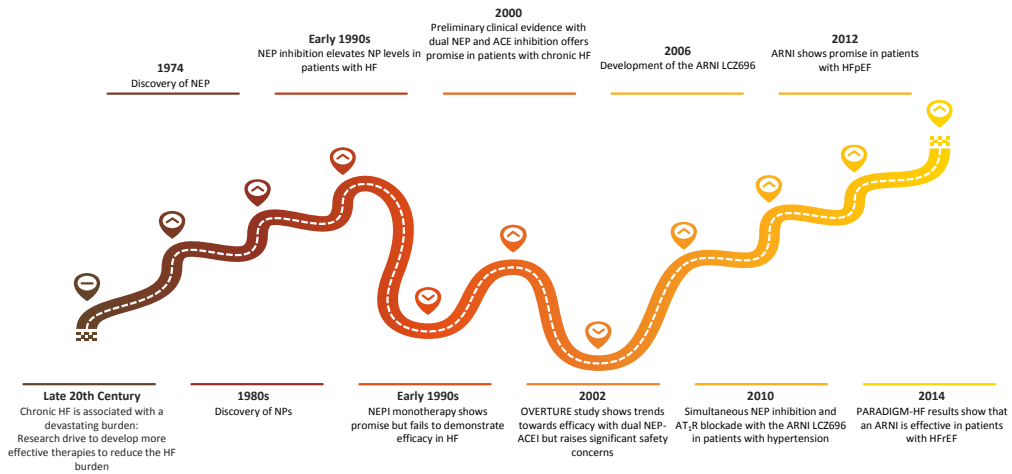
Prof. dr. Petar M. Seferovic
President-elect, Heart Failure Association of the ESC
Corresponding member Serbian Academy of Sciences and Arts

Recent uptadates in the treatment of heart failure

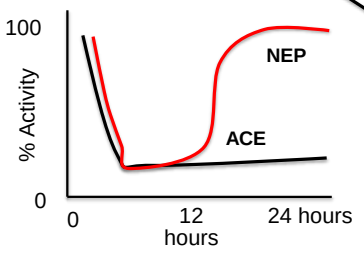
Chair of Internal medicine, Belgrade University School of Medicine
President, Heart failure Society of Serbia

Chronology of ARNI development



ACE-Neprilysin inhibition with omapatrilat

Combined ACE-neprilysin inhibition with omapatrilat once daily



Failure to inhibit neprilysin for 24 hours

↓

Modest (10%) reduction in risk of cardiovascular events

Transient simultaneous enzyme inhibition causes excessive bradykinin

↓

Excess risk of serious angioedema

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

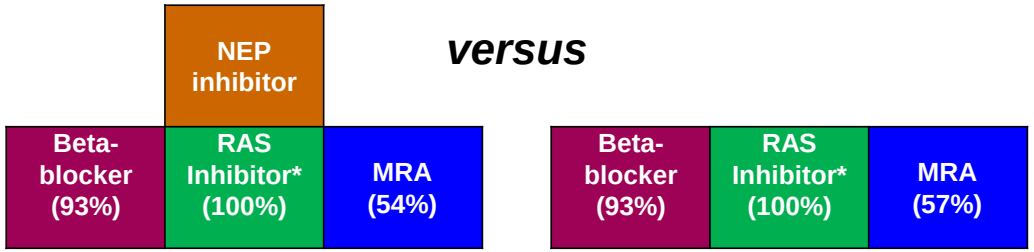
John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

PARADIGM-HF: The most geographically diverse trial in patients with HFrEF

- 8442 patients were randomized at 985 sites in 47 countries

McMurray et al. Eur J Heart Fail. 2014;16:817–25;
McMurray et al. Eur J Heart Fail 2013;15:1062–73

