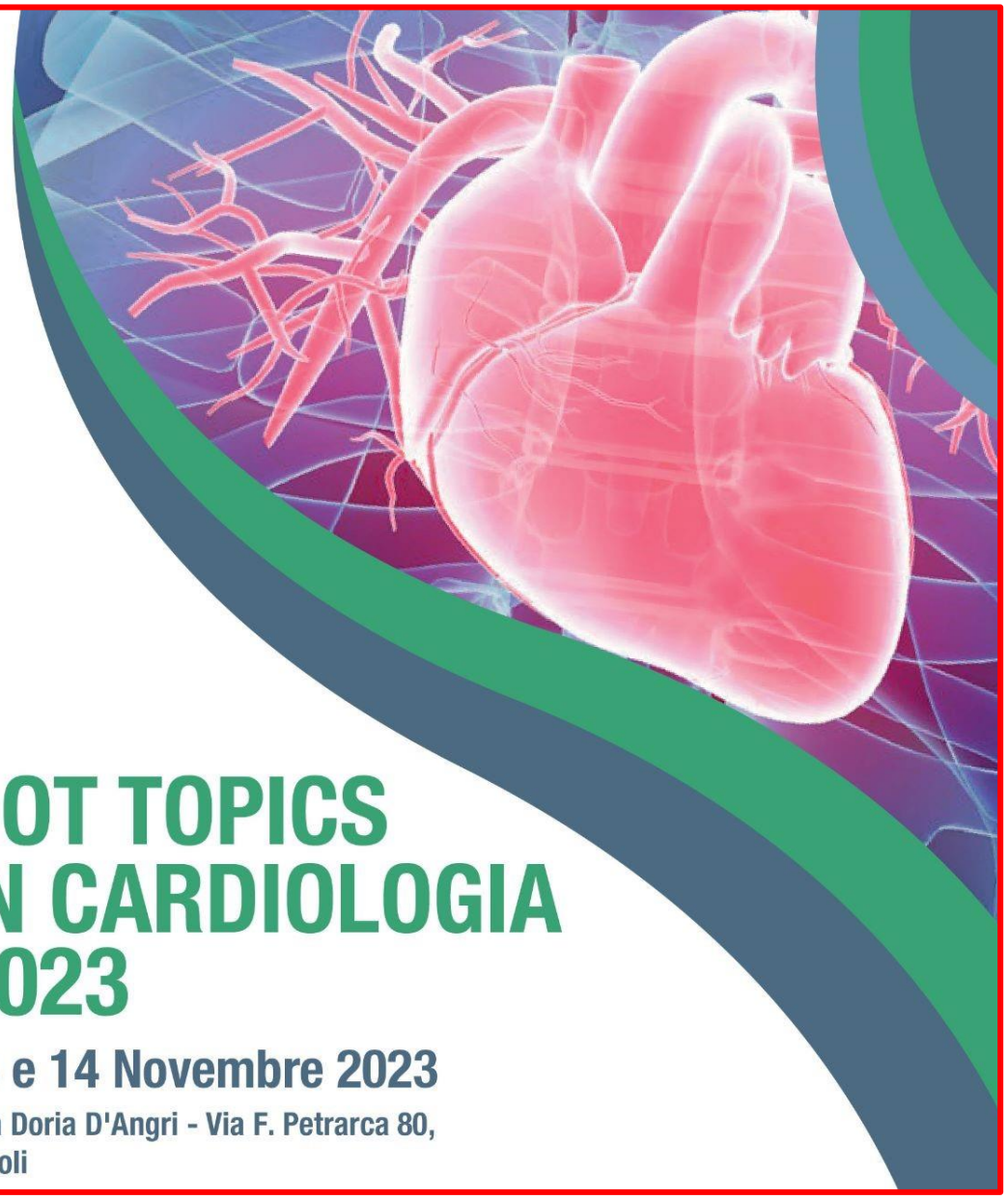


VERICIGUAT : BLOCCO NEUROORMONALE E STIMOLAZIONE OSSIDO NITRICO

Dott. GIUSEPPE PACILEO

UOSD “Scompenso Cardiaco”

AOS DEI COLLI _ NAPOLI

NO CONFLITTO DI INTERESSI

Open access Viewpoint

openheart

Four pillars of heart failure: contemporary pharmacological therapy for heart failure with reduced ejection fraction

Sam Straw ,[1] Melanie McGinlay,[2] Klaus K Witte[1]

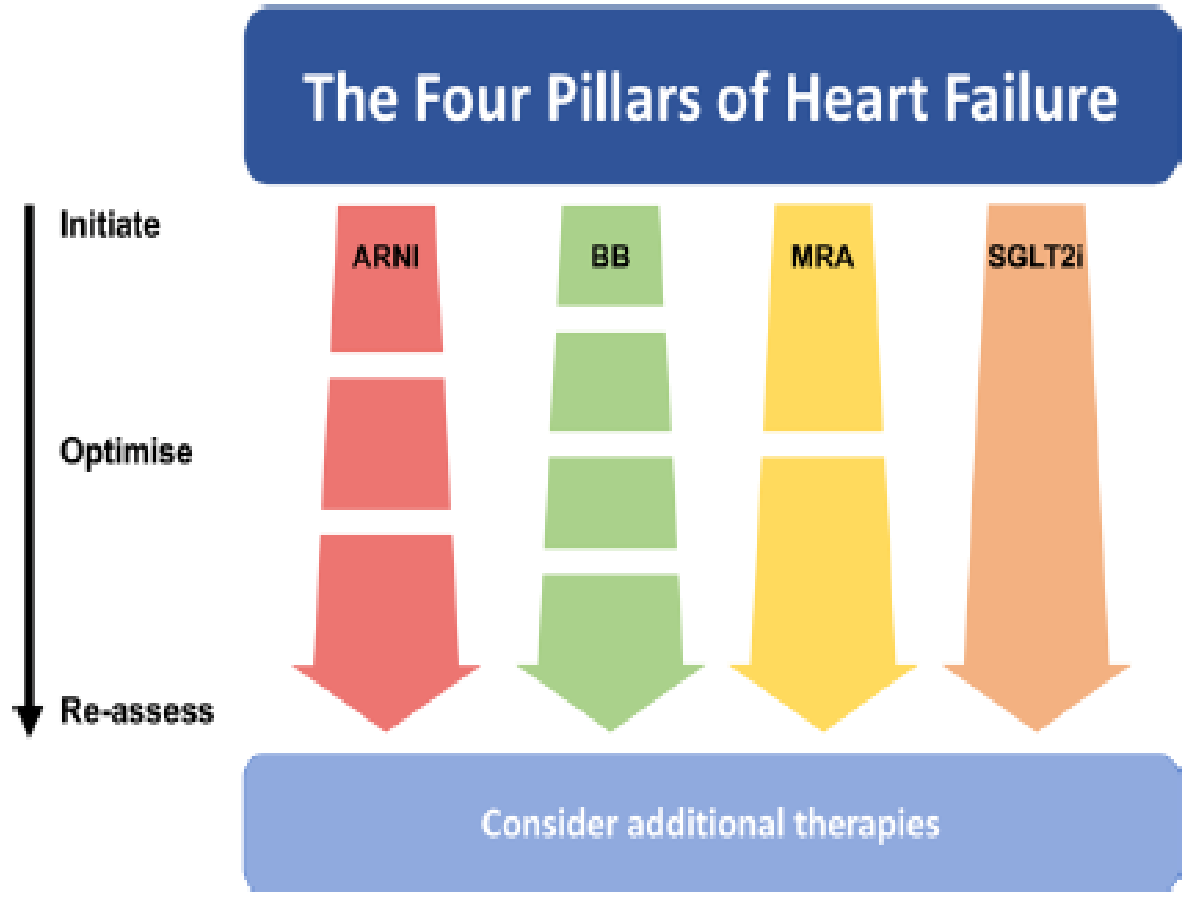
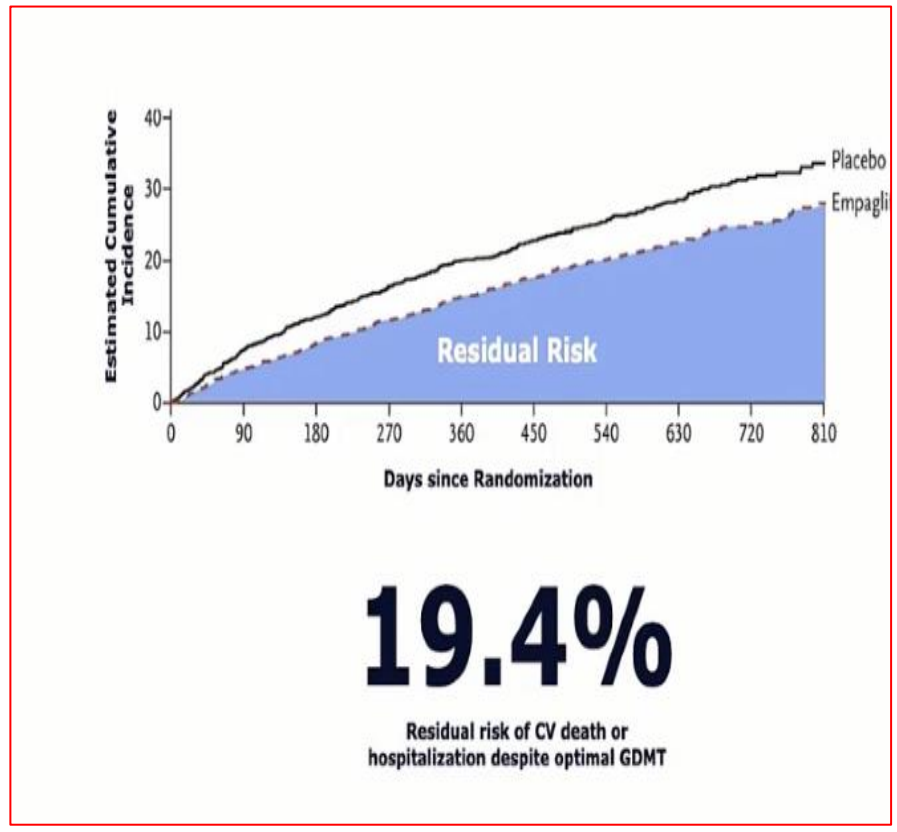


