# Diabetic Chronic Kidney Disease in Type 2 Diabetes Mellitus (Albuminuric/ Non-albuminuric)

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## 16.1 Overview of Clinical Epidemiology

The global diabetes prevalence has reached epidemic proportions and is projected to rise from 9.3% (463 million people) in 2019 to 10.9% (700 million people) by the year 2045 [1]. Approximately 40% of people with diabetes will eventually develop chronic kidney disease (CKD) over lifetime. Type 2 diabetes mellitus (T2DM) is the leading cause of end-stage kidney disease (ESKD) in the USA [2] and worldwide [1]. Since 33% of ESKD patients in the USA have received no prior nephrology care [3], and because renal biopsies in diabetics with ESKD are infrequently performed, causation for T2DM is difficult to assess which makes difficult the true prevalence and incidence of ESKD by T2DM. Diabetic kidney disease (DKD) is associated with increased risks for all-cause and cardiovascular (CV) mortality, and it is well known that most DKD patients die before development of ESKD requiring dialysis. The annual incidence rates of ESKD attributed to DKD are gradually increasing worldwide and vary from 10 to 67 per million patients [2].

DKD is a heterogenous disease. The Developing Education on Microalbuminuria for Awareness of reNal and cardiovascular risk in Diabetes (DEMAND) study assessed the prevalence of DKD in 32,308 T2DM patients from 33 countries without known kidney disease and found that the prevalence of albuminuria was 39% and that of reduced glomerular filtration rate (GFR) 22% [4]. This study reported a wide variation of albuminuria prevalence across different ethnic groups, with

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Hispanic and Asian patients presenting a higher prevalence than Caucasians. A cross-sectional study of a representative sample of Chinese adults found a 5.5-fold higher prevalence of albuminuria (9.4%) than of impaired kidney function (1.7%) [5]. Over the past two decades the proportion of people with T2DM has increased by 4% in the USA, while the prevalence of DKD has reached a plateau of approximately 26–29% [6]. During this period the proportion of patients with albuminuria declined by 5%, whereas the prevalence of patients with decreased eGFR increased by 5% [6]. However, testing for albuminuria in high-risk populations remains low; in 2017, only 43% of patients with T2DM and hypertension in the USA were tested for albuminuria [2] (Box 16.1). The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) study enrolled patients with preserved GFR with and without albuminuria that were followed for a median of 4.8 years, with outcome the development of ESKD requiring dialysis. During the follow-up period, the crude incidence for developing kidney failure among T2DM patients was 11.5 times higher in those with albuminuria, compared to those without albuminuria at baseline. Moreover, among non-albuminuric participants, compared to nondiabetics, T2DM patients exhibited eight times higher risk for developing ESKD [7]. These findings changed the perspective that diabetic nephropathy is a process where albuminuria is an obligatory step preceding the eGFR decline. Microalbuminuria—urinary albumin to creatinine ratio (ACR) of 30–300 mg/g KDIGO stage A2—was long regarded to reflect an initial and potentially reversible stage of DKD. However, and it is now clear that the decline in eGFR might occur independently of albuminuria, and non-albuminuric nephropathy is considered as the main clinical phenotype underlying the global ESKD burden by DKD [8]. The Chronic Renal Insufficiency Cohort (CRIC) study showed that 28% of diabetic patients with CKD patients do not present albuminuria. Compared to albuminuric diabetics, these patients have a significant reduced risk for CKD progression and ESKD [9]. Similarly in the United Kingdom Prospective Diabetes Study (UKPDS), 28% developed eGFR decline, 38% albuminuria, and 14% both conditions over a 15-year follow-up [10]. Sixty-four percent of the diabetic patients who displayed albuminuria did not develop renal impairment, and 51% of patients that developed renal impairment over time remained normoalbuminuric. A high prevalence of non-albuminuric DKD was also observed in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study [11] and in the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study [12] as well as in the National Evaluation of the Frequency of Renal Impairment cO-existing with Noninsulin-dependent diabetes mellitus (NEFRON) study [13].

In type 1 diabetes (T1DM), the absence of albuminuria is more common than in T2DM (about 50%) and carries a lower risk for CKD progression, but still 10% of non-albuminuric diabetics might present a more than 30% loss of eGFR after 4 years of follow-up [14]. In disagreement with these findings, a cohort study in 600 T2DM patients with hypertension and albuminuria below 200 μg/min reported similar trends of eGFR decline among albuminuric and non-albuminuric patients, over

a median follow-up period of 4 years [15]. A longitudinal cohort study in 1984 T2DM patients showed that non-albuminuric T2DM patients might also manifest pathological eGFR loss and even progression to ESKD. In this study the authors reported that the presence and degree of albuminuria affects the eGFR loss rate, with macroalbuminuric patients displaying the steepest eGFR decline, during the follow-up. However, the normoalbuminuric group still experienced rates of renal function loss above the anticipated age-related eGFR decline, and about 20% of the patients who developed ESKD did not manifest transition to macroalbuminuria [16]. Data from the large Joslin Kidney studies also suggest that a 20% of T2DM normoalbuminuric patients might manifest an early, progressive loss of renal function [17]. Therefore, it is important to screen for both albuminuria and eGFR trajectories in T2DM patients.

It was hypothesized that the high prevalence of non-albuminuric DKD might reflect the changes in therapeutic agents and treatment and the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers. However, data from the CRIC study and two small studies in T2DM patients [18, 19] suggest that the shift of the DKD clinical course to non-albuminuric pattern cannot be attributed to treatment with these agents. In the study by Vistisen et al., it was shown that in T2DM patients developing CKD3 stage, the annual loss rate of eGFR across categories of albuminuria (normo-, micro-, and macroalbuminuria) was 1.9, 2.1, and 3.0 ml/min, even after adjustment for treatment with renin-angiotensin system (RAS) inhibitors [16]. In this cohort of normoalbuminuric T2DM patients, the vast majority (90%) manifested the classical initial increase in renal function, followed by a progressive linear decrease in eGFR, whereas the rest (10%) presented an accelerated eGFR decline, followed by a small increase. This progression pattern was associated with significant less treatment with RAS inhibitors and other antihypertensive agents.

