

Prognostic Circulating Neprilysin and Therapeutic Neprilysin Inhibition

Antoni Bayes-Genis

Chair, Heart Institute

Hospital Univesitari Germans Trias i Pujol
Badalona, Barcelona, Spain



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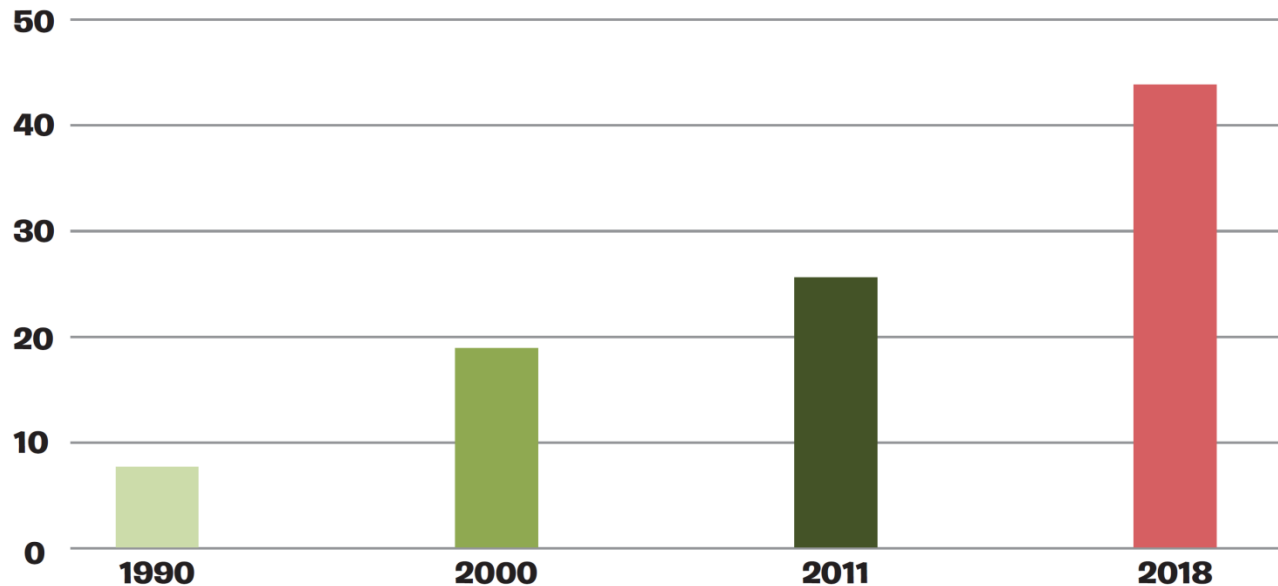
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HF Epidemic... in the WORLD

GLOBAL PREVALENCE OF HEART FAILURE, 1990 - 2018
(in millions)



Based on U.S. Department of Health And Human Services report, Feb. 1994, "Mortality from Congestive Heart Failure - United States, 1980-1999, multiplied by a factor of 4 to estimate global prevalence.

Based on U.S. National Health And Nutrition Examination Survey (1998-1991), National Center for Health Statistics estimate of U.S. prevalence of heart failure (1-2 million), then using the higher range multiplied by a factor of 4 to estimate global prevalence of heart failure.

BCC Research, Cardiac Biomarkers: Technologies and Global Markets, 2014.

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.... In US and Western Europe



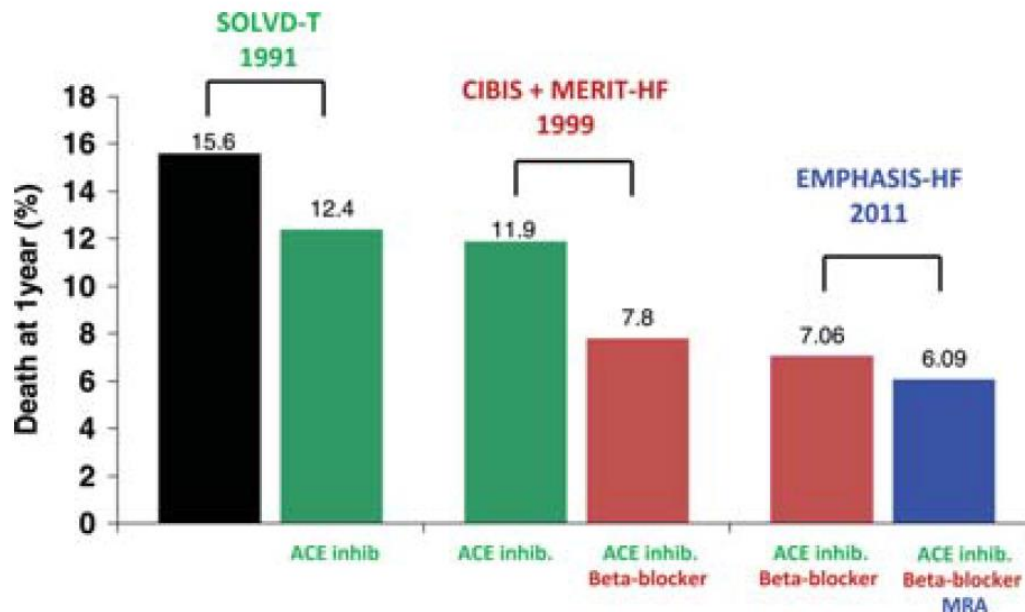
1 in 5 individuals > 40 years will develop HF

HF unmet needs?



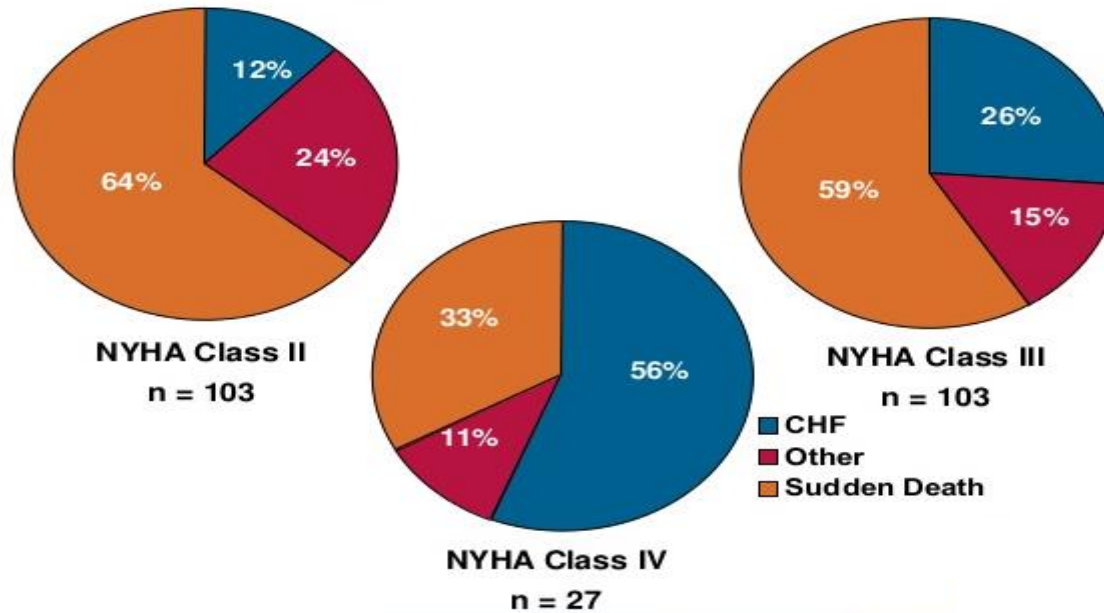
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Excessive mortality despite neurohormonal blockade

