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Review

Effects of glucose-lowering agents on surrogate endpoints and hard clinical renal outcomes in patients with type 2 diabetes

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ABSTRACT

Diabetic kidney disease (DKD) represents an enormous burden in patients with type 2 diabetes mellitus (T2DM). Preclinical studies using most glucose-lowering agents have suggested renal-protective effects, but the proposed mechanisms of renoprotection have yet to be defined, and the promising results from experimental studies remain to be translated into human clinical findings to improve the prognosis of patients at risk of DKD. Also, it is important to distinguish effects on surrogate endpoints, such as decreases in albuminuria and estimated glomerular filtration rate (eGFR), and hard clinical endpoints, such as progression to end-stage renal disease (ESRD) and death from renal causes. Data regarding insulin therapy are surprisingly scarce, and it is nearly impossible to separate the effects of better glucose control from those of insulin per se, whereas favourable preclinical data with metformin, thiazolidinediones and dipeptidyl peptidase (DPP)-4 inhibitors are plentiful, and positive effects have been observed in clinical studies, at least for surrogate endpoints. The most favourable renal results have been reported with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter type-2 inhibitors (SGLT2is). Significant reductions in both albuminuria and eGFR decline have been reported with these classes of glucose-lowering medications compared with placebo and other glucose-lowering agents. Moreover, in large prospective cardiovascular outcome trials using composite renal outcomes as secondary endpoints, both GLP-1RAs and SGLT2is added to standard care reduced renal outcomes combining persistent macro-albuminuria, doubling of serum creatinine, progression to ESRD and kidney-related death; however, to date, only SGLT2is have been clearly shown to reduce such hard clinical outcomes. Yet, as the renoprotective effects of SGLT2is and GLP-1RAs appear to be independent of glucose-lowering activity, the underlying mechanisms are still a matter of debate. For this reason, further studies with renal outcomes as primary endpoints are now awaited in T2DM patients at high risk of DKD, including trials evaluating the potential add-on benefits of combined GLP-1RA–SGLT2i therapies.

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Introduction

In parallel with the type 2 diabetes mellitus (T2DM) worldwide pandemic, diabetic kidney disease (DKD), which is also associated with cardiovascular (CV) morbidity and mortality, has now become the leading cause of end-stage renal disease (ESRD) [1]. Renal impairment in T2DM results in high healthcare utilization and costs [2]. Thus, both the prevention of DKD and

its appropriate early management to retard progression to ESRD represent major challenges in patients with T2DM [3–5].

In addition to inhibition of the renin–angiotensin–aldosterone system (RAAS), tight glucose control is also an established modality for preventing the development and progression of albuminuria [6]. Evidence suggests it can ameliorate estimated glomerular filtration rate (eGFR) declines, although these benefits appear to be most pronounced when applied to T2DM patients with early stages of DKD and longer follow-up durations [7,8]. Most antihyperglycaemic medications can be safely used in patients with mild-to-moderate DKD. However, several glucose-lowering agents are either not advisable or require dose adjustments in cases of more advanced stages of renal disease [6–10]. Of note, metformin, the first-line treatment for pharmacological

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management of T2DM, may now be used in patients with stable, moderate renal dysfunction, according to recent guidelines [11].

Intensive glucose control with the classic glucose-lowering agents, including insulin, reduces the risk of (micro)albuminuria, although evidence is lacking that it can reduce the risk of hard clinical renal outcomes like doubling of serum creatinine levels, ESRD and death due to renal disease, presumably because of too-short follow-ups in most of the available trials [12]. However, as add-ons to standard care, new glucose-lowering agents have demonstrated renoprotective effects beyond just improvement of glucose control [13–16]. In particular, glucagon-like peptide-1 receptor agonists (GLP-1RAs) [17] and, even more impressively, sodium–glucose cotransporter type-2 inhibitors (SGLT2is) [18–21] have shown positive effects on composite renal outcomes, including hard clinical endpoints, in T2DM patients with established CV disease.

The aim of the present narrative review is to analyze and compare the effects of old and new glucose-lowering agents on surrogate renal endpoints and clinical renal outcomes in patients with T2DM (Table 1). The underlying mechanisms responsible for nephroprotection were mainly investigated in in-vitro and in-vivo experiments using animal models, and are here briefly discussed for each pharmacological class.

Metformin

Metformin elicits at least part of its therapeutic activity via activation of the AMP-activated kinase (AMPK) pathway. AMPK is a metabolic sensor that regulates cellular energy balance, transport, growth, inflammation and survival functions; in the kidney, AMPK plays a unique role at the crossroads of energy metabolism, ion and water transport, inflammation and stress [22]. Pharmacological activators of AMPK like metformin have shown renal-protective effects in numerous experimental studies [23]. Renal cells under hyperglycaemic or proteinuric conditions exhibit inactivation of cell defence mechanisms (AMPK and autophagy) and activation of pathological pathways [mammalian target of rapamycin (mTOR), epithelial-to-mesenchymal transition, endoplasmic reticulum stress, oxidative stress] [24]. Activation of AMPK by metformin suppresses endoplasmic reticulum stress by angiotensin II, aldosterone and high glucose levels, and also reduces renal fibrosis related to transforming growth factor (TGF)- β [25]. In a concentration-dependent manner, metformin has also exhibited antiapoptotic effects on human podocytes via activation of AMPK and inhibition of mTOR signalling [26]. Experimental studies in mice concluded that the underlying mechanisms for the protective effects of metformin against renal fibrosis include AMPK α 2-dependent targeting of TGF- β 1 production and AMPK α 2-independent targeting of TGF- β 1 downstream signalling [27]. Other

data have indicated that reduced phosphorylation of acetyl-CoA carboxylase (ACC) after renal injury contributes to the development of tubulointerstitial fibrosis, and that phosphorylation of ACC, a target for energy-sensing AMPK, is required for antifibrotic metformin actions in the kidney [28]. Thus, numerous in-vitro and in-vivo studies have revealed nephroprotective effects with metformin, and these effects have been demonstrated to be mediated via the AMPK–mTOR signalling axis [29].

Metformin activates not only AMPK, but also protein deacetylase SIRT1. In fact, metformin has been shown to prevent the hyperglycaemia-induced reduction of SIRT1 protein levels while ameliorating glucose uptake into podocytes and decreasing glomerular filtration barrier permeability. Indeed, the potentiating effect of metformin on high-glucose-induced insulin-resistant podocytes seems to be dependent on SIRT1 activity in addition to AMPK, thereby arguing in favour of pleiotropic effects with metformin action [30]. Recent experimental data in a rat model of chronic kidney disease (CKD) showed that kidneys from the metformin group exhibited significantly less cellular infiltration, fibrosis and inflammation, and that metformin protected against the development of severe renal failure (while preserving calcium phosphorus homeostasis) and vascular calcification. Of note, these positive effects were independent of any glucose-lowering effect in this model using non-diabetic rats [31]. Overall, these preclinical data suggest that the potential benefits of metformin on renal outcomes in patients with T2DM may well extend beyond its antihyperglycaemic activity.

