# Renal Effects of Angiotensin-Converting Enzyme Inhibitors That Result in Cost Savings and Improved Patient Outcomes

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**Background:** In some patients with renal disease, use of angiotensin-converting enzyme (ACE) inhibitors is thought to improve renal function, whereas in others their use leads to worsening. Many questions remain about the categories of patients that benefit from ACE inhibitor use.

**Objective:** To clarify the use of ACE inhibitors in patients with renal disease.

**Study Design:** A literature review focusing on various renal diseases, ACE inhibitors, and criteria of cost effectiveness was performed.

**Results:** Almost 100 clinical studies were reviewed. Treatment with ACE inhibitors seems to have beneficial effects in type 1 and type 2 diabetes mellitus with nephropathy, AIDS nephropathy, and other nondiabetic renal diseases. Use of these agents in these diseases decreases the progression of renal disease and the need for dialysis, resulting in potential cost savings and improved quality of life. Data supporting goal blood pressures indicate the need to aggressively decrease this risk factor. Use of ACE inhibitors is hazardous in bilateral renal artery stenosis, particularly with volume depletion, but may be valuable in patients with unilateral stenosis. In African Americans, ACE inhibitor treatment is likely to be of benefit, although required doses may be higher than for whites, and caution must be exercised in certain situations. The potential efficacy of angiotensin receptor blockers and other new drugs that affect the renin-angiotensin system is assessed.

**Conclusions:** Use of ACE inhibitors has benefit in renal disease states characterized by increased glomerular perfusion pressure; their use in other renal disease states, particularly those characterized by reduced glomerular perfusion pressure, may be risky. The benefits conferred by ACE inhibitor therapy are so dramatic in terms of cost savings and improved quality of life that their use in certain clinical situations should be strongly encouraged in managed care and other practice settings.

***(Am J Manag Care 2001;7:283-295)***

Since their introduction in the early 1980s, angiotensin-converting enzyme (ACE) inhibitors have attained widespread use in the treatment of congestive heart failure, hypertension, diabetic nephropathy, and other less common renal and hemodynamic conditions.[1] Although use of these agents has been widespread, there seems to be uncertainty concerning their use in varying clinical situations.[1-3] For example, although ACE inhibitor treatment is beneficial for most patients with congestive heart failure,[1] recently published data[2,4] suggest that use of these agents is less than expected. Although this may reflect the 5% to 10% of patients who are intolerant of ACE inhibitors, primarily because of intractable cough, this underuse may also reflect provider uncertainty. A major area of uncertainty is the use of ACE inhibitors in patients with renal disease: in some patients with renal disease, these agents are thought to improve renal function, whereas in others their use leads to worsening. We review pertinent clinical studies in humans to clear-

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This study was supported in part through the Research Service, Department of Veterans Affairs, Northern California Health Care System, Martinez, CA.

The views expressed in the article do not necessarily represent the views of the Department of Veterans Affairs or of the US government.

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ly describe patients with renal disease in whom use of ACE inhibitors improves renal function, those in whom their use leads to deterioration, and areas of remaining uncertainty.

## ··· METHODS ···

Computerized MEDLINE searches for articles published between January 1, 1985, and July 31, 1999, were performed. Only clinical trials published in English were selected, using the following keywords: angiotensin-converting enzyme inhibitor, angiotensin-converting enzyme inhibition, chronic renal failure, renal disease, diabetes mellitus, angiotensin cost benefit, angiotensin II blocker, and renal artery stenosis. To focus on areas of uncertainty, we excluded articles referring to hypertension and congestive heart failure. Other relevant citations were extracted from the obtained articles. We focused on peer-reviewed clinical trials; review articles were used primarily for clarification of current guidelines and as potential sources of relevant references. Basic science (animal) articles were referred to only occasionally and only for historical perspective.

## ··· OVERVIEW ···

Angiotensin-converting enzyme inhibitors are a class of medications that have been in use in the United States since the introduction of captopril in 1981. Although preparations differ in details of structure and pharmacokinetics, these agents share a mechanistic similarity in that they interfere with the enzymatic conversion of angiotensin I to angiotensin II, leading to reduced production of this potent vasoconstrictor. In addition, since ACE is identical to kinase II, inhibiting this enzyme leads to an accumulation of the vasodilator bradykinin. As a result of these activities, ACE inhibitor use leads to vasodilation, systemically and within the kidney.[6] Other endopeptidases, such as neutral endopeptidase, are not significantly affected by ACE inhibitors.[7] Neutral endopeptidase is widely expressed in the kidneys, lungs, and vascular wall[8] and primarily degrades a variety of natriuretic peptides, specifically atrial, brain, and endothelial natriuretic peptides. Omapatrilat, a novel peptidase inhibitor, simultaneously inhibits neutral endopeptidase and ACE.[7]

