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REVIEW

Renal Outcomes in Type 2 Diabetes: A Review of Cardiovascular and Renal Outcome Trials

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ABSTRACT

The development of chronic kidney disease (CKD) in people with diabetes is commonplace, and is frequently associated with a significant and unfavourable impact on patient outcomes along with a substantial economic burden. With the development of novel classes of drug therapies in diabetes, there has been a recent focus on cardiovascular safety measures, with dedicated cardiovascular outcome trials (CVOTs) carried out for all new diabetes medications. More recently, there has been a growing regulatory view that such trials should report more specific renal outcomes to ensure simpler comparability between drugs and drug classes. This article explores some of the possible mechanisms by which these drugs may improve renal function in people with diabetes, and it reviews important CVOTs that have reported renal outcomes to date. These include CVOTS of sodium-glucose cotransporter-2 inhibitors (EMPA-REG OUTCOME study, CANVAS study, CREDENCE trial, DECLARE-TIMI trial and DAPA-HF study), dipeptidyl peptidase-4 inhibitors (EXAMINE trial, SAVOR-TIMI 53, TECOS trial and CARMELINA trial) and glucagon-like peptide-1 analogues (ELIXA trial, LEADER trial, SUSTAIN-6 trial, PIONEER-6 trial, EXSCEL trial, HARMONY Outcomes study and the REWIND study). Ongoing cardiovascular and renal outcome studies such as Dapa-CKD, EMPA-KIDNEY, EMPEROR-Preserved and EMPEROR-Reduced are also discussed. The heterogeneity of patient characteristics and reported renal outcomes, which hinders comparisons between trials and drug classes, is highlighted. Novel classes of diabetes therapies present an important opportunity for nephroprotection beyond the blockade of the renin–angiotensin–aldosterone system in this high-risk group. Clinicians should be aware of such benefits when prescribing these medications for people with, and possibly those without, type 2 diabetes.

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Key Summary Points

Cardiovascular outcome trials often report a degree of heterogeneity in renal outcomes in secondary analyses, complicating comparisons between medications.

This article outlines the mechanisms by which diabetes medications influence renal function as well as the renal outcomes reported by cardiovascular and renal outcome trials of newer diabetes therapies to date.

Trial data indicate that SGLT-2 inhibitors, DPP-4 inhibitors and GLP-1 analogues all reduce the rate of decline in albuminuria in people with diabetes and chronic kidney disease, and that SGLT-2 inhibitors also reduce the rate of glomerular filtration rate (GFR) decline in this cohort.

Further work should focus on reporting consistent renal outcome measures in cardiovascular and renal outcome trials to facilitate simpler comparisons between drugs and drug classes.

INTRODUCTION

Diabetes mellitus is the principal cause of end-stage renal disease (ESRD) worldwide; it is responsible for up to 50% of all incident cases [1]. Diabetic kidney disease (DKD) affects about 30% of people with type 1 diabetes (T1D) and 40% of people with type 2 diabetes (T2D) [2]. DKD is clinically defined as a persistently raised urinary albumin-to-creatinine ratio (ACR) ($\geq$ 30 mg/g) and/or a consistent reduction in the estimated glomerular filtration rate (eGFR) ($<$ 60 ml/min/1.73 m^2) [3]. In people with diabetes, the development of DKD increases the risk of death at least fivefold compared to people with normal renal function, and in those who develop ESRD, the risk of death is increased up to 100-fold [2]. This increased risk occurs due to higher rates of both cardiovascular and noncardiovascular events [4].

Currently, management to reduce the incidence and progression of DKD focusses on improving risk factors such as glycaemic and blood pressure control. Indeed, the only licensed drug therapies specifically for renoprotection in people with DKD involve blockade of the renin–angiotensin–aldosterone system (RAAS). The use of medicines within these drug classes improves renal outcomes in people with diabetes. One meta-analysis observed that angiotensin-converting enzyme (ACE) inhibitors reduce the incidence of ESRD (odds ratio (OR) 0.71) or the likelihood of a doubling of the serum creatinine (OR 0.58) compared with placebo. Similarly, angiotensin-receptor blockers (ARBs) were noted to reduce the incidence of ESRD (OR 0.73) or the likelihood of a doubling of the serum creatinine (OR 0.76) compared with placebo [5]. Nevertheless, there remains a high residual risk for the development of DKD and ESRD in this cohort, meaning that there is a considerable opportunity to improve patient outcomes [6]. Additionally, the economic burden of DKD is substantial; it cost the National Health Service in the UK almost £1 billion in 2010/11, and is projected to cost almost £1.3 billion in 2035/36, ignoring other costs associated with the treatment of diabetes [7]. Thus, there is growing interest in therapies that may prevent or delay the development of DKD, and trials evaluating the safety of newer classes of diabetes medications are increasingly reporting on specific renal outcomes in this cohort.

The aim of this manuscript is to review the renal outcomes reported from these trials and to discuss the use of these diabetes therapies to prevent or delay the progression of DKD.

REGULATORY VIEW ON RENAL OUTCOMES

In 2008, the US Food and Drug Administration (FDA) published its expectations to support the pharmaceutical industry in cardiovascular outcome trials (CVOTs) for the development of

new medical therapies for T2D [8]. This guidance was later supported by similar recommendations from the European Medicines Agency (EMA) [9]. Studies on renal endpoints were generally performed as secondary measures from these CVOTs, with a degree of variability in the definition of such renal outcomes between CVOTs. More recently, trials focussing on renal endpoints have reported their results with a more specific and homogeneous set of renal outcome measures.

