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Angiotensin II Type 1 Receptor Blockade – Certainties, Probabilities, Possibilities

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Hypertension and atherosclerosis are important risk factors for heart disease. Both conditions damage blood vessels, the heart, and kidneys, causing endothelial dysfunction, vascular and ventricular remodeling and hypertrophy. These processes eventually lead to either the formation of unstable coronary atheromatous plaque and acute myocardial infarction, or progressive left ventricular dysfunction, heart failure, and death. The renin-angiotensin-aldosterone system has been implicated in nearly every step of this progression. Angiotensin II type 1 receptor blockade is the newest approach to intervention in the renin-angiotensin-aldosterone system. This report will review the established and future role of this approach in the treatment of cardiovascular disorder.

An overview of the renin-angiotensin system in cardiovascular disease

The renin-angiotensin-aldosterone system (RAAS) plays a pathophysiologic role in nearly every stage in the progression of atherosclerosis and hypertension to end-stage heart failure (HF). The pleiotropic effects of angiotensin which contribute to the development of hypertension include vasoconstriction, sympathetic activation, sodium retention, and vascular smooth cell growth stimulation, all of which are involved in raising blood pressure and inducing end organ damage (Figure 1). Angiotensin promotes vascular growth by activating autocrine and paracrine growth factors such as fibroblast growth factor, and by transforming growth factor ß-1 and platelet-derived growth factor.[1] These factors are, in turn, regulated by endothelium-derived vasodilator anti-growth factors. In the rat, infusion of angiotensin II, but not norepinephrine, has been found to increase superoxide production via NADH/NADPH oxidase activation, with the increase in blood pressure associated with impaired endothelial function.[2] When the angiotensin type 1 receptor (AT_1) blocker (ARB) losartan was administered concomitantly with angiotensin II in this study, the vascular superoxide production and relaxation was normalized. These data suggest that in hypertension associated with activated RAAS, the key pathologic mechanisms are increased oxidative stress and impaired endothelial function mediated by stimulation of the AT_1 receptor. The pleiotropic actions of angiotensin which contribute to the inflammatory process in atherosclerosis include the production of oxidized low density lipoprotein (LDL) particles which stimulate the production of adhesion and chemo-attractant molecules, as well as cytokine and growth factors. Angiotensin can also be formed locally by activated macrophages and fibroblasts, where it is responsible for vascular smooth muscle replication, hypertrophy, and migration, as well as for stimulating metalloproteinases and extracellular matrix expansion and degradation.[1-4] Many of these processes eventually lead to the formation of unstable plaques in the arteries. Angiotensin also has prothrombotic properties as well as the ability to activate platelets.[5] All of these characteristics contribute to the thrombotic process and eventually to acute myocardial infarction (MI).

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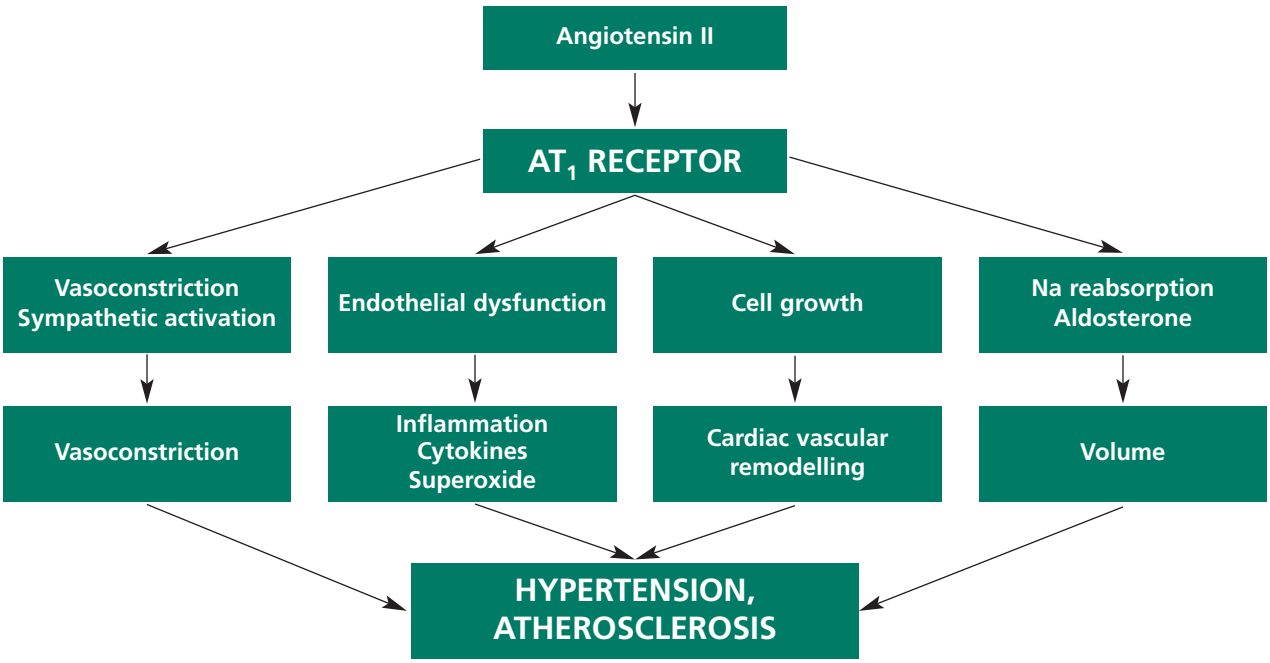
Figure 1: Pleiotrophic cardiovascular effects of angiotensin.



