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Perspective

Verisiguat: A New Kid in Town. But One Size does not Fit all Heart Failure

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Leaving in the Corona-virus era, brings a lot of digital innovations including the first LBCT presentation virtually. The Victoria [1] study presented virtually at ACC 2020 and published simultaneously at NEJM presented the results of verisiguat, a novel oral soluble guanylate cyclase stimulator, that enhances the cyclic guanosine monophosphate (GMP) pathway by directly stimulating soluble guanylate cyclase through a binding site independent of nitric oxide, and it sensitizes soluble guanylate cyclase to endogenous nitric oxide by stabilizing nitric oxide binding to the binding site [2].

This Phase III trail of the new drug verisiguat was tried in very high risk patients with Heart Failure. It was an event driven double-blind trial vs placebo. The primary endpoint was met but without reduction of cardiovascular mortality only due to the reduction of hospitalizations due to worsening Heart Failure. This comes in contrast with the latest trails in patients with heart failure (DAPA-HF [3] and PARADIGM-HF [4]) showing not only reduction of hospitalizations but also a mortality benefit.

Does that mean that this drug and this new class of guanylate cyclase stimulators are of less benefit than the other pharmaceutical classes?

That's too early to comment. There are some significant differences in this trial compared to the latest ones that we need to take in consideration.

1. Very short median follow up: In an event driven trial median follow up depends on the number of events. Here in contrast with a lot of other studies we had a median follow up of only 11 months (much shorter than DAPA-HF 18 months and PARADIGM-HF 27 months). Significantly more events that predicted.
2. Significantly advanced clinical condition of HF: Median nt-pro BNP was 2821 pg/ml, (while in DAPA-HF 1437 pg/ml and PARADIGM-HF 1615 pg/ml). Class III-IV NYHA in 41% of participants vs DAPA-HF 33% and PARADIGM-HF 25%.
3. The number of events is more than double from other trials. Victoria had 34,4% vs 30,7%, DAPA-HF 15,1% vs 11,5%, paradigm-hf 13,8% vs 11%. And the absolut risk reduction was greater than in the other studies. ARR 3,7%, DAPA-HF 3,6%, paradigm-hf 2,8%.
4. In the subgroup analyses we have two categories that show significant heterogeneity and are not consistent with the results. Patients over 75 years old vs patients younger than that age and the highest quartale of NT-pro BNP patients.

Why then with so many events and patients in a significantly deteriorated clinical condition we don't see a mortality benefit?

Could it be that by trying to get more events and finish the study earlier, we arrive to include heart failure patients that cannot benefit any more from interventions that could significantly reduce mortality in the rest of the cohort?

If the most severe patients are not getting benefit from this drug shouldn't there be a specific sub-analyses for the rest of the cohort and possibly another study in better defined patients?

Heart Failure is a complicated and with adverse prognosis disease in the majority of patients. We need to stratify better our patients because one size doesn't fit all patients.

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