REVIEW

# Recognition, Pathogenesis, and Treatment of Different Stages of Nephropathy in Patients With Type 2 Diabetes Mellitus

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**Nephropathy is a common microvascular complication among patients with type 2 diabetes mellitus and a major cause of kidney failure. It is characterized by albuminuria (≥300 mg/d) and a reduced glomerular filtration rate and is often present at the time of diabetes diagnosis after the kidney has been exposed to chronic hyperglycemia during the prediabetic phase. A low glomerular filtration rate (<60 mL/min/1.73 m²) is also an independent risk factor for cardiovascular events and death. Detection of diabetic nephropathy during its initial stages provides the opportunity for early therapeutic interventions to prevent or delay the onset of complications and improve outcomes. An intensive and multifactorial management approach is needed that targets all risk determinants simultaneously. The strategy should comprise lifestyle modifications (smoking cessation, weight loss, increased physical activity, and dietary changes) coupled with therapeutic achievement of blood glucose, blood pressure, and lipid goals that are evidence-based. Prescribing decisions should take into account demographic factors, level of kidney impairment, adverse effects, risk of hypoglycemia, tolerability, and effects on other risk factors and comorbidities. Regular and comprehensive follow-up assessments with appropriate adjustment of the therapeutic regimen to maintain risk factor control is a vital component of care, including referral to specialists, when required.**

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**AACE = American Association of Clinical Endocrinologists; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACE = angiotensin-converting enzyme; ADA = American Diabetes Association; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; $HbA_{1c}$ = hemoglobin $A_{1c}$; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MDRD = Modification of Diet in Renal Disease; NKF = National Kidney Foundation; RR = relative risk**

Diabetes is estimated to affect 23.5 million (10.7%) of Americans 20 years of age or older[1]; it is a major cause of chronic kidney disease (CKD) and is recognized as the most common cause of end-stage renal disease (ESRD) in the United States.[2-4] Approximately 40% of US adults with diagnosed or undiagnosed diabetes had some degree of CKD in the 1999-2006 National Health and Nutrition Examination Survey.[4-6] Even among adults with undiagnosed diabetes or prediabetes, the prevalence of kidney damage or dysfunction was substantial (17.7%).[6] The presence of CKD also adds considerably to the cost of diabetes management.[4,7] For example, a recent analysis of a US managed care database showed that total direct health care costs were significantly higher for patients with diabetes and CKD than for those with diabetes alone (unadjusted annualized mean per patient cost, $18,444 vs $6631; $P<.001$).[7]

The mechanisms involved in the pathogenesis of diabetic nephropathy are multiple and complex. Early hemodynamic changes of glomerular hyperperfusion and hyperfiltration are followed by leakage of albumin from the glomerular capillaries and structural changes such as glomerular basement membrane thickening, glomerular hypertrophy, glomerulosclerosis, mesangial cell expansion, and podocyte injury and loss.[8] Clinical manifestations of diabetic nephropathy include a decrease in the glomerular filtration rate (GFR) and an increase in levels of urinary albumin excretion (although a substantial proportion of patients with type 2 diabetes mellitus have a low GFR without albuminuria[9]). Pathologic findings on kidney biopsy in patients with type 2 diabetes are complex and heterogeneous.[10] Nevertheless, only about one-third of patients with diabetes develop nephropathy. Poorly controlled glucose levels, blood pressure, and cholesterol activate inflammatory mediators, and patients with a genetic predisposition progress to advanced stage nephropathy.[8,11]

Besides heralding the onset of deteriorating kidney function in patients with diabetes, albuminuria is an independent risk marker for all-cause mortality and adverse cardiovascular events, including myocardial infarction, stroke, hospitalization for congestive heart failure, and peripheral artery disease.[3,12-14] Cardiovascular risk also increases proportionally and independently as the GFR declines in patients with type 2 diabetes mellitus.[15,16]

The precise pathophysiologic basis for the association between deteriorating kidney function and cardiovascular disease is unclear, although a number of hypotheses have been proposed. Many patients with long-standing diabetes have generalized atherosclerosis (clinical or subclinical). This is manifested in a variety of ways, including increased vascular stiffness with wide pulse pressures and significant

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**Article Highlights**

- Early detection of diabetic nephropathy during its initial stages provides opportunity for therapeutic interventions to prevent or delay onset of complications and improve outcomes
- Diabetic nephropathy is characterized by albuminuria (≥300 mg/d) and a reduced glomerular filtration rate (GFR) often present at the time of diabetes diagnosis
- Presence of stage 3 or higher chronic kidney disease (estimated GFR <60 mL/min/1.73 $m^2$) is associated with a high cardiovascular risk
- An intensive and multifactorial management approach is needed that targets all risk determinants simultaneously. The strategy should comprise lifestyle modifications (smoking cessation, weight loss, increased physical activity, and dietary changes) coupled with therapeutic achievement of blood glucose, blood pressure, and lipid goals that are evidence-based
- Treating abnormal lipid profiles in people with advanced kidney disease with low doses of 2 different agents reduces cardiovascular mortality
- Small limited and sustained increases in serum creatinine of up to 30% after institution of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be tolerated because they are associated with slower declines in kidney function if blood pressure is controlled
- Micro- or low levels of albuminuria (30-299 mg/d) is NOT indicative of diabetic nephropathy but is associated with endothelial dysfunction and heightened cardiovascular risk

increases in serum creatinine when renin–angiotensin system blockers are given. Although these findings suggest the presence of renal artery stenosis, later investigations show no evidence of renal artery stenosis. This intrarenal hypoperfusion leads to low-grade ischemia and can harm the kidney over the long term.[17] In addition, increasing levels of albuminuria reflect systemic vascular endothelial dysfunction and injury to the podocytes.[18-20]

Hyperglycemic damage to the vascular glycocalyx[18,21] may disrupt its function as a barrier between the blood and the endothelium and its role in regulating vascular permeability to macromolecules, adhesion of circulating cells, and flow-mediated dilatation. Other factors implicated include reduced levels of vitamin D that contribute to increased vascular calcifications.[22]

Diabetes is considered a coronary heart disease risk equivalent (ie, it confers a level of risk for major coronary events equal to that of existing heart disease)[23] and, as discussed previously, CKD also imparts a high level of risk for cardiovascular disease.[3,24] Thus, for patients with both diabetes and CKD, the risk of cardiovascular events is extremely high. A multifaceted management strategy aimed at controlling CKD risk factors (many of which are also cardiovascular risk factors) is advocated[3,25,26] and is associated with improvements in both kidney and cardiovascular outcomes.[27-29] Such an approach should target hyperglycemia, hypertension, dyslipidemia, obesity, smoking, and platelet activity according to evidence-based recommendations with appropriate agents and lifestyle modifications.

