Vericiguat in Patients with Atrial Fibrillation and Heart Failure with Reduced Ejection Fraction: Insights from the VICTORIA trial

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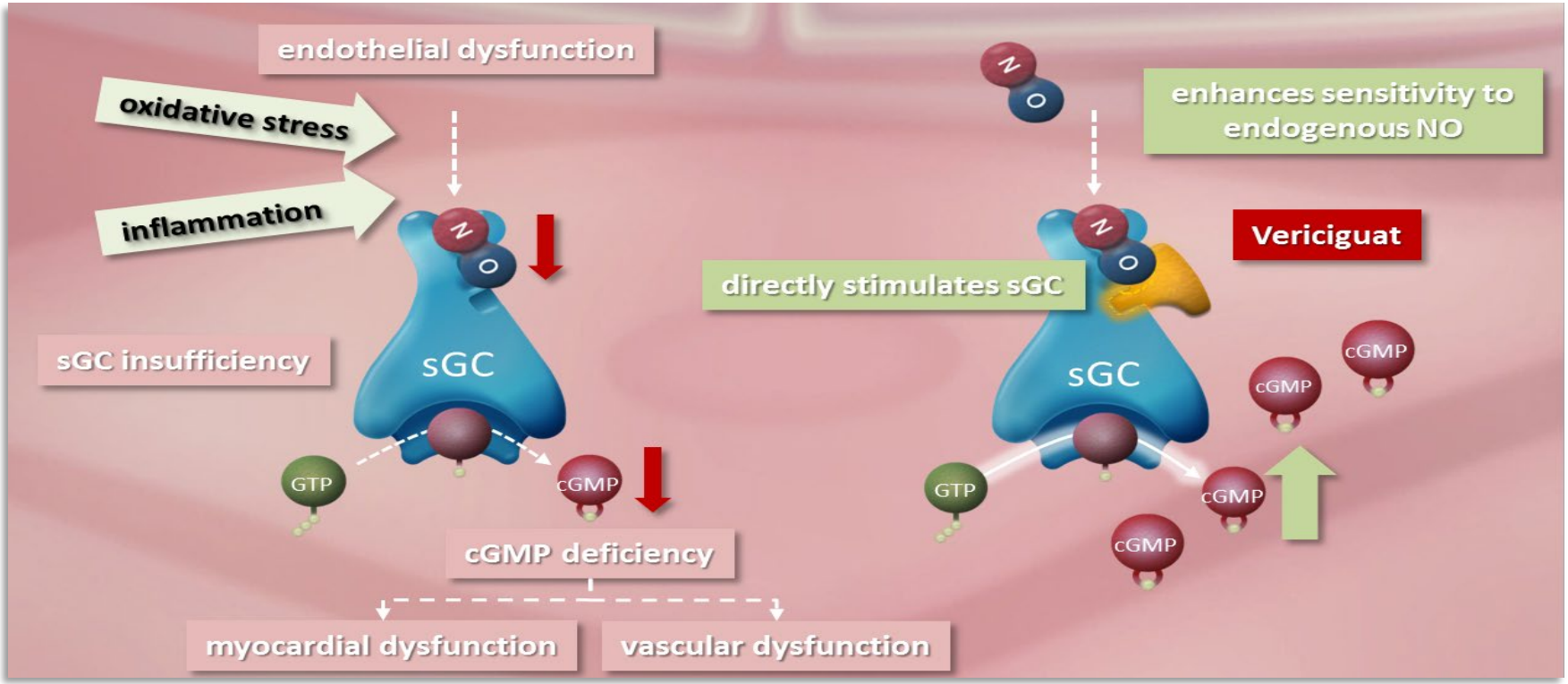
Vericiguat: sGC Stimulation as a Novel Mechanism With a Dual Mode of Action



cGMP=cyclic guanosine monophosphate; GTP=guanosine triphosphate; NO=nitric oxide; sGC=soluble guanylate cyclase.