**Box 16.1**

- T2DM is the leading cause of ESKD worldwide.
- The annual incidence rates of ESKD attributed to DKD are gradually increasing worldwide and vary from 10 to 67 per million patients.
- Among T2DM patients, the prevalence of albuminuria is higher than the prevalence of reduced eGFR.
- In the USA, during the past 20 years, the prevalence of DKD has reached a plateau of approximately 26–29%.
- During this period the proportion of patients with albuminuria declined by 5%, whereas the prevalence of patients with decreased eGFR increased by 5%.
- Non-albuminuric nephropathy is considered as the main clinical phenotype underlying the global ESKD burden by DKD.

## 16.2 Pathophysiology, Risk Factors, and Novel Biomarkers

Risk factors for DKD and DKD progression do not coincide in albuminuric and non-albuminuric patients**.** First and foremost, albuminuria per se induces kidney damage [20], and this phenomenon in large part accounts for the much slower progression toward kidney failure in non-albuminuric patients as compared to albuminuric ones. In albuminuric T2DM patients, the prevalence of diabetic retinopathy increases progressively across CKD stages, while in non-albuminuric patients, the prevalence of low ankle-brachial index (an indicator of macrovascular disease) goes along with the eGFR decline [21]. These observations suggest that the main mechanism that drives progression in non-albuminuric DKD individuals might be macroangiopathy, as opposed to microangiopathy in albuminuric individuals. Repeated episodes of acute kidney injury of various severities have also been suspected as responsible for the evolution of non-albuminuric DKD toward renal failure [22]. In line with this hypothesis, a nonlinear eGFR decline pattern is more frequent among DKD patients than in nondiabetic CKD patients [23]. Urinary concentration tumor necrosis factor alpha (TNF-a), an inflammatory mediator implicated in the progression of DKD, was strictly associated with the ACR in the whole population of patients with DKD and was much lower among non-albuminuric T2DM patients [24] than among albuminuric diabetics pointing to different degrees of inflammation among the two clinical phenotypes of DKD.

Non-albuminuric DKD is more prevalent in T2DM women than in men, probably due to the action of estrogens [10, 12, 25]. Even at late CKD stages (stage 4), despite the low eGFR, female gender has been independently associated with preservation of normoalbuminuria [26]. Data from the Swedish National Diabetes Register [25] showed that advanced age, increased systolic blood pressure (BP), low body mass index (BMI), poor glycemic control, and high triglycerides are independently associated with both decline of renal function and development of albuminuria, whereas female gender was an independent predictor of the eGFR decline only. In the Atherosclerosis Risk in Communities (ARIC) Study, high glycated hemoglobin (HbA1c) predicted incident CKD (defined as a eGFR < 60 ml/min/1.73 $m^2$) and this relationship was independent of albuminuria [27]. In a diverse high-risk population of T2DM patients with preserved renal function, higher systolic BP and black race were risk factors for developing treated ESKD, irrespective of the degree of albuminuria [7]. In the UK Prospective Diabetes Study, development of incident CKD or albuminuria was independently associated with Indian-Asian race and high systolic BP, whereas female sex, smoking, and decreased waist circumference predicted renal dysfunction independently of albuminuria. Therefore, these risk factors for CKD apply to both, albuminuric and non-albuminuric DKD patients [10]. Overall, high HbA1c and high systolic BP appear to be coherent risk factors for non-albuminuric DKD.

**Box 16.2**

- The main mechanism that drives progression of non-albuminuric DKD is macroangiopathy, as opposed to microangiopathy in albuminuric DKD.
- High HbA1c and high systolic BP appear to be coherent risk factors for non-albuminuric DKD.
- The biological pathways that promote progression of DKD include the following:
  - Production of advanced glycation end products (AGEs).
  - Reactive oxygen species (ROS).
  - Activation of protein kinase C (PKC).
  - Stimulation of the hexosamine and polyol pathway.
  - Systemic hypertension and alterations in renal hemodynamics.
  - Autophagy.
  - SGLT and cell hypoxia.
  - Urinary microRNAs and the mitochondria.

Several biological pathways may induce and promote the progression of DKD. Hyperglycemia is central to renal damage both in albuminuric and non-albuminuric DKD, and this applies to both, type 1 and 2 diabetes. The hyperglycemia-derived glycolysis triggers several metabolic pathways in DKD, including production of advanced glycation end products (AGEs), reactive oxygen species (ROS), activation of protein kinase C (PKC), and stimulation of the hexosamine and polyol pathway (Box 16.2).

### 16.2.1 Hyperglycemia, AGEs, Asymmetric Dimethyl Arginine, and the PKC Pathway

Glucose causes slow, non-enzymatic glycation of protein and the products are compounds characterized by an imine (C=N) bond (Schiff bases). Further molecular arrangements of these bases generate reversible production of Amadori compounds that can undergo oxidation, dehydration, cyclization, and condensation reactions that produce protein-bound compounds, the AGEs. This process is slow at normal glucose levels, but it is much accelerated in hyperglycemia, like in diabetes. AGEs typically alter the structure and function of cytosolic molecules and intracellular proteins and upregulate several signaling genes and proinflammatory and profibrotic pathways. High levels of AGEs induce dose-dependent increases of fibronectin, collagen, vascular endothelial growth factor (VEGF), and the inflammatory mediators, transforming growth factor beta 1 (TGF-β1) and TNF-a. VEGF associates with alterations in the capillary permeability and intrarenal blood flow and contributes to the development of albuminuria [28, 29].

In the early stages of experimental diabetic nephropathy, hyperglycemia upregulates the activity of nitric oxide (NO) synthase, and the resulting increase in NO bioavailability at kidney level dilatates the afferent arteriole and magnifies angiotensin II effects on the efferent arteriole [30]. On the other hand, the diabetic milieu in the kidney decreases the activity of dimethylarginine dimethylaminohydrolase (DDAH), an enzyme which metabolizes asymmetric dimethylarginine (ADMA), thereby increasing the levels ADMA at kidney level. This effect contributes to inflammation, oxidative stress (OS), and albuminuria and can be reversed by intrarenal injection of DDAH-1 [31]. At more advanced stages of nephropathy, accumulation of the endogenous inhibitor of NO, ADMA, reduces NO bioavailability triggering eGFR decline, severe albuminuria, and hypertension [32].

Hyperglycemia also upregulates the PKC pathway and by this pathway stimulates the expression of VEGF, fibronectin, collagen, and TGF-β, all effects leading to accumulation of extracellular matrix (ECM) and thickening of the basal membrane.

