Novel therapies for diabetic kidney disease

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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, atrasentan, 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
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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 Diamicon 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 m², and should be discontinued once eGFR falls below 45 ml/min per 1.73 m² 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 m². 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,

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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 m² 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 m².^{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 m².^{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 m², 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 coamilofide 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,

Kosiborod *et al.* reported that in more than 300,000 patients, the use of SGLT2is was associated with reduced risks of hospitalization for heart failure and all-cause death compared with other glucose-lowering agents,²¹ and similar benefits have been reported in a large, real-world general practice cohort.²³ While renal and safety endpoints in these analyses have not been reported, these analyses provide some reassurance that results from trials such as EMPA-REG OUTCOME are translating into cardiovascular benefits in clinical practice, and that benefits appear to outweigh any potential risks outside of the clinical trial setting.

Based on the strong mechanistic rationale for renal protection through natriuresis-based pathways rather than via glycosuria, mechanistic studies and clinical trials are currently under way in patients without diabetes to determine whether benefits observed in patients with diabetes extend to those without diabetes, including the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD), and the recently announced renal endpoint trial with empagliflozin in patients with and without diabetes. Finally, the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial is due to report in 2019 and will further elucidate the role of SGLT2 inhibition as a renal protective therapy. Additional insights into this area will be obtained in other cardiovascular safety trials that also include secondary renal endpoints, including the Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial with ertugliflozin and the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) with dapagliflozin.²⁴

Incretin-based agents: glucagon-like peptide-1 receptor agonists and dipeptidylpeptidase-4 inhibitors

Incretin-based agents are another class of therapy that, while used primarily to control hyperglycemia in patients with type 2 diabetes, also have a variety of other nonglycemic effects on blood pressure and natriuresis, as well as effects on anti-inflammatory pathways. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have further benefits related to significant weight reduction through induction of nausea, changes in gastrointestinal motility, and possible central nervous system pathways.²⁵

Similar to SGLT2 inhibitors, GLP-1 RA agents are associated with a proximal tubular natriuresis, which is due to inhibition of sodium–hydrogen exchanger-3.²⁶ As a consequence, studies in healthy patients, individuals with obesity, and those with type 2 diabetes have uniformly reported significant increases in fractional excretion of sodium.^{27–31} As a consequence, it would be expected that GLP-1 RA agents should stimulate tubuloglomerular feedback, leading to afferent vasoconstriction and reductions in renal blood flow and GFR. However, the above mechanistic studies and clinical

trials have failed to show such effects on renal function. The lack of renal hemodynamic vasoconstriction in response to GLP-1 RAs may be as a result of direct vasodilatory action of GLP-1 at the afferent arteriole, which offsets vasoconstriction induced by tubuloglomerular feedback, resulting in overall neutral GFR effects.³²

Despite this apparent lack of effect on renal hemodynamic function or surrogate markers of glomerular pressure such as GFR, GLP-1 RA agents reduce albuminuria in patients with type 2 diabetes.²⁵ In addition to cardiovascular benefits in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) with liraglutide and semaglutide, respectively, these agents were associated with a significant reduction in the composite renal endpoint defined as progression to macroalbuminuria, doubling of serum creatinine, dialysis, or renal death.^{33,34} In both studies, the renal benefit was due to a reduced progression to macroalbuminuria. Given the apparent lack of effect on glomerular pressure, effects on albuminuria may instead be due to suppression of inflammation-related pathways.

