Hypertension is a cause and consequence of chronic renal disease. Data from the United States Renal Data System (USRDS) identifies systemic hypertension as the second most common cause of end-stage renal disease, with diabetes mellitus being the first. Renal failure in patients with hypertension has many causes, including functional impairment secondary to vascular disease and hypertensive nephrosclerosis. Even in those in whom hypertension is not the primary process damaging the kidney, elevations in systemic blood pressure may accelerate the rate at which kidney function is lost. This accelerated loss of kidney function occurs particularly in patients with glomerular diseases and clinically evident proteinuria.

Hypertension may damage the kidney by several mechanisms. Because autoregulation of glomerular pressure is impaired in chronic renal disease, elevations in systemic blood pressure also are associated with increased glomerular capillary pressure. Glomerular hypertension results in increased protein filtration and endothelial damage, causing increased release of cytokines and other soluble mediators that promote replacement of normal kidney tissue by fibrosis. An important factor contributing to progressive renal disease is activation of the renin-angiotensin system, which not only tends to increase blood pressure but also promotes cell proliferation, inflammation, and matrix accumulation.

Numerous studies in experimental animals suggest that antihypertensive drugs can slow the progression of chronic renal disease. Drugs that inhibit the renin-angiotensin system may be more effective than are other agents in retarding renal disease progression.

For many reasons, the effects of angiotensin II receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors may not
Hypertension and the Kidney

be identical. Calcium channel blockers also are beneficial in some settings; however, this effect is critically dependent on the degree of blood pressure reduction.

The relationship between hypertension and progression of chronic renal disease has been examined in a number of clinical trials. Individuals with systemic hypertension are at increased risk for developing end-stage renal disease. The rate at which kidney function is lost increases in patients with poorly controlled systemic hypertension. Antihypertensive therapy can slow the rate of loss of kidney function in patients with diabetic and nondiabetic renal disease. Studies suggest that ACE inhibitors are particularly useful in patients with hypertension and proteinuria of over 1g/24 h. Calcium channel blockers also may slow the progression of renal disease; however, whether all classes of calcium channel blockers have equivalent renal protective effects is uncertain.

Patients with hypertension and chronic renal disease should be treated aggressively. A 24-hour urine collection determines the extent of proteinuria. The patient who excretes more than 1 g/24 h of protein or who has diabetes mellitus should receive an ACE inhibitor. The target in this group of patients is to reduce the blood pressure to lower than 120/80 mm Hg. Most often, reaching this goal requires the use of combinations of antihypertensive agents, diuretics, or calcium channel blockers. Patients who excrete less than 1 g/24 h of protein may be treated according to standard recommendations with diuretics, beta blockers, ACE inhibitors, or other agents. The target blood pressure for this group of patients is lower than 130/85 mm Hg.

Hypertension and Kidney Damage

![Diagram of Hypertension and Kidney Damage]

**FIGURE 6-1** Hypothesis identifying systemic hypertension as a central factor contributing to the progression of chronic renal disease. After partial loss of kidney function resulting from an undefined primary renal disease, a number of secondary processes develop that promote progressive kidney failure. Activation of the renin-angiotensin system is a common event in patients with chronic renal disease. In these patients, renin levels are either elevated or at least not appropriately suppressed for the degree of volume expansion, elevation in blood pressure, or both. Activation of the renin-angiotensin system and the relative salt and water excess contribute to the development of systemic hypertension in most patients with chronic renal disease. Systemic hypertension and a decrease in preglomerular vascular resistance lead to an increase in hydraulic pressure within the glomerular capillaries. Glomerular hypertension has a number of adverse effects, including increased protein filtration, which promotes release of cytokines and growth factors by mesangial cells and downstream tubular epithelial cells. A partial loss of kidney function also is a potent stimulus for compensatory renal growth. Glomerular hypertrophy and hypertension combine to increase capillary wall tension, promoting endothelial cell activation and injury, again causing release of cytokines and growth factors and recruitment of inflammatory cells. These mediators stimulate processes such as apoptosis, causing loss of normal kidney cells and increased matrix production, which leads to glomerular and interstitial fibrosis and scarring. As additional nephrons are damaged secondarily the cycle is repeated and amplified, causing progression to end-stage renal failure. All—angiotensin II.
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**FIGURE 6-2**

