Elevations in serum creatinine with RAAS blockade: why isn’t it a sign of kidney injury?
Michael J. Ryan and Katherine R. Tuttle

Introduction
The renin–angiotensin–aldosterone system (RAAS) is thought to have evolved as a means to conserve salt and water in order to maintain tissue perfusion at livable levels in a very low sodium environment. Although it conferred a survival advantage in the distant past, RAAS appears to have become a liability in the high salt culture of modern times. There is an epidemic of chronic kidney disease (CKD), in part due to a dramatic increase in the prevalence of overeating in the world [1]. CKD is associated with a higher risk for cardiovascular disease, and the association is not completely accounted for by traditional risk factors, such as diabetes, hypertension, and hyperlipidemia [2–5]. Both obesity and CKD are associated with increases in activity of RAAS [7,8,9,10].

RAAS is therefore one of the most important pharmacologic targets for treating hypertension, preventing cardiovascular disease, and slowing the progression of kidney disease.

Progressive kidney disease: role of the renin–angiotensin–aldosterone system
CKD may affect 16.8% of the US population, and it is estimated that there will be 700,000 patients with end stage renal disease (ESRD) in America by 2015 [11]. Total Medicare costs for CKD and ESRD patients neared $42 billion and $20 billion in 2005, respectively, levels that certainly contribute to concerns about solvency of the federally funded Medicare program that supports most ESRD care in the United States [12].

Significant reductions in renal mass trigger a sequence of events that results in proteinuria, glomerulosclerosis, tubulointerstitial inflammation and fibrosis, and ultimately ESRD. Angiotensin II (AgII) mediates hemodynamic effects (reviewed below) and a constellation of oxidative and inflammatory reactions that impact the growth and proliferation of mesangial cells and podocytes that contribute to progressive glomerular injury and tubulointerstitial fibrosis [13,14,15,16].

Purpose of review
The aim of this article is to review the pertinent physiology and pathophysiology of the renin–angiotensin–aldosterone system (RAAS), summarize the proven beneficial cardiovascular and renal effects of RAAS blockade, examine clinical situations in which RAAS blockade may induce reductions in glomerular filtration rate, and explore why increases in serum creatinine in the setting of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy do not necessarily signify the presence of clinically relevant kidney failure.

Recent findings
RAAS inhibition appears to reduce the likelihood of atrial fibrillation. RAAS inhibition leads to improved insulin sensitivity and glycemic control, but does not appear to prevent diabetes. The beneficial effects of ACEi/ARB therapy extend to those with significant renal disease. Combination ACEi/ARB is safe, and reduces proteinuria more than either agent alone in patients with macroalbuminuric nephropathy. Acute deteriorations in renal function that result from RAAS inhibition are usually reversible.

Summary
RAAS blockade exerts potent hemodynamic, antihypertensive, and antiinflammatory effects, and slows progression of kidney disease beyond that due to lowering of blood pressure. The benefit extends to those with advanced disease. In spite of established benefit, ACEi and ARB therapy remains underutilized, in part due to concerns about acute deteriorations in renal function that result from interruption of the RAAS.

Keywords
acute kidney injury and dual RAAS blockade, angiotensin II receptor blocker, angiotensin-converting enzyme inhibitor, renin–angiotensin system
The two most important pharmacologic approaches to inhibiting the RAAS include angiotensin converting enzyme (ACE) inhibitors (ACEis) and angiotensin receptor blockers (ARBs), which affect the action of AgII on cells. Aliskerin, a renin inhibitor, has recently been approved by the US Food and Drug Administration for the treatment of hypertension [17*].

**Evidence benefits of blockade of the renin–angiotensin–aldosterone system for cardiovascular disease and progressive renal disease**

The RAAS not only modulates salt and water balance, it regulates the vascular response to injury and inflammation. In patients with heart disease and reduced left ventricular function, there is accentuated activation of the RAAS with upregulation of ACE, increased production of AgII, and increased degradation of bradykinin, all of which contribute to atherosclerosis, cardiac fibrosis and left ventricular (LV) hypertrophy [18,19].