Nevertheless, such positive preclinical results are still awaiting further clinical translation [32]. Indeed, human data are still rather scarce. In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of T2DM patients with urinary albumin > 50 mg/L (the only surrogate marker used as a renal outcome in this landmark study) did not differ significantly between the metformin group (23%), the conventional diet-treated group (23%) and the intensive (sulphonylurea or insulin) group (24%) over a median follow-up of 10.7 years [33]. In A Diabetes Outcome Progression Trial (ADOPT), a 5-year study comparing initial therapy with metformin vs glyburide (glibenclamide) and rosiglitazone in T2DM patients, the urinary albumin/creatinine ratio (UACR) rose slowly in the metformin group, whereas it initially fell with rosiglitazone and glyburide over the first 2 years, then rose slowly over time. On the other hand, the late decline in eGFR with metformin was more pronounced than with rosiglitazone, but less marked than with glyburide [34].

Most clinical studies have been interested in the safety issues of metformin in T2DM patients with renal impairment as regards risk of lactic acidosis rather than the impact of metformin on surrogate or clinical renal outcomes (for reviews, see Crowley et al. and Inzucchi et al. [35,36]). Nevertheless, based on the relevant clinical

Table 1
Effects of glucose-lowering agents on renal surrogate endpoints and clinical outcomes in preclinical animal models and clinical studies in patients with type 2 diabetes.

Medications	Preclinical results	Clinical results		
	In-vitro and in-vivo data	Reduction of albuminuria	Slowing of eGFR reduction	Less progression to ESRD
Metformin	Positive	Not proven	Not proven	Not proven
Sulphonylureas	None	No ^a	No ^a	No ^a
Glinides	None	No data	No data	No data
Alpha-glucosidase inhibitors	Rare	No data	No data	No data
Thiazolidinediones	Positive	Yes	Not proven	Not proven
DPP-4 inhibitors	Positive	Yes	Not proven	Not proven
GLP-1 receptor agonists	Positive	Yes	Yes	Not proven
SGLT2 inhibitors	Positive	Yes	Yes	Yes
Insulin therapy	Rare	Not proven ^b	Not proven ^b	Not proven ^b

eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; SGLT2: sodium–glucose cotransporter type 2.

^a Less favourable results compared with metformin in observational studies.

^b Impossible to discriminate from possible effects due to better glucose control.

observations, metformin appears to be a promising drug in the treatment of progressive renal damage [37]. Several observational findings demonstrated better renal outcomes in T2DM patients initiated or treated with metformin than in those initiated or treated with sulphonylureas (see below). However, because of the possible biases inherent in observational studies, randomized controlled trials (RCTs) are the essential next step to confirm these findings.

Sulphonylureas

In contrast to the huge amount of experimental animal data supporting the renal-protective effects of metformin [37], no such data are available in the literature for sulphonylureas [38,39].

In the above-mentioned ADOPT study comparing initial therapy with the sulphonylurea glyburide vs. metformin and rosiglitazone in newly diagnosed T2DM patients, a late decline in eGFR was observed in all three groups, albeit more marked with glyburide than with either metformin or rosiglitazone over the 5-year follow-up [34]. The Action in Diabetes and Vascular disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) reported that intensive glucose control using modified-release (MR) gliclazide prevented ESRD in patients with T2DM [40]: after a median duration of 5 years, intensive glucose control significantly reduced microalbuminuria by 9%, macroalbuminuria by 30% and risk of ESRD by 65% [hazard ratio (HR): 0.35, $P = 0.02$], although there were very few such events (only 7 vs. 20 ESRD cases). However, this effect on ESRD was confirmed in the subsequent ADVANCE-ON trial after a median of 5.4 additional years (29 vs. 53 events; HR: 0.54, $P < 0.01$), and the benefit was greater in patients with earlier-stage DKD and with well-controlled blood pressure [41]. Of note, the experimental design of the study did not allow separation of the effects of sulphonylurea per se from that of better glucose control.

Using electronic health records from two primary-care networks and compared with metformin as the reference, sulphonylurea exposure in newly diagnosed T2DM patients trended towards an association with an increased risk of developing proteinuria [adjusted hazard ratio (aHR): 1.27, 95% confidence interval (CI): 0.93–1.74], but showed a clear association with an increased risk of eGFR reduction to < 60 mL/min/1.73 m² (aHR: 1.41, 95% CI: 1.05–1.91) [42].

Several retrospective comparisons were performed using the US Veterans Affairs national database. In a cohort of 93,577 T2DM patients who had filled an incident oral antidiabetic drug prescription and had an eGFR ≥ 60 mL/min/1.73 m² at inclusion, sulphonylurea users compared with metformin users had an increased risk of the primary outcome (persistent decline of $\geq 25\%$ in eGFR from baseline or a diagnosis of ESRD: aHR: 1.22, 95% CI: 1.03–1.44) [43]. These results were confirmed in 13,238 veteran T2DM patients who initiated either sulphonylurea or metformin treatment. A higher risk of kidney function decline or death was seen with sulphonylurea compared with metformin, and the difference appeared to be independent of changes in glycated haemoglobin (HbA_{1c}), systolic blood pressure and body mass index (BMI) over time [44]. Of 175,296 patients with newly diagnosed T2DM and DKD, initiation of a sulphonylurea vs. metformin was associated with a substantial increase in mortality across all ranges of eGFR evaluated (HR ranged from 1.25 to 1.69). The biggest absolute risk increase was observed in those with moderate-to-severe decreases in eGFR (30–44 mL/min/1.73 m²) [45].

In a real-world cohort of T2DM patients with albuminuria (urinary albumin creatinine ratio [UACR] > 30 mg/g) who initiated either sulphonylurea or sitagliptin as add-on dual therapy to metformin (data extracted from the computerized medical records

of a large managed-care organization in Israel), while both pharmacological approaches reduced albuminuria, sulphonylureas seemed to provide less of a reduction in albuminuria independent of glycaemic control compared with the DPP-4 inhibitor [46].

Another real-life study investigated the effects of two commonly prescribed sulphonylureas on kidney outcomes in 4486 T2DM patients treated with either glibenclamide or gliclazide for > 2 years and followed for a median duration of 4.7 years [47]. In a matched cohort using propensity scores with 12,122 person-years of follow-up, there was no significant difference between the two sulphonylureas in risk of ESRD or doubling of creatinine, although there was a trend towards higher risks in the glibenclamide group than in the gliclazide group, reaching statistical significance in some subgroups [47].

