Diabetic Nephropathy for the Primary Care Physician: More than Microalbuminuria

Case Study and Commentary, Jeffrey A. Giullian, MD, Peale Chuang, MD, and Julia B. Lewis, MD

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, accounting for approximately 45% of incident and 55% of prevalent cases in the past 10 years [1–3]. The frequency of diabetic nephropathy–induced ESRD has increased dramatically from 7000 new cases in 1984 to over 41,000 in 2003 [4]. This trend has begun to slow somewhat in recent years. However, the number of Americans with diabetes mellitus (DM) has more than doubled over the past 2 decades, from 5.8 million in 1980 to 13.8 million in 2003 [5] and is expected to double again in the coming decade, mostly as a result of the increased incidence of type 2 diabetes [6]. In 2003, Medicare spent nearly $17 billion to cover the health expenses of over 400,000 patients with ESRD [4], and experts predict an increase in this expenditure to $28.3 billion by the year 2010 [7]. This phenomenal growth in both new patients and health care costs has led experts to describe diabetic nephropathy as “a medical catastrophe of worldwide dimensions” [8]. As such, any strategies that prevent the development or delay the progression of diabetic nephropathy are of paramount importance.

Between 25% and 40% of patients with DM will develop diabetic nephropathy [9–11]. African Americans, Mexican Americans, Native Americans, and Polynesians with diabetes are at even higher risk than Caucasians for developing diabetic nephropathy [12]. Over the past decade and a half, several studies have led to the development of specific interventions that delay progression of this disease. These therapies are most effective when instituted early, making timely detection during the asymptomatic phase of diabetic nephropathy crucial for at-risk individuals. In this case-based review, we will present a general overview of diabetic nephropathy and discuss several relevant clinical studies that have evaluated the efficacy of common therapies. In addition, the recommendations recently set forth by the American Diabetes Association (ADA), the National Kidney Foundation (NKF), and other expert bodies will be discussed.

**CASE 1**

**Initial Presentation**

A 45-year-old white woman presents to her primary care physician for an annual health physical.

From the Division of Nephrology, Vanderbilt University School of Medicine, Nashville, TN.
Table 1. Risk Factors for Developing Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic predisposition</td>
<td>Positive family history for kidney disease in a first-degree relative</td>
</tr>
<tr>
<td>Racial backgrounds at increased risk:</td>
<td>African Americans</td>
</tr>
<tr>
<td></td>
<td>Hispanics (Mexican Americans)</td>
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<tr>
<td></td>
<td>Native Americans (Pima Indians)</td>
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<td></td>
<td>Maori and South Pacific Polynesians</td>
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<td>Uncontrolled hypertension</td>
<td>Poor glycemic control</td>
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<td></td>
<td>Smoking</td>
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<td></td>
<td>Hyperlipidemia</td>
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<tr>
<td>Presence of microvascular disease:</td>
<td>Retinopathy</td>
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<tr>
<td></td>
<td>Neuropathy</td>
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<td></td>
<td>Peripheral vascular disease</td>
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</table>

Table 2. Stages of Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Renal hypertrophy with glomerular hyperfiltration (low or normal serum creatinine concentration)</td>
</tr>
<tr>
<td>2</td>
<td>Glomerular lesions present (glomerular basement membrane thickening and mesangial expansion); no abnormal protein in the urine</td>
</tr>
<tr>
<td>3</td>
<td>Microalbuminuria with mild to moderate decrease in glomerular filtration rate</td>
</tr>
<tr>
<td>4</td>
<td>Overt diabetic nephropathy with proteinuria and moderate to severe decrease in glomerular filtration rate</td>
</tr>
<tr>
<td>5</td>
<td>End-stage renal disease</td>
</tr>
</tbody>
</table>

**History and Physical Examination**

The patient says she has been healthy and denies any history of serious or chronic medical illnesses. Her blood pressure (BP) is 140/85 mm Hg and her body mass index (BMI) is 29 Kg/m$^2$. The remainder of the physical examination is unremarkable. The physician orders some routine laboratory studies including electrolytes, liver function tests, and hematologic cell counts. Test results are within normal limits except for a serum glucose level of 195 mg/dL.

The patient returns the following week and is diagnosed with DM based on results of a glucose tolerance test. Her hemoglobin A$_1c$ (HbA$_1c$) is 8.5%. The patient reveals that her 65-year old father developed ESRD from diabetes and has been on dialysis for the past 2 years. She is concerned that she will also develop ESRD and need dialysis.

- **What risk factors are associated with development of diabetic nephropathy and ESRD?**

Diabetic nephropathy may develop in up to 40% of patients with diabetes. Several risk factors increase the likelihood of developing diabetic nephropathy; such as persistently elevated BP [13,14], poor glycemic control [15–18], genetic predisposition including family history and race [19–24], hyperlipidemia [13,15,25], and smoking [26–29] (Table 1). In addition, the quantity of albuminuria (proteinuria) in an individual predicts the rate of progression of renal dysfunction, with a more rapid decline in kidney function occurring in diabetic patients excreting higher amounts of urinary protein [30,31]. Based on this patient’s positive family history of diabetic nephropathy in a first-degree relative, borderline hypertension, and poor glycemic control, she is at increased risk of developing diabetic nephropathy.

- **What is diabetic nephropathy?**

Diabetic nephropathy is a clinical disorder characterized by the presence of increased urinary albumin excretion and/or persistently reduced glomerular filtration rate (GFR). The natural progression of diabetic nephropathy has classically been divided into 5 stages (Table 2) [32]. Normal-sized or mildly enlarged kidneys with normal or mildly elevated GFR characterizes stage 1. Stage 2 is distinguished by the presence of glomerular basement membrane thickening and mesangial expansion on microscopic evaluation of renal biopsy tissue. Both the first and second stages are generally clinically silent. By stage 3, microalbuminuria (defined in the next section) is present, usually occurring at least 5 to 10 years after the onset of diabetes. A fraction of patients with stage 3 diabetic nephropathy will have spontaneous regression of microalbuminuria [33]. Without treatment, however, patients may progress to stage 4 diabetic nephropathy with overt albuminuria (also referred to as macroalbuminuria or proteinuria) detectable by routine dipstick urinalysis. Stage 4 is associated with a decline in renal function and the albuminuria is predictive of further decline in GFR [34]. Subsequently, some patients evolve to stage 5, defined as ESRD requiring renal replacement therapy. This natural history and timeline has best been described in patients with type 1 diabetes. In the general clinic population, the time of onset of type 2 diabetes is often unclear and may be delayed by many years. Hence, this group of patients may present with advanced stages of diabetic nephropathy at the time of initial diabetes diagnosis. Additionally, death from cardiovascular disease often precedes progression to...
advanced renal dysfunction or renal failure in patients with type 2 diabetes [35].

- What tests are recommended to screen for diabetic kidney disease?

