Chronic Kidney Disease in Type 2 Diabetes: Implications for Managing Glycemic Control, Cardiovascular & Renal Risk

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Abstract

This review examines the current literature relating to diabetes related kidney disease (DKD) and the optimal management of cardio-renal risk. DKD develops in approximately 40% of patients with type 2 diabetes mellitus. The mainstay of therapy is to reduce the progression of DKD by optimising hyperglycaemia, blood pressure, lipids and lifestyle. Evidence supports the role for renin-angiotensin system blockade in limiting the progression of DKD. Recent data from diabetes related cardiovascular outcome trials and renal specific trials have provided a novel insight on the additional benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in reducing the progression of DKD as well as cardiovascular risk. Lessons have been learnt from CREDENCE and there are expectations that DAPA-CKD and EMPA-KIDNEY will further support the benefits of SGLT2 inhibition in relation to DKD. As a consequence, international guidelines have been updated to reflect the positive benefits. In addition novel steroidal mineralocorticoid receptor antagonists offer a potential role in future years. The review examines the current evidence and future approach to optimising outcomes for renal protection in patients with diabetes.

Key words

Diabetes-related nephropathy; Diabetic Nephropathy; Chronic kidney disease; Type 2 diabetes; Sodium-glucose cotransporter-2 inhibitors; Angiotensin-converting enzyme inhibitors; Angiotensin II receptor blockers; Glucagon like peptide-1 receptor agonists; Dipeptidyl peptidase-4 (DPP-4) inhibitors.

1. Introduction

Diabetes is a major risk factor for cardiovascular disease (CVD) and is a leading cause of chronic kidney disease (CKD). Diabetes-related nephropathy (also known as diabetic

nephropathy [1] or diabetic kidney disease [DKD]) develops in approximately 40% of patients with type 2 diabetes mellitus [2]. Furthermore, between 1990-2012, the number of deaths attributed to DKD rose by 94% [2, 3]. The World Health Organisation estimate that deaths related to diabetes will double by 2030 [4]. Notably, most of the excess risk is associated with CVD mortality [5]. As for other diabetes related complications, the traditional approach to reducing the progression of DKD involves the optimal management of hyperglycaemia, blood pressure, lipids and lifestyle. Whilst evidence supports a role for renin-angiotensin-aldosterone system (RAS) blockade in limiting the progression of DKD, recent data from cardiovascular outcome trials and renal specific trials has provided a novel insight on the additional benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in reducing the progression of DKD as well as cardiovascular risk. This review examines the current evidence approach to optimising outcomes for renal protection in patients with diabetes.

2. Search strategy

Publications were identified through searches of Medline, PubMed, Web of Science and Google Scholar for articles published between 1980 to 2019. Search terms included “diabetes kidney disease,” “diabetic nephropathy,” “chronic kidney disease,” “diabetes cardiovascular outcome trials,” “microvascular,” “dipeptidyl peptidase inhibitor,” “glucagon like peptide”, “sodium glucose transporter inhibitor”, “cardiovascular”, “macrovascular”, “type 2 diabetes”. For consideration, studies had to be published in English and articles were excluded if they were case reports, editorials, small studies or studies that the authors felt had methodological limitations.

3. Diabetes related kidney disease: Diagnosis and prognosis

3.1 Diagnosis

DKD is a clinical diagnosis based on the measurement of the estimated glomerular filtration rate (eGFR) and albuminuria. Patients typically exhibit a long duration of diabetes and the presence of other microvascular complications such as retinopathy [2, 6, 7]; however patients with type 2 diabetes may not have co-existing retinopathy. DKD is identified clinically by a persistently high urinary albumin: creatinine ratio (UACR) ≥30 mg/g (or ≥3.4 mg/mol) and/or a sustained reduction in eGFR below 60 mL/min per 1.73 m^2 [8]. Diabetes is likely to be the main cause of CKD, if these features are present. Other potential causes should be considered in the presence of a rapid decrease in eGFR, a sudden increase in albuminuria, nephritis, hypertension, and the presence of an active urinary sediment with cellular casts, the absence of diabetes-related retinopathy in patients with type 1 diabetes, or signs or symptoms of other systemic diseases associated with declining renal function. A renal biopsy can confirm the diagnosis, but is usually not required unless atypical features are present [9]. Renal disease in diabetes is heterogeneous in nature and the role of biopsy is controversial. The routine diagnosis of nephropathy in patients with diabetes has not demonstrated an impact on renal prognosis or mortality [10].

Microalbuminuria is a non-invasive marker of early renal involvement and usually occurs five years following the onset of diabetes. It is thought to be predictive of progression to nephropathy and reflects podocyte loss or endothelial damage. The pathogenesis of DKD is multifactorial and exhibits a decline in eGFR which usually progresses over ten years in type 1 diabetes, but can be more variable in type 2 diabetes [11]. The American Diabetes Association (ADA) recommend that screening for albuminuria can be performed on a spot urine sample by measuring the UACR, therefore negating the need for a 24 hour urine collection [12]. It is worth noting that UACR may demonstrate biological variability so that two

of three samples collected within a three to six month period should be abnormal. Furthermore, exercise, infection, fever, marked hyperglycaemia and hypertension may elevate UACR [12]. The eGFR should be calculated from serum creatinine using a validated formula, and many laboratories routinely report eGFR along with serum creatinine. An eGFR <60 mL/min per 1.73 m^2 is generally considered abnormal, though optimal thresholds for clinical diagnosis are debated [13]. Increased urinary albumin excretion is currently considered the best indicator of DKD risk. However, early progressive renal decline may precede the onset of microalbuminuria and elevated levels typically only appear after significant structural changes in the kidney have already occurred [14]. Furthermore, deterioration to end stage renal disease (ESRD) may also occur in spite of normalbuminuria. In the future, biomarkers associated with glomerular and tubulointerstitial histopathology may inform clinicians earlier in relation to the risk of progressive renal impairment due to DKD [15].

The stages of CKD are summarised in table 1. Different publications provide varied descriptions of the stages of DKD [12, 16]. The majorities define stages based on eGFR. All guidance appear to agree that at any stage of CKD, the degree of albuminuria is associated with the progression of CKD, and CVD risk and mortality.

3.2 Prognosis

Whilst microalbuminuria is confirmatory evidence of DKD, the progression to macroalbuminuria is not absolute and regression to normoalbuminuria may occur [17]. Previous studies report that 80% of patients with microalbuminuria progress to macroalbuminuria over a six to fourteen year period. However with improved control of blood glucose, blood pressure and lipids, the progress may change. For patients with type 1

diabetes, the Diabetes Control and Complications Trial (DCCT) showed that 58% of patients with microalbuminuria regressed to normoalbuminuria over 6 years [18]. Similarly in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 50% of patients regressed to normoalbuminuria over 10 years [19]. This effect was due to improved management of glucose and cardiovascular risk factors [20, 21]. The improvement in microalbuminuria was also associated with an 89% reduction in decreased eGFR.

With respect to type 2 diabetes, the clinical picture is different. Over a median follow-up of fifteen years in the United Kingdom Prospective Diabetes Study (UKPDS), 38% had microalbuminuria and 29% had a reduced eGFR [22]. The progression from normoalbuminuria to microalbuminuria, and from microalbuminuria to macroalbuminuria was approximately 2% per year. At fifteen years after diagnosis, 40% of participants had macroalbuminuria and 30% an eGFR <60 mL/min per 1.73 m^2 or a doubling in serum creatinine. Gaede et al, also showed that with multifactorial intervention for patients with type 2 diabetes, 31% of participants with microalbuminuria progressed to macroalbuminuria, whereas 31% regressed to normoalbuminuria during 7.8 years of follow-up. Another 38% remained microalbuminuric during this time period [23]. There appear to be differences in progression and regression of microalbuminuria relating to different ethnic background. For example, in Pima Indians, a study has reported that 7.3% of patients had microalbuminuria at enrollment with 17% at five years, 25% at ten years and 28% at fifteen years. The prevalence of macroalbuminuria was 50% during a median follow-up of twenty years [24]. It should of course be cknowledged that the above studies are now historical and pateints are currently treated with RAS blockade, more stringent glycemic control and multifactorial interventions (as discussed below) and therefore the progression and regression patterns of DKD may be different.