Imaginary autoregulation curves in normal and diseased kidneys. Plotted on the y-axis are renal plasma flow (RPF), glomerular filtration rate (GFR), and glomerular capillary hydraulic pressure \( P_{GC} \) with undefined units. Ordinarily, RPF, GFR, and \( P_{GC} \) remain relatively constant over a wide range of perfusion pressures within the physiologic range, from approximately 80 to 140 mm Hg. Because autoregulatory ability is impaired in the kidneys of persons with chronic renal disease, these patients who develop systemic hypertension also are likely to have glomerular hypertension.

**FIGURE 6-3**

Mechanism of autoregulation of glomerular capillary pressure in a single glomerulus from a normal kidney. A, Baseline. B, Increased perfusion pressure. Glomerular pressure is determined by three factors: mean arterial pressure (MAP) or perfusion pressure, and the relative resistance of both the afferent and efferent arterioles. The initial response to an increase in MAP is an increase in afferent arteriolar resistance \( R_A \), preventing transmission of the elevated systemic pressure to the glomerular capillaries. Efferent arteriolar resistance \( R_E \) also may decline. This decrease decompresses the glomerulus, helping to limit the increase in glomerular capillary hydraulic pressure \( P_{GC} \), and maintains constant renal plasma flow.

**FIGURE 6-4**

Mechanism of failure of autoregulation in a glomerulus from a damaged kidney. A, Baseline. B, Increased perfusion pressure. To compensate for a partial loss of function, surviving glomeruli undergo adaptive changes to increase the filtration rate. These include a reduction in afferent \( R_A \) and efferent \( R_E \) arteriolar resistances, tending to increase renal plasma flow and the glomerular filtration rate. In this setting, an increase in mean arterial pressure (MAP) is transmitted directly to the glomerular capillaries, resulting in glomerular capillary hypertension, increased protein filtration, and hemodynamically mediated capillary injury. \( P_{GC} \) — glomerular capillary hydraulic pressure.
Effects of Antihypertensive Agents on Experimental Kidney Injury

In five separate studies, rats with experimental renal disease were given similar antihypertensive agents. Studies were conducted in several different animal models of hypertension and renal disease, including the following: uninephrectomized spontaneously hypertensive rats (Unx SHR); rats with a remnant kidney given either relatively high-dose (remnant-HD) or low-dose (remnant-LD) drug therapy; rats with desoxycorticosterone-salt–induced hypertension (Doc-salt); and rats with nephrotoxic serum nephritis (NSN), an immune-mediated form of glomerular disease (NSN) [1–5]. In all these studies, untreated rats were compared with those receiving a combination of three antihypertensive agents (triple therapy), including hydralazine, reserpine, and a thiazide diuretic. In rats with remnant kidneys, separate studies examined the effects of low or high doses of these agents. A close correlation was revealed between the degree of reduction in glomerular capillary pressure produced by triple therapy and subsequent development of glomerular sclerosis. The data are consistent with the hypothesis that antihypertensive agents lessen glomerular injury by reducing glomerular capillary pressure. In the studies in rats with remnant kidneys, only a relatively high dose of the drugs was effective in reducing pressure and injury, suggesting that aggressive antihypertensive therapy is more likely to slow progression of renal disease. This finding is particularly true for antihypertensive combinations that include direct vasodilators, such as the triple-therapy regimen. By dilating the afferent arteriole, regimens such as these tend to further impair autoregulation of glomerular pressure in the setting of chronic renal disease. (From Weir and Dworkin [6]; with permission.)