This patient has type 2 DM caused by a relative deficiency of insulin production accompanied by peripheral tissue resistance to insulin. In the United States, over 90% of incident cases of diabetes are type 2 [36]. The ADA recommends screening for diabetic nephropathy immediately following the diagnosis of type 2 DM, as these individuals may have had longstanding diabetes prior to diagnosis and may have already sustained renal injury. In contrast, the time of onset of type 1 DM is easily established and screening for microalbuminuria is recommended 5 years after diagnosis [37]. Regardless of the type of diabetes, patients whose initial screen is negative for microalbuminuria should be screened yearly thereafter.

Screening for diabetic nephropathy requires checking the patient’s serum creatinine level and checking the urine for the presence of albumin. Albumin is generally the most prevalent protein circulating in the blood. The kidney normally excretes very little albumin into the urine, as the glomerular filtration barrier prevents passage of the majority of albumin into the urinary space. In addition, epithelial cells of the proximal tubule reabsorb much of the albumin that enters the urinary space. Only a minute amount of albumin is filtered and even less is lost in the urine. On average, only 8 to 10 mg of albumin is excreted each day. Normal urinary albumin excretion has been arbitrarily defined as less than 30 mg daily. Microalbuminuria refers to albumin excretion between 30 and 300 mg daily, while overt albuminuria or macroalbuminuria refers to levels greater than 300 mg per day. The term proteinuria refers to the urinary excretion of multiple proteins; albumin accounts for 15% to 60% of total proteinuria.

Along with checking serum creatinine levels, initial screening for kidney disease includes a simple dipstick urinalysis, looking specifically for the presence of elevated urinary protein excretion [37]. Most dipstick urinalysis tests are adequate for determining the presence of overt albuminuria but will not recognize smaller amounts of albumin in the urine. For this reason, a negative dipstick urinalysis for proteinuria does not rule out diabetic nephropathy. Rather, a negative dipstick test necessitates further examination for the presence of small amounts of albumin in the urine, referred to as microalbuminuria (defined as 30–300 mg/day).

Urinary albumin and total protein excretion rates may be quantified in a 24-hour urine collection or by shorter collection times such as 4 hours, 6 hours, or overnight collections. Microalbuminuria in these timed collections is defined as a urinary albumin excretion rate between 20 and 200 µg per minute of collection time. These levels correlate to 30 and 300 mg, respectively, of albumin excretion daily.

The spot urine protein-to-creatinine ratio or the albumin-to-creatinine ratio (ACR) are now more commonly used than the above noted timed collections for determining the level of total protein or albumin in the urine. The ACR is convenient since it does not necessitate a timed collection and reduces collection errors. Recent reviews and guidelines [37–39] define a normal ACR as less than 30 µg albumin/mg creatinine, microalbuminuria as 30 to 299 µg/mg, and overt albuminuria as 300 µg/mg or greater. (Table 3). However, these current classifications of normal and abnormal urinary albumin loss, using the ACR, do not account for differences in creatinine excretion in men versus women. In general, women excrete less creatinine into the urine due to lower overall muscle mass. Thus, a female excreting 100 mg of albumin into the urine daily will have a higher ACR than a male excreting the same amount due to the differences of urinary creatinine excretion. Future reviews and guidelines will likely incorporate this important gender difference when describing normal versus abnormal values.

Regardless of which method is used to determine urine albumin levels, the test should be performed on 3 different urine samples collected separately within a several-month period. Recurrent testing increases accuracy, as urinary protein excretion may vary significantly day to day due to confounding factors including fever, heavy exercise, and prolonged periods of standing [40].

Further Evaluation

On serial measurements, the patient is found consistently to have microalbuminuria. Her serum creatinine level is 1.0 mg/dL.

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**Table 3. Definitions of Urinary Albumin Excretion in Diabetic Nephropathy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Urinary Dipstick for Protein</th>
<th>Timed Collection, µg/min</th>
<th>24-Hour Collection, mg/24 hr</th>
<th>Spot Urinary Albumin/Creatinine Ratio, µg/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Negative</td>
<td>&lt; 20</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Negative</td>
<td>20–199</td>
<td>30–299</td>
<td>30–299</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>Positive</td>
<td>≥ 200</td>
<td>≥ 300</td>
<td>≥ 300</td>
</tr>
</tbody>
</table>

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Patients with early diabetic nephropathy often have low or normal serum creatinine levels, corresponding to a supraphysiologic GFR, often 50% higher than expected for age [41,42]. This early stage of diabetic nephropathy (stage 1) is associated with glomerular hyperfiltration, renal hypertrophy, and intraglomerular hypertension. Eventually, hyperfiltration and glomerular hypertension lead to sclerosis and irreversible kidney damage. Therefore, aggressive treatment at this early hyperfiltration phase, before creatinine rises, may be very effective at slowing the progression of diabetic nephropathy [43].

Three formulas are commonly used to estimate a patient’s renal function based on serum creatinine: the Cockcroft-Gault equation [44], the Modification of Diet in Renal Disease (MDRD) equation [45], and the modified MDRD equation [46]. Calculated by the modified MDRD equation, this patient’s estimated GFR is greater than 60 mL/min/1.73 m² (Table 4). The rate of renal function decline varies greatly from patient to patient, making it difficult to predict with certainty when a particular individual will develop ESRD. Historically, if left untreated, the GFR of a patient with diabetic nephropathy will decline 6 to 12 mL/min/year [47,48] potentially necessitating renal replacement therapy for this patient in less than 5 years. With treatment, however, the rate of decline in renal function can decrease to only 3 to 5 mL/min/year [49–51], delaying this patient’s onset of ESRD for approximately 10 to 17 years.

**Follow-up**

This patient’s BP on follow-up visits and home measurements averages 140/85 mm Hg.

Over the past decade, BP goals have become increasingly more stringent as epidemiologic studies report a strong, consistent correlation between BP and diabetic complications such as ESRD, coronary events, and stroke. Unfortunately, unequivocal evidence from trials, in which diabetic patients are randomized to different BP goals, do not conclusively demonstrate further improvement in renal outcomes below a BP target of 140/90 mm Hg.

The United Kingdom Prospective Diabetes Study (UKPDS) enrolled over 1100 hypertensive type 2 diabetic patients with an average initial mean BP of 160/94 mm Hg and randomized patients to tight BP control (average BP achieved, 144/82 mm Hg) or to a less restrictive BP goal (average BP achieved, 154/87 mm Hg) with a median 8.4-year follow-up. The tight BP treatment goal, which resulted in a greater than 10-mm Hg reduction in systolic blood pressure (SBP) compared with the less restrictive BP goal, resulted in a 29% relative risk reduction for the development of microalbuminuria and a 39% relative risk reduction for developing macroalbuminuria [52]. At the end of treatment, however, the 2 cohorts had similar serum creatinine levels, suggesting that BP control did not affect overall kidney function in terms of solute clearance. It remains unclear if more stringent BP control, defined as less than 130/80 mm Hg [53], would have improved overall kidney function.