Primary prevention of CKD, early detection of disease, and prompt intervention with appropriate, evidence-based measures will delay CKD onset or progression, improve kidney and cardiovascular outcomes, and reduce resource utilization.[30] Despite these benefits, CKD is both underdiagnosed and undertreated,[31-34] and awareness of CKD among patients and providers is low.[3] Improvements in CKD screening among patients with diabetes (a high-risk population) and proactive implementation of an early, intensive, and multifactorial management strategy are needed to reduce the burden of CKD in this population.[27,35]

## SCREENING AND DIAGNOSIS

Professional bodies concerned with management of patients with diabetes recommend that all patients with type 2 diabetes be screened annually for CKD, starting at diagnosis.[3,25,26] Urinary albumin excretion should be evaluated from the albumin-to-creatinine ratio in a random spot sample (Table 1). Because of fluctuations in urinary albumin excretion, at least 2 of 3 samples collected within a 3- to 6-month time frame should be used to categorize the degree of albuminuria and avoid false-positive results. Common causes of transient increases in albuminuria into microalbuminuria (currently termed *low-level albuminuria* [30-299 mg/d]) include fever, high-salt diet, vigorous exercise in the previous 24 hours, any infection, dehydration, hematuria, marked hyperglycemia, very high blood pressure, and congestive heart failure.[3,26]

Evaluation of urinary albumin excretion alone is insufficient to assess the presence and severity of CKD because some patients with type 2 diabetes can have advanced stage nephropathy in the absence of albuminuria.[36,37] Serum creatinine should also be measured annually in all patients; the

TABLE 1. **Definitions of Abnormalities in Albumin Excretion**

| Category | Spot collection (mg/g creatinine) | 24-h collection (mg/24 h) | Timed collection (μg/min) |
|---|---|---|---|
| Normal | <30 | <30 | <20 |
| Microalbuminuria (low-level albuminuria) | 30-299 | 30-299 | 20-199 |
| Albuminuria | ≥300 | ≥300 | ≥200 |

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TABLE 2. **The Chronic Kidney Disease Epidemiology Collaboration Equation for Estimating Glomerular Filtration Rate on the Natural Scale**

| Race and sex | Serum creatinine level (mg/dL) | Equation |
|---|---|---|
| Black | | |
| Female | ≤0.7 | $GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$ |
| | >0.7 | $GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$ |
| Male | ≤0.9 | $GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$ |
| | >0.9 | $GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$ |
| White or other | | |
| Female | ≤0.7 | $GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$ |
| | >0.7 | $GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$ |
| Male | ≤0.9 | $GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$ |
| | >0.9 | $GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$ |

Expressed for specified race, sex, and serum creatinine (Scr) level. To convert glomerular filtration rate (GFR) from mL/min/1.73 m$^2$, multiply by 0.0167. From *Ann Intern Med*,[40] with permission.

GFR is then estimated from serum creatinine and used to stage the level of CKD.[3,25,26] Laboratories report estimated GFR (eGFR) alongside serum creatinine. Otherwise, the Modification of Diet in Renal Disease (MDRD) equation can be used to calculate eGFR from the serum creatinine value.[38,39] This equation takes into account the variables of age, sex, and ethnicity, which are important determinants of serum creatinine. For example, in elderly patients, the age-related decrease in GFR is not paralleled by an increase in serum creatinine levels because of a concomitant age-related decline in creatinine generation.[38] An eGFR calculator based on the MDRD formula is available on the National Kidney Disease Education Program Web site at http://www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm. The recently proposed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[40] appears to provide a more accurate estimate of GFR from serum creatinine than the MDRD equation, especially at higher GFR values.[41] This equation more closely resembles the actual measured GFR, in that is has reduced the bias in the equation. It has made the equation far more accurate, especially in people with a GFR greater than 60 mL/min/1.73 m$^2$. Measurements of GFR using the older MDRD equation, currently used by most laboratories, have been compared with GFR values obtained using the CKD-EPI equation.[41] For individuals with an eGFR of 30 to 59 mL/min/1.73 m$^2$, bias was decreased from 4.9 to 2.1 mL/min/1.73 m$^2$ (57% improvement); for an eGFR of 60 to 89 mL/min/1.73 m$^2$, bias was decreased from 11.9 to 4.2 mL/min/1.73 m$^2$ (61% improvement); and for an eGFR of 90 to 119 mL/min/1.73 m$^2$, bias was decreased from 10.0 to 1.9 mL/min/1.73 m$^2$ (75% improvement). A limitation of this comparison of equations was the inclusion of a limited number of elderly and racial/ethnic minorities with measured GFR. Table 2 shows how to calculate GFR from the CKD-EPI equation, taking into account age, sex, race, and serum creatinine level.[40]

TABLE 3. **Kidney Disease: Improving Global Outcomes Definitions of GFR and Albuminuria Stages in Chronic Kidney Disease**

| GFR stage | Description | Range (mL/min/1.73 m$^2$) |
|---|---|---|
| 1 | Increased and optimal | >90 |
| 2 | Mild | 60-89 |
| 3a | Mild to moderate | 45-59 |
| 3b | Moderate to severe | 30-44 |
| 4 | Severe | 15-29 |
| 5 | Kidney failure | <15 |
| **Albuminuria stage** | **Description** | **Range (mg/g)** |
| 1 | Optimal and high normal | <30 |
| 2 | High | 30-299 |
| 3 | Very high | >300 |

GFR = glomerular filtration rate.
Adapted from *Kidney Int*,[42] with permission from Macmillan Publishers Ltd.

