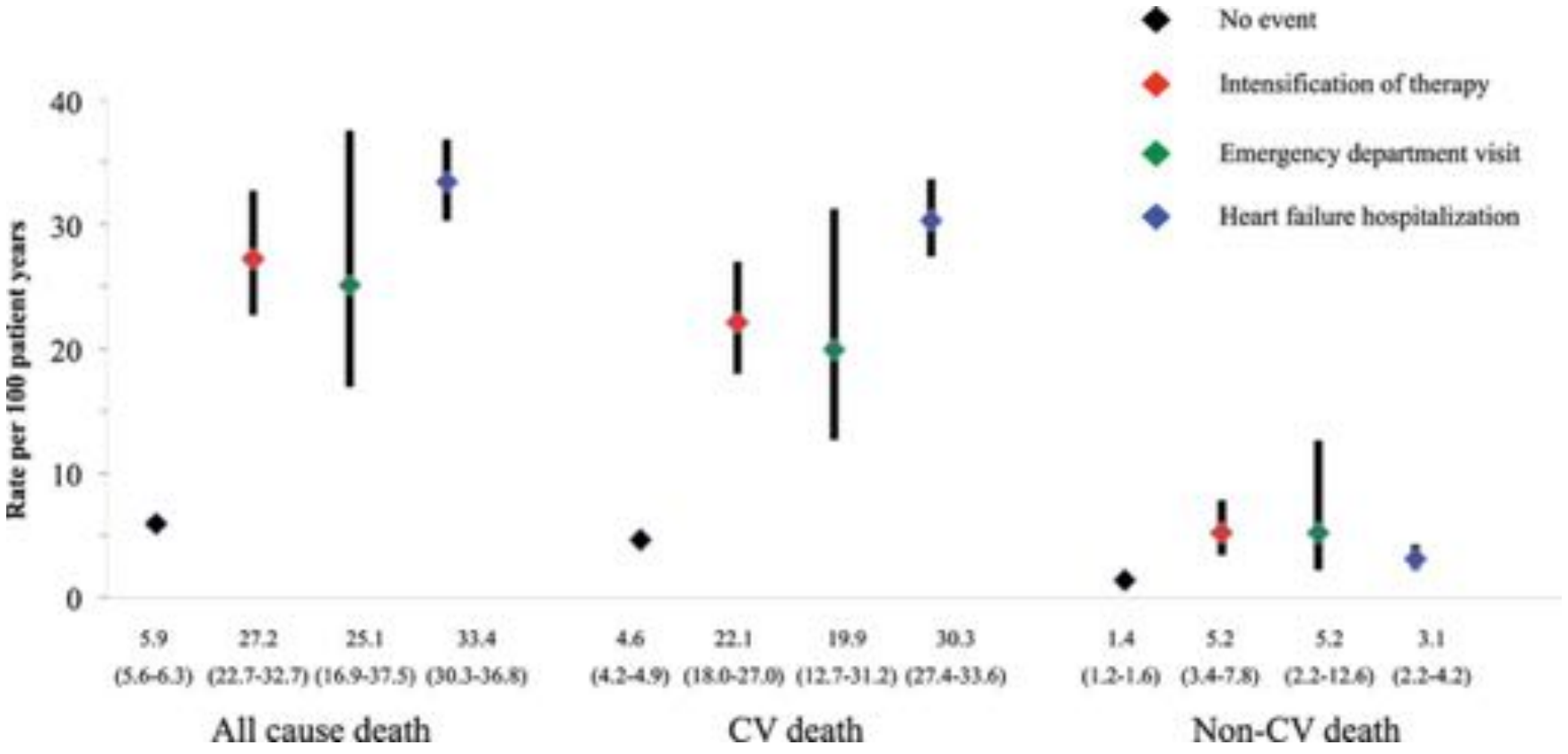


Worsening HF death



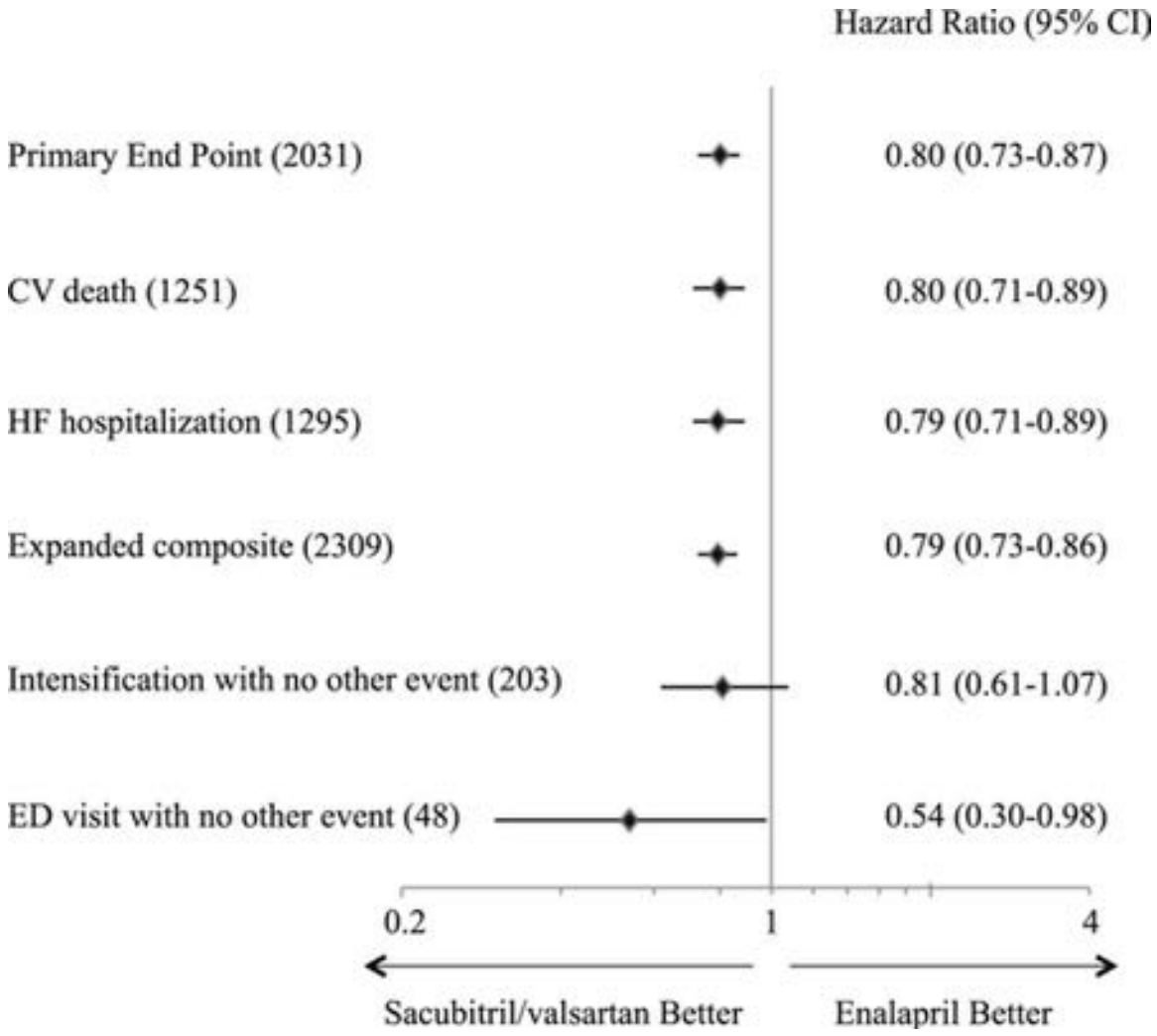
Akshay S. Desai et al. Eur Heart J 2015;36:1990-1997

Mortality (%) after a first event or in patients with no event.



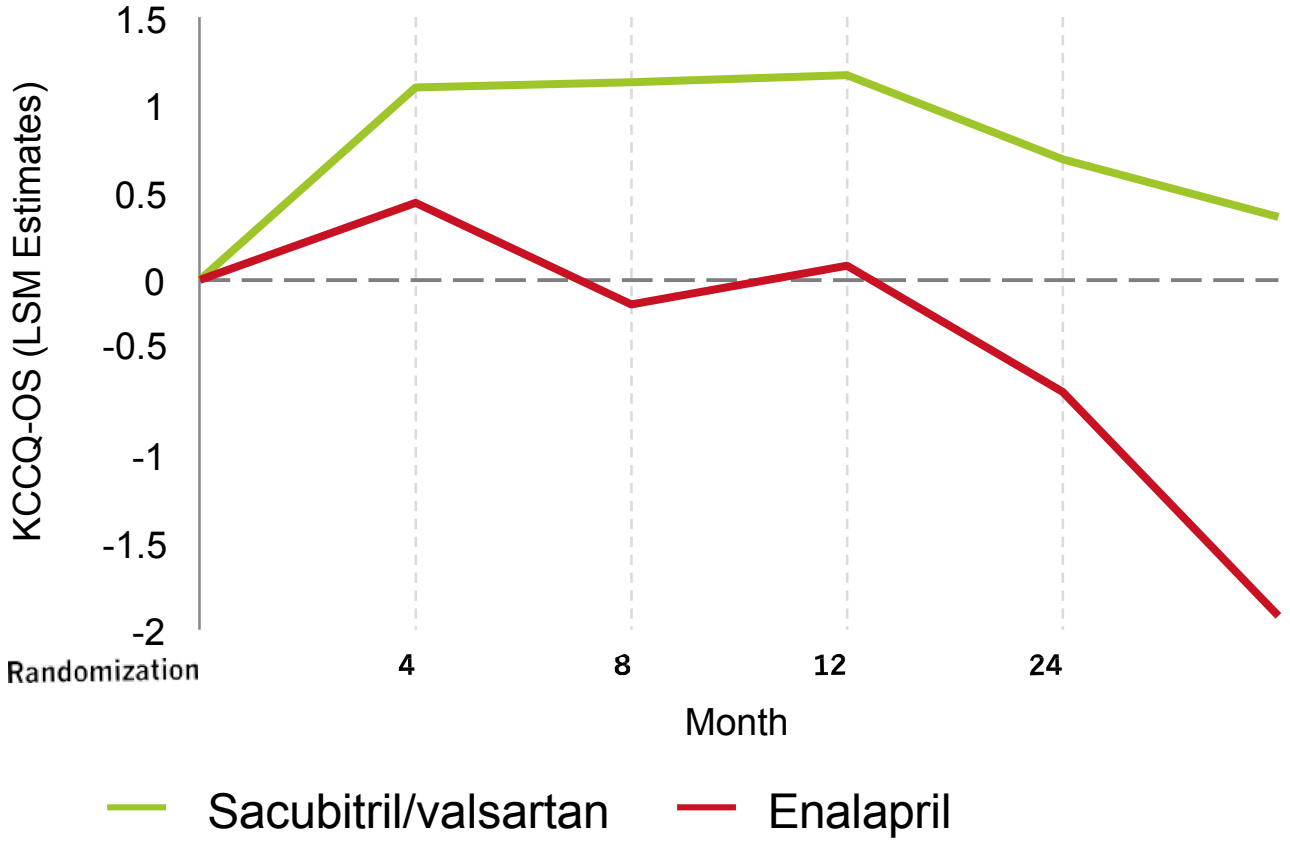
Naoki Okumura et al. Circulation. 2016;133:2254-2262

Effect of sacubitril/valsartan versus enalapril for each outcome.



Naoki Okumura et al. Circulation. 2016;133:2254-2262

Persistent improvement in KCCQ scores with sacubitril/valsartan vs enalapril through 36 months

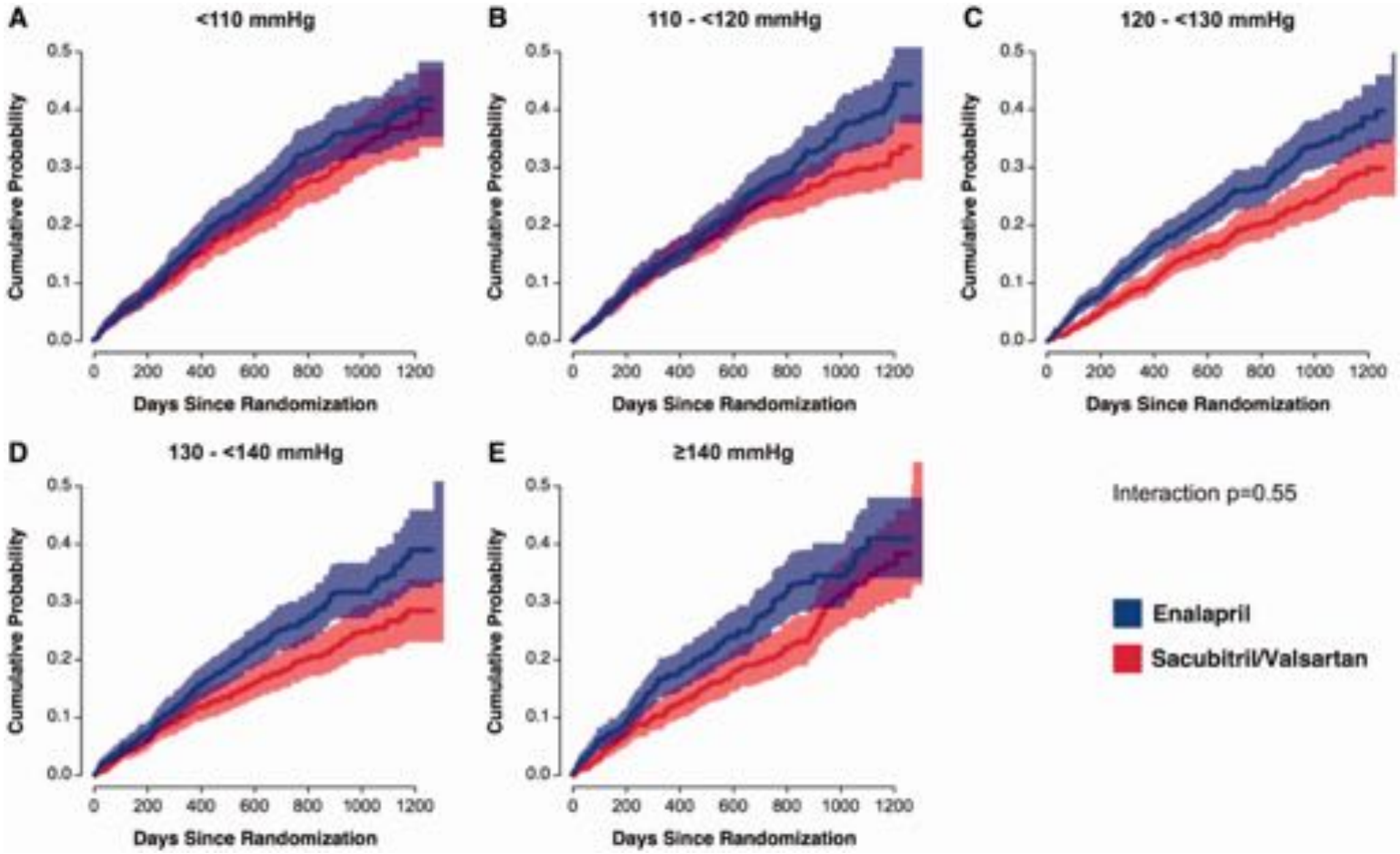


Lewis EF et al. Circ Heart Fail. 2017;10:e003430.

Effect of LCZ696 on Clinical Outcomes: The MAGGIC Risk Score Category

Simpson et al. J Am Coll Cardiol. 2015;66(19):2059-2071.

Kaplan-Meier event curves for the primary endpoint in patients subdivided according to different SBP subgroups

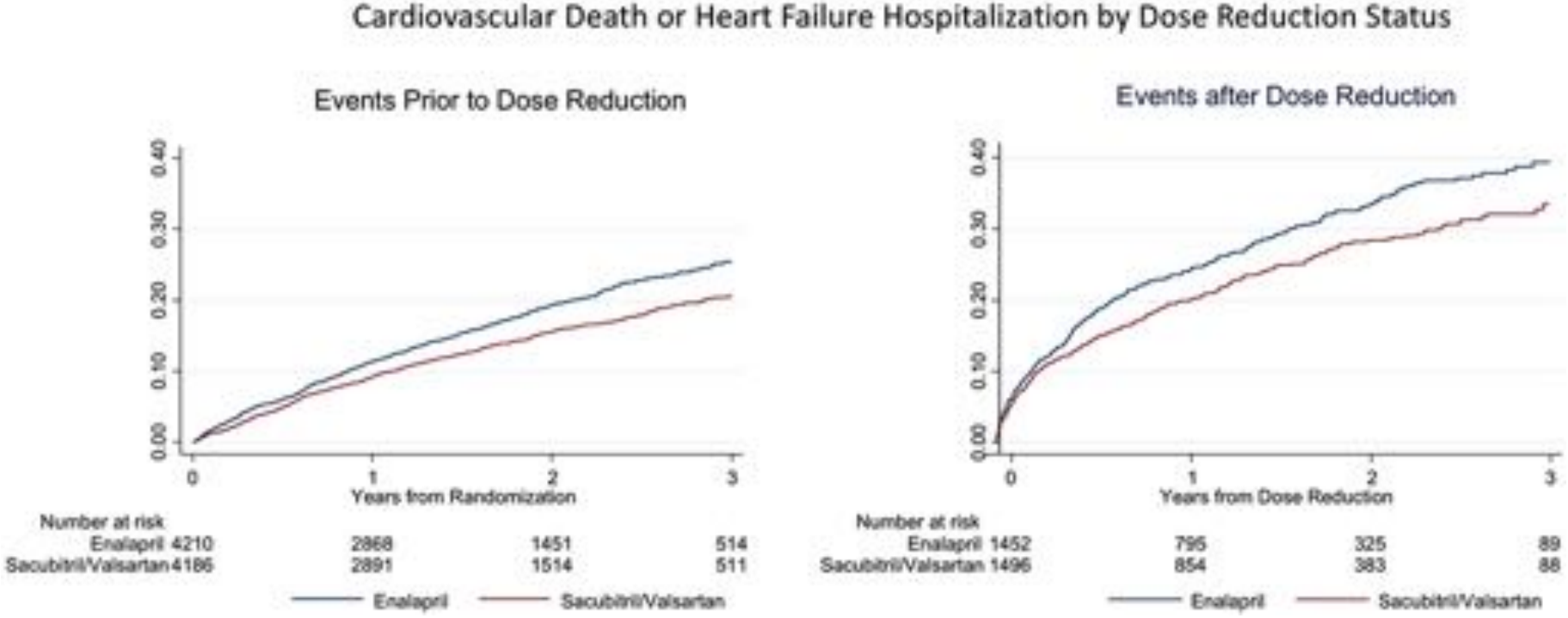


Bohm et al. Eur Heart J. Published online February 01, 2017. doi:10.1093/eurheartj/ehw570

