New pharmacological strategies for protecting kidney function in type 2 diabetes

Muskiet, Marcel H A; Wheeler, David C; Heerspink, Hiddo J L

Published in:
Lancet Diabetes & Endocrinology

DOI:
10.1016/S2213-8587(18)30263-8

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
New pharmacological strategies for protecting kidney function in type 2 diabetes

Marcel H A Muskiet, David C Wheeler, Hiddo J L Heerspink

Type 2 diabetes is the leading cause of impaired kidney function, albuminuria, and renal replacement therapy globally, thus placing a large burden on health-care systems. Current treatment strategies rely on intensive glucose lowering as well as strict blood pressure control through blockade of the renin–angiotensin–aldosterone system. Such approaches might slow decline in kidney function, but many patients progress to end-stage kidney failure despite optimal therapy. In recent clinical trials, new-generation glucose-lowering drug classes, the sodium-glucose co-transporter-2 inhibitors and agents that target the incretin pathway, have been shown to improve kidney outcomes in patients with type 2 diabetes. Other new approaches, which have been developed on the basis of an improved understanding of the mechanisms that contribute to kidney damage in the context of diabetes, include use of drugs that block endothelin receptors (eg, atrasentan) and non-steroidal mineralocorticoid receptors (eg, finerenone). In this Review, we provide an overview of recent clinical data relevant to these new therapeutic approaches for management of kidney disease in the context of type 2 diabetes.

Introduction

Patients with type 2 diabetes who develop a reduction in estimated glomerular filtration rate (eGFR) to less than 60 mL/min per 1.73 m², albuminuria (eg, urinary albumin-to-creatinine ratio [UACR] >3 mmol/mol), or both, sustained over at least 3 months, are considered to have chronic kidney disease according to current international guidelines.1 Chronic kidney disease identified in the context of type 2 diabetes is usually referred to as diabetic nephropathy or diabetic kidney disease, even when kidney histology has not been formally assessed by biopsy. The clinical assumption that kidney dysfunction is a consequence of diabetes might be reinforced by the presence of other diabetes complications (such as retinopathy) and by blood tests excluding other causes of chronic kidney disease, such as systemic vasculitis or myeloma. A diagnosis of chronic kidney disease in a person with type 2 diabetes has important implications in terms of prognosis. Not only is the risk of developing end-stage kidney disease increased, potentially requiring renal replacement therapy (such as dialysis or kidney transplantation), but patients with diabetes and chronic kidney disease are also at substantially increased risk of mortality and non-fatal cardiovascular events compared with people with diabetes but without chronic kidney disease.2 The risk of these adverse outcomes is further increased at lower levels of eGFR and higher levels of albuminuria.3 As the prevalence has increased, type 2 diabetes has emerged as the leading cause of chronic kidney damage. Monitoring for the development and progression of chronic kidney disease can be achieved through regular blood testing to allow estimation of glomerular filtration rate (GFR) and analysis of urine samples (preferably early morning) for UACR.

The aims of medical management in diabetic kidney disease are to reduce the level of albuminuria and prevent a progressive decline in eGFR. Identification of renin–angiotensin–aldosterone system (RAAS) inhibition as an effective renoprotective strategy in patients with type 2 diabetes in the early 2000s was a major step forward, but was followed by several years without much progress.4 However, emerging data from clinical outcome trials suggest that new-generation glucose-lowering drug classes (sodium-glucose co-transporter-2 [SGLT2] inhibitors and certain incretin-based therapies) might protect the kidney through mechanisms not directly related to glucose lowering.5,6 Furthermore, there are several novel pharmacological agents under development that target newly identified mechanistic pathways underlying diabetic kidney disease (figure 1). In this Review, we summarise 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 programmes.

Current treatment strategies in diabetic kidney disease

Recommended treatment strategies for patients with type 2 diabetes and chronic kidney disease are to initiate appropriate lifestyle changes (eg, weight management, physical activity, dietary recommendations, and smoking cessation) and to target high blood pressure and poor glycaemic control.

Glycaemic control

Optimisation of glycaemic control reduces the risk of microvascular complications in diabetes, including the onset and progression of albuminuria and, in post-hoc follow-up analysis of the ADVANCE trial, the risk of end-stage kidney disease.7,8 Yet reaching and maintaining HbA1c targets can be more challenging in patients with diabetic kidney disease because an eGFR lower than 60 mL/min per 1.73 m² restricts the use, or dose, of several oral and injectable glucose-lowering drugs.9 For example, most guidelines recommend discontinuation of metformin when eGFR falls below 30 mL/min per 1.73 m² to reduce the risk of lactic acidosis, a rare but
serious adverse effect." Accumulation of sulfonylureas and their active metabolites because of reduced renal excretion increases the likelihood of hypoglycaemia, and necessitates the avoidance of first-generation agents (eg, tolbutamide) and dose restriction of some second-generation agents (eg, glimepiride) in patients with chronic kidney disease. Largely because of these risks, arguments have been made for less stringent HbA1c targets for patients with type 2 diabetes and low eGFR levels by some experts.

**Blood pressure control**

The best method to assess blood pressure in patients with type 2 diabetes (eg, whether to use resting office readings or 24 h assessment) is not universally agreed and guidelines differ in recommending target systolic and diastolic pressures. Lower targets (eg, <130/80 mm Hg) are generally considered appropriate to reduce cardiovascular risk and slow eGFR decline once albuminuria develops. Although most classes of antihypertensive medication can be used to control hypertension in patients with type 2 diabetes and chronic kidney disease, guidelines generally recommend inclusion of angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors in the antihypertensive regimen, on the basis of evidence from randomised controlled trials done almost two decades ago. These RAAS blockers reduce albuminuria, probably by reducing intraglomerular pressure, and might also prevent renal inflammation and fibrosis. Although renoprotective in the longer term, their use might be limited by acute reductions in eGFR or the development of hyperkalaemia. There are few studies directly comparing ACE inhibitors with ARBs in diabetic kidney disease, but the available data suggest that the two classes have similar beneficial effects on kidney outcomes. 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 might have a detrimental effect on eGFR as a result of intravascular volume depletion.

