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The emerging role of angiotensin receptor blockers in the therapy of chronic heart failure

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Blockade of the renin-angiotensin-aldosterone system (RAAS) is the most established therapeutic approach in the management of patients with heart failure. Within this approach, the angiotensin-converting enzyme (ACE) inhibitors (ACEIs) reduce mortality and morbidity and have been the cornerstone of therapy of patients with left ventricular dysfunction and heart failure for nearly two decades. Increasing evidence, however, supports an important role of non-ACE mediated pathways for the generation of angiotensin II (Ang II). As a result, Ang II production persists despite ACE inhibition, which then may explain the persistently high event rate in patients with heart failure despite therapy with ACEIs. The Ang II receptor blockers (ARBs) theoretically produce a more complete blockade of Ang II generation; these agents, either alone or in combination with ACEIs, by blocking Ang II from all sources, may be superior to ACEIs. Clinical experience with the use of ARBs in heart failure is still emerging. This review will summarize the relevant background information and data from recently completed and ongoing outcome studies on the use of ARBs as well as their therapeutic implications for patients with chronic heart failure.

Chronic heart failure represents a major public health problem in industrialized nations. In the United States, heart failure accounts for 40,000 deaths and close to one million hospital admissions annually.[1] One of the hallmarks of heart failure is a relentlessly progressive clinical course manifested as repeated emergency room visits and hospital admissions, as well as a high mortality in afflicted patients.[2,3] Accordingly, the design of novel therapies that will favorably alter the progressive course of heart failure is of great importance.

The RAAS and the progression of heart failure

There is convincing evidence that the RAAS plays a crucial role in the pathogenesis and progression of heart failure. One of the end products of RAAS, Ang II, is known to exert several deleterious effects on the cardiovascular system via the stimulation of the type-1 Ang II (AT_1) receptor. These effects of Ang II include vasoconstriction, water and sodium retention, myocyte and smooth muscle hyperplasia, myocardial and vascular wall fibrosis, direct myocardial cytotoxic effects, altered gene expression and increased levels of plasminogen activator inhibitor-1.[4-11] In addition, Ang II also potentiates the activity of other neurohormonal systems such as the sympathetic nervous system, arginine vasopressin, aldosterone, and endothelin,[4,12,13] all of which can exert some of the deleterious effects described above. Finally, increased Ang II may stimulate oxygen free radical formation and therefore exacerbate oxidative stress.[14] Increased free oxygen radicals accelerate the consumption of nitric oxide (NO),[15] while at the same time, NO may be reduced because of increased breakdown of bradykinin, with attendant loss of its beneficial counter-regulatory effects.[4] These effects of Ang II over time induce adverse cardiac remodeling characterized by left ventricular (LV) dilatation, hypertrophy, and changes in chamber configuration, all of which predispose to progression of LV dysfunction and the heart failure phenotype.

Inhibition of the RAAS: Rationale for angiotensin receptor blockade therapy in heart failure

ACEIs have been a cornerstone of therapy for patients with LV dysfunction and heart failure for close to two decades. The benefits of ACEIs have been demonstrated in patients post myocar-

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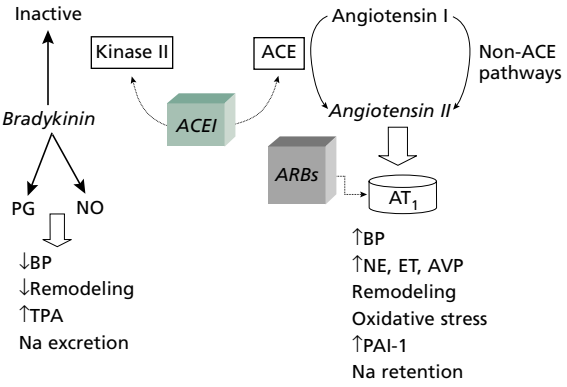
Figure 1: Site of action of ACEIs and ARBs