Stasch JP, et al. *Nature*. 2001;410(6825):212-215; Evgenov OV, et al. *Nat Rev Drug Discov*. 2006;5(9):755-768;
Stasch JP, Evgenov OV. *Handb Exp Pharmacol*. 2013;218:279-313.

VICTORIA: Inclusion Criteria

“Chronic HF”

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

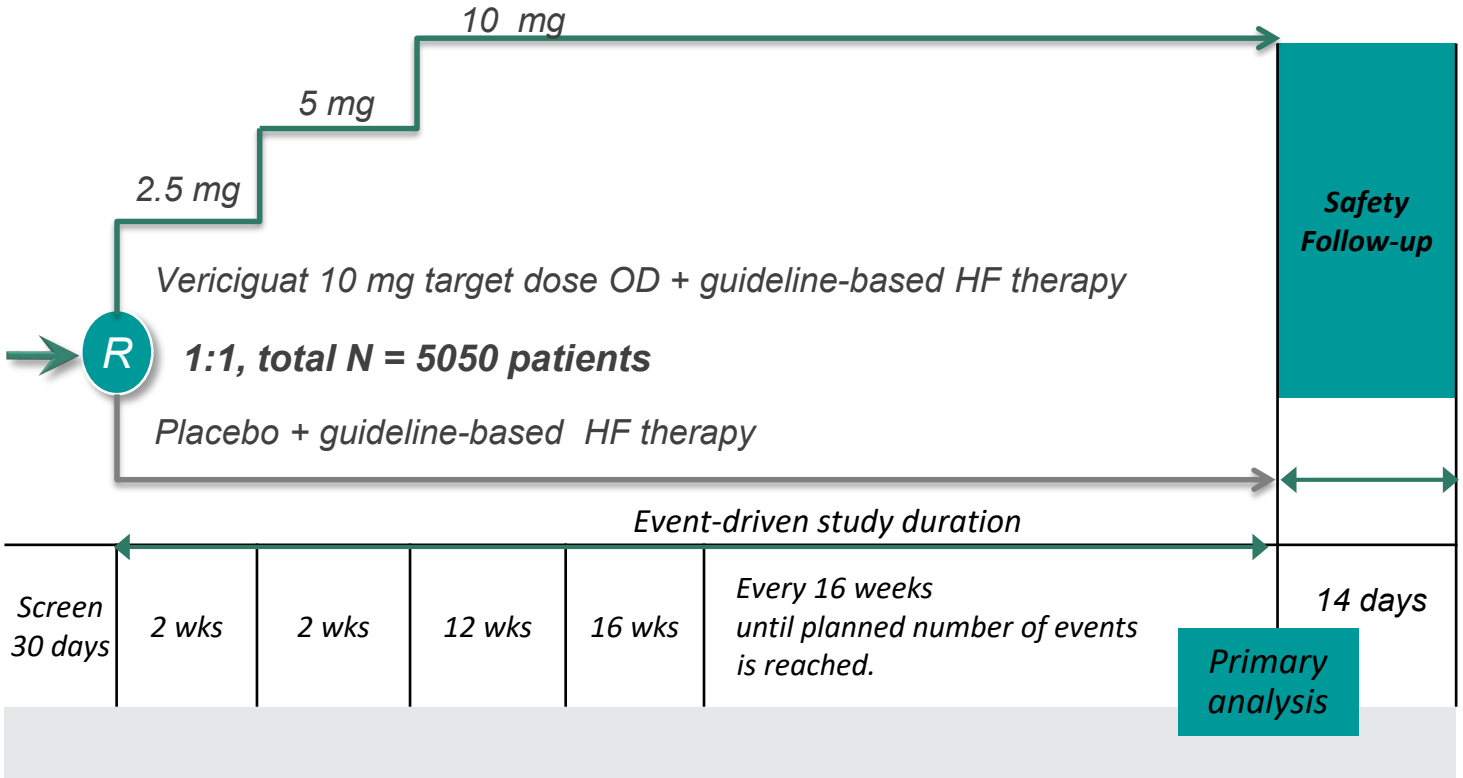
after

“Worsening event”

