Diabetic Kidney Disease
Challenges, Progress, and Possibilities

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Abstract
Diabetic kidney disease develops in approximately 40% of patients who are diabetic and is the leading cause of CKD worldwide. Although ESRD may be the most recognizable consequence of diabetic kidney disease, the majority of patients actually die from cardiovascular diseases and infections before needing kidney replacement therapy. The natural history of diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining GFR, and ultimately, ESRD. Metabolic changes associated with diabetes lead to glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial inflammation and fibrosis. Despite current therapies, there is large residual risk of diabetic kidney disease onset and progression. Therefore, widespread innovation is urgently needed to improve health outcomes for patients with diabetic kidney disease. Achieving this goal will require characterization of new biomarkers, designing clinical trials that evaluate clinically pertinent end points, and development of therapeutic agents targeting kidney-specific disease mechanisms (e.g., glomerular hyperfiltration, inflammation, and fibrosis). Additionally, greater attention to dissemination and implementation of best practices is needed in both clinical and community settings.

Introduction

It took more than three millennia from the first description of diabetes in 1552 BC to the recognition of an association between diabetes and kidney disease, but it took only several decades for diabetic kidney disease (DKD) to become the leading cause of ESRD in the United States (1,2). This microvascular complication develops in approximately 30% of patients with type 1 diabetes mellitus (DM1) and approximately 40% of patients with type 2 diabetes mellitus (DM2) (2,3).

The increasing prevalence of DKD parallels the dramatic worldwide rise in prevalence of diabetes (4,5). In the United States, the prevalence of diabetes among adults increased from 9.8% in the 1988–1994 time period to 12.3% in the 2011–2012 time period (6). Worldwide, in the year 2015, 415 million people were estimated to have diabetes; by 2040, prevalence is projected to increase to 642 million, with disproportionate growth in low- to middle-income countries (7).

The driving force behind the escalating prevalence of diabetes is the global pandemic of obesity (4). Between the years 1980 and 2000, the overall prevalence of obesity in adults snowballed from 15% to 31% in the United States (8). By 2013–2014, the adjusted prevalence of obesity was up to 35% among men and 40% among women (9).

Kidney disease attributed to diabetes is a major but under-recognized contributor to the global burden of disease. Between 1990 and 2012, the number of deaths attributed to DKD rose by 94% (10). This dramatic rise is one of the highest observed for all reported chronic diseases (11). Notably, most of the excess risk of all-cause and cardiovascular disease (CVD) mortality for patients with diabetes is related to the presence of DKD (12).

Risk Factors
DKD risk factors can conceptually be classified as susceptibility factors (e.g., age, sex, race/ethnicity, and family history), initiation factors (e.g., hyperglycemia and AKI), and progression factors (e.g., hypertension, dietary factors, and obesity) (Table 1) (13). Two of the most prominent established risk factors are hyperglycemia and hypertension.

Hyperglycemia
In normoalbuminuric patients with DM1, poor glycemic control is an independent predictor of progression to development of proteinuria (albuminuria) and/or ESRD (14). Two landmark trials conducted with patients with early-stage DM1 or DM2 showed that intensive blood glucose control early in the course of disease exhibits a long-lasting favorable effect on the risk of DKD development (15,16). This “legacy effect,” also named “metabolic memory,” suggests that early intensive glycemic control can prevent irreversible damage, such as epigenetic alterations, associated with hyperglycemia (17). In patients with DM1, an intensive glucose control intervention targeting a hemoglobin A1C (HbA1C) level ≤7% reduced the 9-year risks of developing microalbuminuria and macroalbuminuria by 34% and 56%, respectively, compared with standard care (18). After a median follow-up of 22 years, the intensive therapy group had approximately 50%
lower risk of a low eGFR (<60 ml/min per 1.73 m²), and the average rate of eGFR loss was significantly reduced from 1.56 ml/min per 1.73 m² per year with standard therapy to 1.27 ml/min per 1.73 m² per year with intensive therapy (19). Similarly, in patients with newly diagnosed DM2, 10 years of an intensive glycemic control intervention targeting an HbA1C of 7% produced a 24% reduction in development of microvascular complications, including DKD, compared with conventional therapy (20,21). After 12 years, intensive glycemic control resulted in a 33% reduction in the risk of development of microproteinuria or “clinical grade” proteinuria and a significant reduction in the proportion of patients with a doubling of the blood creatinine level (0.9% versus 3.5%) relative to the conventional therapy group (20,21).

