REVIEW ARTICLE

An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines

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Abstract

Diabetic nephropathy (DN) is a major healthcare challenge. It occurs in up to 50% of those living with diabetes, is a major cause of end-stage kidney disease (ESKD) that requires treatment with dialysis or renal transplantation, and is associated with significantly increased cardiovascular morbidity and mortality. DN is a clinical syndrome characterized by persistent albuminuria and a progressive decline in renal function, but it is increasingly recognized that the presentation and clinical course of kidney disease in diabetes is heterogeneous. The term diabetic kidney disease (DKD) is now commonly used to encompass the spectrum of people with diabetes who have either albuminuria or reductions in renal function. In this article, the clinical presentation and approach to diagnosis of DKD will be discussed, as will its prognosis. The general principles of management of DKD will also be reviewed with reference to current international guidelines.

1 | INTRODUCTION

Diabetic nephropathy (DN) is a clinical syndrome characterized by persistent albuminuria and a progressive decline in renal function, and the term infers the presence of a typical pattern of glomerular disease. DN is reported to occur in 20% to 50% of those living with diabetes and is the single commonest cause of end-stage kidney disease (ESKD) in many populations, accounting for 28% of those commencing renal replacement therapy (RRT) in the United Kingdom,[1] with corresponding figures of 44% in the United States and 38% in Australia.[2] DN is typically associated with arterial hypertension and increased cardiovascular morbidity and mortality; outcomes for people with type 1 (T1DM) or type 2 (T2DM) diabetes who develop DN are significantly worse than those who do not. Despite the large and increasing number of people affected by these sometimes devastating consequences, DN is also an area that has seen significant therapeutic advances. Well-evidenced interventions, such as inhibition of the renin-angiotensin-aldosterone-system (RAAS), have contributed to

sustained improvements in patient outcomes over the last four decades.[3,4] There is increasing awareness that DN is not always relentlessly progressive, that there is significant variation in individual rates of chronic kidney disease (CKD) progression and that regression of albuminuria is not uncommon.[5] The emergence of newer therapeutic agents, such as the sodium-glucose cotransporter 2 inhibitors (SGLT2i), provide further optimism.

As the first in this series of articles, this article will provide an overview of the diagnosis, prognosis and treatment goals for DN. This will include a discussion of the heterogeneity of kidney disease that can occur in people with diabetes, particularly in T2DM, and how the classical paradigm of DN is not always observed in clinical practice. Indeed, the term diabetic kidney disease (DKD) is increasingly used to refer to persistent albuminuria or a reduction in eGFR in the setting of diabetes and moves away from connotations of specific underlying renal pathology. When discussing albuminuria, we will follow the recommendations of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD, which suggested the use of three

TABLE 1 KDIGO definitions of albuminuria category[6]

Measure	Urinary albumin categories		
	Normal or mildly increased (A1)	Moderate increased (A2)	Severely increased (A3)
Albumin excretion rate (mg per 24 h)	<30	30-300	>300
Albumin-to-creatinine ratio (mg/g)	<30	30-300	>300
Albumin-to-creatinine ratio (mg/mmol)	<3	3-30	>30

Note: KDIGO guidelines adopt conversion rates between the different albuminuria categories that have been rounded for pragmatic reasons and clinical applicability. The exact conversion rate between ACR values in mg/g and mg/mmol is ×0.1131.

categories to describe severity of albuminuria and that the terms micro- and macro-albuminuria should no longer be used.[6] These categories are summarized in Table 1, with urinary albumin-to-creatinine ratio (ACR) values of 3 to 30 mg/mmol or 30 to 300 mg/g (corresponding to micro-albuminuria) referred to as "moderately increased" (A2); and ACR values of >30 mg/mmol (>300 mg/g), corresponding to macro-albuminuria, referred to as "severely increased" (A3).

2 | DIAGNOSIS

2.1 | Clinical features of DN

The hallmark of established DN is persistent albuminuria (category A3, severely increased), with co-existing retinopathy and no evidence of alternative kidney disease. In T1DM, this definition is highly specific, that is, if these features are present then the histological picture will almost certainly be that of diabetic glomerulopathy.[7] It is rare for DN to manifest in people with T1DM in the first 10 years following diagnosis, but between 10 and 20 years the incidence of DN is approximately 3% per year. Overall, approximately 15% of people with T1DM have severe (A3) albuminuria and a further 15% display moderate (A2) albuminuria.[2] After 20 years, the incidence rate declines so that people with normal renal function and normal urinary albumin excretion after 30 years of T1DM are at lower risk of developing DN.[8] Therefore, the risk of developing DN varies between individuals and is dependent not only on duration of T1DM, but it is also influenced by other factors, such as glycaemic control, blood pressure and genetic susceptibility.

T2DM accounts for 90% of diabetes globally, so the majority of people who develop DN do so because of T2DM.[9] The epidemiology of DN in T2DM shows more variation than in T1DM, with a wider range of reported prevalence rates across different countries and ethnic groups.[2] For example, a cross-sectional study that randomly screened 28 538 people from 33 countries who had T2DM but without known kidney disease reported that the prevalence rates of albuminuria were a third higher in Asian and Hispanic groups (55%) as compared to

Caucasians (40.6%).[10] There is likely to be a polygenic component that explains some of this variation between ethnic groups. This is supported by observations of familial clustering of DN and genome-wide association studies that have identified genetic susceptibility loci.[11]

