

Progression of Renal Disease: Renoprotective Specificity of Renin-Angiotensin System Blockade

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Recent guidelines for management of patients with chronic kidney disease recommend both lower optimal BP targets and agents that block the renin-angiotensin system (RAS) for specific additional BP-independent renoprotection. Although there are other compelling rationales to use RAS blockade in patients with chronic kidney disease, including its antihypertensive effectiveness and ability to counteract the adverse effects of diuretics, a critical review of the available scientific evidence suggests that the specificity of renoprotection that is provided by RAS blockade has been greatly overemphasized. Little evidence of truly BP-independent renoprotection is observed in experimental animal models when ambient BP is assessed adequately by chronic continuous BP radiotelemetry. Although the clinical trial evidence is somewhat stronger, nevertheless, even when interpreted favorably, the absolute magnitude of the BP-independent component of the renoprotection that is observed with RAS blockade is much smaller than what is due to its antihypertensive effects.

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The recognition that chronic kidney disease (CKD), regardless of cause, tends to progress to ESRD has led to extensive investigations of the underlying mechanisms and of therapeutic strategies to combat such progression. Although controversy persists about the relative pathogenetic importance of the individual mechanisms (*vide infra*), a general consensus has emerged regarding the therapeutic approach to slow the progression of both diabetic and nondiabetic nephropathies. All recent guidelines now recommend aggressive BP control to essentially normotensive levels (systolic BP approximately 125 to 130 mmHg), particularly in patients with proteinuric CKD (1,2). In addition, these guidelines recommend the initial use of agents that block the renin-angiotensin system (RAS) because they are believed to provide class-specific renoprotection that is independent of and additional to that achieved by reduced BP alone. Although widely accepted, the experimental and clinical evidence for this latter postulate is less definitive, and the magnitude of such protection likely is much smaller than claimed. Nevertheless, it needs to be emphasized that the issue is more of scientific than clinical practice relevance. Hypertension in patients with CKD usually is volume dependent and relatively difficult to control without adequate diuretic use (3,4). RAS blockers are very effective antihypertensives in aggressively diuresed patients and additionally counteract the tendency to potassium and magnesium wasting that occurs with such diuretic use. Therefore, the antihypertensive synergy of diuretics and RAS blockade and their antagonism of each other's adverse effects makes this combination an effective and logical initial regimen for patients with CKD (3,4).

Accordingly, the following discussion is addressed primarily to the scientific evidence of BP-independent renoprotection by RAS blockade and not its clinical usage.

Pathogenesis of CKD Progression

The continued progression of CKD, even when the original renal disease is quiescent, led to the concept that after a critical loss of functional renal mass, pathogenetic mechanisms for progression that were intrinsic to the loss of functional nephrons *per se* were initiated and eventually led to the loss of the remaining nephrons (5–7). This concept received strong support from observations in the rat remnant kidney model of five-sixths renal ablation (uninephrectomy + infarction of two thirds of the contralateral kidney). Although the remnant one sixth of renal tissue initially was normal histologically and functionally, the rats developed hypertension, increasing proteinuria, and progressive glomerulosclerosis (GS) over time (8). On the basis of micropuncture studies, it was hypothesized that the increased function of the normal remnant glomeruli that occurred as a part of the compensatory response was maladaptive and led to progressive GS (9). Subsequent investigations revealed that of the determinants of this hyperfiltration, it was the increases in glomerular pressure (P_{GC}) but not blood flow that were pathogenic (10,11). The increases in P_{GC} were ascribed to the greater dilation of the afferent as compared with the efferent arteriole. This relative efferent arteriolar vasoconstriction was attributed to the tonic vasoconstrictor effects of angiotensin II (AngII), because angiotensin-converting enzyme (ACE) inhibitors were shown to dilate the efferent arteriole and reduce P_{GC} (10,11). Therefore, AngII was believed to play a major role in the pathogenesis of the glomerular hypertension that was postulated to be intrinsic to the glomerular hemodynamic maladaptation. The hemodynamic hypothesis received additional support from observations in experimental diabetes

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that also showed hyperfiltration, increased P_{GC} , and an effectiveness of RAS blockade in reducing P_{GC} and GS (11,12).

Controversy soon developed as other investigators attributed a greater pathogenetic importance to increased and/or dysregulated growth factor expression that was associated with the structural glomerular hypertrophy after renal mass reduction (RMR) (13–16). The observation that substitution of a low-protein diet greatly reduced the hyperfiltration and hypertrophy in both RMR and diabetes models and also protected against GS was consistent with both “hemodynamic” or “hypertrophy” theories (5–7,9,11,13–16). However, it is of note that despite the differences in interpretations, the “hypertrophy” theory also ascribed a central pathogenetic role to AngII. Increased locally generated AngII was postulated to trigger multiple downstream pathways that led to proteinuria and increased expression and/or activity of profibrotic mediators such as TGF- β and plasminogen activator inhibitor-1, *etc.* (13–18). Such pathways have been demonstrated clearly in *in vitro* systems and evidence also obtained for their *in vivo* activation. Nevertheless, the interpretation that such activation *in vivo* is a primary event and not a response to glomerular injury *per se* from any cause, including barotrauma, is based on the specific BP-independent renoprotection that is claimed to be provided by RAS blockade. However, RAS blockade, even as monotherapy, is a very effective antihypertensive regimen in most rodent models in contrast to humans with CKD. Therefore, the primary *in vivo* evidence of the deleterious effects of AngII, whether glomerular hemodynamic or direct tissue damage promoting, primarily rests on the large number of studies that have shown greater renoprotection with RAS blockade than that achieved by equivalent BP reductions with other classes of antihypertensive agents (11,14–21). In addition, BP-independent renoprotection also has been inferred on the basis of the apparent dissociation between the antihypertensive and renoprotective dose-response relationships of RAS blockade in these models (16,18,22–24). For instance, renoprotection has been observed at dosages that seem not to lower BP. In like manner, an increase in renoprotection has been seen with dosages that seem to exceed the maximally antihypertensive dose. To address the critical limitations of such evidence, it first is useful to review briefly the pathophysiology of hypertensive renal damage and the reasons for the now widely recognized enhanced vulnerability of patients with CKD to even moderate hypertension.