A new classification system for CKD has been proposed by Kidney Disease: Improving Global Outcomes (KDIGO), which defines different stages of GFR and categories of albuminuria (Table 3).[42] Stages 1 and 2 are defined according to the GFR and presence of kidney damage on urinalysis, imaging, or biopsy; stages 3 through 5 are defined on the basis of GFR alone. These abnormalities must be present for at least 3 months to exclude cases of acute kidney injury. The likelihood of certain clinical diagnoses, including diabetic nephropathy, can be evaluated from consideration of both the GFR and the level of albuminuria.[42] Findings suggesting an alternative cause of CKD include an absence of diabetic retinopathy, a low or rapidly decreasing GFR, rapidly increasing proteinuria or nephrotic syndrome, active urinary sediment, signs or symptoms of other systemic disease, or a greater than 30% decrease in GFR within 2 to 3 months after angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) initiation in the absence of dehydration, bilateral renal artery stenosis, or heart failure.[3]

Detection of diabetic kidney disease is only of value if it triggers initiation and continual assessment of an effective management strategy by the primary care physician. Referral to a nephrologist is appropriate if the GFR deteriorates rapidly or if difficult management issues are encountered.

## LIFESTYLE MODIFICATIONS

Lifestyle improvements are a first step in diabetes management, irrespective of the presence of CKD.[25,26] These should comprise measures to encourage smoking cessation, weight loss, and increased physical activity, as well as dietary changes (Table 4).



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TABLE 4. **Multifactorial Approach to Treatment in Patients with Diabetic Nephropathy**[a]

| |
|---|
| Lifestyle modifications |
| Avoidance or cessation of smoking |
| Weight reduction (maintain normal body weight [BMI, 18.5-24.9]) |
| Physical activity (engage in regular aerobic physical activity, such as brisk walking for ≥30 minutes per day, most days of the week) |
| Low protein diet (limit protein intake to 0.8-1.0 g/kg body weight per day in early-stage CKD and to ≤0.8 g/kg per day in late-stage CKD) |
| Adopt DASH eating plan (consume a diet rich in fruits, vegetables, and low-fat dairy products, with a reduced content of saturated and total fat) |
| Dietary sodium reduction (reduce dietary sodium intake to ≤100 mmol/d (2.4 g of sodium or 6 g of sodium chloride) |
| Moderate alcohol intake (limit consumption to ≤2 drinks per day for most men or 1 drink/day for women and lighter-weight individuals) |
| Achieve glycemic control (<7% $HbA_{1c}$)[b] |
| Achieve blood pressure <130/80 mm Hg, using an ACE inhibitor or ARB as first-line treatment |
| Achieve LDL-C <100 mg/dL (<70 mg/dL is an alternative therapeutic option for very high-risk patients), using statins as first-line treatment |
| Prevent anemia with erythropoietin |
| Antiplatelet therapy: low-dose aspirin 75-162 mg/d in selected individuals according to clinical judgment |

[a] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CKD = chronic kidney disease; DASH = Dietary Approaches to Stop Hypertension; $HbA_{1c}$ = hemoglobin $A_{1c}$; LDL-C = low-density lipoprotein cholesterol.
[b] The American Association of Clinical Endocrinologists guidelines recommend a glycemic goal of <6.5%.
Data from *Endocr Pract.*[25]

### Smoking

Smoking appears to promote onset and progression of diabetic kidney disease.[43-45] Several studies have reported a higher prevalence of microalbuminuria and macroalbuminuria and reduced GFR (<60 mL/min/1.73 $m^2$) among patients with type 2 diabetes who smoked compared with their nonsmoking counterparts.[45] A range of structural and functional kidney changes have been identified in smokers with diabetes, although the precise mechanisms by which smoking exerts its nephrotoxic effects require clarification. One hypothesis is that activation of multiple cellular pathways in smokers with diabetes results in accumulation of reactive oxygen species and a loss of kidney redox homeostasis.[45] Smoking cessation appears to be effective at preventing progression of early nephropathy in patients with type 2 diabetes.[44,46] Consequently, support should be provided to help patients quit smoking through education and counseling, smoking cessation delivery systems, and use of antismoking medications (eg, nicotine-replacement therapy).[43,47] Smoking cessation will also reduce the cardiovascular risk.

### Weight Loss

Many patients with type 2 diabetes are overweight (body mass index [BMI], calculated as the weight in kilograms divided by the height in meters squared, 25.0-29.9) or obese (BMI ≥30.0). These conditions are associated with an increased incidence and rate of progression of CKD as well as an increased risk of renal cell carcinoma and nephrolithiasis.[48,50] In particular, obesity appears to independently heighten CKD risk and progression in the setting of diabetes.[48] Adverse hemodynamic, structural, and functional changes are observed in the kidneys of obese individuals.[48] However, as with smoking, the mechanisms behind such obesity-induced kidney injury, especially in a diabetic milieu, are complex and yet to be fully elucidated.[48,49] Weight loss, by nonsurgical or surgical interventions, has been shown to reduce proteinuria and microalbuminuria and stabilize kidney function in various populations, including those with type 2 diabetes.[51] These findings are likely to be attributable, in part, to a concomitant reduction in blood pressure. Additional long-term studies are needed to evaluate the durability of the effects of weight loss on the kidneys and whether they translate into improved outcomes, such as slowing the development of ESRD. Nevertheless, weight loss is recommended for overweight or obese patients with diabetes.[52] Weight loss will not only improve glycemic control but will also reduce the risk of cardiovascular disease through beneficial effects on blood pressure, dyslipidemia, and serum markers of inflammation.[52] The weight loss goal should be individualized to the patient and should be both achievable and maintainable; the National Kidney Foundation (NKF) recommends a target BMI of 18.5-24.9 (ie, within the normal range) for patients with diabetes and CKD.[3] However, this target is unrealistic for most overweight or obese patients with type 2 diabetes and is rarely achieved. Weight management programs should comprise lifestyle measures (dietary restriction and increased physical activity) and antiobesity medications if needed, coupled with appropriate support and counseling.[26,52] Bariatric surgery should be considered only for patients with type 2 diabetes with a BMI greater than 35.[26]

### Dietary Modifications

Protein restriction may have benefits in patients with diabetic nephropathy in terms of slowing the progression of albuminuria, the decline in GFR, and the development of ESRD.[3,25,26] Patients with early-stage CKD should be advised to limit their protein intake to 0.8 g/kg body weight per day; the target for those with late-stage CKD is 0.8 g/kg or lower per day.[25,26] Adopting the Dietary Approaches to Stop Hypertension (DASH) diet, reducing sodium intake (≤2.4 g/d of sodium or ≤6 g of salt), and limiting alcohol consumption (≤2 drinks/day for most men or 1 drink/day in women and lighter-weight individuals) will have a posi-



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tive effect on blood pressure.[53,54] Dietary changes to improve diabetic dyslipidemia should comprise reductions in saturated fat, trans fat, and cholesterol intake, together with increases in omega-3 fatty acids (eg, 1 g/d of fish oil), viscous fiber, and plant stanols/sterols.[25,26] Weight loss and increased physical activity also have beneficial effects on the lipid profile.

