Module 2

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Clinical Background on Heart Failure

Learning objectives

After completing this chapter you will be able to:

- Outline the main goals of the treatment of HFrEF
- Identify the important pathophysiological targets of HFrEF treatments
- Describe the classes of drugs currently available for treating HFrEF
- Understand the guidelines currently in place for clinical management of HFrEF
- Discuss the challenges and unmet needs in the treatment of HFrEF
- Describe emerging treatment strategies of interest in HFrEF

Sections

Current HFrEF Treatments
Guidelines for the Treatment of HFrEF
Treatment Challenges and Unmet Needs in HFrEF
Emerging Treatment Strategies for HFrEF

Goals of management in HFrEF

Therapeutic approaches differ for HFrEF and HFpEF[1]

The goals of HFrEF therapy are:[3]


Improve clinical status


Improve functional capacity


Improve quality of life


Prevent hospitalisations


Reduce mortality

HFrEF

- **Management has evolved from symptom control to disease-modifying therapy**
  - The aim is to improve the ability of the heart to act as a pump, and inhibit unfavourable cardiac remodelling[2]

HFpEF

- **Similar advances to the treatment of HFrEF have been elusive, and there are still no convincing therapeutic advances to alter its natural history[4]**
  - The main focus is the identification and treatment of comorbid conditions such as hypertension[1]

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

1. Zeitler EP, et al. *J Atr Fibrillation*. 2015;8:1250. 2. Shantsila E, et al. *Circulation*. 2014;130:387-389. 3. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200. 4. Mehra MR. Heart failure: management. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. Volume 2. 19th ed. New York, NY: McGraw Hill Education; 2015:1507-1516.

What's new in guidelines with regard to goal of HFrEF treatment?

The goals of treatment in patients with HF:

- reduce mortality
- prevent hospital admission
- improve clinical status, functional capacity and quality of life

*…**preventing HF hospitalization and improving functional capacity** are important benefits to be considered if mortality excess is ruled out.*

Ponikowski P et al. 2016 ESC HF Guidelines
Eur Heart J 2016 & Eur J Heart Fail 2016

There are three major goals of treatment for patients with HFrEF:

(i) reduction in mortality

(ii) prevention of recurrent hospitalizations due to worsening HF

(iii) improvement in clinical status, functional capacity, and QOL.

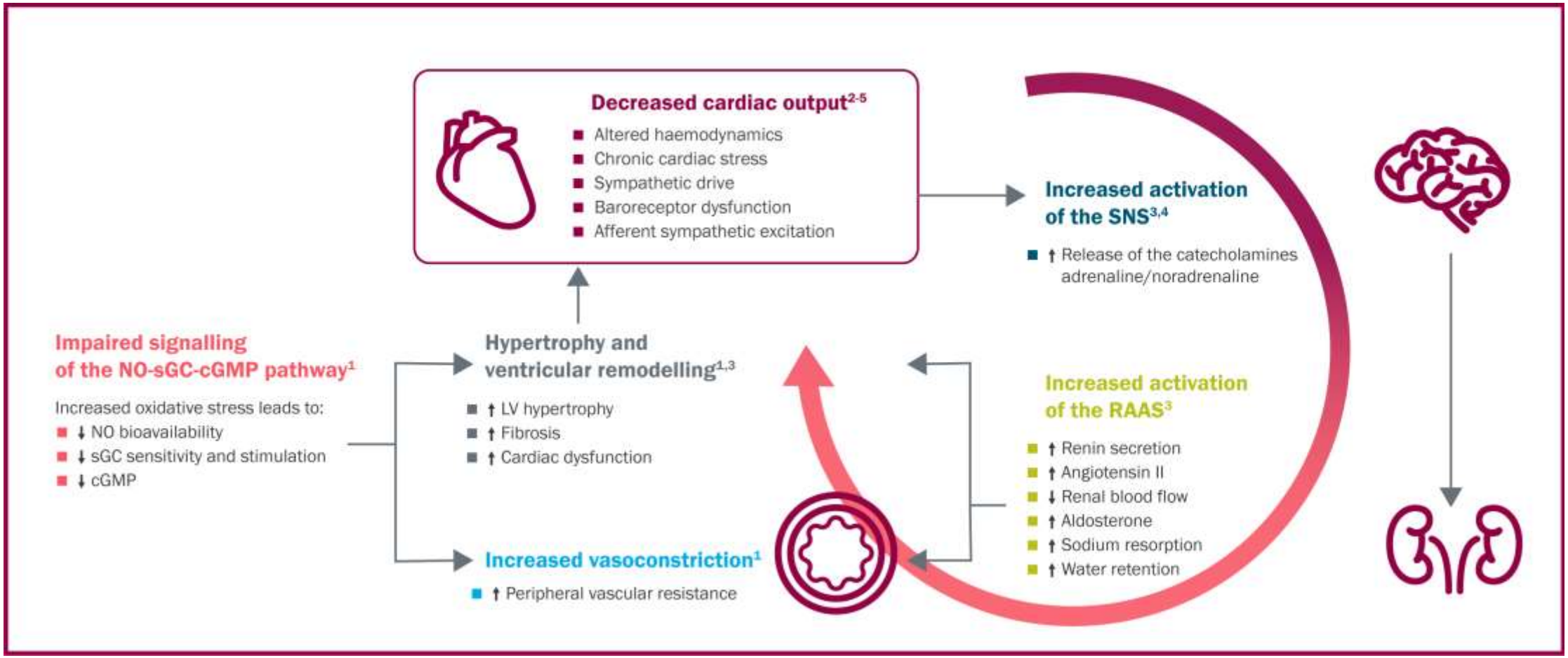
Pharmacotherapy is the **cornerstone of treatment for HFrEF** and should be implemented before considering device therapy, and alongside non-pharmacological interventions.

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

Current pathophysiological targets in the treatment of HFrEF

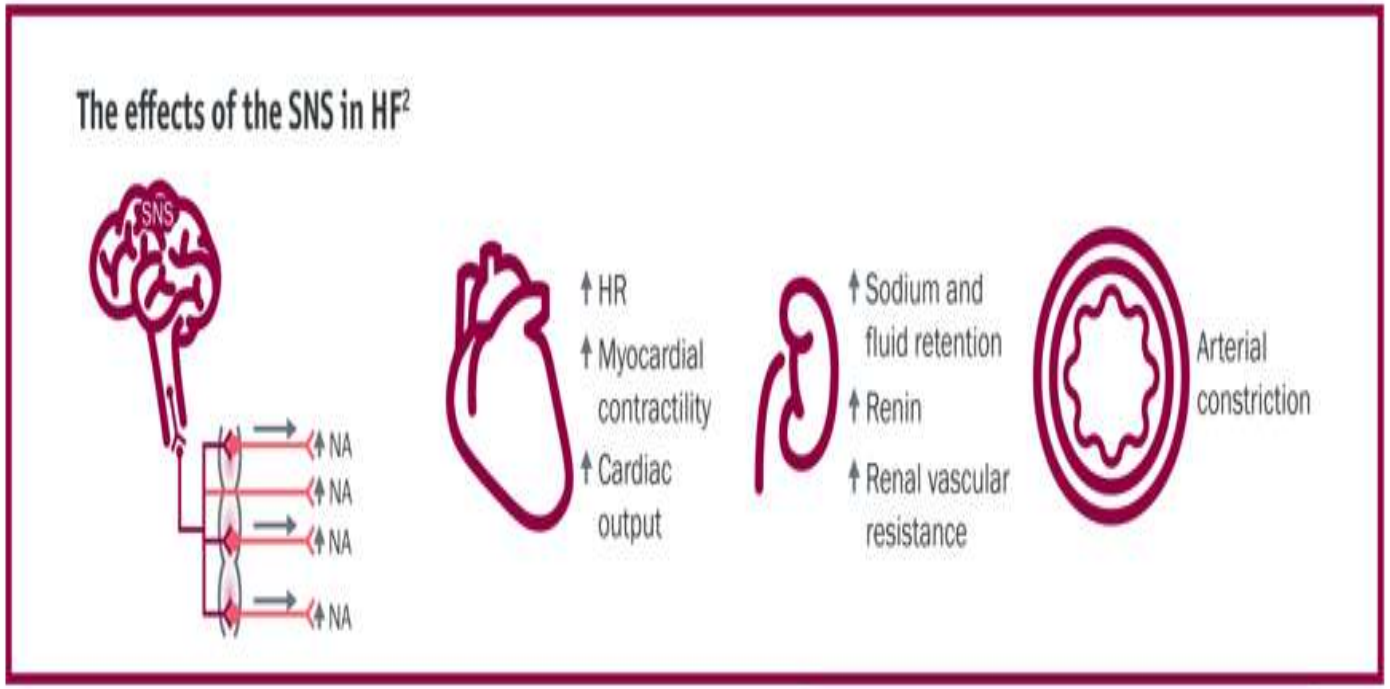
PP-VER-ALL-0104-1 January 2021

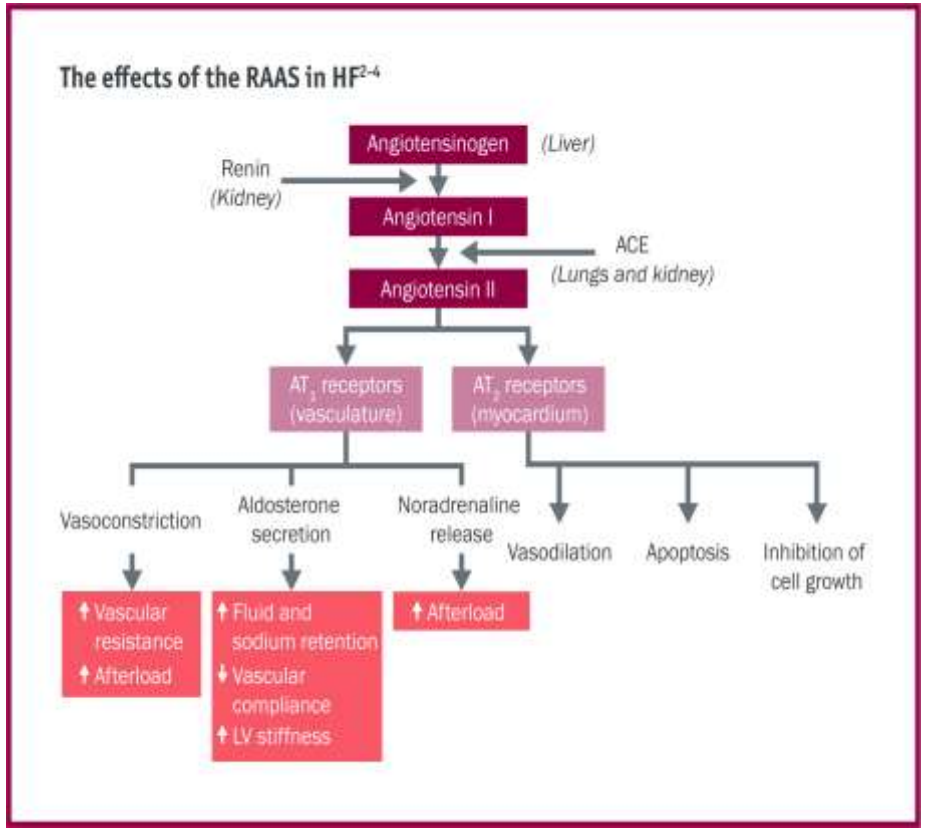
Overview of Contributors to Heart Failure Pathology



cGMP, cyclic guanosine monophosphate; HF, heart failure; LV, left ventricle; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; sGC, soluble guanylate cyclase; SNS, sympathetic nervous system.

Overview of Contributors to Heart Failure Pathology





Over time, reduced cardiac output leads to cardiac remodelling and progressive deterioration of the heart[1]

Damage to heart muscle[3]

↓ Cardiac output

↓ Blood pressure

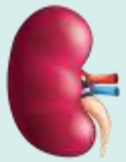
Body compensatory mechanisms[3]

Sympathetic Nervous System (SNS)

Contracts peripheral blood vessels

↑ blood pressure

Renin-Angiotensin-Aldosterone System (RAAS)



Fluid retention

↑ Preload (amount of blood entering heart)

↑ Sodium reabsorption

Short-term[1-4]

↑ Cardiac output, adequate volume for circulation

Over time[4]

Cardiac remodelling

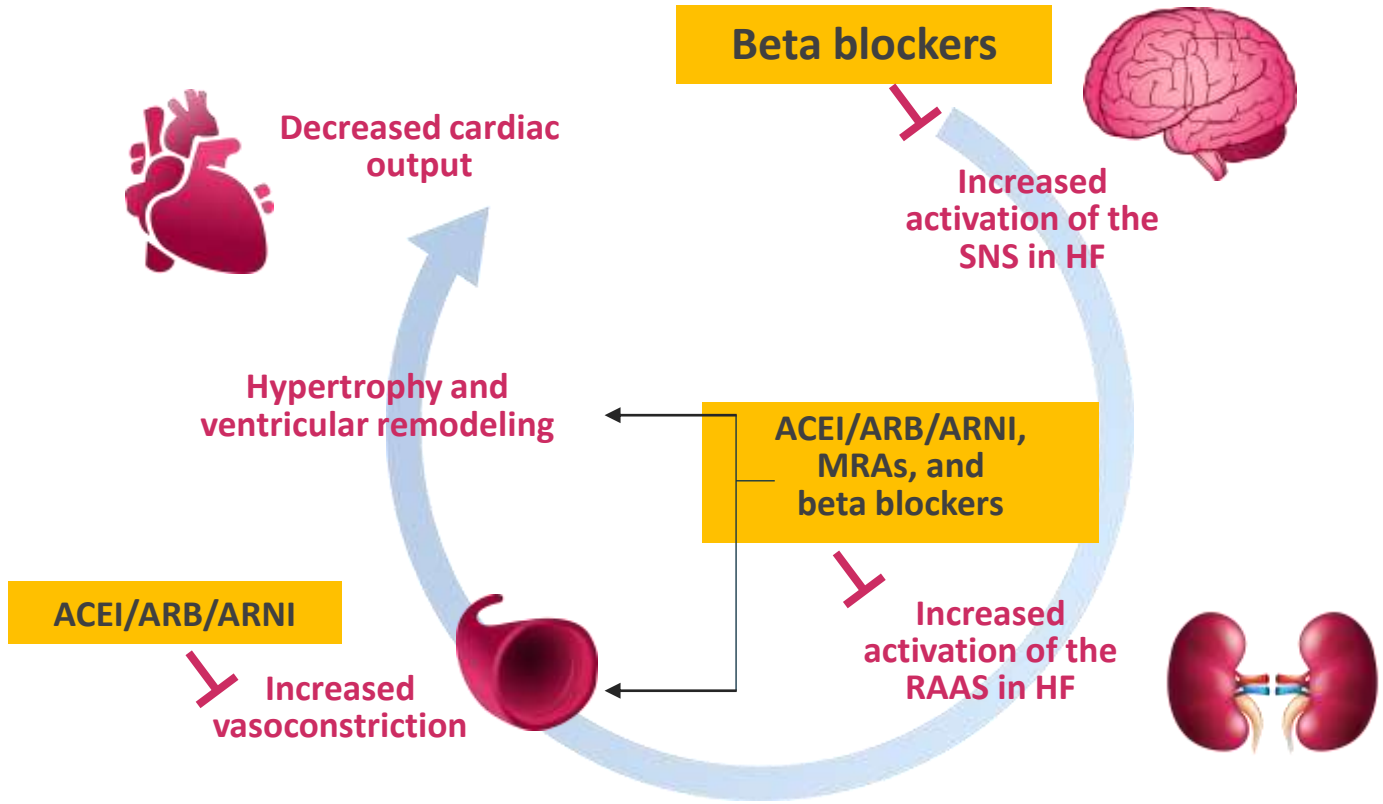
e.g. hypertrophy (thickening of the cardiac muscle wall)

Suppressing the process of cardiac remodeling and maintaining cardiac function form the main concepts of treatment for chronic HF[2]

RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Zardkoohi O, et al. Atrial fibrillation, heart failure, and the autonomic nervous system. In: Gronda E, Vanoli E, Costea A, eds. *Heart Failure Management: The Neural Pathways*. Cham, Switzerland: Springer International Publishing; 2016:25-41. 2. Kato M. The concept of heart failure: chronic diseases accompanied by an attack of acute exacerbation. In: Sato N, ed. *Therapeutic Strategies for Heart Failure*. Tokyo, Japan: Springer; 2018:1-15. 3. King M, Casey BR, Rodenberg RE. Heart failure. In: South-Paul JE, Matheny SC, Lewis EL, eds. *Current Diagnosis & Treatment: Family Medicine*. 4th ed. New York, NY: McGraw Hill; 2011:212-223. 4. Givens RC, Schulze PC. Molecular changes in heart failure. In: Eisen H, ed. *Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care*. London: Springer-Verlag; 2017:1-26.

