# Novel therapies for diabetic kidney disease

David Z.I. Cherney[1] and George L. Bakris[2]

[1]Department of Medicine, Division of Nephrology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; and [2]Department of Medicine, American Society of Hypertension Comprehensive Hypertension Center, University of Chicago Medicine, Chicago, Illinois, USA

**Over the past 30 years there have been many complementary therapies developed to achieve glycemic control and have an impact on cardiovascular outcomes, as well as reduce the risk of microvascular disease. The 2 most notable new entries have been the sodium–glucose cotransporter 2 (SGLT2) inhibitors and the glucagon-like peptide-1 (GLP-1) agonists. Both these classes of agents have demonstrated reductions in cardiovascular event rates as well as reductions in blood pressure and weight. Moreover, while both have demonstrated a benefit in slowing nephropathy progression, the SGLT2 inhibitors appear to have a significantly greater effect compared with the GLP-1 agents. There is an ongoing trial specifically powered for renal disease progression, CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy). Additionally, there are 2 other classes of agents being tested to slow nephropathy progression, a selective endothelin-1 receptor antagonist, atrasantan, in the SONAR (Study of Diabetic Nephropathy With Atrasentan) trial and a nonsteroidal mineralocorticoid receptor antagonist, finerenone, in the FIDELIO (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus) trial. These and other studies are discussed.**

*Kidney International Supplements* (2018) **8,** 18–25; https://doi.org/10.1016/j.kisu.2017.10.005

KEYWORDS: cardiovascular; diabetic kidney disease; endothelin; heart failure; incretin; inflammation; mineralocorticoid; SGLT2 inhibition; uric acid



**Correspondence:** *David Z.I. Cherney, Toronto General Hospital, 585 University Ave., 8N-845, Toronto, Ontario M5G 2N2, Canada. E-mail: david.cherney@uhn.ca*

Current approaches to the management of patients with type 2 diabetes include management of hyperglycemia to achieve target hemoglobin A1c ($HbA_{1c}$) levels below 7% in most patients, as well as blood pressure control and the use of agents that block the renin-angiotensin-aldosterone system (RAAS). From a renal perspective, the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post-Trial Observational Study (ADVANCE-ON) reported that while there were no effects on cardiovascular outcomes or mortality, intensive glycemic control reduced the risk of microvascular complications including end-stage renal disease.[1] Previous trials in patients with type 2 diabetes have also demonstrated that RAAS inhibitors are effective primary and secondary prevention strategies.[2] Unfortunately, despite the use of these therapeutic approaches, more than 30% of patients with type 2 diabetes develop diabetic kidney disease, highlighting the urgent need to identify novel therapies. Accordingly, our aim was to review evidence from recent clinical trials that have reported the impact of therapeutic agents on nephropathy endpoints, or that are in the process of conducting clinical trials in this area.

## Sodium–glucose cotransporter 2 inhibitors

The inhibition of sodium–glucose cotransporter 2 (SGLT2) leads to blockade of sodium–glucose cotransport at the proximal tubule, leading to both glucosuria and natriuresis, as reviewed in detail elsewhere.[3] SGLT2 inhibitors (SGLT2is) are approved for use as glucose-lowering agents owing to their effects on glucosuria leading to reductions in $HbA_{1c}$ (~0.7%). Furthermore, the negative calorie balance promotes weight loss (~2–3 kg), while natriuresis has been linked with blood pressure lowering, anti-albuminuric effects, and reduced glomerular pressure, as discussed below.[4–6] Importantly, $HbA_{1c}$ lowering is attenuated with progressive renal function decline owing to reduced glucose filtration and consequent glucosuria.[7–9] As a result, the SGLT2is canagliflozin and empagliflozin are approved to be initiated in patients with estimated glomerular filtration rate (eGFR) above 60 ml/min per 1.73 $m^2$, and should be discontinued once eGFR falls below 45 ml/min per 1.73 $m^2$ owing to their lesser therapeutic effects on $HbA_{1c}$ reduction, while dapagliflozin is approved for use in patients with eGFR above 60 ml/min per 1.73 $m^2$. Interestingly, and in contrast to the reduced glucosuria-related clinical effects of SGLT2 inhibition (lowered $HbA_{1c}$ and weight reduction), factors that are related to natriuresis such as blood pressure, albuminuria,

and glomerular pressure reductions appear to be ameliorated in patients with and without impaired renal function.[7–9]

