
Therapeutic advances in HFrEF patients who have had a previous worsening HF event

Bayer Symposium
Saturday, 29 August 2020

Disclaimer

- This virtual symposium is provided to an audience of international healthcare professionals from around the world for scientific discussion and scientific exchange. The compounds presented are investigational or are being investigated for uses that have not been approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), or other health authorities

Welcome and Introductions

Carolyn S.P. Lam, MBBS, FRCP, PhD
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Professor of Duke-NUS Cardiovascular Academic Clinical Program

Disclosures

- Supported by a Clinician Scientist Award from the National Medical Research Council of Singapore
- Received research support from:
 - AstraZeneca, Bayer, Boston Scientific, Medtronic, Roche Diagnostics, and Vifor Pharma
- Served as consultant or on the Advisory Board/ Steering Committee / Executive Committee for:
 - Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc., Eko.ai Pte Ltd, JanaCare, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Stealth BioTherapeutics, The Corpus, Vifor Pharma, and WebMD Global LLC
- Serves as co-founder and non-executive director of EKo.ai Pte Ltd.
- Patents:
 - 1. Patent pending: PCT/SG2016/0502171
 - 2. Patent application No.: 16/216,9292

Agenda



Time	Topic	Speaker	
12:45	Welcome and introductions	Carolyn Lam (Singapore, SGP)	
12:50	Stimulating sGC: VICTORIA trial reveals improved outcomes in patients with HFrEF	Burkert Pieske (Berlin, GER)	
13:05	New insights from a deep dive into VICTORIA data and its potential impacts	Justin Ezekowitz (Edmonton, CAN)	
13:15	Putting the VICTORIA trial into perspective with contemporary HFrEF clinical trials	Javed Butler (Mississippi, US)	
13:25	Panel discussion and live Q&A	ALL	
13:45	Session close		

A Clinical Case....

Andrew was diagnosed with HFrEF 2 years ago ...

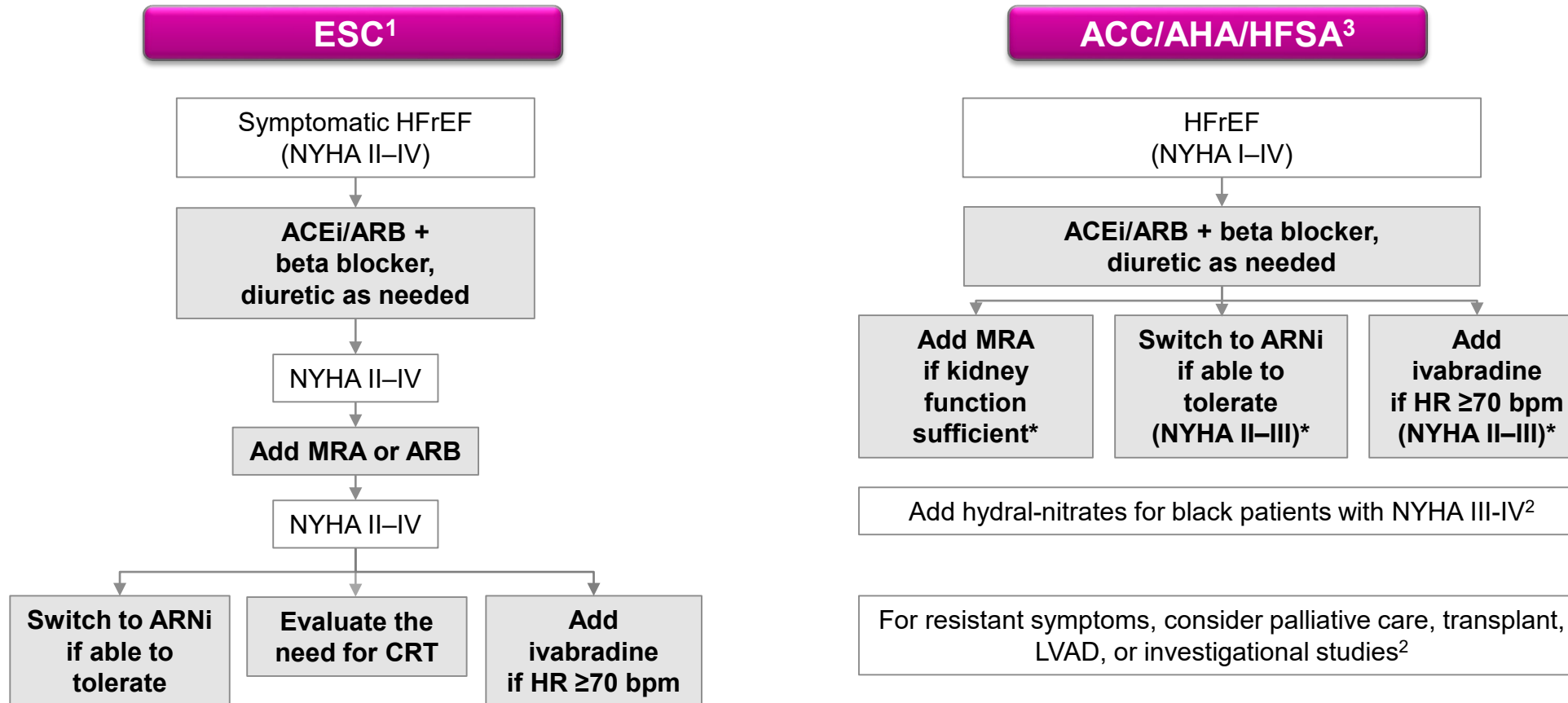
You are seeing him 3 months after his first HF hospitalisation



“
*My first hospitalisation
was terrifying and I'll do
everything I can to
prevent another visit*
”

Characteristic	Value
Age (years)	62
NYHA class	III
LVEF (%)	35
Comorbidities	Afib / CAD / Prior MI (No T2D)
eGFR (ml/min/1.73 m ²)	55
Heart Rate (bpm)	74
Current SBP (mmHg)	110

The EU and US Guidelines for Treating Patients with Symptomatic Chronic HF¹⁻³

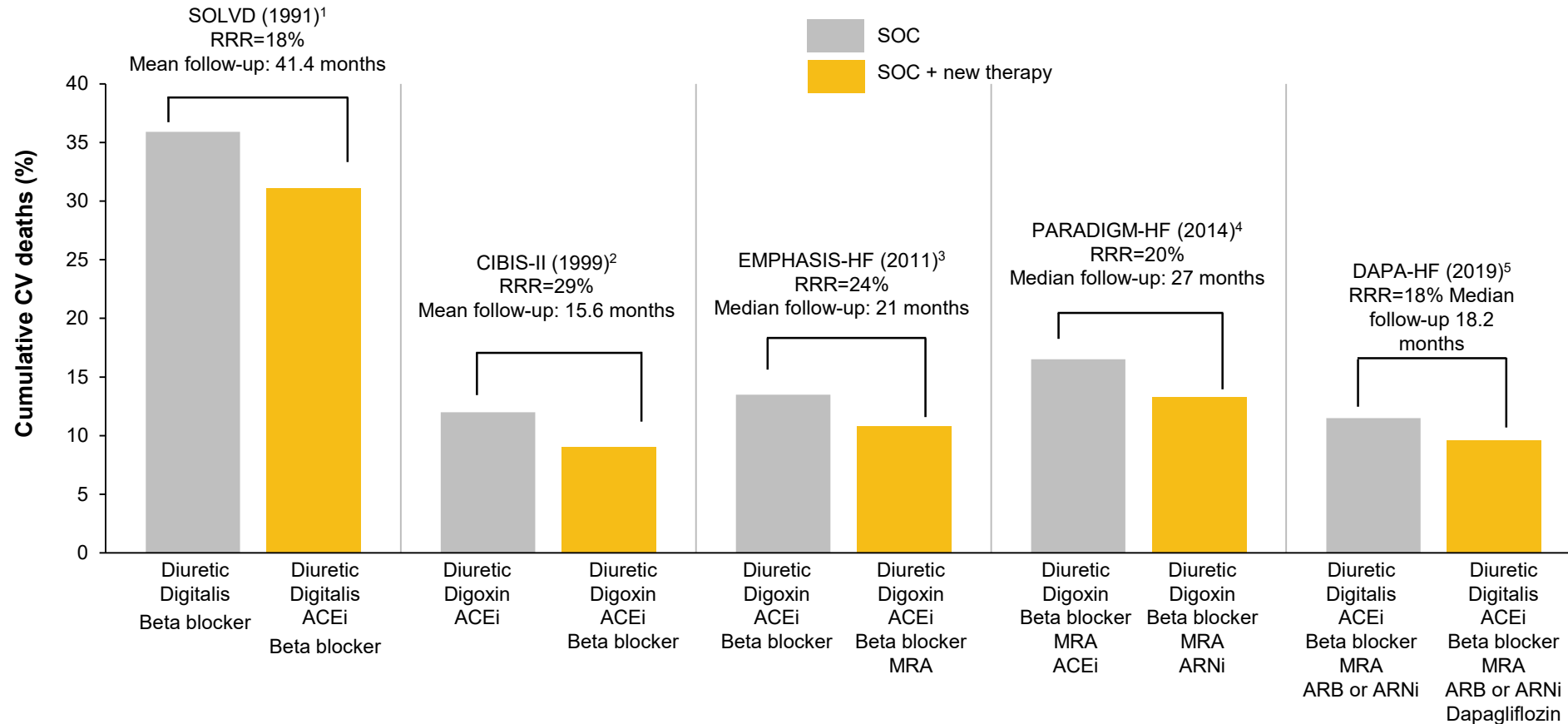


*The listed therapies are not mutually exclusive, and no order is inferred.

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; CRT, cardiac resynchronisation therapy; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; HR, heart rate; LVAD, left ventricle assist device; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

1. Ponikowski P et al. *Eur Heart J*. 2016;18:891–975; 2. Yancy CW et al. *J Am Coll Cardiol*. 2017;70:776–803; 3. Yancy CW et al. *J Am Coll Cardiol*. 2018;71:201–230.

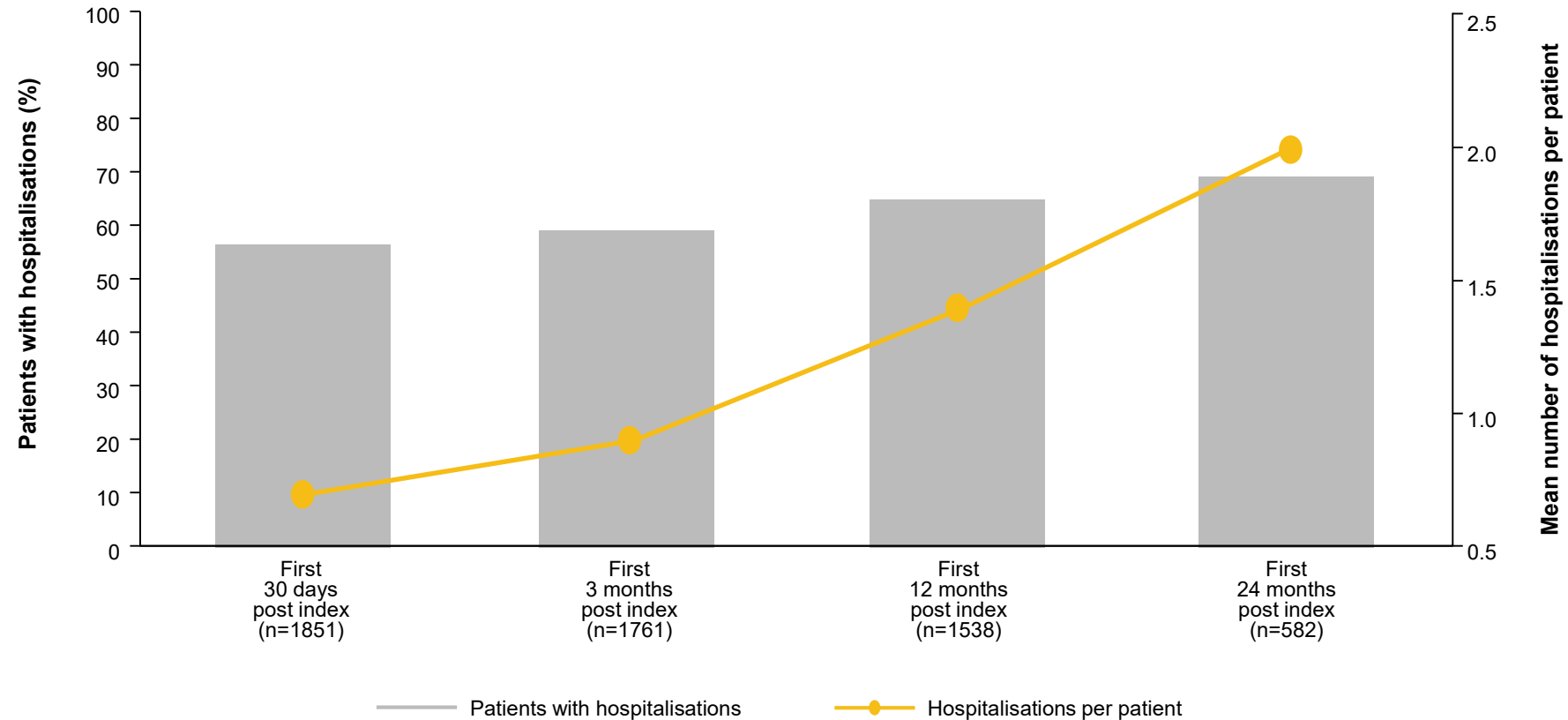
Residual Risk in HFrEF Remains Despite the Use of Available HF Medications¹⁻⁵



ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RRR, relative risk reduction.