Pathophysiology of Hypertensive Renal Damage

The extent to which a peripheral target organ, including the kidney, sustains damage from hypertension is expected to be proportional to the degree of its BP exposure. Therefore, it is not systemic BP *per se* that determines the severity of renal damage but the degree to which it is transmitted to the renal microvasculature. However, BP is fundamentally labile and exhibits spontaneous, rapid, and often large fluctuations when continuously monitored in the conscious state, and such time-dependent variability is exaggerated further in hypertensive states (3,4,25). Therefore, the conventional intermittent tail-cuff BP measurements that have been used to demonstrate the BP-independent renoprotective superiority of RAS blockade (11–13,15–24) are inherently inadequate to define the quantitative relationships between “BP load” and renal damage

(3,4,25,26), but as long as the normally efficient renal autoregulatory mechanisms are intact, as is the case in the vast majority of patients with essential hypertension (Figure 1), the transmission of BP elevations, episodic or sustained, to the renal microvasculature is expected to be largely prevented (reviewed in [3,4]). However, if BP elevations become so severe as to exceed the range of autoregulatory protection, then acute disruptive vascular and glomerular injury (malignant nephrosclerosis) is expected to ensue. By contrast, if renal autoregulation is impaired, as is observed after severe (approximately three-fourths) RMR (Figure 1), then the BP threshold for glomerular injury is expected to be greatly reduced with transmission of even modest and transient BP elevations to the glomerular capillaries (27–30). Moreover, under such conditions, P_{GC} is expected to exhibit considerable lability in parallel with the labile systemic pressures. Therefore, isolated P_{GC} measurements like isolated BP measurements may not provide an accurate index of chronic glomerular capillary pressure exposure. In addition, P_{GC} measurements may be compromised by surgery and anesthesia-induced activation of RAS and neurohormonal systems (3,4). In any event, the pattern of renal damage in such states is predominantly that of GS, and hypertensive vascular injury is not observed in the absence of hypertension that is severe enough to cause vascular damage.

The availability of BP radiotelemetry for direct and chronic continuous BP monitoring over weeks and months in conscious unrestrained animals now has made it possible to critically examine such quantitative relationships between ambient BP load, defined on the basis of several thousand BP measurements in each individual animal, and renal damage. As Figure 2 illustrates, the observed threshold relationships between such radiotelemetrically measured average systolic BP and renal damage in models of malignant nephrosclerosis and five-sixths renal ablation are precisely those that are predicted by the differences in the renal autoregulatory capacity in these models (Figure 1) (26,31,32). In this context, it is of interest that recent data suggest that it may be the systolic BP that serves as a trigger for the myogenic autoregulatory response (32), given the stronger correlations of renal damage that are observed with systolic BP, both experimentally and clinically (1,2,30–32). Figure 2 additionally shows that the large variability in the severity of GS that is observed in individual animals after five-sixths renal ablation can be accounted for largely by the differences in their ambient BP load. Accordingly, animals that do not develop significant hypertension after five-sixths RMR, as a result of either genetic differences or the method used for RMR (surgical excision instead of infarction), also are relatively resistant to the development of GS after five-sixths RMR (33–35). Moreover, these data suggest that glomerular hypertension that is severe enough to result in significant GS is not intrinsic to the compensatory adaptation response but rather represents the enhanced glomerular transmission of an elevated systemic BP. In this context, it is important to note that more modest reductions in functional renal mass, such as after uninephrectomy, do result in preglomerular vasodilation and increased fractional glomerular BP transmission (4,11,29). However, the increase is relatively small, and as renal autoregulatory capac-

