הלב הוא לא רק איבר מטרה של סוברת, הוא גם איבר אנדוקריני

ד"ר אבישי גרופר

מנהל מרפאות המערך הקרדיולוגי, שיבא, תל השומר

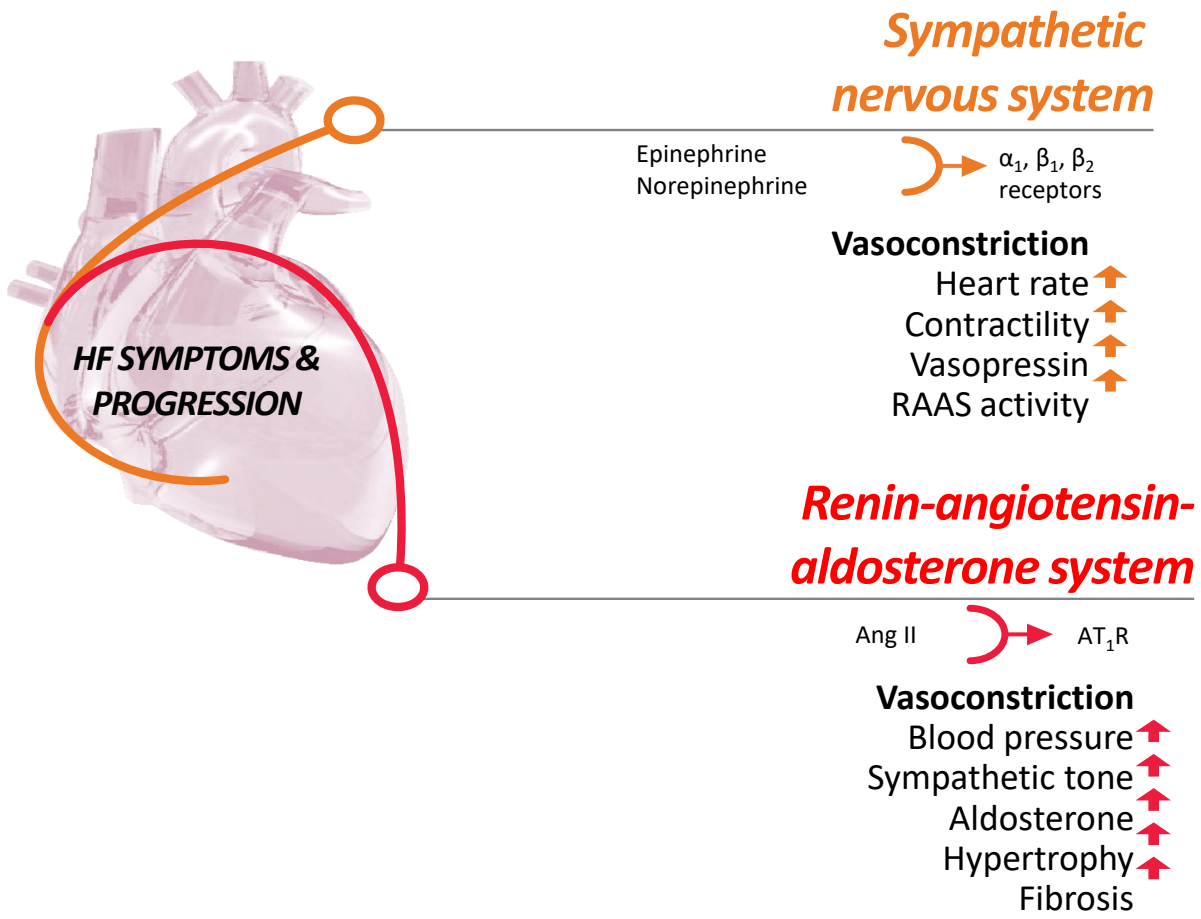
יו"ר החוג לאי ספיקת לב באיגוד הקרדיולוגי

SHEBA Tel HaShomer | The Leviev Cardiothoracic & Vascular Center

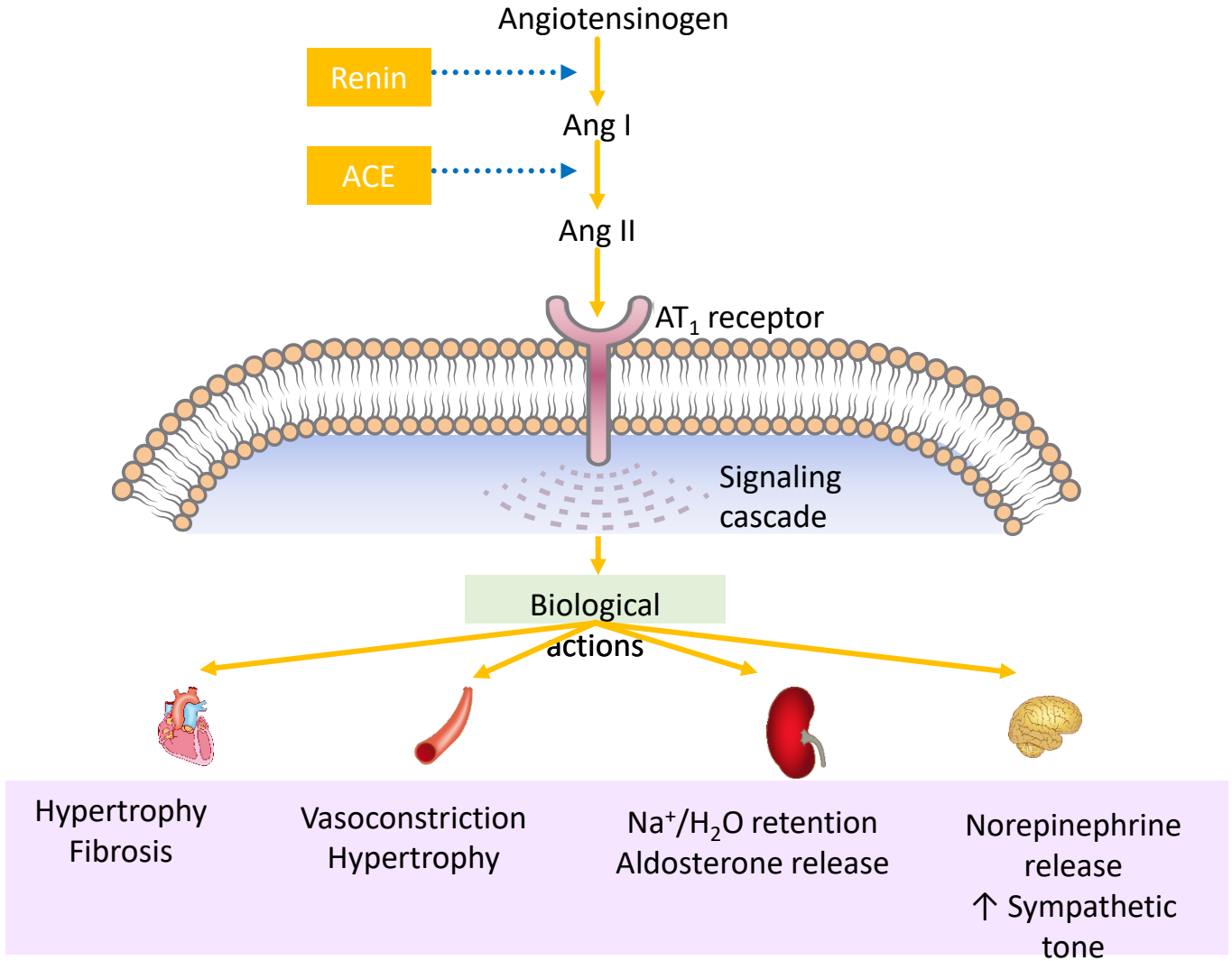
TEL AVIV UNIVERSITY אוניברסיטת תל אביב

האיגוד הקרדיולוגי בישראל ISRAEL HEART SOCIETY

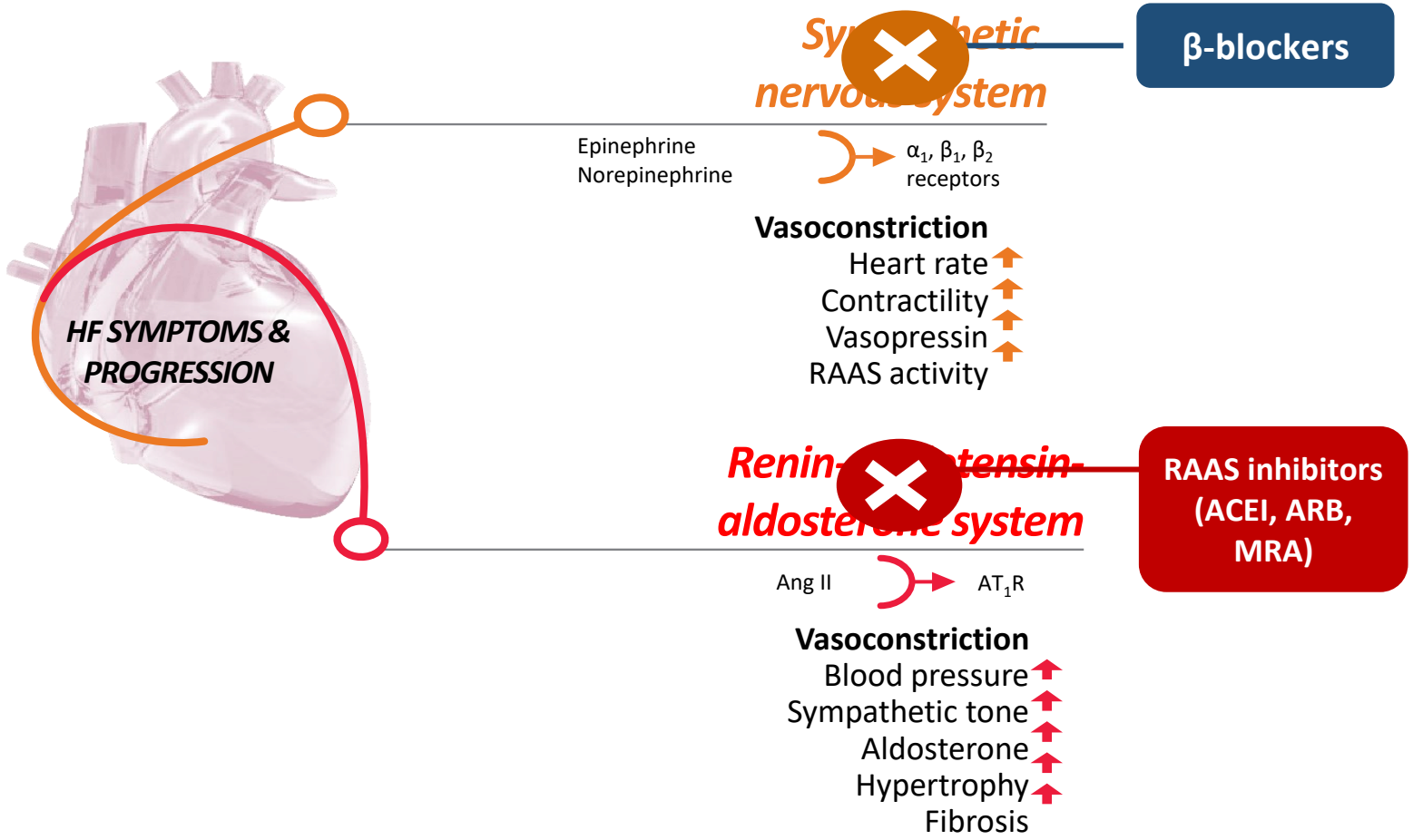
Decline in systolic function leads to activation of three major neurohormonal systems



