

Class Effects of Angiotensin-Converting Enzyme Inhibitors

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Abstract

This review discusses important issues related to the use of angiotensin-converting enzyme inhibitors (ACEIs). ACEIs have been shown in clinical trials to slow progressive renal, cardiac, and vascular disease. The Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends ACEIs as alternative first-line therapy in patients with essential hypertension (HTN), congestive heart failure, and in hypertensive diabetics who also have renal disease. Many of the therapeutic benefits derived from ACEIs are thought to be class effects. There are certain distinctive pharmacokinetic and pharmacodynamic features for some of the ACEIs such as differences in absorption, protein binding, half-life, and metabolic disposition. In appropriate doses, they all lower blood pressure similarly. In the treatment of HTN and hypertensive renal disease, a class effect appears to be

applicable when selecting an agent. It is less likely that ACEIs are interchangeable in the treatment of congestive heart failure because maximal cardioprotective tissue effect rather than blood pressure normalization is the goal. In addition, for some agents clinical trials that demonstrate decreased morbidity or mortality are currently lacking.

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Since they were introduced into the healthcare market almost 20 years ago, angiotensin-converting enzyme inhibitors (ACEIs) have become vital tools in the medical therapy of hypertension (HTN) and cardiovascular disease.¹ Following the introduction of captopril in 1981, the first compound of this class, the ACEI field has quickly mushroomed to include approximately 20 ACEIs that are marketed worldwide and 10 that are available in the United States.^{2,3}

Captopril ushered in an era of remarkable success in cardiovascular therapy. Its efficacy in reducing blood pressure (BP) in a number of renin-dependent models of HTN was only a precursor of what this class of drugs would do for the management of cardiovascular disease.⁴ In addition to their vasodepressor properties, ACEIs were shown experimentally to slow

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progressive renal, cardiac, and vascular disease and attendant morbidity and mortality. Thus, additional indications for ACEIs were sought in the areas of congestive heart failure (CHF), post-myocardial infarction (post-MI), and diabetic nephropathy (Table 1). A full description of the tissue protective properties of ACEIs exceeds the scope of this review. The reader is referred to a number of scholarly reviews on these topics.⁴⁻¹⁰

Understanding the current role of ACEIs in the management of HTN and cardiovascular diseases requires a knowledge of the epidemiology and pathophysiology of HTN as well as its sequelae. Current opinion concerning these issues will be discussed. Although many of the therapeutic gains from ACEI therapy are class

effects, there do exist certain distinctive pharmacokinetic and pharmacodynamic features for some of the ACEIs. Where indicated, such differences in class members will be discussed. ACEIs also have proven useful for a number of off-label indications; these areas will be addressed as well.

... HYPERTENSION ...

Epidemiology

HTN is a worldwide epidemic that affects all ages but primarily occurs in adults. The prevalence of HTN increases dramatically with age: 50% of the population older than age 60 years are hypertensive. Comparisons of the prevalence of HTN in different populations of the world can only be made with the utmost caution because of differing cut points for the definition of HTN, varying quality of the BP measurements and surveys, differing age and ethnic group proportions, and widely varying socioeconomic conditions. Four rigorous national health surveys have been reported in the past decade, 2 in developed countries—the United States and Canada—and 2 in developing countries—Egypt and China (Table 2).¹¹

The current trend in HTN therapy is to seek lower BP values. The ideal BP, both systolic and diastolic, is still debated and ultimately will vary according to patient-type and disease-state subset. In spite of a growing realization of the HTN paradigm of “lower is better,” the control rates in the United States and in most industrialized countries appear to have either plateaued or decreased during the past several years.^{12,13} For example, the National Health and Nutrition Examination Survey (NHANES III) Phase-2, reports a 27% BP control rate, defined as less than 140/90 mm Hg, for the years 1991 through 1994 (Table 3). The BP control rate was 29% in a similar survey conducted from 1988 to 1991.¹² If today’s rigor-

Table 1. FDA-Approved Indications for ACEIs

Drug	Hypertension	Congestive Heart Failure	Diabetic Nephropathy	Left Ventricular Dysfunction
Captopril	•	•	•	• (post-MI)
Benazepril	•			
Enalapril	•	•		• (asymptomatic)
Fosinopril	•	•		
Lisinopril	•	•		
Moexipril	•			
Perindopril	•			
Quinapril	•	•		
Ramipril	•	•		
Trandolapril	•	• (post-MI)		• (post-MI)

Post-MI: Post-myocardial infarction.

ous standards of a goal BP of 120/80 mm Hg were to be applied, control rates would drop to 10% in most industrialized countries.

The epidemiology of HTN is to a degree age-, gender-, and ethnic-dependent, which may influence the selection of an antihypertensive agent. HTN prevalence increases with age. Whereas HTN is more common before the age of 40 years in males, it occurs more frequently in females with advancing age. The prevalence of HTN is much greater in the African-American population, irrespective of age or gender.¹² The NHANES III, Phase 2 of 1991 to 1994 estimates the prevalence of high BP in adults age 20 years and older to be 35% for African-American males and 34.2% for African-American females. This is an incidence rate approximately 2 times more frequent than that observed in white or Hispanic males and females.¹² The percentage of well-controlled Hispanic hypertensives was only 14% in the most recent NHANES survey.¹² Fewer hypertensive men are aware of their HTN or are treated and controlled than are hypertensive females.

Etiology and Pathophysiology

As much as 95% of all HTN is of unknown cause. HTN clusters in families, with a stronger contribution from the father than the mother. Estimates of the genetic contribution to HTN range from 30% to 60%.¹⁴ Environmental factors influence the expression of a hypertensive trait, although the boundaries between genes and the environment are blurred by the recognition that intrauterine growth retardation is an apparently strong predictor of subsequent HTN.¹⁵ No doubt multiple factors are involved in the genesis of HTN, although in most cases initiating factors are only detectable for a short period of time. Increased pressure typically alters vascular wall structure and function with

loss of vascular compliance. This fact is a unifying concept for many forms of HTN.

HTN may find its origin in several readily definable abnormalities such as hyperkinetic circulation, increased

Table 2. Comparison of Hypertension Surveys in 4 Countries

Country	%			
	Prevalence	Awareness	Treated	Controlled
United States	20.4	73	55	21
Canada	22.0	58	39	16
Egypt	26.3	37	24	8
China	13.6	25	13	3

These studies were performed following standardized protocols using trained personnel. Nationwide cross-sectional studies of randomly selected subjects were carried out. The results were adjusted for age and gender. Awareness indicates the % of subjects who knew that they had HTN; Treated indicates the % of HTN subjects on HTN treatment; and Controlled indicates the % of hypertensive subjects whose blood pressure was observed to be less than 140/90 mm Hg. Source: Adapted from Reference 11.

