AT₁-receptor blockers in hypertension and heart failure: clinical experience and future directions

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Introduction

In various manifestations of cardiovascular disease, blockade of the renin–angiotensin system by angiotensin converting enzyme (ACE) inhibitors has been shown to prevent or delay disease progression effectively and improve prognosis in terms of mortality and morbidity. Angiotensin type 1-receptor (AT₁-receptor) blockers, on the other hand, are used for more specific and efficacious blockade of the renin–angiotensin system, by blocking the deleterious effects of the activated renin–angiotensin system selectively and effectively at the receptor level. The introduction of this pharmacological principle is in line with the general development of more refined drug interaction with biological systems. Several AT₁-receptor blockers are available, and those currently accessible for clinical use are listed in Table 1.

Pharmacological differences exist between AT₁-receptor blockers (Table 2), but no definite data indicate that these differences have clinical relevance. Indeed, according to the American Food and Drug Administration, there are no differences between AT₁-receptor blockers in terms of blood pressure lowering. However, recent results from studies in patients with heart failure using different AT₁-receptor blockers are conflicting, raising the question of whether clinically relevant differences might exist.

Losartan, first registered in Sweden in September 1994 for use in hypertension, is the first and, so far, the most extensively documented substance in this group. In many countries, several AT₁-receptor blockers have since become available for clinical use, including for the treatment of heart failure (Table 1). Clinical experience in general practice is extensive and AT₁-receptor blockers have been prescribed to several million patients worldwide. A substantial number of clinical studies on AT₁-receptor blockers have been performed in patients with hypertension and, to a somewhat lesser extent, in patients with heart failure. All AT₁-receptor blockers available for clinical use have adequate blood pressure lowering effects, are extremely well tolerated and have a good safety record. Mortality and morbidity studies on several thousand patients with hypertension, heart failure, diabetes with renal failure, and post myocardial infarction, are currently ongoing using various AT₁-receptor blockers. Since AT₁-receptor blockers for the treatment of cardiovascular disease seem very promising and appear to have come to stay this review will document their current clinical use in hypertension and heart failure, and also summarize ongoing clinical trials in the field.

Inhibition of the renin–angiotensin system

The importance of neurohormonal activation in the development and progress of cardiovascular disease processes such as myocardial remodelling is well known, and the renin–angiotensin system plays a central role in this[1–8]. The end product of the renin–angiotensin system, angiotensin II, exerts a number of harmful effects on the cardiovascular system via the AT₁-receptor (Table 3).

Angiotensin II potentiates the activity of other neurohormonal systems and thereby exerts harmful cardiovascular effects, contributing to the remodelling process. Sympathetic adrenergic system activation is facilitated, and the release of vasopresin/anti-diuretic hormone, aldosterone, and endothelin is enhanced[4–6]. In addition, free oxygen radicals are formed as a consequence of increased angiotensin II levels, thereby accelerating the consumption of nitric oxide[9]. Concomitantly, nitric oxide levels are decreased due to increased breakdown of bradykinin[10], and the positive effects of nitric oxide, crucial to vascular function, are diminished[9,11]. The effects of nitric oxide are listed in Table 4.

Key Words: Angiotensin type-1 receptor blockers, hypertension, heart failure, review.


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Figures 1 and 2 illustrate the principles of ACE inhibition and AT₁-receptor antagonism. Experimental studies have shown that ACE inhibitors, besides inhibiting the formation of angiotensin II, could have desirable effects by decreasing the breakdown of bradykinin\[12\]. The auto-/paracrine effects of bradykinin are shown in Table 5.