1. SOLVD Investigators. *N Engl J Med.* 1991;325:293–302; 2. CIBIS-II Investigators. *Lancet.* 1999;353:9–13; 3. Zannad F et al. *N Engl J Med.* 2011;364:11–21; 4. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 5. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008.

Patients with Hospitalisations and Number of Hospitalisations per Patient up to 2 Years After Worsening HF Event

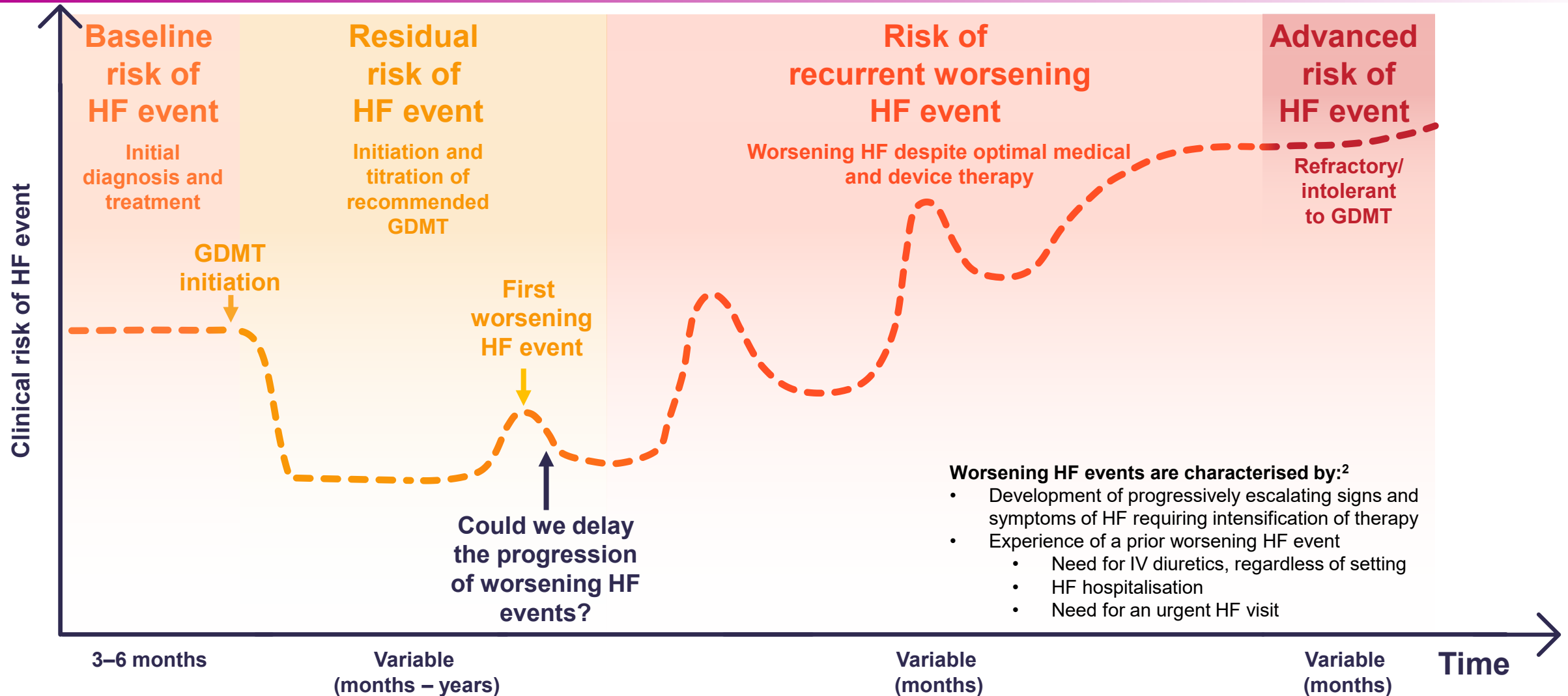


56% of patients were rehospitalised within 30 days of the worsening HF event, and the number of HF-related hospitalisations increased over time

Note that 'worsening HF' 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 hospitalised setting. HF, heart failure

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

Patients with Symptomatic Chronic HF can Progressively Worsen Over Time¹



GDMT, guideline-directed medical therapy; HF, heart failure; IV, intravenous

1. Modified from Greene SJ et al. *Circ Heart Fail.* 2020;13:e007132; 2. Butler J et al. *J Am Coll Cardiol.* 2019;73:935–944.

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Stimulating sGC: VICTORIA Trial Reveals Improved Outcomes in Patients with HFrEF

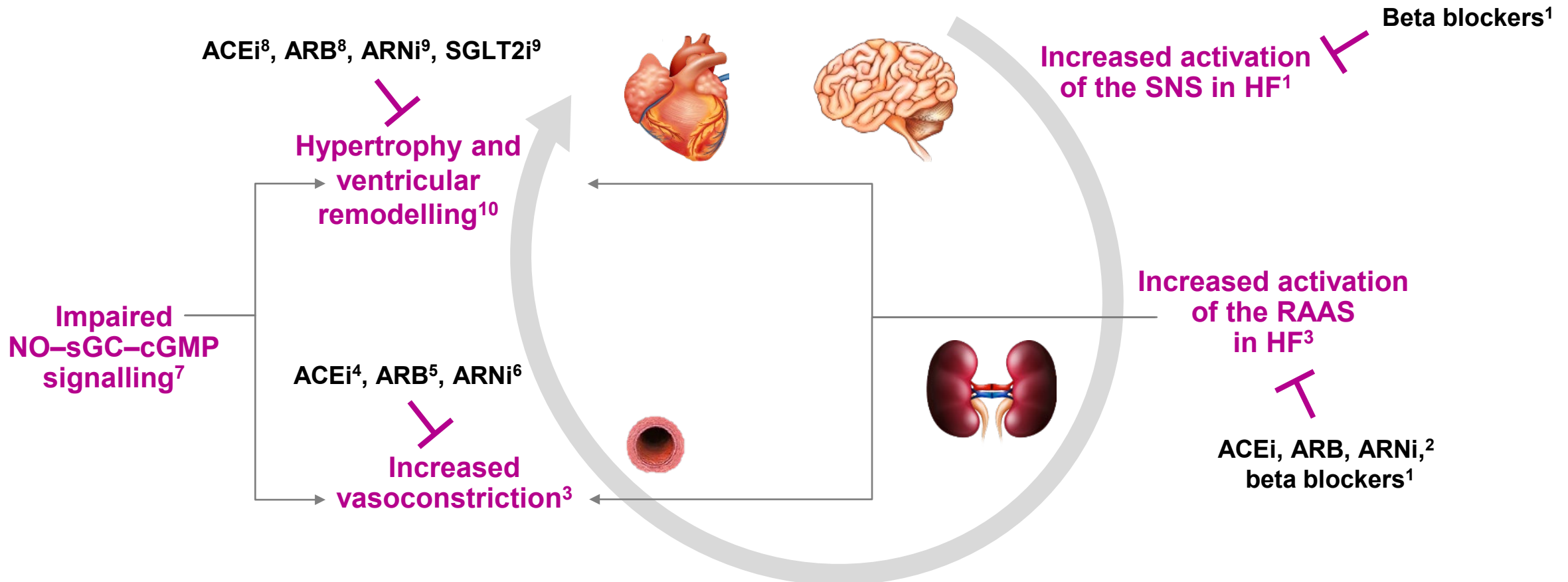
*Burkert Pieske, MD
Professor of Medicine
Head of Cardiology
Charité University Medicine, Berlin
German Heart Center, Berlin
Germany*

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 - Novartis, Bayer Healthcare, Merck, Servier, Astra-Zeneca, BMS, Daiichi-Sankyo, and Medscape

Some Established Pathways Contributing to HFrEF Are Already Medically Addressed¹⁻¹⁰

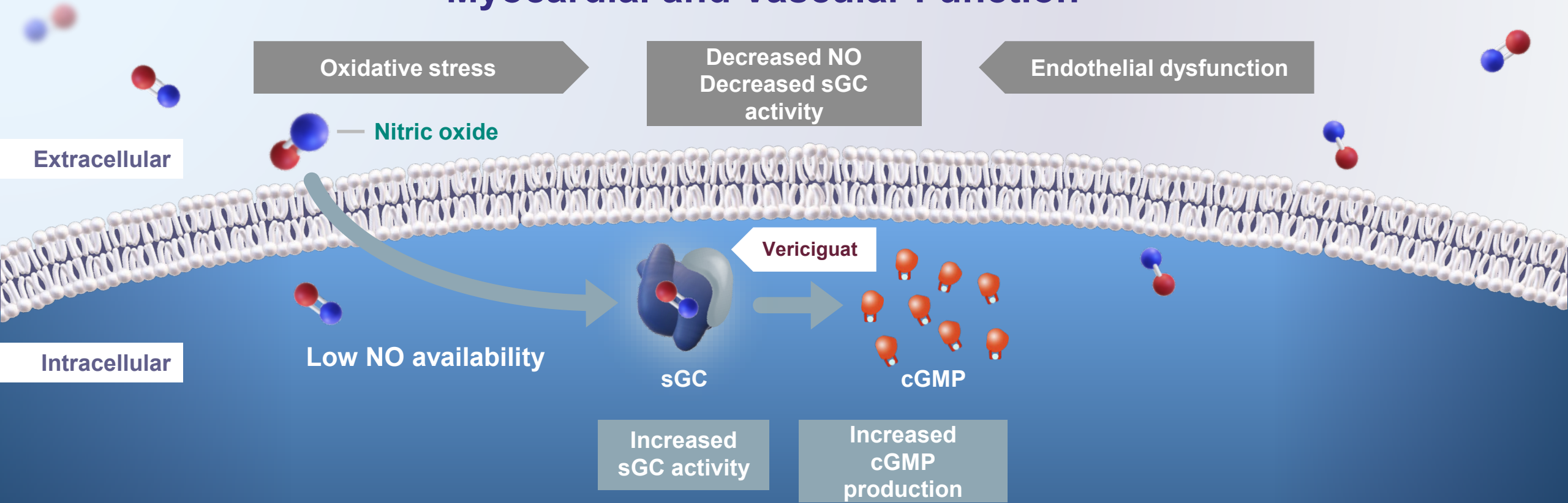


MRA and diuretics increase Na⁺ resorption and increased water retention

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

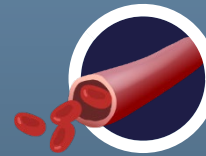
1. Triposkiadis F et al. *J Am Coll Cardiol*. 2009;54:1747-1762; 2. Yancy CW et al. *J Am Coll Cardiol*. 2017;70:776-803; 3. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Elsevier/Saunders; 2015; 4. Enseleit F et al. *J Cardiovasc Pharmacol*. 2001;37:S21-S30; 5. Kobori H et al. *Curr Pharm Des*. 2013;19:3033-3042; 6. Ponikowski P et al. *Eur J Heart Fail*. 2016;18:891-975; 7. Gheorghide M et al. *Heart Fail Rev*. 2013;18:123-134; 8. Cohn JN et al. *J Am Coll Cardiol*. 2000;35:569-582; 9. Matsumura K & Sugiura T. *Cardiovascular Ultrasound* 2019;17:26. doi: 10.1186/s12947-019-0177-8; 10. Jia G et al. *Hypertension*. 2018;72:537-548.