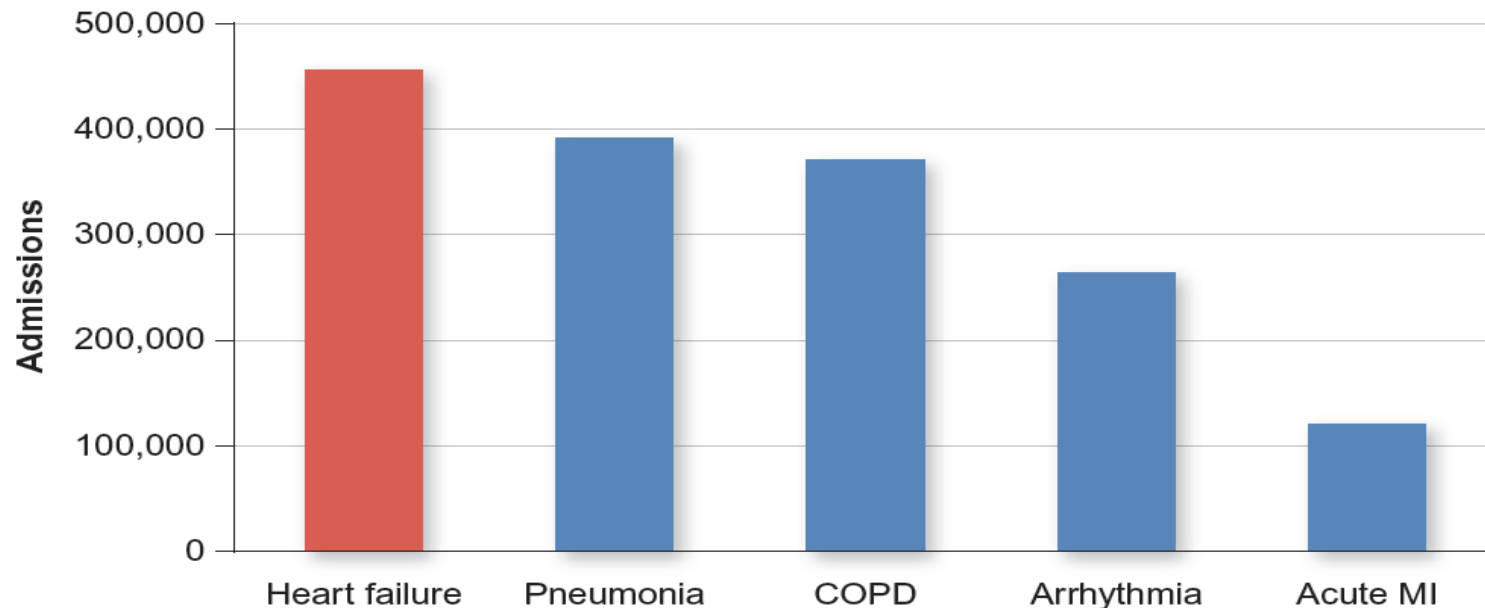


HF progresses and mortality remains high despite optimal neurohormonal blockade

Sudden death accounts for 50% of HF mortality



Too many HF admissions and readmissions

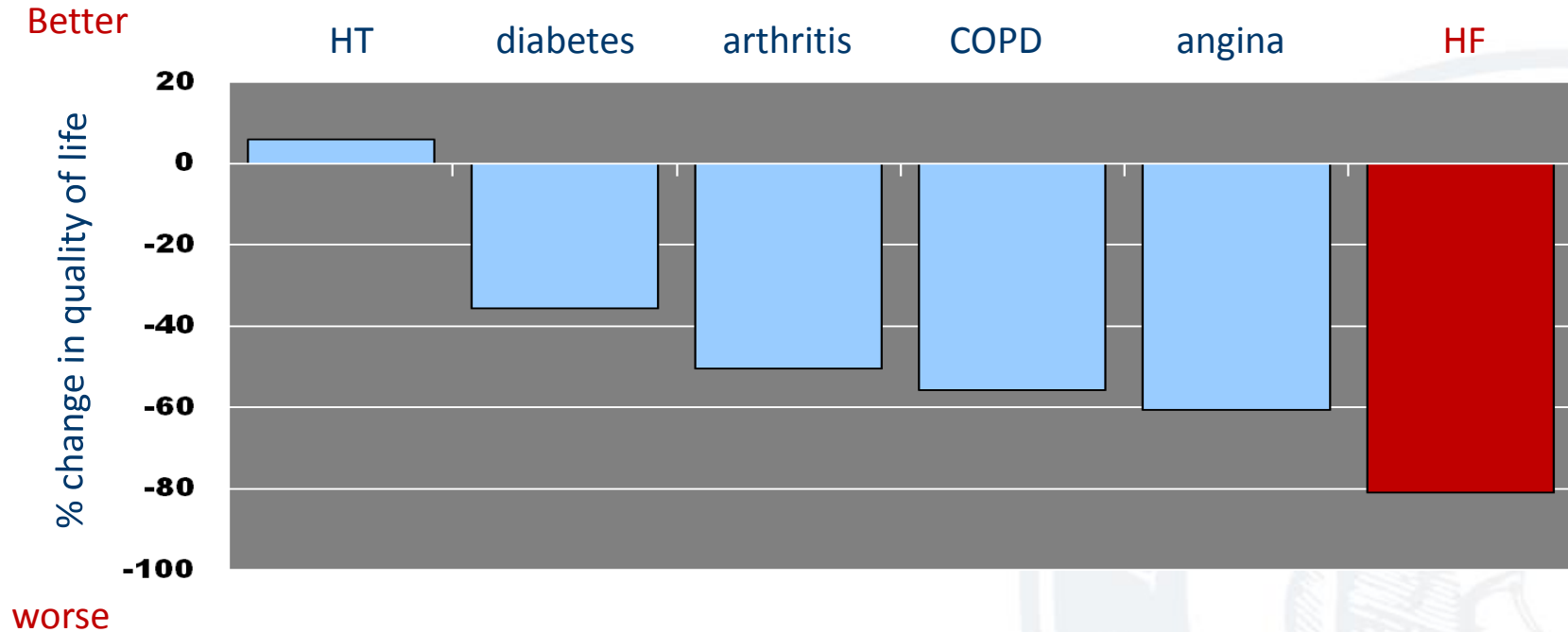


Centers for Medicare & Medicaid Services. Medicare Provider Utilization and Payment Data: Inpatient. 2013



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... and poor quality of life