**Evidence-based renoprotective strategies**

The notion of specifically protecting the kidney in patients with type 2 diabetes arose largely from studies of ARBs done 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 about 20% compared with conventional therapies. Data from previous animal studies suggested that such renoprotective effects were due to reductions in intraglomerular pressure, believed to result from the ability of these drugs to selectively vasodilate the efferent arteriole of the glomerulus. This mechanism of action was thought to explain the acute reductions in eGFR observed in many patients on initiation of these drugs, which need to be considered in the context of their longer-term benefit on kidney function. Post-hoc analyses of these trials have lent support to the hypothesis that renoprotection was conferred as a result of RAAS blockade, rather than via the effects on systemic blood pressure.

**The search for new therapies**

Despite widespread use of RAAS inhibitors as part of the antihypertensive regimen in clinical practice, there remains a high residual risk of progressive kidney disease, emphasising the need for new therapies. Following RENAAL and IDNT, investigators tried to show that maximising RAAS blockade by combination of an ARB with either an ACE inhibitor (VA NEPHRON-D) or the direct renin inhibitor aliskiren (ALTITUDE) would have an additional benefit on kidney outcomes. Although combination therapy led to greater reductions in albuminuria and blood pressure, these trials were stopped prematurely for safety and futility reasons, respectively.

Alternative therapeutic approaches that have been tried unsuccessfully include administration of the glycosaminoglycan sulphodexide (Sun-MACRO), targeting of the endothelin receptor with the antagonist avosentan (ASCEND; see Endothelin receptor antagonists), and activation of the nuclear factor erythroid 2-related factor 2 with bardoxolone methyl (BEACON). Despite such setbacks, the growing prevalence of type 2 diabetes and the increasing cost of managing the associated complications have driven the search for new therapies. Large-scale clinical trials have been required to prove cardiovascular safety (in addition to HbA\textsubscript{1c} lowering) of new glucose-lowering drugs by regulatory agencies. These cardiovascular outcome trials have not only indicated generally favourable adverse effect profiles of newer drug classes, but have also identified potential drug-specific renoprotective benefits associated with the use of some SGLT2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor antagonists. Other new therapeutic approaches include mineralocorticoid receptor antagonists (MRAs; figure 1).

**SGLT2 inhibitors**

The kidneys have an important role in normal glucose homoeostasis through gluconeogenesis, use of glucose as a metabolic fuel, and re-absorption of most filtered glucose by the sodium-glucose co-transporters (SGLT1 and SGLT2) located in the luminal membrane of the proximal tubule. 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.

In patients with poorly controlled diabetes, the maximum renal glucose reabsorptive capacity is increased compared with normal glucose-tolerant individuals, probably because of upregulation of SGLT2. As such, inhibition of SGLT2 was identified as an attractive therapeutic target. Four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) have been approved by the US Food and Drug Administration and the European Medicines Agency for use as glucose-lowering drugs in patients with type 2 diabetes. SGLT2 inhibitors dose-dependently increase urinary glucose excretion by about 70–80 g per day in healthy individuals without diabetes, and decrease HbA\textsubscript{1c} by 0.5–0.8% in patients with type 2 diabetes, depending on baseline HbA\textsubscript{1c} and kidney function. 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, sulfonylureas, DDP-4 inhibitors, GLP-1 receptor agonists, or basal insulin. Glucose-lowering efficacy seems to be enhanced in patients with poor glycaemic control (HbA\textsubscript{1c} >8.0%). Beyond glycaemic control, SGLT2 inhibitors have been shown to decrease bodyweight by 2–3 kg, partly as a direct consequence of a negative caloric balance due to increased urinary glucose excretion (1 g of glucose equates to 4 kcal). However, despite ongoing glycosuria, weight loss does not usually continue after 6 months, probably because of compensatory changes in metabolism and increased appetite and food intake.

As the reabsorption of glucose and sodium are coupled, SGLT2 inhibition leads to a dose-dependent natriuresis. Although the natriuretic effect of these drugs dissipates after 2–3 days and sodium and fluid balance re-equilibrate, a reduction in plasma volume of about 7%, along with an increase in haematocrit and reduction in systolic blood pressure of about 2–4 mm Hg, have been reported. The antihypertensive effects of SGLT2 inhibitors seem to be independent of concomitant antihypertensive medications (including diuretics and RAAS inhibitors).
The beneficial effects of SGLT2 inhibitors on cardio-renal outcomes have been established in three landmark placebo-controlled cardiovascular outcome trials, EMPA-REG OUTCOME (empagliflozin), the CANVAS Program (canagliflozin), and the DECLARE-TIMI 58 trial. In EMPA-REG OUTCOME, which included 7020 patients with type 2 diabetes with established cardiovascular disease, empagliflozin reduced the risks of the composite primary outcome (major adverse cardiovascular events [MACE]) by 14% (95% CI 1–26%; p=0.04) relative to placebo after a median follow-up of 3.1 years. Similarly, in the CANVAS Program, which included 1042 patients with type 2 diabetes and high cardiovascular risk, canagliflozin reduced the risk of the primary MACE outcome by 14% (95% CI 3–25%; p=0.02) relative to placebo after a mean of 118.2 weeks. In DECLARE-TIMI 58, among 17 160 patients with type 2 diabetes, including 10 186 without prior cardiovascular disease, dapagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure by 17% but did not result in a lower rate of MACE overall in this population. Importantly, all three SGLT2 inhibitors slowed the progression of eGFR decline and reduced the risk of a composite renal outcome by approximately 40%. These effects were achieved in all three studies, which enrolled patients with baseline eGFR greater than 30 mL/min per 1.73 m² (creatinine clearance greater than 60 mL/min in DECLARE) who were already well managed, with about 80% of all participants prescribed an RAAS inhibitor. Despite these results, it is important to realise that EMPA-REG OUTCOME, CANVAS, and DECLARE were not designed to assess the renoprotective effects of SGLT2 inhibitors. Dedicated kidney outcome trials (currently in progress) are required before recommendations on the use of SGLT2 inhibitors as a renoprotective drug can be included in updated clinical practice guidelines.