Renal outcome measures reported by CVOTs include [10]:

1. Progression of albuminuria
2. Changes in the eGFR (typically defined as a decline of 30–50% from baseline, or a doubling of serum creatinine)
3. Incidence of ESRD (usually defined as the need for renal replacement therapy, RRT)
4. Death from a renal cause.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

NEWER DIABETES THERAPIES: POTENTIAL FOR NEPHROPROTECTION

Several classes of drug have been introduced over the last 15 years for the treatment of diabetes that may directly improve renal function, including sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogues. Interestingly, secondary outcomes reported by CVOTs have indicated that these drugs may directly improve renal function beyond changes in glycaemic control.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

This class of medications exert their action by inhibiting the sodium-glucose cotransporter-2 protein in the proximal convoluted tubule, preventing the reuptake of both sodium and glucose. The consequent increased urinary excretion of glucose is responsible for the improved glycaemia and weight loss. Moreover, the reduced tubular reabsorption of sodium and glucose promotes natriuresis, reducing blood pressure [11, 12]. One meta-analysis reported significant reductions in the progression of albuminuria, the risk of worsening renal impairment, the need for a renal transplant, and death from a renal cause [13].

There are two main mechanisms by which SGLT-2 inhibition fosters nephroprotection, which can be broadly categorised into haemodynamic and tubular factors [14]. The haemodynamic changes are a result of increased sodium delivery to the macula densa, a consequence of reduced sodium (and glucose) reabsorption in the proximal convoluted tubule. This results in increased local secretion of vasoconstrictors such as adenosine that reduce and thereby preserve glomerular blood flow, which typically manifests clinically as an initial decline in eGFR that stabilises over years and is generally comparable to the effect of drugs that blockade the RAAS. This concept was demonstrated well by Cherney and colleagues [15], who explored the impact of empagliflozin on renal hyperfiltration in participants with T1D and normal renal function. The administration of empagliflozin attenuated renal hyperfiltration in participants with eGFR > 135 ml/min/1.73 m^2 and did not alter renal function in those with a normal eGFR. This important observation highlights that SGLT-2 inhibitors can influence the glomerular hyperfiltration that characterises the earlier stages of diabetic nephropathy, thereby lessening its progression [12, 15, 16].

Beyond the impact of SGLT-2 inhibition on renal haemodynamics, administering these drugs reduces markers of inflammation and renal fibrosis. This is important in chronic kidney disease (CKD), as proinflammatory molecules are elevated in CKD—they cause the disease and contribute to its progression [17]. In people with diabetes, increased activity of SGLT-2 receptors secondary to hyperglycaemia results in the increased production of proinflammatory cytokines. In mouse models at least, production of these proinflammatory cytokines is

attenuated by the administration of SGLT-2 inhibitors such as dapagliflozin or empagliflozin, leading to reduced glomerulosclerosis and tubulointerstitial fibrosis [17, 18]. These drugs also preserve renal function by addressing risk factors for renal disease: they reduce blood pressure and improve hyperglycaemia and weight loss [12, 16]. The combined effect of stabilising the GFR, reduced tubulointerstitial fibrosis and improved risk factors for renal disease explains the reduced incidence and progression of albuminuria in people with diabetes who are using SGLT-2 inhibitors.

Empagliflozin

The EMPA-REG OUTCOME study primarily aimed to evaluate the cardiovascular safety of empagliflozin (10 mg or 25 mg) versus placebo [19]. A total of 7020 people with T2D and established cardiovascular disease aged $\geq$ 18 years with HbA_{1c} 7.0–9.0% and eGFR > 30 ml/min/1.73 m^2 were randomised and followed for a median of 3.1 years. At baseline, 25.9% of participants had eGFR < 60 ml/min/1.73 m^2. Whilst primary outcomes focussed on cardiovascular safety, renal outcomes were established in a secondary analysis. The definitions used for the renal outcomes are presented in Table 1. Participants receiving empagliflozin had a reduced occurrence of the renal composite outcome versus placebo (12.7 vs 18.8%). Fewer participants using empagliflozin developed macroalbuminuria, presented a doubling of serum creatinine or required the initiation of RRT [20]. Renal outcomes are shown in Table 2.

Canagliflozin

The CANVAS Program aimed to evaluate the cardiovascular safety of canagliflozin (100 mg or 300 mg) versus placebo [21]. A total of 10,142 participants with T2D (HbA_{1c} 7.0–10.5%) who were aged $\geq$ 30 years and had a history of significant cardiovascular disease or were aged $\geq$ 50 years and had $\geq$ 2 significant risk factors for cardiovascular disease were observed for a median of 126.1 weeks. At baseline, 20.1% of participants had eGFR < 60 ml/min/1.73 m^2. The definitions used for renal outcomes are summarised in Table 1. The composite renal outcome was acquired by fewer participants using canagliflozin than by those using placebo [5.5 vs 9.0 participants per 1000 patient years; hazard ratio (HR) 0.60]. Notably, canagliflozin use was associated with a reduced incidence of macroalbuminuria progression (HR 0.58) compared to participants receiving placebo. Further renal outcomes are detailed in Table 2 [22].

