

Verquvo training module 4



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Recap



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Question 1

- What is heart failure?

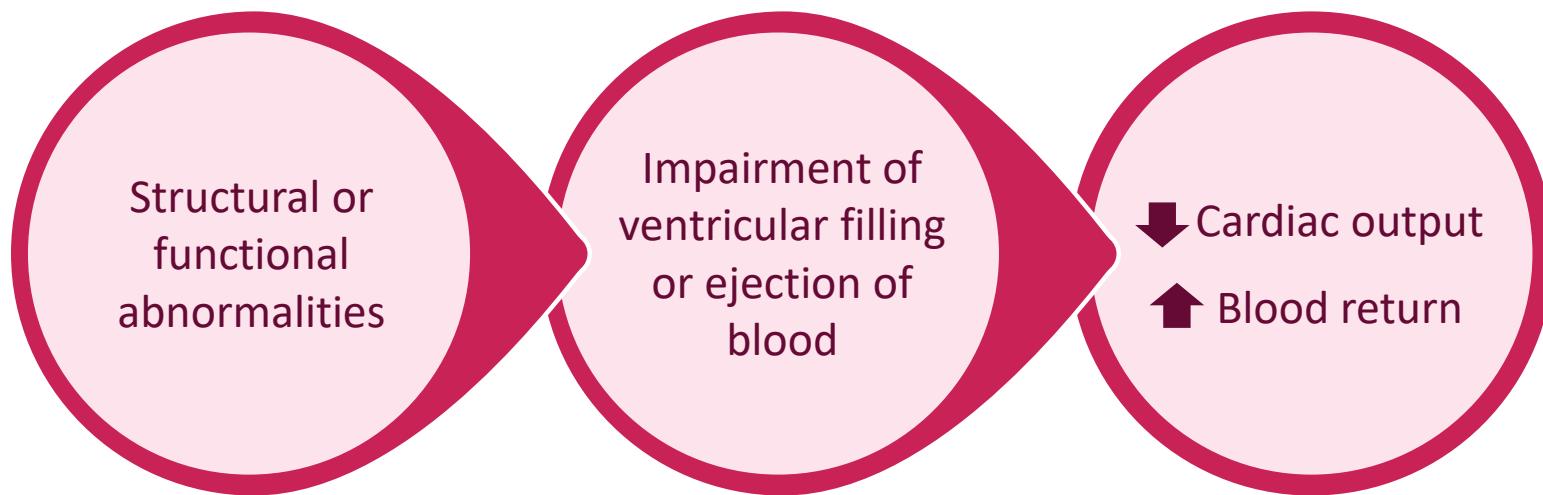


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Heart failure is a complex clinical syndrome¹



Clinical guidelines issued by the European Society of Cardiology (ESC) in 2016 define HF as:²

“...a clinical syndrome characterised by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.”

ESC, European Society of Cardiology; HF, heart failure.

1. Yancy CW, et al. Circulation. 2013;128:e240-327. 2. Ponikowski P, et al. Eur Heart J. 2016;37:2129-2200.



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Question 2

- How do current guidelines classify heart failure based on ejection fraction?



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2021 ESC HF Guidelines: what is new ?

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF <40%	LVEF 40–49%
	3	–	1. Elevated levels of natriuretic peptides ^b ; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Identifying HFmrEF as a separate group will stimulate research into underlying characteristics, pathophysiology and treatment of this population



Table 3 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
	2	LVEF \leq 40%	LVEF 41–49% ^b
	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

Question

- What is the main pathophysiology for the occurrence of heart failure?

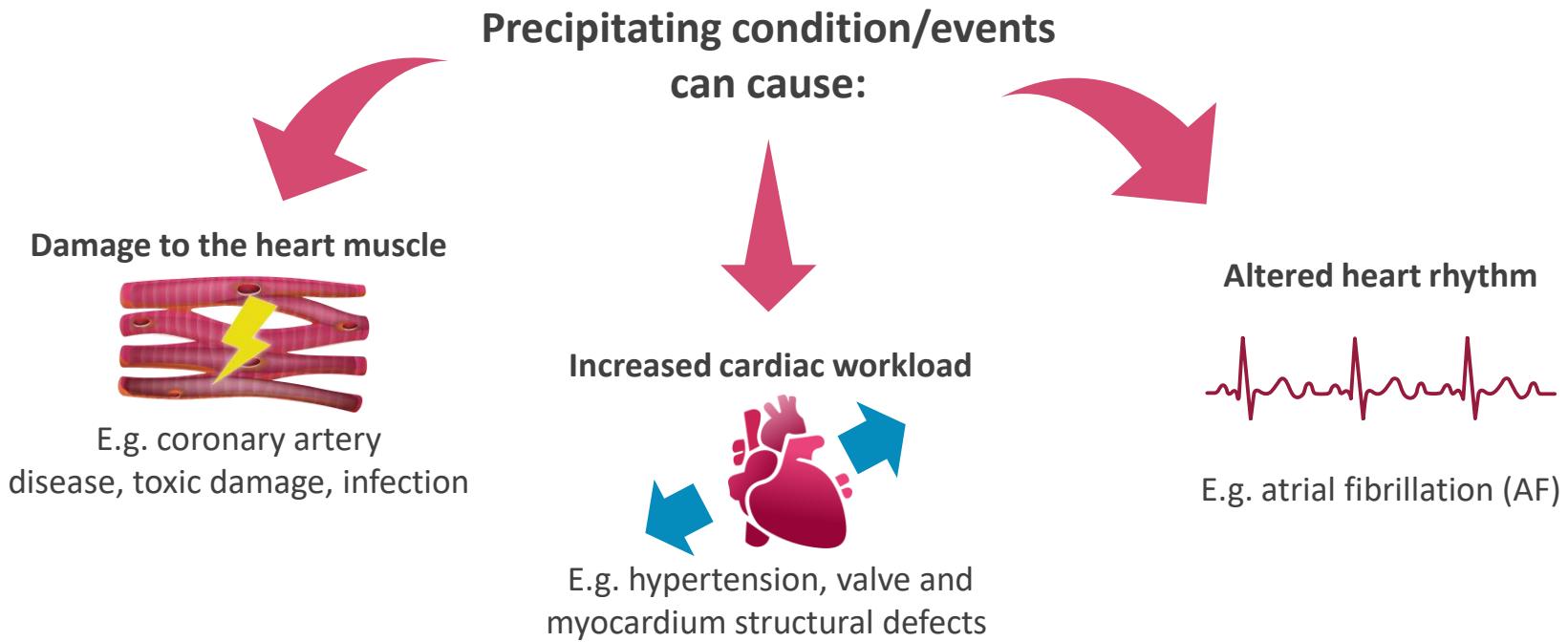


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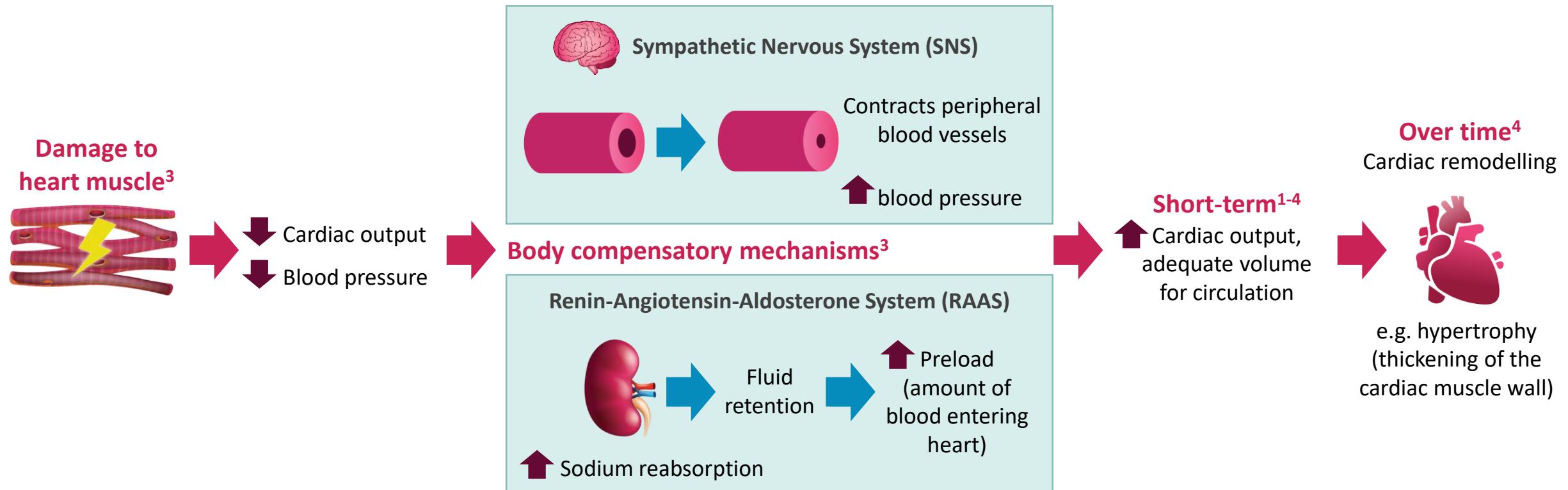
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How do precipitating conditions/events lead to heart failure?¹



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

Over time, reduced cardiac output leads to cardiac remodelling and progressive deterioration of the heart¹



Suppressing the process of cardiac remodeling and maintaining cardiac function form the main concepts of treatment for chronic HF²

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

1. Zardkooohi 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.



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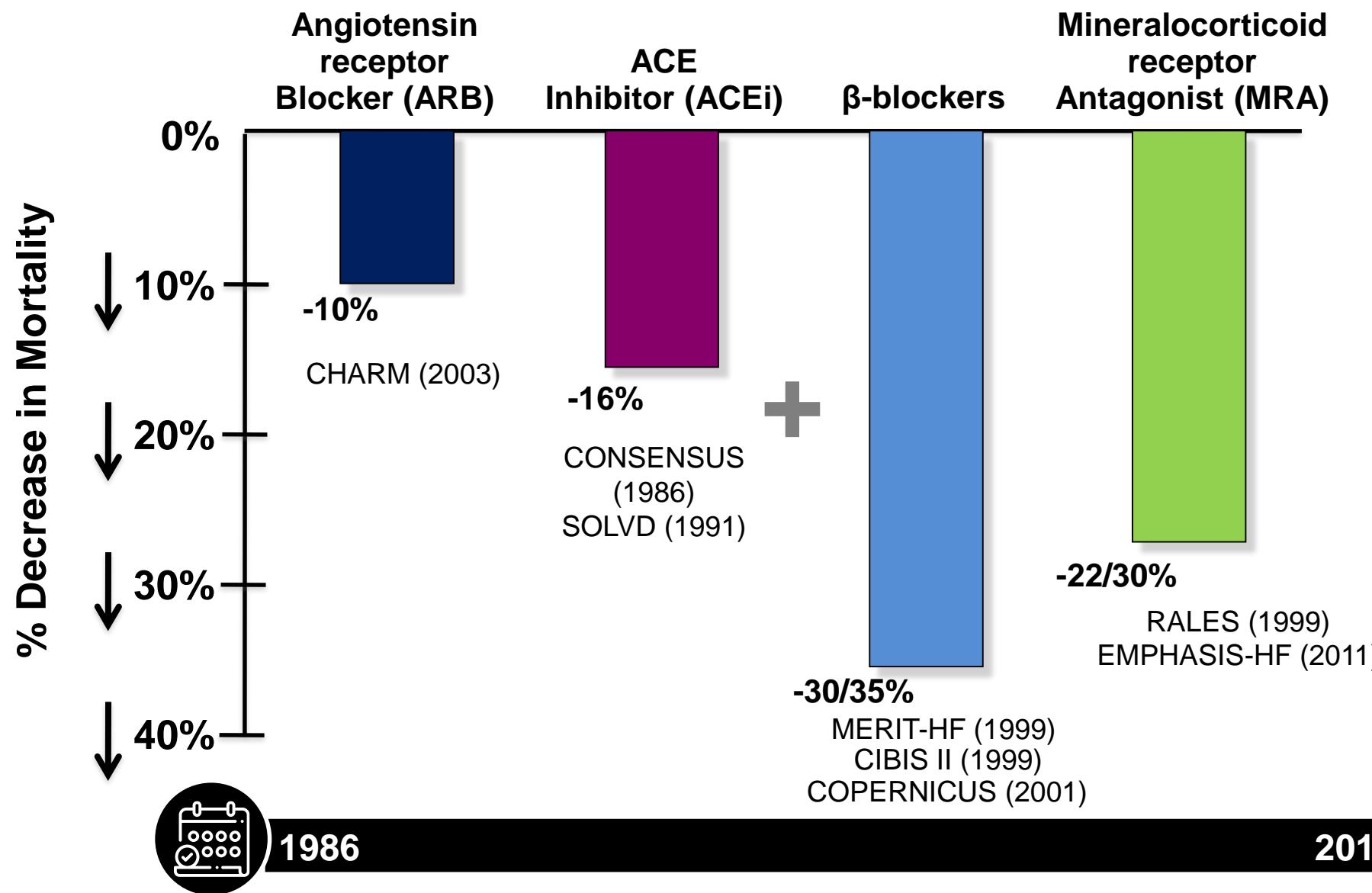
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Question 4