Subsequently, the Appropriate Blood Pressure Control in Diabetics (ABCD) trial enrolled 950 patients with type 2 diabetes and compared intensive diastolic blood pressure (DBP) control (10 mm Hg below baseline DBP) versus moderate BP control (DBP, 80–90 mm Hg). Additionally, this trial evaluated the calcium channel blocker nisoldipine versus the angiotensin-converting enzyme inhibitor (ACEI) enalapril as first-line antihypertensive agents. In the subset of 480 normotensive diabetic patients (baseline DBP, 80–89 mm Hg) enrolled in this trial, those randomized to intensive BP control (average BP achieved, 128/75 mm Hg) were less likely to develop microalbuminuria or albuminuria as compared with those maintained at a slightly higher BP (average BP achieved, 137/81 mm Hg) [51]. Similar to the UKPDS study, there was no statistically significant difference in creatinine clearance between the 2 groups. Somewhat

### Table 4. Glomerular Filtration Rate (GFR) Estimating Equations

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>$(140–\text{age}) \times \text{weight [kg]} \times (0.85 \text{ if female})$ $72 \times \text{creatinine [mg/dL]}$</td>
</tr>
<tr>
<td>Modification of Diet in Renal</td>
<td>$170 \times (\text{Cr_{serum}}^{0.809} \times (\text{age})^{–0.176} \times (0.762 \text{ if female}) \times (1.180 \text{ if black}) \times (\text{BUN_{serum}}^{0.170} \times (\text{Alb}^{0.318})$</td>
</tr>
<tr>
<td>Disease (MDRD)</td>
<td></td>
</tr>
<tr>
<td>Modified MDRD</td>
<td>$186.3 \times (\text{Cr_{serum}}^{1.154} \times (\text{age})^{–0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$</td>
</tr>
</tbody>
</table>

**NOTE:** All estimated GFR (eGFR) units are mL/min/1.73 m². Alb = albumin; BUN = blood urea nitrogen.

**What is this patient’s current renal function and how many years will pass before she develops ESRD from diabetic nephropathy?**

**Is initiation of antihypertensive medication recommended at this time and will this delay progression of kidney disease?**

![Insert image here](image-url)
surprising, however, the cohort that began the study with hypertension did not experience renal benefit from intensive BP control but did achieve lower overall incidence of death with intense BP control [54].

The effect of BP control has also been studied in patients with type 1 diabetes [51,55]. In 1999, Lewis and colleagues randomized 129 type 1 diabetic patients with overt diabetic nephropathy (urinary protein excretion > 500 mg/24 hr) to strict BP control (mean arterial pressure [MAP], < 92 mm Hg) or more liberal BP control (MAP, 100–107 mm Hg), and followed these groups prospectively for 2 years [51]. The authors found no statistically significant difference in the rate of decline in creatinine clearance between the 2 groups. After 2 years, however, the lower BP group had less proteinuria (532 vs. 1723 mg/24 hr). Whether or not this decrease in proteinuria represents a clinically important improvement in renal function remains unproven.

Regardless of the renal effects of BP control, strong evidence suggests that treating hypertension in patients with diabetes prevents other serious complications, such as coronary artery disease, stroke, and retinopathy [56,57]. The Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC VII) recommends a goal BP less than 130/80 mm Hg in all patients with diabetes [53]. This recommendation follows the results of the Hypertension Optimal Treatment (HOT) trial, which found a 51% reduction in major cardiovascular events in diabetic patients randomized to a DBP less than 80 mm Hg compared with a target group of patients with a DBP around 90 mm Hg after an average 3.8 years of follow-up. Organizations such as the NKF and the ADA have also adopted this recommendation [58,59]. Adequately controlling BP in this population often requires multiple drug therapies and can rarely be achieved with a single antihypertensive alone [60].

Additionally, cases of overt albuminuria may warrant further BP reduction to less than 125/75 mm Hg, as suggested by the MDRD study. This trial found that patients with a GFR between 25 and 55 mL/min/1.73 m² and over 3 g of proteinuria daily had a slower decline in GFR over 3 years when randomized to a MAP of 92 mm Hg compared with patients randomized to a MAP of 107 mm Hg. Also, patients with proteinuria between 1 and 3 g daily had a modest reduction in GFR decline over 3 years when randomized to the lower BP goal. This finding was a secondary endpoint, and there was no difference in the rate of decline of GFR in patients with lower levels of urinary protein excretion. Also, only 3% of the volunteers in this study had DM and patients with insulin-dependent DM were excluded from this study [61].

**Follow-up**

The patient starts an oral hypoglycemic agent and, on follow-up examination, her HbA1c is 7.5%.

- **Will improved glycemic control delay progression of diabetic nephropathy?**

In patients with either type 1 or type 2 diabetes, several studies have reported a strong association between glycemic control and the development of microvascular complications including diabetic nephropathy [62,63]. Two large studies, the Diabetes Control and Complications Trial (DCCT) [64] and the UKPDS [65] investigated the renoprotective aspects of improved glycemic control.

The DCCT compared intensive and conventional glycemic control in 1441 teenagers and young adults with type 1 diabetes over a mean follow-up of 6.5 years. Intensive therapy was defined as the use of an insulin pump or at least 3 insulin injections daily with a goal preprandial glucose between 70 and 120 mg/dL. Conventional therapy required only 1 or 2 daily insulin injections and absence of hyperglycemic symptoms. Patients with normo- or microalbuminuria were included, but those with macroalbuminuria were not enrolled. The intensive treatment arm (mean HbA1c achieved, 7%) had improved outcomes compared with standard treatment (mean HbA1c, achieved, 9%).

In this trial, 2 cohorts were evaluated: 726 patients without retinopathy or microalbuminuria at baseline (primary prevention cohort) and another 715 patients with mild retinopathy and normo- or microalbuminuria on study entry (secondary intervention cohort). Intensive blood glucose control reduced the risk of developing microalbuminuria by 34% in the primary prevention cohort and by 43% in the secondary intervention cohort. In the secondary intervention group, the risk of developing overt albuminuria was reduced 56% with strict glycemic control. Since patients with more advanced renal dysfunction were excluded, the trial was not powered to detect differences in serum creatinine levels.

Other beneficial effects noted in the DCCT trial included a reduced risk of developing diabetic retinopathy and neuropathy. Notably, tight glycemic control was not without risk. Aggressive control of glucose led to weight gain and an increased occurrence of hypoglycemic episodes [64].