The CREDENCE trial was designed not to evaluate the cardiovascular safety of canagliflozin but rather to assess the renal safety of canagliflozin (100 mg) in people aged $\geq$ 30 years with T2D (HbA_{1c} 6.5–12.0%) and pre-existing renal disease (ACR 300–5000 mg/g and eGFR 30–89 ml/min/1.73 m^2) compared to placebo [23]. A total of 4401 participants were randomised and observed for a median of 2.6 years. The definitions used for renal outcomes are summarised in Table 1. There was a reduced risk of observing the renal composite outcome in participants using canagliflozin versus placebo (11.1 vs 15.5%, HR 0.70). A doubling of serum creatinine occurred in 5.4% of participants using canagliflozin versus 8.6% using placebo (HR 0.60), ESRD occurred in 5.3% of participants using canagliflozin compared with 7.5% using placebo (HR 0.68), and renal death occurred in 0.1% using canagliflozin and 0.2% using placebo. The mean urinary ACR was 31% lower during follow-up in participants using canagliflozin compared with those using placebo. The authors estimated that canagliflozin use over 2.5 years reduced the incidence of ESRD by 24 per 1000 patients (number needed to treat (NNT): 43). Indeed, reductions in the proportions of participants using canagliflozin who attained either the primary composite outcome, the renal-specific composite outcome, ESRD, RRT or renal death, cardiovascular death or death from any cause could be seen from just 12 months postrandomisation. Specific renal outcomes are detailed in Table 2.

Dapagliflozin

The DECLARE-TIMI 58 trial aimed to evaluate the cardiovascular safety of dapagliflozin

Table 1 Definition of the reported renal outcomes in each of the CVOTs for SGLT-2 inhibitors, DPP4 inhibitors and GLP-1 analogues

Trial	Renal composite outcome	Albuminuria	eGFR/creatinine	ESRD
EMPA-REG OUTCOME [19, 20]	Progression to macroalbuminuria, doubling of serum creatinine with eGFR $\leq$ 45 ml/min/1.73 m^2, ESRD, renal death	Incident microalbuminuria (urinary ACR 30–300 mg/g) Incident macroalbuminuria (urinary ACR > 300 mg/g)	Doubling of serum creatinine and eGFR < 45 ml/min/1.73 m^2	Need for RRT
CANVAS Program [21, 22]	Sustained $\geq$ 40% decrease in eGFR, ESRD or renal death	New microalbuminuria, or new macroalbuminuria with $\geq$ 30% increased urinary ACR	Sustained 40% reduction in eGFR for $\geq$ 30 days	Sustained eGFR < 15 ml/min/1.73 m^2 for > 30 days, dialysis $\geq$ 30 days or renal transplant
CREDENCE trial [23]	Doubling of serum creatinine, ESRD, or death from renal or cardiovascular disease	Comparison of urinary ACR versus placebo	Sustained doubling of serum creatinine	Sustained eGFR < 15 ml/min/1.73 m^2 for > 30 days or need for dialysis for $\geq$ 30 days or renal transplant
DECLARE-TIMI 58 [24, 26]	Sustained $\geq$ 40% decrease in eGFR to $\leq$ 60 ml/min/1.73 m^2, ESRD, renal or cardiovascular death	Comparison of urinary ACR versus placebo	Sustained $\geq$ 40% decrease in eGFR to $\leq$ 60 ml/min/1.73 m^2	Sustained eGFR < 15 ml/min/1.73 m^2, or dialysis for $\geq$ 90 days, or renal transplant
DAPA-HF study [27]	Sustained $\geq$ 50% decrease in eGFR, ESRD, renal death	Not reported	Sustained $\geq$ 50% decrease in eGFR	Sustained eGFR < 15 ml/min/1.73 m^2 $\geq$ 28 days, or need for continuous RRT
EXAMINE trial [44]	Not reported	Not reported	Changes in eGFR over the study	Need for renal dialysis
SAVOR-TIMI 53 [45, 46]	Doubling of serum creatinine or ESRD	Categorical change in urinary ACR from baseline	Doubling of serum creatinine	Need for renal dialysis, transplant or serum creatinine > 530 μmol/L
TECOS trial [47, 48]	Not reported	Comparison of urinary ACR versus placebo	Changes in eGFR over the study	Not reported