In later stages of DKD, as GFR declines, both renal and non-renal related DKD complications develop. Anaemia and bone disease develop earlier in patients with DKD and furthermore a greater degree of tubulointerstitial fibrosis, is associated with earlier onset and more sever forms of anaemia. In fact, patients with DKD are more likely to have deficiency of erythropoietin and vitamin D compared to patients without diabetes and CKD. [25]. Hepcidin is a key iron regulatory hormone, levels of which are elevated in inflammatory states such as CKD, resulting in functional iron deficiency anaemia. A bi-directional relationship exists between iron and glucose metabolism. Serum hepcidin levels have been shown to be elevated in type 2 diabetes [26] and one of the pleiotropic effects of hepcidin is to worsen insulin resistance. The cross talk between iron metabolism and diabetes, in addition to the frequent use of angiotensin-converting enzyme inhibitors (ACEi) in diabetes may explain the earlier onset of renal anaemia in DKD [27]. Furthermore diabetes may be associated with lower levels of parathyroid hormone as a consequence of insulin deficiency or insulin resistance, as insulin is a cofactor for parathyroid hormone release [28].

Glycated haemoglobin (HbA1c) is widely used as the gold standard index to assess glycaemic control in diabetes; indicating average glucose levels over the preceding 120 days. However in CKD, the prognostic value of HbA1c has limitations due to uraemia, concomitant anaemia, red blood cell lifespan and consequent iron or erythropoietin therapy [29]. Glycated albumin (GA) has been suggested as a more reliable biomarker for evaluating glycaemic control in advanced CKD. As it is calculated as a ratio it is not influenced by total serum albumin levels. It is believed that GA may provide a more reliable short term index of glycaemic control of the preceding two to three weeks, as well as a predictor of cardiovascular complications in patients with diabetes and DKD [30].

With respect to mortality, death from CVD, infection and ERSD are evident. The UKPDS observed that the mortality rate after the onset of DKD in those with a creatinine >177 µmol/L or those receiving renal replacement therapy was 20% per year [31].

4. From pathophysiology to therapeutics targets

Advanced glycation end-product (AGE) generation, growth factor amplification, haemodynamic and hormonal changes ensue as a result of the diabetes milieu. In addition, the release of reactive oxygen species and other inflammatory mediators cause microvascular renal injury and subsequent diabetes related change. Glomerular hyperfiltration and hypertension, and renal hypertrophy manifest clinically as albuminuria and elevated blood pressure. Renal morphological changes in type 2 diabetes include early glomerular basement membrane thickening, mesangial expansion (figure 1) and late nodular (Kimmelstiel-Wilson) type or diffuse glomerulosclerosis related to DKD (figure 2) [11].

DKD is complex and encompasses not only albuminuria, but also atheroembolic disease, ischemic nephropathy, and interstitial fibrosis. Many pathophysiologic pathways are involved in the development of DKD. Current treatment regimens focus on cardiovascular risk reduction, optimisation of glycaemic control, blood pressure lipids, weight management and inhibition of the RAS system.

4.1 Haemodynamic factors

Glomerular hyperfiltration occurs in the early stages of DKD and is defined as an eGFR greater than two standard deviations above normal (usually an eGFR between 120-140

mL/min per 1.73 m^2) [32]. It is worth noting that there is an intraindividual variability of GFR, which can be affected by the severity of hyperglycaemia [33]. In addition, eGFR may be influenced by gender, ethnicity and age. The prevalence of glomerular hyperfiltration differs between type 1 and type 2 diabetes. Patients with type 1 diabetes of ten years duration have a prevalence rate of 34-67%, while the prevalence in those with type 2 diabetes is 6-23% [32]. The lower prevalence of glomerular hyperfiltration in patients with type 2 diabetes may be explained by the presence of pre-existing comorbidities such as hypertension, dyslipidaemia and obesity, which are associated with renovascular diseases.

Glomerular hyperfiltration is thought to be a result of a disproportionate difference in vascular resistance between afferent and efferent arterioles. In diabetes mellitus, RAS activation leads to increased angiotensin II levels, which subsequently results in efferent arteriolar vasoconstriction and aldosterone release [34]. At the same time, increased circulating vasodilators, such as atrial natriuretic peptide and nitric oxide (NO), and insulin resistance or relative insulin deficiency result in a reduction in afferent arteriolar resistance [32]. This results in increased glomerular pressure, increased glomerular hyperfiltration and subsequent glomerular sclerosis.

Elevated levels of angiotensin II are associated with increased albuminuria and nephropathy [35, 36]. Angiotensin II is also associated with increased inflammation, oxidative stress, fibrosis and endothelial dysfunction. Agents that result in RAS blockade have a long track record in reducing the doubling rate of creatinine, albuminuria, and progression to nephropathy, ESRD, and death. Their benefit is largely attributed to reduced vasoconstriction of the efferent arteriole, which consequently reduces hyperfiltration. Therefore, RAS blockade alleviates this effect and as a consequence, agents such as

ACEi, angiotensin II receptor blockers (ARB), and spironolactone have beneficial effects on DKD.

Tubular function also plays a role in glomerular haemodynamics via a tubuloglomerular feedback mechanism. Sodium and glucose reabsorption are increased during moderate hyperglycaemia (blood glucose >10 mmol/L (180 mg/dL) due to upregulation of SGLT-2 and SGLT-1 receptors in the proximal tubules. Increased glucose and sodium reabsorption in the proximal tubules leads to reduced sodium delivery to the macular densa portion of the distal tubules. As a result, afferent arteriolar tone is reduced with increased renal plasma flow and glomerular filtration [37]. SGLT-2 inhibition increases sodium delivery to the distal tubules, resulting in afferent arteriolar vasoconstriction and a subsequent reduction in renal blood flow and glomerular filtration. This is supported by observations from SGLT-2i trials, which demonstrated a small decrease in eGFR at initiation of therapy of approximately 5 mL/min per 1.73 m^2 and a favourable renal outcome [38-40].

4.2 Metabolic factors

Hyperglycaemia results in increased glycolysis, which subsequently increases the activity of the mitochondrial electron transport chain, which in turn up-regulates superoxide production. This excess superoxide results in oxidative stress and up regulates four distinct metabolic pathways: the polyol pathway, hexosamine pathway, production of AGEs, and the activation of protein kinase C (PKC) [41]. The polyol pathway is a non-glycolytic pathway, resulting in reduced activity of the antioxidant, glutathione and subsequent increased oxidative stress [41]. In addition, the end-product of the polyol pathway, fructose, has been found to be potentially nephrotoxic in animal studies [42]. The hexosamine pathway is associated with increased transcription of inflammatory cytokines including tumour necrosis

factor-α (TNF-α) and transforming growth factor-β1 (TGF-β1) [41]. Increased TGF-β1 is thought to be responsible for renal cell hypertrophy and increased mesangial matrix components, two pathologic hallmarks of DKD. AGEs, resulting from irreversible glycation of proteins, damage cells by disrupting the function of intercellular and extracellular proteins. AGEs are also involved in activation of inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α; growth factors such as vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF) and the production of reactive oxygen species [41]. VEGF is linked to abnormal intrarenal blood flow and increased capillary permeability [43]. CTGF is a profibrotic contributing to glomerular membrane thickening [44]. The activation of PKC increases prostaglandin E_2 and NO formation [41], which contribute to afferent arteriolar vasodilation. Therefore, the net effect of these pathways and subsequent activation of inflammation and increased oxidative stress is development of proteinuria, hypertension and decline in eGFR.

5. Managing chronic kidney disease in patients with diabetes

The therapeutic aim in patients with DKD is to avoid cardiovascular and renal associated mortality along with reducing the progression of CKD. Evidence supports addressing glycaemic control, the use of RAS blockade, lipid-lowering measures, blood pressure control, lifestyle modification and multiple interventions.

5.1 Glucose control

The efficacy of strict glycaemic control depends in part upon the stage of CKD and the evidence is best established in type 1 diabetes. The DCCT comprised of 1,441 participants with type 1 diabetes without CVD and with normal renal function that were randomised to intensive (HbA1c <6.05% [43 mmol/mol]) versus conventional (HbA1c 9.0% [75 mmol/mol])

glycaemic control. Only 73 individuals had microalbuminuria at the start of the study [18]. Following 6.5 years of follow-up, intensive glucose control reduced the occurrence of microalbuminuria by 39% and macroalbuminuria by 54%. However, there were approximately three times as many severe hypoglycaemic episodes in the intensive control arm. There was no reduction in cardiovascular events in the DCCT (note, that the age was 13-39 years). The same subjects were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, which observed a 42% reduction in any cardiovascular event 10 years after both groups had similar glycaemic control, implying that the cardiovascular effect of intensive glycaemic control persisted after control was loosened [45].

