Diabetes and Hypertension: Blood Pressure Control and Consequences

Matthew R. Weir

Diabetes and hypertension are the leading causes of end-stage renal disease in the Western world. Inadequate control of both systemic and glomerular capillary pressure in diabetics results in increasing hydraulic force and mechanical stretch on the glomeruli, with a subsequent increase in proteinuria and ultimately glomerulosclerosis. Therapeutic strategies that combine systemic and glomerular capillary pressure reduction result in reduced proteinuria and are ideal for preventing renal injury. Both experimental and clinical studies have demonstrated the importance of intensive control of blood pressure, preferably to systolic blood pressure (SBP) ≤ 130 mm Hg to delay progression of renal disease. In particular, drugs that block the renin-angiotensin system (RAS) offer the advantage of consistently reducing glomerular capillary pressure and proteinuria relative to changes in systemic blood pressure. This combination of events is ideal for delaying progression of renal disease. However, the use of drugs that block the RAS is not a surrogate for maintaining tight control of blood pressure. Am J Hypertens 1999;12:170S–178S © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Diabetes, hypertension, angiotensin II, RAS, renal disease.

Hypertension and diabetes are the most common causes of end-stage renal disease in the United States. Moreover, they contribute even more substantially in the development of cardiovascular disease (CVD). In 1997, more than 35% of patients entering dialysis had been diagnosed with diabetes and hypertension. The prognosis for patients with diabetic renal disease has improved considerably due to more aggressive therapy to reduce blood pressure and proteinuria. Diabetic patients without proteinuria tend to have lower systemic blood pressure than proteinuric patients. Clinical studies have demonstrated that the onset of microalbuminuria often coincides with a clinically apparent increase in blood pressure. In fact, systemic blood pressure correlates more with changes in urinary microalbumin excretion than with many of the variables in diabetic patients including glycemic control, age, duration of diabetes, gender, and body mass index. Blood pressure tends to increase more consistently in patients with microalbuminuria than in diabetic patients without it. Even modest increases in blood pressure within the so-called “normal” range (110/70 to 130/80 mm Hg) can be indicative of progressive nephropathy. Therefore, it makes sense to intervene as soon as possible to prevent blood pressure elevation to greater than 110–120/70–80 mm Hg to prevent increased risk of renal disease.

The benefits of reducing blood pressure on renal function in diabetic patients were first demonstrated in the late 1970s by Mogensen, who discovered that tighter control of blood pressure to a level below normotensive (<130/80 mm Hg) reduced renal disease progression rates. This was subsequently confirmed by long-term studies by Parving et al. Parving et al employed standard antihypertensive

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therapies (diuretics, β-blockers, and vasodilators) to demonstrate that reducing blood pressure to 129/84 mm Hg was associated with a reduction in albuminuria and a 50% decrease in the rate of renal disease progression.11

In this review, I will discuss the implications of renal autoregulation and intensive blood pressure control, and how these factors have an impact on our decisions about blood pressure treatment and choice of therapy. The mechanistic effects of renin-angiotensin system (RAS) blockade and its benefits on blood pressure and renal function will be discussed in light of both experimental and clinical trials. A review of the antagonistic effects of dietary salt on the effects of drugs that block the RAS will be reviewed, with emphasis on clinical relevance. Mechanistic differences between angiotensin-converting enzyme (ACE) inhibitors and angiotensin type-1 receptor blockers (ARB) will also be reviewed, with a discussion on the impact they have on blood pressure, proteinuria, and the rate of progression of renal disease. An argument will be made for tighter control of blood pressure, preferably to systolic blood pressure (SBP) < 130 mm Hg. This lower blood pressure should be the goal regardless of whether or not drugs that block the RAS are used. Drugs that block the RAS, such as ACE inhibitors or ARB, are beneficial for renal function and should be routinely employed to control blood pressure and proteinuria in diabetic hypertensives. However, they should not be used in lieu of proper blood pressure control.

RENAL AUTOREGULATION: HOW LOW SHOULD YOU REDUCE SYSTEMIC BLOOD PRESSURE?