Table 1 continued

Trial	Renal composite outcome	Albuminuria	eGFR/creatinine	ESRD
CARMELINA trial [49]	Sustained $\geq$ 40% decrease in eGFR and eGFR $\leq$ 60 ml/min/1.73 m^2, ESRD, renal death	Microalbuminuria (ACR 30–300 mg/g) or macroalbuminuria (urinary ACR $\geq$ 300 mg/g)	Sustained $\geq$ 40% decrease in eGFR and eGFR $\leq$ 60 ml/min/1.73 m^2	Need for renal dialysis $\geq$ 30 days or renal transplant
ELIXA trial [50, 51]	Not reported	Mean percentage change in urinary ACR, progression to macroalbuminuria	Doubling of the serum creatinine, changes in eGFR	Not reported
LEADER trial [52, 53]	New macroalbuminuria, doubling of serum creatinine with eGFR $\leq$ 45 ml/min/1.73 m^2, need for continuous RRT or renal death	New macroalbuminuria (urinary ACR > 300 mg/g or urinary albumin > 300 mg/24 h)	Doubling of the serum creatinine with eGFR $\leq$ 45 ml/min/1.73 m^2	Need for continuous RRT
SUSTAIN-6 trial [54]	New macroalbuminuria, doubling of serum creatinine with eGFR $\leq$ 45 ml/min/1.73 m^2, need for continuous RRT or renal death	New macroalbuminuria (urinary ACR > 300 mg/g or urinary albumin > 300 mg/24 h)	Doubling of the serum creatinine with eGFR $\leq$ 45 ml/min/1.73 m^2	Need for continuous RRT
PIONEER-6 [55]	Not reported	Not reported	Changes in eGFR ratio from baseline to end of treatment	Not reported
EXSCEL trial [56, 57]	New macroalbuminuria, sustained $\geq$ 40% decrease in eGFR or RRT or renal death	New macroalbuminuria	Sustained $\geq$ 40% decrease in eGFR	Need for RRT
HARMONY Outcomes study [58]	Not reported	Not reported	Changes in eGFR over the study	Not reported

Table 1 continued

Trial	Renal composite outcome	Albuminuria	eGFR/creatinine	ESRD
REWIND study [59]	New macroalbuminuria, sustained ≥ 30% decrease in eGFR or chronic RRT	New macroalbuminuria (urinary ACR > 33.9 mg/mmol)	Sustained ≥ 30% decrease in eGFR	Need for continuous RRT

eGFR estimated glomerular filtration rate, *ESRD* end-stage renal disease, *ACR* albumin-to-creatinine ratio, *RRT* renal replacement therapy

(10 mg) in people aged ≥ 40 years with T2D and multiple risk factors or a previous history of cardiovascular disease and HbA_{1c} of 6.5–12.0% [24]. A total of 17,160 participants were randomised to receive dapagliflozin or placebo and were followed for a median of 4.2 years. At baseline, just 7.4% of participants had eGFR ≤ 60 ml/min/1.73 m^2, and the definitions used for renal outcomes are summarised in Table 1. Participants using dapagliflozin were less likely to attain the composite renal outcome compared to placebo (1.5 vs 2.8%, HR 0.53). In those using dapagliflozin, there was a reduced risk of a sustained decline in eGFR ≥ 40% to < 60 ml/min/1.73 m^2 and a reduced risk of ESRD or renal death compared to placebo. Participants using dapagliflozin had a mean urinary ACR that was 29% lower than in those using placebo [25, 26]. The specific renal outcome measures are presented in Table 2.

The DAPA-HF study evaluated the cardiovascular safety of dapagliflozin (10 mg) in T2D and non-T2D people aged ≥ 18 years with symptomatic heart failure, left ventricular ejection fraction ≤ 40% and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/ml [27]. A total of 4744 patients (42% with T2D) were randomised to either study group and followed for a median of 18.2 months. The definitions used for renal outcomes are summarised in Table 1. The composite renal outcome occurred in 1.2% of people receiving dapagliflozin and 1.6% of people receiving placebo (HR 0.71). Unfortunately, at the time of writing, no further data relating to renal outcomes were available.

VERTIS-CV

The VERTIS-CV study aims to evaluate the cardiovascular and renal efficacy of ertugliflozin (5 mg or 15 mg) versus placebo [28]. A total of 8252 participants aged ≥ 40 years with T2D (HbA_{1c} 7.0–10.5%) and established atherosclerotic cardiovascular disease were randomised. At baseline, 22.0% of participants had eGFR < 60 ml/min/1.73 m^2, and 9.0% of participants had macroalbuminuria. Whilst the trial design and the baseline characteristics of the participants have been published, the results of this trial were not available at the time of writing.

INCRETIN-BASED THERAPIES

There are two drug classes that utilise the incretin system: DPP4 inhibitors and GLP-1 analogues. Incretins such as GLP-1 and gastric inhibitory polypeptide (GIP) are secreted by the distal small bowel following the ingestion of glucose, and act to stimulate insulin secretion from the β cells of the pancreas. Whilst GLP-1 analogues exert their action directly, DPP-4 inhibitors prevent the degradation of incretins. Drugs in both of these classes have been associated with nephroprotection [29].

Whilst the degree of nephroprotection associated with DPP-4 inhibitor use is debated, one meta-analysis reported that their use does reduce the progression of albuminuria and, in general, has a neutral impact on the GFR [30]. Interestingly, people with T2D and albuminuria have been observed to have higher urinary DPP-

