Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

VICTORIA TRIAL

Κουτρουλός Μάριος-Βασίλειος
Ειδικευόμενος Καρδιολογίας
Πανεπιστημιακή Καρδιολογική Κλινική
Π.Γ.Ν.Αλεξανδρούπολης
Διευθ: καθ Τζιακάς Δημήτριος

NO CONFLICT OF INTERESTS

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Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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- A phase 3,randomized,double-blind, placebo-controlled trial
- The effect of vericiguat in patients with HFrEF who had a recent worsening HF event

Thank-you to all 616 VICTORIA Investigative Sites and Patients

(n = # randomized)

Canadian **VIGOUR** Centre
Bridging Hearts and Minds

Duke Clinical Research Institute

Trial Organization

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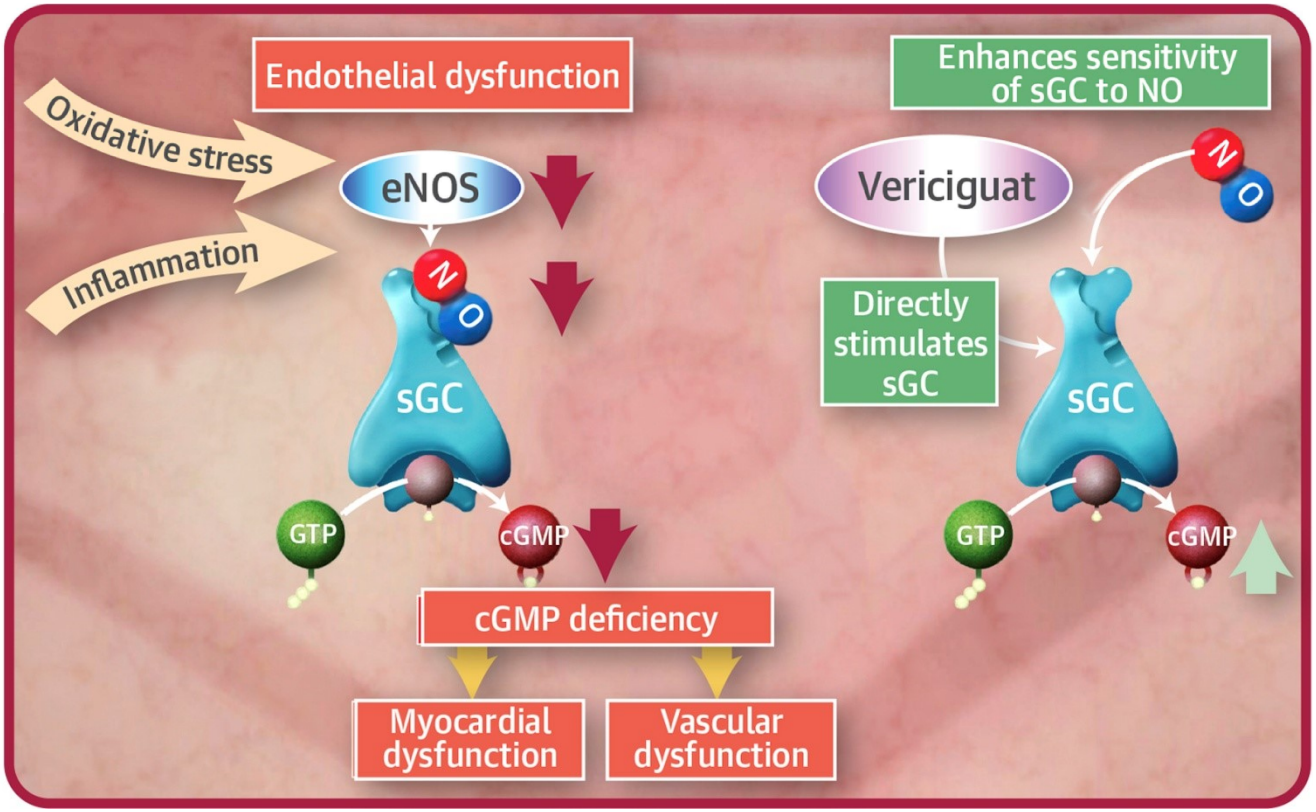
Vericiguat increases sGC activity to improve Myocardial and Vascular function



