Angiotensin-Converting Enzyme Inhibitors

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Key Points and Recommendations

- In addition to hypertension, angiotensin-converting enzyme inhibitors are indicated for treatment of patients at high risk for coronary artery disease, after myocardial infarction, with dilated cardiomypathy, or with chronic kidney disease.
- The most familiar angiotensin-converting enzyme subtype, angiotensin-converting enzyme-1 (kininase II), cleaves the vasoconstrictor octapeptide angiotensin II from its inactive decapeptide precursor, angiotensin I, while simultaneously inactivating the vasodilator bradykinin.
- Biochemical pathways within and around the renin-angiotensin system are *highly species-specific;* there is little evidence that "angiotensin-converting enzyme bypass pathways" have major clinical implications in humans.
- Dietary sodium loading can diminish or abolish the antihypertensive effect of an angiotensin-converting enzyme inhibitor, while salt restriction or concomitant diuretic therapy enhances it.
- Dose-response curves with angiotensin-converting enzyme inhibitors are quite flat but their peak effects vary in different individuals.
- Increased serum creatinine (decreased glomerular filtration rate) during acute or chronic angiotensin-converting enzyme inhibition identifies individuals likely to experience long-term renal protective benefits.
- Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy due to fetal toxicity.
- Use of angiotensin-converting enzymes can be limited by idiosyncratic reactions (cough or angioedema), hyperkalemia (usually in cardiac or renal failure or with combined renin-angiotensin blockade) or hypotension (usually with severe volume-depletion or cardiac failure).

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Agents that block angiotensin-converting enzyme (ACE) and the formation of angiotensin II (Ang II) have become mainstays of cardiovascular and renal medicine. Peptide relatives of modern ACE inhibitors were first identified in extracts from *Bothrops* venom. Further pharmacologic development culminated in the synthesis in the 1970s of the first oral agent, captopril. Development of this breakthrough drug involved some of the most sophisticated physical chemistry of its time: crystallization and 3-dimensional modeling of the active catalytic site of the ACE molecule, an accomplishment for which its developers received several prestigious awards.[1] Other ACE inhibitors with more attractive pharmacodynamic effects have since been developed, and most ACE inhibitors, alone and in combination with diuretic or amlodipine, are now available generically. General understanding of the impact of renin-angiotensin system (RAS) inhibition has been hampered by its biochemical, physiological, and phylogenetic complexity and by the sheer volume of information available. By early 2010, there were more than 24,400 citations under the MESH term "angiotensin-converting enzyme inhibitors." The intent of this review is to integrate relevant human basic science and outcome data in order to promote a sophisticated yet practical approach to clinical use of ACE inhibitors. In areas of controversy, original source documentation is cited whenever possible.

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THE RAS

The RAS is a phylogenetically ancient system that is intrinsic and ubiquitous in animal and human tissue.[2] It seems likely that its original function in primitive animals with open sinusoidal circulatory systems was to influence growth and development and to integrate metabolic, secretory, and structural needs. These effects did not fully disappear as the RAS evolved into a more more complex circulatory control system that included renal and endocrine functions. From this perspective, the RAS has always been a whole-body system and the impact of RAS blockade is best understood as a series of linked changes in function and structure. A critical concept is that the biochemical pathways within and around the RAS are *highly species-specific*.[2] This fact helps explain why there are sometimes opposing observations in animals and humans. The ensuing discussion is limited as much as possible to human tissues and physiology and the corresponding clinical effects. In some cases, widely held beliefs are inconsistent with sound but lesser-known basic observations.

Classical RAS Pathophysiology

The strategic position squarely between major vasopressor and vasodepressor systems makes ACE an

attractive target for pharmacologic interruption. The most familiar ACE subtype, now called ACE-1, allows local cleavage of the vasoconstrictor octapeptide Ang II from its inactive decapeptide precursor, Ang I, while simultaneously inactivating the vasodilator bradykinin via its innate actions as kininase II. ACE-1 is found in most tissues but the highest concentrations are found in the kidney and lung. As a result, bradykinin generated in peripheral tissues is almost completely removed in a single pass through the lung.[3] The absence of bradykinin from the arterial circulation strongly suggests that bradykinin's predominant hemodynamic role is to modulate venous return rather than systemic arteriolar dilation, largely through reduced venomotor tone, central blood volume, and cardiac filling pressure. Thus, although it has been postulated that bradykinin-dependent effects contribute to the arterial dilator actions of ACE-1 inhibitors,[4] such effects are probably minor in essential hypertension. In contrast, when high cardiac filling pressures are necessary to maintain cardiac stroke volume in ventricular dysfunction, bradykinin-dependent effects may differentiate ACE inhibition from other forms of RAS blockade.

