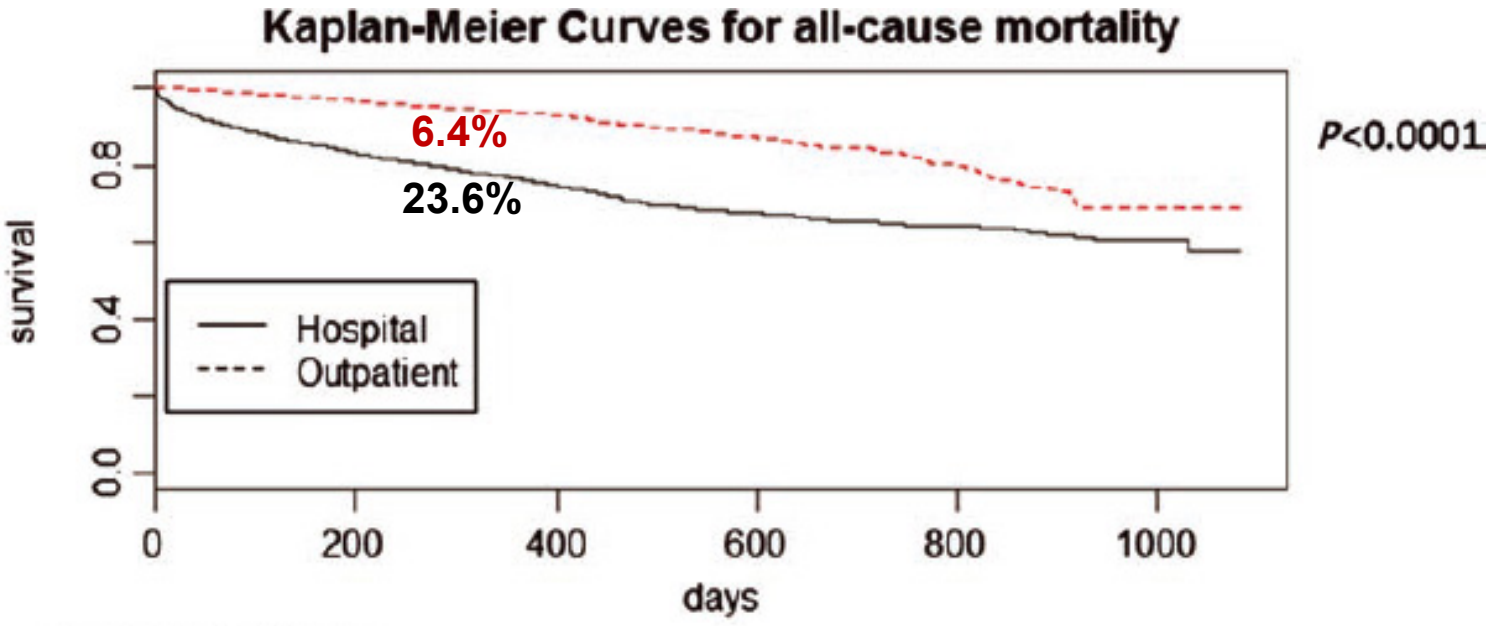
What's optimal medical therapy for heart failure?

Prof. Dr. Marco Metra

Cardiology. University and Hospitals of Brescia

All-cause mortality in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT)

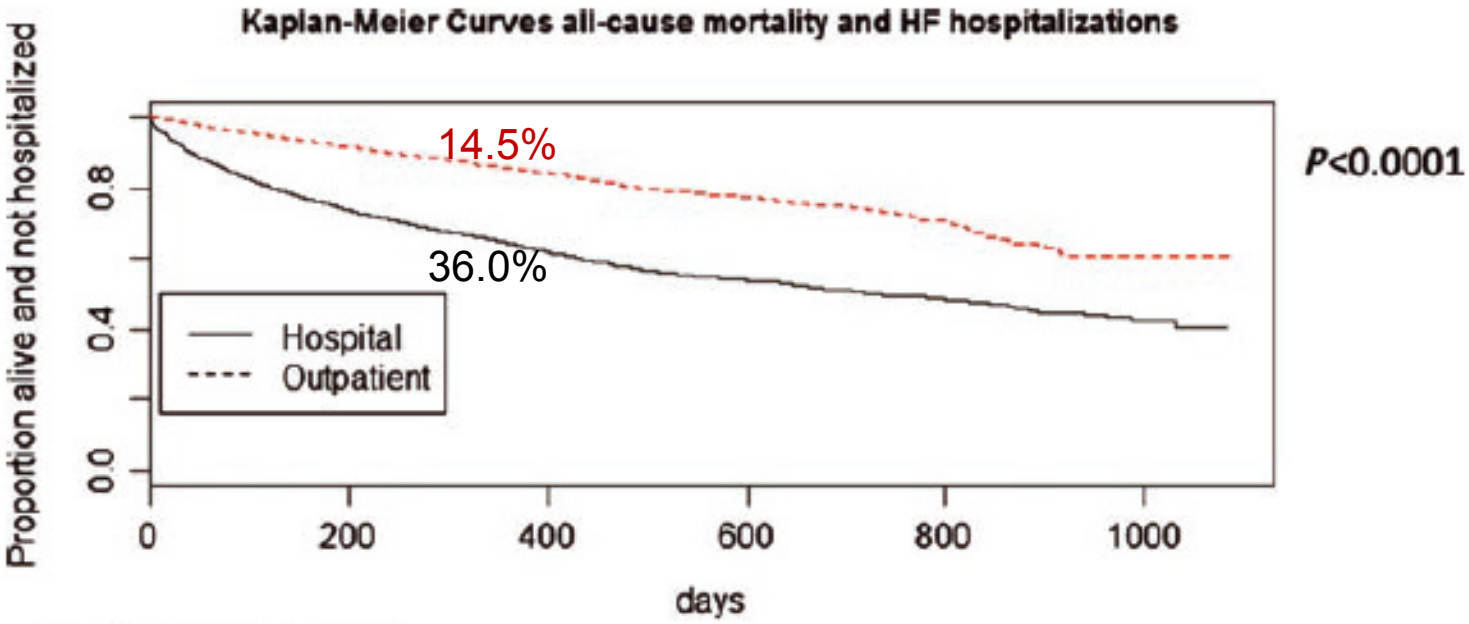


Number of Patients at Risk:

Hospital	5038	3874	1656	763	384	100
Outpatient	7401	6892	2367	700	246	69

Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-625

All-cause mortality and HF-hospitalizations in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT)



Number of Patients at Risk:

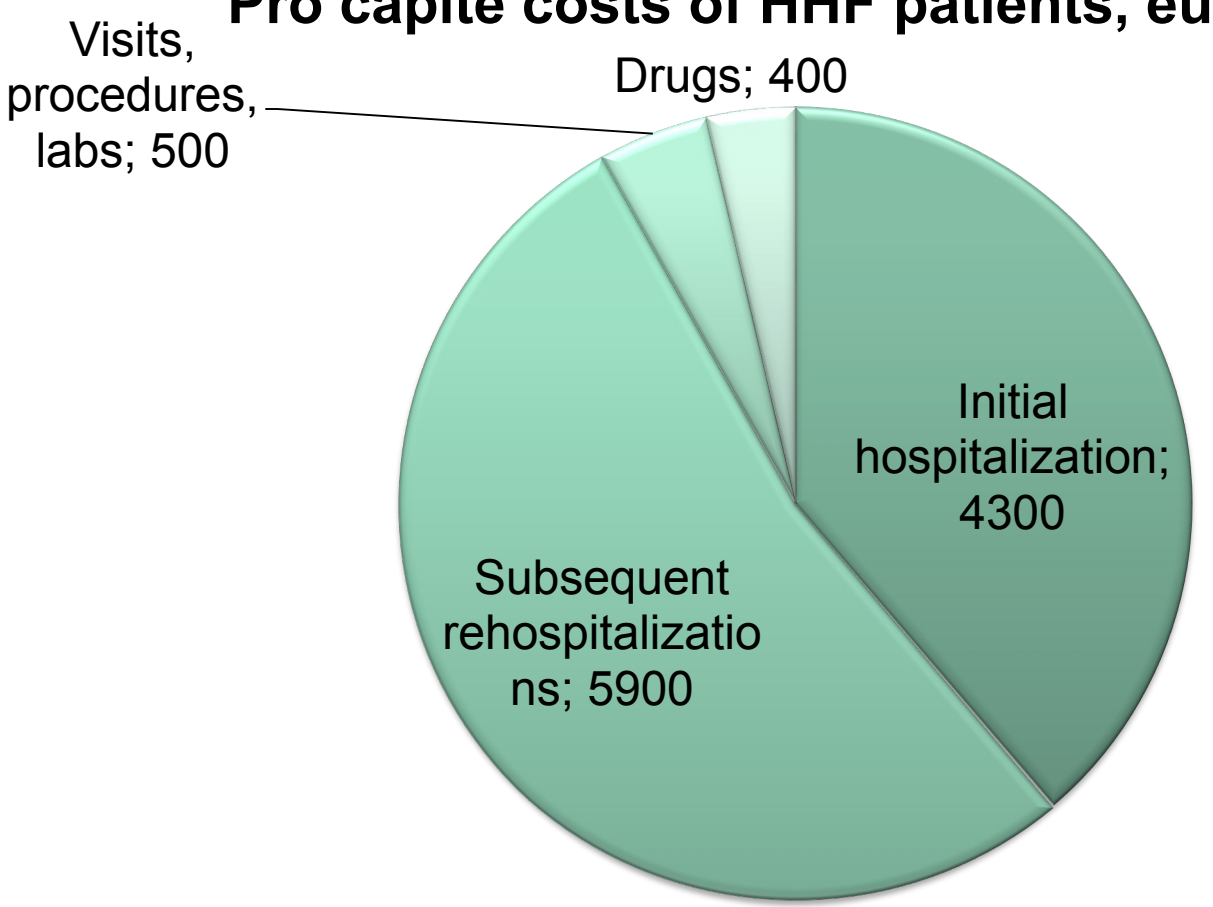
Hospital	4958	3369	1457	708	336	52
Outpatient	7378	6513	2221	684	242	67

Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-625

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

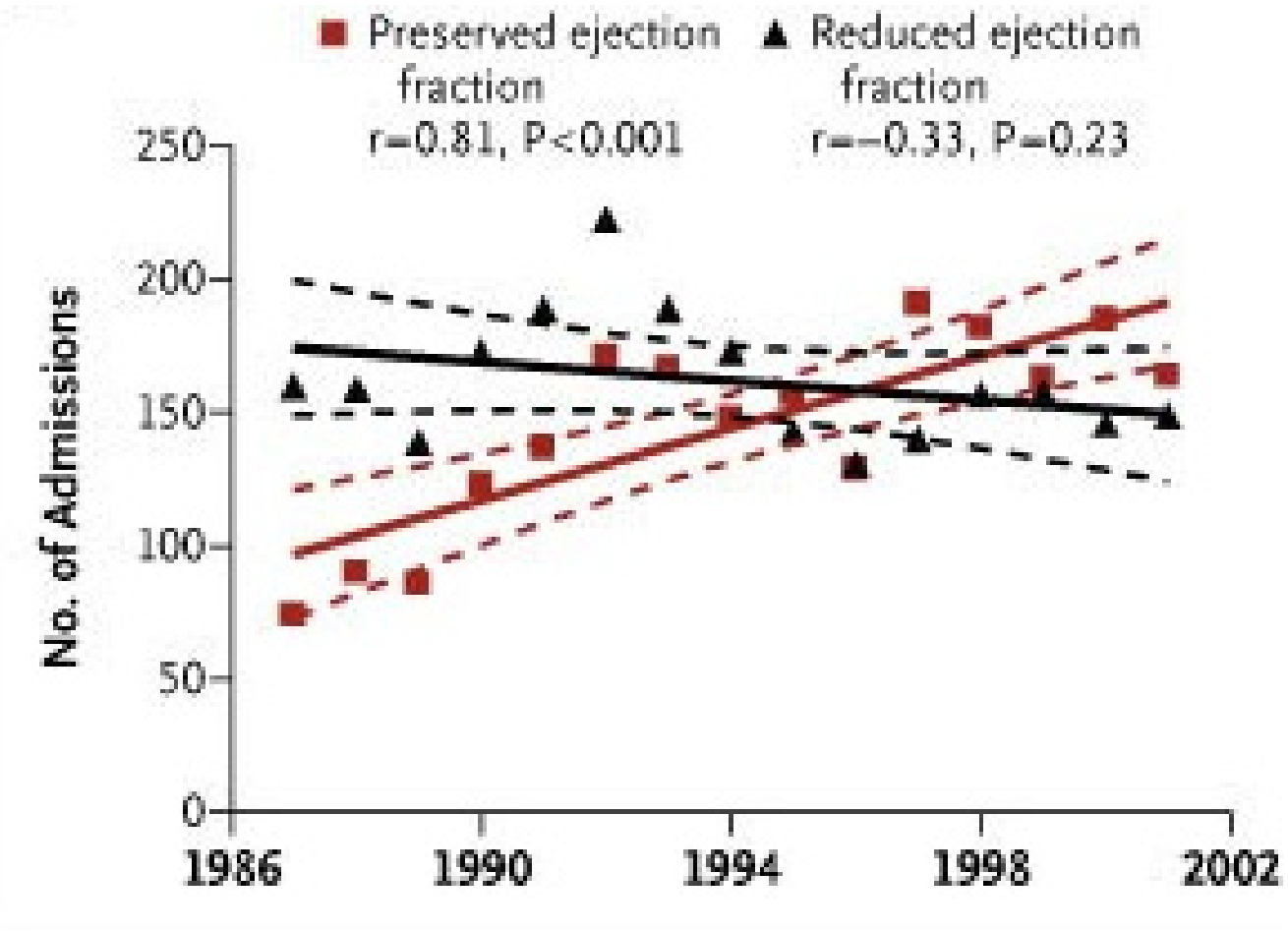
Giovanni Corrao[1]*, Arianna Ghirardi[1], Buthaina Ibrahim[1], Luca Merlino[2], and Aldo Pietro Maggioni[3]

Pro capite costs of HHF patients, euros/year



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

Secular Trends in the Prevalence of Heart Failure with Preserved Ejection Fraction

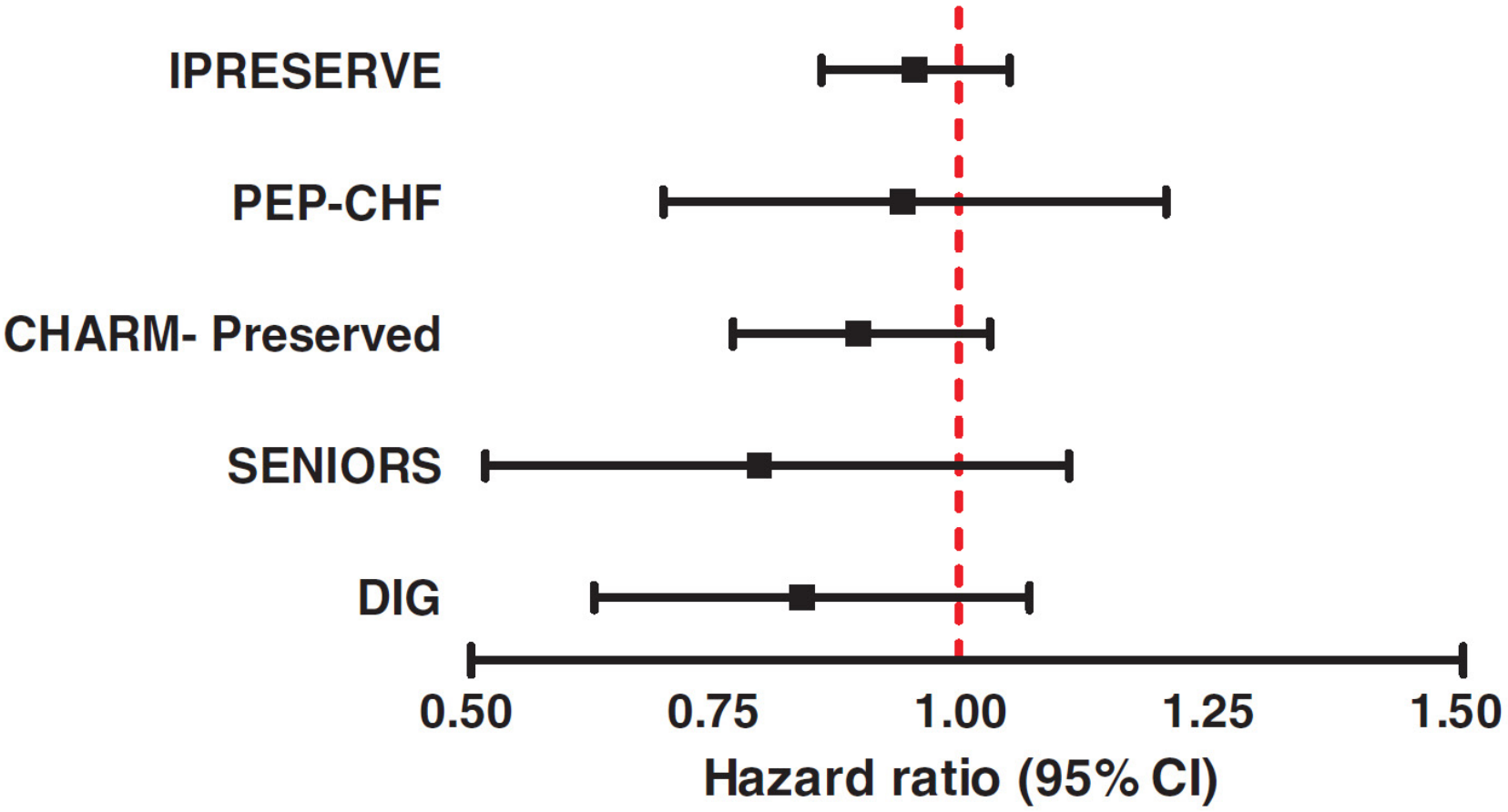


Owan T et al. N Engl J Med 2006;355:251-259

Optimal medical therapy for HF

1. HFpEF

Large trials in HFpEF – no benefit

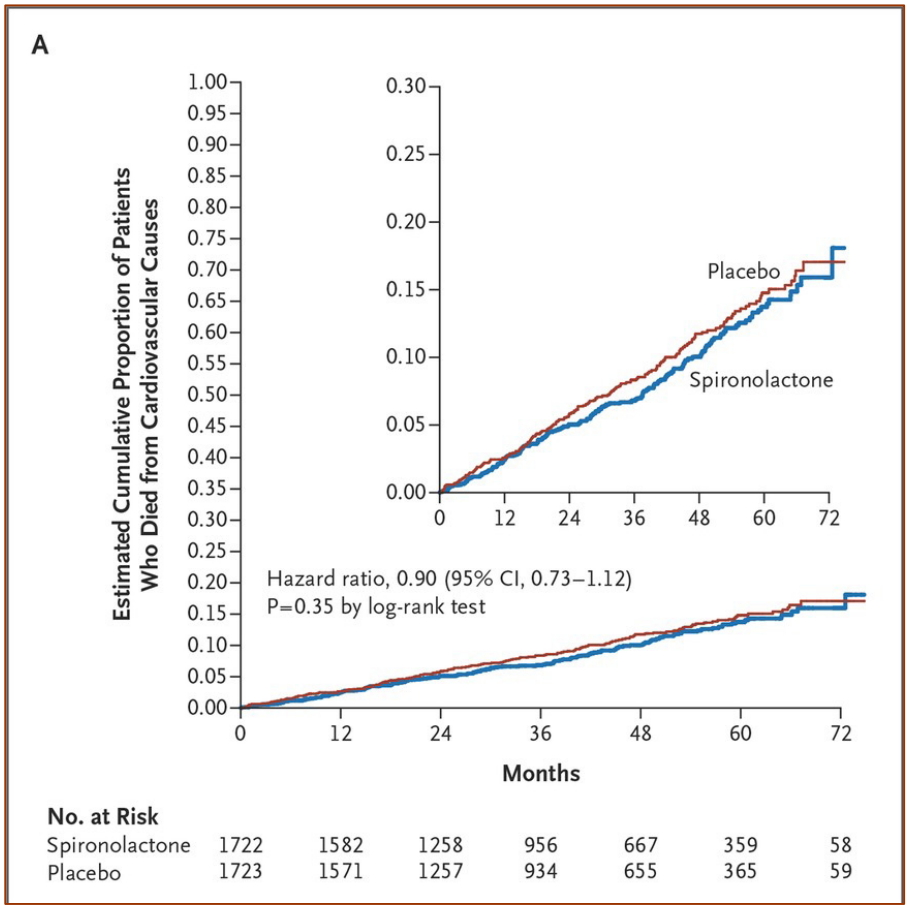


CI=confidence interval

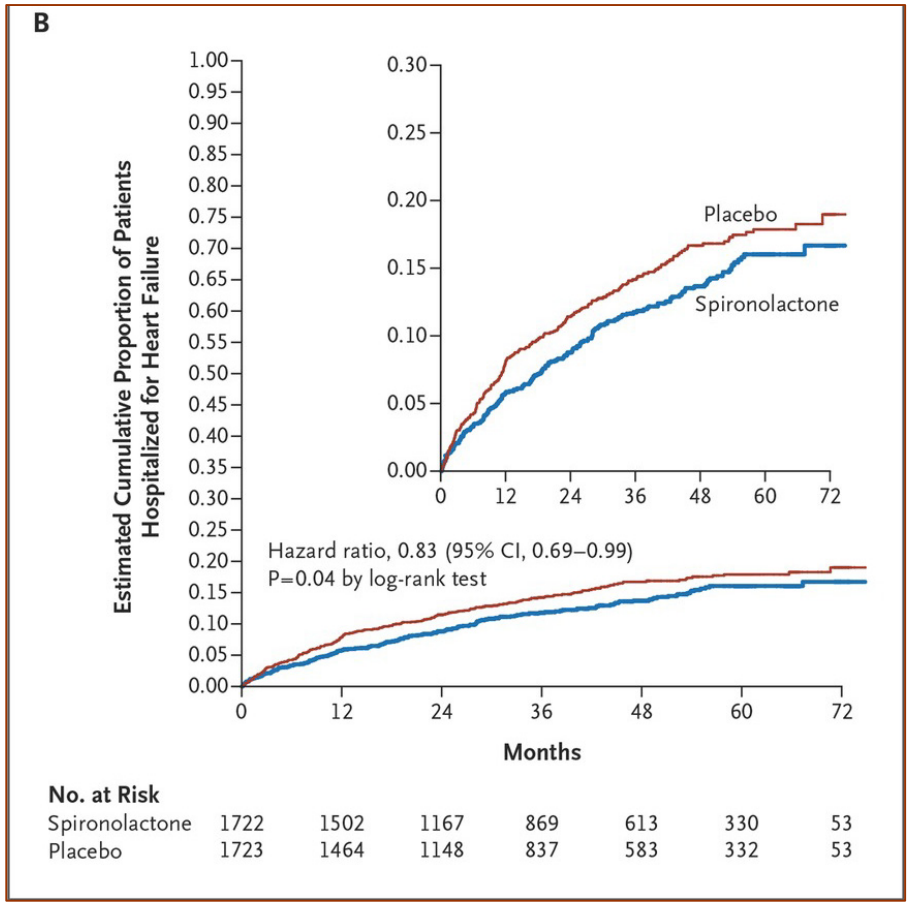
Redfield MM, et al. Circ Heart Fail 2012;5;653–9

TOPCAT: Time to the Two Components of the Primary Outcome.