Table 3. Trends in the Awareness, Treatment, and Control of High Blood Pressure in Adults, United States, 1976-1994

	NHANES II (1976-1980)	NHANES III (Phase 1: 1988-1991)	NHANES III (Phase 2: 1991-1994)
Awareness	51	73	68
Treatment	31	55	53
Control*	10	29	27

NHANES: National Health and Nutrition Examination Survey. *Systolic BP less than 140 mm Hg and diastolic BP less than 90 mm Hg. Data are percentage of adults age 18 to 74 years with systolic BP 140 mm Hg or greater, diastolic BP of 90 mm Hg or greater, or taking antihypertensive medications. Source: Reference 1.

circulating blood volume, or increased peripheral resistance with or without increased vascular stiffness. In turn, certain accompanying factors may have a permissive effect on how early in life HTN presents and the rate at which the disease progresses. Not all such factors have been identified, although those most commonly considered include the dietary intake of nutrients such as sodium, potassium, and calcium, the degree of sympathetic nervous system activity, insulin resistance and hyperinsulinemia, the level of activation of the renin-angiotensin aldosterone (RAA) axis, and endothelial dysfunction.¹⁶

Two of these factors warrant additional consideration: endothelial dysfunction and the level of RAA axis activation. In the hypertensive patient, the vascular wall is both functionally and structurally abnormal. Thus, HTN may be both cause and consequence of endothelial dysfunction. Vascular cellular function is impaired as the result of an interplay of environmental, genetic, and pathologic events.¹⁷ The target for much of the early change in vascular function is endothelial cells—a continuous monolayer lining the entire inner surface of all blood vessels and the heart. The endothelium is especially prone to injury since it is subjected to wide swings in BP and is in direct contact with many potentially pathogenic substances, such as low-density lipoprotein cholesterol and angiotensin-II.^{18,19} Endothelial cell dysfunction/injury has become an area of intense clinical interest with a wide range of conditions, such as HTN, hypercholesterolemia, smoking, diabetes, and diet—the main risk factors for cardiovascular disease. All such conditions are capable of producing a state of abnormal endothelial cell function.^{18,19}

The RAA axis is implicated in multiple facets of the HTN syndrome including both its origin and progression. Increased activity of the RAA

axis has been recognized for several years as an important element in the progression to end-organ damage. Thus, left ventricular hypertrophy (LVH), CHF, post-MI ventricular remodeling, and nephropathic conditions have all been linked with increased activity in this axis.³ There is general agreement that the RAA axis and, in particular, angiotensin-II is involved in cardiovascular homeostasis but maybe more as a growth factor than as a pressor hormone.²⁰ The possibility that there is a direct and clinically relevant growth-promoting effect of angiotensin-II seems more plausible, particularly because a complete renin-angiotensin system has been demonstrated within various tissues, including vessel walls, heart, and brain.²¹

A cardiovascular risk factor syndrome has also been reported in which HTN, glucose intolerance, underlying insulin resistance, compensatory hyperinsulinemia, and dyslipidemia (elevated triglycerides and reduced high-density lipoprotein cholesterol) are clustered. Various components of this syndrome are readily identifiable in the borderline hypertensive patient well before fixed HTN has developed.²²⁻²⁴ Abdominal obesity appears to be a promoter of this syndrome both in HTN and in general. The tendency of these atherogenic traits to cluster with elevated BP was found in the Framingham Study to increase stepwise with baseline obesity and sequenced weight gain. A 5-lb weight increase was associated with a 30% increase in atherogenic risk factor clustering in patients with HTN.

Sequelae

Untreated HTN inevitably results in premature death from cardiovascular disease. The complications of chronically elevated BP are a consequence of either HTN or atherosclerosis, although it is unusual for these to be mutually exclusive. Those complications derived directly from HTN are

more likely to be governed by direct pressure transmission, whereas atherosclerotic complications have multiple causes, with HTN playing a variable role in their genesis (Table 4).

The ability to effectively control BP in at least a portion of the population has dramatically reduced the morbidity and mortality attributed to HTN. For example, age-adjusted death rates for stroke and coronary artery disease have declined by 60% and 53%, respectively. The reduction in stroke mortality is particularly significant in women age 50 years and older, with 50% of the benefit among white women and nearly two thirds of the benefit among African-American women traced to reduction in BP.²⁵ However, additional improvement in morbidity and mortality has not been forthcoming; since 1993, age-adjusted stroke rates have risen slightly and the slope of the age-adjusted rate of decline in coronary artery disease appears to be leveling.²⁶ Furthermore, rates have increased for the incidence of end-stage renal disease for which HTN is the second most common antecedent,²⁷ and the prevalence of CHF, wherein the large majority of patients have antecedent HTN.²⁸

Presentation Mode

Elevated BP is often inadvertently discovered in otherwise asymptomatic patients, for example, at a community BP screening or incidentally during evaluation for another problem. HTN should never be diagnosed from a single elevated measurement unless significantly elevated BP—that is, 180 mm Hg (systolic) or 110 mm Hg (diastolic)—coexists with end-organ damage. The belief that untreated HTN is an asymptomatic illness also may need to be reexamined. Increasingly, intervention trials with active drug therapy show an improvement in quality of life as BP is reduced.²⁹ Therefore, in the future, the presence of symptoms may become an additional indication for

therapy in an otherwise untreated hypertensive patient.

Initial Evaluation of the Hypertensive Patient

In the initial evaluation of the hypertensive patient, a thorough medical history must be obtained. The initial physical examination in a newly diagnosed hypertensive patient should include a careful assessment for the presence of target organ damage or reversible causes of HTN. The initial laboratory examination, a process that can typically be accomplished by obtaining an electrocardiogram, urinalysis, and chemistry profile, is also designed to look for evidence of target organ damage or secondary HTN. Several possible causes exist for secondary HTN. In the elderly, renal artery stenosis is a common cause of HTN, and in the young, primary hyperaldosteronism should always be considered. For a complete listing of potentially reversible causes of HTN, including common disease states and medications, the reader is referred to several recent reviews on

Table 4. Complications of Hypertension

<p>Hypertensive</p> <ul style="list-style-type: none"> Accelerated or malignant hypertension Encephalopathy Cerebral hemorrhage Left ventricular hypertrophy Congestive heart failure Renal insufficiency Aortic dissection <p>Atherosclerotic</p> <ul style="list-style-type: none"> Cerebral thrombosis Myocardial infarction Coronary artery disease Claudication syndromes

this topic.^{1,30}

Nonpharmacologic Therapy

The treatment of HTN is complex. Stage I or II HTN may respond to non-pharmacologic or lifestyle modification forms of therapy. Several proposed lifestyle modifications are outlined in Table 5.¹ Lifestyle modifications are to be encouraged regardless of the status of pharmacologic therapy. Effective implementation of lifestyle modifications may sometimes normalize BP thereby obviating the need for continued pharmacologic therapy. On occasion, this change may go unrecognized. Therefore, the dosage and number of antihypertensive medications generally should be reduced if HTN has been effectively controlled for at least 1 year, particularly if successful lifestyle modifications have been instituted.³¹ Any such reduction in antihypertensive medication dose should be undertaken in a deliberate, slow, and progressive manner.