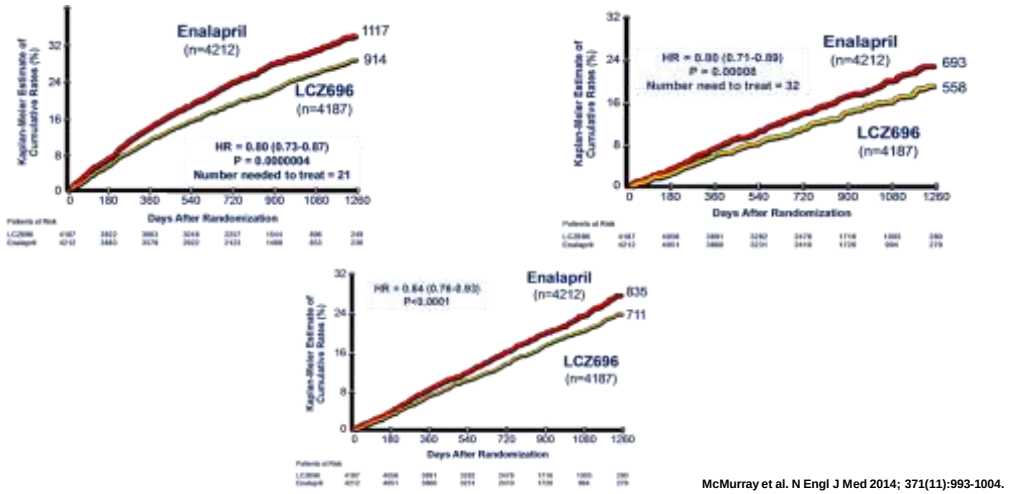
PARADIGM-HF: Treatment comparison



*RAS blocker: valsartan in NEP inhibitor group and enalapril in control group

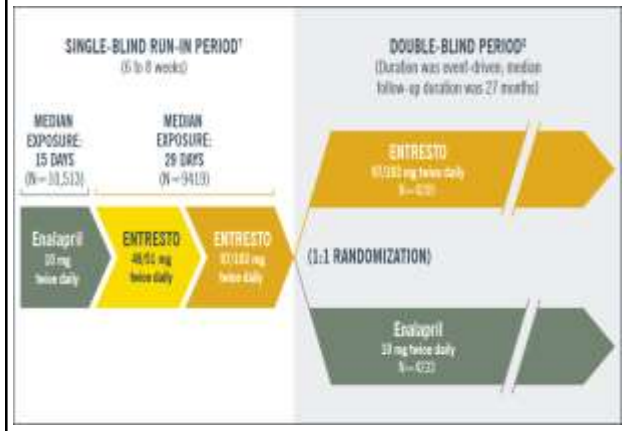
PARADIGM-HF Primary Results

Significant Reduction in Primary Endpoints (CV death or heart failure hospitalization), CV Death and All-Cause Mortality



McMurray et al. N Engl J Med 2014; 371(11):993-1004.

PARADIGM-HF: far from being ideal

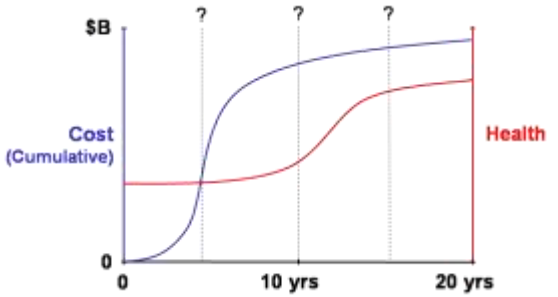


- **Selected patients**
  - Too young
  - No hospitalized patients
  - Not enough NYHA class IV patients
  - BNP/NT proBNP level required for enrollment
- **ACE inhibitor before enrollment**
- **Run-in period**
- **Only one trial**
- **Safety concerns?**
- **Too costly**

Thinking for optimal decision making in using HF drugs

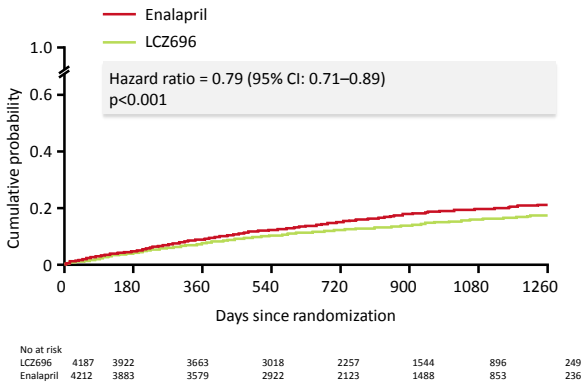
- Better treatment of HF if it is affordable
- The cost of HF (suffering and lives) by using new vs. standard medications
- Cost and suffering vs confort and benefit

COST vs BENEFIT in medical treatment
The price of life ?



- Several breast cancer drugs extents life, but regulators reject its approval because they are too expensive

PARADIGM-HF: far from being ideal



McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

- **Selected patients**
  - Too young
  - HF hospitalizations: enalapril 1079 vs sacubitril/valsartan 851
  - Not enough NYHA class IV patients
  - BNP/NT proBNP level required for enrollment
- **ACE inhibitor before enrollment**
- **Run-in period**
- **Only one trial**
- **Safety concerns?**
- **Too costly**

ESC Long-term registry (ambulatory patients with LVEF <40%)

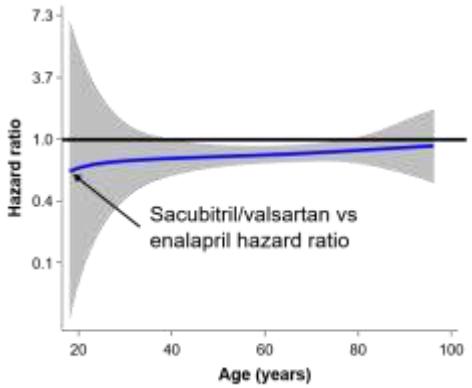
	ESC HF registry N=5460	PARADIGM-HF N=8399
Age (yr)	64±12.6	64±11.4
Age ≥75 yrs (%)	21.9	18.6
Male (%)	78	78
LVEF (%)	29.1	29.5
HR bpm	73	73
SBP (mmHg)	122	122
NYHA class I/II (%)	69	75
NYHA class III/IV (%)	31	25
1 year mortality (%)	8.8	~9*