Figure 1 Initiation and optimisation of the Four Pillars of Heart Failure. All agents are initiated in parallel. This is followed by up-titration in one, two or three steps, as required. Additional therapies are then considered as a final step. ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta-blocker; MRA, mineralocorticoid receptor antagonists;SGLT2i, sodium-glucose co-transporter 2inhibitors.

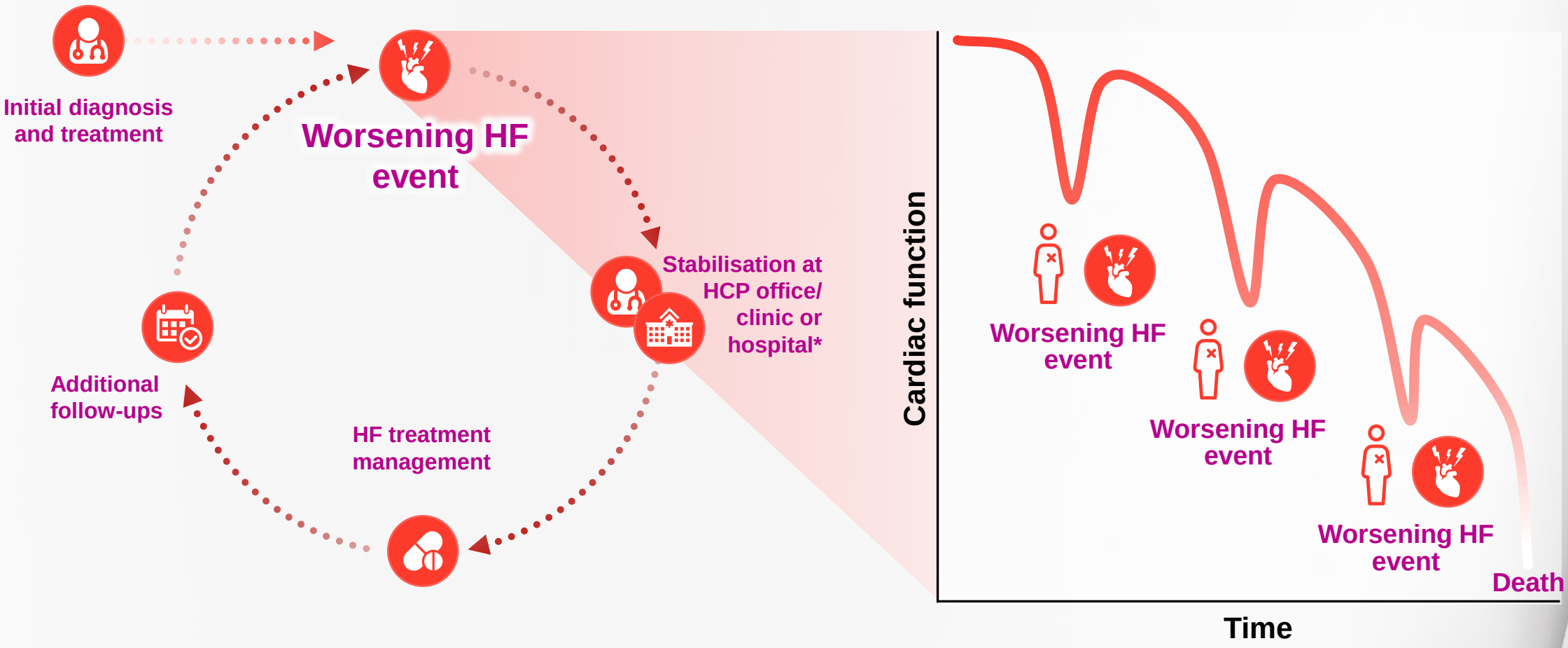
The war against heart failure: the *Lancet* lecture

Eugene Braunwald



Packer M. NEJM 2020

HF is a progressive condition: patients with HF are caught in a vicious cycle and progressively worsen over time

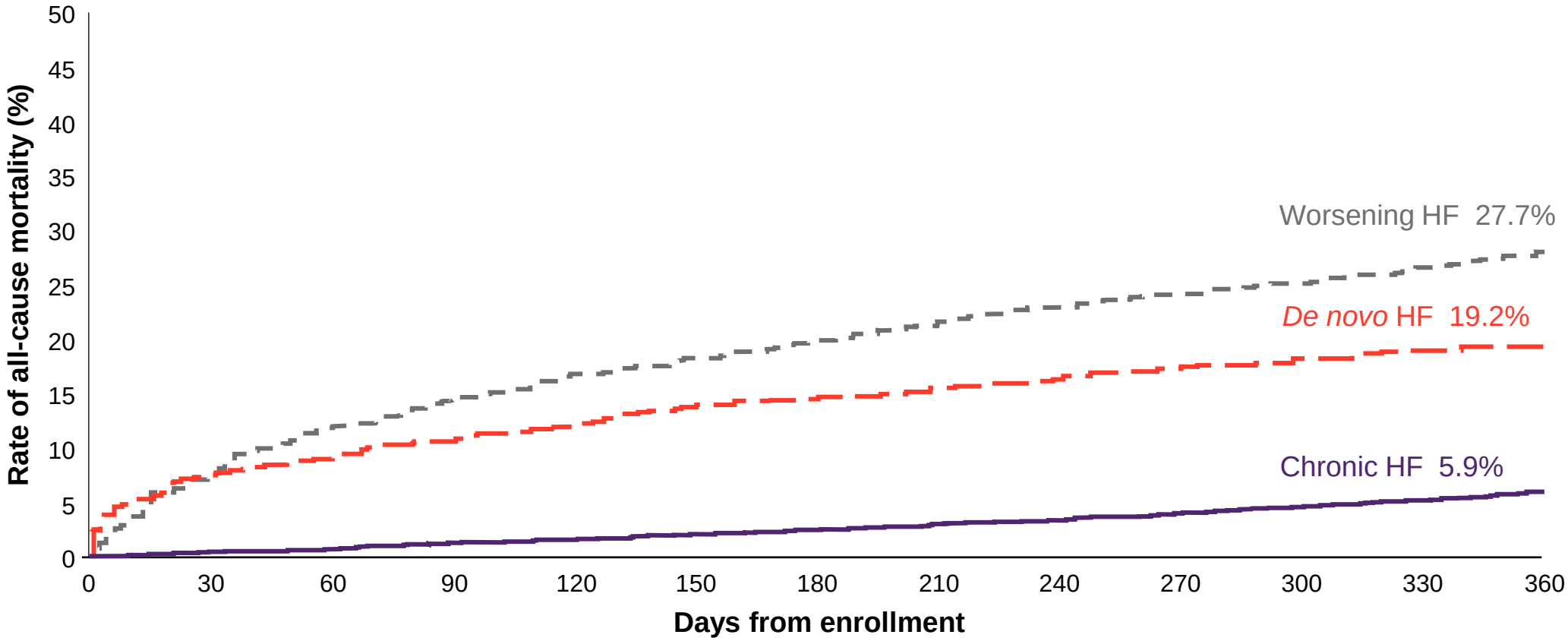


Adapted from Gheorghiade et al. *Am J Cardiol.* 2005 and Cowie et al. *ESC Heart Fail.* 2014.
*Adjustment of and potential addition to current therapy.
HCP, healthcare professional; HF heart failure.

1. **Gheorghiade M** et al. *Am J Cardiol*. 2005;96:11G–17G; 2. Cowie MR et al. *ESC Heart Fail*. 2014;1:110–145.