J Am Coll Cardiol HF. 2018 Feb, 6 (2) 96–104

– 2nd in this class

Follows riociguat (ADEMPAS), FDA approved for PAH 2013

– SOCRATES-REDUCED

Change in NTproBNP over 12 weeks, statistically NS

- PRIMARY OUTCOME : CV death or first HF hospitalization
- SECONDARY OUTCOMES :

1. *Components of the primary composite endpoint*
2. *Total HF hospitalizations; first and recurrent –*
3. *Composite of all-cause mortality or first HF hospitalization –*
4. *All-cause mortality*

INCLUSION CRITERIA

- *History of chronic HF (New York Heart Association [NYHA] Class II-IV) on standard therapy before qualifying HF decompensation*
- *Previous HF hospitalization within 6 months prior to randomization or intravenous (IV) diuretic treatment for HF (without hospitalization) within 3 months.*
- *Brain natriuretic peptide (BNP) levels: sinus rhythm ≥ 300 pg/mL; atrial fibrillation ≥ 500 pg/mL and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels: sinus rhythm ≥ 1000 pg/mL; atrial fibrillation ≥ 1600 pg/mL within 30 days prior to randomization*
- *Left ventricular ejection fraction (LVEF) of <45% assessed within 12 months prior to randomization by any method*

"Chronic HF"

- NYHA class II–IV
- LVEF < 45%
- Guideline based HF therapies

after

"Worsening event"

- Recent HFH or IV diuretic use
- With very elevated natriuretic peptides (BNP or NT-proBNP)

BNP ≥ 300 & pro-BNP ≥ 1000 pg/ml NSR
BNP ≥ 500 & pro-BNP ≥ 1600pg/ml AF

Patients may have been randomized as an inpatient or outpatient but must have met criteria for clinical stability (e.g., SBP ≥ 100 mmHg, off IV treatments ≥ 24 hours)

