# Insufficienza cardiac cronica : il ruolo di vericiguat

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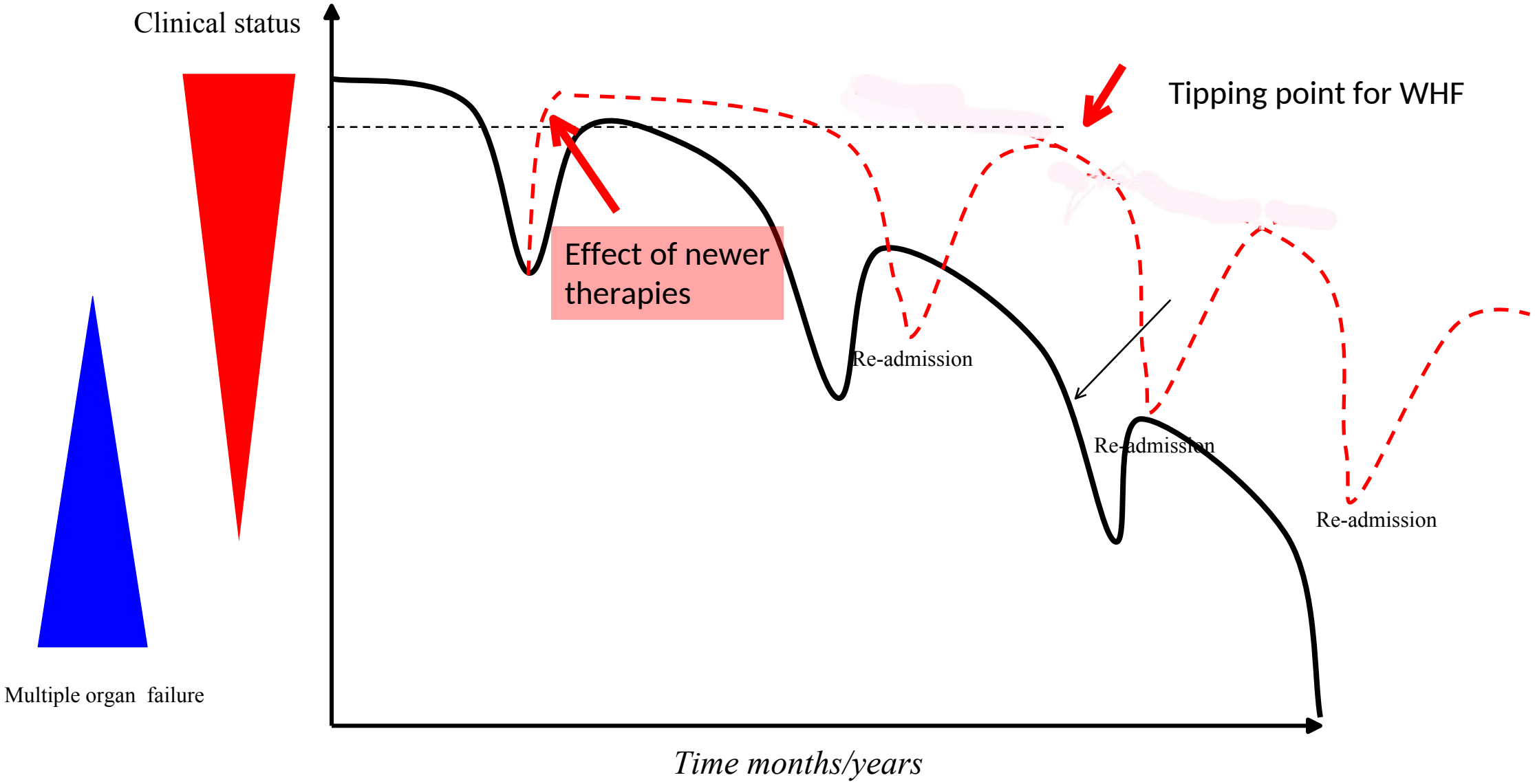
# Clinical evolution of patients with Heart Failure



# Clinical Trajectories in Heart Failure

## New onset/ de novo HF:

- Newly diagnosed HF
- No former history of HF

## Improving HF:

- Improving symptoms/signs and or functional capacity

## Persistent HF:

- Persistent HF with ongoing symptoms/ signs and or limited functional capacity

Do not use "Stable HF" instead, use "Persistent"

## HF in Remission:

- Resolution of symptoms and signs of HF, with resolution of previous structural/functional heart disease after a phase of symptomatic HF

Do not use "Recovered HF" instead, use "HF in Remission"

## Worsening HF:

- Worsening symptom/signs/ functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies
- and/or hospitalization

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HFSA HEART FAILURE SOCIETY OF AMERICA

HFA Heart Failure Association

CHFS SCIC Canadian Heart Failure Society Société canadienne d'insuffisance cardiaque

CSANZ Cardiac Society of Australia and New Zealand

The Japanese Heart Failure Society

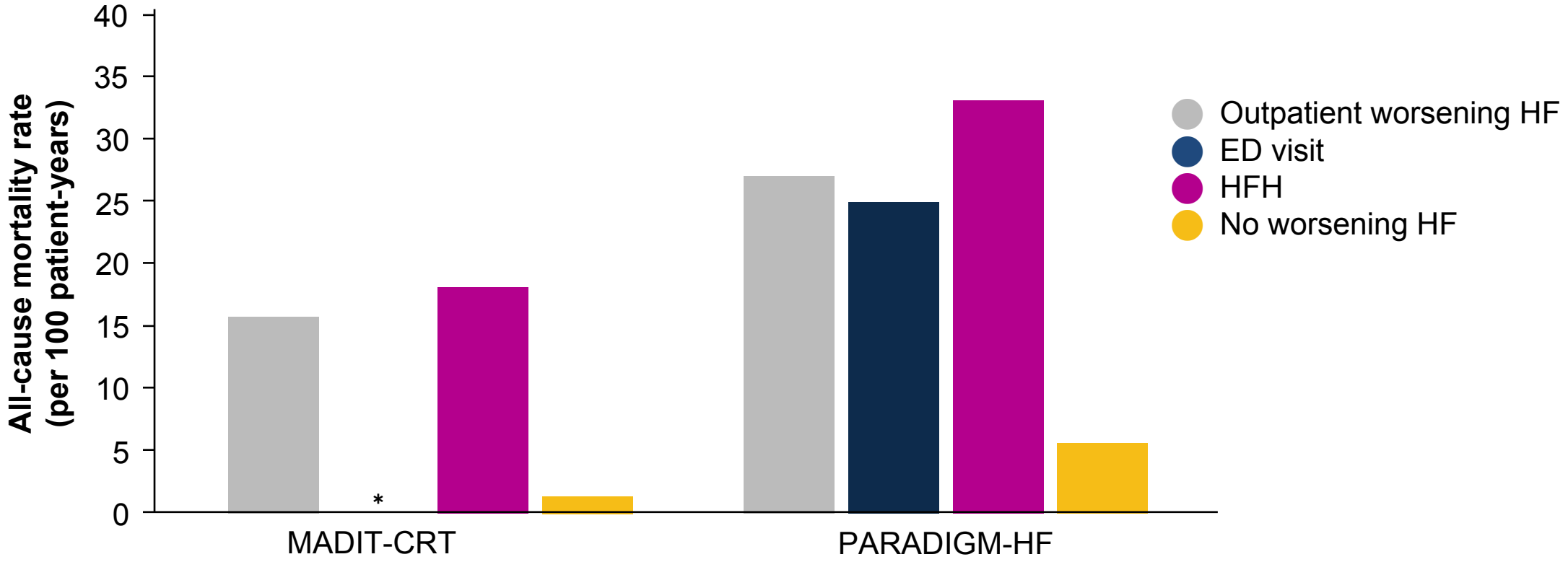
Chinese Heart Failure Association

Bozkurt, et al. Universal Definition and Classification of Heart Failure, Journal of Cardiac Failure, 2021, ISSN 1071-9164, https://doi.org/10.1016/j.cardfail.2021.01.022.

# Worsening HF Events Are Associated with Increased Mortality Risk, Regardless of Care Location[1]

## Risk of mortality after a worsening HF event treated in the outpatient setting, in the ED or in hospital






*Data for ED visits in MADIT-CRT were not reported.
ED, emergency department; HF, heart failure; HFH, heart failure hospitalization.