### 16.2.2 Phosphofructokinase and the Hexosamine Pathway

Glucose is fundamental for the production of energy in the cell. This normally occurs by phosphorylation of this molecule by the enzyme hexokinase. However, in the presence of sustained hyperglycemia, hexokinase is overwhelmed and excess glucose is diverted to the polyol pathway where it is converted to sorbitol by aldose reductase and then to fructose by sorbitol dehydrogenase. Fructose is then metabolized by fructokinase, a reaction triggering ATP depletion, proinflammatory cytokine expression, and OS. Wild-type mice with streptozotocin-induced diabetes exhibit high renal expression of aldose reductase; high levels of sorbitol, fructose, and uric acid; and low levels of ATP, all changes pointing to activation of the fructokinase pathway. Experimental data in mice indicate that enhanced fructokinase activity is toxic to the proximal tubule, triggering kidney injury and proteinuria and kidney dysfunction which are in large part prevented in fructokinase-deficient mice [33].

The hexosamine pathway is activated by the third step of glycolysis (phosphorylation of fructose-6-phosphate, catalyzed by the enzyme phosphofructokinase, see above) and produces sugar molecules in which a hydroxyl group is replaced by an amine group (amino sugars), and the most abundant of these sugars is *N*-acetyl-D-glucosamine. In this pathway, fructose-6-phosphate is converted to glucosamine-6-phosphate (GlucNAc-6-P) by the rate-limiting enzyme glutamine: fructose-6-phosphate aminotransferase (GFAT), which uses glutamine as an amino donor. GlucNAc-6-P is further converted in a rapid manner to uridine-5-diphosphate-*N*-acetylglucosamine (UDP-GlucNAc), the precursor for all other amino sugars that are necessary for the biosynthesis of glycoproteins, glycolipids, proteoglycans, and glycosaminoglycans. Because glucosamine levels of extracellular fluids are below the limit of detection (i.e., <0.02 mmol/L), cellular uptake of

glucosamine is negligible under physiologic conditions. However, in the presence of excess glucosamine, this compound is avidly taken up by the glucose transporter and phosphorylated by hexokinase yielding GlucNAc-6-P, thereby bypassing the rate-limiting enzyme GFAT. The activation of the hexosamine pathway upregulates the transcription and expression of TGF-β1 and TNF-a associated with endothelial apoptosis, thickening of the basement membrane, and kidney injury [34, 35]. The causal role of TGF-β1 in diabetic nephropathy in experimental models is supported by the observation that the administration of a neutralizing anti-TGF-β prevents renal damage in the same models [36].

### 16.2.3 Systemic Hypertension and Alterations in Renal Hemodynamics

Systemic hypertension is a risk factor of primary importance for the risk of CKD in the diabetic population. In newly diagnosed T2DM patients, every 10 mm Hg increase in systolic BP portends a 15% risk excess for the incidence DKD and albuminuria [10].

The hyperglycemic environment activates the RAS and several other metabolic and hormonal mediators, resulting in kidney hypertrophy and glomerular hyperfiltration both at single nephron and whole kidney level. Vasodilators, such as nitric oxide, cyclooxygenase-2 (COX-2) prostanoids, and atrial natriuretic peptide, reduce vascular renal resistances and dilate the afferent arteriole [37]. On the other hand, the role of angiotensin II, an efferent arteriole vasoconstrictor, in renal hemodynamics is of paramount importance [38]. Other glomerular vasoconstrictors with a prevailing action on the efferent side of the microcirculation of the kidney such as thromboxane A2 and endothelin-1 (ET-1) contribute to increase the GFR in experimental models and in human disease [37]. In type 1 normoalbuminuric and normotensive diabetic adolescents, the renal hemodynamic response to hyperglycemia is gender dependent [39]. Indeed, in a Canadian study testing the effect of hyperglycemia on renal hemodynamics, during clamped euglycemia, effective renal plasma flow (ERPF) and renal blood flow (RBF) were higher and renal vascular resistance (RVR) lower in males than in females. During clamped hyperglycemia, females presented increases in RVR and the filtration fraction (FF) and reductions in RBF and ERPF, whereas no significant renal hemodynamic changes occurred in males. Furthermore, in the face of similar changes in blood pressure after ACE inhibition, this intervention reduced the eGFR and the filtration fraction only in females [39]. Thus, females exhibit an unfavorable renal response to hyperglycemia but a protective renal hemodynamic response to ACE inhibition.

Like angiotensin II, also ET-1 promotes efferent arteriolar vasoconstriction as well as inflammation, fibrosis, endothelial dysfunction, and hypertension in kidney diseases. Moreover, this autacoid triggers mesangial hypertrophy and ECM accumulation and increases glomerular permeability, thus resulting in increased albuminuria and deterioration of kidney function [40].

The prevalence of glomerular hyperfiltration is largely dependent on the duration of hyperglycemia. Probably due to advanced age, hypertension-induced glomerulosclerosis, and age-dependent kidney senescence, the prevalence of hyperfiltration among T2DM patients is lower than that in T1DM (6–23% and 34–67%, respectively) [37]. Glomerular hyperfiltration has been repeatedly associated with subsequent eGFR reduction and albuminuria worsening. Among T2DM patients with hyperfiltration at baseline, those who maintained hyperfiltration after treatment with ACE inhibitors presented a higher risk for developing albuminuria and an accelerated eGFR loss (5.2 ml/min and 2.4 respectively) as compared to those in whom hyperfiltration was corrected by ACE inhibition [15]. Thus, early correction of whole kidney hyperfiltration mitigates the progression of DKD.

### 16.2.4 Autophagy

Autophagy is a regulated biological process in which a special type of newly formed vesicles, the autophagosomes, phagocytize and degrade cytoplasmic content. This phenomenon is important for cell biology because it serves to eliminate aging cells and long-lived proteins and damaged organelles. The optimal level of cell autophagy depends on tissues, age, and contingent physiology needs. To maintain their homeostasis, podocytes have an increased basal autophagy level. Exposure of podocytes to hyperglycemia leads to decreased autophagy and induces severe podocyte injury, and studies in obese T2DM patients documented defective autophagy in proximal tubular cells in these patients. This alteration has long been implicated in podocyte injury and death and in the progression of DKD [41, 42]. Impaired tubular autophagy in patients with DKD triggers tubular hypertrophy, inflammation, and fibrosis, through the pathway of p53/microRNA-214 [43].The causal role of disturbed autophagy is supported by the observation in experimental models with T2DM that dietary restriction exerts anti-inflammatory effects and restores both autophagy and kidney injury [44]. However, a recent biopsy study in T1DM, 10 years after pancreas transplantation and restoration of euglycemia, showed a significant reversal of DKD (assessed by reduction in basal membrane width and ECM accumulation) despite the fact that the injury of podocytes remained unchanged or even deteriorated [45].

