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Manipulation of the Renin-Angiotensin System

Michael M. Givertz, MD

Since the initial description of angiotensin II–mediated hypertension 40 years ago, basic and clinical investigations of the renin-angiotensin system (RAS) have resulted in a broader understanding of cardiovascular pathophysiology and significant advances in therapy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists are now widely prescribed for the treatment of hypertension and left ventricular (LV) dysfunction; more recently, the aldosterone receptor antagonist, spironolactone, has proven beneficial in severe heart failure. This article will focus on our current understanding of the RAS and how pharmacological manipulation of this system can improve clinical outcomes in patients with cardiovascular disease.

Pathophysiological Rationale for RAS Manipulation

Renin is released by juxtaglomerular cells in the kidney in response to renal hypoperfusion, decreased sodium delivery, and sympathetic activation (Figure 1). Angiotensinogen produced by the liver is cleaved by renin to yield the inactive decapetide angiotensin I. Circulating angiotensin I is, in turn, converted to angiotensin II in the lungs by the action of ACE. ACE, or kininase II, also plays a key role in the kallikrein-kinin system by cleaving bradykinin to inactive peptides. In addition to the hormonal effects of circulating angiotensin II, all of the necessary components of the RAS exist in several organs and tissues, including the heart, kidneys, and vasculature.

Angiotensin II exerts its actions in target organs and tissues by binding to both angiotensin II type 1 and 2 (AT$_1$ and AT$_2$) receptors, although adverse effects in humans seem to be mediated primarily by the AT$_1$ receptor (Figure 1). In the kidney, angiotensin II causes sodium and water retention and efferent arteriolar vasoconstriction. Constriction of the systemic vasculature by angiotensin II causes hypertension, whereas coronary vasoconstriction may cause myocardial ischemia and arrhythmias. Angiotensin II–stimulated secretion of aldosterone by the adrenal cortex and arginine vasopressin by the posterior pituitary contributes to extracellular volume expansion and sympathetic activation. Of particular relevance to the progression of cardiovascular disease is the recognition that angiotensin II and aldosterone exert pleiotropic effects in the heart and systemic vasculature that result in myocardial and vascular remodeling. Important biological events include cellular hypertrophy, interstitial fibrosis, apoptosis, inflammation, and thrombosis. Increasing evidence points to the RAS as a major contributor to the progression of atherosclerosis.

Pharmacology of RAS Manipulation

Several classes of drugs inhibit the RAS (Figure 2) and slow the progression of cardiovascular disease. ACE inhibitors decrease the formation of angiotensin II and inhibit the breakdown of bradykinin. In turn, increased bradykinin levels result in the formation of nitric oxide and other endogenous vasodilators. Most ACE inhibitors are formulated as pro-drugs, require esterification in the liver, and are cleared by the kidneys. Differences in tissue affinity exist, but they have not been shown to impact clinical outcomes. Circulating angiotensin II levels decrease with short-term ACE inhibitor therapy but return to normal, pretreatment levels with long-term ACE inhibition. This “escape” phenomenon may be due, in part, to non-ACE pathways of angiotensin I metabolism (eg, myocardial chymase), and it provides the rationale for the development of angiotensin receptor antagonists.

The angiotensin receptor antagonists bind competitively to and dissociate slowly from AT$_1$ receptors. Circulating angiotensin II levels increase during therapy due to the loss of negative feedback. There are 6 angiotensin receptor antagonists approved for the treatment of hypertension, which vary in bioavailability from 15% (eprosartan) to 70% (irbesartan) and in half-life from 2 hours (losartan) to 24 hours (telmis-
artan). All are highly protein-bound and, except for telmisartan, are excreted in the bile and by the kidney.

Spironolactone competitively inhibits aldosterone-sensitive sodium channels in the cortical collecting tubule of the kidney and causes sodium and free water excretion and potassium retention. β-Adrenergic antagonists, in addition to blocking the tissue effects of norepinephrine, inhibit renin release by the kidney by ≈60% and thereby indirectly attenuate RAS activation. Investigational agents for manipulating the RAS include vasopeptidase inhibitors, which inhibit both ACE and neutral endopeptidase, and renin inhibitors.

