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Updates in Heart Failure Therapy: New Drugs and Indications

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Heart failure (HF) is a structural or functional cardiac disorder resulting in reduced cardiac output and/or elevated cardiac pressures. In the United States, about 6.2 million adults have HF, and the prevalence is expected to increase to over 8 million adults by 2030.[1,2] It is further classified into HF with reduced ejection fraction (HFrEF = left ventricular ejection fraction ≤ 40%) and HF with preserved ejection fraction (HFpEF = left ventricular ejection fraction ≥ 50%). Until recently, guideline directed medication therapy (GDMT), including select renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs), are the only medications that have demonstrated a mortality benefit in HFrEF.[3] The purpose of this newsletter is to review evidence on cardiovascular (CV) outcomes for expanded indications (**Table 1**) of sacubitril/valsartan, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and the recently FDA-approved vericiguat.

Table 1. New or Expanded Heart Failure Indications

Drug	Adult Heart Failure Indications	Target Dose
Vericiguat[4]	To reduce risk of CV death & HF hospitalization following a HF hospitalization or IV diuretic use in HFrEF	10 mg once daily
Sacubutril/ Valsartan[5]	To reduce risk of CV death & HF hospitalization in chronic HF. Benefits most evident if LVEF is below normal.	97 mg/ 103 mg twice daily
Dapagliflozin[6]	To reduce risk of CV death and HF hospitalization in adults with HFrEF	10 mg once daily

Abbreviations: CV – cardiovascular; HF- heart failure, HFrEF – heart failure with reduced ejection fraction; LVEF- left ventricular ejection fraction; mg - milligram

Vericiguat: New Heart Failure Medication

Vericiguat is a soluble guanylate cyclase (sGC) stimulator, causing vasodilation through the nitric oxide pathway.[4] Common side effects include hypotension and anemia. It is contraindicated with concurrent use of long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors and in pregnancy.[4]

Approval was based on the VICTORIA trial (**Table 2 and 3**), a placebo-controlled, multicenter, double-blind, randomized controlled trial (RCT) that compared vericiguat to matching placebo in patients with HFrEF and on GDMT.[7] By the median follow-up of 10.8 months, a statistically significant reduction in CV death and HF hospitalizations occurred with vericiguat versus placebo (35.5% vs. 38.5%; hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.82 to 0.98; p = 0.02), primarily driven by HF hospitalizations (**Table 3**).[7] There was no significant reduction in CV death or all-cause mortality. Vericiguat should not be used for HFpEF. A 6-month study in HFpEF resulted in an increase of CV death with vericiguat 10 mg daily compared to placebo (4.6% vs. 1.5%, respectively) and did not improve physical functioning.[8]

The VICTORIA trial has limited generalizability since it enrolled a higher risk population of patients with worsening HF, defined as hospitalization within the previous 6 months or use of intravenous (IV) diuretics within 3 months.[7] This resulted in a study population with more advanced HF. Sixty seven percent of patients had a recent HF hospitalization and 41% of patients had NYHA Class III or IV, compared to 29-33% in other landmark HF trials.[7, 9-12]

Vericiguat should be reserved as a last line, add-on treatment to optimized GDMT for patients with advanced, symptomatic HFrEF with a recent decompensation.[7] Moderate quality evidence suggests that for this population, vericiguat reduces HF hospitalization and CV death but does not reduce overall mortality.[7]

Table 2. Summary of Recent Heart Failure Trials

Trial	Treatment Arms	Population	Mean Baseline LVEF
PARADIGM HF[9]	Sacubitril/Valsartan vs. Enalapril	HFrEF (EF ≤ 35%)	30%
PARAGON HF[10]	Sacubitril/Valsartan vs. Valsartan	HFpEF (EF ≥ 45%)	58%
VICTORIA[7]	Vericiguat vs. Placebo	Advanced HFrEF (EF ≤ 45%)	29%
DAPA HF[11]	Dapagliflozin Vs. Placebo	HFrEF (EF ≤ 40%)	31%
EMPEROR Reduced[12]	Empagliflozin Vs. Placebo	HFrEF (EF ≤ 40%)	28%

Abbreviations: EF: ejection fraction; HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction

Sacubitril/Valsartan: Expanded Indication

Sacubitril/valsartan was previously approved for use in HFrEF, based on the PARADIGM-HF trial (**Table 2**).[5,9] In February 2021, the FDA labeling was expanded to include all adult patients with HF regardless of EF.[5] The expansion was based on PARAGON-HF, an active-control, double-

blind, RCT study (**Table 2**). Patients with symptomatic HFpEF who tolerated sacubitril/valsartan in an initial run-in period were randomized to a target dose of either valsartan 160 mg twice daily or sacubitril/valsartan 97/103 mg twice daily with median follow-up of 35 months.[10]

