Verquvo training module 5

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Recap

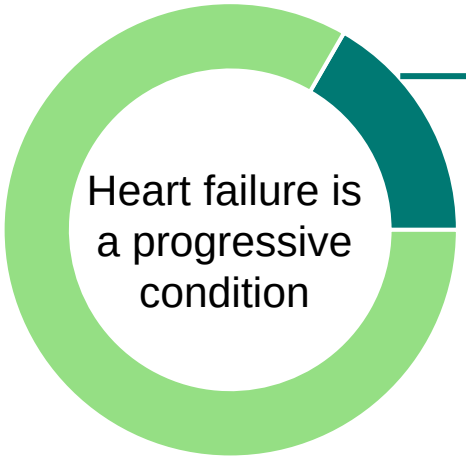
Define worsening heart failure(WHF)?

Why does WHF represent an area of high unmet need?

What is the MOA of vericiguat?

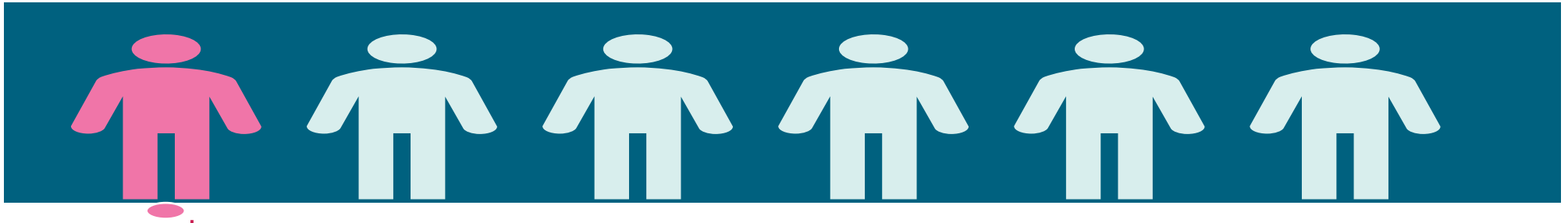
What is the PK-PD profile of vericiguat?

Despite a period of stabilization, patients with HFrEF may experience a worsening HF event



Worsening chronic HF is characterized by:[1-3]

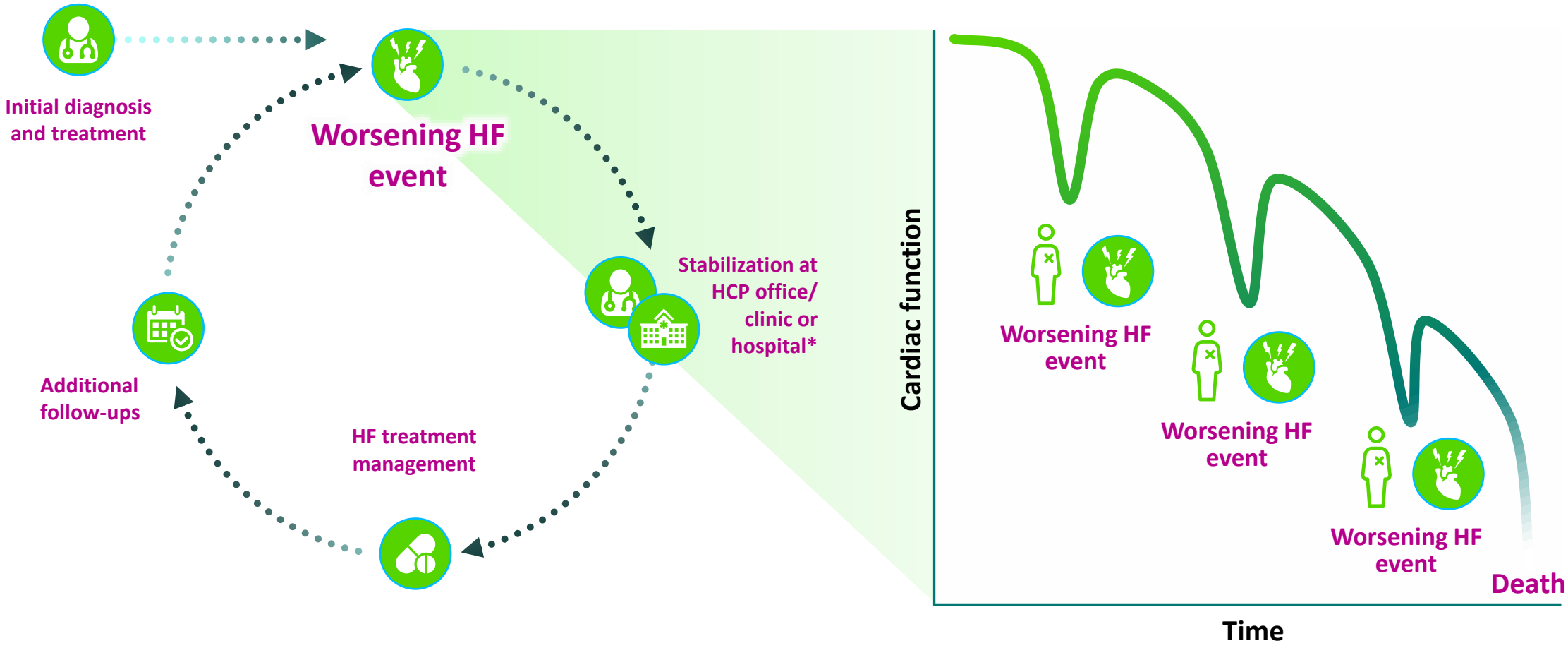
- Development of progressively **escalating signs and symptoms of HF** requiring intensification of therapy
- Experience of a prior worsening HF event:
  - Need for IV diuretics, regardless of setting
  - HF hospitalisation
  - Need for an urgent HF visit



In a real-world study linking registry and claims data of >11,000 patients with HFrEF, 1 in 6 patients developed worsening HF* within 18 months of initial diagnosis[1]

*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 hospitalised setting.
HF, heart failure; HFrEF, heart failure with reduced ejection fraction.
1. Butler J, et al. *J Am Coll Cardiol*. 2019;73(8):935-944. 2. Greene SJ, et al. *JAMA Cardiol*. 2018;3(3):252-259. 3. EMA CPMP/EWP/235/95, Rev.2. Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. 20 July 2017. Accessed July 23, 2019.

Patients with HF can progressively worsen over time[1,2]



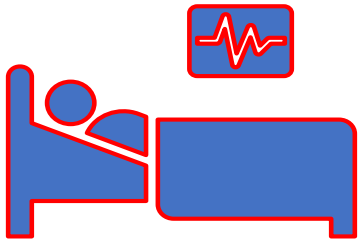
Adapted from Gheorghiade et al. *Am J Cardiol*, 2005 and Cowie et al. *ESC Heart Fail,* 2014.
*Adjustment of and potential addition to current therapy.
HCP=health care provider; HF=heart failure.
1. Gheorghiade M et al. *Am J Cardiol*. 2005;96(6A):11G-17G. 2. Cowie MR et al. *ESC Heart Fail*. 2014;1(2):110-145.

Vericiguat

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

Despite GDMT, patients remain at risk of CV death and HFH[1–4] Worsening heart failure represents an area of high unmet need

Chronic worsening HF accounts for ~80% of HFH cases[6]



1 in 2 patients will be hospitalized again within 30 days of their worsening HF event[5]

1 in 5 patients will die within 2 years of their worsening HF event[5]

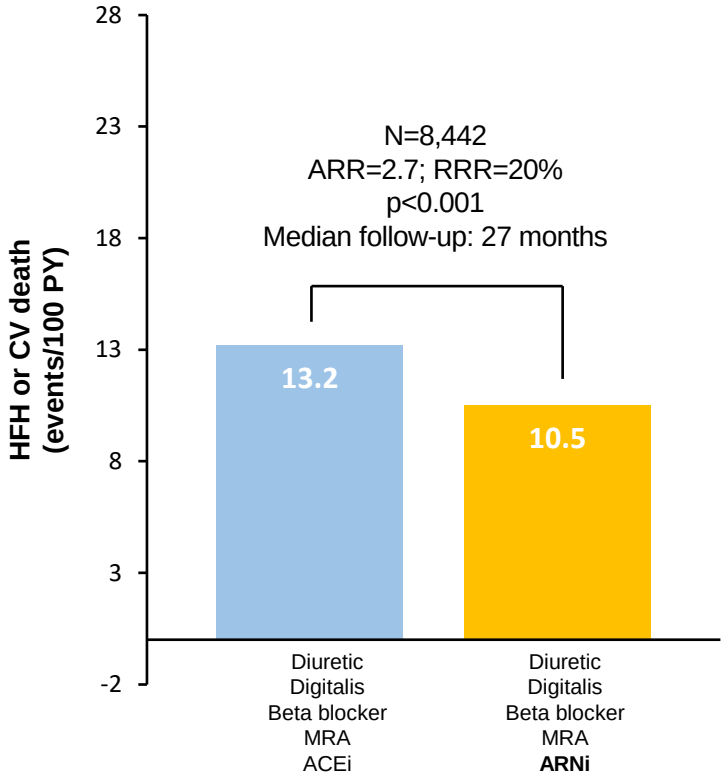
Optimisation of existing treatment and new options are required for patients following worsening HF events[5]

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

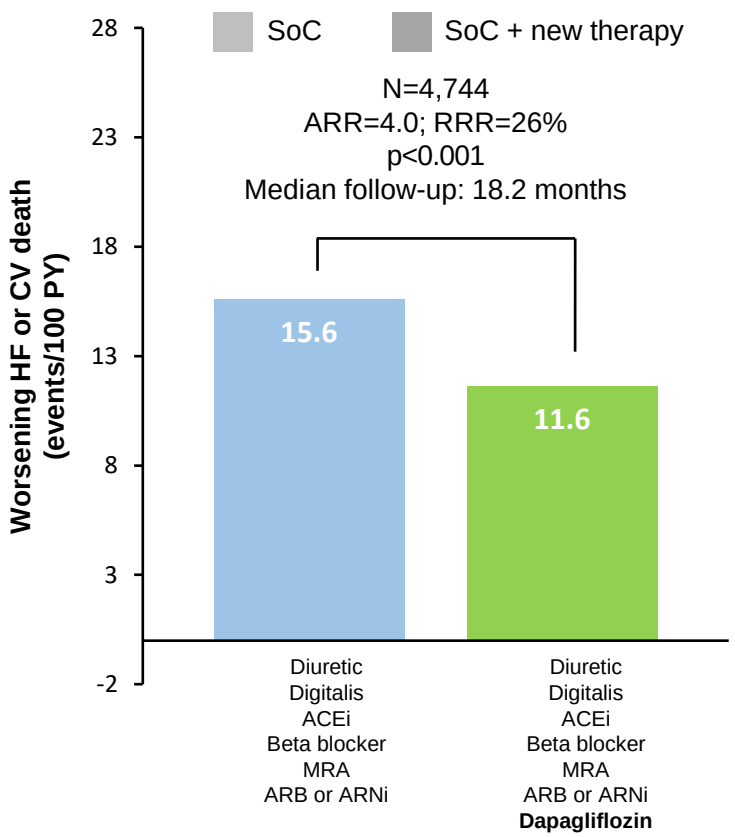
1. McMurray JJV et al. *N Engl J Med*. 2014;371:993–1004; 2. McMurray JJV et al. *N Engl J Med*. 2019;381:1995–2008; 3. Packer M et al. *N Engl J Med*. 2020;383:1413–1424; 4. Teerlink JR et al. *N Engl J Med*. 2021;384:105–116; 5. Butler J et al. *J Am Coll Cardiol*. 2019;73:935–944; 6. Gheorghiade M et al. *J Am Coll Cardiol.* 2013;61:391–403.

Despite improved outcomes with contemporary therapy in patients with HFrEF, significant residual risk remains[1–4]

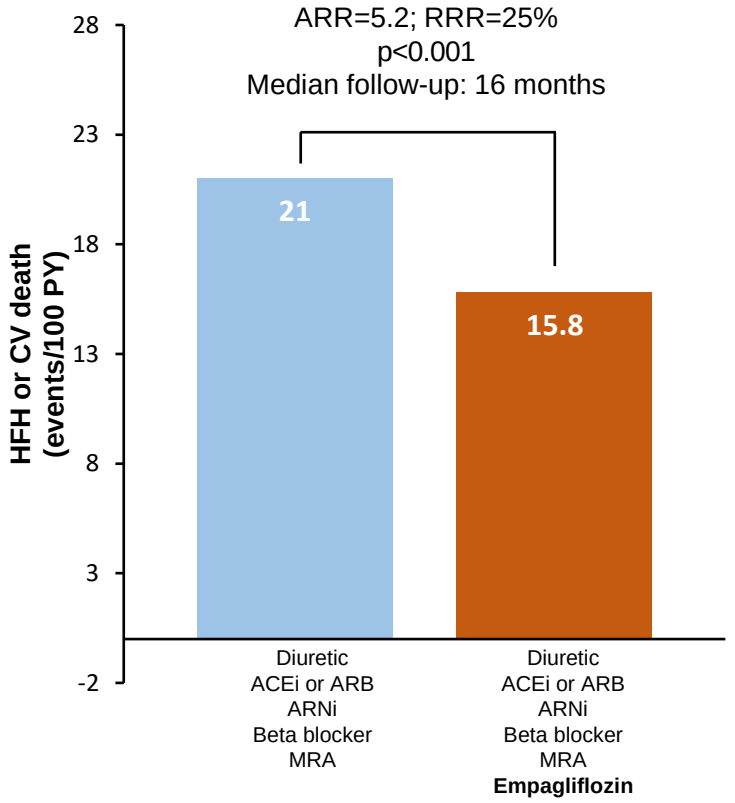
PARADIGM-HF (2014)[1,2]



DAPA-HF (2019)[2,3]



EMPEROR-Reduced (2020)[2,4]

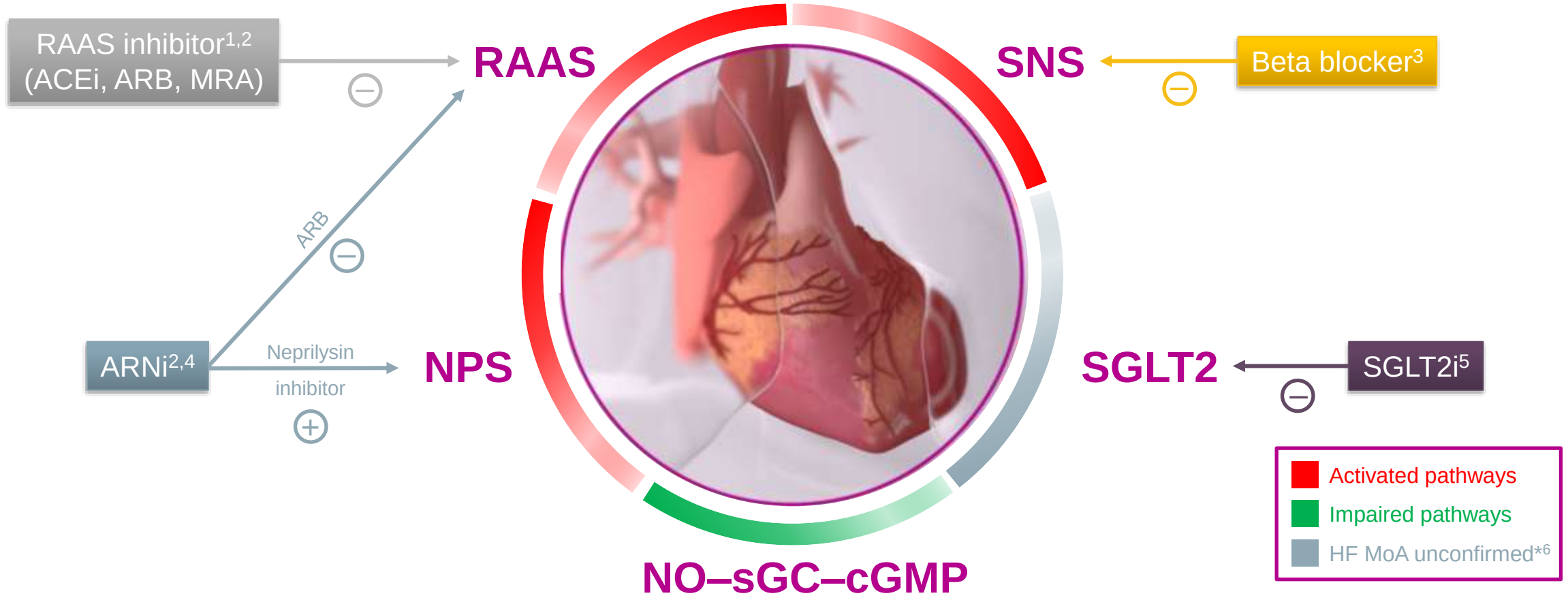


Major medical therapies listed. Each HF study was conducted independently, and no head-to-head HF studies have been completed that allow for direct comparisons.

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 JJV *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 JJV *et al. N Engl J Med* 2019;381:1995–2008; **4.** Packer M *et al. N Engl J Med* 2020;383:1413–1424.

