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Angiotensin Converting Enzyme Inhibitors: Comparative Structure, Pharmacokinetics, and Pharmacodynamics

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Summary. **Angiotensin converting enzyme (ACE) inhibitors are a novel class of antihypertensive and anticongestive heart failure agents with wide patient and physician acceptability. By blocking the formation of angiotensin II in blood and tissues, all ACE inhibitors significantly lower systemic vascular resistance, lower blood pressure, and improve cardiac function, while maintaining or enhancing perfusion of vital organs: kidneys, brain, and heart. Captopril is the first oral ACE inhibitor with an active sulfhydryl group. Enalapril and lisinopril are potent nonsulfhydryl inhibitors of ACE characterized by weak chelating properties. The side effects of skin rashes, pruritis, taste abnormalities, oral ulcers, pemphigus, and blood dyscrasias have been considered to be strongly characteristic of penicillaminelike drugs, including the sulfhydryl ACE inhibitors. The class effects of cough, angioedema, hyperkalemia, nonoliguric functional renal insufficiency, and hypotension can occur with equal frequency with all ACE inhibitors. It is unclear whether the many yet investigational ACE inhibitors would have distinct advantages over captopril, enalapril, lisinopril, and enalaprilat. This paper reviews the comparative structure and clinical pharmacology of the three commercially available but chemically different oral ACE inhibitors.**

Key Words. **ACE inhibitors, sulfhydryl groups, class side effects, enalapril, captopril, lisinopril**

Angiotensin converting enzyme (ACE) inhibitors have ushered in a new era in the pathophysiologic understanding and treatment of systemic hypertension and congestive heart failure. Goldblatt and coworkers [1] first introduced the concept of the renin-angiotensin system in experimental hypertension in 1934. It was only in 1971 that Ondetti et al. [2] reported the isolation of a nonapeptide from the venom of the Brazilian snake *Bothrops jararaca*, which was later synthesized as the first ACE inhibitor teprotide, SQ20881. Ondetti, Cushman, and coworkers [3,4] designed and synthesized captopril, the first oral ACE inhibitor with an active sulfhydryl group. Enalapril and lisinopril are potent nonsulfhydryl specific inhibitors of ACE characterized by weak chelating properties [5]. This paper reviews the clinical relevance of the comparative structure and the pharmacokinetic and pharmacodynamic properties of the commercially available oral ACE inhibitors.

Angiotensin I Converting Enzyme (Kininase II)

Angiotensin I converting enzyme (ACE), first described by Skeggs et al. [6], catalyzes the conversion of angiotensin I by cleaving the carboxyl terminal dipeptide His-Leu from the decapeptide to form angiotensin II, an octapeptide. Angiotensin II is a potent stimulus for aldosterone release, resetting of sympathetic autonomic tone, and stimulation of vasopressin-arginine peptides, in addition to its stimulatory effects on the cardiovascular system and direct potent vasoconstriction of the arterioles (Figure 1). These neurohumoral effects of angiotensin II result in a markedly increased systemic vascular resistance and afterload, and retention of sodium and water with a modest increase in preload, thus producing and aggravating hypertension and congestive heart failure. The ACE inhibitors, by lowering the angiotensin II levels in blood and tissues, reverse the hemodynamic, neurohumoral, and metabolic abnormalities of hypertension and congestive heart failure. There is considerable controversy about the differential effects of ACE inhibitors on prostanoid production, which may have biologic implications in patients with low-renin hypertension or congestive heart failure. Bradykinin, through direct vasodilatation and possible prostaglandin release, may have a salutary effect in congestive heart failure by lowering preload (Figure 1).