McMurray J. Eur Heart J 1998; 19 (supp. P): P9

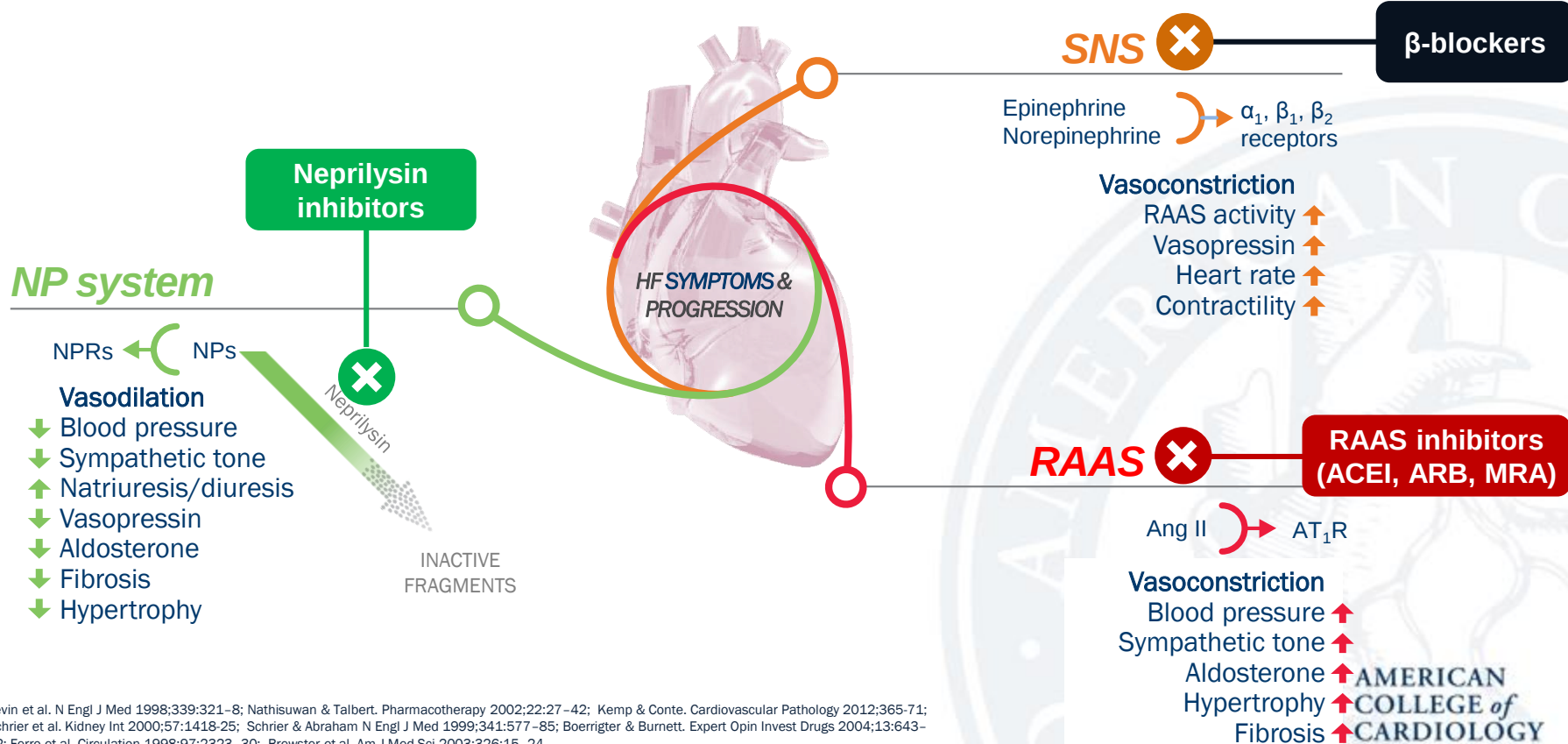


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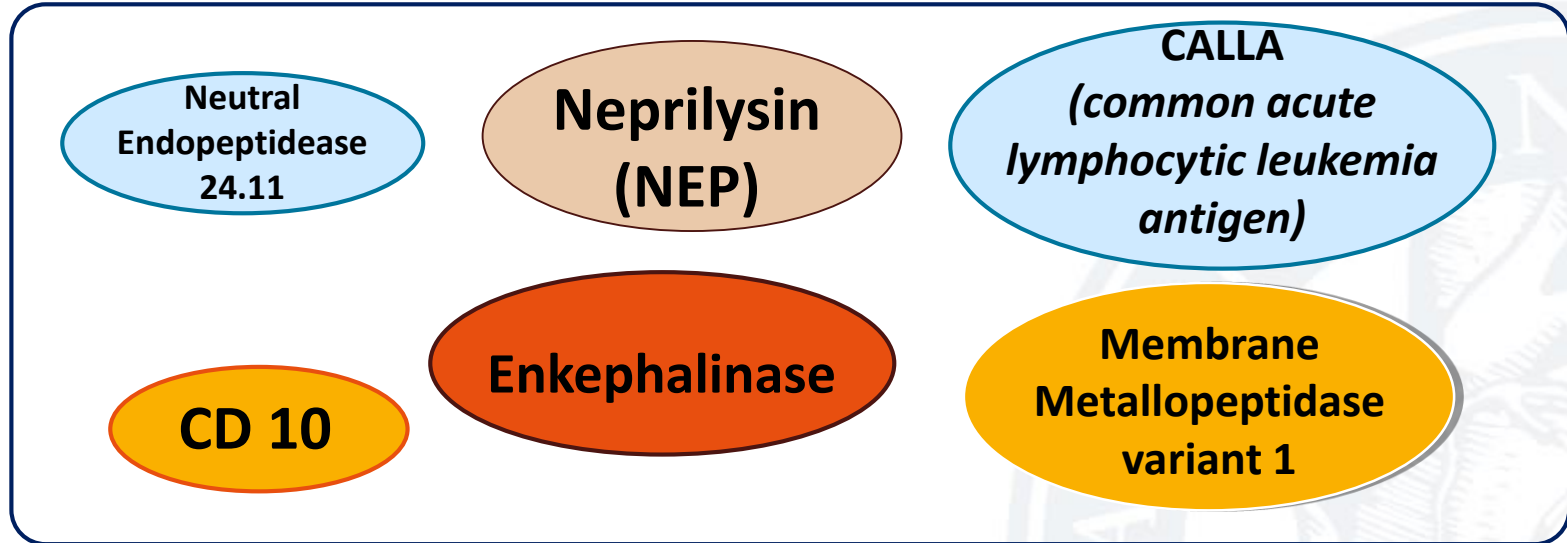
New Mechanism of action: Neprilysin inhibition



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Neprilysin: a long journey

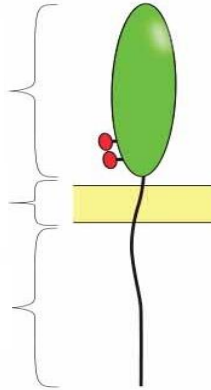


NEP: a “ubiquitous” transmembrane receptor

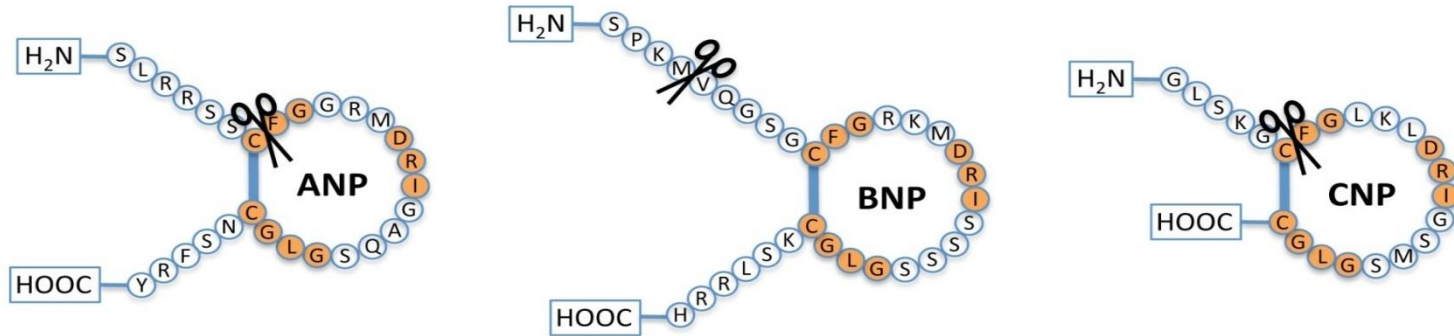
Large CT **Extracellular domain** (55-750 aa)
with a Zn atom at the active site

A single **transmembrane** helix

Short NT **Intracellular domain** (27 aa)

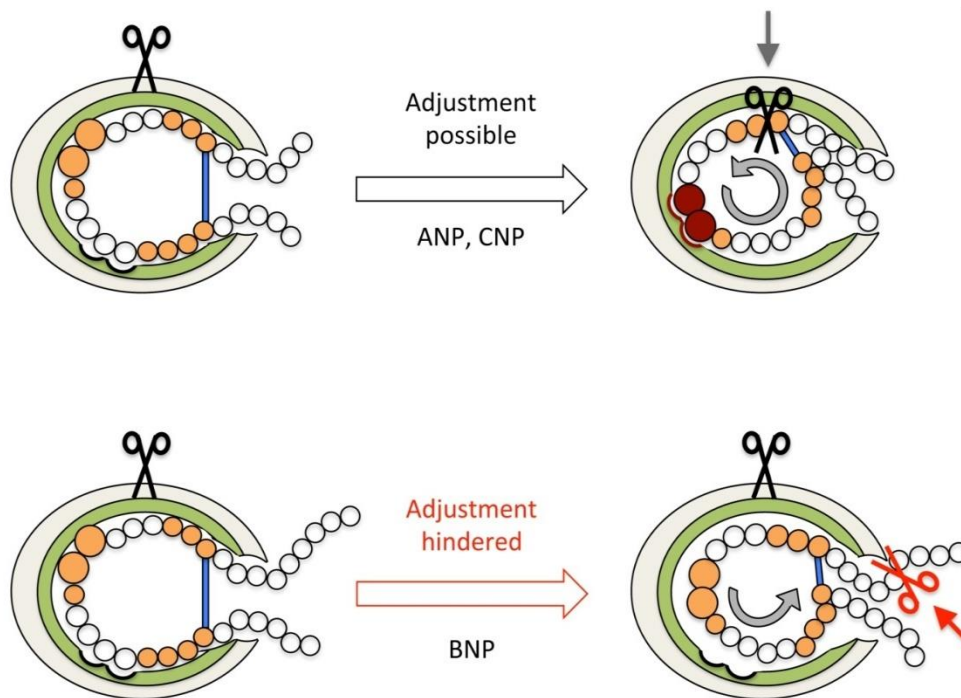


Primary sites of cleavage by NEP on human ANP, BNP and CNP

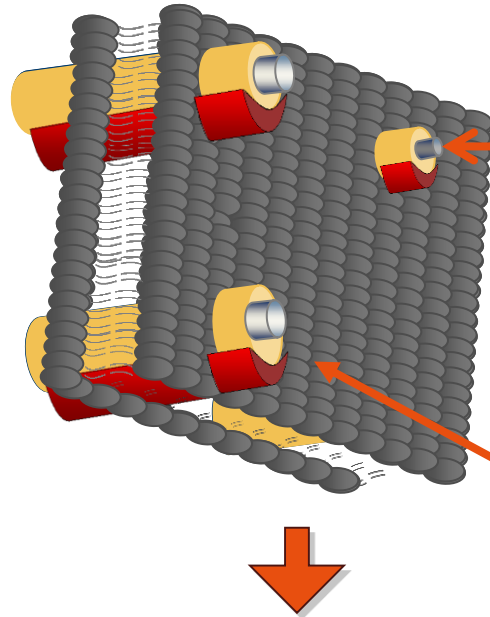


 NEP cleavage sites

Interaction of individual NPs with neprilysin



NEP: a «promiscuous» transmembrane receptor



Endogenous vasoactive peptides

Vasodilators: NPs, adrenomedullin, bradykinin.

Vasoconstrictors: angiotensin I- II, endothelin 1.

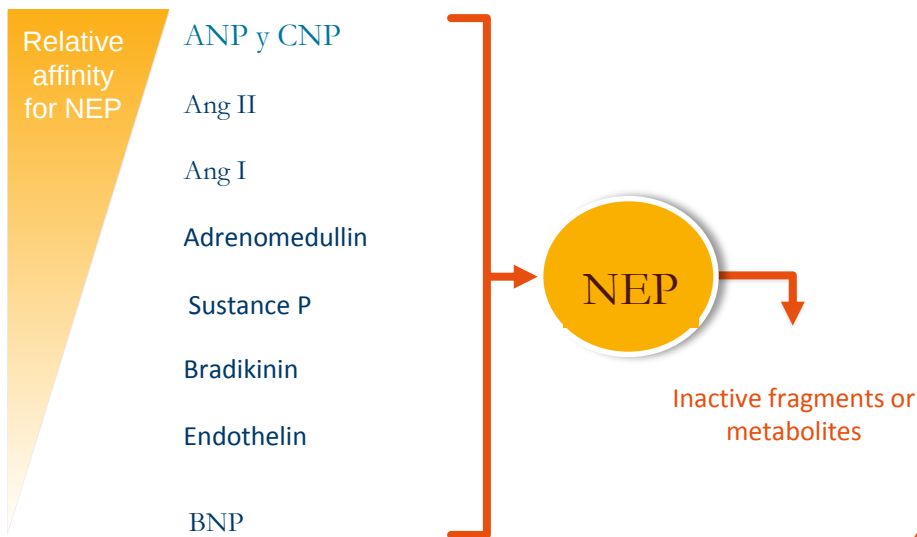
Other peptides

Opioids, substance P, gastrin, β -amyloid

Inactive
metabolites

Neprilysin has many substrates that are metabolized with differing levels of affinity

