Angiotensin-Converting Enzyme Inhibitors

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Abstract—ACE inhibitors have achieved widespread usage in the treatment of cardiovascular and renal disease. ACE inhibitors alter the balance between the vasoconstrictive, salt-retentive, and hypertrophic properties of angiotensin II (Ang II) and the vasodilatory and natriuretic properties of bradykinin and alter the metabolism of a number of other vasoactive substances. ACE inhibitors differ in the chemical structure of their active moieties, in potency, in bioavailability, in plasma half-life, in route of elimination, in their distribution and affinity for tissue-bound ACE, and in whether they are administered as prodrugs. Thus, the side effects of ACE inhibitors can be divided into those that are class specific and those that relate to specific agents. ACE inhibitors decrease systemic vascular resistance without increasing heart rate and promote natriuresis. They have proved effective in the treatment of hypertension, they decrease mortality in congestive heart failure and left ventricular dysfunction after myocardial infarction, and they delay the progression of diabetic nephropathy. Ongoing studies will elucidate the effect of ACE inhibitors on cardiovascular mortality in essential hypertension, the role of ACE inhibitors in patients without ventricular dysfunction after myocardial infarction, and the role of ACE inhibitors compared with newly available angiotensin AT1 receptor antagonists. (Circulation. 1998;97:1411-1420.)

Key Words: angiotensin ■ blood pressure ■ bradykinin ■ drugs ■ renin

Angiotensin-converting enzyme inhibitors were developed as therapeutic agents targeted for the treatment of hypertension. Since the initial application of these agents, several additional clinical indications have been identified and approved. This review summarizes the pharmacology of ACE inhibitors and their current clinical indications.

Mechanism

ACE, or kininase II, is a bivalent dipeptidyl carboxyl metallopeptidase present as a membrane-bound form in endothelial cells, in epithelial or neuroepithelial cells, and in the brain and as a soluble form in blood and numerous body fluids.1 ACE, or kininase II, cleaves the C-terminal dipeptide from Ang I and bradykinin and a number of other small peptides that lack a penultimate proline residue. Thus, ACE is strategically poised to regulate the balance between the RAS and the kallikrein-kinin system.

The RAS plays a pivotal role in blood pressure regulation (Fig 1). Reduced sodium delivery at the macula densa, decreased renal perfusion pressure, and sympathetic activation all stimulate secretion of renin by the juxtaglomerular cell, the classic source of renin in the circulating RAS.2 Alternatively, renin may be produced locally in tissues.3,4 Renin cleaves the inactive decapeptide Ang I from the prohormone angiotensinogen, a noninhibiting member of the serpin superfamily of serine protease inhibitors.5 Ang II is then cleaved from Ang I by the action of ACE.6 Ang II is a potent vasoconstrictor, acting directly on vascular smooth muscle cells.7 In addition, Ang II interacts with the sympathetic nervous system both peripherally and centrally to increase vascular tone.8 Ang II causes volume expansion through sodium retention (via aldosterone9 and renal vasoconstriction) and fluid retention (via antidiuretic hormone).10 At the cellular level, Ang II promotes migration, proliferation, and hypertrophy.11-15 Most of these effects of Ang II appear to be mediated through the AT1 receptor, although recent studies are defining roles for the AT2 and AT4 subtype receptors.16

As mentioned earlier, in addition to catalyzing the formation of Ang II, ACE (or kininase II) catalyzes the degradation of bradykinin.6 In specific tissues or organs, bradykinin causes smooth muscle contraction (eg, uterine and ileal), increased vascular permeability, stimulation of peripheral and C fibers, and augmentation of mucous secretion.17 More importantly, however, bradykinin promotes vasodilation by stimulating the production of arachidonic acid metabolites, nitric oxide, and endothelium-derived hyperpolarizing factor in vascular endothelium.18 In the kidney, bradykinin causes natriuresis through direct tubular effects.19 Most of the physiological effects of bradykinin appear to be mediated through the B1 receptor.20