Correlation between systolic blood pressure and glomerular injury in rats with remnant kidneys. In these rats, blood pressure was continuously monitored by implanting a blood pressure sensor in the abdominal aorta connected telemetrically to a receiver. The time-averaged blood pressure in rats with remnant kidneys that were untreated or given the angiotensin-converting enzyme inhibitor enalapril or triple therapy (combination of hydralazine, reserpine, and a thiazide diuretic) was correlated with morphologic evidence of glomerular injury. A close correlation was found between the average blood pressure and extent of glomerular injury that developed in these rats. It is proposed that, because of impaired autoregulation in chronic renal disease, elevations in systemic blood pressure are associated with glomerular hypertension in these rats. The higher the systemic pressure, the higher the glomerular pressure is predicted to be and the more glomerular injury is observed. These data provide additional evidence that systemic hypertension produces glomerular injury by causing elevation in glomerular pressure, and that antihypertensive therapy reduces injury by reducing glomerular capillary pressure. (From Griffen and coworkers [7]; with permission.)
The Role of Hypertension in Progression of Chronic Renal Disease

### FIGURE 6-7
The wall tension hypothesis. A, Normal. B, Chronic renal failure. After a partial loss of kidney function, compensatory adaptations within surviving nephrons include renal vasodilation. Vasodilation leads to an increase in glomerular capillary pressure and compensatory renal growth associated with an increase in the radius of the glomerular capillaries. According to the LaPlace equation, wall tension in a blood vessel is equal to the product of the transmural pressure and the radius of the vessel. In a surviving glomerular capillary of a damaged kidney, therefore, wall tension increases not only because of the increase in glomerular pressure but also because of an increase in capillary radius. Elevations in wall tension contribute not only because of the increase in glomerular pressure but also because of an increase in capillary radius. Elevations in wall tension contribute to progressive renal disease by damaging the endothelial and epithelial cells lining the glomerular capillaries. By reducing wall tension, maneuvers that decrease either glomerular pressure or glomerular capillary radius are predicted to be beneficial. P_{GC}—glomerular capillary hydraulic pressure; R_{GC}—glomerular capillary radius; T—tension. (From Dworkin and Benstein [8]; with permission.)

### FIGURE 6-8
Scanning electron micrographs of vascular casts of glomeruli from normal or uninephrectomized rats. A, A glomerulus from a rat having had a sham operation, showing a uniform capillary pattern. (Panels B–D display casts from uninephrectomized rats.) B, A uniform pattern with most capillaries being approximately the same size. C and D, Nonuniform patterns in which individual capillary loops (indicated by asterisks) are markedly dilated. In dilated capillary loops, wall tension is elevated and capillary wall damage is most likely to occur. The segmental nature of the capillary dilation may explain why glomerular sclerosis that eventually develops in remnant kidneys is also focal in early stages of the disease process. (Panels A–D ×=320.) (From Nagata and coworkers [9]; with permission.)
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Role of the Renin Angiotensin System

The central role of angiotensin II (AII) in promoting progressive kidney failure. Based on studies in which the renin-angiotensin system has been blocked and renal injury ameliorated, it has been suggested that activation of this system is a crucial factor promoting progressive kidney failure. Increased activity of the renin-angiotensin system also may help explain the association between hypertension and progression of renal disease. AII may promote renal injury by several mechanisms. Activation of the renin-angiotensin system is one mechanism leading to an increase in systemic blood pressure, the result of peripheral vasoconstriction. Glomerular hypertension results not only from the increase in systemic blood pressure but also because of the ability of AII to constrict efferent arterioles, contributing to an increase in glomerular pressure. Glomerular hypertension damages the glomerular capillary wall and promotes injury by multiple mechanisms (see Fig. 6-1). An increase in glomerular pressure tends to increase protein filtration directly. In addition, evidence suggests that AII alters the permeability of the glomerular capillary wall to macromolecules, directly increasing protein filtration. By activating mesangial and epithelial cells, proteinuria itself is a factor promoting progressive kidney failure. Evidence also exists that AII directly stimulates production of various growth factors and cytokines by kidney cells, including transforming growth factor-beta and platelet-derived growth factor. Release of these factors has been linked to the development of glomerular sclerosis and interstitial fibrosis. AII also stimulates proliferation and growth of kidney cells that contribute to progression of renal disease.