Metabolism of vasoactive peptides by NEP



Implications for NEP inhibition

NEP substrates can have opposing biological actions

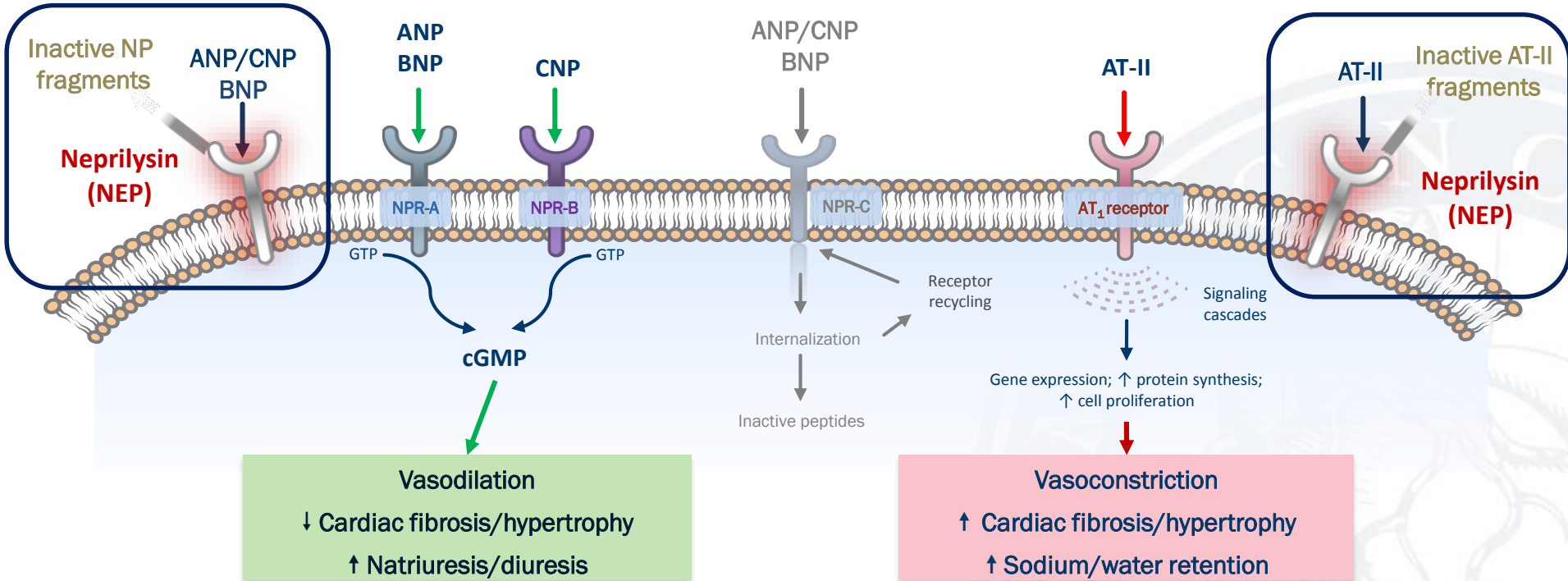
Overall effect is dependent upon the **net effect** on NEP metabolism of individual substrates

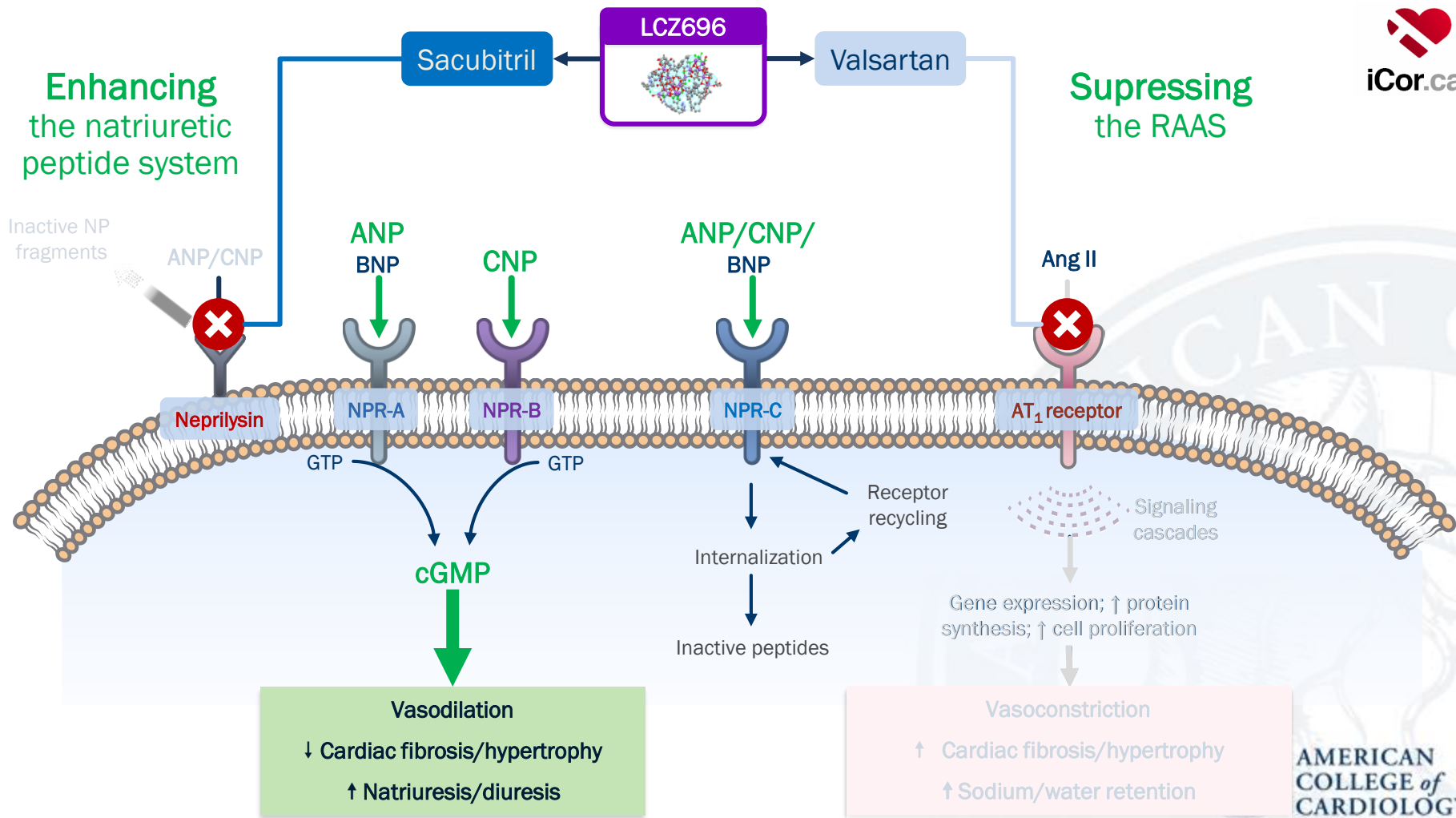
Benefits in enhancing NP system may be offset by increased Ang II

