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Review

Diabetic kidney disease: update on clinical management and non-glycaemic effects of newer medications for type 2 diabetes

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***Abstract*:** Type 2 diabetes is a leading cause of chronic kidney disease worldwide and continues to increase in prevalence. This in turn has significant implications for healthcare provision and the economy. In recent years there have been multiple advances in the glucose-lowering agents available for the treatment of diabetes, which not only modify the disease itself but also have important benefits in terms of the associated cardiovascular outcomes. The cardiovascular outcome trials of agents such as glucagon-like peptide-1 receptor agonists (GLP-RAs) and sodium glucose cotransporter 2 inhibitors (SGLT-2) have demonstrated significant benefits in reducing major adverse cardiovascular events, admissions for heart failure and in some cases mortality. Secondary analysis of these trials has also indicated significant renoprotective benefit. Canagliflozin and Renal Outcomes in Type 2 Diabetes Mellitus and Nephropathy (CREDENCE) a renal-specific trial, has shown major benefits with canagliflozin for renal outcomes in diabetic kidney disease, and similar trials with other SGLT-2 inhibitors are either underway or awaiting analysis. In this article we review current goals of treatment of diabetes and the implications of advancing renal impairment on choice of treatments. Areas discussed include the diagnosis of diabetic kidney disease and current treatment strategies for diabetic kidney disease ranging from lifestyle modifications to glycaemic control. This review focuses on the role of GLP-RAs and SGLT-2 inhibitors in treating those with diabetes and chronic kidney disease with some illustrative cases. It is clear that these agents should now be considered first choice in combination with metformin in those with diabetes and increased cardiovascular risk and/or reduced renal function, and in preference to other classes such as dipeptidyl peptidase-4 (DPP-4) inhibitors or sulphonylureas.

Keywords: albuminuria, chronic kidney disease, diabetic kidney disease, diabetes mellitus, renal outcomes, sodium glucose cotransporter 2 inhibitors

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Introduction

For almost two decades the management of diabetic kidney disease (DKD) in type 2 diabetes has been centred on optimising glycaemic and blood pressure control, with preferential use of antihypertensive agents that attenuate activity of the renin–angiotensin–aldosterone system (RAAS). Although several different categories of glucose-lowering agents have been developed during this time, the most recent additions, glucagon-like peptide 1 receptor agonists (GLP-RAs) and sodium glucose linked transporter 2 (SGLT-2) inhibitors, have been found in large, randomised controlled trials (RCTs) to have very important benefits not only in terms of diminishing cardiovascular complications but now in ameliorating renal disease. Consequently, we have entered an era in which the boundaries concerning specialty-specific disease are being dissipated. Nephrologists and other suitably skilled renal care workers are

having to adapt skills in diabetology, while diabetologists, diabetic specialist nurses and primary care physicians are in turn required to focus more on the renal function and kidney disease of their patients than they did before. The parallels are similar in the world of cardiology, particularly concerning heart failure.

In this review we have concentrated on DKD and have summarised the evidence that underpins our latest approach to optimal kidney care of patients with type 2 diabetes. To show how this has now changed we conclude the article with some short case examples to demonstrate the opportunities that have arisen with new therapies.

Review methodology

A literature search was carried out that included the published literature from 2015 until October 2020 that focused on the management of DKD. Information was retrieved from PubMed through the National Library of Medicine using keyword such as 'diabetic kidney disease', 'SGLT2 inhibitors and diabetic kidney disease', 'GLP-RA and diabetic kidney disease'. The search yielded 750 papers which included RCTs, meta-analyses and systematic reviews. These articles were evaluated based on how relevant the article was, if the article addressed a research question related to treatment and outcomes of DKD. Articles were excluded if they were deemed irrelevant to the purposes of this review. Sixty-two of these were considered relevant to the topic. Other manuscripts were located through reference lists of relevant articles. Some articles were included that were published before 2015 as they had established important concepts and knowledge which were relevant to the topic.

Background context: diabetes, pre-diabetes and DKD

The growth in international prevalence of diabetes over the past half century has been huge. It was estimated in 1964 that 30 million had diabetes[1] and five decades later that estimate rose to 382 million;[2] in 2015 it was estimated that there were 415 million cases among adults in 220 countries worldwide[3] and this number may be 642 million by 2040. This burden has major healthcare impacts in terms of morbidity and mortality, with diabetes being the 15th most important cause of life years lost in 2015 closely followed by chronic kidney disease (CKD) in 17th place.[4] Diabetes also has a significant financial impact on the global economy, with an estimated cost of $1.3 trillion in 2015 increasing to $2.1 trillion in 2030, which as represented as a percentage of global gross domestic product (GDP) equates to a change from 1.8% in 2015 to 2.2% in 2030.[5]

Those with type 2 diabetes have a higher morbidity and mortality, predominantly as a result of associated macrovascular and microvascular complications, and it is the leading global cause of end stage kidney disease (ESKD) ahead of hypertension and glomerulonephritis.[6] A recent large observational study has shown that 42.3% of patients with diabetes will have evidence of renal disease,[7] and it highlighted the increased 10-year cumulative all-cause mortality among those with diabetes. Much of this increased risk is attributable to cardiovascular events, with the non-cardiovascular mortality rate being similar to those without diabetes. The combination of diabetes and kidney disease, manifest by albuminuria, reduced glomerular filtration rate (GFR) or both, confers the greatest risk.

