Cardiorenal Effects of the Renin-Angiotensin-Aldosterone System

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Hemodynamic stability in humans is highly dependent on proper functioning of the renin-angiotensin-aldosterone system (RAAS). This cascade plays an integral role in maintaining vascular tone, cardiac function, and optimal salt and water homeostasis. Overactivity of this peptide hormone system can result in pathology, and experimental evidence suggests that the RAAS contributes significantly to untoward cardiorenal effects. This article examines the evidence regarding the RAAS in cardiac and renal pathology and reviews the role of pharmacologic inhibitors of the RAAS in preventing and ameliorating kidney and heart disease.

OVERVIEW OF THE RAAS

The RAAS plays a primary role in the preservation of hemodynamic stability in humans. Changes in cardiac pump function, coronary blood flow, and systemic arterial compliance underlie the role of the RAAS on the cardiovascular system in maintaining circulatory integrity. Renal effects of the RAAS are geared primarily toward regulating extracellular fluid volume, sodium and water homeostasis, and electrolyte balance. The RAAS achieves this through complementary interactions with hemodynamic effects produced by other vasomotor systems, including the sympathetic nervous system and several vasoactive hormones (eg, endothelin, nitric oxide, adenosine, and atrial natriuretic peptide). These complementary interactions allow the RAAS to respond to a variety of threats that may compromise blood pressure stability, extracellular fluid volume homeostasis and, ultimately, critical end-organ perfusion.

The RAAS comprises a cascade of peptide hormones (**Figure 1**) whose synthesis is primarily triggered by the release of renin from the kidney. Renin cleaves the substrate angiotensinogen (secreted by the liver), resulting in the biologically inactive peptide angiotensin I. Angiotensin I then is efficiently converted in the bloodstream to the octapeptide angiotensin II by angiotensin-converting enzyme (ACE). This ubiquitous proteolytic enzyme is synthesized in pulmonary endothelial cells, endothelial cells of the vasculature, and cell membranes of the heart, kidneys, and brain. ACE produces angiotensin II following the systemic delivery of angiotensin I to organs where ACE activity occurs. As seen in Figure 1, however, non-renin and non-ACE pathways that are capable of generating angiotensin II also exist and have been termed *ACE-independent* pathways.

Systemic delivery of angiotensin I is fundamental to RAAS function; however, many organ tissues also possess angiotensinogen, ACE, and the alternate pathway enzymes noted above. The presence of these components in organs, termed *tissue RAAS*, permits local regulation of this cascade independent of systemic angiotensin I synthesis or delivery.[1–3]

The final step in the RAAS is the production of aldosterone in the zona glomerulosa of the adrenal gland. Additionally, experimental evidence suggests that angiotensin II may generate aldosterone in cardiac and other tissue.[4] Aldosterone then acts by binding to its mineralocorticoid receptor.
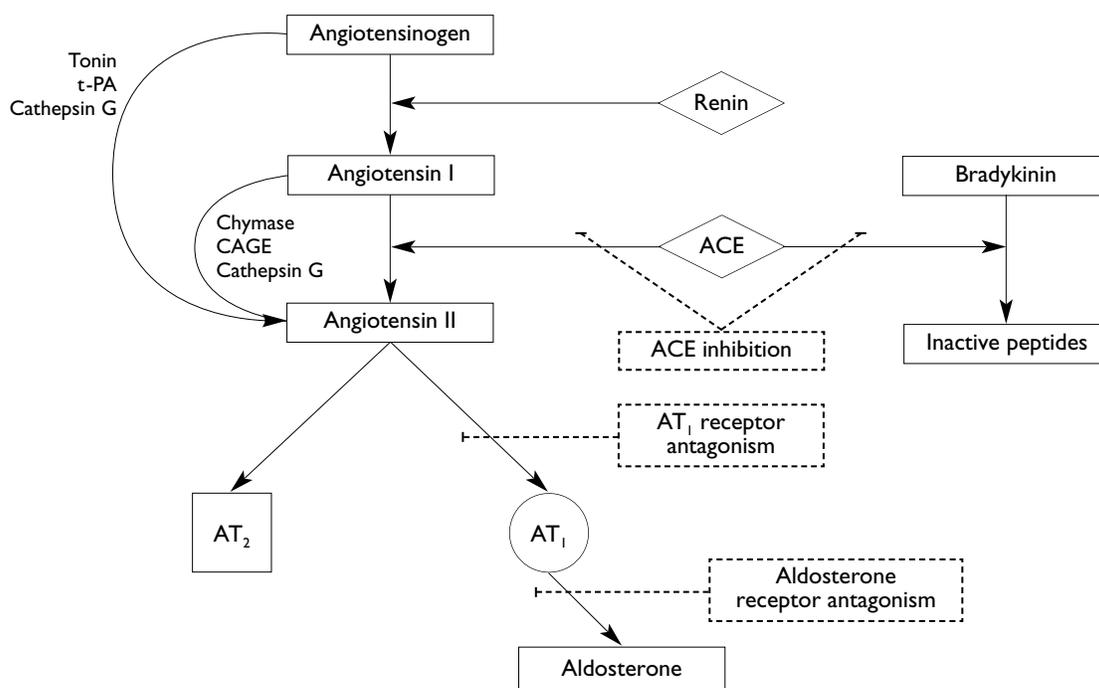
ANGIOTENSIN II RECEPTOR SUBTYPES