Within the renal RAS, the rate of renin release from juxtaglomerular cells is physiologically rate-limiting but ACE-1 can become a second rate-limiting step in the presence of an ACE inhibitor. Systemically, the major effects of RAS blockade can be attributed to reduced circulating and local concentrations of Ang II and the attendant effects on systemic arterioles, renal hemodynamics, the adrenal zona glomerulosa, and the sympathetic nervous system. Blood pressure (BP) modulation by Ang II appears to be at least partly dependent on its direct arteriolar constrictive effects but chronic infusions of either renin or Ang II, at least at higher doses, are met with rapid tachyphylaxis and diminution or disappearance of the corresponding pressor effects of Ang II.[5] ACE-1 is present in abundance in human glomeruli,[6] allowing renin-dependent variations in the rate of generation of Ang II, which, in turn, modulate renal vascular resistance, efferent arteriolar tone, and glomerular filtration pressure. ACE-1 inhibitors reduce adrenal aldosterone release in response to acute stimuli such as posture or salt-depletion[7] but have little effect on plasma aldosterone chronically.[8] A more comprehensive explanation of the BP-lowering effects of ACE inhibitors is offered by extensive observations that the brain and the cerebral vasculature respond to both local and systemic RAS systems. Because of fenestrated capillaries in circumventricular organs such as the area postrema, increased circulating (or locally generated) Ang II causes a net disinhibition of sympathetic nervous system outflow,[9,10] which results in the maintenance of an inappropriately high BP.[9,10]

Tissue vs Endocrine RAS Components

The RAS system is ubiquitous in excitatory and secretory tissues and in growing or remodeling tissues.[11,12] There is cross-talk between the renal-endocrine system and local tissue systems[11,12] such that angiotensinogen released by the liver passes freely across cell membranes in many tissues, some of which (adipocytes, fibroblasts, neurons, glial cells, leukocytes, and various glandular cells) also synthesize angiotensinogen locally. Similarly, renin produced predominantly in the kidney can be taken up by various other tissues but neuroendocrine and cardiovascular cells can generate renin locally. ACE-1 is thought to act as an ectoenzyme signaling molecule on the surface of these many cell lines and can be upregulated in conditions of tissue injury such as myocardial infarction or ongoing atherosclerosis. Given the interpenetration of circulating and tissue systems, the concept of "tissue ACE inhibition" probably has little useful clinical meaning.

Alternate RAS Pathways

Several ACE-1 bypass mechanisms have been described that allow generation of Ang II in the absence of ACE-1, but there is substantial tissue and species-specificity in these pathways. ACE-2 in some tissues produces the heptapeptide Ang 1–7, which has similar but weaker effects than Ang II[13] and may provide a counter-regulatory balance to Ang II.[14] ACE-2 is not blocked substantially by current ACE inhibitors but its clinical impact on physiological and structural changes during chronic ACE inhibition in humans is not fully known. In the heart and muscular arteries, the primary non-ACE pathway appears to be tissue chymase, which can generate Ang II even when ACE-1 is blocked.[15,16] Again, the clinical significance of these observations is unclear because ACE inhibitors and angiotensin receptor blockers (ARBs, which act distal to ACE or chymase) have similar effects on BP, cardiac and vascular structure and function, and cardiac outcomes (see Clinical Benefits section).

Structural Effects

Ang II generated systemically or locally has important structural as well as functional effects. Some of the chronic antihypertensive effect of ACE inhibition may be attributable to withdrawal of the trophic effect of Ang II on vascular smooth muscle, which increases arteriolar wall thickness and sustains increased systemic vascular resistance. As would be predicted by such an effect, ACE inhibitors reverse arteriolar hypertrophy in humans[17] and also promote regression of left ventricular hypertrophy.[18] Further, Ang II affects matrix protein composition in the heart and blood vessels by promoting the synthesis and deposition of collagen and other structural proteins via stimulation of fibroblast growth factor-2[19] and other trophic substances.

