

Comprehensive Care for People With Diabetic Kidney Disease

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■ **IN BRIEF** Diabetic kidney disease carries a heavy burden, both economically and in terms of quality of life, largely because of its very high risk for vascular disease. Coordinated, multidisciplinary care with attention to appropriate, timely screening and preventive management is crucial to reducing the morbidity and mortality of this devastating disease.

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) and a significant risk factor for progressive macro- and microvascular disease. Increasing albuminuria and declining estimated glomerular filtration rate (eGFR) are both independent and additive risk factors for subsequent vascular complications. Given the increased risk that DKD poses for other micro- and macrovascular complications of diabetes, comprehensive management is crucial. We will review the costs of DKD; the safety and efficacy of blood pressure-independent effects of renin angiotensin aldosterone system (RAAS) inhibition in slowing its progression; and the heightened risk for vascular disease associated with DKD. We will then review the evidence and recommendations for screening and treatment of extra-renal vascular complications and the utility of the patient-centered medical home for comprehensive care of patients with DKD.

Costs of DKD

In 2012, Medicare spent >\$24 billion for the health care needs of people with DKD (1). Although this population only comprises 5% of the Medicare population, these ex-

penditures account for 11% of the Medicare budget. The costs increase incrementally with chronic kidney disease (CKD) stage, with the greatest expenditures for patients on renal replacement therapy (1,2). In comparison to people with diabetes who do not have CKD, the health care costs for a person with stage 5 CKD not yet on dialysis is more than twofold higher and for someone with ESRD requiring dialysis is more than sixfold higher (3). Similarly, the health care costs for someone with either macroalbuminuria (defined as a urine albumin:creatinine ratio ≥ 300 $\mu\text{g}/\text{mg}$) or an eGFR < 60 mL/min/1.73 m² are 50% higher than for a person with diabetes without these criteria (3).

As will be discussed, comorbid cardiovascular complications are more prevalent in the diabetic population with versus without CKD, and the presence of cardiac disease further increases medical costs. Annualized health care expenditures per person with diabetes are as follows: \$10,325 for those without CKD or congestive heart failure (CHF); \$23,312 for those with CKD but not CHF; and \$35,452 for those with both CKD and CHF (1). The total economic cost for DKD is even higher, because the

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estimates listed here do not account for work days lost, unemployment, or the need for social assistance with progressive morbidities.

RAAS Inhibition for Slowing Progression of DKD

Modifiable risk factors to slow the progression of DKD include glycaemic and blood pressure control and the use of ACE inhibitors or angiotensin II receptor blockers (ARBs). Blood pressure and glycaemic control are covered elsewhere in this issue of *Diabetes Spectrum* (p. 175 and p. 214). Hence, only the blood pressure-independent effects of RAAS blockade will be discussed here.

The first landmark trial of RAAS inhibition was in type 1 diabetes and demonstrated that, for every 11 people treated with captopril, 1 death or case of ESRD could be prevented (4). The beneficial effect of ACE inhibitors was subsequently replicated in two ARB trials in people with type 2 diabetes with baseline macroalbuminuria (5,6). ARBs were also shown to reduce the progression of micro- to macroalbuminuria in a dose-dependent manner (7). ACE inhibitors and ARBs have been proven to be of equal efficacy in type 2 diabetes, and it is likely that this also extends to type 1 diabetes (8).

These positive results using ACE inhibitors or ARBs for the delay of diabetic nephropathy led to clinical trials for the primary prevention of microalbuminuria. Results have been conflicting, and the largest trial that demonstrated a decrease in the incidence of albuminuria also found a significantly higher rate of fatal cardiovascular events (9,10). Hence, in the absence of microalbuminuria or hypertension, ACE inhibitor or ARB therapy is not recommended (11).

Enthusiasm regarding the use of ACE inhibitors or ARBs in nephropathy also led to investigation of dual ACE inhibitor-ARB therapy and dual treatment with a direct renin inhibitor on the background of an ACE inhibitor or ARB. These trials

were stopped prematurely because of safety concerns (hyperkalemia and acute kidney injury), and there was no evidence of benefit to combination RAAS therapy with respect to primary outcomes (12,13).

Numerous small trials have demonstrated the antiproteinuric effect of mineralocorticoid blockade in DKD (14), but this has yet to be studied in well-powered trials using hard outcomes. Given the failure of other trials examining dual RAAS blockade in nephropathy, this is unlikely to occur.

Macrovascular Complications of DKD

Cardiovascular Events and Death

The presence of kidney disease in diabetes portends a much greater risk for cardiovascular events and death. This increased risk is mediated by both albuminuria and declining eGFR (15). It has been estimated that, even after adjustment for baseline sociodemographic and clinical risk factors, every tenfold increase in baseline albuminuria carries a 2.5-fold higher risk for cardiovascular events and a 3.9-fold higher risk for cardiovascular death (15). Every halving of baseline eGFR carries a 2.2- and 3.6-fold greater risk for cardiovascular events and death, respectively.

