REVIEW

New Pharmacological Strategies for Protecting Kidney Function in Type 2 Diabetes

Marcel H.A. Muskiet MD[1]

David C. Wheeler MD[2]

Hiddo J.L. Heerspink PharmD PhD[3]

[1] Diabetes Centre, Department of Internal Medicine, VU University Medical Centre, Amsterdam, The Netherlands

[2] Centre for Nephrology, University College London, London, United Kingdom

[3] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

Corresponding Author:

David C. Wheeler MD

Centre for Nephrology, University College London

Rowland Hill Street, London NW3 2PF, UK

Email: d.wheeler@ucl.ac.uk

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[H1]Summary

Diabetes is the leading cause of impaired kidney function, albuminuria and renal replacement therapy in virtually all regions of the world and places a large burden on health care systems. Current treatment strategies rely on intensive glucose-lowering and strict blood pressure control, targeting blockade of the renin-angiotensin-aldosterone system. Such approaches may slow decline in kidney function, but many patients progress to end-stage kidney failure despite optimal therapy. In recent clinical trials, two new-generation glucose-lowering drug classes; the sodium-glucose co-transporter (SGLT)2 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists have been shown to improve both kidney and cardiovascular outcomes in patients with type 2 diabetes. Other new approaches, based on an improved understanding of the mechanisms that contribute kidney damage in the context of diabetes, include use of drugs that block endothelin receptors (e.g. atrasentan) and non-steroidal mineralocorticoid receptors (e.g. finerenone). Here we review recent clinical data relevant to these new therapeutic approaches in the management of kidney disease in the context of type 2 diabetes.

[H1]Introduction

Patients with type 2 diabetes mellitus (T2DM) who develop a reduction in estimated glomerular filtration rate (eGFR) to <60 ml/min/1.73m^2, albuminuria (e.g. urinary albumin:creatinine ratio [UACR] >3 mmol/mol), or both, sustained over at least 3 months, are considered to have chronic kidney disease (CKD) according to current international guidelines.[1] CKD identified in the context of T2DM is usually referred to as “diabetic nephropathy” or “diabetic kidney disease” (DKD) even when kidney histology has not been formally assessed by biopsy. The assumption that kidney dysfunction is a consequence of diabetes may be reinforced by the presence of other diabetic complications (such as retinopathy) and by blood tests excluding other causes of CKD such as system vasculitis or myeloma. A diagnosis of CKD in a person with T2DM has important implications in terms of prognosis. Not only is the risk of developing end-stage kidney disease (ESKD) increased, potentially requiring renal replacement therapy (such as dialysis or kidney transplantation), but patients with diabetes and CKD are also at substantially higher risk of mortality and non-fatal cardiovascular events when compared to those with diabetes but without CKD.[2] The risk of these adverse outcomes is further increased at lower levels of eGFR and higher rates of urinary albumin excretion.[1] Monitoring for the development and progression of CKD can be achieved through regular blood testing to allow estimation of GFR and analysis of urine samples (preferably early morning) for UACR. The aims of medical management in DKD are to reduce the level of albuminuria and prevent a progressive decline in eGFR. The identification of renin-angiotensin-aldosterone system (RAAS)-inhibition as an effective renoprotective strategy in T2DM patients in the early 2000’s was a major step forward, but several years have subsequently passed without much progress.[3] However, emerging data from clinical outcome trails indicate that new-generation glucose-lowering drug-classes (i.e. sodium-glucose co-transporter [SGLT-2] inhibitors and certain incretin-based therapies) may protect the kidney through mechanisms not directly related to glucose-lowering.[4, 5] Furthermore, there are a number of novel pharmacological agents under development that target newly identified mechanistic pathways underlying DKD. This review summarizes our current knowledge of the clinical benefits of new strategies that are either approved for clinical use, or have shown promising efficacy and safety in advanced development programs (**Figure 1**).

[H1]Current treatment strategies in diabetic kidney disease

Recommended treatment strategies for patients with T2DM and CKD are to initiate appropriate lifestyle changes (e.g. weight management, physical activity, dietary recommendations and smoking cessation) and to target high blood pressure and poor glycaemic control.

[H2]Glycaemic control

Optimisation of glycaemic control reduces the risk of microvascular complications in diabetes, including the onset and progression of albuminuria and in a secondary analysis of the ADVANCE trial, the incidence of ESKD.[5, 6] Yet reaching and maintaining HbA1c-targets can be more challenging in patients with DKD because an eGFR <60 mL/min/1.73m^2 restricts the use, or dose, of several oral and injectable glucose-lowering agents.[7] For example, most guidelines recommend discontinuation of metformin when eGFR falls <30 mL/min/1.73m^2 to reduce the risk of lactic acidosis, a rare but serious

adverse effect.[8] Accumulation of sulphonylureas and their active metabolites due to reduced renal excretion increases the likelihood of hypoglycaemia, and necessitates the avoidance of first generation agents (e.g. tolbutamide) and dose restriction of some second-generation agents (e.g. glimepiride) in patients with CKD.[9] Largely because of these risks, arguments have been made for less stringent HbA1c-targets for patients with T2DM and low eGFR levels by some experts.[10]

[H2]Blood pressure control

The best method to assess blood pressure in patients with T2DM (e.g. whether to use resting office readings or 24h-assessment), is not universally agreed and guidelines differ in recommending target systolic and diastolic pressures.[5, 11] Lower targets (e.g. <130/80 mmHg) are generally considered appropriate to reduce cardiovascular risk and slow eGFR-decline once albuminuria develops. While most classes of antihypertensive medication are used to control hypertension in patients with T2DM and CKD, current guidelines generally recommend inclusion of angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEi) in the antihypertensive regimen, based on evidence from randomized controlled trials conducted almost two decades ago (see below).[5] RAAS-blockers reduce albuminuria, probably by reducing intraglomerular pressure and may also prevent renal inflammation and fibrosis. Although renoprotective in the longer-term, their use may be limited by acute reductions in eGFR and/or the development of hyperkalaemia. There are few studies directly comparing ACEi with ARBs in DKD but the available data suggest that the two classes have comparable beneficial effects on kidney outcomes.[12] Declining kidney function is often associated with fluid retention, which exacerbates hypertension resulting in peripheral and pulmonary oedema. Loop diuretics are often used to offset volume expansion and treat associated symptoms, but may have a detrimental effect on eGFR as a result of intravascular volume depletion.

[H1]Evidence-based renoprotective strategies

The concept of specifically protecting the kidney in patients with T2DM arose largely from studies of ARBs conducted in the late 1990s. In two clinical outcome trials reported in 2001, IDNT and RENAAL, the use of irbesartan and losartan respectively reduced the likelihood of adverse kidney outcomes by approximately 20% when compared to conventional therapies.[13, 14] Prior animal studies indicated that such renoprotective effects were due to reductions in intraglomerular pressure, thought to result from the ability of these agents to selectively vasodilate the efferent arteriole of the glomerulus.[15, 16] This mechanism of action was thought to explain the acute reductions in eGFR observed in many patients on initiation of these agents, which need to be considered in the light of their longer-term benefit on kidney function. Post-hoc analyses of these trials helps to support the hypothesis that renoprotection was conferred as a result of RAAS-blockade, rather than the effects on systemic blood pressure.[17]

[H1]The search for new therapies

Despite widespread use of RAAS-inhibitors as part of the antihypertensive regimen in clinical practice, there is a high residual risk of progressive kidney disease highlighting a need for new therapies.[3, 5] Following RENAAL and IDNT, investigators tried to show that maximizing RAAS blockade by a combination of an ARB with either an ACEi (VA NEPHRON-D)[18] or the direct renin inhibitor aliskiren

(ALTITUDE)[19] would have an additional benefit on kidney outcomes. Although combination therapy led to greater reductions in albuminuria and blood pressure, both trials were stopped prematurely for safety and futility reasons, respectively.

Alternative therapeutic approaches that have been tried unsuccessfully include administration of the glycosaminoglycan sulodexide (Sun-MACRO)[20], targeting of the endothelin receptor with the antagonist avostentan (ASCEND)[21] and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) with bardoxolone methyl (BEACON).[22] Despite such setbacks, the expanding problem of T2DM and the growing cost of managing the associated complications has driven the search for new therapies. Large-scale clinical trials have been required to prove cardiovascular safety (in addition to HbA1c-lowering) of new agents by regulatory agencies. These cardiovascular outcome trials (CVOTs) have not only indicated generally favourable adverse effect profiles of newer drug-classes, but also identified potential drug-specific renoprotective benefits associated with the use of SGLT2 inhibitors (empagliflozin and canagliflozin) and glucagon-like peptide (GLP)-1 receptor antagonists (GLP1-RAs; liraglutide and semaglutide). Other new therapeutic approaches include endothelin receptor and mineralocorticoid receptor antagonists (**Figure 1**).

