Clinical Impact of Renin-Angiotensin System Blockade: Angiotensin-Converting Enzyme Inhibitors vs. Angiotensin Receptor Antagonists

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Clinical trials have proved that blockade of the renin-angiotensin-aldosterone system (RAAS) offers primary and secondary protection of the cardiovascular system, brain, and kidneys. Drugs that interrupt the RAAS do so by several diverse mechanisms but it remains to be fully proved whether these mechanistic differences are associated with meaningful differences in clinical outcomes. This review summarizes current information about the basic mechanisms of action of three classes of anti-RAAS drugs: angiotensin-converting enzyme (ACE) inhibitors, combined ACE-neutral endopeptidase inhibitors, and angiotensin receptor antagonists as well as results of major clinical outcome trials with these agents. Basic and clinical science information is then blended with insights from the clinical pharmacology of anti-RAAS drugs to address four current controversies in clinical medicine: whether ACE inhibitors and angiotensin receptor antagonists are interchangeable, optimal dosing of available agents, potential justification of ACE inhibitor/angiotensin receptor antagonist combinations, and first-line use of anti-RAAS drugs in antihypertensive therapy. (J Clin Hypertens. 2002;4(6 suppl 2):11–19, 31) ©2002 *Le Jacq Communications, Inc.*

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Our appreciation of the value of drugs that block the renin-angiotensin-aldosterone system (RAAS) has increased steadily over the past two decades so that today, many physicians routinely identify angiotensin-converting enzyme (ACE) inhibitors as preferred first-line antihypertensive agents.[1] It is also recognized that anti-RAAS drugs are especially valuable in high-risk hypertensive patients, a realization that provided the impetus for the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) in 1997 to recognize "compelling" clinical trial evidence that ACE inhibitors exerted favorable effects on the natural history of heart failure, myocardial infarction, and diabetic nephropathy.[2]

Amid the many successes, numerous controversies and uncertainties have arisen regarding the exact mechanisms by which anti-RAAS drugs work and in practical matters of how best to use the various subclasses of RAAS blockers. New basic science discoveries about "tissue renin-angiotensin systems," alternate pathways of angiotensin metabolism, and angiotensin receptor subtype interactions have not yet been matched by appropriate human studies that fully identify their potential clinical importance. Yet future interpretation of clinical significance is likely to become even more complicated because of ongoing interest in the development of new compounds with additional mechanisms of action, including ACE-neutral endopeptidase (NEP) inhibitors.[3] This review is intended to provide interested practitioners with a foundation for interpretation of basic and clinical issues regarding anti-RAAS drugs.

ACE INHIBITORS

Appreciation of the far-reaching effects of the RAAS has arisen largely from discoveries that have occurred since the release of ACE inhibitors over 20 years ago. We now understand a great deal more about the ubiquitous and pervasive nature of the RAAS in excitable and secretory tissues and the wide variety of biochemical and clinical consequences that arise from blockade of ACE.[4] These effects can be divided arbitrarily into biochemical-hormonal, hemodynamic, and cellular-structural mechanisms.

Biochemical-Hormonal Mechanisms

The fundamental mechanism of action of ACE inhibitors is simultaneous inhibition of the formation of the pressor octapeptide angiotensin II (Ang II) and inhibition of the breakdown of the vasodilator peptide bradykinin.[5,6] Inhibition of ACE reduces the rate of conversion of Ang I, an inactive decapeptide, into the active octapeptide Ang II. Ang II is a formidable multidimensional pressor hormone that defends or raises blood pressure via several interacting mechanisms, virtually all of which are diminished by ACE inhibition. Direct arteriolar constriction is caused by Ang II type 1 (AT_1)-receptor-mediated cytosolic calcium release within vascular smooth muscle cells.[7] Indirect arteriolar and venous constriction is the result of multi-level stimulatory effects of Ang II on the sympathetic nervous system and concomitant facilitation of release of other vasoactive substances such as vasopressin and endothelin. Extracellular fluid volume expansion results via aldosterone release.[5,6] Recent suggestions that other angiotensins—most notably Ang 1-7, which may interact with the biologic effects of Ang II—can affect blood pressure[8] requires further confirmation. It has been shown that blood pressure can be increased equally by infusion of renin or Ang II.[9]

Additional antihypertensive actions of ACE inhibitors appear to depend partly on the potentiation of bradykinin, nitric oxide stimulation, and vasodilator prostaglandin release.[5] Acute administration of bradykinin inhibitors during ACE inhibition tends to diminish the antihypertensive effect of ACE inhibition.[10,11] Recent opinion suggests that bradykinin also exerts favorable effects on cardiovascular structural remodeling, probably through the stimulation of nitric oxide.[11]

Hemodynamic Effects

ACE inhibitors reduce cardiac preload and afterload in a very balanced fashion.[6] On the arterial side, reduction in Ang II allows arteriolar dilation and improved arterial compliance, which reduces afterload. On the venous side, bradykinin enhancement causes active endothelially mediated venodilation,[12] which tends to reduce cardiac preload. The venodilatory effects of ACE inhibitors are quite apparent in dilated cardiomyopathies, where therapy for excessive preload improves the overall hemodynamic profile.[13] The importance of venomotor effects in sustaining inappropriately high cardiac preload in human hypertension, however, has been systematically overlooked, largely because venomotor properties are not measured clinically. If hemodynamic studies are performed in the sitting or upright position, where active venoconstriction is necessary to maintain cardiac filling, the abilities of nitrates and other venodilators such as ACE inhibitors to reduce cardiac filling and cardiac output become more apparent. Because of the balanced reduction of preload and afterload by ACE inhibitors, and because of direct antisympathetic effects within the central nervous system,[5,6] ACE inhibition is not accompanied by reflex tachycardia, another feature that protects against cardiac overload.