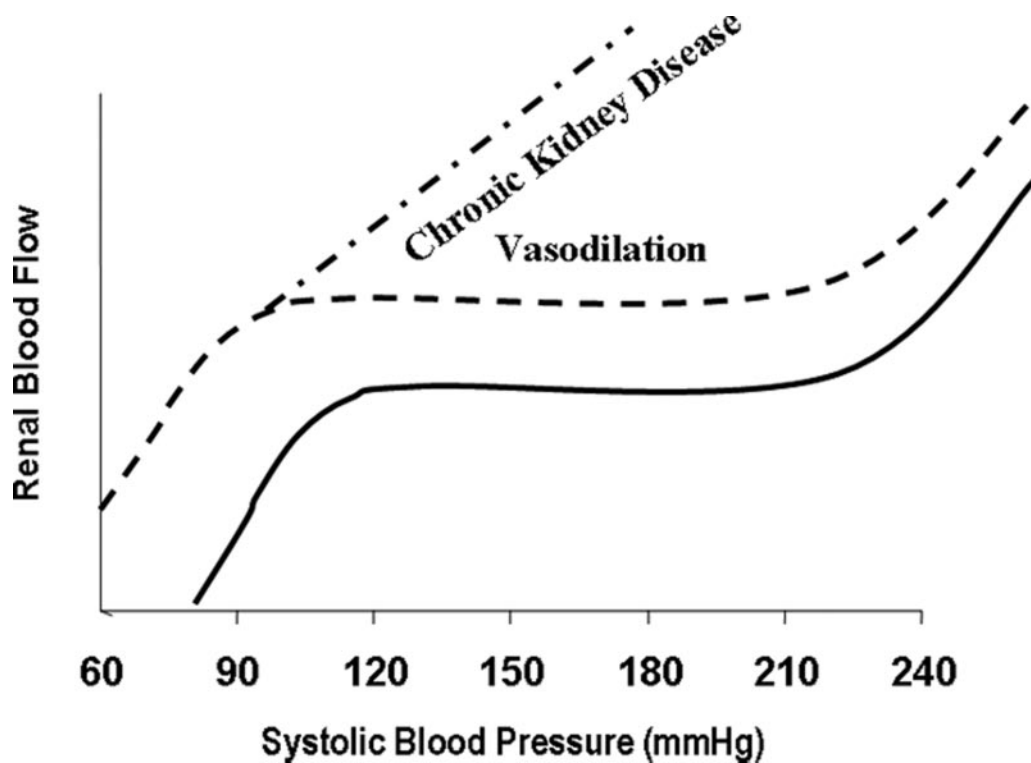


Figure 1. Renal autoregulatory patterns in normal rats with intact renal mass, with vasodilation but preserved autoregulation such as after uninephrectomy, and in the five-sixths renal ablation model of chronic kidney disease (CKD; vasodilation and impaired autoregulation).

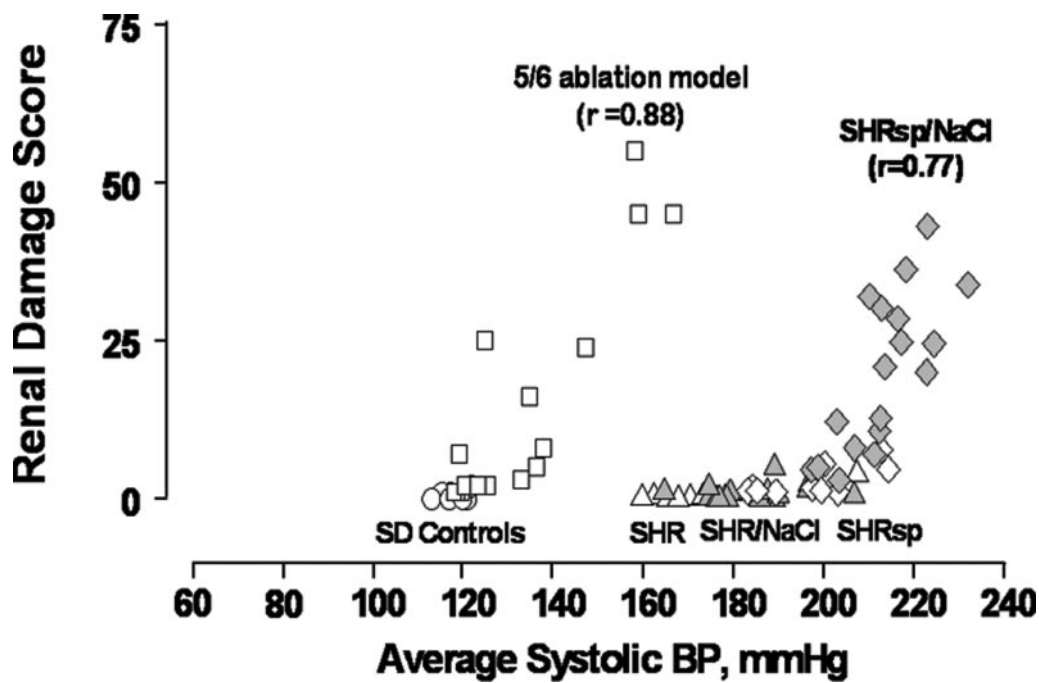


Figure 2. Relationship between renal injury and systolic BP in rat models with intact autoregulation (normotensive Sprague-Dawley [SAD; circles], spontaneously hypertensive rat [SHR; triangles], stroke-prone SHR [SHRsp; diamonds], SHR [gray triangles], and SHRsp [gray diamonds] placed on increased dietary salt intake) and in the five-sixths remnant kidney model (squares) with impaired autoregulation. The renal damage score represents a composite of vascular and glomerular damage scores in the SHRsp and percentage of glomerulosclerosis (GS) in the five-sixths ablation model. Reprinted with permission from references (25,31).

ity is preserved, only a modest increase in susceptibility to GS is observed. Therefore, the increase in susceptibility to enhanced BP transmission after functional loss of renal mass and/or diabetes is expected to be variable and depend on the degree of preglomerular vasodilation and autoregulatory impairment. Accordingly, differences in susceptibility to hypertensive injury, whether as a result of alterations in autoregulatory capacity (genetic or acquired) and/or intrinsic local tissue susceptibility (genetic or acquired), are predicted to be reflected in differences in the BP threshold or in the slope of the relationship between BP and GS (increase in renal damage/mmHg increase in BP). Consistent with such predictions, substitution of a low-protein diet in the five-sixths ablation model reduces preglomerular vasodilation, preserves renal autoregulation, and provides protection by increasing the BP threshold and flattening the slope of the relationship between BP and GS (27,36). Conversely, interventions that have a deleterious impact on renal autoregulatory capacity, such as calcium channel blockers (CCB), have the opposite effect on these quantitative relationships (3,4,37) (*vide infra*). It is of note, however, that such interpretations of the consequences of impaired renal autoregulation are valid only with a vasodilated preglomerular vasculature. With vasoconstriction, as during acute renal failure, impaired autoregulation may increase primarily the susceptibility to renal ischemia, when BP is reduced (4).