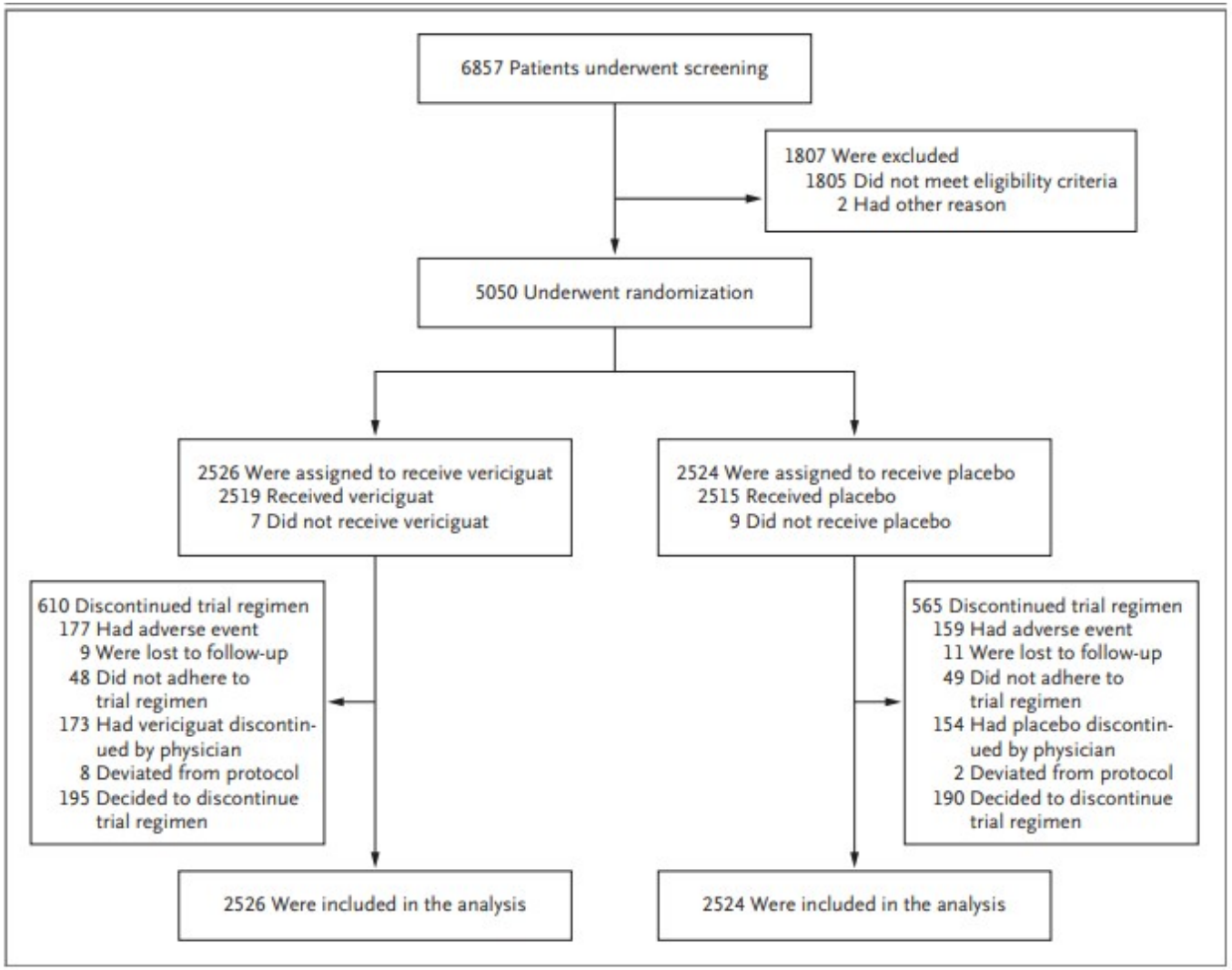
30-day screening period without run-in

EXCLUSION CRITERIA

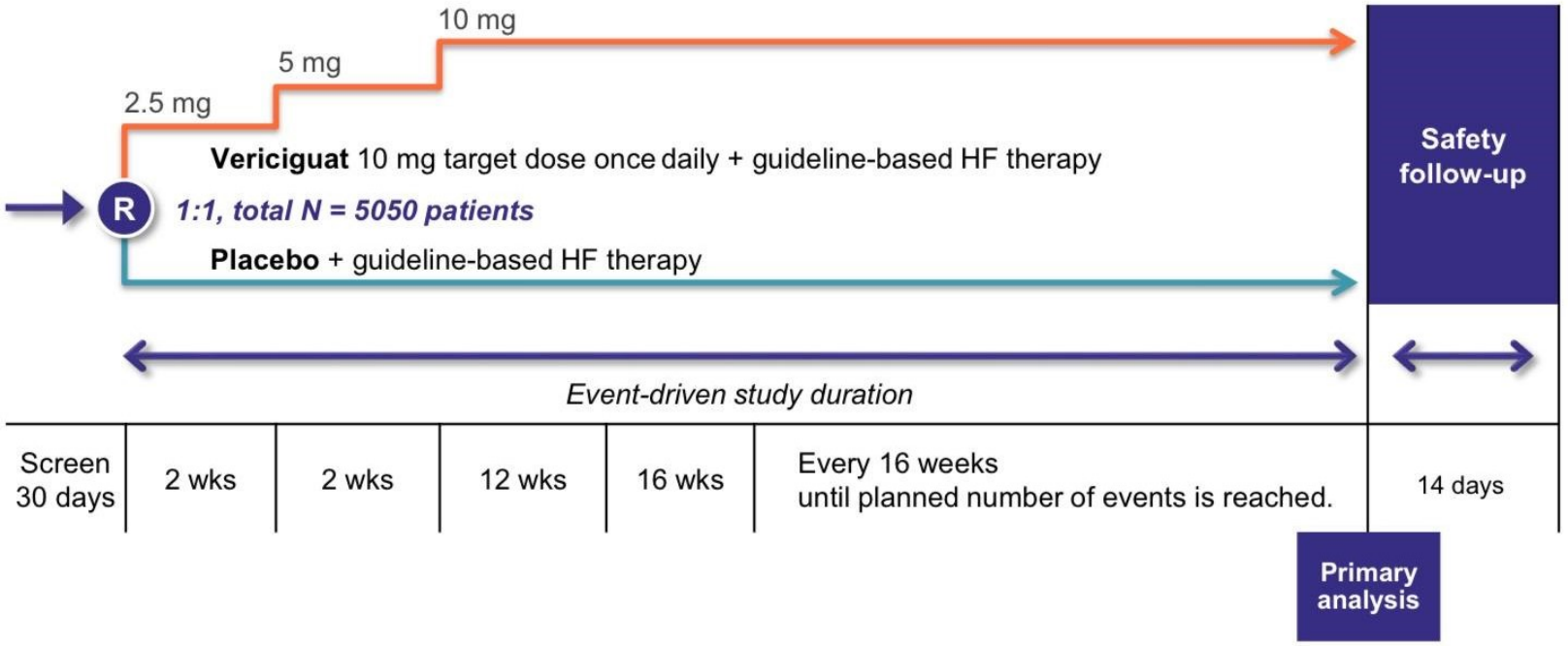
- *Clinically unstable at the time of randomization(IV treatment within 24 hours, systolic blood pressure (SBP) <100 mmHg)*
- *Long-acting nitrates, PDE5 type inhibitors, riociguat*
- *Awaiting heart transplantation (United Network for Organ Sharing Class 1A / 1B or equivalent), receiving continuous IV infusion of an inotrope, or has/anticipates receiving an implanted ventricular assist device*
- *Estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m2 or chronic dialysis*

