Simposio: Farmaci 2018

Sacubitril/ valsartan: dagli studi clinici al mondo reale

Prof. Marco Metra
Cardiologia, Brescia

The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

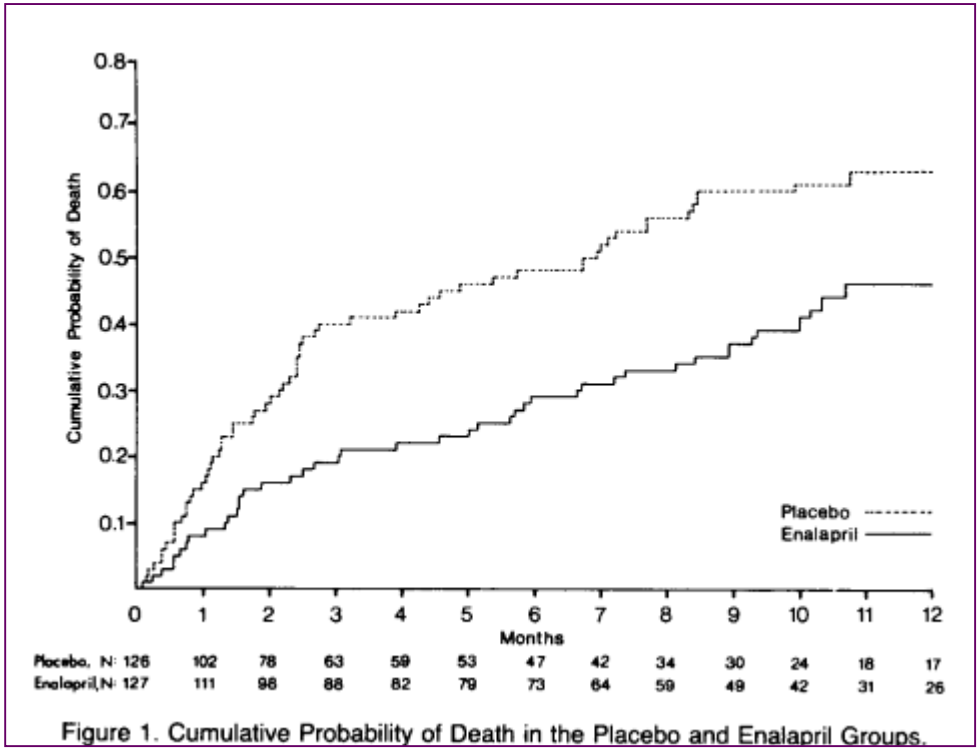
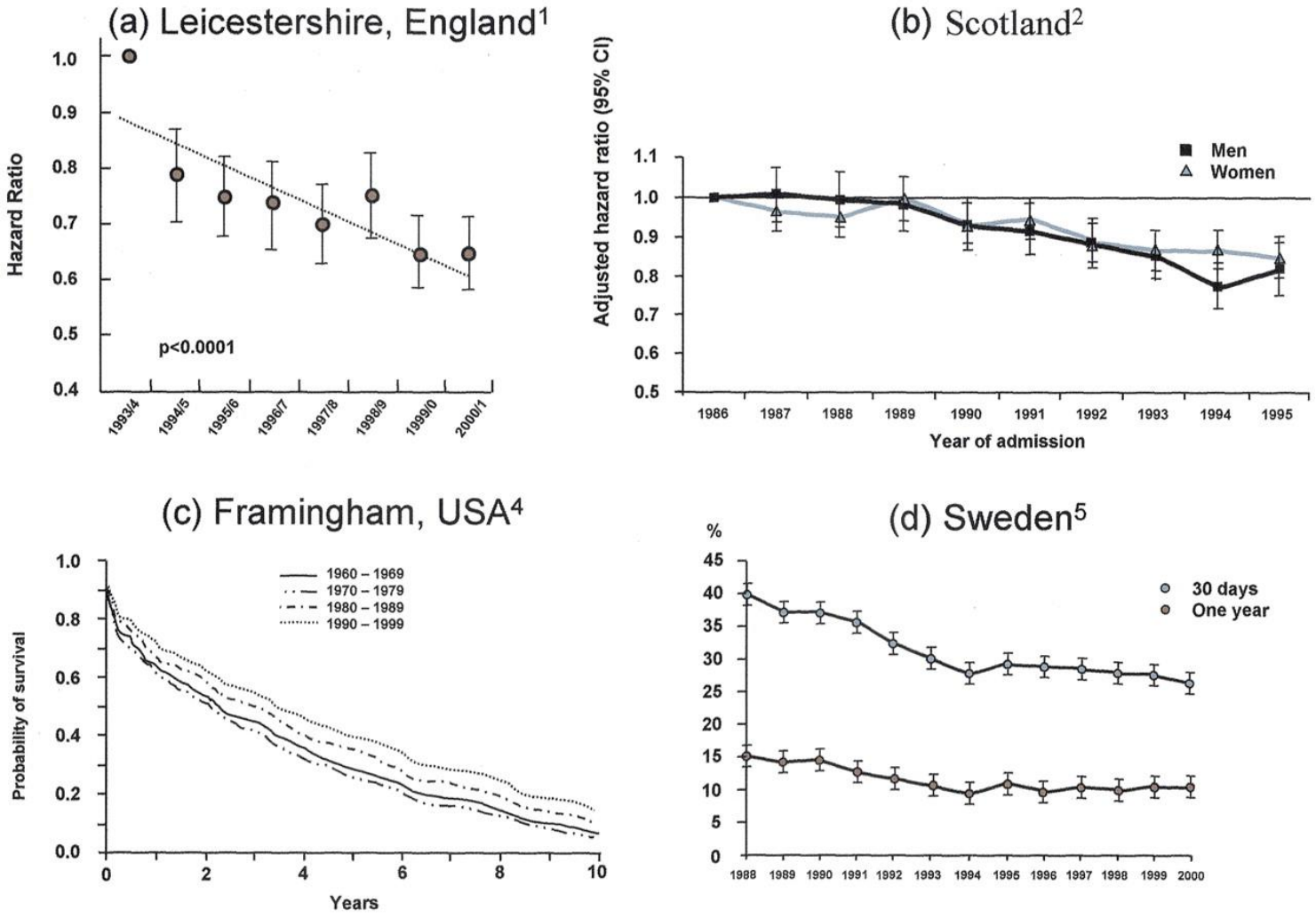


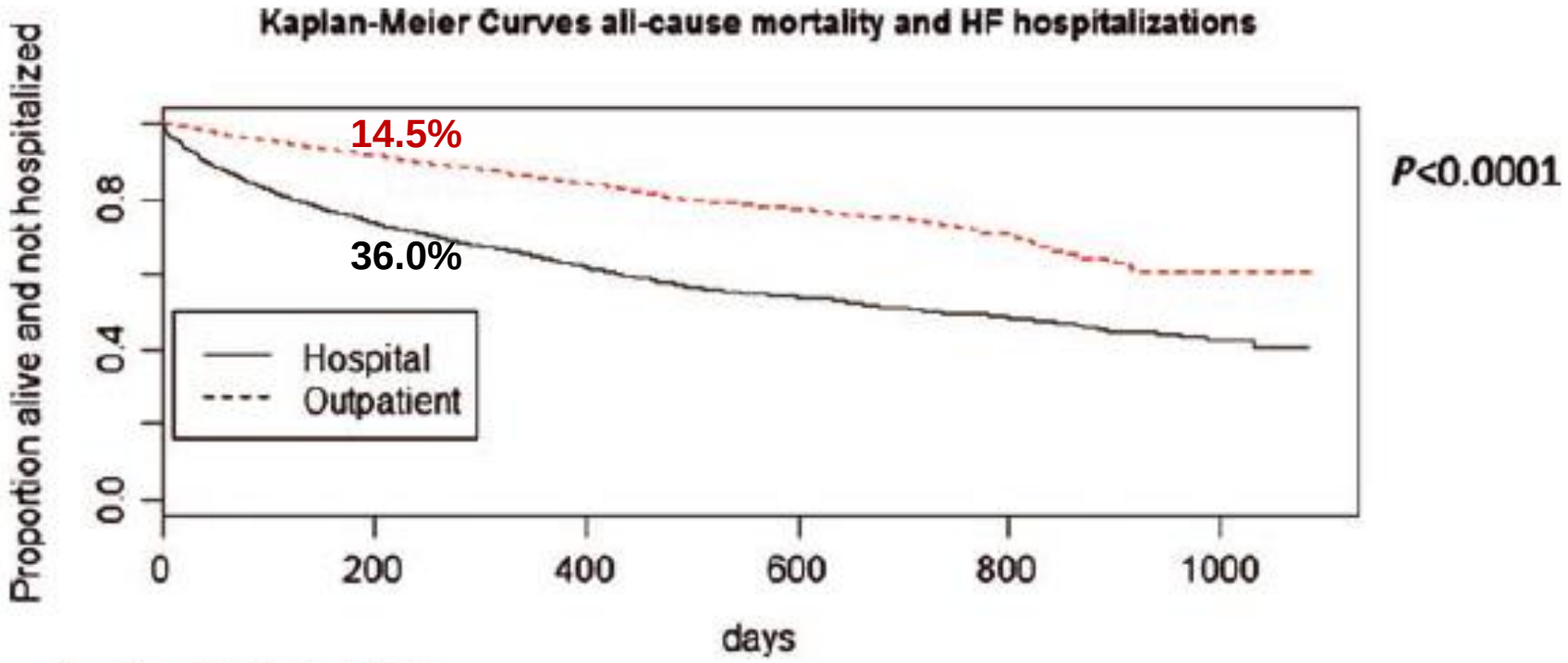
Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

Evidence of improving survival from heart failure in the general population



[1]Blackledge et al., Heart 2003; 89:615; [2]MacIntyre et al., Circulation 2000;102:1126; [3]Levy et al., NEJM 2002; 347:1397; [4]Scahufelberger et al., EHJ 2004; 25:300; McMurray, J. J.V. et al. J Am Coll Cardiol 2004;44:2398-2405

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



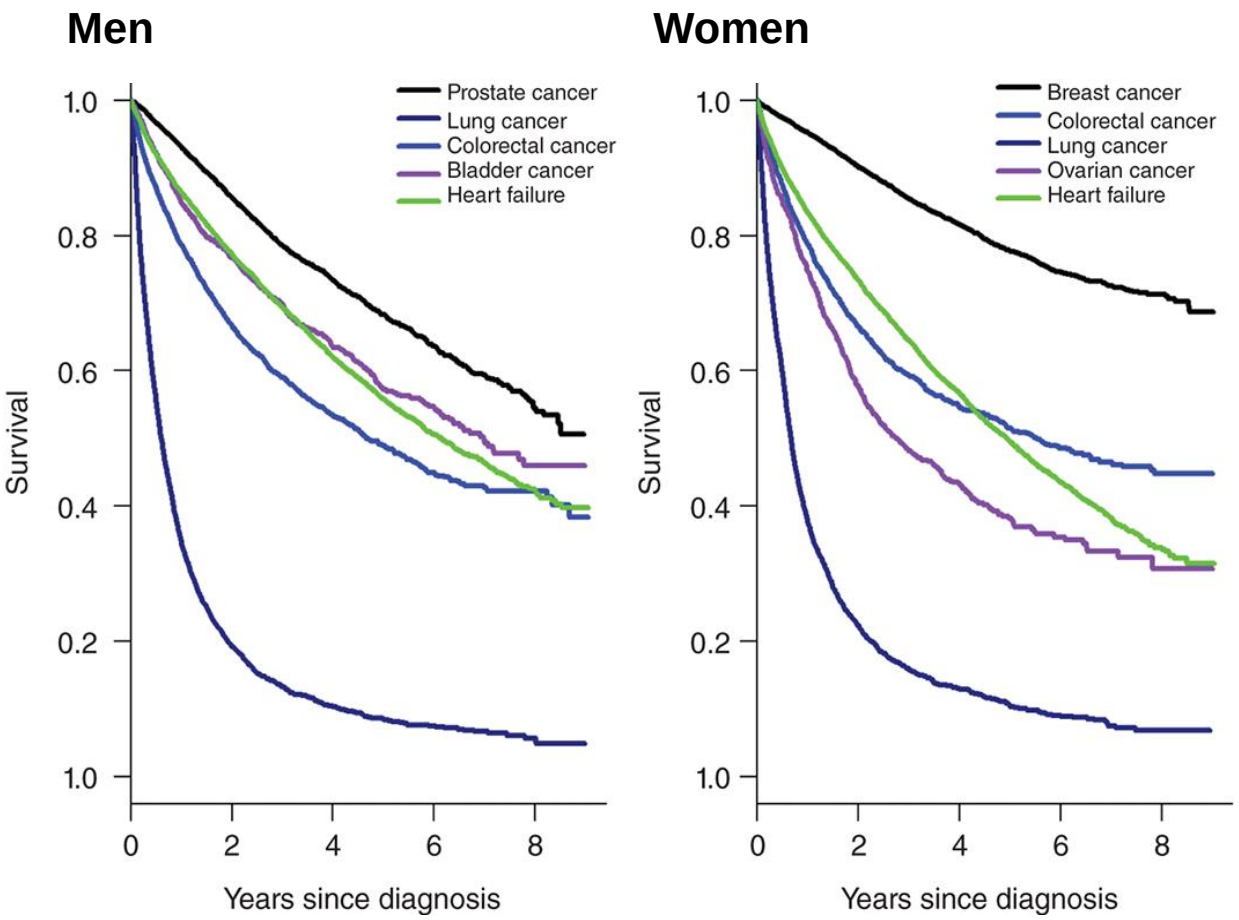
Number of Patients at Risk:

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

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.822

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

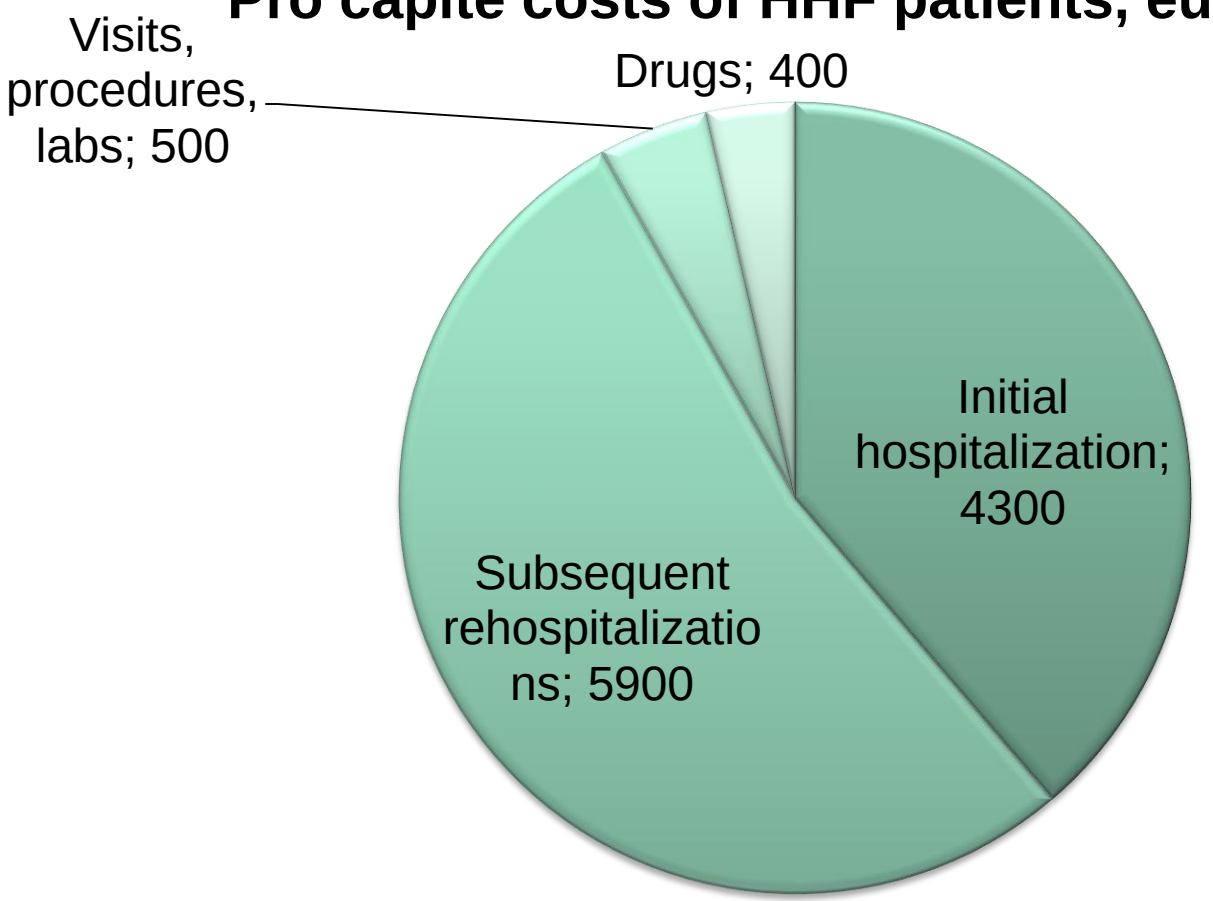


Mamas et al. Eur J Heart Fail 2017; 19: 1096-1105

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

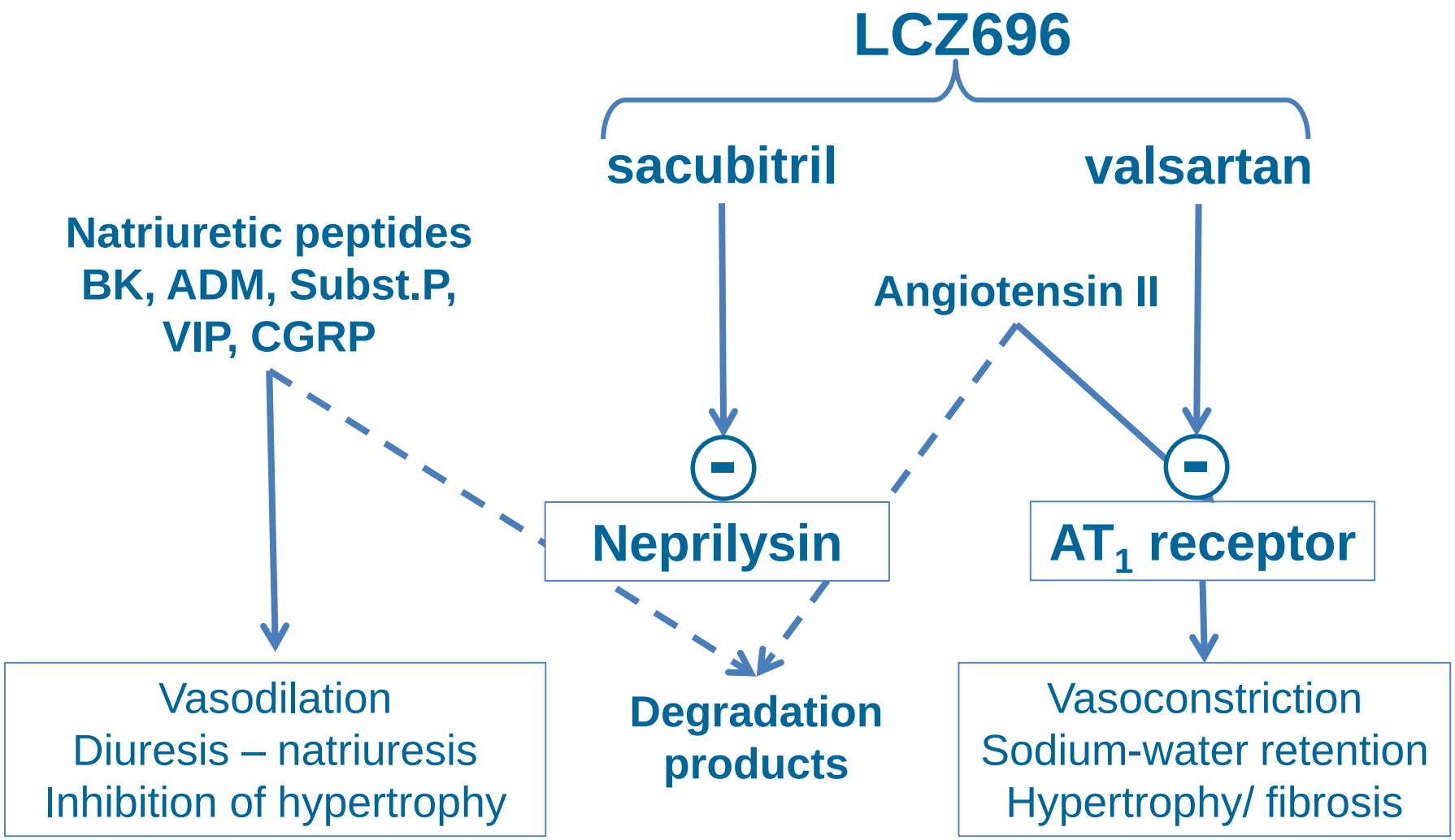
Giovanni Corrao[1]*, Arianna Ghirardi[1], Buthaina Ibrahim[1], Luca Merlino[2], and Aldo Pietro Maggioni[3]

