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REVIEW

Empagliflozin in Adults with Chronic Kidney Disease (CKD): Current Evidence and Place in Therapy

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Abstract: Chronic kidney disease guidelines and disease modifying therapy have seen a dramatic shift in the last 5 years. The SGLT2 inhibitor class of medications has been catapulted from hyperglycemia management medications, to cardiovascular and kidney disease improvement therapies. Multiple trials looking at dedicated cardiovascular and kidney endpoints have resulted in favorable results. This review will target empagliflozin and the exciting journey that it has taken along this path. Empagliflozin has been studied for hyperglycemia, cardiovascular, and kidney hard outcome endpoints. Both patients with diabetes and without have been rigorously studied and shown surprising results. The major implications for patients on empagliflozin will be shown. Future studies and directions are highly anticipated to add to the growing knowledge of the SGLT2 inhibitor class, as well as discover possibilities for new disease states to benefit from empagliflozin.

Keywords: empagliflozin, SGLT2, chronic kidney disease, cardiovascular disease, diabetes, end stage kidney disease

Introduction

Hyperfiltration is the driving force that leads nephrons to glomerulosclerosis and eventually results in chronic kidney disease (CKD) and end-stage kidney disease (ESKD). It has therefore been intuitive that decreasing hyperfiltration is the major paradigm for slowing the progression of CKD.

A little over 2 decades ago, we first witnessed the landmark trials involving a class of drugs, the renin angiotensin aldosterone inhibitors (RAASi) that addressed this paradigm and paved the way to how we have managed patients with diabetic kidney disease (DKD), as a means to slow progression of CKD. Since that time, this space has been dead silent until the recent introduction of a novel class of therapeutics, the sodium glucose co-transporter 2 inhibitors (SGLT2i). The US Food and Drug Administration (FDA) approved the first SGLT2ii in early 2013, followed by the report of the mandatory cardiovascular outcome safety trials. Overall, the trials reported to date show that SGLT2i do not increase cardiovascular (CV) risk. Several of these SGLT-2i have been associated with clinically meaningful reductions in major cardiovascular events (MACE) and CV death. All-cause mortality reduction was demonstrated by empagliflozin, and other SGLT2i safety trials reported reductions in congestive heart failure (CHF). In these trials, there was an impressive reduction in the risk for hard kidney endpoints (ESKD, need for dialysis or doubling of serum creatinine [DSC], or death), with relative risk reductions between 40% and 24%.[1,2] These reductions, along with the effects of SGLT2i on cardiac outcomes, are much larger than those obtained with RAASi. In the earlier CV safety trials, kidney endpoints were either secondary or exploratory only. Several trials have been published since, looking at specific kidney endpoints.[1,2] This review will highlight the pharmacology, safety and efficacy, and key findings of the recent SGLT2i trials particularly, Empagliflozin, and the latest developments.

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Pharmacology of Sodium Glucose Cotransporter (SGLT)

The kidney glomeruli normally filter approximately 120–180 grams of glucose from plasma each day but less than 0.5 grams are excreted in the urine. Glucose is known to be freely filtered in the glomerulus and then reabsorbed in the proximal convoluted tubule (PCT). The maximum kidney glucose reabsorptive capacity (TmG) is calculated at 375 mg/min and glucose is filtered at 125 mg/min or 180 mg/day, in the average human (assuming a normal estimated glomerular filtration rate (eGFR)). Moreover, glucosuria appears when glycemia exceeds 180 mg/dL in patients with type 1 or type 2 diabetes mellitus and this phenomenon develops because the filtered glucose load exceeds the TmG leading to glucosuria.