- *Severe hepatic insufficiency such as with hepatic encephalopathy*
- *Interstitial Lung Disease*
- *Cardiac Commorbidities*
- *Current alcohol and/or drug abuse*
- *Pregnancy*

TRIAL DESIGN



Study Design



PATIENT BASELINE CHARACTERISTICS

	Vericiguat (N=2526)	Placebo (N=2524)
Age mean (SD)	67.5(12.2)	67.2(12.2)
Male sex	1921(76.0%)	1921(76.1%)
Female sex	605(24.0%)	603 (23.9%)
HF hosp <3 mos	1673(66.2%)	1705(67.6%)
HF hosp 3 to 6 mos	454(18.0%)	417(16.5%)
IV diuretic for HF (<3mos)	399(15.8%)	402(15.9%)
EF % (SD)	29.0(8.3)	28.8(8.3)
NYHA class III-IV	1045 (41.4%)	1024 (40.6%)
NT-proBNP pg/ml	2804	2821
Triple guide-based therapy	1480(58.7%)	1529(60.7%)
ICD, BV pacemaker (or both)	813(32.2%)	802(31.8%)

Comparing the Benefit of Novel Therapies Across Clinical Trials. CIRCULATION, Vol.142, No.8

	PARADIGM-HF[1]		DAPA-HF[2]		VICTORIA[3]	
	Comparator	Sacubitril/Valsartan	Comparator	Dapagliflozin	Comparator	Vericigu
Median follow-up, mo	27		18		11	
Trial characteristics						
Comparator	Active (enalapril)		Placebo		Placebo	
Run-in phase	Yes (2 of them)		No		No	
Left ventricular ejection fraction, mean, %	29		31		29	
Estimated glomerular filtration rate, mean, $mL \cdot min^{-1} \cdot 1.73m^{-2}$	68		66		61	
Atrial fibrillation, %	37		40		45	
NT-proBNP, median, pg/mL	1615		1437		2821	
New York Heart Association class III–IV, %	25		33		41	

