Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***SGLT-2 inhibitors (Update)***
-August 2017-

Background:

The FDA has currently approved three SGLT-2 inhibitors, two of which have completed FDA-mandated cardiovascular outcomes trials. Last year, in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG), empagliflozin not only reduced cardiovascular events, but also mortality.[1] This year, the Canagliflozin Cardiovascular Assessment Study (CANVAS) demonstrated equivocal cardiovascular benefits, no mortality benefit, and significant harms in those receiving canagliflozin.[2] The DECLARE-TIMI 58 cardiovascular study of dapagliflozin will be completed in April 2019 (ClinicalTrials.gov Identifier: NCT01730534). Uncertainty remains regarding the current data, long-term benefits and harms, and differentiation among SGLT-2 inhibitors. Following a review of SGLT2 inhibitors at the August 2017 NPTC meeting on their cardiovascular outcomes, net benefit and place in therapy, **no modifications were made to the National Core Formulary** (NCF).

Discussion:

EMPA-REG enrolled 7,020 patients with Type 2 diabetes mellitus (T2DM) and HgbA1c values between 7.0-10.0%. All patients had established cardiovascular disease (CVD) and were observed for a median duration of 3.1 years. Empagliflozin reduced the primary outcome of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal cardiovascular accident (CVA) by 6.5 events per 1000 patient-years (pt-yrs). Mortality decreased by 9.2 events per 1000 pt-yrs, primarily driven by a reduction in CV mortality of 7.8 events per 1000 pt-yrs. Heart failure hospitalization decreased by 5.1 events per 1000 pt-yrs. The number needed to treat (NNT) for the primary outcome was 63; for total mortality, the NNT was 38; and for cardiovascular mortality, the NNT was 45.[1] Based on this evidence, the FDA approved empagliflozin for an additional indication to "reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease."

CANVAS enrolled 10,142 T2DM patients with HgbA1c values between 7.0-10.5%. Established CVD was not required in all patients at study enrollment; patients over 50 years old could be enrolled without established CVD if deemed at high risk (≥2 risk factors for CVD). As a result, the CANVAS population had lower overall CV risk than the EMPA-REG population. The results must therefore be compared with caution. Canagliflozin reduced the primary outcome of CV death, nonfatal MI, or nonfatal CVA by 4.6 events per 1000 pt-yrs. Heart failure hospitalization declined by 3.2 events per 1000 pt-yrs however mortality did not decrease. Despite the improved time-to-event rate, patients treated with canagliflozin had absolute increases of 0.3% for the primary outcome, 0.4% for total mortality and 0.3% for CV mortality. This data was originally available in Table S6 of the Supplementary Appendix, but was later removed.[2] It is plausible that canagliflozin decreases early events but increases later events, thereby increasing time-to-event while not decreasing total events.

Both empagliflozin and canagliflozin improved renal outcomes. Patient-oriented outcomes were only included in post hoc analyses, but the results were highly significant. The NNT for empagliflozin to prevent the composite endpoint of doubled creatinine/renal replacement/renal death was 71.[3]

Empagliflozin did not increase the rate of significant side effects, aside from the expected increase in genital mycosis. For women, the number needed to harm for genital mycosis was 14. Canagliflozin increased lower-limb amputations by nearly two-fold, from 3.4 events to 6.3 events per 1000 pt-yrs ($p<0.001$). The FDA has now required a boxed warning on the label for this adverse event. Fractures also significantly increased in canagliflozin patients by 3.5 events per 1000 pt-yrs, a 29% relative increase. Ketoacidosis, hypoglycemia, hypotension, hyperkalemia and UTIs were not significantly increased in either trial.[1,2,6] There have been case reports published of euglycemic diabetic ketoacidosis (DKA) with

these agents. A recent review by the American Association of Clinical Endocrinologists points out that euglycemic DKA occurred before these agents were initially administered, and it is not clear whether the frequency increased. They conclude that euglycemic DKA occurs infrequently and the risk-benefit ratio overwhelmingly favors continued use.[7]

Several meta-analyses note that SGLT-2 inhibitors decrease body weight by approximately 2 kilograms[4], reduce systolic and diastolic blood pressures by about 2 mm Hg[5], and cause trivial yet clinically insignificant changes in lipid parameters. In general, SGLT-2 inhibitors have few drug interactions, with dapagliflozin and empagliflozin having fewer than canagliflozin (Lexicomp, accessed 7/15/2017).

Findings:

In CANVAS, canagliflozin reduced the incidence of CV death, nonfatal MI or nonfatal CVA, the primary outcome, however there was concern expressed by the NPTC that canagliflozin may actually increase risk over time (evidenced by increased total events with canagliflozin over study duration). There was also a trend, though non-significant, toward increased risk of mortality with canagliflozin. Renal outcomes are reassuring however, which seem to be a class effect. Risk of both amputations and fractures were increased.

EMPA-REG demonstrated that empagliflozin reduced the incidence rate of the primary outcome (CV death, nonfatal MI or nonfatal CVA), overall mortality, cardiovascular mortality, hospitalization for heart failure, and renal outcomes, without increasing adverse events beyond genital mycosis.

Conclusions:

Despite positive outcomes for empagliflozin, the NPTC voted against NCF inclusion at this time for the following reasons:

- Benefits are shown in only a single, drug manufacturer-funded study without independent oversight or analysis.
- EMPA-REG included only patients with established cardiovascular disease. The impact of empagliflozin in T2DM patients outside this study population (without CVD) remains undefined.
- Long-term effects are unknown. It is uncertain whether benefits outweigh harms for those without established cardiovascular disease. HgbA1c lowering is modest and may diminish significantly over time.
- The CANVAS study demonstrated safety concerns (adverse effects) that may be class effects.

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.

References:

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