In kidney physiology, glucose cannot be reabsorbed through the walls of the PCT, so it requires assistance of glucose transport by cotransporters present in the PCT. The sodium glucose co-transporters, SGLT1 and SGLT2 are members of the SLC5 gene family, a subdivision of sodium cotransporters. SGLT1 is predominantly expressed in the small intestine and to a lesser extent in the kidneys, particularly in the cortex, whereas SGLT2 is present in the kidney cortex.[3] SGLT2 is present in the first and second segment (S1 and S2) of the PCT and is responsible for 90% of glucose reabsorption. SGLT1 is mostly present in the luminal membrane of the S3 segment.[4] This cotransporter in S1 has a high capacity/low affinity whereas in S2 and S3, it has high-affinity and low-capacity glucose/galactose co-transporter. The SGLT proteins engage the Na/K ATPase pump localized in the basolateral membrane leading to a decline in the intracellular sodium concentration accomplishing a sodium gradient which generates a downhill gradient to transport one glucose molecule against the uphill glucose gradient in the apical membrane of the PCT. The ratios of sodium to glucose cotransport inside the cell are 1:1 and 2:1 for SGLT2 and SGLT1, respectively.[5] This subsequently is then transferred into the blood by the glucose transporters, GLUT1 and GLUT2 which are present on the basolateral membrane of the PCT.

SGLT2i are a class of drugs that promote the kidney excretion of glucose by inducing glucosuria, decreasing both the TmG and the threshold for glucose reabsorption, and although they are not first-class agents for the treatment of type 2 diabetes, they have become an important component in the management of patients with diabetes, as well as in patients with heart failure and CKD, as described below.

SGLT2 intercedes in the reabsorption of 90% of filtered glucose, however, SGLT2i only increase glucosuria by approximately 50% of the filtered glucose load. This phenomenon takes place because SGLT1 located mostly in the S2 and S3, operates below its maximal transport capacity given the fact that the SGLT2 already reabsorbed 90% of the filtered glucose.[4] So, when SGLT2 is inhibited, this results in the delivery of a large load of glucose to the SGLT1 transporter which at that point, is at its full reabsorptive capacity, which can explain why we see less than 50% of the filtered glucose in the urine. Currently SGTL2i drug class are not approved for use in patients with Type 1 diabetes mellitus. There is fear of metabolic acidosis and possible ketoacidosis with SGLT2i exposure. These patients have not been included in the major trials and the data cannot be extrapolated to this group.

Empagliflozin Pharmacology Characteristics

Empagliflozin is a SGLT2 inhibitor with the higher selectivity for SGLT2 over SGLT1 (over >2500 fold). Its bioavailability is around 75% and is rapidly absorbed after oral administration. Empagliflozin has a Tmax of 1.5 hours and binds to proteins by 86% and its half-life life (T1/2) is 13 hours and is eliminated mostly by the fecal (40%) and kidney (55%) route.[5]

After initiating a SGLT2i there is typically a decline in eGFR, an effect that is reversible overtime or after the medication is stopped. Several models of diabetes-related hyperfiltration have shown that increased distal natriuresis to the macula densa activates the tubuloglomerular feedback, likely via an adenosine-related mechanism, however this has been debated by other findings suggesting that that main effect is a post-glomerular vasodilation, rather than preglomerular vasoconstriction.[6] This may explain the accompanied lowering microalbuminuria effects seen with these medication class. Other long term positive effects can be explained by a reduction in the intraglomerular pressure.[7]

In healthy individuals, empagliflozin has been shown to be rapidly absorbed after it is administered orally. Increases in exposure to urinary albumin appears to be dose-proportional over the range of empagliflozin doses (0.5–800 mg). Similar findings have been reported with doses between 1 and 100 mg in healthy Japanese patients.[8] These findings can be explained as Japanese individuals generally have less weight. It has also been noticed that when empagliflozin is administered with food, there is a slight delayed absorption, although Cmax was lower under fed conditions than when the drug is given in fasting conditions, these findings appeared to be non-clinically significant, and drug can be administered with food.

Plasma concentrations of empagliflozin at higher doses such as 100 mg, have been reported to be detectable for up to 72 hours. Furthermore, the FDA and according to the International Conference on Harmonization (ICH) guidelines,[9] recommends that clinical trials implement strategies and collect data in one region to determine if there are differences in ethnic factors in other regions. For instance, there are no differences in pharmacokinetic parameters between Egyptians and white Germans and no dose adjustment is needed in these populations[10] when 25 mg of empagliflozin is being administered.