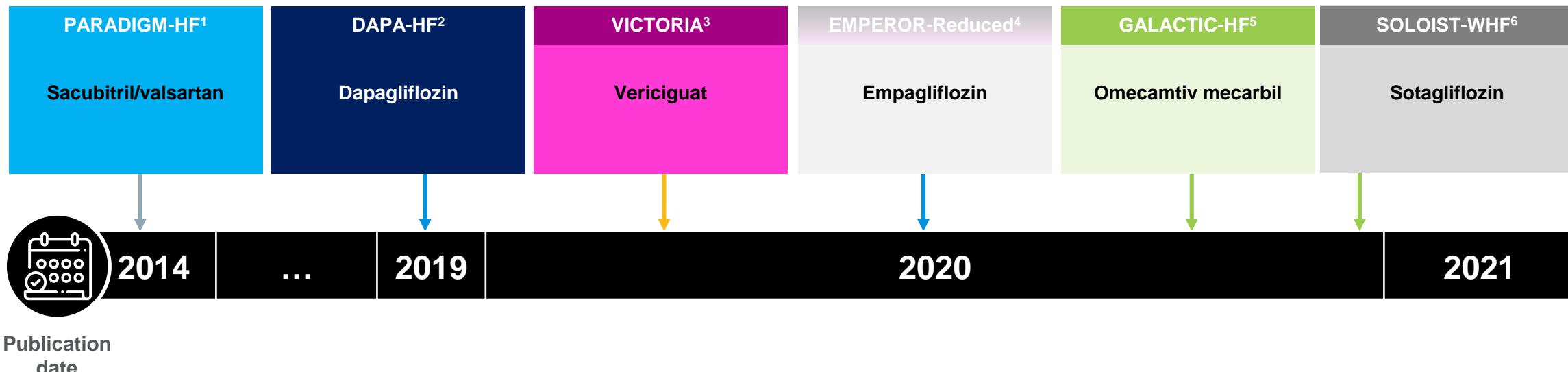
What are the pharmacological modalities for the management of HFrEF?



RCTs in HFrEF: in 30 yrs Progressive Benefit Increased, Mainly when ACEi/ARB were Added to β -blockers & MRA



...but Huge Improvements were Achieved in the Last 6 yrs by Means Seminal RCTs!



ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; EU, European Union; HF, heart failure; HFH, heart failure hospitalisation; HFrEF, heart failure reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; sGC, soluble guanylate cyclase; SGLT1/2i, sodium–glucose cotransporter 1/2 inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor

1. McMurray JJV et al. *N Engl J Med.* 2014;371:993–1004; 2. McMurray JJV, et al. *N Engl J Med.* 2019;381:1995–2008; 3. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893;
4. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 5. Teerlink JR et al. *Eur J Heart Fail.* 2020. doi:10.1002/ejhf.2015; 6. Bhatt DL, et al. *N Engl J Med* 2020; doi: 10.1056/NEJMoa2030183 [Epub ahead of print]; 7. FDA news release. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure>; 8. <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/forxiga-1> [accessed November 2020]; 9. Seferović PM et al. *Eur J Heart Fail.* 2020;22:1984–1986; 10. <https://www.astrazeneca.com/media-centre/press-releases/2020/forxiga-approved-in-the-eu-for-heart-failure.html> [accessed 5 Nov 2020]

Question 5

- What are the key trials you are aware of?



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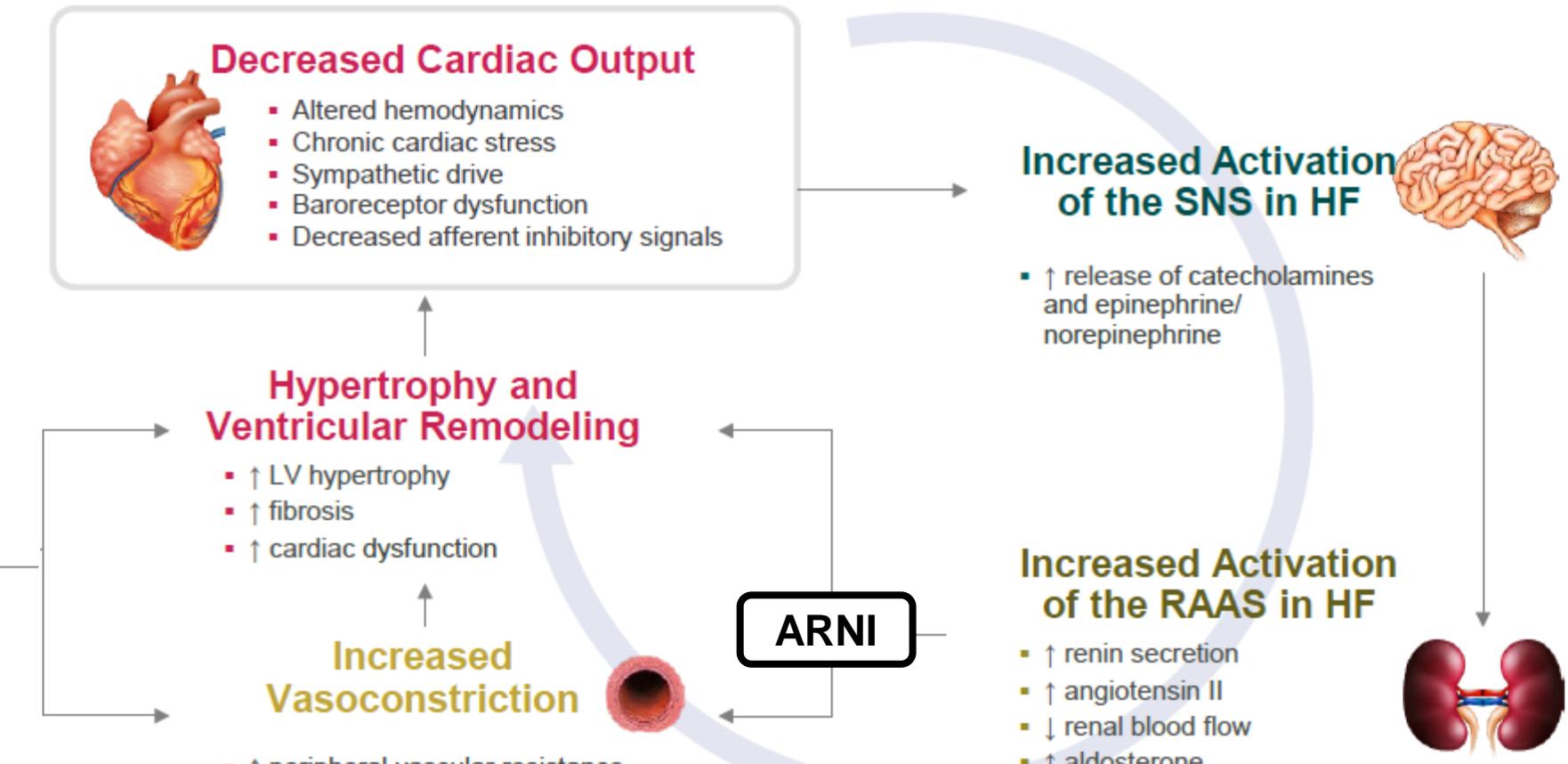
Emerging Therapies and Targets in HFrEF

ARNI
sacubitril/valsartan:
PARADIGM-HF¹ (2014)

Endothelial Dysfunction
Impaired Signaling of the NO-sGC-cGMP Pathway

Increased oxidative stress leads to
▪ ↓ NO bioavailability
▪ ↓ sGC sensitivity and stimulation
▪ ↓ cGMP

sGC stimulator
vericiguat:
VICTORIA³ (2020)



1. McMurray JJV et al. *N Engl J Med* 2014; 2. McMurray JJV et al. *N Engl J Med* 2019; 3. Armstrong PW et al. *N Engl J Med* 2020; 4. Packer M et al. *N Engl J Med* 2020; 5. Teerlink JT et al. *N Engl J Med* 2020; 6. Bhatt ML et al. *N Engl J Med* 2020

SGLT2i
dapagliflozin: DAPA-HF² (2019)
empagliflozin: EMPEROR-Reduced⁴ (2020)
sotagliflozin: SOLOIST- WHF⁶ (2020)

Question 6

- Describe the pharmacology of ARNI?

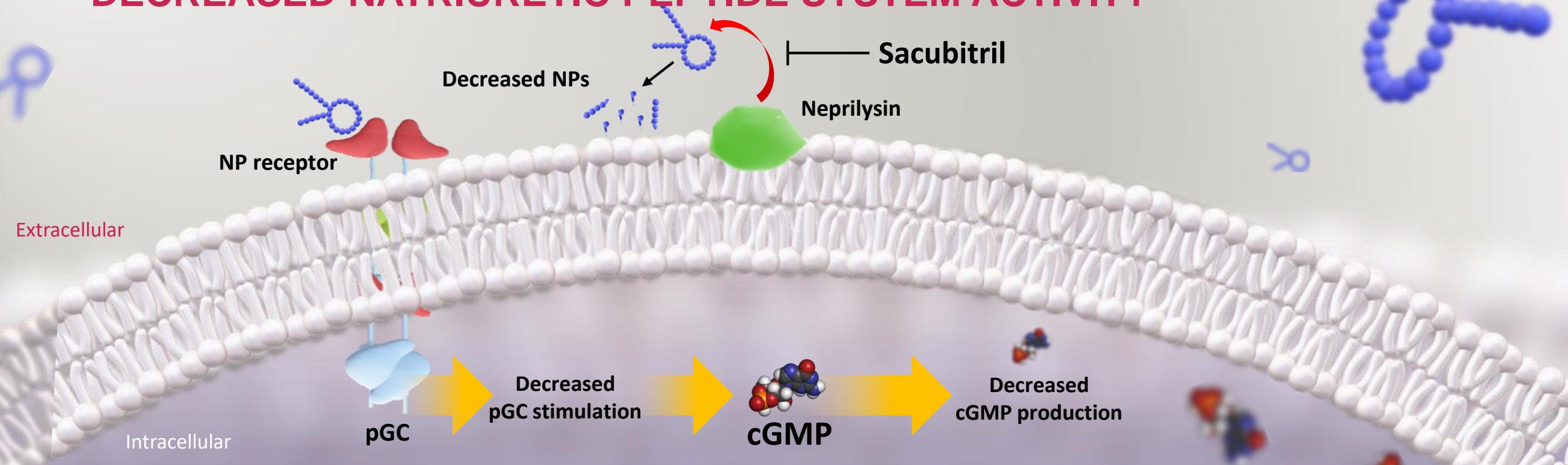


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THE DEVELOPMENT OF HF AND SACUBITRIL: DECREASED NATRIURETIC PEPTIDE SYSTEM ACTIVITY



- **PATHOPHYSIOLOGY:** Prolonged activation of the SNS and RAAS facilitates the increased release of NPs to counter-regulate worsening HF; as HF progresses NPs may be degraded by neprilysin¹⁻³
- **MECHANISM OF ACTION:** Sacubitril's active metabolite inhibits neprilysin, an endopeptidase that degrades NPs³
- **CLINICAL EFFECT:** Sacubitril enhances the helpful, counterregulatory NP system; this increases vasodilation, reduces hypertrophy and fibrosis, and increases Na⁺ and fluid excretion⁴

cGMP = cyclic guanosine monophosphate; HF = heart failure; Na⁺ = sodium; pGC = particulate guanylate cyclase; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system.

