

The Role of SGLT-2 Inhibitors in Heart Failure: An Interview With Darren K. McGuire, MD, MHSc

An editor from The American Journal of Managed Care® spoke with Darren K. McGuire, MD, MHSc, to discuss the impact of the results of cardiovascular outcome trials on the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with heart failure in real-world clinical practice. McGuire is professor of medicine, director of the cardiology clinical trials unit, and director of the Parkland Hospital and Health System outpatient cardiology clinics at the University of Texas Southwestern Medical Center in Dallas.

DIABETES AND CARDIOVASCULAR DISEASE

Atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF) represent major causes of morbidity and mortality for patients with diabetes. Heightened attention to reducing ASCVD risk factors has resulted in decreases in the rate of ASCVD among patients with diabetes.¹ However, the burden of cardiovascular disease remains substantial. McGuire pointed out that patients with diabetes are now equally likely to have a heart attack as they are to have HF. “It’s only been [over] the last 5 to 7 years where we’ve really gotten a better understanding of the critical importance of considering heart failure as part of the cardiovascular complications of type 2 diabetes,” said McGuire.

Despite recognition that diabetes and cardiovascular disease are intricately linked, the impact of glucose-lowering medications on cardiovascular risk and outcomes remained largely unknown for many years. “We didn’t even know if the medications available were safe,” said McGuire.

The FDA eventually heeded the call for further research, and in 2008 mandated that manufacturers of new diabetes drugs submit evidence from cardiovascular outcomes trials (CVOTs) showing that their drug was not associated with an unacceptable increase in cardiovascular risk.² What followed were not just much-needed safety data from clinical trials, but also, said McGuire, the discovery that some medications used in the management of diabetes “can be incrementally beneficial from a cardiovascular perspective.”

SGLT-2 INHIBITOR CARDIOVASCULAR OUTCOME TRIALS

“One of the most remarkable observations...is the powerful effect of the SGLT-2 inhibitors and the consistent effect across trials and agents on heart failure risk,” said McGuire. The first CVOT to report results was the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess

Glucose (EMPA-REG OUTCOME) study, which showed that treatment with empagliflozin yielded a 35% reduction in hospitalization for HF among patients with diabetes and cardiovascular disease ($P = .002$) versus placebo.³

Although enrollment criteria were not identical, similar impacts on hospitalization for HF were seen with canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) and with dapagliflozin in the Dapagliflozin Effect on Cardiovascular Events—Thrombosis in Myocardial Infarction 58 (DECLARE—TIMI 58) trial, which showed reductions of 33%⁴ and 27%,⁵ respectively. Most recently, preliminary data from the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular (VERTIS-CV) trial suggest that treatment with ertugliflozin yields a similar reduction.⁶

As CVOT results came in, it became “quickly clear that [the effect of SGLT-2 inhibitors on HF risk] was not related to glycemic control,” according to McGuire. The SGLT-2 inhibitors reduce blood sugar by increasing urinary excretion of glucose and inducing modest diuretic and natriuretic effects. “We’re now discovering that...[with the SGLT-2s,] there may be direct off-target effects that have nothing at all to do with SGLT-2, and nothing to do with glucose control,” said McGuire.

SGLT-2 INHIBITORS AS HEART FAILURE MEDICATIONS

Positive CVOT results led researchers to question whether SGLT-2 inhibitors could improve HF outcomes in patients without diabetes. The Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial randomly assigned 4744 patients with HF with reduced ejection fraction (HFrEF) to either dapagliflozin or placebo. Importantly, the study population featured a nearly equal split of patients with and without diabetes. After 18.2 months, patients in the dapagliflozin group were 26% less likely to experience the primary outcome of worsening HF or cardiovascular death ($P < .001$).⁷ Rates of the primary outcome were similar in patients with and without diabetes.⁷

Results for cardiovascular death and worsening renal function also favored dapagliflozin.⁷

McGuire referred to DAPA-HF as a “landmark revolutionary trial,” citing that it “now adds to the level 1A indicated therapies like angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, β -blockers, [and] mineralocorticoid antagonists.” Results of the EMPEROR-Reduced trial, which is comparing empagliflozin with placebo for HFrEF patients both with and without diabetes, will help to distinguish whether the results of DAPA-HF represent a class effect.

Stakeholders must work together to provide optimal care for patients with HF by incorporating SGLT-2 inhibitors into appropriate clinical situations.

McGuire, as well as the residents and fellows in his training program, have been quick to embrace the evidence from CVOTs. “We have begun using [the SGLT-2s] as routine cardiovascular medications in our cardiology clinics...using them very much like we use a statin,” he said. Notably, patients with diabetes and HF visit their cardiologist nearly 7 times as often as they do their endocrinologist,⁸ highlighting the need for cardiologists to become more actively involved in prescribing glucose-lowering therapies that mitigate HF risk. McGuire noted that cardiologists as a whole are doing “dismally” when it comes to prescribing SGLT-2s to appropriate patients.

OVERCOMING BARRIERS TO SGLT-2 INHIBITOR USE

Cardiologists have not traditionally encountered medications that lower both cardiovascular risk and blood sugar. McGuire suspects that many are hesitant to get involved in blood sugar management. To overcome this, he encourages cardiologists to start disconnecting the cardiovascular benefits of SGLT-2 inhibitors from their glucose-lowering benefits and to approach their use from a more pure cardiovascular risk–management standpoint.

When cardiologists do prescribe SGLT-2 inhibitors, having a systematic means of communicating with other care providers is essential. This communication “engages the coproviders in a team approach, [so that there is an] understanding [that] we’re not stepping on their toes and we’re not embarking on glucose

management in their clinic, but that we are using these medications for further cardiovascular benefits,” said McGuire.

McGuire also cited cost and access as potential barriers to expanding the use of SGLT-2 inhibitors. Uninsured patients may not be able to afford these medications until a generic SGLT-2 inhibitor is available. Similarly, patients with insurance may face limitations based on coverage by third-party payers who are attempting to minimize their costs. McGuire proposed a reevaluation of the cost-effectiveness of SGLT-2s given the strong evidence of their clinical benefits. “I think from a societal perspective the potency of these drugs, especially SGLT-2 inhibitors, [at] reducing heart failure has a real, major impact on health care costs and health care utilization,” he said.

CONCLUSIONS

Diabetes and HF are intricately linked, and patients with both conditions are more likely to experience adverse health outcomes. Since 2008, new glucose-lowering therapies have been required to demonstrate cardiovascular safety in clinical trials. The SGLT-2 inhibitors have not only proved themselves in terms of cardiovascular safety, but have also consistently shown their ability to reduce hospitalizations for HF in patients with diabetes. The results of DAPA-HF indicate that this benefit extends to patients without diabetes. Insurers, cardiologists, endocrinologists, and primary care providers must work together to provide optimal care for patients with HF by incorporating SGLT-2 inhibitors into appropriate clinical situations. •

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