In summary, ACE regulates the balance between the vasodilatory and natriuretic properties of bradykinin and the vasoconstrictive and salt-retentive properties of Ang II. ACE inhibitors alter this balance by decreasing the formation of Ang II and the degradation of bradykinin (Fig 1). ACE inhibitors alter the balance between the vasoconstrictive, salt-retentive, and hypertrophic properties of angiotensin II (Ang II) and the vasodilatory and natriuretic properties of bradykinin and alter the metabolism of a number of other vasoactive substances. ACE inhibitors differ in the chemical structure of their active moieties, in potency, in bioavailability, in plasma half-life, in route of elimination, in their distribution and affinity for tissue-bound ACE, and in whether they are administered as prodrugs. Thus, the side effects of ACE inhibitors can be divided into those that are class specific and those that relate to specific agents. ACE inhibitors decrease systemic vascular resistance without increasing heart rate and promote natriuresis. They have proved effective in the treatment of hypertension, they decrease mortality in congestive heart failure and left ventricular dysfunction after myocardial infarction, and they delay the progression of diabetic nephropathy. Ongoing studies will elucidate the effect of ACE inhibitors on cardiovascular mortality in essential hypertension, the role of ACE inhibitors in patients without ventricular dysfunction after myocardial infarction, and the role of ACE inhibitors compared with newly available angiotensin AT1 receptor antagonists. (Circulation. 1998;97:1411-1420.)

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inhibitors also alter the formation and degradation of several other vasoactive substances such as substance P, but the contribution of these compounds to the therapeutic or adverse effects of ACE inhibitors is uncertain.

Pharmacology

ACE inhibitors differ in the chemical structure of their active moieties, in potency, in bioavailability, in plasma half-life, in route of elimination, in their distribution and affinity for tissue-bound ACE, and in whether they are administered as prodrugs. ACE inhibitors may be classified into three groups according to the chemical structure of their active moiety. Captopril is the prototype of the sulphydryl-containing ACE inhibitors; others are fentiapril, pivalopril, zofenopril, and alacepril. In vitro studies suggest that the presence of the sulphydryl group may confer properties other than ACE inhibition to these drugs, such as free-radical scavenging and effects on prostaglandins; however, the clinical relevance of these effects remains to be demonstrated. Fosinopril is the only FDA-approved ACE inhibitor that contains a phosphinyl group as its reactive moiety. The majority of the other ACE inhibitors contain a carboxyl moiety. The half-lives and routes of elimination for selected ACE inhibitors appear in Table 1. Captopril differs from other ACE inhibitors by its short half-life. With the exception of fosinopril, trandolapril, and spirapril, ACE inhibitors are cleared predominantly by the kidney. For this reason, dose reductions are required in the setting of impaired renal function. The majority of ACE inhibitors are administered as prodrugs that remain inactive until esterified in the liver. These prodrugs have enhanced oral bioavailability compared with their active drugs. ACE is present in plasma as well as in tissues, and there are differences in the relative tissue affinity of ACE inhibitors. For example, Fabris and coworkers examined the binding of various ACE inhibitors to heart homogenates and found the order of potency to be quinaprilat > benazaprilat > perindoprilat > lisinoprilat > fosinoprilat. Several investigators have shown that the effects of ACE inhibitors on blood pressure correlate better with tissue ACE levels than with circulating ACE, but the clinical significance of differences in tissue binding has not been established.

Humoral Effects

The effects of ACE inhibitors on the RAS in humans is well documented. ACE inhibitors block the pressor response to intravenous Ang I but not Ang II. When ACE inhibitors are given short-term, endogenous levels of Ang II and aldosterone decrease, whereas PRA and Ang I increase, at least in part because of loss of feedback inhibition. The resulting increase in Ang I levels may result in degradation of Ang I to Ang 1–7, a vasodilator, or in formation of Ang II via non–ACE-mediated pathways, although the role of these alternative degradation products in humans is controversial. With chronic ACE inhibition, Ang II and aldosterone levels tend to return toward pretreatment levels. The contribution of bradykinin to the hemodynamic effects of ACE inhibitors in humans is uncertain. ACE inhibitors potentiate the hypotensive effects of intravenous bradykinin in humans. However, endogenous bradykinin is difficult to measure because of its short half-life, and investigators have reported that bradykinin levels are either increased or unchanged during ACE inhibition. Similarly, prostaglandin levels have been reported to be increased or unchanged in patients treated with ACE inhibitors. The recent availability of specific bradykinin (B2) receptor antagonists has begun to shed light on the contribution of bradykinin to the actions of ACE inhibitors. In animal models, coadministration of a bradykinin antagonist attenuates the antihypertensive effect of ACE inhibitors. Recent data suggest that B2 antagonism blunts the hypotensive effects and reduces the endothelium-dependent vasodilator effects in humans as well.

Hemodynamic Effects

ACE inhibitors decrease systemic vascular resistance but cause little change in heart rate. In normotensive and hypertensive subjects with normal left ventricular function, ACE inhibitors have little effect on cardiac output or pulmonary capillary wedge pressure. In the kidneys, ACE inhibitors cause increased renal plasma flow and promote salt excretion. Glomerular filtration is usually unchanged; thus, filtration fraction is decreased.

