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## TERAPIA MEDICA OTTIMIZZATA NELLO SCOMPENSO CARDIACO

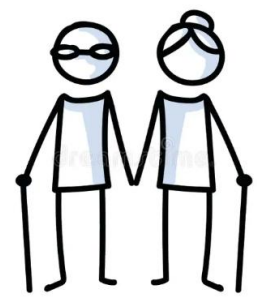
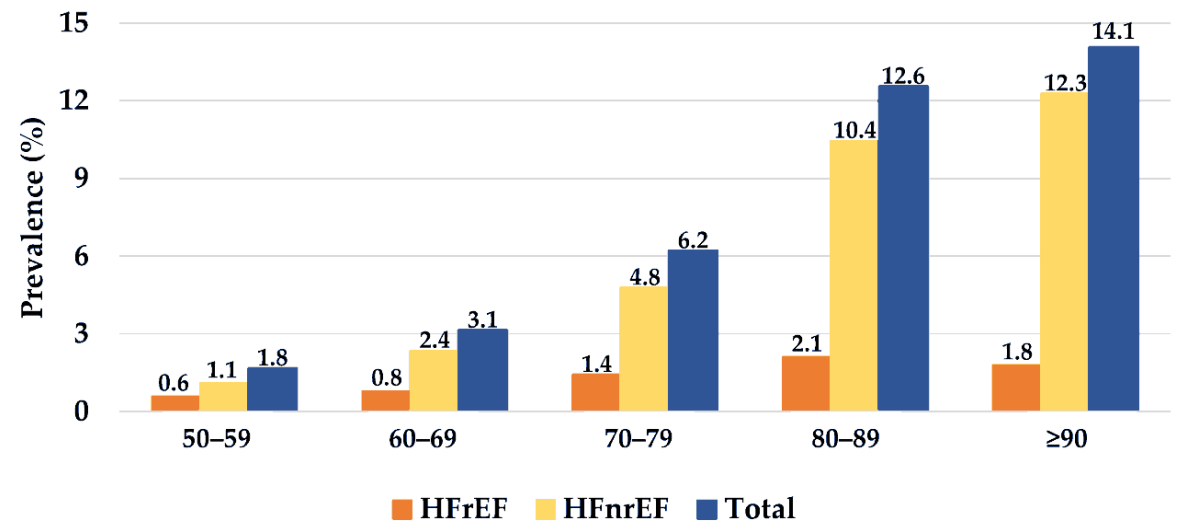
# Vericiguat: non solo worsening HF

Domenico Acanfora

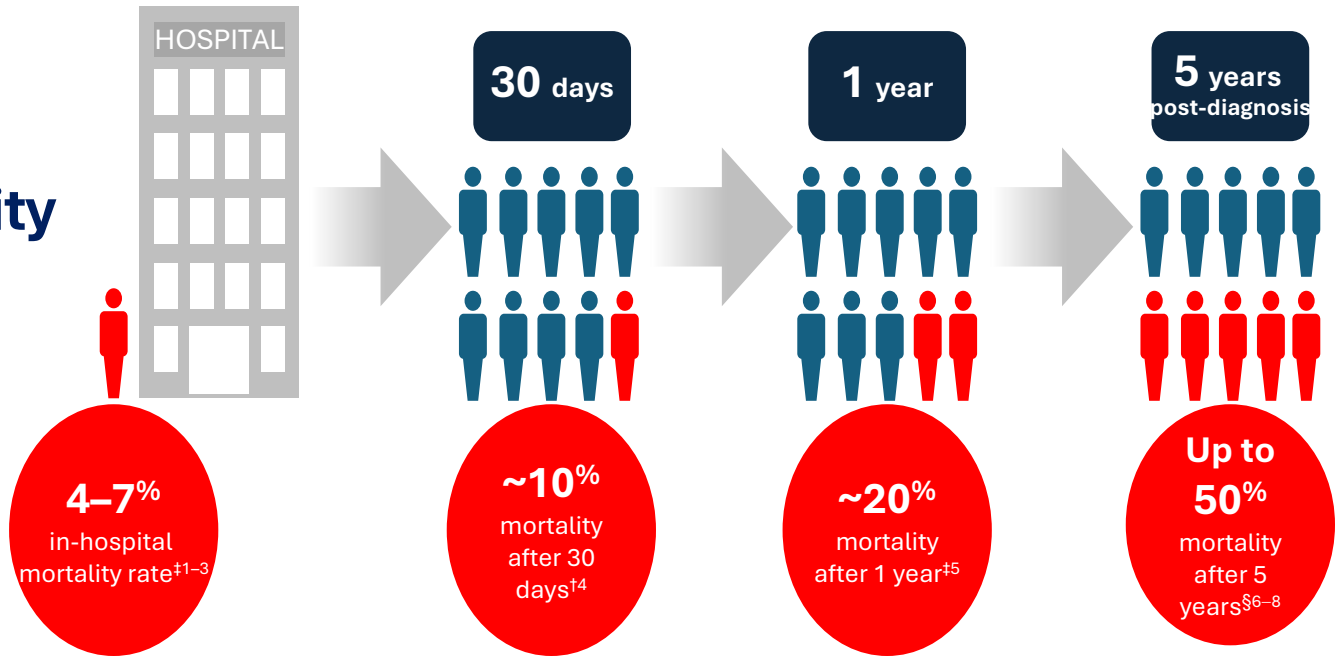


Il Dottor Domenico Acanfora dichiara che non sussistono conflitti di interesse tra la sua persona e le aziende sponsor dell'evento, così come richiesto dall'art. 48, comma 25, del D.L. 269/2003, convertito in Legge n. 326 del 25 novembre 2003

# HF is a major and growing public health problem



## HF is associated with significant mortality



1. Dickstein et al. Eur Heart J 2008;29:2388-442; 2. Go et al. Circulation 2013;127:e6-e245; 3. Allender et al. Coronary Heart Disease Statistics 2008; 4. Hung et al. Hong Kong Med J 2000;6:159-62; 5. Hunt et al. J Am Coll Cardiol 2009;53:e1-90; 6. Kearney et al. Lancet 2005; 365:217-23



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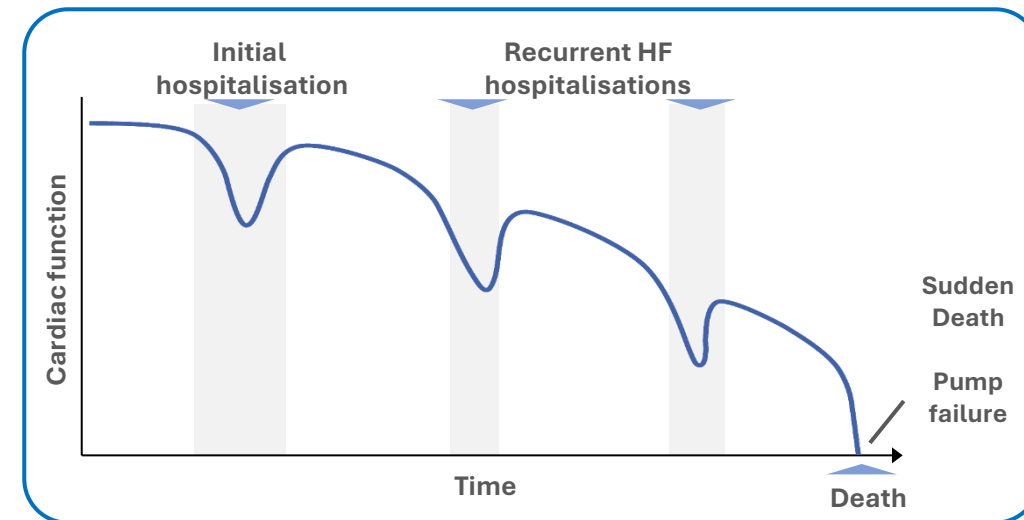
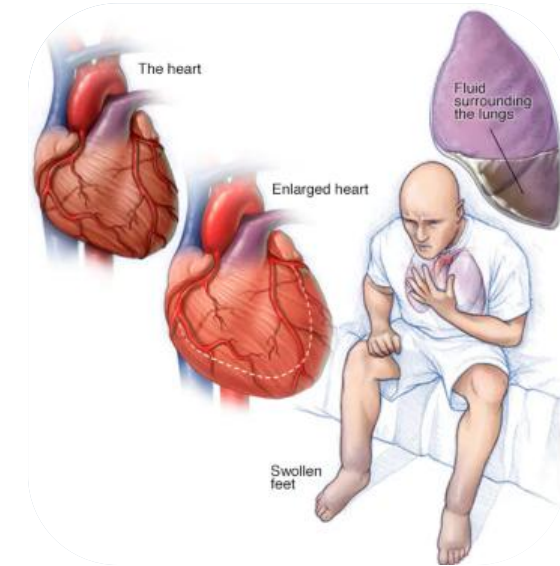
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# Heart failure definition

- **ESC<sup>1</sup>:** Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.<sup>1</sup>
- **ACCF/AHA<sup>2</sup>:** HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.<sup>2</sup>
- **JCS/JHFS<sup>3</sup>:** HF is a clinical syndrome consisting of dyspnoea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart.



# Universal definition and classification of HF report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society.



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## HF with reduced EF (HFrEF):

- HF with LVEF  $\leq 40\%$

## HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41–49%

## HF with preserved EF (HFpEF):

- HF with LVEF  $\geq 50\%$

## HF with improved EF (HFimpEF):

- HF with a baseline LVEF  $\leq 40\%$ , a  $\geq 10$  point increase from baseline LVEF, and a second measurement of LVEF  $> 40\%$

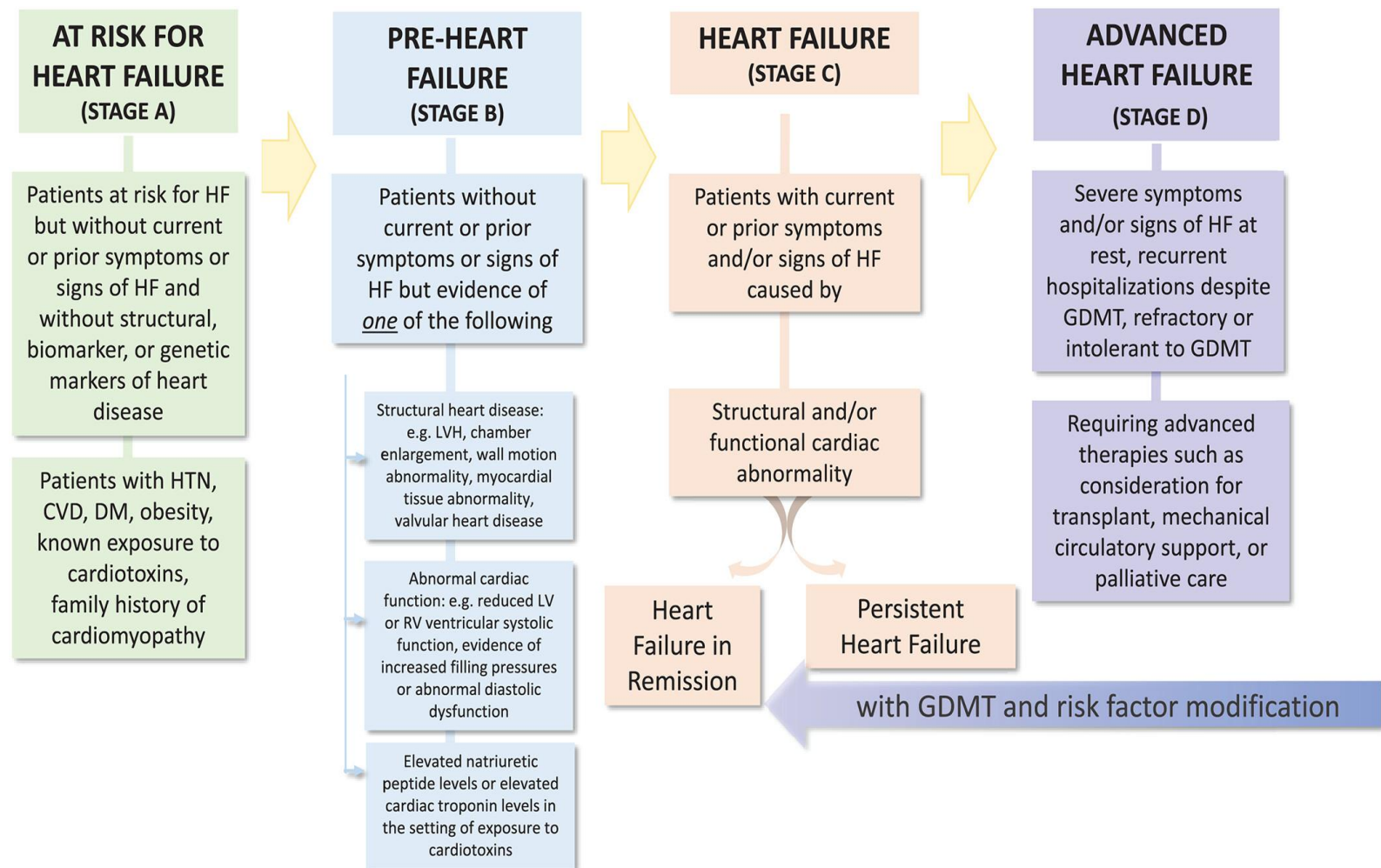
# Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure



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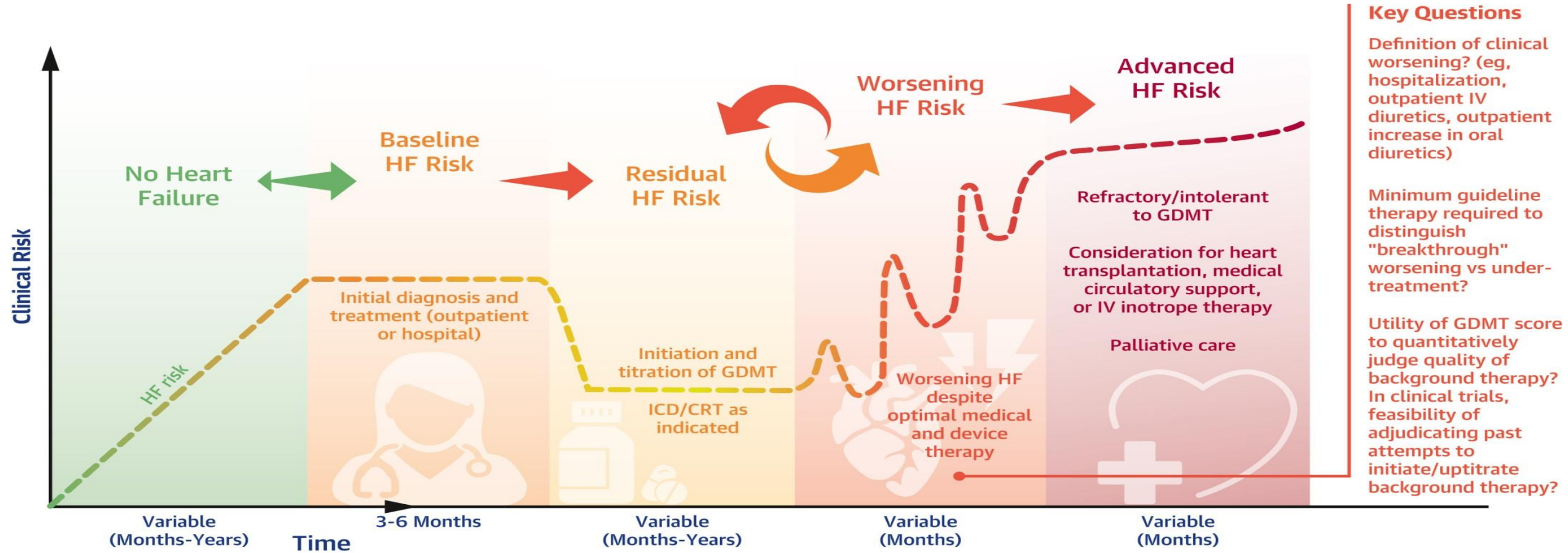
# Progression of HF Clinical Risk Over Time