In the heart, angiotensin modulates myocyte growth, matrix formation, and degradation and therefore plays an important role in the process of ventricular remodeling and dilatation post MI.[6-8] The multiple activities of angiotensin provide the rationale for blocking the RAAS to protect the heart, blood vessels, and kidneys, while providing an explanation for the observed clinical benefits of AT_1 receptor blockade.

What we know about AT_1 receptor blockade: the certainties

Efficacy, tolerability, and possibly organ protection are the three key attributes that underscore the increasing acceptability of ARBs in the treatment of hypertension. It has generally been assumed from short-term studies that individual drug classes are of similar efficacy when used in *unselected* groups of patients with essential hypertension. A recent rotational study conducted in a middle-aged Caucasian population, however, suggested that agents that inhibited the RAAS tended to be more effective in lowering blood pressure than agents that did not inhibit this system. A similar trend was found in studies that addressed the treatment of hypertension in a high-risk patient population.[9,10] These observations raise the possibility that in some patients with essential hypertension, there may be a fundamental abnormality of the RAAS and other peptide systems at the tissue level that results in the altered structure and function of small arteries.[11] Furthermore, older studies have sometimes ignored the important phenomenon that there are marked differences within the hypertensive population with regard to treatment response. This is clearly accounted for by the underlying heterogeneity in both the etiology and the pathophysiology of the disease.

Recent data have suggested that the ARBs are at least as effective as other classes of agents in lowering blood pressure.[12] However, multiple factors need to be considered when comparing drugs and classes of drugs, since both pharmacokinetic and pharmacodynamic factors will influence the response to individual drugs. In making these comparisons, it is important to construct full dose-response relationships for the evaluation of efficacy. The most recent comparison was a study by Malmqvist on hypertensive women in which the diuretic hydrochlorothiazide (HCTZ), the angiotensin-converting enzyme (ACE) inhibitor enalapril, and the ARB candesartan cilexetil were dose-titrated to commonly-employed maximal clinical dosages. The doses were candesartan (up to 16 mg), enalapril (up to 20 mg), and HCTZ (up to 25 mg). Their preliminary results, interestingly, revealed a greater decline in both systolic and diastolic arterial pressures with candesartan cilexetil than with the diuretic or ACE inhibitor.[13]

Moreover, frequency of adverse events, including cough, was least in the candesartan-treated patients. One crossover study investigated intra-individual differences in response to an ARB in combination with an ACE inhibitor. The study showed that there was a marked reduction in blood pressure with the combination of the ARB and the ACEI.

A second feature that identifies ARBs as a unique class of antihypertensive agents is their exceptional tolerability. In placebo-controlled studies with several ARBs, including candesartan cilexetil, irbesartan, losartan, and valsartan, no differences were detected between the active drugs and placebo in terms of their side-effect profiles. This feature has translated into an improvement in patient compliance. As a result, it is probable that blood pressure control would be improved in patients on ARBs.

There is currently a wealth of evidence from animal models of hypertension in which treatment with ARBs has been found to reverse vascular, cardiac, and renal structural abnormalities associated with hypertension.[14] An important observation from these experimental studies is that many types of benefit are achieved with doses of ARBs too small to lower arterial blood pressure. This suggests a direct organ-protective effect.