Clinical Indications

Hypertension

ACE inhibitors effectively lower the mean, systolic, and diastolic pressures in hypertensive patients as well as in salt-depleted normotensive subjects. The acute change in blood pressure correlates with pretreatment PRA and angiotensin levels, such that the greatest reductions in blood pressure are seen in patients with the highest PRA. However, with long-term therapy, a greater percentage of patients achieve a decrease in blood pressure, and the antihypertensive effect no longer correlates with pretreatment PRA. The mechanism for this increased efficacy with chronic administration is not clear but may involve the kallikrein-kinin system or production of vasodilatory prostaglandins.

Figure 1. Schematic of RAS and kallikrein-kinin system. ACE is strategically poised to regulate the balance between Ang II and bradykinin.
Although ACE inhibitors are generally effective in reducing blood pressure, they appear to be less potent in hypertensive blacks than whites. In a Veterans Administration Cooperative Study Group trial, captopril reduced blood pressure significantly more in white patients with mild to moderate hypertension than in black patients at 7 weeks.87 Similarly, ACE inhibitors and β-blockers were less effective than calcium channel blockers in young and elderly black men.79 One possible explanation for these data is that hypertensive blacks tend to have low renin levels more often than do whites.80–82 In support of this, coadministration of drugs that increase PRA, such as diuretics, abolishes the racial differences in response to ACE inhibitors.78,83 Weir et al83 suggested that the mechanism through which ACE inhibitors lower blood pressure differs in blacks and whites. This group observed a dissociation between the potency of ACE inhibitors for decreasing plasma ACE activity and their antihypertensive potency in blacks; however, in some dose groups, baseline ACE activity was higher in the blacks than in the whites studied. Nevertheless, this study underscores the need to use higher doses of ACE inhibitors for blacks.

One of the hallmarks of ACE inhibitors is that they lower peripheral vascular resistance without causing a compensatory increase in heart rate.58–61 The lack of heart rate response to ACE inhibitors contrasts with the effect of other vasodilators, such as calcium channel blockers and direct-acting vasodilators, on heart rate and may reflect an effect of ACE inhibitors on baroreceptor sensitivity as well as inhibition of the normal tonic influence of Ang II on the sympathetic nervous system.84–86 During ACE inhibition, heart rate responses to postural changes and exercise are not impaired.87

The goal of antihypertensive therapy is not only to lower blood pressure but, more importantly, to alter the risk of end-organ damage and mortality. To date, trials of ACE inhibitors in the treatment of essential hypertension have focused on the end point of blood pressure reduction. For this reason, the Joint National Committee for the Detection, Evaluation, and Treatment of High Blood Pressure VI has not recommended ACE inhibitors as first-line therapy for uncomplicated hypertension. ACE inhibitors are indicated for the treatment of hypertension with coexistent conditions such as congestive heart failure and diabetic nephropathy.88 Clinical trials testing the effect of ACE inhibitors on cardiovascular mortality in patients with essential hypertension are under way. These include the Captopril Prevention Project89 and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).90 It should be emphasized that existing data suggest that ACE inhibitors will have a favorable effect on cardiovascular mortality. ACE inhibitors lack adverse metabolic effects,91 and they have been shown to cause regression of left ventricular hypertrophy.92–93 Finally, they have already been shown to reduce mortality in patients with congestive heart failure94–96 and diabetic nephropathy.99

### Congestive Heart Failure and Left Ventricular Dysfunction

ACE inhibitors favorably alter hemodynamics in patients with systolic dysfunction. ACE inhibitors reduce afterload, preload, and systolic wall stress100–103 such that cardiac output increases without an increase in heart rate. ACE inhibitors promote salt excretion by augmenting renal blood flow and by reducing the production of aldosterone and antidiuretic hormone. Since 1987, several large, prospective, randomized, placebo-controlled trials have demonstrated that treatment with ACE inhibitors results in a reduction in overall mortality in patients with congestive heart failure due to systolic dysfunction.94–98 These trials are summarized in Table 2 and have had a major impact on the management of congestive heart failure. The reduction in mortality has been seen even in patients with asymptomatic left ventricular dysfunction.104,111 This reduction in mortality results primarily from a reduction in progression of congestive heart failure,94,96,97 although the incidence of sudden death96 and MI10 may also decrease.