Currently available classes of agents for symptomatic HFrEF[1-4] target compensatory mechanisms activated in HFrEF



ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor agonist; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200. 2. Benjamin EJ, et al. *Circulation*. 2018;137(12):e67-e492. 3. Dickstein K, et al. *Eur J Heart Fail*. 2008;10(10):933-989. 4. Maggioni AP, et al. *Eur J Heart Fail*. 2016;18(4):402-410.

Beta Blockers

- Beta blockers **are part of first-line treatment in HFrEF**, as **they reduce morbidity and mortality** in patients by **preventing ventricular remodelling and causing vasodilation**[1]

Mechanism of action

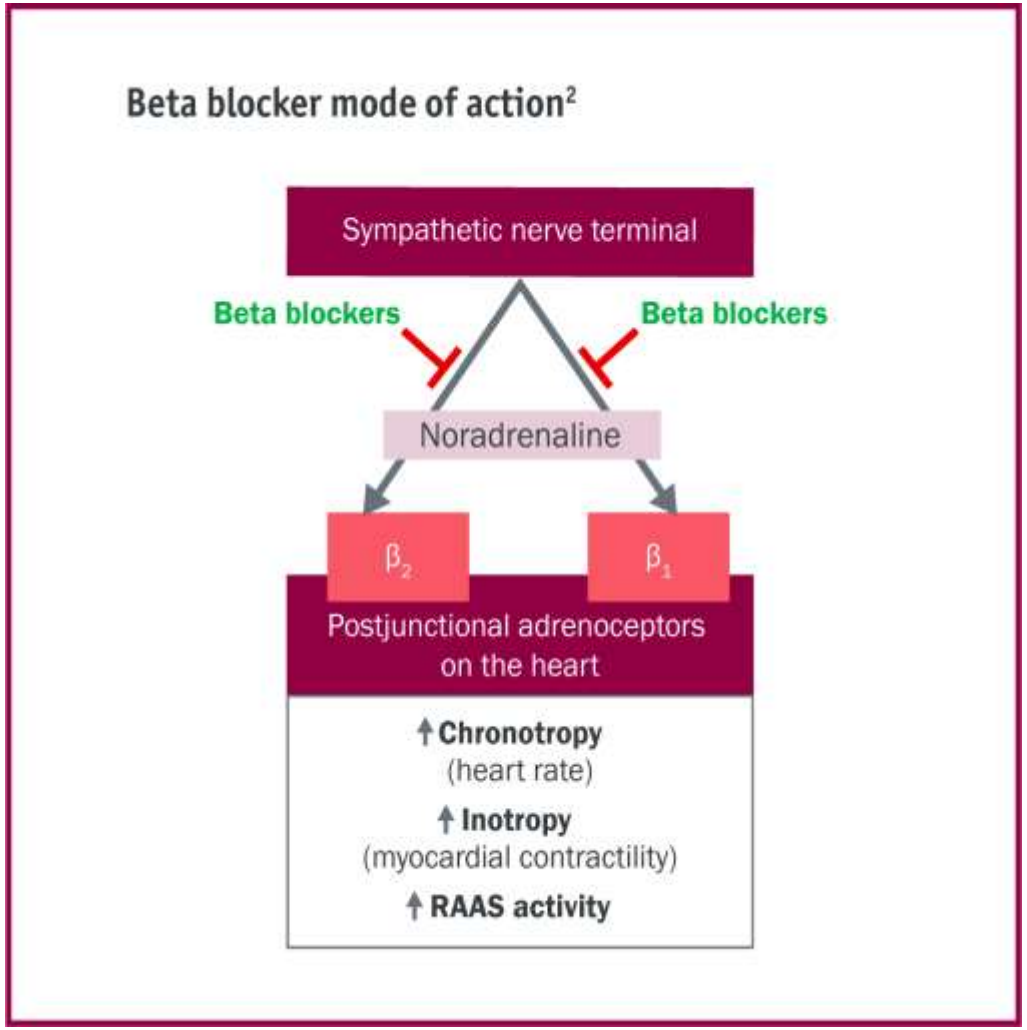
Contraindications and adverse effects

Pivotal clinical trials

Mechanism of action

Activation of the SNS is an early neurohormonal compensatory mechanism observed in patients with HF2

- The pharmacological action of beta blockers is to **attenuate sympathetic nervous system (SNS) activity** and **decrease RAAS activity**[2]
  - **Beta-1 receptors** predominate in **the heart**, and their activation leads to increased **heart rate, myocardial contractility and velocity of contraction**
  - **Beta-2 receptors** are present to a lesser degree in the heart (similar effects to beta-1 receptors), but are **predominant in vascular smooth muscle (vasodilator activity) and bronchi (bronchodilator activity)**



Beta blockers used for HF

Beta Blocker	Starting dose	Target dose
Bisoprolol	1.25 mg OD	10 mg OD
Carvedilol	3.125 mg BID	25 mg BID
Metoprolol succinate	12.5- 25mg OD	200mg OD
Nebivolol	1.25 mg OD	10mg OD

- Beta-blockers should be initiated in **clinically stable, euvolaemic, patients at a low dose and gradually uptitrated to the maximum tolerated dose**.
- In patients admitted with AHF, betablockers should be cautiously initiated in hospital, once the patient is haemodynamically stabilized.

Contraindications and adverse effects

Contraindications[1-3]	Adverse effects[1,2]
• Severe bradycardia • Second- or third-degree heart block • Cardiogenic shock • Decompensated HFrEF • Sick sinus syndrome • Bronchial asthma • Severe reversible airway disease	• Hypotension • First-degree heart block • Severe bradycardia • Oedema • Depression • Dizziness • Weakness • Fatigue • Abdominal pain/diarrhoea

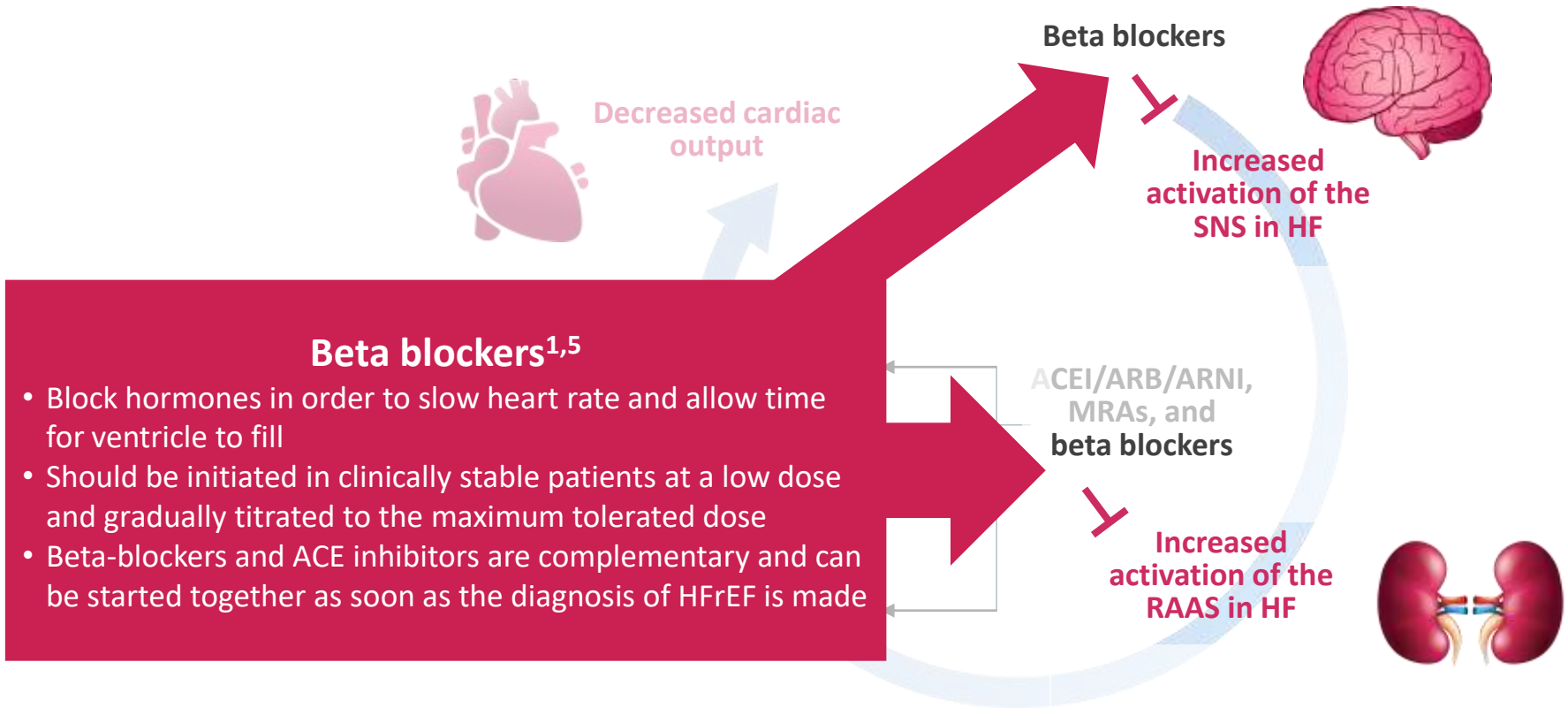
HFrEF, heart failure with reduced ejection fraction.

Pivotal clinical trials

Study	Drug	Main outcome
CIBIS-II (1999)[4]	Bisoprolol vs. placebo	Significant mortality benefit and fewer hospital admissions in symptomatic HFrEF patients taking bisoprolol vs. placebo
MERIT-HF (1999)[5]	Metoprolol vs. placebo	Improved survival in patients with symptomatic chronic HFrEF taking metoprolol vs. placebo
COPERNICUS (2001)[6]	Carvedilol vs. placebo	Lower annual mortality rate in the carvedilol group vs. placebo in patients with severe chronic HFrEF
COMET (2003)[7]	Carvedilol vs. metoprolol	Lower rates of all-cause mortality in the carvedilol group vs. metoprolol in patients with symptomatic chronic HFrEF
SENIORS (2005)[8]	Nebivolol vs. placebo	Lower event rate of the composite of all-cause mortality or CV hospitalisation in the nebivolol group vs. placebo in patients with chronic HF aged ≥70 years

CV, cardiovascular; HF, heart failure; HFrEF, HF with reduced ejection fraction.

Key points- Beta blockers



Beta blockers[1,5]

- Block hormones in order to slow heart rate and allow time for ventricle to fill
- Should be initiated in clinically stable patients at a low dose and gradually titrated to the maximum tolerated dose
- Beta-blockers and ACE inhibitors are complementary and can be started together as soon as the diagnosis of HFrEF is made

ACEI, ACE inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor agonist; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200. 2. Benjamin EJ, et al. *Circulation*. 2018;137(12):e67-e492. 3. Dickstein K, et al. *Eur J Heart Fail*. 2008;10(10):933-989. 4. Maggioni AP, et al. *Eur J Heart Fail*. 2016;18(4):402-410. 5. Yancy CW, et al. *J Am Coll Cardiol*. 2018;71(2):201-230.

Angiotensin-Converting Enzyme Inhibitors

- ACEi are part of first-line therapy in HF, improving circulation by causing relaxation of blood vessels and lowering of blood pressure[1-4]

Examples of ACEi include:[4]

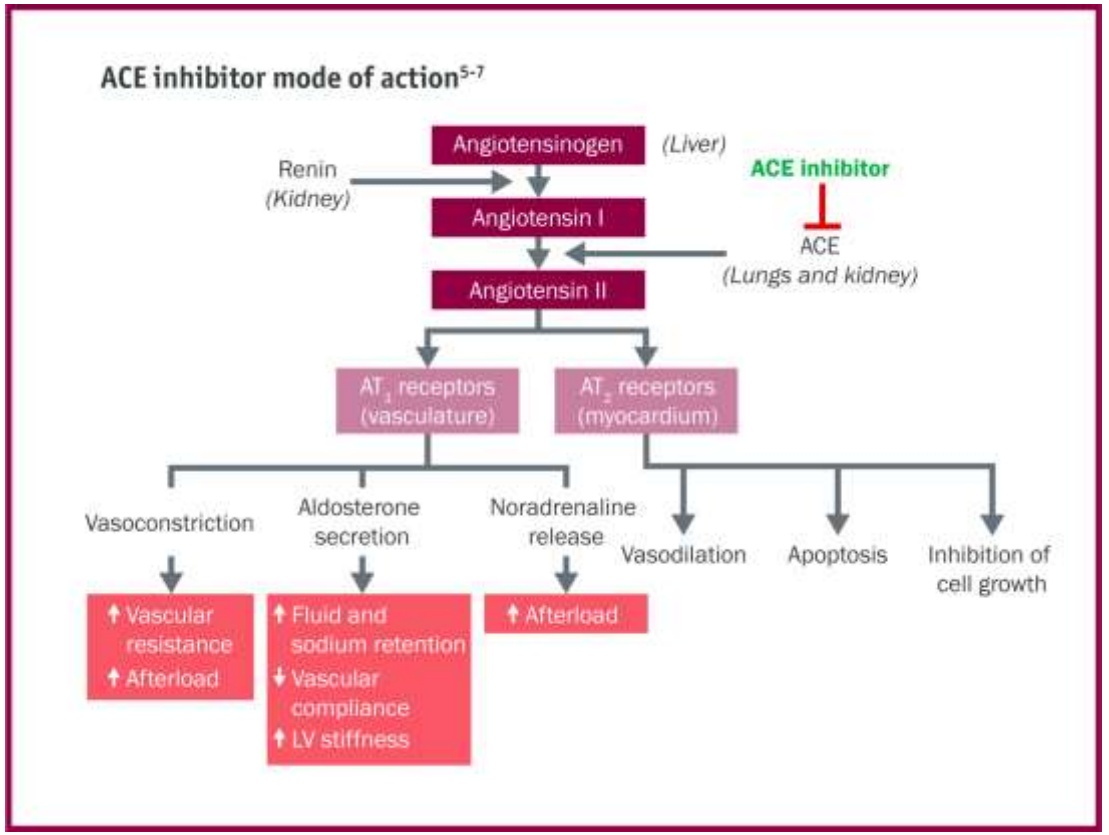
- Captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril

- Mechanism of action
- Contraindications and adverse effects
- Pivotal clinical trials

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*

Mechanism of action

- The **ACE is an enzyme that converts angiotensin I to angiotensin II**[5]
- ACEi interrupt the RAAS at an early stage by directly inhibiting the action of ACE and the generation of angiotensin II[5]
- By decreasing angiotensin II levels, ACEi promote vasodilation of both veins and arteries, decreasing both preload and afterload[5–7]

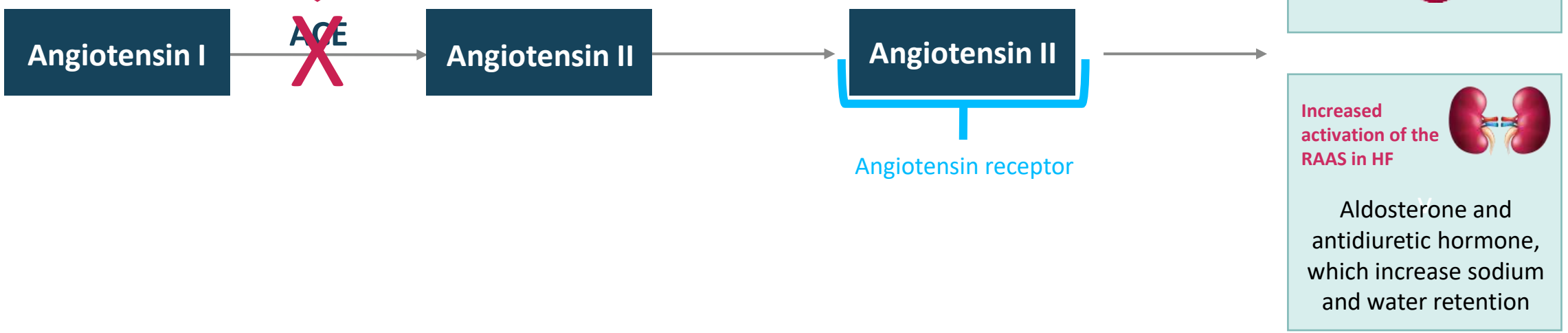


ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; AT, angiotensin II; LV, left ventricular.

Current treatment targets

ACE Inhibitors (ACEIs)[1]

- Reduce mortality and morbidity in patients with symptomatic HFrEF
- Recommended in patients with asymptomatic left ventricular systolic dysfunction



ACEI, angiotensin-converting enzyme; HF, heart failure; RAAS, renin–angiotensin–aldosterone system.

1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200.

Contraindications and adverse effects

Contraindications[8,9]	Adverse effects[9]
• Impaired kidney function (eGFR <30 mL/min/1.73 m^2; serum potassium >5.0 mEq/L; serum creatinine >2.5 mg/dL) • Bilateral renal artery stenosis • Significant aortic stenosis • Hypertropic and restrictive cardiomyopathy	• Hypotension • Worsening kidney function • Hyperkalaemia • Cough

eGFR, estimated glomerular filtration rate.

