Mechanism of action and Evidence of ARNI in Chronic heart failure(CHF)

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Outline:

1. Introduction: definitions, stages, natural history and pathophysiology of heart failure

2. Mechanism of action of ARNI

3. Evidence of ARNI in chronic heart failure

Introduction: Scope of the Problem of Heart failure

- **Major public health problem** resulting in substantial **morbidity**, **mortality**, and **healthcare expenditures**

Prevalence	Incidence	5-Yr Mortality	Hospital Discharges	Total Cost
5,700,000	915,000	~ 50%	1,023,000	$30.7 billion

- ~ **25%** of hospitalized patients for HF **readmitted within 30 days**
  - High incidence of hospitalizations a **major cost driver**

- Despite treatment advances, large numbers of eligible pts do **not receive 1 or more evidence-based HF therapies**

- Mozaffarian D, et al. Circulation. 2016;133:e38-e60
- Dharmarajan K, et al. JAMA. 2013;309:355-363
- Albert NM, et al. JAMA. 2009;302:1658-1665.

Definition of Heart failure

- Is not a single pathological diagnosis, but a clinical syndrome
- Consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue)
- Accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema)
- Due to a structural and/or functional abnormality of the heart
- Resulting in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise

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

Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

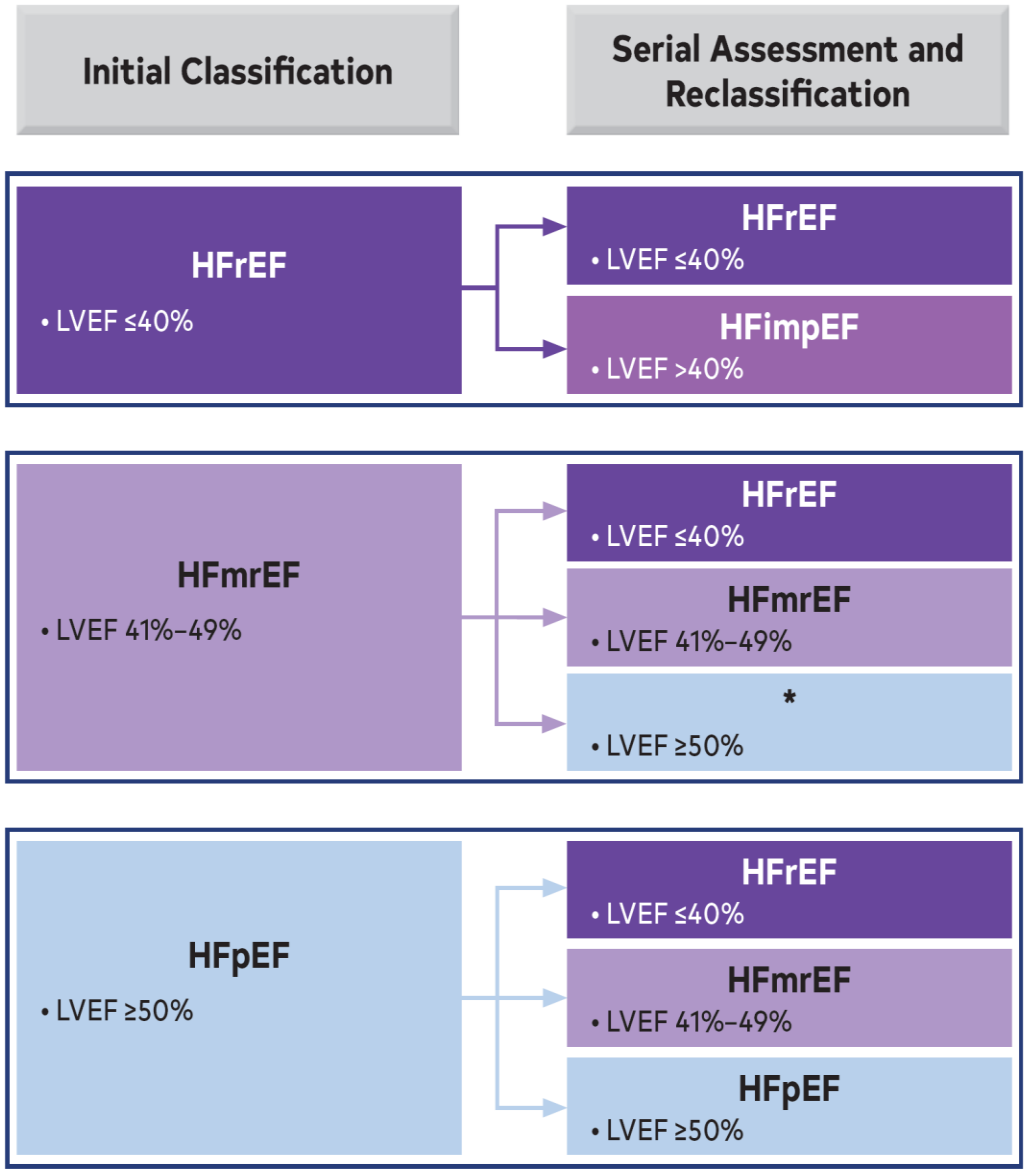
HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

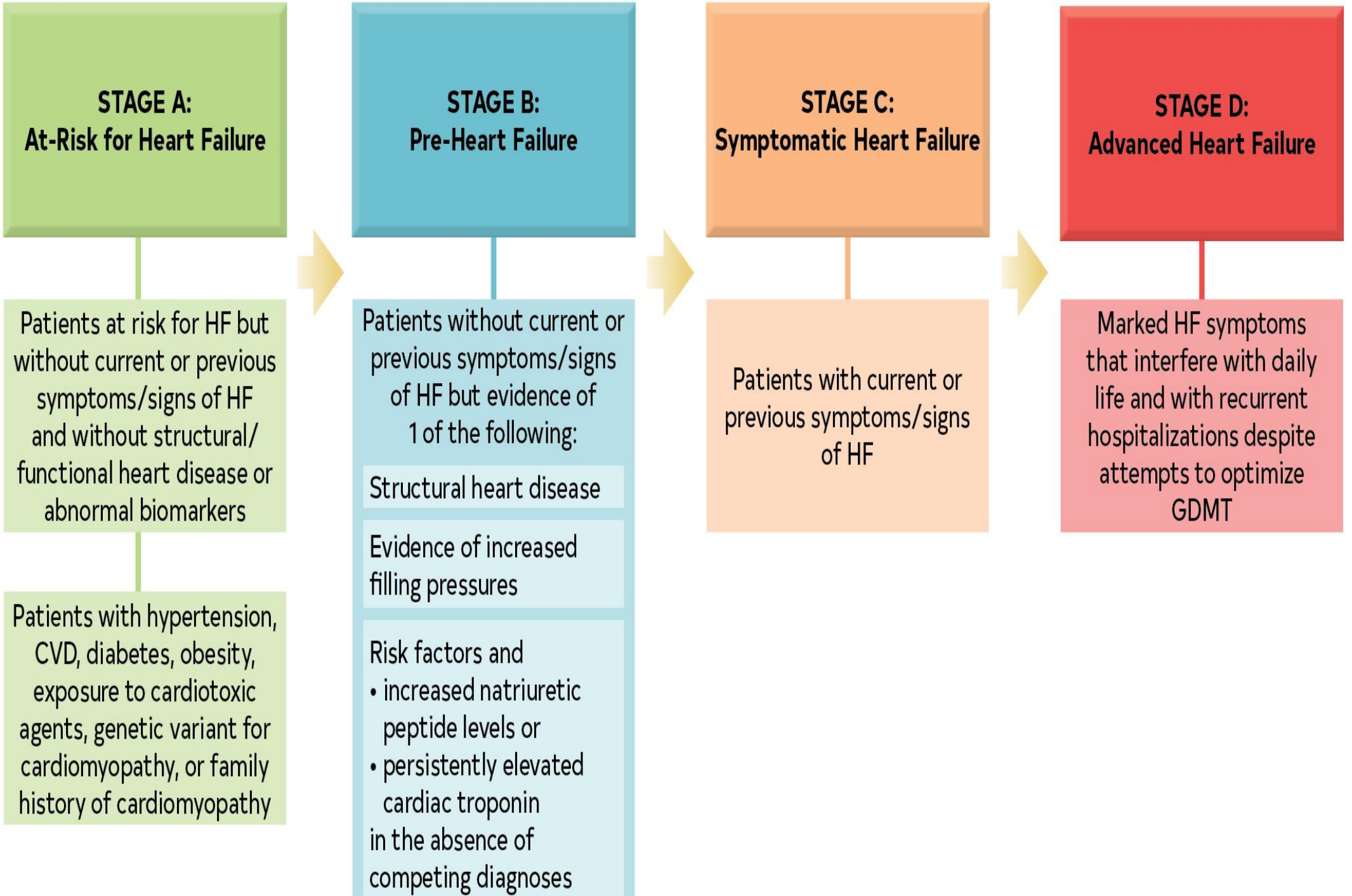
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Classification and Trajectories of HF Based on LVEF



- **Patients with a history of overtly reduced LVEF (≤40%), who later present with LVEF ≥50%**
- **Should be considered to have "recovered HFrEF" or "HF with improved LVEF" (rather than HFpEF)**
- **Continued treatment for HFrEF is recommended**