In contrast with SGLT2is and GLP-1 RAs, the results of cardiovascular safety trials with dipeptidylpeptidase-4 (DPP-4) inhibitors including the Trial to Evaluate Cardiovascular Outcomes After Treatment with Sitagliptin (TECOS), Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care (EXAMINE) trial, and Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial were neutral,^{35–38} aside from possible adverse effects related to heart failure in the SAVOR-TIMI trial. From a renal perspective, DPP-4 inhibitors have neutral effects on blood pressure and heart rate, but have been shown to increase natriuresis. In patients with type 2 diabetes, sitagliptin increases natriuresis, as reflected by total fractional sodium excretion. More recent experimental work has shown that natriuresis associated with DPP-4 inhibition is independent of GLP-1 and is related to increased stromal cell-derived factor-1 α (SDF-1 α), leading to a distal natriuresis³⁹ beyond the macula densa. When SDF-1 α is inhibited pharmacologically with AMD3100, the natriuretic effect of DPP-4 inhibition is abolished. More recent data in patients with type 2 diabetes have corroborated this hypothesis, because sitagliptin increases total sodium excretion but not fractional excretion of lithium—a marker of proximal renal tubular sodium reabsorption.⁴⁰ As a consequence of the distal nature of the natriuresis, the increase in sodium delivery does not affect the macula densa. Consequently, renal function is not influenced by DPP-4 inhibition, as reflected by direct or indirect measures of GFR.⁴¹

In clinical trials, similar to the lack of effect on cardiovascular outcomes or mortality, DPP-4 inhibition does not impact renal endpoints. In a secondary analysis of the

SAVOR-TIMI 53 trial, saxagliptin reduced urinary albumin excretion at 1 and 2 years into the trial, but did not impact renal endpoints such as doubling of creatinine, dialysis, or renal death.⁴² Similar to effects observed with saxagliptin, patients treated with sitagliptin in TECOS did not demonstrate a reduction in hard renal endpoints, although there was a small but statistically significant effect on urinary albumin excretion, and a difference of approximately 1 ml/min per 1.73 m²—which was lower in the sitagliptin group than placebo—by the end of the study.⁴³ Similar anti-albuminuric effects of DPP-4 inhibitors have been reported with linagliptin, which is frequently used by nephrologists owing to a lack of renal dose adjustment in patients with impaired kidney function. In a *post hoc* analysis of previous glycemic control trials, linagliptin treatment reduced albuminuria by a modest amount even after controlling for important clinical variables.⁴⁴ Surprisingly, however, in the recent Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With Linagliptin (MARLINA-T2D) trial, conducted over 24 weeks, albuminuria and impaired renal function failed to demonstrate a significant impact on albuminuria.⁴⁴ The renal and cardiovascular impact of linagliptin over more prolonged periods of time is being examined in patients with pre-existing diabetic nephropathy in the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) and Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trials, which are not yet complete.

Endothelin-1A receptor blockade

Diabetes is associated with increased endothelin-1 (ET-1) activity, and is associated with an increased risk of renal disease.^{45–48} ET-1A receptor (ET1AR) stimulation is responsible for mediating the vasoconstrictive and sodium-retaining effects of ET-1,^{49–51} while stimulation of the ET-1B receptor brings about mediation of the vasodilatory and natriuretic effects of ET-1. As a consequence, selective ET1AR blockers have been developed to reduce blood pressure, glomerular hypertension, and proteinuria associated with diabetic nephropathy,^{52–54} although the clinical effects on these parameters differ between specific agents based on the level of receptor selectivity.⁵¹ In previous studies, avosentan was first used in patients with macroalbuminuria and preserved renal function, and demonstrated a significant reduction in albuminuria throughout the range of doses used by 28.7% to 44.8%, but also increased the risk of edema.⁵⁵ In a subsequent trial in patients with overt nephropathy, Mann *et al.* reported that avosentan reduced albuminuria by over 40%, but was also associated with increased risk of edema and congestive heart failure.⁵³ Based on available data, avosentan may have promoted sodium retention through antagonism of the ET-1B receptor, owing to loss of ET-1A selectivity at higher doses.⁵⁶

Therefore, to take advantage of the beneficial effects of ET1AR inhibition⁵⁷ while at the same time minimizing risks

associated with ET1BR blockade, contemporary trials using atrasentan such as Reducing Residual Albuminuria in Subjects With Type 2 Diabetes and Nephropathy With Atrasentan (RADAR) and Study of Diabetic Nephropathy With Atrasentan (SONAR) have targeted appropriate dose regimens^{58,59}; in the SONAR trial the further step was taken of using an adaptive trial design, as described elsewhere. In the RADAR study, atrasentan reduced albuminuria by 36%,^{60,61} and also improved measures of mitochondrial dysfunction.⁶² In the SONAR trial, as described in detail elsewhere, patients with eGFR of 25 to 75 ml/min per 1.73 m² and a urine albumin-creatinine ratio of at least 300 mg/g are being enrolled. The primary outcome of the SONAR trial is the time to the first occurrence of a component of the composite renal endpoint of doubling of serum creatinine or the onset of end-stage renal disease.^{61,63,64}