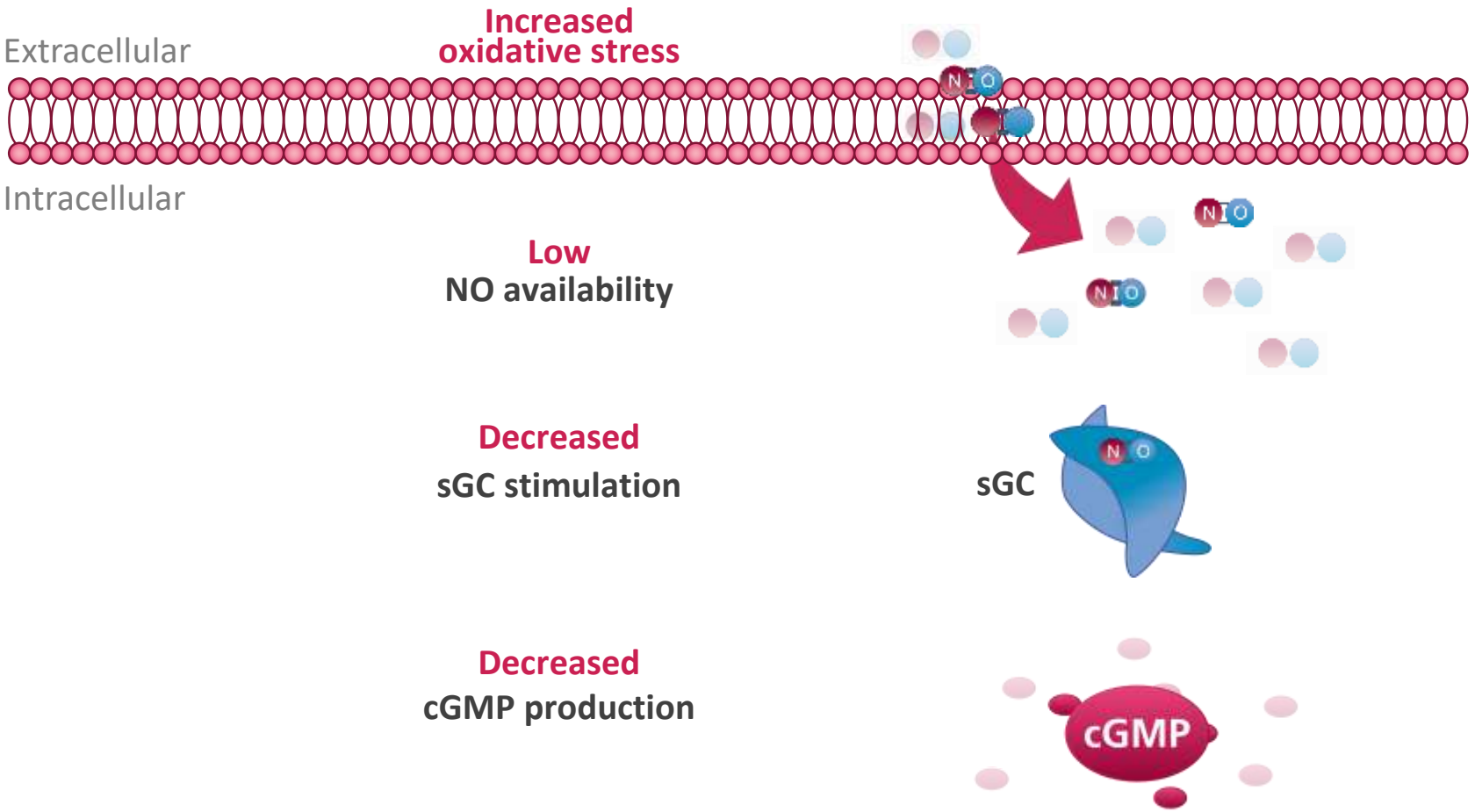
Current Therapies Target Established Activated Pathways[1–6]



*The mechanism(s) by which SGLT2is mediate their cardioprotective effects is unclear but there are several postulated mechanisms which include improving hemodynamics, controlling sympathetic stimulation, inhibiting fibrosis and cardiac remodelling, improving cardiac efficiency and output, modulating the overall cytosolic sodium and calcium concentrations, and altering the adipokine levels.[6] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; cGMP, cyclic guanosine monophosphate; HF, heart failure; MoA, mechanism of action; MRA, mineralocorticoid receptor antagonist; NO, nitric oxide; NPS, natriuretic peptide system; RAAS, renin–angiotensin–aldosterone system; sGC, soluble guanylate cyclase; SGLT2, sodium–glucose cotransporter 2; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SNS, sympathetic nervous system.

1. Mann DL *et al*. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 10th edn. Philadelphia, PA: Elsevier/Saunders; 2015; 2. Yancy CW *et al*. *J Am Coll Cardiol* 2017; 70:776–803; 3. Triposkiadis F *et al*. *J Am Coll Cardiol* 2009;54:1747–1762; 4. Ponikowski P *et al*. *Eur J Heart Fail* 2016;18:891–975; 5. Matsumura K & Sugiura T. *Cardiovasc Ultrasound* 2019;17:26; 6. Nightingale B. *Cardiol Res* 2021;12:60–66.

In HF, the NO-sGC-cGMP pathway is medically unaddressed[1-4]



Clinical Effects of an Impaired NO-sGC-cGMP Pathway[1]

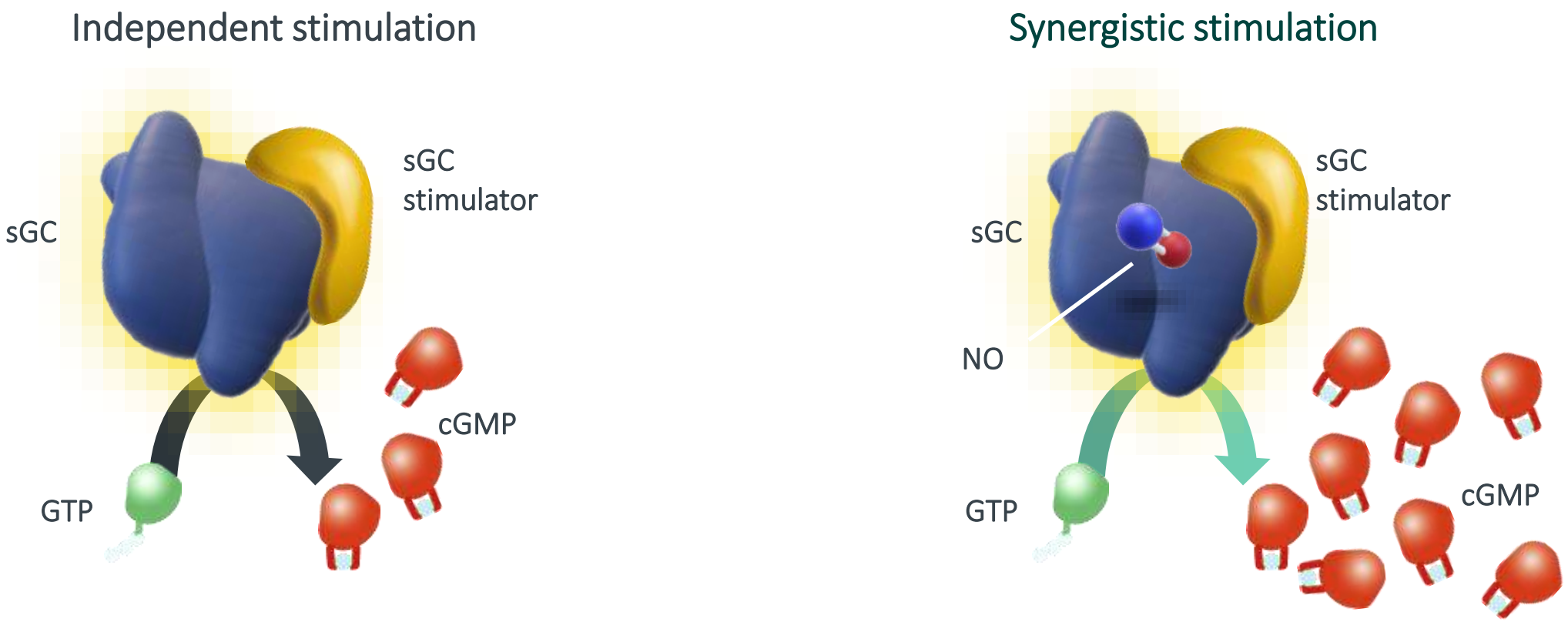
- ↓ Myocardial function
- ↑ Left-ventricular remodelling
- ↓ Vascular function
- ↑ Fibrosis
- ↑ Inflammation

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. Borbély A, et al. *Circ Res*. 2009;104(6):780-786.

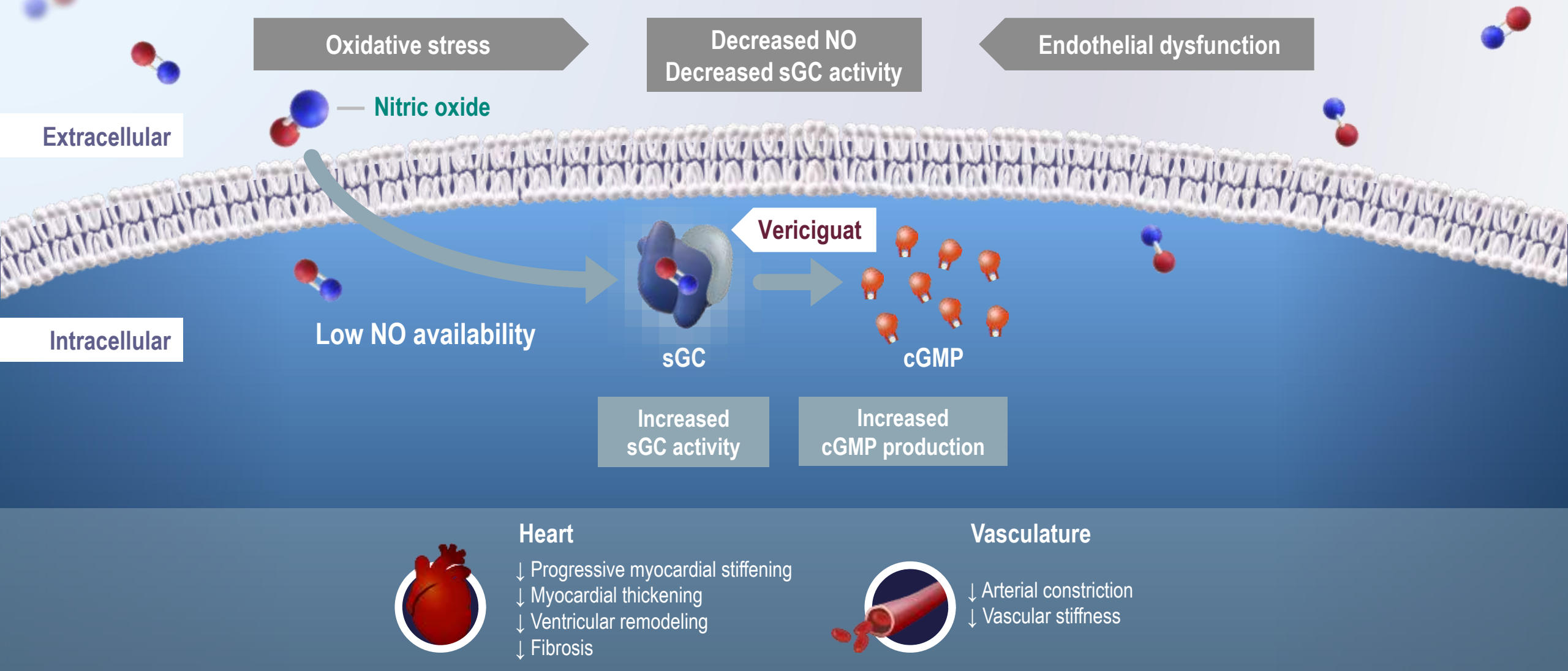
sGC Stimulators Can Act Independently From or Synergistically With NO[1,2]



cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylate cyclase.

1. Follmann M et al. *Angew Chem Int Ed Engl*. 2013;52:9442–9462; 2. Sandner P. *Biol Chem*. 2018;399:679–690.

Vericiguat has a unique MOA it increases sGC activity to improve myocardial and vascular function[1–8]



Heart

- ↓ Progressive myocardial stiffening
- ↓ Myocardial thickening
- ↓ Ventricular remodeling
- ↓ Fibrosis

Vasculature

- ↓ Arterial constriction
- ↓ Vascular stiffness

cGMP, cyclic guanosine monophosphate; HF, heart failure; MoA, mechanism of action; NO, nitric oxide; sGC, soluble guanylate cyclase.

1. Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123. 2. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Elsevier/Saunders; 2015. 3. Boerrigter G et al. *Handb Exp Pharmacol.* 2009;191:485. 4. Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225. 5. Felker G & Mann D. *Heart Failure: A Companion to Braunwald's Heart Disease*. Elsevier; 2020. 6. Armstrong PW et al. *JACC Heart Fail*. 2018;6:96; 7. Follmann M et al. *J Med Chem* 2017;60:5146; 8. Mathar I et al. *Circulation.* 2018;138:A15553.

Vericiguat pharmacodynamic and pharmacokinetics

ADME Profile	
Absorption	• Rapidly absorbed[3] – 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 dose[3]
Distribution	• Mainly in plasma[3]
Metabolism	• N-glucuronidation (major metabolic pathway); 9.0% in urine as vericiguat[1]
Elimination	• Clears from plasma in t1/2 ~20 hours[3] • Balanced in urine (53.1%) and feces (45.2%)[1]

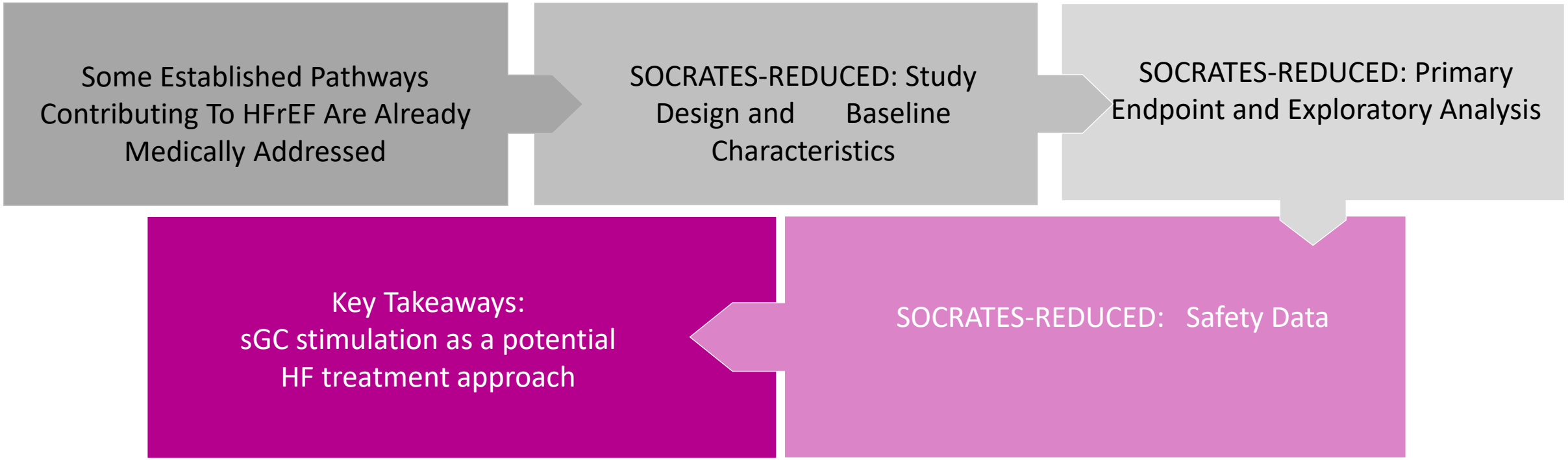
Co-medication	Effect on PK/PD[1,2]
Sacubitril/valsartan	• **No clinically relevant** PK/PD interaction[2]
Warfarin and aspirin[2]	• **No clinically relevant** PK/PD interaction • No dose adjustment of warfarin • No dose adjustment of aspirin
Nitrates [5,6]	• **No significant effect** on BP or HR with SL nitrates (VENICE study) • **No significant effect** on BP or HR with concomitant long-acting nitrates (VISOR study)
Effect of vericiguat on PK (digoxin; midazolam)[1]	• **No clinically relevant** PK interaction • No dose adjustment of digoxin • No dose adjustment of co-medications metabolized by CYP3A4
Effect of PK on vericiguat (ketoconazole, rifampicin, mefenamic acid)[1]	• **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.

Early clinical development of Vericiguat



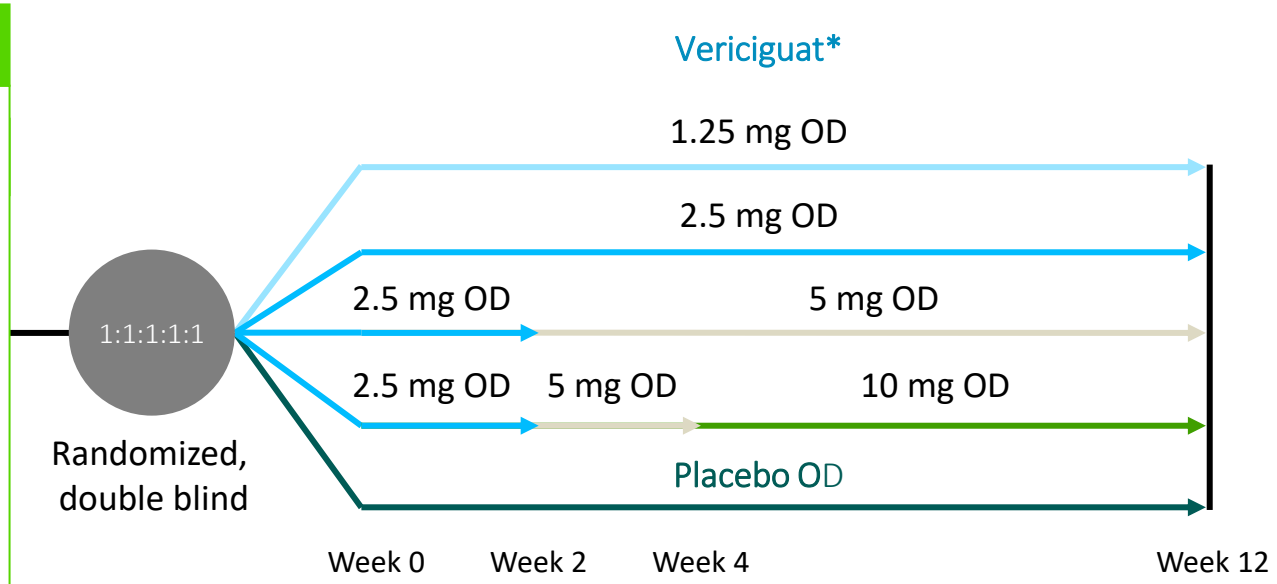
Section 3: Phase II SOCRATES-REDUCED Study

SOCRATES-REDUCED: Study Design

N=456

Patient population:

- LVEF <45%
- NYHA class II-IV
- Worsening chronic HF requiring hospitalization or IV diuretic treatment for HF without hospitalization
- NT-proBNP ≥1000 or BNP ≥300 (SR)
- NT-proBNP ≥1600 or BNP ≥500 (AF)
- eGFR ≥30 mL/min/1.73 m^2



Primary endpoint†:
Change from baseline to Week 12 in log-transformed NT-proBNP of the pooled vericiguat (2.5/5/10 mg) vs the placebo group

Secondary endpoints:
Safety and tolerability and PK/PD

Select exploratory endpoints:

- Clinical outcomes (CV death, recurrent hospitalization for worsening HF, nonhospitalized worsening HF)
- Echocardiography parameters (LVEF, LVEDV, LVESV)

*The 4 vericiguat treatment groups targeted a maximal dose of 1.25 mg, 2.5 mg, 5 mg, and 10 mg daily. All active treatment groups except the 1.25-mg OD group started with 2.5 mg OD at randomization (visit 1). Study protocol specified up-titration (ie, dose doubling) or sham titration of dose at week 2 (visit 2) and week 4 (visit 3) after randomization. †Secondary analyses of the primary endpoint were prespecified to investigate a dose-response relationship by linear regression model.

AF=atrial fibrillation; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HFH=heart failure hospitalization; HFrEF=heart failure with reduced ejection fraction; IV=intravenous; LVEDV=left ventricular end-diastolic volume; LVEF=left ventricular ejection fraction; LVESV=left ventricular end-systolic volume; NP=natriuretic peptide; NT-proBNP=N-terminal pro-B type natriuretic peptide; NYHA=New York Heart Association; PD=pharmacodynamic; PK=pharmacokinetic; PRO=patient-reported outcome; OD=once daily; SR=sinus rhythm.

