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EMPA-REG OUTCOME: The Nephrologist's Point of View

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ABSTRACT

There is increasing evidence that sodium glucose cotransporter 2 (SGLT2) inhibitors have renoprotective effects, as demonstrated by the renal analyses from clinical trials including Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), CANagliflozin Treatment And Trial Analysis versus SUlphonylurea (CANTATA-SU), and the dapagliflozin renal study. The potential mechanisms responsible are likely multifactorial, and direct renovascular and hemodynamic effects are postulated to play a central role. This report reviews the renal outcomes data from key SGLT2 inhibitor clinical trials, discusses the hypotheses for SGLT2 inhibitor-associated renoprotection, and considers the main renal safety issues associated with SGLT2 inhibitor treatment.
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Since the publication 15 years ago of the Irbesartan Diabetic Nephropathy Trial (IDNT)[1] and the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study,[2] which investigated the renoprotective effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with type 2 diabetes (T2DM) and nephropathy, there have been no new interventions or approved medications for the treatment of diabetic kidney disease (diabetic nephropathy).[3-8] Although the progression of kidney disease has decreased with advances in blood pressure (BP) control and renin-angiotensin-aldosterone system (RAAS) blockade, many patients with T2DM still suffer from chronic kidney disease (CKD) and will progress to end-stage renal disease and require dialysis. The prevalence of T2DM is increasing,[9] and improved life expectancy is leading to a higher proportion of elderly patients with T2DM; an escalating demand for clinical nephrology services, including an increase in the requirement for renal dialysis, can be expected.[10] Consequently, there is a profound and urgent need for new drug therapies that prevent, treat, or slow the progression of diabetic kidney disease given that current treatments are only moderately effective.[11]

PATHOPHYSIOLOGY OF DIABETIC KIDNEY DISEASE

In diabetes, chronic hyperglycemia causes substantial morbidity and mortality due to the resulting macrovascular disease (ie, atherosclerotic cardiovascular disease) and

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microvascular disease (ie, kidney disease, retinopathy, and neuropathy).[12] Diabetic kidney disease develops gradually over many years and has several separate but interrelated stages, including reversible glomerular hyperfiltration, normal glomerular filtration and normoalbuminuria, normal or decreasing glomerular filtration and microalbuminuria, declining glomerular filtration and macroalbuminuria, and end-stage renal disease.[13] Several well-defined pathophysiologic mechanisms of diabetic kidney disease have been described, including hemodynamic, metabolic, and inflammatory pathways, as reviewed in detail by Toth-Manikowski and Atta.[14] In the hemodynamic pathways of diabetic kidney disease, RAAS activation leads to increased levels of angiotensin II, causing efferent arteriolar vasoconstriction and hyperfiltration; there is also increased expression of another efferent arteriolar vasoconstrictor, endothelin-1.[14] In terms of metabolic pathways, hyperglycemia leads to generation of free oxygen radicals, causing inhibition of glyceraldehyde-3-phosphate dehydrogenase, which prevents normal glycolysis and results in a backlog of glycolysis precursors, leading to upregulation of the polyol and hexosamine pathways and the production of advanced glycation end-product precursors and cofactors for protein kinase C activation.[14] These metabolic effects are associated with various pathophysiologic processes affecting the kidney, including increased transcription of inflammatory cytokines, renal cell hypertrophy, increased mesangial matrix components, and damage to the glomerular basement membrane, which contribute to glomerular hyperfiltration.[14] With regard to the inflammatory pathways, hyperglycemia results in 1) increased expression of nuclear factor-κB, a transcription factor that regulates gene expression relating to processes including inflammation, immunity, and apoptosis; 2) activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway, which relays extracellular chemical signals to gene promoters; and 3) increased expression of inflammatory cytokines, such as interleukins and tumor necrosis factor-α.[14] Other pathways that may also contribute to diabetic kidney disease include decreased podocyte autophagic activity and upregulation of sodium glucose cotransporter 2 (SGLT2) expression, both of which are associated with hyperglycemia.[14]

MECHANISM OF ACTION OF SGLT2 INHIBITORS

SGLT2 inhibitors are glucose-lowering agents that target the kidney to reduce the reabsorption of glucose and promote glucose excretion in the urine, thereby reducing hyperglycemia in patients with T2DM. Three SGLT2 inhibitors − canagliflozin, dapagliflozin, and empagliflozin − have been approved for the treatment of T2DM by regulatory agencies in the United States (US), European Union (EU), and other parts of the world. Three more SGLT2 inhibitors − ipragliflozin, luseogliflozin, and tofogliflozin − have regulatory approval in Japan, but are not currently available in either the US or EU markets; other SGLT2 inhibitors are in clinical development as well. The mechanism of action of SGLT2 inhibitors has been described in detail in previous reviews.[15,16] Briefly, effectively all of the glucose filtered by the kidney in a healthy individual is reabsorbed and returned to the blood circulation, and a negligible amount is excreted in the urine.[15] Renal glucose reabsorption is predominantly mediated by SGLT2, with lesser involvement by its family member SGLT1. Evidence suggests that in patients with T2DM, the expression and activity of SGLT2 is increased in the presence of hyperglycemia, resulting in additional glucose reabsorption and preservation of elevated blood glucose levels.[15,17] Pharmacologic inhibition of SGLT2 in the kidney reduces the capacity for renal glucose reabsorption by up to 50%.[18] As SGLT2 reabsorbs sodium and glucose in a cotransport manner, SGLT2 inhibitors also cause natriuresis and are associated with an antihypertensive effect.[19] The mechanism of SGLT2 inhibition occurs independently of insulin secretion, and is not affected by pancreatic β-cell function or the degree of insulin resistance.[15] (A review of the efficacy and safety of SGLT2 inhibitors is presented by Thrasher in this issue.[20]) In addition to their glucose-lowering effect, increasing evidence suggests that SGLT2 inhibitors have renoprotective effects, as discussed below.

SUMMARY OF RENAL FUNCTION RESULTS FROM EMPA-REG OUTCOME AND OTHER PHASE III EMPAGLIFLOZIN STUDIES

The cardiovascular and renal outcomes data from EMPA-REG OUTCOME have been described.[21,22] Briefly, the study population included patients with T2DM, established cardiovascular disease, and an estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2.[21,22] Patients were randomized (N = 7020) to receive either empagliflozin (10 mg or 25 mg) or placebo once daily, in addition to standard care.[21] Prespecified renal outcomes included incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria (defined as urinary albumin:creatinine ratio [U_{ACR}] $\geq$30 mg/g).[22] Several additional prespecified renal microvascular outcomes and a post hoc renal composite outcome were also analyzed.[22] Patients in EMPA-REG OUTCOME had the following baseline characteristics: mean age, ~63 years; mean BP, ~135/77 mm Hg; mean duration of T2DM >10 years, ~57%; baseline eGFR $\geq$60 and <90 mL/min/1.73 m^2, ~52%; received RAAS inhibition with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, ~80%; and U_{ACR}<30 mg/g, ~59%.[21] The median observation period was 3.1 years.[21] Empagliflozin treatment (10-mg and 25-mg pooled dose group) was associated with a statistically significant 39% reduction in relative risk of incident or worsening nephropathy vs placebo (**Figure 1A**).[22] Statistically significant relative risk reductions for empagliflozin vs placebo were also observed for progression to macroalbuminuria, doubling of serum