Incretin-based drugs and the kidney in type 2 diabetes

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Pleiotropic effects of type 2 diabetes management strategies on renal risk factors

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Abstract

In parallel with the type 2 diabetes pandemic, diabetic kidney disease has become the leading cause of end-stage renal disease worldwide, and is associated with high cardiovascular morbidity and mortality. As established in landmark randomised trials and recommended in clinical guidelines, prevention and treatment of diabetic kidney disease focuses on control of the two main renal risk factors, hyperglycaemia and systemic hypertension. Treatment of systemic hypertension with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers is advocated because these drugs seem to exert specific renoprotective effects beyond blood pressure lowering. Emerging evidence shows that obesity, glomerular hyperfiltration, albuminuria, and dyslipidaemia might also adversely affect the kidney in diabetes. Control of these risk factors could have additional benefits on renal outcome in patients with type 2 diabetes. However, despite multifactorial treatment approaches, residual risk for the development and progression of diabetic kidney disease in patients with type 2 diabetes remains, and novel strategies or therapies to treat the disease are urgently needed. Several drugs used in the treatment of type 2 diabetes are associated with pleiotropic effects that could favourably or unfavourably change patients' renal risk profile. We review the risk factors and treatment of diabetic kidney disease, and describe the pleiotropic effects of widely used drugs in type 2 diabetes management on renal outcomes, with special emphasis on antihyperglycaemic drugs.

Introduction

Roughly 387 million adults are living with diabetes worldwide and, mainly because of the relentless increase in type 2 diabetes incidence, this estimate is projected to rise to 592 million by 2035.[1] Of various diabetes-related microvascular and macrovascular complications, about 20–40% of patients with type 2 diabetes will ultimately develop diabetic kidney disease,[2] formerly referred to as diabetic nephropathy. Diabetic kidney disease is defined as diabetes with albuminuria (≥30 mg urinary albumin excretion [UAE]/24 h), impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), or both.[3] However, gold standard diagnosis requires renal biopsy to exclude other causes of chronic kidney disease, which might be appropriate in some clinical circumstances, such as absence of diabetic retinopathy, rapidly decreasing glomerular filtration rate (GFR), or rapidly increasing albuminuria.[4] In parallel with the increase in so-called diabesity prevalence, diabetic kidney disease has now become the leading cause of end-stage renal disease in developed and developing nations.[5] Additionally, diabetic kidney disease results in high cardiovascular morbidity and mortality, and decreased health-related quality of life.[6] As a result, diabetic kidney disease has a heavy economic health-care burden.

The natural course of diabetic kidney disease progresses through several clinical stages.[7] Initially, renal hypertrophy and glomerular hyperfiltration can be recorded. Then, after a clinically asymptomatic stage, patients develop microalbuminuria (30–300 mg UAE/24 h), followed by macroalbuminuria (>300 mg UAE/24 h), and a subsequent decline in GFR. Finally, end-stage renal disease might develop. However, not all patients with renal impairment have albuminuria, which challenges the notion that proteinuria precedes GFR loss in type 2 diabetes and might suggest a new phenotype in diabetic kidney disease.[8] Also, regression from microalbuminuria to normoalbuminuria has been described,[4] although it is often attributed to intensified glycaemic and blood pressure control. In patients with newly diagnosed type 2 diabetes from the UK Prospective Diabetes Study (UKPDS) in the 1990s, incidences were 25% for microalbuminuria, 5% for macroalbuminuria, and 1% for the composite of plasma creatinine more than 175 μmol/L or progression to end-stage renal disease after 10 years of follow-up.[9] Notably, the low number of patients progressing from macroalbuminuria to end-stage renal disease might be explained by the 19% annual mortality (mostly due to cardiovascular disease) in this group. However, more contemporary data are needed to establish the transition rate seen in clinical practice nowadays.

The pathophysiological changes of diabetic kidney disease in type 2 diabetes involve complex interactions between metabolic and haemodynamic factors on a background of genetic predisposition. Chronic hyperglycaemia has a central role in the development and progression of diabetic kidney disease, whereas a cluster of cardiometabolic abnormalities (including obesity, systemic hypertension, glomerular hyperfiltration, albuminuria, and dyslipidaemia) also contribute early on in the disease course. In accordance with this complex aetiology, multifactorial therapy aimed to improve renal outcome in patients with type 2 diabetes is recommended, including lifestyle interventions (eg, diet and exercise to achieve weight loss, and smoking cessation) and pharmacological management of glucose, blood pressure, and

lipids (Panel 1). With respect to blood pressure control, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in particular are recommended in clinical guidelines[2,10,11] because these inhibitors of the renin-angiotensin-aldosterone system (RAAS) have shown renoprotective effects beyond their ability to decrease blood pressure. RAAS inhibition/se has been shown to attenuate the progression of diabetic kidney disease in major landmark trials, in which renal risk is high and the associated mortality surpasses that of all treated types of cancer combined.[12] Even when several risk factors are targeted simultaneously, residual risk for the development of diabetic kidney disease remains. The Steno-2 trial[13] investigated cardiovascular and renal outcomes of an intensive multifactorial intervention (including lifestyle interventions, strict glycaemic control, blood pressure management, lipid regulation, and treatment with RAAS inhibitors and aspirin) in patients with type 2 diabetes and microalbuminuria. 25% of these patients still developed diabetic kidney disease after 7.8 years of intervention and 5.5 years after trial follow-up (Figure). As a result, novel strategies or new therapeutic drugs to reduce this residual renal risk in patients with type 2 diabetes are urgently needed.

Panel 1. Recommendations for type 2 diabetes management to prevent onset and progression of chronic kidney disease, in addition to cardiovascular disease

Lifestyle interventions

Bodyweight management (general)

Modest weight loss might provide clinical benefit in some individuals (not rated); use intensive lifestyle interventions and continued support to achieve this (A); bariatric surgery might be an option when BMI >35 kg/m^2 (B).

Bodyweight management (chronic kidney disease)

Achieve BMI 20–25 kg/m^2, according to country-specific demographics (1D); also suggested to lower blood pressure (1D).

Physical activity (general)

Aim for ≥150 min/week of moderate-intensity aerobic physical activity, spread over ≥3 days/week with ≤2 consecutive days without exercise (A); in absence of contraindications, do resistance training two times or more/week (A).

Physical activity (chronic kidney disease)

≥30 min daily, five times/week, compatible with cardiovascular health and exercise tolerance (1D); also suggested to lower blood pressure (1D).

Dietary sodium restriction (general and chronic kidney disease)

Lowering intake to <2 g (<90 mmol) sodium/day (corresponds to <5 g sodium chloride) (1C); also suggested to lower blood pressure (1D).

Dietary protein restriction (general)

Lowering intake of protein to 0.8 g/kg/day of ideal bodyweight daily (2C).

Dietary protein restriction (chronic kidney disease)

Avoid high protein intake (more than 1.3 g/kg/day) in patients at risk of chronic kidney disease progression (2C).

Smoking cessation (general and chronic kidney disease)

Smoking cessation (A and 1D).

Panel 1. (continued)

Pharmacological interventions

Glycaemic control (general and chronic kidney disease)

Aim for HbA_{1c} about 7.0% (53 mmol/mol) (1A), HbA_{1c} <7.0% is not recommended in patients at risk of hypoglycaemia (1B), HbA_{1c} >7.0% is suggested in patients with comorbidities or limited life expectancy and risk of hypoglycaemia (1C).