Glomerular capillary pressure is carefully regulated due to the unique vascular anatomy of the glomerulus. The glomerulus is arranged in series between two resistance vessels—the afferent and efferent arterioles. These arterioles respond to a variety of stimuli, allowing the independent regulation of glomerular capillary pressure. In general, an increase or decrease in systemic blood pressure causes directionally similar changes in glomerular capillary pressure. An increase in afferent vessel tone is associated with a reduction in glomerular capillary pressure. Conversely, glomerular capillary pressure may increase in response to elevation in efferent vessel tone. Healthy vessels will respond almost instantly to changes in systemic blood pressure so that glomerular capillary pressure remains relatively constant over a wide range of perfusion pressures.12 The ability of the glomerulus to regulate pressure may be impaired by renal disease or by different medications. As systemic blood pressure rises, the kidney increases afferent glomerular arteriolar tone so as to limit too much pressure from entering the glomerulus. However, at SBP ≥ 150 mm Hg, this protective mechanism may be limited and the resultant glomerular capillary hypertension may cause injury.13 In patients with diabetic renal disease, disease of the afferent arteriole may further impair its ability to limit systemic blood pressure from entering the glomerulus. In addition, increased efferent glomerular arteriolar tone is often present in diabetics, possibly due to the excessive vascular responsiveness to angiotensin II. This combination of events results in elevated glomerular capillary pressure.14 Consequently, a therapeutic strategy that reduces systemic blood pressure (Figure 1)15 and efferent glomerular arteriolar tone is ideal for limiting glomerular injury in diabetics.16

Angiotensin II is a powerful vasoconstrictor in the kidney. It vasoconstricts both the afferent and efferent glomerular arterioles. However, the efferent arterioles may be more sensitive than the afferent arterioles to the vasoconstrictive effects of angiotensin II. Therefore, drugs that block the RAS subsequently lower glomerular capillary pressure as they lower systemic blood pressure. In contradistinction, other drug classes that do not attenuate the RAS do not consistently lower glomerular capillary pressure in concert with reducing systemic blood pressure. Although the precise relation between systemic and glomerular capillary pressure cannot always be assumed to be exact, it is safe to say that the lower the systemic blood pressure, the greater the likelihood of lower glomerular capillary pressure. Drugs such as calcium channel blockers (CCB) or direct acting vasodilators preferentially dilate the afferent glomerular arterioles. Thus, if blood pressure is not reduced sufficiently, a paradoxical increase in glomerular capillary pressure could occur.

FIGURE 1. Cross-section of the glomerulus exposed to essential hypertension. As mean arterial pressure (MAP) rises, it induces preglomerular vasoconstriction with an increase in afferent glomerular arteriolar resistance (RA) and a resultant fall in renal plasma flow (RPF). There is no overall change in glomerular capillary pressure (Pgc) because of an increase in efferent glomerular resistance (RE) due to activation of the intrarenal renin angiotensin system. There is a decline in glomerular ultrafiltration coefficient (Kf). Reprinted with permission from Reference 15.
TABLE 1. BENEFITS OF RAS BLOCKADE FOR RENAL PROTECTION

<table>
<thead>
<tr>
<th>Hemodynamic effects</th>
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<td>Reduction in systemic blood pressure</td>
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<td>Reduction in glomerular capillary pressure</td>
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<td>? Reduction in proteinuria</td>
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<td>Nonhemodynamic effects</td>
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<td>? Stimulation of extracellular matrix degradation</td>
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<td>? Inhibition of macrophage/monocyte infiltration</td>
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These understandings about glomerular hemodynamics and renal autoregulation suggest more intensive and sustained control of blood pressure will control glomerular capillary pressure and reduce the likelihood of renal injury. In addition, drugs that block the RAS provide additional advantages in that they consistently reduce systemic and glomerular capillary pressures.

**BENEFITS OF RAS BLOCKADE**

Experimental and clinical studies have demonstrated the benefits of drugs that block the RAS on delaying progression of diabetic and nondiabetic renal disease. These results are summarized in Table 1.

The hemodynamic benefits of RAS blockade are more important than the nonhemodynamic benefits. Constant reduction of blood pressure has been demonstrated to be the most important benefit of ACE inhibitors in both experimental and clinical studies of progressive renal disease. Nonhemodynamic benefits such as the stimulation of extracellular matrix degradation or inhibition of macrophage/monocyte infiltration into glomerular vascular beds are beneficial but less important than intensive systemic and glomerular capillary pressure control.