Pro capite costs of HHF patients, euros/year



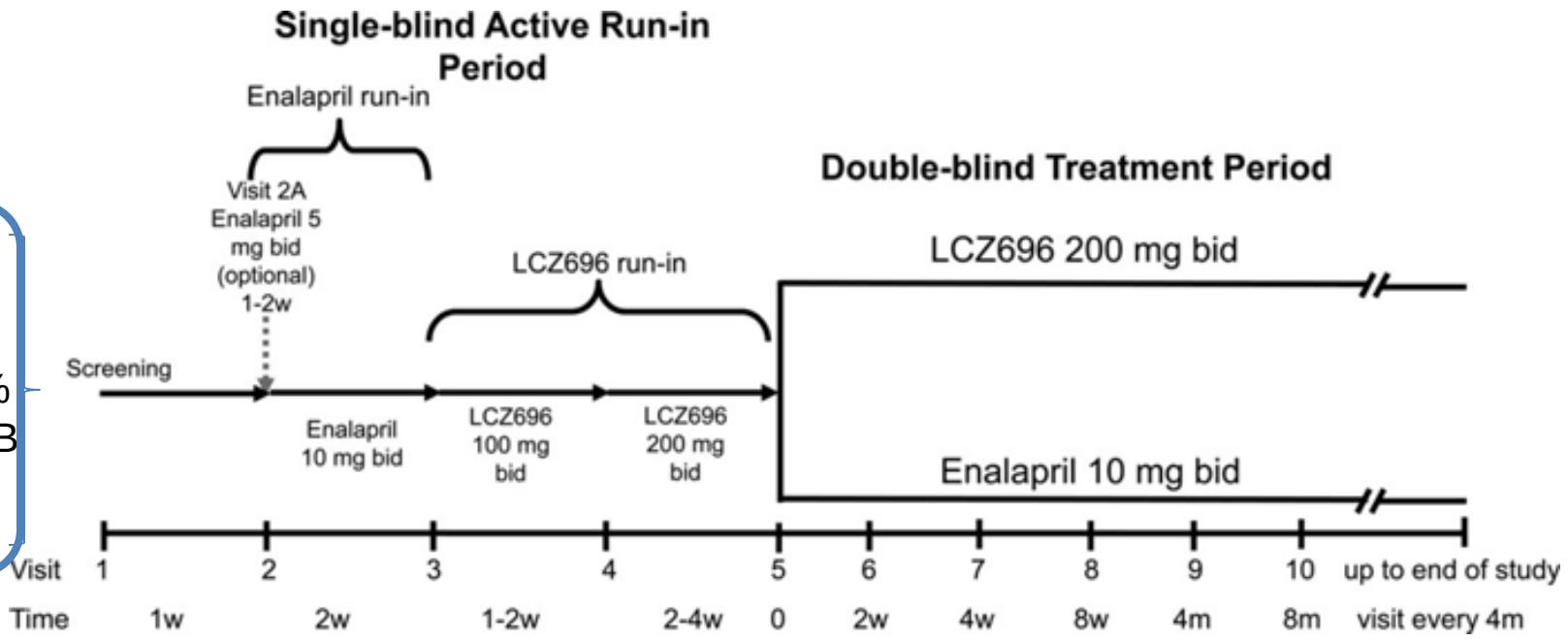
Corrao et al. Eur J Heart Fail 2014; 16, 729–736

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



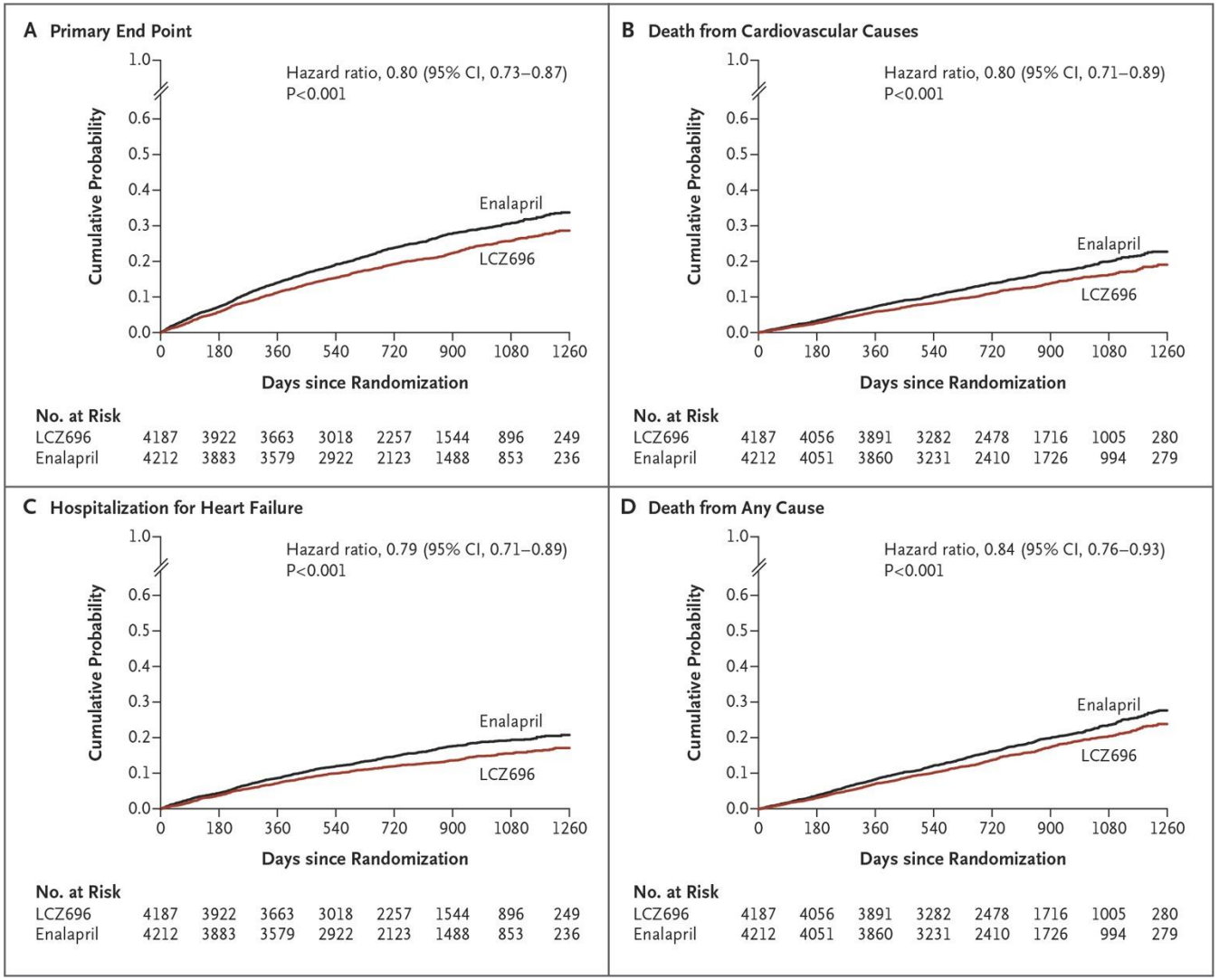
Dual Angiotensin Receptor and Neprilysin inhibition (ARNI) as an alternative to ACE inhibition in patients with chronic systolic HF. Design of the PARADIGM-HF Trial

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



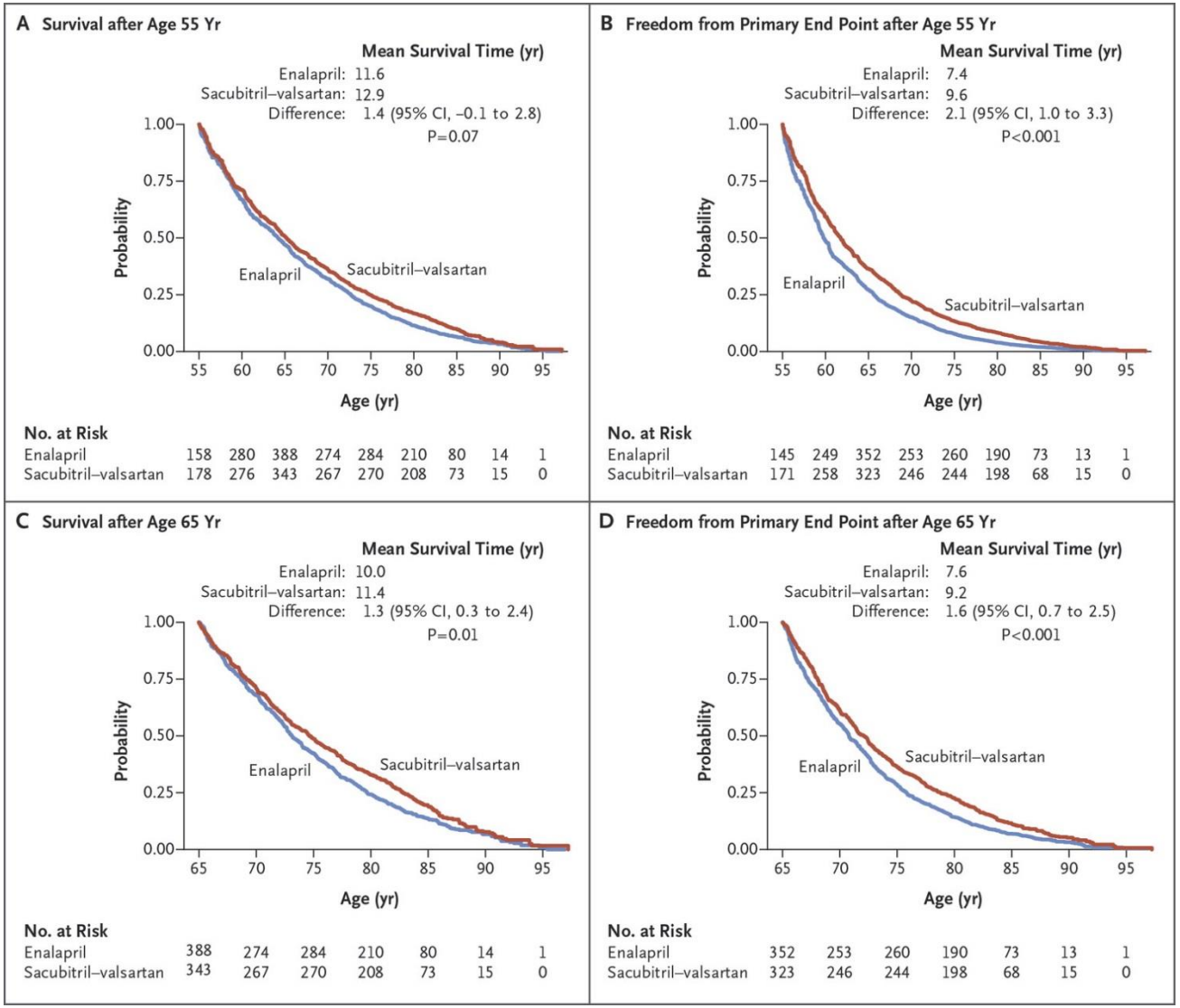
McMurray et al. European Journal of Heart Failure; 15: 1062-73

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



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

Probability of Death from Any Cause or the Primary End Point Extrapolated from the PARADIGM-HF Trial, According to Age



Claggett B et al. N Engl J Med 2015;373:2289-2290.

2016 ESC Guidelines

Recommendation	COR	LOE
An ACEI is recommended in addition to a beta-blocker for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, beta-blocker, and MRA.	**I**	**B**

2016 ACC/AHA/HFSA Focused Update

Recommendation	COR	
The clinical strategy of inhibition of the renin–angiotensin system with ACEIs OR ARBs OR ARNI in conjunction with evidence-based beta-blockers and aldosterone antagonists in select patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality.	I	A
In patients with chronic symptomatic HFrEF in NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.	**I**	**B**
ARNI should not be administered concomitantly with an ACEI or within 36 h of the last dose of an ACEI.	III	A
ARNI should not be administered to patients with a history of angioedema.	III	A

Sacubitril/valsartan vs. enalapril

- **Quali parametri**
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dose di ACE inibitore
  - Comorbilità
- Costo- efficacia

PARADIGM-HF: baseline clinical characteristics

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index§	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)

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

PARADIGM-HF: baseline clinical characteristics (II)

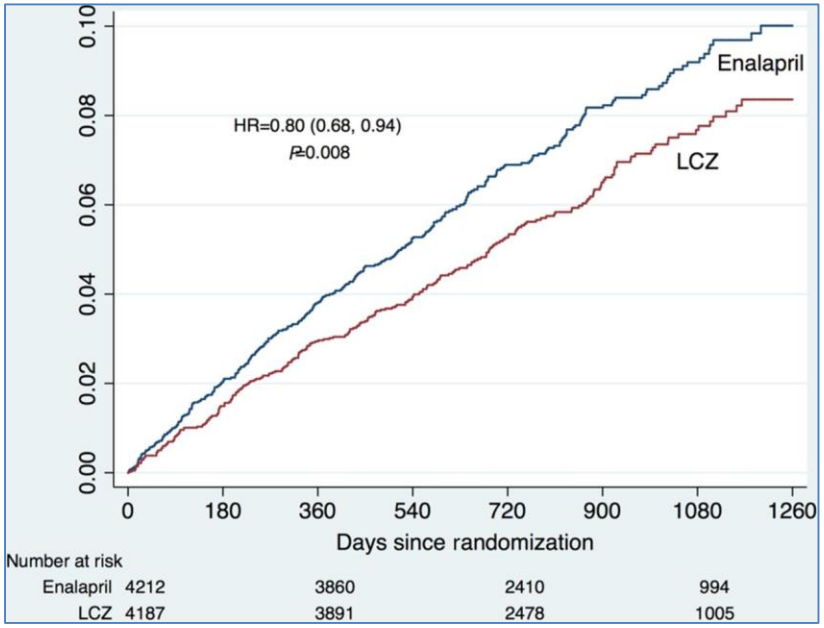
Table 1. (Continued.)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

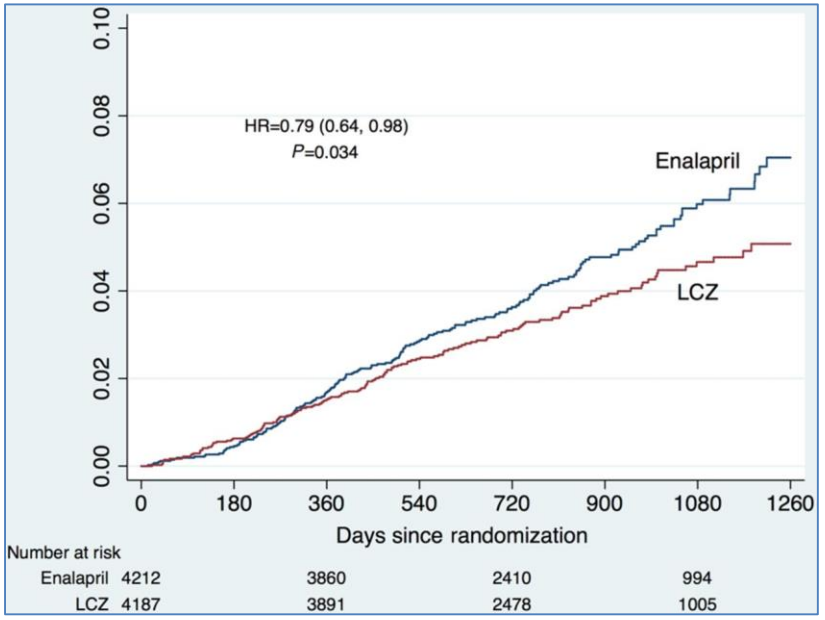
McMurray JJV et al. N Engl J Med 2014;371:993-1004