ACEis and ARBs have consistently demonstrated a significant reduction in cardiovascular morbidity and mortality in multiple, large, prospective, randomized trials, and are considered standard therapy for patients with cardiovascular disease [20*]. They appear to have a dose dependent beneficial effect on atherosclerosis progression [21], and may also prevent the development and recurrences of atrial fibrillation [22*,23].

Control of hypertension slows the rate of progression of nephropathy in both diabetic and nondiabetic CKD, irrespective of the class of medicine, but agents that block the RAAS alter glomerular hemodynamics, reduce intraglomerular pressure and hyperfiltration, and thereby reduce proteinuria, which slows progression of CKD beyond that seen with blood pressure (BP) reduction alone [24**,25]. The benefits of ACEi and ARB therapy in diabetic and nondiabetic kidney diseases are stronger in patients with a greater degree of proteinuria, and the effect is present over all levels of baseline glomerular filtration rate (GFR) [24**,26–28]. The antiproteinuric effects of RAAS are enhanced with concomitant low salt [29] and low protein diets [30].

The ‘BP-independent’ effects of RAAS blockade are also likely important in renoprotection [31,16*] particularly for patients with proteinuric kidney diseases for which the GFR is under 60 ml/min/1.73 m².

Based on a large body of experimental and clinical research, a consensus has developed in the last decade that RAAS blockade with ACEis or ARBs, or a combination of both, reduces proteinuria and slows progression more effectively than other agents in patients with nephropathy [32*,33**,34*].

Although there is scientific rationale for using agents that block RAAS for primary prevention of kidney disease in patients with early stage, nonproteinuric nondiabetic nephropathies, the evidence of benefit of RAAS inhibition is less robust, and it appears that BP control is of greater importance [35**].

**Common clinical dilemmas**

The American College of Cardiology and American Heart Association have issued practice guidelines strongly recommending ACEis as standard therapy for secondary prevention in cardiovascular patients [36]. The *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) and the recently updated *National Kidney Foundation Kidney Disease Outcomes Quality Initiative* (NKF-KDOQI) guidelines recommend a goal BP under 130/80, and that ACEis or ARBs be used as first line therapy in patients with hypertension and kidney disease accompanied by proteinuria [37].

Although there has been improvement in the recognition and successful treatment of hypertension, the BP control rates remain low at 36.8% in 2003–2004 [38]. In patients with CKD, the percentage of those with hypertension who achieved the designated target BP (<130/80) was less than 20% [39]. In spite of the established beneficial effects of using inhibition of the RAAS system in patients with atherosclerosis with and without LV dysfunction and in patients with CKD, many patients do not receive inhibitors of the RAAS system [40–44].

The reasons for underuse of ACEis/ARBs in patients at risk for cardiovascular disease and or patients with kidney disease are not known, but it is likely that safety concerns contribute to underutilization. One of the frequent reasons for discontinuation of ACEis is the worry about worsening of renal function.

**Worsening of kidney function with use of angiotensin- converting enzyme inhibitors/angiotensin receptor blockers: who is at risk?**

Although the exact incidence of ACEi or ARB-induced acute renal insufficiency is not known, an acute increase in serum creatinine with RAAS blockade is most likely to occur in one of several situations: in patients in whom GFR is highly dependent on AgII, such as in severe high-grade bilateral renal artery stenosis or arterial stenosis in a renal transplant; in extracellular volume deletion, such as with nausea, vomiting, diarrhea, or diuretics [45]; in patients with substantial reductions in mean arterial pressure for which renal perfusion pressure cannot be maintained, such as those with congestive heart failure.
glomerular structure [51]; in patients taking vasoconstrictor medications, such as NSAIDS, cyclooxygenase-2 inhibitors, [47,48] or cyclosporine [49]; and in patients with preexisting renal disease [50].