Thus, sulphonylureas appear to exert less of a nephroprotective effect, especially compared with metformin, although results from observational studies require confirmation by RCTs. In addition, no study specifically investigated the effects of other insulin-secreting agents, such as repaglinide and nateglinide, on UACR or any other renal outcomes.

Alpha-glucosidase inhibitors

In animal models, the alpha-glucosidase inhibitor acarbose suppressed blood glucose levels in mildly insulin-deficient rats and reduced the number of anionic sites in the glomerular basement membrane, which might help to prevent its increased permeability leading to albuminuria [48]. However, human data are scarce [49]. In T2DM patients not well controlled by sulphonylureas and metformin, additional acarbose therapy for 6 months provided similar glycaemic control and changes in eGFR and UACR compared with pioglitazone [50].

In the recent Acarbose Cardiovascular Evaluation (ACE) trial to evaluate the effects of acarbose on CV and diabetes outcomes in Chinese patients with coronary heart disease and impaired glucose tolerance, after a median follow-up of 4.4 years, incidental impaired renal function (defined as eGFR < 30 mL/min/1.73 m², doubling of baseline serum creatinine or halving of baseline eGFR) did not differ between the acarbose group and the placebo group (41/3272 vs. 50/3250, respectively; HR: 0.81, 95% CI: 0.54–1.23; $P = 0.33$) [51].

Glitazones

Of all the glucose-lowering agents, thiazolidinediones (TZDs) are those with the greatest anti-inflammatory activity [52], an effect that may contribute to nephroprotection [53]. TZDs may also interfere with most of the pathogenetic pathways involved in the development and progression of DKD, as they have been shown to reduce hyperglycaemia and insulin resistance, lower arterial blood pressure, improve endothelial function, reduce inflammatory processes and oxidative stress, lower TGF- β and downregulate the RAAS [54,55]. Data from several animal and human studies support the notion that TZDs reduce UACR and may prevent the development of renal impairment [55]. In a meta-analysis of 15 RCTs (five with rosiglitazone and 10 with pioglitazone) involving 2860 T2DM patients, treatment with TZDs significantly decreased UACR and protein excretion [56]. However, in patients with advanced diabetic nephropathy, no reduction in proteinuria was observed in patients treated with pioglitazone compared with glipizide for 4 months [57]. In a study that compared add-on pioglitazone with basal insulin, both treatments improved glycaemic control, but only pioglitazone was observed to be advantageous by preserving renal function when used as an

add-on therapy for T2DM patients in whom sulphonylurea and metformin regimens had failed [58].

In a small study of T2DM patients with microalbuminuria, rosiglitazone compared with either nateglinide or placebo significantly reduced albumin excretion and ameliorated glomerular hyperfiltration at an early stage of T2DM as well as incipient DKD, while also improving nitric oxide bioavailability and renal endothelial dysfunction [59]. In ADOPT, initial monotherapy with rosiglitazone slowed the rise of UACR compared with metformin, preserved eGFR compared with glyburide, and lowered blood pressure relative to both active comparators over a 5-year period [34]. In a post-hoc analysis from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), patients who had DKD and were treated with pioglitazone compared with placebo were less likely to reach the composite endpoint of all-cause death, myocardial infarction and stroke, independently of the severity of renal impairment. However, there was an unexpectedly greater decline in eGFR with pioglitazone (between-group difference: 0.8 mL/min/1.73 m²/year) than with placebo [60]. Clinical renal outcomes were not investigated in the study.

Therefore, whether the use of TZDs has a positive or negative impact on renal outcomes in T2DM patients remains an open, unanswered question [61]. In the recently published large-scale prospective Insulin Resistance Intervention after Stroke (IRIS) trial, which demonstrated significant risk reductions of both recurrent stroke and myocardial infarction with pioglitazone compared with placebo as add-ons to standard care, no renal endpoints were reported on [62]. Thus, the relative lack of evidence demonstrating the effects of TZDs on hard renal outcomes mandates the need for well-designed RCTs focused on this particular objective [55].

DPP-4 inhibitors

DPP-4is are incretin-based therapies that lower blood glucose levels without inducing hypoglycaemia or weight gain while having good CV safety profiles [63]. Their glucose-lowering efficacy is maintained in T2DM patients at all stages of CKD, and they are safe to use [64–66]. However, it is recommended to reduce doses of alogliptin, saxagliptin, sitagliptin and vildagliptin according to reductions in eGFR to guarantee consistent drug exposures to these medications, which are excreted *via* the kidneys [67,68]. In contrast, as linagliptin has biliary rather than renal excretion, its usual dose may be maintained whatever the state of renal function [69].

Several recent reviews have explored the effects of DPP-4is on surrogate renal outcomes [70–72]. Renal protection has been demonstrated in various animal models implicating different underlying mechanisms independent of glucose control, including: upregulation of GLP-1 and GLP-1 receptors; inhibition of renal DPP-4 activity; attenuation of inflammasome activation, reduction of oxidative stress; mitochondrial dysfunction and apoptosis; suppression of connective-tissue growth factor; limitation of TGF- β -related fibrosis and nuclear factor (NF)- κ B p65-mediated macrophage infiltration; reduction of renal tubulointerstitial fibronectin; upregulation of stromal cell-derived factor-1; suppression of advanced glycation end-products; regulation of proliferation of preglomerular vascular smooth muscle and mesangial cells; and attenuation of rises in blood pressure [70–73]. However, despite such promising results in animal models, data on surrogate biological markers of renal function (UACR, eGFR) and clinical renal outcomes (progression to ESRD) are still relatively scanty in patients with T2DM, and mostly demonstrate the safety rather than true efficacy of DPP-4is regarding renal protection [70].

In overweight patients with T2DM without DKD, 12-week treatment with sitagliptin had no measurable effect on renal

haemodynamics, and was not associated with sustained changes in tubular function or alterations in markers of renal damage [74]. The Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) was mainly a CV outcome trial to demonstrate the CV safety of sitagliptin [75]. In a post-hoc analysis of TECOS, renal outcomes were evaluated over a median period of 3 years, with participants categorized at baseline into different eGFR stages [76]. Kidney function declined at the same rate in both treatment groups, but with a marginally lower yet constant eGFR difference (–1.3 mL/min/1.73 m²) in those participants assigned to sitagliptin compared with those receiving placebo [76] (Table 2).