The characteristic description of DKD involves progression of glomerular hyperfiltration to microalbuminuria and then overt proteinuria with reducing GFR, and ultimately leading to ESKD necessitating dialysis.[8] However, more recent studies have shown a more complex and non-linear relationship with the possibility of albuminuria regressing and a progressive decline in GFR in the absence of albuminuria.[9] A biopsy is now rarely necessary to make a diagnosis as a clinical diagnosis suffices in those with typical features (albuminuria and/or loss of GFR and evidence of non-renal microvascular disease such as neuropathy and retinopathy) and diabetes $\geqslant$10 years. This approach is supported by the largest study of renal biopsies performed in those with type 2 diabetes. Among 620 patients based in the US with a median time from diagnosis of 10 years, 37% of the biopsies were consistent with DKD, 27% had evidence of both DKD and non-DKD, whereas 36% did not have findings consistent with DKD on their biopsy.[10] The most common pathological findings in those without DKD were glomerulopathies such as focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy and pauci-immune glomerulonephritis, as well as hypertensive nephrosclerosis and acute tubular necrosis. The

best predictor of DKD was the presence of diabetes for ⩾12 years supporting the contention that a clinical diagnosis is sufficient unless atypical features are present.

DKD is a microvascular complication of diabetes.[11] There may be evidence of microvascular complications at the time of diagnosis of type 2 diabetes or perhaps even before.[12] Pre-diabetes is a general term given to a stage between normal glucose tolerance and overt type 2 diabetes. There are currently two definitions of this, one from the American Diabetes Association[13] and the second from the International Expert Committee and World Health Organization,[14] both of which are based on fasting blood glucose and/or haemoglobin A1c (HbA1c) concentrations. The findings of the Maastricht Study, an observational population-based cohort study of those free of other types of diabetes, support the concept that microvascular dysfunction precedes and contributes to the complications of diabetes such as nephropathy.[15] Other observational studies have raised an interest in pre-diabetes as a modifiable risk factor for DKD. One such study from Norway prospectively followed 1261 patients aged 50–62 years without diabetes for a median of 5.6 years. Pre-diabetes was defined as per the guidelines above, and it was associated with development of glomerular hyperfiltration and abnormal albuminuria (cardinal early features of DKD). The findings were robust and persisted after adjustment for both hypertension at baseline (all patients had ambulatory blood pressure recording) and change in anti-hypertensive treatment at follow-up.[16] This would suggest that early intervention of blood pressure and glycaemic control should play a key role in the management of those with impaired glucose tolerance.

Pathophysiology of DKD

The pathophysiology of DKD is a complex interplay between haemodynamic changes, oxidative stress, inflammation, hypoxia and activation of the RAAS, ultimately leading to fibrosis.

Glomerular hyperfiltration ultimately leads to albuminuria and the development of DKD. The mechanism of this involves alteration of the glomerular microvasculature. In the early stages of diabetes large quantities of filtered glucose lead to upregulation of SGLT-2 thus increasing the absorption of glucose and chloride. This leads to decreased delivery of sodium chloride to the macula densa region of distal tubules which causes dilation of the afferent arteriole through tubule–glomerular feedback. Concurrently, there is vasoconstriction of the efferent arteriole due to increased levels of angiotensin II. The result is intra-glomerular hypertension causing physical stress to capillaries and the mesangium and additionally a profibrotic response.[17]

Hyperglycaemia also triggers oxidative damage through the production of reactive oxygen species and advanced glycation end (AGE) products which are pro-inflammatory as a result of increased production of cytokines. These in turn lead to disruption of the endothelium causing further vasoconstriction and podocyte damage, inflammation and fibrosis.[18]

The hallmark of DKD is mesangial cell proliferation that results from activity of the transforming growth factor beta (TGF-β) system which is triggered by both hyperglycaemia and angiotension II. TGF-β leads to glomerular extracellular matrix production but it concomitantly decreases the production of matrix metalloproteinases which are key in degradation of the matrix.[19] Macrophages are also activated by both TGF-β and AGE and are an important source of tumour necrosis factor alpha (TNF-α), a cytokine which plays a key role in the progression of DKD by stimulating hypertrophy, podocyte and tubular injury and also triggering other cytokine cascades.[20] Accumulation of macrophages correlates strongly with serum creatinine and interstitial fibrosis in animal studies, and conversely reductions in albuminuria, creatinine, histopathological changes and levels of inflammatory cytokines levels are seen with blockade of TNF-α.[21]

As DKD progresses there is a clear relationship between the degree of fibrosis and tubular atrophy with declining estimated glomerular filtration rate (eGFR).[22]

Current treatment strategies for attenuation or prevention of diabetic nephropathy

Blood pressure control

The Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines recommend that target blood pressure in DKD should be ⩽130/80 mmHg for patients with urine albumin

excretion of 0.3 mg/24 h.[23] However, this is based on observational data that demonstrate an association between albuminuria and worse cardiorenal outcomes. Larger trials such as the landmark UK Prospective Diabetes Study Group (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) randomly assigned patients with diabetes to intensive *versus* less tight blood pressure control and showed that, although intensive blood pressure control did reduce the risk of developing microalbuminuria, this did not lead to reduction in the risk of renal failure, dialysis or renal transplantation during long-term follow-up.[24,25]

