Interrupting the Renin-Angiotensin System: The Role of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists in the Treatment of Hypertension

Michael A. Weber

The renin-angiotensin system has two roles in clinical hypertension: its vasoconstrictor properties directly govern blood pressure, and its actions on arterial smooth muscle, connective tissue, and endothelial integrity affect cardiovascular prognosis. Additionally, the direct actions of angiotensin II on the function and structure of the heart and renal vasculature influence clinical events. Angiotensin-converting enzyme (ACE) inhibitors have produced functional and clinical outcome benefits in clinical trials of patients with congestive heart failure, systolic dysfunction after myocardial infarction, and diabetic nephropathy. Similar favorable trends have been noted in observational studies in hypertension. Because such enzymes as chymase can substitute for ACE, the ACE inhibitors may not completely block angiotensin II formation, although they enhance bradykinin accumulation and secondarily stimulate nitric oxide and vasodilatory prostaglandins.

Angiotensin II receptor blockers (ARB) selectively block the angiotensin II type 1 (AT₁) receptor that not only mediates the known effects of angiotensin II but, according to recent reports, might be responsible for sequestering angiotensin II molecules in renal and cardiac cells. Moreover, by increasing plasma concentrations of angiotensin II, the ARB stimulate the unblocked angiotensin II type 2 (AT₂) receptors, which—if they exist in meaningful numbers in human hypertension—mediate additional vasodilatory and antiproliferative effects. The contrasting actions of these two classes of drugs might be clinically relevant. For example, they may have additive antihypertensive efficacy; they have differing effects on renal plasma flow; and in a small pilot study of patients with congestive heart failure, the ARB demonstrated an apparent advantage in survival. Ongoing clinical trials will try to determine whether the effects of ARB can equal or even exceed the beneficial effects of ACE inhibitors on cardiovascular prognosis.


KEY WORDS: Renin-angiotensin system, hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, cardioprotection.
The outcomes of treating hypertension are conveniently classified as short-term, intermediate, and long-term. Short-term outcomes pertain to the immediate results of treating hypertension and focus on such issues as changes in blood pressure and the tolerability of the treatment being offered. Intermediate outcomes are surrogates for target organ changes and include such measures as left ventricular muscle mass, renal function, proteinuria, and vascular changes. Ultimately, though, the long-term outcomes—particularly when viewed on a population basis—are the most critical. These outcomes include determination of whether particular treatments of hypertension effectively prevent strokes, coronary events, and other cardiovascular sequelae of hypertension. The recent Sixth Report of The Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) has endorsed this classification of outcomes in hypertension therapy.

Evaluation of trials in hypertension with clinical endpoints has shown that stroke is reduced by most blood pressure–lowering therapies but that the prevention of coronary events is less readily achieved. Most of these trials have been based on older forms of antihypertensive pharmacologic therapy, usually diuretics and β-blockers or other sympatholytic therapies. Data from the clinical trials with newer antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and calcium channel blockers are not yet available. Explanations for the relatively disappointing results in preventing coronary events with traditional therapies include three possibilities: (1) high blood pressure is part of a syndrome of cardiovascular risk factors, sometimes termed the hypertension syndrome, and failure to deal with concomitant problems of lipid disorders and other related abnormalities can explain the persistent high incidence of coronary disease; (2) blood pressure reductions have not been sufficiently rigorous; (3) the hypothesis that hypertension is associated with a concomitant vascular pathogenetic factor, such as increased activity of the renin-angiotensin system, has not been adequately addressed by appropriate therapies.

The chief features of the hypertension syndrome are shown in Table 1. This constellation of abnormalities appears to be inherited and should be suspected in all patients with hypertension. Underlying these abnormalities might be increased activity of the sympathetic nervous system or the renin-angiotensin system, each of which can play a role in creating or worsening other cardiovascular risk factors. This, in turn, raises the possibility that effective blockade of these systems might have advantages beyond blood pressure–lowering effects in providing cardiovascular protection.