FIGURE 6-9

Angiotensin-converting enzyme (ACE) inhibitors and low-dose triple therapy. The effects of ACE inhibitors are compared with those of low-dose triple therapy on systemic and glomerular pressure, proteinuria, and morphologic evidence of glomerular injury in rats with remnant kidneys. Both ACE inhibitors and triple therapy caused similar reductions in mean arterial pressure in rats with remnant kidneys; however, glomerular pressure declined only in the group treated with ACE inhibitors, by approximately 10 mm Hg. ACE inhibitor—induced reductions in systemic and glomerular pressure were associated with a reduction in proteinuria and morphologic evidence of glomerular injury. The data suggest that ACE inhibitors are superior to low-dose triple therapy in preventing glomerular injury in chronic renal disease. The data support the importance of increased glomerular pressure as a determinant of glomerular injury. ACE inhibitors may be more effective than are other agents, specifically because of their ability to reduce glomerular pressure. It should be noted, however, that significant reductions in glomerular pressure and injury may be achieved even with the triple-therapy regimen when significantly higher doses than those used in the current study are administered (see Figs. 6-5 and 6-6). A asterisk indicates P < 0.05 versus remnant. (Data from Anderson and coworkers [10].)
The Role of Hypertension in Progression of Chronic Renal Disease

### FIGURE 6-11
Effect of renal vein constriction on glomerular protein filtration. The role of angiotensin II (AII) in modulating macromolecular clearance across the glomerular capillary wall has been examined by Yoshioka and coworkers [11]. These authors used a model of renal vein constriction to increase glomerular pressure and markedly increase protein filtration. They calculated the volume flux through the small selective pores (effective pore radius, 40–50 Å) within the glomerular capillary wall and through the large nonselective pores. **A**, Volume fluxes under control conditions (hatched bars) and during renal vein constriction (open bars). Renal vein constriction causes an increase in filtration through large nonselective pores, which accounts for increased protein filtration. **B**, Effects of renal vein constriction were again examined, alone (open bars) and during administration of the AII receptor antagonist saralasin (hatched bars). Saralasin reduced volume flux through the large pores, indicating that increased endogenous AII action was largely responsible for proteinuria during renal vein constriction. (From Yoshioka and coworkers [11]; with permission.)

### FIGURE 6-12 (see Color Plate)
Local activation of the renin-angiotensin system and production of fibrogenic cytokines in experimental chronic renal disease. In situ reverse transcriptase was performed in rats with remnant kidneys to examine the level of gene expression for angiotensinogen and transforming growth factor-beta (TGF-beta). Rats still had not developed widespread morphologic evidence of glomerular injury 24 days after subtotal nephrectomy. **A**, At this point in time (arrows), staining for angiotensinogen messenger RNA (mRNA) was observed along the wall of a dilated capillary loop (CL) and in an adjacent cluster of mesangial cells. **B**, TGF-beta mRNA was present in an identical pattern in a contiguous section (arrows). **C** and **D**, Staining for angiotensinogen (panel C) and TGF-beta (panel D) is examined in kidneys from rats treated with the angiotensin receptor antagonist losartan from the time of nephrectomy. Administration of losartan markedly reduced expression of both factors in remnant kidneys. The findings are consistent with the hypothesis that endothelial injury is associated with increased angiotensinogen production and local activation of the renin-angiotensin system, leading to increased expression of TGF-beta and progressive glomerular fibrosis. (From Lee and coworkers [12]; with permission.)
Angiotensin II (AII) may be a proinflammatory molecule. The effect of AII on production of the chemokine RANTES was examined in cultured glomerular endothelial cells. **(A)** Effects of AII on secretion of RANTES by cultured glomerular endothelial cells. AII markedly stimulated RANTES secretion. Of note is that AII-induced RANTES secretion was prevented by incubation with the AT2 receptor antagonists SCP-42112A (CGP) or PD 1231777 (PD) but not by the AT1 receptor antagonist losartan (los). These findings suggest AT2 receptors mediate the increase in secretion of RANTES. **(B)** Results of a chemotactic assay for human monocytes. Migration of monocytes was assessed using a modified Boyden chamber. Migration of monocytes was stimulated by conditioned medium from glomerular endothelial cells that were exposed to AII. This effect was blocked by incubation of the medium with an anti-RANTES antibody but not by control serum. The anti-RANTES antibody alone was also without effect, as was AII in the absence of conditioned media. The findings are consistent with the hypothesis that AII promotes glomerular inflammation by binding to AT2 receptors, promoting RANTES secretion and infiltration of inflammatory monocytes and macrophages. fg—femtograms. (From Wolf and coworkers [13]; with permission.)
The Role of Hypertension in Progression of Chronic Renal Disease

