Aldosterone Antagonism in Chronic Kidney Disease

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Mini-Review

Aldosterone antagonism in chronic kidney disease (CKD). By reducing blood pressure (BP) and disproportionately decreasing intraglomerular pressure, this class of drugs also reduces proteinuria and slows progression of CKD (1,2). Given the high prevalence of cardiovascular disease in this population, it is noteworthy that ACE inhibitors also decrease the incidence of stroke, myocardial infarction (MI), and cardiovascular mortality in patients who are at high cardiovascular risk (3). More recently, data reporting similar benefits of angiotensin receptor blockers (ARB) support their use in the treatment of CKD as well, especially in individuals with type 2 diabetes (4). Furthermore, one sizable study suggested that the combination of an ACE inhibitor and ARB may be more effective than either agent alone (5). Parving and colleagues (6) called attention to the effects of high-dose ARB therapy, up to three times the recommended dose, as an additional means of effectively interrupting the renin-angiotensin-aldosterone system (RAAS). By logical extension, further blockade of the RAAS by direct antagonism of aldosterone may also prove beneficial. Indeed, aldosterone seems to be a potent effector of renal injury (7–9). In the rare cases of primary aldosteronism and its functional analogue, the even more rare Liddle’s syndrome, the observed renal injury probably is independent of the more proximal elements of the RAAS (10,11).

Animal models provide an expeditious tool for assessing pathophysiologic change and the efficacy of intervention. The classic model of primary aldosteronism, the mineralocorticoid–nephrectomy–high-salt model of hypertension, develops systemic and glomerular capillary hypertension and sustains renal damage (12). In the remnant kidney model of CKD, ACE inhibitors and ARB attenuate renal injury (13). However, this protection, which is associated with suppression of aldosterone secretion, is abrogated by exogenous aldosterone infusion with return of hypertension, proteinuria, and nephrosclerosis. These results support a direct role for the mineralocorticoid in promoting renal disease. In the stroke-prone spontaneously hypertensive rat, the mineralocorticoid receptor blocker spironolactone reduces proteinuria and nephrosclerosis independent of any effect on BP or volume status (14,15). Other animal models, including radiation nephritis (16), cyclosporine toxicity (17), diabetes (18), obstruction (19), and other models of hypertension (20,21), implicate aldosterone in the pathogenesis of progressive kidney disease. Most of these studies of experimental disease implicate aldosterone by virtue of the benefits of the mineralocorticoid receptor antagonists spironolactone and eplerenone. Human studies are of limited scope and also have focused on the effects of these receptor blockers but tend to corroborate the major role of aldosterone in renal injury.

Mechanisms of Aldosterone Action
Blood Pressure and Sodium and Potassium Balance

Sodium and potassium balance are strongly influenced by aldosterone. Aldosterone controls sodium reabsorption in the distal nephron through regulation of the epithelial sodium channel (ENaC). In turn, aldosterone acts as a key determinant of volume status and thereby BP. Patients with primary aldosteronism are characterized by volume expansion and hypertension. A similar phenotype is observed in patients with Liddle’s syndrome, in whom mutations in ENaC cause its constitutive activity. Even in people with primary hypertension, aldosterone often seems to play a role. Indeed, subjects in the Framingham Offspring cohort who had higher serum aldosterone levels but within the normal range were at increased risk for developing hypertension (22).

Aldosterone directly and indirectly influences ENaC expression (Figure 1). In the classic model of steroid hormone action, aldosterone binds to a cytoplasmic mineralocorticoid receptor. This complex translocates to the nucleus, which results in increased transcription of target genes such as ENaC subunits (23). Another genomic target of aldosterone is serum- and glucocorticoid-regulated kinase 1 (Sgk1). This enzyme is under transcriptional control by aldosterone (24,25) and is responsible for phosphorylating and thereby inhibiting Nedd4-2, a regulatory protein that promotes ENaC degradation (26,27). Therefore, aldosterone regulates sodium reabsorption by controlling ENaC trafficking as well.