Moreover, increased mortality rates in diabetes are predominantly accounted for by the increased prevalence of kidney disease in this population. The 10-year cumulative all-cause mortality rates in people with DKD (defined as a urine albumin:creatinine ratio >30 $\mu\text{g}/\text{mg}$ or eGFR <60 $\text{mL}/\text{min}/1.73$ m^2), diabetes but no kidney disease, or neither diabetes nor kidney disease are 31.1, 11.5, and 7.7%, respectively (16).

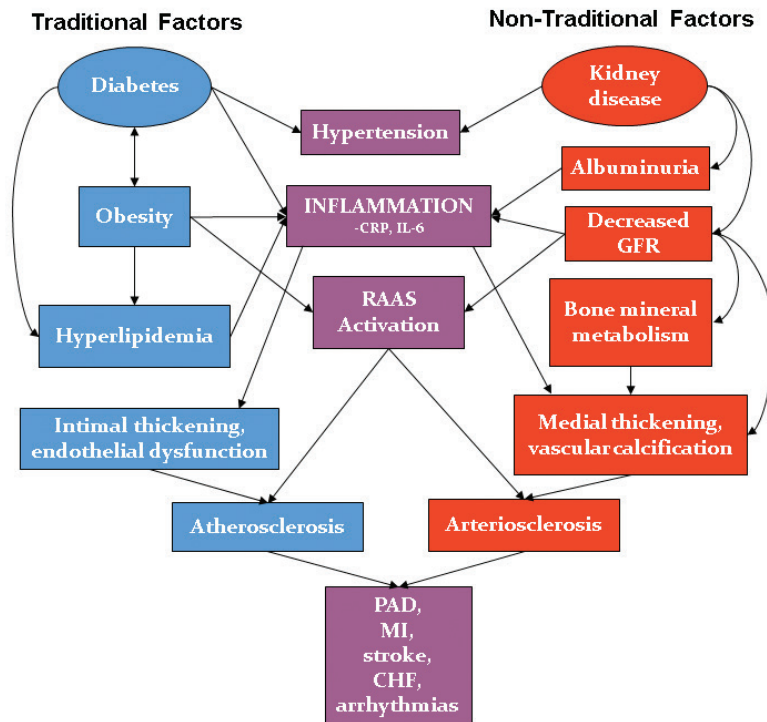
This increased risk for cardiovascular events and death in kidney disease is the result of a combination of traditional and nontraditional risk factors (Figure 1). Hyperlipidemia and resistant hypertension are more prevalent in people with than in those

without CKD. Endothelial dysfunction, inflammation, volume overload, anemia, electrolyte disturbances, and aberrant bone mineral metabolism occur with advancing CKD. These pathogenic factors result in left ventricular remodeling, hypertrophy, arterial stiffness, and accelerated atherosclerosis and arteriosclerosis (17,18).

Despite the elevated risk for vascular disease in CKD, the current recommendation is not to screen asymptomatic patients with normal resting electrocardiograms (19). This guideline was set for a number of reasons. There are no data regarding benefit, and there is significant cost and risk with exposure to unnecessary radiation and nephrotoxic contrast dye used for cardiac catheterizations. People with DKD are already at maximal risk for coronary artery disease (CAD) and hence should be receiving intensive medical therapy and lifestyle modification, which together are similar to invasive revascularization with regard to long-term benefit (18).

Peripheral Artery Disease

A greatly underappreciated complication of CKD is peripheral artery disease (PAD), which is an extremely common and poor prognostic indicator, especially in the setting of diabetes. In stage 3 CKD, the prevalence of PAD is 25.7% compared to 18.5% for CAD and 10.9% for transient ischemic attack or stroke (1). Diabetes and kidney disease have an additive effect on neuropathy, poor wound healing, and PAD, leading to repetitive trauma and nonhealing foot ulcerations (20). As with coronary disease, aberrant bone-mineral metabolism in CKD results in a vascular calcification, which in part accounts for the increased risk of PAD. Because of the severity of neuropathy that often accompanies CKD, these patients often present with nonhealing ulcers and dry gangrene rather than claudication, as is typically the case in patients without CKD (21). The presence of macroalbuminuria



■ **FIGURE 1.** Schematic of traditional and non-traditional risk factors that account for the greatly increased risk of macrovascular disease in people with DKD. CRP, C-reactive protein; IL-6, interleukin 6; MI, myocardial infarction; PAD, peripheral artery disease.

and worsening eGFR significantly increases the likelihood of ulcer non-healing and subsequent need for amputation (21,22).

