Pre-randomization NT-proBNP trajectory and outcomes in the VICTOR trial

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Introduction

- Heart failure (HF) with reduced ejection fraction (HFrEF) is associated with a high risk of mortality.[1,2]
- Vericiguat is a soluble guanylate cyclase stimulator approved for the treatment of people with HFrEF following hospitalisation for HF (HHF) or who needed an outpatient visit requiring intravenous diuretic therapy.[3,4]
- The VICTOR trial (NCT05093933) evaluated over 6100 adult participants with symptomatic chronic HFrEF who had not experienced recent worsening HF (eg, no recent HHF).[5]
- In the VICTOR trial, enrolment was enriched using screening N-terminal pro-B-type natriuretic peptide (NT-proBNP) thresholds of 600–6000 ng/L (900–6000 ng/L if in atrial fibrillation [AFib]).[6] However, NT-proBNP levels may have fluctuated between screening and randomisation.

Aim of the study

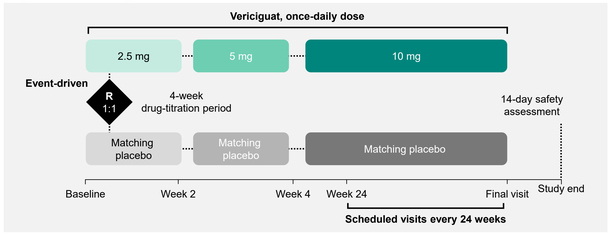
To evaluate the impact of different NT-proBNP trajectories between screening and randomisation on outcomes in the VICTOR trial.

Methods

Design

- The VICTOR trial was a phase 3, double-blind, randomised, placebo-controlled trial, designed to assess the effects of vericiguat (target dose 10 mg) *versus* placebo in ambulatory patients with HFrEF and no recent worsening HF event.[5,6]
- The study rationale and design have been described previously.[5,6]
- The study design is shown in **Figure 1**.
- The primary endpoint of VICTOR was a composite of time to first occurrence of cardiovascular (CV) death or HHF. The trial was powered to assess the effect of vericiguat on the hierarchical secondary outcome of CV death.
  - The primary and key secondary endpoints are outlined in **Table 1**.
- For this analysis, the participants in the VICTOR trial were categorised by screening-to-randomisation NT-proBNP trajectory into 3 groups: 'Stable' (staying within 600–6000 ng/L), 'Drop' (falling below 600 [or 900 ng/L in AFib]), or 'Rise' (rising above 6000 ng/L).

Figure 1. Design of the VICTOR trial[5,6]



Primary endpoint
- Time to first occurrence of CV death or HHF

Hierarchical secondary endpoints

Time to:
- CV death
- First HHF
- Total HHF events (first and recurrent events)
- All-cause death/HHF
- All-cause death

CV, cardiovascular; HHF, hospitalisation for heart failure; R, randomised.

Table 1. VICTOR trial: primary, key secondary, and exploratory endpoints[5,6]

Primary endpoint
Time from randomisation to the first occurrence of CV death or HHF
Secondary endpoints
Time from randomisation to CV death, time to first event of HHF, time to total (first and recurrent) HHF, time to the first event of all-cause death or HHF, and time to all-cause death
Exploratory endpoints
Time from randomisation to the first event of HHF or urgent HF visit; time to the first event of CV hospitalisation; total number of HHF events; change from baseline in health status (measured by the Kansas City Cardiomyopathy Questionnaire and EQ-5D-5L questionnaire); and slope of change in estimated glomerular filtration rate from baseline

CV, cardiovascular; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HF, heart failure; HHF, hospitalisation for heart failure.

Statistical analysis

- Endpoints were assessed using Cox proportional hazard models with covariates of stratification factors defined by baseline New York Heart Association class, treatment, NT-proBNP trajectory subgroup, and treatment-by-subgroup interaction.
- A trend test was performed using a separate Cox proportional hazard model in which NT-proBNP subgroup was coded as a numeric covariate.
- All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

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Results

Participants

- There were 6105 participants randomised; 3053 were assigned to vericiguat and 3052 to placebo.
- Baseline characteristics of the study population have been published previously.[5] The mean age was 67 years, 24% were women, mean left ventricular ejection fraction was 30%, and 79% had New York Heart Association class II symptoms.
- Overall, 94% of participants were on beta-blockers, 94% were on a renin–angiotensin system modulation agent (including 56% on an angiotensin receptor/neprilysin inhibitor), 78% were receiving a mineralocorticoid receptor antagonist, and 59% were on a sodium–glucose cotransporter-2 inhibitor.
  - Overall, 84% were being treated with at least 3 guideline-directed medical therapies.