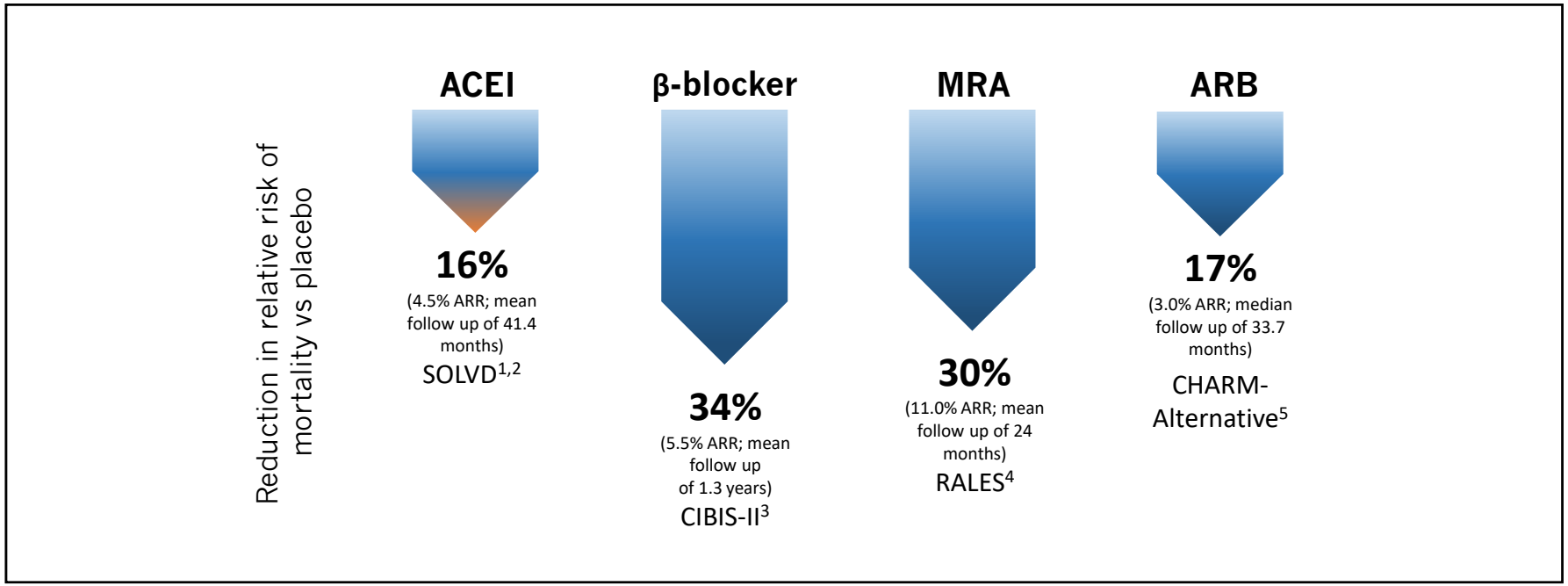
The RAAS is activated in HF – initially compensatory and subsequently pathological



Decline in systolic function leads to activation of three major neurohormonal systems



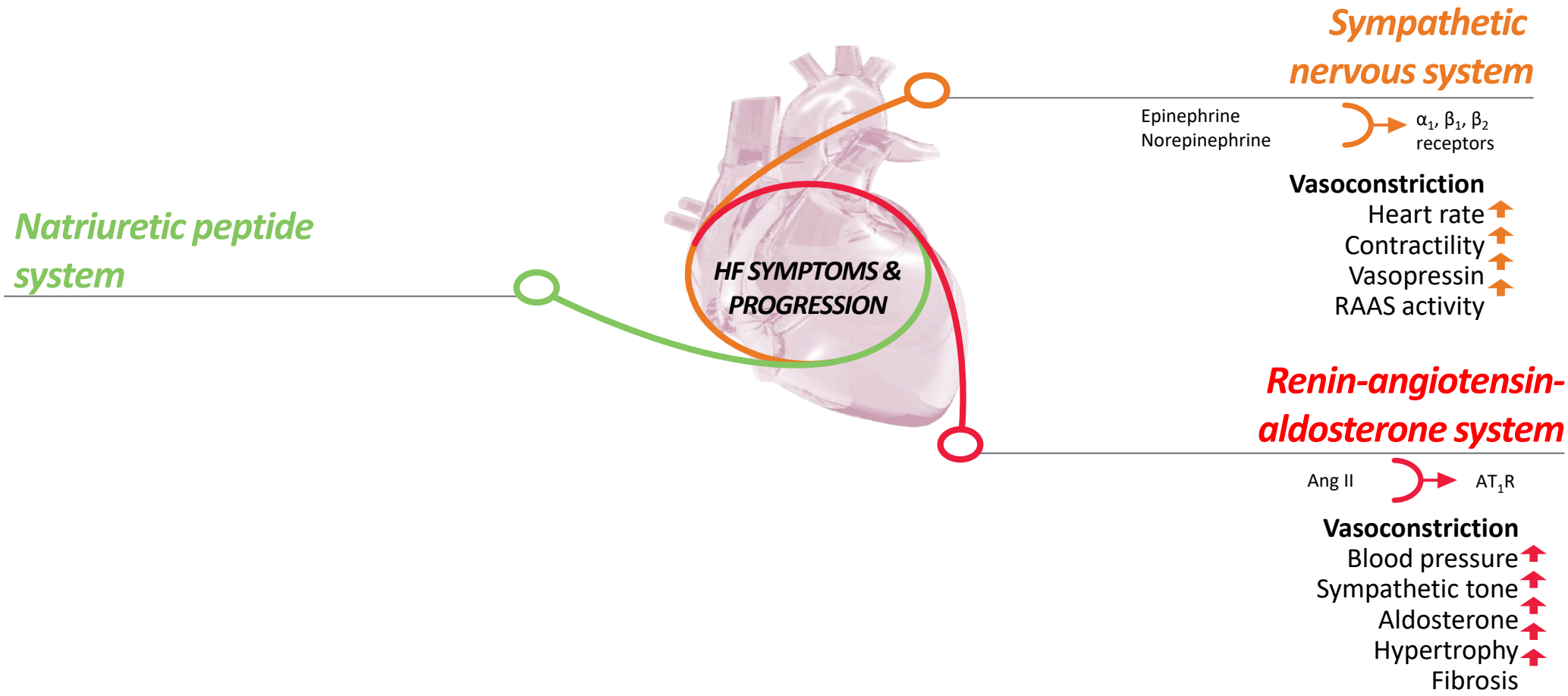
Mortality in HFrEF remains high despite the introduction of new therapies that improve survival



However, significant mortality remains – ~50% of patients die within 5 years of diagnosis[6–8]

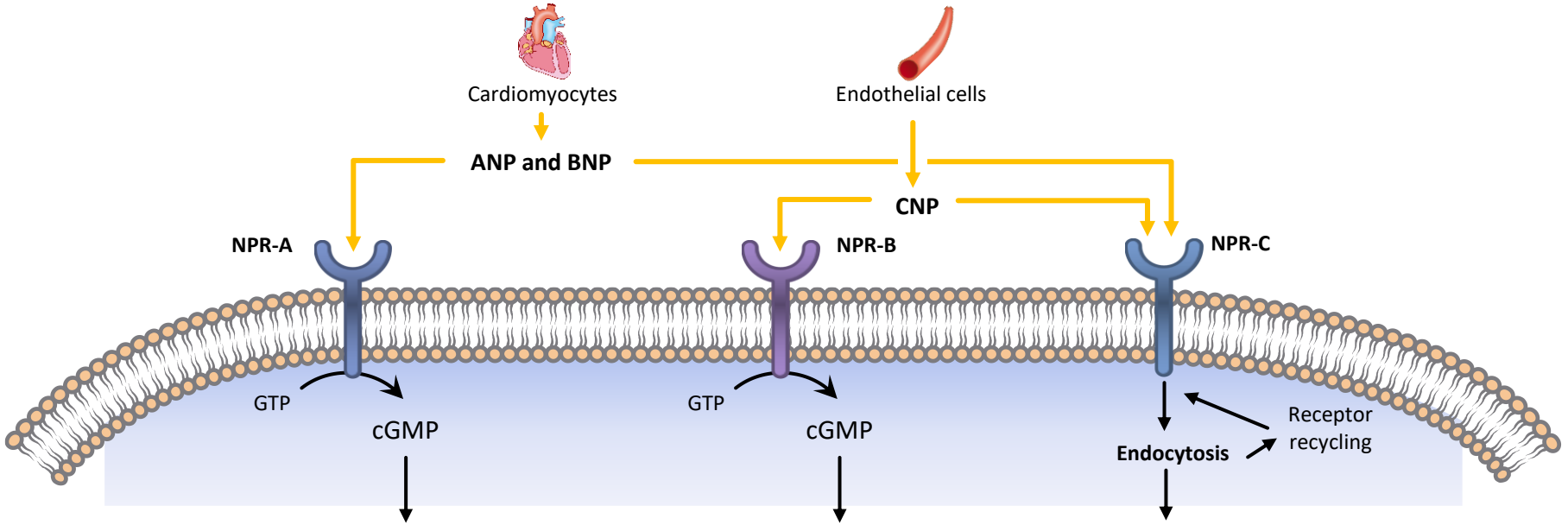
1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Granger et al. Lancet 2003;362:772–66. 6. Go et al. Circulation 2014;129:e28-e292; 7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 1996;334:1397–402

Decline in systolic function leads to activation of three major neurohormonal systems