For type 2 diabetes, the picture is less clear. The UKPDS, which examined sulphonylurea and insulin therapy, showed no real benefit on cardiovascular outcome but did demonstrate a 24% reduction in microvascular disease including DKD. After 12 years, intensive glycaemic control resulted in a 33% reduction in the risk of developing microalbuminuria or macroalbuminuria and a significant reduction in the proportion of patients with a doubling of serum creatinine (0.9% versus 3.5%) relative to the conventional therapy group [46, 47]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) [48], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [49], and the VA Diabetes Trial (VADT) [50] studies with respect to cardiovascular effects, ranged from no benefit to increased risk with an increased total and cardiovascular mortality risk being observed in ACCORD. In ADVANCE, after a median of 5 years, intensive glucose control significantly reduced the risk of ESRD by 65%, microalbuminuria by 9% and macroalbuminuria by 30%. The progression of albuminuria was significantly reduced by 10% and its regression significantly increased by 15% [51].

Shurraw et al in a sample of 23,296 patients observed that a HbA1c > 9% was more prevalent in people with non-hemodialysis-dependent CKD and was associated with worse renal outcomes. Of interest, the excess risk of kidney failure associated with a higher HbA1c was highest among people with better kidney function. This suggests that timely glycaemic control is important [52].

5.2 Hypertension

In the UKPDS study, patients with newly diagnosed type 2 diabetes, treating to a target blood pressure of <150/85 mmHg over a median of fifteen years resulted in a 37% risk reduction of microvascular complications compared to those treated to a target of <180/105 mmHg [22]. Each 10 mmHg increase in mean systolic blood pressure was associated with a 15% increase in the risk of development of both micro- and macroalbuminuria and impaired renal function defined as eGFR <60 mL/min per 1.73 m^2 or doubling of the blood creatinine level. A baseline systolic blood pressure >140 mmHg in patients with type 2 diabetes has been associated with higher risk of ESRD and death [53, 54]. Many guidelines recommend a target of 140/90 mmHg for patients with diabetes regardless of CKD [55-57]. Other guidelines suggest a target of 130/80 mmHg in the presence of micro or macroalbuminuria [57, 58]. In summary, those patients at low risk with diabetes and normoalbuminuria could be treated to a target of 140/90 mmHg, while those at high risk or significant macroalbuminuria should have a lower target of 130/80 mmHg.

5.2.1 Choice of antihypertensive agents

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: Angiotensin-converting enzyme inhibitors (ACEi) have been widely studied in relation to DKD. Captopril was the first agent to demonstrate a reduction in the progression of

albuminuria and renal function in patients with type 1 diabetes [59-61]. Evidence for patients with type 2 diabetes in reducing new onset microalbuminuria and macroalbuminuria is provided for the combination of perindopril and indapamide from the ADVANCE trial [62]. Of interest, serum creatinine and ESRD were not affected. In addition, the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) demonstrated a delay in the onset of microalbuminuria [63].

With respect to Angiotensin II receptor blockers (ARB), in the irbesartan Diabetic Nephropathy Trial (IDNT) in patients with type 2 diabetes, irbesartan reduced the risk of ESRD or a doubling of serum creatinine by 20-23% compared to amlodipine or placebo [63]. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial of patients with type 2 diabetes and nephropathy, losartan reduced the risk of ESRD or doubling of serum creatinine by 25-28% compared to placebo [64]. Olmesartan in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial of patients with type 2 diabetes was also associated with a reduction in the progression to microalbuminuria [65].

The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial compared the ACEi enalapril with the ARB, telmisartan, in type 2 diabetes patients with early DKD. In the DETAIL trial, 250 participants with early DKD were randomly assigned to enalopril or telmisartan. This trial indicated that telmisartan was not inferior to enalopril in reducing a decline in eGFR over five years [66]. With the lack of data for ARBs in type 1 diabetes, most clinicians prefer initiating treatment with an ACEi for DKD. For the primary prevention of DKD, a meta-analysis of 11,906 participants found that ACEis reduced the risk of new onset microalbuminuria, macroalbuminuria, or both when compared to placebo (relative risk

0.71; 95% confidence interval [95% CI]: 0.56–0.89) [67]. However, similar benefits could not be demonstrated for ARBs. Therefore, there is no proven benefit in starting ARB treatment in normotensive, normoalbuminuric type 1 or type 2 diabetes. Neither ACEi nor ARB are currently recommended in normotensive, normoalbuminuric patients for the primary prevention of DKD [35].

Studies have also evaluated the combined ACEi and ARB approach to DKD. Early studies in patients with diabetes supported combination therapy for lowering albuminuria and blood pressure versus either alone [68-70], however the effects on the preservation of eGFR have not been demonstrated. In the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) there was no beneficial effect on renal, outcomes but a delayed progression to microalbuminuria and macroalbuminuria, and improved regression to microalbuminuria and normoalbuminuria was observed [71]. In the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study, the addition of lisinopril to losartan treatment failed to reduce the composite endpoint of a 50% reduction in eGFR, ESRD or death [72]. Combination treatment was also associated with an increase in acute kidney injury and hyperkalaemia and therefore, the dual ACEi and ARB treatment strategy has essentially been abandoned.

Aldosterone antagonists: In patients with diabetes, spironolactone appears to reduce proteinuria on its own or in combination with ACEi or ARB [73, 74]. The combination of aldosterone antagonists and other RAS inhibitors increases the risk of hyperkalaemia and there is lack of long-term data relating to renal function with combination blockade. Therefore the combination of aldosterone antagonists and ACEi or ARB is unclear and carries the risk of hyperkalaemia.

Calcium channel blockers: In type 2 diabetes, verapamil and diltiazem have been shown to lower proteinuria [75]. Furthermore, the addition of verapamil to lisinopril or trandolapril has been observed to be additive in reducing albuminuria and slowing the decline in eGFR [53, 75]. In the MicroAlbuminuria Reduction With VALsartan (MARVAL) study where patients with type 2 diabetes were randomised to valsartan or amlodipine, valsartan was more effective than amlodipine in reducing albuminuria, including remission to normoalbuminuria [76].

Diuretics: Thiazide diuretics when combined with an ACEi reduced albuminuria in patients with type 2 diabetes, but the combination is associated with postural hypotension [21].

5.3 Lipid-lowering agents

Studies in type 1 diabetes [77] and type 2 diabetes [5, 78] show an association between abnormalities in apolipoprotein B, HDL-cholesterol and triglycerides with the risk of DKD. There is paucity in the available literature with respect to renal outcomes. Simvastatin [79] and rosuvastatin [80] have been shown to reduce albuminuria in patients with type 2 diabetes. Furthermore, in the Heart Protection Study, simvastatin was associated with a slower decline in eGFR compared to placebo, a difference that was greater in patients with diabetes [81]. Atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS) improved the annual decline in eGFR, particularly in those with albuminuria [82].

5.4 Lifestyle and diet

Smoking cessation, weight control, and increased physical activity should be encouraged. Smoking is an independent risk factor for DKD. Smokers have a higher prevalence of

proteinuria and a higher rate of eGFR decline compared to non-smoker [83]. Obesity is a risk factor for CVD, hypertension and diabetes, but also an independent risk factor for the development of CKD and ESRD [84]. A direct causal link between obesity and ESRD exists, independent of associated co-morbidities. Glomerular hyperfiltration is thought to occur as a precursor to CKD in the diabetic population [34]. In addition, patients with diabetes and co-existing obesity have a two-fold increased risk of new onset kidney disease [85].

The beneficial role of low dietary protein intake (<0.6 g/kg/day) in DKD remains unclear. Some studies have demonstrated that a low dietary protein intake (<0.6 g/kg/day) is associated with a reduction in the rate of eGFR decline [86], while others did not support these findings [87]. On the other hand, a high protein intake (>20% of daily calories from protein or a protein intake >1.3 g/kg/day) has been associated with progression of DKD as measured by increased albuminuria, a rapid decline in eGFR and increased CVD mortality [88]. The ADA therefore recommends to limit protein intake to 0.8 g/kg/day for patients with non-dialysis-dependent CKD [89].

Dietary sodium restriction has been shown to enhance the antiproteinuric effect of ACEi and have beneficial effect on blood pressure and cardiovascular risk. A low salt diet should be considered for patients with a reduced eGFR, for whom urinary sodium excretion may be impaired. The ADA suggests that dietary sodium restriction (<2300 mg/day) may be useful but recommends that an individualised target is needed, based on co-morbidities and concurrent medication use, with the support of a renal dietician. [89].

