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Review

The potential of GLP-1 receptor agonists in type 2 diabetes and chronic kidney disease: from randomised trials to clinical practice

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***Abstract*:** Chronic kidney disease (CKD) affects around 10% of the global population and is most often caused by diabetes. Diabetes with CKD (diabetic kidney disease, DKD) is a progressive condition that may cause kidney failure and which contributes significantly to the excess morbidity and mortality in these patients. DKD is treated with direct disease-targeting therapies like blockers of the renin–angiotensin system, sodium–glucose cotransporter-2 (SGLT-2) inhibitors and non-steroidal mineralocorticoid receptor antagonists as well as indirect therapies impacting hyperglycaemia, dyslipidaemia, obesity and hypertension, which all together reduce disease progression. While no glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are currently indicated to improve kidney outcomes, accumulating evidence from cardiovascular outcomes trials (CVOTs) corroborates a kidney-protective effect in people with T2D and CKD, and GLP-1 RAs are now mentioned in international treatment guidelines for type 2 diabetes (T2D) with CKD. GLP-1 RAs are indicated to improve glycaemia in people with T2D; certain GLP-1 RAs are also approved for weight management and to reduce cardiovascular risk in T2D. Ongoing pivotal trials are assessing additional indications, including T2D with CKD. In this article, we review and discuss kidney outcomes from a multitude of completed clinical trials as well as real-world evidence and ongoing clinical trials.

Keywords: diabetic kidney disease, chronic kidney disease, type 2 diabetes, diabetes, GLP-1 receptor agonists, kidney outcomes

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Introduction

Diabetes is the most common cause of chronic kidney disease (CKD),[1] and diabetes with CKD is often referred to as diabetic kidney disease (DKD).[2,3] DKD is a serious progressive disease that contributes markedly to the high burden of morbidity or mortality associated with diabetes.[3,4] While undiagnosed in a large group of the affected individuals, the estimated worldwide prevalence of CKD is around 9–10% of the total population based on data from 2017[4] with some projections suggesting an even higher occurrence.[5] Around 30% of people with type 1 diabetes and 40% of those with type 2 diabetes (T2D) develop DKD.[6] DKD is the most prevalent cause of kidney failure, accounting for almost 50% of all cases.[7,8]

The pathophysiology of CKD and DKD is not described in all details, and it is often not possible to fully separate the two definitions.[1–3] Accordingly, while we in the present review use the DKD term, others have argued that describing the condition as 'diabetes with CKD' better reflects that the dysfunctional kidney in people with diabetes and kidney disease may in some cases be the result of various acute and chronic conditions not specifically caused by diabetes, such as acute kidney injury, glomerular atherosclerosis and

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kidney-specific vascular disease.[2] Nevertheless, the interrelated metabolic derangements associated with especially T2D, such as hyperglycaemia, dyslipidaemia, obesity and hypertension play a major role in the aetiology of DKD.[2] The prevailing hypothesis is that DKD represents the renal manifestation of the toxic excess glucose levels characterising type 1 diabetes and T2D alike, which leads to diverse pathogenic processes throughout the body, including in the endothelial cells in the kidney and elsewhere. In CKD, including DKD, the ensuing renal dysfunction manifests clinically as excess urinary excretion of proteins, including albumin, and reduced glomerular filtration rate (GFR),[2] both of which are individual risk markers for CKD and cardiovascular disease (CVD) progression.[9,10]

The recent introduction of sodium–glucose cotransporter-2 (SGLT-2) inhibitors[11,12] and a third-generation, non-steroidal mineralocorticoid receptor antagonist, finerenone,[12,13] has greatly improved the treatment armamentarium for DKD. Some SGLT-2 inhibitors have been proven effective in reducing the risk of kidney failure and cardiovascular events.[14–16] Nevertheless, current treatment options remain sparse and of insufficient efficacy on preventing progression of CKD; people with DKD continue to experience declining kidney function, they often suffer from poor health-related quality of life, and some ultimately develop kidney failure and a need for kidney replacement therapy.[4] Thus, additional efficacious and well-tolerated therapeutic strategies to prevent or manage DKD are still needed.

In this article, we review current evidence supporting the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as kidney-protective agents in the management of T2D with CKD. GLP-1 RAs are efficacious and well-tolerated glucose-lowering agents regardless of kidney function.[17] In addition, GLP-1 RAs have proven benefits on weight loss, and certain members of the drug class reduce cardiovascular risk.[17] Because no dedicated kidney outcomes trial has yet been completed with GLP-1 RAs, none of the agents are currently indicated to improve kidney outcomes. However, one such outcomes trial is ongoing with the GLP-1 RA semaglutide (FLOW, Clinicaltrials.gov ID NCT03819153). At this time, the drug class is recommended as second-line therapy (after metformin and SGLT-2 inhibitors) in current guidelines to improve glycaemic control and reduce cardiovascular risk in people with T2D and CKD.[18,19]

The GLP-1 RA drug class

GLP-1 is a hormone of the incretin system and is secreted from the L-cells of the intestines upon food intake. The biology of the hormone has been comprehensively reviewed by others.[20] Briefly (Figure 1), GLP-1 receptors are present in many tissues; however, their current therapeutic use in diabetes primarily exploits the ability of GLP-1 to reduce blood glucose by potentiating insulin release and by reducing glucagon secretion, both in a blood glucose-dependent manner. Furthermore, because GLP-1 increases satiety via effects in the brain, the drug class has also been developed for weight management, that is, weight reduction and maintenance in people with obesity or overweight. The half-life of endogenous GLP-1 is short (1–2 min), mainly due to the rapid degradation by dipeptidyl peptidase IV (DPP-IV). The pharmacological use of GLP-1 has been made possible by the discovery of the exendin-4 peptide in the Gila monster; this peptide activates the human GLP-1 receptor but is resistant to DPP-IV-mediated degradation. In addition, human native GLP-1 has been modified using recombinant technologies to also resist DPP-IV degradation and, for example, to facilitate the formation of circulating albumin-bound depots for even longer durations of action following subcutaneous (s.c.) or oral administration.