1981
Discovery
of ANP[1]
1980s

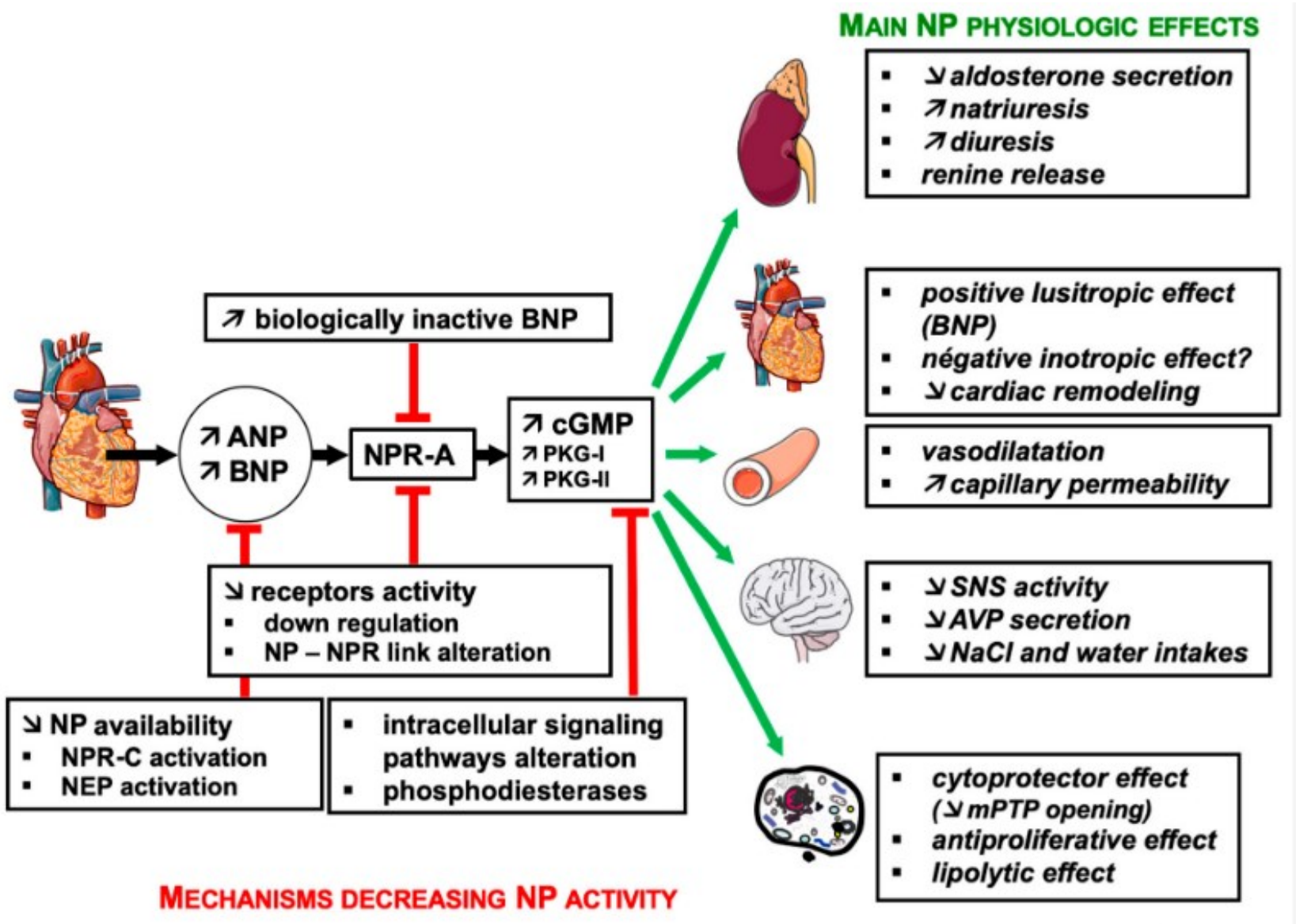
The heart is releasing natriuretic peptides in response to mechanical stretch. Natriuretic peptides mediate a wide range of physiological effects via their receptors that counter some effects of RAAS activation



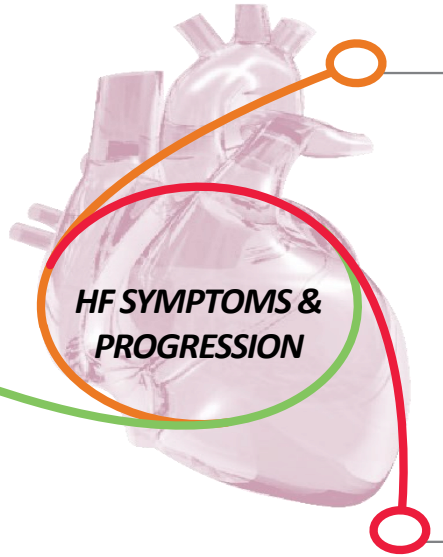
- Vasodilation
- Antihypertrophy
- Antiproliferation
- Vascular regeneration
- Myocardial relaxation
- Diuresis, natriuresis
- Antiapoptosis
- Anti-aldosterone
- Renin secretion inhibition
- Reduced sympathetic tone
- Lipolysis

- Vasodilation
- Antihypertrophy
- Antiproliferation
- Vascular regeneration
- Venodilation
- Antifibrosis

Inactivation of NPs


MAIN NP PHYSIOLOGIC EFFECTS
↘ aldosterone secretion
↗ natriuresis
↗ diuresis
renine release
positive lusitropic effect (BNP)
négative inotropic effect?
↘ cardiac remodeling
vasodilatation
↗ capillary permeability
↘ SNS activity
↘ AVP secretion
↘ NaCl and water intakes
cytoprotector effect (↘ mPTP opening)
antiproliferative effect
lipolytic effect
↗ biologically inactive BNP
↗ ANP
↗ BNP
NPR-A
↗ cGMP
↗ PKG-I
↗ PKG-II
↘ receptors activity
down regulation
NP – NPR link alteration
↘ NP availability
NPR-C activation
NEP activation
intracellular signaling pathways alteration
phosphodiesterases
MECHANISMS DECREASING NP ACTIVITY

Decline in systolic function leads to activation of three major neurohormonal systems



Sympathetic nervous system

Epinephrine
Norepinephrine
→ α_1, β_1, β_2 receptors

Vasoconstriction
- Heart rate ↑
- Contractility ↑
- Vasopressin ↑
- RAAS activity ↑

Natriuretic peptide system

NPRs ← NPs

Vasodilation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↑ Natriuresis/diuresis
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- Hypertrophy

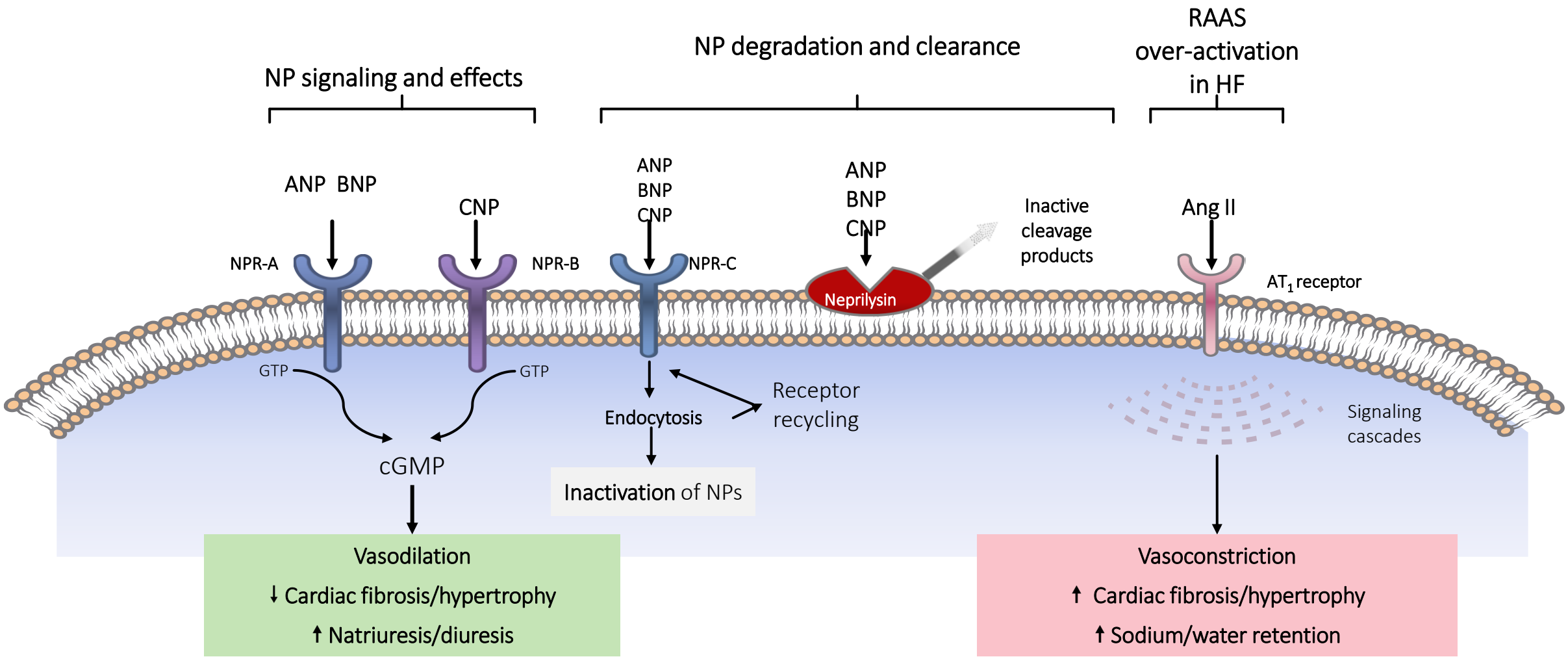
Renin-angiotensin-aldosterone system

Ang II → AT_1R

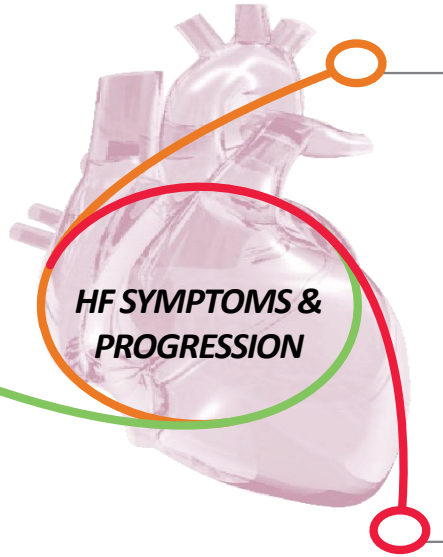
Vasoconstriction
- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis


1981
Discovery of ANP[1]
1980s
1988
NEP identified as the primary enzyme responsible for degrading ANP

Natriuretic peptides are cleared by NPR-C and neprilysin



Decline in systolic function leads to activation of three major neurohormonal systems



Sympathetic nervous system

Epinephrine
Norepinephrine
→ α_1, β_1, β_2 receptors

Vasoconstriction
- Heart rate ↑
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- RAAS activity ↑

Natriuretic peptide system

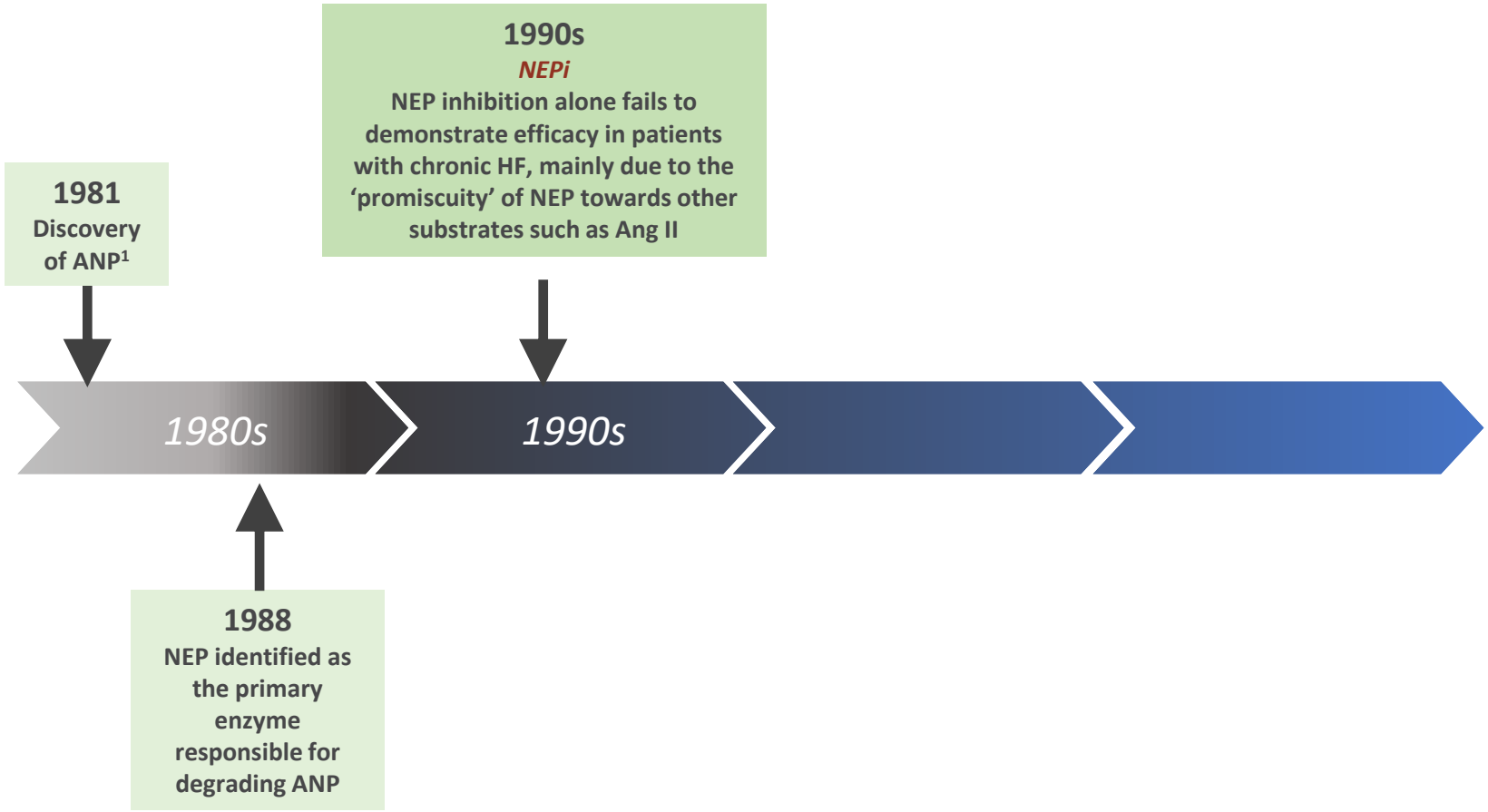
NPRs ← NPs

Vasodilation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↑ Natriuresis/diuresis
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- Hypertrophy