Table 2 Renal outcomes in SGLT-2 inhibitor cardiovascular outcome trials

Trial	Composite renal outcome measure	Progression of albuminuria	eGFR/ creatinine	Incidence of ESRD	Death from a renal cause
EMPA-REG OUTCOME (empagliflozin) *n* = 7020	Empagliflozin: 12.7% Placebo: 18.8% (HR 0.61)	Empagliflozin: 11.2% Placebo: 16.2% (HR 0.62)	Empagliflozin: 1.5% Placebo: 2.6% (HR 0.56)	Empagliflozin: 0.3% Placebo: 0.6% (HR 0.45)	Empagliflozin: 0.1% Placebo: 0.0%
CANVAS Program (canagliflozin) *n* = 10,142	Canagliflozin: 5.5[a] Placebo: 9.0[a] (HR 0.60)	New macroalbuminuria: Canagliflozin: 15.1[a] Placebo: 27.6[a] (HR 0.58)	Canagliflozin: 5.3[a] Placebo: 8.7[a] (HR 0.60)	Canagliflozin: 0.4[a] Placebo: 0.6[a] (HR 0.77)	Canagliflozin: 0.0[a] Placebo: 0.2[a]
CREDENCE trial (canagliflozin) *n* = 4402	Canagliflozin: 11.1% Placebo: 15.5% (HR 0.70)	Mean urinary ACR 31% less versus placebo	Canagliflozin: 5.4% Placebo: 8.6% (HR 0.60)	Canagliflozin: 5.3% Placebo: 7.5% (HR 0.68)	Canagliflozin: 0.1% Placebo: 0.2%
DECLARE-TIMI 58 (dapagliflozin) *n* = 17,600	Dapagliflozin: 1.5% Placebo: 2.8% (HR 0.53)	Mean urinary ACR 29% less versus placebo	Dapagliflozin: 1.4% Placebo: 2.6% (HR 0.54)	Dapagliflozin: 0.1% Placebo: 0.2% (HR 0.31)	Dapagliflozin: 0.1% Placebo: 0.1% (HR 0.60)
DAPA-HF (dapagliflozin) *n* = 4744	Dapagliflozin: 1.2% Placebo: 1.6% (HR 0.71)	Not reported	Not reported	Not reported	Not reported

The number of participants in each trial is denoted by *n*

eGFR estimated glomerular filtration rate, *ESRD* end-stage renal disease, *HR* hazard ratio, *ACR* albumin-to-creatinine ratio

[a] Results presented as the number of participants with an event per 1000 patient years

4 activity than people with T2D but not albuminuria [31]. Additionally, Wolke and colleagues [32] reported that people with higher DPP-4 activity had a lower GFR than those with lower DPP-4 activity. There are several mechanisms by which DPP-4 inhibitors reduce albuminuria whilst maintaining a neutral impact on the GFR. Evidence from preclinical studies demonstrates that DPP-4 inhibitors reduce oxidative stress, inflammation, endothelial dysfunction and fibrosis within the kidney [33]. Moreover, DPP-4 inhibitors stimulate natriuresis in people with T2D, exerting their effect on the distal renal tubule [34]. However, some authors argue that, considering the natriuretic response to DPP-4 inhibitors is blunted in mice with diabetes [35], DPP-4 inhibitors reduce albuminuria in people with diabetes via their impact on oxidative stress, inflammation and fibrosis rather than through their haemodynamic impact [30].

The use of GLP-1 analogues improves renal outcomes by two key mechanisms: haemodynamic changes and anti-inflammatory effects. Firstly, GLP-1 induces natriuresis and diuresis, as demonstrated by the infusion of GLP-1 or a GLP-1 analogue in healthy participants [36, 37] and in people with T2D [38, 39]. This is likely

mediated directly via inhibition of the sodium–hydrogen exchanger 3 (NHE3) in the proximal tubular cells, which augments tubuloglomerular feedback by increasing the sodium load at the macula densa. Furthermore, GLP-1 analogues have been observed to reduce plasma renin and angiotensin levels, further promoting natriuresis and reducing albuminuria [40]. The net impact of these effects is stimulation of afferent arteriolar vasodilatation and inhibition of efferent arteriolar vasoconstriction, resulting in a neutral impact on GFR in general [41]. The mechanism by which these drugs reduce albuminuria remains unclear, though several possible mechanisms have been suggested, including the natriuretic effect of GLP-1 analogues, reductions in inflammation and oxidative stress, and reductions in body weight, blood pressure and hyperglycaemia [40, 42, 43].

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Alogliptin

The EXAMINE trial evaluated the cardiovascular safety profile of alogliptin (6.25 mg, 12.5 mg or 25 mg, dependent on eGFR) in T2D patients (HbA_{1c} 6.5–11.0%) hospitalised for acute coronary syndrome 15–90 days prior to randomisation [44]. A total of 5380 patients were recruited into the trial, with a median follow-up of 533 days. At baseline, 29.1% of participants had eGFR < 60 ml/min/1.73 m^2. During the study, 0.9% of participants using alogliptin were initiated on renal dialysis compared with 0.8% of participants using placebo. Participants using alogliptin had similar changes in their eGFR to participants receiving placebo. The reported renal outcomes are presented in Table 3.

Saxagliptin

The SAVOR-TIMI 53 trial primarily assessed the cardiovascular safety of saxagliptin (2.5 mg or 5 mg, dependent on eGFR) versus placebo [45]. A total of 16,492 participants aged ≥ 40 years with T2D (HbA_{1c} 6.0–12.0%) and a history or significant risk of cardiovascular disease were followed for a median duration of 2.1 years. At baseline, 15.6% of participants had eGFR < 50 ml/min/1.73 m^2. At the end of treatment, participants using saxagliptin were more likely to have an improved urinary ACR and less likely to have a worse urinary ACR than participants receiving placebo. Participants receiving saxagliptin demonstrated a mean improvement in urinary ACR of 34.3 mg/g compared with placebo. There was no significant difference in the renal composite outcome (saxagliptin 2.2% vs placebo 2.0%), doubling of serum creatinine (saxagliptin 2.02% vs placebo 1.82%), initiation of RRT (saxagliptin 0.61% vs placebo 0.67%) or renal death between groups [46]. Specific renal outcome measures are detailed in Table 3.