5.5 Multifactorial risk factor reduction

The Steno-2 trial of patients with type 2 diabetes with microalbuminuria demonstrated that multifactorial risk factor reduction with reduced dietary fat, light to moderate exercise, smoking cessation, tight glycaemic control (HbA1c <6.5% [48 mmol/mol]), tight blood pressure control (130/80 mmHg), the use of ACEi, and lipid lowering medications (cholesterol <4.5 mmol/L) had a beneficial effect [90]. Patients receiving multifactorial intervention had significantly lower risk of overt nephropathy (hazard ratio, HR 0.39, 95% CI: 0.17-0.87) compared to those receiving regular management. Therefore, as for all diabetes related complications a multi risk factor reduction strategy is essential. In addition, a post hoc analyses was conducted which examined the impact of intensified, multifactorial treatment on renal outcomes in patients with type 2 diabetes and microalbuminuria enrolled in the Steno-2 Study over a total follow-up up to 21 years. Progression to macroalbuminuria was significantly reduced in the intensive therapy group (HR 0.48, 95% CI: 0.31-0.84]. The decline in GFR was significantly different at 3.1 mL/min per 1.73 m^2 in the intensive therapy group compared to 4.0 mL/min per 1.73 m^2 in the conventional therapy group. Furthermore, ESRD combined with renal death was significantly lower (HR: 0.53, 95% CI: 0.35-0.8) [91].

5.6 Metabolic acidosis

Patients with DKD are at increased risk of metabolic acidosis due to type IV renal tubular acidosis, which is complicated by hyperkalaemia [92]. This tubular transport defect can limit the ongoing use of renoprotective anti-proteinuric ACEi therapy. Treatment includes a low-potassium diet, diuretics to promote renal potassium wasting and base supplementation, traditionally with oral sodium bicarbonate tablets. Bicarbonate supplementation slows progression of CKD and improves nutritional status [93]. The use of metformin is limited with advanced CKD (eGFR <30 ml/min per 1.73 m^2) due to the risk of metformin-associated lactic acidosis. The ongoing Evaluation of Effect of TRC101 on Progression of Chronic

Kidney Disease in Subjects With Metabolic Acidosis (VALOR-CKD) (NCT03710291, https://clinicaltrials.gov/ct2/show/NCT03710291, accessed October 2019) is a phase 3b randomised, double blinded, placebo controlled trial investigating the impact of veverimer (TRC101) in delaying CKD progression in metabolic acidosis. It includes CKD of diabetes aetiology and is due to complete in 2022.

5.7 Current guidelines

Several guidelines are available relating to the management of DKD. These include the National Kidney Foundation [1], ADA [12], NICE (https://www.nice.org.uk/guidance/CG182, accessed October 2019), and the Renal Association (https://renal.org/guidelines/endorsed-guidelines, accessed October 2019), which contain the most recent updated advice relating to managing hyperglycaemia, hypertension and lipids. Furthermore, the ADA and European Association for the Study of Diabetes (EASD) Consensus Report of 2018 provide clarity in relation to glucose-lowering medication in type 2 diabetes, such that an SGLT2i such as canagliflozin or empagliflozin is recommended as second line following metformin if CKD predominates and the eGFR is in the licensed range for use [94, 95]. Clearly consideration may need to be given to local geographical practice and availability of medication and resources. These guidelines are available on-line and will not be discussed further in this review article.

6. The diabetes cardiovascular outcome trials and renoprotection

Whilst cardiovascular outcome studies have the main aim of assessing the cardiovascular safety of newer diabetes medications, great insight has been gained with respect to the effects of SGLT2i and glucagon like peptide-1 receptor agonists (GLP-1RA) on renal function.

6.1 Sodium-glucose cotransporter-2 inhibitors

With respect to SGLT2is, all appear to be associated with a small decrease in eGFR at initiation of therapy of approximately 5 mL/min per 1.73 m^2. Considerable insight and attention have focussed on data obtained from cardiovascular outcome studies focusing on SGLT2is. It should of course be noted that the participants recruited into the trials did differ as shown in table 2. As shown within the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) more than 99% of participants had established CVD. Within the Canagliflozin Cardiovascular Assessment Study (CANVAS) 66.6% had established CVD and 34.4% had multiple risk factors, where as in Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58), 40.6% had established CVD and 59.4% had multiple risk factors. CANVAS demonstrated that canagliflozin was associated with a 27% reduction in the progression of albuminuria, with a 40% reduction in the composite endpoint of a reduced eGFR, the need for renal replacement therapy, and death from any renal cause [96]. Of note there was an initial fall in mean eGFR with canagliflozin from 76 to 73 mL/min per 1.73 m^2 at three months, but eGFR remained stable through six years while gradually declining during the period of observation with placebo. In EMPA-REG, empagliflozin was associated with effects on albuminuria and eGFR [39]. An initial decline in eGFR was observed with empagliflozin, however during the course of the study, eGFR was consistently higher with empagliflozin, although this was less clear in trial participants with a baseline eGFR <60 mL/min per 1.73 m^2. Empagliflozin also reduced the development of acute renal failure. Further analysis showed empagliflozin to be associated with a reduction in albuminuria, regardless of the baseline urine albumin level [97]. With respect to dapagliflozin, DECLARE-TIMI 58 examined renal outcomes [40, 98]. In DECLARE–TIMI 58, 17,160 patients with type 2

diabetes, HbA1c 6.5-12.0 % (47.5-113.1 mmol/mol), with either established atherosclerotic CVD or multiple risk factors, and creatinine clearance of at least 60 mL/min were randomised to 10 mg dapagliflozin or placebo once daily over a median follow-up of 4.2 years. The study included a prespecified secondary cardiorenal composite outcome defined as a sustained decline of at least 40% in eGFR to less than 60 mL/min per 1.73m^2, ESRD (defined as dialysis for at least 90 days, renal transplant, or confirmed sustained eGFR <15mL/min per 1.73 m^2), or death from renal or cardiovascular causes; a prespecified renal-specific composite outcome was the same but excluding death from cardiovascular causes. The cardiorenal secondary composite outcome was significantly reduced with dapagliflozin versus placebo (HR 0.76, 95% CI: 0.67-0.87, P<0.0001); excluding death from cardiovascular causes, the HR for the renal-specific outcome was 0.53, 95% CI: 0.43-0.66, P<0.0001. There was a 46% reduction in sustained decline in eGFR and the risk of ESRD or renal death was lower in the dapagliflozin group than in the placebo group (HR 0.41, 95% CI: 0.20-0.82, P=0.012). As in CANVAS and EMPA-REG, six months after randomisation, the mean decrease in eGFR was larger in the dapagliflozin group than in the placebo group, but this equalised by two years, and at three and four years the mean decrease in eGFR was less with dapagliflozin than with placebo.

6.2 Glucagon like peptide-1 receptor agonists

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the significant 13% reduction in the primary composite outcome of cardiovascular death, myocardial infarction, and stroke was found on subgroup analysis to particularly occur among participants with stage 3 CKD, having an eGFR 30-59 mL/min per 1.73 m^2 [99]. No significant effect on eGFR was found with liraglutide, although both those receiving and not receiving the drug showed a decline in eGFR from approximately 75 to

65 mL/min per 1.73 m^2 over the two year period of observation. Liraglutide administration was associated with a significant reduction in albuminuria, with a 25% lower likelihood of developing of macroalbuminuria, with the UACR being approximately 20% lower among treated participants, regardless of the baseline level of eGFR. Similarly, in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, a 34% increase in the UACR was reported among participants receiving placebo, but the increase was 24% among those receiving lixisenatide [100]. For semaglutide, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), it was reported that persistent macroalbuminuria developed among 2.7% of those receiving semaglutide, but among 4.9% of those receiving placebo [101]. For dulaglutide, the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial demonstrated a lower incidence of new macroalbuminuria in the dulaglutide group (8.9%) compared to the placebo group (11.3%), with a HR 0.77, 95% CI: 0.68-0.87, P<0.0001 [102]. Renal Outcomes were also evaluated in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) where a 40% decrease in a composite endpoint of eGFR decline, renal replacement, renal death or new macroalbuminuria was siobserved [103].

6.3 Dipeptidyl peptidase-4 (DPP-4) inhibitors

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) Thrombolysis in Myocardial Infarction (TIMI) 53 trial, saxagliptin was associated with significantly less worsening and more improvement in microalbumin levels at one year, at two years, and by the end of treatment [104]. The reduction in microalbumin levels was similar in patients with and without renal impairment. Interestingly, there was no relationship between improvement in albuminuria and improvement in HbA1c. The other DPP4i cardiovascular outcome trials have not reported effects of these agents on renal

function or albuminuria, but studies of sitagliptin and linagliptin suggest that these agents may also reduce albuminuria [105].

