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Angiotensin Receptor Blockers: Evidence for Preserving Target Organs

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Summary: Hypertension is a major problem throughout the developed world. Although current antihypertensive treatment regimens reduce morbidity and mortality, patients are often noncompliant, and medications may not completely normalize blood pressure. As a result, current therapy frequently does not prevent or reverse the cardiovascular remodeling that often occurs when blood pressure is chronically elevated. Blockade of the renin-angiotensin system (RAS) is effective in controlling hypertension and treating congestive heart failure. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) inhibit the activity of the RAS, but these two classes of antihypertensive medications have different mechanisms of action and different pharmacologic profiles. Angiotensin-converting enzyme inhibitors block a single pathway in the production of angiotensin II (Ang II). In addition, angiotensin I is not the only substrate for ACE. The ACE inhibitors also block the degradation of bradykinin that may have potential benefits in cardiovascular disease. Bradykinin is, however, the presumed cause of cough associated with ACE inhibitor therapy. Data from clinical trials on ACE inhibitors serve to support the involvement of the RAS in the development of cardiovascular disease. Angiotensin receptor blockers act distally in the RAS to block the Ang II type 1 (AT_1) receptor selectively. Thus, ARBs are more specific agents and avoid many side effects. Experimental and clinical trials have documented the efficacy of ARBs in preserving target-organ function and reversing cardiovascular remodeling. In some instances, maximal benefit may be obtained with Ang II blockade using *both* ARBs and ACE inhibitors. This review describes clinical trials that document the efficacy of ARBs in protecting the myocardium, blood vessels, and renal vasculature.

Key words: angiotensin-converting enzyme, angiotensin receptor blockers, angiotensin receptor subtypes, heart failure, hypertension, myocardial hypertrophy, myocardial infarction

Introduction

Hypertension remains a major problem in the United States, producing increased morbidity and mortality in the 50 million Americans who are hypertensive.[1] Elevated blood pressure (BP) is associated with significant increased risk for stroke, heart failure (HF), coronary artery disease, end-stage renal disease (ESRD), and sudden death.

The prevalence of hypertension is affected by age, gender, ethnic background, and income. It occurs commonly in the elderly,[2] predominantly in women.[1] This is of particular note since, in 1996, more women than men died of complications of hypertension. Blacks develop hypertension earlier than Caucasians; moreover, decade for decade, hypertension is more severe in blacks.[1] People with lower incomes and educational levels also tend to have higher BP.

Among hypertensive individuals, BP is controlled adequately with antihypertensive treatment in 27.4% and controlled poorly in another 26.2%; nearly 15% do not take any medications.[1] In addition, hypertension often goes unrecognized; about one third of hypertensive Americans are unaware that their BP is high.[2] These figures show that despite a diagnosis of hypertension, current antihypertensive treatment leaves much to be desired. Since they specifically block the actions of angiotensin II (Ang II), angiotensin receptor blockers (ARBs) offer a unique opportunity to lower BP effectively and to address target-organ issues with little development of side effects.

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Problems with Current Antihypertensive Medications

Evidence from clinical trials indicates that currently available antihypertensive medications reduce the morbidity and mortality associated with increased BP. Unfortunately, 30 to 50% of hypertensive patients do not comply with their treatment regimens.[3] Factors associated with noncompliance include side effects of the medication, age, apathy about the consequences of missed doses, use of home remedies, employment, and cost. Failure to take medications regularly may account for target-organ damage in many patients.[4]

In addition, the duration of action of antihypertensive medications is an issue in intermittently compliant patients. Drugs with a rapid onset and short duration of action are suboptimal because this profile may be associated with sudden decreases in BP with the onset of the drug's action, followed by rapid disappearances of the antihypertensive effect when doses are missed. Also, missed doses of some short-duration agents (e.g., short-acting beta blockers) may be accompanied by excessive sympathetic discharge and the possibility of potentially fatal arrhythmias.

Many currently available antihypertensive drugs have notable side effects.[2] For example, diuretics can produce various biochemical abnormalities, such as hypokalemia, and can also decrease magnesium. Peripheral adrenergic inhibitors can cause diarrhea. Patients treated with beta blockers are at risk for fatigue, bradycardia, HF, insomnia, impaired peripheral circulation, and asthma. Although angiotensin-converting enzyme (ACE) inhibitors have many benefits, cough is an irritating side effect.

