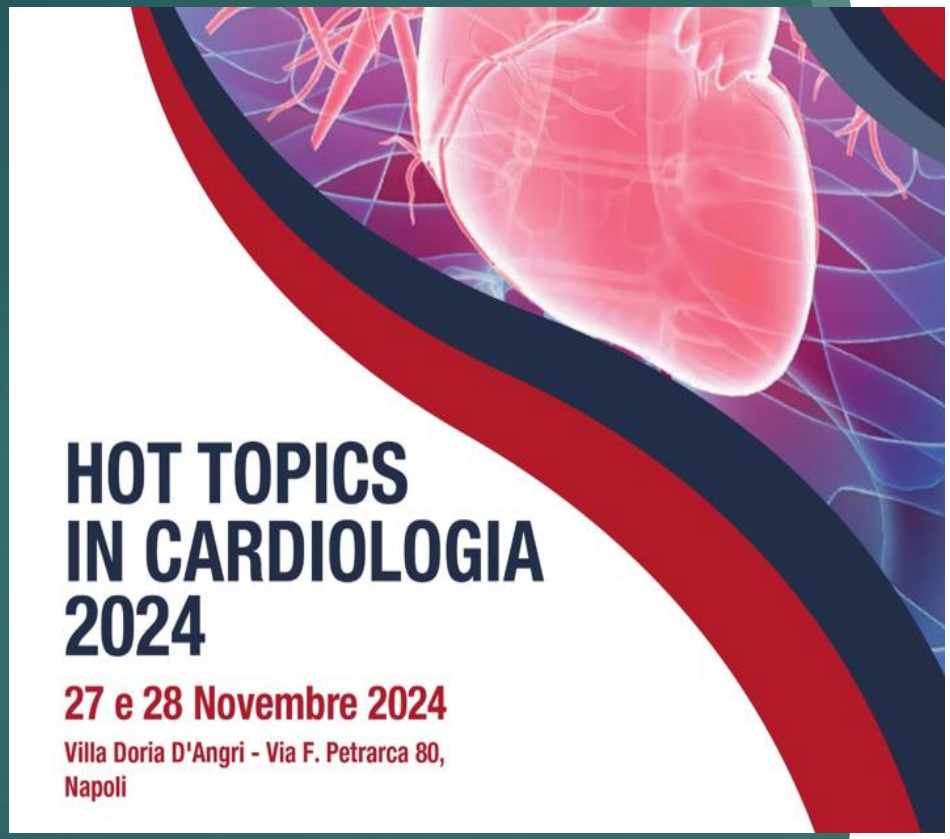
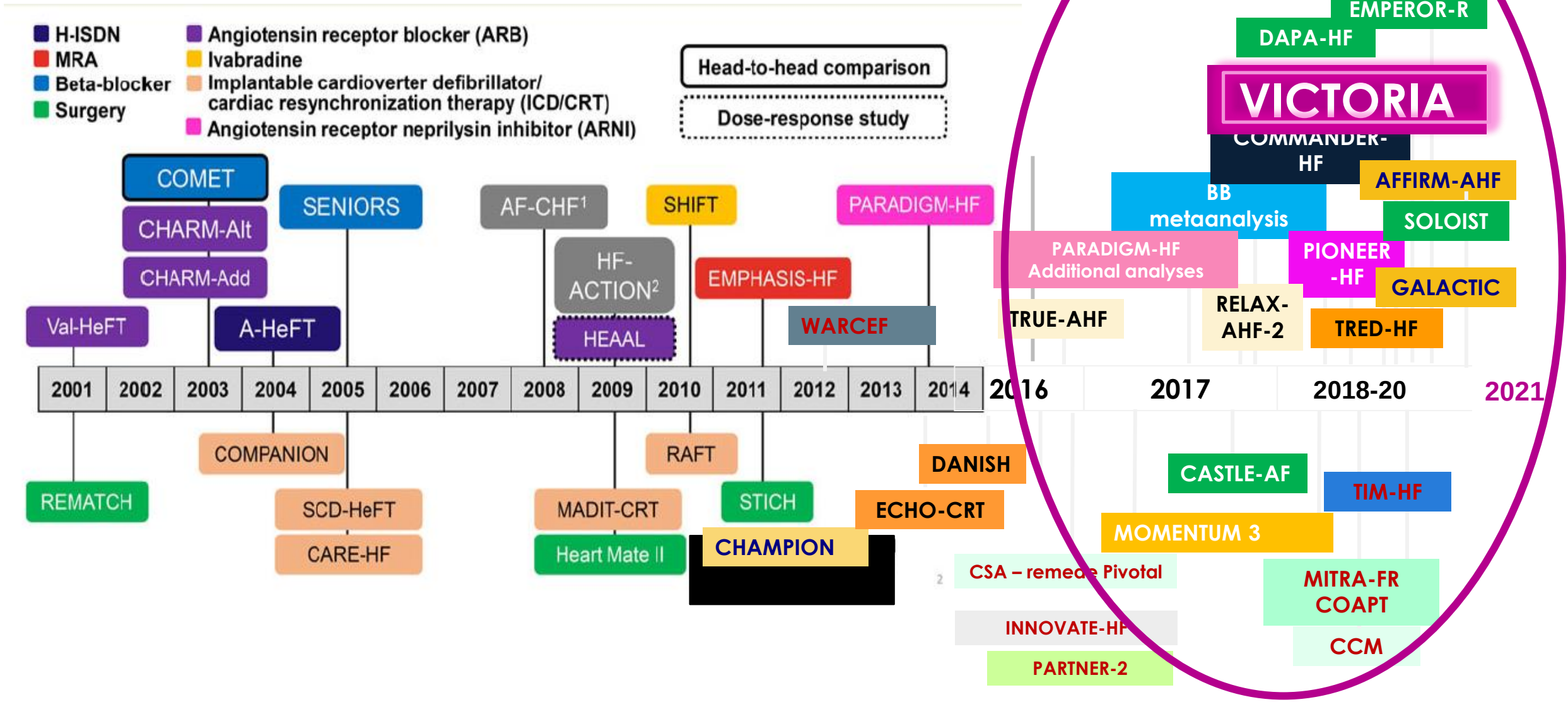


Vericiguat: trattare lo scompenso cardiaco a frazione di eiezione ridotta attraverso un nuovo meccanismo d'azione

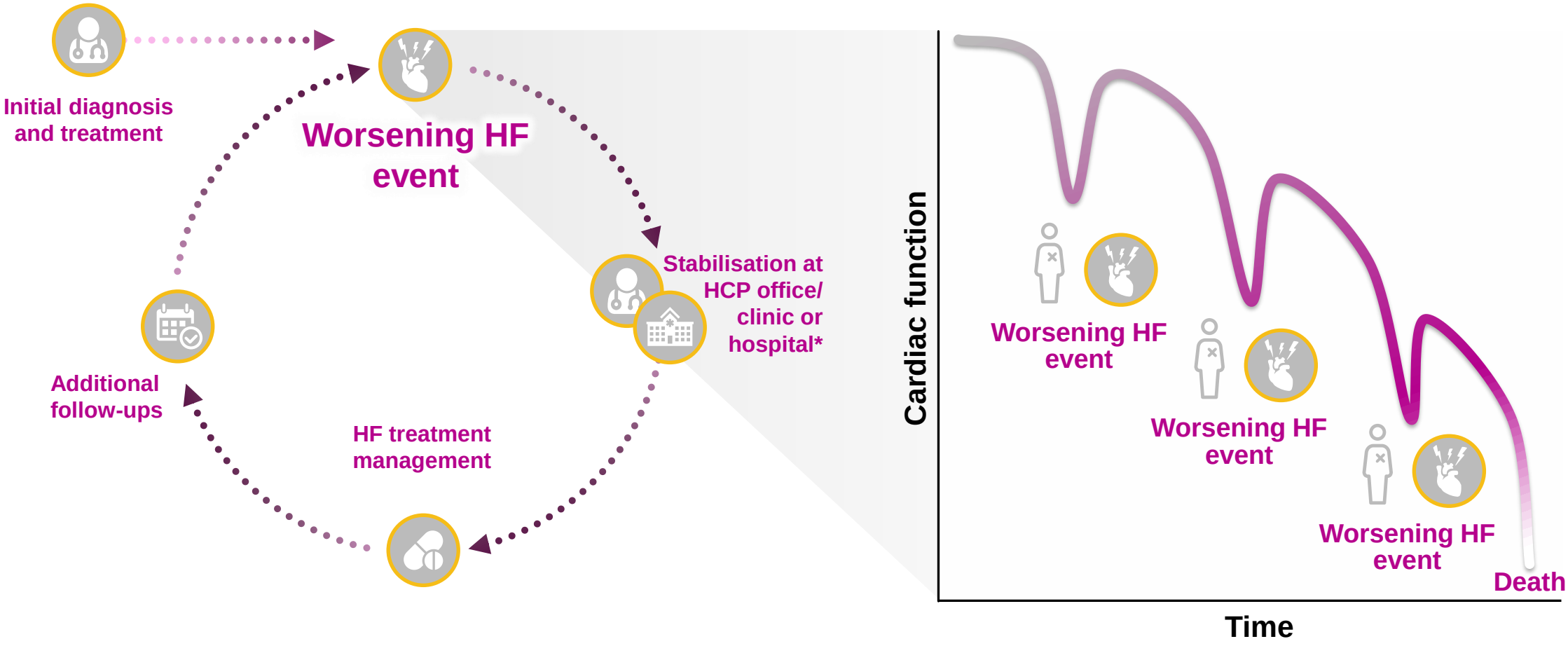
Dott. Fabio Marsico, MD, PhD,
Cardiologia con UTIC AORN Cardarelli

Clinical trials in HFrEF patients*(in the 21st century)*



Modified from McMurray JJV; Eur Heart J 2015;36:3467-70

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

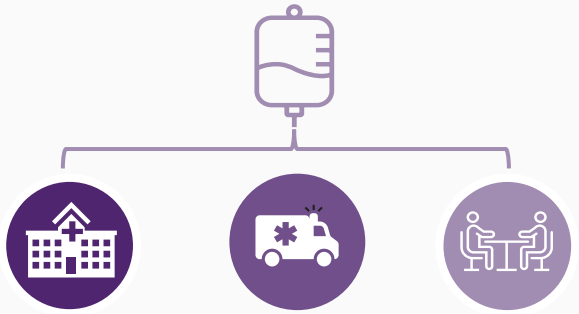


Adapted from Gheorghiade et al. *Am J Cardiol.* 2005 and Cowie et al. *ESC Heart Fail.* 2014.
*Adjustment of and potential addition to current therapy.
HCP, healthcare professional; HF heart failure.
1. Gheorghiade M et al. *Am J Cardiol*. 2005;96:11G–17G; 2. Cowie MR et al. *ESC Heart Fail*. 2014;1:110–145.