The GLP-1 RA drug class comprises the exendin-4-based peptides exenatide, lixisenatide and efpeglenatide, and the human recombinant peptide RAs dulaglutide, liraglutide and semaglutide (Table 1). These agents are indicated (or currently in development as regards efpeglenatide) to improve glycaemic control in people with T2D[17] and for weight management (liraglutide and semaglutide).[21,22] Certain GLP-1 RAs are available to reduce incident cardiovascular risk in people with T2D and established CVD or multiple cardiovascular risk factors (dulaglutide, liraglutide and once-weekly s.c. semaglutide).[23] Most GLP-1 RAs are administered *via* s.c. injections on a daily or, for the newer-generation GLP-1 RAs, weekly basis. A tablet-based once-daily option for oral administration is available for semaglutide.[24] Finally, albiglutide, a GLP-1 RA constructed as a GLP-1/albumin fusion protein was previously marketed in the United States and EU for use in T2D.[25]

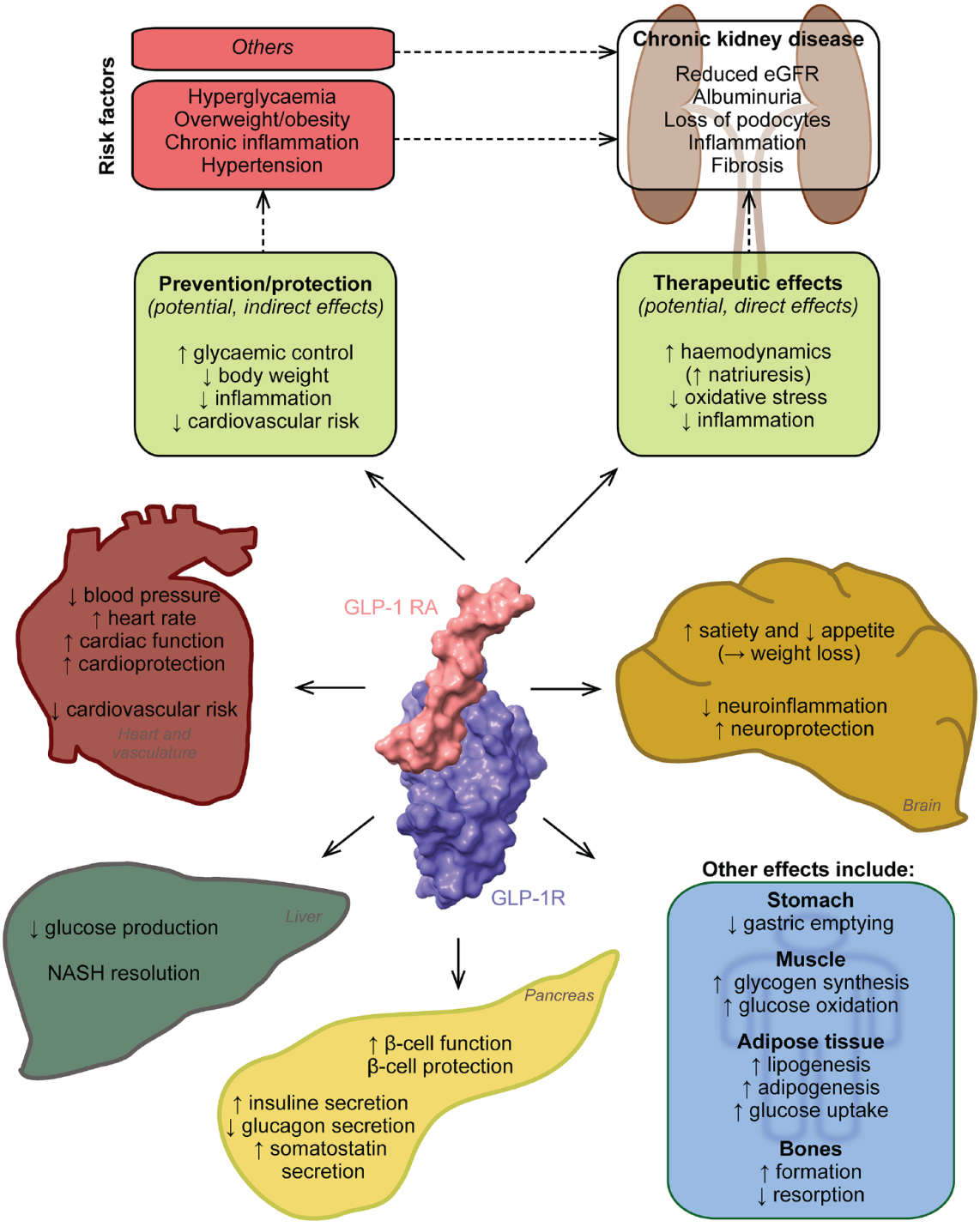

Figure 1. Potential kidney-protective and other effects of GLP-1 receptor agonists.
Chronic kidney disease can have multiple causes, including those associated with diabetes, such as chronic hyperglycaemia, overweight or obesity, chronic inflammation and hypertension. GLP-1 RA treatment improves glycaemic control, and reduces, body weight, inflammation and hypertension. These effects are suggested to help prevent or attenuate progression of kidney disease. GLP-1 RA therapy may also address chronic kidney disease directly, and can also impact several other tissues and organs, including the heart and vasculature, as well as the brain, liver, pancreas and others. Dashed arrows indicate putative effects and actions; full-line arrows indicate well-established effects of GLP-1 RAs on key target organs and tissues. The GLP-1 RA depicted is semaglutide bound to the extracellular domain of the GLP-1 receptor (GLP-1R); rendered in ChimeraX based on the crystal structure published as 4zgm (PDB). Additional details are available in the text.

Table 1. Cardiovascular outcomes trials for GLP-1 receptor agonist.

Compound	Indication(s) and dose	Cardiovascular outcomes trials (type 2 diabetes indication)						
				Baseline characteristics				
			Population and median follow-up	eGFR (ml/min/1.73 m²)	SBP/DBP (mmHg)	HbA_{1c} (%)	BMI (kg/m²)	Age (years)
Exendin-4-based GLP-1 receptor agonists								
Lixisenatide	T2D: 10 or 20 μg per day, s.c.	ELIXA[26] *n* = 6068	T2D + ACS 2.1 years	78	129/78	7.7	30	60
Exenatide	T2D: 2 mg per week, s.c.	EXSCEL[27] *n* = 14,752	T2D ± CVD 3.2 years	77	135/76	8.1	33	62
Efpeglenatide	N/A; 4 or 6 mg per week, s.c.	AMPLITUDE-O[28] *n* = 4076	T2D ± CVD 1.8 years	72	135/77	8.9	33	65
Human-based GLP-1 receptor agonists								
Dulaglutide	T2D: 1.5 or 3 mg per week, s.c. CVD: 1.5 or 3 mg per week, s.c.	REWIND[29] *n* = 9901	T2D ± CVD 5.4 years	78	137/79	7.3	32	66
Liraglutide	T2D: 1.2 or 1.8 mg per day, s.c. WM: 3.0 mg per day, s.c. CVD: 1.2 or 1.8 mg per day, s.c.	LEADER[30] *n* = 9340	T2D ± CVD 3.8 years	80	136/77	8.7	33	64
Semaglutide, s.c.	T2D: 0.5 or 1 mg per week, s.c. WM: 2.4 mg per week, s.c. CVD: 0.5 or 1 mg per week, s.c.	SUSTAIN 6[31] *n* = 3297	T2D ± CVD 2.1 years	76	136/77	8.7	33	65
Semaglutide, oral	T2D: 7 or 14 mg per day, oral	PIONEER 6[32] *n* = 3183	T2D ± CVD 1.3 years	74	136/76	8.2	32	66

Indications and regimen are according to the US prescribing information and may differ across regions. Data are means.
ACS, acute coronary syndrome; BMI, body mass index; CVD (indication), reduction of risk of major adverse cardiovascular events in people with type 2 diabetes and at high cardiovascular risk according to the prescribing information; CVD (trial population), people with established cardiovascular disease or with cardiovascular risk factors; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; N/A, not available or not applicable; n, number of randomised participants; s.c. subcutaneous; SBP, systolic blood pressure; T2D, type 2 diabetes; WM, weight management.