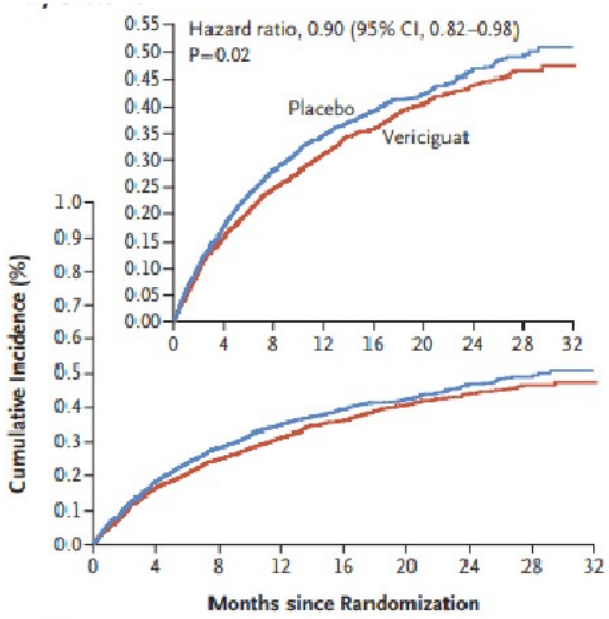
Primary and Secondary Outcomes

	Vericiguat (N=2526)		Placebo (N=2524)		Treatment Comparison	
	%	Events/ 100 Pt-Yrs	%	Events/ 100 Pt-Yrs	HR (95%)*	P-value†
PRIMARY COMPOSITE OUTCOME	35.5	**33.6**	38.5	**37.8**	0.90 (0.82–0.98)	0.019
HF hospitalization	27.4		29.6			
Cardiovascular death‡	8.2		8.9			
SECONDARY OUTCOMES						
Cardiovascular death	16.4	**12.9**	17.5	**13.9**	0.93 (0.81–1.06)	0.269
HF hospitalization	27.4	**25.9**	29.6	**29.1**	0.90 (0.81–1.00)	0.048
Total HF hospitalizations		**38.3**		**42.4**	0.91 (0.84–0.99)	0.023
Secondary composite outcome	37.9	**35.9**	40.9	**40.1**	0.90 (0.83–0.98)	0.021
HF hospitalization	27.4		29.6			
All-cause mortality‡	10.5		11.3			
All-cause mortality	20.3	**16.0**	21.2	**16.9**	0.95 (0.84–1.07)	0.377

For patients with multiple events, only the first event contributing to the composite endpoint is counted in the table.
**Hazard ratio (Vericiguat over Placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).*
†From log-rank test stratified by the stratification factors defined by region and race.
‡Mortality components of the primary and secondary composite outcomes were not preceded by a heart failure hospitalization.
Based on data up to the primary analysis cutoff date (18Jun2019). CI indicates confidence interval; HF, heart failure; HR, hazard ratio.