Needs to be complemented by simultaneous RAAS suppression

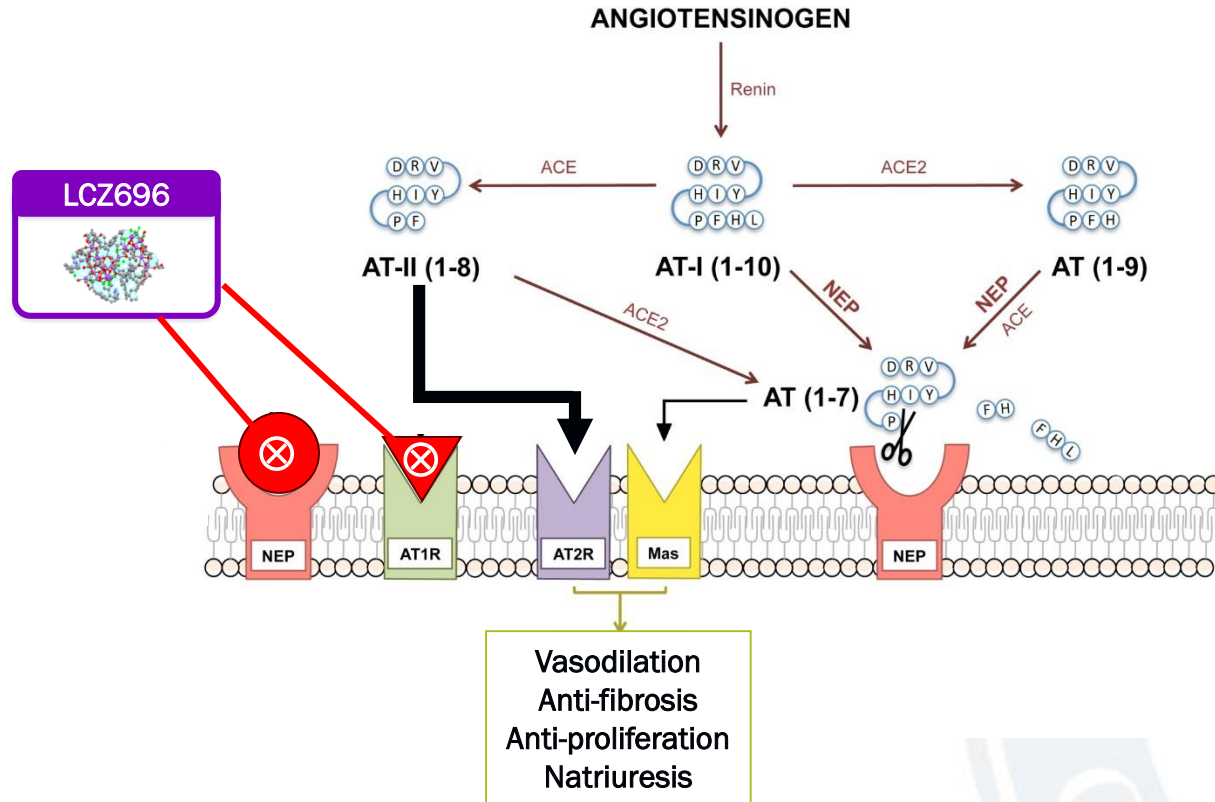


NEP inhibition alone increases NPs and AT-II

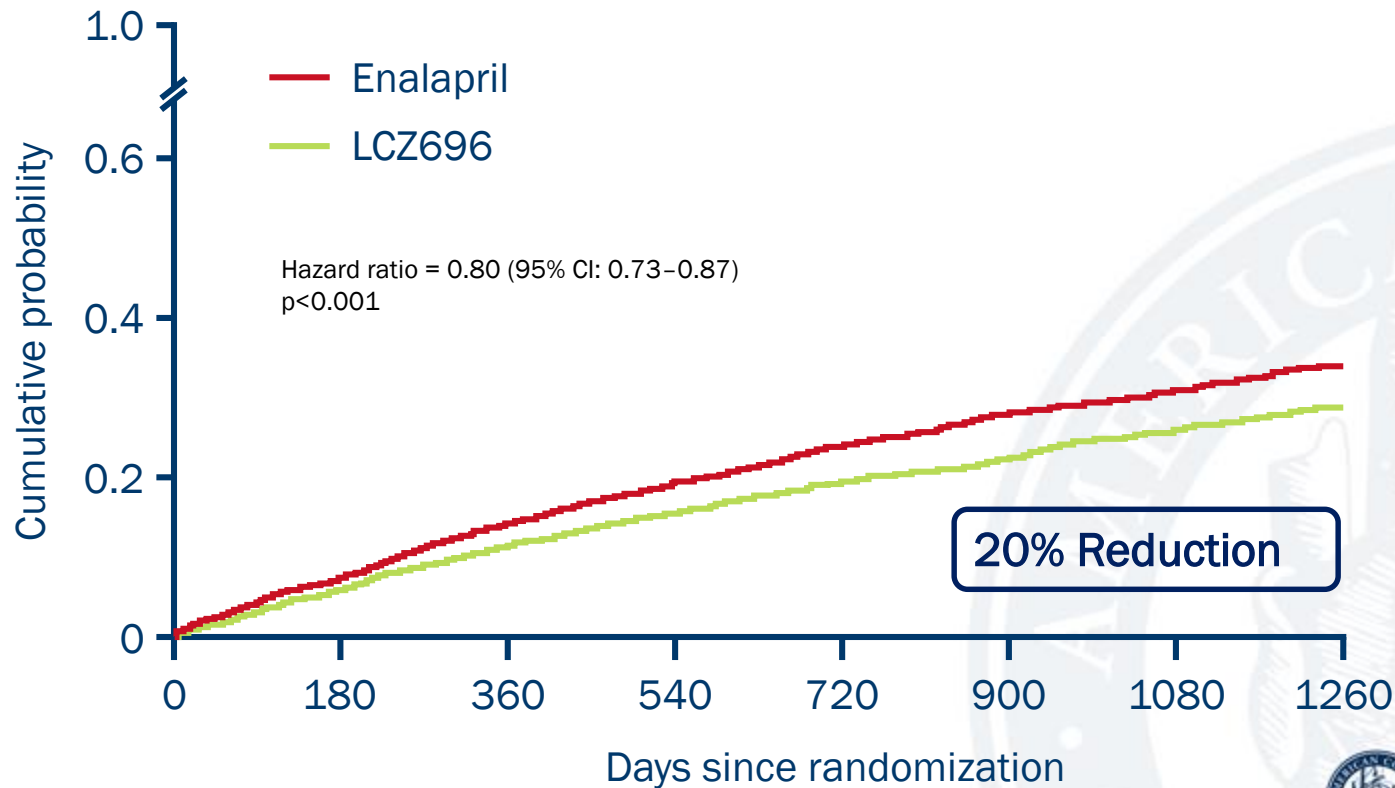




Sac/Val in the Angiotensin pathway



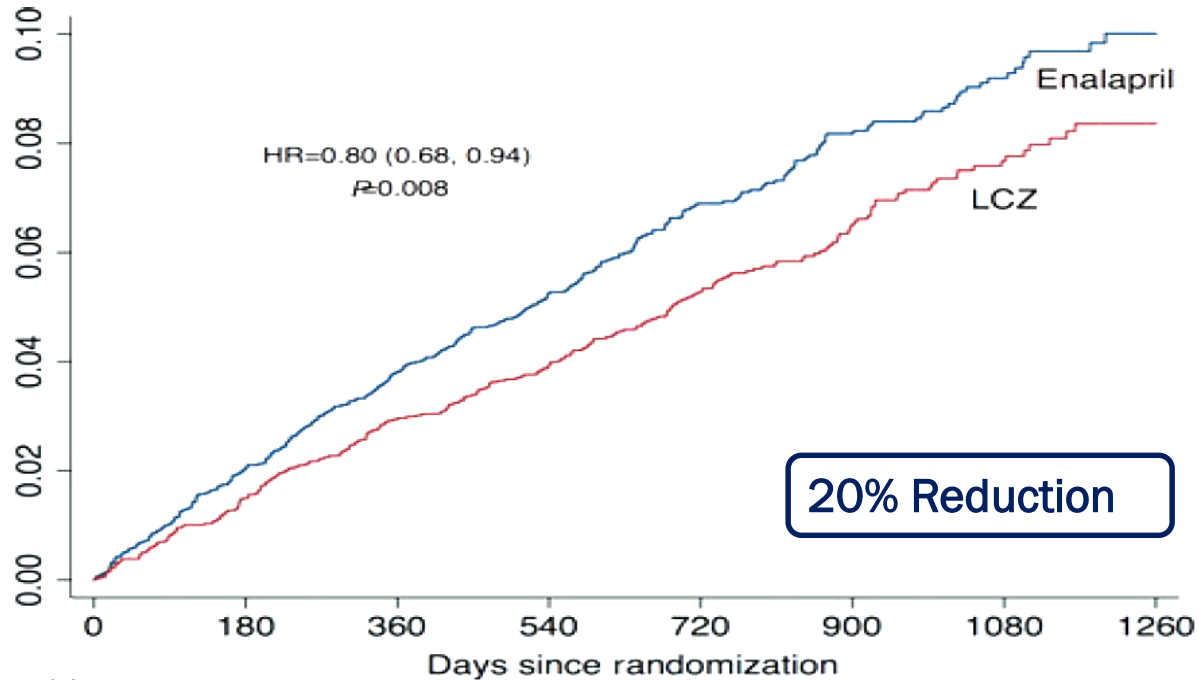
Death from CV causes or first hospitalization for HF



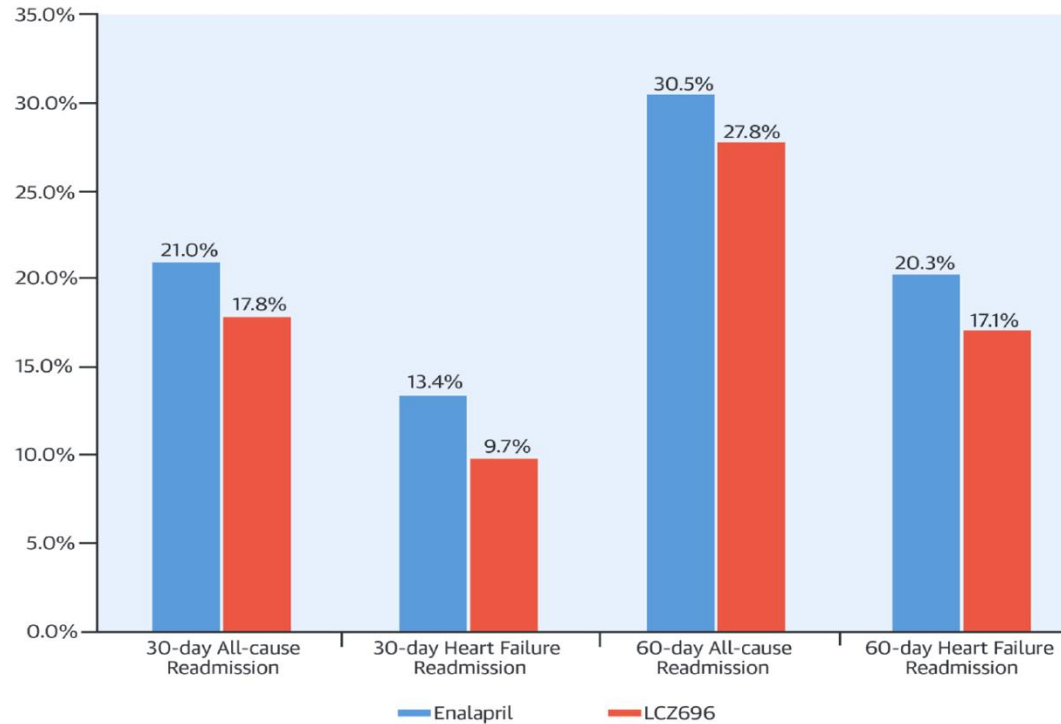
Sudden Death



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30- and 60-day HF readmissions



Desai et al. J Am Coll Cardiol 2016;68:241-8



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Is it safe?