Renin-Angiotensin System and Blood Pressure Control

The renin-angiotensin system (RAS) is important in both the short- and long-term control of BP. Through the actions of binding to the Ang II type 1 receptor (AT_1), Ang II, the major effector hormone of the RAS, produces fluid and sodium retention and vasoconstriction. Blockade of the RAS is a widely accepted means of controlling hypertension and treating congestive HF (CHF). Both ACE inhibitors and ARBs attenuate the effects of Ang II, ACE inhibitors by impairing the conversion of angiotensin I (Ang I) to Ang II, and ARBs by antagonizing Ang II at its target, the type 1 (AT_1) receptor. Both approaches are effective in treating hypertension. The ACE inhibitors also produce some of their beneficial effects by interfering with the metabolism of the vasodilator bradykinin resulting in its elevated levels.[5]

Angiotensin II Receptors

Humans have multiple types of angiotensin receptors, but two, AT_1 and AT_2, have been well characterized. Both receptors belong to the superfamily of seven transmembrane domain G protein–coupled receptors although they share only a 34% sequence bonding. The receptors use a transmembrane signaling system with three separate components to mediate their actions. An extracellular ligand specifically identified by a cell surface receptor triggers activation of a G protein located on the cytoplasmic face of the plasma membrane; this, in turn, changes the activity of an effector element, usually an enzyme or ion channel, which changes the concentration of an intracellular second messenger. Receptor type as well as target tissue and effector mechanisms all determine the biologic activities of Ang II.

Angiotensin II type 1 receptor: Binding of Ang II to the AT_1 receptor produces various G protein–coupled and G protein–independent effects. These interrelated events produce vascular smooth muscle contraction, hyperplasia and hypertrophy of vascular smooth muscle cells, and formation of extracellular matrix.[6]

An experimental model of human essential hypertension using spontaneously hypertensive rats showed that blocking the effects of AT_1 receptor stimulation with AT_1 receptor antisense can prevent the development of hypertension and prevent the associated pathophysiologic changes of left ventricular hypertrophy (LVH), multifocal fibrosis, and perivascular fibrosis.[7]

Angiotensin II type 2 receptor: The AT_1 receptor is widely expressed in the human tissue, while the AT_2 receptor is located predominantly in the heart, adrenal medulla, reproductive tissue, vascular endothelium, and the central nervous system in adults. In contrast, it is abundant and ubiquitous in fetal tissue.[6, 8–10] This unequal distribution raises the possibility that the AT_2 receptor may play a critical role in the regulation of cellular growth and differentiation.

Under physiologic conditions, binding of Ang II to the AT_2 receptor appears to inhibit angiogenesis.[11] Some of the growth-regulatory effects of the AT_2 receptor may be mediated through induction of programmed cell death.[12] In vascular injury, myocardial infarction (MI), HF, wound healing, and peripheral nerve injury, the AT_2 receptor may be upregulated to control excessive growth mediated by the AT_1 receptor or other growth factors.[11]

Yin-yang activity of angiotensin II receptor subtypes: The activities of the body's neurohumoral systems are evenly balanced under physiologic conditions. For example, the glucose-lowering effects of insulin are countered by glucagon; the activity of parathyroid hormone on calcium is balanced by the hypocalcemic effects of calcitonin; and the outflow of the sympathetic and parasympathetic nervous systems are finely tuned. Likewise, such yin-yang dualism is expressed by the Ang II receptor subtypes. While stimulation of the AT_1 receptor is associated with vasoconstriction and cell growth, stimulation of the AT_2 leads to vasodilation and cell differentiation. This dichotomy becomes particularly important in patients treated with ARBs. The AT_1 receptor blockade is accompanied by increased plasma levels of Ang II. When the AT_1 receptor sites are effectively blocked, Ang II selectively binds to the unoccupied AT_2 receptors.[13] The resulting unopposed action of the AT_2 receptor pathway has numerous potential benefits in patients with disordered cardiovascular physiology, including attenuation of AT_1 receptor pressor-mediated effects, reversal of the cardiac remodeling produced by untreated hypertension, and protection of target organs.