1. Pieske B et al. *Eur J Heart Fail*. 2014;16(9):1026-1038. 2. Gheorghiade M et al. *JAMA*. 2015;314(21):2251-2262.

Vericiguat

SOCRATES-REDUCED: Baseline Characteristics

		Vericiguat			
	Placebo (n=92)	**1.25 mg (n=91)**	**2.5 mg (n=91)**	**2.5 to 5 mg (n=91)**	**2.5 to 10 mg (n=91)**
Age (years, mean)	67	68	68	67	69
NT-proBNP (pg/mL, median)	4043	3670	2721	2644	2805
Hospitalization/IV diuretic for HF (%)	77/23	79/21	84/17	75/25	75/25
LVEF (%, mean)	28.6	29.5	29.2	31.5	29.3
Systolic blood pressure (mmHg, mean)	124	126	125	125	128
Atrial fibrillation (%)	33	35	33	33	35
Diabetes mellitus (%)	45	40	59	43	54
Chronic kidney disease (%)	41	39	45	41	39
Hypertension (%)	76	78	77	75	86

HF=heart failure; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal pro-B type natriuretic peptide.
Gheorghiade M et al. JAMA. 2015;314(21):2251-2262.

Vericiguat

SOCRATES-REDUCED: Baseline Characteristics (cont'd)

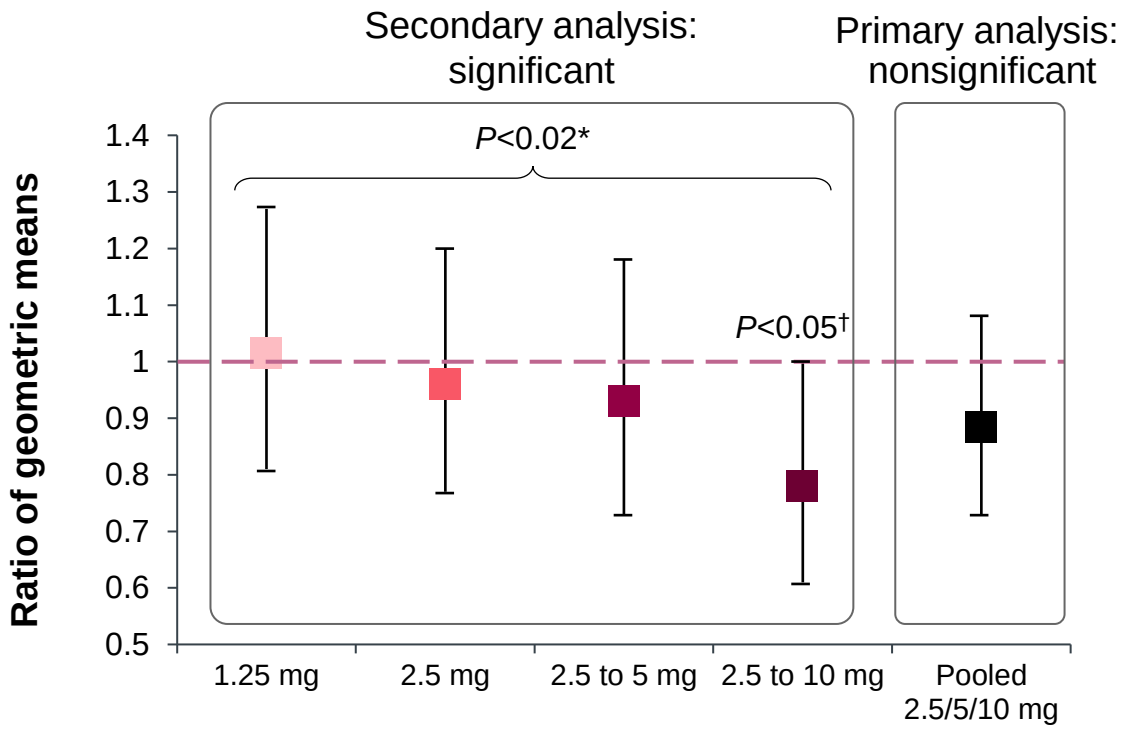
		Vericiguat			
	Placebo (n=92)	1.25 mg (n=91)	2.5 mg (n=91)	2.5 to 5 mg (n=91)	2.5 to 10 mg (n=91)
Initial worsening CHF presentation, n (%)					
Time from stabilization to R, days (mean ± SD)	15.0 ± 9.9	14.8 ± 9.7	15.0 ± 9.5	14.3 ± 8.9	13.0 ± 10.8
Ischemic HF etiology, n (%)	51 (55.4)	46 (50.5)	57 (62.6)	42 (46.2)	46 (50.5)
Hospitalization	71 (77.2)	72 (79.1)	76 (83.5)	68 (74.7)	68 (74.7)
IV diuretic	21 (22.8)	19 (20.9)	15 (16.5)	23 (25.3)	23 (25.3)
NYHA class at baseline, n (%)					
I/II	54 (58.7)	44 (48.4)	47 (51.7)	44 (48.4)	51 (56.0)
III/IV	38 (41.3)	47 (51.6)	44 (48.4)	47 (51.7)	40 (44.0)

HF=heart failure; IV=intravenous; NYHA=New York Heart Association; R=randomization; SD=standard deviation.

Gheorghiade M et al. JAMA. 2015;314(21):2251-2262.

SOCRATES-REDUCED: Primary Endpoint

Primary Endpoint:
Change From Baseline of NT-proBNP at 12 weeks



There was no statistically significant difference on change in NT-proBNP in the pooled 2.5/5/10 mg vericiguat dose arms compared to placebo (*P*=0.15) at 12 weeks

In the secondary exploratory analysis to assess optimal dose for phase 3 studies:

- Higher vericiguat doses were associated with greater reductions in NT-proBNP level (*P*<0.02), which suggests a dose-response relationship
- The 10-mg arm demonstrated greater reductions in NT-proBNP compared to placebo at week 12 (*P*=0.048)

Error bars indicate 90% confidence intervals. *Exploratory analysis of decreasing slope among vericiguat dose groups. †Exploratory pairwise comparison of 10-mg target dose group with placebo; 1-sided test.
NT-proBNP=N-terminal pro-B type natriuretic peptide.
Gheorghiade M et al. *JAMA*. 2015;314(21):2251-2262.

SOCRATES-REDUCED: Adverse Events

AEs, n (%)	Placebo (n=92)	Vericiguat 1.25 mg (n=91)	Vericiguat 2.5 mg (n=90)	Vericiguat 2.5 to 5 mg (n=91)	Vericiguat 2.5 to 10 mg (n=91)
Any AE	71 (77.2)	64 (70.3)	71 (78.9)	67 (73.6)	65 (71.4)
Any study drug-related AE	13 (14.1)	10 (11.0)	13 (14.4)	12 (13.2)	15 (16.5)
AE with outcome of death	5 (5.4)	6 (6.6)	4 (4.4)	2 (2.2)	4 (4.4)
Any study drug-related SAE	3 (3.3)	1 (1.1)	1 (1.1)	1 (1.1)	4 (4.4)
Discontinuation of study drug due to AE	7 (7.6)	10 (11.0)	9 (10.0)	8 (8.8)	8 (8.8)
Discontinuation of study drug due to SAE	5 (5.4)	6 (6.6)	2 (2.2)	5 (5.5)	7 (7.7)
Hypotension*,†	6 (6.5)	5 (5.5)	6 (6.7)	4 (4.4)	14 (15.4)
Asymptomatic	1 (1.1)	2 (2.2)	3 (3.3)	2 (2.2)	5 (5.5)
Symptomatic	5 (5.4)	3 (3.3)	3 (3.3)	2 (2.2)	10 (11.0)
Syncope	1 (1.1)	0	2 (2.2)	1 (1.1)	4 (4.4)
Acute kidney injury	3 (3.3)	5 (5.5)	2 (2.2)	1 (1.1)	3 (3.3)

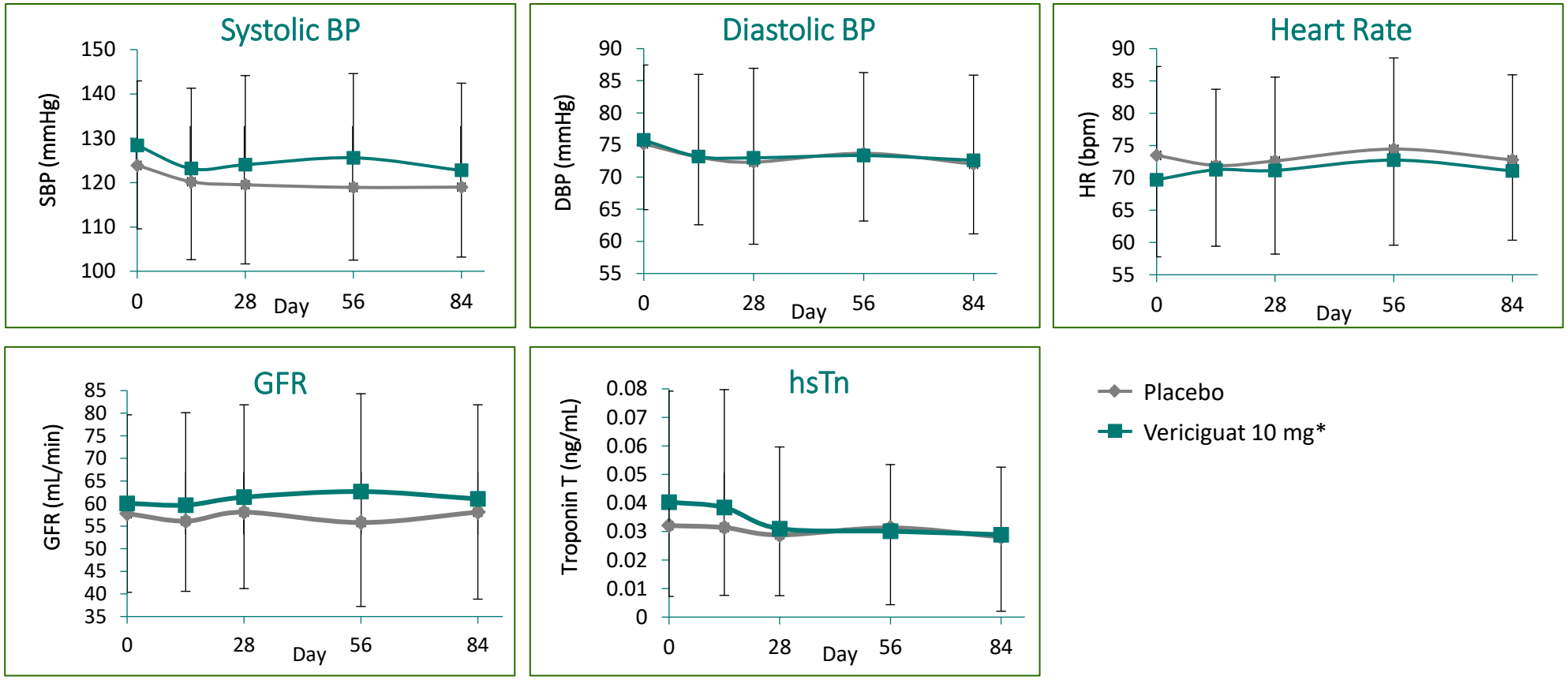
- Although investigator-reported episodes of treatment-emergent hypotension and syncope were more frequent among patients in the highest-dose vericiguat group, these events did not prompt excess study drug discontinuation, and there were no significant differences in 12-week follow-up blood pressure and heart rate measurements among patients randomized to receive 10-mg vericiguat or placebo

Syncope and hypotension were the most frequent treatment-emergent events in the 10-mg vericiguat group

*One patient had preferred term “orthostatic hypotension” reported.
†One patient had symptomatic and asymptomatic hypotension.
AE=adverse event; SAE=serious adverse event.
1. Gheorghiade M et al. JAMA. 2015;314(21):2251-2262. 2. Gheorghiade M. AHA 2015.

Vericiguat

SOCRATES-REDUCED: BP, HR, Renal Function, and Troponin[1,2]



Changes in BP, HR, renal function, and troponin from baseline to 12 weeks were similar between the placebo and 10-mg vericiguat groups

*10 mg: 2.5 to 10 mg arm.

Mean longitudinal changes and standard deviations in BP, HR, renal function, and troponin are shown.

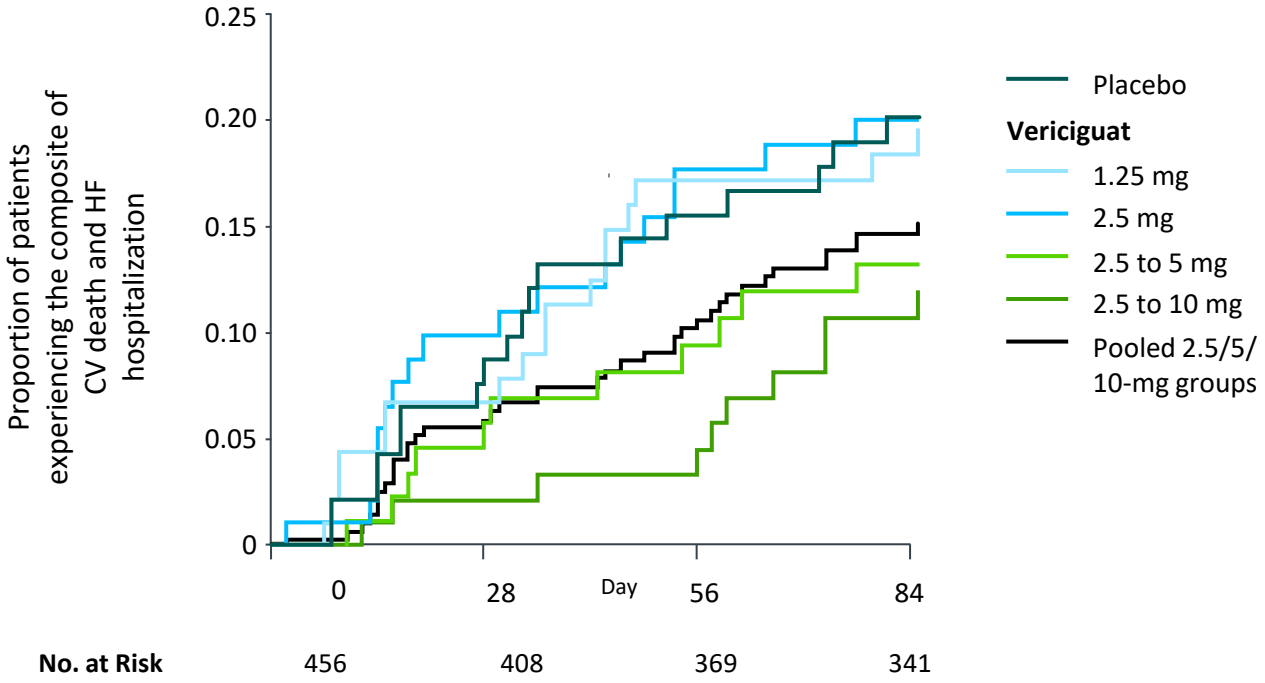
BP=blood pressure; DBP=diastolic blood pressure; GFR=glomerular filtration rate; HR=heart rate; hsTn=high-sensitivity troponin; SBP=systolic blood pressure.

1. Gheorghiade M et al. JAMA. 2015;314(21):2251-2262. 2. Gheorghiade M. AHA 2015.

Vericiguat

SOCRATES-REDUCED: Exploratory Analysis

Exploratory Endpoint:
Time to Composite of CV Death or HF Hospitalization



- Although SOCRATES-REDUCED was not powered for clinical events, rates of mortality and HF hospitalization were generally numerically lower among patients receiving vericiguat, particularly among those randomized to the 2 highest-dose vericiguat groups
- The rate of the composite of cardiovascular death or HF hospitalization was:

Treatment	Rate of composite CV death and HFH
Vericiguat	
10 mg	11.1%
5 mg	12.1%
2.5 mg	19.8%
1.25 mg	18.7%
Placebo	19.6%

CV=cardiovascular; HF=heart failure; HFH=heart failure hospitalization.
Gheorghiade M et al. JAMA. 2015;314(21):2251-2262.

Vericiguat

Key Findings from SOCRATES-REDUCED

In the dose-finding, confirmatory study SOCRATES-REDUCED, 10 mg vericiguat once daily (OD):

Yielded concurrent improvements in N-terminal pro B-type natriuretic peptide (NT-proBNP) and left ventricular ejection fraction (LVEF)

Demonstrated a similar safety profile compared with placebo when added to current HF treatment options

There was no statistically significant difference in NT-proBNP between the pooled vericiguat (2.5/5/10 mg) and placebo groups

However, secondary analyses showed a dose–response relationship and a significant effect at the highest vericiguat dose

Although not powered for clinical endpoints, exploratory analyses from the SOCRATES-REDUCED study support that the composite of CV death and HF hospitalisation occurred less frequently in the vericiguat 2.5- to 5-mg and 2.5- to 10-mg groups compared with placebo

Vericiguat was well tolerated in patients with chronic HFrEF

71.8% of patients randomised to receive the highest vericiguat dose reached the 10-mg daily target dose

The key results are presented in detail in the following pages

Section 4: Phase III VICTORIA Study

Rationale for the Phase III VICTORIA Study

The rationale and design of the phase III VICTORIA study were informed by key takeaways from SOCRATES-REDUCED[1]:

Positive findings in the secondary and exploratory analyses supported the decision to proceed with a phase III study[2]

Reassuring safety and tolerability data further supported this decision[1,2]

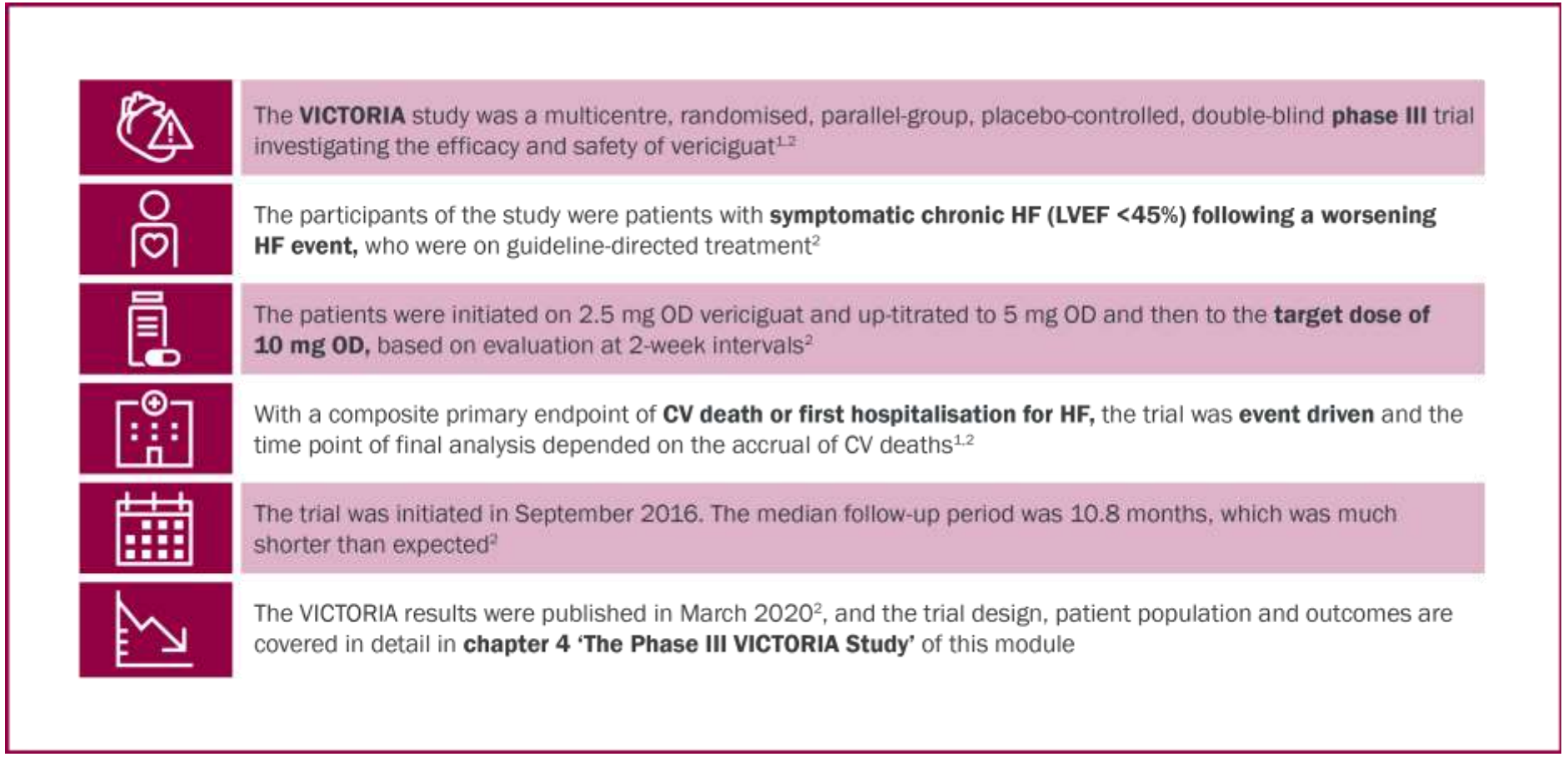
The dosing regimen (2.5 to target 10 mg) was chosen based on the dose-finding data[1]

The exploratory analysis on CV death and HF hospitalisation informed the VICTORIA primary endpoint[1]

The safety findings on symptomatic hypotension and syncope informed VICTORIA safety endpoints of interest[1,2]

The inclusion of patients with a recent episode of worsening chronic HF led to the patient inclusion criteria for phase III[2,3]

What is the VICTORIA Study?



CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; OD, once daily.

Section 1: Study Design and Patient Characteristics

VICTORIA Study Design

The **VICTORIA** study was a randomised, parallel-group, placebo-controlled, double-blind, event-driven, multicentre, phase III trial investigating the effect of vericiguat in adult patients with symptomatic chronic heart failure (HF) following a worsening HF event, and ejection fraction (EF) less than 45%[1,2]

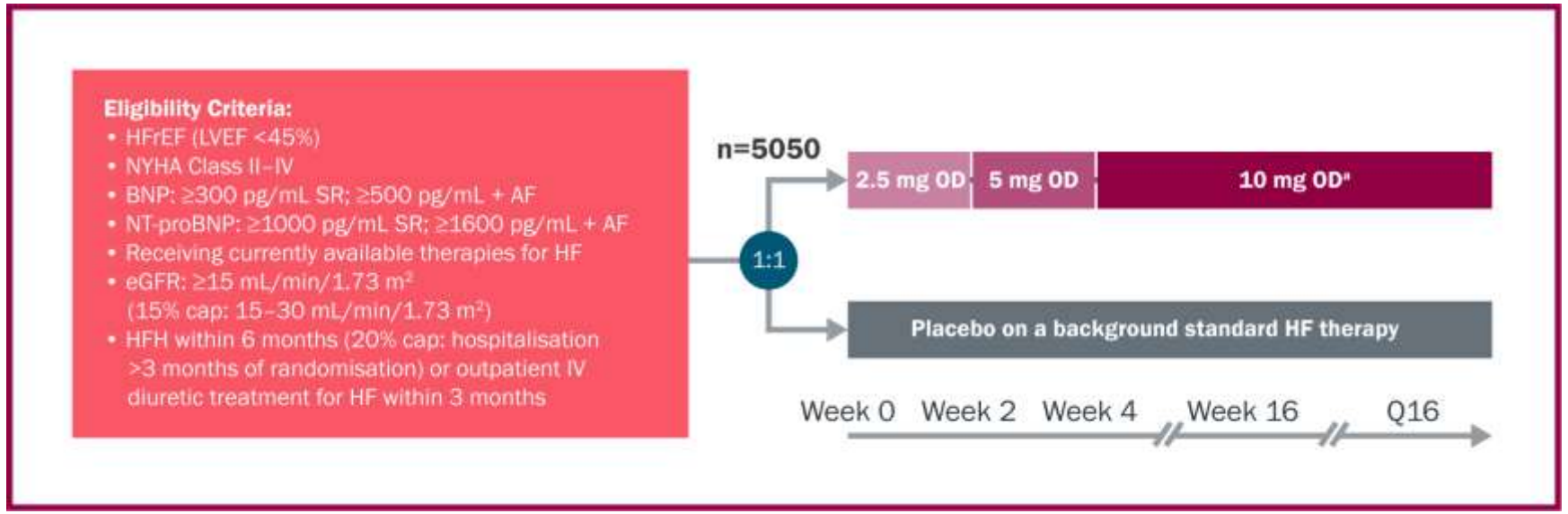
Study design

Endpoints

VICTORIA Study Design

The **VICTORIA** study was a randomised, parallel-group, placebo-controlled, double-blind, event-driven, multicentre, phase III trial investigating the effect of vericiguat in adult patients with symptomatic chronic heart failure (HF) following a worsening HF event, and ejection fraction (EF) less than 45%[1,2]

Study design



[a]*If the 10 mg target dose was not reached, then up-titration was considered at subsequent study visits, based on protocol-specified criteria.*

AF, atrial fibrillation; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalisation; HFrEF, heart failure with reduced ejection fraction; NT-proBNP; N-terminal pro-hormone BNP; NYHA, New York Heart Association; OD, once daily.

VICTORIA Study Design

The **VICTORIA** study was a randomised, parallel-group, placebo-controlled, double-blind, event-driven, multicentre, phase III trial investigating the effect of vericiguat in adult patients with symptomatic chronic heart failure (HF) following a worsening HF event, and ejection fraction (EF) less than 45%[1,2]

Endpoints

Primary endpoint:

- Time to first occurrence of the composite of cardiovascular (CV) death and HF hospitalisation (up to approximately 3.5 years)

Secondary endpoints (up to approximately 3.5 years):

- Time to CV death
- Time to first HF hospitalisation
- Time to first and subsequent HF hospitalisations
- Time to all-cause mortality
- Time to composite all-cause mortality or HF hospitalisation

Pop up 1

Exploratory endpoints and subgroup analyses

Exploratory and Subgroup Analyses in VICTORIA[1,2]

Exploratory endpoints	Subgroup analyses
• Time to first HF event (either HF hospitalisation or urgent HF visit) • Time to first CV hospitalisation • Total number of HF hospitalisations (first and recurrent) • Change in health-related QoL (KCCQ and EQ-5D) • Relationships between treatment effect, baseline biomarkers and genetic variation	• Age, sex, race • Geographic region • Index event (HFH 0–3 months, HFH 3–6 months, IV diuretic therapy 0–3 months) • eGFR at randomisation (≤30 ml/min/1.73 m^2, >30 to ≤60 ml/min/1.73 m^2, >60 ml/min/1.73 m^2) • NYHA class at baseline • Baseline NT-proBNP by quartiles • Use of ARNI at baseline • Baseline EF (<35% vs ≥35% and (<40% vs ≥40%)

ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life.

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 Designed to Study Patients with Symptomatic Chronic HF Who Had a Previous Worsening HF Event[1–5]

'Symptomatic chronic HF'

- NYHA class II–IV
- LVEF <45%
- On available HF therapies

&

'Worsening HF event'

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

Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability (e.g. SBP ≥100 mmHg, off IV treatments ≥24 hours)

There was no run-in period

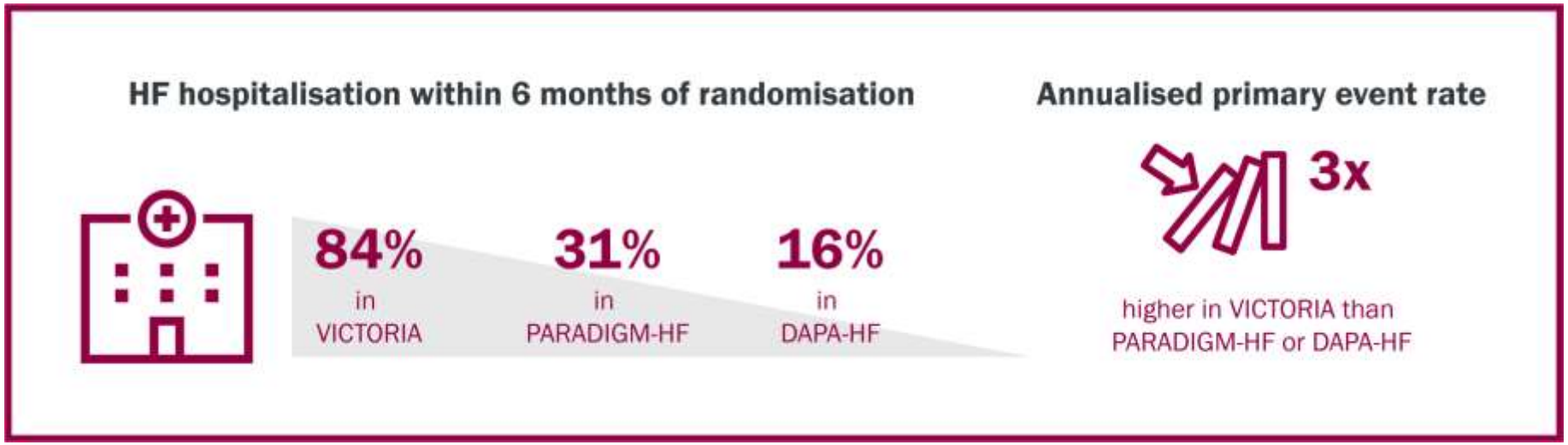
HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

1. Armstrong PW *et al. JACC Heart Fail.* 2018;6:96–104; 2. Armstrong PW *et al. N Engl J Med*. 2020;382:1883–1893; 3. Hicks KA *et al. Circulation.* 2015;132:302–361; 4. European Medicines Agency. 2017CPMP/EWP/235/95, Rev.2. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf. [accessed 9 Feb 2021]; 5. Butler J *et al. Circulation.* 2020;142:717–719.

Vericiguat

Clinical Characteristics in Key HFrEF Trials

Patients in VICTORIA had a higher risk of CV events (CV death, HF hospitalisation) than those studied in recent HF trials[1–6]



Select baseline characteristics
Differences between studies

Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug vs. another.
HF, heart failure.

VICTORIA Baseline Characteristics (1)

Selected baseline characteristics	Vericiguat (n=2526)	Placebo (n=2524)
Sex, n (%)		
Male	1921 (76.0)	1921 (76.1)
Female	605 (24.0)	603 (23.9)
Age, years		
Mean ± SD	67.5±12.2	67.2±12.2
Geographical region, n (%)		
Eastern Europe	848 (33.6)	846 (33.5)
Western Europe	443 (17.5)	446 (17.7)
Asia-Pacific	592 (23.4)	591 (23.4)
Latin and South America	362 (14.3)	362 (14.3)
North America	281 (11.1)	279 (11.1)

SD, standard deviation.

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

VICTORIA Baseline Characteristics (2)

Selected baseline characteristics	Vericiguat (n=2526)	Placebo (n=2524)
NYHA class, n (%)		
I	0	2/2523 (0.1)
II	1478/2523 (58.6)	1497/2523 (59.3)
III	1010/2523 (40.0)	993/2523 (39.4)
IV	35/2523 (1.4)	31/2523 (1.2)
LVEF*		
Mean ± SD at screening	29.0±8.26	28.8±8.34
Ejection fraction <40%, n (%)	2158 (85.8)	2158 (85.6)

*LVEF was a historical value (within 12 months prior to randomisation) recorded at screening visit. Data on LVEF were missing for 10 patients in the vericiguat group and 4 patients in the placebo gr
LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

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

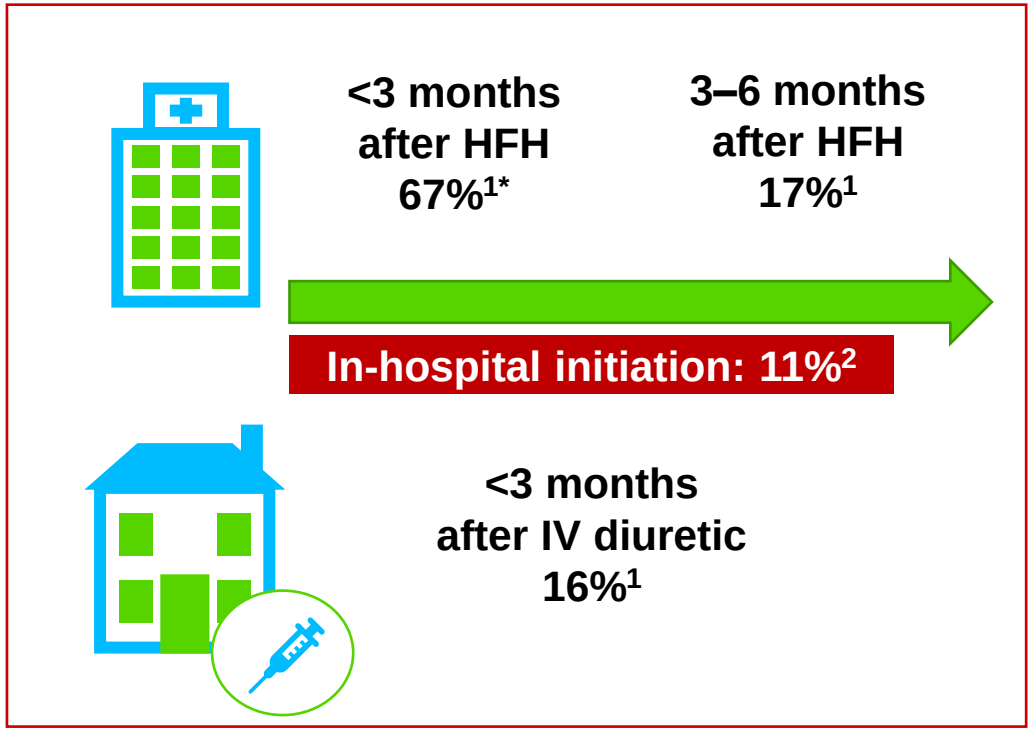
VICTORIA Baseline Characteristics (3)

Selected baseline characteristics	Vericiguat (n=2521)	Placebo (n=2519)
Baseline SoC medications, n (%)		
Beta blockers	2349 (93.2)	2342 (93.0)
ACEi/ARB	1847 (73.3)	1853 (73.6)
MRA	1747 (69.3)	1798 (71.4)
Sacubitril/valsartan	360 (14.3)	371 (14.7)
3 SoC medications*	1480 (58.7)	1529 (60.7)
Baseline SoC device, n (%)		
Implantable cardioverter-defibrillator	696 (27.6)	703 (27.9)
Biventricular pacemaker	370 (14.7)	369 (14.6)

*SoC medications can include beta blockers, ACEis, ARBs, MRAs and sacubitril/valsartan.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SoC, standard of care.
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

The majority of VICTORIA patients had received multiple HF therapies before randomization and all randomized patients had a worsening HF event

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)
Beta blocker	2349 (93.2%)	2342 (93.0%)
ACEi/ARB	1847 (73.3%)	1853 (73.6%)
MRA	1747 (69.3%)	1798 (71.4%)
ARNi (sacubitril/valsartan)	360 (14.3%)	371 (14.7%)
Patients on triple therapy, n (%)*	1480 (58.7%)	1529 (60.7%)
ICD, n(%)	696(27.8%)	703(27.9%)
Biventricular pacemaker n(%)	370(14.7%)	369(14.8%)



Patients could be enrolled in VICTORIA up to 6 months after HF hospitalisation or up to 3 months after an episode of worsening HF requiring IV diuretics without hospitalisation[1]

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; SD, standard deviation
Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

*Study drug was initiated in hospital in 11% of patients.[2]
HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous.

Current treatments for HFrEF were established based on large randomized, controlled trials, focused on patients with more *stable chronic HFrEF*

Key details	PARADIGM HF (N=8399)[1] Sacubitril/valsartan	DAPA-HF (N=4744)[2] Dapagliflozin	EMPEROR-Reduced (N=3730)[3] Empagliflozin	VICTORIA (N=5050)[5] Vericiguat
eGFR cut-off	≥30 ml/min/1.73 m^2	≥30 ml/min/1.73 m^2	≥20 ml/min/1.73 m^2	≥15 ml/min/1.73 m^2
Recent HF decompensation	Not required	Not required	Not required	HFH within 6 months or IV diuretic use for HF within 3 months
Median NT-proBNP	1608	1437	1906	2816
HFH<6 months	31%	16%	NA	84%
IV diuretic for HF (without hospitalisation) within 3 months, n (%)	NR	NR	NR	15.9%
NYHA III-IV	25%	32%	25%	41%
eGFR <60 ml/min/1.73 m^2	37%	41%	48%	53%
Primary endpoint event rate (control arm)	**13.2 events/ 100 PY**	**15.6 events/ 100 PY**	**21.0 events/ 100 PY**	**37.8 events/100 PY**

100% focus on WHF patients

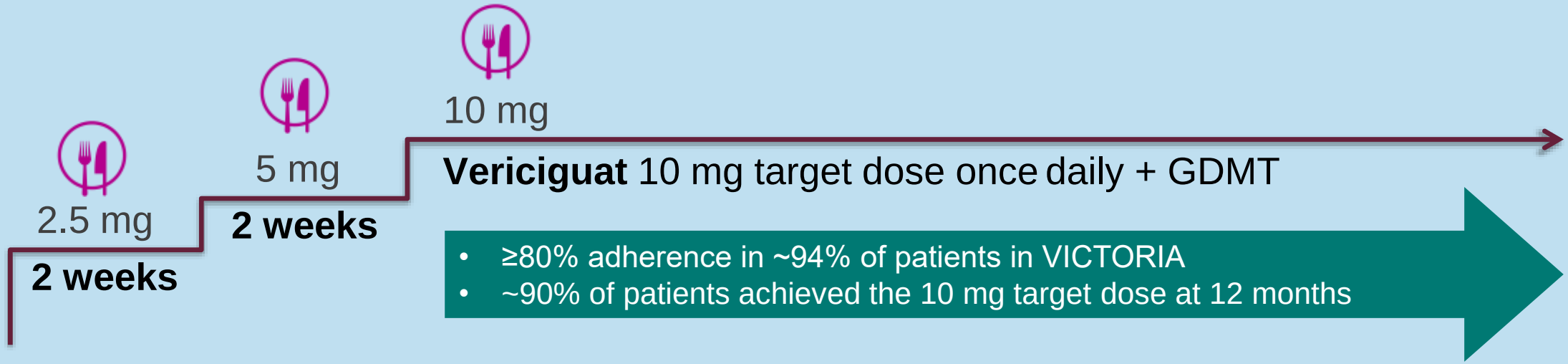
Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.