Clinical trials with ARBs

The clinical efficacy and tolerability of ARBs in hypertensive patients and the organ-protective effect demonstrated in animal models should ideally be translated into reduced adverse clinical outcomes in patients with hypertension. In this regard, the effects of ARBs on morbidity and mortality in hypertension, compared to traditional antihypertensive therapy, are currently under investigation in large-scale randomized-controlled clinical trials.

- The Losartan In Hypertension For End-point reduction (LIFE) trial is one which examines the effect of an ARB on mortality in patients with hypertension. Losartan is compared with atenolol in patients with hypertension and left ventricular hypertrophy (LVH). The outcomes are mortality, morbidity and LVH. Recruitment for the study has been completed (over 9,000 patients enrolled) and follow-up is expected to terminate in 2001.
- The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study will include 14,400 patients over 50 years of age with hypertension and at least one other risk factor. In this study, valsartan will be compared to amlodipine with cardiac mortality as the primary endpoint. Target number of events is 1450; the study is expected to run for over four years.
- Another important trial, the Study on COnigition and Prognosis in Elderly (SCOPE) will recruit 4,000 patients, aged 70-89 years, with blood pressure of 160-179/90-99 mm Hg and a Mini-Mental score of more than 24. The ARB candesartan cilexetil will be compared to placebo. Primary endpoint will be any major cardiovascular event and secondary endpoints will include Mini-Mental score and quality of life.

The results of these three trials will hopefully demonstrate improvement in prognosis in patients with hypertension who remain at high risk of developing cardiovascular disease.

AT_1 receptor blockade: Probabilities

Significant therapeutic successes that have been achieved by inhibition of the RAAS in congestive heart failure (CHF) suggest that the ARBs may also be useful in this condition. The efficacy of ACE inhibitors in CHF has been proven in several large-scale studies such as CONSENSUS and SOLVD.[15,16] Recently, the RALES study showed that the aldosterone antagonist spironolactone could prolong survival in patients with severe CHF.[17] This trial, as well as the ATLAS study which demonstrated that high-dose lisinopril was superior to a low-dose in preventing total death and hospitalization, suggests that a greater inhibition of the RAAS may result in further reduction in mortality and morbidity in patients with CHF.

There are strong theoretical grounds for believing that ARBs may be pharmacologically superior to the ACE inhibitors. By selectively binding to the AT_1 receptors, these agents prevent the deleterious effects of angiotensin II, regardless of whether angiotensin II was generated from ACE or "alternative pathways," such as chymase. Furthermore, selective AT_1 receptor blockade may result in increased stimulation of the angiotensin II type 2 (AT_2) receptor subtypes, possibly antagonizing the vasoconstrictive and proliferative effects from AT_1 receptor stimulation by angiotensin II.[18] On the other hand, ARBs, unlike ACE inhibitors, do not enhance kinins to the same degree as the ACE inhibitors, an effect believed to mediate ACE inhibitor-induced cough.[19]

Thus, ARBs should theoretically be at least as effective as the ACE inhibitors in CHF, and perhaps even more so. What is the current clinical evidence to support or refute this hypothesis?

ARBs versus placebo

Clinical experience with the use of ARBs in CHF is still relatively limited. Most studies that have compared ARBs with placebo have involved short-term hemodynamic assessments. Almost all of these studies have confirmed hemody-

namic improvement in comparison with placebo.[20] In a study of 926 patients with CHF and New York Heart Association (NYHA) functional class II and III symptoms by Riegger et al, the ARB candesartan cilexetil was found to produce a dose-dependent improvement in exercise tolerance compared to placebo, as measured by treadmill walking time.[21] Whether this longer-lasting hemodynamic effect will be translated to a reduced incidence of clinical events in patients with CHF must await results from large-scale studies. However, it is unlikely that any more data comparing ARBs and placebo in the absence of ACE inhibitors will be available in the foreseeable future. The only exceptions would be the ACE inhibitor-intolerant arm and the CHF with preserved systolic function arm of the ongoing Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) study. These patients either cannot tolerate ACE inhibitors, or ACE inhibition has not been proven to reduce mortality, ie, in those with preserved systolic function.

ARBs versus ACE inhibitors

Current evidence for the benefit of ARBs versus ACE inhibitors is limited to the results of two relatively small studies that compared an ARB directly to an ACE inhibitor.