CV death

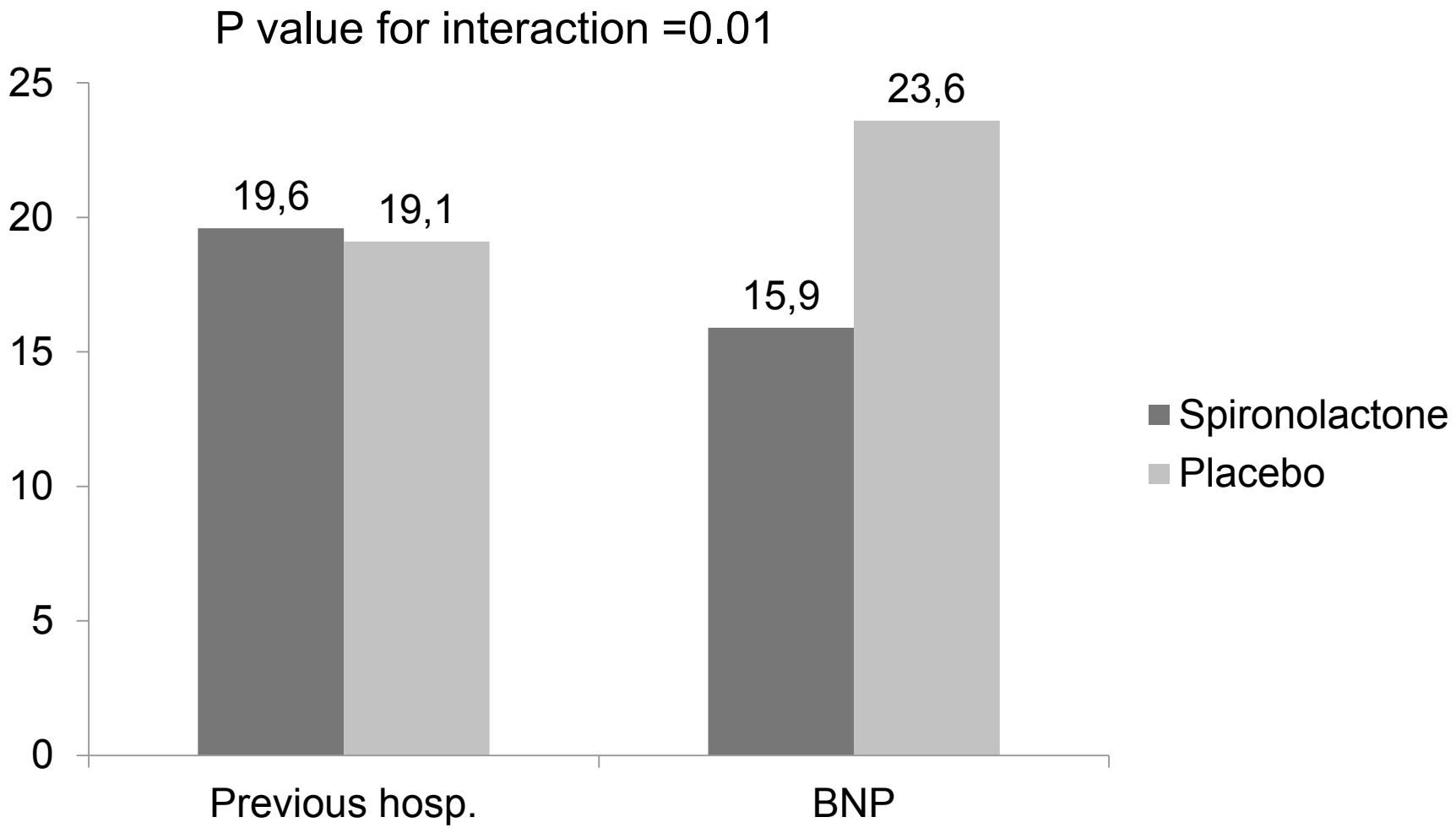


HF Hospitalization



Pitt B et al. N Engl J Med 2014;370:1383-1392

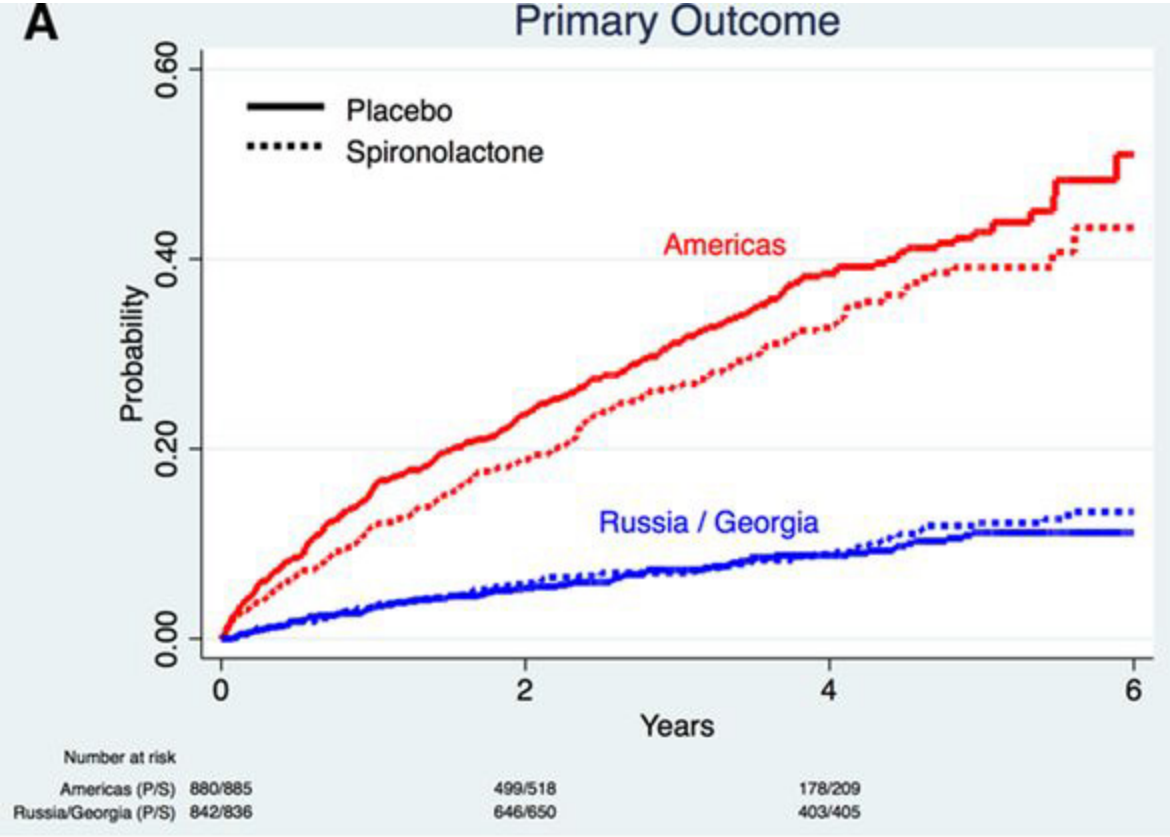
TOPCAT: Subgroup analysis by randomization stratum



From Pitt B et al. N Engl J Med 2014;370:1383-1392

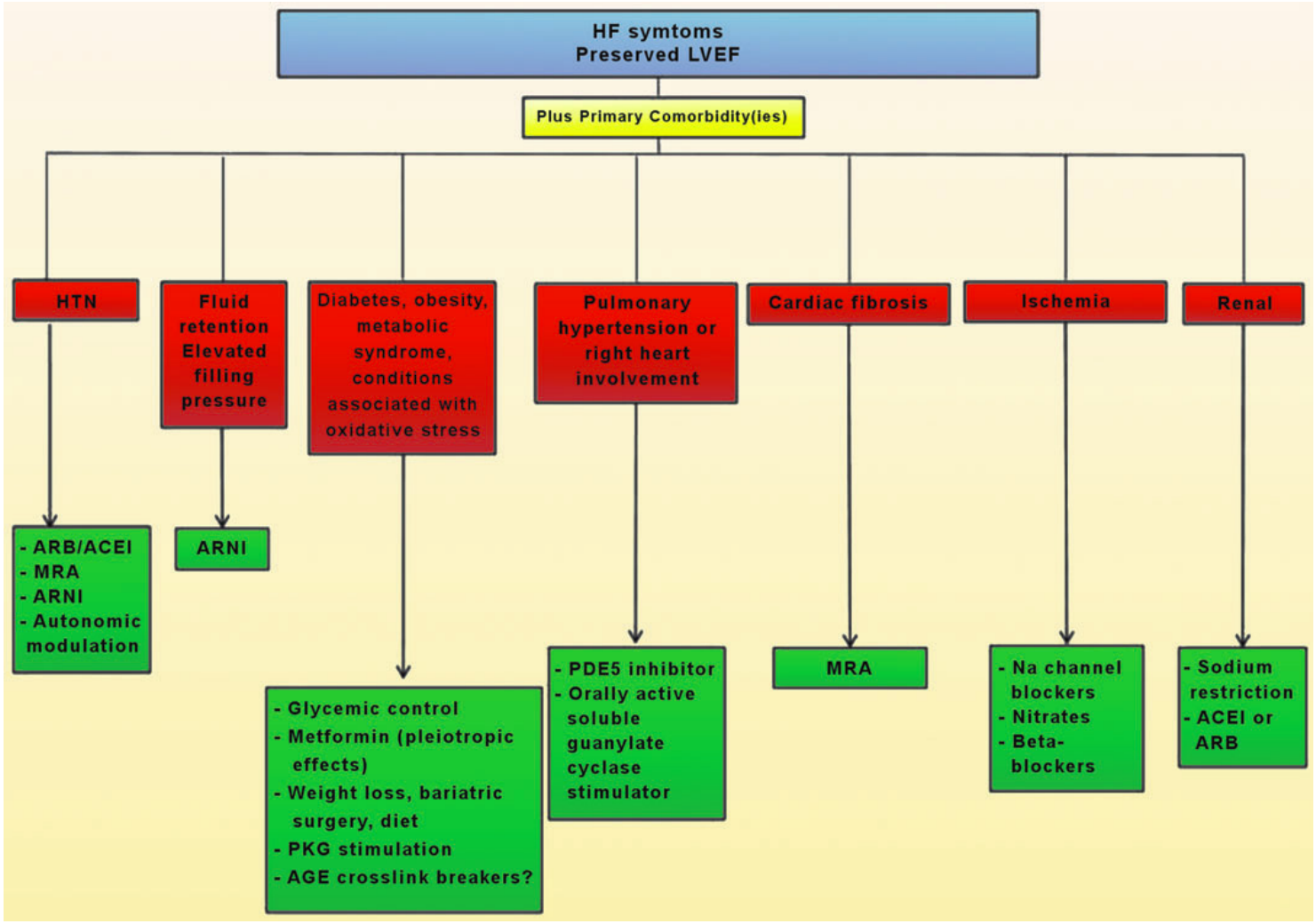
Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

Marc A. Pfeffer, MD, PhD; Brian Claggett, PhD; Susan F. Assmann, PhD; Robin Boineau, MD; Inder S. Anand, MD; Nadine Clausell, MD, PhD; Akshay S. Desai, MD, MPH; Rafael Diaz, MD; Jerome L. Fleg, MD; Ivan Gordeev, MD; John F. Heitner, MD; Eldrin F. Lewis, MD, MPH; Eileen O'Meara, MD; Jean-Lucien Rouleau, MD; Jeffrey L. Probstfield, MD; Tamaz Shaburishvili, MD, PhD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Nancy K. Sweitzer, MD, PhD; Sonja M. McKinlay, PhD; Bertram Pitt, MD



Marc A. Pfeffer et al. Circulation. 2015;131:34-42

Potential approach for matching key HFpEF phenotypes with therapeutic interventions.

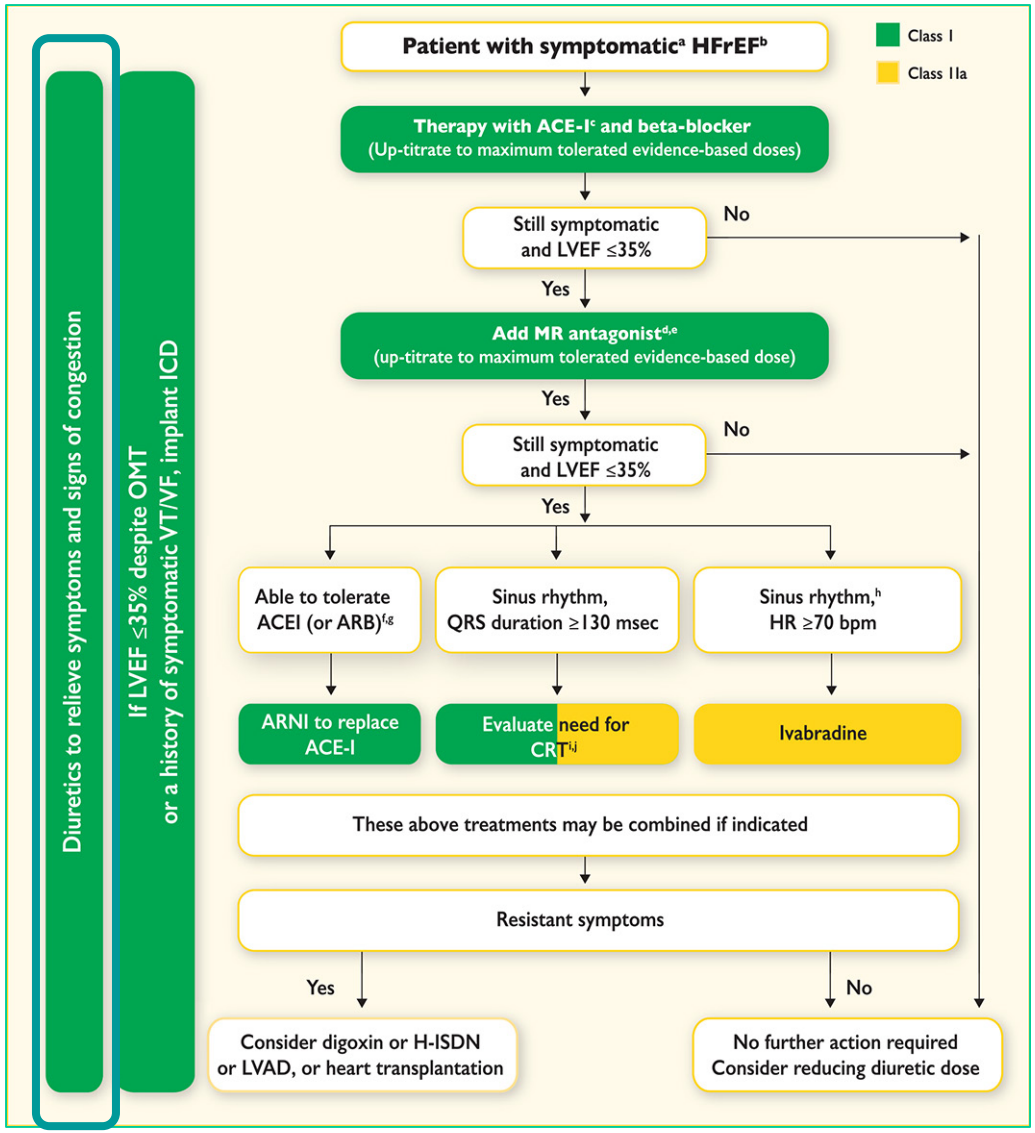


Senni et al. Eur Heart J. 2014 Oct 21;35(40):2797-815

Optimal medical therapy for HF

1. HFpEF
2. Diuretics

Therapeutic algorithm for a patient with symptomatic HFrEF



Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

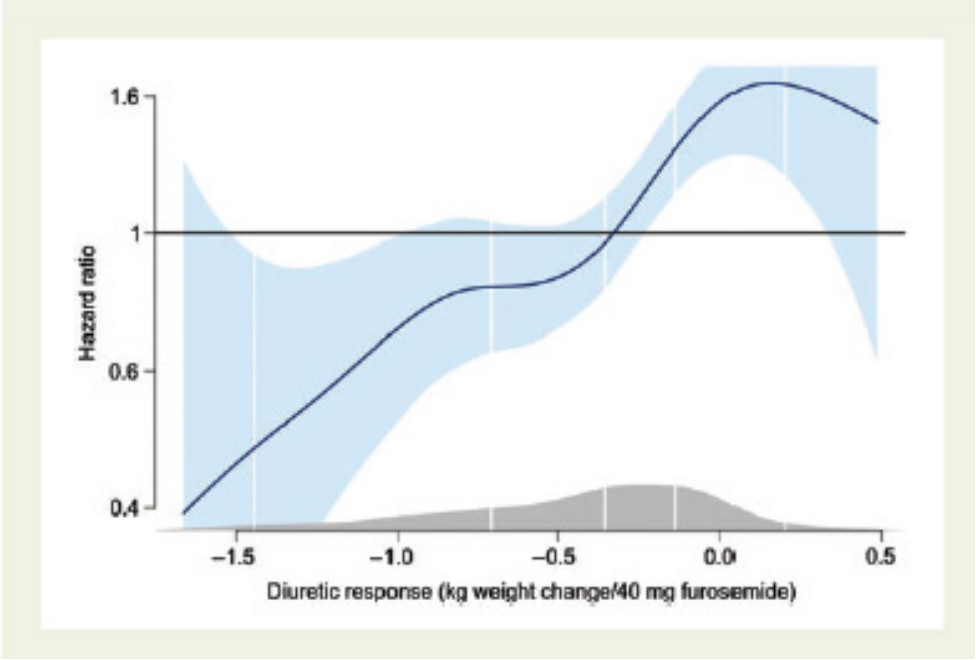
European Heart Journal Advance Access published February 28, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu065