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Omapatrilat

Active bradykinin



ACE

APP

NEP

DPP-4

Inactive bradykinin

Sac/Val

Active bradykinin



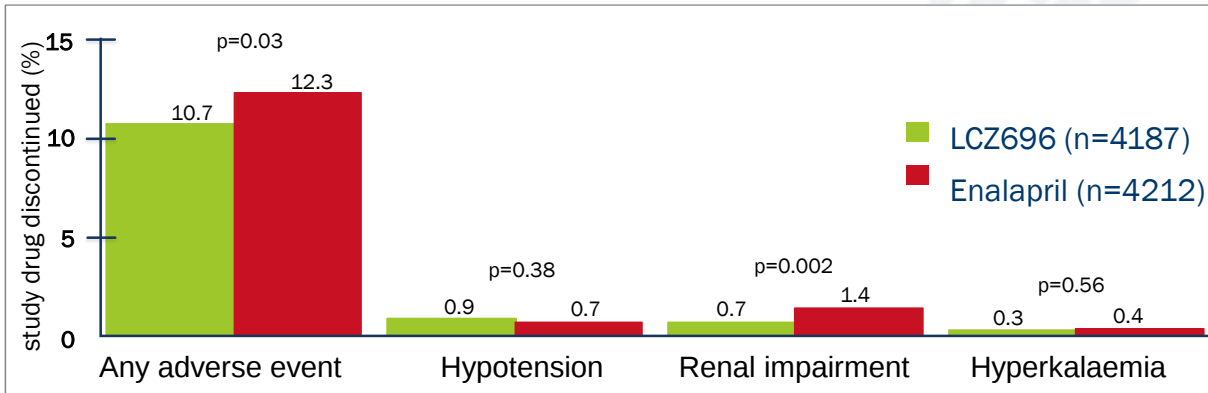
ACE

APP

NEP

DPP-4

Inactive bradykinin

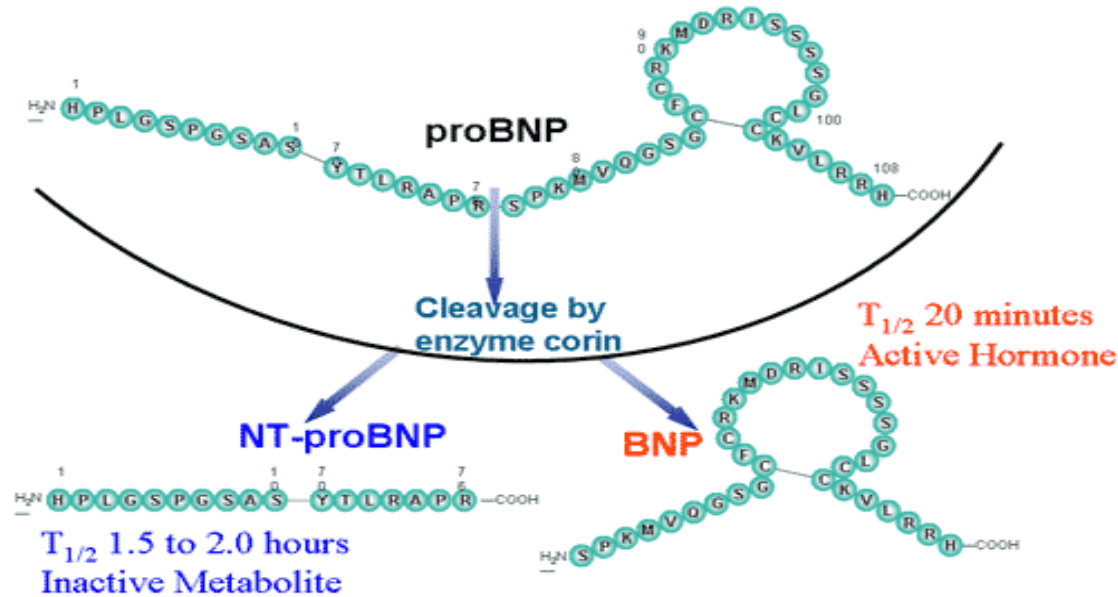


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What about biomarkers?



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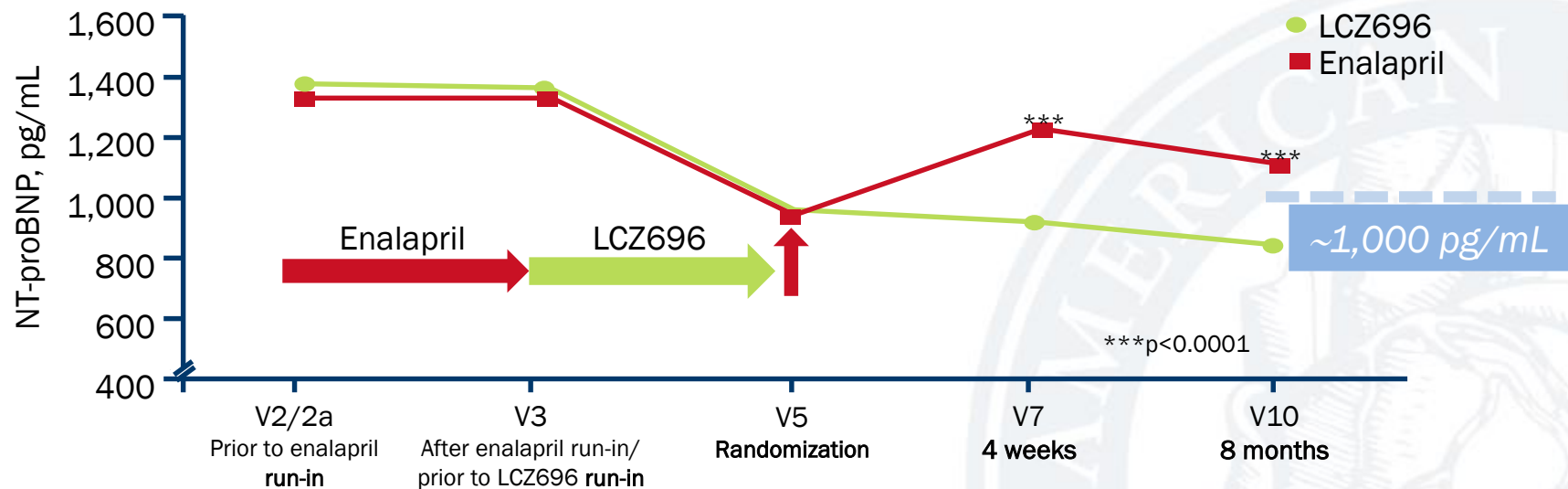
NOT
cleaved by NEP