### 16.2.5 Sodium Glucose Cotransporter (SGLT) and Cell Hypoxia

Due to enhanced proximal sodium reabsorption mainly mediated by the SGLT2, sodium delivery to the macula densa is reduced in diabetic patients. This causes a reflex reduction of afferent arteriole resistance and glomerular hyperfiltration. SGLT2 inhibition reduces proximal glucose reabsorption and glomerular

hyperfiltration and mitigates OS and fibrosis in the kidney [46]. Along with the hypothesis that the macula densa is key to the hemodynamic alterations induced by hyperglycemia, randomized controlled trials testing the effect of SGLT2 on renal function coherently detected a small, initial eGFR decrease followed by a substantial attenuation of DKD progression in the long term [47, 48]. In this regard, it should be noted that among T2DM patients with eGFR below 45 ml/min, the long-term renoprotective effects of SGLT2 inhibitors occur without causing the early short-term eGFR decline, thus suggesting that the mechanisms affected by SGLT2 inhibition might be other than hyperfiltration [49].

Chronic cell hypoxia has been suggested to be a primary driver of DKD. T2DM causes oxygen imbalance by compromising oxygen delivery (due to diabetes-induced microvascular injury) in the face of a high oxygen demand by enhanced kidney sodium reabsorption coupled with glucose reabsorption, a process mainly mediated by SGLT2. The hyperglycemia-associated hypoxic damage mediates capillary injury, inflammation, fibrosis, and nephron loss in diabetes [50], and the renoprotective effect of SGLT2 inhibitors might be at least partially attributed to improvement of kidney hypoxic status allowed by these drugs.

### 16.2.6 Urinary microRNAs and the Mitochondria

In recent years, urinary microRNAs (miRNAs) have been associated with clinical and histopathologic parameters in DKD and are now implicated in the progression of this disease. In both non-albuminuric and albuminuric T2DM patients, urinary miRNA-192 is strongly associated with the expression of TGF-β, and the degree of albuminuria [51] and urinary exosomal miRNA-29 is a marker of kidney fibrosis [52]. Moreover, in diabetic animals, the increase of miRNA-451-5p levels in urine exosomes precedes albuminuria and kidney fibrosis and is a potential biomarker of early DKD [53]. miRNA dysregulation in diabetes is extensive, and two recent meta-analyses reported that seven miRNAs (miR-21-5p, miR-29a-3p, miR-126-3p, miR-192-5p, miR-214-3p, miR-342-3p, and the hsa-miR-770 family) are substantially dysregulated in blood or urine from DKD patients compared to controls [54, 55].

The mitochondria are considered the powerhouse of the cell because these cell organelles generate most of the cell's supply of ATP which is used as a source of chemical energy. Interestingly, increased mitochondrial oxidation might be both the cause and the effect of hyperglycemia, and, once established, such an alteration activates proinflammatory, profibrotic, and apoptotic mediators. Mitochondrial DNA changes have been detected in blood, urine, and other tissues of DKD patients. Monitoring the molecular alterations in mitochondrial DNA might predict incident DKD and might also serve as a potential therapeutic target [56], an issue intensively investigated in experimental studies. Figure 16.1 summarizes the main and novel pathophysiologic mechanisms underlying development of DKD.

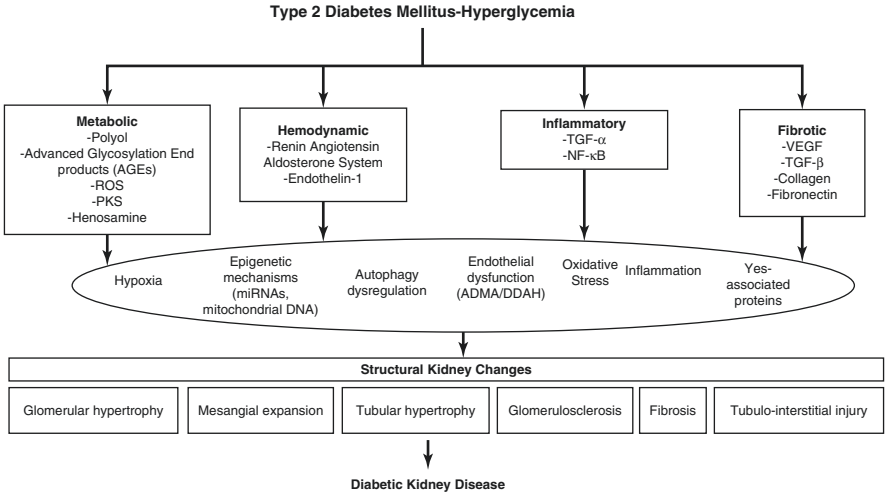


**Fig. 16.1** Main and novel pathophysiologic mechanisms underlying development of DKD

## 16.3 Novel Biomarkers of DKD

Both albuminuria (which is believed to be the first sign of DKD) and eGFR are characterized by significant variability and lack of accuracy in the detection and prediction of DKD progression. This is attributed to the fact that these two biomarkers are not linked to the molecular alterations responsible for DKD but are the actual result of kidney injury. Developing novel biomarkers that reflect pathophysiologic alterations at a preclinical stage is now perceived as an unmet clinical need. To improve the prediction of DKD, "omics" studies identified novel proteins and metabolites that may predict the course of this disease. Among those, the CKD273 urinary proteome-based classifier that consists of collagen fragments and proteins involved in inflammation and fibrosis is now considered the most accurate predictor of DKD progression in longitudinal and cross-sectional studies [57]. In a longitudinal study of T2DM patients, the CKD273 classifier was a stronger and more accurate predictor of macroalbuminuria (AUC, area under the curve, = 0.93) as compared to microalbuminuria (AUC = 0.67). Moreover, this classifier predicted the occurrence of macroalbuminuria 4.9 years before the actual occurrence of this alteration, compared with only 3.4 years for microalbuminuria [58]. The Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria (PRIORITY) study showed that various clinical risk factors for DKD were associated with the CKD273 score, including old age, male gender, longer duration of T2DM, lower eGFR, and higher albuminuria [59]. A post hoc analysis of the Diabetic Retinopathy Candesartan Trials (DIRECT-Protect 2 study) in T2DM patients showed that this classifier predicts the development of microalbuminuria independently of age, gender, albuminuria, eGFR, and HBA1c, with hazard ratio of 2.5 and AUC of 0.79 [60].