1. Felker GM et al. *Heart Failure*. 4th ed. Elsevier; 2020. 2. Liu RC. *Am J Cardiovasc Drugs*. 2018;18:473–482. 3. Entresto [package insert]. Kenilworth, NJ: Merck Pharmaceuticals, Inc. 2020. 4. ENTRESTO is a unique combination of valsartan PLUS sacubitril, a neprilysin inhibitor. Entresto website. www.entrestohcp.com/mechanism-of-action. Accessed August 13, 2020.



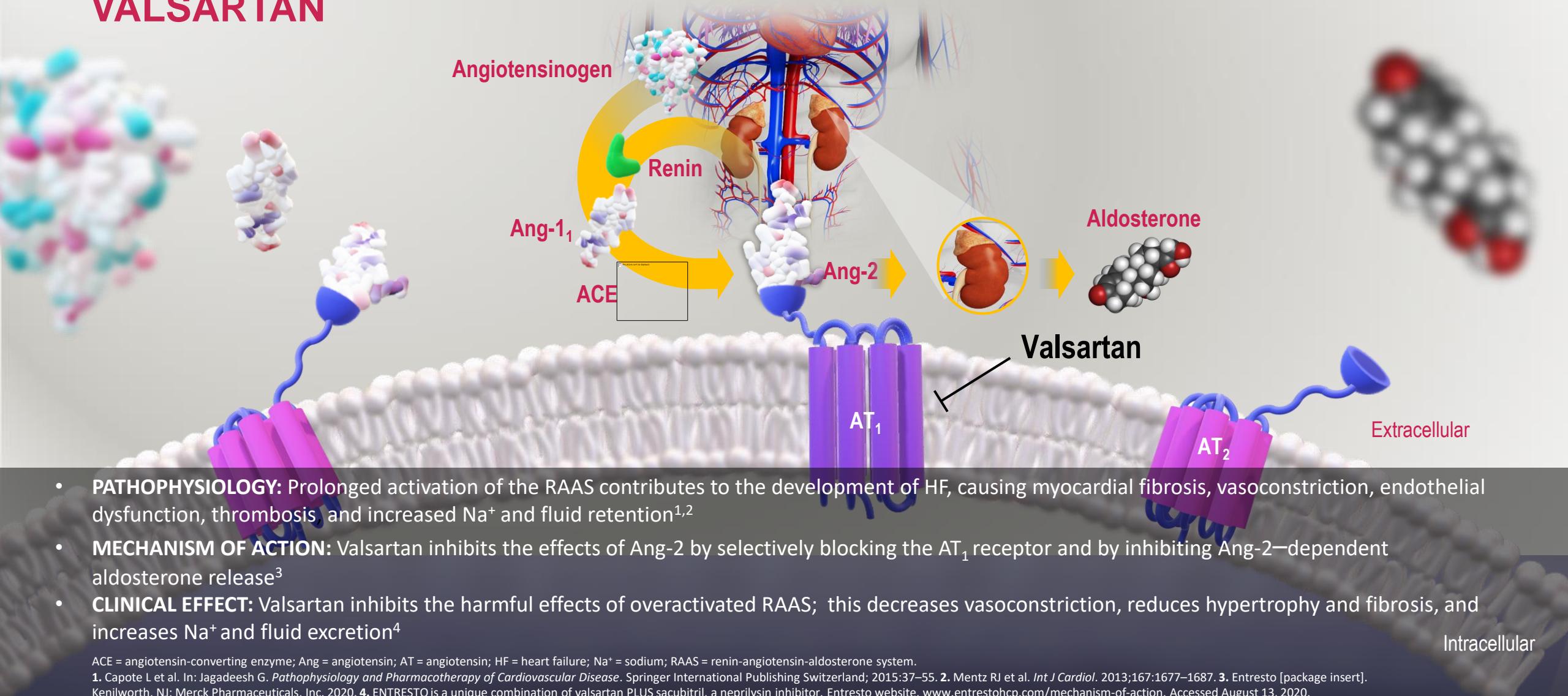
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EFFECTS OF RAAS ACTIVATION, THE DEVELOPMENT OF HF, AND VALSARTAN



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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.

Contraindications and adverse effects

Contraindications¹¹

- 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

Adverse effects¹¹

- Angioedema
- Impaired renal function
- Hyperkalaemia
- Dizziness
- Cough

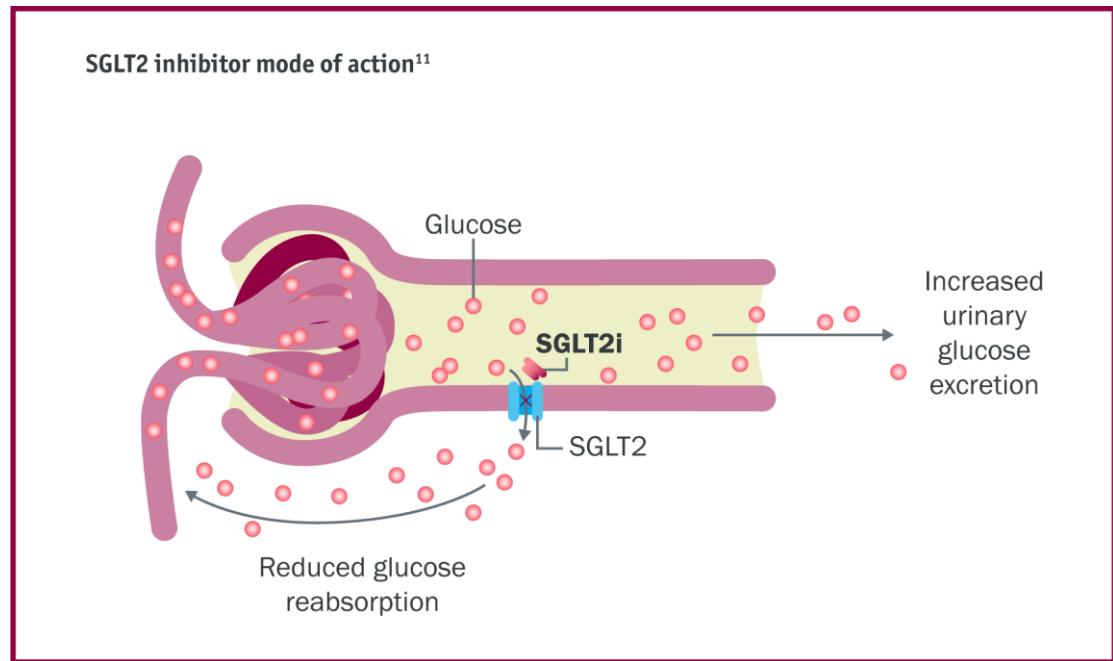
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Question 7

- What is the mechanism of action of SGLT2 inhibitors?

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 circulation¹⁰
 - 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 urine¹¹
 - This leads to reduction of blood glucose, blood pressure, inflammation, oxidative stress, arterial stiffness, and SNS activity¹¹
 - Mediate natriuresis, which reduces both systolic and diastolic pressures¹¹
 - 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 function¹¹



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.

Question 9

- What are the recent trials of SGLT2 Inhibitors in HFrEF?



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Contraindications and adverse effects

Contraindications¹⁶

- Prior serious hypersensitivity reaction to given SGLT2i
- Severe renal impairment (eGFR <30 mL/min/1.73 m²) 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

Adverse effects¹⁶

- 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.

Question 9

- Provide a recap of the landmark trials for ARNI and SGLT2 Inhibitors in HFrEF?

	PARADIGM-HF¹ sacubitril/ valsartan	DAPA-HF² dapagliflozin	EMPEROR-Reduced³ empagliflozin	SOLOIST-WHF⁶ 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

Heart Failure

What is Symptomatic chronic HF following a worsening HF event?



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Challenges in the Definition of a ‘Worsening HF Event’

- There are numerous criteria that define a ‘worsening HF event’¹
 - In order to qualify as an episode of worsening HF, objective evidence of the following should be provided:
 - Signs and symptoms of deteriorating clinical conditions
 - Signs of cardiac overload and changes in biomarkers
 - The need for acute treatments for chronic HF should be included, such as:
 - Increase in diuretic dose
 - IV diuretics
 - IV vasodilators/inotropes
- “*There is no widely accepted nomenclature for HF syndromes requiring hospitalisation*”²
 - Patients are described as having:
 - Acute HF
 - Acute HF syndromes
 - **Acute(ly) decompensated HF**
 - **This last phrase has its limitations (e.g., does not make the important distinction between those with a de novo presentation of HF from those with worsening of previously chronic stable HF)**

Outpatient Worsening Chronic Heart Failure as a Target for Therapy

**Worsening CHF can be managed
as a hospitalized, in the ED, or as an outpatient**

- There are no strong evidence-based guideline recommendations or therapies for WCHF management other than optimization of chronic HF therapy
- Nature and time course of clinical deterioration that precedes hospitalization is highly variable
 - a minority of patients may experience relatively rapid and severe deterioration (acute event) requiring hospitalization/ED visit
 - most may have symptoms of worsening for a longer period; this prolonged course of clinical deterioration offers a potential window of opportunity for intervention before hospitalization, not previously considered

**Outpatient WCHF is defined as
the deterioration of HF signs and symptoms**

**in a patient with chronic HF after a period of clinical stability that
requires escalation of therapy without an urgent need for hospitalization or ED presentation**

Over the clinical course of HF, several factors should be closely monitored, particularly in patients with worsening HF

Common factors that can contribute to worsening HF¹

NYHA functional class

Acute myocardial ischemia

Uncontrolled hypertension

Atrial fibrillation and other arrhythmias

Nonadherence with medication regimen, sodium, or fluid restriction

Medications with negative inotropic effect

Medications that increase sodium retention (NSAIDs, thiazolidinediones, steroids)

Excessive alcohol intake or illicit drug use

Anemia

Hyper or hypothyroidism

Acute infections (upper respiratory infection, pneumonia, urinary tract infections)

Additional acute cardiovascular diagnoses (aortic valve disease, endocarditis, myopericarditis)

Careful evaluation of the primary etiology of the heart disease and potential aggravating factors is necessary

*Note that worsening HF here is defined as the lack of clinical improvement, the worsening of HF symptoms, and acutely decompensated heart failure.

HF=heart failure; NSAIDs=nonsteroidal anti-inflammatory drugs; NYHA>New York Heart Association.

1. Holenberg SM et al. *J Am Coll Cardiol*. 2019. pii: S0735-1097(19)36183-2. doi: 10.1016/j.jacc.2019.08.001. 2. Mehta RJ, O'Connor CM. *Nat Rev Cardiol*. 2016;13(1):28-35.

