Vericiguat training module 6

Verquvo vericiguat

MA-M_VER-IN-0188-1

BAYER MERCK

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Recap

Verquvo
vericiguat

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VICTORIA Targeted a Distinct Patient Population Compared to Contemporary HF Trials

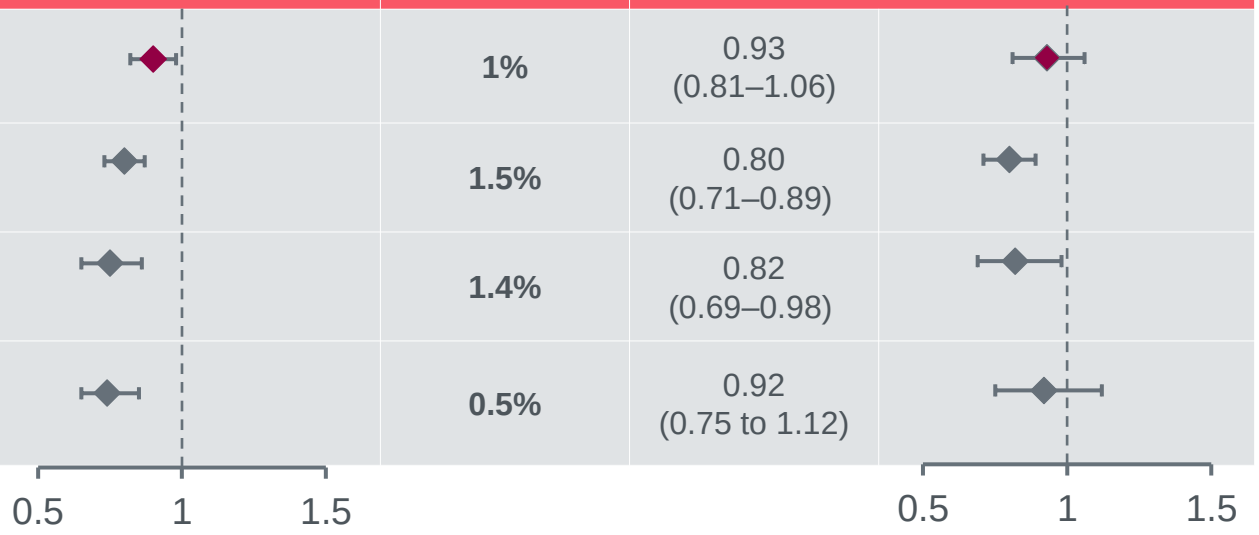
	PARADIGM-HF	DAPA-HF	EMPEROR-REDUCED	VICTORIA
Median NT-proBNP (pg/ml)[1-5]	1,608*	1,437	1,907#	2,816
HF hospitalization within 6 months[3-6]	31%	16%	31% *HFH within 12m*	84%
Proportion of patients with eGFR < 60 mL/min/1.73m^2 (3-5,7)	37%	41%	48%	53%¶
Primary outcome§ Event rates in placebo arms / 100 pt-yr[3,8]	13.2	15.6	21.0	37.8

*At screening before run-in; one month after randomization, 24% of the baseline NT-proBNP levels >1000 pg/ml had fallen to ≤1000 pg/ml; #average between 2 empagliflozin & placebo arms as overall median not reported;
¶For VICTORIA, cut off was ≤ 60 mL7min/1.73m$^{2;}$
§For VICTORIA & PARADIGM-HF, primary endpoint was a composite of CV death or HF hospitalization; for DAPA-HF, primary endpoint was a composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy for HF) or CV death

1. Zile MR et al. J Am Coll Cardiol 2016;68:2425-2436; **2.** Docherty KF et al. Eur Heart J. 2020. doi: 10.1093/eurheartj/ehaa183; **3.** Packer M et al. N Engl J Med. 2020;383(15):1413-1424; **4.** Armstrong PW et al. New Eng J Med. 2020;382(20):1883-92; **5.** McMurray JJV et al. Eur J Heart Fail. 2019;21(11):1402-1414; **6.** Solomon SD et al. JACC Heart Fail. 2016;4(10):816-822; **7.** McMurray JJV et al. Eur J Heart Fail. 2014;16(7):817-25; **8.** Butler J et al. Circulation. 2020 Aug 25;142(8):717-719

VICTORIA Delivered Competitive ARR to ARNI and SGLT2i Landmark Trials

	Median NT-proBNP (pg/ml)	Primary endpoint*		CV death	
		ARR/100 patient-years	HR (95%CI)	ARR/100 patient-years	HR (95% CI)
'Verquvo' VICTORIA[1,2]	2,816	**4.2%**	0.90 (0.82–0.98)	**1%**	0.93 (0.81–1.06)
Sacubitril/Valsartan PARADIGM-HF[1,3,4]	1,608#	**2.7%**	0.80 (0.73–0.87)	**1.5%**	0.80 (0.71–0.89)
Dapagliflozin DAPA-HF[1,5,6]	1,437	**4%**	0.74 (0.65–0.85)	**1.4%**	0.82 (0.69–0.98)
Empagliflozin EMPEROR-REDUCED[7]	1,907§	**5.2%**	0.75 (0.65–0.86)	**0.5%**	0.92 (0.75 to 1.12)



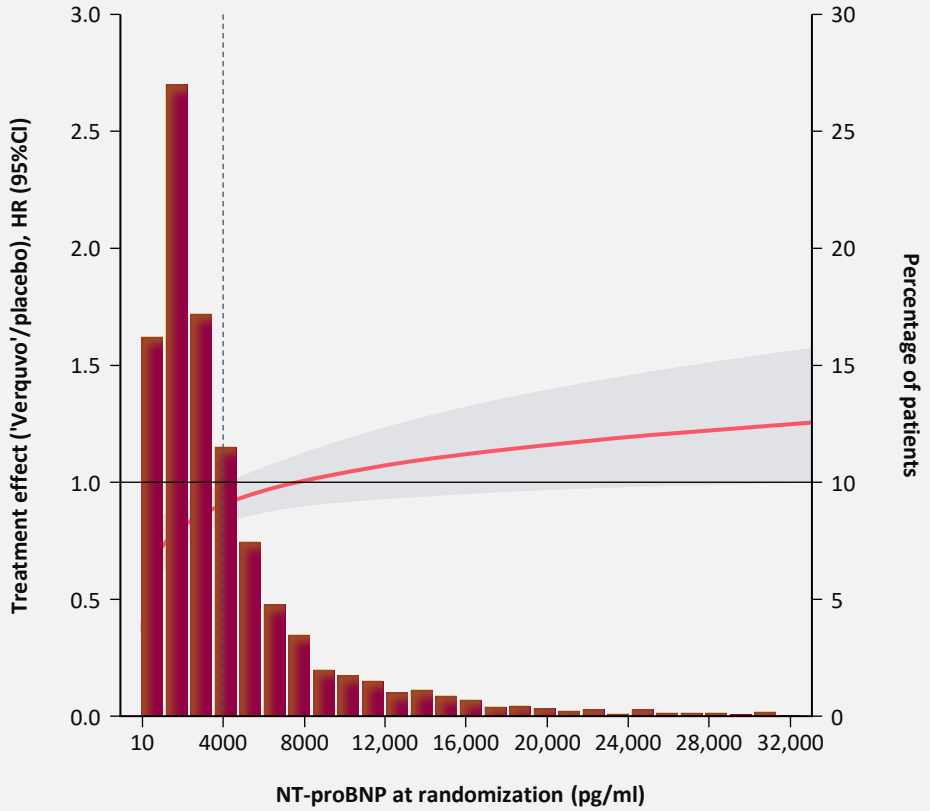
RESULTS ARE NOT INTENDED FOR DIRECT COMPARISON & FOR INTERNAL USE ONLY – NOT FOR EXTERNAL DISTRIBUTION

*For VICTORIA & PARADIGM-HF, primary endpoint was a composite of CV death or HF hospitalization; for DAPA-HF, primary endpoint was a composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy for HF) or CV death; #At screening before run-in; one month after randomization, 24% of the baseline NT-proBNP levels >1000 pg/ml had fallen to ≤1000 pg/ml; §average between 2 empagliflozin & placebo arms as overall median not reported

1. Butler J et al. Circulation. 2020 Aug 25;142(8):717-719; **2.** Armstrong PW et al. New Eng J Med. 2020;382(20):1883-92; **3**. Docherty KF et al. Eur Heart J. 2020. doi: 10.1093/eurheartj/ehaa183;
4. McMurray JJV et al. N Engl J Med. 2019;381:1995–2008; **5.** Zile MR et al. J Am Coll Cardiol 2016;68:2425-2436; **6.** McMurray JJ et al. N Engl J Med. 2014;371:993–1004; **7.** Packer M et al. N Engl J Med. 2020;383(15):1413-1424

Treatment Effect with 'Verquvo' Differed Across NT-proBNP Levels at Randomization

Primary composite outcome



Efficacy with 'Verquvo' was maintained in patients with baseline NT-proBNP levels as high as 8,000 pg/ml

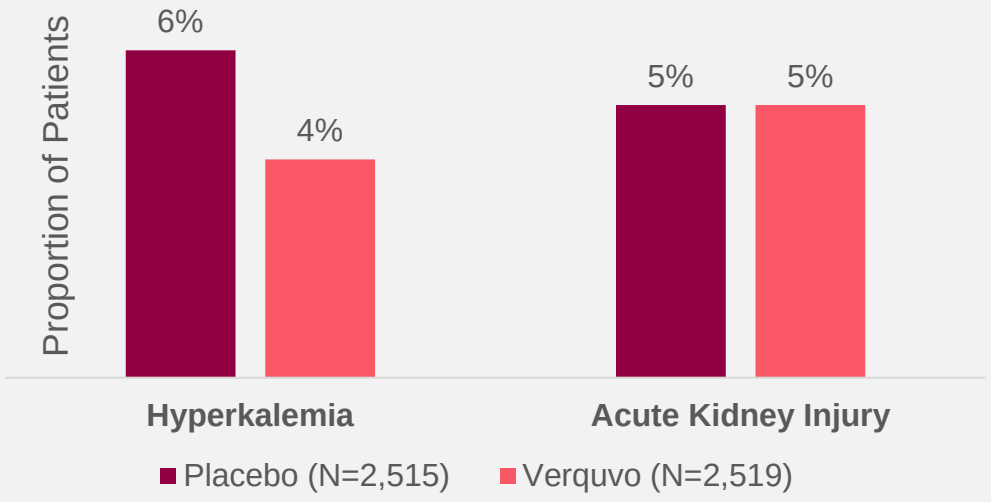
Baseline NT-proBNP (pg/mL)	N	ARR	HR (95% CI)
≤ 4000	3,100	6.8	0.77 (0.68-0.88)
≤ 8000	4,133	5.4	0.85 (0.76-0.95)
> 8000	672	-12.7	1.16 (0.94-1.41)

Ezekowitz AJ et al. JACC Heart Fail. 2020;8(11):931–939

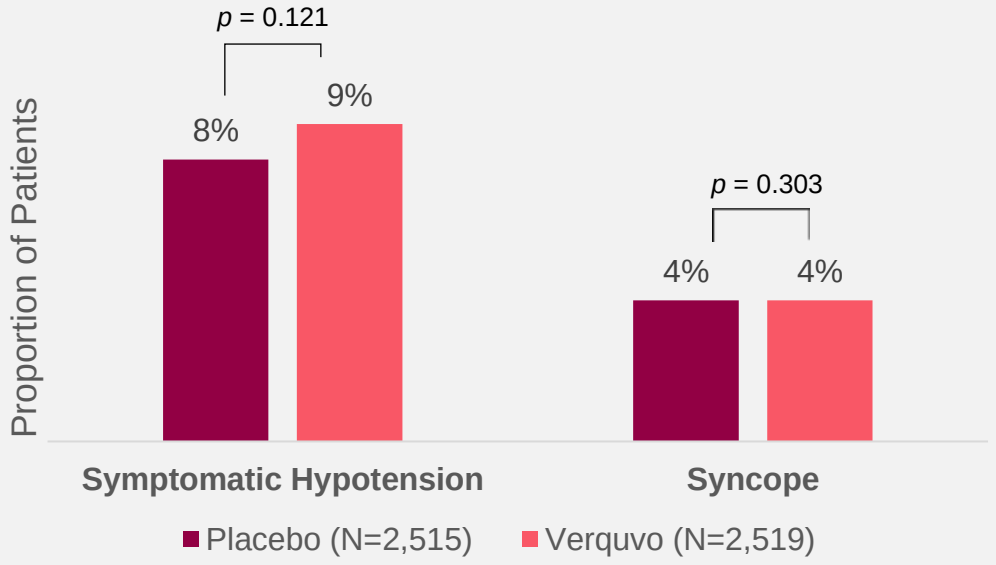
'Verquvo' Delivered an Overall Safety Profile Comparable to the Placebo Arm in VICTORIA, which Meant Nearly 95% of Patients Stayed on Treatment

After approximately 12 months, target dose of 'Verquvo' 10 mg was achieved in 89.2% (vs placebo: 91.4%)

No hyperkalemia or decreases in eGFR observed across the study population



Rates of symptomatic hypotension and syncope were similar to placebo



The total proportion of patients who experienced adverse events was same in both cohorts (81%)
Only 7% of patients receiving 'Verquvo' discontinued due to AEs

Armstrong PW et al. New Eng J Med. 2020;382(20):1883-92;

For Vulnerable HF Patients, the VICTORIA Study Delivered

HIGH UNMET NEED

1 in 2 patients re-hospitalized 30 days following a worsening event[1]

HIGH EFFICACY

ARR 4.2% overall and NNT of 24[2]

EXCLUSIVE PATIENT POPULATION

The only study exclusively in worsening HF patients with 3x higher event rates *vs* contemporary HF trials[2]