Both in type 1 and 2 diabetes, the CKD273 identifies patients who experience a decline of eGFR to below 60 mL/min, even in the absence of albuminuria [61]. Since the CKD273 classifier is thought to predict the response of mineralo-receptor blockade in T2DM, the ongoing PRIORITY trial [62] will use this score to stratify treatment response (spironolactone-derived prevention of albuminuria). Thus, the potential of urinary "omics" markers like the CKD273 classifier in DKD extends from the early detection of DKD to progression, prognosis, and prediction of response to treatment (Box 16.3).

**Box 16.3**
- CKD273 classifier is a novel biomarker of DKD.
- It includes several collagen fragments and proteins involved in inflammation and fibrosis.
- It predicts macroalbuminuria more accurately, as compared to microalbuminuria.
- CKD273 score correlates with old age, male gender, long duration of T2DM, low eGFR, and high albuminuria.

## 16.4 Therapeutic Advancements

Diabetic subjects without renal dysfunction and without albuminuria do not exhibit any excess risk for renal function loss over time as compared to individuals in the general population matched for age and gender. The question whether the lack of albuminuria may afford the same protection in diabetic individuals with established renal dysfunction (CKD stage 3) was examined by Vistisen in 935 persons with T1DM and 1984 with T2DM during up to 16 years of follow-up at the Steno Diabetes Center in Copenhagen [16]. In this study, the yearly eGFR loss over the following 10 years was dose-dependently associated with the presence and the magnitude of albuminuria both in T1DM (normoalbuminuria 1.9 ml/min/1.73 $m^2$, microalbuminuria 2.3 ml/min/1.73$m^2$, and 3.3 mL/min/1.73 $m^2$ for macroalbuminuria) and T2DM (1.9 ml/min/1.73$m^2$, 2.1 ml/min/1.73$m^2$, and 3.0 ml/min/1.73$m^2$). The 14% of T1DM and the 10% of T2DM individuals with CKD and normoalbuminuria developed an early decline in the eGFR. These subgroups were characterized by a lower use of lipid-lowering drugs, RAS blockers, and other antihypertensive treatment suggesting that these interventions may slow CKD progression in non-albuminuric DKD. Remarkably, in this contemporary cohort the rate of eGFR loss in micro- and macroalbuminuric T1DM and T2DM patients (between 2.1 and 3.3 mL/min/1.73 $m^2$ per year) was substantially less than in historical cohorts in Denmark [63, 64] and in England [65] which was in the 10–20 mL/min/1.73 $m^2$ per year range. This spectacular improvement in kidney outcomes underlines the achievements of primary and secondary prevention of DKD of the last three decades.

As to **primary prevention of DKD**, a trial of caloric restriction in non-albuminuric obese individuals with T2DM and high or normal eGFR showed that

this intervention reduced the high eGFR in hyperfiltering patients, improved insulin sensitivity, and reduced albuminuria even though this parameter was already within the normal range at baseline [66]. However, glomerular hyperfiltration per se, i.e., unassociated with albuminuria, is a surrogate of uncertain clinical relevance. Therefore, the renal effect of calorie restriction and other non-pharmacologic or pharmacologic interventions in these patients should be assessed in trials based on classical clinical endpoints like eGFR loss >50%, dialysis and transplantation, or by detailed studies of the rate of eGFR loss over time [67]. Given the very low rate of eGFR fall registered in normoalbuminuric individuals with diabetes without renal dysfunction, these trials should be done in normoalbuminuric patients with established DKD, particularly in the subset of patients (about 10%, see above) manifesting an early decline in eGFR.

Four drug trials, the BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) [68], the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) [69], the Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention (ROADMAP) [70], and the DIabetic REtinopathy Candesartan Trial and the progression of retinopathy in type 2 diabetes-Prevent 2 (DIRECT Protect-2) [71], reported that ACEi like perindopril in BENEDICT and angiotensin II receptor blockers (ARBs) like olmesartan and candesartan in the other two trials prevent the onset of albuminuria in hypertensive, normoalbuminuric patients with T2DM. However, none of these trials were based on established clinical renal endpoints and/or the rate of the eGFR decline. Furthermore, olmesartan in ROADMAP was associated with increased mortality risk, despite albuminuria reduction. Overall, for the lack of studies based on clinical endpoints, ACEis and ARBs are not recommended for primary prevention of DKD in T2DM in the clinical practice guidelines by the American Diabetes Association current (11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes 2019) which is in line with the recent recommendation by KDIGO (Kidney Disease: Improving Global Outcomes Diabetes Work Group, 2020).

As to **secondary prevention of DKD**, RAS inhibitors are established agents for the treatment of albuminuric DKD in T2DM. This is because of landmark trials published in 2001, the Irbesartan Diabetic Nephropathy Trial (IDNT) [72] and the Reduction of End Points in Non-Insulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan (RENAAL) [73] in DKD patients with ACR over 300 mg/g. In both trials RAS blockade was associated with a reduction in the risk for the classical combined renal endpoint (serum creatinine doubling or progression to ESKD). However, the residual risk in these studies was still substantial, ranging from 6 to 8/100 patient-years for individual outcomes and 11/100 patient-years for the composite outcome. Given the global burden of diabetes in the world population, the search for novel therapies to prevent DKD progression is a public health priority. Over the last decade new antidiabetic agents (SGLT2 inhibitors, GLP-1RA, and DDP-4 inhibitors) and new antihypertensive agents with unique nephroprotective properties have enlarged the armamentarium applied to treat DKD. Furthermore, new K-binders allow a better control of hyperkalemia, a relevant side effect of RAS blockers and aldosterone antagonists.