Increases in plasma K⁺ increase aldosterone secretion (28). The mineralocorticoid also has been shown to increase expression of the renal outer medullary potassium channel, which enhances K⁺ secretion (29). This effect is synergistic with sodium reabsorption; the latter allows for an increase in luminal negativity in the renal tubules and thereby facilitates K⁺ secretion. Aldosterone also acts through Sgk1 to amplify this effect. Sgk1 seems to work in concert with the Na⁺/H⁺ exchange.
regulating factor to increase renal outer medullary potassium channel activity (30). This finding is supported by the sgk1 knockout mouse, which has impaired renal K\(^+\) clearance (31). In addition to renal epithelia, aldosterone exerts control over ENaC expressed in intestinal, salivary, and sweat epithelial tissue, where it also participates in sodium and potassium homeostasis (32).

A number of other nonhemodynamic pathways of aldosterone action have begun to be explored and are discussed next. However, several observations give predominance to aldosterone’s ability to raise arterial and, probably, glomerular pressure as a major mode of damage to the kidney and the organism as a whole. The requirement for concomitant high salt intake in most animal models of injury and the absence of tissue injury in forms of secondary aldosteronism without hypertension both argue for a key role of hypertension (33,34). Also, the appearance of kidney failure in a person with Liddle’s syndrome, in whom aldosterone levels are suppressed, suggests that classic salt-dependent hypertension is very important, whatever other aldosterone-dependent pathways may be at work (10).

### Vasculature

Extra-adrenal tissue may synthesize aldosterone. The vasculature, the kidney, and the heart have been reported as synthetic sites (35–37). However, none of these potential sources contributes significantly to plasma levels, because the concentration of aldosterone falls essentially to zero with adrenalectomy. Furthermore, recent data have questioned the notion of cardiac synthesis of aldosterone (38,39). However, given the presence of mineralocorticoid receptors in many nonepithelial tissues, including the vasculature and the heart, these nontraditional targets indeed may respond to aldosterone regardless of whether they produce it (40).

Beyond the well-documented effect of aldosterone to expand extracellular volume with the net result of hypertension, direct vascular actions of aldosterone have been proposed. Systemic vascular resistance has been reported to change modestly in response to acute aldosterone infusion in normal humans (41). However, the magnitude of change was small and reversed within 10 min, making the results difficult to interpret. Indeed, other studies of rapid changes in vascular tone in humans are inconsistent (42–44).
Rabbit glomerular afferent and efferent arterioles constrict in response to aldosterone *ex vivo* (45). In this model, increased calcium flux plays an important role, and calcium channel blockade can inhibit the effect. Aldosterone can induce a rapid rise in free intracellular calcium in single endothelial cells, although this effect is not diminished by spironolactone (46). However, aldosterone also can counteract rabbit glomerular afferent arteriole vasoconstriction *ex vivo* within minutes through a nitric oxide–dependent pathway (47,48). It is interesting that spironolactone blunts the attenuation of vasoconstriction but not its augmentation, suggesting divergent pathways early in the signaling cascade (45,47). Therefore, although aldosterone may have a physiologic role in modulating vascular tone, the data at present are conflicting. Scott and colleagues (48) suggested that when endothelial damage removes its nitric oxide–dependent counterregulation, vasoconstriction may predominate.

Aldosterone also induces endothelial swelling in cultured monolayers, which can be blocked by either spironolactone or amiloride (49,50). As a result, endothelial cell stiffness increases as well as basolateral deposition of a proteinaceous substance, highlighting a potential role for the mineralocorticoid in vascular endothelial dysfunction (51).