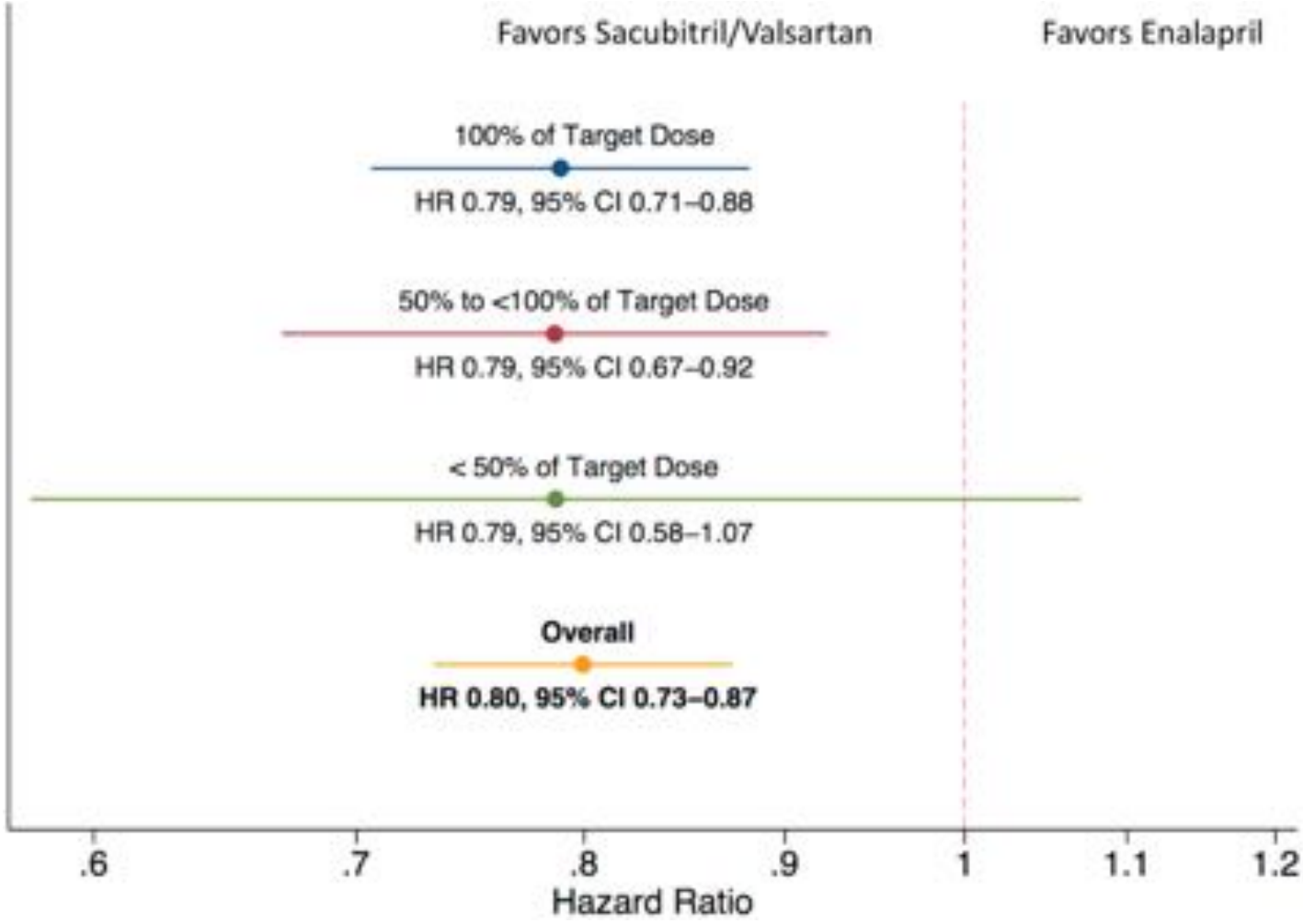
European Journal of Heart Failure (2016)
doi:10.1002/ejhf.580

Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Orly Vardeny[1], Brian Claggett[2], Milton Packer[3], Michael R. Zile[4], Jean Rouleau[5], Karl Swedberg[6], John R. Teerlink[7], Akshay S. Desai[2], Martin Lefkowitz[8], Victor Shi[8], John J.V. McMurray[9], Scott D. Solomon[2]*, for the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators



Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial



Vardeny et al. European Journal of Heart Failure 10 JUN 2016 DOI: 10.1002/ejhf.580

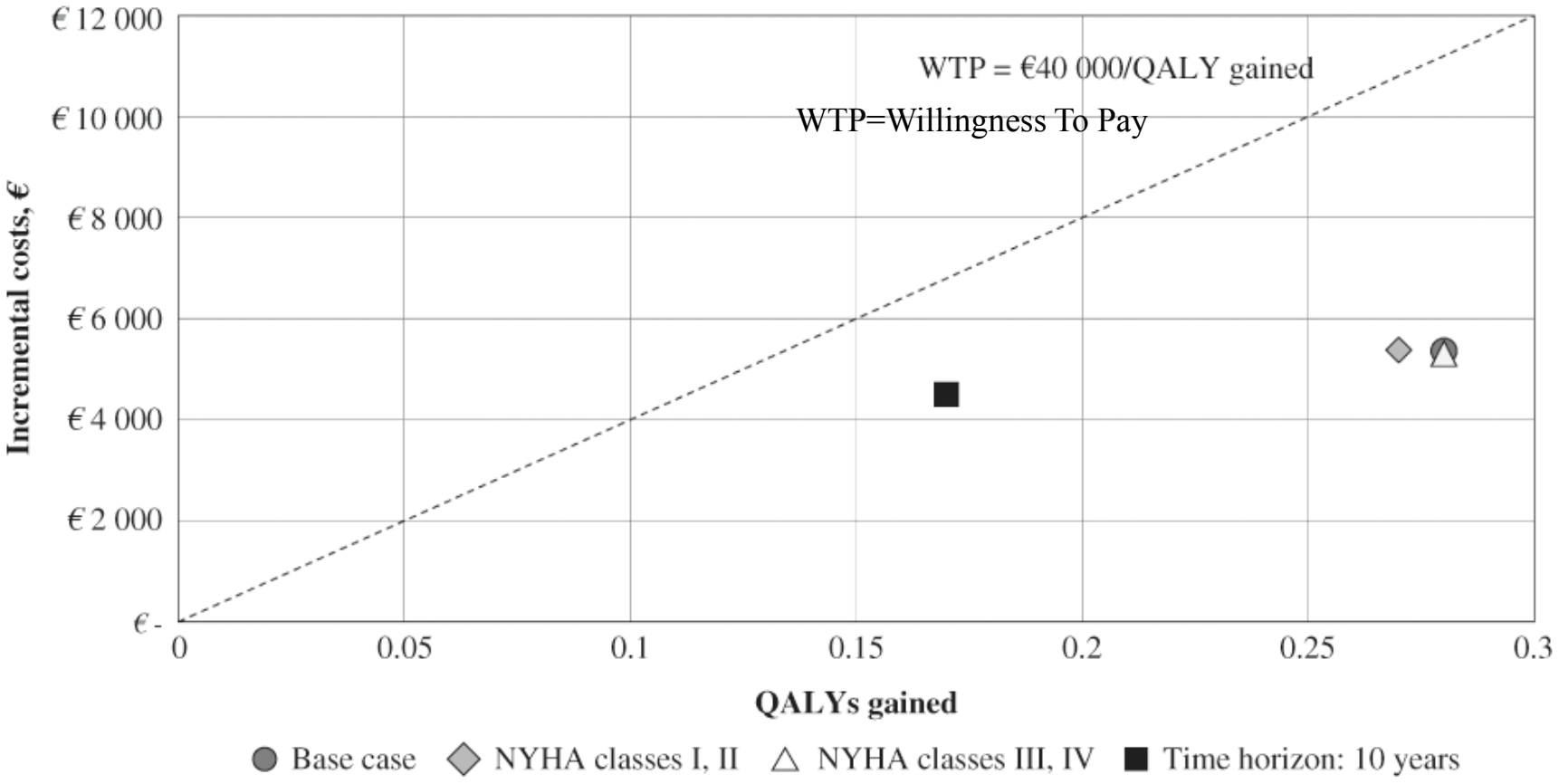
Cost – efficacy of sacubitril/valsartan versus enalapril in HFrEF

Table 1 Model parameters: clinical characteristics, event probabilities, costs and utility values.

Input	Value (range)	Parameter distribution	References
Age, years, mean (range)	71 (60.0–80.0)	Normal	Senni et al. (2014)[1]
Female, %	33.6%	Beta	Senni et al. (2014)[1]
Race and region, %			
White	100%	NA	Assumption
Western Europe	100%	NA	Assumption
NYHA class, %			
I	3.5%	NA	Kristensen et al. (2016)[8]
II	77.1%		
III	19%		
IV	0.4%		
LVEF, %, mean (range)	31.6% (31.1–32.1%)	Normal	Senni et al. (2014)[1]
Event probabilities			
Cardiovascular mortality: sacubitril/valsartan HR	0.80 (0.71–0.89)	LogNormal	PARADIGM-HF trial[7,8]
Hospitalization: sacubitril/valsartan HR	0.84 (0.78–0.91)	LogNormal	PARADIGM-HF trial[7,8]
Monthly probability of hospitalization (enalapril)	0.044 (0.038–0.051)	Beta	PARADIGM-HF trial[7,8]
Discontinuation: sacubitril/valsartan HR	0.89 (0.81–0.99)	LogNormal	PARADIGM-HF trial[7,8]
Monthly probability of discontinuation (enalapril)	0.0104 (0.0050–0.0210)	Beta	PARADIGM-HF trial[7,8]
Costs, €			
Sacubitril/valsartan, per month	126.36	NA	Italian Medicines Agency[9]
Enalapril, per month	9.91		
Background therapy, per month	23.55		
Per hospitalization	4898.11 (3673.58–6122.63)	Gamma	Kristensen et al. (2016)[8] Gazzetta Ufficiale della Repubblica Italiana[10]
HF management, per month	52.42 (39.32–65.53)	Gamma	Maggioni et al. (2016)[1]
Utility			
Baseline utility	0.78 (0.663–0.897)	Beta	PARADIGM-HF trial[7,8]
Utility effect of sacubitril/valsartan	+0.011 (+0.004–+0.017)	Beta	PARADIGM-HF trial[7,8]

D'Angiolella LS, Cortesi PA, Pitotti C, Ritrovato D, Mantovani LG, Senni M. et al. Eur J Heart Fail 28 AUG 2017 DOI: 10.1002/ejhf.919

Incremental costs (€) and quality-adjusted life years (QALYs) gained in comparisons of sacubitril/valsartan with enalapril



D'Angiolella LS, Cortesi PA, Pitotti C, Ritrovato D, Mantovani LG, Senni M. et al. Eur J Heart Fail 28 AUG 2017 DOI: 10.1002/ejhf.919

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations for diagnostic tests in patients with heart failure

Recommendations	Class [a]	Level [b]
The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:		
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C
- natriuretic peptides	IIa	C

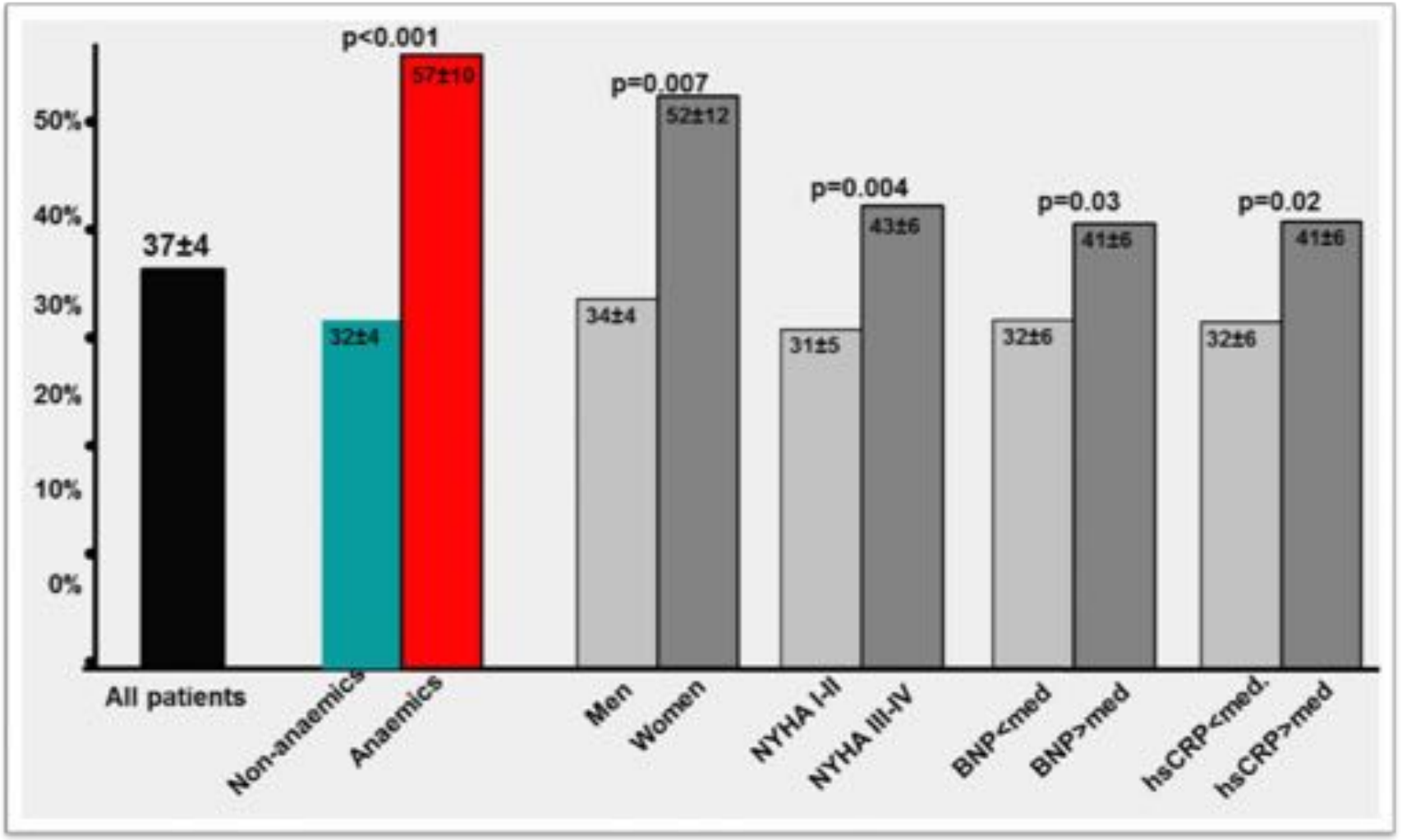
European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

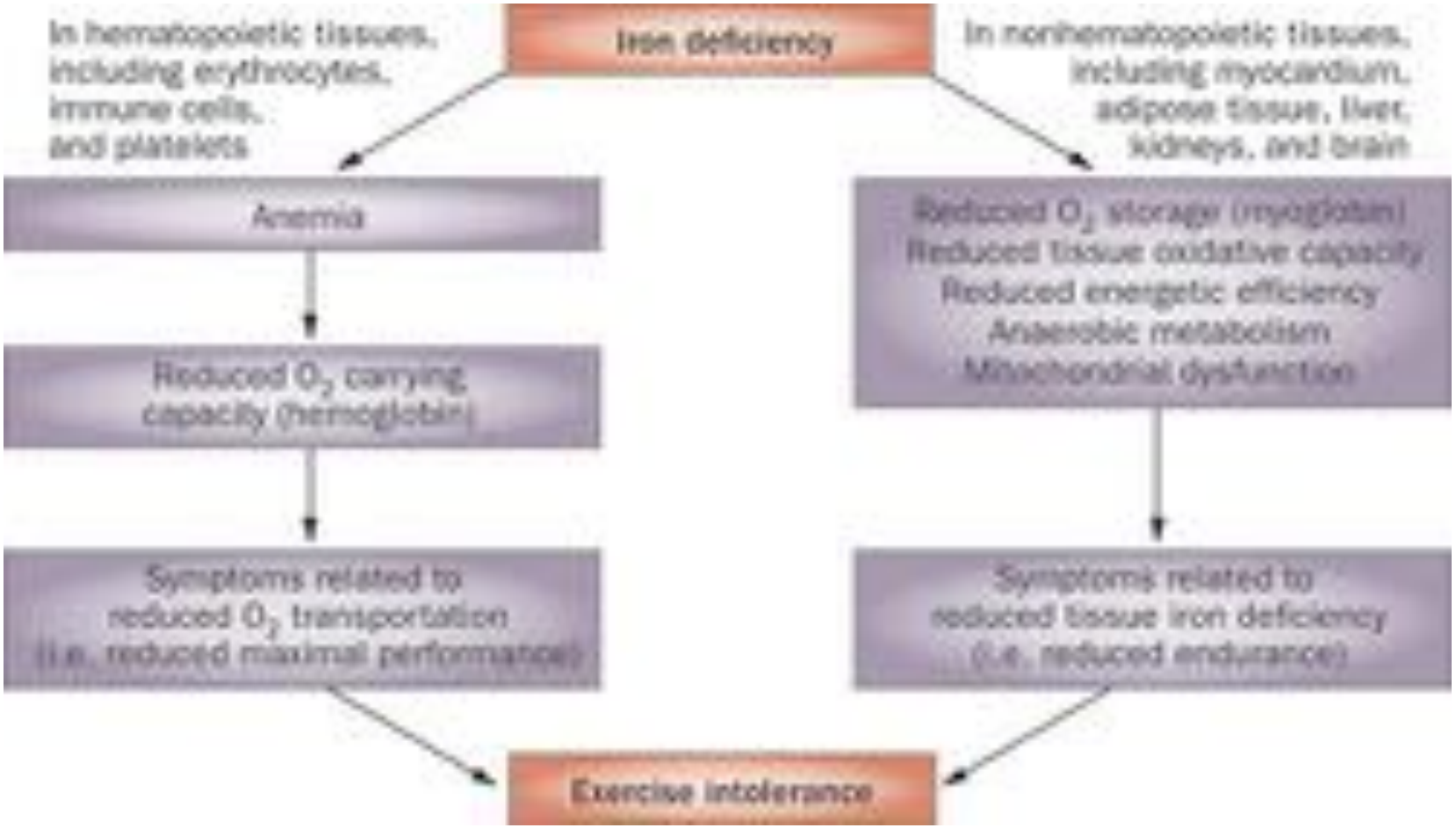
Recommendations	Class [a]	Level [b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A

Prevalence of iron deficiency (ID) in CHF
ID: ferritin <100 μg/dL, or 100-299 μg/dL with TSat <20%



Jankowska E A et al. Eur Heart J 2010;31:1872-1880

Role of iron deficiency in the pathogenesis of exercise intolerance



van Veldhuisen, D. J. et al. (2011) Nat. Rev. Cardiol. doi:10.1038/nrcardio.2011.77