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 study [77], there were no meaningful differences between the saxagliptin vs placebo treatment arms, respectively, in any of the prespecified renal safety outcomes: doubling of serum creatinine (2.02% vs. 1.82%); initiation of chronic dialysis, renal transplantation, or serum creatinine > 6.0 mg/dL (0.61% vs. 0.67%); and the composite of doubling of serum creatinine, initiation of chronic dialysis, renal transplantation and serum creatinine > 6.0 mg/dL (2.2% vs. 2.0%) [78] (Table 2). Overall changes in eGFR during follow-up were similar in the saxagliptin and placebo arms. However, a significant reduction in UACR was observed with saxagliptin compared with placebo (–34.3 mg/g; $P < 0.004$), driven mainly by decreased levels in patients with macroalbuminuria at baseline (–283 mg/g; $P = 0.002$), although changes in UACR did not correlate with those in HbA_{1c} [78]. The frequency of UACR progression was significantly lower with saxagliptin compared with placebo in all patients except those with severe renal impairment. Other renal endpoints appeared at relatively balanced rates in patients treated with saxagliptin compared with placebo, irrespective of renal impairment [79]. Also, in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), changes in eGFR from baseline (whatever the baseline level) and rates of initiation of dialysis were similar between alogliptin and placebo [80] (Table 2).

Finally, pooled analyses of placebo-controlled RCTs with linagliptin revealed a 28% reduction in UACR (95% CI: –47 to –2; $P = 0.0357$) [81] and 16% reduction in risk of composite DKD events (HR: 0.84, 95% CI: 0.72–0.97; $P = 0.02$) compared with placebo [82]. However, because of the limitations of such retrospective analyses of rather short-term trials, the potential of linagliptin to improve kidney disease outcomes still warrants further investigation. Indeed, in the Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin (MARLINA-T2D), a dedicated phase-III placebo-controlled RCT in patients with inadequately controlled T2DM and evidence of DKD (UACR with 30–3000 mg/g creatinine despite a stable background of single RAAS blockade, and eGFR ≥ 30 mL/min/1.73 m²), linagliptin significantly improved glycaemic control with no significant effect on UACR compared with placebo and no significant change in placebo-adjusted eGFR [83]. Although there was no conclusive evidence of renoprotective effects in the 24-week MARLINA-T2D trial, previous research had suggested that clinically evident renal benefits might develop with longer-term treatment [84].

Overall, the renal-protective potential of DPP-4is remains largely unproven in humans and merits further investigation [70,72]. Several reasons may explain why DPP-4is failed to positively impact renal outcomes in RCTs. First, they were designed to demonstrate non-inferiority, rather than superiority, with CV outcomes as primary endpoints. Furthermore, adjustment of glucose-lowering therapies was allowed, which resulted in only a small HbA_{1c} difference between the active-treatment and placebo groups. Finally, the RCTs were most likely too short-term,

Table 2
Renal outcomes reported with dipeptidyl peptidase-4 inhibitors (DPP-4is) in patients with type 2 diabetes and high cardiovascular risk.

Studies	DPP-4is vs comparator	Active vs. placebo (n)	Median follow-up (years)	Baseline mean eGFR	Change in eGFR vs. placebo	Baseline UACR (mg/g)	Change in UACR (mg/g) vs. placebo	New-onset persistent macro	Doubling of serum creatinine	Progression to ESRD requiring RRT	Composite renal outcome	Death from any cause ^a
TECOS [75,76]	Sitagliptin vs. placebo	7332 vs. 7339	3.0	74.9	-1.34 (-1.76 to -0.91), P < 0.0001	10.3 (3.5–34.6)	-0.18 (-0.35 to -0.02), P = 0.031	NA (micro: 7.8% vs. 7.9%)	NA	1.4% vs. 1.5%	NA	1.01 (0.90–1.14), P = 0.88
SAVOR-TIMI 53 [77,78]	Saxagliptin vs. placebo	8280 vs. 8212	2.1	72.5	NA	203.6 (79.2–848.4)	-34.3 (NA), P < 0.004	2.2% vs 2.8%	1.1 (0.89–1.36), NS	0.7% vs. 0.9%, 0.90 (0.61–1.32), NS ^b	1.08 ^c (0.88–1.32), P = 0.46	1.05 (0.74–1.50), P = 0.79
EXAMINE [80]	Alogliptin vs. placebo	2701 vs. 2679	1.5	71.1	No difference ^d	NA	NA	NA	NA	0.9% vs. 0.8%	NA	0.88 (0.71–1.09), P = 0.23

Results are expressed as hazard ratios (95% confidence interval).
eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio; macro/micro: macroalbuminuria/microalbuminuria; ESRD: end-stage renal disease; RRT: renal replacement therapy; NA: not available; NS: not significant.

^a Includes renal death, as those results are lacking in publications (presumably very few events).

^b includes serum creatinine > 6 mg/dL.

^c doubling of serum creatinine, dialysis, renal transplantation, serum creatinine > 6 mg/dL.

^d basal eGFR (mL/min/1.73 m²): ≥ 90, -6.7 vs. -4.5; < 90 but ≥ 60, 0.6 vs. 1.0; < 60 but ≥ 30, 1.1 vs. 2.1; < 30, 0.2 vs. 1.6.

lasting only 1.5 to 3 years. Thus, there is an urgent need for long-term RCTs that are adequately powered and based on hard renal outcomes to ascertain (or contradict) the therapeutic benefits of DPP-4is in patients with T2DM and DKD.

The placebo-controlled Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial aimed to evaluate the effects of linagliptin on both CV and kidney outcomes in a study population of T2DM patients at high risk of CV and/or kidney events [85]. The recruited population in this unique study differed from those of previous studies with DPP-4is in that ≥ 60% of patients had signs of renal dysfunction (either eGFR < 60 mL/min/1.73 m² or albuminuria), in contrast to < 25% in other trials. While the primary outcome was the classic three-point combination of major CV events, the key secondary outcome was a composite of time to first sustained appearance of ESRD, ≥ 40% decrease in eGFR from baseline and kidney-related death. The results were presented at the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD; 4 October 2018), but have yet to be published. No significant differences were observed between the linagliptin and placebo groups for either CV or renal composite endpoints. Linagliptin was associated with a significant reduction in albuminuria with no effective change in eGFR.

