

Mineralocorticoid Receptor Blockers and Chronic Kidney Disease

Gaurav Jain, Ruth C. Campbell, and David G. Warnock

Division of Nephrology, Department of Medicine, University of Alabama at Birmingham

The increasing prevalence of chronic kidney disease (CKD) and the public health initiatives for detection and slowing its progression have placed special emphasis on controlling proteinuria and the renin-angiotensin-aldosterone system (RAAS). In addition to the traditional blockers of angiotensin-converting enzyme and angiotensin receptors, mineralocorticoid receptor blockers (MRBs) have come into focus as anti-proteinuric agents with moderate anti-hypertensive effects. The beneficial effects of MRBs on mortality in patients with cardiac disease have been well described. We review the role of aldosterone in end-organ damage, the rationales for using MRBs as adjuncts to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in treating CKD, and the adverse effects that may occur when these agents are used in combination. Suggestions are included for avoiding serious adverse events in CKD patients treated with MRBs. There is a clearly defined need for prospective outcome studies focused on cardiovascular mortality as well as progression of CKD in patients treated with MRBs and other inhibitors of the RAAS.

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There are compelling indications for the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in treating patients with chronic kidney disease (CKD), hypertension, and proteinuria, with the expressed goal of preventing progression to ESRD (1). Proteinuria appears to be an independent predictor of renal and cardiovascular outcomes (2,3). Anti-proteinuric therapy is an important part of treatment for slowing progression of CKD (4,5).

Increased aldosterone levels are seen in patients treated with ACEIs and ARBs (“escape” or “breakthrough”), supporting the use of MRBs as adjuncts to ACEIs or ARBs (6–8). As summarized in two recent meta-analyses (9,10), adding MRBs to ACEIs or ARBs: a) reduces proteinuria; b) hyperkalemia can be clinically significant when the estimated GFR (eGFR) is <30 ml/min/1.73 m², when other drugs that increase serum potassium are used, and when oral potassium supplements are given; and c) the long-term effects of combined therapy on renal outcomes and mortality need to be defined.

Randomized controlled trials demonstrate a beneficial effect of adding MRBs to ACEIs or ARBs on survival in patients with left ventricular dysfunction (11,12). MRBs are now widely used in many patients with less severe heart disease, although the supporting evidence is not as strong as for the severe heart failure studies (13). The beneficial cardiac effects of MRBs have not been demonstrated in patients with eGFR <60 ml/min/1.73 m².

Recent work has explored the cellular mechanisms of inter-

actions between mineralocorticoid and angiotensin II, type I (AT-1) receptors. Our purpose is to review this information, provide rationales for using MRBs in combination with other inhibitors of the RAAS, and to better define the potential benefits and risks of combined therapy in CKD patients. Our hope is that consulting nephrologists will then be better prepared to evaluate, explain, and apply these recent advances with reference to the care of CKD patients.

Mineralocorticoid and Angiotensin II Receptor Interactions

Aldosterone increases expression of vascular ACE activity and AT-1 receptors, resulting in increased local generation and responses to angiotensin II (14). In addition to these synergistic effects, intracellular “cross-talk” between mineralocorticoid, AT-1, and EGF (EGF) receptors may underlie end-organ damage (15,16). These processes have been well characterized in the heart, where aldosterone and angiotensin II induce cardiac fibrosis and remodeling (17,18). Zhang *et al.* (19) elegantly described the interplay between systemic angiotensin II, AT-1, and mineralocorticoid receptors in cardiomyocytes. This study demonstrated that angiotensin II leads to left ventricular hypertrophy, which is inhibited by MRBs, and provides new insights into the interactions between AT-1 and mineralocorticoid receptors, involving activation of gp91 phox-containing NADPH oxidase, reactive oxygen species, activation of matrix metallo-proteinases, increased collagen deposition, and vascular smooth muscle migration and vascular remodeling (Figure 1).