There is also greater heterogeneity in T2DM in clinical presentation and in the underlying pathological lesions of DKD. This includes greater variation in the timing between diagnosis of diabetes and development of DN, with up to 3% of those with T2DM having already developed albuminuria at time of diagnosis. This usually results from a period of preceding undiagnosed diabetes or pre-diabetes,[12] although it can occasionally signify alternative renal pathology. Furthermore, DN occurs without co-existing retinopathy in as many as a third of cases, a scenario that is much more common in T2DM as compared to T1DM.[13,14] Additionally, while the presence of persistent albuminuria with co-existing retinopathy in T2DM indicates DN in the majority of cases,[14] this is not always so. Prospective biopsy studies of T2DM in which kidney biopsies were taken for research (as opposed to clinical reasons that introduce selection bias and increase the risk of finding alternative diagnoses[15]) have reported that a small proportion (<10%) of those with both severe (A3) albuminuria and retinopathy had non-diabetic forms of kidney disease.[13,16] However, this has not been a universal finding, with other studies reporting 100% specificity for the combination of severe (A3) albuminuria and retinopathy to predict the classical histological appearance of DN.[14] Some of this variation may reflect differences in the epidemiology of DN in T2DM in different populations, but study design, biopsy practice and the generally small sample sizes of studies in which renal biopsy is performed may also contribute. Of greater importance is the growing appreciation of the wider spectrum of renal pathology that underlies DKD in T2DM. In one study of 52 patients with T2DM and clinical features of DN (urine protein excretion 900-9200 mg/24 h, serum creatinine 80-796 μmoL/L [0.9-9 mg/dL], no data on retinopathy), renal biopsy findings varied between those with classical diabetic glomerulopathy (36.5%), predominantly ischaemic changes (30.8%) and another glomerular disease superimposed on DN (32.7%).[17] Similar findings were reported in 34 people with T2DM and moderate (A2) albuminuria, in whom diabetic changes were seen in 10 biopsies (29.4%), ischaemic/fibrotic changes in 14 (41.2%) and minimal pathology reported in the remaining 10 (29.4%).[18]

2.2 | Histological features of DN

Kidney biopsy is used to make the diagnosis in only a minority of cases of DN, but the typical histological features are described in an international classification system. Classes I to IV are characterized by thickening of the glomerular basement membrane, mesangial expansion, nodular sclerosis (Kimmelstiel-Wilson lesion) and severe glomerulosclerosis, respectively.[19] In addition to these characteristic glomerular features, interstitial fibrosis and tubular atrophy (IFTA), interstitial fibrosis, arteriolar hyalinosis and arteriosclerosis are frequently also present. The pathophysiology of DKD is discussed further elsewhere in this issue of Diabetes, Obesity and Metabolism.

2.3 | Moderately increased albuminuria (A2)

As well as indicating increased cardiovascular risk in both T1DM and T2DM,[20,21] the traditional paradigm is that the onset of moderately increased albuminuria (A2), previously termed microalbuminuria, predicts the onset of established DN.[22-25] A number of studies have reported this relationship in both T1DM and T2DM. Hovind et al recruited 286 people with T1DM between 1979 and 1984 who were followed prospectively for a median of 18 years.[25] Of the 79 who developed moderately increased (A2) albuminuria, 27 (34%) subsequently progressed to severe (A3) albuminuria. The authors reported that although spontaneous regression to normal albumin excretion did occur (in the absence of RAAS inhibitors), it was rare and was not observed once severe (A3) albuminuria had developed. Similar results are seen in a number of other observational studies and interventional trials, as well as in T2DM.[26] In the HOPE trial, in which participants at increased cardiovascular risk were randomized to ramipril or placebo, moderate albuminuria (A2) at baseline was present in 31.8% of the 3577 people with T2DM.[27] After 4.5 years, 225 (20%) participants with and 41 (2%) without baseline microalbuminuria developed overt nephropathy (relative risk [RR] 14, 95% CI 10–19, $P < .001$). These observations led to the conclusion that in many cases, moderate (A2) albuminuria represents the first clinically detectable stage of DN, which without intervention will progress to more advanced and less reversible stages of kidney disease in a significant proportion of affected individuals. This is also supported by the development of histological lesions of diabetic glomerulopathy by the time that moderate albuminuria is detected (and sometimes even before any clinical manifestations are apparent).[28] However, other data challenge this concept and suggest that the traditional paradigm of an inexorable progression from moderate albuminuria through severe albuminuria to progressive fall in eGFR is not seen in all people with DN. In particular, the rates of regression of albuminuria may be greater than previously appreciated in both T1DM and T2DM. Perkins et al reported regression of albuminuria in 386 people with T1DM and moderate (A2) albuminuria who were evaluated over a 6-year follow-up period.[5] After 6 years, the cumulative incidence of progression to severe (A3) albuminuria was 19% (95% CI 14-23%). Over the same time period, the cumulative proportion of those that regressed to normo-albuminuria was 59% (95% CI 54-64%), an observation that was not explained by RAAS inhibition. In a separate study, regression from moderate (A2) albuminuria to normo-albuminuria in a cohort of T2DM was reported to occur in 23.6% of cases.[29]

