Sodium/Glucose Cotransporter 2 Inhibitors in Patients With Diabetes Mellitus and Chronic Kidney Disease

Turning the Page

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The link between cardiovascular disease (CVD) and diabetes mellitus has long been recorded, extending back to the advent of insulin therapy, when that therapeutic advance increased patient survival, allowing atherosclerotic complications to become more evident.[1] Attention to the relationship between diabetes mellitus and CVD grew, fostered by forces such as the epidemic of obesity and diabetes mellitus, improved post–myocardial infarction survival, and increasing data linking these 2 common, chronic problems. For example, the East-West Study placed the cardiovascular risk of diabetes mellitus in a context easily grasped by cardiologists: the chances of a future myocardial infarction in those with diabetes mellitus and no CVD history equaled those of myocardial infarction survivors with no history of diabetes mellitus.[2] Although still debated, this "cardiovascular risk equivalency" offered an easy shorthand that helped recast the nature and treatment of diabetes mellitus. The arrival of new glucose-lowering drugs and therapeutic strategies created expectations about the next chapter to come: glucose lowering in diabetes mellitus would decrease cardiovascular events. That story, however, unfolded with unexpected twists, including a new subplot concerning the cardiovascular safety of glucose-lowering agents. Ultimately, a long, often disappointing, contradictory saga of the "glucose paradox" emerged; although hyperglycemia increases cardiovascular risk, lowering glucose levels did not reverse this relationship.[3] Even when the cardiovascular safety of a drug was established, no cardiovascular risk reduction was found.[4] In the past 2 years, 2 classes of antidiabetic drugs have demonstrated an improved primary major cardiovascular end point in a large prospective trial using 2 different agents within each class, namely glucagon-like peptide–1 agonists (liraglutide, semaglutide) and sodium/glucose cotransporter 2 (SGLT2) inhibitors (empagliflozin, canagliflozin).[5–8] The page had finally turned to a new chapter of cardiometabolic therapeutics.

Decreasing cardiovascular events with a glucose-lowering agent carries a key question: Why did those drugs work? For SGLT2 inhibitors, their mechanism of action is predicated on their action in the kidney: decreased glucose reabsorption causing glucosuria, thus lowering hemoglobin A1C levels.[9] In the landmark EMPA-REG OUTCOME trial [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], empagliflozin, compared to usual care, decreased the primary end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 14% while reducing cardiovascular mortality by 38%.[7] Given that SGLT2 inhibitors act primarily on tubules in the kidney, did this class also demonstrate a benefit among those with a reduced estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}, the definition of stage 3 chronic kidney disease (CKD)? In this issue of *Circulation,* Wanner et al[10] add to the initial EMPA-REG results, further evaluating outcomes among the one third of the 7020 EMPA-REG subjects

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with an estimated glomerular filtration rate between 30 and 59 mL·min^{-1}·1.73 m^{-2} with albuminuria. Empagliflozin significantly reduced all cardiovascular events and all-cause mortality in these patients with CKD, with the greatest decline being manifest in heart failure hospitalization. The magnitude of benefit did not differ between those with renal dysfunction and the total cohort. Even those with an estimated glomerular filtration rate <45 mL·min^{-1}·1.73 m^{-2} had outcomes similar to those of patients with better kidney function. It is noteworthy that blood pressure and weight declined similarly in those with and without CKD; hence, these changes are not directly related to osmotic diuretic effects of the drug. As such, none of the benefits seen in the subjects with CKD treated with empagliflozin, which increases urinary glucose disposal, can be linked directly to degree of glucose loss in the urine.

These EMPA-REG results establish the SGLT2 inhibitor empagliflozin as a means of reducing cardiovascular risk in those with type 2 diabetes mellitus and CKD. They also highlight the important, sometimes overlooked, and still incompletely understood interplay between CKD and CVD.[11] CKD independently increases cardiovascular risk while augmenting the progression of kidney dysfunction and intensifying other drivers of atherosclerotic complications: worsening diabetes mellitus, raising triglycerides, and increasing blood pressure. Independent of questions about risk equivalency, the cardiovascular risk of diabetes mellitus is now broadly recognized.[12] The combination of CKD and diabetes mellitus earmarks a distinct group of patients at particularly high risk for untoward cardiovascular outcomes. Just as diabetes mellitus manifests itself across a wide spectrum of clinical diseases and associated cardiovascular risks, CKD also involves a broad range of pathology and associated risk of cardiovascular complications. The cardiovascular risk of CKD may not be fully appreciated by clinicians or appreciated as driving a need for intervention, an oversight perhaps supported by cardiovascular risk calculators that do not incorporate CKD as a distinct factor. The EMPA-REG renal data add to the tasks for clinicians seeing patients with diabetes mellitus and CKD, asking that they not only recognize and manage cardiovascular risk but also consider how different glucose-lowering therapies affect cardiovascular outcomes, including among those with CKD.

One barrier to physician engagement with CKD among those with diabetes mellitus and high cardiovascular risk may be missing data. The landscape for studies evaluating how different therapies, including glucose-lowering agents, modify cardiovascular events in stage 3 (glomerular filtration rate, 30–59 mL/min) and stage 4 (glomerular filtration rate, 15–29 mL/min) CKD has been limited (Table). By including such patients, EMPA-REG has provided noteworthy findings. For SGLT2 inhibitors, although glucose lowering and diuresis decline in those with CKD, the reduction in blood pressure and cardiovascular events with these agents does not, suggesting a diuresis-independent effect on hypertension and a glucose-independent cardiovascular benefit. Deeper consideration of mechanisms at work with SGLT2 inhibitors is needed, including complex issues such as whether SGLT2 inhibition modifies CKD progression and cardiovascular complications through similar or distinct pathways.

