Differences between angiotensin converting enzyme inhibitors and receptor blockers

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INTRODUCTION — Angiotensin converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension. They have also been effective in a number of other disorders, prolonging survival in patients with heart failure, coronary heart disease, and acute myocardial infarction, and slowing the rate of progression in chronic renal failure, particularly diabetic nephropathy. One limiting side effect in a minority of patients is cough, a side effect that does not appear to occur with increased frequency with the angiotensin receptor blockers. The latter drugs are as effective as the ACE inhibitors in the treatment of hypertension [1]. (See "Renin-angiotensin system inhibition in the treatment of hypertension" ). It remains unclear, however, whether they are ACE inhibitors without cough or whether they have some differences in activity.

The evidence that there are clinically important differences between these two classes of drugs will be reviewed here. There is also evidence that there may be circumstances when combination therapy is beneficial.

MECHANISMS OF ACTION — Angiotensin II is an oligopeptide of eight amino acids, formed from its precursor, angiotensinogen by a series of two enzymatic cleavages. Angiotensinogen is released into the circulation by the liver. Renin, produced by the kidney, in response to glomerular hypoperfusion, catalyzes cleavage of angiotensinogen to angiotensin I, an inactive decapeptide. Angiotensin I is in turn cleaved by angiotensin converting enzyme to produce angiotensin II. Angiotensin II binds to its specific receptors and exerts its effects in the brain, kidney, adrenal, vascular wall, and the heart. (See "Chapter 2B: Renin-angiotensin system" ).
There are two well-described subtypes of angiotensin II receptors, designated AT1 and AT2, both of which have a high affinity for angiotensin II [2,3].

- The AT1 subtype mediates the vasoconstrictor effect of angiotensin II and is generally thought to mediate angiotensin II-induced growth in the left ventricle and the arterial wall [4].

- The actions of the AT2 receptor are less well understood. AT2 receptors are expressed in greater abundance in fetal tissues, followed by a decline in expression after birth [5,6]. Their role in development has not been elucidated [3,4]. In vivo data in a model of angiotensin II-induced hypertension showed that exposure of a specific inhibitor of the AT2 receptor (PD123319) prevented angiotensin II-induced arterial hypertrophy [7]. This and other observations suggest that the AT2 receptor plays a greater role in stimulating growth in the arterial wall.

**Receptor activation** — There are two major differences between the ACE inhibitors and angiotensin II receptor antagonists: the receptors that are affected; and the effect on kinins (show figure 1). Angiotensin II can activate both AT1 and AT2 receptors. As a result, inhibition of angiotensin II formation with an ACE inhibitor will diminish the activity of both receptor subtypes. The inhibition of angiotensin II production occurs both systemically and at tissue sites of local renin-angiotensin systems. (See "Actions of angiotensin II on the heart").

In contrast, the angiotensin II receptor antagonists only diminish AT1 activity. Thus, there is no change in AT2 receptor-mediated effects.

**Effect on kinins** — Converting enzyme is also a kininase. As a result, inhibiting this enzyme with an ACE inhibitor may lead to increased kinin levels, an effect not seen with the angiotensin II receptor antagonists. It is presumed that the absence of kinin accumulation accounts for the lack of cough with the angiotensin II receptor antagonists. (See "Major side effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers"). However, kinin accumulation may also mediate some of the beneficial effects of ACE inhibition.

- Increased kinins may contribute to the hypotensive action of ACE inhibitors by releasing nitric oxide from vascular endothelial cells. The potential importance of kinins in this response was illustrated in a study in humans who were treated with an ACE inhibitor (quinaprilat), or a bradykinin B2-receptor antagonist (icatibant), or both [8]. ACE inhibition increased flow-dependent vasodilation (as determined by ultrasound and Doppler of the radial artery); this effect was abolished, and flow-dependent vasodilation was actually reversed by the addition of
the bradykinin B2 receptor antagonist. The effect of the combination was similar to that seen with icatibant alone.

A significant role for bradykinin in the induction of hypotension with ACE inhibitors was also found in a single-blinded, randomized study of 20 normotensive and 7 hypertensive individuals [9]. An ACE inhibitor alone (25 mg of captopril), captopril plus a bradykinin B2-receptor antagonist (icatibant), an angiotensin II subtype 1-receptor antagonist alone (75 mg of losartan) and placebo were randomly administered on four separate study days. Icatibant significantly ameliorated the hypotensive response to captopril (10.5 versus 15.0 mmHg for combination therapy and captopril alone, respectively, p = 0.001); in addition, combination therapy resulted in the same degree of blood pressure lowering as that observed with losartan alone (10.5 versus 11.0 mmHg). The elevation in plasma renin activity associated with ACE inhibition was reversed with icatibant, suggesting that bradykinin was responsible for this effect.

- Increased kinins may contribute to another effect of ACE inhibitors, the ability to improve insulin sensitivity which can lower the blood glucose in patients with type 2 diabetes. (See "Treatment of hypertension in diabetes mellitus", section on Choice of antihypertensive agents). In one study in rats, the enhancement of insulin sensitivity by enalapril was inhibited by a kinin antagonist whereas no change in insulin sensitivity was seen with losartan [10]. The effect of kinins may be mediated in part by increased blood flow to skeletal muscle, thereby promoting insulin delivery and glucose uptake.

Rationale for combined therapy — There is reason to believe that combined therapy with an ACE inhibitor and angiotensin receptor antagonist might have an additive effect. With ACE inhibitors, the fall in angiotensin II leads to increased renin release, which partially returns angiotensin II levels toward baseline. In addition, ACE inhibitors only block the formation of angiotensin II that is mediated by angiotensin converting enzyme. There is evidence that alternative enzymatic pathways, particularly involving chymase, exist for the production of angiotensin II within the myocardium [11-13].

A similar effect may occur in the blood vessels. In a mouse model, overexpression of vascular chymase leads to an elevation in blood pressure [14]. It remains to be proven that this effect is mediated by increased local production of angiotensin II.

CLINICAL IMPLICATIONS — Although initial studies in a variety of disease states were performed with ACE inhibitors, it has been expected and in many cases demonstrated that similar benefits could be achieved with ARBs. In addition, combination therapy with both classes may be more effective than monotherapy with either drug in heart failure and chronic renal failure.
The following is a summary of the clinical settings in which these drugs have been used. The specific data are discussed in detail separately:

- To slow the progression of proteinuric diabetic and nondiabetic chronic renal failure. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease" and see "Treatment and prevention of diabetic nephropathy").

- To improve hemodynamics and survival in patients with heart failure due to systolic dysfunction. (See "ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use" and see "Angiotensin II receptor blockers in heart failure due to systolic dysfunction: Therapeutic use").

- To lower the blood pressure in patients with hypertension and also allow more rapid regression of left ventricular hypertrophy. (See "Renin-angiotensin system inhibition in the treatment of hypertension" and see "Renin-angiotensin system inhibition in the treatment of hypertension" and see "Clinical implications and treatment of left ventricular hypertrophy in hypertension").

It has also been suggested that ACE inhibitors and ARBs improve outcomes in patients at high risk for a cardiovascular event. However, it is likely that this beneficial effect is due to blood pressure reduction rather than a specific consequence of blockade of the renin-angiotensin system. (See "Choice of antihypertensive drug and blood pressure goal in patients at increased risk for a cardiovascular event").

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REFERENCES


GRAPHICS
Comparison of the actions of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

ACE: angiotensin converting enzyme; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

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