Annual foot exams are recommended universally for people with diabetes, and in the presence of signs or symptoms of disease, ankle-brachial index (ABI) should be measured. Because of the high prevalence of PAD in CKD patients, screening in asymptomatic DKD patients of any age is supported by American Diabetes Association recommendations.

The greatest increase in PAD prevalence occurs with an eGFR <60 mL/min/1.73 m² in diabetes (23), so this is a reasonable criterion for performing screening. If results are normal, screening should be repeated every 5 years (24).

Although ABI is the preferred diagnostic test for PAD in the general population, this test performs poorly in patients with CKD because of

the presence of vascular calcification and incompressible arteries. A normal ABI is considered to be between 0.9 and 1.3, and a result <0.9 signifies probable PAD. The presence of medial arterial calcification results in falsely elevated ABIs. Hence, results are difficult to interpret in CKD.

Similar to ABI, a toe-brachial index (TBI) can be performed with more robust results in the presence of CKD because vessels supplying the toes are less susceptible to medial arterial calcification. A TBI <0.7 is diagnostic of PAD.

Use of Antiplatelet Agents

There is a dearth of evidence regarding the use of antiplatelet agents in patients with DKD for the primary or secondary prevention of cardiovascular events. A large, meta-analysis of CKD subgroups from 44 clinical trials showed that antiplatelet use decreased the risk of myocardial infarction (MI) but not stroke or cardiovascular mortality (25). The

risk-benefit ratio for antiplatelet agent therapy for primary or secondary prevention in the setting of CKD can be best framed according to the cardiovascular risk of individual patients (Table 1) (25). Antiplatelet therapy confers an additional benefit for hemodialysis patients, preventing an estimated 200 vascular access thromboses/patency failures per 1,000 patients treated. In six comparative efficacy trials, there were no differences in the risk-benefit ratio for different antiplatelet agents in CKD strata.

Cholesterol Targets and Therapy

There is no direct benefit to statin therapy with regard to CKD progression. However, statins should be used judiciously in DKD because of the high prevalence of macrovascular disease. Guidelines for lipid surveillance and cholesterol lowering are slightly different for DKD patients with an eGFR <60 mL/min/1.73 m². Two large meta-analyses of relevant clinical trials have concluded that initiating statin therapy in CKD patients who are not on dialysis reduces the risk for cardiac events, but statins do not confer this benefit in patients on renal replacement therapy (26). Patients who are already on statin therapy when they begin dialysis may continue it, but statins should generally not be initiated in the dialysis population. A caveat to this is that statins may be considered in dialysis patients who have had a recent cardiovascular event or who have PAD (27).

For people with diabetes and stage 3–5 CKD not requiring dialysis, statin therapy does not need to be titrated to specific lipid targets (28). Dosages consistent with clinical trials in patients without CKD are appropriate. Escalating statin doses increases the risk for adverse events, and the benefit of higher statin doses or lower cholesterol levels in CKD is unknown (26). Furthermore, although the risk for

TABLE 1. Absolute Benefits and Risks of Antiplatelet Treatment on MI and Major Bleeding Events per 1,000 Patients Treated

Cardiovascular Risk Group*	MIs Prevented	Major Bleeding Incurred
Low (2% per year)	2/1,000	7/1,000
Intermediate (10% per year)	13/1,000	7/1,000
High (25% per year)	32/1,000	7/1,000

Adapted from ref. 25.

*Low cardiovascular risk: CKD but without clinical evidence for CVD; intermediate cardiovascular risk: CKD and preexisting CVD and/or on dialysis; high cardiovascular risk: CKD and recent acute cardiovascular event.

cardiovascular events increases with worsening eGFR, the incremental benefit of lowering cholesterol in more advanced CKD is reduced (29). This may be in part because of the relatively higher risk as kidney disease progresses for nonatherosclerotic cardiovascular events such as arrhythmias and CHF. Clinical practice guidelines recommend obtaining an initial fasting lipid panel on patients with CKD to identify those with potential secondary hyperlipidemia, who may benefit from subspecialty referral (28). Treatment with fibrates is not recommended for people with diabetes and CKD who have mild to moderate hypertriglyceridemia because of the lack of data regarding clinical benefit in this population and the trend of rising creatinine levels associated with fibrate therapy (28).

Retinopathy and DKD

The association between DKD and retinopathy is partly dependent on the presence of albuminuria. Retinopathy of any severity occurs in ~30% of normoalbuminuric people with diabetes who have a reduced eGFR (<60 mL/min/1.73 m²) compared to 40–50% of patients with albuminuria regardless of the presence of reduced eGFR (30). Moreover, patients with more advanced CKD (stages 3–5) are more likely to have vision-threatening retinopathy than those with CKD stages 1–2 (31).