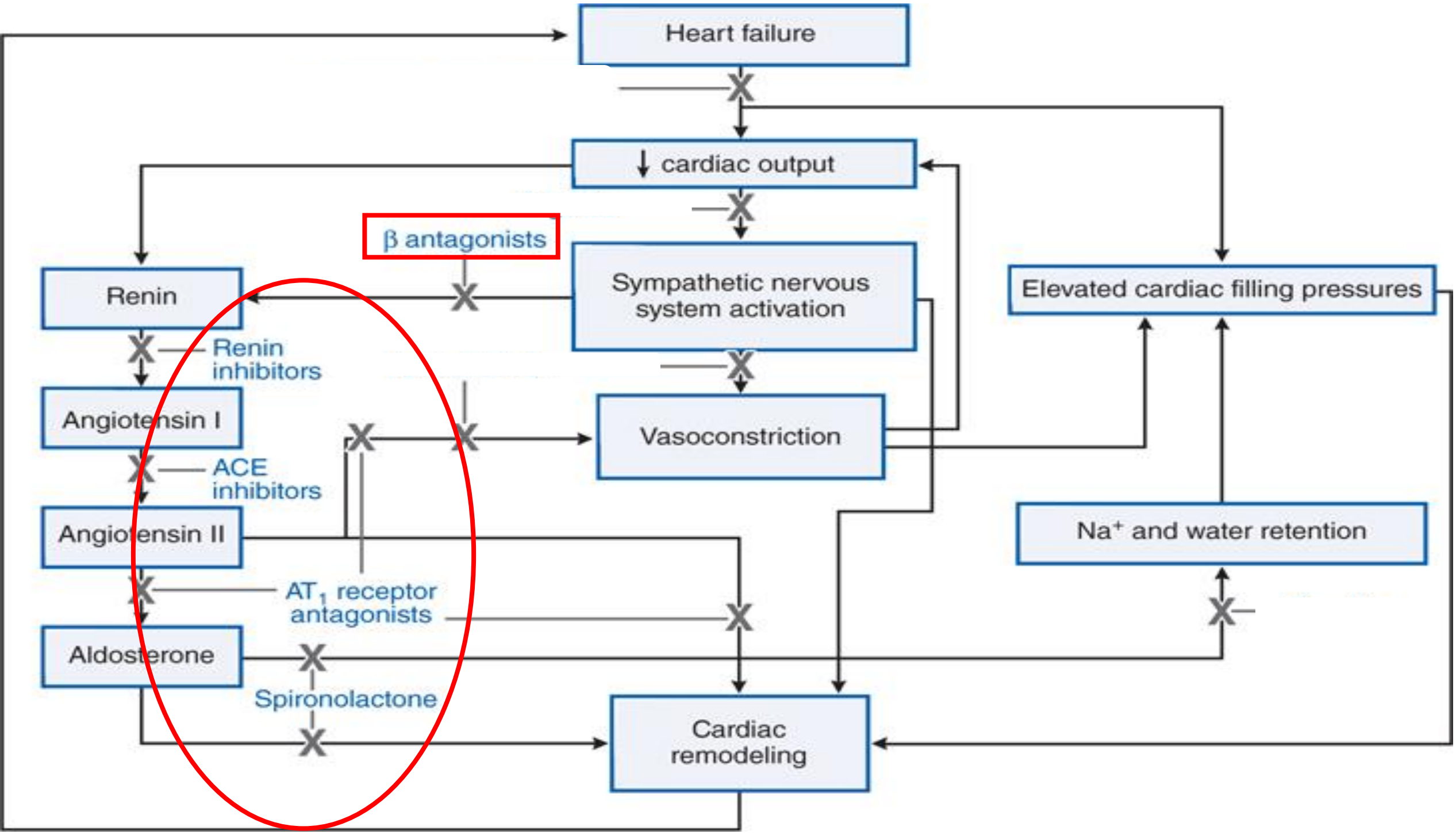
Worsening HF is associated with a four-fold increase in 1-year mortality risk compared with chronic HF

One-year all-cause mortality rate in patients hospitalized with acute HF or outpatients with chronic HF, prospectively enrolled in the IN-HF outcome registry (N=5,610)[1]



HF, heart failure.

Reference: 1. Tavazzi L *et al. Circ Heart Fail* 2013;6:473–481.


Heart failure
↓ cardiac output
β antagonists
Sympathetic nervous system activation
Renin
Renin inhibitors
Angiotensin I
ACE inhibitors
Angiotensin II
AT1 receptor antagonists
Aldosterone
Spironolactone
Vasoconstriction
Elevated cardiac filling pressures
Na+ and water retention
Cardiac remodeling

PATHWAY

Pathway	Receptor/target	Second messenger	Adaptive effects	Maladaptive effects	Drugs
Sympathetic nervous system	β_1	G_s > AC > cAMP > PKA	Increased contractility and relaxation	Excitation contraction uncoupling Apoptotic pathways Alterations in β_1 signals	*Selective β blockers (e.g., bisoprolol)*
	α_1	G_q > PLC-β_1 > DAG, IP3, PKC > MEF-2 ROS		Pro-fibrotic and pro-hypertrophic genes expression	*Non-selective β blockers (e.g., carvedilol)*
Renin–angiotensin–aldosterone system	AT-1	G_q > NADPH oxidase – ROS JAK/STAT > PTK PLC > DAG, IP3, PKC Tyrosine kinase—MAPK		Vasoconstriction, inflammation, proliferation, atherosclerosis Inflammation, growth, proliferation DAG, IP3 > vasoconstriction Inflammation, growth, proliferation	*ACE inhibitors, AT-1 antagonists (ARBs)*
	AT-2	Bradykinins > NO > cGMP G_q > PP2A, PTP > ↓ MAPK	Vasodilation, blunt in inflammation, growth and proliferation		*ACE inhibitors*
	MR	Tissues with 11-β-HSD2: Kidney: sodium-water retention vSMCs: galectin-3; PKB; PlGF Endothelium: ICAM, Tissues without 11-β-HSD2: Cardiomyocytes Macrophages: M1 phenotype	Increased contractility	Hypertension Fibrosis; apoptosis; atherosclerosis Leukocytes adhesion Hypertrophy, electric instability, oxidative stress Fibrosis and damage	*MR antagonists (MRAs)*
Natriuretic peptides	NPR-A	GC > cGMP > PKG	Vasodilation, diuresis, natriuresis, inhibition of cardiac hypertrophy and remodeling, suppression of ADH, blunt in SNS discharge		*Angiotensin receptor/Neprilysin inhibitor*
	NPR-B		Inhibition of vSMC proliferation, LDLox migration, ET-1 release		
	NPR-C	Internalization of NPs for degradation		Blunt in NPs effects	
Nitric oxide	Guanylate cyclase	cGMP	Vasodilation and muscular relaxation		**Soluble guanylate cyclase stimulators (vericiguat) and activators**

The Nobel Prize in Physiology or Medicine 1998

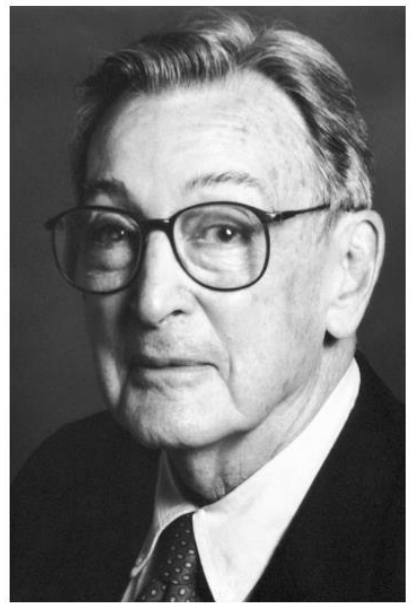


Photo from the Nobel Foundation archive.

Robert F. Furchgott

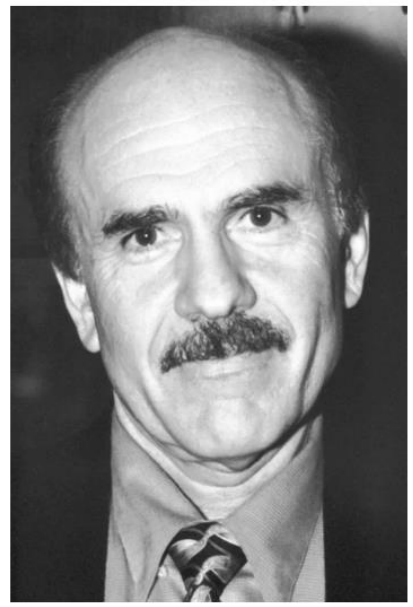


Photo from the Nobel Foundation archive.

Louis J. Ignarro

Photo from the Nobel Foundation archive.