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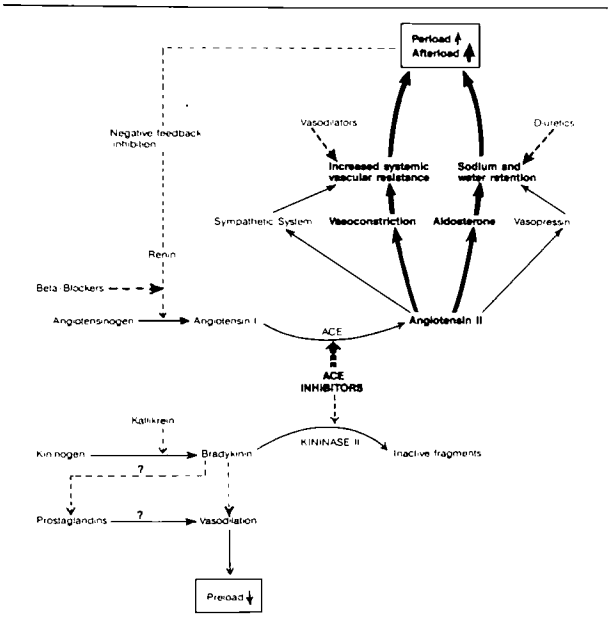

Fig. 1. Cardiovascular homeostasis and renin-angiotensin-aldoesterone and kallikrein-kinin-prostaglandin systems. The relative importance of angiotensin II effects and ACE inhibition are indicated by the width of the arrows and the boldness of the print, the widest arrow and the boldest print being the most important.

Table 1. Comparative data on ACE activity and biliary excretion of angiotensin converting enzyme inhibitors

Agent	I_{50}nM	Log P	MW	Biliary excretion
Sulfhydryl ACE inhibitors				
Captopril	23	1.016	217	±
Pivalopril	17	2.169	245	+
Rentiapril	7	2.043	281	+
Zofenopril	8	3.121	325	+ +
Nonsulfhydryl ACE inhibitors				
Enalapril	1–5	0.161	348	±
Perindopril	2	0.554	340	±
Ramipril	4	1.034	388	+
Quinapril	3	1.442	396	+
Cilazapril	2	NA	389	NA
Delapril	40	1.974	424	+ +
Lisinopril	1	−2.439	405	±
Phosphorus-containing ACE inhibitors				
Fosinopril	11	> 2	453	+ +
SQ 29,852	36	−0.771	440	±

I_{50} = active ACE inhibitor concentration required for 50% inhibition of rabbit lung ACE; log P = logarithm of the octanol:water partition coefficient; MW = molecular weight. The higher the log P and MW, the higher the lipophilicity and biliary excretion of the ACE inhibitor; biliary excretion: ± = minimal, + + = maximal. Adapted from Ondetti [41].

Development of Oral ACE Inhibitors

Captopril [3] and enalapril [5] were developed independently by two major United States research laboratories. There are obligatory and auxiliary binding sites on the ACE for the sulfhydryl and nonsulfhydryl ACE inhibitors. All of the in-vivo active ACE inhibitors have a prominent zinc-binding moiety, which was originally shown to bind with the sulfhydryl end terminal of captopril [2]. Enalapril and analogs, however, despite the lack of the sulfhydryl moiety, have many interactions with the active sites of the ACE enzyme. These involve additional sites binding with the imino group of the alanyl residue and phenethyl groups of enalapril [7]. With the exception of lisinopril and cilazapril, most of the enalapril analogs were created with the modification of the lysine residue. Lisinopril is the lysine derivative of enalaprilat and does not require hydrolysis to become an active ACE inhibitor, unlike enalapril, which is a prodrug. All of the enalapril analogs, except lisinopril, are considerably more lipophilic and, just like captopril analogs, have a larger molecular size; these properties are probably responsible for the increased biliary excretion of these analogs. The recently developed phosphorus-containing ACE inhibitors [8, 9] have a somewhat different structure-activity relationship than captopril and enalapril analogs. To maximize activity, the bridge between the phosphorus and amide bond in fosinopril is one atom shorter than in SQ29852, although both compounds are well absorbed orally. Both have in-vitro ACE inhibition similar to that of captopril, but are longer acting in vivo. Fosinopril, unlike SQ29852, has a higher molecular weight and lipophilicity with considerably higher biliary excretion. The relative inhibition of ACE by captopril and analogs, enalapril and analogs, and phosphorus-containing ACE inhibitors is shown in Table 1. There are over a dozen other ACE inhibitors undergoing clinical investigative studies in hypertension and congestive heart failure [10]. It is too early to tell whether these ACE inhibitors will be superior to the already available ACE inhibitors.