Angiotensin II mediates all of its physiologic actions by activating 2 well-characterized angiotensin II receptor subtypes (**Figure 2**), the angiotensin II–type 1 (AT_1) and angiotensin II–type 2 (AT_2) receptors. Both receptor subtypes are G-coupled polypeptides that contain approximately 360 amino acids and have 7 cell membrane–spanning regions.[5] Major differences clearly separate the ultimate actions of these receptor subtypes: their genes reside on different chromosomes (AT_1 on chromosome 3 and AT_2 on chromosome X), and they share a sequence homology of only approximately 30%.

The AT_1 receptor is widely distributed in the healthy adult. Areas of expression include the systemic

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Figure 1. The renin-angiotensin-aldosterone system and its inhibitors. ACE = angiotensin-converting enzyme; AT_1 = angiotensin II type 1 receptor; AT_2 = angiotensin II type 2 receptor; CAGE = chymostatin-sensitive angiotensin II–generating enzyme; t-PA = tissue plasminogen activator.

vasculature, kidney, adrenal gland, heart, liver, and brain. The AT_2 receptor is found ubiquitously in the fetus, where it regulates normal organ development. In adults, it is present only in the adrenal medulla, uterus, ovary, vascular endothelium, and distinct brain areas. Of interest, the AT_2 receptor is upregulated in pathologic tissues, probably to help counterbalance the adverse effects of AT_1 receptor actions. Most important to recognize is that these receptors are functionally distinct. The AT_1 receptor clearly mediates the recognized hemodynamic actions of angiotensin II, including vasoconstriction. Also, the endocrine and mitogenic effects associated with angiotensin II are promoted through AT_1 receptor stimulation.[5,6] Angiotensin II triggers several signal transduction pathways through its interactions with the AT_1 receptor.[6] In contrast, the AT_2 receptor is thought to modulate organ development in the fetus and to possess both vasodilatory and antiproliferative effects.[6] Activation of AT_2 by angiotensin II stimulates signal transduction pathways that include a variety of phosphatases as well as the bradykinin/nitric oxide/cyclic GMP cascades.[7] The actions of the activated AT_2 receptor appear to antagonize the untoward effects of the AT_1 receptor (Figure 2).