Cellular and Structural Effects

It has been shown that blood pressure can be increased equally by infusion of renin or Ang II.[9] Most excitable (nerve or muscle) and secretory (glandular) cells produce most of the components of the RAAS intracellularly.[4] This "tissue renin-angiotensin system" responds to hormonal and local environmental stimuli and is believed to be important in the regulation of cell structure and function. Much attention has been paid in recent years to the question of how much the individual contributions of circulating and "tissue" RAAS determine a given biologic effect. But closer scrutiny suggests that significant confounding occurs because circulating components of the RAAS are quite avidly taken up by blood vessels and other tissues.[9,14] These bidirectional movements of RAAS components across cell membranes suggest that it may be clinically irrelevant to assign respective contributions of circulating and tissue RAAS components to a given process. Instead, it may be more appropriate to view overall RAAS activity as the sum of the circulating (hormonal) and "tissue" RAAS components and to focus on inhibition of the entire system rather than to decide which component predominates in a given situation.

One of the breakthroughs in understanding the RAAS came with the realization that Ang II modifies both function and structure. In addition to its short-term hormonal and vasoconstrictive effects, Ang II also promotes pro-growth forces such as hypertrophy and hyperplasia of vascular smooth muscle.[4,15] Current views hold that Ang II-induced cell hypertrophy or hyperplasia are counterbalanced by depressor-antigrowth effects of bradykinin and

nitric oxide.[16] These basic cellular changes also affect the basic anatomic structure of the heart and vasculature.[4,15] More recently it has been found that Ang II tends to favor the formation of superoxide radicals, which are thought to be important mediators of tissue damage and atherosclerosis.[17]

Clinical Benefits

ACE inhibitors have a large number of major clinical trials documenting their abilities to protect target organs. All ACE inhibitors marketed in the United States are indicated for the treatment of both systolic and diastolic hypertension and most ACE inhibitors (captopril, enalapril, lisinopril, ramipril, fosinopril, trandolapril) have received indications for the treatment of heart failure. Captopril has also been approved for secondary cardiovascular risk reduction in individuals with prior myocardial infarction[18] and more recently ramipril has been approved for primary and secondary cardiovascular protection in diabetics and other individuals at high risk for coronary artery disease (in the Heart Outcomes Prevention Evaluation [HOPE]).[19] In diabetic and nondiabetic renal diseases, ACE inhibition markedly reduces albuminuria and extends the time to dialysis or transplantation.[20,21] Reports also indicate a benefit of ACE inhibitors (with a diuretic) in the prevention of recurrent stroke.[22] In almost all of these trials, some confounding of the benefit of ACE inhibitors is present because multiple medications were used to achieve blood pressure lowering.

A variety of other potential clinical benefits are documented in smaller studies. ACE inhibitors are more effective than diuretics[23] or β blockers[24] in reducing

Table. Evidence for Clinical Outcome Benefits by Specific Drug Classes in High-Risk Hypertension With Target Organ Damage. Studies* Included Have Been Published Since the JNC VI Report in 1997

	Drug Class				
	Diuretic	β Blocker	Calcium Antagonist	ACE Inhibitor	ARA
High-Risk Comorbid Condition					
• Systolic hypertension	JNC VI[2] SHEP[67] STOP-2[31]	JNC VI[2] STOP-2[31]	Syst-Eur[68] STOP-2[31]	STOP-2[31]	
• Post myocardial infarction		JNC VI[2]		JNC VI[2]	
• High CAD risk				HOPE[19]	
• Left ventricular hypertrophy					LIFE[69]
• Heart failure	JNC VI[2]	MERIT[70] COPERNICUS[70]	PRAISE (neutral outcome)[71]	JNC VI[2]	ELITE I[72],II[44] Val-HeFT[45]
• Diabetes with proteinuria	UKPDS[73]	UKPDS[73]	UKPDS[73] ABCD (negative CVD outcome)[74]	Lewis, et al.[20] UKPDS[73] JNC VI[2]	RENAAL[47] IDNT[48] IRMA2[33] LIFE[46]
• Nondiabetic renal failure				REIN[75] AASK[32]	
• Stroke/TIA	SHEP[67]	SHEP[67] (with diuretic)	Syst-Eur[68]	PROGRESS[22] (with diuretic)	LIFE[69]

