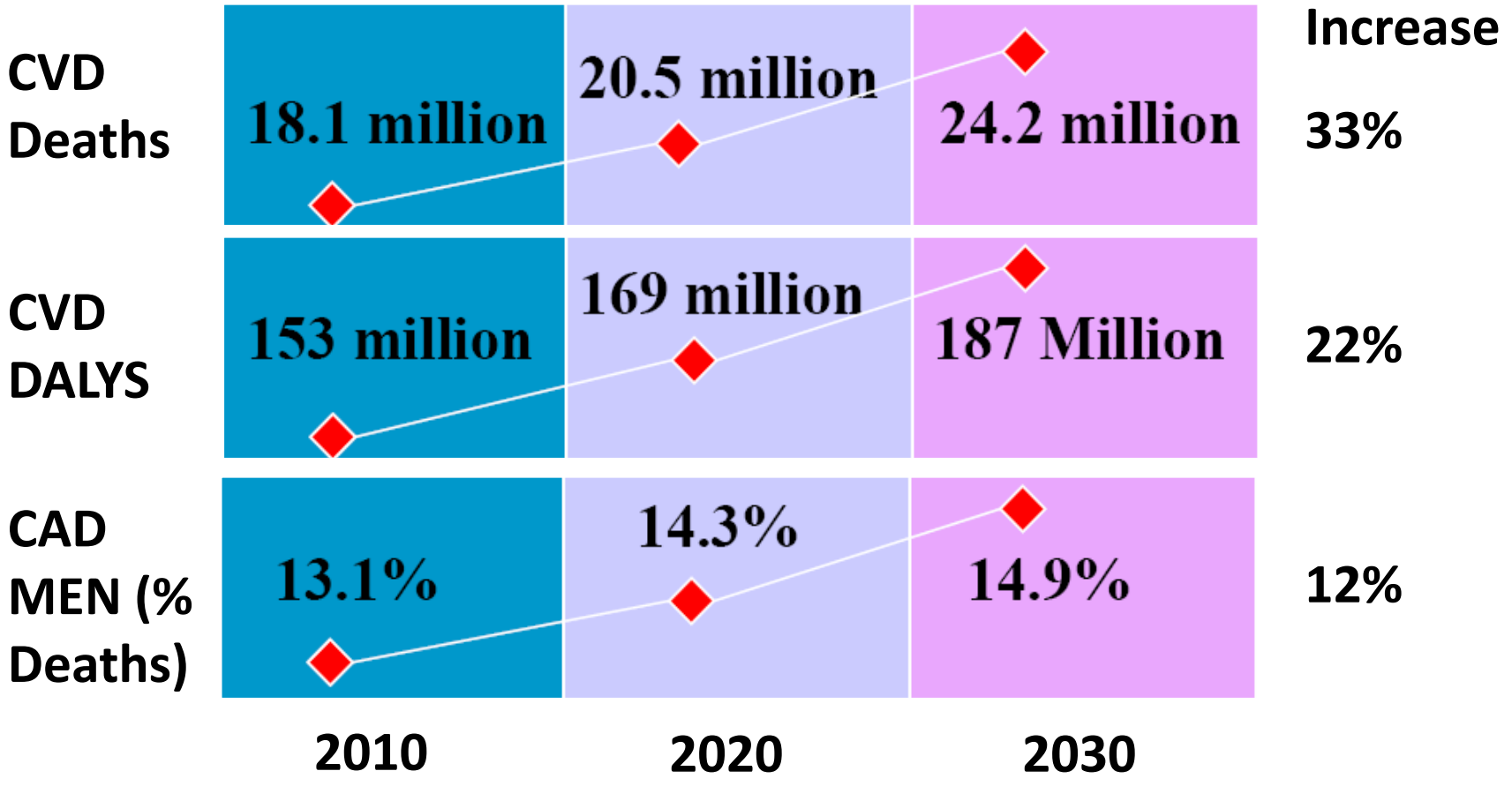
LCZ696: LA NUOVA RIVOLUZIONE NELLA TERAPIA DELLO SCOMPENSO CARDIACO

Dario Leosco

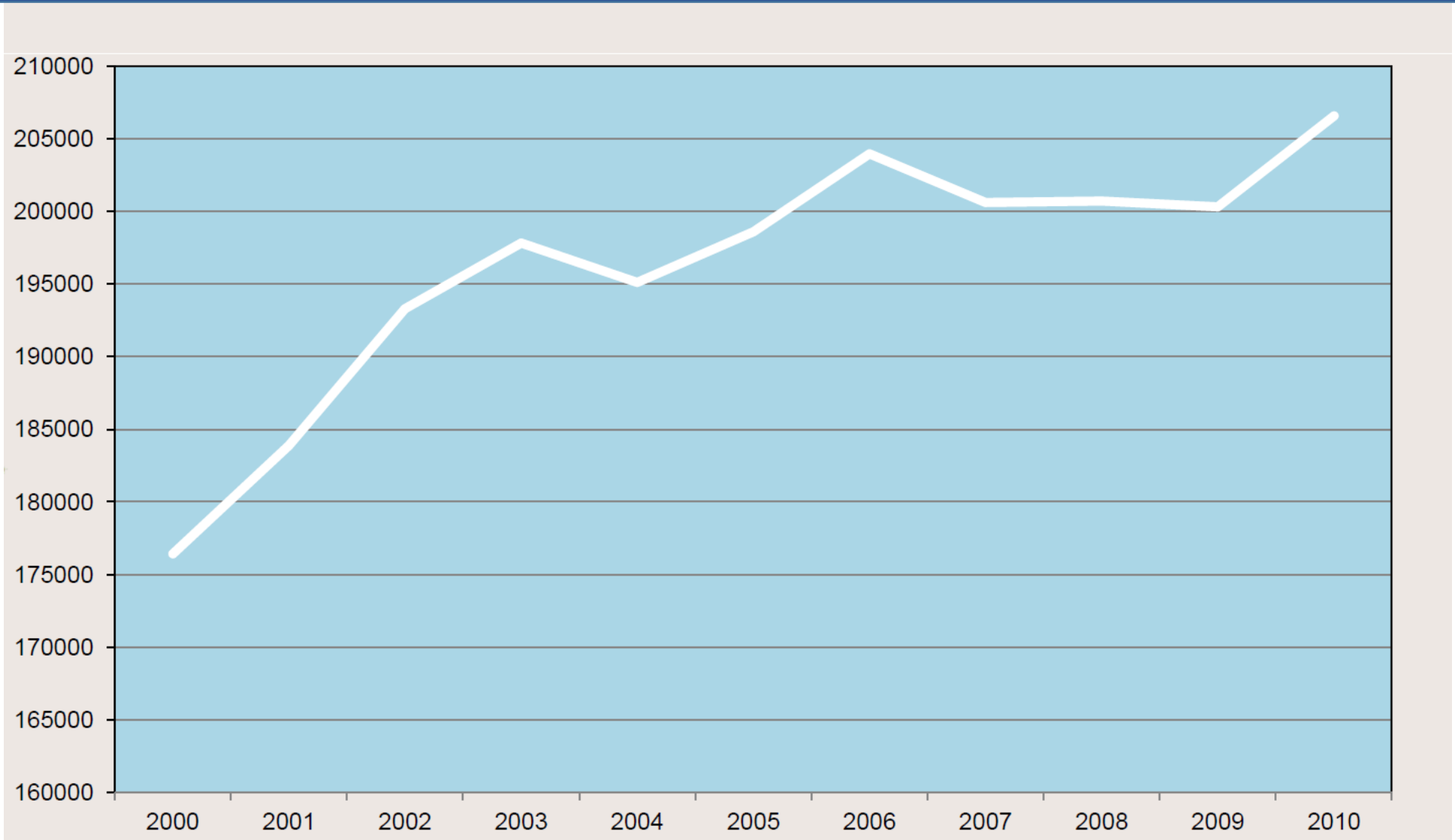
Università di Napoli Federico II

Projected changes in cardiovascular diseases



WHO Atlas of Heart Disease and Stroke '04

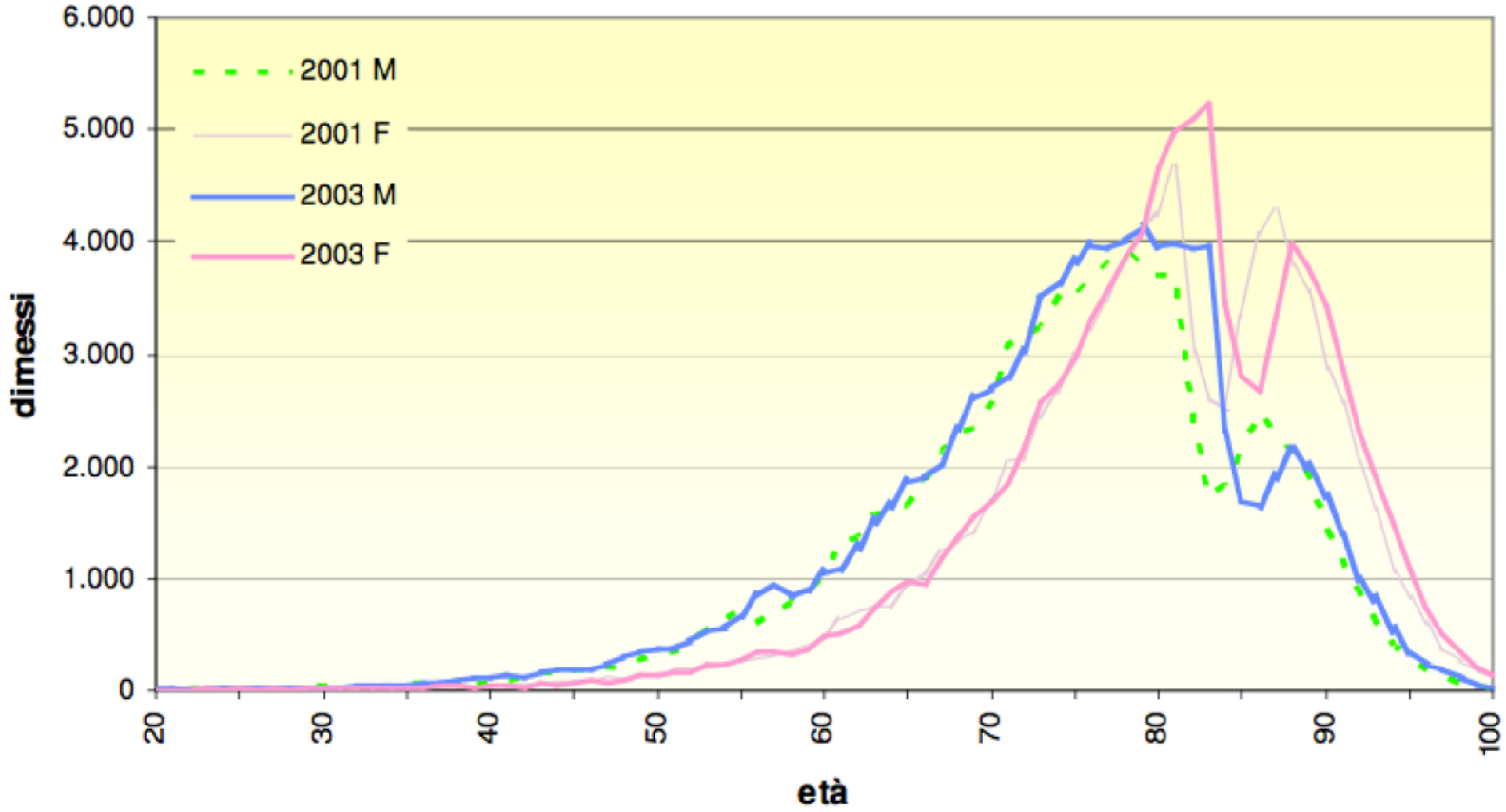
Ricoveri per scompenso cardiaco (DRG 127) in Italia
(Fonte Ministero della Salute)



Ricoveri per scompenso cardiaco (DRG 127) in Italia
(Fonte Ministero della Salute)

• Tasso ospedalizzazione	4-5/mille abitanti
• Andamento negli anni progressivo	aumento
• Durata media ricovero	9 gg
• Reparto di ricovero	Medicina 60% Cardiologia 25% Altri reparti 15%

Ricoveri per scompenso cardiaco in Italia per età
(Fonte Ministero della Salute)



Fonte: Ministero della Salute – SDO 2001 e 2003

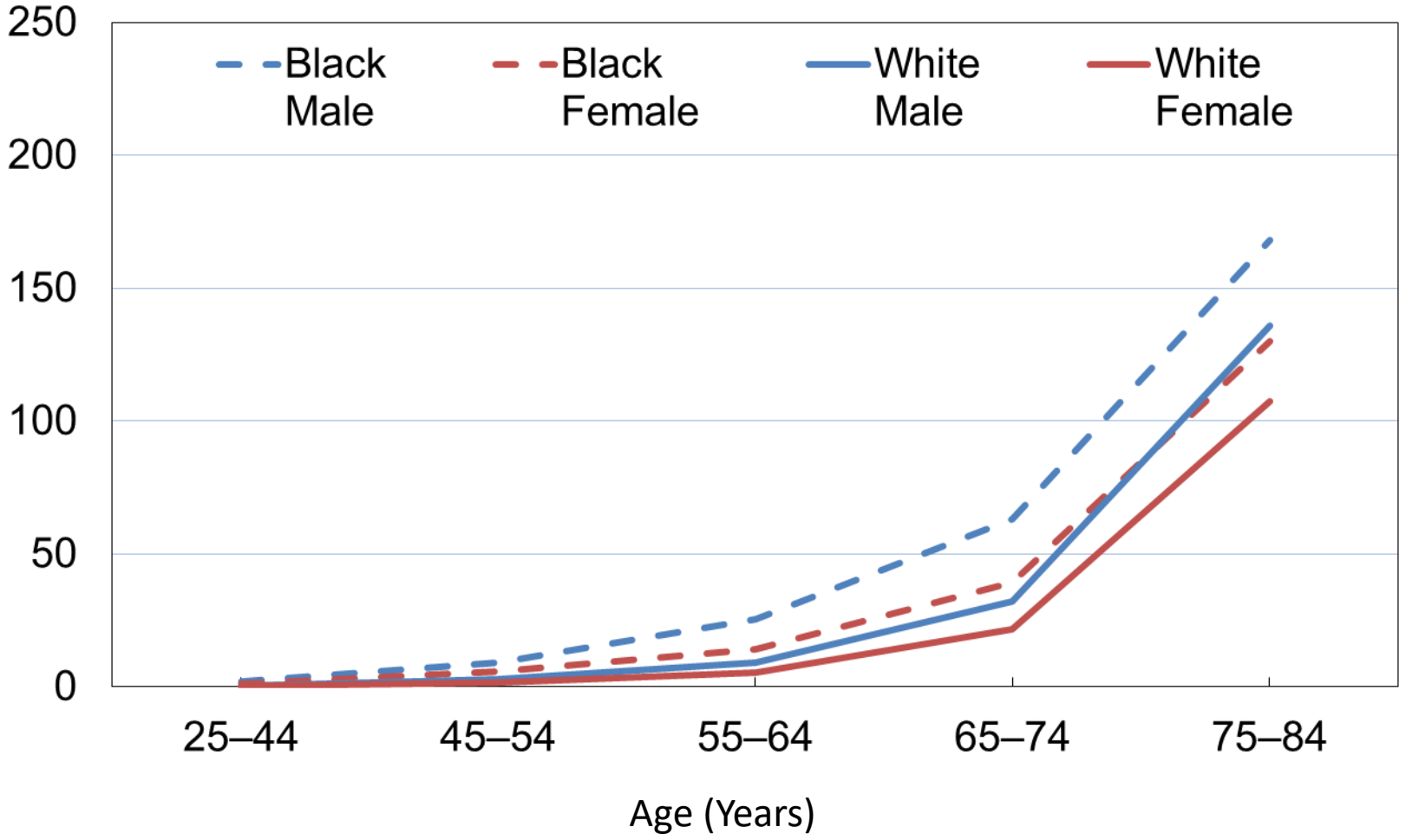
Re-ospedalizzazioni per riacutizzazioni di scompenso cardiaco