2.4 | Methodological aspects of assessing albuminuria

In addition to varying clinical trajectories, the assessment of albuminuria is made more complex due to marked intra-individual variation in albumin excretion. In a cohort of proteinuric CKD patients who submitted three separate urine samples, the coefficient of variation for ACR was 29.7% (in random samples) and 32.5% (in early morning samples).[30] This variability is also seen with measurements of urine albumin excretion
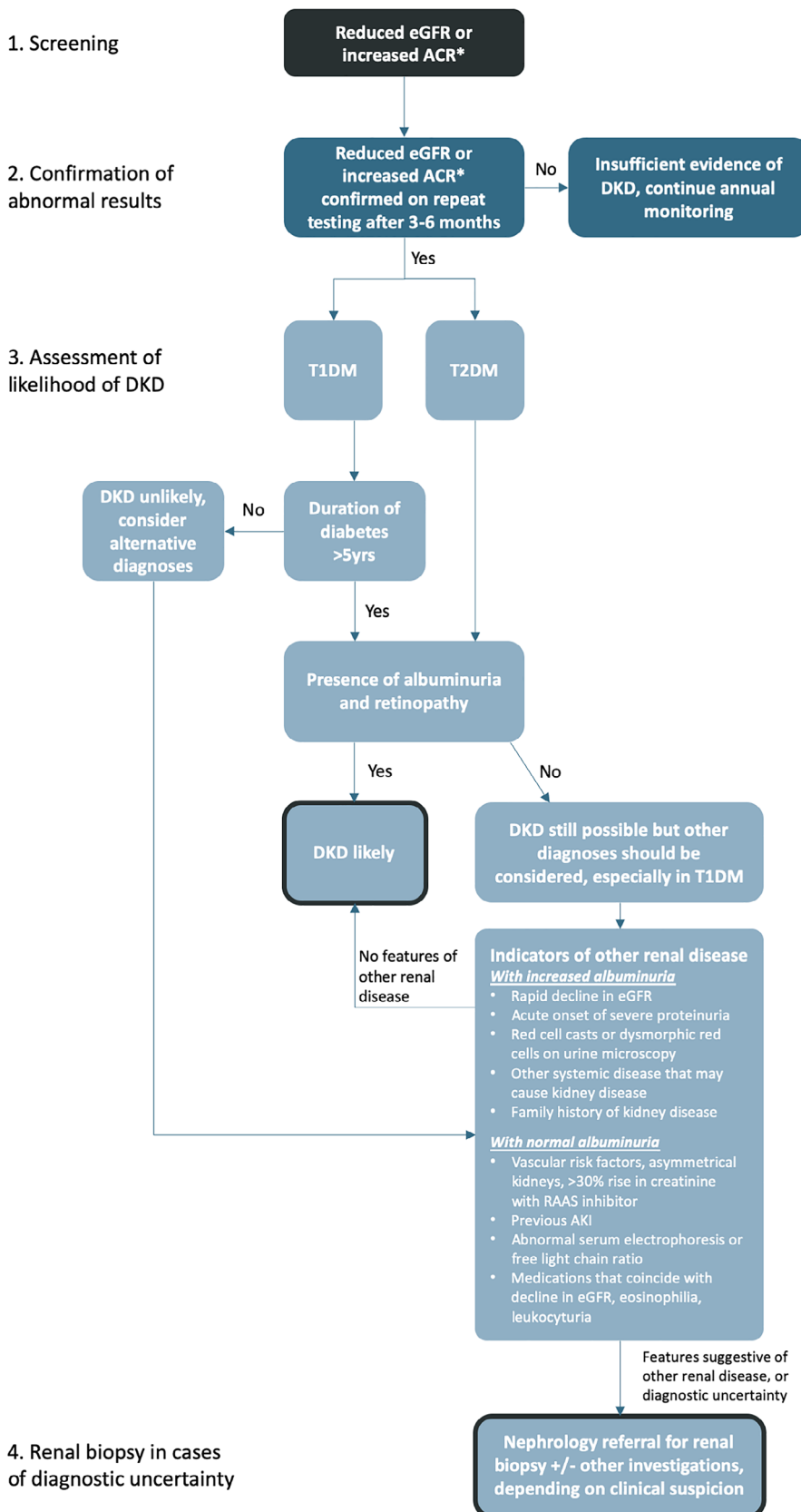
rate, where it is further exaggerated by the challenges of accurate collection of timed or 24-hour urine samples.[31] This, coupled to the inconvenience of measuring albumin excretion, means that ACR is the preferred method for assessing albuminuria in clinical practice. Most guidelines, including those from the American Diabetes Association (ADA), the National Institute for Health and Care Excellence (NICE) and the European Association for the Study of Diabetes (EASD) suggest annual screening with ACR to detect moderate (A2) albuminuria in all people with diabetes, with a requirement for repeat testing to confirm elevated results.[32-34] It is also important to consider this biological variation in ACR values when monitoring serial changes or response to treatment, and caution should be taken when interpreting change between two measures; examining serial trends is a more reliable approach. Finally, clinicians should be aware of conditions that may result in transient increases in albuminuria and risk erroneous diagnosis. These include urinary tract infection; active systemic infection/inflammation; heavy exercise in the preceding 12 to 24 hours; heart failure; severe hypertension; menstruation; and severe hyperglycaemia. In addition, urinary ACR results can be difficult to interpret in the setting of long-term urinary catheters and in those with an ileal conduit. Urine dipstick testing is not useful for quantifying albuminuria and is not recommended for monitoring the degree of albuminuria over time.[35]

2.5 | Non-albuminuric DKD

It is increasingly recognized that reductions in eGFR can occur in the setting of normal urinary albumin excretion in both T1DM and T2DM.[36,37] In general, non-proteinuric CKD often points towards aetiologies that are ischaemic in nature or in which tubulo-interstitial pathologies predominate.[38,39] However, non-proteinuric DN has also been described in association with the typical histopathological changes of diabetic glomerulopathy.[40,41] Yamanouchi et al retrospectively identified 526 renal biopsies from patients with eGFR values of <60 mL/min/1.73 m^2 that had the typical pathological findings of DN.[41] Of these, 88 (16.7%) had non-proteinuric DN (ACR <300 mg/g) and 438 (83.3%) had proteinuric DN (ACR ≥300 mg/g). In the group without overt proteinuria, 19 (3.6%) had normo-albuminuria, and 69 (13.1%) had moderately increased (A2) albuminuria. Nevertheless, as observed in many forms of CKD, it appears that the degree of proteinuria remains a strong predictor of risk of progression, and that non-proteinuric DN has a better prognosis.[42] In the study by Yamanouchi et al, those with non-proteinuric DN had less severe pathological lesions and lower blood pressure. Additionally, the non-proteinuric group had much better 5-year CKD progression-free survival of 86.6% (95% CI 72.5-93.8) compared with 30.3% (95% CI 22.4-38.6) for the proteinuric group ($P < 0.001$).[41] The lower risk of CKD progression or the development of ESKD in non-albuminuric DKD vs DN with significant albuminuria has been reported in a number of other studies.[43,44] However, this should not mask that the development of non-albuminuric DKD is a significant risk factor for death and major cardiovascular events compared to those without kidney disease; again risks are even greater when albuminuria is also

present.[45] There are several possibilities that may explain the occurrence of non-proteinuric DN. These include co-existing vascular disease or tubulo-interstitial fibrosis that in fact are the dominant processes, that eGFR decline has resulted from previous episodes of AKI (either recognized or subclinical) or that albuminuria has been reduced by RAAS inhibitors.[46] The challenge of diagnosing DN is

1. Screening

Reduced eGFR or increased ACR*

2. Confirmation of abnormal results

Reduced eGFR or increased ACR* confirmed on repeat testing after 3-6 months

No → Insufficient evidence of DKD, continue annual monitoring

Yes

3. Assessment of likelihood of DKD

T1DM   T2DM

DKD unlikely, consider alternative diagnoses ← No ← Duration of diabetes >5yrs

Yes

Presence of albuminuria and retinopathy

Yes → DKD likely

No → DKD still possible but other diagnoses should be considered, especially in T1DM

No features of other renal disease

Indicators of other renal disease
With increased albuminuria
- Rapid decline in eGFR
- Acute onset of severe proteinuria
- Red cell casts or dysmorphic red cells on urine microscopy
- Other systemic disease that may cause kidney disease
- Family history of kidney disease