Pivotal clinical trials

Study	Drug	Main outcome
CONSENSUS (1987)[10]	Enalapril vs. placebo	Significant mortality benefit in patients with severe congestive HF treated with enalapril vs. placebo
SOLVD (1991)[11]	Enalapril vs. placebo	Enalapril reduced mortality and HF hospitalisations in patients with chronic HFrEF vs. placebo

HF, heart failure; HFrEF, HF with reduced ejection fraction.

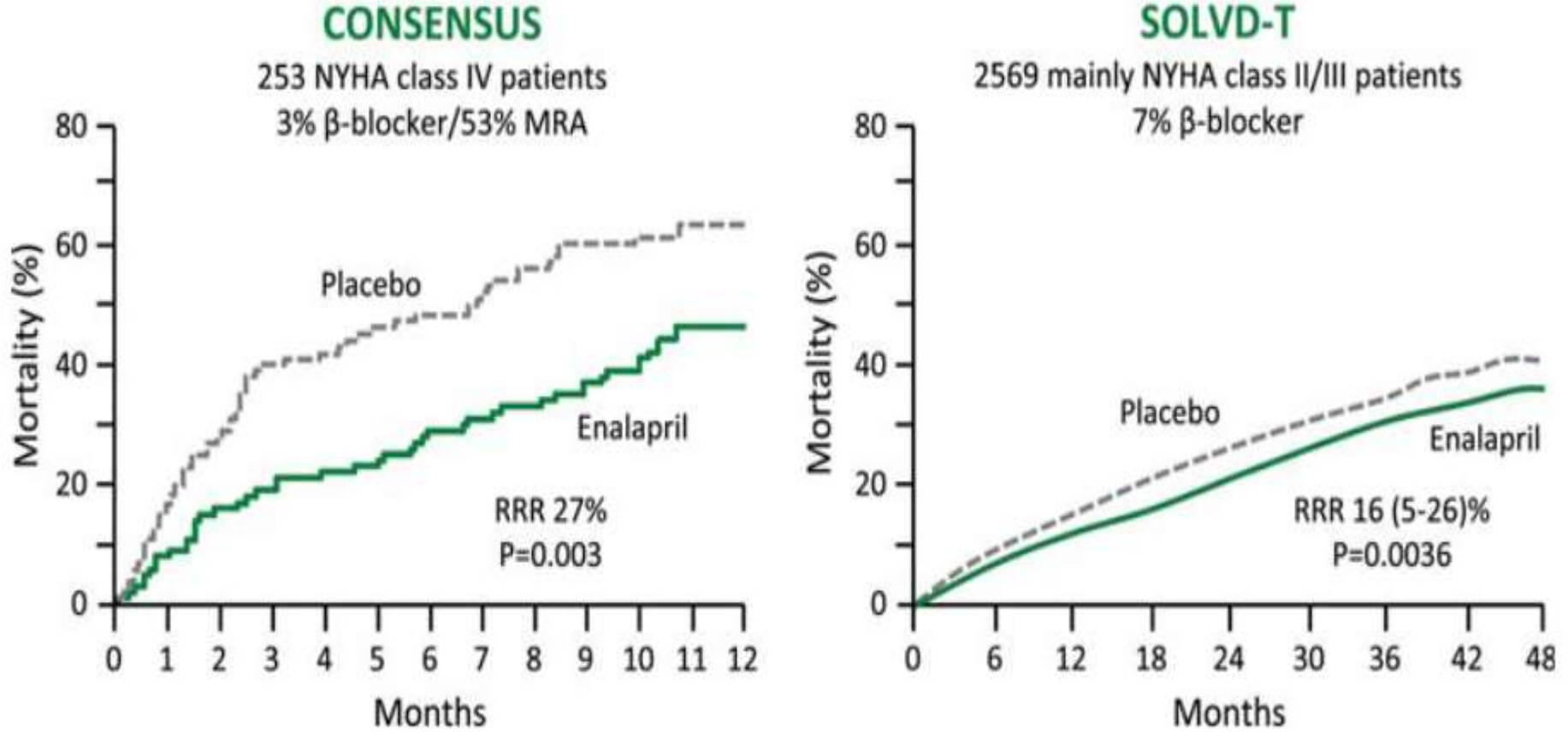


Figure 2 Trials comparing an angiotensin-converting enzyme (ACE) inhibitor to placebo in patients with systolic heart failure. Outcome is cumulative mortality.[1,13]

Angiotensin Receptor Blockers

- ARBs are part of first-line therapy in HF[a], improving circulation by causing relaxation of blood vessels and lowering of blood pressure[1–4]

Mechanism of action

Contraindications and adverse effects

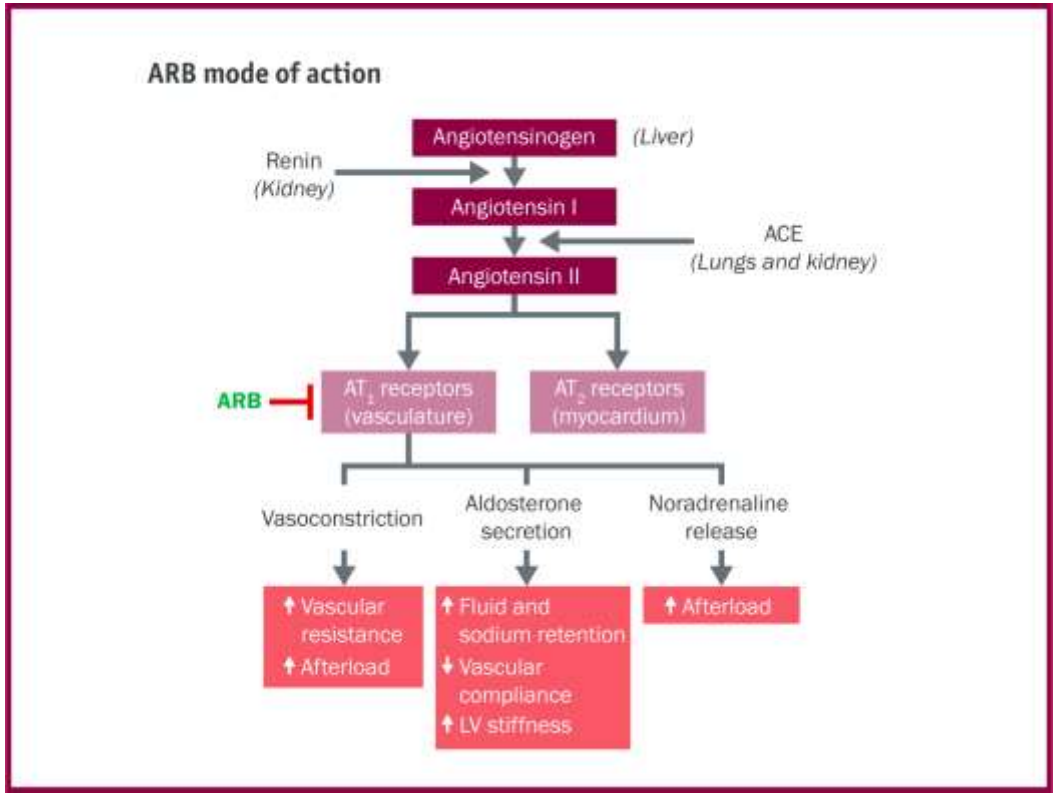
Pivotal clinical trials

[a]*Alternative to ACEi in case of contraindication.*

Mechanism of action

- Angiotensin II binds to angiotensin II receptor type 1 (AT_1), which is responsible for much of the cardiac remodelling induced by angiotensin II[4-7]
- **ARBs selectively block the binding of angiotensin II to the AT_1 receptor[4]**
- ARBs produce haemodynamic, neurohormonal and clinical effects consistent with inhibition of the RAAS[1]

- Although their mechanism of action is similar to that of ACE inhibitors, **ARBs do not cause an inhibition of kininase**, which **reduces the incidence of cough in comparison with ACE inhibitors.**



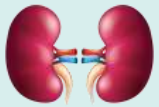
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT, angiotensin II; LV, left ventricular.

Current treatment targets

Angiotensin receptor blockers (ARBs)[1]
- **Inhibits angiotensin II** by blocking its receptor

Vasoconstriction

Increased activation of the RAAS in HF



Aldosterone and antidiuretic hormone, which increase sodium and water retention

ACEI, angiotensin-converting enzyme; HF, heart failure; RAAS, renin–angiotensin–aldosterone system.

1. Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-2200.

ARB's- ESC 2021

- The place of ARBs in the management of HFrEF has changed over the last few years.
- They are now recommended for patients **who cannot tolerate ACE-I or ARNI because of serious side effects**.
- **Candesartan** in the CHARM-Alternative **study reduced CV deaths** and HF hospitalizations in patients who were not receiving an ACE-I due to previous intolerance.
- Valsartan, in addition to usual therapy, including ACE-I, reduced HF hospitalizations in the Val-HeFT trial.

- **No ARB has reduced all-cause mortality in any trial**.

Pivotal clinical trials

Study	Drug	Main outcome
ELITE-II (2000)[9]	Losartan vs. captopril	Similar rates of all-cause mortality, sudden death and resuscitated arrests between the treatment groups in HFrEF patients aged >60 years
ValHeFT (2001)[10]	Valsartan vs. placebo	Similar overall mortality between the treatment groups but improved hospitalisation rates, NYHA class and EF for the valsartan group vs. placebo in patients with chronic HF
CHARM-Alternative (2003)[11]	Candesartan vs. placebo	Reduced composite of CV death or HF hospitalisation in the candesartan group vs. placebo in patients with chronic HFrEF who were intolerant to ACEi
CHARM-Added (2003)[12]	Candesartan vs. placebo	The addition of candesartan to ACEi led to reduced composite of CV death or HF hospitalisation in the candesartan group vs. placebo in patients with chronic HFrEF

ACEi, angiotensin-converting enzyme inhibitor; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced EF; NYHA, New York Heart Association.

Contraindications and adverse effects

Contraindications[3,8]	Adverse effects[8]
• Bilateral renal artery stenosis • Severe aortic stenosis • Elevated serum potassium (>5.0 mEq/L) • Elevated serum creatinine (>2.5 mg/dL) • Impaired kidney function (eGFR <30 mL/min/1.73 m^2) • NOTE: ARBs should not be used in patients taking both an ACEi and an MRA due to the risk of hyperkalaemia, hypotension and kidney dysfunction	• Hypotension • Worsening kidney function • Hyperkalaemia • Cough (<2% of treated patients)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist.

Mineralocorticoid Receptor Antagonists

- Mineralocorticoid receptor antagonists (MRAs) are used in HF therapy to **further reduce blood pressure on top of ACEis/ARBs and beta blockers**[1,2]
- Two MRAs are currently available: **Spironolactone and eplerenone**[3]
- Careful patient selection and risk assessment with availability of close monitoring is essential in initiating the use of MRAs[1]

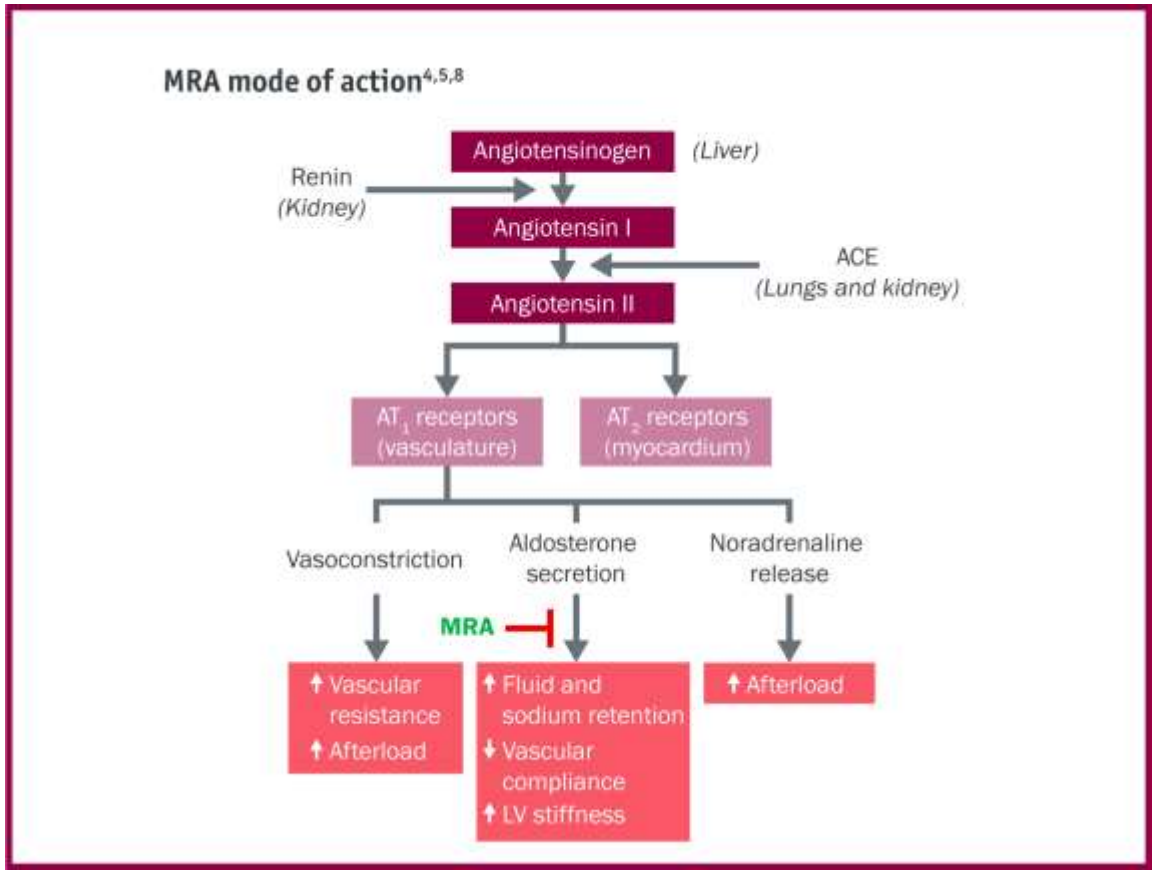
Mechanism of action

Contraindications and adverse effects

Pivotal clinical trials

Mechanism of action

- Activation of the RAAS in HF leads to the secretion of the mineralocorticoid **aldosterone** from the adrenal glands[4,5]
- **Aldosterone binds to specific MRs in the distal tubule of the kidney,** promoting **sodium reabsorption in exchange for potassium excretion[6]**
- MRAs, also known as **aldosterone antagonists**, block the action of aldosterone at the late distal tubule and collecting duct of the kidney[6,7]
- This promotes **sodium (and water) excretion into the collecting duct and urine,** while conserving potassium in the blood[6,7]



ACE, angiotensin-converting enzyme; AT, angiotensin II; LV, left ventricular; MRA, mineralocorticoid receptor antagonist.

MRA classes

- MRAs (spironolactone or eplerenone) are recommended, in addition to an ACE-I and a beta-blocker, in all patients with HFrEF to reduce mortality and the risk of HF hospitalization.
- They also improve symptoms.

Beta Blocker	Starting dose	Target dose
Spironolactone	25 mg OD	50 mg OD
Eplerenone	25 mg OD	50 mg OD

Contraindications and adverse effects

Contraindications[2,6]	Adverse effects[3,6]
• Elevated serum potassium (≥5.0 mEq/L) • Elevated creatinine (>2.5 mg/dL) • Administration of another potassium-sparing diuretic or potassium supplements • NOTE: Clinically unsafe to use MRAs with two ACEi/ARBs due to the risk of hyperkalaemia	• Worsening kidney function • Hyperkalaemia • Gynaecomastia (only with spironolactone)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

RCT evaluating effects of MRA on mortality and HFH

Table 2

Summary of RCT evaluating effects of MRA on mortality and HF hospitalizations in patients with HF and reduced LVEF.

RCT: randomized controlled trial, LVEF: left ventricular ejection fraction, MI: myocardial infarction, NYHA: New York Heart Association, HF: heart failure, HR: hazard ratio, CI: confidence interval, CV: cardiovascular.