1. Greene SJ *et al*. *JAMA Cardiol*. 2018;3:252–259.

# EMA Guidance on HF



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
CPMP/EWP/235/95, Rev.2
Committee for Medicinal Products for Human Use (CHMP)

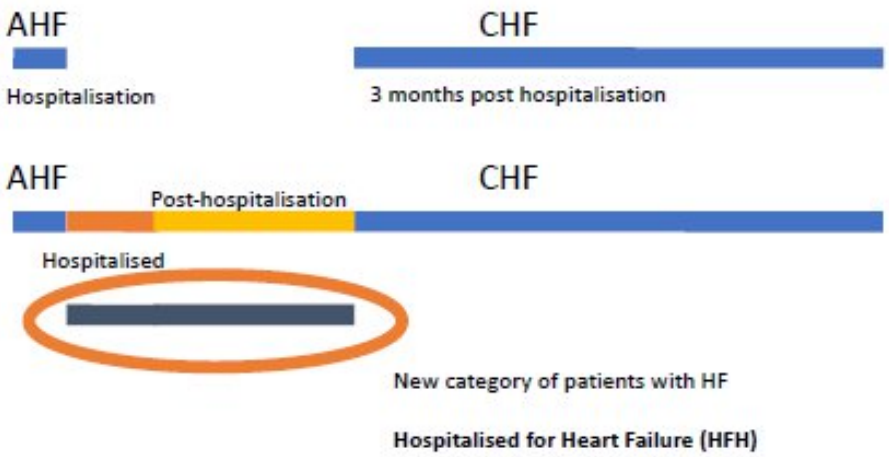
Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure

| | |
|---|---|
| **Draft agreed by Cardiovascular Working Party** | 24 November 2015 |
| **Adopted by CHMP for release for consultation** | 28 January 2016 |

The main therapeutic goals in the treatment of CHF are to reduce cardiovascular mortality and to prevent deterioration of the clinical status and hospitalisations; these goals should represent the primary aim of new agents developed for the treatment of CHF.

**4.1.2. Worsening of heart failure**

An episode of worsening of heart failure (WHF) may qualify as an episode managed either in a hospital setting or on an outpatient basis by an emergency visit



# VICTORIA Was Designed to Study Patients with Symptomatic Chronic HF Who Had a Previous Worsening HF Event[1–5]

***'Symptomatic chronic HF'***

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

**&**

***'Worsening HF event'***

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

**Patients may have been randomised as an inpatient or outpatient but must have met criteria for clinical stability (SBP ≥100 mmHg and/or off IV treatments ≥24 hours)**

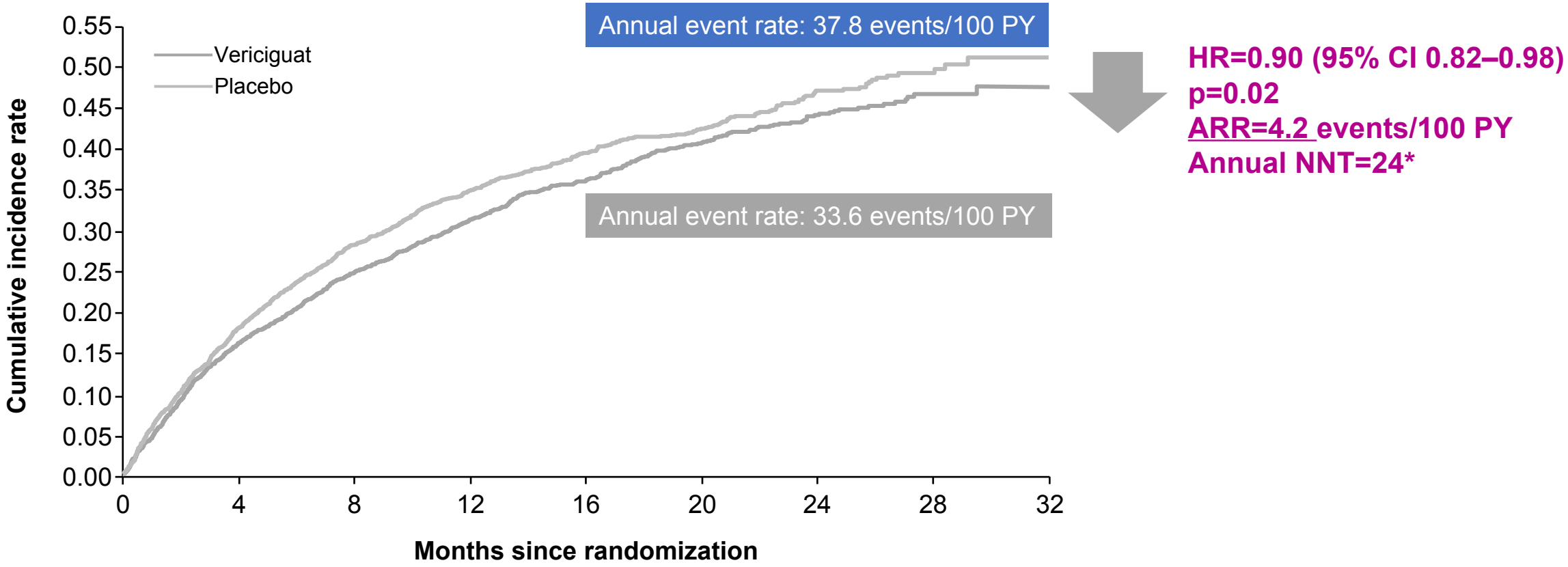
**There was no run-in period**

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; 3. Hicks KA et al. *Circulation.* 2015;132:302–361; 4. European Medicines Agency. 2017. CPMP/EWP/235/95, Rev.2. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf. [accessed 9 Feb 2021]; 5. Butler J et al. *Circulation.* 2020;142:717–719.

# Vericiguat Significantly Reduced the Annualized Absolute Rate of Time to HFH or CV Death by 4.2 Events/100 PY[1]

## Time to CV death or first HFH

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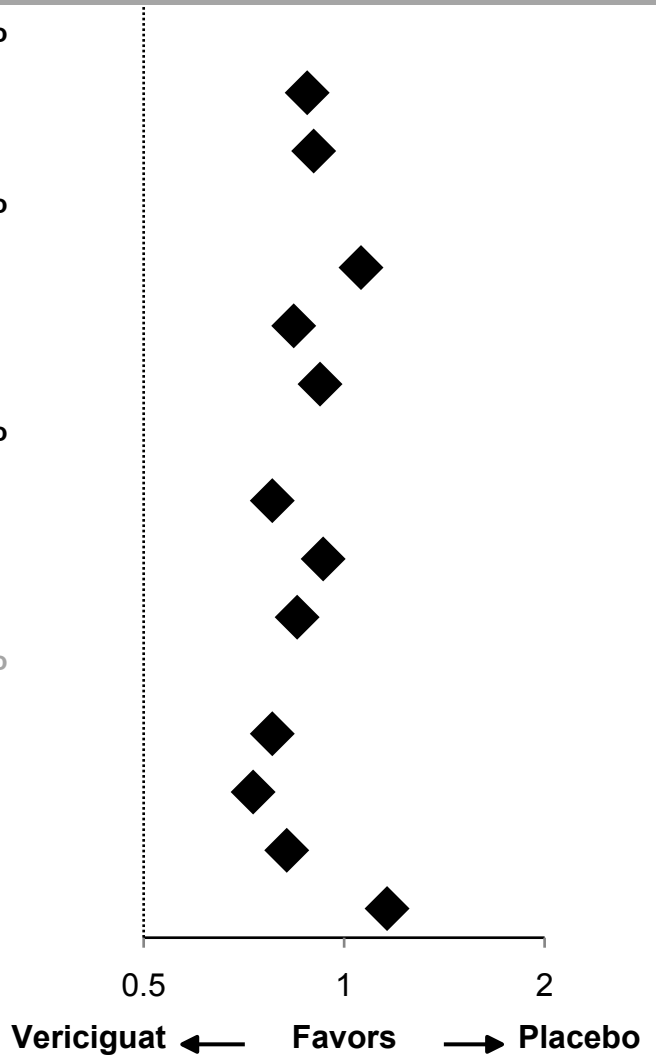
Median treatment duration for primary endpoint: 10.8 months.
*Calculations: annual NNT = 100/4.2 = 24.
ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; NNT, number needed to treat; PY, patient-years.
1. Armstrong PW *et al*. *N Engl J Med* 2020;382:1883–1893.