Blood pressure control (general)

When blood pressure >120/80 mmHg advise lifestyle changes (weight loss if overweight, reduce sodium intake and increase potassium intake, moderation of alcohol intake, increased physical activity) (B); use pharmacological therapy to reduce blood pressure to <140/80 mmHg (B); systolic blood pressure <130 mmHg might be appropriate for some individuals, such as younger patients, if it can be achieved without undue treatment burden (C).

Blood pressure control (chronic kidney disease)

Reduce blood pressure to ≤140/90 mmHg in patients with urinary albumin excretion <30 mg/24 h (1B) and ≤130/80 mmHg if urinary albumin excretion ≥30 mg/24 h (2D); encourage lifestyle modifications as described above to lower blood pressure in addition to reducing alcohol intake to no more than two standard drinks/day for men and one for women (2D).

Renin-angiotensin-aldosterone system inhibition (general)

Include angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in antihypertensive management (C).

Renin-angiotensin-aldosterone system inhibition (chronic kidney disease)

Use angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in patients with urinary albumin excretion 30–300 mg/24 h (2D) or urinary albumin excretion >300 mg/24 h (1B).

Lipid control (general)

Advise lifestyle modification (optimise dietary fat intake, weight loss if indicated, and increased physical activity) to improve lipid profile (A); add statin to lifestyle therapy in patients with: overt cardiovascular disease (A) (aim for LDL cholesterol <2.6 mmol/L [B] or optional <1.9 mmol/L [B]), without cardiovascular disease but aged >40 years and ≥1 cardiovascular disease risk factors* (A), with LDL cholesterol>2.6 mmol/L or several cardiovascular disease risk factors*; triglycerides <1.7 mmol/L and HDL cholesterol >1.0 mmol/L in men and >1.3 mmol/L in women are desirable (C) but LDL cholesterol targeted statin therapy is the preferred strategy.

Lipid control (chronic kidney disease)

Start statin treatment in patients aged 18–49 years without end-stage renal disease† (2A). In patients aged ≥50 years with estimated glomerular filtration rate <60 mL/min/1.73 m^2, but without end-stage renal disease, start treatment with a statin, or statin and ezetimibe combination (1A). Start statin in patients aged ≥50 years with chronic kidney disease and estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 (1B).

Chronic kidney disease is defined as present markers of kidney damage or glomerular filtration rate less than 60 mL/min/1.73 m^2 for more than 3 months, or both. Recommendations are graded (1=recommended; 2=suggested) and the quality of the supporting evidence is rated (A=high; B=moderate; C=low; D=very low) according to chronic kidney disease guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) group.[10,11,14] When these guidelines do not address the non-chronic kidney disease diabetes patient population, recommendations are not graded but the level of evidence is rated (A=clear [or supportive] evidence from well done [generalisable], adequately powered, randomised clinical trials or compelling non-experimental evidence; B=supportive evidence from well conducted cohort studies; C=supportive evidence from poorly controlled or uncontrolled studies) according to the diabetes guideline by the American Diabetes Association.[2] *Cardiovascular disease risk factors are family history of cardiovascular disease, hypertension, smoking, or dyslipidaemia. †End-stage renal disease is defined as chronic dialysis or kidney transplantation.

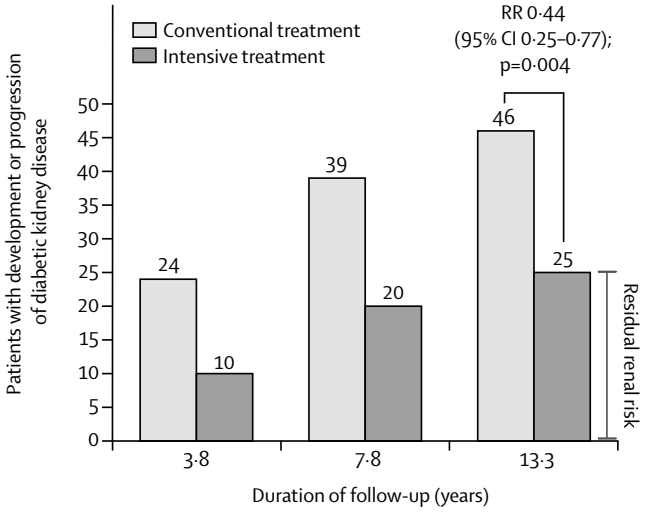

Figure1. Residual renal risk in Steno-2. Based on data from Gaede and colleagues.[13] In the Steno-2 trial, intensive multifactorial treatment—with lifestyle interventions, strict control of hyperglycaemia (with metformin, sulfonylureas, and insulin), and management of systemic hypertension (including the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers) and dyslipidaemia, in addition to aspirin —did not eliminate the risk of diabetic kidney disease in 160 patients with type 2 diabetes with persistent microalbuminuria.

Type 2 diabetes management can involve a diverse range of antihyperglycaemic drugs, of which several display effects beyond the ability to decrease glucose, so-called pleiotropic actions that target diabetic kidney disease risk factors. In this Review, we appraise current renoprotective management in type 2 diabetes, and assess favourable and unfavourable pleiotropic actions of widely used antihyperglycaemic drugs on renal risk factors. Although many of these actions can also target cardiovascular outcomes, an in-depth discussion of these outcomes is beyond the scope of this Review.

Glycaemic control

Chronic hyperglycaemia is a fundamental cause of renal complications in patients with diabetes through the induction of renal glucotoxicity and adverse renal haemodynamic effects.[15] So far, results of several randomised clinical trials[16] have shown the value of intensive glycaemic control on renal outcome in patients with type 2 diabetes, with short-term and long-term disease duration (Table 1). The first landmark trial to investigate this issue was the UKPDS,[17] in which 3867 patients newly diagnosed with type 2 diabetes were randomly assigned to intensive blood glucose-lowering treatment (achieved HbA_{1c} 7.0%) or conventional treatment (achieved HbA_{1c} 7.9%) for a duration of 10 years. Reductions were seen in microalbuminuria (24%) and macroalbuminuria (33%), and doubling of serum creatinine (60%) in the intensive versus the conventional treatment group. After 10 years of post-trial follow-up, in which the previous

differences in HbA_{1c} levels disappeared between the groups, a lasting benefit in the reduction of microvascular disease (renal failure, retinal photocoagulation, or vitreous haemorrhage) was seen in the original intensive treatment group.[18] These findings suggested that early exposure to hyperglycaemia predisposes patients to the development and progression of diabetic complications, a phenomenon known as the legacy effect. More recently, three major and two small randomised trials have revisited the effects of intensive glucose lowering in patients with type 2 diabetes and a disease duration ranging from 8 to 12 years; a systematic review and meta-analysis of these trials,[16] including more than 28 000 patients with type 2 diabetes, supports the implication of intensive glycaemic control on the reduction of microalbuminuria and macroalbuminuria, although effects on the hard renal endpoint end-stage renal disease did not reach statistical significance (risk ratio [RR] 0.69, 95% CI 0.46–1.05). In a secondary analysis of the ADVANCE trial,[19] a reduced incidence of end-stage renal disease (–65%, 95% CI –17 to –85) was seen in the intensive treatment group. Although the number of end-stage renal disease events was low in this trial, the benefit was sustained after an additional 6-year monitoring phase after the initial trial (–46%, 95% CI –15 to –66).[20] Thus, evidence that supports a renoprotective effect of glycaemic control on diabetic kidney disease is mainly based on albuminuria reduction, which was mainly achieved with metformin, sulfonylureas, and insulin (Table 1). By contrast, evidence of glucose lowering according to other surrogate endpoints (including serum creatinine doubling and eGFR decrease) and the hard renal endpoint end-stage renal disease is very limited, and no proof for prevention of renal death exists. Adequately powered trials with hard renal endpoints as prespecified outcomes (Panel 2) are essential to show definite renal benefit of intensive glucose regulation in type 2 diabetes.