[H2]SGLT2 inhibitors

The kidneys play an important role in normal glucose homeostasis through gluconeogenesis, utilization of glucose as a metabolic fuel and re-absorption of most filtered glucose by the sodium glucose co-transporters 1 and 2 (SGLT1 and SGLT2, respectively) located in the luminal membrane of the proximal tubule.[23] The majority (80-90%) of filtered glucose is reabsorbed by the high-capacity low-affinity SGLT2 in the early S1 segment of the proximal convoluted tubule, whereas the remaining 10-20% is reabsorbed by the low-capacity high-affinity SGLT1 in the more distal S2/S3 segment.[23, 24] In patients with poorly controlled diabetes, the maximum renal glucose reabsorptive capacity is increased compared to normal glucose-tolerant individuals, likely because of upregulation of SGLT2.[25, 26] As such, inhibition of SGLT2 appeared an attractive therapeutic target. Four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin) have been approved by the FDA and EMA for use as glucose-lowering drugs in patients with T2DM.[23, 27]

SGLT2 inhibitors dose-dependently increase urinary glucose excretion by approximately 70-80 gram per day in healthy non-diabetic individuals[27], and decrease HbA1c by 0.5 to 0.8% in T2DM patients, depending on baseline HbA1c and kidney function.[28] SGLT2 inhibitors can be used in combination with other anti-hyperglycaemic drugs and their glucose-lowering efficacy is not reduced when used as an adjunct to metformin, sulphonylureas, DDP-4 inhibitors, GLP-1RA's, or basal insulin.[29] Glucose lowering efficacy appears to be enhanced in patients with poor glycaemic control (HbA1c >8.0%).[28] Beyond glycaemic control, SGLT2 inhibitors have been shown to decrease body weight by 2-3 kg[5, 23], in part as a direct consequence of a negative caloric balance due to increased urinary glucose excretion (1g of glucose equates 4 kilocalories). However, despite on-going glycosuria, weight loss does not usually continue after six months, likely due to compensatory changes in metabolism and increased appetite and food intake.[30, 31]

As the reabsorption of glucose and sodium are coupled, SGLT2 inhibition leads to a dose-dependent natriuresis.[32] Although the natriuretic effect of these drugs dissipates after 2-3 days and

sodium and fluid balance re-equilibrate, an ~7% reduction in plasma volume, along with an increase in haematocrit and reduction in systolic blood pressure of ~2-4 mmHg have been reported.[28] The antihypertensive effects of SGLT2 inhibitors appear to be independent of concomitant antihypertensive medications (including diuretics and RAAS-inhibitors).[33, 34]

The beneficial effects of SGLT2 inhibitors on cardio-renal outcomes have been established in two landmark placebo-controlled cardiovascular outcome studies, the EMPA-REG OUTCOME trial[35] and the CANVAS Clinical Trial Program.[36, 37] In EMPA-REG OUTCOME, involving 7020 T2DM patients with established cardiovascular disease, empagliflozin reduced the risks of the composite primary MACE outcome by 14% (95% CI 1-26%; P=0.04) relative to placebo after a median follow-up of 3.1 years.[35] Similarly, in the CANVAS Program, involving 10,142 patients with T2DM and high cardiovascular risk, canagliflozin lowered the rate of the primary MACE outcome by 14% (95% CI 3-25%; P=0.02) relative to placebo after a mean of 118.2 weeks.[36] Importantly, both SGLT2 inhibitors slowed the progression of eGFR-decline and reduced the risk of a composite renal outcome by approximately 40% in the study populations who had a baseline eGFR >30 ml/min/1.73m^2 that were already well managed, with ~80% of all participants prescribed a RAAS-inhibitor.[36-40] Despite these results, it is important to realize that neither EMPA-REG OUTCOME or CANVAS were designed to assess the renoprotective effects of SGLT2 inhibitors.[41] Dedicated kidney outcome trials (as described below) are required before recommendations on the use of SGLT2 inhibitors as a renoprotective drug can be included in updated clinical practice guidelines.[4]

The renoprotective benefits of SGLT2 inhibitors are likely to be explained by several mechanisms. Like ACEi and ARBs, these agents are thought to have favourable effects on renal haemodynamics (**Figure 2**). Their proximal natriuretic effect, possibly enhanced by functional blockade of the sodium-hydrogen exchanger 3 (NHE3)[42], increases sodium delivery to the downstream juxtaglomerular apparatus.[43] In turn, tubulo-glomerular feedback signalling is activated, resulting in afferent arteriolar vasoconstriction and decreased renal blood flow, attenuating glomerular hyperfiltration which is a characteristic of DKD.[16] In long-term trials, SGLT2 inhibitors consistently reduce eGFR after treatment initiation over a wide range of baseline values, with the reduction reversed after washout of the study drugs, collectively suggesting renal haemodynamic actions.[44] Such early reductions in eGFR predict a slower subsequent decline in kidney function on long-term treatment, as reviewed in detail elsewhere.[16, 23, 45] SGLT2 inhibitors may also reduce renal hypoxia, which is typically observed in diabetic kidneys.[46] By reducing sodium and glucose transport activity in the proximal tubule, energy and oxygen demands decrease, resulting in preservation of tubular cell structural integrity and possibly function.[46]

SGLT2 inhibitors are currently not licenced for use in patients with DKD and eGFR <45 mL/min/1.73m^2 in most countries (**Table 1**), since their efficacy in terms of glucose lowering is attenuated in stages 3b-5 CKD.[47-49] However, body weight, blood pressure and albuminuria lowering effects persist in these.[50, 51] Additionally, subgroup analyses from the EMPA-REG OUTCOME and CANVAS trials suggested that the efficacy of SGLT2 inhibitors to reduce the risks of cardiovascular and renal outcomes do not depend on eGFR.[36, 52] In recognition of these findings, Health Canada allows physicians to consider their use when indicated for cardiovascular and renal protection down to an eGFR of 30 mL/min/1.73m^2.

Effects of SGLT2 inhibitors in slowing progressive kidney function loss appear to be independent of glycaemic control. In a secondary analysis of CANTATA-SU, a 2-year clinical phase-III registration trial comparing canagliflozin with the SU-derivative glimepiride, the rate of kidney function decline was significantly lower in the canagliflozin arm, while glycaemic control was similar between the two classes.[53] Also, *post-hoc* analyses of EMPA-REG OUTCOME and earlier stage phase-III studies indicated that UACR-lowering was statistically independent of concomitant changes in HbA1c.[4, 39] Collectively, these data suggest that renoprotective effects are unlikely to be mediated by improvements in glycaemic control but rather by other mechanisms as described above. Renal outcomes trials of SGLT2 inhibitors in DKD patients are ongoing. One of these, CREDENCE (NCT02065791)[54] has recently been stopped early at the recommendation by the data safety monitoring committee, based on achievement of pre-specified kidney efficacy criteria. Finally, since glomerular hyperfiltration is involved in the pathophysiology of various kidney diseases beyond DKD, there is a rationale to extend the use of SGLT2 inhibitors in non-DKD such as CKD induced by obesity, secondary focal segmental glomerulosclerosis or hypertensive nephrosclerosis.[55] As such, the dedicated renal outcome study Dapa-CKD trial (dapagliflozin; NCT03036150) is recruiting patients with CKD with or without T2DM, with a recent announcement for plans for a similar study assessing empaglilfozin (EMPA-KIDNEY trial[56]).