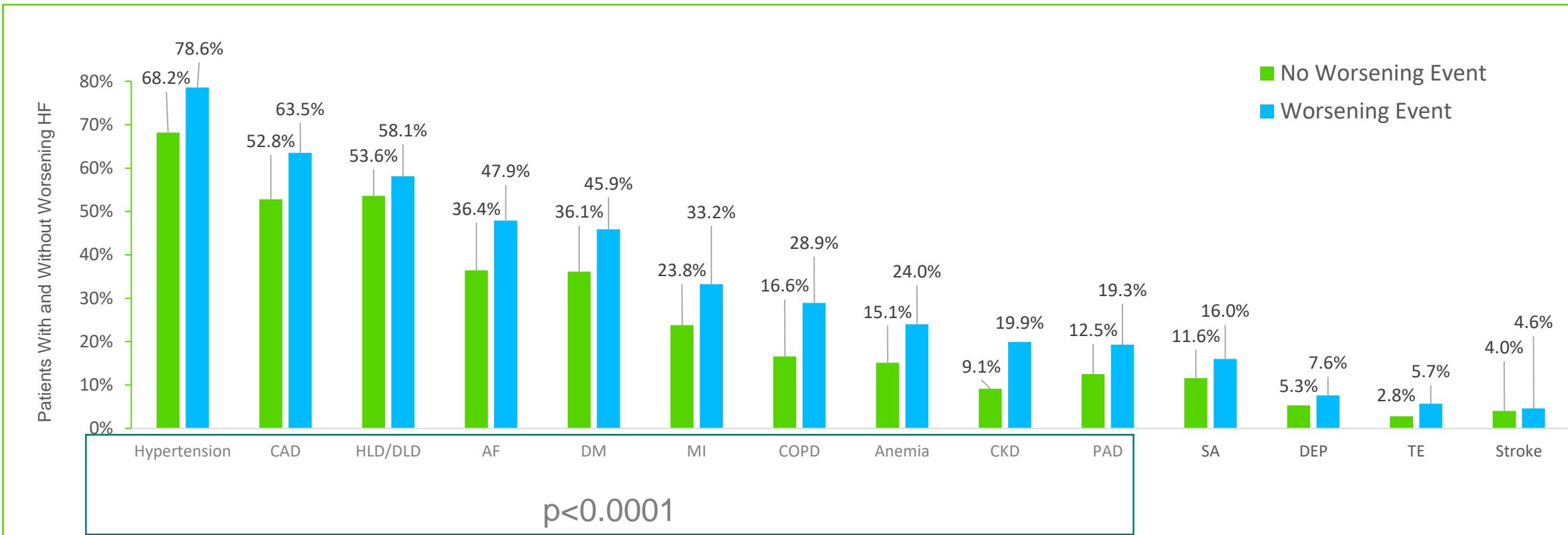


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Rates of comorbidities are higher among patients who developed worsening HF

Comorbidities in Patients With and Without Worsening HF



Although the comorbidity burden was high overall, all rates of comorbidities were higher in those with worsening HF

Note that worsening is defined in PINNACLE-HF as the development of progressively escalating symptoms and signs of HF requiring IV diuretic treatment in the outpatient, ED, or hospitalized setting.

Stroke frequency does not include transient ischemic attack or intracerebral hemorrhage.

AF=atrial fibrillation; CAD=coronary artery disease; CKD=chronic kidney disease (stage III or IV); COPD=chronic obstructive pulmonary disease; DEP=depression; DM=diabetes mellitus (type 1, 2, primary, or secondary); ED=emergency department; HF=heart failure; HLD/DLD=hyperlipidemia/dyslipidemia; IV=intravenous; MI=myocardial infarction; PAD=peripheral artery disease; SA=sleep apnea; TE=thromboembolism

Butler J et al. J Am Coll Cardiol. 2019;73(8):935-944.

BEST STUDY



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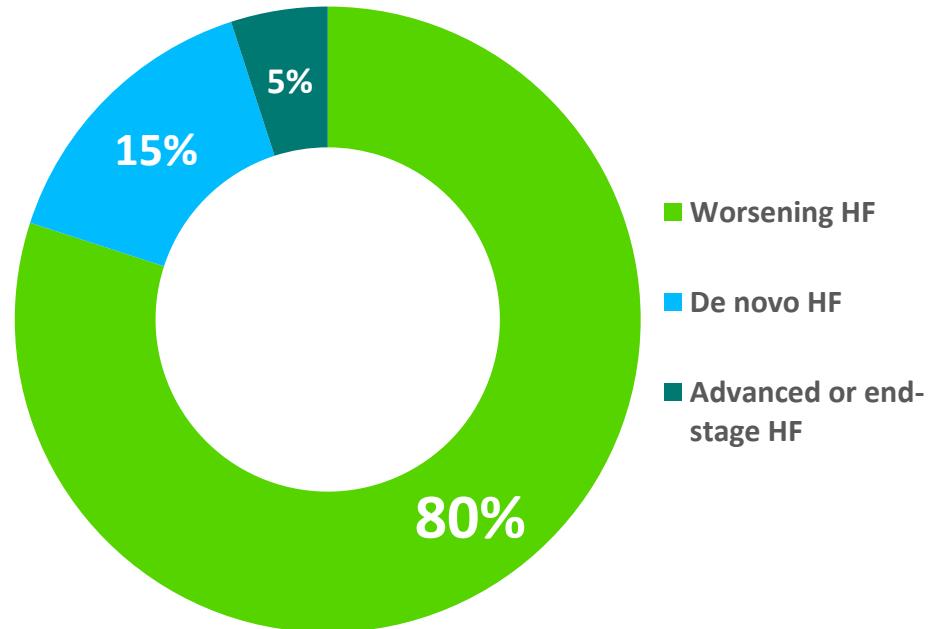
Why does worsening Heart failure represent an area of high Unmet need?



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Worsening chronic heart failure represents an area of high unmet need



**Chronic worsening HF
accounts for ~80% of HFH
cases¹**

HF markedly affects a patient's quality of life by reducing their independence and ability to carry out day-to-day activities²

HF, heart failure; HFH, heart failure hospitalization.

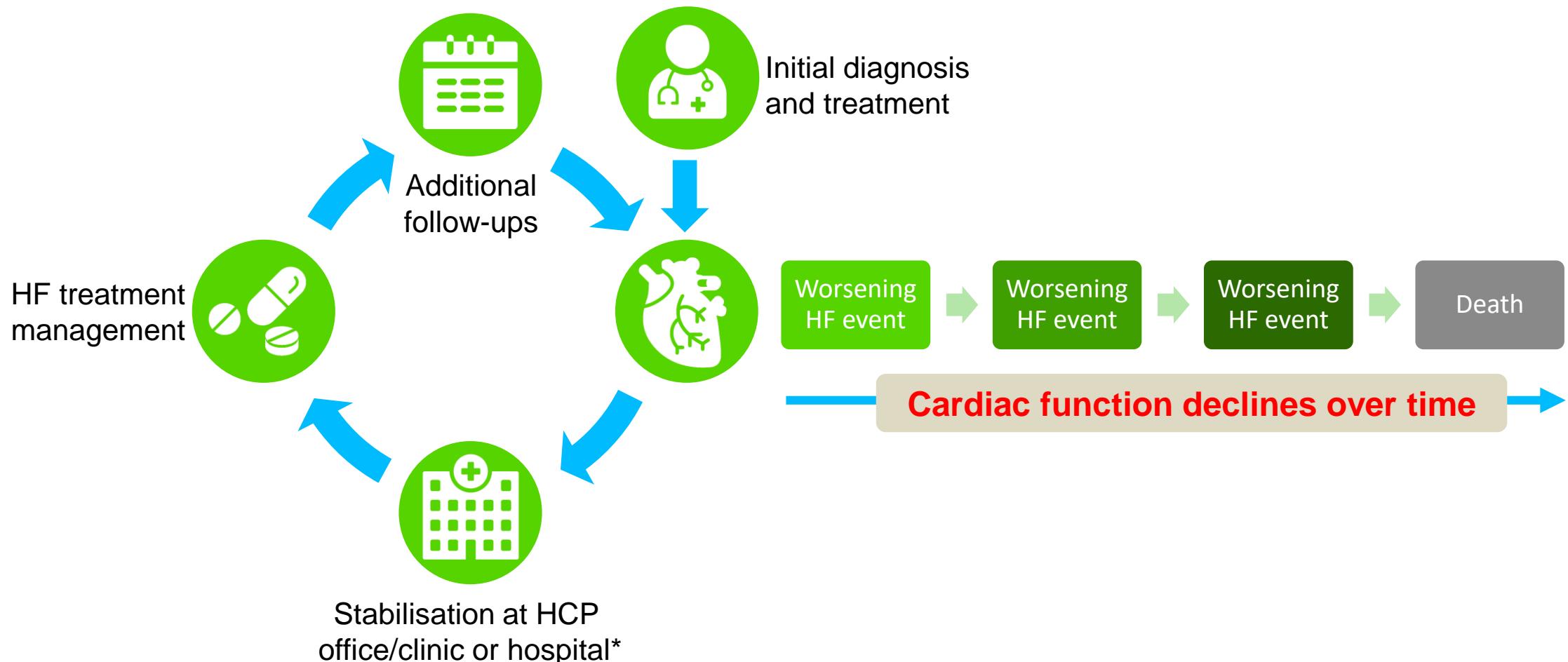
1. Gheorghiade M et al. *J Am Coll Cardiol* 2013;61:391–403; 2. Ponikowski P et al. *ESC Heart Fail* 2014;1:4–25.



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Patients with chronic heart failure are in a cycle of recurrent events^{1–3}



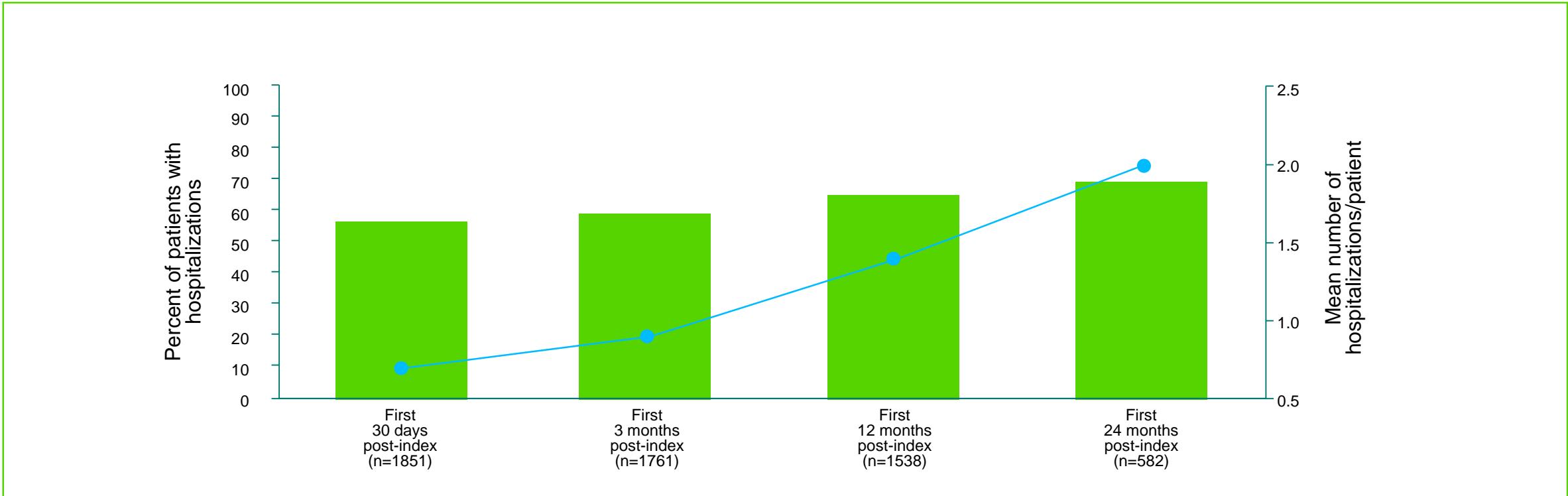
*Adjustment of and potential addition to current therapy.

HCP, healthcare professional; HF, heart failure.

1. Gheorghiade M et al. *Am J Cardiol* 2005;96:11G–17G. 2. Cowie MR et al. *ESC Heart Fail* 2014;1:110–145. 3. Greene S et al. *Circ Heart Fail* 2020;13:e007132.

1 in 2 patients will be hospitalized again within 30 days of their worsening HF event⁵

Patients With Hospitalizations & Number of Hospitalizations per Patient Through 2 Years After Worsening HF Event



56% of patients were rehospitalized within 30 days of the worsening HF event, and the number of HF-related hospitalizations increased with time

Note that worsening is defined in PINNACLE-HF as the development of progressively escalating symptoms and signs of HF requiring intravenous diuretic treatment in the outpatient, emergency department, or hospitalized setting.

HF=heart failure.

