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New Drug Approvals in Cardiology

Beta-blockers (BB) and renin-angiotensin-aldosterone (RAAS) inhibitors have been the mainstay of guideline directed medical therapy (GDMT) for patients with heart failure (HF). Over the past few decades, major advances in understanding pathophysiology of HF has led to evolving treatment paradigms.[1] Introduction of these new therapies has expanded the cardiovascular medication armamentarium and facilitated individualized management of HF patients. Vericiguat (Verquvo®) is a novel soluble guanylate cyclase (sGC) stimulator. It works by enhancing the production of cyclic guanosine monophosphate, independent of nitric oxide, resulting in vascular smooth muscle relaxation and myocardium contraction. Vericiguat is Food and Drug Administration (FDA) approved for symptomatic HF in patients with an ejection fraction (EF) less than 45% as an adjunctive therapy. The recommended starting dose is 2.5mg once daily, which can be titrated biweekly to a maximum of 10 mg daily as tolerated based on blood pressure and HF symptoms. There are no specific hepatic or renal dysfunction dose adjustments provided by the manufacturer for patients with estimated glomerular filtration rate less than 15 mL/min/1.73m^2 or Child-Pugh class C. This medication has a linear pharmacokinetic profile with high bioavailability (93%) when administered with food. For patients unable to swallow, tablets may be crushed and mixed with water immediately before administration. As demonstrated in the pre-clinical studies, vericiguat is metabolized by glucuronidation and theoretically has a low risk for drug-drug interactions. However, patients with long-acting nitrites and phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil were excluded from the trial; therefore, concomitant use of vericiguat with these agents is not recommended. Significant adverse drug reactions reported include hypotension (16%), anemia (10%), dyspnea (4%) and nausea (4%). Vericiguat label contains a US boxed warning for fetal harm with in-utero exposure based on animal studies. Hence, females of reproductive potential must use effective forms of contraception prior to the start and for one month after stopping the treatment. The primary monitoring parameter includes blood pressure. This medication was granted FDA approval in January of 2021 based on the results of the landmark trial, VICTORIA, conducted by Armstrong et al.[2]

The VICTORIA trial was a multinational, randomized, double-blind, placebo-controlled study that assessed effects of vericiguat 10mg daily in HF patients with an EF of less than 45% and New York Heart Association (NYHA) class II or higher. The VICTORIA trial required enrollment within 6 months of HF hospitalization or within 3 months of intravenous diuretic therapy without hospitalization. The primary outcome was a composite of death from cardiovascular causes or first hospitalization for HF. Over a median of 10.8 months, the primary outcome occurred in 35.5% in the vericiguat group and 38.5% in the placebo group (P= 0.02). This trial concluded that treatment with vericiguat lowered the incidence of the composite of death from cardiovascular causes or hospitalization for HF. Analysis of components of primary outcomes illustrated incidence of hospitalization was lower in vericiguat compared with placebo (P=0.02), with no significant difference in incidence of death from any cause (P=0.38). With a median follow-up of 10.8 months, the absolute rate reduction in high-risk population was calculated to be 4.2 events per 100 patient-years, translating to a number needed to treat of 28 patients over a 12-month period. Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group versus 7.9% in the placebo group.[3]

The GDMT for HF with reduced EF (HF*r*EF) consists of an angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker or angiotensin receptor-neprilysin inhibitor (preferred) and evidence-based

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BB followed by the addition of aldosterone receptor antagonist. Sodium-glucose cotransporter-2 inhibitors should be considered for HF*r*EF with NYHA class II-IV. In addition, hydralazine plus isosorbide dinitrate and ivabradine or digoxin would be beneficial in symptomatic patients meeting specific criteria for these agents. The 2021 Focused Updates to the 2017 Journal of the American Cardiology Guidelines on HF regard vericiguat as an important treatment target in hemodynamically stable HF with EF of less than 45%.[4] The concern remains about the optimal strategy to maximize efficacy and tolerability of above therapies as clinicians must recognize the nuances with each agent. For example, digoxin, ivabridine and vericiguat have shown to improve HF hospitalization, choosing one versus the other depends on various patient and drug specific components. The selection criteria should take into account HF symptoms, co-morbidities, hemodynamic parameters, adherence, cost and the intended clinical benefit. In short, with the availability of existing and emerging therapies for HF, it is crucial to understand current evidence and explore remaining gaps in knowledge in order to provide optimal care to our patients diagnosed with HF.[5]

References:

1. Udelson JE, Stevenson LW. The Future of Heart Failure Diagnosis, Therapy, and Management. *Circulation*. 2016;133:2671–2686.
2. Vericiguat [package insert]. Whitehouse Station, NJ. Merck; 2021.
3. Armstrong PW, Pieske B, Anstrom KJ, et al; VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020; 382(20):1883-1893.
4. Maddox T, Januzzi J, Allen L, et al; 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction. *KIDNEYS*. 2021; 10(3):179-180.
5. Lee A, Natarajan P, Kar-Hang cheng R, et al; The Role of Vericiguat in the Expanding Realm of Heart Failure Pharmacotherapy: An Overview of the VICTORIA Trial. *American College of Cardiology*. 2021.