Mechanism of Action of ACE Inhibitors

The interaction of the three chemically different classes of ACE inhibitors with the renin-angiotensin systems is dependent on their intrinsic potency to bind with the angiotensin converting enzyme and their pharmacokinetic properties. Until recently, the renin-angiotensin system was considered primarily a circulating endocrine system. There is increasing evidence to suggest that inhibition of tissue ACE activity, particularly in the vasculature, rather than

the plasma ACE inhibition, contributes significantly to the hemodynamic improvement noted after ACE inhibitor administration. Dzau [11] has recently summarized the presence of the renin-angiotensin system in tissues such as blood vessels, kidneys, adrenals, brain, and elsewhere. This was supported by the demonstration of messenger RNA for angiotensinogen (the only known precursor of angiotensin peptides) in several extrarenal and extrahepatic tissues of the rat. Campbell [12] has suggested that the major site of angiotensin I and angiotensin II production may be the peripheral vascular tissues and that circulating angiotensin II represents a spillover from the tissue sites of angiotensin production. ACE inhibitors not only block serum ACE, but exert their action by inhibiting tissue ACE, which may have distinct patterns in different models of hypertension [13]. This may explain why long-term antihypertensive and anticongestive heart failure effects of ACE inhibitors do not always correlate with the pretreatment plasma renin levels. Likewise, the duration of action of an ACE inhibitor may be more dependent on the tissue ACE inhibition than on the plasma elimination half-life of the drug.

The available data on the ACE inhibitors' effects on the arachidonic-acid cascade (prostaglandins), kallikrein-kinin, and bradykinin degradation are controversial [14]. The inhibition of these hormone systems may occur at the tissue level, such as the vascular smooth muscle and renal medullary cells, thus increasing the production of prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2) during treatment with captopril in patients with hypertension or congestive heart failure [15, 16]. Circulating bradykinin levels have also been reported to be elevated in some studies after captopril administration in hypertensive and congestive heart failure patients [17, 18]. It is known that sodium restriction leads to a high-renin state and enhanced prostaglandin response [16]. Further evidence that prostaglandins may partially mediate the captopril hemodynamic responses is provided by the marked (up to 50%) attenuation of the blood-pressure lowering effect of captopril in hypertensive patients by indomethacin, a potent inhibitor of prostaglandin synthesis [15, 16]. This attenuation of the captopril effect by concomitant use of nonsteroidal antiinflammatory drugs may be of clinical significance in hypertensive patients who are not receiving diuretics. Another nonsteroidal antiinflammatory agent, sulindac, unlike indomethacin, inhibits systemic, but not renal, prostaglandin synthesis, and it does not markedly attenuate the blood-pressure lowering effect of captopril [19]. These studies suggest a possible role for renal prostaglandins in partially mediating the antihypertensive effect of captopril. It has been noted that in rats made hypertensive by the continuous infusion of angiotensin II, there are no important nonangiotensin mechanisms involved in the antihypertensive effect of enalapril [20]. There is one study reported in abstract form [21] suggesting a possible role for prostaglandins in low-renin essential hypertension patients given enalapril. However, an extensive review of the effects of enalapril on kallikrein-kinin and prostaglandin systems does not support the notion that inhibition of these systems is clinically important for the antihypertensive effects of enalapril [22].

Pharmacokinetics of ACE Inhibitors

The major differences between oral ACE inhibitors are primarily related to their structure, binding to active sites on ACE, and whether the ACE inhibitor, when administered, is an active compound or a prodrug. The sulfur moiety of captopril and its sulfhydryl analogs binds to the zinc ion of the ACE. The sulfhydryl group of captopril, however, easily undergoes oxidation and disulfide exchange reactions, which accounts for the short duration of ACE inhibition by captopril. Enalapril, a potent ACE inhibitor with a carboxyl group as a zinc ligand, and its nonsulfhydryl analogs bind to the ACE at auxillary zinc ligand sites (seven for enalapril vs. five for captopril). Enalapril is a prototype of the prodrug ACE inhibitors that were developed to increase the rate of oral absorption, to prolong the duration of ACE inhibition, and to minimize the occurrences of some side effects such as skin rashes, taste disturbances, and neutropenia. The prodrugs are inactive until converted by the liver into the active ACE inhibitor through deesterification. Food can significantly modify the absorption rate of captopril, but not that of enalapril and lisinopril. In one study, captopril absorption was decreased by almost 50%, and its rate of absorption was also significantly decreased in the fed state in humans [23]. There was no effect of food on the absorption of enalapril and thus no dosage adjustment is necessary for enalapril, unlike captopril [24]. There were no significant differences in single, oral-dose captopril, enalapril, and lisinopril pharmocokinetics in young (18–35 years old) and elderly (60–75 years old) healthy subjects. There appears to be no reason to decrease the total daily dosage of the presently available oral ACE inhibitors on the basis of patient age unless there is concomitant moderate- (glomerular filtration rate of < 20–30 ml/min/1.73 m^2) to-severe renal function impairment. There is an increased elimination half-life and reduced clearance of the oral ACE inhibitors with progressive renal function impairment.