# VICTORIA: Primary Composite Endpoint Outcomes Across a Range of Prespecified Subgroups[1]

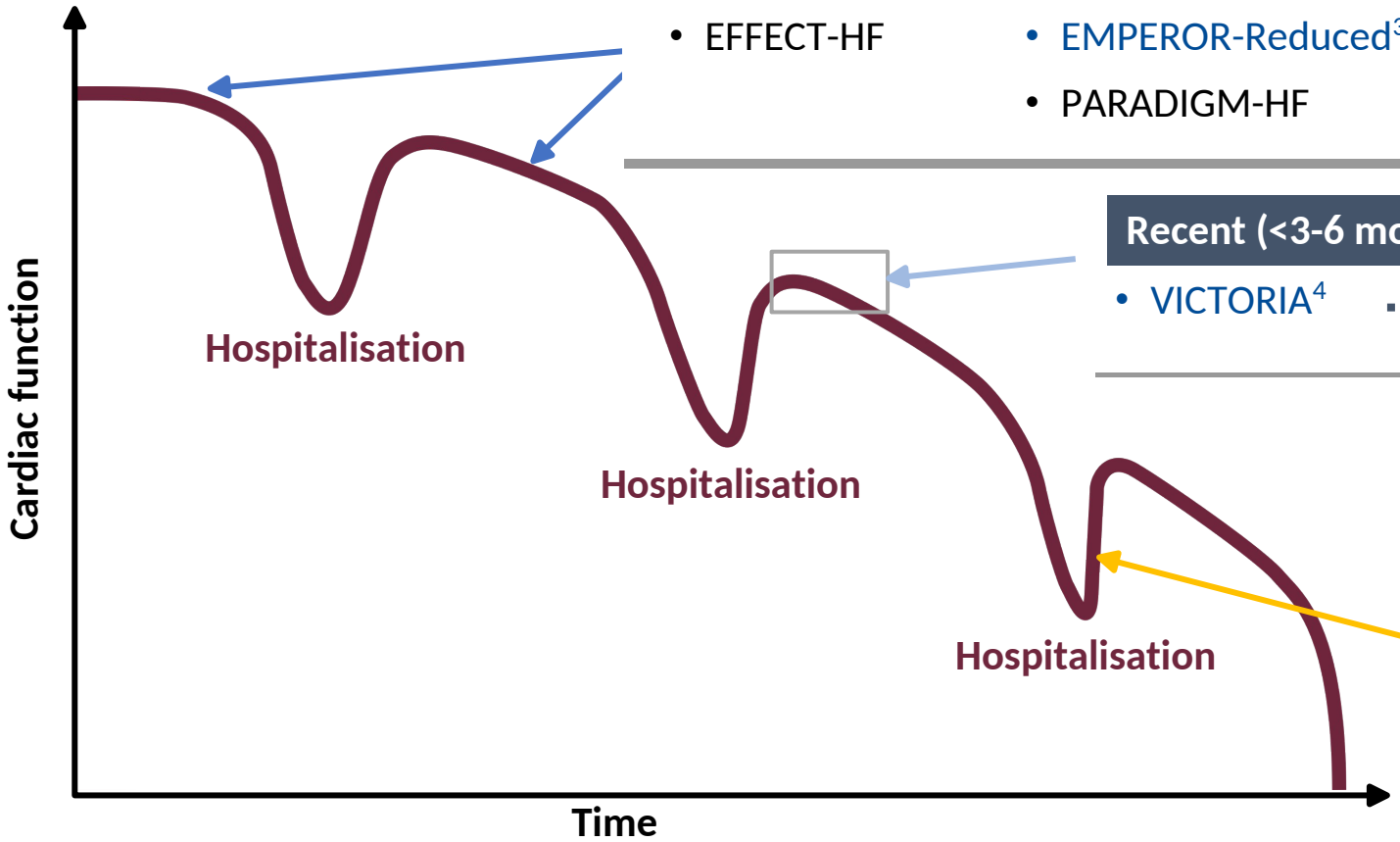
| Subanalysis | Event rate | Hazard ratio | 95% CI |
|---|---|---|---|
| **Use of sacubitril/valsartan at baseline** | **Number of events, vericiguat/placebo** | | |
| Yes | 134/153 | 0.88 | (0.70–1.11) |
| No | 760/818 | 0.90 | (0.81–0.99) |
| **eGFR at baseline (ml/min/1.73 m$^2$)** | **Number of events, vericiguat/placebo** | | |
| ≤30 | 143/128 | 1.06 | (0.83–1.34) |
| >30 to ≤60 | 392/455 | 0.84 | (0.73–0.96) |
| >60 | 346/372 | 0.92 | (0.80–1.07) |
| **Index event** | **Number of events, vericiguat/placebo** | | |
| IV diuretic <3 months | 96/120 | 0.78 | (0.60–1.02) |
| Hospitalization <3 months | 660/701 | 0.93 | (0.84–1.04) |
| Hospitalization 3–6 months | 141/151 | 0.85 | (0.67–1.07) |
| **NT-proBNP at baseline by quartiles (pg/ml)** | **Number of events, vericiguat/placebo** | | |
| 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) |




CI, confidence interval; eGFR, estimated glomerular filtration rate; IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile.

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

# Effects of therapies across the HF continuum




**Chronic HF**

- FAIR-HF
- CONFIRM-HF
- EFFECT-HF
- PARAGON-HF[1]
- DAPA-HF[2]
- EMPEROR-Reduced[3]
- PARADIGM-HF

| Control Event Rate |
|---|
| 14.6 per 100 py<br>Total HHF/CV death |
| 15.6 per 100 py<br>First HHF/CV death |
| 21.0 per 100 py<br>First HHF/CV death |

**Recent (<3-6 months) AHF**

- VICTORIA[4]

| Control Event Rate |
|---|
| 37.8 per 100 py<br>First HHF/CV death |

**Prior to D/C following hospitalisation**

- EVEREST
- ASTRONAUT
- SOLOIST-WHF

| Control Event Rate |
|---|
| 76.3 per 100 py<br>Total HHF/CV death |
| 72.51 per 100 py<br>Total HHF/CV death |

1. Solomon SD, et al for the PARAGON-HF Investigators and Committees. *N Engl J Med*. 2019;381(17):1609–1620; 2. McMurray JJV, et al for the DAPA-HF Trial Committees and Investigators. *N Engl J Med*. 2019;381(21):1995–2008; 3. Packer M, et al for the EMPEROR-Reduced Trial Investigators. *N Engl J Med*. 2020;383(15):1413–1424; 4. Armstrong PW, et al for the VICTORIA Study Group. *N Engl J Med*. 2020;382(20):1883–1893; 5. Ponikowski P, et al for the AFFIRM-AHF investigators. *Lancet*. 2020:10.1016/S0140-6736(20)32339-4.

# In Contrast With Other Contemporary HF Trials, Most Patients in the VICTORIA Trial had HF Hospitalisation <6 Months Prior to Randomisation[1–10]

