Item S1. SGLT2 Inhibitors Background and Evidence Review

Additional Background

Chronic kidney disease (CKD) is a major national public health concern affecting approximately 37 million adults in the United States[1] and is the 10th leading cause of death, predominately due to cardiovascular disease.[2,3] Pharmacotherapy to reduce cardio-renal risk remains imperative. Despite strong evidence in randomized controlled trials of the benefits of SGLT2i therapy, there is considerable underutilization of SGLT2i in patients with CKD.[4,5] There is an unmet need for an effective and timely evidence-based tool to support the implementation of this impactful therapy. A clinical pathway, in conjunction with other support strategies such as electronic medical record resources, has been shown to be an effective method of research translation to overcome clinical inertia.[6,7] Here, we review the evidence surrounding SGLT2i and present a clinical pathway that can be used by nephrologists, nephrology advanced practice providers (APPs), and other clinicians to aid in prescribing SGLT2i therapy for patients with CKD.

SGLT2i Background and Brief Evidence Review

Sodium-glucose cotransporter-2 (SGLT2) is expressed in the proximal tubule of the kidney and is responsible for the active transport of glucose across the cell membrane, which reabsorbs approximately 90% of the filtered glucose.[8] SGLT2 inhibition decreases the kidney glucose threshold, which results in glycosuria, a reduction in plasma glucose, and an osmotic diuresis with increased urine output.[9,10] There is an accompanying natriuresis, which leads to afferent arteriolar vasoconstriction via tubuloglomerular feedback.[10] The downstream effect is a decrease in intraglomerular pressure, which is thought to reduce kidney function decline over time.[10]

Pharmacotherapy to block SGLT2 and promote glycemic control in type 2 diabetes

received FDA approval in 2013.[11] The first SGLT2i approved was canagliflozin, followed by empagliflozin, dapagliflozin, and most recently ertugliflozin.[11] Subsequent to the indication for glucose reduction, several large cardiovascular outcome trials (CVOTs) demonstrated significant cardiovascular benefits of SGLT2i in patients with type 2 diabetes.[12-14] EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) and CANVAS Programs (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) both saw a 14% relative risk reduction with SGLT2i use as compared to placebo in major adverse cardiovascular endpoints (MACE), defined by the composite of death from cardiovascular disease, non-fatal myocardial infarction, or non-fatal stroke.[12,13] While DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) did not demonstrate the same benefits for MACE, there was a 17% relative risk reduction in cardiovascular death or hospitalization for heart failure with SGLT2i use as compared to placebo, an effect that was consistent across all levels of renal function and albuminuria status.[14,15]

In patients with heart failure with reduced and preserved ejection fraction, several studies showed similar benefit.[16-18] Specifically, in heart failure with reduced ejection fraction, DAPA-HF (Dapagliflozin in Patients with Heart Failure with Reduced Ejection Fraction) and EMPEROR-Reduced (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure) demonstrated a 26% and 22% risk reduction respectively for the composite of heart failure hospitalization or cardiovascular death with SGLT2i as compared to placebo.[16,17] Similarly, in patients who had heart failure with preserved ejection fraction, EMPEROR-Preserved (Empagliflozin in Heart Failure with a Preserved Ejection Fraction) demonstrated a 21% reduced risk.[18] The trials enrolled patients with CKD (eGFR $\geq$ 30 ml/min/1.73m^2 for DAPA-HF and $\geq$20 ml/min/1.73m^2 for EMPEROR-Reduced and EMPEROR-Preserved) and results were similar regardless of diabetes and severity of CKD.[18-21] Overall, these trials showed a consistent benefit of SGLT2i in heart

failure management which led to varying new indications to reduce the risk of hospitalization for heart failure and cardiovascular death.[11]

The secondary analyses of the CVOTs that focused on adverse kidney outcomes provided strong evidence of kidney protection from the SGLT2i in patients with CKD.[13,20-27] In EMPA-REG OUTCOME, empagliflozin as compared to placebo conferred a 39% relative risk reduction for secondary composite endpoint of urine albumin/creatinine >300 mg/g, doubling of creatinine with an eGFR of ≤45 ml/min/1.73m^2, incident end-stage kidney disease (ESKD), or kidney related death, with no difference in results between those with and without CKD.[20] Importantly, there was a 55% relative risk reduction for progression to ESKD with the use of empagliflozin as compared to placebo.[20] CANVAS Program produced similar results for these secondary composite outcomes.[13,21] Each study saw an initial decrease in eGFR in both arms, which then stabilized in the treated group and declined in the placebo group. Overall, there was an annual eGFR decline of 0.19 and 0.33 ml/min/1.73m^2 in the treated arm as compared to 1.67 and 0.85 ml/min/1.73m^2 in the placebo group for EMPA-REG OUTCOME and CANVAS Program respectively.[20,21] Subsequent analyses demonstrated that these findings were similar for subjects with CKD across a spectrum of eGFR.[21,23] Notably, over 80% of subjects in both studies were on renin-angiotensin receptor (RAS) blockers, and these findings were similar regardless of the presence of RAS blockade.[12,13, 21,23]

CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) was the first trial to assess kidney outcomes in a CKD population with type 2 diabetes at high risk for CKD progression.[24] CREDENCE showed that SGLT2i use as compared to placebo conferred a 30% and 34% relative risk reduction in the primary composite outcome (serum creatinine doubling, ESKD, or death due to kidney or cardiovascular cause) and secondary endpoints (composite of ESKD, serum creatinine doubling, or death due to kidney causes), respectively.[24]

Further analysis revealed that the beneficial kidney effects of SGLT2i seen in CREDENCE and other trials were consistent across strata of eGFR and albuminuria status.[25,26] Additionally, SGLT2i use blunted the slope of eGFR decline over time, similar to the analyses in the CVOTs.[17,18,22,25,26] The evidence from CREDENCE led to a new FDA indication of canagliflozin for the treatment of diabetic kidney disease in 2019, the first medication to gain such approval in approximately 20 years.[11]

While the prior trials focused on patients with type 2 DM, questions remained as to whether the beneficial effects extended to patients without DM, particularly given the DAPA-HF results that showed similar efficacy of dapagliflozin in patients with and without DM. Likewise, EMPEROR-Reduced and EMPEROR-Preserved saw preservation of the eGFR slope with SGLT2i use in patients with CKD with and without diabetes.[17-19] DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease), which enrolled patients with and without type 2 DM, demonstrated that dapagliflozin as compared to placebo reduced the primary endpoint (a composite of a sustained decline in the eGFR of ≥50%, ESKD, or death from kidney or cardiovascular causes) by approximately 40%.[27] The results were similar regardless of diabetes status. As a result of the DAPA-CKD findings, dapagliflozin gained an FDA indication in 2020 for treatment of CKD (specifically reduction of sustained eGFR decline, ESKD, hospitalization for heart failure, and cardiovascular death) irrespective of diabetes or albuminuria status for those who are at risk of progression.[28] Based on the benefits seen in the trials and the new FDA indications, the major clinical practice guidelines, including Kidney Disease Improving Global Outcomes (KDIGO), now overwhelmingly support the use of SGLT2i in patients with CKD and type 2 diabetes.[29-31]

Evidence Translation through Clinical Pathway

The pathway in **Figure 1** reflects the most current evidence and indications, and it is intended to be dynamic to account for additional trial data that is expected to emerge. It is

suggested to use this pathway in print and/or electronic form in the clinical setting and is designed for use by both specialty and primary care providers. In our academic nephrology practice, the pathway is displayed as laminated cards in visible locations in exam rooms. As additional support, the pathway has been extrapolated into a best practice alert in the electronic medical record. This best practice alert "triggers" on appropriate patients during an office visit and serves as a prompt for the provider to consider SGLT2i therapy in patients meeting appropriate criteria. Mirroring the pathway, this alert contains a systematic process for SGLT2i initiation and monitoring. Further details on operationalizing this pathway through a quality improvement project at our institution are forthcoming and will be reported on in a future paper. Of fundamental importance, clinical-behavioral change is complex, and utilization of the pathway should be supported with peer-peer discussions and provider buy-in.

Additional Side Effects

The CANVAS trial saw in increase in fracture and amputation with the use of SGLT2i in patients with normal and reduced kidney function, which raised early concerns over their use in patients with a history of foot/lower limb ulceration or peripheral arterial disease.[13] Subsequent trials and post-marketing surveillance did not identify an increased fracture and amputation risk in patients on SGLT2i and cited peripheral arterial disease as the most important predictor of amputation.[24,25,32] The pathway advises to avoid SGLT2i use with critical limb ischemia and to monitor for foot/lower limb ulceration with annual (or more frequent) exams and to hold SGLT2i with any concerning findings.

Cost

Cost is an important barrier to SGLT2i use and requires attention when operationalizing the clinical pathway. Out-of-pocket expenses for these medications can be high, with a reported list price for dapagliflozin of approximately $530/month without insurance coverage.[33] Medicare part

D coverage varies depending on prior payments in the year but are generally high at over $1000 annually.[34] Despite high individual costs, however, several cost analyses on kidney and cardiovascular outcomes found that the SGLT2i were cost-effective at an individual and societal level.[35-38] Of particular interest to nephrologists, one study showed that the two year delay of dialysis conferred by dapagliflozin use could result in a $30,000,000 per 5,000 patients cost reduction over a ten year period.[39] High and shifting costs will affect prescribing uptake. Discussion of SGLT2i with patients should include cost and can be aided with pharmacy involvement and various voucher programs.

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