Hyperglycemia Studies for Empagliflozin

In the middle 2010s, SGLT2i including empagliflozin underwent clinical trials as hyperglycemic therapy. At that time, patients with advanced CKD were excluded from Phase 1 trials related to safety and tolerability.[11] We have selected landmark trials that helped establish the validity, safety, and efficacy of empagliflozin. The 2013 EMPA-REG MONO Phase 3 clinical trial randomized adults with glycosylated hemoglobin (HbA1c) 7–10% on no prior therapy to placebo, sitagliptin, or 10 or 25mg doses of empagliflozin. Compared to placebo, empagliflozin decreased A1c by 0.74 and 0.85% depending on dose, which was a statistically significant difference comparable to the 0.73% difference seen with sitagliptin. As secondary efficacy endpoints, investigators discovered systolic blood pressure was reduced by an average of 3.7mmHg and body weight was reduced by an average of 2.5kg (in 25mg dosage group) which was significant compared to sitagliptin and placebo.[12] The finding of lowered weight was consistent in the 2014 EMPA-REG MET trial, in which empagliflozin was added on to metformin, with a similar reduction in weight of 2.5kg in the 25mg group.[13] In this trial, systolic blood pressure as an exploratory outcome was lowered by an average of 4.8 mmHg in the 25 mg dose group.

After EMPA-REG MONO and EMPA-REG MET, additional trials demonstrated efficacy of empagliflozin as an add-on therapy to metformin and sulfonylurea (EMPA-REG METSU[14]) and pioglitazone (EMPA-REG PIO[15]), making the SGLT2i a well-established choice for second-and third-line medication for patients with diabetes. Notably, the addition of empagliflozin to sulfonylurea increased the incidence of reported hypoglycemia events, but the incidence of hypoglycemia was not increased when combined with pioglitazone. Both trials demonstrated decreased systolic blood pressure and body weight in patients using empagliflozin compared to sulfonylurea or pioglitazone alone.

The final success story for empagliflozin as a hyperglycemia therapy was the 2015 publication of EMPA-REG BASAL trial.[16] This study enrolled patients with sub optimally controlled diabetes (HbA1c > 7%) despite basal insulin and, in some patients, the concomitant use of metformin or sulfonylurea. In patients enrolled at 18 weeks, HbA1c decreased by 0.7% with addition of empagliflozin 25mg compared to 0.1% in placebo. This effect was lessened slightly by week 78, as investigators were permitted to increase basal insulin if needed after week 18, but a significant improvement in A1c was still noted. As in prior studies, the addition of empagliflozin showed significant decrease in body weight at either 10 or 25 mg doses, however a statistically significant decrease in systolic blood pressure was only seen with 10 mg dose.

Overall, empagliflozin emerged as a reasonable treatment option for patients with diabetes, either as a monotherapy, an additional non-insulin therapy, or as an addition to insulin therapy. The American Diabetes Association recommendations were broadened in 2020 to specify that patients with Type 2 Diabetes with atherosclerotic cardiovascular disease or kidney disease should have a SGLT2i or GLP-1 agonist as part of their glucose lowering strategy. It should be noted, however, that this recommendation was added as a response to trials (discussed later) demonstrating improved cardiovascular and kidney risk in this patient population.

Most trials did demonstrate an increased incidence of urinary or genital tract infections with use of empagliflozin, which has been a major criticism of SGLT2i. It is critically important to note that patients with eGFR <30mL/min/m^2 were excluded from these earlier hyperglycemia trials. When comparing the different SGLT2i medications, the side effects do appear to be a class effect and all patients need to be warned of potential infection risk and hypovolemia.[17]

Kidney Studies for SGLT2i and Empagliflozin

The kidney benefits of SGLT2i have been earlier discovered in all cardiovascular studies, as secondary outcomes (EPMA-REG, CANVAS[18]) and will be discussed later in the cardiovascular section of this review. The first trial addressing kidney outcomes as the primary outcome was the CREDENCE trial in 2019.[1] CREDENCE randomized 4401 patients with T2DM, CKD (eGFR 30-≤90 mL/min/1.73 m^2) and albuminuria (300–5000 mg/g), who have been stable on renin–angiotensin system blockade for 4 weeks or more to receive Canagliflozin 100 mg or placebo. The study was stopped early after an interim

analysis with a median follow-up of 2.62 years. Canagliflozin caused a 30% relative risk reduction of primary composite outcome (ESKD, doubling of the serum creatinine level, or death from renal or cardiovascular causes). The canagliflozin group also had a 31% lower risk of cardiovascular death, myocardial infarction, or stroke (HR 0.80; 95% CI, 0.67 to 0.95; P = 0.01) and hospitalization for heart failure (HR 0.61; 95% CI, 0.47 to 0.80; P < 0.001).