*Patients with AF or atrial flutter were required to have an NT-proBNP level ≥900 pg/ml, regardless of their history of HFH

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SR, sinus rhythm

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. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 4. Teerlink JR et al. *N Engl J Med.* 2021;384:105–116; 5. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

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



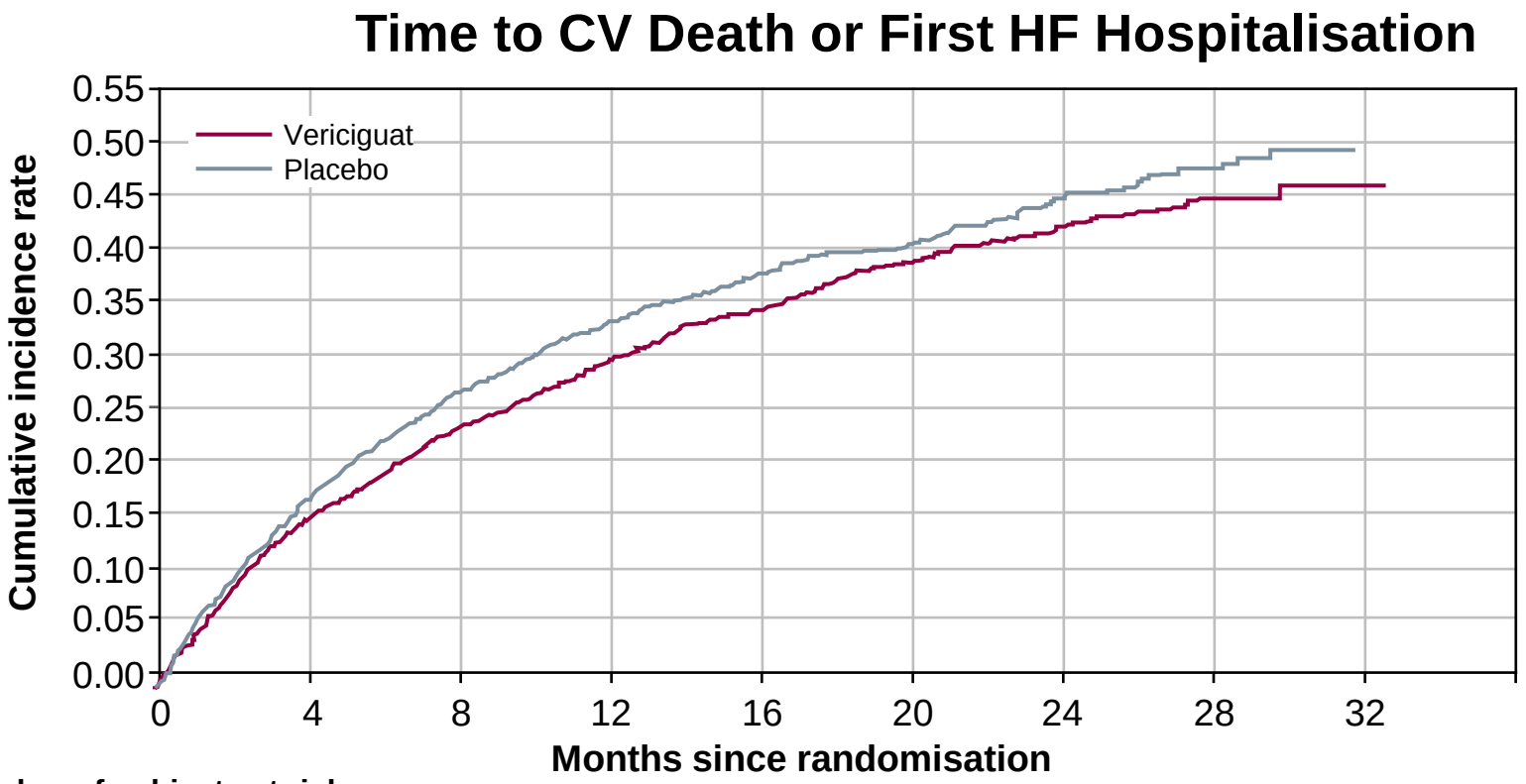
→ One tablet per day with meal/food
→ Titration guided by evaluation of blood pressure and clinical symptoms
→ No dosage adjustment for geriatric patients or patients with moderate renal or hepatic impairment

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

Vericiguat

End of Section 1

Vericiguat Significantly Reduced the Annualised Absolute Risk of the Primary Outcome of Time to HFH or CV Death by 4.2%[1]



Number of subjects at risk

Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

- Median treatment duration for primary endpoint: 10.8 months
- Annual event rate for vericiguat vs placebo per 100 patient-years was 33.6% versus 37.8%, respectively

HR=0.90 (95% CI 0.82–0.98)

P=0.02

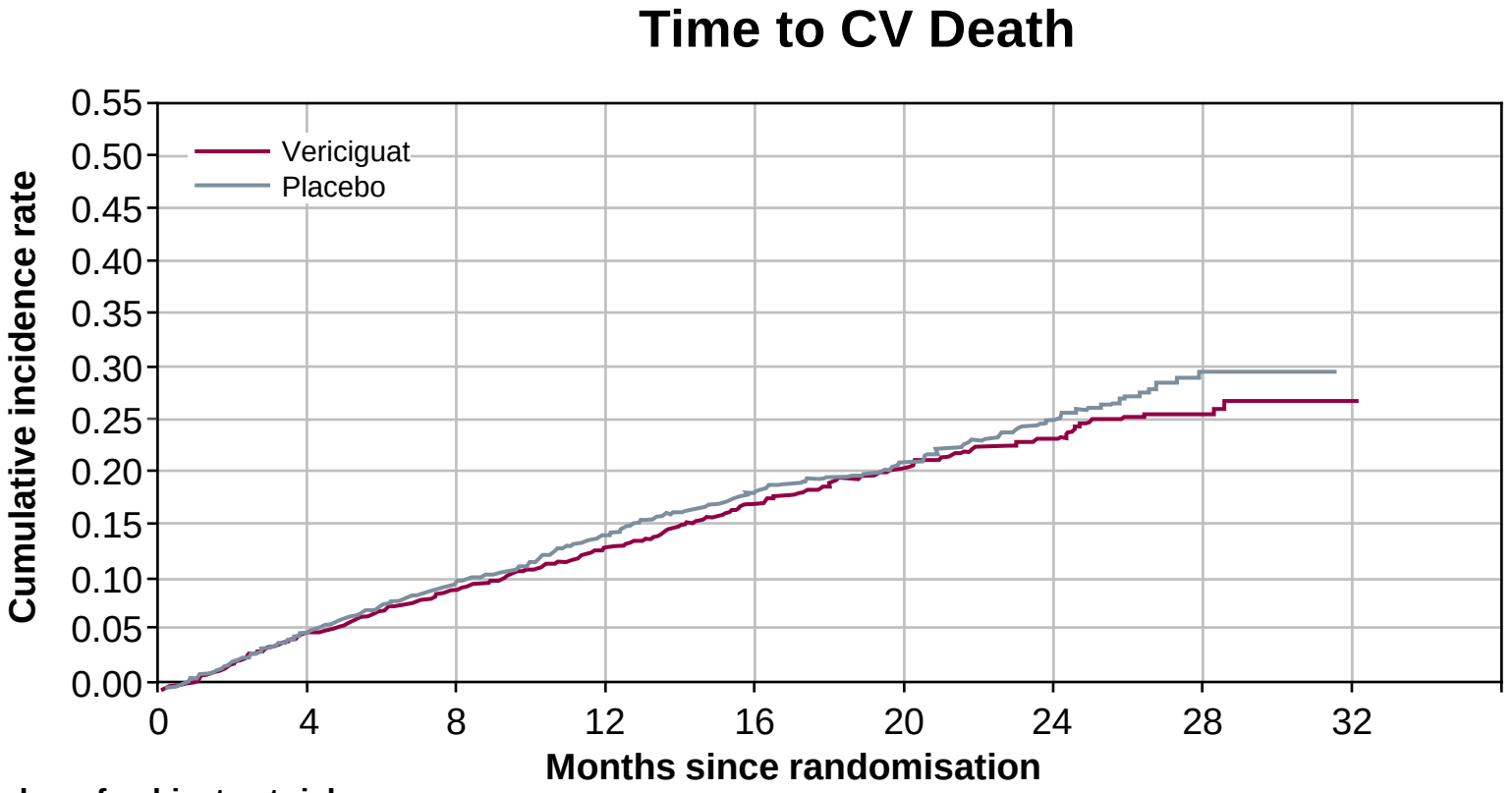
ARR: 4.2% per year*

Annual NNT: 24#

*Annual ARR: 37.8–33.6=4.2%; #Annual NNT: 100/4.2=24.
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, hospitalisation for heart failure; NNT, number needed to treat.

1. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928.

The Secondary Endpoint of Cardiovascular Death Was Directionally Consistent with the Primary Endpoint, with ARR of 1%[1]



Number of subjects at risk

Vericiguat	2526	2376	1968	1468	1070	779	487	185	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

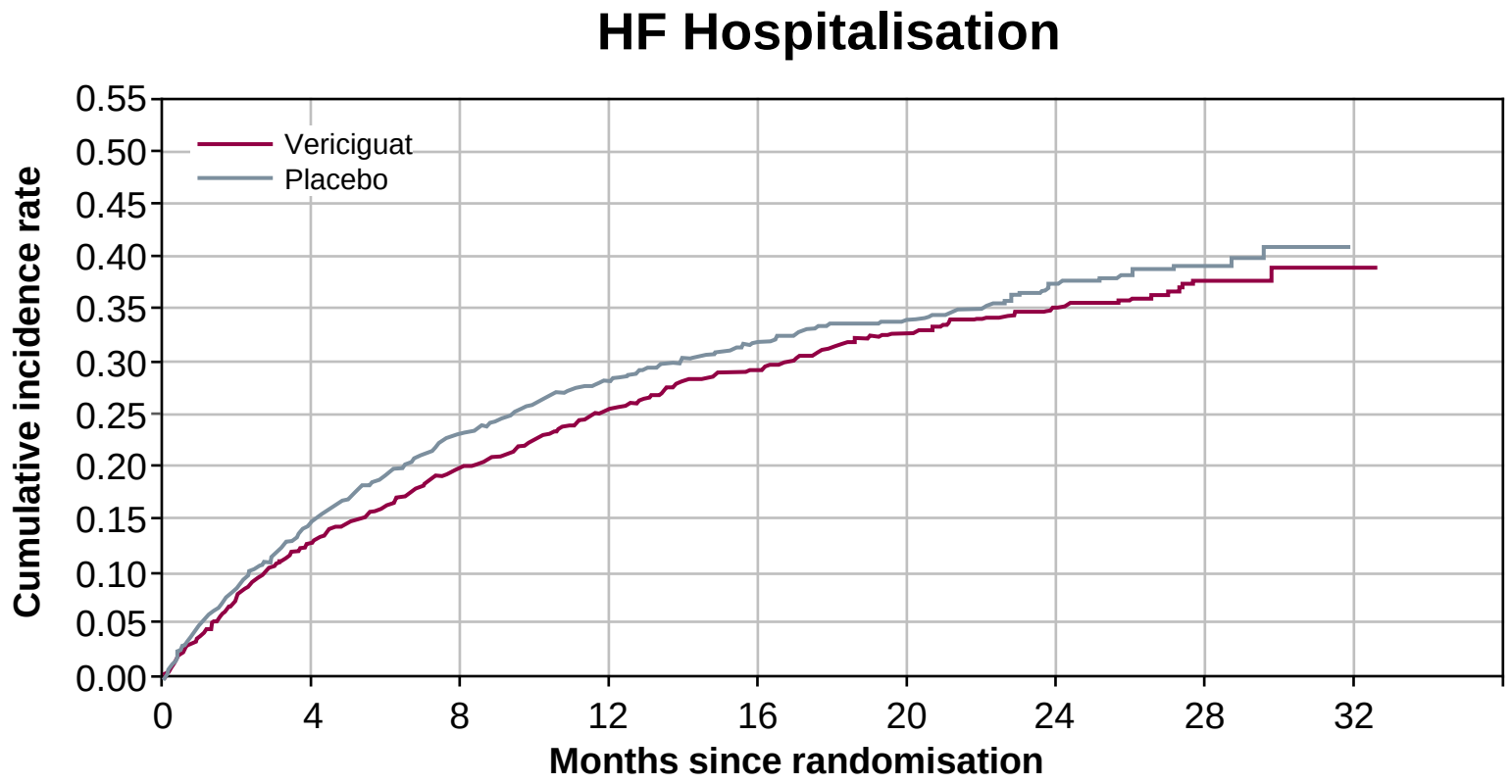
- Median treatment duration: 10.8 months
- Annual event rate for vericiguat vs placebo per 100 patient-years was 12.9% versus 13.9%, respectively

HR=0.93 (95% CI 0.81–1.06)

ARR: 1.0% per year*

*Annual ARR: 13.9–12.9=1.0%.
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
1. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928.

Vericiguat Significantly Reduced the Annualised Absolute Risk of HFH by 3.2%[1]



Number of subjects at risk

Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

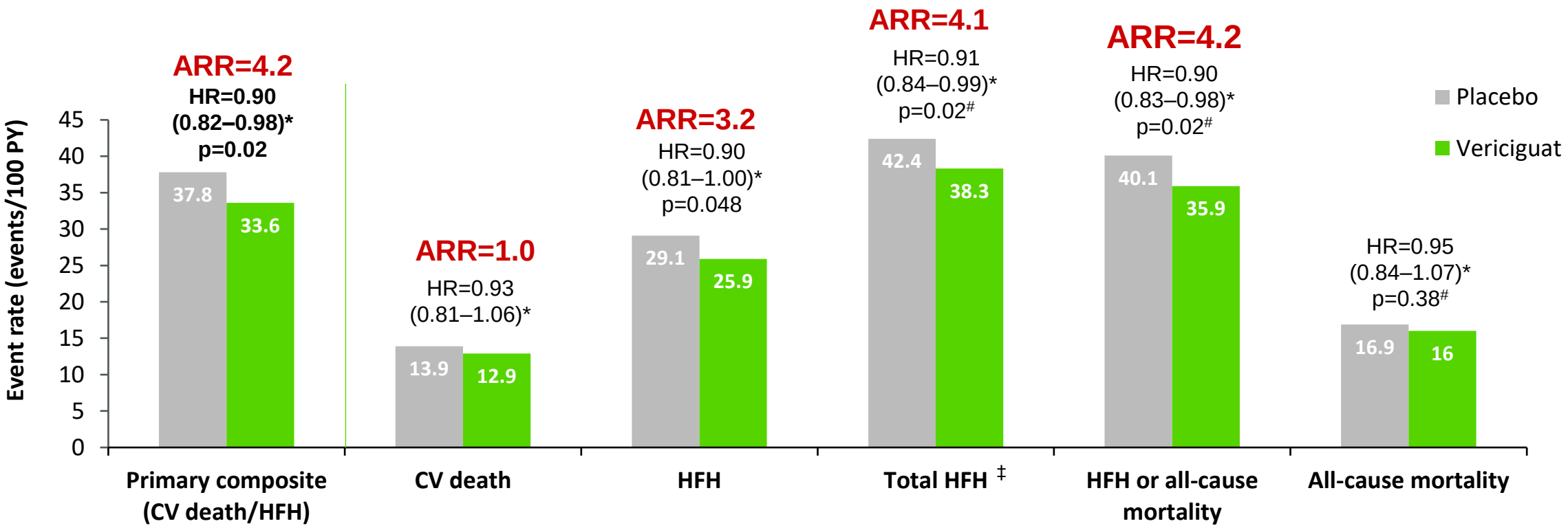
- Median treatment duration: 10.8 months
- Annual event rate for vericiguat vs placebo per 100 patient-years was 25.9% versus 29.1%, respectively

HR=0.90 (95% CI 0.81–1.00)

ARR: 3.2% per year*

*Annual ARR: 29.1–25.9=3.2%.
ARR, absolute risk reduction; CI, confidence interval; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio.
1. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928.

VICTORIA: Primary and Secondary Outcomes[1]



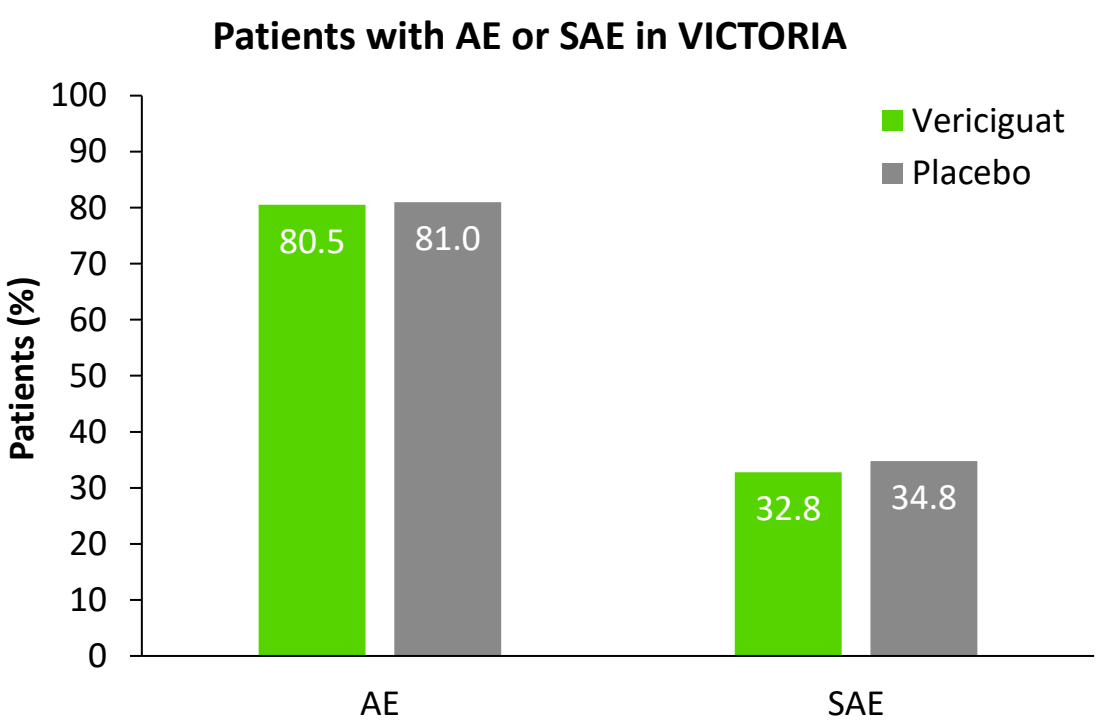
The primary composite outcome, total HFH and the composite of HFH or all-cause mortality were significantly reduced with vericiguat vs placebo

Worsening symptoms requiring hospitalization or IV diuretic use in the outpatient setting. 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).
ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; IV, intravenous; PY, patient-years.