**FIGURE 6-15**
Subclasses of angiotensin receptors. Another theoretical reason the actions of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor antagonists may differ. All of the AII receptor antagonists currently available for clinical use selectively block the AT1 receptor. This receptor appears to transduce most of the well-known effects of AII, including vasoconstriction, stimulation of cell growth, and secretion of aldosterone. Increasingly, however, potentially important actions of other angiotensin receptors are being discovered. For example, AT2 receptors may be involved in regulation of apoptosis and modulation of inflammation by way of secretion of RANTES (see Fig. 6-13) [13,15]. AT4 receptors bind other angiotensins preferentially and may promote endothelially mediated vasodilatation [16]. Activity of all pathways is reduced after administration of ACE inhibitors, whereas only AT1 receptor-mediated events are blocked by drugs currently available. Whether these differences will have important consequences for progression of renal disease is currently unknown.

**FIGURE 6-16**
Shown are results of studies comparing the effects of angiotensin II (AII) receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors on experimental renal injury. AII receptor antagonists were as effective as were ACE inhibitors in the remnant kidney model; streptozotocin-induced diabetic rats; the puromycin aminonucleoside model of progressive glomerular sclerosis, preventing interstitial fibrosis associated with obstructive uropathy; and an inherited model of glomerular sclerosis, the Munich-Wistar Furth/Ztm rat [17–21]. In contrast, AII receptor antagonists were somewhat less effective than were ACE inhibitors in several other animal models of chronic renal disease, including uninephrectomized spontaneously hypertensive rats, obese Zucker rats, and the passive Heymann nephritis model of membranous glomerulonephritis [22–24]. Clinical trials are necessary to determine whether these classes of drugs will be equally effective in preventing progressive renal disease in humans.

**FIGURE 6-17**
Three calcium channel blockers and their effects in experimental animals. The results of several studies examining the effects of three different dihydropyridine calcium channel blockers on hemodynamics and injury in the uninephrectomized spontaneously hypertensive rat model of progressive glomerular sclerosis are summarized. The three drugs produced graded declines in mean arterial pressure (MAP), with nifedipine causing the greatest and amlodipine the least reduction in systemic pressure. Micropuncture determinations of glomerular capillary hydraulic pressure (P_{GC}) revealed that only nifedipine and felodipine caused glomerular pressure to decline significantly. These drugs reduced both the protein excretion rate (PROT) and morphologic evidence of glomerular injury (SCLER). The data are consistent with the hypothesis that antihypertensive agents ameliorate renal damage by reducing glomerular pressure and that, for calcium channel blockers, significant reductions in P_{GC} occur only when drug administration causes a marked decline in systemic pressure. (From Dworkin [25,26]; with permission.)
**The Effect of Hypertension on Renal Disease**

### ROLE OF HYPERTENSION IN CHRONIC RENAL DISEASE

<table>
<thead>
<tr>
<th>Cause</th>
<th>Contributors to disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal artery stenosis or occlusion</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Atheroembolic disease</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>Tubulointerstitial disease (?)</td>
</tr>
<tr>
<td></td>
<td>Adult-onset polycystic kidney disease (?)</td>
</tr>
</tbody>
</table>

**FIGURE 6-18**

The impact of hypertension on the incidence of end-stage renal disease (ESRD) is vastly underestimated if one considers only those patients in whom systemic hypertension is the primary process resulting in loss of kidney function. The group of patients in whom ESRD is attributed to hypertension undoubtedly includes persons with renal disease of several causes. Some of these causes are occlusive disease of the main renal arteries as a result of atherosclerotic disease, atheroembolic disease of the kidneys, and hypertensive nephrosclerosis. The exact incidence of these processes within the hypertensive population with chronic renal disease is unknown. Even more commonly, poorly controlled systemic hypertension accelerates the rate of loss of kidney function in many patients in whom the primary cause of renal injury is another process altogether. This fact is particularly true in patients with glomerular diseases such as diabetic nephropathy and chronic glomerulonephritis [27,28]. Whether systemic hypertension also contributes to loss of kidney function in patients with tubulointerstitial or cystic disease of the kidney is less certain [29].