ELITE

The Evaluation of Losartan in the Elderly Study (ELITE), was a pilot study designed to evaluate the safety and efficacy of losartan compared with that of the ACE inhibitor captopril in ACEI-naive elderly patients with CHF.[21] Of note, patients were admitted to the study as ACEI-naive if they had been on ACEI for < 7 days. Seven hundred and twenty-two patients with NYHA class II to IV symptoms were randomized to losartan 50 mg daily or captopril 150 mg daily. The primary endpoint was renal function (a persistent increase in serum creatinine ≥ 26.5 µmol/L). The secondary endpoint was composite of death and/or hospitalization for heart failure. After 48 weeks, there was no difference between groups in the frequency of sustained rise in serum creatinine, the primary endpoint of the trial (10.5% in both groups). Nevertheless, tolerability was significantly better in the losartan-treated patients, with fewer patients discontinuing the medication early (12%) than in the captopril-treated patients (21%). Although there was no significant difference in the composite secondary endpoint, one unexpected finding was a significant difference in total mortality (4.8% in the losartan group, 8.7% in the captopril group (RR 0.54, CI, 0.31-0.95, p=0.035). This difference was primarily due to a reduction in sudden death. To confirm these findings, the ELITE-II study with total mortality as the primary endpoint has just been completed and the results will be available in November 1999.

RESOLVD

In the pilot study, the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial, 768 patients with NYHA II to IV symptoms and LVH fraction < 40% were randomized to candesartan cilexetil alone (4, 8, or 16 mg), combination therapy (candesartan 4 or 8 mg with enalapril 20 mg daily), or enalapril 20 mg daily. The primary endpoints were six-minute walk distance, safety, tolerability, neurohormonal status, left ventricular ejection fraction, and quality of life. There were no significant differences between candesartan cilexetil and enalapril on most of the endpoints. Candesartan cilexetil and enalapril were equally well-tolerated.[22]

SPICE

Clinicians encounter a considerable number of patients with CHF who are intolerant to ACE inhibitors. The management of these patients at present is mostly empirical. The Study of Patients Intolerant of Converting Enzyme inhibitors (SPICE) was designed to assess the effects of the ARB candesartan cilexetil in such patients.[23] Two hundred and seventy patients who could not tolerate ACE inhibitors were randomized in a 2:1 ratio to candesartan (4, 8, or 16 mg) or placebo. The median age of these patients was 67 years, 71% had heart failure due to coronary artery disease, and NYHA functional class was II for 54 % and III for 41%. The intolerance was due to cough, hypotension, and renal dysfunction in 67%, 15%, and 11% of the patients, respectively. The primary endpoint of the pilot study was tolerability, while the secondary endpoints included safety, clinical events, functional status, and quality of life. The overall result was that candesartan cilexetil was well tolerated; the assigned treatment was continued to 12 weeks in 82.7% of patients given candesartan, compared to 86.6% of patients given placebo (difference not significant). The results of SPICE indicate that patients who are intolerant of ACE inhibitors can tolerate treatment with candesartan cilexetil. This supports further studies of ARBs in patients with CHF who cannot tolerate ACE inhibitors. This question is currently being addressed in the CHARM study.

ARBs in combination with ACE inhibitors

Combined therapy with ARBs and ACE inhibitors is theoretically appealing since the combination potentially produces more complete blockade of the RAAS, while at the same time, preserves bradykinin, an important mechanism for the benefit of the ACE inhibitors.

RESOLVD

The only study that has reported the effect of combination therapy is the RESOLVD study discussed earlier. This study found that the combination of enalapril and candesartan was more effective in suppressing plasma aldosterone and natriuretic peptide levels (BNP), improving left ventricular ejection fraction, preventing the increase of ventricular volumes and the reduction in arterial pressure than either agent alone.[22] All three regimens were well tolerated. There were no differences between the three groups in incidences of deaths and hospitalizations although the study was not designed to assess clinical events.

The results of RESOLVD support further studies of combined ACE inhibitor and ARB therapy in CHF. Indeed, these studies are currently underway. The Valsartan Heart Failure Trial (Val-HeFT) study is expected to include over 5000 patients with symptomatic CHF and systolic dysfunction. At baseline, patients are already optimized on ACE inhibitor therapy. They are then randomized to valsartan or placebo, with the background (open-label) therapy on ACE inhibitors. The primary endpoint is mortality. Target events are 906 deaths; expected completion date is 2002.

