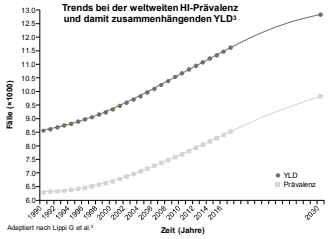
Kardio-Update 2022

HART & herzlich am See - Symposium

1

Herzinsuffizienz ist ein grosses weltweites Gesundheitsproblem[1,2,3]

~64 Millionen Patienten weltweit sind von einer Herzinsuffizienz betroffen und die Prävalenz wird voraussichtlich mit der alternden Bevölkerung zunehmen[1,2]



- Die HI-Prävalenz und die damit assoziierten YLD sind seit 1990 um 36 % angestiegen[3]
- Es wird erwartet, dass HI-bezogene YLD bis 2030 um weitere ~10% zunehmen werden[3]
- Es wird erwartet, dass die HI-Prävalenz bis 2030 um weitere ~15% zunehmen wird[3]

YLD, Years Lost due to Disability (durch Behinderung verlorene Jahre)

2

HI-Patienten haben ein sehr hohes Mortalitäts- und Hospitalisierungsrisiko[1-3]

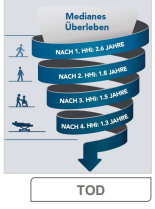
9 von 10 PATIENTEN

sind symptomatisch, selbst mit dem aktuellen Behandlungsstandard[1,a]

Fast ein Drittel der Patienten mit HFrEF hat ein hohes Risiko für Hospitalisierung oder CV-bedingten Tod, darunter auch solche, die stabil erscheinen[2]

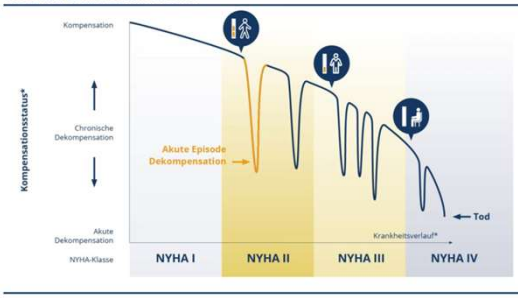
Auf Grundlage der NYHA-Klassifikation über einen Zeitraum von 4 Jahren, aus der CHARM-Studie von 2004[2]

Jede HHI lässt das Mortalitätsrisiko weiter ansteigen[3,b]



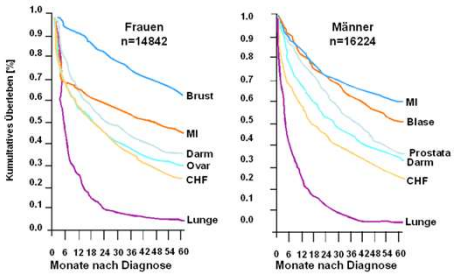
3

Wie verläuft eine Herzinsuffizienz?



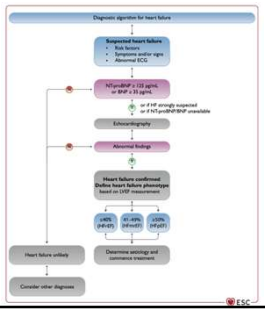
4

Prognose der Herzinsuffizienz im Vergleich



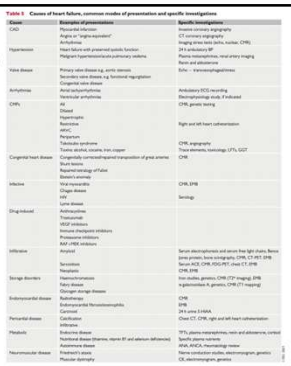
5

Abklärung der Herzinsuffizienz



6

Ursachen der Herzinsuffizienz



7

Einteilung der Herzinsuffizienz

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41 – 49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

©ESC 2021

8

The New England
Journal of Medicine

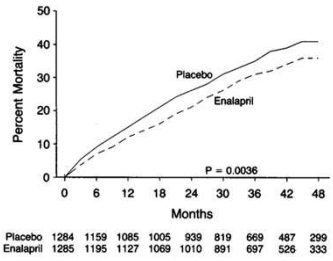
Volume 325 AUGUST 1, 1991 Number 5

EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

9

Anfänge der Herzinsuffizienz-Therapie



Placebo	1284	1159	1085	1005	939	819	669	487	299
Enalapril	1285	1195	1127	1069	1010	891	697	526	333

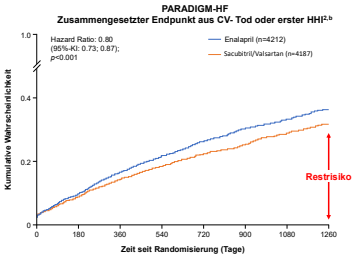
Figure 1. Mortality Curves in the Placebo and Enalapril Groups.