The UKPDS trial examined 3867 patients with type 2 diabetes and compared intensive versus conventional control. In this trial, intensive glucose control for nonoverweight patients was achieved with insulin or a sulfonylurea, while overweight patients could also be randomized to metformin. The goal premeal glucose was 72 to 126 mg/dL. Glucose in the conventional control group was initially maintained with lifestyle changes alone. If fasting glucose was greater than 270 mg/dL, patients in the conventional control group were also randomized to insulin, sulfonylurea, or metformin.

The mean achieved HbA1c in the intensive control
group was 6.6% by year 5 and 70% by year 10. In the conventional control group, mean achieved HbA1c at year 5 was 74% and 79% by year 10. The median follow-up was 11 years. Patients treated with intensive glycemic control had less risk of developing microalbuminuria, proteinuria, or doubling of serum creatinine after 9 years of treatment. Similar to findings in the DCCT trial, hypoglycemic episodes were more common in the intensive control group [65]. The results of each of these large studies show that glycemic control reduces progression of early diabetic nephropathy. Whether strict glycemic control also improves renal outcomes in patients with more advanced diabetic nephropathy is unknown.

A smaller study published prior to the UKPDS also deserves mention. In this study, 110 Japanese type 2 diabetic patients with either normo- or microalbuminuria (55 of each) were randomized to tight or conventional blood glucose control and followed prospectively over a 6-year period. The patients in the tight glucose control arm achieved an average HbA1c of 7.1% versus 9.4% in the conventional group, a much wider difference than that achieved in UKPDS. In this study, less than 8% of the patients with normoalbuminuria at baseline randomized to tight blood glucose control developed microalbuminuria, while 28% of patients in the conventional blood glucose control group developed either microalbuminuria or albuminuria. Among patients who began the study with microalbuminuria, 11.5% in the tight blood sugar control group versus 32% in the conventional blood sugar control group had further progression of their kidney disease. Overall, the patients with type 2 diabetes randomized to tight glucose control had a 70% relative risk reduction for progression of kidney disease based upon urinary albumin excretion. The authors also reported a statistically significant reduction in the development and/or progression of diabetic retinopathy and neuropathy in the patients randomized to tight glucose control [66].

Taken together, these studies clearly demonstrate that improved glycemic control in patients with either type 1 [64] or type 2 [65,66] diabetes delays the onset of diabetic nephropathy and slows progression of renal disease in those with early diabetic nephropathy. The ADA currently recommends a target HbA1c less than 70%, while the American College of Endocrinology and the American Association of Clinical Endocrinologists advocate an even lower HbA1c goal of 6.5% [67,68]. In lieu of strong evidence, either target is reasonable, as long as patients are counseled regarding the increased risk of hypoglycemia. In the case presented, the HbA1c has declined from 8.5% to 7.5%. However, the patient would benefit from further glucose reduction.

Recent evidence demonstrates that therapy that blocks the renin-angiotensin system (RAS), either with ACEI or angiotensin receptor blockers (ARBs), preserves renal function in patients with diabetic nephropathy. RAS blockade is effective in hypertensive and normotensive individuals alike.

The RAS cascade begins with the protein angiotensinogen, synthesized in the liver. The enzyme renin, produced primarily in the kidney, converts angiotensinogen to angiotensin I. Next, the angiotensin-converting enzyme, found in several tissues including kidney, vascular endothelium, lung, heart, and brain [69], cleaves angiotensin I to angiotensin II. Mediated by its interaction with the angiotensin II type 1 (AT1) receptor, angiotensin II acts as one of the body’s most potent vasoconstrictors [70]. Angiotensin II is also involved in synthesis of aldosterone in the adrenal cortex (Figure).

Medications that block the action of angiotensin-converting enzyme delay progression of diabetic nephropathy. Published in 1993, the first large randomized trial to demonstrate this effect revealed that captopril, a short-acting ACEI, improved outcomes in patients with type 1 diabetes and significant proteinuria. In this trial, 409 patients with more than 500 mg/24 hour urinary protein excretion received either captopril (207 patients) or placebo (202 patients). Throughout the trial, BP remained similar between both the treatment and placebo groups. Patients in the treatment arm benefited from a 50% reduction in the combined endpoint of death, dialysis, or transplantation. This improvement was independent of the BP-lowering effects of the ACEI [71].

Subsequently, a smaller, underpowered study reported that patients with type 2 diabetes also benefited when treated with a similar ACEI, enalapril [72]. In this study, 94 patients with type 2 diabetes with microalbuminuria and normal BP were followed over a 7-year period. In the first 5 years, patients were randomized to either enalapril or placebo. For the final 2 years of the study, enalapril was optional. Treatment with enalapril led to an absolute risk reduction of 42% for development of nephropathy, and patients who received enalapril maintained a stable serum creatinine and urinary albumin excretion. Furthermore, patients in the enalapril group who stopped taking the medication for the final 2 years of the study had increased urinary albumin excretion after discontinuing the ACEI.

More recently, 3577 patients with type 2 diabetes and without overt albuminuria were randomized in a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, which evaluated the effects of the ACEI ramipril. Randomization to ramipril reduced the risk of a cardiovascular event (stroke, myocardial infarction, or cardiovascular death) by 25%. Treatment with ramipril also led to a 24% reduction in the development of overt diabetic nephropathy, regardless of whether microalbuminuria was present upon enrollment. By the end of the trial, however, study participants in

- Aside from reducing serum glucose and BP, do other interventions delay progression of diabetic nephropathy?
the ramipril arm had slightly lower average SBP and DBP. After accounting for this difference, the improvement in primary outcomes remained statistically significant. Additionally, aside from cough, adverse effects requiring cessation of treatment were nearly identical between the ACEI and placebo arms [73].

The latest studies addressing blockade of the RAS in diabetic nephropathy have focused on the efficacy of ARBs. This medication class blocks the RAS by preventing angiotensin II from binding to one of its receptors, the AT$_1$ receptor. A potential advantage of the ARB class over ACEI is that angiotensin II can be formed through non–angiotension-converting enzyme pathways, and thus ACEI may not as effectively block the RAS as ARBs. Also, ARBs selectively block the AT$_1$ receptor without affecting the angiotensin II type 2 (AT$_2$) receptor, which may have cardio- and renoprotective effects when bound by angiotensin II [74].

Several large clinical trials have provided substantial evidence that treatment with an ARB delays progression of diabetic nephropathy in patients with type 2 diabetes and diabetic nephropathy. In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group (IRMA II) trial, 590 patients with hypertension, type 2 diabetes, and microalbuminuria were randomized to placebo versus either 150 mg or 300 mg daily of the ARB irbesartan. The primary outcome was progression to overt nephropathy, defined as greater than 200 µg/min albuminuria on an overnight collection (corresponding to > 300 mg/day albuminuria). Patients randomized to irbesartan 150 mg/day had nearly half the risk of progression compared with the placebo group, while those randomized to 300 mg/day of irbesartan were one third as likely to progress, indicating a dose-dependent response.