Pharmacokinetics and

Pharmacodynamics of Hypertension Therapy

Several antihypertensive drug classes are available for the treatment of HTN, with some of them, such as diuretics, having been in use for more than 40 years. The reader is referred to several recent reviews for a full description of the available drug classes.^{32,33} The remainder of this review will center on the ACEIs and their use in cardiovascular disease states, including HTN. As a prelude to this discussion, several pharmacokinetic and pharmacodynamic issues regarding dose-response relationships are addressed.

Dose-response relationships are increasingly relevant to the titration of an individual antihypertensive agent or to the decision on what represents the optimal dose for 2 antihypertensive medications given together. A number of factors influence the response to an antihypertensive medication, including demographic considerations such as race and age. For example, African-American hypertensives are generally less responsive to ACEIs, yet in many cases if dose escalation occurs, their response differs little from that observed in white hypertensives who have received lower doses.³⁴

An additional response consideration relates to differences between short- and long-term response to dosing. With short-term response, variables such as drug formulation, circadian BP rhythms, and inherent sensitivity to a medication dictate the extent to which BP drops. With long-term response, it is now well-recognized for several drug classes, such as ACEIs and angiotensin 1-receptor antagonists (AT₁-RA), that their full BP lowering effect does not become evident until several weeks after therapy has begun. Thus, the dose-response relationship for an antihypertensive compound can vary as a function of the duration of dosing.³⁵

The time at which response is

Table 5. Lifestyle Modifications for Hypertension Prevention and Management

- | |
|---|
| <ul style="list-style-type: none"> ■ Lose weight if overweight ■ Limit alcohol intake to no more than 1 ounce (30 mL) of ethanol, 24 ounces (720 mL) of beer, 10 ounces (300 mL) of wine, or 2 ounces of 100-proof whiskey per day ■ Increase aerobic physical activity (30 to 45 minutes several times a week) ■ Reduce sodium intake to no more than 100 mmol per day (2.4 g of sodium or 6 g of sodium chloride) ■ Maintain adequate dietary intake of potassium (90 mmol per day) ■ Maintain adequate intake of dietary calcium and magnesium for general health ■ Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health |
|---|

assessed is relevant because it establishes in part the extent and duration of effect. In this regard, peak, trough, or trough-to-peak ratios for BP response have been considered as measures of efficacy. Trough BP readings are particularly useful in defining whether BP control has been effectively maintained throughout a dosing interval.³⁶ Therefore, individual members of a drug class can be distinguished. In the ACEI drug class, several compounds, such as captopril and enalapril, may require multiple daily doses to affect BP control (Table 6). In addition, the effect of many ACEIs may wane at the end of a dosing interval thereby necessitating a repeat dose. This phenomenon may be both pharmacokinetically and pharmacodynamically driven, with the latter being based on the underlying character of the HTN being treated.³⁷

A primary consideration in the dose-response relationship for an antihypertensive medication is the extent to which known counterregulatory mechanisms are activated. Such factors include volume expansion secondary to renal sodium retention, tachycardia triggered by baroreceptor stimulation, and peripheral vasoconstriction resulting from activation of the renin-angiotensin or sympathetic nervous systems. To the extent that these responses are initiated, the initial BP reduction with an antihypertensive medication can be effectively abolished or significantly attenuated. Several of the antihypertensive drug classes fail to activate these counterregulatory systems when they reduce BP. For example, the ACEIs effectively reduce BP without increasing pulse rate, inducing salt-and-water retention, or triggering renin-axis or sympathetic nervous system activation. Thus, ACEI therapy

establishes an environment conducive to both short- and long-term maintenance of reduced BP in the treated hypertensive.^{2,4}

An additional dose-effect consideration arises from how a compound is systemically eliminated. As a corollary to this, a specific drug dose may not always equate with a predictable blood level. For example, most ACEIs, clonidine, and the beta-blocker atenolol are eliminated primarily by renal mechanisms. These compounds will accumulate in the setting of a diminished glomerular filtration rate (GFR) if dosed in an unadjusted manner.³⁸ Failure to recognize this pharmacologic nuance may result in an exaggerated or prolonged antihypertensive effect as well as a significant increase in the incidence of concentration-related side effects (eg, sedation with clonidine).

A number of antihypertensive

Table 6. Dosage Strengths and Treatment Guidelines for Oral Angiotensin-Converting Enzyme Inhibitors

Drug	Strengths mg	Hypertension mg •day/frequency	Heart Failure mg •day/frequency
Benazepril	5, 10, 20, 40	20-40 /qd → b.i.d.	Not FDA approved
Captopril	12.5, 25, 50, 100	50-450 /b.i.d. → t.i.d.	18.75-150 /t.i.d.
Enalapril	2.5, 5, 10, 20	10-40 /qd → b.i.d.	5-20 /qd → b.i.d.
Fosinopril	10, 20	20-40 /qd → b.i.d.	20-40 /qd
Lisinopril	2.5, 5, 10, 20, 40	20-40 /qd	5-20 /qd
Moexipril	7.5, 15	7.5-30 /qd → b.i.d.	Not FDA approved
Perindopril	2, 4, 8	4-16 /qd	Not FDA approved
Quinapril	5, 10, 20, 40	20-80 /qd → b.i.d.	20-40 /qd → b.i.d.
Ramipril	1.25, 2.5, 5, 10	2.5-20 /qd → b.i.d.	10 /b.i.d.
Trandolapril	1, 2, 4	1-4 /qd	1-4 /qd

compounds must gain access to deep-tissue compartments to achieve their desired effect. An example of one such drug is the central α -agonist, clonidine. Clonidine is available in oral and transdermal forms. The pharmacokinetics of clonidine differ substantially for each of these delivery modes. When clonidine is administered orally, a typical peak and valley pattern for drug concentration emerges, whereas transdermal clonidine administration provides a more steady-state pattern. The latter still provides sufficient drug for entry into the central nervous system where it can affect BP reduction yet far fewer side effects occur because in a traditional sense peak blood concentrations do not occur.³⁹