10

Bei Anwendung aktueller HI-Therapien bleibt ein **Restrisiko** für Tod oder HHI, was den Bedarf für neue HI-Wirkstoffe unterstreicht[1,2]

Aktuell gebräuchliche Behandlungen gegen Herzinsuffizienz[1,a]

- ACE-Hemmer
- ARB
- β-Blocker
- Schleifendiuretikum
- Mineralocorticoid-Antagonist
- Sacubitril/Valsartan



[a]Liste nicht vollständig, es können andere Behandlungen angewendet werden; [b]Daten der PARADIGM-HF-Studie
ACE, Angiotensin-Converting-Enzym; ARB, Angiotensin-Rezeptor-Blocker; KI, Konfidenzintervall; CV, kardiovaskulär; HI, Herzinsuffizienz; HHI, Hospitalisierung wegen Herzinsuffizienz
1. Ponikowski P, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;37:2129–2200; 2. McMurray JJV, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 2014;371:993–1004

11

Therapie der Herzinsuffizienz

Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril*	6.25 mg t.i.d.	50 mg t.i.d.
Enalapril	2.5 mg b.i.d.	10–20 mg b.i.d.
Lisinopril*	2.5–5 mg o.d.	20–35 mg o.d.
Ramipril	2.5 mg b.i.d.	5 mg b.i.d.
Trandolapril*	0.5 mg o.d.	4 mg o.d.
ARNI		
Sacubitril/valsartan	49/51 mg b.i.d.†	97/103 mg b.i.d.
Beta-blockers		
Bisoprolol	1.25 mg o.d.	10 mg o.d.
Carvedilol	3.125 mg b.i.d.	25 mg b.i.d.*
Metoprolol succinate (CR/XL)	12.5–25 mg o.d.	200 mg o.d.
Nebivolol*	1.25 mg o.d.	10 mg o.d.
MRA		
Eplerenone	25 mg o.d.	50 mg o.d.
Spironolactone	25 mg o.d.*	50 mg o.d.
SGLT2 inhibitor		
Dapagliflozin	10 mg o.d.	10 mg o.d.
Empagliflozin	10 mg o.d.	10 mg o.d.
Other agents		
Candesartan	4 mg o.d.	32 mg o.d.
Losartan	50 mg o.d.	150 mg o.d.
Valsartan	40 mg b.i.d.	160 mg b.i.d.
Ivabradine	5 mg b.i.d.	7.5 mg b.i.d.
Vericiguat	2.5 mg o.d.	10 mg o.d.
Digoxin	62.5 µg o.d.	250 µg o.d.
Hydralazine/ Isosorbide dinitrate	37.5 mg t.i.d./20 mg t.i.d.	75 mg t.i.d./40 mg t.i.d.

12

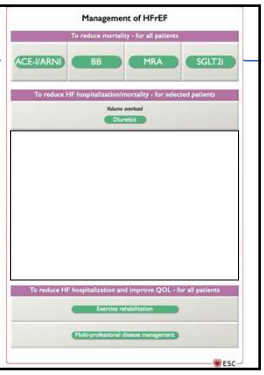
Symptome der Herzinsuffizienz

Table 6 Symptoms and signs typical of heart failure

Symptoms	Signs
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitations
Palpitation	Pleural effusion
Dizziness	Tachycardia
Syncope	Irregular pulse
Bendopnea*	Tachypnoea
	Cheyne-Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

13

Therapie-Algorithmus der Herzinsuffizienz



14

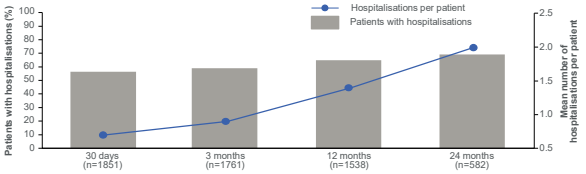
Vericiguat (Verquvo®): Background and VICTORIA Study Data

MAAT VER-CH-0029 01.2022

15

More Than Half of Patients with Chronic HF may Require Rehospitalisation Within a Month of a Worsening HF Event

Patients with hospitalisations and number of hospitalisations per patient through 2 years post index worsening HF event

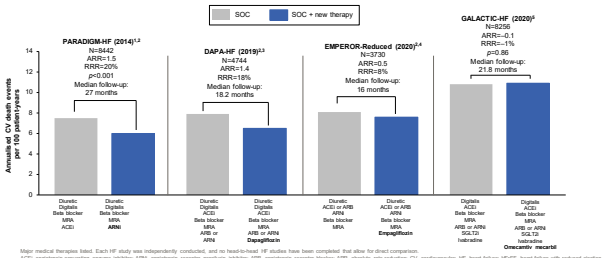


56% of patients were re-hospitalised within 30 days of the worsening HF event and the number of HF-related hospitalisations increased over time

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

16

High Persisting Risk in HFrEF Remains Despite the Use of HF Medications[1–5]

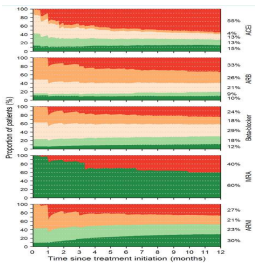


Major medical therapies listed. Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison.
ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; ARB, angiotensin receptor blocker; ARR, absolute rate reduction; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RRR, relative risk reduction; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SOC, standard of care.