JNC=Joint National Committee; ACE=angiotensin-converting enzyme; ARA=angiotensin receptor antagonist; SHEP=Systolic Hypertension in the Elderly; STOP-2=Swedish Trial in Old Patients with Hypertension; Syst-Eur=Systolic Hypertension in Europe; CAD=coronary artery disease; MERIT=Metoprolol Controlled Release Randomized Intervention; COPERNICUS=Carvedilol Prospective Randomized Cumulative Survival; PRAISE=Prospective Randomized Amlodipine Survival Evaluation; UKPDS=United Kingdom Prospective Diabetes Study; ABCD=Appropriate Blood Pressure Control in Diabetes; CVD=cardiovascular disease; REIN=Randomized Efficacy in Nephropathy; PROGRESS=Perindopril Protection Against Recurrent Stroke Study; TIA=transient ischemic attack; *most studies defined in text.

large arterial stiffness. They are more effective than β blockers and at least as effective as diuretics in regressing left ventricular hypertrophy.[25] ACE inhibition improves insulin sensitivity[26] and forestalls the development of overt clinical diabetes.[19] There is a beneficial effect of ACE inhibitors on endothelial dysfunction[27] and remodeling of arteriolar smooth muscle hypertrophy in hypertension.[28] ACE inhibitors have been shown to increase plasminogen activator inhibitor-1.[6] It has even been reported that ACE inhibitors reduce the incidence of new cancers.[29] Additional clinical trials are being conducted to prove whether ACE inhibitors can achieve other important benefits such as prevention of blindness or dementia.[30] Whether these theoretical benefits exceed those achieved by a diuretic (with or without a β blocker) remains to be proven in uncomplicated essential hypertension.

In more complicated cases of hypertension (Table), the beneficial impact of ACE inhibition is substantial. In diabetics, morbidity and mortality are reduced to a greater degree when ACE inhibitors are part of a treatment program but overall cardiovascular event rates appear to be reduced equally by a regimen that includes a diuretic and β blocker. ACE inhibitor-based therapy has been found to be superior to calcium antagonist-based therapy with respect to coronary heart disease events, heart failure incidence, and renal disease progression (Swedish Trial in Old Patients with Hypertension [STOP-2],[31] African American Study of Kidney Disease and Hypertension [AASK],[32] and Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria [IRMA].)[33]

Adverse Effects

ACE inhibitors are well tolerated and have been shown to actually improve the quality of life in patients with hypertension.[34] It is clinically important to recognize that the adverse effects of ACE inhibitors are generally idiosyncratic and *not dose-dependent*. The most common ACE inhibitor side effect, cough, occurs in 10%–20% of the treated population.[35] It has been long speculated that the cough is related to accumulation of bradykinin but recent data point to a metabolic difference in susceptible individuals that leads to accumulation of an abnormal bradykinin metabolite, des-Arg9-bradykinin.[36] The most serious potential adverse effect of ACE inhibitors is angioedema, which occurs in less than about 1% of the population,[37] but newer data suggest that blacks are two to three times more susceptible than whites to ACE inhibitor-induced angioedema (Omapatrilat Cardiovascular Treatment Assessment vs. Enalapril [OCTAVE]).[38] Nevertheless, any potential racial differences in efficacy and safety are relatively small when compared to the potential benefits of ACE inhibition on blood pressure and target organs and it would be inappropriate to conclude that ACE inhibitor use in blacks should be curtailed based on differences in tolerability.

Hyperkalemia during ACE inhibition occurs as a result of reduced aldosterone secretion in the setting of reduced distal tubular sodium delivery. Serum potassium values rarely reach critical ranges unless patients also have advanced renal failure or practice marked sodium restriction. In these cases, an increase in dietary salt along with increased diuretic therapy, especially with loop diuretic-thiazide combinations, is usually highly effective in controlling hyperkalemia.[39] Clinically significant hypotension with ACE inhibitors generally occurs only in individuals who are markedly sodium-depleted (especially in those who have been "over-diuresed"), patients with advanced heart failure, or those taking multiple vasodilators.

COMBINED ACE-NEP INHIBITORS

Recently, there has been a modification to the ACE inhibitor class. By adding a side chain that simultaneously inhibits NEP (which is ordinarily responsible for the degradation of natriuretic peptides or atriopeptins), a new potent antihypertensive subclass, combined ACE-NEP inhibition, has been formed.

Physiologic Effects of Atriopeptins

Atriopeptins are potent endogenous vasodilators whose actions are similar in many respects to bradykinin; both hormones have short plasma half-lives and stimulate the nitric oxide-cyclic guanosine monophosphate vasodilator cascade in vascular smooth muscle.[40] There are three major atriopeptin isoforms synthesized in the heart: atrial natriuretic peptide (ANP), brain natriuretic peptide, and vascular natriuretic peptide. All are vasodilators that also cause natriuresis. ANP and brain natriuretic peptide inhibit a variety of vasoconstrictors such as endothelin, cause inhibition of sympathetic nervous and RAAS activity, and blunt cell proliferation and hypertrophy. All three atriopeptins are degraded by NEPs, which are ubiquitous peptide scavenger enzymes. At present, no orally active analogs of ANP are available, so the clinical approach to enhancing the biologic effects of ANP has been to administer molecules that inhibit NEP.