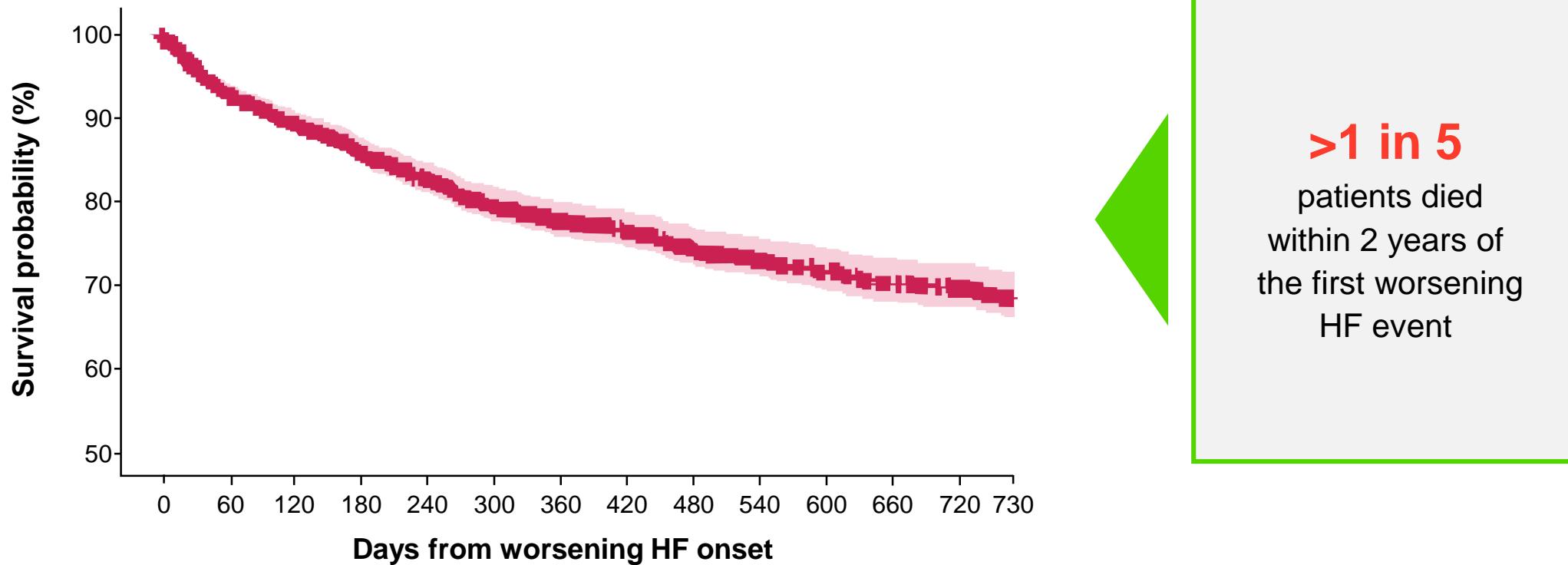
Butler JF et al. J Am Coll Cardiol. 2019;73(8):935-944.

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Each worsening HF event has a lasting impact on patients

- Days from onset of worsening HF* to death/censor in patients with worsening HF in the PINNACLE registry (N=1,851)



* Worsening HF event was defined as a requirement for IV diuretic treatment in a healthcare setting or heart failure hospitalization. HF, heart failure; IV, intravenous.

Reference: 1. Butler J et al. J Am Coll Cardiol 2019;73:935–944.

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WORSENING HF included in the ESC 2021 guidelines

New onset/ de novo HF	Worsening HF	Improving HF	Persistent HF	HF in remission
<ul style="list-style-type: none">• Newly diagnosed HF• No former history of HF	<ul style="list-style-type: none">• Worsening symptom/signs/functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies• and/or hospitalization	<ul style="list-style-type: none">• Improving symptoms/signs and/or functional capacity	<ul style="list-style-type: none">• Persistent HF with ongoing symptoms/signs and/or limited functional capacity	<ul style="list-style-type: none">• Resolution of symptoms and signs of HF, with resolution of previous structural/functional heart disease after a phase of symptomatic HF



“Worsening HF” in VICTORIA³

- 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.

Current treatment gaps in Worsening Heart Failure?

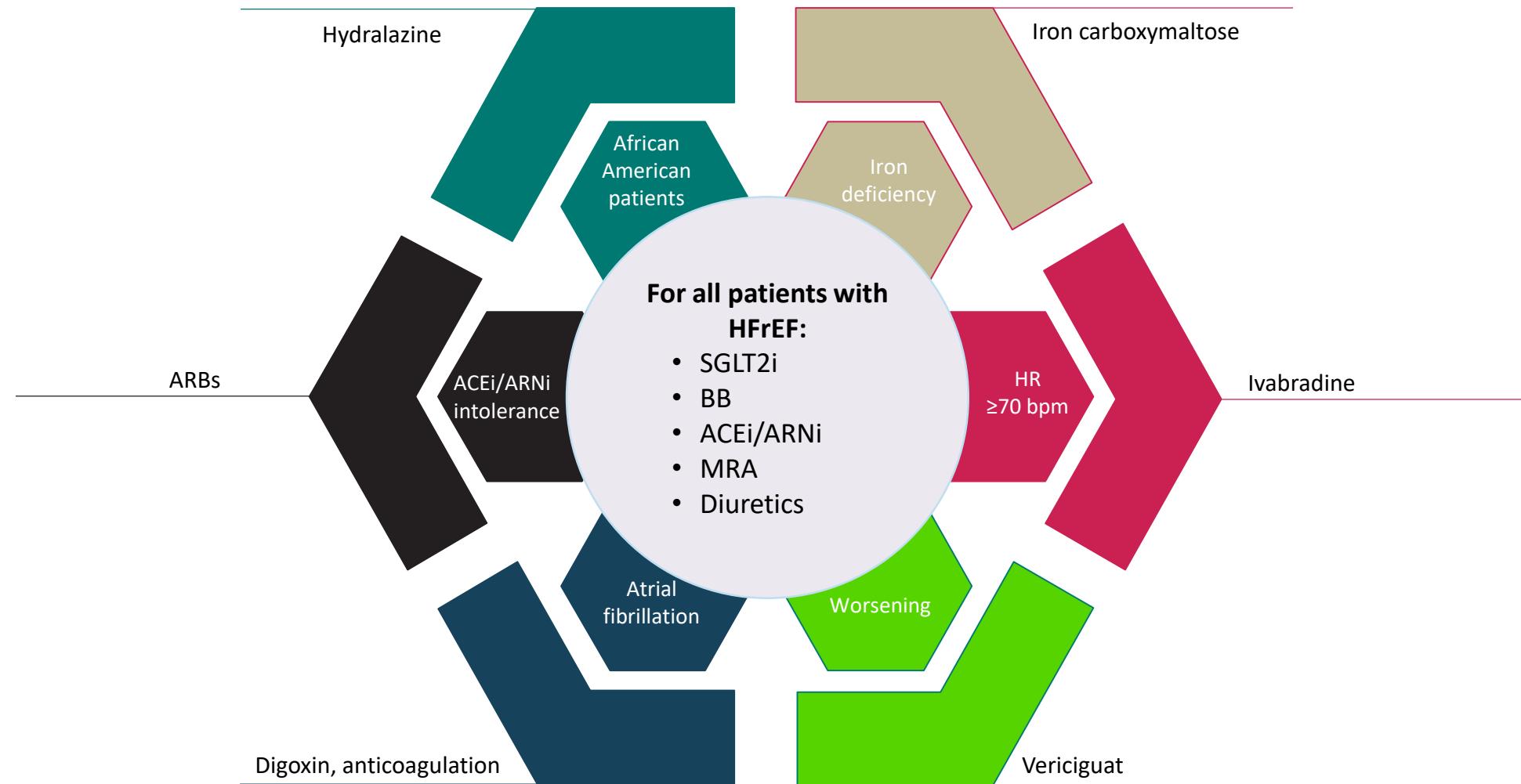


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Guidelines recommend quadruple therapy for all patients with HFrEF, with additional therapies for some patients^{1,2}



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ESC 2021 guidelines: Drugs recommended in all patients with HFrEF¹

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.

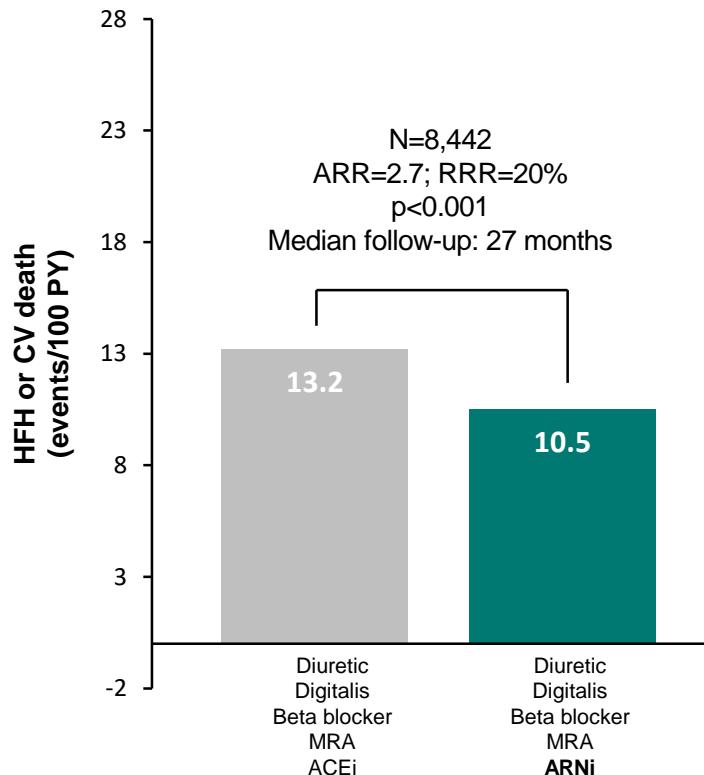
Reference: 1. McDonagh EM, Gami LS, et al. Eur Heart J 2021; doi:10.1093/eurheartj/ehab368.

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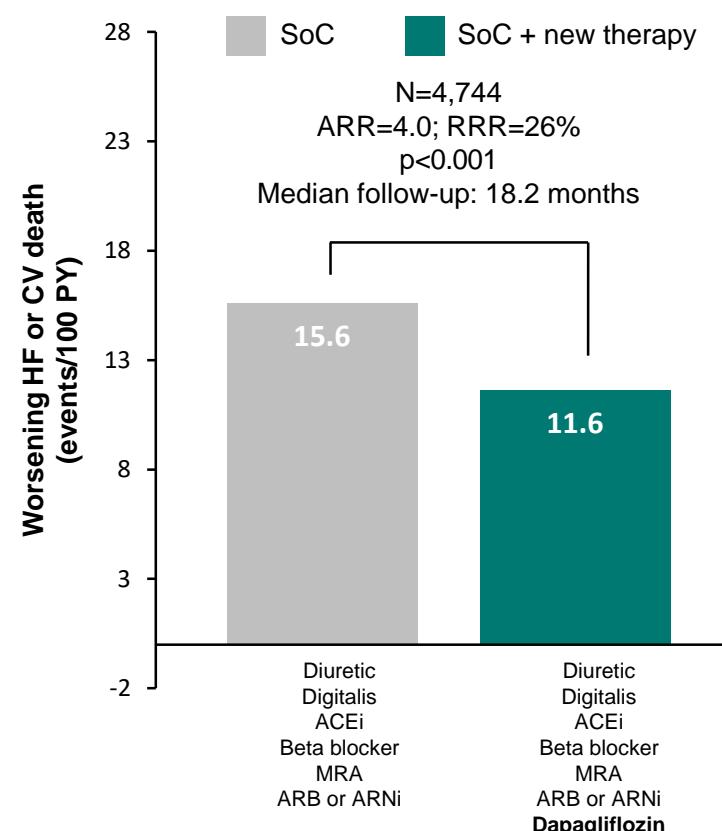
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Despite improved outcomes with contemporary therapy in patients with HFrEF, significant residual risk remains¹⁻⁴