Vericiguat Increases sGC Activity to Improve Myocardial and Vascular Function¹⁻⁸



Heart

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



Vasculature

- ↓ Arterial constriction
- ↓ Vascular stiffness

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

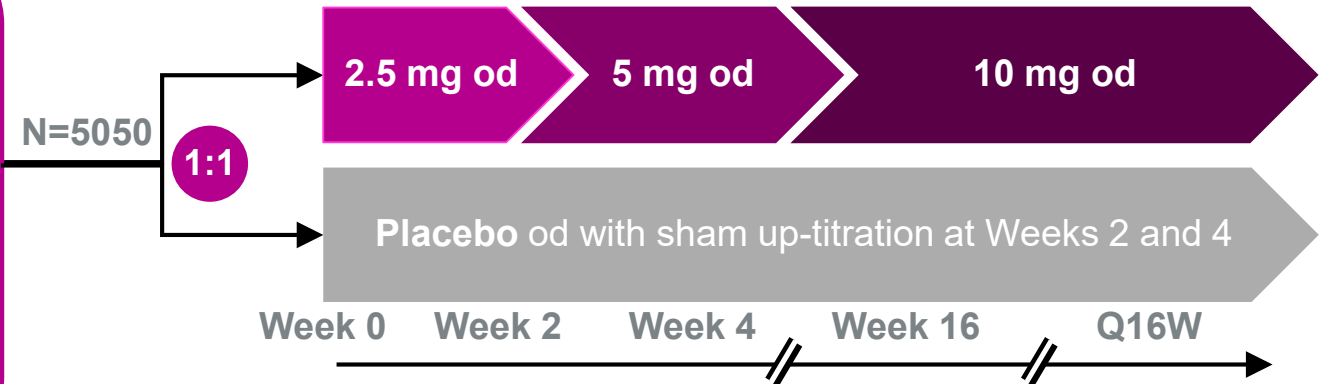
1. Gheorghiu M et al. *Heart Fail Rev.* 2013;18:123–134. 2. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* Elsevier/Saunders; 2015; 3. Boerrigter G et al. *Handb Exp Pharmacol.* 2009;191:485–506. 4. Breitenstein S et al. *Handb Exp Pharmacol.* 2017;243:225–247; 5. Felker G & Mann D. *Heart Failure: A Companion to Braunwald's Heart Disease.* Elsevier; 2020; 6. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 7. Follmann M et al. *J Med Chem.* 2017;60:5146–5165; 8. Mathar I et al. *Circulation.* 2018;138:A15553

VICTORIA Study Design^{1,2}

Design: randomised, parallel-group, placebo-controlled, double-blind, event-driven, international phase III trial
Objective: evaluate the effect of vericiguat in patients with symptomatic chronic HF following a worsening HF event

Eligibility criteria

- HFrEF (LVEF <45%)
- NYHA class II–IV
- BNP: ≥300 pg/ml; SR ≥500 pg/ml +AF
- NT-proBNP: ≥1000 pg/ml; SR ≥1600 pg/ml +AF
- eGFR: ≥15 ml/min/1.73 m²
(15% cap: 15–30 ml/min/1.73 m²)
- HF hospitalisation within 6 months or IV diuretic treatment for HF within 3 months



Primary endpoint: Time to first occurrence of the composite of CV death and HF hospitalisation

After approximately 12 months, 10 mg target dose was achieved: vericiguat (89.2%); placebo (91.4%)

VICTORIA Baseline Characteristics: Index Event

Selected baseline characteristics	Vericiguat (n=2526)	Placebo (n=2524)
HF hospitalisation within 3 months	1673 (66.2)	1705 (67.6)
HF hospitalisation at 3–6 months	454 (18.0)	417 (16.5)
IV diuretic for HF (without hospitalisation) within 3 months	399 (15.8)	402 (15.9)

~84% of patients randomised had an index HF hospitalisation
within 6 months

VICTORIA Was Designed to Study Patients with Symptomatic Chronic HF Following a Worsening HF Event¹⁻⁴

'Symptomatic chronic HF'

NYHA class II–IV

LVEF <45%

On available HF therapies

&

'Worsening HF event'

Recent HF decompensation
(HF hospitalisation or IV diuretic use)

Elevated natriuretic peptides

Patients may have been randomised as an inpatient or outpatient but must have met criteria for clinical stability (e.g., SBP \geq 100 mmHg; off IV treatments \geq 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. Hicks KA et al. *Circulation.* 2015;132:302–361; 3. EMA. CPMP/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 23 July 2020; 4. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086

VICTORIA Baseline Characteristics: Gender, Age and Geographical Region

Selected baseline characteristics	Vericiguat (n=2526)	Placebo (n=2524)
Gender, n (%)		
Male	1921 (76.0)	1921 (76.1)
Female	605 (24.0)	603 (23.9)
Age (year)		
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)

VICTORIA Baseline Characteristics: NYHA Class and LVEF

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 group
 LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation
 Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

VICTORIA Baseline Characteristics: Standard of Care Therapies at Baseline

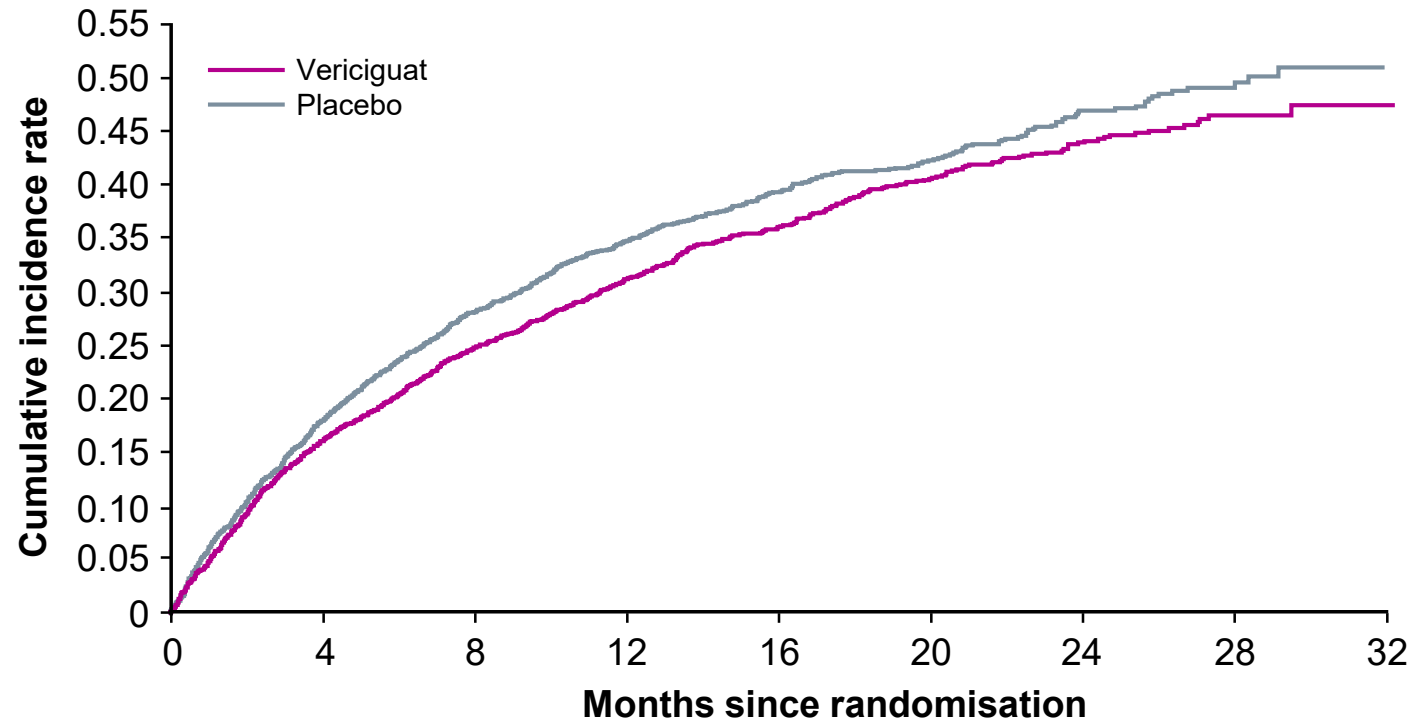
Selected baseline characteristics	Vericiguat (n=2526)	Placebo (n=2524)
Baseline SoC medications, n (%)		
Beta blockers	2349 (93.2)	2342 (93.0)
ACEi/ARB	1847 (73.3)	1853 (73.6)
MRA	1747 (69.3)	1798 (71.4)
3 SoC medications*	1480 (58.7)	1529 (60.7)
Sacubitril/valsartan	360 (14.3)	371 (14.7)
Baseline SoC 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, RAAS inhibitors, and MRAs

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SoC, standard of care
Armstrong PW et al. *N Engl J Med.* 2020;382:1883-1893

Cumulative Incidence Rate of the Primary Endpoint

Time to CV death or first HF hospitalisation



- Median treatment duration for primary endpoint: 10.8 months
- Annual event rates for vericiguat and placebo per 100 patient-years were 33.6 and 37.8, respectively

$p=0.02$

HR=0.90 (95% CI 0.82–0.98)

ARR=4.2% per year

Annual NNT=24*

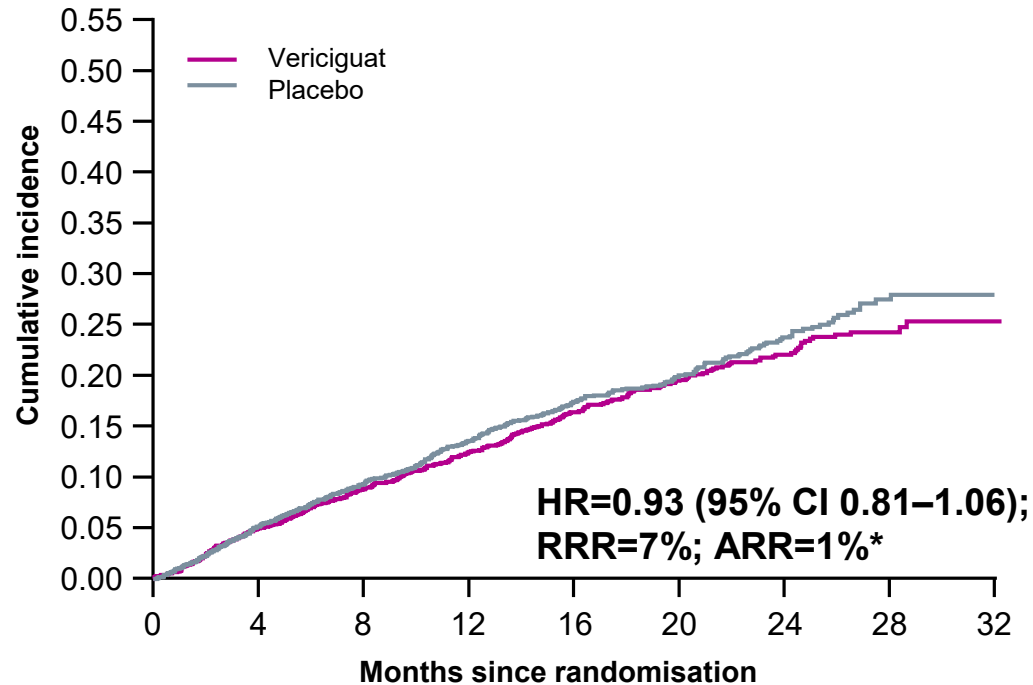
Number of subjects at risk

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

*Annual NNT: $100/4.2 = 24$. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NNT, number needed to treat
Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