FAVORABLE SAFETY

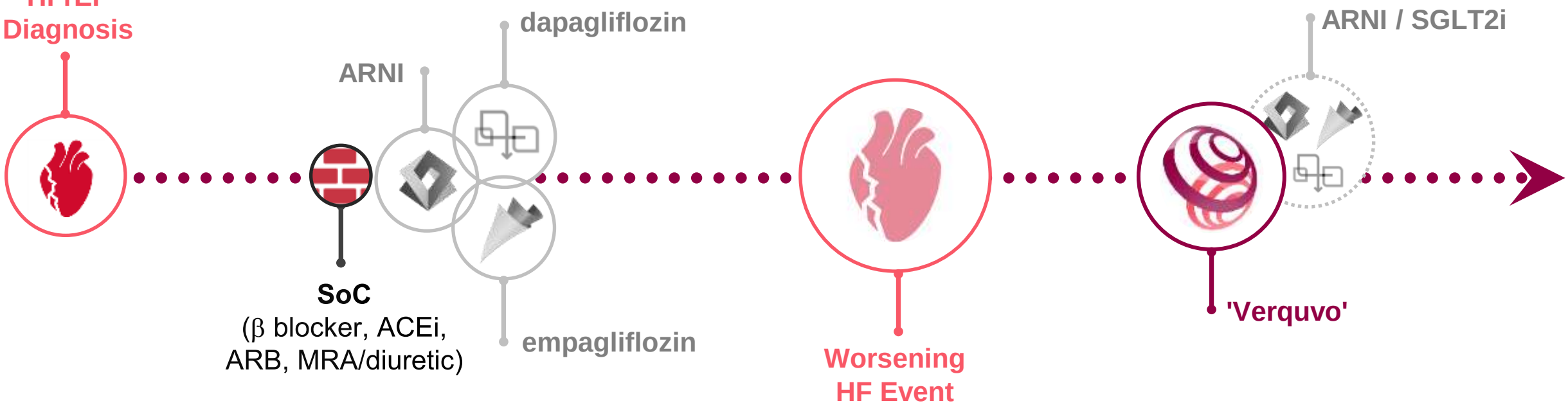
Overall safety profile in VICTORIA comparable to placebo arm (even hypotension) & can be used in conjunction with any HF therapy[2]

1. Butler J et al. J Am Coll Cardiol. 2019;773(8):935-944; **2.** Armstrong PW et al. New Eng J Med. 2020;382(20):1883-92

'Verquvo' will be Well Placed as a 2nd Line Therapy but Will Face Strong Competition

Foundational use at HFrEF Diagnosis
1st Line

Added on to SoC after worsening event
2nd Line



Specifically, 'Verquvo' will be Positioned as the Stabilizing Force for Patients at Higher Risk Following a Worsening HF Event

For HFrEF patients who **have experienced a worsening HF event** (within the last 6 months) and for Initiators of therapy, who aim to **safely change the trajectory of worsening** HF patients

Verquvo vericiguat is the **stabilizing force following a worsening HF event** that can be **added to any** HF background therapy

- Only 'Verquvo' will restore the myocardial function and change the course of HF progression by unlocking the potential of the **currently untapped sGC-cGMP pathway** in HF
- That **empowers you to save lives and keep patients out of the hospital**, especially for when they need it most
- HCPs have the potential to **transform patients' lives** by setting them on a new path to fight worsening HF

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Clear Patient Profiles like Andrew & Betty at Launch are Critical to Ensure Early Adoption

'Verquvo' for efficacy & new MoA

Andrew

In-hospital for worsening HF on ARNI

CAD/MI/AF + HF diagnosed 2 years ago

1st event a year ago

2nd event now

"I was terrified—I couldn't breathe, lying in the hospital bed alone, I didn't think I would see my family again. I want to stay out of the hospital and keep doing what I love."

'Verquvo' for tolerability

Betty

Hypotension risk with ARB/BB/MRA

Renal impairment +
HF diagnosed a year ago with event

1st event a year ago

2nd event 3 months ago

"I'm scared of my blood pressure dropping and getting dizzy all the time. I want to feel secure and get back to living my life"

Case based discussion:
Defining right patients for vericiguat

Speaker:

Speaker

Refractory to GDMT

Meet Andrew* – A 68-Year-Old Man with HFrEF

Andrew was diagnosed with HFrEF 2 years ago. He experienced a first worsening event 6 months ago, following which he was initiated on sacubutril/Valsartan 49/51mg BD. He is recently rehospitalised for a second time with decompensated HF. He has been successfully recompensated with IV diuretics and his condition has stabilised. You are seeing him as an inpatient just prior to discharge

Characteristics of patient at stabilisation	Value
Age (years)	68
NYHA class	III
LVEF (%)	35
NT-proBNP (pg/ml)	2250
eGFR (ml/min/1.73 m^2)	55
Heart rate (bpm)	69
Current SBP (mmHg)	110
Comorbidities	AF/CAD/prior MI
Current HF therapies	**Optimised SoC:** Torasemide orally 10 mg 1-1-0; sacubitril/valsartan 49/51 mg 1-0-1, bisoprolol 5 mg 1-0-1, eplerenone 25 1-0-0, dapagliflozin 10 mg 1-0-0, Rivaroxaban 20 mg 0-0-1, metformin 850 mg 1-0-1

*Fictitious case study.

AF, atrial fibrillation; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SoC, standard of care.

Andrew is an inpatient just prior to discharge, how do we optimize treatment of Andrew to prevent another HFH?

Andrew*

68 years old

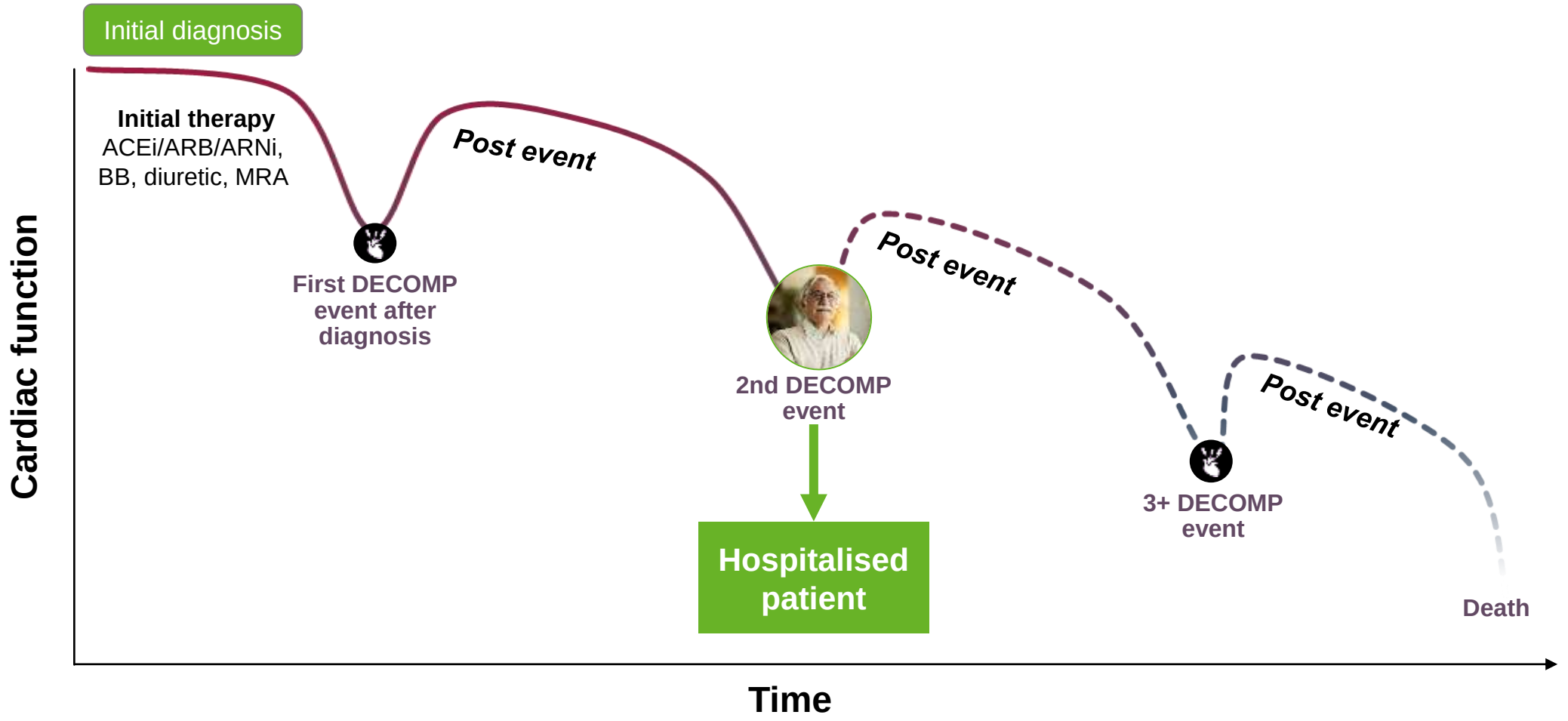
- Symptomatic HFrEF with two previous worsening HF events
  - Diagnosis with HFrEF 2 years ago
  - First HFH 6 months ago
  - Second HFH recently
- Optimized background therapy
- AF/CAD/prior MI

"I thought my HF was under control, but being hospitalized was really scary. I hope I don't have to go through that again."

* Fictitious case study.

AF, atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.

In VICTORIA, **Vericiguat Was Initiated Following a Recent Worsening HF Event, Even in Patients Already Receiving GDMT**[1,2]

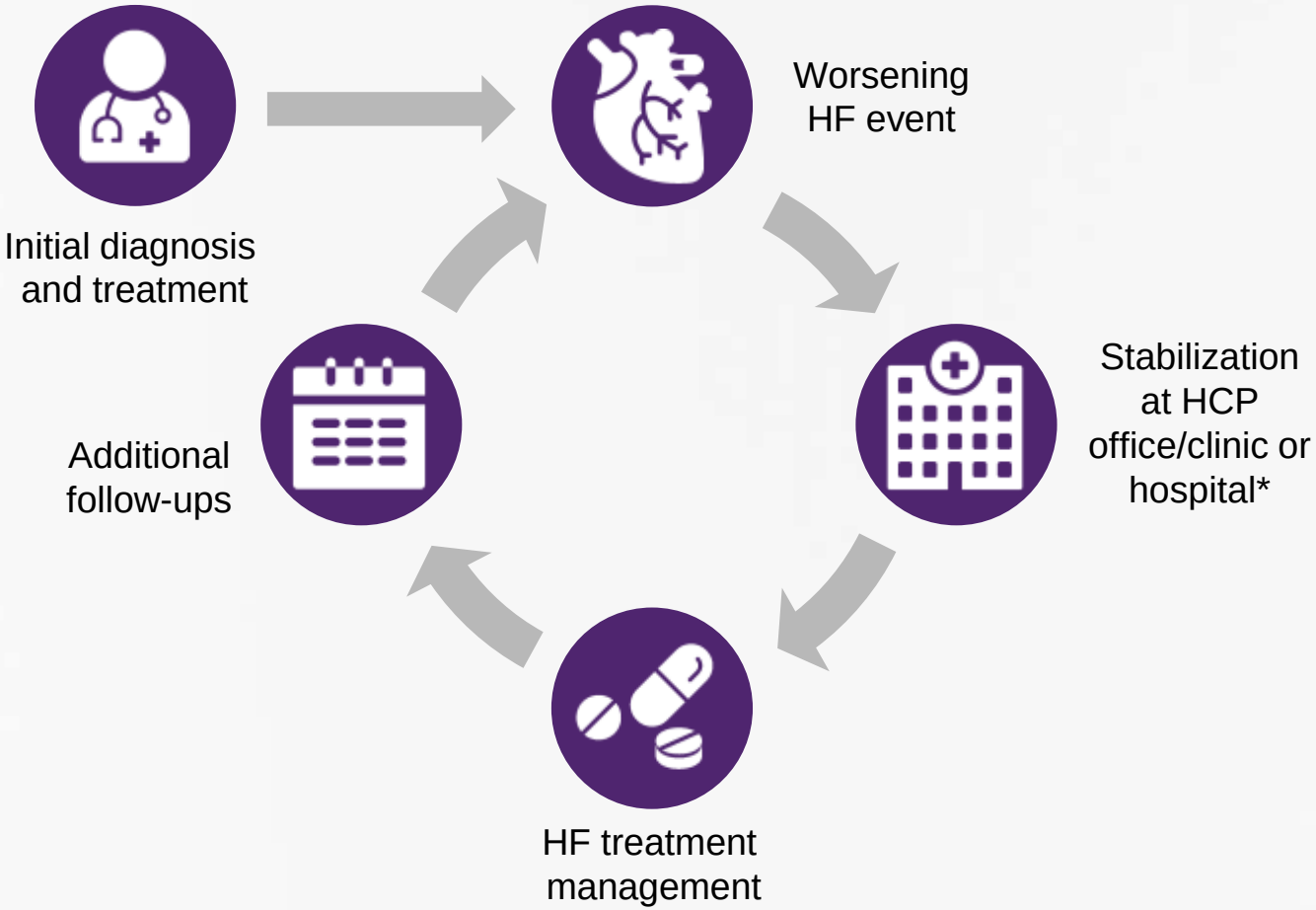


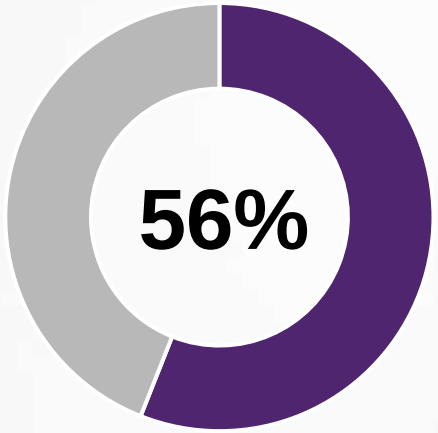
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; DECOMP, decompensation; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist.

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Gheorghiade M et al. *Am J Cardiol*. 2005;96:11G–17G.

Heart Failure

Patients like Andrew have a high risk of recurrent hosptialization[1–3]





In a large US registry (N=11,064), **over half** of patients were rehospitalized **within 30 days** of a worsening HF event[3]

* Adjustment of and potential addition to current therapy.

References: 1. Cowie MR *et al. ESC Heart Fail* 2014;1:110–145; **2.** Greene S *et al. Circ Heart Fail* 2020;13:e007132; **3.** Butler J *et al. J Am Coll Cardiol* 2019;73:935–944.

Guidelines recommend optimization of treatment prior to Andrew's hospital discharge and regular follow-ups[1]

Recommendations	Class	Level
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment	I	C
It is recommended that evidence based oral medical treatment be administered before discharge	I	C
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy	I	C
Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin <100 ng/ml or serum ferritin 100–299 ng/ml with TSAT <20%, to improve symptoms and reduce hospitalizations	IIa	B

HF, heart failure; TSAT, transferrin saturation.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021;42:3599–3726.