YES
cleaved by NEP

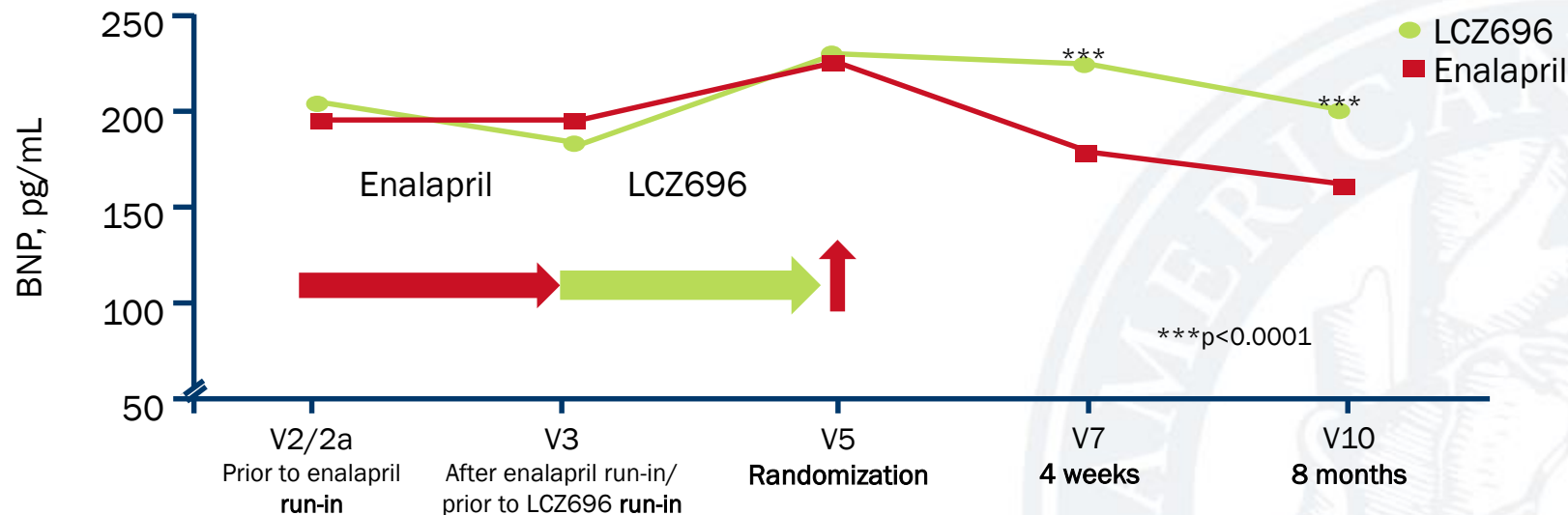


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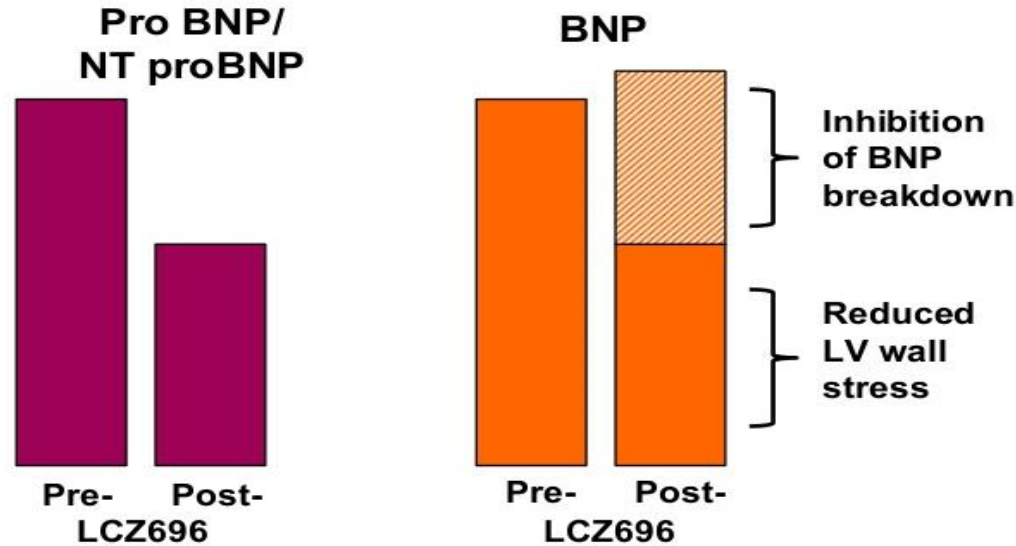
LCZ696 significantly reduced levels of NT-proBNP



Sustained BNP reflects NEP inhibition with LCZ696



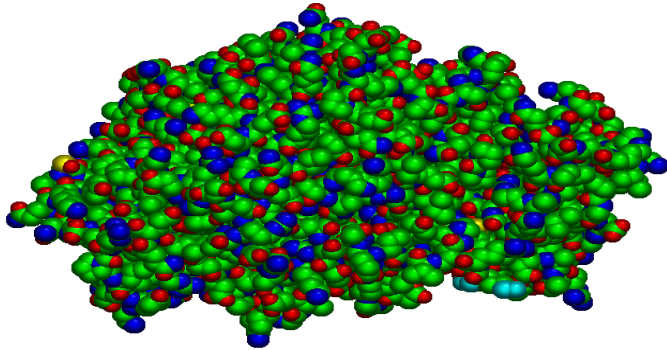
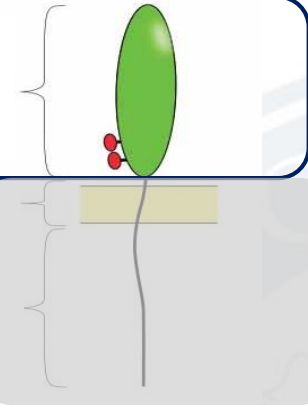
...So, what NP should I use: BNP or NT-proBNP?



NT-proBNP: remains a good **biomarker** for diagnosis, prognosis, monitoring
BNP: changes its role from biomarker to **biotarget**

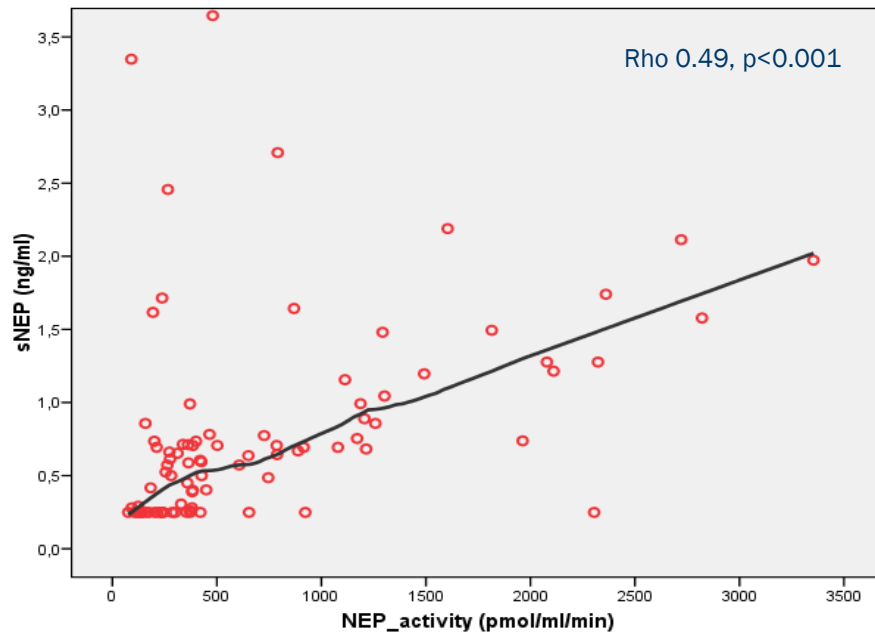
NEP may be found as a circulating peptide: sNEP

Large CT **Extracellular domain** (55-750 aa)
with a Zn atom at the active site



NEP extracellular domain, Human 55-750

Is sNEP catalytically active?



Bayes-Genis A, et al. J Heart Lung Transpl 2016;35:684-5.

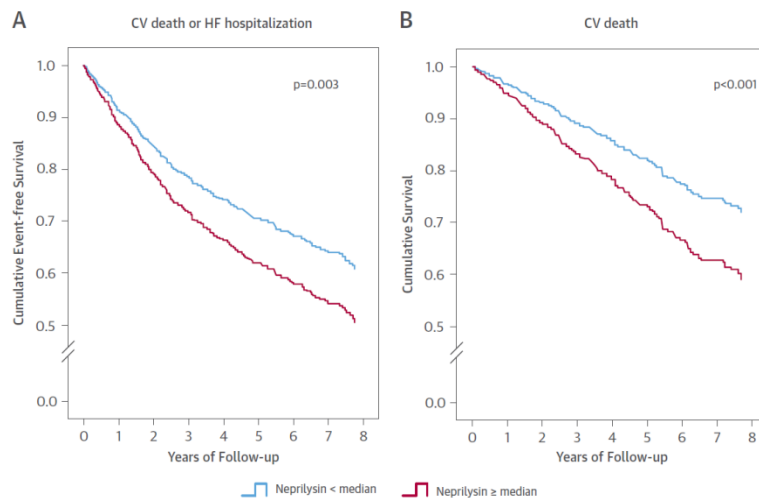


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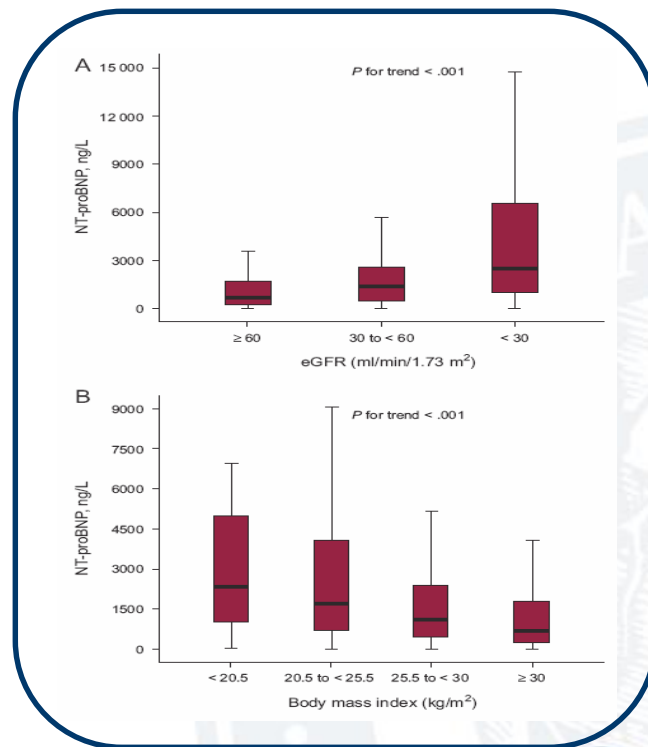
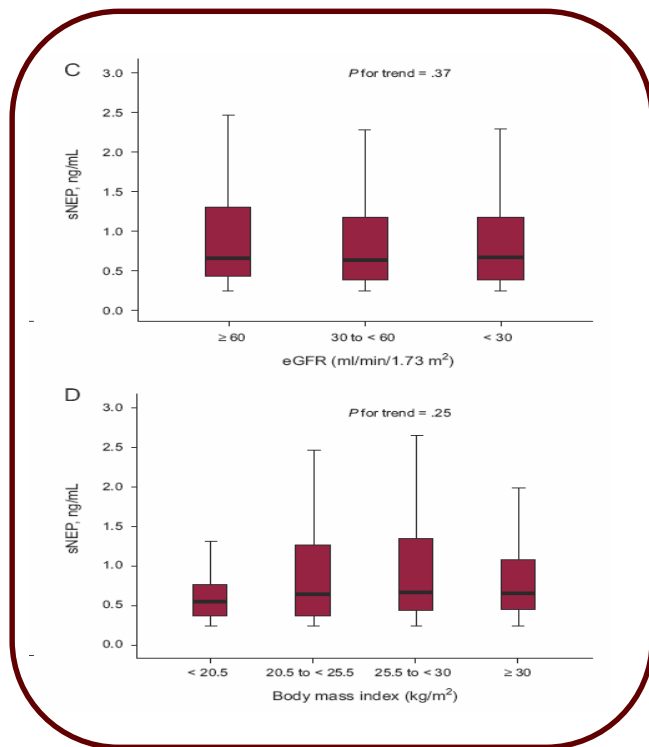
sNEP and prognosis in chronic HF