Table 2. *Summary of pharmacokinetic and pharmacodynamic effects of single doses of the approved angiotensin converting enzyme inhibitors in healthy subjects and hypertensive patients*

ACE inhibitor	SH group	Prodrug	Dose (mg)	Blood-pressure lowering effect* Onset (min)	Peak (hrs)	Duration (hrs)	Metabolism	Excretion	Serum half-life
Captopril	Yes	No	25–100	15–30	1–2	6–10	Extensive to disulfides	Urine, ⅓ unchanged, 95% in 24 hrs	2 hrs
Enalapril	No	Yes	5–20	60–90	2–4	18–30	None except to enalaprilat	60–75% in urine in 72 hrs	11 hrs
Lisinopril	No	No	5–10	50–120	4–6	18–30	None	28% in urine 56% in feces in 24 hrs	12 hrs
Enalaprilat	No	No	1.25	15	1–4	6–8	None	92% in urine	5 hrs

*The magnitude and duration of blood pressure effect is dependent on the dose and half-life of the ACE inhibitor.

There are preliminary studies with ACE inhibitors alone or in combination with diuretics and other drugs in type I and type II diabetes mellitus with mild-to-moderate uncomplicated hypertension. Glucose metabolism was unaffected by ACE inhibitors, and the antihypertensive effects were similar in diabetic and nondiabetic hypertensive patients. There was usually a significant decrease in the proteinuria or microalbuminuria after several weeks to months of ACE inhibition in diabetic hypertensive [25] or diabetic nonhypertensive patients [26]. The reduction in the proteinuria and microalbuminuria has been attributed to the improvement in the glomerular hypertension of the remaining functioning glomeruli after ACE inhibition. These patients, however, should have frequent serial renal function assessments and electrolyte monitoring for early diagnosis of nonoliguric azotemia or hyperkalemia, which may occur with ACE inhibition. Large long-term studies are underway to study renal protective effects of ACE inhibition in hypertensive patients with diabetic nephropathy.

Pertinent data from the pharmacokinetic studies following single doses of captopril [15], enalapril [22], and lisinopril [27] are summarized in Table 2. The bioavailability of captopril is decreased by 30–50% when coadministered with food, and absorption is similarly decreased when the drug is given with antacids. Bioavailability of oral enalapril and enalaprilat is about 40%, but enalapril oral absorption is not affected by food. Approximately 70% of captopril and 60% of enalapril is absorbed by healthy, fasting subjects. Mean maximal blood concentrations after single oral doses of 10–100 mg captopril are dose related. Peak serum concentrations of enalapril are reached in about 1 hour. Enalapril undergoes deesterification, primarily in the liver, to form enalaprilat, which reaches peak serum concentrations 3–4 hours after oral enalapril. Enalaprilat is <50% protein bound, and unchanged enalapril and enalaprilat are excreted in the urine and feces. Lisinopril absorption is lower than that of enalapril and 25% of it is bioavailable. Peak serum concentrations are reached in about 6 hours, with detectable lisinopril serum concentrations for up to 72–96 hours of the single dose.