7. Renal outcome trials with SGLT2 inhibitors: CREDENCE, DAPA-CKD and EMPA-KIDNEY

Whilst cardiovascular outcome trials provide exciting results related to renal outcomes, they enrolled a small proportion of patients with CKD at baseline and furthermore, they were not primarily designed to assess renal end points, but rather included secondary renal outcome measures. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was designed to assess the effects of canagliflozin primarily on renal outcomes in participants with type 2 diabetes and albuminuria related CKD [38]. This double-blind, randomised trial compared canagliflozin versus placebo in people with type 2 diabetes with a baseline eGFR of 30-90 mL/min per 1.73 m^2 and a UACR ratio >300-5000 mg/g. Participants received a stable dose of either an ACEi or ARB. The primary outcome for the trial was a composite of ESRD (dialysis, kidney transplantation, or a sustained eGFR <15 mL/min per 1.73 m^2), doubling of serum creatinine, or death from kidney or cardiovascular causes. The trial of 4,401 participants and 50% with a history of CVD, was stopped as during a median of 2.62 years, as benefit was observed with canagliflozin. The primary outcome was reduced by 30% in those treated with canagliflozin (HR 0.70, 95% CI: 0.59-0.82, P<0.001). In addition, the kidney-specific composite outcome (ESRD, doubling of creatinine, or kidney-related death) was positive (HR 0.66, 95% CI: 0.53-0.81, P<0.001). Canagliflozin treatment was also associated with a lower risk for several cardiovascular-related outcomes.

Whilst CREDENCE has a focus on patients with type 2 diabetes, two other clinical trials are underway examining the effects of SGLT2is in patients with CKD, not exclusively with diabetes. These trials are summarised in table 3. A study to evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) will end in November 2020 (https://clinicaltrials.gov/ct2/show/NCT03036150, accessed October 2019). This study is currently recruiting 4,000 participants randomised to dapagliflozin (5mg or 10 mg) or placebo in participants with an eGFR of 25-75 mL/min per 1.73 m^2 and albuminuria (UACR 200-5000 mg/g) receiving a stable dose of ACEi or ARB. The study is recruiting both patients with type 2 diabetes and those without (type 1 diabetes is an exclusion). The primary outcome (up to four years) is the time to the first occurrence of any of the components of the composite of a ≥50% sustained decline in eGFR or reaching ESRD or CV death or renal death. In addition a Multicentre International Randomized Parallel Group Double-blind Placebo-controlled Clinical Trial of EMPAgliflozin Once Daily to Assess Cardio-renal Outcomes in Patients With Chronic KIDNEY Disease (EMPA-KIDNEY) will come to completion in June 2022 (https://clinicaltrials.gov/ct2/show/NCT03594110, accessed October 2019). This study is recruiting 5,000 participants randomised to empagliflozin or placebo. The sample consists of participants with evidence of CKD at risk of kidney disease progression defined by at least 3 months before and at the time of screening visit by an eGFR 20-45 mL/min per 1.73m^2 or an eGFR ≥45 to <90 mL/min per 1.73m^2 with a UACR ≥200 mg/g (or protein: creatinine ratio ≥300 mg/g). In addition, participants are already receiving an ACEi or ARB. One exclusion includes patients with type 2 diabetes and prior atherosclerotic CVD with an eGFR >60 mL/min per 1.73m^2. The primary composite outcome is time to first occurrence of (i) kidney disease progression (defined as ESRD, a sustained decline in eGFR to <10 mL/min per 1.73m^2, renal death, or

a sustained decline of ≥40% in eGFR from randomisation) or (ii) Cardiovascular death (with a median follow-up approximately 3.1 years).

The results of DAPA-CKD and EMPA-KIDNEY will clearly provide considerable insight into the effects of SGLT2is in relation to CKD. The data is likely to support the results of CREDENCE. These studies will provide insight into whether the SGLT2is have a class effect in addition to whether the effects are observed in patients with and without type 2 diabetes. At present, the current SGLT2i labelling recommends dose reductions on the basis of eGFR because of diminished glucose-lowering effect with reduced kidney function, with use not recommended for empagliflozin, canagliflozin, and dapagliflozin in patients with an eGFR<45 mL/min per 1.73 m^2 (and not to be initiated with an eGFR<60 mL/min per 1.73 m^2). CREDENCE demonstrates that canagliflozin use in patients with an eGFR below this threshold is safe and provides kidney benefit. This finding suggests that SGLT2is may offer an alternative for patients unable to tolerate ACEi or ARB therapy because of hyperkalaemia, although further evidence is needed to demonstrate improvement in kidney outcomes in the absence of background ACEi or ARB use [106].

8. Newer therapies in the future

As discussed already, steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone appear to have beneficial effects in the setting of DKD. In addition these agents have been used in the management of hypertension, primary aldosteronism and heart failure. More recently, novel nonsteroidal MRAs with improved safety profiles have been developed, including BR-4628 (Bayer), finerenone (Bayer, Leverkusen, Germany), PF-03882845 (Pfizer, Groton, CT), SM-368229 (Dainippon Sumitomo Pharma, Osaka, Japan), and AZD9977 (AstraZeneca, Cambridge, UK), among

others [107-110]. At present, none of the agents are currently marketed. Animal based research has shown that these agents may have beneficial effects in alleviating the effects of acute kidney injury in the setting of ischaemia and hypoperfusion. In a phase 2a clinical trial comparing the efficacy and safety of finerenone with spironolactone in patients with CKD and heart failure (MinerAlocorticoid Receptor Antagonist Tolerability Study: ARTS), participants receiving finerenone (2.5-10 mg once daily) had a lower incidence of hyperkalaemia and reduced albuminuria from baseline compared with those receiving spironolactone [111]. In the ARTS-Diabetic Nephropathy (ARTS-DN) trial, the addition of 7.5-20 mg of finerenone to RAS blocker therapy reduced the UACR in patients with DKD [112]. This study observed that the placebo-corrected mean ratio of the UACR at day 90 relative to baseline, was reduced in the finerenone 7.5mg, 10mg, 15mg, and 20mg per day groups (for 7.5 mg, 0.79 [90% CI: 0.68-0.91, P=0.004] for 10 mg, 0.76 [90% CI: 0.65-0.88, P=0 .001]; for 15 mg, 0.67 [90% CI: 0.58-0.77, P<0.001]; for 20 mg, 0.62 [90% CI: 0.54-0.72, P<0.001]). Of interest, many participants were receiving an ACEi or an ARB. This effect was replicated in a Japanese population [113]. Therefore, whilst there is encouraging clinical evidence for non-steroidal MRAs in reducing proteinuria in the setting of CKD, further studies to investigate the effectiveness are required to ascertain benefit which is over and beyond the existing therapies described in this review.

9. Conclusions

We provide an empirical and structured review examining the available literature relating to diabetes related CKD, incorporating the current information provided from cardiovascular outcome and renal outcomes from trials relating to diabetes and cardiorenal data. The mainstay of therapy consists of managing hyperglycaemia, blood pressure control, lipid management, and lifestyle modification along with maximising cardiovascular risk factors.

Over recent years there has been controversy in relating to screening for microalbuminuria in patients with type 2 diabetes. With the development in agents that alter the progression of albuminuria there is clearly a justified rationale to screen for this to allow those patients with identified early CKD (with microalbuminuria and a normal eGFR) to be initiated on disease modifying therapies. However, a proportion of patients will develop ESRD do not have microalbuminuria or have very microabuminuria and the effect various mecication that alter the risk of DKD may be independent of microalbuminuria. The exciting data related to SGLT2is has changed the clinical mind-set relating to the potential of reducing the progression of DKD and the subsequent diabetes related renal complications and the associated cardiovascular mortality. These studies have gained the interest of renal and cardiology specialists and provides the opportunity for close collaboration. This is evident by the fact that the renal association along with cardiac societies such as the European Cardiac Society and the American College of Cardiologists and the American Heart Association have gained an interest in the role that these agents play in reducing cardiovascular risk. There has also been early adoption of the use of SGLT2is on these guidelines. Information from EMPA-KIDNEY and DAPA-RENAL will hopefully support the data provided by CREDENCE and we might expect in the near future that SGLT2is would be part of standard therapy in the prevention of DKD, perhaps focussing on patients with all stages of proteinuria and reduced eGFR. There are also promising developments in relation to non-steroidal MRAs but more clinical trials are required within this area to understand the efficacy above and beyond the currently available agents.