Ferid Murad

"for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system"

The NO–sGC–cGMP pathway is a new target in HFrEF settings

System/organ	Drug
Increased activation of the SNS[1]	Beta blockers[1]
Increased activation of the RAAS[2]	ACEi, ARB, ARNi,[3] beta blockers[1]
Increased vasoconstriction[3]	ACEi,[4] ARB,[5] ARNi[6]
Hypertrophy and ventricular remodelling[7]	ACEi,[8] ARB,[5] ARNi,[6] beta blockers,[8] SGLT2i[9]
Impaired NO–sGC–cGMP signalling[10]	**sGC stimulator**

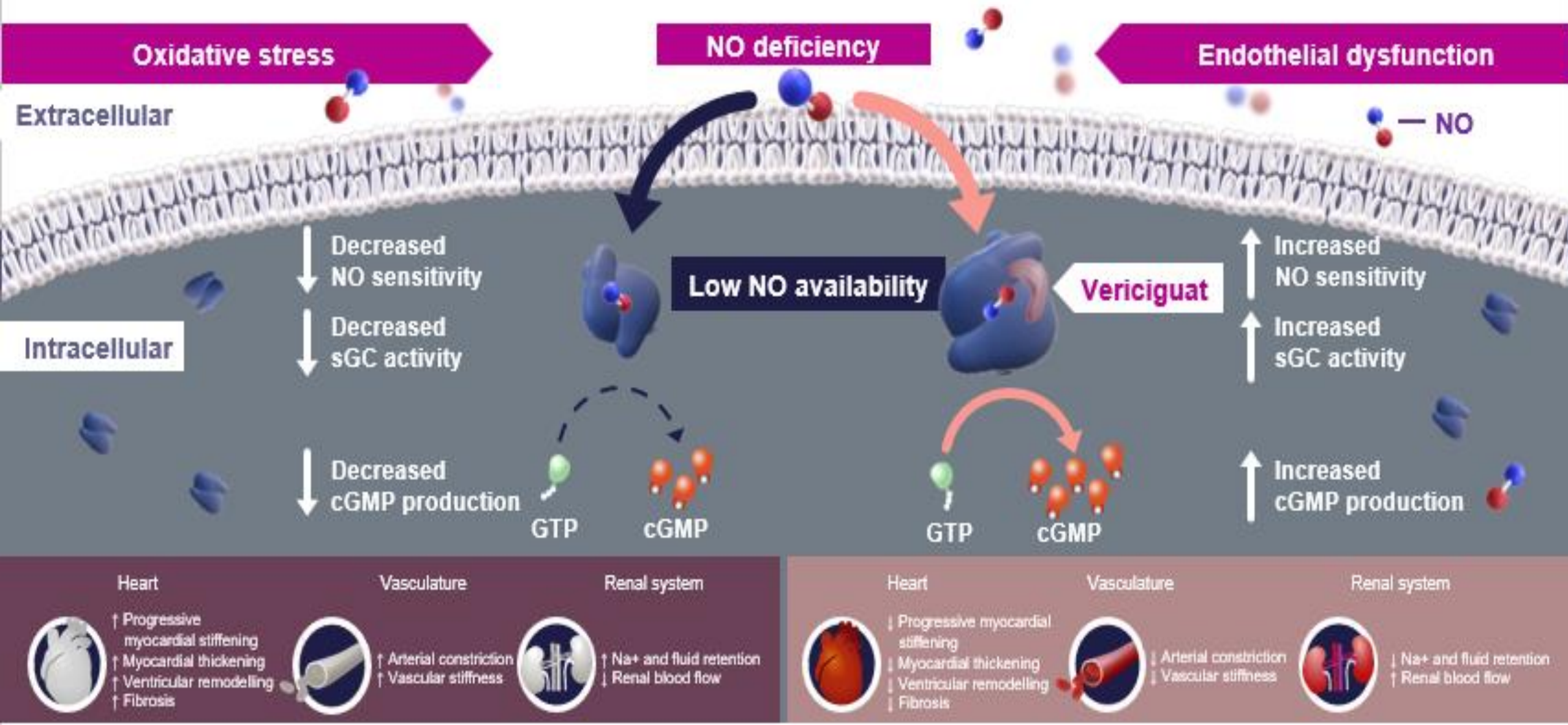
Inhibitors

Stimulator

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; cGMP, cyclic guanosine monophosphate; HFrEF, heart failure with reduced ejection fraction; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; sGC, soluble guanylate cyclase; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SNS, sympathetic nervous system.

1. Triposkiadis F et al. *J Am Coll Cardiol.* 2009;54:1747–1762; 2. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th edn. Elsevier/Saunders; 2015; 3. Yancy CW et al. *J Am Coll Cardiol*. 2017;70:776–803; 4. Enseleit F et al. *J Cardiovasc Pharmacol*. 2001;37:S21–S30; 5. Kobori H et al. *Curr Pharm Des*. 2013;19:3033–3042; 6. Ponikowski P et al. *Eur J Heart Fail*. 2016;18:891–975; 7. Nauta JF et al. *Eur J Heart Fail*. 2020;22:1147–1155; 8. Cohn JN et al. *J Am Coll Cardiol*. 2000;35:569–582; 9. Matsumura K & Sugiura T. *Cardiovasc Ultrasound.* 2019;17:26; 10. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123–134; 11. CIBIS-II Investigators. *Lancet.* 1999;353:9–13; 12. MERIT-HF Investigators. *Lancet.* 1999;353:2001–2007; 13. CONSENSUS Investigators. *N Engl J Med.* 1987;316:1429–1435; 14. SOLVD Investigators. *N Engl J Med.* 1991;325:293–302; 15. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 16. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 17. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 18. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 19. Hartupee J & Mann D. *Nat Rev Cardiol.* 2017;14:30–38.

MoA of Vericiguat



VICTORIA Phase III: study design

Primary objective: **To evaluate the efficacy of vericiguat in comparison with placebo against a background of contemporary HF therapies in increasing the time to first occurrence of the composite of CV death or HFH**

N=5050

Symptomatic chronic HFrEF population:

- EF <45%
- Chronic HF with NYHA class II–IV
- Receiving HF SOC*
- Prior HFH within 6 months or outpatient IV diuretic for HF within 3 months
- Elevated natriuretic peptides
- SBP ≥100 mmHg
- eGFR ≥15 ml/min/1.73 m^2

Randomised, double-blind

1:1

2.5 mg od → 5 mg od → 10 mg od

Vericiguat

Up-titration at 2-week intervals

Placebo

Event-driven study duration
Median follow-up: 10.8 months

Primary endpoint: Time to first occurrence of composite of CV death or HFH

Secondary endpoints:

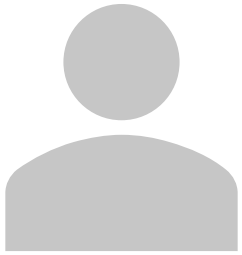
- Time to CV death
- Time to first HFH
- Time to total (first and recurrent) HFHs
- Time to total first occurrence of composite of all-cause mortality or HFH
- Time to all-cause mortality
- Safety and tolerability

*Note: all subjects received standard HF treatment following locally relevant guidelines such as ACCF/AHA and ESC Guidelines for the Management of Heart Failure

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FDA, Food and Drug Administration; HF, heart failure; HFH, heart failure hospitalisation; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; od, once daily; NT-proBNP, N-terminal pro B-type natriuretic peptide; QoL, quality of life; SBP, systolic blood pressure.

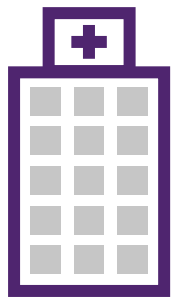
1. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 2. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928.

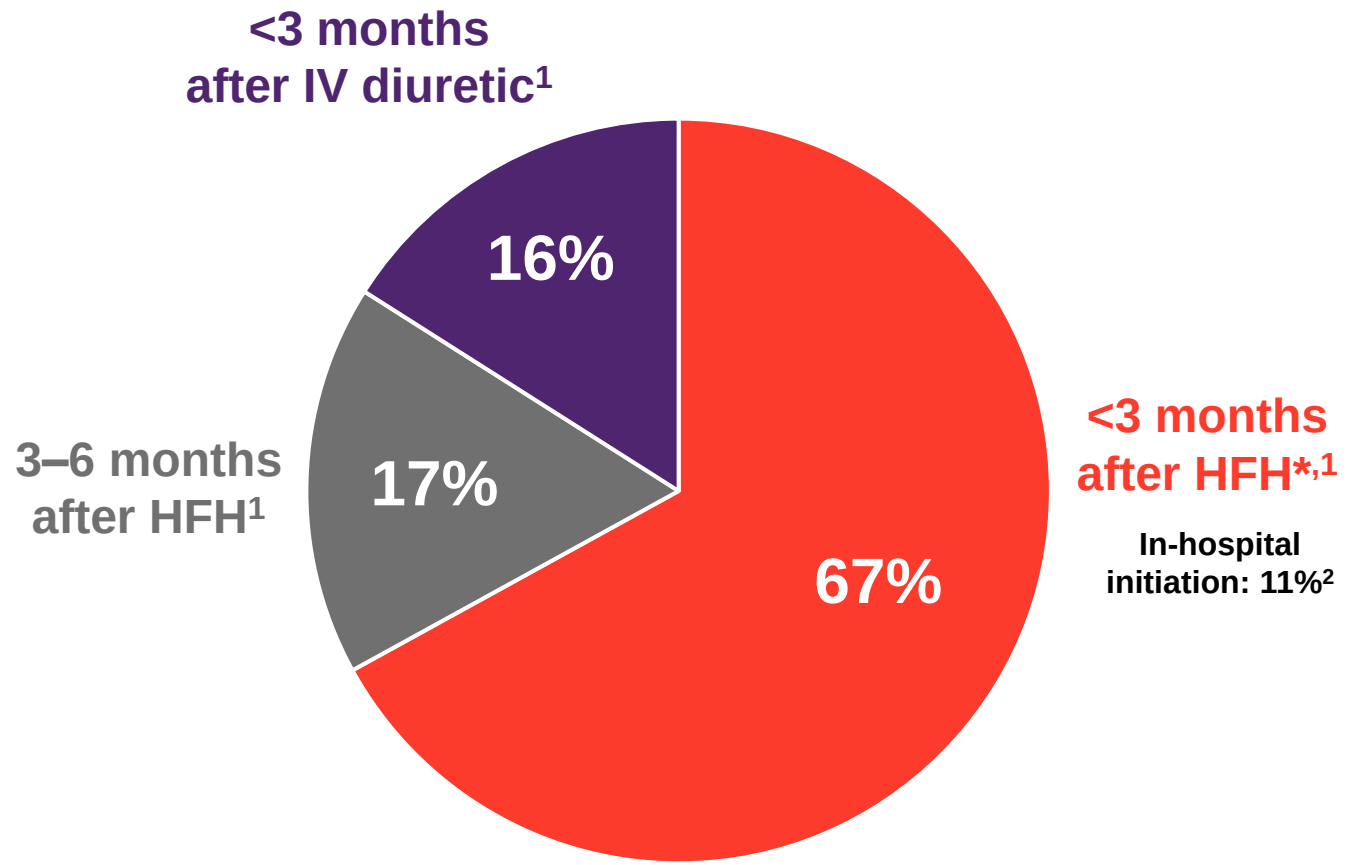
VICTORIA was specifically designed to study patients that recently experienced a worsening HF event