**How much of an increase in serum creatinine is tolerable with the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy?**

The kidney displays highly efficient autoregulation such that under steady-state conditions, renal blood flow (RBF) is independent of BP over a wide range of pressures. Autoregulation functions to maintain extracellular fluid volume in spite of variations in BP, and to preserve glomerular structure [51**,52].

Under normal conditions, the vasoactive states of the afferent and efferent arterioles of the glomerulus are regulated via a complex interplay between systemic mechanisms (the sympathetic nervous system, natriuretic peptides, and vasopressin) paracrine factors (nitric oxide, endothelin, and prostaglandins), and the RAAS. The kidney is unique in that it has components of the RAAS in the tubular and interstitial compartments [53,54**], and functional investigations and biopsy studies in humans emphasize augmentation of the intrarenal RAAS in patients with diabetic and nondiabetic kidney disease [55–58].

A reduction in nephron mass is accompanied by profound alterations in renal hemodynamics characterized by glomerular capillary hypertension, glomerular hypertrophy, and hyperfiltration [59]. AgII acts to constrict both the afferent and efferent arterioles, but has a much stronger effect on the efferent arteriole [60**,61]. Experiments in animals and humans demonstrate that the administration of an ACEi or ARB results in a greater decrease in efferent as compared with afferent resistance, and renal plasma flow increases. An increase, a fall, or no change in GFR may result, depending on the underlying disease and status of the RAAS [62,63].

With loss of nephron mass autoregulation may be impaired and GFR may be more dependent on RBF [64,65]. The presence of RAAS inhibition also prevents the glomerulus from compensating via Ag II-mediated vasoconstriction in the efferent arteriole. Experimental studies demonstrate that acute reduction in GFR with initiation of RAAS inhibition may be as high as 40% [62].

In the clinical setting, the initial fall in GFR with RAAS inhibition (represented by an increase in serum creatinine level) is thought to be primarily functional based on current understanding of underlying renal hemodynamics. In support of this concept, Bakris and Weir [66] reviewed 12 randomized clinical trials that evaluated progression in patients with CKD and found that an increase in serum creatinine of 30% or less above baseline after initiation of ACEi or ARB therapy was common, generally occurred within 2 weeks, and was not associated with long-term harm. The initial fall in GFR associated with initiation of RAAS inhibition is usually reversible with discontinuation of ACEi or ARB therapy [67]. The NKF-KDOQI guidelines suggest that the dose of ACEi or ARB be reduced and GFR monitored more frequently if the serum creatinine increases by over 30% after initiation of RAAS inhibition [27]. There are no randomized trials that specifically address the question of what level of increase in serum creatinine should prompt withdrawal of ACEi or ARB therapy. Diuretics [45] and relative hypotension [68] appear to potentiate RAAS inhibitor-induced acute deterioration in kidney function.

**My patient is about to receive contrast. Should the angiotensin-converting enzyme inhibitor or angiotensin receptor blocker be discontinued?**

Contrast-induced nephropathy (CIN), defined as an acute decline in renal function after the administration of radiocontrast, is the third leading cause of acute renal failure in hospitalized patients [69]. The single most important risk factor for CIN is preexisting renal failure [70], a situation in which RAAS blockade would likely be present. The question of whether an ACEi predisposes to CIN is not resolved. Prospective randomized controlled trials in which prophylactic use of captopril was given prior to contrast showed conflicting results [71,72]. One observational study [73] evaluating the use of ACEIs prior to contrast found ACEIs to be a risk factor for CIN, whereas another found ACEIs to be protective [74]. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial (see below) should help clarify whether ARBs impact the incidence of CIN.