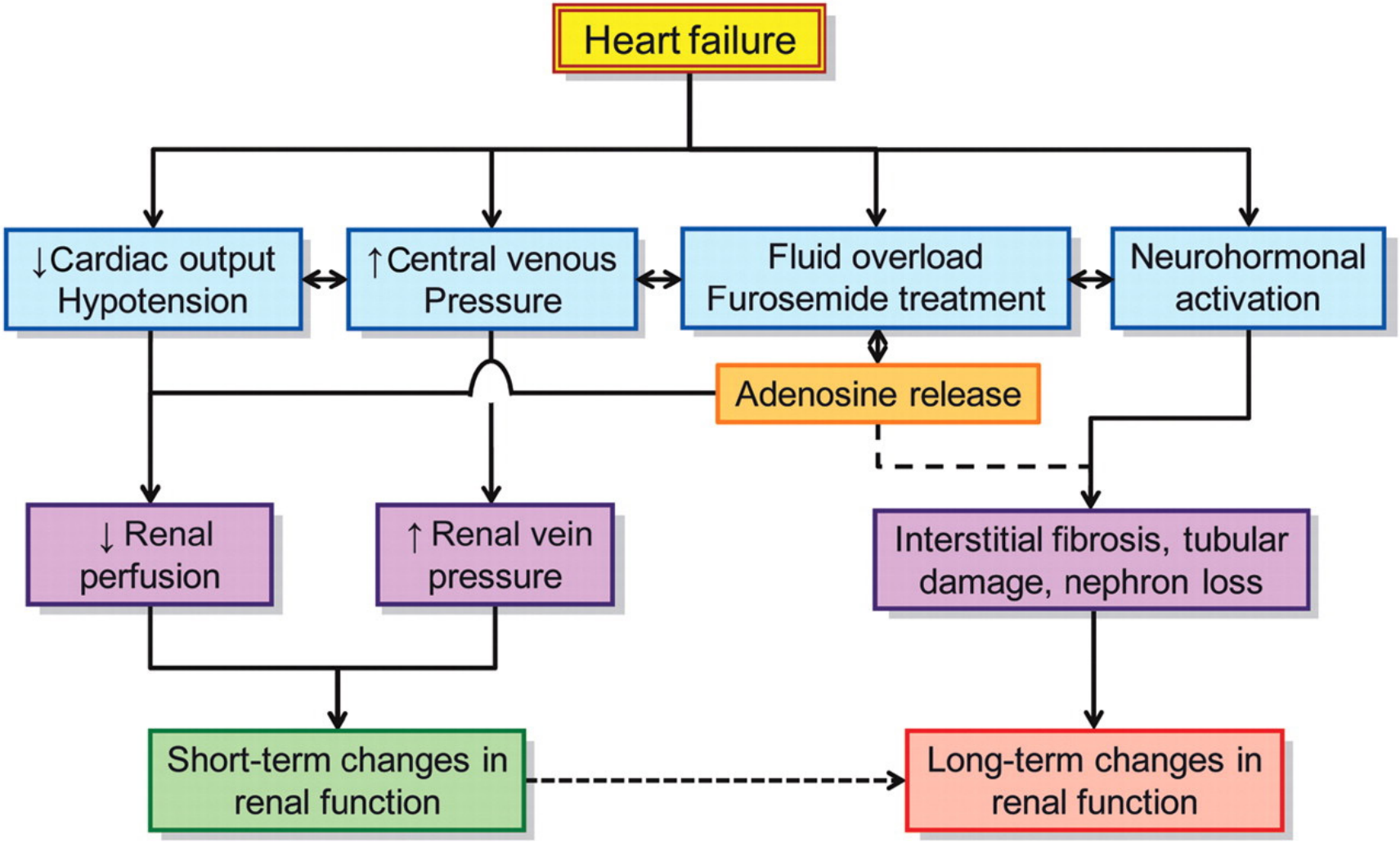
CLINICAL RESEARCH
Heart failure/cardiomyopathy

Diuretic response in acute heart failure: clinical characteristics and prognostic significance

Mattia A. E. Valente[1], Adriaan A. Voors[1]*, Kevin Damman[1], Dirk J. Van Veldhuisen[1], Barrie M. Massie[2], Christopher M. O'Connor[3], Marco Metra[4], Piotr Ponikowski[5], John R. Teerlink[2], Gad Cotter[6], Beth Davison[6], John G.F. Cleland[7], Michael M. Givertz[8], Daniel M. Bloomfield[9], Mona Fiuzat[3], Howard C. Dittrich[10], and Hans L. Hillege[1,11]

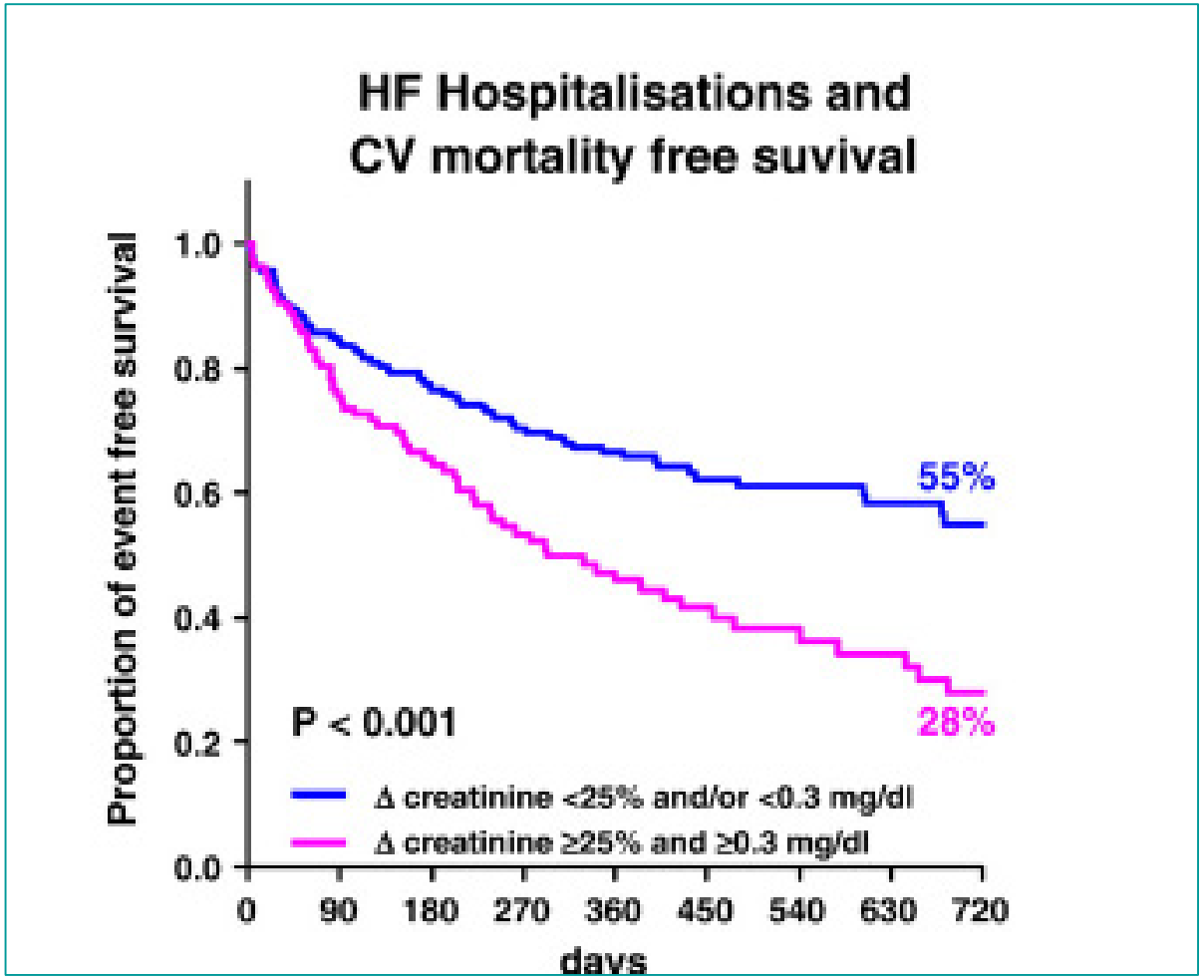


Mechanisms of worsening renal function in HF



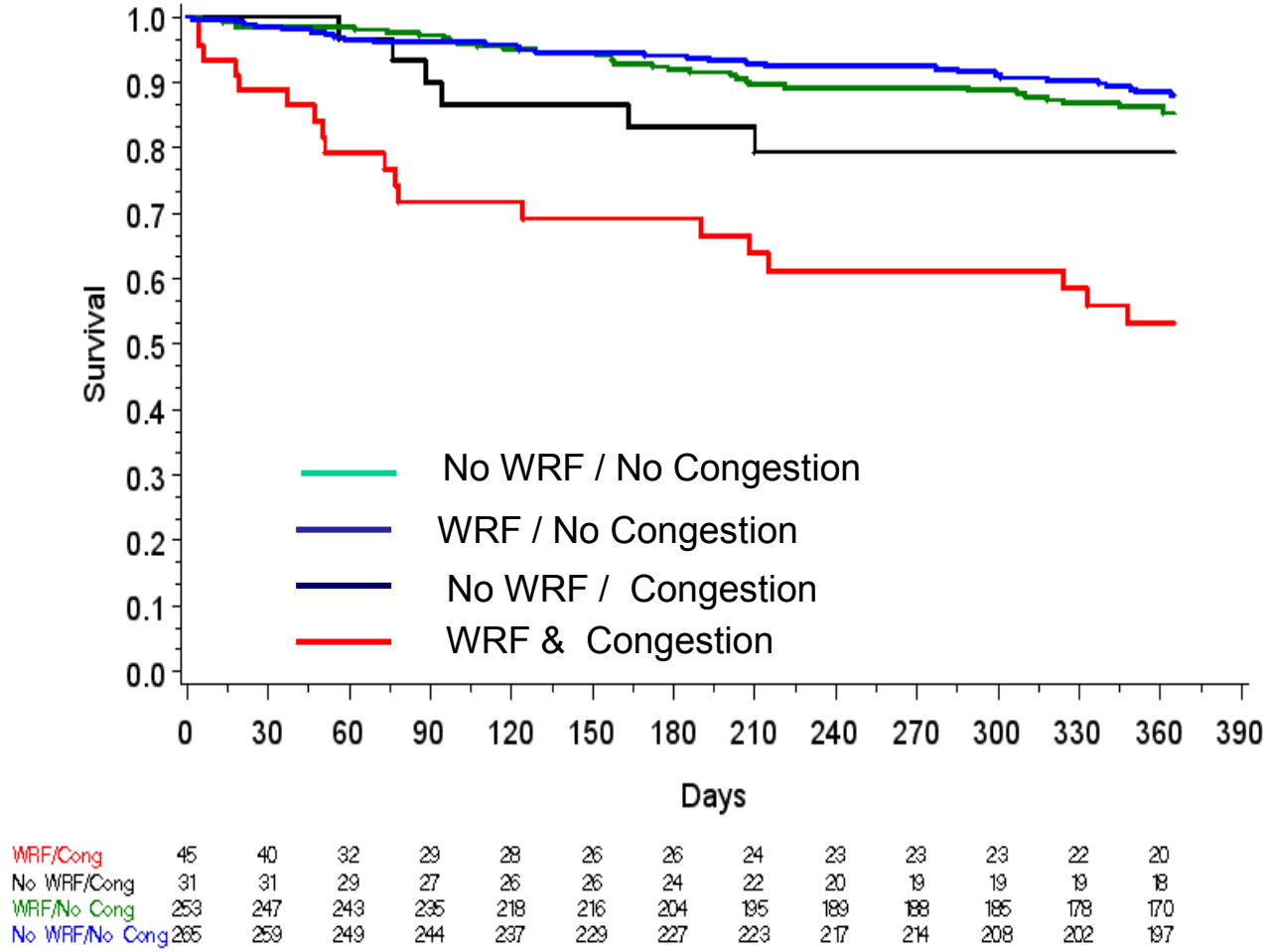
Metra M et al. Eur Heart J 2012;33:2135-2142

Prognostic Significance of Worsening Renal Function in AHF



Metra et al. Eur J Heart Fail 2008; 10: 188

When an increase in serum creatinine is not an ominous prognostic sign in patients with acute heart failure: the role of congestion and its interaction with renal function



Metra et al. Circ Heart Fail 2012; 5:54-62

Treatment of insufficient diuretic response / diuretic resistance

1. Check adherence and fluid intake
2. Increase a dose of diuretic
3. Administer loop diuretic twice (or more times) daily or on empty stomach
4. Add an MRA/increase dose of an MRA
5. Combine loop diuretic and thiazide/metolazone
6. Consider switching from furosemide to torasemide
7. Consider short-term i.v. infusion of loop diuretic
8. Consider ultrafiltration

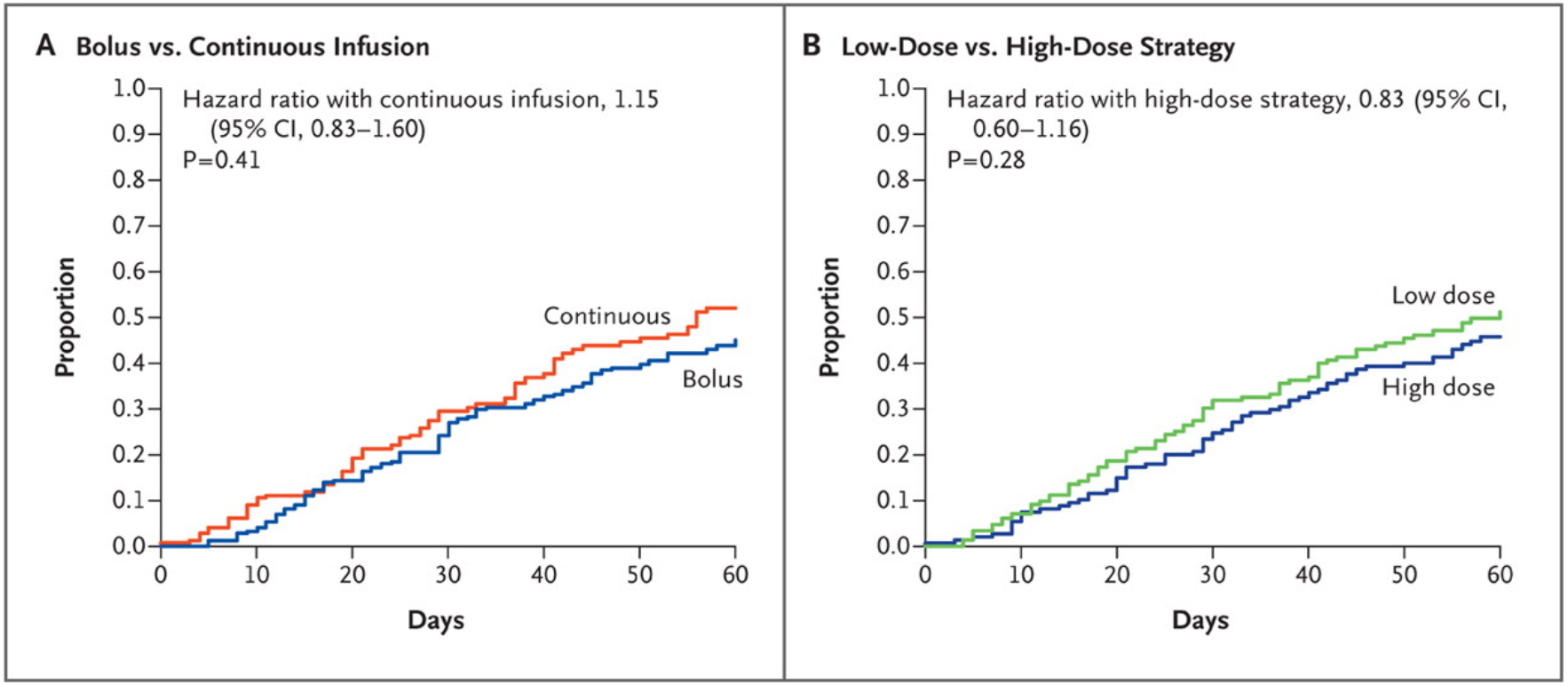
Modified from
Ponikowski et al. Eur J Heart Fail 2016; 8, 891–975 & web tables

Treatment of worsening renal function

1. Check for hypovolaemia/dehydration
2. Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim
3. If using concomitant loop and thiazide diuretic, stop thiazide diuretic
4. Consider reducing a dose of ACE inhibitor/ARB
5. Withhold an MRA
6. Consider haemofiltration/dialysis

Modified from
Ponikowski et al. Eur J Heart Fail 2016; 8, 891–975 & web tables

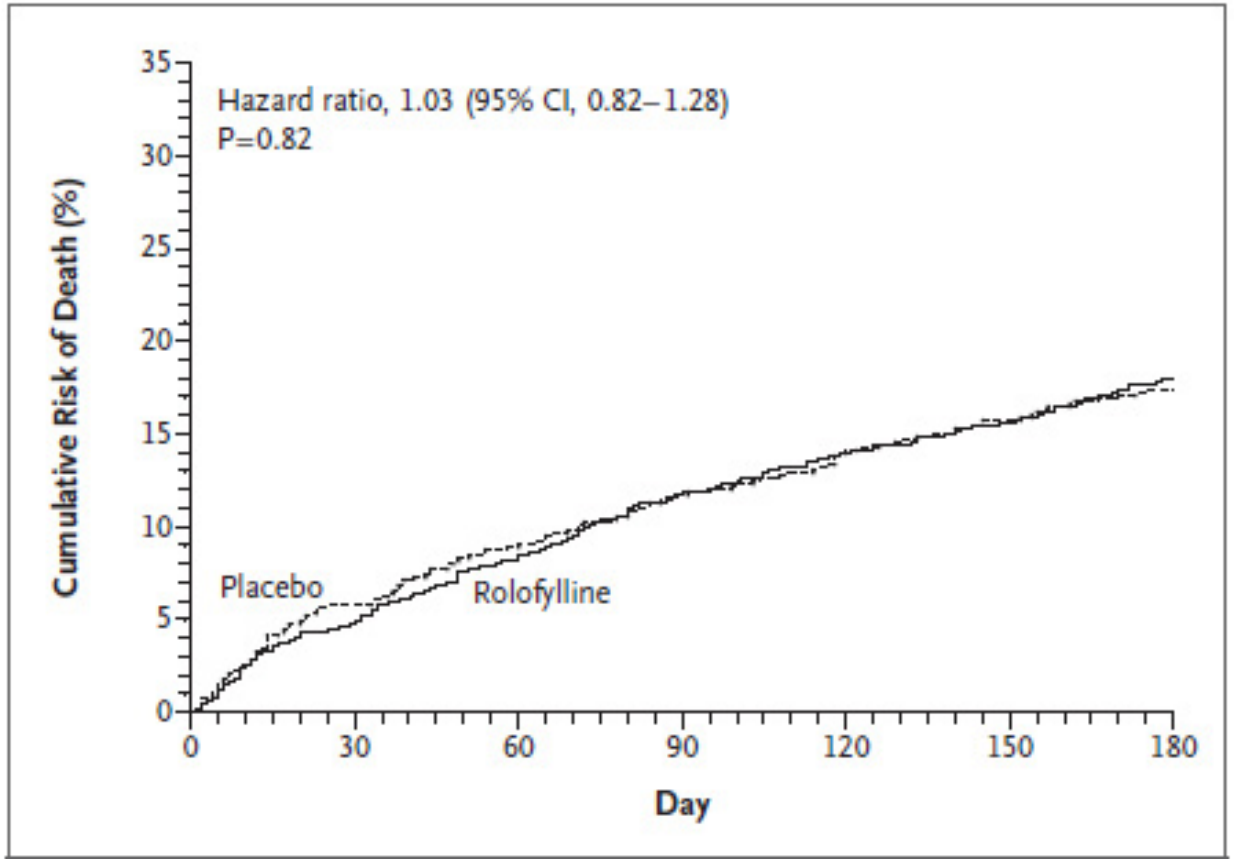
Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.



Felker GM et al. N Engl J Med 2011;364:797-805.

