The incidence of hypertensive end-stage renal disease continues to increase annually. To reduce this incidence, it is necessary to control systolic and diastolic hypertension. Reversible causes should always be sought in any hypertensive patient who develops renal insufficiency. Blood pressure should be reduced to 130/85 mm Hg, and in African Americans with hypertensive renal failure, reducing the blood pressure to 120/75 mm Hg may be beneficial. Any antihypertensive treatment regimen that effectively lowers blood pressure will help slow progressive renal failure. Whenever possible, an angiotensin-converting enzyme inhibitor should be part of the treatment, since these drugs have been shown to be renoprotective beyond their antihypertensive effect in certain renal disease categories.

While the number of hypertensive patients receiving treatment and reaching a goal blood pressure in the United States is twice that in 1980, the frequency of end-stage renal disease (ESRD) has been increasing annually. This review presents information concerning the pathophysiological mechanisms of hypertensive renal disease and recommends treatment strategies based on clinical trial data that should be helpful in slowing the increase in the incidence of hypertensive ESRD.

THE PROBLEM OF HYPERTENSIVE RENAL DISEASE

Since 1972, chronic dialysis and/or renal transplantation, when clinically appropriate, has been available as a Medicare benefit to patients of all ages with ESRD. By the early 1980s, outpatient dialysis was universally available throughout the United States. Since that time, the annual number (incidence) of new cases of ESRD has been growing exponentially. The average annual increase in the number of patients beginning chronic dialysis from 1986 through 1995 was 13% (Figure 1). The incidence of patients entering chronic dialysis or transplantation is a surrogate for the actual incidence of ESRD, since few patients with ESRD elect not to undergo dialysis.

End-stage renal disease occurs most frequently among older and minority patients, particularly African Americans, although there have also been annual increases in ESRD incidence among Asian Americans, Hispanic Americans, and Native Americans. The most common cause of ESRD nationally is diabetes mellitus, most frequently type 2, or adult onset; however, it is followed closely by hypertension in causing ESRD (Figure 2). In the southeastern United States, where the incidence of high blood pressure is greater than in any other region of the country, hypertension is the most frequent cause of ESRD, followed closely by diabetes mellitus.

PATHOPHYSIOLOGY OF HYPERTENSIVE RENAL DISEASE

Hypertension may result from any form of renal disease that leads to a reduced number of functioning nephrons because of dietary sodium and water retention. Renal failure also can result from uncontrolled hypertension. The greater the severity of the hypertension, the greater the risk of renal failure, although it has been sug-
suggested that many of the new cases of hypertensive ESRD currently being seen result from poorly controlled stage 1 hypertension. Although any primary renal disease can occur in a hypertensive patient, renal failure most commonly results from nephrosclerosis, a progressive proliferative lesion within the wall (media) of renal arterioles.

Renal failure typically progresses, regardless of underlying cause, as a continuous function of mean arterial pressure. Systemic hypertension causes afferent glomerular arteriolar vasoconstriction, which activates the intrarenal renin-angiotensin system. Increased intrarenal angiotensin II and other factors sustain glomerular filtration by maintaining transglomerular filtration pressures through increased efferent glomerular arteriolar resistance. This increased efferent arteriolar resistance reduces flow to the vasa recta, producing renal tubular ischemia leading to additional nephron loss. The remaining nephrons increase in size in an attempt to accommodate the increased filtration load per nephron.

With continued dietary intake of salt and water, intravascular volume expands, which is a major cause of the systemic hypertension in patients with renal disease. The renin angiotensin is activated or at least not appropriately suppressed for the degree of intravascular volume expansion. Thus, the increased angiotensin II contributes to the systemic hypertension. Eventually, renal autoregulation is lost and afferent glomerular resistance gives way to systemic hypertension, producing glomerular hyperfiltration and glomerular injury. In the glomerulus, there is increased intracapillary pressure and increased capillary wall tension. Proteinuria parallels the glomerular hyperfiltration. The severity of proteinuria parallels progressive renal failure and increasing systemic hypertension. The increased angiotensin II is a factor in the proteinuria by decreasing the size-selective sieving of the glomerular basement membrane. Proteinuria may also injure tubular cells, causing the release of cytokines, growth factors, and mediators of inflammation, as well as exposing tubules to filtered hormones and growth factors normally excluded by the glomerular macromolecule filtration barrier.