Screening-to-randomisation NT-proBNP analysis

- By the time of randomisation, NT-proBNP levels remained stable in 4888 (80%) participants, dropped below the eligibility threshold in 832 (13.6%) participants, and rose above 6000 ng/L in 172 (2.8%) participants.
- For the primary composite endpoint of CV death or HHF, or for the single endpoints of CV death or all-cause death, no significant differences were observed across the 'Drop', 'Stable', and 'Rise' subgroups (hazard ratio [HR] and 95% confidence interval [CI], 0.92 [0.57–1.50], 0.95 [0.83–1.08], and 0.63 [0.39–1.01]; p-trend=0.26 for the primary composite endpoint; 0.75 [0.40–1.41], 0.86 [0.72–1.02], and 0.48 [0.25–0.94]; p-trend=0.36 for CV death; and 0.78 [0.45–1.33], 0.85 [0.73–0.99], and 0.65 [0.38–1.13]; p-trend=0.66 for all-cause death, respectively).
- No differences across the 3 subgroups were observed for either the composite of all-cause death or any HF event (ie, HHF, urgent HF visit, or oral diuretic intensification) and the composite of CV death or any HF event (**Table 2**).

Table 2. Screening-to-randomisation NT-proBNP trajectory subgroups analysis

		Vericiguat (N=3053)			Placebo (N=3052)				
Endpoints	**NT-proBNP trajectory**	**Events/Total (%)**	**Annual (%)†**	**KM (95% CI)‡**	**Events/Total (%)**	**Annual (%)†**	**KM (95% CI)‡**	**HR (95% CI)§**	**P for trend‖**
Primary endpoint (CV death or HHF)	Drop to <600 ng/L (<900 ng/L for AFib)¶	32/420 (7.6)	4.6	14.6 (9.3–22.6)	34/412 (8.3)	4.9	10.7 (7.5–15.3)	0.92 (0.57–1.50)	0.256
	Consistently stable#	466/2447 (19.0)	12.1	25.9 (23.4–28.6)	487/2441 (20.0)	12.8	28.4 (25.8–31.3)	0.95 (0.83–1.08)	
	Rise above 6000 ng/L††	29/85 (34.1)	25.1	42.4 (30.6–56.4)	40/87 (46.0)	39.8	53.8 (42.0–66.6)	0.63 (0.39–1.01)	
CV death	Drop to <600 ng/L (<900 ng/L for AFib)¶	17/420 (4.0)	2.4	10.3 (5.6–18.6)	22/412 (5.3)	3.1	7.0 (4.4–11.0)	0.75 (0.40–1.41)	0.359
	Consistently stable#	247/2447 (10.1)	6.0	14.1 (12.2–16.2)	283/2441 (11.6)	6.9	17.7 (15.6–20.2)	0.86 (0.72–1.02)	
	Rise above 6000 ng/L††	13/85 (15.3)	9.9	21.1 (12.3–34.8)	25/87 (28.7)	20.4	38.8 (26.8–54.0)	0.48 (0.25–0.94)	
First HHF	Drop to <600 ng/L (<900 ng/L for AFib)¶	17/420 (4.0)	2.4	6.2 (3.3–11.6)	15/412 (3.6)	2.2	4.7 (2.8–7.9)	1.11 (0.56–2.23)	0.247
	Consistently stable#	297/2447 (12.1)	7.7	17.1 (14.9–19.5)	304/2441 (12.5)	8.0	18.0 (15.9–20.5)	0.97 (0.82–1.13)	
	Rise above 6000 ng/L††	21/85 (24.7)	18.3	32.6 (21.7–47.0)	27/87 (31.0)	26.8	43.2 (30.7–58.2)	0.68 (0.38–1.20)	
All-cause mortality	Drop to <600 ng/L (<900 ng/L for AFib)¶	24/420 (5.7)	3.3	12.6 (7.5–20.6)	30/412 (7.3)	4.2	11.1 (7.2–17.0)	0.78 (0.45–1.33)	0.66
	Consistently stable#	313/2447 (12.8)	7.6	18.4 (16.3–20.8)	362/2441 (14.8)	8.9	21.4 (19.2–23.9)	0.85 (0.73–0.99)	