The renoprotective benefits of SGLT2 inhibitors are likely to be explained by several mechanisms. Like ACE inhibitors and ARBs, these drugs are believed 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), increases sodium delivery to the downstream juxtaglomerular apparatus. 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 diabetic kidney disease. 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. Such early reductions in eGFR predict a slower subsequent decline in kidney function on long-term treatment. SGLT2 inhibitors might also reduce renal hypoxia, which is typically observed in the kidneys of people with diabetes. 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 not currently licensed for use in patients with diabetic kidney disease and an eGFR below 45 mL/min per 1.73 m² in most countries (table I), since their efficacy in terms of glucose lowering is attenuated in stages 3b–5 chronic kidney disease.35–38 However, the effects of the drugs in reducing bodyweight, blood pressure, and albuminuria persist in these populations.34,35 Additionally, findings from subgroup analyses of EMPA-REG OUTCOME and the CANVAS Program suggest that the efficacy of SGLT2 inhibitors to reduce the risks of cardiovascular and renal outcomes does not depend on eGFR.36,56 In recognition of these findings, Health Canada allows physicians to consider the use of SGLT2 inhibitors when indicated for cardiovascular and renal protection down to an eGFR of 30 mL/min per 1.73 m².

The effects of SGLT2 inhibitors in slowing progressive kidney function loss seem to be independent of glycaemic control. In a secondary analysis of CANTATA-SU, a 2-year, phase 3 registration trial comparing canagliflozin with the sulfonylurea glimepiride, the rate of kidney function decline was significantly lower in the canagliflozin group, whereas the glycaemic control was similar between the two classes.37 Also, data from post-hoc analyses of EMPA-REG OUTCOME and earlier phase 3 studies suggested that UACR lowering was statistically independent of concomitant changes in HbA₁c.40,46 Collectively, these data suggest that renoprotective effects are unlikely to be mediated by improvements in glycaemic control, but rather by the other mechanisms outlined earlier. Renal outcome trials of SGLT2 inhibitors in patients with diabetic kidney disease are ongoing. One of these, CREDENCE (canagliflozin; NCT02065791),48 was stopped early at the recommendation of the data safety monitoring committee, on the basis of achievement of prespecified kidney efficacy criteria. Finally, since glomerular hyperfiltration is involved in the pathophysiology of various kidney diseases beyond diabetic kidney disease, there is a rationale to extend the use of SGLT2 inhibitors in non-diabetic kidney disease such as chronic kidney disease induced by obesity, secondary focal segmental glomerulosclerosis, or hypertensive nephrosclerosis.49 As such, a dedicated renal outcome trial of dapagliflozin (DAPA-CKD; NCT03036150) is recruiting patients with chronic kidney disease with or without type 2 diabetes, with an announcement for plans for a similar study assessing empagliflozin (EMPA-KIDNEY trial).50

Incretin-based therapies
Glucagon-like peptide-1 (GLP-1) is secreted from gut enteroendocrine L-cells at low tonic rates in the fasting and interprandial state. Circulating levels of this gut hormone rise briskly within minutes of food intake.51,52 Initial studies focused on its role as an incretin hormone, partly responsible for the roughly 70% amplification of insulin secretion in the context of nutrient (particularly glucose) ingestion—the so-called incretin effect.53 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.54

The incretin effect is severely reduced or absent in patients with type 2 diabetes,55 which is regarded as a key pathophysiologically defective that contributes to glucose intolerance.56 The insulinotropic and glucose-lowering response to exogenous GLP-1 is preserved in human type 2 diabetes,57 suggesting that pharmacological efforts aimed at therapeutic amplification of GLP-1-induced glucose-lowering in this population are 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 min), primarily by DPP-4, to a metabolite that stimulates insulin secretion.4 These findings prompted two strategies to extend and maintain incretin activity in type 2 diabetes: first, the use of injectable GLP-1 receptor agonists that are resistant to DPP-4 cleavage and provide supraphysiological concentrations of ligands to the GLP-1 receptor; and second, the use of oral DPP-4 inhibitors, which prevent degradation of endogenously secreted GLP-1 and glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide, GIP), another incretin hormone.58

Several incretin-based drugs with different structures, modes of administration, and pharmacokinetic properties (separating the GLP-1 receptor agonist class into short-acting [prandial] and long-acting compounds) have been introduced as treatments for type 2 diabetes.59–62 GLP-1 receptor agonists 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.4 Although less effective when compared with GLP-1 receptor agonists, DPP-4 inhibitors promote reductions in HbA₁c of 0.6–0.9%.48 Given their glucose-dependent mode of action, incretin-based drugs are associated with low risk of hypoglycaemia, and they are generally well tolerated.52,54–56,58

As pharmacokinetic data and clinical experience with GLP-1 receptor agonists in patients with type 2 diabetes and chronic kidney disease are scarce, caution or discontinuation is advised when kidney function is severely impaired (table I). DPP-4 inhibitors are well tolerated in stages 3b–5 chronic kidney disease,6 although most manufacturers recommend dose reductions, with the exception of linagliptin, which is mainly eliminated through biliary excretion.39

As with SGLT2 inhibitors, off-target effects of incretin-based drug classes might favourably modify the
cardiorenal risk profile and effects on clinical outcomes beyond glycaemia. First, GLP-1-receptor-mediated reductions in appetite and food intake result in a loss of roughly 0·8–1·4 kg in bodyweight, albeit with much variation in individual responses and within-class differences. DPP-4 inhibitors tend to have no effect on bodyweight, as they do not induce satiety. Second, sustained GLP-1 receptor agonist treatment consistently reduces systolic blood pressure by about 2–3 mm Hg, whereas DPP-4 inhibitors have no uniform antihypertensive effect. Third, incretin-based therapies modestly improve fasting and particularly postprandial lipid profiles. Fourth, GLP-1 might modulate inflammation or fibrosis at multiple sites. Finally, GLP-1 has been implicated in the enteroendocrine regulation of water and electrolyte balance (the putative gut–renal axis), specifically by enhancing renal solute excretion in response to acute solute ingestion, forming a feed-forward loop between the gut and the kidneys. GLP-1-receptors have been identified at various locations in the kidney, including proximal tubule.72–74 As with SGLT2 inhibitors, such proximal natriuresis would be expected to stimulate tubuloglomerular feedback (TGF) signalling, leading to afferent vasoconstriction and a reduction in renal plasma flow, hence reducing glomerular filtration rate.87

### Table 1: Antihyperglycaemic drugs available in Europe and North America with dose reductions in chronic kidney disease