### Fibrosis: TGF-β and Plasminogen Activator Inhibitor-1

TGF-β has been implicated in the pathogenesis of many progressive renal diseases and their models (52,53). Nephrosclerosis, a common final pathway that is accelerated by TGF-β, is caused by an imbalance between fibrotic and fibrinolytic activities. Brown et al. (54,55) demonstrated that this balance is influenced by the RAAS through plasminogen activator inhibitor-1 (PAI-1), which is profibrotic. TGF-β upregulates PAI-1 gene expression in endothelial cells (56,57), and PAI-1 activation is induced synergistically by aldosterone and angiotensin II (AngII), although not by aldosterone alone (58).

In one study of hypertensive men, spironolactone abolished the relationship between aldosterone and PAI-1 levels (59). In normotensive rats, aldosterone infusion increased urinary TGF-β (60) without a significant increase in BP. This effect was not altered by amiloride but was attenuated by spironolactone. These data suggest that aldosterone may upregulate PAI-1 *via* the mineralocorticoid receptor and TGF-β signaling. However, TGF-β also may play a physiologic role, because it is present in normal tissue as well. *In vitro*, TGF-β counters the Na⁺ transport that is induced by exposure to aldosterone (61). *In vivo*, TGF-β synthesis and excretion increase in response to salt loading (62). Therefore, TGF-β may act in a regulatory manner either to enhance sodium excretion directly or to antagonize aldosterone.

### Mitogen-Activated Protein Kinase and Oxidative Stress

Terada et al. (63) examined the role of aldosterone in mesangial cell proliferation and found that rat mesangial cells and glomeruli also express the mineralocorticoid receptor. Exogenous aldosterone stimulated mesangial proliferation through mitogen-activated protein kinase (MAPK) activation and by inducing the promoter activity of cyclin D1 and cyclin A. Concomitant administration of spironolactone blunted these effects.

Aldosterone also has been implicated as a stimulus for reactive oxygen species production *via* upregulation of NADPH oxidase (64). Nishiyama et al. (65) showed that rats that received an infusion of aldosterone had increased NADPH subunit expression, markers of oxidative stress, and MAPK activity. Concomitant eplerenone or tempol administration blunted oxidative stress and MAPK activity. Tempol, in contrast to eplerenone, did not normalize the expression of two of three NADPH subunits analyzed. In further studies, the same group extended this general finding to cultured mesangial cells, suggesting that the hemodynamic actions of aldosterone are not required (66). Aldosterone also may contribute to oxidation through its stimulation of citrate synthase, a central enzyme in the Krebs cycle. Ullian et al. (67) showed that this effect of aldosterone occurs even in the glomerulus. Therefore, increased oxidative stress may lead to MAPK pathway activation as a result of mineralocorticoid receptor signaling.

### Nongenomic Actions

Aldosterone can change several markers of cellular signaling within minutes (Figure 1). These effects cannot be explained by its classic genomic actions. Indeed, the effects occur well before any increase in protein expression and are not affected by inhibitors of transcription or protein synthesis (68,69). Therefore, these are so-called “nongenomic” actions. In addition to sodium flux, other rapid or early events such as calcium flux (70), changes in intracellular pH (71), and protein kinase C activity (72) have been demonstrated in response to aldosterone. There are conflicting data as to whether these effects are mediated by the classic mineralocorticoid receptor or an independent pathway, because some studies show inhibition by mineralocorticoid antagonists, whereas others do not (73). Indeed, many of the above-mentioned actions of aldosterone, especially the reported direct vascular actions, are temporally “nongenomic” or at least partially so. The pleiotropic effects of aldosterone most likely occur through the “classic” mineralocorticoid receptor and gene transcription in parallel with other distinct “rapid” signaling pathways. However, distinct physiologic roles for the nongenomic pathway have yet to be assigned definitively.

### Pharmacology

Spironolactone and eplerenone are steroid analogues with structural similarity to aldosterone and thereby function as competitive antagonists. Compared with spironolactone, eplerenone is equally potent but more specific for the mineralocorticoid receptor by virtue of a 9,11-epoxy moiety that decreases its binding to androgen and progesterone receptors (74). Both drugs are metabolized hepatically, although spironolactone has multiple active metabolites, whereas eplerenone has none (75). This results in a shorter effective half-life and therefore quicker time to peak response for eplerenone.