USA:	25%	a 1 mese
	50%	a 6 mesi
Italia:	30-40%	a 6 mesi

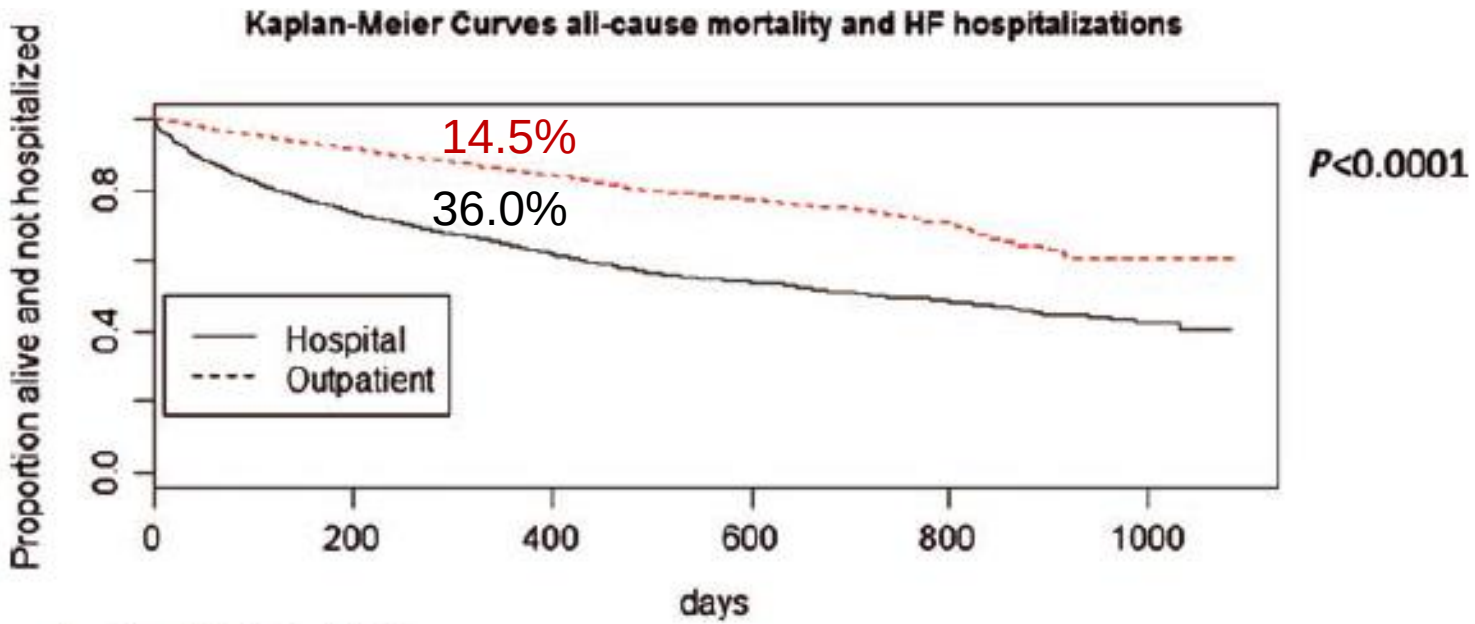
Andamento negli anni:
incremento progressivo

Significato prognostico negativo:
re-ospedalizzazioni associate a prognosi peggiore

Death Rates for HF* as the Underlying Cause by Age, Race, & Sex. U.S., 2008



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

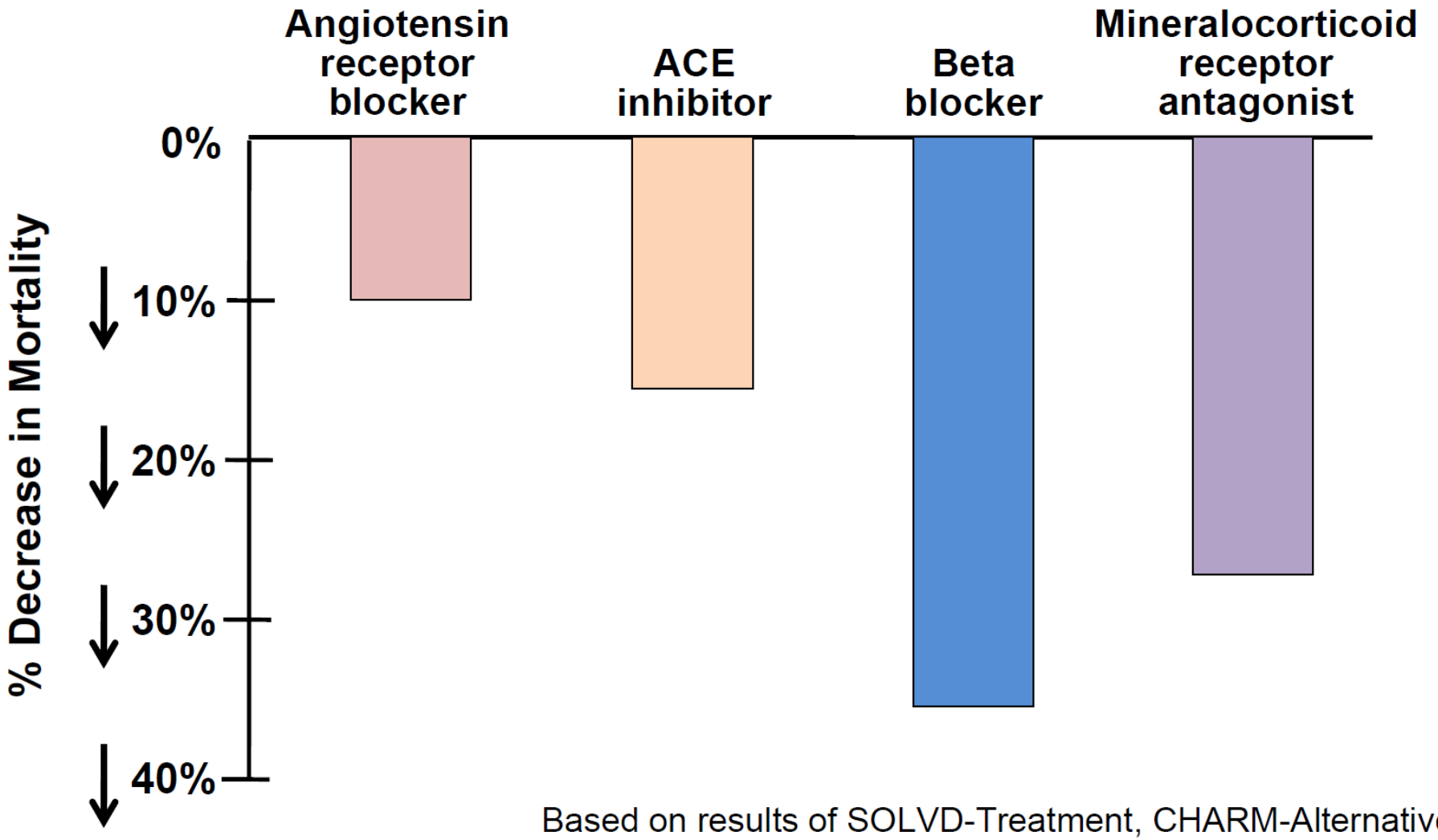


Number of Patients at Risk:

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

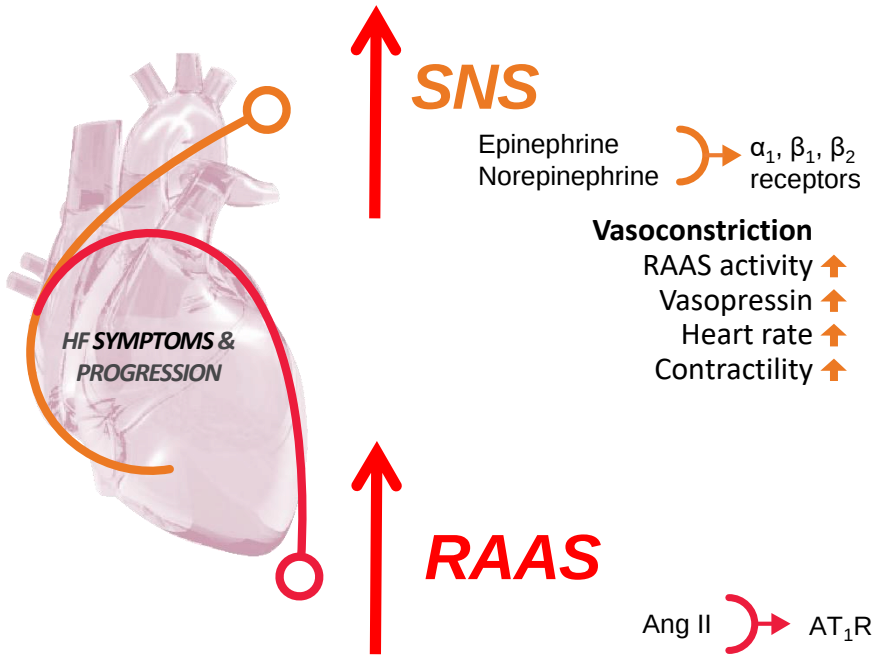
Crespo-Leiro et al. Eur J Heart Fail 2016; 18:613-625

The potent pharmacologic battery for HF treatment

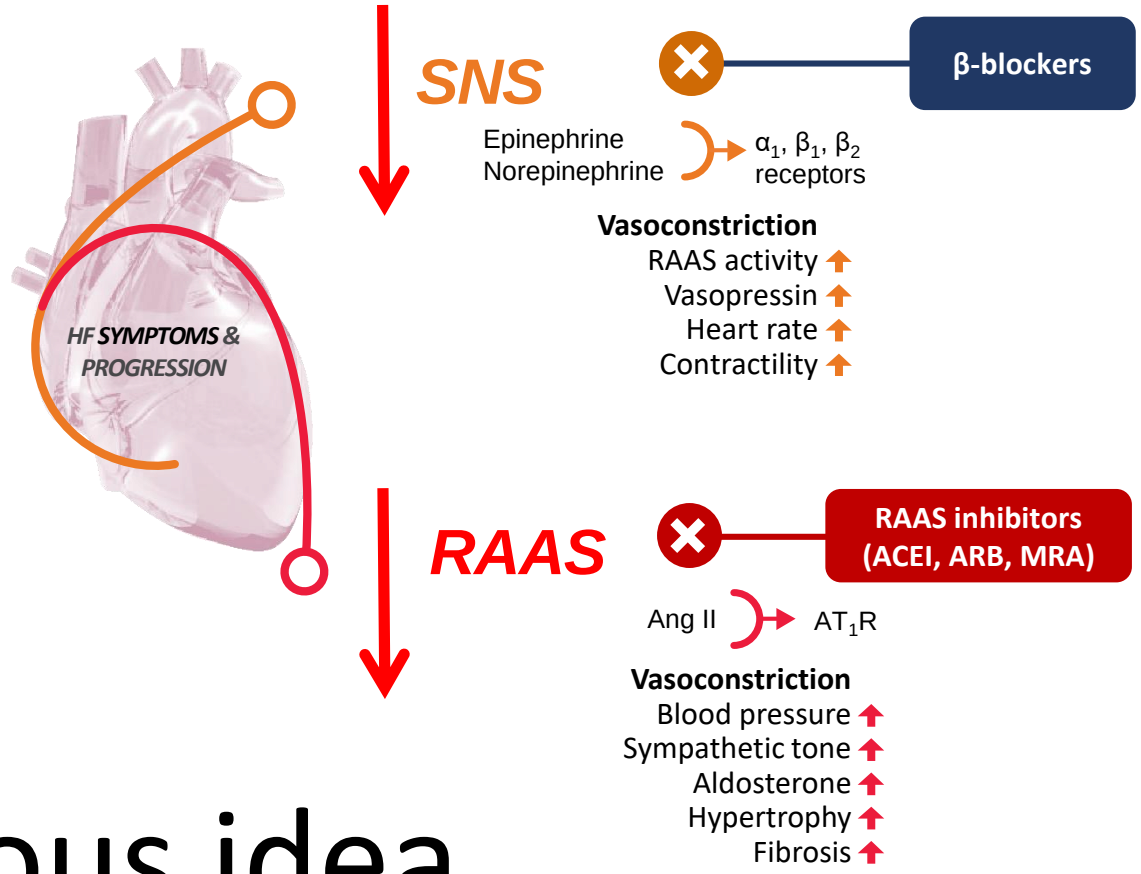


Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

Compensatory mechanisms in the initial phase of HF become detrimental in the long term

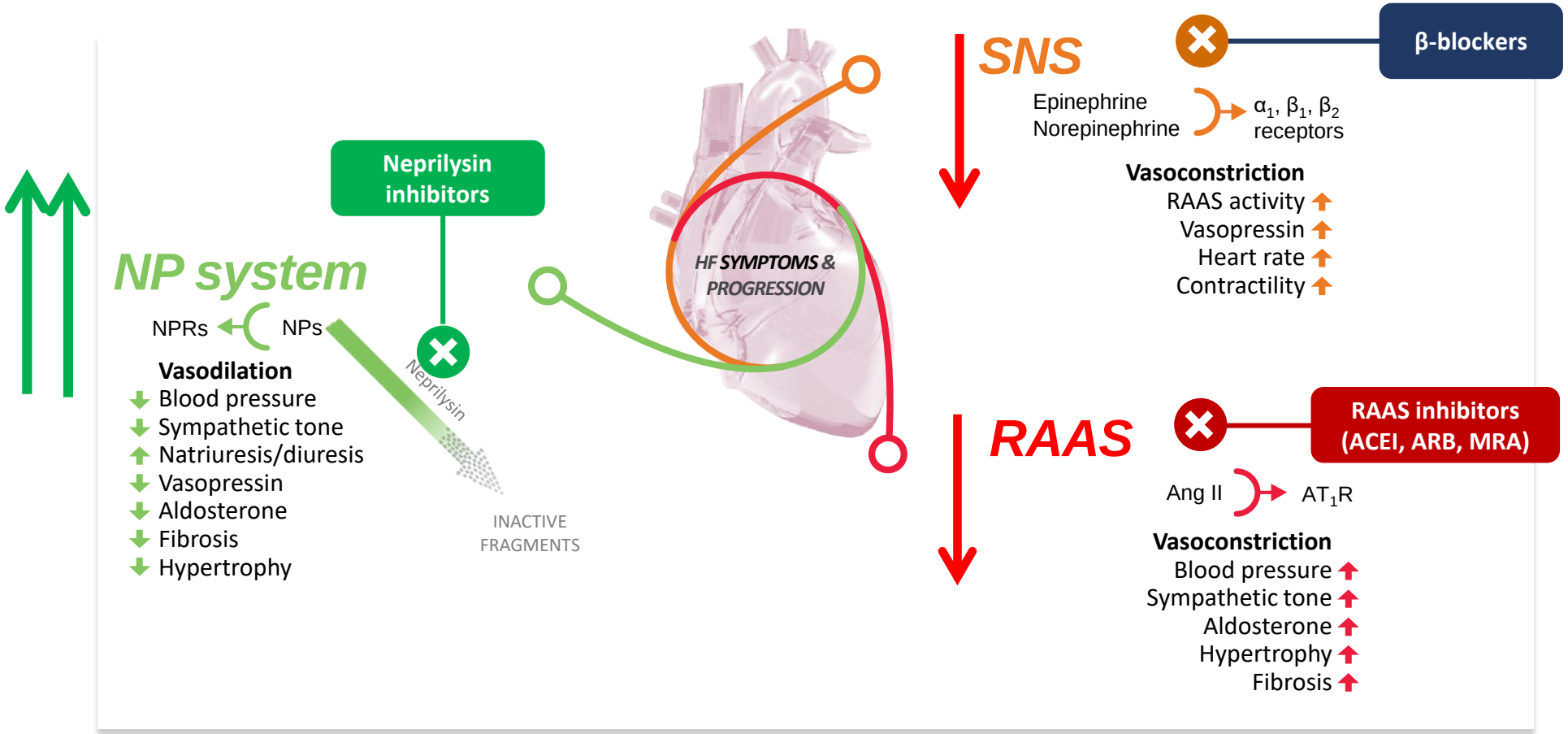


Therefore..! Why do not block SNS and RAAS?