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

Sudden cardiac death

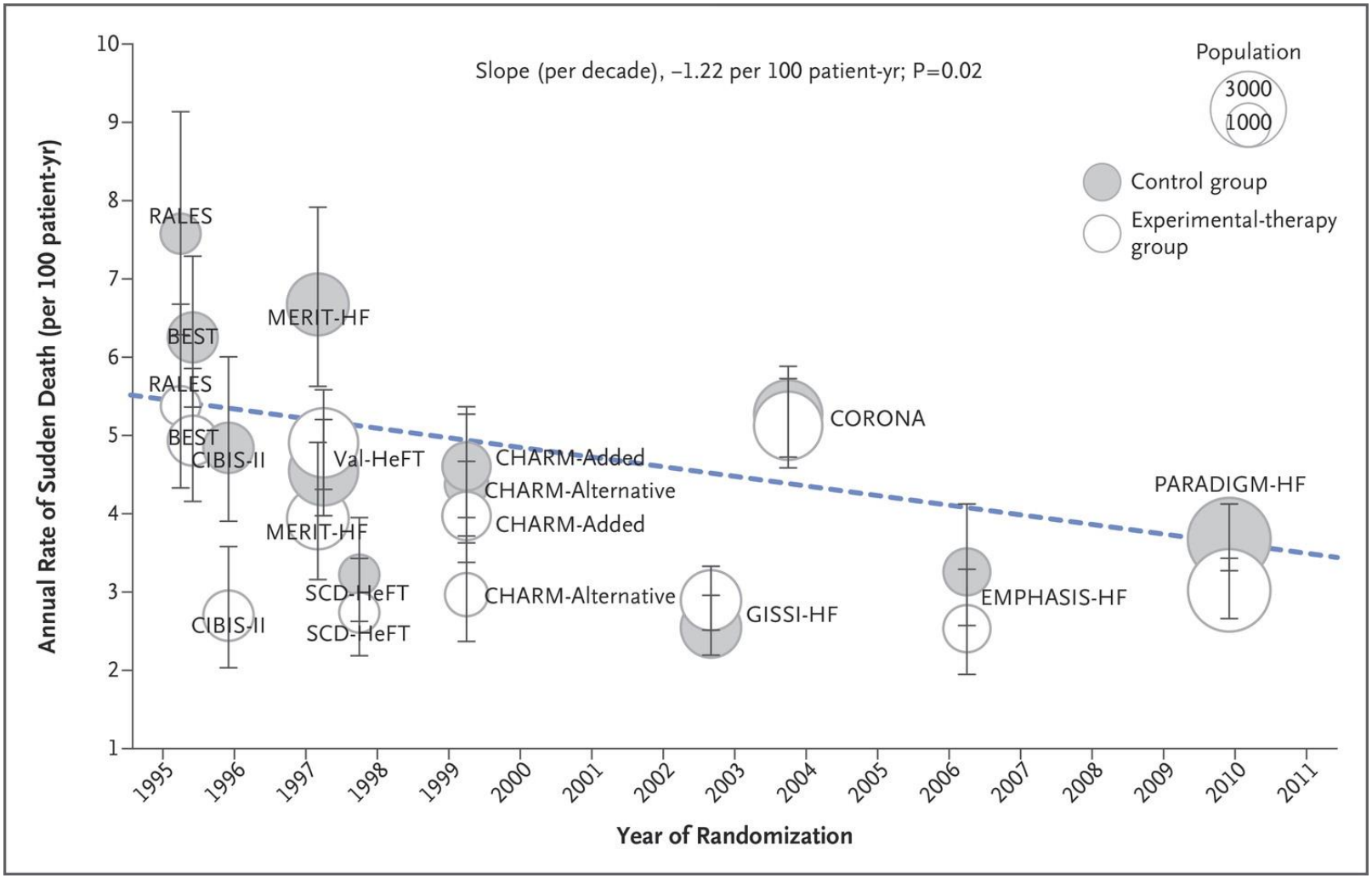


Worsening HF death



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

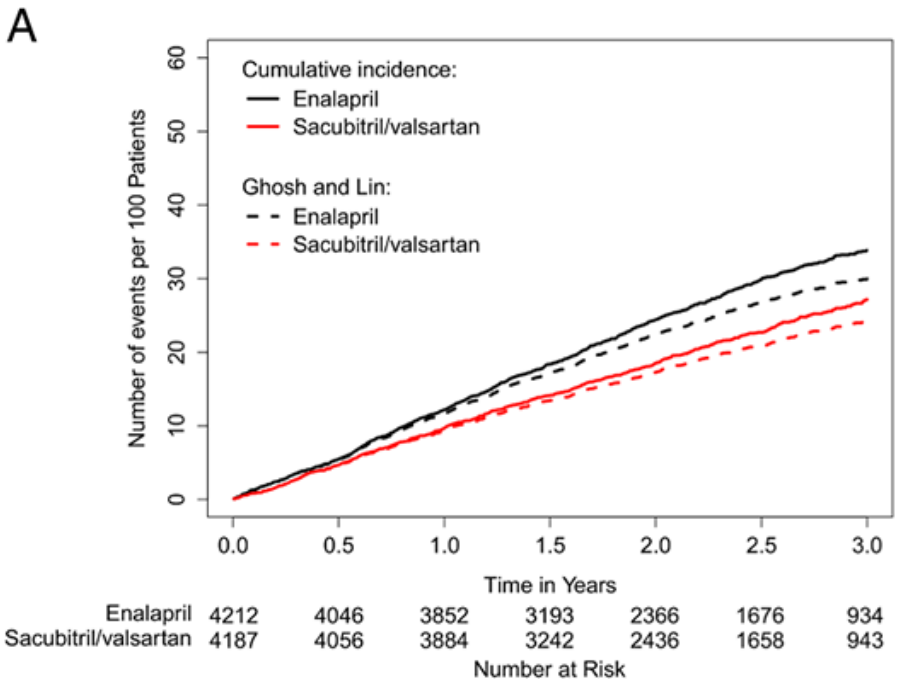
Declining risk of Sudden Death across Trial Groups over Time.



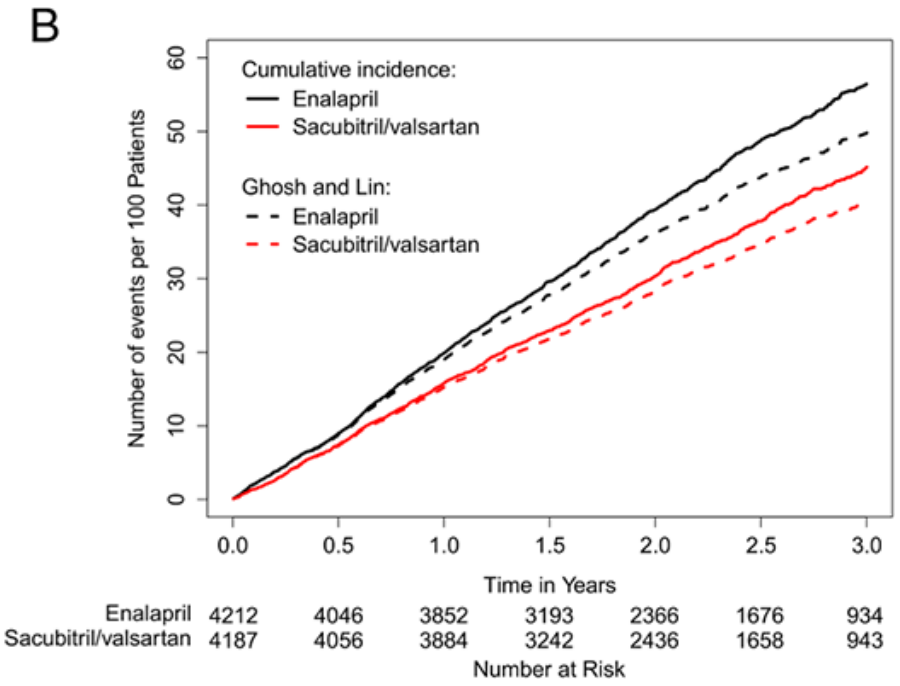
Shen L et al. N Engl J Med 2017;377:41-51.

Effect of sacubitril/valsartan on recurrent events in PARADIGM-HF

Heart failure hospitalizations

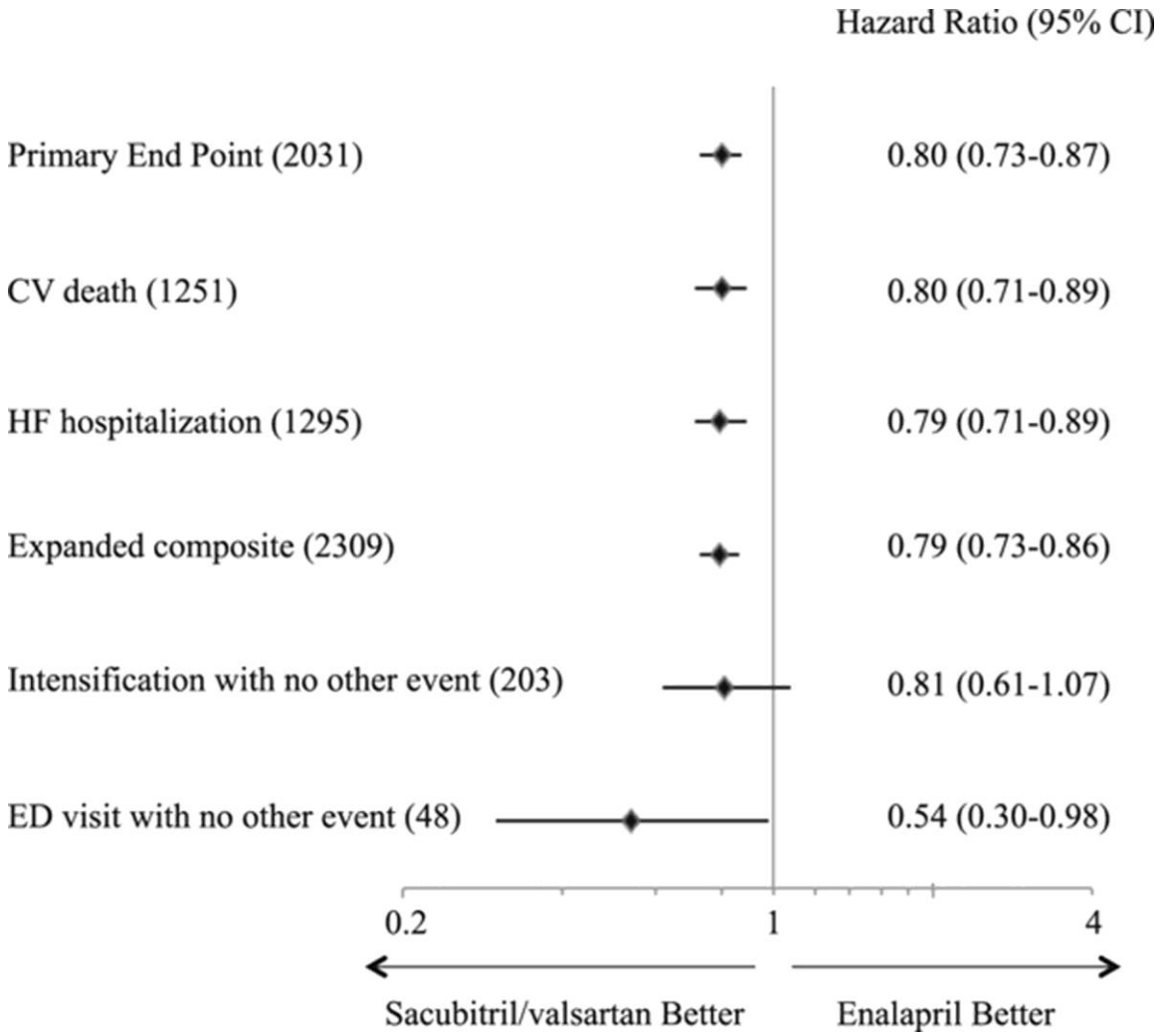


Primary composite endpoint



Mogensen et al. Eur J Heart Fail 12 FEB 2018 DOI: 10.1002/ejhf.1139

Effect of sacubitril/valsartan versus enalapril for each outcome.



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

Sacubitril/valsartan vs. enalapril

- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dose di ACE inibitore
  - Comorbilità
- Costo- efficacia

Journal of Cardiovascular Nursing
Vol. 00, No. 0, pp 00–00 |

From Theory to Practice

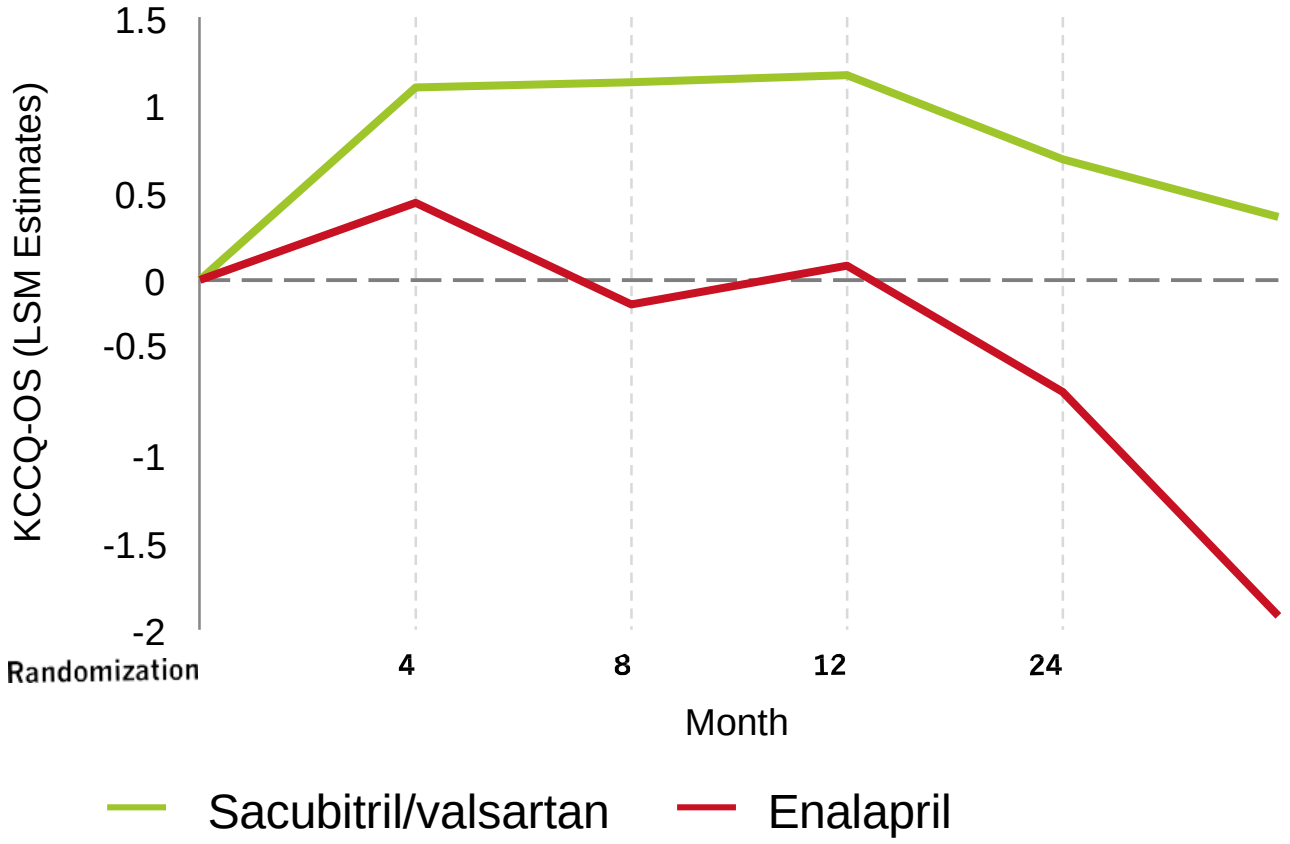
The Diuretic Potential of Sacubitril/Valsartan: A Tale of 2 Patients

Sabrina M. Hormann, PharmD; Lindsay E. Davis, PharmD, BCPS, ASH-CHC, TTS; Elizabeth K. Pogge, PharmD, MPH, BCPS-AQ (Cardiology), FASCP

Background: Heart failure prevalence continues to rise in the United States causing significant morbidity and mortality and costing billions in healthcare expenditures. Consensus guidelines updated in 2016 recommend an angiotensin receptor–neprilysin inhibitor (ARNi) as a therapeutic option in lieu of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for the management of stage C heart failure with reduced ejection fraction (HFrEF). For chronic HFrEF patients with New York Heart Association class II or III symptoms tolerating an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, a change in therapy to an ARNi is recommended to further reduce morbidity and mortality. **Purpose:** We present a brief case series of 2 patients initiated on ARNi therapy for treatment of HFrEF and evaluate their fluid status and diuretic needs before and after ARNi dose optimization. **Conclusions:** After titration to target-dose ARNi therapy, both patients demonstrated improved fluid and electrolyte balance, as well as a reduction in diuretic therapy requirements, suggesting a mechanism of diuresis attributable to ARNi therapy. **Clinical Implications:** Angiotensin receptor–neprilysin inhibitor therapy seems to promote a clinically relevant diuresis in heart failure patients because of increased levels of functioning natriuretic peptides. Awareness of this diuretic potential may allow for optimization of heart failure regimens with pharmacologic agents demonstrated to improve morbidity and mortality, while preventing adverse effects that may occur with overdiuresis.

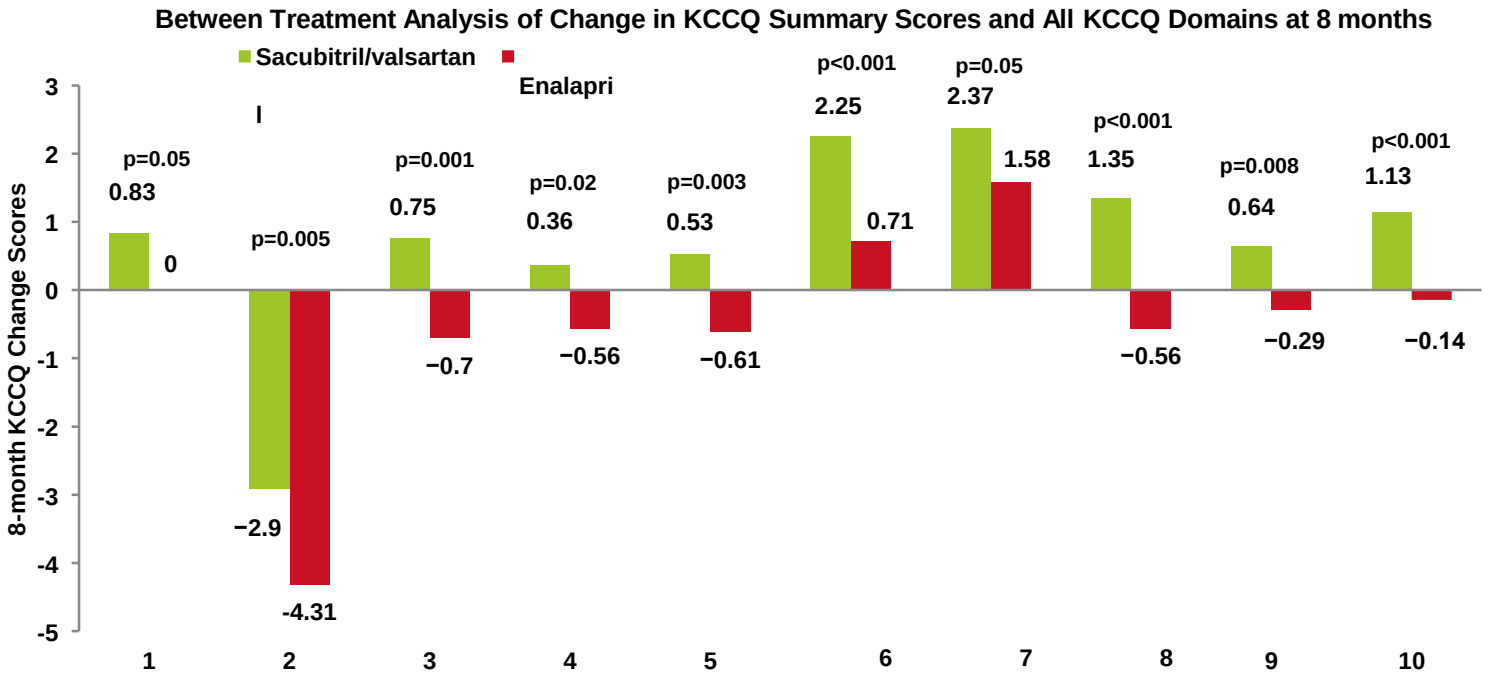
KEY WORDS: angiotensin receptor–neprilysin inhibitor, case report, diuretic, heart failure, sacubitril/valsartan

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



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

Sacubitril/valsartan vs enalapril improved all domains of the Kansas City Cardiomyopathy Questionnaire scores: 8 months data