HETEROGENEITY OF BP EFFECTS OF ACE INHIBITION

A major factor in the overall efficacy of ACE inhibition is the wide degree of heterogeneity in activity of

the RAS between and within humans. Physiologically, the RAS is intimately linked with the sympathetic nervous system and participates in complex stress responses and in early hypertension.[20] Obesity and the early stages of renal failure cause parallel activation of the sympathetic nervous system and RAS,[21] but much greater degrees of RAS activation are found in cardiac failure.[22] Adequate BP responses to chronic ACE inhibitor monotherapy (historically defined as a decrease in BP of at least 10 mm Hg or achievement of BP <140/90 mm Hg) occur in less than half the population with essential hypertension. It is reasonably clear that there are potential environmental, age-related, and genetic explanations for this response heterogeneity.

Salt and Volume Dependency

Dietary sodium loading can diminish or abolish the antihypertensive effect of an ACE inhibitor and, conversely, dietary salt restriction tends to enhance an ACE inhibitor's effect on BP.[23] The efficacy of an ACE inhibitor is also generally dependent on the state of activation of the RAS prior to therapy but, in principle, pharmacologic paralysis of the RAS itself causes a form of "volume-dependent" hypertension. Neither volume status alone nor the degree of "salt-sensitivity" of an individual fully explains the variability in ACE inhibitor responses, however, because ACE inhibitors are effective at lowering BP in salt-sensitive (those whose BPs increase disproportionately during controlled sodium loading) and salt-resistant hypertensive patients.[24] A "nonmodulator" subgroup of salt-sensitive individuals has been described in whom a high-salt diet increases BP but does not cause normal renal vasodilation or suppression of aldosterone release. Chronic ACE inhibition corrects this defect[25] but the relative roles of genes, environment, and other influences in the non-modulator phenotype is the subject of ongoing investigation.

Aging and Race

Plasma renin activity declines steadily with age[26] but the reasons for this "atrophic" pattern are not known. In drug development studies that include individuals with high diastolic BP, age is not a strong predictor of ACE inhibitor response.[27] In clinical practice, however, blunted response to ACE inhibition in older individuals is often seen. There is a very broad overlap in the range of plasma renin activity between blacks and whites but mean plasma renin activity tends to be lower in black cohorts[28] and the antihypertensive efficacy of ACE inhibitor monotherapy is generally reduced in blacks compared with whites.[29] Genetic mechanisms for this racial difference have not been elucidated. Recent British Hypertension Society/National Institute for Health and Clinical Excellence guidelines have recommended that initial monotherapy with an ACE inhibitor (or ARB) be reserved for individuals younger than 55 but there are few data to support this recommendation.[29] It must be emphasized that: (1) the observed range of plasma renin values and ACE inhibitor responses are very wide across all age and demographic groups, and (2) the combination of any ACE inhibitor with either a diuretic or calcium channel blocker achieves roughly the same magnitude of BP reduction in older and younger people of all races.

Genetic Variation

A known genetic variant is an insertion/deletion polymorphism of the ACE-1 enzyme (I and D alleles) that correspond to a non-coding region of the ACE enzyme. I/I homozygous individuals tend to have lower plasma ACE activity than their D/D counterparts,[29] but the antihypertensive efficacy of ACE inhibitors is not affected by either allele.[31] D/D individuals, however, may be more susceptible to target organ damage such as atherosclerosis, ventricular hypertrophy,[32] and progressive renal disease but this remains controversial.[33] A sex interaction occurs because ACE inhibition is generally renoprotective in women but is more beneficial in D/D men than I/D or I/I men.[33]

CLINICAL BENEFITS

In addition to their original indication for hypertension, ACE inhibitors are currently indicated for treatment of patients at high risk for coronary artery disease, after myocardial infarction, with dilated cardiomyopathy, or with chronic kidney disease. Despite the absence of formal studies or indications, they also have widespread off-label use in vascular conditions such as peripheral arterial disease and scleroderma.

