INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *SGLT-2 Inhibitors (Update)*
-August 2024-

Background:

In November 2019, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) conducted a drug class review of sodium-glucose cotransporter-2 inhibitors (SGLT2i), focusing on updated guidelines from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE). At that time, the NPTC added empagliflozin due to new data regarding renal and cardiovascular outcomes in patients with diabetes. This class of medications was re-evaluated at the Fall 2024 meeting with emphasis on use in heart failure and chronic kidney disease. Recommendations from the European Society of Cardiology (ESC) and U.S.-based disease guidelines, along with numerous RCTs of individual agents supported the NPTC's decision.[1,2] Following clinical review and analysis, the NPTC made **no modifications** to the IHS National Core Formulary.

Discussion:

Heart Failure (HF) is a common condition affecting more than 6 million Americans over the age of 20 and is increasing in prevalence due to the aging population.[3] Each year more than one million new cases of HF are diagnosed in adults ≥55 years old.[3] Along with increasing prevalence, the American Heart Association has forecasted that the total direct medical costs of HF will increase from $21 billion in 2012 to $53 billion in 2030.[4] Causes of HF include those of cardiac etiology in addition to chronic diseases such as diabetes mellitus (DM) and chronic kidney disease (CKD).[5] Diabetes is the number one cause of CKD and American Indian/Alaska Natives are twice as likely to develop kidney failure compared to whites.[6] CKD is a progressive disorder that affects more than 10% of the world's population, representing over 800 million people.[7]

Currently, there are six FDA approved SGLT2i, namely bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin. Dapagliflozin and empagliflozin are the only two agents that have been evaluated in patients with HF or CKD, without type 2 diabetes. There are four landmark HF outcomes trials assessing the benefits of dapagliflozin and empagliflozin in HF patients with and without type 2 diabetes. The primary outcomes were worsening HF and cardiovascular (CV) death. Two of the four trials, DAPA-HF and EMPEROR-Reduced, enrolled patients with HF with reduced ejection fraction (HFrEF), with an estimated glomerular filtration rate (eGFR) ≤40.[8,9] The EMPEROR-Reduced trial included patients with an eGFR ≥20 which is lower than patients in the DAPA-HF trial, which were required to have an eGFR ≥30. A meta-analysis comparing these two trials showed identical treatment effect, with SGLT2i use resulting in a significant 26% reduction in the combined risk of CV death or first hospitalization for HF; 25% reduction in the composite of recurrent hospitalizations for HF or CV death; 31% reduction in the risk of first hospitalization for HF; 13% reduction in all-cause mortality, and a 14% reduction in CV death.[10] These findings extend the therapeutic role of dapagliflozin and empagliflozin beyond patients with diabetes. Also, the benefits of SGLT2i are in addition to conventional therapy, making them one of the four pillars of HFrEF treatment. The conventional approach recommends that SGLT2i be implemented over a 6-month time frame. However, the rapid approach recommends SGLT2i initiation as soon as possible in conjunction with a beta-blocker, with all three steps ideally achieved within 4 weeks.[11] Volume depletion, renal adverse events, bone fractures, and lower limb amputations were found to be balanced between the active treatment groups and respective placebo groups in each trial. There were zero cases of ketoacidosis in EMPEROR-Reduced and only 3 patients (0.1%) had diabetic ketoacidosis in DAPA-HF. Dapagliflozin and empagliflozin are both comparable in safety and tolerability.