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.473

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

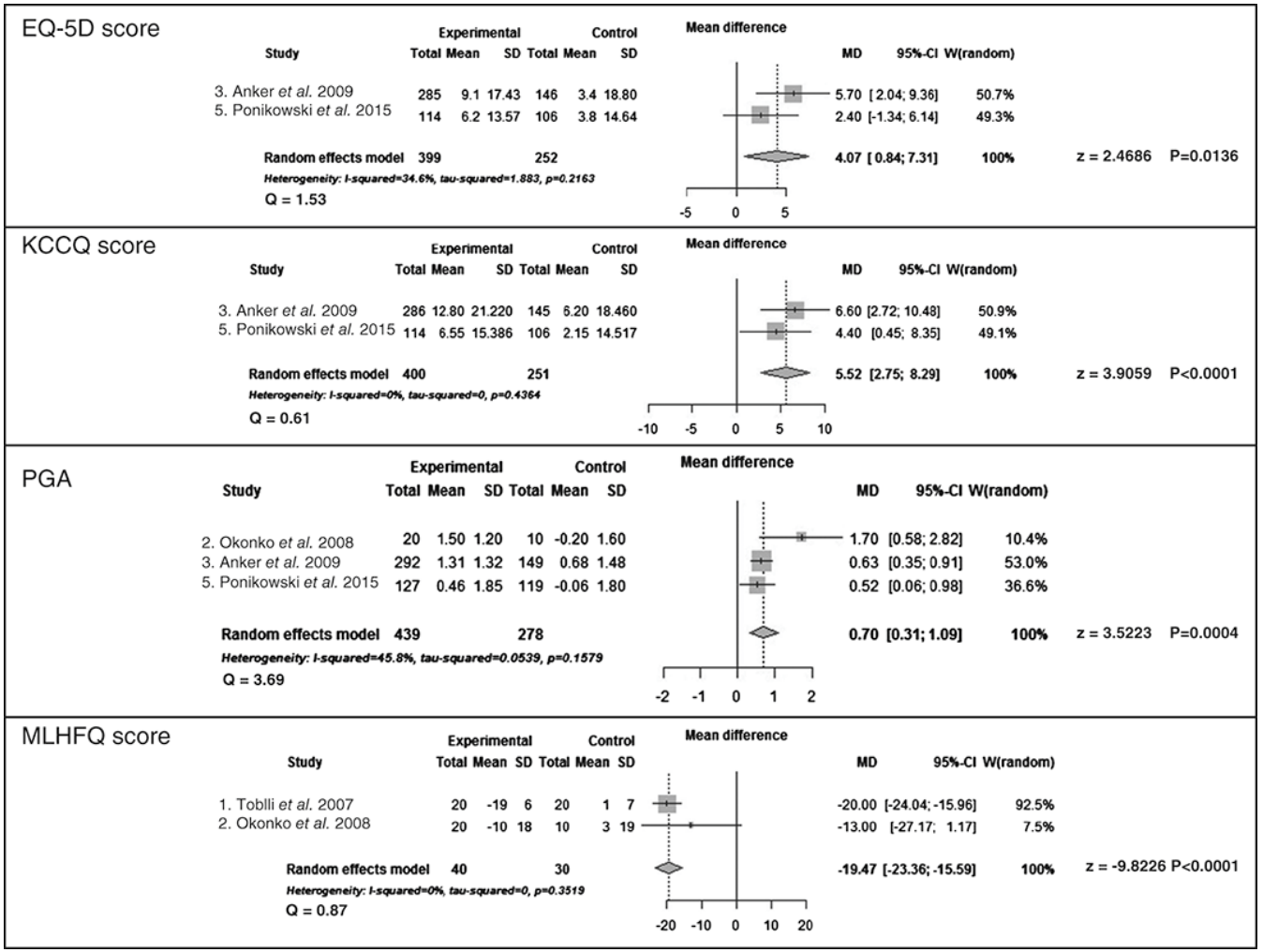
Ewa A. Jankowska[1,2]*, Michał Tkaczyszyn[1,2], Tomasz Suchocki[3], Marcin Drozd[1,2], Stephan von Haehling[4], Wolfram Doehner[5,6], Waldemar Banasiak[2], Gerasimos Filippatos[7], Stefan D. Anker[4], and Piotr Ponikowski[2,8]

Table 1 Continued

Baseline characteristics of studied groups according to the assigned treatment/placebo	Tobili et al. (2007)[10]		Okonko et al. (2008)[10] FERRIC-HF study		Anker et al. (2009)[11] FAIR-HF study		Beck-da-Silva et al. (2013)[20] IRON-HF study		Ponikowski et al. (2015)[11] CONFIRM-HF study	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Number of patients randomized	20	20	24	11	304[F]	155[F]	10	6	150	151
No. of patients who completed the study (= reached endpoint)	20	20	20	10	278	135	–*	–*	133	128
Age (years)	76 ± 7	74 ± 8	64 ± 14	62 ± 11	68 ± 10	67 ± 11	67 ± 8	69 ± 10	69 ± 10	70 ± 9
Female sex (%)	–*	–*	29	27	52	55	33	33	45	49
NT-proBNP (pg/mL)	334 ± 125	268 ± 115	–*	–*	–*	–*	–*	–*	3511 ± 5006	3600 ± 4555
LVEF (%)	31 ± 4	31 ± 2	30 ± 7	29 ± 6	32 ± 6	33 ± 6	25 ± 9	31 ± 7	37 ± 8	37 ± 7
NYHA class	2.9 ± 0.7	2.9 ± 0.6	3.5 ± 0.5[S]	3.5 ± 0.5[S]	3.8 ± 0.4[S]	3.8 ± 0.4[S]	No data	No data	2.5 ± 0.5[S]	2.4 ± 0.5[S]
Ischaemic HF aetiology (%)	60	65	75	73	80.6	79.4	22.2	66.7	83	83
Ferritin (μg/L)	73 ± 30	71 ± 21	62 ± 37	88 ± 62	53 ± 55	60 ± 67	185 ± 146	95 ± 138	57 ± 48	57 ± 42
TSAT	20 ± 1	20 ± 1	20 ± 8	21 ± 9	18 ± 13	17 ± 8	19 ± 10	14 ± 6	20 ± 18	18 ± 8
Haemoglobin (g/dL)	10.3 ± 0.6	10.3 ± 0.5	12.6 ± 1.2	12.2 ± 1.0	11.9 ± 1.3	11.9 ± 1.4	11.2 ± 0.6	10.9 ± 0.7	12.37 ± 1.41	12.42 ± 1.30
Anaemia (%)	100	100	50	55	65	61	100	100	53	48

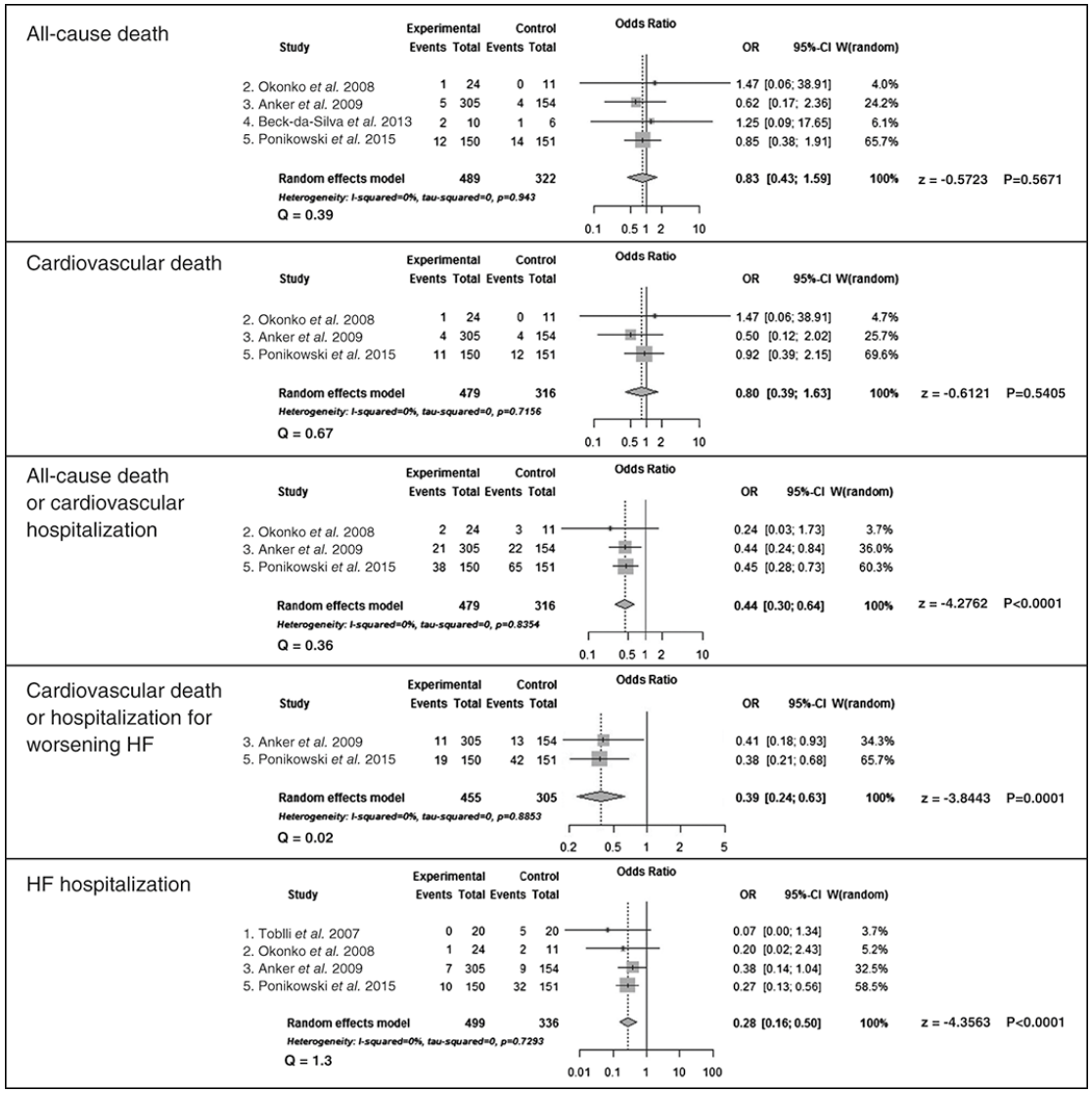
Continuous variables are presented as a mean ± standard deviation of the mean.
CrCl, creatinine clearance; EQ-5D, European Quality of Life–5 Dimensions; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; IVC, iron sucrose; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living With Heart Failure Questionnaire; 6MWT, 6-min walking test; peak VO_2, peak oxygen consumption; PGA, Patient Global Assessment; TSAT, transferrin saturation.
*Given zero events in both the iron and placebo arm, this study was excluded from the analysis.
†Complete data (mean ± SD) regarding the change from baseline not available for the treatment and control arms separately.
‡Indirect data from the meta-analysis of Kapoor et al.[11]
§304 patients were randomized to FCM but one patient assigned to the placebo group received FCM instead and therefore the number of patients treated was 305.
¶No data available in the paper or additional materials online.
#Mean NYHA class as a continuous variable was calculated by the authors of this meta-analysis.

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials



European Journal of Heart Failure
28 JAN 2016 DOI: 10.1002/ejhf.473
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.473/full#ejhf473-fig-0004

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

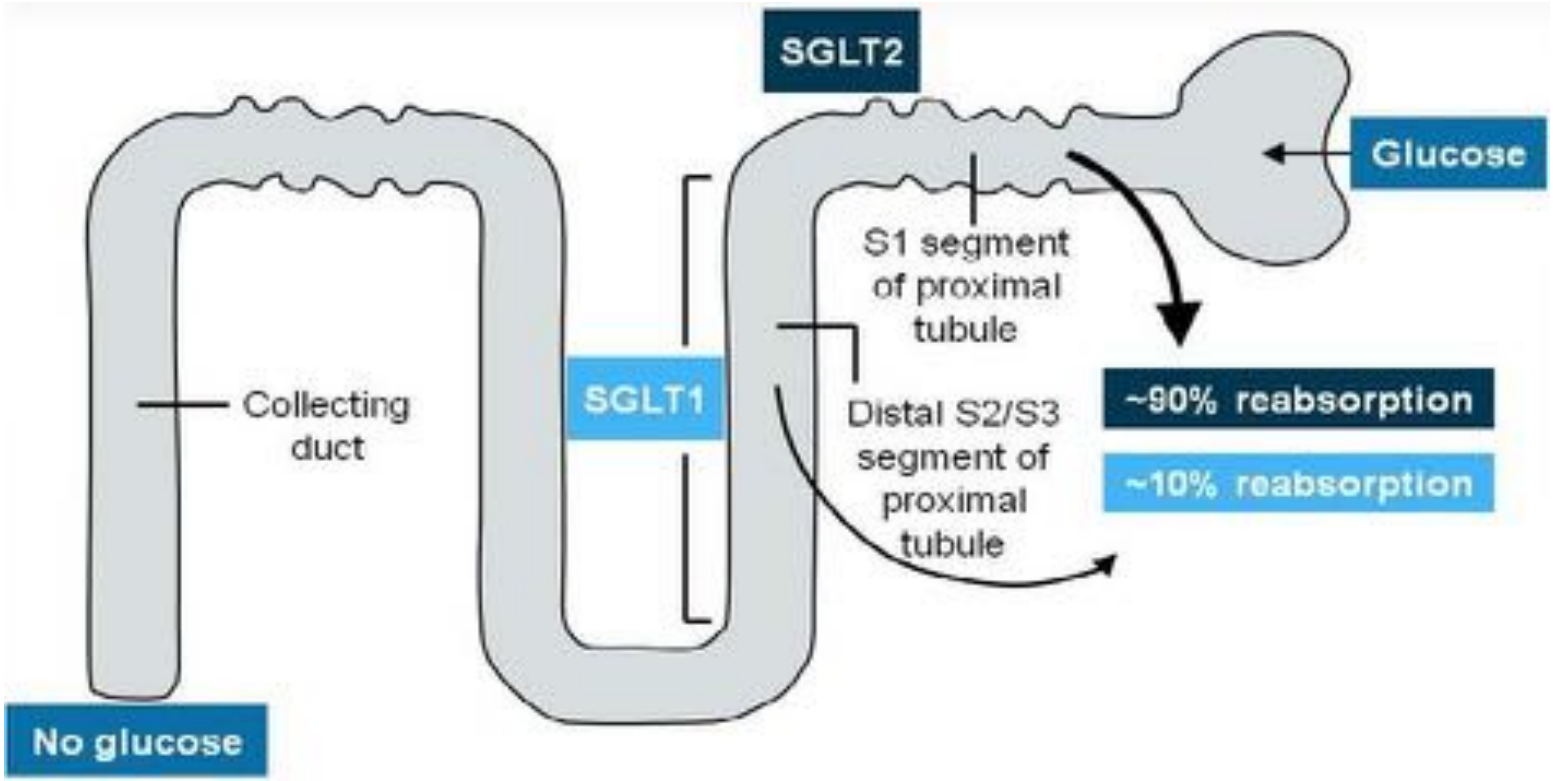


Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

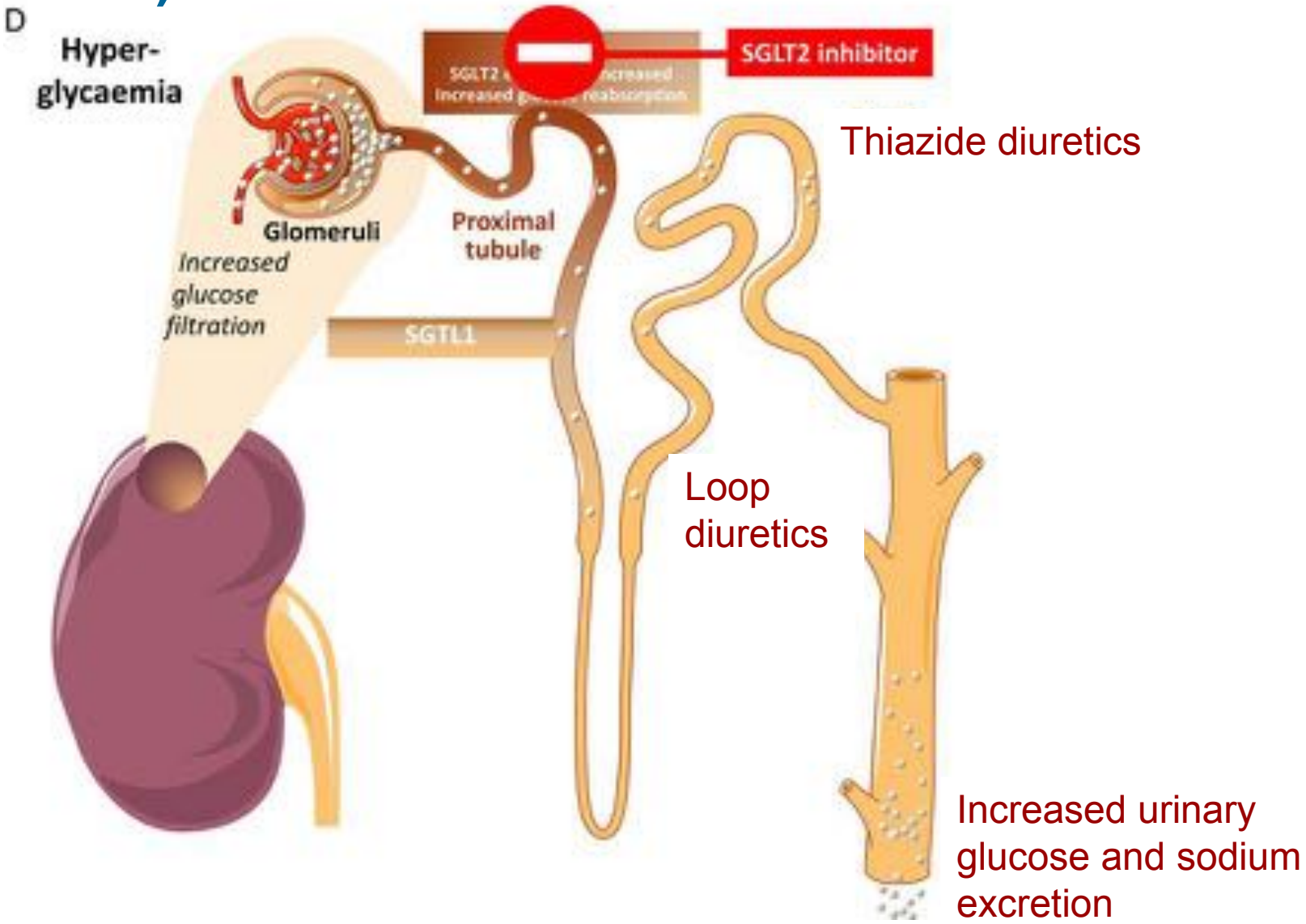
Recommendations	Class [a]	Level [b]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy. in order to prevent sudden death and prolong life.	I	B

SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?