Antihypertensives, RAS Blockade, and Renoprotection in Experimental Models

The data shown in Figure 2 indicate that the renoprotection that is provided by an antihypertensive agent will depend not only on the achieved BP reductions but also on the existent threshold and slope relationships between BP and renal damage in a given individual animal or model. For instance, with intact autoregulation, even modest BP lowering to below the threshold for renal damage is expected to prevent malignant nephrosclerosis. By contrast, preventing GS in CKD models with impaired autoregulation would require that BP be reduced well into the normotensive range, although the steeper the slope, the greater would be the impact of any given BP reduction. These differences probably account for the much greater success that has been achieved in preventing malignant nephrosclerosis and hypertensive strokes than in preventing CKD progression. Such analysis also provides a rigorous method to examine the BP dependence of the protection that is provided by antihypertensive agents. BP-independent protection would be expected to raise the BP threshold or make the slope flatter (3,4,36). Conversely, if the protection is proportional to the achieved BP reductions without a change in the threshold or slope of the relationship, then the observed renoprotection can be attributed purely to its antihypertensive efficacy (37–42).

When such more accurate quantitative methods are used to examine the renoprotection that is provided by RAS blockade in either the malignant nephrosclerosis (Figure 3A) or the five-sixths renal ablation model (Figure 3B), such protection can be accounted for entirely by the achieved BP reductions without any evidence of significant BP-independent effects on the relationship between BP and renal injury (38–40). Moreover, the observed differences in

renoprotection with the varying doses of either the ACE inhibitors or the AT₁ receptor blockers (ARB) are found to parallel closely the radiotelemetrically measured differences in BP in the five-sixths ablation model (39). BP radiotelemetry also has shown that conventional tail-cuff BP measurements are not adequate to ensure that equivalent BP reductions have been achieved when antihypertensive regimens are compared. For instance, the much-cited renoprotective superiority of RAS blockade over the triple-therapy regimen of hydralazine, hydrochlorothiazide, and reserpine in the remnant kidney model (11,19–21) could be shown clearly by BP radiotelemetry to be due in fact to the antihypertensive superiority of RAS blockade that is not detected by the tail-cuff method (38). Similarly, differences in the renoprotection that are noted between the standard and the high-dose triple therapy regimens (23,43) also could be accounted for by differences in achieved BP (38).

The proportionality between glomeruloprotection and radiotelemetrically measured BP reductions that are seen with either RAS blockade or the triple-therapy regimens is consistent with the essential neutrality of these antihypertensive regimens with respect to their effects on renal autoregulation and glomerular BP transmission (3,4,37–39). This is in clear contrast to CCB, which have been shown to impair renal autoregulatory responses, in animals with both intact and reduced renal mass (37,44–46). These effects are not unexpected, given that the myogenic renal autoregulatory responses have been demonstrated to be dependent on pressure-induced depolarization and calcium entry through voltage-gated calcium channels (47–49). Of additional relevance, the effects of CCB, particularly the dihydropyridine CCB, on renal autoregulation seem to be additive to that of reduced renal mass. Dosages of dihydropyridine CCB that cause only an approximately 40 to 50% impairment in normal rats (47) completely abolish renal autoregulatory capacity in the remnant kidneys of rats with five-sixths ablation (37,44,45). Therefore, the likelihood and the magnitude of the adverse effects of CCB on renal autoregulation are likely to increase with increasing loss of functional of renal mass. In any event, as would be predicted, the additional impairment in renal autoregulation by CCB (enhancement of glomerular BP transmission) results in a further lowering of the BP threshold and an increase in the steepness of the slope of the relationship between BP and GS as also illustrated in Figure 3B (4,37,44,45). Greater GS is observed at any given BP elevation in CCB-treated as compared with untreated animals with five-sixths ablation, and GS is not prevented unless BP is reduced well into the normotensive range (Figure 3B). Consistent with such interpretations, CCB also abolish the low-protein diet-conferred protection in the five-sixths ablation model by reversing the beneficial effects of the low-protein diet on renal autoregulation (36). Similarly, CCB are ineffective in providing protection against GS that is observed in experimental diabetes or with aging, despite their antihypertensive efficacy (50,51). Nevertheless, it needs to be emphasized that the net effects of CCB in any given animal or model will depend on the balance between the beneficial effects of BP reduction and the deleterious effects on glomerular BP transmission. Therefore, when capillary beds are the primary site of hypertensive injury and