ACC/AHA Stages of HF



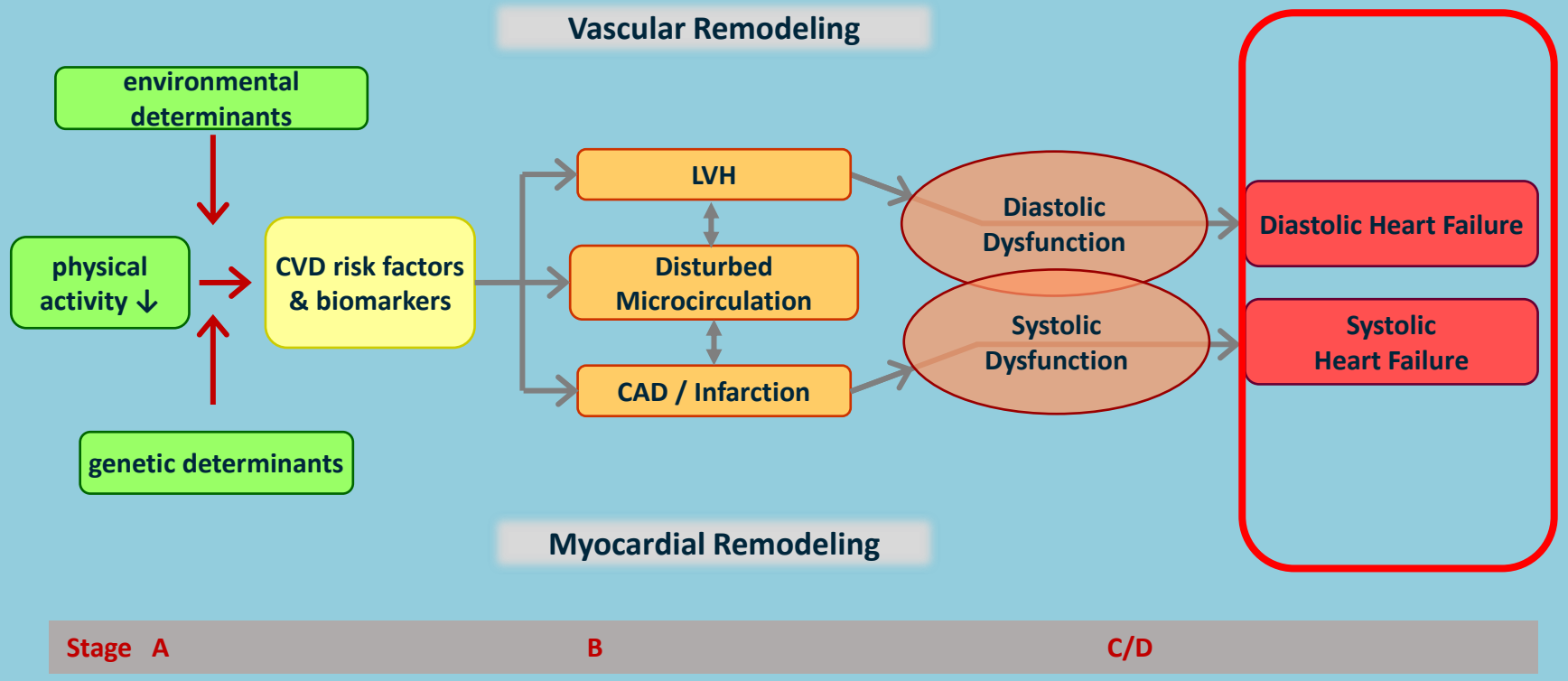
The ACC/AHA stages of HF are shown.

ACC indicates American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.

Natural history of Heart Failure

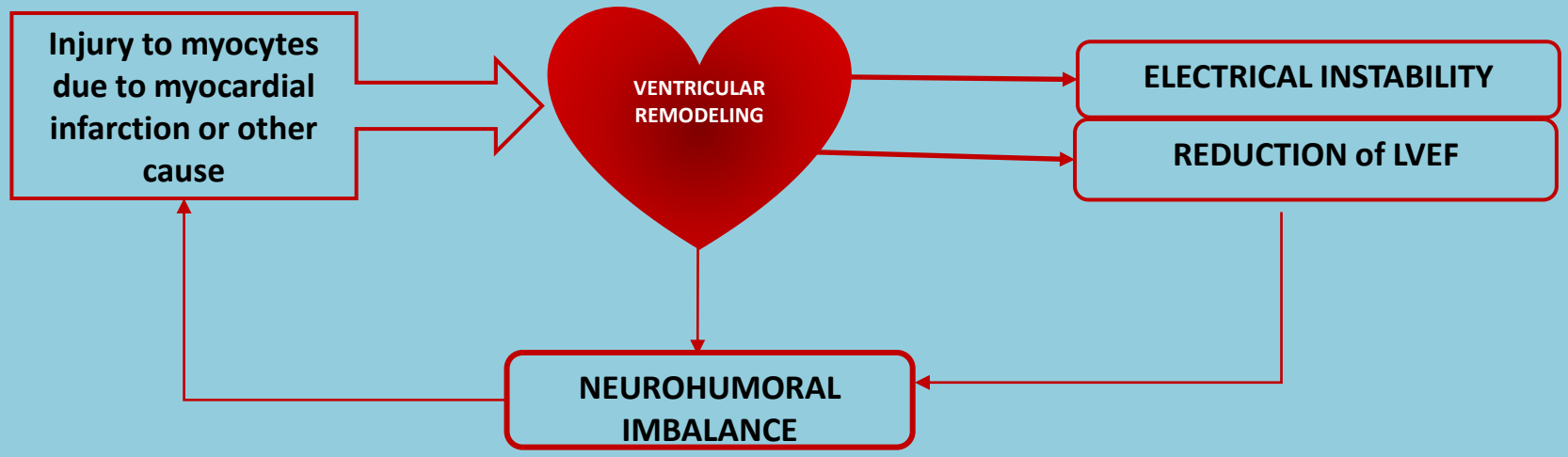
HF is a silently progressing disease

The cardiovascular continuum



Krum, Gilbert. Lancet 2003;362:147–58
McMurray et al. Eur Heart J 2012;33:1787–847

Pathophysiology of HF

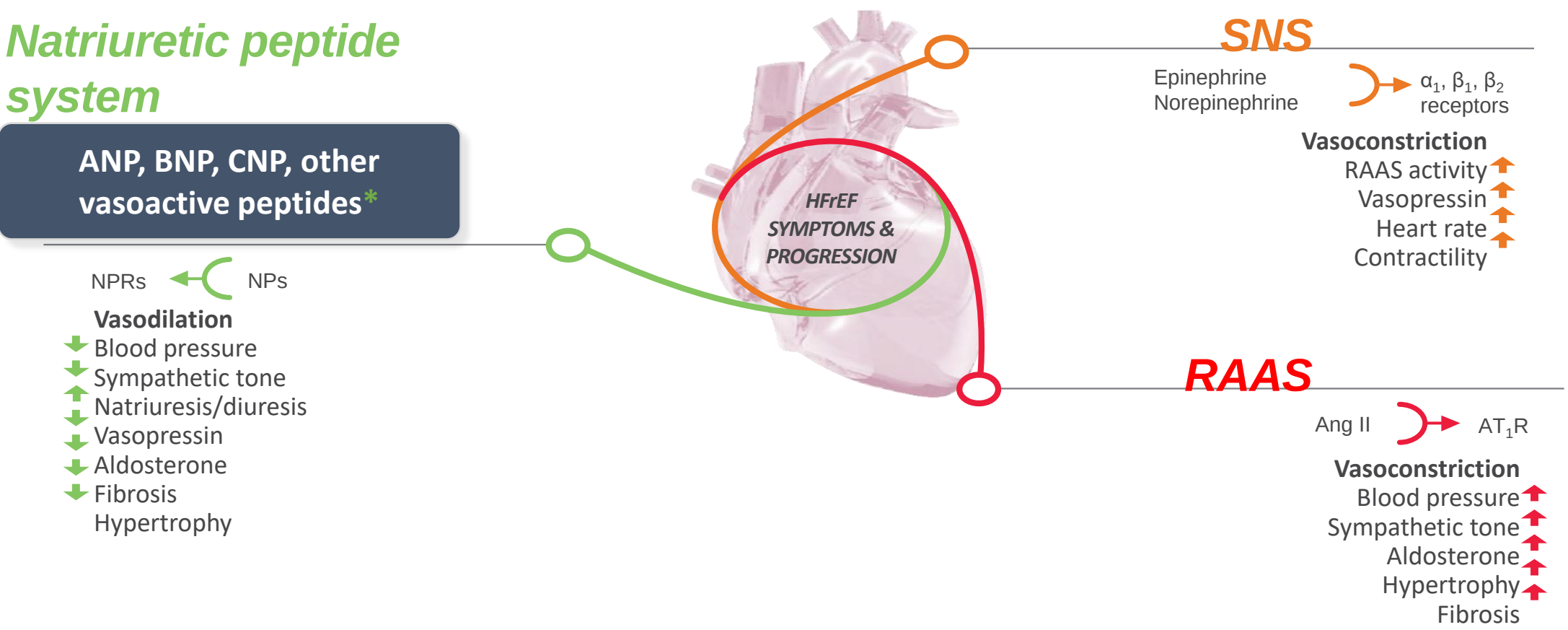


An imbalance occurs in three key neurohumoral systems:

- The renin–angiotensin–aldosterone system
- The sympathetic nervous system
- The natriuretic peptide system

1. McMurray JJ. N Engl J Med 2010;362:228–238
2. Shah AM. Lancet 2011;378:704–712

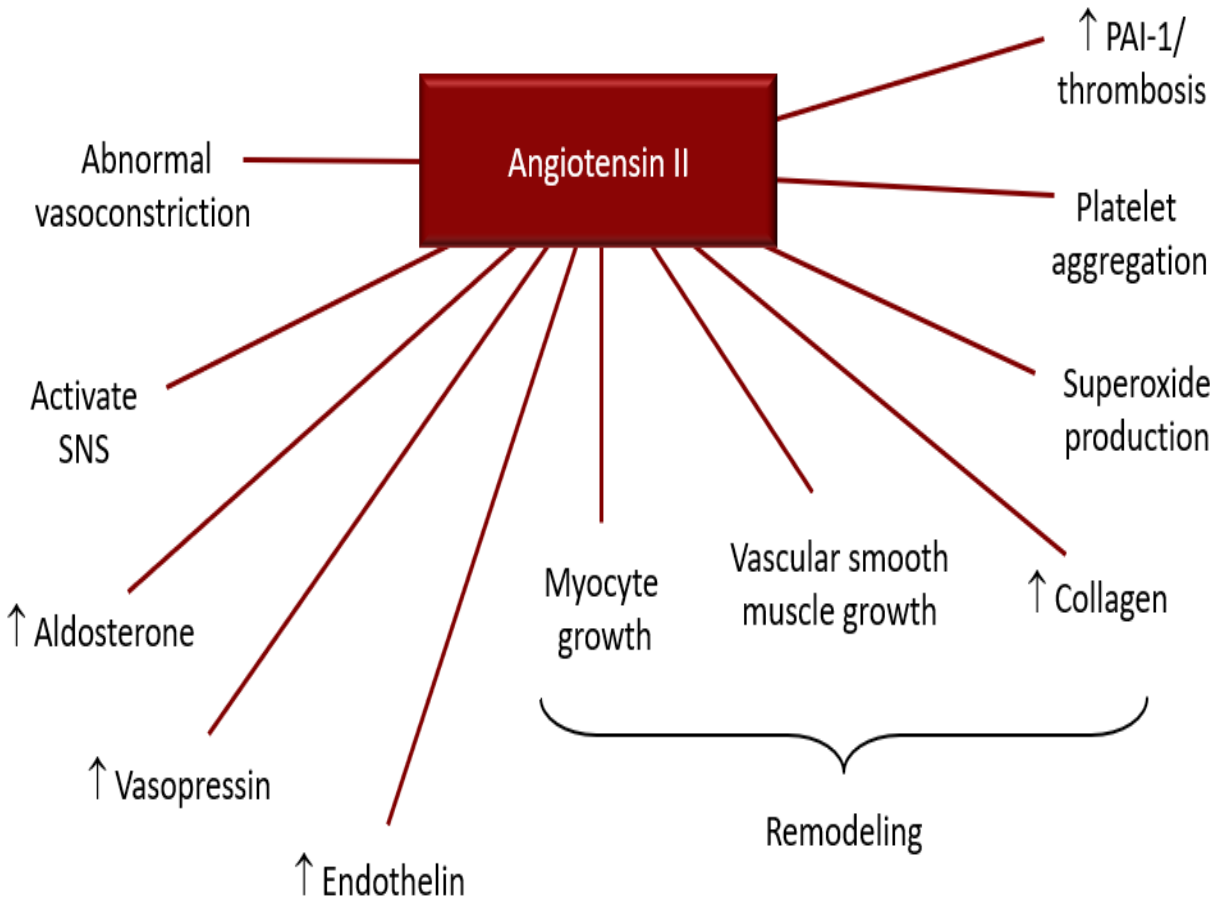
Natriuretic peptide system



- In the initial phase of HF, activation of the SNS and the RAAS are compensatory, maintaining blood pressure (BP) and cardiac output (CO).
- With continuous and overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy, causing cascade of potentially harmful long-term effects
- Activation of the natriuretic peptide system is protective, which can counterbalance the adverse effects due to overactivation of the other two systems

Deleterious Effects of Norepinephrine(SNS) and Angiotensin II(RAAS)

- **Increased left ventricular volumes and pressure**
  - Peripheral vasoconstriction
  - Impaired sodium excretion by the kidneys
- **Left ventricular hypertrophy**
- **Arrhythmias**
  - Increased automaticity of cardiac cells
  - Increased triggered activity in the heart
  - Increased risk of hypokalemia
- **Apoptosis**
  - Stimulation of cellular growth and oxidative stress



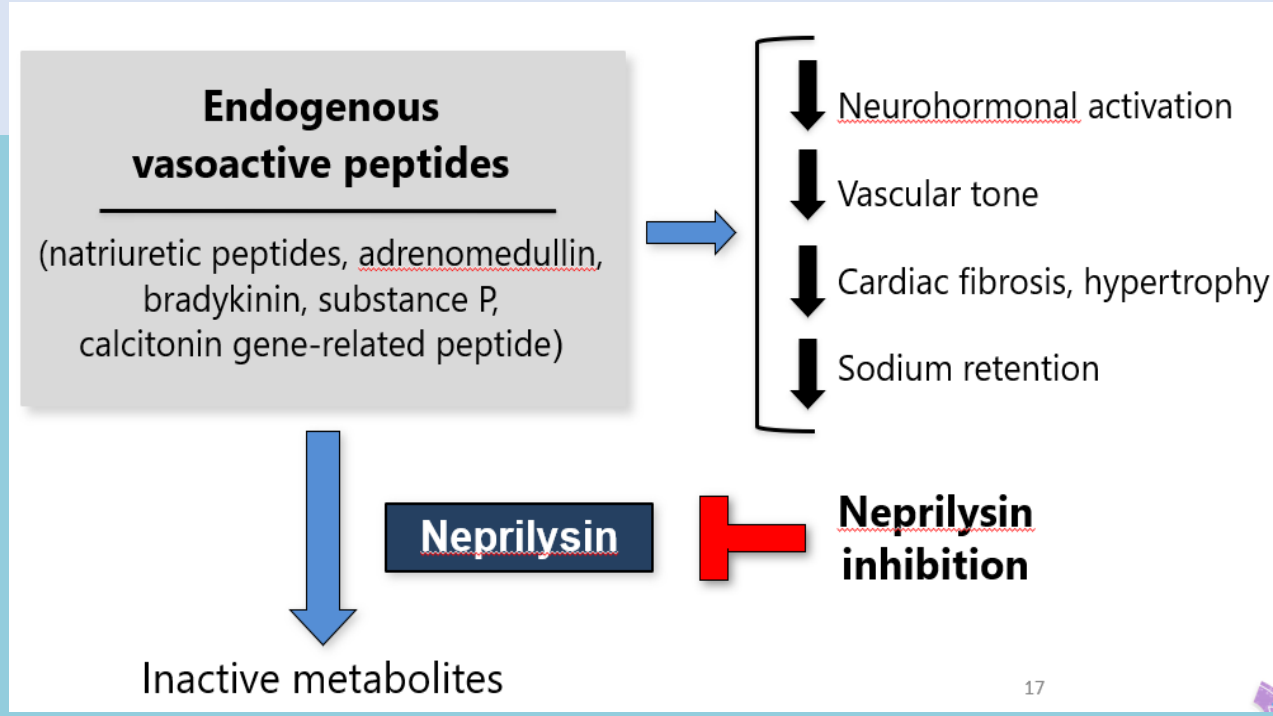
PAI-1, plasminogen activator inhibitor-1; SNS, sympathetic nervous system

Burnier M, et al. *Lancet*. 2000;355:637-645.
Brown NJ, et al. *Adv Intern Med*. 2000;45:419-429

Neprilysin as a Therapeutic Target
(Neutral endopeptidase)