Patients could be enrolled in VICTORIA:

- Up to 6 months after HFH
- Up to 3 months after an episode of worsening HF requiring IV diuretics without hospitalization[1]

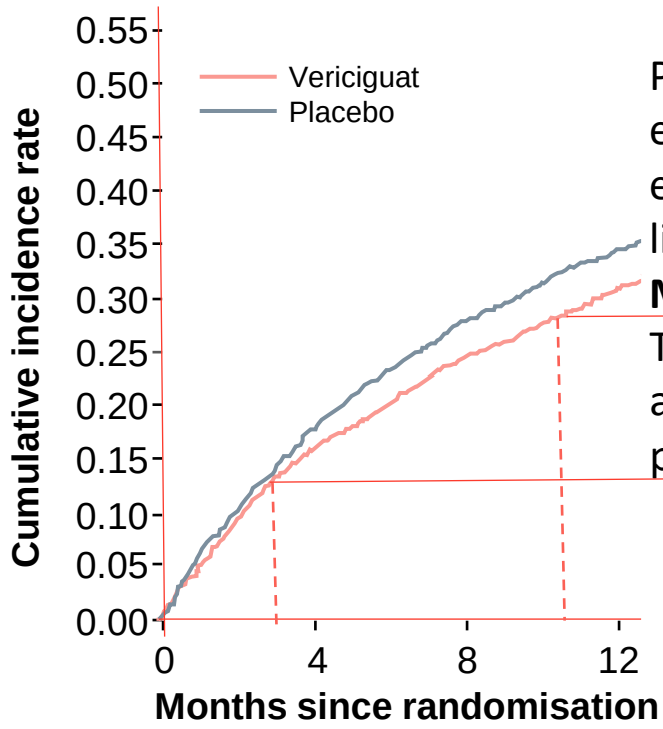




(Armstrong PW et al. N Engl J Med 2020)

Vericiguat reduced primary endpoint by means 4.2% (ARR) in a relatively short exposure time (10.8 months)

Time to CV death or first HFH



Number of subjects at risk				
Vericiguat	2526	2099	1621	1154
Placebo	2524	2053	1555	1097

Prespecified events were accrued earlier than expected, thereby leaving a relatively short exposure time and potentially limitir

Media

The difference favoring vericiguat appeared after approximately **3 months** of treatment and pe

Annual NNT: 24#

ARR: 4.2% per year*

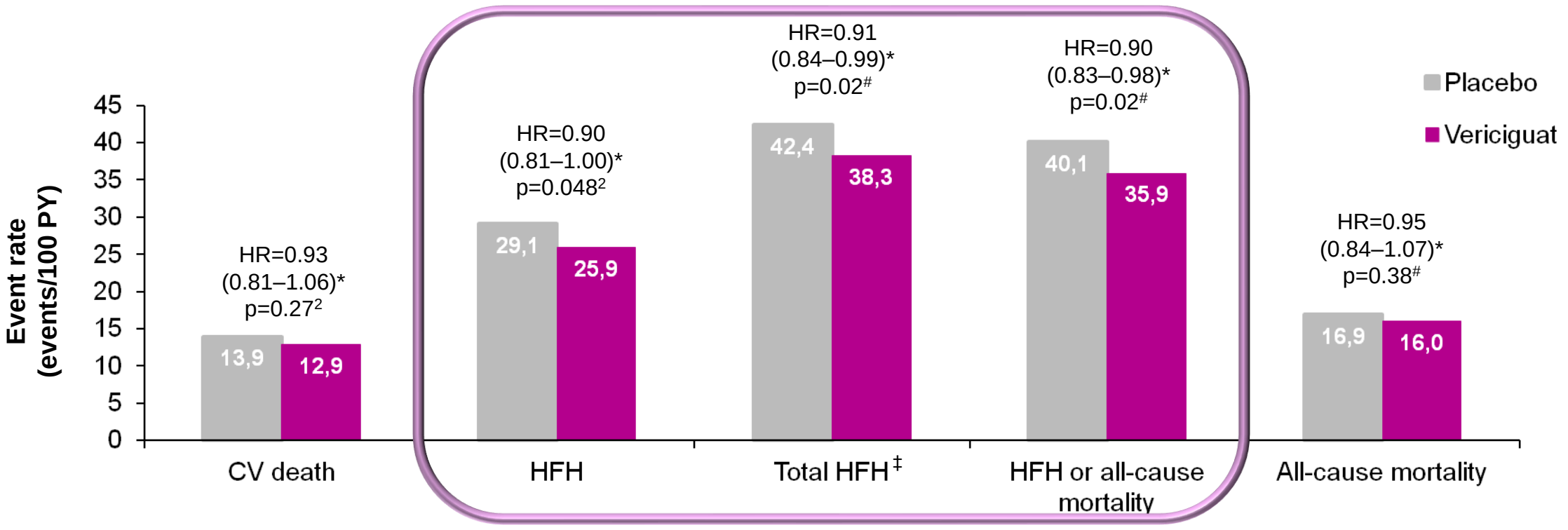
HR=0.90 (95% CI 0.82–0.98)
P=0.02

Annual NNT: 24#

ARR: 4.2% per year*

Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

VICTORIA: Secondary Outcomes[1]



HFH, total HFH and the composite of HFH or all-cause mortality were significantly reduced with vericiguat vs placebo

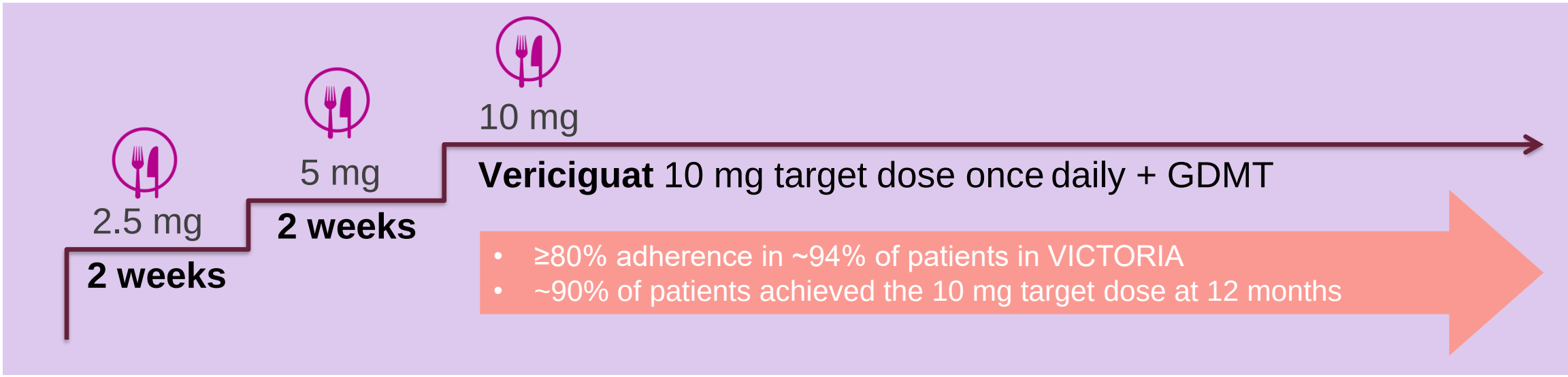
For patients with multiple events, only the first event contributing to the composite endpoint is counted.

*HR (vericiguat over placebo) and 95% CI from Cox proportional hazard model controlling for stratification factors (defined by region and race). [#]From log rank test stratified by the stratification factors defined by region and race. ‡Patients could have been hospitalized more than once. Based on data up to the primary completion date (18 June 2019).

CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; PY, patient-years.

1. Armstrong PW *et al*. *N Engl J Med*. 2020;382:1883–1893; 2. US Food and Drug Administration. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214377Orig1s000IntegratedR.pdf [accessed June 2021].