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# Potential Approaches to Background Drug Therapy for Heart Failure Patients

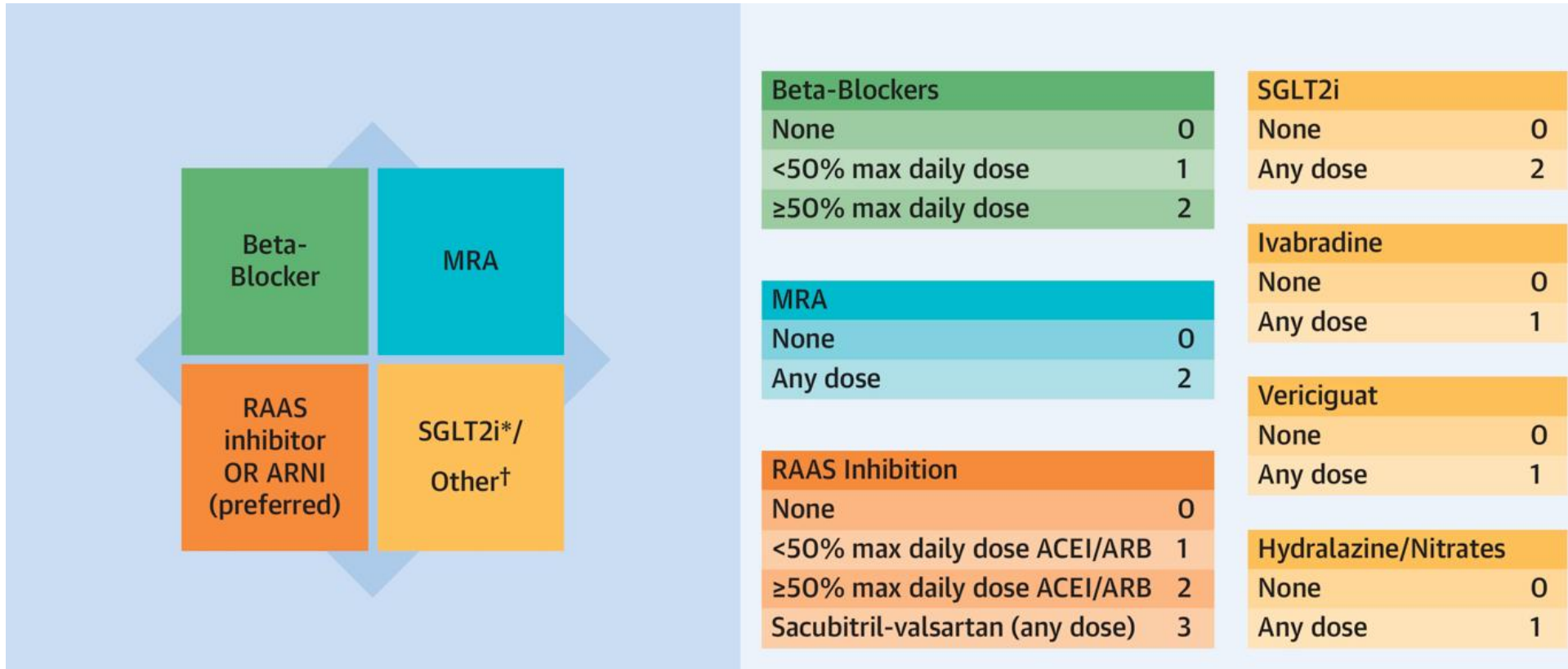


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- A. Sub-optimal: score <3, or no heart failure-specific beta-adrenergic antagonist or no ACE inhibitor, ARB, or ARNI, without documented intolerance to these agents.
- B. Acceptable: score = 3–4 if treated with a heart failure-specific beta-adrenergic antagonist and an ACE inhibitor, ARB, or ARNI, unless the patient has a documented intolerance to these agents.
- C. Optimal: score ≥5 if treated with a heart failure-specific beta-adrenergic antagonist and an ACE inhibitor, ARB, or ARNI, unless the patient has a documented intolerance to these agents.

# Trajectory of heart failure (HF) and goals of treatment in HF stages.

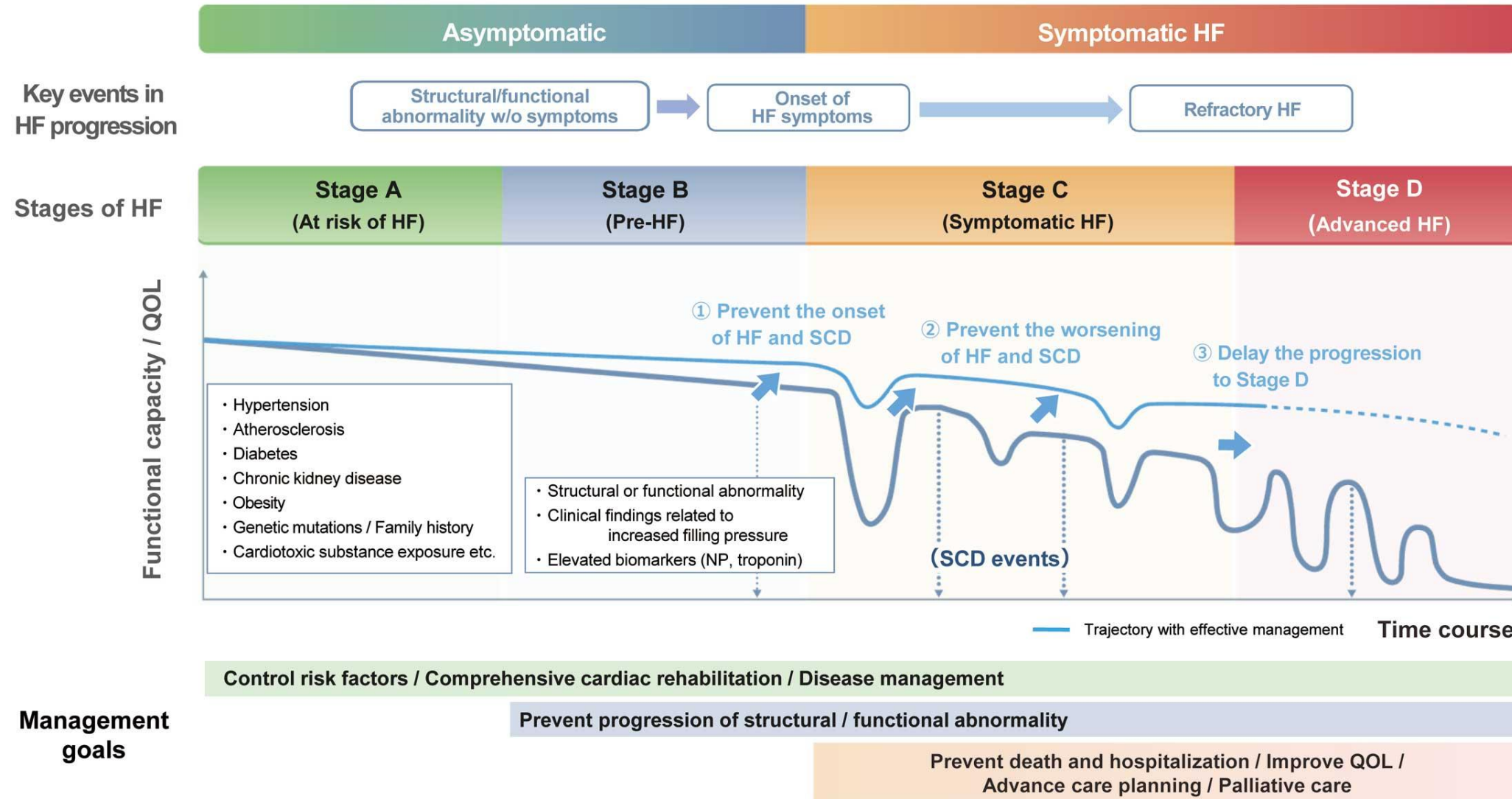


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# Overview of heart failure therapy

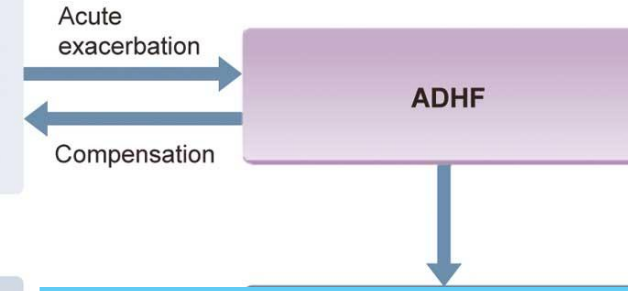
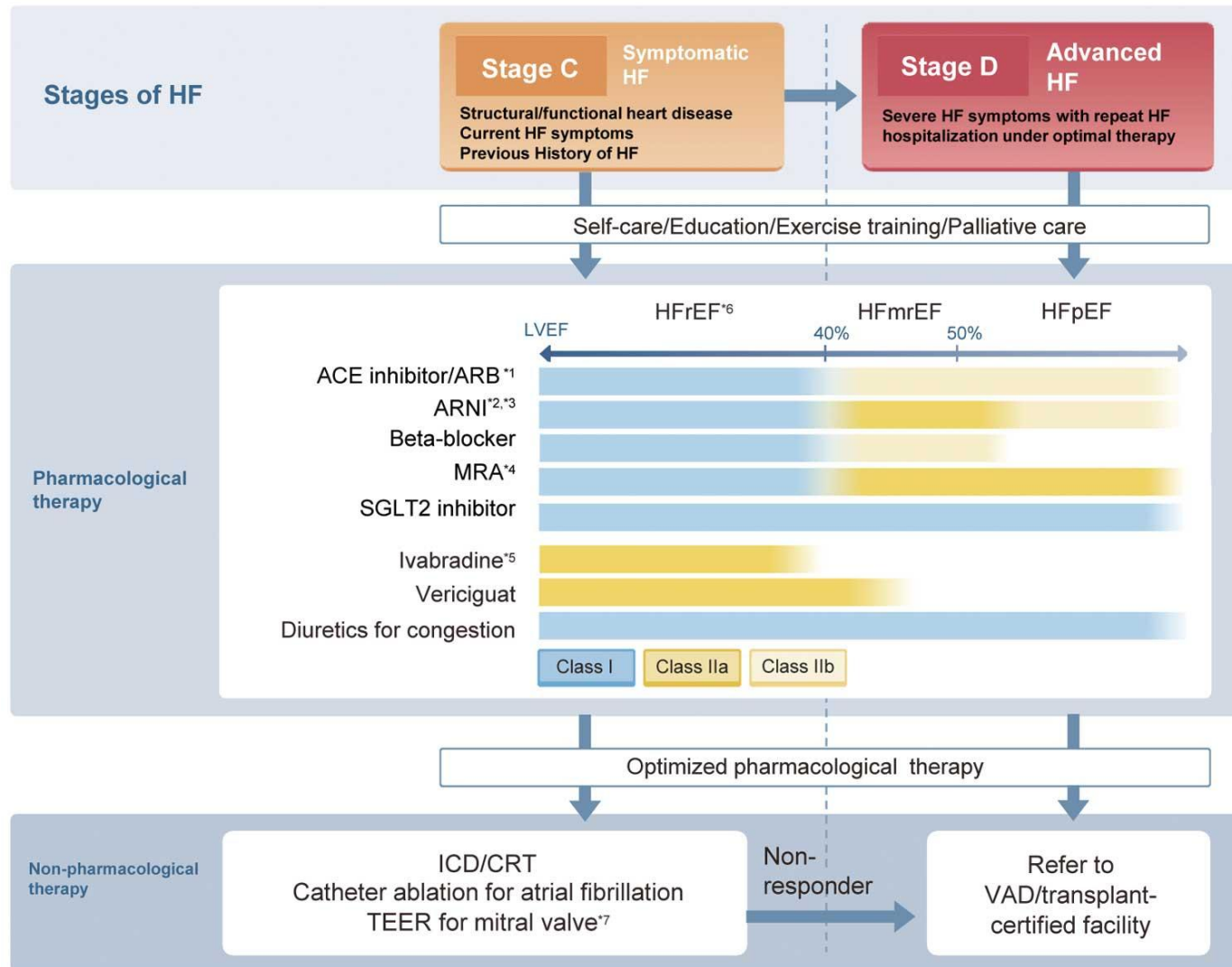


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**•Rapid infusion of normal saline or Ringer's solution (≥200 mL over 15–30 min) can be considered in patients without evidence of fluid overload.**

**•Administration of inotropic agents can be considered to maintain cardiac output and tissue perfusion.**

**•Short-term use of mechanical circulatory support can be considered, taking into account the patient's age, cognitive function, comorbidities, and social factors.**

- \*1 In HFpEF, ARBs have class IIb recommendation
- \*2 Consider switching from ACE inhibitors or ARBs
- \*3 First choice for hospitalized HF without ACE inhibitors or ARBs
- \*4 In HFmrEF and HFpEF, finerenone is class Iia recommendation, and spironolactone and eplerenone are class IIb recommendation
- \*5 For sinus rhythm with >75 beats/min
- \*6 Continue GDMT for HFrEF in HFimpEF
- \*7 Functional severe MR with LVEF ≥20%