As described above, these molecules are able to antagonize some but not all of aldosterone’s actions. This suggests either that aldosterone can signal through a mineralocorticoid re-
ceceptor–distinct pathway or that differential mineralocorticoid receptor localization somehow favors access to aldosterone but not spironolactone or eplerenone. As an example of the latter, an open-ring water-soluble aldosterone antagonist, RU28318, completely abrogated aldosterone’s influence on Na⁺/H⁺ exchanger activity, whereas spironolactone had no effect in a human vascular preparation \textit{ex vivo} (76).

**Stimuli**

Aldosterone levels have been measured in at least one cross-sectional study of people with varying GFR. The levels tend to rise with decreasing GFR, similar to the case in the remnant kidney model in the rat (77). The stimuli to excess aldosterone secretion are probably several. As a primary regulator of volume status, aldosterone secretion is significantly upregulated by extracellular volume depletion and conversely downregulated by volume expansion, largely through the actions of AngII. As a survival mechanism, such a response would have been crucial during times of sodium scarcity. However, as posited by Vasan et al. (22), downregulation presumably would not have been as important a survival advantage. The net effect of this imperfect feedback may be that mildly elevated aldosterone levels may not represent much of a short-term liability with hypertension and tissue damaged expressed only over years. In any case, renin and presumably AngII levels tend to remain relatively constant in cross-sectional studies of people with a range of GFR (77,78). That is, despite the rising prevalence of hypertension with worsening GFR, renin generally is not suppressed. In animal models of reduced renal mass, uninephrectomy and renal infarction lead to greater plasma aldosterone levels, hypertension, proteinuria, and glomerulosclerosis when compared with equivalent surgical reduction (79). In the infarcted kidney, the peri-infarct region has increased renin production (80). As a human correlate, it is conceivable that “micro-infarcts” or regional ischemia of the renal parenchyma similarly leads to increased or at least unsuppressed renin and provides tonic support for aldosterone production.

Potassium homeostasis seems to be an additional important cause for aldosterone secretion in CKD as an adaptation to fixed potassium intake in the setting of decreased GFR (81). Indeed, in the remnant kidney model, increased dietary potassium leads to increased urinary aldosterone secretion and hypertension (81). In fact, patients with “hyporeninemic hypoaldosteronism” are characterized by hyperkalemia and low plasma aldosterone and typically have diabetic or interstitial renal disease. Given the prevalence of CKD with comorbid diabetes, it is possible that analysis of patients with CKD will not reveal an association between progression of renal disease and aldosterone levels unless those patients with hyporeninemic hypoaldosteronism are considered.

**Human Studies**

Although aldosterone antagonists have shown promising results in a number of animal models, large long-term studies of their use in people with renal disease are lacking. However, several short-term investigations suggested that spironolactone or eplerenone may prove to be useful and safe agents in the treatment of CKD and ESRD. At present, the beneficial effects have been limited to short-term surrogate end points, such as reductions in proteinuria and BP (Table 1).

**Aldosterone Antagonists in CKD**

In one of the first preliminary reports, Chrysostomou and Becker (82) found a 54% decrease in proteinuria from baseline after 4 wk by adding spironolactone 25 mg/d in eight patients with persistent overt proteinuria (>1 g/d). The aldosterone receptor blocker was added to the previous long-term ACE inhibitor therapy. Some of this effect may have been secondary to an estimated 10-mmHg decrease in mean BP. Also, the study was small but did not include a control group. The patients were only compared with their baseline. The same investigators subsequently carried out a double-blind, randomized, controlled trial with 41 patients who had persistent proteinuria (>1.5 g/d) and were assigned to ACE inhibitor; ACE inhibitor and ARB; ACE inhibitor and spironolactone; or ACE inhibitor, ARB, and spironolactone (83). Confirming earlier results, the ACE inhibitor and spironolactone combination led to a 41% greater reduction in proteinuria compared with ACE inhibitor alone and a 26% greater reduction compared with ACE inhibitor and ARB after 3 mo of treatment. Triple therapy was not significantly more effective than an ACE inhibitor and spironolactone. These differences persisted through 6 mo of follow-up. These outcomes were independent of BP, which did not differ within or between groups through the first 6 mo. In both studies, >60% of patients had diabetic nephropathy.