**FIGURE 6-19**

Hypertension prevalence corresponds with decreased glomerular filtration rate (GFR). Hypertension is common in glomerular, tubular, vascular, and interstitial renal disease and becomes increasingly prevalent as renal function declines. In almost 200 patients screened for the Modification of Diet in Renal Disease study, the prevalence of hypertension increased as the GFR decreased and hypertension was almost universal as the GFR approached 10 mL/min [29].

**FIGURE 6-20**

Multifactorial mechanisms for hypertension in clinical renal disease. An increased intravascular volume, owing to decreased renal excretion of sodium and water as the glomerular filtration rate declines, is probably the primary cause. Activation of sympathetic tone and involvement of the renin-angiotensin system, which is inappropriately stimulated in the setting of volume expansion, have been demonstrated in renal failure. Decreased activity of nitric oxide and other vasorelaxants and increased activity of endothelin and other endogenous vasoconstrictors also are probably contributory.
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**FIGURE 6-21**
Consistent relationship between hypertension and progressive renal disease. Analysis of the Modification of Diet in Renal Disease study, which involved patients with a heterogeneous miscellany of renal diagnoses, showed that the degree of elevation of the mean arterial blood pressure correlated with the decline in the glomerular filtration rate [30]. This finding has been confirmed in cohorts of patients with the same renal disease. In immunoglobulin A (IgA) nephropathy, eg, the presence of high blood pressure at diagnosis is a strong predictor for development of end-stage renal disease. In this study by Radford and coworkers [31] of 148 patients with IgA nephropathy, 69 patients with hypertension had a much higher risk of proceeding to renal failure than did the 79 patients who were normotensive.

**FIGURE 6-22**
Relationship between hypertension and renal failure. Johnson and Gabow [32] studied over one thousand patients with autosomal dominant polycystic kidney disease. These authors demonstrated that the time of renal survival was much shorter for patients with hypertension compared with patients whose blood pressure was normal (see Fig. 6-21). Renal survival was defined as the time period before the need for dialysis. HBP—high blood pressure; NBP—normal blood pressure.

**FIGURE 6-23**
Hypertension accelerates progression of renal failure in children and adults. For 2 years, Wingen and coworkers [33] followed almost 200 children and adolescents with renal disease, aged 2 to 18 years. Here, renal survival is defined as stability of the creatinine clearance rate. Compared with patients with systolic blood pressures lower than 120 mm Hg, those with systolic blood pressures higher than 120 mm Hg had more rapid development of renal death. Renal death was defined as a decrease in the creatinine clearance rate by 10 mL/min/1.73 m².
hypertension to later development of renal failure. In over 300,000 men screened for the Multiple Risk Factor Intervention Trial, Klag and coworkers [34] showed that a single blood pressure measurement was strongly correlated with the risk of end-stage renal disease (ESRD) later in life. Even men with high-normal blood pressures (defined as a systolic pressure of 130 to 139 mm Hg or a diastolic blood pressure of 85 to 89 mm Hg) were at a statistically significant greater risk for ESRD than were men with blood pressures under 120/80 mm Hg. This risk increases sequentially with the higher stage of hypertension. This study used definitions of hypertension discussed in the Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-5). Stage I hypertension is defined as a systolic pressure of 140 to 159 mm Hg and a diastolic pressure of 90 to 99 mm Hg. Stage II hypertension is defined as a systolic pressure of 160 to 179 mm Hg and a diastolic pressure of 100 to 109 mm Hg. Stage III hypertension is a systolic pressure of 180 to 209 mm Hg and a diastolic pressure of 110 to 119 mm Hg. Stage IV hypertension is a systolic pressure of 210 mm Hg or higher and a diastolic blood pressure of 120 mm Hg or greater. The highest relative risk for renal failure was among persons with stage III or IV hypertension.
The Role of Hypertension in Progression of Chronic Renal Disease