Pharmacodynamic Effects of ACE-NEP Inhibitors

ACE-NEP inhibitors, which suppress the formation of Ang II and simultaneously inhibit breakdown of bradykinin and natriuretic peptides, exert potent anti-

hypertensive effects in animals with both "low-renin" and "high-renin" forms of hypertension.[41] Early observations suggesting, that combined ACE-NEP inhibitors are more potent antihypertensive drugs than ACE inhibitors alone[41] have been confirmed in the large clinical trial OCTAVE.[38] Why the ACE-NEP inhibitor combination is superior in potency to ACE inhibitors alone is an interesting phenomenon given that "pure" NEP inhibitors cause no marked effects on blood pressure, even in the setting of heart failure.[42]

Clinical Aspects

Large-scale trials with the first ACE-NEP inhibitor, omapatrilat (OCTAVE)[38] are now completed. Omapatrilat was more effective in lowering systolic and diastolic blood pressure than ACE inhibitors but was no more effective in blacks than ACE inhibitors. In OCTAVE, omapatrilat use was associated with a significantly higher overall incidence of nonfatal angioedema compared to enalapril (2.2% vs. 0.7%), a problem that was amplified in African Americans (5.5% vs. 2.2%, respectively). The mechanisms for these differences remain unknown but are presumed to be related to abnormal bradykinin metabolism.[37] Based on these safety concerns, no ACE-NEP inhibitor is currently approved for clinical use.

ANGIOTENSIN RECEPTOR ANTAGONISTS (ARAs)

Drugs that specifically block the actions of Ang II at the peripheral AT_1 receptors have been successfully used clinically for almost a decade and their role in the crowded field of antihypertensive drugs is expanding. Wheras ACE inhibitors block the generation of Ang II, the ARAs block the effects of this vasoconstrictor at the tissue or vascular level.

Physiologic and Pharmacologic Mechanisms

The vast majority of the clinically relevant effects of Ang II receptor antagonists (ARAs) are related to the direct blockade of AT_1 receptors on peripheral tissues, especially on cell membranes of excitable and secretory tissues. Currently available ARAs have little effect on other known Ang II receptors, including the AT_2 and AT_4 receptors, whose functions are not fully understood. AT_1 receptors activate cells by stimulating the release of calcium from intracellular stores. The physiologic ramifications of AT_1 receptor blockade reflect the actions of the hormone Ang II. ARAs increase plasma renin activity via inhibition of the negative feedback loop by which Ang II suppresses juxtaglomerular cell renin release. As a result, the levels of circulating Ang I and Ang II are actually increased during chronic ARA therapy, but the effects of Ang II remain blocked. Additional stimulation of the AT_2 receptor by increased Ang II during chronic ARA therapy may augment the depressor effect of the drugs. ARAs cause a balanced hemodynamic effect that reduces both cardiac output and systemic resistance with no reflex tachycardia, a pattern similar to ACE inhibitors.

Clinical Benefits

In an early heart failure trial in which losartan was investigated for its effects on renal function (no adverse effects were found), the drug was incidentally found to be superior to captopril in reducing mortality (Evaluation of Losartan in the Elderly [ELITE I]).[43] In the larger follow-up trial that followed (ELITE II),[44] captopril and losartan were both beneficial in their abilities to reduce mortality (about 10%) and heart failure rehospitalization rates (about 30%–40%). Roughly equal reductions in heart failure rehospitalization rates were observed in the subgroup of ACE-intolerant individuals in the Valsartan Heart Failure Trial (Val-HeFT).[45] As a result, valsartan has been deemed "approvable" by the Food and Drug Administration (FDA) for the treatment of heart failure in ACE inhibitor-intolerant patients. ARAs have most recently been shown to exert a favorable effect on left ventricular hypertrophy, an important precursor of heart failure. Preliminary reports of the Losartan Intervention For Endpoint reduction in hypertension (LIFE)[46] study, which compared losartan to atenolol in patients with documented left ventricular hypertrophy, indicate a more favorable effect of ARAs than β blockers on cardiovascular morbidity and mortality, especially in reducing the incidence of stroke. In high-risk patients with diabetic renal disease ARAs have been proved to be beneficial in comparison to standard therapy (that did not include an ACE inhibitor) in two large randomized trials in high-risk type 2 diabetic patients with nephrotic-range proteinuria.[47,48] Losartan in RENAAL (Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study)[47] and irbesartan in IDNT (Irbesartan Diabetic Nephropathy Trial)[48] both reduced the composite end point (rate of doubling of serum creatinine, death, and time to initiation of end-stage renal therapy) and the rate of albumin excretion. Neither study demonstrated that ARAs reduce mortality rates in this high-risk population but in RENAAL, the end-stage renal disease incidence rate and the rate of heart failure hospitalization were significantly decreased by losartan therapy compared to treatments that did not include an

ARA. Beneficial effects of ARAs have also been demonstrated in lower risk type 2 diabetics with normal glomerular filtration rates in the IRMA 2 study,[33] where irbesartan reduced the microalbumin excretion rate in a dose-dependent fashion. It should again be emphasized that in all of these trials a majority of subjects also received a diuretic.