One of the hemodynamic effects of ACE inhibitors that distinguishes them from other antihypertensives is renal: ACE inhibitors have a potent effect on reducing glomerular capillary pressure that other agents with a similar effect on systemic blood pressure lack. This reduction of glomerular pressure with use of ACE inhibitors is a consequence of vasodilation of efferent and afferent renal vessels. The primary effect is on efferent pressures; the reduction in efferent pressure reduces intraglomerular capillary pressure and glomerular filtration rate (GFR). Although there is vasodilation of afferent vessels, the resulting increase in glomerular flow does not lead to glomerular hypertension because of the predominant efferent arteriolar effect. By decreasing angiotensin II levels, ACE inhibitors also reduce preload (fluid volume filling the heart resulting from increased intravascular fluid volume or volume redistribution[9]), which is also different from some other antihypertensives. Angiotensin receptor blockers (ARBs) have hemodynamic effects comparable to those of ACE inhibitors.

It is important to distinguish between acute effects of ACE inhibitor use, caused by an immediate decrease in GFR resulting from a drop in blood pressure, and long-term outcomes, reflecting chronic renal effects. With long-term use, GFR may actually increase because of an increase in cardiac output resulting from systemic vasodilation and a subsequent increase in glomerular blood flow. Understanding these hemodynamic effects of ACE inhibitor therapy is crucial to predicting clinical utility and response. In some forms of renal disease, elevation of glomerular pressure leads to hyperfiltration and to progressive renal dysfunction.[10-12] As will be shown, in conditions such as diabetic nephropathy, AIDS nephropathy, and others, reduction of glomerular pressure has therapeutic benefit. In other types of renal disease, such as bilateral renal artery stenosis, glomerular pressure is necessary to maintain renal function, and its reduction may lead to a worsening of renal function.

### Diabetic Nephropathy

Diabetic nephropathy is the leading cause of adult end-stage renal disease in the United States[13] and is responsible for an enormous burden of healthcare costs, including dialysis, transplantation, premature death, and unemployment. Once undergoing dialysis, mortality rates among diabetics (~30% per year) exceed those of colon cancer. The cost of caring for patients with diabetic end-stage renal failure in the United States approached $2 billion in 1991.[14] For more than 2 decades, the role of hypertension in promoting and maintaining diabet-

ic nephropathy has been well described.[15] We have described the effect of blood pressure on albumin excretion, a marker of nephropathy, in normotensive diabetics.[16] Although the focus of this article is directed to the impact of blood pressure control and, in particular, the role of ACE inhibitor therapy on the progression of diabetic nephropathy, glycemic control, as outlined in the Diabetes Control and Complications Trial,[17] and other factors[13] also have an important impact on the progression of diabetic nephropathy.

The course of diabetic nephropathy is better defined for type 1 than for type 2 diabetes mellitus, but the precise mechanisms leading to renal failure are unknown. Microalbuminuria (<300 mg/d, a level at which urine protein dipstick test results are negative) is a hallmark of early diabetic kidney disease. In addition to monitoring albumin or protein excretion rates, creatinine-based measurements (eg, serum creatinine or creatinine clearance), despite drawbacks (eg, impact of tubular secretion, dietary meat content, and inaccuracies of timed collections), are widely used as markers of renal function. Early in the course of diabetic nephropathy, perhaps reflective of hyperglycemia, there is nephromegaly and hyperfiltration, with an increased GFR for both type 1 and type 2 diabetics. As kidney disease progresses, glomerulosclerosis occurs, as does overt proteinuria and decline in renal function. During this time of disease progression, GFR declines and may decrease to the reference range from its previously elevated state. About 5 years after onset of clinical nephropathy (>300 mg albumin excreted per day, or dipstick-positive urine), most patients with type 1 diabetes mellitus progress to dialysis.[18]

**Type 1 Diabetes Mellitus and ACE Inhibitors**

Most treatment studies of diabetic nephropathy are in patients with type 1 disease. In 1976, in the pre-ACE inhibitor era, Mogensen[19] described the benefit of blood pressure control on reducing the rate of renal function decline.[20,21] Subsequent works[22,23] clarified how diabetic nephropathy resulted from glomerular damage and the contributory role of glomerular hemodynamic effects; animal studies[24,25] emphasized the potential impact of ACE inhibitor therapy. These early findings were recently confirmed by Yip and colleagues,[26] who, in a 10-year study, reported that although levels of albumin excretion and systemic blood pressure were the main risk factors for renal decline, glomerular hyperfiltration (reflected in part by intraglomerular pressure) also played an important role.