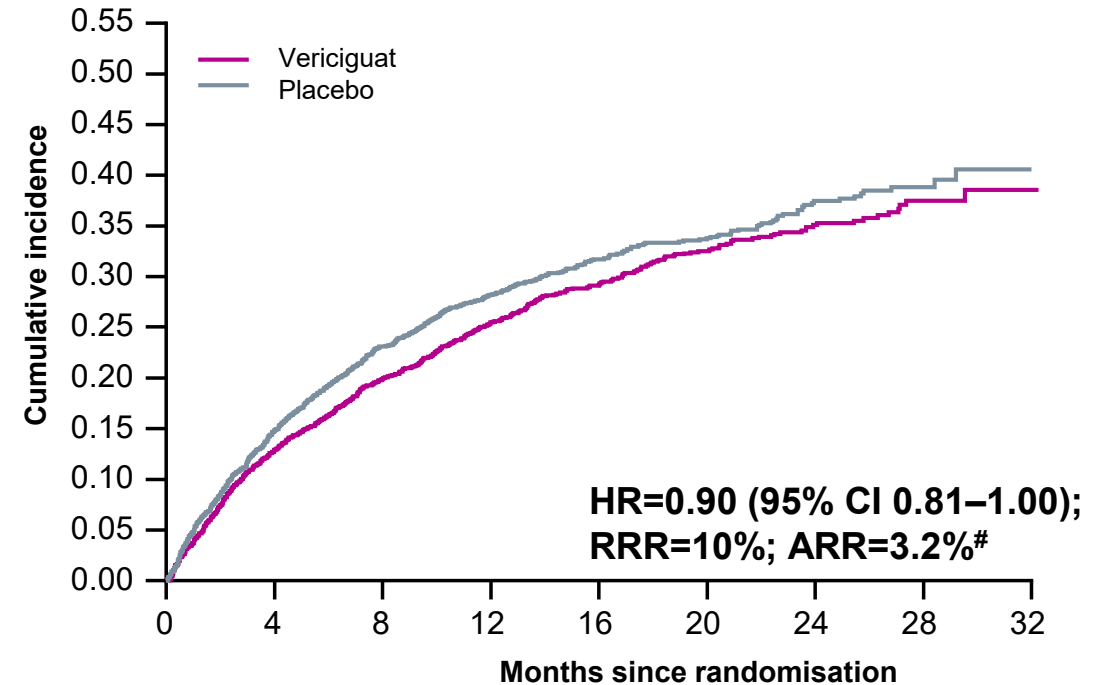
Cumulative Incidence Rates of the Individual Components of the Primary Endpoint^{1,2}

Time to CV death



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

Time to HF hospitalisation



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

*Annual ARR: 13.9–12.9=1%; #annual ARR: 29.1–25.9=3.2%

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; RRR, relative risk reduction

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086.

Secondary Outcomes and Components

	Vericiguat (n=2526)		Placebo (n=2524)		Treatment comparison	
	%	Events/ 100 pt-yr	%	Events/ 100 pt-yr	HR (95% CI)*	p-value#
Total HF hospitalisations‡		38.3		42.4	0.91 (0.84–0.99)	0.02
Composite of first HF hospitalisations and all-cause mortality	37.9	35.9	40.9	40.1	0.90 (0.83–0.98)	0.02
HF hospitalisation	27.4		29.6			
All-cause mortality§	10.5		11.3			

Based on data up to the primary analysis cut-off date (18 Jun 2019). For patients with multiple events, only the first event contributing to the composite endpoint is counted in the table. *HRs (vericiguat over placebo) and CIs 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 geographic region and race; †patients could have been hospitalized more than once; §mortality components of the primary and secondary composite outcomes were not preceded by a HF hospitalisation

CI, confidence interval; HF, heart failure; HR, hazard ratio; pt-yr, patient-years

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

Subgroup Analysis of Primary Endpoint – ITT (1)

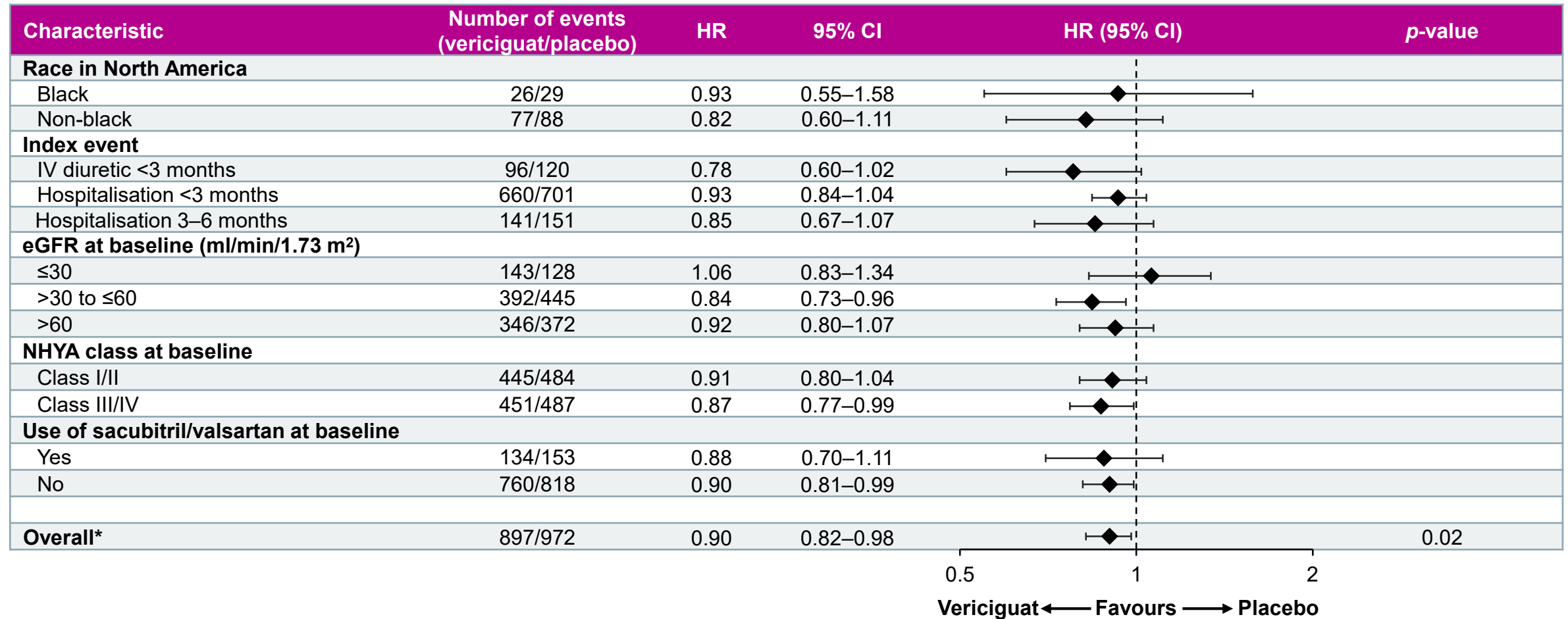
Characteristic	Number of events (vericiguat/placebo)	HR	95% CI	HR (95% CI)	p-value
Gender					
Male	704/762	0.90	0.81–1.00		
Female	193/210	0.88	0.73–1.08		
Age group (years)					
<65	290/348	0.81	0.70–0.95		
≥65	607/624	0.94	0.84–1.06		
Age group (years)					
<75	579/669	0.84	0.75–0.94		
≥75	318/303	1.04	0.88–1.21		
Race					
White	593/635	0.91	0.81–1.02		
Asian	199/207	0.91	0.75–1.11		
Black	41/50	0.85	0.56–1.28		
Other	64/80	0.80	0.57–1.11		
Geographical region					
Eastern Europe	310/345	0.87	0.75–1.01		
Western Europe	173/178	0.96	0.78–1.18		
North America	103/117	0.85	0.65–1.10		
Latin and South America	100/116	0.83	0.63–1.08		
Asia-Pacific	211/216	0.96	0.79–1.16		
Overall*	897/972	0.90	0.82–0.98		0.02

0.5 1 2
 Vericiguat ← Favours → Placebo

*Primary endpoint p-value

CI, confidence interval; HR, hazard ratio; ITT, intention to treat
 Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

Subgroup Analysis of Primary Endpoint – ITT (2)

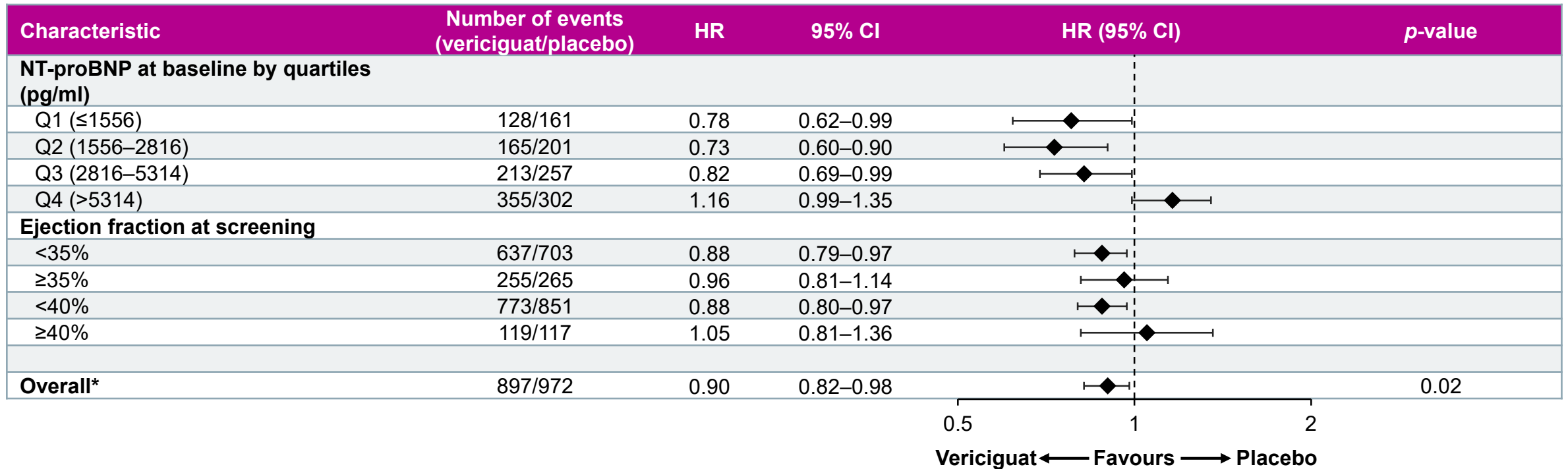


*Primary endpoint p-value

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ITT, intent-to-treat; IV, intravenous; NYHA, New York Heart Association

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

Subgroup Analysis of Primary Endpoint – ITT (3)



*Primary endpoint p-value

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile
 Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

VICTORIA Safety Profile (1): AE and SAE Incidence

	Vericiguat		Placebo		Total	
	n	%	n	%	n	%
Patients in population	2519		2515		5034	
With ≥1 AE	2027	80.5	2036	81.0	4063	80.7
With SAEs	826	32.8	876	34.8	1702	33.8

The overall AE profiles and incidence of SAEs were similar between vericiguat and placebo

SAEs Within a System Organ Class:

More anaemia developed with vericiguat (7.6%) than with placebo (5.7%)
The electrolyte balance was similar between vericiguat and placebo

VICTORIA Safety Profile (2):

Patients with adverse events of clinical interest: Symptomatic hypotension and syncope

	Vericiguat (n=2519)	Placebo (n=2515)	Difference in % vs placebo	
			Estimate (95% CI)	p-value
Symptomatic hypotension	229 (9.1)	198 (7.9)	1.2 (-0.3 to 2.8)	0.121
Syncope	101 (4.0)	87 (3.5)	0.6 (-0.5 to 1.6)	0.303