With these clear kidney benefits of Canagliflozin on albuminuric CKD patients with T2DM, the second kidney outcomes trial using dapagliflozin was published in 2020. The DAPA-CKD randomized 4304 patients with CKD (eGFR 25–75 mL/min/1.73m^2), with or without diabetes, albuminuria (200 to 5000 mg/g), who have been stable on renin–angiotensin system blockade for 4 weeks or more to receive dapagliflozin 10 mg or placebo.[2] Once again, the study was stopped earlier because of efficacy. Dapagliflozin group had a 44% relative risk reduction of primary composite of a sustained decline in the estimated GFR of at least 50%, ESKD, or death from kidney or cardiovascular causes (HR 0.56, 95% CI, 0.45 to 0.68; P < 0.001). The cardiovascular benefits of dapagliflozin, or the SGLT2i class, were clearly apparent with 29% relative risk reduction of a composite of death from cardiovascular causes or hospitalization for heart failure. The effect of dapagliflozin was surprisingly similar in CKD patients with or without diabetes. Major trials with the different SGLT2i can be seen in Figure 1. Another real-world trial looking at kidney outcomes with SGLT2i use was CVD-REAL 3.[19] This observation trial showed SGLT2i use was associated with a reduced eGFR decline (difference in slope for SGLT2i vs other glucose-lowering drugs 1.53 mL/min/1.73 m2 per year, 95% CI 1.34–1.72, p < 0.0001) and a lower incidence of major kidney events (hazard ratio 0.49, 95% CI 0.35–0.67; p < 0.0001). As well, these findings were consistent across subgroups and different regions throughout the world.

Empagliflozin specific kidney outcome trial was recently published (EMPA-KIDNEY). The EMPA-KIDNEY is the third of the kidney outcome trials for the SGLT2i class. EMPA-KIDNEY randomized 6609 patients to empagliflozin 10mg, versus placebo, to test its effect on kidney disease progression (ESKD, a sustained eGFR below 10mL/min/1.73m^2, kidney death, or a sustained ≥40% decline in eGFR) and cardiovascular death.[20] EMPA-KIDNEY included patients with more advanced CKD without albuminuria (eGFR > 45 down to 20mL/min/1.73m^2) or patients with CKD stage 1–3a (eGFR 45->90 mL/min/

Selected Clinical Trials of SGLT2 inhibitors in CVD and CKD

	N	T2DM	CKD (eGFR)	1° Composite Outcome	HR (95 CI)	Takeaway
EMPA-REG OUTCOME	7,020	100%	25.9% (74)	CV death, nonfatal MI, or nonfatal stroke	0.86 (0.74-0.99)	Empagliflozin lowered CV events in T2DM + ASCVD; signal for SGLT2i in HF and CKD.
CANVAS	10,142	100%	21.9% (76)	CV death, nonfatal MI, or nonfatal stroke	0.86 (0.75-0.97)	Canagliflozin lowered CV events in T2DM + ASCVD or ASCVD risk; signal for SGLT2i in HF and CKD.
DECLARE-TIMI 58	17,160	100%	9.2% (85)	1. CV death or HHF* 2. MACE	*0.83 (0.73-0.95)	Dapagliflozin lowered CV death or HHF, but had no effect on MACE, in T2DM + ASCVD or ASCVD risk.
CREDENCE	4,401	100%	100% (56)	ESKD, 2x SCr, renal or CV death	0.70 (0.59-0.82)	Canagliflozin lowered adverse kidney events in CKD + T2DM; first renal outcomes trial in SGLT2i.
DAPA-CKD	4,304	67%	100% (43)	≥50% decline eGFR, ESKD, renal or CV death	0.61 (0.51-0.72)	Dapagliflozin lowered adverse kidney events for patients with CKD, with or without T2DM.
DAPA-HF	4,744	42%	41% (66)	CV death or worsening HF	0.74 (0.65-0.85)	Dapagliflozin improved HF outcomes in HFrEF on GDMT, with or without T2DM.
EMPEROR-REDUCED	3,730	50%	48% (62)	CV death or HHF	0.75 (0.65-0.86)	Empagliflozin improved HF outcomes in HFrEF on GDMT, with or without T2DM.