CHARM

As mentioned earlier, CHARM is a large outcome study designed to define the clinical benefits of candesartan cilexetil in a broad spectrum of patients with symptomatic left ventricular dysfunction. CHARM is unique because it will evaluate patients with heart failure and preserved systolic function, as well as reduced left ventricular ejection fraction. This trial will recruit 6,500 patients from 26 countries and will integrate three distinct clinical trials involving different patient groups as follows:

- patients with reduced left ventricular ejection fraction (LVEF ≤40%) who cannot tolerate ACE inhibitors;
- patients with LVEF ≤40% and treated with an ACE inhibitor (combination therapy);
- patients with preserved left ventricular function (LVEF >40%) who are not treated with an ACE inhibitor.

In each of the study arms, patients will be randomized to treatment with either candesartan cilexetil or placebo. The primary objective of each of the three trials is to examine the effects on the combined endpoint of cardiovascular mortality or heart failure hospitalization. The program is designed so that the three studies can be combined to evaluate the effect of candesartan cilexetil on all-cause mortality. CHARM will therefore have the ability to address the question of whether candesartan can meet the need for a better therapy in different subgroups of patients with CHF. This is the largest investigation to be conducted in patients with CHF. The average follow-up will be 2.7 years. The study, which is recruiting rapidly and is ahead of schedule, is anticipated to complete randomization in 2000, and terminate in 2002 with results available by the second quarter of 2003.

ARBs post-MI

The role of ARBs in patients with left ventricular dysfunction and/or CHF following acute MI is also being actively investigated. OPTIMAAL will randomize about 5000 of these high-risk patients to losartan or captopril. The study will go on until 937 deaths have occurred, with a minimum follow-up of six months. The primary end point is all-cause mortality. The conclusion of this study is expected in 2000. The VALIANT trial addresses the same high-risk post-MI patient population. This study has three randomization arms: valsartan, valsartan and captopril, and captopril. Target event is 2700 deaths. Expected completion date is 2002 to 2003.

AT_1 receptor blockade: Possibilities

Extensive evidence has documented the role of angiotensin II in the pathogenesis of cardiovascular disease. As reviewed earlier, the efficacy of ACE inhibitors in the treatment of hypertension, CHF, and diabetic nephropathy has been well documented. The ARBs are also effective in the treatment of hypertension, and the preliminary data in CHF are encouraging. There is now ample evidence to suggest that angiotensin II contributes to the pathogenesis of vascular disease through a variety of mechanisms. The relationship between angiotensin II and oxidative stress has been reviewed earlier.[2] Angiotensin II enhances macrophage lipid peroxidation both *in vitro* and *in vivo*.[3] This effect seems to be dose-dependent and involves the binding of angiotensin II to its receptor on the macrophage surface. Angiotensin II can also increase the activity of the macrophage-oxidized LDL receptors, which

bind to LDL and lead to the formation of a modified lipoprotein, which is then taken up by macrophages at an enhanced rate through the scavenger receptors. Administration of an ACE inhibitor reduces LDL peroxidation in patients with hypertension and in atherosclerotic apo E deficient mice. In these mice, the reduced LDL peroxidation is associated with a marked reduction of the atherosclerotic lesion area. A similar effect was seen in these mice with the ARB, losartan, suggesting that an ARB can retard the process of atherosclerosis.

Other links between angiotensin II and atherosclerosis may include the expression of vascular inflammatory genes such as the vascular cell adhesion molecule (VCAM-1). In rats infused with norepinephrine or angiotensin II, only the angiotensin II infused rats exhibited increases in aortic VCAM-1 protein and mRNA expression.[24] Oral losartan abolished the hypertensive response as well as the VCAM-1 expression. Angiotensin II has now also been shown to increase inflammatory signals in vascular smooth muscle cells (VSMC). In human VSMC, angiotensin stimulated interleukin-6 (IL-6) production, this effect was abolished by the administration of losartan.[25] Furthermore, the proinflammatory transcription factor, nuclear factor kappa B, which is necessary for transcription of most cytokine genes, was also increased by angiotensin II. Therefore, inflammatory activation of the blood vessel wall appears to be yet another mechanism for the pro-atherogenic effect of angiotensin II.

As reported in a prior *Scientific Update*, the recently presented HOPE study has demonstrated that the ACE inhibitor ramipril reduces cardiovascular events in high risk patients. Since the AT_1 receptor mediates most of the pathological vascular actions of angiotensin II, there is a strong probability that ARBs will be of value to patients at risk for cardiovascular events.

In summary, theoretical, experimental, and early clinical studies suggesting the possibility of the beneficial use of ARBs in a variety of cardiovascular diseases, as well as their proven efficacy in hypertension, promise that this class of agents will be an important therapeutic modality in the new millennium.

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