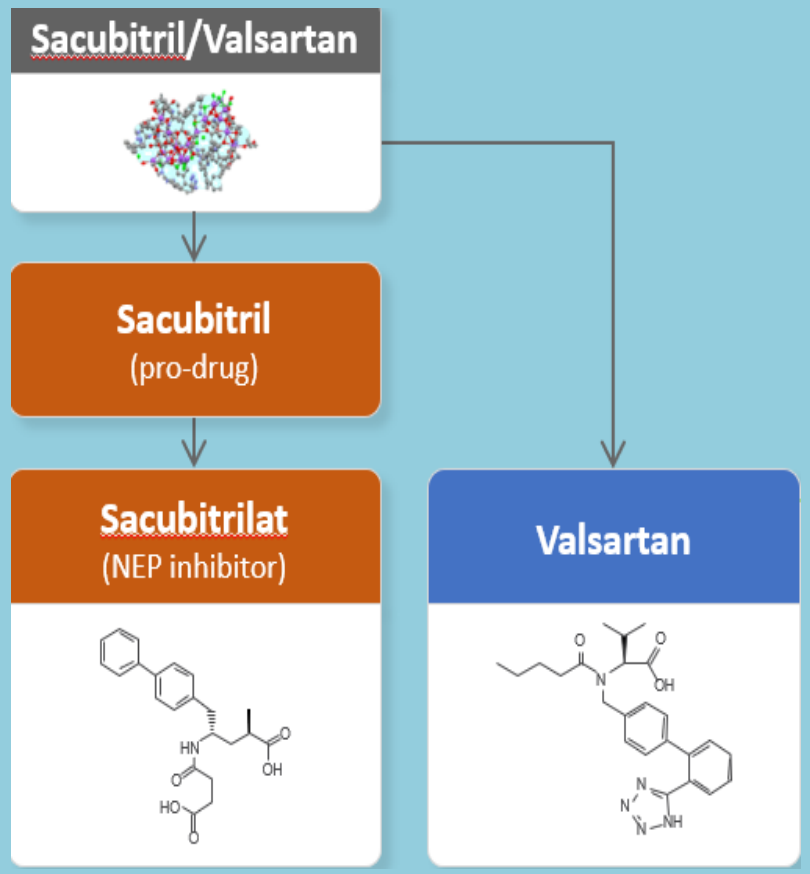
- **B-type natriuretic peptide (BNP)**
  - Produced by ventricles in response to increased pressure and volume load
- **Atrial natriuretic peptide (ANP)**
  - Produced by atria in response to atrial stretch

- Both reduce preload and afterload:
  - Sequester plasma (short-term)
  - Renal salt and water excretion
  - Antagonize RAAS
  - Antagonize hypertrophic effects of angiotensin II



- Neprilysin breaks down endogenous vasoactive peptides, including the natriuretic peptides
- Inhibition of neprilysin potentiates the action of those peptides

- In the past, the focus of HF therapy has been on blocking SNS and RAAS pathways
- Third major neurohormonal system: Natriuretic peptide system is counter-regulatory to RAAS, with many beneficial physiologic effects
- LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI)
- Following oral administration, dissociates into the prodrug sacubitril (AHU377), further metabolized to LBQ657, and valsartan
- Simultaneously inhibit neprilysin via the active metabolite (LBQ657) and block angiotensin (AT_1) receptor via valsartan

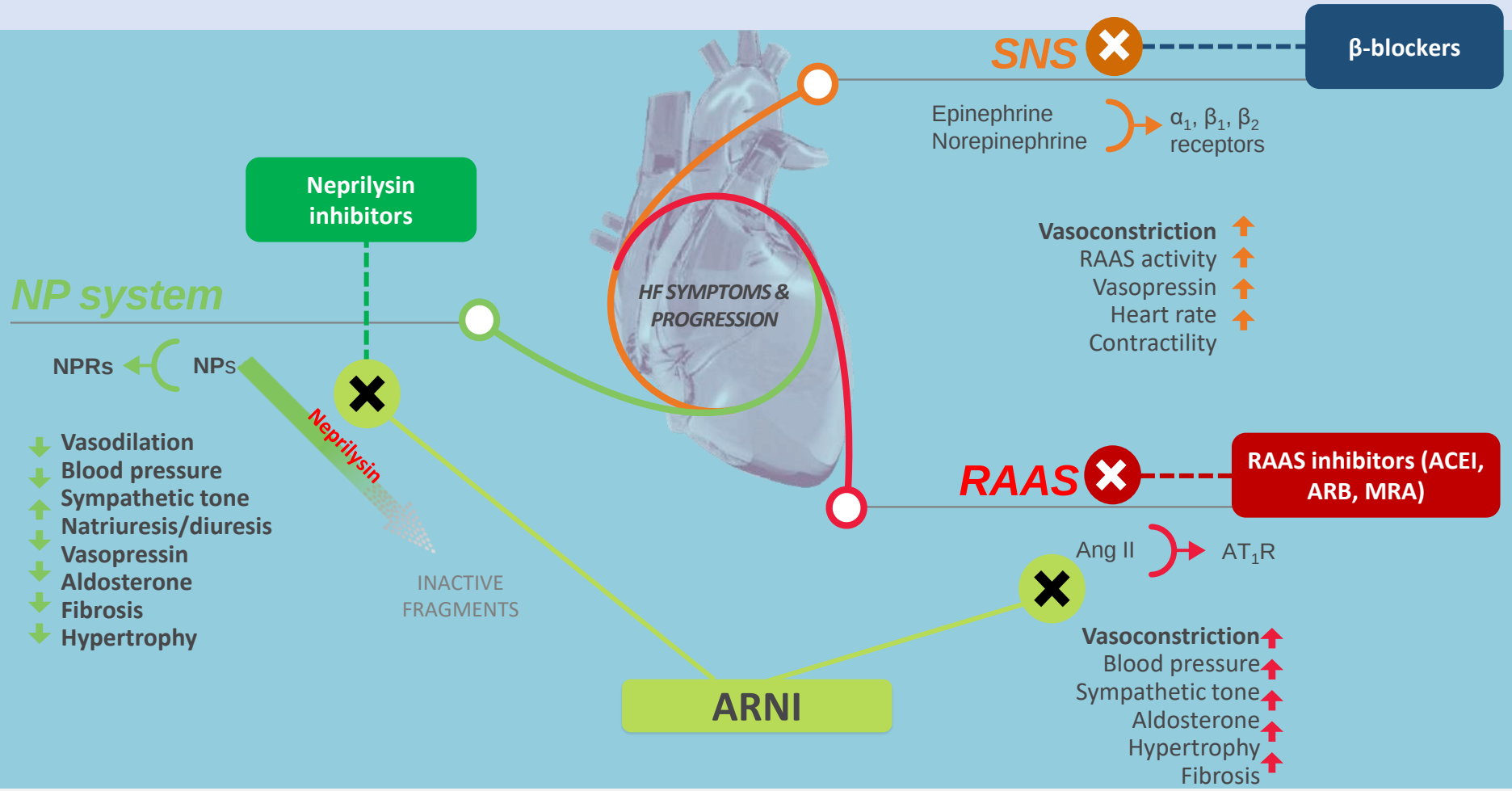


- Inhibition of neprilysin enhances the effects of natriuretic peptides, including vasorelaxation, natriuresis and diuresis and inhibition of cardiac fibrosis and hypertrophy

- Since neprilysin is involved in the breakdown of Ang II, simultaneous suppression of the RAAS by LCZ696 is important to offset any potential effects of an increase in Ang II, resulting from neprilysin inhibition

- Through simultaneous blockade of the AT_1 receptor, suppresses the long-term harmful effects of RAAS over-activation, such as increased blood pressure, sodium and water retention

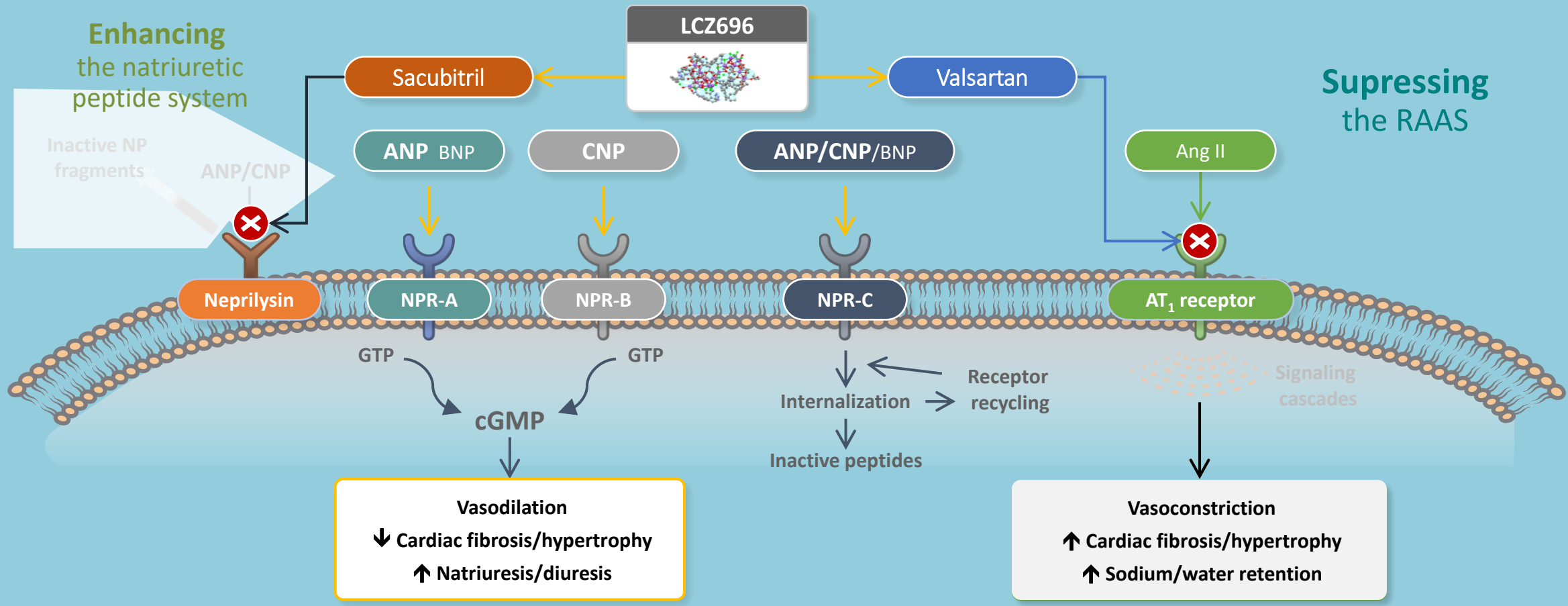
Evolution of Pharmacologic Approaches in Heart Failure