There are important differences in the metabolism of the three types of ACE inhibitors. The metabolism of captopril is complex, and about 50% of it is metabolized mainly by disulfide formation with endogenous thiol compounds including glutathione, cystine, and proteins. These disulfides can regenerate captopril and constitute a diploid form of the drug [28]. This may, in part, explain the relatively high incidence of captopril-related side effects, such as skin rashes and taste disturbances, and rare but life-threatening occurrences of neutropenia. One of the metabolites, S-methyl captopril, is present in significant concentrations in the circulation. Captopril can also be converted into disulfides through its interaction with oxygen-derived free radicals and may serve as a free-radical scavenger. The disulfides can be converted to free captopril, and the system can function as a recyclable antioxidant, which may play an added role in the cardioprotective effects of the ACE inhibitors in acute myocardial infarction [29]. Enalapril and its nonsulfhydryl analogs, and the phosphorus-containing ACE inhibitors, undergo a very limited metabolism, except for the conversion to active drug if an ester prodrug ACE inhibitor is utilized. Lisinopril is not significantly metabolized in humans and is primarily excreted unchanged in the urine. Most of captopril is excreted unchanged in the urine by tubular secretion, with 94% being recovered within 6 hours. The primary route of elimination of enalapril appears to be renal. Enalaprilat has polyphasic elimination kinetics with

Table 3. *Summary of acute hemodynamic effects of angiotensin converting enzyme inhibitors in congestive heart failure patients*

ACE inhibitor	No. of pts.	Dose (mg)	Mean percent maximal change from baseline*								
			MAP	HR	CI	SVI	SVR	PVR	PCWP	RAP	PAP
Captopril	99	25–100	−24	−11	+35	+34	−37	−39	−42	−46	−29
Enalapril	73	2.5–10	−24	−11	+40	+54	−41	−47	−41	−45	−29
Lisinopril	70	1.25–10	−19	NS	+22	NA	−30	−22	−36	NS	−38

*Significantly different from baseline values unless indicated otherwise; MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; PAP = pulmonary artery pressure; − = decrease; + = increase; NS = not statistically significant; NA = not available. Adapted from Brogden et al. [15], Gomez et al. [30], and Lancester and Todd [27].

strong binding to serum ACE with a terminal half-life of 30–35 hours. Enalapril accumulation can occur in patients with moderate-to-severe renal impairment, just as with captopril, and reduction in the daily total dosage is necessary for both captopril and enalapril. Monitoring captopril plasma concentrations is of little value in establishing the optimum dose, since neurohumoral and hemodynamic responses do not correlate well with plasma levels. Although in patients with hepatic dysfunction conversion of enalapril to enalaprilat is delayed, steady-state plasma concentrations of enalaprilat are similar in patients with congestive heart failure and in those with hypertension after repeated doses of enalapril. Lisinopril has polyphasic elimination kinetics, with the terminal phase representing saturable binding of lisinopril to plasma ACE. Dosage reduction of lisinopril is necessary in patients with severe renal impairment. The pertinent pharmacokinetic characteristics of the yet many investigational ACE inhibitors have been recently summarized [10].

Pharmacodynamic Properties of ACE Inhibitors

Pharmacodynamic studies with ACE inhibitors support the hypothesis that the favorable acute hemodynamic effects are predominantly due to ACE inhibition, with a consequent reduction in blood and tissue angiotensin-II levels and a subsequent decrease in aldosterone secretion. The acute hemodynamic changes in hypertensive patients after a single, oral dose of an ACE inhibitor produces a significant decrease (10–20%) in the systolic and diastolic blood pressures and lowering of the systemic vascular resistance (10–36%), usually without clinically significant changes in the heart rate or cardiac output [15, 22, 27]. In patients with congestive heart failure, there are, however, dramatic decreases (37–45%) in right atrial pressure, pulmonary capillary wedge pressure, pulmonary and systemic vascular resistance, and significant decreases (24–29%) of mean arterial and pulmonary artery pressure within 30–90 minutes of the oral, single dose of an ACE inhibitor. Cardiac output, cardiac index, stroke index, and stroke work index similarly increase by an average of 20–44% (Table 3). The beneficial hemodynamic and clinical effects of ACE inhibition are maintained during long-term treatment of congestive heart failure patients [15, 27, 30]. Most acute studies have shown a correlation between high pretreatment renin activity and a more marked acute hemodynamic response with ACE inhibition in congestive heart failure. There is, however, no consistent correlation between pretreatment renin levels and the long-term hemodynamics or clinical response with ACE inhibition. After single-dose administration of the ACE inhibitors, the onset of hemodynamic effects are quicker with captopril in comparison with enalapril and lisinopril. In most clinical studies, dose increment of the ACE inhibitors generally results in some prolongation of the hemodynamic effects, although the magnitude of the hemodynamic response is essentially the same at low and high doses of the ACE inhibitors [15, 22, 27].

