Letter to the Editor

Dear Editor:

In a recent article in *The Journal for Nurse Practitioners*,[1] the authors robustly presented the clinical trial data evidence, mechanism of action (MOA), use, and prescribing of sodium-glucose cotransporter-2 inhibitors (SGLT2is) in heart failure (HF).

Although they provide a very detailed MOA for SGLT2is in HF, the exact mechanism is unclear. What we do know in HF for this class of drugs is that they effect glucose excretion, diuresis by way of interstitial volume (not intravascular), and natriuresis, which leads to decreased arterial pressure and stiffness and a shift to a keto-based myocardial metabolism.[2] With increased use, we may gain the exact MOA.

The authors were clear to explain that dapagliflozin was the only SGLT2i that has shown a risk reduction in cardiovascular and all-cause mortality in heart failure with reduced ejection fraction (HFrEF). In fact, dapagliflozin was the first SGLT2i granted approval by the Food and Drug Administration for the treatment of New York Heart Association class II to IV, stage C HFrEF patients based on survival and reduced hospitalizations. They further acknowledged that in cardiovascular outcome trials, hospitalizations for HF were the "primary driver." It is important to acknowledge that a recent systematic review and meta-analysis of 17,000 patients by Butler et al[3] concluded that SGLT2is significantly reduced HF hospitalizations, adverse renal outcomes, and mortality consistently in diabetic and nondiabetic patients with HFrEF. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic HFrEF) trial where the primary outcomes were cardiovascular death or HF hospitalization for empagliflozin versus placebo (19.4% vs 24.7%; hazard ratio 0.75; 95% confidence interval, 0.65-0.86; $P < .001$), the results were significant irrespective of diabetics or nondiabetics.[4]

McDermott and colleagues are correct that beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and cardiac resynchronization therapy are proven therapies in HF. However, newer therapies have come to market that have changed the standard of care in HF. The four foundational medication therapy classes include: beta-blockers, renin-angiotensin-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists, and SGLT2is. ARNIs are now preferred over angiotensin inhibitors and angiotensin system inhibitors.[5] Given the fact that these guideline directed medication therapies (GDMTs) target different pathways, these foundational medications are recommended for rapid and additive benefits for both morbidity and mortality.[5]

An important effect of SGLT2 is are that they do not contribute to significant hypotension. Although hypotension was a potential side effect in the trials, no absolute difference was noted in systolic blood pressure (−2.4 vs −1.7, $P > .05$) in the EMPEROR-Reduced trial.[4] This is one of the reasons SGLT2is can be initiated early in therapy.

Finally, the cost of newer drugs like SGLT2is and ARNIs often inhibits the ability to optimize and/or up-titrate GDMT. These costs are not nominal, particularly in Medicare patients once they reach their maximum benefit plan or "donut hole," which can be a driver to discontinue the more costly GDMTs.

It is important for providers and patients to understand the outcome data, MOA, adverse effects, and potential barriers to the implementation of GDMT such as cost in order to make the best-informed decisions about their plan of care.

References

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