GLP-1 receptor agonists

GLP-1RAs act on the traditional risk factors of progressive kidney disease, including improvement of glucose control, lowering of blood pressure and weight reduction. Moreover, GLP-1RAs may also have direct effects on the kidney, including the intrarenal RAAS, ischaemia/hypoxia, apoptosis and neural signalling (for a review, see Thomas [17]). However, the mechanisms that may underlie any direct actions in the kidney have yet to be established [86]. The GLP-1 receptor seems to be expressed in glomeruli and arterioles, whereas kidney-protective actions independent of the GLP-1 receptor have been proposed. GLP-1 induces natriuresis by reducing sodium/hydrogen exchanger isoform 3 (NHE3)-dependent sodium reabsorption in the proximal tubule [17,87]. GLP-1RAs have also been shown to reduce inflammation, macrophage infiltration, oxidative stress and type-IV collagen accumulation in the kidney [17,88]. Because the beneficial actions of liraglutide are known to be inhibited by a specific adenylate cyclase inhibitor and a selective protein kinase A (PKA) inhibitor, cAMP and PKA-dependent pathways downstream of GLP-1 receptor activation may play a critical role in renal protection [88]. In both in-vivo and in-vitro studies, liraglutide prevented epithelial-to-mesenchymal transition, which plays a significant role in the development of renal fibrosis, by inhibiting activation of the TGF-β1/Smad3 and ERK1/2 signalling pathways, and decreasing extracellular matrix secretion and deposition [89]. Renal GLP-1 receptors have been found to be present in afferent arteriolar vascular smooth muscle cells, glomerular endothelial cells and macrophages, juxtaglomerular cells and proximal tubule, while GLP-1 has been reported to increase GFR, renal blood flow, and fractional excretion of both sodium and potassium [90].

GLP-1RAs are safe to use in T2DM patients with DKD [67]: 12-week treatment with liraglutide had no measurable effects on renal haemodynamics, and led to no observable sustained changes in either tubular function or markers of renal damage [74]. In another study, short-term liraglutide treatment also did not affect renal haemodynamics, but did decrease proximal tubular sodium reabsorption. Furthermore, a reduction in angiotensin II concentration was observed, which may contribute to renal protection [91].

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study of CV outcomes [92], the prespecified secondary renal outcome was a composite of

new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, ESRD and death from renal disease [93]. After a median follow-up of 3.84 years in T2DM patients at high risk of CV disease, this renal outcome was observed in fewer participants in the liraglutide than in the placebo group (268/4668 patients vs. 337/4672, respectively; HR: 0.78, 95% CI: 0.67–0.92; $P = 0.003$; Table III). However, this result was driven primarily by the new onset of persistent macroalbuminuria, whereas no significant differences were observed for persistent doubling of serum creatinine, ESRD and death due to renal disease (Table 3). The decline in eGFR was slightly lower in the liraglutide than in the placebo group (estimated 36-month trial ratio: 1.02, 95% CI: 1.00–1.03; $P = 0.01$), corresponding to a 2% lower decrease with liraglutide: -7.44 vs. -7.82 mL/min/1.73 m²). Rates of renal adverse events (AEs) were similar in both liraglutide and placebo groups (15.1 AEs and 16.5 AEs per 1000 patient-years, respectively), including rates of acute kidney injury (7.1 AEs and 6.2 AEs per 1000 patient-years, respectively) [93].

In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), after a median follow-up of 2 years, new or worsening nephropathy was less frequently reported in T2DM patients treated with semaglutide vs. placebo (HR: 0.64, 95% CI: 0.46–0.88; $P < 0.01$). Again, however, this composite outcome was largely driven by a reduction in new-onset macroalbuminuria, whereas doubling of serum creatinine concentrations resulting in eGFRs ≤ 45 mL/min/1.73 m², ESRD and death from renal causes were unaffected [94] (Table III). In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), a reduction in new-onset macroalbuminuria was reported in patients treated with once-weekly exenatide compared with placebo (2.2% vs 2.8%, respectively; $P = 0.03$), with no significant changes in either microalbuminuria (7.2% vs. 7.5%, respectively) or ESRD requiring renal replacement therapy (0.7% vs. 0.9%) after a median follow-up of 3.2 years [95] (Table 3).

In T2DM patients who had had recent acute coronary events from the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), 74.3% had normoalbuminuria, 19.2% had microalbuminuria and 6.5% had macroalbuminuria [96]. After 108 weeks, the placebo-adjusted, least-squares mean percentage changes in UACR from baseline with lixisenatide were negligible in patients with normoalbuminuria, but reached -21.10% (95% CI: -42.25 – 0.04 ; $P = 0.0502$) in patients with microalbuminuria, and -39.18% (95% CI: -68.53 to -9.84 ; $P = 0.0070$) in those with macroalbuminuria. Lixisenatide was also associated with a reduced risk of new-onset macroalbuminuria compared with placebo when adjusted for baseline HbA_{1c} (HR: 0.808, 95% CI: 0.660–0.991; $P = 0.0404$). However, no significant differences in eGFR decline were identified between treatment groups in any UACR subgroup. In addition, the proportion of patients with renal AEs was low and did not significantly differ between treatment groups [96].

Integrated data from nine phase-II/-III trials in T2DM patients ($n = 6005$) showed that dulaglutide had no effect on eGFR, but did decrease UACR slightly without increasing kidney AEs compared with either placebo or active comparators [97]. In the 52-week AWARD-7 trial of patients with T2DM and moderate-to-severe DKD, once-weekly dulaglutide resulted in glycaemic control similar to that achieved with insulin glargine with no greater reduction in UACR, but with significantly less of a decline in eGFR ($P = 0.005$ for dulaglutide 1.5 mg and $P = 0.009$ for dulaglutide 0.75 mg vs. insulin) [98]. This was confirmed by a US study in a real-life setting where initiation of dulaglutide therapy, compared with insulin glargine, was associated with a significantly smaller decrease in eGFR over a 1-year period [99]. Overall, these short-term data suggest that dulaglutide has the potential to exert renal protection in patients with T2DM, an effect that should be

Table 3 Renal outcomes reported for glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with type 2 diabetes and high cardiovascular risk.

Studies	GLP-1RA dose vs. comparator	Active vs. placebo (n)	Median follow-up (years)	Baseline mean eGFR	Baseline UACR	Change in UACR	New-onset persistent macro	Doubling of serum creatinine	Progression to ESRD requiring RRT	Composite renal outcome	Death from any cause ^a
LEADER [92,93]	Liraglutide 1.8 mg once daily vs. placebo	4668 vs. 4672	3.84	80.4	Micro: 26.3%; macro: 10.5%	-17% (-12 to -21), $P < 0.001$	0.74 (0.60–0.91), $P = 0.004$	0.89 (0.67–1.19), $P = 0.43$	0.87 (0.61–1.24), $P = 0.44$	0.78 ^b (0.67–0.92), $P = 0.003$	0.85 (0.74–0.97), $P = 0.02$
SUSTAIN-6 [94]	Semaglutide 0.5 or 1.0 mg once daily vs. placebo	1648 vs. 1649	2	NA	NA	NA	0.54 (0.37–0.77), $P = 0.001$	1.28 (0.64–2.58), $P = 0.48$	0.91 (0.40–2.07), $P = 0.83$	0.64 ^c (0.46–0.88), $P = 0.005$	1.05 (0.74–1.50), $P = 0.79$
EXSCEL [95]	Exenatide ER 2 mg once weekly vs. placebo	7356 vs. 7396	3.2	76.6	NA	NA	2.2% vs. 2.8%	NA	0.7% vs. 0.9%	NA	0.86 (0.77–0.98), P not tested