Despite the great success of novel therapies to spare and salvage vision in diabetic retinopathy, nearly 25% of people with diabetes do not receive routine eye screenings (32). Screening

for diabetic retinopathy for patients with CKD is the same as for those without CKD and should occur at least every 2 years if there is no evidence of retinopathy. In the presence of any retinopathy, screening should occur at least annually, and more frequently depending on the severity of retinal lesions. It is important to actively screen pregnant women as early as possible in gestation because pregnancy can trigger a significant acceleration in retinopathy progression.

Telemedicine using a nonmydriatic camera operated by a trained technician in the primary care setting has been shown to increase screening rates from 56 to 94% (33). However, fundus photography is not equivalent to an in-person comprehensive eye examination, which should still occur initially and periodically thereafter (11).

Models of Health Care Delivery and the Role of the Nephrologist

Multiple longitudinal studies have demonstrated the value of multifactorial intervention for patients with DKD. Reductions in hard outcomes have been cited, including progression to ESRD, cardiovascular events, and all-cause mortality (34–36). The benefits of simultaneous blood pressure and glycemic control are additive, and there may be additional benefits of targeting lipids and taking prophylactic aspirin. Moreover, nutritional and lifestyle interventions also likely reduce the risk of micro- and macrovascular outcomes

in DKD patients (37). Weight loss, smoking cessation, a heart-healthy diet, and exercise have all shown beneficial effects with regard to the progression of CKD and macrovascular complications (37).

Imperative to achieving targeted performance measures is the presence of a multidisciplinary team heavily weighted with nonphysician providers, including pharmacists, certified diabetes educators, dietitians, and social workers. Outreach programs aimed at reaching patient populations at highest risk to assess and intervene in otherwise unknown barriers to care are becoming increasingly common. Such multidisciplinary care is integral to the conceptual framework of the “medical home,” a model of health care delivery that has attracted increasing attention from public health, managed care, and political organizations (38). Effects of the medical home model in patients with diabetes have included reductions in hard outcomes such as incident ESRD and amputations (39). The beneficial effects of this intensive, integrated form of care are presumably mediated by improved adherence to medication, diet, and lifestyle changes (40). However, some have noted an effect on outcome measures even in the absence of an effect on intermediate performance measures such as A1C and blood pressure (41).

Much of the care for CKD stages 1–3 can occur in the primary care office, although providers must be knowledgeable about bone-mineral and anemia complications, which can occur in stage 3 CKD. Referral to a

nephrologist should be considered under certain clinical scenarios such as rapidly worsening eGFR >5 mL/min/1.73 m² per year, sudden-onset nephrotic-range proteinuria, microscopic hematuria, and resistant hypertension. Once eGFR is <30 mL/min/1.73 m², nephrology referral is extremely important to educate and prepare patients for the possibility of dialysis or transplantation (11).

Summary

With the rising incidence of diabetes, the prevalence of advanced stages of DKD will continue to rise. The nephrology labor force will not be sufficient to care for the projected pandemic of DKD. Hence, primary care providers and diabetologists will need to bear some of this burden.

Clearly, novel therapies are desperately needed, but, at present, ACE inhibitor or ARB therapy is the only specific treatment available and must be used judiciously where appropriate. It is concerning that, despite solid evidence of their beneficial effect, only 40% of people with DKD are currently treated with an ACE inhibitor or ARB (42).

The economic and social costs of DKD encompass not only the expense of renal replacement therapy, but also the vastly greater risk for concomitant vascular diseases. PAD may be the most common form of macrovascular disease in CKD (1) and does not receive nearly the attention it requires to prevent nonhealing ulcers, critical limb ischemia, and amputation. TBIs should be assessed routinely for all patients with DKD and an eGFR <60 mL/min/1.73 m².

CKD has been deemed an angina equivalent. Therefore, all patients with DKD should be on maximal medical therapy. Aspirin should be used in all people with diabetes and ESRD and in the setting of a recent vascular event, and statins should be used universally in DKD patients unless contraindicated.

Retinopathy is another area in which we can greatly improve the

lives of our patients. By employing cost-effective, nonmydriatic cameras and telemedicine, we can ensure that people receive early interventions that are proven to reduce the incidence of blindness (11).

The complexity of multisystemic disease in patients with DKD demands a well-organized, multidisciplinary team approach to minimize progression of renal disease and micro- and macrovascular events. Multifactorial interventions, medical home care models, and patient-centered outreach programs are crucial. Such changes will demand a restructuring of health care delivery and payment systems and will require community, financial, and political support. Every health care worker needs to subscribe to this change, because nothing short of this will reduce the economic and social costs of DKD that will otherwise accrue.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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