An additional deep-tissue compartment consideration relates to the issue of ACEI therapy and "tissue binding." Several of the ACEIs, such as quinapril and ramipril, are highly lipophilic and have a strong affinity for the angiotensin-converting enzyme (ACE) found at the tissue level. Accordingly, they may affect a greater overall suppression of total body ACE activity. Although this current concept is provocative, it has not translated into a substantially different pattern for BP reduction compared to what has been observed with ACEIs, which are less tissue bound. Alternatively, there are data to suggest that endothelial dysfunction is differentially improved with the more tissue-bound ACEIs, although this too remains of poorly defined clinical significance.⁴⁰

A final consideration in defining a dose-response relationship for an antihypertensive medication resides in the well-recognized influence of volume contraction on enhancing drug effect and thereby the extent to which BP drops. Whether volume contraction is the initial step in the treatment of HTN or arises as the result of a diuretic being added to nondiuretic antihypertensive thera-

py, BP typically diminishes. When diuretic therapy is considered as adjunct therapy, 2 phenomena can be anticipated. First, an additive or synergistic relationship typically develops between a diuretic and the other form of therapy, and second, the amount of the first drug being administered can generally be reduced, consistent with the known amplifying effect of diuretic therapy. This pharmacologic practice is illustrated by combining a diuretic with an ACEI. Thus, diuretic therapy primes the system, sensitizing it to the effect of an ACEI and resulting in an additional reduction in BP. Accessing this facilitating effect has been simplified by the availability of several fixed-dose combination antihypertensive products that are comprised of an ACEI and a diuretic.⁴¹

...ANGIOTENSIN-CONVERTING
ENZYME INHIBITORS ...

**Pharmacologic Therapy:
Mechanism of Action of
Angiotensin-Converting Enzyme
Inhibitors**

It is important to know how ACEIs interact with the RAA axis and how they differ from other compounds also known to lessen RAA axis activity. ACEIs modify RAA axis activity by decreasing plasma angiotensin-II production as do beta-blockers (beta-blockers decrease plasma renin activity [PRA]); whereas, AT₁-RA curb angiotensin-II effect by blocking the Type I angiotensin-receptor.⁴²

The locus of activity of ACEIs within the RAA axis is at an ACE, which is pluripotent in that it catalyzes the conversion of angiotensin-I into angiotensin-II and controls the degradation of bradykinin and several other vasoactive peptides.⁴³ Although ACEIs effectively curb the generation of angiotensin-II from angiotensin-I, they do not prevent angiotensin-II from being produced by nonACE-

dependent pathways.⁴⁴ Such pathways rely on chymase and other proteases to independently produce angiotensin-II in myocardial and vascular tissue,⁴⁵ with the ensuing gradual rise in angiotensin-II levels, despite continuation of an ACEI, being termed "angiotensin escape."^{46,47}

The presence of angiotensin-II ordinarily dampens upstream production in the RAA axis. When ACEIs are given, by virtue of their temporarily diminishing angiotensin-II, there is a disinhibition of renin secretion from the juxtaglomerular apparatus by angiotensin-II.⁴⁸ As this controlling influence dissipates, the concentration of both PRA and angiotensin-I increases. This surplus of angiotensin-I is one source of substrate for these alternative pathways and provides a partial explanation for the phenomenon of angiotensin-II escape.

Because ACEIs only transiently reduce angiotensin-II levels (days into weeks) other mechanisms for their BP-lowering effect need to be considered, particularly if the manner in which they reduce BP is examined.^{43,45,46} When first administered, ACEIs transiently reduce BP, commensurate with the preexisting level of RAA axis activation.⁴⁹ With long-term therapy, the relationship between the fall in BP and pretreatment levels of angiotensin-II fades.⁵⁰ This latter observation makes renin profiling of little practical value in predicting the efficiency with which an ACEI reduces BP⁵¹; instead, the BP response achieved shortly after the initiation of ACE inhibition provides a better predictive index of long-term response. In many patients who have received chronic ACEIs, BP falls to levels well below those seen at the beginning of therapy, despite the aforementioned phenomenon of angiotensin-II escape. Although the precise explanation for the persistent decline in BP with ACEIs is not yet identified, changes in bradykinin concentrations appear to have some

influence on this process.⁵²

How ACEIs interact with the kallikrein-kinin system is a matter of considerable interest. ACE processes peptides other than angiotensin-II, which has important functional implications. For example, bradykinin is broken down by kininases, one of which (kininase II) is identical with ACE. Thus, in theory, administration of an ACEI should elevate tissue or circulating bradykinin concentrations. In turn, bradykinin stimulates the production of endothelium-derived relaxing factor and promotes the release of prostacyclin (PGI₂). When circulating bradykinin concentrations were measured in ACEI-treated patients, the values obtained were found to be inconsistently elevated.^{53,54} It is possible though that tissue bradykinin increases with ACEI therapy and thereby influences vascular tone locally, reducing BP.

The exact contribution of prostaglandins to the antihypertensive effect of ACEIs is still uncertain. The evidence supporting a role for increased vasodilatory prostaglandins in the BP-lowering effect of ACEIs remains circumstantial.⁵⁵ Although circulating levels of prostaglandin E₂ and PGI₂ metabolites are not noticeably altered by ACEIs, it has been recognized for some time that nonsteroidal anti-inflammatory drugs (NSAIDs) blunt the BP-lowering effect of ACEIs.⁵⁶ Low-dose aspirin (100 mg/day or less) has no significant effect on ACEI-induced BP reduction. Higher doses of aspirin (more than 236 mg/day) can on occasion blunt the antihypertensive response to ACEIs.^{57,58}

An ACEI's vasodepressor response is believed to be because of reduced activity in both the central and the peripheral sympathetic nervous system (SNS).⁵⁹ ACEI administration does not produce a consistent change in circulating catecholamines. ACEIs also do not alter circulatory reflexes and thereby do not increase heart

rate when BP is lowered.⁶⁰ Finally, ACEIs improve endothelial function, facilitate vascular remodeling, and favorably alter the viscoelastic properties of blood vessels.⁶¹ These additional attributes of ACEIs may explain why long-term BP reduction with an ACEI typically exceeds that observed in shorter terms.

Pharmacokinetics

The first orally active ACEI was the drug captopril, a sulfhydryl-containing compound with both a rapid onset of action and a short duration of effect. Subsequently, enalapril, a more long-acting compound, became available. Enalapril like other ACEIs, with the exception of lisinopril and captopril, undergoes metabolic conversion to an active diacid form, a process that occurs within the liver and the intestinal wall. An early theory held that

the formation of the active metabolite of an ACEI could be suppressed in the presence of hepatic impairment, such as in advanced CHF, but any such alteration in diacid formation has not proved clinically relevant.⁶² Pharmacokinetic parameters of several ACEIs are listed in Table 7.

