CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will screen for nephropathy in their diabetic patients and take steps to slow its progression

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Detecting and controlling diabetic nephropathy: What do we know?

ABSTRACT

Diabetic nephropathy is becoming increasingly common with the aging of our population and the obesity epidemic. The major ways to prevent or slow its progression are by reducing blood pressure, controlling blood sugar, and inhibiting the renin-angiotensin-aldosterone axis. New therapeutic agents are also being tried.

KEY POINTS

The progression from no proteinuria to microalbuminuria to clinical proteinuria parallels glomerular changes of thickening of the basement membrane, mesangial expansion, and the development of Kimmelstiel-Wilson nodules and sclerosis.

Blood pressure control to 130/80 mm Hg slows microvascular and macrovascular disease, but the goal should not be lower in older patients with diabetes.

Glycemic control slows microvascular disease: the goal for most patients for hemoglobin A_{1c} is 7.0%. Tighter control may increase cardiovascular risk.

Either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is the first-line treatment for diabetic nephropathy; combining the two is no longer recommended.

If more aggressive treatment is needed, a diuretic or spironolactone (with potassium monitoring) can be added.

The role of sodium bicarbonate and new agents such as blockers of transcription factors is still emerging.

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Diabetes is on the rise, and so is diabetic nephropathy. In view of this epidemic, physicians should consider strategies to detect and control kidney disease in their diabetic patients.

This article will focus on kidney disease in adult-onset type 2 diabetes. Although it has different pathogenetic mechanisms than type 1 diabetes, the clinical course of the two conditions is very similar in terms of the prevalence of proteinuria after diagnosis, the progression to renal failure after the onset of proteinuria, and treatment options.[1]

DIABETES AND DIABETIC KIDNEY DISEASE ARE ON THE RISE

The incidence of diabetes increases with age, and with the aging of the baby boomers, its prevalence is growing dramatically. The 2005–2008 National Health and Nutrition Examination Survey estimated the prevalence as 3.7% in adults age 20 to 44, 13.7% at age 45 to 64, and 26.9% in people age 65 and older. The obesity epidemic is also contributing to the increase in diabetes in all age groups.

Diabetic kidney disease has increased in the United States from about 4 million cases 20 years ago to about 7 million in 2005–2008.[2] Diabetes is the major cause of end-stage renal disease in the developed world, accounting for 40% to 50% of cases. Other major causes are hypertension (27%) and glomerulonephritis (13%).[3]

Physicians in nearly every field of medicine now care for patients with diabetic nephropathy. The classic presentation—a patient who has impaired vision, fluid retention with edema, and hypertension—is commonly seen in dialysis units and ophthalmology and cardiovascular clinics.

TABLE 1

Screening for diabetic nephropathy

Test	When	Normal
Blood pressure	Each office visit	< 130/80 mm Hg
Urinary albumin	Type 2: Annually beginning at diagnosis Type 1: Annually, 5 years after diagnosis	< 30 mg/day or < 20 µg/min or < 30 µg/mg creatinine

BASED ON INFORMATION IN MOLITCH ME, DEFRONZO RA, FRANZ MJ, ET AL; AMERICAN DIABETES ASSOCIATION. NEPHROPATHY IN DIABETES. DIABETES CARE 2004; 27(SUPPL 1):S79–S83.

CLINICAL PROGRESSION

Early in the course of diabetic nephropathy, blood pressure is normal and microalbuminuria is not evident, but many patients have a high glomerular filtration rate (GFR), indicating temporarily "enhanced" renal function or hyperfiltration. The next stage is characterized by microalbuminuria, correlating with glomerular mesangial expansion: the GFR falls back into the normal range and blood pressure starts to increase. Finally, macroalbuminuria occurs, accompanied by rising blood pressure and a declining GFR, correlating with the histologic appearance of glomerulosclerosis and Kimmelstiel-Wilson nodules.[4]

Hypertension develops in 5% of patients by 10 years after type 1 diabetes is diagnosed, 33% by 20 years, and 70% by 40 years. In contrast, 40% of patients with type 2 diabetes have high blood pressure at diagnosis.

Unfortunately, in most cases, this progression is a one-way street, so it is critical to intervene to try to slow the progression early in the course of the disease process.