*enalapril group

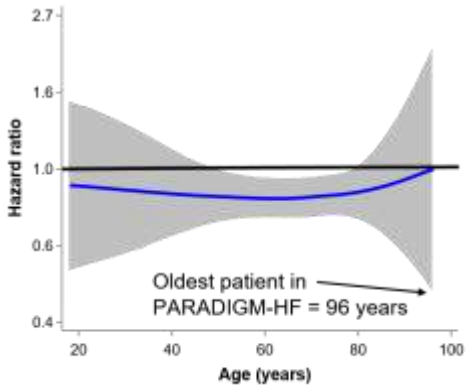
Chioncel et al Eur J Heart Fail. 2017 Apr 6. doi: 10.1002/ejhf.813. [Epub ahead of print]

Benefit of sacubitril/valsartan according to age in PARADIGM-HF

Heart failure hospitalization

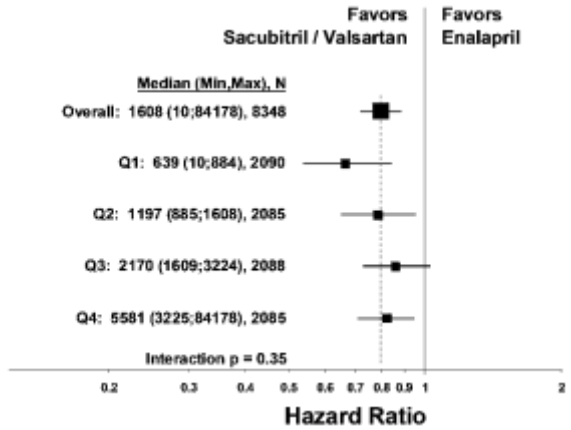


All-cause mortality



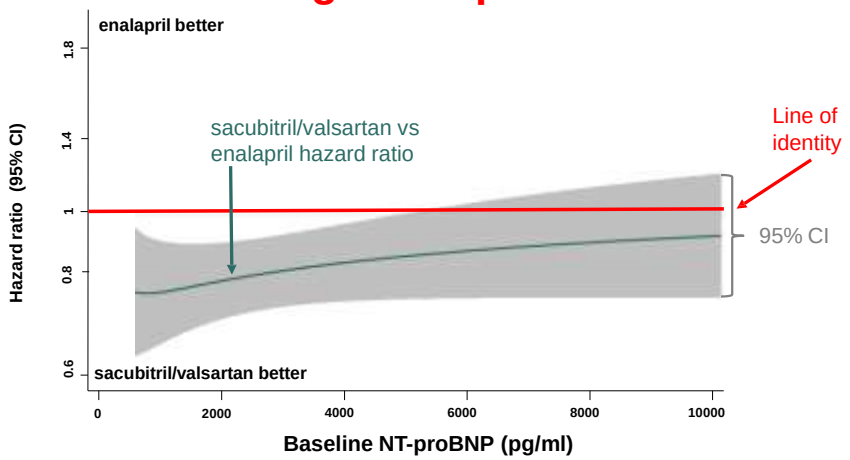
Jhund PS, et al. Eur Heart J. 2015;36:2576-84.

Effect of treatment on primary endpoint according to NT-proBNP level



Zile et al. JACC 2016;68:2425–36

Effect of treatment on all-cause mortality according to NT-proBNP level



Zile et al. JACC 2016;68:2425–36

Prior ACE inhibition

- **Protocol: *"Patients must be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d equivalent for at least 4 weeks before Visit 1"***
- **So you COULD start your ACE inhibitor naïve patient on half-dose ACE inhibitor for a month before switching sacubitril/valsartan……**

Practicing physician: comfort vs. benefit

- My patient is “stable” on current therapy
- Why change anything?
- I’ll wait and see how he is doing

763 of 2309 (33%) of FIRST primary endpoints (intensification of medical therapy, ED visit, HF hospitalization or CV deaths) were CV DEATHS

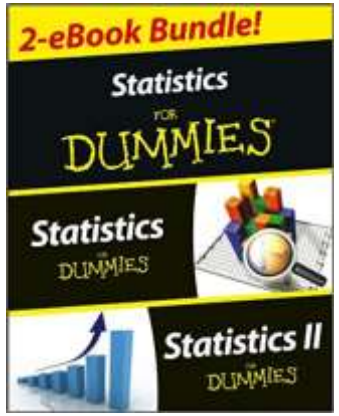
467 of these 763 deaths (61%) were SUDDEN

McMurray et al. N Eng J Med 2014;371:993-1004; Desai As et al Eur Heart J. 2015;36:1990-7.