The evidence on the anti-hypertensive agents of choice in the setting of DKD is clear, with the use of RAAS inhibition as first line treatment strongly based on evidence from large RCTs published in 2001, which include both the (Reduction of Endpoints in Non-Insulin Dependent Diabetes with Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT). In IDNT the use of irbesartan in the early stages of DKD, in patients with normal renal function and microalbuminuria, led to a reduced likelihood of developing macroalbuminuria.[26] The benefit of RAAS inhibition has also been shown in more advanced DKD (patients with reduced GFR and significant albuminuria >300 mg/24 h), as highlighted by the RENAAL trial. Treatment with losartan reduced the risk of a composite outcome of death, ESKD or doubling of creatinine by 16% and reduced the median decline of eGFR by 0.8 ml/min/1.73 m^2 per year,[27] whereas the IDNT study showed the benefit of irbesartan in patients with a similar advanced DKD phenotype and hypertension with a 20% and 23% reduction of a similar primary outcome, compared to either placebo or amlodipine, respectively.[28] Losartan was also shown to reduce proteinuria by an average of 35% in the RENAAL trial whereas the IDNT trial showed a dose dependent effect with a reduction of 24% in the 150 mg irbesartan group [95% confidence interval (CI) 19–29] and 38% in the 300 mg group, which was statistically significant ($p < 0.001$). The benefit of a reduction of albuminuria with anti-hypertensive treatment, irrespective of the nature of therapy, has long been associated with a diminished rate of decline in GFR and an overall improved prognosis,[29,30] but it is clear that renin–angiotensin blockade has independent benefits. The evidence for angiotensin II receptor blocker (ARB) benefit in type 2 diabetes exceeds that of angiotensin-converting enzyme inhibitors (ACE-Is) but these two categories of RAAS inhibitors are often used interchangeably in clinical practice due to the class effect.[31]

A synergistic effect of dual blockade with the use of combination therapy of ACE-I/ARB in high-risk patients was effectively ruled out by the Ongoing Telmisartan and in Combination with Ramipril global Endpoint Trial (ONTARGET).[32] Over a median follow-up of 56 months dual RAAS blockade was associated with significantly worse outcomes, with a greater number of events such as doubling of creatinine, dialysis, or death. No cardiovascular or mortality benefit was observed with combination treatment and a higher rate of complications such as hyperkalemia and acute kidney injury was observed with dual therapy. ONTARGET examined those with established atherosclerotic disease or diabetes. A smaller trial, Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for treatment of Diabetic Nephropathy (VA-NEPHRON D), followed 5 years later examining the effect of a combination of losartan and lisinopril in those who exclusively had type 2 diabetes and evidence of DKD. The trial involved 1448 patients and was stopped early with a median follow-up of 2.2 years due to safety concerns of an increased risk of adverse events. As with its predecessor, VA-NEPHRON D also showed an increased risk of hyperkalemic episodes [hazard ratio (HR) of 2.8] and acute kidney injury (HR 1.7) with no benefit in terms of mortality.[33] Although both trials demonstrated a reduction in proteinuria with dual RAAS blockade this was in the absence of slowing long-term progression.

Lifestyle modification: weight loss and diet

Being a microvascular complication of diabetes, DKD is associated with hyperglycaemia, hypertension, and increased body mass index (BMI) within the metabolic syndrome. A healthy lifestyle has been shown to reduce the risk of cardiovascular events in the general population.[34] The Finnish Diabetic Nephropathy (FinnDane) study, a large cohort of 1400 participants with type 1 diabetes,[35] demonstrated that the intensity of physical activity may have an impact on the progression of DKD. DKD was classified according to the degree of

albuminuria, and progression during follow-up was defined as any change to a higher class of albuminuria or development of ESKD. After 8 years follow-up the cumulative progression rate was 5.9%, 6.9% and 15.4% among participants in the high, moderate, and low intensity physical activity groups, respectively. However, the Diabetes Control and Complications Trial (DCCT), also examining risk factors for the development of complications in type 1 diabetes, found no association between intensity of physical activity and the development of albuminuria over a mean follow-up of 6.5 years.[36] Of note, these studies were based on self-reported physical activity which is prone to significant bias.

In type 2 diabetes the Look AHEAD (Action for Health in Diabetes) Trial[37] was a multicentre RCT examining the effect of intensive lifestyle modification on cardiovascular events in those patients who were also overweight or obese. The participants were randomly assigned to either an intensive lifestyle intervention or to a diabetes support and educational programme. The trial found no significant reduction in cardiovascular events but there was also an analysis of the impact of the intervention on other outcomes such as nephropathy. Defining very high risk CKD as either eGFR <30 ml/min/1.73 m^2, eGFR $\leqslant 45$ ml/min/1.73 m^2 with urine ACR (Albumin to Creatinine Ratio) >30 mg/g or eGFR <60 ml/min/1.73 m^2 and urine ACR >300 mg/g, the incidence of this end point was 31% lower in the intensive intervention arm.[38] Over 10 years of follow-up those in the intensive intervention arm had a 4 kg weight reduction. Hence reducing the risk of DKD progression is likely to require a combination of lifestyle modification, weight loss and pharmacological interventions.