Diabetes is the major cause of end-stage renal disease in the developed world

SCREENING FOR DIABETIC NEPHROPATHY

Nephropathy screening guidelines for patients with diabetes are provided in TABLE 1.[5]

Blood pressure should be monitored at each office visit (TABLE 1). The goal for adults with diabetes should be to reduce blood pressure to 130/80 mm Hg. Reduction beyond this level may be associated with an increased mortality rate.[6] Very high blood pressure (> 180 mm Hg systolic) should be lowered slowly. Lowering blood pressure delays the progression from microalbuminuria (30–299 mg/day or 20–199 µg/min) to macroalbuminuria (> 300 mg/day or > 200 µg/min) and slows the progression to renal failure.

Urinary albumin. Proteinuria takes 5 to 10 years to develop after the onset of diabetes. Because it is possible for patients with type 2 diabetes to have had the disease for some time before being diagnosed, urinary albumin screening should be performed at diagnosis and annually thereafter. Patients with type 1 are usually diagnosed with diabetes at or near onset of disease; therefore, annual screening for urinary albumin can begin 5 years after diagnosis.[5]

Proteinuria can be measured in different ways (TABLE 2). The basic screening test for clinical proteinuria is the urine dipstick, which is very sensitive to albumin and relatively insensitive to other proteins. "Trace-positive" results are common in healthy people, so proteinuria is not confirmed unless a patient has repeatedly positive results.

Microalbuminuria is important to measure, especially if it helps determine therapy. It is not detectable by the urinary dipstick, but can be measured in the following ways:

- Measurement of the albumin-creatinine ratio in a random spot collection
- 24-hour collection (creatinine should simultaneously be measured and creatinine clearance calculated)
- Timed collection (4 hours or overnight).

The first method is preferred, and any positive test result must be confirmed by repeat analyses of urinary albumin before a patient is diagnosed with microalbuminuria.

Occasionally a patient presenting with proteinuria but normal blood sugar and hemoglobin A_{1c} will have a biopsy that reveals morphologic changes of classic diabetic nephropathy.

TABLE 2

Definitions of microalbuminuria and microalbuminuria

	Normal	Microalbuminuria	Macroalbuminuria
Urine dipstick	Negative	Negative	Positive
Urine albumin excretion rate (μg/min)	< 20	20–200	> 200
Urine albumin excretion rate (mg/24 h)	< 30	30–300	> 300
Urine albumin-to-creatinine ratio (mg/g)	< 30	30–300	> 300

Most such patients have a history of hyperglycemia, indicating that they actually have been diabetic.

Proteinuria—the best marker of disease progression

Proteinuria is the strongest predictor of renal outcomes. The Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) study was a randomized, placebo-controlled trial in more than 1,500 patients with type 2 diabetes to test the effects of losartan on renal outcome. Those with high albuminuria (> 3.0 g albumin/g creatinine) at baseline were five times more likely to reach a renal end point and were eight times more likely to have progression to end-stage renal disease than patients with low albuminuria (< 1.5 g/g).[7] The degree of albuminuria after 6 months of treatment showed similar predictive trends, indicating that monitoring and treating proteinuria are extremely important goals.

STRATEGY 1 TO LIMIT RENAL INJURY: REDUCE BLOOD PRESSURE

Blood pressure control improves renal and cardiovascular function.

As early as 1983, Parving et al,[8] in a study of only 10 insulin-dependent diabetic patients, showed strong evidence that early aggressive antihypertensive treatment improved the course of diabetic nephropathy. During the mean pretreatment period of 29 months, the GFR decreased significantly and the urinary albumin excretion rate and arterial blood pressure rose significantly. During the mean 39-month period of antihypertensive treatment with metoprolol, hydralazine, and furosemide or a thiazide, mean arterial blood pressure fell from 144/97 to 128/84 mm Hg and urinary albumin excretion from 977 to 433 μg/min. The rate of decline in GFR slowed from 0.91 mL/min/month before treatment to 0.39 mL/min/month during treatment.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial[9] enrolled more than 11,000 patients internationally with type 2 diabetes at high risk for cardiovascular events. In addition to standard therapy, blood pressure was intensively controlled in one group with a combination of the angiotensin-converting enzyme (ACE) inhibitor perindopril and the diuretic indapamide. The intensive-therapy group achieved blood pressures less than 140/80 mm Hg and had a mean reduction of systolic blood pressure of 5.6 mm Hg and diastolic blood pressure of 2.2 mm Hg vs controls. Despite these apparently modest reductions, the intensively controlled group had a significant 9% reduction of the primary outcome of combined macrovascular events (cardiovascular death, myocardial infarction, and stroke) and microvascular events (new or worsening nephropathy, or retinopathy).[10]