The active run-in

- The best way to examine the differences in effect of sacubitril/valsartan vs. evidence-based dose of enalapril
- Mirror usual clinical practice
- Routinely employed in different ACEi trials (SOLVD)

Statistical nonsense



- Single trial power !?
- For class I, Level A recommendation:
  - ❖two trials with P<0.05
  - ❖a meta-analysis

PARADIGM-HF: Statistical robustness

P in a single trial	Number of trials with P <0.05 to provide same strength of evidence	PARADIGM-HF: Effect on primary endpoint	PARADIGM-HF: Effect on cardiovascular death
0.05	1		0.00008
0.00125	2		
0.00003125	3		
0.00000078	4	0.0000004	
0.0000000195	5		

Based on formula $(0.025)^n$ x2 (personal communication Stuart Pocock)

Jhund & McMurray Heart 2016

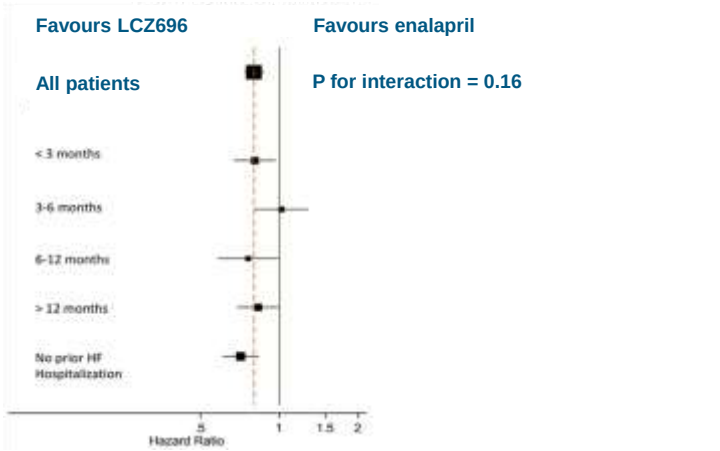
Dementia and neprilysin inhibition

- **Neprilysin is one of >20 amyloid beta-peptide clearance mechanisms in the brain – including ACE!**
- **No hard evidence that neprilysin has effect on development of dementia (or evidence in PARADIGM-HF)**
- **Neprilysin inhibition DOES reduce mortality, hospitalization and worsening of HRQL**

Dementia/cognition-related adverse events (MedRA)

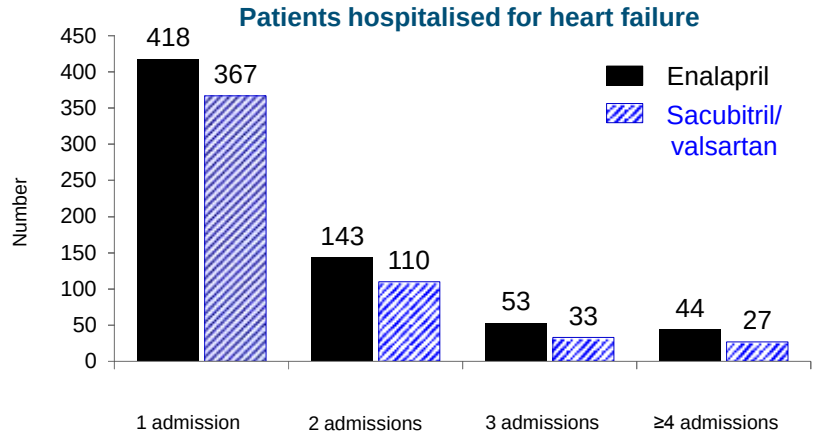
SMQ Dementia	Sacubitril/valsartan N=4203 n (%)	Enalapril N=4229 n (%)	Sac/val vs Enalapril Relative Risk (95% CI)
Broad SMQ Dementia	**86 (2.05)**	**83 (1.96)**	1.029 (0.761, 1.391)
Narrow SMQ Dementia	**12 (0.29)**	**15 (0.35)**	0.793 (0.371, 1.695)

PARADIGM-HF: Treatment effect according to prior hospitalization



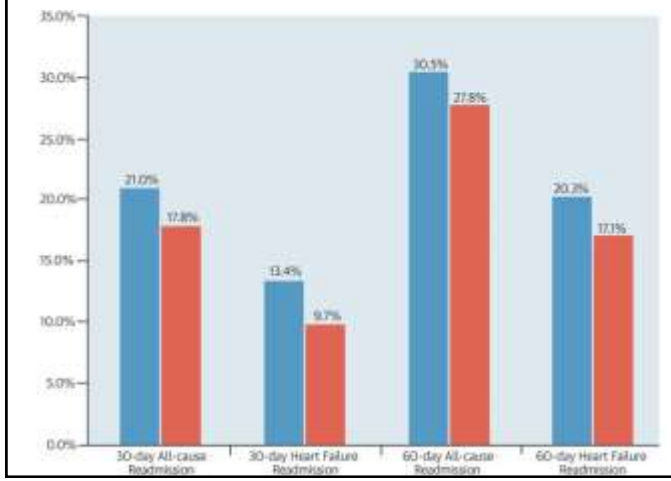
Desai AS et al. JAMA Cardiol. 2017;2(1):79–85

PARADIGM-HF: First and repeat heart failure hospitalizations



Packer M, et al. Circulation. 2015:131:54-61.