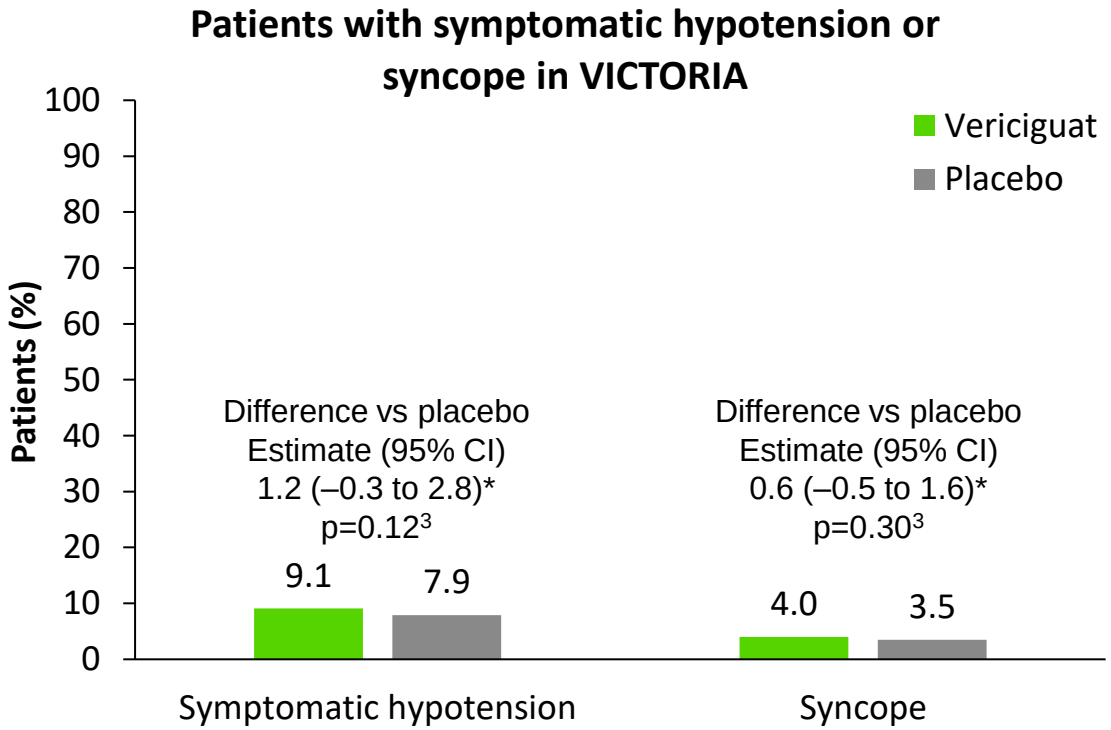
1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893.

Vericiguat added to background therapies is well tolerated in patients with HFrEF following a worsening HF event[1,2]

Rates of AEs and SAEs were numerically lower with vericiguat *vs* placebo



No significant difference in symptomatic hypotension or syncope



* Based on the Miettinen & Nurminen method. Note: includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug. Based on data up to the primary analysis cut-off date (18 June 2019).

AE, adverse event; CI confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SAE, serious adverse event.

References: 1. Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893; **2.** Lam C *et al. J Am Heart Assoc* 2021;10:e021094; **3.** Armstrong PW *et al. N Engl J Med* 2020(Suppl);382:1883–1893.

Vericiguat

VICTORIA in context: Annualised event rate (events per 100 patient-years at risk)

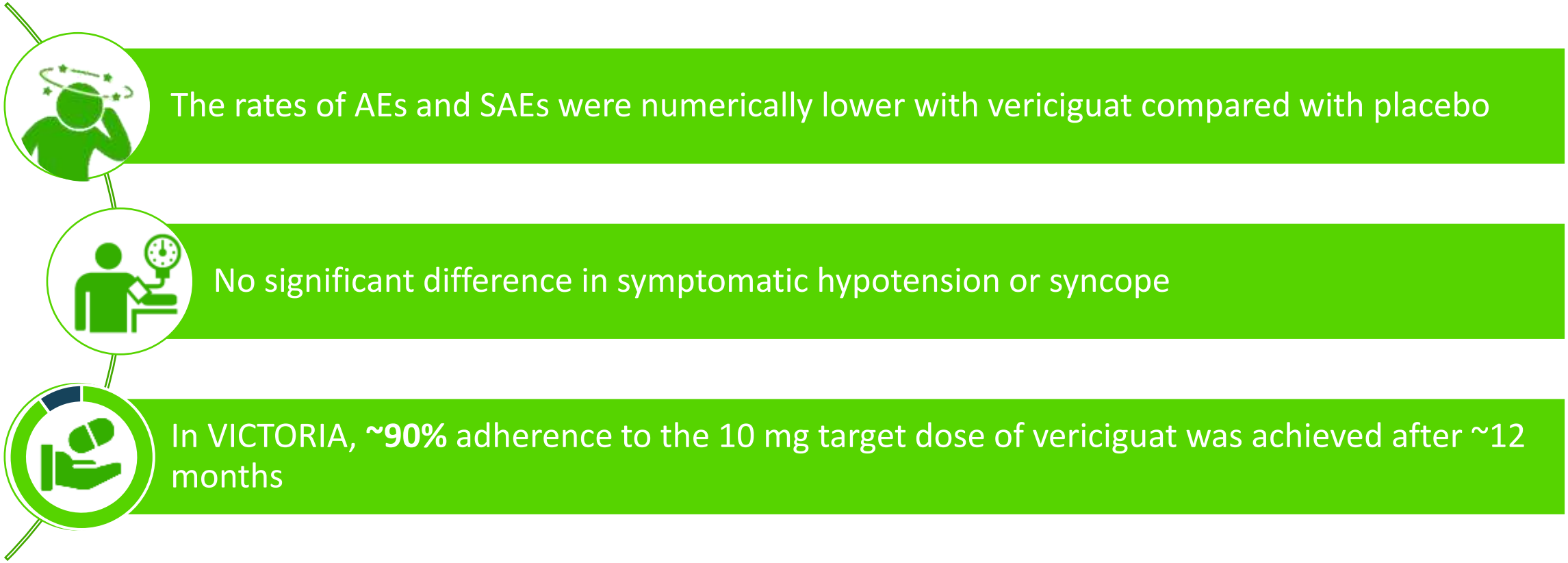
	PARADIGM-HF[1,2]		DAPA-HF[1]		EMPEROR-Reduced[1]		VICTORIA[1]	
	Comparator	Sacubitril/ valsartan	Comparator	Dapagliflozin	Comparator	Empagliflozin	Comparator	Vericiguat
Annualised event rate (events per 100 patient-years at risk)								
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	37.8	33.6
Absolute rate reduction	**2.7**		**4.0**		**5.2**		**4.2**	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	13.9	12.9
Absolute rate reduction	**1.5**		**1.4**		**0.6**		**1.0**	
First HFH	7.7	6.2	9.8	6.9	15.5	10.7	29.1	25.9
Absolute rate reduction	**1.6**		**2.9**		**4.8**		**3.2**	

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

1. Butler J et al. *Eur J Heart Fail*. 2020;22:1991–1993; 2. McMurray JJV et al. *Eur Heart J.* 2015;36:434–439; 3. Teerlink JR et al. *N Engl J Med.* 2021;384:105–116

Vericiguat added to GDMT is well tolerated in patients with HFrEF following a worsening HF event

- **Vericiguat has a favourable safety profile suitable for patients with multiple comorbidities requiring polypharmacy**

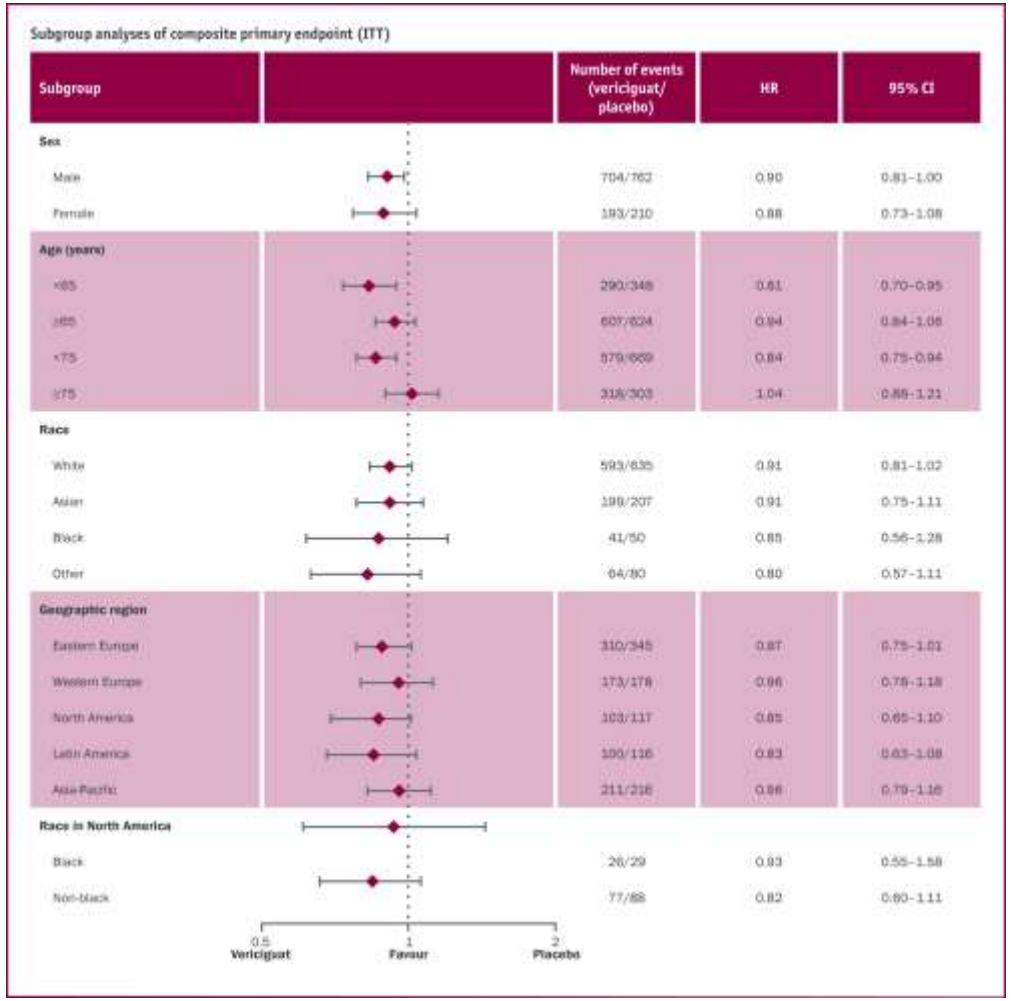


Worsening symptoms requiring hospitalisation or IV diuretic use in the outpatient setting.
AE, adverse event; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; SAE, serious adverse event.
Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893.

Demographic and Geographic Subgroup Analyses (ITT)

Subgroup analyses of composite primary endpoint (ITT)

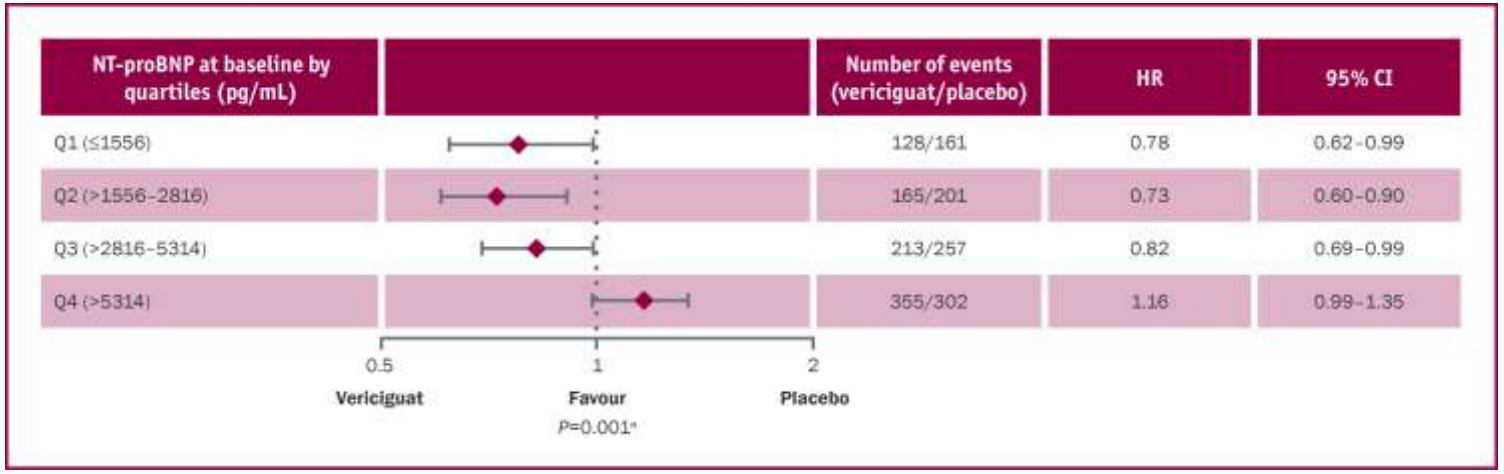
- Regardless of sex, race or geographic region, vericiguat reduced the risk of the composite of hospitalisation for HF or CV death compared with placebo when given in combination with available HF therapies in patients with symptomatic chronic HF following a worsening HF event[1]
- The findings were consistent among demographic and geographic subgroups for CV death and HF hospitalisation[1]



CI, confidence interval; HR, hazard ratio; ITT, intention to treat.

Disease-Related Subgroup Analyses (ITT): NT-proBNP

- When given in combination with available HF therapies in patients with symptomatic chronic HF following a worsening HF event, maximal benefit with vericiguat was demonstrated in patients with baseline NT-proBNP <5314 pg/mL (HR: 0.73–0.82)[1,2]



Pop up 1

Measuring NT-proBNP

Pop up 2

Examining baseline NT-proBNP levels in recent HF studies and in the real world

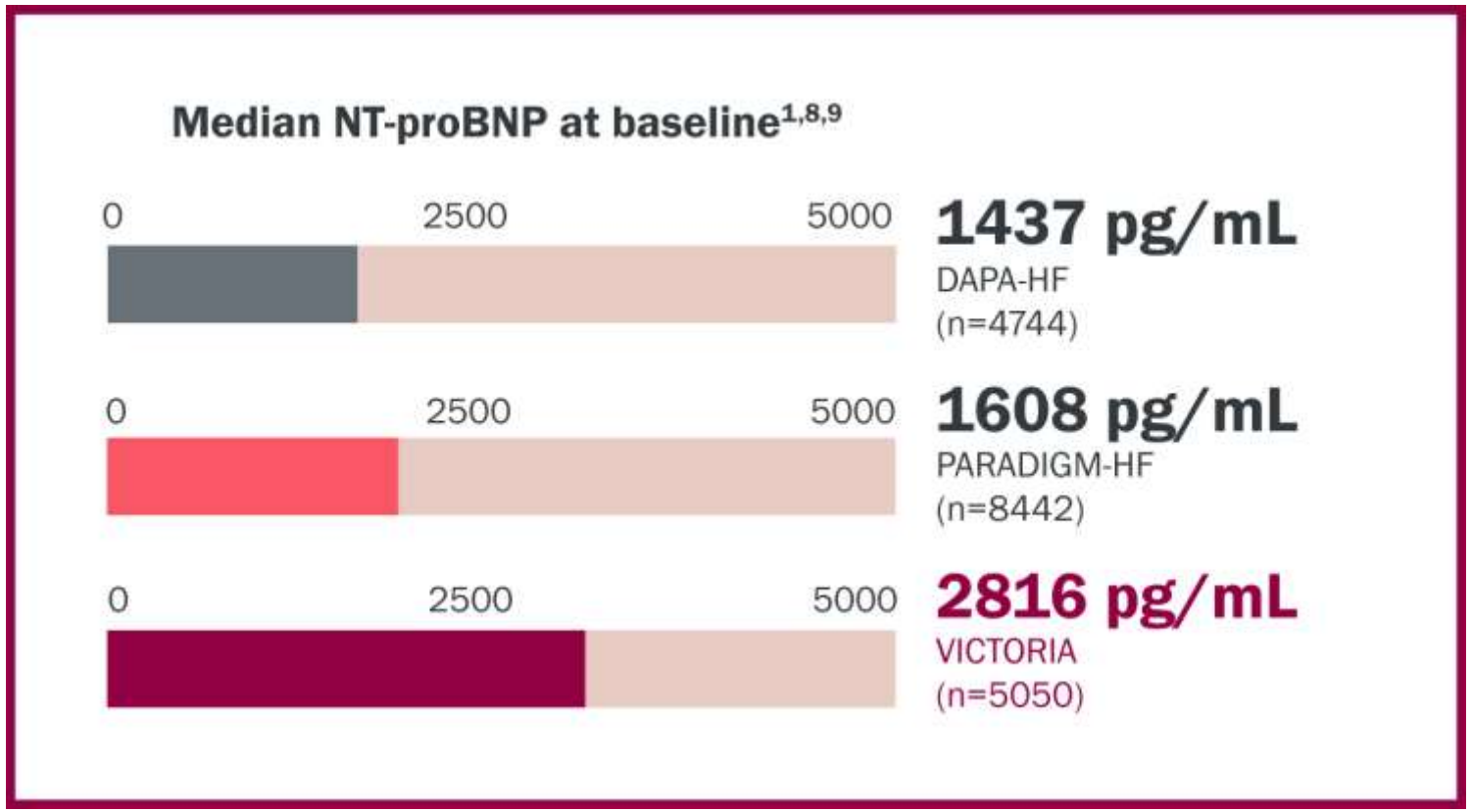
[a]P-value for treatment by subgroup interaction from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction.
CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Pop up 1:
Measuring NT-proBNP

- Recall from chapter 1 that natriuretic peptides are hormones – mainly secreted by the heart – that have important properties in stimulating the release of sodium, potassium and water from the kidneys[3,4]
- Measuring natriuretic peptides, such as BNP and NT-proBNP, as an initial diagnostic test can be helpful when echocardiography or other imaging techniques are not immediately available[5,6]
- Elevated natriuretic peptides help establish an initial working diagnosis by identifying patients who require further cardiac investigation; patients with normal plasma natriuretic peptide concentrations do not require echocardiography because they are unlikely to have HF[5,6]
- The upper limit of concentration in the serum in the non-acute setting is 35 pg/mL for BNP and 125 pg/mL for NT-proBNP[6]
- Note that the higher the NT-proBNP plasma level the higher the risk of CV events[7]

Pop up 2:
Examining baseline NT-proBNP levels in recent HF studies

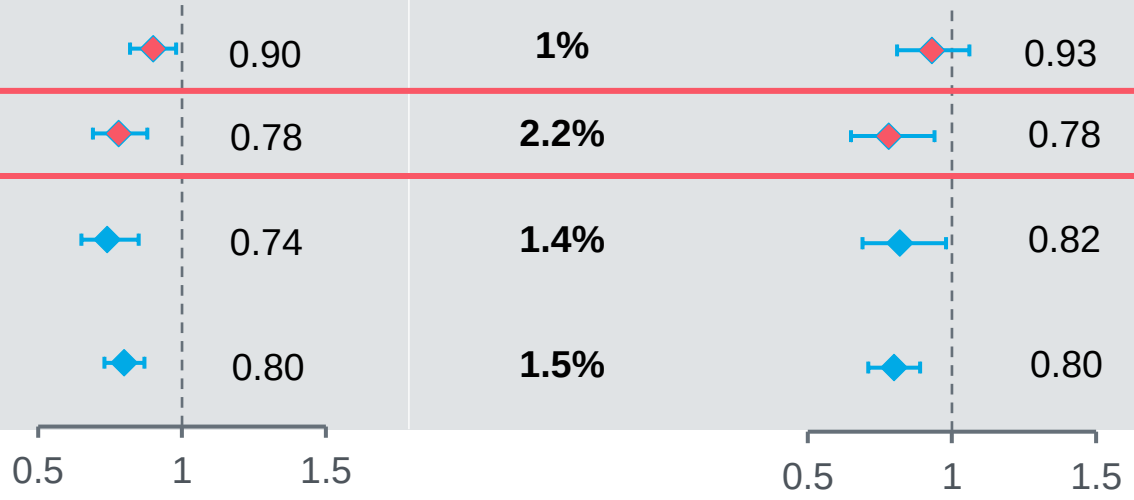
- The median NT-proBNP in VICTORIA was 2× higher than in PARADIGM-HF or DAPA-HF[1,8,9]



NT-proBNP, N-terminal pro-hormone brain natriuetic peptide.

