

16. KARDIOLOGIE-SYMPOSIUM
DES HERZZENTRUMS HIRSLANDEN ZENTRALSCHWEIZ

19. Oktober 2023 Radisson Blu Luzern



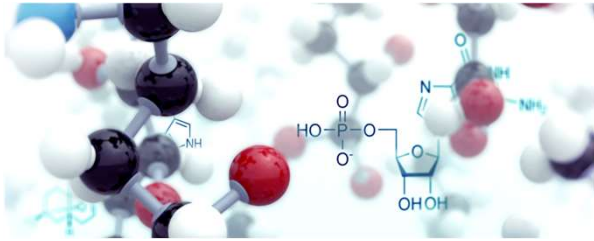
VERQUVO

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1

Vericiguat (Verquvo®):
Treatment for heart failure patients with reduced ejection fraction after decompensation



2

Heart failure: 5 yr Outcomes & Epidemiology




Region	Country	Prevalence
North America	Canada	3.0%
	USA	2-4.2%
Europe	Sweden	2.2%
	Germany	4.0%
	Belgium	3.3%
	Italy	1.4%
Asia	China	1.3-3.5%
	Japan	0.8%
	India	0.3%
	Spain	2.1%

HF is the #1 reason for hospitalisation in patients aged >65 years, with 24% of patients re-hospitalised within 30 days of discharge^{2,3}

Approximately 50% of patients diagnosed with HF will die within 5 years⁴

There are 150.000 Heart Failure Patients in Switzerland*

Herztransplantationen und Personen auf der Herz-Warteliste, 2007-2019



■ Anzahl Herztransplantationen
■ Anzahl Personen auf der Herz-Warteliste (jeweils Jahr)

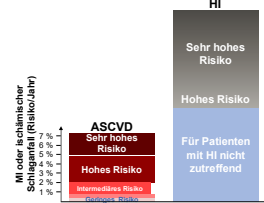
*Mohacs, P., et al., Ein Curriculum für Herzinsuffizienz ist als Grundlage für die Entwicklung erforderlicher nationaler Strukturen umgänglich: Postkongress 'Herzinsuffizienz Curriculum' der Arbeitsgruppe Herzinsuffizienz der SGG. Cardiovascular Medicine, 2018, 23(03): p. 26-32
11. Sponswagen et al., Eur J Heart Fail 2020; 22(4): 495

3

Prognose von Patienten mit ASCVD / Herzinsuffizienz / Krebs

Selbst die Untergruppen von HFrEF-Patienten mit dem geringsten Risiko weisen höhere Ereignisraten auf als ASCVD-Patienten mit hohem oder sehr hohem Risiko!

Prognose bei Herzinsuffizienz ist vergleichbar mit vielen Krebsarten⁵



MI oder ischämischer Schlaganfall (Risiko/Jahr)

ASCVD
Sehr hohes Risiko

Hohes Risiko

Intermediate Risiko

Sehr hohes Risiko

Hohes Risiko

Für Patienten mit HI nicht zutreffend

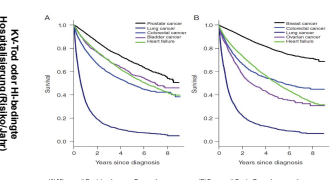
HI

KV-Risk oder HFrEF-Risk (Risiko/Jahr)

Sehr hohes Risiko

Hohes Risiko

Für Patienten mit HI nicht zutreffend



A: Männer mit Prostata-, Lungen-, Darm- oder Blasenkrebs oder mit Herzinsuffizienz