Angiotensin-Converting Enzyme Inhibition

Acute inhibition of ACE decreases Ang II levels. However, with chronic ACE inhibition, plasma Ang II returns to pretreatment concentrations and remains free to bind to its receptors.[14] Studies in normal volunteers have shown that ACE inhibition is associated with an increase in the levels of both renin and Ang I; the latter is then partially converted to Ang II through both ACE and non-ACE pathways.[15] Much of this ACE-independent conversion of Ang I to Ang II appears to result from the action of chymase, a chymotrypsin-type serine protease predominantly found in mast cells.[16] Although both ACE and chymase are present in the tissues of the human left ventricle, about 80% of the Ang II–forming activity in left ventricular (LV) tissue is due to chymase, not ACE.[17] Thus, tissue chymase and other enzymes may serve as a pathway for the persistence of the effects of Ang II in patients treated with therapeutic dosages of ACE inhibitors.

Angiotensin Receptor Blockade

Controlling hypertension with angiotensin receptor blockade uses receptor antagonists that compete selectively with Ang II for binding to the AT_1 receptor. Early AT_1 receptor antagonists, such as saralasin, sarilesin, and sarmesin, were Ang II peptide analogues that were easily degraded by the digestive system and could not be administered orally. These first-generation Ang II antagonists also were limited by their short duration of action, partial agonist activity, and activity that blocked both AT_1 and AT_2 receptors.[8]

Within the last several years, a number of ARBs have been marketed for the treatment of hypertension (Table I). These agents are as effective as ACE inhibitors, calcium-channel antagonists, and beta blockers in the treatment of hypertension.[14] Their effects on systemic hemodynamics are comparable with those of ACE inhibitors, while their effects on renal hemodynamics are routinely greater.[18] The ARBs also have favorable tolerability: in clinical trials, the incidence of side effects in patients given ARBs is comparable with that reported with placebo.

Angiotensin receptor blockers should not be considered a single class since there are a number of therapeutically significant pharmacokinetic differences between the individual agents. For example, not all ARBs show a similar dose-response relationship: losartan, the prototype agent, has a flatter dose response than valsartan, which has a steeper dose-response curve.

TABLE I Pharmacologic features of current angiotensin receptor blockers

Trade name	Generic name	Active metabolite	Bioavailability (%)	Half-life (h)	Protein binding (%)
Diovan®	Valsartan	No	25	6	95.0
Cozaar®	Losartan	Yes	33	2[a]	98.7[a]
Avapro®	Irbesartan	No	70	13	90.0
Atacand®	Candesartan	Yes	42	7	99.5
Micardis®	Telmisartan[b]	No	50	24	99.5
Teveten®	Eprosartan[c]	No	13	6	98.25

When a range has been reported, the number in the table represents a mean value. Adapted from Ref. No. 14 with permission.

[a] Data are for losartan itself; its active metabolite EXP 3171 has a half-life of 6–9 h and is 99.8% protein bound.

[b] Source: Ref. No. 67.

[c] Source: Ref. No. 8.

Evidence for Preserving Target Organs

The risk for cardiovascular disease is determined by many factors, including age, gender, history of smoking, dyslipidemia, diabetes, high BP, and family history of cardiovascular disease.[2]

The importance of risk has been addressed by the World Health Organization (WHO) and the International Society of Hypertension.[19] Their joint 1999 Guidelines for the Management of Hypertension state: "Blood pressure levels are continuously related to the risks of cardiovascular disease and the definition of hypertension. . . is, therefore, arbitrary." In addition, they emphasize that "much blood pressure–related disease occurs among individuals who would normally be considered normotensive." Hypertension has been shown by the Framingham Study to occur in isolation only 20% of the time. Clustering with other cardiovascular risk factors that markedly influence the impact of hypertension is the rule. Approximately 25% of patients already have evidence of cardiovascular disease at the time hypertension is diagnosed.[20]

In an attempt to help clinicians stratify cardiovascular risk in hypertensive patients, the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) provided guidelines for risk stratification and treatment according to BP stage, other commonly accepted cardiovascular risk factors, and target-organ damage/clinical cardiovascular disease (TOD/CCD).[2] The importance of target organs to the JNC VI mode of risk stratification is emphasized by the placement of patients into the highest-risk group (C) if they have TOD/CCD, even if their BP is just high-normal. Because hypertension tends to be accompanied by target-organ damage, dyslipidemia, glucose intolerance, insulin resistance, and LVH, therapy usually has to be individualized. In contrast to some of the other antihypertensive agents, ARBs may be useful in any of these accompanying conditions.