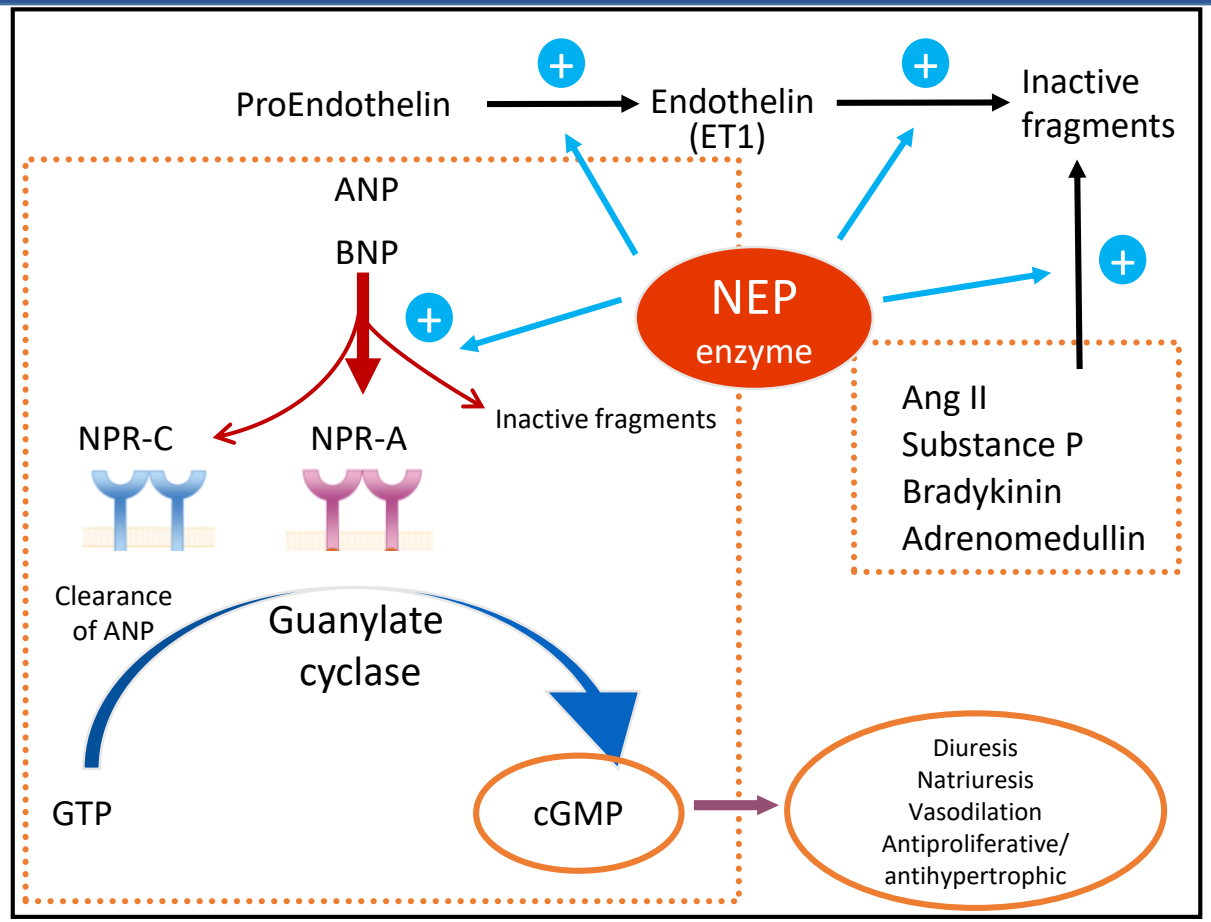


A tremendous idea

Evolution of pharmavologic approaches in HF: Neprilysin inhibition

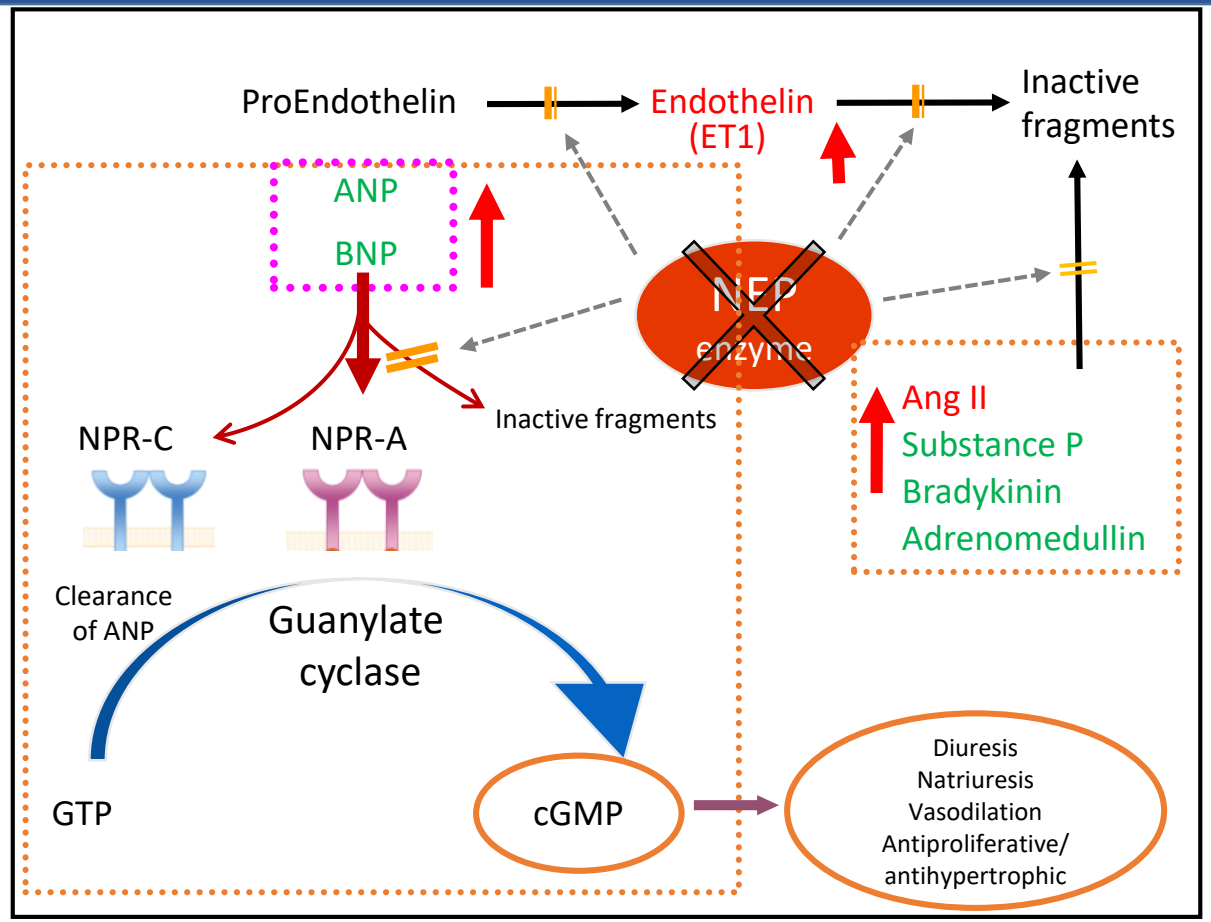


Neprilysin is responsible for NP degradation, but not only...



- **NEP is the major enzyme responsible for degrading the NPs (ANP, BNP, CNP)[1,3-5]**
- **NEP catalyzes the degradation** of other vasoactive peptides:
  - **vasodilating peptides**
    - substance P[6]
    - bradykinin[1]
  - **vasoconstrictor peptides**
    - ET-1[7]
    - Ang II[1]
- NEP converts big ET-1 to the active vasoconstrictor peptide ET-1[8]

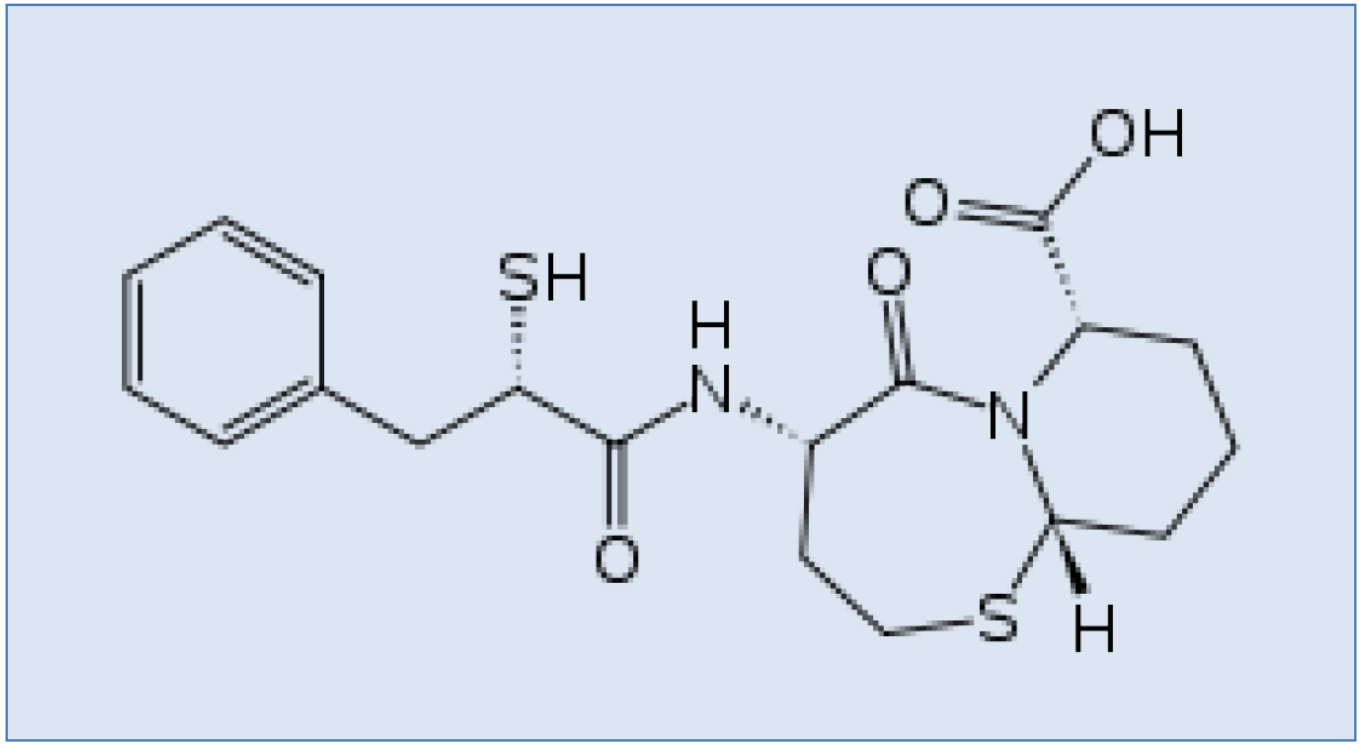
Neprilysin inhibition enhances the effects of NPs and of other vasoactive peptides



- **Neprilysin (NEP) is the major enzyme responsible for degrading NPs[5]**
  - BNP, not NT-proBNP, is a NEP substrate[6]
- **Inhibition of NEP enhances the effects of NPs[7]**
- **Studies suggest the potential effects of NEP inhibitors may be offset by an increase in Ang II levels[2,5,7]**

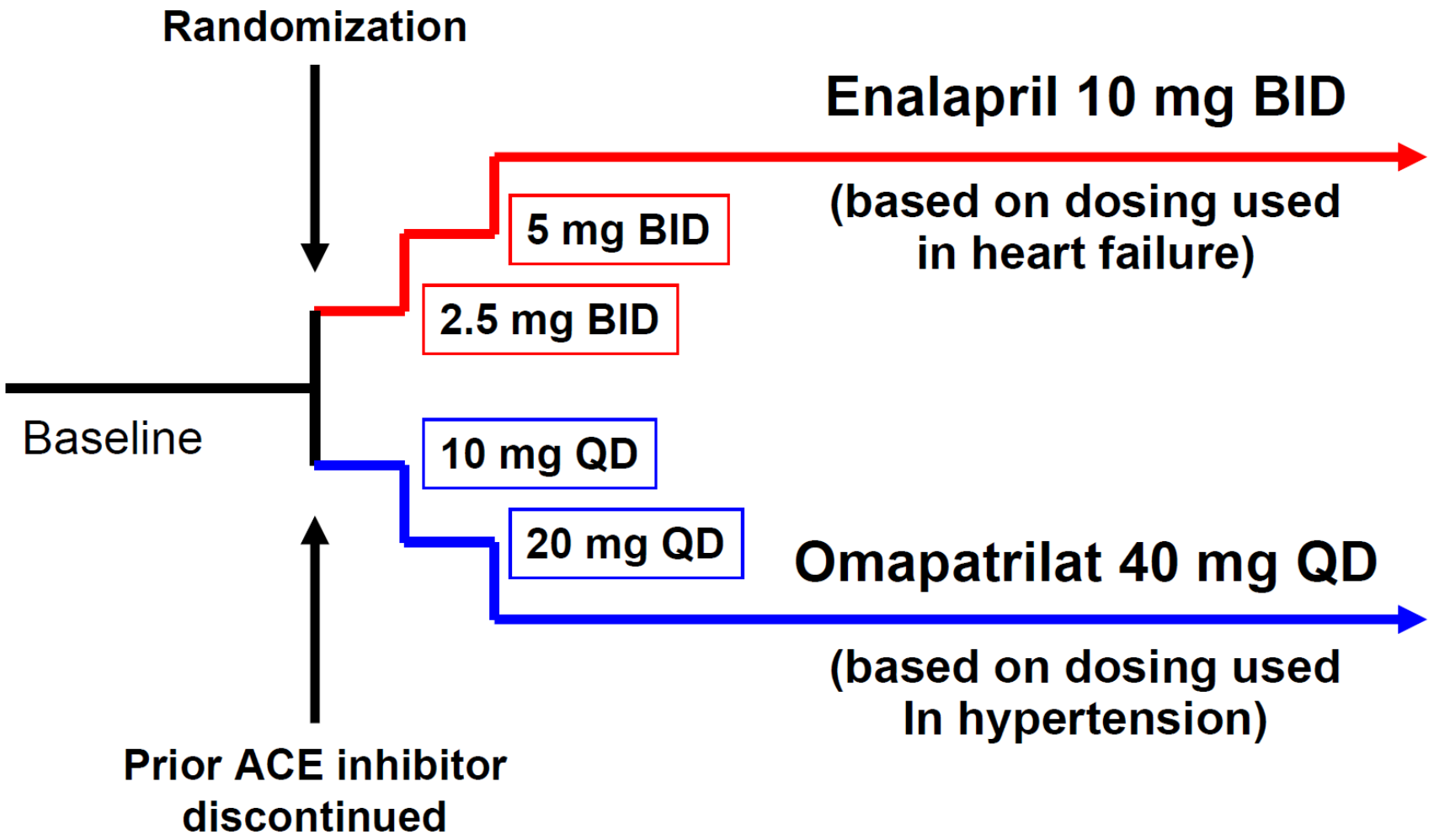
Simultaneous inhibition of Neprilysin and ACE WHY NOT ???