Additionally, many patients randomized to irbesartan had regression of albuminuria and were more likely to revert to normoalbuminuria than the placebo group. This beneficial effect was also dose-dependent, as urinary albumin excretion declined 24% in the low-dose group and 38% in the high-dose irbesartan group. Additionally, a higher percentage of patients had restoration of normoalbuminuria in the 300 mg group (34%) as compared with the 150 mg group (24%). As the only large clinical trial examining different doses of ARB, this trial importantly demonstrates that a maximum dose of this ARB is more efficacious than a lower dose [75].

Published at the same time as IRMA II, the results of 2 large trials evaluating the effects of ARB in patients with type 2 diabetes and macroalbuminuria also revealed renoprotective effects. These 2 trials were the Irbesartan in Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study.

IDNT included 1715 patients randomized either to the ARB irbesartan, the calcium channel blocker amlodipine, or to placebo and followed for an average of 2.6 years. The primary endpoint was a composite of doubling of serum creatinine, onset of ESRD, or death for any reason. Patients who received irbesartan had a 20% lower risk of reaching the
primary endpoint compared with placebo and a 23% lower risk compared with patients treated with the calcium channel blocker. There was a 30% reduced relative risk of doubling of baseline serum creatinine and a 23% reduced relative risk of needing renal replacement treatment when comparing irbesartan with either placebo or amlodipine [76].

The second clinical trial, RENAAL, included 1513 patients randomized to either the ARB losartan or placebo and followed for an average 3.4 years, with similar results as IDNT. Again, the primary endpoint was a composite of doubling of serum creatinine, ESRD, or death from any cause. Treatment with the ARB resulted in a 16% relative risk reduction for the primary endpoint, even when adjusted for minor changes in BP between the 2 groups. Additionally, adverse clinical events leading to discontinuation of the study drug occurred less frequently in the losartan group than in the placebo group (17% vs. 21%) [77].

In both studies, analysis of secondary endpoints revealed that treatment with an ARB led to reduced albuminuria and a slower rate of serum creatinine rise. Losartan was associated with a 15% relative reduction in the rate of GFR decline compared with placebo. Similarly, patients treated with irbesartan had a slower reduction in creatinine clearance (−5.5 mL/min in the irbesartan arm versus −6.3 mL/min and −6.8 mL/min in the placebo and amlodipine arms) [76,77].

More recently, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) reported that the use of the ACEI trandolapril in normoalbuminuric, hypertensive patients with type 2 diabetes significantly delayed the onset of microalbuminuria [78]. On the other hand, efficacy of ACEI and ARB for primary prevention of diabetic nephropathy in normotensive individuals remains debatable [52,73,79]. In comparing available evidence, by far the largest body of clinical trial data demonstrates the efficacy and importance of RAS inhibition in patients with early (microalbuminuria) or late (macroalbuminuria, proteinuria) diabetic nephropathy. In light of this compelling data, inhibition of the RAS is paramount in the treatment of diabetic nephropathy.

Limited evidence also suggests that other measures may help preserve renal function in patients with diabetes. These interventions include dietary modification [80,81], smoking cessation [82], and the use of cholesterol-lowering medications [83]. Protein and phosphorus restriction in patients with type 1 diabetes and albuminuria slows reduction of GFR over a mean of 37 months of follow-up [80]. Additionally, a small study found protein restriction alone decreased the risk of ESRD or death (combined endpoint) but did not improve the overall rate of renal function decline [81]. Given the already restricted diet most diabetic patients follow, further protein restriction is often difficult to accomplish. Notably, smoking has been shown to be independently associated with diabetic nephropathy and renal disease [26–28], and smoking cessation alone may reduce progression of renal disease by 30% [82].

Although only limited data is available, in a meta-analysis including 362 patients (253 with diabetes) from 13 studies, HMG-CoA reductase inhibitors (statins) decreased proteinuria and preserved renal function in patients with chronic kidney disease and these renoprotective properties were not entirely explained by the lipid-lowering effects of these medications [82]. In the Heart Protection Study (HPS), a large randomized study with over 20,000 patients including nearly 6000 diabetic patients (90% with type 2 diabetes), simvastatin 40 mg daily reduced the rate of major vascular events by 25% and delayed loss of renal function [84]. Irrespective of the potential renoprotective effects of statins, the results of the Collaborative Atorvastatin Diabetes Study (CARDS) suggest that all type 2 diabetic patients should be treated with statins. In this randomized, placebo-controlled trial, atorvastatin reduced the risk of cardiovascular events and death by 32% [85].

In the future, other prospective targets for prevention of diabetic nephropathy include endothelin antagonists [86], advanced glycation end-product formation prevention [87–89], direct renin inhibitors [90], aldosterone inhibitors [91], and sulodexide, an oral proteoglycan that may restore the negative charge of the glomerular/basement membrane [92].

- Is the ARB class of medications superior to the ACEI class? Are there any benefits for combining these medications for increased blockade of the RAS?

Although ARBs and ACEIs are often categorized together since both block the RAS, it is important to recall that they block the RAS by entirely different mechanisms and should be considered separately when deciding on appropriate treatment for diabetic nephropathy. As described in the previous section, ARBs may provide more complete blockade of the RAS than ACEI, as angiotensin II can form through non-ACE pathways. Additionally, ARB do not block the AT1 receptor, which may have cardioprotective effects when stimulated by angiotensin II [74]. Conversely, a theoretical advantage of ACEI over ARB is the inhibition of bradykinin breakdown. Bradykinin acts as a potent vasodilator and thus may have additional BP-lowering effects.

Few studies have compared ACEI head-to-head with ARB in patients with diabetes. A small, prospective, double-blind study compared the ARB losartan to the ACEI enalapril in 92 patients with type 2 diabetes with early diabetic nephropathy and found no difference at 1 year in loss of renal function or urinary albumin excretion [93]. Subsequently, a larger, longer-duration trial, the Diabetics Exposed to Telmisartan...
and Enalapril study (DETAIL) evaluated 250 patients with type 2 diabetes, the majority of whom had microalbuminuria or low-level macroalbuminuria. Patients were randomized to the ARB telmisartan or the ACEI enalapril and followed for 5 years. The primary endpoint was change in GFR. At the end of the trial, there was no statistically significant difference in GFR decline between the 2 treatment arms (~17.5 mL/min with telmisartan vs. ~15.0 mL/min with enalapril) in spite of improved BP control in the telmisartan arm (~6.9 vs. ~2.9 mm Hg). However, the dosages of the 2 medications were not equivalent. Per the study protocol, telmisartan was prescribed at full dose (80 mg daily), whereas the dose of enalapril was half of maximum (20 mg daily) [94].

At this time, evidence from large clinical trials and hence, clinical guidelines, support the use of ACEI in patients with type 1 diabetes–induced nephropathy. The evidence supports the use of either medication class for patients with type 2 diabetes and microalbuminuria, while those with type 2 diabetes and overt albuminuria should be prescribed an ARB.