Sitagliptin

The TECOS trial primarily assessed the cardiovascular safety of sitagliptin (50 mg or 100 mg, dependent on eGFR) compared with placebo [47]. In total, 14,671 participants aged ≥ 50 years with T2D (HbA_{1c} 6.5–8.0%) and established cardiovascular disease were followed up for a median of 3.0 years. At baseline, just 9.4% of participants had eGFR < 50 ml/min/1.73 m^2. The mean change in eGFR in participants was -4.0 ml/min/1.73 m^2, compared with -2.8 ml/min/1.73 m^2 in those receiving placebo over 48 months. From the limited data available on urinary ACR collected in this trial, participants using sitagliptin demonstrated a marginally lower (by 0.18 mg/g) mean urinary ACR than participants receiving placebo [48].

Linagliptin

The CARMELINA trial primarily assessed the cardiovascular safety of linagliptin (5 mg) in people aged ≥ 18 years with T2D (HbA_{1c} 6.5–10.0%), and included participants at high cardiovascular and renal risk [49]. In total, 6979 participants were randomised to receive linagliptin or control, and were observed for a median 2.2 years. At baseline, 74% and 15.2% of participants had eGFR 30–59 ml/min/1.73 m^2

Table 3 Renal outcomes in incretin-based therapy cardiovascular outcome trials

Trial	Composite renal outcome measure	Progression of albuminuria	eGFR/creatinine	Incidence of ESRD	Death from a renal cause
EXAMINE trial (alogliptin) *n* = 5380	Not reported	Not reported	Alogliptin vs placebo[a]: eGFR < 30: + 0.2 vs + 1.6 eGFR 30–59: + 1.1 vs + 2.1 eGFR 60–89: + 0.6 vs + 1.0 eGFR ≥ 90: − 6.7 vs. − 4.5	Alogliptin: 0.9% Placebo: 0.8%	Not reported
SAVOR-TIMI 53 (saxagliptin) *n* = 16,492	Saxagliptin: 2.2% Placebo: 2.0: (HR 1.08)	Worsened UACR: Saxagliptin: 13.3% Placebo: 15.9%	Saxagliptin: 2.02% Placebo: 1.82% (HR 1.1)	Saxagliptin: 0.61% Placebo: 0.67% (HR 0.90)	Saxagliptin: 0.1% Placebo: 0.1%
TECOS trial (sitagliptin) *n* = 14,671	Not reported	Sitagliptin: − 0.18 mg/g vs placebo	Sitagliptin: − 4.0[a] Placebo: − 2.8[a]	Not reported	Not reported
CARMELINA trial (linagliptin) *n* = 6979	Linagliptin: 9.4% Placebo: 8.8% (HR 1.04)	Linaglipitin: 35.3% Placebo: 38.5% (HR 0.86)	Linaglipitin: 7.5% Placebo: 6.9%	Linaglipitin: 1.8% Placebo: 1.8%	Linaglipitin: 0.03% Placebo: 0.03%
ELIXA trial (lixisenatide) *n* = 6068	Not reported	Mean change in urinary ACR (lixisenatide vs placebo): normoalbuminuria (− 1.69 vs − 11.69%), microalbuminuria (− 21.10 vs − 42.45%), or macroalbuminuria (− 39.18 vs − 68.53%)	Lixisenatide: 1.35% Placebo: 1.15% (HR 1.16)	Not reported	Not reported

Table 3 continued

Trial	Composite renal outcome measure	Progression of albuminuria	eGFR/creatinine	Incidence of ESRD	Death from a renal cause
LEADER trial (liraglutide) *n* = 9340	Liraglutide: 5.7% Placebo: 7.2% (HR 0.78)	Liraglutide: 3.4% Placebo: 4.6% (HR 0.74)	Liraglutide: 1.9% Placebo: 2.1% (HR 0.89)	Liraglutide: 1.2% Placebo: 1.4% (HR 0.87)	Liraglutide: 0.17% Placebo: 0.11% (HR 1.59)
SUSTAIN-6 trial (semaglutide) *n* = 3297	Semaglutide: 3.8% Placebo: 6.1% (HR 0.64)	Semaglutide: 2.7% Placebo: 4.9% (HR 0.54)	Semaglutide: 1.1% Placebo: 0.8% (HR 1.28)	Semaglutide: 0.7% Placebo: 0.7% (HR 0.91)	Not reported
PIONEER-6 (semaglutide) *n* = 3183	Not reported	Not reported	eGFR ratio (baseline:end of study) Exenatide: 0.98 Placebo: 0.98	Not reported	Semaglutide: 0% Placebo: 0.1%
EXSCEL trial (exenatide) *n* = 14,752	Exenatide: 5.8% Placebo: 6.5% (HR 0.85)	Exenatide: 2.2% Placebo: 2.8%	Exenatide: 3.5% Placebo: 4.6%	Exenatide: 0.7% Placebo: 0.9%	Exenatide: 1.0% Placebo: 0.9%
HARMONY Outcomes (albiglutide) *n* = 9463	Not reported	Not reported	Change in GFR (albiglutide vs placebo): 8 months: − 1.11[a] 16 months: − 0.43[a]	Not reported	Not reported
REWIND study (dulaglutide) *n* = 9901	Dulaglutide: 17.1% Placebo: 19.6% (HR 0.85)	Dulaglutide: 8.9% Placebo: 11.3% (HR 0.77)	Dulaglutide: 9.2% Placebo: 10.1% (HR 0.89)	Dulaglutide: 0.3% Placebo: 0.4% (HR 0.75)	Not reported