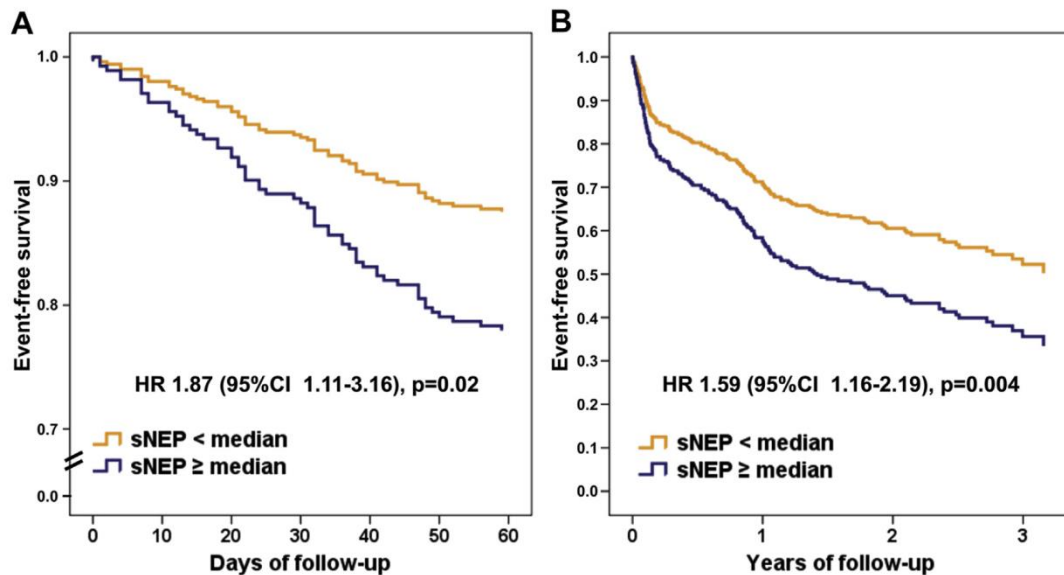
	Composite Primary Endpoint			Cardiovascular Death		
	HR	95% CI	P value	HR	95% CI	P value
sNEP	1.18	1.07 - 1.31	0.001	1.18	1.05 - 1.32	0.006

18% Increased Risk



sNEP vs. NTproBNP: eGFR and BMI





- High sNEP in AHF with prognostic value argues in favour of initiating LCZ696 within hospital admission

Clinical studies using sNEP for HF prognostication

TABLE 2 Clinical Studies Using sNEP for HF Prognostication

First Author (Ref. #)	HF Setting	n	Age, yrs	LVEF, %	NT-proBNP, ng/l	Female, %	Assay	Lot No.	Matrix	sNEP, pg/ml
Bayés-Genís et al (90)	HFrEF	1,069	66.2	33.5	1,302	28.2	SK00724-01 Aviscera Bioscience (Santa Clara, CA)	20111893	Serum	642
Vodovar et al (41)	ADHF	469	74	45	5,682	47	SEB785Hu USCN Life Science (Wuhan, China)	NA	Plasma	314
Bayés-Genís (93)	ADHF	350	72.6	46.6	3,953	53.1	SK00724-01 Aviscera Bioscience	20112070	Serum	670
Goliasch et al (92)	HFpEF	144	72	62	1,148	65	SEB785Hu USCN Life Science	NA	Plasma	2,862

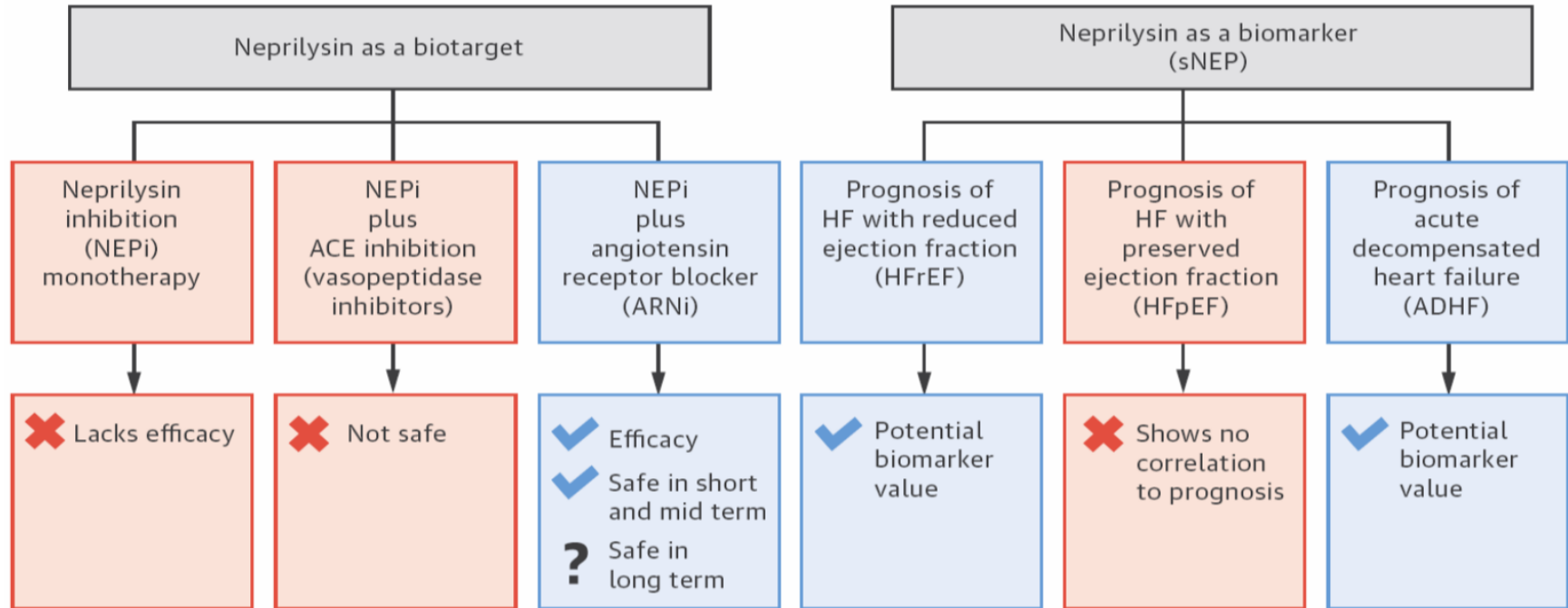
ADHF = acutely decompensated heart failure; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NA = not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sNEP = soluble neprilysin.

Performance of the marketed sNEP assays

TABLE 3 Performance Characteristics of the 4 Commercially Available Assays for sNEP

	Coating Antibody	Detection Antibody	Assay Range, pg/ml	Intraassay CV, %	Interassay CV, %	Protocol	Controls Provided	Cross-Reactivity Studies
SK00724-01 Aviscera Bioscience (Santa Clara, CA)	Polyclonal	Polyclonal	125–8,000	6	12	2-step (sandwich)	Positive control, 500 pg/ml	Human ECE-1 and ECE-2 Human NEP-2 Mouse Kell
SEB785Hu USCN Life Science (Wuhan, China)	Not specified	Not specified	31–2,000	10	12	2-step (sandwich)	None	NA
EK0851 Boster Bio (Pleasanton, CA)	Monoclonal	Polyclonal	125–8,000	5.6	7.3	2-step (sandwich)	None	NA
FIVEphoton Biochemicals (San Diego, CA)	Monoclonal	Polyclonal	5–1,000	NA	NA	Single-step	None	NA
CV = coefficient variation (highest reported) according to the manufacturer; ECE = endothelin-converting enzyme; NEP = neprilysin; other abbreviations as in Table 2 .								

Take-home message





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