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Approval (agency [year] or year)</th>
<th>Dosing</th>
<th>Plasma half-life (h)</th>
<th>Elimination route</th>
<th>Use in patients with renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga (EU), Forxiga (USA)</td>
<td>EMA (2012), FDA (2014)</td>
<td>5–10 mg once per day</td>
<td>12.9</td>
<td>Renal 75%, faeces 21%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>2013</td>
<td>100–300 mg once per day</td>
<td>10.6–13.1</td>
<td>Renal 34%, faeces 52%</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Steglatro</td>
<td>2017</td>
<td>5–15 mg once per day</td>
<td>11.0–17.0</td>
<td>Renal 50%, faeces 41%</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>2005</td>
<td>5–10 μg twice per day</td>
<td>2.4 (short-acting)</td>
<td>Mainly renal</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>EMA (2009), FDA (2010)</td>
<td>0.6–1·2–1·8 mg once per day</td>
<td>11·6–13·0 (long-acting)</td>
<td>Peptidases, renal 6%, faeces 5%</td>
</tr>
<tr>
<td>Euxetide</td>
<td>Bydureon</td>
<td>EMA (2011), FDA (2012)</td>
<td>2 mg once per week</td>
<td>Not specified (long-acting)</td>
<td>Mainly renal</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia (EU), Adlyxin (USA)</td>
<td>EMA (2013), FDA (2016)</td>
<td>10–20 μg once per day</td>
<td>3.0 (short-acting)</td>
<td>Mainly renal</td>
</tr>
<tr>
<td>Albglutide</td>
<td>Eperzan (EU), Tanezum (USA)</td>
<td>2014</td>
<td>30–50 mg once per week</td>
<td>120.0 (long-acting)</td>
<td>Peptidases, renal</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>2017</td>
<td>0.75–1.5 mg once per week</td>
<td>112.8 (long-acting)</td>
<td>Peptidases, renal</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
<td>2017</td>
<td>0.5–1.0 mg once per week</td>
<td>165.0–184.0 (long-acting)</td>
<td>Peptidases, renal</td>
</tr>
</tbody>
</table>

| **DPP-4 inhibitors** | | | | | |
| Sitagliptin | Januvia | FDA (2006), EMA (2007) | 100 mg once per day | 12.4 | Renal 87%, faeces 13% | No adjustment | Dose reduction (50 mg per day) | Dose reduction (25 mg per day) |
| Vildagliptin | Galvus | 2007 | 50 mg twice per day | 2.0 | Renal 85%, faeces 15% | No adjustment | Dose reduction (50 mg per day) | Dose reduction (25 mg per day) |
| Saxagliptin | Onglyza | 2009 | 5 mg once per day | 2.5 | Renal 12–29%, faeces 22% | No adjustment | Dose reduction (2.5 mg per day) | Dose reduction (2.5 mg per day) |
| Linagliptin | Trajenta (EU), Tradjenta (USA) | 2011 | 5 mg once per day | 12.0 | Renal –5%, faeces –80% | No adjustment | No adjustment | No adjustment |
| Alogliptin | Nesina (USA) | 2013 | 25 mg once per day | 11.0 | Renal –76%, faeces –13% | No adjustment | Dose reduction (12.5 mg per day) | Dose reduction (6.25 mg per day) |

CrCl=creatinine clearance. DPP-4=dipeptidyl peptidase-4. EMA=European Medicines Agency. ESRD=end-stage renal disease. EU=European Union. FDA=US Food and Drugs Administration. GLP-1=glucagon-like peptide-1. SGLT2=sodium–glucose co-transporter-2. The pharmacokinetic profiles of exenatide once per week and exenatide twice per day are similar, except that subcutaneous absorption is prolonged with the once per week formulation. Data derived from SPCs and Muskiet et al,56 Tahraní et al,65 and Deacon.16

### Figure 1: Dose adjustment based on renal function

- **Mild** (CrCl ≥ 90 mL/min): No adjustment
- **Moderate** (CrCl 30–50 mL/min): Dose reduction
- **Severe or ESRD** (CrCl < 30 mL/min): Not recommended

**Table 1: Antihyperglycaemic drugs available in Europe and North America with dose reductions in chronic kidney disease**
reduction in renal blood flow and GFR. However, in patients with type 2 diabetes, mechanistic studies and clinical trials have not identified (consistent) effects of GLP-1 receptor agonists on renal haemodynamics or acute reductions in (estimated) GFR on initiation of therapy. This finding might be explained by direct nitric oxide-dependent vasodilatory actions of GLP-1 receptor agonists at the afferent arteriole, which might override or offset vasoconstriction induced by TGF (figure 2). Renal response to DPP-4 inhibition might be even more complicated, as DPP-4 inhibitors induce natriuresis, at least partly independently of GLP-1.

Data from placebo-controlled phase 3 trials of GLP-1 receptor agonists in patients with type 2 diabetes have shown inconsistent effects on albuminuria and generally no effect on eGFR. In the SCALE Diabetes trial, 56 weeks of liraglutide resulted in dose-dependent reductions in UACR, whereas the 26-week LIRA-RENAL trial in patients with type 2 diabetes and moderate-to-severe kidney impairment did not show reductions in UACR. In a small crossover trial in patients with type 2 diabetes and albuminuria who were on RAAS inhibitors, liraglutide given for 12 weeks reduced 24 h urinary albumin excretion by 32% compared with placebo, independent of HbA1c reductions and possibly driven by blood pressure lowering. Integrated data from nine registration trials of dulaglutide, which included 6005 patients with type 2 diabetes, showed lower UACRs than with placebo (−16.7% vs 10.0%), insulin glargine (−16.7% vs 3.7%), and other active comparators (−20.0% vs −12.5%). Although no differences in serum creatinine levels were observed over 104 weeks, fewer patients receiving dulaglutide rather than insulin glargine experienced a 40% decline in eGFR at any point during a 1-year treatment period. In the AWARD-7 trial, which included 577 patients with type 2 diabetes and moderate-to-severe chronic kidney disease, 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.