In addition to these glomerular basement membrane changes, there is expansion of the mesangium and an increase in renal interstitial fibrosis. There can also be calcification of the interstitum. Angiotensin II has been demonstrated, in vitro, to be active in this mesangial expansion by increasing transport of blood-borne macromolecules such as IgG, stimulating the production of fibrogenic cytokines, such as transforming growth factor β, and reducing the activity of interstitial proteinases, such as plasmin and metalloproteinases, which should normally prevent interstitial fibrosis.

The importance of the renin-angiotensin system in progressive hypertensive renal failure also has been demonstrated by the observations that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blocking agents (ARBs) reduce glomerular filtration pressure in the animal model of hypertensive renal failure with reduced kidney mass and slow progressive renal failure beyond the drugs’ systemic antihypertensive effect.

Nephrosclerosis shares similarities with coronary atherosclerotic vascular disease. It occurs simultaneously with coronary and carotid atherosclerosis. Anatomically, nephrosclerosis, like coronary artery disease, occurs at branching points of renal arterioles, and there is smooth muscle hypertrophy within the wall of the affected arteriole. Experimentally, it increases with and is reduced by the treatment of systemic hypertension and hypercholesterolemia. There is not yet sufficient clinical trial data to recommend hypercholesterolemia treatment to slow the progression of nephrosclerosis. The relationship of nephrosclerosis in hyperten-
sive renal failure to other coronary artery disease risk factors has not been defined.

**STRATEGIES TO SLOW PROGRESSIVE RENAL FAILURE IN HYPERTENSIVE PATIENTS**

**Early Recognition and Evaluation of Renal Insufficiency**

Patients at risk of developing ESRD are those with renal insufficiency, African Americans, Hispanic Americans, and those with diabetes mellitus, high blood pressure, or proteinuria. Renal insufficiency should be identified early in the course of renal disease. Small elevations in serum creatinine level reflect major reductions in kidney function. For example, a serum creatinine level greater than 115 µmol/L (1.3 mg/dL) in a patient older than 60 years reflects a 50% loss of glomerular filtration rate, as does a level greater than 133 µmol/L (1.5 mg/dL) in a younger patient.24 Reversible causes of renal failure should always be sought and treated. Initial examination of patients with renal insufficiency should include urinalysis to detect proteinuria and/or hematuria (signs of glomerular disease) and a renal sonogram to exclude lower urinary tract obstruction and to determine the size of the kidneys. (Kidneys with hypeerechogenic cortex on ultrasonography that are less than 8 cm long are considered end stage.24)

**Blood Pressure Treatment Goal**

Blood pressure should be controlled to 130/85 mm Hg with whatever antihypertensive therapy is necessary.8 Controlling systolic as well as diastolic blood pressure is important in slowing progression of renal failure.21,25 Lowering blood pressure to 120/75 mm Hg may be beneficial for African Americans with renal insufficiency or in patients with renal disease and proteinuria in excess of 1 g/d.8,26,27

**Lifestyle Modification Focus**

While weight loss and increased moderate aerobic exercise can assist hypertension control in any hypertensive patient, reducing dietary sodium to a level lower than that recommended for uncomplicated hypertension (<6 g of sodium) is especially helpful in reducing high blood pressure in patients with renal insufficiency.8,24,26 In addition, dietary sodium restriction will enhance the antihypertensive and antiproteinuric effect of ACEIs. Dietary protein restriction as a means to slow progressive renal failure is controversial; however, it will improve uremic symptoms in patients with advanced renal failure.29,30 If dietary protein restriction is instituted, close attention must be paid to total caloric intake to prevent malnutrition. Dietary potassium and phosphorus restriction in patients with creatinine clearances less than 0.50 mL/s (30 mL/min) is needed to prevent hyperkalemia and to help prevent secondary hyperparathyroidism.