Overall, there was no statistical difference between sacubitril/valsartan and valsartan for the primary composite outcome of CV deaths and HF hospitalization (12.8 events per 100 patient years vs. 14.6; risk ratio [RR] 0.87; 95% CI 0.75 to 1.01; p=0.06).[10] HF hospitalizations were the primary driver of this outcome. Greater benefit was shown for the prespecified subgroup of patients with LVEF below the median of ≤ 57% (RR 0.78; 95% CI 0.64-0.95) than patients with LVEF above the median (RR 1.00; 95% CI 0.81-1.23).[10]

Despite failing to meet the primary outcome, the FDA expanded approval based on a re-analysis of the data.[13] The re-analysis found a statistically significant benefit (RR 0.84; 95% CI 0.74 to 0.97; p=0.014) after the composite endpoint was expanded to include HF urgent care visits and reexamination of unconfirmed HF hospitalizations.[13]

Sacubitril/valsartan's benefits remain most evident when EF is markedly reduced (≤40%) and should be used judiciously with higher baseline EF. Although expert consensus guidelines consider initiating sacubitril/valsartan without prior exposure to an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), a trial of an ACEI or ARB prior to initiation is a recommended strategy by the National Institute for Health and Care Excellence (NICE).[14, 15] This is also supported by pivotal trials, which used extensive run-in periods that excluded patients who could not tolerate RAAS inhibitors.[9,10] In PARADIGM-HF, over 20% of patients were unable to tolerate target doses and it is unclear if lower doses have any clinic benefit in HFrEF.

Table 3. Cardiovascular Outcome Results in HFrEF[7,9,11,12]

	CV death & HF hospitalization ARR/NNT	All-cause mortality ARR/NNT	CV Death ARR/NNT
Sacubitril/Valsartan*	4.7% / 22	2.8% / 36	3.2% / 32
Vericiguat ±	3.0% / 34	NS	NS
Dapagliflozin ±	4.9% / 21	2.3% / 44	1.9% / 53
Empagliflozin±	5.3% / 19	NS	NS

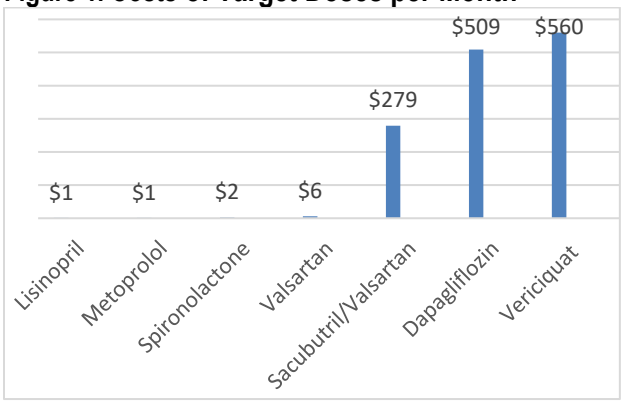
Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; HF: heart failure; NNT: number needed to treat; NS: not significant
*Active comparator: enalapril. ± Versus placebo

Updates to SGLT2 Inhibitor Use in Heart Failure

SGLT2 inhibitors have been shown to reduce HF hospitalizations in patients with diabetes and CV disease.[16,17] More recent data suggests empagliflozin and dapagliflozin may benefit patients with heart failure, with or without diabetes. Dapagliflozin was FDA approved for HFrEF based on the DAPA-HF trial (**Table 2 and 3**), demonstrating a reduction in worsening HF (defined by hospitalization or requiring intravenous therapy for HF) or CV death (HR 0.74; 95% CI; 0.65 to 0.85; p<0.001) with dapagliflozin compared to placebo in patients with HFrEF, with or without type 2 diabetes (T2D).[11] As of January 2021, empagliflozin is under FDA review for patients with HFrEF based on the EMPEROR-Reduced trial (**Table 2 and 3**).[12]

Based on these data, dapagliflozin is an add-on option to optimized GDMT (RAAS inhibitor, beta blocker, and an MRA) for treatment of symptomatic chronic HFrEF in adults.[18] No direct comparisons between dapagliflozin and other drugs have been made. When used with diuretic therapy, patients should be counseled on the risks of hypovolemia and acute kidney injury when initiated.

Figure 1. Costs of Target Doses per Month



*Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC).
**Vericiguat cost based on Average Wholesale Cost (AWP) minus 20% AAAC.

Conclusion

New drugs and indications provide additional options for patients with HF who remain symptomatic while on GDMT. However, very few patients are on GDMT at target doses. Attempts to optimize these cost-effective treatments (**Figure 1**) and address barriers to adherence should happen before adding on additional medications to already complex drug regimens.

For Oregon Health Plan (OHP) Fee-For Service (FFS):

- Sacubitril/valsartan and vericiguat require prior authorization (PA).
- Trial and failure with ACE-I/ARB is required to confirm tolerance.
- For HFrEF, optimization of an ACE-I/ARB and target dose beta blocker should be prioritized before adding additional therapies.
- Vericiguat should not be used for HFpEF or in less severe HFrEF
- SGLT2 inhibitor use should be prioritized for patients with HFrEF and T2D.

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