Patients with HFrEF, are at high risk of a worsening HF event

What is a "worsening HF event"?

A decompensation event requiring IV diuretic treatment in[1,2]:



What is the risk of a worsening HF event?

~1 in 6 patients suffer a WHF event within 18 months of HFrEF diagnosis[2]

In one year, ~1 in 3 HF patients will experience a WHF event[3]

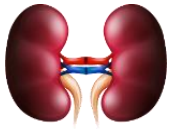
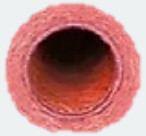
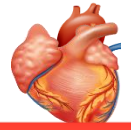
When might a worsening HF event happen?

Can occur across the whole disease lifecycle, not just in advanced HF[2,4]

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; WHF, worsening heart failure.

1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 2. Butler J et al. *J Am Coll Cardiol*. 2019;73:935–944; 3. Mentz RJ et al. ACC, 2020: Presentation no. 1205–134; 4. Greene SJ et al. *Circ Heart Fail*. 2020;13:e007132.

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

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

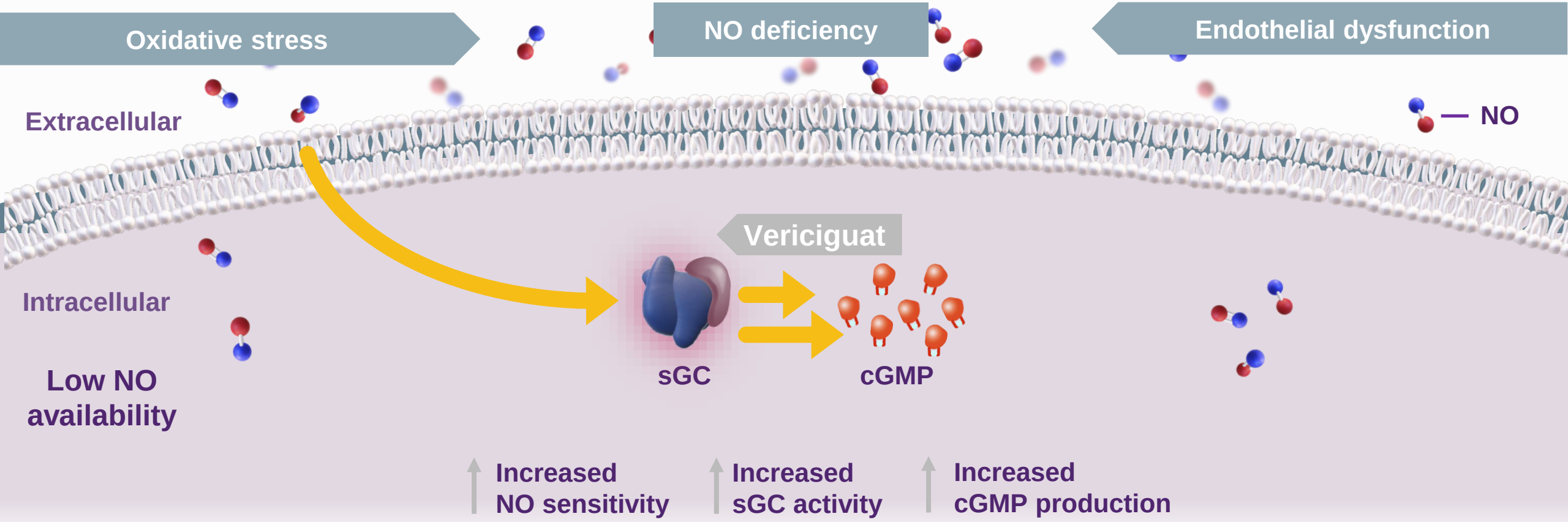
Inhibitors

Stimulator

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

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

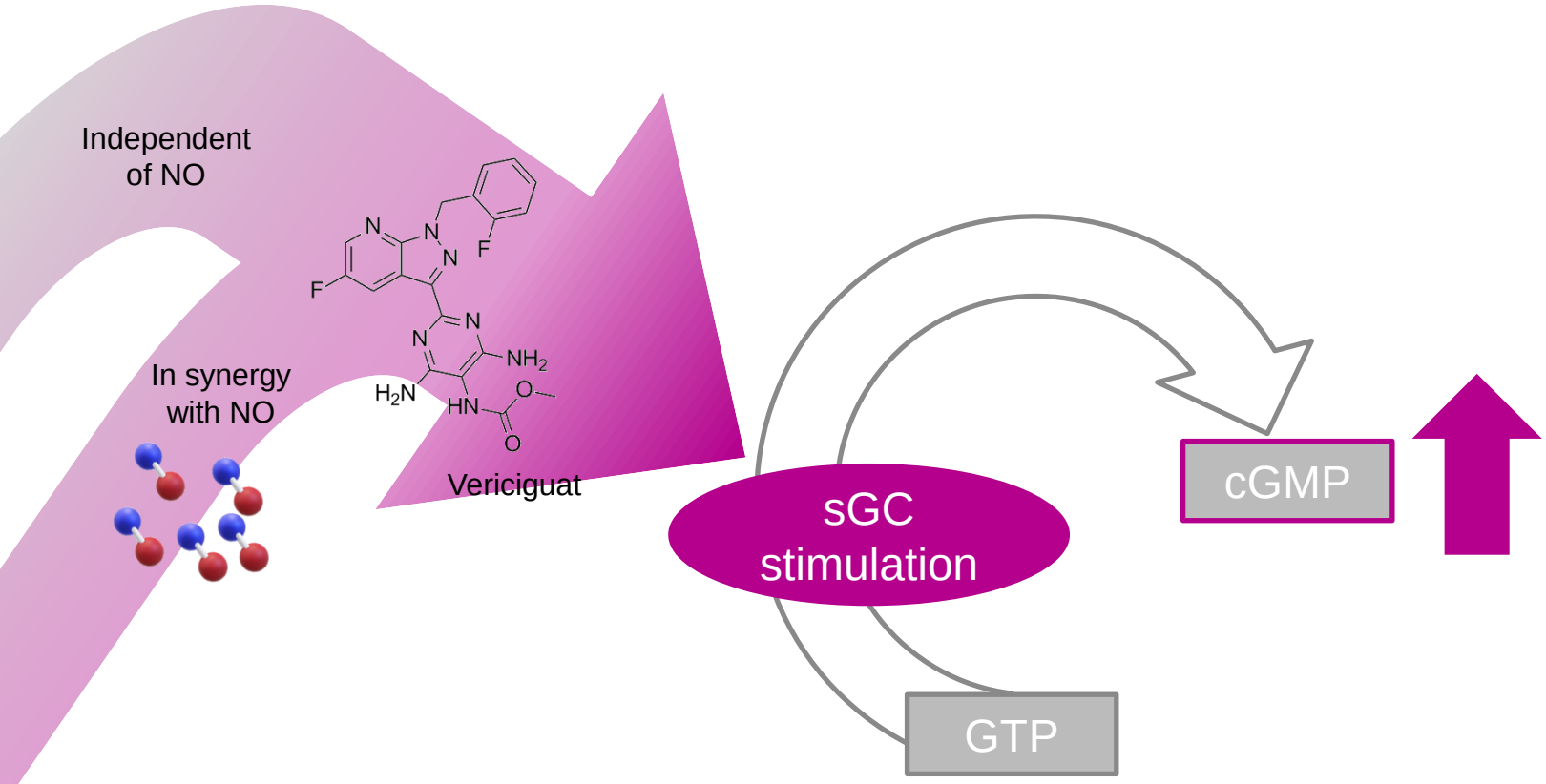
sGC stimulation targets an untapped pathway implicated in the development and progression of HF[1–5]

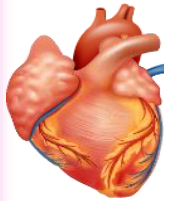


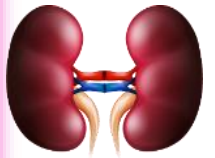
cGMP, cyclic guanosine monophosphate; HF, heart failure; NO, nitric oxide; sGC, soluble guanylate cyclase.

References: 1. Gheorghiade M *et al. Heart Fail Rev* 2013;18:123–134; **2.** Boerrigter G *et al. Handb Exp Pharmacol* 2009;191:485–506; **3.** Breitenstein S *et al. Handb Exp Pharmacol* 2017;243:225–247; **4.** Armstrong PW *et al. JACC Heart Fail* 2018;6:96–104; **5.** Follmann M *et al. J Med Chem* 2017;60:5146–5161.

Vericiguat: simplified mechanism of action







- Improved myocardial function
- Reduced left ventricular remodeling
- Improved vascular function
- Decreased fibrosis
- Decreased inflammation

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

1. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 2.Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123–134; 3. Sandner P et al. *Handb Exp Pharmacol*. 2021;264:355–394.

VICTORIA trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

VICTORIA was designed to study patients with symptomatic chronic HF with previous, recent worsening HF event

'Symptomatic chronic HF'

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

&

'Worsening HF event'

- Recent HF decompensation
  - HF hospitalization
  - 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. 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. 2017. 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 9 Feb 2021]; 5. Butler J *et al*. *Circulation.* 2020;142:717–719.