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Conflicts of interest

J.W.S reports obtaining personal fees in relation to advisory boards and lectures for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, AstraZeneca, MSD, NovoNordisk, NAPP. These payments are not related to this review article. K.E.B. has no conflicts of interest to declare. T.M. reports receiving educational travel grant from NAPP and Boehringer Ingelheim and honoraria from AstraZeneca. These payments are not related to this review article.

Author contributions

All authors contributed to all aspects of this manuscript and approved the final manuscript.

Table legends

Table 1: Classification and prognostic risk of chronic kidney disease (CKD) according to estimated Glomerular Filtration Rate and presence of albuminuria (mg/mmol) adapted from KDIGO clinical guidelines [114]

At any stage of CKD, the degree of albuminuria, observed history of eGFR loss, and cause of kidney damage (including possible causes other than diabetes) may also be used to characterise CKD, gauge prognosis, and guide treatment decisions. Green = low risk (if no other markers of kidney disease, no CKD). Yellow = moderately increased risk. Orange = high risk. Red = very high risk.

Table 2: Baseline characteristics of participants recruited into EMPA-REG, CANVAS and DECLARE-TIMI 58

Table 3: SGLT-2 inhibitor clinical trials in CKD populations

† Doubling of serum creatinine, renal death.

* Includes cardiovascular death, non-fatal MI, non-fatal stroke, hospitalised congestive heart failure and hospitalised unstable angina.

Figure legends

Figure 1: Electron micropscopic appearance of diabetes related kidney disase

1A: Thickened glomerular capillary basement membranes.

2B: Mesangial expansion by extracellular amorphous material.

Figure 2: Diabetes related kidney disease

2A: Silver stain showing marked nodular expansion of the mesangial matrix (Kimmelstiel-Wilson) nodule, on light microscopy.

2B: Glomerulus with features of diffuse mesangiosclerosis on light microscopy.

Table 1

Stage	eGFR (mL/mil/1.73m^2)	Description	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
1	>90	Normal or high	Low	Moderate	High risk
2	60-89	Mild reduction	Low	Moderate	High risk
3A	45-59	Mild-moderate reduction	Moderate	High risk	Very high risk
3B	30-44	Moderate-severe reduction	High risk	Very high risk	Very high risk
4	15-29	Severe reduction	Very high risk	Very high risk	Very high risk
5	<15	Kidney failure	Very high risk	Very high risk	Very high risk

Table 2

Baseline characteristics	EMPA-REG	CANVAS	DELCARE
Mean age (years)	63.1	63.3	63.9
Gender (% male)	71.5	64.2	62.6
HBA1c (%)	8.1	8.2	8.3
Duration of diabetes (years)	>10	13.5	11.9
Insulin use (%)	48.2	50.2	40.5
Mean eGFR (mL/min/1.73m^2)	74.1	76.5	85.2
Micro/macroalbuminuria (%)	40.6	30.2	30.3
Myocardial infarction (%)	46.6	29.1	20.9
Ischaemic stroke (%)	23.3	12.7	6.5
Heart failure (%)	10.1	14.4	10.0

Table 3

	CREDENCE	EMPA-KIDNEY	DAPA-CKD
Composite Primary outcome	• ESRD (Dialysis, renal transplant). • Sustained eGFR <15 mL/min per 1.73 m^2. • Doubling of serum creatinine. • Death from kidney or cardiovascular causes.	• ESRD (Dialysis, kidney transplant). • Sustained eGFR <10 mL/min/1.73m^2. • Renal death. • Sustained decline of ≥40% in eGFR.	• ESRD (Dialysis, renal transplant, sustained eGFR <15 mL/min/1.73m^2), • Sustained ≥50% decline in eGFR, or death from kidney or cardiovascular causes.
Secondary outcome measures	• Time to the first occurrence of an event in the composite endpoint of CV death and hospitalised congestive heart failure. • Time to the first occurrence of an event in the composite endpoint of CV death, non-fatal MI, and non-fatal Stroke. • Time to the first occurrence of hospitalised congestive heart failure. • Time to the first occurrence of an event in the renal composite endpoint†.	• Time to first hospitalisation for heart failure or cardiovascular death. • Occurrences of all-cause hospitalisation (first and recurrent). • Time to death from any cause. • Time to first occurrence of kidney disease progression. • Time to cardiovascular death. • Time to cardiovascular death or ESRD.	• Time to the first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death. • Time to the first occurrence of either of the components of the composite: CV death or hospitalisation for heart failure. • Time to death from any cause.

	• Time to cardiovascular death • Time to all-cause death. • Time to the first occurrence of an event in the cardiovascular composite endpoint*.		
Number of participants	4401	5000	4000
Inclusion criteria	• Age ≥30 years. • eGFR 20–45 or eGFR 45–90 mL/min/1.73 m^2 with UACR ≥200 mg/g. • Type 2 diabetes (HbA1c 6.5–12%). • eGFR 30–90 mL/min/1.73 m^2. • Stable maximally tolerated RAS blockade • UACR 300–5000 mg/g.	• Age ≥18 years. • eGFR 20–45 or eGFR 45–90 mL/min/1.73 m^2 with UACR ≥200 mg/g. • Clinically appropriate doses of ACE inhibitor or ARB, unless not tolerated.	• Age ≥18 years. • eGFR 25–75 mL/min/1.73 m^2. • Stable maximally tolerated ACE inhibitor or ARB if not contraindicated • UACR 200–5000 mg/g.

References

1. National Kidney F. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60:850-86.
2. Alicic RZ, Rooney MT and Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical journal of the American Society of Nephrology : CJASN. 2017;12:2032-2045.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128.
4. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378:31-40.
5. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case-control study in 13 countries. Circulation. 2014;129:999-1008.
6. Standards of Medical Care in Diabetes-2016: Summary of Revisions. Diabetes care. 2016;39 Suppl 1:S4-5.
7. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;64:510-33.
8. Vassalotti JA, Piraino B and Szczech LA. A decade after the KDOQI CKD guidelines: impact on the National Kidney Foundation. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60:689-91.
9. Nazar CM. Diabetic nephropathy; principles of diagnosis and treatment of diabetic kidney disease. Journal of nephropharmacology. 2014;3:15-20.
10. Bermejo S, Pascual J and Soler MJ. The current role of renal biopsy in diabetic patients. Minerva medica. 2018;109:116-125.
11. Gonzalez Suarez ML, Thomas DB, Barisoni L and Fornoni A. Diabetic nephropathy: Is it time yet for routine kidney biopsy? World journal of diabetes. 2013;4:245-55.
12. American Diabetes A. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2019. Diabetes care. 2019;42:S124-S138.
13. Delanaye P, Glassock RJ, Pottel H and Rule AD. An Age-Calibrated Definition of Chronic Kidney Disease: Rationale and Benefits. The Clinical biochemist Reviews. 2016;37:17-26.
14. Bonventre JV. Can we target tubular damage to prevent renal function decline in diabetes? Seminars in nephrology. 2012;32:452-62.
15. Yamanouchi M, Skupien J, Niewczas MA, et al. Improved clinical trial enrollment criterion to identify patients with diabetes at risk of end-stage renal disease. Kidney international. 2017;92:258-266.
16. Haneda M, Utsunomiya K, Koya D, et al. A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. Journal of diabetes investigation. 2015;6:242-6.
17. Caramori ML, Fioretto P and Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? Diabetes. 2000;49:1399-408.