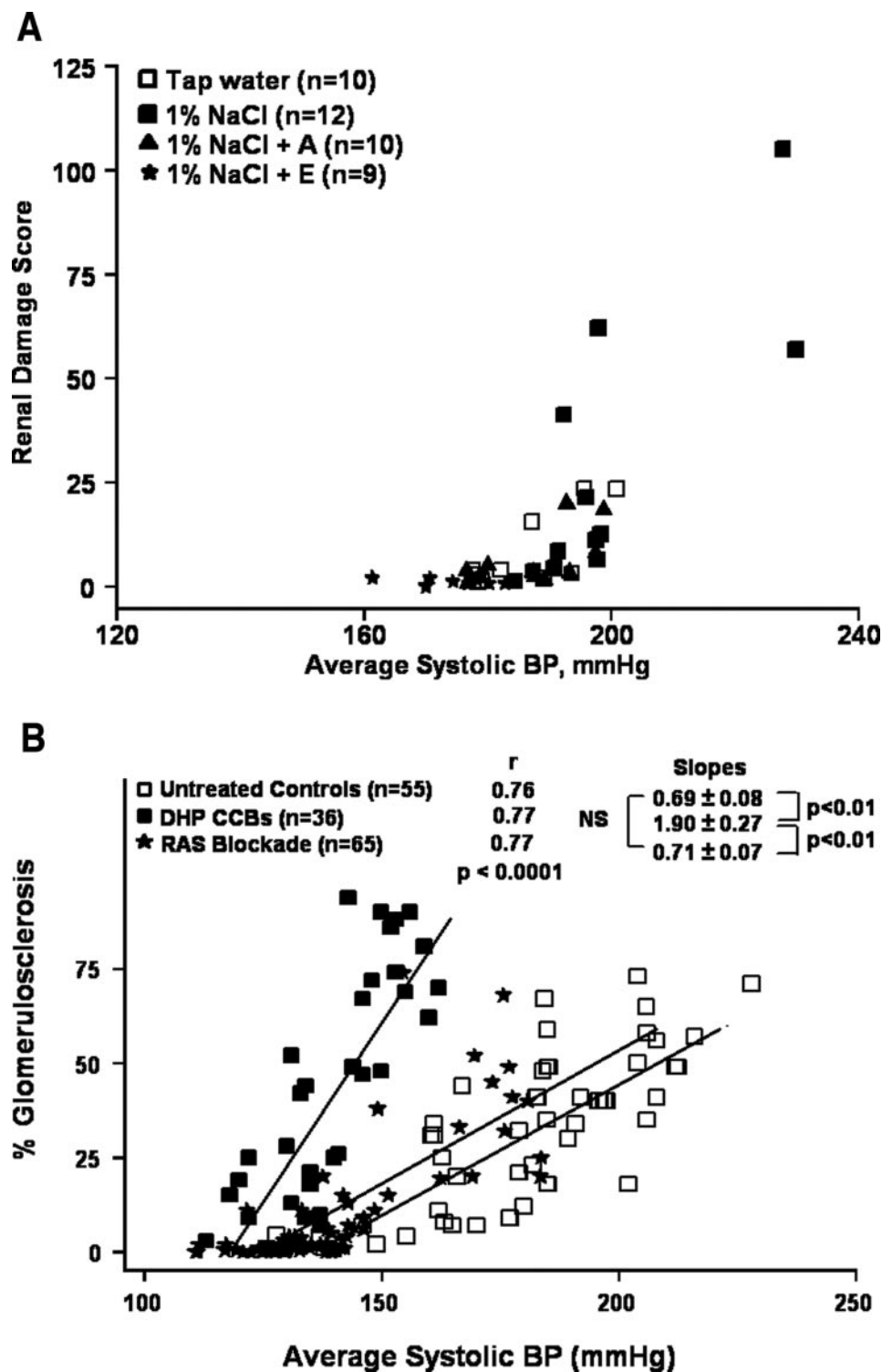


Figure 3. (A) BP dependence of the renoprotection by enalapril and Aldactone as illustrated by their effects on the relationship between average systolic BP during the final 3 wk and renal damage scores in the malignant nephrosclerosis model in the SHRsp, given either tap H₂O or 1% NaCl as drinking fluid for 8 wk before being killed. Linear regression analysis for SHRsp with an average systolic BP <200 mmHg (n = 25): r = 0.48, slope, 0.06 ± 0.02, P < 0.02; for SHRsp with an average systolic BP >200 mmHg (n = 16): r = 0.86, slope, 1.5 ± 0.24, P < 0.0001; and combined for all SHRsp (n = 41): r = 0.80, slope, 0.84 ± 0.01, P < 0.0001. Reprinted with permission from reference (40). (B) BP dependence of the renoprotection provided by the angiotensin-converting enzyme inhibitor benazepril and the AT₁ receptor blocker losartan in the five-sixths renal ablation model as illustrated by their effects on the relationship between average systolic BP and GS at the time of killing after approximately 7 wk. The doses of benazepril used were 25, 50, and 100 mg/L and of losartan were 50, 120, and 180 mg/L of drinking water (37). Also shown are data obtained in rats that had five-sixths ablation and were treated with the dihydropyridine calcium channel blockers (39,44,45).

autoregulation is already impaired, as in the five-sixths ablation model, the adverse effects are likely to dominate unless complete normotension is achieved. By contrast, when larger vascular segments are the primary target and/or the injury depends primarily on the severity of hypertension, as is true of malignant nephrosclerosis and hypertensive injury to other target organs, CCB are likely to be very effective because of their antihypertensive potency (1,4,52).

In this context, it also is of note that despite the widely emphasized potential of AngII and aldosterone to activate profibrosis pathways (13–17,53), little evidence of such activation is observed in normotensive states that are characterized by substantial increases in AngII and/or aldosterone (4). Examples include a low-salt diet, decreased central volume (cirrhosis, minimal-change disease), or the clipped kidney in the two kidney-1 clip model of hypertension (4). Similarly, administration of even large amounts of exogenous aldosterone to animals that are prevented from becoming hypertensive (maintained on a low-salt diet) fails to cause any target organ damage (4). Of relevance, some recent data using the AT₁ receptor knockout mice are even more definitive in regard to the general issue of RAS-mediated target organ injury. Earlier studies had noted that AT₁ receptor^{-/-} mice developed cardiac hypertrophy comparable to the wild-type mice in response to increases in pressure load, indicating that the presence of the AT₁ receptor was not necessary for hypertensive cardiac hypertrophy (54). More recent studies have shown that its presence is not sufficient even when exogenous AngII is administered in the absence of hypertension. In an elegant series of renal cross-transplantation experiments between AT₁ receptor^{-/-} and wild-type mice, followed by exogenous AngII infusion, Crowley *et al.* (55) showed that whereas the presence of AT₁ receptors in the kidney is necessary for the hypertensive response to AngII, the adverse cardiac hypertrophy responses are entirely dependent on the presence of hypertension. In the absence of hypertension (kidneys from AT₁^{-/-} mice transplanted into wild-type mice), no cardiac hypertrophy is observed despite the presence of both cardiac AT₁ receptors and high concentrations of exogenously infused AngII. Using a similarly elegant approach in a chimeric mouse preparation with both AT₁ receptor^{-/-} and AT₁^{+/+} cells in the same kidney, comparable phenotypic responses to exogenous AngII-induced hypertension were observed in both types of glomerular cells (56). Autosomal dominant pseudohypoaldosteronism type 1 in adults (PHA-1) and Liddle's syndrome may be considered similar parallel experiments of nature in humans (57,58). PHA-1 is associated with high renin and aldosterone levels but normotension and little evidence of target organ damage. By contrast, individuals with Liddle's syndrome (genetically increased activity of the epithelial sodium channel) and hypertension but suppressed renin and aldosterone levels exhibit substantial target organ damage (57,58). Collectively, such data showing that hypertension is both necessary and sufficient, whereas AngII is neither necessary nor sufficient in the pathogenesis of target organ damage, provide persuasive evidence against the BP-independent direct tissue damage-promoting effects of AngII *per se* and thereby undermine the theoretical basis of the class-specific BP-independent protection by RAS blockade.