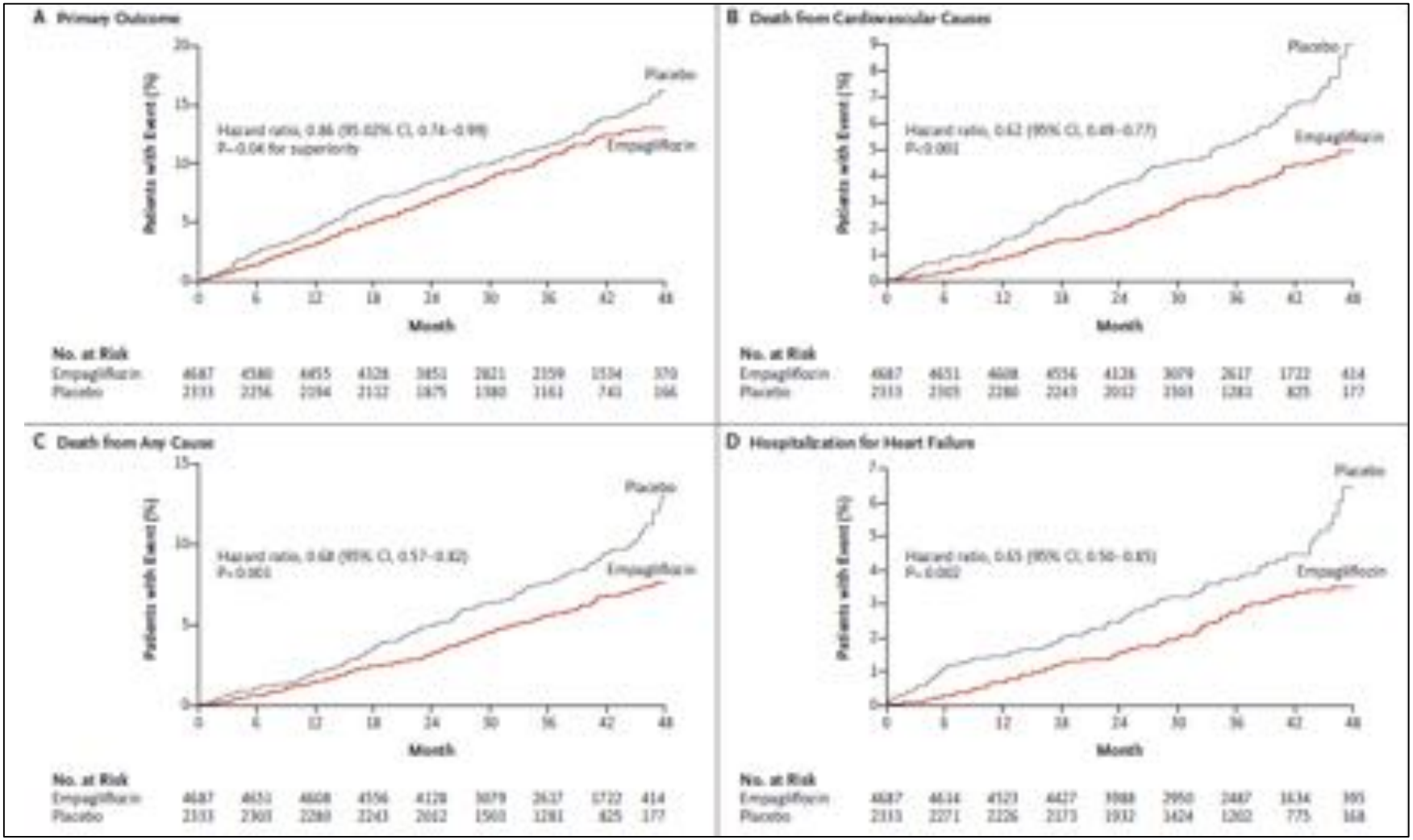


The sodium-glucose cotransporter-2 (SGLT2) inhibitors in antidiabetic treatment



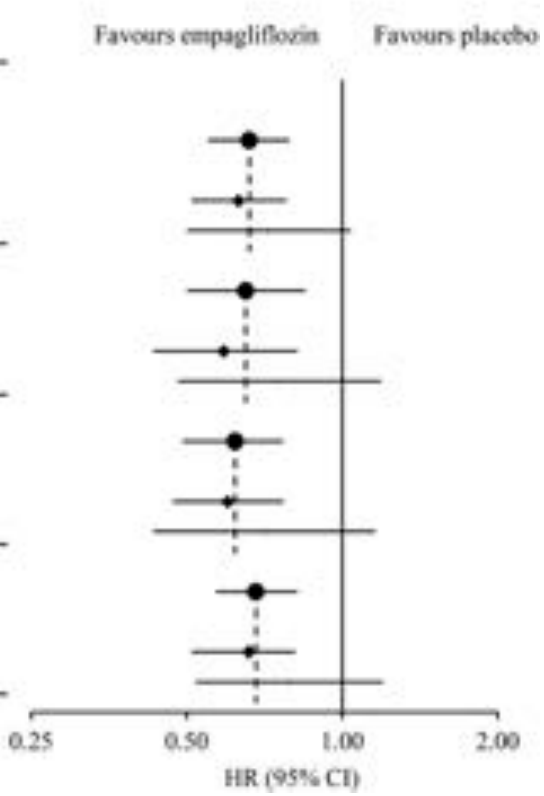
Modified from Nikolaus Marx, and Darren K. McGuire Eur Heart J 2016;37:3192-3200

Empaglifozin, cardiovascular outcomes and mortality. EMPA-REG Outcome trial



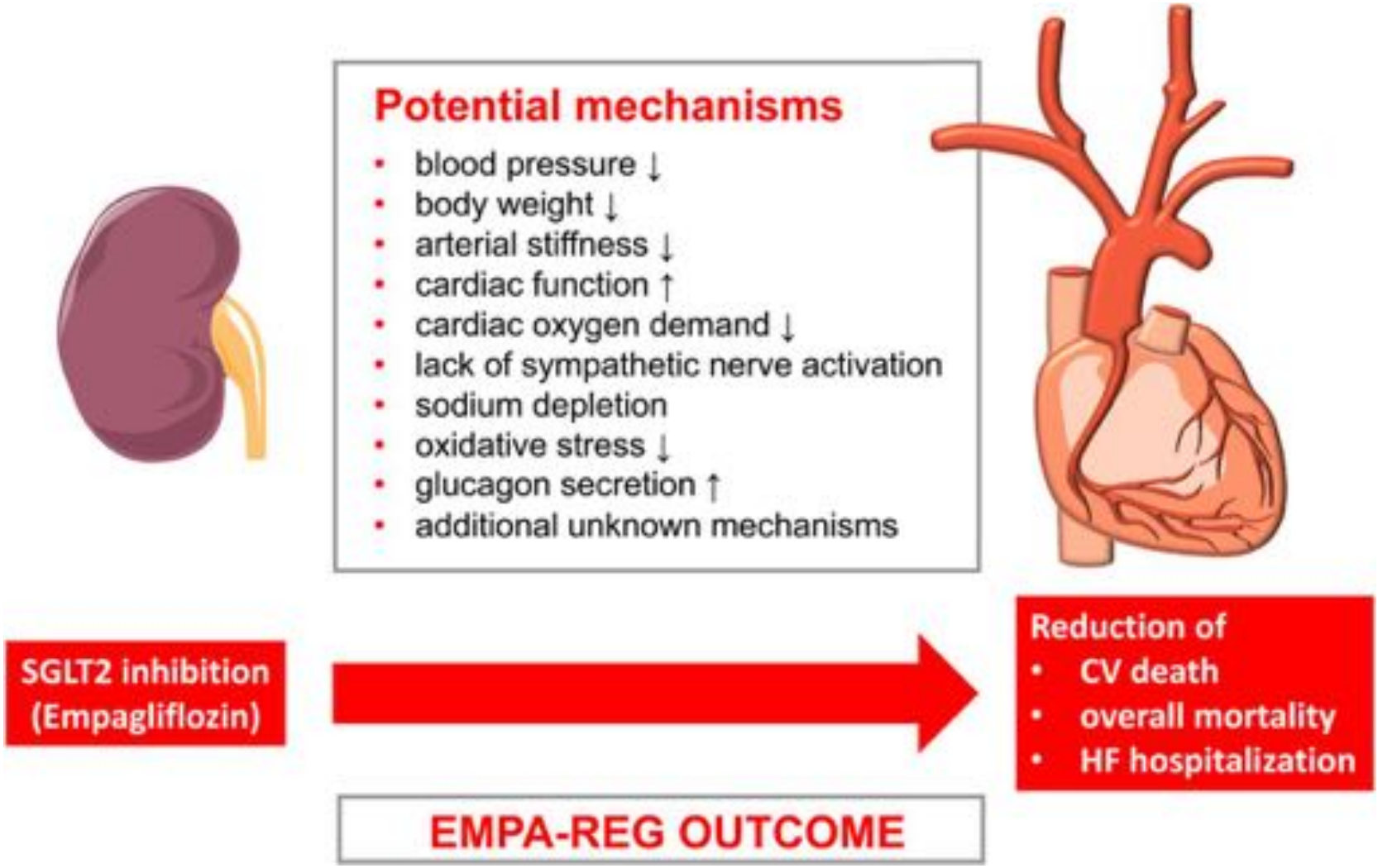
Outcomes in patients with and without heart failure at baseline in EMPA-REG Outcome trial

	Empagliflozin		Placebo		HR (95% CI)
	n with event/*n*	%	*n* with event/*n*	%	
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.72 (0.50–1.04)
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)



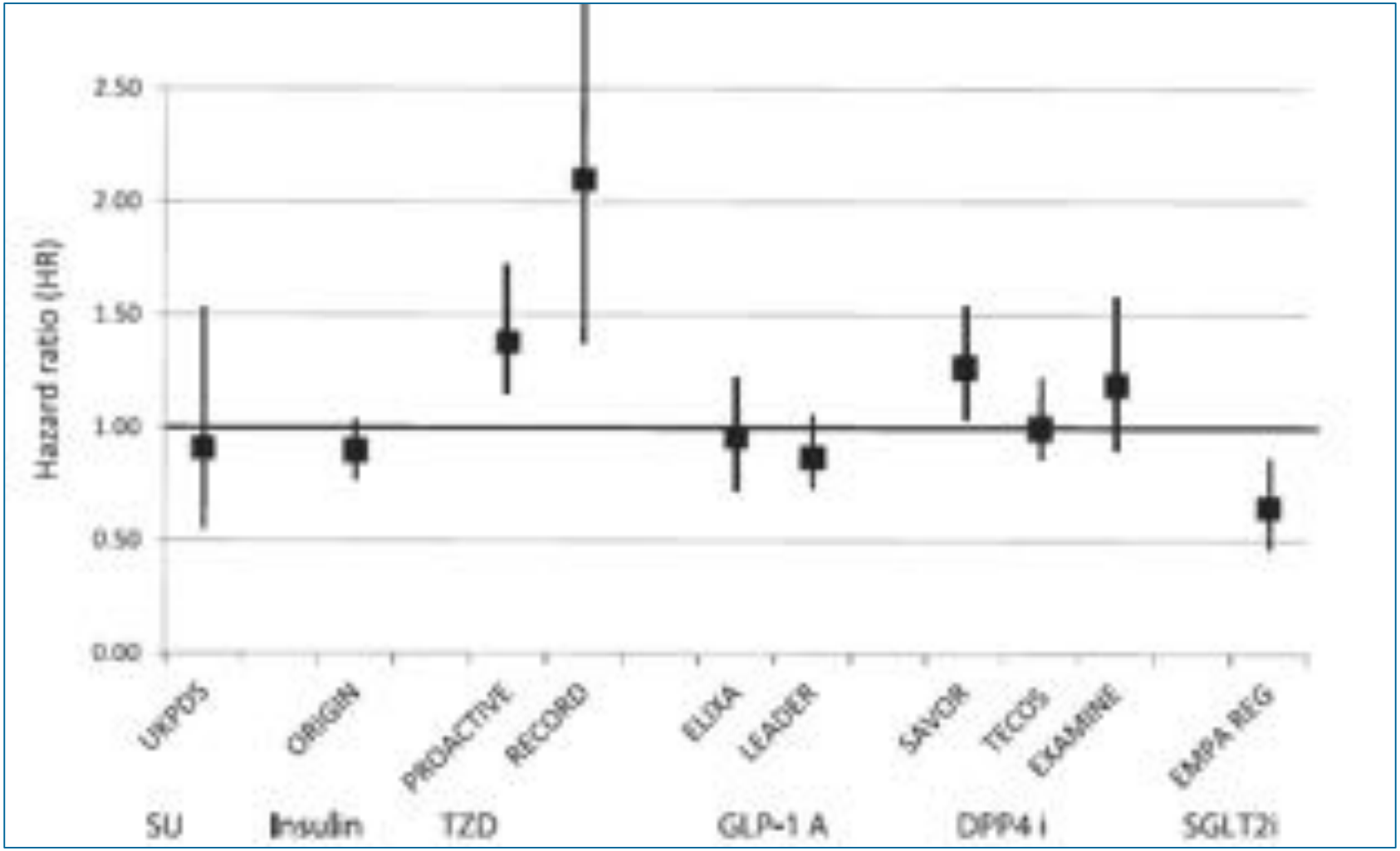
David Fitchett et al. Eur Heart J 2016;37:1526-1534

Potential mechanisms involved in the reduction of CV events (cardiovascular death, total mortality, and HF hospitalization) observed in the EMPA-REG OUTCOME



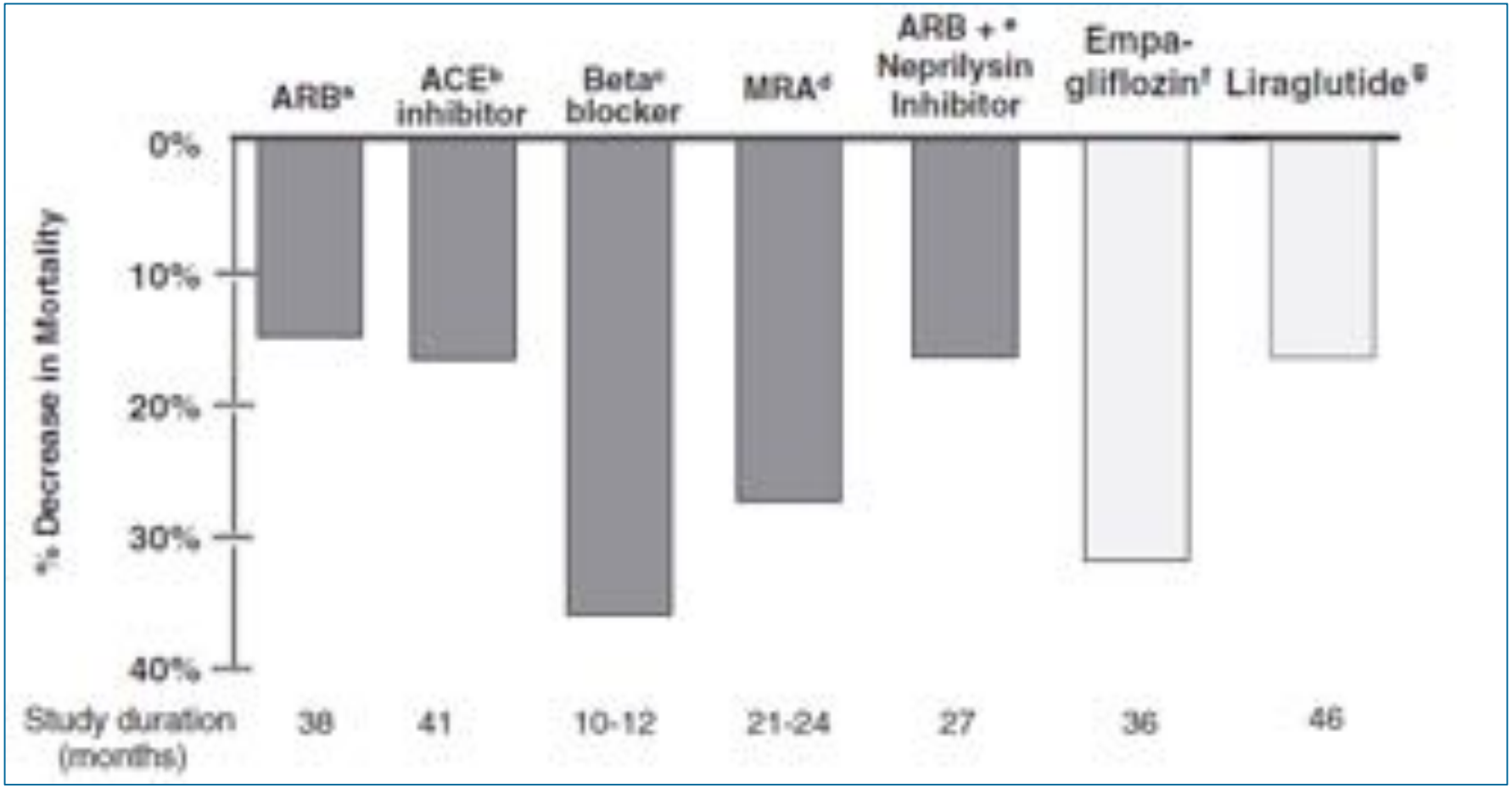
Nikolaus Marx, and Darren K. McGuire Eur Heart J 2016;37:3192-3200

Impact of glucose-lowering drugs on HF hospitalizations



Fitchett, Udell, Inzucchi Eur J Heart Fail 2016. doi:10.1002/ejhf.633

Comparison of all-cause mortality reductions in HF trials and in CV outcomes trials in diabetics



Fitchett, Udell, Inzucchi Eur J Heart Fail 2016. doi:10.1002/ejhf.633

Table. Ongoing Trials with SGLT-2 Inhibitors

Drug	Cohort	Primary Endpoint
Canagliflozin*	Chronic HF	Change from baseline aerobic exercise capacity at 12 weeks Change from baseline ventilator efficiency at 12 weeks
Dapagliflozin*	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*	HFpEF HFrEF	Time to first adjudicated CV death or adjudicated hospitalization for HF
Luseogliflozin	HFpEF	Change in BNP at 12 weeks
Ertugliflozin	n/a	n/a
Sotagliflozin	n/a	n/a

* Currently approved by Food and Drug Administration and European Medicines Agency

European Journal of Heart Failure (2015) 17, 828–836
doi:10.1002/ejhf.309

Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm: a nationwide cohort study

Emil Wolsk[1]*, Morten Lamberts[1], Morten L. Hansen[1], Paul Blanche[2], Lars Køber[3], Christian Torp-Pedersen[4], Gregory Y. H. Lip[5,†], and Gunnar Gislason[1,6,†]

[1]Department of Cardiology, Gentofte Hospital, University of Copenhagen, Gentofte, Denmark; [2]Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark; [3]The Heart Centre, Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [4]Institute of Health, Science and Technology, Aalborg University, Aalborg, Denmark; [5]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; and [6]The National Institute of Public Health, University of Southern Denmark, Odense, Denmark

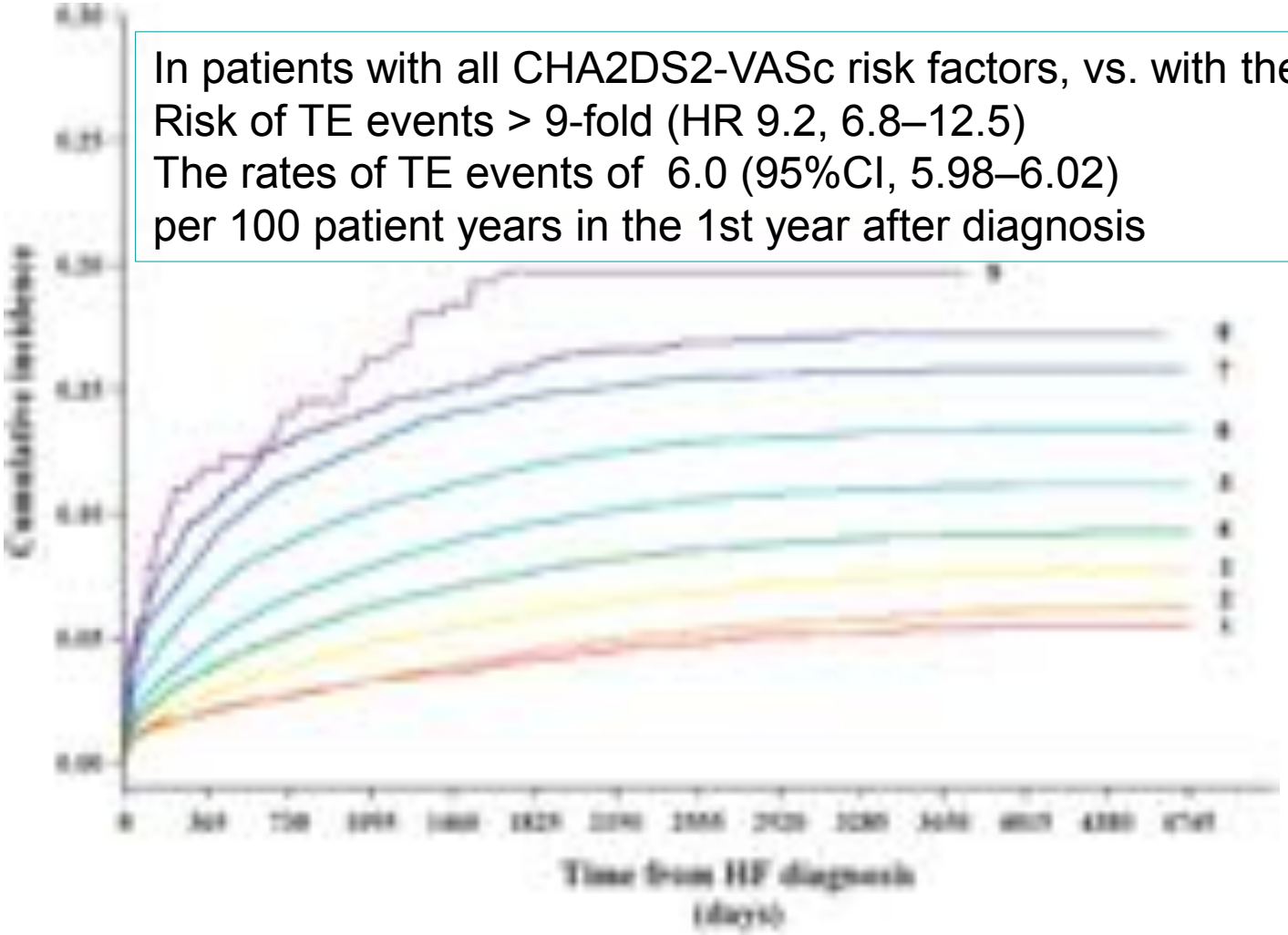
Received 7 January 2015; revised 25 February 2015; accepted 20 May 2015; online publish-ahead-of-print 2 July 2015

Aims Patients with heart failure in sinus rhythm are at an increased risk of thromboembolic complications. So far, validated risk stratification tools are lacking for such patients, which makes the decision to initiate anti-thrombotic treatment difficult.