Indications

Hypertension
ACE inhibitors and angiotensin receptor antagonists are indicated for the treatment of mild, moderate, or severe hypertension (Table). Both classes of drugs cause dose-dependent reductions in systolic and diastolic pressure without reflex tachycardia. The decrease in blood pressure tends to correlate with baseline plasma renin activity. Compared with calcium-channel blockers and β-blockers, ACE inhibitors and angiotensin receptor antagonists are equally effective in lowering blood pressure, tend to be better tolerated, and cause greater reduction in LV hypertrophy. These agents exert additional antihypertensive effects when combined with a thiazide diuretic, and there is no rebound hypertension after withdrawal. The antihypertensive effects of angiotensin receptor antagonists are independent of sex, age, and race, and are well tolerated in the elderly. In contrast, ACE inhibitors are less potent in blacks and have a withdrawal rate of up to 15% in patients >60 years.

ACE inhibitors are particularly effective in hypertensive patients with coexisting LV dysfunction or diabetic nephrop-
Evaluation of Losartan In The Elderly (ELITE) study suggested a survival benefit of losartan versus captopril, but ELITE II failed to demonstrate the superiority of angiotensin receptor blockade. For heart failure patients who remain symptomatic on an ACE inhibitor, the addition of an angiotensin receptor antagonist has the theoretic potential to block RAS activation maximally, reduce heart failure symptoms, and improve clinical outcomes. The recently completed Valsartan in Heart Failure Trial (Val-HeFT) examined >5000 patients with mild-to-moderate heart failure and showed that valsartan, when added to an ACE inhibitor, reduced heart failure hospitalizations by 28% but had no effect on mortality. A trend toward worse outcomes was observed in patients taking a β-blocker in addition to an ACE inhibitor and angiotensin receptor blocker. Another large trial (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity [CHARM]) is currently underway to evaluate the survival benefit of candesartan when used as an alternative or in addition to an ACE inhibitor. An important arm of this study will address optimal RAS blockade in patients with diastolic heart failure.

Despite treatment with an ACE inhibitor or angiotensin receptor antagonist, patients with heart failure may demonstrate elevated aldosterone levels. Mechanisms of “aldosterone escape” include alternative stimuli for aldosterone synthesis (eg, adrenocorticotropic hormone and endothelin), potassium-dependent aldosterone secretion, and reduced aldosterone clearance. Spironolactone has been used infrequently as a potassium-sparing diuretic in patients with refractory ascites, edema, and hypokalemia. Although there has been concern about the potential for serious hyperkalemia when spironolactone is added to an ACE inhibitor, recent evidence suggests that spironolactone is safe and effective in treating chronic heart failure. The Randomized Aldactone Evaluation Study (RALES), which randomized >1600 patients with severe heart failure and low ejection fractions to spironolactone or placebo, was stopped early because of a 30% reduction in mortality in the spironolactone group. In addition, spironolactone improved symptoms and reduced heart failure hospitalizations.

### Myocardial Infarction

Animal models and human studies demonstrated that ACE inhibitors attenuate LV remodeling after myocardial infarction. Subsequent large, randomized, controlled trials have shown that ACE inhibitors reduce cardiovascular and all-cause mortality, prevent or delay the onset of heart failure, and decrease the risk of stroke after a myocardial infarction. Although it is generally agreed that ACE inhibitors should be initiated early after acute myocardial infarction (on day 1 or 2), a selective versus broad-inclusion strategy is still debated. Long-term trials, including the Survival and Ventricular Enlargement Trial (SAVE), Acute Infarction Ramipril Efficacy Study (AIRE), and Trandolapril Cardiac Evaluation (TRACE), selectively enrolled high-risk patients with LV dysfunction or heart failure after a myocardial infarction and demonstrated a 20% reduction in mortality. Long-term therapy also reduced the risk of progressive heart failure and stroke. Short-term trials after myocardial infarction (Fourth