The reduction of proteinuria is independent of changes in systemic blood pressure, perhaps due to the improvement of glomerular permselectivity of proteins. Reducing proteinuria is beneficial for the kidney because it reduces the phagocytic uptake of glycosylated proteins within the mesangial beds of the glomeruli and the renal tubules. Consequently, this reduces cytokine production and elaboration of soluble mediators of fibrosis and growth. It is likely that with more intensive control of blood pressure, the nonhemodynamic effects of RAS blockade become less important, whereas at higher levels of blood pressure these properties may be of greater magnitude. There is experimental data that supports the concept that RAS blockade drugs have beneficial effects on kidney structure independent of blood pressure. However, these benefits have not been proved in human clinical studies, as patients who derived renoprotective benefit from ACE inhibitors have almost always had lower systemic blood pressures.

**EXPERIMENTAL STUDIES: BENEFITS OF BLOOD PRESSURE REDUCTION**

The best experimental studies assessing the relationship between systemic blood pressure, glomerular injury, and the impact of antihypertensive therapy have employed radiotelemetric monitoring to accurately assess average systemic blood pressure. This technology offers consistent blood pressure measurement, as opposed to intermittent measurement with tail-cuff monitoring. Griffen et al discovered a strong correlation between systemic blood pressure and glomerular injury in rats with remnant kidneys. They found that the autoregulation of renal blood flow was impaired in rats with renal disease, and their glomerular capillary pressure varied directly with changes in systemic blood pressure. This has important implications when one evaluates the impact of antihypertensive therapy. Lowering blood pressure is always important. But how the drugs affect glomerular hemodynamics and the autoregulation of blood flow to the kidney is of considerable significance.

Drugs that block the RAS consistently reduced both systemic and glomerular capillary pressure. The magnitude of pressure reduction correlates directly with the development of glomerulosclerosis. Calcium channel blockers impair autoregulation because they preferentially dilate the afferent arteriole as they lower blood pressure. The slope of the relationship between blood pressure and renal injury is steep in experimental studies when using CCB, indicating that there is a marked dependency of blood pressure reduction in protecting against glomerulosclerosis. Regardless of the antihypertensive therapy employed in experimental studies, the likelihood of renal injury decreases with the reduction of blood pressure (Figure 2).

The experimental studies using the more sophisticated radiotelemetric blood pressure monitoring discussed previously reveal the important relationship between blood pressure reduction and attenuation of renal injury regardless of therapy. These observations are in contrast to studies using the tail-cuff method for measuring blood pressure, which have demonstrated that drugs that block the RAS are more renoprotective. However, this inconsistency in data between the tail-cuff method and the radiotelemetric methods may be related to the inherent variability of the intermittent tail-cuff measurement and its inaccuracy in evaluating hypertensive vascular load in the kidney. However, the studies using both tail-cuff and radiotelemetric methods of measuring blood pressure consistently show that lowering blood pressure retards diabetic and nondiabetic glomerulosclerosis.
sure, particularly SBP. Findings from the Multiple
Epidemiologic evidence strongly supports the concept
studies have consistently demonstrated the benefits of
In a large metaanalysis of clinical trials, Kasiske et
In patients with type 1 diabetes, two clinical trials have helped us learn more about the
importance of blood pressure control on the progression of renal disease. Viberti et al27 studied 92 patients
with type 1 and type 2 diabetes and persistent microalbuminuria without hypertension (mean blood
pressure was 124/77 mm Hg). Patients were randomized to receive either the ACE inhibitor captopril or a
placebo. After a 2-year follow-up, the mean blood pressure in the captopril group was 122/74 mm Hg
compared with 126/76 mm Hg in the placebo group. This 4/2 mm Hg difference was statistically significant
(P < .05) and was associated with the prevention of urinary albumin excretion and progression to clinical
proteinuria (Figure 3). This indicates that treatment of normotensive microalbuminuric diabetics can be ben-
eficial in delaying the likelihood of overt nephropathy. However, it does not answer the question whether it
was a specific benefit of the ACE inhibitor or blood pressure reduction.