Prior to the publication of the Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, experimental data demonstrated that SGLT2 inhibition reduces intraglomerular hypertension, proteinuria, and histological evidence of glomerular and tubulointerstitial injury, as reviewed elsewhere.[3,10] While the mechanisms responsible for these effects are not yet fully understood, one unifying hypothesis involves the impact of natriuresis on tubuloglomerular feedback.[3] Briefly, by increasing delivery of sodium and chloride to the macula densa, increased reabsorption of sodium chloride leads to increased metabolism of adenosine triphosphate, which is broken down to adenosine. Adenosine produced at the macula densa then binds to the adenosine type 1 receptor at the afferent arteriole, leading to vasoconstriction and to declines in renal blood flow and intraglomerular pressure. As a result, SGLT2 inhibition is associated with decreased hyperfiltration in animals and in humans with type 1 diabetes, and also increases urinary adenosine excretion, as reviewed in detail elsewhere.[3,11] Similarly, in patients with type 2 diabetes, initiation of an SGLT2 inhibitor influences renal function, reflected by a 4 to 6 ml/min per 1.73 $m^2$ acute dip in eGFR, which is thought to reflect an SGLT2 inhibitor-induced decline in glomerular pressure.[12] Changes in eGFR occur in patients with and without impaired renal function, at least down to eGFR 30 ml/min per 1.73 $m^2$.[7–9] Furthermore, SGLT2 inhibition reduces urinary albuminuria excretion by 30% to 50% in patients with type 2 diabetes, and also across a range of eGFR levels down to 30 ml/min per 1.73 $m^2$.[13,14] Importantly, changes in albuminuria occur independently of changes in blood pressure, weight, or $HbA_{1c}$ reduction, implicating a role for intrarenal hemodynamic mechanisms instead.[7–9,13]

To determine the cardiovascular safety of agents in the SGLT2 inhibitor class, empagliflozin 10 mg and 25 mg doses were compared with placebo in EMPA-REG OUTCOME in more than 7000 patients with type 2 diabetes with previous cardiovascular disease.[12] Empagliflozin was associated with a significant 14% reduction in the 3-point major adverse cardiac event of death, nonfatal myocardial infarction, or nonfatal stroke, driven by a 38% reduction in death from cardiovascular causes, without significant reductions in either nonfatal myocardial infarction or stroke. Death from any cause was reduced by 32%, and hospitalization for heart failure by 35%. In addition to beneficial effects on cardiovascular outcomes, the risk of the secondary composite renal endpoint of new onset or worsening nephropathy was significantly reduced with empagliflozin, defined as new-onset macroalbuminuria, doubling of creatinine and glomerular filtration rate (GFR) below 45 ml/min per 1.73 $m^2$, initiation of renal replacement therapy, and death due to renal disease.[15] Empagliflozin also reduced the composite of doubling of creatinine, initiation of renal replacement therapy, and death due to renal disease.

More recently, data from the CANVAS Program further support the findings of EMPA-REG OUTCOME.[10] The CANVAS Program integrated data from 2 trials that enrolled 10,142 individuals with type 2 diabetes and elevated cardiovascular risk. Participants were randomly assigned to canagliflozin or placebo and followed for a mean of 3.6 years. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The authors found that the primary efficacy endpoint was reduced with canagliflozin compared with placebo by 14% ($P < 0.0001$ for noninferiority; $P = 0.0158$ for superiority), and the risk of hospitalization for heart failure was reduced by 23%. The renal composite endpoint of sustained 40% reduction in eGFR, need for renal replacement therapy, or renal death was reduced by 40%. Adverse reactions were consistent with the previously reported risks of canagliflozin except for an almost doubling of the number of lower-extremity amputations, largely among those who already had amputations. Thus, there are now 2 SGLT2 inhibitor outcome trials with a documented reduction in cardiovascular events as well as evidence of renoprotection.

The mechanisms responsible for the increase in lower-extremity amputation risk with canagliflozin, which has not been reported with other SGLT2is, is not known. However, it is perhaps relevant that a previous administrative database analysis from the Netherlands reported that in patients with type 2 diabetes, the use of thiazide diuretics, alone or in combination with other agents, had a higher risk of lower-extremity amputation compared with the use of any nonthiazide antihypertensive drug (adjusted odds ratio 7.04; 95% confidence interval [CI] 1.10–45.30), and this risk increased with longer exposure.[16] In the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, 20.6% of participants had diabetes mellitus; participants using coamilozide had more peripheral vascular disorders compared with nifedipine users (5.3% and 3.0%, respectively; $P < 0.0001$). In contrast, in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 33% of participants had diabetes mellitus; those randomized to doxazosin, amlodipine, or lisinopril had a similar risk of peripheral arterial disease compared with subjects randomized to chlorthalidone.[17–20]

Further evidence for the cardiovascular protective effects associated with SGLT2 inhibition has recently been published using administrative databases to assess real-world evidence.[21,22] For example, Nyström *et al.* reported that in Swedish national health administrative databases, in all patients with type 2 diabetes who were new users of SGLT2is ($n = 21{,}758$), the risks of all-cause death (hazard ratio [HR] 0.44; 95% CI 0.28–0.70) and fatal or nonfatal cardiovascular disease (HR 0.51; 95% CI 0.30–0.86) were significantly reduced with dapagliflozin versus insulin over 1.5 years.[22] In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) trial,