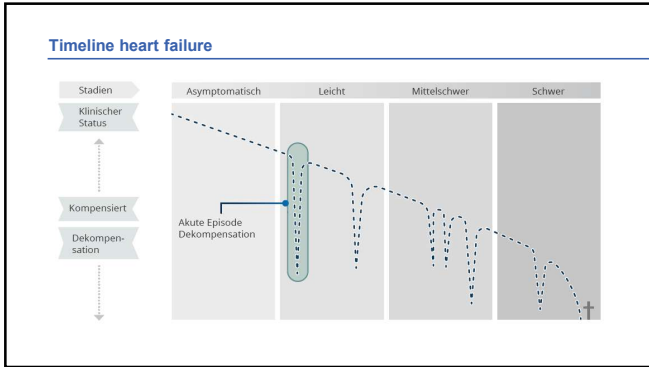
B: Frauen mit Brust-, Darm-, Lungen- oder Eierstockkrebs oder mit Herzinsuffizienz

Legend for A: Prostatakrebs, Lungenkrebs, Darmkrebs, Blasenkrebs, Heart failure

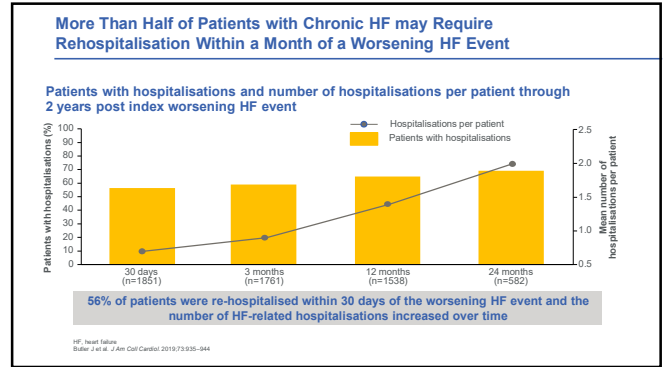
Legend for B: Brustkrebs, Eierstockkrebs, Darmkrebs, Lungenkrebs, Heart failure

5. Givens SJ et al., JAMA 2017;317(22):2281-2292; 2. Matusik NR et al., Eur J Heart Fail 2017; 19(9):1050-1054

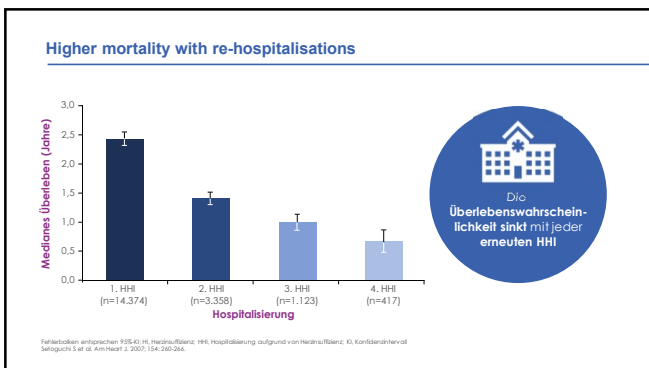
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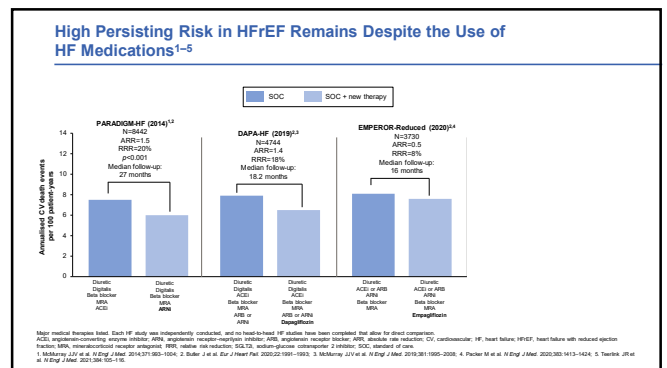
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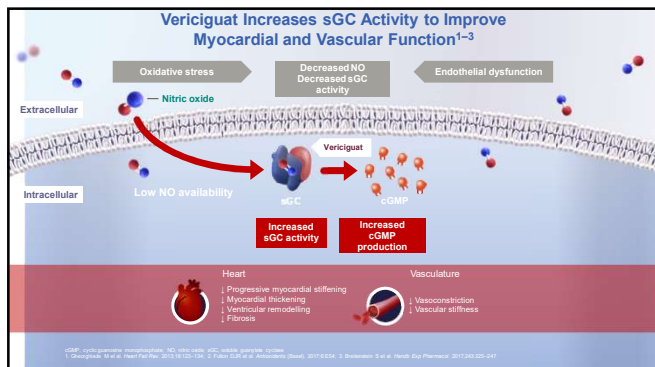
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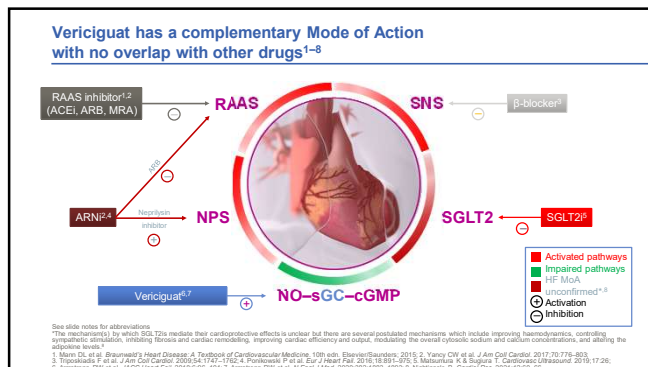
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8