Glycaemic control

Glycaemic control is an important contributory factor to mortality as diabetes patients with a mean HbA1c of $<6\%$ (42 mmol/mol) or $\geqslant 9\%$ (63 mmol/mol) are associated with a higher risk for all-cause mortality in comparison to those with tighter glycaemic control (i.e. HbA1c of 6–6.9%). Interestingly, HbA1c was not associated with the risk of ESKD.[39]

Some large studies such as the DCCT[40] in patients with type 1 diabetes, the Japanese study in non-obese patients with type 2 diabetes[41] and the UK Prospective Diabetes Study[24] have shown a benefit of intensive over less intensive glycaemic control in the development and progression of microvascular complications.[24] However, the ACCORD study, which randomly assigned patients with type 2 diabetes and cardiovascular risk factors to intensive *versus* standard treatment, has cast doubt on the level of benefit; it was terminated early due to higher mortality rates in the intensive arm,[42] but secondary renal outcomes showed that intensive treatment was associated with a significantly lower incidence of albuminuria, both micro (21%) and macro (31%), but with a 7% higher rate of doubling of creatinine. No effect on the development of ESKD was shown. Despite this renoprotective benefit the effect on mortality raised concern about the long-term management of these patients.

The choice of glucose-lowering agents in patients with DKD depends on:

- The glycaemic target for treatment: this has not been well established in those with advanced DKD. HbA1c levels may not be accurate in those with advanced CKD or ESKD due to altered red blood cell life span, the effect of EPO (erythopoetin) administration and metabolic acidosis. KDIGO guidelines advise the avoidance of intensive glycaemic control in those with significant co-morbidities or those at particular risk of hypoglycaemia.[23]
- The risks associated with treatment (e.g. hypoglycaemia, cardiovascular events, lactic acidosis): Metformin-associated lactic acidosis is a rare event occurring in 7.4 events per 100,00 person-years among those on treatment. This risk is increased in patients with renal impairment taking a high dose of metformin.[43] Current recommendations suggest that those receiving metformin should have dose adjustment with lower eGFR; National Institute for Health and Care Excellence (NICE) guidelines recommend dose reduction if eGFR is <45 ml/min/1.73 m^2 and metformin discontinuation when eGFR is <30 ml/min/1.73 m^2.[44] The risk of hypoglycaemia associated with sulfonylureas is well documented, with one study reporting an episode in 605 people over 34,053 person-years of treatment consistent with an annual risk of 1.8%.[45]
- Patient choice.

In this exciting era for treatment of type 2 diabetes certain classes of oral glucose-lowering agents have come to the fore in offering renoprotective benefits independent of glycaemic control. The evidence for each of these 'newer' treatment classes that include DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors, will be discussed in turn. Much of the renal evidence has derived from secondary outcomes in large RCTs, which were primarily designed to satisfy US Food and Drug Administration (FDA) requirements to ensure cardiovascular safety of new anti-diabetic therapies that have followed the adverse risk profile that emerged with rosiglitazone.[46]

DPP-4 inhibitors

First line therapy for type 2 diabetes is usually metformin, which has a long confirmed cardiovascular risk profile, but over the past 15 years DPP-4 inhibitors have been used in preference in patients intolerant of metformin, and those with stage 4 or worse CKD, and very often as add-on therapy when a second glucose-lowering agent is required. DPP-4 is an enzyme expressed on most cell types that deactivates bioactive peptides including GLP-1.[47] GLP-1 stimulates the pancreatic secretion of insulin and reduces glucagon secretion, and hence inhibition of DPP-4 enhances glycaemic control. In a pooled analysis of RCTs encompassing 5466 patients that examined the effect of linagliptin *versus* placebo on renal end points (incidence of new albuminuria, deteriorating renal function, halving of eGFR and acute kidney injury), linagliptin significantly reduced the overall renal event hazard by 16%, but this was largely due to the effect on incident albuminuria as reduction in renal function, halving of eGFR and acute renal failure were comparable in both groups.[48] The Saxaliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 Trial (SAVOR-TIMI 53) randomly assigned 16,492 patients with type 2 diabetes and high cardiovascular risk and varying renal function to treatment with saxagliptin or placebo and followed them for a median of 2.1 years.[49] Saxagliptin did not confer any cardiovascular event benefit but an analysis of renal outcomes showed that saxagliptin was associated with an improvement in albuminuria for all baseline albuminuria categories. The change in albuminuria did not correlate with HbA1c. There was no difference between the groups in terms of change in eGFR, doubling of creatinine or initiation of renal replacement therapy.[50] The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) is the most recent RCT comparing the addition of linagliptin *versus* placebo in patients at high risk of both cardiovascular disease and CKD, and it had primary cardiovascular and secondary renal end points;[51] 74% of patients had CKD and 43% had an eGFR of <45 ml/min/1.73 m^2. Linagliptin was non-inferior to placebo in terms of cardiovascular events and there was no signal that it increased heart failure, important as this end point had previously been highlighted as a concern with DPP-4 inhibitors as a class. Linagliptin was again shown to reduce the progression of albuminuria but had no effect on other renal outcomes.

These trials support the fact that DPP-4 inhibitors have a modest impact on albuminuria but not on renal functional decline and they do not confer any cardiovascular benefit. They are safe for use in renal impairment, and linagliptin can be used in patients with ESKD. Other DPP-4 inhibitors such as sitagliptin, saxagliptin and alopgliptin do require dose adjustment with advancing renal impairment.