Renal Hemodynamic Effects of ACE Inhibition

In healthy subjects ACE inhibition produced an increase in renal blood flow and a decrease in renovascular resistance [15, 22]. Restriction of sodium intake markedly increased the renal response to ACE inhibition. Long-term captopril administration in essential hypertension patients usually resulted in little change in renal blood flow and effective renal plasma flow. Enalapril, however, significantly increased both parameters in essential hypertension patients. There was no change in the glomerular filtration rate with both ACE inhibitors. ACE inhibition can cause a decrease in glomerular filtration (sometimes markedly) on the stenotic side, without much change in the nonstenotic kidney, in patients with unilateral renal vas-

cular hypertension. Following ACE inhibition, the reduction in renal blood flow in the stenotic kidney is counterbalanced by an increase in the renal blood flow of the unaffected kidney in patients with unilateral renal artery stenosis. The ACE-inhibitor-related functional renal insufficiency is a rare occurrence in renovascular hypertensive patients, unless there is critical (hemodynamically significant) bilateral renal artery stenosis, renal artery stenosis of the single functioning kidney, or severe bilateral nephrosclerosis in essential hypertensive patients [31, 32]. Sodium excretion was increased in some patients with essential hypertension but not in others, while the mean potassium excretion was unchanged during captopril treatment. Enalapril, however, produced modest natriuresis with fractional increased excretion of sodium during acute and prolonged treatment. Marginal increases in serum potassium concentrations were noted after captopril and enalapril therapy. Diuretic-induced hyperaldosteronism and hypokalemia was attenuated by ACE inhibition in the hypertensive patient [22].

Renal Protective Effects of ACE Inhibition

The potential renal protective effects of ACE inhibition in patients with essential hypertension with moderate-to-severe renal disease have been reported by Bauer and coworkers [33]. The blood pressure of 23 patients with essential hypertension was strictly controlled with enalapril or enalapril and hydrochlorothiazide. In patients with moderately impaired renal function, there was a 33–50% increase in inulin clearance (glomerular filtration rate) and a 39% increase in effective renal plasma flow during 3 years of enalapril treatment. The filtration fraction and urinary protein excretion were unchanged. Bauer et al. [28] concluded that long-term blood-pressure control with enalapril either preserved or improved renal function in essential hypertensive patients. Experimentally, proteinuria and glomerular injury were prevented with enalapril treatment of rats with reduced renal mass or with streptozotocin-induced diabetes mellitus [34, 35]. It has been suggested that glomerular hypertension due to elevated glomerular capillary hydraulic pressure is critical for eventual glomerular destruction with normal aging, diabetes mellitus, or chronic renal disease [34–36]. It is noteworthy that controlling systemic hypertension with drugs other than ACE inhibitors did not prevent glomerular injury in the rats, since the glomerular capillary pressure was not reduced with conventional drugs [34, 37]. This has led to the hypothesis that interruption of the renin-angiotensin system, particularly at the tissue level, improves intrarenal hemodynamics and retards glomerular destruction. Short-term (8 weeks) enalapril treatment has been shown to reduce proteinuria in essential hypertensive patients [38]. Long-term enalapril treatment in the same patients showed a tendency for the protein excretion to return towards pretreatment levels in patients with moderately impaired renal function. Captopril treatment in essential hypertensive patients had variable effects on renal parameters [39, 40]. Although ACE inhibition is well tolerated in the vast majority of renovascular hypertensive patients, nonoliguric functional renal insufficiency may occur rarely in some patients with critical bilateral renal artery stenosis or renal artery stenosis of the single-functioning kidney. This occurs after inhibition of intrarenal of angiotensin II production, which had previously maintained the "protective" efferent arteriolar constriction necessary to preserve glomerular filtration in the ischemic kidney [31]. There are no clinical data yet available comparing the renal protective effects (including the renal function and urinary protein excretion) of ACE inhibitors with other antihypertensive agents in equipotent doses that lower the systemic blood pressure but may not improve the glomerular hypertension. Further long-term studies are already underway to determine if the renal protective effects of long-term ACE inhibition in essential hypertensive patients with and without moderately impaired renal function are "class" effects or are ACE "agent" specific.