Repressing SGLT2 action in the kidney decreases glucose reabsorption in the proximal tubule, raising distal delivery of sodium chloride and fluid, thus restoring tubuloglomerular feedback and reducing glomerular hyperfiltration.[13] The data that SGLT2 inhibitors reduce sympathetic tone are still under investigation with variable results. Along with glucose, SGLT2 inhibition increases excretion of uric acid, a molecule implicated in adverse vascular responses.[9] SGLT2 inhibition raises levels of glucagon, which has multiple vascular effects. Urinary glucose excretion wastes energy; this effect, along with diuresis, likely underlies the modest but significant weight loss

Table. Clinical Renal Characteristics in Recent GLP1 and SGLT2 Inhibitor Cardiovascular Outcome Trials in Diabetes Mellitus

	Clinical Trial					
	LEADER	EXSCEL	SUSTAIN-6[6]	ELIXA	EMPA-REG	CANVAS
Drug class	GLP1	GLP1	GLP1	GLP1	SGLT2i	SGLT2i
Primary cardiovascular end point	Positive	Neutral	Positive	Neutral	Positive	Positive
Baseline eGFR, mL·min^{-1}·1.73 m^{-2}	75	76	?	76	74	77
eGFR <60 mL·min^{-1}·1.73 m^{-2}, % study	23	21.6	29	23.2	25.9	16
eGFR <30 mL·min^{-1}·1.73 m^{-2}, % study	2.4	0.03	0.5	0.1	NA	NA

? indicates unknown, data not available; CANVAS, Canagliflozin Cardiovascular Assessment Study (NCT01032629); eGFR, estimated glomerular filtration rate; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (NCT01147250); EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (NCT01131676); EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial: A Trial to Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly in Patients With Type 2 Diabetes Mellitus (NCT01144338); GLP1, glucagon-like peptide–1 receptor; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes and Results (NCT0117904); NA, not applicable; Neutral, no evidence for cardiovascular benefit on trial primary endpoint; Positive, positive cardiovascular benefit on trial primary endpoint; SGLT2i, sodium/glucose cotransporter 2 inhibitor; and SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (NCT01720446).

seen with SGLT2 inhibitors, which may improve other cellular and systemic responses to stressors such as ischemia.[14] Particularly intriguing is evidence that branched-chain amino acid metabolism is altered in diabetes mellitus and improved by SGLT2 inhibition.[15] Glucose and fatty acids are used as fuel for active tissues, with ketone bodies and branched-chain amino acids serving as alternative energy resources. Few organs demand as much energy as the heart, which may be a particular issue for patients with diabetes mellitus and heart failure. SGLT2 inhibitors modestly increase circulating ketones, an efficient energy substrate that may improve myocardial function and perhaps cardiac ischemia and arrhythmia.[14] As investigators who have long chased the complex intersection of diabetes mellitus, CVD, and renal disease know, benefits from inhibiting SGLT2 may well involve the combined effects on these and other pathways.

The advent of randomized, prospective, controlled clinical trial data that treating diabetes mellitus can improve cardiovascular outcomes is auspicious. Beyond the initial report of the SGLT2 inhibitor empagliflozin decreasing cardiovascular events in patients with diabetes mellitus, we now have more evidence that empagliflozin, which acts in the kidney, still decreases blood pressure and improves cardiovascular outcomes, including cardiovascular mortality, even when significant CKD is present. These results provide new clinical opportunities and force more immediate, pressing clinical application of what we now know. The presence of CKD, a powerful force in worsening cardiovascular outcomes in the setting of diabetes mellitus, arguably among the more definitive cardiovascular risk equivalents a clinician will encounter, requires attention. Aggressive cardiovascular risk reduction may be easier for the physician to pursue when the clinical situation is obvious: Q waves on an ECG, a history of coronary stenting, or a chest scar from coronary bypass. More challenging is recognizing the cardiovascular risk lurking when CKD and diabetes mellitus are present together, even without these more glaring CVD signals. Because of the positive prospective clinical trial data from EMPA-REG, this increased attention has to include consideration of SGLT2 inhibitors as an intervention that improves cardiovascular outcomes in high-risk patients with diabetes mellitus and CKD. These novel SGLT2 inhibitor findings also stimulate new questions: What other patient groups may benefit from such agents? Are there other ways to target this pathway? How do these renal-acting agents retain their beneficial effects in the presence of significant CKD, and can they protect the kidney from further decline in settings of high CVD risk? The page has turned again. The next page awaits.

DISCLOSURES

Dr Plutzky reports being a consultant to Aegerion, Boehringer-Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi, and Vivus. Dr Bakris reports being a consultant to Merck and Relypsa; serving on the clinical trial steering committee for AbbVie (SONAR [Study of Diabetic Nephropathy With Atrasentan]), Janssen (CREDENCE [Computed Tomographic Evaluation of Atherosclerotic Determinants of Myocardial Ischemia]), and Vascular Dynamics (CALM-FIM [Controlling and Lowering Blood Pressure With the MOBIUSHD]); and being the principal investigator for Bayer (FIDELIO [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus]).

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FOOTNOTES

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