The molecular mechanisms of receptor cross-talk and interactions are being defined, and may include physical associations in caveolae/lipid rafts; AT-1 receptor dimerization; and transactivation through common receptor tyrosine kinases, subcellular redistribution, and post-translational modification of the cognate receptors by phosphorylation, and ubiquityla-

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Correspondence: Dr. David G. Warnock, ZRB 614, 1530 3rd Avenue South, Birmingham, Alabama 35294-0007. Phone: 205-934-9509; Fax: 205-934-1879; E-mail: dwarnock@uab.edu

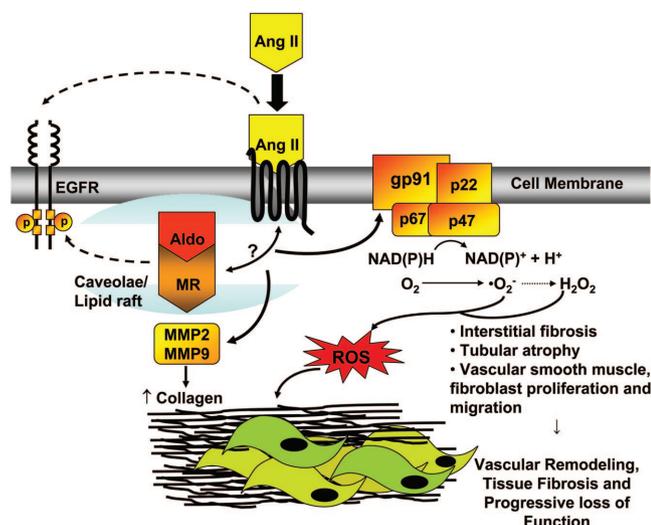


Figure 1. Molecular mechanisms that may link angiotensin receptors, and EGF receptors with mineralocorticoid receptors in renal epithelial cells. Dietary salt excess may also increase of intrarenal angiotensin II and reactive oxygen species (27). Aldo, aldosterone; Ang II, angiotensin II; EGFR, EGF receptor; MMP, matrix metalloproteinase; MR, mineralocorticoid receptor; ROS, reactive oxygen species. (Adapted, with permission from references (17,18)).

tion mediated by extracellular signal-regulated kinase 1/2, c-Src, RhoA/Rho kinase, Ki-ras2A, protein kinase B, and NADPH oxidase (14,17,19–24).

While these studies have focused on cardiomyocytes and vascular smooth muscle cells, the recent finding that Rac1 GTPase can modify mineralocorticoid receptor function (25) in association with podocyte damage and proteinuria in the absence of increased systemic aldosterone levels provides an important link between the cardiac and vascular findings and aldosterone-mediated renal injury, fibrosis, and decreased function (25,26).

Dietary salt may also play an important role in these processes. Dietary salt excess increases proteinuria and aggravates glomerulosclerosis in patients with CKD (27). Salt restriction has beneficial effects that are not reproduced by diuretic treatment (28). Even in states with high-circulating systemic aldosterone levels (29–31), hypertension and target organ damage do not develop unless dietary salt intake is elevated. Inappropriate increase of intrarenal angiotensin II and generation of reactive oxygen species appear to be the major culprits responsible for target organ damage related to dietary salt excess (27,32). Avoiding excess dietary sodium intake is an important adjunct to treating CKD patients with inhibitors of the RAAS, with the goals of controlling BP and minimizing target organ damage.

The Protective Effects of MRBs

Aldosterone receptors have been discovered in a wide variety of tissues, including adipose tissue, vascular endothelial cells, cardiomyocytes, and the brain. High aldosterone levels are associated with inflammatory markers, including IL-6, IL-1 β , monocyte chemo-attractant protein-1, reactive oxygen spe-

cies, increased type IV collagen production, and alterations of plasminogen activator inhibitor and osteopontin expression (26,33–35).

Hospitalization rates, mortality, and cardiac events decreased significantly in patients with heart failure when MRBs were added to ACEIs or ARBs. In the Randomized Aldactone Evaluation Study (RALES), spironolactone reduced the relative risk of death in patients with advanced heart failure (11). The Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated a significant reduction in the composite end point of death or hospitalization for cardiovascular causes when eplerenone was given to patients with left ventricular dysfunction following acute myocardial infarction (12). Consensus treatment guidelines for heart failure (36) include MRBs as standard therapy in patients with moderate to severe heart failure.

