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Victoria Trial: Vericiguat Joins the Big League, or does it?

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Abstract

The VICTORIA trial showed Vericiguat once daily (titrated up to 10 mg) significantly reduced its primary end-point, the composite of death from cardiovascular causes or first hospitalization for heart failure, in 5050 class II-IV HFrEF patients (LVEF<45%). This a landmark trial, one of the largest we have seen in heart failure, and it had some very important novel features; it only recruited patients with a recent (within 6 months) worsening of their heart failure, a group known to be at increased risk of subsequent events, and it included more severe heart failure than most recent trials with NTproBNP levels nearly twice that of Paradigm-HF or DAPA-HF. VICTORIA had a substantially higher mortality rate but an apparently less impressive hazard ratio (HR) 0.90 (0.82 – 0.98) compared to Paradigm's 0.80 (0.73 – 0.87) and DAPA's 0.74 (0.65 –0.85). This must be considered against a healthy absolute risk reduction at 4.2% compared to Paradigm's 2.7% and DAPA's 4.0%, due to the higher risk patients in VICTORIA. Another very important difference with VICTORIA is that it included the higher risk recently discharged HF patients, and patients with eGFR's down to 15 ml per minute per 1.73 m^2 of body-surface area, possibly suggesting a special place for Vericiguat in treating these at-risk subsets of HFrEF patients, but for the fact that the cohort between 15 and 30mL/min/1.73m^2 of eGFR was only around 10.0%, and the point estimate for the HR for this small group was above 1.0 at 1.06 (0.83-1.34). Also the sub-grouping by NTproBNP level was highly significantly interacting (p<0.001) with the lower three quartiles all being significantly in favour of Vericiguat and the highest quartile (>5,314 pg/mL) being almost significantly worse on Vericiguat with a HR of 1.16 (0.99-1.35). So the two major areas where Vericiguat may have received special notice appear to be less impressive when we look in detail at the trial results. How do we therefore place Vericiguat in the wake of VICTORIA? It is a proven therapy in a disease which still has residual high rates of clinical mortality and morbidity. It conveyed a benefit on top of other therapies, thus it should be not ignored and may indeed be a very effective therapy in some patients.

Keywords: Heart Failure; Clinical trials; sGC stimulators; Therapy

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Introduction

Heart failure with reduced ejection fraction (HFrEF) has multiple therapies that have been shown to improve the important combined end-point of mortality and prevention of unplanned heart failure hospitalisation. These include (in some only in selected patients) both drugs (ACE inhibitors, selected beta-blockers, mineralocorticoid receptor antagonists, ivabradine and sacubitril/valsartan) and devices (ICD and CRT). To that august list we must now add Vericiguat, a soluble guanylate cyclase (sGC) stimulator[1].

We learned back on November 18th 2019 from a press release that the VICTORIA study has met its primary efficacy endpoint[2]. "Vericiguat reduced the risk of the composite endpoint of heart failure hospitalization or cardiovascular death in patients with worsening chronic heart failure with reduced ejection fraction (HFrEF) compared to placebo when given in combination with available heart failure therapies." It took until March 28th that to learn the details, with a simultaneous presentation at a webcast (that replaced the ACC conference this year due to COVID-19) and NEJM paper[3].

In the VICTORIA trial, Vericiguat once daily (titrated up to 10 mg) compared to placebo, both on top of guideline-recommended therapy, reduced its primary end-point, the composite of death from cardiovascular causes or first hospitalization for heart failure, in 5050 class II-IV HFrEF patients (LVEF<45%). This a landmark trial. It is one of the largest we have seen in heart failure, it proved a clinically very important end-point and it achieved this through a novel mode of action that was not neurohormonal modulation. This is very much to be applauded. Why then did I have cause recently to suggest the results may be less than dramatic, a case that appears to have been proven correct? [4]. It is partly an issue of perception. In a therapeutic field where

nothing does more than relieve symptoms, we would hail as a dramatic breakthrough something that reduces the burden of hospitalisation, yet in heart failure we view such treatments as second-rung; instead we demand a mortality/morbidity composite end-point to be significantly reduced, and to be associated with suggestive benefit in both components of death and HF related hospitalisation (or similar). The problem in heart failure is that we have so many effective therapeutic options (at least 7 in the broader HFrEF population, as noted above), that we have become complacent, not only wanting mortality separately to be significant, but also demanding a very much reduced hazard ratio (HR). As Butler et al[5] have pointed out in discussing the VICTORIA trial results, HR's perhaps should not be directly compared, because they are not linearly related to risk reduction, either relative or absolute.