Rolofylline, an Adenosine A_1–Receptor Antagonist, in Acute Heart Failure

Barry M. Massie, M.D., Christopher M. O'Connor, M.D., Marco Metra, M.D., Piotr Ponikowski, M.D., John R. Teerlink, M.D., Gad Cotter, M.D., Beth Davison Weatherley, Ph.D., John G.F. Cleland, M.D., Michael M. Givertz, M.D., Adriaan Voors, M.D., Paul DeLucca, Ph.D., George A. Mansoor, M.D., Christina M. Salerno, M.S., Daniel M. Bloomfield, M.D., and Howard C. Dittrich, M.D., for the PROTECT Investigators and Committees*



New Engl J Med 2010;363:1419-28

Original Investigation

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

Horng H. Chen, MBBCh; Kevin J. Anstrom, PhD; Michael M. Givertz, MD; Lynne W. Stevenson, MD; Marc J. Semigran, MD; Steven R. Goldsmith, MD; Bradley A. Bart, MD; David A. Bull, MD; Josef Stehlik, MD; Martin M. LeWinter, MD; Marvin A. Konstam, MD; Gordon S. Huggins, MD; Jean L. Rouleau, MD; Eileen O'Meara, MD; W. H. Wilson Tang, MD; Randall C. Starling, MD, MPH; Javed Butler, MD, MPH; Anita Deswal, MD; G. Michael Felker, MD; Christopher M. O'Connor, MD; Raphael E. Bonita, MD, ScM; Kenneth B. Margulies, MD; Thomas P. Cappola, MD, ScM; Elizabeth O. Ofili, MD; Douglas L. Mann, MD; Víctor G. Dávila-Román, MD; Steven E. McNulty, MS; Barry A. Borlaug, MD; Eric J. Velazquez, MD; Kerry L. Lee, PhD; Monica R. Shah, MD, MHS, MSJ; Adrian F. Hernandez, MD, MHS; Eugene Braunwald, MD; Margaret M. Redfield, MD; for the NHLBI Heart Failure Clinical Research Network

Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	**Placebo (n = 119)**	**Dopamine (n = 122)**		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.12 (0.06 to 0.18)	0.01 (−0.08 to 0.10)	.72
Nesiritide strategy	**Placebo (n = 119)**	**Nesiritide (n = 119)**		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8574 (8014 to 9134)	279 (−618 to 1176)	.49
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.07 (0.01 to 0.13)	−0.04 (−0.13 to 0.05)	.36

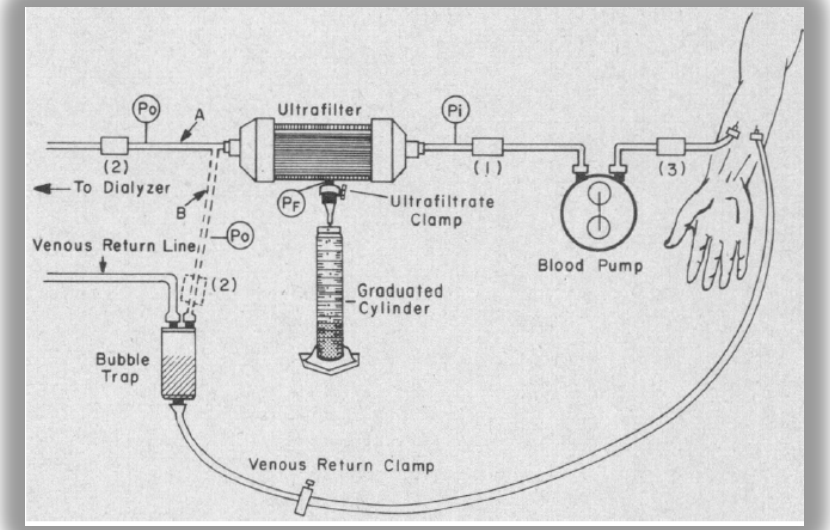
Ultrafiltration - Not a novel therapy

The New England
Journal of Medicine

Volume 291 OCTOBER 10, 1974 Number 15

TREATMENT OF SEVERE FLUID OVERLOAD BY ULTRAFILTRATION

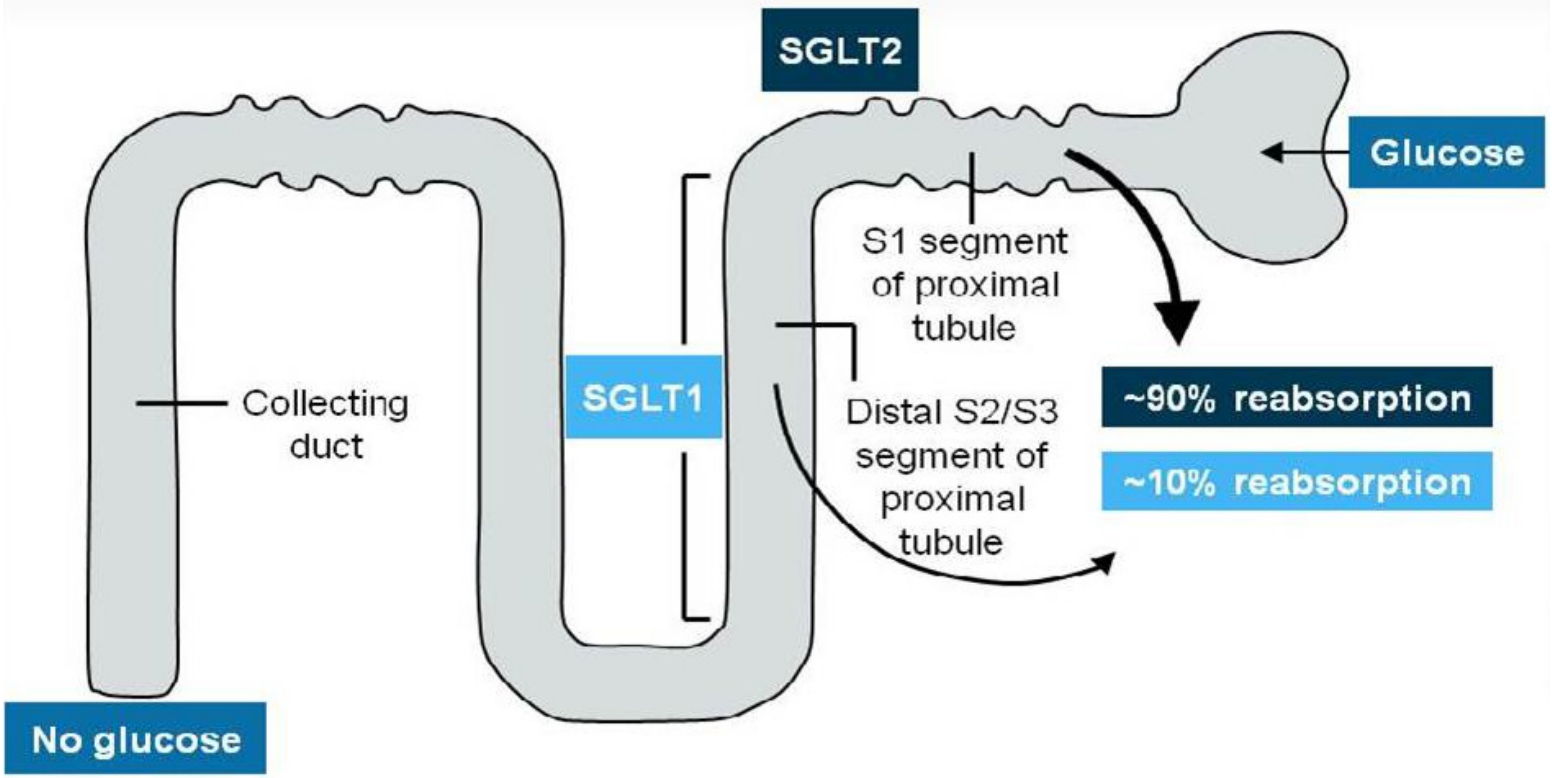
MARC ELIOT SILVERSTEIN, M.D., CHERYL A. FORD, B.S., MICHAEL J. LYSAGHT, M.S., AND LEE W. HENDERSON, M.D.



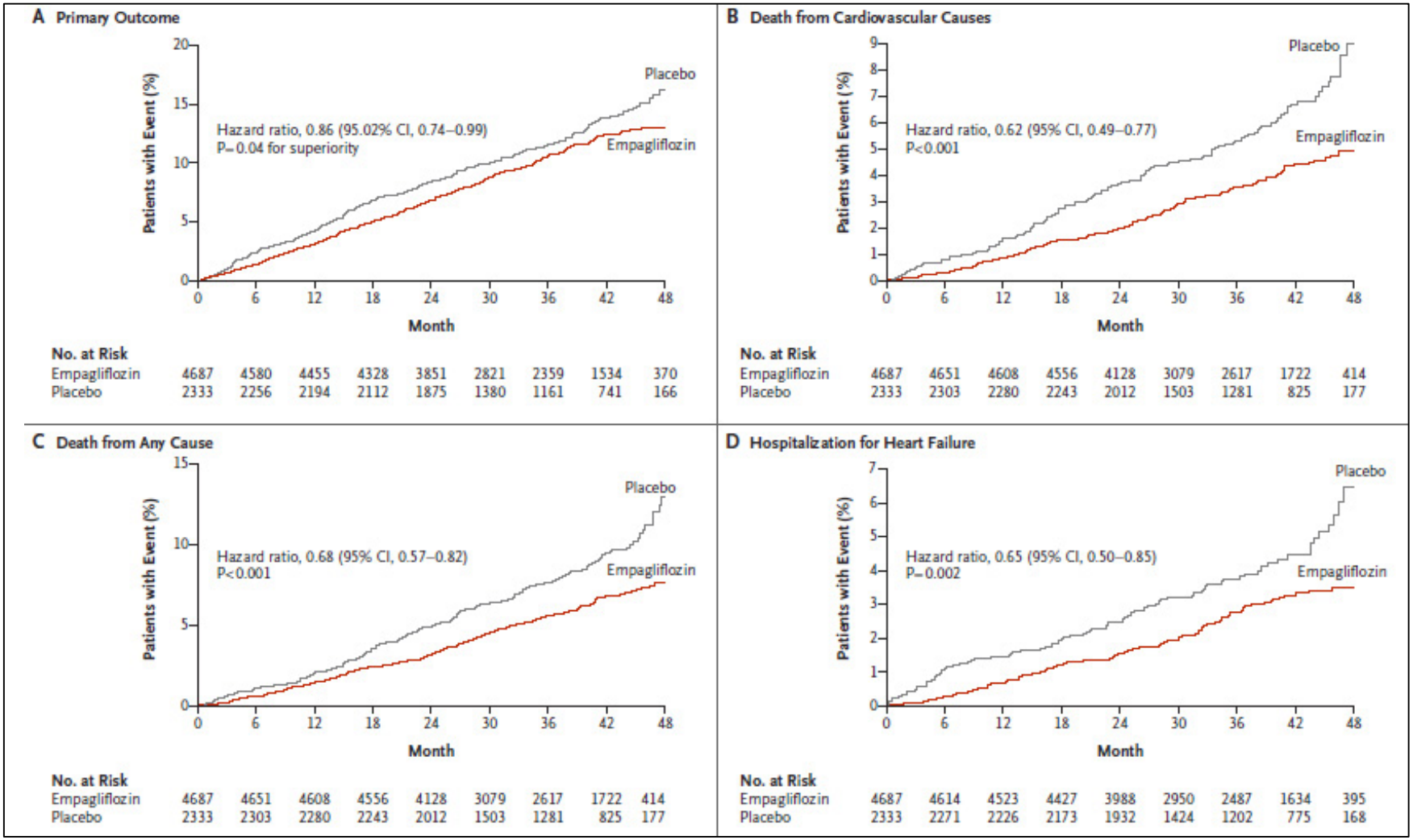
tated. Complications of ultrafiltration were rare and included leg cramps and orthostatic hypertension. The solute concentrations in the ultrafiltrate were identical to plasma water, thereby avoiding electrolyte and acid-base disturbances. This therapy is simpler and safer than peritoneal dialysis or hemodialysis; we speculate that it could logically be extended to patients with refractory chronic edematous states or with pulmonary edema. (N Engl J Med 291:747-751, 1974

SGLT-2 inhibitors

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

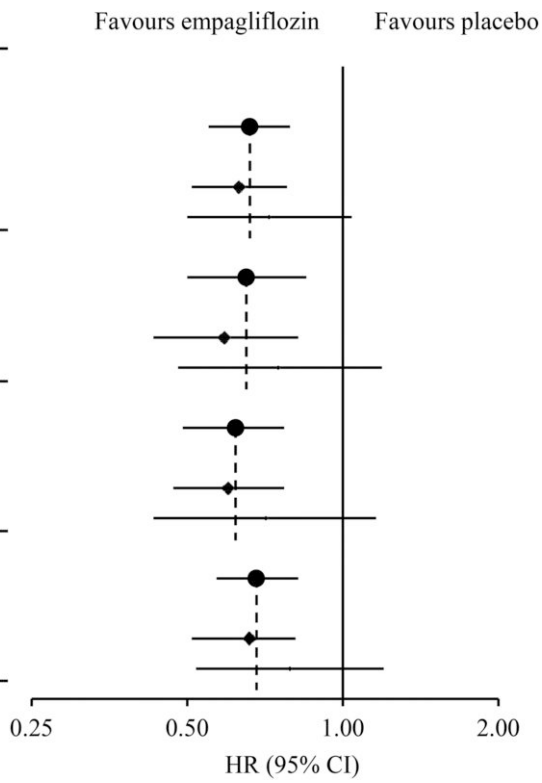


Empaglifozin, cardiovascular outcomes and mortality. EMPA-REG Outcome trial



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)

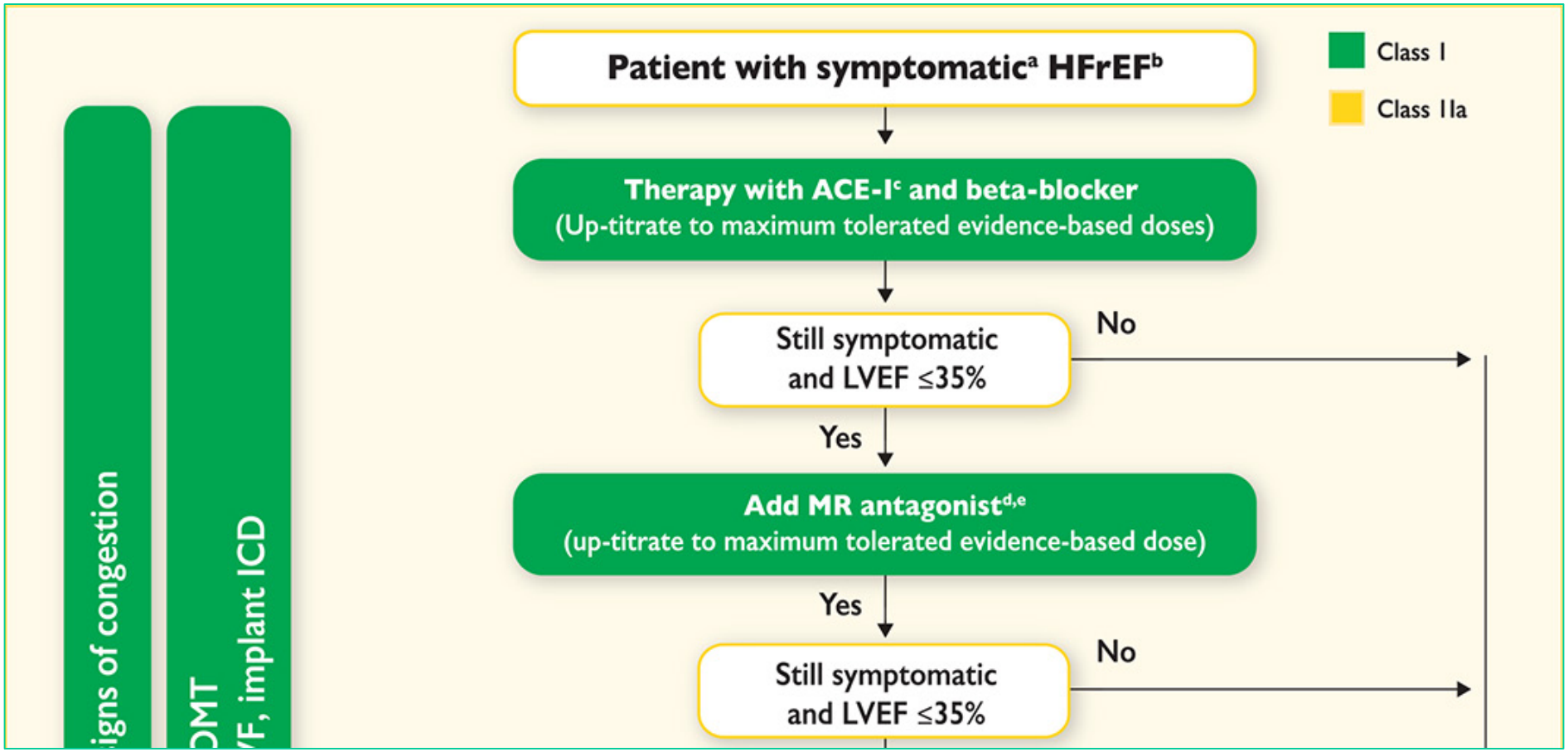


David Fitchett et al. Eur Heart J 2016;37:1526-1534

Optimal medical therapy for HF

1. HFpEF
2. Diuretics
3. Neurohormonal antagonists

Therapeutic algorithm for a patient with symptomatic HFrEF



Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

European Journal of Heart Failure Advance Access published August 26, 2013

European Journal of Heart Failure
doi:10.1093/eurjhf/hft134

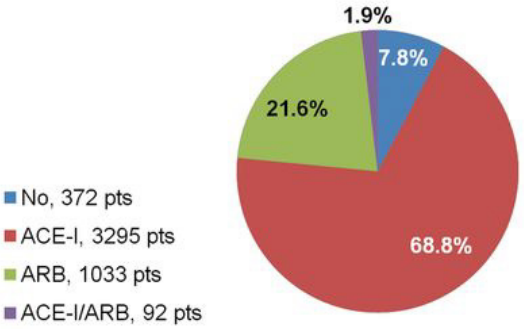
Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry

To evaluate how recommendations of European guidelines regarding pharmacological and non-pharmacological treatments for heart failure (HF) are adopted in clinical practice.

The ESC-HF Long-Term Registry is a prospective, observational study conducted in 211 Cardiology Centres of 21 European and Mediterranean countries, members of the European Society of Cardiology (ESC). From May 2011 to April 2013, a total of 12 440 patients were enrolled, 40.5% with acute HF and 59.5% with chronic HF. Intravenous treatments for acute HF were heterogeneously administered, irrespective of guideline recommendations. In chronic HF, with reduced EF, renin–angiotensin system (RAS) blockers, beta-blockers, and mineralocorticoid antagonists (MRAs) were used in 92.2, 92.7, and 67.0% of patients, respectively. When reasons for non-adherence were considered, the real rate of under-treatment accounted for 3.2, 2.3, and 5.4% of the cases, respectively. About 30% of patients received the target dosage of these drugs, but a documented reason for not achieving the target dosage was reported in almost two-thirds of them. The more relevant reasons for non-implantation of a device, when clinically indicated, were related to doctor uncertainties on the indication, patient refusal, or logistical/cost issues.