Omapatrilat

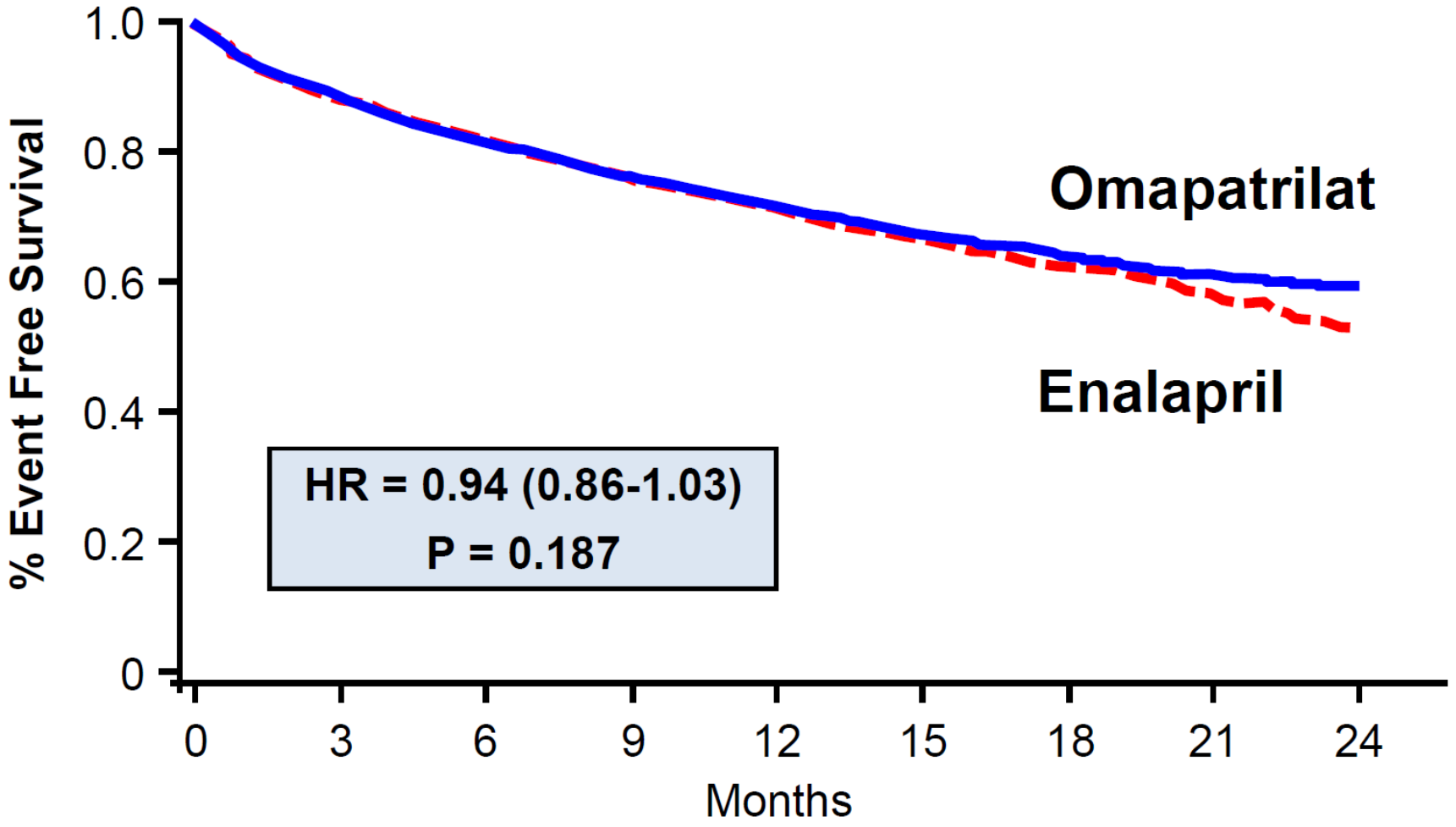


Dual inhibitor of ACE and neprilysin

Design of the Overture trial (n=5770)



OVERTURE: Death or hospitalizations for HF
Primary endpoint



Effects of Omapatrilat in the OCTAVE trial

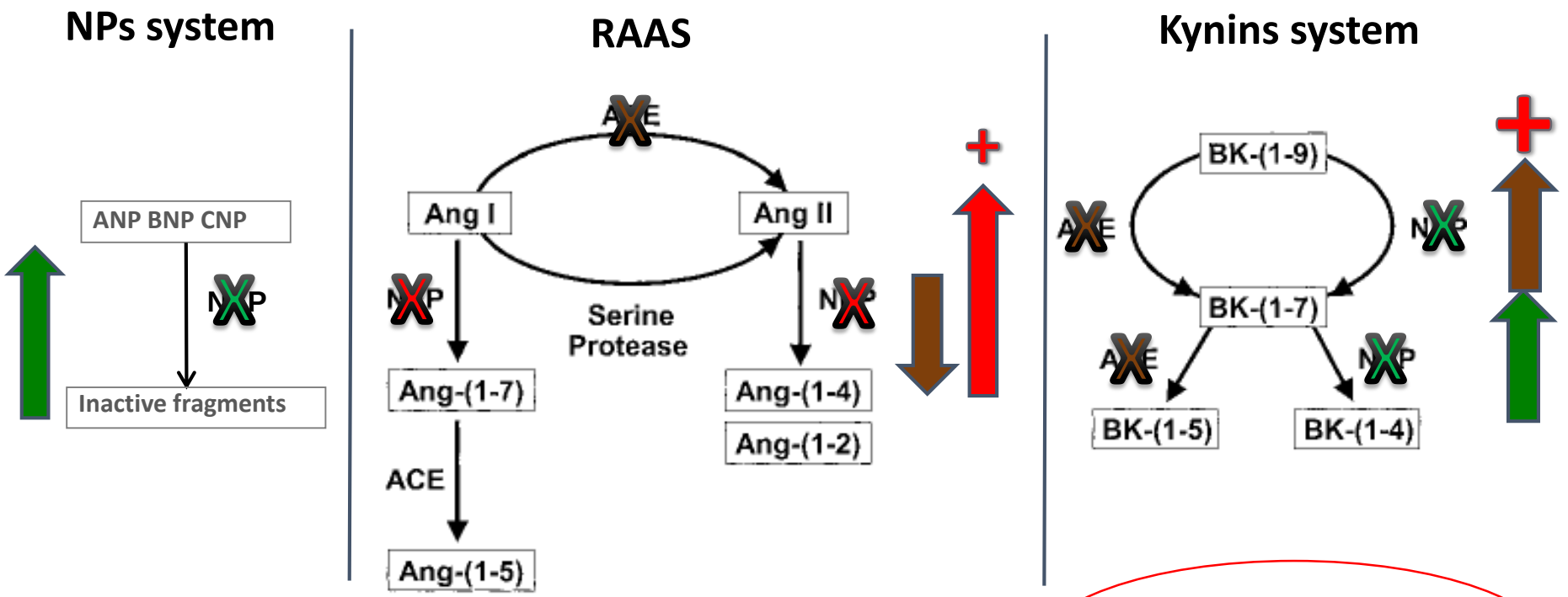
Incidence of angioedema in 25,302 patients with hypertension

2.17%	vs	**0.68%**
Omapatrilat		**ACE inhibitor**

Some of the cases were life-threatening

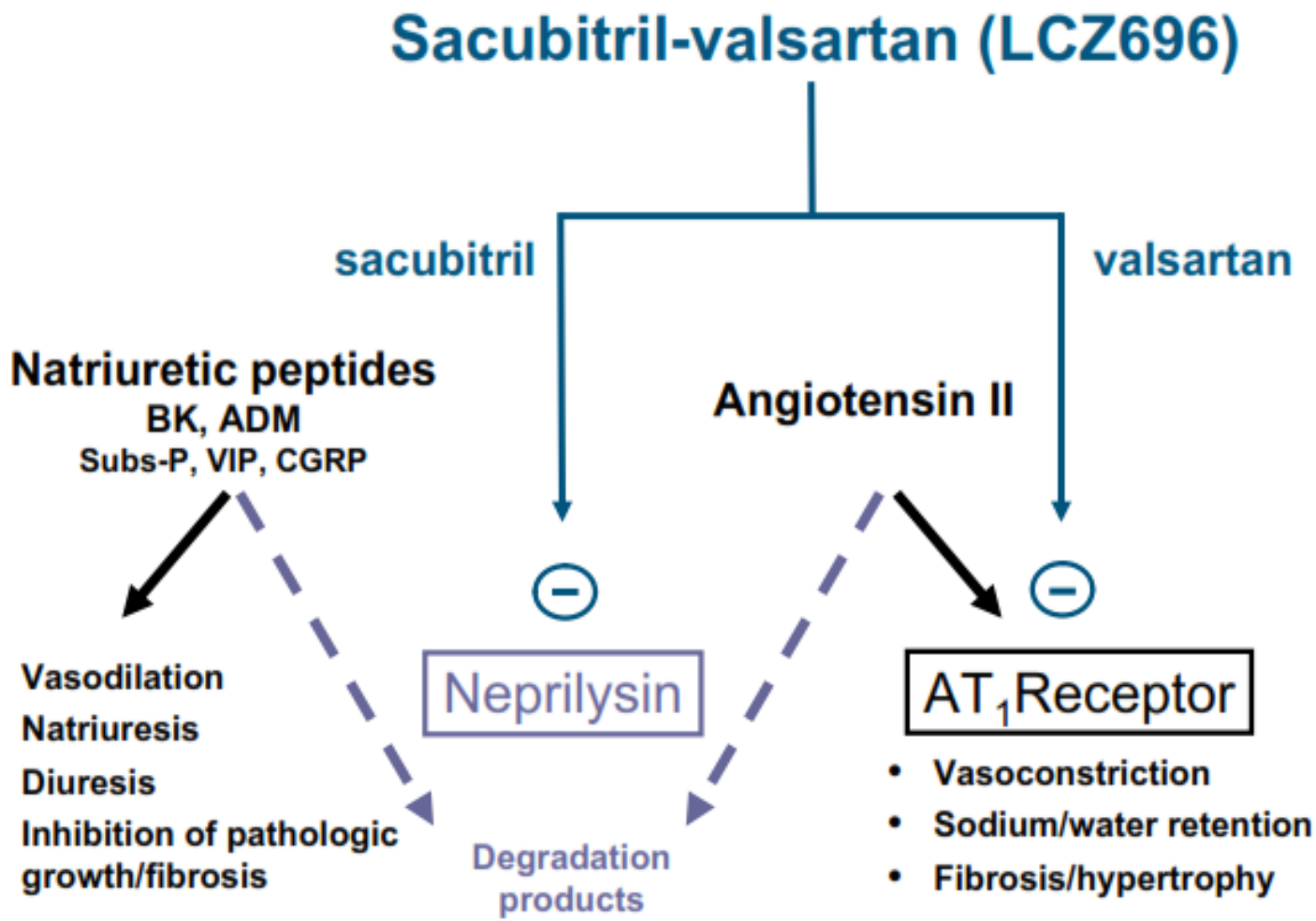
Neprilysin/ACE inhibition effects

Neprilysin/ACE inhibitor (Omapatrilat)



exceded activation = WARNING!!

Angiotensin Receptor Neprilysin Inhibition (ARNI)



McMurray Eur J Heart Fail. 2015;17:242-7

A Comparison of Angiotensin Receptor-Neprilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

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

Aim of the PARADIGM-HF trial

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

LCZ696 400 mg daily ⟺ **Enalapril 20 mg daily**

SPECIFICALLY DESIGNED TO REPLACE CURRENT USE OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AS THE CORNERSTONE OF THE TREATMENT OF HEART FAILURE

PARADIGM-HF

- Largest clinical trial ever in chronic heart failure
- Designed prior to obtaining any Phase I or II data in patients with heart failure.
- Carried out without any Phase II “proof-of-concept” or dose-finding study
- First trial designed to evaluate the effect of a drug on cardiovascular mortality in 15 years.

PARADIGM-HF was designed to show incremental effect on cardiac death

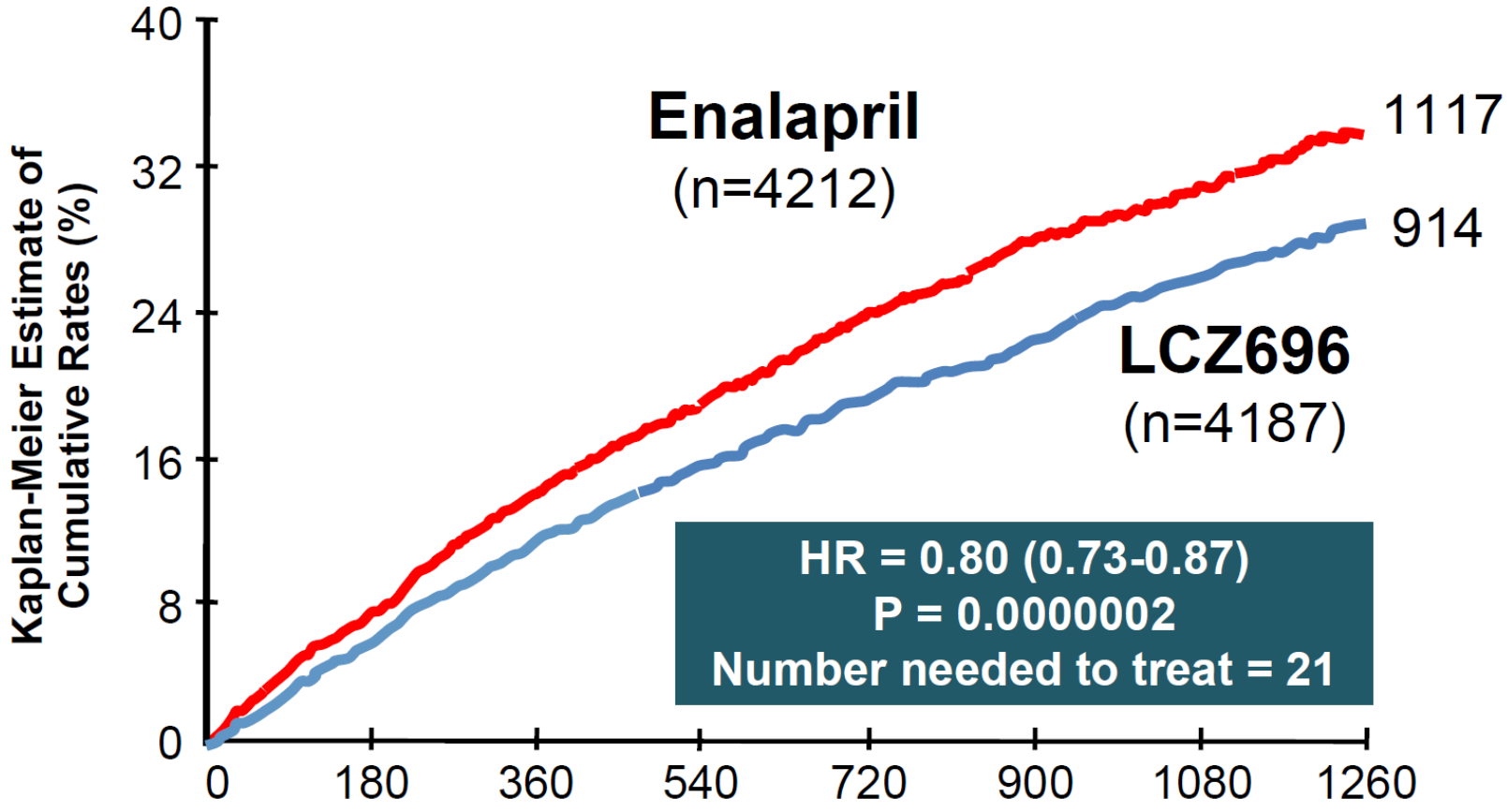
Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial

The sample size of the trial was determined by effect on **cardiovascular mortality**, not the primary endpoint

The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on **cardiovascular mortality** (in addition to the primary endpoint)

Difference in cardiovascular mortality of 15% between LCZ696 and enalapril was prospectively identified as being clinically important (n=8000 yielded 80% power)

