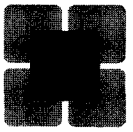

BEN H. BROUHARD, MD, EDITOR

Use of angiotensin-converting enzyme inhibitors in chronic progressive renal disease

BEN H. BROUHARD, MD; KIMBERLY C. IRWIN, MD; ROBERT J. CUNNINGHAM, MD; NICHOLAS T. STOWE, PHD

■ Chronic renal insufficiency is a progressive, self-perpetuating process which is influenced in part by activation of the intrarenal renin-angiotensin system. Oral angiotensin-converting enzyme inhibitors are being studied in animals and humans to determine whether they slow the decline in renal function characteristic of progressive renal disease. In animals that have reduced renal mass, streptozotocin-induced diabetes mellitus, or puromycin aminonucleoside nephrosis, these agents can reduce proteinuria, decrease the frequency of sclerotic glomeruli, and normalize intrarenal hemodynamics. They also may decrease glomerular hypertrophy that occurs after renal ablation. In human trials, angiotensin-converting enzyme inhibitors decrease proteinuria by altering the glomerular capillary permeability. The effect of these agents on progressive disease may be influenced by how soon therapy is begun and how long it is continued.

□ INDEX TERMS: ANGIOTENSIN-CONVERTING ENZYME INHIBITORS; RENAL DISEASE, CHRONIC PROGRESSIVE □ CLEVE CLIN J MED 1991; 58:184–190

CHRONIC RENAL disease often progresses to end-stage renal failure.[1] Progression is seen in a wide variety of renal diseases, including polycystic kidney disease, diabetic glomerulopathy, focal segmental sclerosis, and chronic pyelonephritis. Many factors have been implicated in this process, including abnormalities of lipoprotein metabolism,[2] high dietary protein and phosphate intake,[3] abnormalities of the prostaglandin system,[4] and abnormalities of the coagulation system.[5]

Recent investigations also indicate that activation of the renin-angiotensin system is a factor, raising the possibility of treatment with angiotensin-converting enzyme (ACE) inhibitors.

From the Departments of Pediatrics (B.H.B., K.C.I., R.J.C.), Hypertension and Nephrology (B.H.B., R.J.C., N.T.S.), Urology (N.T.S.), and Heart and Hypertension Research (B.H.B.), and the Nephro-Urology Research Laboratory (N.T.S.).

Address reprint requests to B.H.B., Department of Pediatrics, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

INTRARENAL HEMODYNAMICS AND THE RENIN-ANGIOTENSIN SYSTEM

An early study that used the 5/6 nephrectomy rat model[6] indicated that abnormal intrarenal hemodynamics could generate a sequence of events that leads to end-stage renal failure. The investigators suggested that reduced total renal mass leads to chronic renal vasodilation; the subsequent increase in glomerular blood flow increases the glomerular filtration rate (GFR) in the remaining intact nephrons. The increased GFR is accompanied by increased glomerular capillary hydrostatic pressure with subsequent increases in transmembrane pressure across the glomerular capillary basement membrane. These changes are also associated with diminished sieving properties of the glomerular basement membrane, leading to

increased protein flux and overt proteinuria.

The increase in macromolecular flux across the glomerular basement membrane stimulates glomerular mesangial cell proliferation. The concomitant increase in mesangial matrix gives rise to focal segmental sclerosis. This further limits glomerular capillary basement membrane surface area, which decreases the glomerular filtration rate even more.