Reason for non-use of recommended treatments in patients with reduced EF

A



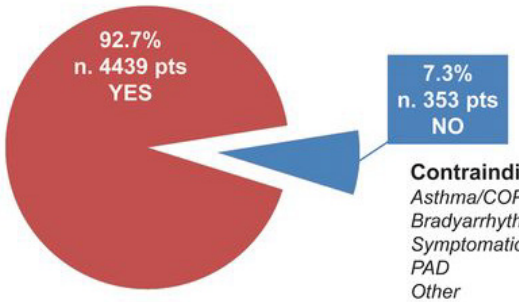
Contraindicated	**n. 94 (2.0%)**
Severe renal dysfunction	*n. 61 (64.9%)*
Symptomatic hypotension	*n. 13 (13.8%)*
Hyperkalemia	*n. 8 (8.5%)*
Other	*n. 12 (12.8%)*

Not tolerated	**n. 123 (2.6%)**
Worsening renal function	*n. 22 (17.9%)*
Symptomatic hypotension	*n. 83 (67.5%)*
Hyperkalemia	*n. 6 (4.9%)*
Angioedema	*n. 2 (1.6%)*
Other	*n. 10 (8.1%)*

Real undertreatment **n. 155 (3.2%)**

ACE-I= angiotensin converting enzyme inhibitor
ARBs= angiotensin receptor blockers;

B



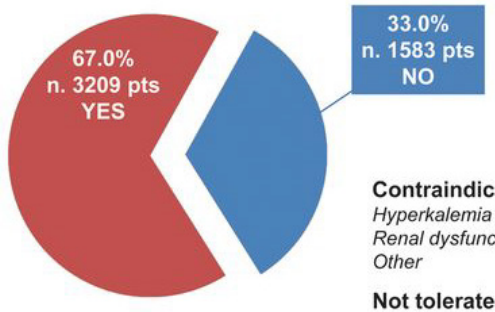
Contraindicated	**n. 78 (1.6%)**
Asthma/COPD	*n. 28 (35.9%)*
Bradyarrhythmia	*n. 11 (14.1%)*
Symptomatic hypotension	*n. 11 (14.1%)*
PAD	*n. 3 (3.8%)*
Other	*n. 25 (32.1%)*

Not tolerated	**n. 165 (3.4%)**
Bronchospasm	*n. 39 (23.6%)*
Symptomatic hypotension	*n. 46 (27.9%)*
Bradyarrhythmia	*n. 22 (13.3%)*
Worsening HF	*n. 36 (21.8%)*
Other	*n. 22 (13.3%)*

Real undertreatment **n. 110 (2.3%)**

COPD=chronic obstructive pulmonary disease;
HF=heart failure; PAD=peripheral artery disease

C



Contraindicated	**n. 268 (5.6%)**
Hyperkalemia	*n. 94 (35.1%)*
Renal dysfunction	*n. 153 (57.1%)*
Other	*n. 21 (7.8%)*

Not tolerated	**n. 147 (3.1%)**
Hyperkalemia	*n. 53 (36.1%)*
Worsening renal function	*n. 34 (23.1%)*
Gynecomastia	*n. 34 (23.1%)*
Other	*n. 26 (17.7%)*

Not indicated **n. 908 (18.9%)**

Real undertreatment **n. 260 (5.4%)**

MRAs=mineralcorticoid receptor antagonists

Maggioni A P et al. Eur J Heart Fail 2013;15:1173-1184

Number of patients at target of recommended doses in ESC-HF registry

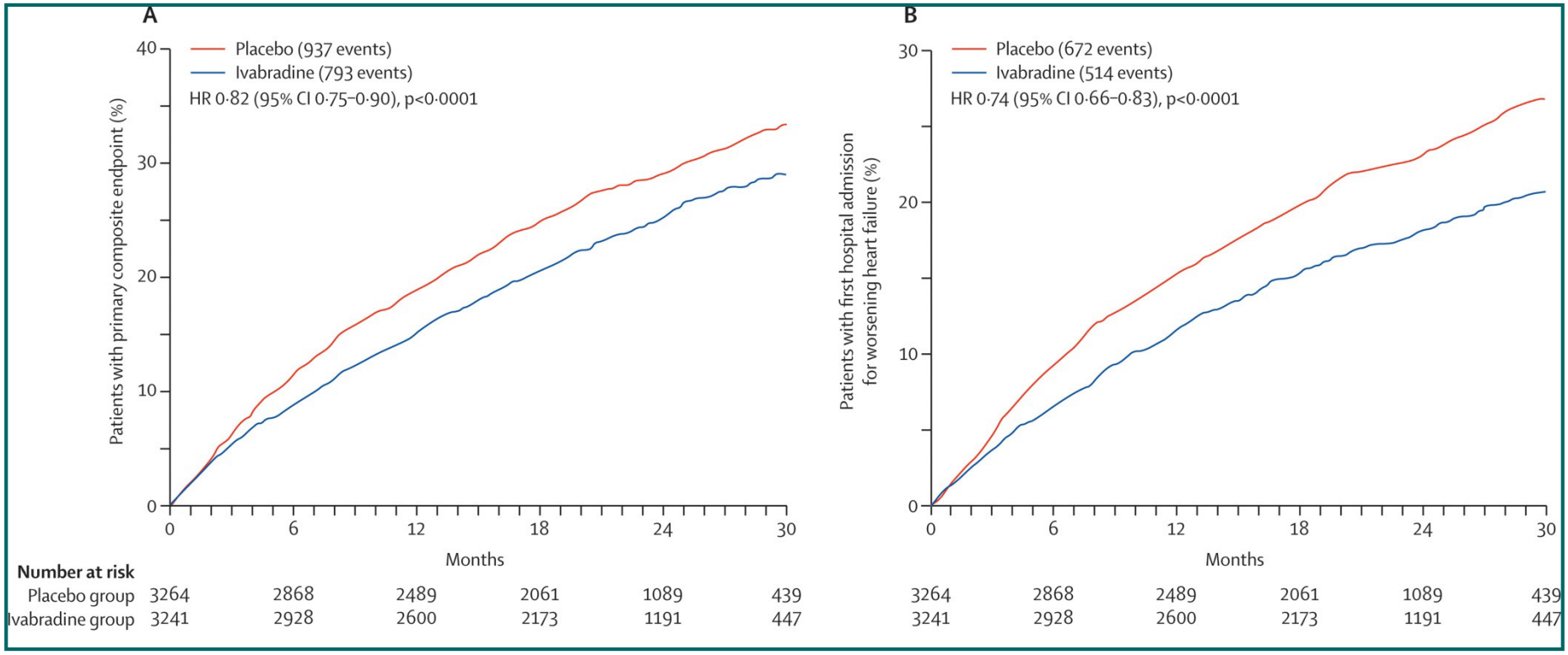
	At target, *n* (%)	Not at target, *n* (%)	Reason for not at target, *n* (%)	
ACE-I (4710 pts)	1380 (29.3)	3330 (70.7)	1123 (33.7)	Still in up-titration
			866 (26.0)	Symptomatic hypotension
			264 (7.9)	Worsening renal function
			85 (2.6)	Hyperkalaemia
			29 (0.9)	Cough
			5 (0.2)	Angioedema
			958 (28.8)	Other/unknown
ARBs (1500 pts)	362 (24.1)	1138 (75.9)	369 (32.4)	Still in up-titration
			295 (25.9)	Symptomatic hypotension
			115 (10.1)	Worsening renal function
			25 (2.2)	Hyperkalaemia
			1 (0.1)	Angioedema
			333 (29.3)	Other/unknown
Beta-blockers (6468 pts)	1130 (17.5)	5338 (82.5)	1871 (35.1)	Still in up-titration
			904 (16.9)	Symptomatic hypotension
			586 (11.0)	Bradyarrhythmia
			185 (3.5)	Worsening HF
			146 (2.7)	Bronchospasm
			56 (1.1)	Worsening PAD
			33 (0.6)	Sexual dysfunction
			1557 (29.2)	Other/unknown
MRAs (4226 pts)	1290 (30.5)	2936 (69.5)		
			864 (29.4)	Still in up-titration
			350 (11.9)	Hyperkalaemia
			284 (9.7)	Worsening renal function
			60 (2.0)	Gynaecomastia
			1378 (46.9)	Other/unknown

Maggioni A P et al. Eur J Heart Fail 2013;15:1173-1184

SHIFT: cumulative event curves

CV death or HF hospitalization (primary end-point)

HF hospitalization (secondary end-point)

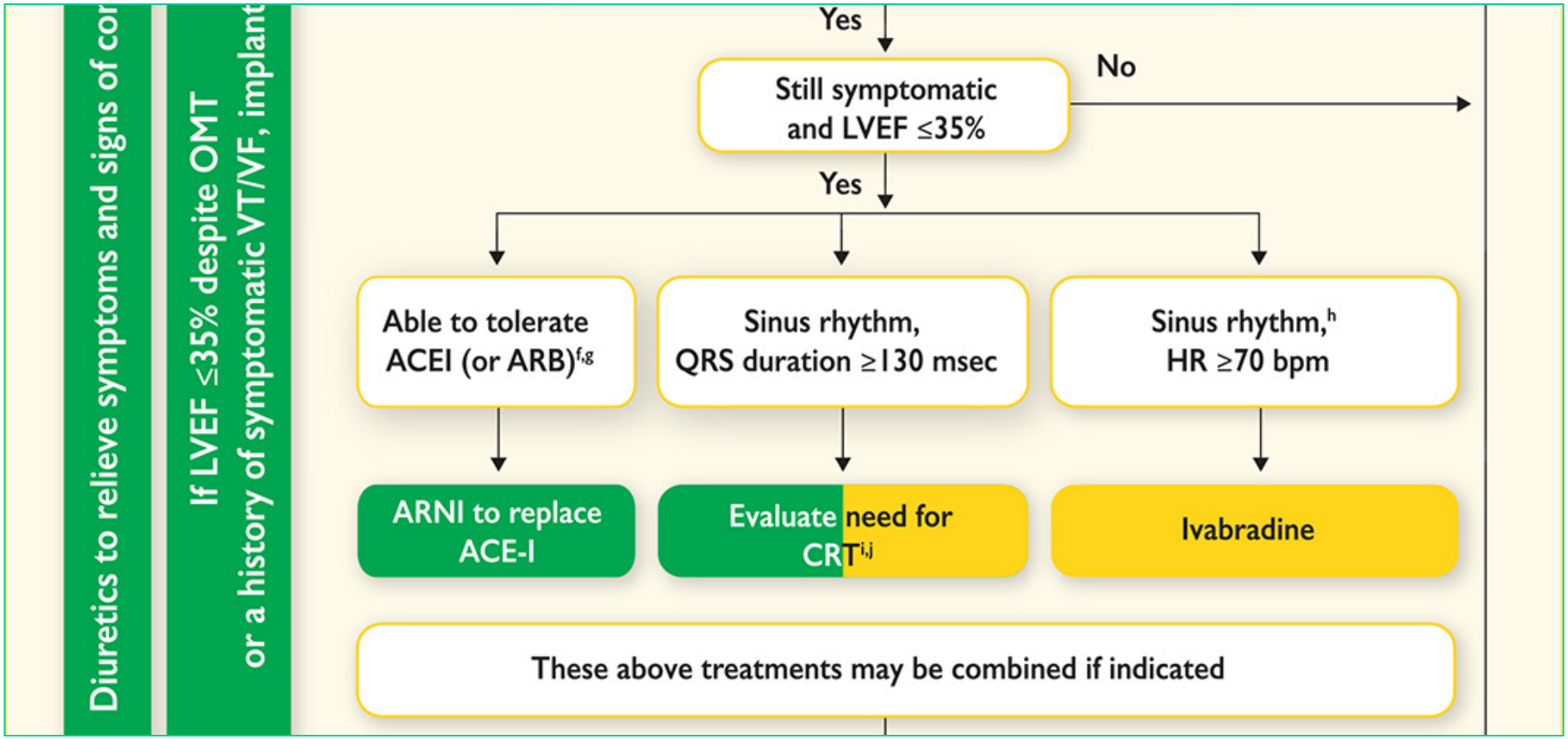


Swedberg et al. The Lancet, 376: 875 – 885

Optimal medical therapy for HF

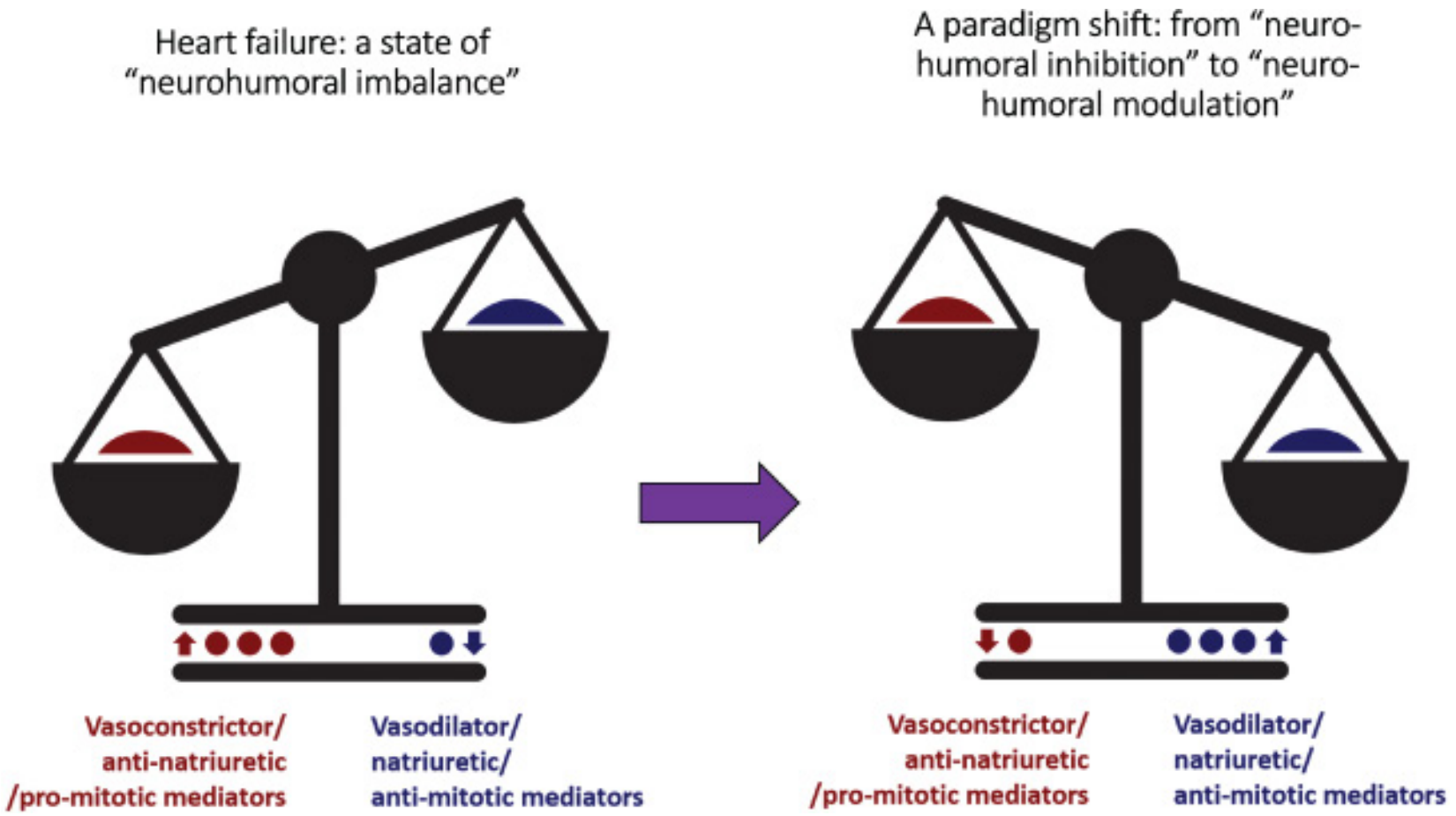
1. HFpEF
2. Diuretics
3. Neurohormonal antagonists
4. New neurohormoanl antagonists (ARNI)

Therapeutic algorithm for a patient with symptomatic HFrEF



Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

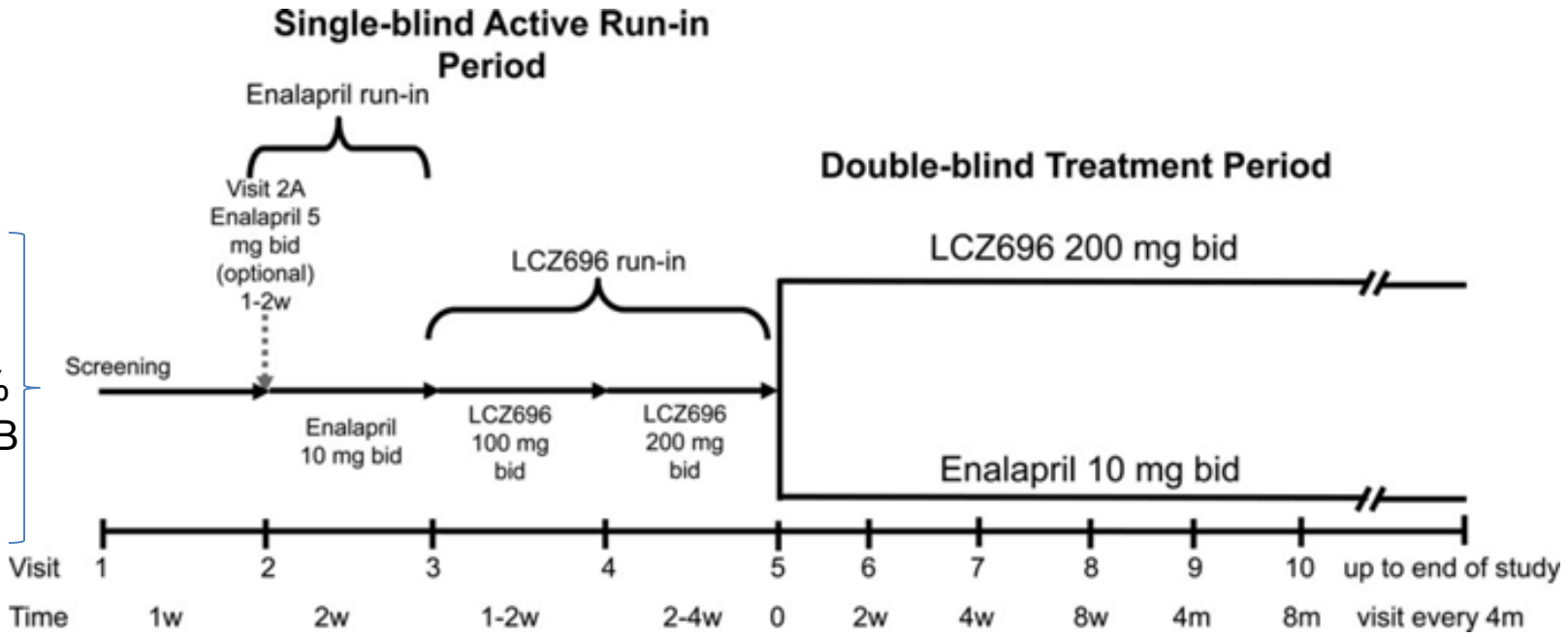
Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances



McMurray. Eur J Heart Fail 2015 Mar;17(3):242-7. doi: 10.1002/ejhf.250

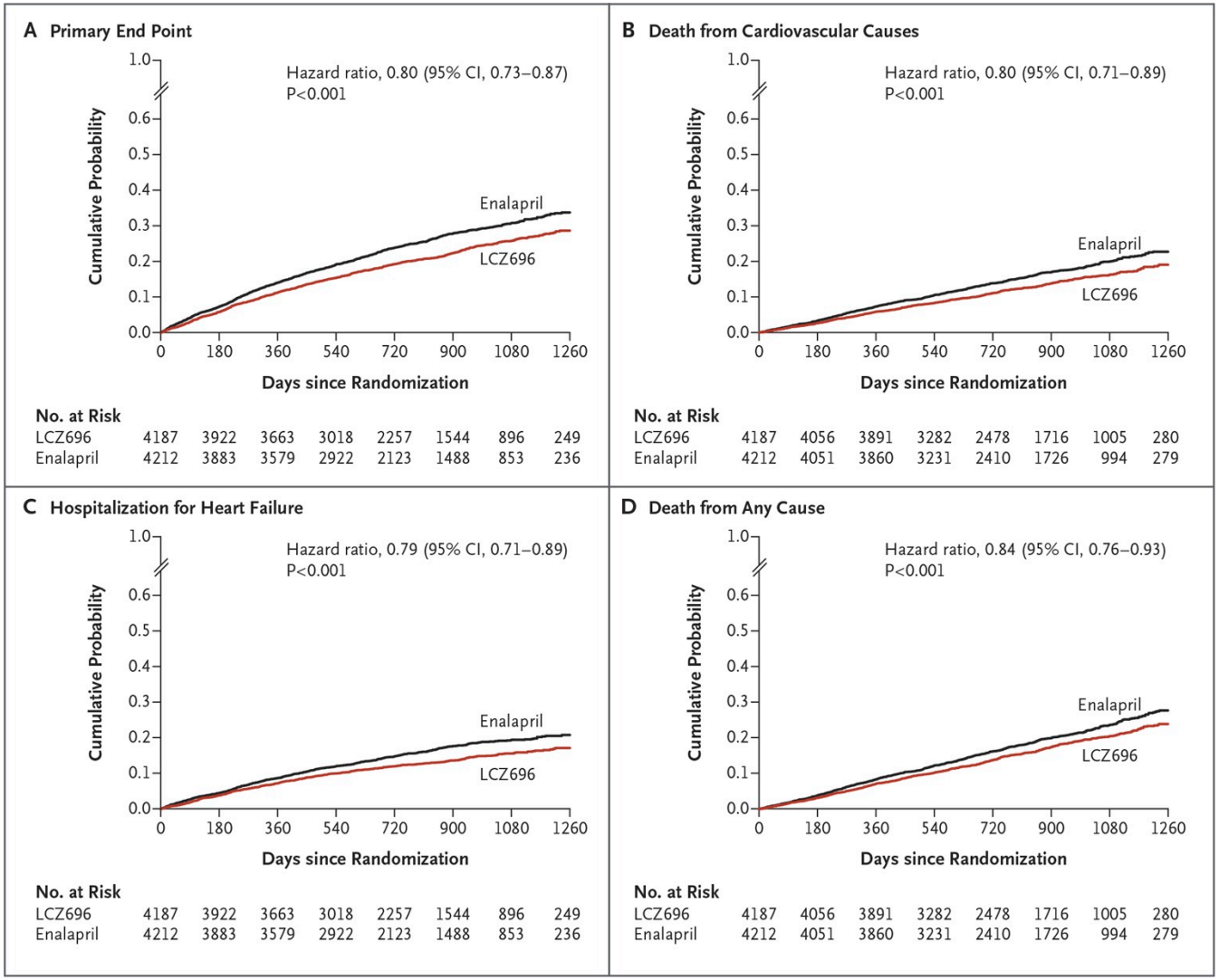
Dual Angiotensin Receptor and Neprilysin inhibition (ARNI) as an alternative to ACE inhibition in patients with chronic systolic HF. Design of the PARADIGM-HF Trial