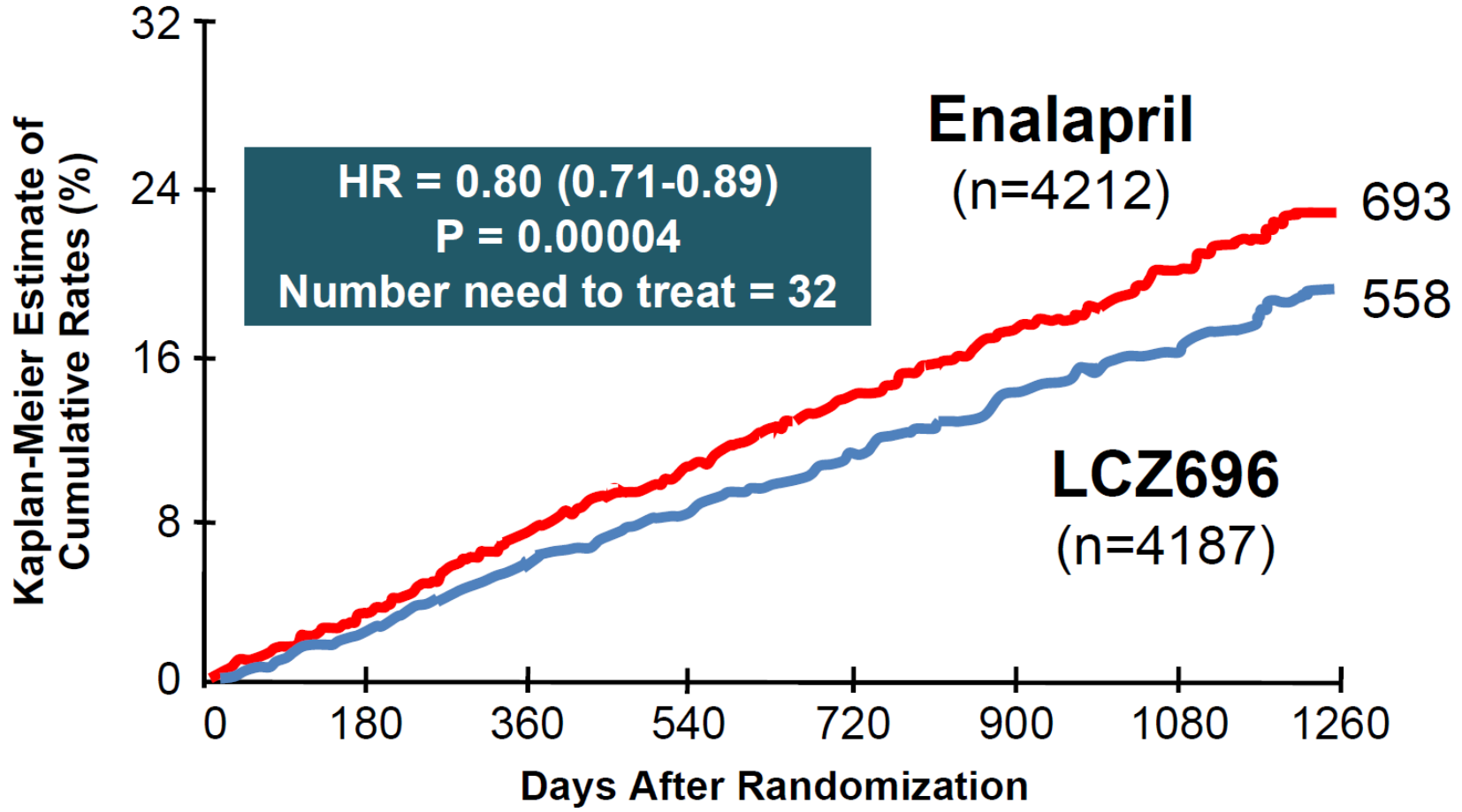
PARADIGM-HF: Cardiovascular Death or HF Hospitalization (Primary end-point)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

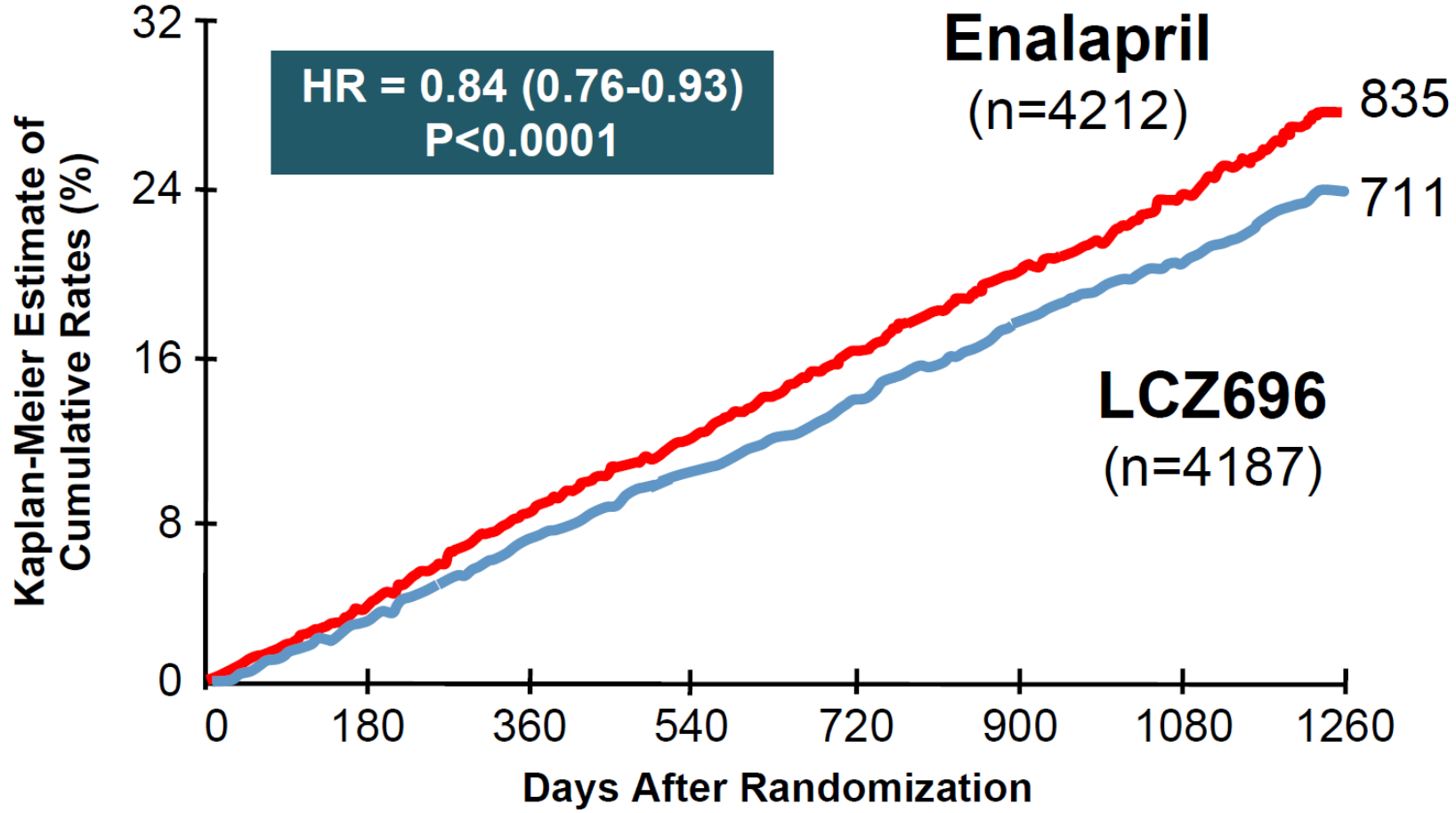
PARADIGM-HF: Cardiovascular Death



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: All cause Death



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: Additional findings

LCZ696 was also *more effective* than enalapril in . . .

- Reducing the risk of a heart failure hospitalization by *incremental* 21%
- *Incrementally* improving symptoms and physical limitations of heart failure

LCZ696 was *better tolerated* than enalapril . . .

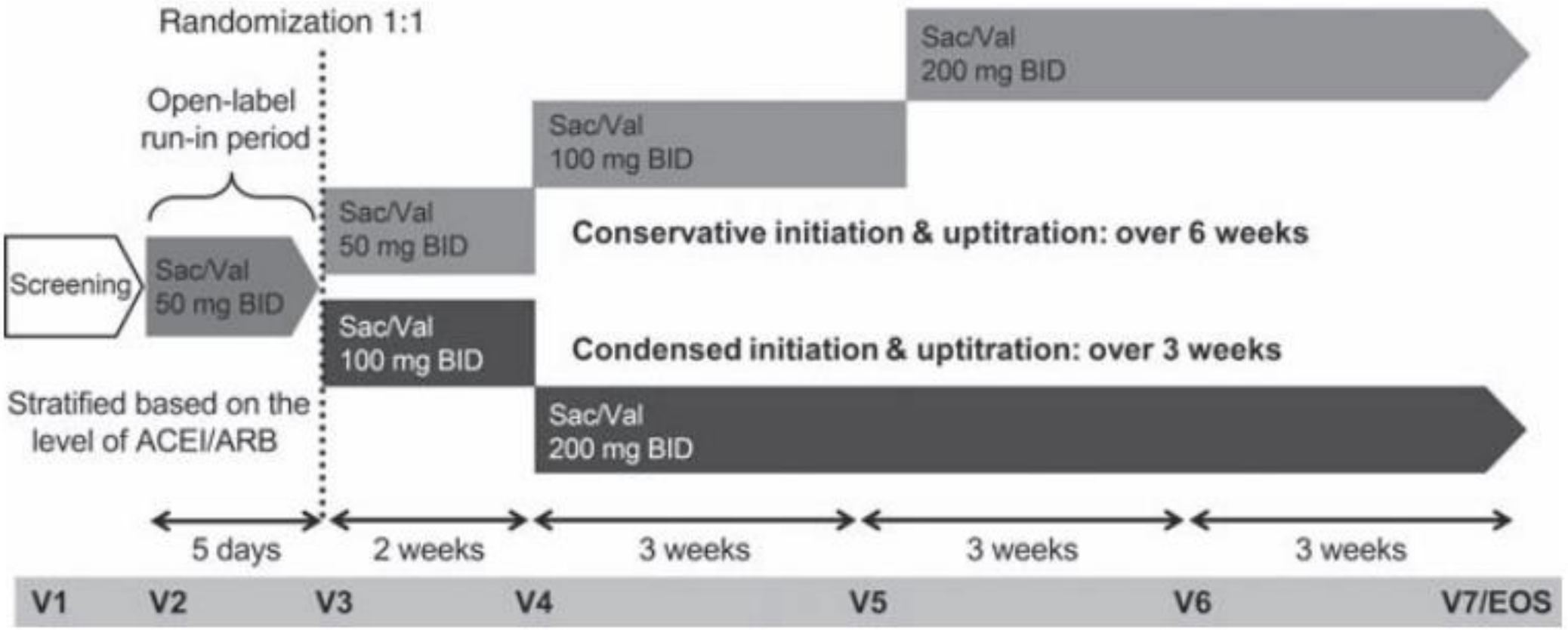
- Less likely to cause cough, hyperkalemia or renal impairment or be discontinued for an adverse event
- More hypotension, but no increase in discontinuations
- No increase in risk of serious angioedema

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine > 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

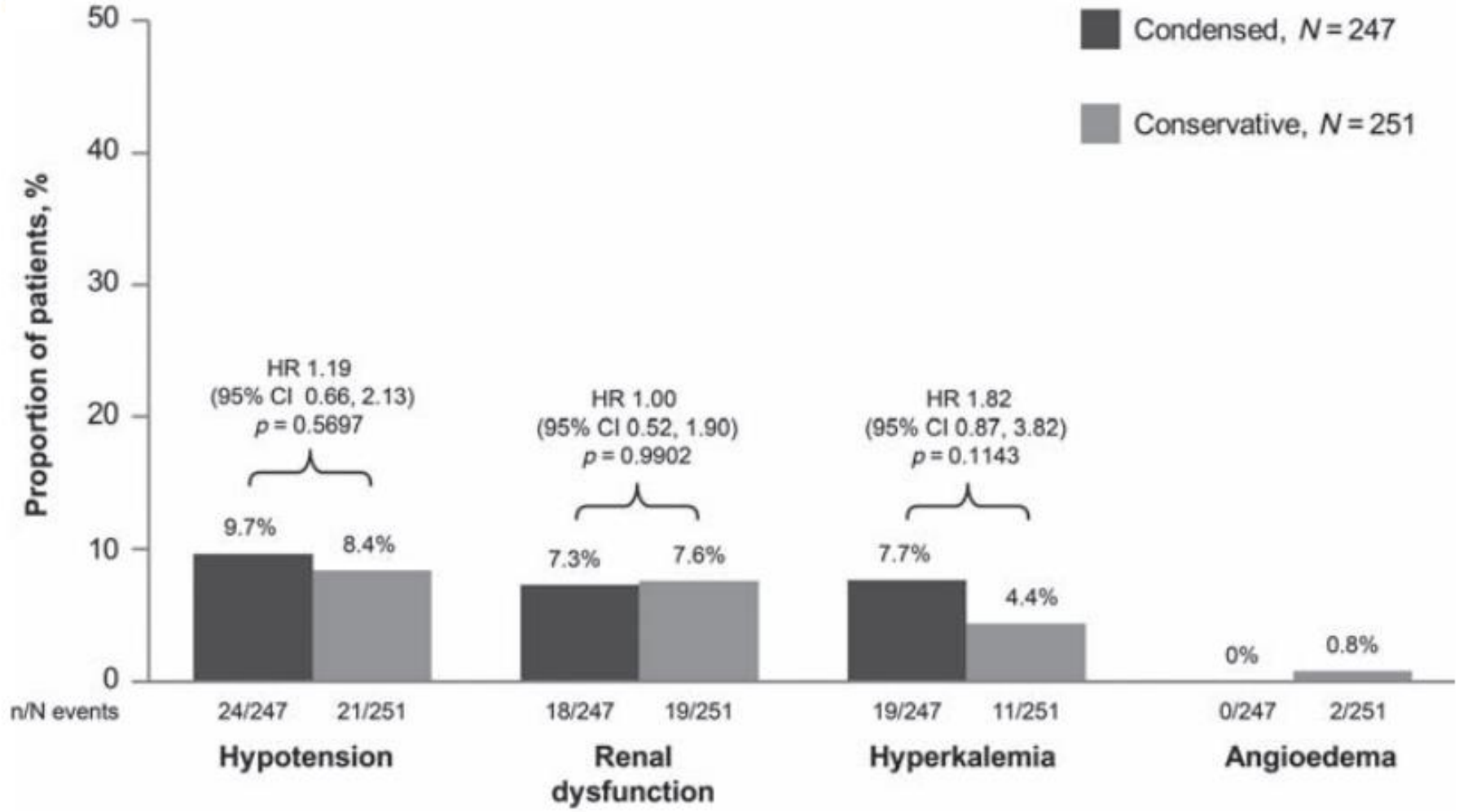
August 30, 2014, at NEJM.org.

TITRATION, a double-blind, randomized comparison of two LCZ uptitration regimens



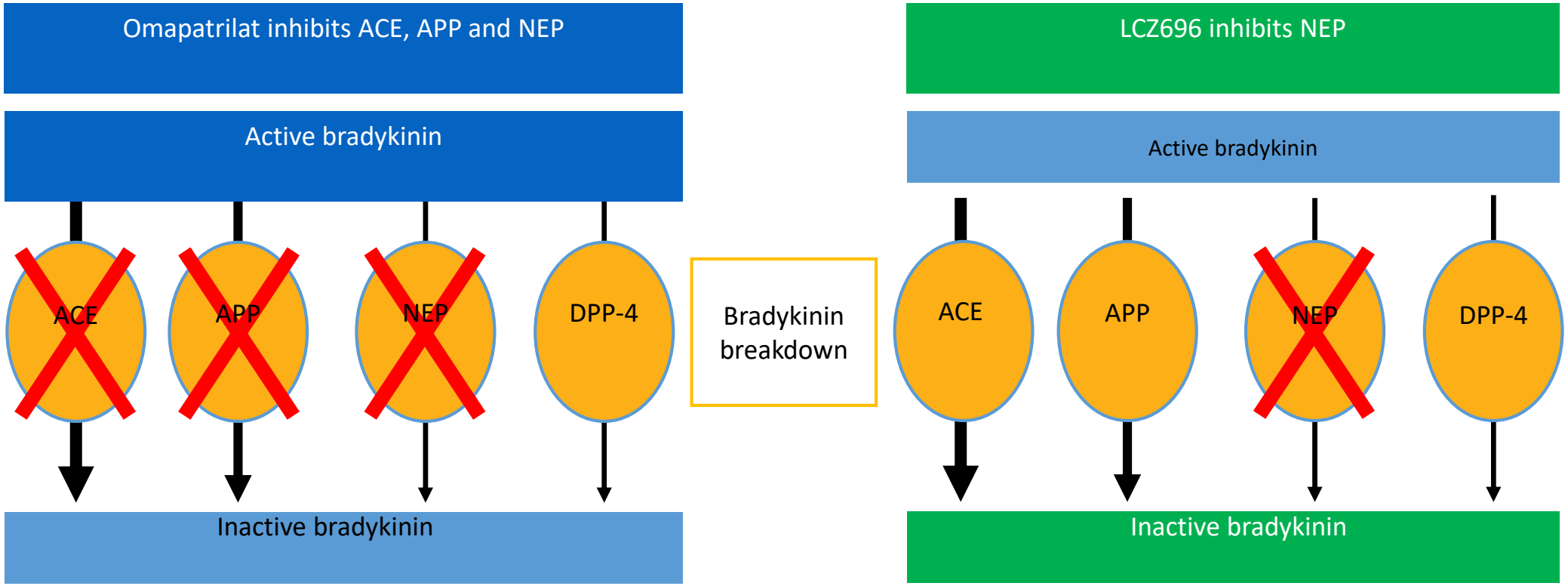
Senni et al. Eur J Heart Fail 2016; 18: 1193-1202

