Baseline Cardiac Troponin T, Clinical Outcomes and Vericiguat Treatment Effect in Heart Failure with Reduced Ejection Fraction Study

Insights from the VICTORIA Trial

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BACKGROUND

- Vericiguat is a soluble guanylate cyclase stimulator that can result in systemic and pulmonary vasodilation as well prevention and even reversal of left ventricular hypertrophy and fibrosis in experimental models.
- In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial (NCT02861534) vericiguat reduced the primary composite of cardiovascular death (CVD) or heart failure (HF) hospitalization (HFH) in HF with reduced ejection fraction (HFrEF).
- Placebo events/100 patient years at risk were 37.8, 13.9 and 29.1 respectively for the primary endpoint, CVD and HFH in this high-risk study population.
- **We hypothesized that baseline cardiac troponin T (cTnT) was associated with the primary endpoint, its components and vericiguat's benefit.**

METHODS

- High sensitivity cTnT (hs-cTnT) was measured at baseline in 4614 of 5050 VICTORIA participants (Roche Diagnostics, detection limit 3 ng/L).
- The association of hs-cTnT with the CVD/HFH was expressed as hazard ratios (HR) and 95% confidence intervals (CI) per standard deviation (SD) increase in the log transformed scale, and interaction with treatment (Tx) was tested. Associations were adjusted for the (i) VICTORIA risk model [includes NT-proBNP], and (ii) MAGGIC Risk Score.

RESULTS

- Median cTnT was 30 (IQ range Q1=19, Q3=49) ng/L.
- In participants with hs-cTnT measurements baseline characteristics were similar between vericiguat versus placebo assignment.
- Increasing baseline hs-cTnT was associated with an increased risk of the CVD/HFH (Table).
- Similar associations occurred with CVD (1.22; 1.13-1.32) and HFH (1.21; 1.13-1.29) even with the optimized VICTORIA risk model inclusive of NT-proBNP. The Table and Figures demonstrate the relationship between the composite outcome (and its components) and baseline levels of hs-cTnT: Histograms show the percent distribution of patients
- For the primary outcome, a Tx interaction with hs-cTnT was present when adjusting for the MAGGIC Risk Score, but not the VICTORIA risk model (Table, Figure 1). Higher treatment effect of Vericiguat was observed at lower baseline cTnT level, especially when below the Q3 threshold.
- However, a significant Tx interaction remained for CVD (p=0.04), but not HFH (p=0.38) when using the VICTORIA risk model (Figures 2 and 3).

CONCLUSION

- Baseline hs-cTnT was significantly associated with CVD and HFH in VICTORIA and exhibits a spectrum of CVD risk associated with vericiguat treatment.
- hs-cTnT appears important in identifying high-risk HFrEF and lower baseline hs-cTnT was associated with a greater effect of vericiguat on CVD.

In the VICTORIA trial vericiguat reduced the primary outcome of CV death/HF hospitalization in patients with HFrEF.

Measuring cTnT at baseline improved risk-stratification even when including a comprehensive model of clinical co-variates and NT-proBNP level. Baseline cTnT was significantly associated with cardiovascular death and heart failure hospitalization in VICTORIA.

A higher baseline cTnT level appears important in identifying high-risk HFrEF and a lower cTnT level was associated with a greater effect of vericiguat for reducing cardiovascular death.

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DISCUSSION

VICTORIA is a clinical trial that treated a population of HFrEF patients with higher event rates compared to other contemporary trials. In this setting hs-cTnT identified patients at progressively higher risk of an adverse endpoint even when accounting for NT-proBNP, which was previously shown to be prognostic and associated with Tx effect. Increasing baseline hs-cTnT identified vericiguat Tx benefit through the 3rd quartile (49 ng/L) and maintained a significant interaction for CVD, but not HFH when accounting for another cardiac specific biomarker, NT-proBNP.

TABLE

Association between baseline hs-cTnT level* with the primary composite and individual outcomes and vericiguat treatment effect

	Adjusted for VICTORIA risk model†			Adjusted for MAGGIC score‡		
Outcome	**HR (95% CI) per SD**	**p**	**Interaction p**	**HR (95% CI) per SD**	**p**	**Interaction p**
Primary	1.21(1.14-1.27)	<0.01		1.42(1.35-1.48)	<0.01	
Treatment			0.12			<0.01
CV death	1.22(1.13-1.32)	<0.01		1.53 (1.43-1.63)	<0.01	
Treatment			0.04			<0.01
HF hospitalization	1.21(1.13-1.29)	<0.01		1.38 (1.31-1.46)	<0.01	
Treatment			0.38			0.08

* hs-cTnT levels are on the log scale; HRs are per SD increase in the log-transformed biomarker level
† Ezekowitz JA. J Am Coll Cardiol HF 2020; 8:931-9
‡ Pocock SJ. Eur Heart J 2013; 34:1404-13

FIGURE 1

VICTORIA-adjusted treatment effect of vericiguat by hs-cTnT at randomization: CVD/HFH

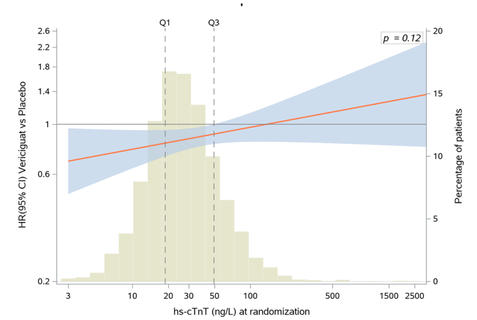


FIGURE 2

VICTORIA-adjusted treatment effect of vericiguat by hs-cTnT at randomization: CVD

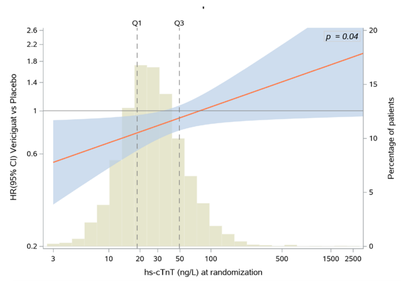
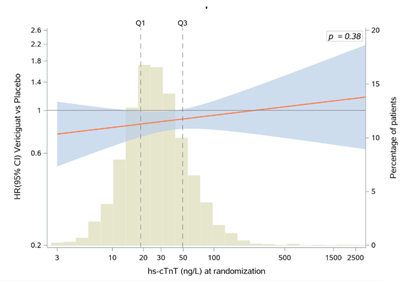


FIGURE 3

VICTORIA-adjusted treatment effect of vericiguat by hs-cTnT at randomization: HFH



DISCLOSURE INFORMATION

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