As mentioned earlier, it is not yet clear to what extent bradykinin contributes to the beneficial therapeutic effects or adverse effects of ACE inhibitors. Since the advent of specific AT1 antagonists, a number of studies comparing ACE inhibitors with AT1 antagonists are now under way. The first of these, the Evaluation of Losartan in the Elderly (ELITE) study, reported nearly equivalent effects of losartan and the short-acting ACE inhibitor captopril on the progression of congestive heart failure in elderly patients; however, there was an unexpected reduction in the incidence of sudden death in the losartan group.112 There was no difference between captopril and losartan in the incidence of renal insufficiency. Whether large-scale trials comparing AT1 receptor antagonists with longer-acting ACE inhibitors will confirm these data remains to be seen.

Although ACE inhibitors improve outcome in patients with systolic dysfunction, many patients with hypertension expe-
rience congestive heart failure due to diastolic dysfunction related to left ventricular hypertrophy. In animal models, ACE inhibitors have been shown to reverse ventricular remodeling by blocking the trophic effects of Ang II on cardiac myocytes.113,114 ACE inhibitors have been shown to reverse left ventricular hypertrophy in patients with hypertension.60,92,93 A meta-analysis of the effects of several anti-hypertensive agents suggested that ACE inhibitors were the most effective agent in reducing left ventricular hypertrophy.115 Studies examining mortality in patients with congestive heart failure due to diastolic dysfunction are needed.

Left Ventricular Dysfunction After MI
On the basis of studies demonstrating that ACE inhibition could reduce progressive enlargement after MI in experimental animals116 as well as in humans,117 it was hypothesized that ACE inhibition might improve clinical outcome in patients after MI. Several large, prospective, randomized trials have now examined the effect of ACE inhibitors on mortality after MI (Table 2).97,118–121 The vast majority of these trials have shown a decrease in cardiovascular mortality and a slowing of the progression to congestive heart failure in patients treated with ACE inhibitors. The optimal timing and dosage of ACE inhibitor after MI are not known. In CONSENSUS II, intravenous enalaprilat was administered within 24 hours of MI.118 There was a significant increase in early hypotension in the enalaprilat-treated group and, in contrast to other studies with enalaprilat, there was no improvement in survival. On the other hand, zofenopril, captopril, and lisinopril started within 24 hours after MI in the SMILE,120 ISIS-4,119 and GISSI-3 trials,121 respectively, did reduce mortality. In the majority of trials, ACE inhibitor was administered 3 to 16 days after MI. It is likely that patients are more sensitive to the hypotensive effects of ACE inhibitors in the immediate post-MI period. An extensive discussion of the issues surrounding the administration of ACE inhibitors after MI is beyond the scope of the present review, but these issues were recently reviewed by Pfeffer122 and by Borghi and Ambrosioni.123

Atherosclerotic Vascular Disease
Studies in patients with left ventricular dysfunction have suggested the possibility that ACE inhibitors decrease the frequency of ischemic events. For example, in the SAVE and SOLVD trials, ACE inhibitors reduced the incidence of recurrent MI and angina in patients with left ventricular dysfunction or mild congestive heart failure by >20%.110,111 Nevertheless, it is not known whether ACE inhibitors will prevent ischemic events in patients with normal ventricular function. However, there is experimental evidence that ACE inhibition can retard the development of atherosclerosis. In animal models of atherosclerosis, including apolipoprotein E
Diabetic Nephropathy

The RAS and increased glomerular capillary pressure have been implicated in the progression of renal dysfunction due to a number of renal diseases, including diabetic nephropathy. Ang II increases glomerular capillary pressure by decreasing arterial pressure and by selectively dilating efferent arterioles. In addition, Ang II causes mesangial cell growth and matrix production. Numerous animal studies and small clinical trials have suggested that ACE inhibitors significantly reduce the loss of kidney function in diabetic nephropathy. ACE inhibitors prevent progression of microalbuminuria to overt proteinuria. A large, prospective, placebo-controlled study has shown that captopril slows the progression of nephropathy in patients with insulin-dependent diabetes mellitus, as measured by the rate of decline in creatinine clearance and the combined end points of dialysis, transplantation, and death. A second large-scale, prospective, double-blind study extended these observations by showing a protective effect of ACE inhibitors in patients with a variety of renal diseases, including glomerulopathies, interstitial nephritis, nephrosclerosis, and diabetic nephropathy. The exception was polycystic kidney disease. Importantly, the protective effect of ACE inhibition was independent of the severity of renal insufficiency.

Ongoing studies will determine whether ACE inhibitors other than captopril are also effective in slowing progression of nephropathy and will also clarify the value of ACE inhibitors in slowing progression of renal disease in patients with non–insulin-dependent diabetes mellitus. This is particularly relevant when one considers that, whereas 89% of the patients in the captopril trial were white, non–insulin-dependent diabetes mellitus is two times more prevalent among blacks than whites. As mentioned above, blacks are resistant to the antihypertensive effects of ACE inhibitors; thus, it remains to be determined whether there are ethnic differences in the renal protective effects of ACE inhibitors.