### 16.4.1 SGLT2 Inhibitors

SGLT2 inhibitors are glucose-lowering agents endowed with relevant protective effects for the kidney and the CV system. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was the first of a series of randomized controlled trials showing that treatment with a SGLT2 inhibitor, empaglifozin, improves CV outcomes and reduces DKD progression both in non-albuminuric and albuminuric patients [47, 74, 75]. In this trial, empagliflozin substantially reduced the eGFR decline across all albuminuria strata. In the same vein, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial showed that canagliflozin decreases the risks for doubling of serum creatinine, progression to ESKD, death from kidney causes, or CV disease in patients with DKD [76]. Importantly, these agents reduced proteinuria, and canagliflozin slowed DKD progression also in patients with severe DKD (eGFR < 30 ml/min) [77]. In both, EMPA-REG and CREDENCE, initiation of treatment with these drugs was followed by an acute drop in eGFR in more than 50% of patients. However, the long-term clinical benefit of treatment was independent of this initial renal-hemodynamic effect [74, 78]. Besides nephroprotection, empaglifozin [79] and canagliflozin [80] stimulate erythropoiesis via increased erythropoietin levels. A third SGLT2 inhibitor, dapaglifozin (DAPA), exhibits the same cardioprotective and nephroprotective effects of empaglifozin and canagliflozin also in nondiabetic CKD patients. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial randomized 4304 patients with eGFR between 25 and 75 ml/min and ACR ranging from 200 to 5000 mg/g to either 10 mg per day of dapagliflozin or placebo. About 1/3 of participants had nondiabetic CKD. After a median follow-up of 2.4 years, dapagliflozin significantly decreased total mortality, progression to ESKD, and the risk for a ≥ 50% reduction in baseline eGFR, in both DKD and nondiabetic CKD patients [81]. In patients with DKD stage 3b-4, dapagliflozin caused clinically significant reductions in BP, albuminuria, and body weight, but failed to decrease HbA1c [49]. Therefore, the beneficial effects of this drug are independent of glycemic control. Even though affording the same beneficial effects for renal and CV prevention of the previously discussed SGLT2 inhibitors, another drug of this class, sotagliflozin, increased the risk of volume depletion, diarrhea, and diabetic ketoacidosis [82]. This trial, the Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease (SCORED), was interrupted for the lack of funding after 14 months. Longer trials with sotagliflozin are still needed to evaluate the safety of this compound in patients with DKD.

The previously discussed large CV and renal outcome trials in patients with T2DM have shown that SGLT2 inhibitors improve CV and renal outcomes, and, in particular, they are quite effective for reducing the risk of hospitalization for heart failure [83–85]. Other trials with the same agents focusing on diabetic and nondiabetic patients with heart failure have now shown that they are unquestionably beneficial in this population. Indeed, a meta-analysis [86] of two large trials in nondiabetic and diabetic patients with heart failure, the Dapagliflozin and Prevention

of Adverse Outcomes in Heart Failure (DAPA-HF) [87] and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) [88] showed that these drugs reduce the risk of CV death or hospitalization for heart failure (composite outcome). However, neither trial had sufficient power to assess the effects on all-cause or CV death or adverse renal events (secondary outcomes). Overall, based on the very positive effects of SGLT2 inhibitors for CV and renal protection, the new KDIGO guideline for the treatment of T2DM with DKD recommends SGLT2 inhibitors as first-line therapy [89] in patients with eGFR above 30 ml/min. Even though the previously mentioned post hoc analysis of the CREDENCE study by Bakris [77] demonstrated that canagliflozin may prevent CKD progression in patients with eGFR < 30 ml/min/1.73m$^2$, this analysis was based on 170 patients only. Ongoing studies, namely, the Effects of Dapagliflozin in Nondiabetic Patients with Proteinuria (DIAMOND) trial that recruited participants with eGFR down to 25 ml/min per 1.73 m$^2$ [90] and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-Kidney) trial [91] that includes patients with an eGFR down to 20 ml/min per 1.73 m$^2$, will clarify whether the benefit of SGLT2 inhibition apply also to patients with eGFR < 30 ml/min/1.73m$^2$.

A recent observational study based on electronic healthcare databases from seven Canadian provinces and the UK reported that, compared to dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT2 inhibitors are associated with a 2.7-fold increased risk for incident diabetic ketoacidosis events [92]. Therefore, the use of SGLT2 needs caution in patients with risk factors for diabetic ketoacidosis, such as alcoholism, drug abuse, and pancreatic insufficiency. Other risks of SGLT2 inhibitors include volume depletion and genital mycotic infections.

### 16.4.2 GLP-1RA and DDP-4 Inhibitors

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) or incretin mimetics are of proven value for the management of T2DM, because they can reduce body weight, appetite, and HbA1c while having a decreased risk of hypoglycemia. In patients with T2DM who were at high CV risk, the rate of CV death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo in the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN) trial [93]. As for SGLT2 inhibitors, the benefit of this drug went beyond CV outcomes. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was indeed the first of a series of GLP-1 analogues showing that liraglutide reduces (−22% in this trial) the risk of new-onset persistent macroalbuminuria, serum creatinine doubling, progression to ESKD, or death [94]. Interestingly, the renoprotective effect of liraglutide was driven almost completely by a decrease in new-onset macroalbuminuria and not by effects on ESKD or doubling serum creatinine. A recent meta-analysis of seven trials including 56,000 T2DM patients [95] confirmed that diverse GLP-1RA (a class effect) causes a 17%

decrease in the same composite renal outcome, which was largely driven by a significant decrease in macroalbuminuria (HR, 0.76, 95% CI 0.68–0.86, $p = 0.003$). However, GLP-1 RA failed to show any beneficial effect on microalbuminuria, eGFR decline, and progression of DKD toward kidney failure. On the other hand, post hoc analyses of the SUSTAIN-6 and the Peptide Innovation for Early Diabetes Treatment-6 (PIONEER-6), two large trials in T2DM patients at high CV risk, showed that semaglutide mitigated the reduction of the eGFR over time [96]. Of note, this renoprotective effect was documented in all patients and across different eGFR strata, and patients with baseline eGFR ranging from 30 to 60 ml/min were those who mostly benefited from the treatment. Based on these data, the recent KDIGO guidelines recommend use of GLP-1 RA in T2DM patients with DKD unable to achieve optimal glycemic control despite treatment with metformin or SGLT2 inhibitors or when these drugs are contraindicated [89].