Results are expressed as hazard ratios (95% confidence interval).
 eGFR: estimated glomerular filtration rate (mL/min/1.73 m²); UACR: urinary albumin/creatinine ratio; ESRD: end-stage renal disease; RRT: renal replacement therapy; Micro: microalbuminuria; NA: not available; ER: extended release.
^a Includes renal death, as those results are lacking in publications (presumably very few events).
^b Includes persistent doubling of serum creatinine, ESRD, death due to renal disease; another composite endpoint was persistent doubling of serum creatinine, need for continuous RRT (ESRD; HR: 0.85, 95% CI: 0.66–1.10, $P = 0.20$).
^c new or worsening nephropathy defined as new-onset persistent macroalbuminuria (macro), persistent doubling of serum creatinine, creatinine clearance < 45 mL/min/1.73 m² (as per Modification of Diet in Renal Disease equation), need for continuous RRT, death due to renal disease.

confirmed in long-term studies using clinical hard endpoints [100]. Further renal data will also become available when the results of the ongoing CV outcome trial, Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND), are published.

In the recently published Harmony Outcomes trial, albiglutide was superior to placebo as regards major CV AEs in patients with T2DM and CV disease (HR: 0.78, 95% CI: 0.68–0.90; $P = 0.0006$ for superiority) [101]. A slight yet significant difference in eGFR between patients in the albiglutide group and those in the placebo group was noted at 8 months (-1.11 mL/min/1.73 m², 95% CI: -1.84 to -0.39), but tended to disappear at 16 months (-0.43 mL/min/1.73 m², 95% CI: -1.26 – 0.41). No increased risk of severe renal AEs was reported with albiglutide. No other renal endpoint data, including changes in albuminuria, are available from this trial.

Divergent results have been reported in recent meta-analyses investigating the effects of GLP-1RAs on microvascular complications. In the first meta-analysis of 51 trials to report valuable information on renal endpoints, GLP-1RAs lowered the incidence of nephropathy [Mantel–Haenszel (MH) odds ratio (OR): 0.74, 95% CI: 0.60–0.92; $P = 0.005$], and was significantly different vs placebo, but not vs any other class of active comparators [102]. In another meta-analysis of 77 randomized trials involving 60,434 T2DM patients, treatment with GLP-1RAs was associated with significant reductions in all-cause and CV mortality, but with no significant decrease in risk of nephropathy (risk reduction: 0.866, 95% CI: 0.625–1.199; $P = 0.385$) [103]. In yet another meta-analysis of 60 studies involving 60,077 T2DM patients, GLP-1RAs marginally reduced UACR compared with placebo and other antidiabetic agents [weighted mean difference (WMD): -2.55 mg/g, 95% CI: -4.37 to -0.73 , and -5.52 mg/g, 95% CI: -10.89 to -0.16 , respectively], but resulted in no clinically relevant changes in eGFR [104]. Of note, as the commercially available GLP-1RAs may differ by a range of properties, whether or not there is a class effect when considering cardiorenal protection remains an open question [105,106].

SGLT2 inhibitors

SGLT2is exert their glucose-lowering effects by promoting glucosuria, an effect that also results in body-weight and fat-mass reductions. In addition to these effects, they increase natriuresis and osmotic diuresis, thereby lowering arterial blood pressure and plasma overload [107], all factors that may contribute to better CV and renal outcomes and rates of mortality [108]. In addition, switching from low-dose thiazide diuretics to SGLT2is has improved various metabolic parameters (HbA_{1c}, fasting plasma glucose, serum uric acid, BMI, visceral fat area) without affecting blood pressure in patients with T2DM and hypertension [109].

SGLT2is certainly represent the most promising pharmacological class of glucose-lowering agents not only for CV factors, but also for renal protection in T2DM patients [21,110]. In recent years, numerous excellent and extensive reviews devoted to this topic have summarized their preclinical and clinical data, and provided several hypotheses to explain the nephroprotective effects of these new antidiabetic agents [18,19,21,111–115]. SGLT2i effects on the kidney are most likely explained by multiple pathways beyond systemic effects via reductions in blood glucose, body-weight and blood pressure. SGLT2is are associated with reduced glomerular hyperfiltration, an effect mediated through increased natriuresis, and restored tubuloglomerular feedback independently of glycaemic control. Increased sodium and chloride delivery to the macula densa following SGLT2 inhibition results in activation of renal tubuloglomerular feedback, leading to afferent vasoconstriction

and attenuation of diabetes-induced renal hyperfiltration [21,111]. This effect may explain the early decline in eGFR commonly observed after initiation of SGLT2i therapy. This initial drop is followed by a slower decline of eGFR thereafter compared with placebo, an effect presumably explained by preservation of glomerular integrity due to a reduction in intraglomerular pressure [21,111]. In addition, SGLT2is may improve renal oxygenation and cellular energy metabolism [21] while also reducing intrarenal inflammation [116], thereby slowing the progression of kidney function decline.

Recent results for biomarkers have suggested that the albuminuria-lowering effect of SGLT2is may be the result of decreased intraglomerular pressure or less tubular cell injury possibly related to decreased inflammation [117] and perhaps also linked to reduced activity of the intrarenal renin–angiotensin system [118]. SGLT2is also lower serum uric acid levels [119,120], an independent risk factor for diminished eGFRs in patients with T2DM [121,122].

Because of their specific mechanism of action targeting the kidney, SGLT2is lose part of their glucose-lowering activity when eGFR falls to < 45 – 60 mL/min/1.73 m², which means that their use is no longer indicated and should be interrupted if levels are below this threshold [123,124]. Nevertheless, the blood-pressure-lowering effects of SGLT2is appear to be maintained [125,126], and reductions in both major CV events and mortality have been reported in subgroup analyses of T2DM patients with eGFRs < 60 mL/min/1.73 m² in CV outcome trials [127,128]. However, even though SGLT2is consistently reduce systolic blood pressure [129], this specific effect apparently plays a minor role in the improvement of either CV [130] or renal [131] outcomes.