An issue left largely unresolved by these results, as well as most others reviewed below, is whether the benefit of spironolactone lies in its diuretic effect or in its ability to modulate the non–volume-mediated effects of aldosterone. Indeed, other studies have shown that addition of a thiazide diuretic to ACE inhibitor or ARB therapy also can reduce proteinuria further (84,85). Although one randomized trial of patients with type 2 diabetes showed that spironolactone still could decrease proteinuria when added to diuretics and a maximum dose of ACE inhibitor or ARB (86), whether a diuretic such as amiloride that is targeted at ENaC could be as efficacious as the mineralocorticoid receptor blockers has not been studied in-depth. If action outside of ENaC activity were provoked by aldosterone, then one would predict that the receptor blockers would be more widely effective than amiloride. An animal study of aldosterone’s ability to stimulate TGF-β did show that this effect of aldosterone could be blocked by spironolactone but not amiloride (60). Furthermore, a randomized, controlled trial of hypertensive patients who already were taking a diuretic reported that spironolactone reduced endothelin-1 levels, whereas amiloride did not, although amiloride treatment led to a greater reduction in BP (87). Another study showed that amiloride, in a similar manner to eplerenone, was able to inhibit the nongenomic vasoconstrictor effect of aldosterone as well as its effect on Na⁺/H⁺ exchanger activity (88). Taken together, these findings suggest that the actions of amiloride and aldosterone antagonists only partially overlap, although whether this has any clinical significance remains to be determined.
Another issue that is worth further consideration is the role of aldosterone antagonism with concomitant ACE inhibition or ARB therapy. Whereas a number of the animal models have responded to therapy with spironolactone alone, the remnant kidney model had very little response (13). In any case, most of the current human studies have compared the combination of spironolactone or eplerenone and ACE inhibition with ACE inhibition alone. Because ACE inhibitors and ARB are standards of care, this likely will remain a general design for any future studies. However, this combined approach has appeal even beyond the ethical exigencies. Spironolactone alone can induce a secondary activation of renin and presumably AngII, as do other diuretics (89,90). This reaction may exaggerate the direct deleterious actions of AngII. The majority of studies reviewed here included ACE inhibitor or ARB therapy either at prespecified doses that are equivalent to the maximum conventional dose or at doses that are titrated to a target BP. Although “ultra-high” doses of ACE inhibitors or ARB were not used, aldosterone antagonism theoretically would not be superfluous as an adjunct to such therapy either. For example, even in low renin states, hyperkalemia stimulates aldosterone secretion. Furthermore, in the stroke-prone spontaneously hypertensive rat, volume expansion leads to decreased plasma renin levels but increased vascular aldosterone synthesis (35). Presumably, aldosterone antagonism would be beneficial in these conditions regardless of the degree of ACE inhibition or angiotensin receptor blockade.

Sato et al. (91) examined the effects of adding spironolactone 25 mg/d to an ACE inhibitor in 13 patients with type 2 diabetes and persistent albuminuria, creatinine clearances >60 ml/min, and evidence of what they termed “aldosterone escape.” These patients had been on an ACE inhibitor for 40 wk before spironolactone was added, and “aldosterone escape” was defined as an increase in plasma aldosterone concentration comparing pre- and post-ACE inhibitor treatment levels. After a 24-wk study period, there was a significant decline in albuminuria as well as left ventricular mass index. Of note, BP and serum potassium levels remained unchanged throughout the study period.