AVP, arginine vasopressin; BP, blood pressure; ET, endothelin; NE, norepinephrine; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PG, vasodilator prostaglandins; TPA, tissue plasminogen activator

dial infarction (MI)[16,17] and in patients with LV dysfunction, ranging from those who are asymptomatic to those with advanced symptoms of heart failure.[18-20] In these patient populations, the treatment benefits include improved LV function, relief of symptoms, decrease in hospitalizations, and improvement of survival. A great majority of these benefits may be related to the ability of ACEIs to retard LV remodeling.[21]

In addition to blocking the formation of Ang II through the ACE pathway, ACEIs also prevent the breakdown of bradykinin, which by itself or through release of NO, exerts vasodilator and antitrophic properties (Figure 1). Indeed, data from experimental models of heart failure have attributed the beneficial hemodynamic and anti-remodeling effect of ACEIs to increased bradykinin.[22,23] On the other hand, increased bradykinin has also been purported as a mechanism for some of the common side effects of ACEIs, such as cough and angioneurotic edema.[24]

Despite their established role in the treatment of heart failure, ACEIs have not completely solved the problem: patients are plagued with persistent or recurrent severe symptomatic episodes and mortality rate remains high. In some patients with heart failure, plasma Ang II levels return to pre-treatment levels or remain persistently elevated despite ACE inhibition and this phenomenon is associated with clinical deterioration or a lack of response to therapy.[25] Indeed, a recent study in patients with heart failure has demonstrated that even maximally recommended doses of ACEIs (eg, 150 mg of captopril) do not completely prevent ACE-mediated formation of Ang II, as measured by the pressor response to ascending doses of angiotensin I (Ang I).[26] These phenomena can be explained by the presence of functional non-ACE mediated enzyme pathways capable of catalysing the conversion of Ang I to Ang II.[27] As shown in Figure 1, these enzymes include human heart chymase, cathepsin G, and trypsin. Since ACEIs do not seem to offer complete protection against the detrimental effects of Ang II, the Ang II receptor blockers (ARBs), by blocking the AT_1 receptors that mediate nearly all of the known harmful effects of Ang II, may offer advantages relative to ACEIs. On the other hand, by not preventing the breakdown of bradykinin, the ARBs may be less efficient than ACEIs, at least for LV anti-remodeling, even though ARBs could be devoid of the presumed bradykinin-mediated side effects of ACEIs.

ARBs in the treatment of heart failure

The theoretical basis for the use of ARBs in the treatment of heart failure is buttressed by emerging clinical findings in patients with heart failure. Initial short-term studies comparing ARBs (mostly losartan) with placebo have demonstrated that ARBs are well tolerated and exert beneficial hemodynamic effects, but appear to confer little benefit on surrogate endpoints such as exercise tolerance and neurohormonal activation when compared with ACEIs.[28-31] There has been only one study that has reported beneficial effects of an ARB on exercise tolerance when compared to placebo.[32] In the STRETCH study, conducted in 844 patients with heart failure and New York Heart Association (NYHA) functional class II and III symptoms, the ARB candesartan cilexetil was found to produce a dose-dependent improvement in exercise time and Dyspnea Fatigue Index score when compared to placebo. Whether this longer-lasting hemodynamic effect will be transcribed to a reduction of clinical events in patients with heart failure is unclear and needs to be confirmed in large-scale studies. However, with the exception of specific patient population or subgroup analyses from large outcome trials, it is highly unlikely that any further data comparing ARBs and placebo in the *absence* of background therapy ACEIs will be forthcoming.

Are ARBs better than ACEIs in improving clinical outcomes in heart failure?

To date there is only one trial that directly compared the effect of an ARB vs ACEI on hard clinical outcomes such as total mortality. The Losartan Heart Failure Survival Study (ELITE II) was a multicentre, multinational, double-blind, randomized study comparing losartan (50 mg daily) with captopril (150 mg daily) in patients with heart failure and systolic left ventricular dysfunction.[33] Over 3000 patients were recruited from 289 sites in 46 countries. The *primary* objective of ELITE II was to test the hypothesis that losartan was superior to captopril in reducing total mortality.