The other important clinical trial of hypertensive type 1 diabetes subjects was conducted by the Collaborative Study Group.4 In this study, 409 patients with rates of urinary protein excretion > 500 mg/day and serum creatinine < 2.5 mg/dL were randomized to receive either an ACE inhibitor or other medication (not an ACE inhibitor, ARB, or CCB) to reduce blood pressure to < 140/90 mm Hg. The results of the study found that the patients receiving the ACE inhibitor

CLINICAL STUDIES

Epidemiologic evidence strongly supports the concept that the risk of developing progressive nephropathy
increases proportionately with systemic blood pressure, particularly SBP.24 Findings from the Multiple
Risk Factor Intervention Trial (MRFIT) established the association of high SBP and the increased risk of de-
veloping renal injury. This association suggests that it may be necessary to reduce blood pressure to levels
even lower than the traditional target of 140/90 mm Hg to protect kidney function.24,25

Clinical trials assessing the rate of progression of renal disease have always focused on the mean arte-
rarial pressure (MAP), which is defined as the diastolic blood pressure (DBP) plus one-third of the difference
between the SBP and DBP. Unfortunately, this means that the MAP is heavily weighted on DBP and may
not reflect absolute risk. For example, using the traditional MAP of 92 mm Hg as the goal blood pressure
for patients in renal disease clinical trials, patients with blood pressures of 125/75 or 156/60 mm Hg
would have the same MAP, yet have a dramatic dif-
ference in SBP and pulse pressure. The latter group
might be more likely to develop renal disease, thus confounding our assessment of the impact of treated MAP on the rate of progression of renal disease.

Despite the lack of a precise risk equation using DBP, SBP, or pulse pressure measurements, clinical
studies have consistently demonstrated the benefits of reducing blood pressure (either the SBP or DBP) to
delay progression of renal disease, particularly in pa-
tients with diabetes and evidence of nephropathy.3,4,11,18 The first clinical trials demonstrating these
benefits are more than 20 years old. These early stud-
ies demonstrated that regardless of the class of antihypertensive therapy, tight blood pressure control
was associated with a reduction in the progression of renal disease. However, many of these studies dem-
onstrated that ACE inhibitors consistently reduced both systemic blood pressure and proteinuria in hy-
pertensive diabetics, which resulted in delayed renal disease progression.3 As we will discuss, the problem
with many of these clinical trials comparing ACE inhibitors with other therapies is that blood pressure reduction is more consistent in the ACE inhibitor-
treated groups than in the control groups. This con-
founds the analysis, as it cannot be determined whether the benefit is related to blood pressure reduc-
tion or an independent factor.

FIGURE 2. Correlation of glomerular injury score and overall averaged systolic blood pressure as determined with radioteleme-
tric monitoring in rats with partial nephrectomy. Rats received either no treatment (open squares), enalapril (closed squares),
triple therapy (open triangles), or high-dose triple therapy (closed triangles) (r = 0.84). Reprinted with permission from Reference 20.
had a slower decline in renal function and displayed a 50% reduction in the risk of death, dialysis, and transplantation. However, the MAP during all follow-up visits was 96 mm Hg in the ACE inhibitor group and 100 mm Hg in the placebo group (P < .05).

The decrease in blood pressure in patients with pre-existing hypertension (defined as > 140/90 mm Hg) was 2 mm Hg greater in the captopril group than in the placebo group (P < .16). The decrease in blood pressure in patients without hypertension was 5 mm Hg greater in the captopril group compared to the placebo group (P < .001). Despite the dramatic differences in outcome between the ACE inhibitor group and the placebo group, the question remains whether the benefit is due to reduced blood pressure as opposed to an independent factor.