In VICTORIA, Adherence to the Target Dose of Vericiguat Was High[1]

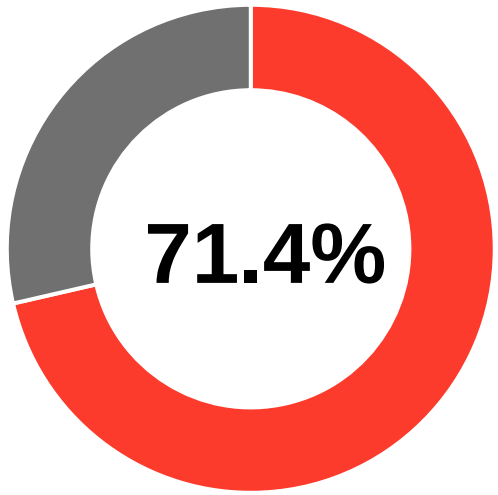


→ One tablet per day with meal/food
→ **Titration guided by evaluation of blood pressure and clinical symptoms**
→ No dosage adjustment for geriatric patients or patients with moderate renal or hepatic impairment

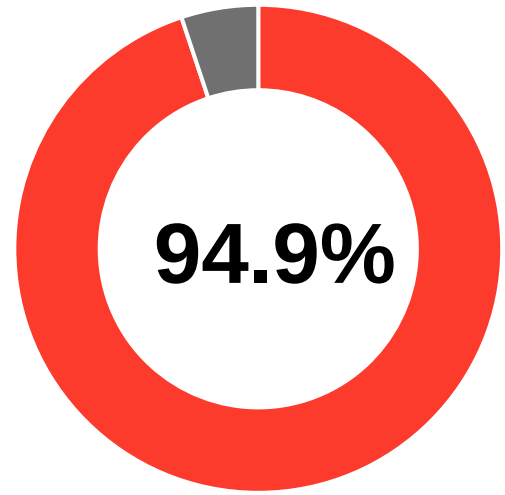
GDMT, guideline-directed medical therapy.
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

The patient population in Q1–3 of VICTORIA reflects most patients seen in clinical practice

Percentage of patients with NT-proBNP ≤5,000 pg/ml following a worsening HF event in two large US databases[1,2]



of **patients hospitalized with a worsening HF event** have **NT-proBNP ≤5,000 pg/ml at discharge***[2]

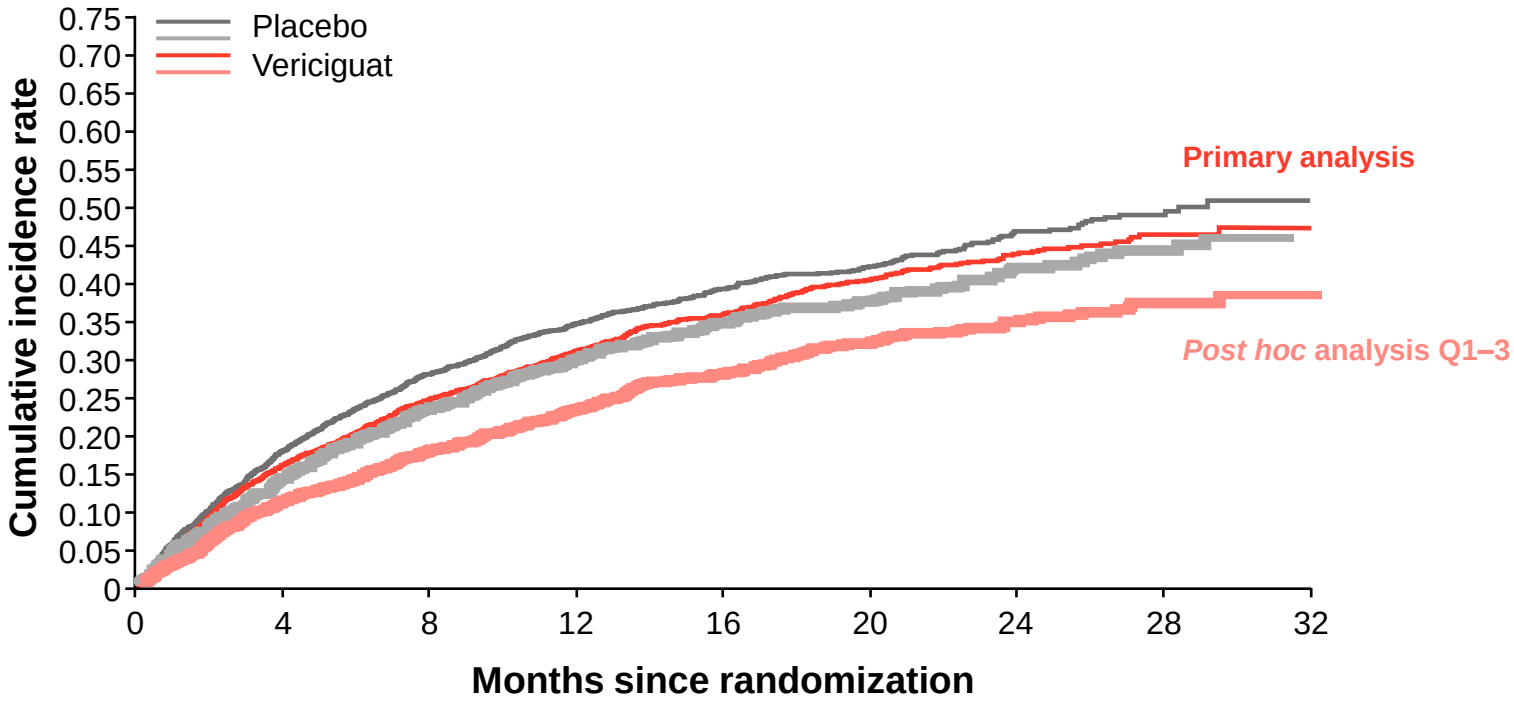


of **outpatients with a previous worsening HF** event have **NT-proBNP ≤5,000 pg/ml**[#1]

(Armstrong PW et al. N Engl J Med 2020)

A *post hoc* analysis showed even greater benefit of vericiguat in patients most frequently seen in clinical practice

Time to primary endpoint in NT-proBNP groups Q1–3 (≤5,314 pg/ml) *vs* entire VICTORIA population[1,2]



VICTORIA population
HR=0.90 (95% CI 0.82–0.98); p=0.02
ARR=4.2 events/100 PY
Annual NNT=24*

Baseline NT-proBNP Q1–3
HR=0.78 (95% CI 0.69–0.88); p<0.001
ARR=7.2 events/100 PY
Annual NNT=14*

Number of patients at risk

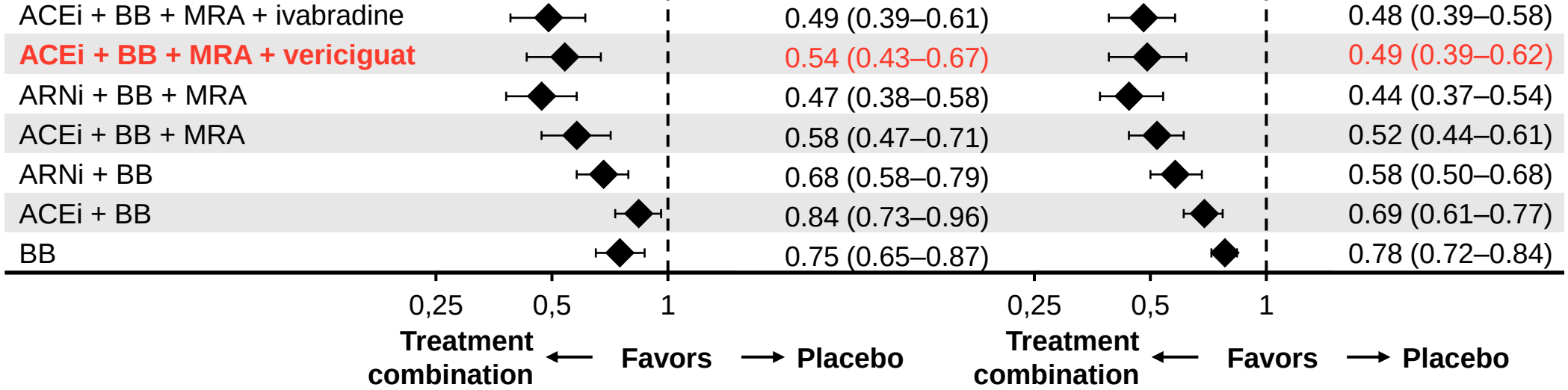
VICTORIA	Vericiguat	2,526	2,099	1,621	1,154	826	577	348	125	1
	Placebo	2,524	2,053	1,555	1,097	772	559	324	110	0
Q1–Q3	Vericiguat	1,798	1,586	1,268	919	658	472	290	105	1
	Placebo	1,806	1,540	1,192	839	604	435	261	89	0

(Armstrong PW et al. N Engl J Med 2020)

In combination with other HF therapies, vericiguat substantially improves CV outcomes

CV outcomes according to treatment combination in a large network meta-analysis (N=95,444)[1]