Readmission after hospitalization in PARADIGM-HF



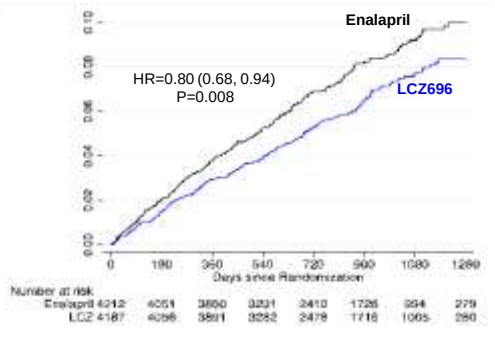
Enalapril

LCZ696

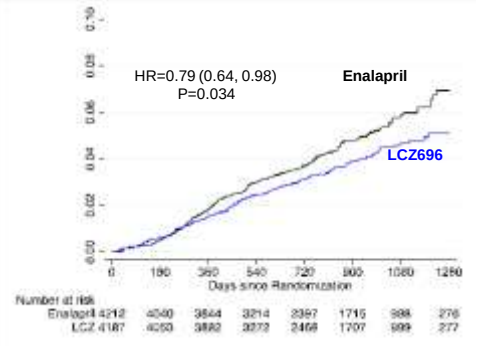
Desai AS et al., JACC 2016; 68:241-248

Sacubitril/valsartan (LCZ696) and main modes of death in HF

Sudden death

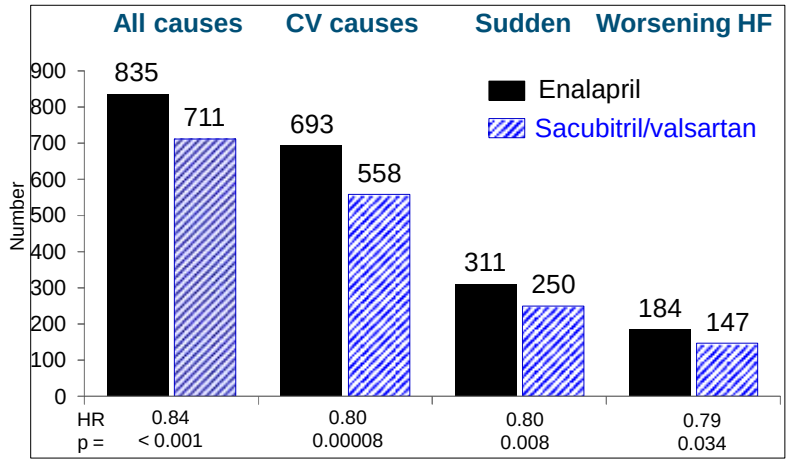


Death due to worsening HF



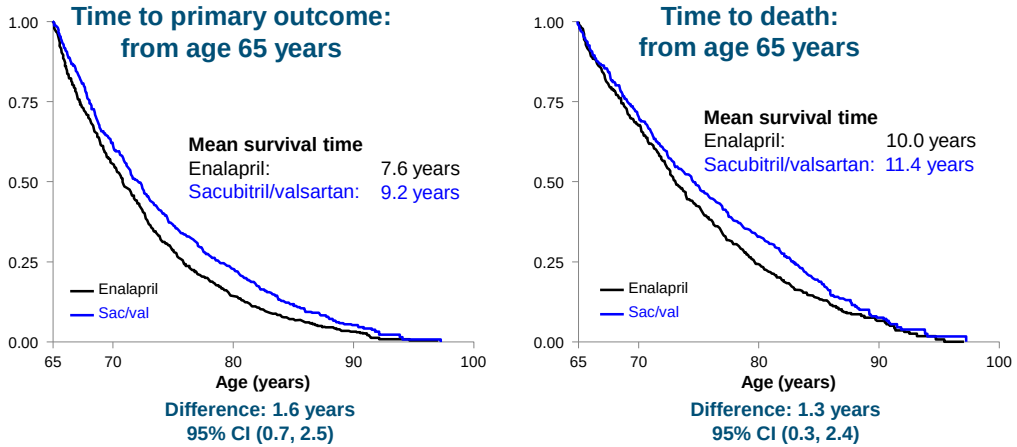
Desai AS et al. JAMA Cardiol. 2017;2(1):79–85

