Title: **Vericiguat, sacubitril/valsartan and more evidence that we are failing our patients**

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The understanding of the efficacy and safety of combinations of pharmacological therapies has become ever more important as the number of drugs available to treat heart failure has increased. Beyond these general considerations, there may also be particular combinations of treatments where there is a more specific question. One example is the addition of vericiguat to background treatment with sacubitril/valsartan. Both stimulation of soluble guanylyl cyclase (sGC) by vericiguat and inhibition of neprilysin (which breaks down natriuretic and other vasoactive peptides) by sacubitril increase the intracellular second messenger cyclic guanosine monophosphate (cGMP).[1] Among other downstream effects, cGMP causes vasodilatation by inducing smooth muscle

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relaxation in arteries and veins. It is reasonable to speculate that the effect of vericiguat added to sacubitril/valsartan may depend on the level of intracellular cGMP stimulated by sacubitril/valsartan. If cGMP levels are already maximally stimulated by sacubitril/valsartan, vericiguat may have only a small additional benefit. Conversely, if the intracellular concentration of cGMP is submaximally stimulated, the addition of vericiguat may be more beneficial (but hypotension may also be more frequent). Consequently, there was a strong rationale for the analyses undertaken by Senni and colleagues using data from the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial.[2,3] While the question is clear, the answer is less so, for two reasons. First, the overall effect of vericiguat in VICTORIA was small, with a 10% reduction (HR 0.90, 95%CI 0.82, 0.98) in the primary composite endpoint of time-to-first heart failure hospitalization or death from cardiovascular causes, driven by a 10% relative risk reduction in heart failure hospitalization (HR 0.90, 95%CI 0.81, 1.00).[3] Second, relatively few patients were treated with sacubitril/valsartan at baseline (n=731 out of 5040; 14.5%), a point we will return to later (in a perfect world, the proportions taking and not taking sacubitril/valsartan should have been reversed!). With the small effect of vericiguat and few events in patients treated with sacubitril/valsartan, the analyses carried out had the power to identify only a very large difference between the effect of vericiguat in the two subgroups defined by baseline sacubitril/valsartan use. With these important caveats, the main finding in VICTORIA was that the hazard ratio for the effect of vericiguat, compared to placebo, on the primary endpoint was 0.88 (95%CI 0.70, 1.11) in patients receiving sacubitril/valsartan at baseline and 0.90 (0.81, 0.99) in those not. This represents the best, unbiased, answer to the question about the efficacy of combined therapy although does not exclude the possibility of an interaction between these two treatments for the reasons discussed above.

Senni and colleagues carried out additional analyses which took into account sacubitril/valsartan started after randomization and the duration of treatment with sacubitril/valsartan.[2] While well-intentioned, these analyses are problematic because they introduce several biases. As can be seen

from the central illustration in their paper, sacubitril/valsartan was started more commonly after randomization in the placebo group, compared with the vericiguat group. While, ironically, this is probably evidence that vericiguat was exerting a beneficial effect, it also tells us that the two randomized treatment groups were diverging in their clinical course following randomization and that sacubitril/valsartan was probably being initiated as a "rescue therapy" in patients exhibiting clinical worsening. This "drop-in" phenomenon where there is asymmetrical use of other effective therapies is seen in all trials where the new agent is superior to placebo – indeed there was a very similar experience in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) as shown in the Figure.[4] The interpretation of post-randomization subgroups and non-randomized therapy is, therefore, particularly challenging.[5]

Sadly, the most clinically relevant finding in this report from the VICTORIA trial was the demonstration of persistently low use of sacubitril/valsartan, a therapy that improves patient well-being, reduces hospital admission, and increases overall survival, despite the Class I indication for this treatment in guidelines.[6] The asymmetrical use of sacubitril/valsartan in the placebo group, likely in response to worsening heart failure, suggests that clinical inertia continues to characterise clinician behaviour and remains a threat to our patients.[7] Why do we not try and treat our patients as early and best we can? Why do we wait until something goes wrong before we act? What about the patients whose first manifestation of deterioration is sudden death; it is too late for them. Will this underuse of treatment also lead the pharmaceutical industry to stop developing new drugs for heart failure? How do we make this better – that is the question for all of us?

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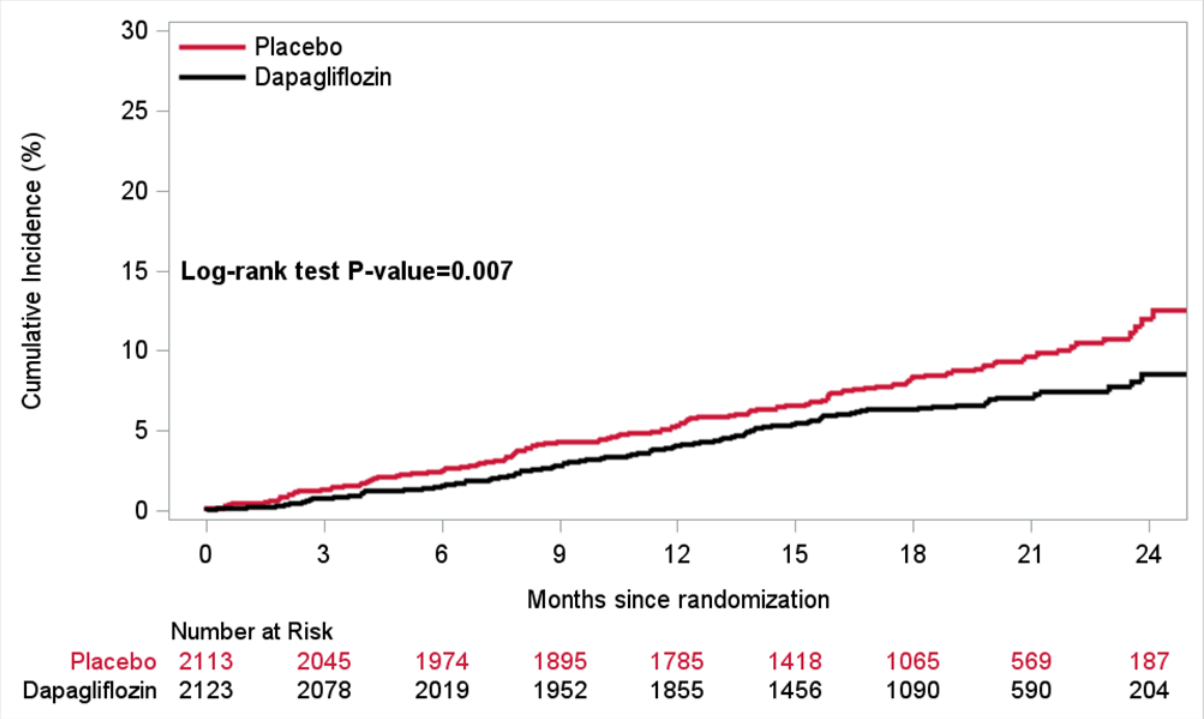
Figure: Initiation of “open-label” sacubitril/valsartan after randomization in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) according to the therapy randomly assigned i.e., placebo or dapagliflozin.



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