Kidney-related efficacy results with GLP-1 RAs

As outlined above, there is a well-established strong association between DKD/CKD and cardiovascular mortality and morbidity, including a markedly increased risk of heart failure (HF) and atherosclerotic CVD.[33] Indeed, the cardiovascular prognosis following a diabetes diagnosis greatly worsens if the person also develops CKD.[34] On the other hand, DKD may also precipitate or exacerbate CVD.[35] In response to injuries or impaired function, the kidney may be involved in mechanisms that mediate aberrant vascular changes, which can essentially initiate a vicious circle leading to progressive loss of kidney function. Because of the strong association between CKD and CVD, clinical trials investigating the cardiovascular effects of GLP-1 RAs in populations enriched for high cardiovascular risk de facto also comprise many participants at high risk of kidney disease.[36] Therefore, currently, the

most robust evidence on the kidney-beneficial effects of GLP-1 RAs is data collected in the dedicated cardiovascular outcomes trials (CVOTs) completed for all GLP-1 RAs (Table 1 and Figure 2). Some of the CVOTs were in fact enriched for people with pre-existing kidney disease, and most have evaluated kidney outcomes as secondary or exploratory endpoints. Composite kidney outcomes have been used across the CVOTs, and even though the definitions and components of the composites have differed slightly, they are sufficiently alike to allow for comparisons across trials and for meta-analysis. Outcomes definitions are available in Figure 2. In general, analysis of data from these CVOTs has indicated that GLP-1 RAs may offer kidney-protective benefits (Figure 1). It is important, however, to be aware that kidney outcomes were evaluated as secondary endpoints and that the trials were not powered or otherwise specifically designed to confirm the effects of GLP-1 RAs on kidney-related clinical outcomes and on kidney function and kidney damage [usually evaluated using estimated GFR (eGFR) and albuminuria]. While albuminuria has been shown to be well correlated with clinical kidney outcomes, it remains a surrogate endpoint with the relatively lowest importance following the clinical outcomes and eGFR, including eGFR slope.