A more recent placebo-controlled, randomized study in 20 patients with type 1 diabetes also supports the addition of spironolactone to ACE inhibitor or ARB therapy (92). After treatment for 2 mo, the patients who received spironolactone experienced a 30% decline in albuminuria. There also was a significant decrease in daytime, although not 24-h, BP. However, despite the short study period and the exclusion of

**Table 1. Studies of aldosterone antagonists in CKD**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>n</th>
<th>Intervention</th>
<th>Δ Proteinuria</th>
<th>Δ SBP/DBP (mmHg)</th>
<th>Reference</th>
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<tr>
<td>Type II DM</td>
<td>215</td>
<td>ACEI vs EpI</td>
<td>-45%</td>
<td>-20/-15</td>
<td>94</td>
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<tr>
<td></td>
<td></td>
<td>vs EpI+ACEI</td>
<td>-62%</td>
<td>-20/-13</td>
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<td></td>
<td></td>
<td></td>
<td>-74%</td>
<td>-22/-16</td>
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<td>-13/-11</td>
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<td>-15/-11</td>
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<tr>
<td>HTN</td>
<td>494</td>
<td>ACEI vs EpI</td>
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<td>-62%</td>
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<tr>
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<td></td>
<td>-33%</td>
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<td>95</td>
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<tr>
<td>+ MA^b</td>
<td>64</td>
<td>ACEI vs EpI</td>
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<tr>
<td>Type II DM</td>
<td>46</td>
<td>+ACEI</td>
<td>-50%</td>
<td>NA</td>
<td>98</td>
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<tr>
<td></td>
<td></td>
<td>+Spiro</td>
<td>-52%</td>
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<tr>
<td>Nondiabetic chronic GN</td>
<td>42</td>
<td>Existing ACEI/ARB</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>+Spiro</td>
<td>NS</td>
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<tr>
<td>Proteinuria (&gt;1.5 g/d), majority DM</td>
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<td>ACEI vs ACEI+ARB</td>
<td>NS</td>
<td>NS</td>
<td>83</td>
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<td></td>
<td></td>
<td>vs Spiro+ACEI+ARB</td>
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<td></td>
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<td></td>
<td>-52%</td>
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<tr>
<td>HTN</td>
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<td>CCB vs EpI</td>
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<td>-20/-7</td>
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<td>-33%</td>
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<td>-60%</td>
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<td>-28%</td>
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^aSBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; ACEI, ACE inhibitor; EpI, eplerenone; Spiro, spironolactone; MA, microalbuminuria; GN, glomerulonephritis; CCB, calcium channel blocker; NS, not significant; NA, not applicable.

^bSubgroup analysis.
patients with a baseline \( K^+ > 4.5 \) mEq/L, one patient was withdrawn because of hyperkalemia.

Aldosterone antagonism also may be beneficial in nondiabetic renal disease. Adding spironolactone 25 mg/d to an ARB after 6 mo of isolated ARB therapy in 22 patients with a diagnosis of chronic glomerulonephritis resulted in further BP reduction and a 13% decrease in proteinuria (93). The mean serum creatinine was 1.5 mg/dl before and after spironolactone. Changes in serum potassium were NS after addition of spironolactone.

The more selective mineralocorticoid receptor antagonist eplerenone also showed benefit in CKD. In the largest study yet reported, >200 patients who had type 2 diabetes with hypertension and microalbuminuria were randomly assigned to eplerenone 200 mg/d, enalapril 40 mg/d, or the combination of eplerenone 200 mg/d and enalapril 10 mg/d (94). After 24 wk, the eplerenone group demonstrated a greater reduction in the urine albumin to creatinine ratio (UACR) compared with ACE inhibitor alone (62 versus 45% from baseline), and the combination group showed the greatest reduction (74% from baseline). The changes in BP among the groups were similar at the end of the 24-wk study. Hyperkalemia, however, was a concern that led to withdrawal for 18% of patients in the combination group versus 7 and 2% for the eplerenone and enalapril groups, respectively. This study has yet to be reported in a full publication. However, a smaller randomized study of patients with diabetic nephropathy with longer follow-up compared spironolactone with cilazapril with similar findings (95). At 36 wk, spironolactone was superior to cilazapril in reducing proteinuria. After 36 wk, each group received both spironolactone and cilazapril. At 60 wk, the original ACE inhibitor group showed a significant 38% further decline in proteinuria, whereas the original spironolactone group experienced only a 12% decline, suggesting that at least at 36 wk, the mineralocorticoid blocker remained more potent than the ACE inhibitor. In this study, BP changes were similar for both groups.