# Vericiguat, a novel soluble guanylate cyclase (sGC) stimulator.



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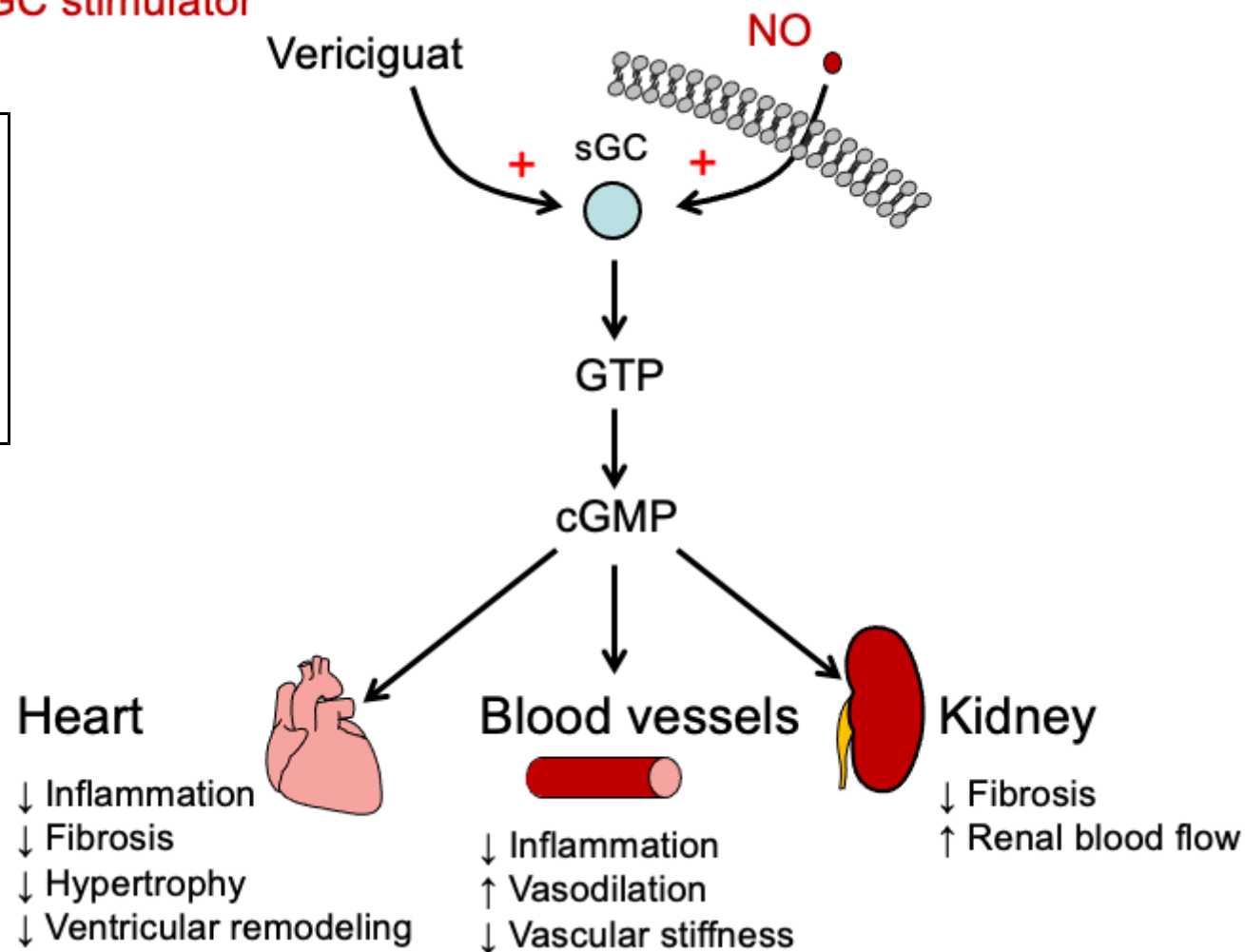
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**HF Pathophysiology**  
Oxidative stress  
Endothelial dysfunction  
Decrease NO  
Decreased sGC activity

sGC stimulator



# The benefit of vericiguat following a recent worsening HF event was studied in the VICTORIA trial<sup>1,2</sup>



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VICTORIA<sup>HF</sup>

## Study population<sup>1</sup>

### Symptomatic chronic HFrEF

- NYHA Class II–IV
- LVEF <45%
- On available SoC therapy

### After a worsening HF event

- Recent HF decompensation
- Elevated natriuretic peptides\*

## Study drug initiation

- Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability<sup>#1,2</sup>
- There was no run-in period<sup>1</sup>



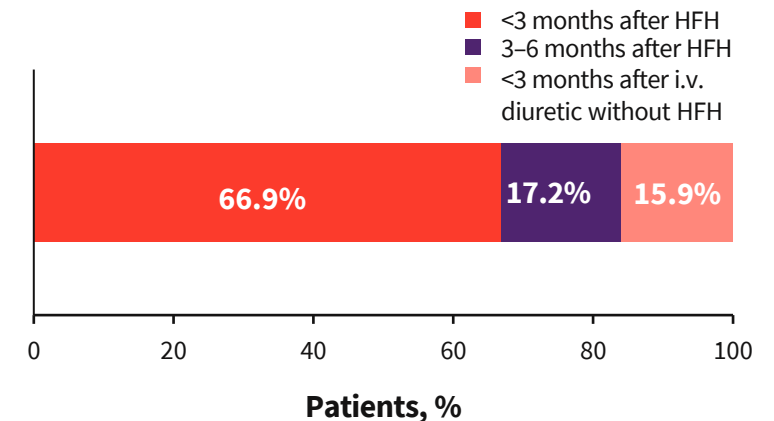
## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

### Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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

### Patients with recent HF decompensation<sup>1</sup>



# In VICTORIA, vericiguat demonstrated a favorable safety profile and a significant reduction in CV death or first HFH vs placebo<sup>1</sup>



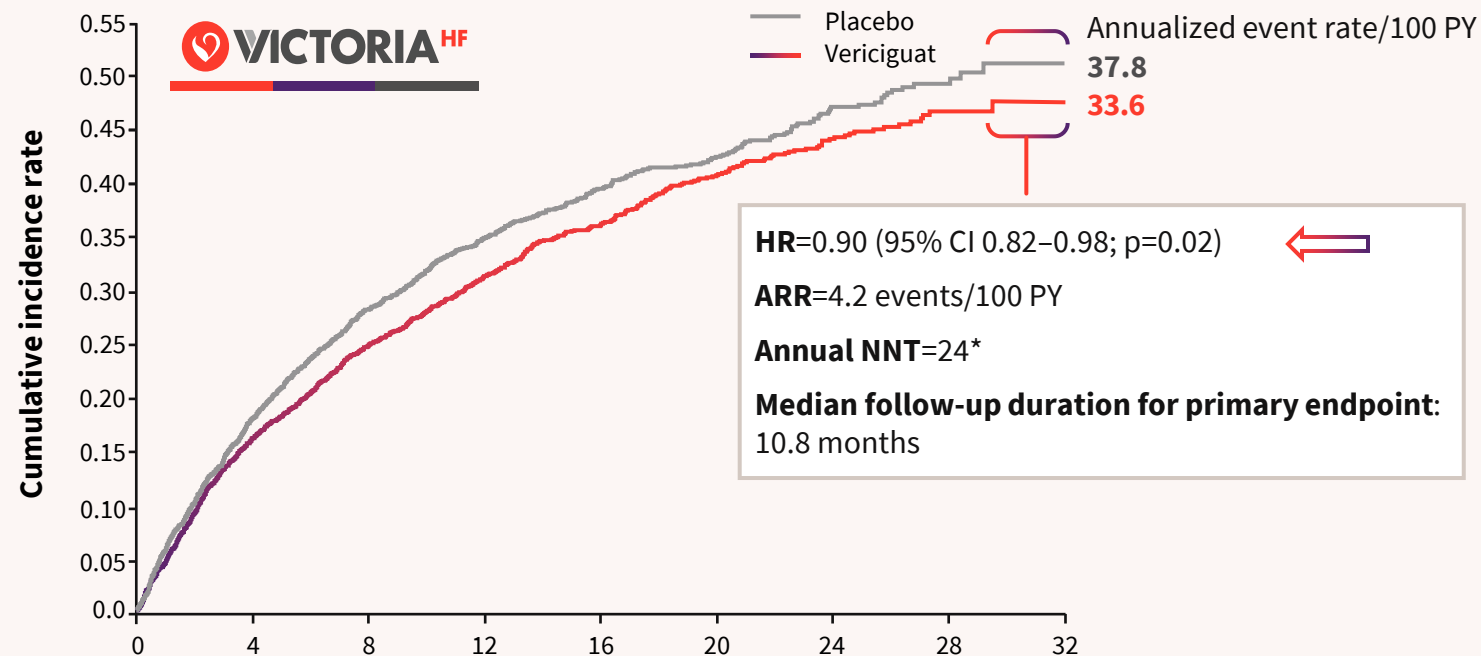
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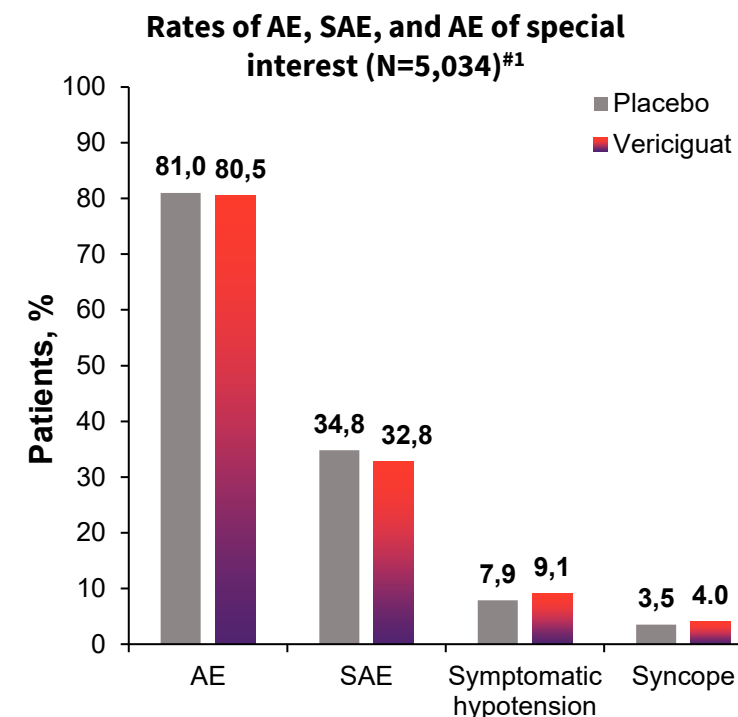


## Composite primary endpoint of time to CV death or first HFH<sup>1</sup>



	Number of patients at risk								
	Months since randomization								
	0	4	8	12	16	20	24	28	32
<b>Vericiguat</b>	2,526	2,099	1,621	1,154	826	577	348	125	1
<b>Placebo</b>	2,524	2,053	1,555	1,097	772	559	324	110	0

## Vericiguat was generally well tolerated with a similar safety profile to placebo<sup>1,2</sup>



The benefit of vericiguat on reducing CV death or first HFH was consistent across the full range of eGFR and irrespective of baseline SBP<sup>‡§3,4</sup>

Adapted from Armstrong PW *et al.* 2020.<sup>1</sup>

\* Calculation for annual NNT: 100/4.2=24. # The most frequently reported adverse reaction under treatment with vericiguat was hypotension (16.4%).<sup>‡</sup> Treatment should not be initiated in patients with SBP <100 mmHg.<sup>§</sup> Vericiguat is not recommended in patients with eGFR <15 ml/min/1.73 m<sup>2</sup> at treatment initiation or on dialysis.<sup>‡</sup> AE, adverse event; ARR, absolute rate reduction; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; NNT, number needed to treat; PY, patient-years; SAE, serious adverse event.

Reference: 1. Armstrong PW *et al.* *N Engl J Med* 2020;382:1883-1893; 2. Armstrong PW *et al.* *N Engl J Med* 2020;382(suppl 1-45):1883-1893; 3. Lam CSP *et al.* *J Am Heart Assoc* 2021;10:e021094; 4. Voors AA *et al.* *Eur J Heart Fail* 2021;23:1313-1321.

# Evidence generation in ambulatory patients with HFrEF and no recent worsening HF<sup>1</sup>



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Phase 3, double-blind, placebo-controlled, 1:1 randomized, event-driven trial<sup>1</sup>

## Composite primary endpoint<sup>1</sup>

Time to first occurrence of HFH or CV death

## Key secondary endpoint\*<sup>1</sup>

Time to CV death

## Key eligibility criteria<sup>1</sup>

- LVEF  $\leq 40\%$  within 12 months
- NYHA class II–IV on GDMT
- No HFH within 6 months or outpatient i.v. diuretic use within 3 months
- NT-proBNP level within 30 days
  - SR: 600–6,000 pg/ml; AF: 900–6,000 pg/ml
- eGFR  $\geq 15$  ml/min/1.73 m<sup>2</sup> and not on chronic dialysis



Follow-up continued until target number of CV death events was reached (n=590)

## Sample size<sup>#1</sup>

- Provision of  $\sim 95\%$  power for the composite primary endpoint
- Designed and powered for CV death

\* Additional secondary efficacy endpoints included time to: first HFH, total HFH (first and recurrent) HFH, first HFH or all-cause death and all-cause death.<sup>1</sup> # Assuming a hazard ratio of 0.80.<sup>1</sup> ‡ Titration schedule identical to VICTORIA.<sup>4</sup> AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IC, insuficiencia cardíaca; IC-FEr, insuficiencia cardíaca con fracción de eyección reducida; i.v., intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; od, once daily; q24w, every 24 weeks; SR, sinus rhythm.

References: 1. Reddy YNV et al. *Eur J Heart Fail* 2025;27:209–218; 2. Saldarriaga CI et al. *Eur J Heart Fail* 2025; <https://doi.org/10.1002/ejhf.3598>; 3. Armstrong PW et al. *N Engl J Med* 2020;382:1883–1893.