On the other hand, there are not any outcome studies that demonstrate a benefit on survival, or progression of ESRD in patients with eGFR <60 ml/min/1.73 m² who are treated with ACEIs or ARBs in combination with MRB therapy (9,10). Nevertheless, the beneficial effects of MRBs on cardiovascular outcomes cannot be ignored, especially with the finding that moderately advanced CKD confers an independent, increased risk of death and cardiovascular events (37). There are competing risks between cardiovascular death and progression to ESRD (38–41). Because different risk factors may be involved, it may not be appropriate to combine mortality and progression to ESRD in a composite end point for outcome studies (38,41). Nevertheless, the possibility that there are beneficial effects of MRBs on cardiac outcomes in CKD patients as well as on progression to ESRD is well worth considering.

MRBs and Aldosterone “Escape” or “Breakthrough”

Aldosterone escape or breakthrough occurs when patients are treated with ACEIs or ARBs; serum aldosterone levels may increase compared with values obtained before treatment was started, and proteinuria may increase with more rapid loss of kidney function (6,8). While the aldosterone escape or breakthrough phenomenon provides a rationale for the use of MRBs as an adjunct to ACEIs or ARBs, circulating aldosterone levels may not have to be elevated for there to be a beneficial response to MRBs (42).

There is recent interest in oral renin inhibitors as anti-hypertensive agents, and it has been proposed that aliskiren might treat aldosterone escape (43). The available evidence shows that aliskiren reduces plasma aldosterone in short-term studies (44,45), similar to what has been described with ACE inhibitors and ARBs (7), but aldosterone escape has not yet been examined in patients receiving long-term aliskiren treatment.

Combinations of MRBs with Other Inhibitors of the RAAS

In addition to aldosterone escape or breakthrough (46), and beneficial effects even when plasma aldosterone is not elevated, there are other rationales for combining MRBs with other RAAS inhibitors (Table 1). Studies in the heart (19,47) and kidney (25) imply that upregulation or activation of mineralocorticoid receptor density/activity at the local tissue level may

Table 1. Rationales for combined therapy with MRBs and other RAAS inhibitors

Use of MRBs with ACEIs or ARBs

1. Aldosterone “escape” or “breakthrough” (6, 8, 46)
2. Beneficial effects of MRBs can be demonstrated even in the absence of elevated systemic circulating aldosterone levels (42)
3. Upregulation or activation of mineralocorticoid receptors at the target organ level implies that tissue damage can occur even with normal systemic levels of aldosterone (19, 25, 47)
4. MRBs, ACEIs, and ARBs reduce oxidative stress and generation of reactive oxygen species (20, 21, 33, 34, 49, 50)

Use of MRBs with ARBs Rather than ACEIs

5. The specificity of ARBs may be permissive of beneficial effects of angiotensin II mediated through non-AT-1 receptor pathways; ACEIs reduce angiotensin II generation and would not necessarily favor non-AT-1 receptor effects (48)
6. There may be beneficial effects of individual ARBs that are not explained by class effects or inhibition of AT-1 receptors (49, 50)
7. Current cost differential between ARBs and ACEIs does not favor using ARBs alone as a first-line therapy in CKD (51)

ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; AT-1, angiotensin II type-1 receptor; CKD, chronic kidney disease; MRBs, mineralocorticoid receptor blockers; RAAS, renin-angiotensin-aldosterone system.

play an important role in aldosterone-mediated organ damage in the absence of increased circulating levels of aldosterone. Intracellular cross-talk between mineralocorticoid and AT1 receptors provides another theoretical basis for the combined therapy with MRBs and ARBs (Figure 1). Finally, the appreciation that there are other effects of angiotensin II (48) or specific effects of some ARBs that are not mediated through classical AT-1 receptors (37,49,50) suggests a theoretical advantage of using MRBs with ARBs rather than ACEIs. ARBs are currently more expensive than ACEIs (51), but generic ARBs may become available in 2010, so cost should have less influence on clinical decision making.