### TABLE 1. CHARACTERISTICS OF THE HYPERTENSION SYNDROME

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tr>
<td>Elevated blood pressure</td>
<td>In hypertension, the criterion for &quot;normal&quot; blood pressure is ≈ 130/85 mm Hg and the criterion for &quot;optimal&quot; blood pressure is ≈ 120/80 mm Hg. These criteria are based on the consideration by JNC VI of available epidemiologic data. The recent Hypertension Optimal Treatment (HOT) Trial confirmed that there was a clinical endpoint advantage in reducing blood pressures to as close to 80 mm Hg as possible, particularly in high-risk patients. Similarly, the Modification of Diet in Renal Disease (MDRD) Study had concluded that prevention of deterioration in renal function was best achieved with blood pressure values &lt; 120/75 mm Hg. In achieving these aggressive goals, such newer drugs as the ARB and the ACE inhibitors may be of particular importance because they combine efficacy with minimal side effects.</td>
</tr>
<tr>
<td>Dyslipidemias; exaggerated cardiovascular risk when blood pressure and lipid abnormalities coexist</td>
<td></td>
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<tr>
<td>Insulin resistance; tendency toward glucose intolerance</td>
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<tr>
<td>Truncal obesity</td>
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<tr>
<td>Microalbuminuria; early changes in renal function reserve</td>
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<tr>
<td>Increased activity of vascular coagulation factors</td>
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<tr>
<td>Reduced arterial compliance</td>
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<td>Hypertrophy and altered diastolic function of left ventricle</td>
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Beyond the role of blood pressure itself and the metabolic changes associated with the hypertension syndrome, the renin-angiotensin system may contribute directly to the adverse clinical consequences of hypertension. Therefore, ACE inhibitors and ARB could potentially benefit short-term, intermediate, and long-term treatment outcomes. More than 25 years ago, Brunner and Laragh and their colleagues provided data suggesting that increased activity of the renin-angiotensin system, independent of its hemodynamic effects, had an adverse impact on prognosis in hypertension, particularly on the probability of myocardial infarction (MI). This hypothesis was later confirmed in a larger, prospective study. In addition, as part of a separate hypothesis, high blood pressure could be attributed directly to a vasoconstrictor action of the renin-angiotensin system in patients with evidence of high plasma renin activity.

Explored in more detail, angiotensin II—the vasoactive product of this system—has two broad types of action. First, it works as a powerful vasoconstrictor that can be responsible for increasing the blood pressure in hypertension and, of similar importance, for
increasing the hemodynamic afterload in congestive heart failure (CHF). The other action of angiotensin II produces a long-term effect in which its trophic properties are paramount. Angiotensin II works directly on the vascular walls to produce medial hypertrophy, stimulate connective tissue growth, and disrupt the endothelium, thereby accelerating the process of atherosclerosis. Indeed, as summarized in Table 2, it regulates a wide variety of genes that potentially affect vascular growth, clotting mechanisms, and the formation of vasoactive substances. From Kurtz and Gardner, with permission.

Angiotensin II also works in the glomerular circulation of the kidney. It increases constriction of the efferent arterioles, raises hydraulic pressure, and thus disrupts the integrity of the glomerular basement membrane and associated structures. This causes proteinuria, nephrosclerosis, and ultimately renal insufficiency. Additionally, angiotensin II works directly on the heart, promoting hypertrophy of the myocytes and leading to left ventricular hypertrophy, another hallmark of hypertension. For these reasons, the ACE inhibitors and, more recently, the ARB are being tested to determine whether they have a beneficial impact on cardiovascular outcomes in hypertension.

PHARMACOLOGY

The ACE inhibitors and the ARB interrupt the renin-angiotensin system in different ways. As shown in Figure 1, the ACE inhibitors act primarily on the ACE, limiting conversion of angiotensin I to the active hormone angiotensin II. The ACE, however, is a kinase that has an important role in breaking down the vasodilatory bradykinin. Therefore, the effect of an ACE inhibitor is not solely to block formation of angiotensin II, but also to enhance concentrations of bradykinin. In turn, bradykinin facilitates production of nitric oxide and vasodilatory prostaglandins. Ultimately, then, the ACE inhibitor has effects on angiotensin II, bradykinin, nitric oxide, and prostaglandins, all of which have blood pressure–lowering properties and, perhaps just as important, antigrowth properties in vascular, cardiac, and renal tissues.

A potential limiting factor to the effectiveness of the ACE inhibitor (Figure 1) is that its blockade of angiotensin II formation may not be complete. The ACE is only one of several enzymes that can exhibit the proteolytic action that converts angiotensin I to angiotensin II. Chymase, for example, may be an important alternative pathway in humans for the formation of angiotensin II. For this reason, ARB may provide a more specific and effective approach for blocking the actions of angiotensin II.