Structure-Activity Relationship of ACE Inhibitors in Cardiovascular Diseases

All ACE inhibitors exert their antihypertensive and anticongestive effects primarily by lowering the circulating and tissue levels of angiotensin II. The ACE inhibitors have variable effects on the kallikrein-kinin-prostaglandin systems [41]. The "agent"-specific differences are for most part related to the chemical structure and the clinical pharmacologic differences between the ACE inhibitors [42]. There are preliminary data suggesting that the sulfhydryl group of captopril may serve as recyclable antioxidant by scavenging superoxide anions and may improve reperfusion-induced cardiac dysfunction [29]. Restoration of blood supply to the ischemic myocardium provoked ventricular fibrillation in 37.5% of control dogs but in only 9% of enalaprilat- and 0% of captopril-treated animals [29]. A stereoisomer of captopril, SQ 13,534, did not reduce the incidence of ventricular fibrillation (40% with SQ 13,534 vs. 37.5% of control dogs), suggesting that the antifibrillatory actions may be related to ACE

inhibition and not to free-radical scavenger properties of SQ 14,534 and captopril [29]. In the dog experiments the intravenous dose of captopril (5 mg/kg), enalaprilat (1.6 ± 0.13 mg/kg), and SQ 14,534 (5 mg/kg) was many times higher than the recommended dose of captopril and enalaprilat for the treatment of hypertension and congestive heart failure. Further studies are needed at lower doses of the ACE inhibitors in in-vivo and in-vitro free radical experiments. The clinical adverse reactions, such as skin rashes, pruritis, taste disturbances, oral ulcers, pemphigus, and blood dyscrasias, have been considered to be strongly characteristic of "penicillaminelike" drugs including captopril, all with an active sulfhydryl group [43]. With reduced captopril doses and more careful patient selection, the more serious reactions (blood dyscrasias) are no longer found, but disturbances of taste perception, skin rashes, pruritis, and oral mucosal ulcers are still encountered with captopril [43]. Oral absorption of captopril is significantly affected by food, and it has a shorter duration antihypertensive effect. The oral absorption of the nonsulfhydryl ACE inhibitors, enalapril and lisinopril, is unaffected by food, and they have a longer duration of antihypertensive effects and a miniminal incidence of the sulfhydryl-related side effects.

It is quite apparent that long-term compliance with antihypertensive therapy is critically linked to the frequency of daily administration of the medication, the adequacy of blood pressure control, and the lack of frequent or serious metabolic and clinical side effects. The ACE inhibitors introduced since 1980 for hypertensive treatment have emerged as the preferred agents for treating most hypertensive patients. They are effective in about 60% of mild-to-moderate essential hypertensive patient as monotherapy [15, 22, 27, 44, 45] and in over 90% in combination with a thiazide diuretic [15, 22, 27, 46, 47]. ACE inhibitors in combination with a diuretic and digitalis have improved the symptoms, exercise tolerance, cardiac hemodynamics, and mortality of congestive heart failure patients [15, 22, 27, 48, 49]. There has been some concern of either more frequent or prolonged hypotension with long-acting ACE inhibitors in patients with congestive heart failure on the basis of a study that employed 8–16 times the recommended starting dose of enalapril and captopril in such patients [50, 51]. Subsequent extensive clinical experience with enalapril [49, 52] and lisinopril [27] has shown that the long-acting ACE inhibitors are as effective and safe as captopril in chronic congestive heart failure patients, although only captopril and enalapril are approved for general use in such patients [51]. Intravenous enalaprilat is now available for short-term treatment of moderate-to-severe hypertension [52]. In conclusion, ACE inhibitors are a unique class of agents with expanding clinical use in the treatment of hypertension and congestive heart failure.

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