T2DM – type 2 diabetes mellitus; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; CV – cardiovascular; MI – myocardial infarction, ASCVD – atherosclerotic cardiovascular disease; SCr – serum creatinine; ESKD – end-stage kidney disease; HF – heart failure; GDMT – guideline-directed medical therapy; MACE – major adverse cardiac events; HHF – hospitalization for heart failure

Figure 1 Selected clinical trials of SGLT2 inhibitors in CVD and CKD. *Significant for CV death or HHF but not for MACE. With permission from Jefferson Triozzi. Available from: https://www.grepmed.com/images/12169/ebm-table-inhibitors-cvd-visualabstract.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CV, cardiovascular; MI, myocardial infarction; SCr, serum creatinine; ESKD, end state kidney disease; HF, heart failure; GDMT, guideline-directed medical therapy; MACE, major adverse cardiac events; HHF, hospitalization for heart failure.

1.73m^2) with urinary albumin:creatinine ratio ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g). The mean age was 63.8 years, 54% had no history of DM, and the mean eGFR was 37.5 mL/min/1.73 m$^{2.}$ With a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin arm and in 558 of 3305 patients (16.9%) in the placebo arm (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P < 0.001). The results were also consistent among patients with and without diabetes. This data was comparable to previous hard outcome benefits of canagliflozin and dapagliflozin trials. This data was presented at the American Society of Nephrology Kidney Week meeting 2022 with great fanfare and excitement.

SGLT2 inhibitors are becoming and should be a first-line treatment, together with RAAS blockers, for the management of patients with CKD given their cardiorenal benefits. Their safety continues to be confirmed with more large randomized trials. Specifically, the issue of amputation and fracture that earlier were seen in the CANVAS trial, are now in line with placebo in the DAPA-CKD and EMPA-KIDNEY trial. Mycotic and urinary tract infections do remain an issue, but better screening and monitoring with real-world use experience should make these issues less frequent.

Cardiovascular Studies for Empagliflozin

The first sign that empagliflozin could provide cardiac benefits was the 2015 EMPA-REG OUTCOME trial.[21] This multicenter, double-blinded, randomized controlled trial (RCT) was designed to evaluate the cardiovascular outcomes of added empagliflozin to patients with type 2 diabetes. Though stroke and MI did not occur less frequently in the treatment group, there was a significant reduction in cardiovascular death, hospitalization for heart failure or all-cause mortality. This trial showed that empagliflozin had a protective effects against CV events, worsening of kidney function and proteinuria even in these very high-risk patients and did not show any safety concerns. Treatment benefit was consistent between patients with or without large proteinuria and tended to be statistically larger on regression (>30% reduction vs baseline) of albuminuria and eGFR slope in patients with nephrotic range proteinuria. A comprehensive meta-analysis looking at SGLT2i trials and cardiovascular events up to 2018 revealed SGLT2i use reduced major adverse cardiovascular events by 11% (HR 0.89 [95% CI 0.83–0.96], p = 0.0014).[22] The significant benefits were seen in those with atherosclerotic cardiovascular disease but not in those without.