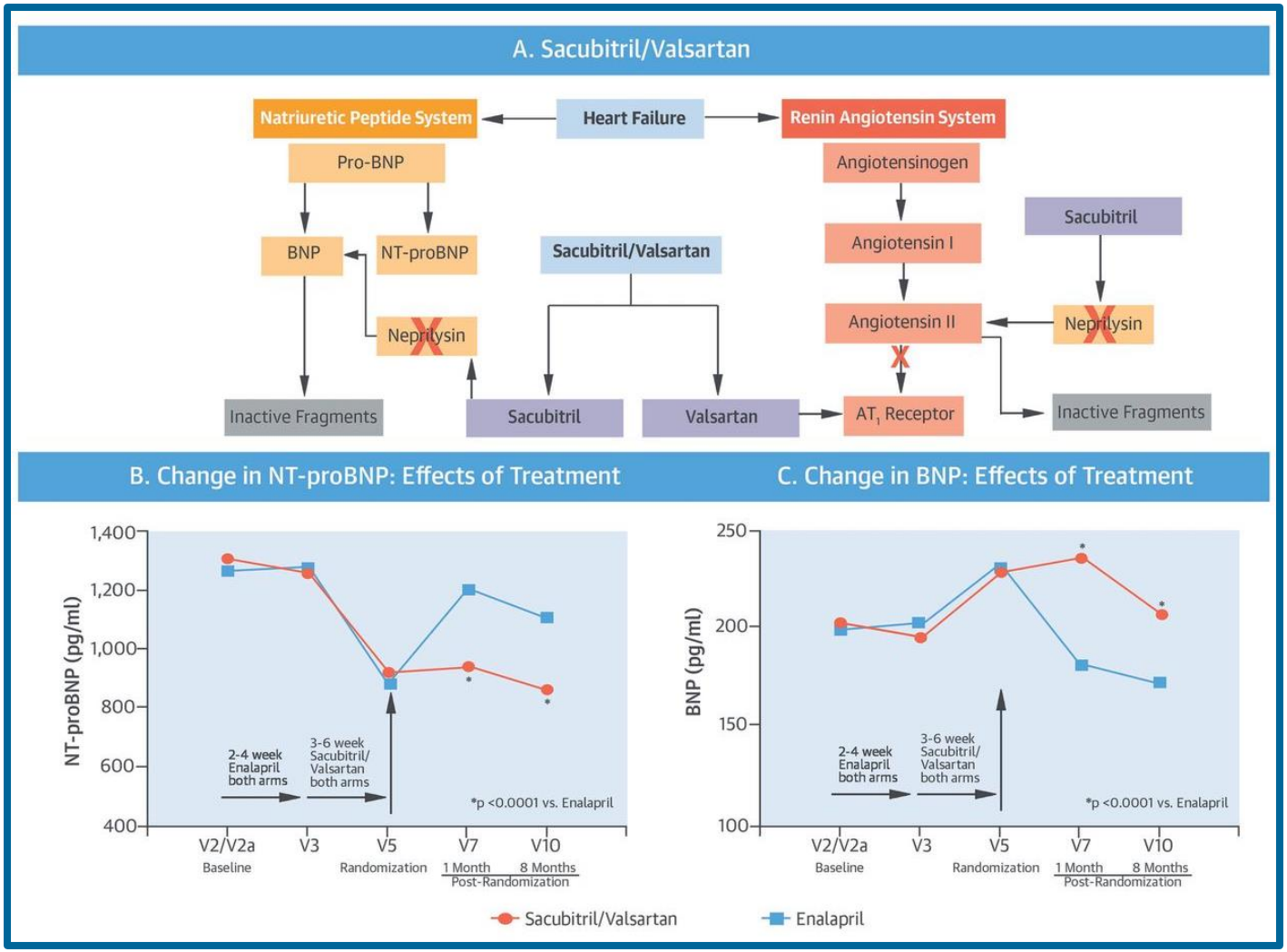
1=Physical limitation	2=Symptom stability	3=Symptom frequency	4=Symptom burden	9=KCCQ-CS
5=Total symptom score	6=Quality of life	7=Self efficacy	8=Social limitation	10=KCCQ-OS

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

Sacubitril/valsartan vs. enalapril

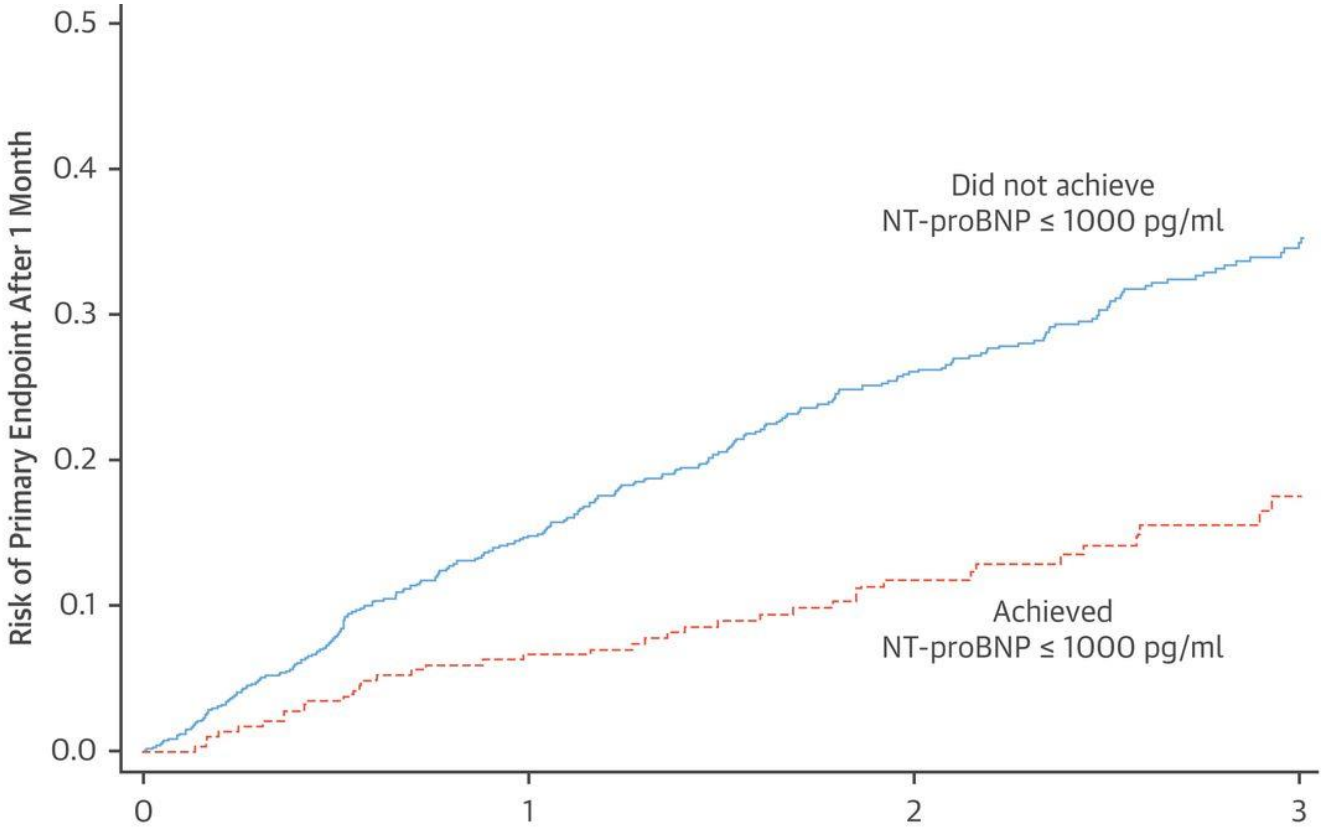
- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dose di ACE inibitore
  - Comorbilità
- Costo- efficacia

NT-proBNP and BNP changes in PARADIGM-H



Michael R. Zile et al. JACC 2016;68:2425-2436

Effects on Risk of Primary Endpoint if NT-proBNP Achieved or Did Not Achieve a Value of <1,000 pg/ml 1 Month After Randomization



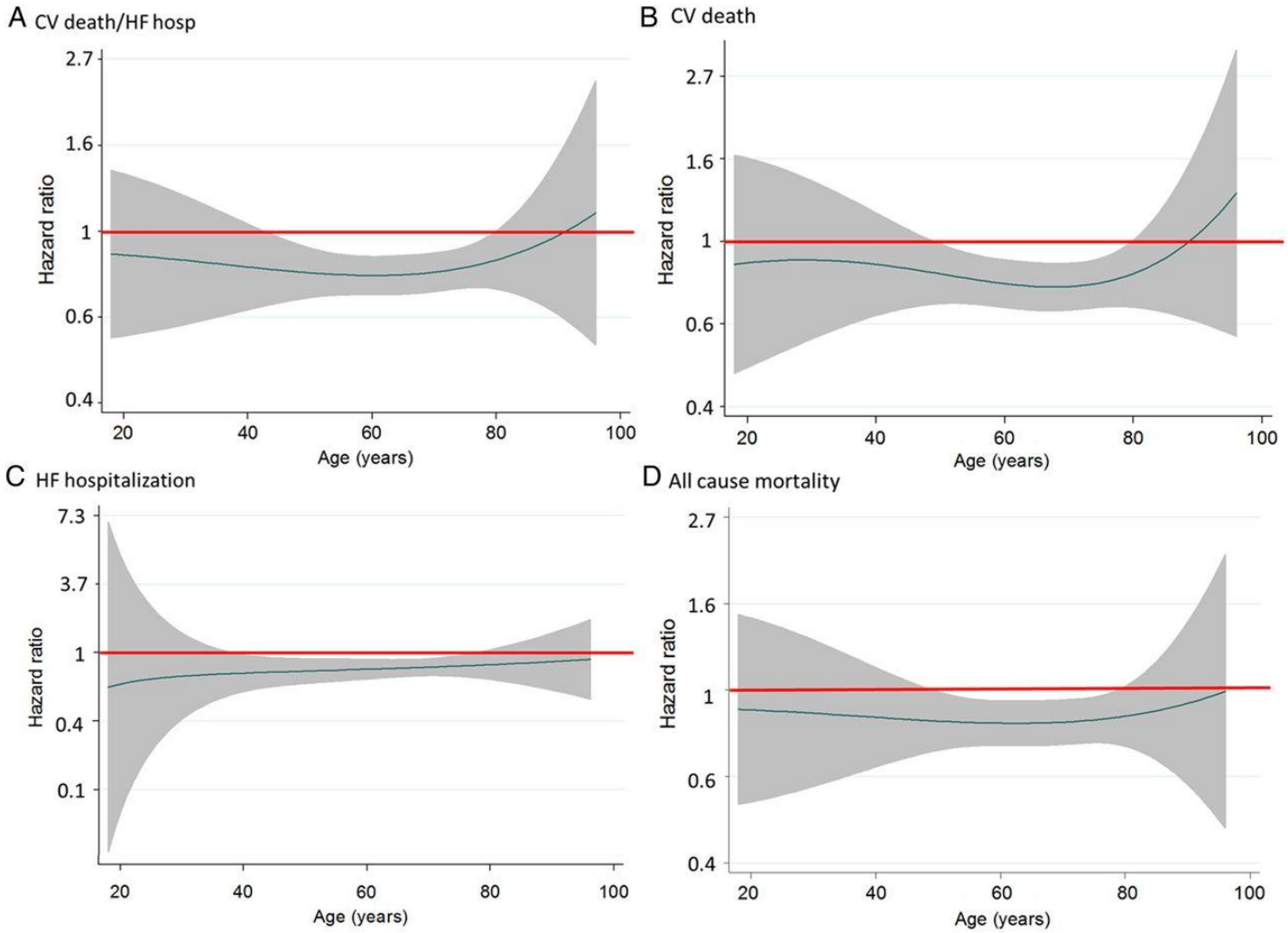
Number at risk				
Did not achieve NT-proBNP < 1000 pg/ml	903	746	476	191
Achieved NT-proBNP ≤ 1000 pg/ml	287	263	174	74

Michael R. Zile et al. JACC 2016;68:2425-2436

Sacubitril/valsartan vs. enalapril

- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dose di ACE inibitore
  - Comorbilità
- Costo- efficacia

Clinical outcomes according to age.

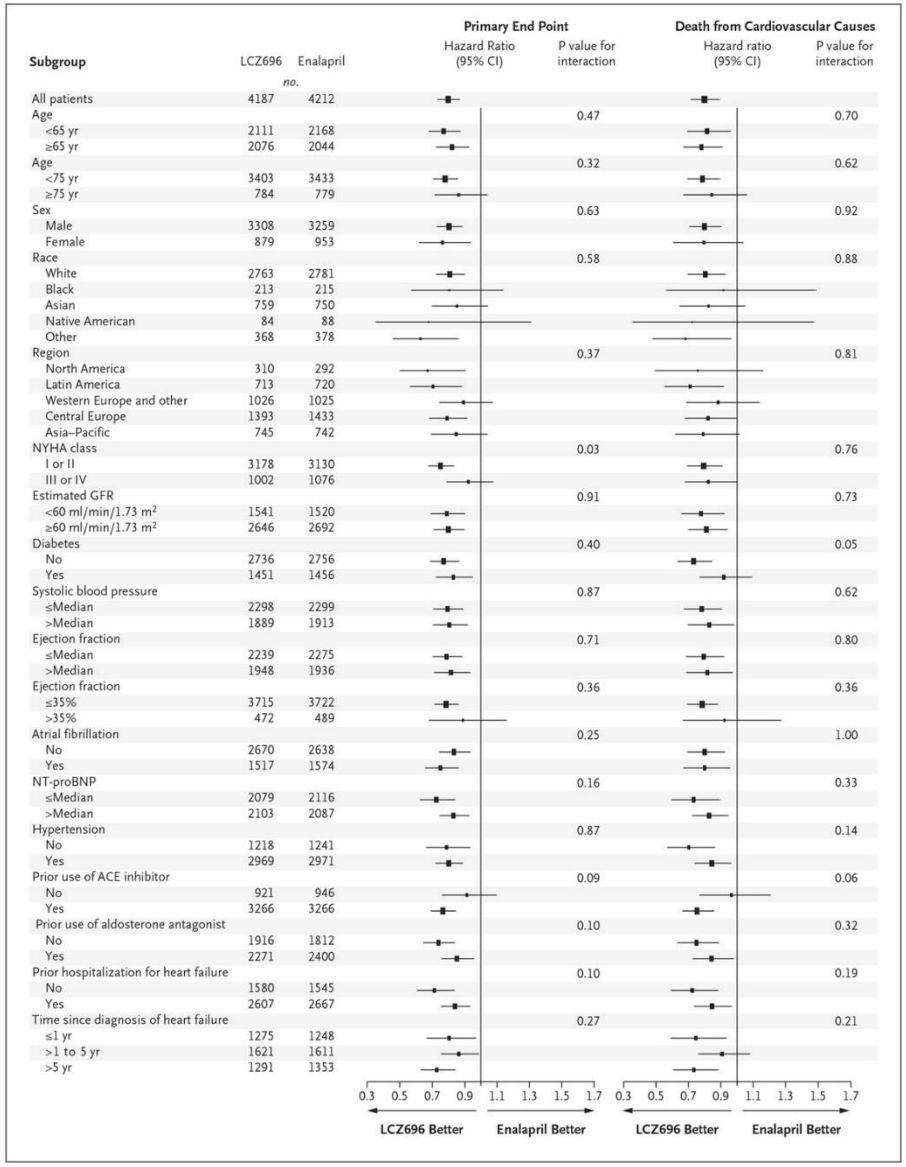


Pardeep S. Jhund et al. Eur Heart J 2015;36:2576-2584

Sacubitril/valsartan vs. enalapril

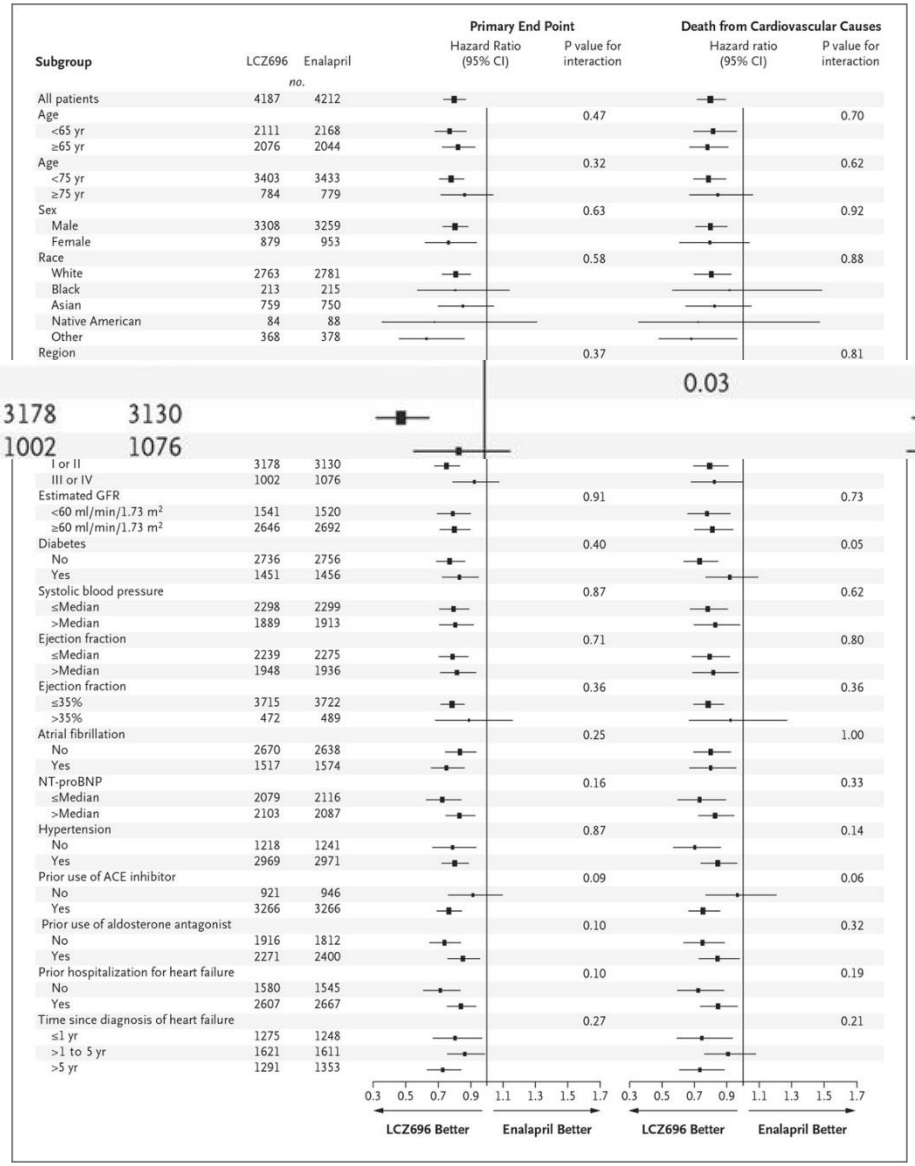
- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dose di ACE inibitore
  - Comorbilità
- Costo- efficacia

PARADIGM-HF: Prespecified Subgroup Analyses.



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

PARADIGM-HF: Prespecified Subgroup Analyses.



NYHA class 0.03 0.76
I or II 3178 3130
III or IV 1002 1076

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

JACC: HEART FAILURE
VOL. 4, NO. 10, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.05.002

Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation

The PARADIGM-HF Trial

Scott D. Solomon, MD,[a] Brian Claggett, PhD,[a] Milton Packer, MD,[b] Akshay Desai, MD,[a] Michael R. Zile, MD,[c] Karl Swedberg, MD,[d] Jean Rouleau, MD,[e] Victor Shi, MD,[f] Martin Lefkowitz, MD,[f] John J.V. McMurray, MD[g]

ABSTRACT

OBJECTIVES This study assessed whether the benefit of sacubtril/valsartan therapy varied with clinical stability.