Tight glycaemic control might differentially affect renal and cardiovascular endpoints in patients with longstanding type 2 diabetes. As such, the ACCORD trial[26] (target HbA_{1c} <6.0%) was prematurely discontinued after 3.5 years because of increased cardiovascular and all-cause mortality, which was shown to particularly affect patients with chronic kidney disease. Thus, from available evidence, expert panels and guidelines recommend individualised HbA_{1c} targets of about 7.0% to prevent or delay progression of microvascular complications in type 2 diabetes (Panel 1).[2,10]

Renoprotection beyond glycaemic control

Obesity

Most patients with type 2 diabetes are overweight or obese (about 80%).[27] In addition to hyperglycaemia, all other renal risk factors described are highly associated with excess bodyweight.[28] Therefore, it can be assumed that obesity harms the diabetic kidney indirectly, by negatively affecting these renal risk factors, although associated hormonal and inflammatory factors could also contribute.[28] In a historical cohort of 320 252 adults from the general population, BMI predicted end-stage renal disease in a stepwise and independent manner after 15–35 years of follow-up,[29] whereas in patients with type 2 diabetes, visceral adiposity was a strong predictor for microalbuminuria development.[30] A systematic review and meta-analysis[31] of generally small, uncontrolled, and short-term trials in overweight and obese

Table 1. Effect of intensive glucose control on renal endpoints in patients with type 2 diabetes

	Kumamoto (1995)	**UKPDS 33 (1998)**	**UKPDS 34 (1998)**
Type 2 diabetes duration (mean years)	6.5/10.2*	0	0
Number of patients	110	3867	753
Follow-up (median years)	6.0	11.1	10.7
Primary agent(s)	Insulin	Sulfonylurea or insulin	Metformin plus sulfonylurea
HbA_{1c} at inclusion	9.1%/9.2%*	7.0 %	7.3 %
HbA_{1c} at study end in intensive group (mean, SD, or median, IQR)	7.1 (SD 1.1)	7.0% (IQR 6.2–8.2)	7.4% (SD ..)
HbA_{1c} at study end in standard group (mean, SD, or median, IQR)	9.4% (SD 1.5)	7.9% (IQR 6.9-8.8)	8.0% (SD ..)
Microalbuminuria (RR [95% CI])	0.44† (0.16–1.17)	0.76‡ (0.62–0.91)	1.00 (0.77–1.30)
Macroalbuminuria (RR [95% CI])	0.11† (0.01–1.94)	0.67‡ (0.42–1.07)	..
Doubling of serum creatinine (RR [95% CI])	..	0.40‡ (0.14–1.20)	..
Renal death (RR [95% CI])	..	1.63 (0.21–12.49)	2.40 (0.22–26.39)
End-stage renal disease (RR [95% CI])	..	0.73 (0.25–2.14)	1.20 (0.17–8.49)

Data taken from Coca and colleagues,[16] and Turner and colleagues.[17] Data for microalbuminuria and macroalbuminuria from the UKPDS 33 were reported in 3-year intervals—data from the 9-year timepoint were chosen for these renal endpoints. Intensive glucose control was stopped in the ACCORD trial and data for renal outcome were reported at transition to standard therapy (follow-up 3.5 years) and at study end (follow-up 5 years). Renal outcome of the main analyses are shown in this Table. RR=risk ratio. *The first value represents the result in the primary-prevention cohort; the second value, in the secondary-prevention

participants with and without type 2 diabetes reported on the effect of weight loss on renal outcome. This study showed that each kilogram of weight loss was associated with a 1.1 mg decrease in microalbuminuria and a 110 mg decrease in total protein excretion.[31] A secondary analysis of the landmark Look AHEAD trial[32] specifically addressed the renoprotective effects of weight loss through diet and increased physical activity. In this open-label randomised study in 5145 patients with type 2 diabetes, a mean bodyweight decrease of 4 kg reduced the incidence of very-high-risk chronic kidney disease by 31% at 8 years of follow-up.[32] However, as lifestyle interventions are generally associated with slight bodyweight reduction and weight regain at long-term follow-up,[32] bariatric surgery might be useful in selected patients. A 3-year randomised trial[33] showed that bariatric surgery reduces bodyweight by about 20 kg versus medical management in obese patients with poorly regulated type 2 diabetes. In addition to benefits in the primary endpoint (HbA_{1c} 6.0% or less, with or without diabetes drugs), a 38% reduction in albuminuria was reported.

Effects of antihyperglycaemic drugs on bodyweight

Antihyperglycaemic drugs have differential effects on bodyweight, which might change renal outcome either positively (bodyweight reduction) or negatively (bodyweight increase) beyond

ADVANCE (2008 and 2013)	VA Diabetes Feasibility (2000)	ACCORD (2008 and 2010)	VADT (2009 and 2011)
8	8	10	12
11140	153	10251	1791
5.0	2.0	3.5	5.6
Gliclazide (90.5%)	Insulin	Metformin (86.9%) and sulfonylurea (73.8%)	Rosiglitazone and metformin (BMI ≥27), or glimepiride (BMI <27)
7.2%	9.7 %	8.3%	9.4%
6.5% (SD 0.9)	7.1% (SD 0.1)	6.4% (IQR 6.1–7.0)	6.9% (SD ..)
7.3% (SD 1.3)	9.1% (SD ..)	7.5% (IQR 7.0–8.1)	8.4% (SD ..)
0.92‡ (0.86–0.98)	0.26‡ (0.13–0.52)	0.88‡ (0.80–0.96)	0.74 (0.51–1.07)
0.79‡ (0.67–0.93)	0.35 (0.11–1.13)	0.72‡ (0.60–0.86)	0.56‡ (0.33–0.96)
1.10 (0.78–1.55)	..	1.10 (0.96–1.26)	1.00 (0.74–1.35)
0.84§ (0.43–1.64)	..	..	..
0.35‡ (0.18–0.70)	..	0.91¶ (0.73–1.15)	0.64‖ (0.25–1.64)

cohort. †The cumulative worsening of microalbuminuria and macroalbuminuria was significantly lower in the intensive group (RR 0.32, p=0.005); reported values are calculated on the basis of original data.[16] ‡Shows significant result. §Composite of end-stage renal disease and renal death. ¶Composite of initiation of dialysis or end-stage renal disease, or renal transplantation, or rise of serum creatinine >291.72 µmol/L in absence of an acute reversible cause. ‖Reported as GFR <15 mL/min.

glycaemic control, although no studies have directly investigated such effects. Sulfonylureas, thiazolidinediones, and insulin are known to increase weight by 2.2–3.4 kg,[34] whereas metformin[35] and dipeptidyl peptidase-4 (DPP-4) inhibitors[34] are weight neutral (Table 2). Glucagon-like peptide-1 (GLP-1) receptor agonists consistently reduce bodyweight in patients with type 2 diabetes by 2.8 kg (95% CI −3.4 to −2.3),[36] probably by satiety promotion and reduction in caloric intake. Similar analyses show that sodium-glucose cotransporter-2 (SGLT-2) inhibitors also reduce bodyweight (−1.8 kg, 95% CI −3.5 to −0.1),[37] which is explained by their initial diuretic effects and sustained glycosuria-related loss of calories. However, the sustained glycosuria-related loss of calories might be blunted by increased caloric intake after prolonged treatment with the drug.[38]