ACEIs are structurally heterogeneous. For example, the active chemical side group or ligand on captopril, which binds to ACE, is a sulfhydryl group; for fosinopril, it is a phosphinyl group, with the remaining ACEIs containing a carboxyl group. The side group on an ACEI is one factor that has been suggested as being responsible for differing pharmacological responses among these compounds. Thus, the sulfhydryl group on captopril is purported to act as a recyclable free radical scavenger, and for this reason, captopril may retard the process of atherogenesis and pro-

Table 7. Pharmacokinetic Parameters of Angiotensin-Converting Enzyme Inhibitors

Drug	Onset/Duration (hrs)	Peak Hypotensive Effect (hrs)	Protein Binding (%)	Effect of Food on Absorption	Serum Half-life	Elimination
Benazepril	1/24	2-4	>95	None	10-11	Renal/some biliary
Captopril	0.25/dose-related	1-1.5	25-30	Reduced	<2	Renal, as disulfides
Enalapril	1/24	4-6	50	None	11	Renal
Fosinopril	1/24	2-6	95	None	11	Renal = hepatic
Lisinopril	1/24	6	10	None	13	Renal
Moexipril	1/24	4-6	50	Reduced	2-9	Renal/some biliary
Quinapril	1/24	2	97	Reduced	2	Renal>hepatic
Ramipril	1-2/24	3-6	73	Reduced	13-17	Renal
Trandolapril	2-4/24	6-8	80-94	None	16-24	Renal>hepatic

fect from myocardial infarction and diabetes.⁶³ This has not been clinically substantiated. In addition, captopril directly stimulates prostaglandin synthesis, whereas other ACEIs indirectly accomplish this by increasing bradykinin concentrations.⁶⁴ Alternatively, the sulfhydryl group is believed to lead to a higher incidence of skin rashes and dysgeusia. The presence of a phosphinyl group on fosinopril has been proffered as the reason for its low incidence of cough⁶⁵ and its ability to improve diastolic dysfunction.⁶⁶ With the latter, the phosphinyl group may facilitate the myocardial penetration or the retention of fosinopril.

Although ACEIs can be distinguished by differences in absorption, protein binding, half-life, and metabolic disposition, they lower BP in a similar manner. Rarely, beyond the issue of frequency of dosing, do these pharmacologic subtleties govern selection of an agent. This being said, 2 pharmacologic considerations for the ACEIs have generated considerable recent debate and warrant additional discussion.

The active diacid of only 2 ACEIs, fosinopril andtrandolapril, is eliminated to any significant degree by hepatic routes.³⁸ For all other ACEIs, elimination is accomplished almost exclusively by renal clearance mechanisms with varying degrees of filtration and tubular secretion occurring.^{67,68} This property of combined renal and hepatic elimination typically minimizes accumulation of these compounds in renal failure because they are being dosed to a steady state.^{67,68} To date, although a direct adverse effect from ACEI accumulation has not been identified, the longer that drug concentrations remain elevated the more likely BP will remain down. Thus, the major adverse consequence of drug accumulation may be prolonged hypotension and the organ-specific sequelae of such hypotension.⁶⁹

The second debated feature of ACEIs concerns the concept of tissue

binding. As noted earlier, some ACEIs, such as quinapril and ramipril, are highly lipophilic and thereby bind to tissue ACE for prolonged periods of time.¹⁰ It was originally believed that compound lipophilicity would favorably distinguish these compounds relative to BP control and end-organ protection. Unfortunately, there have been few direct head-to-head trials between ACEIs that are highly tissue bound and those with more limited tissue binding. In situations where such comparisons have occurred, the results do not convincingly support the claim of overall superiority for lipophilic ACEIs.^{10,70}

Because in most instances there is very little that pharmacokinetically separates one ACEI from another, the cost of an ACEI has become a critical issue in determining which compound is selected.⁷¹ The question of price often neglects the fact that only a small number of ACEIs have been specifically studied for their ability to protect end organs. Class effect is a phrase often invoked to legitimize use of a less costly ACEI when a higher-priced agent has been the one specifically studied in a disease state, such as CHF or diabetic nephropathy.^{72,73} The concept of class effect may be applicable in the treatment of diabetic nephropathy in which the primary goals are reducing BP and decreasing proteinuria. Under these conditions, substituting a less costly ACEI is reasonable if reductions in BP and protein excretion are comparable to those achieved with a more costly ACEI. Thus, in HTN and hypertensive renal disease, after dose equivalency is established, one ACEI can be substituted for another.

Alternatively, in the case of CHF, BP normalization is not a specific treatment goal because BP is commonly low in the more advanced stages of CHF. Rather, dose titration to a presumed maximal tissue effect dose is the desired goal. In CHF, dosage recommendations for ACEIs,

such as enalapril and captopril, propose dose titration to amounts greater than those ordinarily required for BP control.⁷⁴ Thus, the success of an ACEI in CHF may derive from multiple properties other than simply ACE inhibition. Here, myocardial binding, degree of change in plasma aldosterone, and changes in other neuropeptides degraded by the ACE may contribute to the overall cardioprotective effects of ACEIs.⁷⁵ Because not all ACEIs have been thoroughly studied in CHF, particularly relative to these secondary response parameters, it is less likely that ACEIs are interchangeable in the treatment of CHF (Table 1). Furthermore, true dose equivalence in the ACEI class is not established for the treatment of the CHF nor post-MI patient.

Hypertension Treatment and Hemodynamics

Several hemodynamic effects occur with the administration of an ACEI (Table 8).²⁻⁴ The underlying disease being treated frequently dictates the magnitude of change in many of these hemodynamic parameters. This is particularly so in the treatment of CHF and renal failure. In addition, many of these hemodynamic changes are accentuated in the presence of an activated RAA axis, which may develop with diuretic therapy or a low-salt diet. The latter is a well-established risk factor for first-dose hypotension with an ACEI.⁴⁹

The reduction in BP with an ACEI occurs independent of either a decrease in cardiac output or an increase in heart rate.^{60,76} Occasionally, cardiac output increases with ACEI therapy particularly if cardiac output is reduced when therapy is started.⁷⁷ The fall in peripheral vascular resistance with ACEI therapy can lead to a decrease in cardiac filling pressures.⁶⁰ Angiotensin-II can also actively participate in the regulation of coronary vascular tone and coronary blood

flow, if the RAA axis is activated. Conversely, treatment with an ACEI can reverse this angiotensin-II-mediated decline in coronary blood flow.⁷⁸ Several small trials, generally of short duration, assessing the effects of ACEIs on severity of angina or on objective measures of myocardial ischemia, have reported conflicting results in this regard.⁷⁹