Since the EMPA-REG OUTCOME Trial, patients with cardiac illness have undergone dedicated cardiovascular trials regardless of diabetic status. The EMPEROR-Reduced Trial in 2020 was a RCT of 3730 patients with heart failure with reduced ejection fraction (HFrEF) with left ventricular ejection fraction (LVEF) of 40% or less.[23] Patients were given empagliflozin 10mg daily or placebo in addition to standard medical therapy. The primary outcome of composite of cardiac death or hospitalization for worsening heart failure was significantly reduced in the treatment group (primarily driven by a 31% lower risk of hospitalization). Importantly, the primary outcome benefit remained significant whether patients had diabetes or not. Additionally, the rate of decline of eGFR was significantly slower in the treatment group by 1.8mL/min/m^2 year annually over 2 years as well, though this was not the primary outcome. Of note, nearly half the patients had eGFR<60mL/min/1.73m^2. While not the first time SGLT2i had shown benefit in HF patients, this trial extended the reach of the previously published DAPA-HF trial because patients enrolled had lower ejection fractions and elevated BNP – the primary event occurred more frequently and thus demonstrated benefit in a sicker subset of patients.[24]

The subsequently published 2021 EMPEROR-Preserved trial enrolled 5988 patients with Class 2–4 HF with EF>40%.[25] This group of 5988 patients, as in the EMPEROR-Reduced trial, received either placebo or 10mg per day of empagliflozin. Over the course of the study period, patients randomized to the empagliflozin arm were significantly less likely to be hospitalized for heart failure, which drove the positive composite outcome of cardiovascular death or heart failure hospitalization. The EMPULSE trial was completed in 2022 and helped address some of the questions regarding initiation of SGLT2i. This trial randomized 530 patients hospitalized with either decompensated HF exacerbations or new onset HF (not yet on goal directed medical therapy) to receive placebo versus empagliflozin.[26] The primary outcome was the clinical benefit, defined as a hierarchical composite of all-cause mortality, number of heart failure events and time to first heart failure event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days. Significantly more patients in the treatment group saw clinical benefit. This effect was consistent regardless of whether HF was acute and whether the patient had diabetes. Importantly the safety analyses did not reveal a difference in arms.

It has not all been positivity for empagliflozin – the much smaller EMPERIAL studies in 2021 studied the impact of SGLT2i on exercise ability and symptoms in patients with HFrEF (EMPERIAL-Reduced) or HFpEF (EMPERIAL-Preserved).[27] Both studies enrolled just over 300 patients and tested primary endpoint of change in 6-minute walk distance and self-reported dyspnea score over 12 weeks. The changes in these outcomes were nonsignificant.

There has been much discussion if the SGLT2i class medications are individually beneficial or if there is an overall class effect. This debate has been getting quieter and quieter as the CV study endpoints continue to point as a positive effect that is repeatable, no matter which SGTL2i is studied. A nice review shows that when you compare and combine the CV data endpoints, significant improvement is present in all three SGLT2i medications studied.[28] An interesting and strategic plan by the trialists has been to include different patient types and lower eGFR levels. It has been very satisfying to see significant cardiovascular and kidney improvements with sicker and sicker populations.

The most notable ongoing trial in cardiology remains the EMPACT-MI study. Scheduled to complete in early 2023, this study will be investigating the potential heart failure benefit of empagliflozin in patients who have had a recent myocardial infarction. The primary outcomes will be time to first HF hospitalization or mortality. If positive, this study will enable clinicians to start treatment even earlier in disease course than did EMPULSE.[29]

Future Study of Empagliflozin

The past and present use of empagliflozin has focused on glucose control and lowering HgbA1c. Some off label use has been tried by clinicians for weight management and even volume removal. But the future will focus on entirely unrelated mechanistic pathways when compared with hyperglycemia. As stated above, several landmark trials have proven benefits of heart failure with reduced and preserved ejection fraction. The improvements in HF hospitalizations, cardiovascular deaths, and biomarkers in HF are very exciting.[30] The continued empagliflozin FDA label change to include HF patients without diabetes is very encouraging and backed by the data presented. What will remain to be seen is how real-world data and use will emerge in the cardiovascular community. Dapagliflozin and canagliflozin both as well have a cardiac indication for CV disease and heart failure, canagliflozin specifically in diabetic heart failure. It is nice to have several tools in our medical toolbox to treat these previously deficient patients, but empagliflozin having a major market share will be determined in the coming years.