**Antihypertensive Drug Recommendations for Patients With Hypertension and Renal Disease**

The most important action to slow progressive renal failure is to control hypertension by whatever means necessary. Controlling hypertension with any antihypertensive agent slows the progression of renal insufficiency. All classes of antihypertensive drugs are effective in controlling blood pressure in patients with renal insufficiency. Hypertension in such patients may be resistant to control, and multiple antihypertensive drugs may be needed.8,21 Hypertensive patients with renal insufficiency should receive an ACEI, unless contraindicated, since these drugs have been shown to be renoprotective beyond their antihypertensive effects.

A diuretic is usually also needed to achieve blood pressure control because of the sodium retention that occurs with renal disease. Thiazide diuretics are not effective with advanced renal insufficiency (creatinine clearance <0.50 mL/s [<30 mL/min]; typically, serum creatinine level ≥221 µmol/L [≥2.5 mg/dL] in a 70-kg man). Loop diuretics (furosemide, bumetanide, or ethacrynic acid) are needed with more severe renal insufficiency.31 Doses greater than 200 mg of furosemide or 100 mg of ethacrynic acid per day should be avoided because of the risk of ototoxic effects. Combining a loop diuretic with a long-acting thiazide diuretic such as metolazone is effective in patients with edema resistant to a loop diuretic alone. Potassium-sparing diuretics should be avoided in renal insufficiency. Patients receiving high-dose diuretics should be observed closely with serial measurement of weight and electrolytes to prevent extracellular volume depletion and potassium or magnesium losses.31

Since sustained blood pressure control has been demonstrated to be the most effective method to slow progressive hypertensive renal failure, additional antihypertensive drugs from any other class of agents should be added to the ACEI and diuretic to reach the goal blood pressure. Because of the possible beneficial renal effects of some calcium-channel–blocking agents (CCBs), these agents should be useful as a third class of drug.32 Possible mechanisms by which CCBs may be renoprotective are the reduction of systemic blood pressure, prevention or reduction of renal hypertrophy, modulation of mesangial traffic of macromolecules, reduction in metabolic activity of remnant kidneys, amelioration of uremic nephrocalcinosis, attenuation of mitogenic renal growth factors, possible prevention of pressure-induced calcium entry, and reduction of free radical formation.33

**ANTIHYPERTENSIVE DRUGS THAT ARE RENOPROTECTIVE**

**Angiotensin-Converting Enzyme Inhibitors**

Angiotensin-converting enzyme inhibitors slow the progression of hypertensive renal disease by several mechanisms. They are renoprotective by reducing systemic and glomerular hypertension and mesangial proliferation and fibrosis.9,18,34,35 These renoprotective effects may be mediated through mechanisms other than reduction in angiotensin II synthesis. When ACEIs block converting enzyme and the production of angiotensin II, there is a simulta-
With advanced renal failure (creatinine clearance <0.50 mL/s [<30 mL/min]), patients are at increased risk of hyperkalemia, which ACEIs can worsen. Repeated serum creatinine and electrolyte measurements should be obtained soon after an ACEI is begun in any patient with renal insufficiency to detect any decrease in renal function or hyperkalemia. A persistent increase of the serum creatinine level greater than 88 µmol/L (1.0 mg/dL) above a baseline serum creatinine value indicates worsening of renal function. The ACEIs can reduce renal function in patients with bilateral renal artery stenosis or renal artery stenosis to a solitary kidney. They can cause hyperkalemia in older patients and some patients with type 2 diabetes mellitus who have hyporeninemic hypoaldosteronism. If goal blood pressure is not reached with an ACEI and a diuretic, another class of antihypertensive agents should be added.