Because of the growing appreciation for the role of intraglomerular pressure in diabetic nephropathy, ACE inhibitor therapy may be of particular benefit.[12] Bain and colleagues,[27] in a clinical trial designed to evaluate captopril therapy in nephropathic type 1 diabetics, randomized more than 400 patients, 59% of whom were hypertensive, to active drug or placebo treatment. At entry, there was an association between reduced GFR and hypertension, proteinuria, and hypercholesterolemia but not to duration of diabetes, percentage of life as a diabetic patient, or degree of glycemic control.[27] These workers[28] subsequently reported the beneficial impact of captopril therapy. More recently, studies[29,30] in adults have shown that use of captopril results in less progression of microalbuminuria to overt proteinuria, reduction of albumin excretion, and preservation of creatinine clearance. In a study[31] of normotensive children with type 1 diabetes mellitus and microalbuminuria, captopril therapy lowered blood pressure, reduced albumin excretion rates, and maintained GFR.

Results of other studies[32,33] confirm that treatment of hypertensive type 1 diabetic patients is cost effective; captopril treatment of patients with type 1 diabetes and nephropathy has resulted in about a 50% reduction in the risk of both progressive renal insufficiency and the combined endpoint of death, dialysis, and transplantation.[28] Results of a cost-benefit analysis[34] suggested that captopril therapy had a profound and significant impact on dialysis-years avoided (20.01 dialysis-years avoided per 100 patients treated, or 2.4 months per patient), with a concomitant savings in healthcare expenditures, about a 30% reduction in cost. This economic perspective has been extended by Kiberd and Jindal,[35] who used a Markov model to propose that routine treatment of patients with type 1 diabetes mellitus with ACE inhibitors without urinary screening could have significant cost benefit, particularly if high-risk individuals could be identified.

In summary, current evidence strongly suggests a beneficial role for ACE inhibitor therapy in type 1 diabetes mellitus with microalbuminuria or clinical albuminuria, regardless of blood pressure. This evidence is the basis of current American Diabetes Association (ADA) guidelines.[13]

**Type 2 Diabetes Mellitus and ACE Inhibitors**

Although the natural history of patients with type 2 diabetes mellitus with overt nephropathy is incompletely understood, available data[36-40] suggest that it is similar to that of patients with type 1 disease. Gall et al[41] reported that 20% of albuminuric type 2 dia-

betics developed end-stage renal failure during 5 years of observation despite aggressive attempts at blood pressure control. In the United States, type 2 diabetics are older than those with type 1 disease at the onset of nephropathy[42] and are at higher risk of developing other or superimposed renal diseases.[13] Urinalysis results demonstrating any abnormality other than proteinuria (eg, pyuria, hematuria, or casts) suggest concurrent nondiabetic renal disease and warrant further evaluation.

There is substantial evidence supporting a beneficial effect of ACE inhibitor therapy in type 2 diabetics with hypertension. This should be expected because many patients with type 2 disease also have hypertension and are frequently diagnosed as having diabetes only after several years of mild, undetected disease. Studies have reported that recently diagnosed type 2 diabetics frequently have significant alterations in renal hemodynamic values, including increased GFR and effective renal plasma flow, with reduced renovascular resistance[43,44]; a significant proportion (~15%) of newly diagnosed type 2 diabetics have microalbuminuria at the time of diagnosis.[44] Others[45] have reported glomerular hyperfiltration in microalbuminuric type 2 diabetics compared with normoalbuminuric patients. Bauer et al[46] reported that nephropathic type 1 and type 2 diabetics with controlled blood pressures demonstrated decreased urinary protein excretion with enalapril treatment for 18 months. These beneficial effects could be anticipated because there are no striking differences in nephropathological changes between type 1 and type 2 diabetics.[13] It has been suggested[47] that increased ACE localization in glomeruli may be a factor in increased renin-angiotensin system activity in glomeruli in patients with type 2 diabetic nephropathy.

Although, to our knowledge, ACE localization has not been addressed specifically in type 1 diabetics, Metzger et al[48] reported that endothelial cells from diseased kidneys expressed ACE, whereas ACE is usually absent in endothelial cells from normal kidneys. This ACE "neoexpression" may be selective for glomerular endothelial cells in diabetes mellitus.[48] Curiously, the activity of the renin-angiotensin system (RAS) in the circulation is low in diabetic patients. The beneficial impact of ACE inhibitor therapy may be mediated by interfering with the hemodynamic[49] and direct glomerular[50] effects of angiotensin II and may be caused by activity of tissue, as opposed to circulating, ACE.[45] Angiotensin-converting enzyme gene polymorphism may play a role here as well.[47]

The effects of ACE inhibitor therapy in normotensive type 2 diabetics with nephropathy have also been studied. Ravid and colleagues[51] described their 5-year follow-up of normotensive type 2 diabetic patients with microalbuminuria (30-300 mg/d) randomized to either enalapril or placebo treatment. In the enalapril group, albumin excretion and creatinine level remained stable, whereas in those treated with placebo, both albuminuria and creatinine level increased. Glycosylated hemoglobin level and body mass index remained unchanged.[51] A 7-year follow-up study[52] found that benefits continue. Similar findings in other studies[53-55] of healthy or mildly hypertensive patients have been reported with use of enalapril, captopril, or ramipril. In a recent meta-analysis, Kasiske and colleagues[56] evaluated 100 studies of more than 2400 patients and found that ACE inhibitor therapy decreased proteinuria independent of changes in blood pressure, treatment duration, type of diabetes, stage of nephropathy, or study design. Reductions in proteinuria obtained by using agents other than ACE inhibitors could be explained entirely by changes in blood pressure.[56]

In hypertensive type 2 diabetics without proteinuria, it is important to lower blood pressure using any antihypertensive agent.[57] Again, although use of ACE inhibitors may be particularly beneficial based on their hemodynamic effect, other antihypertensives may need to be added to correct blood pressure.