ACEIs lower BP without diminishing cerebral blood flow.⁸⁰ This phenomenon is suggested to represent a favorable effect of ACE inhibition on cerebral autoregulatory ability and is of possible relevance to the treatment of HTN in the elderly.⁸¹ Furthermore, ACEIs decrease capacitance vessel tone, which may explain why ACEIs can alleviate the peripheral edema associated with calcium channel blocker (CCB) therapy.⁸² ACEIs do not limit the peak heart rate response to exercise, although they do effectively reduce the peak BP response.⁸³ The addition of a diuretic to an ACEI does not alter the hemodynamic profile of ACE inhibition except in the instance of exercise, wherein the exercise-related increase in cardiac output may be blunted.⁸⁴

ACEIs routinely increase effective renal plasma flow (ERPF) while maintaining GFR. The rise in ERPF evoked by ACEIs is characterized by a preferential vasodilation of the efferent arteriole.^{6,85} The arithmetic consequence of this is a drop in the filtration fraction (GFR/ERPF), a well-accepted marker for ACEI effect on the kidney. When GFR is heavily reliant on efferent arteriolar tone—as in CHF, dehydration, or renal artery stenosis—and an ACEI is administered, GFR may drop acutely.⁸⁶

Diuretics and beta-blockers are still commonly employed as first-step therapy for HTN, although increasingly ACEIs are seen as a suitable first-step alternative.^{1,87,88} The enthusiasm for the use of ACEIs is not efficacy-related because ACEIs have efficacy comparable to, but not better than,

most other drug classes, with response rates from 40% to 70% in Stage I or II HTN.⁸⁹ Clinical trial results do not reflect conditions in actual practice. In this regard, ACEIs are heavily prescribed because this class is believed to be well tolerated, end-organ protective, and a treatment with which patients will be compliant over the long term.⁹⁰ This enthusiasm for the use of ACEIs is justified when comorbid conditions exist in the hypertensive patient. Such enthusiasm becomes somewhat less justified in the routine uncomplicated hypertensive unless quality of life is anticipated to improve with an ACEI regimen. There exists a paucity of information concerning long-term cardiovascular morbidity and mortality for ACEIs versus conventional therapy. Where such comparative data is available, ACEIs do not differ from conventional therapy in how they affect change in cardiovascular and cardiorenal morbidity and mortality.^{91,92}

There are very few predictors of response to ACEIs. When HTN is accompanied by high PRA values, such as in renal artery stenosis, the response to an ACEI can be particularly profound.⁹³ In most other cases, there is a tenuous relationship between the pre- or the post-treatment PRA value and the vasodepressor response to an ACEI. Although certain patient types, including the low-renin, salt-sensitive individuals, such as the diabetic, African-American, or elderly hypertensive, demonstrate lower response rates to ACEI monotherapy, there still remain a significant number of patients so profiled that will respond to ACEIs.⁴

The low-renin state, characteristic of the elderly hypertensive, differs from other low-renin forms of HTN in that it develops not as a response to volume expansion but rather because of senescence-related changes in PRA.⁹⁴ Thus, the elderly generally respond well to ACEIs at conventional doses,⁸¹ although senescence-relat-

ed renal failure, which slows the elimination of these drugs, complicates interpretation of such treatment successes. The African-American hypertensive, who as a group tend to have lower PRA levels, is perceived as being poorly responsive to ACEIs when compared to whites.⁹⁵ Yet, in many instances, if careful dose titration occurs BP will eventually nor-

Table 8. Predominant Hemodynamic Effects of Angiotensin-Converting Enzyme Inhibitors

Hemodynamic Parameter	Effect	Clinical Significance
■ Cardiovascular		
Total peripheral resistance	Decreased	These parameters contribute to a general decrease in systemic blood pressure
Mean arterial pressure	Decreased	
Cardiac output	Increased or no change	
Stroke volume	Increased	
Preload and afterload	Decreased	
Pulmonary artery pressure	Decreased	
Right atrial pressure	Decreased	
Diastolic dysfunction	Improved	
■ Renal		
Renal blood flow	Usually increased	Contributes to the renoprotective effect of these agents
Glomerular filtration rate	Variable, usually unchanged but may ↓ in renal failure	
Efferent arteriolar resistance	Decreased	
Filtration fraction	Decreased	
■ Peripheral Nervous System		
Biosynthesis of noradrenaline	Decreased	Enhances blood pressure lowering effect and resets baroreceptor function
Reuptake of adrenaline	Inhibited	
Circulating catecholamines	Decreased	

malize.³⁴ This response pattern suggests that eliminating even small amounts of PRA, as exist in the African-American hypertensive, is important to BP control.

All 10 ACEIs are Food and Drug Administration-approved for the treatment of HTN. ACEIs are now recognized by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) as an option for first-line therapy in patients with essential HTN, especially in those with diabetes who also have renal disease and in patients with CHF.¹ Considerable dosing flexibility exists with the available ACEIs. Enalaprilat is the sole ACEI available in an intravenous form.³

Results from several head-to-head trials support the comparable antihypertensive efficacy and tolerability of the various ACEIs. However, there are differences within the ACEIs class such as the time to onset of effect and to maximum BP reduction. These differences do not translate into different response rates if comparable doses of different ACEIs are given. Typical variables, which confuse the interpretation of study results, have included differences in study design/methodology, dose frequency, and dose amount. ACEIs labeled as once daily vary in their ability to reduce BP through a 24-hour dosing cycle, as defined by having a trough-to-peak ratio greater than 50%.⁹⁶ Unfortunately, the trough-to-peak ratio as an index of duration of BP control often misrepresents the true BP reduction achieved by a compound.⁹⁷ Because of this, dosing instructions for many of these compounds include the proviso to administer a second daily dose if the antihypertensive effect has dissipated by the end of the dosing interval. Therefore, additional prospective clinical trials will be required to clarify the issue of duration of effect for the various ACEIs.

The question, what to do if an ACEI does not normalize BP, is often raised. One approach is simply to raise the dose; however, the dose-response curve for ACEIs, like most antihypertensive agents, is flat after the initial dose titration step.³⁷ Responders to ACEIs typically do so at doses well below those necessary for prolonged 24-hour suppression of ACE. In addition, the maximal vasodepressor response to an ACEI does not occur until several weeks after therapy has begun. Thus, only with complete failure to respond to an ACEI should an alternative drug class be substituted. If a partial response has occurred then therapy with an ACEI can be continued in anticipation of an additional drop in BP over the ensuing weeks. Alternatively, an additional compound such as a diuretic, CCB, or peripheral α -blocker can be combined with an ACEI to affect better BP control.