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

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)

VICTORIA: Study Design



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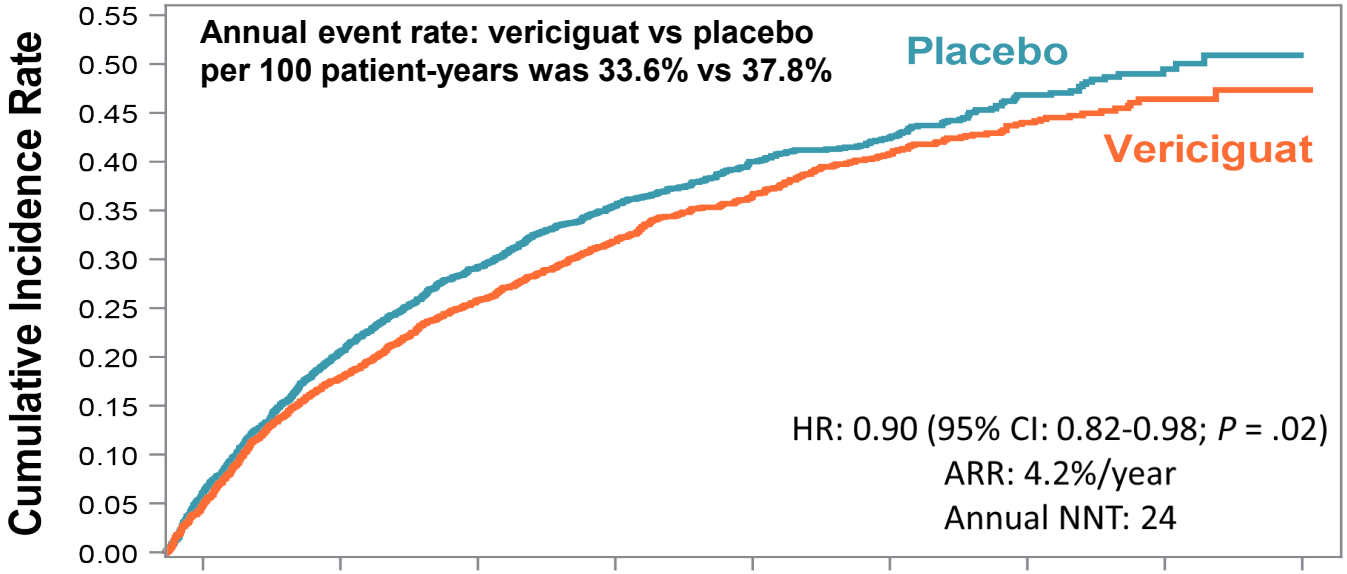
VICTORIA: Primary Composite Endpoint CV Death or First HF Hospitalization



Number at Risk:

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

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Background of VICTORIA AF Study

- Atrial fibrillation (AF) is the most frequent arrhythmia complicating HFrEF
- Whether AF is an independent predictor of poor outcome rather than a reflection of the underlying HF severity remains unclear
- Recommended HF treatments (ACE inhibitors, beta-blockers, or MRAs) *may* reduce the incidence of AF in patients with HFrEF
- The effects of some guideline-recommended treatments may differ according to whether AF is present or not
- High prevalence of AF in the VICTORIA trial (45% reported Hx of AF)
- Relationship between AF and outcomes as well as vericiguat's treatment benefit in this population are unknown

Objectives

- Determine the relation between the clinical outcomes and presence of AF at baseline and occurrence of new-onset AF post-randomization
- Assess subsequent relationship of new-onset AF on clinical outcomes.
- Evaluate whether the treatment effects of vericiguat were related to the presence of AF at baseline

Methods

Data on AF at a randomization visit based on:

- medical history available from the case report forms
- investigator evaluation of an electrocardiogram performed at randomization