Adverse Effects and Interactions

The reported side effect profiles of ARAs are similar to placebo in hypertension and heart failure. ARAs can thus be characterized as having a wide therapeutic window, with virtually no dose-dependent side effects. This finding, taken together with some data of improved outcomes at higher doses, suggests higher doses might provide better target organ protection. A possible exception to the benefits of ARAs in heart failure is their potential lack of safety in combination with β blockers. In ELITE II, mortality was higher with the β blocker-losartan combination than with β blocker-captopril[44] and in Val-HeFT, valsartan caused higher mortality than placebo in individuals receiving both ACE inhibitors and β blockers.[45] However, potential mechanisms explaining the increased mortality of the β blocker-ARA combination are not known at this time.

CRITICAL CLINICAL ISSUES

Despite the explosion of knowledge regarding the mechanisms and impact of anti-RAAS drugs, several critical clinical issues and questions remain to be addressed.

Are ARAs Functionally Equivalent to ACE Inhibitors?

There are at least two possible points of differentiation in the mechanisms of action of ACE inhibitors and ARAs: potential benefit of AT_2 receptor activation with ARAs and degree of bradykinin potentiation by ACE inhibitors. The increased Ang II during chronic ARA therapy is not believed to be harmful because the AT_1 receptor is blocked and effects of Ang II are proportionally diminished. Additional AT_2 receptor stimulation has been thought to potentiate the vasodilatory and antihypertrophic effects of ARAs[49] but the relative merits of chronic AT_2 receptor stimulation are still unclear. Plasminogen activator inhibitor-1 is reduced chronically in insulin-resistant hypertensives by ACE inhibition but not by ARA. (D. Vaughan, personal communication, 2002) but whether this finding is clinically significant remains to be established.

Blood pressure response patterns in hypertension also suggest that ACE inhibitors and ARAs overlap substantially. Theoretically, ARAs should be effective in more individuals than ACE inhibitors, yet both drugs are effective as monotherapy in less than 50% of hypertensives. Like ACE inhibitors, they are consistently more effective as monotherapy in "high-renin" forms of hypertension[50] and less effective as monotherapy in "low-renin" subgroups such as blacks.[51]

Careful examination of the pattern of end organ protection with ACE inhibitors and ARAs reveals similar beneficial effects of both drug classes on hypertension and the associated conditions of albuminuria, progression of renal disease, and heart failure.[52] A number of outcome studies with regard to cardiovascular end points (Heart Outcomes Prevention Evaluation [HOPE] and others) favor ACE inhibitors, largely because they have been investigated for a longer period of time and to a greater extent than ARAs (See Table). Overall it seems appropriate to conclude that because the biologic effects of ACE inhibitors and ARAs overlap to a great extent, their benefits in hypertension and in cerebrovascular and renal diseases are quite similar and that the two subclasses may be functionally interchangeable in most conditions. Significant points requiring additional clarification include whether ARAs can be administered safely in combination with β blockers in heart failure and whether ACE inhibitors are preferred in coronary artery disease. If the answer is negative, a clear point of differentiation will have been established.

Whether or not ACE inhibitors and ARAs are equivalent in lowering blood pressure or protecting target organs, there is at least one subgroup of individuals in whom ACE inhibitors and ARAs are clearly not fully interchangeable: those who develop side effects on one or the other drug.

What Are the Optimal Doses of ACE Inhibitors and ARAs?

In general, there is a reluctance among practitioners to employ higher doses of anti-RAAS drugs, a phenomenon that may contribute to suboptimal reductions in morbidity and mortality. The principal reasons for underdosing include a general lack of knowledge of the pharmacodynamics of anti-RAAS drugs, inappropriately low FDA-approved dose ranges, and lack of useful clinical markers for dosing the drugs in conditions such as heart failure.

The most important reason for underdosing of anti-RAAS drugs is probably the general lack of understanding of their pharmacodynamic effects. The concept of routine clinical underdosing is supported by recent studies demonstrating that the usual

clinical doses of lisinopril, an ACE inhibitor, do not fully block the pressor effects of infused Ang I.[53] Low doses of ARAs similarly fail to achieve effective 24-hour duration of action and also fail to fully block the pressor effects of infused Ang II.[54] Twenty-four hour duration of antihypertensive effect is also commonly ignored in favor of data relating to peak effects, which occur at about 2–4 hours after each dose for virtually all ACE inhibitors. Underdosing is also the result of a general failure to recognize that clinical end points such as the reduction in proteinuria may require higher doses of ACE inhibitors and ARAs, plus the use of other medications, than those that lower blood pressure.[55] Although blood pressure affords a clear titratable end point in hypertension, dosing in heart failure is much more difficult because of the lack of a clinical variable to be monitored. In this setting it is necessary to turn to population-based outcome studies, where inadequate doses of anti-RAAS cause unnecessary rehospitalizations for heart failure.[56,57] Despite these findings, low-dose therapy with ACE inhibitors (less than 20 mg daily of enalapril or equivalent) and ARAs (less than 100 mg daily of losartan or equivalent) remains prevalent.[58] In the treatment of heart failure, clinicians should first recall that because the vast majority of side effects of ACE inhibitors and ARAs are *not dose-dependent*, there is no valid clinical reason to use lower doses. Physicians attempting to minimize side effects by using low doses are therefore more likely to minimize the beneficial effects than the adverse effects. In summary, for ACE inhibitors and ARAs in general, there are few compelling reasons *not* to use the maximum amounts listed in the product literature.

Is It Necessary to Combine ACE Inhibitors and ARAs to Achieve Full RAAS Blockade?