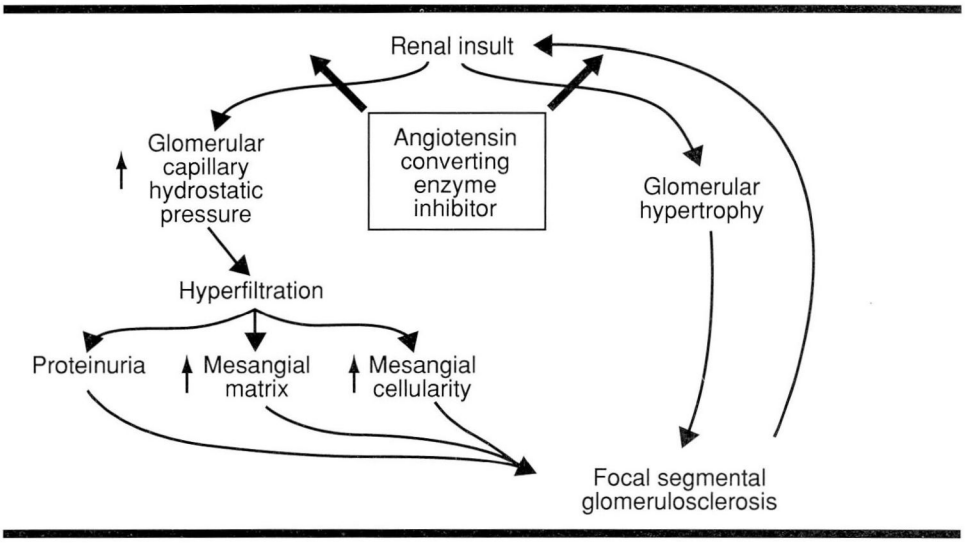

FIGURE 1. Angiotensin-converting enzyme inhibitors may slow or prevent the progression of chronic renal disease. Two potential mechanisms have been hypothesized: The agents may normalize altered intrarenal hemodynamics by decreasing glomerular capillary hydrostatic pressure; or they may lessen glomerular hypertrophy.

The renin-angiotensin system has been shown to markedly alter intrarenal hemodynamics.[7] Activation of the intrarenal renin-angiotensin system, with production of the vasoconstrictor angiotensin II, increases efferent glomerular arteriolar resistance. This raises the glomerular capillary hydrostatic pressure and leads to proteinuria. The associated changes in intrarenal hemodynamics lead to end-stage renal disease. Because orally administered ACE inhibitors limit the production of angiotensin II, several experimental and clinical trials have tested the efficacy of these agents in preventing the decline in GFR that characterizes chronic progressive renal disease.

Several models, including renal disease induced by nephrectomy or by nephrotoxins, have been used to test the hypotheses that angiotensin-converting enzyme inhibitors (1) diminish the hemodynamic abnormalities associated with decreased renal mass; and (2) decrease the frequency of focal segmental glomerulosclerosis, the histologic abnormality that characterizes end-stage renal disease.

Reductions in renal mass stimulate the intrarenal renin-angiotensin system. The activated renin-angiotensin system preferentially increases efferent glomerular arteriolar resistance. This causes the observed increase in hydrostatic pressure across the glomerular basement membrane. This fundamental abnormality in intrarenal hemodynamics, with subsequent proteinuria, mesangial proliferation, and mesangial sclerosis, perpetuates the renal injury (*Figure 1*). Enalapril and captopril prevent the formation of angiotensin II that occurs with activation of the renin-angiotensin system. This action blocks the increase in efferent arteriolar tone and hydrostatic pressure.

ACE INHIBITION IN RENAL ABLATION MODELS

Studies of renal ablation models suggest that ACE inhibition may minimize the glomerular hypertrophy associated with glomerular sclerosis, but the agent apparently must be started at the onset of disease, rather than later, for an effect to be achieved.

Beukers and colleagues[8] initially used the unilateral nephrectomy model of chronic renal insufficiency in rats. After nephrectomy, the animals were followed for either 1 month or 7 months. Compared to untreated controls, animals that received captopril, 500 mg/L of drinking water starting at the time of nephrectomy, had significantly less focal segmental sclerosis and proteinuria, and had no changes in glomerular filtration rate. When captopril administration was delayed until 7 months after nephrectomy, with the animals evaluated 4 months later, the incidence of proteinuria and sclerosis was comparable to that in the untreated, control animals. Thus, it appears that captopril therapy needs to start at the onset of the insult or disease, rather than later in the course of the disease.

Other investigators[9–11] have found that enalapril, 50 mg/L to 100 mg/L of drinking water, given to rats with

a 5/6 reduction in renal mass produced no change in GFR compared to untreated rats. However, there were marked decreases in both proteinuria and sclerosis. Anderson and co-workers[10] and Yoshida and colleagues[11] have shown significant decreases in glomerular capillary hydraulic pressure with the use of enalapril, leading to decreased transmembrane pressure across the glomerular basement membrane. This decrease in glomerular perfusion pressure was associated with decreased proteinuria and fewer histologic abnormalities than in untreated animals.

Yoshida and associates[11] hypothesized that ACE inhibitors may exert their protective effects by limiting glomerular hypertrophy that occurs in the remaining intact glomeruli after renal ablation. Preliminary data[12] suggest that ACE inhibitors have a direct effect on glomerular hypertrophy in vitro. Yoshida's group[11] demonstrated a positive relationship between the total planar area of the glomerulus (a measure of hypertrophy) on histologic examination and the degree of sclerosis. They suggested that early in the course of progressive renal disease, glomerular hypertrophy is associated with increasing degrees of sclerosis. Once glomerular hypertrophy reaches a certain level, the sclerotic process continues, but the glomerulus contracts and the planar area of the glomerulus becomes smaller.