Classification of AF

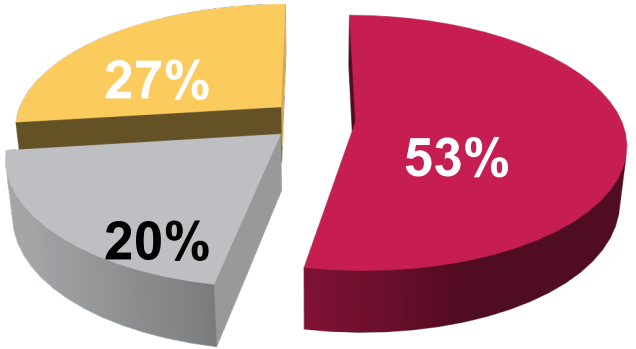
- **not known AF**
- **intermittent AF** (history of AF alone, without AF on ECG at randomization),
- **AF present on randomization ECG**.

Post-randomization onset AF was assessed among patients without AF at randomization (with not known AF and intermittent AF).

Results

Of 5050 patients randomized, 5010 with recorded AF status at baseline were analysed

AF status at baseline



Differences in clinical characteristics

Patients with either type of AF were:
older, more often male, more frequently in NYHA class III–IV at randomization, had poorer renal function, more prevalent history of stroke, COPD, and anaemia, less prevalent T2DM, higher MAGGIC risk scores and higher NT-proBNP levels vs those without AF.

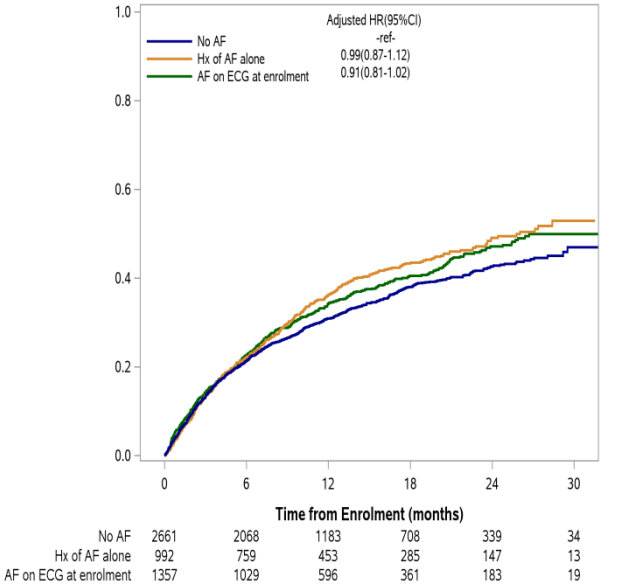
Antithrombotic therapy was used more frequently in patients with either type of AF.

Patients with intermittent AF had the lowest use of triple medical therapy, highest use of ICD and biventricular pacemakers.

