EDITORIALS

Vericiguat — Another Victory for Targeting Cyclic GMP in Heart Failure

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Pivotal advances in basic scientific investigation have led to innovative drugs that have reduced the burden of cardiovascular disease in humans. There is no better example than the Nobel Prize–winning work of Furchgott, Ignarro, and Murad, who discovered that nitric oxide is an endothelial relaxing factor that mediates its favorable cardiovascular actions with the effector molecule 3′,5′-cyclic guanosine monophosphate (GMP).[1] Subsequent studies established that the key target of nitric oxide is activation of soluble guanylyl (sometimes called "guanylate") cyclase, which generates cyclic GMP. Indeed, cyclic GMP has emerged as a key intracellular second messenger that mediates protective cardiovascular, renal, neurohormonal, and metabolic actions in the maintenance of whole-body homeostasis.[2]

Studies have also established that a family of peptides called the natriuretic peptides, which include atrial natriuretic peptide, B-type natriuretic peptide, and C-type natriuretic peptide, are also cyclic GMP activators. These peptides function through particulate guanylyl cyclase, which is a family of membrane-bound receptors (in contrast to soluble guanylyl cyclase, which is localized within the cell).[3] Because of the importance of this pathway, the use of cyclic GMP–augmenting drugs has emerged as a key strategy in the treatment of heart failure. Sacubitril–valsartan, which augments natriuretic peptides through inhibition of neprilysin, highlights the enormous potential of cyclic GMP–augmenting therapy for heart failure.[4]

The promising results with vericiguat reported by Armstrong and coworkers[5] in this issue of the *Journal* (first published on March 28 at NEJM.org) constitute another victory for cyclic GMP–based therapy for heart failure. Vericiguat is a soluble guanylyl cyclase stimulator that augments soluble guanylyl cyclase activation induced by nitric oxide, but unlike nitrovasodilators, it does not induce tolerance with long-term administration.[6] It also may directly activate soluble guanylyl cyclase and increase formation of cyclic GMP. Vericiguat is the product of the pioneering work of Stasch and coworkers at Bayer. In 2001, they reported the development of the first orally available soluble guanylyl cyclase stimulator (BAY 41-2272) that binds to a regulatory site on the alpha subunit of soluble guanylyl cyclase.[7] Shortly afterward, my colleagues and I reported that BAY 41-2272 reduced blood pressure, mediated systemic and renal vasodilatation, and increased cardiac output in a large-animal model of heart failure.[8] Further advances in drug development led to the first-in-class soluble guanylyl cyclase stimulator riociguat, which was approved for the treatment of pulmonary hypertension.

In a phase 2 randomized trial led by Gheorghiade and colleagues, vericiguat, another agent in this class, was investigated in patients with heart failure who were in clinically stable condition.[9] In the Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study (SOCRATES-REDUCED), these investigators used a dose-finding, placebo-controlled strategy, with the primary outcome being a reduction in the level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) from baseline to week 12. Although there was no significant benefit of vericiguat with respect to the primary outcome, an exploratory secondary analysis suggested a dose–response relationship in which higher doses of vericiguat were associated with greater reductions in levels of NT-proBNP.

With consideration of the data from SOCRATES-REDUCED, Armstrong and coworkers designed the phase 3 Vericiguat Global Study

in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA), which involved 5050 patients who had advanced symptomatic heart failure with reduced ejection fraction and who had recently been hospitalized or had received intravenous diuretic therapy. A key design aspect of VICTORIA was the recruitment of sicker patients with higher NT-proBNP levels than those in previous heart-failure trials; this selection resulted in high event rates. Furthermore, the patients were older than those in previous large-scale heart-failure trials; this factor is clinically relevant, since heart failure is often a disease of the elderly. On the basis of the findings in SOCRATES-REDUCED, the target dose of vericiguat in VICTORIA was 10 mg once daily. The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure. Although the incidence of the primary outcome was significantly lower in patients who received vericiguat than in those who received placebo, this result was driven by a lower incidence of hospitalization in the vericiguat group, and there was no significant between-group difference in the incidence of death from any cause. Vericiguat generally had a favorable side-effect profile, although symptomatic hypotension and syncope were more common in patients who received vericiguat than in those who received placebo.

What are the next steps based on this successful trial involving patients with heart failure and reduced ejection fraction? The results of an ongoing study of vericiguat in patients with heart failure with preserved ejection fraction (ClinicalTrials.gov number, NCT03547583) are anxiously awaited, since cyclic GMP therapies such as sacubitril–valsartan and another soluble guanylyl cyclase stimulator, praliciguat, have been unsuccessful in these patients. In this era of precision medicine, better information is also needed regarding which patients with heart failure benefit most from soluble guanylyl cyclase stimulation. To guide therapy, would measurement of plasma or urinary cyclic GMP levels be helpful, or would measurement of nitric oxide levels identify the patients with the best response? Would measurement of atrial natriuretic peptide be important? Approximately 25% of patients with heart failure lack activation of atrial natriuretic peptide and have low cyclic GMP levels.[10] Furthermore, it would be helpful to understand whether targeting both soluble guanylyl cyclase and particulate guanylyl cyclase with combinations of drugs (such as vericiguat with sacubitril–valsartan) would be synergistic or would increase the incidence of adverse events such as hypotension and syncope. These are key questions that warrant further clinical investigation.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Atezolizumab plus Bevacizumab — A Landmark in Liver Cancer

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More than a decade ago, sorafenib became the first systemic therapy that conferred a meaningful survival benefit in the treatment of advanced hepatocellular carcinoma.[1] Since then, no treatment had surpassed the effect of sorafenib in the first line until the regimen of atezolizumab