VICTORIA Phase III: study design

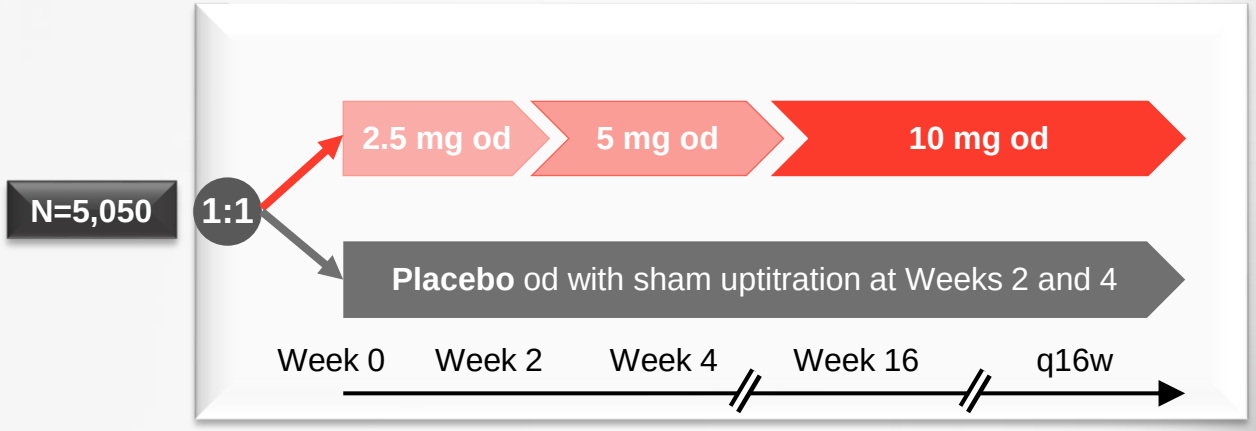
Design: International, parallel-group, event-driven, randomized, double-blind, placebo-controlled, Phase 3 trial

Objective: Evaluate the effect of vericiguat in patients with symptomatic chronic HF following a worsening HF event

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

Eligibility criteria

- **HFrEF (LVEF <45%)**
- **NYHA class II–IV**
- **BNP: SR ≥300 pg/ml AF ≥500 pg/ml**
- **NT-proBNP: SR, ≥1,000 pg/ml; AF, ≥1,600 pg/ml**
- **eGFR ≥15 ml/min/1.73 m²**
- **HF hospitalization within 6 months or IV diuretic treatment for HF within 3 months**
- **SBP ≥100 mmHg**



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

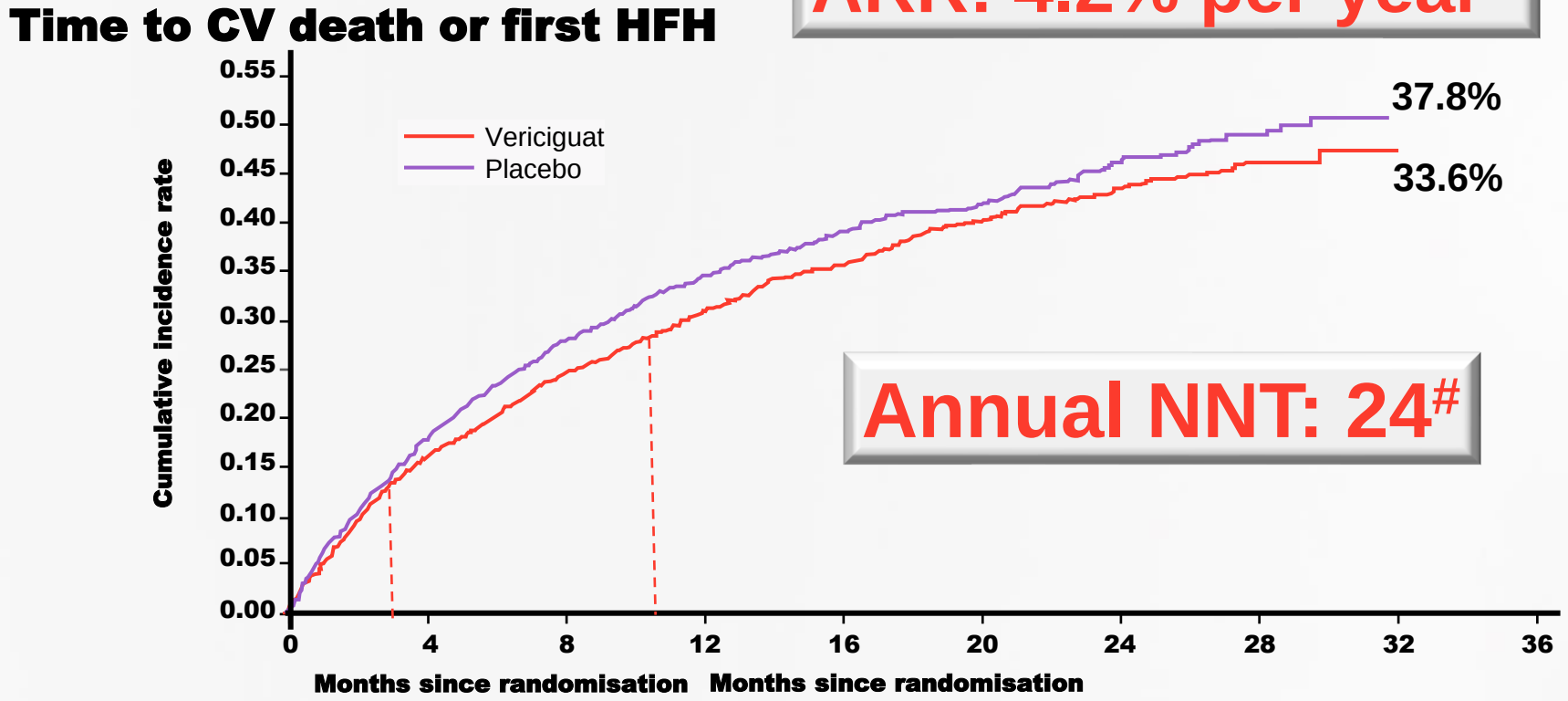
After approximately 12 months, 10 mg target dose was achieved: vericiguat, 89.2%; placebo, 91.4%[2]

AF, atrial fibrillation; BNP, brain natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; od, once daily; q16w, every 16 weeks; SR, sinus rhythm.

References: 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.

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

ARR: 4.2% per year*



Annual NNT: 24#

HR=0.90 (95% CI 0.82–0.98)
P=0.02

Annual NNT: 24#

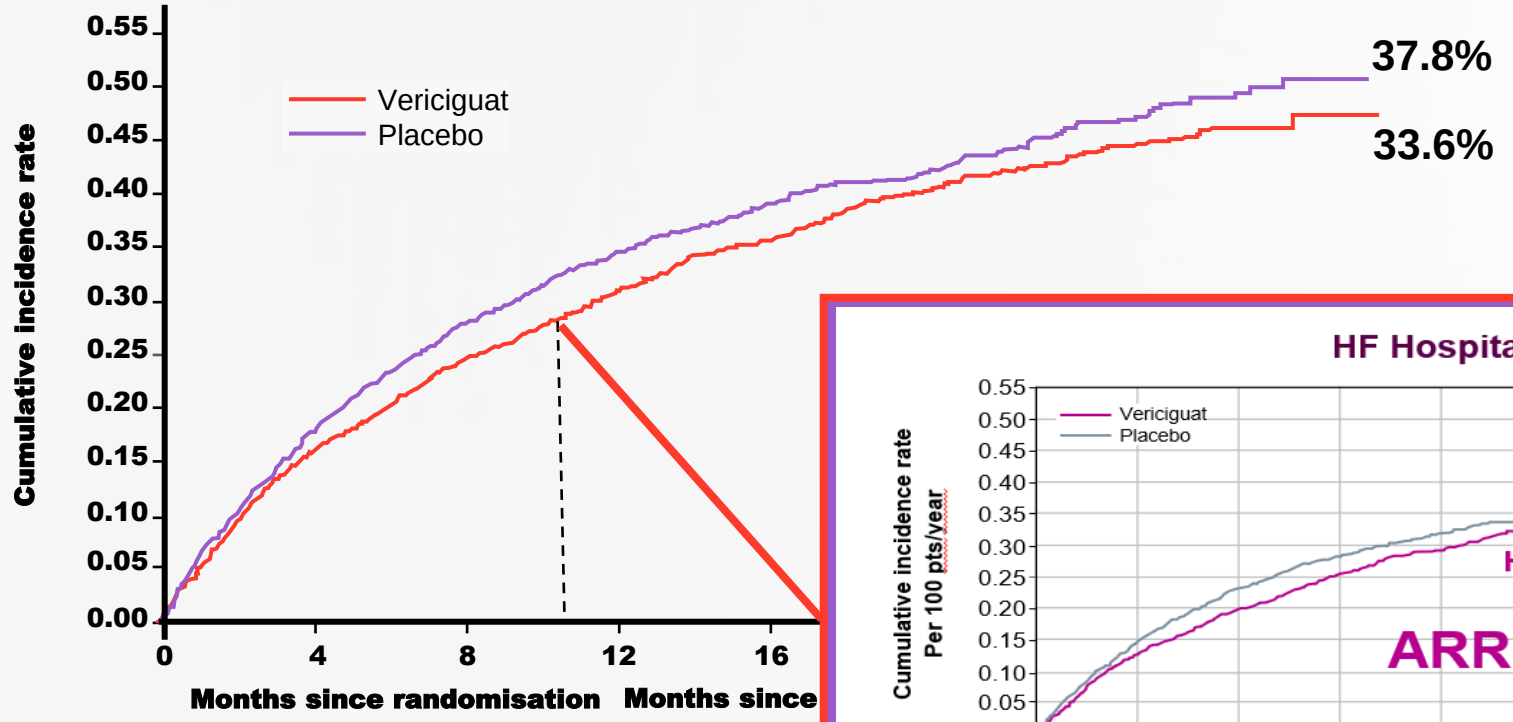
ARR: 4.2% per year*

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

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

Vericiguat reduced HFH by means 3.2% (ARR)

Time to CV death or first HFH



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Number of subjects at risk					
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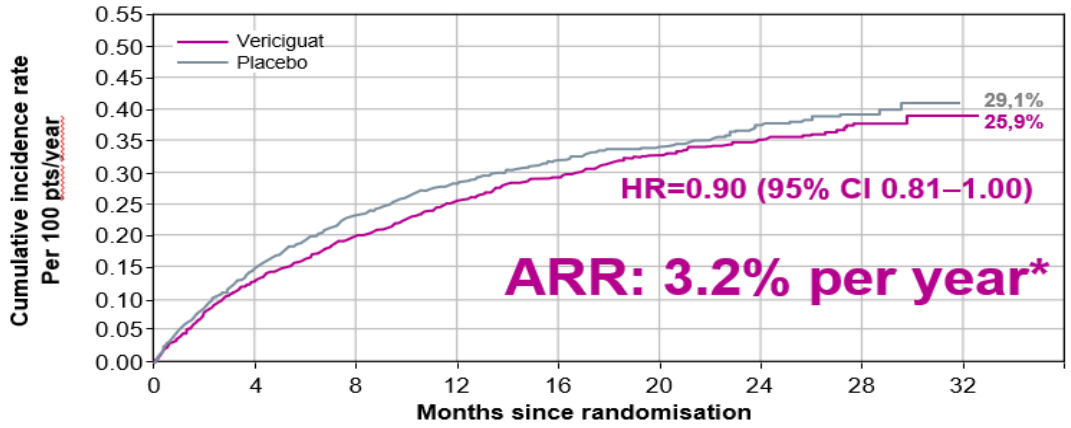
Placebo	2524	2053	1555	1097	772

HF Hospitalisation



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

*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.