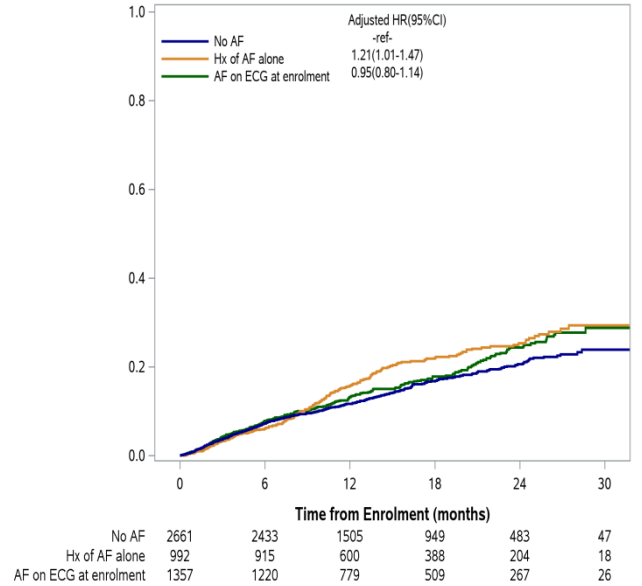
Results

Association Between AF Status at Randomization and Study Outcomes

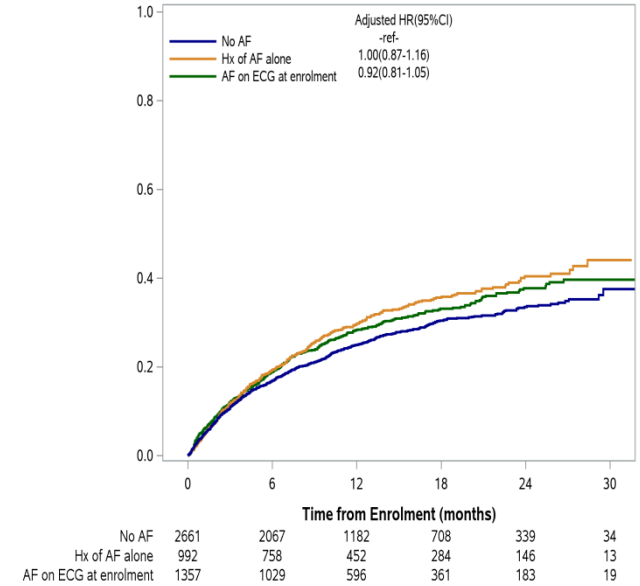
Primary composite outcome
(CV death or HF hospitalization)



CV death



HF hospitalization



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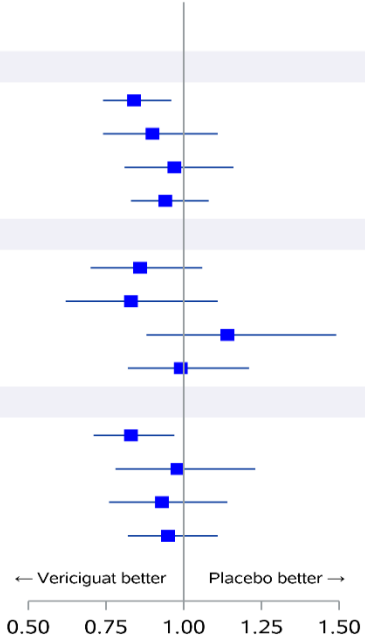
Results

Association Between the AF Status at Randomization and Efficacy of Vericiguat

Outcome	Events, n(%)	HR (95% CI)	P-int.	Event rate/100 per-yrs. Vericiguat	Placebo
Primary Outcome			0.45		
No AF	921/2661(34.6%)			31.2	36.2
Intermittent AF	408/ 992(41.1%)			36.6	40.6
AF on ECG	519/1357(38.2%)			36.7	37.8
Any AF	927/2349(39.5%)			36.6	39.0
CV death			0.18		
No AF	404/2661(15.2%)			11.2	13.2
Intermittent AF	200/ 992(20.2%)			13.8	17.0
AF on ECG	238/1357(17.5%)			15.3	12.6
Any AF	438/2349(18.6%)			14.6	14.5
HF hospitalization			0.44		
No AF	698/2661(26.2%)			23.3	27.6
Intermittent AF	322/ 992(32.5%)			30.3	30.8
AF on ECG	403/1357(29.7%)			27.9	29.9
Any AF	725/2349(30.9%)			28.9	30.3