PARADIGM-HF: Cause/mode of death



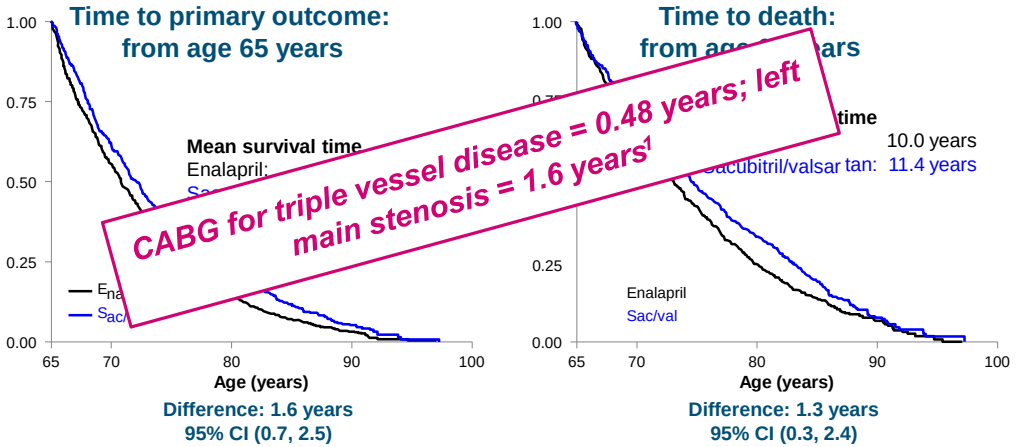
McMurray JJV, et al. N Engl J Med. 2014;371:993-1004. Desai AS, et al. Eur Hear J. 2015:38:1990-7.

PARADIGM-HF: estimated long-term event-free survival gain at various ages



Claggett B, et al N Engl J Med. 2015;373:2289-90.

PARADIGM-HF: estimated long-term event-free survival gain at various ages



Claggett B, et al N Engl J Med. 2015;373:2289-90.

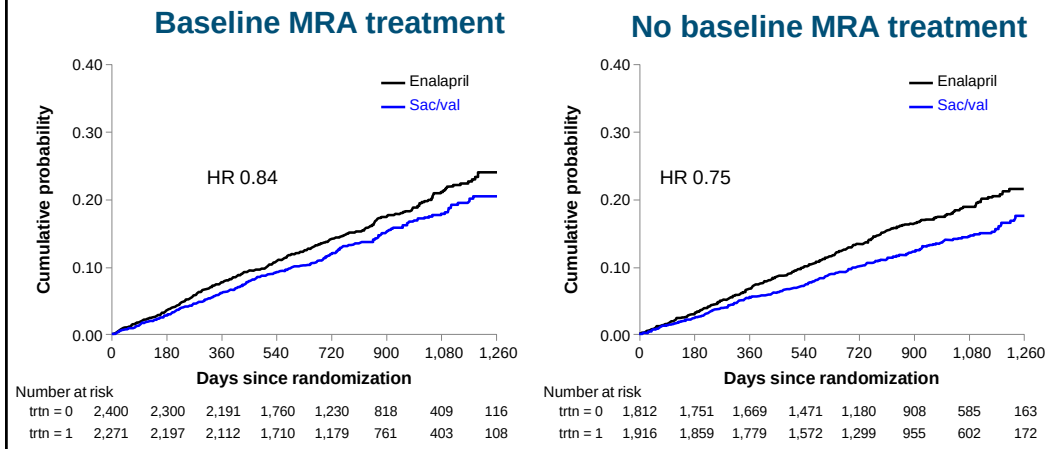
Incremental benefits of sacubitril/valsartan according to background β-blocker use

Cardiovascular death or HF hospitalization

		Number	HR	95% CI	Interaction P value
Beta-blocker	No	588	0.61	0.45-0.83	0.062
	Yes	7811	0.82	0.75-0.90	
Beta-blocker % target dose	<50%	4167	0.82	0.75-0.94	0.908
	≥50%	3644	0.82	0.72-0.92	

Okumura N, et al. JACC 2016;67:1217-050 .

Additional benefit of sacubitril/valsartan in patients taking an MRA: Cardiovascular death



Okumura N, et al. JACC 2016;67:1217-050 .

PARADIGM-HF: Risk of hyperkalaemia

Research

JAMA Cardiology | Original Investigation

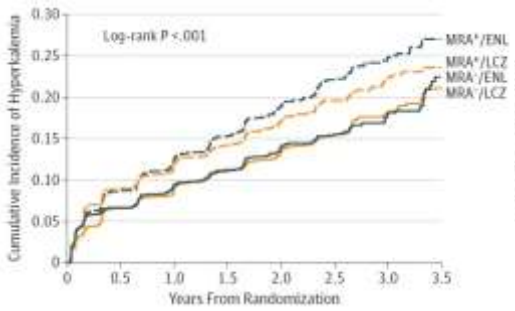
Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril
A Secondary Analysis of the PARADIGM-HF Trial

Akshay S. Desai, MD, MPH; Orly Vardeny, PharmD; Brian Claggett, PhD; John J. V. McMurray, MD; Milton Packer, MD; Karl Swedberg, MD, PhD; Jean L. Rouleau, MD; Michael R. Zile, MD; Martin Lefkowitz, MD; Victor Shi, MD; Scott D. Solomon, MD