Kidney outcome data have been collected as secondary and exploratory endpoints in previous (table 2) and ongoing (table 3) cardiovascular safety trials of GLP-1 receptor agonists and DPP4 inhibitors in patients with type 2 diabetes and high cardiovascular risk. In ELIXA, which assessed the cardiovascular safety of lixisenatide versus placebo in 6068 patients with type 2 diabetes and a previous acute coronary event, the percentage change in UACR showed a modest difference in favour of the GLP-1 receptor agonist after 25 months of follow-up (24% vs 34%). However, in the total population, post-hoc adjustment for HbA1c levels attenuated the lixisenatide-induced kidney benefit, suggesting some glucose dependency. Nevertheless, in a recent exploratory analysis of ELIXA, lixisenatide was associated with a lower risk of new-onset macroalbuminuria after adjustment for baseline and on-trial HbA1c and other traditional renal risk factors. Both LEADER (lixisenatide) and SUSTAIN-6 (semaglutide) included a prespecified composite kidney outcome, defined as progression to macroalbuminuria, doubling of serum creatinine, end-stage kidney disease (ESKD), or kidney death. The kidney composite outcome was reduced by 22% with lixisenatide in 9340 patients after 3–8 years and 36% by semaglutide in 3297 patients after 104 weeks. 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, or systolic blood pressure. Finally, lixisenatide modestly slowed eGFR decline by 2% compared with placebo after 36 months (−7.44 vs −7.82 mL/min per 1.73 m²), the clinical relevance of which is uncertain.

In parallel to its finite effect on cardiovascular outcomes or mortality, DPP-4 inhibitor therapy might have, at best, a modestly beneficial effect on kidney endpoints in at-risk patients with type 2 diabetes. In a pooled analysis of placebo-controlled trials, lixisenatide reduced kidney disease events by 16%, driven by an 18% reduction in moderate albuminuria and a 14% reduction in severe albuminuria, with no effects on eGFR. Moreover, combined data from randomised controlled trials including 217 patients with type 2 diabetes and albuminuria suggested that linagliptin reduced UACR by 28%, independent of HbA1c or systolic blood pressure. However, MARLINA-T2D, which included 360 patients with type 2 diabetes on stable RAAS inhibition and was sufficiently powered to test superiority of linagliptin in reducing albuminuria, did not confirm these findings. Five cardiovascular outcome trials involving DPP-4 inhibitors have provided data on kidney endpoints. In a secondary analysis of SAVOR-TIMI 53, which included 16492 patients with type 2 diabetes at high risk of cardiovascular events, saxagliptin led to reclassification of patients into a lower UACR category, irrespective of baseline UACR. 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 affect other more clinically relevant kidney endpoints after 2–1 years. In TECOS, which included 14671 patients, there was no clinically relevant difference in either eGFR or UACR between the sitagliptin and placebo groups. In the MK-3102-018 cardiovascular outcome trial, which was terminated early in 2016 based on a business decision by the sponsor not to submit a marketing application, there were no clinically meaningful changes from baseline in eGFR at any timepoint between the once-weekly DPP-4 inhibitor omarigliptin and placebo in 4202 patients with type 2 diabetes and established cardiovascular disease after a median follow-up of 96 weeks. Finally, in CARMELINA, linagliptin versus placebo did not significantly affect the secondary kidney composite outcome (sustained >40% decrease in eGFR from baseline, ESKD or renal death) in 6979 patients with type 2 diabetes at high cardiovascular risk.
high cardiovascular risk

Effect of new-generation glucose-lowering drugs in completed cardiovascular outcome trials on secondary and exploratory renal outcomes in patients with type 2 diabetes and kidney disease. GLP-1=glucagon-like peptide-1. HR=hazard ratio. NR=not reported. SGLT2=sodium-glucose co-transporter-2. UACR=urinary albumin-to-creatinine ratio. *All patients in all trials had type 2 diabetes, effects on more clinically relevant kidney outcomes (ie, impaired eGFR and microalbuminuria or macroalbuminuria) after a median of 2-2 years. In exploratory renal analyses, the progression of the albuminuria category occurred less frequently in the linagliptin group (hazard ratio [HR] 0·86; 95% CI 0·7-0·95).9

Although incretin-based therapies (particularly GLP-1 receptor agonists) might improve albuminuria in type 2 diabetes, effects on more clinically relevant kidney outcomes such as time to starting dialysis remain uncertain. The results of active-comparator studies that include secondary kidney endpoints such as CAROLINA (NCT01243424; comparing lixinaglipitin and glimepiride) and GRADE (NCT01794413; comparing exenatide and sitagliptin, glimepiride, and insulin glargine) are anticipated. However, by contrast with SGLT2 inhibitors, there are no ongoing studies of incretin-based therapies recruiting patients with diabetic kidney disease with a primary objective of determining the effects of these drugs on kidney endpoints.

Endothelin receptor antagonists

The endothelin family comprises three endothelins (ET-1, ET-2, and ET-3) that bind to either the ET, or the receptor or risk (ie, impaired eGFR and microalbuminuria or macroalbuminuria) after a median of 2-2 years. In exploratory renal analyses, the progression of the albuminuria category occurred less frequently in the linagliptin group (hazard ratio [HR] 0·86; 95% CI 0·7-0·95).9

Although incretin-based therapies (particularly GLP-1 receptor agonists) might improve albuminuria in type 2 diabetes, effects on more clinically relevant kidney outcomes such as time to starting dialysis remain uncertain. The results of active-comparator studies that include secondary kidney endpoints such as CAROLINA (NCT01243424; comparing lixinaglipitin and glimepiride) and GRADE (NCT01794413; comparing exenatide and sitagliptin, glimepiride, and insulin glargine) are anticipated. However, by contrast with SGLT2 inhibitors, there are no ongoing studies of incretin-based therapies recruiting patients with diabetic kidney disease with a primary objective of determining the effects of these drugs on kidney endpoints.