Since ACEI and ARB exert their effects by different mechanisms, combining these 2 medications may provide maximum RAS blockade. The largest study to evaluate the effects of combination therapy was the Candesartan And Lisinopril Microalbuminuria (CALM) study. In this study, 199 patients with type 2 diabetes were randomized to the ACEI lisinopril alone, the ARB candesartan alone, or both lisinopril and candesartan. These patients were followed prospectively for 12 weeks. Combination therapy more effectively reduced BP and urinary albumin excretion than either agent alone [95]. Given the short course of treatment, however, this study lacked hard clinical endpoints such as doubling of serum creatinine or progression to ESRD. Additionally, medication doses were not maximized in any arm.

Hypothetically, the use of both an ACEI and an ARB together may further delay progression of diabetic nephropathy, but evidence for combination therapy remains limited. Nevertheless, the use of an ACEI with an ARB may be warranted in patients in whom overt albuminuria persists despite maximum therapy with a single agent [96]. Additionally, the use of an ARB, at higher than standard doses, may further reduce microalbuminuria. A small, randomized crossover study of 52 hypertensive patients with type 2 diabetes demonstrated that irbesartan 900 mg/day reduces microalbuminuria 15% more than the 300 mg daily dose after 2 months of follow-up. SBP and DBP were not different between the groups. Those patients with baseline urinary albumin excretion levels higher than the mean of the study group tended to benefit the most from the high-dose ARB. However, GFR did decline more in the high-dose groups compared with lower-dose irbesartan (~4 mL/min vs. ~7 and ~8 mL/min in 300-, 600-, and 900-mg doses). Despite mild increases in potassium with all 3 doses of irbesartan, in this closely monitored group of patients no one developed hyperkalemia during the study (defined as > 5.5 mmol/L) [97]. In actual clinical practice, however, the risk of hyperkalemia may increase with such high doses of ARB.

- Should this patient’s level of proteinuria be rechecked after starting RAS blockade?

Proteinuria itself may promote further kidney disease [30,31,98-99], and reduction of proteinuria is associated with a delay in progression of diabetic nephropathy [100,101]. Post hoc analyses of both the IDNT and RENAAL trials have demonstrated that a sustained decrease of albuminuria is associated with reduced risk of progression to ESRD [101,102]. Additionally, a recent follow-up report on the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial, which enrolled 8206 hypertensive individuals (approximately 13% diabetic), demonstrated that the baseline level of albuminuria correlated with risk of future cardiovascular event [103]. More importantly, patients with reduced albuminuria by the end of the study benefited with less risk of suffering a cardiovascular event. Based upon growing literature associating the level of albuminuria with cardiovascular risk and progression of kidney disease [104,105], it may be beneficial to use the maximum tolerated doses of ACEI or ARB therapy.

- Are other diabetic complications associated with nephropathy?

Nephropathy is an independent risk factor for development of other diabetic complications including cardiovascular disease and retinopathy [34,106]. In addition, nephropathy imparts an increased overall risk of morbidity and mortality compared to diabetes alone [107]. Given the high prevalence of cardiovascular disease among diabetic patients and the added risk from nephropathy, this high-risk population requires aggressive screening for cardiovascular disease. Thus, intervening upon modifiable risk factors of cardiac disease such as cholesterol, blood pressure and smoking is crucial.

**Follow-up**

Over the next 5 years, the patient’s daily urinary albumin excretion steadily increases to 2.5 g.

- Does this increase simply reflect progression of her diabetic nephropathy?
Aside from diabetic nephropathy alone, uncontrolled hypertension can lead to increasing albuminuria. In these cases, further treatment of hypertension, beyond ACEI or ARB therapy, may decrease urinary albumin excretion [108]. Additionally, abnormal urinary albumin excretion occurs in several other glomerular diseases, including membranous nephropathy, focal segmental glomerular sclerosis, minimal change disease, and others. Five to 10% of patients with type 2 diabetes may have a non–diabetes-related etiology of their renal failure [109–111]. Certain clinical situations, such as short duration of diabetes or evidence of another systemic disease, increase the likelihood of nondiabetic renal disease [112]. Although this patient’s rise in albumin excretion likely represents progression of diabetic nephropathy, she should be referred to a nephrologist for further evaluation.

- Are there risks associated with these classes of medications?

No class of medications is completely risk-free. ACEI, by reducing bradykinin breakdown, may lead to cough, and both the ACEI and ARB can cause acute renal failure or life-threatening hyperkalemia.

After starting a patient on any RAS-blocking medication, serum creatinine and potassium should be checked within 2 weeks [38,39]. A 30% to 35% increase in serum creatinine may be expected when initiating ACEI or ARB therapy [113] and does not necessarily constitute worsening renal function. Higher levels of acute serum creatinine rise, however, may require dose reduction or cessation of the drug and may indicate renal artery stenosis [114]. Both volume depletion and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of acute renal failure during treatment with these medications.

Female patients of childbearing age should be counseled regarding the potential teratogenic effects of ACEI and ARB therapy. Fetal exposure to these drugs at any point during pregnancy may lead to severe cardiac, central nervous system and renal disorders or even fetal death [115–117].

CASE 2
Initial Presentation

An 18-year-old white man with a history of type 1 DM since the age of 6 years presents for a physical examination so that he can participate in college sports.

History and Physical Examination

The patient’s BP is 115/65 mm Hg and his BMI is 24 Kg/m². He is on an insulin pump and states that he has had excellent glycemic control over the past few years, with blood glucose generally ranging from 80 mg/dL to 130 mg/dL and a recent HbA₁c of 6.5%. He states at his last examination over a year ago, he was told his kidney function was normal, and his annual eye examination last month was negative for any signs of retinopathy. His maternal aunt has developed diabetic nephropathy and he is concerned. The patient has a serum creatinine of 1.1 mg/dL and no microalbuminuria.

- Does this patient have any renal dysfunction?

Approximately 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy. However, the contrary is not always true, as retinopathy can occur in the absence of renal abnormalities [118]. The concordance in type 2 diabetic patients is lower (55%–65%) [107,119]. The presence of 1 microvascular complication may be a clue for damage in a separate organ but does not guarantee it.

Despite lacking retinopathy and microalbuminuria, this patient’s estimated GFR is only 90 mL/min/1.73 m² (by the modified MDRD equation), possibly representing an early stage of chronic renal disease. However, this equation was designed for an older population and may underestimate GFR in young people. Additionally, if this football player is particularly muscular, the MDRD may underestimate this patient’s true GFR. In this case, a 24-hour urine collection for creatinine clearance may help estimate his true renal function. The Crockcroft-Gault equation may overestimate true GFR, while the MDRD equation tends to underestimate it [120].

- Should this patient be started on an ACEI to protect his kidneys?