For examination of whether the aldosterone antagonist had a BP independent effect, eplerenone was compared with enalapril (96) and amlopidine (97) in hypertensive patients, some of which had microalbuminuria. Compared with the ACE inhibitor, eplerenone lowered BP to a similar extent at 6 and 12 mo. In the small subset of patients with microalbuminuria, eplerenone decreased the UACR by 62 versus 26% in the enalapril group at 6 mo, although no data were given for the comparative effect at 12 mo. In the other study, amlopidine and eplerenone both reduced systolic BP to a similar extent, but eplerenone reduced the UACR 52 versus only 10% for the CCB after 6 mo (97).

Proteinuria and BP control are important indicators of kidney disease that correlate with disease severity and rate of progression. One study showed a strong correlation between aldosterone levels and degree of proteinuria (98), whereas others supported this relationship (91,93). Even though data thus far are encouraging for the use of aldosterone antagonists in reducing proteinuria and BP, larger studies with longer term follow-up are needed to validate these benefits. For example, aldosterone escape merely may be delayed rather than prevented by using aldosterone antagonists. Finally, studies with the usual firm end points, such as change in GFR, occurrence of ESRD, occurrence of cardiovascular disease, and death, would be highly desirable. Unfortunately, in the largest trials to date that used spironolactone and eplerenone and demonstrated a mortality benefit, those of patients with New York Heart Association class III/IV heart failure or left ventricular dysfunction after MI, excluded patients with advanced renal disease (99,100).

Subgroup analysis also may be important to identify which patients would benefit from therapy without a significant risk for hyperkalemia. One study pooled data for 1286 patients who were treated with eplerenone and compared the effect on serum \( K^+ \) levels across a range of estimated creatinine clearances, albeit the vast majority had creatinine clearances >60 ml/min (101). Although there was a significant increase in serum \( K^+ \) with eplerenone use, this was regardless of renal function, and serum \( K^+ \) remained within normal limits for all groups. Furthermore, there was no difference in serum \( K^+ \) among groups that were stratified by renal function. Nonetheless, strategies for risk stratification within the CKD population would optimize treatment regimens. Aside from level of GFR, capacity for handling excess potassium also may be material. For example, determining changes in serum \( K^+ \), fractional excretion, or the transtubular gradient for potassium in response to a \( K^+ \) load may lend more insight into which patients are most susceptible to hyperkalemia. On the other side of the risk/benefit ratio, aldosterone levels might help to identify those who may gain the greatest benefit from using mineralocorticoid receptor antagonists.

**Aldosterone Antagonists in ESRD**

Once patients have progressed to ESRD, aldosterone levels may remain elevated (77,102–104). Emerging data suggest a potential benefit for aldosterone antagonists in this setting as well. Obviously, at this stage, the additional benefit of aldosterone antagonism would be extrarenal. Therefore, reduction in BP, improvement in vascular function, or reduction in left ventricular hypertrophy would be the outcomes that could be envisioned. Aldosterone antagonists have been proved effective in heart failure and after MI in people with adequate renal function. To our knowledge, there are no data as to whether such benefits would accrue to the ESRD patient with heart failure or after MI.