Hypertension

All ACE inhibitors were originally indicated for the treatment of essential hypertension and by implication for the prevention of cardiovascular, cerebrovascular, and renal complications of hypertension. Individual names of available ACE inhibitors, indications, and dosing characteristics are presented in the Table. In the largest outcome trial that included ACE inhibitors (lisinopril in the Antihypertensive Lipid-Lowering Heart Attack Trial [ALLHAT]), the BP-lowering effects of enalapril-based therapy were slightly inferior to chlorthalidone or amlodipine but the reduction in the primary end point (fatal and nonfatal myocardial infarction) was not different from thiazide-type diuretic or amlodipine.[34] In a different population predominantly at risk for ischemic heart disease (International Verapamil-Trandolapril Study [INVEST]), the perindopril-verapamil combination achieved the same BP and outcome benefits as a diuretic–β-blocker combination.[35] In a similar population (Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT]), however, the investigation was terminated prematurely on ethical grounds. Even though the difference in the primary ischemic heart disease–related end point had not yet reached statistical significance, mortality was reduced to

TABLE. Available ACE Inhibitors Indicated for Hypertension

Drug Generic (Brand)	Usual Total Dose,[a] mg/d	Doses Per Day[b]	Generic	Single-Pill Combinations (Brand)	Generic Combination
Benazapril (Lotensin)	20–40	1	Yes	+HCTZ (Lotensin HCT)	Yes
				+Amlodipine (Lotrel)	Yes
Captopril (Capoten)[c,d,f]	75–300	2 or 3	Yes	+HCTZ (Capozide)	Yes
Cilazapril (Inhibace)	2.5–5	1	Yes	+HCTZ (Inhibace Plus)	Yes
Enalapril (Vasotec)[c,d,e]	20–40	1 or 2	Yes	+HCTZ (Vaseretic)	Yes
Fosinopril (Monopril)[c]	20–40	1	Yes	+HCTZ (Monopril HCT)	Yes
Lisinopril[c,d] (Prinivil, Zestril)	20–40	1	Yes	+HCTZ (Prinzide, Zestoretic)	Yes
Moexipril (Univasc)	15–30	1	Yes	+HCTZ (Uniretic)	Yes
Perindopril (Aceon)[e]	8–16	1	Yes	+HCTZ (Aceon Plus)	No
Quinapril (Accupril)[c]	40–80	1	Yes	+HCTZ (Accuretic)	Yes
Ramipril (Altace)[c,d,e]	10–20	1	Yes	No	No
Trandolapril (Mavik)[c,d]	4–8	1	No	No	No

Abbreviations: ACE, angiotensin-converting enzyme; HCT/HCTZ, hydrochlorothiazide. [a]Usual total daily maintenance dosage for hypertension; doses in heart failure may be less. [b]Interval dosage strength = usual total daily dose/doses per day. Indications: [c]heart failure, [d]post-myocardial infarction, [e]reduction of high cardiovascular disease risk, [f]diabetic nephropathy.

a greater degree by an amlodipine-ACE inhibitor combination than with a β-blocker–diuretic combination.[36]

High Coronary Disease Risk

This indication arose largely from the Heart Outcomes Prevention Evaluation (HOPE) study.[37] In this study, the combined coronary disease end point was reduced by 22% with ramipril compared with placebo. The results were initially attributed to an unspecified protective effect of ACE inhibitor that was "independent of BP" because the reported difference in clinic BPs between treatment arms was only about 3/2 mm Hg. Subsequent analyses, however, have revealed irregularities in clinic BP measurement techniques. Further, in a small cohort with peripheral arterial disease, ramipril reduced 24-hour ambulatory BP by about 10/4 mm Hg, a difference of sufficient magnitude to explain the benefits of ACE inhibitor compared with placebo.[38]

Post–Myocardial Infarction

There has been extensive clinical testing of ACE inhibitors in survivors of myocardial infarction who are at heightened risk for major cardiovascular events, including reinfarction, sudden death, chronic heart failure (HF), and stroke. Major randomized, placebo-controlled clinical trials such as the Sleep Apnea Cardiovascular Endpoints Study (SAVE), the Acute Infarction Ramipril Efficacy (AIRE), the Trandolapril Cardiac Evaluation (TRACE), and SMILE have convincingly demonstrated improved survival post-myocardial infarction, particularly when there is left ventricular dysfunction or acute pulmonary congestion.[39–43] Survival benefits have also been achieved with ACE inhibitors in broader populations of acute myocardial infarction survivors, including the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3), Fourth International Study of Infarct Survival (ISIS-4), and the Chinese Cardiac Studies.[44–46] Mortality risk in individuals with ischemic heart disease increases in proportion to the number and severity of the associated comorbidities and to the degree of loss of functional myocardium, but the consistency of benefits attributable to ACE inhibitors has led to the highest grade of evidence and the strongest recommendation for their use in all patients post-myocardial infarction.[47] A further enhancement of the mortality benefit may be possible via addition of a β-blocker to ACE inhibitor in this group.[48] Comparison studies have pitted ACE inhibitors against other RAS blockers. The Evaluation of Losartan in the Elderly (ELITE II) and the Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trials found superior outcomes with the ACE inhibitors compared with the ARBs.[49,50] In the larger Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Function, or Both (VALIANT) trial, end points such as survival, development of HF, recurrent myocardial infarction, and cardiovascular death were comparable between the ACE inhibitor and ARB. Combining ACE inhibitors with ARBs did not further improve outcomes but did increase the number of reported side effects, particularly hypotension.[51]

