

## REVIEW

# Antihypertensive Therapy in the Presence of Proteinuria

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The presence of proteinuria is a well-known risk factor for both the progression of renal disease and cardiovascular morbidity and mortality, and decreases in urine protein excretion level were associated with a slower decrease in renal function and decrease in risk of cardiovascular events. Increased blood pressure has a major role in the development of proteinuria in patients with either diabetic or nondiabetic kidney disease, and all recent guidelines recommend a blood pressure goal less than 130/80 mm Hg in patients with proteinuria to achieve maximal renal and cardiovascular protection. Drugs interfering with the renin-angiotensin system, ie, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, should be used as first-line antihypertensive therapy in patients with proteinuria because they seem to have a blood pressure-independent antiproteinuric effect, and if blood pressure levels are still out of goal, a diuretic should be added to this regimen. A combination of an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker or other classes of medications shown to decrease protein excretion, such as nondihydropyridine calcium antagonists or aldosterone receptor blockers, should be considered to decrease proteinuria further. This review provides an extended summary of current evidence regarding the associations of blood pressure with proteinuria, the rationale for currently recommended blood pressure goals, and the use of various classes of antihypertensive agents in proteinuric patients.

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**INDEX WORDS:** Proteinuria; kidney disease; hypertension; angiotensin-converting enzyme (ACE) inhibitors; angiotensin-receptor blockers (ARBs).

A normally functioning kidney will excrete a small amount of protein in urine. The composition of this protein excretion is about 20% low-molecular-weight proteins, 40% Tamm-Horsfall mucoprotein secreted by the distal tubules, and 40% high-molecular-weight albumin.<sup>1</sup> The first 2 types of protein are not detectable using conventional dipsticks, but albumin is measured routinely in the evaluation of abnormal urinary protein excretion. Urinary albumin excretion (UAE) rates between 30 and 300 mg/d (0.03 and 0.3 g/d) if

measured in a 24-hour urine collection, 20 and 200  $\mu\text{g}/\text{min}$  ( $34 \times 10^{-8}$  to  $34 \times 10^{-7}$  g/s) if measured in a timed urine collection, or 30 and 300 mg/g (0.03 and 0.3 g/g) if measured with the use of urinary albumin-creatinine ratio in a spot urine collection are characterized as microalbuminuria, whereas every albumin or protein excretion greater than these levels represents albuminuria or clinical proteinuria (Table 1).<sup>2,3</sup> Although current knowledge suggests that microalbuminuria be considered as a marker of abnormal vascular function and risk factor for cardiovascular disease,<sup>4</sup> proteinuria is a typical manifestation of overt nephropathy and is associated with both faster deterioration in kidney function and increased risk of cardiovascular disease.<sup>5,6</sup>

In the general population, the prevalence of proteinuria is low. For example, in the US adult population, it was estimated at around 1.3%, ranging from 1% in white individuals to 2.4% in black individuals.<sup>7</sup> However, proteinuria appears more often with increasing age ( $\sim 3.9\%$  in people  $>70$  years)<sup>7</sup> and is much more common in individuals with hypertension or diabetes.<sup>8</sup> For example, without specific interventions, 80% of patients with type 1 diabetes and 20% to 40% of those with type 2 diabetes and microalbuminuria

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**Table 1. Definitions of Microalbuminuria and Macroalbuminuria or Proteinuria**

Urine Collection Method		Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Albumin	24-Hour collection (mg/d)	<30	30-299	>300
	Timed collection ( $\mu$ g/min)	<20	20-199	>200
	Spot urine albumin-creatinine ratio (mg/g)	<30	30-299	>300
Total protein	24-Hour collection (mg/d)	<300	Not applicable	>300
	Timed collection ( $\mu$ g/min)	<20	Not applicable	>200
	Spot urine protein-creatinine ratio (mg/g)	<200	Not applicable	>200

*Note:* Modified from the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative<sup>2</sup> and American Diabetes Association guidelines.<sup>3</sup> To convert albumin or total protein in mg/d to g/d, multiply by 0.001; albumin or total protein in  $\mu$ g/min to g/s, multiply by 0.00000017; albumin- or total protein-creatinine ratio in mg/g to g/g, multiply by 0.001.

will progress to macroalbuminuria during 10 to 15 years.<sup>3</sup>

Hypertension is a well-recognized cause of chronic kidney disease, and blood pressure (BP) level directly influences the development of proteinuria.<sup>2</sup> Conversely, hypertension can be a consequence of kidney disease because many abnormalities present in an individual with nephropathy could result in BP elevation.<sup>9</sup> Interventions that decrease BP levels in patients with proteinuria and mild-to-moderate renal insufficiency consistently were shown to slow the progression of kidney disease.<sup>10</sup> According to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative Working Group guidelines, the goals of antihypertensive therapy in patients with chronic kidney disease are to decrease BP, as well as decrease the risk of cardiovascular disease and slow the progression of kidney disease in patients with or without hypertension.<sup>2</sup> Because proteinuria is associated with both risk of cardiovascular disease and progression to end-stage renal disease (ESRD) and decreases in proteinuria correlate with decreases in cardiovascular morbidity and mortality and preservation of kidney function,<sup>11</sup> changes in urinary protein excretion level would best reflect the effect of antihypertensive treatment in these patients.

This review discusses the natural history of proteinuria development in relation to abnormal BP levels, the rationale for currently recommended BP goals in patients with proteinuria, and the evidence for the various nonpharmacological and pharmacological approaches to achieve these goals.