RCT	Drug	*n*	LVEF	NYHA class	Etiology of HF	Primary end-point (CV deaths and HF hospitalizations)	HR (95% CI) P value	Death for any cause, HR (95% CI), P value
RALES	Spironolactone	1663	≤35%	III to IV	Ischemic and non-ischemic	38.1% vs. 50.5%	0.68 (0.59–0.78) <0.001	0.70 (0.60–0.82) P < 0.001
EPHESUS	Eplerenone	6642	≤40	II to IV, even class I if diabetes is present	Post-MI (2 weeks)	26.6% vs 30.0%	0.87 (0.79–0.95) 0.002	0.85 (0.75–0.96) P = 0.008
EMPHASIS	Eplerenone	2737	≤30%, ≤35% if QRS > 130 ms	II	Ischemic and non-ischemic	18.3% vs 25.9%	0.63 (0.54–0.74) <0.001	0.76 (0.62–0.93) P = 0.008

Pivotal clinical trials

Study	Drug	Main outcome
RALES (1999)[9]	Spironolactone vs. placebo	Patients with severe HFrEF in the spironolactone group experienced lower all-cause mortality rates vs. placebo
EPHESUS (2003)[10]	Eplerenone vs. placebo	Eplerenone reduced morbidity and mortality in patients with HFrEF after MI vs. placebo
EMPHASIS-HF (2011)[11]	Eplerenone vs. placebo	Eplerenone reduced the risk of CV death and HF hospitalisation in patients with chronic HFrEF and mild symptoms vs. placebo

CV, cardiovascular; HF, heart failure; HFrEF, HF with reduced ejection fraction; MI, myocardial infarction.

Angiotensin Receptor and Neprilysin Inhibitor

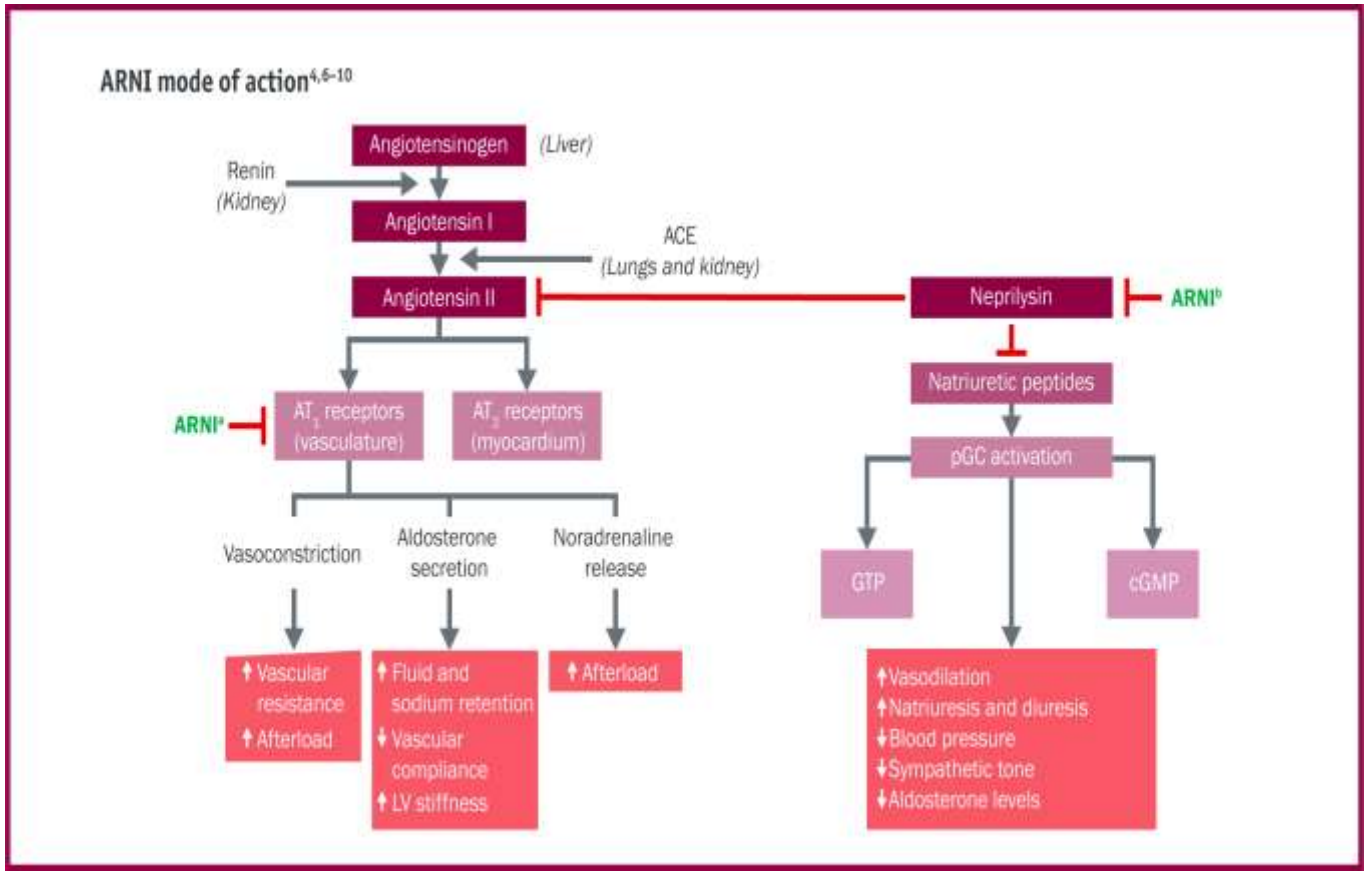
- The ARNI **sacubitril/valsartan** was approved for the treatment of HFrEF in 2015[1]
- Recommended in patients with **chronic symptomatic HFrEF who tolerate ACEi/ARB,** to **reduce morbidity and mortality**[2,3]

Mechanism of action

Contraindications and adverse effects

Mechanism of action

- That the natriuretic peptide system is a compensatory mechanism in HF, which works antagonistically to the RAAS and has favourable effects on HF pathogenesis[4]
- **Neprilysin is a neutral endopeptidase** that inactivates several vasoactive peptides[5]
- **Neprilysin inhibitors** decrease the inactivation of vasoactive peptides, such as natriuretic peptides, promoting their downstream effects[5]
- Since angiotensin II is also a substrate for neprilysin, neprilysin inhibitors raise angiotensin levels, which explains the additional rationale for **co-administration of ARB[5]**



ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor neprilysin inhibitor; AT, angiotensin II; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; LV, left ventricular; pGC, particulate guanylate cyclase.

Sacubitril-valsartan *(Entresto)*

- Dosage form
  - Combination tablet

- Available dosages
  - 24-26 mg (50 mg)
  - 49-51 mg (100 mg)
  - 97-103 mg (200 mg)

- Indicated regimen
  - One tablet by mouth twice daily

Initial dosing

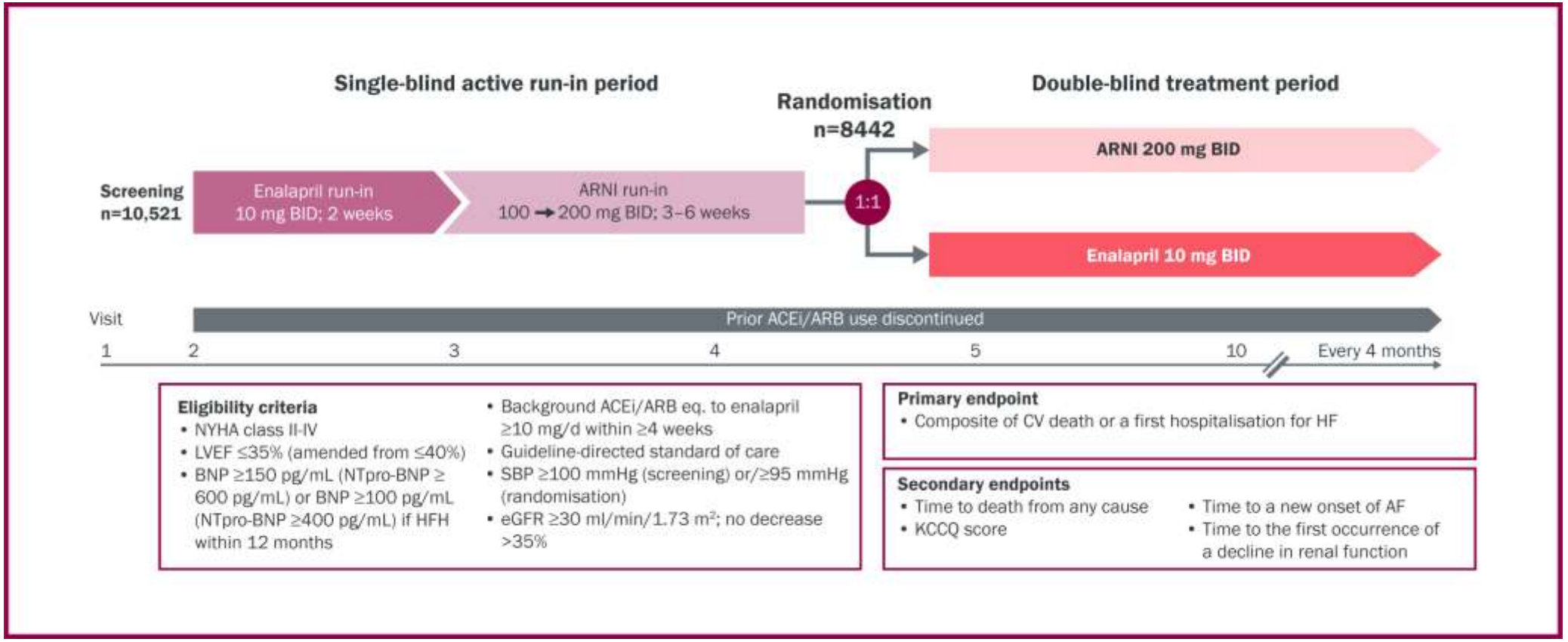
- ACE/ARB naive patients
  - Initiate sacubitril-valsartan 24/26 mg BID. If tolerated, double dose in 2-4 weeks. Goal dose 97/103 mg.

- Patient on ACE-inhibitor (≤10 mg enalapril/day or equivalent)
  - Initiate sacubitril-valsartan 24/26 mg BID. If tolerated, double dose in 2-4 weeks. Goal dose 97/103 mg.

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)

PARADIGM HF
Trial design[1,2]



ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BID, twice daily; BNP, B-type natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, HF hospitalisation; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal proBNP; NYHA, New York Heart Association; SBP, systolic blood pressure.

Concertina:
Baseline characteristics[2,3]

Characteristic	Sacubitril/ valsartan (n=4187)	Enalapril (n=4212)
Age, years	63.8±11.5	63.8±11.3
Female sex, n (%)	879 (21.0)	953 (22.6)
Systolic blood pressure, mmHg	122±15	121±15
Clinical features of HF		
Ischaemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
LVEF, %	29.6±6.1	29.4±6.3
Median NT-proBNP, pg/mL (IQR)	***1631 (885–3154)***	***1594 (886–3305)***
NYHA class III/IV, n (%)	***1002 (23.9)***	***1076 (25.5)***
Hospitalisation for HF	**2607 (62.3)**	**2667 (63.3)**
Hospitalisation for HF in previous 6 months	***2620 (31.2)[a]***	
Medical history, n (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Treatments at randomisation, n (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta blocker	3889 (93.1)	3912 (92.9)
MRA	2271 (54.2)	2400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)
Pre-trial use of ACEi	3266 (78.0)	3266 (77.5)
Pre-trial use of ARB	929 (22.2)	963 (22.9)

[a]*Calculated from 8399 patients.*

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Results

Outcome[2]	Sacubitril/valsartan (n=4187)		Enalapril (n=4212)		HR (95% CI)	*P*-value	ARR[4]
	Values	*Events/ 100 PY*[5]	Values	*Events/ 100 PY*[5]			
Primary composite outcome, n (%)							
CV death or first HF hospitalisation	914 (21.8)	10.5	1117 (26.5)	13.2	0.80 (0.73–0.87)	<0.001	**2.7**
CV death	558 (13.3)	6.0	693 (16.5)	7.5	0.80 (0.71–0.89)	<0.001	**1.5**
First HF hospitalisation	537 (12.8)	6.2	658 (15.6)	7.7	0.79 (0.71–0.89)	<0.001	**1.5**
Secondary outcomes, n (%)							
Death from any cause	711 (17.0)	7.6	835 (19.8)	9.0	0.84 (0.76–0.93)	<0.001	**1.4**
Change in KCCQ clinical summary score at 8 months	−2.99±0.36		−4.63±0.36		1.64 (0.63–2.65)	0.001	
New-onset atrial fibrillation	84 (3.1)		83 (3.1)		0.97 (0.72–1.31)	0.83	
Decline in renal function[a]	94 (2.2)		108 (2.6)		0.86 (0.65–1.13)	0.28	

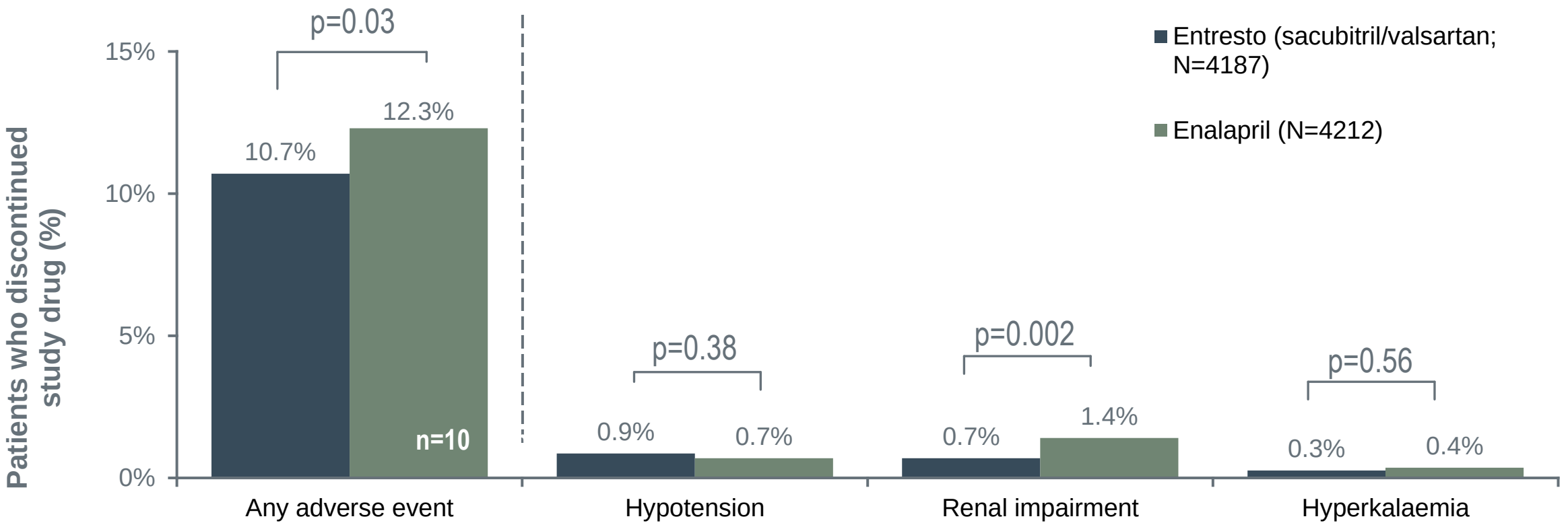
[a]Defined as end-stage renal disease or a decrease of 50% or more in the eGFR from the value at randomisation or a decrease in the eGFR of >30 mLmin/1.73 m^2, to <60 mL/min/1.73 m^2.

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; PY, patient-years.