Two types of the angiotensin II receptor, type 1 (AT1) and type 2 (AT2), appear to be relevant in understanding the actions of the ARB. These agents—of which losartan, irbesartan, valsartan, candesartan, and telmisartan are now approved for use in the United States—selectively block the AT1 receptor. The principal properties of this receptor are shown in Table 3. It is clear that the AT1 receptor mediates the known actions of angiotensin II that are relevant to hypertension and CHF, specifically its vasoconstrictor and vascular growth effects. This receptor is constantly expressed in the cardiovascular system and in other relevant tissues throughout the body. The clinically available ARB are highly selective for the AT1 receptor, and have no effect at the AT2 receptor. The role of the AT2 receptor is not completely defined. Indeed, the AT2 receptor may not even exist in meaningful numbers in healthy adult humans. It plays an important role in the fetus, and in the adult it is expressed chiefly in response to injury. However, it is possible that such conditions as established hypertension and CHF could...
TABLE 3. ANGIOTENSIN II RECEPTORS AND THE EFFECTS OF BLOCKADE

<table>
<thead>
<tr>
<th>Vascular AT₁ receptors</th>
<th>Constantly expressed</th>
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<tr>
<td></td>
<td>Mediate vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Mediate angiotensin II arterial wall growth effects</td>
</tr>
<tr>
<td>Vascular AT₂ receptors</td>
<td>Expressed only after injury (sustained hypertension might provoke expression)</td>
</tr>
<tr>
<td></td>
<td>Mediate vasodilation</td>
</tr>
<tr>
<td></td>
<td>Mediate antiproliferative actions</td>
</tr>
<tr>
<td></td>
<td>Activate other factors (e.g., nitric oxide)</td>
</tr>
<tr>
<td>Potential double action of selective AT₁ blockers</td>
<td>Directly block vasoconstrictor and growth actions of angiotensin II at AT₁ receptors</td>
</tr>
<tr>
<td></td>
<td>Increase circulating angiotensin II levels</td>
</tr>
<tr>
<td></td>
<td>Unblocked AT₂ receptors (if expressed), stimulated by increased angiotensin II activity, mediate vasodilation and growth inhibition</td>
</tr>
<tr>
<td>Net effects: AT₁ blockade + AT₂ stimulation</td>
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AT₁, angiotensin II type 1; AT₂, angiotensin II type 2.

change or damage cardiovascular tissue sufficiently to prompt expression of the AT₂ receptor and make it clinically relevant. Some of this receptor’s attributes are shown in Table 3. In essence, its effects oppose those of the AT₁ receptor. It has vasodilatory and growth-inhibitory effects and can mediate apoptosis. Recently, studies have shown that, at least in the kidney, stimulation of the AT₂ receptor might produce nitric oxide and possibly even increase tissue concentrations of bradykinin.

The ARB, then, might actually have a dual mechanism of action (Table 3). Pivotal to this is the fact that the selective blockade of the AT₁ receptor, with consequent interruption of the negative feedback action of angiotensin II on renin release, promotes marked elevations of plasma angiotensin II. Therefore, even as the AT₁ receptor is being blocked by the drug, the unblocked AT₂ receptor is exposed to heightened angiotensin II stimulation. Studies in cell culture preparations have confirmed the relevance of this dual action in inhibiting cell growth. However, it has not yet been possible to test the relevance of this innovative concept to the clinical and prognostic effects of the ARB in human clinical practice.

Recent research has demonstrated the very interesting finding that cells in the kidney and in the myocardium have the ability to take up angiotensin II molecules. Presumably the angiotensin II is sequestered and may then exhibit delayed functional or structural actions at local tissues sites. This uptake of angiotensin II occurs at AT₁ receptor sites, indicating that the selective ARB may be uniquely effective in preventing this phenomenon.

Currently, several clinical trials are under way to determine whether the addition of ARB to ACE inhibitors in patients being treated for CHF can improve hemodynamics, modify the adverse neuroendocrine profile of heart failure, and most importantly, enhance prognosis in these patients. Major trials with clinical endpoints comparing the two classes of drugs are yet to be completed, although one short-term pilot study in CHF indicated a possible mortality advantage for the ARB. If the ACE inhibitors and ARB have separate actions, it is possible that they could produce additive clinical effects when given together. One report focusing on blood pressure effects has suggested that the combined use of these two types of agents produces additive effects, although issues related to study design and optimal dosing of each of the agents make it difficult to reach firm conclusions. Even so, it is becoming apparent that these two types of agents are sufficiently different that it would be inappropriate to assume that they would have equal effects on the cardiovascular system.