Angiotensin II Receptor Blocking Agents

The effects of ACEIs and ARBs may not be the same in renal disease. Since ACEIs do not block tissue-converting enzyme completely, ARBs may offer additional renal benefit, since they do completely block the effect of angiotensin II at the angiotensin tissue 1 (AT₁) receptor. There is incomplete knowledge concerning all of the renal effects mediated by angiotensin II through the various AT receptors (AT₁, through AT₄). It is known that the vasoconstrictor effect of angiotensin II on the afferent and efferent glomerular arterioles is mediated through the AT₁ receptor, as are the glomerular effects, which reduce glomerular surface area and the glomerular basement membrane sieving coefficient. These renal angiotensin II hemodynamic and glomerular effects can be blocked by ARBs, producing a reduction in efferent glomerular resistance, a reduction in glomerular pressure, an increase in glomerular surface area, and a reduction in the glomerular filtration constant.

The role of other angiotensin II renal receptors in progressive renal disease is not yet known. Experimental studies have demonstrated that renal AT₂ receptors may mediate apoptosis, and the AT₄ receptor may promote endothelial-dependent vasodilation.

There has been some comparison of ACEIs and ARBs in several experimental models of renal disease. In general, ARBs were as effective as ACEIs in slowing progressive renal failure in the remnant hypertensive kidney, diabetic rat, puromycin amonucleoside glomerular disease, obstructive uropathy, and the genetic model of glomerular sclerosis, the MWF/Ztm rat. On the other hand, ARBs were somewhat less effective than an ACEI in preventing kidney damage in spontaneously hypertensive rats subjected to nephrectomy, obese Zucker rats, and the Heyman model of membranous glomerulonephritis.

There is limited clinical experience with ARBs in hypertensive renal failure. In a small series of patients with nondiabetic renal disease, the AT₁-blocking drug losartan reduced systemic hypertension, increased renal plasma flow, reduced proteinuria, and maintained the glomerular filtration rate. The ARBs may have beneficial effects in hypertensive renal failure; however, there are insufficient data from human trials. Currently, this class of drugs cannot be recommended as an alternative to ACEIs in such patients except for patients who have experienced intolerable side effects with an ACEI.

Calcium-Channel Blocking Agents

Calcium-channel blockers preferentially antagonize preglomerular vasoconstriction, which, theoretically, should not favor attenuation of glomerular hypertension. However, as detailed in a recent review, these agents have additional properties that may contribute to their ability to afford renal protection under diverse experimental conditions and perhaps in clinical disorders. The CCBs have been reported to prevent renal injury by retarding renal growth, reducing mesangial entrapment of macromolecules, and attenuating the mito-
genic effect of diverse cytokines and growth factors, such as platelet-derived growth factor and platelet-activating factor. Nifedipine, verapamil, and diltiazem have been shown to inhibit the mesangial growth effects of platelet-derived growth factor and thrombin, while amloidipine has been shown to inhibit the in vitro proliferation of mesangial cells. Verapamil has been shown to slow progressive renal failure in the reduced mass model of nephroclerosis, to protect mitochondria from hypoxic injury, and to increase survival of ischemic renal tubular cells in vitro.

Only recently have long-term clinical trials assessed the renoprotective effects of CCBs. Although few, the available studies suggest that CCBs may be beneficial in stabilizing renal failure. Some studies using CCBs in hypertensive patients with renal insufficiency have demonstrated an increase in glomerular filtration rate or preservation of renal function; however, other trials have not. Although there is not enough current evidence to consider CCBs as renoprotective beyond their antihypertensive effect, these agents can be effective antihypertensive agents in patients with renal insufficiency.

Other Classes of Antihypertensive Agents

Animal studies and human clinical trials have demonstrated that blood pressure reduction with any class of antihypertensive agent will slow the progression of hypertensive renal failure, but the renal protective benefit is attributable solely to their systemic antihypertensive effect.

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