The hemodynamic effects of ACE inhibitors may yield benefits even in normotensive type 2 diabetic individuals: enalapril therapy will attenuate the expected decline in renal function in normotensive normoalbuminuric type 2 diabetics.[58]

As for type 1 diabetes mellitus, a cost-benefit analysis has been done for type 2 diabetes mellitus. Rodby and colleagues[59] calculated, based primarily on data from type 2 diabetes mellitus, that the use of captopril in either type 1 or type 2 diabetic nephropathy will provide substantial savings. The cumulative healthcare cost savings for 1995 through 2004, if captopril therapy were started in 1995 for diabetics with nephropathy, would total $2.4 billion.[59] Kiberd and Jindal[60] used a medical decision analysis model to suggest that routine treatment of Pima Indians—a group at high risk for type 2 diabetes mellitus—with ACE inhibitors would be cost effective compared with the current practice of screening followed by treatment. Golan and colleagues,[61] using modeling techniques simulating the progression of diabetic nephropathy, suggested that

treating all middle-aged type 2 diabetics with ACE inhibitors is cost effective compared with screening. A major challenge in clinical practice is to document the presence and extent of diabetic nephropathy; we[62] reported that diabetics are inadequately screened (only about 25% of a clinic population of almost 3000 diabetics had a quantitative measurement of urinary albumin or protein; of those screening positive with microalbuminuria, only one third received ACE inhibitors). This inadequate screening rate persisted despite repeated educational interventions so that although the clinic diabetic population grew to almost 5000, the percentage screened remained at 25% and the fraction of screened individuals receiving ACE inhibitors remained at one third.[63]

**Blood Pressure Control and Diabetes**

Recent recommendations clarify goal blood pressure for diabetics. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (JNC VI) clarifies the distinction between normotension and the different degrees of hypertension and recommends a goal blood pressure of <130/85 mm Hg for diabetics.[3] The ADA also currently recommends a goal blood pressure of <130/85 mm Hg for nonpregnant diabetic adults. For individuals with isolated systolic hypertension, the ADA goal systolic blood pressure is 160 mm Hg for those with pressures >180 mm Hg or a reduction of 20 mm Hg for those whose systolic blood pressure is 160 to 179 mm Hg.[13,57,64] These recommendations vary from those of the JNC VI, in which the goal systolic blood pressure is <140 mm Hg. In addition, the ADA currently recommends ACE inhibitor therapy for all hypertensive diabetics—type 1 and type 2—with microalbuminuria or clinical albuminuria, normotensive type 1 diabetics with microalbuminuria, and probably normotensive type 2 diabetics with microalbuminuria (**Table**[13]). In addition to recommendations of the ADA, similar guidelines and cautions regarding ACE inhibitors have been proposed by the National Kidney Foundation.[65]

Several lines of evidence support these recommendations for type 2 diabetics. The Appropriate Blood Pressure Control in Diabetes trial[66-69] evaluated 950 type 2 diabetic patients, of whom 470 were hypertensive, and compared the effects of moderate (goal diastolic blood pressure, 80-89 mm Hg) vs intensive (goal diastolic blood pressure, 75 mm Hg) control of blood pressure on the incidence and progression of diabetic complications. The results of this trial suggest that ACE inhibitors should be the initial antihypertensive agent used in type 2 diabetes and hypertension, in large part because of the beneficial renal and systemic hemodynamic effects of ACE inhibitors and in lesser part because of an increased incidence of coronary events in patients treated with long-acting calcium channel blockers compared with ACE inhibitors. Blood pressure, blood glucose, and lipid values were comparable between the 2 treatment arms.[68] Although beyond the scope of this article, other data[70] suggest that the combination of ACE inhibitor therapy and calcium channel blockade may offer the greatest reduction in cardiovascular event rate.