Contemporary Heart Failure Trials: Inclusion Criteria

Characteristic	PARADIGM-HF[1]	DAPA-HF[2,3]	EMPEROR-Reduced[4–6]	VICTORIA[8–10]
Patients (N)	8399	4744	3730	5050
Primary endpoint	CV death or first HFH	CV death or first HFH*	CV death or first HFH	CV death or first HFH
LVEF	≤35%	≤40%	≤40%	<45%
eGFR	≥30 ml/min/1.73 m^2	≥30 ml/min/1.73 m^2	≥20 ml/min/1.73 m^2	>15 ml/min/1.73 m^2
NT-proBNP (pg/ml)	• BNP ≥150 (NT-proBNP ≥600) • If hospitalised for a HF event within 12 months BNP ≥100 (NT-proBNP ≥400)	Patients in SR: • NT-proBNP ≥600 or ≥400 if HFH ≤12 months Patients with AF or atrial flutter: • NT-proBNP ≥900	EF ≤30% • NT-proBNP ≥1200 (AF); ≥600 (SR) EF 31–35% • NT-proBNP ≥2000 (AF); ≥1000 (SR) EF 36–40% • NT-proBNP ≥5000 (AF); ≥2500 (SR) EF ≤40%‡ • NT-proBNP ≥1200 (AF); ≥600 (SR)	Patients in SR: • BNP ≥300 • NT-proBNP ≥1000 Patients with AF: • BNP ≥500 • NT-proBNP ≥1600
Prior HF event	No current ADHF (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy)	No current ADHF or HFH <4 weeks prior to enrolment	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	Prior HFH ≤6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF ≤3 months prior to randomisation

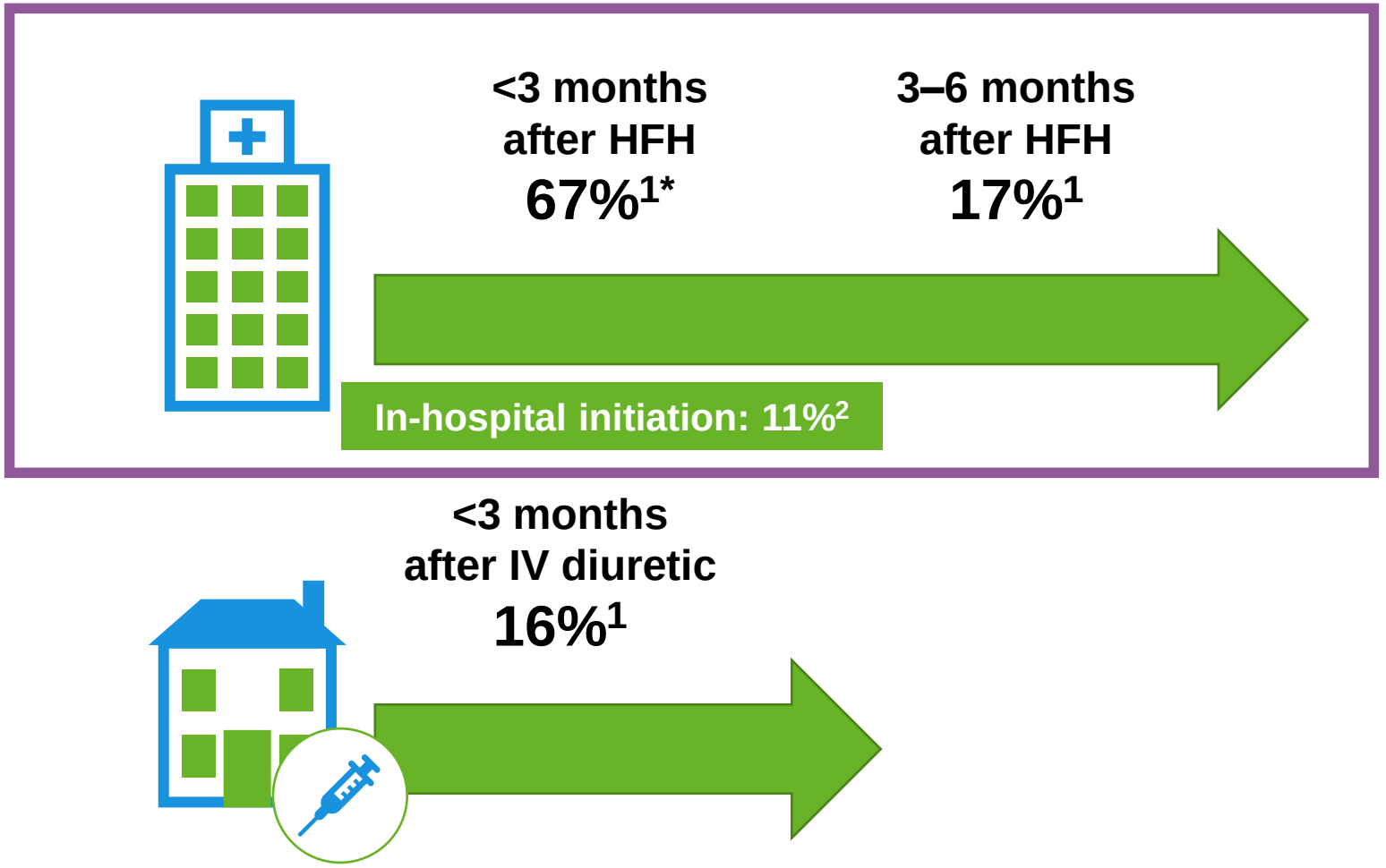
*HFH or urgent visit resulting in IV therapy for HF; # The primary outcome was a composite of a HF event or cardiovascular death; ‡Patient hospitalised for HF within the 12 months prior to screening.

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; IV, intravenous; LVEF, left ventricular ejection fraction; MSL, medical science liaison; NT-proBNP, N-terminal pro-brain natriuretic peptide; SR, sinus rhythm; Tx, treatment.

1. McMurray JJV et al. *N Engl J Med.* 2014;371:993–1004; 2. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:665–675; 3. McMurray JJV et al. *N Engl J Med* 2019;381:1995–2008; 4. Packer M et al. *Eur J Heart Fail.* 2019;21:1270–1278; 5. ClinicalTrials.gov. NCT03057977. https://clinicaltrials.gov/ct2/show/NCT03057977 [accessed November 2020]; 6. Packer M et al. *N Engl J Med* 2020;383:1413–1424; 7. Teerlink JR et al. *N Engl J Med.* 2020; doi: 10.1056/NEJMoa2025797 [Epub ahead of print]; 8. Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104; 9. Pieske B et al. *Eur J Heart Fail.* 2019;21:1596–1604; 10. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893.

Patients like Andrew Were Enrolled in VICTORIA[1,2]

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

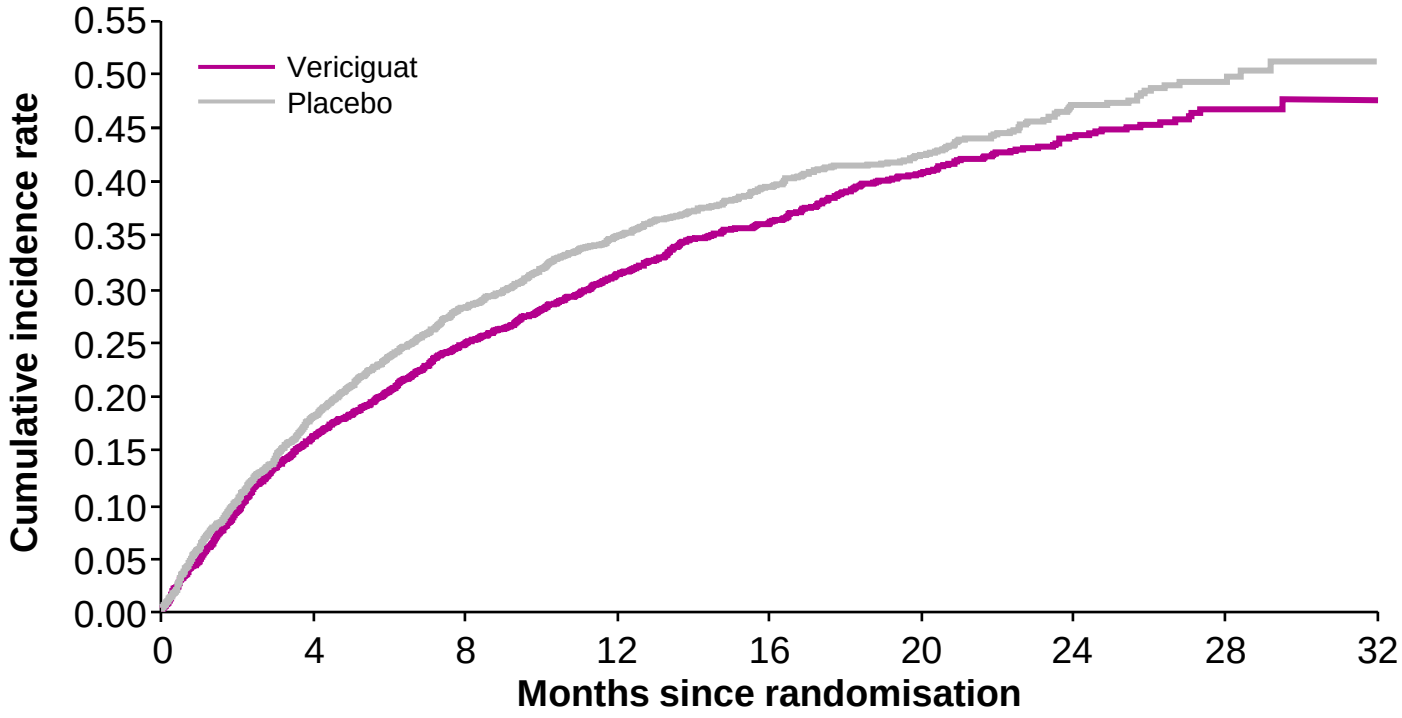


*Study drug was initiated in hospital in 11% of patients.[2]
HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous.
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 2. Lam CSP et al. *JAMA Cardiol.* 2020. doi: 10.1001/jamacardio.2020.6455 [Epub ahead of print].

Heart Failure

Vericiguat Significantly Reduced the Annualised Absolute Rate of Time to HFH or CV Death by 4.2 events/100 patient-yr[1]

Time to CV death or first HFH



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

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

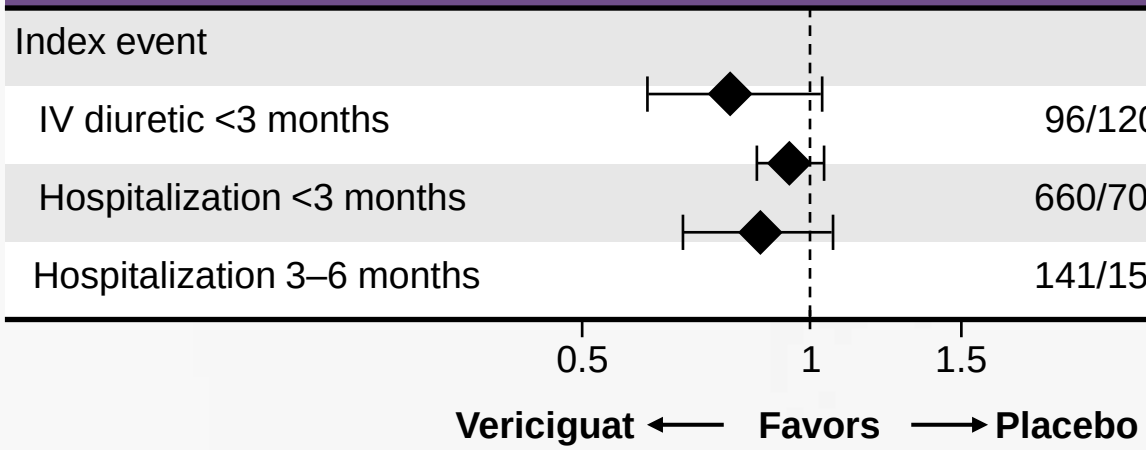
HR=0.90 (95% CI 0.82–0.98); *p*=0.02
ARR=4.2 events per 100 patient-yr
Annual NNT=24*

*Calculations: annual NNT = 100/4.2 = 24.
ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalisation; HR, hazard ratio; NNT, number needed to treat; yr, year.
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

Patients like Andrew benefited from adding vericiguat to GDMT irrespective of time from index event[1,2]

Incidence of the primary endpoint in VICTORIA according to time from the index event[1,2]

	Number of events vericiguat/placebo	Hazard ratio	95% CI	p–interaction[2]
Index event				
IV diuretic <3 months	96/120	0.78	(0.60–1.02)	0.43
Hospitalization <3 months	660/701	0.93	(0.84–1.04)	
Hospitalization 3–6 months	141/151	0.85	(0.67–1.07)	



Among patients with worsening HF, those closest in proximity to their index event were at highest risk of CV death or HFH. The benefit of vericiguat was consistent irrespective of risk in worsening HF[2]

CI, confidence interval; CV, cardiovascular; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; IV, intravenous.

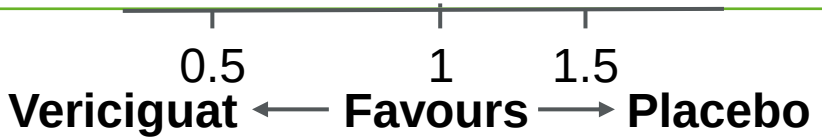
References: 1. Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893; **2.** Lam CSP *et al. JAMA Cardiol.* 2021;6:706–712.

Patients in VICTORIA Were Well Managed[1]

~60% of patients were on triple therapy at baseline (e.g. beta blockers, ACEi/ARB/ARNi and MRA)

The primary composite endpoint outcomes were directionally consistent irrespective of use of sacubitril/valsartan at baseline

	Number of events vericiguat/placebo	Hazard ratio	95% CI
Use of sacubitril/valsartan at baseline			
Yes	134/153	0.88	0.70–1.11
No	760/818	0.90	0.81–0.99

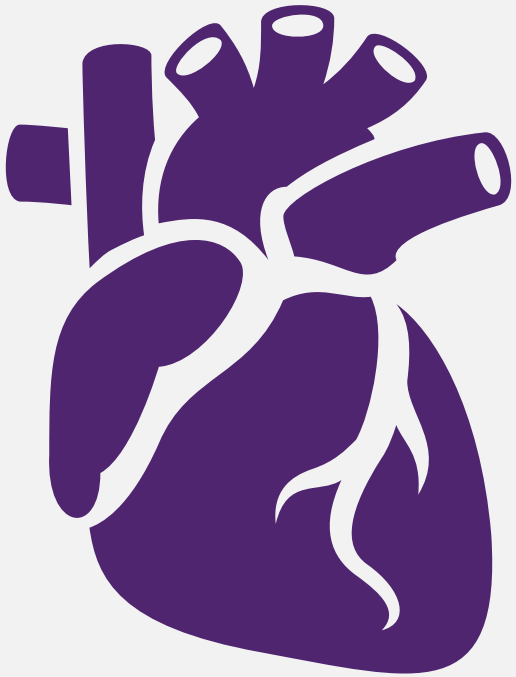


ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; MRA, mineralocorticoid receptor antagonist.