Mineralocorticoid receptor antagonists

When added to RAAS inhibitors, mineralocorticoid receptor antagonists (MRAs) reduce albuminuria and markers of inflammation and fibrosis in the kidney.^{65–70} Unfortunately, the use of agents such as spironolactone and eplerenone in this class in the setting of chronic kidney disease (CKD) is limited by the risk of hyperkalemia due to impaired distal tubular potassium secretion. In contrast, finerenone is a nonsteroidal MRA with greater receptor selectivity than spironolactone and higher receptor affinity than eplerenone. In the Mineralocorticoid Receptor Antagonist Tolerability Study–Heart Failure (ARTS-HF), finerenone reduced albuminuria in patients with CKD and heart failure and had a lower risk of hyperkalemia than spironolactone.⁷¹ In the more recent ARTS–Diabetic Nephropathy (ARTS-DN) study performed in patients with type 2 diabetes, macroalbuminuria, and eGFR of 60 ml/min per 1.73 m² or lower finerenone reduced albuminuria in a dose-dependent manner. The risk of hyperkalemia leading to discontinuation was 2.1%, 3.2%, and 1.7% in the finerenone 7.5, 15, and 20 mg/d groups, respectively.⁷² Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) are ongoing, separate phase 3 trials that are examining the effects of finerenone on diabetic nephropathy and cardiovascular outcomes,^{73,74} and are expected to report in 2019.

Anti-inflammatory agents

Progression of diabetic nephropathy has been closely linked with the activation of proinflammatory pathways. As a consequence, a variety of anti-inflammatory and antifibrotic agents have been used in both experimental studies and clinical trials. While the experimental literature is replete with positive studies showing beneficial effects on albuminuria and markers of fibrosis, human mechanistic studies and clinical trials have been comparatively disappointing. As a complete

analysis of neutral studies involving these agents is beyond the scope of this review, here we focus on agents that have reported promising results or that are the subject of ongoing clinical trials. We have omitted agents that are not currently under clinical development such as pyridorin.⁷⁵ Agents that target Janus kinase–signal transducer and activator of transcription signaling such as baricitinib have demonstrated promising effects in patients with type 2 diabetes and nephropathy, reflected by significant reductions in albuminuria and decreases in cytokines and tumor necrosis factor receptors that are closely linked with the initiation and progression of diabetic kidney disease. To date, no additional studies with this agent are registered in patients with diabetes or kidney disease.⁷⁶ For a more complete review of this topic and other agents in early clinical development such as the pentoxifylline derivative CTP-499, the CCR2/CCL2-targeting drug CCX140-B, and emapticap pegol, readers are directed to work by Perez-Gomez *et al.*⁷⁶

Uric acid levels are strongly associated with the development of renal disease in animal models through a variety of pathways, including activation of neurohormones such as the RAAS, and increased production of cytokines or chemokines. Higher uric acid levels in animals promote cardiovascular and renal injury in animals—an effect that can be attenuated with uric acid-lowering agents including xanthine oxidase inhibitors such as allopurinol and febuxostat.⁷⁷ In humans, uric acid is associated with the presence of hypertension and with an increased risk of CKD development, although the direction of the association remains controversial.^{78–80} In patients with type 1 diabetes or type 2 diabetes, higher uric acid levels, even within the normal range, are associated with an increased risk of albuminuria and with accelerated GFR reduction. In patients with type 1 diabetes, uric acid levels are associated with higher blood pressure, higher levels of albuminuria within the normal range, and higher HbA_{1c}.⁸¹ From a renal perspective, uric acid levels are negatively correlated with GFR and renal blood flow, and positively correlated with total renal vascular resistance and afferent resistance.⁸² As in animal models, uric acid therefore appears to be associated with afferent vasoconstriction, which could promote renal ischemia. Owing to the strong mechanistic rationale for uric acid lowering, as described elsewhere, the Preventing Early Renal Loss in Diabetes (PERL) study is being performed in approximately 450 patients with type 1 diabetes and pre-existing albuminuria or evidence of impaired renal function.⁸³