PARADIGM HF

- **Primary outcome of CV death or hospitalisation for HF occurred in 21.8% of the ARNI group vs. 26.5% of the enalapril group (median follow-up: 27 months)[2]**
- Study stopped early due to benefit[2]
- Consistent benefit among all subgroups[2]
  - The risk of the primary outcome was higher in patients with more recent hospitalisation for HF, but there was no difference of differential treatment effect across the spectrum of time since hospitalisation[3]
- Higher rate of symptomatic hypotension with ARNI – however, this did not lead to an increased rate of discontinuation of the therapy[2]

PARADIGM-HF: Fewer adverse events leading to permanent study drug discontinuation



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

Contraindications and adverse effects

Contraindications[11]	Adverse effects[11]
• Hypersensitivity • Angioedema with previous ACEi or ARB use • Within 36 h of ACEi use • Concomitant aliskiren use in patients with diabetes **Not recommended** • Severe hepatic impairment (Child-Pugh C) • Pregnancy/breastfeeding **Cautions** • Renal artery stenosis • Volume depletion • Hyponatraemia	• Angioedema • Impaired renal function • Hyperkalaemia • Dizziness • Cough

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

SGLT2 Inhibitors

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) have been used for patients with type 2 diabetes (T2D) for improvement of glycaemic control since 2012, and have been tested in CV outcome trials, as per the guidance of the US Food and Drug Administration (US FDA)[1,2]
- Results of these trials suggested potential for this class in patients with HF and T2D, and possibly those with, or at risk of HF without T2D[3]
- The European Society of Cardiology (ESC) Heart Failure Association (HFA) 2019 Clinical Practice Update included a statement that 'canagliflozin, dapagliflozin, empagliflozin should be considered in T2D patients with/at risk of CVD **to prevent or delay onset of HF hospitalisation**'[4]
  - SGLT2 inhibitors should be prioritised over metformin[5]
- **Dapagliflozin was approved in the US for the treatment of HFrEF in May 2020[9]**

[a]Sotagliflozin is an SGLT2/1 inhibitor.[1]

- SGLT2is, including empagliflozin, dapagliflozin and sotagliflozin,[a] are under investigation in phase III trials for their potential to reduce the risk of HF hospitalisations or CV death in patients with HFrEF with or without T2D
  - DAPA-HF, the first study of an SGLT2i in HF, was positive[6]
  - EMPEROR-Reduced and SOLOIST-WHF were also positive[7,8]

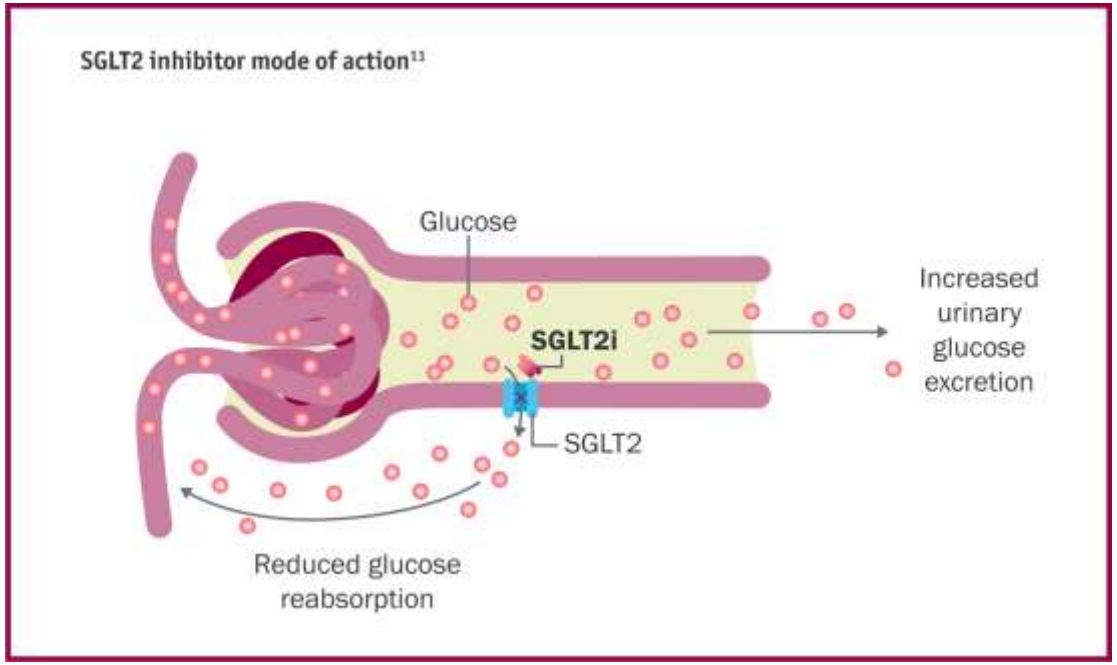
Mechanism of action

Pivotal CV outcome trials

Contraindications and adverse effects

Mechanism of action

- **SGLT2 is expressed almost exclusively in the early segment of the kidney's proximal tubule,** and accounts for up to 90% of the reabsorbed glucose from the glomerular filtrate back into circulation[10]
  - SGLT1 is responsible for reabsorption of the residual glucose (10–20%)[10,11]
- **SGLT2 inhibitors:**
  - Inhibit the physiological reabsorption of glucose and sodium in the kidneys, resulting in their excretion in the urine[11]
    - This leads to reduction of blood glucose, blood pressure, inflammation, oxidative stress, arterial stiffness, and SNS activity[11]
  - Mediate natriuresis, which reduces both systolic and diastolic pressures[11]
  - Mediate natriuresis and glycosuria, which reduce plasma volume and lower cardiac preload[11,12]
    - This may decrease central aortic pressure and reduce afterload, indirectly leading to improved LV function[11]



SGLT2 drives the sodium-coupled glucose entry across the membrane. Sodium levels are maintained by a basolateral sodium/potassium-ATPase, an energy-dependent pump that pumps potassium into the cell and sodium out of the cell. Glucose leaves the cell down into the blood through facilitative glucose transporters (GLUT2). SGLT2is work to stop this process.[11]
SGLT2, sodium-glucose co-transporter 2; SGLT2i, SGLT2 inhibitor.

Pivotal CV outcome trials

	EMPA-REG OUTCOME[13]	DECLARE-TIMI 58[14]
Drug	Empagliflozin (vs. placebo)	Dapagliflozin (vs. placebo)
Patients, n	7020	17,160
Patient population	• T2D with high risk of CV events	• T2D with, or at risk of, atherosclerotic CVD
Primary endpoint	• Patients who received empagliflozin had a lower rate of the primary composite CV outcome of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke, vs. placebo	• Compared with placebo, dapagliflozin did not result in a higher or lower rate of the primary safety and efficacy outcome of MACE,[a] but did result in a lower rate of the primary efficacy outcome of a composite of CV death or HF hospitalisation, across multiple subgroups
Further results	• Patients who received empagliflozin had a lower rate of death from any cause and of HF hospitalisation, vs. placebo	• Additional analysis showed that dapagliflozin reduces HF hospitalisation in a broad spectrum of patients with T2D and high CV risk regardless of EF, with the greatest absolute risk reduction in patients at highest risk, and reduces CV death and all-cause mortality in patients specifically with HFrEF[15]

[a]CV death, myocardial infarction or ischaemic stroke.
CV, cardiovascular; CVD, CV disease; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.

Pivotal Heart Failure Trial on SGLT2 Inhibitors: DAPA-HF

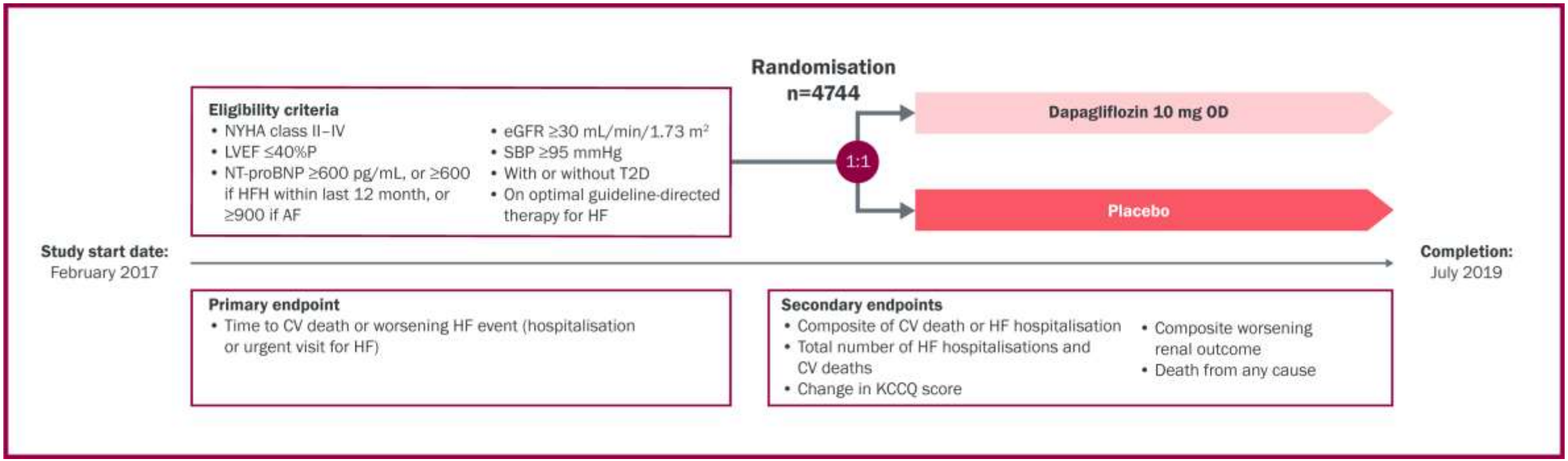
- DAPA-HF: International, multicentre, phase III randomised clinical trial evaluating dapagliflozin on morbidity and mortality in patients with chronic HFrEF[1]
- The risk of a worsening HF event or death from CV causes was lower in the dapagliflozin group than in the placebo group, regardless of the presence or absence of diabetes[2]

Concertina 1: Trial design[1–3]

Concertina 2: Baseline characteristics[2,4]

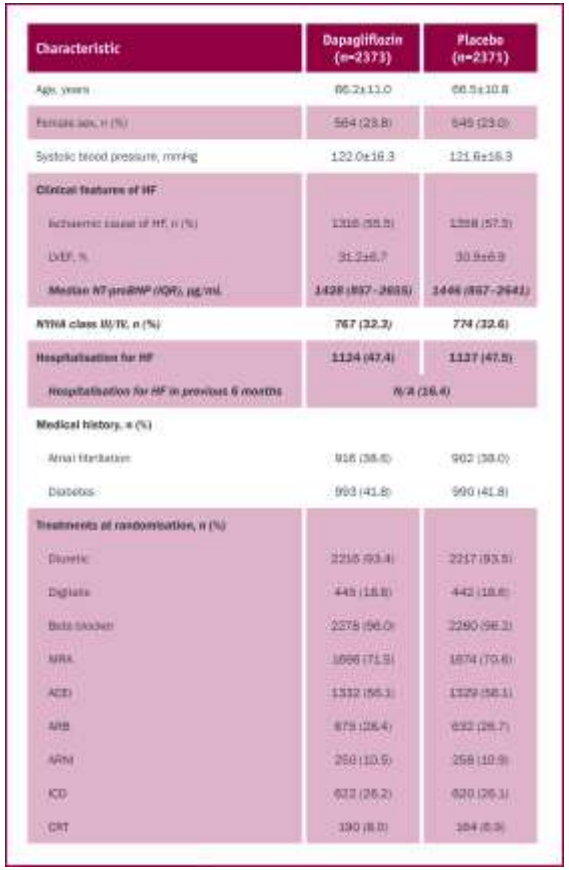
Concertina 3: Results[2]

DAPA HF
Trial design[1–3]



AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OD, once daily; SBP, systolic blood pressure; T2D, type 2 diabetes.

DAPA HF
Baseline characteristics[2,4]



Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Age, years	66.2±11.0	66.5±10.8
Female sex, n (%)	564 (23.8)	545 (23.0)
Systolic blood pressure, mmHg	122.0±16.3	121.6±16.3
Clinical features of HF		
Ischaemic cause of HF, n (%)	1316 (55.5)	1358 (57.3)
LVEF, %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR), pg/mL	*1428 (897–2655)*	*1446 (887–2641)*
NYHA class III/IV, n (%)	767 (32.3)	774 (32.6)
Hospitalisation for HF	1124 (47.4)	1137 (47.9)
Hospitalisation for HF in previous 6 months	*N/A (16.4)*	
Medical history, n (%)		
Atrial fibrillation	916 (38.6)	902 (38.0)
Diabetes	993 (41.8)	990 (41.8)
Treatments at randomisation, n (%)		
Diuretic	2216 (93.4)	2217 (93.5)
Digitalis	445 (18.8)	442 (18.6)
Beta blocker	2278 (96.0)	2280 (96.2)
MRA	1696 (71.5)	1674 (70.6)
ACEi	1332 (56.1)	1329 (56.1)
ARB	679 (28.4)	632 (26.7)
ARNI	250 (10.5)	258 (10.9)
ICD	622 (26.2)	620 (26.1)
CRT	190 (8.0)	184 (7.8)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronisation therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Concertina: Results[2]

Outcome	Dapagliflozin (n=2373)		Placebo (n=2371)		HR (95% CI)	P-value	ARR
	Values	Events/ 100 PY	Values	Events/ 100 PY			
Primary composite outcome, n (%)	386 (16.3)	11.4	502 (21.2)	15.6	0.74 (0.65–0.85)	<0.001	4.9
Hospitalization or an urgent visit for HF	237 (10.0)		326 (13.7)		0.70 (0.59–0.82)		
Hospitalization for HF	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59–0.83)		2.9
Urgent HF visit	10 (0.4)		33 (1.4)		0.45 (0.20–0.93)		
CV death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69–0.98)		1.4
Secondary outcomes, n (%)							
CV death or HF hospitalization	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65–0.85)	<0.001	3.9
Total no. of HF hospitalizations and CV deaths	567		742		0.73 (0.65–0.84)	<0.001	
Change in KCCQ score at 8 months	0.1±18.8		3.3±19.2		1.18 (1.11–1.26)	<0.001	
Worsening renal function[a]	28 (1.2)		39 (1.6)		0.71 (0.44–1.16)		
Death from any cause	276 (11.6)	7.9	329 (13.9)	9.3	0.80 (0.71–0.91)		2.3

[a]*A composite outcome of a reduction of ≥50% in the eGFR sustained for ≥28 days, ESRD, or death from renal causes. ESRD was defined as an eGFR of <15 mL/min/1.73 m^2 that was sustained for ≥8 days, long-term dialysis treatment (sustained for ≥28 days), or kidney transplantation.*

- Safety: Discontinuations due to adverse events were comparable in both arms (<5%)
  - Change in systolic blood pressure from baseline was significantly higher for dapagliflozin vs. placebo: -1.92±14.92 vs. -0.38±15.27 mmHg (HR: -1.27; 95% CI -2.09 to -0.45; P=0.002)
- Looking more closely at KCCQ response, more patients in the dapagliflozin group than in the placebo group had an increase of at least 5 points (the minimal clinically important difference) in the total score (58.3 vs. 50.9%; OR: 1.15; 95% CI 1.08 to 1.23) and fewer had significant deterioration (25.3 vs. 32.9%; OR: 0.84; 95% CI 0.78 to 0.90) (both P<0.001)

ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; PY, patient-years.

EMPEROR-Reduced study design

Design: Randomised, double-blind, placebo-controlled, phase III study

Objective: Investigate the safety and efficacy of empagliflozin versus placebo on top of SOC in patients with HFrEF

Eligibility criteria

- Age ≥18 years*
- Diagnosed HF (NYHA class II–IV)
- LVEF ≤40%
- Elevated NT-proBNP#
- Receipt of SOC for HF and stable for ≥1 week before visit 1
- Written consent provided

Median follow-up: 16 months

Primary endpoint: Time to first event of CV death or HFH

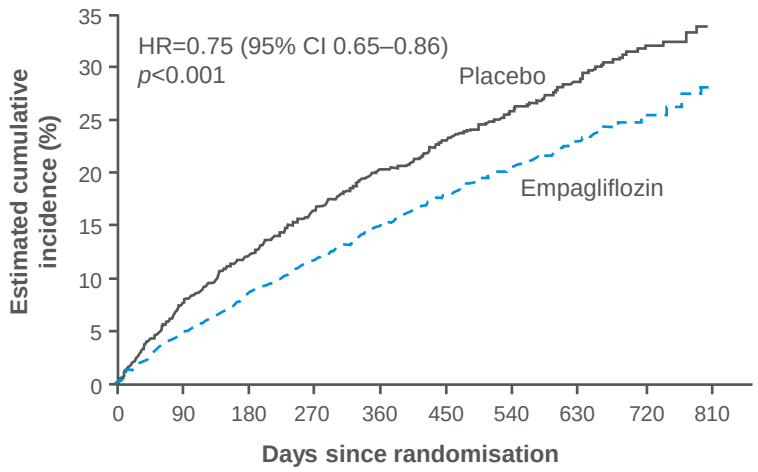
*For Japan only: Age ≥20 years; #NT-proBNP cut-off was double in patients with atrial fibrillation
CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFH, heart failure hospitalisation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; od, once daily; SOC, standard of care

Packer M et al. *N Engl J Med*. 2020;383:1413–1424

Heart Failure

EMPEROR-Reduced: Empagliflozin reduced time to composite of CV death or HFH, but not CV death alone

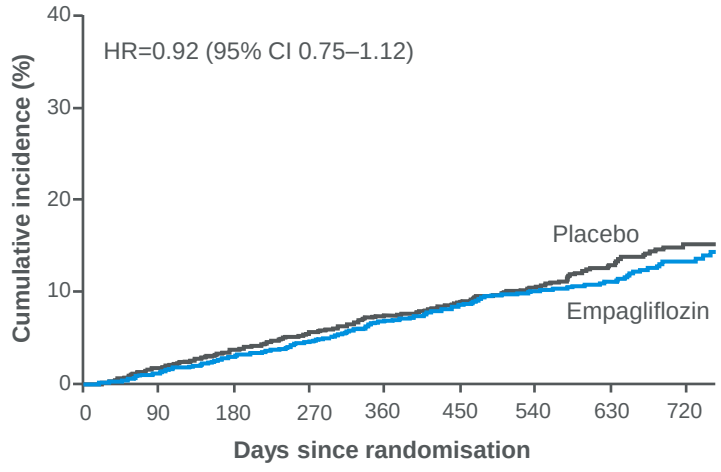
Primary outcome (CV death or HFH)