Heart Failure

The ability of ACE inhibitors to improve survival in individuals with HF due to systolic dysfunction was first demonstrated in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial and later confirmed by the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial in symptomatic individuals with reduced left ventricular ejection fraction (LVEF <35%).[52,53] Reduced HF hospitalization rates were found in the SOLVD treatment trial and the SOLVD prevention trial in asymptomatic individuals

with reduced LVEF.[54] Initial reports of the SOLVD prevention study did not demonstrate mortality benefit, but longer-term follow-up has revealed reduced mortality with chronic ACE inhibitor therapy.[55] The Vasodilator-Heart Failure Trial II (V-HeFT II) found similar mortality benefits when the combination of hydralazine/isosorbide dinitrate was compared with enalapril,[56] while in ELITE II, losartan 50 mg daily was less effective than captopril 50 mg 3 times daily in patients with symptomatic HF.[49] In individuals with preserved systolic function, a sustained benefit of perindopril was not observed.[57] Other ACE inhibitors have not been sufficiently studied.

Chronic Kidney Disease

The benefit of ACE inhibitors in the treatment of kidney disease was first noted in rodent models of reduced renal mass or diabetes[58] but several randomized trials have extended these observations to clinical medicine. The first RAS blocker studied in diabetic nephropathy was captopril, which proved to be superior to non-RAS agents in delaying time to occurrence of a composite renal end point (doubling of serum creatinine, end-stage renal disease, or death) and in reducing albuminuria.[59] The greatest benefits occurred in patients with baseline serum creatinine >2.0 mg/dL, in patients whose proteinuria remitted, and in patients who achieved lower BPs during follow-up. A meta-analysis of 11 randomized controlled trials comparing the efficacy of ACE inhibitor–based and non–ACE inhibitor–based therapy demonstrated a positive effect on the rate of progression of kidney disease at every level of achieved BP or achieved proteinuria.[60] Separating the effects of ACE inhibitors from those attributable to BP-lowering itself remains difficult, however, because there is consistently better systolic BP control with ACE inhibition. In type 1 diabetes, it appears that maintenance of low BP itself (<120/80 mm Hg) retards diabetic mesangial expansion, with little additional benefit of ACE inhibition.[61]

In nondiabetic kidney disease, ACE inhibitors are also effective in preserving renal function, especially in patients with proteinuria. In the Modification of Diet and Renal Disease Study (MDRD),[62] patients with nondiabetic kidney disease (glomerular filtration rate [GFR] 13–55 mL/min) were treated with ACE inhibitors and reduced dietary salt and protein. In those with severe proteinuria (>3 g daily), lower BPs (<125/75 mm Hg) were associated with better outcomes within 8 months compared with traditional BP goals (<140/90 mm Hg), but it took 24 months to see the advantage of lower BPs in patients with 1 g to 3 g of proteinuria. For those with <1 g protein, there was no advantage of lower BP goal at 3 years. The Ramipril Efficacy in Nephropathy (REIN) trial in patients with nondiabetic kidney disease also found that ramipril preserved renal function, but the positive impact on glomerular filtration rate was proportional to the baseline albumin excretion rate.[63] In the African American Study of Kidney Disease (AASK), nondiabetic patients with presumed hypertensive nephrosclerosis were randomized into a 3 × 2 factorial study that tested 3 drugs (ramipril, metoprolol, and amlodipine) and 2 BP targets (<140/90 mm Hg or <125/75 mm Hg) for a period of 5 years.[64] Ramipril was superior in protecting against the composite renal end point (>50% or >25 mL/min loss of GFR from baseline, end-stage renal disease occurrence, or death) but there was no benefit of the lower target BP unless the urine protein:creatinine ratio exceeded 0.22 g/mg.[65] In a subsequent report after 7 to 10 years of additional follow-up, GFR loss continued in all individuals despite the presence of ACE inhibitors.[66] Nevertheless, renal benefits of ACE inhibition persist during the progression of nondiabetic kidney disease irrespective of the initial level of serum creatinine, and the incidence of serious adverse events including hyperkalemia remains low.[67]