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

Vericiguat shows a good safety profile

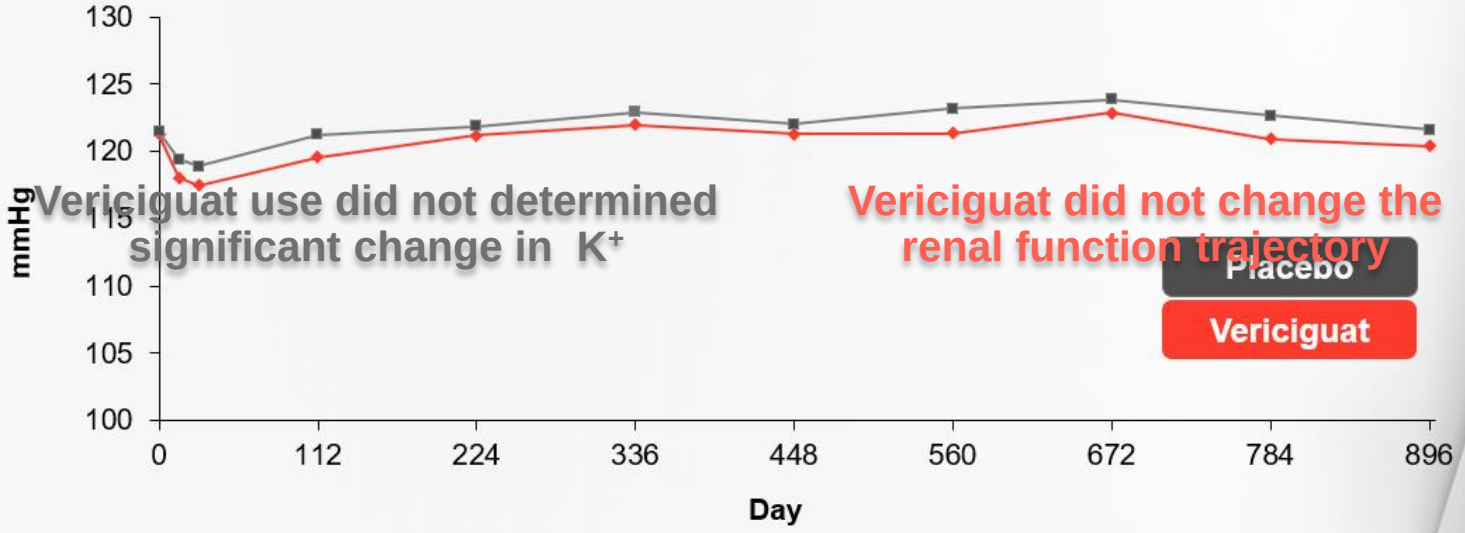
Systolic Blood Pressure Over Time

K+

Patients at risk of hyperkalemia[2]

Patients with renal impairment[2]

Patients at risk of hypotension[1]



Vericiguat use did not determined significant change in K^+

Vericiguat did not change the renal function trajectory

Patients at risk of hypotension[1]

Between-arm differences in mean values between vericiguat and placebo arm (1 to ~1.5 mmHg)

BP, blood pressure.
1. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928; 2. Data on file.

First analysis of real-world use of vericiguat on a nation-wide level and that may contribute to a better understanding of novel GDMT implementation in routine clinical practice

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-024-03654-0

RESEARCH

Real-world characteristics and use patterns of patients treated with vericiguat: A nationwide longitudinal cohort study in Germany

Fabian Kerwagen[1,2] · Christoph Ohlmeier[3] · Thomas Evers[4] · Stefan Herrmann[5] · Inga Bayh[4] · Alexander Michel[6] · Silvia Kruppert[7] · Joanna Wilfer[7] · Rolf Wachter[8] · Michael Böhm[9] · Stefan Störk[1,2]

Received: 17 January 2024 / Accepted: 19 February 2024

Abstract

Purpose Vericiguat reduced clinical endpoints in patients experiencing worsening heart failure in clinical trials, but its implementation outside trials is unclear.

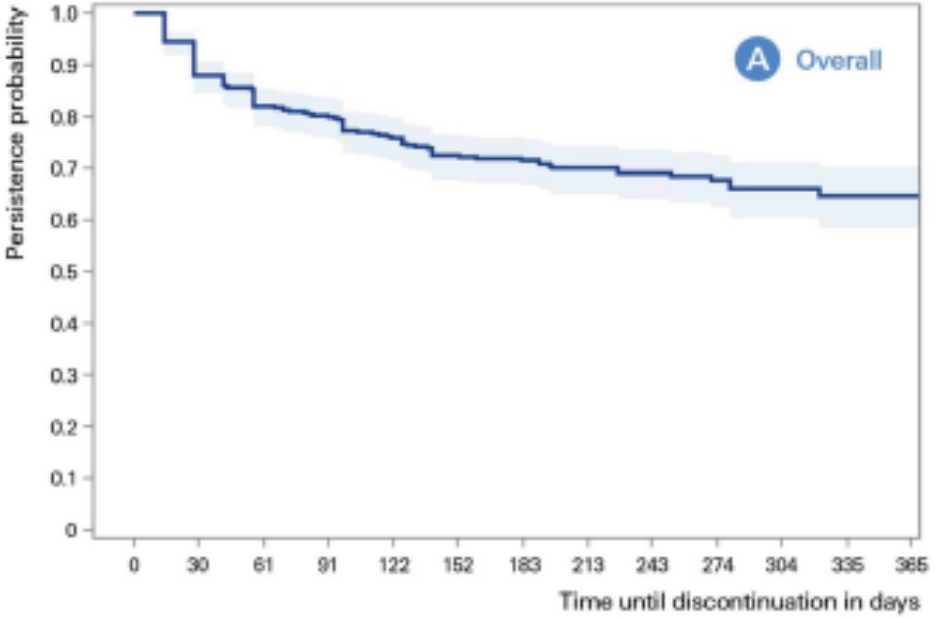
Methods This retrospective analysis of longitudinally collected data was based on the IQVIA™ LRx database, which includes ~ 80% of the prescriptions of the 73 million people covered by the German statutory health insurance.

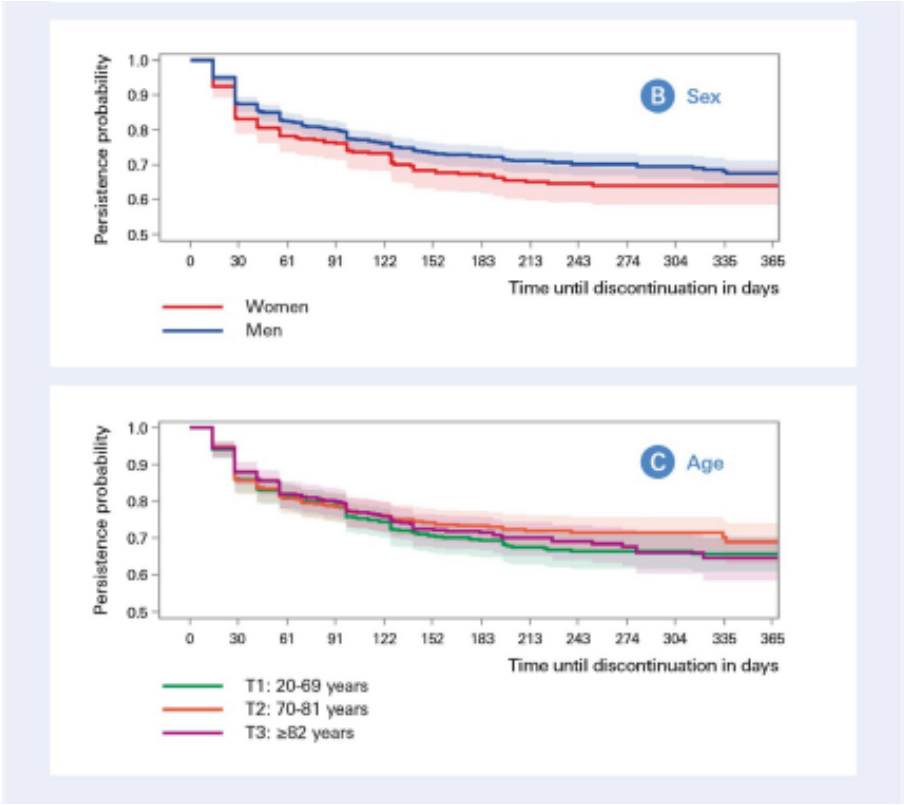
Results Between September 2021 and December 2022, vericiguat was initiated in 2916 adult patients. Their mean age was 73 ± 13 years and 28% were women. While approximately 70% were uptitrated beyond 2.5 mg, only 36% reached 10 mg. Median time to up-titration from 2.5 mg to 5 mg was 17 (quartiles: 11–33) days, and from 2.5 to 10 mg 37 (25–64) days, respectively. In 87% of the patients, adherence to vericiguat was high as indicated by a medication possession ratio of ≥ 80%, and 67% of the patients persistently used vericiguat during the first year. Women and older patients reached the maximal dose of 10 mg vericiguat less often and received other substance classes of guideline-recommended therapy (GDMT) less frequently. The proportion of patients receiving four pillars of GDMT increased from 29% before vericiguat initiation to 44% afterwards.

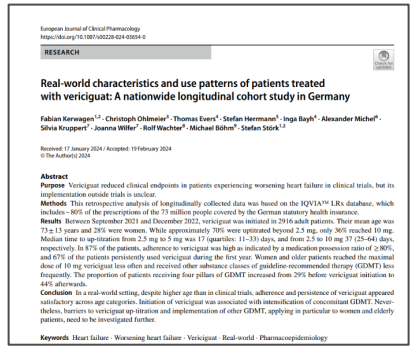
Conclusion In a real-world setting, despite higher age than in clinical trials, adherence and persistence of vericiguat appeared satisfactory across age categories. Initiation of vericiguat was associated with intensification of concomitant GDMT. Nevertheless, barriers to vericiguat up-titration and implementation of other GDMT, applying in particular to women and elderly patients, need to be investigated further.

Keywords Heart failure · Worsening heart failure · Vericiguat · Real-world · Pharmacoepidemiology

67.1% of Vericiguat initiators were observed to have persistent therapy during first twelve months after initiation, adherence was 87% consistent in all categories of ages/sex







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Eur J Clin Pharmacol. 2024 Mar 12. doi: 10.1007/s00228-024-03654-0.