[H2]Incretin-based therapies

GLP-1 is secreted from gut enteroendocrine L-cells at low tonic rates in the fasting/interprandial state. Circulating levels of this gut-hormone rise briskly within minutes of food intake.[57, 58] Initial studies focused on its role as an incretin-hormone, in-part responsible for the ~70% amplification of insulin secretion in the context of nutrient (particularly glucose) ingestion; i.e. the “incretin-effect”.[59] This finding was rapidly followed by the demonstration that the glucoregulatory actions of GLP-1 also include suppression of glucagon secretion, inhibition of gastric emptying rate and small bowel motility and reduction in appetite and food intake, transduced by a single GLP-1 receptor (GLP-1R) located in many organs including the kidney (see below).[58]

The incretin effect is severely reduced or absent in patients with T2DM[59], and is regarded as a key pathophysiological defect that contributes to glucose intolerance.[60] The insulinotropic and glucose-lowering response to exogenous GLP-1 is preserved in human T2DM[61], suggesting that pharmacological efforts aimed at therapeutic amplification of GLP-1-induced glucose-lowering in this population was worthwhile. However, the GLP-1 peptide is unstable *in-vivo* and continuous infusion would be required to overcome this problem, limiting clinical application. Circulating GLP-1 is rapidly inactivated (<2 minutes), primarily by DPP-4, to a metabolite that stimulates insulin secretion.[62] These findings prompted two strategies to extend and maintain incretin activity in T2DM, firstly the use of injectable GLP-1RAs that are resistant to DPP-4 cleavage and provide supraphysiological concentrations of ligands to the GLP-1R, and secondly the use of oral DPP-4 inhibitors (DPP-4is), which prevent degradation of endogenously secreted GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), another incretin-hormone.[62]

Several incretin-based drugs with different structures, modes of administration and pharmacokinetic properties (separating the GLP-1RA class into short-acting [prandial] and long-acting

compounds) have been introduced as treatments for T2DM,[58, 62] GLP-1RAs reduce fasting glucose and HbA1c-levels by 0.5-1.3%, the reductions achieved depending on choice of agent, dose, baseline HbA1c and background therapy.[62] Although less effective when compared to GLP-1RAs, DPP-4is promote reductions HbA1c of 0.6-0.9%.[62] Given their glucose-dependent mode of action, incretin-based drugs are associated with low rates of hypoglycaemia, and are generally well tolerated.[57, 58, 62] As pharmacokinetic data and clinical experience with GLP-1RAs in patients with T2DM and CKD are limited, caution or discontinuation is advised when kidney function is severely impaired (**Table 1**). DPP-4is are well tolerated in stages 3b to 5 CKD[62], although most manufacturers recommend dose reductions, with the exception of linagliptin, which is mainly eliminated through biliary excretion.[62]

As with SGLT2 inhibitors, "off-target" effects of incretin-based drug-classes may favourably modify cardio-renal risk profile and impact on clinical outcomes beyond glycaemia.[5] Firstly, GLP-1R-mediated reductions in appetite and food-intake result in a loss of ~0.8-1.4 kg in body weight[63], albeit with much variation in individual responses and within-class differences. DPP-4is tend to be weight-neutral as they do not induce satiety.[62, 64] Secondly, sustained GLP-1RA-treatment consistently reduces systolic blood pressure by ~2-3 mmHg[5, 62, 65], while DPP-4is have no uniform antihypertensive effect.[5, 62] Thirdly, incretin-based therapies modestly improve fasting and particularly postprandial lipid-profiles.[5] Fourthly, GLP-1 may modulate inflammation/fibrosis at multiple sites. Finally, GLP-1 has been implicated in the enteroendocrine regulation of water and electrolyte balance (the putative "gut-renal axis"[66]), specifically by enhancing renal solute excretion in response to acute solute ingestion, forming a feed-forward loop between the gut and the kidneys.[62] GLP-1Rs have been identified at various locations in the kidney, including pre-glomerular vascular smooth muscle cells and proximal tubular cells, emphasizing a potential physiological role of GLP-1 in kidney function.[62] Administration of GLP-1 and GLP-1RAs induces natriuresis, diuresis and urinary alkalinisation in healthy males[67, 68] and T2DM patients, possibly mediated by inhibition of NHE3 in the brush border of the proximal tubule.[69-71] As with SGLT2 inhibitors, such proximal natriuresis would be expected to stimulate TGF-signalling, leading to afferent vasoconstriction and a reduction in renal blood flow and GFR. However, in T2DM patients, mechanistic studies and clinical trials have failed to identify (consistent) effects of GLP-1RAs on renal haemodynamics[69-72] or acute reductions in (estimated) GFR upon initiation of therapy.[62] This may be explained by direct NO-dependent vasodilatory actions of GLP-1RAs at the afferent arteriole, which may override or offset vasoconstriction induced by TGF (**Figure 2**).[68] Renal response to DPP-4 inhibition may be even more complicated, as they induce natriuresis, at least in-part *independent* of GLP-1[66, 73]

Data from placebo-controlled phase-III trials of GLP-1RAs in patients with T2DM have shown inconsistent effects on albuminuria and generally no effect on eGFR. In SCALE Diabetes, 56 weeks of liraglutide resulted in dose-dependent reductions in UACR[74], whereas the 26-week LIRA-RENAL trial in T2DM patients with moderate to severe kidney impairment did not demonstrate reductions in UACR .[75] In a small crossover trial in albuminuric T2DM patients on RAAS-inhibitors, liraglutide given for 12 weeks reduced 24h urinary albumin excretion by 32% compared with placebo, independent of HbA1c-reductions and possibly driven by blood pressure-lowering.[76] Integrated data from nine registration trials of dulaglutide, which included 6005 patients with T2DM, showed lower UACRs than with placebo (-16.7% vs 10.0%), insulin glargine (-16.7% versus 3.7%) and other active comparators (-20.0% vs -

12.5%).[77] Although no differences in serum creatinine levels were observed over 104 weeks, fewer patients receiving dulaglutide than insulin glargine experienced a 40%-decline in eGFR at any point during a 1-year treatment period.[77] More recently, in AWARD-7, involving 577 patient with T2DM and moderate-to-severe CKD, dulaglutide versus once-daily titrated insulin glargine (with similar HbA1c-reductions) resulted in a higher eGFR after 52-weeks, and reduced UACR in patients with baseline macroalbuminuria.[78]

Kidney outcome data have been collected as secondary and exploratory endpoints in recent (Table 2) and ongoing (Table 3) cardiovascular safety trials of GLP1-RAs and DPP4-is.[62] In ELIXA, which assessed the cardiovascular safety of lixisenatide in 6,068 patients with T2DM and a prior acute coronary event, the percentage change in UACR showed a modest difference in favour of the GLP-1RA after 25 months of follow up (24% versus 34%).[79] However, in the total population, *post-hoc* adjustment for HbA1c levels attenuated (p=0.07) the lixisenatide-induced kidney benefit, suggesting some glucose-dependency. Both LEADER (liraglutide)[80] and SUSTAIN-6 (semaglutide)[81] included a prespecified composite kidney outcome, defined as progression to macroalbuminuria, doubling of serum creatinine, ESKD, or kidney death. The kidney composite was reduced by 22% with liraglutide in 9,340 T2DM patients after 3.8 years[80] and 36% by semaglutide in 3,297 patients after 104 weeks[81], respectively. Notably, in both trials, the effects were driven by a 26-46% reduction in macroalbuminuria, rather than more clinically relevant kidney endpoints. In LEADER, the difference in kidney outcome was not altered by adjustment for change in glycaemic control, bodyweight and systolic blood pressure.[82] Finally, liraglutide modestly slowed eGFR-decline by 2% compared to placebo after 36-months (-7.44 versus -7.82 mL/min/1.73m^2, respectively), of which the clinical relevance is uncertain.[80]

In parallel to their lack of effect on cardiovascular outcomes or mortality, DPP-4i therapy may have at best a modestly beneficial effects on kidney endpoints in at-risk T2DM patients. In a recent pooled analysis of placebo-controlled trials, linagliptin reduced kidney disease events by 16%, driven by an 18%-reduction in moderate and 14%-reduction in albuminuria, with no effects on eGFR.[83] Moreover, combined data from randomised controlled trials including 217 albuminuric T2DM patients indicated that linagliptin reduced UACR by 28%, independent of HbA1c or systolic blood pressure.[84] However, MARLINA-T2D™, which included 360 T2DM patients on stable RAAS-inhibition, and was sufficiently powered to test superiority of linagliptin in reducing albuminuria, did not confirm these findings.[85] Three CVOTs involving a DPP-4is have provided data on kidney endpoints. In a secondary analysis of SAVOR-TIMI 53, involving 16,492 at-risk T2DM patients, saxagliptin led to reclassification of patients into a lower UACR category, irrespective of baseline UACR.[86] An overall mean reduction in UACR of 34 mg/g was seen with saxagliptin which was independent of HbA1c-lowering, although the drug did not impact on othermore clinically relevant kidney endpoints after 2.1 years. In TECOS, which randomized 14,671 T2DM patients to either sitagliptin or placebo, there was no clinically relevant between-group difference in either eGFR or UACR.

Although incretin-based therapies (particularly GLP-1RAs) may improve albuminuria in T2DM, effects on more clinically relevant kidney outcomes such as time to starting dialysis remain uncertain. The results of CARMELINA (NCT01897532), which examines cardio-renal effects of prolonged linagliptin-therapy in patients with pre-existing DKD, or active-comparator studies that include

secondary kidney endpoints such as CAROLINA (NCT01243424; comparing linagliptin and glimepiride) and GRADE (NCT01794143; comparing liraglutide, sitagliptin, glimepiride and insulin glargine) are anticipated. However, in contrast to SGLT2 inhibitors, there are no ongoing studies of incretin-based therapies recruiting patients with DKD with a primary objective of determining the effects of these drugs on kidney endpoints.