With normal albuminuria
- Vascular risk factors, asymmetrical kidneys, >30% rise in creatinine with RAAS inhibitor
- Previous AKI
- Abnormal serum electrophoresis or free light chain ratio
- Medications that coincide with decline in eGFR, eosinophilia, leukocyturia

Features suggestive of other renal disease, or diagnostic uncertainty

4. Renal biopsy in cases of diagnostic uncertainty

Nephrology referral for renal biopsy +/- other investigations, depending on clinical suspicion

FIGURE 1 Schematic of a clinical approach for the diagnosis of diabetic kidney disease (DKD). * indicates ACR = urinary albumin creatinine ratio, albumin excretion rate is also appropriate. AKI, acute kidney injury; RAAS, renin-angiotensin-aldosterone system

further illustrated by an autopsy study in which 20 of 106 (19%) persons with T1DM or T2DM and with histological evidence of DN had no albuminuria and no ante-mortem diagnosis of DN.[47]

2.6 | Clinical approach to diagnosis of DKD

In many cases, DKD is a clinical diagnosis. A kidney biopsy is the gold standard test for diagnostic and prognostic information, but in most centres is usually only performed when an alternative renal pathology is suspected.

2.6.1 | Screening

DKD usually does not cause symptoms, so guidelines from the ADA and KDIGO group recommend that all people with diabetes should have renal function and albuminuria measured at diagnosis and annually thereafter in T2DM; in T1DM, this can start from 5 years after diagnosis.[32,48] Albuminuria is best assessed using ACR measurements on spot urine samples (ideally early morning samples); timed or 24-hour urine collections to measure albumin excretion are also appropriate although less convenient and more prone to collection errors. Renal function should be assessed using a serum-creatinine based eGFR calculation (CKD-EPI equation recommended due to its superior performance in the eGFR range 60-90 mL/min/1.73 m^2).

2.6.2 | Confirmation of persistent abnormalities

If a reduction in eGFR or an increase in albuminuria is detected, this should be confirmed on repeat testing over 3 to 6 months; a minimum of two elevated ACR levels more than 3 months apart are required before an individual is considered to have increased albuminuria.[32] This is to differentiate from transient changes as well as to account for the intra-individual variation that is seen in ACR. Similarly, two eGFR values below 60 mL/min/1.73 m^2 at least 90 days apart are required to make a diagnosis of CKD.

2.6.3 | Clinical diagnosis of DKD

In T1DM, a clinical diagnosis of DKD can be made when there is persistent moderate (A2) or severe (A3) albuminuria or a persistent reduction in eGFR to <60 mL/min/1.73 m^2, occurring at least 5 years after onset of diabetes. In over 95% of cases, diabetic retinopathy will also be present,[7] and there should be no clinical suggestions of alternative kidney disease (see later). Albuminuria is not required to make a diagnosis of DKD in the setting of a persistently reduced eGFR, but this clinical scenario should prompt consideration of other forms of non-albuminuric kidney disease (see later), as should albuminuria in the absence of retinopathy.

In T2DM, the clinical diagnosis can be more challenging due to the increased heterogeneity of clinical presentation, although the same principles of persistent albuminuria or persistently reduced eGFR apply. Again, albuminuria does not have to be present to make a diagnosis of DKD providing eGFR is persistently <60 mL/min/1.73 m^2. Longer duration of diabetes and presence of retinopathy are important pointers towards the diagnosis when they are present, but neither a short duration of diabetes nor absence of retinopathy are useful to rule out DKD in T2DM. It is therefore important to evaluate for features that may indicate alternative forms of kidney disease and proceed to renal biopsy when there is diagnostic uncertainty. This approach to diagnosis is summarized in Figure 1.

2.6.4 | Features that may indicate alternative forms of kidney disease

Non-diabetic forms of kidney disease may be suggested by the following:

- Atypical trajectory of eGFR decline or onset of albuminuria. Rapid declines in eGFR (>5 mL/min/year) or sudden onset of albuminuria are not typical of DN, nor is severe albuminuria in the first 5 years of T1DM. Looking at serial eGFR trends will help to identify previous episodes of AKI, which are increasingly recognized to be associated with CKD onset and progression.[49-51]
- Very severe albuminuria (ACR > 300 mg/mmol or > 3000 mg/g) or nephrotic syndrome. Although DN is a well-recognized cause of nephrotic syndrome, primary glomerular disease is more likely in this setting, particularly when the nephrotic syndrome has an acute onset.
- Active urinary sediment. Non-visible haematuria is not a classical finding in DN but can occur. The presence of haematuria on urinalysis is not particularly helpful and has poor ability to discriminate between diabetic and non-diabetic kidney disease with a c-statistic of only 0.59 (0.54-0.63).[52] However, the presence of red cell casts or dysmorphic red cells on urine microscopy is much more likely to signify an alternative pathology, typically a glomerulonephritis.
- Diagnosis of or clinical features that are suspicious for another systemic disease that commonly causes kidney disease (e.g., connective tissue disorders, HIV).
- Family history of non-diabetic forms of kidney disease.

2.6.5 | Differential diagnoses to consider in the setting of non-albuminuric DKD

Although non-albuminuric DN is well described, this presentation should prompt evaluation for the following:

- Ischaemic nephropathy. Suggested by vascular disease elsewhere, smoking history, hypertension, aortic disease or asymmetric kidneys on renal ultrasound. Sometimes, this scenario is incorporated under the umbrella term of DKD (ie, without renal biopsy), and several of the risk factors for ischaemic nephropathy are very common

in people with diabetes. Renovascular disease can also be suggested by large (>30%) declines in eGFR after initiation of RAAS inhibitors.

- Dysproteinaemia-related renal disease. There are a variety of renal diseases associated with dysproteinaemias that are initially screened for with serum electrophoresis and assay of serum free light chains. This includes monoglonal gammopathy of renal significance, defined as a clonal proliferative disorder that produces a nephrotoxic monoclonal immunoglobulin, but does not meet the treatment criteria for a specific haematological malignancy.[53]

- Previous episodes of AKI.

- Tubulointerstitial nephritis (TIN), classically associated with eosinophilia and urinary leukocytes but can present with normal urinary sediment. TIN is often due to medications (eg, non-steroidal anti-inflammatory drugs, proton-pump inhibitors, antibiotics, diuretics), and a careful medication history to establish temporal links between initiation of culprit medications and onset of eGFR decline can be useful. Diagnosis requires kidney biopsy.