In patients with ESRD, dialysis represents the prime mechanism for \( K^+ \) elimination. This situation may limit the risk for hyperkalemia from pharmacotherapy. However, concern has been expressed that patients with ESRD may be more dependent on aldosterone during interdialytic periods for intestinal elimination or intracellular shift to achieve potassium homeostasis. Several studies have shown that these latter concerns are likely to be unimportant in practice. Saudan et al. (105) examined the effect of 25 mg of spironolactone administered three times weekly after hemodialysis (HD).
sessions in 14 patients with ESRD in a nonblinded, nonrandomized manner. Compared with control HD patients, there was no significant change in serum K⁺ levels during a 4-wk study period. The majority of these patients were on an ACE inhibitor or ARB. In a similar study, 25 mg of spironolactone was given daily to HD patients for 4 wk (106). Serum K⁺ was checked before each HD session, and the patients’ own baseline K⁺ values served as controls. There was no difference observed between baseline values and those after 4 wk of therapy. Even higher doses of spironolactone seem to be safe and effective short term. Eight oligo-anuric HD patients were given 50 mg of spironolactone twice daily for 2 wk (107). There were no significant changes in serum K⁺ levels or urine K⁺ excretion. However, there was a statistically significant fall of 10.6 mmHg in pre-HD systolic BP in the spironolactone group.

Michea et al. (108) investigated the ability of nine long-term HD patients to handle an oral potassium load (0.3 mEq K⁺/kg) with carbohydrates after 2 wk of therapy with spironolactone 50 mg three times weekly. An important caveat is that this study excluded patients with diabetes and those who were on an ACE inhibitor or ARB. There was no difference in plasma K⁺ levels after the K⁺ load while on spironolactone compared with K⁺ loading before spironolactone and K⁺ loading after receiving placebo. Moreover, predialysis plasma K⁺ remained <5.5 mEq/L throughout the trial period. In this study, there was no significant reduction in BP. However, the doses of spironolactone were lower than those in the report by Gross et al. (107), which found an antihypertensive effect. Therefore, administration of an aldosterone receptor blocker to patients who have ESRD and are on long-term HD seems free of risk for hyperkalemia, at least in the short term, and may improve control of hypertension. Aside from serum potassium and BP, the known effects of aldosterone antagonism in ESRD are limited. In Michea’s study, the expression of ENaC mRNA in peripheral blood mononuclear cells decreased from an elevated level in response to spironolactone. The pathophysiologic significance of the monocyte ENaC is unclear, but that the levels could be reduced to normal indicates heightened aldosterone activity in ESRD, at least in this tissue.

Compared with the trials of aldosterone antagonists in CKD, those that involve patients with ESRD are even smaller and with yet shorter study periods. However, they do raise the possibility that these agents may be beneficial. One small retrospective report described a positive association between aldosterone levels and survival for patients who had ESRD and were on HD (109). Perhaps, as the authors suggested, this reflected that these people (n = 12) merely had better nutrition and therefore higher K⁺ intakes. Further prospective interventional studies are needed to confirm the safety of the mineralocorticoid receptor blockers and their effects on BP. Other end points such as improvement in vascular function, left ventricular hypertrophy, cardiovascular morbidity, and death, also need to be investigated.

Conclusion
Aldosterone plays a significant role in the pathogenesis of renal disease. Although its potentially nonhemodynamic actions are intriguing and may contribute to its injurious effects, a number of observations suggest that its ability to raise arterial and probably glomerular capillary pressures is a major mechanism of injury. Initial studies that detailed its pathophysiologic mechanisms and the efficacy of aldosterone blockade in animals and humans are encouraging. Nevertheless, we believe that because of the potential serious toxicity, especially in patients with pre-ESRD, and lack of more definitive studies, at present these agents should not be used routinely as a means of treating people with CKD or ESRD. Furthermore, clinical studies are warranted to address more definitively the safety and the efficacy of aldosterone antagonism in CKD and ESRD.

References
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37. Xue C, Stray-Gundersen H: Local renal aldosterone system and its regulation by salt, diabetes, and angiotensin II type 1 receptor. Hypertension 46: 584–590, 2005


47. Uhrenholt TR, Schjerning J, Hansen PB, Norregaard R,


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