GLP-1 receptor agonists

GLP-1 is produced in L cells of the small intestine and binds to GLP-1 receptors expressed in various tissues including pancreatic beta cells, gastric mucosa, kidney, heart, skin, immune cells and the hypothalamus. Its main effect is to stimulate glucose-dependent insulin release from the pancreatic islets,[52] but it also downregulates glucagon secretion. In diabetes there is an impaired response to GLP-1; GLP-1 agonists bind to the GLP-1 receptor in the pancreatic islets and stimulate insulin release. The GLP-1 receptor agonists also help reduce body weight by a combination of delaying gastric emptying and increased satiety, effects which explain the increased risk of adverse gastrointestinal symptoms in comparison to placebo.[53]

There are several currently available GLP-1 receptor agonists. RCTs which were primarily cardiovascular outcome trials have examined the effect of liraglutide, administered daily by subcutaneous (SC) injection (LEADER trial)[54] and semaglutide, administered by weekly SC injection

(SUSTAIN-6),[55] demonstrating significant lowering of cardiac events in type 2 diabetes. In both trials patients were deemed high risk for cardiovascular complications having either an established cardiovascular condition (coronary artery disease, cerebrovascular disease, peripheral vascular disease or heart failure) or risk factors for cardiovascular disease (albuminuria, proteinuria, hypertension, left ventricular hypertrophy/dysfunction or Ankle Brachial Index <0.9). In LEADER[56] 81.3% of patients had established cardiovascular disease, 72.4% had CKD stage 3 or worse, with a mean duration of diabetes of 12.8 years. It was a similar cohort in SUSTAIN[57] as 83% of patients had cardiovascular disease, CKD or both.

Significant improvements in weight loss and blood pressure control were observed in both studies, and these are likely to have contributed to cardiovascular benefits. The secondary outcomes of both studies published in 2016 included renal outcomes such as onset of proteinuria, doubling of creatinine and the need for renal replacement therapy. Both trials demonstrated a lower rate of renal outcomes driven predominantly by lower rates of macroalbuminuria.

These studies indicate that GLP-1 analogues have a positive effect on albuminuria, with some slowing of GFR decline. A particular advantage of this class of medication is that it can be administered safely at very low levels of renal function (e.g. to patients with eGFR as low as 15 ml/min/1.73 m^2).

There have been several other trials examining the cardiovascular benefits of GLP-RAs involving the agents albiglutide, lixisenatide, exenatide and dulaglutide. In the Harmony outcomes trial (Albiglutide and Cardiovascular Outcome in patients with Type II diabetes and cardiovascular disease) the addition of a weekly SC injection of albiglutide (30–50 mg) to standard care *versus* placebo was shown to reduce the risk of major cardiovascular events by 22% (HR 0.78, 95% CI 0.68–0.90) in those with type 2 diabetes and cardiovascular disease.[56] This trial had a shorter median follow-up of 1.6 years than either LEADER (3.8 years) or SUSTAIN 6 (2.1 years) yet highlighted a benefit among those with significant cardiovascular disease. Among the 9463 participants 71% had coronary artery disease, 25% had peripheral artery disease and 25% had cerebrovascular disease.

The evaluation of Lixisenatide in Acute Myocardial Infarction (ELIXA) trial examined the effect of lixisenatide in those with type 2 diabetes who had an acute coronary event (acute myocardial infarction or admission for unstable angina) within the previous 180 days.[57] In comparison to the other trials this was a neutral trial which illustrated that the addition of lixisenatide did not alter the rate of major cardiovascular events. However, there was a signal for potential renal benefit with a modest difference in the percentage of change in urine ACR in favour of lixisenatide over placebo (24% *versus* 34%, $p=0.004$ increase in urine ACR at 24 months).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial randomly assigned patients with type 2 diabetes with or without previous cardiovascular disease to receive SC injections of extended-release exenatide (2 mg) or placebo on a once weekly basis.[58] Similar to the other studies the outcome was a composite of major cardiovascular events. Again, this trial was neutral illustrating non-inferiority to placebo with respect to cardiovascular safety. The lack of cardiovascular benefit may be related to shorter median follow-up or lower baseline glycated haemoglobin level (8%) in comparison to that in the LEADER trial (8.7%).

Dulaglutide was studied in Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND) a multicentre RCT of the addition of a weekly injection of 1.5 mg dulaglutide to an existing glucose-lowering regimen in participants with type 2 diabetes with either pre-existing cardiovascular disease, or cardiovascular risk factors, *versus* placebo.[59] This trial was also a cardiovascular outcome trial and it found that with a median follow-up of 5.4 years (longer than the previously mentioned trials) the primary composite outcome of major cardiovascular events was lower in those treated with dulaglutide 12% *versus* 13.4% (HR 0.88, 95% CI 0.79–0.99). However, this study had lower baseline rates of both cardiovascular disease and CKD at 31.5% and 22.2%, respectively.

A subsequent meta-analysis[60] of the above trials in 2019 involving 56,004 patients found that GLP-RAs reduced major cardiovascular events by 12% (HR 0.88, 95% CI 0.82–0.94; $p<0.0001$), all-cause mortality by 12% (HR 0.88, 95% CI 0.83–0.95; $p=0.001$) and admission for heart failure by 9% (HR 0.91, 95% CI 0.83–0.99;

$p = 0.028$). In terms of renal outcomes GLP-RAs were shown to reduce a composite outcome of new onset macroabuminuria, deteriorating renal function, progression to ESKD or death attributable to a renal cause by 17% (HR 0.83, 95% CI 0.78–0.89; $p < 0.001$) which was mainly driven by reduction in albuminuria. This further highlights the significant benefit of the addition on GLP-RAs in the management of those with type 2 diabetes in terms of mortality, cardiovascular events and renal events.