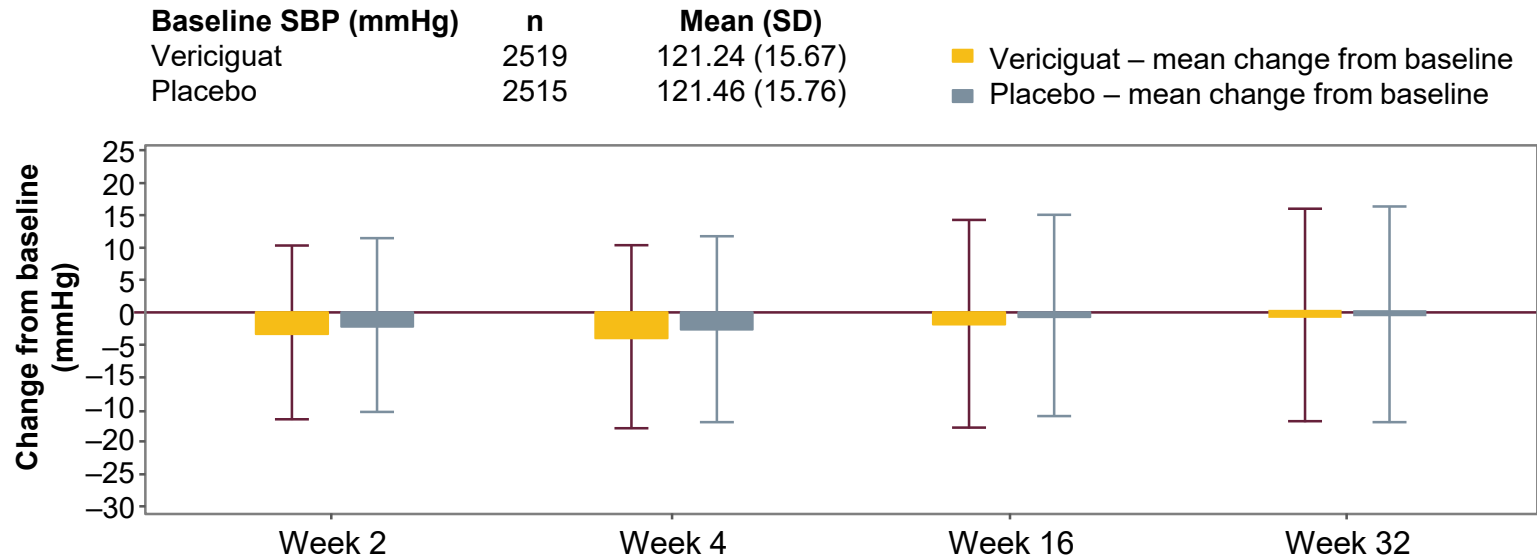
Values presented as n (%)

AE, adverse event; CI, confidence interval

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

VICTORIA Safety Profile (3): Change in SBP

Mean change in SBP from baseline over time



Number of subjects with SBP assessments at each time point

Vericiguat	2516	2388	2147	1769
Placebo	2513	2388	2173	1774

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

Summary

Mechanism of action^{1,2}

- Vericiguat enhances the cGMP pathway, leading to improved myocardial and vascular function in HF

Efficacy²

- Vericiguat significantly reduced the annualised absolute risk of the VICTORIA composite outcome of time to HF hospitalisation or CV death by 4.2%
- The effect of vericiguat on the primary outcome was consistent across most prespecified subgroups
- The impact of NT-proBNP quartiles on treatment effect needs further analysis

Patient population²

- VICTORIA included patients with symptomatic chronic HF (LVEF <45%) who had a previous worsening HF event despite currently available HF therapies

Safety²

- Overall AE profile of vericiguat comparable to that of placebo
- Rates of symptomatic hypotension and syncope were similar between vericiguat and placebo
- No decreases in eGFR
- Despite decreases in SBP and DBP occurring early in the titration phase, no further clinically relevant reductions in BP were subsequently observed

AE, adverse event; BP, blood pressure; CV, cardiovascular; cGMP, cyclic guanosine monophosphate; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide

1. Gheorghiade M et al. *Heart Fail Rev.* 2013;18:123; 2. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

New Insights from a Deep Dive into VICTORIA Data and Their Potential Impacts

*Justin Ezekowitz MB, BCH, MSc
Professor of Medicine
Department of Medicine
University of Alberta
Edmonton, Alberta, Canada*

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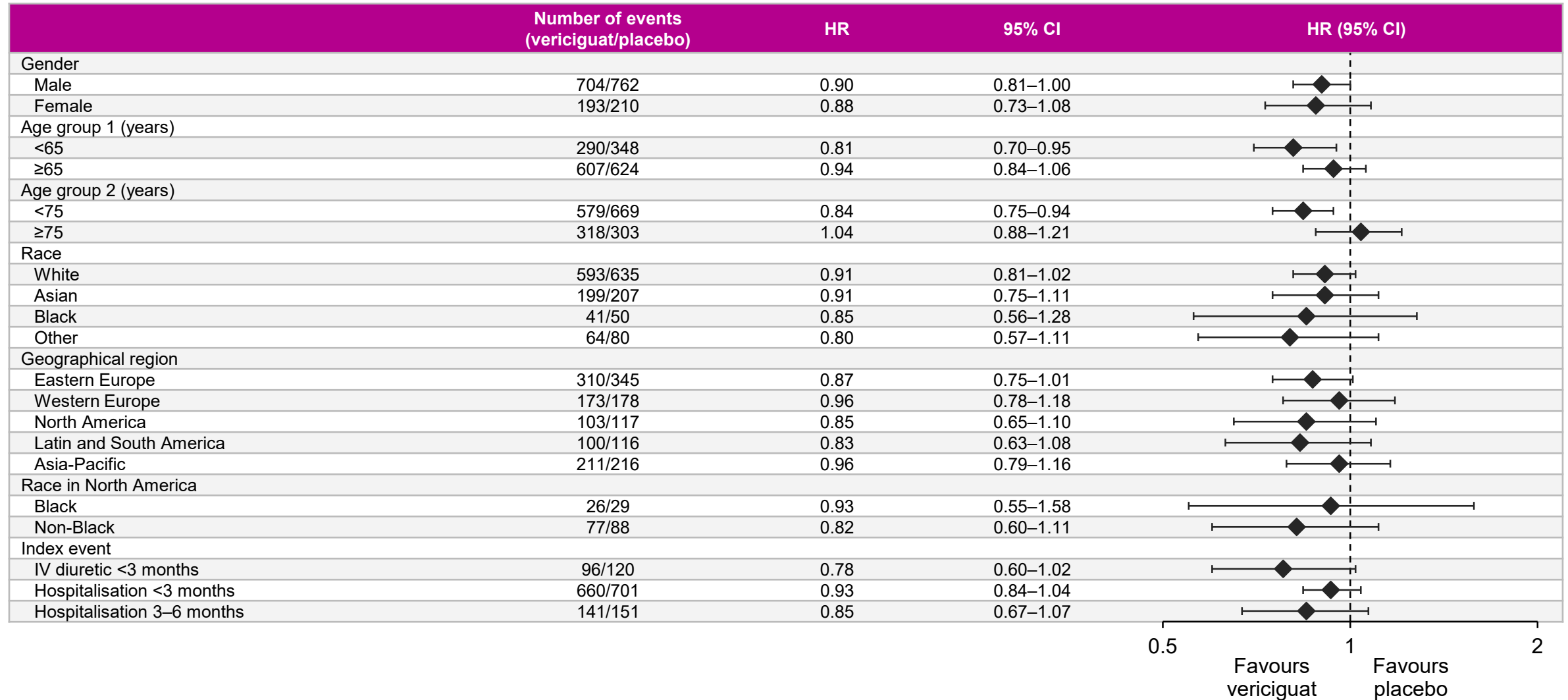
- Available online: thecvc.ca
- VICTORIA: Executive Committee
- The VICTORIA trial was funded by Bayer and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

The VICTORIA Trial

Vericiguat in patients with symptomatic chronic HF (and LVEF <45%) who had been receiving GDMT and had a previous worsening HF event

- Compared with placebo, vericiguat reduced the primary outcome of CV death or HF hospitalisation in patients with HFrEF in VICTORIA
- The effect of vericiguat on the primary outcome was consistent across most prespecified subgroups
- A prespecified subgroup analysis identified an interaction between treatment and the primary outcome according to NT-proBNP levels

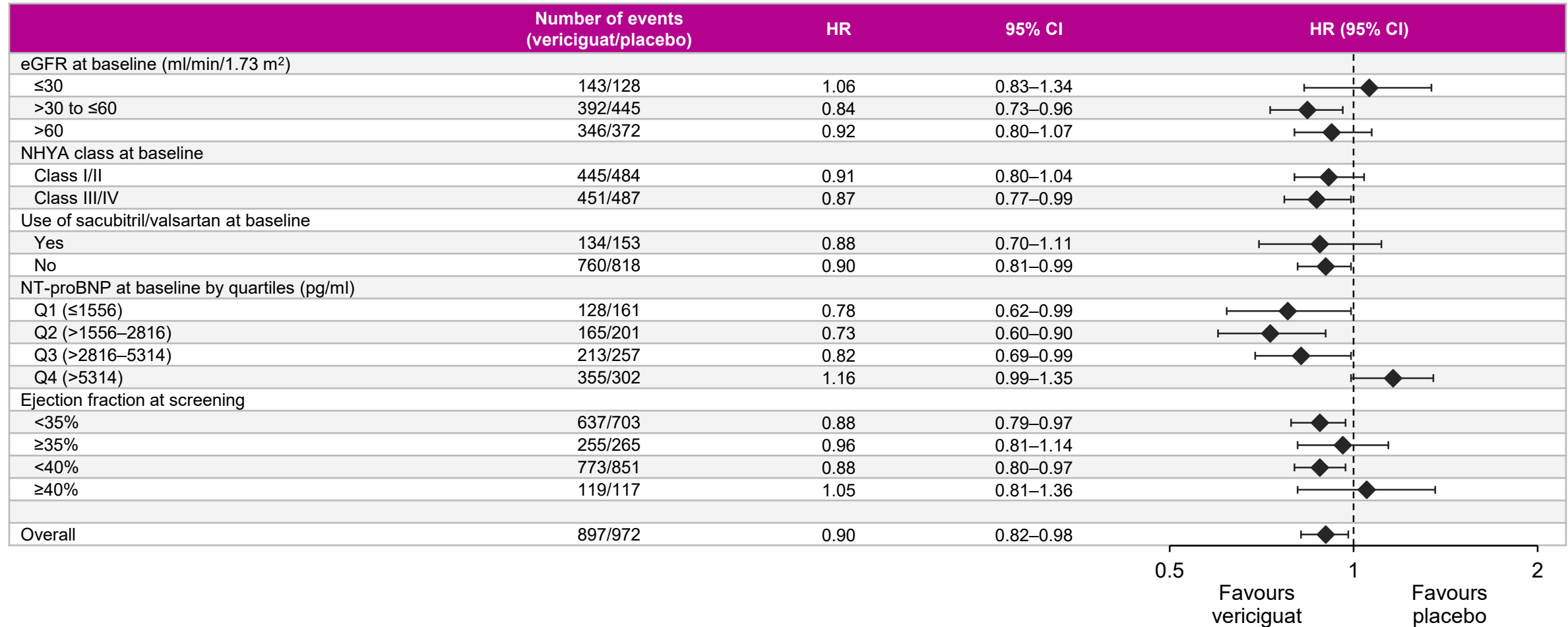
The Effect of Vericiguat on the Primary Outcome was Consistent Across Most Prespecified Subgroups (1)



CI, confidence interval; HF, heart failure; HR, hazard ratio; IV, intravenous.