PRIMARY OUTCOME
CV death or first HF hospitalazation

event reduction
4.2/100 patient-yr

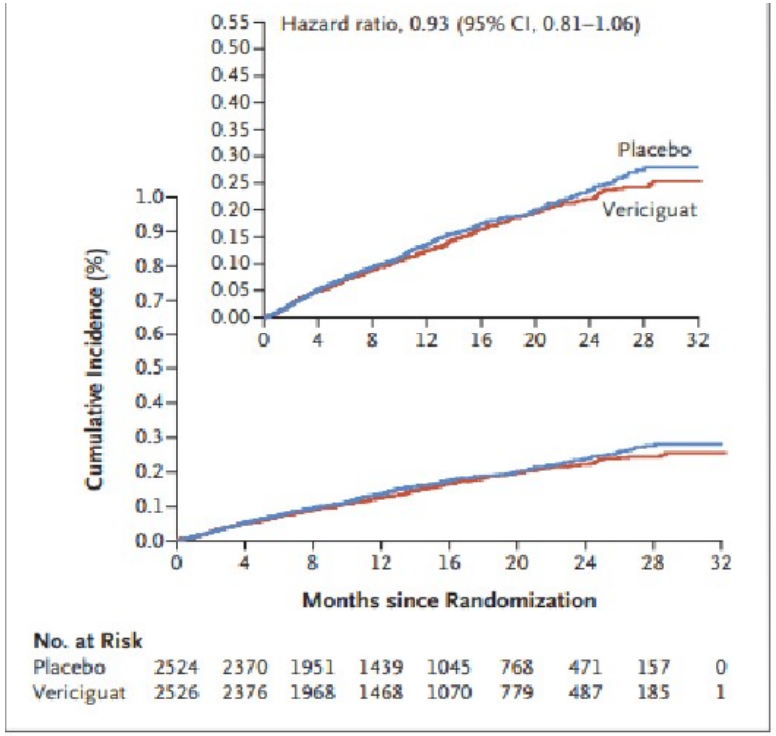


No. at Risk

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

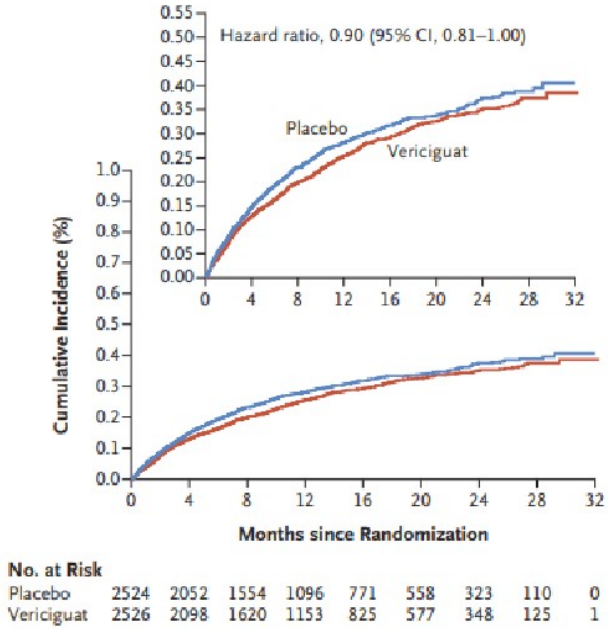
CV DEATH

NS


Hazard ratio, 0.93 (95% CI, 0.81–1.06)
Placebo
Vericiguat
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2524 2370 1951 1439 1045 768 471 157 0
Vericiguat 2526 2376 1968 1468 1070 779 487 185 1