Monotherapy with an ACE inhibitor (or ARA) is effective in lowering blood pressure in about one half of the population. It is also true that the response patterns within individuals and groups are similar for both drug subclasses.[59] These findings suggest a strong overlap in mechanisms of action of ACE inhibitors and ARAs.

On the other hand, because only about one half of the population does not respond to either class, it is possible that Ang II generated by non-ACE pathways including chymases may be clinically important.[60] These findings have caused some experts to conclude (perhaps prematurely) that "ACE inhibitor escape" is an intrinsic feature of chronic therapy with ACE inhibitors and that monotherapy with ACE inhibitors is limited in its benefits. There is some evidence suggesting a return to baseline of plasma Ang II during chronic ACE inhibition[61] but it should be pointed out that this oft-quoted study utilized a nonspecific assay system that obscured the actual changes in circulating Ang II and thus should not be interpreted to suggest that ACE escape actually occurs. Even if "non-ACE" pathways are found in man, significant population heterogeneity seems likely and individual effects may be different than population effects.

The question of the need for combination therapy with ACE inhibitors and ARAs is also confounded by the problem of inadequate dosing. Based on animal pharmacology studies, the amount of ACE inhibitor necessary to achieve maximum blood pressure lowering is probably 3–30 times more than has been used routinely in clinical studies. It is thus entirely predicable that studies employing the lowest doses of an ACE inhibitor often found an added benefit of combination therapy with an ACE inhibitor and ARA,[62] whereas studies employing higher ACE inhibitor doses (e.g., enalapril 40 mg daily) have typically failed to demonstrate an additive effect of ACE inhibitors and ARAs.[63] Overall, it does not seem likely that substantial additive effects of ACE inhibitors and ARAs will occur in most people because of the overlap in the basic mechanisms of action (i.e., RAAS blockade) of the two classes. A more effective antihypertensive combination is either an ACE inhibitor or ARA with a diuretic.

Should ACE Inhibitors or ARAs Be First-Line Therapy in Hypertension?

The JNC established a precedent in 1997 by recommending specific drugs for high-risk cases[2] based on clinical trial evidence that certain drugs had demonstrated particularly favorable outcomes in those at the highest risk for adverse cardiovascular outcomes (individuals with diabetes, renal disease, ischemic heart disease and heart failure). Since 1997, additional studies have been completed and an expanded list of "compelling indications" can be created (see Table). These new studies in systolic hypertension[64] diabetes with proteinuria,[33,47,48] high-risk cardiac patients without overt hypertension,[19] and individuals with all forms of progressive renal disease[21] have added greatly to our knowledge of the value of anti-RAAS drugs. In the case of isolated systolic hypertension, the National Heart, Lung and Blood Institute (NHLBI) clinical advisory statement issued in May, 2000 identifies ACE inhibitors as effective agents.[65] Perhaps what is most striking about the observed pattern (see Table) is that anti-RAAS drugs confer distinct benefits in all conditions tested to date. This statement also stands in contrast to studies that sug-

gest poorer cardiovascular outcomes with other drug classes such as α blockers[66] or calcium antagonists.[64] A review of the more recent trials is found on page 20 of this supplement.

The value of ACE inhibitors and ARAs in high-risk conditions brings about an obvious question: if anti-RAAS drugs are effective agents in the most complicated forms of hypertension, isn't it logical to assume that these same agents will be more effective at preventing the development of target organ damage? It remains unclear whether all target organ damage is the result of elevated pressure per se or whether there is a specific "toxic" role of Ang II and other hormones in addition to the effects of blood pressure. Definitive differences between drug classes may be demonstrated by the huge Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT)[66] study but the absence of between-class differences in ALLHAT results could easily be falsely negative because of the relatively short duration of follow-up, the heterogeneity of clinical conditions in the study subjects, and the relatively low doses of the study drugs that were used. For the present, the physician is left to interpret the incomplete existing data that point to superiority of RAAS blockers and to decide whether it is important to treat patients now or to wait for "definitive" clinical results that in fact may never come. It seems logical to include the use of an agent that blocks the RAAS system as one of the preferred initial medications in addition to diuretics and perhaps β blockers.

CONCLUSIONS

Despite the advances made in understanding the basic and clinical science of anti-RAAS drugs, there are important unanswered questions about the clinical implications of the different mechanisms of action of ACE inhibitors and ARAs. It is indisputable that drugs that interrupt the RAAS can improve and extend the lives of many people. For these benefits to occur, however, clinicians must be sure to use adequate doses of ACE inhibitors and ARAs and to concentrate *less* on the potential between-drug differences and *more* on improving overall blood pressure control by using more effective drug combinations, especially ACE inhibitor-diuretic and ARA-diuretic combinations. On balance, the bulk of current evidence is consistent with the recommendation that ACE inhibitors and ARAs are appropriate first-line and second-line agents in hypertension.

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REFERENCES

1 Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. *Arch Intern Med*. 2000;160(15): 2281–2286.

2 The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med*. 1997;157(21): 2413–2446.

3 Burnett JJ. Vasopeptidase inhibition: a new concept in blood pressure management. *J Hypertens*. 1999;17:S37–S43.

4 Bader M, Peters J, Baltatu O, et al. Tissue renin-angiotensin systems: new insights from experimental animal models in hypertension research. *J Mol Med*. 2001;79:76–102.