Number at risk

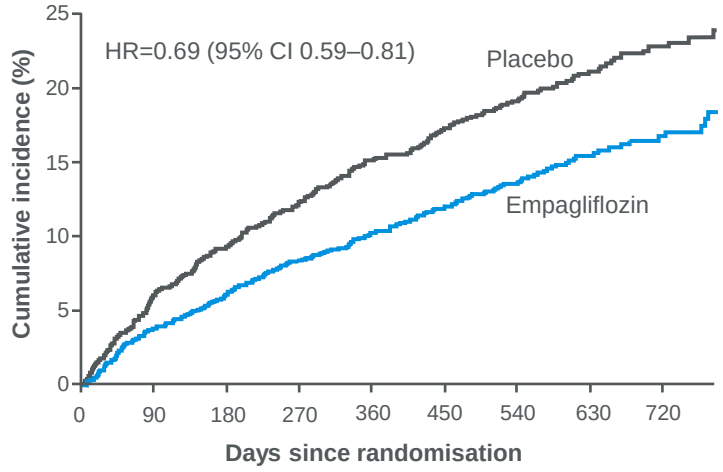
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

CV death



1867	1825	1770	1534	1294	1027	743	507	282
1863	1829	1772	1537	1289	1015	742	506	281

HFH



1867	1715	1612	1345	1108	854	611	410	224
1863	1763	1677	1424	1172	909	645	423	231

HFH indicates time to first HFH
CV, cardiovascular; HFH, heart failure hospitalisation
Packer M et al. *N Engl J Med*. 2020;383:1413–1424

Heart Failure

Key details of the DAPA-HF and EMPEROR-Reduced studies

		DAPA-HF (N=4744)[1–3] Dapagliflozin	EMPEROR-Reduced (N=3730)[4] Empagliflozin
Inclusion/ exclusion criteria	NT-proBNP cut-off (pg/ml)	≥600 or ≥400 if HFH within 12 months or ≥900 if AF	EF ≤30%: ≥600, or ≥1200 if AF EF 31–35%: ≥1000, or ≥2000 if AF EF 36–40%: ≥2500, or ≥5000 if AF EF ≤40% and HFH within 12 months: ≥600, or ≥1200 if AF
	Recent HF decompensation	No current ADHF or hospitalisation due to decompensated HF <4 weeks prior to enrolment	Chronic HF ≥3 months No current ADHF requiring IV diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomisation
Baseline characteristics	Median NT-proBNP, pg/ml	1437	1907
	NYHA class III or IV	32%	25%
	Prior HFH	16% within 6 months	31% within 12 months
	Mean eGFR, ml/min/1.73 m^2	66	62
	eGFR <60 ml/min/1.73 m^2	41%	48%
Primary endpoint event rate (control arm)		15.6 events/100 PY	21.0 events/100 PY

EMPEROR-Reduced included a higher-risk patient population than DAPA-HF

Note: The total population values have not been reported for EMPEROR-Reduced, so the average of the mean or median values from the individual study arms was calculated in some cases. Each study was conducted independently, and no head-to-head studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug vs another
AF, atrial fibrillation; ADHF, acute decompensated heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PY, patient-years

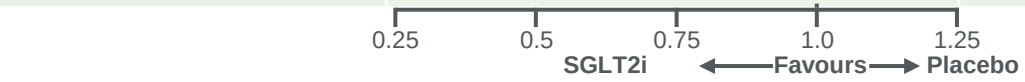
1. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 2. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 3. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:665–675;
4. Packer M et al. *N Engl J Med*. 2020;383:1413–1424

Heart Failure

DAPA-HF and EMPEROR-Reduced meta analysis: Is there a benefit for CV death?

Is the lack of CV death benefit in EMPEROR-Reduced due to the higher risk patient population compared with that of DAPA-HF?

All-cause mortality	HR (95% CI)	No. of events/no. of patients (%)		HR	95% CI
		SGLT2i	Placebo		
EMPEROR-Reduced		249/1863 (13.4)	266/1867 (14.2)	0.92	(0.77–1.10)
DAPA-HF		276/2373 (11.6)	329/2371 (13.9)	0.83	(0.71–0.97)
Total				0.87	(0.77–0.98)
Test for overall treatment effect *p*=0.018					
Test for heterogeneity of effect p=0.39					
CV death					
EMPEROR-Reduced		187/1863 (10.0)	202/1867 (10.8)	0.92	(0.75–1.12)
DAPA-HF		227/2373 (9.6)	273/2371 (11.5)	0.82	(0.69–0.98)
Total				0.86	(0.76–0.98)
Test for overall treatment effect *p*=0.027					
Test for heterogeneity of effect p=0.40					



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor

Zannad F et al. *Lancet*. 2020;396:819–829

Heart Failure

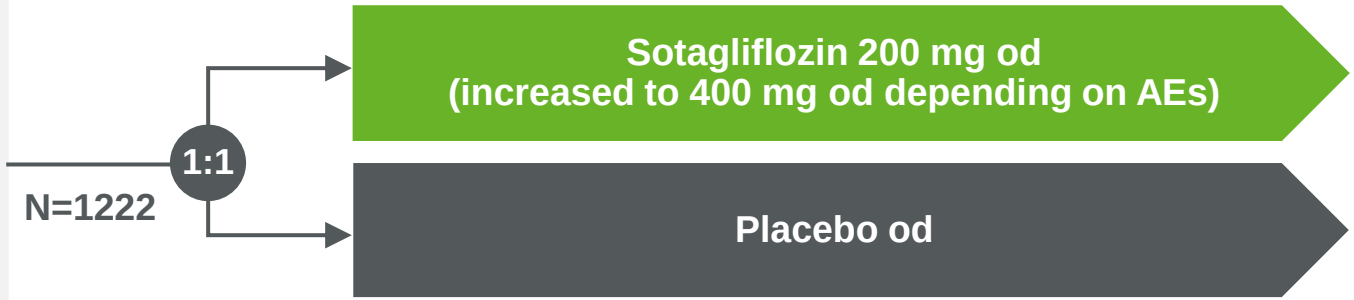
SOLOIST-WHF study design

Design: Randomised, double-blind, placebo-controlled, phase III trial

Objective: Investigate the efficacy and safety of sotagliflozin versus placebo in patients with **T2D who were recently treated for worsening HF (HFrEF or HFpEF)** when initiated soon after the episode of decompensated HF

Eligibility criteria

- Age 18–85 years
- HFH or urgent visit for worsening HF and received treatment with IV diuretic therapy
- T2D diagnosis prior to or during the index admission
- Prior diagnosis of HF ≥3 months
- Receiving treatment with a loop diuretic for HF for ≥30 days prior to index event
- On beta-blockers and RAAS inhibitors if LVEF <40%, unless contraindicated
- eGFR ≥30 ml/min/1.73 m^2
- Written consent provided



Median follow-up: 9.0 months

Primary endpoint: Total number of deaths from CV causes and hospitalisations and urgent visits for HF (first and subsequent events)

AE, adverse events; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFH, heart failure hospitalisation; LVEF, left ventricular ejection fraction; od, once daily; RAAS, renin-angiotensin-aldosterone system; T2D, type 2 diabetes

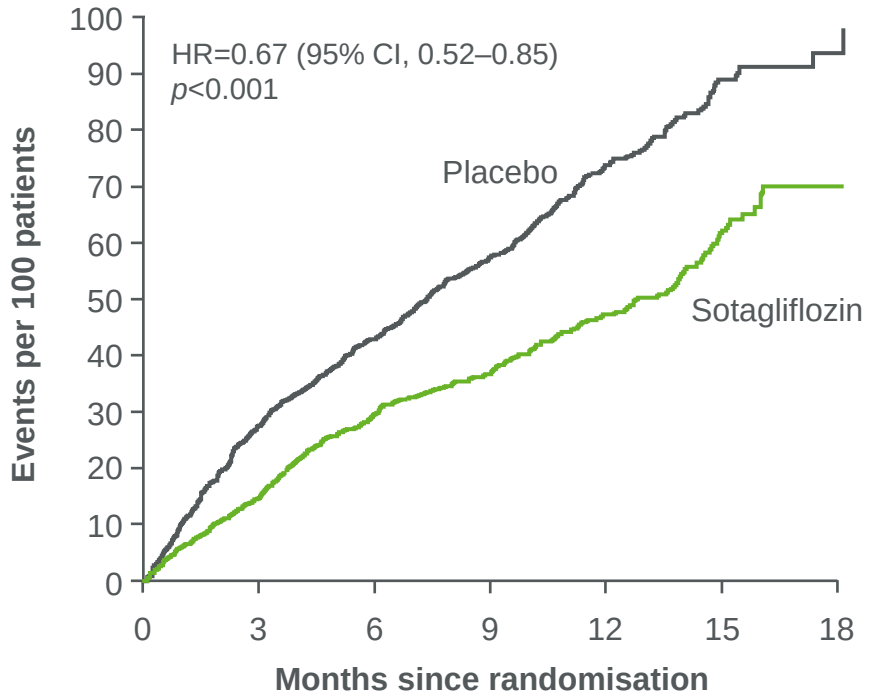
Bhatt DL, et al. *N Engl J Med* 2021;384:117–128

Heart Failure

SOLOIST-WHF: Sotagliflozin reduced the total CV deaths or hospitalisations/urgent visits for HF

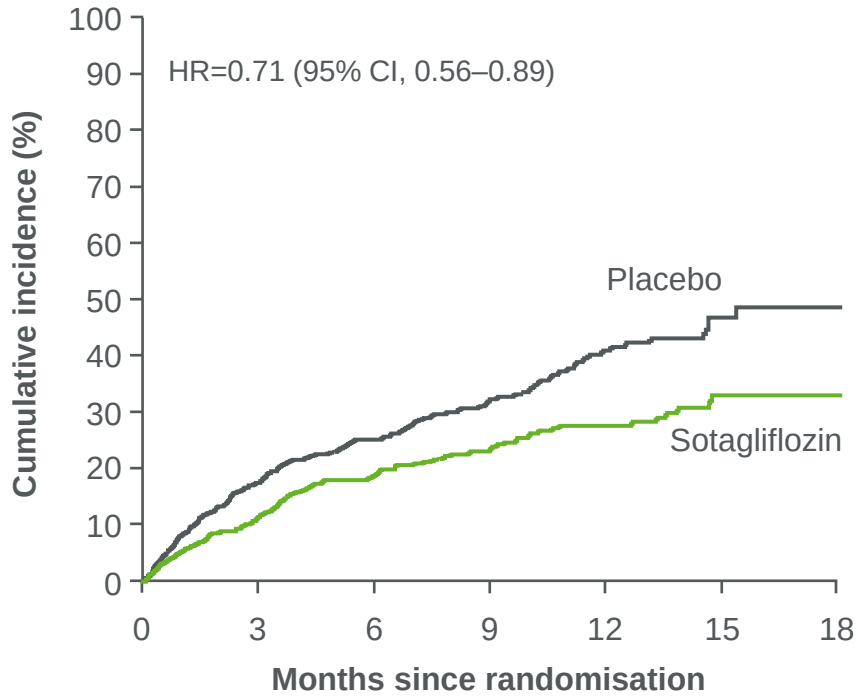
Primary endpoint

Total number of CV deaths and hospitalisations and urgent visits for HF (first and subsequent events)



No. at risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

First occurrence of either CV death or HFH



No. at risk							
Placebo	614	461	345	241	144	66	14
Sotagliflozin	608	498	374	266	171	76	25

CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio

Bhatt DL, et al. *N Engl J Med* 2021;384:117–128

Heart Failure

Contraindications and adverse effects

Contraindications[16]	Adverse effects[16]
• Prior serious hypersensitivity reaction to given SGLT2i • Severe renal impairment (eGFR <30 mL/min/1.73 m^2) being treated for glycaemic control without established CVD or multiple CV risk factors • Dialysis **Cautions** • Volume depletion • Ketoacidosis in diabetes • Urinary tract infections • Hypoglycaemia • Fournier's gangrene • Genital mycotic infections	• Female genital mycotic infections • Nasopharyngitis • Urinary tract infections

Note: Contraindications, cautions and adverse effects for dapagliflozin.
CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Putting data into context

	PARADIGM-HF[1] sacubitril/ valsartan	DAPA-HF[2] dapagliflozin	EMPEROR-Reduced[3] empagliflozin	SOLOIST-WHF[6] sotagliflozin
Number of patients at randomisation	8442	4744	3730	1222
Diabetes mellitus at baseline,* %	34.6	41.8#	49.8	100
LVEF	≤35%	≤40%	≤40%	HFrEF and HFpEF‡
Recent HF decompensation	Not required	Not required	Chronic HF ≥3 months	HFH or worsening HF and received treatment with IV diuretic therapy
Primary endpoint	First HFH or CV death	Worsening HF (unplanned hospitalisation/urgent visit resulting in IV therapy for HF) or CV death	First HFH or CV death	Total number of CV deaths and hospitalisations and urgent visits for HF§

	PARADIGM-HF[1]		DAPA-HF[1]		EMPEROR-Reduced[1]		SOLOIST-WHF[3]	
	Control	Sacubitril/ valsartan	Control	Dapa-gliflozin	Control	Empa-gliflozin	Control	Sota-gliflozin
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	76.3	51.0
ARR	2.7		4.0		5.2		25.3	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	12.5	10.6
ARR	1.5		1.4		0.6		1.9	
First HF hospitalisation	7.7[4]	6.2[4]	9.8	6.9	15.5	10.7	NR	NR
ARR	1.6		2.9		4.8		NR	

Guidelines update

Key updates from ESC 2021 guidelines in the management of chronic HF[1]

New concepts

A change of the term ‘heart failure with mid-range ejection fraction’ to ‘**heart failure with mildly reduced ejection fraction**’ (HFmrEF)
A new **simplified treatment algorithm** for HFrEF, now including ARNi as first-line with ACEi and excluding ARBs from first-line therapies
The addition of a treatment algorithm for HFrEF according to **phenotypes**
Updated treatments for most non-cardiovascular comorbidities including diabetes, hyperkalemia, iron deficiency and cancer

New recommendations

Recommendation	Class
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACEi (or ARNi), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization	IIb

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

Changes in the classification of HF from the 'Universal definition and classification of HF' consensus statement[1,2]

New onset/ de novo HF	Worsening HF	Improving HF	Persistent HF	HF in remission
• Newly diagnosed HF • No former history of HF	• Worsening symptom/signs/ functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies • and/or hospitalization	• Improving symptoms/signs and/or functional capacity	• Persistent HF with ongoing symptoms/signs and/or limited functional capacity	• Resolution of symptoms and signs of HF, with resolution of previous structural/ functional heart disease after a phase of symptomatic HF

"Worsening HF" in VICTORIA[3]

- Recent HF decompensation
  - HF hospitalization within 6 months
  - Outpatient IV diuretic use within 3 months

HF, heart failure; IV, intravenous.

References: 1. Bozkurt B *et al. J Cardi Fail* 2021;27:387–413; **2.** Bozkurt B *et al.* ESC. 27–30 August 2021; presentation; **3.** Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893.