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



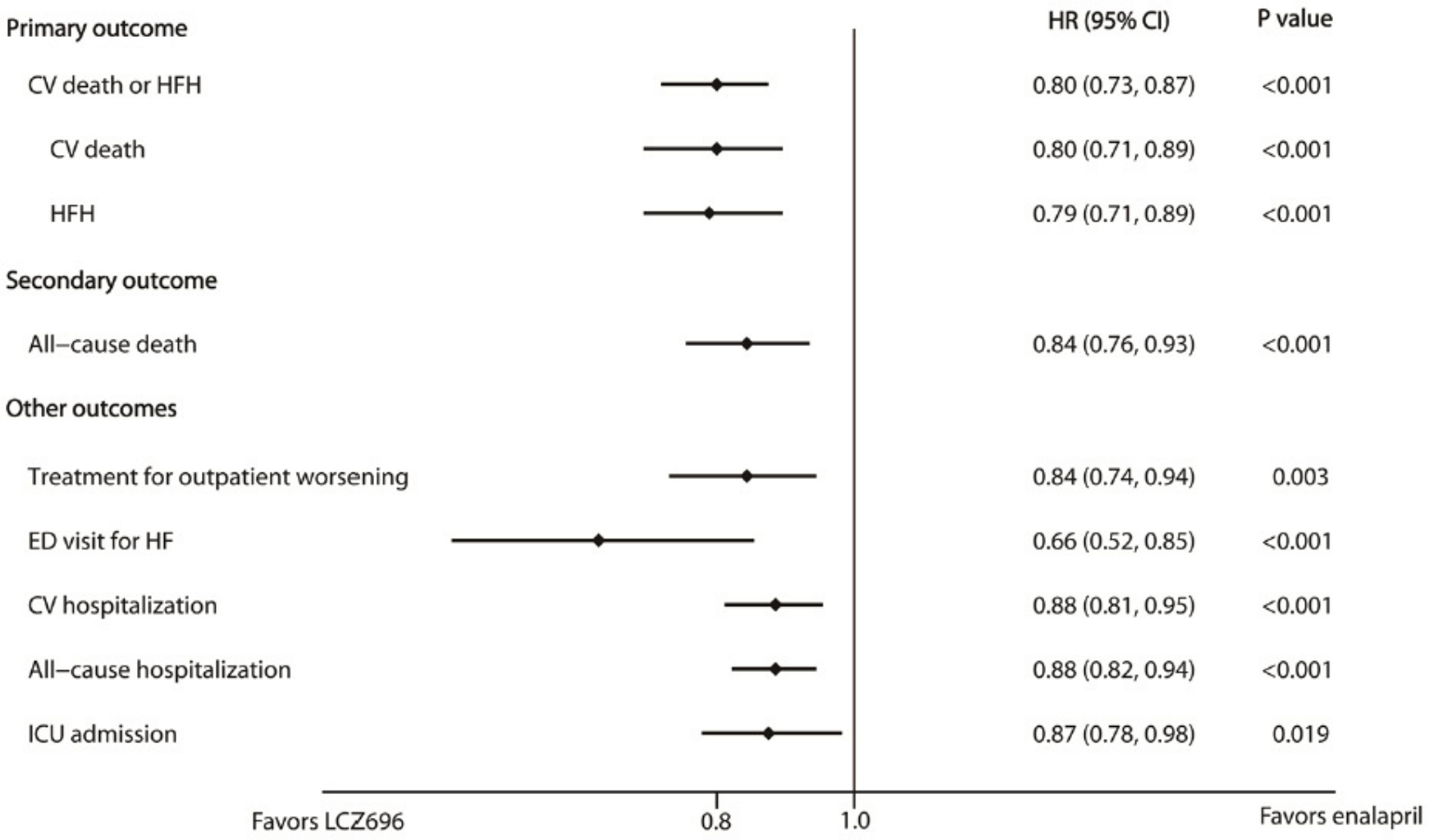
McMurray et al. European Journal of Heart Failure; 15: 1062-73

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



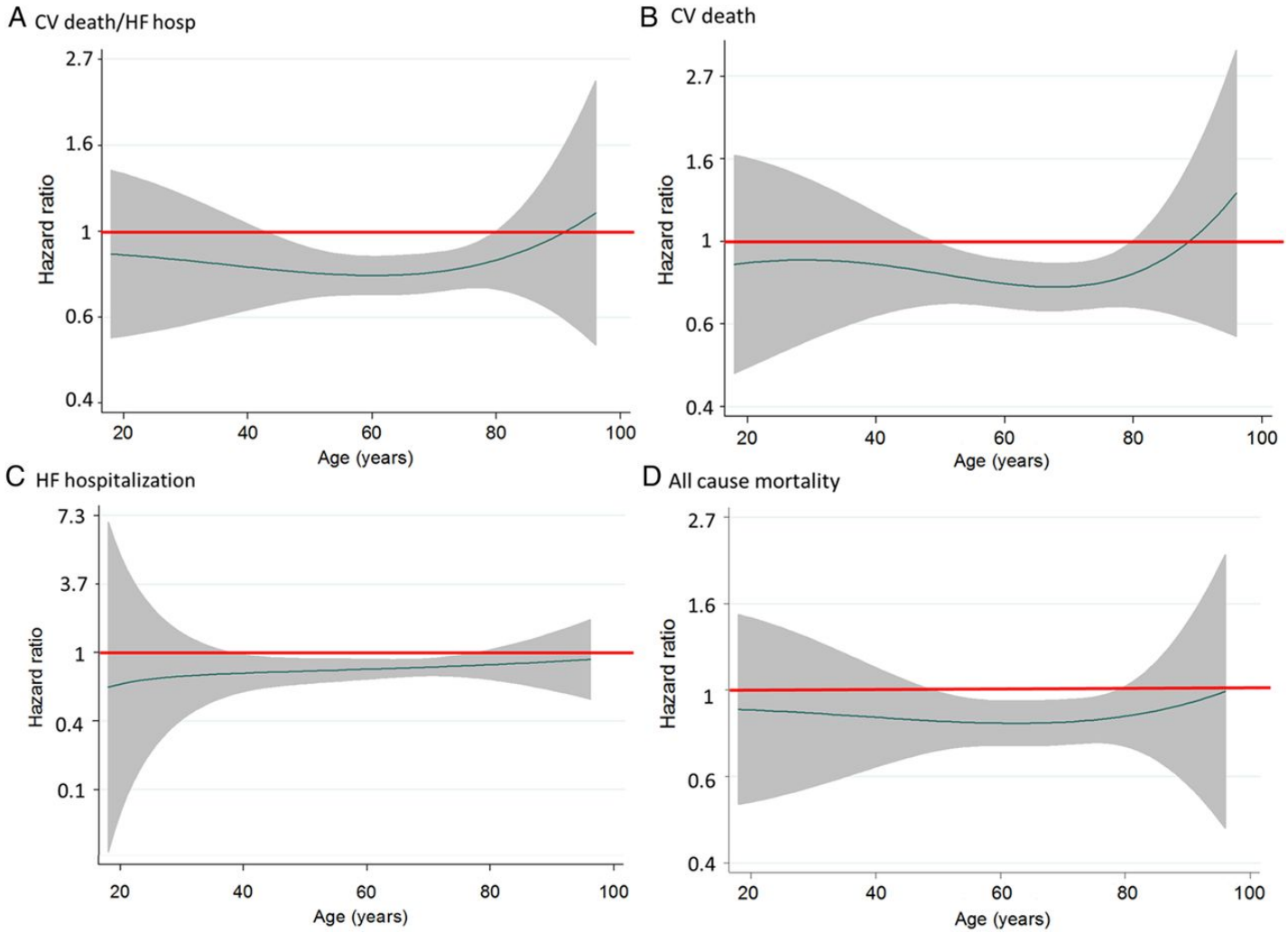
McMurray JJV et al. N Engl J Med 2014;371:993-1004

Key clinical outcomes in PARADIGM-HF



McMurray. Eur J Heart Fail 2015 Mar;17(3):242-7. doi: 10.1002/ejhf.250

Clinical outcomes according to age



Jhund et al. Eur Heart J 2015;36:2576-2584

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	Class [a]	Level [b]	Ref [c]
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162

Sacubitril/valsartan in clinical practice

- Tolerability

Adverse Events during Randomized Treatment.

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (P=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (P=0.002); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (P=0.56).

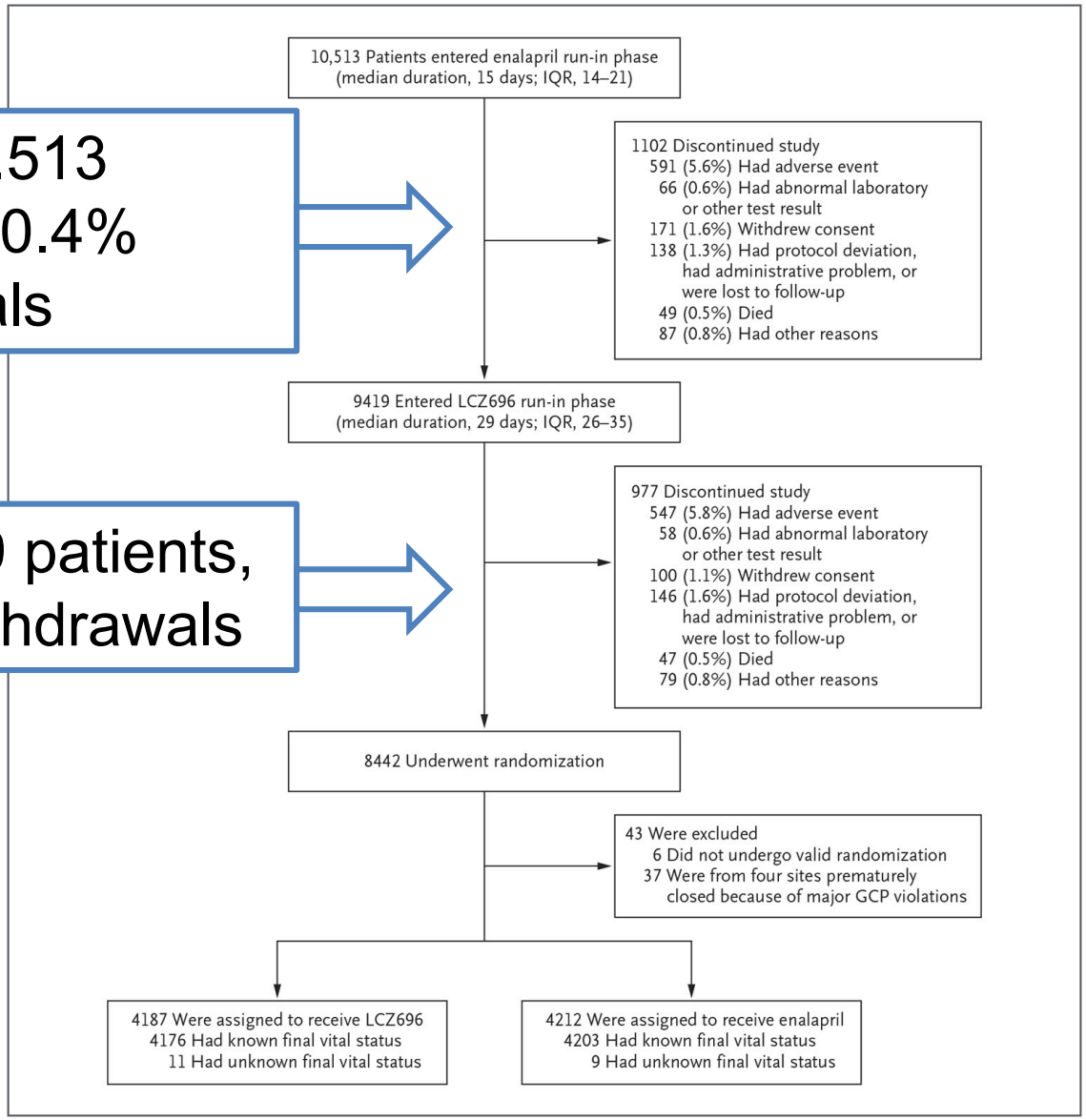
† Angioedema was adjudicated in a blinded fashion by an expert committee.

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

Screening Criteria, Run-in Periods, and Randomization.

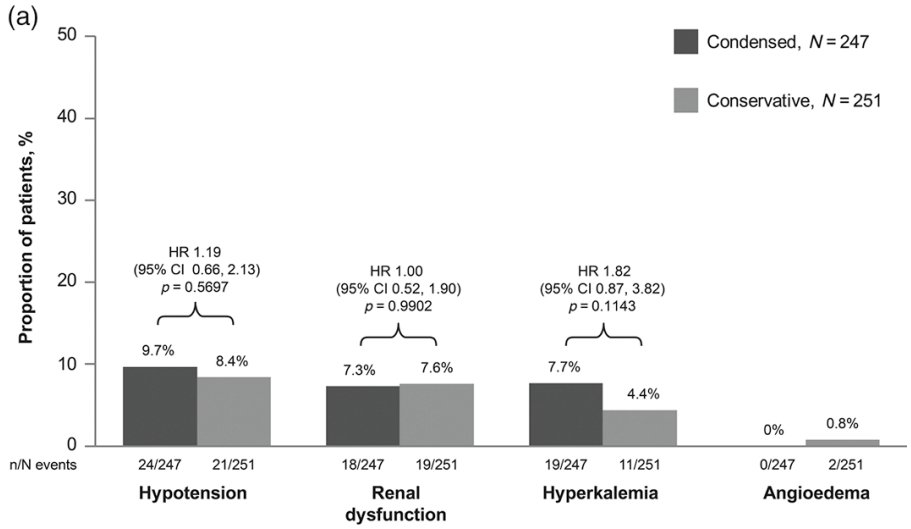
1.102/ 10.513 patients,10.4% withdrawals

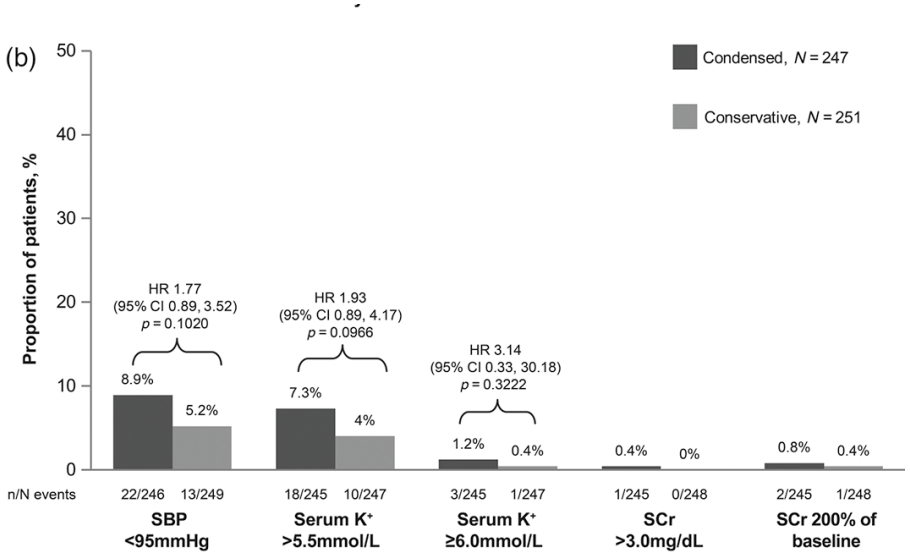
977/ 9419 patients, 10.4% withdrawals



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

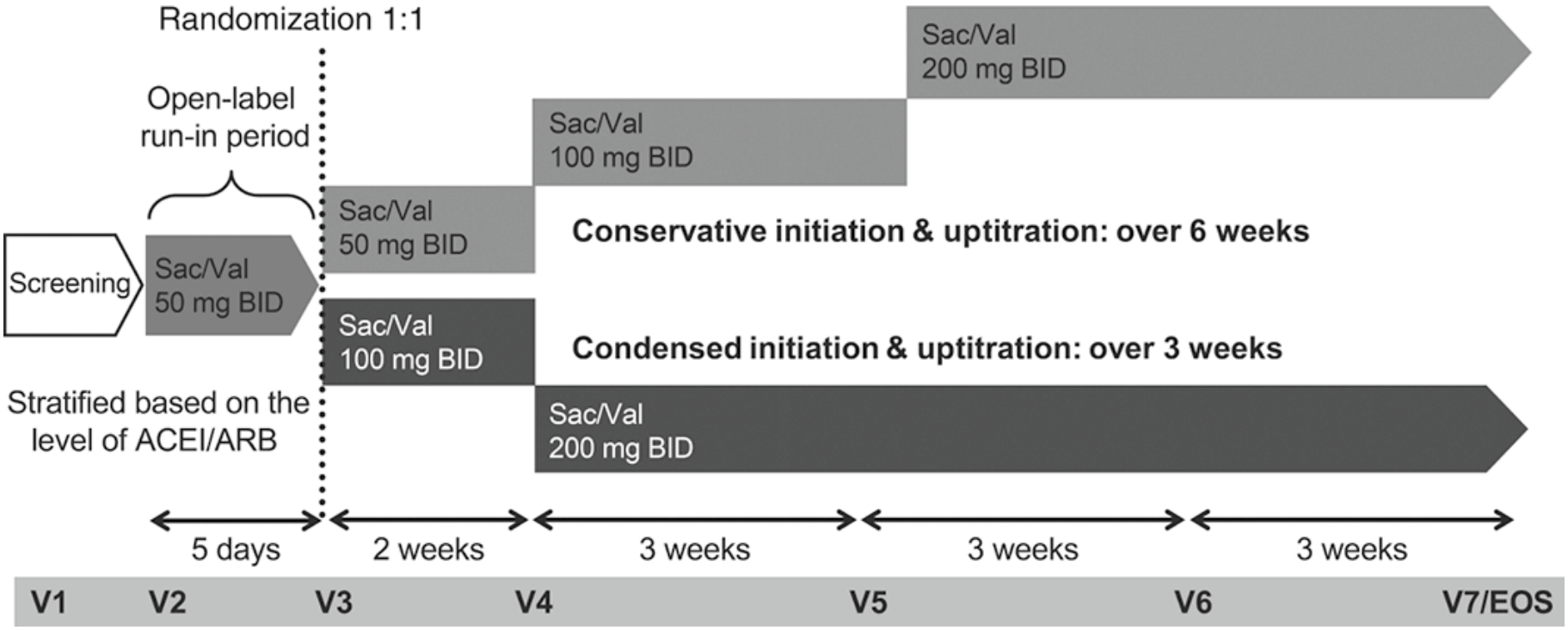
Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens





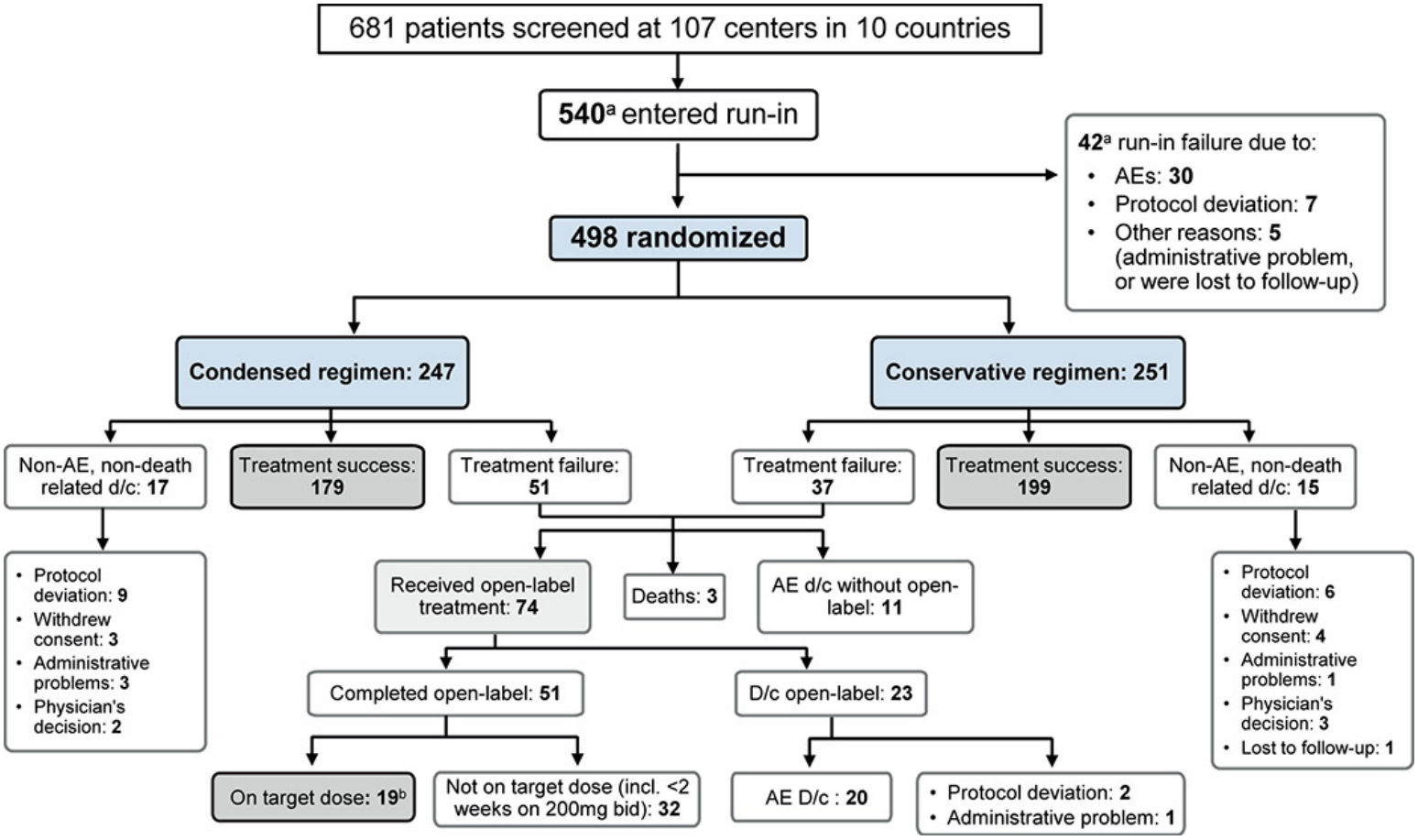
Senni et al. Eur J Heart Fail 2016; 18: 1193-1202