1. McMurray JJV et al. *N Engl J Med*. 2014;371:993–1004; 2. Butler J et al. *Eur J Heart Fail*. 2020;22:1991–1993; 3. McMurray JJV et al. *N Engl J Med*. 2019;381:1995–2008; 4. Packer M et al. *N Engl J Med*. 2020;383:1413–1424; 5. Teerlink JR et al. *N Engl J Med*. 2021;384:105–116.

17

Lower than target doses are frequent



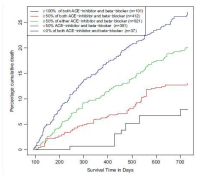
- Registry data with 68 172 new users of HF drugs over 12 months[1]
- Results:
  - In patients new on treatment, 10-30% reached recommended dose of SoC
  - discontinuation was common (24-55%)

1. Savarese G. et al. European Journal of Heart Failure (2021) doi:10.1002/ejhf.2271

18

Lower than target doses are associated with higher risk for mortality and/or HF related hospitalization[1-4]

Lower than target doses are associated with higher risk for mortality and/or HF related hospitalization[1] – as well in patients with recent worsening HF[2]



Patients not reaching recommended dose because of symptoms, side effects and non-cardiac organ dysfunction had the highest mortality rate[2]

PARADIGM-HF:
1. 10% of patients not tolerating full dose: sorted out in run-in-period[3]
2. 40% of patients: dose reduction →impact on efficacy [3,4]

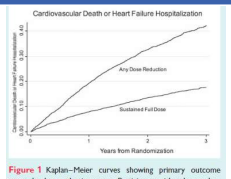
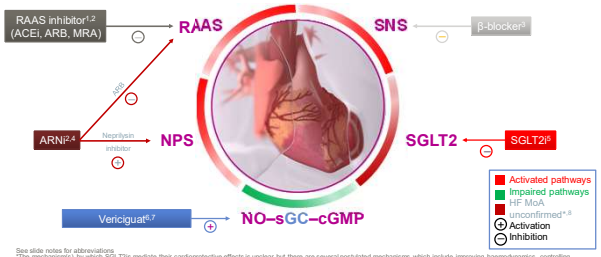


Figure 1 Kaplan–Meier curves showing primary outcome events by dose reduction status. Participants with a dose reduction had a higher risk of the primary event compared with those who remained on full study medication doses.

1. Ouwerkerk W. et al. European Heart Journal (2017)38, 1883–1890; 2. Bistola V. et al. European Journal of Heart Failure (2021) 23, 1170–1181. 3. McMurray JJV et al. N Engl J Med. 2014;371:993–1004 4. Verdery O. et al. European Journal of Heart Failure (2016)18,1228–1234

19

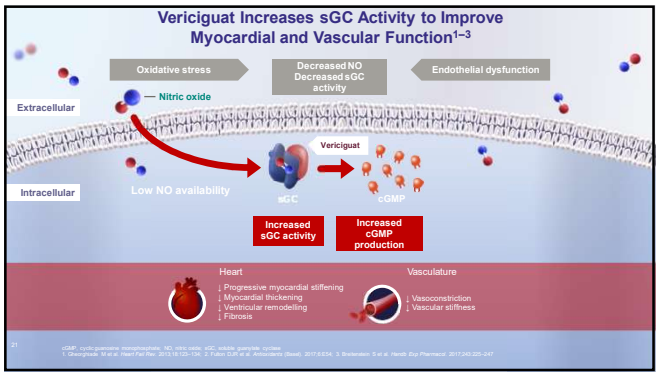
Vericiguat has a complementary Mode of Action with no overlap with other drugs[1–8]



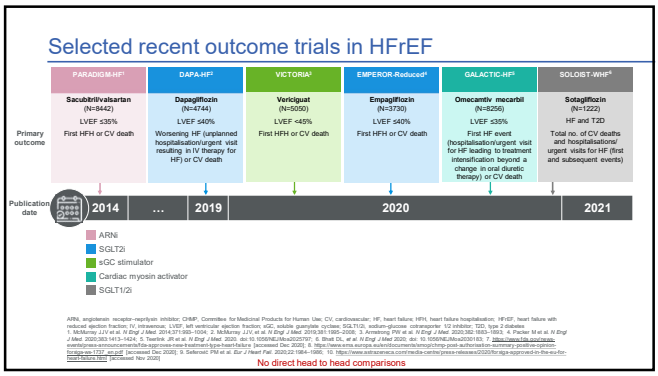
See slide notes for abbreviations
*The mechanism(s) by which SGLT2is mediate their cardioprotective effects is unclear but there are several postulated mechanisms which include improving haemodynamics, controlling sympathetic stimulation, inhibiting fibrosis and cardiac remodelling, improving cardiac efficiency and output, modulating the overall cytosolic sodium and calcium concentrations, and altering the adipokine levels.[8]

1. Mann DL et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 10th edn. Elsevier/Saunders; 2015; 2. Yancy CW et al. *J Am Coll Cardiol*. 2017;70:776–803; 3. Triposkiadis F et al. *J Am Coll Cardiol*. 2009;54:1747–1762; 4. Ponikowski P et al. *Eur J Heart Fail*. 2016;18:891–975; 5. Matsutsuka K & Sugiura T. *Cardiovasc Ultrasound*. 2019;17:26; 6. Armstrong PW et al. *JACC Heart Fail*. 2018;6:96–104; 7. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 8. Nottingale R. *Cardiol Res*. 2021;12:60–66.