**FIGURE 6-27**
Two patient groups in the study of diet in renal disease. The Modification of Diet in Renal Disease (MDRD) study involved two patient groups. The group in which patients had moderate renal dysfunction (glomerular filtration rate [GFR] between 25 and 55 mL/min) was called Study 1. The other group, which included patients who had more severe renal dysfunction (with a GFR between 13 and 24 mL/min) was called Study 2. The effects of the lower blood pressure (BP) target on patients with proteinuria in Studies 1 and 2 are shown. The y-axis divides patients in Studies 1 and 2 into three groups, depending on urinary protein excretion. The x-axis represents the rate of GFR decline. In the subset of patients in the MDRD trial in both Studies 1 and 2 who had massive proteinuria (protein over 3 g/24 h), the lower blood pressure had an especially salutary effect: the decline in GFR was much slower [37].

**FIGURE 6-28**
Proteinuria as a marker for progressive renal disease. Nephrotic proteinuria may be a more important and independent marker for progression of renal disease than is hypertension. That is, patients in whom massive proteinuria and hypertension coexist have the worst renal prognosis. In a study of over 400 patients with renal insufficiency followed over 2 years, Locatelli and coworkers [38] found that patients who had both a mean blood pressure (BP) higher than 107 mm Hg and protein excretion of 1 to 3 g/24 h had the lowest rates of renal survival.

**FIGURE 6-29**
The effect of reduction of proteinuria on the stabilization of renal function. The observations that the potentially correctable factors of hypertension and proteinuria predict the decline of renal function lead to the hypothesis that antihypertensive agents in the angiotensin-converting enzyme (ACE) inhibitor class may be especially important in treatment of hypertension in renal disease. Praga and coworkers [39] investigated 46 patients with nondiabetic renal disease and massive proteinuria treated with the ACE inhibitor captopril. These authors found that proteinuria was decreased by about half. In patients with the greatest reduction in proteinuria (group A), a greater stabilization of renal function occurred over time when compared with those (group B) whose reduction in proteinuria was less.
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**FIGURE 6-30**
Large study of patients with diabetes mellitus and renal disease randomly assigned to captopril or placebo. Lewis and coworkers [40] have studied the use of the angiotensin-converting enzyme inhibitor captopril in patients with type I diabetes mellitus who have diabetic nephropathy and proteinuria. Captopril provides strong protection against progression of renal disease. Those patients treated with captopril had a significant decrease in proteinuria and a slower rate of disease progression, as defined by the time to doubling of the serum creatinine, as compared with patients randomized to placebo.

**FIGURE 6-31**
Study of patients with renal disease not associated with diabetes randomly assigned to ramipril or placebo. A study structured similarly to that in Figure 6-30 examined the use of the angiotensin-converting enzyme inhibitor ramipril in over 150 patients with nondiabetic renal disease [41]. The primary conclusion of the study is summarized. Blood pressure and proteinuria decreased more significantly in the patients treated with ramipril. This group had significantly lower rates of decline in glomerular filtration rate (GFR) over time. This effect was increasingly striking as the baseline level of proteinuria increased and was most pronounced in patients with a urinary protein excretion of over 7 g per 24 hours.

**FIGURE 6-32**
Meta-analysis of over 1500 patients with renal insufficiency. A recent meta-analysis examined randomized studies comparing an angiotensin-converting enzyme inhibitor (ACE) to other antihypertensive agents [42]. None of the individual studies showed that the relative risk for development of end-stage renal disease (ESRD) was statistically lower in patients treated with ACE inhibitors. The pooled relative risk, incorporating data from all the studies, however, was lower in the cohort groups treated with ACE inhibitors.
Calcium channel blockers. Calcium channel blockers are prescribed widely to patients with normal renal function and affect renal protein excretion variably. The general consensus is that the nondihydropyridine calcium channel blockers diltiazem and verapamil decrease proteinuria, whereas the dihydropyridine agents have minimal or minor effects on proteinuria.