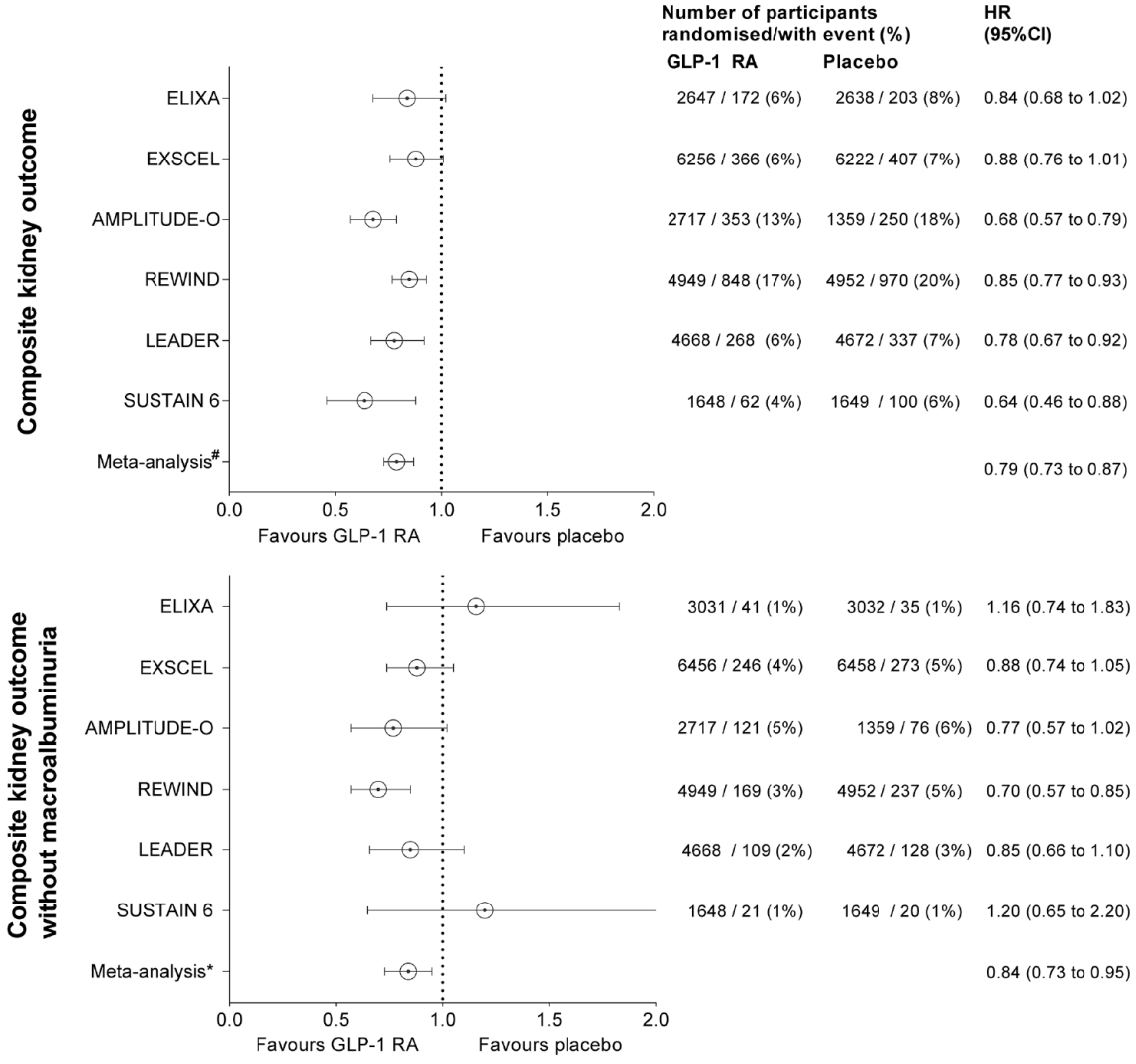

Figure 2. *(Continued)*

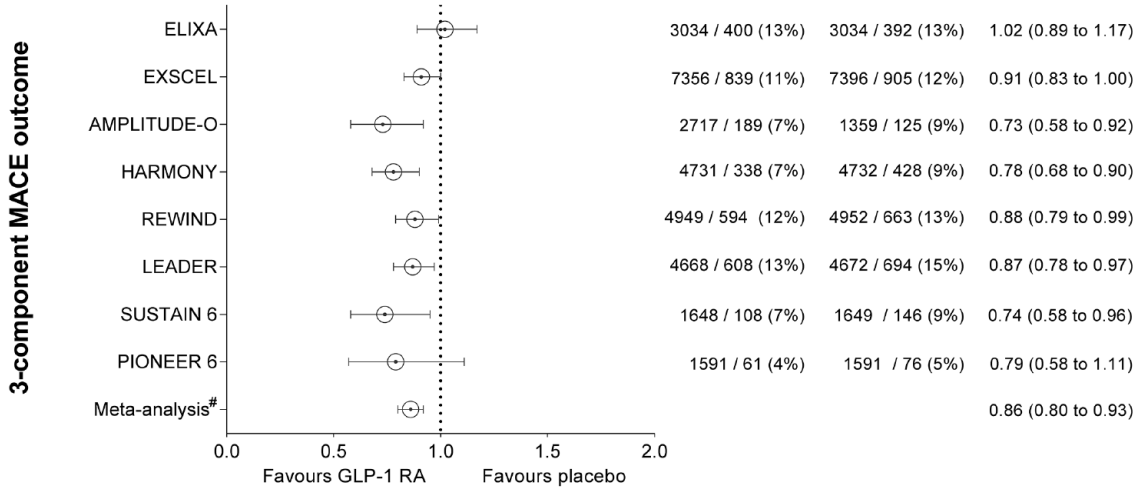

Figure 2. Kidney outcomes and primary MACE outcome from CVOTs with GLP-1 receptor agonists.
#Meta-analysis (random effects) from Sattar *et al.*[37] *Meta-analysis using the random effects method that assumes varying treatment effects across the included cardiovascular outcomes trials; $I^2 = 28.7$. CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event; RA, receptor agonist. Composite kidney outcome[37]: ELIXA: new-onset macroalbuminuria; EXSCEL: new-onset persistent macroalbuminuria, ⩾40% worsening of eGFR, kidney replacement therapy, death due to kidney disease; AMPLITUDE-O: new macroalbuminuria with UACR increase ⩾30% from baseline, sustained eGFR decrease ⩾40% from baseline, sustained eGFR < 15 ml/min/1.73 m^2, or kidney replacement therapy (⩾90 days).; REWIND: new-onset macroalbuminuria, ⩾30% eGFR decrease, kidney replacement therapy; LEADER and SUSTAIN 6: new-onset macroalbuminuria, doubling of serum creatinine, kidney replacement therapy, death due to kidney disease. Composite kidney outcome without macroalbuminuria: ELIXA[38]: doubling of serum creatinine; EXSCEL[39]: ⩾40% worsening of eGFR, kidney replacement therapy, death due to kidney disease; AMPLITUDE-O[28]: kidney function outcome [eGFR of at least 40% for 30 days or more, end-stage kidney disease (defined as dialysis for ⩾90 days, kidney transplantation, or an eGFR of < 15 ml per minute per 1.73 m^2 for ⩾30 days), or death from any cause]; REWIND[40]: sustained ⩾40% worsening of eGFR; LEADER[30]: persistent doubling of serum creatinine (and eGFR < 45 ml/min/1.73 m^2) or need for continuous renal replacement therapy (end-stage kidney disease); SUSTAIN 6 (Novo Nordisk, data on file): doubling of serum creatinine; kidney replacement therapy, death due to kidney disease. 3-component MACE: cardiovascular death, myocardial infarction and stroke.[37]

Lixisenatide: ELIXA

Lixisenatide was evaluated for its cardiovascular effects in the ELIXA CVOT.[26,38] This trial was different from the remainder of the CVOTs discussed in this review in that only ELIXA enrolled people with a recent acute coronary syndrome. Moreover, although lixisenatide like some other GLP-1 RAs is to be dosed once daily, the half-life of lixisenatide is considerably shorter (2–3 h) than that of all other once-daily GLP-1 RAs.

Lixisenatide reduced the urinary albumin-to-creatinine ratio (UACR); the placebo-adjusted reductions were statistically significant in participants with macroalbuminuria (39.2%; 95% CI = −68.5 to −9.8) but not in those with normoalbuminuria (1.7%; 95% CI = −11.7 to 8.3) or microalbuminuria (21.1%; 95% CI = −42.3 to 0.04). A nominal benefit was shown in terms of the effect of lixisenatide on the risk of new-onset macroalbuminuria (HR = 0.84; 95% CI = 0.68–1.02) (Figure 2); when adjusting for baseline HbA_{1c}, a statistically significant relative risk reduction of 19% was found (0.81; 95% CI = 0.66–0.99).[38]

Exenatide: EXSCEL

Exenatide is an exendin-4-based GLP-1 RA, the cardiovascular effects of which were investigated in the EXSCEL CVOT.[27] Kidney outcomes were reported separately using two pre-specified composite outcomes[41]; one with and one without new macroalbuminuria. For each of the two outcomes, a relative risk reduction of 12% was shown for exenatide based on the unadjusted HR of 0.88 (Figure 2). The relative risk reduction for the outcome that includes new macroalbuminuria was statistically significant when adjusting for various demographic factors (HR = 0.85, 95% CI = 0.73–0.98). Onset of macroalbuminuria during the EXSCEL trial was less frequent with exenatide than with placebo but the difference was not

statistically significant (adjusted HR = 0.84, 95% CI = 0.70–1.07).

Efpeglenatide: AMPLITUDE-O

The most recently completed CVOT among the GLP-1 RAs is the AMPLITUDE-O trial, which evaluated the once-weekly exendin-4-based GLP-1 RA efpeglenatide *versus* placebo.[28] Efpeglenatide was associated with a statistically significant 32% relative risk reduction (HR = 0.68; 95% CI = 0.57–0.79) for the composite kidney outcome, including macroalbuminuria compared with placebo (Figure 2). For a pre-defined kidney function outcome (⩾40% eGFR decline for ⩾30 days, kidney failure or all-cause death), a HR of 0.77 (95% CI = 0.57–1.02) was found (Figure 2). In addition, efpeglenatide treatment appeared to attenuate the decline in eGFR when compared with placebo [estimated treatment difference 0.87 ml/min/1.73 m^2 (95% CI = 0.27–1.51)].

Dulaglutide: REWIND and AWARD-7

Most data on the renal effects of the GLP-1 RA dulaglutide originate from the REWIND CVOT in individuals with T2D and increased CV risk,[29] as well as from the AWARD-7 randomised controlled trial comparing dulaglutide *versus* glargine for metabolic effect in people with T2D and advanced CKD.[42] In REWIND, dulaglutide statistically significantly reduced the risk of a pre-defined kidney outcome by 15% *versus* placebo (HR = 0.85, 95% CI = 0.77–0.93) (Figure 2), driven mainly by the lower incidence of new-onset macroalbuminuria (HR = 0.77, 95% CI = 0.68–0.87), whereas there were nominal but no statistically significant effects on the two other components [sustained decline in eGFR of at least 30% (HR = 0.89, 95% CI = 0.78–1.01) and need for chronic kidney replacement therapy (HR = 0.75, 95% CI = 0.39–1.44)].[29] A sensitivity analysis found a statistically significant relative risk reduction in terms of a sustained decline in eGFR of at least 50% (HR = 0.56, 95% CI = 0.41–0.76). In AWARD-7, a secondary endpoint was the decline in eGFR, which was statistically significantly more subtle after 1 year in participants treated with dulaglutide (especially the highest dose tested, that is, 1.5 mg once weekly) compared with those treated with insulin glargine.[42] Of note, the eGFR decline was in general more pronounced in AWARD-7 participants with pre-existing macroalbuminuria (urinary UACR > 300 mg/g).