SGLT-2 inhibitors

SGLT-2 inhibitors have come to the fore as a remarkably interesting class of oral glucose-lowering agents due to their pleiotropic effects that have been demonstrated in several RCTs (Table 1). SLGT-2 is predominantly expressed in the convoluted segment of the proximal tubule and is responsible for approximately 90% of tubular glucose reabsorption. The remaining 10% is under the influence of SGLT-1 located in the adjacent straight segment of the proximal tubule. In diabetes, tubular reabsorption of glucose is increased, an effect which limits glycosuria, but which contributes to hyperglycaemia.[61] The SGLT-2 inhibitors increase renal excretion of glucose which in turn leads to lower blood glucose levels in type 2 diabetes. Not only do the SGLT-2 inhibitors lower HbA1c, but they also contribute to weight loss and improved blood pressure control. This effect is independent of insulin and hence they tend not to cause hypoglycaemia when used with other oral glucose-lowering agents. Their effectiveness may be blunted by advancing renal impairment.

Currently four agents are approved for the treatment of type 2 diabetes either as monotherapy or in combination with other glucose-lowering agents, especially metformin. These include canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. The RCTs have shown that SGLT-2 inhibitors have several pleiotropic effects including: (a) eeight loss of 2–3 kg as a result of osmotic diuresis and loss of calories;[62] (b) persistent reductions in systolic and diastolic blood pressure of 5 and 2 mmHg, respectively, as seen in a 2017 meta-analysis;[63] (c) alteration of lipid profile by reducing plasma triglycerides and increasing both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol;[64] (d) although the impact on liver histology has not been confirmed SGLT-2 inhibitors have been associated with reduced alanine aminotransferase (ALT), aspartate aminotransferase (AST), body weight and fatty liver index in those with non-alcoholic steato-hepatitis;[65] (e) natriuresis leading to reduced pre-load, blood pressure and arterial stiffness with consequent improvement in sub-endocardial blood flow in those with heart failure;[66] (f) reduction in intra-glomerular pressure leading to reduction in albuminuria.[67]

There have been several large RCTs investigating the cardiovascular safety of SGLT-2 inhibitors, all with secondary renal outcomes. The Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG) randomly assigned 7020 patients with type 2 diabetes and cardiovascular disease to empagliflozin at two doses (10 mg or 25 mg) *versus* placebo.[68] Thirty-two per cent of the patients had CKD as manifest by eGFR <60 ml/min/1.73 m^2 and/or urine ACR >300 mg/g. Empagliflozin was associated with improved cardiovascular outcomes but also improved kidney outcomes. The latter consisted of a lowered rate of macroalbuminuria (38%), a reduction of 44% in terms of doubling of creatinine and the initiation of renal replacement therapy was reduced by 55% across the range of eGFR and treatment doses, although the number of ESKD end points was very small. Although there was significant renal benefit observed in EMPA-REG it was not a dedicated renal outcomes trial.

The recently published Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-REDUCED) trial predominantly examined the benefit of empagliflozin *versus* placebo in addition to recommended therapy in those with class II to IV heart failure and left ventricular ejection fraction of 40% or less; 1856 participants had diabetes (50%). The study found a consistent reduction in the risk of hospitalisations for heart failure regardless of diabetic status (HR 0.72 with diabetes and 0.78 without diabetes) and across the continuum of HbA1c. There was also a renal benefit highlighted with reduced slope of decline of eGFR and progression to ESKD in the empagliflozin arm regardless of the severity of renal impairment at baseline.[69]

The Canagliflozin Cardiovascular Assessment Study (CANVAS) programme involved two RCTs, CANVAS and CANVAS-RENAL, which

Table 1. Renal end points in cardiovascular outcome trials (CVOTs), renovascular outcome trials (RVOTs) and heart failure studies for SGLT-2 inhibitors.