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens



European Journal of Heart Failure
Volume 18, Issue 9, pages 1193-1202, 12 MAY 2016 DOI: 10.1002/ejhf.548
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.548/full#ejhf548-fig-0001

Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

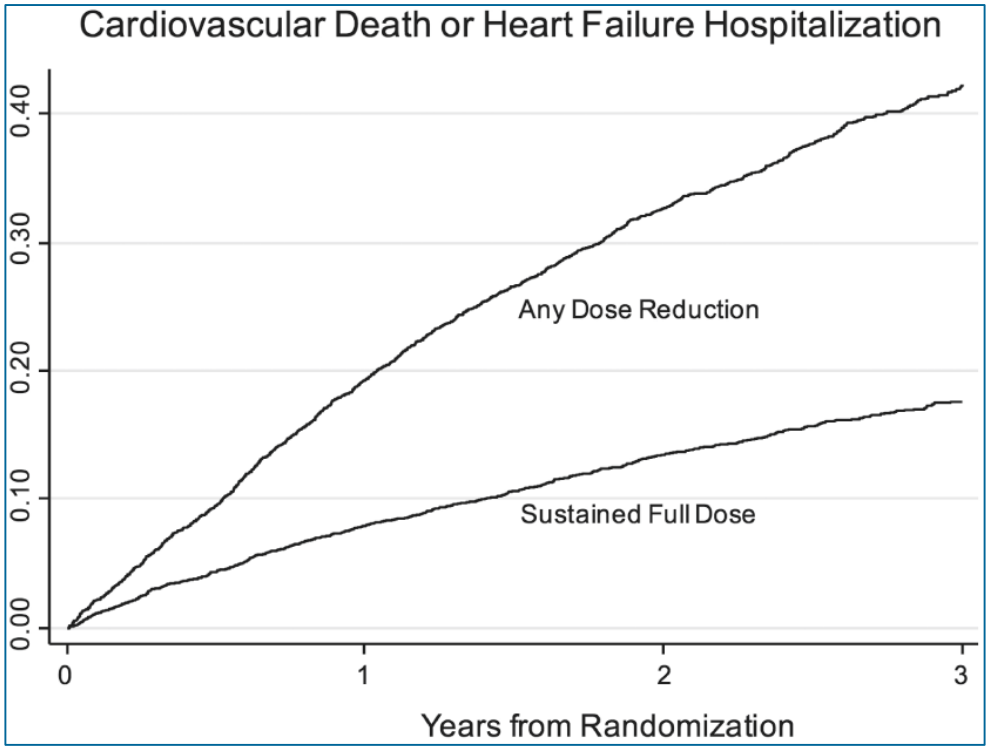


European Journal of Heart Failure
Volume 18, Issue 9, pages 1193-1202, 12 MAY 2016 DOI: 10.1002/ejhf.548
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.548/full#ejhf548-fig-0002

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



European Journal of Heart Failure (2016)
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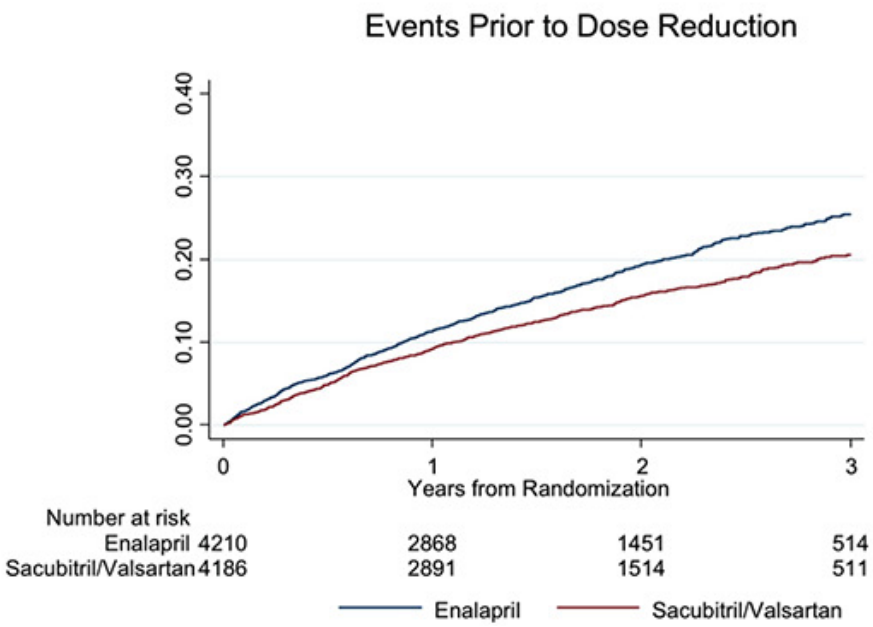
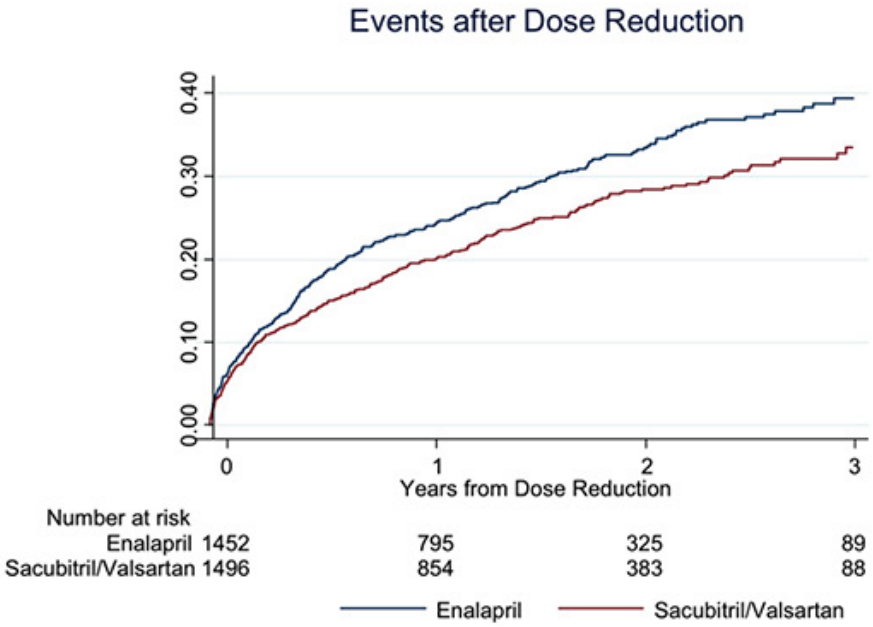
Cardiovascular Death or Heart Failure Hospitalization by Dose Reduction Status





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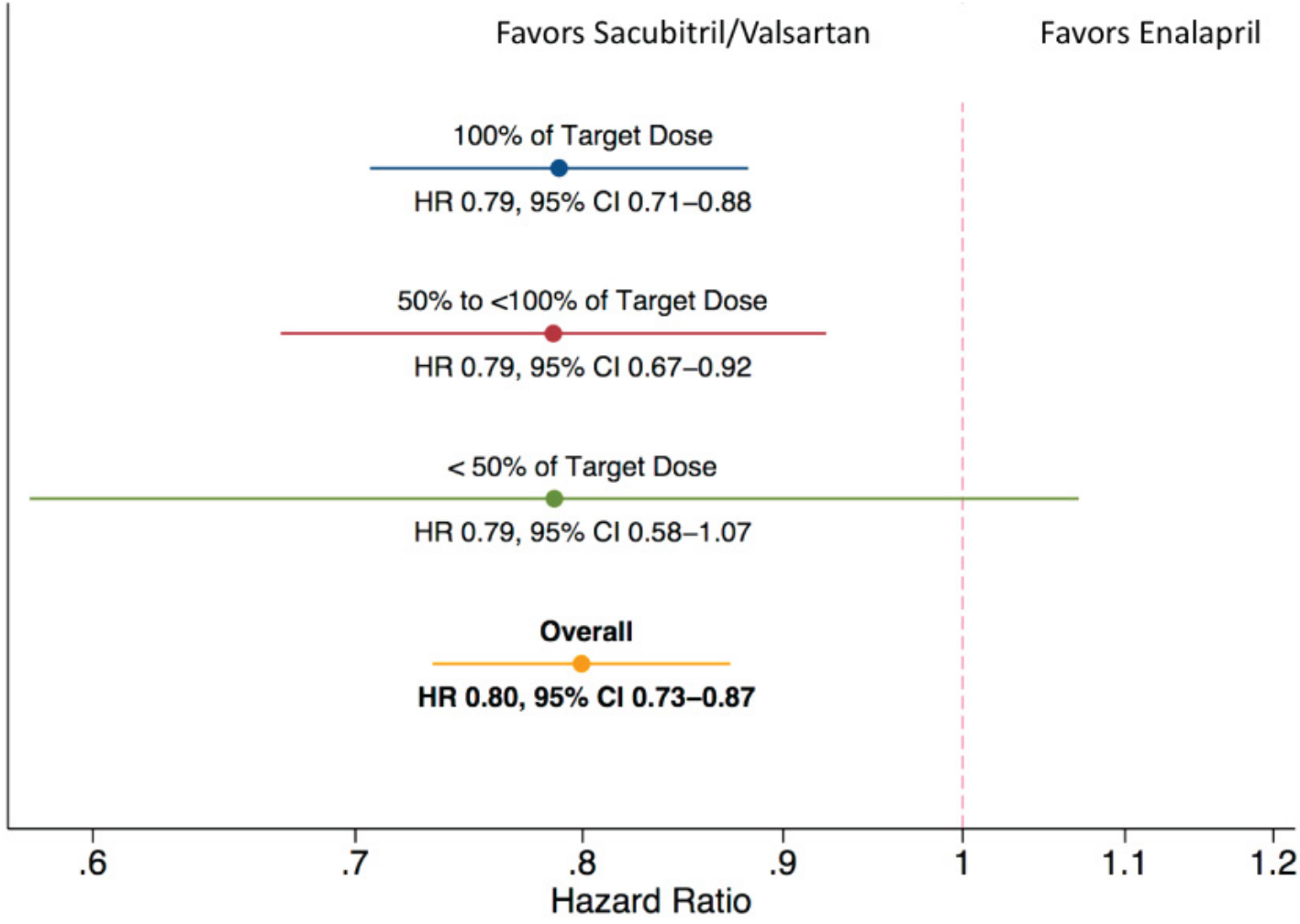


Vardeny et al. European Journal of Heart Failure 10 JUN 2016 DOI: 10.1002/ejhf.580

Sacubitril/valsartan in clinical practice

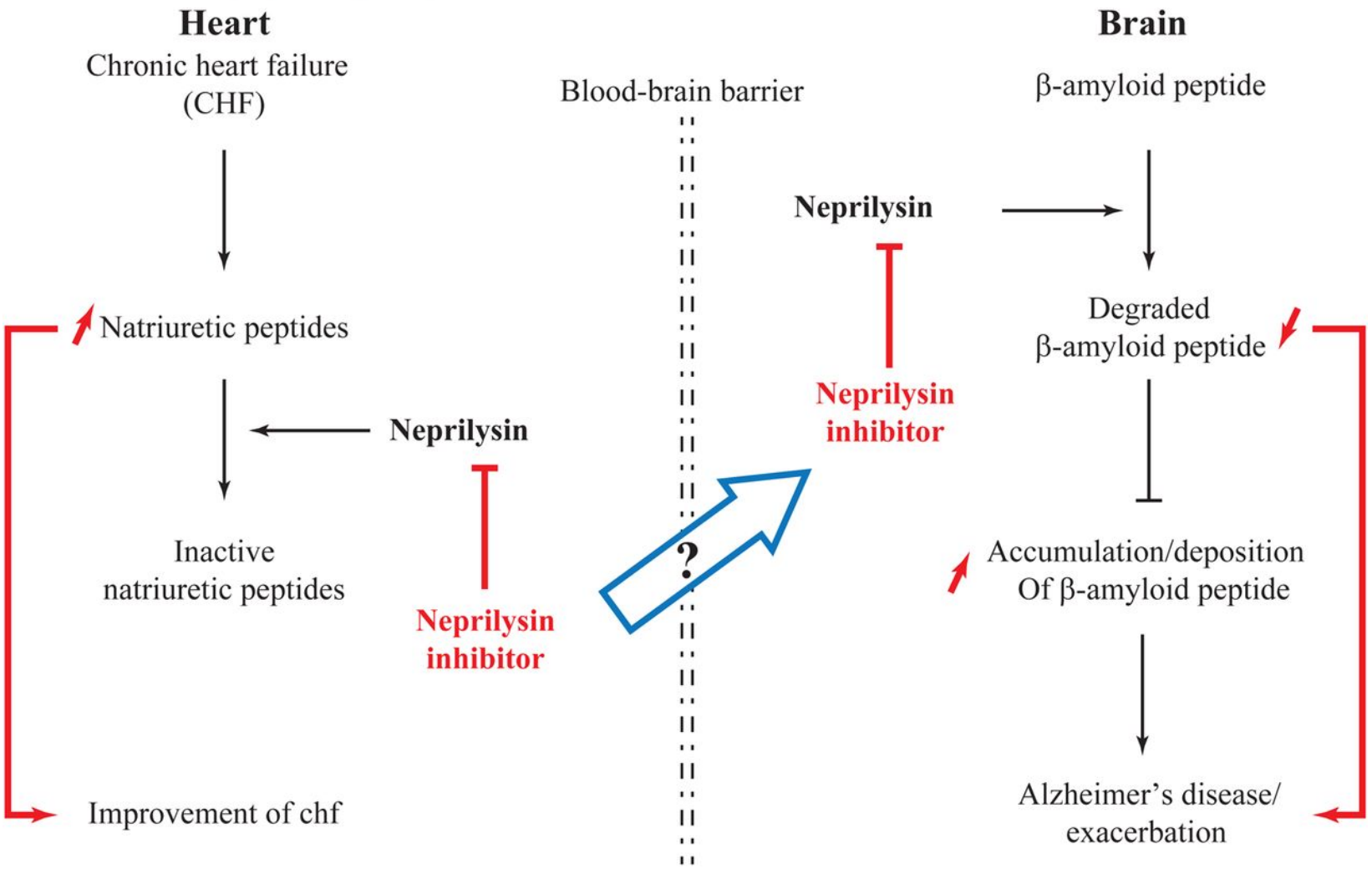
- Tolerability
- Long-term safety

European Heart Journal (2015) 36, 902–905
doi:10.1093/eurheartj/ehv015

CURRENT OPINION

Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split?

Nicolas Vodovar[1], Claire Paquet[1,2], Alexandre Mebazaa[1,3,4], Jean-Marie Launay[1,5,6], Jacques Hugon[1,2,4], and Alain Cohen-Solal[1,4,7]*



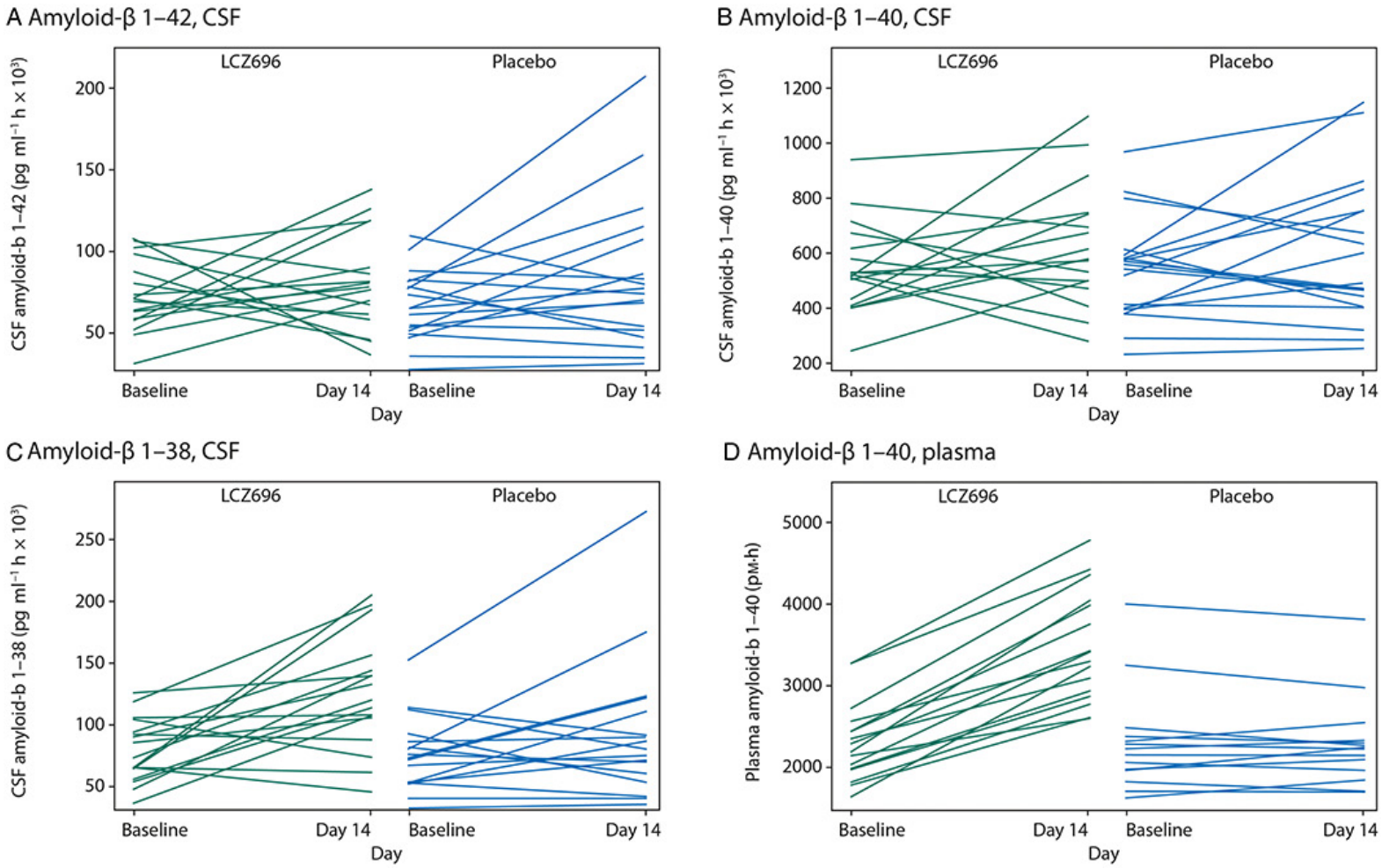
British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) •• ••–••

PHARMACODYNAMICS

The effect of LCZ696 (sacubitril/valsartan) on amyloid-β concentrations in cerebrospinal fluid in healthy subjects

Thomas H. Langenickel[1], Chiaki Tsubouchi[1], Surya Ayalasomayajula[2], Parasar Pal[3], Marie-Anne Valentin[1], Markus Hinder[1], Stanford Jhee[4], Hakop Gevorkyan[5] and Iris Rajman[1]