CARDIAC EFFECTS OF THE RAAS
Myocardial Effects

The heart is densely populated with angiotensin II receptors. As a result, stimulation of the angiotensin II signal transduction pathways promotes various important actions in the myocardium. Such observed effects include myocyte hypertrophy with left ventricular hypertrophy (LVH), apoptosis in myofibroblasts, collagen deposition within muscle fibers, and fibrosis of myocardial tissue.[8–11] These changes carry significant consequences as LVH represents an important risk factor for the development of congestive heart failure (CHF). Also, potentially lethal cardiac arrhythmias and sudden death occur more frequently with a hypertrophied left ventricle.[12]

LVH may develop from a number of clinical disease states. Poorly controlled hypertension, obesity, type 2 diabetes, and insulin resistance with hyperinsulinemia all may promote LVH.[13,14] Excessive levels of insulin in combination with angiotensin II and/or aldosterone enhance the proliferative effects of these substances on myocardial cells.[15–17] Collagen deposition in myocardial tissue also is increased by this combination of hormones on heart tissue.[15–17] Enhanced expression of

matrix metalloproteinase and augmented oxidative stress represent further pathologic consequences of angiotensin II.[18,19] Angiotensin II may be particularly active in the setting of myocardial ischemia or hypertrophy. Experimental evidence demonstrates heightened activity and increased AT_1 receptor density in nearby noninfarcted tissue following experimental myocardial infarction.[20,21] Similar findings have been noted upon examination of the heart in patients with clinical CHF.[22,23]

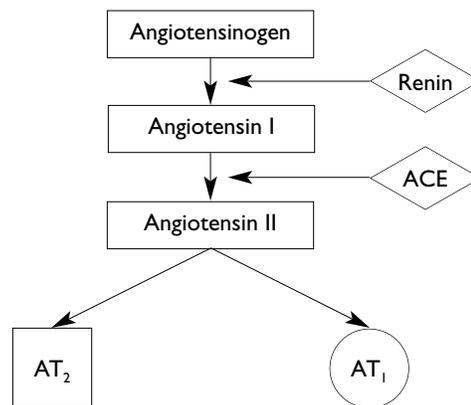**Effects on the Coronary Circulation**

Angiotensin II promotes arterial vasoconstriction, vessel wall hypertrophy, formation of atherosclerotic plaques, tissue inflammation, and prothrombotic effects in the coronary arteries.[24,25] In the experimental setting, angiotensin II can directly produce significant atherosclerosis, even in the absence of hypertension or hyperlipidemia.[26] These proatherosclerotic effects likely are derived from angiotensin II–induced activation of inflammatory cytokines,[27,28] monocyte chemoattractant proteins,[29] and vascular adhesion cell molecules.[30,31] Experimental models demonstrate prevention of these atherosclerotic effects with inhibition of angiotensin II formation with ACE inhibitors.[32]

The expression of plasminogen activator inhibitor–1 (PAI-1), a recognized prothrombotic moiety that opposes the natural fibrinolytic activity of tissue plasminogen activator, also is partially regulated by angiotensin II.[33] The role of angiotensin II in this process is supported by clinical trials that reveal significant suppression of PAI-1 following myocardial infarction[34] and CHF[35] with ACE inhibition. Of interest, ACE inhibitor therapy in large clinical trials is associated with a favorable reduction in acute coronary events, an effect that occurred despite modest blood pressure lowering. These findings raise the possibility that RAAS inhibition has a direct, positive influence on the atherosclerotic process itself.[36]

Interruption of the RAAS appears important in the modification of various forms of heart disease. Prospective clinical trials in patients who have undergone coronary revascularization have documented significant reductions in cardiovascular and all-cause mortality, myocardial infarction, and CHF in patients receiving ACE inhibitors.[37]

Influence on the Systemic Arterial Circulation

Activation of the RAAS directly promotes hypertension through vasoconstriction and smooth muscle cell hyperplasia, while also stimulating the sympathetic nervous system. Normal vascular remodeling is disturbed

Figure 2. Properties of angiotensin II receptor subtypes. ACE = angiotensin-converting enzyme; AT_1 = angiotensin II type 1 receptor; AT_2 = angiotensin II type 2 receptor; PAI-1 = plasminogen activator inhibitor–1.