20



21



22

Differences between PARADIGM-HF, DAPA-HF, EMPEROR-Reduced, GALACTIC-HF and VICTORIA (1)

Inclusion/exclusion criteria

	PARADIGM HF (N=8399)[1] sacubitril/valsartan	DAPA-HF (N=4744)[2] dapagliflozin	EMPEROR-Reduced (N=3730)[4] empagliflozin	GALACTIC-HF (N=8256)[5] omecamtiv mecarbil	VICTORIA (N=6050)[3] Vericiguat
NT-proBNP cut-off	≥600 pg/ml or ≥400 pg/ml if HFH <12 months	≥600 pg/ml or ≥400 pg/ml if HFH <12 months*	≥600 to ≥2500 or ≥1200 to or ≥5000 if AF, according to EF	≥400 pg/ml or ≥1200 pg/ml if AF or flutter	≥1000 pg/ml (SR) or ≥1600 pg/ml if AF
eGFR cut-off	≥30 ml/min/1.73 m²	≥30 ml/min/1.73 m²	≥20 ml/min/1.73 m²	≥20 ml/min/1.73 m²	≥15 ml/min/1.73 m²
LVEF cut-off	≤35%	≤40%	≤40%	≤35%	<45%
Recent HF decompensation	Not required	Not required	Not required	Inpatients or had either made an urgent ED visit or been hospitalised for HF within 1 year before screening (outpatients)	HFH within 6 months or IV diuretic use for HF within 3 months

Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.
*Patients with AF or atrial flutter were required to have an NT-proBNP level ≥600 pg/ml, regardless of their history of HFH.
ACEIs, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SR, sinus rhythm.
1. McMurray JJV et al. N Engl J Med. 2014;371:993–1004; 2. McMurray JJV et al. N Engl J Med. 2019;381:1995–2008; 3. Packer M et al. N Engl J Med. 2020;383:1413–1424; 4. Teerlink JR et al. N Engl J Med. 2020; doi: 10.1056/NEJMoa2032786; 5. Armstrong PW et al. N Engl J Med. 2020;382:1883–1893

No direct head to head comparisons

23

Differences between PARADIGM-HF, DAPA-HF, EMPEROR-Reduced, GALACTIC-HF and VICTORIA (2)

Baseline characteristics*

	PARADIGM HF (N=8399)[1–4] sacubitril/valsartan	DAPA-HF (N=4744)[2,5] Dapagliflozin	EMPEROR-Reduced (N=3730)[7] empagliflozin	GALACTIC-HF (N=8256)[5] omecamtiv mecarbil	VICTORIA (N=6050)[3] vericiguat
Median NT-proBNP, pg/ml	1608	1437	1907	2001	2816
NYHA class III or IV	25%	32%	25%	47%	41%
HFH <6 months ago	31%	16%	NR[6]	NR	84%
eGFR, ml/min/1.73 m²	68 (mean)	66 (mean)	62 (mean)	59 (median[2])	62 (mean)
eGFR <60 ml/min/1.73 m²	37%	41%	48%	52%	53%[3]
Median follow up (months)	27	18.2	16	21.8	10.8
Primary endpoint event rate (control arm)	13.2 events/ 100 PY	15.6 events/ 100 PY	21.0 events/ 100 PY	26.3 events/ 100 PY	37.8 events/ 100 PY

Note: In trials where the total population values have not been reported, the mean or median values from the individual study arms were averaged
Each HF study was independently conducted, and no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug versus another.
*Some values in table were derived from different patient n-numbers than shown due to data availability. †In the EMPEROR-Reduced study, HFH was reported in 512 months (31%). ‡In the GALACTIC-HF study, median eGFR (IQR) values are reported for the omecamtiv mecarbil and placebo arms. §eGFR ≤60 ml/min/1.73 m²
eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalisation; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PY, patient-years
1. McMurray JJV et al. Eur J Heart Fail. 2014;16:817–825; 2. Solomon SD et al. JACC Heart Failure. 2016;4:816–822; 3. McMurray JJV et al. N Engl J Med. 2014;371:993–1004; 4. Butler J et al. Circulation. 2020;142:717–719; 5. McMurray JJV et al. Eur J Heart Fail. 2019;21:1402–1411; 6. McMurray JJV et al. N Engl J Med. 2019;381:1995–2008; 7. Packer M et al. N Engl J Med. 2020;383:1413–1424; 8. Teerlink JR et al. N Engl J Med. 2020; doi: 10.1056/NEJMoa2032786; 9. Armstrong PW et al. N Engl J Med. 2020;382:1883–1893