## PRESERVING KIDNEY FUNCTION THROUGH GLYCEMIC CONTROL

Hyperglycemia is a contributing factor to diabetic complications, including diabetic nephropathy. Thus, good glycemic control is one logical measure that will help prevent development of kidney disease and may slow progression of existing CKD in patients with type 2 diabetes (Table 4).

### Evidence for the Benefits of Glycemic Control on Kidney Function

In the UK Prospective Diabetes Study (UKPDS 33), patients with newly diagnosed type 2 diabetes were randomized to receive intensive glycemic control or conventional treatment.[55] For 10 years, hemoglobin $A_{1c}$($HbA_{1c}$) values were significantly lower with intensive vs conventional treatment (7.0% vs 7.9%), and reductions were also observed in the intensive treatment group in microalbuminuria (relative risk [RR] at 9 years for intensive strategy vs conventional strategy, 0.76; 99% confidence interval [CI], 0.62-0.91; *P*<.001), proteinuria (RR, 0.67; 99% CI, 0.42-1.07; *P*=.026), and a doubling of serum creatinine (RR, 0.40; 99% CI, 0.14-1.20; *P*=.027). Furthermore, early intensive glycemic control was associated with a long-term decrease in the risk of a composite microvascular end point, which included kidney failure (24% relative reduction at 10 years; *P*=.001).[56]

Intensive glucose control ($HbA_{1c}$ 6.5% vs 7.3% in the standard care comparator group) was also associated with a significant reduction in renal events in patients with type 2 diabetes in the Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE).[57] This included new or worsening nephropathy (4.1% vs 5.2%; hazard ratio [HR], 0.79; 95% CI, 0.66-0.93; *P*=.006), notably, the development of macroalbuminuria (2.9% vs 4.1%; HR, 0.70; 95% CI, 0.57-0.85; *P*<.001), as well as new-onset microalbuminuria (23.7% vs 25.7%; HR, 0.91; 95% CI, 0.85-0.98; *P*=.02). A trend toward a reduction in the need for renal replacement therapy or death from renal causes (0.4% vs 0.6%; HR, 0.64; 95% CI, 0.38-1.08; *P*=.09) was also observed, although there was no effect on doubling of serum creatinine (1.2% vs 1.1%; HR, 1.15; 95% CI, 0.82-1.63; *P*=.42). Similarly, in the Veterans Affairs Diabetes Trial (VADT), worsening of albuminuria (9.1% vs 13.8%; *P*=.01) and progression from normo- to micro- to macroalbuminuria (2.9% vs 5.1%; *P*=.04) was also significantly less in patients with type 2 diabetes who were assigned to intensive glycemic control vs standard therapy ($HbA_{1c}$ 6.9% vs 8.4%).[58] However, the more intensive regimen had minimal (nonsignificant) effects on severe kidney complications (doubling of serum creatinine, creatinine >3 mg/dL, or GFR <15 mL/min) or on the rate of GFR decline.

In the Diabetes Control and Complications Trial (DCCT), significantly lower $HbA_{1c}$ levels were achieved in patients with type 1 diabetes who were receiving intensive insulin therapy compared with conventional insulin therapy.[59] This superior glycemic control with intensive therapy was associated with significant reductions in the occurrence of microalbuminuria (39% reduction; 95% CI, 21%-52%) and albuminuria (54% reduction; 95% CI, 19%-74%). Follow-up studies showed persistence of the benefits in previously intensively treated patients, even though their glycemic control during the follow-up period was equivalent to that of patients receiving conventional therapy.[60]

Results of these clinical trials suggest that glycemic control has a beneficial effect on albuminuria in patients with type 1 and type 2 diabetes. It also plays a greater role as primary prevention in the early stages of microvascular disease development and a lesser role as secondary intervention after complications are more advanced. Thus, early attainment and maintenance of glycemic control would be expected to reduce the cumulative burden of chronic hyperglycemia and result in an even greater reduction in the risk of complications such as nephropathy.

### Glycemic Goals

The primary target for hyperglycemia management is $HbA_{1c}$, which should be controlled without inducing clinically important hypoglycemia.[26] The American Diabetes Association (ADA) and NKF both recommend achieving an $HbA_{1c}$ level of 7.0% in most patients with diabetes, irrespective of the presence of CKD.[3,26,61] Guidelines from the American Association of Clinical Endocrinologists (AACE) vary slightly, endorsing a more stringent $HbA_{1c}$ goal of 6.5% or less.[25] The early termination of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial generated debate about whether lower is always better. Increased mortality was observed in this trial among patients assigned to intensive therapy (target $HbA_{1c}$ <6.0%) vs those assigned to standard therapy (target $HbA_{1c}$ 7.0%-7.9%).[62] A post hoc analysis of the ACCORD data conducted to explore this finding showed that a higher average on-treatment $HbA_{1c}$ was a strong predictor of death.[63] In the intensive therapy arm, the mortality risk increased approximately linearly over an average $HbA_{1c}$ range of 6.0% to 9.0%; the excess



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risk vs standard therapy was observed only among patients whose average on-treatment $HbA_{1c}$ remained higher than 7.0% (ie, the ADA $HbA_{1c}$ goal). Severe hypoglycemia was higher among patients receiving intensive therapy[64] and was associated with an increased risk of death with both strategies.[65] However, it did not appear to account for the excess mortality in the intensive treatment arm.[65] Although a retrospective cohort analysis of data from patients with type 2 diabetes indicated a U-shaped relationship between $HbA_{1c}$ decile and mortality,[66] no evidence from prospective studies supports this correlation.