VICTORIA Results Demonstrated Greater Clinical Value Among Patients with NT-proBNP Level ≤5314 pg/mL

	Median NT-proBNP (pg/mL)	Primary endpoint*		CV death	
		ARR/100 patient-years	Hazard Ratio (95% CI)	ARR/100 patient-years	Hazard Ratio (95% CI)
VICTORIA[1,2]					
Overall	2,816	**4.2%**	0.90	**1%**	0.93
NT-proBNP Q1-3‡	2,060	**7.2%**	0.78	**2.2%**	0.78
Dapagliflozin DAPA-HF[1,3,4]	1,437	**4%**	0.74	**1.4%**	0.82
Sacubitril/valsartan PARADIGM-HF[1,5,6]	1,608#	**2.7%**	0.80	**1.5%**	0.80



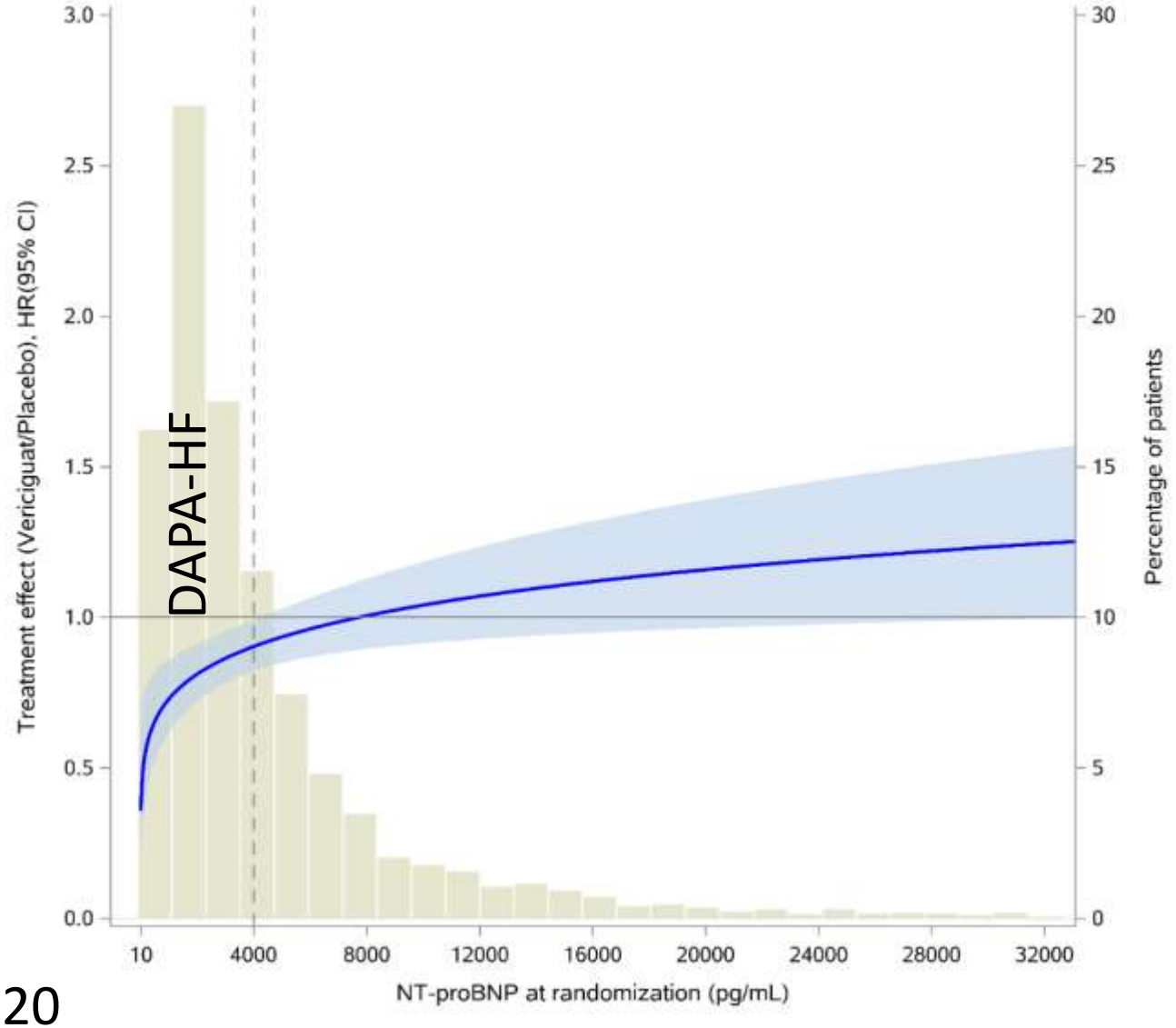
Note: this is not intended as a direct comparison of the different studies.

*For VICTORIA & PARADIGM-HF, primary endpoint was a composite of CV death or HF hospitalization; for DAPA-HF, primary endpoint was a composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy for HF) or CV death; #At screening before run-in; one month after randomization, 24% of the baseline NT-proBNP levels >1000 pg/mlLhad fallen to ≤1000 pg/mL. ‡DATA ON FILE - FOR INTERNAL USE ONLY & NOT FOR DISTRIBUTION.

1. Butler J et al. *Circulation*. 2020. doi: 10.1161/CIRCULATIONAHA.120.047086. **2.** Armstrong P et al. *N Engl J Med*. 2020. doi: 10.1056/NEJMoa1915928; **3**. Docherty KF et al. *Eur Heart J*. 2020. doi: 10.1093/eurheartj/ehaa183; **4**. McMurray JJV et al. *N Engl J M*ed. 2019;381:1995–2008; **5.** Zile MR et al. *J Am Coll Cardiol* 2016;68:2425-2436; **6.** McMurray JJ et al. *N Engl J Med*. 2014;371:993–1004.

Heart Failure

NT-proBNP and Primary Endpoint



<4000 pg/ml:
HR 0.77 (0.68-0.88)

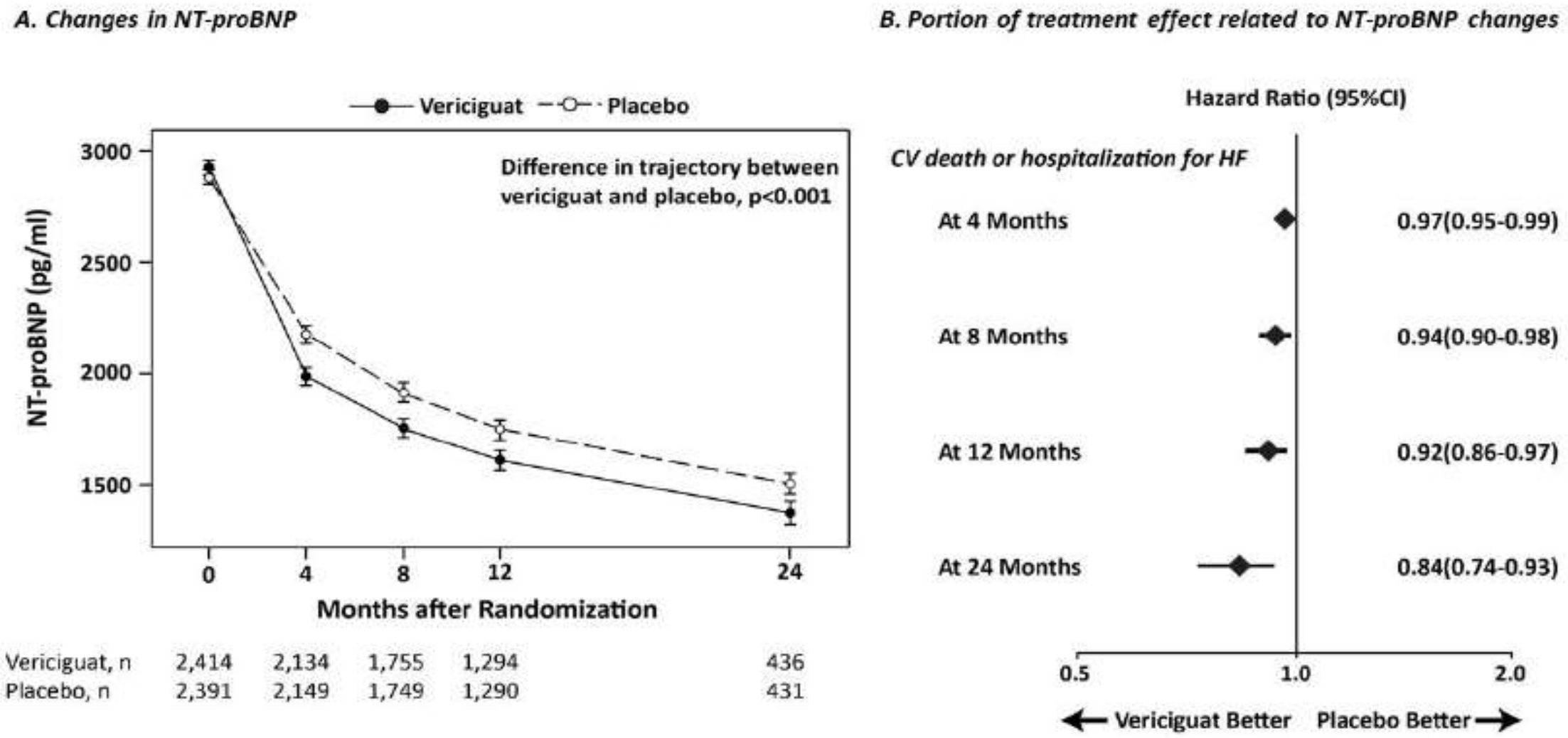
<8000 pg/ml:
HR 0.85 (0.76-0.95)

>8000 pg/ml:
HR 1.16 (0.94-1.41)

Ezekowitz, JACC-HF 2020

Heart Failure

VICTORIA: Changes in NT-proBNP and effects of vericiguat



Conclusions: In patients with worsening HFrEF, vericiguat decreased NT-proBNP during treatment and the change in NT-proBNP was associated with the effect of vericiguat on the primary outcome

Ezekowitz JA et al. presentation at the HFA 2021 Congress

Disease-Related Subgroup Analyses (ITT)

Tab 1/5:
Use of sacubitril/valsartan at baseline

Tab 2/5:
Index events

Tab 3/5:
EF at screening

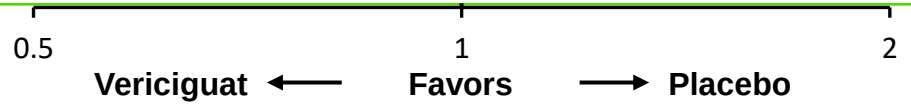
Tab 4/5:
NYHA class at baseline

Tab 5/5:
eGFR at baseline

No significant interaction on the treatment effect of vericiguat was observed based on ARNI use[1]

- Effect of vericiguat on clinical outcomes by baseline ARNi use

Outcome	HR (95% CI)
Patients on ARNi at baseline	
Primary composite outcome	0.94 (0.74–1.20)
CV death	0.81 (0.55–1.20)
HF hospitalization	0.99 (0.76–1.30)
Patients not on ARNi at baseline	
Primary composite outcome	0.89 (0.80–0.98)
CV death	0.95 (0.82–1.11)
HF hospitalization	0.87 (0.78–0.98)



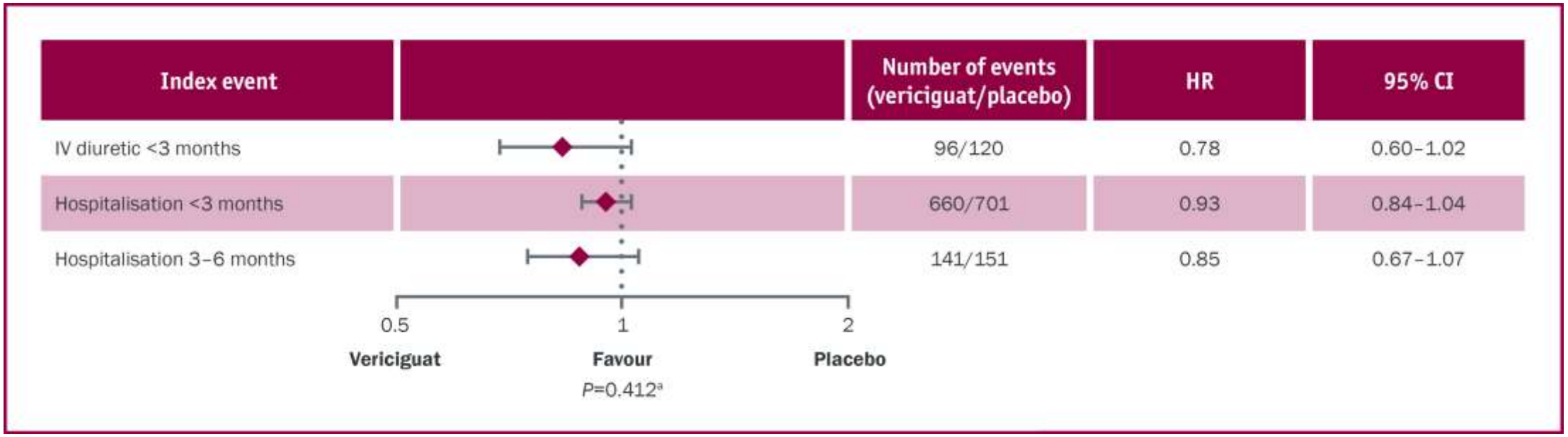
ARNi, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HF, heart failure.

Reference: 1. Senni M *et al.* ESC. 27–30 August 2021, poster.

Vericiguat

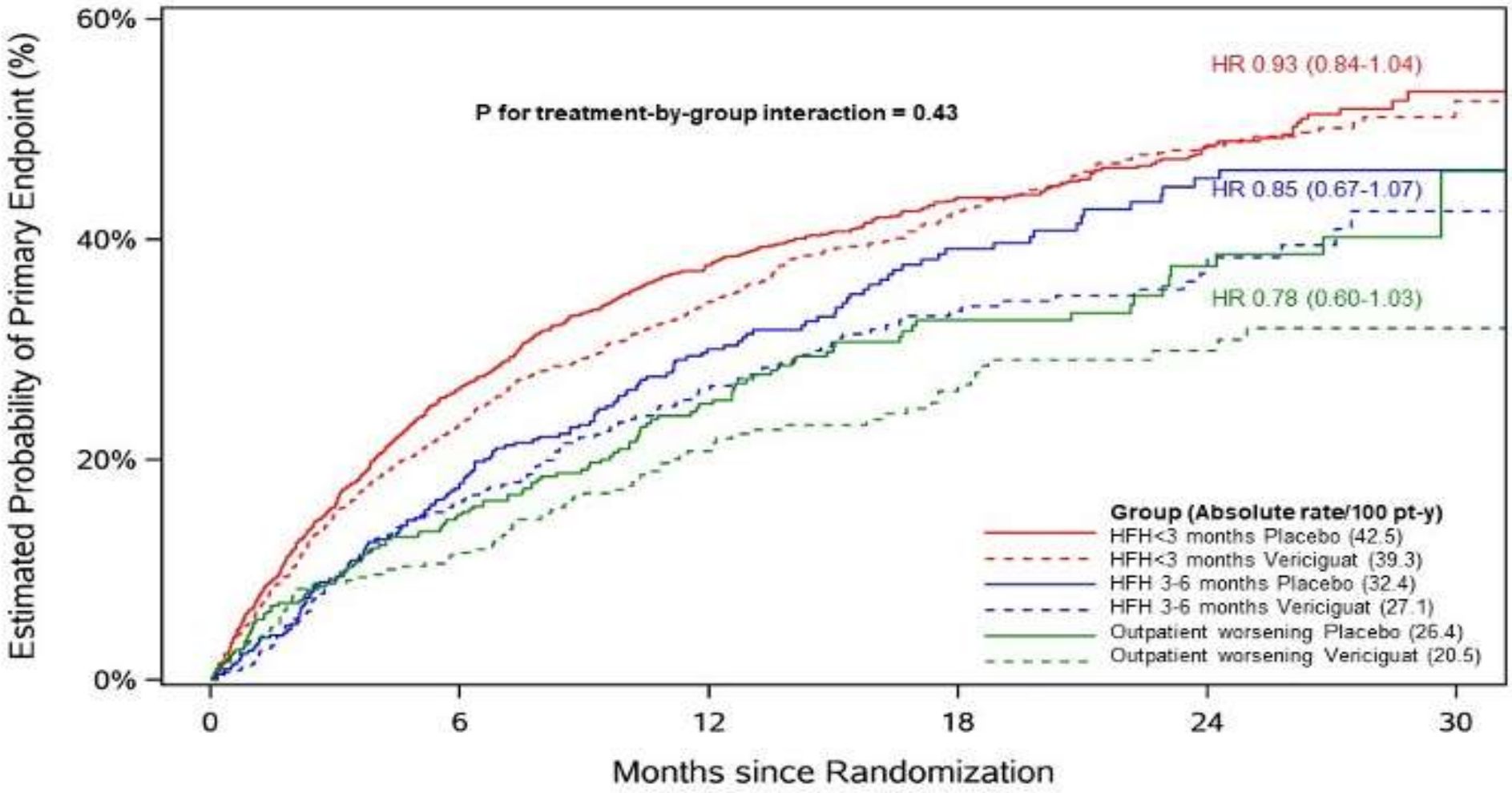
Tab 2/5: Index events

- The primary composite endpoint outcomes were directionally consistent irrespective of the index event[1,2]