Renin-angiotensin-aldosterone system

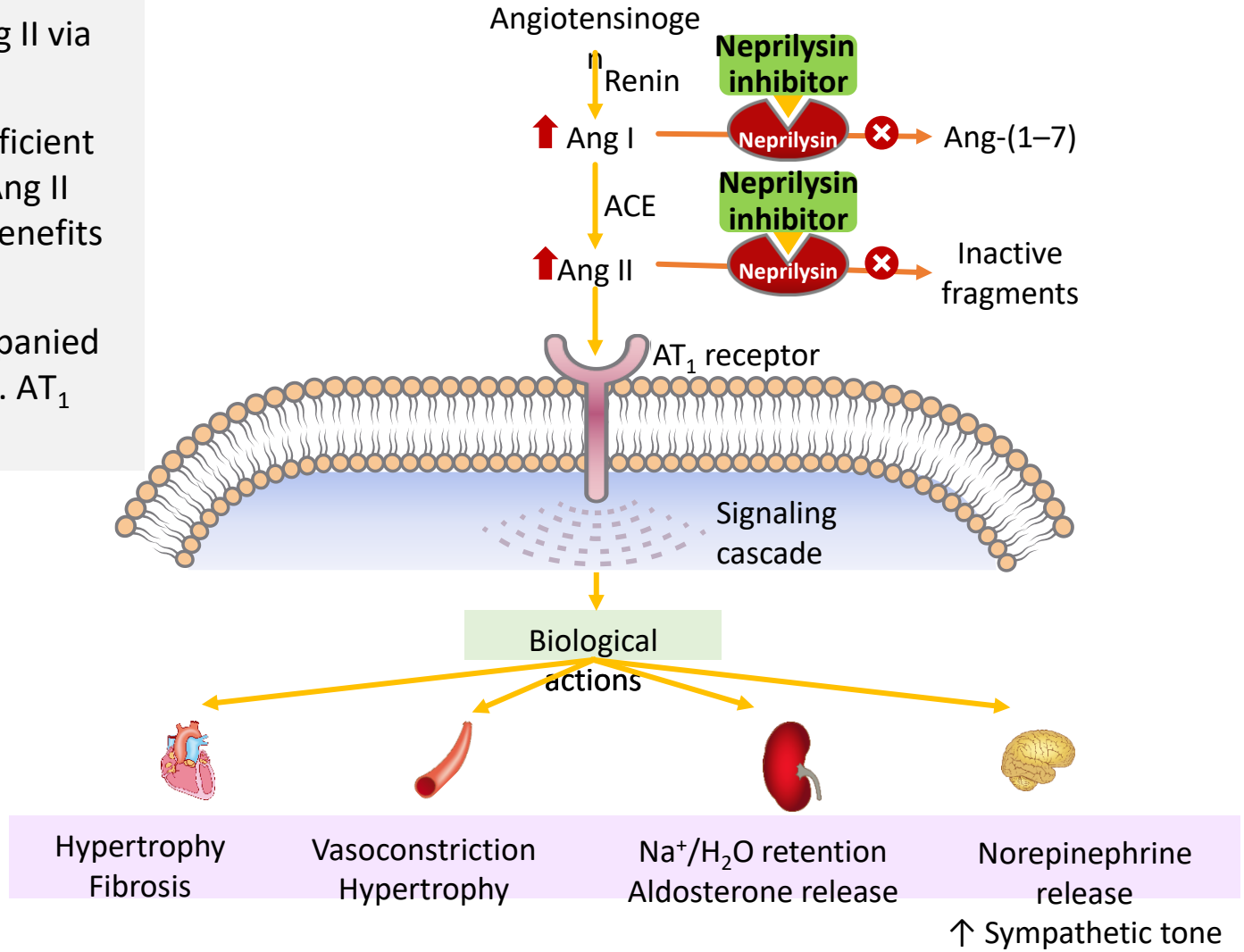
Ang II → AT_1R

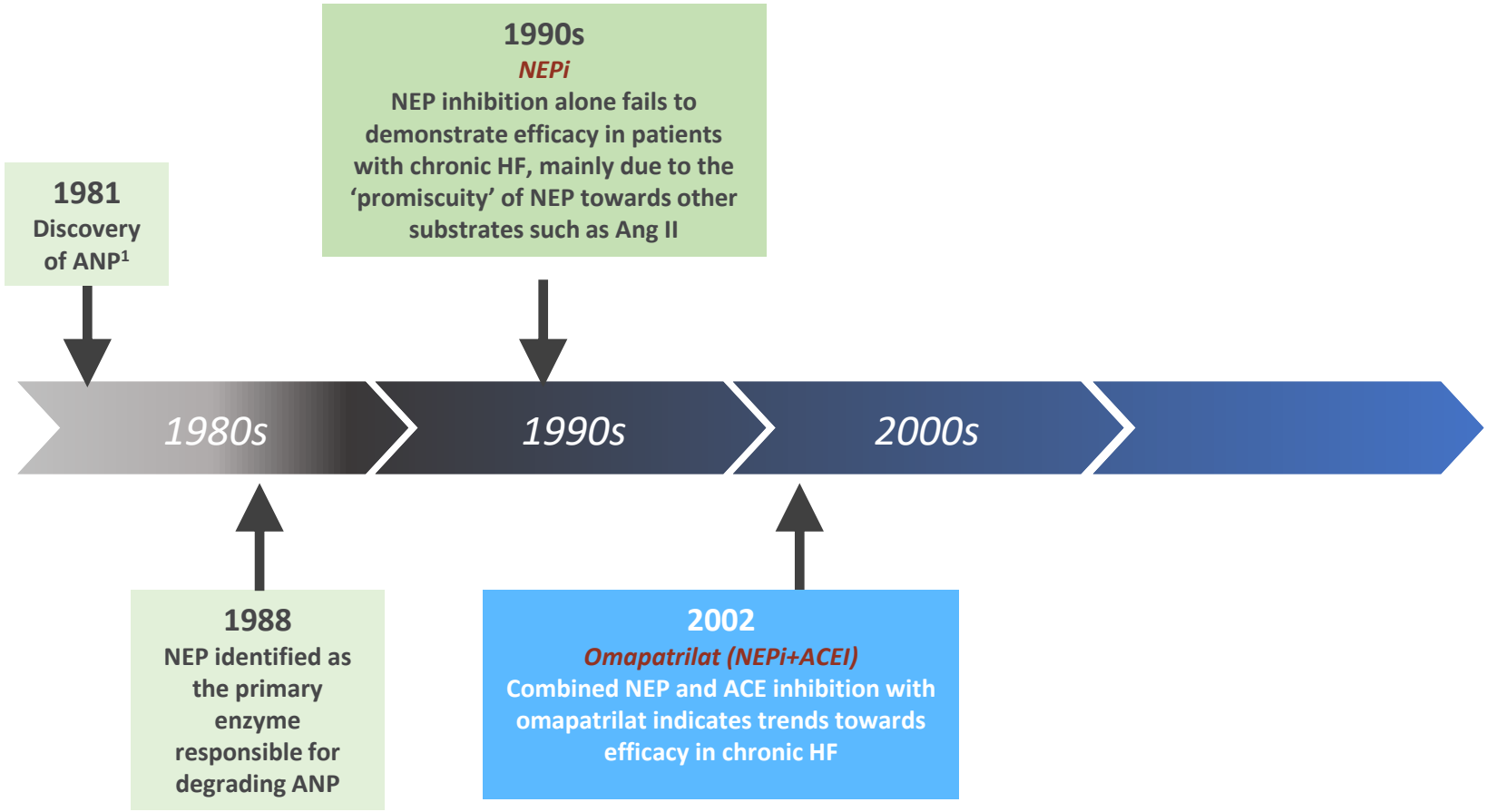
Vasoconstriction
- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis


1990s
NEPi
NEP inhibition alone fails to demonstrate efficacy in patients with chronic HF, mainly due to the 'promiscuity' of NEP towards other substrates such as Ang II
1981
Discovery of ANP[1]
1980s
1990s
1988
NEP identified as the primary enzyme responsible for degrading ANP

Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

- Neprilysin metabolizes Ang I and Ang II via several pathways
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT_1 receptor blockade)




1981
Discovery of ANP[1]
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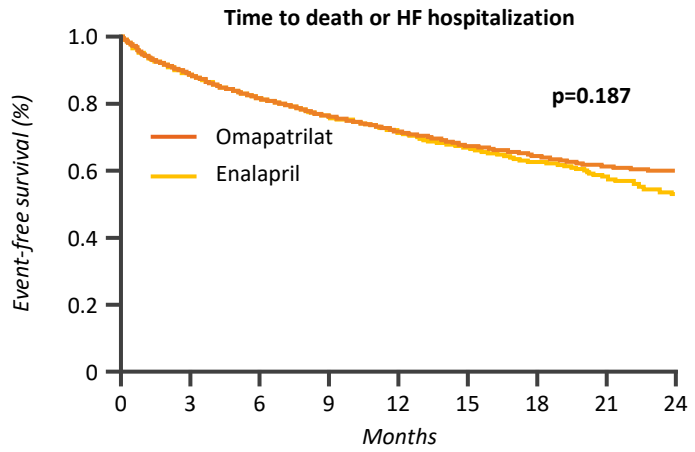
NEP inhibition alone fails to demonstrate efficacy in patients with chronic HF, mainly due to the 'promiscuity' of NEP towards other substrates such as Ang II
1980s
1990s
2000s
1988
NEP identified as the primary enzyme responsible for degrading ANP
2002
Omapatrilat (NEPi+ACEI)
Combined NEP and ACE inhibition with omapatrilat indicates trends towards efficacy in chronic HF

OVERTURE study shows trends towards efficacy with dual NEP-ACEI but raises significant safety concerns