Endothelin receptor antagonists

The endothelin family comprises three endothelins (ET-1, ET-2, and ET-3) that bind to either the ET, or the
<table>
<thead>
<tr>
<th>ClinicalTrials.gov registration number</th>
<th>Drug (class)</th>
<th>n</th>
<th>Main inclusion criteria</th>
<th>Follow-up (years)</th>
<th>Mean age (years)</th>
<th>Mean type 2 diabetes duration (years)</th>
<th>Mean baseline HbA1c (%)</th>
<th>Mean baseline eGFR (mL/min per 1.73 m²)</th>
<th>Mean baseline albuminuria status</th>
<th>Baseline albuminuria status</th>
<th>Trial status (expected completion date)</th>
<th>Renal outcome</th>
<th>Cardiac outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SONAR NCT01858532</td>
<td>Atrasentan (ET, receptor antagonist)</td>
<td>5112</td>
<td>Type 2 diabetes, eGFR 25–75 mL/min per 1.73 m², macroalbuminuria</td>
<td>-4</td>
<td>64.8</td>
<td>16.7</td>
<td>7.8</td>
<td>43.8</td>
<td>Macro 100%</td>
<td>Terminated (December, 2017)</td>
<td>Primary: composite (dSCr, ESKD, renal death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDECE NCT02065791</td>
<td>Canagliflozin (SGLT2 inhibitor)</td>
<td>4401</td>
<td>Type 2 diabetes, macroalbuminuria</td>
<td>Up to 5.5</td>
<td>63.0</td>
<td>15.8</td>
<td>8.3</td>
<td>56.2</td>
<td>Macro 100%</td>
<td>Terminated (July, 2018)</td>
<td>Primary: composite (ESKD, dSCr, cardiovascular death, renal death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIDEJIO-DKD NCT02540993</td>
<td>Finerenone (MRA)</td>
<td>4800</td>
<td>Type 2 diabetes, macroalbuminuria, potassium ≤4.8 mmol/L</td>
<td>Up to 4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Macro 100%</td>
<td>Ongoing (April, 2020)</td>
<td>Primary: composite (ESKD, ≥40% reduction in eGFR, renal death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPA-CKD NCT03036150</td>
<td>Dapagliflozin (SGLT2 inhibitor)</td>
<td>4000</td>
<td>eGFR 25–75 mL/min per 1.73 m², increased albuminuria</td>
<td>Up to 4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Ongoing (November, 2020)</td>
<td>Primary: composite (&lt;50% reduction in eGFR, ESKD, cardiovascular death, renal death)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMFA-KIDNEY NCT03594110</td>
<td>Empagliflozin (SGLT2 inhibitor)</td>
<td>5000</td>
<td>eGFR 20–45 mL/min per 1.73 m² or 45–90 mL/min per 1.73 m² with albuminuria</td>
<td>Up to 3.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Ongoing (June, 2022)</td>
<td>Primary: composite of kidney disease progression (ESKD, eGFR &lt;10 mL/min per 1.73 m², renal death, or ≥40% reduction in eGFR) or cardiovascular death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FREEDOM-CVO NCT01455896</td>
<td>Exenatide DUROS† (GLP-1 receptor agonist)</td>
<td>4156</td>
<td>Type 2 diabetes, CVD history</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Completed (March, 2016)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REWIND NCT01394952</td>
<td>Dulaglutide (GLP-1 receptor agonist)</td>
<td>9901</td>
<td>Type 2 diabetes, CVD risk or history</td>
<td>6</td>
<td>66.2</td>
<td>10.0</td>
<td>7.3</td>
<td>77.7</td>
<td>Micro/macro 35%</td>
<td>Completed (August, 2018)</td>
<td>Secondary: composite (retinopathy, proteinuria, &gt;30% reduction in eGFR, ESKD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAROLINA NCT01243424</td>
<td>Linagliptin* (DPP-4 inhibitor)</td>
<td>6103</td>
<td>Type 2 diabetes, CVD risk or history</td>
<td>8.3</td>
<td>64.0</td>
<td>6.2</td>
<td>7.2</td>
<td>77.0</td>
<td>Micro 21.2% macro 4.3%</td>
<td>Completed (August, 2018)</td>
<td>Secondary: transition in albuminuria classes, change in eGFR, change in UACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIONEER-6 NCT02692716</td>
<td>Semaglutide (GLP-1 receptor agonist [oral])</td>
<td>3183</td>
<td>Type 2 diabetes, CVD risk or history</td>
<td>Up to 1.6</td>
<td>66.1</td>
<td>14.9</td>
<td>8.2</td>
<td>74.2</td>
<td>NR</td>
<td>Completed (September, 2018)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERTIS-CV NCT01986881</td>
<td>Erugliflozin (SGLT2 inhibitor)</td>
<td>8000</td>
<td>Type 2 diabetes, CVD history</td>
<td>Up to 6.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Ongoing (September, 2019)</td>
<td>Secondary: composite (dSCr, ESKD, renal death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGARO-DKD NCT02545049</td>
<td>Finerenone (MRA)</td>
<td>6400</td>
<td>Type 2 diabetes, macroalbuminuria, potassium ≤4.8 mmol/L</td>
<td>Up to 4.4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Macro 100%</td>
<td>Ongoing (June, 2021)</td>
<td>Secondary: composite (ESKD, ≥40% reduction in eGFR, renal death), change in UACR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Table 3 continues on next page)
ET\textsubscript{A} receptor. Generally, ET\textsubscript{A} receptor activation causes vasoconstriction, matrix accumulation, and cell proliferation, whereas ET\textsubscript{B} receptor activation opposes these effects.\textsuperscript{95,96} The endothelin system also has an important role in sodium and water regulation. Although ET\textsubscript{A} activation has a sodium and water retaining effect, ET\textsubscript{B} exerts a natriuresis effect, particularly via ET\textsubscript{B} receptors located in the collecting duct.\textsuperscript{95,96} The endothelin system also has an additional role in sodium and water retention and this effect has made development of endothelin blockers challenging.