- **ARNI: enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression**

- 1. McMurray et al. Eur J Heart Fail 2013;15:1062–73
- Figure references: Levin et al. N Engl J Med 1998;339:321–8 Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42
  Kemp & Conte. Cardiovascular Pathology 2012;365–71
  Schrier & Abraham. N Engl J Med 2009;341:577–85

Sacubitril/Valsartan simultaneously enhances the beneficial effects of the NP system while blocking detrimental effects of the RAAS



ANP: atrial natriuretic peptide; Ang: angiotensin; AT1: angiotensin II type 1; BNP: B-type natriuretic peptide; cGMP: cyclic guanosine monophosphate; CNP: C-type natriuretic peptide; GTP: guanosine triphosphate; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Molkentin. J Clin Invest 2003;111:1275–77; Nishikimi et al. Cardiovasc Res 2006;69:318–28; Guo et al. Cell Res 2001;11:165–80; Von Lueder et al. Circ Heart Fail 2013;6:594–605; Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta & Griendling. Am J Physiol Cell Physiol 2007;292:C82–97; Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9

Evidence of ARNI in chronic heart failure
Clinical Trials

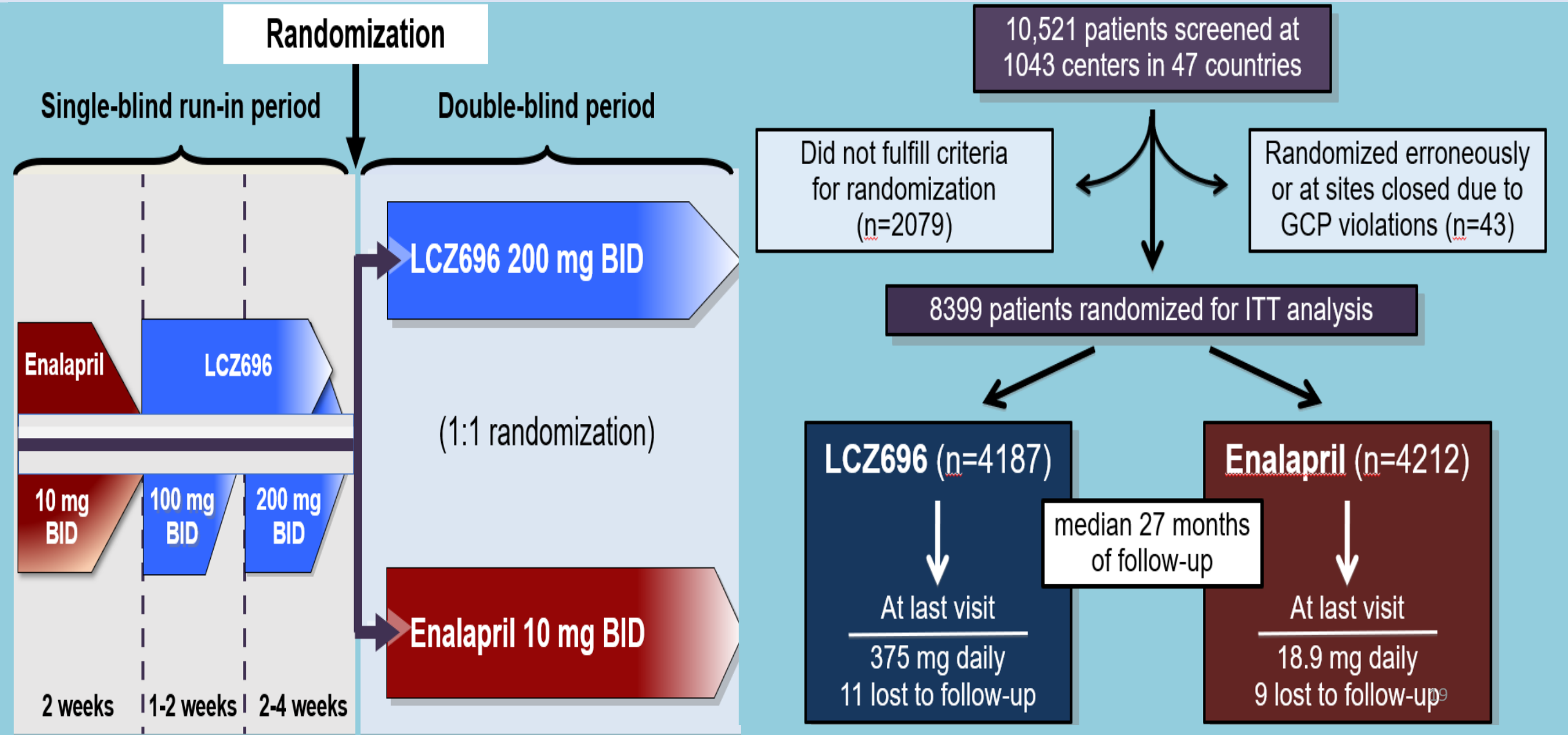
Trial Name	Date Published	Patient Population
PARADIGM-HF	9/11/2014	Heart Failure with Reduced Ejection (HFrEF)
PIONEER-HF	11/11/2018	Decompensated Heart Failure (HF)
PARAGON-HF	9/1/2019	Heart Failure with Preserved Ejection Fraction (HFpEF)

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

- To evaluate the effect of LCZ696 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HFrEF treatment, in delaying time to first occurrence of either CV death or HF hospitalization

- Secondary endpoints:
  - All cause mortality
  - Change from baseline to 8 months in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - Time to new onset of atrial fibrillation
  - Time to first occurrence of a protocol-defined decline in renal function

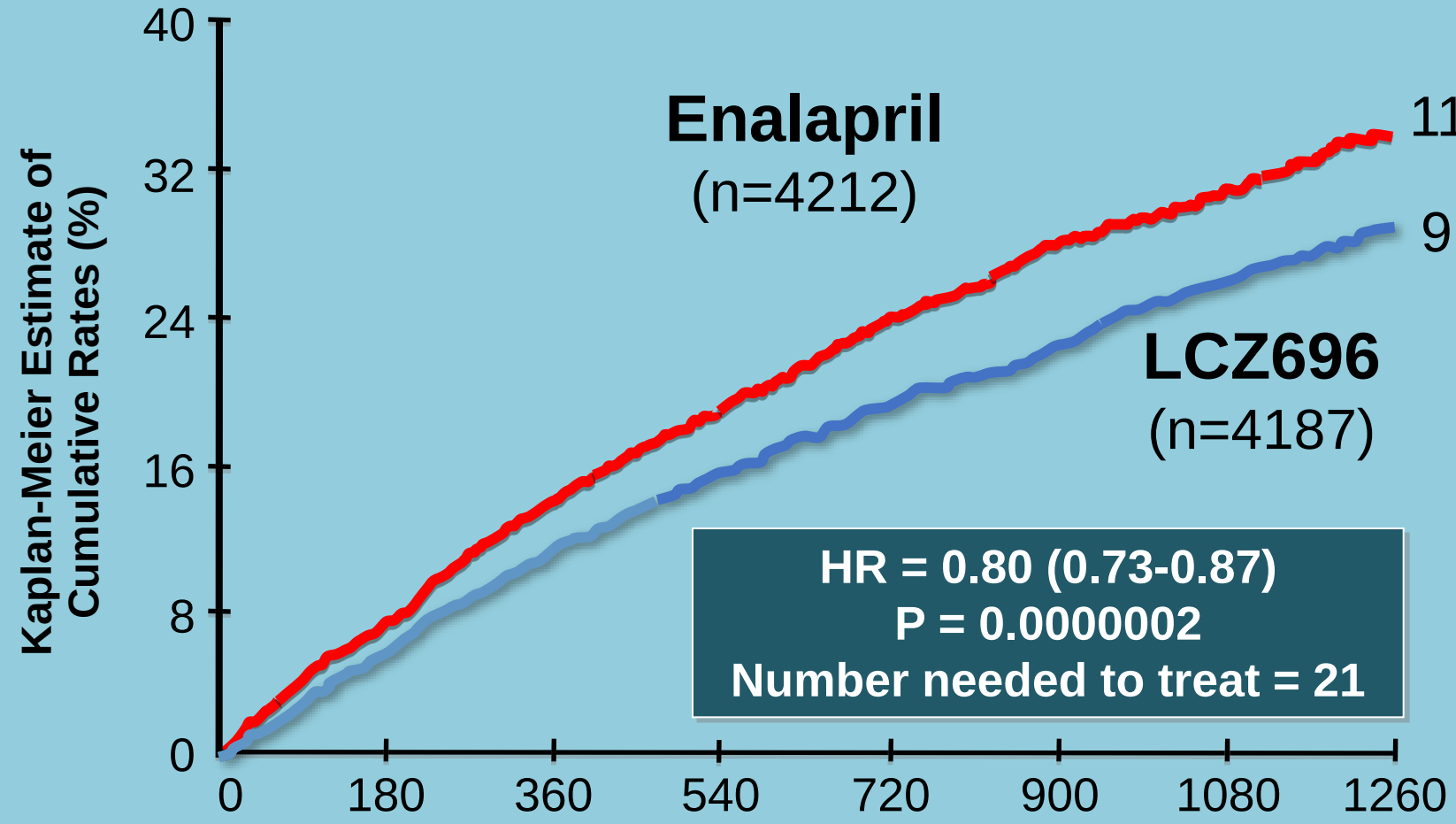
PARADIGM-HF: Study Design and Patient disposition