Diabetic nephropathy progression is a one-way street

A meta-analysis of studies of patients with type 2 diabetes found reduced nephropathy with systolic blood pressure control to less than 130 mm Hg.[11]

The United Kingdom Prospective Diabetes Study (UKPDS) is a series of studies of diabetes. The original study in 1998 enrolled 5,102 patients with newly diagnosed type 2 diabetes.[12] The more than 1,000 patients with hypertension were randomized to either tight blood pressure

TABLE 3

Blood pressure goals in diabetes

Blood pressure < 140/90 mm Hg in all patients
Systolic blood pressure 130–135 mm Hg if it can be done without side effects
Blood pressure < 130/80 mm Hg* if diabetic nephropathy and proteinuria are present (> 300 mg/day)
Consider tighter goals for some patients, but tighter goals may cause more side effects, visits, and costs, with few additional benefits

*Goal may be too low for elderly patients

control or regular care. The intensive treatment group had a mean blood pressure reduction of 9 mm Hg systolic and 3 mm Hg diastolic, along with major reductions in all diabetes end points, diabetes deaths, microvascular disease, and stroke over a median follow-up of 8.4 years.

Continuous blood pressure control is critical

Tight blood pressure control must be maintained to have continued benefit. During the 10 years following the UKPDS, no attempts were made to maintain the previously assigned therapies. A follow-up study[13] of 884 UKPDS patients found that blood pressures were the same again between the two groups 2 years after the trial was stopped, and no beneficial legacy effect from previous blood pressure control was evident on end points.

Proteinuria is the strongest predictor of outcome

Control below 120 mm Hg systolic not needed

Blood pressure control slows kidney disease and prevents major macrovascular disease, but there is no evidence that lowering systolic blood pressure below 120 mm Hg provides additional benefit. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[14] more than 10,000 patients with type 2 diabetes and existing cardiovascular disease or additional cardiovascular risk factors were randomized to a goal of systolic blood pressure less than 120 mm Hg or less than 140 mm Hg (actual mean systolic pressures were 119 vs 134 mm Hg, respectively). Over nearly 5 years, there was no difference in cardiovascular events or deaths between the two groups.[15]

Since 1997, six international organizations have revised their recommended blood pressure goals in diabetes mellitus and renal diseases. Randomized clinical trials and observational studies have demonstrated the importance of blood pressure control to the level of 125/75 to 140/80 mm Hg. The National Kidney Foundation, the American Diabetes Association, and the Canadian Hypertension Society have developed consensus guidelines for blood pressure control to less than 130/80 mm Hg.[16–21] TABLE 3 summarizes blood pressure goals for patients with diabetes.

STRATEGY 2: CONTROL BLOOD SUGAR

Recommendations for blood sugar goals are more controversial.

The Diabetes Control and Complications Trial[22] provided early evidence that tight blood sugar control slows the development of microalbuminuria and macroalbuminuria. The study randomized more than 1,400 patients with type 1 diabetes to either standard therapy (1 or 2 daily insulin injections) or intensive therapy (an external insulin pump or 3 or more insulin injections guided by frequent blood glucose monitoring) to keep blood glucose levels close to normal. About half the patients had mild retinopathy at baseline and the others had no retinopathy. After 6.5 years, intensive therapy was found to significantly delay the onset and slow the progression of diabetic retinopathy and nephropathy.

The Kumamoto Study[23] randomized 110 patients with type 2 diabetes and either no retinopathy (primary prevention cohort) or simple retinopathy (secondary prevention cohort) to receive either multiple insulin injections or conventional insulin therapy over 8 years. Intensive therapy led to lower rates of retinopathy (7.7% vs 32% in primary prevention and 19% vs 44% in secondary prevention) and progressive nephropathy (7% vs 28% in primary prevention at 6 years and 11% vs 32% in secondary prevention).