Systemic hypertension

Systemic hypertension is an early and common problem in patients with type 2 diabetes and substantially contributes to adverse diabetes-related outcomes, including mortality, stroke, heart disease, and development and progression of diabetic kidney disease.[4, 39] Patients with diabetes and advanced renal disease have an especially high incidence of systemic hypertension, and because of impaired renovascular autoregulation and a non-dipping pattern of nocturnal

Panel 2. Diabetic kidney disease monitoring and renal endpoints

A hard endpoint in clinical trials is a characteristic that shows how a patient feels, functions, or survives.[21] Substantial effect on such clinical endpoints shows the efficacy of novel or existing drugs, which is needed for their acceptance by the medical community, guidelines, and regulatory agencies.[21] However, hard endpoints are often impractical because they take a long time to manifest and therefore need large complex studies of long duration or a specific severely diseased population at high risk to develop the endpoint.[21] A surrogate endpoint is a biomarker or physical sign validated (on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence) to predict hard endpoints, and might replace these to increase clinical trial efficacy, especially in earlier stages of a disease. For renoprotection trials in patients with or without diabetes, several hard and surrogate endpoints are used.[21,22] Discussion about whether to accept a 30–40% decrease in estimated glomerular filtration rate (eGFR) or albuminuria as surrogate endpoints is continuing.[22-25]

Established hard endpoints

- End-stage renal disease, defined by renal replacement therapy (dialysis or kidney transplantation) or eGFR <15 mL/min/1.73 m^2
- Renal death, defined as death attributable to kidney failure when renal replacement therapy is not provided or available

Established surrogate endpoint

- Doubling of serum creatinine (corresponds to 57% decrease in eGFR)

Potential alternative surrogate endpoints

- 30–40% decrease in eGFR
- Albuminuria
  - New onset, progression, or regression
  - Microalbuminuria or macroalbuminuria

blood pressure,[40] these patients might be even more susceptible to pressure-induced glomerular damage.

Blood pressure control, irrespective of the intervention or pharmacological drug used, reduces cardiovascular disease risk and decelerates the natural course of diabetic kidney disease.[4] Both UKPDS[41] and ADVANCE[42] showed that the benefits of tight blood pressure control might be similar to, or even more important than, strict glycaemic control for the reduction of renal disease in patients with type 2 diabetes. Finally, blood pressure control could have been the major determinant for the beneficial renal outcome of multifactorial treatment in Steno-2.[43]

Although benefits of blood pressure reduction/se are well established, optimum blood pressure targets remain to be identified. Early observational studies and post-hoc analyses of randomised trials suggested that a blood pressure lower than 130/80 mmHg might be the most appropriate target for patients with diabetes.[11,44] However, results of a meta-analysis[45] including 2272 patients showed no benefit for a reduction in blood pressure to less than 130/80 mmHg compared with less stringent targets, whereas ACCORD disclosed more serious adverse events with tight blood pressure control, including acute kidney failure and electrolyte imbalance.[46] As a result of scarce robust evidence for lower targets, the Kidney Disease—Improving Global Outcomes (KDIGO) group and the Eighth Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure now recommend a blood pressure target of 140/90 mmHg

or less,[11, 47] whereas the American Diabetes Association advocates diastolic blood pressures of less than 80 mmHg,[2] and the European Society of Hypertension and the European Society of Cardiology advocate diastolic blood pressures of less than 85 mmHg,[48] because of suggested benefits in the HOT trial[49] and UKPDS.[50] Subgroup analyses of discussed trials showed that blood pressure targets of 130/80 mmHg or lower could be appropriate in younger individuals[2] or patients with diabetes and albuminuria.[11] Additional trials in progress, such as the SPRINT (NCT01206062), are expected to provide further guidance in the identification of optimum blood pressure targets. Importantly, reliable measurement of blood pressure that includes a 24 h assessment has been advocated because the conventional blood pressure measurements taken in a physican's office are of limited value.[4,6] Therefore, the value of present targets for blood pressure should be interpreted with care in clinical practice.

Clinicians should use a stepwise combination of lifestyle modifications and drug therapy to lower blood pressure in patients with type 2 diabetes (Panel 1). With respect to lifestyle, patients should be encouraged to exercise regularly, maintain a healthy weight, and restrict sodium intake to less than 2 g/day, and excess alcohol ingestion should be avoided.[11] Pharmacological interventions are, however, often warranted in hypertension management in patients with diabetes, especially when kidney function is compromised. Of the antihypertensive drugs used, those that interrupt the RAAS have shown renoprotection that extends beyond their blood-pressure-lowering capacity, as was shown in several trials in patients with diabetes and chronic kidney disease (Panel 1).[51] Benefit was also suggested in normoalbuminuric patients with type 2 diabetes, since ACE inhibition reduced microalbuminuria development by about 50% in BENEDICT, although in ROADMAP, ARB therapy decreased time to onset of microalbuminuria by 23% (see reference 45 for a review on these studies).[51] The pleiotropic benefits of RAAS inhibitors are predominantly attributed to their reduction of albuminuria, and possibly by targeted glomerular hyperfiltration, renal inflammation, and fibrosis. Results of a recent meta-analysis[52] suggested that ACE inhibitors had cardioprotective effects and increased survival in patients with diabetes, an effect that is not shared with ARBs. Diuretics and dietary sodium restriction increase the efficacy of RAAS inhibitors to lower albuminuria, which can result in additional renal benefit.[53] Furthermore, addition of an aldosterone blocker to ACE inhibitor or ARB treatment has been shown to decrease UAE in patients with type 2 diabetes, although caution should be taken because of the increased risk for hyperkalaemia.[11] However, few patients attain present blood pressure goals—with or without RAAS inhibitors—in a real-world setting,[54] and therefore, renal risk related to blood pressure still exists in clinical practice.

Effects of antihyperglycaemic drugs on blood pressure

Metformin and sulfonylureas do not cause clinically relevant blood pressure changes.[55,56]However, thiazolidinediones reduce systolic blood pressure by −3.47 mmHg and diastolic blood pressure by −1.84 mmHg, which might have beneficial effects on diabetic kidney disease development and progression.[57] Although the exact mechanisms by which thiazolidinediones lower blood pressure are unknown, potential actions include increased insulin sensitivity and endothelial function, attenuation of over-activity of the sympathetic nervous system, and downregulation

Table 2. Properties of frequently used antihyperglycaemic drugs in patients with type 2 diabetes.