GDMT therapy prior to vericiguat initiation: SGLT2i and ARNi were used in 51, 1% and 56,6% of patients, respectively

European Journal of Clinical Pharmacology

Table 3 Change of co-prescribed medication during the three months before and after initiation with vericiguat

	Prior to vericiguat initiation (n = 1416)	After to vericiguat initiation (n = 1416)
HF co-medication		
BB	1113 (78.6%)	1202 (84.9%)
ACEi	236 (16.7%)	204 (14.4%)
ARB	179 (12.6%)	168 (11.9%)
ARNi	801 (56.6%)	949 (67.0%)
Any RASi	1113 (78.6%)	1193 (84.3%)
MRA	769 (54.3%)	943 (66.6%)
SGLT2i	724 (51.1%)	1040 (73.4%)
Diuretic medication	1124 (79.4%)	1243 (87.8%)
Digitalis	141 (10.0%)	175 (12.4%)
Ivabradine	82 (5.8%)	104 (7.3%)
HF drug combinations		
≤ 1 drug class	252 (17.8%)	103 (7.3%)
2 drug classes	381 (26.9%)	319 (22.5%)
3 drug classes	375 (26.5%)	375 (26.5%)
4 drug classes	408 (28.8%)	619 (43.7%)
Non-HF co-medication		
Oral anticoagulant	818 (57.8%)	910 (64.3%)
Antiplatelet medication	382 (27.0%)	418 (29.5%)
Lipid-lowering medication	881 (62.2%)	960 (67.8%)
Glucose-lowering medication	445 (31.4%)	431 (30.4%)
Anti-depressant	171 (12.1%)	200 (14.1%)
NSAIDs	177 (12.5%)	157 (11.1%)
Antiobstructive medication	346 (24.4%)	349 (24.6%)
Gout medication	414 (29.2%)	436 (30.8%)

HF heart failure, *BB* beta-blockers, *MRA* mineralocorticoid receptor antagonists, *RASi* renin–angiotensin system inhibitors, *ACEi* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *ARNi* angiotensin receptor–neprilysin inhibitor [ARNi]), *SGLT2i* sodium-glucose co-transporter-2 inhibitors, *NSAIDs* non-steroidal anti-inflammatory drugs

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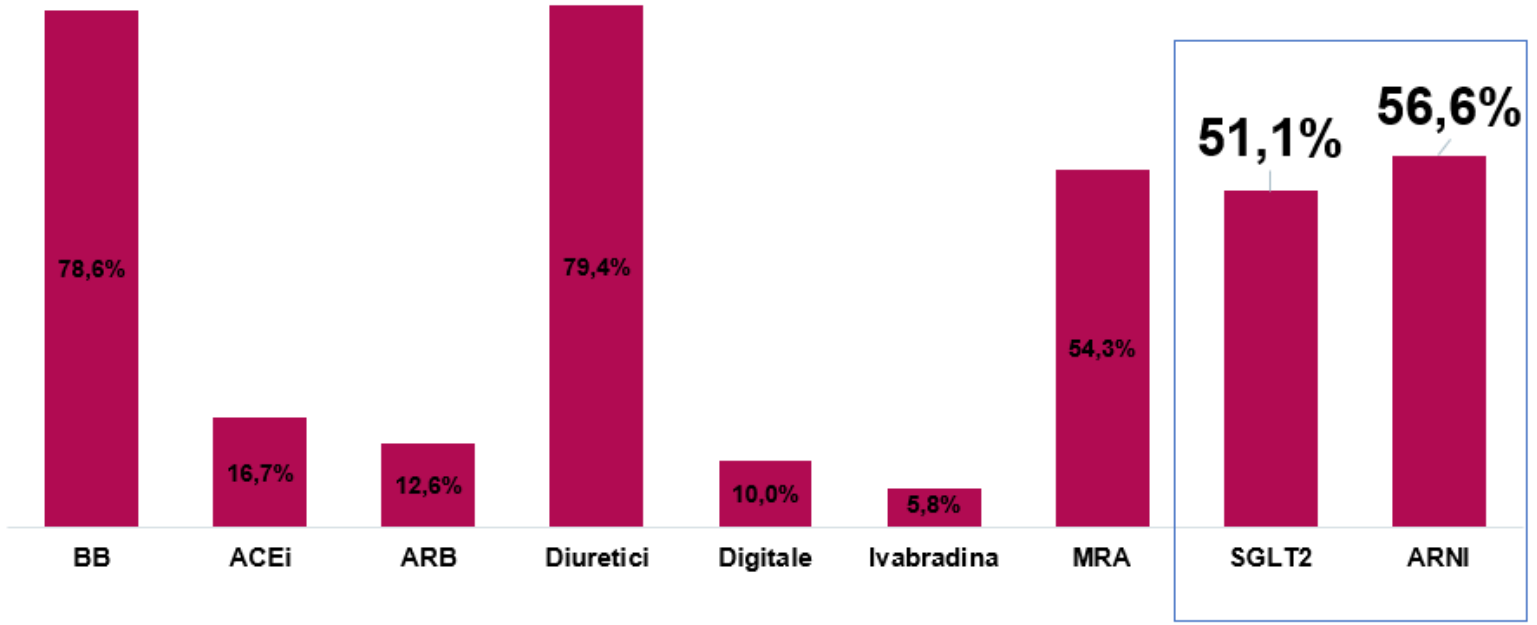
Results Between September 2021 and December 2022, vericiguat was initiated in 2916 adult patients. Their mean age was 73 ± 13 years and 28% were women. While approximately 70% were uptitrated beyond 2.5 mg, only 36% reached 10 mg. Median time to up-titration from 2.5 mg to 5 mg was 17 (quartiles: 11–33) days, and from 2.5 to 10 mg 37 (25–64) days, respectively. In 87% of the patients, adherence to vericiguat was high as indicated by a medication possession ratio of ≥ 80%, and 67% of the patients persistently used vericiguat during the first year. Women and older patients reached the maximal dose of 10 mg vericiguat less often and received other substance classes of guideline-recommended therapy (GDMT) less frequently. The proportion of patients receiving four pillars of GDMT increased from 29% before vericiguat initiation to 44% afterwards.

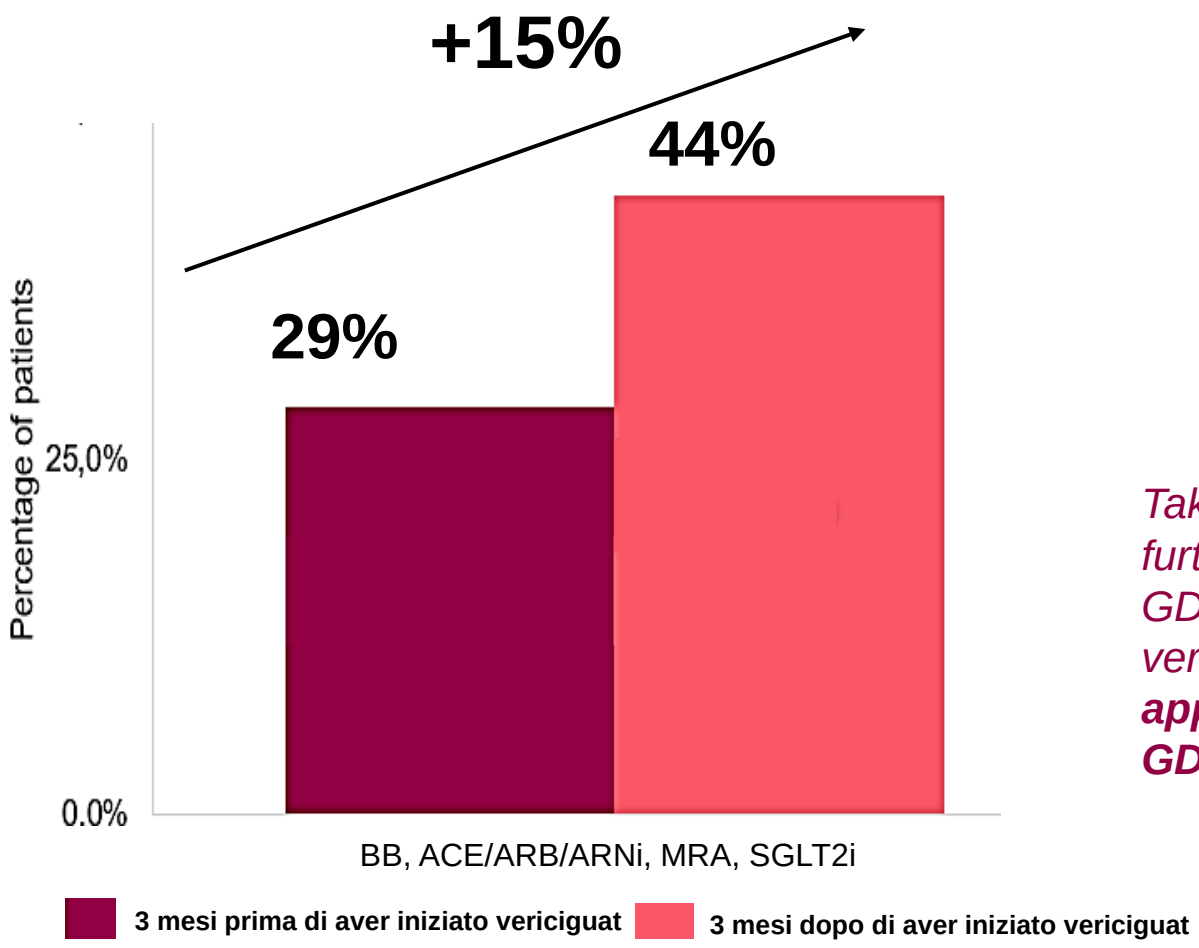
Conclusion In a real-world setting, despite higher age than in clinical trials, adherence and persistence of vericiguat appeared satisfactory across age categories. Initiation of vericiguat was associated with intensification of concomitant GDMT. Nevertheless, barriers to vericiguat up-titration and implementation of other GDMT, applying in particular to women and elderly patients, need to be investigated further.

Keywords Heart failure · Worsening heart failure · Vericiguat · Real-world · Pharmacoepidemiology



Adapted: Eur J Clin Pharmacol. 2024 Mar 12. doi: 10.1007/s00228-024-03654-0.