[H2]Endothelin receptor antagonists

The endothelin family comprises three endothelins (ET-1, ET-2, and ET-3) that bind to either the ET_A and ET_B receptor. In general, ET_A receptor activation causes vasoconstriction, matrix accumulation and cell proliferation, while ET_B receptor activation opposes these effects.[87, 88] The ET system also plays an important role in sodium and water regulation. Although ET_B activation has a sodium and water retaining effect, ET_A exerts a natriuresis, in particular via ET_A receptors located in the collecting duct.[89, 90] Pharmacological blockade of ET receptors is associated with sodium and water retention and this effect has made development of ET blockers challenging.

The ET system is thought to be involved in the development and progression of DKD.[91] Patients with DKD generally exhibit hyperglycaemia, insulin resistance, obesity, dyslipidaemia, RAAS-activation, endothelial dysfunction and increased oxidative stress, all of which increase production of ET-1 in the kidney.[91] Apart from its potent vasoconstrictive effects on the efferent renal vasculature, which can result in a reduction of renal blood flow and glomerular hyperfiltration[16], ET-1 may promote kidney injury by activating pro-inflammatory and pro-fibrotic pathways.[91, 92]

Multiple experimental and clinical mechanistic studies have supported the hypothesis that ET blockade may delay the progression of kidney disease in the long-term. ERA attenuate the vasoconstrictor effect of ET-1 and thereby reduce intraglomerular pressure and hyperfiltration (**Figure 2**). In hypertensive patients with CKD, it has been shown that ERAs caused a significant increase in effective renal blood flow and reduction in filtration fraction, indicating that ET-1 causes vasoconstriction mediated by the efferent arteriole.[93, 94] In addition to hemodynamic effects, a recent study with the ERA atrasentan reported a reduction in albuminuria, possibly through protection of the glycocalyx.[95] Other potential mechanisms of ERA-induced renoprotection involve preservation of podocytes morphology[96], and changes in production of growth-factors and vasoconstrictors II (ATII)[97] Avosentan was the first ERA to be tested in a larger randomized, placebo-controlled trial involving 286 patients with DKD and macroalbuminuria. This 12-week trial showed a dose dependent reduction in proteinuria, with an optimal dose of 10 mg/day Higher dosages (≥25 mg/day) increased the risk of the main adverse outcome, peripheral oedema (12%).[98] Following this dose finding study, a large phase 3 trial testing the effect of avosentan on kidney outcomes (ASCEND) at 25 and 50 mg/day in 1392 patients with T2DM, yet was terminated early because of an excess of congestive heart failure (CHF) and mortality associated with the ERA.[21] These results demonstrate the narrow therapeutic window of ERAs and the importance of careful dose selection to avoid adverse consequences of sodium and fluid retention.

Atrasentan, which has a higher ER_A selectivity than avosentan and may therefore exert less sodium retention, has also been tested in DKD. A phase-2 trial (RADAR), reported that atrasentan (0.75 mg/day and 1.25 mg/day) reduced albuminuria by 35% and 38%, respectively, in 211 patients

with DKD and overt proteinuria after 12 weeks, with the 1.25 mg/day dose leading to more sodium retention.[99] A large phase-3 confirmatory outcome trial (SONAR), evaluating the effect of atrasentan in T2DM patients with CKD stage 2-4, which selected individual recruits based on their initial atrasentan response in terms of albuminuria and body weight,[100] was recently stopped prematurely due a lower than expected number of renal events by that time in the study (rather than safety concerns) with results expected in late 2018.

[H2]Mineralocorticoid receptor antagonists

The steroidal mineralocorticoid receptor (MR) plays an important role in the RAAS. Although traditionally ATII has been considered the key component of the RAAS that mediates end-organ damage, it has become increasingly clear that aldosterone is at least as an important in driving cardiovascular and kidney injury, beyond the effects of renin and ATII.[101] Patients with DKD show increased activity of the MR receptors, which is most likely driven by increased levels of circulating aldosterone, altered cortisol activity and/or elevated local expression of the MR.[102]

Current clinically approved steroid-based MR antagonists (MRAs), including spironolactone and eplerenone, mimic the molecular structure of the natural MR ligands. Clinical trials to date have demonstrated that MRAs further reduce albuminuria and blood pressure in patients with diabetic and non-diabetic kidney diseases when added to a RAAS inhibitor.[103-105] Moreover, a prospective open-label study suggested that spironolactone may stabilize decline in kidney function in patients with proteinuric kidney diseases.[106]However, the use of MRAs is limited in clinical practice by adverse effects. Spironolactone is a poorly selective MRA and inhibits androgen and progesterone receptors, increasing the likelihood of sex hormone related side effects such as gynecomastia, impotence, and menstrual irregularities. occurrence of hyperkalemia. Indeed, addition of both spironolactone and eplerenone to RAAS inhibition increased the risk of hyperkalemia by three to eight fold.[107, 108] This adverse effect is particularly pronounced in elderly patients, patients with diabetes and those with CKD (i.e. the population who may also gain the greatest benefit from MRA's).[109] Preventative measures to avoid hyperkalaemia during MRA-treatment are described in **Box 1**.

In an attempt to more precisely target the MR receptor, potent MRAs which may exhibit less potassium retention, nonsteroidal compounds such as finerenone have been developed.[110] In contrast to spironolactone and eplerenone, which bind to the ligand domain of the MR receptor, finerenone induces a conformational change within the MR receptor complex, thereby ultimately changing the stability and nuclear translocation of the receptor.[111] The efficacy and safety of finerenone has been tested in ARTS-DN, a phase 2 clinical trial in T2DM patients with DKD.[112] A total of 823 patients were randomized to receive once-daily doses of finerenone (7.5, 10, 15, or 20 mg) or placebo, as an adjunct to RAAS-inhibition. Finerenone decreased UACR in a dose-dependent manner. A placebo-adjusted reduction of 21 to 38% was observed from baseline to Day-90. However, there were no differences in the incidence of the prespecified secondary outcome, an eGFR-decrease of 30% or more between the placebo and finerenone groups. The occurrence of hyperkalemia was 1.8% versus 0% in the placebo group, although only patients with a baseline potassium levels <4.8 mmol/L were eligible and few patients with an eGFR <45 mL/min/1.73m^2 and macroalbuminuria were included. The efficacy and safety of finerenone in patients with DKD is currently being tested in the ongoing

FIDELIO-DKD (NCT02540993; expected study completion October 2019) and FIGARO-DKD (NCT02545049; expected study completion February 2020) studies.

[H1]Future perspectives

Many of the new therapies described above, which may improve outcomes for DKD patients, have already been granted marketing authorization by regulatory agencies for non-renal indications or are in advanced stages of development. However, DKD is a multifactorial, heterogeneous disease comprising a variety of complex phenotypes and it seems likely that not all patients will benefit from these drugs. .[113] Between-patient variation in underlying pathophysiology results in a wide diversity of individual drug responses, as described in more detail elsewhere.[114] This variation in individual drug response was addressed in the SONAR trial described above, which selected only responder patients and excluded patients who do not tolerate atrasentan.[100] However, whether non-responders to atrasentan may benefit from an SGLT2 inhibitor, or incretin-based drug-class, or MRA or vice versa is an important question to be answered in the future.

It is also likely that future studies will start combining new therapies to further slow the progression of DKD. Theoretically, the effect of an SGTL-2 inhibitor and an ERAs would be complementary, as the diuretic properties of the SGLT-2 inhibitor can mitigate the sodium/fluid retaining effects of the ERA. In addition, the renal haemodynamic benefit of the SGLT2 inhibitor involve the afferent arteriole via TGF-signalling, whereas the ERA's reduce glomerular pressure by directly reducing efferent arteriolar resistance.

Finally, although nearly all patients with T2DM will require multiple therapies to maintain glycaemic control, no large-scale studies have provided definite data as to which are the best combinations to use. The ideal combination should correct multiple pathophysiological defects in T2DM, whilst being well-tolerated and safe, easy to administer and cost-effective. Based upon their different mechanisms of action in terms of reducing glucose, bodyweight, blood pressure and other cardio-renal risk factors, combination therapy with an SGLT2 inhibitor and GLP-1RAs may be expected to fulfil (most of) these criteria.[115] Hitherto, two trials have assessed this combination in poorly controlled T2DM patients and shown useful reductions in glycaemic measures and additive effects on weight-loss and blood pressure-lowering.[116, 117] Such combination therapy may be even more powerful in slowing the progression of DKD beyond either drug class used alone, but dedicated studies on albuminuria and kidney outcomes are needed to prove this. We believe that well-designed mechanistic studies that aim to characterize individual drug responses based on phenotypical traits, as well as large-sized prospective outcome trials that evaluate the cardio-renal effects of different combinations of drugs, are required in T2DM patients. Hurdles to developing novel therapies to reduce DKD burden and test combinations of drugs in T2DM patients are listed in **Box 2**.