Methods and results We included 136 545 patients admitted with heart failure in sinus rhythm from national registries from 1999 to 2012. Patients receiving oral anticoagulants were omitted from the study. First, we investigated if the CHA_2DS_2-VASc

Thromboembolism according to CHA_2DS_2-VASc classification. Data from 136 545 patients admitted with HF in sinus rhythm from national registries, 1999 to 2012.

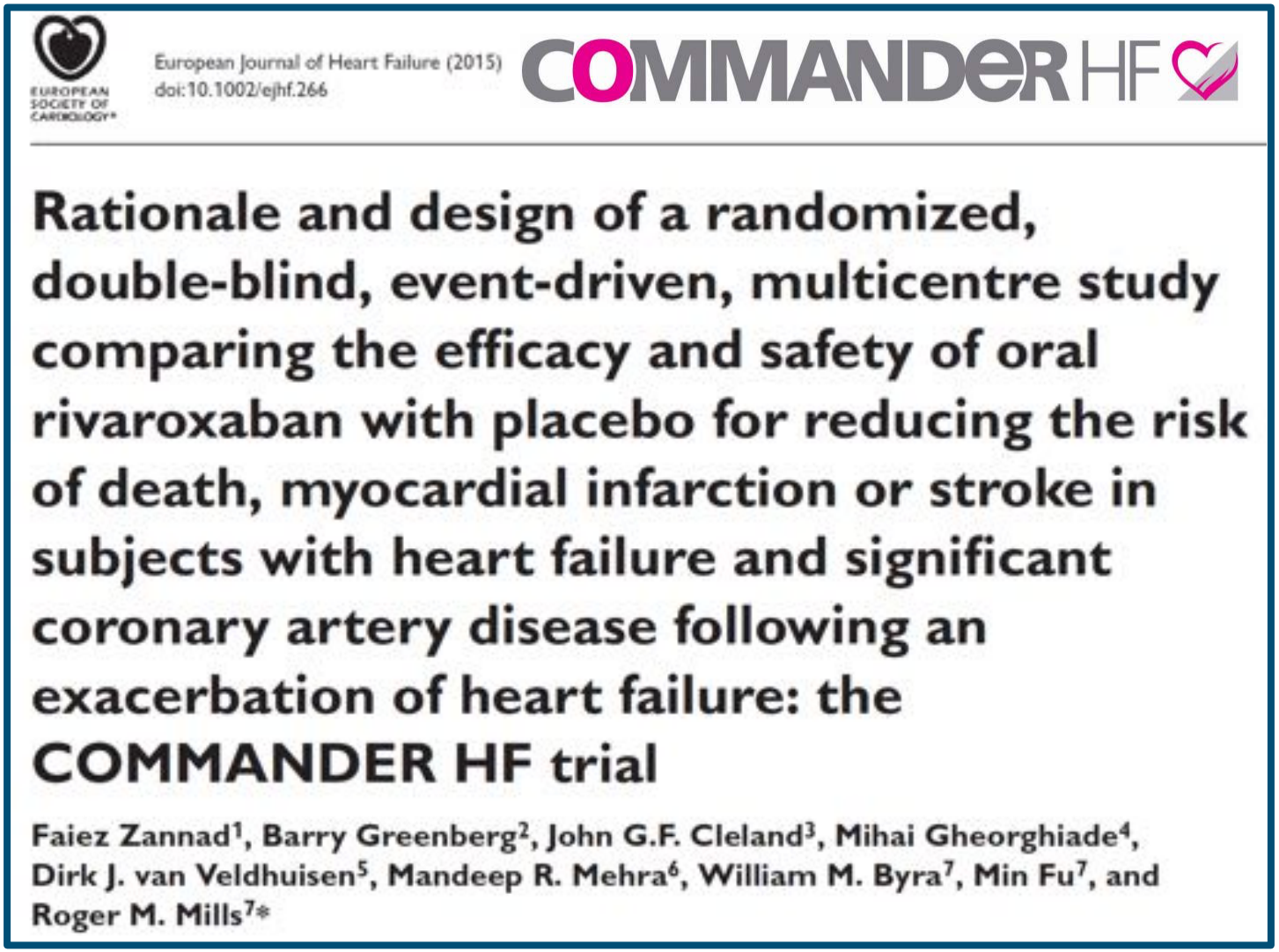
In patients with all CHA2DS2-VASc risk factors, vs. with the others:
Risk of TE events > 9-fold (HR 9.2, 6.8–12.5)
The rates of TE events of 6.0 (95%CI, 5.98–6.02)
per 100 patient years in the 1st year after diagnosis



Wolsk et al. Eur J Heart Fail 2015; 17: 828-836,

COMMANDER HF

Cardiovascular Outcome Modification, Measurement AND Evaluation of Rivaroxaban in patients with Heart Failure



European Journal of Heart Failure (2015)
doi:10.1002/ejhf.266

COMMANDER HF

Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

Faiez Zannad[1], Barry Greenberg[2], John G.F. Cleland[3], Mihai Gheorghiade[4], Dirk J. van Veldhuisen[5], Mandeep R. Mehra[6], William M. Byra[7], Min Fu[7], and Roger M. Mills[7]*

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval.[453,454] Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium[455] and preventing recurrent hyperkalaemia in patients with HF and CKD in the context of treatment with RAAS inhibitors.[456]

A New Era for the Treatment of Hyperkalemia?

Julie R. Ingelfinger, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.

Original Investigation

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia

The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD

Sodium Zirconium Cyclosilicate in Hyperkalemia

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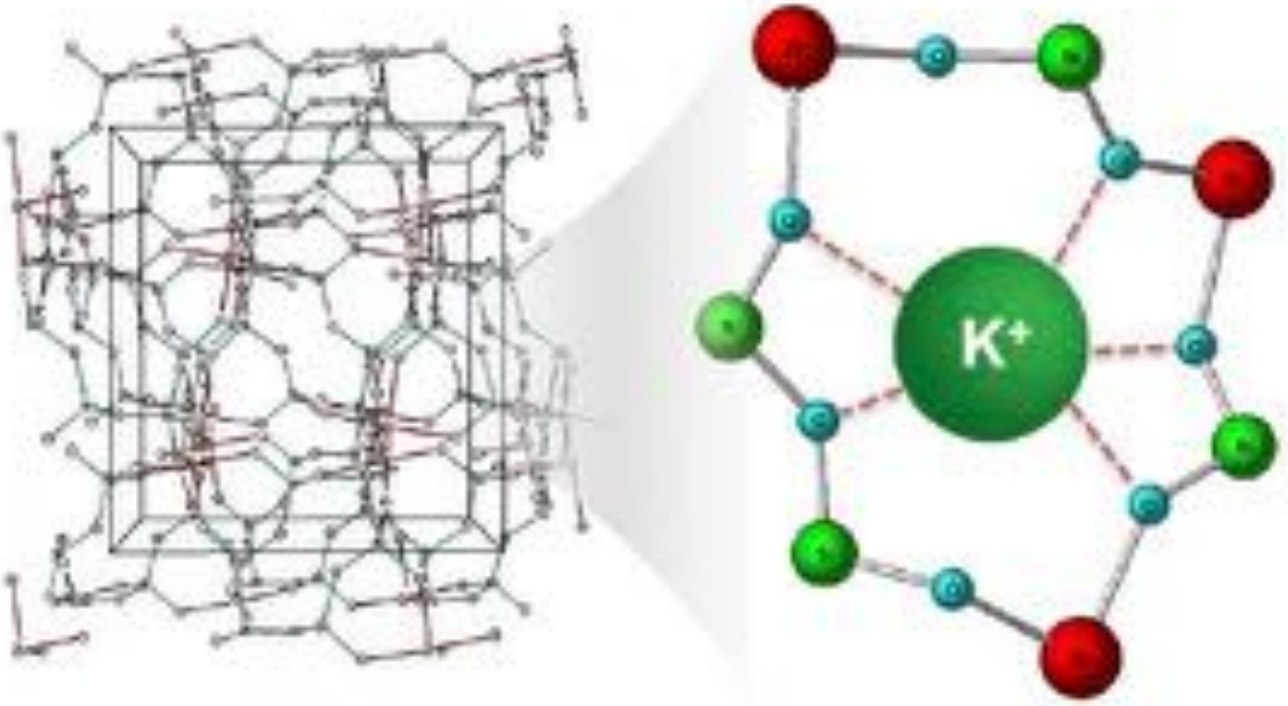
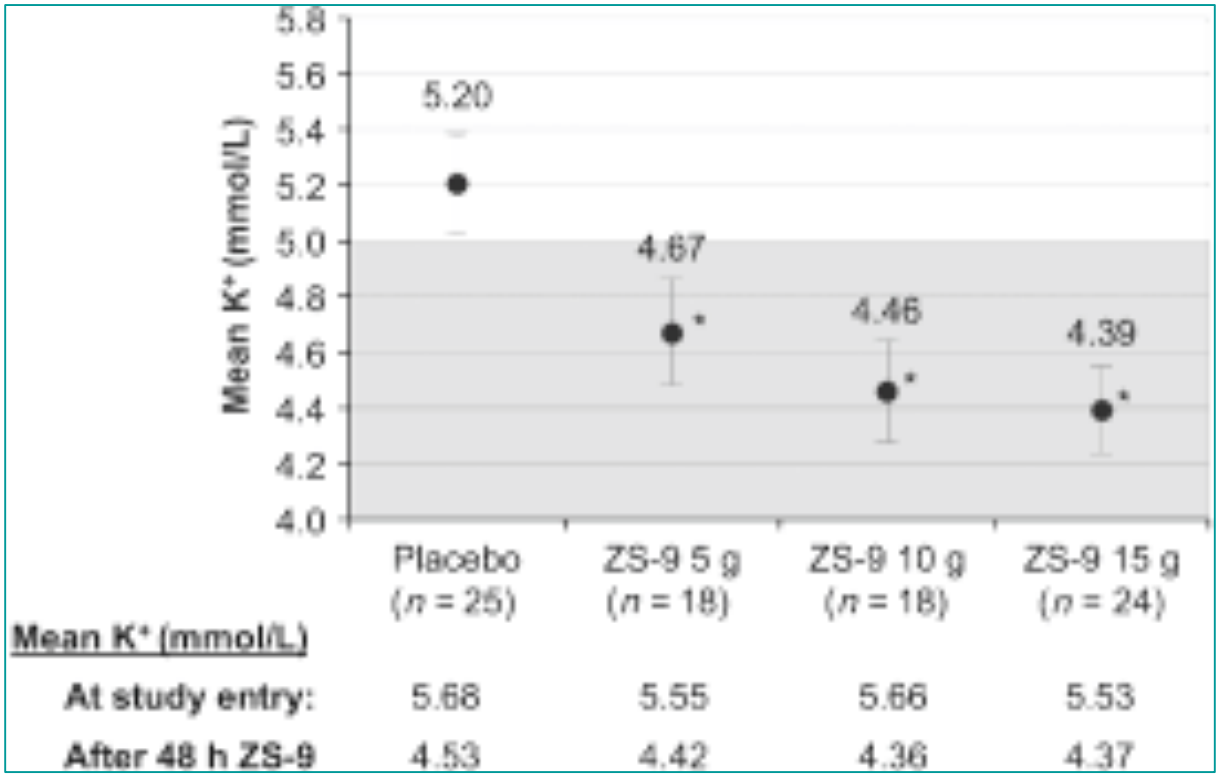


This article was published on November 21, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1411487

K+ = potassium, Z = zirconium, S = silicon

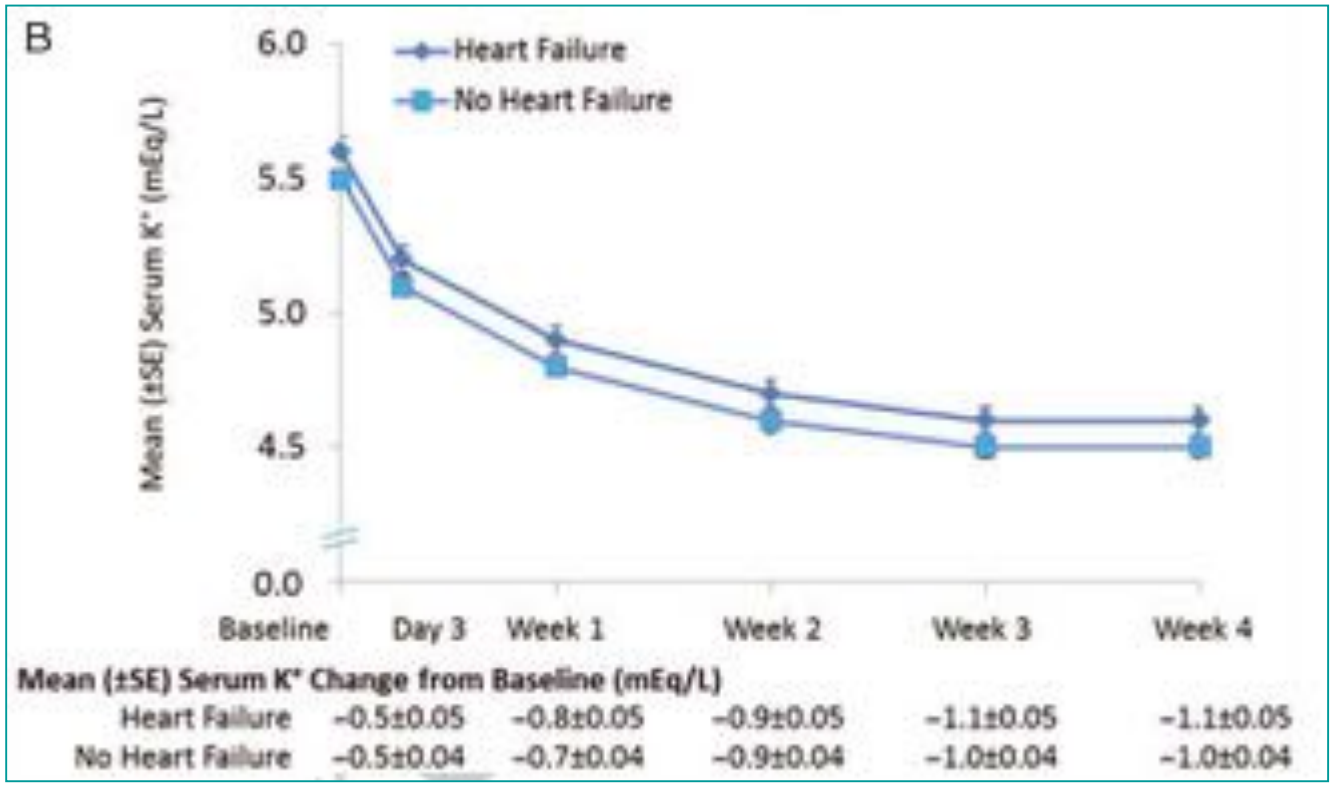
Mean serum potassium after randomization



Mean K⁺ (mmol/L)	Placebo (*n* = 25)	ZS-9 5 g (*n* = 18)	ZS-9 10 g (*n* = 18)	ZS-9 15 g (*n* = 24)
At study entry:	5.68	5.55	5.66	5.53
After 48 h ZS-9	4.53	4.42	4.36	4.37

Anker et al. Eur J Heart Fail; 16 JUN 2015 DOI: 10.1002/ejhf.300

Serum potassium levels over time in OPAL-HK Trial



Mean (±SE) Serum K⁺ Change from Baseline (mEq/L)					
Heart Failure	−0.5±0.05	−0.8±0.05	−0.9±0.05	−1.1±0.05	−1.1±0.05
No Heart Failure	−0.5±0.04	−0.7±0.04	−0.9±0.04	−1.0±0.04	−1.0±0.04

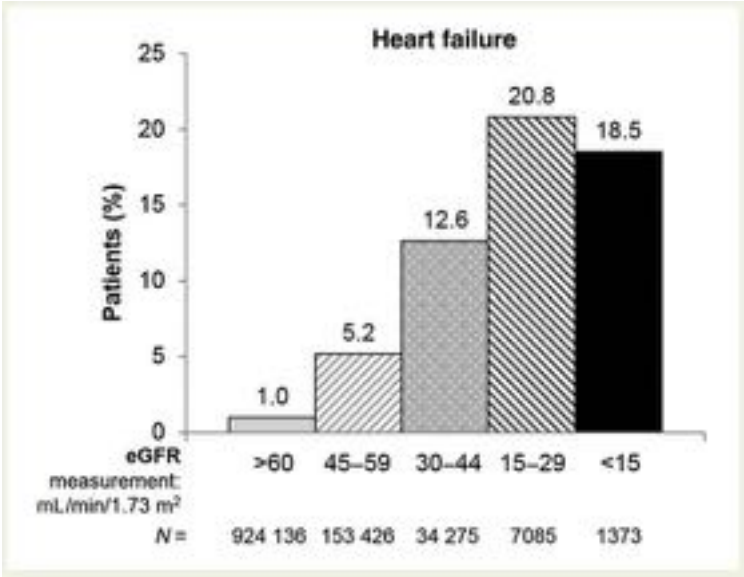
Pitt et al. Eur J Heart Fail; doi:10.1002/ejhf.402

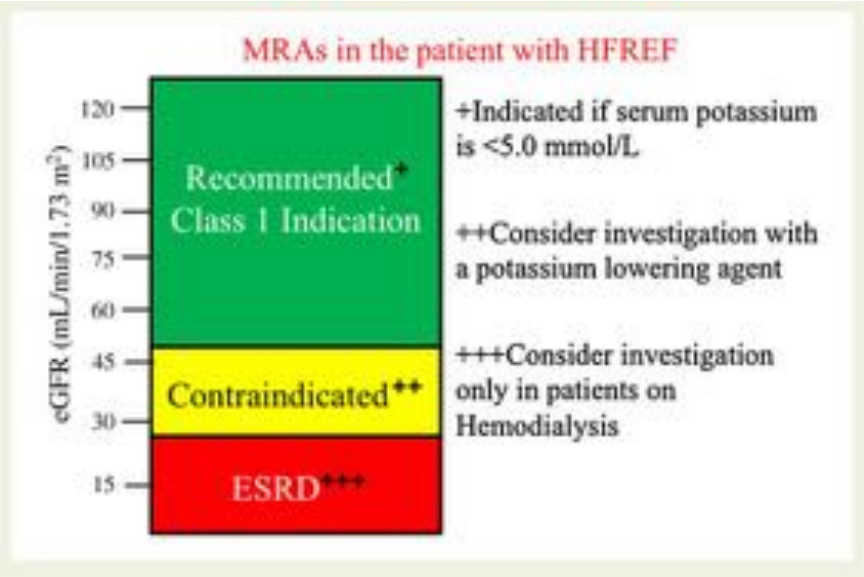
European Heart Journal (2016) **37**, 3130–3134
doi:10.1093/eurheartj/ehw222

CURRENT OPINION

A propitious time for initiating clinical trials in patients with heart failure with reduced ejection fraction and an estimated glomerular filtration rate <30 mL/min with an mineralocorticoid receptor antagonist and a K^+ binder: 'the forbidden fruit'

Murray Epstein[1]* and Bertram C. Pitt[2]