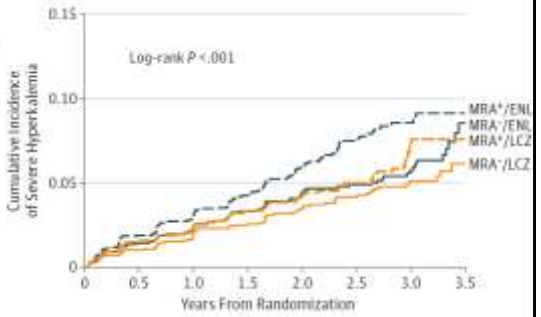
Desai AS et al. JAMA Cardiol. 2017;2(1):79–85

PARADIGM-HF: Incidence of hyperkalaemia according to MRA use at baseline

K^+ >5.5 mmol/l

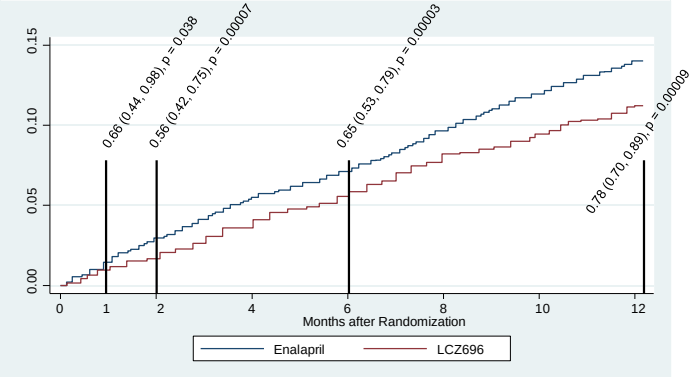


K^+ >6.0 mmol/l

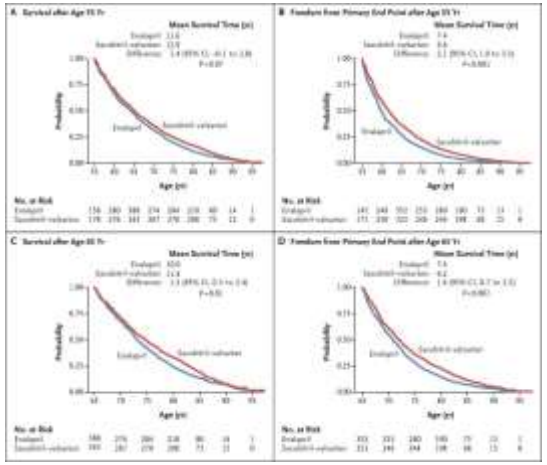


Desai AS et al. JAMA Cardiol. 2017;2(1):79–85

Early Benefit of LCZ696



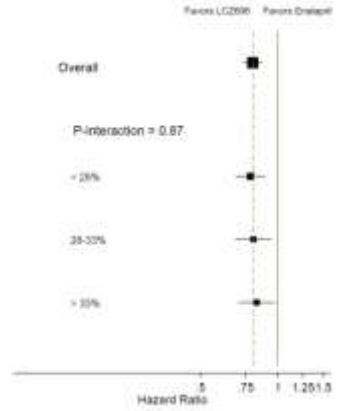
Estimated Long-Term Benefit of 1.5 to 2 Years using Actuarial Methods



Claggett et al. NEJM 2015

LCZ was effective across the spectrum of Ejection Fraction

PARADIGM Enrolled > 2000 patients with EF between 35-40%!



Solomon et al. Circulation HF 2016

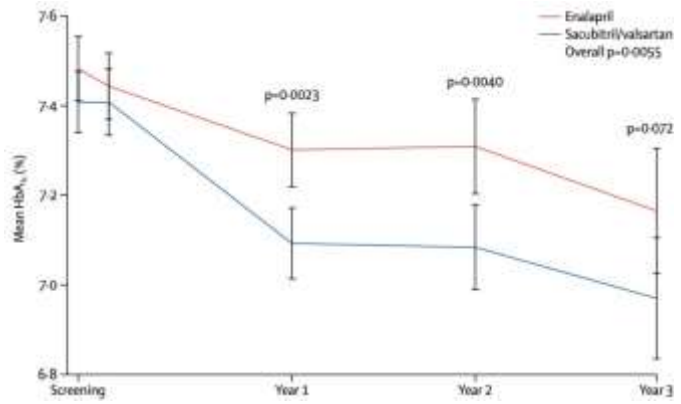
- **A randomized, double blind, trial to evaluate the long-term efficacy and safety profile of the angiotensin receptor neprilysin inhibitor (ARNI), LCZ696, compared with valsartan, in patients with heart failure with preserved ejection fraction (HFpEF)**

Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial

Jelena P Seferovic, Brian Claggett, Sara B Seidelmann, Ellen W Seely, Milton Packer, Michael R Zile, Jean L Rouleau, Karl Swedberg, Martin Lefkowitz, Victor C Shi, Akshay S Desai, John J V McMurray, Scott D Solomon