### Heart Failure

Randomized, controlled trials demonstrated the beneficial effects of ACE inhibitors on clinical status, neurohumoral activation, quality of life, and survival in patients with chronic heart failure due to LV systolic dysfunction. Important hemodynamic and neurohumoral effects include balanced vasodilation, increased bradykinin levels, and inhibition of aldosterone and inflammatory cytokines. Cardiovascular effects include reductions in right and left heart filling pressures, increased cardiac output without reflex tachycardia, and attenuation of myocardial hypertrophy and fibrosis. ACE inhibitors reduce the risk of death due to heart failure, sudden cardiac death, and myocardial infarction; similar mortality benefits have been observed with multiple agents and in a broad range of patients. Maximum dose therapy is recommended and is equally well tolerated as low-dose therapy. ACE inhibitors are generally used with diuretics in patients with fluid retention and with β-blockers in symptomatic patients. Unresolved issues with ACE inhibitors in heart failure include attenuation of effects by aspirin, decreased efficacy in blacks, and benefits in diastolic heart failure. Despite survival benefits, ACE inhibitors remain underused, particularly in the elderly.

For patients with heart failure who are intolerant of or have a contraindication to ACE inhibitors, angiotensin receptor antagonists are an effective alternative. Like ACE inhibitors, angiotensin receptor antagonists reduce systemic vascular resistance and LV filling pressure and increase cardiac index; effects on exercise duration and symptoms are modest. The

### FDA-Approved Indications for Agents That Block the RAS

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>Angiotensin Receptor Antagonists</th>
<th>Spironolactone</th>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Myocardial infarction</td>
<td>Hypertension</td>
<td>Hypokalemia</td>
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<td>Heart failure</td>
<td>Severe heart failure</td>
<td>Asites</td>
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<td>Diabetic nephropathy</td>
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FDA indicates Food and Drug Administration.

athy because of their known beneficial effects in improving outcomes in these settings. In essential hypertension, however, neither ACE inhibitors nor angiotensin receptor antagonists have been shown to reduce cardiovascular morbidity and mortality. When compared with standard therapy (diuretics and β-blockers) in >10,000 patients with diastolic hypertension, captopril exerted no additional benefits on the combined end point of myocardial infarction, stroke, or cardiovascular death. Ongoing controlled trials of ACE inhibitors versus diuretics or calcium-channel blockers (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]) and angiotensin receptor blockers versus β-blockers (Losartan Intervention For Endpoint Reduction in Hypertension Study [LIFE]), calcium channel blockers (Valsartan Antihypertensive Long-term Use Evaluation [VALUE]), and diuretics (Study on Cognition and Prognosis in the Elderly [SCOPE]) will help define the role of these agents in improving clinical outcomes in patients with uncomplicated and high-risk hypertension.

### Myocardial Infarction

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International Study of Infarct Survival [ISIS-4], Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-3 [GISSI 3], and Survival of Myocardial Infarction Long-term Evaluation [SMILE] enrolled more broadly and demonstrated a 7% reduction in mortality, with the greatest benefit seen in high-risk patients (eg, anterior myocardial infarction, heart failure, and diabetes). According to class I American College of Cardiology/American Heart Association guidelines, ACE inhibitors should be given to all patients with acute myocardial infarction and anterior ST elevation, an ejection fraction <40%, or clinical heart failure in the absence of hypotension. Therapy should be continued for at least 6 weeks in all patients and indefinitely in patients with persistent LV dysfunction, although recent data suggest a role for long-term ACE inhibition in all patients with ischemic heart disease. Despite their increasing use in patients with hypertension and heart failure, angiotensin receptor antagonists have not been adequately tested in the setting after myocardial infarction. Large, randomized trials (Valsartan in Acute Myocardial Infarction [VALIANT] and Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan [OPTIMAAL]) involving >20,000 patients are currently underway to define the role of angiotensin receptor antagonists as alternative or adjunctive therapy to ACE inhibitors in high-risk patients after acute myocardial infarction. For now, angiotensin receptor antagonists should only be used in patients who are intolerant of or have a contraindication to ACE inhibitor therapy.