in the presence of hypertension. Imbalance in the normal media-to-lumen ratio in arteries is one of the major consequences of elevated blood pressure.[24] Aberrant vascular remodeling produces a enhanced response to vasoconstrictor substances, thereby increasing arterial impedance and accelerating pulse wave reflection.[38] Intravenous infusion of angiotensin II amplifies sympathetic outflow,[39] and stimulation of the AT_1 receptor augments sympathetic tone.[40] Angiotensin II also enhances the activity of the potent arterial constrictor endothelin-1, further elevating blood pressure and inducing end-organ damage.[41]

Interactions between various complementary and counterbalancing substances are important in maintaining normal function of the vascular endothelium. Activation of the sympathetic nervous system promotes renin release, supporting the view that the RAAS and the sympathetic nervous system act together to modulate circulatory homeostasis and hemodynamic stability. The presence and activity of nitric oxide, a compound that promotes vasodilation and limits vascular hypertrophy, is key to modulating the effects of angiotensin II,

Table. Clinical Trials Evaluating Blockade of the RAAS on Cardiovascular Disease Endpoints

Trial	Drug Regimen	Patients (N)	Endpoint	Risk Reduction (%)*
SOLVD[49]	Enalapril	2569	Mortality from CHF	22
			All-cause mortality	16
			CV mortality	18
SAVE[50]	Captopril	2231	Hospitalization for CHF	22
			All-cause mortality	19
Val-HeFT[51†]	Valsartan	5010	CV morbidity/mortality	13
			All-cause mortality	−2 (NS)
RENAAL[52]	Losartan	1513	Hospitalization for CHF	32
			CV morbidity/mortality	10 (NS)
IDNT[53‡]	Irbesartan	1715	Hospitalization for CHF	23
			CV mortality	9 (NS)
RALES[54]	Spironolactone	1663	Hospitalization for CHF	35
			All-cause mortality	30

CHF = congestive heart failure; CV = cardiovascular; IDNT = Irbesartan Type 2 Diabetic Nephropathy Trial; NS = not statistically significant; RAAS = renin-angiotensin-aldosterone system; RALES = Randomized Aldactone Evaluation Study Investigators; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction; Val-HeFT = Valsartan Heart Failure Trial.

*All drug regimens compared versus placebo.

†Valsartan added to angiotensin-converting enzyme inhibitor.

‡Trial included amlodipine, but results in table reflect comparison only to placebo.

catecholamines, and endothelin. In pathologic states, angiotensin II depletes nitric oxide and impairs normal vascular endothelial cell function.[42]

Aldosterone represents another important cause of hypertension and vascular damage. Aldosterone enhances sympathetic activity and promotes both sodium retention and potassium loss by the kidney.[16]

CARDIAC RESPONSE TO RAAS INHIBITION
Myocardial Response

Most antihypertensive agents facilitate regression of LVH through adequate control of blood pressure.[43] Inhibition of the RAAS appears to promote regression of pathologic LVH more effectively than other antihypertensive agents.[44,45] This finding persists even when angiotensin receptor blockers (ARBs) are compared with β-adrenergic blockers,[46] drugs known to regress LVH. In a randomized controlled trial (LIFE) in which subjects who had hypertension and LVH were examined, losartan (an ARB) reduced hypertrophy more effectively than atenolol (a β-blocker).[46] Regression of LVH is associated with a more favorable prognosis[47] and improved functional capacity in the presence of diastolic dysfunction.[48]

A clinical corollary to the positive effects of RAAS inhibition noted above can be seen in some clinical tri-

als (**Table**).[49–54] In patients who have CHF due to systolic dysfunction, inhibition of the RAAS has provided highly favorable outcomes. ACE inhibitors are now primary therapy to treat heart failure based on several randomized controlled studies documenting improved symptoms and survival.[49,50,55] Potential effects include favorable remodeling of the left ventricle following myocardial infarction and vasodilation with reduction in afterload. Because there are non-ACE pathways for converting angiotensin I to angiotensin II (Figure 1), it has been proposed that ARBs may provide fuller inhibition of the undesired effects of angiotensin II in the heart.