#### THE NATURAL HISTORY OF PROTEINURIA

When evaluating the natural history of proteinuria, a distinction must be made between those

with and without diabetes mellitus. Previous studies of patients with type 1 diabetes showed that average time from diagnosis of diabetes to the development of proteinuria is 19 years, and the strongest predictor of proteinuria is the presence of microalbuminuria.<sup>12,13</sup> This close association between the presence of microalbuminuria and subsequent development of proteinuria in patients with type 1 diabetes was supported further from additional data and, for some years, was considered a definite finding.<sup>14</sup> However, recent evidence showing that 64% of patients with type 1 diabetes and microalbuminuria reverted to normoalbuminuria within 5 years<sup>15</sup> challenges the predictive value of microalbuminuria, and the issue needs to be examined further. In patients with type 2 diabetes, although some evidence relating microalbuminuria to proteinuria development exists, the natural history of proteinuria seems more variable.<sup>16</sup> For example, in a large prospective study from Italy, microalbuminuria increased the risk of developing overt nephropathy by 42%, but other factors, ie, level of glycemic control, were strongly predictive of proteinuria development.<sup>17</sup>

It is important to note that the occurrence of hypertension in relation to abnormal urinary protein excretion is different in patients with type 1 and type 2 diabetes. Patients with type 1 diabetes have increases in systolic and diastolic BP only after the development of microalbuminuria, and these increases could act as an aggravating factor, whereas isolated systolic hypertension without microalbuminuria has not been predictive of overt nephropathy. Conversely, in patients with type 2 diabetes, increases in BP usually precede and can predict the development of abnormal urinary protein excretion.<sup>18,19</sup> Overall, relevant data suggest that abnormal UAE in patients with

type 1 diabetes can reflect continuous damage to the kidney, beginning with microalbuminuria that relates to incipient nephropathy and ending with proteinuria, whereas in patients with type 2 diabetes, abnormal UAE relates primarily to atherosclerotic vascular damage, and varying levels of blood glucose and BP help explain the different courses of nephropathy among different patients.

The natural history of proteinuria in patients with nondiabetic renal disease is much less well defined; the most likely explanation is varied causes of nondiabetic renal disease. However, BP levels also directly influence the development of proteinuria. In a study of 387 hypertensive patients, UAE levels were directly proportionate to systolic, diastolic, and mean BP measured at the office or with an ambulatory monitor.<sup>20</sup> A population study with 1,567 participants showed an 18-mm Hg higher systolic BP in the group of nondiabetic individuals with microalbuminuria than in those without microalbuminuria.<sup>21</sup> In addition, proteinuria clearly correlates with renal function impairment. This was shown by a study of 7,728 individuals without diabetes that stratified subjects into 4 different groups based on baseline albumin excretion: normal (0 to 15 mg/d), high normal (15 to 30 mg/d), microalbuminuria (30 to 300 mg/d), and macroalbuminuria (>300 mg/d). The macroalbuminuria group had a decrease in glomerular filtration rates (GFRs), whereas the high-normal and microalbuminuria groups had increases in GFRs.<sup>22</sup> The explanation for these findings relates to the pathophysiological process of renal function loss in patients with nondiabetic kidney disease.<sup>23</sup> When an insult initiates renal injury and abnormal UAE, the kidney responds by hypertrophy and hyperfiltering. Initially, this allows the kidney to meet the body's demands, but it leads to a vicious circle because hyperfiltering will increase protein leakage, which leads to increased renal damage and loss of more nephrons. The final result of this cascade is both proteinuria and a decrease in GFR.

#### **ROLE OF PROTEINURIA IN SETTING BP GOALS**

All recent relevant guidelines recommend a BP goal less than 130/80 mm Hg for patients with diabetes and/or chronic kidney disease.<sup>2,3,24,25</sup> In patients with diabetes, the rel-

evant evidence derives mainly from 2 outcome trials that randomly assigned subjects to different BP levels, the Hypertension Optimal Treatment trial<sup>26</sup> and the United Kingdom Prospective Diabetes Study (UKPDS) 38,<sup>27</sup> which showed significant decreases in cardiovascular mortality in the groups of patients with diabetes that achieved the lower BP levels. However, it should be noted that in the only study with renal end points that included patients with diabetes and showed a benefit with a low BP goal, the population largely consisted of patients with nondiabetic kidney disease.<sup>28</sup> Thus, there currently is no evidence in favor of a low BP goal to reduce renal disease progression deriving from a uniform diabetic population.

The Modification of Diet in Renal Disease (MDRD) Study provided the first evidence to support a lower BP target in the appropriate chronic kidney disease population. In this study, patients with chronic kidney disease were randomly assigned to a low-BP group with a goal mean BP of 92 mm Hg or less for patients 60 years and younger and 98 mm Hg or less for patients older than 60 years and a group with a goal mean BP less than 107 mm Hg for patients 60 years or younger and 113 mm Hg or less for patients older than 60 years. At the end of the study, patients with baseline proteinuria with protein greater than 1,000 mg/d (>1 g/d) in the low-target group had a significant decrease in proteinuria and significantly slower decrease in GFR compared with patients assigned to the usual-target group.<sup>29</sup> Of note, proteinuria decrease within the first 4 months of the study was associated with a slower subsequent decrease in GFR. Moreover, analysis of data obtained about 7 years after the end of the randomization trial showed that risks of kidney failure and the composite outcome of kidney failure and all-cause mortality were significantly less in the low-target-BP group.<sup>28</sup> In a recent meta-analysis of studies of patients with nondiabetic kidney disease, systolic BP of 110 to 129 mm Hg was associated with the lowest risk of kidney disease progression in patients with urine protein excretion greater than 1,000 mg/d (>1 g/d).<sup>30</sup>

Results of the African American Study of Kidney Disease (AASK), which included African-American patients with hypertensive kidney disease, add support to the notion that patients with significant proteinuria benefit from a lower

BP target. The overall trial showed that patients randomly assigned to a lower mean BP target less than 92 mm Hg derived no benefit from this intervention in comparison to patients randomly assigned to a usual target (mean BP, 102 to 107 mm Hg).<sup>31</sup> However, a post hoc analysis of this trial<sup>32</sup> showed that baseline proteinuria was the key factor that defined its results because the lower BP target preserved renal function in the small subset of patients with proteinuria with protein greater than 1,000 mg/d (>1 g/d).