Vascular Disease and Nephropathy
Several lines of evidence support the use of ACE inhibitors in high-risk patients with vascular disease. Early work by Brunner and colleagues suggested that patients with hypertension and RAS activation are at increased risk of myocardial infarction and stroke. Subsequent studies demonstrated that ACE inhibitors and angiotensin receptor antagonists improve endothelial function in patients with hypertension or diabetes, and ACE inhibitors slow the progression of atherosclerosis in animal models. More recent observations from the SAVE and Studies of Left Ventricular Dysfunction (SOLVD) trials in patients with LV dysfunction suggest that ACE inhibitors reduce the risk of ischemic events. The Heart Outcomes Prevention Evaluation (HOPE) study tested the role of ACE inhibition with ramipril in >9,000 patients with atherosclerosis in the absence of heart failure or LV dysfunction and demonstrated significant reductions in myocardial infarction, stroke, and death. The implication from these data is that attenuation of tissue RAS protects the heart, kidneys, and vasculature from long-term angiotensin II and aldosterone stimulation. Potential mechanisms of benefit include regression of hypertrophy and fibrosis, decreased inflammation and oxidative stress, and increased fibrinolysis. Whether the benefits of ramipril can be generalized to other ACE inhibitors or angiotensin receptor antagonists remains unknown.

Chronic renal insufficiency is common in patients with cardiovascular disease and coexisting hypertension or diabetes. In animal models, ACE inhibitors and angiotensin recep-tor antagonists delay the progressive loss of renal function by normalizing glomerular hemodynamics and attenuating glomerular and interstitial fibrosis. Controlled trials in patients with insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus have shown that ACE inhibitors slow the decline in renal function and decrease the risk of cardiovascular events. In patients with hypertensive nephropathy, ACE inhibitors and angiotensin receptor antagonists decrease albumin excretion, and their effects may be additive. Ongoing randomized studies (Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan [RENAAL], Appropriate Blood Pressure Control in Diabetes—Part 2 With Valsartan [ABCD 2V], and Irbesartan Diabetic Nephropathy Trial [IDNT]) will determine whether angiotensin receptor antagonists exert renoprotective effects and reduce cardiovascular morbidity and mortality in patients with non-insulin-dependent diabetes.

**Adverse Effects**
Increased bradykinin levels may account for important differences in tolerability between ACE inhibitors and angiotensin receptor antagonists. Dry cough occurs in 5% to 15% of patients taking ACE inhibitors, but it has not occurred with angiotensin receptor antagonists. Not infrequently, “ACE inhibitor cough” is a manifestation of pulmonary congestion and improves with diuresis. Angioedema, a potentially life-threatening complication of ACE inhibitors in 0.1% to 0.5% of patients, has been reported only rarely with angiotensin receptor antagonists, and a direct causal link is unproven. First-dose hypotension with ACE inhibitors typically occurs in patients who are volume-depleted due to diuretics and/or sodium restriction. Hyperkalemia can occur with both ACE inhibitors and angiotensin receptor antagonists, especially in patients with chronic renal insufficiency or diabetes or those taking potassium-sparing diuretics or potassium supplements. Similarly, progressive renal dysfunction can occur with either agent in the setting of hypovolemia or renovascular hypertension; this complication is much less common than generally believed, and it is usually reversible. In heart failure patients, transient renal dysfunction can often be avoided by decreasing the diuretic dose on initiation of therapy. Both ACE inhibitors and angiotensin receptor antagonists are contraindicated during pregnancy.

In the RALES study, the incidence of serious hyperkalemia was 2% with spironolactone, which did not differ significantly from placebo. However, the incidence may be higher in elderly patients with coexisting renal dysfunction, and close laboratory monitoring is advised. Adverse effects that may limit the use of spironolactone, particularly in men, include gynecomastia and breast pain. Newer, more selective aldosterone receptor antagonists with improved side effect profiles are being developed for the treatment of heart failure.

**Acknowledgment**
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