The $HbA_{1c}$ targets proposed by the ADA, NKF, and AACE are general recommendations, and clinical judgment should be used to individualize each patient's goal.[25,26,61,67] A balance should be sought between lowering $HbA_{1c}$ and the anticipated long-term benefits vs specific safety issues, taking into account the duration of diabetes, age/life expectancy, comorbidities, macro- or microvascular complications (including diabetic nephropathy), and patient awareness of hypoglycemia.

### Antidiabetic Drug Treatment

Tight glycemic control, rather than use of any specific antidiabetic agent, appears to be the principal factor in decreasing the risk of microvascular complications in clinical trials.[55] A treatment regimen tailored to the individual will maximize his or her likelihood of achieving and maintaining glycemic control while reducing the risk of adverse events. The choice of antidiabetic medication should take into account adverse effects, risk of hypoglycemia, tolerability, ease of use, long-term compliance, cost, nonglycemic effects on comorbidities or risk factors (eg, body weight, blood pressure, and the lipid profile), and any other specific patient considerations.

The presence of kidney disease brings an additional layer of complexity to the management of patients with type 2 diabetes. Kidney function should be assessed before initiation of antidiabetic therapy because the stage of CKD, if present, will influence antidiabetic drug selection.[68] Any potentially harmful or protective effects on the kidneys beyond glucose lowering will also need to be considered in the prescribing decision. Patients with decreased kidney function (CKD stages 3-5) are particularly susceptible to hypoglycemia.[3,69] Impaired clearance of insulin (which is excreted renally) and decreased insulin degradation in peripheral tissues predispose patients with CKD to hypoglycemic episodes.[69,70] Hypoglycemia is also a concern among patients with diminished kidney function, especially at GFR levels below 30 mL/min/1.73 $m^2$, who are receiving treatment with oral antidiabetic drugs that are primarily eliminated by the kidneys.[3,69] Furthermore, CKD is associated with impaired kidney gluconeogenesis due to a decrease in tissue mass.[3] Therefore, patients with CKD must monitor their glucose levels closely and reduce their dose of antidiabetic medication to prevent hypoglycemia, if necessary.

**Metformin.** Patients with mild to moderate CKD can be treated with metformin, but it is contraindicated at serum creatinine concentrations of 1.5 mg/dL or higher in men or 1.4 mg/dL or higher in women because of an increased risk of lactic acidosis.[3,71,72] However, recent studies report use of metformin in patients with eGFRs as low as 45 mL/min/1.73 $m^2$ with no problems.[73] Thus, although use of metformin is reasonable in a young person with a creatinine concentration of 1.5 mg/dL, elderly patients with a creatinine concentration of 1.3 mg/dL may have an eGFR lower than 50 mL/min/1.73 $m^2$ and hence have substantially decreased clearance of metformin. Consequently, a wiser approach is to assess eGFR and not use metformin if the eGFR is lower than 45 mL/min/1.73 $m^2$. Hypoglycemia is unlikely with metformin monotherapy.[3,71,72]

**Sulfonylureas.** As kidney function declines, the clearance of sulfonylureas or their active metabolites also declines and increases the risk of hypoglycemic reactions.[3] Therefore, the initial dose, subsequent dose titrations, and maintenance dosage should be conservative in patients with any degree of kidney dysfunction. First-generation sulfonylureas (acetohexamide, tolazamide, and tolbutamide) should generally be avoided in patients with stage 3 to 5 CKD; chlorpropamide can be used at a reduced dose in patients with a GFR of 50 to 70 mL/min/1.73 $m^2$ but should be avoided if the GFR is lower than 50 mL/min/1.73 $m^2$.[3] Glipizide is the preferred second-generation sulfonylurea for patients with stage 3 to 5 CKD, although glimepiride can also be used if initiated at a low dose.[3] Glyburide is substantially excreted by the kidney and should be avoided in patients with stage 3 to 5 CKD to avoid hypoglycemic reactions.[3]

**Meglitinides.** Both nateglinide and repaglinide can be given to patients with type 2 diabetes and CKD. No dose adjustment is required for nateglinide in patients with mild to severe kidney impairment[74] or for repaglinide in patients with mild to moderate kidney impairment.[75] However, the initial dose of repaglinide should be reduced in patients with severe kidney dysfunction.[75]

**Alpha-Glucosidase Inhibitors.** Acarbose and miglitol are suitable for patients with mild to moderate CKD but are not recommended for patients with severe kidney dysfunction (serum creatinine >2 mg/dL).[3,76,77]

**Thiazolidinediones.** No dose adjustment is necessary with either pioglitazone or rosiglitazone in patients with kidney impairment.[78,79] Furthermore, these drugs have been shown to significantly decrease urinary albumin and protein excretion in patients with diabetes.[80] Whether this translates into improved kidney outcomes in patients with diabetic nephropathy has yet to be investigated.



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**Glucagon-Like Peptide-1 Mimetics.** Exenatide may be used without dose adjustment in patients with mild kidney dysfunction (creatinine clearance [CrCl], 50-80 mL/min),[81] although care is necessary when initiating or increasing exenatide doses in patients with moderate kidney impairment (CrCl, 30-50 mL/min). Exenatide is not recommended for patients with severe kidney impairment (CrCl <30 mL/min) or ESRD. Experience with liraglutide in patients with kidney impairment is limited, and it should be used with caution in this population; no dose adjustment is required.[82]

**Dipeptidyl Peptidase-4 Inhibitors.** Reduction of the sitagliptin dose is unnecessary in patients with mild kidney impairment (CrCl ≥50 mL/min) but is recommended in patients with moderate (CrCl ≥30 to <50 mL/min) or severe (CrCl <30 mL/min) kidney impairment or ESRD.[3,83] Likewise, a reduced dose of saxagliptin is advised for patients with moderate or severe kidney dysfunction (CrCl ≤50 mL/min) or ESRD.[84] Vildagliptin (which is approved in Europe but not the United States) does not require dose reduction in patients with mild renal impairment; however, its use is not recommended in those with moderate or severe renal impairment or in hemodialysis patients with ESRD. Linagliptin, alogliptin, and dutogliptin are dipeptidyl peptidase -4 inhibitors currently in clinical development. Of these, linagliptin may hold promise as a new antidiabetic agent for patients with reduced kidney function because excretion via the kidneys is only a minor route of elimination.[85]

**Insulin.** Doses of insulin are not based on the degree of kidney function but should be titrated to achieve glycemic control without inducing hypoglycemia.[3] Whichever hypoglycemic agent is selected, $HbA_{1c}$ levels and kidney function should be monitored regularly and the antidiabetic regimen adjusted accordingly. Because of the progressive nature of type 2 diabetes,[86] most patients will require a combination of agents to maintain glycemic control over time. These combinations should be selected with care in patients with CKD.