[a]*P-value for treatment by subgroup interaction from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction.*

Index Event HF Event: Outcomes & Treatment Effect

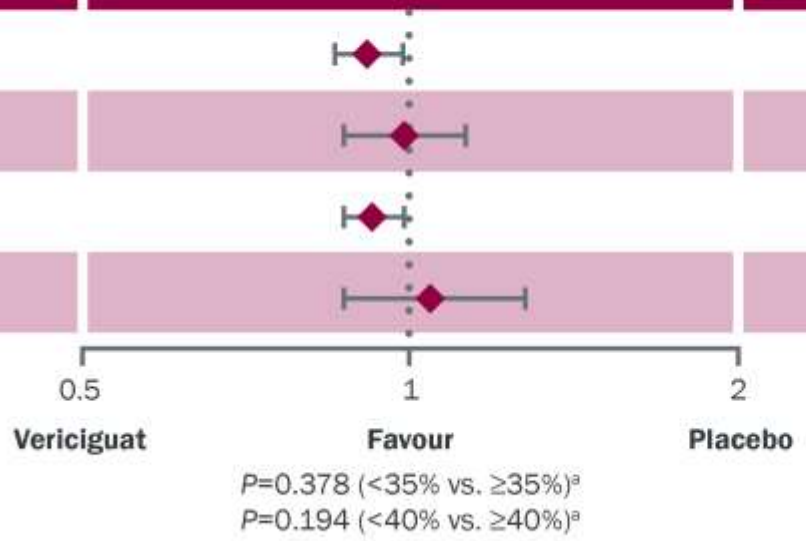


1	1705	1233	701	419	221	27
2	1673	1264	741	436	217	33
3	417	341	215	122	71	9
4	454	373	235	151	86	9
5	402	338	205	131	61	6
6	399	349	205	133	73	14

Lam et al JAMA Card 2020

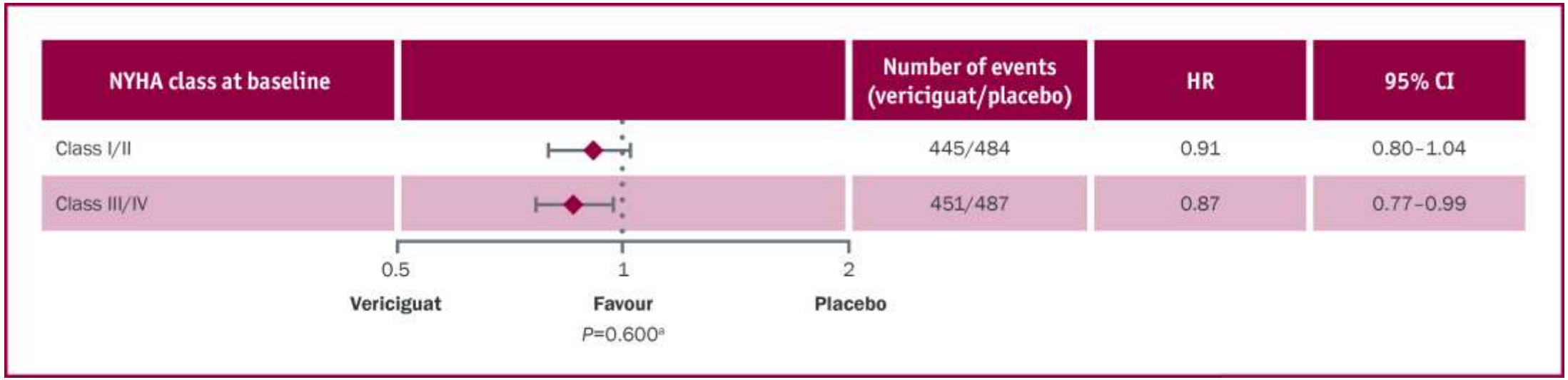
Tab 3/5: EF at screening[1,2]

EF at screening	Number of events (vericiguat/placebo)	HR	95% CI
<35%	637/703	0.88	0.79–0.97
≥35%	255/265	0.96	0.81–1.14
<40%	773/851	0.88	0.80–0.97
≥40%	119/117	1.05	0.81–1.36



[a]*P-value for treatment by subgroup interaction from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction.*

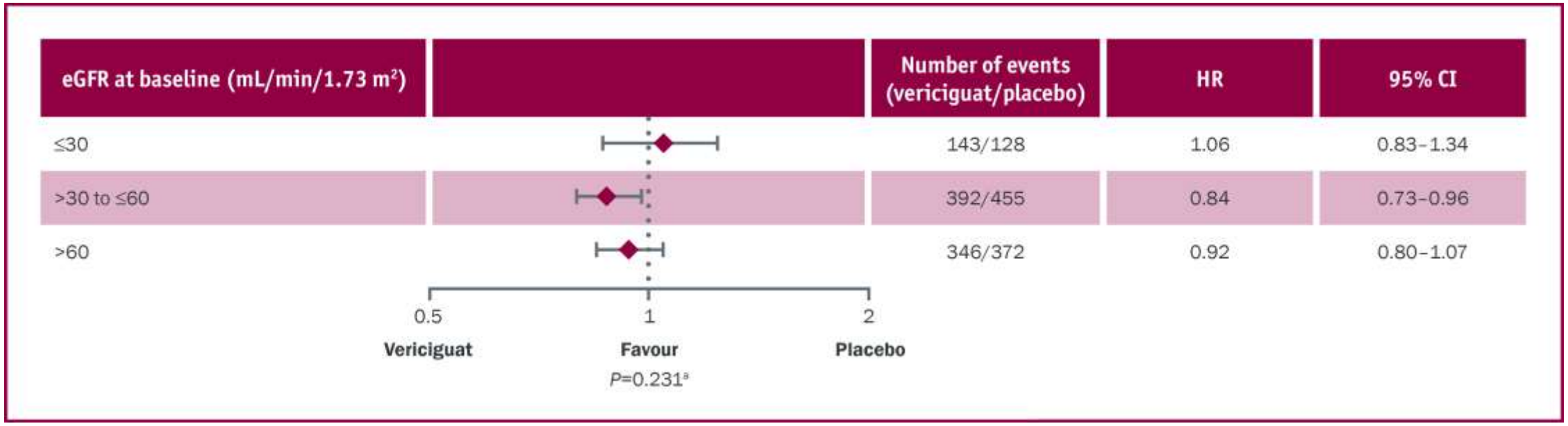
Tab 4/5: NYHA class at baseline[1,2]



[a]*P-value for treatment by subgroup interaction from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction.*

Tab 5/5: eGFR at baseline

- The benefit of vericiguat was observed in patients with a baseline eGFR >30 mL/min/1.73 m2 given in combination with available HF therapies in patients with symptomatic chronic HF following a worsening HF event[1,2]



[a]*P-value for treatment by subgroup interaction from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction.*

VICTORIA: Safety Outcomes
Flip card: 2/2

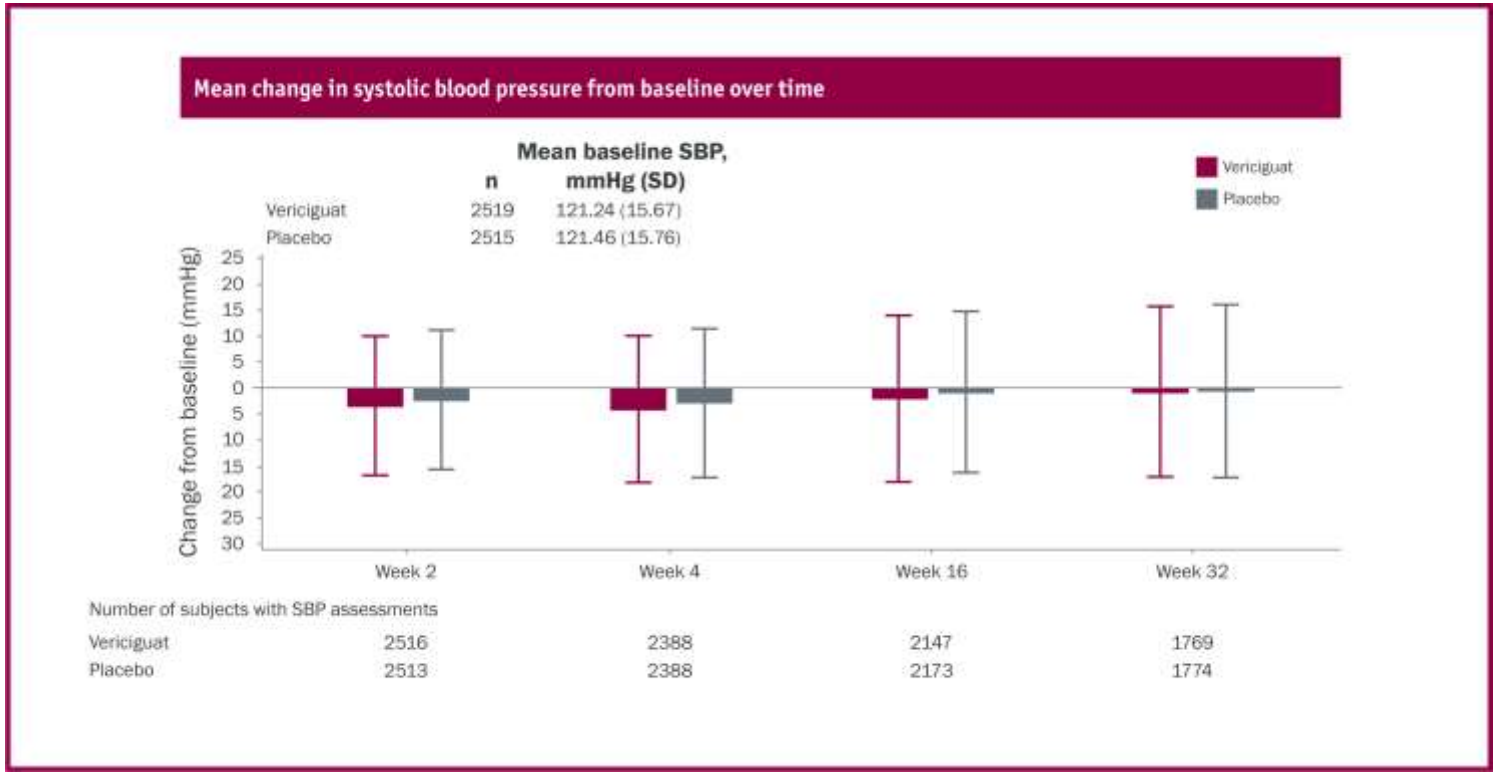
- There were prespecified events of clinical interest: Symptomatic hypotension and syncope
- Small differences in the rates of symptomatic hypotension (9.1% vs. 7.9%; P=0.121) and syncope (4.0% vs. 3.5%; P=0.303) were observed for vericiguat given in combination with available HF therapies compared with placebo in the VICTORIA study; despite decreases in systolic and diastolic blood pressure occurring early in the titration phase, no further clinically relevant reductions in blood pressure were subsequently observed

Adverse event	Vericiguat (n=2519) n (%)	Placebo (n=2515) n (%)	Difference in % vs. placebo	
			Estimate (95% CI)[a]	*P*-value[a]
Symptomatic hypotension	229 (9.1)	198 (7.9)	1.2 (-0.3–2.8)	0.121
Syncope	101 (4.0)	87 (3.5)	0.6 (-0.5–1.6)	0.303

[a]Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column. Estimated differences, confidence intervals and P values are provided in accordance with the statistical analysis plan.
Note: Includes events/measurements from the day of first dose study drug to 14 days after the last dose of study drug. Based on data up to the primary completion date (18 June 2019).
CI, confidence interval.

VICTORIA: Additional Safety Outcomes

- There were very small differences in mean systemic blood pressure values between the vericiguat and placebo arms (1–1.5 mmHg)



- Decreases in SBP occurred early in the titration phase
- No further clinically relevant reductions in BP were observed throughout the remainder of the study

VICTORIA trial evaluated patients with the largest medical need due to persistently elevated event rates, resulting in a much higher baseline-risk patient population compared to contemporary HF trials

Key details	PARADIGM HF (N=8399)[1] Sacubitril/valsartan	DAPA-HF (N=4744)[2] Dapagliflozin	EMPEROR-Reduced (N=3730)[3] Empagliflozin	VICTORIA (N=5050)[5] Vericiguat
eGFR cut-off	≥30 ml/min/1.73 m^2	≥30 ml/min/1.73 m^2	≥20 ml/min/1.73 m^2	≥15 ml/min/1.73 m^2
Recent HF decompensation	Not required	Not required	Not required	HFH within 6 months or IV diuretic use for HF within 3 months
Median NT-proBNP	1608	1437	1906	2816
HFH<6 months	31%	16%	NA	84%
IV diuretic for HF (without hospitalisation) within 3 months, n (%)	NR	NR	NR	15.9%
NYHA III-IV	25%	32%	25%	41%
eGFR <60 ml/min/1.73 m^2	37%	41%	48%	53%
Primary endpoint event rate (control arm)	**13.2 events/ 100 PY**	**15.6 events/ 100 PY**	**21.0 events/ 100 PY**	**37.8 events/100 PY**

100% focus on WHF patients

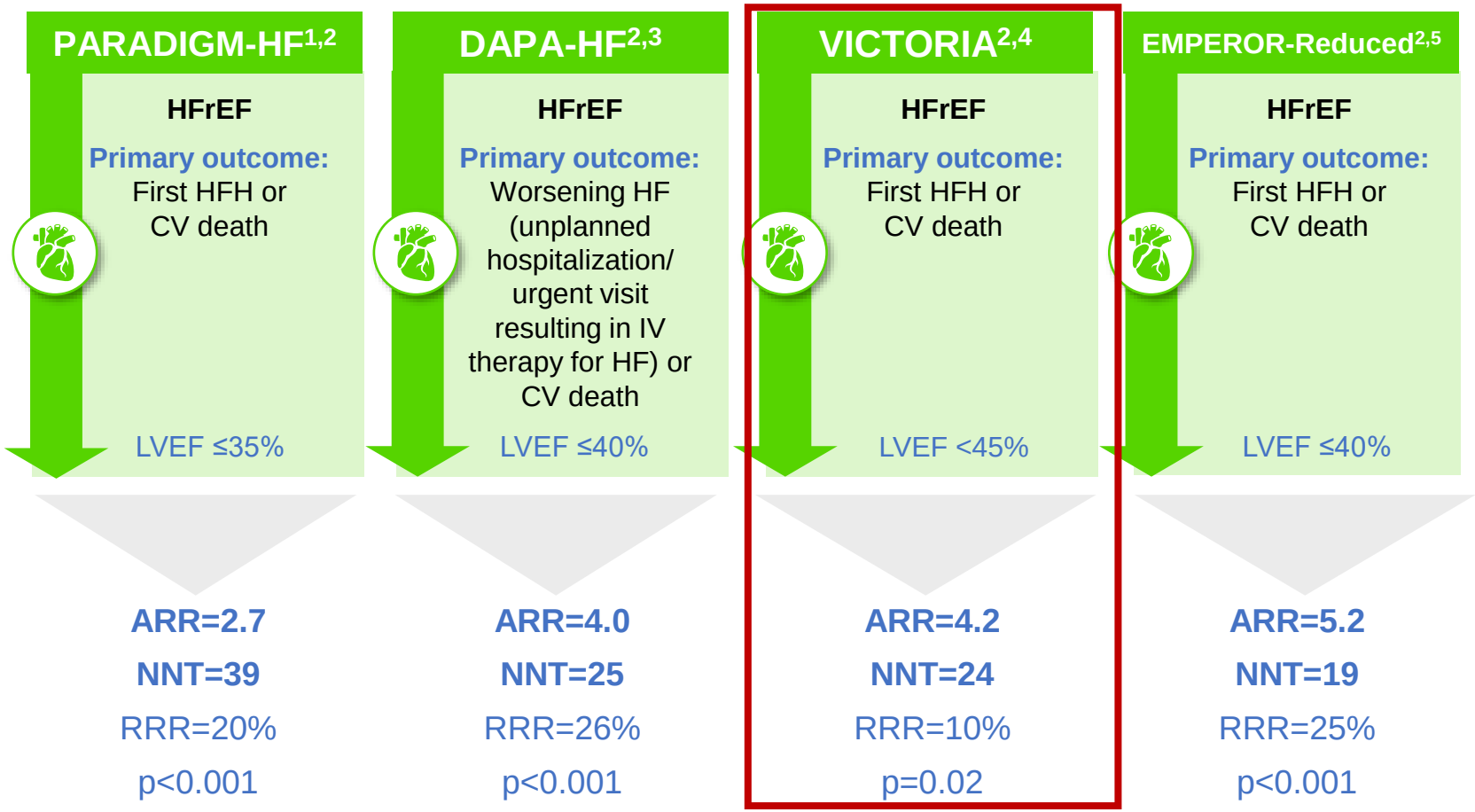
Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.

*Patients with AF or atrial flutter were required to have an NT-proBNP level ≥900 pg/ml, regardless of their history of HFH

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SR, sinus rhythm

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. Packer M et al. *N Engl J Med.* 2020;383:1413–1424; 4. Teerlink JR et al. *N Engl J Med.* 2021;384:105–116; 5. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

In patients with a recent worsening HF event, vericiguat reduced time to HFH or CV death with an ARR of 4.2%[1–6]



Each HF study was conducted independently, and no head-to-head HF studies have been completed that allow direct comparison of the efficacy and/or safety of one drug versus another.
ARR, absolute rate reduction; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; NNT, number needed to treat; PY, patient years; RRR, relative risk reduction.

References: 1. McMurray JJV *et al. N Engl J Med* 2014;371:993–1004; **2.** Chaudhary AG *et al. CJC Open* 2021;3:646–657; **3.** McMurray JJV *et al. N Engl J Med* 2019;381:1995–2008;

Summary: A New Target for an Unmet Need

Vericiguat addresses a new pathophysiological target for a population with substantial medical need

New physiological target in HF[1–2]

Vericiguat, a once-daily soluble guanylate cyclase (sGC) stimulator, targets an untapped pathway in HF to improve myocardial and vascular function

Simple titration

Can be safely combined with other therapies used to treat HF and co-morbidities

New patient population[1–3]

Despite receiving available HF therapies, patients are at increased risk for poor prognosis following a worsening HF event

The VICTORIA population was dramatically different to other contemporary HF trials; it was hyper-focused on symptomatic patients following a worsening HF event

Improved CV outcomes[1]

Vericiguat significantly reduced the risk of HF hospitalisation or CV death by 4.2 events per 100 patient years
(NNT: 24)

Relative risk reduction up to ~30% in NTproBNP Q1–3

Well tolerated[1]

The AE profile was comparable to placebo

Rates of symptomatic hypotension and syncope were similar to placebo

Similar rates of hyperkalaemia and renal outcomes[a] were observed between treatment arms

[a]Acute kidney injury, chronic kidney disease, renal failure and renal impairment.
AE, adverse event; AKI, acute kidney injury; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; NNT, number needed to treat; NT-proBNP, N-terminal pro B-type natriuretic peptide; RRR, relative risk reduction; sGC, soluble guanylate cyclase.

End of Section 2