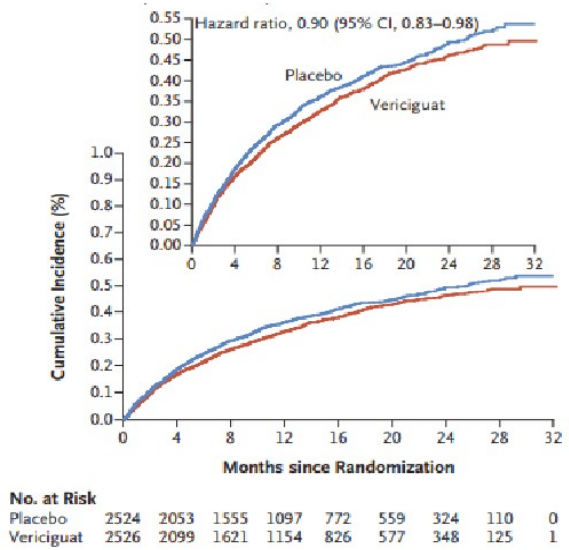
HF Hospitalazation

p-value 0.048

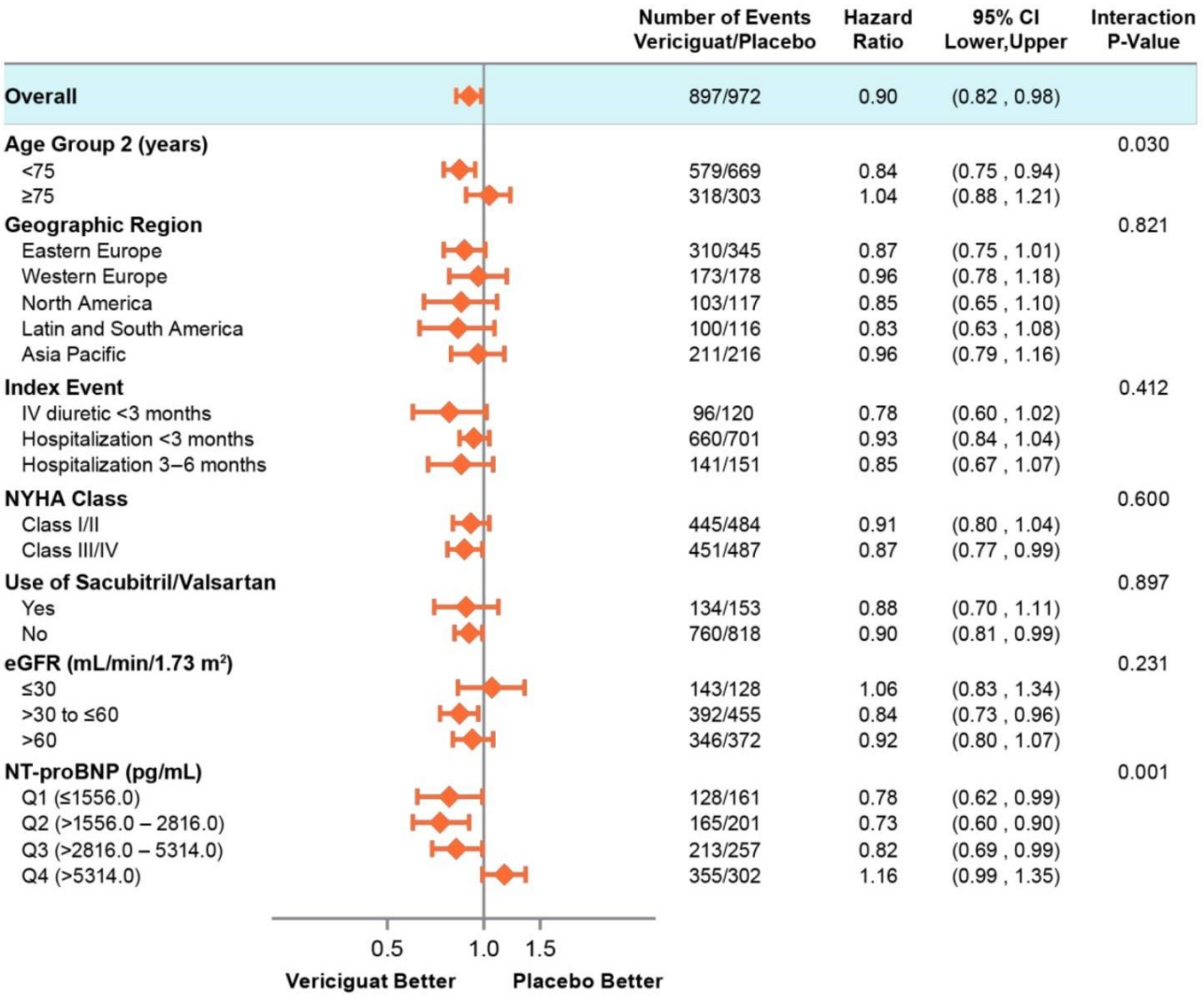


ANY CAUSE DEATH OR HHF

p-value 0.021



Subgroup Analysis



	Number of Events Vericiguat/Placebo	Hazard Ratio	95% CI Lower,Upper	Interaction P-Value
Overall	897/972	0.90	(0.82 , 0.98)	
Age Group 2 (years)				0.030
<75	579/669	0.84	(0.75 , 0.94)	
≥75	318/303	1.04	(0.88 , 1.21)	
Geographic Region				0.821
Eastern Europe	310/345	0.87	(0.75 , 1.01)	
Western Europe	173/178	0.96	(0.78 , 1.18)	
North America	103/117	0.85	(0.65 , 1.10)	
Latin and South America	100/116	0.83	(0.63 , 1.08)	
Asia Pacific	211/216	0.96	(0.79 , 1.16)	
Index Event				0.412
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)	
NYHA Class				0.600
Class I/II	445/484	0.91	(0.80 , 1.04)	
Class III/IV	451/487	0.87	(0.77 , 0.99)	
Use of Sacubitril/Valsartan				0.897
Yes	134/153	0.88	(0.70 , 1.11)	
No	760/818	0.90	(0.81 , 0.99)	
eGFR (mL/min/1.73 m²)				0.231
≤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)	
NT-proBNP (pg/mL)				0.001
Q1 (≤1556.0)	128/161	0.78	(0.62 , 0.99)	
Q2 (>1556.0 – 2816.0)	165/201	0.73	(0.60 , 0.90)	
Q3 (>2816.0 – 5314.0)	213/257	0.82	(0.69 , 0.99)	
Q4 (>5314.0)	355/302	1.16	(0.99 , 1.35)	