The other two HF trials, EMPEROR-Preserved and DELIVER, enrolled HF patients with a preserved ejection fraction (HFpEF) of eGFR >40.[12,13] Of note, current HF guidelines recognize the ejection fraction threshold for HFpEF as ≥50%. These trials revealed a substantial risk reduction of worsening HF and CV death that both dapagliflozin and empagliflozin exhibited in all 4 trials, regardless of ejection fraction. Both trials showed comparable risk reductions for the primary endpoint of time to first hospitalization for HF or CV death. These trials also showed a smaller treatment effect in patients with HFpEF (eGFR >40) compared to HFrEF, 20% vs 25% relative risk reduction, respectively. Overall, SGLT2i exhibited extremely consistent benefits in HF patients with an ejection fraction >40%. A pre-specified analysis done in the DELIVER trial showed a statistical benefit on the primary endpoint of CV death or worsening HF event within 13 days (<2 weeks) after initiation of the SGLT2i (HR=0.45; 95% CI: 0.20-0.99, p=0.046).[14] Another pre-specified analysis of the DELIVER trial showed benefits of a SGLT2i on clinical outcomes and health status were consistent across HF duration as well.[15]

In a post hoc analysis, the frequency of occurrence of early decline in eGFR after initiation of dapagliflozin and its association with outcomes were evaluated in patients with HFrEF.[16] Although a decline in eGFR is generally associated with a poorer prognosis in most situations, an initial decline in eGFR with SGLT2i was instead associated with better CV outcomes and a slower rate of decline in kidney function.

Updated guidelines emphasize the importance of starting an SGLT2i quickly. Due to the mortality benefit seen in the four HF trials, the ESC guidelines gave dapagliflozin and empagliflozin a class 1A indication for patients with HFrEF, HF with mildly reduced ejection fraction (EF 41%-49%), and HFpEF to reduce the risk of HF hospitalization and death.[2]

Lastly, there are three landmark kidney outcomes trials that resulted in SGLT2 inhibitors becoming key kidney protective therapies. The CREDENCE study was the first RCT of an SGLT2i specifically powered for primary kidney outcomes among patients with albuminuric CKD, resulting in a 30% reduction in the primary composite outcome of end stage renal disease (ESRD), doubling of serum creatinine, and renal or CV death.[17] The DAPA-CKD trial was the first kidney outcomes trial to enroll patients with CKD with or without type 2 diabetes.[18] Dapagliflozin showed a 39% risk reduction in the primary outcome, indicating that SGLT2i provide renal protective effects that extend to all patients with CKD regardless of diabetes status (HR=0.61; 95% CI: 0.51-0.72; p<0.001). Results from DAPA-CKD extend findings from the CREDENCE study by demonstrating safety and efficacy of dapagliflozin in a cohort of patients with stage 4 CKD (eGFR <30) more than 3.5-fold larger, and which included patients with CKD without type 2 diabetes. EMPA-KIDNEY was the second kidney outcomes trial to enroll patients with CKD with or without type 2 diabetes.[19] Key differences between DAPA-CKD and EMPA-KIDNEY were the inclusion of many causes of kidney disease not related to diabetes (e.g., polycystic kidney disease, lupus nephropathy), lower eGFR (≥20), and lower levels of albuminuria (UACR ≥200) in EMPA-KIDNEY. The use of empagliflozin resulted in a 28% risk reduction in the primary composite outcome of progression of kidney disease or death from CV causes (HR=0.72; 95% CI: 0.64-0.82; p<0.001).

Both the Kidney Disease Improving Global Outcomes (KDIGO) and the American Diabetes Association (ADA) recommend SGLT2i in patients with type 2 diabetes, CKD, and an eGFR ≥20.[20,21] KDIGO also recommends (grade 1A) use of a SGLT2i in these patients who also have a UACR ≥200, or patients who have CKD and HF, irrespective of the level of albuminuria.

Findings:

SGLT2 inhibitors significantly reduce the risk of mortality and worsening heart failure, and should be considered foundational therapy in all patients with heart failure, irrespective of left ventricular ejection fraction, care setting, or diabetes status. When it comes to CKD, SGLT2 inhibitors provide kidney protective effects in patients with a broad range of baseline eGFRs, regardless of diabetes status or CKD cause. Empagliflozin remains clinically non-inferior to dapagliflozin, and therefore the NPTC voted to make no modifications to the NCF at this time.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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