13



14

The NEW ENGLAND JOURNAL of MEDICINE

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Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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15

VICTORIA Study Design

The VICTORIA study was a randomised, parallel-group, placebo-controlled, double-blind, event-driven, international phase III trial investigating the effect of vericiguat in patients with symptomatic chronic HF/EF following a worsening HF event^{1,2}

Eligibility criteria (N=5050):

- HF/EF (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

Treatment: 2.5 mg OD, 5 mg OD, 10 mg OD* vs Placebo OD with sham up-titration at Weeks 2 and 4.

Timeline: Week 0, Week 2, Week 4, Week 16, Q16W.

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

Secondary endpoints:

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

Exploratory endpoints included changes in KCCQ and EQ-5D from baseline and the relationships among treatment effect, baseline biomarkers and genetic variation.

*If the 10 mg OD target is not reached, up-titration should be considered at subsequent study visits.

1. Armstrong PW, et al. JACC Heart Fail. 2018;6(10):1044-52. 2. Armstrong PW, et al. N Engl J Med. 2020;383:1885-1895.

16

VICTORIA Was Designed to Study Patients with Symptomatic Chronic HF Following a Worsening HF Event^{1,2}

'Symptomatic chronic HF'

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

&

'Worsening HF event'

- Recent HF hospitalisation
- Recent IV diuretic use
- Elevated natriuretic peptides

Main Exclusion Criteria

- Clinically unstable
- Systolic blood pressure <100 mm Hg
- Concurrent or anticipated use of long-acting nitrates of sGC stimulator
- PDES inhibitors
- Receiving IV inotropes, an implantable LV assist device or awaiting heart transplantation
- Correctable, complex, or clinically active cardiac comorbidity
- Prior cardiac valve intervention <3 months or coronary revascularization <90 days
- Unable to provide informed consent
- Females of reproductive age not using an acceptable form of contraception

17

VICTORIA Was Designed to Study Patients with Symptomatic Chronic HF Following a Worsening HF Event^{1,2}

67 % der Patienten wurden in den letzten 3 Monaten nach der Randomisierung hospitalisiert¹

Die VICTORIA-Studie schloss eine Population mit hohem Risiko aber gut behandelter HF ein¹