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

The Effect of Vericiguat on the Primary Outcome was Consistent Across Most Prespecified Subgroups (2)

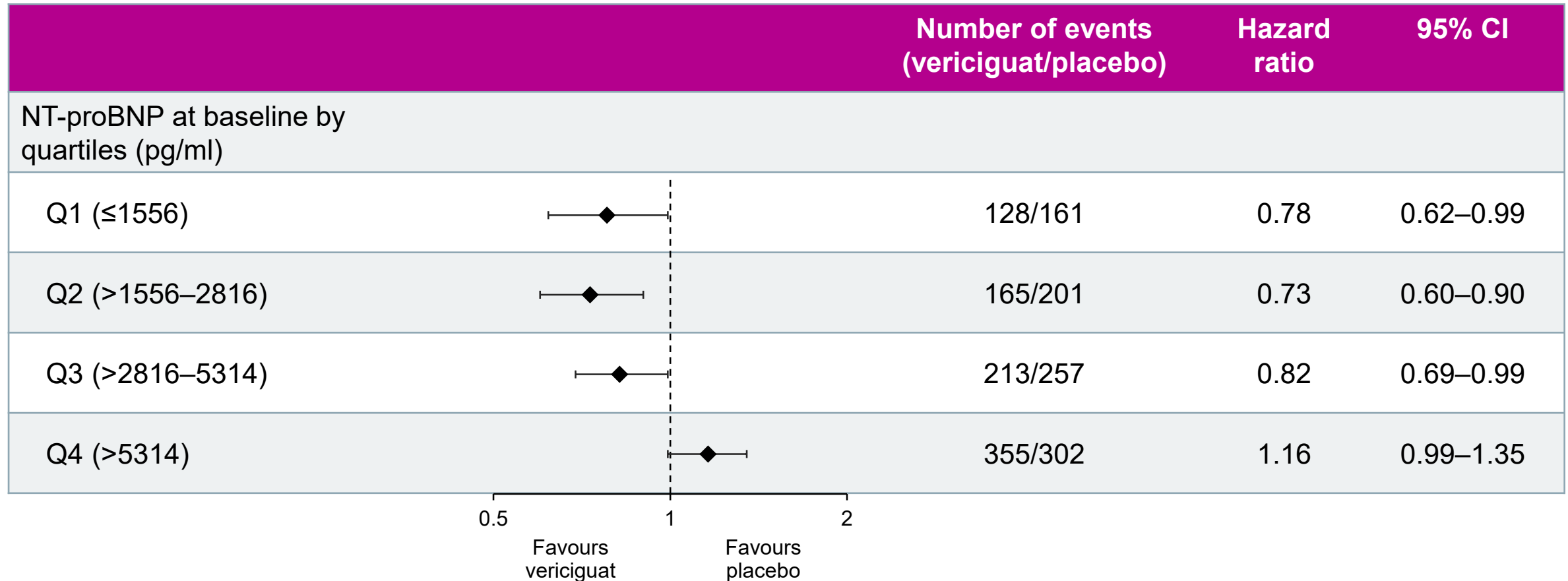


CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile.

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

Subgroup Analysis of Primary Endpoint – ITT

NT-proBNP at baseline by quartiles



NT-proBNP and Clinical Outcomes in VICTORIA

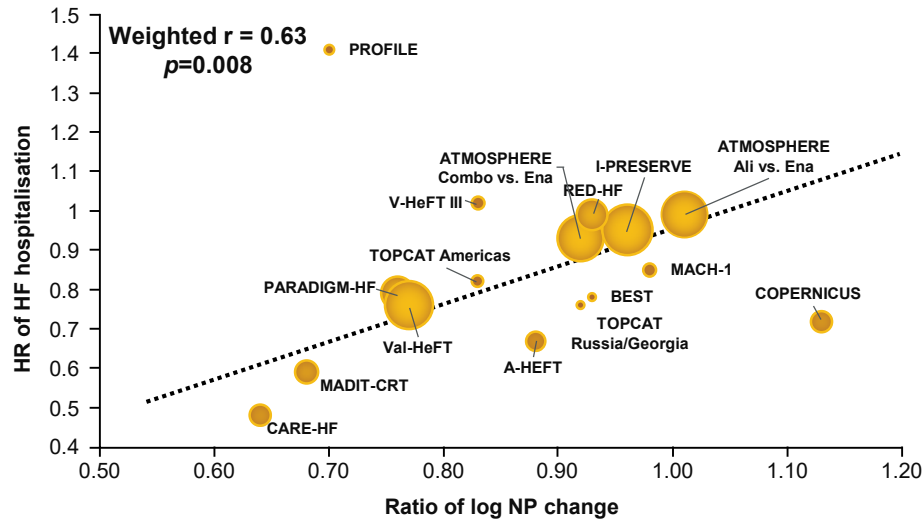
*Justin A. Ezekowitz, Christopher M. O'Connor, Richard W. Troughton,
Wendimagegn Alemayehu, Cynthia M. Westerhout, Adriaan A. Voors,
Javed Butler, Carolyn S. P. Lam, Piotr Ponikowski, Michele Emdin,
Mahesh J. Patel, Burkert Pieske, Lothar Roessig, Adrian F. Hernandez,
Paul W. Armstrong*

Background

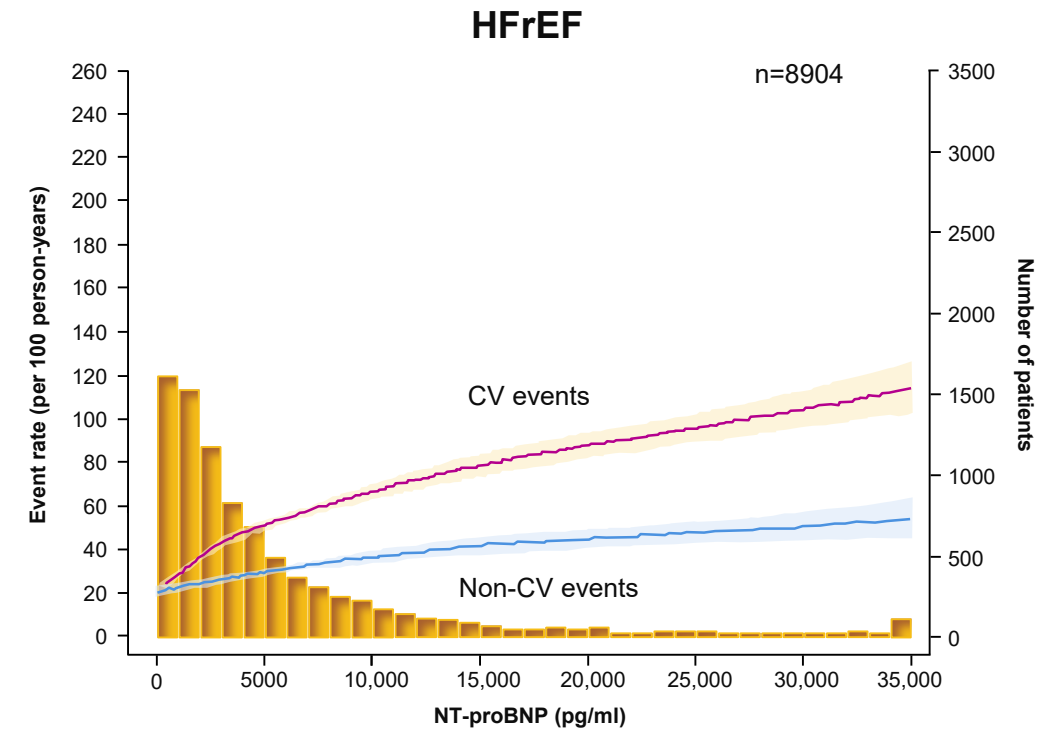
NT-proBNP

- Marker of prognosis in patients with HFrEF
- Inclusion criteria for clinical trials
- Often linked to treatment efficacy

Plot of treatment-related changes in natriuretic peptides against clinical effects on HF hospitalisation¹



Association between continuous NT-proBNP levels and risk of outcomes²

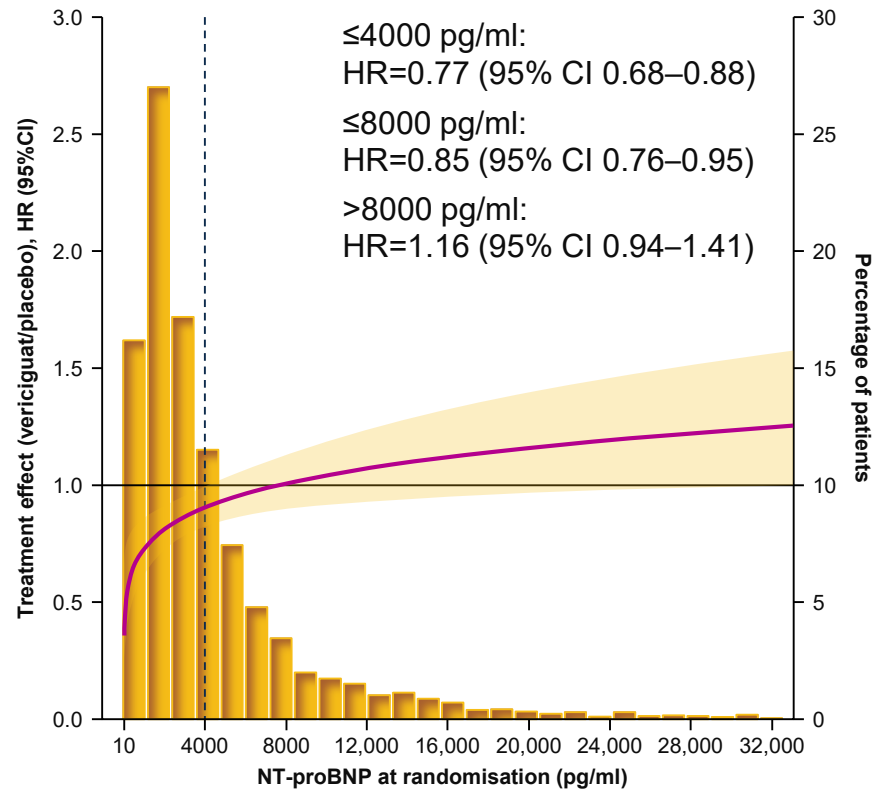


CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

1. Vaduganathan M, et al. *JACC Heart Fail.* 2018;6:564–569; 2. Savarese G et al. *JACC Heart Failure.* 2018;6:246–256.

Association of Vericiguat Treatment Effect on Clinical Outcomes by NT-proBNP at Randomisation

Primary composite outcome

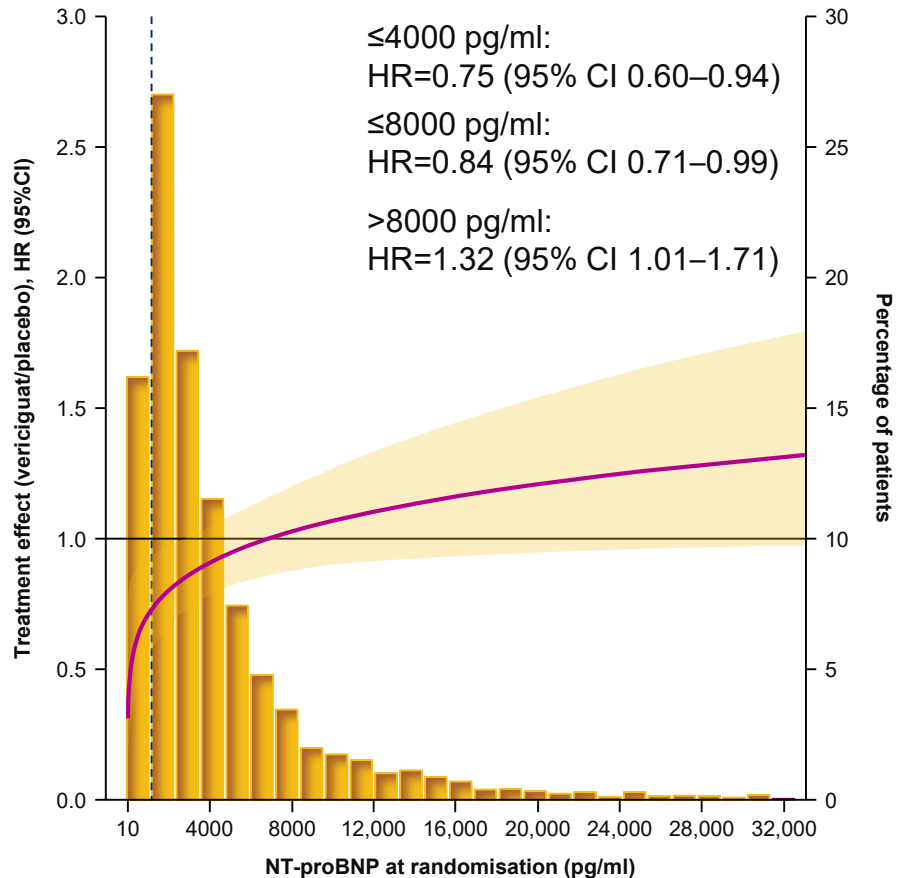


- The treatment effect of vericiguat, compared with placebo, on the primary composite endpoint was:
 - Evident for patients with NT-proBNP ≤8000 pg/ml (86% of the VICTORIA population)
 - Further amplified in patients with NT-proBNP ≤4000 pg/ml (65% of the VICTORIA population)