Hypertension
In patients with newly diagnosed DM2, treating to a target BP of <150/85 mmHg over a median of 15 years resulted in a significant 37% risk reduction of microvascular complications compared with that in patients treated to a target of <180/105 mmHg. Each 10-mmHg increase in mean systolic BP was associated with a 15% increase in the hazard ratio for development of both micro- and macroalbuminuria and impaired kidney function defined as eGFR<60 ml/min per 1.73 m² or doubling of the blood creatinine level (22). Broadly, a baseline systolic BP >140 mmHg in patients with DM2 has been associated with higher risk of basement membrane thickening (14,25,26) (Figure 1). Other glomerular changes include loss of endothelial fenestrations, mesangial matrix expansion, and loss of podocytes with effacement of foot processes (Figure 2). Mesangial volume expansion is detectable within 5–7 years after DM1 diagnosis (14,25,27,28). Segmental mesangiolysis is observed with progression of diabetes and thought to be associated with development of Kimmelstiel–Wilson nodules and microaneurysms, which often present together (29,30) (Figure 3). The exudative lesions result from subendothelial deposits of plasma proteins, which form periodic acid–Schiff-positive and electron-dense deposits and accumulate in small arterial branches, arterioles, and glomerular capillaries as well as microaneurysms. These deposits can result in luminal compromise (e.g., hyaline arteriosclerosis). Similar subepithelial deposits are seen in Bowman’s capsule (capsular drop lesion) and proximal renal tubules. In later stages of diabetes, interstitial changes and glomerulopathy coalesce into segmental and global sclerosis (31). In patients with DM1, GFR, albuminuria, and hypertension are strongly correlated with mesangial expansion and somewhat less strongly associated with glomerular basement membrane width (31) (Figure 4).

Renal structure changes in patients with DM2 are similar to those seen in DM1, but they are more heterogeneous and less predictably associated with clinical presentations (32). Early renal pathology studies described a high prevalence of nondiabetic glomerular disease in the patients with DM2 population, probably because of selection bias: patients who were diabetic and underwent biopsies tended to have atypical presentations of DKD. Conclusions from more recent biopsy studies are more conservative, estimating <10% prevalence of non-DKD in patients with diabetes and albuminuria (24).

Factors underlying the different presentation of DKD in DM2 may include the unreliable timing of DM2 onset compared with DM1, with potentially longer exposure to
hyperglycemia before diagnosis; an older patient population; and a higher burden of atherosclerosis. Additionally, many patients with DM2 are treated with renin-angiotensin system inhibitors before diagnosis of diabetes. An international consensus working group has provided a pathologic classification system to address the heterogeneity of DKD presentation, which includes scoring of glomerular, interstitial, and vascular lesions (Tables 2 and 3) (33).

Natural History
The paradigm of the natural history of DKD continues to evolve. In many patients, DKD clearly does not follow the

Figure 1. | Electron microscope images of structural changes in diabetic kidney disease. Structural changes in diabetic glomerulopathy found with electron microscopy. A indicates marked expansion of the mesangium. B indicates marked diffuse thickening of capillary basement membranes (to three times the normal thickness in this case). C indicates segmental effacement of the visceral epithelial foot processes. Original magnification, ×3500.