In the OVERTURE study, the dual NEP-ACE inhibitor omapatrilat was compared with the ACEI enalapril in 5,770 patients with HFrEF for a mean of 14.5 months*

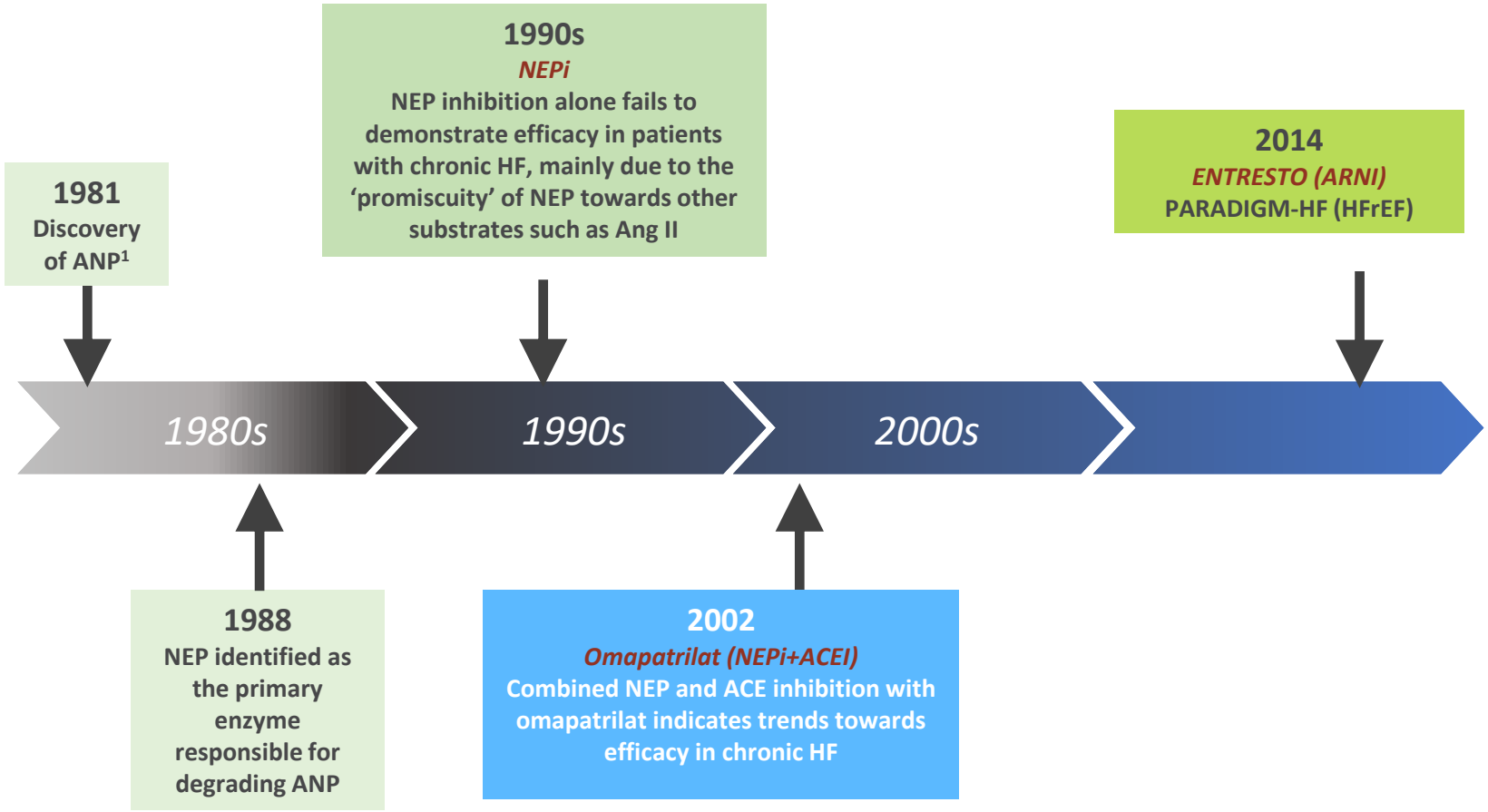


Packer et al. Circulation 2002;106:920–6

Development of omapatrilat was discontinued due to:

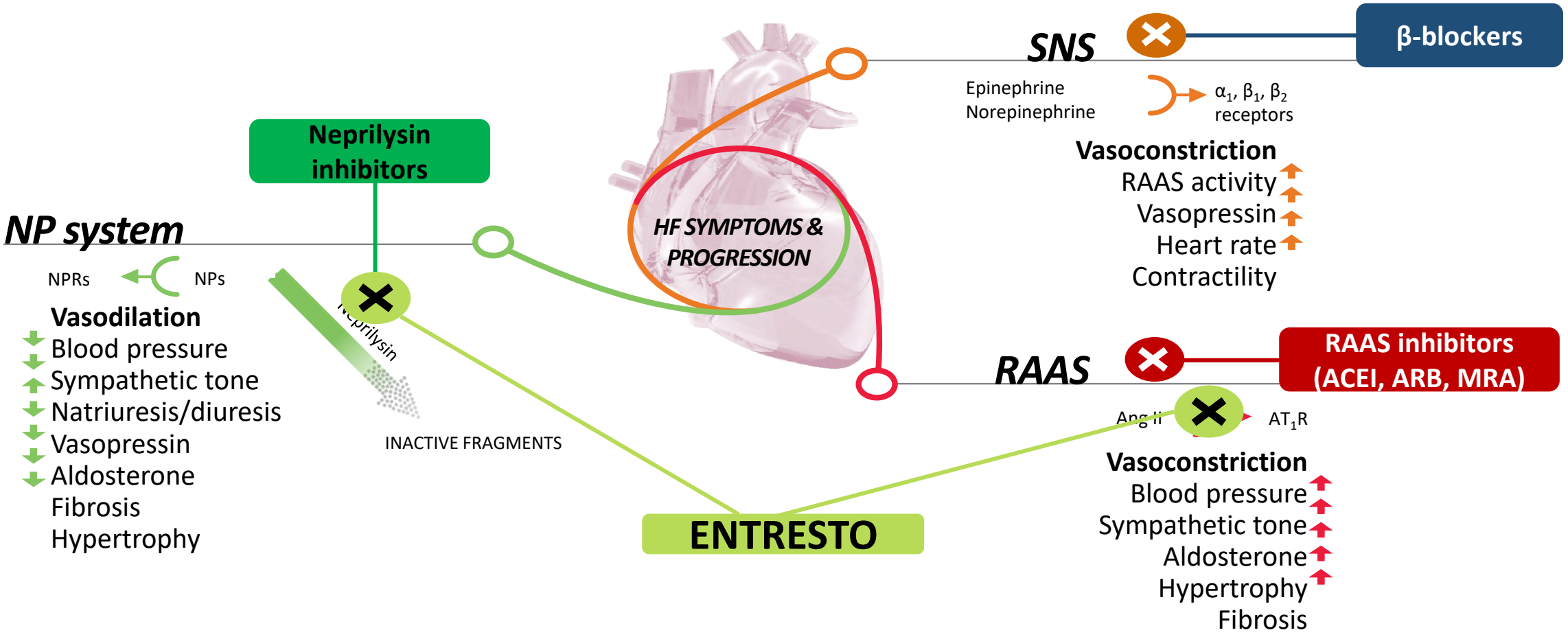
Lack of efficacy
attributed to sub-optimal NEP and ACE inhibition over 24 hours due to the once-daily dosing regimen

Safety concern
unacceptable risk of angioedema (24 patients [0.8%] vs 14 patients [0.5%] for omapatrilat and enalapril, respectively). This was attributed to simultaneous NEP and ACE inhibition leading to elevated bradykinin levels, which are associated with cough and angioedema

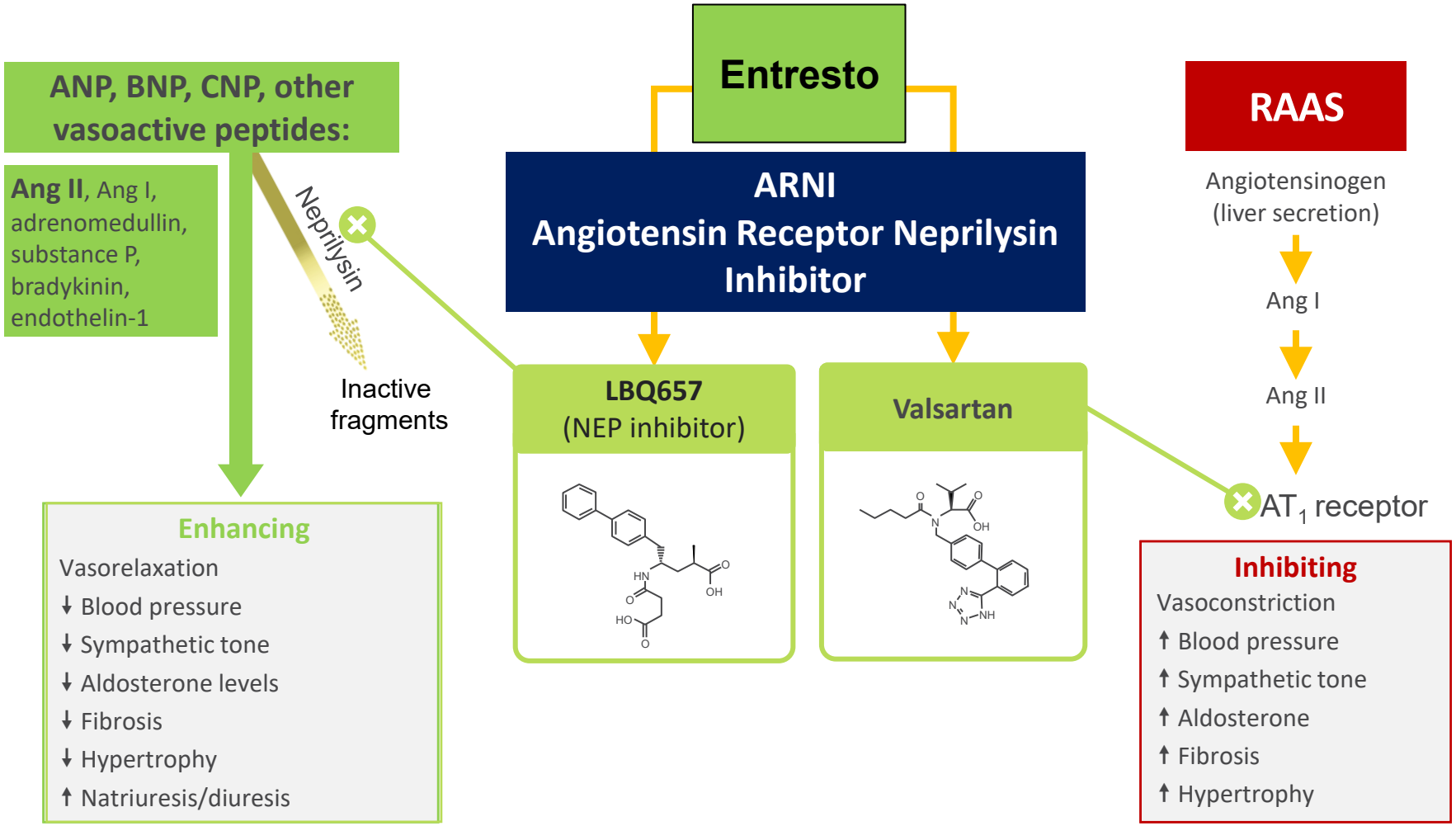

1981
Discovery of ANP[1]
1990s
NEPi
NEP inhibition alone fails to demonstrate efficacy in patients with chronic HF, mainly due to the 'promiscuity' of NEP towards other substrates such as Ang II
2014
ENTRESTO (ARNI)
PARADIGM-HF (HFrEF)
1980s
1990s
2000s
1988
NEP identified as the primary enzyme responsible for degrading ANP
2002
Omapatrilat (NEPi+ACEI)
Combined NEP and ACE inhibition with omapatrilat indicates trends towards efficacy in chronic HF