Liraglutide: LEADER

In LEADER,[43] the CVOT for once-daily liraglutide, a secondary endpoint evaluated a composite kidney outcome (new onset of macroalbuminuria, doubling of serum creatinine, the need for continuous kidney replacement therapy or death from kidney disease), the risk of which was reduced by 22% (HR = 0.78, 95% CI = 0.67–0.92) with liraglutide compared with placebo (Figure 2) primarily driven by a reduction in new-onset persistent macroalbuminuria.[30] Importantly, data from LEADER have shown that liraglutide treatment appears to reduce the cardiovascular risk [as evaluated using the 3-component major adverse cardiovascular event (MACE) outcome] regardless of the presence of CKD.[44]Additional analyses for the cardiovascular effects of liraglutide have been consistent across subgroups by albuminuria or kidney function, and analyses of LEADER have suggested kidney benefits of liraglutide, especially in people with CKD.[44–49] Evaluations of data from LEADER have also contributed to establishing the safety of GLP-1 RAs in people with type diabetes and CKD as reviewed below.[50]

Semaglutide: SUSTAIN 6 and PIONEER 6

The cardiovascular effects of semaglutide were evaluated in the SUSTAIN 6[31] and PIONEER 6[32] CVOTs with once-weekly s.c. semaglutide and once-daily oral semaglutide, respectively. While SUSTAIN 6 included the same composite kidney outcome as evaluated in LEADER, PIONEER 6 evaluated the renal effects of oral semaglutide based on continuous eGFR measurements only. In SUSTAIN 6, s.c. semaglutide once weekly was associated with a statistically significant 36% relative risk reduction for the composite endpoint (Figure 2), which was driven primarily by the macroalbuminuria component.

Pooled analyses of LEADER, SUSTAIN 6 and PIONEER 6

A post hoc analysis using participant-level data pooled from LEADER and SUSTAIN 6 showed that liraglutide and semaglutide treatment was associated with a reduced risk of sustained CKD progression (assessed by eGFR).[51] The benefit was most pronounced in trial participants with pre-existing CKD and micro- and macroalbuminuria; in these participants, the risk of sustained ⩾30%, ⩾40%, ⩾50% or ⩾57% eGFR decline was statistically significantly lower by 35%, 36%,

43% and 44%, respectively (HRs *versus* placebo of 0.65, 0.64, 0.57 and 0.56, respectively; $p < 0.001$) when treated with liraglutide or semaglutide.[51] Likewise, kidney function as assessed by the eGFR slope declined less with liraglutide or semaglutide treatment compared with placebo[52]; this trend was more pronounced in participants who enrolled in LEADER or SUSTAIN 6 with pre-existing kidney disease (eGFR < 60 ml/min/1.73 m^2). Similarly, in comparison with placebo, liraglutide or semaglutide treatment significantly reduced the risk of a persistent 30% reduction in the UACR ($p < 0.0001$) as well as the risk of progressing from normoalbuminuria to micro- or macroalbuminuria ($p < 0.0001$) or from microalbuminuria to macroalbuminuria ($p = 0.0002$).[53]

When pooling data from SUSTAIN 6 and PIONEER 6, the decline in eGFR over a 2-year period was statistically significantly lower with semaglutide than with placebo [estimated treatment difference: 1.21 (95% CI = 0.62–1.80)][54]; again, while statistically significant regardless of pre-existing kidney impairment, the treatment effect at year 2 was numerically more pronounced in participants with a baseline eGFR between 30 and 60 ml/min/1.73 m^2.

Meta-analyses and effectiveness

In a recently updated[55] meta-analysis of kidney outcome data from six of the above-mentioned CVOTs, Sattar and colleagues showed that the GLP-1 RA drug class as a whole appears to be associated with a 21% reduction in incident kidney risk (HR = 0.79; 95% CI = 0.73–0.87) as evaluated using a composite kidney outcome that included macroalbuminuria.[37] Conducting the meta-analysis for this review while leaving out the macroalbuminuria component gave a statistically significant HR of 0.84 (95% CI = 0.73–0.95) (Figure 2). In a different analysis (excluding ELIXA), Sattar *et al.*[37] showed a statistically significant 18% relative risk reduction (HR = 0.82; 95% CI = 0.69–0.98) for a worsening of kidney function.

Results from CVOTs and randomised controlled trials largely represent assessments of efficacy obtained in controlled settings and from certain, pre-defined trial populations; the real-world effectiveness of GLP-1 RAs on kidney outcomes may be different in clinical practice. Interestingly, database studies supplying real-world evidence have indeed corroborated the above-mentioned data from the controlled clinical trials. In a Scandinavian cohort of people seen in clinical practice in Denmark, Norway and Sweden, serious kidney events were fewer in individuals using GLP-1 RAs compared with those who were on DPP-IV inhibitors; the risk of such events was 24% lower with GLP-1 RAs (HR = 0.76, 95% CI = 0.68–0.85).[56] In a Swedish cohort study, the corresponding relative risk reduction (GLP-1 RA use *versus* DPP-IV use) was 28% (adjusted HR = 0.72, 95% CI = 0.53–0.98) for the evaluated composite kidney outcome (sustained doubling of creatinine, kidney failure or kidney death).[57] Similarly, US military veterans using GLP-1 RAs had a 28% lower risk of a composite kidney outcome compared with those in the cohort who used sulfonylureas or DPP-VI inhibitors (HR = 0.68; 95% CI = 0.63–0.74).[58]

Safety and tolerability of GLP-1 RAs in people with CKD

The safety and tolerability of GLP-1 RAs are well established based on the clinical development programmes as well as extensive post-marketing experience.[17,59–61] In general, the drug class is associated with gastrointestinal side effects, primarily nausea, which are transient, related to treatment initiation and dose escalation, and mild to moderate in the majority of cases. To improve tolerability, gastrointestinal side effects are mitigated using a dose-escalation regimen. Gastrointestinal events, which can also include vomiting, may in rare cases lead to dehydration and, especially in people with pre-existing CKD, dehydration can lead to acute kidney injury. This is reflected in the prescribing information for GLP-1 RAs. However, analysis of data for semaglutide pooled from seven of the trials from the clinical development programme (SUSTAIN) did not find an increased risk of acute kidney injury with this GLP-1 RA[62]; similar findings were also apparent for liraglutide in the data from LEADER.[50]

Data from the CVOTs discussed in this review have corroborated the safety and tolerability of the use of GLP-1 RA in people with T2D and CKD. In LEADER, there was no difference in the overall occurrence of adverse events in the liraglutide *versus* placebo group according to the presence or absence of albuminuria,[50] and same trend was observed based on eGFR.

Because GLP-1 RAs function in a blood glucose-dependent manner, the risk of severe hypoglycaemic episodes is low[17] and primarily observed if treatment is combined with insulins or SUs. The risk of severe hypoglycaemia was found to be lower with liraglutide compared with placebo for people with reduced eGFR or albuminuria in LEADER (HRs = 0.63; 95% CI = 0.43–0.91 and 0.57, 95% CI = 0.40–0.82, respectively).[50]

The clearance of drug compounds often happens *via* the kidneys and may be lower when kidney function is impaired. In those cases, the blood concentration and half-life of the compound can be increased, resulting in an elevated risk of side effects. In persons with diabetes and impaired kidney function, many diabetes medications therefore need to be used with caution (e.g. at a reduced dose level) if at all. However, no reduction in dose is required for any of the GLP-1 RAs marketed today according to kidney function. Indeed, most of the agents can be used also in people with advanced CKD, while some are subject to restrictions due to lack of data.