Figure 2. | Normal kidney morphology and structural changes in diabetes mellitus. Diabetic kidney disease induces structural changes, including thickening of the glomerular basement membrane, fusion of foot processes, loss of podocytes with denuding of the glomerular basement membrane, and mesangial matrix expansion.
classic pattern of glomerular hyperfiltration progressing to persistent albuminuria associated with hypertension and declining GFR (34) (Figure 5). The United Kingdom Prospective Diabetes Study (UKPDS) offered a unique opportunity to observe the natural history of DKD in patients with DM2 from early in the course of diabetes. Of enrolled patients, approximately 2% per year progressed from normo- to microalbuminuria and from micro- to macroalbuminuria. At a median of 15 years after diagnosis, 40% of participants developed albuminuria, and 30% developed eGFR, 60 ml/min per 1.73 m² or doubling of the blood creatinine level (22,35). It is noteworthy that 60% of those developing kidney functional impairment did not have preceding albuminuria, and 40% never developed albuminuria during the study (22). This finding underscores the fact that albuminuria is a dynamic, fluctuating condition rather than a linearly progressive process. For example, in the Multifactorial Intervention for Patients with Type 2 Diabetes Study, 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 (36). Recent clinical data from over 20,000 patients with DM1 show lower frequencies of low eGFR (<60 ml/min per 1.73 m²) and albuminuria in this population; 19±13 years after diagnosis, frequencies of low eGFR and albuminuria were 8% and 19%, respectively (37).

In step with the changing paradigm of the natural history of DKD, emerging evidence suggests that the clinical presentation of DKD is altering. A comparison of DKD presentation in adults with diabetes during the time periods between 1988 and 1994 and between 2009 and 2014 shows that the prevalence of albuminuria as a manifestation of DKD decreased from 21% to 16%, that low eGFR (<60 ml/min per 1.73 m²) increased from 9% to 14%, and that severely reduced eGFR (<30 ml/min per 1.73 m²) increased from 1% to 3% (38). Furthermore, lack of albuminuria or low eGFR may not necessarily preclude structural DKD. A recent autopsy study found a considerably higher prevalence of DKD diagnosed histologically compared with that indicated by clinical laboratory testing. Of 168 patients with DM1 or DM2, 106 exhibited histopathologic changes characteristic of DKD. Albuminuria or low eGFR was absent in 20% (20 of 106) of patients throughout life. Moreover, structural changes were highly variable and encompassed almost all histopathologic classes of DKD (39).

In later stages of DKD, as GFR declines, both kidney- and nonkidney-related DKD complications develop. Anemia and bone and mineral metabolism disorders often develop earlier in DKD than in other types of CKD. Predominant tubulointerstitial disease is associated with damage to the peritubular interstitial cells that produce erythropoietin. As a result, patients with diabetes may be prone to erythropoietin deficiency and are nearly twice as likely to have anemia compared with patients with nondiabetic CKD and comparable eGFR (40). Insulin is a cofactor for parathyroid hormone release; therefore, insulin deficiency and/or resistance may be associated with lower parathyroid hormone levels than in other types of CKD (41), which may predispose patients with DKD to adynamic bone disease.

Deaths due to CVDs and infections are highly prevalent and compete with progression to ESRD. In the UKPDS, the overall death rate after onset of DKD in those with blood creatinine levels >2 mg/dl or those receiving kidney replacement therapy was nearly 20% per year (35).

Figure 3. | Diabetic glomerulopathy. Changes in glomerular histology in diabetic glomerulopathy (A) Normal glomerulus. (B) Diffuse mesangial expansion with mesangial cell proliferation. (C) Prominent mesangial expansion with early nodularity and mesangiolysis. (D) Accumulation of mesangial matrix forming Kimmelstiel–Wilson nodules. (E) Dilation of capillaries forming microaneurysms, with subintimal hyaline (plasmatic insudation). (F) Obsolescent glomerulus. A–D and F were stained with period acid–Schiff stain, and E was stained with Jones stain. Original magnification, ×400.
Follow-up data from 2003 showed crude 1-year mortality of patients on dialysis ranging from 6.6% in Japan to 21.5% in the United States (42). Patients on dialysis over age 75 years old are 3.9 times more likely to die than their counterparts in the general population (43).