TITRATION, a double-blind, randomized comparison of two LCZ uptitration regimens

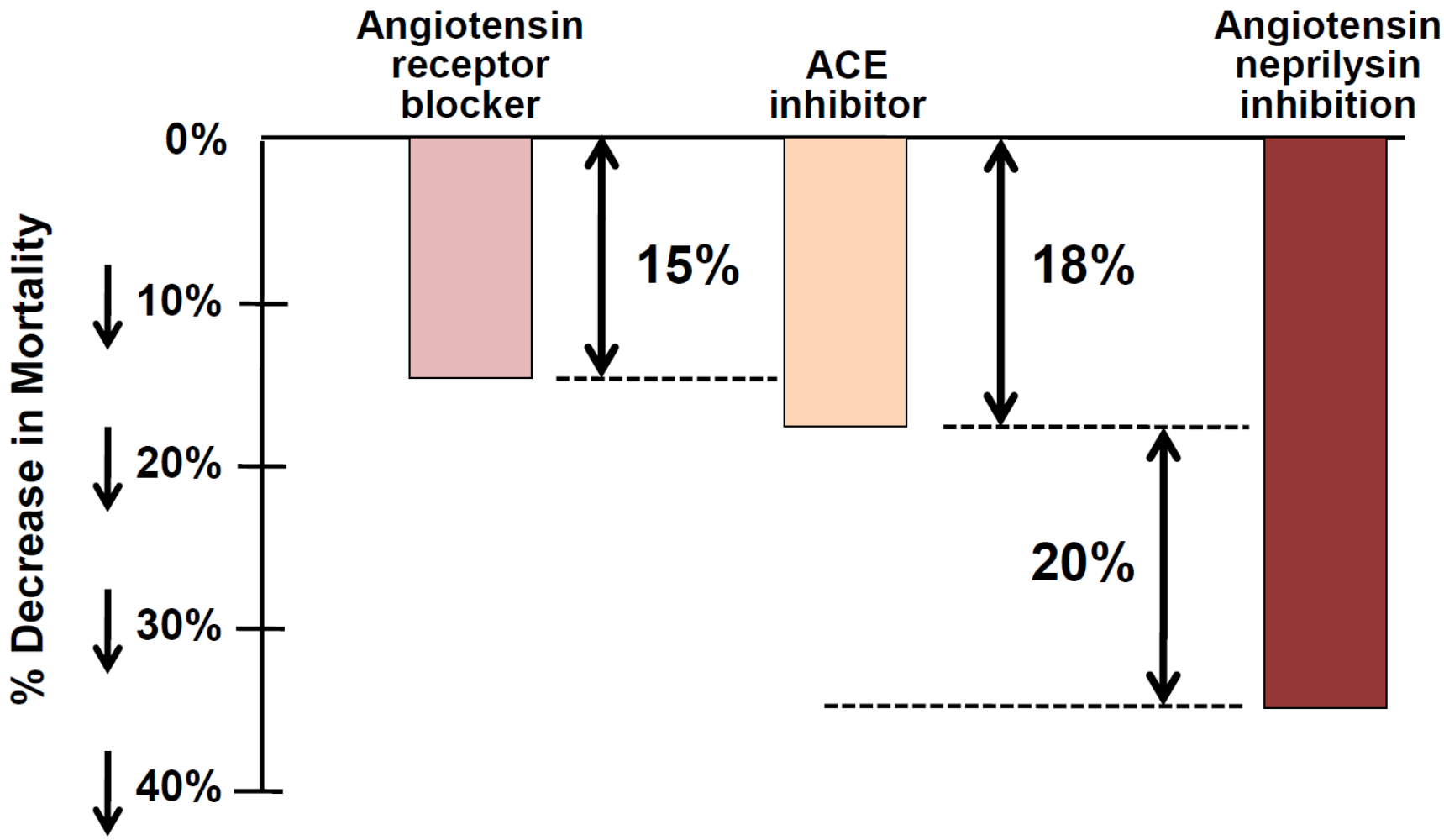


Senni et al. Eur J Heart Fail 2016; 18: 1193-1202

Risk of angioedema with LCZ696 is considered to be low



LCZ696 doubles the effect on cardiovascular death of current RAAS inhibitors



EU & USA: comparison of guidelines and label

	ESC Guideline Recommendations[1]	Sacubitril/valsartan EU LABEL[2]
Class I B	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, a beta-blocker and an MRA[d]	Sacubitril/valsartan is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction

	US Focused Update Recommendations[3]	Sacubitril/valsartan US LABEL[4]
Class I BR	The clinical strategy of inhibition of the renin-angiotensin system with **ACEi** (Level of Evidence: A), **OR ARBs** (Level of Evidence: A), **OR ARNI (Level of Evidence: B-R)** in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, **is recommended for patients with chronic HFrEF to reduce morbidity and mortality**	Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction Sacubitril/valsartan is usually administered in conjunction with other heart failure therapies, in place of an ACEi or other ARB
Class I BR	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, **replacement by an ARNI** is recommended to further reduce morbidity and mortality	

Sacubitril/valsartan in the management of ventricular arrhythmias in HF

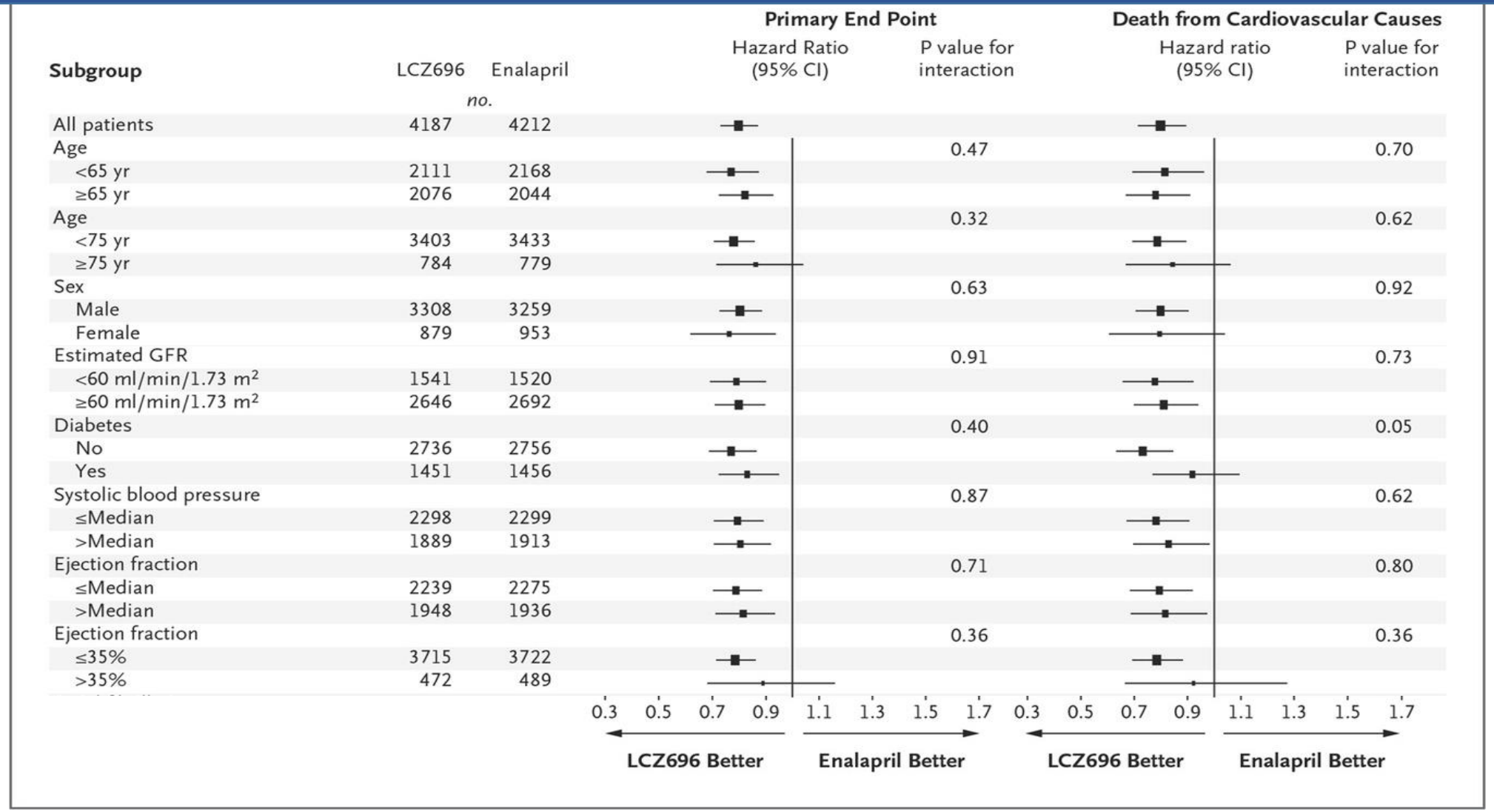
Recommendations for the management of ventricular tachyarrhythmias in heart failure

Recommendations	Class	Level
Treatment with beta-blocker, MRA and **sacubitril/valsartan** reduces the **risk of sudden death** and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients) (Section 10.2).	I	A

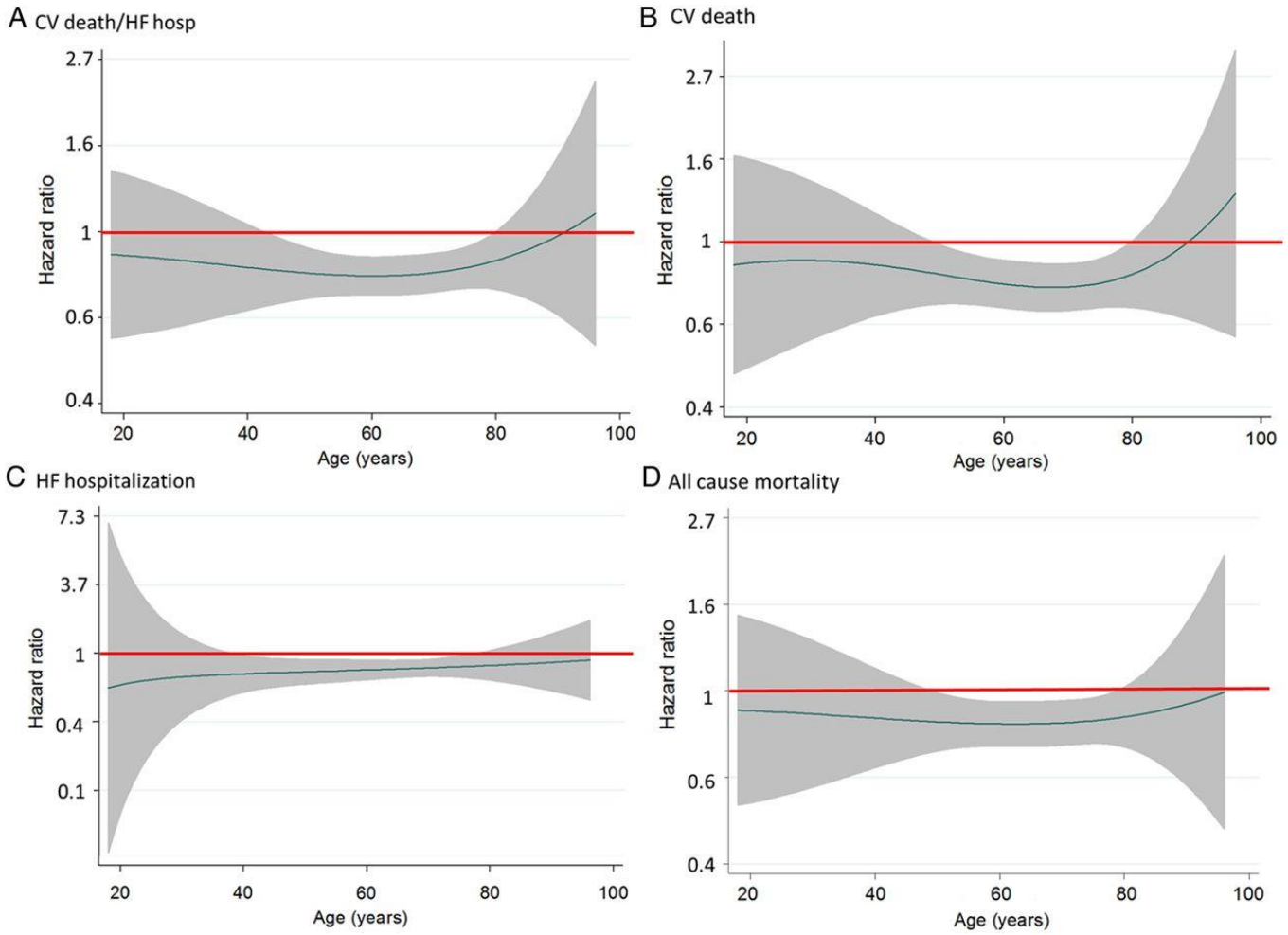
- **Sudden cardiac death accounts for about 39-45% of all the cardiovascular deaths[2,3]**
- **In PARADIGM-HF trial, sacubitril/valsartan significantly reduced the risk of sudden cardiac death compared with enalapril (HR: 0.80, 95% CI 0.68–0.94, P=0.008) in patients with HFrEF[2]**
- **Prevalence of non sustained VT is high in HFrEF, and concerns up to 50% of patients**

LCZ696 (Sacubitril/Valsartan)
Good news for elderly HF patients

PARADIGM HF: The advantage of LCZ696 was seen across all relevant subgroups



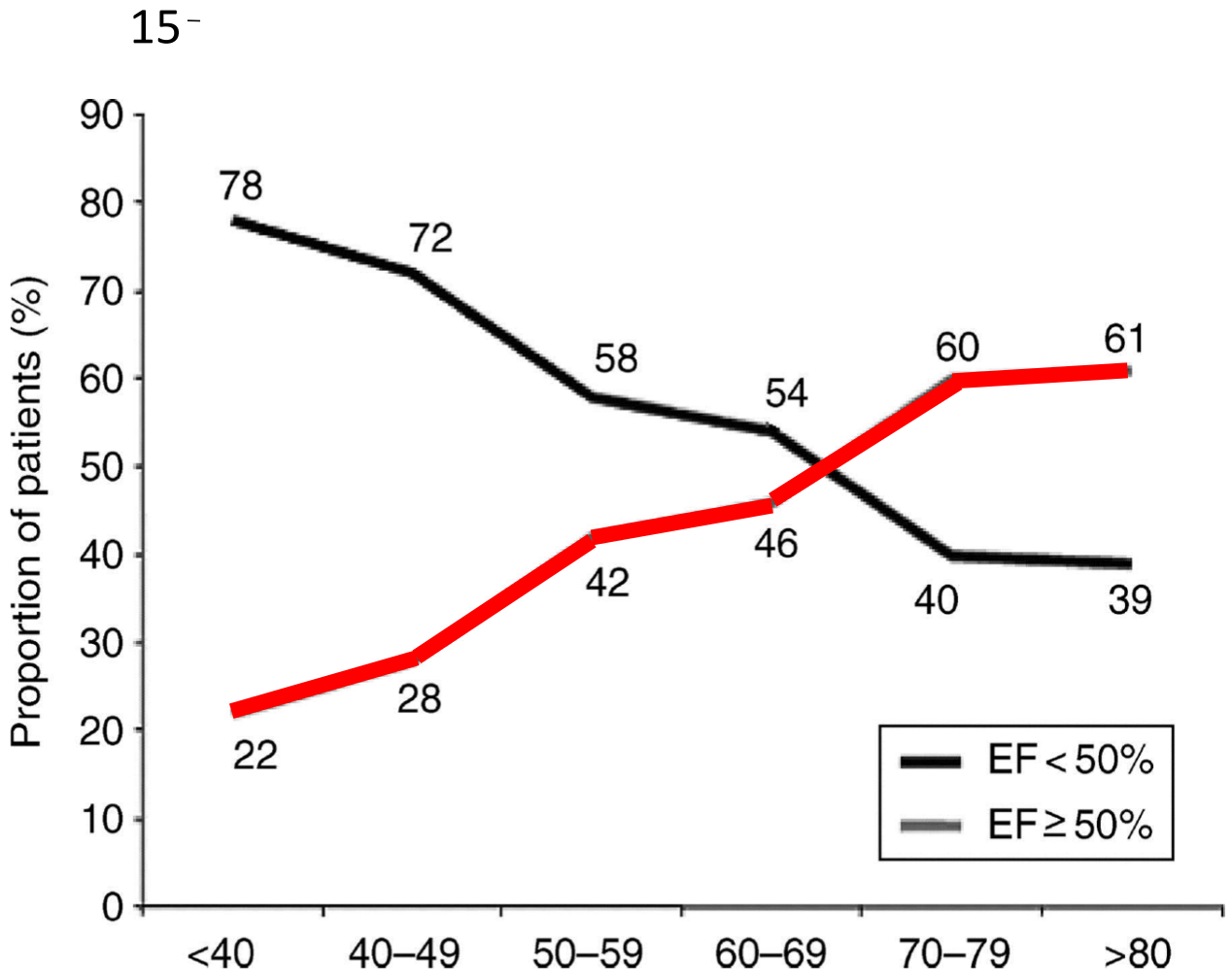
PARADIGM-HF:
Clinical Outcomes according to age