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

Heart Failure

Optimization of therapy before discharge could give Andrew the best chance of favorable outcomes after discharge[1]



Once hemodynamic stabilization is achieved with IV therapy, **treatment should be optimized** before discharge

Treatment optimization has three major aims:

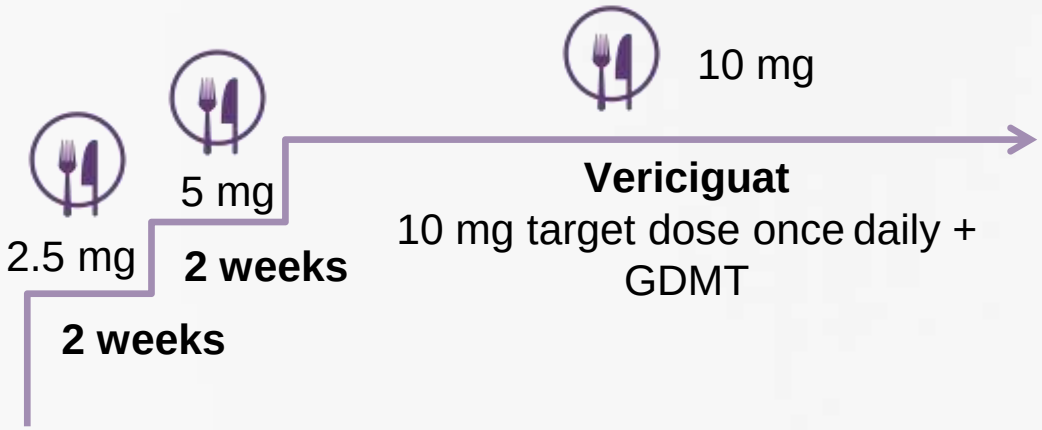
1. Relieve congestion
2. Treat comorbidities, such as iron deficiency, that have an impact on post-discharge outcome
3. Initiate, or restart, **oral GDMT with beneficial effects on outcome**

GDMT, guideline-directed medical therapy; IV, intravenous.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021;42:3599–3726.

In VICTORIA, adherence to the target dose of vericiguat was high[1]

Dosing and adherence



- **≥80% adherence** in ~94% of patients in VICTORIA[1]
- **~90%** of patients achieved the 10 mg **target dose** at 12 months[1]

Administration

- **One tablet** per day with meal/food
- **Crush and mix** with water for patients who have difficulty swallowing[2]
- **Titration** guided by evaluation of blood pressure and clinical symptoms
- **No dosage adjustment** for geriatric patients or patients with moderate renal or hepatic impairment
- **No** clinically relevant **drug–drug interactions**[3,4]
- Vericiguat is suitable for patients requiring **polypharmacy**[4]

GDMT, guideline-directed medical therapy; HF, heart failure.

References: 1. Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893; **2.** Merck. Verquvo® (vericiguat) PI. 2021. [Link]; **3.** Lobmeyer M *et al.* ESC-HF. Athens, Greece, 25–28 May 2019. Poster P1706; **4.** Boettcher M *et al. Clin Pharmacokinet* 2020;59:1407–1418.

Question:

- **Do you agree that this patient could benefit from vericiguat treatment?**
- Yes
- No

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

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

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

No significant difference in symptomatic hypotension or syncope

In VICTORIA, **~90%** adherence to the 10 mg target dose of vericiguat was achieved after ~12 months

Worsening symptoms requiring hospitalisation or IV diuretic use in the outpatient setting.
AE, adverse event; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; SAE, serious adverse event.

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

Heart Failure

Renal impairment

What if Andrew* Had Renal Impairment?

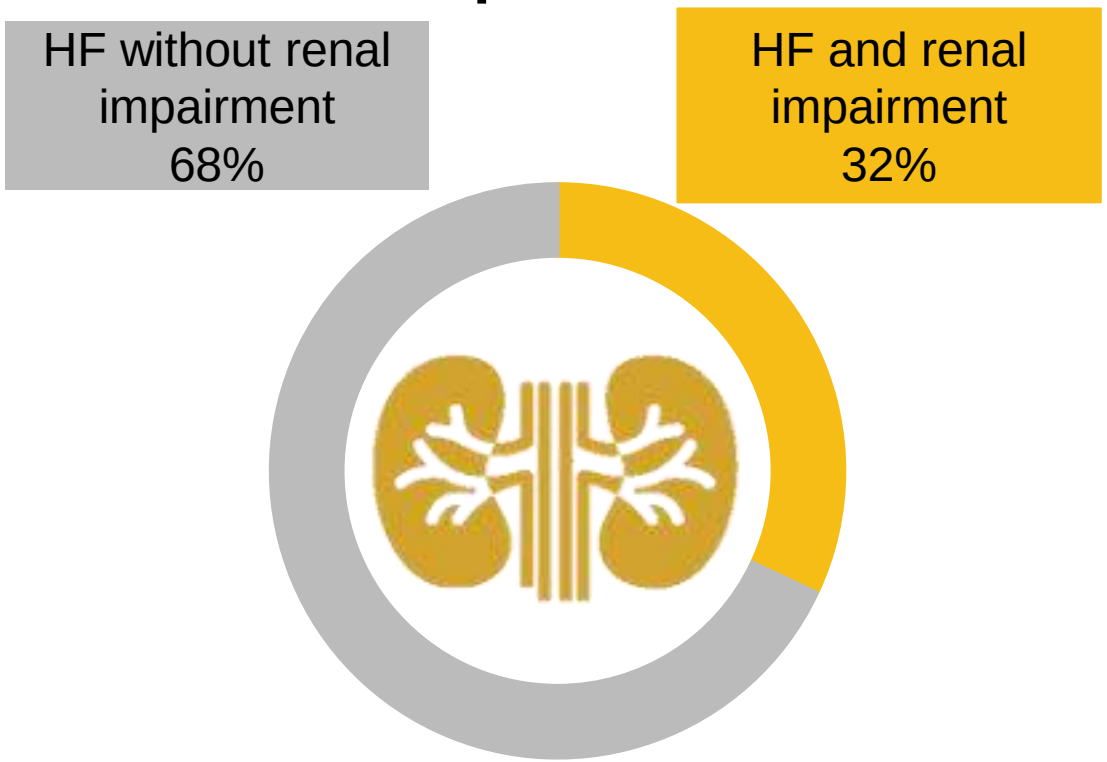
Andrew was diagnosed with HFrEF 2 years ago. He experienced a first worsening event 6 months ago, and was recently rehospitalised for a second time with decompensated HF. He has been successfully recompensated with IV diuretics and his condition has stabilised. You are seeing him as an inpatient with renal impairment just prior to discharge

Characteristics of patient at stabilisation	Value
Age (years)	68
NYHA class	III
LVEF (%)	35
NT-proBNP (pg/ml)	2250
eGFR (ml/min/1.73 m^2)	**28**
Heart rate (bpm)	69
Current SBP (mmHg)	110
Comorbidities	AF/CAD/prior MI
Current HF therapies	Optimised SoC:Torasemide orally 10 mg 1-1-0; sacubitril/valsartan 49/51 mg 1-0-1, bisoprolol 5 mg 0-0-1, eplerenone 25 1-0-0, Rivaroxaban 15 mg 0-0-1, teneligliptin 20 mg OD

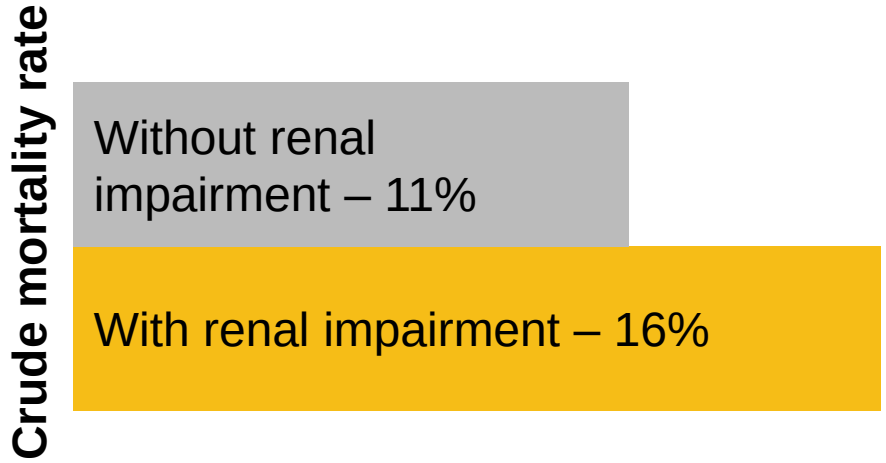
*Fictitious case study.
AF, atrial fibrillation; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SoC, standard of care.

Renal Impairment Is Prevalent in Patients with HF and Is Associated with a Poor Prognosis[1]

32% of patients with HF have renal impairment



Renal impairment was associated with a doubling in mortality rate in patients with HF

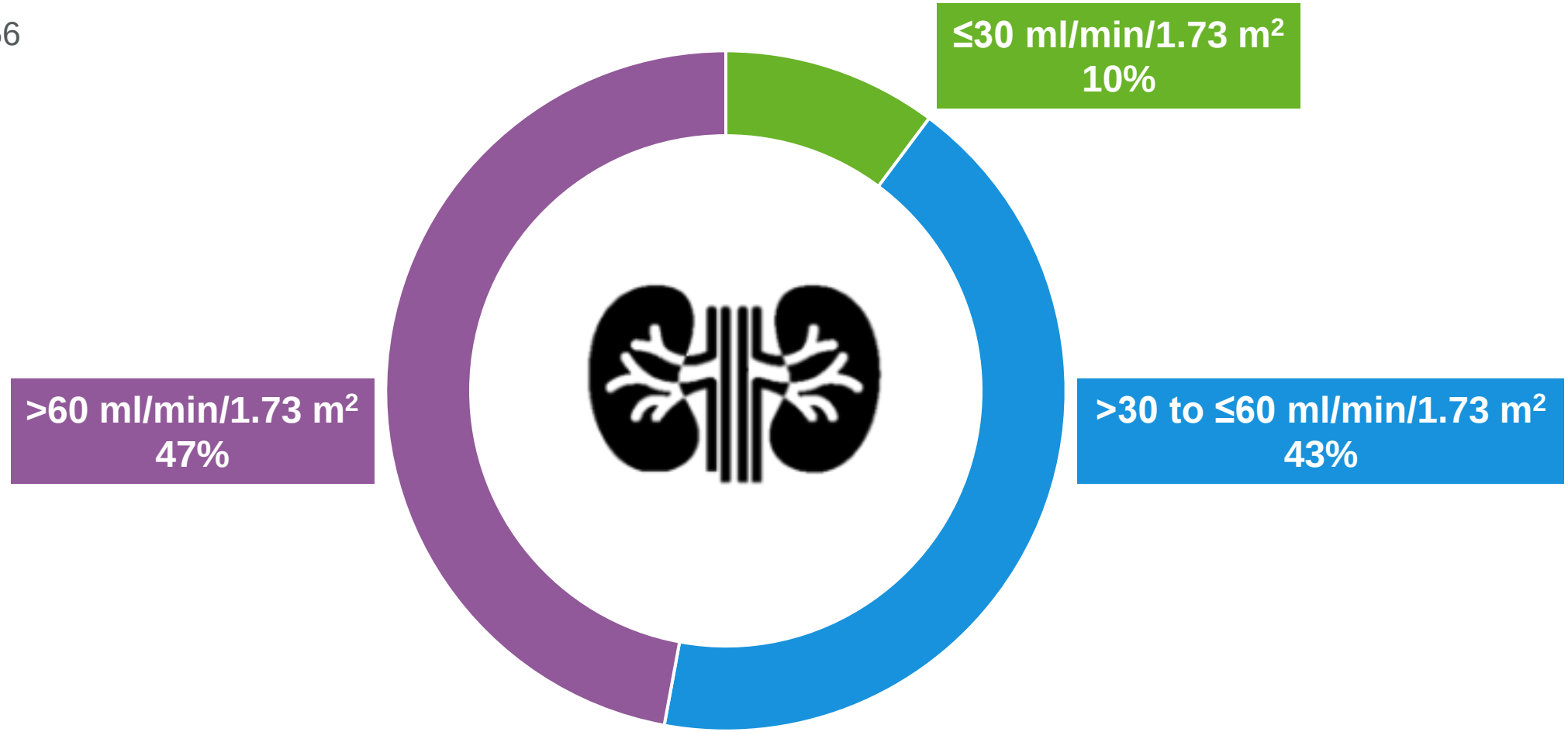


(Odds ratio* 2.34; 95% CI 2.20–2.50; *p*<0.001)

*Unadjusted.
CI, confidence interval; HF, heart failure.
1. Damman K et al. *Eur Heart J.* 2014;35:455–469.

Over Half of Patients in VICTORIA Had an eGFR ≤60 ml/min/1.73 m^2

N=4956



In VICTORIA, the percentage of enrolled patients with an eGFR between 15–30 ml/min/1.73 m^2 was capped at 15%.
eGFR, estimated glomerular filtration rate.