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

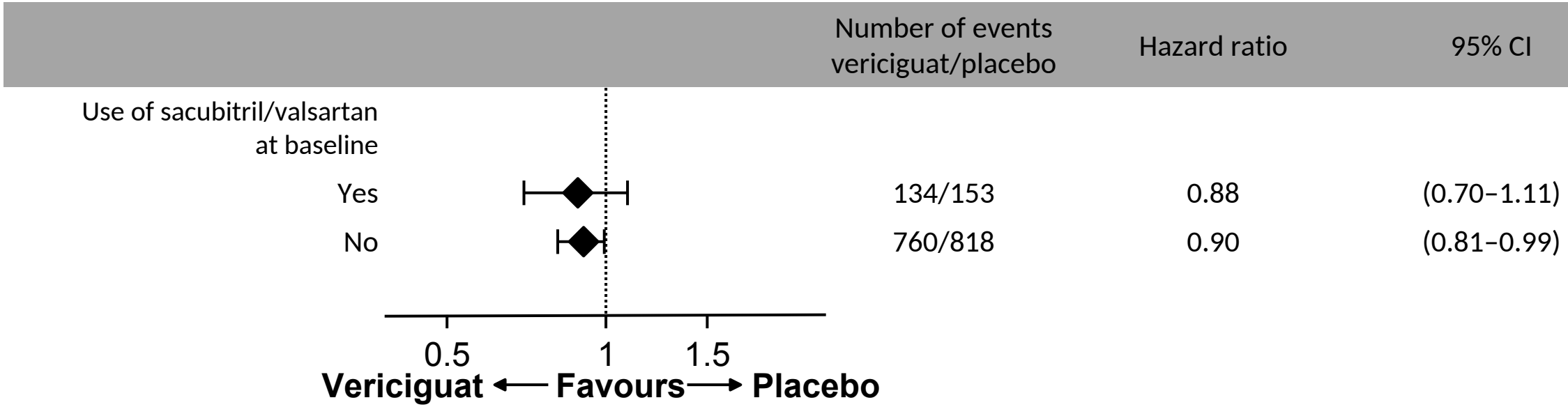
| | PARADIGM-HF[1–3] | DAPA-HF[4,5] | EMPEROR-Reduced[6] | GALACTIC-HF[7] | VICTORIA[8] |
|---|---|---|---|---|---|
| Median NT-proBNP | 1608 pg/ml* | 1437 pg/ml | 1906.5 pg/ml[6] | 2001 pg/ml | 2816 pg/ml |
| HFH within 6 months | 31% | 16.4% | NR‡[6] | NR | 84% |
| NYHA class III/IV at baseline | 25% | 32% | 25%[6] | 47% | 41% |
| Event rates in control arms/100 PY | | | | | |
| Primary outcome | 13.2[9] | 15.6# | 21.0 | 26.3 | 37.8 |
| HFH | 7.7[10] | 9.8 | 15.5 | 19.1 | 29.1 |
| CV death | 7.5[9] | 7.9 | 8.1 | 10.8 | 13.9 |

**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.
*At screening before run-in; 1 month after randomisation, 24% of the baseline NT-proBNP levels >1000 pg/ml had fallen to ≤1000 pg/ml. #The primary outcome was a composite of worsening HF (hospitalisation or an urgent visit resulting in IV therapy for HF) or CV death. Of the patients receiving dapagliflozin, 10 (0.4%) had an urgent HF visit, as compared with 23 patients (1.0%) receiving placebo (HR=0.43; 95% CI 0.20–0.90). ‡In the EMPEROR-Reduced study, HFH was reported for ≤12 months (30.9%).

1. Zile MR et al. *J Am Coll Cardiol.* 2016;68:2425–2436; 2. Solomon SD et al. *JACC Heart Fail.* 2016;4:816–822; 3. McMurray JJ et al. *N Engl J Med.* 2014;371:993–1004; 4. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 5. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 6. Packer M et al. *N Engl J Med*. 2020;383:1413–1424; 7. Teerlink JR et al. *N Engl J Med*. 2021;384:105–116; 8. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893; 9. Butler J et al. *Eur J Heart Fail*. 2020;22:1991–1993; 10. McMurray J et al. *Eur Heart J*. 2015;36:434–439.

# The Primary Composite Endpoint Outcomes Were Directionally Consistent Irrespective of Use of Sacubitril/Valsartan at Baseline[1]

**Use of sacubitril/valsartan**

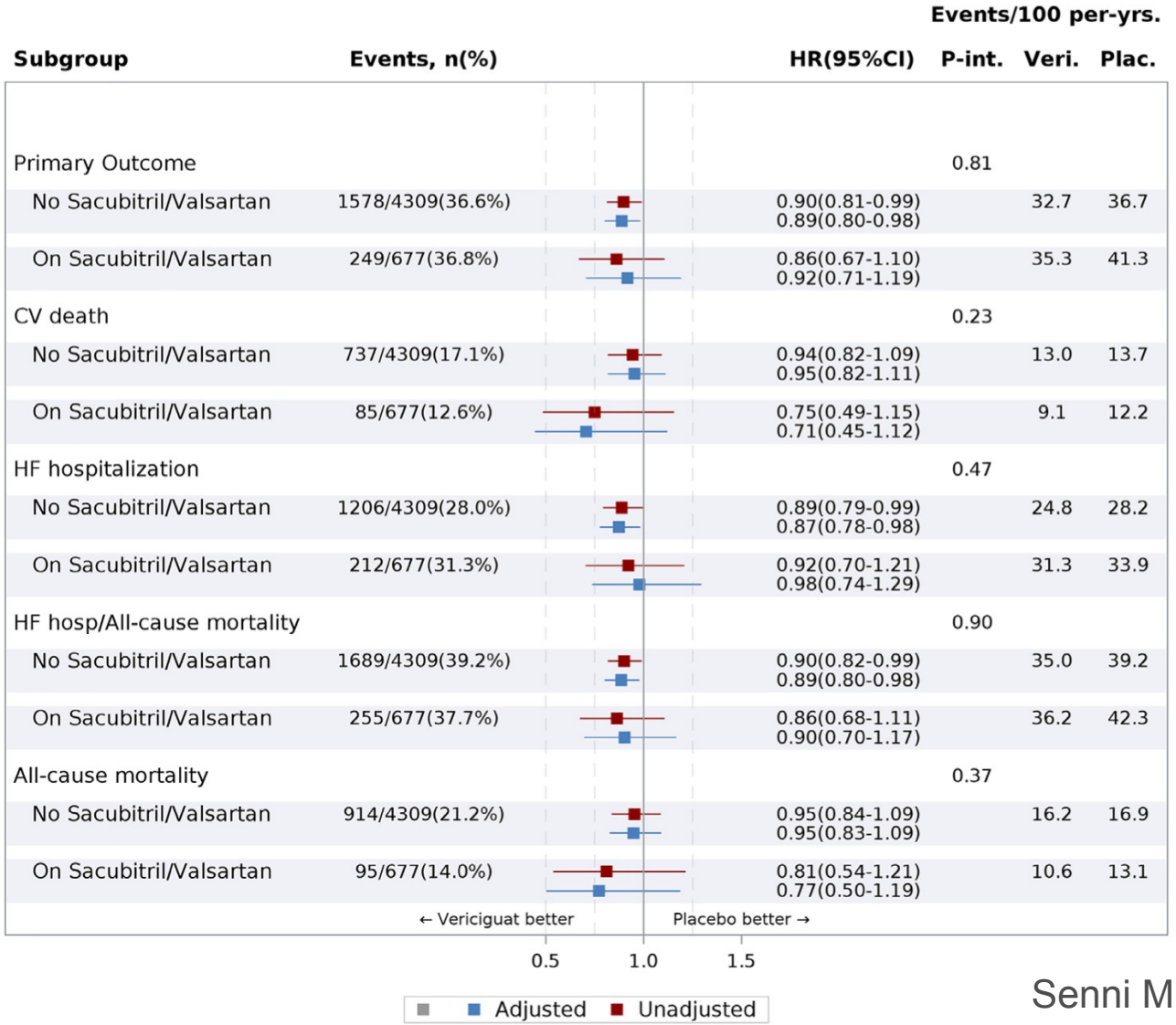



- The effect of vericiguat across the prespecified subgroup defined by the use of sacubitril/valsartan at baseline indicates a generally consistent treatment effect

CI, confidence interval.