Similarly, the United Kingdom Prospective Diabetes Study,[71] which began in 1977, evaluated 1148 hypertensive patients with type 2 diabetes mellitus, of whom 758 were allocated to tight control and 390 were assigned to less tight control of blood pressure. Those assigned to tight blood pressure control, who achieved a blood pressure of 144/82 mm Hg, demonstrated lessened risk of death and complications compared with the less tightly controlled group, whose blood pressure averaged 154/87 mm Hg[72]; blood pressure management compared captopril against atenolol in both groups. Lowering of blood pressure, with either captopril or atenolol therapy, was similarly effective in reducing the incidence rate of diabetic complications (macrovascular endpoints, retinopathy grade, and prevalence of clinical albuminuria[73]), suggesting that in this population, blood pressure reduction may be more important than the drug used. Although beyond the focus of this article, it should be pointed out that β-adrenergic blocking agents also reduce renin activity and circulating angiotensin II concentrations,[74] which may explain some of the benefit obtained in this study. Tight blood pressure control was shown to be cost effective as well, calculated from use of healthcare resources in either treatment group, time free from diabetes-related endpoints, and life-years gained.[75]

The impact of varying degrees of blood pressure control in the treatment of type 1 diabetic patients with nephropathy will be addressed in a 2-year, randomized, prospective, collaborative clinical trial. Patients will receive the ACE inhibitor ramipril as primary therapy and will then be randomized to 1 of 2 groups: an intensive group (goal mean arterial pressure, <92 mm Hg) or a moderate group (goal mean arterial pressure, 100-107 mm Hg). In addition to titration of ramipril, patients will have other antihypertensives added or withdrawn to achieve goal blood pressure.[76]

The Hypertension Optimal Treatment trial[77] demonstrated that in patients with diabetes mellitus (type 1 or 2 not specified), there was a 51% reduction in major cardiovascular events in the group whose goal diastolic blood pressure was ≤80 mm Hg compared with the group whose goal diastolic blood pressure was ≤90 mm Hg. Patients with diabetes represented ~8% of the study population and were equally allocated to all treatment groups. Although only 8% of the study patients were diabetic, there were almost 19,000 patients randomized. Thus, there were roughly 500 diabetic hypertensive patients in each of the 3 diastolic blood pressure target groups: ≤90, ≤85, and ≤80 mm Hg. This study used felodipine as baseline therapy, to which ACE inhibitors, β-adrenergic blocking agents, and diuretics were added. The proportion of patients using each of these drug classes increased with more aggressive goal blood pressure management, suggesting the need for complex multidrug regimens to achieve goal blood pressure.[77] It is not clear if comparable results would have been obtained with an ACE inhibitor-based treatment regimen. In addition, the ongoing Diabetes in Hypertrophie Cardiaque et Ramipril (DIABHYCAR) study[78] in Europe will also shed light on the effect of blood pressure management on the progression of diabetic nephropathy. Diabetes management can be considered a paradigm for the benefit of preventive medicine.[79]

This attention to cost-effective diabetes management is significant for 2 reasons: because of the clinical volume and overall economic burden of diabetes management and because there is significant room for improvement. Peters et al[80] reviewed data on patients served by a California health maintenance organization and assessed the quality of diabetes care provided by comparing the data with ADA guidelines. Disappointingly, 52% of diabetic patients had no urine protein measurements during the year of follow-up; other markers of diabetes management were similarly inadequate.[80] Qualitatively similar findings were reported by the Centers for Disease Control and Prevention[81] based on a nationwide survey, using Health Plan Employer Data and Information Set data, and by Noth et al.[62,63]

In summary, there is considerable evidence that suggests that ACE inhibitors have an important role in the management of diabetic kidney disease for type 1 and type 2 diabetics whether or not there is associated hypertension. Use of ACE

**Table.** Recommended Uses for ACE Inhibitors

| Disease States | ACE Inhibitors Recommended? | References |
|---|---|---|
| Type 1 diabetes mellitus + HTN + MA | Yes | 13, 29, 32, 33 |
| Type 1 diabetes mellitus + HTN + CA | Yes | 13, 28 |
| Type 1 diabetes mellitus + NTN + MA | Yes | 13, 31 |
| Type 2 diabetes mellitus + HTN + MA | Yes | 13, 56-58 |
| Type 2 diabetes mellitus + HTN + CA | Yes | 13, 36-40 |
| Type 2 diabetes mellitus + NTN + MA | Probably | 13, 51 |
| Renal artery stenosis, bilateral or unilateral, with solitary kidney | No | 88 |
| Renal artery stenosis, unilateral, with functioning contralateral kidney | Yes | 88 |
| Nondiabetic chronic renal disease | Yes | 1, 91-98 |
| Renal transplant | Yes | 104-107 |
| AIDS nephropathy | Yes | 110, 111 |
| African American, nondiabetic, with HTN and renal disease | Yes, with caution regarding reduced GFR, possible increased dose requirements, and angioedema | 113-116 |

ACE = angiotensin-converting enzyme; CA = clinical albuminuria; GFR = glomerular filtration rate; HTN = hypertension; MA = microalbuminuria; NTN = normotension.

inhibitors prevents progression to overt nephropathy, is effective even in low levels of blood pressure reduction, and neither masks hypoglycemia nor alters the serum lipid profile.[82] Current evidence also indicates that there is considerable room for improvement in identifying and treating diabetics to retard the progression of renal disease.