Despite not having microalbuminuria, if his creatinine clearance is truly less than 90 mL/min from a 24-hour urine collection, he may have early diabetic kidney disease and treatment would be indicated. ACEI have not specifically been shown to benefit type 1 diabetic patients in terms of primary prevention for patients without microalbuminuria or reduced GFR. Limited data does support the use of an ACEI for primary prevention in normotensive, normoalbuminuric patients with type 2 diabetes [43].

- The patient would like to play football and asks if his renal condition precludes him from playing.

Currently, no evidence exists demonstrating participation
in contact sports increases the risk for developing or accelerating diabetic nephropathy. Several prominent athletes with renal disorders have safely continued to participate in contact sports. General recommendations include avoiding potential nephrotoxins, limiting the use of NSAIDs and minimizing the risk of dehydration. Barring any other contraindication, the presence of kidney disease should not limit athletic participation.

CASE 3
Initial Presentation and History
A 64-year-old Hispanic man presents to a primary care physician to establish care. He has coronary artery disease, hypertension for 20 years, and type 2 diabetes for 15 years. During a recent hospitalization for community-acquired pneumonia, he had a serum creatinine of 2.8 mg/dL and a spot urine ACR of 2500 µg/mg, corresponding to 2.5 g/day of albumin in his urine (approximately equivalent to 5 g of total proteinuria).

**Is referral to a nephrologist necessary at this time?**

The NKF defines chronic kidney disease as a GFR less than 60 mL/min/1.73 m² lasting more than 3 months or any structural or functional kidney damage lasting at least 3 months with or without a change in GFR [121]. This patient’s estimated GFR is 24 mL/min/1.73 m². Assuming this does not improve within a few months, he meets the criteria for chronic kidney disease. The NKF further divides chronic kidney disease into 5 stages (Table 5).

Once patients have a GFR less than 50 to 60 mL/min, they are likely to develop several systemic complications such as anemia, renal osteodystrophy, and electrolyte abnormalities. Additionally, several studies have demonstrated improved patient outcomes with early referral to a nephrologist. This improvement is most prominent in patients with early diabetic nephropathy [122]. Consequences of late referral to a nephrologist include increased morbidity, mortality, and resource utilization [123]. Mortality risk drops when initial evaluation by a nephrologist precedes the need for dialysis by more than 90 to 120 days [124,125].

**Besides referral to a nephrologist, are other actions needed to help preserve this patient’s renal function?**

Since this patient has limited renal function and a progressive deterioration due to diabetic nephropathy, avoiding iatrogenic insults that may hasten the further loss of renal function is important. Certain medications can lead to an acute loss of kidney function in patients with underlying renal insufficiency. Patients should be counseled to avoid nephrotoxic substances such as NSAIDs, aminoglycosides, and certain herbal remedies [126]. Additionally, ensuring proper medication dosing for a given level of renal function is an important step for ongoing renal protection. Finally, in the setting of intravenous contrast for radiologic or cardiovascular procedures, proper hydration and/or the addition of N-acetylcysteine or bicarbonate therapy can serve to minimize the risk to renal function [127,128].

**CONCLUSION**

Early screening for diabetic nephropathy is essential in the care of the diabetic patient. The urine ACR is a convenient and inexpensive means of detecting micro- and even macroalbuminuria. When present, even in the setting of apparent normal serum creatinine, renal damage has occurred. Glycemic and BP control (HbA₁c < 7.0% and BP < 130/80 mm Hg), though not without potential side effects, are important in reducing micro- and macrovascular complications of diabetes, including diabetic nephropathy. ACEI and ARB therapy clearly delay progression of diabetic nephropathy. While either may be beneficial, at this time most evidence points towards the use of ACEI for patients with type 1 diabetes, either class for patients with type 2 diabetes and microalbuminuria and ARB for those with type 2 diabetes and overt albuminuria.

**Table 5. National Kidney Foundation Stages of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Estimated GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt; 15 or dialysis</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate.

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**Author contributions:** conception and design, JAG, PC; drafting of the article, JAG, PC; critical revision of the article, JBL.
### DIABETIC NEPHROPATHY

**Appendix. Relevant Clinical Trials**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Diabetes Type</th>
<th>Nephropathy Included</th>
<th>Intervention</th>
<th>Primary Outcome (of Treated Cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>Type 1</td>
<td>Normo- or microalbuminuria</td>
<td>Glycemic control</td>
<td>Reduction in the development of retinopathy</td>
</tr>
<tr>
<td>UKPDS</td>
<td>Type 2</td>
<td>Normo- or microalbuminuria (~2% overt albuminuria)</td>
<td>Glycemic control HTN treatment</td>
<td>For both studies, treatment led to reduction in all diabetes-related endpoints, diabetes-related death and all-cause mortality</td>
</tr>
<tr>
<td>ABCD</td>
<td>Type 2</td>
<td>Normo-, micro- or overt albuminuria</td>
<td>Diastolic BP control ACEI enalapril vs. CCB</td>
<td>No difference in the change of creatinine clearance for either intervention group</td>
</tr>
<tr>
<td>MDRD</td>
<td>97% Non-diabetic</td>
<td>Reduced GFR, all levels of proteinuria</td>
<td>HTN control Reduced protein intake</td>
<td>No difference in the change of creatinine clearance for either intervention group</td>
</tr>
<tr>
<td>Captopril</td>
<td>Type 1</td>
<td>Overt albuminuria</td>
<td>ACEI captopril</td>
<td>Reduced risk of doubling of serum creatinine</td>
</tr>
<tr>
<td>HOPE &amp; Micro-HOPE</td>
<td>Type 2</td>
<td>Normo- or microalbuminuria</td>
<td>ACEI ramipril</td>
<td>Reduced risk of the combined endpoint of myocardial infarction, stroke or death</td>
</tr>
<tr>
<td>IRMA 2</td>
<td>Type 2</td>
<td>Microalbuminuria</td>
<td>ARB losartan (2 doses)</td>
<td>Reduced risk of progression to overt albuminuria (high dose &gt; low dose &gt; placebo)</td>
</tr>
<tr>
<td>IDNT</td>
<td>Type 2</td>
<td>Overt albuminuria</td>
<td>ARB irbesartan CCB amlodipine</td>
<td>Reduction in the composite endpoint of doubling of serum creatinine, progression to ESRD, or all-cause mortality Not different than placebo</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>Type 2</td>
<td>Overt albuminuria</td>
<td>ARB losartan</td>
<td>Reduction in the composite endpoint of doubling of serum creatinine, progression to ESRD or all-cause mortality</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>Type 2</td>
<td>Normoalbuminuria</td>
<td>ACEI trandilopril, CCB verapamil or combo</td>
<td>Trandilopril delayed onset of microalbuminuria compared with verapamil or placebo</td>
</tr>
<tr>
<td>DETAIL</td>
<td>Type 2</td>
<td>Micro- or overt albuminuria</td>
<td>ACEI enalapril vs. ARB telmisartan</td>
<td>ARB was not inferior to ACEI for change in GFR</td>
</tr>
<tr>
<td>CALM</td>
<td>Type 2</td>
<td>Microalbuminuria</td>
<td>ACEIARB combo therapy</td>
<td>BP and total albumin excretion decreased more with combination therapy than either monotherapy alone</td>
</tr>
<tr>
<td>HPS</td>
<td>Subset: &gt; 90% type 2</td>
<td>Severe renal dysfunction excluded</td>
<td>Statin simvastatin</td>
<td>Reduced risk of coronary or vascular event</td>
</tr>
<tr>
<td>CARDS</td>
<td>Type 2</td>
<td>Normo- or microalbuminuria (~2% overt albuminuria)</td>
<td>Statin atorvastatin</td>
<td>Reduced time to first occurrence of the composite of acute coronary event, coronary revascularization, or stroke</td>
</tr>
<tr>
<td>LIFE</td>
<td>Subset: mostly type 2</td>
<td>Micro- and overt albuminuria</td>
<td>Either the ARB losartan or β blocker atenolol</td>
<td>Higher levels of albuminuria increase the risk for the composite of cardiovascular death, stroke, or myocardial infarction</td>
</tr>
</tbody>
</table>