The results of ELITE-II have been reported in a previous issue of *Cardiology Scientific Update*. There was no significant difference in all-cause mortality between the captopril (15.9%) and losartan groups (17.7%, p=0.16). No difference was observed in sudden death, death due to heart failure, MI, stroke, or non-cardiovascular death between the two arms. Analysis of pre-specified subgroups

that included age, gender, NYHA functional class, and ejection fraction did not suggest that any particular subgroup benefited more or less with either drug. For the secondary and combined endpoints, there was no significant difference in the incidence of sudden death/resuscitated cardiac arrests between the captopril and losartan groups, although there appeared to be a trend favoring captopril. There was no significant difference in all-cause hospitalization, or hospitalization due to heart failure, MI, or stroke/transient ischemic attack. Furthermore, there was no significant difference in the combined endpoint of all-cause mortality and all-cause hospitalization. Finally, heart failure-related events, including hospitalization, death, or discontinuation of drugs, were similar in both groups. Tolerability was significantly better with losartan. A higher number of patients on captopril discontinued the study drug due to an adverse event. The incidence of cough was also significantly lower in the losartan group.

The only hard conclusion one can draw from the ELITE-II study is that, at the dose used in the study, losartan is no better than captopril. The trial was not powered to test for equivalence and therefore does not prove that losartan and captopril are equally effective. One frequently cited concern of the study is that the dose of losartan utilized in the study might have been too low, thereby underestimating the true benefits of losartan. However, hemodynamic studies discussed earlier do not appear to support such a notion.[29] Accordingly, the ELITE-II study has only partially clarified the role of ARBs for the treatment of heart failure.

Does combined ARB and ACEI therapy improve clinical outcomes in heart failure?

As discussed earlier, Ang II production may persist despite ACE inhibition in a great many patients with heart failure, whereas the ARBs may not enhance bradykinin like the ACEIs. Based on these considerations, a theoretically appealing therapeutic approach therefore would be to combine an ACE inhibitor with an ARB. Two pilot studies first explored the therapeutic potential of this approach. In a hemodynamic study, the ARB valsartan was shown to exert beneficial and incremental hemodynamic and neurohormonal effects in patients with heart failure who were already taking ACEIs, including a dose of lisinopril administered in the morning of the hemodynamic study to ensure sustained ACE inhibition.[34] The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study compared the effects of an ARB, candesartan, an ACEI, enalapril, and their combination in a cohort of 768 patients with symptomatic heart failure.[35] The primary goal was to compare the effects of the different regimens on exercise performance, ventricular function, quality of life, neurohormones and tolerability. A secondary goal was to identify the optimal dose of candesartan. The principal findings were the absence of any significant differences between therapies in exercise tolerance, NYHA functional class or quality of life. Of interest, however, was the observation that the combination of candesartan and enalapril decreased arterial blood pressure more than candesartan or enalapril monotherapy, and prevented increases in LV volumes that occurred with the two monotherapies. Combination therapy also had favorable effects on neurohormonal parameters, with reductions observed in plasma natriuretic peptides and aldosterone levels. There was, however, a trend toward a greater number of clinical events in the candesartan or combination groups compared to the enalapril group; however, the study was not designed to assess clinical outcomes. Nevertheless, the results of both pilot studies provided a solid rationale for the following large-scale outcome trials.

The Val-HeFT Study

The Valsartan Heart Failure Trial (Val-HeFT) was designed to test the hypothesis that the ARB valsartan produces a further improvement in clinical outcomes in patients with heart failure who are treated with ACEIs. Five thousand and ten patients with symptomatic heart failure and LV ejection fraction (LVEF) less than 40% accompanied by LV chamber enlargement were recruited from 300 centers in 16 countries. All patients were expected to be on optimal dose of ACEIs. Patients were randomized in a force-titration fashion to placebo or valsartan, 160 mg twice daily (2 to 4 times the dose used in hypertension). There were *two* pre-specified primary outcomes: time to death *and* time to first morbid event which included death, sudden death events with resuscitation, hospitalizations for heart failure, and requirement of intravenous inotropic or vasodilating agents for worsening heart failure. Secondary outcomes included changes from baseline in NYHA functional class, signs and symptoms of heart failure, LVEF, LV diastolic internal diameter, quality-of-life scores, and neurohormonal parameters.