Die Drafachtherapie aus SGLT2-Medikamenten konnte Betablocker, ACE-Hemmer, ARBs und Sacubitril/Valsartan umfassen. ACE: Angiotensin-Converting-Enzym-Inhibitor; ARB: Angiotensinrezeptorblocker; MRA: Mineralocorticoidrezeptorantagonist; SGLT: Standardbehandlung; HF: Herzinsuffizienz mit reduzierter Ejektionsfraktion; IV: intravenös; IQR: Quartilsbreite. 1. Armstrong PW et al. JACC Heart Fail 2018;6:98-104; 2. Armstrong PW et al. N Engl J Med 2020;382:1885-1895

18

The VICTORIA Trial Targeted a Distinct Patient Population in Contrast to Other Contemporary HF Trials

VICTORIA-Patienten haben aufgrund anhaltend erhöhter Ereignisraten den maximalen medizinischen Bedarf, was zu einer Patientenpopulation mit wesentlich höherem Ausgangsrisiko führt

	DAPA-HF ^{1,2}	PARADIGM-HF ³⁻⁵	VICTORIA ^{6,7}
Medianes NT-proBNP (pg/ml)	1437	1608	2816
HI-bedingte Hospitalisierung innerhalb von 6 Monaten (%)	16,4	31	84
NYHA-Klasse III/IV am Ausgangspunkt (%)	32	25	41
eGFR < 60 ml/min/1,73 m ²	41 %	37 %	53 %
eGFR-Grenzwert	≥ 30 ml/min/1,73 m ²	≥ 30 ml/min/1,73 m ²	≥ 15 ml/min/1,73 m ²
Primäres Ergebnis (Ereignisse in den Vergleichsarmen pro 100 PJ)	15,6*	13,2	37,8
HI-bedingte Hospitalisierung	9,8	7,7	29,1
KV-Tod	7,9	7,5	13,9

Notes: *Das ist kein direkter Vergleich der verschiedenen Studien sein. ¹Das primäre Endpunkt für DAPA-HF war der KV-Tod, die Hospitalisierung oder ein dringender Arztbesuch, der zu einer IV-Behandlung wegen HF führte. Primäre Endpunkte in PARADIGM-HF und VICTORIA waren der KV-Todesrate die HI-bedingte Hospitalisierung. ²KV: kardiovaskulär; HI: Herzinsuffizienz; NT-proBNP: N-Terminal des pro-B-Typ natriuretisches Peptid; NYHA: New York Heart Association; PJ: Patient-Jahre. ³McKernan JF et al. Eur J Heart Fail 2015;17:1402-1411; ⁴McKernan JF et al. N Engl J Med 2010;363:1090-1098; ⁵McKernan JF et al. Eur J Heart Fail 2014;16:817-824; ⁶Solomon SD et al. JACC Heart Fail 2018;4:816-822; ⁷McKernan JF et al. Eur Heart J 2015;36:434-439; ⁸Armstrong PW et al. N Engl J Med 2020;382:1885-1895; ⁹Parvati B et al. Eur J Heart Fail 2019;21:1586-1604

19

Vericiguat Significantly Reduced the Annualised Absolute Risk of the Primary Composite Outcome

Time to CV death or first HF hospitalisation

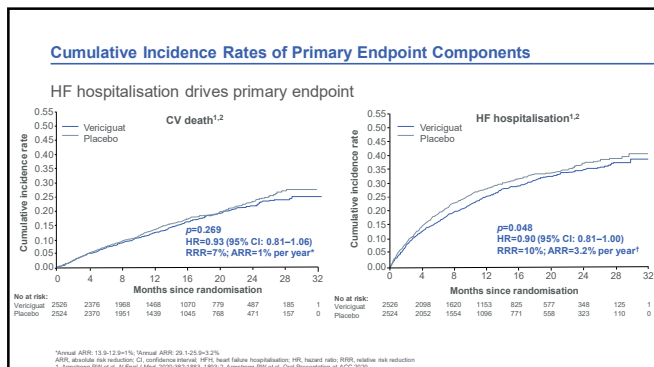
p=0.02
HR=0.90 (95% CI: 0.82-0.98)
ARR=4.2% per year
Annual NNT=24