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Results

Post-randomization, New-onset AF

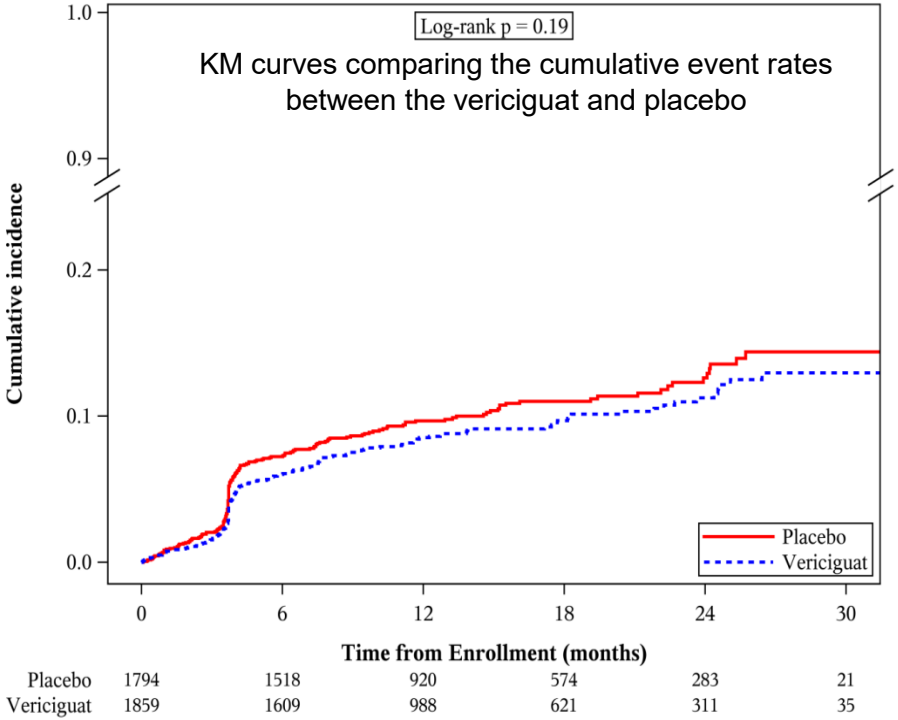
Over a median follow-up of 10.8 months, an episode of post-randomization AF occurred in **345 (9.4%) patients**.
Among them:

- **163 (6.1%) had no prior AF**
- **182 (18.3%) had intermittent AF** previously

(p<0.0001).

The incidence of post-randomization AF did not differ between patients receiving vericiguat and placebo (event rate: 7.5 vs 8.7 per 100 person-years, adjusted HR 0.93, 95% CI 0.75–1.16; p=0.51).

Incidence of post randomization AF



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Associations of post-randomization onset of AF with primary and secondary outcomes

	All Patients (n=3653)	Placebo (n=1794)	Vericiguat (n=1859)	Interaction P-value*
Primary outcome				
Patients with events, no. (%)	1329 (36.4%)	686 (38.2%)	643 (34.6%)	
Adjusted* HR (95% CI)	2.16 (1.76-2.67)	2.11 (1.58-2.81)	2.23 (1.66-2.98)	0.79
Cardiovascular death				
Patients with events, no. (%)	604 (16.5%)	321 (17.9%)	283 (15.2%)	
Adjusted† HR (95% CI)	1.71 (1.29-2.27)	1.83 (1.25-2.68)	1.59 (1.06-2.40)	0.62
HF hospitalization				
Patients with events, no. (%)	1020 (27.9%)	522 (29.1%)	498 (26.8%)	
Adjusted† HR (95% CI)	2.39 (1.90-3.02)	2.40 (1.75-3.30)	2.39 (1.73-3.31)	0.99

*Test of significance of the difference in the association of post-randomization AF with outcome, according to treatment arm.
†Adjusted for VICTORIA prognostic model with NT-proBNP + Medical history of AF.

Summary and Conclusions

- Nearly half of this high-risk population of patients with HFrEF and recent HF decompensation had AF
- Only patients with intermittent AF (but no AF on enrolment ECG) had worse outcomes as compared with those without AF.
- Post-randomization, new-onset AF occurred relatively commonly (in 1 out of 10 patients) during a short follow-up of less than 1 year, was distributed evenly by treatment groups, and was associated with an excess in risk of both the primary and secondary outcomes.
- The beneficial effect of vericiguat was unaffected by any type of AF at baseline

Thank you!

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