The number of participants in each trial is denoted by *n*
eGFR estimated glomerular filtration rate, *ESRD* end-stage renal disease, *HR* hazard ratio, *ACR* albumin-to-creatinine ratio
[a] Units ml/min/1.73 m^2

and < 30 ml/min/1.73 m^2, respectively. The definitions used for renal outcomes are detailed in Table 1. There was no significant difference in the risk of developing the renal composite outcome in participants using linagliptin compared to those using placebo (9.4 vs. 8.8%, HR 1.04). There was a lower proportion of participants using linagliptin who were observed to have significant progression of albuminuria compared to participants receiving placebo (35.3 vs 38.5%, HR 0.86). There were no significant differences in the proportions of participants who developed a sustained ≥ 40% decrease in eGFR, were initiated on RRT or died from a renal cause. Specific reported renal outcomes are presented in Table 3.

GLUCAGON-LIKE PEPTIDE-1 ANALOGUES

Lixisenatide

The ELIXA study was the first CVOT to report outcomes for a GLP-1 analogue; it evaluated lixisenatide (10 μg or 20 μg) against placebo [50]. A total of 6068 participants with T2D (HbA_{1c} 5.5–11.0%) and an acute coronary event within 180 days of screening were observed for a median 25 months. At baseline, 23.2% of participants had eGFR < 60 ml/min/1.73 m^2. The definitions used for renal outcomes are detailed in Table 1. Compared to participants who received placebo, a reduced mean percentage change in the urinary ACR was seen in participants who were prescribed lixisenatide and had normoalbuminuria (− 1.69 vs − 11.69%), microalbuminuria (− 21.10 vs − 42.45%) or macroalbuminuria (− 39.18 vs − 68.53%) at baseline. The significantly reduced risk for developing macroalbuminuria in those receiving lixisenatide was maintained when it was adjusted for the improvement in HbA_{1c} (HR 0.81). Doubling of the serum creatinine level occurred in about 1% of the participants in each study group, and there was no significant difference between groups in renal adverse events [51]. The renal outcomes are presented in Table 3.

Liraglutide

The LEADER study principally aimed to assess the cardiovascular safety profile of liraglutide (1.8 mg) compared with placebo [52]. Over a median of 3.8 years, a total of 9340 participants aged ≥ 50 years with T2D (HbA_{1c} ≥ 7.0%) who had a history of cardiovascular disease and were using liraglutide or placebo were observed. At baseline, 23.1% of participants had eGFR < 60 ml/min/1.73 m^2. The definitions used for renal outcomes are summarised in Table 1. The composite renal outcome was observed less frequently in participants using liraglutide compared with those using placebo (5.7 vs 7.2%, HR 0.78). The authors comment that this was largely driven by a reduction in progression to macroalbuminuria in participants using liraglutide compared to those using placebo (3.4 vs 4.6%, HR 0.74), with no significant differences in the observed rates of a doubling of the serum creatinine, initiation of RRT or renal death [53]. Specific renal outcomes are presented in Table 3.

Semaglutide

The SUSTAIN-6 study assessed the cardiovascular safety of semaglutide (0.5 mg or 1.0 mg weekly) versus placebo [54]. The study observed 3297 participants with T2D (HbA1c ≥ 7.0%) and a previous history or a high risk of cardiovascular disease over a median of 2.1 years. At baseline, 28.5% of participants had eGFR < 60 ml/min/1.73 m^2. Definitions used for renal outcomes are detailed in Table 1. New or worsening nephropathy was observed in 3.8% of the participants using semaglutide compared with 6.1% using placebo (HR 0.64). Again, this was primarily driven by a reduction in incident macroalbuminuria in participants using semaglutide (2.7 vs 4.9%, HR 0.54), with no significant differences in the rate of a doubling of serum creatinine or the rate of initiation of RRT. These results are presented in Table 3.

The PIONEER-6 trial primarily evaluated the cardiovascular safety of oral semaglutide (14 mg) compared with placebo [55]. A total of

3183 participants aged ≥ 50 years with a history or a significant risk of cardiovascular disease were observed for a median of 15.9 months. At baseline, 26.9% of participants had eGFR < 60 ml/min/1.73 m^2. There was no significant reported difference in the eGFR ratio from baseline to the end of treatment (0.98 for both groups) or in the rate of renally related death. At the time of writing, no further renal outcomes were reported.

Exenatide

The EXSCEL trial evaluated the cardiovascular safety of exenatide (2 mg weekly) [56]. In total, 14,752 participants with T2D (HbA_{1c} 6.5–10.0%) with or without a history of cardiovascular disease were observed for a median of 3.2 years. At baseline, 21.6% of participants had eGFR < 60 ml/min/1.73 m^2. Definitions used for renal outcomes are presented in Table 1. A significantly lower proportion of participants attained the renal composite outcome measure in the exenatide group compared to the placebo group (5.8 vs 6.5%, HR 0.85). Rates of macroalbuminuria, worsening eGFR and need for RRT were lower in exenatide-treated participants than in the placebo group [57]. Specific renal outcomes are shown in Table 3.