No direct head to head comparisons

24

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

	PARADIGM-HF[1,2]		DAPA-HF[1]		EMPEROR-Reduced[1]		GALACTIC-HF[3]		VICTORIA[4]	
	Comparator	Sacubitril/ valsartan	Comparator	Dapagliflozin	Comparator	Empagliflozin	Comparator	Omecamtiv mecarbil	Comparator	Vericiguat
Median follow-up	27 months		18 months		16 months		22 months		11 months	
Hazard ratios (95% CI) for key outcomes										
Primary endpoint	0.80 (0.73–0.87)		0.74 (0.65–0.85)		0.75 (0.65–0.86)		0.92 (0.86–0.99)		0.90 (0.82–0.98)	
CV death	0.80 (0.71–0.89)		0.82 (0.69–0.98)		0.92 (0.75–1.12)		1.01 (0.92–1.11)		0.93 (0.81–1.06)	
First HFH	0.79 (0.71–0.89)		0.70 (0.59–0.83)		0.69 (0.59–0.81)		0.95 (0.87–1.03)		0.90 (0.81–1.00)	
Annualised event rate (events per 100 patient-years at risk)										
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8	26.3	24.2	37.8	33.6
Absolute rate reduction	**2.7**		**4.0**		**5.2**		**2.1**		**4.2**	
CV death	7.5	6.0	7.9	6.5	8.1	7.6	10.8	10.9	13.9	12.9
Absolute rate reduction	**1.5**		**1.4**		**0.6**		**-0.1**		**1.0**	
First HFH	7.7	6.2	9.8	6.9	15.5	10.7	19.1	18.0	29.1	25.9
Absolute rate reduction	**1.6**		**2.9**		**4.8**		**1.1**		**3.2**	

CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation
1. Butler J et al. *Eur J Heart Fail* 2020; doi: 10.1002/ejhf.2009; 2. McMurray JJV et al. *Eur Heart J* 2015;36:434–439; 3. Teerlink JR et al. *N Engl J Med* 2020; doi:10.1056/NEJMoa2025797

No direct head to head comparisons

25

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 HFrEF following a worsening HF event[1,2]

Eligibility criteria N=5050
- HFrEF (LVEF <45%)
- NYHA Class II–IV
- BNP: ≥300 pg/mL SR; ≥500 pg/mL + AF
- NT-proBNP: ≥1000 pg/mL SR; ≥1600 pg/mL + AF
- eGFR: ≥15 mL/min/1.73 m² (15% cap: 15–30 mL/min/1.73 m²)
- HF hospitalisation within 6 months or IV diuretic treatment for HF within 3 months

1:1

2.5 mg OD → 5 mg OD → 10 mg OD*

Placebo OD with sham up-titration at Weeks 2 and 4

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.
AF, atrial fibrillation; BNP, B-type natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol 5-dimension; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OD, once daily; SR, sinus rhythm
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

26

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

Patients may have been randomised as an inpatient or outpatient but must have met criteria for clinical stability (e.g. SBP ≥100 mmHg, off IV treatments ≥24 hours). There was no run-in period

HF, heart failure; IV, intravenous; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure
1. Armstrong PW et al. *JACC Heart Fail* 2018;6:96–104; 2. Armstrong PW et al. *N Engl J Med* 2020;382:1883–1893

27

VICTORIA Baseline Characteristics

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)
Mean age, years ±SD	67.5±12.2	67.2±12.2
Male sex, n (%)	1921 (76.0)	1921 (76.1)
Race, n (%)*		
White	1621 (64.2)	1618 (64.1)
Black	123 (4.9)	126 (5.0)
Asian	571 (22.6)	561 (22.2)
Other	211 (8.4)	219 (8.7)
Mean ejection fraction at screening, % ±SD	29.0±8.3	28.8±8.3
Ejection fraction <40%, n (%)	2158 (85.8)	2158 (85.6)
NYHA class III/IV, n/total N (%)†	1045 (41.4)	1024 (40.6)
Other conditions, n/total N (%)‡		
Atrial fibrillation	1098 (43.5%)	1170 (46.4%)
Diabetes mellitus	1226 (48.6%)	1143 (45.3%)
CAD	1511 (59.8%)	1433 (56.8%)

*Race was reported by patient; †From a total of 2523 patients in each group; ‡From a total of 2525 patients in the vericiguat group, and 2523 patients in the placebo group
Armstrong PW et al. *N Engl J Med* 2020;382:1883–1893

28

HF Medications in VICTORIA

Characteristic	Vericiguat (N=2521)	Placebo (N=2519)
Standard-of-care treatment, n (%)		
Beta blocker	2349 (93.2%)	2342 (93.0%)
ACEi/ARB	1847 (73.3%)	1853 (73.6%)
MRA	1747 (69.3%)	1798 (71.4%)
ARNi (sacubitril/valsartan)	360 (14.3%)	371 (14.7%)
Triple therapy	1480 (58.7%)	1529 (60.7%)
Standard-of-care device treatment, n (%)		
Implantable cardioverter defibrillator	696 (27.6%)	703 (27.9%)
Biventricular pacemaker	370 (14.7%)	369 (14.6%)

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

29

Index Events in VICTORIA

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)
Index event, n (%)		
Hospitalisation for HF in previous 3 months	1673 (66.2)	1705 (67.6)
Hospitalisation for HF in previous 3–6 months	454 (18.0)	417 (16.5)
IV diuretic for HF (without hospitalisation) in previous 3 months	399 (15.8)	402 (15.9)
Mean time from initial HFrEF diagnosis to randomisation, years ±SD	4.7±5.5	4.8±5.4