Perspectives on future combination therapies

Based on the mechanism of action of SGLT2is, these agents have the potential to be combined with several other nephroprotective therapies, resulting in synergistic clinical benefits. As SGLT2is induce plasma volume contraction and activate the RAAS, part of the benefit observed in EMPA-REG OUTCOME and the CANVAS Program may have been due to the fact that more than 80% of participants were taking RAAS inhibitors.^{84,85} As a consequence, similar to the

interaction of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with traditional diuretics, the combination of RAAS blockers—including MRAs—with SGLT2is may be a particularly potent combination.

Second, as SGLT2is induce a relative state of volume depletion, these agents have the potential to offset the volume retention and heart failure risk that may be associated with ET1AR antagonists. As these 2 classes of drugs reduce glomerular pressure and proteinuria through different mechanisms, this combination has the potential to derive both renal and cardiovascular protection in patients with diabetes.

Third, among the glucose-lowering agents, SGLT2is lead to a proximal natriuresis, as described above. GLP-1 RAs and DPP-4 inhibitors, on the other hand, induce natriuretic effects through proximal and distal mechanisms, respectively, which may lead to additive plasma volume depletion when used in combination.⁸⁶ Further benefits may result from additive effects on HbA_{1c}, weight reduction, and blood pressure lowering, as shown in the Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy (DURATION-8) trial, leading to further potential renal and cardiovascular protection.⁸⁷ Further synergy might be obtained as a result of SGLT2 inhibition reducing volume and heart failure risk, while GLP-1 RA likely has a beneficial effect on atherosclerosis risk. At the level of the kidney, incretin agents reduce the risk of progression to macroalbuminuria, possibly via different mechanisms: hemodynamic-related reductions with SGLT2 inhibition and anti-inflammatory pathways with incretin-based agents.

In conclusion, over the last 2 years, 2 separate classes of antihyperglycemic therapies—SGLT2 inhibition and GLP-1 RA agents—have demonstrated renal and cardiovascular clinical benefits in patients with type 2 diabetes. For several reasons, it is now critical to understand why these agents have succeeded where so many others have failed. First, it is important to elucidate responsible pathways leading to renal and cardiovascular benefit, because these pathways may help determine whether these agents could have similar CKD and cardiovascular benefits in patients without diabetes. Second, careful mechanistic studies that will help define relevant cardiorenal protective pathways may also help to anticipate and avoid potential side effects, such as acute kidney injury and volume depletion, by effectively counseling patients regarding how to avoid these issues under conditions of illness. Therefore, while progress has been made toward reducing renal and cardiovascular risk in patients with diabetes, a major focus of research and clinical practice needs to be how to avoid side effects such as volume depletion and diabetic ketoacidosis with SGLT2 inhibition agents, fracture and amputation risk with canagliflozin, heart failure with ET1AR antagonists, and hyperkalemia with MRAs.

In summary, several novel agents have been shown to have renal and cardiovascular protective effects in patients with

type 2 diabetes. Over the coming 4 years, additional studies using novel agents may give critical insights into augmenting end-organ protection.

DISCLOSURE

Publication of this article was supported by Bayer AG. DZIC has received speaker or consultant honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Mitsubishi Tanabe, and Sanofi, and operational funding for clinical trials from AstraZeneca, Boehringer Ingelheim, and Merck. DZIC has also received grant support from Janssen. GLB is co-principal investigator of FIDELIO, an international renal outcome trial sponsored by Bayer HealthCare AG. He is also on the steering committee of CREDENCE (Janssen) and SONAR (AbbVie). He is a consultant for AbbVie, Bayer HealthCare AG, Elcelyx, Janssen, GlaxoSmithKline, and Relypsa (who provide direct funding to the University of Chicago).

