Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA)

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Background

Heart failure with reduced ejection fraction remains a burden on our healthcare system even among patients who are receiving guideline-directed medical therapy (GDMT). The average annual heart failure specific hospitalization cost is speculated to be approximately $15,000 per patient, with a large percent of patients requiring readmission within 90 days of their initial discharge.

Vericiguat, a novel oral soluble guanylate cyclase stimulator, enhances the cGMP pathway by directly stimulating soluble guanylate cyclase (sGC) and sensitizes sGC to endogenous nitric oxide (NO) through a binding site independent of nitric oxide by stabilizing NO binding to the binding site. This mechanism is significant because in heart failure,the NO-sGC pathway becomes dysregulated leading to impairment in diastolic relaxation and microvascular dysfunction. In this trial, efficacy and safety of vericiguat in patients with a reduced ejection fraction and recent decompensated heart failure was studied.

Methods

- Multinational, randomized, double-blind, placebo-controlled trial

Inclusion criteria

- ≥ 18 years old
- Have chronic heart failure NYHA class II-IV on standard therapy
- Have left ventricular ejection fraction of < 45% within 12 months prior to randomization
- Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization
- Have BNP or NT-proBNP levels within 30 days prior to randomization as follows:

	NT-proBNP	BNP
Sinus rhythm	≥1000 pg/mL	≥300 pg/mL
Atrial fibrillation	≥1600 pg/mL	≥500 pg/mL

Exclusion Criteria

- Clinically unstable at the time of randomization as defined by:
    - Administration of any IV treatment with 24 hours prior to randomization AND/OR
    - Systolic blood pressure <100 mmHg or symptomatic hypotension

- Has concurrent or anticipated use of long-acting nitrates or NO donors including isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil or transdermal nitroglycerin patch, and molsidomine
- Has concurrent use or anticipated use of PDE5 inhibitors
- Has concurrent use or anticipated use of a sGC stimulator such as riociguat
- Has known allergy or sensitivity to any sGC stimulator
- Is awaiting heart transplant, receiving continuous IV infusion of an inotrope, or has/anticipates receiving a VAD

Cardiac Comorbidity

- Has primary valvular heart disease requiring surgery or intervention, or is within 3 months after valvular surgery or intervention
- Has acute myocarditis, amyloidosis, sarcoidosis, Takotsubo cardiomyopathy
- Has acute coronary syndrome or coronary revascularization within 60 days prior to randomization, or indication for coronary revascularization at time of randomization

Non-cardiac Comorbidity

- Has eGFR < 15 mL/min/1.73m2 or chronic dialysis
- Has severe hepatic insufficiency
- Has malignancy or other non-cardiac condition limiting life expectancy to < 3 years
- Is pregnant or breastfeeding or plans to become pregnant or breastfeed

Patients categorized into three cohorts:

- Hospitalization within 3 months before randomization
- Hospitalization 3 to 6 months before randomization
- Receiving IV diuretic, without hospitalization, within the previous 3 months

Randomly assigned in 1:1 ratio

- 2.5 mg of vericiguat or matching placebo
- Screening period (0-30 days)
    - No run-in period
- Doses increased to 5 mg and ultimately to target dose of 10 mg daily
    - Guided by blood pressure and other clinical symptoms
- Evaluated at weeks 2 and 4, and every 4 months thereafter until the end of the trial

Trial Outcomes

Primary outcome:

- composite of death from cardiovascular causes or first hospitalization for heart failure

Secondary outcomes:

- Components of the primary outcome
- First and subsequent hospitalizations for heart failure
- A composite of death from any cause or first hospitalization for heart failure
- Death from any cause

Safety outcomes of clinical interest:

- symptomatic hypotension
- syncope

Results

- 6857 patients screened between September 25, 2016 and December 21, 2018 in 42 countries
    - 5050 patients enrolled
        - 2526 patients in vericiguat cohort
        - 2524 patients in placebo cohort

- Mean age: 67 years old
- 75% males
- At randomizations:
    - ⅔ of patients had been enrolled within 3 months of their index HF hospitalization
    - 40% were classified as having NYHA Class III HF
    - Mean ejection fraction was 29%
    - Median NT-proBNP level was 2816 pg/mL
    - Concomitant GDMT was essentially balanced between the two cohorts
- Similar adherence to trial drug between cohorts
- At one year, 90% of patient in treatment arm were receiving target dose

<u>Follow-up and Trial Outcomes</u>

- 610 patients and 565 patients in the vericiguat and placebo cohorts, respectively, discontinued the trial regimen
- Median follow-up period was 10.8 months

	Vericiguat (n)	Placebo (n)	
Primary Outcome Composite of death from CV cause or first hospitalization for HF	35.5(897)	38.5(972)	HR 0.90; 95% CI, 0.82 to 0.98; P=0.02
Secondary Outcomes Death from CV cause First Hospitalization for HF Total Hospitalizations for HF Death from any cause or first hospitalization for HF Death from any cause	 16.4(414) 27.4(691) 48.4(1223) 37.9(957) 20.3(512)	 17.5(441) 29.6(747) 52.9(1336) 40.9(1032) 21.2(534)	 HR, 0.93; 95% CI, 0.81 to 1.06 HR, 0.90: 95% CI, 0.81 to 1.00 HR, 0.91: 95% CI, 0.84 to 0.99; P=0.02 HR, 0.9; 95% CI, 0.83 to 0.98; P=0.02 HR, 0.95; 95% CI, 0.84 to 1.07; P=0.38
Adverse Events Symptomatic Hypotension Syncope Anemia -Serious adverse event with anemia	 9.1(230) 4(101) 7.6(192) 1.6(40)	 7.9(199) 3.5(88) 5.7(144) 0.9(23)	 P=0.12 P=0.30

Discussion

In this trial, the rate of composite of death from CV causes or hospitalization for heart failure was lower with vericiguat than with placebo. This trend appeared after approximately 3 months of treatment and was carried throughout the trial. There was an absolute event-rate reduction of 4.2 events per 100 patient-years with a number needed to treat of 24 patients.

There are two previous trials involving patients with HFrEF, PARADIGM-HF and the DAPA-HF trials. In those trials only 25-32% of patients had either NYHA class III or IV heart failure as compared with 41% of patients in this trial.

A strength of this trial was that it looked at a different pathway for the treatment of HFrEF than those previously studied. However, a limitation of the study could be the amount of involvement of the manufacturers in most aspects of the study as well as the relatively short median follow-up time.

Reviewers Thoughts

Some countries have already implemented vericiguat into their HFrEF treatment guidelines, though the guidelines in the US have not been updated to reflect this new medication. Though it seemed to have a short median follow-up, I do feel like it has shown greater results in patient outcomes, especially in regards to cardiovascular deaths and hospitalizations due to heart failure. I do find it imperative to have more treatment options in this patient group but with the recent changes to our guidelines to reflect the new roles of SGLT2 Inhibitors and ARNi, I am not too sure this new drug will make much of an impact for a while. However, given this study's limited serious adverse effects compared to its improvement in outcomes, I would consider

treating a patient with vericiguat should they meet similar characteristics shown through this study.

References:

1. Armstrong, P., Burkert P. *et al.* Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine 2020; 382:1883-1892
2. Urbich, M., Globe, G., Pantiri, K. *et al.* A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014–2020). *PharmacoEconomics* 38, 1219–1236 (2020). https://doi.org/10.1007/s40273-020-00952-0