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

30

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

VICTORIA patients have the largest medical need due to persistently elevated event rates, resulting in a much higher baseline-risk patient population

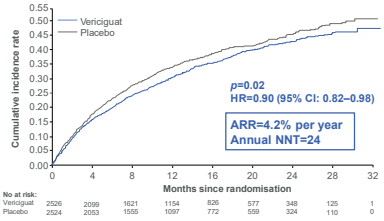
	DAPA-HF[1,2]	PARADIGM-HF[3–5]	VICTORIA[5,7]
Median NT-proBNP (pg/mL)	1437	1608	2816
HFH within 6 months (%)	16.4	31	84
NYHA Class III/IV at baseline (%)	32	25	41
Primary outcome (Events in comparator arms per 100-PY)	15.6*	13.2	37.8
HFH	9.8	7.7	29.1
CV death	7.9	7.5	13.9

Note: this is not intended as a direct comparison of the different studies.
*The primary endpoint for DAPA-HF was CV death or hospitalisation or urgent visit resulting in IV therapy for HF. Primary endpoints for PARADIGM-HF and VICTORIA were CV death or first HFH
CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalisation; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PY, patient-years
1. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 2. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 3. McMurray JJV et al. *Eur J Heart Fail.* 2014;16:817–825; 4. Solomon SD et al. *JACC Heart Fail.* 2016;4:816–822; 5. McMurray JJV et al. *Eur Heart J.* 2015;36:434–439; 6. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 7. Packer S et al. *Eur J Heart Fail.* 2019;21:1596–1604

31

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

Time to CV death or first HF hospitalisation



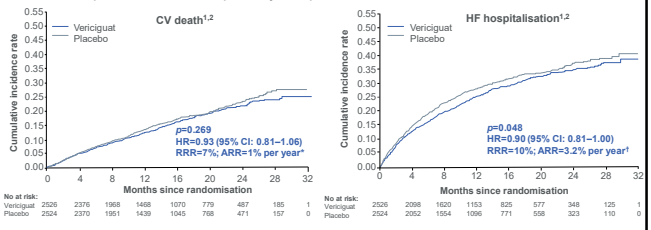
- Median follow-up period: **10.8 months**
- Event rate per 100 patient-years was **33.6%** for **vericiguat** vs **37.8%** for **placebo**

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

32

Cumulative Incidence Rates of Primary Endpoint Components

HF hospitalisation drives primary endpoint



*Annual ARR: 13.9-12.9=1%; †Annual ARR: 29.1-25.9=3.2%
ARR, absolute risk reduction; CI, confidence interval; HFH, heart failure hospitalisation; HR, hazard ratio; RRR, relative risk reduction
1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893 2. Armstrong PW et al. Oral Presentation at ACC 2020

33

Special Benefit of Vericiguat in stabilized Patients with NT-proBNP Levels Up to ≤5314 pg/ml at Baseline[1]

NT-proBNP at baseline

	Number of events Vericiguat/Placebo	Hazard ratio	95% CI
NT-proBNP at baseline by quartiles (pg/ml)			
Q1 (≤1556)	128/161	0.78	0.62–0.99
Q2 (>1556–2816)	165/201	0.73	0.60–0.90
Q3 (>2816–5314)	213/257	0.82	0.69–0.99
Q4 (>5314)	355/302	1.16	0.99–1.35

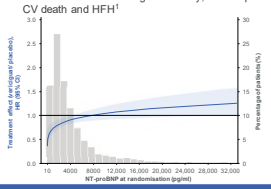
Clinical trials report median NT-proBNP levels at discharge of 2703–4137 pg/ml[2–4]

CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile.
1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893. 2. Bettencourt P et al. *Circulation.* 2004;110:2168–2174; 3. Stienen S et al. *Circulation.* 2018;137:1671–1683;
4. Metra M et al. *Eur J Heart Fail.* 2007;9:776–786.

34

Special Benefit of Vericiguat in stabilized Patients with NT-proBNP Levels Up to 8000 pg/ml[1]

- Relationship between NT-proBNP level at randomisation and vericiguat efficacy, with respect to CV death and HFH[1]



Patients with NT-proBNP ≤8000 pg/ml: positive treatment effect of vericiguat extended to both HFH **and** CV death:

Efficacy for patients with NT-proBNP ≤ 8000 pg/ml (= 86% of the VICTORIA population):

CV Death + HF Hospitalisation	CV Death	HF Hospitalisation
5.4% ARR HR=0.85 95% CI 0.76–0.95)	**0.8% ARR** HR=0.84 95% CI 0.71–0.99)	**4.6% ARR** HR=0.84 (95% CI 0.75–0.95)

Efficacy for patients with NT-proBNP ≤ 4000 pg/ml (= 61% of the VICTORIA population): :

6.8% ARR HR=0.77 95% CI 0.68–0.88)	**1.3% ARR** HR=0.75 95% CI 0.60–0.94)	**5.5% ARR** HR=0.78 (95% CI 0.67–0.90))

Clinical trials report median NT-proBNP levels at discharge of 2703–4137 pg/ml[2–4]

Range of the treatment effect of vericiguat compared with placebo for the primary composite endpoint for NT-proBNP at randomisation, adjusted for the MAGGIC risk score.
CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalisation; HR, hazard ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NT-proBNP, N-terminal pro-brain natriuretic peptide.
1. Ezekowitz JA et al. *J Am Coll Cardiol.* 2020;8:931–939; 2. Bettencourt P et al. *Circulation.* 2004;110:2168–2174; 3. Stienen S et al. *Circulation.* 2018;137:1671–1683;
4. Metra M et al. *Eur J Heart Fail.* 2007;9:776–786.