# VICTOR baseline characteristics align with chronic populations enrolled in other contemporary HFrEF trials<sup>1</sup>



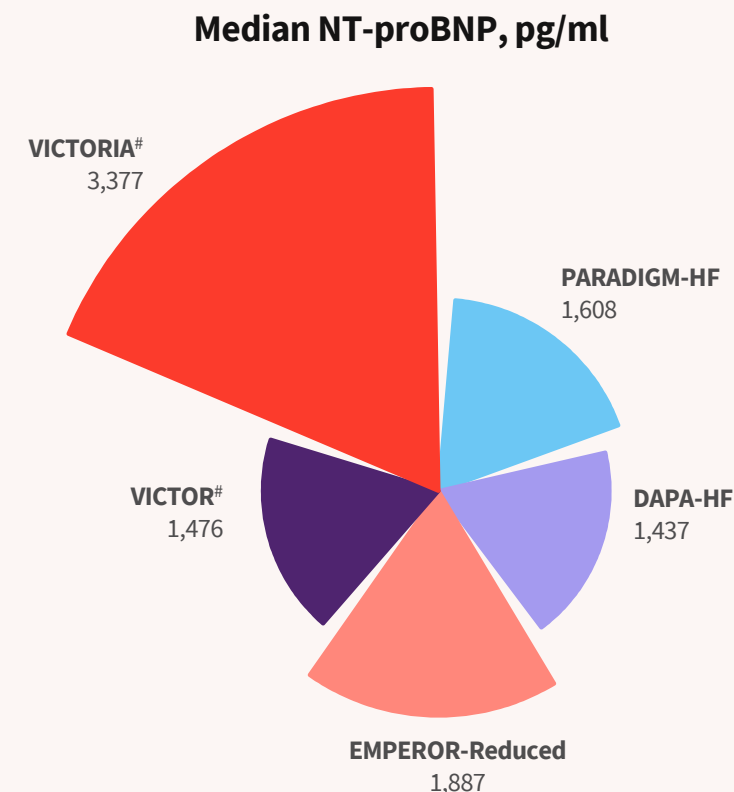
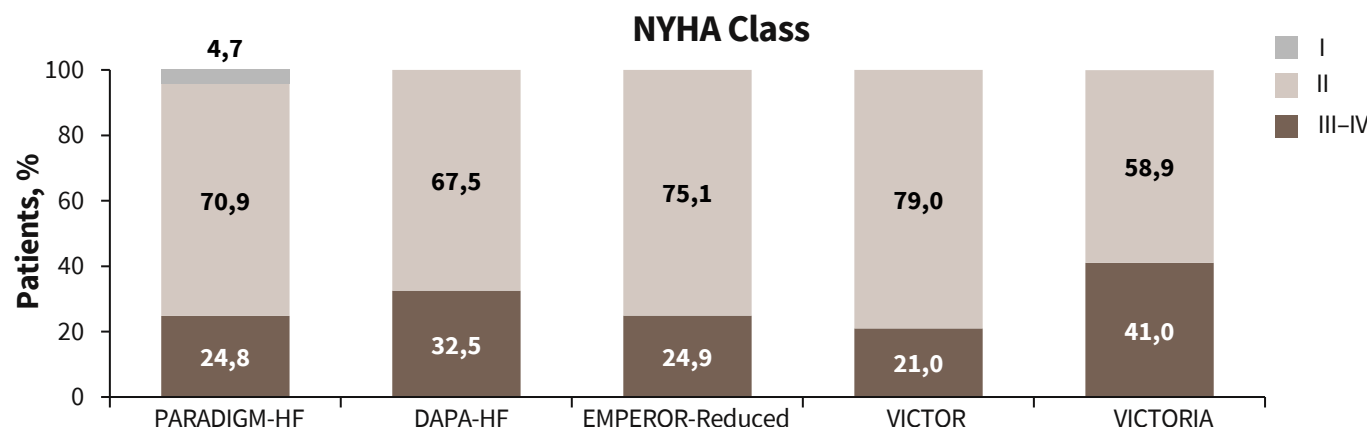
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Baseline characteristic	PARADIGM-HF	DAPA-HF	EMPEROR-Reduced	VICTOR	VICTORIA
Patients randomized, n	8,442	4,744	3,730	6,105	5,050
Mean age, years ± SD	63.8 ± 11.4	66.4 ± 11.0	66.9 ± 11.0	67.0 ± 11.0	67.3 ± 12.2
Female, %	22.0	23.4	23.9	23.6	23.9
No prior HFH, %	37.8	52.6	69.0	47.5	N/A*
<b>Mean laboratory values ± SD</b>					
LVEF, %	29.5 ± 6.2	31.1 ± 6.8	27.5 ± 6.1	30.4 ± 7.0	28.9 ± 8.3
eGFR, ml/min/1.73 m <sup>2</sup>	70.0 ± 20	65.8 ± 19.4	62.0 ± 21.6	70.9 ± 24.0	61.5 ± 27.2



In VICTORIA, the high median NT-ProBNP level of 3,377 pg/ml was indicative of a high-risk population

\* Each HF study was independently conducted; no head-to-head HF studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug vs another.

\* All patients enrolled in VICTORIA had either a HFH ≤6 months or an urgent HF visit <3 months of randomization. # At screening visit. eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N/A, not applicable; NT-proBNP, N-terminal pro-B-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Reference: 1. Saldarriaga CI, et al. *E J Heart Fail* 2025. doi: 10.1002/ejhf.3598.

# Primary composite endpoint

## Time to first HFH or CV death<sup>1</sup>



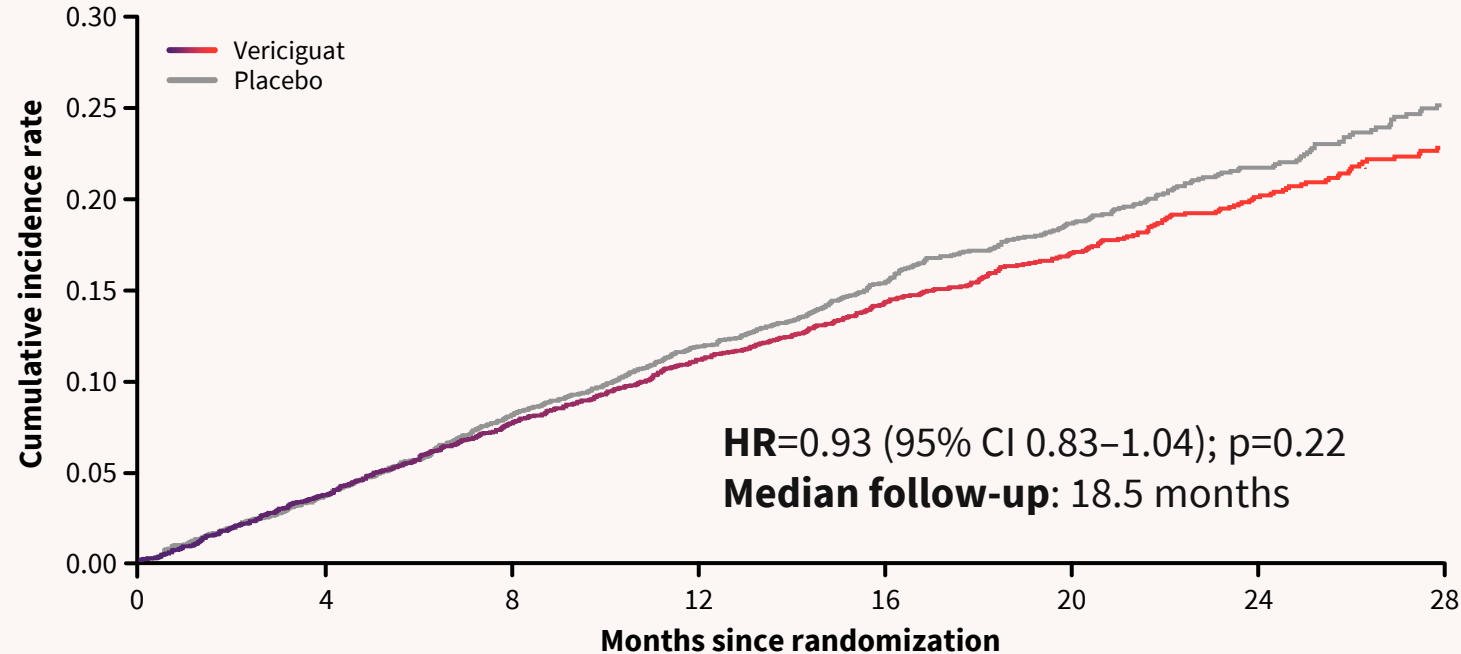
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### Time to first HFH or CV death



#### Number of patients at risk

	0	4	8	12	16	20	24	28
<b>Vericiguat</b>	3,053	2,927	2,797	2,581	1,917	1,352	849	459
<b>Placebo</b>	3,052	2,929	2,771	2,543	1,879	1,314	823	442

Extracted from Butler J *et al.* 2025.<sup>1</sup>

CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-Fer, insuficiencia cardíaca con fracción de eyección reducida.

References: 1. Presented at ESC 2025, publication accepted. Butler J *et al.* *Lancet* Sept 2025;

# Secondary endpoints

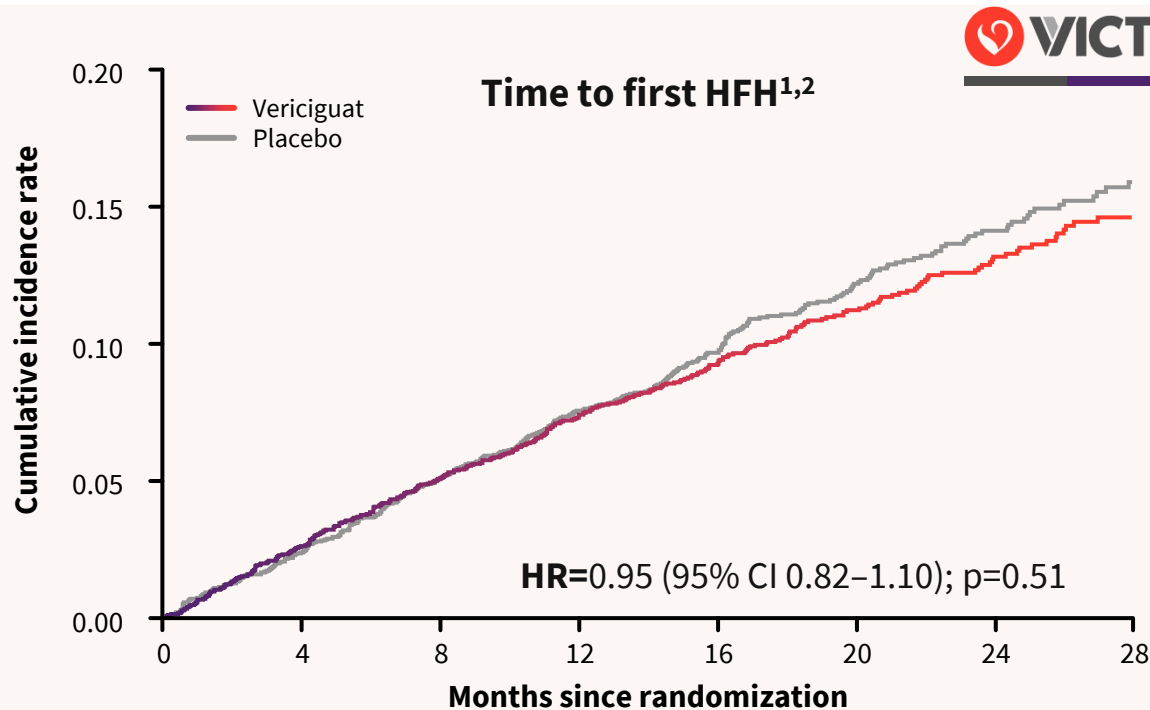
## Time to first HFH or CV death<sup>1</sup>



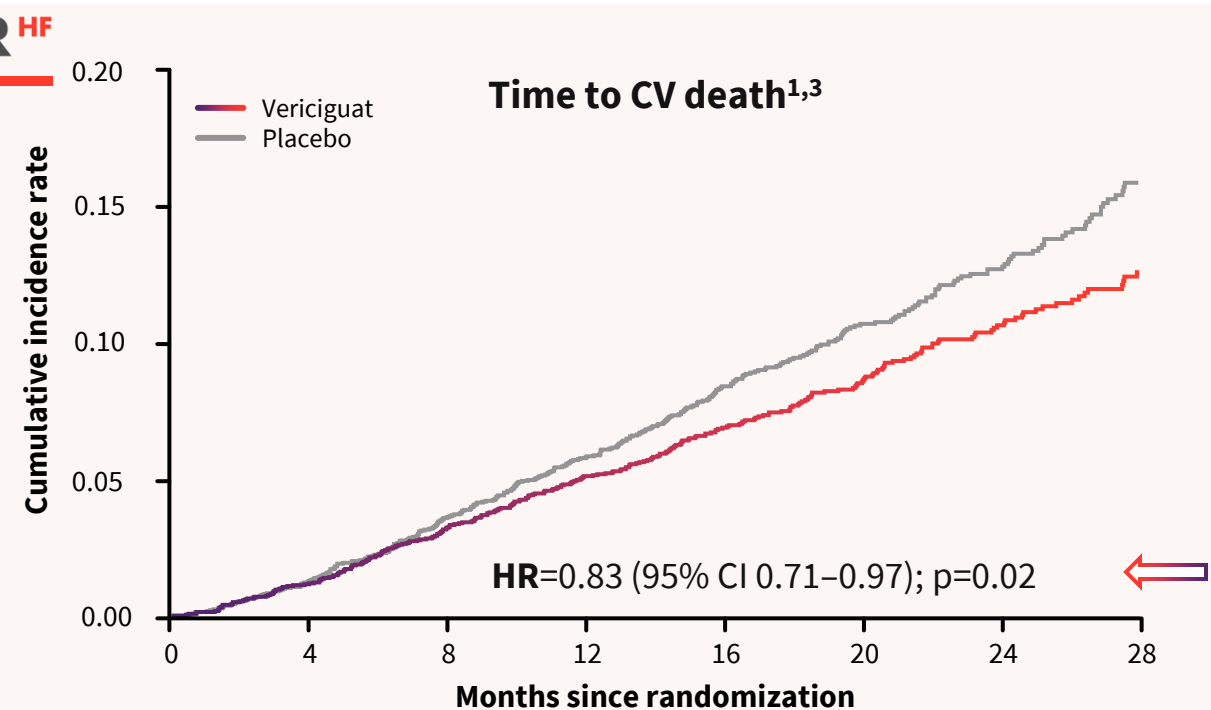
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<b>Placebo</b>	3,052	2,929	2,771	2,543	1,879	1,313	822	442	



Number of patients at risk		0	4	8	12	16	20	24	28
<b>Vericiguat</b>	3,053	3,000	2,928	2,752	2,092	1,516	968	536	
<b>Placebo</b>	3,052	3,003	2,910	2,728	2,050	1,456	940	514	

VICTOR was designed and powered to test whether vericiguat could reduce the risk of CV death vs placebo, as a key secondary endpoint<sup>\*4</sup>

Figures extracted from Zannad F *et al.* 2025 and Butler J *et al.* 2025<sup>2,3</sup>

Analyses were not part of a trial hypothesis testing per prespecified hierarchical testing approach.<sup>1-4</sup> \* Conditional of a positive primary outcome.<sup>4</sup> CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-FER, insuficiencia cardíaca con fracción de eyección reducida. **References:** 1. Presented at ESC 2025, publication accepted. Butler J *et al.* *Lancet* Sept 2025; 2. Presented at ESC 2025, publication accepted. Zannad F *et al.* *J Am Coll Cardiol* 2025; 3. Presented at ESC 2025, publication accepted. Butler J *et al.* *Eur Heart J* Sept 2025; <https://doi.org/10.1093/eurheartj/ehaf665>; 4. Reddy YNV *et al.* *Eur J Heart Fail* 2025;27:209-218;

# Secondary endpoint

## All-cause mortality<sup>1</sup>



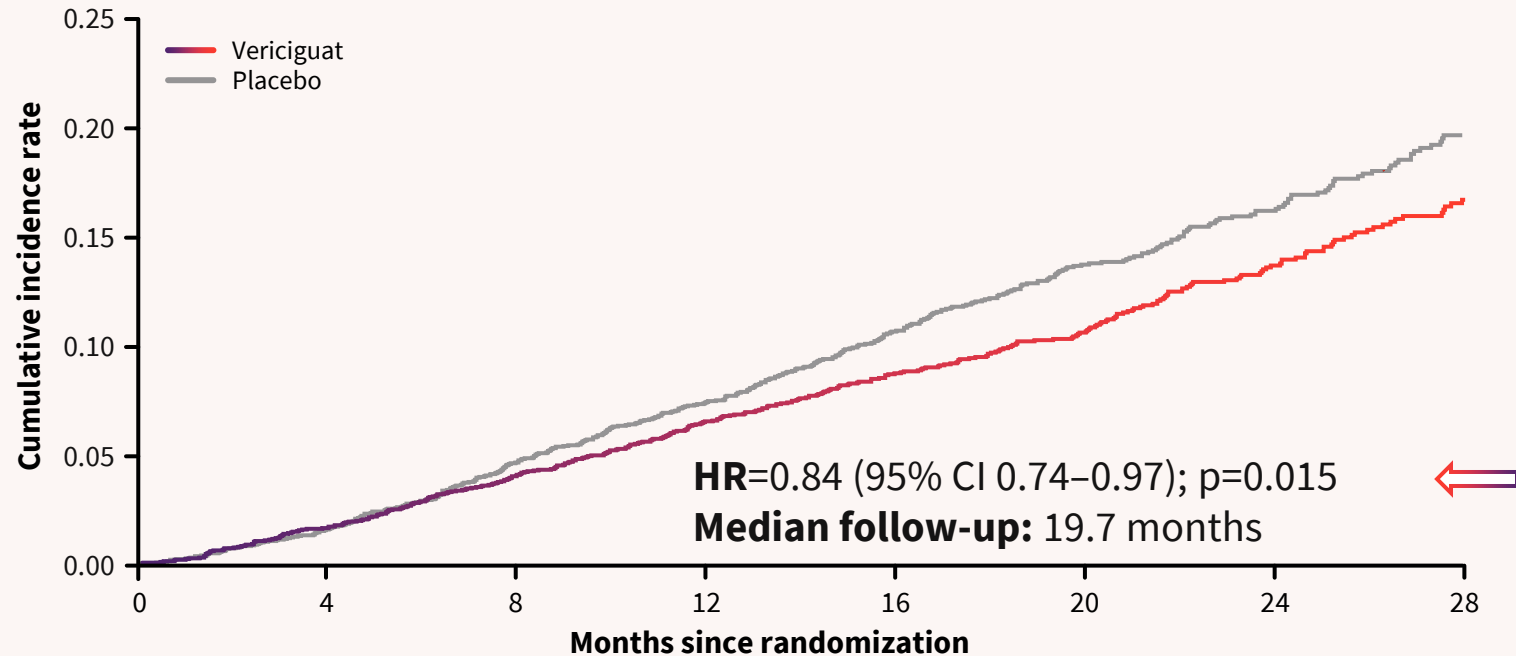
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### Time to all-cause mortality<sup>1,2</sup>



#### Number of patients at risk

	0	4	8	12	16	20	24	28
<b>Vericiguat</b>	3,053	3,000	2,928	2,752	2,092	1,516	896	536
<b>Placebo</b>	3,052	3,003	2,910	2,728	2,050	1,456	940	514

Extracted from Butler *J et al.* 2025.<sup>1</sup>

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CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-Fer, insuficiencia cardíaca con fracción de eyección reducida.