The kidney is the next logical organ to pay attention to when considering empagliflozin for benefits. The SGLT2i class has shown remarkable improvements in CKD progression, dialysis, cardiovascular and overall mortality with canagliflozin and dapagliflozin. EMPA-KIDNEY was well detailed to study CKD patients and has been recently published in 2022.[20] There is much excitement that the data matches what we see in canagliflozin and dapagliflozin in the SGLT2i class. EMPA-KIDNEY studied patients with eGFR down to 20 mL/min/1.73m^2, which further advances the proof that SGLT2i can work with sicker kidney patients safely. Further head-to-head studies are needed, but unlikely to be completed soon with the SGLT2i class given recency of the large clinical trials. As well, patients with Type 1 diabetes mellitus should also be considered who are well controlled as they have the same cardiovascular and kidney risks.

Liver disease is another complex disease state that has unmet needs for corrective treatment. Nonalcoholic fatty liver disease (NAFLD) is a potential disease that could have improvement when taking empagliflozin. A small study of patients with DM and NAFLD received empagliflozin 10 mg daily compared to standard treatments in the MRI-PDFF trial[31] showed that fat fraction of the liver was reduced, although modestly at 5% but did not show any adverse events. The COMBATT2NASH trial will also look at using empagliflozin vs semaglutide vs placebo in patients with nonalcoholic steatohepatitis as an alternative treatment option (Clinicaltrials.gov: NCT04639414). Many therapeutic targets are being investigated for these chronic liver disease patients and empagliflozin may surprise us again for the non-diabetic patient.

Atherosclerosis of blood vessels and resulting distal organ ischemia may be impacted by empagliflozin. In diabetic patients, three months of empagliflozin resulted in significant regression of complex intima medial thickness by 7.9% and was obvious at just one month.[32] Decreased cerebral atherosclerosis could improve cognitive impairment progression and may play a role in dementia.[33] Further studies looking at Alzheimer's research is ongoing to see how empagliflozin and other SGTL2i class drugs alter inflammation, oxidative stress, neurotransmitter imbalance, and synaptic loss.[34]

Further clinical trials are discussed in Table 1. A large group of kidney patients that have not been fully explored are those with a kidney transplant. This group is frequently left out of large controlled trials, but they may serve as patients ripe for benefit as the allograft slowly fails over time. A kidney allograft should function as a native kidney, and in theory

Table 1 Notable Ongoing Clinical Trials Involving Empagliflozin Found at ClinicalTrials.gov

Study Title	Trial Identification	Enrolled	Outcome
Effects of Empagliflozin on Fibrosis and Cirrhosis in Chronic Hep B	NCT05147090	106 patients. Emp vs Placebo	Change in liver stiffness measured by MR elastography
Impact of the SGLT2i Empagliflozin on Urinary Supersaturations in Kidney Stone Formers	NCT04911660, SWEETSTONE	46 patients. Emp vs Placebo	Change in calcium oxalate supersaturation, change in calcium phosphate supersaturation, change in uric acid supersaturation
Empagliflozin and Cardiac Remodeling in People Without Diabetes	NCT04461041, EMPA-HEART 2	164 patients. Emp vs Placebo	Change in Left Vent mass
Empagliflozin and the Preservation of Beta-cell Function in Women with Recent Gestational Diabetes	NCT03215069, EMPA post-GDM	120 patients. Emp vs Placebo	Baseline-adjusted Insulin Secretion-Sensitivity Index-2 at 48 weeks
Real World Safety and efficacy of Empagliflozin With or Without Metformin in T2DM	NCT05164263, EASE	156 patients. Emp + metformin vs Emp alone	Safety and Tolerability of adverse events
Efficacy or Empagliflozin or Linagliptin as an Alternative to Metformin for Treatment of Polycystic Ovary Syndrome	NCT05200793	75 patients. Metformin vs Emp vs Linagliptin	Fertility, follicle-stimulating hormone level, free androgen level, ultrasound changes, menses cycles
The Metabolic Effects of Empagliflozin in Patients with High Risk of Heart Failure	NCT05042973	120 patients. Emp vs Placebo	Epicardial adipose tissue and estimated extracellular volume
Effects of the SGLT2i Empagliflozin in Patients with Euvolemic and Hypervolemic Hyponatremia	NCT04447911, EMPOWER	172 patients. Emp vs Placebo	Change in average daily area under curve for serum sodium concentration
Comparative Effectiveness of Empagliflozin in the US	NCT03363464, EMPRISE	230,000 patients, Emp vs DPP-4 inhibitor vs GLP-1 agonist *Observational trial	3-point major adverse cardiovascular events (MACE), hospitalization for heart failure, Modified MACE, all-cause mortality
Head-to-head Comparison of Empagliflozin and Dapagliflozin	NCT03748810	600 patients. Emp vs Dapagliflozin. Both added to standard of care	Changes in HbA1c from baseline to week 156, change in fasting plasma glucose to week 156
Post Marketing Surveillance of Jardiance in Chronic Heart Failure	NCT05262764	1200 patients on Emp	Incidence of Adverse Drug Reactions
A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack	NCT04509674, EMPACT-MI	5000 patients. Emp vs Placebo	Composite of time to first heart failure hospitalization or all-cause mortality
Empagliflozin-based Quadruple Therapy vs Basal Insulin-based Therapy	NCT05103306, LUCID	300 patients. Emp +SOC, vs Insulin	Changes in HbA1c from baseline to 36 months
The Cardiac Effects of Empagliflozin in Patients with High Risk of Heart Failure	NCT05084235	204 patients. Emp vs Placebo	Left ventricular mass index and maximal oxygen consumption on stress test
A Study to Test Whether Different Doses of BI 690517 Alone or in Combination with Empagliflozin Improve Kidney Function in People with Chronic Kidney Disease	NCT05182840	552 patients. Emp + BI690517 vs BI690517 alone	Change from treatment period baseline in log transformed urine albumin creatinine ratio