Pathophysiology of DKD

Critical metabolic changes that alter kidney hemodynamics and promote inflammation and fibrosis in early diabetes include hyperaminoacidemia, a promoter of glomerular hyperfiltration and hyperperfusion, and hyperglycemia

Table 2. International pathologic classification of glomerular changes in diabetic kidney disease

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild or nonspecific light microscopy changes and electron microscopy–proven GBM thickening</td>
<td>GBM &gt; 395 nm in women and &gt; 430 nm in men 9 yr of age and older; biopsy does not meet any of the criteria mentioned below for classes 2–4</td>
</tr>
<tr>
<td>2a</td>
<td>Mesangial expansion, mild</td>
<td>Mild mesangial expansion in &gt; 25% of the observed mesangium; biopsy does not meet criteria for class 3 or 4</td>
</tr>
<tr>
<td>2b</td>
<td>Mesangial expansion, severe</td>
<td>Severe mesangial expansion in &gt; 25% of the observed mesangium; biopsy does not meet criteria for class 3 or 4</td>
</tr>
<tr>
<td>3</td>
<td>Nodular sclerosis (Kimmelstiel–Wilson lesion)</td>
<td>At least one convincing Kimmelstiel–Wilson lesion; biopsy does not meet criteria for class 4</td>
</tr>
<tr>
<td>4</td>
<td>Advanced diabetic glomerulosclerosis</td>
<td>Global glomerular sclerosis in &gt; 50% of glomeruli; lesions from classes 1–3</td>
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Degree of mesangial expansion: mild mesangial expansion occupies an area smaller than the area of the capillary lumen. Severe mesangial expansion occupies an area greater than the area of the capillary lumen (33). GBM, glomerular basement membrane.
In DM2, systemic hypertension and obesity also contribute to glomerular hyperfiltration via mechanisms, such as high transmitted systemic BP and glomerular enlargement (47). Glomerular hyperfiltration is a well characterized consequence of early diabetes. Overall, it is observed in 10%–40% or up to 75% of patients with DM1 and up to 40% of patients with DM2 (48).

Mechanisms underlying glomerular hyperfiltration in diabetes are incompletely understood (48); however, one plausible mechanism is increased proximal tubular reabsorption of glucose via sodium–glucose cotransporter 2, which decreases distal delivery of solutes, particularly sodium chloride, to the macula densa (49,50). The resulting decrease in tubuloglomerular feedback may dilate the afferent arteriole to increase glomerular perfusion, while concurrently, high local production of angiotensin II at the efferent arteriole produces vasoconstriction. The overall effect is high intraglomerular pressure and glomerular hyperfiltration (47,49) (Figure 7).

**Diagnosis of DKD**

The clinical diagnosis of DKD is on the basis of measurement of eGFR and albuminuria along with clinical features, such as diabetes duration and presence of diabetic retinopathy (51,52). DKD is identified clinically by persistently high urinary albumin-to-creatinine ratio $\geq 30$ mg/g and/or sustained reduction in eGFR below 60 ml/min per 1.73 m² (53). Screening for DKD should be performed annually for patients with DM1 beginning 5 years after diagnosis and annually for all patients with DM2 beginning at the time of diagnosis. In patients with albuminuria, the presence of diabetic retinopathy is strongly suggestive of DKD. The preferred test for albuminuria is a urinary albumin-to-creatinine ratio performed on a spot sample, preferably in the morning (51,52). The eGFR is calculated from the serum creatinine concentration. Although the Chronic Kidney Disease-Epidemiologic Prognosis Initiative equation is more accurate, particularly at eGFR levels in the normal or near-normal range, the Modification of Diet in Renal Disease equation is typically reported by clinical laboratories (52). Confirmation of albuminuria or low eGFR requires two abnormal measurements at least 3 months apart. If features atypical of DKD are present, then other causes of kidney disease should be considered. Atypical features include sudden onset of low eGFR or rapidly decreasing eGFR, abrupt increase in albuminuria or development of nephrotic or nephritic syndrome, refractory hypertension, signs or symptoms of another systemic disease, and $>30\%$ eGFR decline within 2–3 months of initiation of a renin-angiotensin system inhibitor (53).

**Treatment of DKD**

Prevention of diabetic complications, particularly DKD, by long-term intensive glycemic control from early in the course of diabetes is well established for DM1 and DM2.
To the contrary, less stringent goals of HbA1C absence of complications, and a longer life expectancy. Patients with shorter duration of diabetes, younger age, gent goals, such as HbA1C targets for glycemia should be tailored to age, comorbid-

Figure 6. | Different pathways and networks involved in the initiation and progression of diabetic kidney disease. AGE, advanced glycation end product; CTGF, connective tissue growth factor; JAK-STAT, Janus kinase/signal transducer and activator of transcription; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SAA, serum amyloid A; VEGF-A, vascular endothelial growth factor A. *JAK/STAT signaling can be unchanged (↔) or upregulated (↑) in early and later stages of diabetes, respectively.