1. Voors AA et al. *Eur J Heart Fail.* 2021; doi: 10.1002/ejhf.2221 [Epub ahead of print].

Heart Failure

Question

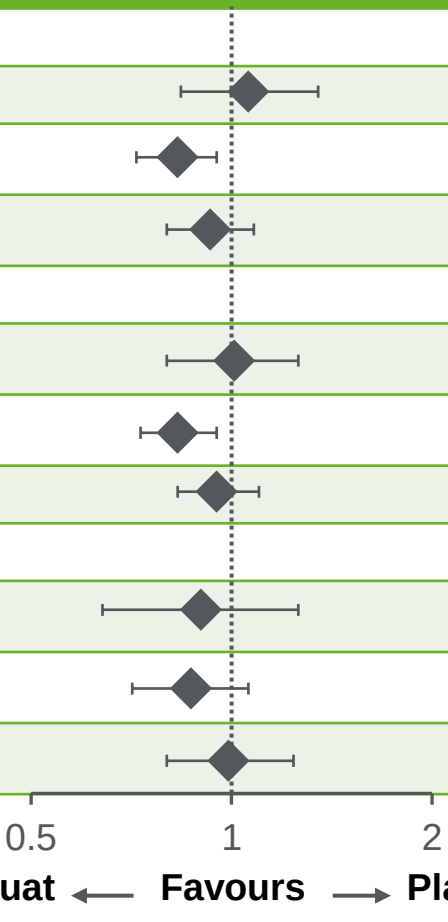
What would be your next line of treatment for this patient?

- Continue with the same treatment
- Stop ARNI and add vericiguat
- Stop ARNI and add SGLT2i
- Stop ARNI, add Vericiguat and SGLT2i

Heart Failure

Vericiguat Provided Benefit in Patients Across eGFR Categories[1]

	1-year Kaplan-Meier event rate		2-year Kaplan-Meier event rate		Hazard ratio	95% CI	p-value
	Vericiguat (%)	Placebo (%)	Vericiguat (%)	Placebo (%)			
HF hospitalisation or CV death							
eGFR ≤30	48.0	47.9	70.4	62.5	1.06	(0.84–1.35)	
eGFR >30 to ≤60	33.7	37.7	45.1	52.1	0.83	(0.72–0.95)	0.17
eGFR >60	25.3	28.9	36.7	38.4	0.93	(0.80–1.08)	
HF hospitalisation or all-cause death							
eGFR ≤30	50.3	52.2	72.9	67.8	1.01	(0.80–1.26)	
eGFR >30 to ≤60	35.1	39.1	46.9	54.2	0.83	(0.73–0.95)	0.22
eGFR >60	26.6	29.6	38.9	40.2	0.95	(0.83–1.10)	
CV death							
eGFR ≤30	17.9	23.6	37.6	36.3	0.90	(0.64–1.26)	
eGFR >30 to ≤60	13.1	14.2	23.1	25.8	0.87	(0.71–1.06)	0.67
eGFR >60	10.5	10.7	17.0	18.7	0.99	(0.80–1.24)	



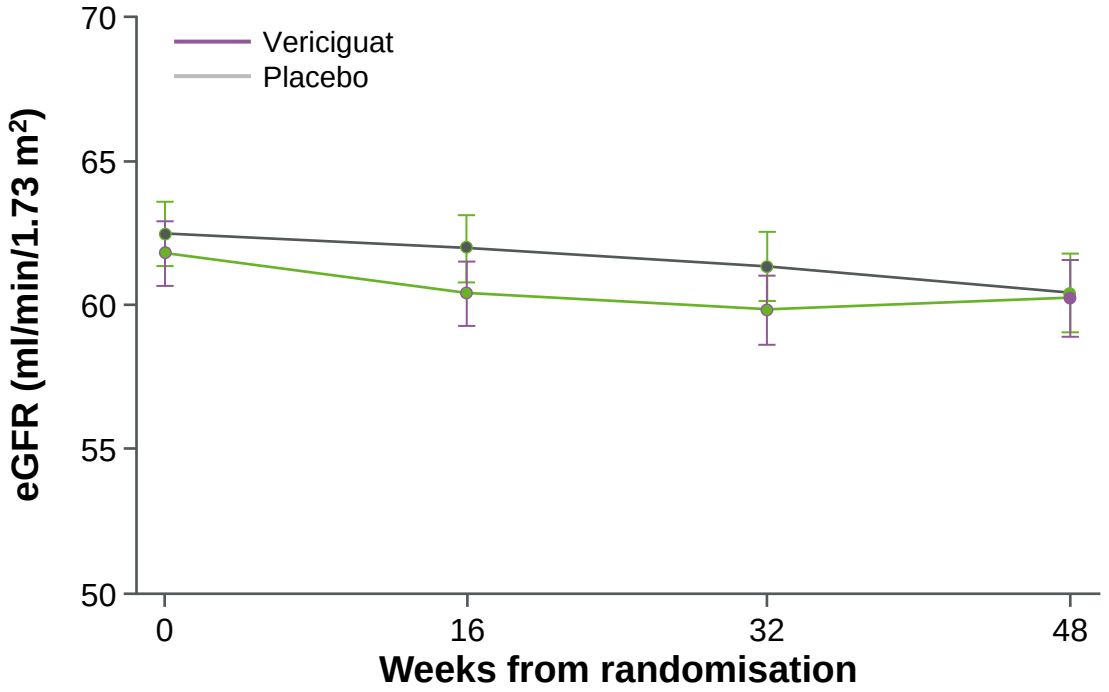
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure.

1. Voors AA et al. *Eur J Heart Fail.* 2021; doi: 10.1002/ejhf.2221 [Epub ahead of print].

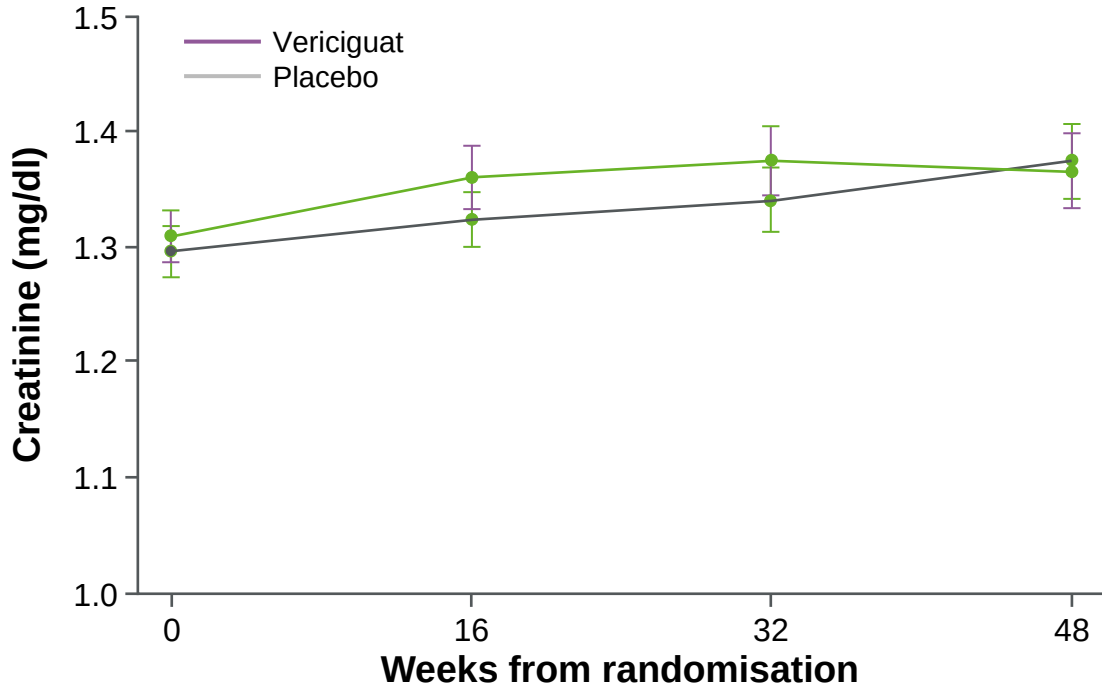
Heart Failure

Impact of Vericiguat on Renal Function Trajectories Was Similar to That of Placebo[1]

Change in eGFR over time



Change in creatinine over time



Patients	Baseline	Week 16	Week 32	Week 48
Placebo	2237	2181	1991	1559
Vericiguat	2196	2155	1971	1553

eGFR, estimated glomerular filtration rate.

1. Voors AA *et al*. *Eur J Heart Fail.* 2021; doi: 10.1002/ejhf.2221 [Epub ahead of print].

Heart Failure

Incidence of Hyperkalemia in VICTORIA Was Similar Between Treatment Arms Even in Patients with Low Renal Function[1]

Adverse event	eGFR ≤30 (ml/min/1.73 m^2)		eGFR <30–≤60 (ml/min/1.73 m^2)		eGFR >60 (ml/min/1.73 m^2)		Overall
	Vericiguat (n=261)	Placebo (n=246)	Vericiguat (n=1060)	Placebo (n=1070)	Vericiguat (n=1153)	Placebo (n=1166)	N=4956
Syncope	11 (4.2%)	10 (4.1%)	48 (4.5%)	38 (3.6%)	41 (3.6%)	37 (3.2%)	185 (3.7%)
Symptomatic hypotension	29 (11.1%)	22 (8.9%)	109 (10.3%)	98 (9.2%)	86 (7.5%)	72 (6.2%)	416 (8.4%)
Hyperkalemia	21 (8.0%)	25 (10.2%)	71 (6.7%)	84 (7.9%)	29 (2.5%)	39 (3.3%)	269 (5.4%)
Worsening renal function by 16 weeks*	47/210 (22.4%)	35/184 (19.0%)	183/892 (20.5%)	173/921 (18.8%)	116/1016 (11.4%)	92/1041 (8.8%)	646/4264 (15.2%)

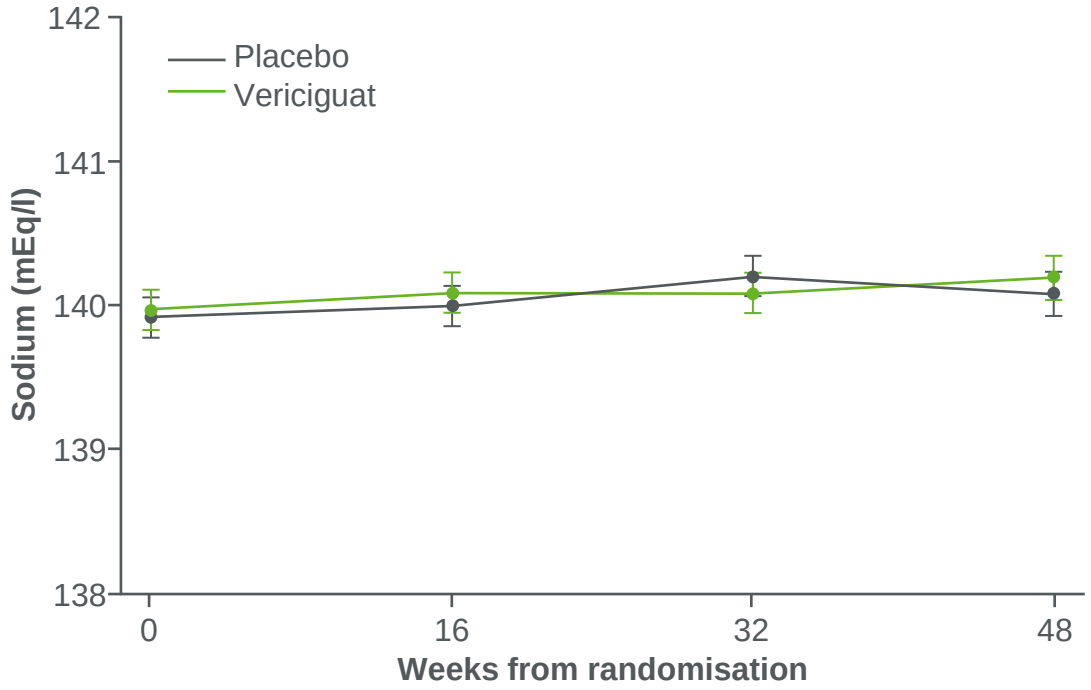
*Worsening renal function was defined as an increase of ≥0.3 mg/dl in creatinine from baseline to Week 16, assessed via a Cox model with respect to subsequent primary events.
eGFR, estimated glomerular filtration rate.

1. Voors AA *et al. Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2221.

Heart Failure

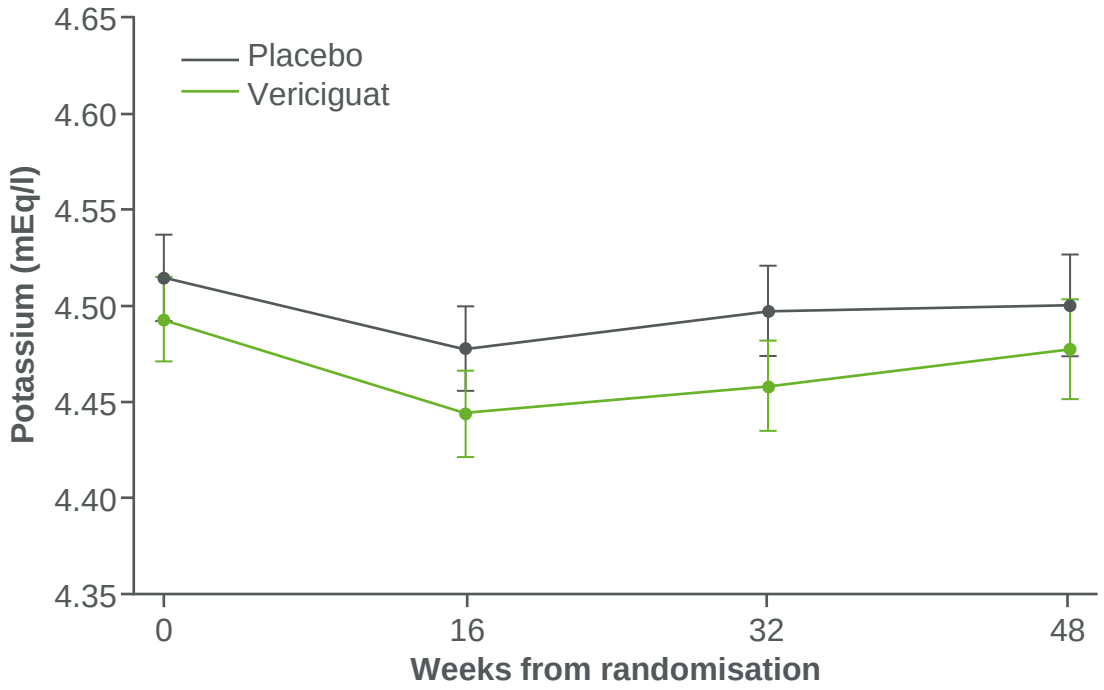
Vericiguat Has no Impact on Sodium and Potassium Levels Over Time[1]

Sodium



Patients	Baseline	Week 16	Week 32	Week 48
Placebo	2236	2186	2000	1559
Vericiguat	2194	2159	1974	1553

Potassium



Patients	Baseline	Week 16	Week 32	Week 48
Placebo	2217	2168	1981	1546
Vericiguat	2170	2140	1952	1543

1. Voors AA et al. *Eur J Heart Fail*. 2021; doi: 10.1002/ejhf.2221 [Epub ahead of print].

Heart Failure

Patients with renal impairment are underserved by current therapies[1–4]

Patients with renal insufficiency are significantly less likely to receive ARNi, ACEi, ARB or MRA

Guidelines recommend caution if using RAASi or diuretics in patients with eGFR <30 ml/min/1.73 m^2

SGLT2is are not recommended for patients with poor renal function

Renal function trajectories were similar between patients treated with 'vericiguat' *vs* placebo[3]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

1. Greene SJ et al. *J Am Coll Cardiol.* 2018;72:351–366; 2. Ponikowski P et al. *Eur Heart J.* 2016;18:891–975; 3. Boehringer Ingelheim International GmbH. Jardiance (empagliflozin) Summary of Product Characteristics. 2019. https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf [accessed April 2021]; 4. AstraZeneca AB. Farxiga (dapagliflozin) Summary of Product Characteristics. 2017. https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf [accessed April 2021].