35

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	5.6	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 ≥2% 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

36

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

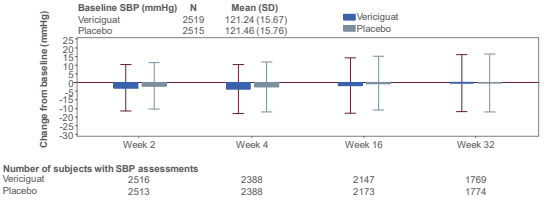
- Symptomatic hypotension and syncope were numerically more common in the patients receiving vericiguat than in those receiving placebo

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

37

Systolic Blood Pressure Declined Slightly in Both Groups Over The First 16 Weeks, Then Returned to Baseline

Mean change in SBP from baseline over time



Number of subjects with SBP assessments

Vericiguat	2516	2388	2147	1769
Placebo	2513	2388	2173	1774

SBP, systolic blood pressure; SD, standard deviation
Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

38

Vericiguat is a simple therapy[1]

Adherence: 93.8% of patients on the vericiguat arm achieved adherence of >80% to the trial drug[2]

Titration: 90.3% of patients were receiving the 10 mg target dose[2]

No clinically relevant interactions with with HF drugs or those used to treat comorbidities[3,4]

1x/d **Once daily** medication

No Monitoring needed

Renal impairment: No dose adjustment required in patients with eGFR ≥15 mL/min/1.73 m2 (without dialysis)

1. Swiss SmPC www.swissmedicinfo.ch 2. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893. 3. Lobmeyer M, et al. Poster P1706. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019. 4. Boettcher M, et al. Poster P1163. Presented at the European Society of Cardiology Heart Failure Congress, 25-28 May 2019.

39

ESC Recommendation 2021 for Pre-discharge and Early Post-discharge FU of Patients Hospitalized for Acute HF[1,2]

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, drugs' 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.
1. Metra M. ESC-HF. 2021. Oral. 2. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

40

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	IIb

- 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

New concepts

A new **simplified treatment algorithm** for HFrEF, now including ARNi as first-line with ACEi and excluding ARBs from first-line therapies

The addition of a treatment algorithm for HFrEF according to **phenotypes** (e.g. effects on BP, renal function and K+ levels; drug-drug interactions; adverse events, comorbidities,..)

Vericiguat may be suitable for a wide range of patients due to its favorable safety profile:

Patients at risk of hypotension | Patients with renal impairment | Patients at risk of hyperkalemia

1. McDonald M *et al. Can J Cardiol* 2021;37:531–546. 2. Rosano GMC *et al. EHJ HF* 2021;23:872-81

41

When and why to use Vericiguat?

When?	Why?
HFrEF Patients **after Decompensation** with NT-proBNP<8000 pg/ml…	• **And** progressing symptoms (beside already receiving SoC) → 1. **Evidence:** Significant reduction of the risk of HF hospitalisation or CV death: **ARR = 5.4 % (NNT= 19); RRR= 15%** and significant Reduction of components of the 1°EP[1] 2. poor prognosis and remaining risk despite SoC
	• **And Tolerability and up-titration issues** with SoC → 3. More promising concept of low dose combination of different MoA before up-titration: Vericiguat has a **complementary MoA** with no overlap with other drugs 4. **Excellent safety profile**: AE over all on Placebo level; the 4 most frequent side effects with SoC not a problem with vericiguat (HR, potassium, BP, creatinine) 5. **Good adherence /OD dosing** with **90.3%** of patients **on target dose → Efficacy !** (full uptitration = full efficacy) 6. **No interaction** with most of the common drugs for HF and comorbidities; Evidence in **Patients with low eGFR**, BP

= Reasons for early combination with Vericiguat

1. Ezekowitz JA et al. *J Am Coll Cardiol.* 2020;8:931–939

42

DELIVER

Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure[1,2,3]

6263 Patients

- ≥40 years of age with or without T2D
- LVEF >40%[a] and evidence of structural heart disease[b] within 12 months
- Symptomatic NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- Elevated NT-proBNP levels
- eGFR[c] ≥25 mL/min/1.73 m²
- Ambulatory or hospitalized off IV HF therapy[d] for ≥24 hours

1:1 randomization

- Dapagliflozin 10 mg
- Placebo

Median follow-up: 2.3 years

Visit 1 (enrollment) Day -21 | Visit 2 Day 1 | Visit 3 Day 30 | Visit 4 Day 120 | Visit 5 Day 240 | Visit 6 Day 360 | Visit 7 Day 480 | Visit 8 Day 600

Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or worsening HF events (hHF or urgent HF visit)
  - Full patient population
  - Patients with LVEF <60%

Secondary Endpoints

- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

[a]Patients with an LVEF ≤40% were also included. [b]LV hypertrophy or LA enlargement; [c]Based on Chronic Kidney Disease-Epidemiology Collaboration Equation; [d]including diuretics; [e]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment).