Stroke Recurrence and Dementia

Stroke protection was claimed for ACE inhibition in the Perindopril Protection Against Recurrent Stroke (PROGRESS) study of stroke recurrence but this benefit occurred only in patients receiving concomitant indapamide therapy.[68] In long-term follow-up, patients with the lowest achieved BPs had the lowest stroke recurrence rate.[69] Specific effects on dementia have not been observed in those without prior stroke[70] and, in general, it seems unlikely that any benefits of ACE inhibition on stroke or dementia are independent of BP reduction.

Peripheral Arterial Disease

ACE inhibitors are commonly recommended for use in PAD patients despite the absence of clinical trials documenting functional improvement in PAD symptomatology. In a retrospective analysis of the INVEST trial, PAD patients with lower BPs had better outcomes than those with higher BPs, but the verapamil–ACE inhibitor combination was not superior to diuretic–β-blocker in reducing composite the cardiovascular end points.[71]

PRACTICAL PHARMACOLOGY

Dosing and Duration

Dose-response curves with ACE inhibition that measure peak BP effects (usually at 2–4 hours) are quite flat, especially at the upper end of the dose range.[72] Low doses (eg, enalapril 10 mg) have similar peak effects but have weaker trough effects, probably because they do not suppress plasma Ang II for a full 24 hours.[73] Because many practitioners use doses that are too low, optimal treatment of hypertension and reduction of cardiovascular events[74] or HF[75] episodes may not be achieved along with unnecessary morbidity, mortality, and health care cost.[76] Despite practitioner fears, first-dose hypotension with any dose of ACE inhibitor is extremely uncommon unless there is

marked volume depletion (sometimes signalled by hyponatremia) or severe ventricular dysfunction. In individuals at risk for these conditions, a low "test dose" may be warranted, but clinical experience also demonstrates that it is feasible to start at maintenance doses (eg, lisinopril 20–40 mg daily) in uncomplicated hypertensive patients not previously taking diuretics or other agents. Prescribing information consistently suggests that ACE inhibitors should be titrated upward from initial low doses, but because many physicians do not titrate drugs, the result is suboptimal BP control.

Acute vs Chronic BP Effects

It is not uncommon for BP to drop within a few days after beginning ACE inhibitor therapy followed by a gradual return back toward pre-treatment baseline values within a few weeks. Usually, this "pseudotolerance" effect is caused by net salt and water retention induced by the chronic reduction in systemic and glomerular filtration pressures. The predominance of the "volume component" in this pattern of "ACE inhibitor escape" is revealed by addition of a diuretic, which restores or enhances the antihypertensive effect of the ACE inhibitor. An alternate explanation for "ACE inhibitor escape" has been proposed, where plasma Ang II levels were reported to be increased during chronic ACE inhibitor therapy, supposedly due to the induction of "ACE bypass pathways" such as tissue chymases. This phenomenon was first described in an extremely small cohort (n=9) using an assay system for Ang II that cross-reacted with Ang I (which increases markedly during chronic ACE inhibition).[77] The phenomenon was immediately publicized by pharmaceutical firms that manufactured ARBs, which were said to work distally to ACE and therefore were touted as being free from the escape problem. Based on clinical experience and newer studies, however, it is highly unlikely that ACE bypass pathways are clinically meaningful. First, there is no appreciable further BP-lowering when an ARB is added to an ACE inhibitor.[78,79] Furthermore, more careful biochemical studies in patients with hypertension[80,81] or HF[82] using a more specific assay for Ang II have clearly demonstrated that chronic ACE inhibition causes persistent reductions in plasma Ang II concentrations both acutely and chronically.