Meta-analyses have examined the effectiveness of the combination approach compared with either class alone on reduction of proteinuria (9,10). Combination therapy may have better efficacy in treating proteinuria, but these same effects can also be achieved by using maximal doses of ACEIs or ARBs alone (52,53). However, if the “maximal” dose exceeds the currently approved dose, there may be reimbursement issues, especially with ARBs (51). If similar effects are achieved with maximal doses of either class alone, then the rationale for combined therapy is weakened, and may not be justified. The ONTARGET Study (54) used fixed dosage combinations of ramipril and telmisartan. The study design has been appropriately criticized (55,56). This large-scale trial provides an excellent example of the disadvantages of using a fixed dose combination of an ACEI and ARB for preserving kidney function, especially in CKD patients who do not have significant proteinuria against which the drug dosing can be titrated.

The use of multiple RAAS blockers has been referred to as “triple” therapy (42,57–61). Nevertheless, because of the added risks of serious adverse events, this approach has not been endorsed in the American College of Cardiology/American Heart Association position paper on treating heart failure (36)

or in recent papers in the cardiology (13) and nephrology literature (55).

We would like to suggest that the combination of MRBs and ARBs could be more rationale, and even more effective than combining MRBs with ACEIs. This suggestion is based on the recent data about AT-1 and mineralocorticoid intracellular receptor cross-talk. Other potentially beneficial effects of specific ARBs could also be noted in this context. Candesartan has a novel effect to reduce reactive oxygen species, which appears to be independent of its classical AT-1 receptor-mediated effects (49,50). Telmisartan may have unique and selective PPAR- γ -modulating activity (37).

There are no clinical studies that demonstrate superiority of one combination compared with the other, but the stage may be set for prospective safety and efficacy studies to evaluate the optimal use of specific combinations of MRBs and ARBs in slowing the course of proteinuric CKD, with an attendant improvement in the cardiovascular outcomes for these patients. In contrast to previous studies in type II diabetes that used a BP target as the primary treatment goal (62,63), our suggested study design would involve dose titration of MRBs or ARBs to reach a proteinuria target of 500 mg/d as the primary study goal (5,64). The primary outcome measures would be reduction in all-cause and cardiovascular mortality, and secondary outcomes focused on slowing progressive loss of kidney function and ESRD. Safety measures would include hyperkalemia and symptomatic hypotension. It does not seem likely that a comparison of ACEIs plus MRBs to ARBs plus MRBs will be carried out with pharmaceutical industry sponsorship, but a properly powered, prospective study with cardiovascular and renal end points could be organized to compare an ARB plus MRB to an ARB plus thiazide diuretic. The differences between MRBs and thiazide, and thiazide-like, diuretics on incidence of insulin resistance and diabetes should not be overlooked (65). A large clinical trial would be needed to evaluate these issues

in patients with CKD. In the meanwhile, it is common nephrologic practice to control dietary salt intake and combine RAAS blocking agents with the goal of reducing proteinuria and progression of CKD.

Adverse Events Associated with MRBs

The common adverse effects associated with spironolactone are breast tenderness, gynecomastia, hyperkalemia, prostatic hypertrophy, erectile dysfunction, and menstrual irregularities. In male patients treated with spironolactone, approximately 10% experience breast tenderness at doses of 25 mg/d (11,12). The incidence of hyperkalemia (>5.5 mEq/L) in a systematic review was 5.5% (9). Another meta-analysis has described the relative risk of hyperkalemia of 1.031 with MRBs used along with ACEIs and or ARBs compared with ACEIs and or ARBs used alone (10). Eplerenone may cause fewer “endocrinologic” side-effects than spironolactone, but it is also a less potent MRB (66,67).

The prescribing information for eplerenone contains an absolute contraindication for patients with eGFR <30 ml/min/1.73 m², serum potassium >5.5 mEq/L, or diabetics with microalbuminuria (66). Spironolactone is contraindicated for patients with “anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia” (67). Patients at risk for MRB-induced hyperkalemia include the elderly; those treated with higher doses of MRBs; diabetic patients; patients with moderately severe CKD; and patients also receiving ACEIs, ARBs, potassium-sparing diuretics, and oral potassium (68). Higher rates of hyperkalemia have been reported with MRB use in community hospital settings due to inappropriate prescribing patterns (69), such as patients being discharged on MRBs and oral potassium supplements, and patients who had overt hyperkalemia during their hospitalizations for heart failure being discharged on a MRB without addressing the hyperkalemia (70). Small studies have shown