3 | PROGNOSIS

People with diabetes who develop kidney disease are at increased risk of CKD progression, ESKD, cardiovascular events and mortality.[20,54] While these high-level statements are undisputed, there are some important methodological considerations relating to the underlying data. These include the influence of ethnicity and clinical variables (eg, blood pressure, glycaemic control, nephron endowment) on rates of CKD progression, so differences in baseline characteristics of study populations may lead to variation in reported outcome rates. The effects from clinical uptake of new effective interventions that slow progression of DN or alter cardiovascular risk, alongside updated guidelines that have advocated more aggressive management approaches (eg, for blood pressure and cholesterol lowering), have impacted upon prognosis over time. Over the last four decades, sustained improvements in patient outcomes have been reported, as well as a differing clinical course of DN; one example is the increasing recognition of regression of albuminuria and stability of eGFR in some people with DN.[3,4] While T1DM is commonly detected at an early point in the natural history of the condition the same is not true for T2DM, making it harder to compare the natural history of DKD between these groups, in addition to the obvious differences in age and baseline comorbidity between T1DM and T2DM populations. Finally, the technical aspects of GFR measurement and estimation as well as assessment of albuminuria, discussed in depth elsewhere, can have important effects on the assessment of CKD progression.[54-58]

In T1DM, there are a number of studies that suggest the development of kidney disease is a major factor underlying increases in mortality. The Finnish Diabetic Nephropathy (FinnDiane) study reported mortality rates in a cohort of 4201 adults with T1DM over a 7-year period, and excess mortality was only observed in those with DKD.[21] Additionally, there was a gradated relationship between severity of renal disease and outcomes: individuals with normo-albuminuria showed no excess mortality beyond the general population (standardized mortality ratio [SMR] of 0.8, 95%CI 0.5-1.1), but the presence of moderate (A2) albuminuria, severe (A3) albuminuria and ESKD was associated exponential increases in SMRs of 2.8, 9.2 and 18.3, respectively. These results are similar to historical data from several decades ago, also suggesting that excess mortality in T1DM was most apparent in those who developed advanced CKD, and in particular those who progressed to ESKD.[59] These high relative risks between people with T1DM who do and do not develop DN are striking, and in part reflect the younger age of the T1DM population and relatively low event rates in the people without kidney disease.

A meta-analysis performed by the CKD Prognosis Consortium provided the opportunity to compare outcomes in people with and without diabetes across similar levels of eGFR and albuminuria, with pooled data from large (>1000 participant) cohort studies that together included over a million participants (13% of these had diabetes, presumed mainly T2DM).[20] As expected, rates of ESKD, mortality and CV mortality were higher with increasing ACR and lower eGFR values. While diabetes as a whole was associated with increased mortality (1.2-1.9 times higher), the risk of mortality was similar between diabetes and non-diabetes groups at fixed eGFR and ACR reference points. In other words, the absolute risks of ESKD, mortality and cardiovascular mortality are higher in CKD patients with diabetes as compared to those without diabetes, but the relative risks of these outcomes are similar throughout the ranges of eGFR and ACR, again showing the importance of the development of CKD upon increasing the risk of adverse outcomes. In T2DM, an important observation is that the risk of mortality and CV mortality is substantially higher than the risk of progressing to ESKD, even though the relative risks between T2DM with and without DN are lower than those observed in T1DM due to the higher event rates in the population without kidney disease.[60]

There is a wide variation in the rates of CKD progression in DKD in terms of both eGFR trajectory and rates of progression to ESKD. Extended follow-up of participants in the Diabetes Control Complications Trial (DCCT) reported an average change in eGFR of -1.37 mL/min/1.73 m^2/year, in a population of T1DM who at baseline had a mean duration of diabetes of 5.9 years and had normal albumin excretion and eGFR.[61] However, after the onset of severe (A3) albuminuria, the average decline in eGFR was more rapid at -5.4 mL/min/1.73 m^2/year,[62] although within this there was wide inter-individual variation. After 10 years of follow up, 32% of participants with severe (A3) albuminuria still had an eGFR >60 mL/min/1.73 m^2, whereas another 16% had progressed to ESKD, the latter equating to an incidence rate of ESKD of 1.4 events/100 person-years.[62] A combined analysis of four cohort studies that included 1518 people with T1DM and DN (persistent severe (A3) albuminuria and CKD stages G1-3) reported incidence rates of ESKD of between 2.2 and 4.1 events/100 person-years.[63]

In T2DM, variation in reported rates of CKD progression and incidence of ESKD is also seen. In a prospective observational study, Rossing et al followed 227 people with T2DM and severe (A3) albuminuria for an average of 6.5 years (minimum follow up 3 years), in whom GFR was measured annually with Chromium-EDTA clearance.[64] The mean decline in eGFR was −5.2 mL/min/year, but a standard deviation of 4.1 mL/min/year suggests that the distribution of eGFR change encompassed declines of as much as −13.4 mL/min/year through to increases of +3.0 mL/min/year. In the Irbesartan Diabetic Nephropathy Trial (IDNT), which randomized people with T2DM, reduced eGFR and severe (A3) albuminuria to irbesartan, amlodipine or placebo, the mean change in creatinine clearance was −5.5 mL/min/1.73 m^2/year in the irbesartan-treated group.[65] Similarly, in the losartan arm of the Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) trial, the average change in eGFR was −4.4 mL/min/1.73m^2/year.[66] Rates of ESKD also show variation. One informative study recruited people from a community health setting and included >42 000 people with diabetes, of whom 8618 (20.2%) had estimated GFR <60 mL/min/1.73 m^2, 7715 (18.0%) had albuminuria and 2641 (6.2%) had both.[67] The rates of progression to ESKD varied from 0.02 to 22 events/100 person-years, with baseline eGFR and degree of albuminuria critical determinants of the rate of progression. This study also highlights the competing risk of mortality, with eGFR and albuminuria also major determinants of survival. Overall, 5 times as many people died as reached ESKD.