The endothelin system is believed to be involved in the development and progression of diabetic kidney disease.\textsuperscript{39} Patients with diabetic kidney disease generally have hyperglycaemia, insulin resistance, obesity, dyslipidaemia, RAAS activation, endothelial dysfunction, and increased oxidative stress, all of which increase production of ET-1 in the kidney.\textsuperscript{39} Apart from its potent vasoconstrictive effects on the efferent renal vasculature, which can result in a reduction of renal blood flow and glomerular hyperfiltration,\textsuperscript{39} ET-1 might promote kidney injury by activating pro-inflammatory and profibrotic pathways.\textsuperscript{93-95}

Data from multiple experimental and clinical mechanistic studies have supported the hypothesis that endothelin blockade might delay the progression of kidney disease in the long term. Endothelin receptor antagonists (ERAs) attenuate the vasoconstrictor effect of ET-1 and thereby reduce intraglomerular pressure and hyperfiltration (figure 2). In patients with hypertension and chronic kidney disease, ERAs cause a significant increase in effective renal blood flow and reduction in filtration fraction, suggesting that ET-1 causes vasoconstriction mediated by the efferent arteriole.\textsuperscript{93,94} In addition to haemodynamic effects, use of the ERA atrasentan led to a reduction in albuminuria in one study, possibly through protection of the glyocalyx.\textsuperscript{95} Other potential mechanisms of ERA-induced renoprotection involve preservation of podocyte morphology\textsuperscript{104} and changes in production of growth factors and vasoconstrictors (eg, angiotensin II).\textsuperscript{105} Atrasentan was the first ERA to be tested in a large, randomised, placebo-controlled trial, which included 286 patients with diabetic kidney disease and macroalbuminuria. This 12-week trial showed a dose-dependent reduction in proteinuria, with an optimal dose of 10 mg per day. Higher doses (25 mg per day) increased the risk of the main adverse outcome, peripheral oedema (12%).\textsuperscript{106} Following this dose-finding study, a large phase 3 trial assessing the effect of atrasentan (at 25 and 50 mg per day) versus placebo on kidney outcomes in 1392 patients with type 2 diabetes (ASCEND) was undertaken, but was terminated early because of an excess of congestive heart failure and mortality associated with the ERA.\textsuperscript{107} These results show 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\textsubscript{A} selectivity than atrasentan and might therefore exert less sodium retention, has also been tested in diabetic kidney disease. In a phase 2 trial (RADAR), atrasentan given at doses of 0.75 mg or 1.25 mg per day, reduced albuminuria versus placebo by 35% and 38%, respectively, in 211 patients...
with diabetic kidney disease and overt proteinuria after 12 weeks, with the 1-25 mg per day dose leading to greater sodium retention. A large phase 3 confirmatory outcome trial (SONAR), evaluating the effect of atrasentan in type 2 diabetes patients with chronic kidney disease stage 2–4, which selected individual participants on the basis of their initial atrasentan response in terms of albuminuria and bodyweight, was stopped prematurely because of a lower than expected number of renal events (rather than safety concerns), with results expected to be reported in 2019.

Mineralocorticoid receptor antagonists

The steroidal mineralocorticoid receptor (MR) has an important role in the RAAS. Although traditionally angiotensin II 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 important in driving cardiovascular and kidney injury, beyond the effects of renin and angiotensin II. Patients with diabetic kidney disease show increased activity of the MRs, which is probably driven by increased levels of circulating aldosterone, altered cortisol activity, or increased local expression of the MR.

Clinically approved steroid-based MRAs, including spironolactone and eplerenone, mimic the molecular structure of the natural MR ligands. Findings from clinical trials have shown that MRAs further reduce albuminuria and blood pressure in patients with diabetic and non-diabetic kidney diseases when added to a RAAS inhibitor. Moreover, results from a prospective, open-label study suggested that spironolactone might stabilise decline in kidney function in patients with proteinuric kidney diseases. 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 gynaecomastia, impotence, and menstrual irregularities, as well as hyperkalaemia. Addition of both spironolactone and eplerenone to RAAS inhibition increases the risk of hyperkalaemia by three to eight times. This adverse effect is particularly pronounced in older patients, patients with diabetes, and those with chronic kidney disease (ie, the population who might also gain the most benefit from MRAs). Preventive measures to avoid hyperkalaemia during MRA treatment are described in panel 1.

In an attempt to more precisely target the MR, potent MRAs that might exhibit less potassium retention—specifically non-steroidal compounds such as finerenone—have been developed. In contrast with spironolactone and eplerenone, which bind to the ligand domain of the MR, finerenone induces a conformational change within the MR complex, thereby ultimately changing the stability and nuclear translocation of the receptor. The efficacy and safety of finerenone has been tested in ARTS-DN, a phase 2 clinical trial in patients with type 2 diabetes with diabetic kidney disease. 823 patients were randomly assigned 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 21–38% was reported from baseline to 90 days. There were no differences in the incidence of the prespecified secondary outcome, an eGFR decrease of 30% or more, compared with placebo. Hyperkalaemia occurred in 12 (1.5%) out of 821 patients assigned to finerenone, compared with none of the 94 patients in the placebo group, although only patients with baseline potassium levels of less than 4.8 mmol/L were eligible and few patients with an eGFR less than 45 mL/min per 1.73 m² and macroalbuminuria were included in the study. The efficacy and safety of finerenone in patients with diabetic kidney disease is being tested in the ongoing FIDELIO-DKD (NCT02540993; expected study completion October, 2019) and FIGARO-DKD (NCT02545049; expected study completion February, 2020) trials.

Future perspectives

Many of the new therapies described in the previous sections, which might improve outcomes for patients with diabetic kidney disease, have already been granted marketing authorisation by regulatory agencies for non-renal indications, or are in advanced stages of development. However, diabetic kidney disease is a multifactorial, heterogeneous disease comprising various complex

Panel 1: Preventive measures to avoid hyperkalaemia in patients with diabetic kidney disease receiving mineralocorticoid receptor agonist therapy

Monitoring serum K^+ during MRA treatment

Enables quick recognition of unusual changes in K^+ levels, but optimal timing and duration of K^+ monitoring unknown

Selection of patients on the basis of indices of mineralocorticoid activity (PRA, urinary Na^+K^+ ratio, FEK, or TTKG)

More specific method of identifying risk of hyperkalaemia than exclusion of known common risk factors such as age, diabetes status, or eGFR, but indices are affected by diet and GFR and methods are not validated

Dietary restriction of potassium intake and use of diuretics

Easy method to reduce risk of developing hyperkalaemia, but long-term compliance with dietary restriction is difficult to maintain

Review of concomitant therapies (for example NSAIDs, β-blockers, and heparin)

Easy method to prevent drug-related alterations in K^+ homeostasis, but physicians are often unaware of all medications taken by the patient, and not all drugs with known interaction can be safely discontinued

Reduce MRA dose

Reduced risk of developing hyperkalaemia, but possible reduced efficacy of MRAs

MRA=mineralocorticoid receptor antagonist. PRA=plasma renin activity. FEK=fractional excretions of K^+. TTKG=transtubular potassium gradient. eGFR=estimated glomerular filtration rate. NSAIDs=non-steroidal anti-inflammatory drugs. Derived from Roscioni et al.
Panel 2: Hurdles to the development of novel therapies to reduce the burden of diabetic kidney disease

Several challenges are apparent for the development of new treatments or combinations of drugs for chronic kidney disease, including factors that must be considered in trial design and the identification of appropriate endpoints and efficacy biomarkers. Additionally, testing of novel therapies aimed at slowing the progression of diabetic kidney disease must be done in patients with diabetes who are already receiving standard care, including optimal risk factor control such as the use of renin-angiotensin–aldosterone system (RAAS) blockers.