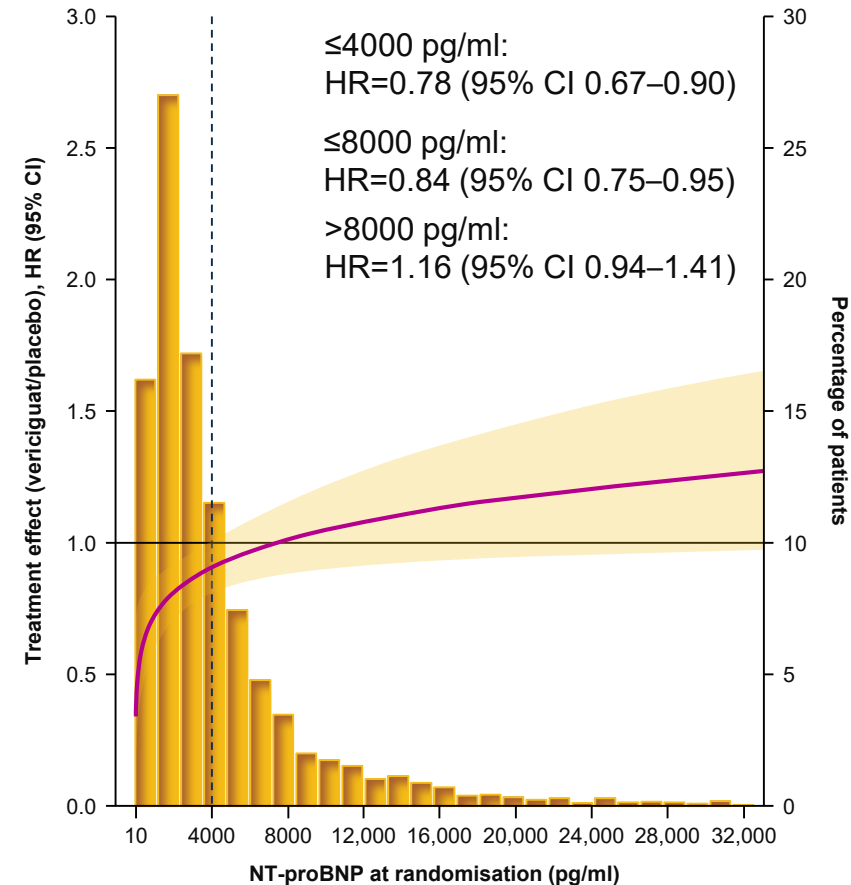
Across the spectrum of NT-proBNP levels, there was an association of treatment effect with vericiguat up to 8000 pg/ml

For Patients with NT-proBNP ≤ 8000 pg/ml, the Treatment Effect of Vericiguat Extended to Both CV Death and HFH

CV death



HF hospitalisation



Erratum: the cut-off values for NT-proBNP levels have been corrected since the original presentation of this data (<4000 pg/ml corrected to ≤ 4000 pg/ml and <8000 pg/ml corrected to ≤ 8000 pg/ml)
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Ezekowitz J et al. ESC-HF. 2020; abstract 29.

Limitations

- Post-hoc analysis using robust statistical methods
- Unmeasured confounders despite adjustment with the MAGGIC risk score

Summary

Overall, the VICTORIA trial demonstrated an HR of 0.90 for CVD/HFH (ARR=4.2% per year)¹

- Treatment effect was consistent across most prespecified subgroups
 - An exception being heterogeneity by NT-proBNP quartiles

Continuous analysis demonstrated that the treatment effect of vericiguat, compared with placebo, on the primary composite endpoint was:²

- Evident for patients with NT-proBNP ≤ 8000 pg/ml
 - 86% of the VICTORIA population
- Further amplified in patients with NT-proBNP ≤ 4000 pg/ml
 - 65% of the VICTORIA population
- Evident for the individual components of CVD and HFH for patients with NT-proBNP ≤ 8000 pg/ml

Putting the VICTORIA Trial Into Perspective with Contemporary HFrEF Clinical Trials

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Patrick H. Lehan Chair in Cardiovascular Research*

Disclosures

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 - Abbott, Adrenomed, Array, Amgen, Applied Therapeutics, AstraZeneca, Bayer, BerlinCures, Boehringer Ingelheim, Corvia, Cardior, CVRx, Eli Lilly, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Limited, and Vifor

Contemporary HF Trials: Inclusion Criteria

Characteristic	DAPA-HF ^{1,2}	PARADIGM-HF ³	VICTORIA ⁴⁻⁶
Patients (N)	4744	8442	5050
Primary endpoint	CV death or first HFH*	CV death or first HFH	CV death or first HFH
LVEF	≤40%	≤35%	<45%
eGFR	≥30 ml/min/1.73 m ²	≥30 ml/min/1.73m ²	>15 ml/min/1.73 m ²
NT-proBNP (pg/ml)	Patients in SR: <ul style="list-style-type: none"> • NT-proBNP ≥600 or ≥400 if HFH ≤12 months Patients with AF or atrial flutter: <ul style="list-style-type: none"> • NT-proBNP ≥900 	<ul style="list-style-type: none"> • BNP ≥150 (NT-proBNP ≥600) • If hospitalised for a HF event within 12 months BNP ≥100 (NT-proBNP ≥400) 	Patients in SR: <ul style="list-style-type: none"> • BNP ≥300 • NT-proBNP ≥1000 Patients with AF: <ul style="list-style-type: none"> • BNP ≥500 • NT-proBNP ≥1600
Prior HF event	No current ADHF or HFH <4 weeks prior to enrolment	62.8% HF hospitalised	Prior HFH ≤6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF ≤3 months prior to randomisation

*HFH or urgent visit resulting in IV therapy for HF

ADHF, acute decompensated heart failure; AF, atrial fibrillation; BNP, brain natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SR, sinus rhythm

1. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:665–675; 2. McMurray JJV et al. *N Engl J Med* 2019;381:1995–2008; 3. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 4. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 5. Pieske B et al. *Eur J Heart Fail.* 2019;21:1596–1604; 6. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

VICTORIA Was Designed to Study Patients with Symptomatic Chronic HF Following a Worsening HF Event¹⁻³

‘Symptomatic chronic HF’

NYHA class II–IV
LVEF <45%

On available HF therapies

&

‘Worsening HF event’

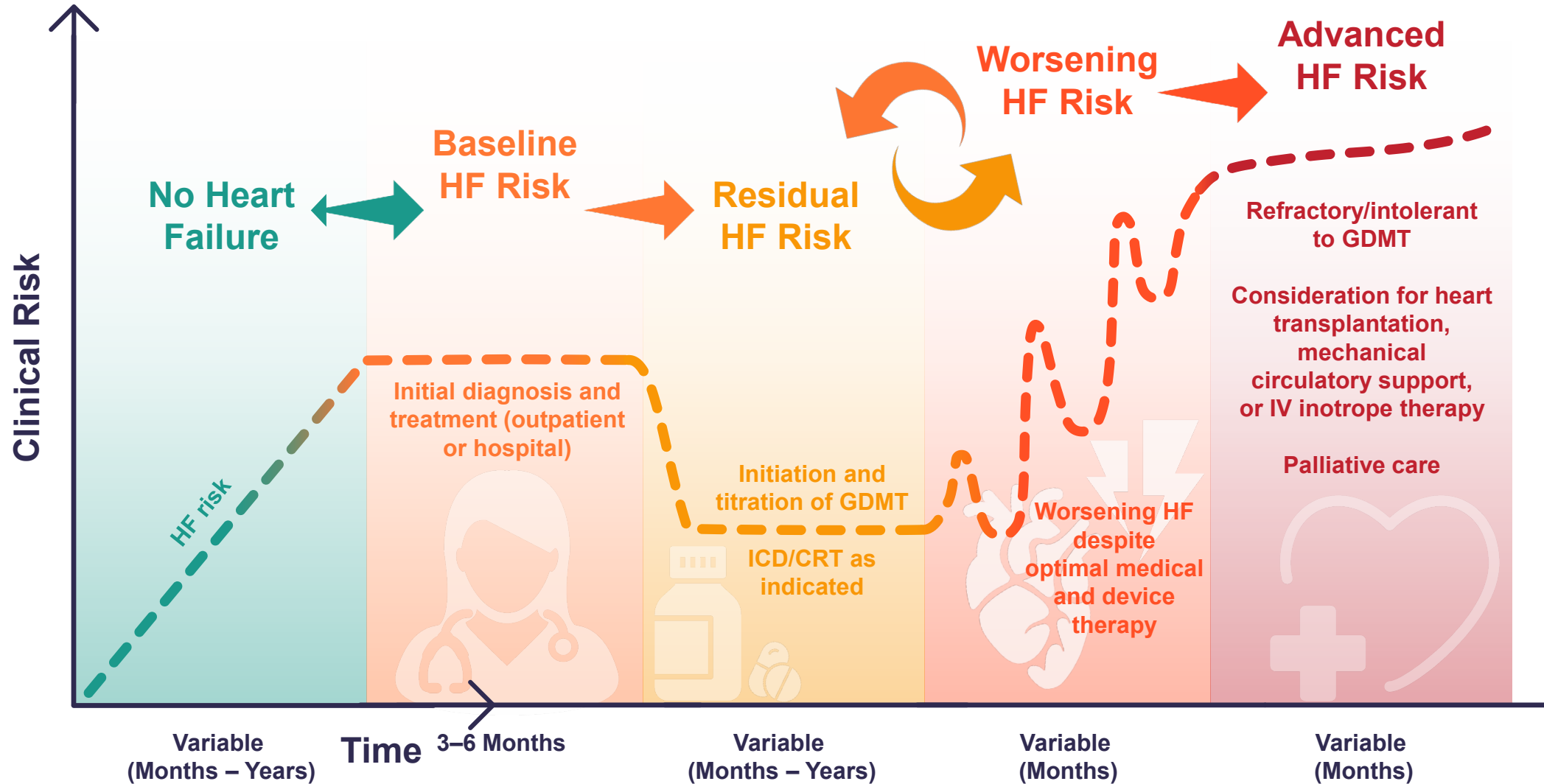
Recent HF decompensation
(HF hospitalisation or IV diuretic use)

Elevated natriuretic peptides

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. EMA. CPMP/EWP/235/95, Rev. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf. Accessed 16 July 2020; 3. Hicks KA et al. *Circulation.* 2015;132:302–361

Patients with Symptomatic Chronic HF Who Had a Previous Worsening Event Can Progressively Worsen Over Time

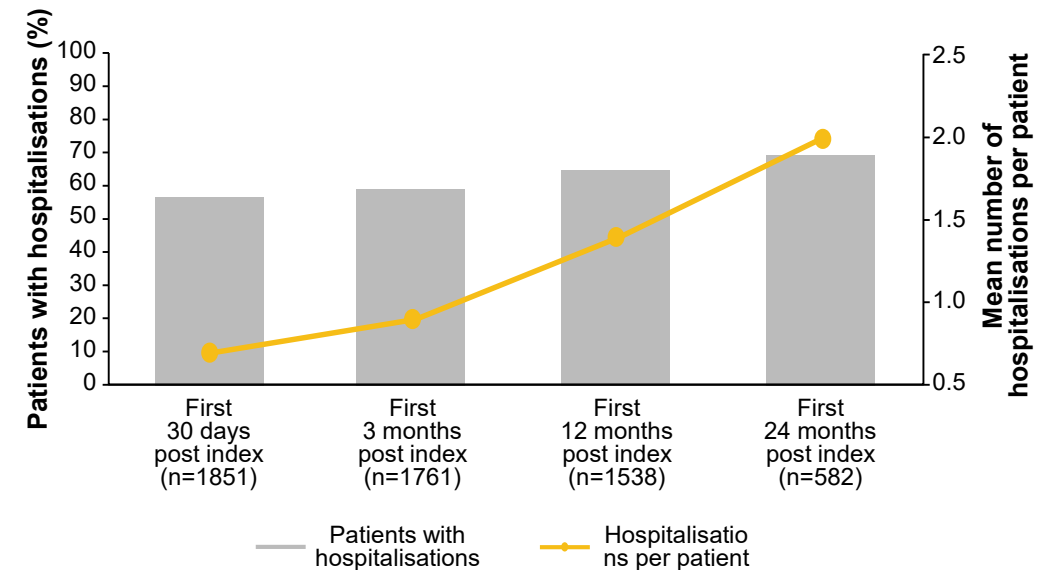


Modified from Green et al. GDMT, guideline-directed medical therapy; HF, heart failure
 Greene SJ, Fonarow GC, Butler J. *Circ Heart Fail.* 2020;13:e007132. DOI: 10.1161/CIRCHEARTFAILURE.120.007132