## PRESERVING KIDNEY FUNCTION THROUGH BLOOD PRESSURE CONTROL

Hypertension and diabetes are commonly associated, such that most individuals with diabetes also have hypertension.[3,26,53] High blood pressure is a key pathogenic factor that contributes to kidney deterioration, and treatment of hypertension is probably the most important intervention in CKD management. Indeed, there is indisputable evidence from many large, randomized clinical trials that correct blood pressure control will delay the development and progression of diabetic kidney disease.[87-91] Early studies such as the UKPDS 38 study provided some evidence that intensive blood pressure control in patients with type 2 diabetes and hypertension has a beneficial effect on kidney function.[87] Patients (N=1148) were randomized to 2 levels of blood pressure control; mean blood pressure over 9 years in the 2 groups was 144/82 mm Hg vs 154/87 mm Hg ($P$<.0001). However, the lower blood pressure group showed no additional benefit with regard to the risk of proteinuria, fatal or nonfatal renal failure, or doubling of serum creatinine concentrations. Keep in mind that this achieved blood pressure level is well above the currently recommended target of less than 130/80 mm Hg. Nevertheless, blood pressure levels lower than 140/90 mm Hg have uniformly been shown to reduce cardiovascular risk.[92]

### Blood Pressure Goals

Current guidelines recommend a blood pressure goal of 130/80 mm Hg for patients with type 2 (and type 1) diabetes, irrespective of the presence of CKD (Table 4).[3,25,26,53] This target is based on the results of randomized clinical trials, such as the UKPDS studies[87,88] and the Hypertension Optimal Treatment trial,[93] that demonstrated the benefits of lowering blood pressure on both macro- and microvascular outcomes in patients with diabetes. Furthermore, early studies equated low levels of albuminuria (microalbuminuria) with kidney disease, and lower levels of blood pressure reduced albuminuria.[89-91,94] We now know that low levels of albuminuria do not equate to the presence of kidney disease, but rather vascular inflammation and cardiovascular risk.[8,95,96]

Recent clinical trials suggest the presence of a J-shaped relationship between blood pressure and cardiovascular outcomes.[97-99] Among patients with diabetes who participated in the International Verapamil SR-Trandolapril study,[97] the risk of the primary end point (all-cause death, nonfatal myocardial infarction, or nonfatal stroke) was increased in the subset of patients with a diastolic blood pressure lower than 70 mm Hg. In the ACCORD blood pressure trial, no additional benefit on a similar composite end point (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) was observed at systolic blood pressures below 120 mm Hg.[98] Furthermore, intensive antihypertensive therapy in ACCORD was associated with a higher incidence of serious adverse events.[98] Thus, the current blood pressure goal of less than 130/80 mm Hg cannot be supported by data from prospective studies. A notable exception, however, is patients with advanced proteinuric kidney disease who have eGFRs lower than 50 mL/min/1.73 $m^2$ with greater than 500 mg/d of proteinuria. Data from long-term follow-up of 2 prospective studies support a blood pressure lower than 130/80 mm Hg in this subgroup to slow nephropathy progression.[100,101]

There is some concern that lower diastolic blood pressure may impair myocardial perfusion.[102] Thus, future evidence-based guidelines are not likely to recommend lower targets for patients with proteinuric kidney disease.



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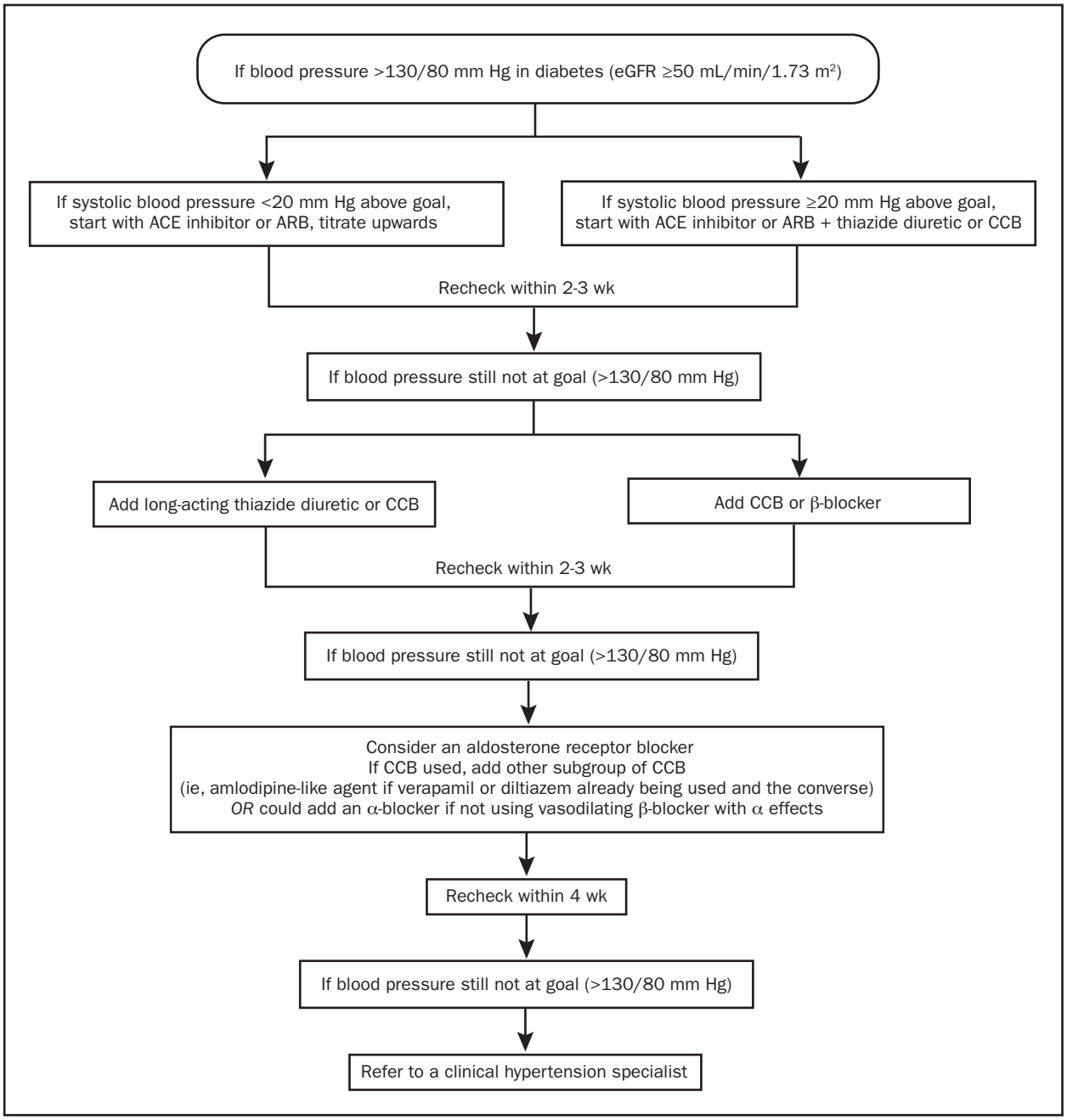


