EDITORIAL

Clinical Credence — SGLT2 Inhibitors, Diabetes, and Chronic Kidney Disease

Julie R. Ingelfinger, M.D., and Clifford J. Rosen, M.D.

The number of people who die from kidney disease every year has risen over the past decade and is now estimated at 5 million to 10 million worldwide. The increase in rates of obesity — along with associated rates of type 2 diabetes, hypertension, and cardiovascular disease — has principally driven the elevated mortality. More than 660,000 Americans have reached the point of requiring intervention for end-stage kidney disease, with 468,000 receiving dialysis and more than 193,000 undergoing kidney transplantation, leading to a major public health and economic burden.[1] Hence, the development of new treatments that may prevent or delay the progression of chronic kidney disease, as well as treat type 2 diabetes, is an important goal.

Tight control of glucose levels and blood pressure slows but does not prevent the onset of diabetic nephropathy.[2] The standard approach for retarding the onset of diabetic nephropathy and stabilizing renal function has been blockade of the renin–angiotensin–aldosterone system, particularly with inhibitors of angiotensin-converting enzyme. This approach was first used in the early 1990s in patients with type 1 diabetes[3]; randomized trials subsequently established that such drugs were also effective in type 2 diabetes.[4] Newer classes of agents have also been tried but have not been successful.

Inhibitors of sodium–glucose cotransporter-2 (SGLT2) were initially approved as a new class of hypoglycemic agents that lowered blood glucose levels in patients with type 2 diabetes by enhancing urinary glucose excretion through the inhibition of SGLT2 in the proximal convoluted tubule, where glucose is reabsorbed. SGLT2 inhibitors reduce the renal threshold of glucose from 180 mg per deciliter (10 mmol per liter) to 40 to 120 mg per deciliter (2 to 7 mmol per liter), thereby effectively lowering blood glucose levels. In 2015, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[5] changed the landscape in diabetes management by showing a lower risk of cardiovascular death among the 4687 patients who received empagliflozin than among the 2333 controls (172 patients [3.7%] vs. 137 patients [5.9%]) (hazard ratio, 0.62; 95% confidence interval [CI], 0.49 to 0.77). Patients in the empagliflozin group also had a lower risk of death from any cause (269 patients [5.7%] vs. 194 patients [8.3%]) (hazard ratio, 0.68; 95% CI, 0.57 to 0.82) and a lower risk of hospitalization for heart failure (126 patients [2.7%] vs. 95 patients [4.1%]) (hazard ratio, 0.65; 95% CI, 0.50 to 0.85). Recently, the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)[6] showed similar cardiovascular benefits, indicating a class effect of SGLT2 inhibitors. Further support for that finding was noted in the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors)[7] and the Health Improvement Network (THIN) trials.[8] As a result, SGLT2 inhibitors are now widely used in patients with type 2 diabetes both to improve glycated hemoglobin levels and to reduce cardiovascular risk.

Recent studies have hinted that medications designed to treat diabetes could also confer renoprotection through a mechanism that differs from those affecting glucose homeostasis.[3,4,7] Among these drugs, the SGLT2 inhibitors appeared to be the most promising.

In the *Journal*, Perkovic et al.[9] now report the primary results of the double-blind, randomized CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, in which 4401 patients with type 2 diabetes and albuminuric chronic kidney disease received 100 mg of canagliflozin or placebo added to renin–angiotensin–aldosterone blockade and baseline diabetic therapy after a 2-week run-in period. All the participants met the criteria of having an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio of more than 300 (with albumin measured in milligrams and creatinine in grams). Sixty percent of the patients had an estimated GFR of 30 to 60 ml per minute per 1.73 m^2. The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, transplantation, or a sustained estimated GFR of less than 15 ml per minute per 1.73 m^2 for 30 days), doubling of the serum creatinine level for at least 30 days, or death from renal or cardiovascular disease. Secondary outcomes included cardiovascular outcomes (death, heart failure, myocardial infarction, or stroke). The trial was halted early (median follow-up, 2.62 years) after a planned interim analysis indicated that the primary outcome had been met.

The relative risk of the primary outcome was nearly 30% lower in the canagliflozin group than in the placebo group. There was also a 20 to 30% lower relative risk of deleterious cardiovascular outcomes. The glycated hemoglobin levels were reduced more by canagliflozin than by placebo, as were blood pressure and body weight. The slope of the decline in the estimated GFR was slower in the canagliflozin group than in the placebo group. Rates of two targeted adverse events, fractures and lower-limb amputations, were similar in the two groups; diabetic ketoacidosis was more frequent in the canagliflozin group than in the placebo group, despite the overall low rates (2.2 vs. 0.2 per 1000 patient-years).

The underlying mechanisms of canagliflozin activity are probably both renal and systemic. SGLT2 inhibition increases glucose and sodium delivery to the distal renal tubule, which is sensed by the juxtaglomerular apparatus as increased glomerular perfusion. This leads to increased vasoconstriction of the afferent arteriole, which decreases glomerular perfusion and intraglomerular pressure. Although these effects decrease the estimated GFR in the short term, as was seen during the first weeks of the CREDENCE trial, over time that effect stabilizes. The level of angiotensin II in the circulation decreases, as does the level of atrial natriuretic peptide, with a subsequent decrease in inflammation and an increase in intrarenal oxygenation. Decreased body weight and sympathetic output, decreased uric acid, and perhaps an increase in glucagon may also contribute.[10] Other hypoglycemic agents, such as inhibitors of dipeptidyl peptidase-4, also suppress oxidative stress, lessening fibrosis and apoptosis, which may retard progression.[4]

Overall, the importance of CREDENCE,[9] a well done and large clinical trial, cannot be overstated. The investigators estimated that among 1000 patients treated for 2.5 years, 22 would need to be treated with canagliflozin to prevent the composite primary outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death. In addition, among the same number of patients, canagliflozin treatment would prevent 22 hospitalizations for heart failure and 25 composite events of cardiovascular death, myocardial infarction, or stroke. Such data are certain to be welcomed by patients with diabetes and chronic kidney disease and by the clinicians who treat them.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Tufts University School of Medicine, Boston, and the Center for Clinical and Translational Research, Maine Medical Center Research Institute, Scarborough (C.J.R.).

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