5 Sica D, Ripley E. Angiotensin-converting enzyme inhibitors. In: Izzo JL Jr, Black HR, eds. *Hypertension Primer*. Baltimore, MD: Lippincott, Williams, and Wilkins; 1999:372–376.

6 Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;97:1411–1420.

7 Marsden PA, Brenner BM, Ballerman BJ. Mechanisms of angiotensin action on vascular smooth muscle, the adrenal, and the kidney. In: Laragh JH, Brenner BM, eds. *Hypertension: Pathophysiology, Diagnosis, and Treatment*. New York, NY: Raven Press; 1990:1247–1272.

8 Ferrario CM, Chappell MC, Dean RH, et al. Novel angiotensin peptides regulate blood pressure, endothelial function and natriuresis. *J Am Soc Nephrol*. 1998;9:1716–1722.

9 Hu L, Catanzaro DF, Pitarresi TM, et al. Identical hemodynamic and hormonal responses to 14-day infusions of renin or angiotensin II in conscious rats. J *Hypertens*. 1998; 19:1285–1298.

10 Gavras I. Bradykinin-mediated effects of ACE inhibition. *Kidney Int*. 1992;42:1020–1029.

11 Waeber B, Brunner HR. Cardiovascular hypertrophy: role of angiotensin II and bradykinin. *J Cardiovasc Pharmacol*. 1996;27(suppl 2):S36–S40.

12 Dachman WD, Ford GA, Hoffman BB, et al. Bradykinin-induced venodilation is not impaired with aging in humans. *J Gerontol*. 1992;47:M166–M170.

13 Baruch L, Anand I, Cohen IS, et al. Augmented short and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin-converting enzyme inhibitor therapy in patients with heart failure. *Circulation*. 1999;99:2658–2664.

14 Campbell DJ, Valentijn AJ. Identification of vascular renin-binding proteins by chemical cross-linking: inhibition of binding of renin by renin inhibitors. *J Hypertens*. 1994;12:879–890.

15 Dzau VJ. Atherosclerosis and hypertension: mechanisms and interrelationships. *J Cardiovasc Pharmacol*. 1990;15(suppl 5): S59–S64.

16 Hornig B, Drexler H. Endothelial function and bradykinin in humans. *Drugs*. 1997;54(suppl 5):42–47.

17 Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. 2001; 87:840–844.

18 Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669–677.

19 Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Eng J Med*. 2000;342(3):145–153.

20 Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329:1456–1462.