Antagonism of the effect of aldosterone, the last product of the RAAS, also appears to provide clinical benefit. In a placebo-controlled study (RALES) of patients with New York Heart Association class III or IV CHF and a left ventricular ejection fraction of less than 35%, the aldosterone antagonist spironolactone significantly reduced mortality after only 2 years of therapy.[54]

In addition to a reduction in angiotensin II and aldosterone synthesis, ACE inhibitors also blunt the breakdown of bradykinin to its inactive metabolites, leading to increased bradykinin and nitric oxide levels. Both favorable and unfavorable effects develop from this action. Positive effects include systemic vasodilation

and potential afterload reduction in patients with CHF. The major detrimental action of increased bradykinin is dry cough, which leads to ACE inhibitor intolerance in 10% to 20% of patients. In contrast, ARBs do not promote significant elevations in bradykinin and rarely induce cough.[56] ARBs may offer additional benefits through their effect to reduce circulating levels of inflammatory cytokines in CHF[57] and to limit pathologic neurohumoral activation.[58]

On the basis of more complete angiotensin II blockade, reduction in inflammation, inhibition of sympathetic activation, and better tolerability, the use of ARBs as CHF therapy has been examined. Great hope for heart failure therapy was raised with the publication of the ELITE study.[59] Data from this trial suggested that ARBs were superior to ACE inhibitors in the treatment of CHF. The ARB losartan was compared with the ACE inhibitor captopril in older patients with heart failure. The primary study endpoint was the effect of an ACE inhibitor and an ARB on renal function. Although no difference in renal function was noted, composite rates of death and hospitalization for CHF were 32% lower in the group receiving losartan. These interesting results spurred the commencement of a larger trial, ELITE II.[60] In ELITE II, however, the ARB was not demonstrated to be superior to the ACE inhibitor.[60] In a similar cohort of CHF patients, no difference in the primary endpoint of mortality was observed between captopril (15.9%) and losartan (17.7%). A recently published trial of patients with type 2 diabetes and nephropathy revealed that losartan, although perhaps not superior to ACE inhibitors, was effective in preventing new CHF in treated patients (32% reduction).[52] Until other data suggest otherwise, the major advantage of the ARBs over ACE inhibitors is their better tolerability.

Dual blockade of the RAAS to fully blunt angiotensin II effects also has been examined in patients with heart disease. Several large studies have evaluated the combination of various ACE inhibitors and ARBs in the treatment of CHF. The Val-HeFT trial studied the addition of valsartan (an ARB) to an existing regimen designed to treat patients with CHF.[51] Ninety-three percent of the subjects were receiving an ACE inhibitor and 35% were receiving a β-blocker. An improvement in overall mortality rate was not observed with the addition of the ARB. However, the frequency of hospitalization for CHF was reduced and a composite of morbidity and mortality rates was significantly better in the ARB-therapy cohort. Combined morbidity and mortality was 45% lower in ACE inhibitor–intolerant subjects who received valsartan, underscoring the benefit of ARBs in this subset of CHF patients. Treatment with 3 different classes of drugs (β-blocker, ACE inhibitor, ARB) that inhibit the RAAS was found to be associated with worse outcomes and should be avoided.[51] There is not yet sufficient data to support the routine combination of ARBs and ACE inhibitors for treatment of CHF.

Response of the Systemic Arterial Circulation

As would be expected, therapeutic inhibition of the RAAS leads to euvolemia, vasodilatation with afterload reduction, and restoration of normal systemic blood pressure. Notable mechanisms include inhibition of the vasoconstrictor influences of angiotensin II and of the sodium-retentive properties of aldosterone. ACE inhibitors and ARBs have been documented to improve endothelium-dependent vasodilation[61] and promote normalization in the media-to-lumen ratio in arteries thickened by hypertension.[62] Additionally, both of these RAAS inhibitors have been noted to counteract the effects of the sympathetic nervous system.[63]

These physiologic effects have been translated into positive clinical outcomes. ACE inhibitors significantly improve the longitudinal prognosis in patients with various cardiovascular disorders, including hypertension, atherosclerosis, and diabetes mellitus.[36] The composite endpoint of myocardial infarction, stroke, or cardiovascular death was reduced by 22% in patients treated with an ACE inhibitor (ramapril) versus placebo in patients receiving conventional therapy.[36] This effect occurred despite equal blood pressure control in both groups. Significant reductions in individual endpoints such as stroke, all-cause mortality, myocardial infarction, cardiac arrest, need for coronary revascularization, and the occurrence of new diabetes also was noted with ACE inhibitor therapy.

