Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials

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The prevalence of type 2 diabetes is catalyzing a pandemic in kidney disease, with ensuing cardiovascular complications. The effort to identify antidiabetic agents capable of promoting benefits that go beyond the bounds of glucose control has produced remarkable outcomes in recent cardiovascular outcomes trials in patients with type 2 diabetes mellitus, many of whom have diabetic kidney disease. Two novel antidiabetic drug classes, sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), improve cardiovascular outcomes in different ways, with SGLT2is reducing the risk of heart failure and cardiovascular death and GLP-1 RAs being associated with reduced risk of myocardial infarction and cardiovascular death. Further mechanistic studies and additional cardiovascular outcome trials are ongoing and are expected to determine whether these benefits are a result of class effect, as well as to delineate optimum timing for intervention and population target.

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When diabetes is associated with kidney disease, the cardiovascular (CV) risk increases substantially. It is known that a high proportion of patients with moderate chronic kidney disease (CKD) will never reach end stage owing to a prior fatal CV event. The current treatment strategies for the management of diabetic kidney disease and the prevention of CV mortality are based on conventional risk factor modification and the use of agents to antagonize the renin-angiotensin and sympathetic nervous systems; however, despite success, there is a pressing need for additional pharmacological treatments to abate the excess risk. This review will focus on describing the epidemiology of CV outcomes in diabetic kidney disease and will detail recent advances in type 2 diabetes mellitus (T2DM) treatment with CV impact, particularly sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Epidemiology of diabetic kidney disease and cardiovascular outcomes

Diabetes is an accelerating health and economic burden worldwide, with an estimated prevalence nearing 600 million by 2030 due to population aging, growth, and lifestyle changes associated with urbanization.[1] CV complications are the leading cause of morbidity and mortality in patients with diabetes, and diabetic kidney disease appears to predominantly account for the increased risk.[2,3] The additive CV hazard between diabetes and CKD has been shown in many settings. Not only is this cohort of patients at increased risk of developing acute coronary syndrome, arrhythmias, and congestive heart failure; their risk of complications and mortality derived from these conditions is striking.[4,5] Among medically treated patients with diabetes undergoing percutaneous coronary intervention (PCI), the presence of CKD has been associated with a significantly higher in-hospital and 1-year mortality rate, as well as longer hospital stays and higher rates of neurological, gastrointestinal, and pulmonary complications.[5] Data from the Bypass Angioplasty Revascularization Investigation (BARI) study among patients with multivessel coronary artery disease undergoing revascularization show an increased risk of death among patients with CKD, independent of and additive to the risk associated with diabetes, reaching close to 70% in 7 years in this group.[6] Both diabetes and CKD are risk factors for the development of atrial fibrillation[7,8] and are associated with an increased risk of stroke with this arrhythmia.[9,10] Given the notoriously high

prevalence of bleeding in patients with impaired kidney function and the paucity of data from drug and procedure trials involving patients with a reduced estimated glomerular filtration rate, the balance between stroke prevention and the avoidance of bleeding in this group becomes especially challenging.[11,12] When it comes to heart failure, diabetes is an independent risk factor for progression of disease, and regardless of the etiology, the concomitant presence of T2DM and CKD is associated with worse prognosis.[13,14]