**References:** **1.** Presented at ESC 2025, publication accepted. Butler *J et al. Lancet* Sept 2025; **2.** Presented at ESC 2025, publication accepted. Butler *J et al. Eur Heart J* Sept 2025; <https://doi.org/10.1093/eurheartj/ehaf665>;

**3.** Reddy YNV *et al. Eur J Heart Fail* 2025;27:209-218.

# Post hoc analyses

## Time to sudden cardiac death and HF-related death<sup>1</sup>



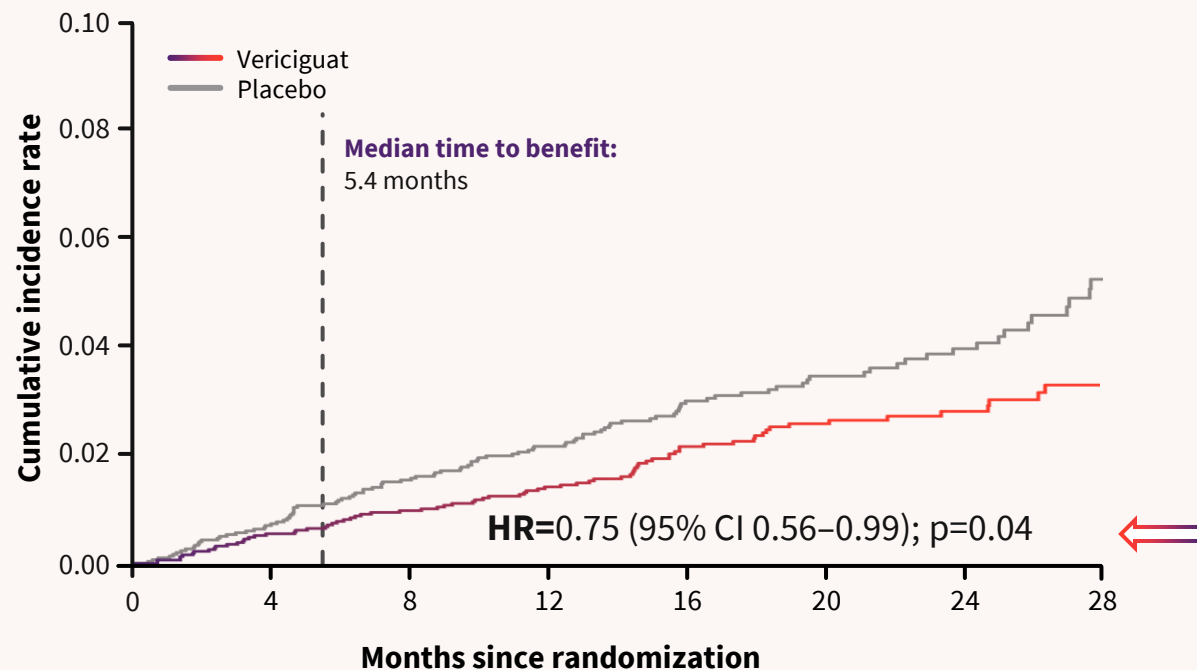
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### Time to sudden cardiac death<sup>1,2</sup>

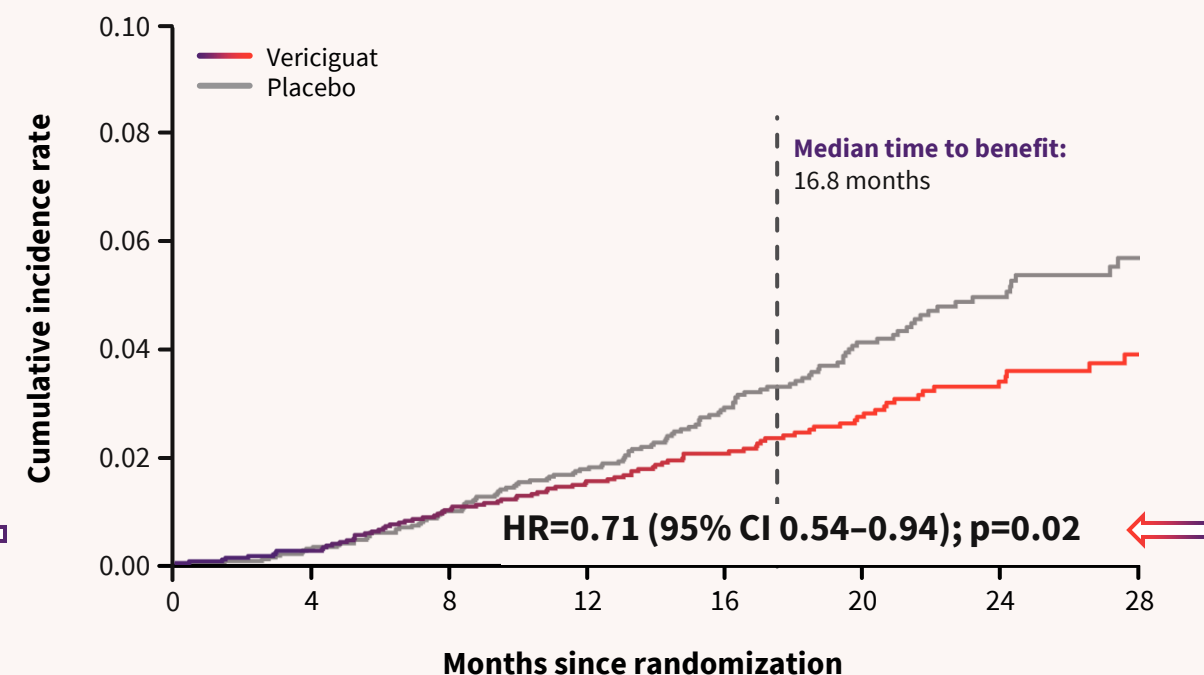


Number of patients at risk

<b>Vericiguat</b>	3,053	3,000	2,928	2,752	2,092	1,516	968	536
<b>Placebo</b>	3,052	3,003	2,910	2,728	2,050	1,456	940	514



### Time to HF-related death<sup>1,2</sup>



Number of patients at risk

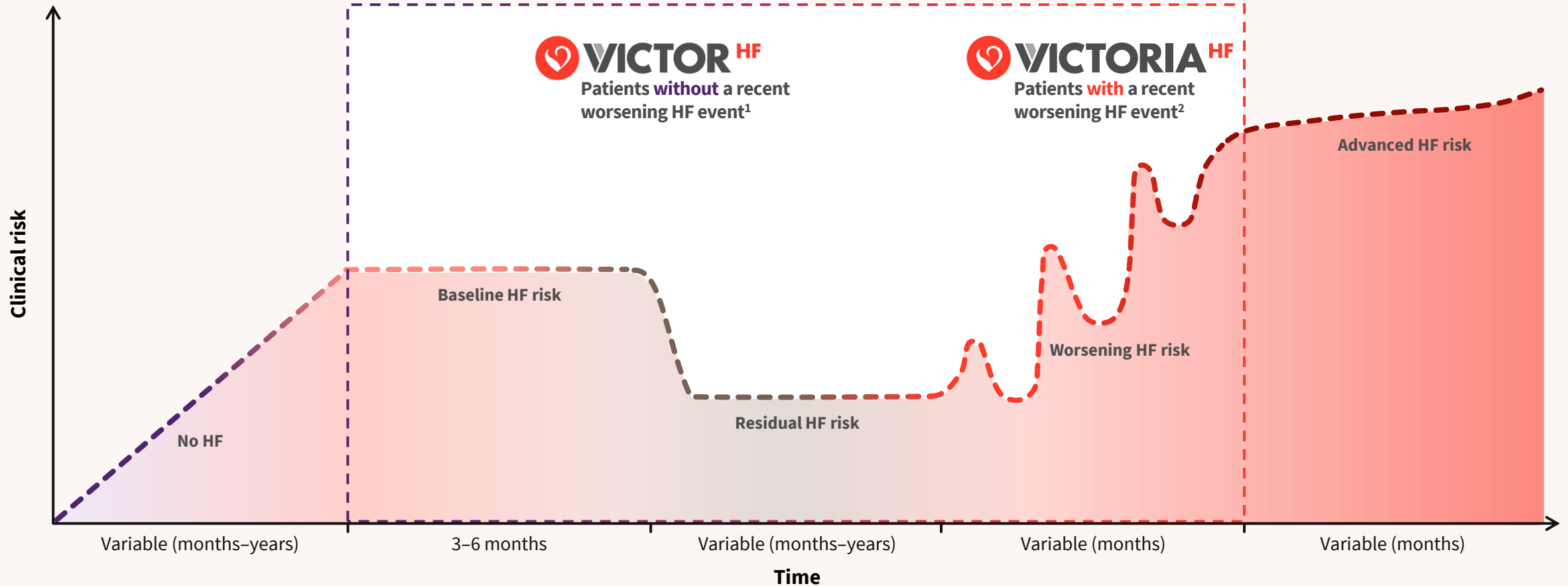
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Extracted from Butler J *et al.* 2025.<sup>1</sup>

CI, confidence interval; CV, cardiovascular; HF, heart failure; HFREF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-FEr, insuficiencia cardíaca con fracción de eyección reducida.

References: 1. Presented at ESC 2025, publication accepted. Butler J *et al.* *Lancet* Sept 2025; 2. Presented at ESC 2025, publication accepted. Butler J *et al.* *Eur Heart J* Sept 2025; <https://doi.org/10.1093/eurheartj/ehaf665>;

# Together, VICTOR and VICTORIA have generated evidence for vericiguat across the spectrum of risk in HFrEF1–3



 **VICTORIA<sup>HF</sup>**  
Patients **with** a recent  
worsening HF event<sup>2</sup>

 **VICTOR<sup>HF</sup>**  
Patients **without** a recent  
worsening HF event<sup>1</sup>

 **Vericiguat**  
A pooled analysis of  
VICTOR—VICTORIA



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# Vericiguat for patients with heart failure and reduced ejection fraction across the risk spectrum: an individual participant data analysis of the VICTORIA and VICTOR trials

*Faiez Zannad, Christopher M O'Connor, Javed Butler, Ciaran J McMullan, Kevin J Anstrom, Irina Barash, Marc P Bonaca, Maria Borentain, Stefano Corda, Davis Gates, Justin A Ezekowitz, Adrian F Hernandez, Carolyn S P Lam, Eldrin F Lewis, JoAnn Lindenfeld, Robert J Mentz, Piotr Ponikowski, Yogesh N V Reddy, Giuseppe M C Rosano, Clara Saldarriaga, Michele Senni, Pedro P Teixeira, James Udelson, Alessia Urbinati, Vanja Vljajnic, Adriaan A Voors, Aiwen Xing, Mahesh J Patel, Paul W Armstrong, for the VICTORIA and VICTOR Study Groups*

www.thelancet.com Published online August 30, 2025 [https://doi.org/10.1016/S0140-6736\(25\)01682-4](https://doi.org/10.1016/S0140-6736(25)01682-4)  
The Lancet, Volume 406, Issue 10510, 1351 - 1362

# A pooled population representing the Vericiguat spectrum of risk in HFrEF<sup>1</sup>

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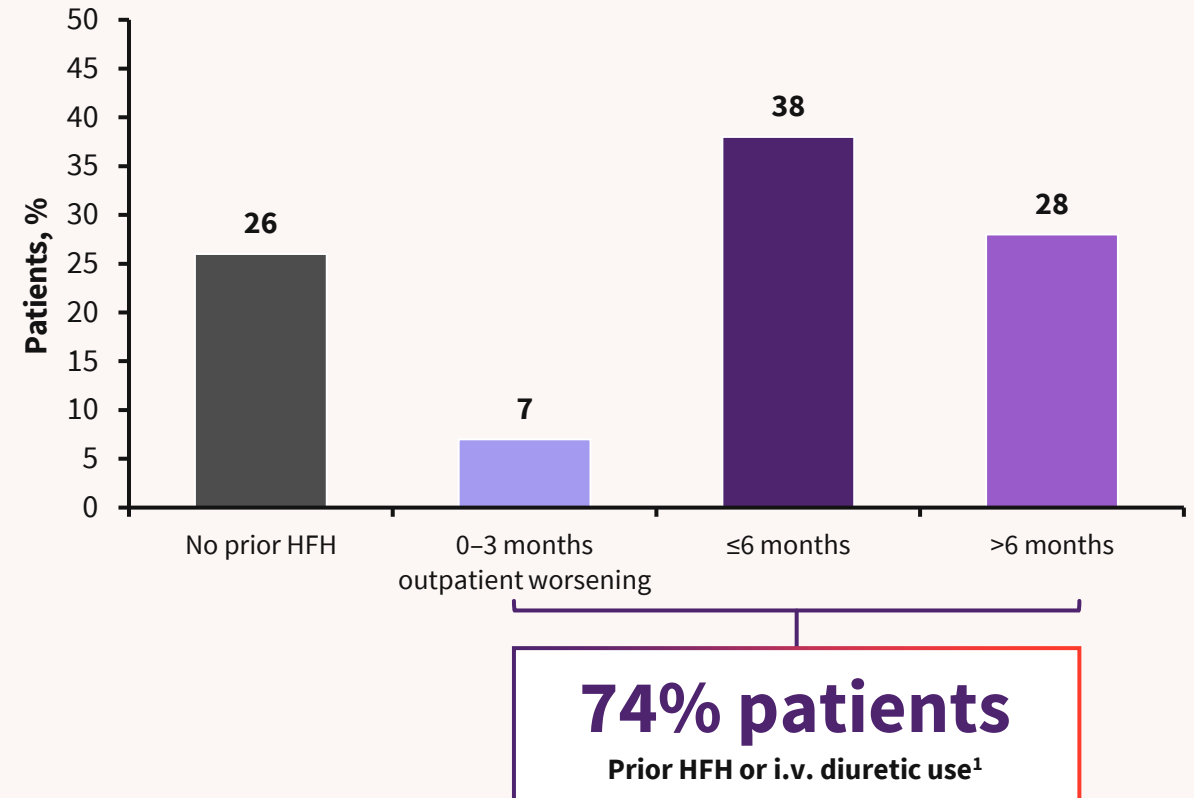
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Baseline characteristic <sup>1</sup>	N=11,155
Median age (IQR), years	68 (60–75)
Sex, female	24%
Mean LVEF ± SD at screening	30 ± 8%
Median NT-proBNP (IQR)*	1,864 (1,036–3,537) pg/ml
<b>NYHA class</b>	
II	70%
III–IV	30%
Mean eGFR ± SD	67 ± 26 ml/min/1.73 m <sup>2</sup>
<b>Co-morbidities</b>	
Ischemic heart disease	64%
Diabetes	44%
Atrial fibrillation	41%