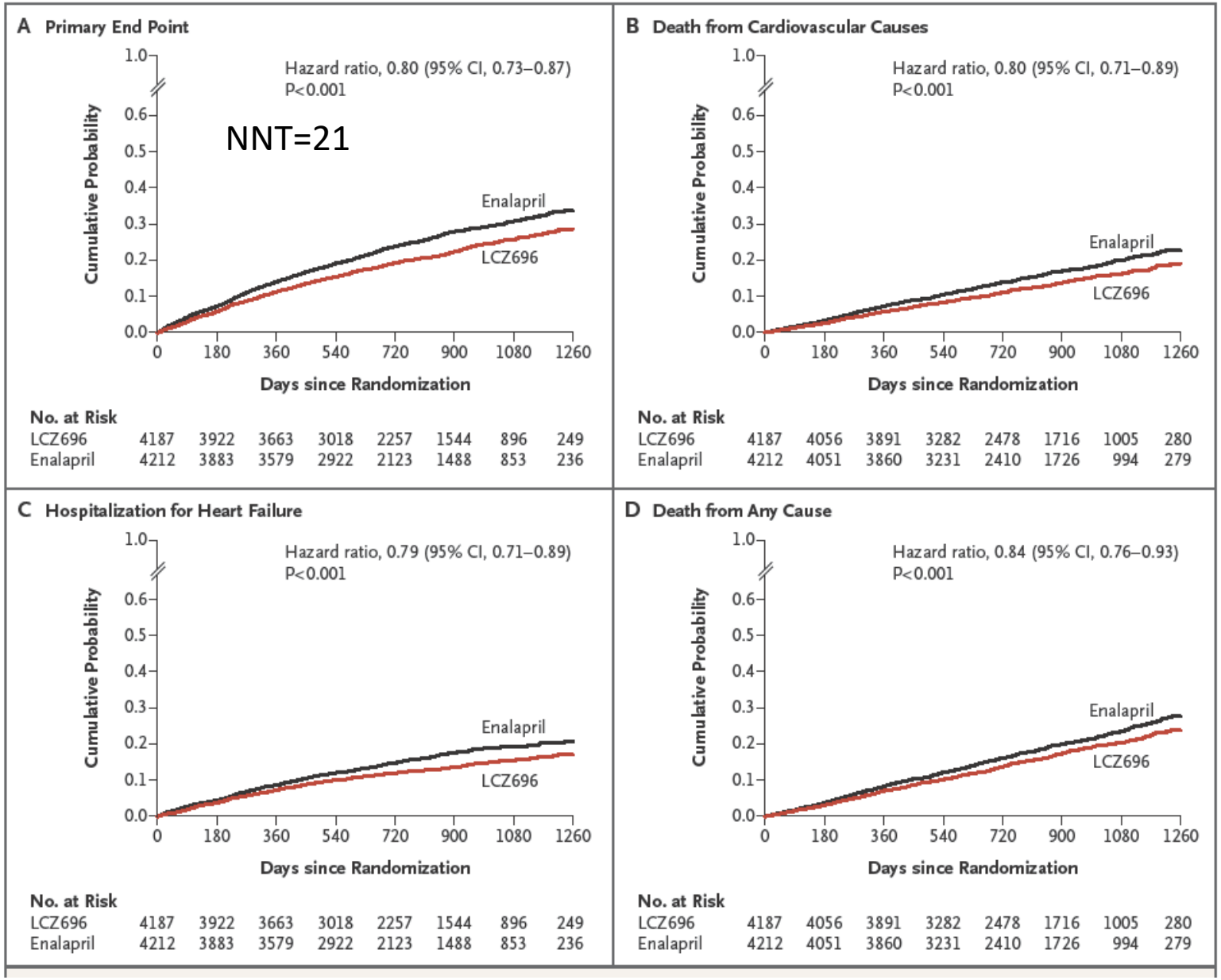
Evolution of pharmacologic approaches in HF:

ENTRESTO as a new alternative to an ACEI or ARBs in patients with HFrEF



LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT_1 receptors (via valsartan)