	Rise above 6000 ng/L††	22/85 (25.9)	16.7	33.1 (22.3–47.3)	31/87 (35.6)	25.3	44.9 (32.4–59.5)	0.65 (0.38–1.13)	
First HHF, UHF, or ODI	Drop to <600 ng/L (<900 ng/L for AFib)¶	44/420 (10.5)	6.5	13.6 (9.8–18.8)	41/412 (10.0)	6.2	13.1 (9.5–18.0)	1.04 (0.68–1.60)	0.297
	Consistently stable#	579/2447 (23.7)	16.5	30.2 (27.8–32.8)	635/2441 (26.0)	18.5	35.9 (33.1–38.9)	0.90 (0.80–1.00)	
	Rise above 6000 ng/L††	34/85 (40.0)	33.4	46.8 (34.9–60.3)	39/87 (44.8)	46.8	51.7 (40.1–64.5)	0.74 (0.47–1.18)	
First all-cause mortality, HHF, UHF, or ODI	Drop to <600 ng/L (<900 ng/L for AFib)¶	64/420 (15.2)	9.5	23.0 (17.2–30.3)	66/412 (16.0)	9.9	22.6 (17.3–29.2)	0.94 (0.67–1.33)	0.479
	Consistently stable#	771/2447 (31.5)	22.0	39.8 (37.1–42.6)	849/2441 (34.8)	24.7	45.8 (42.9–48.7)	0.89 (0.81–0.98)	
	Rise above 6000 ng/L††	46/85 (54.1)	44.9	60.8 (48.6–73.2)	50/87 (57.5)	60.0	60.6 (49.7–71.8)	0.77 (0.52–1.15)	
First CV death, HHF, UHF, or ODI	Drop to <600 ng/L (<900 ng/L for AFib)¶	57/420 (13.6)	8.4	20.8 (15.1–28.2)	59/412 (14.3)	8.9	18.7 (14.3–24.3)	0.94 (0.65–1.35)	0.379
	Consistently stable#	726/2447 (29.7)	20.7	37.3 (34.7–40.0)	797/2441 (32.7)	23.2	43.9 (41.0–47.0)	0.89 (0.81–0.99)	
	Rise above 6000 ng/L††	41/85 (48.2)	40.0	53.9 (42.0–66.8)	48/87 (55.2)	57.6	59.4 (48.3–70.8)	0.72 (0.47–1.09)	

†Total participants with an event/time at risk in years.
‡KM estimate and CI at 2.5 years.
§HR (vericiguat *vs* placebo) and CI from Cox proportional hazard model with covariates of the stratification factors, treatment, subgroup, and treatment-by-subgroup interaction. The HR estimates for the subgroup of 'Rise above 6000 ng/L' are based on very limited data; results are exploratory and should be interpreted with caution.
‖Based on a separate Cox proportional hazard model with the same covariates in which subgroup was coded as a numeric covariate.
¶Screening NT-proBNP of 600–6000 ng/L (900–6000 ng/L for AFib) and drop to <600 ng/L (<900 ng/L for AFib) at randomisation.
#Screening NT-proBNP of 600–6000 ng/L (900–6000 ng/L for AFib) and consistently stable between 600–6000 ng/L (900–6000 ng/L for AFib) at randomisation.
††Screening NT-proBNP of 600–6000 ng/L (900–6000 ng/L for AFib) and rose above 6000 ng/L at randomisation.
AFib, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HHF, hospitalisations for heart failure; HR, hazard ratio; KM, Kaplan–Meier; NT-proBNP, N-terminal pro B-type natriuretic peptide; ODI, oral diuretic initiation or intensification; UHF, urgent visit for heart failure.

Conclusions

- In this *post hoc* analysis of the VICTOR trial, no differences in outcomes were observed across 3 subgroups of NT-proBNP trajectory between screening and randomisation.
- The estimates for the 'Rise' subgroup are based on very limited data.

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