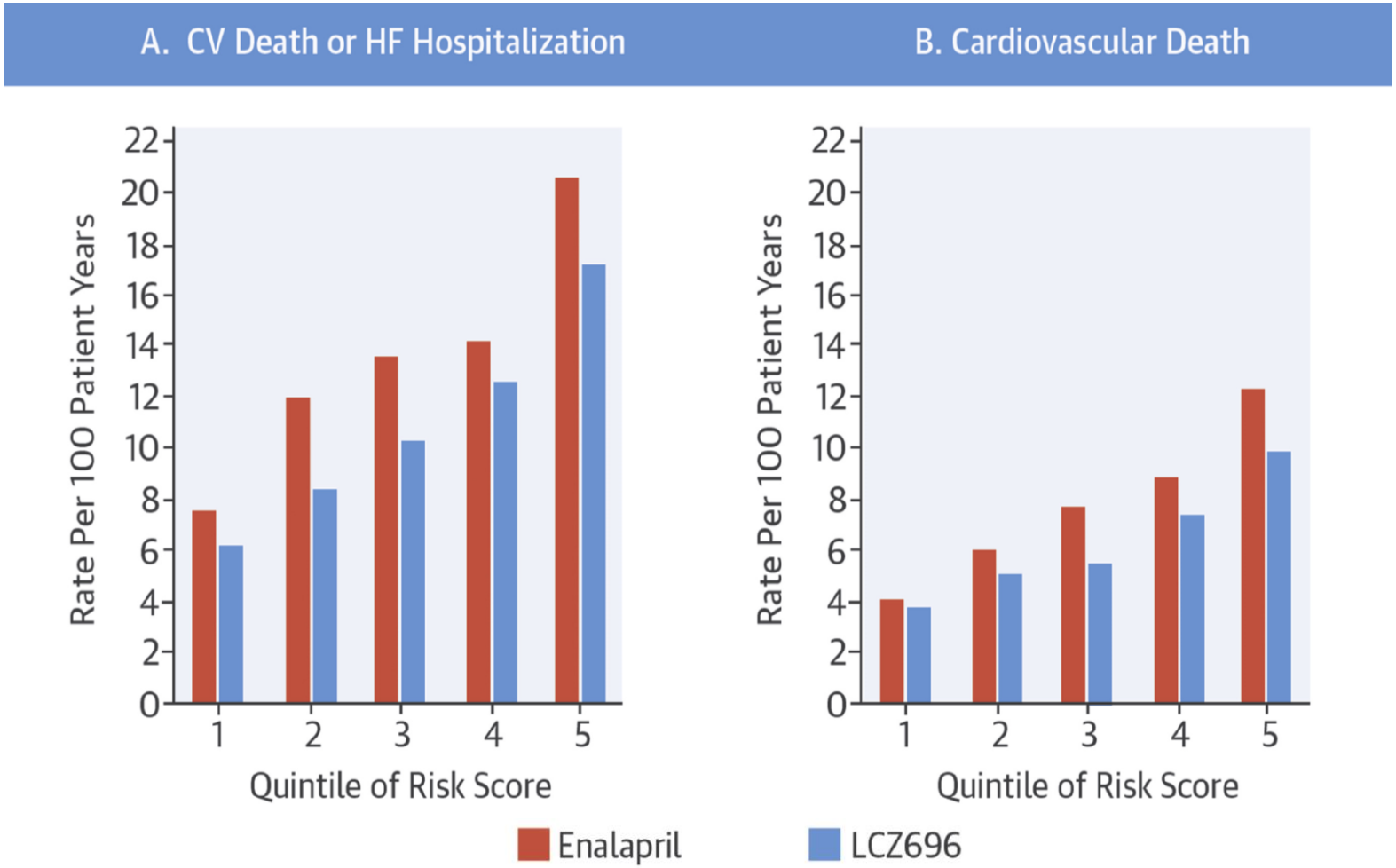
BACKGROUND Despite the benefit of sacubitril/valsartan therapy shown in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, it has been suggested that switching from an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be delayed until occurrence of clinical decompensation.

METHODS Outcomes were compared among patients who had prior hospitalization within 3 months of screening (n = 1,611 [19%]), between 3 and 6 months (n = 1,009 [12%]), between 6 and 12 months (n = 886 [11%]), >12 months (n = 1,746 [21%]), or who had never been hospitalized (n = 3,125 [37%]).

RESULTS Twenty percent of patients without prior HF hospitalization experienced a primary endpoint of cardiovascular death or heart failure (HF) hospitalization during the course of the trial. Despite the increased risk associated with more recent hospitalization, the efficacy of sacubitril/valsartan therapy did not differ from that of enalapril according to the occurrence of or time from hospitalization for HF before screening, with respect to the primary endpoint or with respect to cardiovascular or all-cause mortality.

CONCLUSIONS Patients with recent HF decompensation requiring hospitalization were more likely to experience cardiovascular death or HF hospitalization than those who had never been hospitalized. Patients who were clinically stable, as shown by a remote HF hospitalization (>3 months prior to screening) or by lack of any prior HF hospitalization, were as likely to benefit from sacubitril/valsartan therapy as more recently hospitalized patients. (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]; NCT01035255) (J Am Coll Cardiol HF 2016;4:816–22) © 2016 by the American College of Cardiology Foundation.

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



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

Sacubitril/valsartan vs. enalapril

- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dosi di ACE inibitore
  - Comorbilità
- Costo- efficacia

European Journal of Heart Failure (2016) **18**, 716–726
doi:10.1002/ejhf.531

STUDY DESIGN

A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF

Adriaan A. Voors[1]*, Stefan D. Anker[2], John G. Cleland[3], Kenneth Dickstein[4,5], Gerasimos Filippatos[6], Pim van der Harst[1], Hans L. Hillege[1], Chim C. Lang[7], Jozine M. ter Maaten[1], Leong Ng[8], Piotr Ponikowski[9], Nilesh J. Samani[8], Dirk J. van Veldhuisen[1], Faiz Zannad[10], Aeilko H. Zwinderman[11], and Marco Metra[12]

Aims Despite major improvements in pharmacological and device treatments, heart failure remains a syndrome with high morbidity and mortality, poor quality of life, and high health-care costs. Given the extensive heterogeneity among patients with heart failure, substantial differences in the response to therapy can be expected. We hypothesize that individualized therapy is an essential next step to improve outcomes in patients with heart failure.

Methods The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) included 2516 patients with worsening signs and/or symptoms of heart failure from 11 European countries, who were considered to be on suboptimal medical treatment. Another 1738 patients from Scotland were included in a validation cohort. Overall, both patient cohorts were well matched. The majority of patients were hospitalized for acute heart failure, and the remainder presented with worsening signs and/or symptoms of heart failure at outpatient clinics. Approximately half of the patients were in New York Heart Association class III, and 7% vs 34% of patients of the index vs validation cohort had heart failure with preserved ejection fraction. According to study design, all patients used diuretics, but owing to the inclusion criteria of both cohorts, patients were not on optimal, evidence-based medical therapy. In the follow-up phase, uptitration to guideline-recommended doses was encouraged.

Conclusion By using a novel systems biology approach, incorporating demographics, biomarkers, genome-wide analysis, and proteomics, a model that predicts response to therapy will be developed, which should be instrumental in developing alternative therapies for patients with suboptimal response to currently recommended therapies and thus further improve care for patients with heart failure.

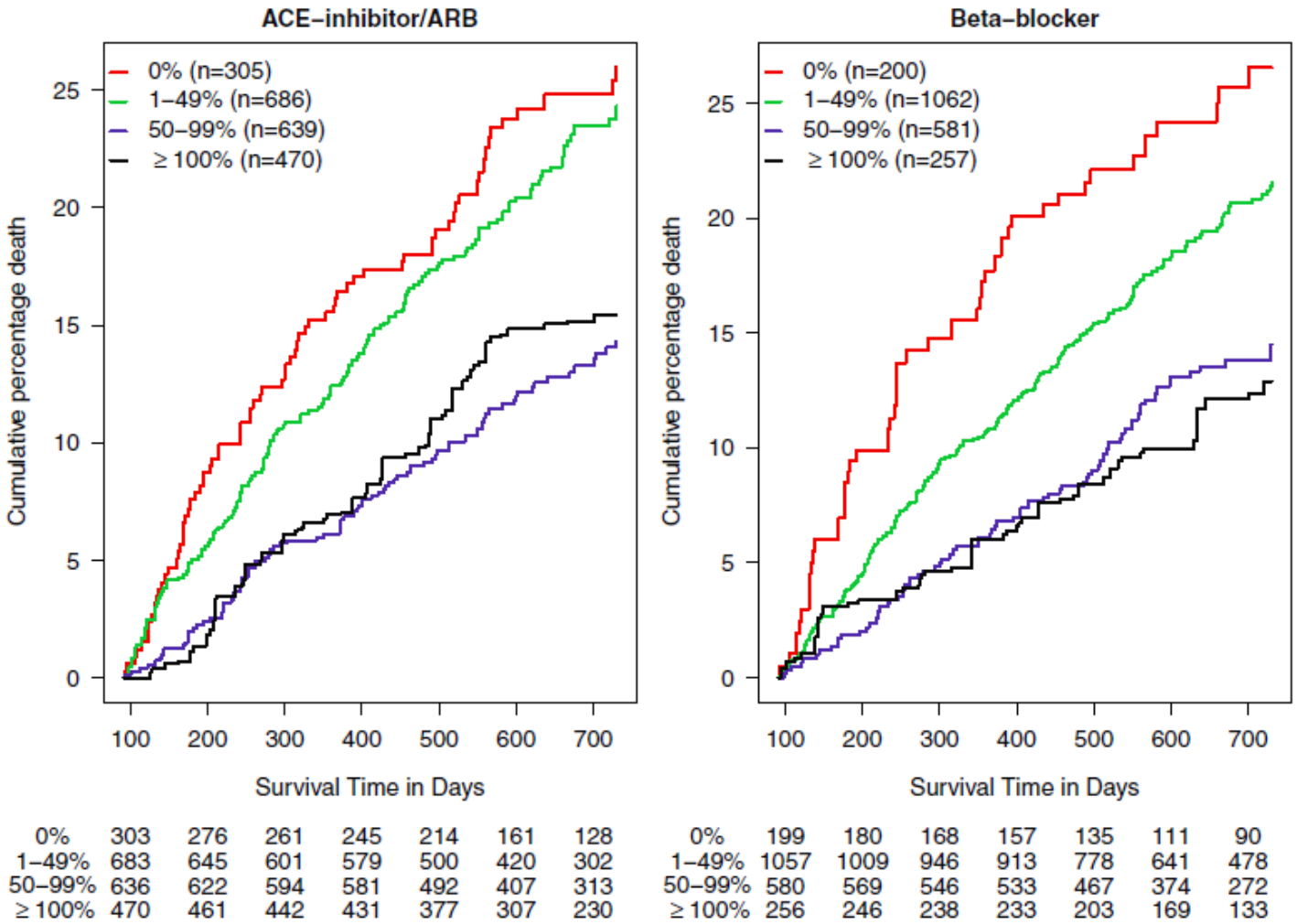
European Heart Journal (2017) **38**, 1883–1890
doi:10.1093/eurheartj/ehx026

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study

W. Ouwerkerk[1], A.A. Voors[2]*, S.D. Anker[3], J.G. Cleland[4], K. Dickstein[5,6], G. Filippatos[7], P. van der Harst[2], H.L. Hillege[2], C.C. Lang[8], J.M. ter Maaten[2], L.L. Ng[9], P. Ponikowski[10], N.J Samani[9], D.J. van Veldhuisen[2], F. Zannad[11], M. Metra[12], and A.H. Zwinderman[1]

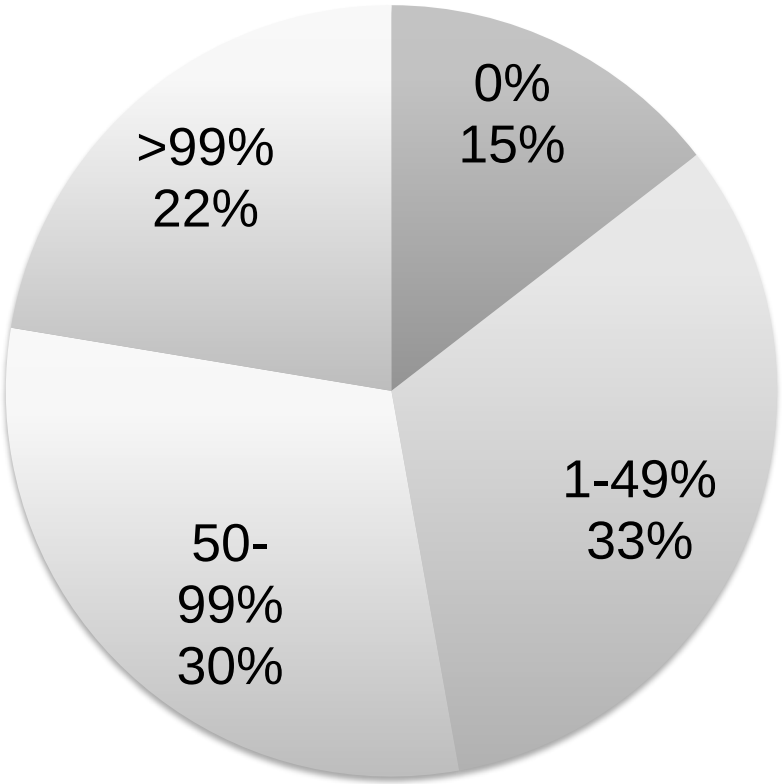
Adjusted mortality rate for patients achieving target doses of ACEi/ARBs or beta-blockers: results from BIOSTAT-HF



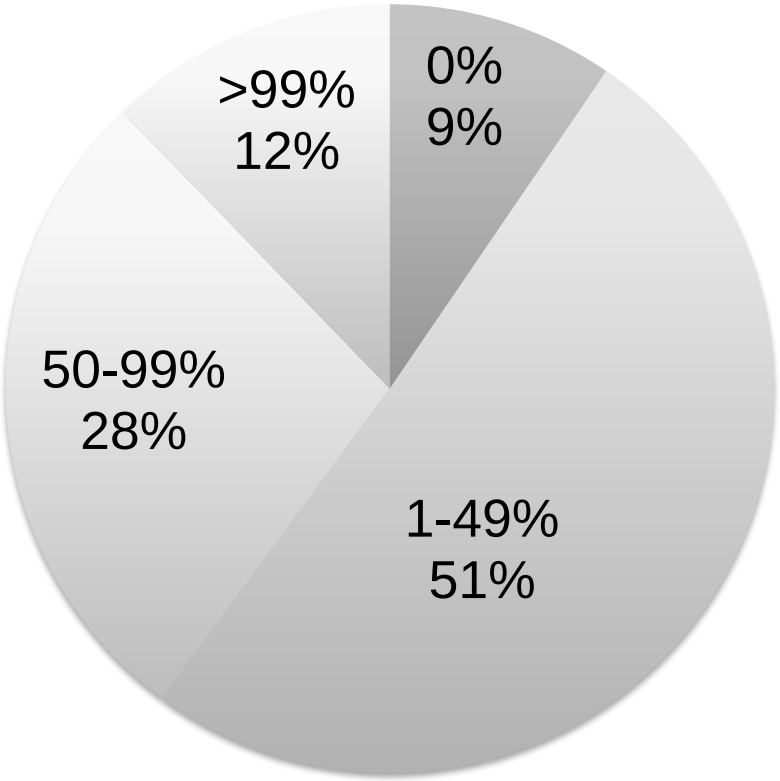
Voors et al. Eur Heart J. 2017;38(24):1883-1890. doi:10.1093/eurheartj/ehx026

Average percentage achieved of the recommended dose

ACEi/ARB



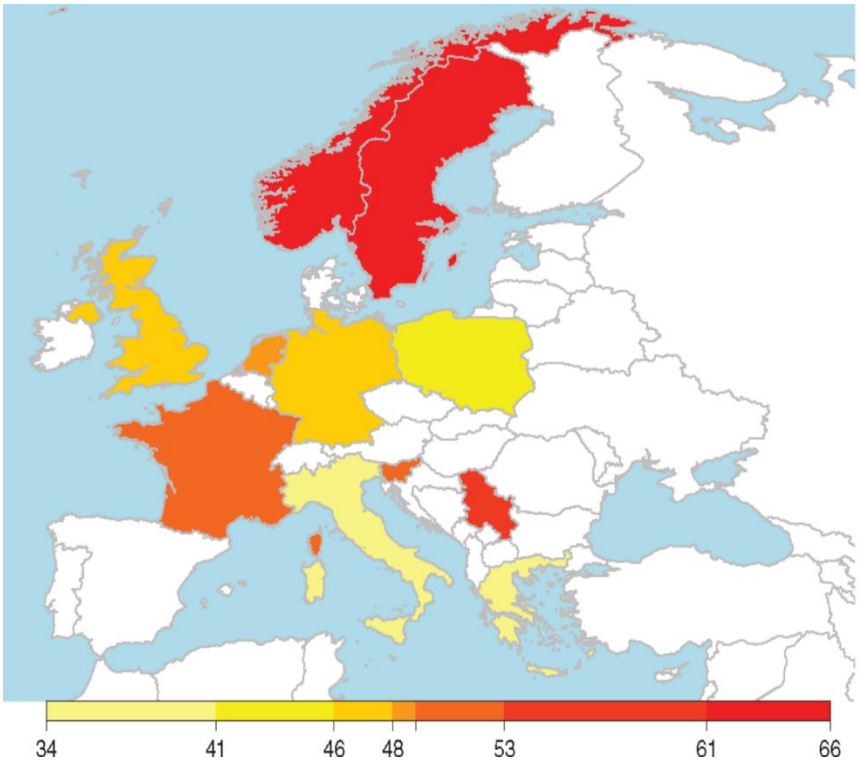
Beta-blockers



Ouwerkerk et al Eur Heart J. 2017;38(24):1883-1890.