ABCD = Appropriate Blood Pressure Control and Diabetics; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; BP = blood pressure; CALM = Candesartan And Lisinopril Microalbuminuria; CARDS = Collaborative Atorvastatin Diabetes Study; CCB = calcium channel blocker; CHF = congestive heart failure; DETAIL = Diabetics Exposed to Telmisartan and Enalapril; DCCT = Diabetes Control and Complications Trial; ESRD = end stage renal disease; GFR = glomerular filtration rate; HOPE = Heart Outcomes Prevention Evaluation; HPS = Heart Protection Study HTN = hypertension; IDNT = Irbesartan in Diabetic Nephropathy Trial; IRMA = Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group; LIFE = Losartan Intervention For Endpoint Reduction in Hypertension; MDRD = Modification of Diet in Renal Disease; RENAAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; UKPDS = United Kingdom Prospective Diabetes Study.

**References**

<table>
<thead>
<tr>
<th>Renal or Secondary Outcome (of Treated Cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced microalbuminuria and albuminuria</td>
</tr>
<tr>
<td>Reduced risk of microalbuminuria</td>
</tr>
<tr>
<td>Less microalbuminuria and albuminuria</td>
</tr>
<tr>
<td>Reduced risk of increased albumin secretion in a subset of patients</td>
</tr>
<tr>
<td>Slower rate of GFR decline in subset of patients with over 1 g of proteinuria and strict HTN control</td>
</tr>
<tr>
<td>Less death and renal failure</td>
</tr>
<tr>
<td>(Micro-HOPE) Less progression to overt albuminuria</td>
</tr>
<tr>
<td>Higher rate of regression of microalbuminuria, especially in high-dose group; no difference in the rates of decline of creatinine clearance</td>
</tr>
<tr>
<td>No difference in cardiovascular outcomes except lower risk of hospitalization for CHF</td>
</tr>
<tr>
<td>No difference in cardiovascular morbidity and mortality except greater time to first hospitalization for CHF</td>
</tr>
<tr>
<td>No significant difference in GFR</td>
</tr>
<tr>
<td>No overall difference in the rate of albumin excretion</td>
</tr>
<tr>
<td>Slight decrease in GFR in the combination group and ACEI group compared with the ARB group</td>
</tr>
<tr>
<td>Slower decline of estimated GFR (rise of serum creatinine)</td>
</tr>
<tr>
<td>Reduced risk of each of the primary outcomes individually</td>
</tr>
<tr>
<td>Risk increases stepwise as baseline and 1-year treated albuminuria levels increase</td>
</tr>
</tbody>
</table>


119. Manaviat MR, Afkhami M, Shoja MR. Retinopathy and


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CME EVALUATION: Diabetic Nephropathy for the Primary Care Physician: More than Microalbuminuria

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. A 42-year-old woman was diagnosed with type 2 diabetes 5 years ago. Routine dipstick urinalyses have been negative for proteinuria. Her serum creatinine level is 1.0 mg/dL, corresponding to an estimated glomerular filtration rate (GFR) of around 60 mL/min/1.73 m². What is the next step in determining if she has significant microalbuminuria?
   A. Repeat dipstick urinalysis in 1 to 2 years
   B. Obtain a 24-hour urine collection and if more than 200 mg of albumin present, begin treatment with an angiotensin receptor blocker (ARB)
   C. Obtain 3 separate urine collections over the next several months and check the albumin-to-creatinine ratio in each. If she consistently has greater than 30 mg of albumin in these collections, she has microalbuminuria.
   D. As the patient’s creatinine is only 1.0 mg/dL, she does not require further testing at this time

2. Which of the following treatment strategies have been proven to reduce the risk of developing microalbuminuria in normotensive patients with type 2 diabetes?
   A. HMG-CoA reductase inhibitor (statin) therapy if started early
   B. ABR therapy if used in maximum doses
   C. Calcium channel blocker treatment
   D. None of the above have been proven as primary prevention for normotensive normoalbuminuric patients

3. A 34-year-old woman with type 1 diabetes is started on an angiotensin-converting enzyme inhibitor (ACEI). Two weeks after initiating treatment, she returns to the office for a routine lab check. Her potassium level is 4.6 mEq/L (reference range, 3.5–5.1 mEq/L), but her serum creatinine level has risen from 1.5 mg/dL to 1.8 mg/dL. What should be done with regard to her ACEI?
   A. Stop the ACEI immediately and recheck labs in 1 week to ensure that creatinine has returned to pretreatment levels
   B. Stop the ACEI and start an ARB, then recheck labs in 1 to 2 weeks
   C. Continue the patient on the ACEI, as a 30% rise in serum creatinine may be expected
   D. Start the patient on scheduled doses of ibuprofen to counteract the glomerular efferent arteriolar vasodilation effects of the ACEI

4. In a patient who is diagnosed with type 2 diabetes, when is it appropriate to begin screening for microalbuminuria?
   A. At the time of the initial diagnosis
   B. 5 years after the initial diagnosis
   C. 10 years after the initial diagnosis
   D. Only screen if the patient has hypertension, elevated serum creatinine, or diabetic retinopathy

5. In patients with type 2 diabetes, treatment with an HMG-CoA reductase inhibitor (statin) may:
   A. Slow the rate of GFR loss (creatinine rise)
   B. Reduce the risk of a coronary artery or other vascular event
   C. Lead to increased risk of developing diabetic retinopathy
   D. Both A & B
EVALUATION FORM: Diabetic Nephropathy for the Primary Care Physician: More than Microalbuminuria

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