Vericiguat is specifically recommended for worsening HF in ESC 2021 guidelines[1]

Recommendations	Class	Level
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II–IV who have had **worsening HF** despite treatment with an **ACEi (or ARNi), a beta blocker and an MRA** to reduce the risk of CV mortality or HFH	IIb	B

Inclusion in the guidelines before EU approval is in contrast with other unlicensed therapies (e.g. omecamtiv mecarbil)

Worsening HF is referred to in the guidelines for the **first time**, and vericiguat is **specifically recommended** for this patient group

Guidelines **do not require the use of all foundational therapies** prior to vericiguat initiation

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; EU, European Union; HF, heart failure; HFH, heart failure hospitalization; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

Disease-modifying therapies in HFrEF

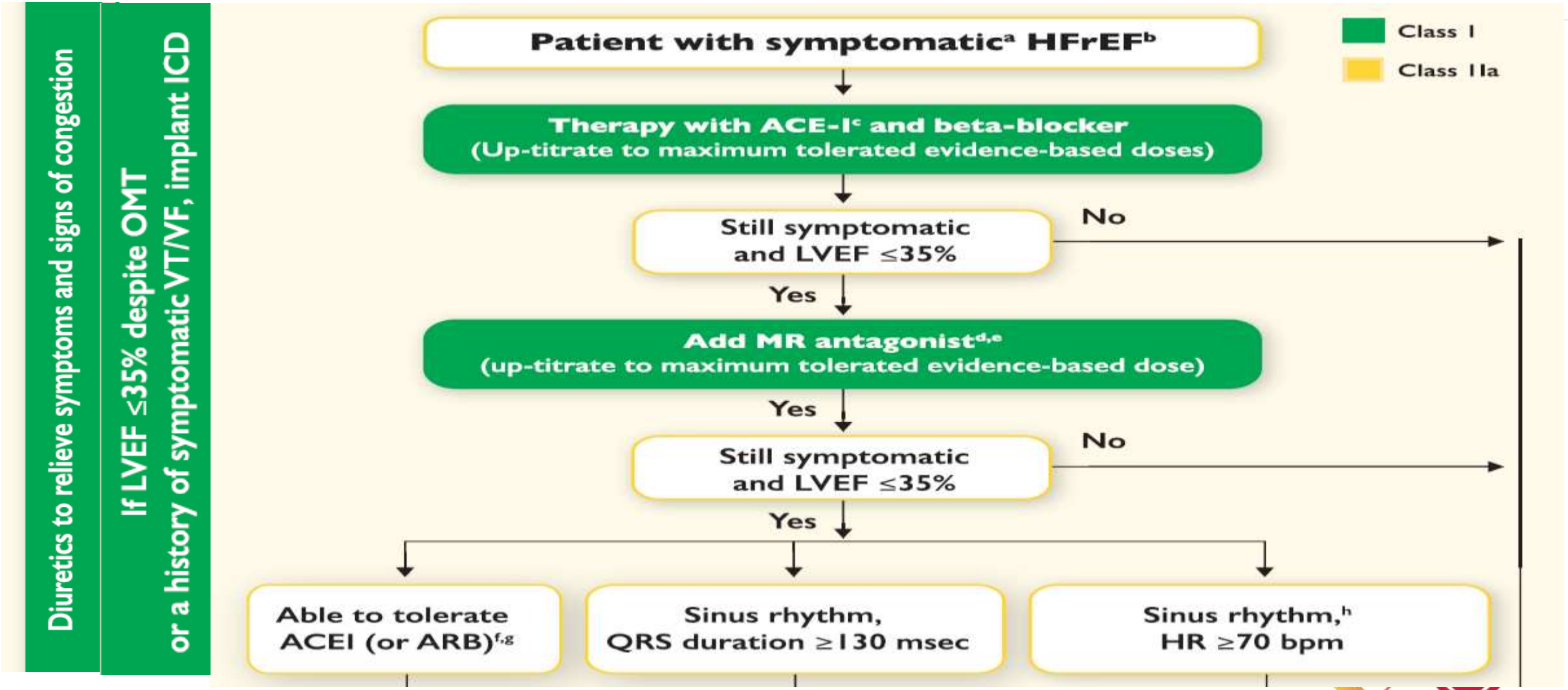
Evidence-based doses of disease-modifying drugs, including vericiguat, in key randomized trials in patients with HFrEF[1]

	Starting dose	Target dose
ACEi		
Captopril*	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10–20 mg bid
Lisinopril#	2.5–5 mg od	20–35 mg od
Ramipril	2.5 mg bid	5 mg bid
Trandolapril*	0.5 mg od	4 mg od
ARNi		
Sacubitril/valsartan	49/51 mg bid‡	97/103 mg bid
Beta-blockers		
Bisoprolol	1.25 mg od	10 mg od
Carvedilol	3.125 mg bid	25 mg bid¶
Metoprolol succinate (CR/XL)	12.5–25 mg od	200 mg od
Nebivolol§	1.25 mg od	10 mg od
MRA		
Eplerenone	25 mg od	50 mg od
Spironolactone	25 mg od**	50 mg od
SGLT2 inhibitor		
Dapagliflozin	10 mg od	10 mg od
Empagliflozin	10 mg od	10 mg od
Other agents		
Candesartan	4 mg od	32 mg od
Losartan	50 mg od	150 mg od
Valsartan	40 mg bid	160 mg bid
Ivabradine	5 mg bid	7.5 mg bid
Vericiguat	**2.5 mg od**	**10 mg od**
Digoxin	62.5 µg od	250 µg od
Hydralazine/isosorbide dinitrate	37.5 mg tid/ 20 mg tid	75 mg tid/ 40 mg tid

* Indicates an ACEi where the dosing target is derived from post-myocardial infarction trials.
# Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive randomized, placebo-controlled trial and the optimum dose is uncertain.
‡ Sacubitril/valsartan may have an optional lower starting dose of 24/26 mg bid for those with a history of symptomatic hypotension.
§ Indicates a treatment not shown to reduce CV or all-cause mortality in patients with heart failure (or shown to be non-inferior to a treatment that does).
¶ A maximum dose of 50 mg bid can be administered to patients weighing over 85 kg.
** Spironolactone has an optional starting dose of 12.5 mg in patients where renal status or hyperkalemia warrant caution.
ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; bid, twice daily; CR, controlled release; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; od, once daily; SGLT2, sodium–glucose cotransporter 2; tid, three times daily; XL, extended release.

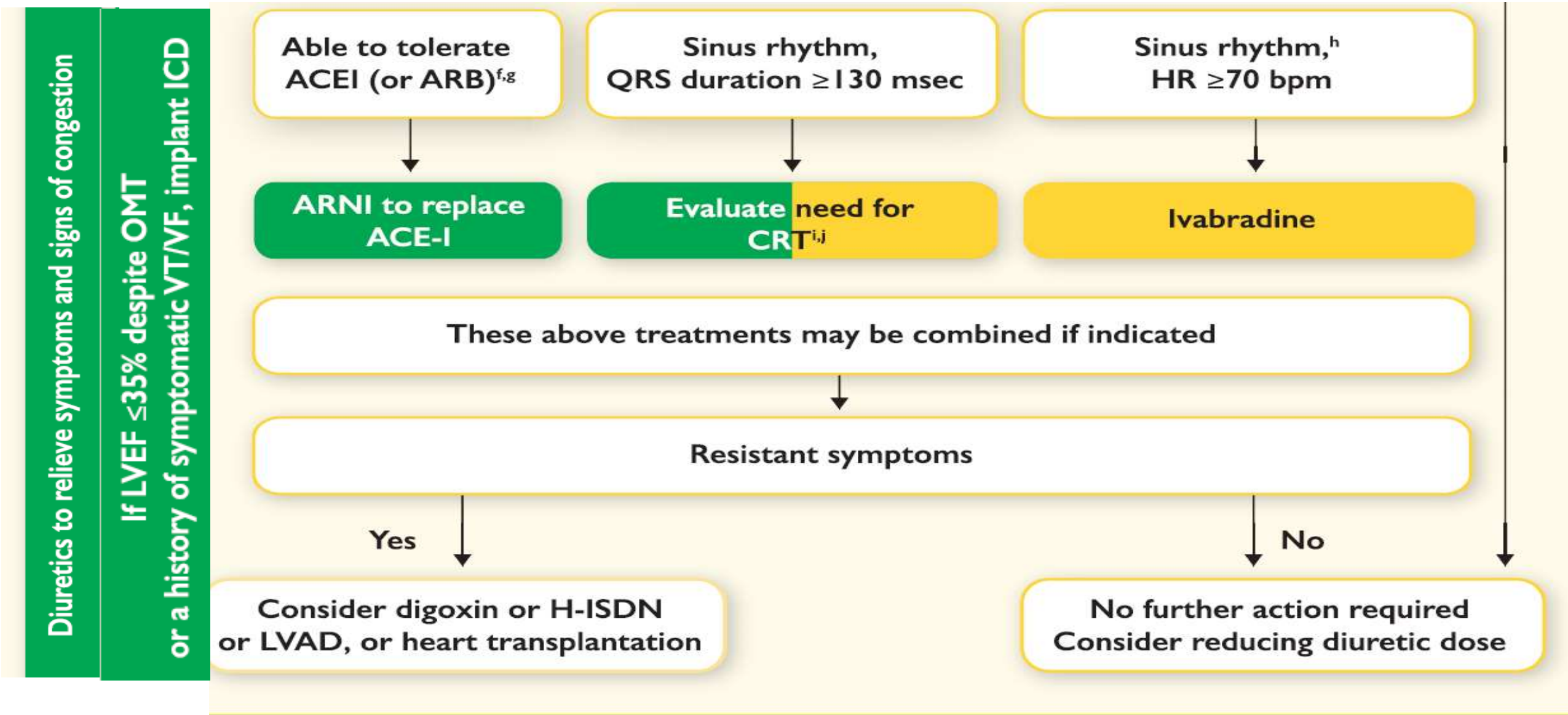
Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

New therapeutic algorithm for HFrEF



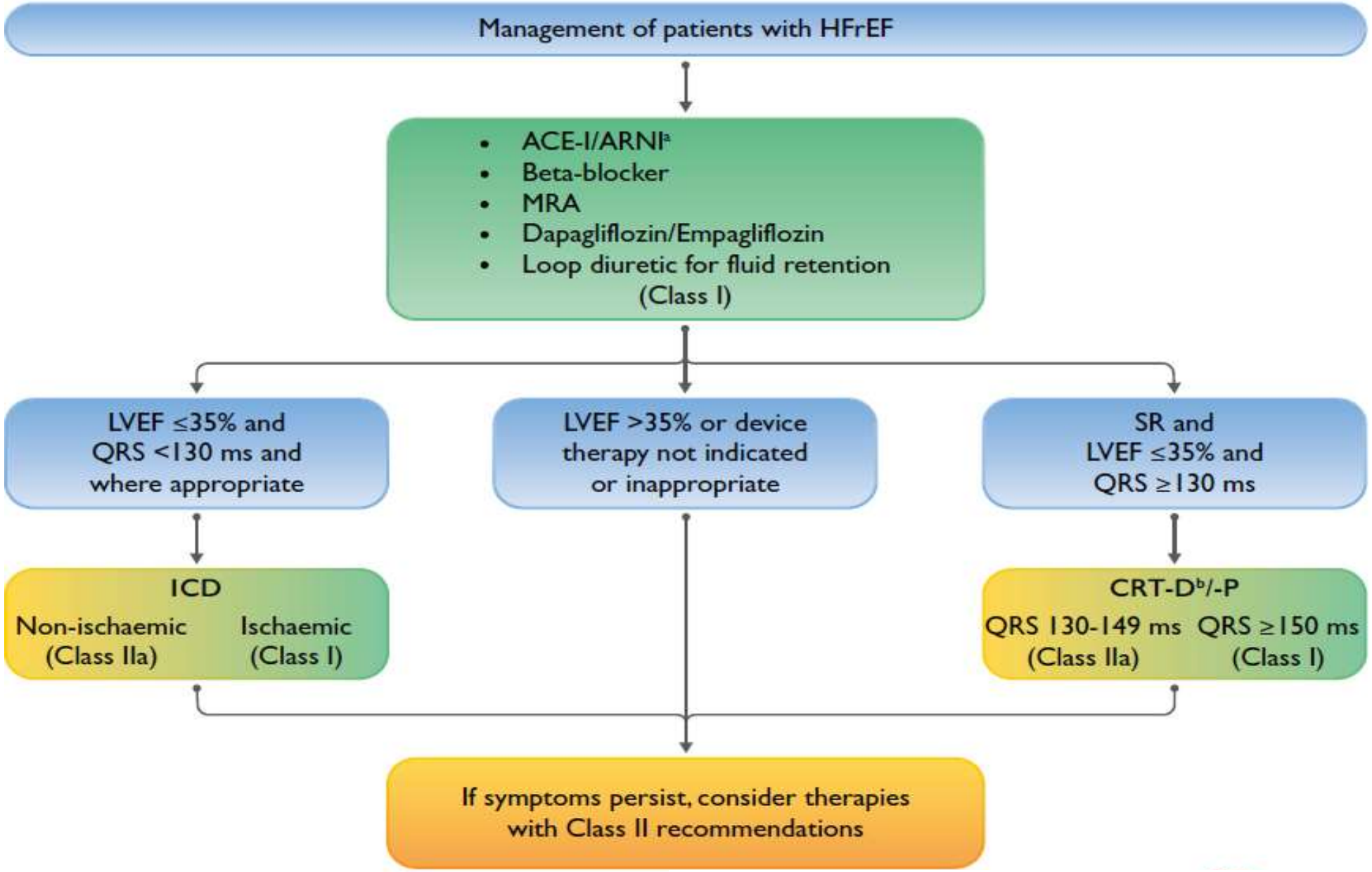
Ponikowski P et al. 2016 ESC HF Guidelines
Eur Heart J 2016 & Eur J Heart Fail 2016

New therapeutic algorithm for HFrEF



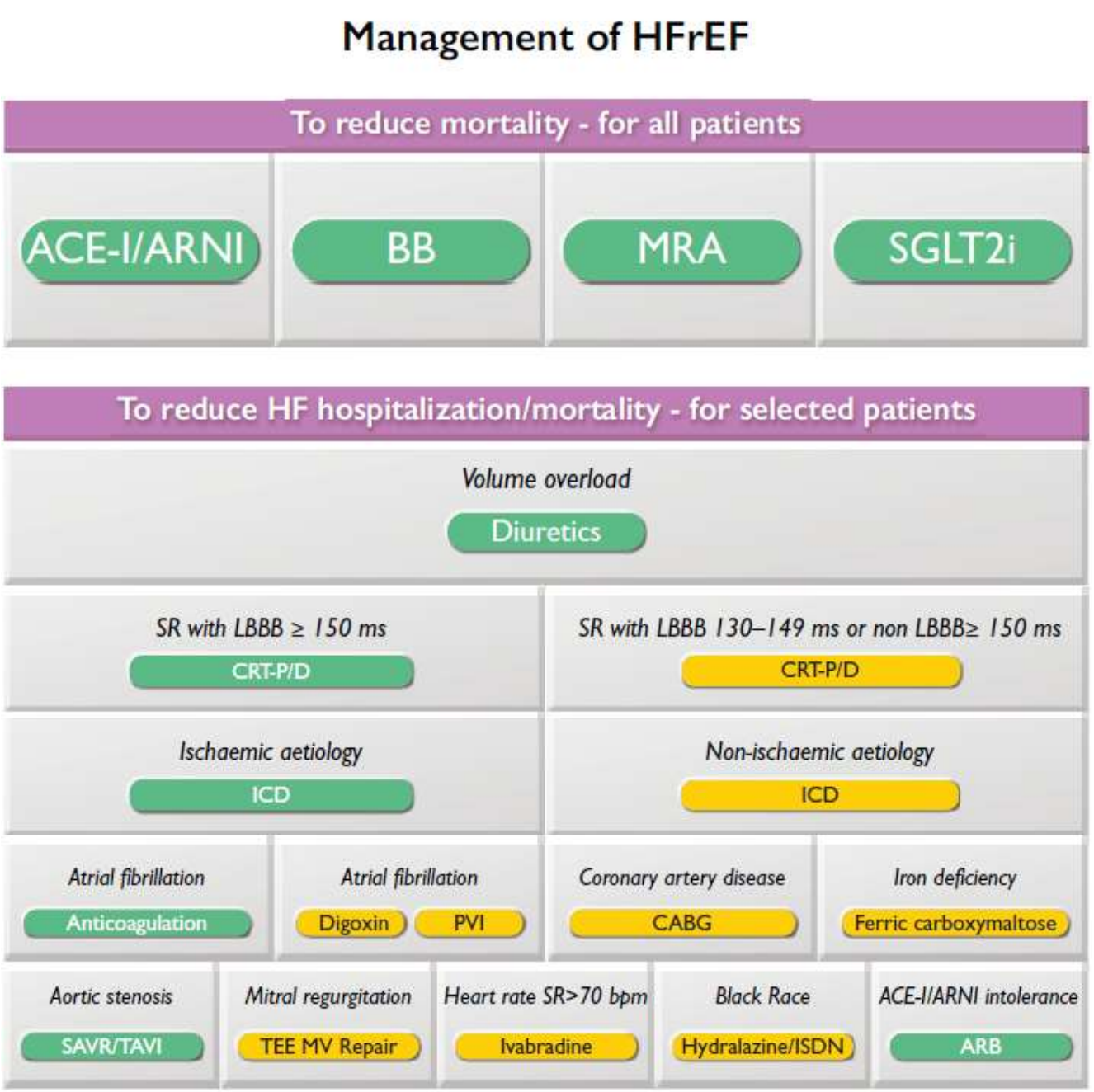
Ponikowski P et al. 2016 ESC HF Guidelines
Eur Heart J 2016 & Eur J Heart Fail 2016