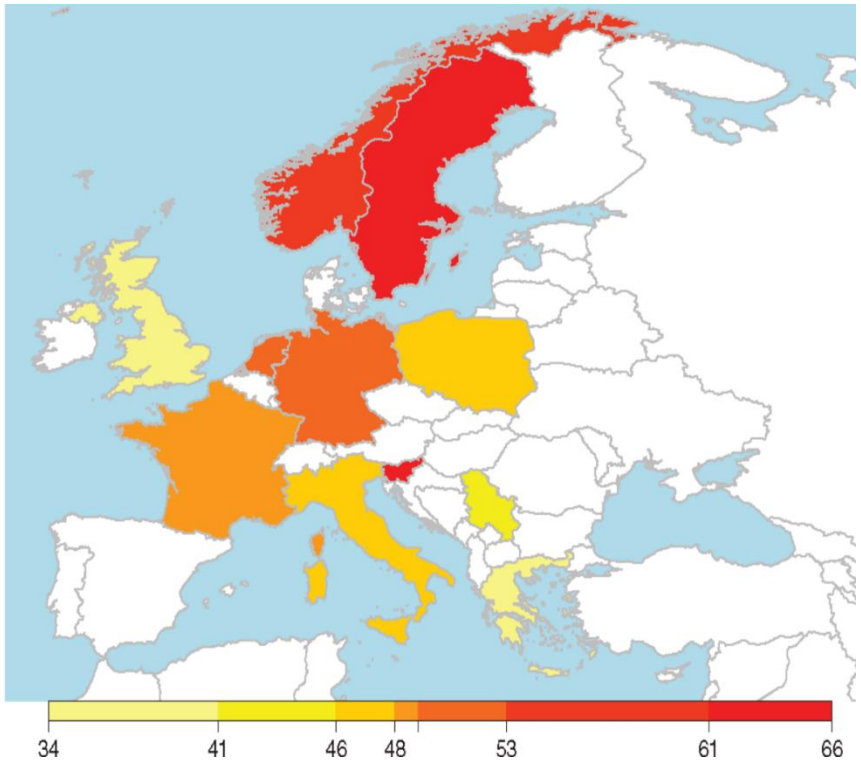
Average percentage achieved of the recommended dose per country

ACE inhibitor/ ARB



Average percentage achieved of the recommended dose

Beta-blocker



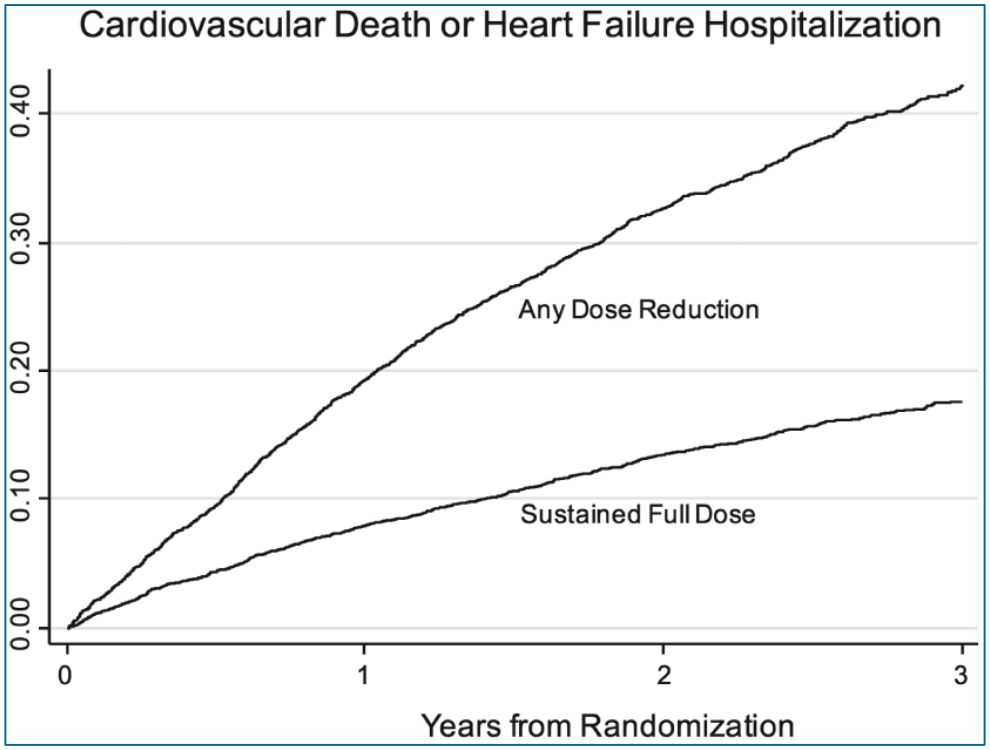
Average percentage achieved of the recommended dose

Ouwerkerk et al Eur Heart J. 2017;38(24):1883-1890.

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

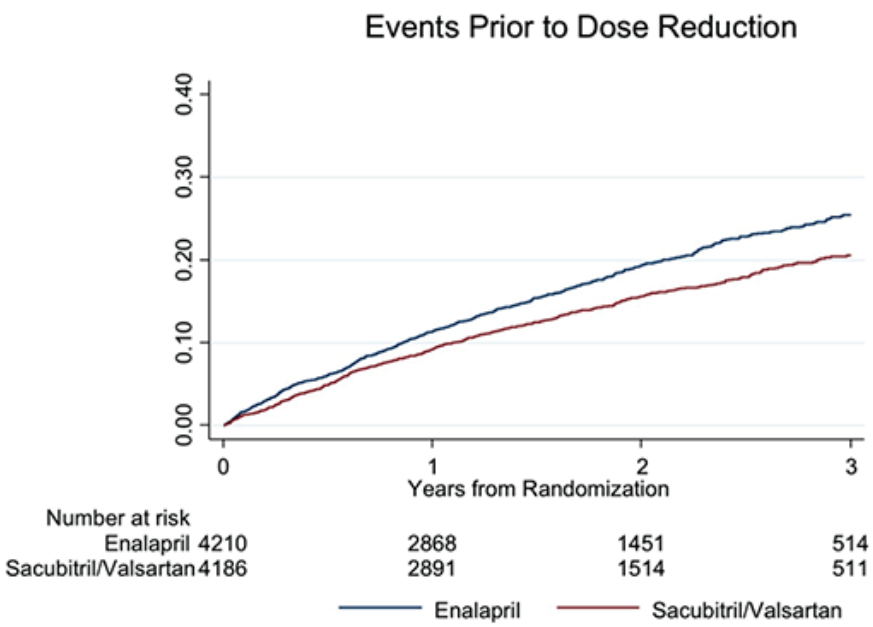


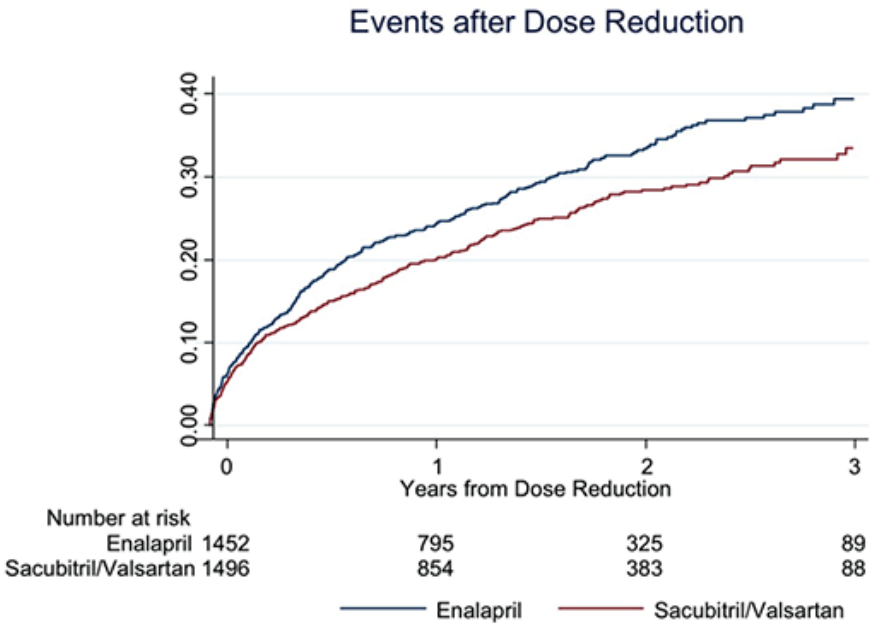
European Journal of Heart Failure (2016)
doi:10.1002/ejhf.580

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

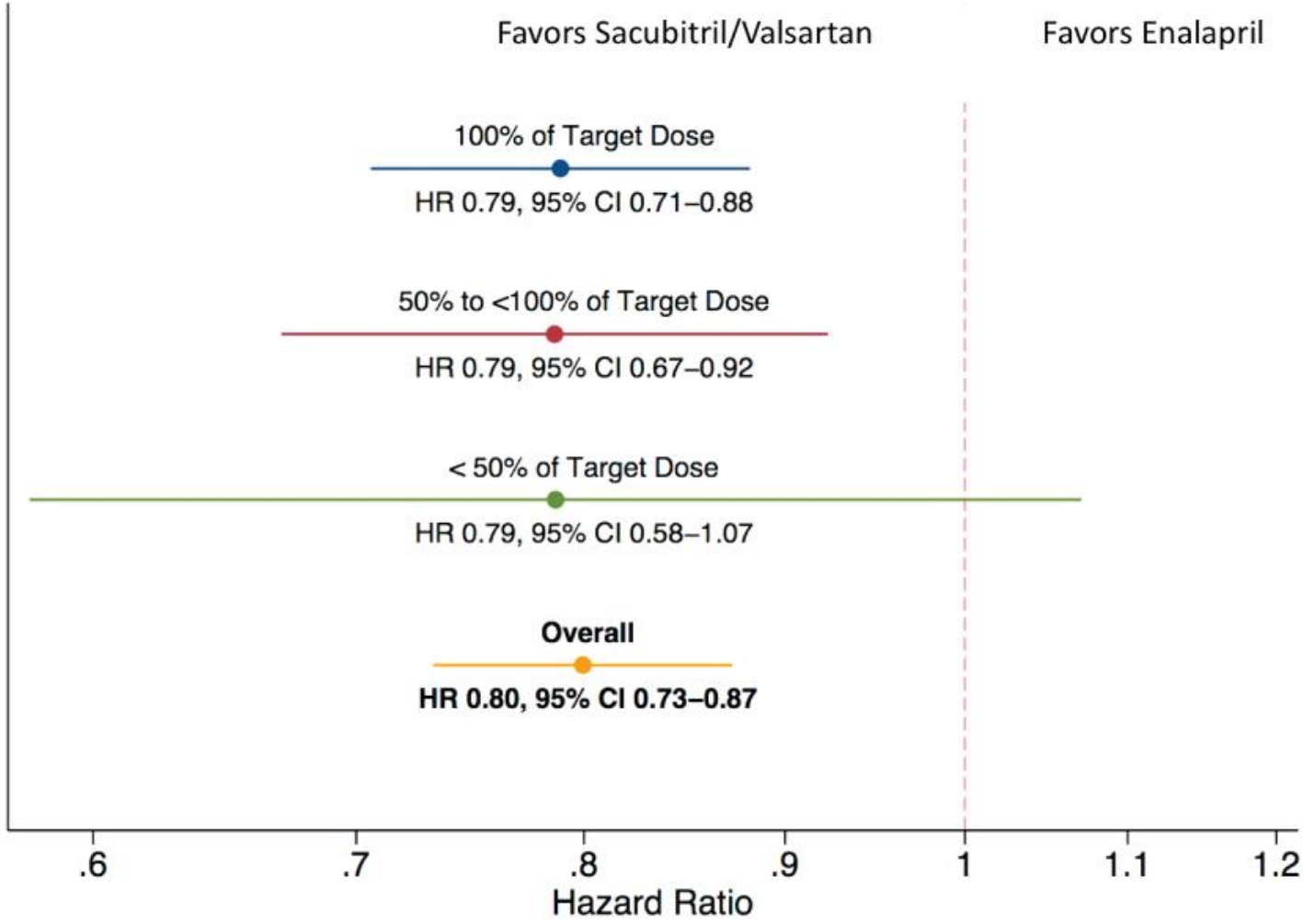
Orly Vardeny[1], Brian Claggett[2], Milton Packer[3], Michael R. Zile[4], Jean Rouleau[5], Karl Swedberg[6], John R. Teerlink[7], Akshay S. Desai[2], Martin Lefkowitz[8], Victor Shi[8], John J.V. McMurray[9], Scott D. Solomon[2]*, for the Prospective Comparison of ARNI with ACEI to Determine Impact on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

Cardiovascular Death or Heart Failure Hospitalization by Dose Reduction Status





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

Sacubitril/valsartan vs. enalapril

- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dosi di ACE inibitore
  - Comorbilità
  - Tolleranza
- Costo- efficacia

Risk Related to Pre–Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction

Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

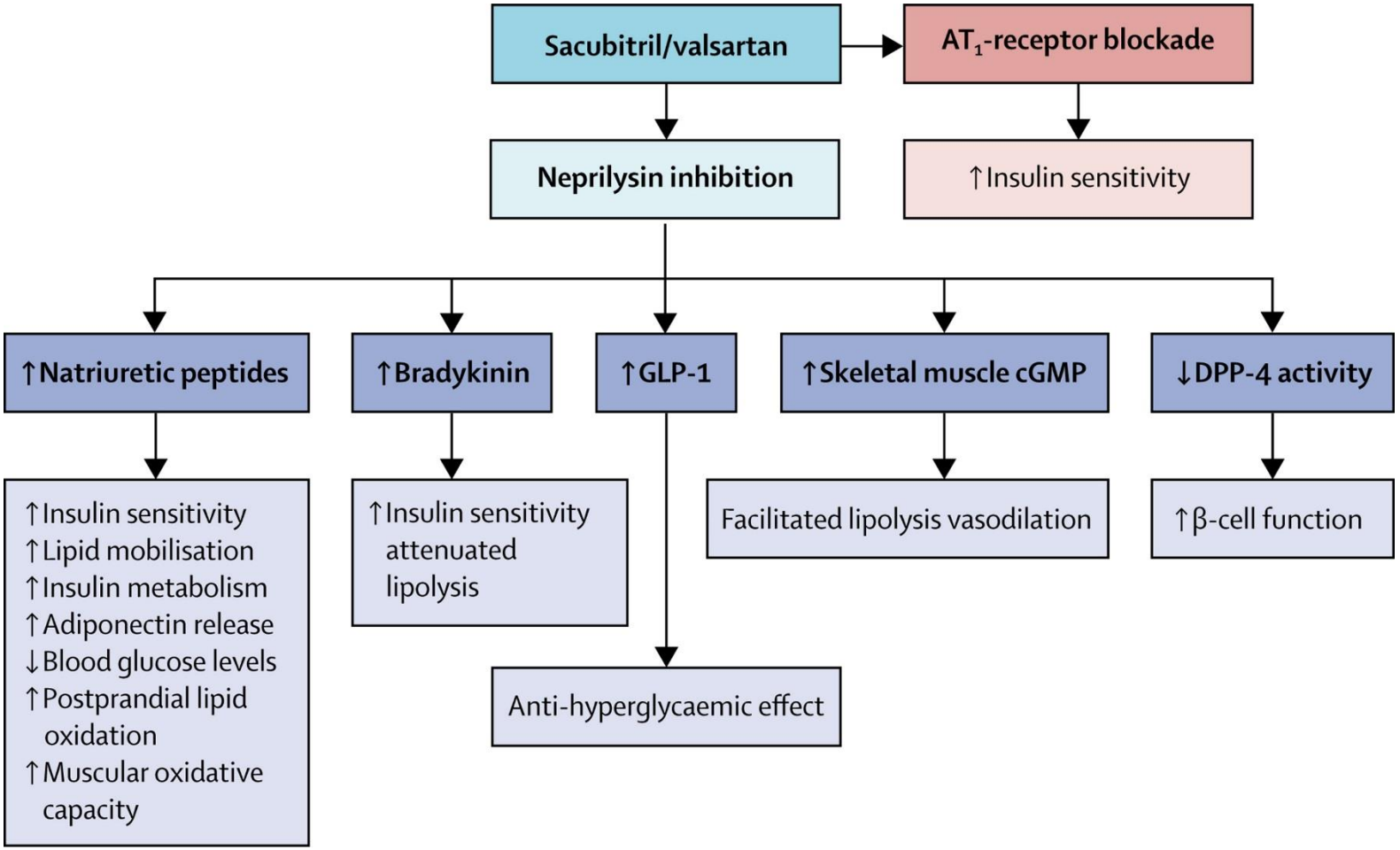
Søren L. Kristensen, MD, PhD; David Preiss, MD, PhD; Pardeep S. Jhund, MB, PhD; Iain Squire, MD; José Silva Cardoso, MD, PhD; Bela Merkely, MD, PhD, DSc; Felipe Martinez, MD; Randall C. Starling, MD, MPH; Akshay S. Desai, MD; Martin P. Lefkowitz, MD; Adel R. Rizkala, PharmD; Jean L. Rouleau, MD; Victor C. Shi, MD; Scott D. Solomon, MD; Karl Swedberg, MD; Michael R. Zile, MD; John J.V. McMurray, MD; Milton Packer, MD; for the PARADIGM-HF Investigators and Committees*

Table 3. Treatment Effects of LCZ696 (Sacubitril/Valsartan) According to History of Diabetes Mellitus and Glycemic Status

	Overall	Normoglycemia	Pre–Diabetes Mellitus	Undiagnosed Diabetes Mellitus	Diabetes Mellitus	*P* Values for Interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
HF hospitalization or cardiovascular death	0.80 (0.73–0.87)	0.68 (0.56–0.83)	0.76 (0.63–0.91)	0.97 (0.77–1.22)	0.87 (0.77–0.98)	0.13
Cardiovascular death	0.80 (0.71–0.89)	0.62 (0.48–0.80)	0.76 (0.61–0.96)	0.86 (0.65–1.15)	0.92 (0.77–1.09)	0.09
HF hospitalization	0.80 (0.71–0.89)	0.85 (0.65–1.12)	0.73 (0.57–0.93)	0.88 (0.65–1.20)	0.79 (0.67–0.94)	0.78
All-cause mortality	0.84 (0.76–0.93)	0.68 (0.55–0.85)	0.77 (0.63–0.95)	0.91 (0.69–1.18)	0.97 (0.83–1.14)	0.06
Significant worsening in KCCQ clinical score (≥5) at 8 mo†	0.83(0.76–0.92)‡	0.73 (0.60–0.89)‡	0.86 (0.71–1.04)‡	0.93 (0.71–1.21)‡	0.86 (0.74–1.01)‡	0.14

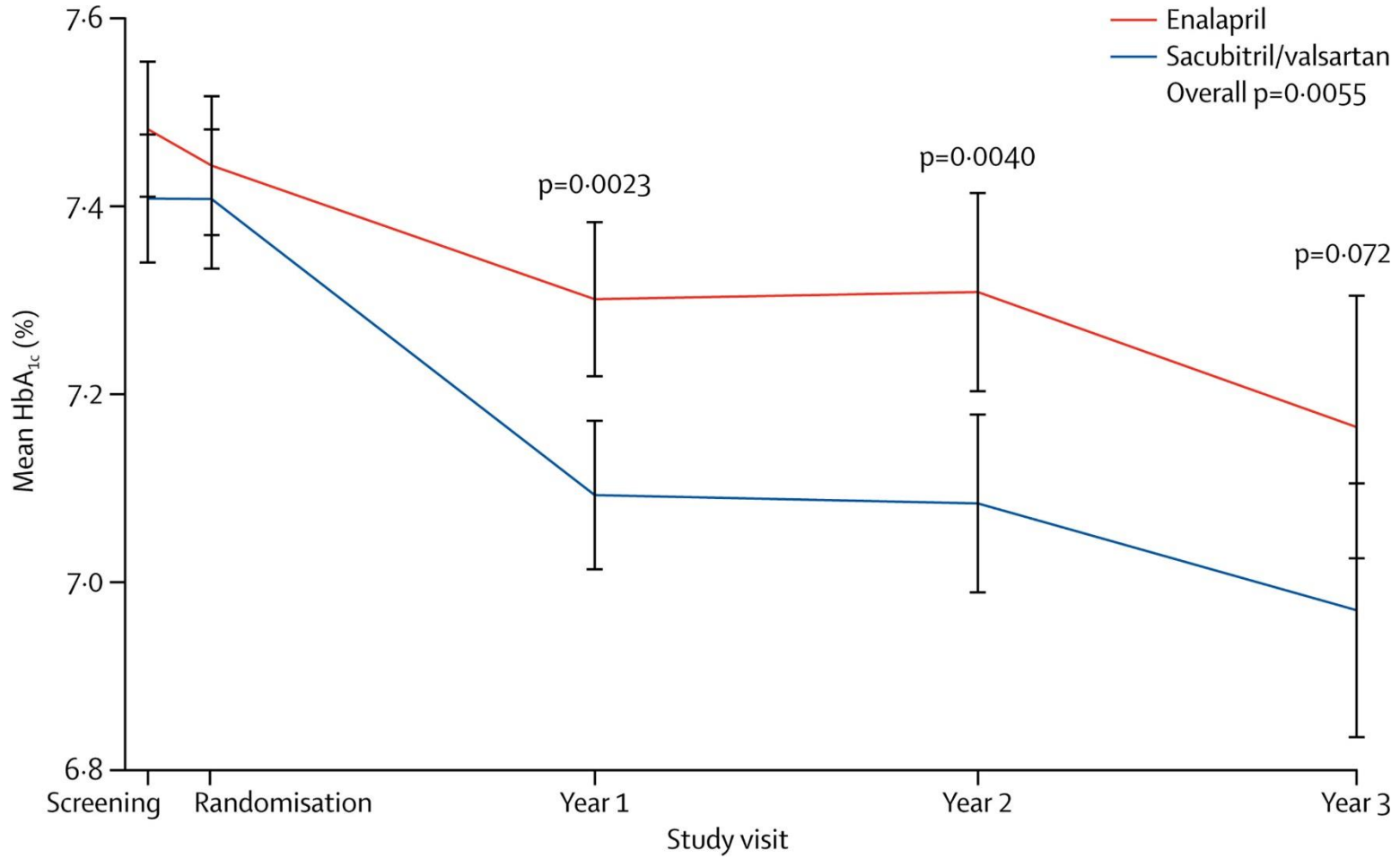
(*Circ Heart Fail.* 2016;9:e002560. DOI: 10.1161/CIRCHEARTFAILURE.115.002560.)