Left Ventricular Hypertrophy

In the presence of sustained increases in afterload, the myocardium undergoes a series of adaptations to maintain its function.[21] For example, the increase in end-diastolic volume stretches the myocardial fibers, which respond with increased

contractility via the Frank-Starling mechanism. Neurohumoral mechanisms, including the release of norepinephrine by adrenergic cardiac nerves and activation of the RAS, also augment myocardial contractility. Finally, myocardial fibers hypertrophy in a process involving a continuum of events that include changes in muscle fibers, interstitial connective tissue, and the vasculature.[22] Early in this process, the myocardium will revert to normal if the stress is removed, but eventually the physiologic increase in muscle fiber size becomes pathologic.

The process of remodeling in pathologically hypertrophic hearts is recognized on several levels: Myocytes continue to increase in size; collagen strands increase in number and thickness, and the amount of type III collagen increases temporarily; capillaries and interstitium increase in size and amount, respectively.

This increase in noncontractile elements appears to contribute significantly to the increase in myocardial mass in a pathologically hypertrophic myocardium.[22]

It has been suggested that Ang II plays a major role in the development of pathologic myocardial hypertrophy. The beneficial effects of ACE inhibition in inducing LVH regression may be due to blockade of the direct effects of this hormone unrelated to BP control.[23] For example, regression of cardiac hypertrophy can be achieved by doses of ACE inhibitor that do not affect BP. Angiotensin-induced cardiac remodeling may be due in part to the influence of angiotensin on cellular pathways and growth factors mediated through the AT_1 receptor. For example, acting through the AT_1 receptor, Ang II upregulates proto-oncogenes, including *c-fos, c-jun, jun-B, Egr-1, and c-myc*.[24] Upregulation of these genes in myocardial cells of rats produces ventricular hypertrophy independent of BP plus a shift to a fetal type of myocardium.[25]

Meta-analyses have suggested that ACE inhibitors are very effective agents for reversing LVH in patients with systemic hypertension.[26, 27] Since LVH regression may be associated with an improved prognosis,[28] the influence of ARBs on LVH is of great interest. In one randomized, double-blind trial,[29] 69 patients with essential hypertension and echocardiographic features of LVH, 56 of whom were previously untreated, were given either valsartan or atenolol. After 8 months of treatment, the LV mass index of the valsartan-treated patients decreased 21 g/m^2 from baseline, compared with only a 10 g/m^2 decrease from baseline for patients given the beta blocker. Since the two groups experienced similar reductions in systolic and diastolic BP, this evidence suggests that cardiac remodeling was reversed in patients treated with the ARB and that valsartan had a significant pharmacologic effect beyond BP reduction. This study further supports data suggesting the potential benefits of attentuation of the growth-promoting actions of Ang II.[29]

Chronic Heart Failure

Heart failure represents a clinical complex of symptoms including shortness of breath, congestion, and fatigue. Most cases in industrialized countries have been linked to ischemic heart disease. Epidemiologic studies have also suggested an association with hypertension. Whatever the etiology, ultimately myocardial exhaustion—marked by distinct morphologic, functional, and neurohumoral abnormalities—ensues. Ultrastructural changes include reduced myocardial volume relative to myofibrillar volume and decreased surface densities of the T-tubular and diadicjunctional systems.[30] On light microscopy, capillary density is reduced, areas of reactive interstitial fibrosis are present, and foci of myocytic drop-out are recognizable.[30, 31] The latter appears to be a consequence of a proapoptotic shift involving the entire population of cardiac muscle cells.[32]