In patients with nondiabetic kidney disease and lower urine protein levels, the evidence for such a low BP goal is not as strong. In the MDRD trial, no significant benefit in renal protection was apparent in the subgroup of patients with proteinuria less than 1,000 mg/d (<1 g/d) of protein.<sup>29</sup> In the cohort of patients with urine protein excretion less than 1,000 mg/d (<1 g/d) in the AASK trial, there was a nonsignificant trend toward a slower decrease in GFR.<sup>31,32</sup> That meta-analysis provided additional support of these findings because it showed no significant association between systolic BP and risk of kidney disease progression in patients with proteinuria with protein less than 1,000 mg/d (<1 g/d; Fig 1).<sup>30</sup>

The Ramipril Efficacy in Nephropathy (REIN) trial 2 has been considered as evidence to contradict low BP goals in patients with proteinuria.<sup>33</sup> In this study, patients with nondiabetic nephropathy and urine protein excretion greater than 1,000 mg/d (>1 g/d) already treated with the angioten-

sin-converting enzyme (ACE) inhibitor ramipril were assigned to either conventional (diastolic BP < 90 mm Hg) or intensified (systolic/diastolic BP < 130/80 mm Hg) treatment with the addition of the dihydropyridine calcium antagonist felodipine. At the end of the treatment period, cumulative incidence of ESRD, rate of GFR decrease, and residual proteinuria were similar in the 2 arms. However, this study was underpowered to detect a difference in decrease in GFR between the 2 BP groups because median follow-up was only 1.6 years and there was only a 4.1/2.8-mm Hg difference in BP between treatment groups throughout the study.

When all the evidence is pooled (Table 2), it is clear that a BP goal less than 130/80 mm Hg definitely must be sought, except for patients with diabetes and those with nondiabetic chronic kidney disease and proteinuria with protein greater than 1,000 mg/d (>1 g/d). In patients without diabetes with proteinuria with protein between 300 and 1,000 mg/d (0.3 and 1 g/d), strong consideration also should be given for this target until specific trials clarify the issue.

### TREATMENT OF HYPERTENSION AND PRESERVING RENAL FUNCTION IN PATIENTS WITH PROTEINURIA

#### Nonpharmacological Approaches

Overall, managing hypertension in Western societies on both sides of the Atlantic has proved

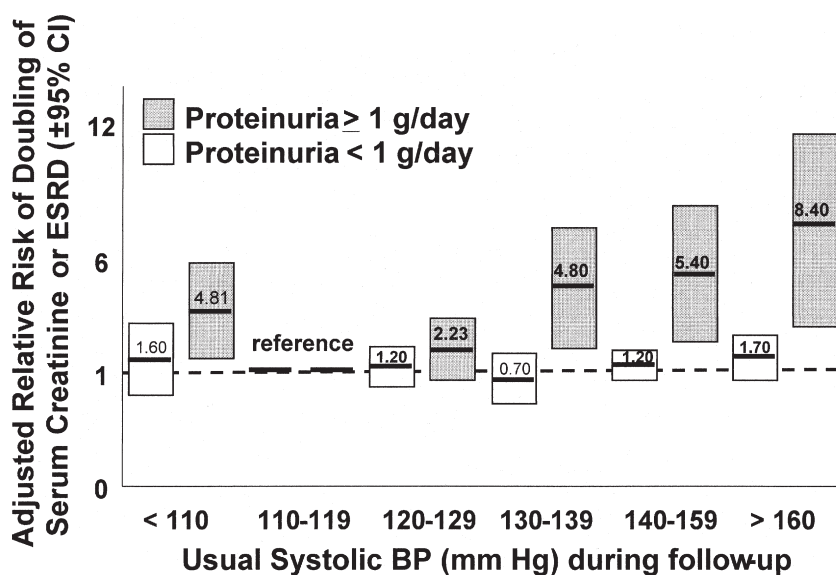


Figure 1. Relative risk of kidney disease progression based on systolic BP and urine protein excretion levels. Results based on a meta-analysis of 11 randomized controlled trials. The reference group is defined at a systolic BP of 110 to 119 mm Hg. Modified from Jafar et al.<sup>30</sup>

**Table 2. Characteristics of Studies Evaluating the Impact of Different BP Levels on Renal Outcomes**

	MDRD <sup>35</sup>	AASK <sup>31</sup>	REIN-2 <sup>33</sup>
Mean follow-up (y)	6.2	3.8	3
Baseline GFR (mL/min/1.73 m <sup>2</sup> )	32	46	35
Baseline level of protein excretion (mg/d)	1,090	530	2,850
Difference in renal outcomes between higher and lower BP groups	No difference*	No difference*	No difference

Note: To convert GFR in mL/min to mL/s, multiply by 0.01667; protein in mg/d to g/d, multiply by 0.001.

\*Subgroup analyses of these studies showed that patients with proteinuria with protein greater than 1 g/d have slower decreases in GFR when BP less than 125/75 mm Hg is achieved.

very difficult because control rates are only about 30% in the United States and less than 10% of the overall hypertensive population in various European countries.<sup>34</sup> The presence of chronic kidney disease makes hypertension management even harder. Such lifestyle changes as weight loss, exercise, and alcohol moderation should have a central role in helping manage hypertension in all patients, but low-protein diets, low sodium intake, and smoking cessation have been proposed to have additional importance in terms of kidney function preservation and hypertension control in patients with proteinuria.

The MDRD is the largest trial to date to evaluate the role of a low-protein diet for kidney function.<sup>35</sup> The trial randomly assigned patients with chronic kidney disease and proteinuria to 2 BP groups, as discussed previously, and either a low-protein (0.58 g/kg/d) or very-low-protein diet (0.28 g/kg/d). The very-low-protein group had a marginally ( $P = 0.07$ ) slower decrease in GFR than the low-protein group in 3 years, indicating a trend toward renal function preservation when protein consumption decreases. These results are strengthened by a meta-analysis showing that a low-protein diet reduces the decline in GFR by 0.53 mL/min/y (0.01 mL/s/y).<sup>36</sup> However, physicians must balance this benefit with the difficulty that most patients have adhering to a strict diet restricting protein intake and must be vigilant in monitoring patients for signs of malnutrition.

Hypertension in patients with chronic kidney disease is related to a large extent to salt sensitivity. This was shown previously in a study comparing response to salt loading in patients with kidney disease and healthy subjects. Both groups were able to increase their fractional excretion of sodium after a salt load, but patients with kidney disease also showed increases in BP.<sup>37</sup>

This was a result of the increase in extracellular volume caused by the high salt intake and inability of the impaired functioning kidneys to deal with this volume expansion. High dietary sodium intake in patients with proteinuria is particularly deleterious for additional reasons. For example, the presence of a high salt load itself will increase the oncotic pressure of the glomerular filtrate, which leads to more protein pulled into urine.<sup>38</sup> In addition, excessive dietary sodium intake (ie, >6 g/d) will attenuate the effects of many antihypertensive medications on proteinuria reduction.<sup>39</sup> Thus, recommending a daily dietary sodium intake of 2 to 4 g in patients with chronic kidney disease will help BP management and decrease urinary protein excretion.