In addition to studying the effects of blood pressure control, the UKPDS also studied the effects of intensive blood glucose control.[24,25] Nearly 4,000 patients with newly diagnosed type 2 diabetes were randomized to intensive treatment with a sulfonylurea or insulin, or to conventional treatment with diet. Over 10

years, the mean hemoglobin A_{1c} was reduced to 7.0% in the intensive group and 7.9% in the conventional group. The risk of any diabetes-related end point was 12% lower in the intensive group, 10% lower for diabetes-related death, and 6% lower for all-cause mortality. There was also a 25% reduction in microvascular disease (retinopathy and nephropathy). However, the intensive group had more hypoglycemic episodes than the conventional group and a tendency to some increase in macrovascular events. A legacy effect was evident: patients who had intensive treatment had less microvascular disease progression years after stopping therapy.

Tight glycemic control reduces nephropathy, but does it increase cardiovascular risk?

Earlier trials provided strong evidence that blood glucose control prevents or slows retinopathy and nephropathy. The critical question is, "At what expense?" Although diabetes is the most common cause of kidney failure in the United States, most people with diabetes do not die of kidney failure, but of cardiovascular disease. Two recent large trials had different results regarding glycemic control below hemoglobin A_{1c} of 7.0% and macrovascular risk, creating a controversy about what recommendations are best.

The ADVANCE trial, enrolling 11,140 patients with type 2 diabetes, was largely conducted in Australia and used the sulfonylurea glipizide for glycemic control. Compared with the group that received standard therapy (n=5,569), the intensive-treatment group (n=5,571) achieved mean hemoglobin A_{1c} levels of 6.5% compared with 7.3% in the standard group, and had less nephropathy, less microalbuminuria, less doubling of creatinine, and a lower rate of end-stage renal disease (4% vs 5% in the standard therapy group). No difference between the two groups was found in retinopathy. Rates of all-cause mortality did not differ between the groups.[9]

The ACCORD trial had more than 10,000 subjects with type 2 diabetes and took place mostly in the United States. Using mainly rosiglitazone for intensive therapy, the intensive group achieved hemoglobin A_{1c} levels of 6.4% vs 7.5% in the standard-therapy group. The trial was stopped early, at 3.7 years, because of a higher risk of death and cardiovascular events in the group with intensive glycemic control. However, the intensive-therapy group did have a significant decrease in microvascular renal outcomes and a reduction in the progression of retinopathy.[14,26]

In summary, tighter glycemic control improves microvascular complications—both retinopathy and nephropathy—in patients with type 2 diabetes. The benefit of intensive therapy on macrovascular complications (stroke, myocardial infarction) in long-standing diabetes has not been convincingly demonstrated in randomized trials. The UKPDS suggested that maintaining a hemoglobin A_{1c} of 7% in patients newly diagnosed with type 2 diabetes confers long-term cardiovascular benefits. The target hemoglobin A_{1c} for type 2 diabetes should be tailored to the patient: 7% is a reasonable goal for most patients, but the goal should be higher for the elderly and frail. Reducing the risk of cardiovascular death is still best done by controlling blood pressure, reducing lipids, quitting smoking, and losing weight.

STRATEGY 3: INHIBIT THE RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

Blood pressure control slows kidney and cardiovascular disease

Components of the renin-angiotensin-aldosterone system are present not only in the circulation but also in many tissues, including the heart, brain, kidney, blood vessels, and adrenal glands. The role of renin-angiotensin-aldosterone system blockers in treating and preventing diabetic nephropathy has become controversial in recent years with findings from new studies.

The renin-angiotensin-aldosterone system is important in the development or maintenance of high blood pressure and the resultant damage to the brain, heart, and kidney. Drug development has focused on inhibiting steps in the biochemical pathway. ACE inhibitors block the formation of angiotensin II—the most biologically potent angiotensin peptide—and are among the most commonly used drugs to treat hypertension and concomitant conditions, such as renal insufficiency, proteinuria, and heart failure. Angiotensin receptor blockers (ARBs) interact with the angiotensin AT1 receptor and block most of its actions. They are approved by the US Food

and Drug Administration (FDA) for the treatment of hypertension, and they help prevent left ventricular hypertrophy and mesangial sclerosis. Large studies have shown that ACE inhibitors and ARBs offer similar cardiovascular benefit.

The glomerulus has the only capillary bed with a blood supply that drains into an efferent arteriole instead of a venule, providing high resistance to aid filtration. Efferent arterioles are rich in AT1 receptors. In the presence of angiotensin II they constrict, increasing pressure in the glomerulus, which can lead to proteinuria and glomerulosclerosis. ACE inhibitors and ARBs relax the efferent arteriole, allowing increased blood flow through the glomerulus. This reduction in intraglomerular pressure is associated with less proteinuria and less glomerulosclerosis.