Renal Function

Decreased GFR (increased serum creatinine) can occur with any drug that reduces systemic and renal perfusion pressure but the increase in serum creatinine is often transient. Patterns observed with ACE inhibitors are somewhat more complex. ACE inhibitors are almost never the sole cause of any clinically significant permanent loss of renal function but there is a strong clinical trend to discontinue ACE inhibitors after small increases in serum creatinine. This over-reaction to modest changes in GFR can lead to inappropriate withdrawal of ACE inhibitors from patients with cardiac or renal disease whose well-being depends on them. Susceptibility to ACE inhibitor–induced increases in serum creatinine is not uniform and is more pronounced with advanced age, chronic kidney disease (particularly stage 4), advanced diabetes mellitus, renal artery stenosis, or HF or who have undergone significant diuresis.[83] Increases in serum creatinine (or decreases in GFR) of about 30% are common during the initiation of ACE inhibition,[83] corresponding to an increase in serum creatinine from 1.0 mg/dL to 1.3 mg/dL (or from 2.0 mg/dL to 2.6 mg/dL). ACE inhibitors are expected to cause long-term reductions in GFR because they reduce glomerular perfusion pressure. Such changes do not usually represent true renal injury. In fact, the *failure* of serum creatinine to increase acutely and chronically with ACE inhibition is an unwelcome sign, particularly in diabetics because it strongly suggests that the drugs have not reduced glomerular filtration pressure and thus are unlikely to slow the progression to end-stage renal disease.[83,84]

Comparative RAS Pharmacology

Any agent that inhibits the RAS exhibits a pattern of responses common to other RAS blockers (including β-blockers, ARBs, and renin inhibitors).[85] In practical terms, the magnitude of the BP response to ACE inhibitors (or ARBs) can be interpreted as a rough marker of the degree of pretreatment RAS activation. All RAS blockers work most effectively when the RAS is already activated (eg, salt-depletion or dilated cardiomyopathy) and are less effective in low-renin states (eg, salt-overload, some older individuals, and many African Americans).[86] Overall, because ACE inhibitors and ARBs are equally efficacious in improving outcomes in HF and renal failure,[87] it is reasonable to consider that they are interchangeable with regard to efficacy, although not necessarily with regard to tolerability.

RAS Blocker Combinations

If an adequate dose of any single RAS-blocking agent is used, there is little additional benefit of adding a β-blocker or an ARB with respect to BP-lowering effects.[78,88] An ACE inhibitor–ARB combination does not improve outcomes post-myocardial infarction[51] but the combination may be useful in some individuals with HF[89] irrespective of the prior dose of ACE inhibitor.[90] In renal disease, combination ACE inhibitor-ARB therapy may lead to greater reduction in proteinuria[88,91] but also causes a negative effect on the rate of progression of nephropathy.[88] In contrast, combining an ACE inhibitor with a vasodilator drug with a complementary mechanism of action leads to additional BP-lowering and the potential for better outcomes. An expert consensus from the American Society of Hypertension has recommended ACE inhibitor–diuretic and ACE inhibitor–CCB combinations while not recommending ACE inhibitor–β-blocker or ACE inhibitor–ARB combinations.[92] There is little evidence of improved blood efficacy in uncomplicated

hypertension when ACE inhibitors are combined with renin inhibitors, central sympatholytics, or other antihypertensive drug classes.

Adverse Effects

ACE inhibitors can produce a variety of beneficial and adverse effects that are considered to be class-specific rather than drug-specific, so an adverse event with any ACE inhibitor generally precludes the use of any other ACE inhibitor. ACE inhibitors are contraindicated in women who are pregnant or likely to become pregnant because of the possibility of fetal defects or death. Cough and angioedema are idiosyncratic reactions that, by definition, are dose-independent. Hypotension during ACE inhibition is generally a reflection of marked salt-depletion or an additive drug interaction with diuretics. Hypotension may also occur when ACE inhibitors are combined with other vasodilators such as nitrates or α-blockers, especially in individuals with HF and low ejection fraction. Hyperkalemia is largely limited to individuals with reduced kidney function or low renal blood flow, as in advanced HF or stage 4 chronic kidney disease, especially if high dietary potassium intake is maintained. In diabetics, hyperkalemia can be seen in individuals whose glucose values are grossly uncontrolled and hyporeninemic hypoaldosteronism (type IV renal tubular acidosis), which is usually found in association with diabetic kidney disease. Use of multiple RAS blockers, aldosterone antagonists, high-potassium diets, or marked sodium restriction diets further exacerbate hyperkalemia.

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