Hypotension on up-titration of GDMT

Meet Betty* – A 59-Year-Old Woman with HFrEF

Betty was diagnosed with HFrEF 1 year ago, and was admitted to hospital 4 months later with cardiac decompensation. Three months ago, she was rehospitalised with a second worsening event and was shifted from ACEi to ARNI. She is now presenting as an outpatient with syncope resulting from up-titration of GDMT

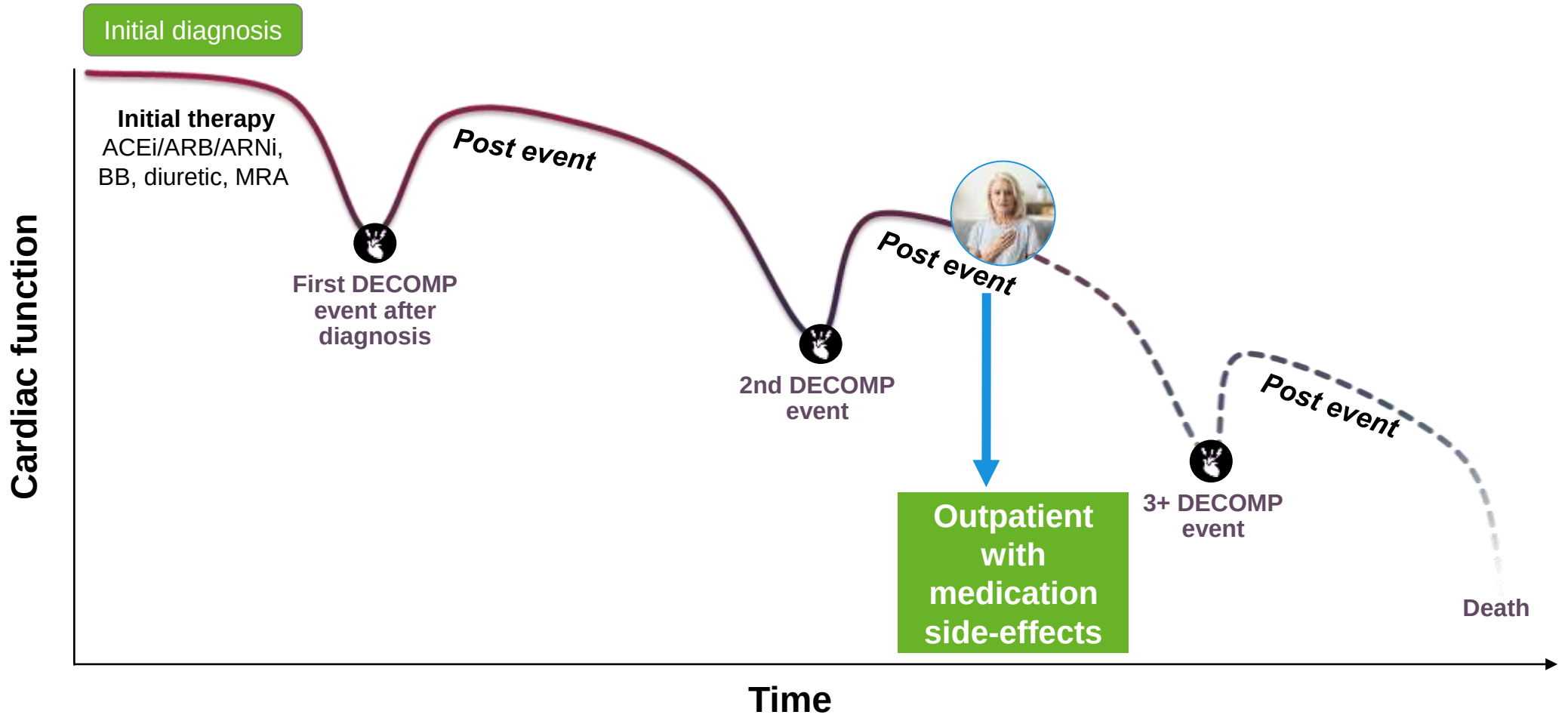
Characteristics of patient at stabilisation	Value
Age (years)	59
NYHA class	III
LVEF (%)	32
NT-proBNP (pg/ml)	1970
eGFR (ml/min/1.73 m^2)	40
Heart rate (bpm)	69
Current SBP (mmHg)	100
Comorbidities	aHTN/CKD
Current HF therapies	**BB (bisoprolol 10 mg od) sacubitril/valsartan 49/51 mg 1-0-1, MRA (eplerenone 50 mg od) Torsemide 10mg bd) Dapagliflozin 10mg OD**

*Fictitious case study.

aHTN, antihypertensive; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SoC, standard of care.

Heart Failure

In VICTORIA, Vericiguat Was Initiated Following a Recent Worsening HF Event, Even in Patients Already Receiving GDMT[1,2]



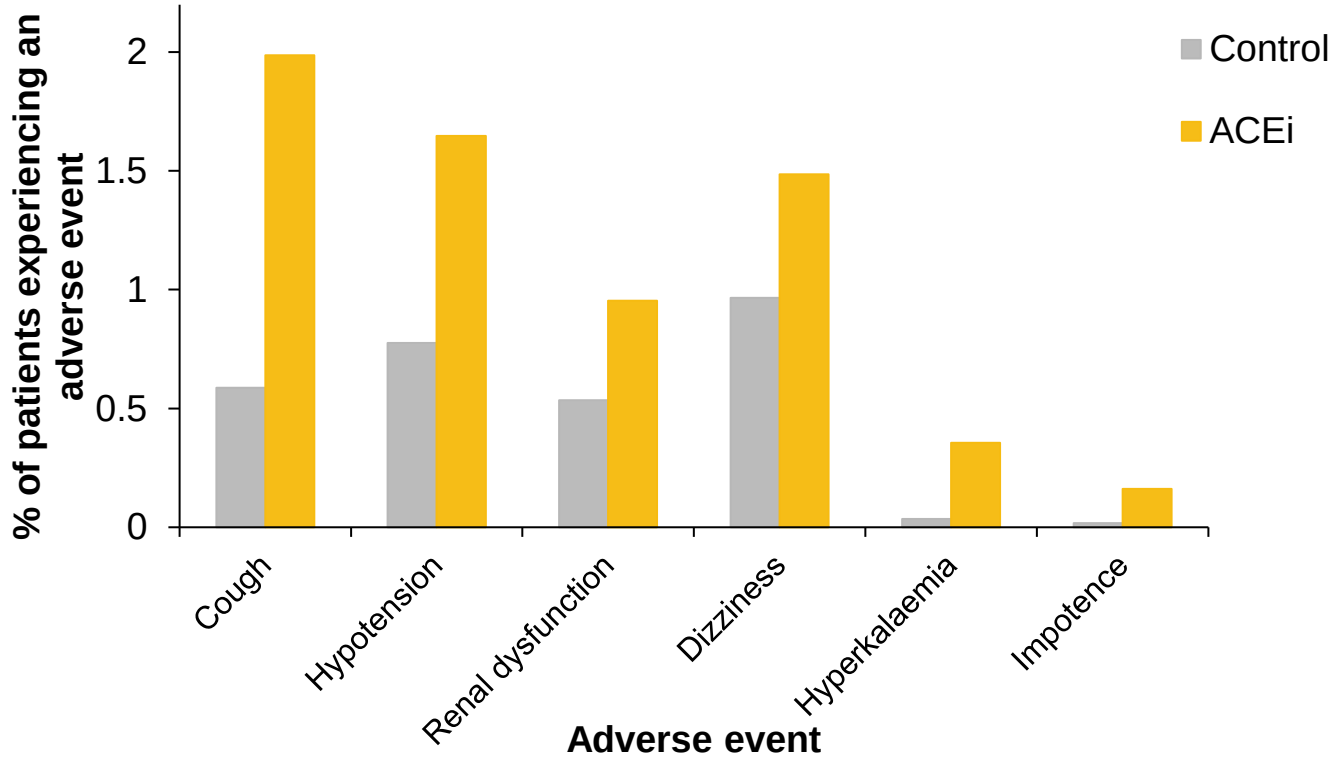
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; DECOMP, decompensation; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist.

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Gheorghiade M et al. *Am J Cardiol*. 2005;96:11G–17G.

Heart Failure

Adverse Events Associated with GDMT May Cause Treatment Discontinuation[1]

- Treatment discontinuation resulting from adverse events in a meta-analysis of 51 RCTs



ACEi use was associated with a significant increase in therapy discontinuation due to adverse events, including hypotension and syncope

A patient could be withdrawn for more than one reason.
ACEi, angiotensin-converting enzyme inhibitor; GDMT, guideline-directed medical therapies; RCT, randomised controlled trial.
1. Agustí A et al. *Drug Saf.* 2003;26:895-908.

Heart Failure

Patients with HFrEF often suffer from medication side effects, making adherence challenging[1]

Patient factors commonly associated with non-use and subtarget dosing of GDMT[1]

- Worsening renal function
- Hyperkalemia
- Hypotension
- Older age
- Lower body mass index

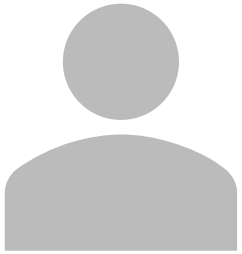
There is the need for novel therapies to be developed that are:

- **Effective**
- **Well tolerated (e.g. no concerns with hypotension, renal function or hyperkalemia)**

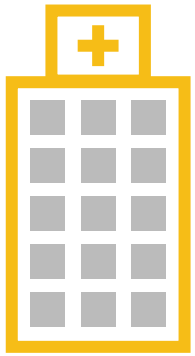
GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction.

Reference: 1. Greene SJ *et al. Heart Fail Rev.* 2021; https://doi.org/10.1007/s10741-021-10077-x.

Patients like Betty Were Enrolled in VICTORIA[1,2]



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



<3 months after HFH
67%[1*]

3–6 months after HFH
17%[1]

In-hospital initiation: 11%[2]

<3 months after IV diuretic
16%[1]

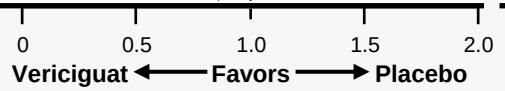
*Study drug was initiated in hospital in 11% of patients.[2]
HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous.
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 2. Lam CSP et al. *JAMA Cardiol.* 2020. doi: 10.1001/jamacardio.2020.6455 [Epub ahead of print].

Vericiguat demonstrated efficacy irrespective of Betty's background HF therapy[1]

Effect of vericiguat according to GDMT

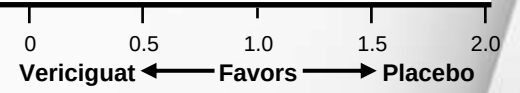
Basic adherence

	Vericiguat (%)	Placebo (%)	GDMT	n	HR (95% CI)*	$p_{interaction}$*
ACEi/ARB	73.3	73.6	No	1,340		0.544
			Yes	3,700		
ARNi	14.3	14.7	No	4,309		0.906
			Yes	731		
RAASi	–	–	No	636		0.418
			Yes	4,404		
Beta blocker	93.2	93.0	No	349		0.359
			Yes	4,691		
MRA	69.3	71.4	No	1495		0.168
			Yes	3,545		
Triple therapy#	58.7	60.7	No	2,031		0.296
			Yes	3,009		



Dose-corrected adherence

	Vericiguat (%)	Placebo (%)	GDMT	n	HR (95% CI)*	$p_{interaction}$*
ACEi/ARB	40.0	42.0	No	1,749		0.710
			Yes	1,215		
ARNi	84.0	88.5	No	80		0.361
			Yes	504		
RAASi	–	–	No	1,744		0.825
			Yes	1,713		
Beta blocker	48.4	50.7	No	2,237		0.001
			Yes	1,837		
MRA	43.9	46.3	No	401		0.431
			Yes	1,901		
Triple therapy#	82.9	82.3	No	639		0.147
			Yes	2,602		