In patients with T2DM at high CV risk recruited for the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) [120], empagliflozin was associated with slower progression of kidney disease, as reflected by reduced albuminuria and a smaller decline in eGFR, and lower rates of clinically relevant renal AEs, including progression to ESRD, compared with placebo when added to standard care [132] (Table 4). Also, a detailed post-hoc analysis supports both short-term and long-term benefits of empagliflozin on UACR, irrespective of albuminuria status at baseline [133]. At week 12, the placebo-adjusted geometric mean ratio of UACR changes from baseline with empagliflozin were -7% ($P = 0.013$), -25% ($P < 0.0001$) and -32% ($P < 0.0001$) in patients with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively, and these UACR reductions were maintained at 164 weeks. Indeed, patients treated with empagliflozin were more likely to experience sustained improvements from microalbuminuria to normoalbuminuria (HR: 1.43, 95% CI: 1.22–1.67; $P < 0.0001$) and from macroalbuminuria to microalbuminuria or normoalbuminuria (HR: 1.82, 1.40 to 2.37; $P < 0.0001$), and less likely to experience sustained deterioration from normoalbuminuria to microalbuminuria or macroalbuminuria (HR: 0.84, 0.74 to 0.95; $P = 0.0077$) [133]. Of note, reductions in major CV events and mortality were also consistent across baseline categories of eGFR and UACR [127]. In patients with prevalent DKD at baseline (2250 of the whole cohort of 7020 patients), empagliflozin compared with placebo reduced the risks of CV death by 29% (HR: 0.71, 95% CI: 0.5–0.98), all-cause mortality by 24% (HR: 0.76, 95% CI: 0.59–0.99) and hospitalization for heart failure by 39% (HR: 0.61, 95% CI: 0.42–0.87). The effects of empagliflozin on these outcomes were consistent across all baseline categories of eGFR and UACR [127].

In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, prespecified outcomes included a composite of sustained and adjudicated doubling of serum creatinine, ESRD and death from renal causes, the individual components of this

Table 4 Renal outcomes reported with sodium–glucose cotransporter type-2 inhibitors (SGLT2is) in patients with type 2 diabetes and high cardiovascular risk.

Studies	SGLT2i daily dose vs. comparator	Active vs. placebo (n)	Median follow-up (years)	Baseline mean eGFR	Annual GFR decline (slope difference)	Baseline UACR (g/g)	Change in UACR (%)	New-onset persistent macro	Doubling of serum creatinine	Progression to ESRD requiring RRT	Composite renal outcome	Death from any cause ^a
EMPA-REG OUTCOME [120,132,133]	Empagliflozin 10 or 25 mg vs. placebo	4687 vs. 2333	3.1	74.2	1.48 (NA), P < 0.001	Micro: 29% macro: 11%	Range: –15% to –49% ^b	0.62 (0.54–0.72), P < 0.001	0.56 (0.39–0.79), P < 0.001	0.45 (0.21–0.97), P = 0.04	0.61 ^c (0.53–0.70), P < 0.001	0.68 (0.57–0.82), P < 0.001
CANVAS [134,135]	Canagliflozin 100–300 mg vs. placebo	5795 vs. 4347	2.4	76.5	1.2 (1.0–1.4), NA	Median: 11.3 (IQR: 6.5–33.0), micro or macro: 27%	–18% (–16 to –20), NA	0.73 (0.67–0.79), NA	0.50 (0.30–0.84), NA	0.77 (0.30–1.97), NS	0.60 ^d (0.47–0.77), P < 0.001	0.87 (0.74–1.01), NS

Results are expressed as hazard ratios (95% confidence interval).

eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio; ESRD: end-stage renal disease; NA: not available; IQR: interquartile range; NS: not significant.

^a Includes renal death, as those results are lacking in publications (presumably very few events).

^b Normoalbuminuria at baseline: –15%, 95% CI: –22 to –7, P = 0.0004; microalbuminuria (micro) at baseline: –42%, 95% CI: –49 to –34, P < 0.0001, macroalbuminuria (macro) at baseline: –49%, 95% CI: –60 to –36, P < 0.0001.

^c Progression to macro: doubling of serum creatinine, initiation of renal replacement therapy (RRT), death due to renal disease; another post-hoc outcome was doubling of serum creatinine, initiation of RRT, death due to renal disease (HR: 0.54, 95% CI: 0.40–0.75, P < 0.001).

^d Sustained 40% reduction in eGFR, need for RRT, death due to renal causes; another composite endpoint was sustained doubling of serum creatinine, ESRD, death due to renal causes (HR: 0.53, 95% CI: 0.33–0.84).

composite outcome, annual reductions in eGFR and changes in UACR [134,135]. The composite renal outcome presented less frequently in the canagliflozin group compared with the placebo group, with consistent findings across the prespecified patient subgroups. Annual eGFR declines were slower and mean UACRs were lower in participants treated with canagliflozin than with placebo. After a rather short median follow-up of 2.4 years, only a numerical trend for less progression to ESRD requiring renal replacement therapy was noted [135] (Table IV). Renal outcomes (HR: 0.59, 95% CI: 0.44–0.79 vs. HR: 0.63, 95% CI: 0.39–1.02; P = 0.73 for interaction) were similarly reduced in the secondary and primary CV prevention cohorts, respectively [136]. In addition, the relative effects on most of the CV and renal outcomes were similar across all eGFR subgroups [128].

Canagliflozin compared with glimepiride slowed the progression of renal disease over 2 years in patients with T2DM together with reductions in albuminuria and declines in eGFR independently of its glycaemic effects [137]. These renoprotective effects of canagliflozin were confirmed in a 1-year open-label study of Japanese T2DM patients with CKD, which also showed a reduction in tubulointerstitial markers [138]. The large-scale ongoing prospective Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) compares the efficacy and safety of canagliflozin vs. placebo in preventing clinically important kidney and CV outcomes (primary outcome is a composite of ESRD, doubling of serum creatinine and renal or CV death) in patients with T2DM and established CKD [139]. A similar study is also ongoing with dapagliflozin [A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (Dapa-CKD); ClinicalTrials.gov identifier: NCT03036150] to confirm and extend the preliminary positive results for albuminuria over 2 years with dapagliflozin therapy in T2DM patients with renal impairment [140].

Nevertheless, even though SGLT2is have elicited considerable enthusiasm, they may be associated with AEs, some of which are potentially severe, thereby requiring that individual benefit–risk ratios be taken into consideration [141,142]. Indeed, despite the encouraging renal outcomes described above, scattered reports have suggested the possible risk of acute kidney injury that may, on occasions, require renal replacement therapy [143]. Therefore, several mechanisms have been proposed to explain this risk with SGLT2is, including: effective volume depletion (with dehydration or diuretic therapy); excessive decline in transglomerular pressure (with concomitant RAAS blockade); and induction of renal medullary hypoxic injury (triggered by, for example, non-steroidal anti-inflammatory drugs) [123,142]. Given the higher proportion of reports of acute renal failure with SGLT2is in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database [144], the FDA now requires that acute kidney injury be listed as a potential side-effect of SGLT2is while cautioning careful prescription of these drugs with the other above-mentioned medications.