Patients with Symptomatic Chronic HF Who Had a Previous Worsening HF event Are in Need of New Treatment Strategies

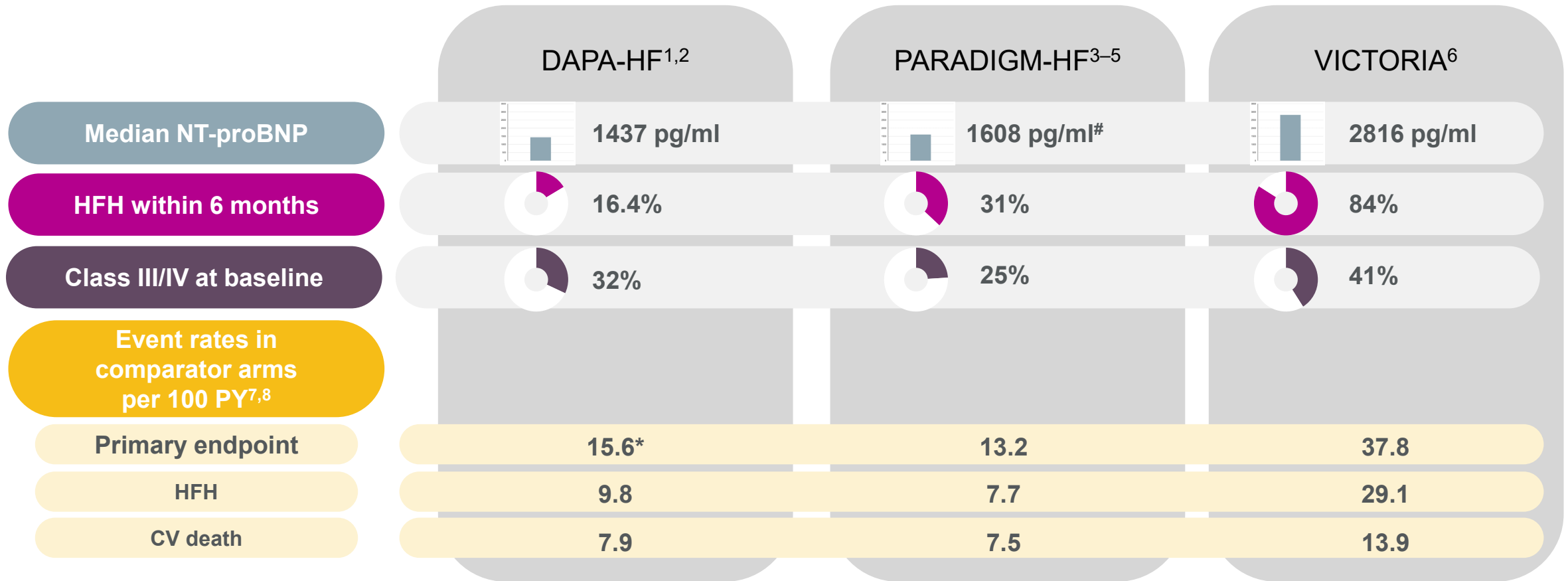
- ~17% of patients developed worsening HF within 1.5 years of HFrEF diagnosis
- In patients with symptomatic chronic HF who had a previous worsening HF event*:
 - The 2-year mortality rate was ~23%
 - Rehospitalisation within 30 days of the worsening HF event was 56%

Patients with hospitalisations and number of hospitalisations per patient up to 2 Years after worsening HF event



*Consisting 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
Butler J et al. *J Am Coll Cardiol.* 2019;73:935–944

Contemporary HF Trials: Study Characteristics at Baseline



Note: this is not intended as a direct comparison of the different studies. *The primary endpoint was a composite of worsening HF (hospitalisation or an urgent visit resulting in IV therapy for HF) or CV death. Of the patients receiving dapagliflozin, 10 (0.4%) had an urgent HF visit, compared with 23 patients (1.0%) receiving placebo (HR=0.43 [95% CI 0.20–0.90]); [#]At screening before run-in; 1 month after randomisation, 24% of the baseline NT-proBNP levels >1000 pg/ml had fallen to ≤1000 pg/ml

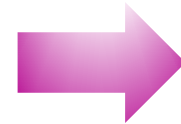
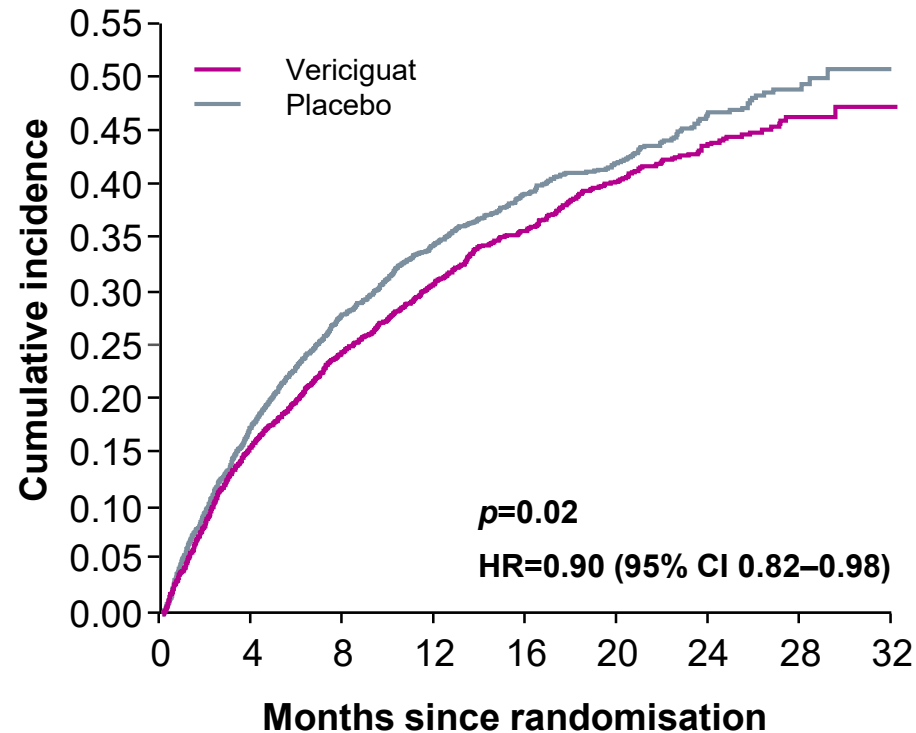
CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide; PY, patient-years

1. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 2. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 3. Zile MR et al. *J Am Coll Cardiol.* 2016;68:2425–2436; 4. Solomon SD et al. *JACC Heart Fail.* 2016;4:816–822; 5. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 6. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 7. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086;

8. McMurray JJV et al. *Eur Heart J* 2015;36:434–439

Results from the VICTORIA Trial: Primary Endpoint and Components

Time to CV death or first HF hospitalisation¹



Primary endpoint ²		
Annualised event rates	Guideline-directed therapies	Vericiguat
Primary endpoint*	37.8	33.6
ARR	4.2	
Components of the primary endpoint ²		
Annualised event rates	Guideline-directed therapies	Vericiguat
CV death	13.9	12.9
ARR	1.0	
First HFH	29.1	25.9
ARR	3.2	

Annual NNT for the composite endpoint of CV death or first HFH = 24[#]

*The primary endpoint was a composite of death from CV causes or first HFH; [#]annual NNT: 100/4.2 = 24

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; NNT, number needed to treat

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883-1893; 2. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086

Ongoing HF Trials: Study Design Comparison with VICTORIA

Characteristic	VICTORIA ^{1,2}	EMPEROR-Reduced ^{3,4}	GALACTIC-HF ^{5,6}
Patients (N)	5050	2850 (planned)	8256
Primary endpoint	CV death or first HFH	CV death or first HFH	CV death or first HFH
Inclusion criteria			
LVEF	<45%	≤40%	≤35%
eGFR	>15 ml/min/1.73 m ²	≥20 ml/min/1.73 m ²	≥20 ml/min/1.73m ²
NT-proBNP (pg/ml)	Patients in SR: <ul style="list-style-type: none"> • BNP ≥300 • NT-proBNP ≥1000 Patients with AF: <ul style="list-style-type: none"> • BNP ≥500 • NT-proBNP ≥1600 	EF ≤30% <ul style="list-style-type: none"> ▪ NT-proBNP ≥1200 (AF); ≥600 (SR) EF 31–35% <ul style="list-style-type: none"> ▪ NT-proBNP ≥2000 (AF); ≥1000 (SR) EF 36–40% <ul style="list-style-type: none"> ▪ NT-proBNP ≥5000 (AF); ≥2500 (SR) EF ≤40%* <ul style="list-style-type: none"> ▪ NT-proBNP ≥1200 (AF); ≥600 (SR) 	Patients without AF: <ul style="list-style-type: none"> ▪ BNP ≥125 pg/ml ▪ NT-proBNP ≥400 pg/ml Patients with AF: <ul style="list-style-type: none"> ▪ BNP ≥375 pg/ml ▪ NT-proBNP ≥1200 pg/ml
Prior HF event	Prior HFH ≤6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF ≤3 months prior to randomisation	Chronic HF ≥3 months No current ADHF requiring IV diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomisation	<ul style="list-style-type: none"> • Chronic HF (HF Tx ≥30 days pre-randomisation) • Current HF hospitalisation or ≤1 year of screening: <ul style="list-style-type: none"> – Hospitalisation for HF, or – Urgent ER for HF

*Patient hospitalised within the 12 months prior to screening.

ADHF, acute decompensated heart failure; AF, atrial fibrillation; BNP, brain natriuretic peptide; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ER, emergency room; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide; SR, sinus rhythm

1. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 2. Pieske B et al. *Eur J Heart Fail.* 2019;21:1596–1604; 3. Packer M et al. *Eur J Heart Fail.* 2019;21:1270–1278; 4. ClinicalTrials.gov. NCT03057977.

<https://clinicaltrials.gov/ct2/show/NCT03057977> Accessed July 2020; 5. ClinicalTrials.gov. NCT02929329. <https://clinicaltrials.gov/ct2/show/NCT02929329> Accessed July 2020; 6. Teerlink JR et al. *JACC Heart Fail.* 2020;8:329–340

Summary

- In VICTORIA, the rationale for selecting patients with “symptomatic chronic HF who had a worsening HF event” was to focus on a population with substantial unmet need¹
 - Despite use of guideline-directed medical therapy, these patients are at increased risk of poor prognosis²
- The VICTORIA patient population is a distinct patient cohort at high risk of a worsening HF event, due to the following:
 - 100% of patients had a recent HF event; 84% had HF hospitalisation ≤6 months prior to randomisation³
 - High comparator arm event rate of the primary endpoint (37.8 per 100 PY) as compared with that in the comparator arm of DAPA-HF and PARADIGM-HF (15.6 and 13.2 per 100 PY, respectively)⁴
 - High median NT-proBNP value at baseline (2816 pg/ml)³
 - High proportion of patient with NYHA class III/IV at baseline (41%)³
- VICTORIA showed an ARR of 4.2% in the primary endpoint with an annual NNT of only 24, which is reflected by the high event rates in the primary endpoint and its components in the comparator arm despite guideline-directed medical therapy^{3,4}

ARR, absolute risk reduction; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NNT, number needed to treat; NYHA, New York Heart Association; PY, patient-years

1. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 2. Butler J et al. *J Am Coll Cardiol.* 2019;73:935–944; 3. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 4. Butler J et al. *Circulation.* 2020; doi: 10.1161/CIRCULATIONAHA.120.047086

A Clinical Case....

Andrew was diagnosed with HFrEF 2 years ago ...

You are seeing him 3 months after his first HF hospitalisation



“
*My first hospitalisation
was terrifying and I'll do
everything I can to
prevent another visit*
”

Characteristic	Value
Age (years)	62
NYHA class	III
LVEF (%)	35
NT-proBNP (pg/ml)	2800
Current therapies*	ARNi / BB / MRA / Loop Diuretic
Comorbidities	AF / CAD / Prior MI
eGFR (ml/min/1.73 m ²)	55
Heart Rate (bpm)	74
Current SBP (mmHg)	110

*Unless stated otherwise, the patients are on the optimal guideline-directed doses for each medication

AF, atrial fibrillation; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2D, type 2 diabetes