In summary, safety and tolerability of the GLP-1 RAs have been thoroughly investigated in people with CKD and are well established.

Mechanisms of action

Currently, the mechanisms of action underlying the potential kidney-protective benefits of GLP-1 RAs in DKD are not fully elucidated (Figure 1). It has been speculated that the beneficial effects on CKD risk factors, such as blood glucose, systolic blood pressure and body weight indirectly improve kidney function, and mediation analyses using data from the LEADER, SUSTAIN 6 and REWIND CVOTs suggest that these effects partially, but only to a minor extent, explain the potential kidney benefits of GLP-1 RAs.[29,46] Nevertheless, considering the importance of obesity/overweight in CKD[63,64] and that SGLT2 inhibitors only modestly reduce body weight, the weight-reducing benefit of GLP-1 RAs may arguably be of importance in the management of CKD. In AWARD-7, a clinical benefit on kidney function (attenuated eGFR decline) of dulaglutide was observed even though glycaemic equipoise was ensured using an active comparator (insulin glargine), indicating that the kidney benefit was not driven by improvements in glycaemic control.[42]

Multiple direct actions have been suggested, including reductions in inflammation and oxidative stress and improved kidney oxygenation or perfusion; however, only a few smaller non-clinical and clinical studies have explored this. Furthermore, these studies have primarily focussed on the acute-phase response immediately after GLP-1 exposure in the setting of normal kidney function with or without diabetes.

While the effects of GLP-1 and GLP-1 RAs on oxidative stress have only been sparsely studied,[65,66] accumulating evidence are available to suggest that GLP-1 RAs reduce systemic inflammation and that semaglutide specifically down-regulate the expression of several pro-inflammatory genes.[67–70] Additional studies are warranted to investigate whether the potential anti-inflammatory effects of GLP-1 receptor agonism may in fact play a role in the potential kidney-protective benefit of the GLP-1 RA drug class or certain of the specific compounds.

Changes in kidney haemodynamics induced by GLP-1 RAs might depend on baseline kidney function and these observations have not been consistent across studies.[71–75] In the acute phase, GLP-1 RA therapy has been shown to induce natriuresis, and the increased salt delivery in the distal nephron could reduce intraglomerular pressure *via* tubular glomerular feedback.[76] Moreover, the compounds also suppress angiotensin II and renin,[71–75] thereby modulating the renin–angiotensin–aldosterone system (RAAS). The relevance of these findings is not fully established, however, and should be investigated in mechanistic clinical trials.

Summary and future perspectives

While results from the large, controlled clinical trials, meta-analyses and the available real-world evidence implies a potential kidney-protective effect of GLP-1 RAs in people with T2D and high cardiovascular risk, a dedicated, properly powered kidney outcomes trial in participants with CKD remains needed to confirm this hypothesis. To that end, the FLOW trial has been initiated (Clinicaltrials.gov ID NCT03819153); FLOW is a multinational, randomised, placebo-controlled, outcomes trial with a composite kidney outcome as the primary, confirmatory endpoint. The trial is currently ongoing testing the 1.0 mg s.c. version of the GLP-1 RA semaglutide *versus* placebo on top of standard of

care. As the primary objective, FLOW will evaluate whether semaglutide can delay the progression of kidney impairment and lower the risk of death from kidney failure or CVD in people with T2D and CKD, of whom the vast majority enrolled in the trial has been selected for very high risk of CKD progression. FLOW, which will enrol around 3,500 participants, is expected to finalise in mid 2024.

In addition, studies investigating the kidney-specific mechanisms of action for GLP-1 RA are warranted. Here, the REMODEL trial (ClinicalTrials.gov Identifier: NCT04865770), which enrols a trial population similar to the one in FLOW, is ongoing. REMODEL, as well as the SMART trial (ClinicalTrials.gov Identifier: NCT04889183) in people with overweight/obesity and elevated albuminuria but without diabetes, are expected to complement and expand on the scientific insights gained from the FLOW trial.

Another area that needs clarification is if there are particular segments among people with diabetes and CKD that may benefit the most from GLP-1 RA treatment. As discussed above, the most pronounced kidney risk reduction seems to be seen for individuals with pre-existing CKD. Studies like REMODEL and FLOW may provide insights that could help optimising therapy.

Dual agonists activating the GLP-1 receptor and the receptor of the other major hormone of the incretin system, gastric inhibitory polypeptide (GIP), are also in clinical development.[77] Such and other combination therapies that integrate a GLP-1 RA and additional relevant compounds may hold additional potential.[77] Results from the SURPASS programme for tirzepatide have shown that this dulaglutide-based GLP-1/GIP dual agonist provide profound glycaemic and weight-related benefits,[78] which may translate into corresponding kidney-protection. Furthermore, the combination of the once-weekly GLP-1 RA semaglutide and the amylin analogue, cagrilintide, has displayed similar promising efficacy results on body weight that seem to go beyond what is achievable with semaglutide alone.[79] Amylin clearance predominantly happens *via* the renal route,[80] suggesting the effects of amylin, whether beneficial or risk-associated, could be more pronounced in people with CKD.

The current KDIGO guideline recommends blockade of the RAAS and SGLT-2 inhibitors in people with DKD.[18] In addition, the American Diabetes Association now recommends finerenone in case of SGLT-2 inhibitor intolerance or inadequacy.[81] Further expanding the treatment options for people with DKD, GLP-1 RA treatment may provide additional benefits (Figure 1), including body weight reduction. Recent evidence supports the safe combined use of SGLT-2 inhibitors and GLP-1 RAs[82] and that the benefits of finerenone are independent of GLP-1 RA treatment in people with DKD.[83] Thus, combined appropriate use of these three drug classes may offer added or even synergistic benefits to people with DKD.

In conclusion, data from clinical trials and real-world evidence suggest a potential kidney-protective effect of GLP-1 RAs in DKD as reflected by the prioritisation of the drug class in current treatment guidelines.[18] Confirmatory and mechanistic trials are ongoing, which will provide additional insights, potentially allowing for the approved use of GLP-1 RAs to address the profound current unmet medical need for kidney protection in diabetes, alone or in combination with other treatment options.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contributions
Bernt Johan von Scholten: Conceptualization; Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing.

Frederik Flindt Kreiner: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Søren Rasmussen: Data curation; Formal analysis; Methodology; Resources; Writing – review & editing.

Peter Rossing: Data curation; Methodology; Validation; Writing – original draft; Writing – review & editing.