**Is there a level above which angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy is not indicated?**

Post-hoc analyses of the Modification of Diet in Renal Disease Trial (MDRD) and the Ramipril Efficacy in Nephropathy (REIN) trial established that the renoprotective effects of ACEIs in chronic nephropathies are independent of the severity of baseline renal function, and that ACEIs slowed progression of disease even in patients with GFR of 25 ml/min/1.73 m² or lower [75,76]. In a randomized prospective trial to determine whether ACE inhibition is beneficial for patients with non-diabetic advanced renal disease, 140 patients with creatinine 3.1–5.0 mg/dl were randomized to treatment with benazepril or placebo. Treatment with benazepril, as compared to placebo, resulted in a 43% overall reduction in the risk of doubling of serum creatinine, ESRD, or death [77]. It should be noted that 5% of patients were excluded during the 8-week run-in due...
My patient has atherosclerotic renal artery stenosis. Is it safe to administer an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker?

ACE inhibitors successfully control BP in the majority of patients with atherosclerotic renal artery stenosis (ARAS) [79], but have the potential to relax the efferent arteriole, reduce GFR, and precipitate a functional acute renal failure. Patients with renal artery stenosis are often candidates for ACEi or ARB therapy for other indications such as diabetes, congestive heart failure, or chronic kidney disease, and RAAS inhibition may improve survival in patients with ARAS [80].

The renal impairment that may be induced by RAAS blockade is usually rapid in onset, and recovery is equally rapid after withdrawal of the medication. The exact incidence of acute kidney injury (AKI) in patients with ARAS is unknown, but depends on the degree of and locations of stenosis [81]. A significant increase in serum creatinine can sometimes be treated with reduction or discontinuation of diuretics rather than ACEIs [82]. NSAIDs should be avoided. It should also be recognized that decreases in GFR are not unique to RAAS blockade, as any medication that drops systemic BP enough to impair renal perfusion can result in deterioration in renal function. RAAS blockade-induced AKI in patients with ARAS can be severe enough to require dialysis [83], and rarely may be permanent [84].

The benefit of Stent Placement and Blood Pressure and Lipid-lowering for the Prevention of Progression of Renal Dysfunction caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial [85], the CORAL trial [86], and the Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial [87] will help clarify the optimal therapy for patients with ARAS [88], and whether RAAS inhibition is beneficial in ARAS. Until the results of these trials are available, agents that block RAAS should be used with caution in patients with ARAS, and renal function should be monitored closely. As sodium depletion may increase the likelihood of acute AKI, it is probably advisable to reduce intensity of diuretic therapy before initiation of ACEIs or ARBs, especially in patients with reduced LV function.

Are patients on combination angiotensin-converting enzyme inhibitor–angiotensin receptor blocker therapy at greater risk of developing an increase in serum creatinine?

In spite of the proven benefit of blockade of the RAAS in the management of patients with nephropathy, progression of kidney disease occurs. This may be in part due to the fact that ACE inhibitors do not completely prevent formation of AgII by alternative pathways [89], whereas ARBs do not block all AgII type 1 receptors at clinically recommended doses [90*,91**].

Although combination therapy may offer no benefit over monotherapy in patients with low albumin excretion rates and early-stage disease [92], combination of ACEis and ARBs appears to reduce proteinuria in the short term more than either drug alone in patients with macroalbuminuric nephropathy [33**,93], without significant reductions in GFR [94]. Combination therapy should be used with caution in patients with LV dysfunction, as acute worsening of renal function (increased creatinine >0.5 mg/dl) was 2.2-fold more likely with the combination ACEi plus ARB than with the comparator, usually an ACEi alone in one study [95].

The exact mechanisms of the antiproteinuric effects and the optimal dosages for slowing progression of disease are not known [96]. NKF-KDOQI guidelines suggest that ACEi/ARB combination therapy may be used to reduce proteinuria, but that large-scale studies are necessary to clarify the role of combination therapy in patients with CKD [27].

Conclusion

The beneficial effects of blockade of the RAAS are well established in patients at risk for cardiovascular disease and for those with diabetic and nondiabetic nephropathy.

Even patients with advanced CKD may garner protection from kidney disease progression with RAAS blockade. Overall ACEi and ARB are safe if used judiciously. Ongoing clinical trials will help to clarify whether RAAS inhibition should be withheld prior to radiocontrast, the optimal therapy of ARAS, and the role of ACEi/ARB combination therapy in patients with progressive kidney disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 548).