Diabetes promotes renal disease in many ways. Glucose and advanced glycation end products can lead to increased blood flow and increased pressure in the glomerulus. Through a variety of pathways, hyperglycemia, acting on angiotensin II, leads to NF-kapa beta production, profibrotic cytokines, increased matrix, and eventual fibrosis. ACE inhibitors and ARBs counteract many of these.

Tight blood sugar control slows retinopathy and nephropathy, but at what expense?

ACE inhibitors and ARBs slow nephropathy progression beyond blood pressure control

Several major clinical trials[27–32] examined the effects of either ACE inhibitors or ARBs in slowing the progression of diabetic nephropathy and have had consistently positive results.

The Collaborative Study Group[30] was a 3-year randomized trial in 419 patients with type 1 diabetes, using the ACE inhibitor captopril vs placebo. Captopril was associated with less decline in kidney function and a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small difference in blood pressures between the two groups.

The Irbesartan Diabetic Nephropathy Trial (IDNT)[31] studied the effect of the ARB irbesartan vs the calcium channel blocker amlodipine vs placebo over 2.6 years in 1,715 patients with type 2 diabetes. Irbesartan was found to be significantly more effective in protecting against the progression of nephropathy, independent of reduction in blood pressure.

The RENAAL trial,[32] published in 2001, was a 3-year, randomized, double-blind study comparing the ARB losartan at increasing dosages with placebo (both taken in addition to conventional antihypertensive treatment) in 1,513 patients with type 2 diabetes and nephropathy. The blood pressure goal was 140/90 mm Hg in both groups, but the losartan group had a lower rate of doubling of serum creatinine, end-stage renal disease, and combined end-stage renal disease or death.

'Aldosterone escape' motivates the search for new therapies

An important reason for developing more ways to block the renin-angiotensin-aldosterone system is because of "aldosterone escape," the phenomenon of angiotensin II or aldosterone returning to pretreatment levels despite continued ACE inhibition.

Biollaz et al,[33] in a 1982 study of 19 patients with hypertension, showed that despite reducing blood pressure and keeping the blood level of ACE very low with twice-daily enalapril 20 mg, blood and urine levels of angiotensin II steadily rose back to baseline levels within a few months.

A growing body of evidence suggests that despite effective inhibition of angiotensin II activity, non-ACE synthetic pathways still permit angiotensin II generation via serine proteases such as chymase, cathepsin G, and tissue plasminogen activator.

Thus, efforts have been made to block the renin-angiotensin system in other places. In addition to ACE inhibitors and ARBs, two aldosterone receptor antagonists are available, spironolactone and eplerenone, both used to treat heart failure. A direct renin inhibitor, aliskiren, is also available.

Combination therapy—less proteinuria, but…

A number of studies have shown that combination treatment with agents having different targets in the renin-angiotensin-aldosterone system leads to larger reductions in albuminuria than does single-agent therapy.

Mogensen et al[34] studied the effect of the ACE inhibitor lisinopril (20 mg per day) plus the ARB candesartan (16 mg per day) in sub-

jects with microalbuminuria, hypertension, and type 2 diabetes. Combined treatment was more effective in reducing proteinuria.

Epstein et al[35] studied the effects of the ACE inhibitor enalapril (20 mg/day) combined with either of two doses of the selective aldosterone receptor antagonist eplerenone (50 or 100 mg/day) or placebo. Both eplerenone dosages, when added to the enalapril treatment, significantly reduced albuminuria from baseline as early as week 4 ($P < .001$), but placebo treatment added to the enalapril did not result in any significant decrease in urinary albumin excretion. Systolic blood pressure decreased significantly in all treatment groups and by about the same amount.

The Aliskiren Combined With Losartan in Type 2 Diabetes and Nephropathy (AVOID) trial[36] randomized more than 600 patients with type 2 diabetes and nephropathy to aliskiren (a renin inhibitor) or placebo added to the ARB losartan. Again, combination treatment was more renoprotective, independent of blood pressure lowering.

Worse outcomes with combination therapy?

More recent studies have indicated that although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal and cardiovascular outcomes. The multicenter Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[37] randomized more than 25,000 patients age 55 and older with established atherosclerotic vascular disease or with diabetes and end-organ damage to receive either the ARB telmisartan 80 mg daily, the ACE inhibitor ramipril 10 mg daily, or both. Mean follow-up was 56 months. The combination-treatment group had higher rates of death and renal disease than the single-therapy groups (which did not differ from one another).