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

LCZ696 (Sacubitril/Valsartan) in HF with preserved ejection fraction

Percentage of HF pts with preserved and reduced EF by age



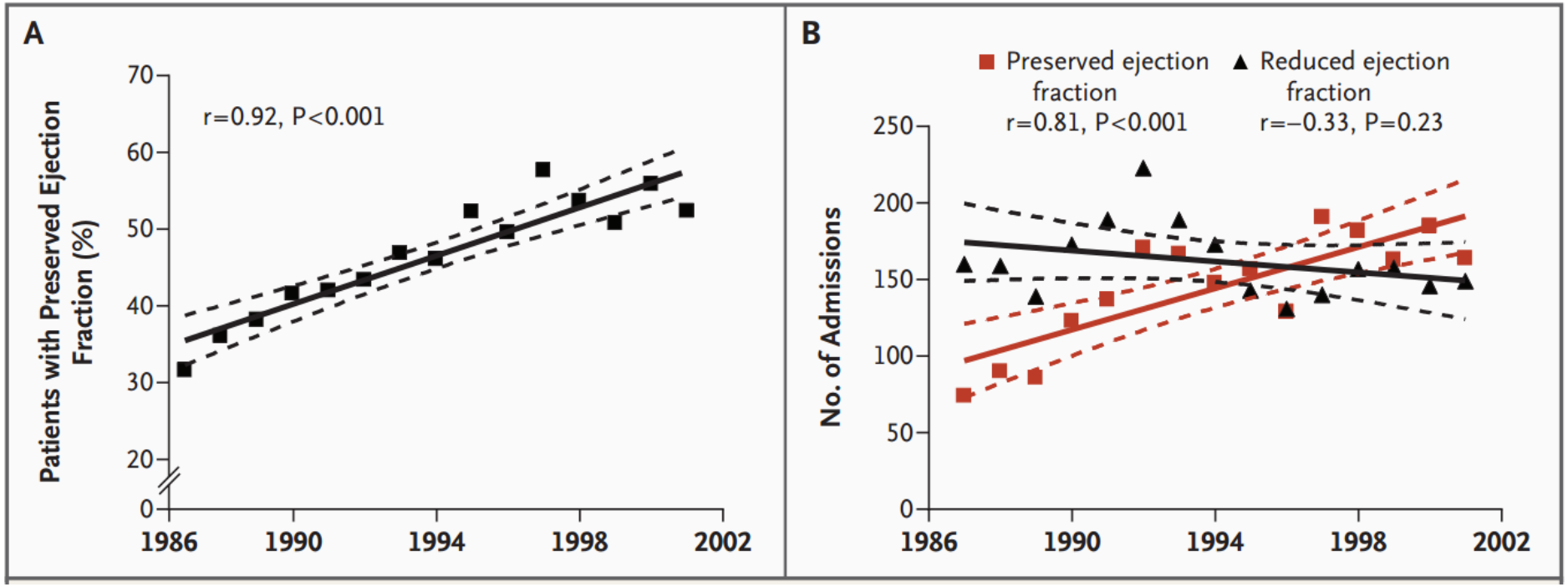
Tribouilloy C et al. Eur Heart J 2008;29:339-347

The NEW ENGLAND JOURNAL of MEDICINE

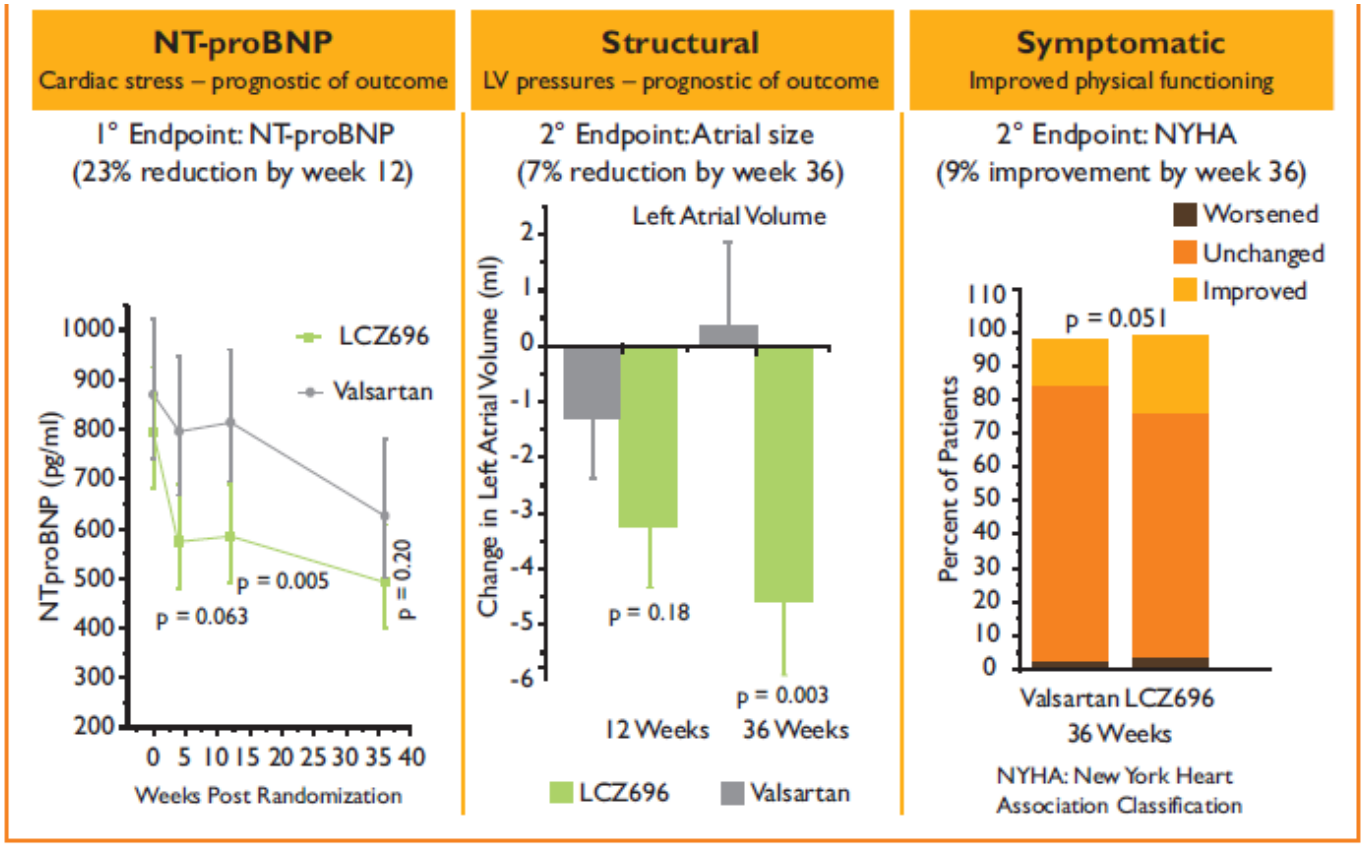
ORIGINAL ARTICLE

Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S., Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H., and Margaret M. Redfield, M.D.

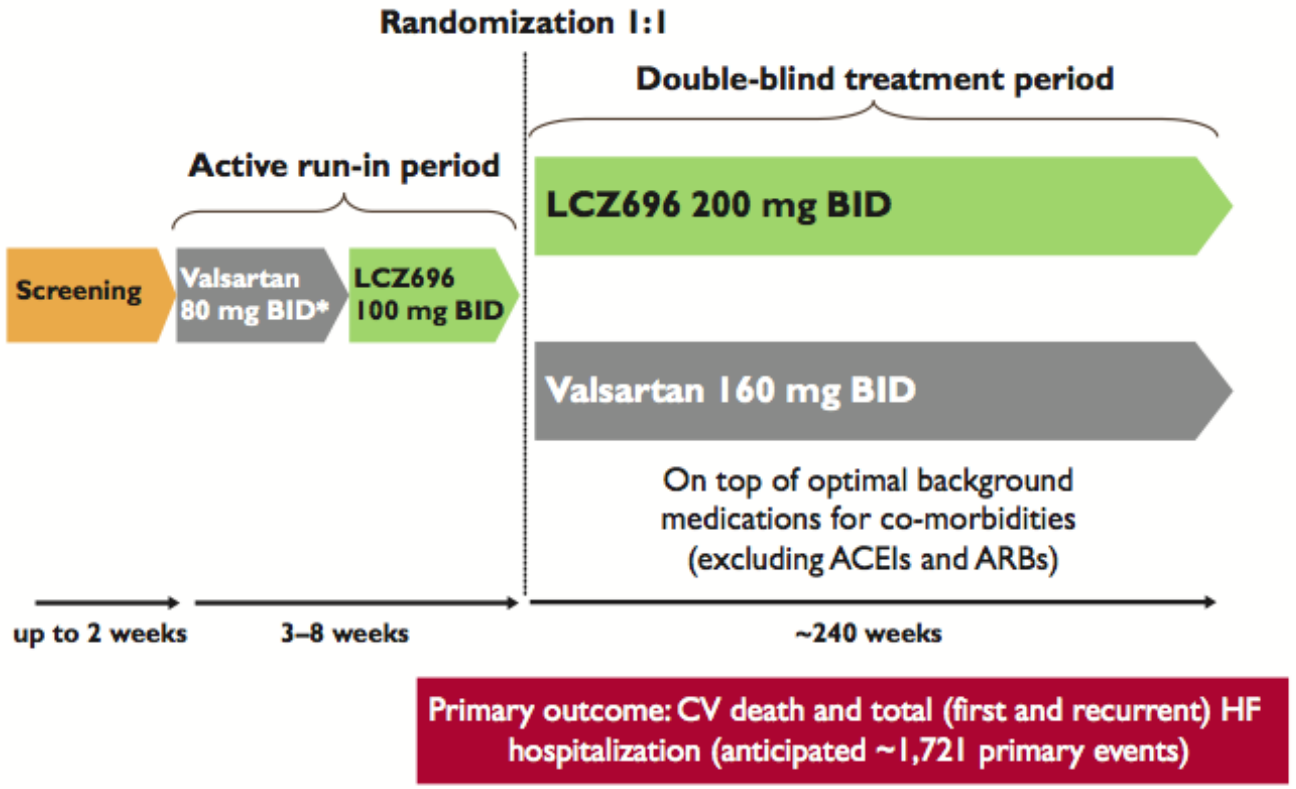


LCZ696 in HF with preserved ejection fraction: a phase 2 double-blind randomised controlled trial PARAMOUNT trial



Solomon et al. Lancet 2012

LCZ696 in HF with preserved ejection fraction: a randomized, double blind, morbidity and mortality trial PARAGON-HF



*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEI or ARB at Visit 1.

LCZ696 (Sacubitril/Valsartan) in older patients with systolic hypertension and an increased pulse pressure

Principal results of the **P**rospective comparison of **A**ngiotensin **R**eceptor neprilysin inhibitor with **A**ngiotensin Receptor blocker **ME**asuring arterial s**T**iffness in the eld**ER**ly (***PARAMETER***) Study

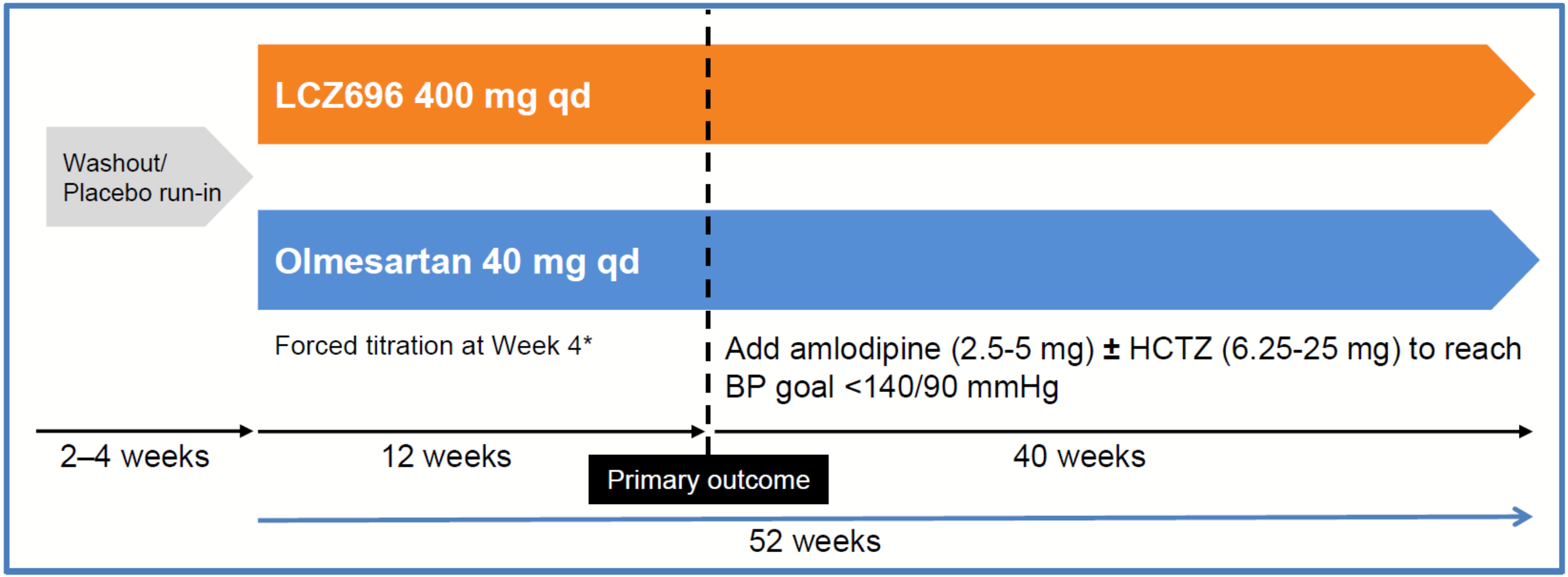
B. Williams,[1] JR. Cockcroft,[2] K. Kario,[3] DH. Zappe,[4] Q. Wang,[5] W. Guo[4]

[1]University College London, London, UK, [2]Cardiff University, Wales, UK, [3]Jichi Medical School, Tochigi, Japan, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, [5]Beijing Novartis Pharma Co. Ltd, Shanghai, China.