[H1]Conclusion

Several promising new approaches are emerging to protect kidney function on patients with T2DM. Such progress should offer hope to the unfortunate patients in whom a progressive loss kidney function leads to ill health and reductions in quality of life. None of these new therapies have as yet been adequately proven in large scale randomised controlled trials assessing clinically relevant kidney endpoints such as 50% reduction in eGFR or the need to initiate renal replacement therapy. Many

such trials are ongoing and several will report within the next 3-5 years. Some of these agents, by virtue of their mode of action, may benefit patients with proteinuric kidney disease resulting from pathological processes other than DKD. Bearing in mind the unmet need, clinicians will no doubt welcome these new therapies and will be tempted to initiate them in CKD patients for other indications (e.g. to reduce cardiovascular risk) before kidney endpoint studies are completed. However, new risks may emerge in CKD patients and for the SGLT2 inhibitors, benefits may be attenuated in patients with advanced (stages 3b-5) CKD. Whatever the results of ongoing trials, we seem to be entering a new era in the management of patients with CKD in the context of T2DM.

Author contributions:

All authors are fully responsible for all content, were involved at all stages of manuscript development, and have approved the final version.

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Search strategy and selection criteria

We searched Medline, PubMed, Google Scholar, and the Cochrane library for English language abstracts and full-texts articles published before 16 July, 2018. We focused on new potentially renoprotective drugs in type 2 diabetes, with particular attention to SGLT2 inhibitors, incretin-based therapies, endothelin receptor antagonist and mineralocorticoid receptor antagonists. The keywords used included: “Diabetic kidney disease”, “Diabetic nephopathy”, “Renoprotection”, “Type 2 diabetes”, “Sodium-glucose cotransporter-2 inhibitor”, “SGLT2 inhibitor”, “Incretin-based therapy”, “Glucagon-like peptide-1”, “GLP-1 receptor agonist”, “Dipeptidyl-peptidase-4 inhibitor”, “DPP-4 inhibitor”, “Endothelin receptor antagonist”, “Mineralocorticoid receptor antagonist”, “MRA”. These keywords were used as single search terms and in combination. We also searched the reference list of original articles, narrative reviews, clinical guidelines, and systematic reviews and meta-analyses for further relevant material. This review is mainly restricted to clinical studies (cohort studies, randomised controlled trials, and meta-analyses of randomised clinical trials).

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Box 1| Preventative measures to avoid hyperkalemia. Derived from Roscioni et.al.[123].

Preventative measure	Advantage	Disadvantage
Monitoring serum K^+ during MRA treatment	Enables quick recognition of unusual changes in K^+ levels	Optimal timing and duration of K^+ monitoring unknown
Selection of patients based on indices of mineralocorticoid activity (PRA, urinary Na^+:K^+ ratio, FEK, or TTKG	More specific method of identifying risk of hyperkalemia than exclusion of known common risk factors such as age, diabetes status or eGFR.	Indices are influenced by diet and GFR; methods are not validated
Dietary restriction of potassium intake and use of diuretics	Easy method to reduce development of hyperkalemia	Long-term compliance with dietary restriction is limited
Review of concomitant therapies (for example NSAIDs, β-blockers and heparin)	Easy method to prevent drug related alterations in K^+ homeostasis	Physicians are often unaware of all medications taken by the patient; not all drugs with known interaction can be safely discontinued
Reduce MRA dose	Reduced chance to develop hyperkalemia	Possible reduced efficacy of MRAs

Box 2│Hurdles to developing novel therapies to reduce DKD burden

When facing the development of new treatments or combinations of drugs for CKD, there are several challenges that should be recognized, include factors that must be considered in the design of trials, as well as the identification of appropriate end-points and efficacy biomarkers. Also, testing novel therapies aimed at slowing DKD progression must be performed in diabetes patients that are already receiving standard of care, that is optimal risk factor control including the use of RAAS-blockers.

Challenges	Difficulties	Alternatives/possibilities
Disease awareness	• Disease awareness in patients with CKD stage 1-3 is ~5% • Physicians may neglect to inform patients that they have CKD	
Clinical trial recruitment	• Recruitment rates for DKD are ~0.20 patients per site per month (~25% of the number of patients enrolled per months for a diabetes trial) • Low rates delay timelines, increase costs and negatively impacts willingness of pharmaceutical companies to invest	• Clinical trial networks and patient registries
Patient selection	• Eliminate likely biological non-responders who decrease trial efficiency *versus* patients heterogeneity with respect to rate of renal function loss • Widespread use of RAAS-blockers confines recruiting patients with high proteinuria and “rapid-progressors” • Increasing numbers of DKD patients progress without developing proteinuria; ~25% do not follow “classic” paradigm	• Development of novel biomarkers can supplement proteinuria in predicting progression of renal disease
Clinical endpoints	• Characterizing the effect of a drug on renal markers (surrogates), *versus* parameters of patients well-being and hard outcome, *versus* a composite of these • Intermediate events/surrogates should match with the appropriate mechanisms of action of the drug (i.e. acute reductions in renal function with RAAS-blockers and SGLT2i)	• Using intermediate eGFR decrements (that is, -30 or -40% or eGFR slope) as surrogates of currently accepted -57% (i.e. doubling of serum creatinine)

Table 1 | Antihyperglycaemic drugs available in Europe and North America with dose reductions in CKD

Agent	Brand name	Approval (agency/year)	Dosing	Plasma half-life (hours)	Elimination route	Use in patients with renal insufficiency		
						Mild (CrCl 50-89 mL/min)	**Moderate** (CrCl 30-50 mL/min)	**Severe or ESRD** (CrCl <30 mL/min)
SGLT2 inhibitors								
Dapagliflozin	Forxiga (EU) Farxiga (US)	EMA/2012 FDA/2014	5–10 mg QD	12.9	Renal 75%; faeces 21%	No adjustment	Not approved	Not approved
Canagliflozin	Invokana	2013	100–300 mg QD	10.6-13.1	Renal 34%; faeces 52%	No adjustment	Not approved	Not approved
Empagliflozin	Jardiance	2014	10–25 mg QD	12.4	Renal 54%; faeces 41%	No adjustment	Not approved	Not approved
Ertugliflozin	Steglatro	2017	5–15 mg QD	11.0-17.0	Renal 50%; faeces 41%	No adjustment	Not approved	Not approved
GLP-1 receptor agonists								
Exenatide BID	Byetta	2005	5–10 µg BID	2.4 (*short*-acting)	Mainly renal	No adjustment	Conservative dose escalation	Not recommended
Liraglutide	Victoza	EMA/2009 FDA/2010	0.6–1.2–1.8 mg QD	11.6–13.0 (long-acting)	Peptidases Renal 6%, faeces 5%	No adjustment	No adjustment	Not recommended
Exenatide QW	Bydureon	EMA/2011 FDA/2012	2 mg QW	NS* (long-acting)	Mainly renal	No adjustment	Not recommended	Not recommended
Lixisenatide	Lyxumia (EU) Adlyxin (US)	EMA/2013 FDA/2016	10–20 µg QD	3.0 (*short*-acting)	Mainly renal	No adjustment	No adjustment	Not recommended
Albiglutide	Eperzan (EU) Tanzeum (US)	2014	30–50 mg QW	120.0 (long-acting)	Peptidases and renal	No adjustment	No adjustment	Not recommended
Dulaglutide	Trulicity	2014	0.75–1.5 mg QW	112.8 (long-acting)	Peptidases and renal	No adjustment	No adjustment	Not recommended
Semaglutide	Ozempic	2017	0.5–1.0 mg QW	165.0–184.0 (long-acting)	Peptidases and renal	No adjustment	No adjustment	Not recommended
DPP-4 inhibitors								
Sitagliptin	Januvia	FDA/2006 EMA/2007	100 mg QD	12.4	Renal 87%; faeces 13%	No adjustment	Dose reduction (50 mg QD)	Dose reduction (25 mg QD)
Vildagliptin	Galvus	2007	50 mg BID	2.0	Renal 85%; faeces 15%	No adjustment	Dose reduction (50 mg QD)	Dose reduction (50 mg QD)
Saxagliptin	Onglyza	2009	5 mg QD	2.5*	Renal 12–29%; faeces 22%	No adjustment	Dose reduction (2.5 mg QD)	Dose reduction (2.5 mg QD)
Linagliptin	Trajenta (EU) Tradjenta (US)	2011	5 mg QD	12.0	Renal ~5%; faeces ~80%	No adjustment	No adjustment	No adjustment
Alogliptin	Nesina (US)	2013	25 mg QD	21.0	Renal ~76%; faeces ~13%	No adjustment	Dose reduction (12.5 mg QD)	Dose reduction (6.25 mg QD)

*The pharmacokinetic profile of exenatide QW and exenatide BID are similar, except that subcutaneous absorption is prolonged with the QW formulation. BID, twice-daily; CrCl, creatinine clearance; DPP, dipeptidyl peptidase; ESRD, end stage renal disease; NS, not specified; QD, once-daily; QW, once-weekly.