that oligo-anuric hemodialysis patients can tolerate spironolactone in low doses (71–73), although the safety issues raised by impaired renal and colonic potassium secretion as well as impaired extra-renal potassium handling need to be much better addressed (74,75). It appears that persistent hyperkalemia may be better tolerated in patients with CKD than those with only mild renal impairment, but the short-term, life-threatening consequences of serum potassium levels that exceed 5.5 mEq/L have recently been re-emphasized (76), as has extra-renal potassium handling (74). Any combination of MRBs with other RAAS inhibitors requires careful and regular monitoring of serum potassium levels. Dietary guidance about potassium intake, concomitant use of diuretics, and avoidance of nonsteroidal anti-inflammatory agents and other drugs that increase serum potassium may help avoid hyperkalemia in patients with CKD treated with MRBs (Table 2).

Conclusions and Future Developments

The addition of MRBs to RAAS inhibitors in CKD can further reduce proteinuria, but can also cause serious adverse events in advanced CKD and patients with baseline hyperkalemia (9,10). The proven benefits of MRBs in left ventricular dysfunction have only been demonstrated in the setting of concomitant ACEI or ARB therapy in patients with eGFR >60 ml/min/1.73 m² (77). Long-term cardiovascular outcomes, renal outcomes, and mortality have not been evaluated in CKD patients receiving MRBs (9,10) and warrant a well designed study.

Aldosterone escape is a rationale for adding MRB to other RAAS blockers. With the recent insights into the cross-talk between AT-1 and mineralocorticoid receptors (18,19), an additional rationale is provided that we believe favors the addition of MRBs to ARBs therapy rather than ACEIs. The rationales for using combined RAAS inhibitor therapy is listed in Table 1, and suggestions for using MRBs in CKD and managing the risks of

Table 2. Suggestions for minimizing and managing serious adverse events in CKD patients treated with MRBs

1. Unless there is a compelling indication, avoid using MRBs in patients with eGFR <60 ml/min/1.73 m².
2. Avoid starting MRB therapy in any patient with baseline serum K⁺ in excess of 5.0 mEq/L.
3. MRBs can be used as adjuncts to ACE inhibitors or ARBs in CKD patients with overt proteinuria (>300 mg/d) in whom maximal doses of ACE inhibitors or ARBs have not achieved the target for proteinuria reduction.
4. MRBs should be started at low doses. Serum K⁺ should be checked 1 wk after starting or changing the MRB dose, and regularly thereafter.
5. Dietary prudence with respect to K⁺ intake and regular bowel habits will help minimize elevations of serum K⁺. Avoid oral K⁺ supplements and salt substitutes.
6. Be cautious using MRBs with more than 1 other inhibitor of the RAAS, with K⁺-sparing diuretics or with any other agent that suppresses renin secretion or activation (calcineurin inhibitors, non-steroidal anti-inflammatory agents, β -blockers, aliskiren, Vitamin D receptor agonists).
7. Concomitant use of thiazides or furosemide may help control serum K⁺ in CKD patients with serum K⁺ >4.5 mEq/L.
8. If serum K⁺ rises above 5.0 mEq/L, decrease the dose of MRB or ACEI or ARB, modify the dietary K⁺ intake and check for constipation.
9. If serum K⁺ is >5.5 mEq/L, stop the administration of MRBs, ACEIs, and ARBs, and modify dietary K⁺ intake. Check 24-h urine for K⁺ and Na⁺ excretion to confirm dietary patterns and interventions.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MRBs, mineralocorticoid receptor blockers; RAAS, renin-angiotensin-aldosterone system.

hyperkalemia are summarized in Table 2. Prospective safety information must be obtained before MRBs are used with any other drug that suppresses renin secretion or activation.

The cardioprotective effects of MRBs in non-CKD patients and their anti-proteinuric potential when used in combination with other RAAS inhibitors and dietary salt restriction in CKD patients are well described. Long-term outcome studies are needed to define the therapeutic role and safety concerns that arise with the use of MRBs in patients with eGFR <60 ml/min/1.73 m², and these outcome studies need to address all-cause mortality as well as slowing progression to ESRD.

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Disclosures

None.

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