



What is the mechanism of action of vericiguat?

- Vericiguat is a soluble guanylate cyclase stimulator(sGC stimulator). In HF, sCG activity and NO bioavailability are decreased due to oxidative stress and endothelial dysfunction, resulting in myocardial and vascular dysfunction.
- Vericiguat restores the NO-sGC-cGNP pathway by directly stimulating sGC and also by enhancing sensitivity to endogenous NO
- The subsequent increase in cGMP may improve myocardial function and vascular tone.



How is vericiguat different than riociguat?



- Vericiguat and riociguat are both sGC stimulators acting as modulators of the NO–sGC–cGMP pathway. These GC stimulators are different molecules with discrete PK/PD profiles and were developed to treat different diseases.
- Riociguat is an approved drug administered three times daily for the treatment of pulmonary hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).
- By contrast vericiguat is given once daily dosing leading to a higher peak-to-trough fluctuation vericiguat concentrations with associated hemodynamic changes. This agent has not been studied in patients with PAH or CTEPH.
- Hence *vericiguat should not be used in PAP or CTEPH patients* because of potentially significant acute hypotensive effects.



What were the special features of the VICTORIA patient population?



- They had worsening HF developed on top of a background of chronic stable HFrEF.
- This population is now recognized as increasingly common i.e. estimated at ~ 1/5 patients annually . Yet they have been rarely studied in clinical trials.
- This population was selected because of their high baseline risk profile: this is known to portend an increased likelihood of cardiovascular death(CVD) or repeat hospitalization for heart failure(HFH).
- All VICTORIA patients had prior chronic HFrEF with a recent worsening HF event; *two thirds had HFH within prior 3 mos, one sixth within the prior 6 mos and one sixth had and emergency visit requiring IV diuretic therapy.*
- Despite excellent background guideline based HF therapy (>60% on triple therapy, >30% ICD/BiV pacemakers) they showed deterioration which vericiguat was able to significantly prevent.



What were the VICTORIA outcomes?

Did the short median follow up (10.8 mos) influence CV death?



- Remarkably, their annualized placebo event rates for the primary composite endpoint was 37.8% (based on a time to first event analysis); *importantly the annualized rate for CV death was 13.9% and for HFH was 29.1%.*
- These events came early and often in VICTORIA and the prespecified target event rate of 782 CV deaths was reached relatively quickly.
- While the CVD reductions were concordant with the overall the treatment benefit of vericiguat, the unexpectedly short follow up time limited exploring a potentially significant late treatment benefit on mortality.
- Nonetheless, the annualized reduction from 13.9 to 12.9% in CV death contributed about ¼ of the treatment benefit seen with vericiguat.



Why the treatment heterogeneity with Quartiles of NT-proBNP?



- The NT-proBNP threshold for inclusion was higher and the median levels at baseline were more than 2 fold greater than in recent HFrEF trials (PARADIGM and DAPA-HF).
- Based on prior studies it was prospectively decided to explore the treatment effect of vericiguat according to baseline NT-proBNP by quartiles.
- An interaction signal for less benefit was observed in the 4th NTproBNP quartile (i.e. those with NT-proBNP <5314pg/ml).
- By contrast, clear benefit was evident in the other 3 subgroups in Q1,2, and 3 (hazard ratios 0.78, 0.73 and 0.82 respectively).
- Because other high risk features signaling very high risk likely coexist in this upper NT-proBNP quartile - *such as advanced age and diminished renal function*- these findings are the subject of ongoing investigation.



What more has been learned about vericiguat and NTproBNP since ACC 2020 and the NEJM original publication?



- New analysis exploring NT-proBNP as a continuous variable demonstrates a vericiguat treatment benefit for 86% of the VICTORIA population with levels <8000 pg/ml. Specifically hazard ratios for the primary composite of 0.85, for CVD 0.84 and for HFH 0.78 (HFA Discovery June 19 2020).
- This benefit is further amplified in the 2/3 of the population with NT-proBNP <4000 pg/ml: for CVD/HFH 0.77, for CVD 0.75 and for HFH 0.78.
- Hence these new data provide further insight into the treatment effect of vericiguat and how the benefit also extends to the individual endpoints of CVD and HFH.



What were the characteristics of VICTORIA patients with NT-proBNP values above 8000pg/ml?



- As expected, they exhibited other high risk features i.e. lower EF, more NYHA Class III and lower GFR.



What is the mechanism of anemia with vericiguat?



- Anemia developed in more patients in the vericiguat group than placebo (7.6% vs 5.6%); of these, 1.6% in vericiguat and 0.9% in placebo were considered serious.
- Change from baseline in Hgb level at week 16 was - 0.38 +/- 1.27 g/dL in vericiguat vs -0.14 +/- 1.30 g/dL in placebo.
- The exact mechanism for anemia is not well understood but may be due to hemodilution secondary to fluid overload, decreased EPO production or other factors. Anemia was also seen with riociguat.
- Etiologies due to bleeding, hemolysis are unlikely. Because ~10% patients in VICTORIA had diminished eGFR < 30 ml/min/m² (mean eGFR 62 ml/min/m² in entire population), this may also be a causal factor.
- Further investigation is underway and more analysis will be forthcoming.



What % of VICTORIA patients were on SGLT2 inhibitors?



- Only ~3% patients in VICTORIA were on SGLT2 inhibitors at baseline.
- No conclusions can be drawn from this analysis.



What % of patients were on sacubitril/valsartan (Entresto)?



- Approximately 15% of patients in VICTORIA were on S/V at baseline.
- As will be evident from the Forest plot in the original NEJM publication vericiguat's treatment effect on the primary endpoint was similar *irrespective of baseline S/V use*.