## Recency of worsening HF prior to randomization<sup>2,3</sup>



Extracted from Zannad F *et al.* 2025.<sup>1</sup>

\* n=10,790 with available data; n=365 with missing data.<sup>1</sup> eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; IC, insuficiencia cardíaca;

IC-Fer, insuficiencia cardíaca con fracción de eyección reducida; IQR, interquartile range; i.v., intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

**References:** **1.** Presented at ESC 2025, Zannad F *et al. Lancet* Sept 2025; **2.** Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893; **3.** Presented at ESC 2025, Butler J *et al. Lancet* Sept 2025;

# Vericiguat reduced the primary composite endpoint across the spectrum of risk in HFrEF vs placebo\*1



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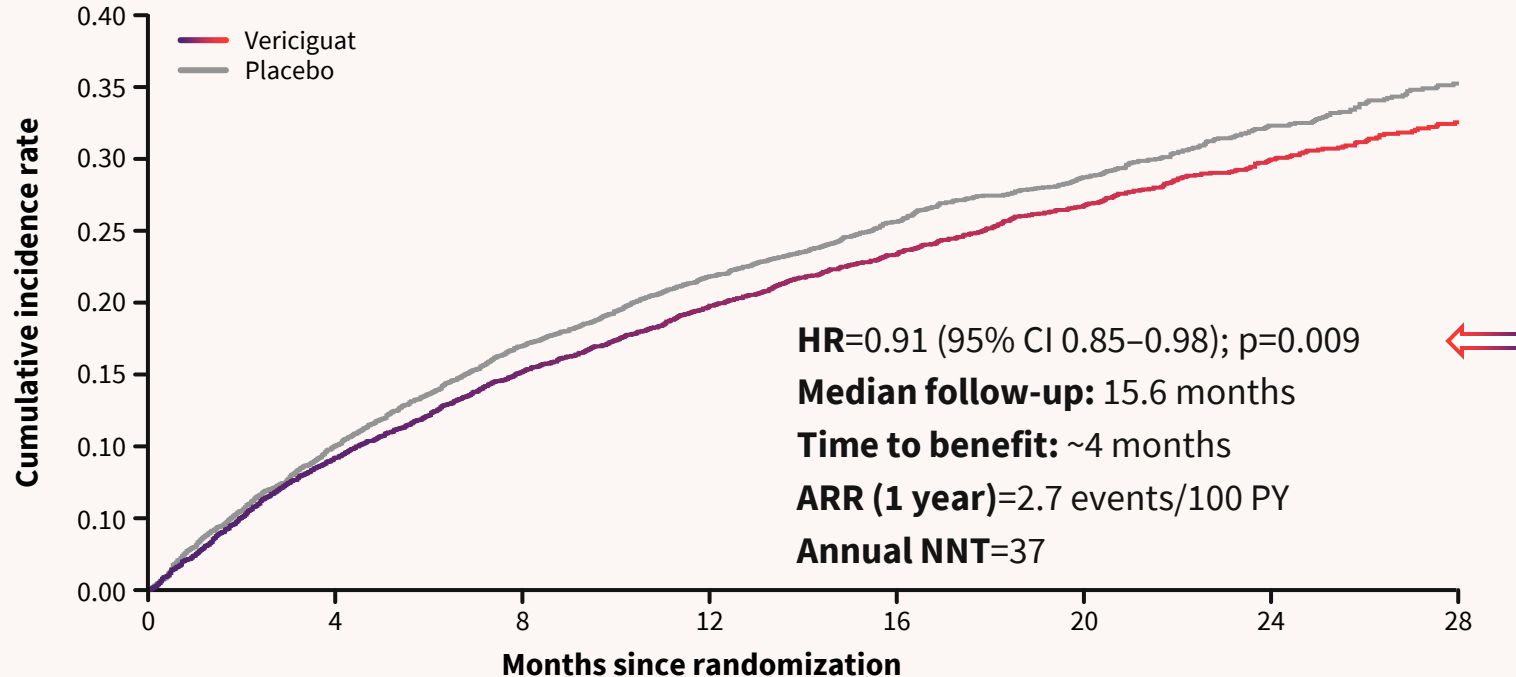


## Primary composite endpoint of time to first HFH or CV death<sup>1</sup>



**Vericiguat**

A pooled analysis of VICTOR–VICTORIA



### Number of patients at risk

	0	4	8	12	16	20	24	28
<b>Vericiguat</b>	5,579	5,026	4,418	3,735	2,743	1,929	1,197	584
<b>Placebo</b>	5,576	4,982	4,326	3,640	2,651	1,873	1,147	552

Extracted from Zannad F *et al.* 2025.<sup>1</sup>

\* P-values were calculated using the stratified log-rank test and are descriptive rather than formal tests for statistical inference.<sup>1</sup>

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NNT, number needed to treat; PY, patient-years. **References: 1.** Presented at ESC 2025, publication accepted. Zannad F *et al.* *Lancet* Sept 2025.

# The benefit of vericiguat was demonstrated in both components of the primary composite endpoint vs placebo\*1



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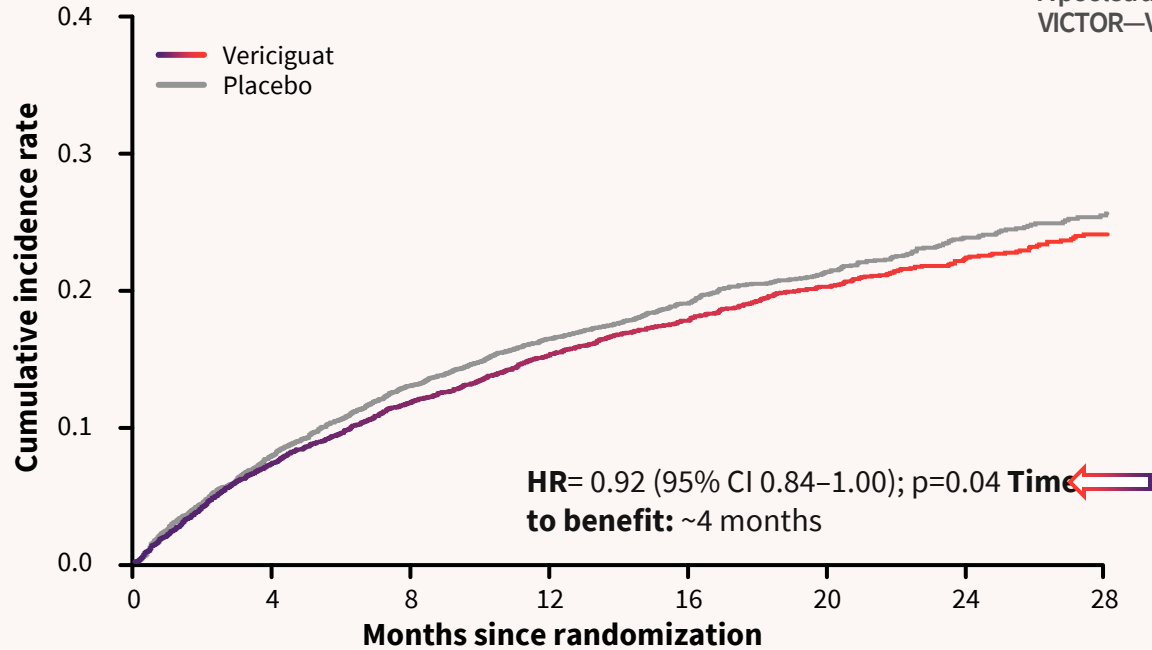
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## Vericiguat

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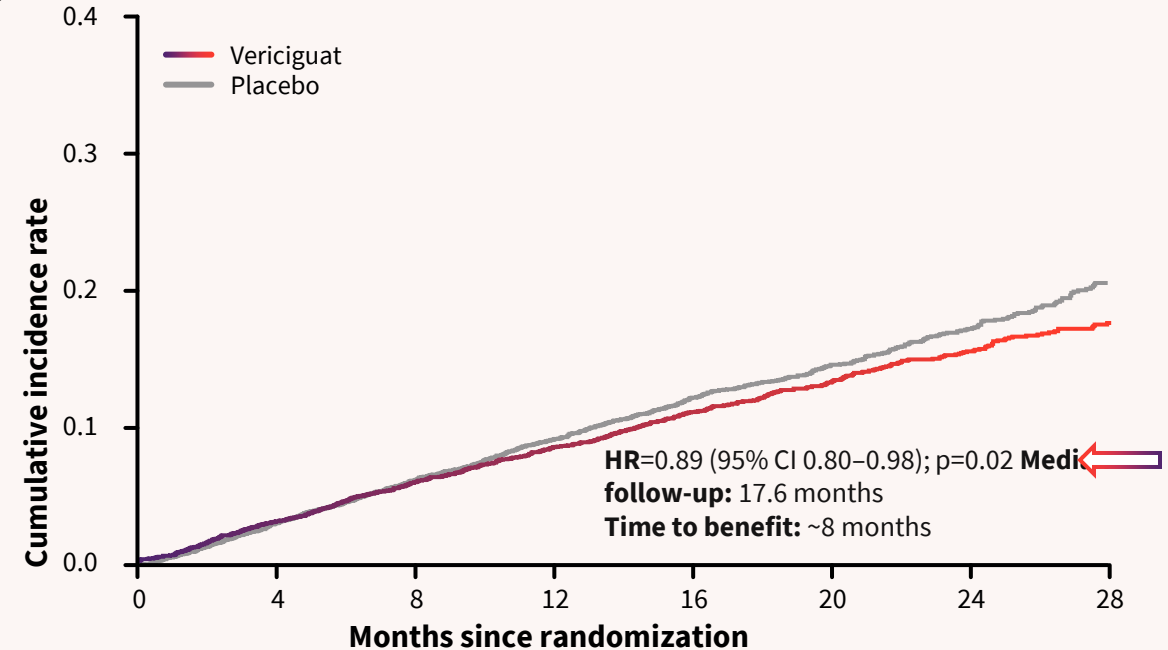
### Time to first HFH<sup>1</sup>



#### Number of patients at risk

<b>Vericiguat</b>	5,579	5,024	4,416	3,734	2,742	1,929	1,197	584
<b>Placebo</b>	5,576	4,981	4,325	3,639	2,650	1,871	1,145	552

### Time to CV death<sup>1</sup>



#### Number of patients at risk

<b>Vericiguat</b>	5,579	5,376	4,896	4,220	3,162	2,295	1,455	721
<b>Placebo</b>	5,576	5,373	4,861	4,167	3,095	2,224	1,411	671

Extracted from Zannad F *et al.* 2025.<sup>1</sup>

\* P-values were calculated using the stratified log-rank test and are descriptive rather than formal tests for statistical inference.<sup>1</sup>

CI, confidence interval; CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization; HFREF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-Fer, insuficiencia cardíaca con fracción de eyección reducida.

References: 1. Presented at ESC 2025, Zannad F *et al. Lancet* Sept 2025;

# An incremental survival benefit was observed for vericiguat vs placebo in well-treated patients across the disease continuum\*1



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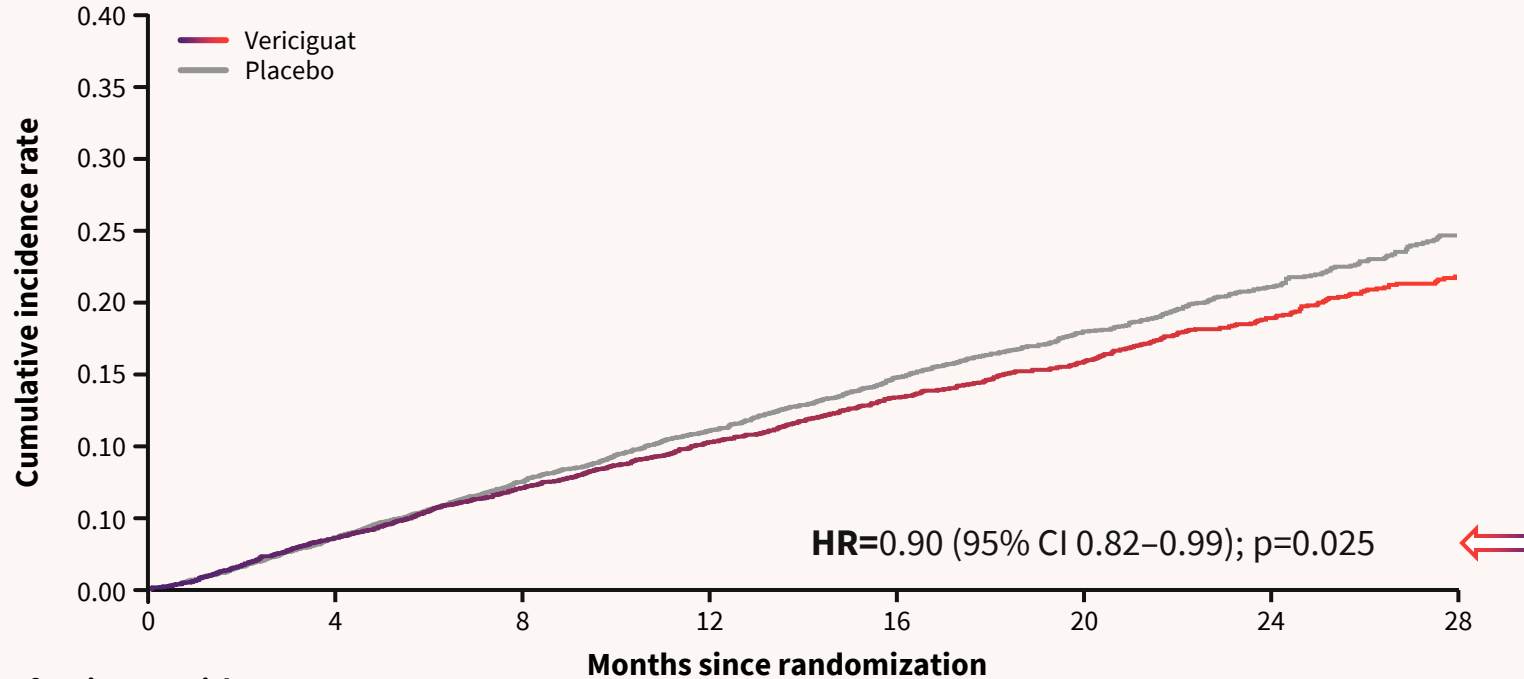
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## Vericiguat

A pooled analysis of VICTOR—VICTORIA

### Time to all-cause mortality<sup>1</sup>



#### Number of patients at risk

	0	4	8	12	16	20	24	28
<b>Vericiguat</b>	5,579	5,376	4,896	4,220	3,162	2,295	1,455	721
<b>Placebo</b>	5,576	5,573	4,861	4,167	3,095	2,224	1,411	671

Extracted from Zannad F *et al.* 2025.<sup>1</sup>

Vericiguat is not approved in Spain for patients with HFrEF without a recent worsening HF event; please refer to local Prescribing Information for full indication and usage in your market.<sup>2</sup>

Vericiguat no está autorizado en España para pacientes con IC-FER sin un episodio reciente de descompensación de la IC; consulte la información de prescripción local para obtener información completa sobre la indicación y el uso en su mercado.<sup>2</sup>

CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; IC-FER, insuficiencia cardíaca con fracción de eyección reducida.