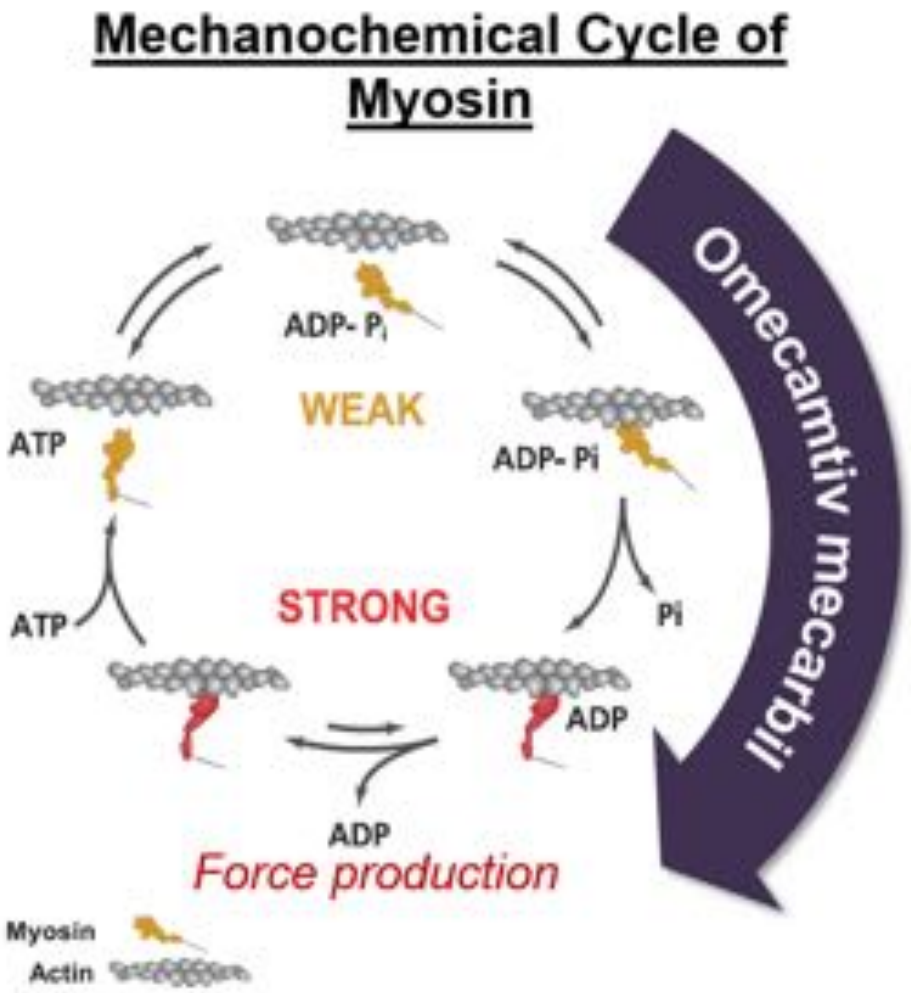




Inotropic agents for the treatment of heart failure

- Sympathomimetic agents
- PDE-3 Inhibitors
- Levosimendan
  - Intermittent administration
- **SERCA Activators, istaroxime**
- **Myosin activators, omecamtiv mecarbil**
- **Mitochondrial targeted peptides, elamipretide**
- **Recombinant neoregulin**

Omecamtiv mecarbil: A small molecule selective cardiac myosin activator



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

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http://dx.doi.org/10.1016/j.jacc.2016.01.031

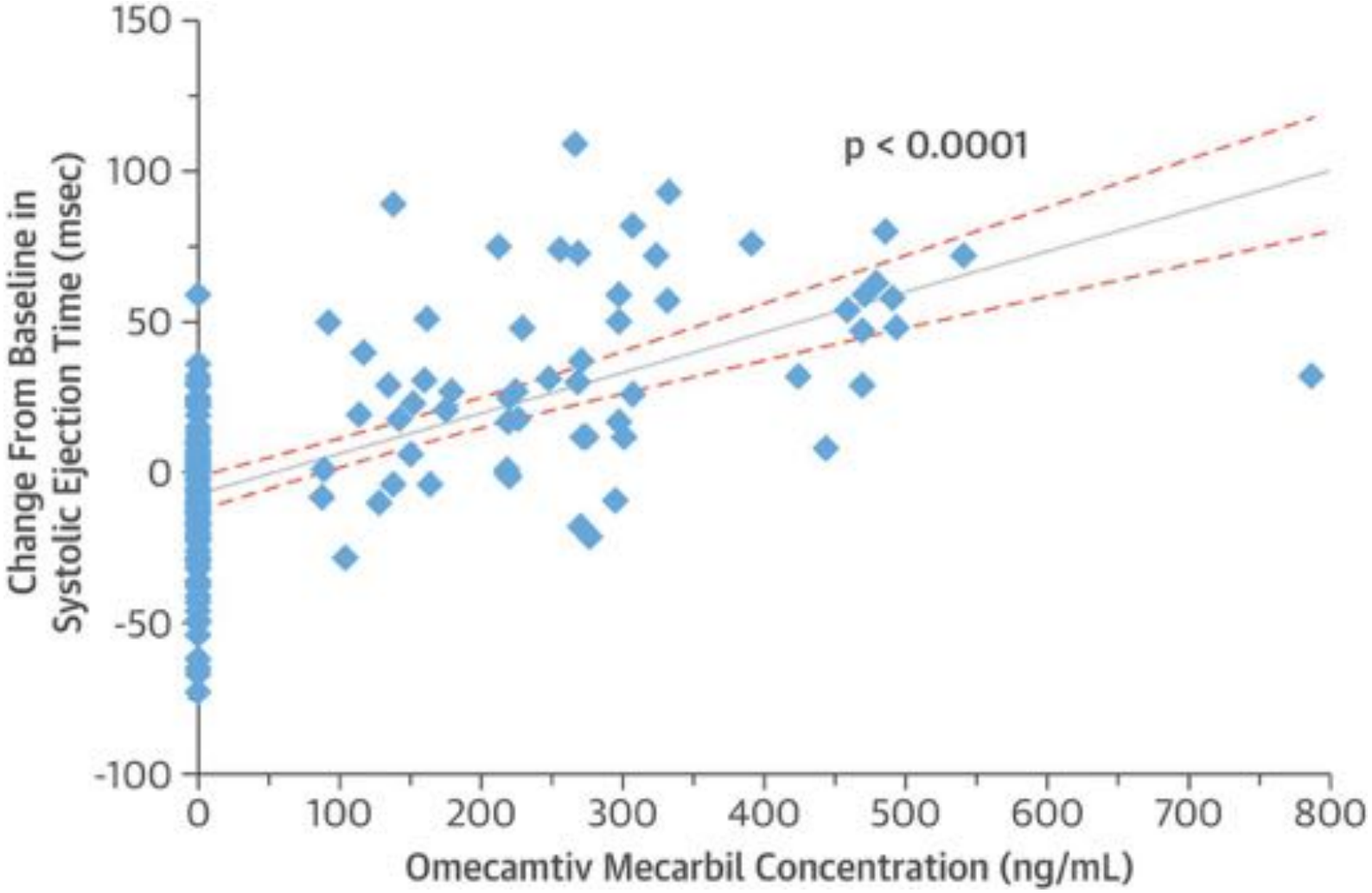
Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

The ATOMIC-AHF Study

John R. Teerlink, MD,[a,b] G. Michael Felker, MD,[c] John J.V. McMurray, MD,[d] Piotr Ponikowski, MD, PhD,[e] Marco Metra, MD,[f] Gerasimos S. Filippatos, MD,[g] Justin A. Ezekowitz, MBBCh, MSc,[h] Kenneth Dickstein, MD, PhD,[i,j] John G.F. Cleland, MD,[k] Jae B. Kim, MD,[l] Lei Lei, PhD,[l] Beat Knusel, PhD,[l] Andrew A. Wolff, MD,[m] Fady I. Malik, MD, PhD,[m] Scott M. Wasserman, MD,[l] on behalf of the ATOMIC-AHF Investigators

CONCLUSIONS In patients with AHF, intravenous OM did not meet the primary endpoint of dyspnea improvement, but it was generally well tolerated, it increased systolic ejection time, and it may have improved dyspnea in the high-dose group. (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure [ATOMIC-AHF]; NCT01300013) (J Am Coll Cardiol 2016;67:1444-55) © 2016 by the American College of Cardiology Foundation.

Left Ventricular Systolic Ejection Time versus plasma omecamtiv mecarbil concentrations in ATOMIC-AHF



John R. Teerlink et al. JACC 2016;67:1444-1455

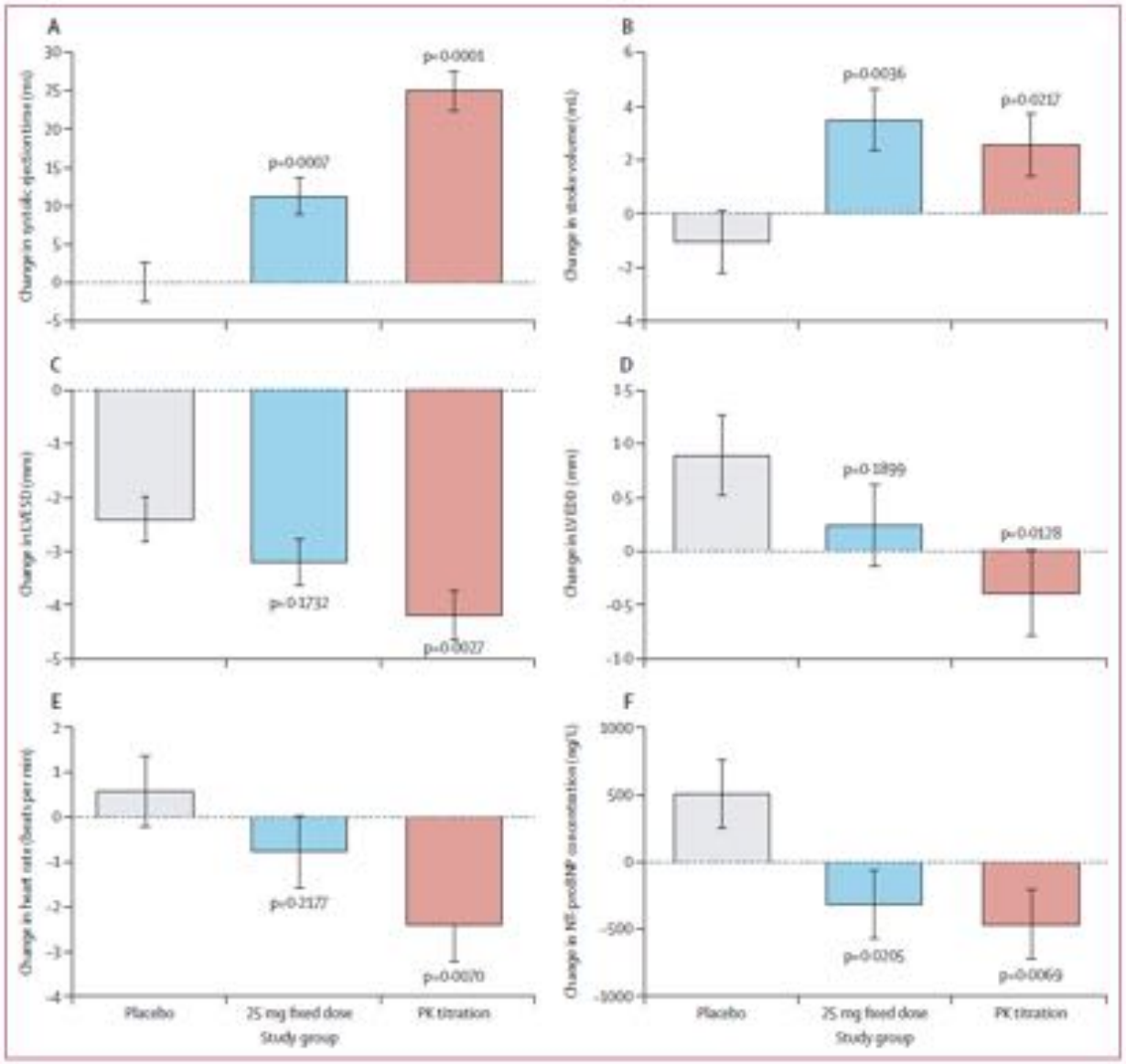
Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial

John R Teerlink, G Michael Felker, John J V McMurray, Scott D Solomon, Kirkwood F Adams Jr, John G F Cleland, Justin A Ezekowitz, Assen Goudev, Peter Macdonald, Marco Metra, Veselin Mitrovic, Piotr Ponikowski, Pranas Serpytis, Jindrich Spinar, János Tomcsányi, Hans J Vandekerckhove, Adriaan A Voors, Maria Laura Monsalvo, James Johnston, Fady I Malik, Narimon Honarpour, for the COSMIC-HF Investigators

Findings From March 17, 2014, to March 5, 2015, we enrolled 150 patients in the fixed-dose omecamtiv mecarbil group and 149 in the pharmacokinetic-titration and placebo groups. Mean maximum concentration of omecamtiv mecarbil at 12 weeks was 200 (SD 71) ng/mL in the fixed-dose group and 318 (129) ng/mL in the pharmacokinetic-titration group. For the pharmacokinetic-titration group versus placebo group at 20 weeks, least square mean differences were as follows: systolic ejection time 25 ms (95% CI 18–32, p<0·0001), stroke volume 3·6 mL (0·5–6·7, p=0·0217), left ventricular end-systolic diameter −1·8 mm (−2·9 to −0·6, p=0·0027), left ventricular end-diastolic diameter −1·3 mm, (−2·3 to 0·3, p=0·0128), heart rate −3·0 beats per min (−5·1 to −0·8, p=0·0070), and N-terminal pro B-type natriuretic peptide concentration in plasma −970 pg/mL (−1672 to −268, p=0·0069). The frequency of adverse clinical events did not differ between groups.

Interpretation Omecamtiv mecarbil dosing guided by pharmacokinetics achieved plasma concentrations associated with improved cardiac function and decreased ventricular diameter.

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

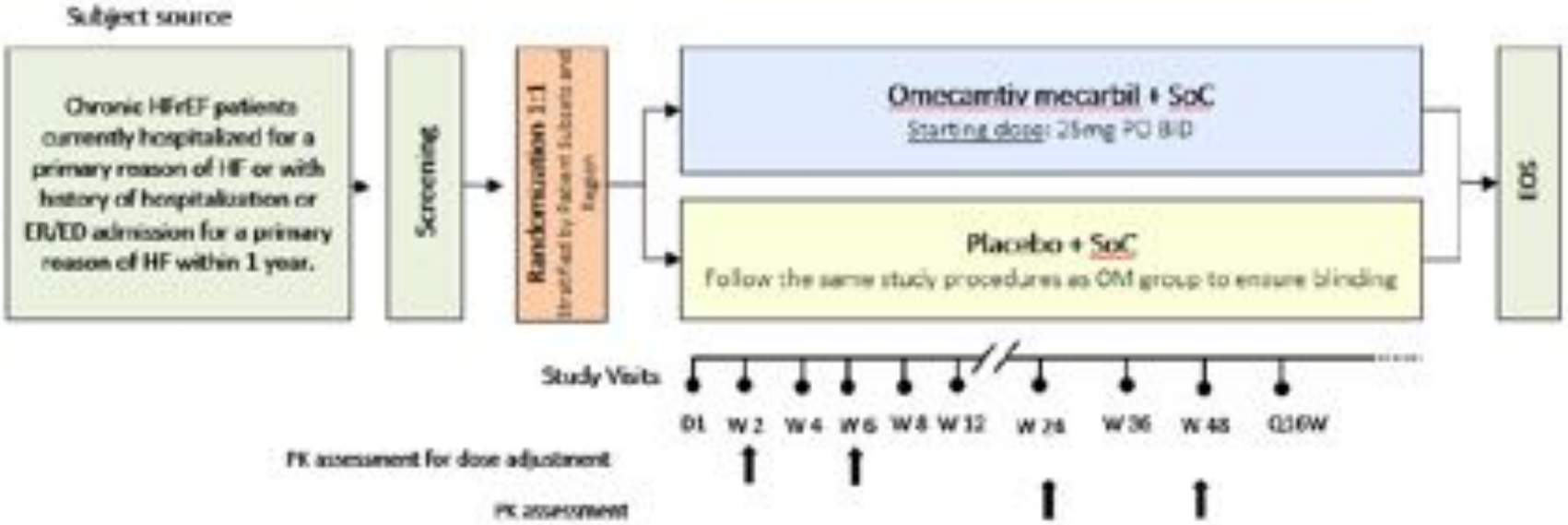
GALACTIC-HF

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

---

Study Design and Treatment Schema

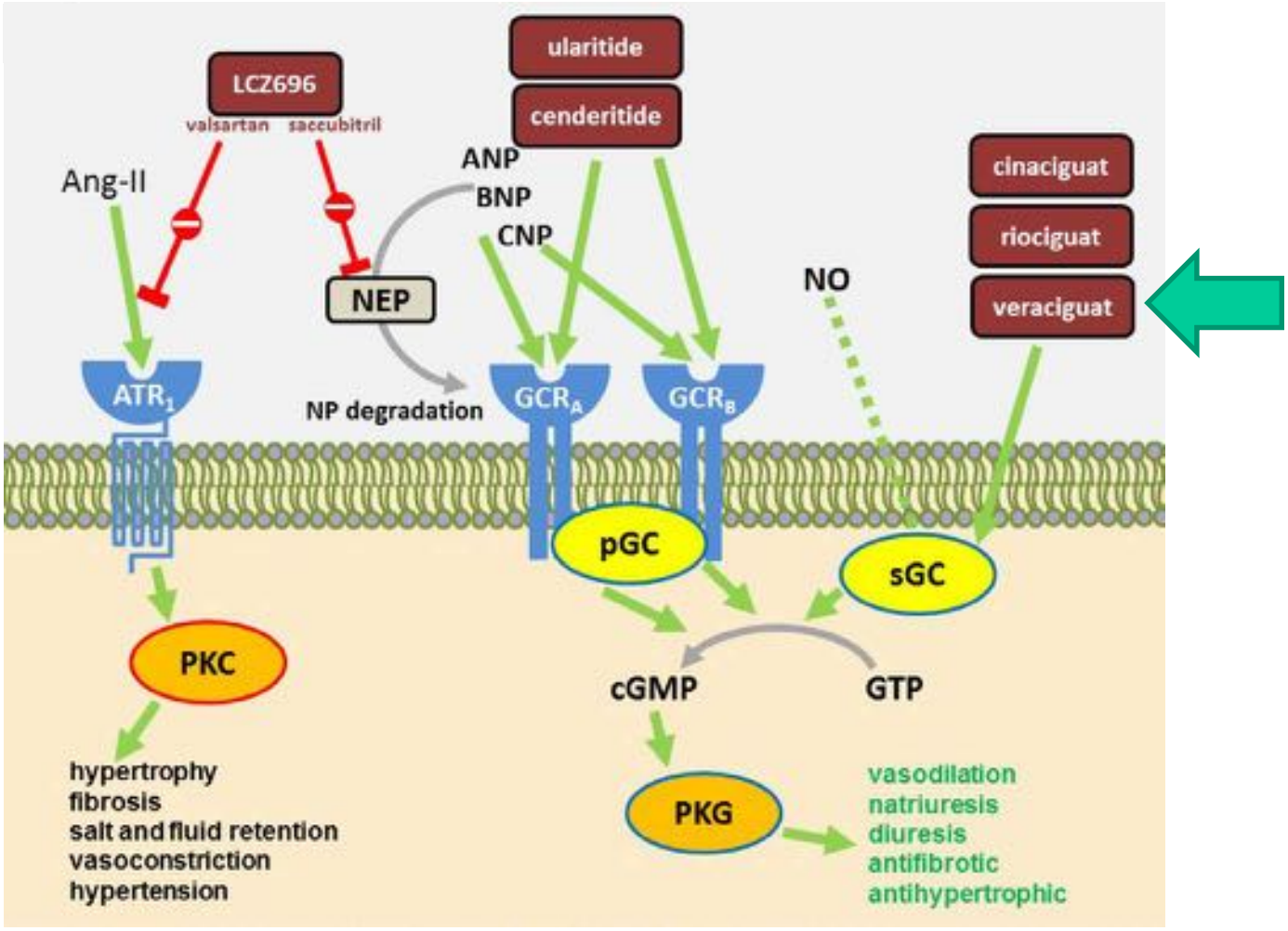
2 years enrollment, approx. 4 years total follow-up/study period



Quali novità nel trattamento dell'insufficienza cardiaca

- Sacubitril/ valsartan
- Iron
- SGLT-2 Inhibitors
- K binders
- Inotropic agents
- Guanilate cyclase activators
- Metabolic agents

Soluble guanylyl cyclase (sGC) stimulation to increase cGMP



Original Investigation

Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction

The SOCRATES-REDUCED Randomized Trial

Mihai Gheorghiade, MD; Stephen J. Greene, MD; Javed Butler, MD, MPH, MBA; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS; Aldo P. Maggioni, MD; Piotr Ponikowski, MD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Elisabeth Kraigher-Krainer, MD; Eliana T. Samano, MD; Katharina Müller, DiplStat; Lothar Roessig, MD; Burkert Pieske, MD; for the SOCRATES-REDUCED Investigators and Coordinators

CONCLUSIONS AND RELEVANCE Among patients with worsening chronic HF and reduced LVEF, compared with placebo, vericiguat did not have a statistically significant effect on change in NT-proBNP level at 12 weeks but was well-tolerated. Further clinical trials of vericiguat based on the dose-response relationship in this study are needed to determine the potential role of this drug for patients with worsening chronic HF.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01951625

JAMA. doi:10.1001/jama.2015.15734
Published online November 8, 2015.