The results of Val-HeFT have been reported in a recent issue of *Cardiology Scientific Update*. The two study groups were comparable in baseline demographics. The ratio of men to women was about 4:1 and 90% of subjects were white. Ischemic etiology constituted 57% of the patients with the majority with NYHA class II (62%) and class III (36%) symptoms. Eighty-five percent of patients were on treatment with diuretics, 67% on digitalis, 35% on β-blockers, and 93% on ACE inhibitors at doses recommended by current guidelines. The average dose of the study medication achieved was 254 mg per day. Data from the primary and key secondary outcomes are shown in Table 1. All-cause mortality was similar for the two treatment groups. However, the valsartan-treated group had a significant 13% reduction in combined all-cause mortality and morbidity. The reduction of this combined primary endpoint was accounted for mostly by a reduction in heart failure hospitalization. As demonstrated in Table 1, heart failure hospitalization was reduced by 28% in the valsartan group and this reduction was highly significant. Signs and symptoms of

Table 1: Val-HeFT Study Endpoints				
Primary endpoints	Valsartan n=2511	Placebo n=2499	Risk ratio (95% C.I.)	P-value
All-cause mortality	494 (19.7%)	484 (19.4%)	1.02 (0.9, 1.15)	0.8
All-cause mortality + morbidity	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.96)	0.009
Secondary endpoints	Valsartan n=2511	Placebo n=2499	Risk ratio (95% C.I.)	P-value
Heart failure hospitalization	349 (13.9%)	463 (18.5%)	0.73 (0.63, 0.83)	0.00001

heart failure, quality-of-life, and LVEF were all significantly improved by valsartan with no excessive adverse effects. In the analysis of pre-specified subgroups, the point estimates trended favorably for valsartan for most of the subgroups, indicating a treatment benefit from valsartan on the combined endpoint, regardless of age, gender, LVEF, or heart failure etiologies. However, for the 7% of patients who were not taking ACEIs, the benefit derived from valsartan was greater than for the patients who were taking ACEIs (this is not an analysis on a pre-specified subgroup).

On the other hand, the opposite trend was observed with the use of β-blockers. A treatment benefit was observed in the 65% of the patients not treated with β-blockers, whereas the point estimate actually favored placebo in the 35% of patients treated with β-blockers. This unfavorable trend for valsartan on patients taking β-blockers, however, was not significant as the 95% confidence intervals crossed unity and were present only in patients taking ACEIs.

Val-HeFT was a well-designed study and, after ELITE-II, was the second major outcome trial of ARBs in heart failure. Val-HeFT demonstrated that an ARB such as valsartan is a well-tolerated and effective treatment for reducing heart failure hospitalizations in patients with moderate heart failure (annual placebo mortality rate of 9%) already on optimal therapy, including ACEIs. The beneficial effect on clinical outcome is accompanied by concurrent and consistent improvements in signs and symptoms of heart failure, quality-of-life, and LVEF. The differential response of the small number (35%) of patients who were on β-blockers not manifesting the benefits that were observed in the overall program is particularly interesting and hypothesis-generating. Indeed, the interesting findings of Val-HeFT heighten the importance of the third and ongoing outcome trial of ARBs in heart failure, namely the CHARM study.

The CHARM and SPICE Studies

Although commonly encountered in clinical practice,[36] patients with heart failure and preserved systolic function have not been studied systematically; currently their treatment has remained largely empirical.[37] Similarly, clinicians frequently encounter patients with heart failure who are intolerant of ACE inhibitors. These patients are therefore denied the benefits of ACEIs. At present, there are still no large-scale studies (including the ELITE-II study) that have documented equivalence of the effect of ARBs and ACEIs on clinical outcomes in heart failure. Therefore, the practice of substituting an ACEI with an ARB in patients who are intolerant to ACEIs is not based on undisputed evidence.