Several population-based studies showed an association between smoking and both accelerated renal function decrease and increased risk of developing abnormal UAE.<sup>40,41</sup> The Heart Outcomes and Prevention Evaluation trial confirmed this finding, showing a 20% greater risk of microalbuminuria or proteinuria development in current smokers compared with nonsmokers.<sup>42</sup> To date, no prospective trial examined the effect of smoking cessation on patients with renal disease and proteinuria. However, on the basis of the cardiovascular benefits of smoking cessation, physicians should recommend this intervention to patients with chronic kidney disease. That this also will serve to decrease proteinuria and preserve renal function is possible, but remains to be established.

### Pharmacological Therapy

Because the overall goal of hypertension management in patients with nephropathy involves not only decreasing BP to less than 130/80 mm Hg, but also slowing the progression of kidney disease and reducing the risk of cardiovas-

cular disease, physicians must be aware of the presence of proteinuria and use antihypertensive agents that also decrease it because this will result in better renal and cardiovascular outcomes.<sup>43</sup>

### **ACE Inhibitors**

Antihypertensive agents that interfere with the renin-angiotensin-aldosterone system, ie, ACE inhibitors and angiotensin receptor blockers (ARBs), are those most consistently found to decrease proteinuria and the rate of renal function deterioration in patients with diabetic and nondiabetic kidney disease, independent of BP levels. For ACE inhibitors, this was shown first in the original trial of the Collaborative Study Group that randomly assigned 409 patients with type 1 diabetes with overt nephropathy (UAE  $\geq$  500 mg/d [ $\geq$ 0.5 g/d]) and mild renal insufficiency (serum creatinine  $\leq$  2.5 mg/dL [ $\leq$ 221  $\mu$ mol/L]) to captopril or placebo therapy<sup>44</sup> (Table 3). After a median follow-up of 3 years, treatment with captopril led to a 43% decrease in risk of the primary end point of doubling of serum creatinine level; 50% decrease in the combined end points of death, need for dialysis therapy, and transplantation; and 30% decrease in UAE in comparison to placebo. Although there were small differences in BP between the 2 groups, these effects were independent of BP levels.

Subsequent studies supported the use of ACE inhibitors to decrease proteinuria and preserve renal function in patients with nondiabetic kidney disease. In the first report of the REIN Study, in patients without diabetes with an average creatinine level of 2.4 mg/dL (212.4  $\mu$ mol/L) and 24-hour urine protein excretion greater than 3,000 mg/d ( $>$ 3 g/d) randomly assigned to ramipril, 5 mg/d, or placebo, ramipril was associated with a 55% decrease in median urine protein excretion from baseline and significant decreases in UAE, GFR decline, and risk of doubling of serum creatinine level or progressing to ESRD compared with placebo. The risk of kidney disease progression still decreased significantly after adjustment for changes in systolic and diastolic BP.<sup>45</sup> In the AASK trial, African-American patients with hypertensive kidney disease, a mean serum creatinine level of 2.2 mg/dL (194.7  $\mu$ mol/L), and 24-hour urine protein excretion of 600 mg/d (0.6 g/d) were randomly assigned to ramipril, amlodipine, or metoprolol.

Patients treated with ramipril had a 36% decrease in the secondary composite outcome of 50% decrease in GFR, ESRD, or death compared with amlodipine and a 22% decrease compared with metoprolol.<sup>31</sup> A previous meta-analysis of patients with nondiabetic chronic kidney disease showed that regimens including an ACE inhibitor were associated with a 31% decrease in progression to ESRD and 30% decrease in the combined end point of doubling of serum creatinine level or progression to ESRD.<sup>46</sup> Finally, in a recent study in which 224 patients with serum creatinine levels of 3.1 to 5.0 mg/dL (274.3 to 442.5  $\mu$ mol/L) and persistent proteinuria (mean urine protein excretion, 1,600 mg/d [1.6 g/d]) were randomly assigned to administration of 20 mg/d of benazepril or placebo on top of conventional antihypertensive therapy,<sup>47</sup> benazepril was associated with a 43% decrease in risk of the primary end point (doubling of serum creatinine level, ESRD, or death), 23% decrease in rate of decline in renal function, and 2.5 times greater decrease in proteinuria compared with placebo after a mean follow-up of 3.4 years, benefits that did not seem attributable to better BP control.

In contrast to these results, findings from more recent studies suggest that the only benefit seen with ACE inhibitors is related to BP decrease. For example, in the UKPDS 39, captopril and atenolol had similar outcomes on microvascular and macrovascular complications in hypertensive patients with type 2 diabetes.<sup>48</sup> Well-controlled animal studies,<sup>49</sup> post hoc data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),<sup>50</sup> and a recent meta-analysis<sup>51</sup> expanded the idea that ACE inhibitors have no unique effects independent of BP decrease for patients with nondiabetic kidney disease. As in the total population of ALLHAT,<sup>52</sup> in patients with a mild (60 to 89 mL/min/1.73 m<sup>2</sup> [1.00 to 1.48 mL/s/1.73 m<sup>2</sup>]) or moderate-severe ( $<$ 60 mL/min/1.73 m<sup>2</sup> [ $<$ 1.00 mL/s/1.73 m<sup>2</sup>]) decrease in baseline GFR, there were no differences in incidence of ESRD or a 50% or greater decrease in GFR between the groups of chlorthalidone, amlodipine, and lisinopril.<sup>50</sup> In the meta-analysis of Casas et al,<sup>51</sup> use of ACE inhibitors or ARBs was shown not to be related to an additional BP decrease, lower risk of doubling of serum creatinine level, or inci-