ACKNOWLEDGMENTS

Editorial support was provided by Eric Southam of Oxford PharmaGenesis, funded by Bayer AG. The development of this supplement was supported by funding from Bayer AG. No person from the sponsor was involved in the development or review of any of the articles. DZIC was supported by funding from the Canadian Institutes of Health Research and the Banting and Best Diabetes Centre, University of Toronto. Finally, the authors are grateful to the study participants, whose time and effort are critical to the success of our research program. DZIC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

- Wong MG, Perkovic V, Chalmers J, et al. Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON. *Diabetes Care*. 2016;39:694–700.
- Lytvyn Y, Bjornstad P, Pun N, et al. New and old agents in the management of diabetic nephropathy. *Curr Opin Nephrol Hypertens*. 2016;25:232–239.
- Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes: cardiovascular and kidney effects, potential mechanisms and clinical applications. *Circulation*. 2016;134:752–772.
- Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2014;16:984–993.
- Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159:262–274.
- Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Investig*. 2014;5:265–275.
- Barnett AH, Mithal A, Manassie J, et al. Empagliflozin in patients with type 2 diabetes mellitus (T2DM) and renal impairment (RI). *American Diabetes Association*. 2013. abstract 1104-P.
- Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int*. 2014;85:962–971.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Obes Metab*. 2014;16:1016–1027.
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
- Rajasekaran H, Lytvyn Y, Bozovic A, et al. Urinary adenosine excretion in type 1 diabetes. *Am J Physiol Renal Physiol*. 2017;313:F184–F191.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
- Heerspink HJ, Johnsson E, Gause-Nilsson I, et al. Dapagliflozin reduces albuminuria in hypertensive diabetic patients using renin-angiotensin blockers. *Diabetes Obes Metab*. 2016;18:590–597.
- Heerspink HJ, Kröpelin TF, Hoekman J, et al. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. *J Am Soc Nephrol*. 2015;26:2055–2064.
- Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334.
- Erkens JA, Klungel OH, Stolk RP, et al. Antihypertensive drug therapy and the risk of lower extremity amputations in pharmacologically treated type 2 diabetes patients. *Pharmacoepidemiol Drug Saf*. 2004;13:139–146.
- Lasagna L. Diuretics vs alpha-blockers for treatment of hypertension: lessons from ALLHAT. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *JAMA*. 2000;283:2013–2014.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2000;283:1967–1975.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
- Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a goal in hypertension treatment (INSIGHT). *Lancet*. 2000;356:366–372.
- Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation*. 2017;136:249–259.
- Nyström T, Bodegard J, Nathanson D, et al. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19:831–841.
- Toulis KA, Willis BH, Marshall T, et al. All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in the health improvement network database. *J Clin Endocrinol Metab*. 2016;102:1719–1725.
- Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res*. 2015;12:90–100.
- Muskiet MH, Smits MM, Morsink LM, et al. The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? *Nat Rev Nephrol*. 2014;10:88–103.
- Thomas MC. The potential and pitfalls of GLP-1 receptor agonists for renal protection in type 2 diabetes. *Diabetes Metab*. 2017;43 Suppl 1, S250–S257.
- Gutzwiller JP, Tschopp S, Bock A, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab*. 2004;89:3055–3061.
- Lovshin JA, Barnie A, DeAlmeida A, et al. Liraglutide promotes natriuresis but does not increase circulating levels of atrial natriuretic peptide in hypertensive subjects with type 2 diabetes. *Diabetes Care*. 2015;38:132–139.
- Skov J, Dejgaard A, Frøkiær J, et al. Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men. *J Clin Endocrinol Metab*. 2013;98:E664–E671.
- Tonneijck L, Smits MM, Muskiet MH, et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. *Diabetologia*. 2016;59:1412–1421.
- Nathanson D, Frick M, Ullman B, et al. Exenatide infusion decreases atrial natriuretic peptide levels by reducing cardiac filling pressures in type 2 diabetes patients with decompensated congestive heart failure. *Diabetol Metab Syndr*. 2016;8:5.
- Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155:1280–1290.

33. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
34. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
35. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326.
36. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242.
37. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327–1335.
38. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247–2257.
39. Takashima S, Fujita H, Fujishima H, et al. Stromal cell-derived factor-1 is upregulated by dipeptidyl peptidase-4 inhibition and has protective roles in progressive diabetic nephropathy. *Kidney Int*. 2016;90:783–796.
40. Lovshin JA, Rajasekaran H, Lytvyn Y, et al. Dipeptidyl peptidase-4 inhibition stimulates distal tubular natriuresis and increases in circulating SDF-1 α 1-67 in patients with type 2 diabetes. *Diabetes Care*. 2017;40:1073–1081.
41. Tonneijck L, Smits MM, Muskiet MH, et al. Renal effects of DPP-4 inhibitor sitagliptin or GLP-1 receptor agonist liraglutide in overweight patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2016;39:2042–2050.
42. Mosenzon O, Leibowitz G, Bhatt DL, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. *Diabetes Care*. 2017;40:69–76.
43. Cornel JH, Bakris GL, Stevens SR, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care*. 2016;39:2304–2310.
44. Groop PH, Cooper ME, Perkovic V, et al. Effects of linagliptin on glycemic control and albuminuria in type 2 diabetes—the MARLINA-T2D™ trial. *American Diabetes Association*. 2016; abstract 17-LB.
45. Cardillo C, Campia U, Bryant MB, et al. Increased activity of endogenous endothelin in patients with type II diabetes mellitus. *Circulation*. 2002;106:1783–1787.
46. De Mattia G, Cassone-Faldetta M, Bellini C, et al. Role of plasma and urinary endothelin-1 in early diabetic and hypertensive nephropathy. *Am J Hypertens*. 1998;11:983–988.
47. Peppas-Patrikiou M, Dracopoulou M, Dacou-Voutetakis C. Urinary endothelin in adolescents and young adults with insulin-dependent diabetes mellitus: relation to urinary albumin, blood pressure, and other factors. *Metabolism*. 1998;47:1408–1412.
48. Shin SJ, Lee YJ, Tsai JH. The correlation of plasma and urine endothelin-1 with the severity of nephropathy in Chinese patients with type 2 diabetes. *Scand J Clin Lab Invest*. 1996;56:571–576.
49. Peppas-Patrikiou M, Scordili M, Antoniou A, et al. Carotid atherosclerosis in adolescents and young adults with IDDM. Relation to urinary endothelin, albumin, free cortisol, and other factors. *Diabetes Care*. 1998;21:1004–1007.
50. Rabelink TJ, Kaasjager KA, Boer P, et al. Effects of endothelin-1 on renal function in humans: implications for physiology and pathophysiology. *Kidney Int*. 1994;46:376–381.
51. Sachidanandam K, Elgebaly MM, Harris AK, et al. Effect of chronic and selective endothelin receptor antagonism on microvascular function in type 2 diabetes. *Am J Physiol Heart Circ Physiol*. 2008;294:H2743–H2749.
52. Krum H, Viskoper RJ, Lacourciere Y, et al. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan hypertension investigators. *N Engl J Med*. 1998;338:784–790.
53. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21:527–535.
54. Raichlin E, Prasad A, Mathew V, et al. Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. *Hypertension*. 2008;52:522–528.
55. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol*. 2009;20:655–664.
56. Smolander J, Vogt B, Maillard M, et al. Dose-dependent acute and sustained renal effects of the endothelin receptor antagonist avosentan in healthy subjects. *Clin Pharmacol Ther*. 2009;85:628–634.
57. Kohan DE, Pollock DM. Endothelin antagonists for diabetic and non-diabetic chronic kidney disease. *Br J Clin Pharmacol*. 2013;76:573–579.
58. Kohan DE, Lambers Heerspink HJ, Coll B, et al. Predictors of atrasentan-associated fluid retention and change in albuminuria in patients with diabetic nephropathy. *Clin J Am Soc Nephrol*. 2015;10:1568–1574.