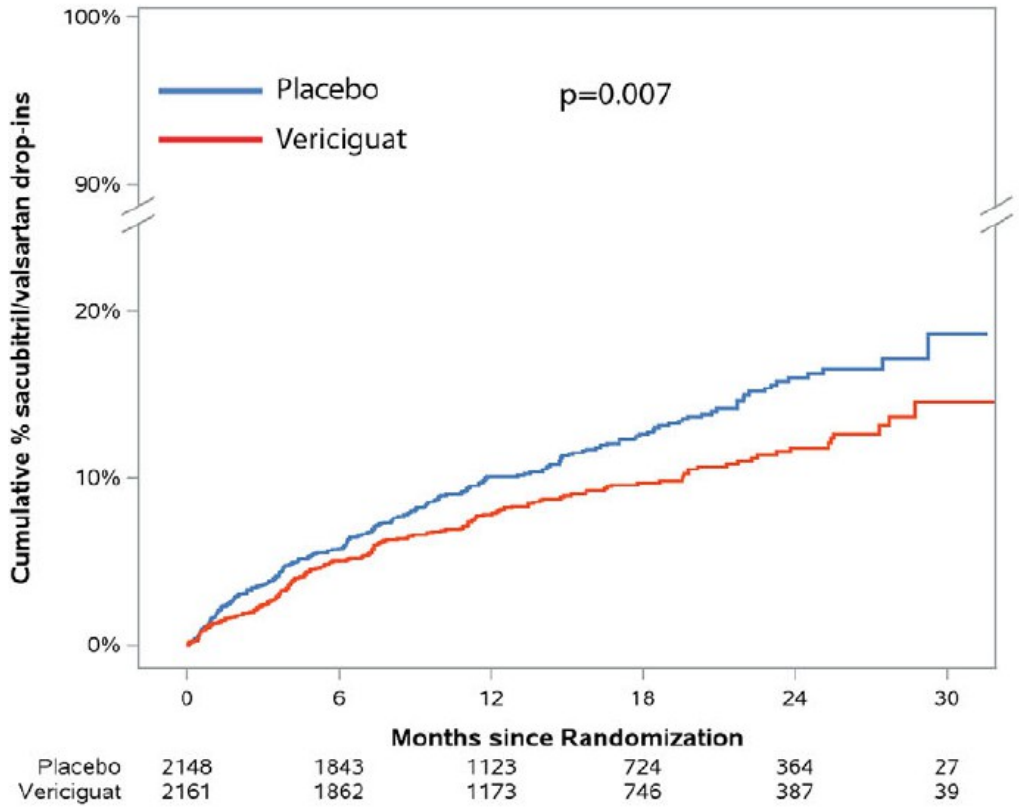
1. Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

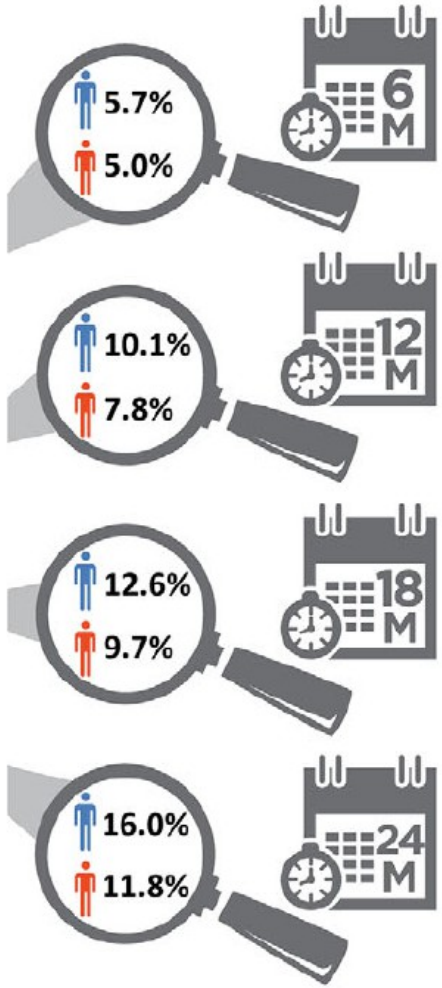
# Effect of vericiguat on outcomes according to sacubitril/valsartan use at randomization for at least 3 months after randomization




Senni M et al. Eur J Heart Fail 2022

# Time to initiation of drop-in therapy with sacubitril/valsartan among sacubitril/valsartan naïve patients at randomization



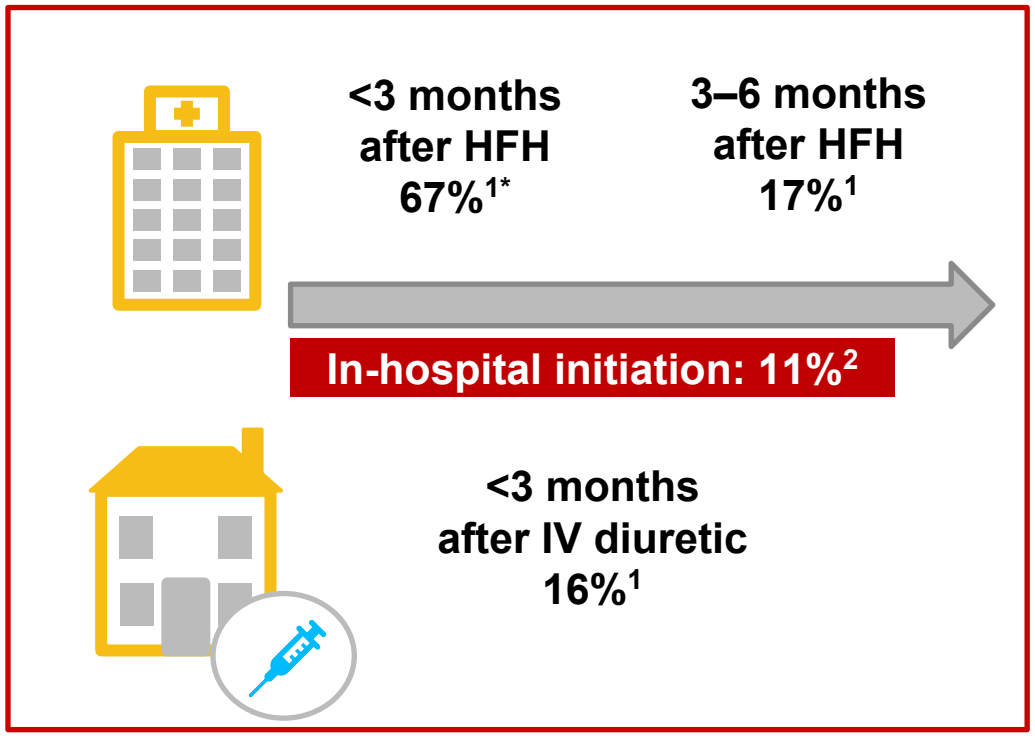

**Significantly more patients in the placebo group (11.7%) had sacubitril/valsartan added than vericiguat (8.7%; log-rank p=0.007).**

***This difference in the pattern of sacubitril/valsartan use appeared early during the follow-up period and widened progressively over time.***

Senni M et al. Eur J Heart Fail 2022

# The majority of VICTORIA patients had received multiple HF therapies before randomization and all randomized patients had a worsening HF event

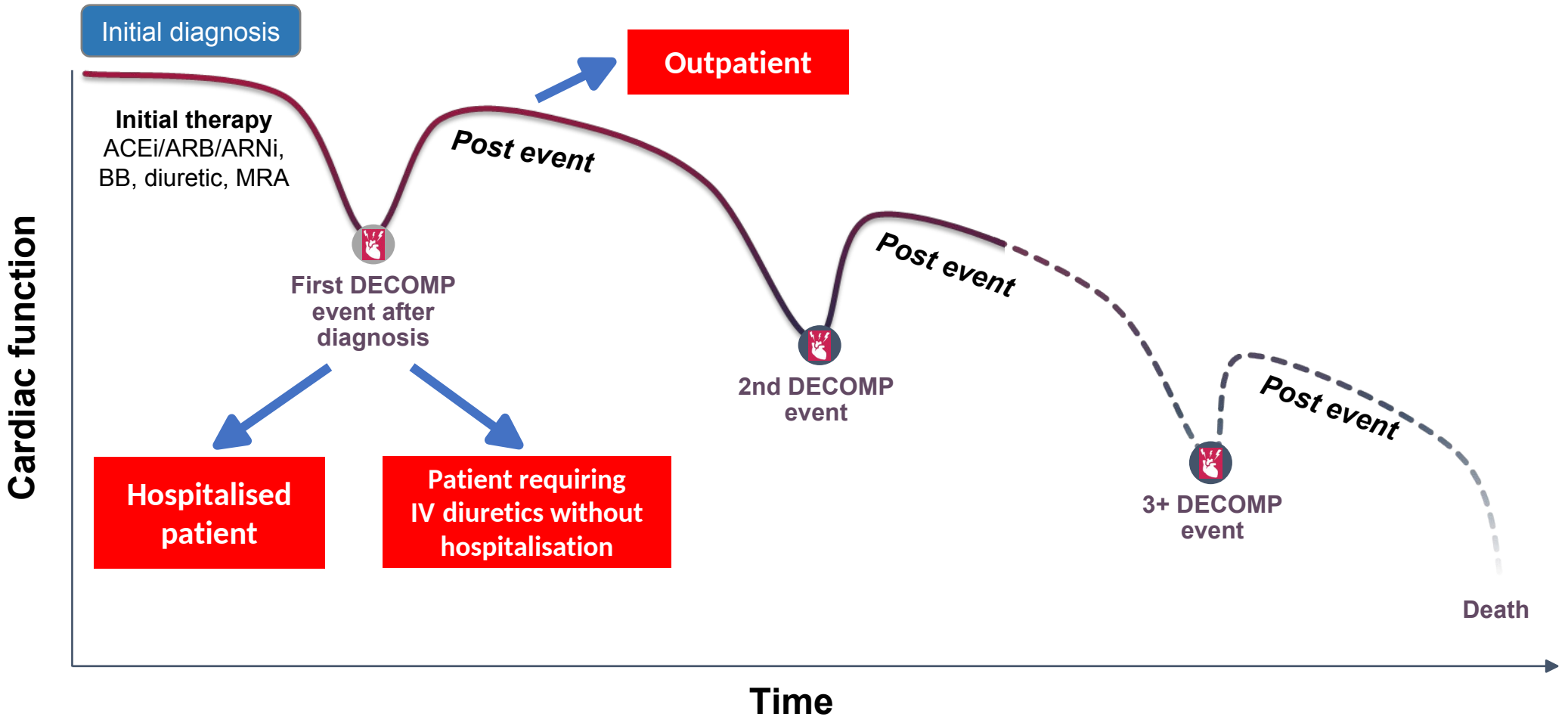
| Characteristic | Vericiguat (N=2526) | Placebo (N=2524) |
|---|---|---|
| **Beta blocker** | 2349 (93.2%) | 2342 (93.0%) |
| **ACEi/ARB** | 1847 (73.3%) | 1853 (73.6%) |
| **MRA** | 1747 (69.3%) | 1798 (71.4%) |
| **ARNi (sacubitril/valsartan)** | 360 (14.3%) | 371 (14.7%) |
| **Patients on triple therapy, n (%)*** | 1480 (58.7%) | 1529 (60.7%) |
| **SGLT2** | 66 (2.6%) | 69 (2.7%) |
| **ICD, n(%)** | 696(27.8%) | 703(27.9%) |
| **Biventricular pacemaker n(%)** | 370(14.7%) | 369(14.8%) |