**Table 3. Long-Term Studies of Antihypertensive Treatment in Patients With Proteinuria With Primary Renal End Points**

	Regimens Compared	No. of Patients	Baseline GFR (mL/min/1.73 m <sup>2</sup> )	Baseline Proteinuria (g/d)	Mean Follow-Up	Main Findings
Diabetic nephropathy						
Captopril trial, 1993 <sup>44</sup>	Captopril v placebo	409	68	1.2	3 y	Captopril led to 43% reduction in risk of doubling of serum creatinine level; 50% reduction in combined end point of death, need for dialysis, and transplantation; and 30% reduction in proteinuria compared with placebo
Bakris et al, 1996 <sup>65</sup>	Lisinopril v non-DHPCCB v atenolol	52	59	3.5	63 mo	No difference in decrease in creatinine clearance between lisinopril and non-DHPCCB groups, significantly greater decrease in atenolol group
Bakris et al, 1997 <sup>66</sup>	Verapamil SR v atenolol	34	62	3.2	54 mo	Verapamil SR associated with slower rate of decrease in creatinine clearance and greater reduction in proteinuria compared with atenolol
Smith et al, 1998 <sup>67</sup>	Diltiazem v nifedipine GITS	21	96	0.9	21 mo	Diltiazem associated with 57% reduction in baseline proteinuria, whereas nifedipine GITS‡ produced no change
RENAAL, 2001 <sup>59</sup>	Losartan v placebo	1,513	54	1.25*	3.4 y	Losartan associated with 16% reduction in risk of doubling of baseline serum creatinine level, progression to ESRD, or death and 35% reduction in albumin-creatinine ratio compared with placebo
IDNT, 2001 <sup>60</sup>	Irbesartan v amlodipine v placebo	1,715	59	2.9	2.6 y	Irbesartan associated with 20% reduction compared with placebo and 23% reduction compared with amlodipine in risk of doubling of baseline serum creatinine level, progression to ESRD, or death and 33% reduction in proteinuria from baseline
REIN-2, 2005 <sup>33</sup>	Conventional v intensified control	338	35	2.9	19 mo†	No difference in renal outcomes
Nondiabetic kidney disease						
MDRD, 1994 (Study B) <sup>29</sup>	Usual v low BP goal	255	20	1.45	2.2 y	Patients with baseline proteinuria > 1 g/d in the low-goal group had slower GFR decrease and decrease in proteinuria compared with those in usual-goal group
AIPRI, 1996 <sup>53</sup>	Benazepril v placebo	583	42	1.8	3 y	Benazepril associated with 53% reduction in risk of doubling of serum creatinine level or ESRD compared with placebo
REIN, 1997 <sup>45</sup>	Ramipril v placebo	166	39	5.3	16 mo	Ramipril associated with significant reductions in UAE, GFR decrease, and risk of doubling of serum creatinine level or progressing to ESRD compared with placebo
AASK, 2001 <sup>31</sup>	Metoprolol v amlodipine v ramipril; usual v low BP goal	1,094	46	0.5	3-4.1 y	Ramipril associated with 36% reduction in secondary composite outcome of 50% decrease in GFR, ESRD, or death compared with amlodipine and 22% reduction compared with metoprolol
Hou et al, 2006 <sup>47</sup>	Benazepril v placebo	224	26	1.6	3.4 y	Patients with baseline proteinuria > 1 g/d in the low-goal group had slower GFR decline compared with those in usual-goal group Benazepril associated with 43% reduction in risk of doubling of serum creatinine level, ESRD, or death; 23% decrease in rate of GFR decline; and 2.5 times greater reduction in proteinuria compared with placebo

Note: To convert GFR in mL/min to mL/s, multiply by 0.01667.

Abbreviations: AIPRI, Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study; SR, sustained release; GITS, gastrointestinal transcapillary system.

\*Urinary albumin-creatinine ratio in grams per gram.

†Median follow-up.

‡Median follow-up changing for the various comparisons.

dence of ESRD in patients with diabetic nephropathy. In patients with nondiabetic kidney, these agents were associated with BP-independent small renal benefits, which were proposed to be uncertain because of evidence of small-study bias.

The lack of benefit seen with ACE inhibitors in these later cases relates to several issues. Most importantly, it seems that baseline UAE level and stage of kidney disease are key factors determining benefit from treatment with an ACE inhibitor. The Collaborative Study Group trial

provides some of the strongest evidence to support this idea because patients in that study with a serum creatinine level greater than 2.0 mg/dL ( $>177 \mu\text{mol/L}$ ) derived the greatest benefit from adding renin-angiotensin-aldosterone system inhibition to a standard antihypertensive regimen because those in the ACE-inhibitor group had a 74% decrease in risk of doubling of serum creatinine level compared with the placebo group. Conversely, only a 4% reduction in this end point was seen with ACE inhibition in patients with a serum creatinine level less than 1.0 mg/dL ( $<88.5 \mu\text{mol/L}$ ).<sup>44</sup> In a previous study of benazepril in patients with kidney disease of various causes, the reduction in the primary end point (doubling of serum creatinine level or need for dialysis therapy) was greater in those with baseline urinary protein excretion greater than 1,000 mg/d ( $>1 \text{ g/d}$ ).<sup>53</sup> In the REIN Study, a higher degree of baseline urinary protein excretion was associated with larger differences in the mean rate of GFR decrease and the percentage of patients reaching the combined end point (doubling of serum creatinine level or ESRD) between the placebo and ramipril groups.<sup>45</sup> Similarly, the mentioned meta-analysis of nondiabetic renal disease<sup>30</sup> showed a better renoprotective action of ACE inhibitors in patients with greater levels of proteinuria.