FIGURE. A suggested approach to achieve blood pressure goal in patients with diabetes. An estimated glomerular filtration rate (eGFR) of ≥50 mL/min/1.73 $m^2$ generally responds well to thiazide diuretics. Chlorthalidone is the suggested thiazide-like diuretic because it is the diuretic used in clinical trials and forms the basis for the cardiovascular outcomes data. Vasodilating β-blockers have a better tolerability profile and fewer metabolic consequences compared with older agents such as atenolol. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.
From *J Am Soc Hypertens*,[54] with permission from Elsevier.

### Antihypertensive Drug Selection

In addition to lifestyle modifications, individuals with type 2 diabetes will generally require 2 or more antihypertensive agents at maximal doses to achieve their blood pressure target. The Figure shows an algorithm proposed by the American Society of Hypertension for the treatment of blood pressure in patients with diabetes and an eGFR of 50 mL/min/1.73 $m^2$ or higher.[54,103]



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Guidelines generally support first-line treatment of patients with diabetes and hypertension, regardless of the presence of CKD, with an agent that targets the renin–angiotensin system (ie, an ACE inhibitor or ARB).[3,26] Large-scale outcomes trials of patients with advanced proteinuric kidney disease demonstrate that inhibitors of the renin–angiotensin system delay the decline in kidney function independent of the benefit attributable to the blood pressure reduction.[104-106] A meta-analysis by Kunz et al[107] supports the concept that combined administration of an ACE inhibitor and an ARB is more effective than either drug alone to further reduce proteinuria in patients with or without diabetes. However, benefit with these agents vs other agents that simply achieve current blood pressure goals has been proven only in patients with advanced proteinuric nephropathy or in those with heart failure but not in those with early nephropathy.[108,109] The ADA also recommends that normotensive patients with diabetes and early-stage nephropathy receive treatment with an ACE inhibitor or ARB.[26] Note, however, that the practice of treating low levels of albuminuria with a blocker of the renin–angiotensin system in normotensive patients cannot be justified on the basis of findings of a recent double-blind, placebo-controlled trial that found no benefit on nephropathy progression.[110]

Initial combination therapy is recommended for patients whose blood pressure is greater than 20/10 mm Hg above the goal (ie, >150/90 mm Hg for those with diabetes).[53,54,111] The combination should comprise an ACE inhibitor or ARB and a second drug, such as a thiazide diuretic, calcium channel blocker, or β-blocker.[26] These can be given either as a fixed or free combination. A loop diuretic rather than a thiazide diuretic should be used in patients with lower levels of kidney function (eGFR <50 mL/min/1.73 $m^2$).[54]

If the blood pressure goal is not reached and maintained with 2 drugs, other antihypertensive agents from different therapeutic classes should be added, as needed. ACE inhibitor/ARB combinations are not advised on the basis of results of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).[112,113] In this trial of patients at high risk of vascular events, 38% of whom had diabetes, combination treatment with telmisartan plus ramipril reduced progression of albuminuria compared with ramipril alone.[113] However, the combination also increased the risk of hyperkalemia, syncope, hypotension, and kidney dysfunction compared with ramipril monotherapy.[112] The definitive answer regarding this question will arise from the currently ongoing VA NEPHRON-D trial.[114]

### General Considerations

Recommendations in hypertension management guidelines provide general advice and should not supplant good clinical judgment; the antihypertensive drug regimen should be tailored to each patient according to specific comorbidities and needs. In addition, blood pressure should be monitored regularly and the antihypertensive regimen adjusted, either through uptitration of doses or use of additional agents, to maintain blood pressure control. Serum creatinine and potassium levels should be monitored if ACE inhibitors, ARBs, or diuretics are used in order to detect development of acute kidney disease and hyperkalemia.[26]

## PRESERVING KIDNEY FUNCTION THROUGH CHOLESTEROL CONTROL

Dyslipidemia is another comorbidity commonly associated with type 2 diabetes. Diabetic dyslipidemia is characterized by elevated triglyceride levels, low high-density lipoprotein cholesterol (HDL-C) levels, and an excess of highly atherogenic, small, dense low-density lipoprotein cholesterol (LDL-C) particles (Table 4).[3,25] Studies in animal models have shown that lipoprotein abnormalities can contribute to the initiation and progression of CKD, regardless of its underlying cause, through a number of pathophysiologic mechanisms.[115,116] Several clinical studies also suggest that dyslipidemia can contribute to CKD progression. In particular, high triglycerides and low HDL-C levels (characteristic features of diabetic dyslipidemia) appear to be associated with a deterioration in kidney function.[117-120] Recently presented data from the Study of Heart and Renal Protection (SHARP) trial[121] indicate that lowering of LDL-C slows the progression of nephropathy and reduces cardiovascular events.