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References

1. Romagnani P, Remuzzi G, Glassock R, *et al.* Chronic kidney disease. *Nat Rev Dis Primer* 2017; 3: 1708820171124.
2. Thomas MC, Brownlee M, Susztak K, *et al.* Diabetic kidney disease. *Nat Rev Dis Primer* 2015; 1: 1501820150101.
3. Oshima M, Shimizu M, Yamanouchi M, *et al.* Trajectories of kidney function in diabetes: a clinicopathological update. *Nat Rev Nephrol* 2021; 17: 740–750.
4. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395: 709–733.
5. Lv JC and Zhang LX. Prevalence and disease burden of chronic kidney disease. *Adv Experiment Med Biol* 2019; 1165: 3–15.
6. Harjutsalo V and Groop PH. Epidemiology and risk factors for diabetic kidney disease. *Adv Chronic Kidney Dis* 2014; 21: 260–266.
7. Helve J, Sund R, Arffman M, *et al.* Incidence of end-stage renal disease in patients with type 1 diabetes. *Diabetes Care* 2018; 41: 434–439.
8. Tuttle KR, Bakris GL, Bilous RW, *et al.* Diabetic kidney disease: a report from an ADA Consensus Conference. *Am J Kidney Dis* 2014; 64: 510–533.
9. Minutolo R, Gabbai FB, Provenzano M, *et al.* Cardiorenal prognosis by residual proteinuria level in diabetic chronic kidney disease: pooled analysis of four cohort studies. *Nephrol Dialysis Transplant* 2018; 33: 1942–1949.
10. Koye DN, Magliano DJ, Reid CM, *et al.* Risk of progression of nonalbuminuric CKD to end-stage kidney disease in people with diabetes: the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2018; 72: 653–661.
11. Wheeler DC, James J, Patel D, *et al.* SGLT2 inhibitors: slowing of chronic kidney disease progression in type 2 diabetes. *Diabetes Ther* 2020; 11: 2757–2774.
12. Shaffner J, Chen B, Malhotra DK, *et al.* Therapeutic targeting of SGLT2: a new era in the treatment of diabetes and diabetic kidney disease. *Front Endocrinol (Lausanne)* 2021; 12: 749010.
13. Pitt B, Filippatos G, Agarwal R, *et al.* Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Eng J Med* 2021; 385: 2252–2263.
14. Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Eng J Med* 2019; 380: 2295–2306.
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al.* Dapagliflozin in patients with chronic kidney disease. *N Eng J Med* 2020; 383: 1436–1446.
16. Tuttle KR, Brosius FC 3rd, Cavender MA, *et al.* SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the national kidney foundation. *Diabetes* 2021; 70: 1–16.
17. Nauck MA, Quast DR, Wefers J, *et al.* GLP–1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art. *Mol Metab* 2021; 46: 101102.
18. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020; 98: S1–S115.
19. Draznin B, Aroda VR, Bakris G, *et al.* 11. Chronic kidney disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care* 2022; 45: S175–S184.
20. Andersen A, Lund A, Knop FK, *et al.* Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol* 2018; 14: 390–403.
21. Alruwaili H, Dehestani B and le Roux CW. Clinical impact of liraglutide as a treatment of obesity. *Clin Pharmacol* 2021; 13: 53–60.
22. Gribble FM and O'Rahilly S. Obesity therapeutics: the end of the beginning. *Cell Metab* 2021; 33: 705–706.

23. Honigberg MC, Chang LS, McGuire DK, *et al*. Use of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and cardiovascular disease: a review. *JAMA Cardiol* 2020; 5: 1182–1190.

24. Meier JJ. Efficacy of semaglutide in a subcutaneous and an oral formulation. *Front Endocrinol (Lausanne)* 2021; 12: 645617.

25. Nauck MA and Quast DR. Cardiovascular safety and benefits of semaglutide in patients with type 2 diabetes: findings from SUSTAIN 6 and PIONEER 6. *Front Endocrinol (Lausanne)* 2021; 12: 645566.

26. Pfeffer MA, Claggett B, Diaz R, *et al*. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Eng J Med* 2015; 373: 2247–2257.

27. Holman RR, Bethel MA, Mentz RJ, *et al*. Effects of once-weekly EXenatide on cardiovascular outcomes in type 2 diabetes. *N Eng J Med* 2017; 377: 1228–1239.

28. Gerstein HC, Sattar N, Rosenstock J, *et al*. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N Eng J Med* 2021; 385: 896–907.

29. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019; 394: 121–130.

30. Mann JFE, Ørsted DD, Brown-Frandsen K, *et al*. Liraglutide and renal outcomes in type 2 diabetes. *N Eng J Med* 2017; 377: 839–848.

31. Marso SP, Holst AG and Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Eng J Med* 2017; 376: 891–892.

32. Husain M, Birkenfeld AL, Donsmark M, *et al*. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Eng J Med* 2019; 381: 841–851.

33. Jankowski J, Floege J, Fliser D, *et al*. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation* 2021; 143: 1157–1172.

34. Lawson CA, Seidu S, Zaccardi F, *et al*. Outcome trends in people with heart failure, type 2 diabetes mellitus and chronic kidney disease in the UK over twenty years. *Eclinicalmedicine* 2021; 32: 100739.

35. Provenzano M, Coppolino G, De Nicola L, *et al*. Unraveling cardiovascular risk in renal patients: a new take on old tale. *Front Cell Dev Biol* 2019; 7: 314.

36. Sheahan KH, Wahlberg EA and Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J* 2020; 96: 156–161.

37. Sattar N, Lee MMY, Kristensen SL, *et al*. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021; 9: 653–662.

38. Muskiet MHA, Tonneijck L, Huang Y, *et al*. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018; 6: 859–869.

39. Bethel MA, Mentz RJ, Merrill P, *et al*. Renal outcomes in the EXenatide study of cardiovascular event lowering (EXSCEL). *Diabetes* 2018; 67: 522.

40. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019; 394: 131–138.

41. Bethel MA, Mentz RJ, Merrill P, *et al*. Microvascular and cardiovascular outcomes according to renal function in patients treated with once-weekly exenatide: insights from the EXSCEL trial. *Diabetes Care* 2020; 43: 446–452.

42. Tuttle KR, Lakshmanan MC, Rayner B, *et al*. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; 6: 605–617.

43. Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Eng J Med* 2016; 375: 311–322.

44. Mosenzon O, Bain SC, Heerspink HJL, *et al*. Cardiovascular and renal outcomes by baseline albuminuria status and renal function: results from the LEADER randomized trial. *Diabetes Obes Metab* 2020; 22: 2077–2088.

45. Persson F, Bain SC, Mosenzon O, *et al*. Changes in albuminuria predict cardiovascular and renal outcomes in type 2 diabetes: a post hoc analysis of the LEADER trial. *Diabetes Care* 2021; 44: 1020–1026.

46. Mann JFE, Buse JB, Idorn T, *et al*. Potential kidney protection with liraglutide and semaglutide: exploratory mediation analysis. *Diabetes Obes Metab* 2021; 23: 2058–2066.