Several large studies employing ARBs to interrupt the RAAS in a variety of subjects with cardiovascular disease are currently underway. Based on experimental data and the clinical trials presented above, it is hoped that the ARBs will maintain efficacy equal to that of ACE inhibitors in improving both short- and long-term cardiovascular outcomes.

RENAL EFFECTS OF THE RAAS
Effects on Sodium Balance

The RAAS has various direct and indirect actions on the kidney that modify systemic blood pressure homeostasis and regulate intravascular volume status. Activation by angiotensin II of the AT_1 receptors present in the kidney stimulates a variety of effects in humans, including modulation of renal vasomotor tone, control of endocrine functions, and regulation of cellular growth and proliferation. Angiotensin II clearly raises blood

pressure through influences on renal hemodynamics and salt and water excretion. The action of angiotensin II on the efferent arteriole augments glomerular filtration rate (GFR) by increasing the glomerular capillary pressure.[3] This effect increases the filtration fraction and, in so doing, modulates the peritubular Starling forces, decreasing hydrostatic pressure and increasing oncotic pressure in the renal interstitium.[3] These peritubular pressure changes favor reabsorption of sodium and fluid by the proximal tubules. Additionally, angiotensin II is able to regulate blood flow in the medullary circulation because the renal medulla is extensively innervated with angiotensin II receptors.[3] Angiotensin II thus reduces medullary blood flow and, as a result, increases sodium and water reabsorption by diminishing the renal interstitial pressure.[3]

In addition to effects of the RAAS on peritubular fluid fluxes, direct actions on the renal tubules also increase sodium and water reabsorption.[3] Angiotensin II stimulates proximal tubular sodium transport through actions on both luminal and basolateral membrane components. On the luminal side, angiotensin II increases Na^+/H^+ antiporter activity, increasing sodium uptake by the cell.[64] On the basolateral membrane, angiotensin II stimulates the $Na+/K^+$-ATPase enzyme and the Na^+/HCO_3^- cotransporter.[65] Sodium reabsorption also is promoted in the loop of Henle and the distal nephron through actions of angiotensin II on the Na^+/K^+-ATPase pump in the medullary thick ascending limb and in the epithelial Na^+ channel in the cortical collecting tubules.[66,67] Finally, aldosterone stimulates sodium reabsorption through the epithelial $Na+$ channel in cells in the distal nephron by activating the mineralocorticoid receptor.[68]

Effects on Cell Proliferation in the Kidney

In addition to its role as a potent vasoconstrictor and regulator of sodium homeostasis, angiotensin II possesses significant mitogenic properties, accomplishing these effects through the activation of AT_1 receptors.[69,70] Angiotensin II induces cell proliferation and tissue remodeling directly as well as indirectly through multiple pathways.[70] One such pathway stimulates the production of a group of cytokines and growth factors including transforming growth factor–β (TGF-β), platelet-derived growth factor, and nuclear factor-κB, ultimately leading to tissue inflammation, fibroblast formation, and collagen deposition. The sum of these effects is the increased development of glomerulosclerosis and tubulointerstitial fibrosis, thereby enhancing progressive renal injury.[69,70] Interestingly, it appears that angiotensin II acts via the AT_2 receptor to counterbalance the inflammatory and promitogenic

actions associated with AT_1 receptor activation.[70] In fact, expression of the AT_2 receptor is upregulated in areas of tissue injury in an effort to limit these untoward effects.