Angiotensin-converting enzyme inhibitors must be used cautiously in certain diabetics. Their use may increase serum creatinine levels, particularly in the presence of underlying renal artery stenosis (see the following subsection), or may cause hyperkalemia.[13] Results of a recent meta-analysis[83] suggest that modest increases in serum creatinine levels of up to 30% that stabilize within the first 2 months of ACE inhibitor therapy may be associated with long-term preservation of renal function. Thus, ACE inhibitor withdrawal should be considered if creatinine levels increase more than 30% above baseline or if hyperkalemia develops.[83] The development of hyperkalemia may suggest development of type IV renal tubular acidosis with hyporeninemic hypoaldosteronism[84] or concomitant nonsteroidal anti-inflammatory drug use.[85]

**Renal Artery Stenosis**

Although renal artery stenosis is an uncommon cause of hypertension, it is more frequently associated with some types of patients, including individuals with peripheral vascular disease and hypertension, where approximately 30% of patients have evidence of renal artery stenosis.[86] Other clinical situations (eg, sudden onset of hypertension and loss of blood pressure control) also increase the probability of renal artery stenosis. In one study,[87] hypertensive drug resistance to 2 agents was a risk factor for renal artery stenosis.

In patients with renal artery stenosis, ACE inhibitor therapy may produce acute renal failure. In the presence of hemodynamically significant renal artery stenosis, the GFR depends on the effect of angiotensin II on efferent arterioles. Treatment with ACE inhibitors dilates efferent arterioles, resulting in a reduction of glomerular perfusion pressure, which may lead to acute renal failure. In the presence of only 1 kidney affected by renal artery stenosis, the other kidney compensates, but in the presence of bilateral renal artery stenosis, or in the case of stenosis of a solitary kidney, treatment with ACE inhibitors results in dilation of the efferent arterioles. This may result in acute renal failure of abrupt onset with an increase in serum creatinine level and hyperkalemia but with normal urinalysis results.[88] Volume depletion, at times secondary to diuretic use, may predispose to this problem. This renal failure is reversible after withdrawal of the ACE inhibitor. The clinician should recall that azotemia after introduction of ACE inhibitors, particularly in patients taking concomitant hypotensive agents, may be multifactorial, and the appropriate response may include alteration of coexisting drugs.

**Nondiabetic Chronic Renal Disease**

Chronic renal disease frequently progresses to end-stage renal disease. Attempts to delay or arrest this progression take many forms, including control of systemic and glomerular hypertension. Hypertension may result from any type of renal disease that reduces the number of nephrons, leading to an inability to excrete salt and water normally.[89] Early detection of hypertensive renal damage is crucial. The most important intervention in terms of slowing progression of renal failure is lowering blood pressure to the goal value. Many patients may require administration of multiple medications, particularly ACE inhibitors.[1,90,91] Mourad[12] pointed out that various disease states, including glomerulonephritides, interstitial nephritis, and hereditary nephropathies, share a hemodynamic adaptation, leading to intraglomerular hypertension. Use of ACE inhibitors has been shown to decrease both types of hypertension (systemic and intraglomerular), and because of the success of using these agents to retard the progression of diabetic renal disease, it is logical to consider whether use of these drugs might also be successful in arresting the progression of nondiabetic renal disease.

A recent meta-analysis[1] of the effect of ACE inhibitor therapy on progression of nondiabetic renal disease included 1594 patients enrolled in 10 studies. A small benefit was found for the 806 patients randomized to ACE inhibitor therapy compared with 788 controls. In those given ACE inhibitors, 52 (6.4%) developed end-stage renal disease compared with 72 controls (9.1%) (95% confidence interval, 0.51-0.97). There was, however, no statistically significant difference in mortality: 17 patients (2.1%) randomized to ACE inhibitor therapy died compared with 12 controls (1.5%).

The effect of treatment with ACE inhibitors on proteinuria and/or albuminuria has also been evaluated in patients with nondiabetic chronic renal disease. In 23 studies of ACE inhibitor treatment ranging from a few weeks to 6 months, there was a

significant decline in protein excretion in 20 studies. The authors also reviewed long-term studies. In 15 studies of at least 12 months' duration, only 6 showed a decrease in protein excretion with ACE inhibitor use. The cause of proteinuria may be important in predicting whether ACE inhibitors will be successful in reducing protein excretion.[92] In a study of low-dose captopril to reduce the proteinuria of adult idiopathic membranous nephropathy, renal function remained stable in the 11 patients who completed the trial (of 14 who enrolled).[93] A decrease in proteinuria was observed after 1 month of therapy that persisted over time and was associated with a trend toward a long-term decrease. An increase in the serum albumin concentration was observed after 6 months of treatment, and serum immunoglobulin levels also increased.