The primary role of effective lipid management in patients with diabetes is to reduce the very high cardiovascular risk. Aggressive management of LDL-C levels with statins has been shown to stabilize kidney function in patients with cardiovascular disease[122-125] and to decrease the risk of major cardiovascular events in patients with coronary heart disease and CKD.[126] Current evidence also suggests that statins can significantly improve the eGFR or delay eGFR decline in patients with type 2 diabetes.[127,128] Statins appear to have little effect on events in patients with diabetes and advanced kidney impairment, indicating a need to prescribe these agents before kidney function declines substantially.[128]

### Lipid Goals

Guidelines issued by the AACE and ADA endorse the National Cholesterol Education Program Adult Treatment Panel III lipid targets.[23,25,26]

**LDL-C.** The goal for LDL-C, the primary target of lipid-lowering therapy, is lower than 100 mg/dL (<2.6 mmol/L). The updated goal of lower than 70 mg/dL (<1.8 mmol/L) in very high-risk patients, such as those with diabetes and



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overt cardiovascular disease, is a therapeutic option. If pharmacologic treatment with a maximum tolerated dose of statin fails to achieve these levels, an alternative goal is to reduce LDL-C by approximately 30% to 40%.

**HDL-C.** Although no specific goals exist for HDL-C, levels greater than 40 mg/dL (1.0 mmol/L) in men and greater than 50 mg/dL (1.3 mmol/L) in women are desirable.

**Triglycerides.** No formal goal is given for triglycerides; a concentration lower than 150 mg/dL (1.7 mmol/L) is optimal. If triglyceride levels are 200 mg/dL or higher (2.2 mmol/L), non–HDL-C should be a secondary therapeutic target; the non–HDL-C goal is 30 mg/dL higher than the LDL-C goal.

### Selection of Lipid-Lowering Therapy

**First-line Therapy.** If lipid targets are not achieved with lifestyle measures alone, statins are the lipid-lowering agents of choice for patients with stage 1 to 4 CKD.[3,25,26] Statins should also be initiated at the time of lifestyle interventions in patients with diabetes at very high cardiovascular risk, regardless of baseline lipid levels. This includes all patients with documented cardiovascular disease and those without cardiovascular disease who are older than 40 years and have at least 1 other cardiovascular risk factor. For patients undergoing maintenance hemodialysis, a statin should not be initiated unless there is a specific cardiovascular indication for treatment.[3] Ezetimibe is an appropriate alternative first-line agent for patients who cannot tolerate statins,[25] and fibrates should be used as primary therapy in patients whose triglyceride levels exceed 400 mg/dL.[25]

**Additional Therapy.** If patients do not attain their lipid goals despite treatment with maximally tolerated doses of statin, addition of other lipid-lowering agents should be considered. Options to further reduce LDL-C levels include ezetimibe, niacin (especially in patients with low HDL-C), a fibrate, or a bile acid sequestrant (eg, colesevelam).[25,26] Statin/fibrate combinations should be used with caution because of an increased risk of rhabdomyolysis. This risk appears to be greater among patients with kidney impairment and appears to be lower with fenofibrate than with gemfibrozil.[25,26]

Continued and regular monitoring of the lipid profile is necessary and should direct appropriate adjustments to the therapeutic regimen to maintain lipid control and reduce the cardiovascular, and possibly renal, risk.

## OTHER INTERVENTIONS

Several other therapeutic measures require consideration in patients with type 2 diabetes, although their effects on the progression of diabetic nephropathy are currently unclear.

### Prevention of Anemia

Patients with stage 4 diabetic nephropathy will develop erythropoietin deficiency as the disease progresses, resulting in anemia. Therefore, patients should be screened regularly for onset of anemia and corrective treatment with erythropoietin initiated to increase the hemoglobin level to 11 g/dL (Table 4).[25] A randomized controlled trial has shown that initiating erythropoietin early in nondiabetic predialysis patients with nonsevere anemia slowed the progression of kidney disease and delayed the initiation of renal replacement therapy.[129] However, whether this practice will delay the course of diabetic nephropathy is currently unknown.

### Antithrombotic Therapy

A review of trials suggests that aspirin may offer a modest benefit in reducing cardiovascular risk in patients with diabetes, although the evidence is equivocal.[130] Nevertheless, current ADA diabetes management guidelines,[26] endorsed by the American Heart Association and American College of Cardiology,[130] recommend low-dose aspirin (75-162 mg/d) for primary prevention in patients at increased cardiovascular risk (ie, a 10-year risk of >10%) and for those with diabetes and existing cardiovascular disease (Table 4). Use of aspirin in other individuals for primary prevention should be governed by clinical judgment, dependent on the level of cardiovascular risk. Any contraindications to aspirin and the likelihood of bleeding must also be considered. Clopidogrel at 75 mg/d is a useful alternative for patients unable to tolerate aspirin, and dual antiplatelet therapy for 1 year with aspirin plus clopidogrel should be considered for patients experiencing an acute coronary syndrome.

## CONCLUSION

Nephropathy is a common complication among patients with type 2 diabetes. Surveys indicate that CKD often develops during the prediabetic stage, secondary to hypertension and other factors, and is present in up to a third of adults at the time diabetes is diagnosed. Screening for CKD should be performed annually, starting at the time of diabetes diagnosis, and should include measures of the eGFR in addition to urinary albumin excretion. Conscientious screening will facilitate detection of kidney impairment earlier, when interventions to prevent or delay progression are more effective.

Optimal management of diabetic nephropathy requires implementation of a multifactorial approach, comprising lifelong lifestyle modification strategies, glycemic control, blood pressure control, and cholesterol management. Physicians should aim to achieve target levels for all risk determinants simultaneously through careful and individu-



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alized selection of antidiabetic, antihypertensive, and lipid-lowering agents according to degree of kidney impairment, patient characteristics, and effects on comorbidities. Moreover, continual monitoring and adjustment of the treatment regimen to maintain control of all risk factors over the long term is needed because of the progressive nature of diabetes. Such a coordinated approach to management should now be intuitive based on our increased understanding of the complex interactions among these risk factors in the development of diabetes complications, especially cardiovascular disease and nephropathy. Therefore, it is disappointing to note that substantial proportions of patients with type 2 diabetes do not attain their glycemic, blood pressure, and LDL-C goals, and the prevalence of obesity continues to increase.

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