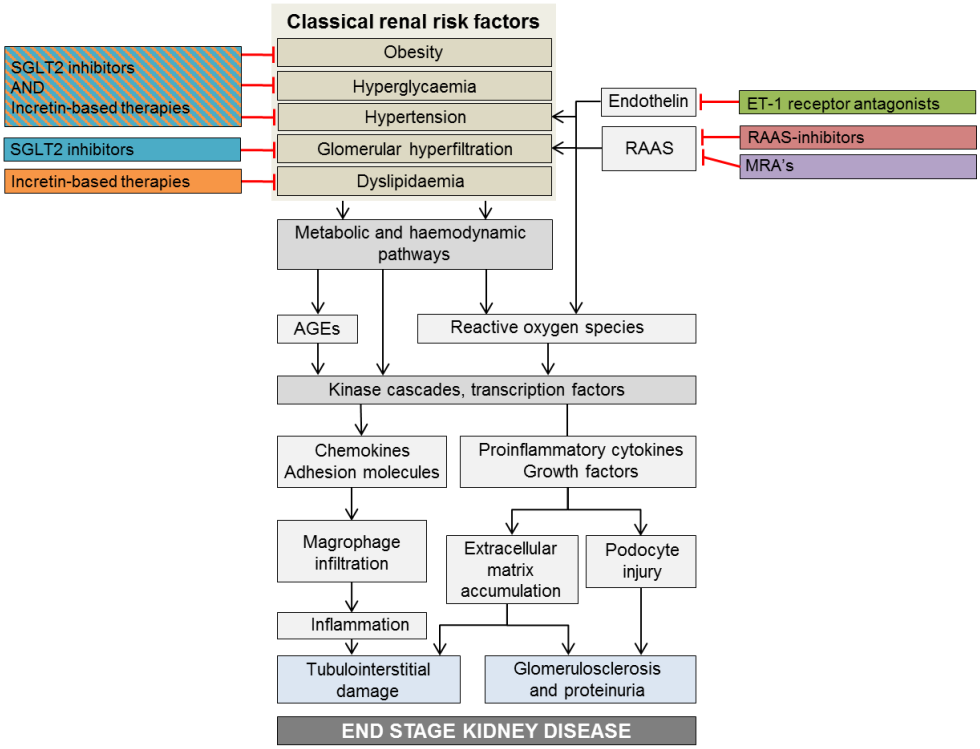
Table 2│Effect of new-generation glucose-lowering drugs in completed cardiovascular outcome trials on secondary/exploratory renal outcomes in patients with type 2 diabetes and high cardiovascular risk

Trial name (year of publication)	**Agent**	**N=**	**Main inclusion criteria**	**Follow-up (yrs)**	**Age (yrs)**	**T2DM duration (yrs)**	**HbA1c** (%)	**BL eGFR** (mL/min/1.73m^2)	**Albuminuria status at BL**	**Renal outcome / endpoints**
SGLT2 inhibitors										
EMPA-REG OUTCOME (2016)	Empagliflozin	7,020	T2DM, CVD history	3.1	63.1	57% >10	8.1	74.0	Micro: 29% Macro: 11%	Secondary: composite (macro, dSCr, ESKD, renal death) HR 0.61 (0.53, 0.70)
CANVAS Program (2017)	Canagliflozin	10,142	T2DM, CVD risk or history	3.6	63.3	13.5	8.2	76.5	Micro: 22.6% Macro: 7.6%	Secondary: composite (macro, dSCr, ESKD, renal death) HR 0.58 (0.50, 0.67)
GLP-1 receptor agonists										
ELIXA (2015)	Lixisenatide	6,068	T2DM, ACS <180 days	2.1	60.3	9.3	7.7	76.0	Micro: 19.2% Macro: 6.5%	Secondary: Change in UACR: Month-24: 34% versus 24%
LEADER (2016/2017)	Liraglutide	9,340	T2DM, CVD risk or history	3.8	64.3	12.7	8.7	80.0	Micro: 26.3% Macro: 10.5%	Secondary: composite (macro, dSCr, ESKD, renal death) HR 0.78 (0.67-0.92)
SUSTAIN-6 (2016)	Semaglutide (s.c.)	3,297	T2DM, CVD risk or history	1.9	64.6	13.9	8.7	NR	NR	Secondary: composite (macro, dSCr, ESKD, renal death) HR 0.64 (0.46-0.88)
EXSCEL (2017)	Exenatide QW	14,752	T2DM, CVD risk	3.2	62.7	12.0	8.0	79.0	NR	Not reported
DPP-4 inhibitors										
EXAMINE (2013)	Alogliptin	5,380	T2DM, ACS <90 days	1.5	61.0	7.2	8.0	71.2	NR	Secondary: eGFR change: >90: -4.5/-6.7; 60-90: 1.0/0.6; 30-60: 2.1/1.1; <30: 1.6/0.2
SAVOR-TIMI 53 (2013)	Saxagliptin	16,492	T2DM, CVD risk or history	2.1	65.1	10.3	8.0	72.6	Micro: 28.1% Macro: 10.4%	Secondary: Change in UACR: 34.3 mg/g. dCr HR 1.1 (0.89-1.36); ESKD HR 0.90 (0.61-1.32)
TECOS (2015)	Sitagliptin	14,671	T2DM, CVD history	3.0	65.5	11.6	7.2	75.1	Micro: 23.3% Macro: 4.8%	Secondary: eGFR difference -1.34 (-1.76, -0.91) UACR difference: -0.18 mg/g (-0.35, -0.02)
MK-3102-018 (2017)	Omarigliptin	4,202	T2DM, CVD history	Up to 3	63.7	12.1	8.0	86.2	NR	Safety: eGFR difference -2.43 (-5.36, 0.51)

Table 3 | Recently completed and ongoing clinical outcome trials evaluating the effect of new drugs in type 2 diabetes on renal endpoints