**Diagnosis**
- Disease awareness in patients with chronic kidney disease stages 1–3 is ~5%
- Physicians might neglect to inform patients that they have chronic kidney disease

**Clinical trial recruitment**
- Recruitment rates for diabetic kidney disease are ~0–20 patients per site per month (~25% of the number of patients enrolled per month for a diabetes trial)
- Low rates delay timelines, increase costs, and negatively affect willingness of pharmaceutical companies to invest
- Clinical trial networks and patient registries could help to address this challenge

**Patient selection**
- Elimination of probable biological non-responders who decrease trial efficiency vs patient heterogeneity with respect to rate of renal function loss
- Widespread use of RAAS blockers restricts recruitment of patients with high levels of albuminuria and so-called rapid progressors
- Increasing numbers of patients with diabetic kidney disease who progress without developing proteinuria; ~25% do not follow the classic paradigm
- Development of novel biomarkers could supplement proteinuria in predicting progression of renal disease

**Clinical endpoints**
- Characterising the effect of a drug on renal markers (surrogates) vs parameters of patient wellbeing and hard outcomes vs a composite of these
- Intermediate events and surrogates should match with the appropriate mechanisms of action of the drug (ie, acute reductions in renal function with RAAS blockers and sodium-glucose co-transporter-2 inhibitors)
- Using intermediate eGFR decrements (ie, 30%, or 40%, or eGFR slope) as surrogates of accepted outcomes (ie, doubling of serum creatinine)

Search strategy and selection criteria

We searched MEDLINE, PubMed, Google Scholar, and the Cochrane Library for English-language abstracts and full-text articles published up to Nov 30, 2018. We focused on new potentially renoprotective drugs in type 2 diabetes, with particular attention paid to sodium-glucose co-transporter-2 (SGLT2) inhibitors, incretin-based therapies, endothelin receptor antagonists, and mineralocorticoid receptor antagonists. The keywords used included “diabetic kidney disease”, “diabetic nephropathy”, “renoprotection”, “type 2 diabetes”, “sodium-glucose co-transporter-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”, and “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. The evidence discussed in this Review is mainly restricted to clinical studies, including cohort studies, randomised controlled trials, and meta-analyses of randomised clinical trials.

as the diuretic properties of the SGLT2 inhibitor could mitigate the sodium and fluid retaining effects of the ERA. Additionally, the renal haemodynamic benefits of SGLT2 inhibitors involves the afferent arteriole via TGF signalling, whereas the ERAs reduce glomerular pressure by directly reducing efferent arteriolar resistance.

Finally, although nearly all patients with type 2 diabetes 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 type 2 diabetes, while being well tolerated and safe, easy to administer, and cost-effective. Based on 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 a GLP-1 receptor agonist might be expected to fulfil (most of) these criteria. Interestingly, two trials have assessed this combination in patients with poorly controlled type 2 diabetes and have shown useful reductions in glycaemic measures and additive effects on weight loss and lowering of blood pressure. Such combination therapy might be even more powerful in slowing the progression of diabetic kidney disease beyond either drug class used alone, but dedicated studies to assess the effects of this combination on albuminuria and kidney outcomes are needed to investigate this possibility. We believe that well designed mechanistic studies that aim to characterise individual drug responses on the basis of phenotypic traits, as well as large-sized prospective outcome trials that assess the cardiorenal phenotypes and it seems probable that not all patients will benefit from these drugs. Between-patient variation in underlying pathophysiology results in a wide diversity of individual drug responses, as described in more detail elsewhere. This variation in individual drug response was addressed in the design of the SONAR trial described previously, which selected only responder patients (albuminuria reduction >30%) and excluded those who do not tolerate atrasentan. However, whether non-responders to atrasentan (in terms of albuminuria) might benefit from an SGLT2 inhibitor, an incretin-based drug, or an MRA is an important question to be answered in the future.

It is also probable that future studies will start combining new therapies to further slow the progression of diabetic kidney disease. Theoretically, the effect of an SGLT2 inhibitor and an ERA would be complementary,
effects of different combinations of drugs, are necessary to advance treatment approaches in patients with type 2 diabetes. Hurdles to overcome in the development of novel therapies to reduce the burden of diabetic kidney disease and test combinations of drugs in patients with type 2 diabetes are outlined in panel 2.

Conclusions

Several promising new approaches are emerging to protect kidney function in patients with type 2 diabetes. Such progress should offer hope to patients in whom a progressive loss of kidney function leads to ill health and reductions in quality of life. None of these new therapies have 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 be reported within the next 3–5 years. Some of these agents, by virtue of their mode of action, might also benefit patients with proteinuric kidney disease resulting from pathological processes other than diabetic kidney disease. Bearing in mind the unmet need, clinicians will no doubt welcome these new therapies and will be tempted to initiate them in patients with chronic kidney disease for other indications (eg, to reduce cardiovascular risk) before kidney endpoint studies are completed. However, new risks might emerge in patients with chronic kidney disease. Whatever the specific findings of ongoing and future trials, we seem to be entering a new era in the management of patients with chronic kidney disease in the context of type 2 diabetes.

Contributors

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

Declaration of interests

MHAM is a consultant for Eli Lilly & Co and Novo Nordisk (all honoraria paid to his employer). DCW has received honoraria or consultancy fees from Akebia, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, and Vifor Fresenius. HJ/LH is a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, and Merck (all honoraria paid to his employer).

References

Review


41 Neuen RL, Okhuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program. Circulation 2018; published online June 25. DOI:10.1161/CIRCULATIONAHA.118.035901.


123 van Baar MJB, van Ruiten CC, Muskiet MHA, van Bloemendaal L, IJzerman van RG, Raalte DH. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018; 41: 1543–56.