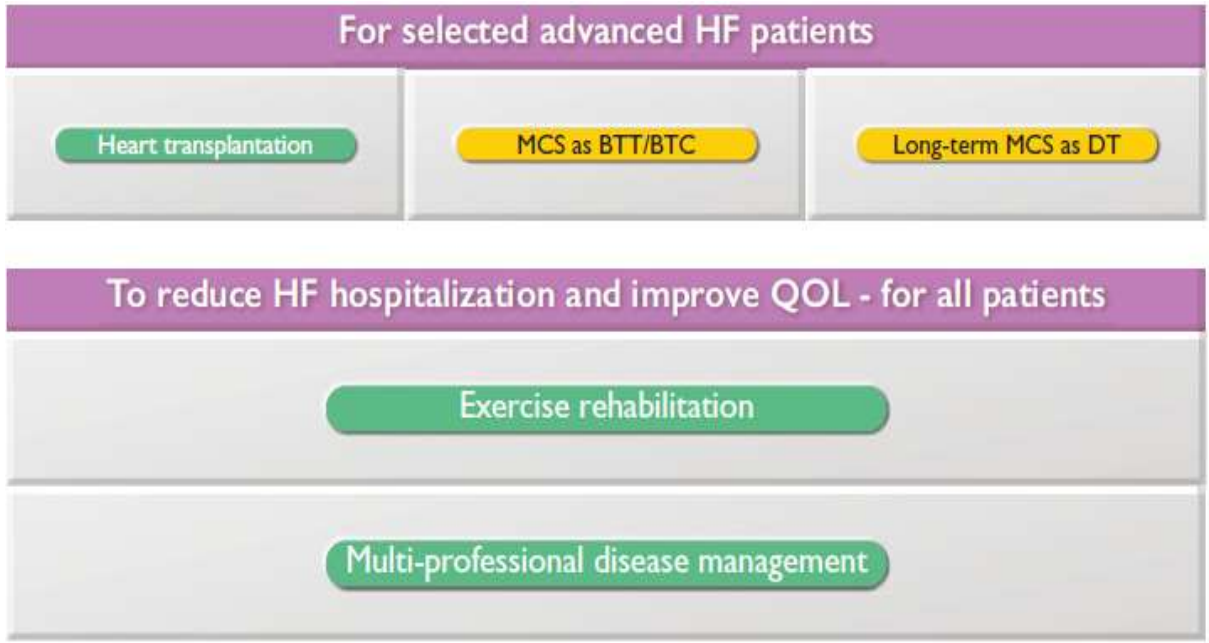
Therapeutic algorithm of Class I Therapy Indications for a patient with HFrEF



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

Strategic phenotypic overview of the management of HFrEF





Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.[141]	IIb	B

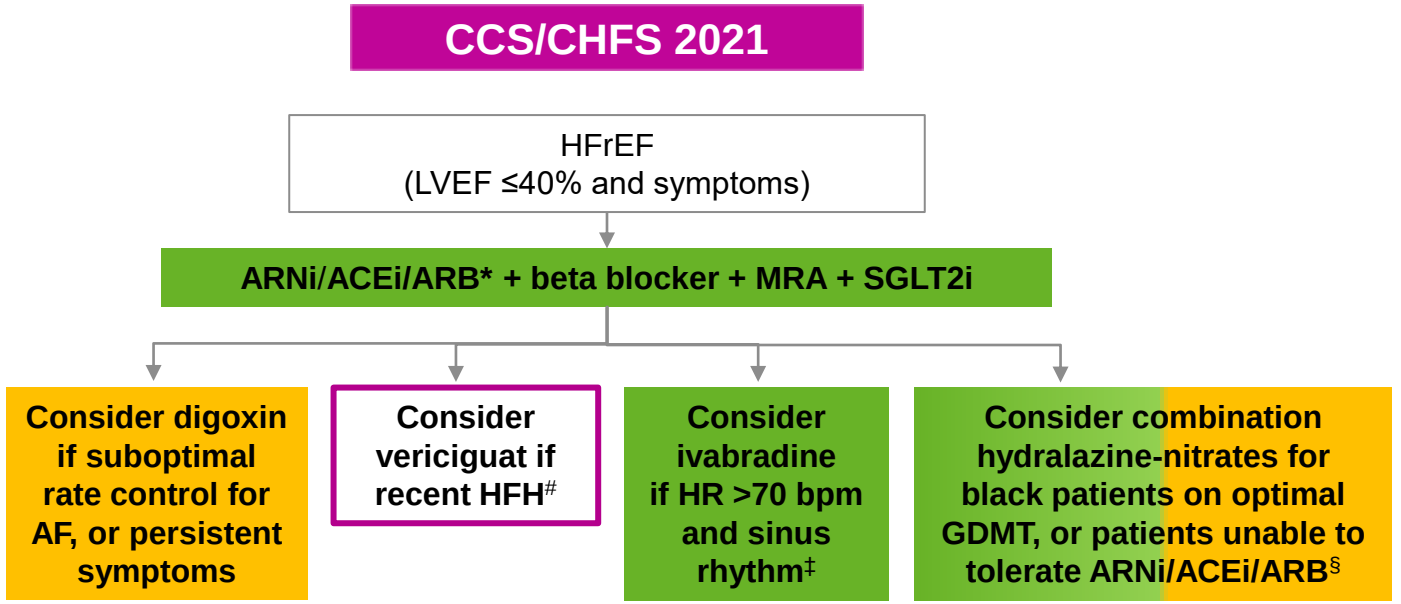
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
European Heart Journal (2021) doi:10.1093/eurheartj/ehab368

Canadian Guidelines for Treating Patients with Symptomatic Chronic HFrEF[1]

Strong

Weak

Not yet approved in Canada



The CCS/CHFS 2021 recommend vericiguat be considered in addition to optimal HF therapies for HFrEF patients with worsening symptoms and HFH in the past 6 months, to reduce the risk of subsequent HFH

*ARNi or ACEi/ARB then substitute ARNi; #Vericiguat is not yet approved for use in Canada; ‡Health Canada has approved ivabradine for patients with HFrEF and HR ≥77 bpm in sinus rhythm; §The recommendation varied from strong to weak depending on the clinical situation.

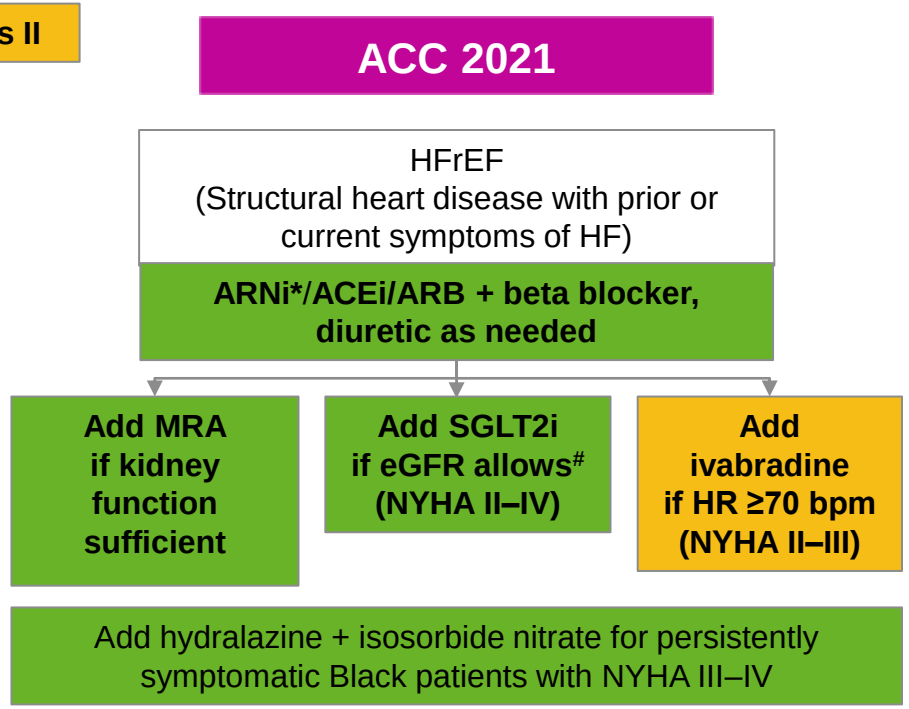
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; CCS, Canadian Cardiovascular Society; CHFS, Canadian Heart Failure Society; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalisation; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

1. McDonald M et al. *Can J Cardiol.* 2021;37:531–546.

ACC Expert Consensus for the Treatment of Patients with Symptomatic Chronic HFrEF[1]

Class I

Class II



No specific recommendations are made in the ACC expert consensus for patients who experience a worsening HF event

Guanylyl cyclase stimulation is mentioned as a pathway shown to improve outcomes for patients with HFrEF

Vericiguat efficacy in HFrEF is mentioned, but it is not yet specifically recommended

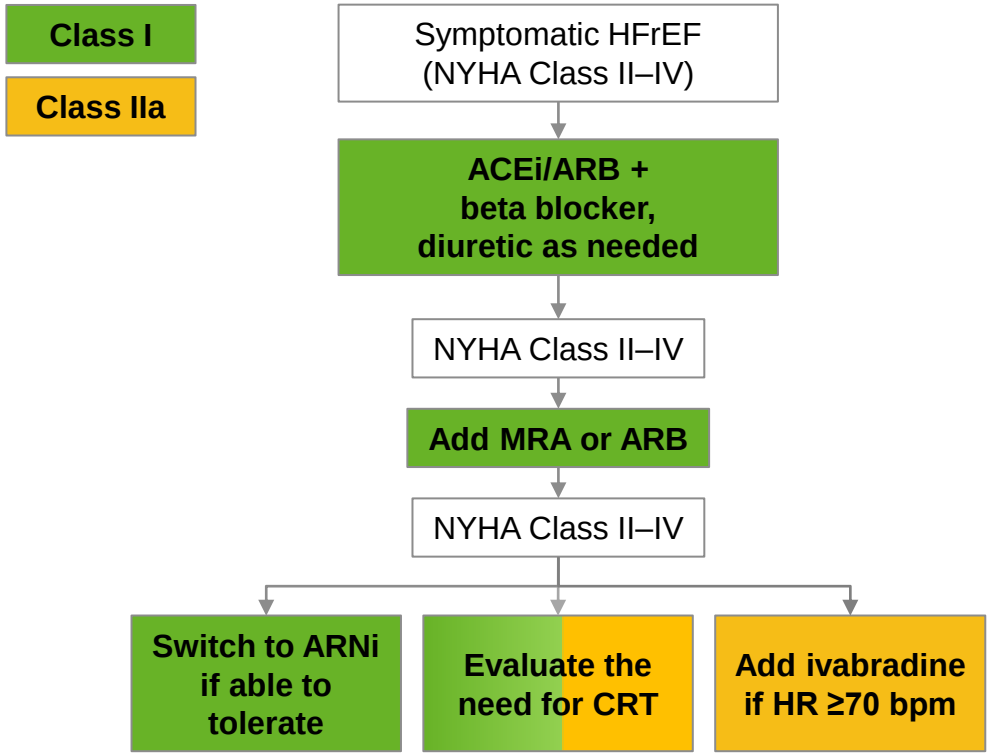
*ARNi is preferred; #ensure eGFR ≥30 ml/min/1.73 m^2 for dapagliflozin and eGFR ≥20 ml/min/1.73 m^2 for empagliflozin before initiation.

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

1. Maddox TM et al. *J Am Coll Cardiol.* 2021;77;772–810.

Four therapies are now recommended as foundational treatments for all patients with HFrEF

ESC 2016[1]



ESC 2021: Key changes[2]

First-line recommendations for HFrEF are now ACEi/ARNi, beta blocker, MRA and SGLT2i

The **SGLT2i** class is now one of the foundational therapies for HFrEF based on evidence from DAPA-HF,[3] EMPEROR-Reduced,[4] and SOLOIST-WHF[5]

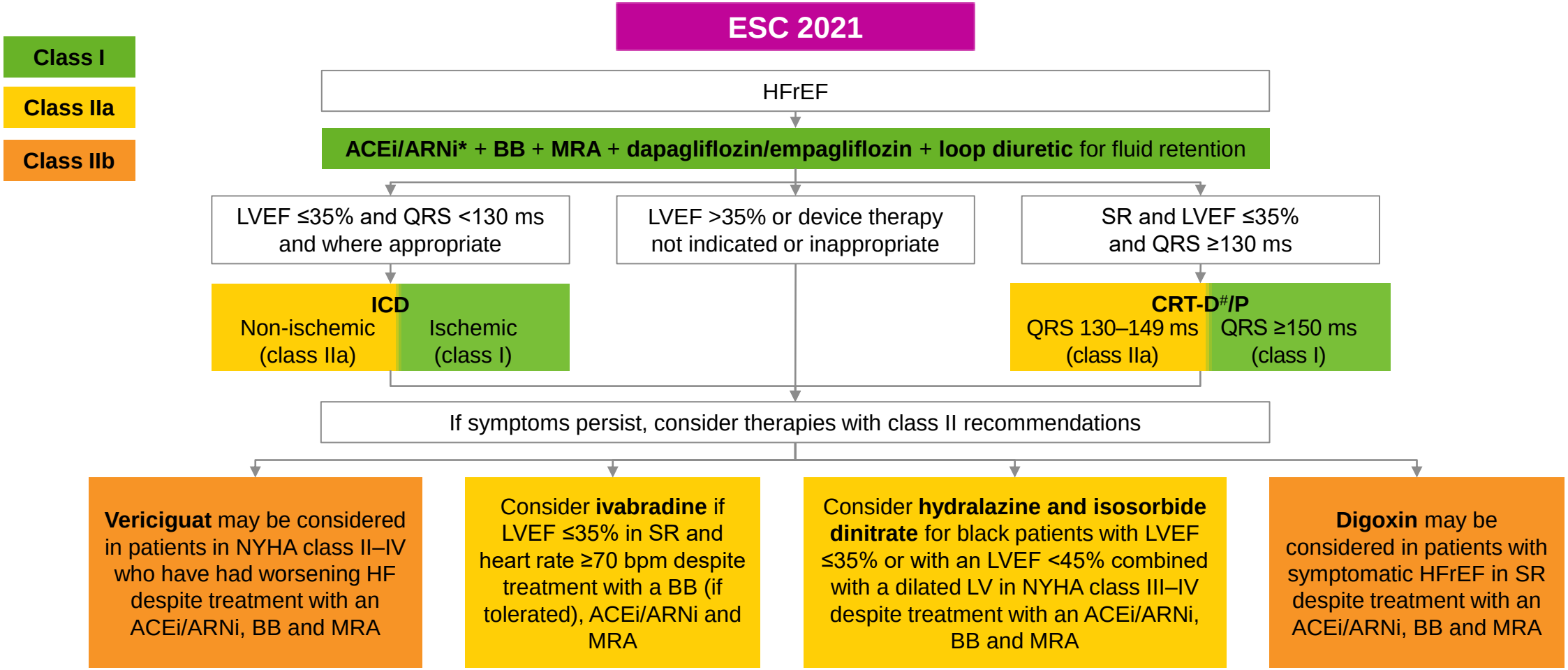
ARNi can now be used first-line in ACEi-naïve patients

ARBs are **no longer** a first-line option, and are recommended only as a replacement for an ACEi

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

References: 1. Ponikowski P *et al. Eur J Heart Fail* 2016;18:891–975; **2.** Metra M. ESC-HF. 29 June–1 July 2021, oral presentation; **3.** McMurray J *et al*. *N Engl J Med* 2019;381:1995–2008; **4.** Packer M *et al*. *N Engl J Med* 2020;383:1413–1424; **5.** Bhatt DL *et al. N Engl J Med* 2021;384:117–128.

ESC 2021 recommendations for the treatment of patients with HFrEF[1]



*ARNi recommended as a replacement for ACEi; an ARB is recommended in patients unable to tolerate an ACEi or ARNi (class I, level B). # Where appropriate.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P,cardiac resynchronization therapy with pacemaker; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QRS, Q, R and S waves; SR, sinus rhythm.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

ESC 2021 guidelines: Drugs recommended in all patients with HFrEF[1]

Recommendations	Class	Level
ACEi is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Dapagliflozin or empagliflozin is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a replacement for ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death	I	B

ACEi, angiotensin-converting enzyme inhibitor; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

New recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute HF[1]

Recommendations	Class	Level
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment	I	C
It is recommended that evidence based oral medical treatment be administered before discharge	I	C
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drugs' tolerance and start and/or uptitrate evidence-based therapy	I	C
Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin <100 ng/ml or serum ferritin 100–299 ng/ml with TSAT <20%, to improve symptoms and reduce hospitalizations	IIa	B

HF, heart failure; TSAT, transferrin saturation.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

Summary

Key changes in the ESC 2021 guidelines

- Foundational therapies for HFrEF are now ACEi/ARNi, beta blocker, MRA and SGLT2i
- Vericiguat is recognized in the guidelines as a disease-modifying therapy
- Vericiguat received a class IIb, level of evidence B recommendation for patients in NYHA class II–IV who have had worsening HF despite treatment with an ACEi (or ARNi), a beta blocker and an MRA to reduce the risk of CV mortality or HFH
- Importantly, the ESC guidelines are the first to mention worsening HF, reflecting a new understanding that this represents a distinct patient population with high unmet need

Phenotyping approach for patients with HFrEF

- A phenotyped approach for HFrEF management is recommended, suggesting that patient profiling will be increasingly important
  - The favourable safety and tolerability profile of vericiguat makes it suitable for use even in hard-to-treat patients
- A new recommendation was included to start evidence-based oral therapy before or shortly after discharge
  - Vericiguat could be an option in these settings

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

References: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368; **2.** Rosano GMC *et al*. *Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2206.