18. Parving HH, Oxenboll B, Svendsen PA, Christiansen JS and Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. Acta endocrinologica. 1982;100:550-5.
19. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U and Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982;1:1430-2.
20. de Boer IH, Afkarian M, Rue TC, et al. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. Journal of the American Society of Nephrology : JASN. 2014;25:2342-50.
21. Hovind P, Tarnow L, Rossing P, Carstensen B and Parving HH. Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. Kidney international. 2004;66:1180-6.
22. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR and Group US. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes. 2006;55:1832-9.
23. Gaede P, Tarnow L, Vedel P, Parving HH and Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2004;19:2784-8.
24. Pavkov ME, Knowler WC, Bennett PH, Looker HC, Krakoff J and Nelson RG. Increasing incidence of proteinuria and declining incidence of end-stage renal disease in diabetic Pima Indians. Kidney international. 2006;70:1840-6.
25. Thomas MC, Cooper ME, Rossing K and Parving HH. Anaemia in diabetes: Is there a rationale to TREAT? Diabetologia. 2006;49:1151-7.
26. Jiang F, Sun ZZ, Tang YT, Xu C and Jiao XY. Hepcidin expression and iron parameters change in Type 2 diabetic patients. Diabetes research and clinical practice. 2011;93:43-8.
27. Martinelli N, Traglia M, Campostrini N, et al. Increased serum hepcidin levels in subjects with the metabolic syndrome: a population study. PloS one. 2012;7:e48250.
28. Moseley KF. Type 2 diabetes and bone fractures. Current opinion in endocrinology, diabetes, and obesity. 2012;19:128-35.
29. Gan T, Liu X and Xu G. Glycated Albumin Versus HbA1c in the Evaluation of Glycemic Control in Patients With Diabetes and CKD. Kidney international reports. 2018;3:542-554.
30. Vos FE, Schollum JB and Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. NDT plus. 2011;4:368-75.
31. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney international. 2003;63:225-32.
32. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017;28:1023-1039.
33. Cherney DZ, Sochett EB, Dekker MG and Perkins BA. Ability of cystatin C to detect acute changes in glomerular filtration rate provoked by hyperglycaemia in uncomplicated Type 1 diabetes. Diabet Med. 2010;27:1358-65.
34. Brenner BM, Lawler EV and Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int. 1996;49:1774-7.
35. Lim A. Diabetic nephropathy - complications and treatment. International journal of nephrology and renovascular disease. 2014;7:361-81.

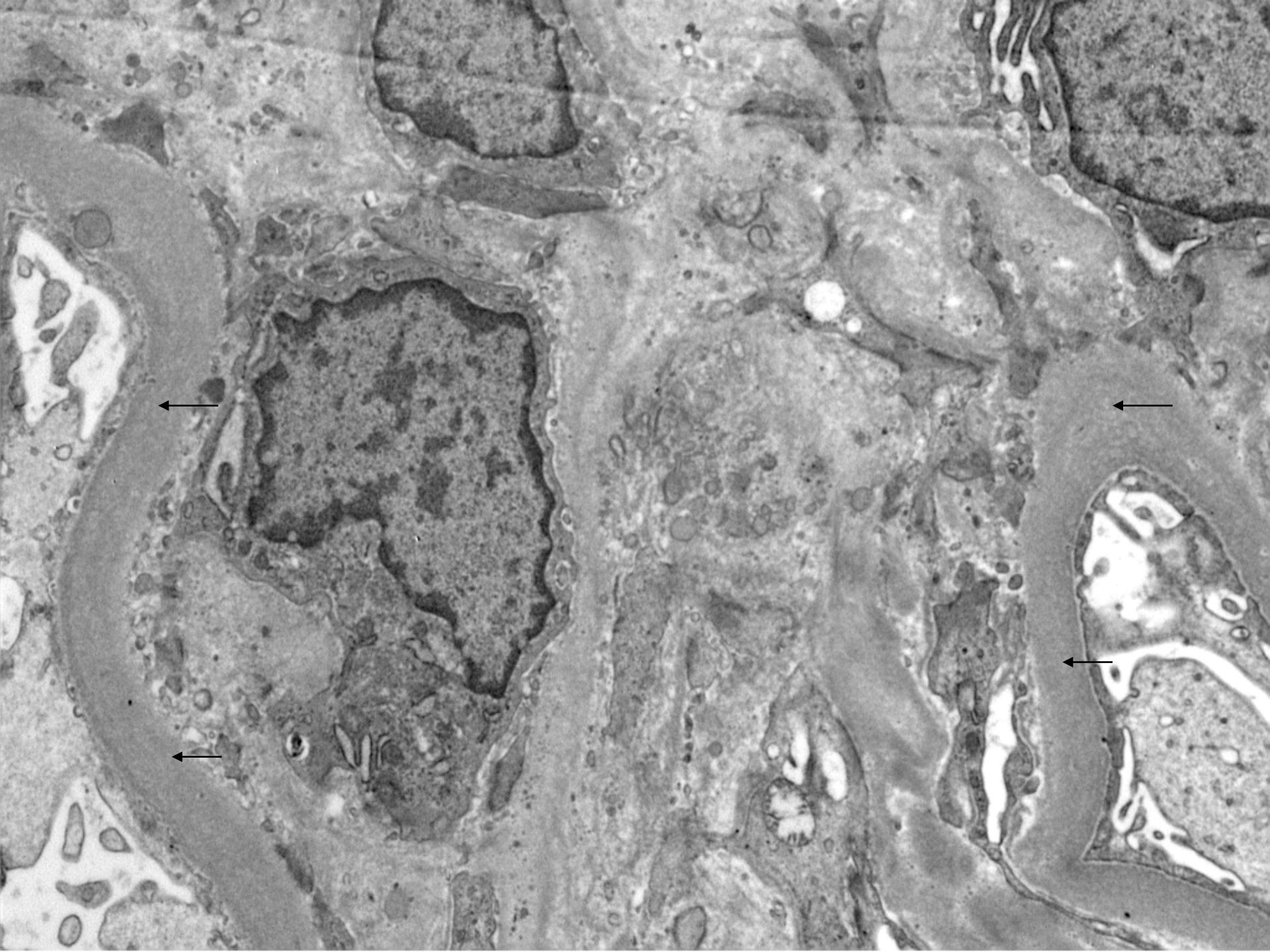
36. Rudberg S, Rasmussen LM, Bangstad HJ and Osterby R. Influence of insertion/deletion polymorphism in the ACE-I gene on the progression of diabetic glomerulopathy in type 1 diabetic patients with microalbuminuria. Diabetes care. 2000;23:544-8.
37. Vallon V and Komers R. Pathophysiology of the diabetic kidney. Compr Physiol. 2011;1:1175-232.
38. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine. 2019;380:2295-2306.
39. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England journal of medicine. 2016;375:323-34.
40. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. The lancet Diabetes & endocrinology. 2019;7:606-617.
41. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813-20.
42. Beckerman P and Susztak K. Sweet debate: fructose versus glucose in diabetic kidney disease. J Am Soc Nephrol. 2014;25:2386-8.
43. Tufro A and Veron D. VEGF and podocytes in diabetic nephropathy. Semin Nephrol. 2012;32:385-93.
44. Mason RM. Connective tissue growth factor(CCN2), a pathogenic factor in diabetic nephropathy. What does it do? How does it do it? J Cell Commun Signal. 2009;3:95-104.
45. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. The New England journal of medicine. 2005;353:2643-53.
46. Bilous R. Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? Diabetic medicine : a journal of the British Diabetic Association. 2008;25 Suppl 2:25-9.
47. Holman RR, Paul SK, Bethel MA, Matthews DR and Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. The New England journal of medicine. 2008;359:1577-89.
48. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. The New England journal of medicine. 2008;358:2545-59.
49. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England journal of medicine. 2008;358:2560-72.
50. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. The New England journal of medicine. 2009;360:129-39.
51. Perkovic V, Heerspink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney international. 2013;83:517-23.
52. Shurraw S, Hemmelgarn B, Lin M, et al. Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Archives of internal medicine. 2011;171:1920-7.
53. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Archives of internal medicine. 2003;163:1555-65.
54. Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. Journal of the American Society of Nephrology : JASN. 2005;16:3027-37.