The combination of all 4 foundational therapies was observed in 29% of the patients prior to initiation of vericiguat but increased to 44% thereafter (n=1,416)



Taken together, the concern that the addition of a further substance class could be at the expense of other GDMT appears unfounded in connection with vericiguat. On the contrary, ***initiation of vericiguat appears to facilitate therapeutic intensification and GDMT optimization*** *(…)*

Adapted: Eur J Clin Pharmacol. 2024 Mar 12. doi: 10.1007/s00228-024-03654-0.

Approximately 70% of the patients were up-titrated to the 5 mg or 10 mg dose

European Journal of Clinical Pharmacology
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RESEARCH

Real-world characteristics and use patterns of patients treated with vericiguat: A nationwide longitudinal cohort study in Germany

Fabian Kerwagen[1,2] · Christoph Ohlmeier[3] · Thomas Evers[4] · Stefan Herrmann[5] · Inga Bayh[6] · Alexander Michel[6] · Silvia Kruppert[7] · Joanna Wilfer[7] · Rolf Wachter[8] · Michael Böhm[9] · Stefan Störk[1,2]

Received: 17 January 2024 / Accepted: 19 February 2024

Abstract

Purpose Vericiguat reduced clinical endpoints in patients experiencing worsening heart failure in clinical trials, but its implementation outside trials is unclear.

Methods This retrospective analysis of longitudinally collected data was based on the IQVIA™ LRx database, which includes ~ 80% of the prescriptions of the 73 million people covered by the German statutory health insurance.

Results Between September 2021 and December 2022, vericiguat was initiated in 2916 adult patients. Their mean age was 73 ± 13 years and 28% were women. While approximately 70% were uptitrated beyond 2.5 mg, only 36% reached 10 mg. Median time to up-titration from 2.5 mg to 5 mg was 17 (quartiles: 11–33) days, and from 2.5 to 10 mg 37 (25–64) days, respectively. In 87% of the patients, adherence to vericiguat was high as indicated by a medication possession ratio of ≥ 80%, and 67% of the patients persistently used vericiguat during the first year. Women and elder patients reached the maximal dose of 10 mg vericiguat less often and received other substance classes of guideline-recommended therapy (GDMT) less frequently. The proportion of patients receiving four pillars of GDMT increased from 29% before vericiguat initiation to 44% afterwards.

Conclusion In a real-world setting, despite higher age than in clinical trials, adherence and persistence of vericiguat appeared satisfactory across age categories. Initiation of vericiguat was associated with intensification of concomitant GDMT. Nevertheless, barriers to vericiguat up-titration and implementation of other GDMT, applying in particular to women and elderly patients, need to be investigated further.

Keywords Heart failure · Worsening heart failure · Vericiguat · Real-world · Pharmacoepidemiology

European Journal of Clinical Pharmacology

Table 2 Up-titration patterns in patients initiating vericiguat

	Total (n = 2129)	Women (n = 565)	Men (n = 1423)	Age tertile 1: 20–69 years (n = 716)	Age tertile 2: 70–81 years (n = 732)	Age tertile 3: ≥ 82 years (n = 681)
First observed dose ("starting dose")						
2.5 mg	1792 (84.2%)	477 (84.4%)	1198 (84.2%)	603 (84.2%)	615 (84.0%)	574 (84.3%)
5 mg	254 (11.9%)	68 (12.0%)	167 (11.7%)	86 (12.0%)	92 (12.6%)	76 (11.2%)
10 mg	83 (3.9%)	20 (3.5%)	58 (4.1%)	27 (3.8%)	25 (3.4%)	31 (4.6%)
Maximal dose reached						
2.5 mg	652 (30.6%)	158 (28.0%)	444 (31.2%)	201 (28.1%)	230 (31.4%)	221 (32.5%)
5 mg	708 (33.3%)	213 (37.7%)	448 (31.5%)	245 (34.2%)	228 (31.1%)	235 (34.5%)
10 mg	769 (36.1%)	194 (34.3%)	531 (37.3%)	270 (37.7%)	274 (37.4%)	225 (33.0%)
Time (days) until up-titration						
to 5 mg	17.0 (11.0–33.0)	16.0 (9.0–34.0)	17.0 (11.0–32.0)	20.0 (13.0–45.0)	16.5 (11.0–29.0)	14.0 (8.0–30.0)
to 10 mg	37.0 (25.0–64.0)	37.0 (24.5–64.5)	39.0 (26.0–64.0)	41.0 (26.0–73.0)	36.5 (25.0–59.0)	34.0 (24.0–55.0)

Data are n (%) or median (quartiles)

the median times until up-titration from 2,5 mg to 10 mg was 37 days

Eur J Clin Pharmacol. 2024 Mar 12. doi: 10.1007/s00228-024-03654-0.

ESC HEART FAILURE
ESC Heart Failure (2024)
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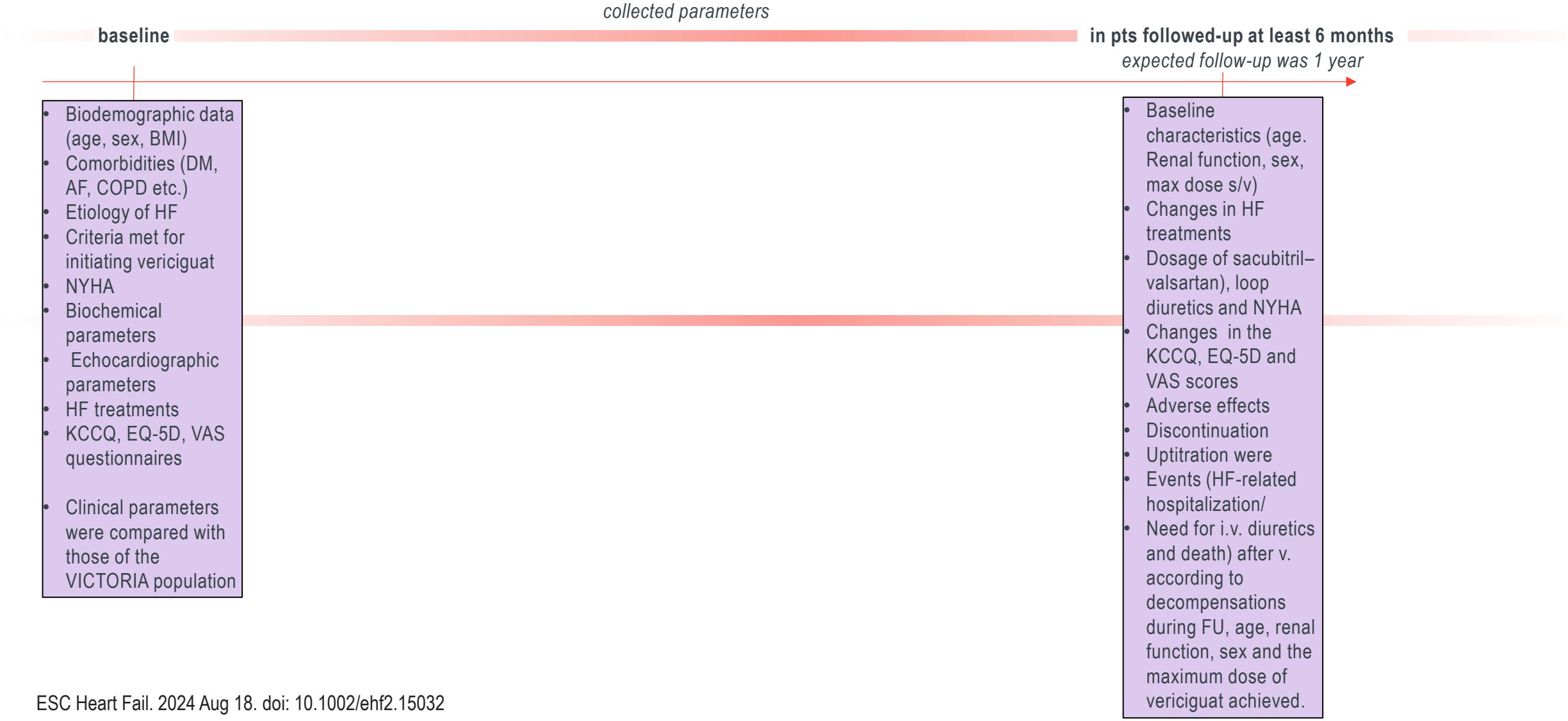
ORIGINAL ARTICLE

Clinical profile, associated events and safety of vericiguat in a real-world cohort: The VERITA study

Mario Galván Ruiz[1]*, Miguel Fernández de Sanmamed Girón[2], María del Val Groba Marco[2], Lorena Rojo Jorge[3], Claudia Peña Saavedra[2], Elvira Martín Bou[2], Rubén Andrade Guerra[2], Eduardo Caballero Dorta[2] and Antonio García Quintana[2]

[1]*Department of Cardiology, Hospital Universitario de Gran Canaria Doctor Negrín, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain;* [2]*Department of Cardiology, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain; and* [3]*Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain*

A prospective and observational cohort study that included patients with HFrEF and recent WHF who initiated or were already taking vericiguat between December 2022 and February 2024 in addition to standard therapy



ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

In clinical practice vericiguat seems being prescribed to patients with a worse risk than in the RCT as in a recent retrospective study from a German registry*…

Table 1 Baseline clinical characteristics of the study population overall and of patients followed up for >6 months.

	Baseline (n = 103)	Follow-up > 6 months (n = 52)	P
Biodemographic data			
Sex, female	28 (27.2%)	11 (21.2%)	0.414
Age, years (mean ± SD)	71.3 ± 9.4	72.0 ± 10.4	0.673
BMI, kg/m^2 (mean ± SD)	28.1 ± 5.8	28.2 ± 5.7	0.919
Follow-up (months), median (IQR)	-	303 (256–365)	-
Comorbidities			
Current smoker	12 (11.7%)	5 (9.6%)	0.702
Former smoker	47 (45.6%)	29 (55.8%)	0.233
Hypertension	89 (86.4%)	50 (96.2%)	0.060
Diabetes	58 (56.3%)	31 (59.6%)	0.694
Dyslipidaemia	86 (83.5%)	48 (92.3%)	0.130
COPD	15 (14.6%)	9 (17.3%)	0.656
Atrial fibrillation	68 (66%)	38 (73.1%)	0.372
Chronic kidney disease	63 (61.2%)	37 (71.2%)	0.220
Aetiology of HF			
Ischaemic	58 (56.3%)	28 (53.8%)	0.771
Dilated non-ischaemic	34 (33%)	20 (38.5%)	0.501
Restrictive	1 (1%)	0	0.620
Toxicity	2 (1.9%)	2 (3.8%)	0.480
Valvular	5 (6.4%)	2 (3.8%)	0.775
Criteria for initiating vericiguat in the VICTORIA trial			
Infusion of levosimendan	8 (7.8%)	6 (11.5%)	0.439
HF-related hospitalization in the previous 3 months	37 (35.9%)	17 (32.7%)	0.690
HF-related hospitalization in the previous 3–6 months	29 (28.2%)	12 (23.1%)	0.499
Intravenous diuretics for HF (without hospitalization) in the previous 3 months	29 (28.2%)	17 (32.7%)	0.559
Number of previous HF hospitalizations/ED visits in the previous 12 months	1.9 ± 1.3	2.3 ± 1.4	0.080
NYHA functional class			
NYHA I	0	1 (2.1%)	
NYHA II	42 (40.8%)	17 (32.7%)	<0.001
NYHA III	61 (59.2%)	35 (67.3%)	

ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032 * Kerwagem et al. Eur J Clin Pharmacol. 2024 Jun;80(6):931-940.