Aldosterone also possesses proinflammatory and promitogenic actions that induce renal injury. As with angiotensin II, aldosterone directly increases expression and production of TGF-β.[71] Formation of this steroid hormone is increased in renal ablation models and has been associated with increased glomerular and tubulointerstitial fibrosis and progressive loss of renal function.[72] It is therefore likely that both aldosterone-induced hypertensive-related pressure injury as well as direct cellular actions of this mineralocorticoid act synergistically to promote kidney damage and scarring.

Role of the RAAS in Kidney Disease

Examination of the various roles of the RAAS demonstrates the importance of this system in maintaining normal hemodynamics and electrolyte balance. In the kidney, heightened tone of the efferent arteriole induced by angiotensin II increases GFR and is a protective response to maintain GFR in states of reduced renal perfusion.[3] However, unregulated and excessive production of angiotensin II is associated with renal injury that can become progressive and irreversible. Examples of this phenomenon include both diabetic and nondiabetic nephropathies.[73–76] Many basic studies and clinical studies in humans have now shown that inhibition of the RAAS reduces the injurious effects of angiotensin II in diabetic and nondiabetic nephropathies.

Nephron loss with a reduction in the number of functioning nephron segments can occur from a variety of renal injuries and promote progressive chronic kidney disease. The remaining nephrons develop glomerular capillary hypertension and increased single-nephron GFR, leading to a process called *hyperfiltration*. Although these changes are initially adaptive to maintaining GFR, over the long term, they have a negative impact on renal function. The importance of hyperfiltration and glomerular hypertension in promoting the progression of chronic renal disease cannot be overstated.[77] Hyperfiltration enhances local RAAS activity in the kidney, further perpetuating renal disease processes.

In diabetic nephropathy, hyperglycemia promotes hyperfiltration and also upregulates expression of the RAAS components in the kidney. Importantly, the combination of an activated RAAS along with advanced glycation end products and other mediators of renal injury contribute significantly to the kidney damage that develops from excessive glomerular capillary pressure and hyperfiltration.[78]

The renal benefits of RAAS blockade also include reductions in pro-inflammatory and profibrotic effects of angiotensin II and aldosterone on renal tissue. Blockade of the RAAS thus may ameliorate renal damage and reduce progression of chronic kidney disease in both the nondiabetic and diabetic forms of nephropathy.

TREATMENT OF KIDNEY DISEASE WITH INTERRUPTION OF THE RAAS

Treatment of kidney disease associated with excessive RAAS activity is achieved by ACE inhibition, angiotensin II receptor antagonism, or aldosterone receptor blockade. Inhibition of ACE activity decreases angiotensin II and aldosterone formation and potentiates the vasodilatory effects of the kallikrein-kinin system by allowing the formation of the endogenous vasodilator bradykinin (Figure 1).[79] The decrease in angiotensin II production also inhibits sympathetic outflow. ACE inhibitors have, therefore, gained widespread application in the treatment of all forms of hypertension. Of particular importance, ACE inhibitors reduce proteinuria and delay progression of renal disease in diabetic nephropathy and in other disorders associated with chronic kidney disease.[79,80] Lewis and coworkers demonstrated a 50% reduction in the time to doubling of serum creatinine level, progression to end-stage renal disease, or death in patients treated with the ACE inhibitor captopril as compared with conventional therapy.[79] In nondiabetic patients with kidney disease, the ACE inhibitor benazepril was associated with an overall risk reduction of 53% in the development of the primary endpoint (doubling of serum creatinine or need for dialysis) as compared with conventional antihypertensive therapy.[80] These effects are likely unique to RAAS inhibition and not attributable to a simple improvement in blood pressure control.