47. Verma S, Bain SC, Buse JB, *et al.* Occurrence of first and recurrent major adverse cardiovascular events with liraglutide treatment among patients with type 2 diabetes and high risk of cardiovascular events: a post hoc analysis of a randomized clinical trial. *JAMA Cardiology* 2019; 4: 1214–1220.
48. Buse JB, Bain SC, Mann JFE, *et al.* Cardiovascular risk reduction with liraglutide: an exploratory mediation analysis of the LEADER trial. *Diabetes Care* 2020; 43: 1546–1552.
49. Zobel EH, von Scholten BJ, Hansen TW, *et al.* The importance of addressing multiple risk markers in type 2 diabetes: results from the LEADER and SUSTAIN 6 trials. *Diabetes Obes Metab* 2021; 24: 281–288.
50. Mann JFE, Fonseca VA, Poulter NR, *et al.* Safety of liraglutide in type 2 diabetes and chronic kidney disease. *Clin J Am Soc Nephrol* 2020; 15: 465–473.
51. Perkovic V, Bain S, Bakris G, *et al.* Sao010 effects of the glucagon-like peptide-1 (GLP-1) analogues semaglutide and liraglutide on renal outcomes – a pooled analysis of the SUSTAIN 6 and LEADER trials. *Nephrol Dialysis Transplant* 2019; 34: gfz101.SaO010.
52. Perkovic V, Bain S, Bakris G, *et al.* FP482 EGFR loss with glucagon-like peptide-1 (GLP-1) analogue treatment: data from SUSTAIN 6 and LEADER. *Nephrol Dialysis Transplant* 2019; 34: gfz106.FP482.
53. Perkovic V, Bain S, Bakris G, *et al.* FP483 effects of semaglutide and liraglutide on urinary albumin-to-creatinine ratio (UACR) – a pooled analysis of SUSTAIN 6 and LEADER. *Nephrol Dialysis Transplant* 2019; 34: gfz106.FP483.
54. Tuttle K, Cherney D, Hadjadj S, *et al.* TO002 reduction in the rate of EGFR decline with semaglutide vs placebo: a post hoc pooled analysis of SUSTAIN 6 and PIONEER 6. *Nephrol Dialysis Transplant* 2020; 35: gfaa141.TO002.
55. Kristensen SL, Rørth R, Jhund PS, *et al.* Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019; 7: 776–785.
56. Pasternak B, Wintzell V, Eliasson B, *et al.* Use of glucagon-like peptide 1 receptor agonists and risk of serious renal events: Scandinavian cohort study. *Diabetes Care* 2020; 43: 1326–1335.
57. Xu Y, Fu EL, Clase CM, *et al.* GLP-1 receptor agonist versus DPP-4 inhibitor and kidney and cardiovascular outcomes in clinical practice in type-2 diabetes. *Kidney Int* 2022; 101: 360–368.
58. Xie Y, Bowe B, Gibson AK, *et al.* Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of kidney outcomes: emulation of a target trial using health care databases. *Diabetes Care* 2020; 43: 2859–2869.
59. Wilding JPH, Batterham RL, Calanna S, *et al.* Once-weekly semaglutide in adults with overweight or obesity. *N Eng J Med* 2021; 384: 989.
60. Pi-Sunyer X, Astrup A, Fujioka K, *et al.* A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Eng J Med* 2015; 373: 11–22.
61. Singh G, Krauthamer M and Bjalme-Evans M. Wegovy (semaglutide): a new weight loss drug for chronic weight management. *J Invest Med* 2021; 70: 5–13.
62. Mann JFE, Hansen T, Idorn T, *et al.* Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a post-hoc analysis of the SUSTAIN 1-7 randomised controlled trials. *Lancet Diabetes Endocrinol* 2020; 8: 880–893.
63. Wang Z, Zhang J, Chan S, *et al.* BMI and its association with death and the initiation of renal replacement therapy (RRT) in a cohort of patients with chronic kidney disease (CKD). *BMC Nephrol* 2019; 20: 329.
64. Hsu CY, McCulloch CE, Iribarren C, *et al.* Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006; 144: 21–28.
65. Li Q, Lin Y, Wang S, *et al.* GLP-1 inhibits high-glucose-induced oxidative injury of vascular endothelial cells. *Sci Rep* 2017; 7: 8008
66. Rizzo M, Abate N, Chandalia M, *et al.* Liraglutide reduces oxidative stress and restores heme oxygenase-1 and ghrelin levels in patients with type 2 diabetes: a prospective pilot study. *J Clin Endocrinol Metab* 2015; 100: 603–606.
67. Rodbard HW, Rosenstock J, Canani LH, *et al.* Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. *Diabetes Care* 2019; 42: 2272–2281.
68. Rakipovski G, Rolin B, Nøhr J, *et al.* The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE(-/-) and LDLr(-/-) mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci* 2018; 3: 844–857.

69. Savchenko LG, Digtiar NI, Selikhova LG, *et al.* Liraglutide exerts an anti-inflammatory action in obese patients with type 2 diabetes. *Rom J Intern Med* 2019; 57: 233–240.

70. Zobel EH, Ripa RS, von Scholten BJ, *et al.* Effect of liraglutide on expression of inflammatory genes in type 2 diabetes. *Scientific Reports* 2021; 11: 1852220210919.

71. Asmar A, Simonsen L, Asmar M, *et al.* Renal extraction and acute effects of glucagon-like peptide-1 on central and renal hemodynamics in healthy men. *Am J Physiol Endocrinol Metabol* 2015; 308: E641–E649.

72. Muskiet MH, Tonneijck L, Smits MM, *et al.* Acute renal haemodynamic effects of glucagon-like peptide-1 receptor agonist exenatide in healthy overweight men. *Diabetes Obes Metab* 2016; 18: 178–185.

73. 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.

74. Skov J, Pedersen M, Holst JJ, *et al.* Short-term effects of liraglutide on kidney function and vasoactive hormones in type 2 diabetes: a randomized clinical trial. *Diabetes Obes Metab* 2016; 18: 581–589.

75. von Scholten BJ, Persson F, Rosenlund S, *et al.* The effect of liraglutide on renal function: a randomized clinical trial. *Diabetes Obes Metab* 2017; 19: 239–247.

76. Muskiet MHA, Tonneijck L, Smits MM, *et al.* GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol* 2017; 13: 605–628.

77. Baggio LL and Drucker DJ. Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. *Mol Metab* 2021; 46: 101090.

78. Rosenstock J, Wysham C, Frías JP, *et al.* Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet* 2021; 398: 143–155.

79. Enebo LB, Berthelsen KK, Kankam M, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet* 2021; 397: 1736–1748.

80. Vine W, Smith P, LaChappell R, *et al.* Nephrectomy decreases amylin and pramlintide clearance in rats. *Horm Metab Res* 1998; 30: 514–517.

81. 11 microvascular complications and foot care: standards of medical care in diabetes-2021. *Diabetes care* 2021; 44: S151–S167.

82. Lam CSP, Ramasundarahettige C, Branch KRH, *et al.* Efpeglenatide and clinical outcomes with and without concomitant sodium-glucose co-transporter-2 inhibition use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. *Circulation* 2021; 145: 565–574.

83. Rossing P, Agarwal R, Anker SD, *et al.* Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: a subgroup analysis from the FIDELIO-DKD trial. *Diabetes Obes Metab* 2021; 24: 125–134.