ACEIs effectively regress LVH in the face of prolonged lowering of BP.⁹⁸ This is an important feature because the presence of LVH portends a significant future risk of sudden death or myocardial infarction.⁹⁹ ACEIs can be safely utilized in patients with coronary artery disease. Although they do not specifically vasodilate coronary arteries, they do improve hemodynamic factors, which dictate myocardial oxygen consumption and thereby would be expected to reduce the risk of ischemia. For example, ACEIs do not reflexly increase myocardial sympathetic tone in hypertensive patients with angina, as occurs with other antihypertensives.¹⁰⁰

ACEIs are also useful in the treatment of either isolated systolic HTN or systolic predominant forms of HTN because they improve arteriolar compliance.¹⁰¹ In addition, ACEIs are useful in the treatment of patients with cerebrovascular disease because they maintain cerebral autoregulatory ability, despite their antihypertensive effects.^{80,102} This is particularly impor-

tant in the treatment of the elderly hypertensive.⁸¹ ACEIs dilate both small and large arteries and can be used safely in patients with peripheral vascular disease and may, on occasion, lessen intermittent claudication symptomology.¹⁰³

ACEIs are also touted as agents of choice in the diabetic hypertensive patient, whether they have diabetic renal disease or not. Such enthusiasm needs to be tempered by the realization that these compounds, when administered as monotherapy, do not effectively reduce BP in many diabetics. This may relate to the fact that many diabetics have a low-renin, volume-expanded form of HTN, which is a form of HTN generally less responsive to an ACEI. This efficacy hurdle can be overcome by the addition of a diuretic to the treatment regimen, or, alternatively, a different antihypertensive drug class may be considered. This rationale for therapy changes when the diabetic demonstrates renal involvement. The data are now impressive in support of ACEIs being a major element of the treatment regimen, irrespective of their BP reducing ability.¹⁰⁴ A final consideration with ACEIs in the hypertensive diabetic relates to their effect on hyperlipidemia or insulin resistance. In this regard, ACEIs have not exhibited a negative effect on serum lipids or insulin resistance.¹⁰⁵⁻¹⁰⁷

End-Organ Disease Therapy/ Congestive Heart Failure

Data from both placebo-controlled and open trials suggest that ACEIs substantially reduce the risk of death and hospitalization for CHF while improving its symptomology.⁸ These agents interfere with the neurohumoral deterioration characteristic of CHF, with angiotensin-II having a vital role in this deteriorative process.¹⁰⁸ Although statistically significant reductions in mortality have been observed only with enalapril, similar trends have been observed

with other ACEIs, including captopril, ramipril, quinapril, and lisinopril.⁸ Furthermore, these agents have demonstrated efficacy and tolerability in the treatment of CHF based on the endpoints of improved exercise tolerance and symptomology. Even though ACEIs are universally recommended as a cost-effective strategy for the treatment of CHF, physician-prescribing practice is such that only approximately 50% of those patients eligible for treatment with ACEIs actually receive it.^{109,110}

Enalapril, captopril, lisinopril, and trandolapril significantly reduce morbidity and mortality rates in patients with myocardial infarction (MI) and depressed ventricular function. There are presently insufficient data to determine whether clinically significant differences exist among the ACEIs in the post-MI setting, given the paucity of head-to-head trials involving these agents and the fact that the studies discussed above varied in length and duration.¹¹¹ Currently, only captopril and trandolapril are approved specifically in post-MI left ventricular dysfunction, although enalapril is approved in asymptomatic left ventricular dysfunction. However, as in patients with CHF, numerous ACEIs have demonstrated benefits in patients after MI, suggesting a probable class effect.¹¹²

Several dosing strategies are effective in reducing morbidity and mortality in patients with systolic left ventricular dysfunction. Most importantly, a systematic effort must be made to reach the target doses shown to be effective in the randomized trials. Emerging data suggest that the lower doses of ACEIs typically employed in clinical practice are less effective than the relatively high doses used in randomized trials.^{75,113} The total daily dose of enalapril and captopril used in community practice is typically in the 10 mg and 50 mg/day range, respectively; whereas, randomized trials used enalapril and captopril

doses approaching 40 and 150 mg/day, respectively. Until convincing evidence otherwise becomes available, the treatment of CHF should include sequential dose titration of an ACEI and should strive for doses employed in the randomized clinical trials. The ability to reach these doses in the CHF patient is typically an issue of tolerance. These patients are prone to the development of hypotension or a decrease in GFR. These dose-limiting side effects in many instances can be tempered by not allowing the patient to become overly volume-contracted.⁶⁹

Renal Failure

JNC-VI recommends the use of ACEIs in patients with HTN and chronic renal disease to control HTN and to slow progressive renal failure.¹ Irrespective of the drug class being used to lower BP, the most important component in the management of the patient with HTN and renal disease remains tight BP control. JNC-VI recommendations advise a goal BP of 130/85 mm Hg, with even a lower value of 125/75 mm Hg being advised for patients with proteinuria in excess of 1 g/day.¹ Although HTN is typically multifactorial in the renal failure patient, in most instances it is volume dependent. Because of the volume dependency of renal failure-related HTN, ACEI monotherapy will not always provide the desired level of BP control. Thus, when treating a renal failure patient, diuretics are often an element of the drug regimen.

ACEIs are useful in a number of clinical trial settings that involve patients with differing forms of nephropathy. Those who benefit from ACEI therapy include insulin- and noninsulin-dependent diabetics with established nephropathy,^{73,114} insulin-dependent patients with microalbuminuria and normal BP,¹¹⁵ and noninsulin-dependent patients with microalbuminuria and normal renal function.¹¹⁶ In addition, several nondiabetic

renal diseases,¹¹⁷⁻¹¹⁹ especially in the setting of significant proteinuria,¹¹⁶⁻¹²⁰ are benefited by ACEI therapy.

ACEI regimens that delay the progression of renal failure include: captopril, 25 mg t.i.d.^{73,115}; enalapril, 5 to 10 mg/day¹¹⁶; benazepril, 10 mg/day¹¹⁷; and ramipril, 2.5 to 5 mg/day.¹¹⁸ Renal failure is presumed to increase the pharmacologic effect of these ACEI doses by decreasing their renal clearance.^{38,67} It remains to be determined whether additional dose titration to doses higher than those cited above would offer additional renal protection. If so, it would likely derive from modification of tissue-based growth factor production or effect and probably not from greater BP reduction. Though not formally tested, it is likely that the majority of the renal effects of an ACEI are class effects.