Trial	Drug	Cohort	Mean eGFR (ml/min/1.73 m²)	Primary end points	Secondary CV end points	Secondary renal end points
				HR (95% CI)		
EMPA-REG CVOT	Empagliflozin 10/25 mg	T2DM with established CVD *N* = 7020	74.1	Composite of CV death, non-fatal MI or non-fatal stroke 0.86 (0.76–0.99)	CV death 0.62 (0.49–0.77) All cause death 0.68 (0.57–0.82) HF admissions 0.65 (0.5–0.85)	Doubling of serum creatinine and eGFR ⩽45, initiation of RRT or kidney related death 0.54 (0.40–0.75) Incident or worsening nephropathy 0.61 (0.53–0.70) Initiation of RRT 0.45 (0.21–0.97)
CANVAS CVOT	Canagliflozin 100/300 mg	T2DM with established CVD (66%) or ⩾3 CVD RF *N* = 10142	76.5	Composite of CV death, non-fatal MI or non-fatal stroke 0.86 (0.75–0.97)	HF admissions 0.67 (0.52–0.87)	Progression of albuminuria 0.73 (0.67–0.79) Reduced composite of 40% reduction in eGFR, RRT or kidney death 0.60 (0.47–0.77)
DECLARE-TIMI CVOT	Ertugliflozin 10 mg	T2DM with established CVD (41%) or ⩾2 CVD RF *N* = 17160	85.3	Composite of CV death, non-fatal MI or non-fatal stroke 0.93 (0.84–1.03) Composite of CV death or HF admission 0.83 (0.73–0.95)	HF admissions 0.73 (0.61–0.88)	⩾40% decrease in eGFR to <60, ESKD or kidney related death 0.53 (0.43–0.66) ESKD 0.31 (01.3–0.79) ESKD kidney related death 0.41 (0.20–0.82)
CREDENCE RVOT	Canagliflozin 100 mg	T2DM with eGFR of 30 to <90 ml UACR >300–500 mg/g. Receiving a stable dose of RAAS inhibition for ⩾4 weeks prior to randomisation *N* = 4401	56.2	Composite of kidney and CV outcome 0.70 (0.59–0.82) ESKD, doubling of serum creatinine or renal death 0.66 (0.53–0.86) ESKD 0.68 (0.54–0.86) Dialysis, kidney transplantation or renal death 0.72 (0.54–0.97)		
EMPEROR-REDUCED HF trial	Empagliflozin 10 mg	Patients with NYHA Class II–IV heart failure and EF of ⩽40% *N* = 3730	61.8	Composite of adjudicated CV death or hospitalisation for HF 0.75 (0.65–0.86)	No. of hospitalisations for HF 0.70 (0.58–0.85)	Rate of decline in eGFR: −0.55 ml/min/1.73m² *versus* 2.28 ml/min/1.73 m²
DAPA-CKD RVOT	Dapagliflozin 10 mg	Patients with eGFR of 25–75 ml. UACR: 200–5000 mg/g *N* = 4304	43.2	Composite of the first occurrence of any of the following: a decline of at least 50% in the estimated GFR, ESKD, kidney transplantation, eGFR of <15 ml per minute per 1.73 or death from renal or CV causes 0.61 (0.51–0.71)	Composite CV outcome defined as hospitalisation for heart failure or death from CV causes; and death from any cause 0.56 (0.45–0.68)	Composite kidney outcome of a sustained decline in the estimated GFR of at least 50%, ESKD or death from renal causes 0.71 (0.55–0.92)

T2DM, type II diabetes mellitus; eGFR, estimated glomerular filtration; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; MI, myocardial infarct; HF, heart failure; RRT, renal replacement therapy; CVDRF, cardiovascular disease risk factors; ESKD, end stage kidney disease; uACR, urine albumin to creatinine ratio.

had a total of 10,142 participants with type 2 diabetes randomly assign to either treatment with canagliflozin or placebo and followed for a mean of 3.6 years.[70] A large proportion of the participants were receiving statins and RAAS inhibition (80%). Treatment with canagliflozin reduced the time to first occurrence of the renal composite end point, a sustained 40% reduction in eGFR, renal death and initiation of renal replacement therapy, in comparison to placebo but again the number of ESKD end points was low.

In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) patients with type 2 diabetes who had or were at risk of atherosclerotic cardiovascular disease were randomly assigned to receive either dapagliflozin or placebo.[71] The patients were followed for a median of 4.2 years, with the primary outcome being a composite of major adverse cardiovascular events. Similar to EMPA-REG and CANVAS, the secondary outcome was a renal composite of ⩾40% decrease in eGFR (to <60 ml/min/1.73 m^2), new ESKD or death from renal or cardiovascular events. The data showed a 47% relative risk reduction with dapagliflozin in these composite renal outcomes, which occurred in 317 patients, an effect mainly driven by a reduction in the doubling of creatinine.

CREDENCE was the first completed 'renal' RCT to investigate a SGLT-2 inhibitor primarily for its renoprotective benefit in those with type 2 diabetes and CKD. In this trial patients with type 2 diabetes and albuminuric CKD were randomly assigned to receive canagliflozin at a dose of 100 mg (which is the usual starting dose for standard hypoglycaemic use) or placebo.[72] All patients were receiving treatment with RAAS blockade and the primary outcome was a composite of doubling of creatinine, ESKD or death from renal or cardiovascular causes. The trial had 4400 participants and was stopped early due to the clear efficacy of canagliflozin at reducing renal events. The relative risk of the primary outcome was 30% lower in those on treatment compared to placebo. Treatment with canagliflozin was also associated with the secondary end points of a lower risk of cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure. Of note, there was no difference in rates of amputation or fracture between the arms of the study, important as an adverse signal for these complications had been detected in the CANVAS trial.

The renoprotective benefits of the SGLT-2 inhibitors have thus been shown in the cardiovascular outcome trials but the level of benefit is substantially less than that seen in CREDENCE, which enrolled CKD patients with a mean eGFR of 56 ml/min/1.73 m^2 and 60% of patients had eGFR <60 ml/min/1.73 m^2. As a consequence, there were 176 sustained renal replacement therapy events adjudicated in CREDENCE, whereas only 11 and 19 similar events were seen in EMPA-REG and CANVAS-R, respectively. What was unclear until the recent publication of Dapagliflozin in patients with Chronic Kidney Disease (DAPA-CKD) was whether the renal benefit shown in CREDENCE was a class effect, or specific to canagliflozin, and whether benefits extended to non-diabetic CKD.