Albiglutide

The HARMONY Outcomes study evaluated the cardiovascular safety of albiglutide (30–50 mg) compared with placebo [58]. A total of 9463 participants aged ≥ 40 years with T2D and a history of cardiovascular disease were observed for a median of 1.6 years. The mean difference in eGFR between participants receiving albiglutide and those receiving placebo was − 1.11 ml/min/1.73 m^2 and − 0.43 ml/min/1.73 m^2 at 8 and 16 months, respectively.

Dulaglutide

The REWIND study evaluated the cardiovascular safety of dulaglutide (1.5 mg) compared with placebo [59]. In total, 9901 participants aged ≥ 50 years with T2D and a history or a high risk of cardiovascular disease were observed for a median of 5.4 years. The composite renal outcome developed less frequently in participants using dulaglutide compared to those using placebo (17.1 vs 19.6%, HR 0.85). Just as for other GLP-1 analogues, this appeared to be principally a result of reduced incident macroalbuminuria (HR 0.77), but the composite outcome was also influenced by reductions in the rates of a sustained decline in eGFR (HR 0.89) and the need for RRT (HR 0.75) [60]. Renal outcome measures are detailed in Table 3.

ONGOING CARDIOVASCULAR AND RENAL OUTCOME TRIALS

Several ongoing trials are evaluating the impact of newer diabetes therapies on renal outcomes. Intriguingly, some of these studies involve people without diabetes.

Dapa-CKD

The Dapa-CKD study aims to compare the impacts of dapagliflozin (5 mg or 10 mg) and placebo on renal and cardiovascular outcomes in CKD patients with or without diabetes [61]. The primary composite outcome is a ≥ 50% sustained decline in eGFR and development of ESRD (sustained eGFR < 15 ml/min/1.73 m^2, chronic dialysis treatment or renal transplant). The estimated enrolment includes 4000 participants aged ≥ 18 years with an eGFR of 25–75 ml/min/1.73 m^2 and albuminuria at baseline (200–5000 mg/g) who are currently treated with ACE inhibitors or ARBs. The study started in February 2017 and it is estimated that it will be completed in November 2020.

EMPA-KIDNEY

The EMPA-KIDNEY study aims to evaluate the effect of empagliflozin (10 mg) on the progression of renal disease or cardiovascular death in diabetic and nondiabetic patients with CKD [62]. The primary composite outcome is a sustained ≥ 40% decline in eGFR or the development of ESRD (sustained decline in eGFR

to < 10 ml/min/1.73 m^2, chronic dialysis treatment or renal transplant) or cardiovascular death. The estimated enrolment is 5000 participants aged ≥ 18 years with eGFR 20–45 ml/min/1.73 m^2 or eGFR 45–90 ml/min/1.73 m^2 with urinary ACR ≥ 200 mg/g treated with either ACE inhibitor or ARB (unless they are not tolerated). The study started in January 2019 and is estimated to be completed in June 2022.

EMPEROR

There are two EMPEROR trials: EMPEROR-Preserved and EMPEROR-Reduced. The EMPEROR-Preserved trial aims to evaluate the safety of empagliflozin (10 mg) versus placebo in about 5750 T2D and non-T2D participants with heart failure and a preserved ejection fraction (EF). Secondary outcomes include the effect of empagliflozin on renal function and mortality [63]. Inclusion criteria include age ≥ 18 years, chronic heart failure, EF > 40%, and elevated NT-proBNP. This trial commenced in March 2017 and is due to complete in November 2020 [64].

The EMPEROR-Reduced trial aims to evaluate the safety of empagliflozin (10 mg) versus placebo in 3600 T2D and non-T2D participants with heart failure and a reduced EF. Secondary outcomes include the effects on renal function and mortality [65]. Inclusion criteria include age ≥ 18 years, chronic heart failure, EF ≤ 40%, elevated NT-proBNP, and that the patient is receiving appropriate medical therapy for their heart failure. This trial commenced in March 2017 and is due to be completed in July 2020 [66].

CONCLUSIONS

As pharmacological therapies for T2D proliferate, it is important to establish the renal safety and efficacy of these medications in order to improve outcomes in this difficult-to-treat group and achieve important economic benefits. The trials published to date indicate that SGLT-2 inhibitors have significant and clinically important benefits for renal outcomes; in particular, they reduce the rate of progression to macroalbuminuria and delay the decline in GFR associated with enduring diabetes. Whilst DPP4 inhibitors may improve the rate of progression of albuminuria in people with T2D, these drugs do not seem to influence the progression of eGFR decline, the incidence of ESRD or the rate of renal death. Moreover, the degree of heterogeneity in the published renal outcomes from DPP4 inhibitor trials is considerable. More consistently and significantly, GLP-1 analogues reduce the progression of albuminuria, but they have no consistently reported impact on changes in eGFR or the incidence of ESRD in this cohort.

Heterogeneity in patient recruitment and reported renal outcomes in CVOTs limits the interpretation of drug class effects on renal disease outcomes. In particular, differences in the degree of renal and cardiovascular disease in participants at baseline are considerable. More recent and ongoing studies show greater emphasis on and consistency towards renal outcomes, and are highly relevant to the future treatment and prevention of DKD in people with T2D.

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