Agent	Glucose-lowering actions	Disadvantages and adverse events	Costs	Bodyweight
Metformin	Decreases in hepatic glucose production	Gastrointestinal intolerance (diarrhoea), lactic acidosis (rare)	$	Neutral
Sulphonylureas	Increases insulin secretion (basal and prandial)	Hypoglycaemia, weight gain, low durability, cardiovascular events‡	$	Gain
Thiazolidinediones	Increases in insulin sensitivity, decreases in hepatic glucose production	Oedema and heart failure, weight gain, bone fractures, bladder cancer‡, cardiovascular events‡	$$	Gain
Insulin	Increases in glucose disposal, decreases in hepatic glucose production	Hypoglycaemia, weight gain, injectable	$ to $$$	Gain
DPP-4 inhibitors	Increases in insulin secretion (glucose-dependent), decreases glucagon secretion (glucose-dependent)	Heart failure‡, pancreatitis‡, pancreatic cancer‡, nasopharyngitis‡	$$$	Neutral
GLP-1 receptor agonists	Increases in insulin secretion (glucose-dependent), decreases in glucagon secretion (glucose-dependent), decreases gastric emptying, increases in satiety	Gastrointestinal side effects (nausea, vomiting, diarrhoea), injectable, pancreatitis‡, pancreatic cancer‡	$$$	Loss
SGLT-2 inhibitors	Increases in urinary excretion of glucose	Genital mycotic infections, urinary tract infections, breast and bladder cancer‡, bone fractures‡	$$$	Loss

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; *Suggests potential reduction in albuminuria beyond glycaemic control; †Based on effects on renal risk factors beyond glucose lowering; ‡Uncertain safety issues.

of the RAAS.[58] For GLP-1 receptor agonists, a meta-analysis[59] of 33 trials including 12 469 patients with type 2 diabetes reported a mean reduction in systolic blood pressure of −2.22 mmHg (95% CI −2.97 to −1.47) compared with oral antihyperglycaemic drugs or placebo. For DPP-4 inhibitors, a review of several studies reported slight blood pressure lowering, but not all do.[60] Various mechanisms might contribute to the antihypertensive effect of incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) in patients, including weight loss, reduced salt intake, increased natriuresis and diuresis, reduced RAAS activity, and improved endothelial function.[60] In a meta-analysis[37] of 27 randomised clinical trials (12 960 participants), SGLT-2 inhibitors also reduced systolic (−3.77 mmHg, 95% CI −2.90 to −4.65) and diastolic blood pressure (−1.75 mmHg, 95% CI −1.23 to −2.27) versus placebo. This finding might be due to their diuretic-like capacity,[61] but might also be partly secondary to weight loss. Although

Blood pressure	Glomerular hyperfiltration	Albuminuria*	Lipids	Renoprotective potential†
Neutral systolic and diastolic	Unknown	Unknown	Total cholesterol decrease, LDL cholesterol decrease, variable HDL cholesterol, triglyceride decrease	Neutral
Neutral systolic and diastolic	Unknown	Unknown	Variable total cholesterol, LDL cholesterol decrease, neutral HDL cholesterol, variable triglycerides	Neutral
Decrease in systolic and diastolic	Decrease	Decrease	Total cholesterol decrease, LDL cholesterol, decrease, HDL cholesterol increase, triglyceride decrease	High
Neutral systolic and diastolic	Uncertain	Unknown	Total cholesterol neutral, neutral LDL cholesterol, HDL cholesterol decrease, triglyceride decrease	Neutral
Decrease or uncertain in systolic and diastolic	Unknown	Decrease	Total cholesterol decrease, LDL cholesterol decrease, HDL cholesterol increase, triglyceride decrease	Moderate
Decrease in systolic and diastolic	Decrease	Decrease	Total cholesterol decrease, LDL cholesterol decrease, HDL cholesterol increase, triglyceride decrease	High
Decrease in systolic and diastolic	Decrease	Decrease	Total cholesterol increase, LDL cholesterol increase, HDL cholesterol increase, triglyceride decrease	High

the blood-pressure-lowering effects of antihyperglycaemic drugs might improve renal outcome, no data from dedicated studies are available.

Glomerular hyperfiltration and albuminuria

Glomerular hyperfiltration and glomerular hypertension in diabetes have been linked to the development and progression of diabetic kidney disease.[62,63] Glomerular hyperfiltration, defined as a GFR of more than 125–140 mL/min/1.73 m^2, is a renal haemodynamic occurrence related to the extent of hyperglycaemia, which is seen early in the course of type 2 diabetes in about 50% of patients.[63] Additionally, hyperfiltration at the single-nephron level to compensate for loss of glomeruli in the natural course of diabetic kidney disease (with normal or reduced GFR) might be common in later stages of type 2 diabetes.[62,64] The mechanisms that underlie

glomerular hyperfiltration with increased GFR might differ from hyperfiltration at the single nephron level in later stages of renal dysfunction, although generally, two major hypotheses exist.[65] First, increased sodium and sodium-glucose coupled reabsorption in the renal proximal tubule, accompanied by upregulation of proximally located sodium–hydrogen exchanger-3, and SGLT-1 and SGLT-2, reduces sodium chloride delivery to the distally located macula densa.[60,63,65] Through inhibition of tubuloglomerular feedback, juxtaglomerular cells reduce resistance of the afferent renal arteriole, leading to augmented glomerular filtration. Combined with tubular hypertrophy, proximal hyper-reabsorption leads to reduced hydrostatic pressure in the Bowman's capsule and further perpetuation of glomerular hyperfiltration.[60] Second, diabetes is associated with dysregulated activity of systemic and renal vasoactive factors, such as angiotensin II, endothelin 1, and atrial natriuretic peptide.[65,66] Collectively, these changes result in less resistance of the afferent compared with the efferent renal arteriole, and subsequent increased intraglomerular pressure and glomerular capillary flow. Ultimately, these changes lead to hyperfiltration and stress-induced glomerular injury.[65,66]

The clinical significance of hyperfiltration is shown by the U-shaped association between eGFR and mortality in patients with diabetes, suggesting an increased risk of death with supranormal kidney function, although confounding factors cannot be excluded.[67] Moreover, increased GFR is associated with albuminuria development, as was summarised in a meta-analysis of ten cohort studies (780 patients with type 1 diabetes) with 11 years of follow-up.[68] Furthermore, several observational studies in type 2 diabetes have linked glomerular hyperfiltration to the development of diabetic kidney disease, although reports have shown some inconsistencies.[69] Additionally, in a recent analysis of 600 hypertensive patients with type 2 diabetes with or without microalbuminuria,[69] patients with persistent hyperfiltration had albuminuria progression and increased loss of GFR, as opposed to patients in which hyperfiltration was ameliorated by intensified metabolic and blood pressure control. Notably, although most studies of hyperfiltration use measured GFR, detection and monitoring of hyperfiltration with eGFR might be unreliable because such estimations consistently underestimate GFR in the hyperfiltration range.[70]

The efficacy of RAAS inhibitors to prevent or delay diabetic kidney disease could partly be explained by their potential to reduce glomerular hyperfiltration, since these drugs relieve angiotensin-II-induced vasoconstriction of the efferent arteriole. As such, in a prospective study[71] in patients with type 1 diabetes and hyperfiltration, high-dose ACE inhibition—titrated to normalise GFR—reduced microalbuminuria by 25% at 18 months of follow-up. However, such targeted therapy does not normalise hyperfiltration in all patients with diabetes.[72] Moreover, in a systematic review of ACE-inhibitor trials,[64] a strong association was reported between an initial decrease in eGFR and long-term preservation of renal function in patients with renal impairment, with and without diabetes. The acute reduction in eGFR in this patient population is compatible with a haemodynamically mediated decrease in intraglomerular pressure and single-nephron hyperfiltration, and is reversible after treatment discontinuation.[64] A more recent post-hoc analysis of the RENAAL trial[73] extended these findings to show a proportional

association between acute ARB-induced eGFR reduction and long-term renal function preservation in patients with type 2 diabetes and diabetic kidney disease. Finally, because high dietary protein intake is associated with increased glomerular pressure and filtration,[62,63] renoprotective effects of a reduction in protein intake might partly be explained by improvement of renal haemodynamics.[10]

Notably, the association between glomerular hypertension and adverse renal outcome might be mediated by its direct association with albuminuria. Intraglomerular hypertension, among other effects, results in stretching of glomerular capillaries, which leads to increased filtration of macromolecules, including albumin. Emerging data show that albumin is not an inert molecule, but could have direct toxic effects on renal tissues.[74] In normal physiological conditions, only small amounts of albumin are filtered by the glomeruli and are effectively reabsorbed in the tubuli.[75,76] However, in conditions of increased glomerular albumin leakage, the tubuli are exposed to increased albumin concentrations, which could activate pro-inflammatory pathways leading to interstitial damage, fibrosis, and ultimately reduced nephron functionality.[77–79] Thus, albuminuria might not only be a marker of the extent of renal damage, but also seems to have a direct damaging effect in the kidney.