ADVERSE EVENTS

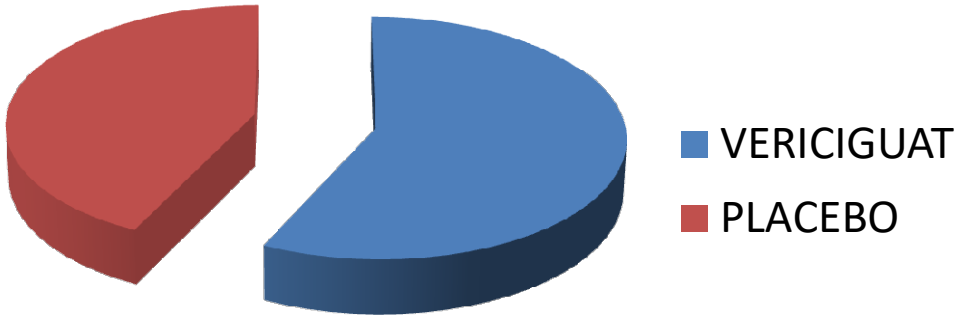
	Vericiguat		Placebo		Difference in % vs. Placebo	
	No.	(%)	No.	(%)	Estimate (95% CI)*	P-value
Patients in population	2519		2515			
Symptomatic hypotension	229	(9.1)	198	(7.9)	1.2 (-0.3 to 2.8)	0.121
Syncope	101	(4.0)	87	(3.5)	0.6 (-0.5 to 1.6)	0.303

**Based on the Miettinen & Nurminen method.*
Note: Includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug.
Based on data up to the primary analysis cutoff date (18Jun2019).
CI indicates confidence interval.

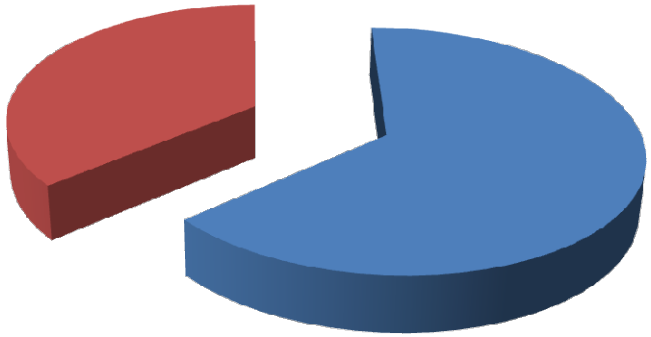
HIGHER RISK OF ANEMIA

in general *serious AE*

7.6% vs 5.7%



1.6% vs 0.9%



STRENGTHS

- *High-risk patient population*
- *Only 0.5% lost to follow-up*
- *Vericiguat engages a new therapeutic target by enhancing the cGMP pathway*
- *Absolute primary event reduction of 4.2/100 patient-years*
- *NNT -24*
- *Once daily medicine*
- *No need for monitoring renal function or electrolytes*

LIMITATIONS

- *Only 15% were on an ARNI*
- *Type of b-blocker not reported*
- *Short duration of study ~ 11 months*
- *Mean BP was 121.4/72.8 mmHg(+-15.7/11mmHg) and mean HR 73bpm (+-13bpm)*
- *Not mentioned: combined with an SGLT-2 inh?*

  Patients receiving Ivabradine?

CONCLUSION

- *Easy to titrate*
- *Generally safe*
- *Well tolerated*
- *May play a useful role in patients with a recent worsening HF event*

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Vericiguat may be considered in patients in NYHA class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	**IIb**

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

COR	LOE	RECOMMENDATION
2b	B-R	1. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death (1).

JAMA | Original Investigation

Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction

The VITALITY-HFpEF Randomized Clinical Trial

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thank you
danke
謝謝
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شكراً جزيلاً
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gracias
obrigado
merci
dziękuję
bedankt
go raibh maith agat
sukriya
kop khun krap
terima kasih
dakujem
arigatō
grazie
takk
tapadh leat
mauruuru
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dankie
kiitos
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спасибо
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blagodaram
barka
welalin
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mersi
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