The importance of the RAS in the pathophysiology of chronic HF has been well established. Physiologic changes include alterations in myocardial blood flow and neurohumoral activation. Activation of the RAS contributes to excessive vasoconstriction and to retention of sodium and water in this disorder. In addition, in response to decreased cardiac output, compensatory neurohumoral mechanisms, including changes in both the sympathetic nervous system and the RAS, may contribute to progressive LV dysfunction. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators have first suggested that neurohumoral activation precedes the development of symptoms.[33] Subsequent studies by Benedict *et al.*[34] went on to demonstrate that elevated plasma norepinephrine (PNE) predicts the development of symptoms in asymptomatic patients. In addition, in patients with HF, neurohormonal activation (increased PNE, plasma renin, and atrial natriuretic peptide) is related to the severity of LV dysfunction independent of functional class or drug therapy. Evidence to support the role for RAS inhibition in patients with HF comes from three major clinical trials. The first, CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) evaluated the effects of enalapril versus placebo in 253 patients with severe HF (New York Heart Association [NYHA] functional class IV) receiving conventional medical therapy. The trial was terminated early because of a significant reduction in mortality in patients treated with enalapril. The SOLVD Treatment Trial evaluated the effects of enalapril added to conventional therapy in 2,569 patients with NYHA functional class II and III, and ejection fractions < 35.[35] Results of the study demonstrated reduced mortality and HF hospitalizations compared with placebo. The SOLVD Prevention Trial evaluated enalapril in 4,228 patients with asymptomatic LV dysfunction and ejection fractions < 35 and found a significant reduction in the incidence of HF and the rate of related hospitalizations. In addition, data showed a nonsignificant trend in the number of cardiovascular deaths.[36] This evidence indicates that ACE inhibitors should be considered in all patients with symptomatic HF as well as in patients with asymptomatic LV dysfunction.

Angiotensin Receptor Blockade

The hemodynamic benefits of AT_1 receptor blockade in patients with congestive heart failure (CHF) have been documented in a number of studies.[37–39] For example, in patients with chronic stable CHF previously untreated with an ACE inhibitor, valsartan produced statistically significant reductions

in mean pulmonary capillary wedge pressure and systemic vascular resistance while significantly increasing cardiac output.[38] Clinical benefits have also been described. The Evaluation of Losartan in the Elderly (ELITE) study[40] compared the effects of losartan and captopril in the elderly. While the trial was neutral in its primary end point, a change in renal function, losartan was superior to captopril in all-cause mortality, sudden death, and combined death and/or hospitalization for HF. Hospitalization for CHF was the same for both drugs; however, adverse effects were described in only 12% of patients on losartan and 21% of patients on captopril.[40]

Combined Angiotensin-Converting Enzyme Inhibition and Angiotensin Receptor Blockade

Studies have documented the presence of alternative pathways for the production of Ang II within the myocardium. Increased activity of these pathways in patients with chronic HF can cause Ang II receptor activation independent of the ACE.[41] Several experimental and clinical studies have evaluated the efficacy of combined ACE inhibitor and ARB therapy in HF.[42–45] This approach allows more complete Ang II blockade by both agents while continuing the favorable ACE inhibitor effect on reducing bradykinin degradation.

Experimentally, the effects of ACE inhibition and Ang II blockade, both alone and combined, have been studied extensively in a porcine model of tachycardia-induced HF.[42, 43, 45] Unique benefits of the combined treatment not seen with either agent alone included normalization of cardiac output both at rest and during exercise, stabilization of the peripheral vascular resistance during exercise, and normalization of LV myocardial blood flow at rest.[42] These findings suggested that combined ACE inhibition and Ang II blockade may provide novel benefits in the CHF setting.

In a multicenter, double-blind, placebo-controlled, dose–response trial, Baruch *et al.* evaluated the hemodynamic and neurohormonal effects of valsartan in patients on standard therapy including ACE inhibitors.[44] Forty-two subjects with symptomatic, stable HF in NYHA classes II to IV were randomized to treatment with valsartan 80 mg twice daily, valsartan 160 mg twice daily, or placebo. A single dose of lisinopril was given on study days to ensure sustained ACE inhibition. Right heart catheterization was performed, and pressures were monitored for 12 hours after the first dose of the study drug on Day 1 and the last dose on Day 28. Reductions in 0 hour trough pulmonary capillary wedge pressure, pulmonary artery diastolic pressure, and systolic BP were seen with valsartan 160 mg compared with placebo at Day 28. More important, 4 weeks of therapy with both doses of valsartan produced a statistically significant decrease in plasma aldosterone levels ($p < 0.001$), and a trend toward PNE suppression. These data also indicated that physiologically active levels of Ang II persist despite ACE inhibition and support the hypothesis that AT_1 receptor blockade can augment the hemodynamic effects of ACE inhibition.[44]

Two studies by Hamroff *et al.* have evaluated the benefits of combined ACE inhibitor and ARB therapy in patients with symptomatic HF (NYHA classes III and IV). The first study in 43 patients determined the safety and tolerability of this combination.[46] The second study in 33 patients demonstrated enhanced peak exercise capacity and symptom relief.[47]

The recently announced Candesartan Cilexetil in Heart Failure: Reduction in Mortality and Morbidity (CHARM) trial is designed to evaluate the safety and efficacy of the ARB candesartan in 6,500 patients with chronic HF. It includes subpopulations of patients with reduced LV function who are intolerant of ACE inhibitor therapy or who are currently receiving therapy with an ACE inhibitor, and patients with preserved LV function. No member of the latter subgroup will receive an ACE inhibitor. The primary endpoints are cardiovascular death and HF hospitalization. Secondary endpoints will evaluate other measures of morbidity and mortality.