The clinical significance of raised albuminuria is its potential to be used as both a target and indicator of efficacy in renoprotective treatments. Various interventions, including RAAS inhibition,[51] corticosteroid treatment,[80] or protein restrictive diet,[81] decrease albuminuria and confer renoprotective effects. Analyses from clinical trials[82–84] show that albuminuria reduction, recorded during the first months of treatment with these drugs, correlates with the amount of long-term renal protection; the larger the initial reduction in albuminuria, the lower the risk of end-stage renal disease during treatment. Trials with dual RAAS blockade showed no additional renal or cardiovascular benefit despite a reduction in albuminuria and blood pressure.[85] This finding is most probably explained by other effects of dual RAAS blockade such as hyperkalaemia, hypotension, or acute kidney injury, which disrupt the relation between blood pressure or albuminuria, with renal and cardiovascular outcomes.

In conclusion, clinical evidence shows that glomerular hypertension and hyperfiltration contribute to diabetic kidney disease, whereas reduction of these renal haemodynamic abnormalities with RAAS inhibitors has renoprotective properties in diabetes, which might be partly mediated by reduction of albuminuria. Nevertheless, prospective studies are needed to assess whether, and to what extent, glomerular hyperfiltration, albuminuria, or both, should be specific treatment targets for diabetic kidney disease prevention.

Effects of antihyperglycaemic drugs on glomerular hyperfiltration and albuminuria

The thiazolidinedione rosiglitazone was shown to reduce raised GFR, filtration fraction (as a proxy for intraglomerular pressure), and albuminuria in patients with type 2 diabetes.[86] Insulin lispro reduces postprandial GFR,[87] although results with other insulin therapies in the fasting state are inconsistent.[88] However, novel antihyperglycaemic drugs in particular have shown

potential to reduce glomerular hyperfiltration and subsequent albuminuria. As such, in 16 men who were obese and had normoalbuminuric hyperfiltration, 25% of whom had newly diagnosed type 2 diabetes, 3 h infusion of the GLP-1 peptide decreased creatinine clearance from 151 to 142 mL/min.[89] Additionally, in an uncontrolled open-label study[90] in 31 patients with type 2 diabetes, 7 week treatment with the GLP-1 receptor agonist liraglutide decreased GFR from 99.5 to 88.5 mL/min/1.73 m^2 and albuminuria by 30%, which both returned to baseline values after 3 week washout of the study drug. A subsequent follow-up of 1 year in 23 patients supported the durability of these effects compared with seven control patients who did not restart treatment.[91] The DPP-4 inhibitors saxagliptin and linagliptin decreased albuminuria by about 25%, independent of the extent of glycaemic control.[92,93] The incretin-based therapies might reduce GFR and albuminuria by direct actions on the renal vasculature, through effects on vasoactive factors, or by restoration of tubuloglomerular feedback through GLP-1-mediated inhibition of the sodium–hydrogen exchanger-3.[60] DPP-4 inhibitors might also reduce albuminuria by attenuating endothelial dysfunction and filtration barrier injury.[94] SGLT-2 inhibitors also reduce glomerular hyperfiltration and albuminuria in clinical studies, probably by restoration of tubuloglomerular feedback[95] or diuresis-induced reduction in atrial natriuretic peptide.[61,66] In 27 patients with type 1 diabetes, short-term treatment with the SGLT-2 inhibitor empagliflozin attenuated hyperfiltration by 33 mL/min/1.73 m^2 during clamped euglycaemia and 44 mL/min/1.73 m^2 during hyperglycaemia.[95] A subsequent analysis[96] showed that these findings were accompanied by reduced intraglomerular pressure. Additionally, two large placebo-controlled studies[97,98] investigated the SGLT-2 inhibitors canagliflozin for 26 weeks and dapagliflozin for 112 weeks in patients with type 2 diabetes and moderate renal impairment. Both trials reported acute eGFR reductions that were independent of blood pressure with the use of the study drug, which stabilised during follow-up. Furthermore, these drugs reduce albuminuria by about 30%,[97,99] independent of glycaemic and blood pressure control.[99]

Dyslipidaemia

Patients with type 2 diabetes frequently have dyslipidaemia, characterised by hypertriglyceridaemia, decreased HDL cholesterol concentrations, and a high proportion of small dense LDL cholesterol concentrations, probably related to obesity and insulin resistance.[100] Dyslipidaemia is a major risk factor for the development of cardiovascular disease and mortality in the general population and in patients with type 2 diabetes.[2,14] With regard to renal risk, a review of several observational studies in type 2 diabetes has shown an association between dyslipidaemia, diabetic kidney disease, and end-stage renal disease.[100] Additionally, a post-hoc analysis of ADVANCE[101] showed that low concentrations of HDL cholesterol are associated with an increased risk of albuminuria, whereas in RENAAL[102] the relative risk of reaching the primary composite endpoint or end-stage renal disease was higher in patients with type 2 diabetes in the upper quartile of total and LDL cholesterol than those in the lowest quartile. How dyslipidaemia or hyperlipidaemia could cause renal damage is unclear, but results of animal studies have shown that glomerular lipid deposition resembles histological features

of atherosclerotic plaques in vessel walls, for which the term glomerular atherosclerosis has been proposed.[100]

Pharmacological management of lipid disorders with statins is important in patients with diabetes, with or without chronic kidney disease, for reduction of cardiovascular risk and mortality.[2,14] Additionally, several randomised trials and post-hoc analyses have investigated the potential effect of statin therapy on renal outcome. A meta-analysis of three trials[103] showed no effect of statin therapy on reduction of end-stage renal disease in patients with chronic kidney disease with or without diabetes (RR 0.97, 95% CI 0.90–1.05). Furthermore, when surrogate renal endpoints were addressed, including serum creatinine doubling, no benefit was seen in a meta-analysis of seven lipid-lowering trials,[103] although significant heterogeneity was reported. Two independent meta-analyses of clinical trials[104,105] have shown a statin-induced reduction in albuminuria, with heterogeneous effects dependent on baseline albuminuria. The PLANET I trial[106] in patients with diabetes and macroalbuminuria has provided evidence that different statins exert different effects on the kidney. In this study, atorvastatin but not rosuvastatin reduced albuminuria, whereas eGFR declined from baseline with rosuvastatin but not with atorvastatin, despite similar lipid-lowering effects.[106] The underlying mechanisms of this differential effect are unclear, but might relate to a rosuvastatin-induced reduction of proximal tubular protein reabsorption.[107] Lipid-lowering drugs, other than statins, might affect diabetic kidney disease risk. In the FIELD trial,[108] 5-year treatment with fenofibrate versus placebo lowered albuminuria by 14% and was associated with a slower decline of eGFR. No differences were seen in hard renal endpoints, although the study was not designed to address this.