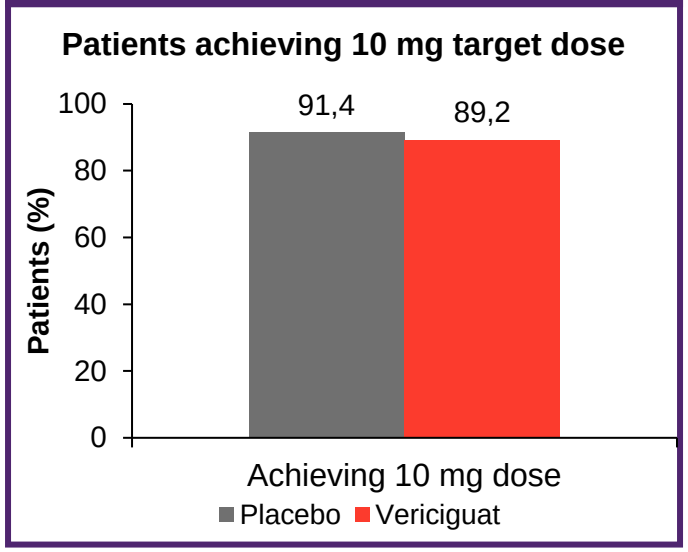
Treatment combination	CV death or HFH	HR (95% CI)	All-cause mortality	HR (95% CI)
ARNi + BB + MRA + SGLT2i		0.36 (0.29–0.46)		0.39 (0.31–0.49)
ARNi + BB + MRA + vericiguat		0.43 (0.34–0.55)		0.41 (0.32–0.53)
ARNi + BB + MRA + omecamtiv		0.44 (0.35–0.56)		0.44 (0.36–0.55)
ACEi + BB + MRA + ivabradine		0.49 (0.39–0.61)		0.48 (0.39–0.58)
ACEi + BB + MRA + vericiguat		0.54 (0.43–0.67)		0.49 (0.39–0.62)
ARNi + BB + MRA		0.47 (0.38–0.58)		0.44 (0.37–0.54)
ACEi + BB + MRA		0.58 (0.47–0.71)		0.52 (0.44–0.61)
ARNi + BB		0.68 (0.58–0.79)		0.58 (0.50–0.68)
ACEi + BB		0.84 (0.73–0.96)		0.69 (0.61–0.77)
BB		0.75 (0.65–0.87)		0.78 (0.72–0.84)



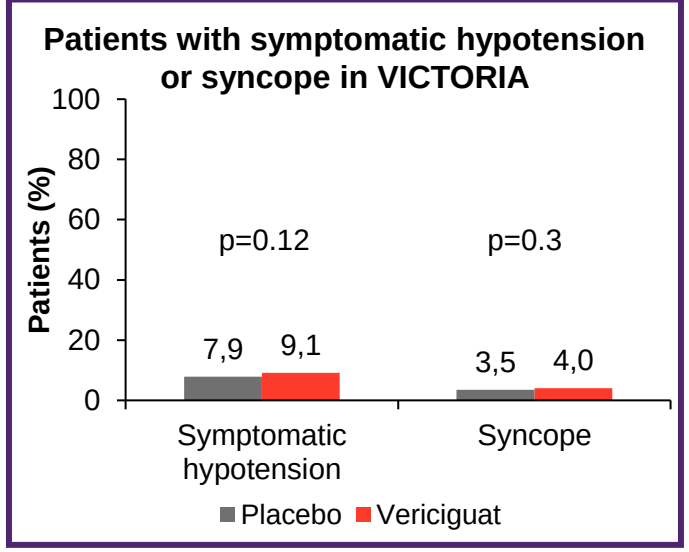
(Tromp *et al.* 2022)

Vericiguat has a favorable safety profile

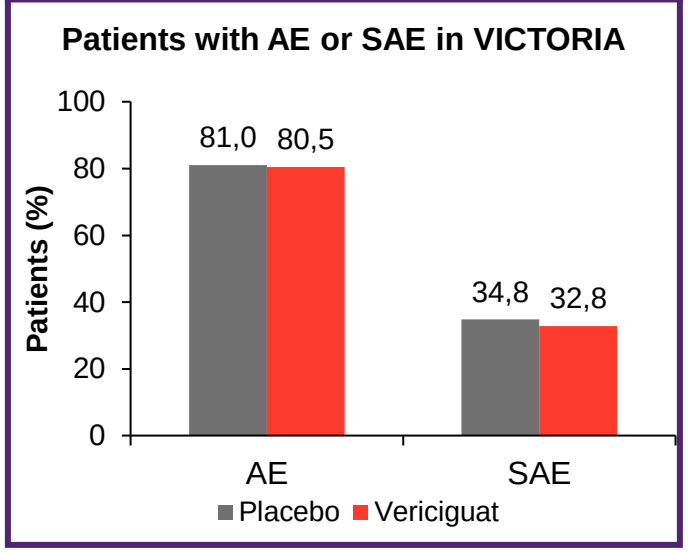
In VICTORIA, **~90%** of patients achieved the target dose of 10 mg of vericiguat after ~12 months[1]



No significant difference in symptomatic hypotension or syncope[1,2]



The rates of AEs and SAEs were numerically lower with vericiguat compared with placebo[1]



(Armstrong PW et al. N Engl J Med 2020)

VERICIGUAT is specifically recommended for worsening HF in ESC 2021 guidelines

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

Vericiguat was included in the guidelines before EU approval

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

Vericiguat is listed among the **disease-modifying drugs** due to the VICTORIA results

(McDonagh TA et al. Eur Heart J 2021)

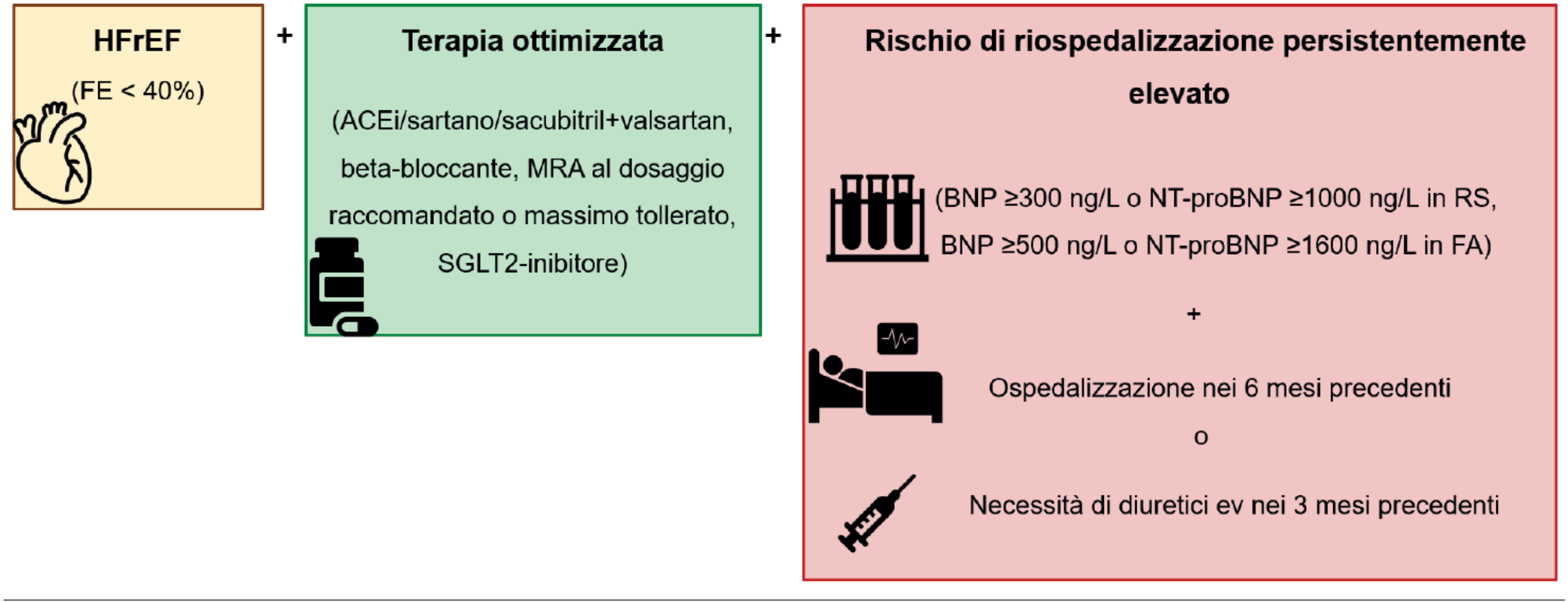
7.3.9.3. Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators

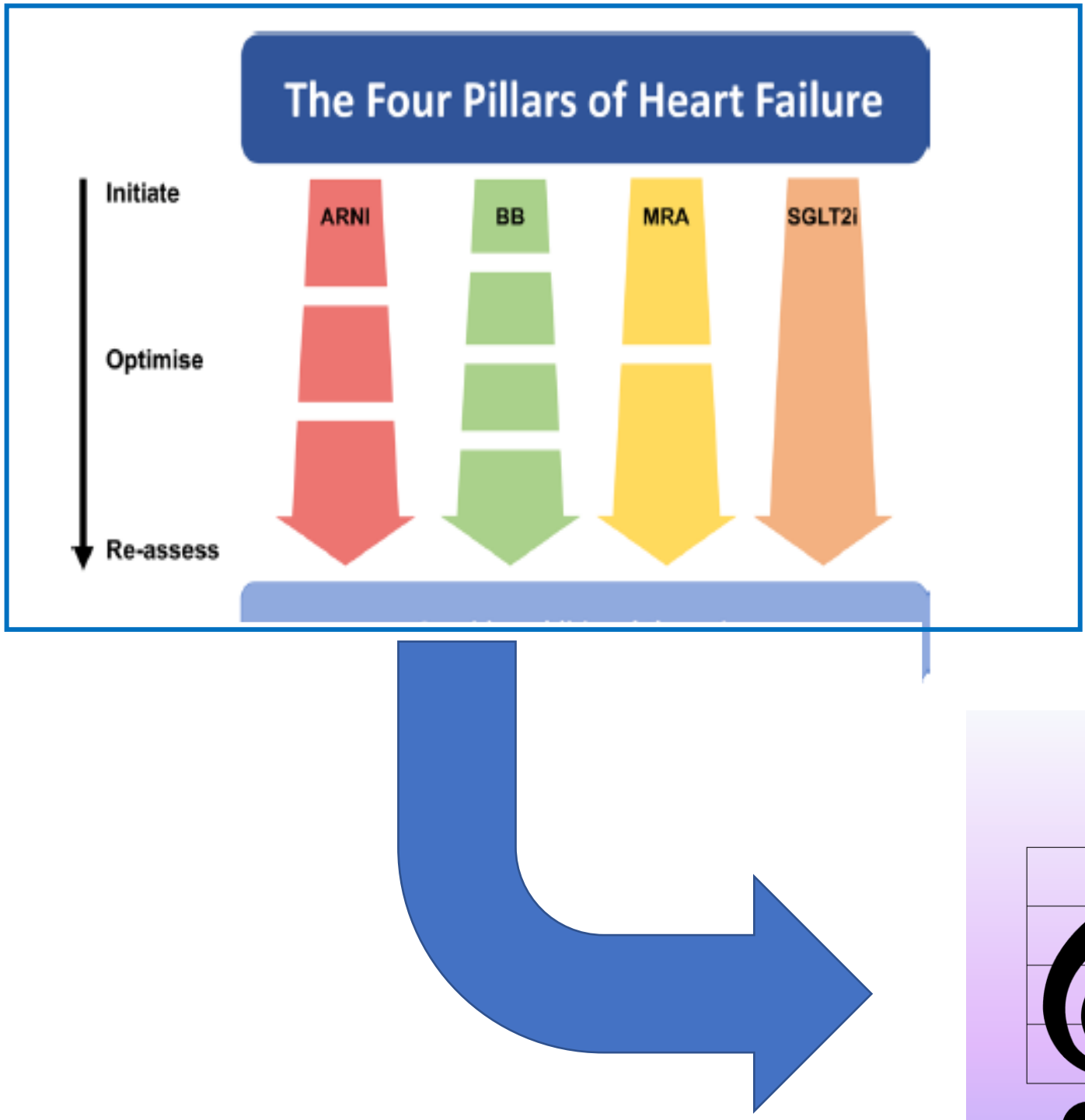
Recommendation for Pharmacological Treatment for Stage C HFrEF: Soluble Guanylyl Cyclase Stimulators
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

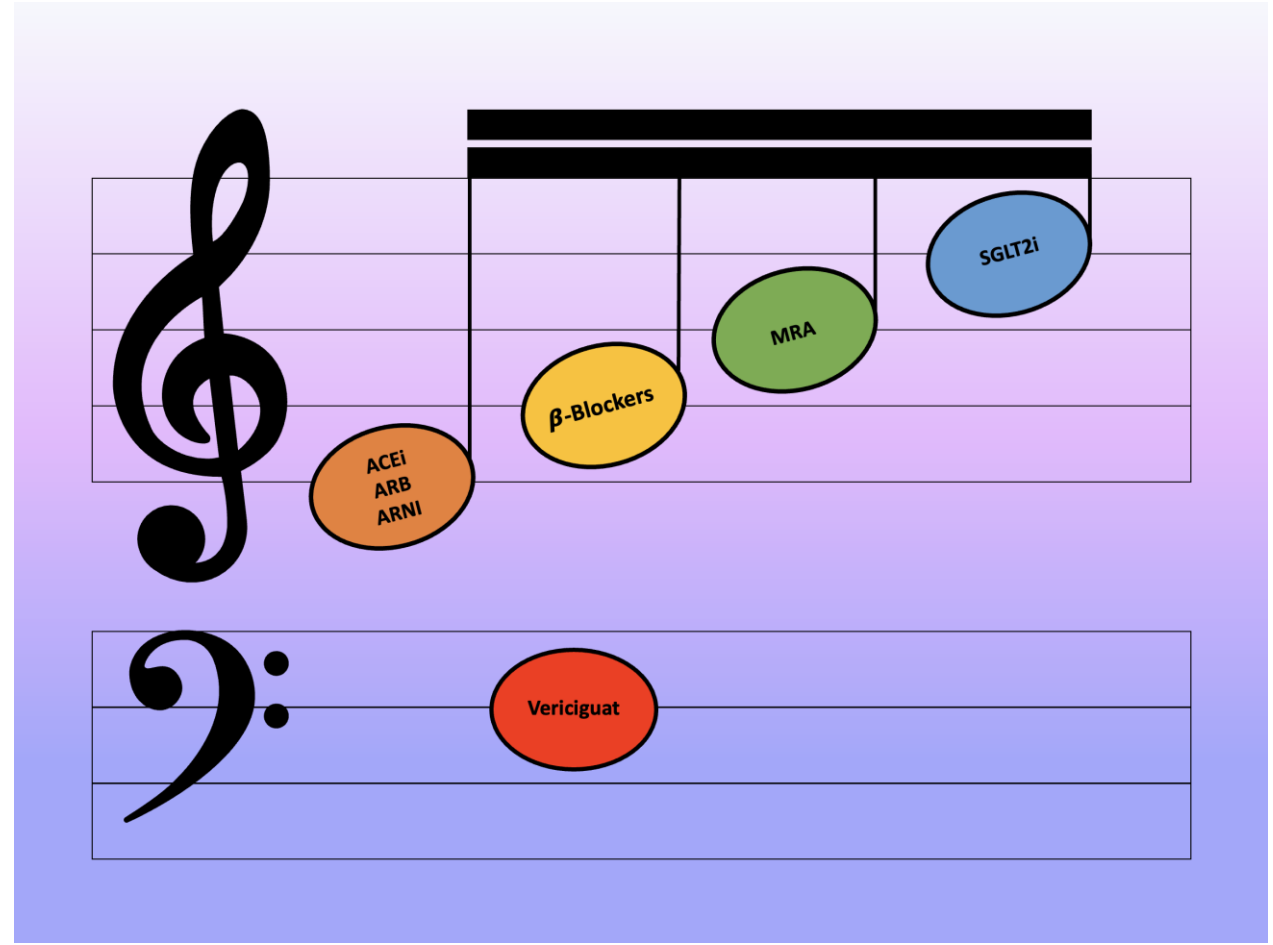
COR	LOE	Recommendation
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.[1]

Position paper ANMCO: Impiego di vericiguat nello scompenso cardiaco: dalle evidenze al posizionamento terapeutico

Stefania Angela Di Fusco[1], Alessandro Alonzo[1], Alberto Aimo[2], Andrea Matteucci[1], Rita Cristina Myriam Intravaia[3], Stefano Aquilani[1], Manlio Cipriani[4], Leonardo De Luca[5], Alessandro Navazio[6], Serafina Valente[7], Michele Massimo Gulizia[8], Domenico Gabrielli[5,9], Fabrizio Oliva[10], Furio Colivicchi[1]







Falco L, Masarone D, Pacileo G, et al. Vericiguat: The Fifth Harmony of Heart Failure with Reduced Ejection Fraction.
***J. Cardiovasc. Dev. Dis.* 2023, *10*, 388.**


thank you
danke
謝謝
gracias
merci
obrigado
dziękuję
teşekkür ederim
go raibh maith agat
ngiyabonga
рахмат
спасибо
Баярлалаа
faafetai lava
kiitos
dankie
nanni
nandri
dhanyavad
hvala
mauruuru
köszönöm
gracie
bayarlalaa
enkosi
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
хвала
asante
manana
obrigada
tenki
murakoze
djiere dieuf
tau
mochchakkeram
mamnun
дякую
akun
dankon
ačiū
spas
welalin
tack
barka
mersi
kia ora
chnorakaloutioun
gratias ago
grácies
sulpáy
sukriya
kop khun krap
taiku
sagolun
sobodi
dēkuji
mèsi
didi madloba
kam sah hamnida
rahmat
তোমাকে ধন্যবাদ
감사합니다
najis tuke
ありがとう
terima kasih
tanemirt
rahmet
grazie
xiexie
ευχαριστώ
arigatô
takk
dakujem
trugarez
dhanyavadagalu
diolch
shukriya
merce
мерси