Clinical Trial Evidence of BP-Independent Protection by RAS Blockade

It is important to note that concurrent with the investigations of CKD progression and renoprotection by RAS blockade in animal models, clinical data that showed an impressive slowing of the progression of diabetic nephropathy with conventional antihypertensives (non-RAS blockers) were being obtained (59,60). Although not randomized controlled trials, these studies provided valuable insights into the importance of BP control in retarding the progression of CKD. A wealth of clinical and epidemiologic evidence since has been accumulated in support of this management principle (1–4). It also is worth noting that the therapeutic superiority of RAS blockade over all other antihypertensive classes initially also was widely postulated for the protection of other cardiovascular target organs. However, extensive clinical trial data and meta-analyses, including data from the largest such trial in high-risk hypertensive patients, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in general have failed to substantiate such postulates (1,61–65). Instead, an overall consensus that emphasizes the primary importance of optimal BP control for most cardiovascular outcomes, with the possible exception of congestive heart failure, has emerged. In fact, on the basis of both cost considerations and efficacy data from ALLHAT, thiazide diuretics, despite the expected stimulation of RAS, are recommended as the initial antihypertensive agents of choice for most patients with hypertension, with other classes being added for specific comorbid conditions (1).

Although the major importance of BP as an independent risk factor also has been emphasized for renal disease progression by recent meta-analyses, RAS blockade is strongly recommended as the initial regimen of choice for renoprotection. This is based on the results of several clinical trials and meta-analyses that have, with a few notable exceptions, shown greater reductions in proteinuria as well as better outcomes for hard renal end points with RAS blockade as compared with other antihypertensive regimens in both diabetic and nondiabetic nephropathies (66–80). For instance, a meta-analysis of patient-level data by Jafar *et al.* (75,76) showed that ACE inhibition was associated with overall relative risk (RR) reductions of 30 to 40% for doubling of serum creatinine and/or ESRD in nondiabetic nephropathy, with the greater benefits being seen in patients with heavier proteinuria. Such data have been interpreted as indicating that the superior renoprotection that is seen with RAS blockade is mediated by BP-independent mechanisms. Support for such conclusions also has been inferred from the greater benefits that are obtained with dual RAS blockade compared with monotherapy with either ACE inhibitors or ARB. However, with the exception of the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Nondiabetic Renal Disease (COOPERATE) trial, which did include a small number of hard end points, most of the other smaller studies have shown improvements only in proteinuria and usually not without additional BP reductions (81–83). In any case, a critical review of the data indicates that the conclusions of BP independence are more ambiguous than has been claimed, and alternative

interpretations have not always been excluded. An illustration is provided by the first of these landmark trials in patients with type 1 diabetic nephropathy by the Collaborative Study Group, which showed a very impressive overall approximately 50% RR reduction for doubling of serum creatinine and/or ESRD in the ACE inhibitor as compared with the placebo group, with almost all of the end points and significant RR reductions (approximately 70%) being observed in patients with entry serum creatinine of ≥ 1.5 mg/dl (66). Although the placebo group did have significantly higher proteinuria at baseline (3.0 versus 2.5 g/24 h; $P < 0.02$), the RR reductions were not significantly altered by adjustment for this difference using proportional hazards regression analysis. However, as discussed in greater detail in a recent review (4), a subsequently published substudy indicates that a substantially greater percentage of the highest risk nephrotic patients, including 14 of the 16 black nephrotic patients, had been assigned to the placebo control group (66 of 202 versus 42 of 207 in the captopril group; $P < 0.002$ by χ^2) (84). It is likely that this disproportionate randomization of 24 more high-risk nephrotic patients largely accounted for the 18 more end points that were reached in the placebo control group. Similarly, ARB therapy was associated with RR reductions of 15 to 35% for hard renal end points in the recent Irbesartan in Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study in type 2 diabetic nephropathy (72,73). However, some insight into the absolute magnitude of the BP-independent renoprotection is provided by the slower decline in GFR by approximately 1 ml/min per yr in the patients who were treated with ARB, as compared with control antihypertensive regimens (approximately 5 versus approximately 6 ml/min per yr/1.73 m²), but given the GFR decline rates of 12 ml/min per yr that have been observed

historically in untreated diabetic nephropathy (59,60), BP reductions *per se* in the non-RAS blockade-treated groups reduced the rate of GFR decline by 6 ml/min per yr, indicating that >80% of the total absolute renoprotection that was provided by RAS blockade was due to its antihypertensive effects.