DAPA-CKD has clarified that other SGLT-2 inhibitors are associated with improved cardiovascular and renal outcomes. This trial involved 4304 participants and was stopped early due to clear efficacy. Over a median follow-up of 2.4 years a clear renal benefit was illustrated with the HR for a renal outcome (defined as sustained decline of eGFR of at least 50%, ESKD or death from a renal cause) of 0.56 (95% CI 0.45–0.68). The HR for a cardiovascular outcome was 0.71 (95% CI 0.55–0.92). Of note, the benefit was similar in those with or without diabetic CKD.[73] EMPA-KIDNEY[74] is due to be completed in 2022, and it will be interesting to see whether it shows similar results. It should also be noted that CREDENCE and the other SGLT-2 RCT demonstrated an improvement in heart failure hospitalisation (a secondary end point in CREDENCE) and this benefit has been conclusively demonstrated in DAPA-HF,[75] in which dapagliflozin was shown significantly to reduce heart failure hospitalisation and death from cardiovascular causes in patients with reduced left ventricular function, irrespective of whether the patients had diabetes (which affected 42%).

As a result of the results of CREDENCE the FDA have approved canagliflozin as a specific treatment for DKD. It can now be initiated in patients with stage 3 CKD (down to eGFR 30 ml/min/1.73 m^2) and those patients who progress to ESKD can continue canagliflozin if already receiving it, but the dose should be adjusted to 100 mg daily. The European Medicines Agency have now extended the licence of canagliflozin to the treatment of diabetics with stage 2 and 3 CKD and albuminuria.[76]

Table 2. Current limitations of glucose lowering agents according to eGFR.

	CKD 1 (eGFR >90 ml/min/1.73m²)	CKD 2 (eGFR 60–89 ml/min/1.73 m²)	CKD 3 (eGFR 30–59 ml/min/1.73 m²)	CKD 4 (eGFR 15–29 ml/min/1.73 m²)	CKD 5 (eGFR <15 ml/min/1.73 m²)
Biguanides					
Metformin	No dose adjustment		Dose reduction (850–1500 mg)	Dose reduction (500 mg) & caution	Avoid
DPP-4 inhibitors					
Sitagliptin	No dose adjustment		Dose reduction		Avoid
Alogliptin				Avoid	Avoid
Saxagliptin			Dose reduction		Avoid in ESKD
Lingliptin					
GLP-RAs					
Albiglutide	No dose adjustment				Avoid
Lixisenatide				Avoid	
Exenatide				Avoid	
Dulaglutide					Avoid in ESKD
Liraglutide					
Semaglutide					
SGLT-2 inhibitors					
Dapagliflozin	No dose adjustment		Do not initiate		
Empagliflozin			Do not initiate		
Canagliflozin			Dose reduction	Do not initiate	

SGLT-2 inhibitors, sodium glucose linked transporter 2 inhibitors; GLP-RAs, glucagon-like peptide 1 receptor agonists.

Summary and practical use of anti-diabetic therapies in patients with CKD

The results of the RCTs involving SGLT-2 inhibitors and GLP-RAs in particular have strengthened the available therapeutic possibilities for treating patients with CKD (Table 2). The combination of improvements in cardiovascular risk and in renal outcomes has led to earlier prioritisation for the introduction of these anti-diabetic classes in the treatment algorithm for diabetes patients. The fact that GLP-RAs can be used in patients with stage 4 CKD, a stage in which metformin cannot be used, is a huge advantage for nephrologists, and the emerging guidance enabling the introduction of canagliflozin throughout the stage 3 CKD continuum is of equal importance. One or other of these anti-diabetic classes should now be first choice for introduction with or after metformin, or in place of it in those intolerant, in patients with diabetes and increased cardiovascular risk or CKD, and in preference to other classes of therapy such as DPP-4 inhibitors or sulphonylureas. Based on the new evidence both the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD) published a consensus in 2018 on the management of patients with type 2 diabetes. For patients with type 2 diabetes and existing cardiovascular disease they now advise the use of either an SGLT-2 inhibitor or GLP-1 agonist with confirmed cardiovascular benefit, and for those with CKD or clinical heart failure with confirmed

Table 3. Renal end points in cardiovascular outcome trials (CVOTs), renovascular outcome trials (RVOTs) and heart failure studies for SGLT-2 inhibitors.

Case	Clinical features	Current diabetic treatment	Anti-hypertensive treatment	Further management prior to new era	Contemporary management
1	62-year-old woman. T2DM for 8 years. Previous TIA. Weight: 77 kg, BMI: 32, Blood pressure: 166/90 mmHg, eGFR: 52 ml/min, uACR: 40 mg/mmol (400 mg/g), HbAIc: 86 mmol/mol	Metformin 1 g BD. Linagliptin 5 mg OD.	Irbesartan 150 mg OD. Bisoprolol 5 mg OD.	Add gliclazide or pioglitazone. Maximise Irbesartan to 300 mg.	Add SGLT-2 inhibitor. Maximise Irbesartan to 300 mg
2	67-year-old man. T2DM for 6 years. Weight: 97 kg, BMI: 36, Angina but non flow limiting CAD at angiography. Blood pressure: 162/92 mmHg,eGFR: 27 ml/min, uACR: 55 mg/mmol (550 mg/g), HbA1c 103 mmol/mol	Metformin 1 g BD. Gliclazide 160 mg BD.	Losartan 100 mg OD. Bisoprolol 5 mg OD.	Stop metformin. Add linagliptin and possibly insulin. Add another anti-hypertensive agent such as calcium antagonist or alpha blocker.	Stop metformin. Add GLP-RA. Add another anti-hypertensive agent such as calcium antagonist or alpha blocker.

atherosclerotic cardiovascular disease the recommendation is the early use of an SGLT-2 inhibitor with confirmed benefit.[77]

The following fictional cases exemplify how our approach to treatment has now changed as a consequence of the new RCT evidence (Table 3).

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Conflict of interest statement

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