Other individual factors may determine the impact of ACE inhibitors on the progression of renal insufficiency. In particular, Rigat et al described an insertion (I)/deletion (D) polymorphism in the ACE gene that correlates with ACE activity such that ACE levels are highest in patients who are homozygous for the ACE D allele, lowest in patients homozygous for the ACE I allele, and intermediate in those who are heterozygous. Yoshida et al reported a greater decrease in proteinuria in response to ACE inhibition in patients with IgA nephropathy who were homozygous for the DD allele. In contrast, other investigators have reported a worse response to therapy in patients who carry the ACE D allele. Obviously, large-scale studies are needed to define the impact of genetic factors on the renal protective effects of ACE inhibitors.

Adverse Effects

The adverse effects of ACE inhibitors (Table 3) can be divided into those that are specific to the entire class and those that are related to chemical structure (specifically, related to the presence of a sulfhydryl group). Like all antihypertensive agents, ACE inhibitors can cause hypotension. The frequency of hypotension is greater in renin-dependent states, such as during low sodium intake and diuretic use, and it is recommended that lower starting doses be used under these conditions. ACE inhibitors can cause hyperkalemia because of a decrease in aldosterone. This effect is usually not significant in patients with normal renal function. However, in patients with impaired kidney function or in patients who are taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, hyperkalemia can occur.

ACE inhibitors can cause a reversible decline in renal function in the setting of decreased renal perfusion, whether this is due to bilateral renal artery stenosis, severe congestive heart failure, or volume depletion. The mechanism is illustrated in Fig 2. When perfusion pressure or afferent arteriolar pressure is decreased in the glomerulus, glomerular filtration is maintained by efferent arteriolar vasoconstriction, an effect of Ang II. Blocking the formation of Ang II, and perhaps increasing the formation of bradykinin, causes selective efferent arteriolar vasodilatation and results in a decrease in glomerular filtration in this setting.
Drug Interactions

As mentioned above, concurrent administration of potassium supplements, potassium-sparing diuretics, or salt substitutes may precipitate hyperkalemia in ACE inhibitor–treated patients in whom aldosterone is suppressed. Patients taking diuretics may be particularly sensitive to the hypotensive effects of ACE inhibitors.146 Nonsteroidal anti-inflammatory drugs may attenuate the antihypertensive effects of ACE inhibitors.47,50,170,171 This effect appears to be more prominent in patients with low renin levels.172

Cost

Captopril is the only ACE inhibitor currently available in a generic form. The average wholesale price per 100 U ranges from $3.41 for 12.5-mg tablets to $14.97 for 100-mg tablets. At present, contract pricing makes the relative cost of the other agents vary from institution to institution. In general, these agents are priced such that the average wholesale price per 100 U runs from $60 to $80. The limited selection of ACE inhibitors available on many formularies today often precipitates patients being changed from one ACE inhibitor to another. However, given the differing potencies, tissue affinities, and bioavailabilities among ACE inhibitors, it is not clear that all agents are equal. Rigorous studies comparing potencies among ACE inhibitors are needed.

Future Directions

This review focuses on the pharmacology of ACE inhibitors and on the broadening clinical applications of this class of compounds. Clearly, the beneficial cardiovascular and renal effects of ACE inhibitors go beyond the original, limited indication for the treatment of hypertension. Although current clinical efforts are directed at the emerging role of ACE inhibitors in preventing cardiovascular events in normotensive subjects, further work needs to be done to characterize molecular and cellular mechanisms responsible for the clinical effects of ACE inhibitors. In particular, the role of bradykinin remains enigmatic. Although ACE inhibition after MI appears to have an established role in clinical practice, the ongoing controversy over the selective versus nonselective use of ACE inhibitors after MI is unlikely to be resolved in the near future. Clinical studies will compare the efficacy of ACE inhibitors and specific AT1 receptor antagonists in the treatment of cardiovascular and renal disease. Finally, studies will determine to what extent individual characteristics such as race and ACE genotype determine responses to ACE inhibitors.

It is clear that ACE inhibitors represent one of the major advances in cardiovascular therapeutics over the past 20 years. It is highly doubtful that even the most enthusiastic advocate of these agents could have anticipated their broad clinical applications. Furthermore, ACE inhibitors, in very tangible terms, have catalyzed research into molecular and cellular mechanisms of vascular disease that is paying large dividends.

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