1. Solomon SD et al. *Eur J Heart Fail.* 2021;23(7):1217-1225. 2. Solomon SD et al. *JACC Heart Fail.* 2022;10(3):184-197. 3. Solomon SD et al. Online ahead of print. *N Engl J Med.* 2022

43

Heart Failure History

Characteristic	Dapagliflozin 10 mg (n=3131)	Placebo (n=3132)
LVEF, %	54.0 ± 8.6	54.3 ± 8.9
LVEF group, n (%)		
≤49%	1067 (34.1)	1049 (33.5)
50-59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
NYHA functional class, n (%)		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Median NT-proBNP (IQR), pg/mL		
Patients not in AF/AFL	729 (472, 1299)	704 (467, 1265)
Patients in AF/AFL	1408 (956, 2256)	1387 (965.5, 2180.5)
KCCQ-TSS[a]	70 ± 23	70 ± 22

HF Therapy, n (%)	Dapagliflozin 10 mg (n=3131)	Placebo (n=3132)
Loop diuretic	2403 (76.7)	2408 (76.9)
ACEI	1144 (36.5)	1151 (36.7)
ARB	1133 (36.2)	1139 (36.4)
Sacubitril-valsartan	165 (5.3)	136 (4.3)
Beta-blocker	2592 (82.8)	2585 (82.5)
MRA	1340 (42.8)	1327 (42.4)

LVEF Group | Recently hospitalized | Prior LVEF <40%

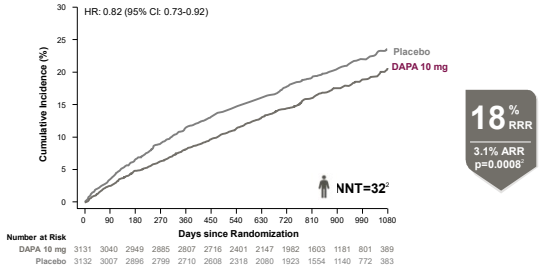
± value is mean ± SD. Percentages might not total 100 because of rounding.

[a]Available for 2903 patients in the dapagliflozin group and 2892 patients in the placebo group.

Solomon SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med.* 2022

44

Primary Composite of CV Death, hHF or Urgent HF Visit[1]



1. Solomon SD et al. Online ahead of print. N Engl J Med. 2022;2. Solomon SD. Presented at ESC Congress; August 26-29, 2022; Barcelona, Spain.

45

Components of the Primary Endpoint[1]

Outcome, n (%)	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	p-value
CV death or worsening HF[a]	512 (16.4)	610 (19.5)	0.82 (0.73-0.92)	0.0008[2]
CV death[b]	231 (7.4)	261 (8.3)	0.88 (0.74-1.05)	
Worsening HF[a]	368 (11.8)	455 (14.5)	0.79 (0.69-0.91)	
hHF	329 (10.5)	418 (13.3)	0.77 (0.67-0.89)	
Urgent HF visit	60 (1.9)	78 (2.5)	0.76 (0.55-1.07)	

[a]Includes hHF or urgent HF visit; [b]Also a prespecified secondary endpoint.
CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio
1. Solomon SD et al. Online ahead of print. N Engl J Med. 2022;2. Solomon SD. Presented at ESC Congress; August 26-29, 2022; Barcelona, Spain.

46

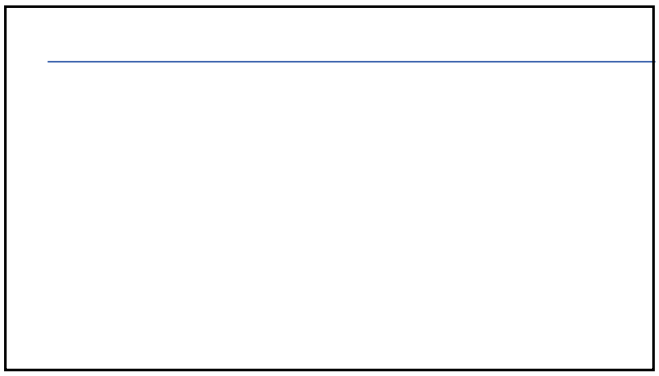
GALACTIC-Studie

47

Zusammenfassung

- Zahl der Herzinsuffizienz-Patienten wird steigen
- Die Echokardiographie besitzt zentrale Bedeutung in der Diagnose
- Therapie erfolgt über multiple Pathways
- Verciguat stellt einen neuen Wirkmechanismus dar
  - Gute Verträglichkeit mit Einmal-Gabe
  - Keinen Einfluss auf den Blutdruck
  - Einsetzbar bei geringer Nierenfunktion
  - Verbesserung der Prognose der Patienten

48



49