The effect of calcium channel blockers on preservation of renal function. Most studies of angiotensin-converting enzyme (ACE) inhibitors versus other agents did not examine calcium channel blockers. In a paper by Zucchelli and coworkers [43], patients with nondiabetic renal diseases and hypertension initially were treated with adrenergic antagonists, diuretics, and vasodilators. These patients were then randomized to treatment with the dihydropyridine calcium entry antagonist nifedipine or to the ACE inhibitor enalapril. The rate of decline in renal function was most rapid in the pre-randomization phase in patients treated with conventional antihypertensive agents, mostly adrenergic antagonists. The rate of decline then slowed after randomization. No significant difference in rates of decline was seen in patients treated with nifedipine compared with those treated with captopril. (From Zucchelli and coworkers [43]; with permission.)

The effect of angiotensin-converting enzyme inhibitors and other antihypertensive agents on stabilization of renal function in non–insulin-dependent diabetes. Bakris and coworkers [52] studied patients with non-insulin-dependent diabetes mellitus, hypertension, proteinuria, and presumed diabetic nephropathy. These patients were randomized to treatment with the angiotensin-converting enzyme inhibitor lisinopril; the beta-blocker atenolol; or a nondihydropyridine calcium channel blocker (NDCCB), either verapamil or diltiazem. The primary conclusion of the study is summarized. The change in glomerular filtration rate as a function of time is depicted in groups of patients receiving lisinopril, calcium channel blockers, or atenolol. The creatinine clearance rate declined in all three groups. However, the slope of the decline was significantly greater in the group treated with atenolol and not significantly different between the groups treated with lisinopril and the calcium entry antagonist.
To determine the choice of antihypertensive agent to delay progression of chronic renal disease. Blacks are at much higher risk than are whites for progression of renal disease. In addition, a more aggressive antihypertensive program may be beneficial to blacks. In the Modification of Diet in Renal Disease study, a trend toward a more gradual decline in renal function in blacks randomized to the low mean blood pressure target was seen [36]. Blacks tend to have a better blood pressure response to administration of diuretics than do whites. In a large study of patients with normal renal function, blacks also responded well to calcium channel blockers [53]. The African-American Study of Kidney Disease and Hypertension (AASK), currently in progress, is examining the hypothesis that a lower-than-usual blood pressure goal will have a renal protective effect in renal disease with hypertension. A preliminary finding from the study is depicted. The study randomized blacks with hypertension to the beta-blocker atenolol, the dihydropyridine calcium channel blocker amlodipine, or the angiotensin-converting enzyme enalapril. In the initial 6 months of the study, the mean arterial blood pressure decreased most significantly in the short term with amlodipine [54]. GFR—glomerular filtration rate.

Management of Hypertension in Clinical Renal Disease

**FIGURE 6-37**

Treatment of patients with renal disease and high-normal or elevated blood pressure (BP). **A**, All patients should have a measurement of 24-hour protein excretion. If the protein excretion is over 1 g/24 h, an angiotensin-converting enzyme (ACE) inhibitor should be started. The goal of hypertension control in patients with azotemia who have massive proteinuria should be a blood pressure of 125/75 mm Hg or lower. It is unlikely that an ACE inhibitor alone will be able to decrease the blood pressure to this level before hyperkalemia or hemodynamically mediated acute renal failure intervenes. A diuretic and medications from other classes, such as a calcium channel blocker, should then be added.

**B**, When protein excretion is less than 1 g/24 h, the blood pressure should be lowered to at least 130/85 mm Hg. No conclusive evidence exists to support the use of one antihypertensive agent or class of agents over another. However, in patients at risk for progressive proteinuria (eg, diabetic patients with microalbuminuria), ACE inhibitors should be used. Given the importance of sodium retention in the hypertension in renal disease, a loop or thiazide diuretic is a reasonable initial treatment. An ACE inhibitor or calcium channel blocker should be added as a second-line agent.