ACE INHIBITION IN TOXIN-INDUCED DISEASE

As in renal ablation models, timing of ACE inhibition appeared to be a factor in some animal models of renal disease induced by nephrotoxins.

Adriamycin-induced renal insufficiency

Four groups of investigators[13–16] have evaluated the effect of angiotensin-converting enzyme inhibitors in chronic renal insufficiency induced in animals by adriamycin. Adriamycin is a known nephrotoxin that gives rise to proteinuria and, ultimately, focal segmental sclerosis. In these studies, ACE inhibitors in relatively large doses did not protect against proteinuria or sclerosis.

Heymann nephritis

Heymann nephritis is a form of experimental renal disease produced when animals are administered antibody against renal tubular cells. The result is progressive decline in renal function, proteinuria, and histologic evidence of focal segmental glomerulosclerosis. In 1987, Hutchison and associates[17] examined the effect of enalapril, 40 mg/kg of body weight, on renal function and histologic findings in animals with Heymann nephritis. They found no difference in glomerular filtration rate compared to untreated controls, but the treated rats had significantly less proteinuria and sclerosis.

Puromycin aminonucleoside nephrosis

The most frequently studied rodent model of experimental renal disease is that of puromycin aminonucleoside (PAN) nephrosis. PAN causes nephrotic syndrome with subsequent focal segmental sclerosis. This experimental model most closely resembles human focal segmental glomerulosclerosis. Radin and co-workers,[18] using captopril, 50 mg/kg of body weight, showed decreased proteinuria in rats made nephrotic with PAN, but little change in the frequency of sclerotic glomeruli compared to untreated animals. Trachtman and colleagues,[19] using a higher dose of captopril, found similar results but also demonstrated no change in glomerular filtration rate in treated *v* untreated animals.

Marinides and associates,[20,21] in two contrasting studies, demonstrated that the natural course of PAN-induced renal disease may influence the effectiveness of ACE inhibitors. Following weekly injections of PAN to induce nephrosis, animals were given enalapril, 10 mg/kg, for 12 weeks and sacrificed 5 weeks after the onset of disease. At the time of sacrifice, there were no changes in proteinuria, frequency of sclerotic glomeruli, or renal function. In a subsequent study,[21] the animals were followed for an additional 3 months after the onset of disease. The investigators observed a marked decrease in the number of sclerotic glomeruli and proteinuria, with no change in glomerular filtration rate. These results suggest that relatively long duration of disease is needed for ACE inhibition to have any therapeutic effect.

Anderson and colleagues[22] supported the Marinides findings[21] when they evaluated the course of disease caused by a single, large dose of puromycin aminonucleoside. They showed that nephrotic syndrome occurred early in the disease process, with hypoproteinemia, proteinuria, and hyperlipidemia. In this early phase, enalapril had no effect on glomerular filtration rate or proteinuria. Two months after injury, there still was little effect on renal function, histologic findings, or proteinuria in the treated animals. After an additional 62 weeks of follow-up, focal segmental sclerosis with increasing proteinuria developed in untreated animals; this group also demonstrated in-

creased glomerular capillary hydraulic pressure characteristic of progressive renal disease. Animals treated with enalapril showed decreased proteinuria and sclerotic glomeruli, and preservation of single-nephron GFR. They also showed decreased glomerular capillary hydraulic pressure, indicating that enalapril normalized intrarenal hemodynamics compared to untreated rats.

Fogo and co-workers,[23] using a shorter follow-up of animals given multiple injections of PAN, found no changes in proteinuria, but decreased frequency of glomerular sclerosis in treated animals compared to untreated animals. ACE inhibitors used in this model of experimental renal disease may preserve renal function and prevent histologic changes weeks to months after the acute insult, but they probably have little protective effect during the acute injury.