**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.

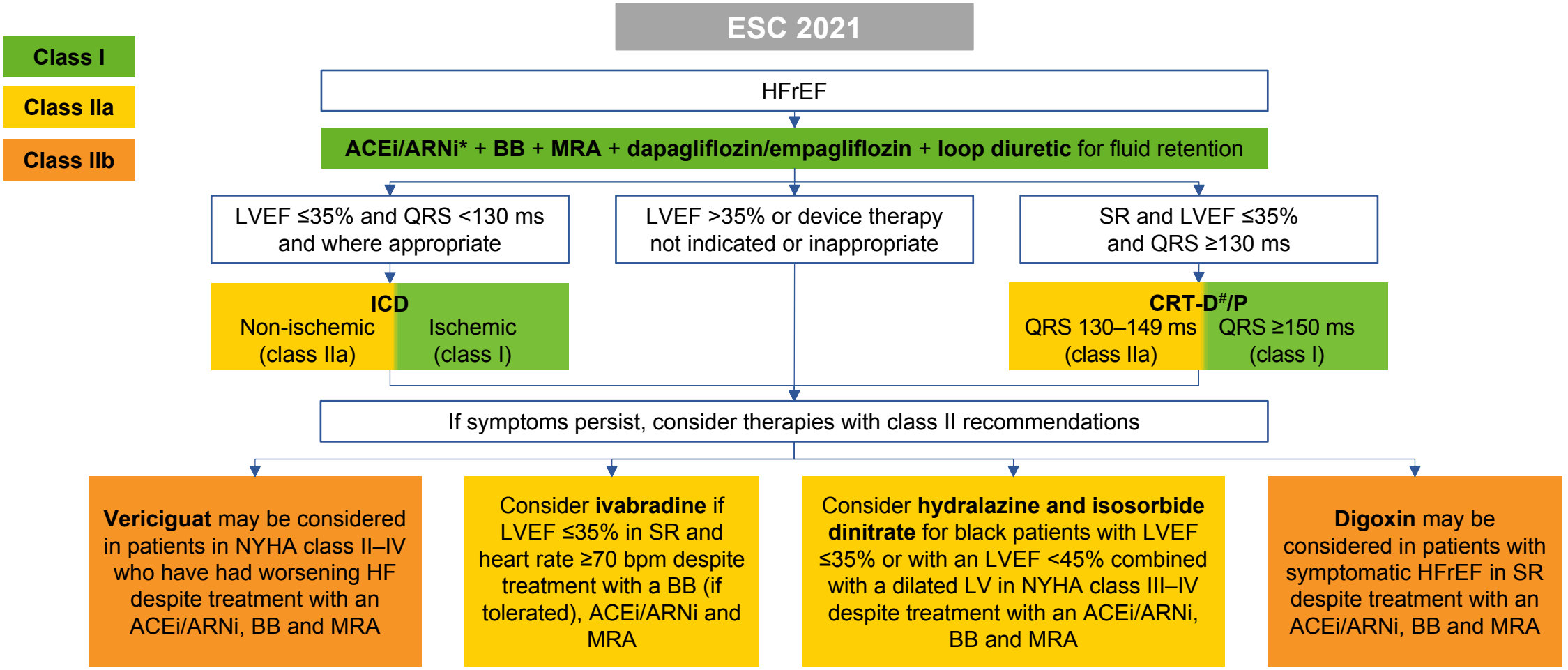
# In VICTORIA, Vericiguat Was Initiated Following a Recent Worsening HF Event, Even in Patients Already Receiving GDMT[1,2]




ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; DECOMP, decompensation; 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.

# ESC 2021 recommendations for the treatment of patients with HFrEF[1]




*ARNi recommended as a replacement for ACEi; an ARB is recommended in patients unable to tolerate an ACEi or ARNi (class I, level B). # Where appropriate.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P,cardiac resynchronization therapy with pacemaker; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QRS, Q, R and S waves; SR, sinus rhythm.

**Reference: 1.** McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

# Vericiguat is specifically recommended for worsening HF in ESC 2021 guidelines[1]

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

**Inclusion in the guidelines before EU approval** is in contrast with other unlicensed therapies (e.g. omecamtiv mecarbil)

**Worsening HF** is referred to in the guidelines for the **first time**, and vericiguat is **specifically recommended** for this patient group

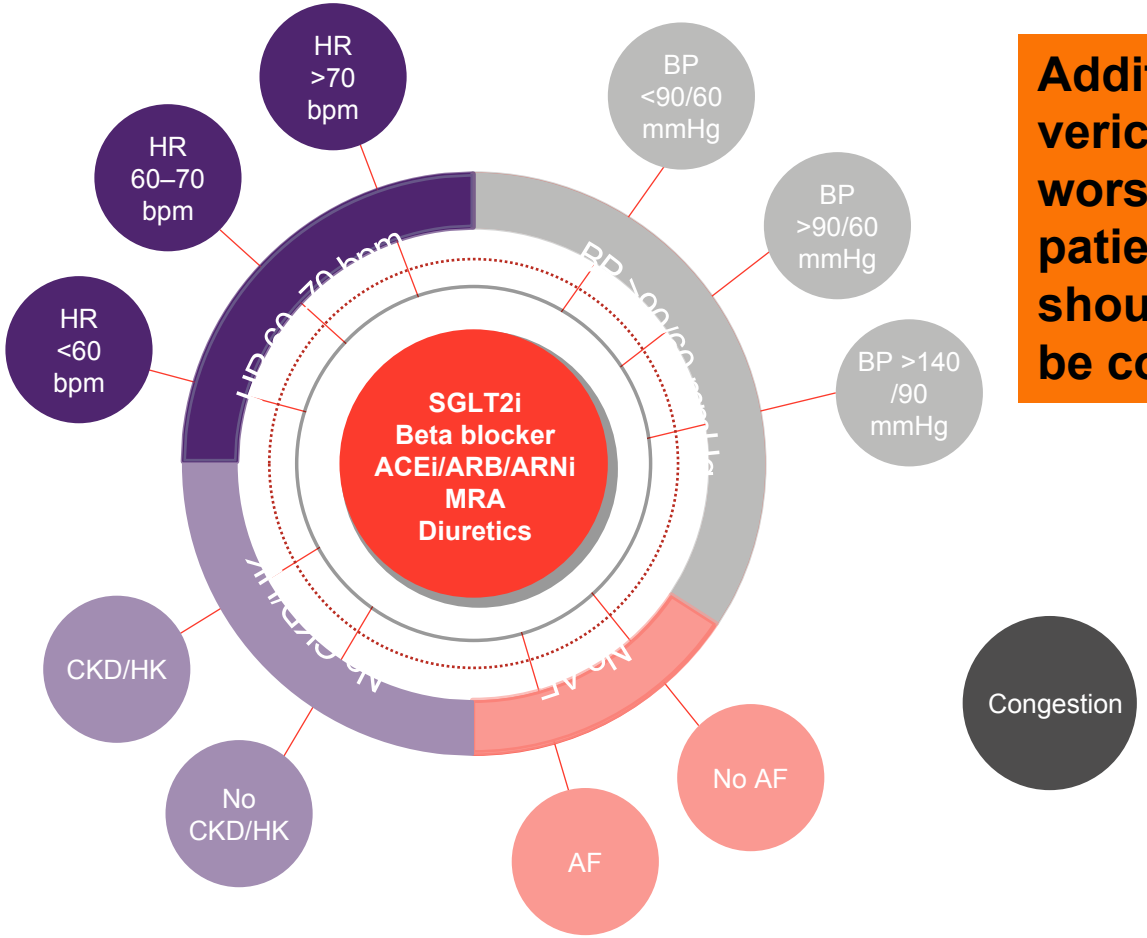
Guidelines **do not require the use of all foundational therapies** prior to vericiguat initiation