(19,22). However, intensive glucose control after onset of complications or in longstanding diabetes has not been shown to reduce risk of DKD progression or improve overall clinical outcomes. Targeting low HbA1C (6%–6.9%) compared with standard therapy in this population did not reduce risk of cardiovascular (CV) or microvascular complications but increased the risk of severe hypoglycemia (54–56). Furthermore, an analysis of patients with DM2 and early-stage CKD showed 30% and 40% higher risks for all-cause mortality and CV mortality, respectively, with intensive glycemic control compared with standard therapy (57). The finding that intensive glycemic control incurs great risk of hypoglycemia and does not benefit the risk of CVD or all-cause mortality has been sustained over the long term (8–10 years). A small benefit of intensive glycemic control on the risk of ESRD was observed, but the absolute number of patients was minute (58). A stratified analysis showed that the greatest benefi of intensive glycemic control for preventing ESRD was seen in participants without kidney disease at study entry, further supporting the concept that intensive glycemic control initiated during early diabetes can prevent DKD (59).

The American Diabetes Association recommends that targets for glycemia should be tailored to age, comorbid-
ties, and life expectancy of individual patients. More stringent goals, such as HbA1C<6.5%, may be reasonable for patients with shorter duration of diabetes, younger age, absence of complications, and a longer life expectancy. To the contrary, less stringent goals of HbA1C<8% are recommended for patients with longstanding diabetes, older age, micro- and macrovascular complications, and limited life expectancy (51). Similarly, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a target HbA1c of about 7.0% to prevent or delay progression of the microvascular complications of diabetes. However, patients at risk for hypoglycemia, such as those with diabetes and CKD, should not be treated to an HbA1c target of <7.0% (53).

For management of hypertension, the Eighth Joint National Committee (JNC-8) recommended initiation of pharmacologic treatment at a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, with treatment goals less than these levels. In the general hypertensive population, including those with diabetes, initial antihypertensive treatment may include a thiazide-type diuretic, a calcium channel blocker, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB). In black patients with diabetes, the JNC-8 recommends initial treatment with a thiazide diuretic or calcium channel blocker. The same BP targets are recommended for those with CKD irrespective of diabetes status. In patients who are diabetic with high levels of albuminuria, the medication regimen should include an ACE inhibitor or an ARB alone or in combination with medication from another drug class (60). The KDIGO guidelines recommend use of an ACE or an ARB and a BP goal <130/80 mmHg in all patients with CKD and albuminuria irrespective of diabetes status (52). There is unambiguous evidence that renin-angiotensin system blockade with either an ACE inhibitor or an ARB reduces the progression of DKD in patients with microalbuminuria (61). However, combination therapy (an ACE inhibitor and an ARB administered together) increases the risk of serious side effects, primarily hyperkalemia and AKI, and offers no clinical benefits (62,63).

Following the liberalized JNC-8 recommendations, target BP goals have been challenged by results of the Systolic BP Intervention Trial (SPRINT). The SPRINT included 9361 nondiabetic participants with hypertension and high CV risk. Participants were randomized to either an intensive (<120 mmHg) or standard (<140 mmHg) systolic BP goal. The trial was terminated early after a median of 3.26 years, because rates of the primary outcome (myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from CV causes) and all-cause mortality were reduced by 25% and 27%, respectively, in the intensively treated group compared with the standard regimen group. These results held across prespecified subgroups defined according to CKD stage, age >75 years old, sex, race, previous CVD, and baseline levels of systolic BP (64,65).