European Journal of Heart Failure (2016) **18**, 1211–1219
doi:10.1002/ejhf.623

REVIEW

Kicking the tyres of a heart failure trial: physician response to the approval of sacubitril/valsartan in the USA

Milton Packer*

Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA

Received 29 April 2016; revised 9 May 2016; accepted 15 June 2016; online publish-ahead-of-print 10 August 2016

Table 3 Adverse event reports related to memory impairment and dementia in the PARADIGM-HF and OVERTURE trials

Trial (average duration of follow-up)	Treatment arm	Memory impairment	Dementia
PARADIGM-HF (median 27 months)	ACE inhibitor ($n = 4212$)	5	10
	Inhibition of both angiotensin and neprilysin ($n = 4187$)	5	6
OVERTURE (mean 14.5 months)	ACE inhibitor ($n = 2884$)	13	6
	Inhibition of both angiotensin and neprilysin ($n = 2886$)	5	1

Sacubitril/valsartan in clinical practice

- Tolerability
- Long-term safety
- **Costs**

JAMA Cardiology | Original Investigation

Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction

Thomas A. Gaziano, MD, MSc; Gregg C. Fonarow, MD; Brian Claggett, PhD; Wing W. Chan, MS; Celine Deschaseaux-Voinet, MPH; Stuart J. Turner, MPH; Jean L. Rouleau, MD; Michael R. Zile, MD; John J. V. McMurray, MD; Scott D. Solomon, MD

Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in HFeEF

Input	Value (Range)	Source
Health		
Probability, median (IQR), mo		
Hospitalization		
Other causes	0.0487 (0.040-0.058)	Trial[3,4]
Heart failure	0.0216 (0.018-0.026)	Trial
All-cause mortality	0.0081 (0.0072-0.0091)	Trial
Sacubitril/valsartan vs enalapril, HR (95% CI)		
Mortality	0.84 (0.76-0.93)	Trial
Hospitalization		
Heart failure	0.79 (0.71-0.89)	Trial
Other causes	0.92 (0.85-0.99)	Trial
Costs, median (range), $		
Hospitalization		
Heart failure	18 158 (12 148-26 595)	Medicare fee schedule/ private payers[9,10]
Other causes	10 467 (7200-12 300)	AHRQ,[11] Pfunter[12]
Annual treatment		
Enalapril	96 (48-1080)	Red Book[13]
Sacubitril/valsartan	4500 (3375-5675)	Red Book[13]

Gaziano et al. JAMA Cardiol 2016; 1:666-672

JAMA Cardiology | Original Investigation

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The ICER of $45 017 per QALY is not only below standard-accepted levels for evaluations of new therapies and interventions, its value also compares well with other accepted cardiovascular therapies when they were first adopted or approved. For example, the ICER for pravastatin before it became generic was $54 000 to $1.4 million per QALY gained,[24] with similar results for other statins.[25,26] In addition, ICERs for implantable cardioverter defibrillators with and without cardiac resynchronization therapy range from $35 000 to $108 000 per QALY,[27,28] whereas the ICERs for percutaneous coronary interventions are approximately $36 000 per QALY[29] and the ICER for left ventricular assist devices range from $120 000 to more than $300 000 per QALY gained.[30]

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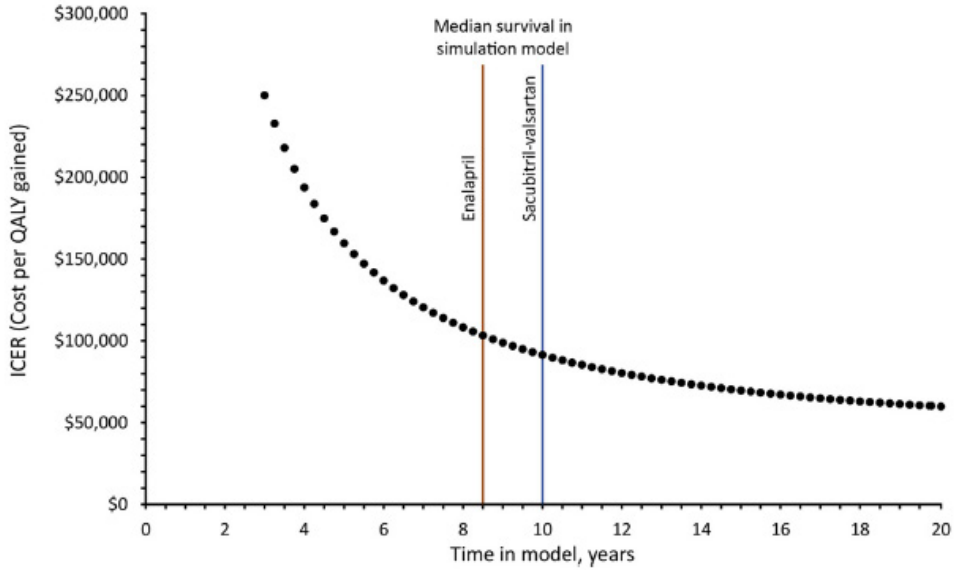
http://dx.doi.org/10.1016/j.jchf.2016.02.007

Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared With Enalapril for the Treatment of Heart Failure With Reduced Ejection Fraction

Jordan B. King, PharmD,[a] Rashmee U. Shah, MD, MS,[b] Adam P. Bress, PharmD, MS,[a] Richard E. Nelson, PhD,[c,d] Brandon K. Bellows, PharmD, MS[a,e]

FIGURE 2 ICER (Cost per QALY Gained) by Duration of Time in Model



Changes in the incremental cost-effectiveness ratio (ICER) over the first 20 years after initiation of either sacubitril-valsartan or enalapril. The earliest measured ICER is at 3 years, which is the duration of follow-up observed in PARADIGM-HF. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Heart Failure's Dark Secret

Does Anyone Really Care About Optimal Medical Therapy?

Milton Packer, MD

Today, most heart failure physicians focus on devices and transplantation; hospital-based management teams devoted only to achieving optimal medical therapy are scarce. The financial demands on heart failure specialists are enormous. A viable business plan can no longer be based on the misguided hope that payers will reimburse generously for prescriptions of digitalis and diuretics; in contrast, cardiac procedures generate meaningful revenues. A growing advocacy now encourages the use of ven-

Circulation. 2016;134:629–631. DOI: 10.1161/CIRCULATIONAHA.116.024498

Optimal medical therapy for HF

1. HFpEF
2. Diuretics
3. Neurohormonal antagonists
4. New neurohormoanl antagonists (ARNI)
5. Management programs

Characteristics and components of management programmes for patients with heart failure

Characteristics

Should employ a multidisciplinary approach (cardiologists, primary care physicians, nurses, pharmacists, physiotherapists, dieticians, social workers, surgeons, psychologists, etc.).
Should target high-risk symptomatic patients.
Should include competent and professionally educated staff.[617]

Components (I)

Optimized medical and device management.
Adequate patient education, with special emphasis on adherence and self-care.
Patient involvement in symptom monitoring and flexible diuretic use.

Components (II)

Follow-up after discharge (regular clinic and/or home-based visits; possibly telephone support or remote monitoring).
Increased access to healthcare (through in-person follow-up and by telephone contact; possibly through remote monitoring).
Facilitated access to care during episodes of decompensation.
Assessment of (and appropriate intervention in response to) an unexplained change in weight, nutritional status, functional status, quality of life, or laboratory findings.
Access to advanced treatment options.
Provision of psychosocial support to patients and family and/or caregivers.

Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

Recommendations for exercise, multidisciplinary management and monitoring of patients with HF

Recommendations	Class [a]	Level [b]
It is recommended that regular aerobic exercise is encouraged in patients with HF to improve functional capacity and symptoms.	I	A
It is recommended that regular aerobic exercise is encouraged in stable patients with HFrEF to reduce the risk of HF hospitalization.	I	A
It is recommended that patients with HF are enrolled in a multidisciplinary care management programme to reduce the risk of HF hospitalization and mortality.	I	A
Referral to primary care for long-term follow-up may be considered for stable HF patients who are on optimal therapy to monitor for effectiveness of treatment, disease progression and patient adherence.	IIb	B
Monitoring of pulmonary artery pressures using a wireless implantable haemodynamic monitoring system (CardioMems) may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization.	IIb	B
Multiparameter monitoring based on ICD (IN-TIME approach) may be considered in symptomatic patients with HFrEF (LVEF ≤35%) in order to improve clinical outcomes.	IIb	B

Ponikowski et al. Eur J Heart Fail 20 MAY 2016 DOI: 10.1002/ejhf.592

Get With The Guidelines Program Participation, Process of Care, and Outcome for Medicare Patients Hospitalized With Heart Failure

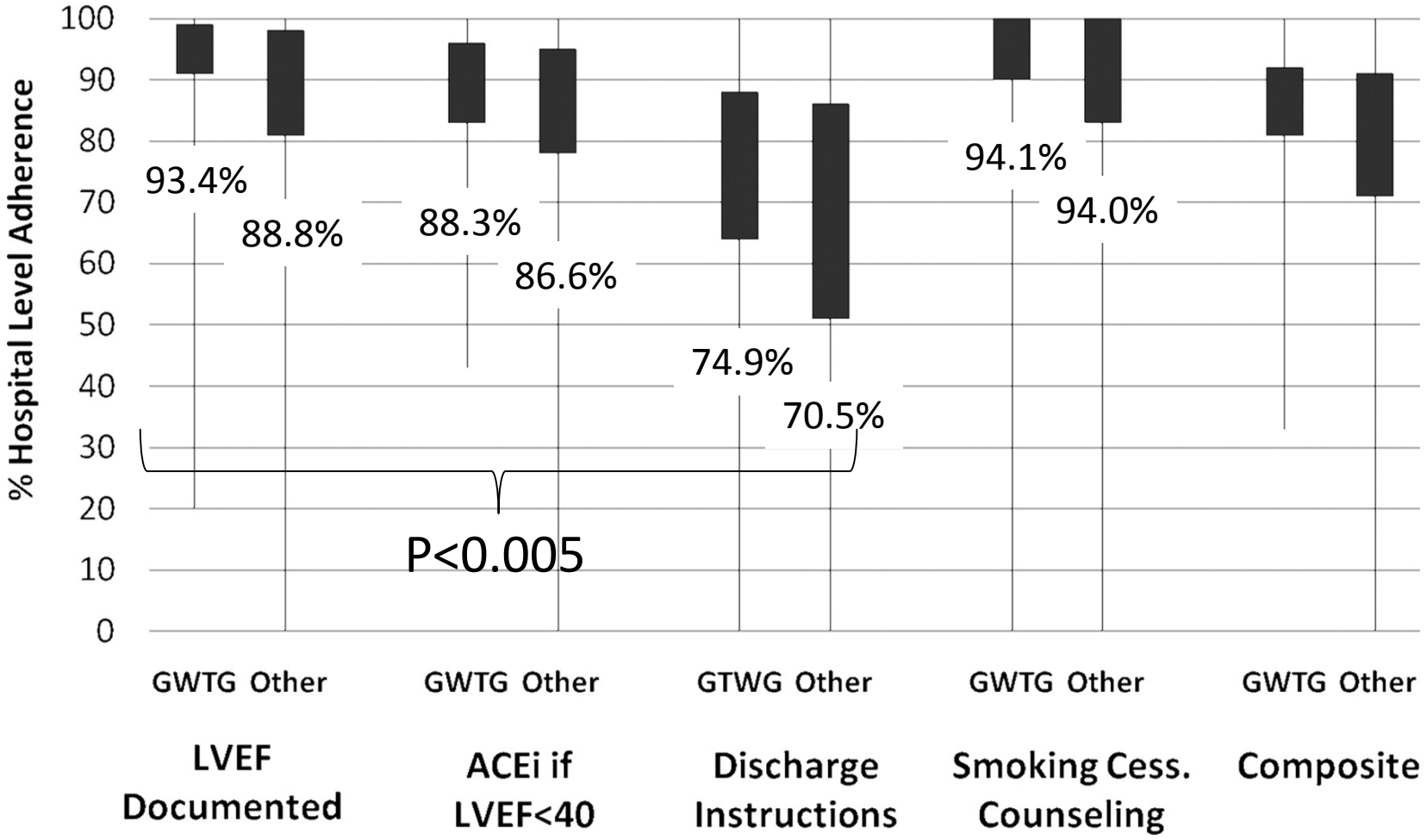
Paul A. Heidenreich, MD, MS; Adrian F. Hernandez, MD, MHS; Clyde W. Yancy, MD; Li Liang, PhD; Eric D. Peterson, MD, MPH; Gregg C. Fonarow, MD

Background—Hospitals enrolled in the American Heart Association's Get With The Guidelines Program for heart failure (GWTG-HF) have improved their process of care. However, it is unclear if process of care and outcomes are better in the GWTG-HF hospitals compared with hospitals not enrolled.

Methods and Results—We compared hospitals enrolled in GWTG-HF from 2006 to 2007 with other hospitals using data on 4 process of heart failure care measures, 5 noncardiac process measures, risk-adjusted 30-day mortality, and 30-day all-cause readmission after a heart failure hospitalization, as reported by the Center for Medicare and Medicaid Services (CMS). Among the 4460 hospitals reporting data to CMS, 215 (5%) were enrolled in GWTG-HF. Of the 4 CMS heart failure performance measures, GWTG-HF hospitals had significantly higher documentation of the left ventricular ejection fraction (93.4% versus 88.8%), use of angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (88.3% versus 86.6%), and discharge instructions (74.9% versus 70.5%) ($P<0.005$ for all). Smoking cessation counseling rates were similar (94.1% versus 94.0%; $P=0.51$). There was no significant difference in compliance with noncardiac process of care. After heart failure discharge, all-cause readmission at 30 days was 24.5% and mortality at 30 days after admission was 11.1%. After adjustment for hospital characteristics, 30-day mortality rates were no different ($P=0.45$). However, 30-day readmission was lower for GWTG hospitals (−0.33%; 95% CI, −0.53% to −0.12%; $P=0.002$).

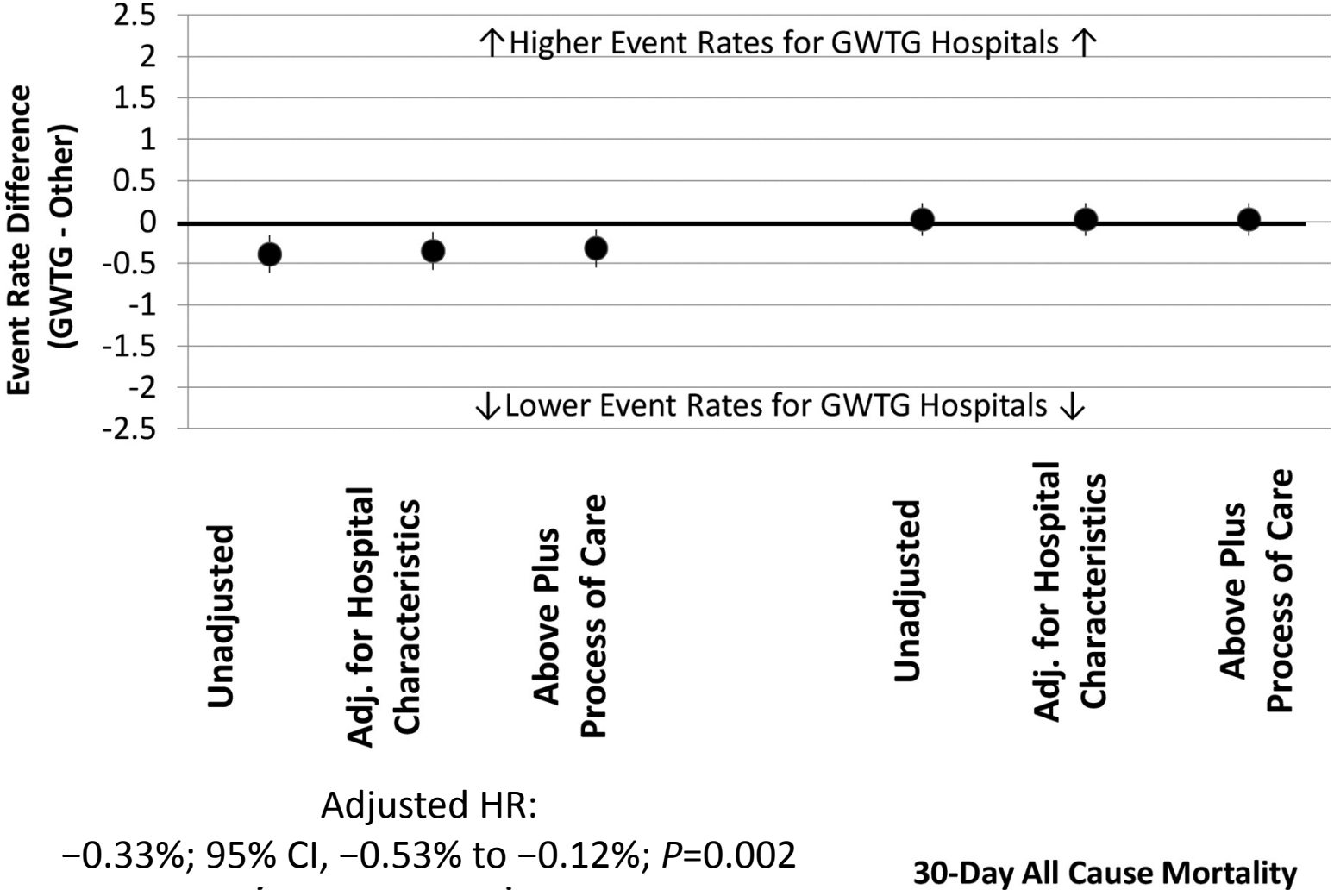
Conclusions—Although there was evidence that hospitals enrolled in the GTWG-HF program demonstrated better processes of care than other hospitals, there were few clinically important differences in outcomes. Further identification of opportunities to improve outcomes, and inclusion of these metrics in GTWG-HF, may further support the value of GTWG-HF in improving care for patients with HF. (***Circ Cardiovasc Qual Outcomes***. 2012;5:37-43.)

Process of care for Get With The Guidelines–Heart Failure (GWTG-HF) hospitals compared with the others



Heidenreich P A et al. Circ Cardiovasc Qual Outcomes. 2012;5:37-43

Get With The Guidelines–Heart Failure (GWTG-HF) and patient outcome.



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Paul A. Heidenreich, MD, MS; Adrian F. Hernandez, MD, MHS; Clyde W. Yancy, MD; Li Liang, PhD; Eric D. Peterson, MD, MPH; Gregg C. Fonarow, MD

Background—Hospitals enrolled in the American Heart Association's Get With The Guidelines Program for heart failure (GWTG-HF) have improved their process of care. However, it is unclear if process of care and outcomes are better in the GWTG-HF hospitals compared with hospitals not enrolled.

Methods and Results—We compared hospitals enrolled in GWTG-HF from 2006 to 2007 with other hospitals using data on 4 process of heart failure care measures, 5 noncardiac process measures, risk-adjusted 30-day mortality, and 30-day all-cause readmission after a heart failure hospitalization, as reported by the Center for Medicare and Medicaid Services (CMS). Among the 4460 hospitals reporting data to CMS, 215 (5%) were enrolled in GWTG-HF. Of the 4 CMS heart failure performance measures, GWTG-HF hospitals had significantly higher documentation of the left ventricular ejection fraction (93.4% versus 88.8%), use of angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (88.3% versus 86.6%), and discharge instructions (74.9% versus 70.5%) ($P<0.005$ for all). Smoking cessation counseling rates were similar (94.1% versus 94.0%; $P=0.51$). There was no significant difference in compliance with noncardiac process of care. After heart failure discharge, all-cause readmission at 30 days was 24.5% and mortality at 30 days after admission was 11.1%. After adjustment for hospital characteristics, 30-day mortality rates were no different ($P=0.45$). However, 30-day readmission was lower for GWTG hospitals (−0.33%; 95% CI, −0.53% to −0.12%; $P=0.002$).

Conclusions—Although there was evidence that hospitals enrolled in the GTWG-HF program demonstrated better processes of care than other hospitals, there were few clinically important differences in outcomes. Further identification of opportunities to improve outcomes, and inclusion of these metrics in GTWG-HF, may further support the value of GTWG-HF in improving care for patients with HF. (***Circ Cardiovasc Qual Outcomes***. 2012;5:37-43.)

Optimal medical therapy for HF

Problem	«Solution»
HFpEF	No specific treatment Treat comorbidieties
Diuretics	Flexible doses Careful patient's follow-up
Neurohormonal antagonists	Always give them, possibly at target doses Follow your patients
Ivabradine	Add to treatment if HR ≥70 bpm in sinus rhythm
ARNI	Alternative to ACEi/ARBs Careful follow-up for tolerability and titration
Disease management programs	Useful, though often not evidence based

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The real improvement	Better patient's follow-up!