TABLE 1
EFFECTS OF ACE INHIBITORS IN DIABETIC NEPHROPATHY

Author	Number of patients	Duration of study (mo)	Change in proteinuria	Change in GFR
Taguma[28]	10	2	10.6 to 6.1 (g/d)	4.75 to 5.0 (creatinine)
Hommel[29]	16	3	1589 to 1075 (μg/min)	99 to 93 (mL/min/1.73 m^2)
Bjorck[30]	14	24	2.9 to 2.8 (g/d)	10.3 to 5.5 (mL/min/yr)
Marre[31]	10	6	124 to 37 (μg/min)	130 to 141 (mL/min/1.73 m^2)
Stornello[32]	12	6	434 to 190 (μg/min)	101 to 105 (mL/min/1.73 m^2)
Valvo[33]	12	6	4.5 to 3.4 (g/d)	57 to 51 (mL/min/1.73 m^2)
Parving[34]	15	12	400 to 350 (μg/min)	112 to 109 (mL/min/1.73 m^2)
Mimran[35]	8	1.5	86 to 51 (μg/min)	0.9 to 0.8 (serum creatinine)
Marre[36]	10	12	90 to 30 (μg/min)	131 to 124 (mL/min/173 m^2)
Morelli[37]	16	3	2.2 to 1.8 (g/d)	73 to 73 (mL/min/1.73 m^2)
Brouhard[38]	3	59	2.1 to 0.3 (g/d)	53 to 37 (mL/min/1.73 m^2)

MWF/Ztm genetic model

Remuzzi and colleagues[24] used enalapril, 50 mg/L of drinking water, in rats with the Munich-Wistar Fromter (MWF) genetic rodent model of progressive renal disease. They followed the animals for 15 to 17 weeks. Proteinuria, focal segmental sclerosis, small contracted glomeruli, and decreased renal function developed in untreated rats. In animals treated with enalapril, there were decreases in glomerular capillary hydraulic pressure, proteinuria, and frequency of sclerosis. Enalapril also appeared to limit glomerular hypertrophy as shown by decreases in glomerular volume in treated animals compared to untreated animals. The fractional clearance of neutral dextrans was also decreased in the treated group, indicating that ACE inhibitors decrease permeability of the glomerular capillary basement membrane wall.

In this genetic model of progressive renal disease, enalapril reversed the intrarenal hemodynamic abnormalities, prevented glomerular hypertrophy, and normalized the pore size of the glomerular basement membrane. It is not clear which of these abnormalities contributes to the decline in renal function and the production of sclerotic glomeruli.

Streptozotocin-induced diabetes

Three studies[25–27] have assessed the effect of ACE inhibitors on the course of renal lesions in insulin-dependent diabetes mellitus induced by streptozotocin. All three showed decreased hyperfiltration early in the course of diabetes, as well as markedly decreased proteinuria and sclerosis. Cooper and associates[26] also demonstrated decreased thickening of glomerular basement membrane, a histologic hallmark of diabetic nephropathy.

COMMENT: ACE INHIBITION IN EXPERIMENTAL RENAL DISEASE

In all of the experimental models, ACE inhibition adequately controlled systemic hypertension when it was present. Except in the adriamycin model, ACE inhibitors limited the progression of renal disease as demonstrated by decreased frequency of sclerotic glomeruli and decreased proteinuria. The mechanism for this preservation of structure and function is not understood.

TABLE 2
EFFECTS OF ACE INHIBITION IN PROTEINURIC RENAL DISEASE

Authors	Number of patients	Drug	Duration of study (mo)	Change in proteinuria	Change in GFR
Trachtman[39]	8	Captopril	3-11	2.8 to 0.7 (protein/creatinine)	93 to 83 (mL/min/1.73 m^2)
Ruilope[40]	15	Captopril	6	4.8 to 1.8 (g/d)	33.4 to 37.8 (mL/min/1.73 m^2)
Heeg[41]	13	Lisinopril	3	4.2 to 2.3 (g/d)	28.7 to 24.5 (mL/min/1.73 m^2)
Ruilope[42]	10	Captopril	12	1.0 to 0.7 (g/d)	28.2 to 34.2 (mL/min/1.73 m^2)
Fitzwater[43]	7	Enalapril Captopril	24	4.0 to 0.63 (g/d)	1.4 to 1.4 (creatinine)

Some models[10,11] demonstrate decreased glomerular capillary hydraulic pressure with subsequent decreases in transmembrane pressure. The derangements in intrarenal hemodynamics may be central to the progressive declines in renal function in these models. Because ACE inhibitors reverse these hemodynamic abnormalities, they preserve renal function.

In at least two models, ACE inhibitors decreased glomerular hypertrophy, which may be the precursor to sclerotic glomeruli.[11,24] In the Remuzzi[24] study, enalapril normalized the increased permeability of the glomerular capillary basement membrane. Whether increased permeability contributes to the development of sclerosis, or is merely an epiphenomenon, is not known.

The timing of administration of an ACE inhibitor may determine its therapeutic effect.[8] For example, Anderson and colleagues[22] found that although ACE inhibitors have no effect during the acute phase of renal injury, they may need to be given at this time in order to show an effect during the chronic phase of the disease.