ARBs also reduce blood pressure to a degree similar to that of other antihypertensive agents.[52,81] Their mechanism of action is based on antagonism of the AT_1 receptor, and, potentially, by stimulation of the AT_2 receptor. Unlike ACE inhibitors, ARBs do not directly modulate the formation of bradykinin.[52] However, animal models suggest that by allowing angiotensin II to bind the AT_2 receptor, ARBs facilitate the formation of bradykinin and other anti-mitogenic substances associated with this receptor pathway.[82] Preliminary information suggests that ARBs reduce proteinuria and prevent progression of diabetic and nondiabetic chronic kidney disease in a fashion similar to ACE inhibitors.[52,81,82] In the RENAAL study, losartan was compared with conventional therapy in 1513 type 2 diabetics with hyper-

tension and nephropathy.[52] Fewer patients in the losartan group reached the primary composite end points of time to doubling of serum creatinine level, progression to end-stage renal disease, or death (16% risk reduction). Similar findings were described in the IDNT study,[53] which evaluated the ARB irbesartan in patients with type 2 diabetes mellitus and nephropathy. Irbesartan therapy was associated with a 19% risk reduction in composite renal end points as compared with placebo over a mean follow-up of 2.6 years. These data suggest that modulation of the RAAS with ARBs in type 2 diabetics is a logical strategy.

The potential renal benefit of dual blockade of the RAAS pathways with ACE inhibitors and ARBs is an area of interest for many researchers. The different pathways through which ACE inhibitors and ARBs modulate the RAAS raise the question whether the combination of these drugs can further reduce proteinuria and progression of chronic kidney disease. Experimental animal studies and preliminary human data suggest that a benefit may exist when therapies are combined. The CALM study, a randomized controlled trial, combined lisinopril (20 mg daily) and candesartan (16 mg daily) to treat hypertension and reduce microalbuminuria in patients with type 2 diabetes mellitus.[83] Dual RAAS blockade over a 24-week period safely reduced systolic/diastolic blood pressure (10 mm Hg/6 mm Hg) more than either monotherapy. Also, combination therapy reduced microalbuminuria (50%) as compared with candesartan (24%) and lisinopril (39%) monotherapy in this group of hypertensive diabetic patients. In contrast to these studies, Agarwal demonstrated that combination therapy with an ARB and ACE inhibitor was not superior to ACE inhibitor therapy alone in decreasing proteinuria in patients with various renal diseases, including diabetic nephropathy.[84] Despite these generally optimistic data, it is premature to draw firm conclusions about dual RAAS therapy in kidney disease.

Aldosterone stimulates renal sodium reabsorption, leading to volume-induced elevations in blood pressure.[68] Aldosterone also has been shown to cause direct injury to the kidney through stimulation of TGF-β and induction of glomerular and tubulointerstitial fibrosis. Antagonism of the mineralocorticoid receptor with spironolactone, a competitive inhibitor of aldosterone, reduces blood pressure by enhancing renal sodium excretion and consequently, may decrease the development of hypertensive renal disease.[68] A direct receptor blocker, eplerenone, appears effective in reducing proteinuria and glomerulosclerosis in animals. It is presently under study in humans. Animal experiments

suggest that spironolactone also may blunt progression of renal disease by limiting the fibroproliferative effects of aldosterone.[71] Preliminary data generated in humans support the potential for renoprotection with aldosterone receptor antagonism.[85] Patients with overt diabetic nephropathy and chronic kidney disease on therapy with the ACE inhibitor enalapril obtained a further reduction in proteinuria with the addition of spironolactone to their treatment regimen. However, because serum potassium levels may rise with this therapy, patients with risk factors for hyperkalemia must be followed closely when prescribed multiple inhibitors of the RAAS.

CONCLUSION

Experimental data and clinical trials clearly document that the RAAS is an important promotor of cardiovascular and renal disease. The hemodynamic consequences of systemic hypertension as well as the direct pro-inflammatory and profibrotic effects of angiotensin II and aldosterone incur maladaptive changes in the cardiovascular system and progressive kidney damage. Therapies directed at various components of the RAAS—namely angiotensin II formation and binding to the AT_1 receptor—have been associated with positive outcomes in clinical trials. A reduction in aldosterone synthesis and binding to the mineralocorticoid receptor also may reduce end-organ damage in the heart and kidneys. These inhibitors of the RAAS should gain widespread use, perhaps in combination, to prevent or blunt damage in these important organ systems. **HP**

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