Why the combination therapy had poorer outcomes is under debate. Patients may get sudden drops in blood pressure that are not detected with only periodic monitoring. Renal failure was mostly acute rather than chronic, and the estimated GFR declined more in the combined therapy group than in the single-therapy groups.

The Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) was designed to test the effect of the direct renin inhibitor aliskiren or placebo, both arms combined with either an ACE inhibitor or an ARB in patients with type 2 diabetes at high risk for cardiovascular and renal events. The trial was terminated early because of more strokes and deaths in the combination therapy arms. The results led the FDA to issue black box warnings against using aliskiren with these other classes of agents, and all studies testing similar combinations have been stopped. (In one study that was stopped and has not yet been published, 100 patients with proteinuria were treated with either aliskiren, the ARB losartan, or both, to evaluate the effects of aldosterone escape. Results showed no differences: about one-third of each group had this phenomenon.)

My personal recommendation is as follows: for younger patients with proteinuria, at lower risk for cardiovascular events and with disease due not to diabetes but to immunoglobulin A nephropathy or another proteinuric kidney disease, treat with both an ACE inhibitor and ARB. But the combination should not be used for patients at high risk of cardiovascular disease, which includes almost all patients with diabetes.

Most people with diabetes die of cardiovascular disease, not kidney disease

If more aggressive renin-angiotensin system blockade is needed against diabetic nephropathy, adding a diuretic increases the impact of blocking the renin-angiotensin-aldosterone system on both proteinuria and progression of renal disease. The aldosterone blocker spironolactone 25 mg can be added if potassium levels are carefully monitored.

ACE inhibitor plus calcium channel blocker is safer than ACE inhibitor plus diuretic

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial[38] randomized more than 11,000 high-risk patients with hypertension to receive an ACE inhibitor (benazepril) plus either a calcium channel blocker (amlodipine) or thiazide diuretic (hydrochlorothiazide). Blood pressures were identical between the two groups, but the trial was terminated early, at 36 months, because of a higher risk of the combined end point of cardiovascular death, myocardial infarction, stroke, and other

major cardiac events in the ACE inhibitor-thiazide group.

Although some experts believe this study is definitive and indicates that high blood pressure should never be treated with an ACE inhibitor-thiazide combination, I believe that caution is needed in interpreting these findings. This regimen should be avoided in older patients with diabetes at high risk for cardiovascular disease, but otherwise, getting blood pressure under control is critical, and this combination can be used if it works and the patient is tolerating it well.

In summary, the choice of blood pressure-lowering medications is based on reducing cardiovascular events and slowing the progression of kidney disease. Either an ACE inhibitor or an ARB is the first choice for patients with diabetes, hypertension, and any degree of proteinuria. Many experts recommend beginning one of these agents even if proteinuria is not present. However, the combination of an ACE inhibitor and ARB should not be used in diabetic patients, especially if they have cardiovascular disease, until further data clarify the results of the ONTARGET and ALTITUDE trials.

STRATEGY 4: METABOLIC MANIPULATION WITH NOVEL AGENTS

Several new agents have recently been studied for the treatment of diabetic nephropathy, including aminoguanidine, which reduces levels of advanced glycation end-products, and sulodexide, which blocks basement membrane permeability. Neither agent has been shown to be safe and effective in diabetic nephropathy. The newest agent is bardoxolone methyl. It induces the Keap1–Nrf2 pathway, which up-regulates cytoprotective factors, suppressing inflammatory and other cytokines that are major mediators of progression of chronic kidney disease.[39]

Pergola et al,[40] in a phase 2, double-blind trial, randomized 227 adults with diabetic kidney disease and a low estimated GFR (20–45 mL/min/1.73 m^2) to receive placebo or bardoxolone 25, 75, or 150 mg daily. Drug treatment was associated with improvement in the estimated GFR, a finding that persisted throughout the 52 weeks of treatment. Surprisingly, proteinuria did not decrease with drug treatment.

As of this writing, a large multicenter controlled randomized trial has been halted because of concerns by the data safety monitoring board, which found increased rates of death and fluid retention with the drug. A number of recent trials have shown a beneficial effect of sodium bicarbonate therapy in patients with late-stage chronic kidney disease. They have shown slowing of the progression of GFR decline in a number of renal diseases, including diabetes.

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