A meta-analysis of 11 randomized showed that RAAS blockade reduced the risk of atrial fibrillation by 19%.

This is a review of the physiology of renin and the history of the development of the renin-angiotensin system (RAS). This review highlights how activation of the renin–angiotensin system RAAS in adipose tissue may represent an important link between obesity and hypertension.

A study of 181 patients demonstrated that elevated BMI and body fat percentage independently predict oxidative stress and inflammation in patients with moderate to severe CKD. The oxidative stress due to obesity likely contributes to the cardiovascular burden in CKD patients.

This is an excellent review of the possible mechanisms, including systemic and glomerular hypertension, cytokines, and growth factors and RAAS, that contribute to progressive renal damage. There is also discussion of the role of podocyte loss, dyslipidemia and proteinuria in progression.

This is a review of the dual effects of RAS blockade with an emphasis on its therapeutic role in type 2 diabetes mellitus and chronic kidney disease. A meta-analysis of 49 studies involving 6181 participants showed that reduction in albuminuria.

This excellent review focuses on BP control vs. RAAS inhibition for patients with early stage, nonproteinuric nephropathy. This is a thorough review of outcome trials that show a continuous association between the level of albumin excretion and the risk for cardiovascular events and overall mortality, and a discussion of therapeutic approaches to reduce impact of proteinuria.

This is a review of beneficial effects of RAAS blockade, including effects on atrial fibrillation and glycemic control.

This is a review of the pathophysiology of insulin resistance, hypertension, obesity, and the associations with CKD.

A study of 184 patients demonstrated that elevated BMI and body fat percentage independently predict oxidative stress and inflammation in patients with moderate to severe CKD. The oxidative stress due to obesity likely contributes to the cardiovascular burden in CKD patients.

This is a review of the pathogenesis of the podocyte and proteinuria in diabetic glomerulopathy. Curr Diabetes Rev 2008; 4:39–45. The authors provide an update on the role of the podocyte as a central target of the effects of the metabolic milieu in the development and progression of diabetic albuminuria.

This study of 181 patients demonstrated that elevated BMI and body fat percentage independently predict oxidative stress and inflammation in patients with moderate to severe CKD. The oxidative stress due to obesity likely contributes to the cardiovascular burden in CKD patients.

This is a review of the dual effects of RAS blockade with an emphasis on BP-dependent and BP-independent effects.


This is a review of the key points of clinical hypertension. J Clin Hypertens (Greenwich) 2007; 9 (11 Suppl 4):4–10.

A meta-analysis of 11 randomized showed that RAAS blockade reduced the risk of atrial fibrillation by 19%.

This is a review of beneficial effects of RAAS blockade, including effects on atrial fibrillation and glycemic control.
Pharmacology and therapeutics


51 Cupples WA, Braam B. Assessment of renal autoregulation. Am J Physiol ** Renal Physiol 2007; 292:F1105–F1123. This is an excellent review of the myogenic mechanism and the tubuloglomerular feedback, and how they contribute both directly and indirectly to autoregulation of RBF and of glomerular capillary pressure.


54 Kobori H, Nagakui M, Navar LG, Nishiyama A. The intrarenal renin–angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007; 59:251–287. This is thorough review of the physiology of intrarenal RAAS and the role of augmentation of intrarenal RAAS in various diseases including both animal and human experiments.


59 Thomson SC, Vallon V, Blantz RC. Kidney function in early diabetes: the role of inflammation. Curr Opin Nephrol Hypertens 2007; 16:46–51. This is a review of Ag BN-oxide interactions and the role of reactive oxygen species in tubuloglomerular feedback, GFR.


88 Weir MR. Effects of renin–angiotensin system inhibition on end-organ protection: can we do better? Clin Ther 2007; 29:1803–1824. This is a critical review of 11 clinical trials of effects of ACE ARB or a combination on target organ damage.