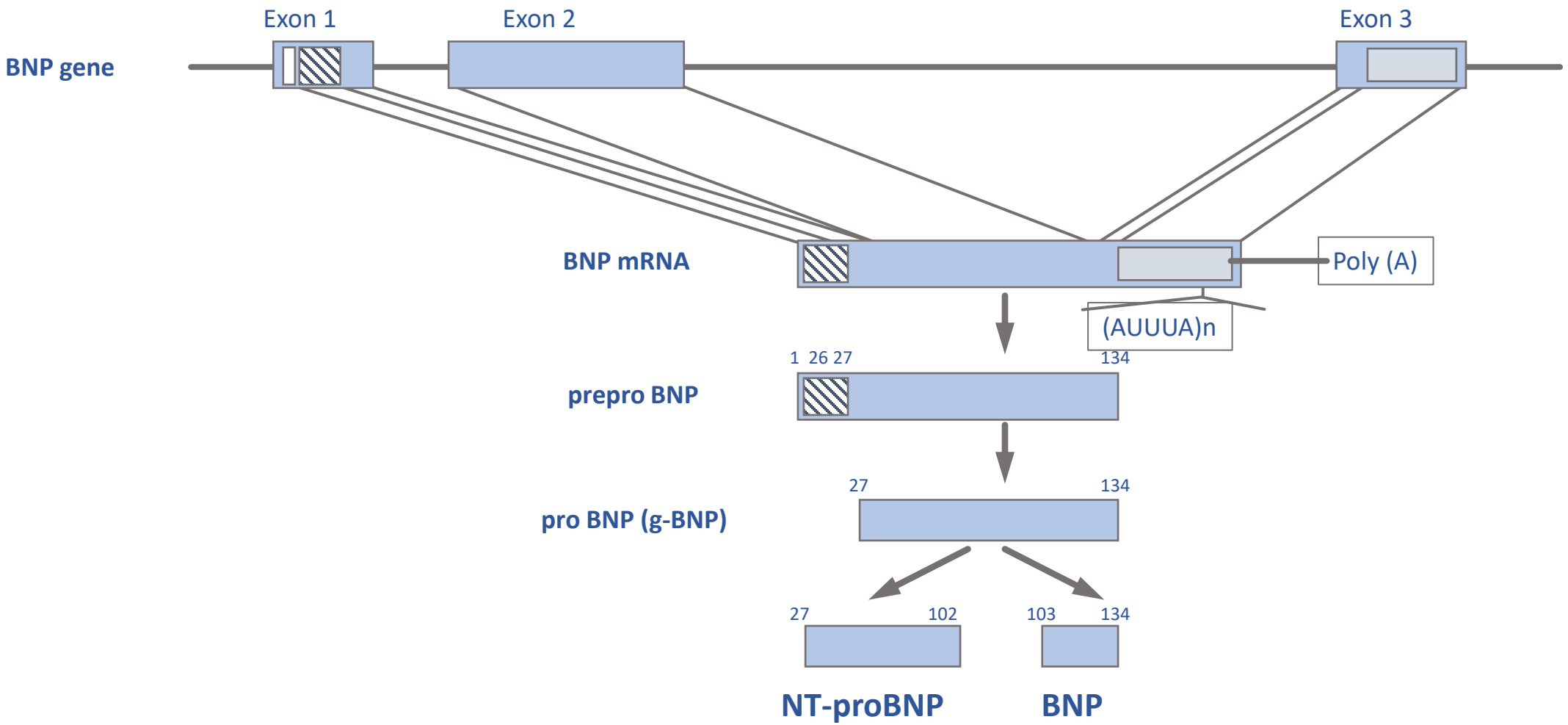




McMurray et al. N Engl J Med 2014;371:993-1004

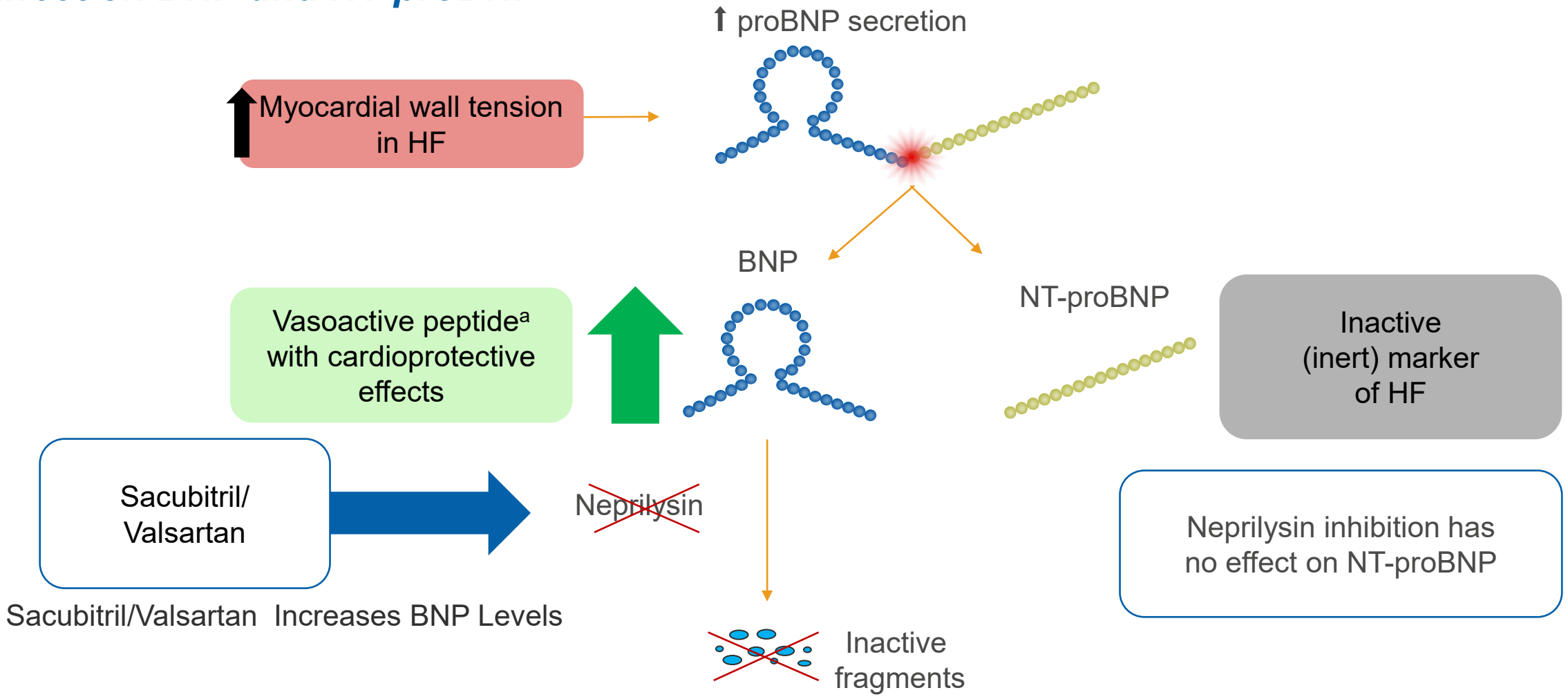
Heart failure biomarkers

BNP and NT-proBNP are formed by cleavage of precursor molecules



Sacubitril/Valsartan

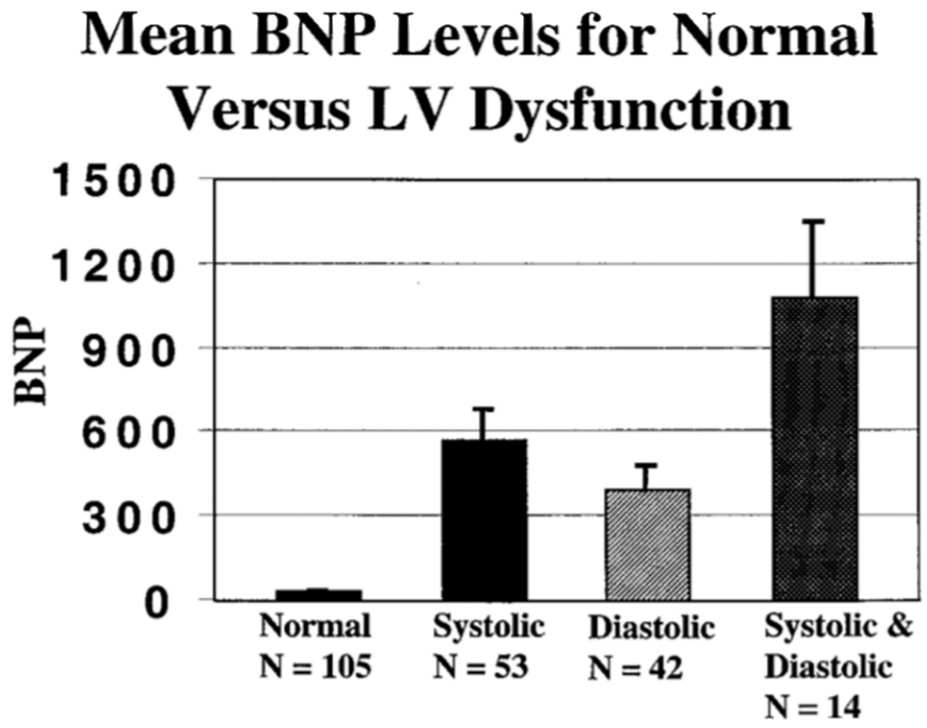
Effect on BNP and NT-proBNP



BNPs, brain natriuretic peptides; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.
[a]Vasoactive peptides include the NPs (atrial NPs, BNPs, C-type NPs), adrenomedullin, and bradykinin.
Modified from Vardeny O et al. Clin Pharmacol Ther. 2013;94:445-448.

Biomarkers: BNP

Though values are generally higher with HFrEF, the values do not adequately differentiate between HFrEF and HFpEF.

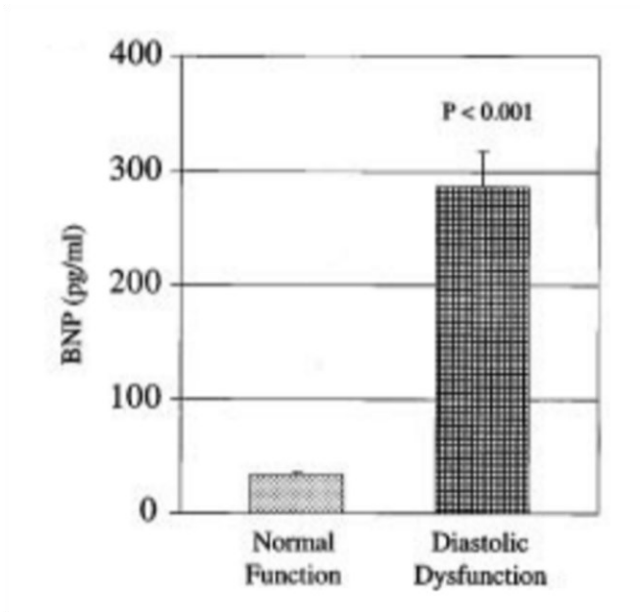


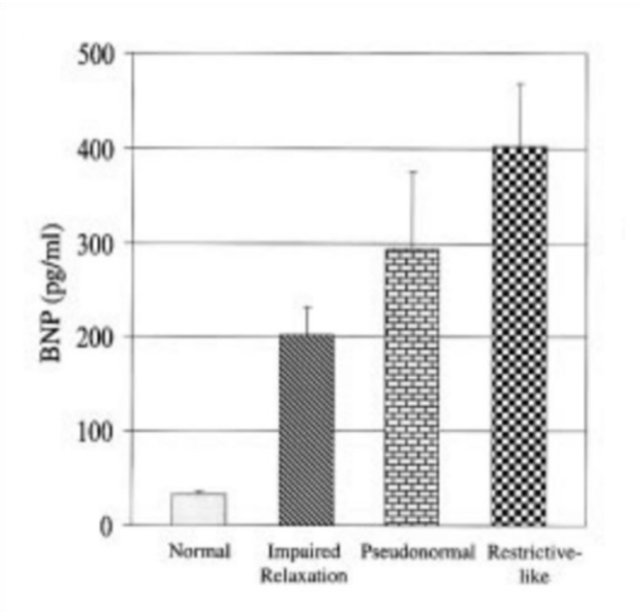
Maisel et al. American Heart Journal, 2001

Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction

Comparison With Doppler Velocity Recordings

Emily Lubien, BS; Anthony DeMaria, MD; Padma Krishnaswamy, MD; Paul Clopton, MS;
Jen Koon, BSN; Radmila Kazanegra, MD; Nancy Gardetto, NP; Erin Wanner, BS; Alan S. Maisel, MD





Am Heart J. 2001;141:367-74.

Recommended diagnostic tests in all patients with suspected chronic heart failure

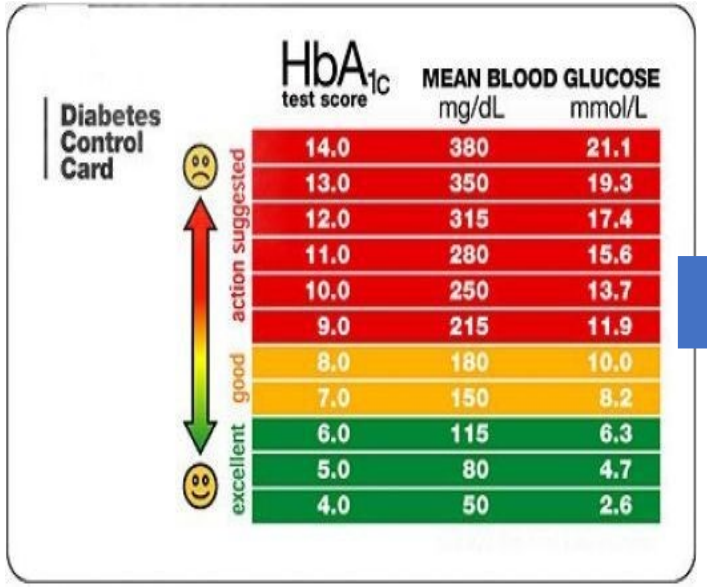
Recommendations	Class	Level
BNP/NT-proBNP[a]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea an electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

BNP = B-type natriuretic peptide; ECG = electrocardiogram; HbA1c = glycated haemoglobin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturation.
[a]References are listed in section 4.2 for this item.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

The change in the paradigm of antidiabetic treatment goals

From glucocentricity to reduction of CV risk and mortality



CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin

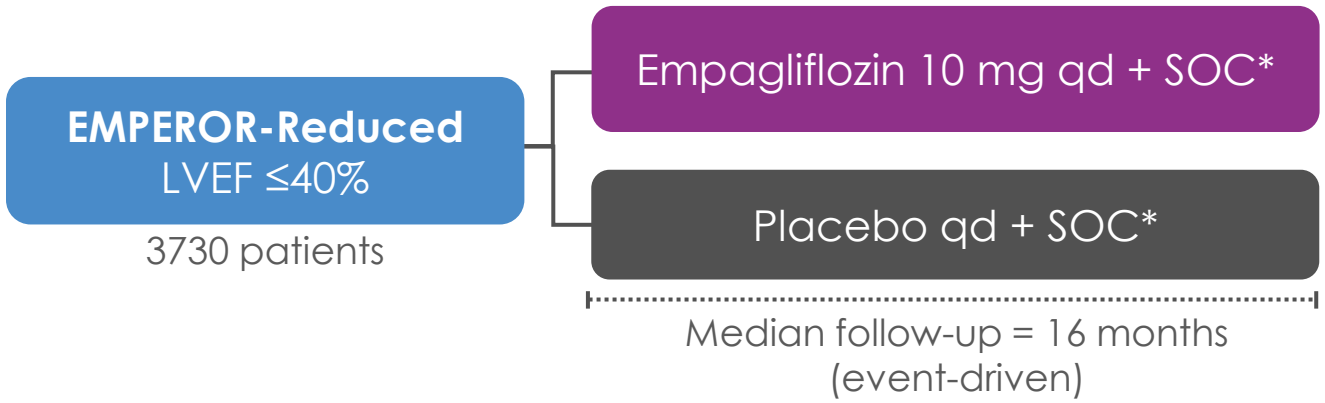
EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HF with **reduced ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1–3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF events**
- **eGFR slope: change from baseline**

*Guideline-directed medical therapy

CV, cardiovascular; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; T2D, type 2 diabetes

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M et al. Eur J Heart Fail 2019;21:1270; 3. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Trial inclusion and exclusion criteria

Inclusion criteria

EMPEROR-Reduced[1,2]		DAPA-HF[3]
Age ≥18 years (Japan, age ≥20 years) at screening		Age ≥18 years
Chronic HF NYHA class II–IV		Chronic HF NYHA class II–IV
HFrEF (LVEF ≤40%)		HFrEF (LVEF ≤40%)
Elevated NT-proBNP		**NT-proBNP ≥600 pg/ml or NT-proBNP ≥400 pg/ml in patients with HHF within 12 months**
EF (%)	**NT-proBNP (pg/ml)** Patients without AF*	Patients without AF†
≥36 to ≤40	≥2500	
≥31 to ≤35	≥1000	
≤30	≥600	
≤40% + HHF within 12 months	≥600	
Further inclusion criteria apply		Further inclusion criteria apply

EMPEROR-Reduced
eGFR <20 ml/min/1.73 m²
or requiring dialysis

eGFR exclusion criteria
Further exclusion criteria apply

DAPA-HF
eGFR <30 ml/min/1.73 m²
or rapidly declining renal function

*The cut off for patients with AF is doubled in EMPEROR-Reduced; †In DAPA-HF patients with AF or atrial flutter were required to have NT-proBNP ≥900 pg/ml regardless of history of HHF
AF, atrial fibrillation; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association
1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Zannad F et al. ESC-HF 2018; poster P1755; 3. McMurray JJV et al. N Engl J Med. 2019;381:1995

Changes in vital signs and laboratory findings

Laboratory and other measurements (change from baseline to 52 weeks)	Empagliflozin (n=1863)	Placebo (n=1867)	Absolute difference (95% CI)
Haematocrit (%) – mean (SE)	1.98 ± 0.10	-0.38 ± 0.10	2.36 (2.08, 2.63)
NT-proBNP (pg/ml) – median (IQR)*	-244 (-890, 260)	-141 (-784, 585)	0.87 (0.82, 0.93)
Body weight (kg) – mean (SE)	-0.73 ± 0.13	0.08 ± 0.13	-0.82 (-1.18 to -0.45)
Systolic blood pressure (mm Hg) – mean (SE)	-2.4 ± 0.4	-1.7 ± 0.4	-0.7 (-1.8 to 0.4)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cr, creatine; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro−B-type natriuretic peptide; LVEF, left ventricular ejection fraction