…but with a higher use of HF therapies than in pts included in the VICTORIA trial

	Baseline (n = 103)	Follow-up > 6 months (n = 52)	P
LVEF, % (mean ± SD)	34 ± 7.5	31.8 ± 7.2	0.083
LVDd, mm (mean ± SD)	61.9 ± 11.8	63.6 ± 8.9	0.362
TAPSE, mm (mean ± SD)	18 ± 3.3	17.4 ± 3.3	0.287
PASP (mean ± SD)	37.5 ± 12.2	37.6 ± 12.3	0.962
Grade III–IV mitral regurgitation	41 (39.9%)	22 (42.3%)	0.765
Grade III–IV tricuspid regurgitation	18 (17.5%)	9 (17.3%)	0.979
Biochemical parameters			
Haemoglobin, g/dL (mean ± SD)	13.8 ± 1.7	13.7 ± 2.0	0.745
N/L ratio, median (IQR)	2.84 (2.0–3.9)	3.04 (2.2–4.37)	0.144
Creatinine (mg/dL), median (IQR)	1.3 (1.1–1.7)	1.43 (1.09–1.75)	0.002
eGFR (mL/min/1.73 m^2), median (IQR)	51 (36–65)	47 (35–60)	0.097
Hb1Ac, % (mean ± SD)	6.6 ± 1.3	-	-
Sodium, mmol/L (mean ± SD)	140 ± 3	139 ± 3.6	0.069
Chlorine, mmol/L (mean ± SD)	101 ± 4.2	100 ± 4	0.157
Potassium, mmol/L (mean ± SD)	4.7 ± 0.6	4.58 ± 0.52	0.221
NT-proBNP (pg/mL), median (IQR)	2034 (910–3372)	2116 (1019–4469)	0.630
CA 125, U/mL median (IQR)	18 (12–29)	16 (11–25)	0.04
Systolic blood pressure (mmHg), median (IQR)	117 (103–128)		
HF treatments			
Beta-blockers	102 (99%)	52 (100%)	0.999
Sacubitril–valsartan	98 (95.1%)	49 (94.2%)	0.808
Dose of sacubitril–valsartan			
No	4 (3.9%)	3 (5.8%)	
12/13 mg	19 (18.4%)	4 (7.7%)	0.023
24/26 mg	41 (39.8%)	11 (21.2%)	
49/51 mg	16 (15.5%)	22 (42.3%)	
97/103 mg	23 (22.3%)	12 (23.1%)	
Aldosterone antagonists	93 (90.3%)	47 (90.4%)	0.985
Dose of aldosterone antagonists			
No	5 (9.6%)	6 (11.8%)	
12.5 mg	13 (25%)	6 (11.8%)	0.372
25 mg	24 (46.2%)	29 (56.9%)	
50 mg	10 (19.2%)	10 (19.6%)	

(*Continues*)

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…but with a higher use of HF therapies & devices than in pts included in the VICTORIA trial

Table 1 (continued)

	Baseline (n = 103)	Follow-up > 6 months (n = 52)	P
SGLT2i	99 (96.1%)	52 (100%)	0.700
Loop diuretics	96 (93.2%)	49 (94.2%)	0.806
Dose of loop diuretics, mg (mean ± SD)	41.5 ± 23.5	38.5 ± 23.7	0.455
Levosimendan	18 (17.5%)	11 (21.2%)	0.579
Devices			
ICD	23 (22.3%)	15 (28.8%)	0.373
Resynchronization therapy	30 (29.1%)	24 (46.2%)	0.036
MitraClip	8 (7.8%)	6 (11.5%)	0.439

In VICTORIA tial 93% of pts were taking BB, 69% MRA, 14% S/V whereas Kerwagen et al. 2024 at baseline 29% were receiving all these molecules

ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

NYHA functional class improved: from 67.3% and 32.7% in classes III and II, respectively, to 22.4% and 75.5%, at study end – *no further changes were reported*

Table 1 Baseline clinical characteristics of the study population overall and of patients followed up for >6 months.

	Baseline (n = 103)	Follow-up > 6 months (n = 52)	P
Biodemographic data			
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Former smoker	47 (45.6%)	29 (55.8%)	0.233
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Diabetes	58 (56.3%)	31 (59.6%)	0.694
Dyslipidaemia	86 (83.5%)	48 (92.3%)	0.130
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Intravenous diuretics for HF (without hospitalization) in the previous 3 months	29 (28.2%)	17 (32.7%)	0.559
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ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

No changes in HF treatments & devices use after follow-up >6 months were reported

Table 1 (continued)

	Baseline (n = 103)	Follow-up > 6 months (n = 52)	P
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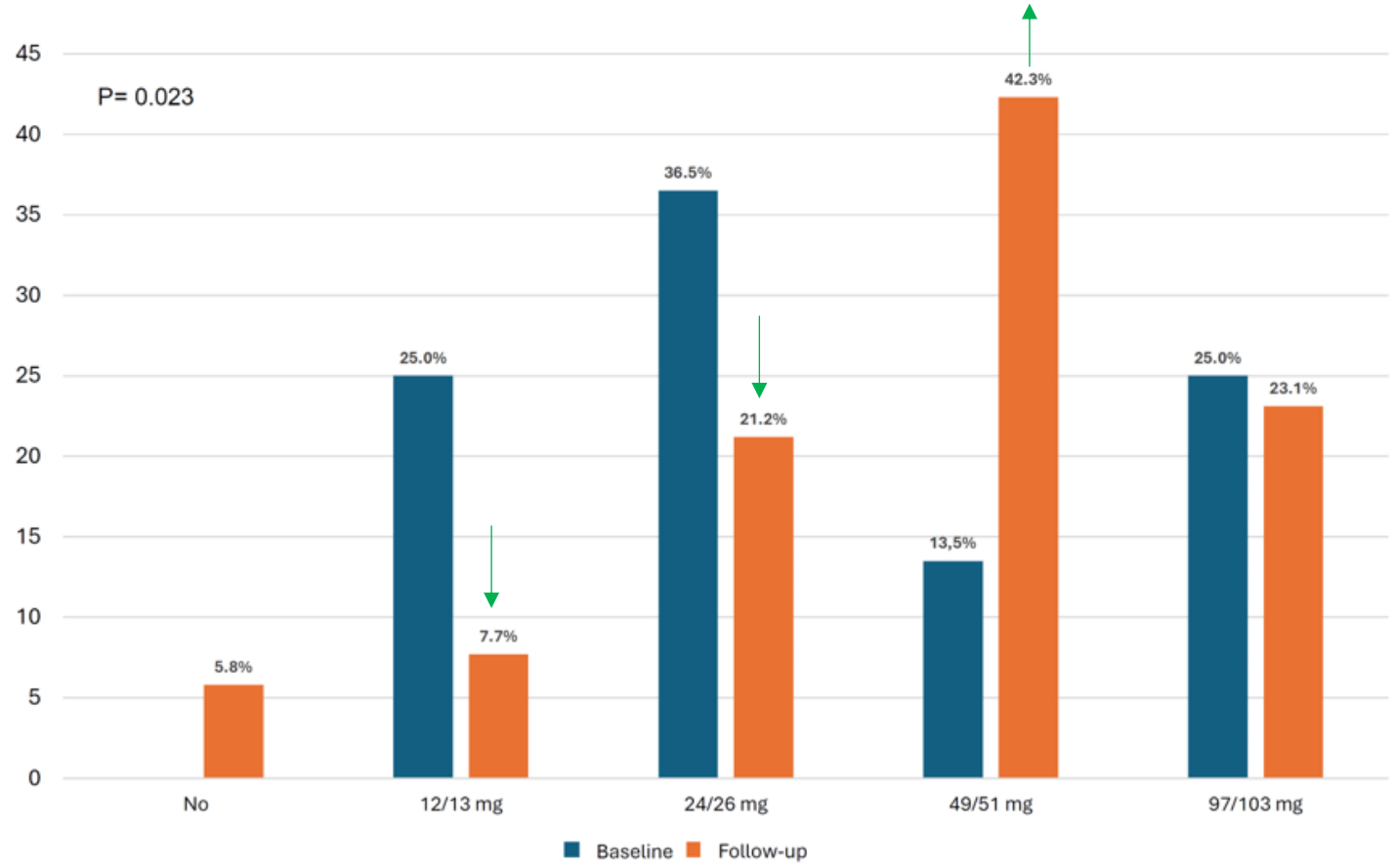
The dosage of sacubitril–valsartan increased significantly after the introduction of vericiguat (>65% of pts received 50-100% maximum dose)

Supplementary figure 1. Change in the dose of sacubitril-valsartan after initiation of treatment with vericiguat (n=52).