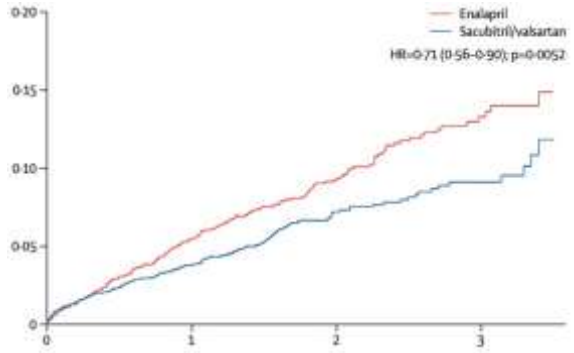
- Heart failure (HF) and diabetes mellitus (DM) frequently co-exist, and DM is an independent risk factor for HF progression
- In PARADIGM-HF, new onset DM was a pre-specified exploratory outcome. Sacubitril/valsartan did not reduce new onset DM in PARADIGM-HF although the number of patients with new onset diagnosis was small (n = 84).
- Another dual neprilysin ACE inhibitor, omapatrilat, improved insulin sensitivity in preclinical studies[2], and sacubitril/valsartan improved insulin sensitivity in obese hypertensive patients[3].
- We assessed the effect of sacubitril/valsartan on glycemic control and on new use of anti-diabetic medications

Improvement in Glycemic Control in Patients treated with Sacubitril/Valsartan



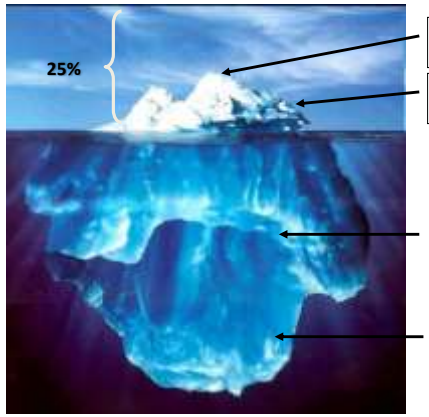
Seferovic et al. Lancet DM 2017

Reduced New Use of Insulin



Seferovic et al. Lancet DM 2017

Who is treating heart failure patients?



CARDIOLOGIST

INTERNAL MEDICINE SPECIALIST

GENERAL PRACTITIONER

OTHER HEALTH CARE PROVIDERS

Hoes et al., Eur Heart J 2008; 19:L2

Vertical integration of the network for heart failure treatment

Inotropes, Devices

Transplant

Specialist/Cardiologist

HF Clinic

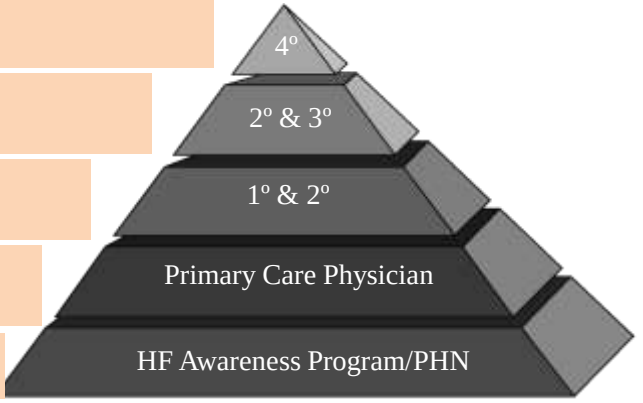
Dosing Optimization-

Family MD & Specialist

Recognition-Initial Therapy

- Family MD

Community Based Awareness/Understanding



European Journal of Heart Failure (2013) 15, 947–959
doi:10.1093/eurjhf/hft092

Organization of heart failure management in European Society of Cardiology member countries: survey of the Heart Failure Association of the European Society of Cardiology in collaboration with the Heart Failure National Societies/Working Groups

Petar M. Seferović*, Stefan Stoerk, Gerasimos Filippatos, Viacheslav Mareev, Ausra Kavoliuniene, Arsen D. Ristić, Piotr Ponikowski, John McMurray, Aldo Maggioni, Frank Ruschitzka, Dirk J. van Veldhuisen, Andrew Coats, Massimo Piepoli, Theresa McDonagh, Jillian Riley, Arno Hoes, Burkert Pieske, Milan Dobrić, Zoltan Papp, Alexandre Mebazaa, John Parissis, Tuvia Ben Gal, Dragos Vinereanu, Dulce Brito, Johann Altenberger, Plamen Gatzov, Ivan Milinković, Jaromir Hradec, Jean-Noel Trochu, Offer Amir, Brenda Moura, Mitja Lainscak, Josep Comin, Gerhard Wikström, and Stefan Anker on behalf of the Committee of National Heart Failure Societies or Working Groups of the Heart Failure Association of the European Society of Cardiology†