The Valsartan Heart Failure Trial (Val-HeFT) has been designed to evaluate the effect of valsartan added to standard HF therapy in 5,000 patients in NYHA classes II to IV. The study will be completed after 906 deaths have been documented. Secondary endpoints will include hospitalization, major morbid events, quality of life measurements, neurohormonal evaluations, and changes in LV size and function. Val-HeFT will evaluate whether the benefits of combination ACE inhibitor–ARB therapy occur in heart failure.

Post Myocardial Infarction

Advances in the management of acute MI over the past several decades have saved many lives. For example, antiplatelet therapy and reperfusion strategies are now the standard of care in patients who are seen in the early hours after an acute MI. Both beta blockers and ACE inhibitors are invaluable in the early and chronic phases post MI. Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have proven beneficial in secondary prevention of MI.

Despite these advances, acute MI continues to be accompanied by significant morbidity and mortality. Although this fact has multiple explanations, postinfarction neurohumoral activation is an important contributor. Sympathetic activation occurs immediately after acute MI. It manifests in many ways, including increases in plasma catecholamines, changes in heart rate variability, alterations in baroreceptor sensitivity, and variations in sympathetic nerve or muscle activity.[48] In addition, both systemic and tissue RAS undergo intense activation.[49] These effects are physiologic and can be beneficial, but this adaptive response can be harmful over the long term and may contribute to development of some of the complications seen after MI. Angiotensin-converting enzyme inhibitor therapy has become a central element in the treatment of CHF, and it plays a critical role in the prevention of post-MI ventricular remodeling.

Post-MI CHF is a common clinical problem[50] that is associated with a twofold increase in both in-hospital and 1-year mortality. In addition, more in-hospital complications and longer hospital stays accompany post-MI HF. Results of both noninvasive and invasive tests can be used to predict the development of in-hospital HF. Higher-risk patients are older and female, have diabetes mellitus and a previous MI, or have an

anterior wall MI. Angiographic predictors include lower ejection fractions and a higher incidence of multivessel disease.[50]

Several recent studies have demonstrated the ability of ACE inhibitors to prevent the long-term development of CHF in patients without LV dysfunction immediately after an acute MI. The Survival and Ventricular Enlargement (SAVE) trial was designed to determine whether long-term ACE inhibitor therapy would reduce morbidity and mortality among survivors of MI.[51] Patients were assigned randomly to treatment with captopril or placebo, and the incidence of cardiovascular events was determined over a follow-up period of 3.0 ± 0.6 years. The SAVE trial demonstrated that LV enlargement and function after infarction, as detected by quantitative two-dimensional echocardiography, are associated with the development of adverse events.[52] In addition, changes in measures of neurohumoral activation (particularly plasma renin activity and atrial natriuretic peptide) at the time of hospital discharge were found to be independent signs of a poor prognosis.[53] Attenuation of ventricular enlargement with captopril in these patients was accompanied by a reduction of events. Captopril also reduced the risk of the following in SAVE enrollees: all-cause mortality, 19% ($p = 0.019$); cardiovascular death, 21% ($p = 0.014$); and MI, 25% ($p = 0.012$).[51]

Results of several other studies also suggested that ACE inhibition offers particular benefit to high-risk survivors of acute MI.[54,55] For example, ramipril administered orally to patients with clinical evidence of either transient or ongoing HF, starting between Days 2 and 9 post MI, substantially reduced premature death from all causes.[55]

Aggressive treatment is warranted to decrease further the mortality associated with acute MI. Since ARBs also inhibit the RAS, but by a different mechanism of action than ACE inhibitors, the actions and effects of these agents may offer similar or even additional benefits when administered to patients immediately post MI. Several clinical trials are in progress to evaluate the role of ARBs post MI. The Optimal Therapy in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) study is a multicenter, double-blind, randomized, parallel, captopril-controlled trial.[56] It is designed to test the hypothesis that, compared with captopril, losartan will decrease the risk for all-cause mortality by 20% in 5,000 high-risk patients ≥ 50 years old, after an acute MI.