In the event, it is imperative to ascertain whether the reported acute renal failure represents true structural kidney injury or a functional decline in eGFR [145]. The available data support the latter, especially in circumstances exposing patients to dehydration. In the EMPA-REG OUTCOME, the number of patients (mostly being treated with RAAS blockers) who developed acute renal failure appeared to be less in the group treated with the SGLT2i than with placebo [132]. In fact, when SGLT2is are properly used in clinical practice, acute kidney injury is a rare event. In addition, a network and cumulative meta-analysis of RCTs has provided diverse results for three SGLT2is regarding risk of renal AEs, thereby indicating that more data from large long-term RCTs and well-conducted observational studies in real-life settings are clearly warranted before any conclusions can be drawn [146].

Insulin

Surprisingly, few data have been published to support the nephroprotective effects of insulin in experimental preclinical studies, which contrasts with the unexpected interest devoted to C-peptide almost a decade ago [147,148]. Yet, several key elements of the insulin-signalling cascade contribute to podocyte function and survival [149], and the insulin receptor is crucial for renal function in the glomeruli and tubules. When signalling is diminished in, for example, insulin-resistant states, it may be responsible for a number of important renal complications, including glomerular disease and albuminuria, leading to hypertension [150]. Also intriguing is the fact that the effects of insulin therapy on renal outcomes have been poorly investigated in patients with T2DM, and that the data from available RCTs are scarce and difficult to interpret for several reasons. In the UKPDS, newly diagnosed T2DM patients were at low renal risk, and the intensive group included sulphonylurea-treated and insulin-treated patients [151,152]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, Veterans Affairs Diabetes Trial (VADT) and ADVANCE, intensification of blood glucose control was based on more insulin therapy, but not exclusively, making it difficult to differentiate the effects of reduction of hyperglycaemia from those of insulin per se [153]. Finally, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial included patients with dysglycaemia, and renal outcomes were not analyzed separately from eye disease [154].

Few studies have provided data on renal endpoints when comparing insulin therapy with other glucose-lowering medications, and none have supported better nephroprotection by insulin. In a retrospective cohort study using data from the UK General Practice Research Database, exogenous insulin therapy compared with metformin monotherapy as the reference was associated with an increased risk of diabetes-related complications, including renal complications. However, differences in baseline characteristics between treatment groups (more advanced and complicated disease in insulin-treated patients) should be considered when interpreting these results [155]. Of the patients who intensified their metformin monotherapy in the US Veterans Affairs national database, the addition of insulin compared with a sulphonylurea was not associated with a lower rate of adverse kidney outcomes (persistent eGFR decline \geq 35% from baseline, a diagnosis of ESRD). In contrast, it was associated with a higher rate of the composite outcome, including death, which was not modified according to baseline eGFR [156]. In the previously mentioned AWARD-7 trial, although insulin glargine was associated with a slightly greater decline in eGFR compared with once-weekly dulaglutide at 52 weeks, both treatments provided similar glycaemic control in patients with T2DM and moderate-to-severe DKD [98]. In a US study within a real-life setting, initiation of insulin glargine compared with dulaglutide therapy was associated with a significantly greater decrease in eGFR after 1 year together with a smaller reduction in HbA1c [99]. Finally, in a study comparing basal insulin with pioglitazone as an add-on therapy for T2DM patients for whom sulphonylurea and metformin regimens had failed, both treatments improved glycaemic control, whereas only pioglitazone proved advantageous in terms of preserving renal function [58].

Combined therapies

DKD in T2DM is a complex disorder that requires multifactorial interventions to minimize the risk, and RAAS inhibitor therapy is the mainstay of DKD prevention [6]. In T2DM patients at high CV risk recruited for four large prospective trials showing significant reductions in renal outcomes (LEADER, SUSTAIN-6, EMPA-REG

OUTCOME, CANVAS), almost three-quarters of all patients were treated with RAAS blockers. The potential complementary mechanism between RAAS inhibitors and SGLT2is has been emphasized, as discussed in a recent review [157].

When focusing on glucose-lowering therapies, a large majority of patients included in the above-mentioned trials were treated with metformin at baseline and throughout the follow-up period. Thus, liraglutide, semaglutide, empagliflozin or canagliflozin were added to the standard care which, in most patients, comprised metformin; the latter, however, was prescribed at similar percentages in both the tested drug and placebo groups.

A promising combination is the association of an SGLT2i with a GLP-1RA: they appear to be synergistic and, at least according to the available short-term data for each pharmacological approach, this combination may yet be the most useful way to protect the kidney (and heart as well) in T2DM patients [158]. However, the strategy still requires further validation in clinical trials with a focus on CV and renal outcomes before it can be recommended for more extensive use in clinical practice, especially as such a drug combination is more expensive. Moreover, whether the addition of pioglitazone might also result in better renal outcomes, as has been postulated for CV outcomes [159], remains an open question.

Conclusion

The overall number of patients with DKD is high and is expected to continue to increase in parallel with the growing global T2DM pandemic. Yet, based on some landmark clinical trials, DKD is preventable by controlling conventional factors, including hyperglycaemia and hypertension, using a combination of lifestyle approaches and multifactorial drug therapies. Of the pharmacological approaches, RAAS inhibitors are considered the cornerstone of renal protection, especially in T2DM patients with (micro)-albuminuria. Nevertheless, the remaining risk of DKD progression is still high.

Improving glucose control remains essential to either prevent or slow the progression of DKD. Yet, despite the numerous positive results in preclinical studies, most glucose-lowering agents have only shown favourable effects on surrogate endpoints, such as albuminuria, in clinical studies, with almost no evidence of positive effects on hard renal outcomes (Table 1). In contrast, GLP-1RAs and SGLT2is have proven their ability to reduce composite renal outcomes including albuminuria, eGFR decline, doubling of creatinine and progression to ESRD or kidney-related death. However, only SGLT2is have proved capable of reducing hard clinical endpoints, such as doubling of creatinine and progression to ESRD, while the positive effects of GLP-1RAs on composite renal outcomes were mainly driven by the reduction of new-onset macroalbuminuria. This is why the updated 2018 consensus report by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) has recommended that, for patients with T2DM and CKD with or without CV disease, the first therapeutic option considered should be an SGLT2i shown to reduce DKD progression or, if contraindicated (eGFR is less than adequate) or not preferred, a GLP-1RA to exert CV protection [160]. Of note, as these nephroprotective effects are independent of glucose-lowering, the underlying mechanisms remain a subject of debate. Besides their positive effects on systemic factors such as blood glucose, body weight and blood pressure, GLP-1RAs and SGLT2is exert their nephroprotection mainly via direct intrarenal effects related to haemodynamic changes or their anti-inflammatory/antioxidative/antifibrotic activities.

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