References: **1.** Presented at ESC 2025, publication accepted. Zannad F *et al.* *Lancet* Sept 2025; **2.** Bayer AG. Vericiguat Summary of Product Characteristics. 2021. [https://www.ema.europa.eu/en/documents/product-information/verquvo-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/verquvo-epar-product-information_en.pdf) [accessed Aug 2025].

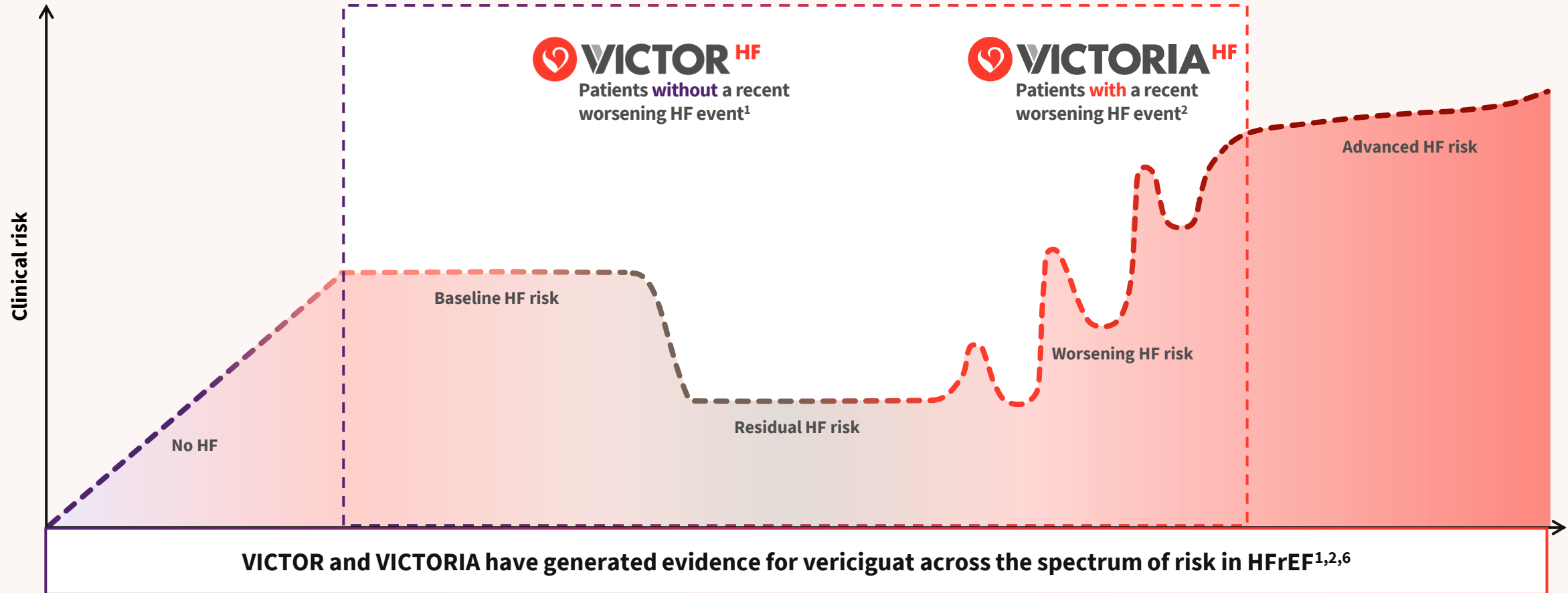
# Vericiguat was studied in 11,155 patients across two outcome-driven trials in the largest Phase 3 HFrEF trial program to date<sup>1-5</sup>



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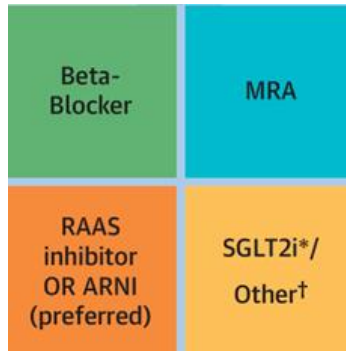


Extracted from Greene SJ *et al.* 2020 and Greene SJ *et al.* 2023.<sup>6,7</sup>

**References:** 1. Presented at ESC 2025, publication accepted. Butler J *et al.* *Lancet* Sept 2025; 2. Armstrong PW *et al.* *N Engl J Med* 2020;382:1883–1893; 3. Saldarriaga CI *et al.* *Eur J Heart Fail* 2025; <https://doi.org/10.1002/ehfj.3598>; 4. Voors AA *et al.* *Nat Med* 2022;28:568–574; 5. Cytokinetics. 2025. <https://clinicaltrials.gov/study/NCT06736574> [accessed Aug 2025]; 6. Greene SJ *et al.* *J Am Coll Cardiol* 2023;81:413–424; 7. Greene SJ *et al.* *Circ Heart Fail* 2020;13:e007132.

# Network meta-analysis of pharmacological treatment in HFrEF

89 randomized controlled trials



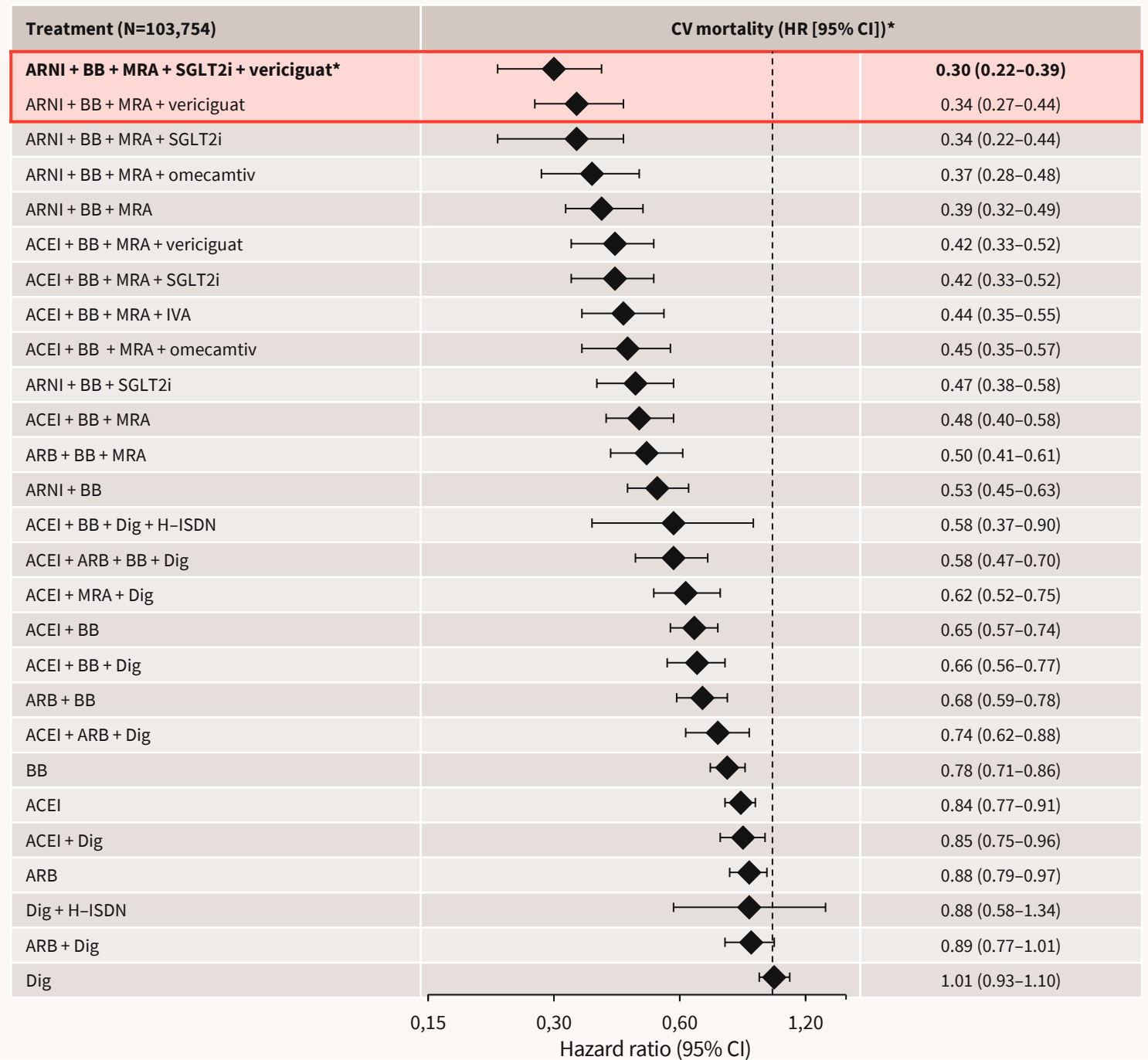
**Benefit of quintuple therapy\***

**70%** Relative risk reduction in CV mortality vs placebo

ARNi + BB + MRA + SGLT2i + Vericiguat

Extracted from Van Essen BJ et al. 2025.

\*Van Essen BJ et al. *J Am Coll Cardiol* 2025; <https://doi.org/10.10.16/j.jacc.2025.08.054>;



# Key takeaways

## The new pillar in HFrEF...



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- Vericiguat has a unique mode of action complementing other GDMT by targeting an unaddressed pathway in HFrEF\*<sup>1-4</sup>
- **VICTORIA** established the role of vericiguat in patients following a recent worsening HF event demonstrating a significant reduction in first HFH or CV death vs placebo<sup>#5</sup>
- In **VICTOR**, a trial designed and powered for CV death, vericiguat showed a consistent and clinically meaningful reduction in CV death and all-cause mortality vs placebo<sup>6</sup>

### In a prespecified pooled analysis, vericiguat...

- Reduced the risk of first HFH or CV death vs placebo in patients across the risk spectrum of HFrEF<sup>7</sup>
- Demonstrated an incremental CV- and all-cause mortality benefit vs placebo in the largest Phase 3 HFrEF trial program to date<sup>7-10</sup>
- Vericiguat was generally well tolerated, with a safety profile comparable with placebo<sup>5-7</sup>



\*Vericiguat is a soluble guanylate cyclase stimulator; foundational therapies in chronic HFrEF include angiotensin receptor–neprilysin inhibitor, beta blockers, mineralocorticoid receptor antagonists and sodium–glucose cotransporter 2 inhibitors.<sup>1,11</sup> # HR = 0.90 (95% CI 0.82–0.98).<sup>5</sup> CI, confidence interval; CV, cardiovascular; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IC, insuficiencia cardíaca; ICFeR, insuficiencia cardíaca con fracción de eyección reducida.

**References:** **1.** Dies RM *et al. Cureus* 2023;15:e49782; **2.** Reddy YNV *et al. Eur J Heart Fail* 2025;27:209–218; **3.** Hulot JS *et al. Expert Opin Pharmacother* 2021; 22:1847–1855; **4.** Butler J *et al. Eur J Heart Fail* 2022;24:2029–2036; **5.** Armstrong PW *et al. N Engl J Med* 2020;382:1883–1893;

**6.** Presented at ESC 2025. Butler J *et al. Lancet* Sept 2025; **7.** Presented at ESC 2025, Zannad F *et al. Lancet* Sept 2025; **8.** Saldarriaga CI *et al. Eur J Heart Fail* 2025; <https://doi.org/10.1002/ejhf.3598>;

**9.** Voors AA *et al. Nat Med* 2022;28:568–574; **10.** Cytokinetics. 2025. <https://clinicaltrials.gov/study/NCT06736574> [accessed Aug 2025]; **11.** McDonagh TA *et al. Eur Heart J* 2021;21:3599–3726;

# Impact of Vericiguat on exercise capacity, quality of life, circulating biomarkers and short-term cardiovascular mortality in elderly heart failure patients after acute decompensation.