The long-term benefit of ACE inhibitor therapy in the treatment of nondiabetic chronic renal disease has been confirmed with recent data from Europe. In the Ramipril Efficacy in Nephropathy core and follow-up studies,[94,95] patients assigned to ramipril therapy had reductions in the rate of GFR decline, risk of doubling of the serum creatinine level, or progression to end-stage renal failure compared with patients treated with conventional antihypertensive therapy. Blood pressure control was comparable in the 2 groups. These benefits were obtained even in patients with severe nephropathy (>3 g urine protein/d) and were sustained for more than 3 years[94,95]; patients with milder degrees of proteinuria also benefited.[96]

In a similar study of nondiabetic chronic renal disease, the ACE Inhibition in Progressive Renal Insufficiency Study Group[91] demonstrated that benazepril therapy was effective in slowing progression of renal dysfunction; this benefit was more pronounced in patients with chronic glomerular disease and proteinuria in excess of 1 g/d.[97] This benefit was apparent for the 3 years of the study. A follow-up study,[98] which extended median treatment follow-up to 6.6 years, confirmed the long-term beneficial effect of ACE inhibition. Employing a statistical model using ACE Inhibition in Progressive Renal Insufficiency study data, van Hout and colleagues[99] concluded that ACE inhibitor therapy was cost effective in nondiabetic chronic renal failure, primarily by increasing the number of years without dialysis.

In summary, ACE inhibitors exert renal protective effects beyond those achieved by blood pressure reduction alone for patients with nondiabetic chronic renal disease.[100] Use of ACE inhibitors results in vasodilation of both efferent and afferent renal vessels, with improvement of renal blood flow and glomerular filtration.[101] The benefit of these modifications in renal blood flow is apparent in individuals in whom there is increased sympathetic activity resulting in intrarenal hypertension. This benefit also involves the intrarenal renin-angiotensin system because of the role of this system as a regulator of renal sympathetic activity.[102]

**Renal Transplantations**

Persistent proteinuria develops in up to 30% of all long-term renal allograft recipients and may progress to nephrotic syndrome. In part because of the increasing number of transplantations, chronic kidney transplant failure has become a major cause of end-stage renal disease, resulting in the need for dialysis or retransplantation.[103] Although the pathogenesis of the kidney failure is multifactorial, proteinuria reflects altered glomerular permselectivity, with alterations in size and charge selectivity of the basement membrane.[103] Angiotensin-converting enzyme inhibitors have been used to treat these individuals. In a study[104] of 22 patients with post-transplant nephrotic syndrome, patients were treated with increasing doses of enalapril for 1 year. Urinary protein excretion decreased after 2 months of this treatment by an average of almost 50%. Creatinine clearance did not change significantly. In another study,[105] the use of fosinopril reduced proteinuria, blood pressure, and renal hemodynamic values in a way that suggested a beneficial effect on intraglomerular hypertension. Similar findings[106] were reported with perindopril therapy. Furthermore, quinapril was recently shown to have antihypertensive efficacy comparable to atenolol in renal transplant patients, with a better maintenance of graft function, as shown by decreased albuminuria; this was thought to reflect the ACE inhibitor effect on efferent glomerular tone. This might be of particular significance in renal transplant patients in whom cyclosporine use may induce vasoconstriction of the afferent glomerular arteriole, leading to a reduction in GFR.[107]

**Renal Disease and AIDS**

Approximately 10% of patients with HIV infection develop an HIV-associated nephropathy characterized by proteinuria and a focal and segmental glomerulosclerosis, suggestive of glomerular hypertension.[108,109] This complication of HIV infection occurs primarily in African American men, perhaps mostly in those who use intravenous drugs. Angiotensin II has been implicated in the pathogenesis of HIV-associated nephropathy. In one study[110]

of 18 patients with biopsy-proven HIV-associated nephropathy, renal survival was enhanced in those receiving captopril vs placebo. The authors suggest that treatment with captopril and antiretroviral therapy may be useful in delaying the rapidly progressing renal failure associated with HIV nephropathy. The effect of this combination may reflect the presumed mechanisms of ACE inhibitors, including reduced angiotensin II levels, reduced tissue growth factor expression, or effects on HIV protease activity. In a case report[111] of a patient with HIV-associated nephropathy, treatment with fosinopril resulted in a marked decrease in 24-hour urinary protein excretion, which returned to baseline levels after discontinuation of drug administration. In this setting, one could speculate that ACE inhibitor use might decrease the need for dialysis by prolonging renal survival.