A number of clinical characteristics have been described that are associated with higher risk of progression of DKD including severity of albuminuria, rate of eGFR decline, systolic blood pressure, haemoglobin A1c, duration of diabetes, serum uric acid, concomitant microvascular complications and positive family history.[68] Tools have been developed to assist clinicians in estimating the risk of progression to ESKD in people with CKD, including DKD. The Kidney Failure Risk Equation uses only four variables (age, sex, eGFR and UACR) to predict 2- and 5-year risk of ESKD. Its good performance has been externally validated in a large study population of 721 357 drawn from 31 cohort studies (c-statistic 0.88), and subgroup analysis confirmed that it performed equally well in people with and without diabetes.[69] In patients with more advanced stage G4 CKD, a risk prediction tool that includes a diagnosis of diabetes has been developed to simultaneously predict the 4-year risks of cardiovascular events, ESKD or death.[70]

4 | TREATMENT GOALS

There are two overarching aims in the management of DN: preserving renal function to reduce the risk of ESKD; and reducing the risks of cardiovascular events and mortality. In addition, people with DKD are also more likely to experience retinopathy, neuropathy and foot ulcers so increased vigilance for these complications is important. Treatment guidelines have been developed by several international and national organizations and are summarized in Table 2.

4.1 | Lifestyle measures

Non-pharmacological interventions are an essential component of any strategy to improve outcomes in patients with DKD and should include weight loss, increased physical activity, reduction in dietary sodium intake and smoking cessation. Unfortunately, these goals are notoriously difficult to achieve; it is essential for patients to be encouraged to be actively involved in their own management and to receive support in achieving mutually agreed treatment goals.

4.2 | Lipid lowering and CV risk reduction

The onset of kidney disease in people with diabetes portends a significant increase in the risk of cardiovascular mortality, and as such aggressive risk factor modification is warranted in all patients. This includes smoking cessation and lipid lowering; the importance of blood pressure lowering is discussed later. There is ongoing debate as to whether lipid lowering therapy has a direct benefit in slowing the progression of DN. In CKD, it has been suggested that hyperlipidaemia may contribute to glomerulosclerosis, and while some studies have suggested that lipid lowering may help to preserve eGFR or reduce albuminuria this has not been conclusively proven.[73-75] In reality, the point may be slightly academic as patients should receive lipid lowering therapy for cardiovascular risk reduction, and it is a component of combination therapy that has been shown to improve outcomes in the Steno-2 trial (discussed later).[76-78]

4.3 | Glycaemic control

Improving glycaemic control has beneficial effects upon the development and progression DN. The DCCT randomized 1441 people with T1DM to intensive insulin therapy (target HbA1c <6.05%, achieved 7.3%) or standard therapy (achieved HbA1c 9.1%).[79] After a mean follow-up of 6.5 years, there was a significant reduction in the development of moderate (A2) and severe (A3) albuminuria in the intensive arm, as well benefits for other microvascular complications. With further follow-up of participants after both control and intervention arms moved to intensive control targets, the development of moderate (A2) and severe (A3) albuminuria remained lower in the intensive arm for an additional 4 years.[80] Long-term outcome assessment has also shown that intensive insulin treatment slowed eGFR decline and reduced the proportion of people who developed a persistent reduction in eGFR to <60 mL/min/1.73 m^2 (50% risk reduction with intensive therapy).[81] In addition, studies performing renal biopsy in people who have undergone pancreas transplantation have shown that the histological changes of diabetic glomerulopathy can reverse, although this may require upwards of 10 years of normoglycaemia.[82]

TABLE 2 Summary of treatment goals for key therapeutic targets in international guidelines on diabetes and CKD

	KDIGO (2012)[6]	EASD (2019)[33,34]	ADA (2020)[32]	NICE (2014)[34,35,71,72]
Dietary sodium	<2 g/day (or < 5 g/day salt)	-	<2300 mg/day	-
Physical activity	>150 min/week moderate intensity	>150 min/week aerobic and resistance activity	>150 min/week aerobic activity	>150 min/week moderate intensity, aerobic activity
Weight loss	Achieve healthy weight (BMI 20-25 kg/m²)	Weight stabilization if BMI ≥ 25 kg/m²	>5% weight loss if BMI ≥ 25 kg/m²	Initial target 5-10% weight loss if BMI ≥ 25 kg/m²
Smoking cessation	Recommended	Obligatory	Advise against tobacco and e-cigarettes	Recommended
Blood pressure	<130/80 if albuminuria[a] present	SBP < 130 mmHg but not <120 DBP < 80 mmHg but not <70 If >65 years: SBP 139-130 mmHg	<130/80 mmHg if 10 year CV risk ≥15% <140/90 if lower risk	<130/80 mmHg
RAASi	All patients with albuminuria[a]	First-line antihypertensive especially if albuminuria[a] or LVH present	First-line antihypertensive if albuminuria[a] present	First-line antihypertensive if albuminuria[a] present
HBA1C[b]	<7% for most patients; Higher target if risk of hypoglycaemia, severe comorbidities, or limited life expectancy	<7% for most patients; <6.5% for early stages of diabetes and younger patients; <8% in elderly or those with severe multimorbidity	<7% for most patients; <6.5% if low risk of hypoglycaemia; <8% if high risk of hypoglycaemia of multimorbidity	<7.0% if risk of hypoglycaemia; <6.5% if low risk of hypoglycaemia; Relax target if: • High risk of hypoglycaemia • Reduced life expectancy • Severe multimorbidity • Elderly or frail
Lipid management	Statin therapy for all patients with diabetes and CKD	Statin therapy as first line; Moderate CV risk: LDL-C < 2.6 mmol/L (100 mg/dL); High CV risk: LDL-C < 1.8 mmol/L (70 mg/dL); Very high CV risk: LDL-C < 1.4 mmol/L (55 mg/dL)	High-intensity statin for all patients aged 50-70 years with multiple CV risk factors; Moderate intensity statin for patients aged 40-75 years without additional CV risk factors	Statin therapy for all patients with diabetes and CKD
Nephrology referral criteria	• CKD stage 4 • CKD progression[c]	-	• CKD stage 4 • Renal diagnosis uncertain • Rapid CKD progression	• CKD 4 • >25% reduction in GFR plus progression to the next CKD category • GFR reduction of >15 mL/min/1.73 m² in 12 months

Note: Details presented here are a summary only. Guidelines emphasize the need for an individualized approach that includes careful consideration of the risks vs benefits of therapy goals and discussion with patients. For further details, please refer to the guideline documents. It should also be noted that the 2019 KDIGO Clinical Practice Guideline on the Management of Diabetes in CKD is currently being finalized for publication, which may differ from the summary presented.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; EASD, European Association for the Study of Diabetes; GFR, glomerular filtration rate; HBA1C, haemoglobin A1C; KDIGO, Kidney Disease Improving Global Outcomes; LDL-C, low density lipoproptein cholesterol; NICE, National Institute for Health and Care Excellence; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure.