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## Inclusion criteria

Age  $\geq 70$  years

Patients with HFrEF within 2 days after acute pulmonary edema

Optimal medical therapy before admission (GDMT)

### Exclusion criteria

Uncorrected primary valvular heart diseases

Active myocarditis

Obstructive hypertrophic or restrictive cardiomyopathy

Administration of vericiguat within 30 days before ward admission

History of hypersensitivity or intolerance to sGC

History of angioedema

Estimated glomerular filtration rate  $< 20$  mL/min/1.73 m<sup>2</sup>

Serum potassium  $> 5.2$  mEq/L

Systolic blood pressure  $\leq 100$  mmHg after 2 days from ward admission

Exercise-limiting angina

Lung disease

Claudication

Severe primary pulmonary, renal, or hepatic disease

Acute coronary syndrome within 30 days before ward admission

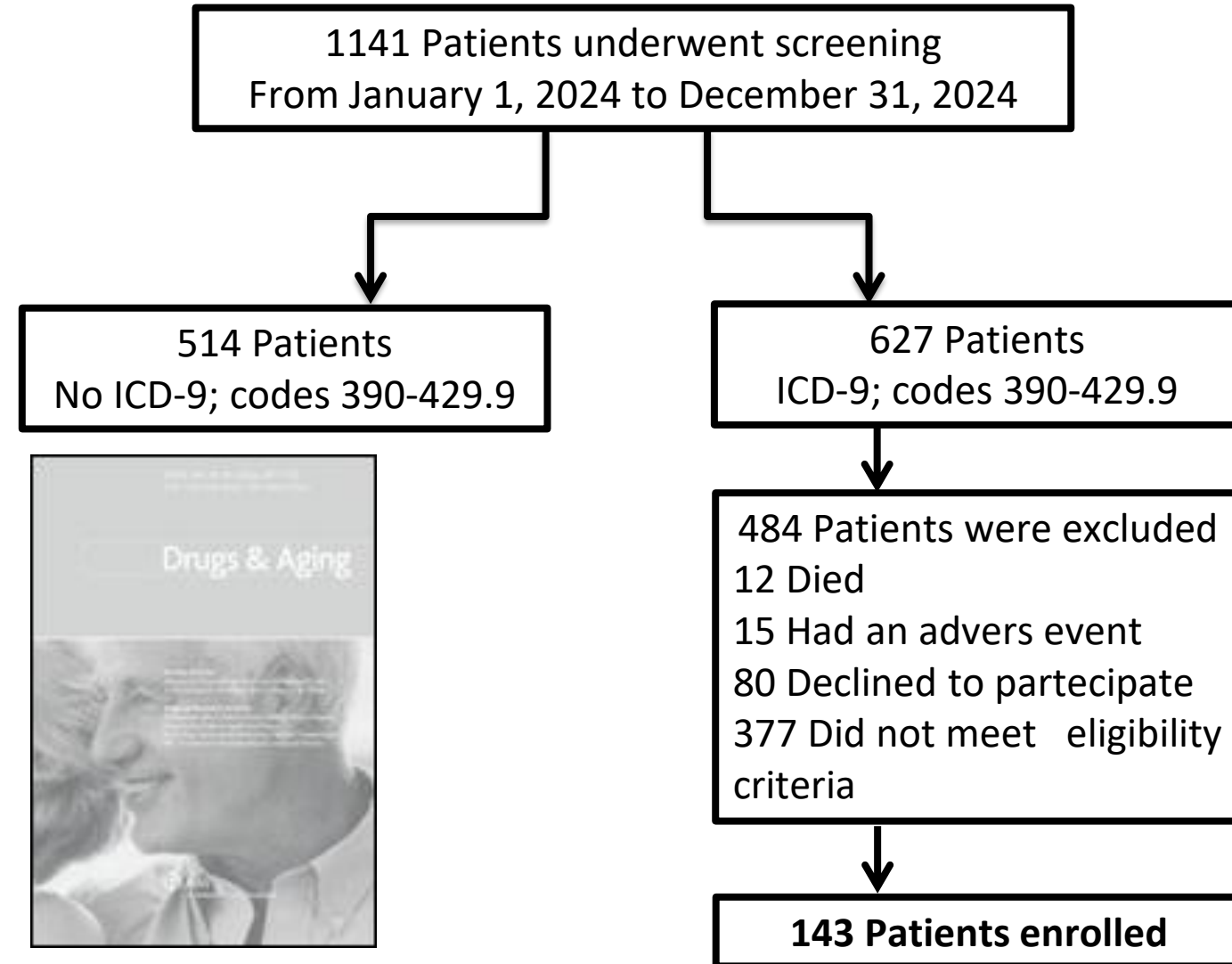
Transient ischemic attack/stroke within 30 days before ward admission

Major cardiovascular surgery within 30 days before ward admission

Percutaneous coronary intervention within 30 days before ward admission

Carotid angioplasty within 30 days before ward admission

HFrEF, heart failure with reduced ejection fraction; sGC, stimulators of soluble guanylate cyclase.



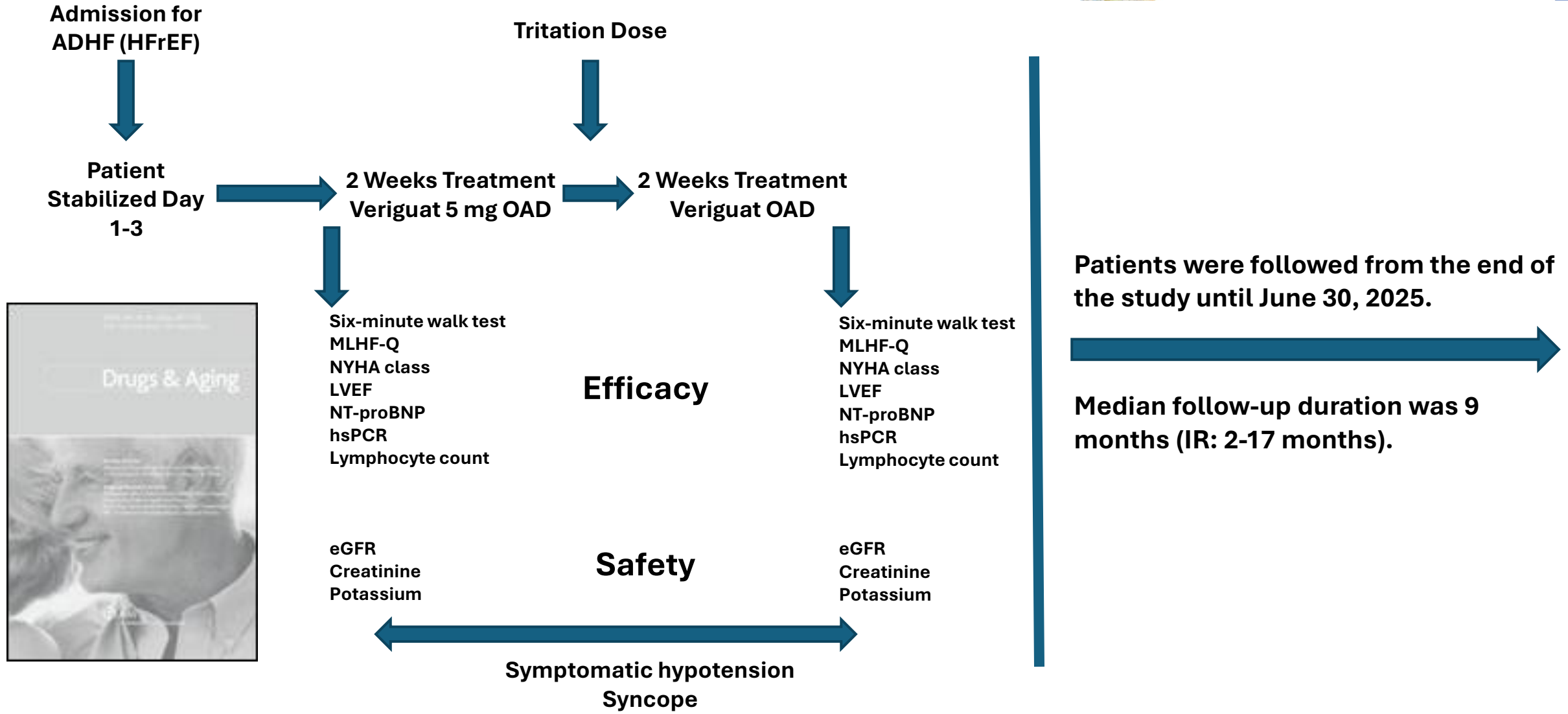
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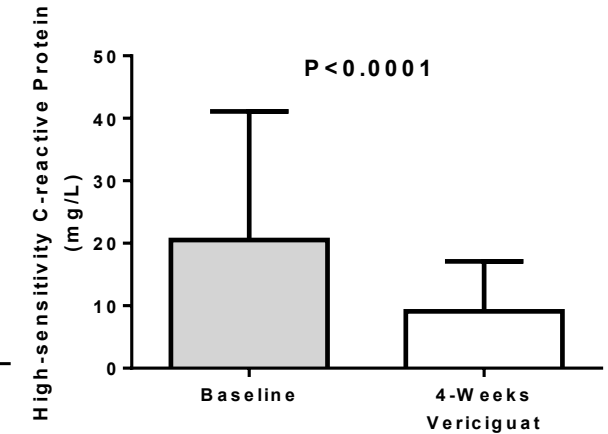
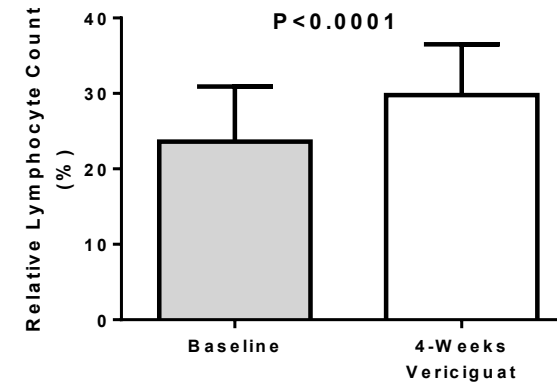
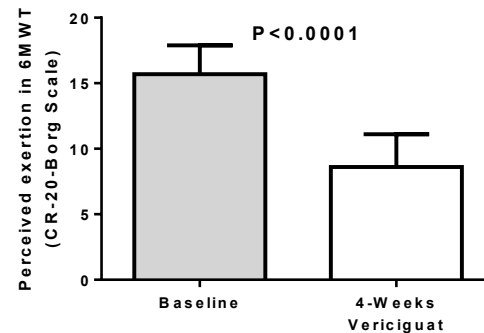
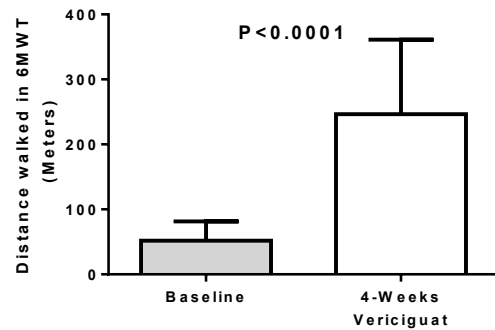
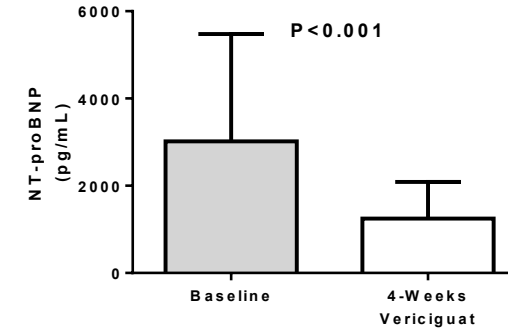
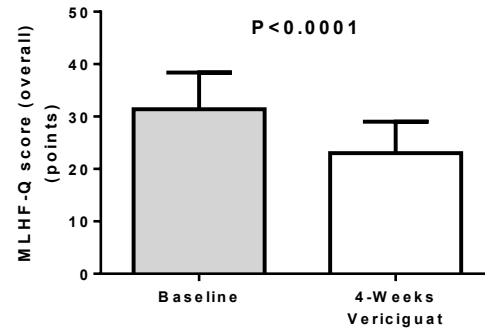
# Impact of Vericiguat on exercise capacity, quality of life, circulating biomarkers and short-term cardiovascular mortality in elderly heart failure patients after acute decompensation.



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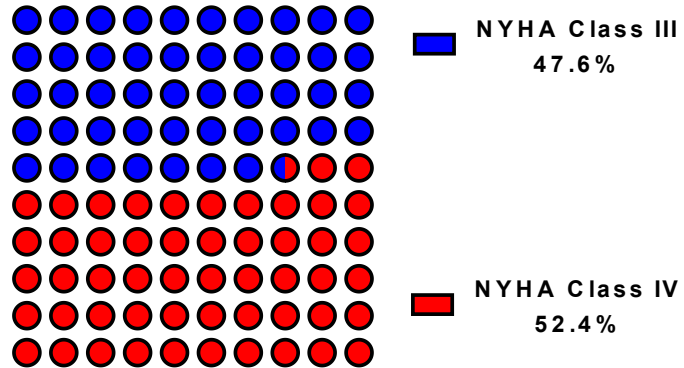
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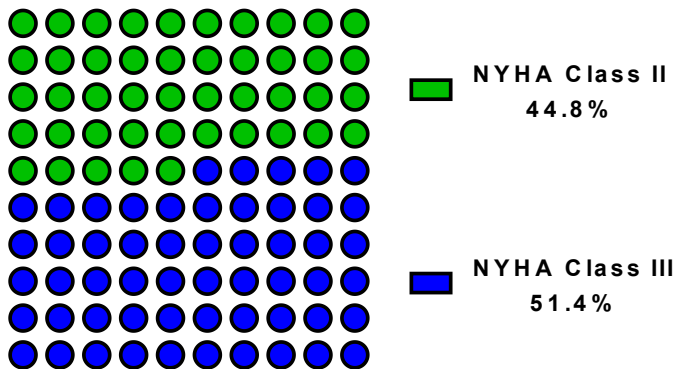
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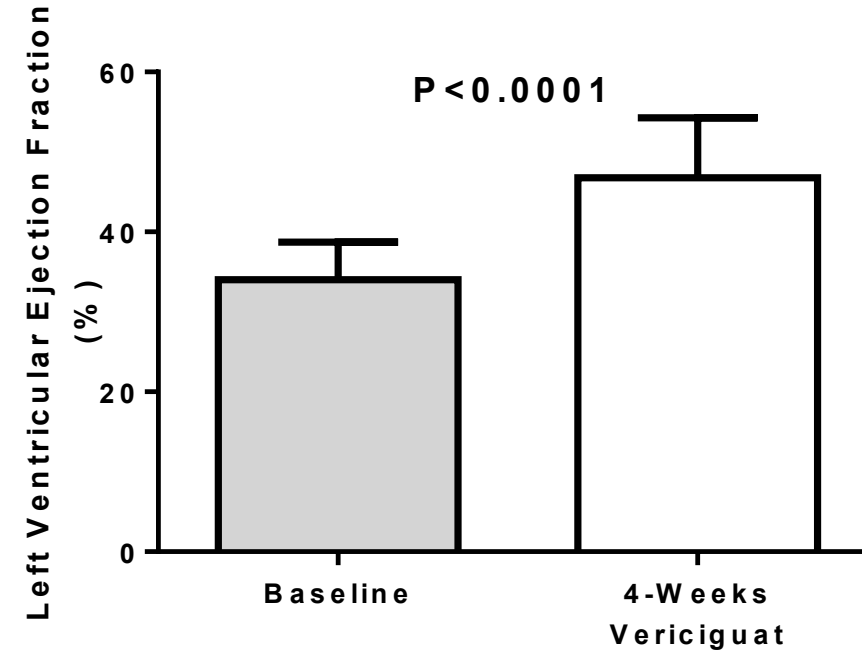
## Baseline



## 4-Weeks Treatment with Vericiguat



$\chi^2=139.8$ ;  $P<0.0001$

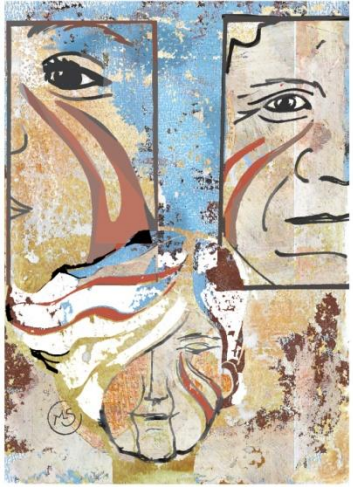


After a median follow-up period of 9 months (IQR 2-17 months), 22 (15.4%) patients died from cardiovascular death.

As expected, age was identified as an independent predictor of all-cause mortality, with a 14% increase in risk for each additional year of age [Hazard Ratio 1.14 (95% CI 1.03–1.27),  $P < 0.05$ ].

No patients experienced any clinically relevant side-effects.





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***“Ora non è il momento di pensare a quello che non hai.***

***Pensa a che puoi fare con quello che hai.”***

***Ernest Hemingway***