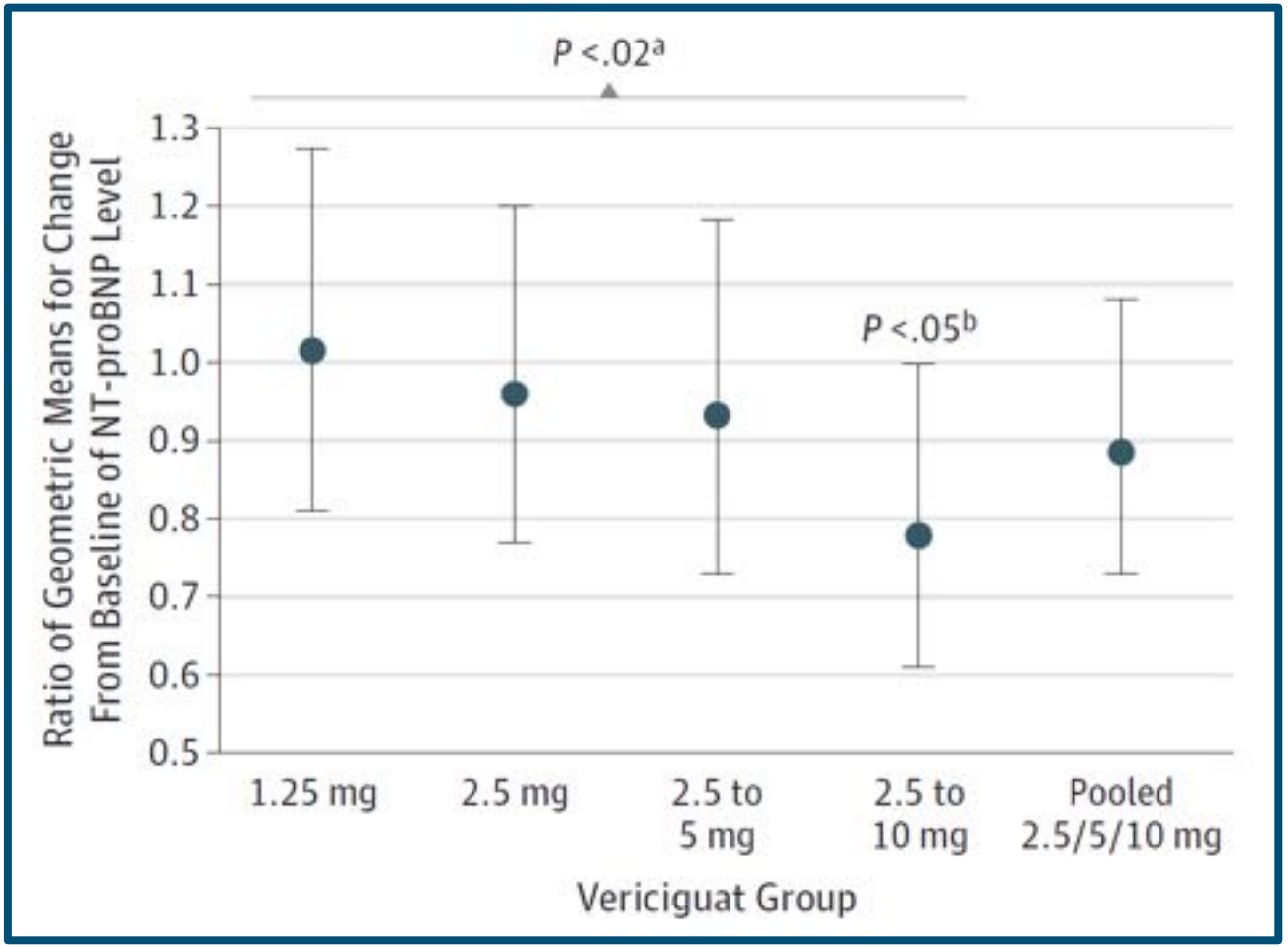
article.

Group Information: SOCRATES-REDUCED Investigators and Coordinators are listed at the end of this article.

Corresponding Author: Mihai Gheorghiade, MD, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, 201 E Huron St, Galter 3-150, Chicago, IL 60611 (mgheorgh@nm.org).

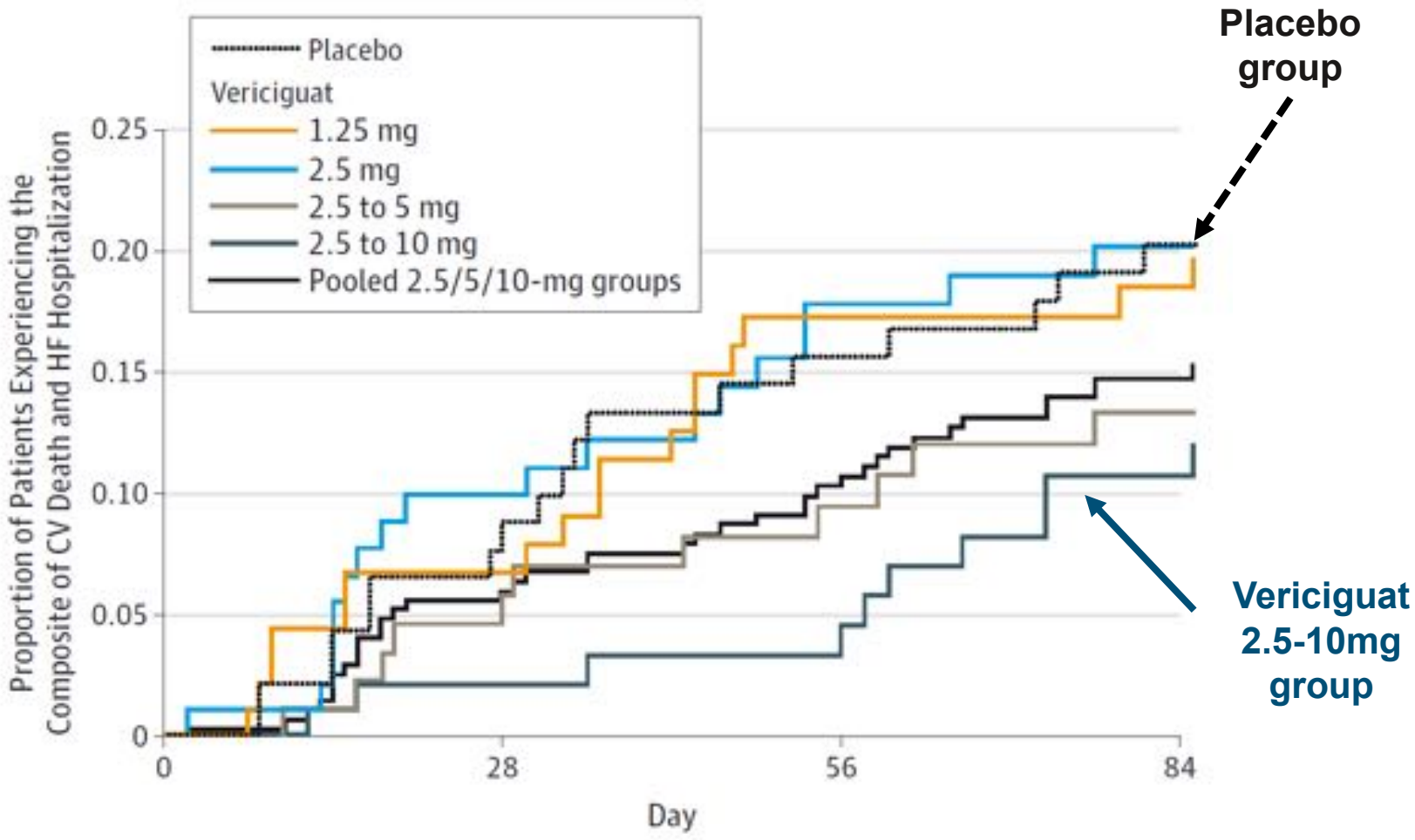
SOCRATES Reduced (Exploratory analyses)

Placebo-corrected change in NT-proBNP from baseline (expressed as a ratio of geometric means)



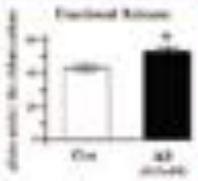
SOCRATES Reduced

CV death or HF hospitalization

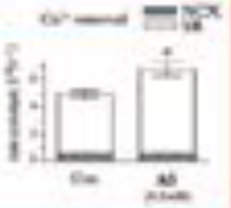


HNO Enhances Contractility and Relaxation

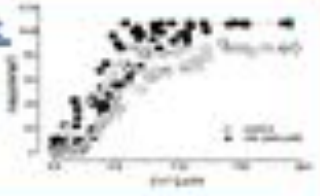
HNO enhances RyR activity[1]:
- Open probability of RyR increased

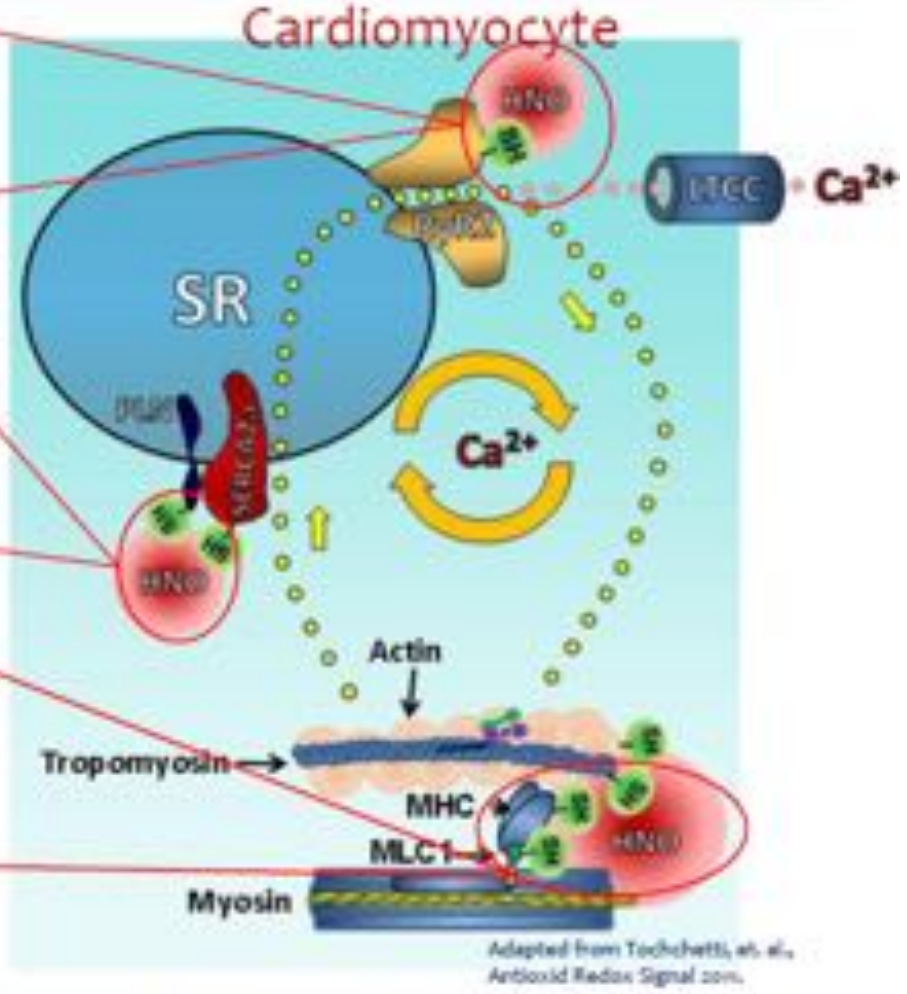


HNO enhances SERCa activity[2,3]:
- Formation of disulfide bonds between Phospholamban monomers



HNO enhances myofilament calcium sensitivity[3,4]:
- Formation of disulfide bonds in Actin, Myosin light chain, and Tropomyosin





Adapted from Tocchetti, et. al., Antioxid Redox Signal 2011.

Ica, L-type calcium current; CONT, control; AS, Angeli's Salt; SR, sarcoplasmic reticulum; NCX, Na-Ca exchanger; RyR, ryanodine receptor

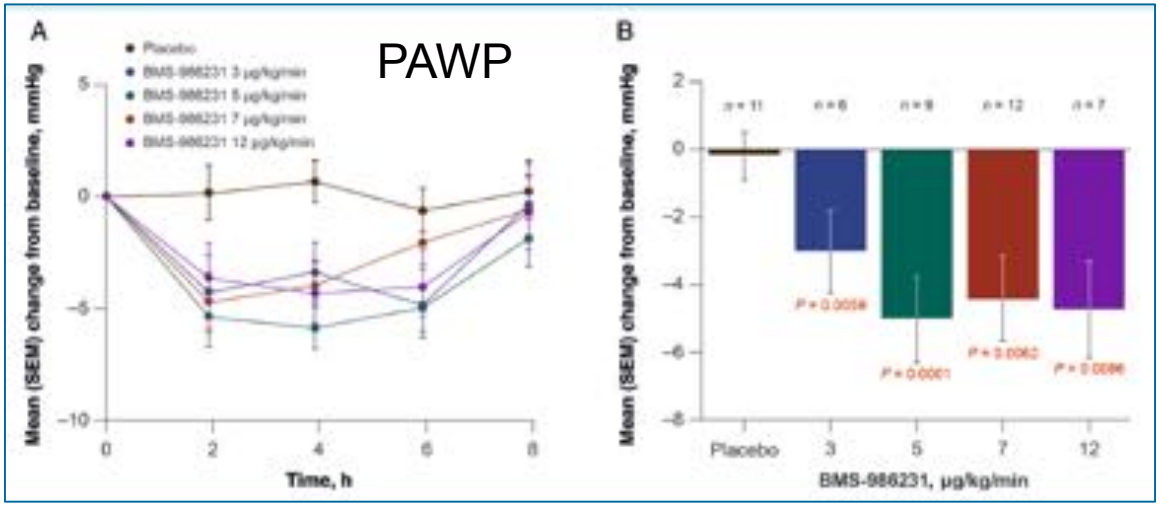
References:
1. Kohr, et al., *Front Biosci*, 2009
2. Tocchetti, et al., *Circ Res*, 2007
3. Dai, et al., *J Physiol*, 2007
4. Murray et al., *JMCC*, 2009
5. Froehlich, et al., *Biochem*, 2008
6. Lancel, et al., *Circ Res*, 2009

European Journal of Heart Failure (2015)
doi:10.1002/ejhf.307

A Phase 2a dose-escalation study of the safety, tolerability, pharmacokinetics and haemodynamic effects of BMS-986231 in hospitalized patients with heart failure with reduced ejection fraction

Cristina Tita[1], Edward M. Gilbert[2], Adrian B. Van Bakel[3], Jacek Grzybowski[4], Garrie J. Haas[5], Mohammad Jarrah[6], Stephanie H. Dunlap[7], Stephen S. Gottlieb[8], Marc Klapholz[9], Parag C. Patel[10], Roman Pfister[11], Tim Seidler[12], Keyur B. Shah[13], Tomasz Zieliński[14], Robert P. Veresh[15], Douglas Cowart[16], Shi Yin Foo[17], Alexander Vishnevsky[18], and Veselin Mitrovic[19]*

PAWP



Chronic Therapy With Elamipretide (MTP-131), a Novel Mitochondria-Targeting Peptide, Improves Left Ventricular and Mitochondrial Function in Dogs With Advanced Heart Failure

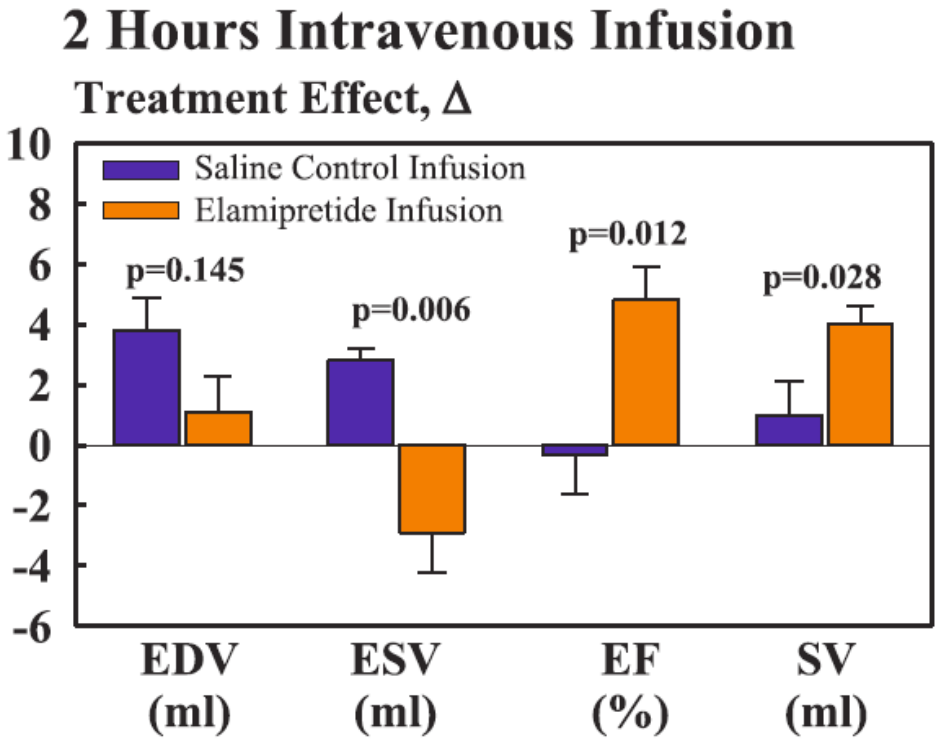
Hani N. Sabbah, PhD; Ramesh C. Gupta, PhD; Smita Kohli, MD; Mengjun Wang, MD; Souheila Hachem, BS; Kefei Zhang, MD

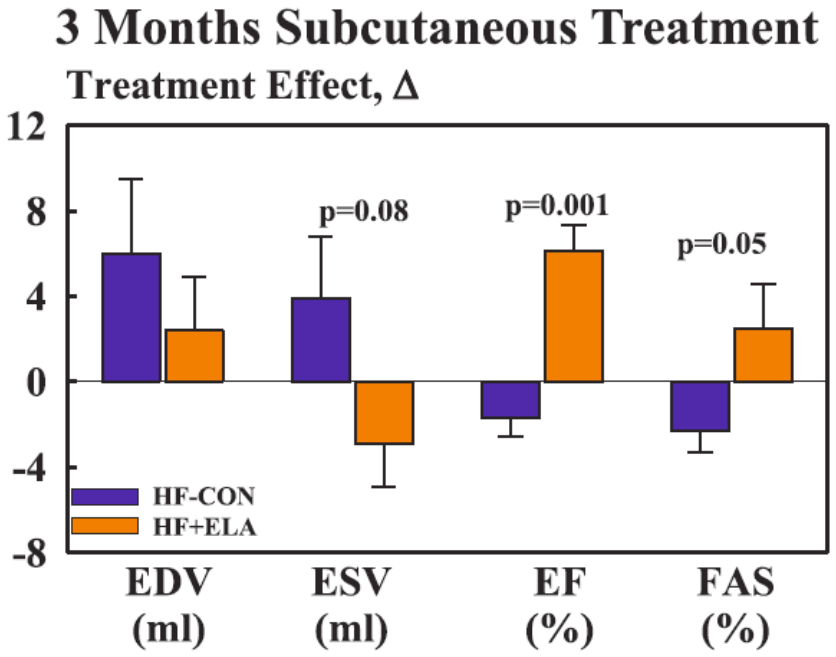
Background—Elamipretide (MTP-131), a novel mitochondria-targeting peptide, was shown to reduce infarct size in animals with myocardial infarction and improve renal function in pigs with acute and chronic kidney injury. This study examined the effects of chronic therapy with elamipretide on left ventricular (LV) and mitochondrial function in dogs with heart failure (HF).