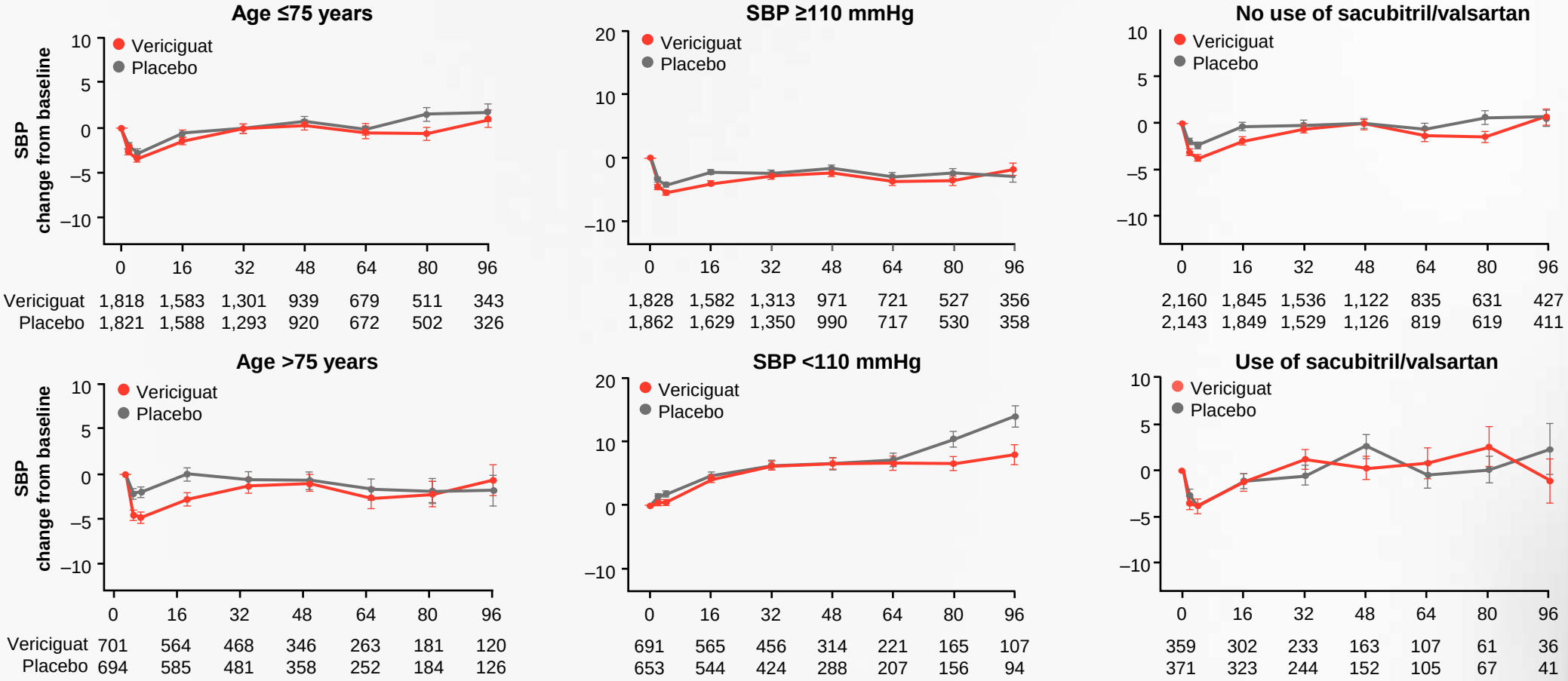
- Adherence:
  - **Basic adherence**: on/off medication
  - **Dose-corrected adherence**: dose ≥50% in indicated patients for medications with evidence-based target doses

* Adjusted for the MAGGIC risk score.
# Triple therapy consisted of an ACEi, ARB or ARNi + beta blocker + MRA.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor.

Reference: 1. Ezekowitz JA *et al.* HFSA. 30 September – 6 October 2020. Abstract 2621.

No excessive blood pressure reductions were observed with vericiguat in potentially vulnerable patients like Betty[1]

SBP trajectories in vulnerable subgroups: Older patients, patients with lower baseline SBP, and patients receiving concurrent ARNi



ARNi, angiotensin receptor–neprilysin inhibitor; SBP, systolic blood pressure.

Reference: 1. Lam CSP et al. *J Am Heart Assoc* 2021;10:e021094.

Vericiguat Has a Favourable Safety Profile[1]

- The overall AE profile and incidence of SAEs were similar with vericiguat compared with placebo
- Discontinuation rate of the trial regimen in VICTORIA was comparable between vericiguat and placebo
- Incidence of organ class SAEs was similar between vericiguat and placebo

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

- Rates of **symptomatic hypotension and syncope** observed with vericiguat were **similar to placebo**
- **Electrolyte balance and renal function were similar between vericiguat and placebo**

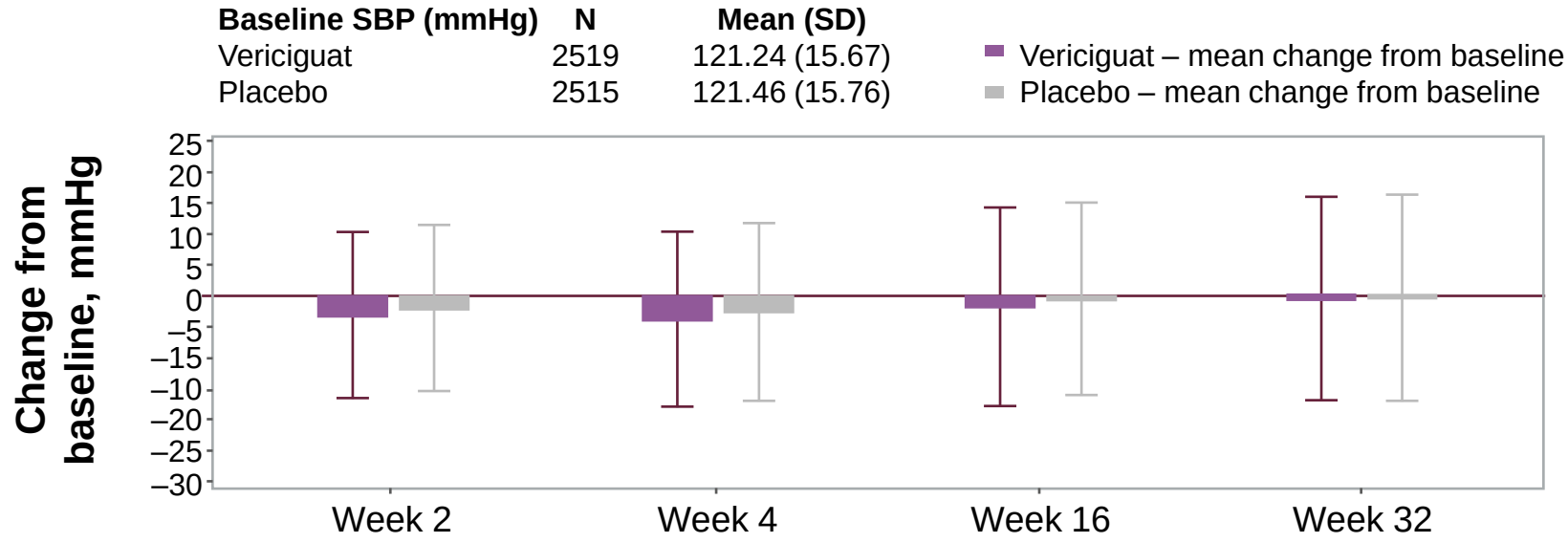
AE, adverse event; SAE, serious adverse event.

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

Heart Failure

There Were Very Small Differences in Mean SBP Values Between the Vericiguat and Placebo Arms[1]

Mean change in SBP from baseline over time



Number of patients 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

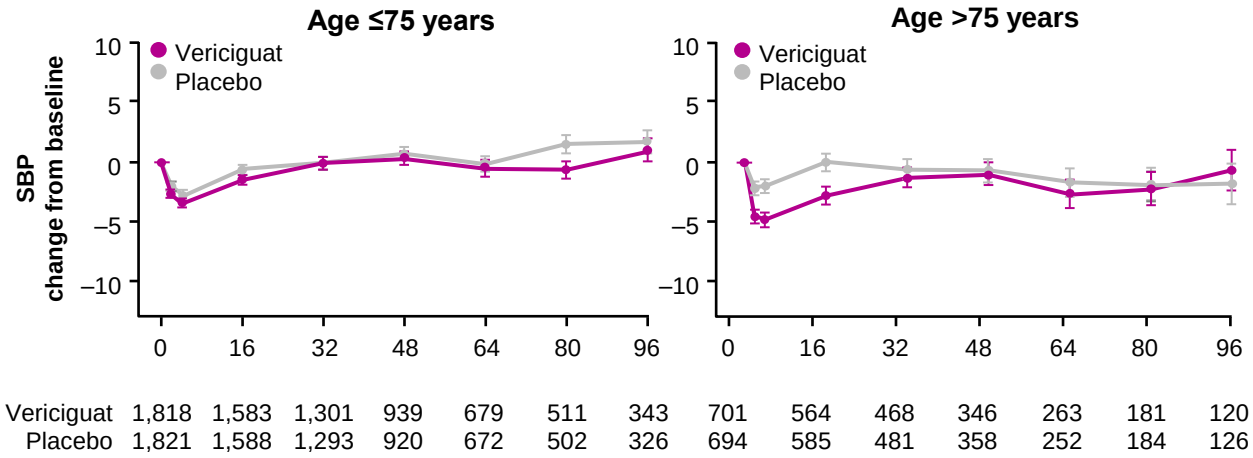
BP, blood pressure; SBP, systolic blood pressure; SD, standard deviation.

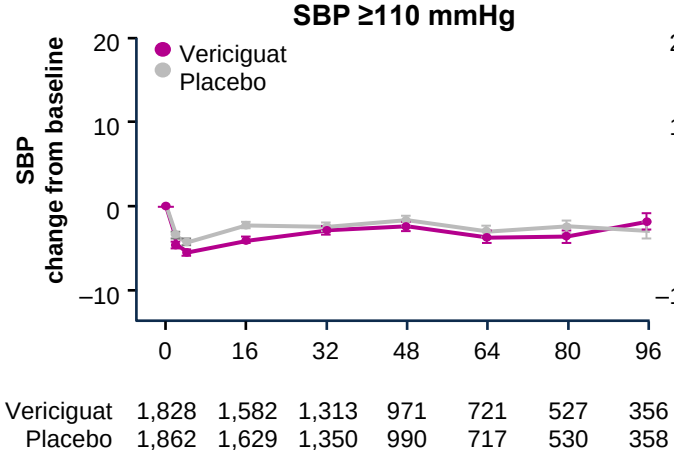
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

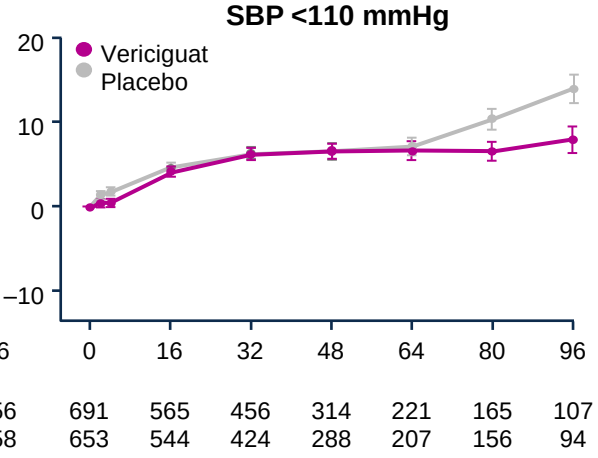
Heart Failure

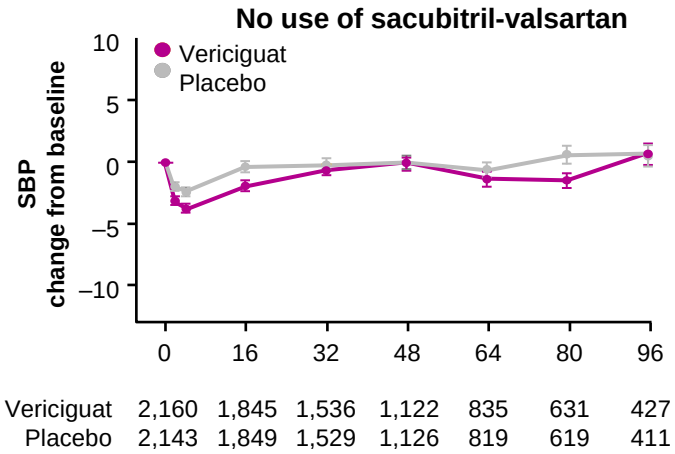
No excessive blood pressure reductions were observed with vericiguat in potentially vulnerable patients[1]

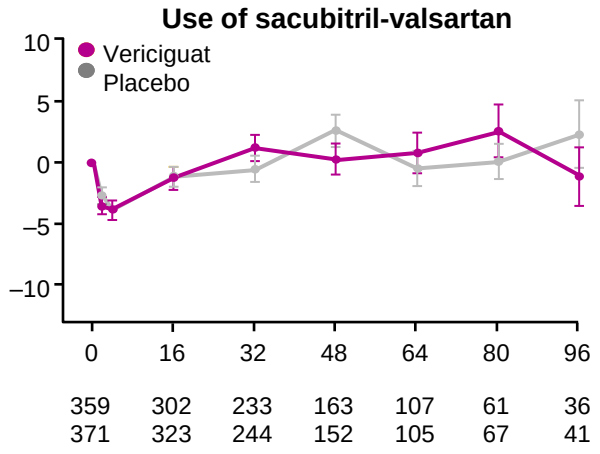
Benefit of vericiguat *vs* placebo on the primary endpoint was similar across the spectrum of baseline SBP ($p_{interaction}$=0.32)









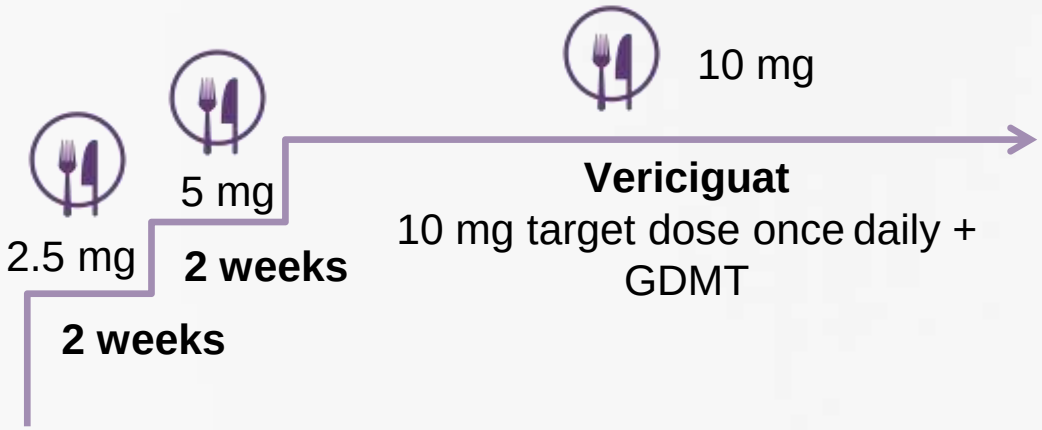


SBP, systolic blood pressure.

Reference: 1. Lam CSP *et al.* ESC-HF. 29 June–July 1 2021; oral presentation.