(…) Patients ***who reduced the dose of sacubitril–valsartan had lower doses of vericiguat****, including the five patients who discontinued the drug (…).*

*(…) In contrast****, patients who titrated the S/V*** *dose also* ***received higher doses of vericiguat (…)***

(…) ***S/V uptitration*** *was* ***not associated*** *with a higher* ***risk of hypotensive*** *episodes (…)*

The introduction of vericiguat may facilitate the optimization of concomitant HF therapies as a ***relationship additive (…)***

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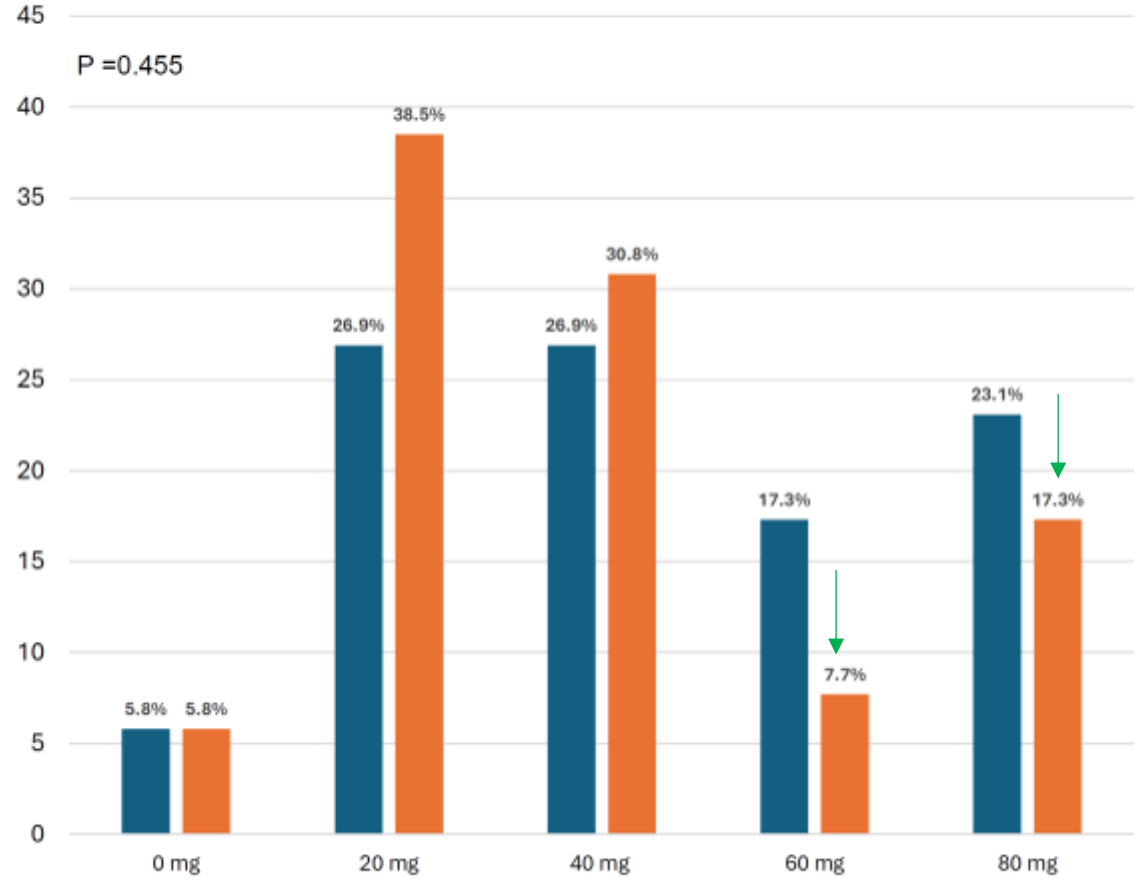
There was a trend towards a reduction in dosage of furosemide during follow-up (from 41.5 ± 23.5 to 38.5 ± 23.7 mg; *P* = 0.455), a lower proportion of patients required high doses of furosemide at study end

Supplementary figure 2. Change in the dose of loop diuretics after initiation of treatment with vericiguat (n=52).



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Adverse effects of vericiguat were uncommon only 9.6% discontinued their treatment because of these effects

Table 2 Adverse effects and uptitration of vericiguat during follow-up (n = 52).

Adverse effect	
Gastrointestinal symptoms	1 (1.9%)
Asymptomatic hypotension	11 (21.2%)
Symptomatic hypotension	7 (13.5%)
Uptitration of vericiguat	
Discontinuation	6 (11.5%)
2.5 mg	2 (3.8%)
5 mg	3 (5.8%)
10 mg	41 (78.8%)
Reasons for discontinuation	
Hypotension	5 (9.6%)
Other	1 (1.9%)

Note: Qualitative variables are presented as absolute (n) and relative (%) frequencies.

*(…) In the **VICTORIA** trial, **symptomatic hypotension** was recorded **in 9.1**% of patients in the vericiguat group (vs. **13.5% in our study**) (…).*

*(…) Even though nearly **all patients received SGLT2 inhibitors (and S/V,** the rate of **hypotension** remained **low (…)***

ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

Most patients (78.8%) achieved the target dose of 10 mg of vericiguat

Table 2 Adverse effects and uptitration of vericiguat during follow-up ($n = 52$).

Adverse effect	
Gastrointestinal symptoms	1 (1.9%)
Asymptomatic hypotension	11 (21.2%)
Symptomatic hypotension	7 (13.5%)
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2.5 mg	2 (3.8%)
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10 mg	41 (78.8%)
Reasons for discontinuation	
Hypotension	5 (9.6%)
Other	1 (1.9%)

Note: Qualitative variables are presented as absolute (n) and relative (%) frequencies.

ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

The median FU was 303 days (similar to VICTORIA): 38.5% of patients were hospitalized for HF or IV diuretics …

Table 3 Events after initiation of treatment with vericiguat (n = 52).

Median follow-up, days (IQR)	303 (256–365)
HF-related hospitalizations/need for i.v. diuretics	20 (38.5%)
Number of HF hospitalizations/need for i.v. diuretics	0.79 ± 1.14
Heart transplant	1 (1.9%)
Death	4 (7.7%)
HF	2 (3.8%)
Non-cardiovascular	2 (3.8%)

Note: Qualitative variables are presented as absolute (n) and relative (%) frequencies; quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) when indicated.
Abbreviations: HF, heart failure; i.v., intravenous.

ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

…before the initiation of vericiguat, the mean *n* of HF-related hospitalizations/decompensations within the previous 12 months was 2.3±1.4; after the initiation of vericiguat decreased to 0.79 ± 1.14 (*P* < 0.001). At study end, 7.7% of patients had died, half of them because of HF

Table 3 Events after initiation of treatment with vericiguat (*n* = 52).

Median follow-up, days (IQR)	303 (256–365)
HF-related hospitalizations/need for i.v. diuretics	20 (38.5%)
Number of HF hospitalizations/need for i.v. diuretics	0.79 ± 1.14
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Non-cardiovascular	2 (3.8%)

Note: Qualitative variables are presented as absolute (*n*) and relative (%) frequencies; quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) when indicated.
Abbreviations: HF, heart failure; i.v., intravenous.

(…) Approx. 36% of pts. were hospitalized in the previous 3 months, 28% between 3 and 6 months and the remaining 28% received i.v. diuretics in the previous 3 months (…)

(…) This indicates that vericiguat can be used in clinical practice for a broad spectrum of patients with HFrEF after a worsening HF event (…).

Thus, it has been reported that the relative efficacy and safety of vericiguat remain unchanged regardless of the index HF event

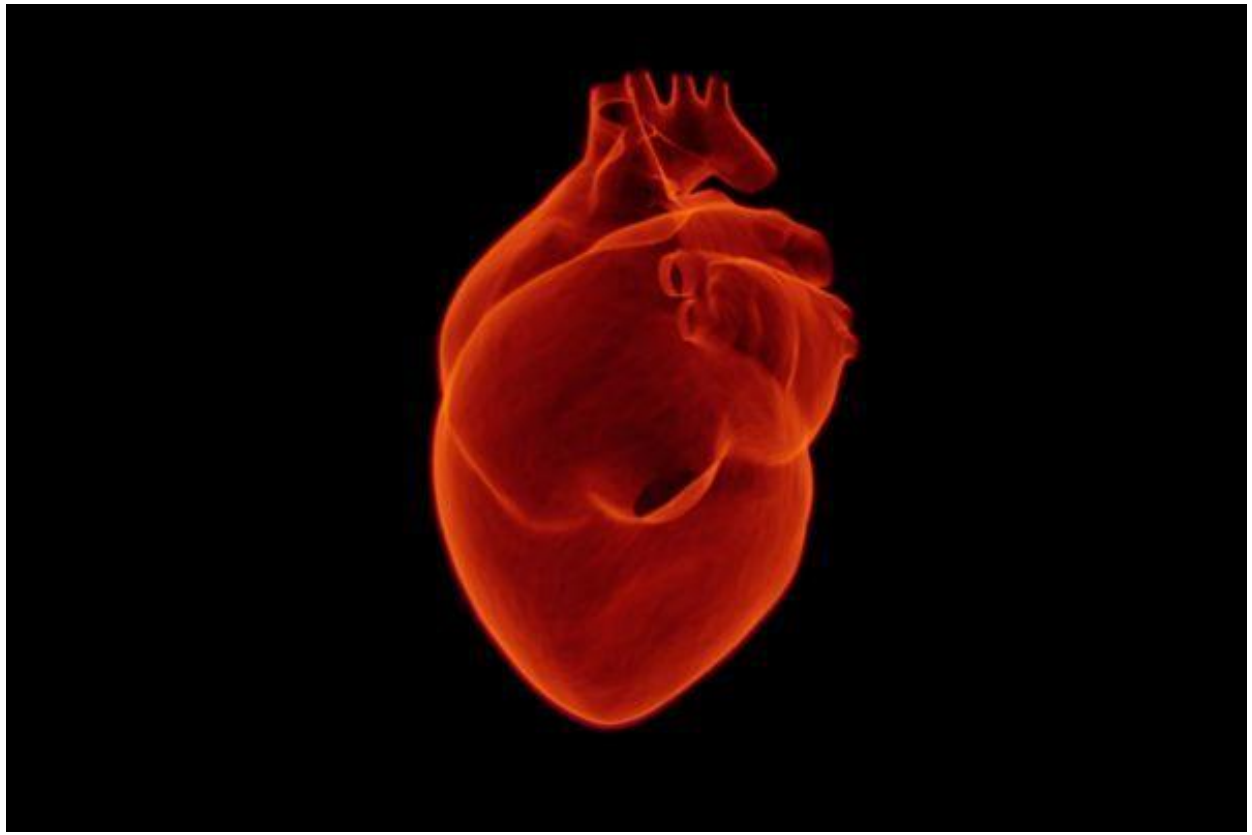
ESC Heart Fail. 2024 Aug 18. doi: 10.1002/ehf2.15032

Vericiguat is specifically recommended and approved for worsening HF[1,2]

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

"Verquvo"* is indicated for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized **after a recent decompensation event requiring IV therapy**[2]

Please refer to relevant SmPCs for region specific indications.
* "Verquvo" is the brand name for vericiguat.
ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; HF, heart failure; HFH, heart failure hospitalization; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SmPC, Summary of Product Characteristics.
References: 1. McDonagh TA *et al. Eur Heart J* 2021;42:3599–3726; **2.** Bayer AG. Verquvo® (vericiguat) SmPC. 2021. [Link].



GRAZIE PER L'ATTENZIONE