Two hypotheses have emerged from these studies: (1) that intrarenal hemodynamic abnormalities cause proteinuria, declining renal function, and sclerotic glomeruli; and (2) that glomerular hypertrophy is the prerequisite for sclerosis and is independent of hemodynamic factors. The data to date suggest that ACE inhibitors normalize these processes.

HUMAN STUDIES

ACE inhibitors have been studied in two groups of patients with proteinuric renal disease—those with diabetic nephropathy, and those with other proteinuric renal diseases.

ACE inhibition in diabetic nephropathy

Ten studies (*Table 1*)[28–37] have documented the effects of ACE inhibitors on proteinuria and glomerular filtration rate in patients with diabetic renal disease. Taguma and colleagues[28] demonstrated that captopril decreased proteinuria in 10 patients after only 2 months of follow-up. Mean protein excretion in this group decreased from 10.6 g/24 h to 6.1 g/24 h; changes in creatinine were minimal. Other studies (*Table 1*) have also shown decreased proteinuria. Renal function, measured by GFR or by serum creatinine concentration, remained stable in these studies.

Morelli and colleagues[37] documented the effects of 3 months of enalapril administration in 16 patients with diabetic renal disease. They observed decreases in proteinuria from 2.2 g/24 h to 1.8 g/24 h, with little change in GFR. These investigators also demonstrated a significant decrease in the fractional clearance of neutral dextrans, indicating decreased glomerular capillary permeability with enalapril in these subjects. When the enalapril was discontinued, increased permeability was again noted. These findings indicate that the increase in glomerular permeability in diabetic nephropathy is reversible, and its normalization with enalapril probably accounts for the decrease in proteinuria. Whether changes in intrarenal hemodynamics accompany the changes in permeability obviously cannot be assessed in humans.

We followed three patients with diabetic nephropathy for an average of 41 months before and 59 months after beginning ACE inhibitor therapy. Renal function declined much faster before treatment than during treatment: ie, 0.95 mL/min/1.73 m2 per month before treatment, compared to 27 mL/min/1.73 m2 per month during treatment. Mean protein excretion decreased from 2.1 g/24 h before treatment to 0.3 g/24 h. Creatinine clearance decreased from a baseline of 53.1 mL/min/1.73 m2 to 37.4 mL/min/1.73 m2 at follow-up. The change in blood glucose, measured by hemoglobin A1C, was insignificant (8.3% to 9.4%). Despite decreases in proteinuria and slowed decline of renal function, the progression of renal disease remained evident. This may reflect the relatively late initiation of therapy.

Other proteinuric diseases

A number of studies (*Table 2*)[38–43] have investigated patients with a renal diseases characterized by proteinuria and various measures of GFR. The studies have involved limited numbers of patients, short follow-up times, and such a wide variety of diseases that no definite conclusion is possible, except that ACE inhibitors decrease proteinuria. Although increased proteinuria has been associated with increased frequency of sclerosis, it is unlikely that limiting proteinuria with ACE inhibitors will prevent progression of renal disease.[22]

Our evaluation43 of two patients with focal segmental sclerosis and nephrotic syndrome, a disease known to progress to end-stage renal failure, indicates that ACE inhibitors may delay the onset of renal failure. Progressive disease is likely, but its rate may be influenced by when the agents are begun in the course of the disease and how long they are continued.43 We have also followed seven patients with asymptomatic focal segmental sclerosis receiving enalapril, 5 mg to 10 mg daily. During an average 24-month follow-up, we have seen virtually no change in serum creatinine and marked decreases in proteinuria.

CONCLUSION

ACE inhibitors are well studied for the control of systemic hypertension. In patients with renal disease, ACE inhibitors can decrease proteinuria by decreasing glomerular capillary permeability which, in the patient with diabetes, is a reversible phenomenon. If started early in the course of the disease, ACE inhibitors may prevent the progressive decline of GFR.

The mechanisms of these protective effects include alterations in intrarenal hemodynamics, normalization of glomerular basement membrane permeability, direct effects on glomerular hypertrophy, and increased glomerular volume during chronic renal injury.

ACKNOWLEDGMENT

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Errata

Two errors occurred in the article, "Management of inflammatory bowel disease: 30 years of observation," by Michener and associates (Cleve Clin J Med 1990; 57:685–691). In *Table 2*, p 686, the entry "Duration of symptoms to diagnosis" should be expressed in months. The last sentence on p 689 should read, "The occurrence of only one colon cancer among patients with ulcerative colitis in the 1975–1984 review period should reassure those with concerns about an association between the two diseases."