Mechanisms by which ARNI may improve glycaemic control



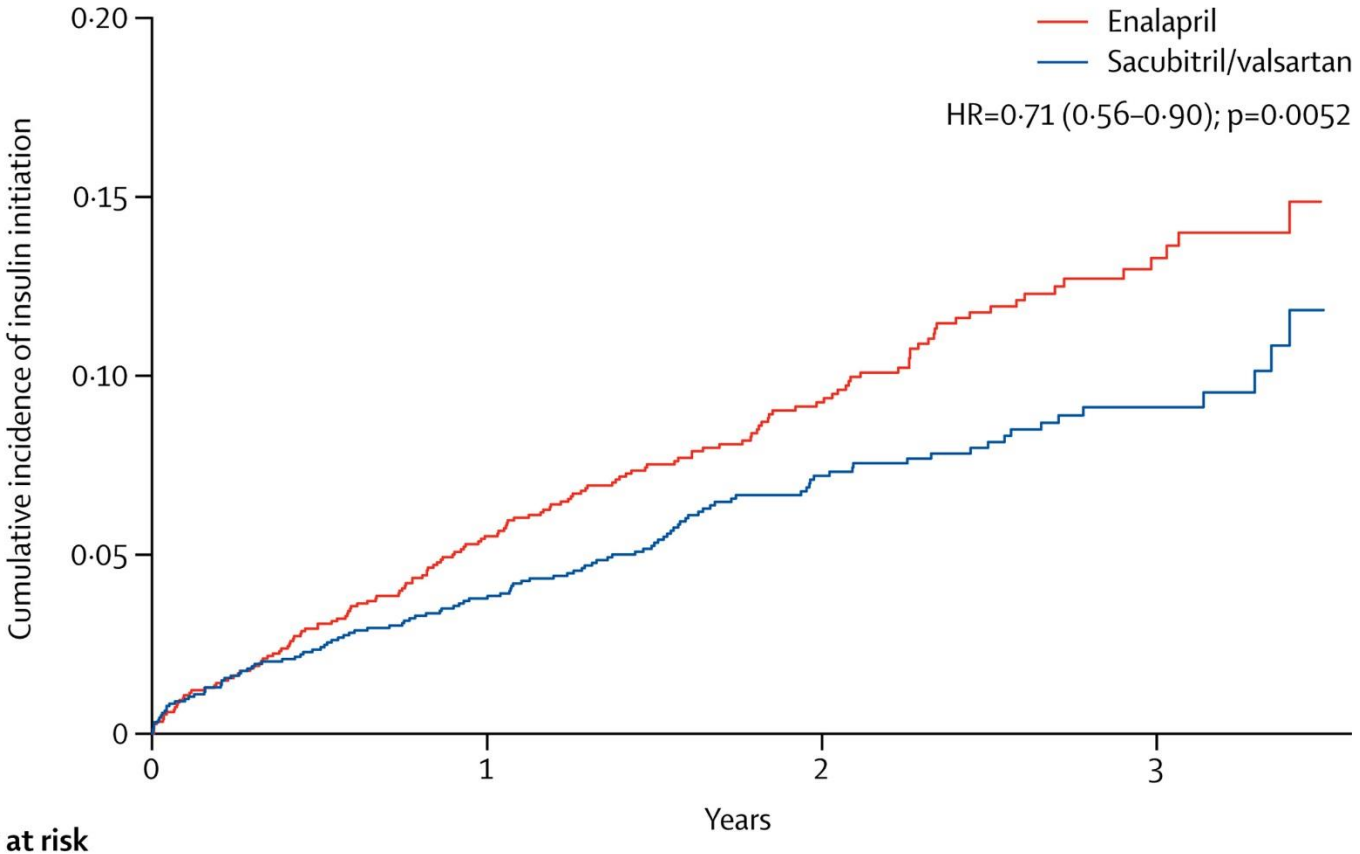
Giamouzis, Butler The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30089-X)

Changes in mean HbA1c in PARADIGM-HF



Seferovic JP et al. The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30087-6)

Kaplan-Meier curves of time to insulin initiation



Number at risk				
Enalapril	1490	1286	786	269
Sacubitril/valsartan	1550	1377	837	284

Seferovic JP et al. The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30087-6)

Sacubitril/valsartan vs. enalapril

- Quali parametri
  - Eventi
  - Qualità di vita
- Monitoraggio efficacia
- Quali pazienti
  - Età
  - Severità
  - Dosi di ACE inibitore
  - Comorbilità
  - Tolleranza
- Costo- efficacia

Adverse Events during Randomized Treatment.

Table 3. Adverse Events during Randomized Treatment.*

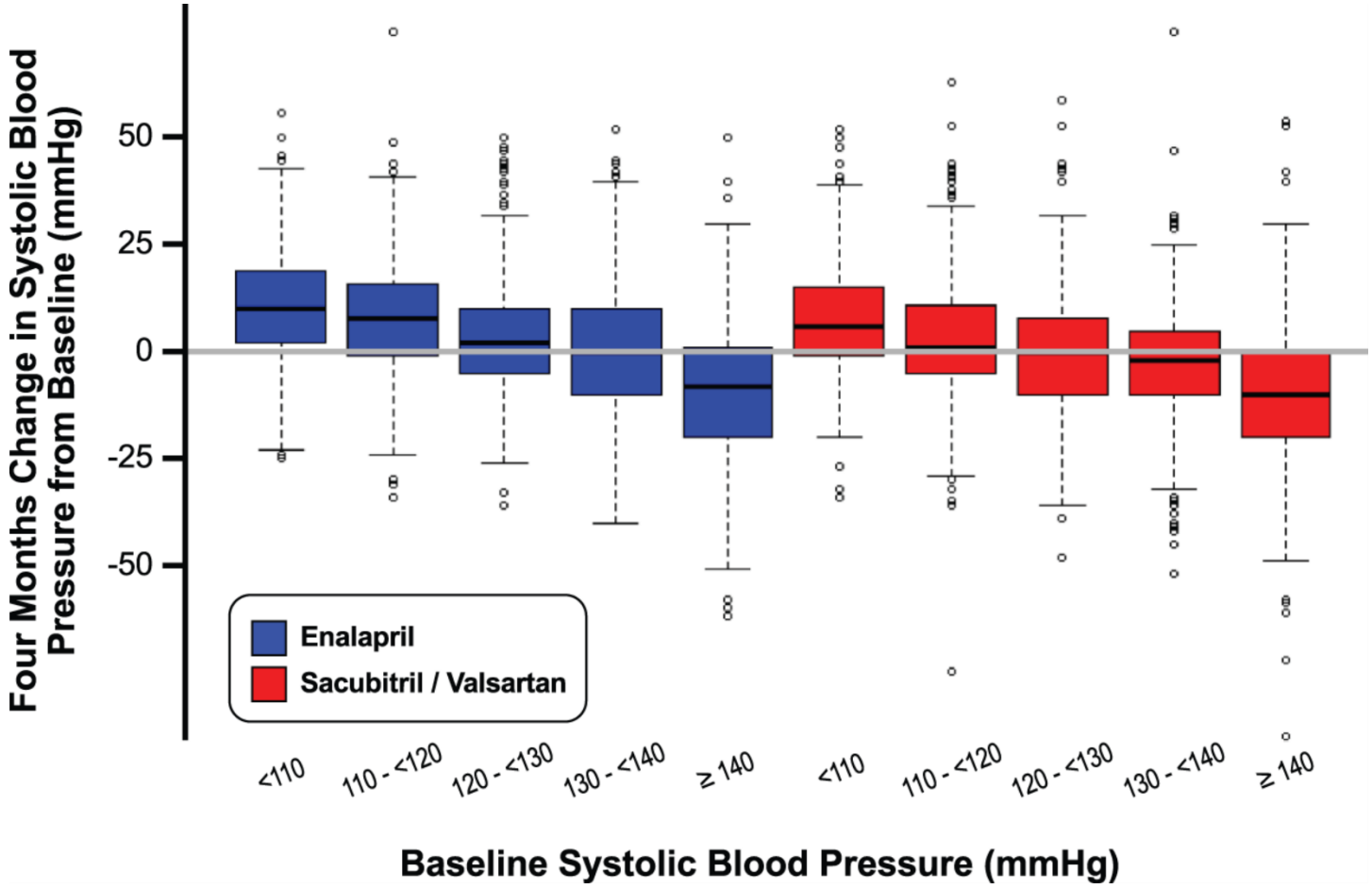
Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated 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.

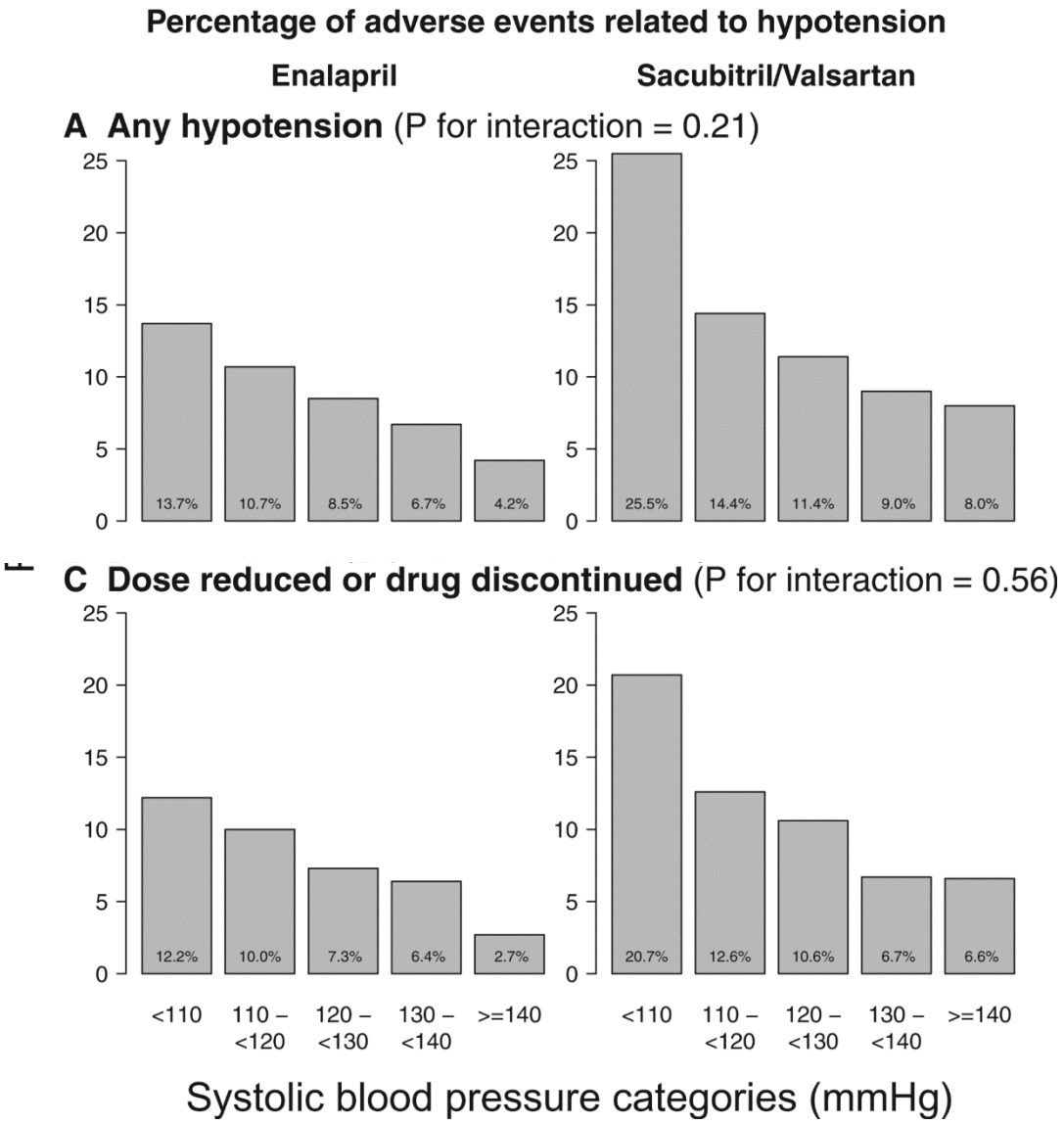
McMurray JJ et al. N Engl J Med 2014;371:993-1004.

PARADIGM-HF: systolic blood pressure change at 4 months according to baseline

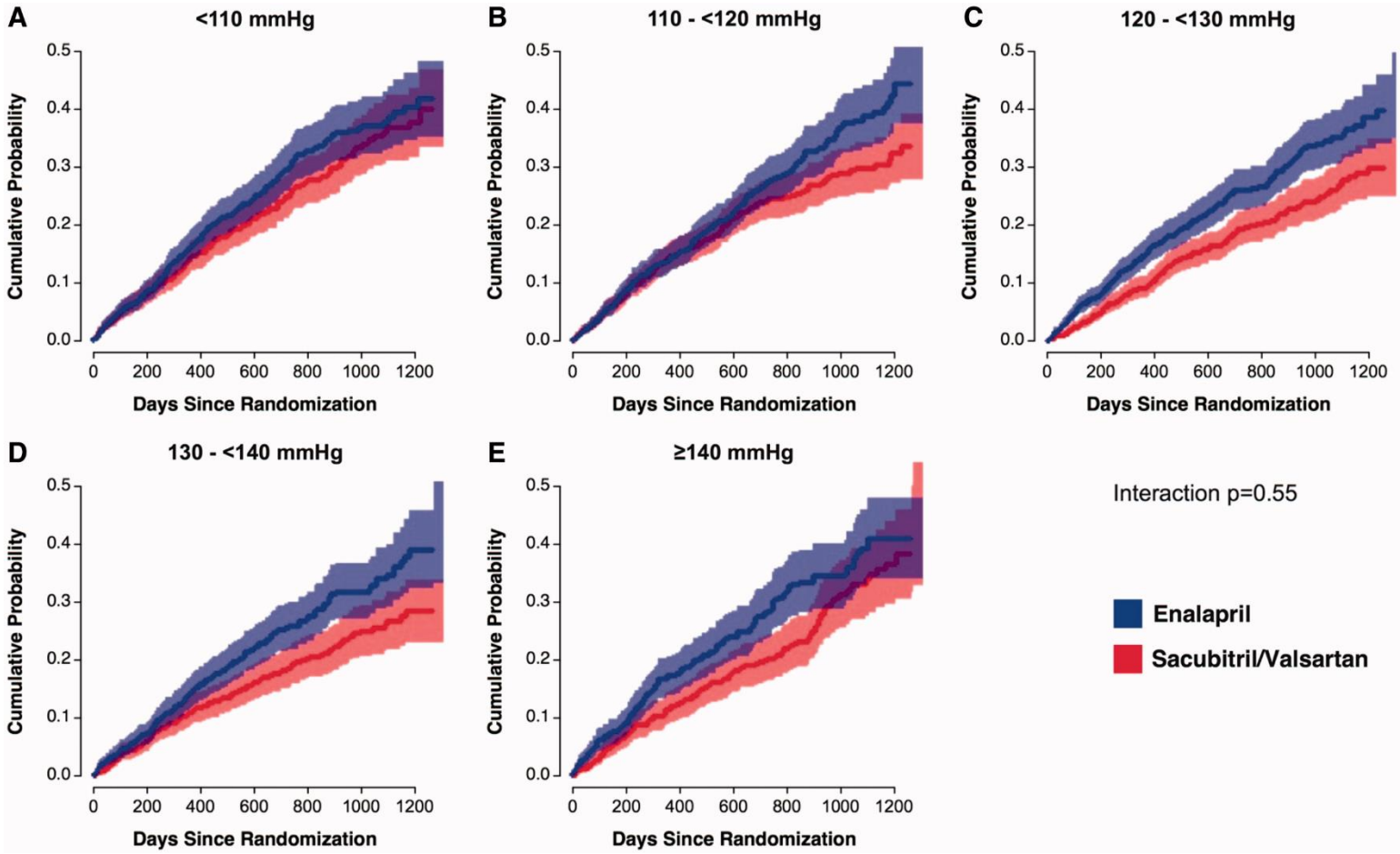


Bohm et al. Eur Heart J. 2017;38(15):1132-1143. doi:10.1093/eurheartj/ehw570

Any report of hypotension or (C) dose reduction or discontinuation of study drug



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



Bohm et al. Eur Heart J. 2017;38(15):1132-1143. doi:10.1093/eurheartj/ehw570

European Journal of Heart Failure (2016) **18**, 1193–1202
doi:10.1002/ejhf.548

RESEARCH ARTICLE

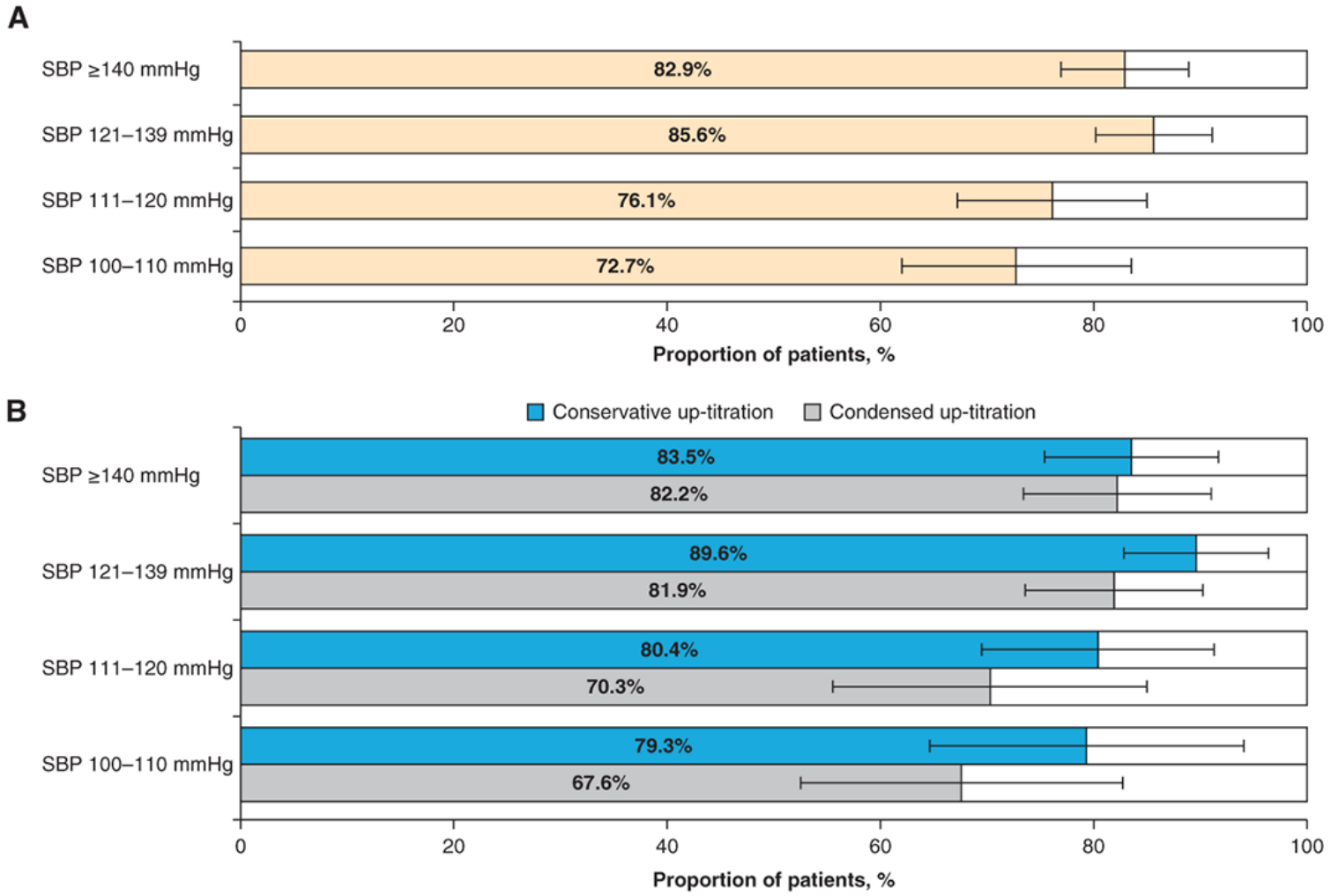
Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens

Michele Senni[1]*, John J.V. McMurray[2], Rolf Wachter[3], Hugh F. McIntyre[4], Antonio Reyes[5], Ivan Majercak[6], Peter Andreka[7], Nina Shehova-Yankova[8], Inder Anand[9], Mehmet B. Yilmaz[10], Harinder Gogia[11], Manuel Martinez-Selles[12], Steffen Fischer[13], Zsolt Zilahi[14], Franco Cosmi[15], Valeri Gelev[16], Enrique Galve[17], Juanjo J. Gómez-Doblas[18], Jan Nociar[19], Maria Radomska[20], Beata Sokolova[21], Maurizio Volterrani[22], Arnab Sarkar[23], Bernard Reimund[24], Fabian Chen[25], and Alan Charney[25]

Table 1 Baseline demographics

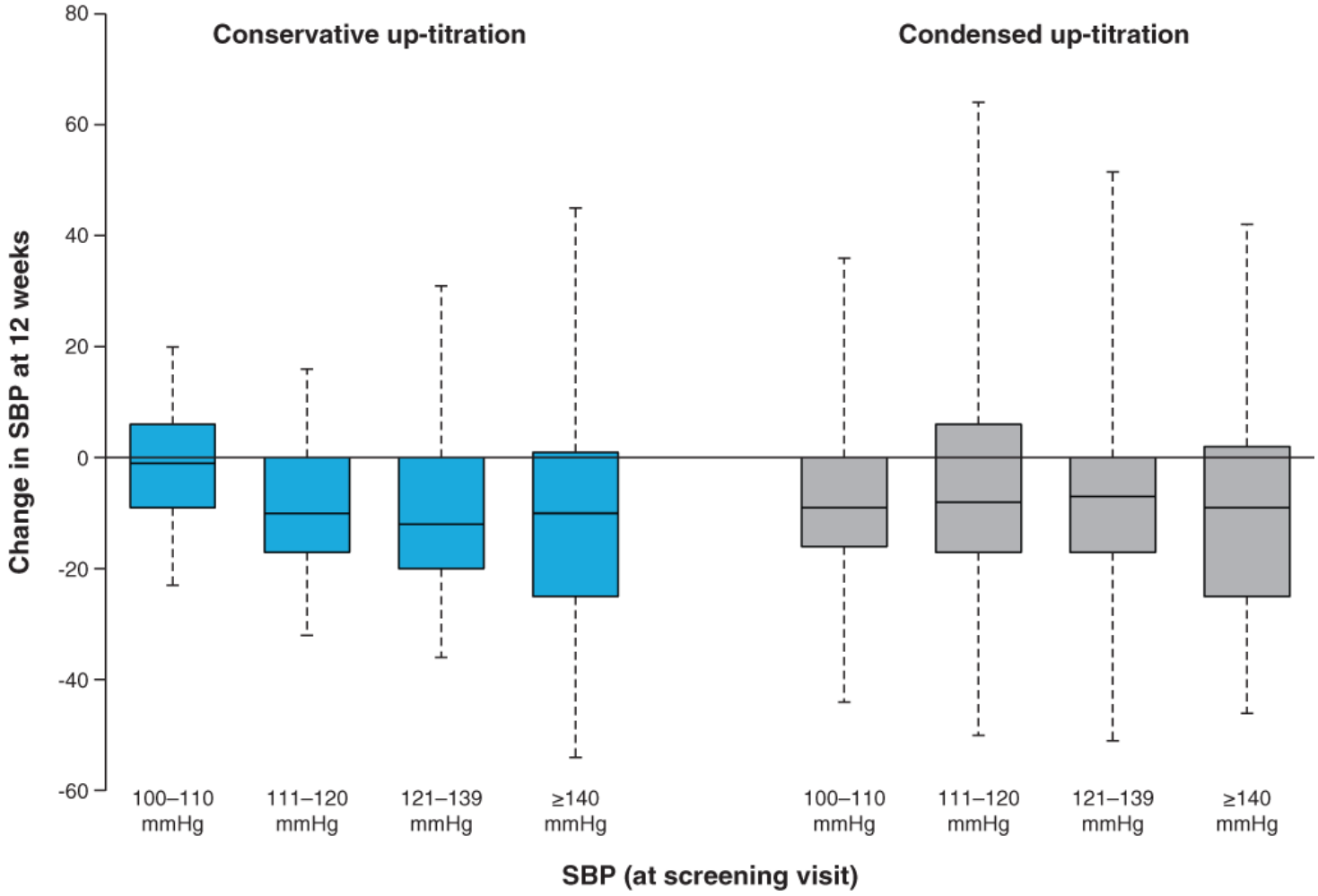
Demographic	Titration regimen		ACEI/ARB dose stratum		Total ($n = 498$)
	Condensed ($n = 247$)	Conservative ($n = 251$)	High ($n = 247$)	Low ($n = 251$)	
Patients composition, *n* (%)					
Inpatient	25 (10.1)	31 (12.4)	17 (6.9)	39 (15.5)	56 (11.2)
Outpatient	222 (89.9)	220 (87.6)	230 (93.1)	212 (84.5)	442 (88.8)
High-dose ACEI/ARB	120 (48.6)	127 (50.6)			247 (49.6)
Low-dose ACEI/ARB	127 (51.4)	124 (49.4)			251 (50.4)
ACEI/ARB-naïve*	17 (6.9)	16 (6.4)			33 (6.6)

Proportion of patients achieving and maintaining the target dose of sacubitril/valsartan 97 mg/103 mg bid without dose interruption/down-titration for 12 weeks



Senni et al. European Journal of Heart Failure 22 NOV 2017 DOI: 10.1002/ejhf.1054

Changes in SBP at 12 weeks according to SBP categories at screening in patients receiving sacubitril/valsartan: data from the TITRATION study



Senni et al. European Journal of Heart Failure 22 NOV 2017 DOI: 10.1002/ejhf.1054

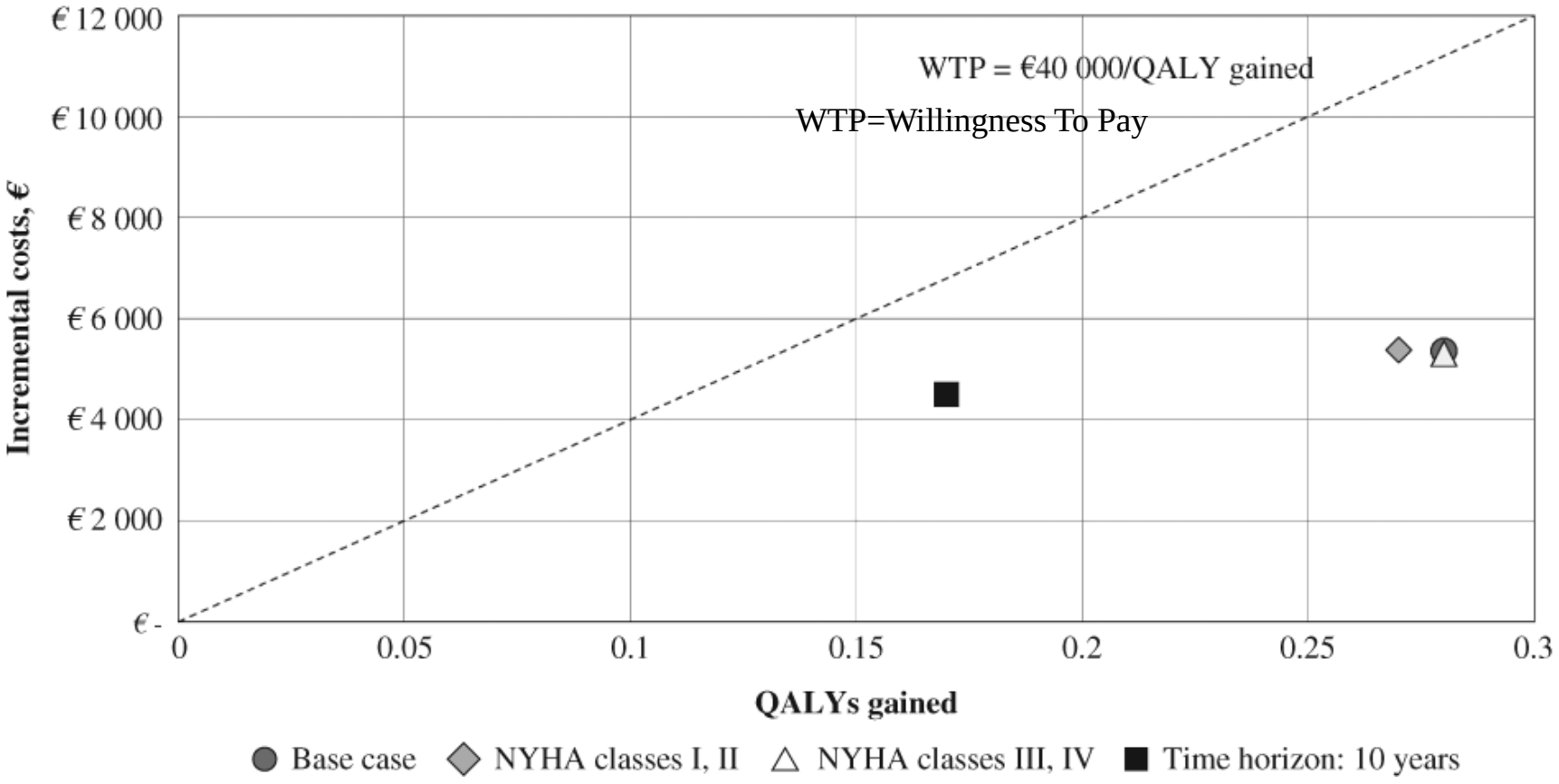
Cost – efficacy of sacubitril/valsartan versus enalapril in HFrEF

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)[2]
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

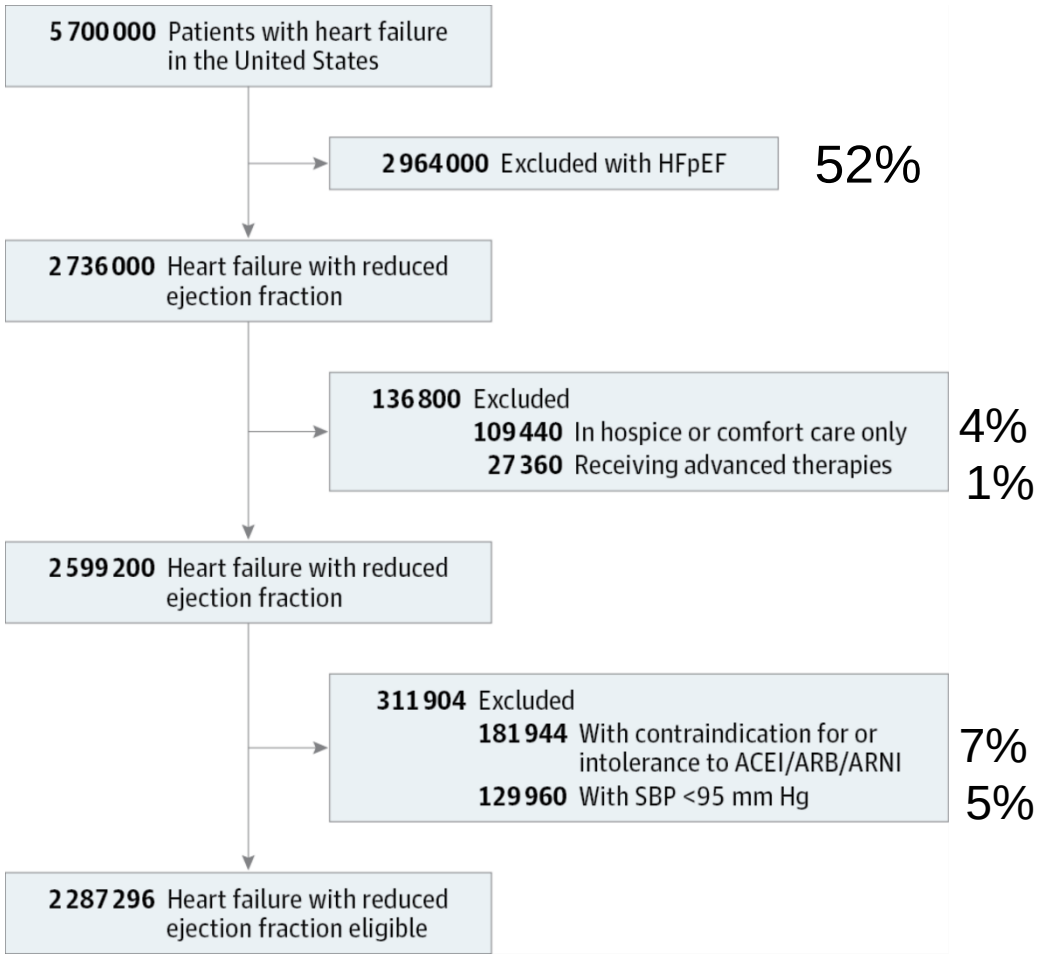


D'Angiolella LS, Cortesi PA, Pitotti C, Ritrovato D, Mantovani LG, Senni M. et al. Eur J Heart Fail 28 AUG 2017 DOI: 10.1002/ejhf.919

JAMA Cardiology | Brief Report

Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure

Gregg C. Fonarow, MD; Adrian F. Hernandez, MD, MHS; Scott D. Solomon, MD; Clyde W. Yancy, MD



JAMA Cardiol. 2016;1(6):714-717. doi:10.1001/jamacardio.2016.1724

JAMA Cardiology | Brief Report

Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure

Gregg C. Fonarow, MD; Adrian F. Hernandez, MD, MHS; Scott D. Solomon, MD; Clyde W. Yancy, MD

IMPORTANCE Angiotensin receptor neprilysin inhibition (ARNI) therapy provided incremental survival benefit to patients with heart failure and reduced ejection fraction (HFrEF) in clinical trials. To date, estimation of the potential benefits that could be gained from optimal implementation of ARNI therapy at the population level have not been quantified.

OBJECTIVE To quantify the projected gains for deaths prevented or postponed with comprehensive implementation of ARNI therapy for patients with HFrEF in the United States.

DESIGN, SETTING, AND PARTICIPANTS Eligibility criteria for ARNI therapy, population-based estimates of patients with HFrEF in the United States, and numbers needed to treat to overt death were obtained from published sources. The potential numbers of deaths prevented or postponed as a result of ARNI were estimated along with multiple-way sensitivity analysis.

MAIN OUTCOME AND MEASURE All-cause mortality.

RESULTS Of 2 736 000 patients with HFrEF patients in the United States, 2 287 296 (84%) were projected to be candidates for ARNI therapy. Optimal implementation of ARNI therapy was empirically estimated to prevent 28 484 deaths a year (range, 18 230-41 017 deaths per year).

CONCLUSIONS AND RELEVANCE A substantial number of deaths in the United States could potentially be prevented by optimal implementation of ARNI therapy. These data support implementation of evidence into practice in a timely manner because this may have a material impact on population health among patients with HFrEF.

JAMA Cardiol. 2016;1(6):714-717. doi:10.1001/jamacardio.2016.1724
Published online June 22, 2016.

Author Affiliations: The Ahmanson–UCLA (University of California, Los Angeles) Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, Los Angeles (Fonarow); Associate Editor for Health Care Quality and Guidelines, *JAMA Cardiology* (Fonarow); Duke Clinical Research Institute, Durham, North Carolina (Hernandez); Associate Editor, *JAMA Cardiology* (Hernandez); TIMI (Thrombolysis in Myocardial Infarction) Study Group, Cardiovascular Division, Brigham and Women's Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts (Solomon); Northwestern University, Feinberg School of Medicine, Chicago, Illinois (Yancy); Deputy Editor, *JAMA Cardiology* (Yancy).

Corresponding Author: Gregg C. Fonarow, MD, Ahmanson–UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, 10833 LeConte Ave, Room A2-237 CHS, Los Angeles, CA 90095-1679 (gfonarow@mednet.ucla.edu).

Conclusioni

- Efficacia di sacubitril/valsartan vs. enalapril su:
  - Mortalità, riospedalizzazioni, qualità di vita
- Monitoraggio dell'efficacia con NT-proBNP plasmatico
- Effetto indipendente da:
  - Età
  - Severità
  - Pressione arteriosa
  - Dose di enalapril
  - Terapie concomitanti
- Buon rapporto costo - efficacia

Trials with sacubitril/ valsartan

Trial	Sample size	Study population	Enrolment criteria	Active comparator†	Primary endpoint
PARADIGM-HF*	8442	HFrEF	• Chronic HF with an EF ≤40% • NYHA class II–IV • Elevated BNP or NT-proBNP • Stable dose of ACEI/ARB equivalent to ≥10 mg of enalapril daily	Enalapril 10 mg	CVM + first HF hospitalization
LIFE	400	HFrEF, NYHA class IV	• Chronic HF with an EF ≤35% • NYHA class IV • Minimum of 3 months of GDMT • SBP ≥90 mmHg • Elevated BNP or NT-proBNP • ≥1 Enrichment criteria‡	Valsartan 160 mg	NT-proBNP over 24 weeks
PIONEER-HF	736	Hospitalized HFrEF	• Chronic HF with an EF ≤40% • Admitted ≥24 h • Elevated BNP or NT-proBNP • SBP ≥100 mmHg • Stable i.v. diuretics for prior 6 h • No recent i.v. vasodilators and/or inotropes	Enalapril 10 mg	NT-proBNP over 8 weeks
PARAMOUNT*	301	HFpEF	• Chronic HF with an EF ≥45% • Elevated NT-proBNP • Chronic oral diuretic therapy • SBP <140 mmHg or <160 mmHg on ≥3 anti-hypertensive agents	Valsartan 160 mg	NT-proBNP over 12 weeks
PARAGON	4500	HFpEF	• Chronic HF with an EF >45% • Elevated NT-proBNP • Chronic oral diuretic therapy • Structural heart disease (i.e. left atrial enlargement or left ventricular hypertrophy) documented on echocardiogram	Valsartan 160 mg	CVM + total HF hospitalizations
PARADISE-MI	4650	High-risk post-MI	• Spontaneous MI between 12 h and 7 days • EF ≤40% or pulmonary congestion requiring i.v. therapy • Haemodynamic stability • ≥1 Risk factor§	Ramipril 5 mg	Time to CVM + HF hospitalization + outpatient HF