Clinical trials involving patients with type 2 diabetes have yielded similar results as studies of patients with type 1 diabetes. Ravid et al evaluated the impact of an ACE inhibitor versus placebo therapy in 156 patients with type 2 diabetes and a MAP > 107 mm Hg (140/90 mm Hg) and urine albumin excretion rates ≥ 30 mg/24 h. Subjects received either placebo or 10 mg a day of enalapril, and were followed for 5 years. At the end of the study, there was a consistent decline in renal function associated with the reduction in albuminuria from the ACE inhibitor therapy (Figure 4). However, MAP increased from 96.1 to 102 mm Hg in patients receiving the placebo, whereas it only increased from 98.2 to 100 mm Hg in patients receiving the ACE inhibitor. This study illustrates the importance of treating “normotensive” normoalbuminuric patients to delay the risk for developing progressive albuminuria. The United Kingdom Prospective Diabetes Study (UKPDS) comprised 1148 patients with type 2 diabetes and hypertension. Participants were randomized to one of two levels of blood pressure reduction groups: less tightly controlled (< 180/105 mm Hg) or more tightly controlled (< 150/85 mm Hg). Subjects were administered either captopril or a β-blocker as the primary therapy and mean follow-up was 8.4 years. The patients in the tightly controlled blood pressure group achieved a mean blood pressure of 144/82 mm Hg, which was 10/5 mm Hg lower than subjects in the less tightly controlled group. This group demonstrated a dramatic reduction in the risk of both macro- and microvascular events (Figure 5). However, between the captopril and atenolol groups, there was no difference in the number of patients progressing to proteinuria or doubling serum creatinine (Table 2). Most of the patients in this clinical trial were titrated taking multiple medications, which may explain the lack of difference between the two primary therapies on the rate of progression of renal disease. Additionally, it has been argued that the short-acting ACE inhibitor captopril was ineffectively
administered as it was only dosed 25 to 50 mg twice a day. Despite these arguments, it is important to note that lower blood pressure remains the critical factor in delaying renal disease progression.

Increasing dietary salt offsets both the antihypertensive and antiproteinuric effects of most antihypertensive drugs, especially ACE inhibitors.\textsuperscript{30,31} This effect may be disastrous for the diabetic hypertensive as reducing blood pressure and proteinuria has clearly been shown to delay progression of renal disease. Consequently, there should be a concerted effort to evaluate dietary salt consumption in diabetic hypertensives and develop clinical strategies to modify salt intake.

\textbf{ACE INHIBITORS VERSUS ARB: EFFECTS ON BLOOD PRESSURE AND PROTEINURIA}

Angiotensin-converting enzyme inhibitors and ARB are pharmacokinetically different (Figures 6,7).\textsuperscript{32,33} An ACE inhibitor inhibits the conversion of angiotensin I to angiotensin II and interferes with the degradation of bradykinin. It is unknown which of these effects is the most important in lowering both systemic blood pressure and glomerular capillary pressure. Clinical studies have demonstrated that although plasma angiotensin II levels return to baseline with chronic ACE inhibitor therapy, blood pressure remains reduced.\textsuperscript{34} This finding raises two interesting questions: why does plasma blood pressure remain reduced, and where is the angiotensin II being formed if not in the plasma? The former question on the mechanism of

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 & Captopril & Atenolol & \textbf{P} \\
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Proportion of patients progressing to a urinary albumin concentration  $\geq$ 50 mg/L & 31\% (48/153) & 26\% (38/146) & .31 \\
Proportion of patients progressing to a clinical proteinuria $> 300$ mg/L & 5\% (7/153) & 10\% (14/146) & .09 \\
\hline
\end{tabular}
\caption{UNITED KINGDOM PROSPECTIVE DIABETES STUDY RENAL DISEASE RESULTS (9 YEARS)\textsuperscript{*}}
\end{table}

* There was no difference in serum creatinine or in the proportion of patients who had a twofold increase in creatinine over a 9-year period.
blood pressure reduction may be related to the ACE inhibitor-induced increase in bradykinin and subsequent stimulation of prostaglandins and nitric oxide. The latter question is more difficult to answer, but may reflect ongoing angiotensin II synthesis within vascular beds, which is unaffected by the ACE inhibitor.

Angiotensin type 1 receptor blockers have no effect on angiotensin II synthesis whether via the ACE or other known enzymatic pathways that exist in vascular beds. These compounds block the angiotensin type 1 binding site in vascular tissue, which is responsible for the vasoconstrictive, growth-promoting, and salt-retentive actions of angiotensin II. In fact, the only similarity between the mechanisms of action of ACE inhibitors and ARB is that they both increase renin activity. This effect reflects a dampening of the activity of the RAS or a reduction of systemic blood pressure. Both drug classes are similarly capable of reducing blood pressure and proteinuria in human subjects.