21 Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus

approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis*. 2000;36:646–661.
22 Mahe I. The PROGRESS study for the prevention of recurrent cerebrovascular accident [French]. *Presse Medicale*. 2001;30:1848.
23 Kool MJ, Lustermans FA, Breed JG, et al. The influence of perindopril and the diuretic combination amiloride+hydrochlorothiazide on the vessel wall properties of large arteries in hypertensive patients. *J Hypertens*. 1995;13:839–848.
24 Barenbrock M, Spieker C, Hoeks AP, et al. Effect of lisinopril and metoprolol on arterial distensibility. *Hypertens*. 1994;23(suppl 1):I161–I163.
25 Schmieder RE, Schlaich MP. Comparison of therapeutic studies on regression of left ventricular hypertrophy. *Adv Exp Med Biol*. 1997;432:191–198.
26 Swislocki ALM, Hoffman BB, Reaven GM. Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am J Hypertens*. 1989;2:419–423.
27 Vanhoutte PM, Boulanger CM, Mombouli JV. Endothelium-derived relaxing factors and converting enzyme inhibition. *Am J Cardiol*. 1995;76:3E–12E.
28 Thybo NK, Stephens N, Cooper A, et al. Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. *Hypertens*. 1995;25(pt 1):474–481.
29 Lever AF, Hole DJ, Gillis CR, et al. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet*. 1998;352:179–184.
30 Hansson L, Lithell H, Skoog I, et al. Study on COgnition and Prognosis in the Elderly (SCOPE): baseline characteristics. *Blood Press*. 2000;9(2–3):146–151.
31 Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751–1756.
32 Sica DA, Douglas JG. The African American Study of Kidney Disease and Hypertension (AASK): new findings. *J Clin Hypertens*. 2001;3:244–251.
33 Parving HH, Lehnert H, Brochner-Mortensen J, et al. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.
34 Testa MA, Anderson RB, Nackley JF, et al. Quality of life and antihypertensive therapy in men. A comparison of captopril with enalapril. The Quality-of-Life Hypertension Study Group. *N Engl J Med*. 1993;328:907–913.
35 Simon S, Moser M, Black HR, et al. Cough and ACE inhibitors. *Arch Intern Med*. 1992;152:1698–1700.
36 Blais CJ, Rouleau JL, Brown NJ, et al. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin-converting enzyme inhibitor-associated angioedema. *Immunopharmacol*. 1999;43:293–302.
37 Prisant LM. Angioneurotic edema. *J Clin Hypertens*. 2001;3:262–263.
38 Black HR. Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE): results of a landmark clinical trial in hypertension. Presented at: An Advanced Approach to the Management of Cardiovascular Disease: The Role of Vasopeptidase Inhibition (VPI). Atlanta, GA: March 20, 2002.
39 Izzo JLJ, Larrabee PS, Scandling JD. Hyperkalemia with enalapril in advanced renal failure. *JAMA*. 1986;255:2605–2606.
40 Burnett JC. The atrial peptide system in cardiac disease. *Am J Hypertens*. 1988;1(4 pt 2):410S–20S.
41 Weber MA. Vasopeptidase inhibitors. *Lancet*. 2001;358:1525–1532.
42 Northridge DB, Newby DE, Rooney E, et al. Comparison of the short-term effects of candoxatril, an orally active neutral endopeptidase inhibitor, and frusemide in patients with chronic heart failure. *Am Heart J*. 1999;38:1149–1157.
43 Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure. *Lancet*. 1997;349:747–752.
44 Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial-the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355:1582–1587.
45 Cohn JN, Tognoni G, for Investigators V. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667–1675.
46 Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:1004.
47 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
48 Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
49 Siragy HM, Carey RM. Angiotensin type 2 receptors: potential importance in the regulation of blood pressure. *Curr Opin Nephrol Hypertens*. 2001;10:99–103.
50 Grossman E, Peleg E, Carroll J, et al. Hemodynamic and humoral effects of the angiotensin II antagonist losartan in essential hypertension. *Am J Hypertens*. 1994;71:1041–1044.
51 Saunders E, Weir MR, Kong BW, et al. A comparison of the efficacy and safety of a β-blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med*. 1990;150:1707–1713.
52 Timmermans P, Duncia JV, Carini DJ, et al. Discovery of losartan, the first angiotensin II receptor antagonist. *J Hum Hypertens*. 1995;9(suppl 5):S3–S18.
53 Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation*. 2000;101:844–846.
54 Latif F, Tandon S, Obeleniene R, et al. Angiotensin II type 1 receptor blockade with 80 and 160 mg valsartan in healthy, normotensive subjects. *J Cardiac Fail*. 2001;7:265–268.
55 Ruggenenti P, Brenner BM, Remuzzi G. Remission achieved in chronic nephropathy by a multidrug approach targeted at urinary protein excretion. *Nephron*. 2001;88:254–259.
56 Luzier AB, Forrest A, Adelman M, et al. Impact of angiotensin-converting enzyme inhibitor underdosing on rehospitalization rates in congestive heart failure. *Am J Cardiol*. 1998;82(4):465–469.
57 Luzier AB, Forrest A, Feuerstein SG, et al. Containment of heart failure hospitalizations and cost by angiotensin-converting enzyme inhibitor dosage optimization. *Am J Cardiol*. 2000;86(5):519–523.
58 Luzier AB, DiTusa L. Underutilization of ACE inhibitors in heart failure. *Pharmacotherapy*. 1999;19(11):1296–1307.
59 Deary AJ, Schumann AL, Murfit H, et al. Double-blind, placebo-controlled crossover rotation of the five principal classes of antihypertensive drugs. *Am J Hypertens*. 2001;14:10A–11A.
60 Urata H, Nishimura H, Ganten D, et al. Angiotensin-converting enzyme-independent pathways of angiotensin II formation in human tissues and cardiovascular diseases. *Blood Press*. 1996;2(suppl):22–28.
61 Biollaz J, Brunner HR, Gavras I, et al. Antihypertensive

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therapy with MK 421: angiotensin II-renin relationships to evaluate efficacy of converting enzyme blockade. *J Cardiovasc Pharmacol*. 1982;4:966–972.

62 Azizi M, Chatellier G, Guyene TT, et al. Additive effects of combined angiotensin-converting enzyme inhibition and angiotensin II antagonism on blood pressure and renin release in sodium-depleted normotensives. *Circulation*. 1995;92:825–834.

63 Agarwal R. Add-on angiotensin receptor blockade with maximized ACE inhibition. *Kidney Int*. 2001;59:2282–2289.

64 Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354(9192):1751–1756.

65 Izzo JL Jr, Levy D, Black HR. Clinical advisory statement: importance of systolic blood pressure in older Americans. *Hypertension*. 2000;35(5):1021–1024.

66 Group ACR. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2000;283:1967–1975.

67 Group SCR. Prevention of stroke by antihypertensive drug treatment in older patients with isolated systolic hypertension. *JAMA*. 1991;265:3255–3264.

68 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997;350:757–764.

69 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.

70 Thackray SD, Witte KK, Khand A, et al. Clinical trials update: highlights of the scientific sessions of the American Heart Association year 2000: Val HeFT, COPERNICUS, MERIT, CIBIS-II, BEST, AMIOVIRT, V-MAC, BREATHE, HEAT, MIRACL, FLORIDA, VIVA and the first human cardiac skeletal muscle myoblast transfer for heart failure. *Eur J Heart Fail*. 2001;3:117–124.

71 Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med*. 1996;335:1107–1114.

72 Pitt B, Segal R, Martinez FA, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747–752.

73 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ*. 1998;317:713–720.

74 Estacio RO, Jeffery RW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med*. 1998;338:645–652.

75 Gisen G. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The REIN Trial. *Lancet*. 1997;349:1857–1863.