Thus, dyslipidaemia probably contributes to chronic kidney disease in patients with type 2 diabetes, although recommendations about use of statin therapy in diabetes, with or without addition of the intestinal cholesterol absorption inhibitor ezetimibe in selected patients (Panel 1), are mainly geared to reduce all-cause and cardiovascular mortality.[109] Whether lipid-lowering drugs confer renoprotection, possibly even through pleiotropic effects on albuminuria or inflammation, needs further studies with hard renal endpoints.

Effects of antihyperglycaemic drugs on lipids

Several antihyperglycaemic drugs improve lipid profiles in addition to their glucose-lowering effect. Although the pleiotropic changes induced by these drugs can be small, they could have important effects on the kidney when added to existing lipid-lowering therapy; however, studies that directly investigate these effects have not been done. Metformin—as monotherapy or in combination with a sulfonylurea—significantly lowers fasting total cholesterol, LDL cholesterol, and triglyceride concentrations, with variable effects on HDL cholesterol, independent of its glycaemic effects.[56] Insulin glargine reduced HDL cholesterol and triglycerides versus standard care (mainly oral antihyperglycaemic drugs) in the ORIGIN trial.[110] The thiazolidinedione pioglitazone improves dyslipidaemia in patients with type 2 diabetes by reducing triglycerides and increasing HDL cholesterol concentrations.[111] GLP-1 receptor agonists and DPP-4

inhibitors reduce triglycerides and LDL cholesterol by the inhibition of hepatic lipid production and intestinal fatty acid uptake.[112,113] Small lipid changes have been reported in trials of SGLT-2 inhibitors, such as inconsistent reductions in triglycerides, and increases in total cholesterol, LDL cholesterol, and HDL cholesterol.[114] Although minimum effect was noted on the ratio of total cholesterol to HDL cholesterol with the use of canagliflozin, the clinical outcomes of reported increases in LDL cholesterol are still uncertain.

Future perspectives

Clinical evidence shows that some of the widely used antihyperglycaemic drugs might favourably target risk factors for diabetic kidney disease beyond their ability to lower glucose. Exploitation of pleiotropic benefits in clinical practice, in addition to established multifactorial treatment, might add value in the reduction of residual renal risk in patients with type 2 diabetes. GLP-1 receptor agonists and SGLT-2 inhibitors, in particular, seem to show beneficial actions on key renal risk factors, such as obesity and hypertension, whereas thiazolidinediones and DPP-4 inhibitors might have alternative renoprotective potential beyond glucose lowering. However, the position of the newest antihyperglycaemic drugs, such as the incretin-based therapies and SGLT-2 inhibitors, in type 2 diabetes management is uncertain, partly because of the scarcity of long-term safety data (potentially unfavourable pleiotropic effects) and costs. In clinical practice, a balance between advantages and disadvantages of these drugs for the individual patient should be made (Table 2). For instance, the thiazolidinediones are not widely used for disease management, especially since rosiglitazone was associated with adverse cardiovascular outcomes; its use was severely restricted in the USA and marketing was suspended in the EU.[115]

Triggered by the negative effects of rosiglitazone, the development of novel diabetes drugs is subject to the 2008 US Food and Drug Administration guidance, requiring large studies of cardiovascular safety. As a result, more than 150 000 patients with type 2 diabetes and high cardiovascular and renal risk are being studied in clinical trials, particularly involving GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors (Table 3). Several of these large randomised trials also include prespecified primary or secondary renal endpoints, or both, thereby possibly providing important clinical data on the effects of these drugs on the kidney. However, since most trials are placebo controlled, estimating drug-specific benefits beyond glucose control is difficult, as are direct comparisons between cardiovascular and renal outcomes of antihyperglycaemic drug classes. Moreover, many trials are of short duration. Therefore, future comparative renoprotection studies that are sufficiently powered and of appropriate duration, with the primary aim of investigation of renal outcome are needed. Finally, since evidence is emerging for a non-proteinuric pathway in diabetic kidney disease, clinical trialists might consider specifically studying patients with type 2 diabetes and progressive renal function loss with no or negligible albuminuria.[8]

Table 3. Randomised cardiovascular safety trials (in progress), with or without renal endpoints, in patients with type 2 diabetes

Trial name	Number of patients	Intervention	Population with type 2 diabetes	Estimated study completion (treatment duration)	Renal endpoints
PPAR-γ agonist					
TOSCA IT (NCT00700856)	3371	Pioglitazone*	HbA_{1c} 7.0–9.0%; metformin monotherapy	December 2018 (48 months)	Secondary: doubling of serum creatinine, creatinine clearance reduction of 20 mL/min, microalbuminuria, overt nephropathy
DPP-4 inhibitor					
TECOS (NCT00790205)	14000	Sitagliptin	HbA_{1c} 6.5–8.0%; CVD history	March 2015 (≤5 years)	Secondary: change in renal function over
MARLINA (NCT01792518)	404	Linagliptin	HbA_{1c} 6.5–10.0%; UACR 30–3,000 mg/g; ACE inhibitors or ARB therapy	November 2015 (24 weeks)	Secondary: time-weighted average of change in UACR
MK-3102 trial (NCT01703208)	4000	Weekly omarigliptin	HbA_{1c} 6.5–10.0%; CVD history	October 2017 (156 weeks)	Not specified
CARMELINA (NCT01897532)	8300	Linagliptin	HbA_{1c} 6.5–10.0%; cardiovascular risk (albuminuria plus CVD or impaired GFR plus UACR, or both)	January 2018 (48 months)	Secondary: composite renal endpoint: renal death, ESRD, and sustained decrease of ≥50% in eGFR
CAROLINA (NCT01243424)	6000	Linagliptin*	HbA_{1c} 6.5–7.5%; CVD, cardiovascular risk factors, or diabetes end organ damage	September 2018 (400 weeks)	Secondary: transitions in albuminuria classes, changes in eGFR, and albuminuria
GLP-1 receptor agonist					
ELIXA (NCT01147250)	6075	Lixisenatide	HbA_{1c} 5.5–11.0%; acute coronary syndrome	February 2015 (108 weeks)	Secondary: change in UACR
LEADER (NCT01179048)	9340	Liraglutide	HbA_{1c} ≥7.0%; age ≥50 years plus CVD; age ≥60 years plus cardiovascular risk factors	October 2015 (≤60 months)	Safety: new-onset macroalbuminuria, doubling of serum creatinine, eGFR ≤45 mL/min, ESRD
SUSTAIN6 (NCT01720446)	3297	Semaglutide	HbA_{1c} ≥7.0%; age ≥50 years plus CVD; ≥60 years plus subclinical CVD	April 2016 (143 weeks)	Secondary: change in UACR

Table 3. (continued)