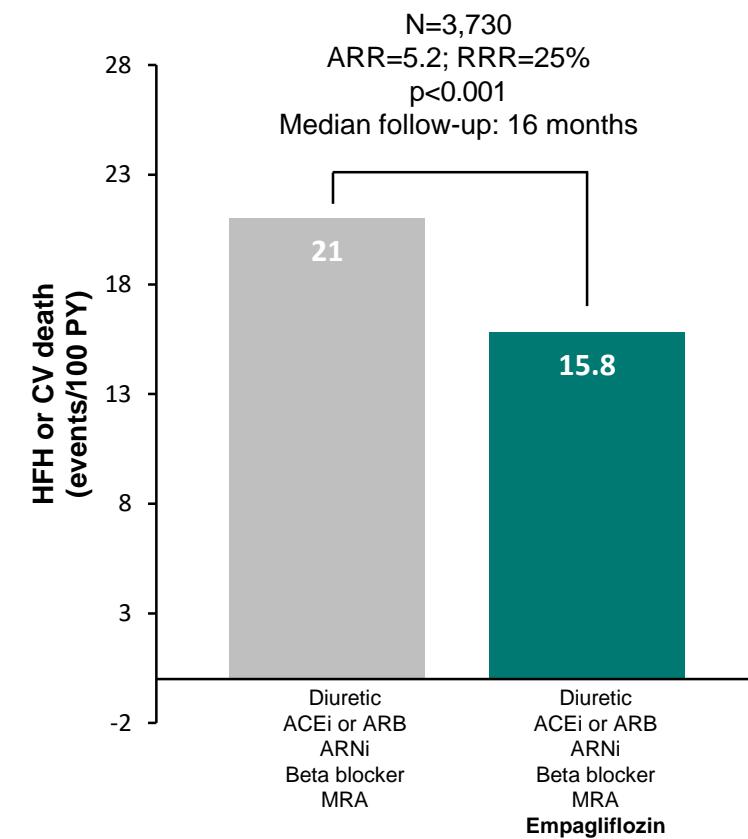
PARADIGM-HF (2014)^{1,2}



DAPA-HF (2019)^{2,3}



EMPEROR-Reduced (2020)^{2,4}



Major medical therapies listed. Each HF study was conducted independently, and no head-to-head HF studies have been completed that allow for direct comparisons.
 ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; ARR, absolute rate reduction; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; PY, patient-years; RRR, relative risk reduction; SoC, standard of care.

References: 1. McMurray J JV et al. N Engl J Med 2014;371:993–1004; 2. Butler J et al. Eur J Heart Fail 2020;22:1991–1993; 3. McMurray J JV et al. N Engl J Med 2019;381:1995–2008;
 4. Packer M et al. N Engl J Med 2020;383:1413–1424.

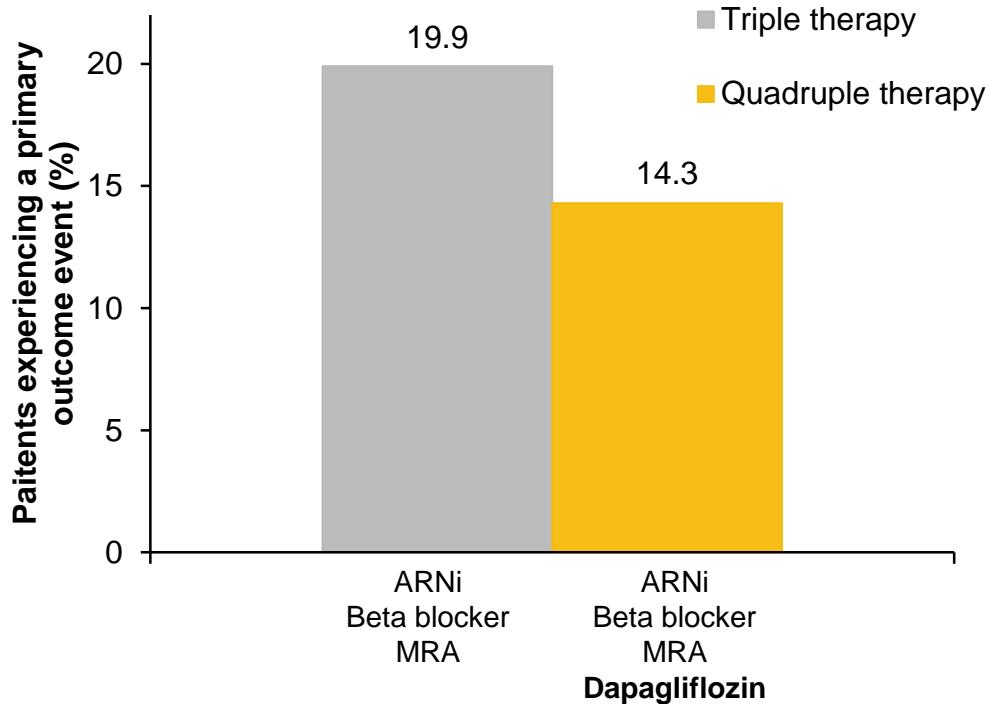
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Even patients receiving all four foundational therapies have a high residual risk of worsening HF and CV death¹

Event rates according to background HF therapy in DAPA-HF



~1 in 7 patients experienced a primary outcome event, despite confirmed use of quadruple therapy (ARNi, beta blocker, MRA and SGLT2i)

14.3% of patients on quadruple therapy had a primary event over the course of the trial#**

* Primary outcome was the composite of an episode of worsening HF or CV death, whichever occurred first.

Median follow-up of 18.2 months.²

ARNi, angiotensin receptor-neprilysin inhibitor; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

References: 1. Dombovy L et al. Eur Heart J 2020;41:2379–2392; 2. McMurray JJV et al. N Engl J Med 2019;381:1995–2008.

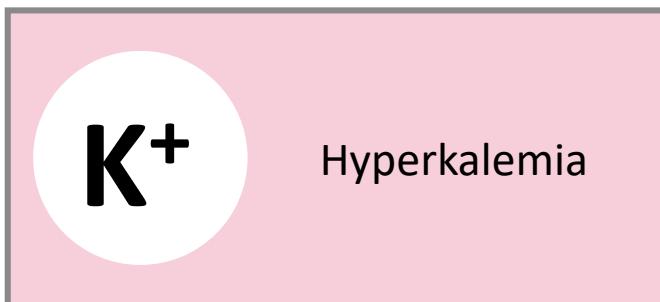


In addition Patients with HFrEF often suffer from medication side effects, making adherence challenging¹

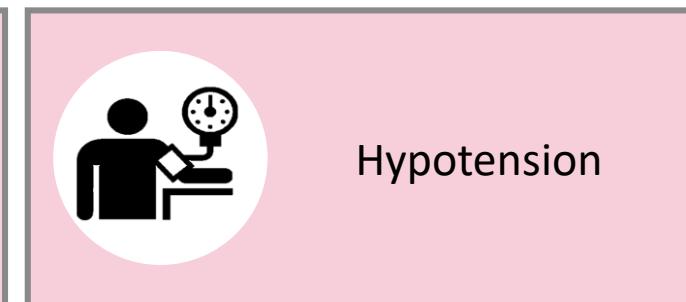
- Patient factors commonly associated with non-use and subtarget dosing of GDMT¹



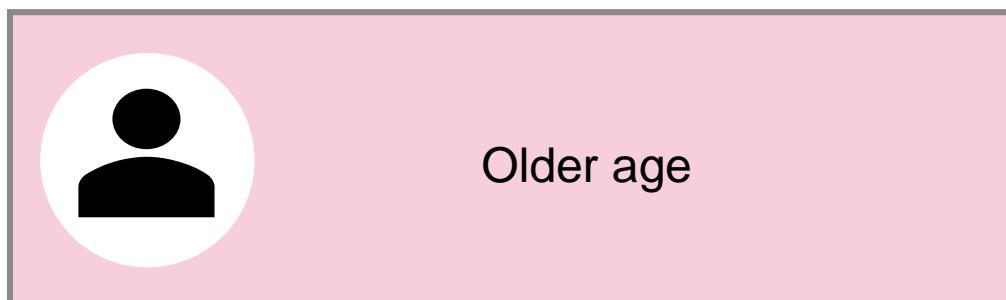
Worsening renal function



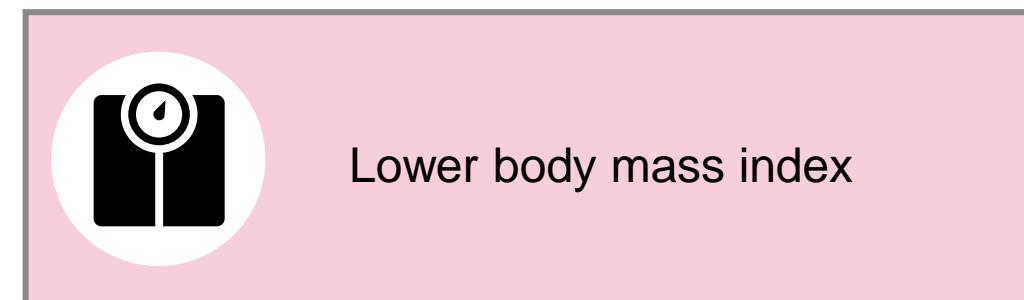
Hyperkalemia



Hypotension



Older age



Lower body mass index

There is the need for novel therapies to be developed that are:

- Effective
- Well tolerated (e.g. no concerns with hypotension, renal function or hyperkalemia)

GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction.

Reference: 1. Greene SJ et al. Heart Fail Rev. 2021; <https://doi.org/10.1007/s10741-021-10077-x>.



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Adverse Effects Limiting Treatment Optimisation

Global clinical data

- In a meta-analysis of 51 randomised controlled trials (RCTs) with information on ACEi withdrawal, 13.8% of the ACEi group and 9.4% of the control group withdrew due to adverse events.
- Cough, hypotension, renal dysfunction, dizziness, hyperkalaemia and impotence were all significantly more prevalent among patients treated with ACEi¹
- PARADIGM-HF: Among the ARNI-treated patients, 54.1% (393/726) of hypotension events led to dose adjustment or temporary discontinuation and 2.2% (16/726) led to permanent discontinuation²
- Despite adherence to guideline-recommended medications in HFrEF being associated with improved outcomes, available guidelines are not being optimally implemented, both in terms of overall use and dosing, most often because of excessive concern about adverse events⁴



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Learning objectives

By the end of this section you will be able to:

- Recall the contributions of the deficient NO-sGC-cGMP pathway to the mechanism of disease in HF
- Explain how vericiguat increases NO-sGC-cGMP signalling
- Differentiate sGC stimulators from other agents that work on the NO-sGC-cGMP pathway

cGMP, cyclic guanosine monophosphate; HF, heart failure; NO, nitric oxide; sGC, soluble guanylyl cyclase.