*NT-proBNP was analyzed with the use of a geometric mean ratio

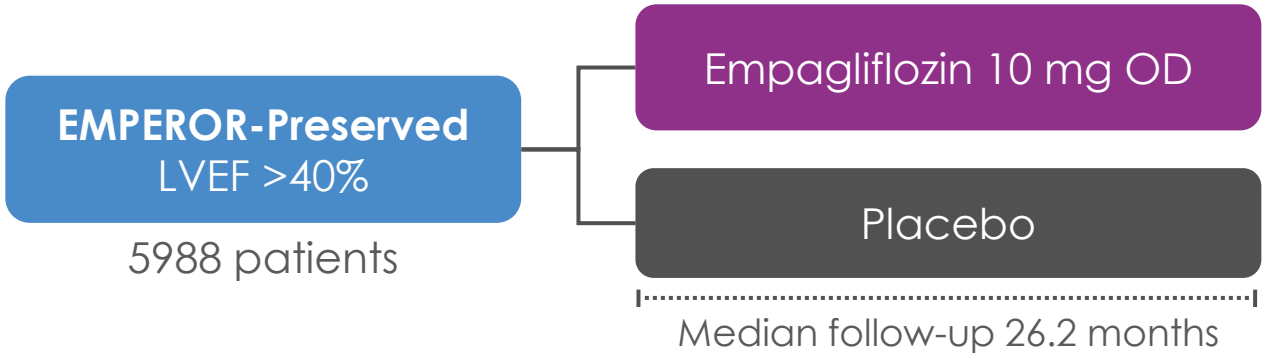
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

EMPEROR-Preserved study design

Phase III trial* in patients with HFpEF

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with **preserved ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)



Patients with structural heart disease* or HHF within 12 months of screening

**left atrial enlargement or LV hypertrophy*

COMPOSITE PRIMARY ENDPOINT

- **Time to first event of adjudicated CV death or adjudicated HHF**

CONFIRMATORY KEY SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF**
- **Slope of change in eGFR (CKD-EPI) from baseline**

Empagliflozin is not indicated for use in patients with heart failure with preserved ejection fraction

*Randomized, double-blind, placebo-controlled trial. *Empagliflozin is not indicated for use in patients with heart failure with preserved ejection fraction

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OD, once daily; T2D, type 2 diabetes.

Anker S *et al. N Engl J Med*. 2021; doi:10.1056/NEJMoa2107038.

EMPEROR-Preserved: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• Symptomatic hypotension and/or SBP <100 mmHg
	• eGFR <20 mL/min/1.73 m^2 or requiring dialysis

Further criteria apply

AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Anker S *et al. N Engl J Med*. 2021; doi:10.1056/NEJMoa2107038.

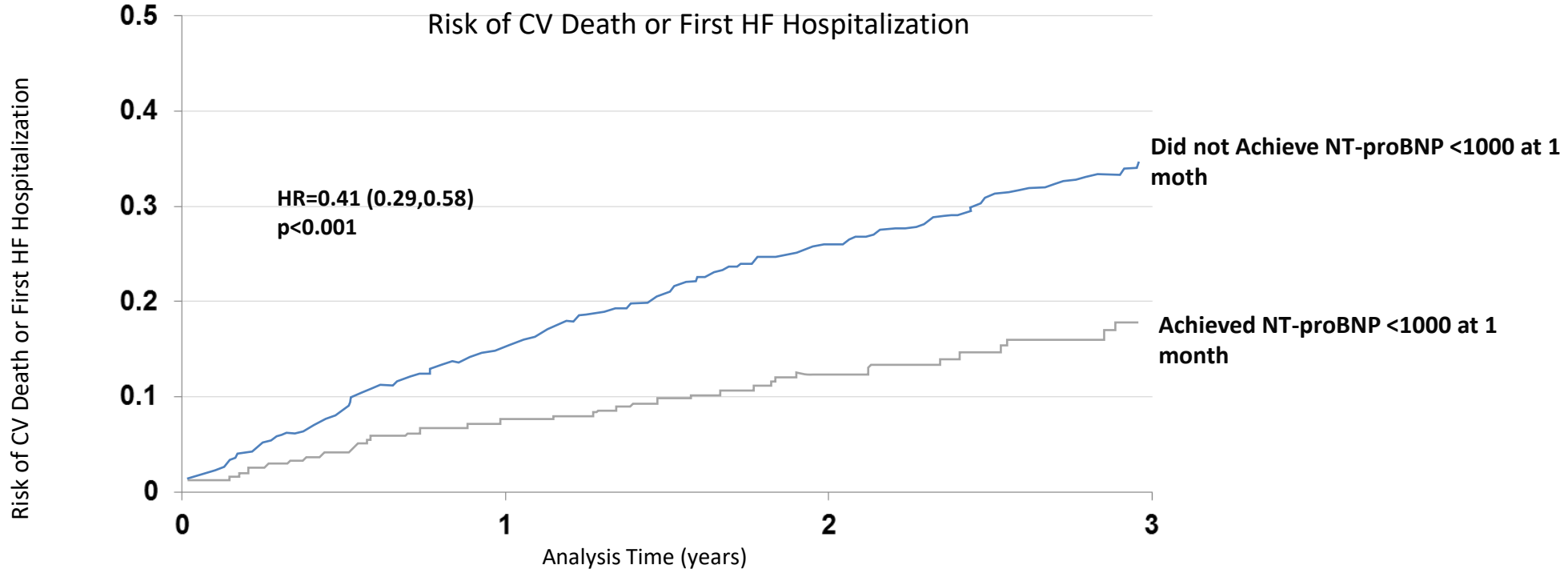
EMPEROR-Preserved: Changes in vital signs and laboratory findings

Laboratory and other measurements (change from baseline to 52 weeks)	Empagliflozin (n=2997)	Placebo (n=2991)	Absolute difference (95% CI)
Glycated haemoglobin in patients with diabetes (%), mean ± SE	–0.16±0.02	0.03±0.02	–0.19 (–0.25, –0.14)
Haematocrit (%), mean ± SE	1.94±0.07	–0.41±0.07	2.36 (2.17, 2.54)
Body weight (kg), mean ± SE	–1.39±0.09	–0.11±0.09	–1.28 (–1.54, –1.03)
Systolic blood pressure (mmHg), mean ± SE	–1.8±0.3	–0.6±0.3	–1.2 (–2.1, –0.3)
Uric acid (mg/dL), mean ± SE	–0.90±0.03	–0.10±0.03	–0.80 (–0.88, –0.72)
NT-proBNP (pg/mL), median (IQR)	–29 (–335, 263)	–9 (–286, 322)	0.95* (0.91, 0.99)

*Geometric mean ratio.
CI, confidence interval; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SE, standard error.
Anker S *et al. N Engl J Med*. 2021; doi:10.1056/NEJMoa2107038.

Relationship of NT-proBNP and Cardiovascular Events

Reduction in NT-proBNP Following HF Treatment is Associated with Reduction in CV Death and HF Hospitalization

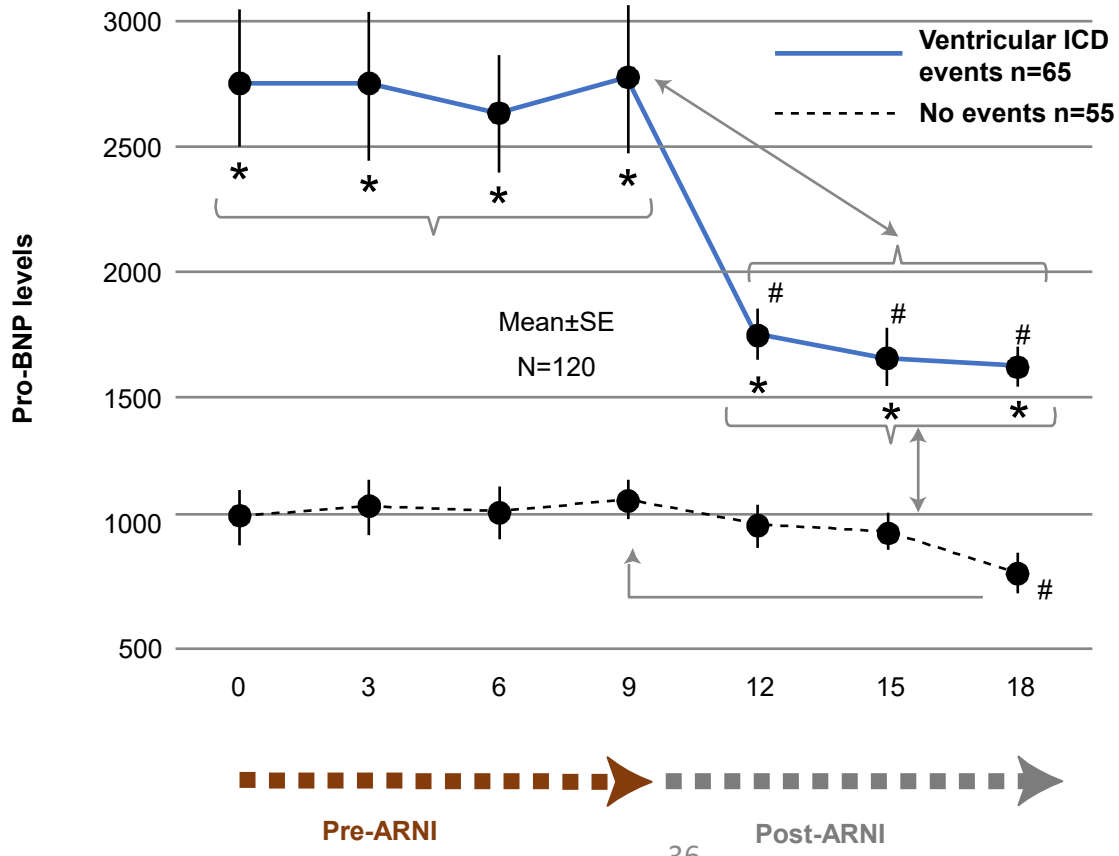


Achieving levels of NT-proBNP <1000 as early as 1 month after randomization to HF therapy was associated with a significant reduction in risk of CV death or first HF hospitalization

This was a post hoc analysis of PARADIGM-HF Study. Analytic variability (imprecision of the test) and biological variability (expected variability within the subject over time) may influence the accuracy of a predictive value of a change in biomarkers. The change from baseline data should therefore be interpreted in light of the influence of the biological variability known to be present in HFrEF patients.
NT-proBNP N-terminal pro–brain natriuretic peptide. HF, Heart Failure. CV, Cardiovascular
Zile MR, et al. *J Am Coll Cardiol.* 2016;68(22):2425–2436.

Sacubitril/valsartan decreases pro-BNP in patients with VA ICD events

- Prior to switching to sacubitril/valsartan (pre-ARNI), pro-BNP levels were significantly elevated in patients with VA ICD events compared with patients without VA
- Following the switch to sacubitril/valsartan (post-ARNI), both groups experienced a decrease in pro-BNP levels, though this effect was more pronounced in the VA ICD group



1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

Summary
Natriuretic peptides

הלב הוא לא רק איבר מטרה של סוכרת,
הוא גם איבר אנדוקריני

תודה על ההקשבה

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