In contrast to the SPRINT, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, which included 4733 patients with diabetes at high risk for CV events, showed that achieving the same systolic BP targets (<120 versus <140 mmHg) did not have a statistically significant effect on the risk of nonfatal myocardial infarction, nonfatal stroke, death from CV cause, or death from any causes (66). One of the possible explanations for this incongruent finding is that the ACCORD Trial was underpowered to show between-group differences,
because CV morbidity and mortality occurred at substantially lower rates than predicted. However, in the SPRINT participants who had CKD at study entry, intensive BP treatment did not reduce incidence of ESRD, cause a 50% decline in eGFR, or cause $30\%$ decline in eGFR to a value of $<60$ ml/min per 1.73 m$^2$. Furthermore, hospitalizations or emergency room visits for AKI occurred more frequently in the intensive treatment group than the standard regimen group (4.4% versus 2.6%; hazard ratio, 1.71) (64,67). Similarly, the ACCORD Trial detected a signal suggestive of a possible negative effect of intensive BP control on kidney function. Even among participants who had normal kidney function at baseline, instances of eGFR $\geq 30$ ml/min per 1.73 m$^2$ were almost doubled in the intensive treatment group (99 in the intensive treatment group versus 52 in the standard treatment group; $P<0.001$) (66).

**Novel Therapies and Approaches**

Despite current approaches to management of diabetes and hypertension and use of ACE inhibitors and ARB, there is still large residual risk in DKD. Novel agents targeting mechanisms, such as glomerular hyperfiltration, inflammation, and fibrosis, have been a major focus for development of new treatments. Agents that have shown promise include ruboxistaurin, a protein kinase C-β inhibitor (68); baricitinib, a selective Janus kinase 1 and Janus kinase 2 inhibitor (69); pentoxifylline, an anti-inflammatory and antifibrotic agent (70); atrasentan, a selective endothelin A receptor antagonist (71,72); and finerenone, a highly selective nonsteroidal mineralocorticoid receptor antagonist (Table 4) (73). However, thus far, there are no available phase 3 clinical trial data for these agents, and none are approved for use in DKD.

Since the year 2008, the US Food and Drug Administration has mandated that new antihyperglycemic therapies seeking approval for the treatment of DM2 must show CV safety. Three agents within the glucagon-like peptide-1 receptor agonist class of medications, lixisenatide, liraglutide, and semaglutide, currently have CV outcome trial data available. The Evaluation of Lixisenatide in Acute Coronary Syndrome Trial showed that the addition of lixisenatide to standard care did not significantly alter the rate of major CV events (74). In contrast, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) Study and the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), fewer participants reached the primary composite CV end point in the liraglutide and semaglutide groups compared with those receiving placebo (hazard ratio, 0.87; $P=0.01$ for superiority and hazard ratio, 0.74; $P<0.001$ for noninferiority, respectively) (75,76). Notably, similar benefits on CV outcomes were observed in the LEADER Study and the SUSTAIN-6 subsets with moderate to severe CKD. Studies in patients with DKD have additionally shown that liraglutide lowered albuminuria levels in patients with normal kidney function or early-stage CKD and showed improved glycemic control in CKD.

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Figure 7. | Normal and diabetic nephron with altered renal hemodynamics.
Table 4. Studies of novel treatments for diabetic kidney disease