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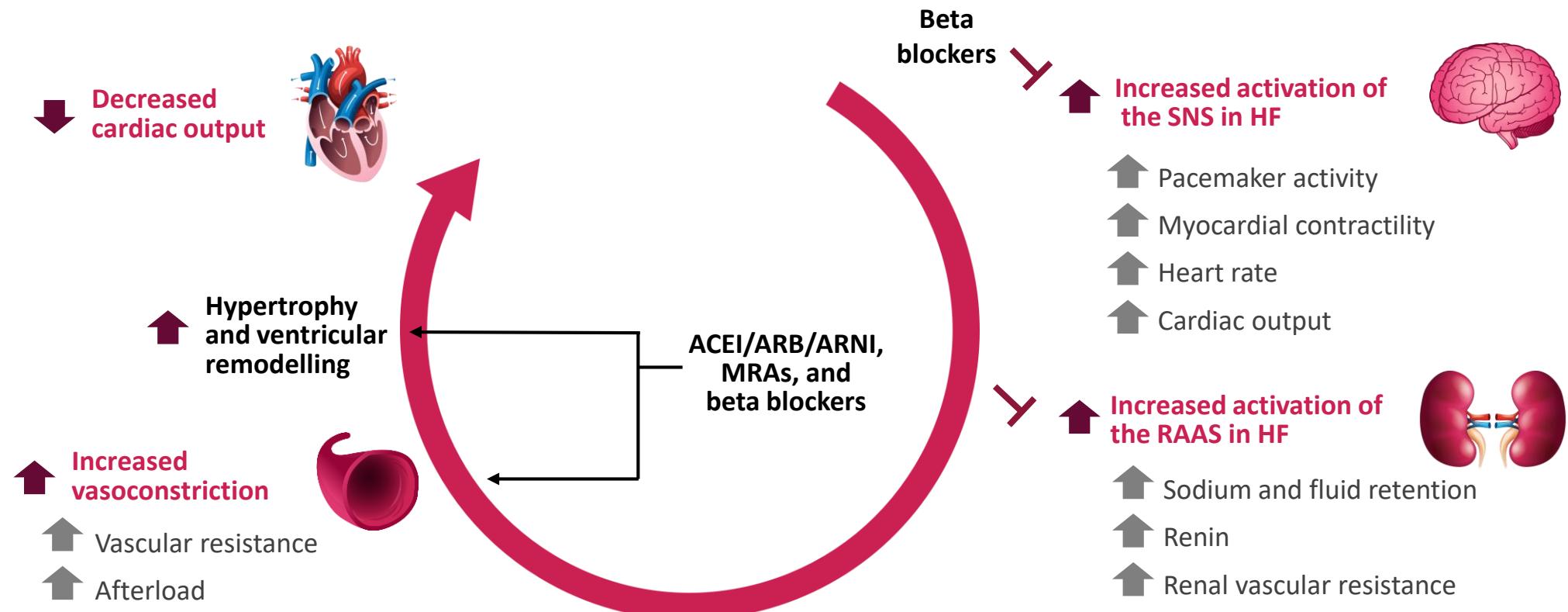
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Current HF targets

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Some Established Pathways Contributing To HFrEF Are Already Medically Addressed¹⁻⁴



Additional treatment strategies are needed to further decrease risk for patients with worsening heart failure

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; 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.

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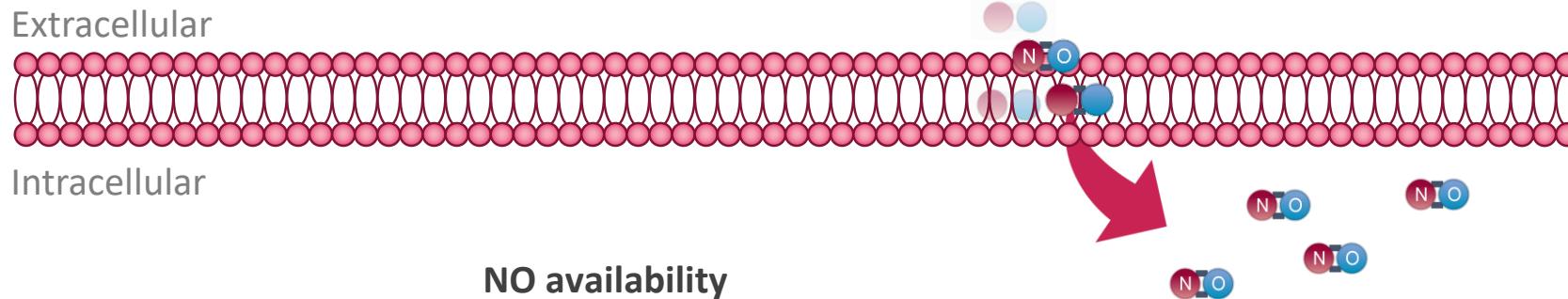
The NO-sGC-cGMP pathway

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The NO-sGC-cGMP pathway: Healthy¹

Extracellular

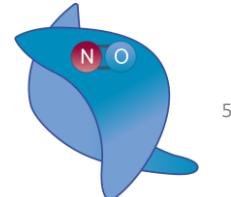


Intracellular

NO availability

sGC stimulation

cGMP production



59



cGMP is key in the regulation
of vasoconstriction,
inflammation and fibrosis¹⁻³

cGMP, cyclic guanosine monophosphate; NO, nitric oxide; sGC, soluble guanylyl cyclase.

1. Kong Q, et al. *Circ Heart Fail*. 2013;6(6):1268-1283. 2. Gheorghiade M, et al. *Heart Fail Rev*. 2013;18(2):123-134. 3. Breitenstein S, et al. *Handb Exp Pharmacol*. 2017;243:225-247.

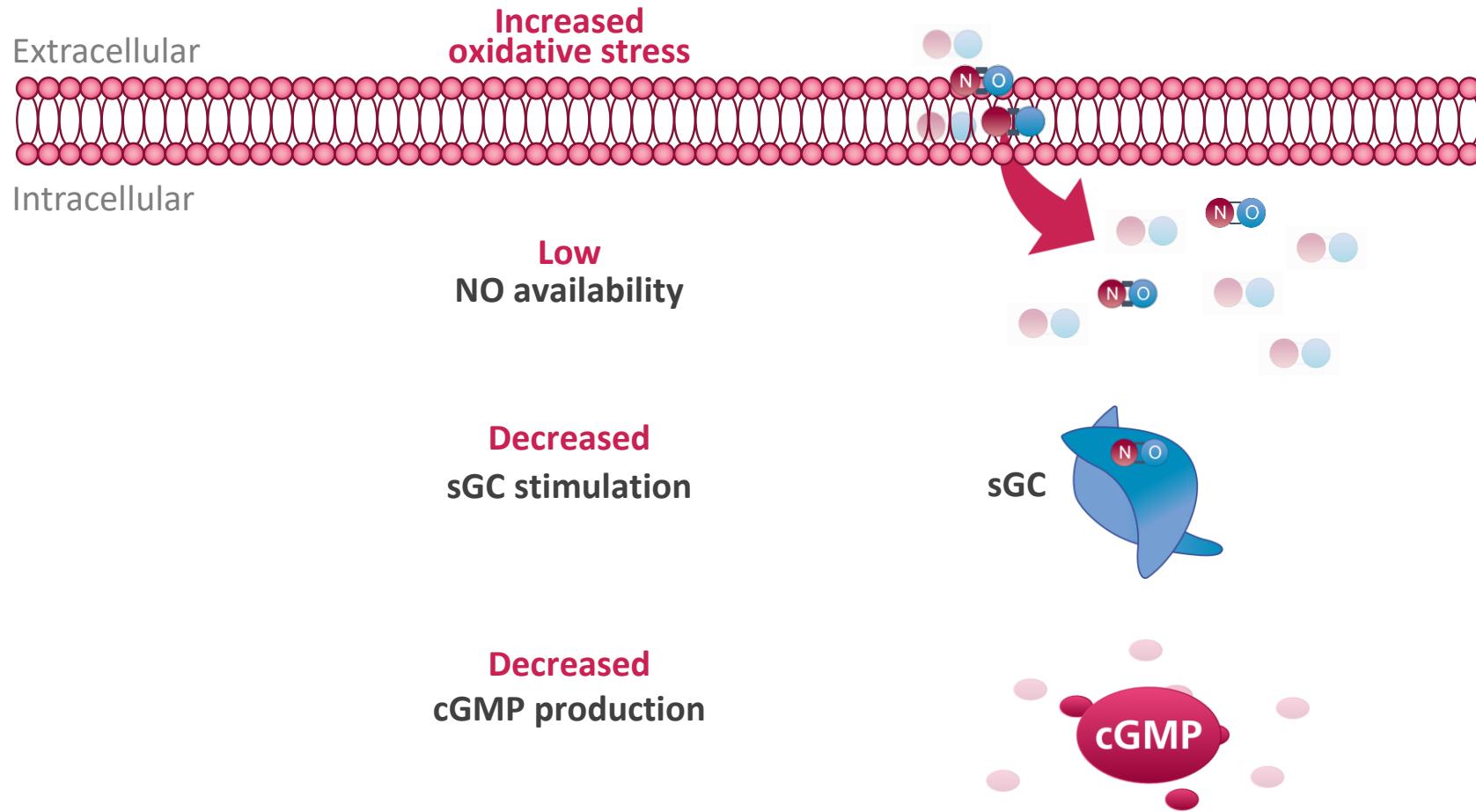


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In HF, the NO-sGC-cGMP pathway is medically unaddressed¹⁻⁴



Clinical Effects of an Impaired NO-sGC-cGMP Pathway¹

- ↓ Myocardial function
- ↑ Left-ventricular remodelling
- ↓ Vascular function
- ↑ Fibrosis
- ↑ Inflammation



Oxidative stress and NO deficiency or relative inefficiency of sGC lead to a decreased production of cGMP and subsequent cardiovascular dysfunction and HF.

cGMP, cyclic guanosine monophosphate; HF, heart failure; LV, left ventricle; NO, nitric oxide; sGC, soluble guanylyl cyclase.

1. Gheorghiade M, et al. *Heart Fail Rev.* 2013;18(2):123-134. 2. Higashi Y, et al. *Circ J.* 2009;73(3):411-418. 3. Fan D, et al. *Fibrogenesis Tissue Repair.* 2012;5(1):15. 4. Buys ES, et al. *Cardiovasc Res.* 2008;79(1):179-186. 5. Cawley SM, et al. *Am J Physiol Heart Circ Physiol.* 2011;301(1):H157-H163. 6. Borbely A, et al. *Circ Res.* 2009;104(6):780-786.

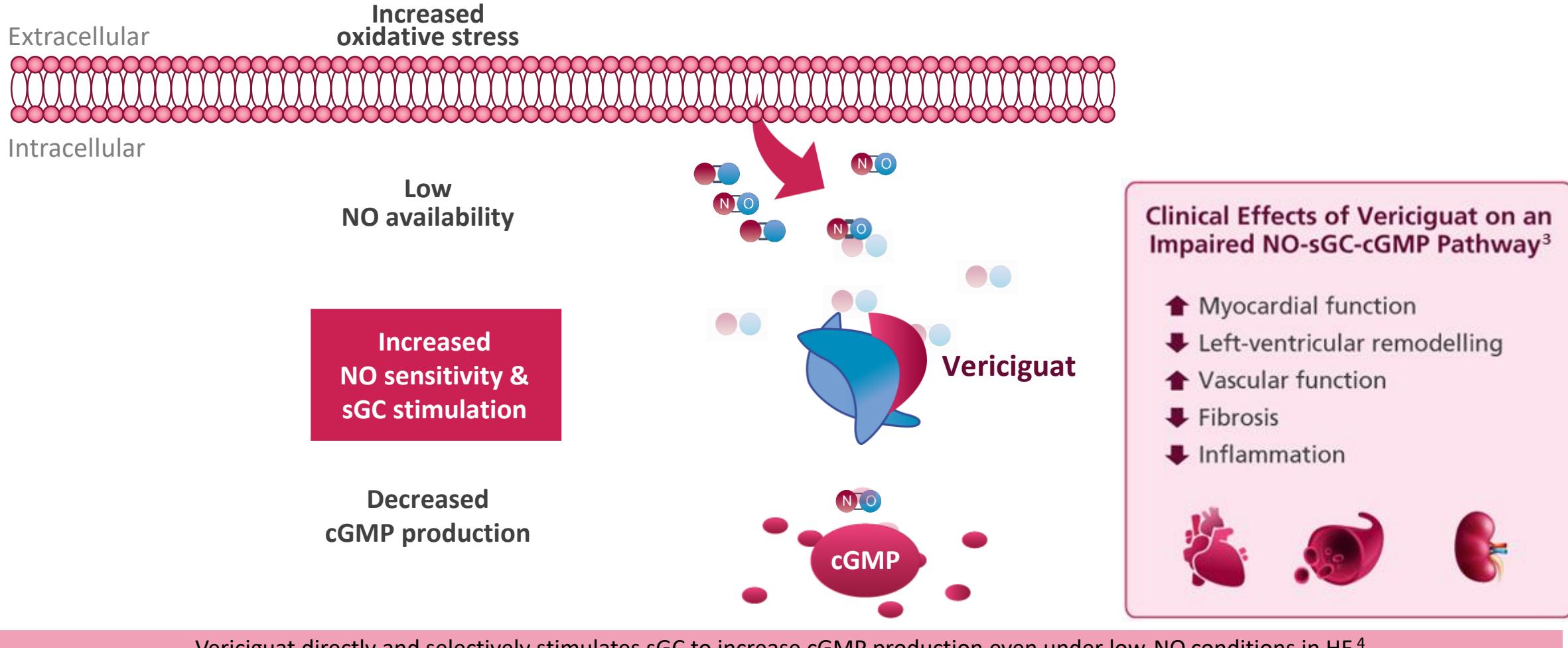


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The NO-sGC-cGMP pathway: Heart failure + vericiguat¹⁻¹²



cGMP, cyclic guanosine monophosphate; HF, heart failure; NO, nitric oxide; sGC, soluble guanylyl cyclase.