In addition, because proteinuria clearly is associated with increased risk of nephropathy progression, a decrease in UAE in proteinuric patients should be related to preservation of renal function. In the REIN trial, the percentage of decrease in proteinuria correlated inversely with decrease in GFR and predicted the decrease in risk of doubling of baseline creatinine level or ESRD. As mentioned, the decrease in risk of renal disease progression was independent of BP changes, but after adjustment for changes in proteinuria, it was no longer significant.<sup>45</sup> In the AASK, although only 33% of participants had proteinuria at baseline, a decrease in proteinuria early in the disease course (6 months) predicted ESRD development at 5 years.<sup>32</sup> This was confirmed from other 2 post hoc analyses of large outcome trials using ARBs,<sup>54,55</sup> discussed next. In ALLHAT, UAE measurements did not take place.<sup>50</sup> Thus, it is difficult to interpret the lack of selective benefit of ACE-inhibitor treatment in this trial. In addition, exclusion criteria in

ALLHAT included heart failure, serum creatinine level in excess of 2.0 mg/dL ( $>177 \mu\text{mol/L}$ ), and current treatment with an ACE inhibitor for underlying kidney disease, and, according to Rahman et al,<sup>50</sup> presumably participants with decreased renal function mostly were patients with ischemic renal disease, for which an overwhelming renoprotective effect of ACE inhibitors is not expected. With regard to the meta-analysis of Casas et al,<sup>51</sup> a great influence of the magnitude of ALLHAT as well as a number of method issues (ie, selection of renal outcomes to be analyzed, ignorance of the previously mentioned issue of proteinuria) recently were proposed to severely hamper relevant conclusions.<sup>56</sup>

The Microalbuminuria, Cardiovascular, and Renal Outcomes substudy of the Heart Outcomes Prevention study showed that adding an ACE inhibitor to the antihypertensive regimen in patients at high risk of cardiovascular events not only decreased the risk of developing overt nephropathy, but also decreased cardiovascular outcomes. The ramipril group had a 25% reduction in the primary outcome (myocardial infarction, stroke, or cardiovascular death) compared with the placebo group.<sup>57</sup> The risk of cardiovascular events increased almost linearly as UAE increased, and risk reduction from using an ACE inhibitor is more pronounced the higher the level of UAE.<sup>58</sup>

Overall, it seems that ACE inhibitors have an important renoprotective effect in addition to BP reduction in patients with proteinuria and advanced kidney disease (ie, stage 3 or higher nephropathy). The higher the degree of baseline urine protein excretion and proteinuria decrease, the more pronounced the effect.

### **Angiotensin Receptor Blockers**

ARBs are a newer class than ACE inhibitors; therefore, data involving ARBs are less abundant. Two large renal outcome trials, the Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial<sup>59</sup> and the Irbesartan in Diabetic Nephropathy Trial (IDNT),<sup>60</sup> showed that ARBs also have renoprotective properties beyond their effect on BP. The RENAAL trial randomly assigned 1,513 patients with type 2 diabetes with a mean creatinine level of 1.9



mg/dL (168  $\mu$ mol/L) and median albumin-creatinine ratio of 1,237 mg/g (1.237 g/g) to the ARB losartan or placebo. After a mean follow-up of 3.4 years, losartan treatment was associated with a 16% reduction in the primary end point of doubling of baseline serum creatinine level, progression to ESRD, or death; 35% decrease in albumin-creatinine ratio; and 15% decrease in rate of decline in estimated creatinine clearance.<sup>59</sup> Subsequently, it was sought to determine whether there was an association between baseline proteinuria, initial decrease in proteinuria, or degree of residual proteinuria and the combined primary end point. Baseline proteinuria level had a nearly linear relationship with risk of achieving the primary outcome. More importantly, the trial showed that for every 50% decrease in albuminuria in the first 6 months after initiating treatment with losartan, there was a 36% risk reduction of the primary end point and 45% reduction for ESRD at trial end. The decrease in proteinuria in the first 6 months of therapy mirrored the nearly linear relationship between baseline proteinuria and renal risk.<sup>54</sup> Interestingly, it was estimated that losartan could delay the need for dialysis therapy or transplantation for 2 years, and the investigators concluded that all renoprotection from losartan use was attributed to antiproteinuric effect of the ARB and was not related to BP.<sup>54</sup>

In the IDNT, 1,715 patients with type 2 diabetes with a mean serum creatinine level of 1.7 mg/dL (150.5  $\mu$ mol/L) and median urinary protein excretion of 2,900 mg/d (2.9 g/d) were randomly assigned to irbesartan, amlodipine, or placebo. The primary end point was the same as with RENAAL. Treatment with irbesartan resulted in a 20% reduction compared with placebo and 23% reduction compared with amlodipine in the primary composite outcome after a mean follow-up of 2.6 years, whereas proteinuria decreased by 33% in the irbesartan group versus 6% in the amlodipine group and 10% in the placebo group.<sup>60</sup> This study also confirmed the relationship between baseline proteinuria and risk of renal disease progression because it showed that for every 2-fold increase in baseline proteinuria level, risk of reaching the primary end point doubled. Irrespective of treatment group, this risk was cut in half with every 50% decrease in proteinuria at 1 year. However, after

1 year of treatment, 40% of patients in the irbesartan group had a greater than 50% decrease in proteinuria compared with 20% in the amlodipine group and 25% in the placebo group. Again, the investigators of this trial attribute the superior renoprotective effect of irbesartan to its antiproteinuric properties.<sup>55</sup>

A recent post hoc analysis of data from the Losartan Intervention for Endpoint Reduction in Hypertension Study showed that UAE decrease with an ARB is related to a decrease in cardiovascular disease risk.<sup>61</sup> The study population of more than 8,000 patients with hypertension and left ventricular hypertrophy followed up for a mean of 4.8 years was stratified into groups by baseline UAE level. Of note, whereas a small percentage of patients in this trial had overt proteinuria, the majority of participants had microalbuminuria. Analysis showed that those with the highest baseline UAE had a 3- to 4-fold greater risk of reaching the primary cardiovascular end point of first occurrence of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction compared with those in the lowest-UAE group. The extent of UAE decrease at 5 years predicted the risk reduction for the primary end point.<sup>61</sup>

In summary, it would appear that ACE inhibitors and ARBs provide similar cardiovascular and renal protection. This similarity was supported by the Diabetics Exposed to Telmisartan And Enalapril Study, which compared the effects of enalapril and telmisartan in 250 patients with type 2 diabetes, hypertension, and UAE between 11 and 999  $\mu$ g/min ( $19 \times 10^{-8}$  and  $17 \times 10^{-6}$  g/s). After 2 years of follow-up, the 2 agents had similar effects on change in GFR, serum creatinine level, UAE, BP, and rates of ESRD, cardiovascular events, and death from all causes.<sup>62</sup> However, there are some who call for the use of ARBs in place of ACE inhibitors because they generally are better tolerated, have a lower incidence of hyperkalemia and cough, and are not associated with the life-threatening complication of angioedema.<sup>63</sup> The greater cost of ARBs makes this argument untenable for some, but ARBs were proved to be cost-effective in the management of nephropathy in various settings.<sup>64</sup> Overall, it is reasonable to use the 2 classes interchangeably in patients with proteinuria in clinical practice.