<table>
<thead>
<tr>
<th>Name of the Study</th>
<th>Tested Intervention/Drugs</th>
<th>Study Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuttle et al., 2005 (68)</td>
<td>Ruboxistaurin (PKC inhibitor)</td>
<td>DM2, macroalbuminuria</td>
<td>Decreased albuminuria, stabilized kidney function</td>
</tr>
<tr>
<td>PIONEER (81)</td>
<td>PYR-311 (anti-AGE treatment)</td>
<td>DM2, HTN, 1.3≤SCr≤3.0 mg/dl, protein-to-creatinine ratio ≥1200 mg/g</td>
<td>Halted</td>
</tr>
<tr>
<td>PREDIAN (70)</td>
<td>Pentoxifylline (anti-inflammatory, antifibrotic action)</td>
<td>DM2, eGFR=15–60 ml/min per 1.73, UAE&gt;300 mg/24 h</td>
<td>Pentoxifylline group: eGFR decline 4.3 ml/min per 1.73 m² less than control group; mean difference in albuminuria of 21%</td>
</tr>
<tr>
<td>Study to Test Safety and Efficacy of Baricitinib in Participants with Diabetic Kidney Disease (69)</td>
<td>Baricitinib, JAK1/2 inhibitor</td>
<td>DM2, eGFR=20–75 ml/min per 1.73 m², macroalbuminuria</td>
<td>Albuminuria reduction by 40% in the highest treatment group; no effect on eGFR</td>
</tr>
<tr>
<td>RADAR and RADAR/JAPAN (71)</td>
<td>Atrasentan (ETA)</td>
<td>DM2, eGFR=30–75 ml/min per 1.73 m², UACR=300–5000 mg/g</td>
<td>35% Reduction of albuminuria</td>
</tr>
<tr>
<td>SONAR, ongoing (72)</td>
<td>Atrasentan (ETA)</td>
<td>HTN, eGFR=15–90 ml/min per 1.73 m², UACR&gt;300–&lt;5000 mg/g</td>
<td>Ongoing</td>
</tr>
<tr>
<td>PERL, ongoing (82)</td>
<td>Allopurinol (xanthine oxidase)</td>
<td>DM1, eGFR=40–99 ml/min per 1.73 m², UAE=18–5000 mg/dl</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ARTS-DN, 2015 (83)</td>
<td>Finerenone (steroid mineralocorticoid receptor antagonist)</td>
<td>DM2, UACR=30 mg/g, eGFR&gt;30 ml/min per 1.73 m²</td>
<td>No difference in eGFR, 17%–40% albuminuria reduction dose dependent</td>
</tr>
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SCr is in milligrams per deciliter. Protein to creatinine ratio is in milligrams per gram. eGFR is in milliliters per minute per 1.73 m². UAE is in milligrams per day. UACR is in milligrams per gram. PKC, protein kinase C; DM2, diabetes mellitus type 2; PIONEER, A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Pyridostin (Pyridoxamine Dihydrochloride) in Subjects With Nephropathy Due to Type 2 Diabetes; PYR-311, pyridoxamine-311; AGE, advance glycation end product; HTN, hypertension; SCr, serum creatinine; PREDIAN, Effect of Pentoxifylline on Renal Function and Urinary Albumin Excretion in Patients with Diabetic Kidney Disease; UAE, urine albumin excretion; JAK1/2, Janus kinases 1/2; RADAR, Reducing Residual Albuminuria in Subjects With Diabetes and Nephropathy With Atrasentan—A Phase 2b, Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Safety and Efficacy; RADAR/JAPAN, RADAR in Japan; ETA, endothelin A; UACR, urinary albumin-to-creatinine ratio; SONAR, A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects With Type 2 Diabetes and Nephropathy; PERL, A Pilot Study of Allopurinol to Prevent GFR Loss in Type 1 Diabetes; DM1, diabetes mellitus type 1; ARTS-DN, A Randomized, Double-blind, Placebo-controlled, Multi-Center Study to Assess the Safety and Efficacy of Different Oral Doses of BAY94-8862 in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Nephropathy.
<table>
<thead>
<tr>
<th>Name of the Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (84)</td>
<td>Saxagliptin (DPP-4 inhibitor)</td>
<td>DM2, HbA1c≥6.5%, high risk for CV events</td>
<td>Improvement in and/or less deterioration in ACR categories from baseline to end of trial ($P=0.02$, $P&lt;0.001$, and $P=0.05$ for normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively); no changes in eGFR</td>
</tr>
<tr>
<td>CARMELINA (85)</td>
<td>Linagliptin (DPP-4 inhibitor)</td>
<td>DM2, 6.5%≤HbA1c≤10%, albuminuria, macrovascular complications, eGFR&gt;15 ml/min per 1.73 m²</td>
<td>In progress, estimated completion in January of 2018</td>
</tr>
<tr>
<td>LEADER (75)</td>
<td>Liraglutide (GLP-1 receptor agonist)</td>
<td>DM2, HbA1c&gt;7%, eGFR&lt;60 ml/min per 1.73 m², CV coexisting disease</td>
<td>Lower incidence of nephropathy (new-onset albuminuria, doubling of SCr and CrCl&lt;45 ml/min per 1.73 m²; need for RRT; death to renal causes [1.5 number of events per 100 patients per year versus 1.9 number of events per 100 patients per year; $P=0.003$])</td>
</tr>
<tr>
<td>AWARD-7, (86)</td>
<td>Dulaglutide (GLP-1 receptor agonist)</td>
<td>DM2, 7.5%≤HbA1c≤10.5%, 15≥eGFR&lt;60 ml/min per 1.73 m²</td>
<td>In progress, estimated completion in July of 2018</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME (78)</td>
<td>Empagliflozin (SGLT-2 inhibitor)</td>
<td>DM2, eGFR&lt;30 ml/min per 1.73 m², high CV risk</td>
<td>44% Relative risk reduction of doubling of SCr (1.5% versus 2.6%); 38% relative risk reduction of progression to macroalbuminuria (11.2% versus 16.2%); 55% relative risk reduction of initiation of RRT (0.3% versus 0.6%); slowing GFR decline (annual decrease 0.19±0.11 ml/min per 1.73 m²; $P=0.001$)</td>
</tr>
<tr>
<td>CREDENCE (87)</td>
<td>Canagliflozin (SGLT-2 inhibitor)</td>
<td>DM2, 6.5%≤HbA1c≤12%, high CV risk, 300 mg/g≥UACR&lt;5000 mg/g, 30≥eGFR&lt;90 ml/min per 1.73 m²</td>
<td>In progress, estimated completion in June of 2019</td>
</tr>
</tbody>
</table>