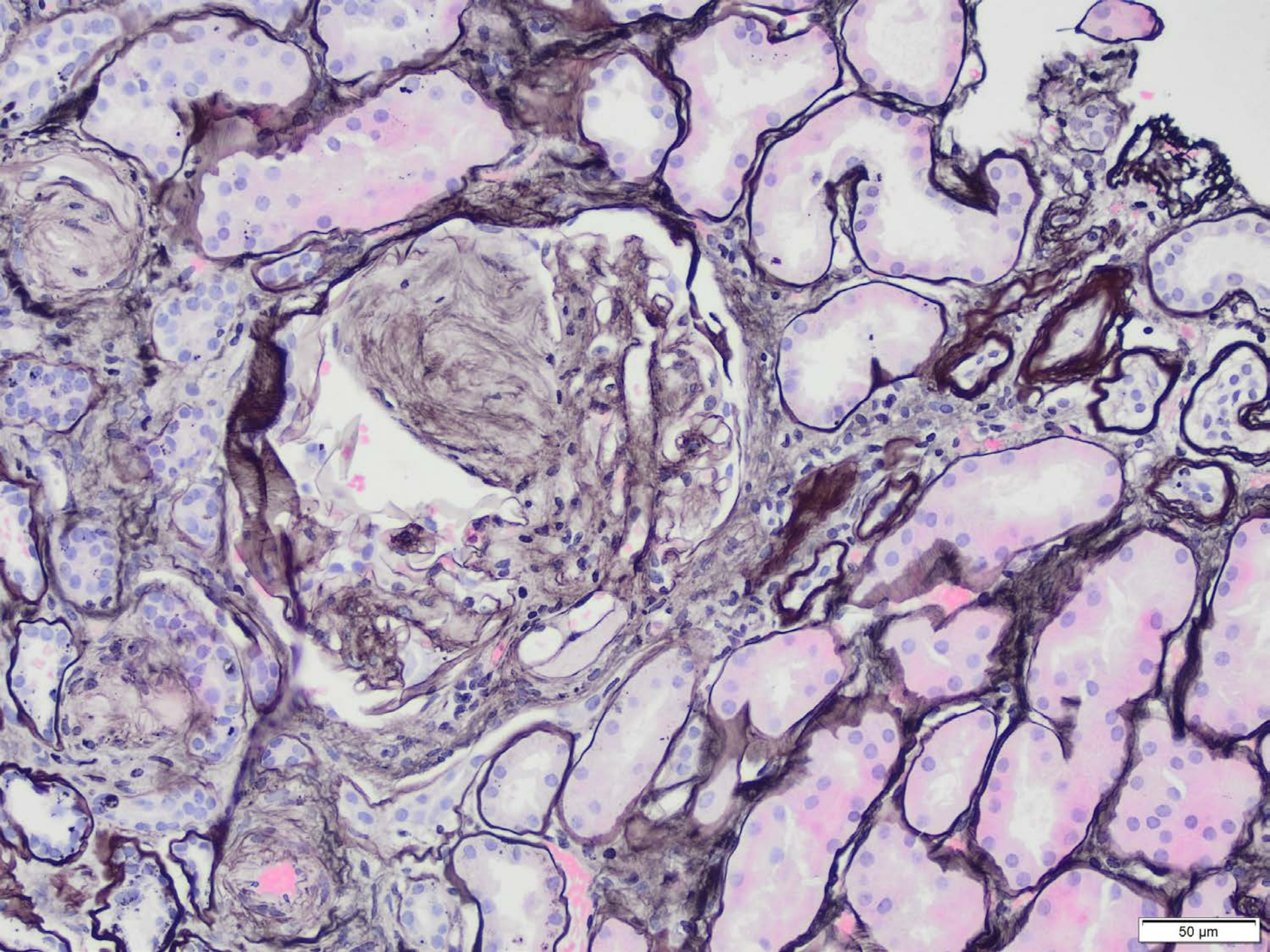
55. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. 2014;311:507-20.
56. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of hypertension. 2013;31:1281-357.
57. Pilmore H, Dogra G, Roberts M, et al. Cardiovascular disease in patients with chronic kidney disease. Nephrology. 2014;19:3-10.
58. Ruzicka M, Quinn RR, McFarlane P, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for the management of blood pressure in CKD. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63:869-87.
59. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. The Microalbuminuria Captopril Study Group. Diabetologia. 1996;39:587-93.
60. Lewis EJ, Hunsicker LG, Bain RP and Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. The New England journal of medicine. 1993;329:1456-62.
61. Viberti G, Mogensen CE, Groop LC and Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. Jama. 1994;271:275-9.
62. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia. 2009;52:2328-2336.
63. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. The New England journal of medicine. 2004;351:1941-51.
64. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. The New England journal of medicine. 2001;345:861-9.
65. Haller H, Ito S, Izzo JL, Jr., et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. The New England journal of medicine. 2011;364:907-17.
66. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. The New England journal of medicine. 2004;351:1952-61.
67. Lv J, Perkovic V, Foote CV, Craig ME, Craig JC and Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. The Cochrane database of systematic reviews. 2012;12:CD004136.
68. Jacobsen P, Andersen S, Jensen BR and Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. Journal of the American Society of Nephrology : JASN. 2003;14:992-9.
69. Jacobsen P, Andersen S, Rossing K, Jensen BR and Parving HH. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. Kidney international. 2003;63:1874-80.
70. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. Bmj. 2000;321:1440-4.

71. Heerspink HJ, Ninomiya T, Perkovic V, et al. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. European heart journal. 2010;31:2888-96.
72. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. The New England journal of medicine. 2013;369:1892-903.
73. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F and Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. Diabetes care. 2005;28:2106-12.
74. Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone in diabetic nephropathy. Kidney international. 2005;68:2829-36.
75. Bakris GL, Copley JB, Vicknair N, Sadler R and Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney international. 1996;50:1641-50.
76. Viberti G, Wheeldon NM and MicroAlbuminuria Reduction With VSI. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002;106:672-8.
77. Krolewski AS, Warram JH and Christlieb AR. Hypercholesterolemia--a determinant of renal function loss and deaths in IDDM patients with nephropathy. Kidney international Supplement. 1994;45:S125-31.
78. Bruno G, Merletti F, Biggeri A, et al. Progression to overt nephropathy in type 2 diabetes: the Casale Monferrato Study. Diabetes care. 2003;26:2150-5.
79. Tonolo G, Velussi M, Brocco E, et al. Simvastatin maintains steady patterns of GFR and improves AER and expression of slit diaphragm proteins in type II diabetes. Kidney international. 2006;70:177-86.
80. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clinical journal of the American Society of Nephrology : CJASN. 2006;1:940-51.
81. Collins R, Armitage J, Parish S, Sleigh P, Peto R and Heart Protection Study Collaborative G. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361:2005-16.
82. Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2009;54:810-9.
83. Sawicki PT, Didjurgeit U, Mühlhauser I, Bender R, Heinemann L and Berger M. Smoking Is Associated With Progression of Diabetic Nephropathy. Diabetes Care. 1994;17:126-131.
84. Hsu CY, McCulloch CE, Iribarren C, Darbinian J and Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144:21-8.
85. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK and Nyren O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006;17:1695-702.
86. Zeller K, Whittaker E, Sullivan L, Raskin P and Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med. 1991;324:78-84.
87. Hansen HP, Tauber-Lassen E, Jensen BR and Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. Kidney Int. 2002;62:220-8.

88. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014;37:2864-83.
89. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42:S124-S138.
90. Pedersen O and Gaede P. Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study. Metabolism: clinical and experimental. 2003;52:19-23.
91. Oellgaard J, Gaede P, Rossing P, Persson F, Parving HH and Pedersen O. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney international. 2017;91:982-988.
92. Umanath K and Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2018;71:884-895.
93. de Brito-Ashurst I, Varagunam M, Raftery MJ and Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. Journal of the American Society of Nephrology : JASN. 2009;20:2075-84.
94. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care. 2018;41:2669-2701.
95. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61:2461-2498.
96. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017;377:644-657.
97. Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. The lancet Diabetes & endocrinology. 2017;5:610-621.
98. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2019;380:347-357.
99. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. The New England journal of medicine. 2017;377:839-848.
100. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. The lancet Diabetes & endocrinology. 2018;6:859-869.
101. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine. 2016;375:1834-1844.
102. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet. 2019;394:131-138.
103. Bethel MA, Mentz RJ, Merrill P, et al. Microvascular and Cardiovascular Outcomes According to Renal Function in Patients Treated With Once-Weekly Exenatide: Insights From the EXSCEL Trial. Diabetes care. 2019.
104. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. The New England journal of medicine. 2013;369:1317-26.

105. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. Jama. 2019;321:69-79.
106. Neumiller JJ and Kalyani RR. How Does CREDENCE Inform Best Use of SGLT2 Inhibitors in CKD? Clinical journal of the American Society of Nephrology : CJASN. 2019.
107. Kolkhof P, Nowack C and Eitner F. Nonsteroidal antagonists of the mineralocorticoid receptor. Current opinion in nephrology and hypertension. 2015;24:417-24.
108. Kolkhof P and Barfacker L. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor antagonists: 60 years of research and development. The Journal of endocrinology. 2017;234:T125-T140.
109. Jaisser F and Farman N. Emerging Roles of the Mineralocorticoid Receptor in Pathology: Toward New Paradigms in Clinical Pharmacology. Pharmacological reviews. 2016;68:49-75.
110. Barrera-Chimal J, Girerd S and Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney international. 2019;96:302-319.
111. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. European heart journal. 2013;34:2453-63.
112. Bakris GL, Agarwal R, Chan JC, et al. Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy: A Randomized Clinical Trial. Jama. 2015;314:884-94.
113. Katayama S, Yamada D, Nakayama M, et al. A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. Journal of diabetes and its complications. 2017;31:758-765.
114. Group KdIGOKCW. KDIGO 2012 clinical practice guidline for the evaluation and management of chronic kidney disease. Kindey International Supplements. 2013;3:1-150.

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