PARADIGM-HF: Summary of baseline characteristics

	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

PARADIGM-HF: Cardiovascular Death or First Heart Failure Hospitalization (Primary Endpoint)



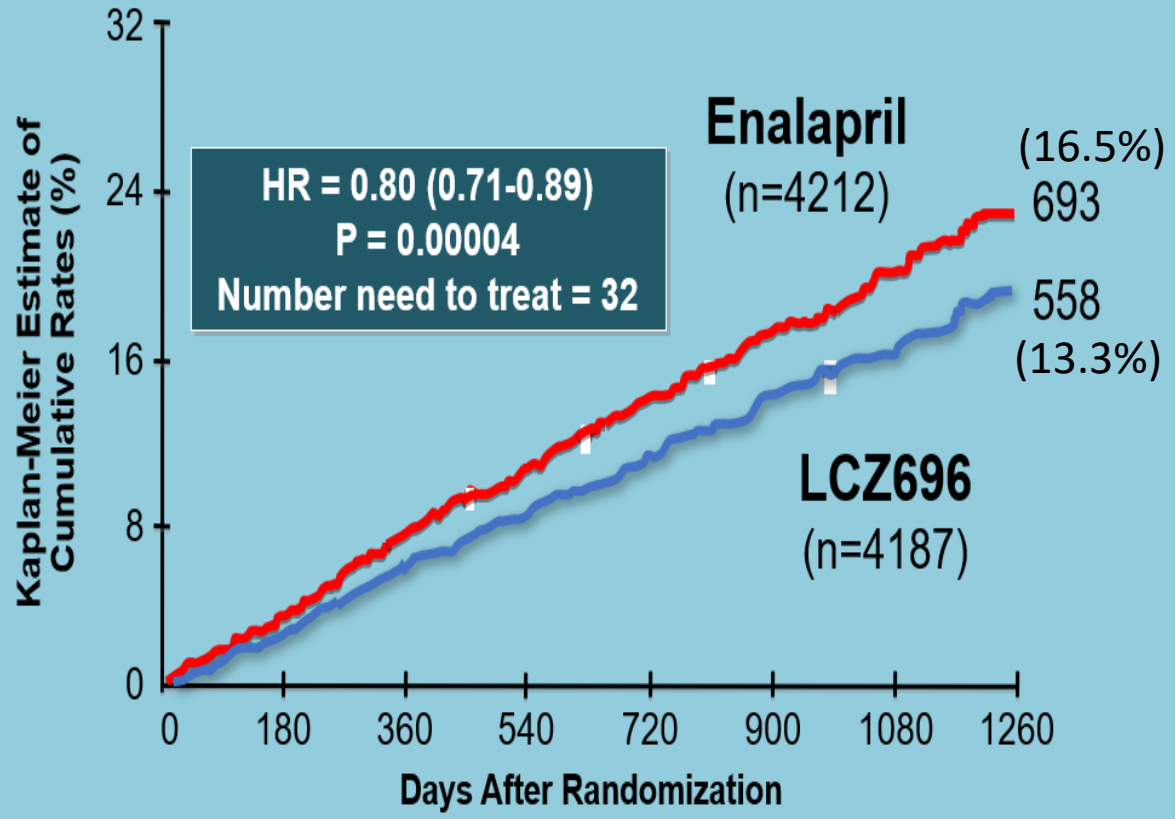
more effective in reducing the risk of death from cardiovascular causes or first hospitalisation for HF

Patients at Risk

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

PARADIGM-HF: Components of primary endpoint

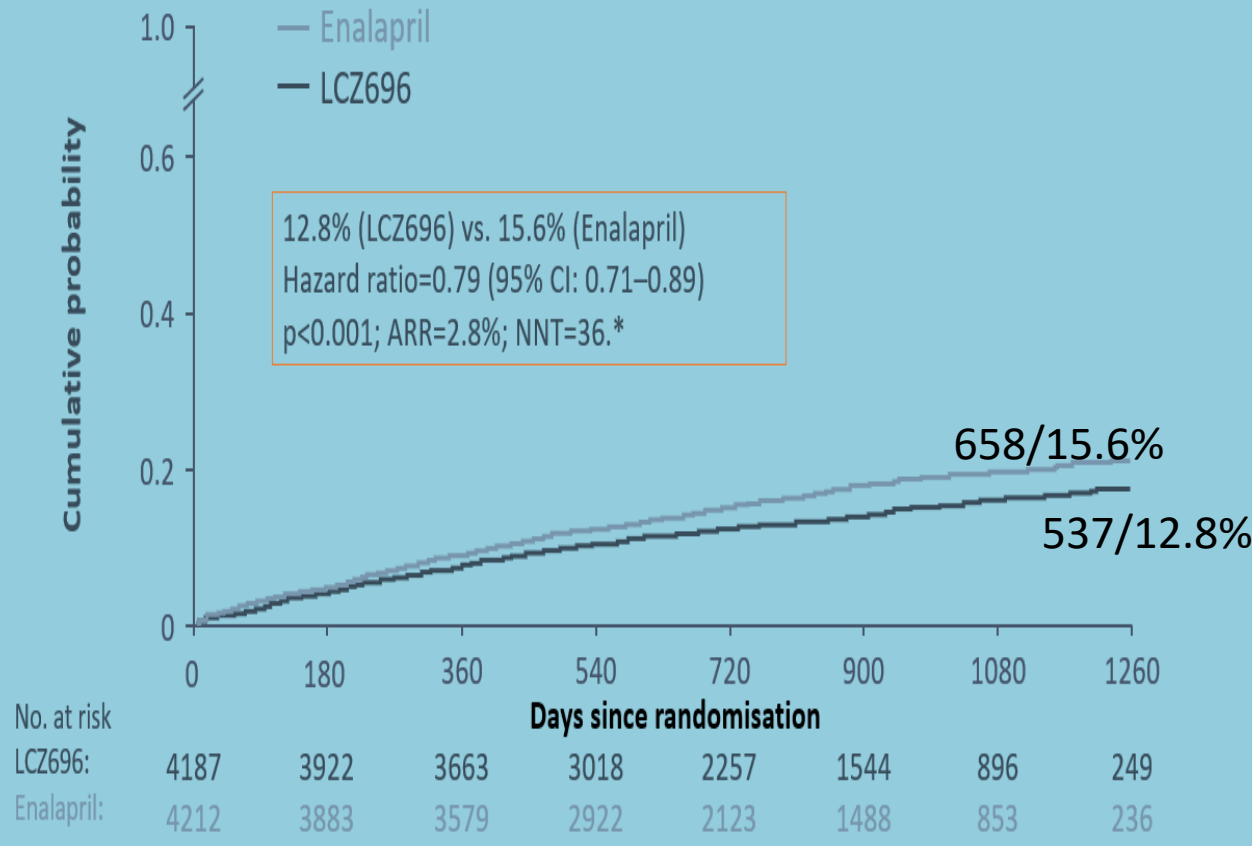
Death from CV causes



Patients at Risk

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

First hospitalisation for HF



No. at risk

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

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**	**0.03**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.002
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

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

- Reducing the risk of CV death and HF hospitalization
- Reducing all-cause mortality
- Improving symptoms and physical limitations