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; ESC, European Society of Cardiology; EU, European Union; HF, heart failure; HFH, heart failure hospitalization; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

**Reference: 1.** McDonagh TA *et al*. *Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

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

## HFA consensus document on patient profiling[1]




**Addition of vericiguat in worsening HF patients should <u>also</u> be considered**

**A range of patient characteristics may impact therapy decisions[1,2]**

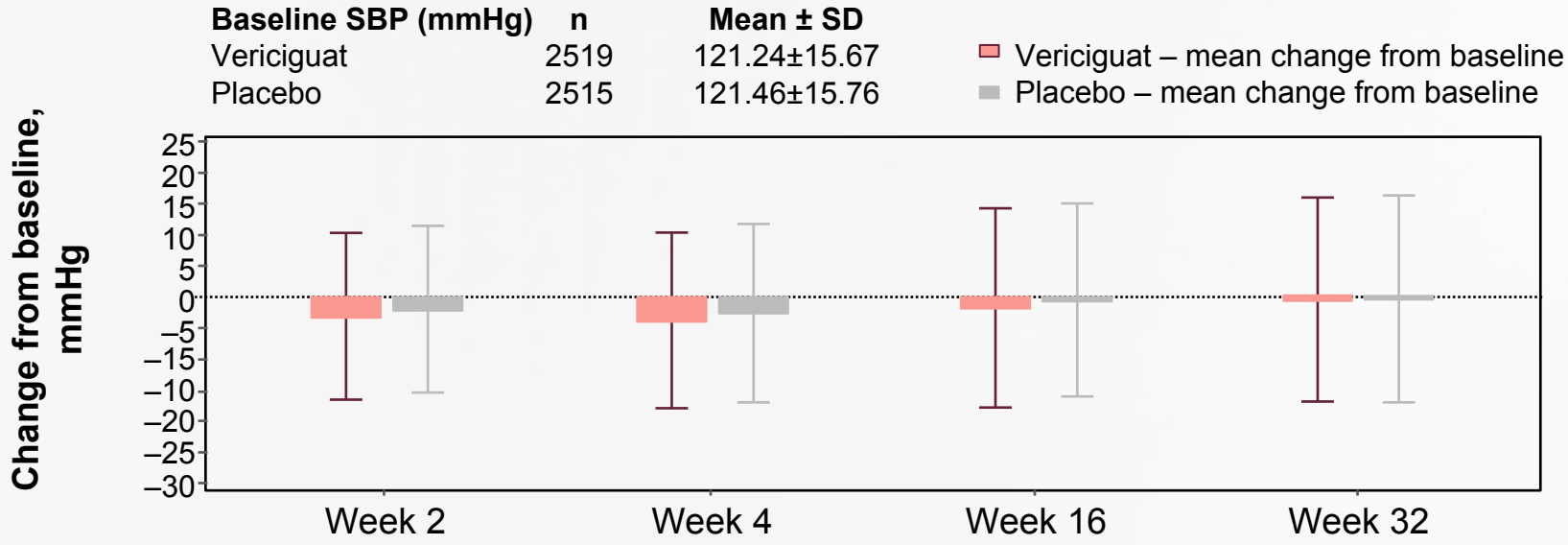
Blood pressure, heart rate, presence of atrial fibrillation, chronic kidney disease or hyperkalemia are **important characteristics when considering medical therapy in patients with HF**[1]

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; HF, heart failure; HFA, Heart Failure Association; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalemia; 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.

# Victoria: Mean SBP Values Between the Vericiguat and Placebo Arms

## 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 |

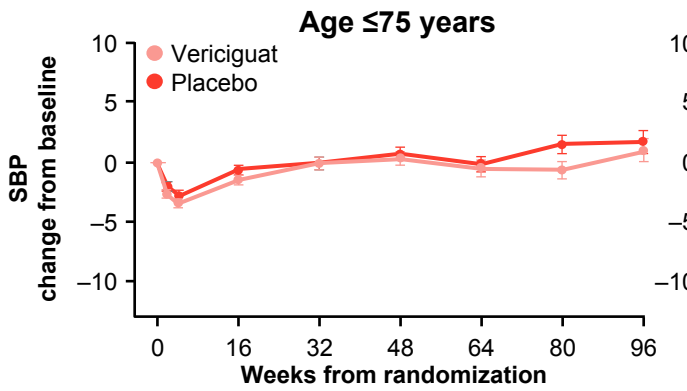
- Decreases in SBP occurred early in the titration phase
- No further clinically relevant reductions in BP were observed throughout the remainder of the study

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

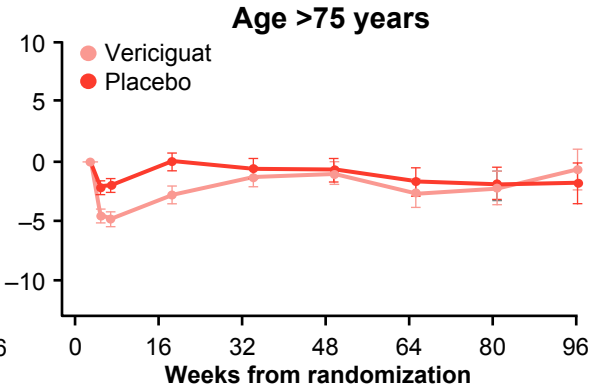
1. Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893.

# No Excessive Blood Pressure Reductions Were Observed with Vericiguat in Patients at Risk of Hypotension

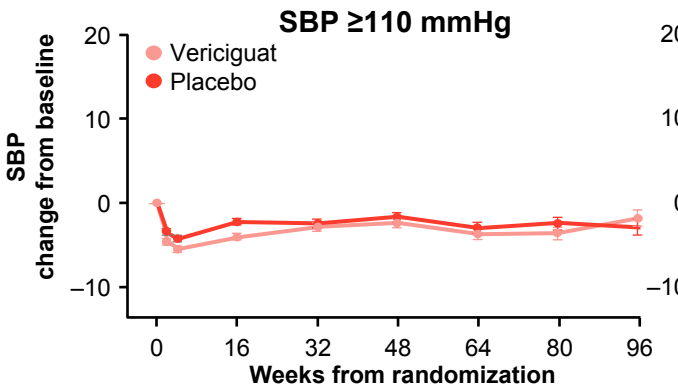
- Benefit of vericiguat *vs* placebo on the primary endpoint was similar across the spectrum of baseline SBP (p-int=0.32)