DPP-4 inhibitors are hypoglycemic agents that stimulate the endogenous production of GLP-1. Data from four randomized controlled trials—the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53) [97], the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) [98], the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) [99], and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) [100]—pointed that among T2DM patients with CV disease, DDP-4 inhibitors have just a minor effect in albuminuria reduction, but no effect on renal endpoints and eGFR decline. Compared to canagliflozin, semaglutide induces a more pronounced weight loss (−1.1 kg) and a greater decrease in HbA1c (−0.5% at 1 year) [101]. However, a recent network meta-analysis of trials comparing new antidiabetic agents showed that SGLT2 inhibitors exhibit a much stronger renoprotective effect than GLP-1RA. Indeed, in this analysis dapagliflozin caused a 47% risk reduction of a composite kidney outcome (kidney death and clinical end-stage kidney disease, represented by progression to kidney transplantation, initiation of maintenance dialysis, or an eGFR < 15 mL/min/1.73 $m^2$ sustained for at least 30 days, and a third variable to represent marked worsening in kidney function, by any one or combination of new-onset macroalbuminuria, a pre-specified percent reduction in eGFR, and doubling of serum creatinine), followed by empagliflozin, canagliflozin, and then semaglutide and liraglutide, whereas linagliptin failed to show a significant beneficial effect [102].

### 16.4.3 Endothelin-1 Antagonists

Evidence that antagonism of endothelin-1 has beneficial effects in experimental models of kidney diseases is well established [103]. The Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death (ASCEND) trial demonstrated that this drug causes a dose-dependent reduction in albuminuria in patients with DKD [104]. However the trial was prematurely stopped due to an

excessive incidence of congestive heart failure in the treatment group, caused by fluid retention [105]. The Reducing Residual Albuminuria in T2DM patients Treated With the Maximum Tolerated Labeled Dose of a Renin Angiotensin System Inhibitor (RADAR) showed that addition of atrasentan to treatment with RAS inhibitors dose-dependently reduced residual albuminuria [106]. Although body weight, a surrogate marker of fluid retention, was significantly increased in the treatment group, there was no difference in the incidence of CV events among groups in this trial. Making treasure of the risk of heart failure triggered by fluid retention in ASCEND and RADAR, the atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR) adopted a special design and enrolled only patients exhibiting early reduction in albuminuria and no substantial fluid overload. This individualized approach excluded approximately 50% of the patients that were initially screened. In the patients that were finally included in the study, the addition of atrasentan to pre-existing treatment with a RAS inhibitor resulted in a 35% reduction of a composite renal outcome of serum creatinine doubling or progression to ESKD [107] and reduced albuminuria status, independently of eGFR and hemoglobin levels [108]. Notwithstanding the strict preselection, edema and anemia, well-known side effects of ET-1, were more frequent in the treatment group but no excess risk for CV outcomes and hospitalizations due to heart failure.

### 16.4.4 Patiromer

International guidelines recommend the use of spironolactone as a fourth-line, add-on therapy in patients with uncontrolled resistant hypertension. Although the prevalence of resistant hypertension is much higher in advanced CKD (stages 3b-4) compared to the general hypertensive population, the use of spironolactone in CKD is limited by the risk of hyperkalemia. Potassium binding agents represent an interesting means for mitigating hyperkalemia by aldosterone antagonists. In this regard, the Patiromer (a K-binder) versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER) trial [109] showed that among patients with uncontrolled resistant hypertension and advanced CKD (eGFR of 25–45 ml/min), the drug meaningfully reduced the risk of hyperkalemia and increased the proportion of patients who continued treatment with spironolactone during a 12-week follow-up, an effect that was independent of diabetes status [110].

### 16.4.5 Finerenone

Finerenone, a nonsteroidal, selective, oral mineralocorticoid receptor antagonist (MRA), has a better safety profile for the risk of hyperkalemia as compared to spironolactone. Furthermore, this drug maintains the beneficial properties of MRAs

including suppression of fibrosis and inflammation. The minerAlocorticoid Receptor antagonist Tolerability Study (ARTS) trial in DKD patients showed that the addition of finerenone to standard treatment with a RAS inhibitor results in a significant, dose-dependent improvement in albuminuria [111]. However, in this study, there was no effect of finerenone in the secondary renal outcome (≥30% reduction on eGFR), which might have been due to the small power of this study for this outcome. This issue was more recently addressed in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial. In this trial 5734 T2DM patients with DKD and moderately increased albuminuria (30–300 mg/g ACR) and diabetic retinopathy or severely increased albuminuria (300–5000 mg/g ACR), that were being treated with ACEi or ARBS, were randomized to either finerenone or placebo. Remarkably, patients in the finerenone group presented a slower decline of eGFR rate, a lower rate of CV mortality and morbidity, and a nonsignificant reduction in mortality and progression to ESKD [112]. Until now no study focused on the possible additive beneficial effect of finerenone in DKD patients already treated with ACEi and SGLT2 inhibitors, which is a question of obvious importance for exploiting in full the new drugs which entered into the therapeutic scenario of DKD in the recent years (Table 16.1).

**Table 16.1** Summary of randomized controlled trials investigating the effects of novel therapeutic agents for management of DKD

| Drug | Trial | Study population | Outcome | Result |
|---|---|---|---|---|
| *SGLT2* | | | | |
| Empagliflozin | EMPA-REG OUTCOME [75, 83] | 4124 T2DM patients with eGFR ≥ 30 ml/min | Progression to macroalbuminuria, doubling of the serum creatinine level, ESKD, or death from renal causes | 6.1% reduction |
| | | | Incident albuminuria | No difference among groups |
| | | 7020 T2DM with high CV risk | Death from CV event, nonfatal stroke, or nonfatal myocardial infarction | 14% reduction |
| | | | Hospitalization for unstable angina | 35% reduction |
| | EMPEROR-REDUCED [88] | 3730 patients with heart failure and EF ≤ 40% | CV death or hospitalization for heart failure | 25% reduction |

(continued)

**Table 16.1** (continued)

| Drug | Trial | Study population | Outcome | Result |
|---|---|---|---|---|
| Canagliflozin | CREDENCE [76, 77, 80] | 4401 T2DM patients with 30 < eGFR < 90 ml/min and UACR of >300–5000 mg/g treated with RASi | Major CV events, CV death | 20% reduction |
| | | | ESKD, doubling of serum creatinine, or death from renal or CV causes | Reduction |
| | | | Anemia events or initiation of treatment for anemia | 35% reduction |
| | | 170 T2DM patients with eGFR < 30 ml/min and UACR of >300–5000 mg/g treated with RASi | Rate of eGFR decline | 66% reduction |
| | | | AKI and kidney-related adverse events | No difference among groups |
| Dapagliflozin | DAPA-CKD [49, 81] | 4304 T2DM patients with 25 < eGFR < 75 ml/min and UACR of >200–5000 mg/g | ESKD, ≥50% eGFR reduction, or death from renal or CV causes | 39% reduction |
| | | | CV death or hospitalization for heart failure | 29% reduction |
| | DECLARE-TIMI 58 [47] | 17,160 T2DM patients with atherosclerotic CV disease OR Multiple risk factors and eGFR > 60 mL/min | ESKD, ≥40% eGFR reduction to less than 60 ml/min, kidney transplantation, or death from renal or CV causes | 24% reduction, including 46% reduction in ≥40% eGFR decline |
| | DAPA-HF [87] | 4744 patients with heart failure and EF ≤ 40% | CV death, hospitalizations/urgent visits for heart failure resulting in intravenous therapy for heart failure | 26% reduction |
| Sotagliflozin | SCORED [82] | 10,584 T2DM patients with 25 < eGFR < 60 ml/min | CV death, hospitalizations/urgent visits for heart failure | 26% reduction |
| | | | Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis | Increase |