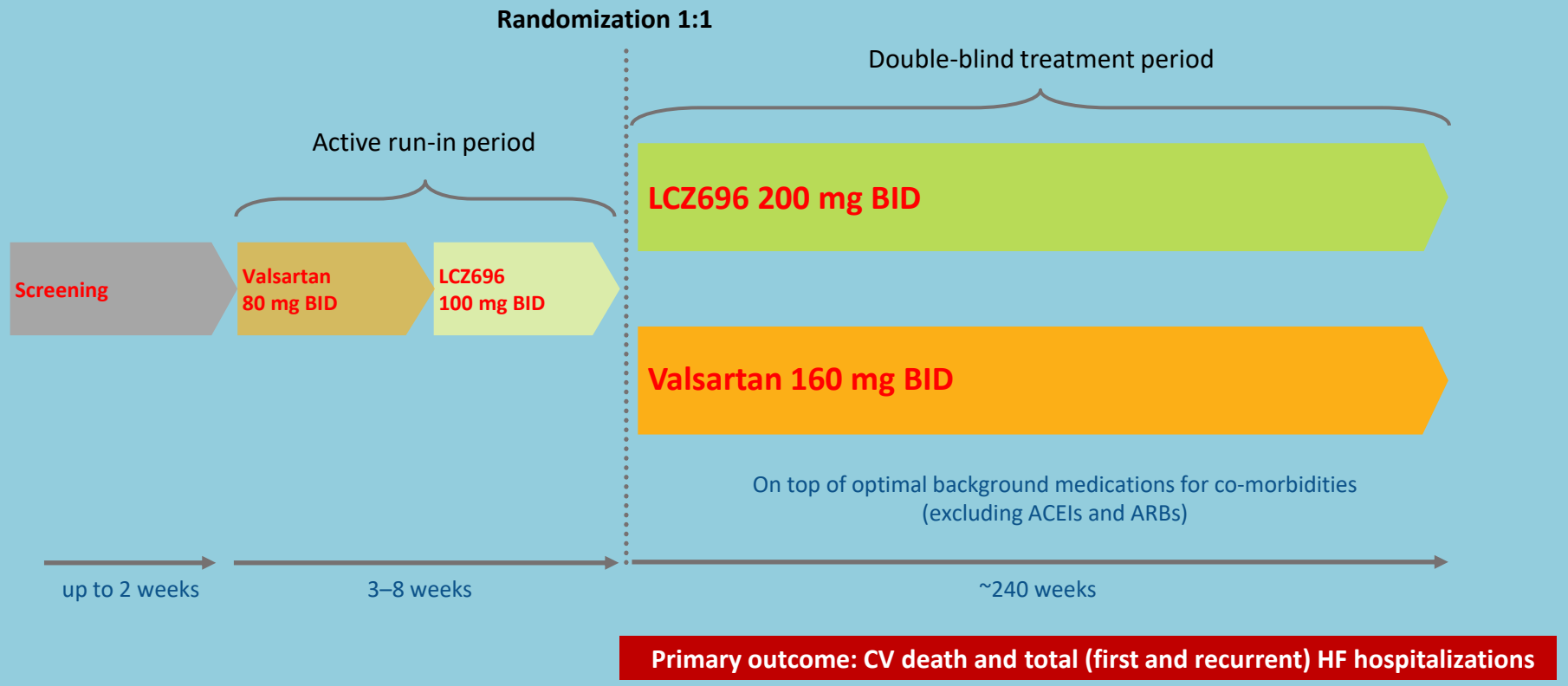
LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

PARAGON-HF: Prospective comparison of ARNI with ARB Global Outcomes in HFpEF

Study design

Target patient population: 4822 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%



Primary outcome: CV death and total (first and recurrent) HF hospitalizations

- *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;

- Solomon et al. Poster presentation at ESC-HF Congress, 25 May 2013; Novartis data on file: GMA&HEOR_LCZ696B_PARAGON-HF study_D2301_001_2.0

PARAGON-HF: Primary and secondary outcomes

Primary outcome:

- Composite of death from cardiovascular causes and total (first and recurrent) hospitalizations for heart failure

Secondary outcomes:

- Change from baseline to 8 months in NYHA class
- Change from baseline to 8 months in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire
- Time to first occurrence of decline in renal function
- All cause mortality

Solomon et al. Poster presentation at ESC-HF Congress, 25 May 2013

PARAGON-HF: Key inclusion and exclusion criteria

Key inclusion criteria:

- Age ≥50 years; LVEF ≥45%
- Symptoms of HF requiring treatment with diuretic(s) for ≥30 days prior to study entry
- Current symptomatic HF (NYHA class II–IV)
- Structural heart disease (LAE and/or LVH)

AND either

HF hospitalization* within 9 months prior to study entry

OR

Elevated NT-proBNP (>300 pg/mL for patients with SR or >900 pg/mL for patients with AF)

Key exclusion criteria:

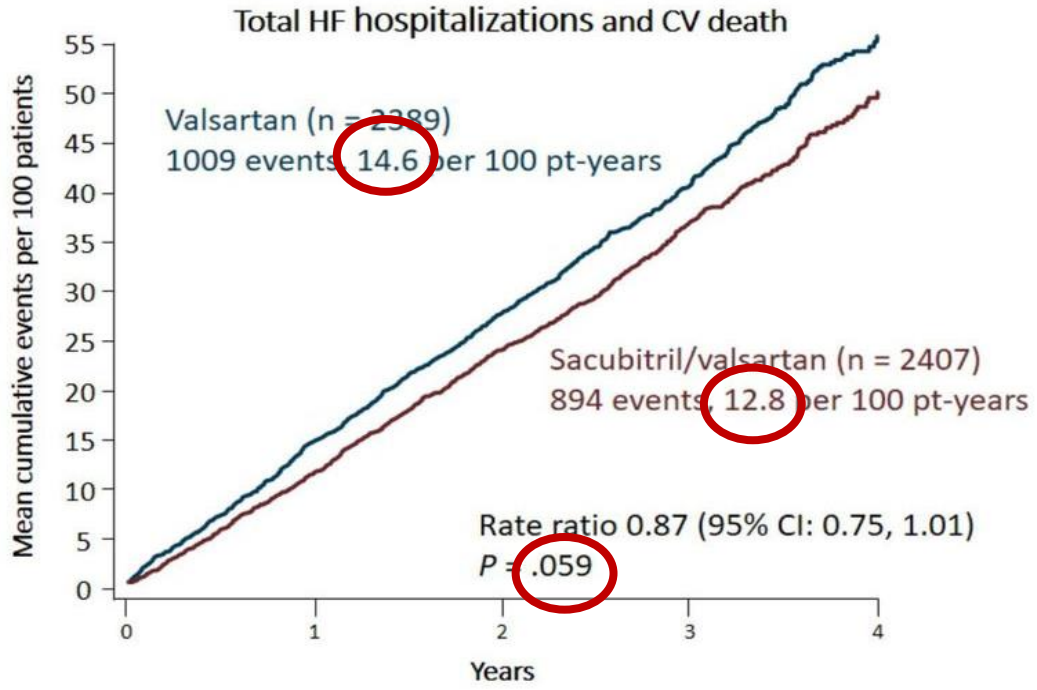
- History of LVEF <45%
- MI, CABG or any event within the 6 months prior to study entry that may have reduced LVEF (unless LVEF confirmed as ≥45%)
- Requirement for treatment with two or more of the following: ACEI, ARB or renin inhibitor
- SBP <110 mmHg OR SBP ≥180 mmHg at study entry*
- Serum potassium >5.2 mmol/L at study entry
- eGFR <30 mL/min/1.73m^2 at study entry

- *If SBP >150 mmHg and <180 mmHg, the patient should be receiving ≥3 antihypertensive drugs

- Solomon et al. Poster presentation at ESC-HF Congress, 25 May 2013

PARAGON-HF: Primary endpoint

PARAGON-HF Primary Results Recurrent Event Analysis of Total HF Hospitalizations and CV Death*



*Semiparametric LWYY method.

Solomon SD, et al. *N Eng J Med.* 2019. [Epub ahead of print].

PARAGON-HF: Summary

- Modest, although statistically nonsignificant, lower rate of hospitalization for HF with ARNI
- No significant difference in risk of death from cardiovascular causes
- Favored ARNI in change in NYHA class and occurrence of decline in renal function
- Higher incidence of hypotension and angioedema in ARNI
- Lower incidence of elevated Cr/K

PIONEER-HF Trial

Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure

Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in patients stabilized from an acute heart failure episode

Primary efficacy outcome:

Time-averaged proportional change in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration from baseline through weeks 4 and 8 when taking an ARNI vs enalapril

Secondary biomarker outcome:

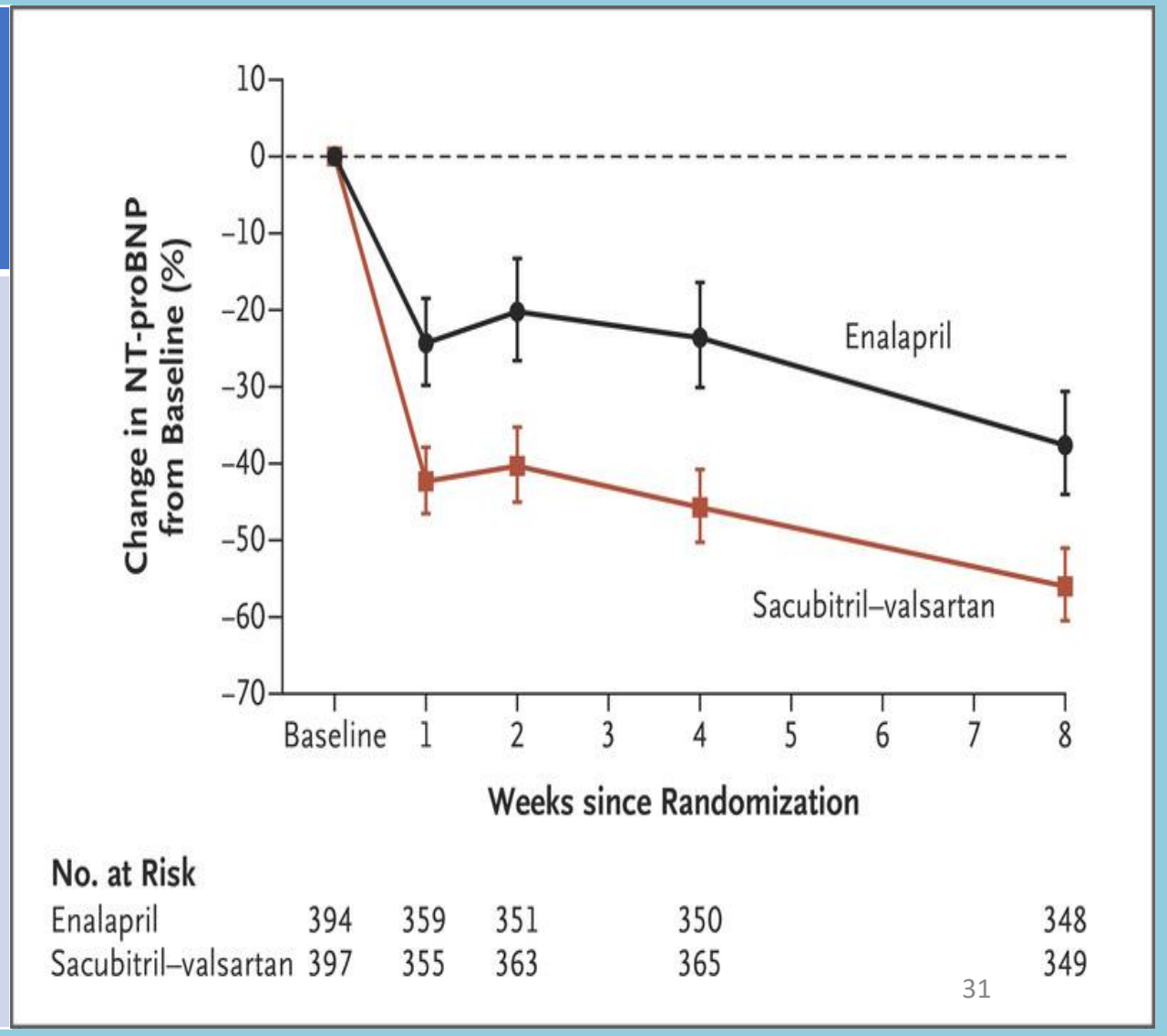
Time-averaged proportional change in the hs Troponin T concentration, BNP concentration, ratio of BNP:NT-proBNP

Key safety outcomes:

Rates of worsening renal function, hyperkalemia, symptomatic hypotension and angioedema

PIONEER-HF: Primary outcome

Primary outcome	Primary outcome results (p-value)
Time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8.	-46.7% v. 25.3% (Ratio of change 0.71, 95% CI 0.63-0.81) **(p<0.001)**

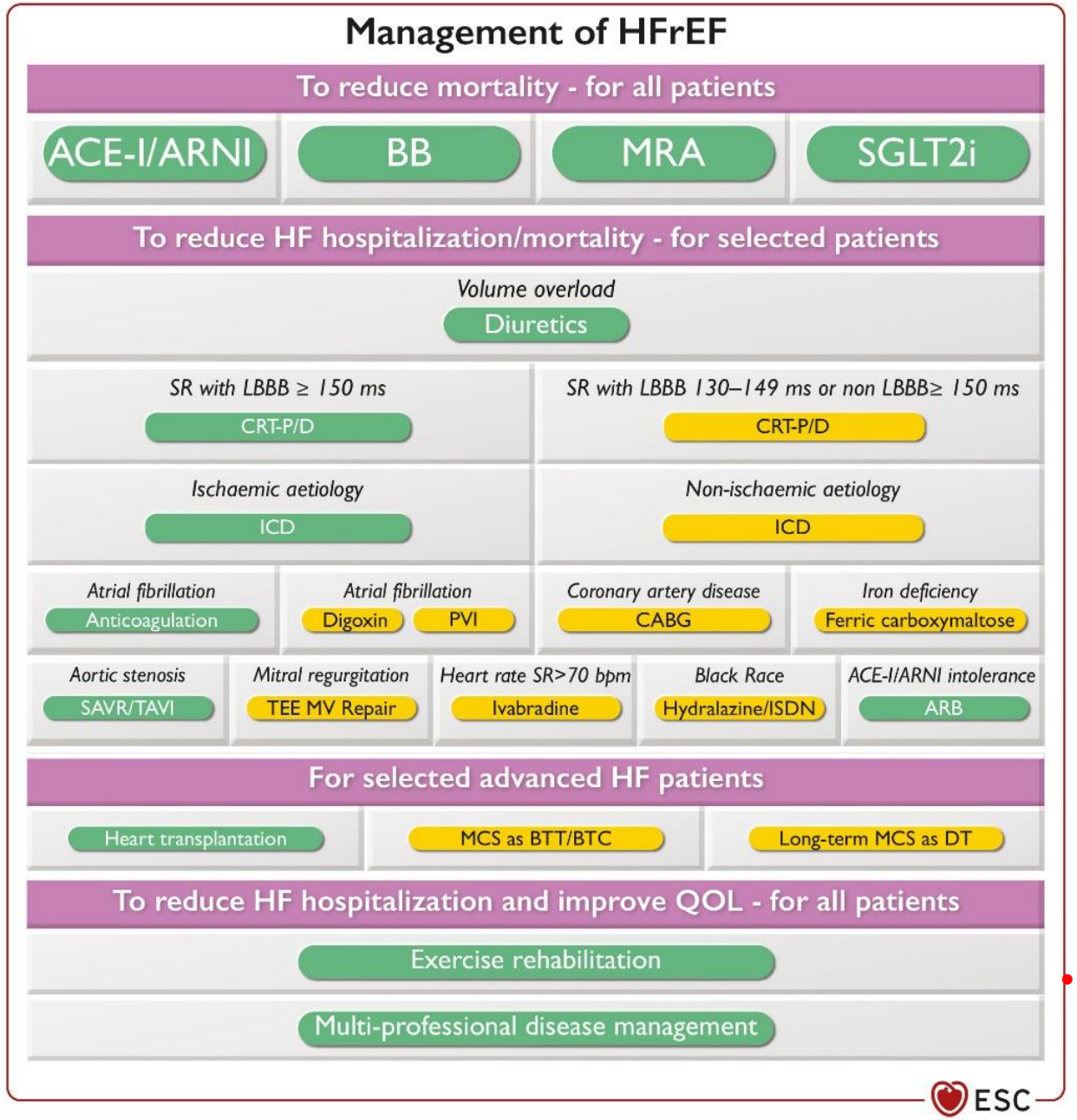


PIONEER-HF: Secondary efficacy outcomes

Secondary outcomes & results: p-value (ratio of change 95% CI)
Change in Troponin T: **0.85 (0.77 to 0.94)**
Change in BNP concentrations: 1.07 (0.92 to 1.23)
Change in ratio of BNP to NT-proBNP: 1.48 (1.38 to 1.58)

PIONEER-HF: Summary

- Initiation of ARNI after hemodynamic stabilization – led to greater reduction in NT-proBNP concentration than Enalapril group
- Difference evident by First week
- Beneficial effect accompanied by Reduction in concentration of hs Troponin T (Prognostic marker)
- Rate of renal dysfunction, hyperkalemia and symptomatic hypotension – not differ significantly
- Exploratory clinical outcomes: lower rate of rehospitalization at 8 weeks in ARNI



Strategic phenotypic overview of the management of heart failure with reduced ejection fraction

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; b.p.m. = beats per minute; BTC = bridge to candidacy; BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see Table 1 for further details on classes of recommendation).
The Figure showsmanagement options with Class I and IIa recommendations. See the specific Tables for those with Class IIb recommendations.

- **4 agents placed side-by-side because positive effects on patient outcomes occur early after treatment initiation and these benefits are additive**

www.escardio.org/guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)[34]

ESC 2021 Guidelines :Recommendations for ARNI use

Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C

1	A	1. In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.

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Value Statement: High Value (A)		6. In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value.
3: Harm	B-R	7. ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi.
3: Harm	C-LD	8. ARNi should not be administered to patients with any history of angioedema.
3: Harm	C-LD	9. ACEi should not be administered to patients with any history of angioedema.

Doses of ARNI

- Patients previously taking >10 mg/day of enalapril or >160 mg/day of valsartan (or equivalent dose of another ACE inhibitor or ARB):
  - Sacubitril 49 mg and valsartan 51 mg twice daily

- Patients previously taking low doses of an ACE inhibitor (≤10 mg/day of enalapril or ≤160 mg/day of valsartan (or equivalent dose of another ACE inhibitor or ARB):
  - Sacubitril 24 mg and valsartan 26 mg twice daily

- Patients not currently taking an ACE inhibitor or an ARB:
  - Sacubitril 24 mg and valsartan 26 mg twice daily

- Double the dose as tolerated after 2 to 4 weeks to the target maintenance dose of sacubitril 97 mg and valsartan 103 mg twice daily

Take Home Message

- Mortality and short-term unplanned rehospitalization in HFrEF remains high despite multiple trials of promising therapies that improve survival

- Sacubitril/valsartan is one of the 4 foundational therapies recommended for patients with HFrEF with achievement of reduction in cardiovascular death, heart failure hospitalizations and all-cause mortality

- Replacing ACE inhibition by an ARNI - shown to improve morbidity and mortality in HFrEF

THANK YOU