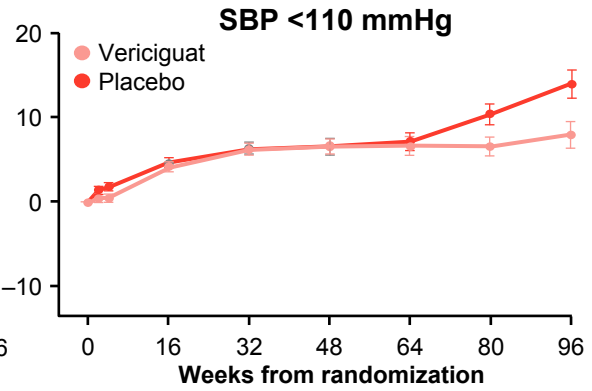

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 1818 | 1583 | 1301 | 939 | 679 | 511 | 343 |
| Placebo | 1821 | 1588 | 1293 | 920 | 672 | 502 | 326 |



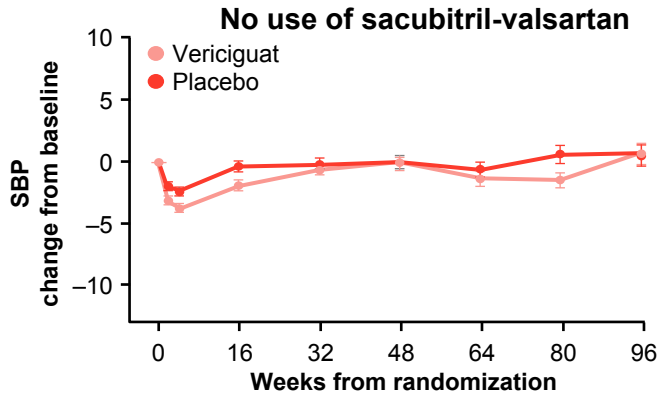

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 701 | 564 | 468 | 346 | 263 | 181 | 120 |
| Placebo | 694 | 585 | 481 | 358 | 252 | 184 | 126 |



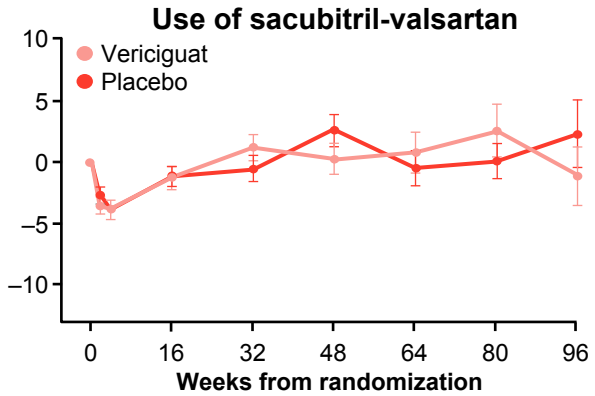

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 1828 | 1582 | 1313 | 971 | 721 | 527 | 356 |
| Placebo | 1862 | 1629 | 1350 | 990 | 717 | 530 | 358 |




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 691 | 565 | 456 | 314 | 221 | 165 | 107 |
| Placebo | 653 | 544 | 424 | 288 | 207 | 156 | 94 |




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 2160 | 1845 | 1536 | 1122 | 835 | 631 | 427 |
| Placebo | 2143 | 1849 | 1529 | 1126 | 819 | 619 | 411 |




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vericiguat | 359 | 302 | 233 | 163 | 107 | 61 | 36 |
| Placebo | 371 | 323 | 244 | 152 | 105 | 67 | 41 |

SBP, systolic blood pressure.

1. Lam CSP *et al.* ESC-HF. 2021

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

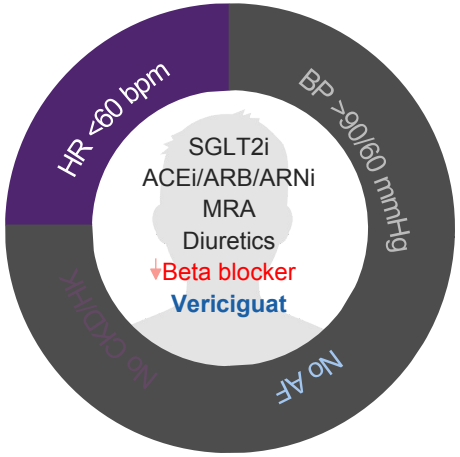
| Adverse event | eGFR ≤30 (ml/min/1.73 $m^2$) | | eGFR <30–≤60 (ml/min/1.73 $m^2$) | | eGFR >60 (ml/min/1.73 $m^2$) | | Overall |
|---|---|---|---|---|---|---|---|
| | Vericiguat (n=261) | Placebo (n=246) | Vericiguat (n=1060) | Placebo (n=1070) | Vericiguat (n=1153) | Placebo (n=1166) | N=4956 |
| 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.

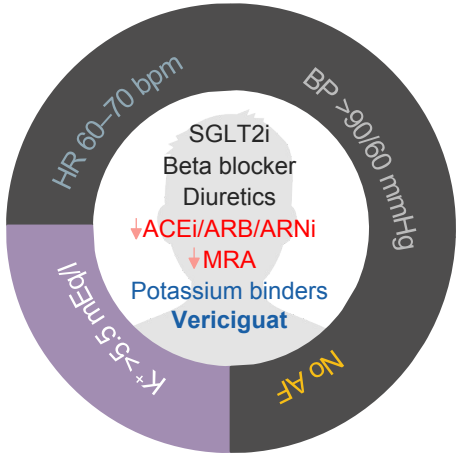
1. Voors AA *et al. Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2221.

# Tailored therapy with vericiguat is particularly recommended when foundational drugs are reduced, discontinued or not tolerated[1]

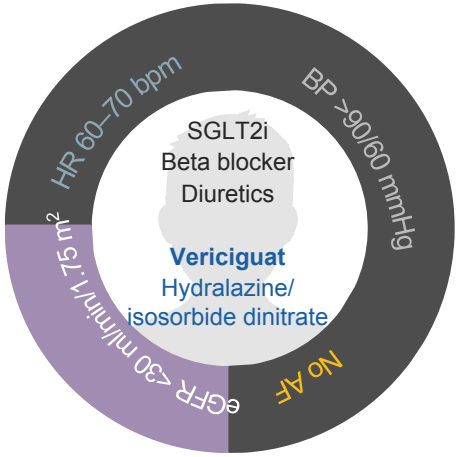
## Addition of vericiguat should be considered:



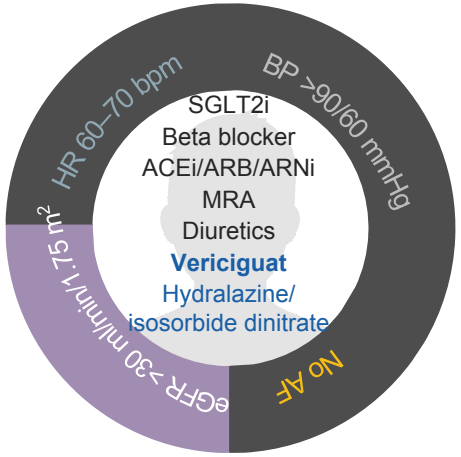

**HR <60 BPM**



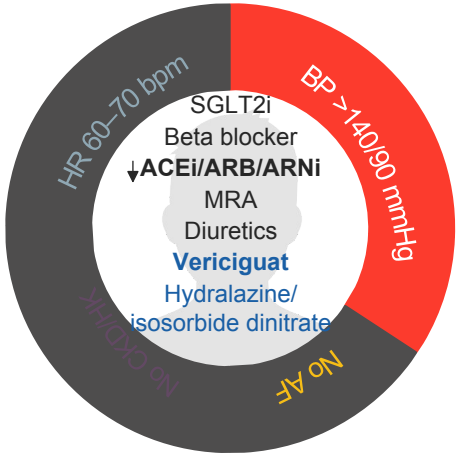

**K+ >5.5 mEq/L**




**eGFR <30 mL/min/1.73 m²**




**eGFR >30 mL/min/1.73 m²**




**BP <140/90 mmHg**

Black text, drugs that should be given to patients; red text, drugs that should be reduced or discontinued; blue text, drugs that should be added.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

**Reference: 1.** Rosano GMC *et al*. *Eur J Heart Fail* 2021; https://doi.org/10.1002/ejhf.2206.

# Conclusions

- **A Personalized Approach in the management of HF patients is reccomended by 2021 ESC Guidelines to address a strong unmet medical need**

- **Thanks to its peculiar MoA, Vericiguat can be safely added to all the existing treatments acting in a synergistic and complementary way**

- **Vericiguat is the only approved treatment tested in HF patients after recent hospitalization regardeless the background therapy**