### Calcium Channel Blockers

The 2 different subtypes of calcium channel blockers, nondihydropyridine (non-DHPCCB) and dihydropyridine (DHPCCB), were shown to have divergent effects on patients with high levels of proteinuria. In previous studies of patients with overt diabetic nephropathy, non-DHPCCBs (verapamil, diltiazem) were associated with decreases in proteinuria and rate of creatinine clearance decline that were greater than those with atenolol<sup>65,66</sup> and no different from those with lisinopril,<sup>65</sup> with similar BP control in the various groups. In another cohort of patients with diabetic nephropathy followed up for 21 months, a DHPCCB, nifedipine XL, produced no change in proteinuria, whereas diltiazem resulted in a proteinuria decrease of about 60%.<sup>67</sup> The mechanism for this difference relates to the more pronounced impairment in renal autoregulation and glomerular pressure transmission produced by DHPCCBs.<sup>68</sup> This relates to increased renal blood flow and gives the mistaken impression of preserved renal function, but comes at the expense of additional increased intraglomerular pressures and permeability to albumin, which, in turn, leads to poorer renal outcomes.

Additional evidence to support a lack of renoprotective properties of DHPCCBs comes from multicenter trials. As mentioned, in the IDNT, amlodipine was associated with a 6% increase in proteinuria versus baseline and 23% greater incidence of the primary end point of doubling of serum creatinine level, onset of ESRD, or death compared with irbesartan.<sup>60</sup> In the nondiabetic population of the AASK trial, the 58% increase in proteinuria at 6 months in those treated with amlodipine correlated with a greater incidence of the composite end point of a 50% or greater decrease in GFR, ESRD, and/or death compared with those treated with ramipril, who had a 20% decrease in proteinuria.<sup>31</sup> Data from the REIN-2 study lead to questions about the ability of DHPCCBs to help toward regression of renal function deterioration in patients with proteinuric kidney disease, even by means of BP decrease, but need to be confirmed from additional studies with longer follow-up.<sup>33</sup>

It has to be noted that these clear differences between effects of calcium channel blocker sub-

classes on the kidney seem to manifest only in patients with advanced disease with proteinuria.<sup>69</sup> In ALLHAT, there were no differences in incidence of ESRD or a 50% or greater decrease in GFR among the groups administered chlorthalidone, amlodipine, and lisinopril.<sup>50,52</sup> However, this finding is not very informative because UAE was not measured, as discussed. The total number of participants with kidney disease and heavy proteinuria are unknown; however, it must have been small because exclusion criteria in ALLHAT included serum creatinine level in excess of 2.0 mg/dL ( $>177 \mu\text{mol/L}$ ) and current treatment with an ACE inhibitor for underlying kidney disease. In the hypertensive Appropriate Blood Pressure Control in Diabetes trial,<sup>70</sup> in which 470 hypertensive subjects were randomly assigned to nisoldipine or enalapril treatment, there was no difference in creatinine clearances between the 2 groups during 5.3 years of follow-up, although enalapril significantly decreased preexisting levels of microalbuminuria. However, almost all participants had normoalbuminuria or microalbuminuria, not microalbuminuria. Moreover, baseline mean creatinine clearance was 84 mL/min/1.73 m<sup>2</sup> (1.40 mL/s/1.73 m<sup>2</sup>) in the overall population and about 75 mL/min/1.73 m<sup>2</sup> (1.25 mL/s/1.73 m<sup>2</sup>) in the subgroup of patients with macroalbuminuria. This is far better kidney function than any trial showing a benefit with renin-angiotensin system blockade. Moreover, the most definite end point of ESRD incidence was not recorded.

The issues mentioned also were exemplified by data resulting from the Bergamo Nephrologic Diabetes Complications Trial, which compared the effect of a non-DHPCCB and an ACE-inhibitor, alone or in combination, on microalbuminuria development in a group of hypertensive normoalbuminuric patients with type 2 diabetes. After a median follow-up of 3.6 years, progression to microalbuminuria was significantly less in subjects treated with trandolapril or the combination (6.0% and 5.7%, respectively) compared with subjects receiving verapamil or placebo (11.9% and 10.0%, respectively).<sup>71</sup> Overall, these notions are in keeping with the mentioned observations about ACE inhibitors, ie, in patients with advanced kidney disease with proteinuria, the focus should be both BP and proteinuria reduction with the use of proper agents, whereas in

those with early kidney disease, the focus should be BP control and cardiovascular risk reduction.

### **Diuretics**

Thiazide diuretics have not been shown to decrease urine protein excretion beyond the amount expected because of BP reduction. However, because most patients with chronic kidney disease and proteinuria would need a combination of 2 or more antihypertensive agents to reach the mentioned BP goals and renal function deterioration is accompanied by salt and water retention, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative guidelines suggest that if BP is not controlled, a diuretic should be the first agent to add to an ACE inhibitor or ARB in patients with proteinuria.<sup>2</sup> It has to be noted that thiazide diuretics become less effective when GFR decreases to less than 40 mL/min/1.73 m<sup>2</sup> (<0.67 mL/s/1.73 m<sup>2</sup>),<sup>72</sup> and to control BP in patients with a GFR less than that level, a loop diuretic (ie, furosemide, torsemide, and so on) is very likely to be needed. If furosemide is used, it should be dosed adequately (ie, 2 to 3 times instead of once daily) because it has a very short duration of action (3 to 6 hours). Recent data suggest that use of such aldosterone receptor antagonists as spironolactone and eplerenone in low doses may be indicated in patients with proteinuric kidney disease, discussed in detail next. However, potassium-sparing diuretics should be avoided in patients with preexisting hyperkalemia, ie, serum potassium level greater than 5.5 mEq/L (>5.5 mmol/L), from either diabetes or renal disease from other causes, and, when used, serum potassium level must be followed up closely and a dose adjustment of the concomitant conventional diuretic therapy always should be considered.