- Median follow-up period: 10.8 months
- Event rate per 100 patient-years was 33.6% for vericiguat vs 37.8% for placebo

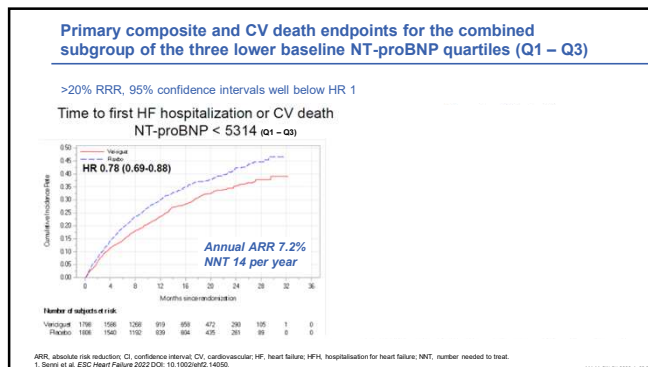
Months since randomisation	Vericiguat	Placebo
0	2526	2524
4	2069	2053
8	1621	1555
12	1164	1097
16	826	772
20	577	559
24	348	324
28	125	110
32	0	0

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;382:1885-1893

20



21



22

Overall AE Incidence and SAE Profile was Similar to Placebo

SAEs within a system organ class (all patients as treated)*

Event, %	Vericiguat (N=2519)	Placebo (N=2515)
≥1 SAEs	32.8	34.8
Blood and lymphatic system disorders	2.1	1.2
Cardiac disorders	8.1	10.7
Cardiac failure	3.2	4.4
GI disorders	4.0	3.7
Infections and infestations	10.7	10.7
Pneumonia	4.0	4.5
Injury, poisoning and procedural complications	2.6	3.1
Metabolism and nutrition disorders	2.9	3.5
Nervous system disorders	3.3	3.3
Renal and urinary disorders	5.9	5.3
Acute kidney injury	2.5	2.0
Respiratory, thoracic and mediastinal disorders	3.5	3.6
Vascular disorders	3.2	3.4

- Incidence of organ class AEs was similar between vericiguat and placebo
- Small imbalances in renal, GI, blood disorders and hypotensive SAEs
- More anaemia developed with vericiguat (7.6%) than with placebo (5.7%)
- Electrolyte balance was similar between vericiguat and placebo

*Incidence 52% in one or more treatment groups
 †AE=adverse event; GI=gastrointestinal; SAE=serious adverse event
 Armstrong PW et al. N Engl J Med 2020;382:1883-1893

23

Adverse Events of Clinical Interest

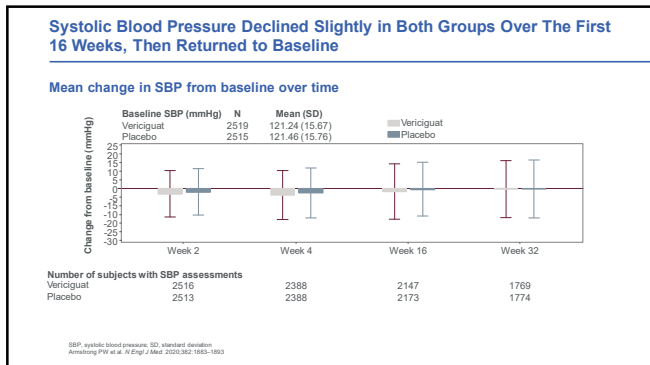
Symptomatic hypotension and syncope

	Vericiguat N=2519	Placebo N=2515	Difference in % vs placebo	
	N (%)	N (%)	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

- Symptomatic hypotension and syncope were numerically more common in the patients receiving vericiguat than in those receiving placebo