[a]Albuminuria is defined as urine albumin excretion >30 mg/day or equivalent (urine albumin-to-creatinine ratio > 3 mg/mmol or > 30 mg/g).

[b]HBA1C values: 8% = 64 mmol/mol; 7.0% = 53 mmol/mol; 6.5% = 48 mmol/mol.

[c]CKD progression defined as >25% reduction in GFR plus progression to the next CKD category; rapid progression defined as a reduction in GFR >5 mL/min/1.73 m²/year.

In T2DM, the evidence is a little more mixed. The United Kingdom Prospective Diabetes Study (UKPDS) randomized 3867 people to intensive control (using oral agents or insulin), or to diet control only. There was a smaller separation in HbA1c levels between the study arms (7.0% vs 7.9%), and while overall events were improved in the intensive arm, differences were not observed in development of moderate or severe albuminuria or doubling of serum creatinine.[83] More positive results were reported from the ADVANCE trial, which randomized 11 140 people with T2DM to intensive (HbA1c 6.5%) or standard (HbA1c 7.3%) glycaemic control.[84] With intensive control, reductions were seen in combined macrovascular and microvascular complications and in particular the incidence or worsening of DN was reduced (4.1% vs 5.2%; hazard ratio 0.79; 95% CI 0.66-0.93). This was defined as the development of severe (A3) albuminuria, doubling of the serum creatinine to at least 200 μmoL/L, the need for renal replacement therapy (RRT), or death due to renal disease. The effect was mainly due to a reduction in the development of severe (A3) albuminuria, with trends towards reductions in the need for RRT or death from renal causes, but no difference in doubling of serum creatinine. The Veterans Affairs Diabetes Trial also reported a reduced rate in the development or worsening of albuminuria with intensive vs standard glycaemic control (9.1% vs 13.8% respectively), although there were no differences between groups in any of the other endpoints, including worsening of renal function, ESKD, cardiovascular events or mortality.[85] Conversely the ACCORD trial, which randomized 10 251 people to intensive or standard glycaemic control, was discontinued early due to higher mortality in the intensive therapy arm and no evidence of benefit elsewhere.[86]

In summary, intensive glycaemic control can reduce the risk of the onset of DN and slows its progression when it has occurred, although does so at the expense of more hypoglycaemic events. This appears true for both types of diabetes although the evidence is clearer in T1DM, and the benefit of more intense glycaemic control seems to decrease at more advanced stages of DKD. However, intensive glycaemic control does not completely eliminate the risk of DN occurring, and there are no data to show that improved glycaemic control reduces the risk of progression to ESKD. The target for glycaemic control should therefore be personalized after careful discussion of the individual risks versus benefits.

For T2DM, the choice of glucose lowering agent also is important. SGLT2i have been shown convincingly to reduce the risk of ESKD, doubling of serum creatinine or death from renal or cardiovascular causes (relative risk reduction 30%; hazard ratio, 0.70; 95% confidence interval, 0.59 to 0.82) in people with T2DM, albuminuric DN (eGFR 30-90 mL/min/1.73 m^2 and severe (A3) albuminuria) and receiving RAAS inhibitors,[87] and are now recommended in ADA Guidelines, "SGLT2i should be considered for patients with type 2 diabetes and CKD who require another drug added to metformin to attain target A1C or cannot use or tolerate metformin"[32] and the EASD Guidelines.[33] It should be noted that the renoprotective effects of SGLT2i are largely independent of their hypoglycaemic effects. These agents will not be discussed in more detail here as they are the focus of specific editorials elsewhere in this edition of *Diabetes, Obesity and Metabolism*.

Glucagon-like peptide 1 (GLP-1) receptor agonists may also have benefit and have the same recommendation regarding their use from the ADA.[32] Data regarding the effects of GLP-1 agonists on DN are largely derived from secondary outcomes of cardiovascular endpoint trials of relatively short duration. In addition, these trials have generally resulted in quite small differences in glycaemic control between intervention and control groups, so it is not clear whether effects are due to differences in glycaemia or whether other mechanisms of action are more important. Liraglutide has been shown to result in fewer people reaching a combined renal endpoint of new-onset severe (A3) albuminuria, doubling of serum creatinine, ESKD or death due to renal disease (HR of 0.78, 95% CI 0.67-0.92), but this was almost entirely driven by a lower incidence of severe (A3) albuminuria.[88] Dulaglutide has also been shown to result in fewer people with T2DM and increased cardiovascular risk reaching a similar combined renal endpoint (18.4% versus 20.6%, HR 0.87, 95% CI 0.79-0.95).[89] In an exploratory analysis, there was also a reduction in the development of new severe (A3) albuminuria (8.9% vs 11.3%, HR 0.77, 95% CI 0.68-0.87).[90] In contrast, there does not appear to be any specific reno-protective effect of dipeptidyl peptidase-4 inhibitors, despite their mechanism of action that increases GLP-1 levels.

4.4 | Preserving renal function

Inhibition of the RAAS is a cornerstone in the management of DN. In T1DM, landmark studies have clearly demonstrated the beneficial effects of angiotensin-converting enzyme inhibitors (ACEi). For example, in 235 normotensive people with T1DM and moderate albuminuria who were randomized to captopril or placebo, captopril resulted in a risk reduction for progression to severe (A3) albuminuria of >60% and smaller increases in albumin excretion rate.[91] Similar trials have confirmed these findings.[92] When captopril has been evaluated in randomized controlled trials in T1DM with severe albuminuria and reductions in eGFR, the risk of a doubling in serum creatinine was shown to be reduced by approximately 50%, with greater magnitude of risk reduction seen in those with lower eGFR values.[93] Even in those with nephrotic range proteinuria, ACEi result in a greater proportion of people achieving a reduction in urinary protein excretion to <1 g/24 h.[94]