**Table 16.1** (continued)

| Drug | Trial | Study population | Outcome | Result |
|---|---|---|---|---|
| *GLP-1RA* | | | | |
| Semaglutide | SUSTAIN [93] | 3297 T2DM patients, with 83% having pre-existing CV disease or CKD or both | Death from CV event, nonfatal stroke, or nonfatal myocardial infarction | Reduction |
| | | | New onset of CKD or worsening pre-existing CKD | Reduction |
| Liraglutide | LEADER [94] | 9340 T2DM patients with<br>Age > 50 years and CV disease or CKD<br>OR<br>Age > 60 years and other specified risk factors of CV disease | New-onset persistent macroalbuminuria, doubling of the serum creatinine level, ESKD, or death from renal causes | 22% reduction (26% reduction in albuminuria, similar rates in doubling of the serum creatinine level, ESKD, or death from renal causes) |
| | | | AKI | No difference among groups |
| Semaglutide | SUSTAIN-6<br>PIONEER-6 [96] | 6480 T2DM | Annual eGFR decline | Reduction by 0.60 ml/min |
| *DDP-4 inhibitors* | | | | |
| Saxagliptin | SAVOR-TIMI 53 [97] | 16,492 T2DM patients (58.8% with normoalbuminuria, 26.8% with microalbuminuria, 9.9% with macroalbuminuria) | Doubling of serum creatinine, ESKD, renal transplantation, or serum creatinine >6.0 mg/dL | No difference among groups |
| | | | eGFR | No difference among groups |
| | | | UACR | Minor reduction in all categories of albuminuria |
| Alogliptin | EXAMINE [98] | 5380 T2DM patients with a recent acute coronary syndrome | Death from CV event, nonfatal stroke, or nonfatal myocardial infarction | No difference among groups |
| | | | HbA1c | Reduction |
| | | | ESKD | No difference among groups |
| Sitagliptin | TECOS [99] | 14,671 T2DM patients with pre-existing CV disease | CV events | No difference among groups |
| | | | eGFR decline | No difference among groups |

(continued)

**Table 16.1** (continued)

| Drug | Trial | Study population | Outcome | Result |
|---|---|---|---|---|
| Linagliptin | CARMELINA [100] | 6991 T2DM patients type 2 diabetes, with a history of vascular disease and UACR > 30 mg/g OR 45 < eGFR < 75 ml/min and UACR > 200 mg/g OR 15 < eGFR < 45 ml/min | CV death, nonfatal myocardial infarction, or nonfatal stroke | No difference among groups |
| | | | ESKD, ≥40% eGFR reduction or death from renal causes | No difference among groups |
| *Endothelin-1 antagonists* | | | | |
| Avosentan | ASCEND [104, 105] | 1392 DKD patients treated with RASi | UACR | Dose-dependent reduction |
| | | | CV events | Increase (reason for premature termination of the study) |
| | | | ESKD, doubling of serum creatinine, or death | No difference among groups |
| Atrasentan | RADAR [106] | 211 T2DM patients, with UACR of 300–3500 mg/g, and 30 < eGFR < 75 ml/min treated with RASi | UACR | Dose-dependent reduction |
| | | | eGFR, office BP measurements, heart failure, peripheral edema, CV events | No difference among groups |
| | | | 24-h systolic and diastolic BP, LDL cholesterol, triglycerides | Reduction |
| | | | Body weight | Increase |
| Atrasentan | SONAR [107, 108] | 2648 T2DM patients, with UACr of 300–5000 mg/g, and 25 < eGFR < 75 ml/min treated with RASi | ESKD or doubling of serum creatinine or death from renal causes | 35% reduction |
| | | | UACR | Reduction, independently of eGFR and Hb |
| | | | Hospitalizations for heart failure | No difference among groups |
| *Potassium binding agents* | | | | |

**Table 16.1** (continued)

| Drug | Trial | Study population | Outcome | Result |
|---|---|---|---|---|
| Patiromer | AMBER [109] | 295 CKD with uncontrolled resistant hypertension and 25 < eGFR < 45 ml/min | Difference in the proportion of patients on spironolactone | Increase in treatment group (16% increase in patients with HF, 22.4% increase in patients without HF), independently of diabetes |
| | | | Change in systolic AOBP | No difference among groups |
| | | | Risk of hyperkalemia | Reduction |
| *Mineralocorticoid receptor antagonist* | | | | |
| Finerenone | ARTS [111] | 821 T2DM treated with RASi | UACR change | Dose-dependent reduction |
| | | | ≥30% eGFR reduction | No difference among groups |
| Finerenone | FIDELIO-DKD [112] | 5734 T2DM with DKD treated with RASi and 30–300 mg/g UACR, 25 < eGFR < 60 ml/min and diabetic retinopathy OR 300–5000 mg/g UACR, 25 < eGFR < 75 ml/min | ESKD, ≥40% eGFR reduction, or death from renal causes | 18% reduction |
| | | | CV death, CV events, hospitalization for heart failure | 14% reduction |

*T2DM* type 2 diabetes mellitus, *CV* cardiovascular, *ESKD* end-stage kidney disease, *EF* ejection fracture, *eGFR* estimated glomerular filtration rate, *UACR* urinary albumin to creatinine ratio, *RASi* renin-angiotensin system inhibitors, *AKI* acute kidney injury, *CKD* chronic kidney disease, *HBA1c* glycated hemoglobin, *BP* blood pressure, *LDL* low-density lipoprotein, *AOBP* automated office blood pressure, *DKD* diabetic kidney disease

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