Methods and Results—Fourteen dogs with microembolization-induced HF were randomized to 3 months monotherapy with subcutaneous injections of elamipretide (0.5 mg/kg once daily, HF+ELA, n=7) or saline (control, HF-CON, n=7). LV ejection fraction, plasma n-terminal pro-brain natriuretic peptide, tumor necrosis factor-α, and C-reactive protein were measured before (pretreatment) and 3 months after initiating therapy (post-treatment). Mitochondrial respiration, membrane potential ($\Delta\psi m$), maximum rate of ATP synthesis, and ATP/ADP ratio were measured in isolated LV cardiomyocytes obtained at post-treatment. In HF-CON dogs, ejection fraction decreased at post-treatment compared with pretreatment (29±1% versus 31±2%), whereas in HF+ELA dogs, ejection fraction significantly increased at post-treatment compared with pretreatment (36±2% versus 30±2%; $P<0.05$). In HF-CON, n-terminal pro-brain natriuretic peptide increased by 88±120 pg/mL during follow-up but decreased significantly by 774±85 pg/mL in HF+ELA dogs ($P<0.001$). Treatment with elamipretide also normalized plasma tumor necrosis factor-α and C-reactive protein and restored mitochondrial state-3 respiration, $\Delta\psi m$, rate of ATP synthesis, and ATP/ADP ratio (ATP/ADP: 0.38±0.04 HF-CON versus 1.16±0.15 HF+ELA; $P<0.001$).

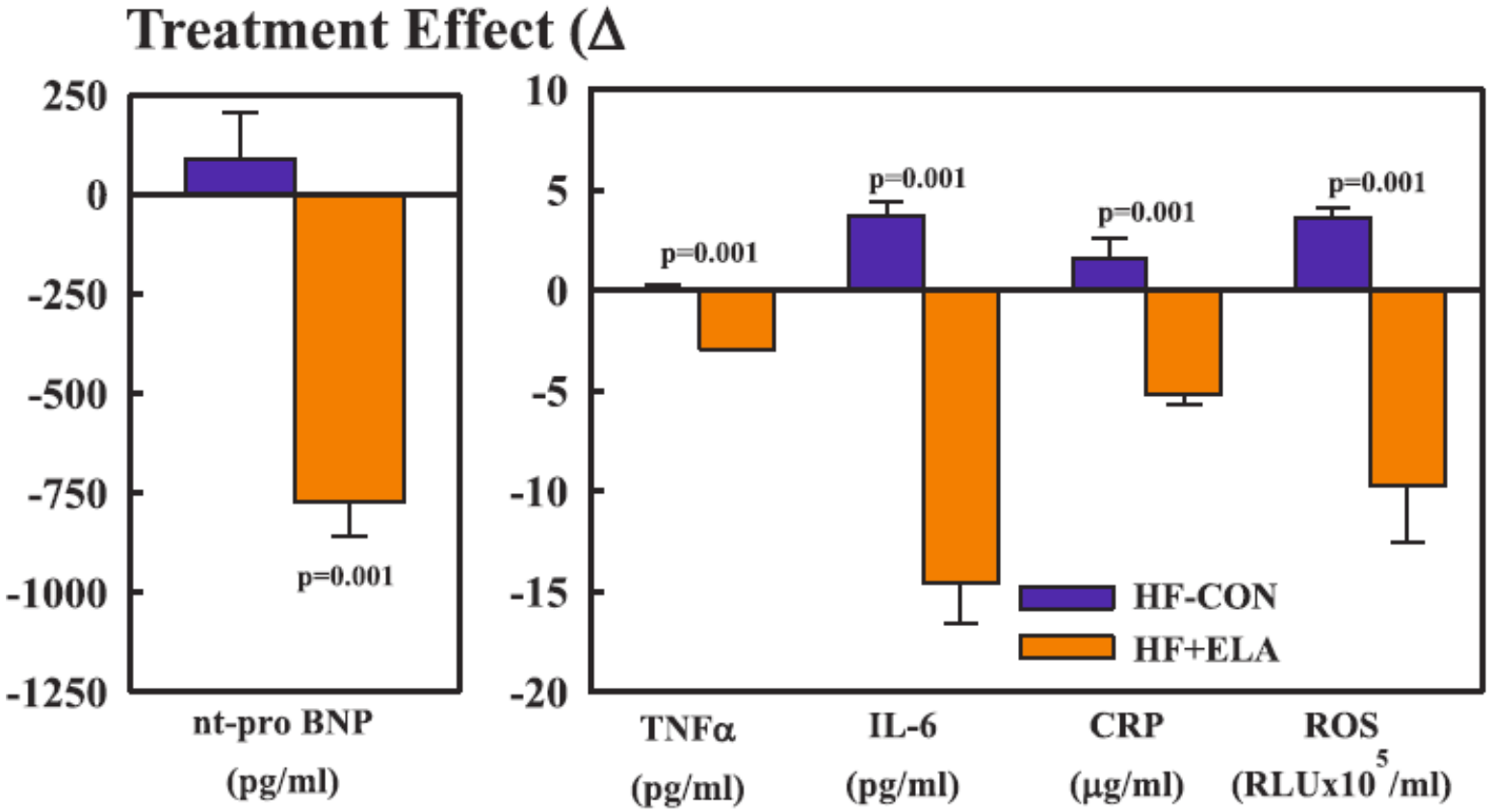
Conclusions—Long-term therapy with elamipretide improves LV systolic function, normalizes plasma biomarkers, and reverses mitochondrial abnormalities in LV myocardium of dogs with advanced HF. The results support the development of elamipretide for the treatment of HF. **(*Circ Heart Fail*. 2016;9:e002206. DOI: 10.1161/CIRCHEARTFAILURE.115.002206.)**

Elamipretide on plasma neurohormones





Elamipretide on plasma neurohormones

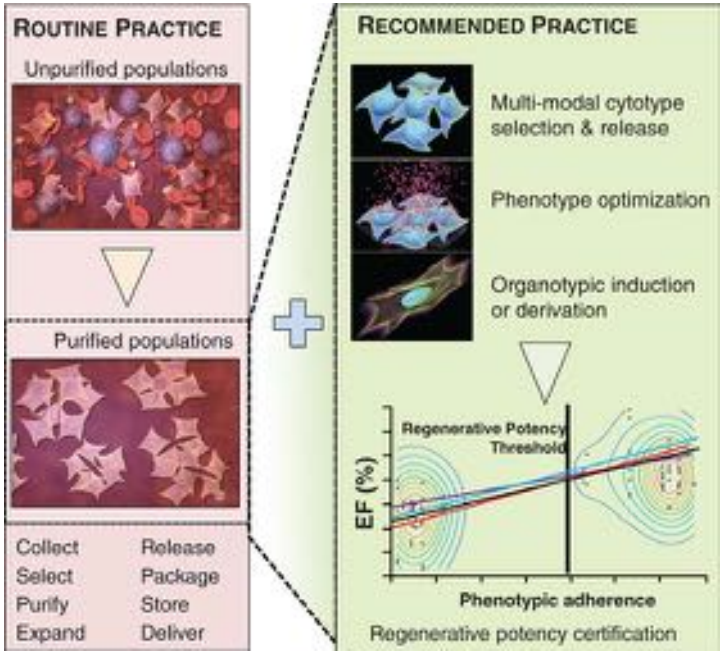


European Journal of Heart Failure (2016) 18, 142–144
doi:10.1002/ejhf.479

EDITORIAL COMMENT

Clinical development plan for regenerative therapy in heart failure

Andre Terzic[1], Atta Behfar[1], and Gerasimos Filippatos[2]*



European Heart Journal (2017) 38, 661–664
doi:10.1093/eurheartj/ehw626

The quest for a successful cell-based therapeutic approach for heart failure

Ana Marie Landin[1] and Joshua M. Hare[1,2]*

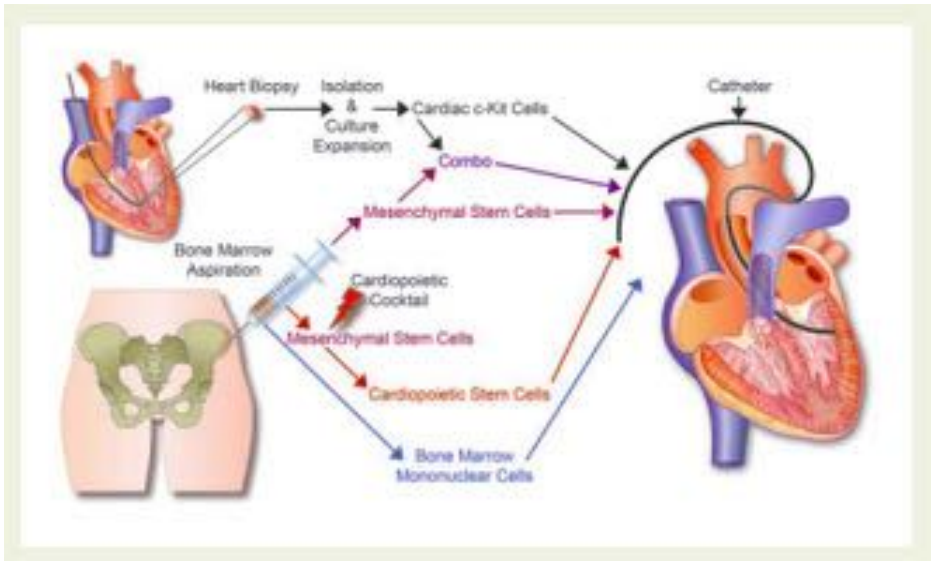


Table 1 Cell types under investigation in cell-based therapy trials for heart failure

Cell types	Application
Unfractionated BM-MNCs	Ischaemic heart failure and chronic heart failure
$CD34^+$ stem cells	Chronic ischaemic failure
Mesenchymal precursor cells	Ischaemic heart failure
Adipose tissue derived MSCs	Ischaemic and non-ischaemic heart failure
Bone marrow-derived MSCs	Ischaemic and non-ischaemic heart failure
Cardiosphere-derived cells	Ischaemic heart failure
Cardiac c-Kit cells	Ischaemic heart failure
Cardiopoietic stem cells	Chronic heart failure
Induced pluripotent cell-derived cardiomyocytes	Chronic heart failure

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doi:10.1002/ejhf.434

Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial design

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European Heart Journal (2016) **0**, 1–13
doi:10.1093/eurheartj/ehw543

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Cardiopoietic cell therapy for advanced ischemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 cli

Jozef Bartunek[1]* Andre Terzic[2]*, Beth A. Davison[3], (
Radovanovic[5], Branko Beleslin[6], Bela Merkely[7], Piot
Wojciech Wojakowski[9], Peter Andreka[10], Ivan G. Ho
Dariouch Dolatabadi[13], Badih El Nakadi[13], Aleksand
Petar M. Seferovic[16], Slobodan Obradovic[17], Marc V
Ivo Petrov[19], Shaul Atar[20,21], Majdi Halabi[21], Valeri L
Jaroslaw D. Kasprzak[23], Ricardo Sanz-Ruiz[24], Guy R.
Nyolczas[25], Victor Legrand[26], Antoine Guédès[27], Al
Francisco Fernandez-Aviles[24], Pilar Jimenez-Queved
Jose Maria Hernandez-Garcia[32], Flavio Ribichini[33], M
Scott A. Waldman[35], John R. Teerlink[36], Bernard J. (
Timothy D. Henry[38], Marco Metra[39], Roger J. Hajjar
Behfar[2], Bertrand Alexandre[41], Aymeric Seron[41], W
Warren Sherman[41], Gad Cotter[3], and William Wijn

[illegible]

Benefit of cardiopoietic mesenchymal stem cell therapy on left ventricular remodelling: results from the Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) study

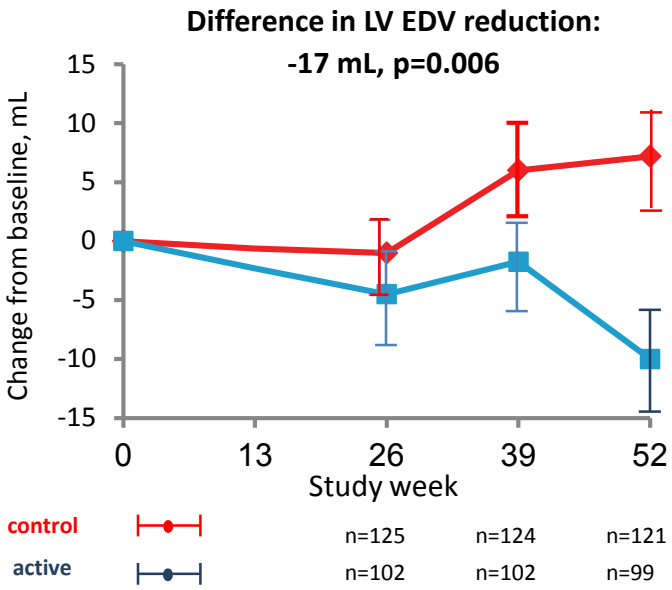
John R. Teerlink[1], Marco Metra[2], Gerasimos S. Filippatos[3], Beth A. Davison[4], Josef Bartunek[5], Andre Terzic[6], Bernard J. Gersh[7], Thomas J. Povsic[7], Timothy D. Henry[8], Bertrand Alexandre[9], Christian Homsy[9], Christopher Edwards[9], Aymeric Seron[9], William Wijns[5,10], and Gad Cotter[4]*, for the CHART Investigators

CHART-1 Clinical Trial

Changes in LV EDV and LV ESV at 52 Weeks

LV volume reduction achieved on top of maximally tolerated standard-of-care

Extent of LV remodeling compares favorably to effects of established HF therapies



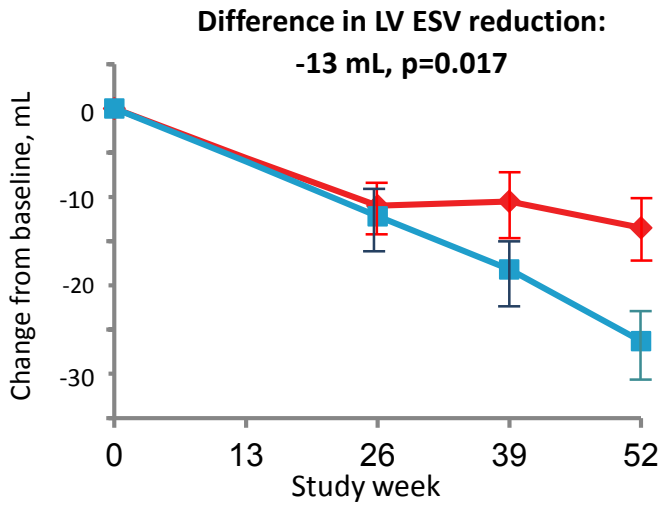


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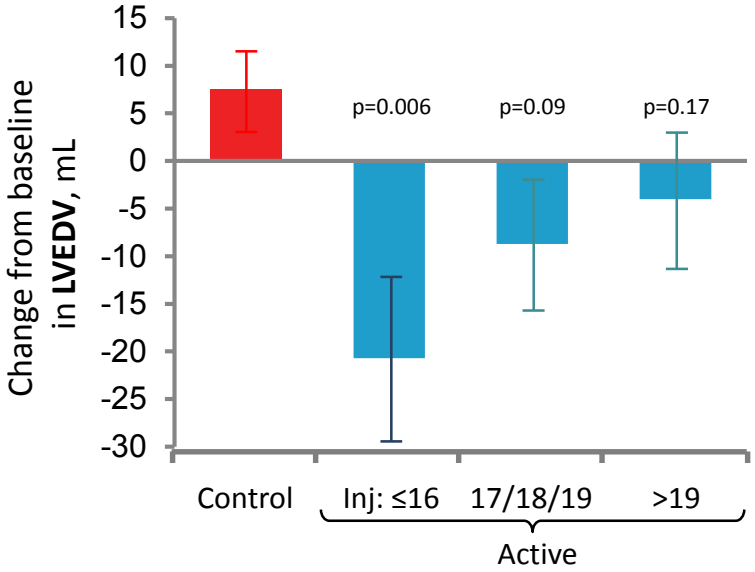
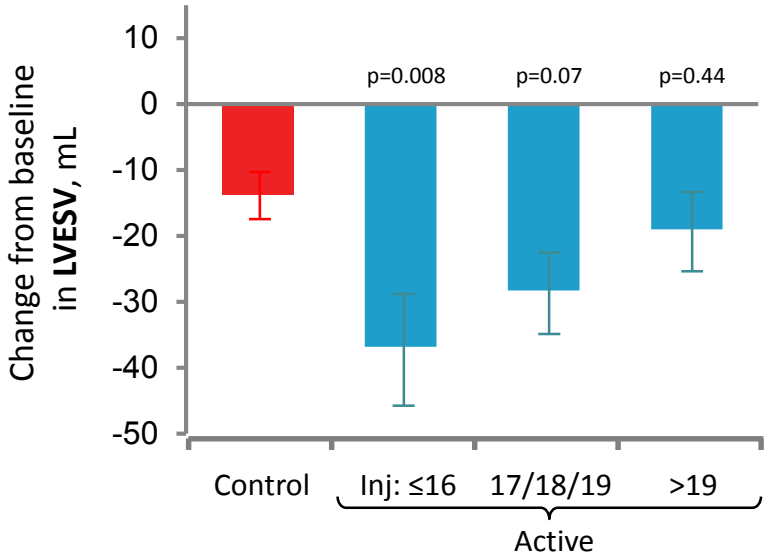
CHART-1 Clinical Trial
Changes in LV EDV and LV ESV at 52 Weeks

Reversed remodeling inversely related to number of injections





P value as compared to control

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Exploratory Analysis at 52 weeks

Hierarchical Outcome as a Function of Baseline LV EDV and Treatment Intensity