VALsartan In Acute myocardial iNfarcTion (VALIANT), another ongoing trial, is comparing the effects of valsartan alone, captopril alone, and combined valsartan and captopril on mortality in approximately 14,500 high-risk patients with acute MI. As a result of its design, VALIANT may help to address many of the complex therapeutic issues facing clinicians as they seek to determine optimal treatment strategies with ARBs, ACE inhibitor, or combined therapy in these patients.

Renal Function

The incidence and prevalence of ESRD in the United States, as measured by the number of patients enrolled in chronic dialysis programs, continues to increase. At the end of 1997, more than 300,000 Americans had ESRD. The incidence and prevalence of chronic renal failure requiring dialysis peaks in patients 60 to 70 years old; men are more commonly affected than women. End-stage renal disease also occurs disproportionately more often in blacks and Native Americans than in Asians and Caucasians.

Hypertension (27.1%) is second only to diabetes mellitus (40.3%) as the disorder most commonly responsible for ESRD.[57] Hypertension is not only a strong independent risk factor for ESRD, it also accelerates the decline of renal function in patients with other diseases of the kidney.[58]

Proteinuria is also an independent risk factor for the progression of renal disease.[59] Consequently, JNC VI issued BP control guidelines that stratify treatment goals for patients with renal disease both with and without proteinuria.[2] Inhibition of the RAS with ACE inhibitors has proven to be so effective that the JNC VI recommends that hypertensive patients with renal insufficiency be treated with an ACE inhibitor.[2]

Renoprotective actions that result from inhibition of the RAS include effects on endothelial cell function, glomerular hypertension and hypertrophy, and mesangial cell proliferation and matrix production.[60] Inhibition of the RAS has been shown to reduce proteinuria, which is the main clinical expression in the short run of disease activity. In patients with type 2 diabetes, ACE inhibition protects against deterioration of renal function and is significantly more effective than BP control alone.[61] Renoprotection also has been demonstrated with ARB. In a randomized, double-blind, placebo-controlled trial, patients with type 2 diabetes and nephropathy, given valsartan, experienced a statistically significant ($p = 0.018$) decrease in microalbumin excretion compared with patients given placebo.[62]

The mechanisms of the BP-independent effects of RAS inhibition are unclear, but experimental evidence suggests that they may be mediated partially by the AT_2 receptor. Whereas the AT_1 receptor is widely distributed throughout the glomeruli and other nephron segments in the kidney of the Sprague-Dawley rat, the AT_2 receptor is localized mainly in the glomeruli.[9] The beneficial effects of AT_2 receptor stimulation have been demonstrated in a renal wrap model of hypertension.[63] As a consequence of Ang II–mediated stimulation of the AT_2 receptor, the kidneys produce bradykinin, which in turn stimulates release of nitric oxide[64] and formation of cyclic guanosine monophosphate (cGMP).[65] Experimental AT_2 receptor blockade in this rat model has led to an increase in BP and a decrease in renal bradykinin.[63] Additional experiments in mice lacking AT_2 receptors showed that these animals are hypersensitive to Ang II.[66] These studies suggest a protective role for the AT_2 receptor in the kidney via counterregulatory vasodilation mediated by bradykinin, nitric oxide, and cGMP. Furthermore, it has been shown that approximately 40% of Ang I is converted to Ang II by non-ACE-dependent pathways in intact human kidney, and this is blocked by ARBs.[18]

Conclusions

Angiotensin receptor blockers offer a number of benefits beyond those offered by the older classes of antihypertensive

agents. These include specificity at a molecular level, virtually no side effects, and reversal of the remodeling that occurs in target organs damaged by the chronic effects of high BP. Both preclinical experiments and clinical trials have documented the efficacy of ARBs in reducing myocardial hypertrophy and improving hemodynamics in acute and chronic HF, and possibly delaying progressive renal failure in patients with type 2 diabetes and nephropathy. Although the evidence requires validation, these studies suggest that inhibition of the RAS through AT_1 receptor blockade may provide benefits to patients beyond those available from ACE inhibitors.

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