The class specificity and BP independence of even this additional renoprotection by ARB need to be interpreted in light of the fact that the achieved clinic BP in the RAS blockade versus control groups in these and many, although not all, other clinical trials in patients with diabetic and nondiabetic nephropathy, have tended to be lower by 2 to 5 mmHg. Therefore, the interpretations of BP independence also depend on the fact that statistical adjustments for differences in achieved clinic BP using Cox proportional hazards regression models have not substantially altered the RR reduction estimates in these studies, and even larger BP differences in some clinical trials have failed to further slow renal disease progression rate (71,74–77). For instance, in the aforementioned meta-analyses by Jafar *et al.* (75), an adjustment for the 4.5 mmHg lower systolic BP in the ACE inhibitor as compared with the control group resulted in a surprisingly small change in RR reduction from 0.64 to 0.67. However, it is possible that the proportional hazards models that were used may not adjust adequately for the very wide differences in the susceptibility to hypertensive glomerular injury that likely are present between individual patients. Such differences are illustrated in Figure 4 and, as discussed earlier, result from differences in BP transmission that are caused by genetic factors and/or the nature and the severity of renal disease (greater losses of functional renal mass are likely to be associated with greater preglomerular vasodilation and autoregulatory impairment). Because of these differences, the impact of any given BP difference is expected to vary markedly across individual patients, depending on the relationship be-

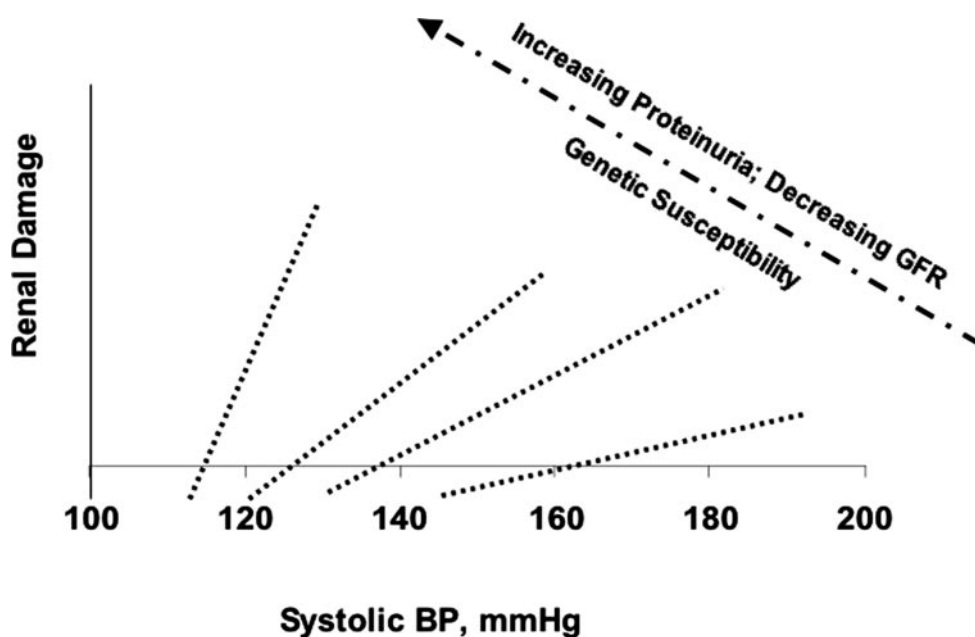


Figure 4. Potential differences in individual susceptibility to hypertensive renal damage. These differences are indicated by the differences in the BP threshold for renal (glomerular) damage and the slope of the relationships between BP and glomerular injury.

tween BP and renal damage. The lower the threshold and the steeper the slope, the greater would be the susceptibility to even small changes in BP in either direction. Moreover, the relationship between BP and renal damage may change during the observation period itself, at least in some patients, because of advancing disease. Such interpretations are consistent with the adverse impact of entry serum creatinine on the rate of disease progression or the greater RR reductions that generally have been observed in such patients (66,75,76).

Likewise, proteinuria has been shown to have a strong adverse impact on the progression of renal disease and the likelihood of adverse outcomes (68,70,75,76,84–86). Although the independent role that is postulated for proteinuria in the mediation of tubular injury and nephron loss remains controversial, there is considerable evidence that proteinuria also may serve as a biomarker for glomerular susceptibility to hypertensive injury (glomerular BP transmission). While a wide variety of heterogeneous mechanisms, including increased P_{GC} , can result in glomerular capillary wall injury and proteinuria, it is likely that the barrier properties of an altered (diseased) capillary wall, regardless of cause, are more sensitive to small changes in capillary pressure. Moreover, as elegantly shown by Kriz and colleagues (87–89), the altered glomerular capillaries may be more susceptible to mechanical (pressure-induced) injury. Given these considerations, it is not surprising that strong interactions have been observed among BP, proteinuria, and/or its response to therapy and the RR for renal disease progression (68,75,76). Conversely, with the higher BP thresholds and/or flatter slopes of the relationship between BP and renal damage, the impact of BP differences is expected to be smaller and the disease progression significantly slower. Indeed, such differences in disease cause and/or baseline characteristics such as lack of substantial proteinuria may be responsible for the slower decline in GFR (approximately 2 ml/min per 1.73 m² per yr) and the small number of hard renal end points that were reached in the African American Study of Kidney Disease and Hypertension (AASK) study (77). Such characteristics also may have contributed to the lack of significant differences that were observed between the patients who were assigned to the usual (mean arterial pressure 102 to 107 mmHg) *versus* the lower BP goal (mean arterial pressure 92 mmHg or less). It is possible that a longer follow-up may be necessary in such states to show differences as was noted for the Modification of Diet in Renal Disease (MDRD) study (90).

In this context of susceptibility to hypertensive glomerular injury, the effects of CCB, particularly the dihydropyridine CCB, are of considerable relevance. As illustrated in Figure 3B, these agents have the clear potential to enhance such susceptibility as a result of their dose-dependent deleterious effects on renal autoregulation that also have been observed in humans (91). Consistent with these adverse effects, therapy with CCB usually results in lesser reduction in proteinuria for a given BP lowering as compared with other antihypertensive agents, including RAS blockade in both diabetic and nondiabetic nephropathies (86,92–95). Accordingly, in the Blood-Pressure Control for Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN-2) study, additional BP reduc-