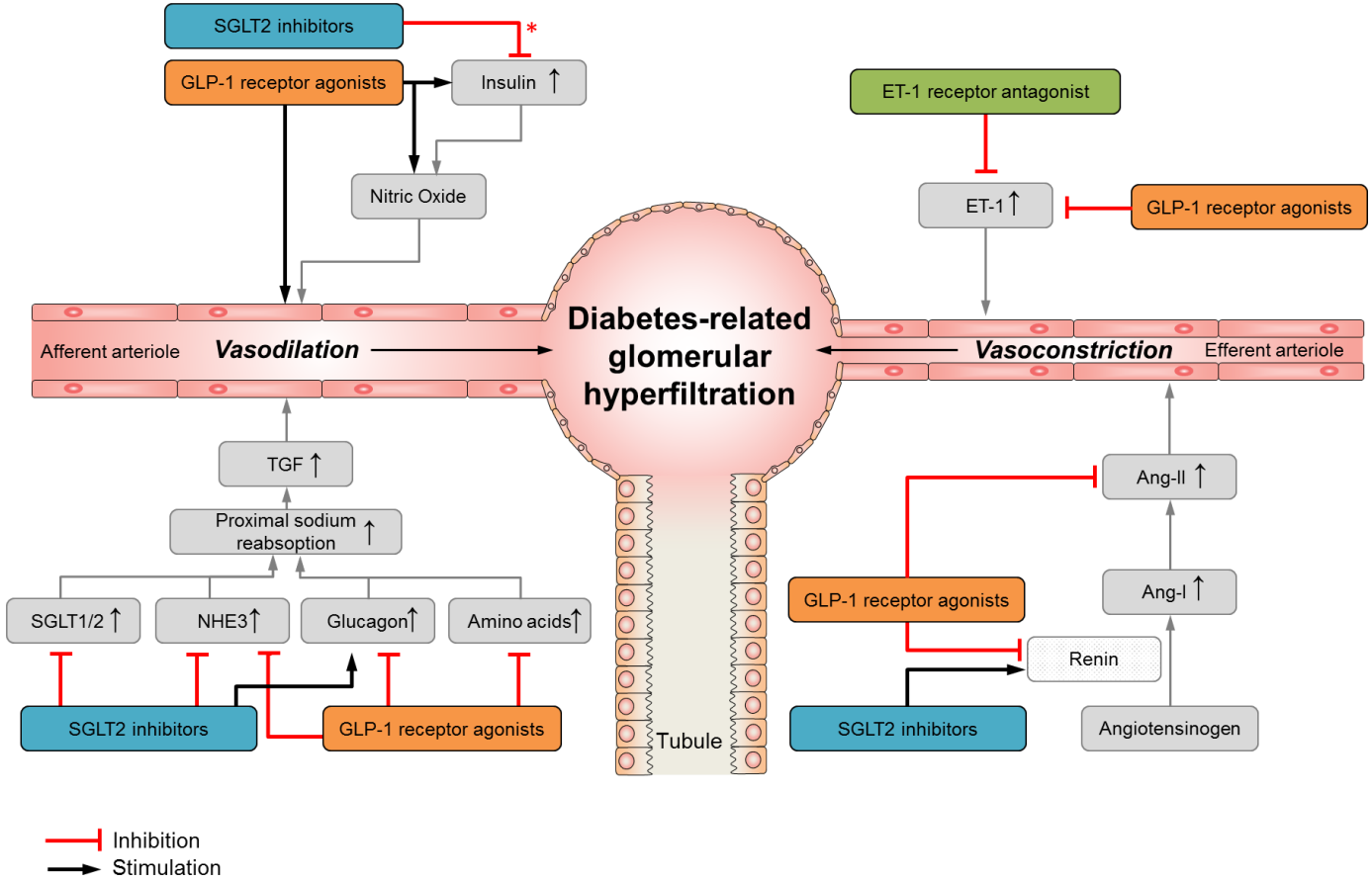
Trial name	ClinicalTrials.gov	Drug-class Agent	N=	Main inclusion criteria	Follow-up (yrs)	Age (yrs)	T2DM duration (yrs)	HbA1c (%)	BL eGFR (mL/min/1.73m^2)	Albuminuria status at BL	Trial status/ expected completion	Renal outcome / endpoints
Renal outcome trials												
SONAR	NCT01858532	ETA-antagonist Atrasentan	5,112	T2DM, eGFR 25-75, macroalbumuria	~4	64.8	16.7	7.8	43.8	Macro: 100%	Terminated Dec-2017	Primary: composite (dSCr, ESKD, renal death)
CREDENCE	NCT02065791	SGLT2 inhibitor Canagliflozin	4,401	T2DM, macroalbuminuria	Up to 5.5	63.0	15.8	8.3	56.2	Macro: 100%	Terminated Jul-2018	Primary: composite (ESKD, dSCr, CV-death, re
FIDELIO-DKD	NCT02540993	MRA Finerenone	4,800	T2DM, macroalbuminuria, potassium ≤4.8	Up to 4					Macro: 100%	Ongoing Okt-2019	Primary: composite (ESKD, ≥40% reduction in e
DAPA-CKD	NCT03036150	SGLT2 inhibitor Dapagliflozin	4,000	eGFR 25-75 mL/min/1.73m^2, increased albuminuria	Up to 4						Ongoing Nov-2020	Primary: composite (>50% reduction in eGFR, E death)
Cardiovascular outcome trials												
FREEDOM-CVO	NCT01455896	GLP-1RA: Exenatide DUROS	4,156	T2DM, CVD history	2	NR	NR	NR	NR	NR	Completed (Mar-2016)	Not reported
CARMELINA	NCT01897532	DPP-4 inhibitor Linagliptin	7,003	T2DM, CKD	4.5	65.8	14.7	7.9	54.6	Micro: 41.5% Macro: 38.6%	Completed (Jan-2018)	Secondary: composite (renal death, ESKD, ≥40
HARMONY Outcomes	NCT02465515	GLP-1RA Albiglutide	9,575	T2DM, CVD history	3 to 5	64.1	13.8	8.7	NR	NR	Completed (Mar-2018)	Not reported
DECLARE-TIMI 58	NCT01730534	SGLT2 inhibitor Dapagliflozin	17,276	T2DM, CVD risk	Up to 6	63.8	11.8	8.3	86.1	Micro: 23.4% Macro: 6.8%	Ongoing Jul-2018	Secondary: composite (≥40% reduction in eGFR death)
REWIND	NCT01394952	GLP-1RA Dulaglutide	9,622	T2DM, CVD risk or history	6.5	66.2	10.0	7.3	77.6	Micro/macro: 35.3%	Ongoing Jul-2018	Secondary: composite (retinopathy, proteinuria, ESKD)
PIONEER-6	NCT02692716	GLP-1RA Semaglutide (oral)	3,176	T2DM, CVD risk or history	Up to 1.6						Ongoing Sep-2018	Not reported
CAROLINA	NCT01243424	DPP-4 inhibitor Linagliptin*	6,041	T2DM, CVD risk or history	8.3	64.0	6.2	7.2	77.0	Micro: 21.2% Macro: 4.3%	Ongoing Mar-2019	Secondary: transition in albuminuria classes, ch UACR
VERTIS-CV	NCT01986881	SGLT2 inhibitor: Ertugliflozin	8,000	T2DM, CVD history	Up to 6.1						Ongoing Sep-2019	Secondary: Composite (dSCr, ESKD, renal deat
FIGARO-DKD	NCT02545049	MRA Finerenone	6,400	T2DM, macroalbuminuria, potassium ≤4.8	Up to 4.4					Macro: 100%	Ongoing Feb-2020	Secondary: composite (ESKD, ≥40% reduction i change in UACR
Heart failure outcome trials												
DAPA-HF	NCT03036124	Dapagliflozin	4,500	T2DM, HFrEF (NYHA II-IV), LVEF ≤40%, high NT-proBNP	Up to 3						Ongoing Dec-2019	Secondary: composite (>50% reduction in eGFR
EMPEROR-Preserved	NCT03057951	Empagliflozin	4,126	HFpEF (NYHA II-VI), LVEF >40%, high NT-proBNP	Up to 3.2						Ongoing Jun-2020	Secondary: eGFR slope, ESKD or ≥40% reducti
EMPEROR-Reduced	NCT03057977	Empagliflozin	2,850	HFrEF (NYHA II-VI), LVEF ≤40%, high NT-proBNP	Up to 3.2						Ongoing Jun-2020	Secondary: eGFR slope, ESKD or ≥40% reducti

Figure 1| Pathyphysiology of diabetic kidney disease and targets of promising renoprotective drugs in type 2 diabetes based on clinical trial data