There are some differences in renal blood flow responses that are evident with both low- and high-salt diets (Figure 8). Angiotensin type 1 receptor blockers have a more robust ability to maintain renal blood flow in the presence of a high-salt diet compared with ACE inhibitors, which may prove to be important in controlling blood pressure, particularly in the low-renin hypertensive. The greater renal blood flow responses with the ARB compared with ACE inhibitors may reflect the renal vascular contribution of angiotensin II production, which may be an important part of the biology of the intrarenal RAS.

There are two large international clinical trials assessing the ability of ARB to delay the progression of renal disease in hypertensive diabetics. One study compares losartan and a traditional non–ACE inhibitor/non–CCB therapy, whereas the other study compares irbesartan, amlodipine, and placebo as the primary antihypertensive therapy. In both clinical trials, additional medications can be added to facilitate reduction of SBP to < 140 mm Hg and < 135 mm Hg, respectively. The latter study will provide an interesting comparison between the mechanistic effects of an ARB (which dilates an efferent glomerular arteriole like an ACE inhibitor) and a CCB (which dilates an afferent glomerular arteriole) on blood pressure, proteinuria, and renal disease progression. An interim analysis of this data does show divergent responses of these two different drug classes on proteinuria. Despite almost identical reductions in blood pressure, the ARB reduced proteinuria whereas the CCB increased it. However, the long-term effects of these primary therapies (taking the additional medications and the ultimate achievement of goal blood pressure into consideration) will soon show whether or not ARB manifest unique kidney function protective properties as opposed to traditional therapies (diuretics, β-blockers, vasodilators) or CCB (amlodipine). Hopefully, these studies will provide some important answers as to whether drugs that block the RAS have unique properties that protect kidney function even at lower levels of blood pressure, unlike other antihypertensive drug classes.

It is unlikely that there will be clinical trials comparing the effects of ACE inhibitors and ARB on the rate of renal disease progression, as both have been seen to protect kidney function in experimental studies, as well as lower blood pressure and proteinuria in human clinical trials. Of interest is a recent clinical trial that suggested these two drug classes might have additional beneficial antiproteinuric effects in human subjects with glomerulonephritis and macroproteinuria. In a clinical trial of a dozen normotensive patients with IgA nephropathy, an ARB was added to an ACE inhibitor. This study is of interest for two reasons: it demonstrates that the drugs may reduce proteinuria independent of blood pressure reduction, and that their mechanisms of action are sufficiently dissimilar that they are complementary in their effects in reducing proteinuria. These observations obviously have substantial clinical importance with regard to strategies for reducing both blood pressure and proteinuria in human diabetic subjects.
CONCLUSIONS

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provides an important consensus opinion that blood pressure in diabetic hypertensives—particularly those with proteinuria—should be reduced to < 130/85 mm Hg, with optimal blood pressure < 120/80 mm Hg.\(^{39}\) This recommendation results from both experimental and human studies of diabetic renal disease, which have shown that reducing blood pressure may delay progression of renal disease. Lower blood pressure, regardless of the choice of drug, will help to preserve renal function. As discussed, even treating diabetics with normo- or microalbuminuria with a blood pressure of 120/70 mm Hg will delay the development of nephropathy.\(^{27}\) There is no evidence in clinical studies, even in patients with substantially compromised renal function, that more intensive control of blood pressure will result in adverse cardiovascular sequelae.\(^{40}\) Thus, there is no J-curve for health care professionals to be concerned about.

Drugs that block the RAS remain the drugs of choice to protect against progressive renal injury largely because of their ability to consistently reduce both systemic and glomerular capillary pressure.\(^{3,18}\) Consequently, they are also more able to consistently reduce proteinuria. Whether drugs that block the RAS have unique blood pressure effects is largely speculative; evidence from clinical trials has demonstrated that they consistently reduce blood pressure in nondiabetic nephropathy.\(^{19}\) A large metaanalysis of diabetic patients revealed lower blood pressure to be the most significant variable in slowing the rate of progression of renal disease.\(^{3}\) Angiotensin type 1 receptor blockers will likely be found to possess similar renal protective effects as ACE inhibitors. This is due to their ability to reduce both systemic blood pressure and proteinuria in human subjects as well as retard histologic evidence of glomerulosclerosis in experimental models.\(^{41}\) Although mechanistically different, these drugs provide similar overall clinical effects and are perhaps best used in combination to take full advantage of their unique antihypertensive and antiproteinuric effects.

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