tions that were achieved with the dihydropyridine CCB felodipine in patients who had nondiabetic nephropathy and were being treated with ACE inhibitors failed to reduce proteinuria or slow progression further (96). Nevertheless, with few notable exceptions (61,66,72,77), the dihydropyridine CCB, because of their excellent antihypertensive potency, usually have been the agents used to achieve equivalent BP reductions in the control groups in these clinical trials. Although an approximately equal proportion of patients in the RAS blockade group often are reported also to have received the CCB, it is very likely that the control groups in general have received higher amounts of these agents so as to substitute for the antihypertensive activity of RAS blockade. In effect, a primarily RAS blockade-based antihypertensive regimen has been compared with a largely CCB-based antihypertensive regimen, and the results generally interpreted as indicating a BP-independent renoprotective superiority of RAS blockade. However, what often has been demonstrated in these studies is a failure to obtain protection with CCB that is proportional to the BP reductions, rather than an achievement of disproportionate renoprotection with RAS blockade. The stronger correlation of progression with BP that is observed in the RAS blockade as compared with the control groups in such studies is consistent with these interpretations (97). This relative inferiority of a CCB-based regimen is likely to be particularly true in patients with advanced proteinuric CKD, such as the participants in the recently reported trial from China (80). Both experimental and clinical data indicate that the balance between the beneficial effects of BP reductions and the adverse effects on BP transmission with CCB may vary depending on the nature and the severity of the underlying renal disease (4,92–94), and this variability may account for their clinically inconsistent adverse effects. For instance, the amlodipine group developed a significantly greater number of hard renal end points as compared with both the ACE inhibitor and the β blocker groups in the AASK trial (77). Similarly, in the IDNT trial, although both the amlodipine and the placebo groups exhibited worse outcomes than the irbesartan group, only the amlodipine group achieved equivalent BP control to the irbesartan group, whereas the BP in the placebo group was significantly higher than that in both of the other groups (72). However, an adverse impact of dihydropyridine CCB on renal outcomes was not observed in the Appropriate Blood Pressure Control in Diabetes (ABCD) and the ALLHAT trials (61,71,74).

Finally, the limitations of BP measurements on which the conclusions of BP-independent therapeutic superiority of RAS blockade are based need to be considered in view of the experimental animal data that are obtained with radiotelemetry. Given the fundamental lability of BP, which is exaggerated further in treated and untreated hypertensive individuals, more caution needs to be exercised in inferring BP independence solely on the basis of isolated and relatively infrequently measured clinic pressures, which additionally often are not controlled for the time of day and/or relationship to drug dosing (3,4,60,97). Such effects may be particularly important in patients with diabetes and/or hypertension, who often do not exhibit the normal nocturnal BP dip (60). In addition, there is evidence of a potential differential

impact of therapeutic agents on central *versus* peripheral pressures (98). The Heart Outcomes Prevention Evaluation (HOPE) sub-study data are relevant to such issues (99). Reductions of 3/2 mmHg in clinic pressures in a subset of 38 ramipril-treated patients, similar to that in the parent study, translated into a reduction of 10/4 mmHg in the average 24-h ambulatory BP (ABP) in the same patients because of a large decrease in nocturnal BP of 17/8 mmHg (ramipril was dosed in the evening). It is not surprising, therefore, that significantly better correlations are observed between 24-h ABP measurements than clinic pressures with markers of cardiovascular target organ damage, including proteinuria (3,4,60), although even intermittent 24-h ABP monitoring may not provide as complete an assessment of the total chronic BP burden as is possible with radiotelemetry in experimental models. In this context, it also is of note that in the very large ALLHAT trial, in which the impact of such potential BP measurement errors would be minimized, a *post hoc* analysis of prespecified renal outcomes did not show better outcomes with an ACE inhibitor over a chlorthalidone-based antihypertensive regimen in patients either with or without diabetes (100). Of interest, when the results of the ALLHAT were included, a recent comprehensive meta-analysis also failed to reveal clear and unambiguous evidence of the renoprotective superiority of RAS blockade (101). Although such evidence is more limited in comparison with the aforementioned renal trials that were conducted specifically in patients with carefully defined preexistent nephropathy and quantified proteinuria, the absolute number of ESRD events in the ALLHAT exceeded that in other trials, including the IDNT and RENAAL trials. Moreover, although the criticisms regarding the somewhat artificial combinations that were necessitated by the study design, such as the exclusion of diuretics from the ACE inhibitor-based regimen, are valid from the clinical practice point of view, they do not undermine the scientific validity of the interpretations of the lack of a broad and general superiority of RAS blockade in preventing ESRD. After all, diuretics activate the RAS, and although they enhance the antihypertensive efficacy of RAS blockade, they are not *per se* expected to improve its BP-independent protective effects.

Collectively, these considerations indicate that the scientific evidence for substantial BP-independent and specific renoprotection by RAS blockade is less compelling than has been claimed. Very little evidence is available in experimental animal models to support either the BP-independent deleterious effects of AngII or of the BP-independent protection by RAS blockade when the 24-h BP load has been measured accurately and continuously. Although the clinical trial evidence is somewhat stronger at least in some subsets of patients, alternative interpretations, at least as of now, have not been excluded definitively. Nevertheless, the availability of agents that block the RAS has represented a great advance in antihypertensive therapy and provided a very effective therapeutic modality to help achieve the optimal BP goals, which presently represents quantitatively the most effective clinically available strategy to retard CKD progression. As alluded to earlier, there are reasons other than the putative renoprotective superiority to use RAS blockade in the initial regimen for patients with CKD. These include their ability to counteract the adverse effects of diuretics, which almost always are required in patients with CKD,

and their great antihypertensive effectiveness in such aggressively diuresed patients. Given that CKD progression, although slower, still continues in most patients even with antihypertensive regimens that include RAS blockade, there is a clear and urgent need to develop truly BP-independent renoprotective interventions for patients with CKD.

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Griffin and Bidani review the specificity of renin-angiotensin system blockade (RAS) for renal disease progression. Gender differences could play a role in the patient response to RAS blockade, according to Miller *et al.* in this month's *JASN* (pp. 2555–2561).