eGFR is in milliliters per minute per 1.73 m². UACR is in milligrams per gram. SAVOR-TIMI, Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications; DPP-4, dipeptidyl peptidase-4 inhibitor; DM2, diabetes mellitus type 2; HbA1c, hemoglobin A1c; CV, cardiovascular; ACR, albumin-to-creatinine ratio; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; GLP-1, glucagon-like peptide-1; Scr, serum creatinine; CrCl, creatinine clearance; AWARD-7, A Study Comparing Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes (T2D) and Moderate or Severe Chronic Kidney Disease (CKD); EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; SGLT-2, sodium-glucose cotransporter 2; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy; UACR, urine albumin-to-creatinine ratio.
stage 3 (75). Recently released data from clinical trials of semaglutide and dulaglutide consistently show reduced risk of albuminuria onset and progression (75,76). The consistency of these data across glucagon-like peptide-1 receptor agonists persuasively suggests a class effect of protection from DKD. The mechanisms of action may be multifactorial and include glycemic control, weight control, and direct effects on the kidney.

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients, a sodium-glucose cotransporter 2 inhibitor, empagliflozin, also showed significantly lowered rates of death from CVD causes (38% relative risk reduction), hospitalization for heart failure (35% relative risk reduction), and death from any cause (32% relative risk reduction) compared with placebo (77,78). Analysis of predefined secondary outcomes showed that empagliflozin also slowed progression of DKD and lowered rates of clinically relevant kidney outcomes among patients with CKD stages 2–4 (78) (Table 5).

Population-Based Approaches

Success of this strategy has been shown by recently available data from the Centers for Disease Control. A 54% decrease in diabetes-related kidney failure occurred between the years 1996 and 2013 among American Indians, a group with a historically high prevalence of diabetes and DKD. Interventions leading to this change included systematic implementation of guidelines for treatment of hypertension and diabetes, regular albuminuria testing, use of ACE inhibitors and ARBs, services to support nutrition, physical activity, and diabetes education (79).

Conclusion

Since the discovery of insulin in the 20th century, research has made significant strides toward understanding and improving the clinical management of diabetes. Although these advances have meaningfully improved outcomes for diabetes complications, such as CVD, these improvements have not translated nearly as well to DKD or ESRD (80). In response, the International Society of Nephrology has convened a Global Kidney Health Initiative to call attention to kidney diseases overall. Key collaborative stakeholders in the quest to fight DKD should include patients, health care providers and payers, advocacy groups, scientists, and governmental agencies. Advocacy and a call to action are essential to effective dissemination and implementation of current best practices. Using public health and population approaches in clinical practice and promoting meaningful and strategic research will be key to improving health outcomes for people with diabetes and DKD.

Disclosures

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