(*Continued*)

Table 1 (Continued).

Study Title	Trial Identification	Enrolled	Outcome
Combined Active Treatment in Type 2 Diabetes with NASH	NCT04639414, COMBATT2NASH	192 patients. Emp vs Emp + Semaglutide vs Placebo	Histological resolution of NASH without worsening fibrosis at 48 weeks
Pharmacological reduction of Right Ventricular Enlargement	NCT04345796, PROVE	180 patients. Carvedilol + Emp vs Carvedilol vs Emp vs Placebo	Change of RV end-systolic volume index
The Efficacy of SLT2i in Patients with CAD and Diabetes undergoing PCI	NCT05333159	1424 patients. Emp or Dapagliflozin or Canagliflozin	Major adverse cardiovascular and cerebrovascular events MACCE at 12 months

Notes: *Significant for CV Death or HHF, but not for MACE.

would have the same physiologic benefits with use of a SGLT2i like empagliflozin. We hope that this group of vulnerable patients will be studied to further lengthen the time of dialysis free survival.

There are many groups throughout the world looking at different uses for empagliflozin for many different disease states. Most trials are small or confirmatory in nature, so wide application will be limited. Yet the SGLT2i class continues to surprise us with better and better findings over the initial hyperglycemia benefit. It is encouraging to see the enthusiasm for research and exploration on how empagliflozin and other SGLT2i class medications can help patients with other debilitating conditions. The story is not over for empagliflozin, and that may be as exciting as the landmark trials we have already completed.

Conclusion

Empagliflozin is the latest SGLT2i drug to show proven benefits in both hyperglycemia, CV disease, heart failure, and now CKD progression. The new EMPA-KIDNEY data proves that it provides benefits in patients with and without diabetes and can be used in those with eGFR down to 20 mL/min/1.73m^2. The medication is further solidified as an important tool to combat CKD progression and avoidance and delay of CV risk factors. Adverse events appear to be minimal and are in line with previous trials and other medications in the SGLT2i class. We encourage clinicians to digest this data and consider adding SGLT2i to RAASi in the appropriate patients. Further guideline changes are expected and we feel encouraged to have advanced therapies like empagliflozin to combat chronic kidney disease.

Disclosure

Dr. Colbert declares as a Consultant for AstraZeneca. Dr Lerma declares honoraria from AstraZeneca and Bayer. Dr Lerma also is advisory board and/or speaker bureau for Astra Zeneca, Bayer, Otsuka, Travere, Vifor, Glaxo Smith Kline, and Boehringer Ingelheim, during the conduct of the study. All other authors report no conflicts of interest in this work.

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