59. Andress DL, Coll B, Pritchett Y, et al. Clinical efficacy of the selective endothelin A receptor antagonist, atrasentan, in patients with diabetes and chronic kidney disease (CKD). *Life Sci*. 2012;91:739–742.
60. de Zeeuw D, Coll B, Andress D, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2014;25:1083–1093.
61. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol*. 2011;22:763–772.
62. Pena MJ, de Zeeuw D, Andress D, et al. The effects of atrasentan on urinary metabolites in patients with type 2 diabetes and nephropathy. *Diabetes Obes Metab*. 2017;19:749–753.
63. Mortensen K, Franzen K, Himmel F, et al. Catheter-based renal sympathetic denervation improves central hemodynamics and arterial stiffness: a pilot study. *J Clin Hypertens (Greenwich)*. 2012;14:861–870.
64. Hering D, Lambert EA, Marusic P, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension*. 2013;61:457–464.
65. Bombardier AS, Kshirsagar AV, Amamoo MA, et al. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis*. 2008;51:199–211.
66. Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. *N Engl J Med*. 2001;345:925–926.
67. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2006;1:940–951.
68. Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone in diabetic nephropathy. *Kidney Int*. 2005;68:2829–2836.
69. Rossing K, Schjoedt KJ, Smidt UM, et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care*. 2005;28:2106–2112.
70. Bolognani D, Palmer SC, Navaneethan SD, et al. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014;4:CD007004.
71. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;34:2453–2463.
72. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA*. 2015;314:884–894.
73. Mahfoud F, Böhm M, Rump LC, et al. Catheter-based renal nerve ablation and centrally generated sympathetic activity in difficult-to-control hypertensive patients: prospective case series. *Hypertension*. 2013;61:e17.
74. Schlaich M, Hering D, Lambert G, et al. Blood pressure and sympathetic nervous system response to renal denervation. *Hypertension*. 2013;61:e13.
75. Grassi G. Renal denervation in cardiometabolic disease: concepts, achievements and perspectives. *Nutr Metab Cardiovasc Dis*. 2013;23:77–83.
76. Perez-Gomez MV, Sanchez-Niño MD, Sanz AB, et al. Targeting inflammation in diabetic kidney disease: early clinical trials. *Expert Opin Investig Drugs*. 2016;25:1045–1058.
77. Lytvyn Y, Perkins BA, Cherney DZ. Uric acid as a biomarker and a therapeutic target in diabetes. *Can J Diabetes*. 2015;39:239–246.
78. Feig DI, Madero M, Jalal DI, et al. Uric acid and the origins of hypertension. *J Pediatr*. 2013;162:896–902.
79. Jalal DI, Chonchol M, Chen W, et al. Uric acid as a target of therapy in CKD. *Am J Kidney Dis*. 2013;61:134–146.
80. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant*. 2013;28:2221–2228.

81. Lytvyn Y, Mahmud FH, Daneman D, et al. Association between plasma uric acid levels and cardiorenal function in adolescents with type 1 diabetes. *Diabetes Care*. 2016;39:611–616.
82. Lytvyn Y, Škrtić M, Yang GK, et al. Plasma uric acid effects on glomerular haemodynamic profile of patients with uncomplicated type 1 diabetes mellitus. *Diabet Med*. 2016;33:1102–1111.
83. Maahs DM, Caramori L, Cherney DZ, et al. Uric acid lowering to prevent kidney function loss in diabetes: the Preventing Early Renal Function Loss (PERL) allopurinol study. *Curr Diab Rep*. 2013;13:550–559.
84. Lambers Heerspink HJ, de Zeeuw D, Wie L, et al. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:853–862.
85. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587–597.
86. Nauck MA, Meier JJ. GLP-1 receptor agonists and SGLT2 inhibitors: a couple at last? *Lancet Diabetes Endocrinol*. 2016;4: 963–964.
87. Frías JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4: 1004–1016.