Clinical Trials Identifier: EUDract number 2012-002899-14; ClinicalTrials.gov NCT01692301
Study code: CLCZ696A2216
Protocol: *Williams B. et al, BMJ Open, 2014*

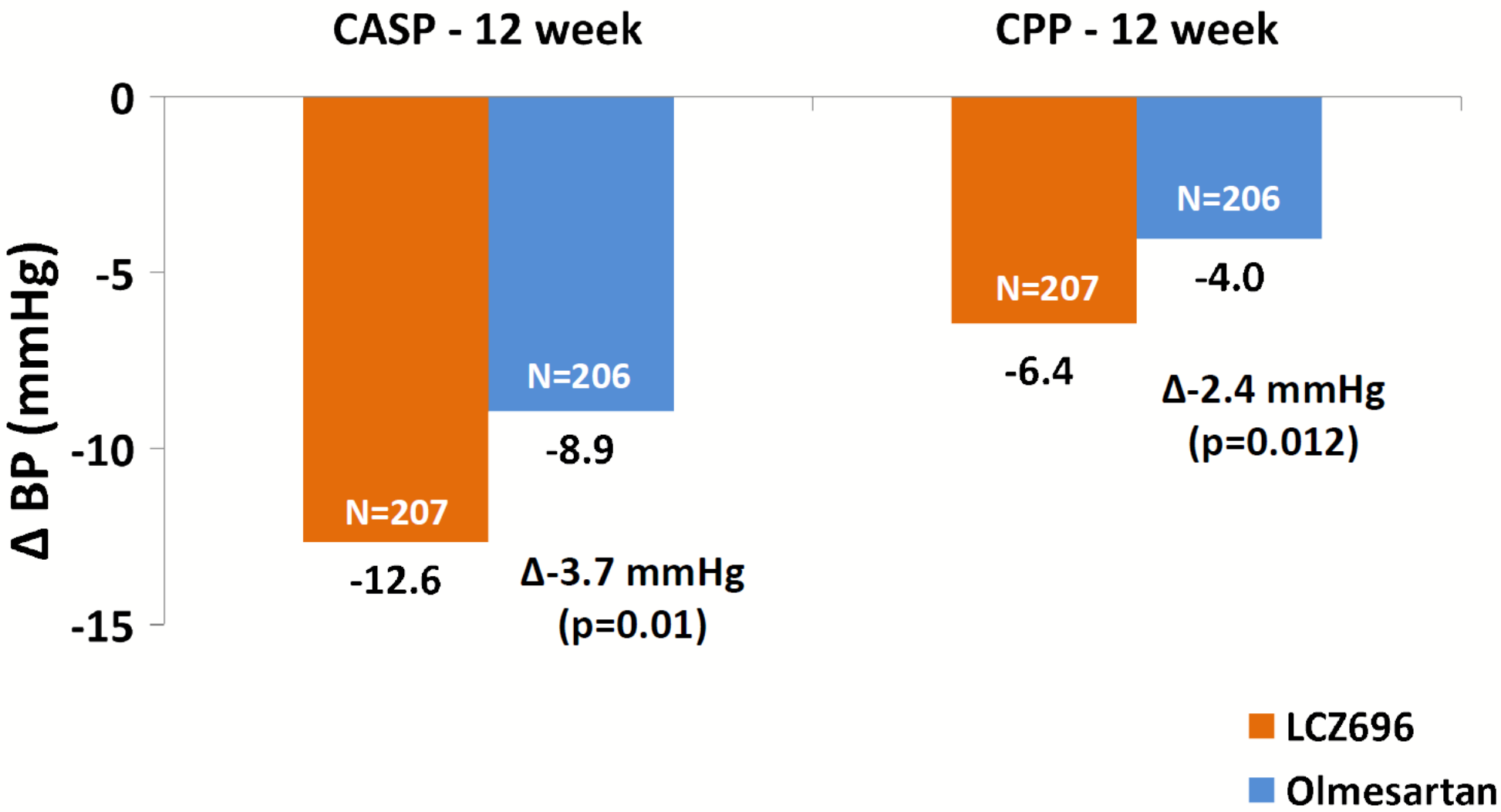
PARAMETER: Study design

Multicenter, randomized, double-blind, active-controlled, 52-week study to evaluate the safety and efficacy of an LCZ696 regimen on central aortic pressures and arterial stiffness in elderly hypertensive patients



Primary and key secondary outcomes:

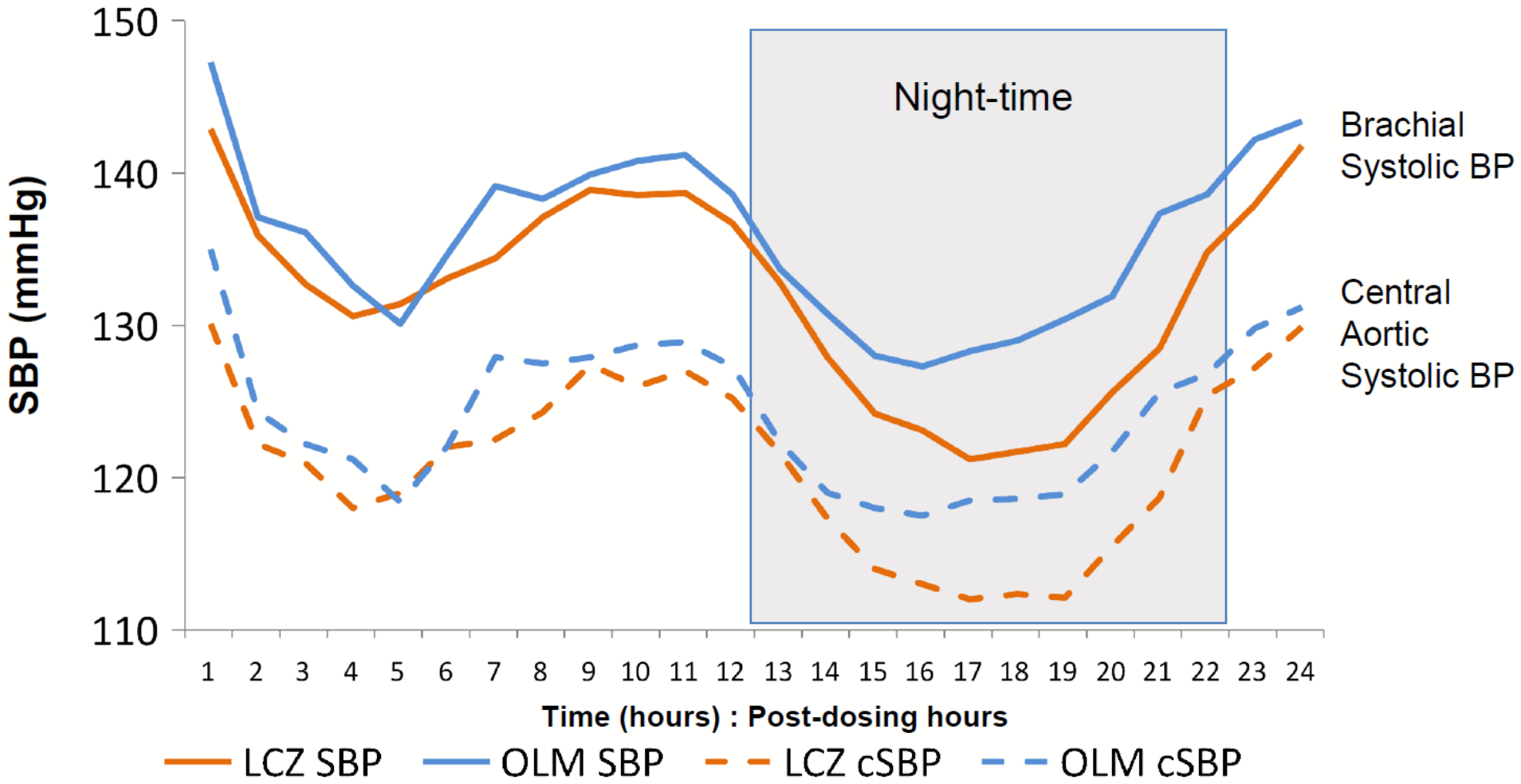
Change from baseline in mean CASP and CPP at Week 12



24-hour brachial and central aortic SBP at Week 12

Mean Δ SBP: -4.1 mmHg, p<0.001 (-13.2 (LCZ696) *vs.* -9.1 (OLM) mmHg)

Mean Δ cSBP: -3.35 mmHg, p<0.001 (-12.1 (LCZ696) *vs.* -8.7 (OLM) mmHg)



An increased risk of Alzheimer disease with neprilysin inhibition???

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

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

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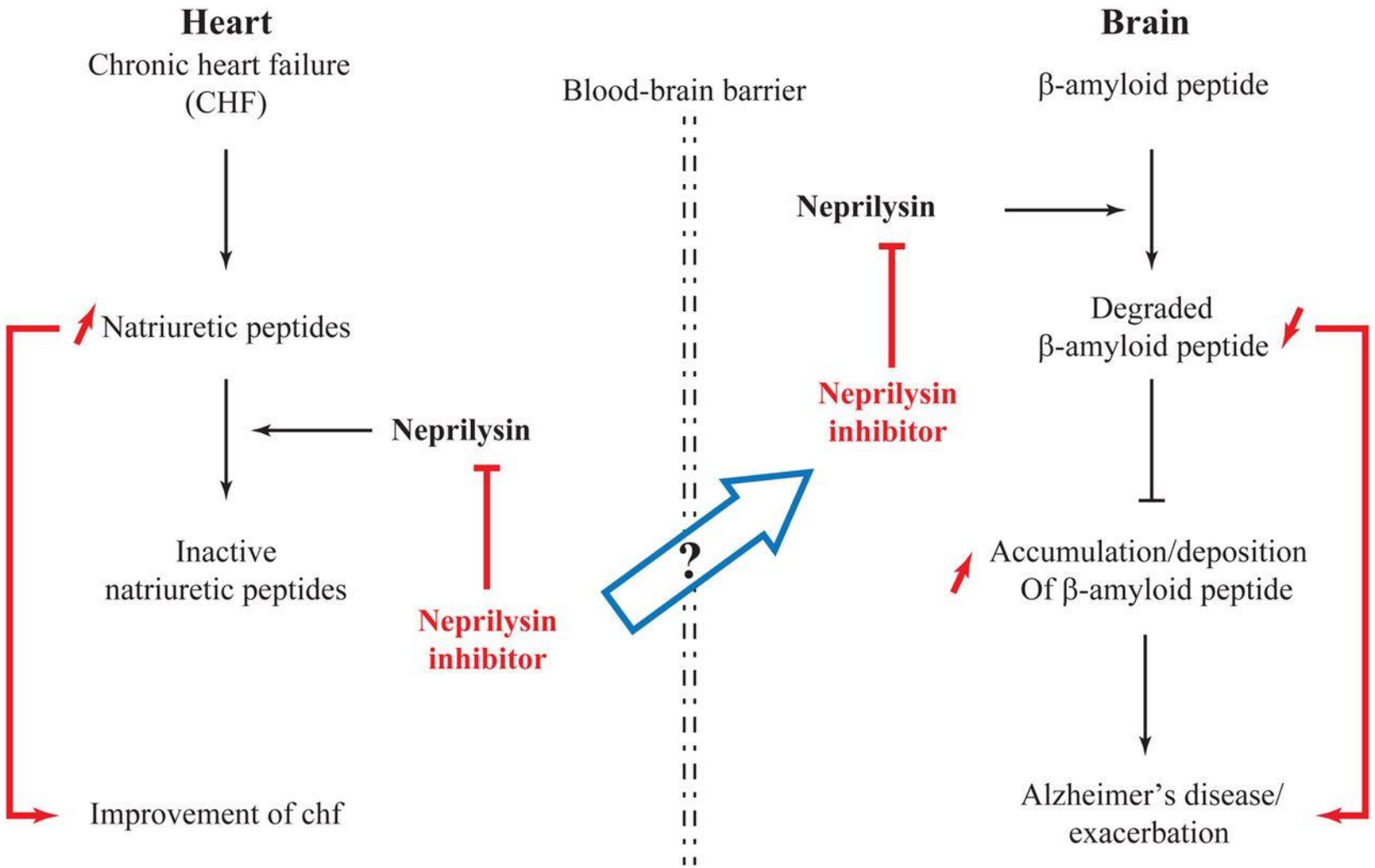
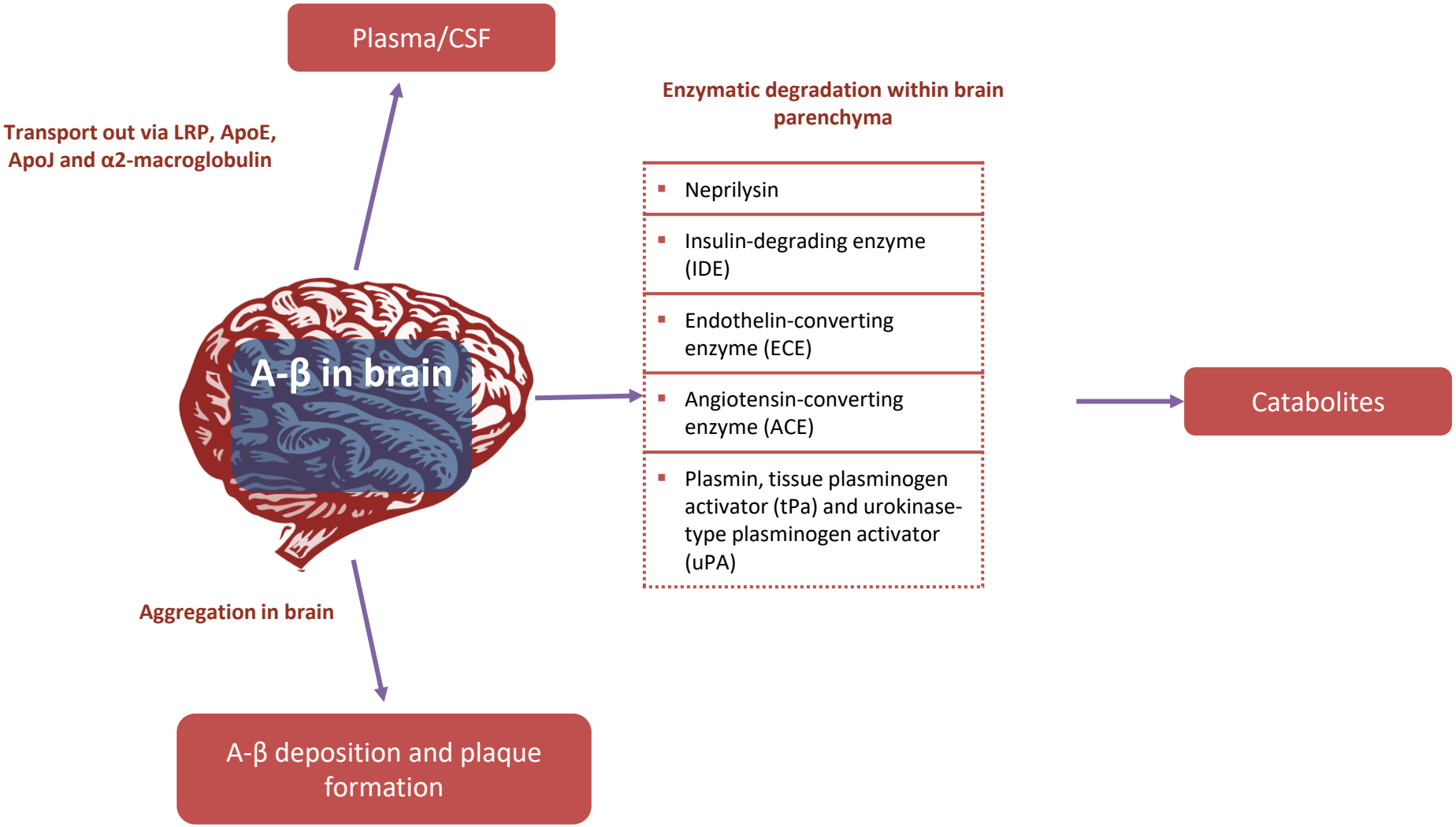


How is A-β processed in the brain?

A-β is transported to and cleared from the brain via several possible routes[1] *(about 20)*



LCZ696 & Amyloid-Beta

- In monkeys, there was an increase in CSF AB biomarkers that was not seen in the brain
- In healthy humans, there was no increase in CSF AB biomarkers associated with AD plaque formation
- In clinical data from PARADIGM-HF no imbalance in cognition, memory, and dementia-related adverse events between the LCZ696 group as compared to the enalapril group was seen

A multicenter, randomized, double blind study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic HF and preserved ejection fraction

Objectives and related endpoints

Objective	Endpoint
Primary To evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in pts with HFprEF	Changes from baseline to 3 years in the CogState Global Cognitive Composite Score (GCCS)
Secondary To evaluate the effects of LCZ696 compared to valsartan on β-amyloid deposition in the brain in a subset of patients using PET	Change from baseline in a cortical composite SUVr (standarized uptake value ratio) at 3 years