*Based on the Miettinen & Nurminen method
 CI=confidence interval
 Armstrong PW et al. N Engl J Med 2020;382:1883-1893

24



25

The urgent need for HF therapies that are well-tolerated and safe in order to ensure compliance^{1,2}

The 4 most common side effects in HF Therapies, that must be uptitrated:²

	Bradycardia	Hypotension	Hyperkalemia	Renal impairment
Verquvo	-	-(+)*	-	-
ARNI	-	+	+	+
ACE-Inhibitors	-	+	+	+
Beta Blockers	+	+	-	-
MRA	-	-(+)*	+	+

* does not occur or does not occur significantly more frequently than with placebo
 + occurs more frequently than with placebo

* Hinkel, affect on blood pressure
 1 Saravahalli et al. Eur J Heart Fail 2021; 23:1495-1511
 2 Escobal et al. Expert Opin Pharmacother 2022; Aug 31:1-11

26

Key updates in the management of chronic heart failure were presented at the congress of the European Society of Cardiology in August 2021.

ESC HF Guidelines 2021

Recommendation	Class
HFREF	
ACEi (ARNI), Beta-blocker, MRA and Dapagliflozin/Empagliflozin are recommended for patients with HFREF to reduce the risk of HF hospitalization and death	I
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 HF hospitalization	Ib

- Vericiguat Inclusion in the guidelines before EU approval
- Worsening HF referred to for the first time and vericiguat specifically recommended for this patient group
- use of all foundational therapies not required prior to vericiguat initiation

1. McDonald M et al. Clin J Cardiol 2021;17:531-546. 2. Rosano GMC et al. EHJ HF 2021;23:872-81

27

Limitatio:

Vergütung von Verquvo® gemäss SL:

Zur Behandlung erwachsener Patienten mit einer rekompensierten symptomatischen chronischen Herzinsuffizienz der NYHA Klassen II-IV, deren linksventrikuläre Auswurfraction (LVEF) vor Behandlung mit Verquvo® < 40% beträgt und die – **trotz vorab optimal eingestellter Basistherapie** die mindestens eine zuvor stabil eingestellte Dosis eines ARNI (Angiotensin-Rezeptorblocker-Nephrisylinhibitor), sowie eines Betablockers, eines Mineralokortikoidrezeptorantagonisten (MRA) und eines SGLT2-Inhibitors enthielt – **eine kürzlich aufgetretene Dekompensation hatten**, die eine i.v.-Therapie erforderte.

Zudem kann Verquvo® bei erwiesener Intoleranz oder Kontraindikation gegenüber einer Substanzklasse der Basistherapien die bestehende Herzinsuffizienztherapie nach Dekompensation ergänzen.

Vor Initiierung der Behandlung mit Verquvo® muss eine ausreichende Stabilisierung nach kürzlich aufgetretener Dekompensation sichergestellt werden, insbesondere bei Patienten mit stark erhöhten NT-proBNP-Spiegeln. Die klinische Stabilisierung schliesst die Behandlung der Volumenüberladung mittels intensiver (intravenöser) Diuretika-Therapie und die Optimierung der Behandlung mit anderen Standardtherapeutika für Herzinsuffizienz ein.

Die Ersterverordnung von Verquvo® darf ausschliesslich durch einen Facharzt für Kardiologie erfolgen.

- Patienten mit Dekompensation trotz Einsatz der Basistherapien (BB, MRA, SGLT2-i, ARNI)
- HI-Basistherapien können aufgrund von Verträglichkeitsproblemen (Intoleranz) nicht oder nur in tiefer Dosierung eingesetzt werden
- HI-Basistherapien können aufgrund von Kontraindikationen (Begleiterkrankungen, Co-Medikationen) nicht eingesetzt werden

28

Management of Worsening HF with Reduced EF

CENTRAL ILLUSTRATION Medical Therapy for Worsening Heart Failure With Reduced Ejection Fraction