1. Breitenstein S, et al. *Handb Exp Pharmacol.* 2017;243:225-247. 2. Buys ES, et al. *Cardiovasc Res.* 2008;79(1):179-186. 3. Gheorghiade M, et al. *Heart Fail Rev.* 2013;18(2):123-134. 4. Armstrong PW, et al. *JACC Heart Fail.* 2018;6(2):96-104. 5. Sandner P. *Biol Chem.* 2018;399(7):679-690. 6. Archer SL, et al. *Proc Natl Acad Sci U S A.* 1994;91(16):7583-7587. 7. Krüger M, et al. *Circ Res.* 2009;104(1):87-94. 8. Vettel C, et al. *Am J Physiol Heart Circ Physiol.* 2014;306(8):H1246-H1252. 9. Borbély A, et al. *Circ Res.* 2009;104(6):780-786. 10. Fan D, et al. *Fibrogenesis Tissue Repair.* 2012;5(1):15. 11. Cawley SM, et al. *Am J Physiol Heart Circ Physiol.* 2011;301(1):H157-H163. 12. Follmann M, et al. *J Med Chem.* 2017;60(12):5146-5161.



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Vericiguat

Pharmacokinetic Properties

Results from phase I studies on vericiguat in healthy individuals revealed the following properties:

Tab 1: Absorption

Tab 2: Distribution

Tab 3: Metabolism

Tab 4: Elimination

Tab 5: Bioavailability

- Vericiguat is rapidly absorbed, showing consistency between 0.5 to 15 mg¹
- Area under the curve (AUC) increases proportionally to the dose¹
- Intake with food prolongs absorption¹
- Administration of 5-mg vericiguat immediate release tablet with a high-fat, high-calorie breakfast led to a delay of absorption: median t_{max} 4 hours (with food) vs. 1.5 hours (without food)
 - AUC and C_{max} were also higher (19% and 9%, respectively)

Pharmacokinetic Properties

Results from phase I studies on vericiguat in healthy individuals revealed the following properties:

Tab 1: Absorption

Tab 2: Distribution

Tab 3: Metabolism

Tab 4: Elimination

Tab 5: Bioavailability

- Vericiguat is mainly bound to plasma proteins (~97.8%; mainly to serum albumin)²
 - For this reason, vericiguat is not expected to be dialysable

Pharmacokinetic Properties

Results from phase I studies on vericiguat in healthy individuals revealed the following properties:

Tab 1: Absorption

Tab 2: Distribution

Tab 3: Metabolism

Tab 4: Elimination

Tab 5: Bioavailability

- The major metabolic pathway of vericiguat is N-glucuronidation, often involved in the metabolism of drugs²
 - The enzymes UGT1A9 and, to a lesser extent, UGT1A1 transform active vericiguat into its inactive metabolite M1²

Pharmacokinetic Properties

Results from phase I studies on vericiguat in healthy individuals revealed the following properties:

Tab 1: Absorption

Tab 2: Distribution

Tab 3: Metabolism

Tab 4: Elimination

Tab 5: Bioavailability

- The half-life of vericiguat 10 mg has been reported as ~20 hours¹
- Vericiguat has a balanced excretion and is eliminated in both the urine (53%) and faeces (45%)²
 - Urine: vericiguat amounts to 9%, while the other components consist of the inactive metabolites M1 (41%) and M15 (1.9%)²
 - Faeces: vericiguat is present as 43% and M15 as 1.6%²

Pharmacokinetic Properties

Results from phase I studies on vericiguat in healthy individuals revealed the following properties:

Tab 1: Absorption

Tab 2: Distribution

Tab 3: Metabolism

Tab 4: Elimination

Tab 5: Bioavailability

- The absolute bioavailability of vericiguat is 93% with food²
- Food intake increases oral bioavailability of vericiguat and lowers patient pharmacokinetic variability; vericiguat should therefore be taken with food¹
- Linear pharmacokinetics were observed after administration of vericiguat across the dose range that was investigated¹

Drug-Drug Interactions

Results from phase I studies on vericiguat revealed no clinically relevant interactions of vericiguat with drugs used for treating HF comorbidities^{1,2}

Co-medication	Effect on PK/PD
ARNI (sacubitril/valsartan)¹	<ul style="list-style-type: none">No clinically relevant PK/PD interaction
Warfarin and aspirin^{1,2}	<ul style="list-style-type: none">No clinically relevant PK/PD interactionNo dose adjustment of warfarinNo dose adjustment of aspirin
Nitrates^{3,4}	<ul style="list-style-type: none">No significant effect on BP or HR with sublingual nitrates (VENICE study)No significant effect on BP or HR with concomitant long-acting nitrates (VISOR study)
PDE5 inhibitors⁵	<ul style="list-style-type: none">Combined treatment of single doses of a PDE5i on top of 10-mg vericiguat resulted in an additional BP-lowering effect by ~5 mm Hg vs. PDE5i alone, independent of the PDE5i doseAdditionally, an increased frequency of transient nervous system disorders was observed
Effect of vericiguat on PK (digoxin; midazolam)²	<ul style="list-style-type: none">No clinically relevant PK interactionNo dose adjustment of digoxinNo dose adjustment of co-medications metabolised by CYP3A4
Effect of PK on vericiguat (ketoconazole, rifampicin, mefenamic acid)²	<ul style="list-style-type: none">No clinically relevant PK interactionNo dose adjustment of vericiguat

ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; HR, heart rate; PD, pharmacodynamic; PDE, phosphodiesterase; PDE5i, phosphodiesterase 5 inhibitor; PK, pharmacokinetic.

Vericiguat pharmacodynamic and pharmacokinetics

ADME Profile		Co-medication	Effect on PK/PD ^{1,2}
Absorption	<ul style="list-style-type: none"> Rapidly absorbed³ <ul style="list-style-type: none"> Consistent between 0.5 mg and 10 mg Food delays absorption, increases oral bioavailability (5 mg, from 77.5% to 93%; 10 mg, from 66.4% to 93%)⁴ AUC increases with proportion to dose³ 	Sacubitril/valsartan	<ul style="list-style-type: none"> No clinically relevant PK/PD interaction²
Distribution	<ul style="list-style-type: none"> Mainly in plasma³ 	Warfarin and aspirin²	<ul style="list-style-type: none"> No clinically relevant PK/PD interaction No dose adjustment of warfarin No dose adjustment of aspirin
Metabolism	<ul style="list-style-type: none"> N-glucuronidation (major metabolic pathway); 9.0% in urine as vericiguat¹ 	Nitrates^{5,6}	<ul style="list-style-type: none"> No significant effect on BP or HR with SL nitrates (VENICE study) No significant effect on BP or HR with concomitant long-acting nitrates (VISOR study)
Elimination	<ul style="list-style-type: none"> Clears from plasma in t_{1/2} ~20 hours³ Balanced in urine (53.1%) and feces (45.2%)¹ 	Effect of vericiguat on PK (digoxin; midazolam)¹ Effect of PK on vericiguat (ketoconazole, rifampicin, mefenamic acid)¹	<ul style="list-style-type: none"> No clinically relevant PK interaction No dose adjustment of digoxin No dose adjustment of co-medications metabolized by CYP3A4
			<ul style="list-style-type: none"> No clinically relevant PK interaction No dose adjustment of vericiguat

No clinically relevant DDIs with drugs used in HF or drugs used to treat comorbidities of HF.^{1,2}

ADME, absorption, distribution, metabolism, elimination; AUC, area under the curve; BP, blood pressure; CYP, cytochrome P450; DDI, drug-drug interaction; HF, heart failure; HR, heart rate; PD, pharmacodynamics; PK, pharmacokinetics; SL, sublingual.

1. Lobmeyer M, et al. Poster P1706. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019. 2. Boettcher M, et al. Poster P1183. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019. 3. Boettcher M, et al. Poster P1182. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019. 4. Bayer 2020. Data on File. 5. Duengen H, et al. Abstract 19938. https://www.ahajournals.org/doi/abs/10.1161/circ.136.suppl_1.19938. Accessed: January 2020. 6. Boettcher M, et al. Poster P1184. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019.



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Pop-up: NO donors¹

Mechanism of action

NO donors (e.g. nitrates) work upstream of sCG stimulators in the NO-sGC-cGMP pathway¹

Benefits

Nitrates demonstrate improved LV function and exercise capacity in combination with hydralazine⁴

Challenges

Biotransformation of nitrates into active NO donors is required¹

Nitrate tolerance limits the long-term effectiveness of these drugs^{1,5}

NO donors can cause endothelial dysfunction, oxidative stress and endothelin 1 increase, and their venoselectivity may restrict the haemodynamic tolerability of these drugs^{1,6,7}

Unlike NO donors, vericiguat directly stimulates the endogenous receptor, sGC, leading to cGMP production regardless of NO bioavailability and under high oxidative stress¹

Pop-up: PDE5 inhibitors

Mechanism of action

PDE5 inhibitors (PDE5i) act downstream of sGC stimulators in the NO-sGC-cGMP pathway, by inhibiting PDE-mediated cGMP degradation¹

Benefits

Some small studies in HF have indicated positive effects of PDE5i; however, there is a lack of large-scale HF trials on this drug class⁸

Challenges

Their action is limited by a dependency on endogenous cGMP production, which is often impaired in HF¹

Another limitation in HF is that PDE5 expression is decreased in the myocardium⁹

Unlike PDE5i, vericiguat directly stimulates sGC to increase cGMP concentration¹

Mechanism of action

Recall from chapter 2 '*Treatment and Guidelines for HFrEF*' that the neprilysin inhibitor component of an ARNI inhibits the degradation of NPs and other vasoactive peptides^{1,10}

This leads to increased cGMP production via the NP-pGC-cGMP pathway, which is driven by a membrane-bound pGC^{1,2}

Benefits

The ARNI sacubitril/valsartan has been shown to reduce the risk of HF hospitalisation and death in patients with symptomatic chronic HFrEF, who are on optimal guideline-recommended therapy¹¹

Challenges

The effect of ARNI is limited by the endogenous levels of NPs¹²

Unlike ARNI, vericiguat directly stimulates sGC to increase intracellular cGMP concentration¹

In a mouse model, directly stimulating sGC significantly increased intracellular cGMP concentration, whereas stimulating pGC had little effect on cGMP production¹³

Discussion

Which patient population
do you think might benefit
most from vericiguat
treatment?

Summary

- Patients living with symptomatic chronic HF, following a worsening HF event are a distinct group within the wider HF patient population, with a high unmet medical need for efficacious treatments to change the trajectory of their disease
- Treatment strategies may include the decision for upfront or sequential combination therapy
- Vericiguat works on an untapped pathway and addresses HF from a different angle
- In the NO-sGC-cGMP pathway:
 - Oxidative stress and NO deficiency or relative inefficiency of sGC lead to a decreased production of cGMP and subsequent cardiovascular dysfunction and HF
 - cGMP plays an essential role in normal cardiovascular function by regulating vasoconstriction, inflammation, hypertrophy and fibrosis
 - The impact of nitrates and PDE5 inhibitors is limited, and they do not directly stimulate sGC
 - PDE5 inhibitors are not approved for use in HF patients and only work downstream to prevent the breakdown of cGMP
 - Vericiguat directly and selectively stimulates sGC to increase cGMP production even under low-NO conditions in HF
 - Vericiguat shows no clinically relevant DDIs with drugs used in HF or drugs used to treat comorbidities of HF

cGMP, cyclic guanosine monophosphate; DDI, drug-drug interactions; HF, heart failure; NO, nitric oxide; PDE5, phosphodiesterase type; sGC, soluble guanylate cyclase; WCHF, worsening chronic heart failure.



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