Trial name	Number of patients	Intervention	Population with type 2 diabetes	Estimated study completion (treatment duration)	Renal endpoints
EXSCEL (NCT01144338)	14000	Weekly exenatide	HbA_{1c} 6.5–10.0%; CVD in about 60%	April 2018 (≤7.5 years)	Not specified
ITCA650 trial (NCT01455896)	4000	Exenatide†	HbA_{1c} >6.5%; CVD history	July 2018 (2 years)	Not specified
REWIND (NCT01394952)	9622	Weekly dulaglutide	HbA_{1c} <9.5%; age ≥50 years plus CVD; age ≥55 years plus subclinical CVD, age ≥60 years plus ≥2 cardiovascular risk factors	April 2019 (6.5 years)	Secondary: time to first occurrence composite microvascular endpoint
SGLT-2 inhibitor					
EMPA-REG OUTCOME (NCT01131676)	7000	Empagliflozin	HbA_{1c} 7.0–10.0% (7.0–9.0% drug naive); high cardiovascular risk	April 2015 (≤5 years)	Secondary: new onset albuminuria or macroalbuminuria, composite microvascular outcome
CANVAS (NCT01032629)	4365	Canagliflozin	HbA_{1c} 7.0–10.5%; high risk of CVD or history of CVD	April 2017 (≤8 years)‡	Secondary: progression of albuminuria
CANVAS-R (NCT01989754)	5700	Canagliflozin	HbA_{1c} 7.0–10.5%; high risk of CVD or history of CVD	April 2017 (78–156 weeks)	Primary: albuminuria progression. Secondary: albuminuria regression, eGFR changes, UACR at last visit
DECLARE-TIMI 58 (NCT01730534)	17150	Dapagliflozin	HbA_{1c} not specified; high cardiovascular risk	April 2019 (≤6 years)	Not specified
CREDENCE (NCT02065791)	3700	Canagliflozin	HbA_{1c} 6.5–10.5%; eGFR 30–90 mL/min; UACR 300–5000 mg/g; ACE inhibitor or ARB therapy	February 2019 (≤66 months)	Primary: composite endpoint (ESRD, doubling of serum creatinine, renal or cardiovascular death). Secondary: renal event primary endpoint

PPAR-γ, peroxisome proliferator-activated receptor gamma; DPP-4, dipeptidyl peptidase-4; CVD, cardiovascular disease; UACR, urinary albumin-creatinine ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; ESRD, end-stage renal disease; *Interventions have an active comparator; TOSCA IT (pioglitazone *vs* sulfonylureas); CAROLINA (linagilptin *vs* glimepiride); †Administered via a DUROS delivery system; ‡CANVAS was originally designed to last for up to 9 years; the last visit from a study participant will now occur when enough major adverse cardiac events are accumulated between the CANVAS and CANVAS-R studies.

Conclusion

During the past decade, much progress has been made to understand renal risk factors and pathophysiological mechanisms of diabetic kidney disease, and to create treatment strategies that reduce diabetic kidney disease risk in patients with type 2 diabetes. Treatment of the main renal culprits (hyperglycaemia and systemic hypertension), and use of RAAS inhibiting drugs have shown beneficial results on renal outcome. Additionally, specific targets of less established risk factors (such as obesity, glomerular hyperfiltration, albuminuria, and dyslipidaemia) could further contribute to prevention of diabetic kidney disease in patients with type 2 diabetes. However, despite multifactorial treatment strategies, substantial residual renal risk remains, which underlines the importance of novel drugs (Panel 3) or therapeutic strategies. Several available antihyperglycaemic drugs exert pleiotropic actions that favourably affect renal risk factors, although results are mechanistic in nature and might not yet direct clinical care. However, exploitation of these benefits could potentially add clinical value in the reduction of renal (and conceivably cardiovascular) risk in the near future, and results of large and long-term randomised trials are eagerly awaited to establish whether these off-target actions affect outcome in type 2 diabetes.

Panel 3. Targeting of renal risk factors in patients with type 2 diabetes with novel drug classes

In addition to pleiotropic effects of current antihyperglycaemic drugs, novel pharmacological drugs that specifically interrupt key pathophysiological pathways of diabetic kidney disease are on the horizon. These emergent drugs might also hold promise in the reduction of the burden of global diabetic kidney disease worldwide. To enhance a treatment strategy, a new therapy should either improve renal outcome in addition to the use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, or be more effective than renin-angiotensin-aldosterone system inhibitors in the prevention of diabetic kidney disease in head-to-head comparisons.

Oxidative stress and inflammation

Experimental evidence shows that the metabolic, haemodynamic, and hormonal abnormalities in the diabetes milieu drive a final common pathway of oxidative stress and inflammation. This pathway can lead to the development and progression of diabetic kidney disease by inducing apoptosis, fibrosis, and proliferation.[116] Therefore, several compounds with antioxidative and anti-inflammatory properties have been developed and are being tested in randomised trials in patients with diabetes, most of them including hard and surrogate renal endpoints.[117] Most notably, among these compounds is bardoxolone methyl, a molecule that activates NFE2L2, and thereby regulates antioxidant genes and inhibits NF-κB. Despite beneficial actions of bardoxolone methyl on estimated glomerular filtration rate in a 52-week phase 2 trial in 227 patients with type 2 diabetes and advanced chronic kidney disease,[118] the large phase 3 BEACON trial[119] was stopped early because of an excess of serious adverse events and mortality in the methyl bardoxolone group, without effect on the primary endpoint (end-stage renal disease or renal death). Therefore, the development of treatments that activate NFE2L2 is on hold until the toxicity of bardoxolone methyl has been investigated.[117] Other potentially promising novel drugs with anti-inflammatory and antifibrotic properties include vitamin D receptor activators and the xanthine derivative pentoxifylline. The results of clinical trials with anti-inflammatory C-C chemokine receptor (CCR)-2 (NCT01440257, NCT01447147) and CCR2/5 (NCT01712061, NCT01752985) antagonists are expected in 2015.[117] However, translation of antioxidative, anti-inflammatory, and antifibrotic strategies from preclinical trials to human diabetic kidney disease has proven difficult so far. Many of the novel

Panel 3. (continued)

and specific strategies are at the proof-of-concept stage, and therefore their therapeutic indication might not be reported for some time.

Endothelin

Renal endothelin 1, almost universally increased in chronic kidney disease, exerts unfavourable renal effects upon binding to endothelin-A receptors located on mesangial and endothelial cells.[120] In addition to induction of inflammation and fibrosis, this hormone probably plays a part in albuminuria development by increasing glomerular pressure, podocyte damage, and permeability to albumin.[65,120] Therefore, selective endothelin-A receptor antagonists were developed that were shown to reduce albuminuria by 35–50% in the ASCEND[120] (avosentan) and RADAR[121] (atrasentan) trials. Albuminuria returned to pretreatment concentrations after cessation of therapy, suggesting a haemodynamic nature of response with these drugs.[121] However, estimated glomerular filtration rate did not change in the 12 week RADAR trial, whereas the ASCEND trial was prematurely terminated because of a dose-dependent, three-fold increase in heart failure compared with placebo, suggesting a narrow therapeutic window of endothelin-A receptor antagonists. Therefore, in the phase 3 SONAR trial (NCT01858532), in progress, patients are exposed to a 6 week treatment period of atrasentan 0.75 mg/day, and only patients who tolerate the drug and show a more than 30% reduction in albuminuria will proceed to a placebo-controlled, double-blind treatment phase. The SONAR trial will provide further insight into the renoprotective actions and clinical safety of this novel drug class and it will simultaneously identify whether the response in albuminuria can be used as a measure for long-term renoprotective efficacy. Notably, the combined endothelin-converting enzyme and neutral endopeptidase inhibitor daglutril does not reduce albuminuria in patients with type 2 diabetes, although this novel drug effectively reduces blood pressure.[122]

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