**African Americans**

Questions remain about the use of ACE inhibitors in African Americans. This is of particular importance given that these individuals, compared with whites, are disproportionately affected by end-stage renal disease of most causes.[112] Whether this is reflective of the observation that African Americans frequently have low-renin hypertension or other factors, such as volume expansion, is unclear. In a pilot study of nondiabetic black men and women with hypertension and nephrosclerosis, Hall and colleagues[113] reported that African Americans treated with either amlodipine, atenolol, or enalapril had comparable blood pressures at 3 months of treatment. By 6 months, amlodipine-treated patients had lower blood pressures than the other 2 groups; similar findings were observed for treatment effects on GFR.[113] Comparable findings were reported by Weir et al,[114] who observed that African Americans had better blood pressure control with isradipine use than enalapril use while maintaining a high-salt diet; these drug differences were blunted on a low-salt diet,[114] suggesting that the dietary prescription may differentially modulate the effect of antihypertensive therapy and that salt sensitivity may attenuate ethnic differences in antihypertensive response. Mitchell and colleagues[115] also reported that both fosinopril and lisinopril reduce blood pressure but decrease GFR in older hypertensive African American patients with renal insufficiency. Guasch et al[116] observed that African Americans with type 2 diabetes mellitus with nephropathy had a significant reduction in proteinuria with captopril use, whereas isradipine therapy caused an increase.

Weir and colleagues[117] analyzed the dose response of trandolapril: African American patients required a dose roughly 2 to 4 times that of white patients to achieve similar blood pressure reductions. Thus, although use of ACE inhibitors may be less effective in African Americans for certain situations, for specific indications, such as diabetic nephropathy, ACE inhibitors remain indicated regardless of ethnicity.[118] For nondiabetic African Americans with hypertension and renal disease, diuretics and calcium channel blockers may be preferred agents; α- and β-adrenergic blocking agents may be effective as well.[119,120] This area requires further study.

**Future Directions**

Although many patients are potential candidates for ACE inhibitor therapy, some do not obtain full benefit, most commonly because of lack of efficacy or adverse effects. In attempts to extend the benefit of disruption of the renin-angiotensin-aldosterone pathway, interference of other steps in this cascade has been explored. Recently, several ARBs (ie, losartan, valsartan, candesartan, and irbesartan) have been introduced[121] that seem to have similar beneficial effects on the kidney as do ACE inhibitors. Results of studies[122-124] suggest that when patients with nondiabetic proteinuria are treated with ARBs for hypertension, the amount of proteinuria decreases. The degree of decrease in proteinuria is similar to that found with ACE inhibitor therapy. After discontinuation of treatment, levels of proteinuria return to baseline. Results of several recent studies[124-126] also provide evidence that use of ARBs reduces protein excretion in hypertensive patients with diabetes. Whether the long-term effects of ARB use on renal disease are similar to those of ACE inhibitor use remains to be established.[127] Because there are non–ACE-dependent pathways for angiotensin II synthesis, angiotensin II blockade may be more protective.

Another recent approach to the inhibition of the renin-angiotensin system has been the development of nonpeptide renin inhibitors. These agents act by inhibiting the enzyme that produces the substrate for ACE; it is effective in the same physiologic pathway as the ACE inhibitor but one reaction earlier. In principle, renin inhibitors should have the same clinical efficacy as ACE inhibitors and ARBs.[121,128] To date, renin inhibitors have primarily been used experimentally to confirm the pathophysiologic role of the renin-angiotensin system, eg, in congestive heart failure.

The ultimate therapeutic potential of these agents is unclear.[129]

## ··· DISCUSSION ···

Angiotensin-converting enzyme inhibitors are powerful and useful drugs that are underused. Although their impact on renal function varies with different disease states, these effects are predictable based on present knowledge of the consequences of glomerular pressure on particular disease states. Use of ACE inhibitors is beneficial for diabetic (both type 1 and type 2), HIV, and posttransplant nephropathies. Benefit also extends to the use of ACE inhibitors in other forms of chronic renal disease, including glomerulonephritides, interstitial nephritis, and hereditary nephropathies characterized by intraglomerular hypertension. Their use in renal artery stenosis, particularly in patients with bilateral stenosis, leads to a deterioration of renal function. There may be racial differences in response to ACE inhibitor therapy that may be explained in part by salt sensitivity and intake. Whether ARBs (or, in the future, renin inhibitors) have the same impact on renal disease remains to be determined. Further studies are needed to optimize the use, timing, and dosing of ACE inhibitors and to identify other patients with renal diseases who will benefit from their use. The recently issued JNC VI guidelines clearly encourages a role for ACE inhibitors in the management of hypertension.[3] We concur with these suggestions and encourage providers to be aware of the powerful, positive effects of these drugs in other renal conditions, both marked by systemic hypertension and not. The available data suggest that these drugs have significant cost benefit and delay more expensive therapies. This observation, coupled with the overall underuse of ACE inhibitors, particularly in diabetic nephropathy, implies that appropriately aggressive use of ACE inhibitors would have a profound and positive impact on health maintenance.

***Acknowledgments***

We appreciate the assistance of George A. Kaysen, MD, PhD, in critically reviewing the manuscript. Barbara Nicholson, MLS, Medical Librarian, VANCHCS, expertly assisted in literature retrieval.

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