In T2DM, the strongest evidence for RAAS inhibition comes from studies of angiotensin receptor blockers (ARBs), in particular from the IDNT and RENAAL trials. IDNT randomized 1715 people with T2DM, reduced eGFR and severe (A3) albuminuria to irbesartan, amlodipine or placebo.[65] Irbesartan resulted in ~20% risk reduction in the composite endpoint of doubling of serum creatinine, ESKD or death from any cause versus either of the other two study arms, effects that were independent of blood pressure. The RENAAL trial showed similar results, in which losartan was compared with placebo in 1513 people with T2DM and DN.[66] The composite endpoint of a doubling of serum creatinine, ESKD or death was reduced by 16% in the losartan

group, who also had significantly lower incidence of doubling of serum creatinine and ESKD when these endpoints were assessed individually. The risk of hospitalization with heart failure was also reduced. Similar results have been replicated in Asian populations,[95] although a degree of uncertainty exists as to whether RAAS inhibition in T2DM delays progression from moderate (A2) albuminuria to overt DN independently of blood pressure lowering effects. However, it seems likely that ACEi have a similar effect on ARBs in T2DM as shown in a secondary analysis of the ADVANCE trial,[96] and an RCT in which 250 people with T2DM and moderate (A2) albuminuria were randomized to telmisartan or enalapril.[97] After 5 years, similar rates of deterioration in measured GFR were observed and there were no differences in other outcome measures of DN. Across several of these studies, it is also clear that greater magnitudes of albuminuria reduction in response to RAAS inhibitors are associated with better outcomes, and these findings are seen across different categories of blood pressure, demonstrating that a reduction in albuminuria is protective.[98] This led to the suggestion that ACEi and ARBs, or one of these agents in combination with direct renin inhibitors, may provide additional benefit due to greater reductions in albuminuria. In fact, when tested in RCTs (ONTARGET and VA NEPHRON-D), dual RAAS blockade did not result in improvements in outcomes but produced higher rates of adverse events, including hyperkalaemia and AKI.[99,100] Dual RAAS blockade should therefore be avoided. Conversely, there are some patients in whom RAAS inhibitors are inadvisable or their dose limited because of hyperkalaemia; agents such as sodium zirconium cyclosilicate and patiromer are now available for the treatment of hyperkalaemia, although it remains to be seen whether these agents improve hard endpoints by allowing increased RAAS inhibition.[101] In summary, RAAS inhibition should be offered to people with T1DM or T2DM with hypertension, with high/normal blood pressure and moderate (A2) or severe (A3) albuminuria and those with reduced eGFR.

Controlling arterial hypertension is fundamental to reducing the risk of progression of CKD and reducing cardiovascular risk. This was confirmed in a meta-analysis that included 40 RCTs with over 100 000 participants, which reported that for each 10 mmHg lowering of systolic BP there was a 17% lower risk of mortality, 11% reduction in cardiovascular events and 17% reduction in the development of albuminuria.[102] These effects were largely similar across different classes of anti-hypertensive agents. Other than RAAS inhibitors, the only other anti-hypertensive agents that may have an additive effect on reduction of albuminuria are the non-dihydropyridine calcium channel blockers, diltiazem and verapamil. Bakris et al randomized 52 people with T2DM, DN and hypertension to an ACEi, a non-dihydropyridine calcium channel blocker or a beta-blocker.[103] Effects were similar between ACEi and calcium channel groups, with greater reductions in albuminuria as compared to the beta-blocker group. However, it has not been shown that reductions in albuminuria with diltiazem or verapamil result in improved outcomes. There is broad consensus between guidelines that in people with diabetes and albuminuria, BP should be lowered to <130/80 mmHg to achieve optimal renal and cardiovascular protection (Table 2), though in those prone to postural hypotension a less stringent target should be considered. Dietary salt restriction can also be an effective component of blood pressure treatment, and the ADA guidelines suggest daily sodium intake of <2300 mg.[32]

4.5 | Combined interventions

In clinical practice, people with diabetes should be assessed and managed holistically, with risk reduction and interventions across the range of macro- and microvascular complications. The Steno-2 trial showed how a combined intervention in T2DM resulted in a number of benefits, including improved survival, reduction of cardiovascular events and slowing of progression of DN.[76-78] The study randomized 160 people with T2DM and moderate (A2) albuminuria to standard treatment or a stepwise implementation of behaviour modification and pharmacological management of hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria. Due to the nature of the intervention, blinding was not possible. Significantly lower rates of progression to nephropathy, retinopathy and autonomic neuropathy were observed (odds ratio for development of severe (A3) albuminuria 0.27, 95% CI 0.1-0.75), as were greater reductions in albumin excretion rates and cardiovascular events. Further analyses of outcomes after the randomized phase of the trial reported a significant reduction in all-cause mortality (HR, 0.54; 95% CI, 0.32-0.89), as well as slower rates of GFR decline (3.1 mL/min/year in the intensive-therapy group compared with 4.0 mL/min/year in the conventional-therapy group), and hinted a reduced risk of progression to ESKD (adjusted hazard ratio in the intensive group of 0.36, 95% CI 0.12–1.05).[78,104] There are few data examining similar approaches in T1DM.[105] A final consideration is implementation of interventions that have been shown to be effective in trials into "real-life" clinical practice. A number of observational studies have reported how this can be challenging, how there are differences between individuals in how easily treatment targets can be attained, and that failure to achieve treatment goals is associated with higher rates of DKD progression.[106,107]

5 | SUMMARY

Diabetic kidney disease is a major healthcare challenge, complicating the course of many people who live with diabetes, and is a major cause of ESKD. The presence of DKD is also strongly associated with CV events and has a major influence on survival. Its presentation and prognosis are heterogeneous and vary between individuals, with non-albuminuric DKD and high rates of regression of albuminuria examples of this, while the severity of albuminuria, particularly when combined with elevated blood pressure, remains an important marker of those at higher risk of progression. Management of DKD requires a holistic approach that combines cardiovascular risk reduction with elements to slow the progression of kidney disease, namely glycaemic control, RAAS inhibition and blood pressure lowering. Effective delivery of these interventions in combination reduces the risks of DKD

progression, as well as other microvascular complications, cardiovascular events and mortality. Several international groups have issued clinical guidelines that largely agree on recommended targets, and in clinical practice these should be tailored for each individual patient.

CONFLICT OF INTEREST

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