Practice Points

- Serum potassium levels and eGFR should be monitored within 2 to 4 weeks after initiating an ACE inhibitor, an ARB, an SGLT2i, finerenone, or with changes in these medications.
- Finerenone can be used for persistent albuminuria in addition to an ACE inhibitor or an ARB and SGLT2i, or in people with CKD in DM who cannot take an SGLT2i.
- In the absence of albuminuria and with normal BP, ACE inhibitors or ARBs do not prevent DKD onset.
- ACE inhibitors and ARBs should not be used together due to increased risks of adverse effects, particularly hyperkalemia and AKI.
- ACE inhibitors and ARBs are not safe for use in pregnant women.

potassium concentration, and albuminuria (UACR ≥30 mg/g) despite a maximum tolerated dose of a renin-angiotensin system inhibitor. **Grade A; BEL 1**

Evidence Base 6: How should DKD or CKD in DM be managed?

DKD or CKD in DM accounts for nearly half of all cases of kidney failure that require kidney replacement therapy (dialysis or transplant) in the United States and occurs in about 40% of persons with T2D and 30% of those with T1D, increasing with duration of DM.[387-389] Classical diabetic nephropathy is represented histologically by the presence of basement membrane thickening, mesangial expansion, podocyte loss, and nodular or diffuse glomerulosclerosis.[197,390] Many other pathological changes (tubulointerstitial inflammation and fibrosis, arteriolar hyalinosis, mesangiolysis, glomerular capillary aneurysms) may also occur as a consequence of DM.[391] The pathologic changes may be present prior to development of albuminuria or low eGFR.[390,392] Consequently, the term DKD is now preferred to diabetic nephropathy. Prevention of microvascular complications including DKD should be a management goal as early as the time of diagnosis of DM. In general, AACE concurs with guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) working group[393] and the Kidney Disease Outcomes Quality Initiative Committee[394] for the diagnosis and management of CKD in persons with DM, also known as DKD.

The KDIGO guidelines recommend phasing out the term microalbuminuria and replacing it with the term albuminuria. Testing for the presence of albuminuria can be done using a spot urine sample or a timed collection, although the former is now preferred for reliability and simplicity. UACR levels >30 mg/g indicate kidney damage and are also a marker of CV risk.[393,394] Increased urinary albumin may be seen in the setting of urinary tract or systemic infection, after exercise, or in the presence of hematuria, so confirmation is necessary to establish the diagnosis of DKD or CKD in DM. A UACR of >300 mg/g indicates greater damage and greater risk for progression to kidney failure and development of CKD complications such as anemia, CVD, and infections. Sudden onset or rapidly increasing albuminuria should prompt additional tests to assess for other types of kidney disease. Table 11 lists correlations between albuminuria, urine dipstick, and tests of total protein excretion.

eGFR should be calculated from the serum creatinine by the Chronic Kidney Disease Epidemiology (CKD-EPI). The CKD-EPI equation is more accurate for calculation of eGFR above 60 mL/min/1.73 m^2 than the prior Modification of Diet in Renal Disease equation, and the CKD-EPI equation is currently preferred.[393] Importantly, the CKD-EPI equation has been updated to a new version that is race agnostic and termed CKD-EPI 2021. The American Society of Nephrology and the National Kidney Foundation have recommended immediate implementation for CKD-EPI 2021 as an important strategy to advance CKD care and reduce health disparities by racial identification.[395-397] Figure 3 depicts the classification system for CKD that incorporates both eGFR and albuminuria in the risk assessment. Note that in Figure 3, stage 3 CKD has been divided into 2 categories: G3a for eGFR 45 to 60 mL/min/1.73 m^2 and G3b for eGFR 30 to 45 mL/min/1.73 m^2. The terminology used to describe CKD provides a composite picture by integrating the cause, eGFR, and UACR. For example, a person with DM, an eGFR of 40 mL/min/1.73 m^2, and an UACR of 250 mg/g creatinine would be categorized as "diabetes/G3b/A2." The "heat grid" shown in Figure 3 indicates the terminology, the level of risk for CVD events and progression of kidney disease by color intensity, and the recommended frequency for monitoring UACR and eGFR.[393,398,399] Progression of CKD is considered rapid if the decline in eGFR is ≥5 mL/min/1.73 m^2 per year or if the person has a rapid increase in albuminuria.

High levels, as well as variability, of both BG and BP are important risk factors for DKD.[89,184,400-403] Prevention of the development of DKD includes optimal control of glycemia and BP with RAAS inhibition as first-line therapy.[394,404,405] Intensive glucose control (A1C levels <7% in T2D and <7.5% in T1D) in several clinical trials was found to reduce the risk of incident albuminuria (A2) and DKD onset.[70,78,90,406-410] However, intensive glucose control has not been shown to diminish DKD or CKD in DM progression and may increase risk of CVD mortality in persons with established DKD or CKD in DM. Moreover, glycemic targets need to be individualized due to increased risk of hypoglycemia in persons with DKD or CKD in DM.

Table 11
Relationship Among Categories for Albuminuria and Proteinuria (KDIGO Work Group 2013 [EL 4; NE])[a,b]

Categories			
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 h)	<30	30-300	>300
PER (mg/24 h)	<150	150-500	>500
ACR (mg/mmol) (mg/g)	<3	3-30	>30
	<30	30-300	>300
PCR (mg/mmol) (mg/g)	<15	15-50	>50
	<150	150-500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Abbreviations: ACR = albumin-to-creatinine ratio; AER = albumin excretion rate; PCR = protein-to-creatinine ratio; PER = protein excretion rate.

[a] Reprinted with permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1-150. [EL 4; NE]

[b] Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered "normal"; ACR 10 to 30 mg/g (1 to 3 mg/mmol) is considered "high normal." ACR >2200 mg/g (>220 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.