### **$\beta$ -Blockers**

In general, there is no direct evidence that conventional  $\beta$ -blockers provide additional renoprotective effects. As mentioned, studies of patients with overt diabetic nephropathy showed that non-DHPCCBs produced significant decreases in proteinuria and rate of creatinine clearance decline compared with atenolol.<sup>38,65</sup> In patients with type 2 diabetes in the UKPDS 39 study, there were no significant differences be-

tween captopril and atenolol in level of BP achieved, incidence of overt nephropathy, and rate of plasma creatinine level doubling, data suggesting that any renoprotective effect is caused by BP lowering.<sup>48</sup> Therefore,  $\beta$ -blockers were suggested to be used in patients with proteinuria as third-line agents to achieve BP control.<sup>2</sup> However, recent data from the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives trial showed that 1 of the newer  $\beta$ -blockers, carvedilol, was associated with significant reductions in risk of microalbuminuria development in hypertensive patients with type 2 diabetes compared with metoprolol.<sup>73</sup> These findings call for a prospective trial examining the effect of this drug in patients with renal disease and proteinuria.

### **$\alpha$ -Blockers**

Although combining effective BP reduction<sup>74</sup> and a beneficial metabolic profile,<sup>75</sup>  $\alpha$ -blockers were not shown to slow renal disease progression or decrease UAE in patients with type 2 diabetes and albuminuria.<sup>76</sup> Moreover, this class of agents also failed to decrease cardiovascular events in patients who had or developed heart failure, evidenced by results of the long-acting  $\alpha$ -blocker arm of ALLHAT, which was stopped early because of an increased incidence of heart failure.<sup>77</sup> Hence, this class should not be preferred as initial or even second-line treatment for hypertension in patients with chronic kidney disease, but as third-line treatment, especially in older men with benign prostatic hypertrophy and urine flow problems.<sup>78</sup>

### **Combination Therapy Approaches to Decrease Proteinuria**

In addition, recent data suggest that specific combinations of antihypertensive agents can be even more effective in proteinuria reduction. For example, combined use of ACE inhibitors and ARBs was shown to decrease proteinuria and slow kidney disease progression more effectively than using ACE inhibitors or ARBs alone. In the Combination Treatment of ARB and ACE-Inhibitor in Non-diabetic Renal Disease trial, 263 patients with nondiabetic kidney disease and mean urinary protein excretion of 2,500 mg/d (2.5 g/d) were randomly assigned to trandolapril, 3 mg/d; losartan, 100 mg/d; or a combination of

the 2 drugs at the same dosages. After 3 years of follow-up, urinary protein excretion decreased significantly more with combined therapy (75.6%) compared with trandolapril (44.3%) or losartan (44.1%) alone. Moreover, the group of patients treated with combined therapy had a 60% to 62% decrease in the primary end point of time to doubling of serum creatinine level or ESRD compared with either the trandolapril- or losartan-treated group.<sup>79</sup> It is important to note that these findings were independent of BP differences because both office and ambulatory BP decreases were similar across all 3 groups.<sup>80</sup> In addition, patients with the greatest decreases in proteinuria at 6 months had the slowest decreases in GFR,<sup>80</sup> a finding also supporting the importance of proteinuria reduction for kidney function preservation. Other studies and a meta-analysis further support the notion that the combination of ACE inhibitors and ARBs is not much use for BP decrease in patients with uncomplicated hypertension, but can be beneficial for proteinuria reduction.<sup>81,82</sup>

Another useful combination could be the addition of an aldosterone receptor antagonist to patients already administered an ACE inhibitor or an ARB, keeping in mind the attention needed to be given to potassium levels, as discussed. The rationale for such a combination is that plasma aldosterone levels increase in patients with chronic kidney disease and may contribute to renal injury,<sup>83</sup> whereas blockade of the renin-angiotensin-aldosterone system with ACE inhibitors or ARBs does not necessarily result in a maintained decrease in plasma aldosterone levels.<sup>84</sup> The addition of spironolactone in proteinuric patients already administered an ACE inhibitor or an ARB decreased proteinuria in pilot studies.<sup>85-88</sup> Moreover, eplerenone, the newer aldosterone receptor antagonist, further reduced UAE in patients with hypertension and left ventricular hypertrophy when added to an ACE inhibitor.<sup>89</sup> Larger future studies are needed to confirm these promising findings.

Combining an ACE inhibitor and a non-DHPCCB previously was shown to decrease proteinuria. The first study to evaluate this combination included 30 patients with type 2 diabetes and renal insufficiency who were randomly assigned to receive either lisinopril alone, verapamil alone, a combination of the 2, or hydrochlor-

othiazide and guanfacine for 1 year. Patients treated with the combination had a 78% decrease in albuminuria compared with a 59% decrease in those treated with lisinopril alone.<sup>90</sup> Also of note, patients receiving the combination therapy had the best side-effect profile of any of the groups. This likely occurred because combining the 2 medications allowed for lower doses of each to be used. However, in a more recent study of 69 patients with nondiabetic nephropathy, the addition of verapamil to trandolapril treatment did not significantly affect proteinuria after 8 months.<sup>91</sup> Thus, this issue needs to be examined further.

## CONCLUSION

Proteinuria is a well known risk factor for the progression of renal disease and cardiovascular morbidity and mortality. To maximize risk reduction, physicians must focus on achieving a target BP less than 130/80 mm Hg in those with UAE greater than 300 mg/d (>0.3 g/d). ACE inhibitors and ARBs should be used as first-line antihypertensive therapy in patients with proteinuria because these classes have a BP-independent antiproteinuric effect and consistently were shown to improve renal and cardiovascular outcomes. If BP levels are still out of goal, initially a thiazide or a loop diuretic and then compounds from the other antihypertensive classes should be added to achieve BP control. Combination therapy with an ACE inhibitor and an ARB or, in addition to such agents, a non-DHPCCB or an aldosterone antagonist should be considered if the degree of proteinuria is still high. Overall, physicians must take aggressive measures to decrease both BP and proteinuria to give their patients maximal renal and cardiovascular protection.

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