In VICTORIA, adherence to the target dose of vericiguat was high[1]

Dosing and adherence



- **≥80% adherence** in ~94% of patients in VICTORIA[1]
- **~90%** of patients achieved the 10 mg **target dose** at 12 months[1]

Administration

- **One tablet** per day with meal/food
- **Crush and mix** with water for patients who have difficulty swallowing[2]
- **Titration** guided by evaluation of blood pressure and clinical symptoms
- **No dosage adjustment** for geriatric patients or patients with moderate renal or hepatic impairment
- **No** clinically relevant **drug–drug interactions**[3,4]
- Vericiguat is suitable for patients requiring **polypharmacy**[4]

GDMT, guideline-directed medical therapy; HF, heart failure.

References: 1. Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893; **2.** Merck. Verquvo® (vericiguat) PI. 2021. [Link]; **3.** Lobmeyer M *et al.* ESC-HF. Athens, Greece, 25–28 May 2019. Poster P1706; **4.** Boettcher M *et al. Clin Pharmacokinet* 2020;59:1407–1418.

Vericiguat may be suitable for vulnerable patients like Betty due to its favorable safety profile[1,2]

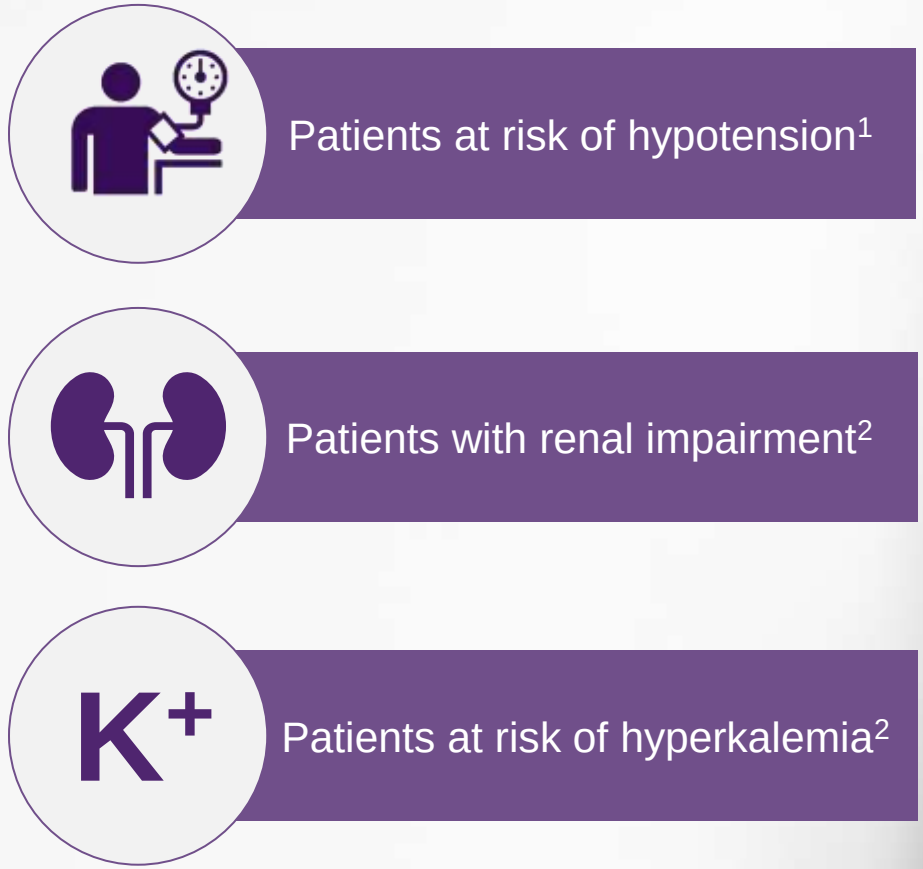
Dosing and adherence

The beneficial effects of vericiguat on the primary composite outcome of VICTORIA (CV death or HFH):

- Persisted regardless of **baseline SBP**
- Were consistent across the **full range of eGFR**

Vericiguat had no clinically relevant impact on:

- **SBP**
- **Renal function**
- **Electrolytes** (potassium and sodium levels)



CV, cardiovascular; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; SBP, systolic blood pressure.

References: 1. Lam CSP *et al. J Am Heart Assoc* 2021;10:e021094; **2.** Voors AA *et al. Eur J Heart Fail* 2021;23:1313–1321.

Question:

- **Do you agree that this patient could benefit from vericiguat treatment?**
- Yes
- No

Key take away

- **Similar rates of symptomatic hypotension and syncope** between patients treated with 'vericiguat' *vs* placebo[1]

- The beneficial effects of vericiguat on the primary composite outcome of VICTORIA (CV death or HFH) **persisted regardless of baseline SBP**

- **No excessive BP reduction with vericiguat in potentially vulnerable patients** predisposed to BP decreases (e.g. older patients, those with lower baseline SBP and patients receiving concurrent ARNi)

Heart Failure

Summary

Guidelines recommend quadruple therapy for all patients with HFrEF, with additional therapies for some patients[1,2]

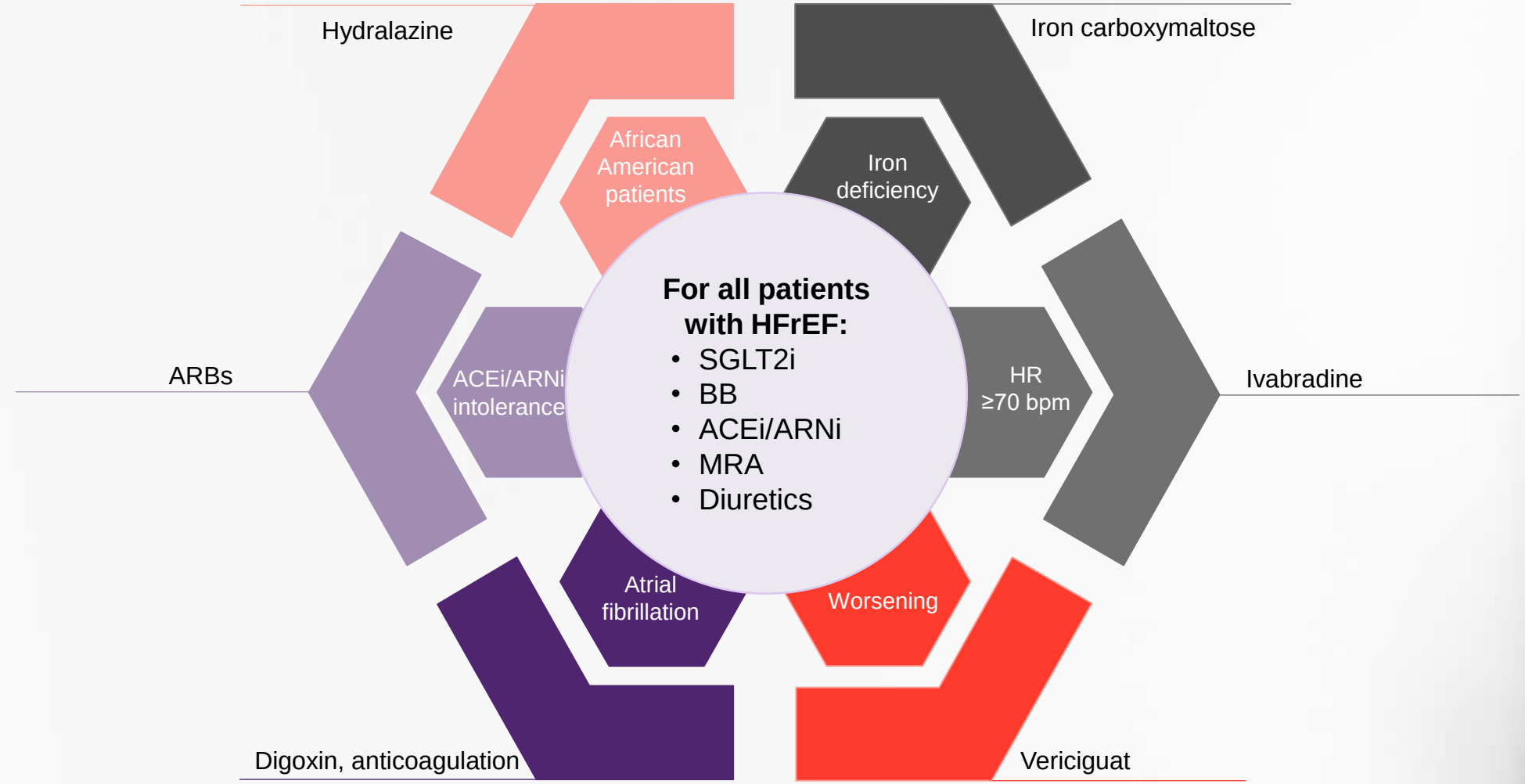


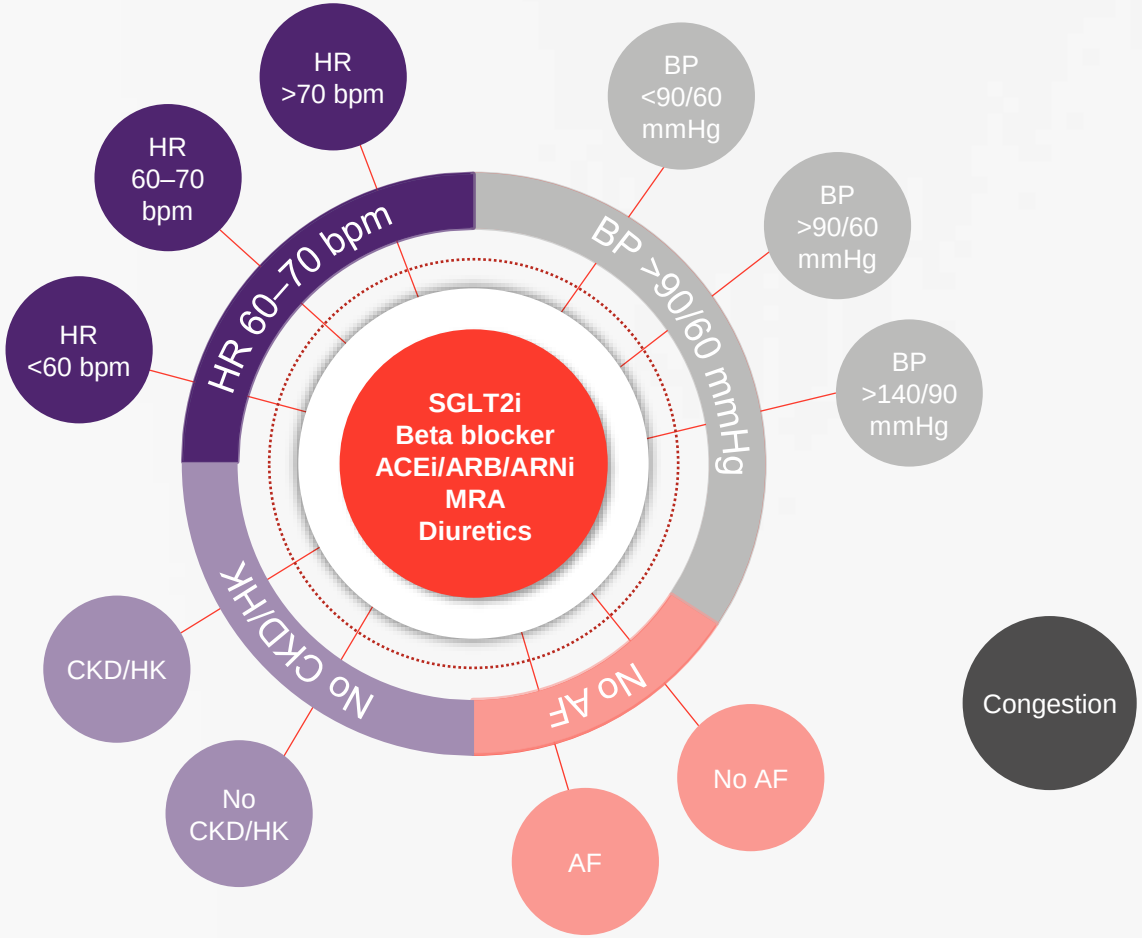
Figure adapted from Edelmann *et al.* 2021.[1]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; bpm, beats per minute; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

References: 1. Edelmann F *et al. Springer Medizin* https://www.springermedizin.de/herzinsuffizienz/sonderbericht-neues-wirkprinzip-herzinsuffizienz-vericiguat/19708516 [accessed 04 Feb 2022];
2. McDonagh TA *et al. Eur Heart J* 2021;36:3599–3726.

Recent guidelines and consensus documents recommend a personalized approach to treating HFrEF[1,2]

HFA consensus document on patient profiling[1]



A range of Andrew and Betty's characteristics may impact therapy decisions[1,2]

Blood pressure, heart rate, presence of atrial fibrillation, chronic kidney disease or hyperkalemia and hypertension are **important characteristics when considering medical therapy in patients with HF**[1]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; HK, hyperkalemia; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

References: 1. Rosano GMC *et al. Eur J Heart Fail* 2021;23:872–881; **2.** McDonagh TA *et al. Eur Heart J* 2021;42:3599–3726.

Vericiguat Could Benefit a Wide Range of Patients following a Worsening HF Event[1]

Patients following a worsening HF event, regardless of:

Location of care (in-hospital/outpatient)

eGFR
>15 ml/min/1.73 m^2

Comorbidities

Other HF therapies

eGFR, estimated glomerular filtration rate; HF, heart failure.

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

Vericiguat Is Recommended for the Comprehensive Medical Treatment of Patients with Worsening HF[1]

+/- ACEi/ARNi

+/- MRA

+/- Beta blocker

+/- SGLT2i

Vericiguat

+/- According to physician clinical decision and patient tolerability.

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

1. Metra M. ESC-HF. 2021. Oral.

Vericiguat Has a Favorable Safety Profile Even in Vulnerable Patients

Patient at risk of hypotension

Similar rates of symptomatic hypotension and syncope between patients treated with 'vericiguat' *vs* placebo[1]

No significant blood pressure reductions observed even in patients at risk of hypotension[2]

Patient with renal impairment

Renal function trajectories were similar between patients treated with 'vericiguat' *vs* placebo[3]

Consistent benefit across eGFR categories[3]

Patient at risk of hyperkalemia

Rates of hyperkalemia were similar between patients treated with 'Vericiguat' *vs* placebo[3]

No significant impact on sodium and potassium levels over time[3]

1. Armstrong PW et al. New Eng J Med. 2020;382(20):1883-92; **2.** Lam CSP *et al.* ESC-HF. 29 June–1 July 2021, oral presentation; **3.** Voors AA *et al*. *Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2221.

Heart Failure