ACEIs have several renal effects that can be inferred to be renoprotective, including decreasing glomerular capillary pressure,¹²¹ protein excretion,¹¹⁶⁻¹²⁰ and transiently reducing GFR.¹²² Early opinion highlighted the ability of ACEIs to decrease glomerular capillary pressures as their predominant renoprotective mechanism.¹²¹ More recent opinion holds that ACEIs modify tissue-based growth factors, which are activated by prior or ongoing renal disease and are stimulated by the presence of angiotensin-II, and thereby slow progressive renal failure.¹²³ The renoprotective effect of ACEIs is most evident in patients with heavy proteinuria (greater than 3 g/day).¹¹⁶⁻¹²⁰

Three factors can be considered as potential modifiers of the renal response to ACEIs. First, a low sodium intake enhances the antiproteinuric effect of ACEIs.^{7,124} Second, short-term studies suggest that dietary protein restriction complements the ACEI effect on protein excretion in nephrotic patients. This implies that protein restriction in combination with ACEI therapy may prove more effective than ACEIs

alone in slowing the progression of renal failure.¹²⁵ A third factor is that of inherited variation in ACE activity. Two common forms of the ACE gene, I (insertion) and D (deletion), give rise to 3 potential genotypes: II, ID, and DD. The DD phenotype is associated with higher circulating ACE levels,¹²⁶ and a greater pressor response to the infusion of angiotensin-I as compared to the II phenotype, with the ID phenotype displaying intermediate characteristics.¹²⁷ In this regard, recent work suggests that GFR declines more rapidly in nephropathic patients with the DD phenotype and that such patients do not demonstrate significant reductions in proteinuria or slowing in the rate of progression of renal failure when given ACEIs.^{128,129}

Off-Label Uses

Several off-label indications exist for ACEIs. For example, ACEIs are known to suppress thirst presumably because angiotensin-II behaves as a dipsogen and ACEIs suppress production of angiotensin-II.^{130,131} In theory, the role of angiotensin-II in thirst drive appears convincing; unfortunately, in practice when this hypothesis has been tested, ACEIs did not slacken thirst in all cases.^{130,131} ACEI use has been associated with the suppression of red blood cell production. In patients with normal renal function, this does not typically result in a clinically significant decline in red blood cell production. Alternatively, in patients with renal insufficiency this can lead to the development of an anemia.¹³² Two possible mechanisms exist by which ACEIs might suppress erythropoiesis.^{133,134} First, ACEIs reduce circulating insulin, like growth factor-I and thereby curb erythropoiesis.¹³³ Second, ACEIs increase plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline, which prevents the recruitment of pluripotent hematopoietic stem cells.¹³⁴ The suppression of

erythropoiesis by ACEIs has been used with positive results in the management of post-transplant erythropoiesis.¹³³ These effects seem to be class effects for ACEIs.¹³⁵ Finally, perhaps as a reflection of increased insulin sensitivity, ACEI use, in particular captopril use, has been accompanied by hypoglycemia both in insulin- and noninsulin-dependent diabetics.¹³⁶ This property is thought to be useful in insulin-resistance states because it may decrease medication requirement for glucose control.

Adverse Effects

After ACEIs were introduced into the healthcare market, a syndrome of "functional renal insufficiency" was observed as a class effect with these drugs. This process was initially recognized to occur in patients with either a solitary kidney and renal artery stenosis or in the setting of bilateral renal artery stenosis. Following these original reports, this phenomenon has been repeatedly observed in several conditions, including dehydration, CHF, and microvascular renal disease.¹³⁷ The theme common to all of these conditions is that GFR is overly dependent upon angiotensin-II-mediated constriction of the efferent or postglomerular arteriole. These aforementioned conditions typically reduced preglomerular or afferent arteriolar flow. Decreased glomerular capillary flow prompts the local production of angiotensin-II within the kidney. The efferent arteriole is sensitive to the effects of angiotensin-II and thereby constricts, returning upstream hydrostatic pressures within the glomerular capillary bed to normal values. Because glomerular capillary pressures determine glomerular filtration, it would follow that efferent arteriolar constriction would maintain GFR. The abrupt removal of angiotensin-II causes this sustaining pressure increase to dissipate, and with this change GFR rapidly diminishes. This

phenomenon of functional renal insufficiency is best treated by discontinuation of the ACEI, careful volume repletion if intravascular volume contraction exists, and, if strongly suspected, investigation for the presence of renal artery stenosis. An additional side effect with ACEIs is that of hyperkalemia.¹³⁸ Hyperkalemia is an uncommon occurrence with ACEIs unless a predisposition to this process exists—as with diabetes or CHF with renal failure—and potassium-sparing diuretics or potassium supplements are being administered. Conversely, ACEIs are known to minimize the diuretic-induced hypokalemia.¹³⁹

A dry, nonproductive cough is a common complication with ACEIs and is seen in about 20% of treated patients.¹⁴⁰ Cough is a class phenomenon with ACEIs and has ostensibly been attributed to increased bradykinin levels or other vasoactive peptides such as Substance P, which may play a second messenger role in triggering the cough reflex.¹⁴¹ Although numerous therapies have been tried, none have consistently eliminated ACEI-induced cough. Usually, the cough will disappear 1 to 2 weeks after the ACEI is discontinued. Nonspecific side effects are generally rare with ACEIs, with the exception of taste disturbances, leukopenia, skin rash, and dysgeusia, which are more frequent in captopril-treated patients.¹⁴¹ The sulfhydryl group found on captopril is implicated in these abnormalities.

Angioneurotic edema is a potentially life-threatening complication of ACEIs. Its incidence is less than 1%, and it can occur quite unpredictably. Typically, angioneurotic edema is not a first-dose phenomenon. It is easily recognized because of its characteristic involvement of the mouth, tongue, and upper airway.¹⁴² A final issue with ACEIs is their capacity to cause birth defects. ACEIs are not teratogenic; rather, when administered during the second and third trimester of preg-

nancy they can result in developmental defects, acute renal failure, or death in the fetus, because the maturing fetus is heavily reliant on angiotensin-II for its proper development.¹⁴³

Drug Interactions

Several class-specific drug interactions occur with ACEIs.¹⁴⁴ Potassium supplements or potassium-sparing diuretics, when given with ACEIs, increase the probability of developing hyperkalemia. NSAIDs, such as indomethacin, reduce the antihypertensive effects of ACEIs particularly in low-renin forms of HTN. The concurrent administration of lithium with an ACEI is associated with a greater likelihood of lithium toxicity.¹⁴⁵ Combining an ACEI with allopurinol is also associated with a higher risk of hypersensitivity reactions, with several reports of the Stevens-Johnson syndrome having occurred with the combination of captopril and allopurinol.¹⁴⁶ Quinapril reduces the absorption of tetracycline by approximately 35%, which may be due to the high magnesium content of quinapril tablets.¹⁴⁵

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