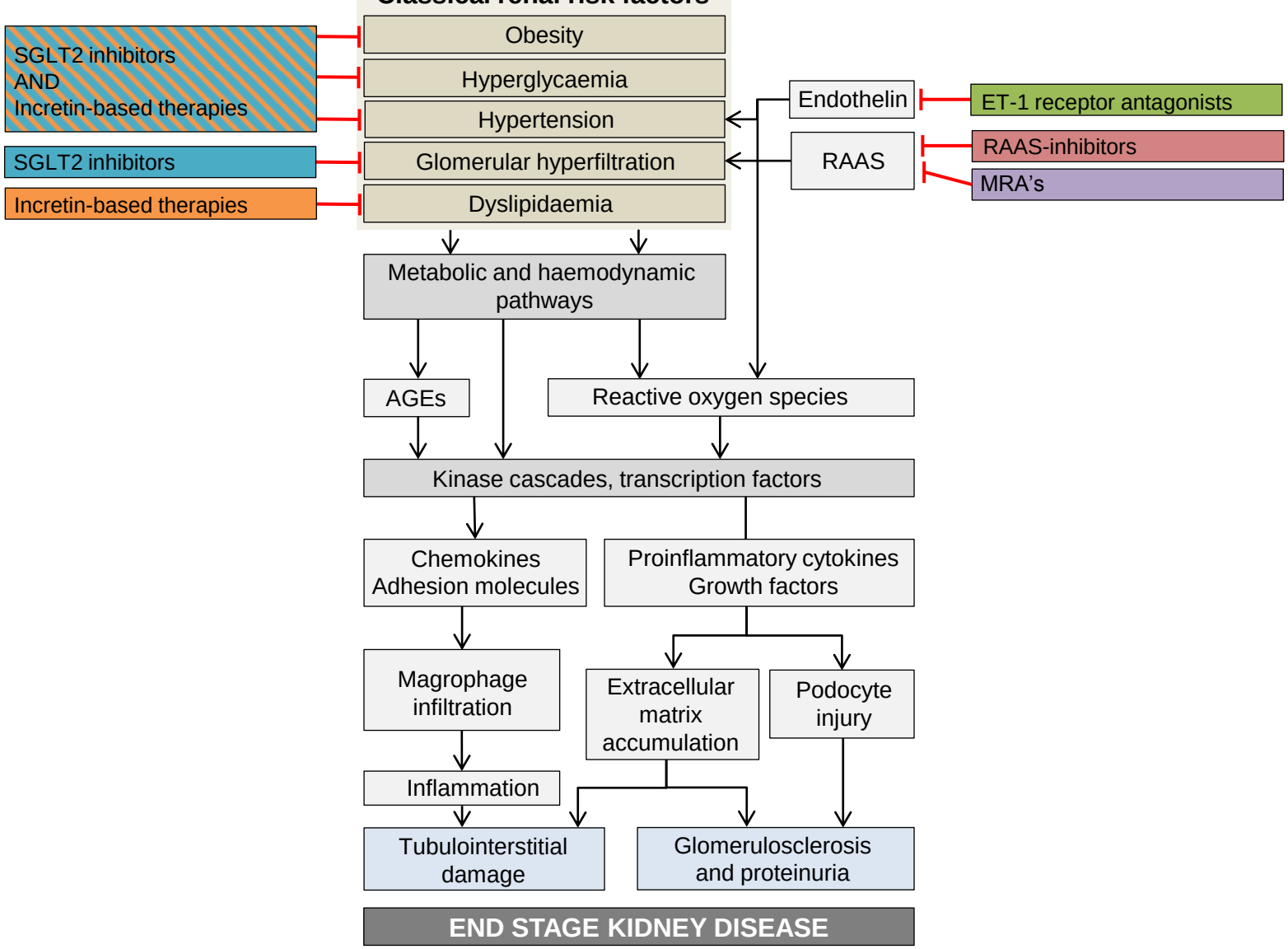
RAAS inhibitors and incretin-based therapies have been associated with *direct* inhibitory effects on (renal) inflammation and ROS-formation, particularly in experimental studies. Clinical studies should test whether these effects are beyond blood pressure and glycaemic control, respectively, by implementing a well-matched control-group. Legend: ACE, angiotensin-converting-enzyme, ARBs, angiotensin-receptor blockers; AGEs, advanced glycation end products; ET-1, endothelin-1; MRA, mineralocorticoid receptor antagonists; RAAS, renin-angiotensin-aldosterone-system; SGLT2, sodium-glucose co-transporter 2.

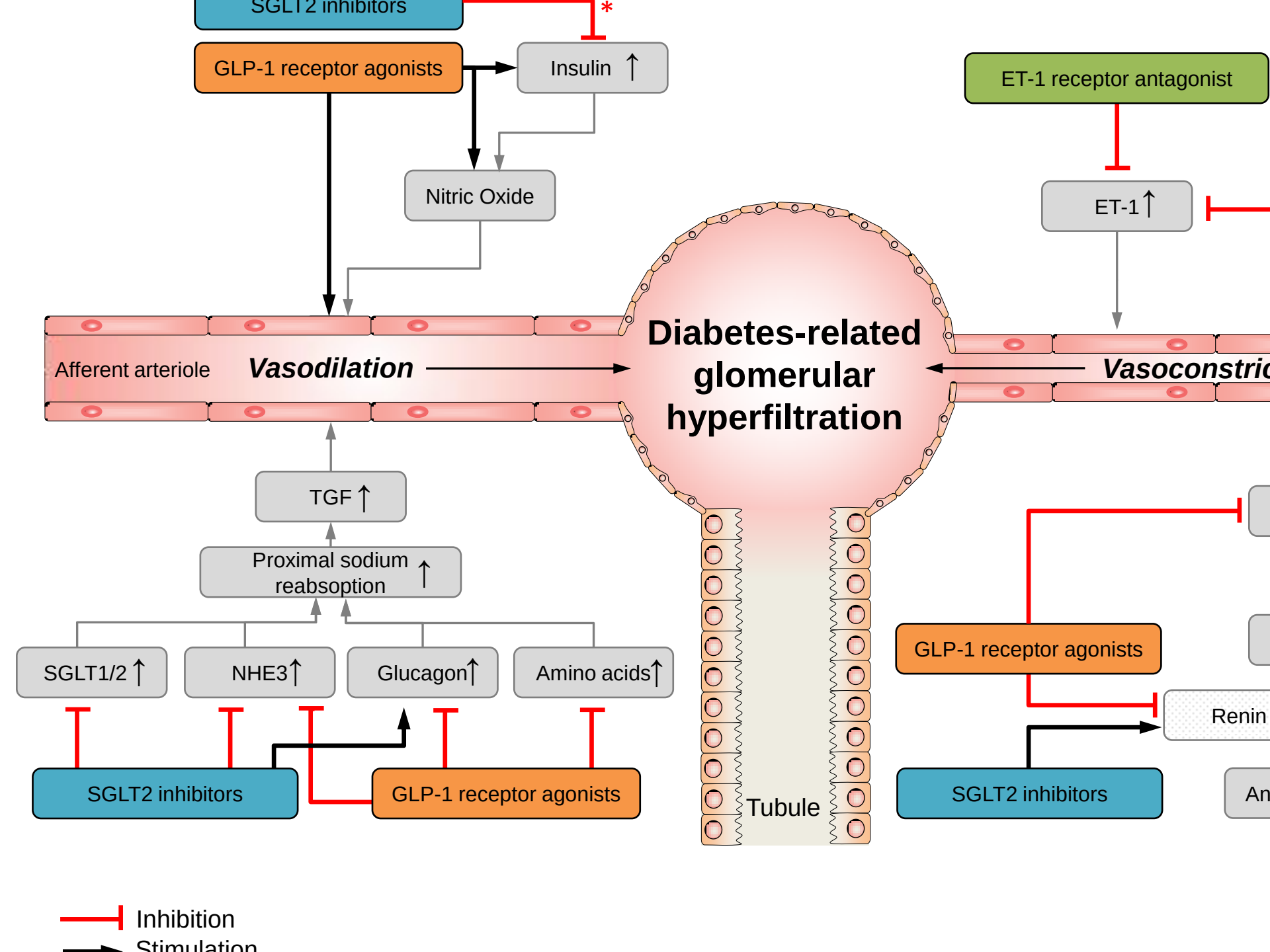
Figure 2 | Putative effects and mechanisms of novel drugs on renal haemodynamics in diabetes-related glomerular hyperfiltration



A protein-rich meal (or amino acid infusion) is known to increase GFR in humans, likely by reducing afferent arteriolar resistance via several mediators and paracrine factors, including glucagon. GLP-1RA's reduce amino-acid uptake by slowing gastric emptying and gastrointestinal uptake and suppress glucagon secretion, possibly reducing postprandial hyperfiltration. Conversely, the robust effect of SGLT2 inhibitors on afferent arteriolar resistance via TGF-activation may be blunted by increasing glucagon, suggesting an added benefit on renal haemodynamics of combination therapy with a GLP-1RA. *SGLT2 inhibitors do not directly inhibit insulin actions, but lead to a reduction in concentration.
Legend: Ang-I, angiotensin-I, Ang-II, angiotensin-II, ANP, atrial natriuretic peptide; ET-1, endothelin-1; GLP-1, glucagon-like peptide-1; NHE3, sodium-hydrogen exchanger 3; SGLT2, sodium-glucose co-transporter 2.

Figure


Classical renal risk factors
Obesity
Hyperglycaemia
Hypertension
Glomerular hyperfiltration
Dyslipidaemia
SGLT2 inhibitors AND Incretin-based therapies
SGLT2 inhibitors
Incretin-based therapies
Endothelin
ET-1 receptor antagonists
RAAS
RAAS-inhibitors
MRA's
Metabolic and haemodynamic pathways
AGEs
Reactive oxygen species
Kinase cascades, transcription factors
Chemokines Adhesion molecules
Proinflammatory cytokines Growth factors
Magrophage infiltration
Extracellular matrix accumulation
Podocyte injury
Inflammation
Tubulointerstitial damage
Glomerulosclerosis and proteinuria
END STAGE KIDNEY DISEASE


SGLT2 inhibitors
GLP-1 receptor agonists
Insulin ↑
Nitric Oxide
ET-1 receptor antagonist
ET-1 ↑
Afferent arteriole
Vasodilation
Diabetes-related glomerular hyperfiltration
Vasoconstric
TGF ↑
Proximal sodium reabsoption ↑
SGLT1/2 ↑
NHE3 ↑
Glucagon ↑
Amino acids ↑
SGLT2 inhibitors
GLP-1 receptor agonists
Tubule
GLP-1 receptor agonists
Renin
SGLT2 inhibitors
An
Inhibition
Stimulation