BLOOD PRESSURE EFFICACY

Direct comparative studies have shown that the ARB and ACE inhibitors have similar antihypertensive efficacy. No meaningful differences have been demonstrated when losartan, candesartan, or valsartan has been compared with ACE inhibitors. Irbesartan has a long duration of action and well-established efficacy, which is discussed elsewhere in this supplement. Of particular note, though, the ARB may have an especially smooth effect on blood pressure throughout the 24-h period. Early studies with this treatment, using ambulatory blood pressure monitoring, showed very consistent blood pressure–lowering effects throughout the 24-h period. More recently, irbesartan has been shown to exhibit antihypertensive efficacy that is highly sustained throughout the day. Indeed, trough/peak ratios for this drug are high.

Another attribute of the ARB is their excellent tolerability. As a class, these agents have side effect profiles that cannot be differentiated from those of placebos. This attribute may be of considerable importance to the practical issues of maintaining patient compliance with therapy and ensuring good long-term blood pressure results. Recently, studies with irbesartan indicated that the incidence of headache with this agent actually was lower than that with placebo. This finding has raised the important concept that hypertension is not a completely symptom-free condition, and that agents such as irbesartan, which have no adverse side effects of their own, have the potential to improve the sense of well-being in patients with hypertension during treatment. Finally, the problem of cough, which may occur in 5% to 20% of patients treated with ACE inhibitors, does not appear to be a problem with ARB. This finding provides another potential clinical
advantage of the newer drug class for patients who have been adversely affected with cough.

**RENAL EFFECTS**

ACE inhibitors have strongly beneficial actions in the kidneys. They reduce proteinuria and slow progression of renal dysfunction, particularly in patients with concomitant conditions such as diabetes mellitus, who are at increased risk for nephropathy. Similar clinical outcome data with ARB are not yet available, although some pivotal long-term trials are currently underway. Studies of renal hemodynamics have shown that ARB decrease renal vascular resistance and increase renal blood flow. A recent report by Hollenberg and colleagues has shown compelling differences between ARB and ACE inhibitors in renal hemodynamic effects. Figure 2 summarizes the different effects of these two drug classes on renal plasma flow in humans, indicating greater effects for the angiotensin II receptor antagonists. These investigators point out the potential role of chymase activity in mediating the formation of angiotensin II, thus making the ACE inhibitors less effective in interrupting the renin-angiotensin system. Additionally, AT1 blockade has been shown to reduce protein excretion in patients with proteinuria. Currently, the effects of irbesartan on renal and cardiovascular endpoints are being assessed in patients with hypertension who have type 2 diabetes in a major international clinical trial.

**METABOLIC EFFECTS**

Antagonists of the renin-angiotensin system do not produce major effects on metabolic measurements. Neither ACE inhibitors nor ARB has meaningful effects on lipid values. Another common association of hypertension is insulin resistance. Both ACE inhibitors and ARB have been shown to moderately improve insulin sensitivity in patients with hypertension, but the clinical benefits of these changes have not been established.

**CARDIOVASCULAR EFFECTS**

Although antihypertensive drugs can have a variety of actions, attention is now focusing on their single most important property: the ability to decrease the incidence of major clinical events, such as MI and strokes, and to prolong life. Clinical trials have already established that diuretics and possibly calcium channel blockers can decrease the incidence of strokes and other cardiovascular events, although their effect on major coronary syndromes is less compelling.

Data on the ACE inhibitors suggest that these agents are beneficial, although prospective clinical trials in hypertension have not yet been completed. In patients with CHF or with impaired left ventricular systolic function after MI, there is evidence that these agents decrease the probability of recurrent MI and improve survival. In patients with type 1 diabetes and nephropathy, there is a protection of renal function and a tendency to reduce cardiovascular events and mortality.

The specific hypertension experience with ACE inhibitors thus far has depended on observational studies. In a study of one large cohort followed up prospectively as part of a work site treatment program, it was possible to compare the effects of various antihypertensive agents on the incidence of major cardiovascular events. This study reported that patients receiving ACE inhibitors were less likely than those receiving other classes of drugs to experience serious clinical outcomes. Similarly, a large population of patients with hypertension followed up in a Glasgow clinic had significantly better treatment outcomes when they received ACE inhibitors than when they received non–ACE inhibitor therapy.

Data on the ARB are not yet available. It is noteworthy, though, that the members of this new class of drugs in use in the United States—including irbesartan, losartan, and valsartan—are already being studied in clinical trials to determine their effects in providing cardiac and renal protection and in improving survival. Clinical trials with irbesartan are described elsewhere in this supplement.
REFERENCES