Conventional cardiovascular risk factor control

Traditional risk factor modification remains the cornerstone of treatment for patients with CKD and diabetes. The Kidney Disease: Improving Global Outcomes (KDIGO)[15] and Kidney Disease Outcomes Quality Initiative (KDOQI)[16] guidelines support the control of blood pressure (BP) and lipids to decrease the risk of CV mortality. For patients with urine albumin excretion < 30 mg in 24 hours, treatment is recommended to maintain a BP that is consistently no higher than 140 mm Hg systolic and 90 mm Hg diastolic (evidence grade 1B), while for patients with albumin excretion higher than 30 mg in 24 hours, the goal is to keep BP consistently no higher than 130 mm Hg systolic and 80 mm Hg diastolic (evidence grade 2D). The weak evidence level for the more strict control in the latter group derives from the lack of data from trials. The ACCORD trial in patients with diabetes[17] failed to show a reduction in rates of fatal and nonfatal major CV events when comparing intensive therapy with the goals of maintaining systolic BP $<$ 120 mm Hg and $<$ 140 mm Hg. Conversely, the SPRINT trial in patients without diabetes[18] showed a reduction in CV events and all-cause mortality among patients treated to a target systolic BP of 120 mm Hg compared with 140 mm Hg. Additionally, strict BP control in SPRINT was not associated with improved renal outcomes. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the preferred agents recommended by KDIGO and KDOQI when albumin excretion exceeds 30 mg in 24 hours (evidence grade 2D).

Strategies to reduce low-density lipoprotein cholesterol levels, such as statins or statin and ezetimibe combination, are recommended for patients with diabetes and CKD, including those who have undergone kidney transplantation (evidence grade 1B). Owing to lack of mortality benefit, statin therapy may not be started in patients treated with dialysis (evidence grade 1B); however, the risks and benefits of reducing nonfatal CV events need to be considered.

When it comes to smoking cessation, evidence is less established. Although multiple studies have tried to quantify the impact of smoking on progression of kidney dysfunction and consequent increased CV disease risk, methodologic issues have been relevant. A large cross-sectional study with 32,208 patients with T2DM with the goal of defining the prevalence and determinants of onset of albuminuria found smoking to be an independent risk factor for microalbuminuria.[19] The impact of smoking exposure on CV morbidity and mortality has been well documented in the population with CKD, both before dialysis and in those undergoing dialysis;[20] however, most studies included both patients with and those without diabetes. Despite the lack of prospective, randomized evidence specific for the cohort of patients with diabetic nephropathy, guidelines recommend providing smoking cessation counseling as an integral part of CKD treatment, regardless of the etiology.

Treatment of diabetes with the goal of reducing cardiovascular events

Until recently, there were no therapies for T2DM with proven CV benefits beyond the foundation of therapy with metformin and a strategy for glycemic control. Indeed, a decade ago the available treatment arsenal for diabetes was limited and included medications associated with weight gain, fluid retention, and hypoglycemia, effects that are deleterious to the CV system. In 2008, the regulatory guidance for the approval of new glucose-lowering medicines evolved to require large-scale CV outcome trials (CVOTs) with systematic assessment of overall and CV safety. The criteria to rule out excess CV risk were an upper bound of the 2-sided 95% confidence interval (CI) for the hazard ratio (HR) of major adverse cardiac events (MACEs) in the active treatment arm of $<$1.80 over the course of the trial and $<$1.30 at trial completion. Since then, several CVOTs have started; 4 of these, involving 2 SGLT2is and 2 GLP-1 RAs, have had positive primary composite outcomes for superiority against placebo: Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), Caanagliflozin Cardiovascular Assessment Study (CANVAS), Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) (Tables 1–3).[21–24] Additionally, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial has been completed and has met its primary endpoint of noninferiority, as announced recently; results are due to be disclosed in the near future.[25]

Empagliflozin is one of the SGLT2is approved for use in the USA, along with canagliflozin and dapagliflozin, while ertugliflozin is currently under review by the US Food and Drug Administration (FDA) for approval. This class of medications works by targeting the sodium–glucose cotransporter 2 located at the S1 segment of the proximal tubule, inhibiting urinary glucose reclamation and thereby increasing glucosuria and lowering plasma glucose independently of insulin. By decreasing the reabsorption of glucose at the proximal tubule, SGLT2 inhibition also causes natriuresis, increasing the availability of sodium to the macula densa, which prevents excessive afferent arteriole dilation and reduces the single-nephron glomerular filtration rate, halting the vicious cycle responsible for hyperfiltration in diabetic kidney disease[26–28] Additionally, the natriuretic and osmotic diuretic effect of SGLT2 inhibition leads to an increase in