The VICTORIA trial had some very important novel features; it only recruited patients with a recent (within 6 months) worsening of their heart failure, a group known to be at increased risk of subsequent events, and it included more severe heart failure than most recent trials with NTproBNP levels nearly twice that of the two most recent major HFrEF trials, Paradigm-HF[6] and DAPA-HF[7]. These differences were borne out, for a much higher annual mortality rate was seen, 13.6% in the placebo group compared to Paradigm-HF, where the comparator rate was 7.5% and DAPA-HF, where the placebo rate was 7.9%. This means that the apparently less impressive HR in VICTORIA of 0.90 (0.82 – 0.98) compared to Paradigm's 0.80 (0.73 – 0.87) and DAPA's 0.74 (0.65 –0.85) is actually misleading, for in absolute risk reduction VICTORIA and the effect of Vericiguat are as impressive as the earlier two trials at 4.2% compared to Paradigm's 2.7% and DAPA's 4.0%, the reason being the substantially higher risk seen in the patients in VICTORIA.

Another very important difference with VICTORIA is that it included the higher risk recently discharged HF patients, a group under-represented in most HFrEF trials, and for the first time in any major M+M trial in HFrEF patients eGFR's down to 15 ml per minute per 1.73 m^2 of body-surface area. These differences may be thought to give the trial special significance and the therapy, Vericiguat, a special mention in any recommendations on how to treat HFrEF, as particularly noteworthy for these two subsets of HF patients. There is a problem, however, for the cohort between 15 and 30mL/min/1.73m^2 (the more common cut-off in HFrEF trials) was capped at 15% of the trial and ended up being only 10.0%, with an extra 0.2% actually being <15mL/min/1.73m^2 at baseline. Our guidelines for HFrEF management are silent at present for what to recommend in HFrEF below an eGFR of <30mL/min/1.73m^2 because no previous outcome trial had recruited these patients. Thus, the VICTORIA trial may have gained a unique place in the guidelines because it is the first drug to be tested for the group between 15 and 30 mL/min/1.73m^2. Sadly, we still do not know the answer to this patient group, for although the sub-group analysis was too under-powered to carry any certainty. But the fact is the point estimate of the HR for the small group of <30mL/min/1.73m^2 was above 1.0 at 1.06 (0.83-1.34). Also, although we would not normally take sub-group differences into account when assessing the efficacy of drugs, we should consider them if three things are true: the interaction term is significant and the interaction is both clinically meaningful and mechanistically plausible. In VICTORIA, as presented live, the sub-grouping by NTproBNP level, was highly significantly interacting (p<0.001), with the lower three quartiles all being significantly in favour of Vericiguat and the highest quartile (>5,314 pg/mL) being almost significantly worse on Vericiguat with a HR of 1.16 (0.99-1.35). For the renal function, the interaction was not significant, but given it was this sub-group where we had not previous trial data, we can argue this result gives no convincing evidence for a benefit.

How do we therefore place Vericiguat in the wake of VICTORIA? It is a proven therapy in a disease which still has residual high rates of clinical mortality and morbidity. It conveyed a benefit on top of other therapies, thus it should be not ignored and may indeed be a very effective therapy in some patients despite already being on optimised guideline recommended therapy, but with the proviso that there were only 15% of patients on Sacubitril/valsartan with virtually none on Dapagliflozin, so that the added efficacy on top of these two recent treatments is less certain.

Where does this place us? As we look forward to revised European guidelines in the next year or two, can we expect to see changes in the main treatment algorithm? Yes, for we have DAPA-HF and now Victoria, both being large positive mortality and morbidity trials. Will Vericiguat get as strong a recommendation as Dapagliflozin? We cannot yet tell, but do we know the algorithm will get more complex, because we have not seen such a substantial number of drug classes individually recommendable in the past and the optimum way to commence them all, i.e. in what order and whether they can be started contemporaneously with each remain unclear. The three most recent therapeutic classes, sacubitril/valsartan, dapagliflozin and Vericiguat given together, could be considered later than the older drug classes, but the situation may get even more complicated with the expected results of GALATIC-HF testing the effect of the myosin activator, Omecamtiv Mecarbil[8], in an even larger mortality and morbidity trial soon to be available[9]. This will also have a lower limit of renal function at entry, down to 20mL/min/1.73m^2 and also a much lower BP cut-off, down to 85mmHg, and it will include substantial numbers of patients recruited during a hospital admission, so it may truly give information about treatment efficacy in groups of HFrEF presently lacking such data. In future we may indeed need to consider individual patient factors in deciding in which order to initiate the multiple classes of drug we could in future use for our HFrEF patients, because we will hopefully have many classes of effective agents with modes of action and trial inclusion/exclusion criteria that allow us to personalise our recommendations more that we have ever done in the past.

Declarations of Interest

The author declares not the authors declare.

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The author state that he abides by the requirements for ethical publishing in biomedical journals.[10]

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