SPICE

To this end, the pilot Study of Patients Intolerant of Converting Enzyme inhibitors (SPICE) was designed to assess the effects of the ARB, candesartan cilexetil, in such patients.[38] In the SPICE registry,[39] 9580 patients with LVEF < 35% were surveyed in 105 centres from 8 countries between 1996-1997. Nine percent of patients were withdrawn from ACEIs due to intolerance from cough, renal insufficiency, or hypotension. In the SPICE study,[38] 270 patients, intolerant to ACEIs, were randomized in a 2:1 ratio to candesartan (4, 8, or 16 mg) or placebo. The median age was 67 years and 71% had heart failure due to coronary artery disease. The percentage of patients with NYHA functional class II was 54%, while 41% were class III. 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 to ACE Is can tolerate treatment with candesartan cilexetil and support further studies of ARBs in patients with heart failure who are intolerant to ACEIs.

CHARM

CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) is a large outcome study that will define the clinical benefits of the ARB blocker candesartan cilexetil in a broad spectrum of patients with symptomatic heart failure. CHARM is unique because it is the first large-scale study to evaluate patients with heart failure and

Figure 2: Patient Characteristics

	Val-HeFT	CHARM (Study Arm 006)
NYHA Class (%)		
II	62	24
III	36	73
IV	1.7	3
EF (%)	27	28
Age (years)	62	64
Male (%)	80	79
Digoxin (%)	67	58
Beta blocker (%)	34	55
Spironolactone (%)	2	17
Diuretics (%)	85	90

preserved systolic function (in addition to those with reduced LVEF), as well as patients who are intolerant to ACEIs. This trial will recruit approximately 7450 patients from 26 countries and will consist of 3 integrated clinical trials involving different patient groups as follows:

- Patients with reduced LVEF (≤40%) who are intolerant to ACEIs (Study Arm 003)
- Patients with LVEF ≤40% treated with ACEIs (combination therapy) (Arm 006)
- Patients with preserved LV function (LVEF >40%) (Arm 007)

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 such that the 3 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 whether candesartan can meet the need for a better therapy in different subgroups of patients with heart failure and, hopefully, overcome some of the limitations of presently available therapies. CHARM may also address some of the issues not addressed or raised by the Val-HeFT study. A preliminary comparison of patient characteristics of the Val-HeFT and CHARM is shown in Figure 2. It is quite likely that CHARM will address a sicker heart failure patient population with a higher number of patients on β-blockers and spironolactone, more reflective of contemporary practice.

CHARM will be the largest investigation to be conducted in patients with heart failure. The first patient was recruited in March, 1999. Recruitment has been ahead of schedule and is completed for Study Arms 006 and 007. The average follow-up will be 2.5 years. It is anticipated that randomization for the entire program will end in 2001, the study will end in the third quarter of 2002 and results will be available at the second quarter of 2003.

Conclusion

The role of the ARBs in the treatment of heart failure continues to evolve as more and more data become available. Studies to date indicate that these agents are at least as good as ACEIs in improving the hemodynamics and symptoms of heart failure and that they are much better tolerated than ACEIs. Large-scale outcome trials to date, however, have indicated that some ARBs, such as losartan, are no better than ACEIs in improving mortality. The combined use of ARBs and ACEIs is theoretically appealing and appears to produce further beneficial effects on hemodynamics and cardiac remodeling, as well as symptom relief, while reducing hospitalizations due to heart failure, but with no benefit on total mortality. The ongoing CHARM study will hopefully further address the issues of total and cardiovascular mortality, demonstrate interactions with other forms of neurohormonal blockade, and help optimize the therapy of patients with heart failure and preserved systolic function, as well as those who are intolerant to ACEIs.

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