	Oral Medical Therapy	IV therapy
Step #1: Rapid sequence or simultaneous initiation of disease-modifying therapies	<p>Quadruple therapy: ARNI*, BB, MRA, SGLT2i</p> <p>Quintuple therapy with vericiguat</p> <ul style="list-style-type: none"> Prioritize initiating low doses to maximize tolerability Prioritize initiating multiple/all medications prior to dose escalation of any one medication 	<p>IV iron</p> <p>Among patients with iron deficiency[†]</p>
Step #2: Dose escalation of oral therapies, as tolerated	<p>Quadruple therapy: ↑ ARNI*, ↑ BB, ↑ MRA, Continue SGLT2i</p> <p>Quintuple therapy with vericiguat</p> <ul style="list-style-type: none"> Achieve maximally tolerated or target doses within 4–6 weeks 	<p>Strength of recommendation and benefit</p> <ul style="list-style-type: none"> Proven to improve HF outcomes, including mortality Foundational therapy to be utilized in all eligible patients, as tolerated Proven to improve HF outcomes other than mortality Therapy should be strongly considered, as tolerated

Figures adapted from Greene et al. (2023).
*ACE/ARB is strongly recommended when use of ARNI is not feasible. † Ferritin <100 µg/L or 100–250 µg/L with transferrin saturation <20%. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; HF-pH2O2, hydrogen peroxide-producing; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; HF-pH2O2, hydrogen peroxide-producing; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HF, heart failure; IV, intravenous; MRA, mineralocorticoid receptor antagonist; HF-pH2O2, hydrogen peroxide-producing.

29

Summary

- New Patient population** with recent decompensation
- New Mode of Action** complementary, with no overlap with other drugs
- Improved outcomes for HFH and CV death**
Significant annual reduction of the risk of HF hospitalisation or CV death.
ARR = 4.2% (NNT= 24), RRR= 10%
- Well tolerated and simple**
AE over all on Placebo level, 90.3% of patients on target dose (full up-titration = full efficacy)
No clinically relevant interactions with most drugs; used for HF and comorbidities
- No Monitoring needed**
No correlation between Vericiguat and eGFR, Worsening renal function or Serum Potassium



Start with **2.5 mg once daily**

Double the dose after 2 weeks to **5 mg once daily**

Double again after 2 weeks to reach **target maintenance dose of 10 mg once daily**

To be taken with food. For patients who are unable to swallow whole tablets, Vericiguat may be crushed and mixed with non-sparkling water immediately before administration.¹

1. Sandoz SMCPC www.vericiguat.com/uk

30

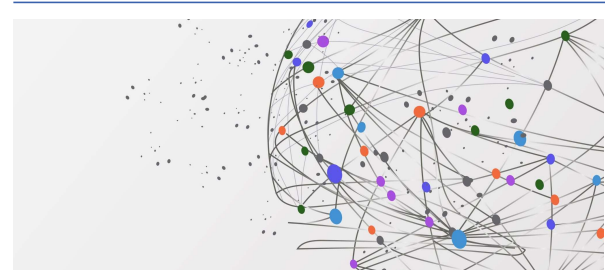
Take home

- Reduced cGMP activity resulting from ineffective stimulation of soluble guanylate cyclase (sGC) due to endothelial dysfunction plays a key role in the **pathophysiology of heart failure** and contributes to disease progression.
- Vericiguat** – a sGC stimulator increasing intracellular cGMP – is a new oral treatment for heart failure and provides a **novel approach** to tackle the pathophysiology of heart failure.
- Treatment with vericiguat is associated with a significant **reduction** in the combined endpoint of **cardiovascular mortality and heart failure hospitalisation**, mainly driven by a reduction in hospital admissions.
- Patients with **advanced HFrEF** and a **recent history of acute decompensation** despite optimal medical heart failure therapy are optimal candidates for starting treatment with vericiguat.

31

31

Thank You for your attention



32