One important problem with long-term ACE inhibition is that after some time plasma levels of angiotensin II return to pre-treatment levels, at least in some patients\[13,14\]. This phenomenon occurs despite the fact that circulating ACE is effectively blocked and appears to be related to the progress of the cardiovascular disease\[14\]. Furthermore, in healthy volunteers it has been shown that angiotensin II levels increase after exercise despite effective blockade of ACE activity\[15\]. The formation of angiotensin II, despite effective ACE inhibition, may be explained by the activity of alternative enzymes capable of catalysing the conversion of angiotensin I to angiotensin II\[16\]. One such enzyme, which may be potentially important in humans, is human heart chymase\[17\]. Other enzymes known to catalyse this conversion include cathepsin G, and trypsin. Another reason why suppression of angiotensin II is insufficient during ACE inhibition may be because tissue ACE, for example in the myocardium, may not be effectively inhibited. Since ACE inhibitors do not seem to offer complete protection against the detrimental effects of angiotensin II, AT₁-receptor blockers may offer advantages relative to ACE inhibitors by effectively blocking the AT₁-receptor, which mediates all known harmful effects of angiotensin II.

On the other hand, by not inhibiting the breakdown of bradykinin AT₁-receptor blockers may be less efficient than ACE inhibitors. However, experimental studies indicate that bradykinin may cause increased release of norepinephrine from sympathetic nerves in the ischaemic myocardium, thereby causing harm\[18,19\]. Thus, it may be beneficial not to inhibit the breakdown of bradykinin, as in the case of AT₁-receptor blockade. Conversely, the negative chronotropic effect of bradykinin, mediated by intrinsic cardiac cholinergic neurons, endows bradykinin with the capacity for cardioprotection, especially since this effect is further pronounced as a response to catecholamine-induced tachycardia\[20\]. It is therefore difficult to say whether bradykinin is advantageous or harmful in this context.

<table>
<thead>
<tr>
<th>Countries (n)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Losartan</td>
<td>X</td>
</tr>
<tr>
<td>Valsartan</td>
<td>X</td>
</tr>
<tr>
<td>Candesartan</td>
<td>31</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>38</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>26</td>
</tr>
</tbody>
</table>


Table 1 AT₁-receptor blockers available for clinical use worldwide by 1 October 1998

The mode of receptor antagonism may vary depending on the model used.
Experimental studies indicate that angiotensin II may have desirable effects through stimulation of the AT₂-receptor\[21–23\] (personal communication 1998, T Unger, Kiel, Germany) (Table 6), which is upregulated in certain pathological conditions which have undergone tissue damage\[1,24\]. During treatment with a selective AT₁-receptor blocker, the AT₂-receptor is left unblocked and is therefore susceptible to stimulation by angiotensin II. At the same time, ACE is not inhibited and can catalyse the conversion of angiotensin I to angiotensin II. Furthermore, the negative feedback on the formation of renin, normally seen due to stimulation of the AT₁-receptor by angiotensin II, is lost, resulting in increased levels of angiotensin II and intense stimulation of the AT₂-receptor.

Several experimental studies indicate that nitric oxide production may be increased during AT₂-receptor stimulation\[25–29\], and although this may be achieved through some bradykinin-dependent mechanism\[25,27\], bradykinin levels seem not to be increased (Fig. 2). Experimental studies indicate that the peptide angiotensin(1–7) may be formed from both angiotensin I and II, through the actions of endopeptidase\[30\]. This peptide may cause nitric oxide to increase via stimulation of a specific AT₁,γ-receptor or the AT₂-receptor. Furthermore, through the AT₁-receptor, angiotensin II causes formation of superoxide that can degrade nitric oxide\[31\]. Consequently, during AT₁-receptor blockade more nitric oxide is available since superoxide formation is decreased. Thus, it seems that the increased activity of nitric oxide seen with ACE inhibitor treatment is also present during treatment with AT₁-receptor blockers. Based on experimental findings, AT₁-receptor blockers therefore have the potential to counteract the deleterious consequences of neurohormonal activation seen in cardiovascular disease more effectively than ACE inhibitors.

**AT₁-receptor blockers in the treatment of hypertension**

In clinical studies, AT₁-receptor blockers have been shown to lower blood pressure as effectively as...
other antihypertensive agents such as beta-receptor blockers, diuretics, calcium-channel blockers, and ACE inhibitors[32–50] (Table 7). It usually takes 4 to 6 weeks to achieve a full blood pressure lowering effect. The addition of a small dose of a thiazide diuretic improves the blood pressure lowering effect[37,44,47,55,56].

There are some data indicating potential differences between various AT1-receptor blockers as regards blood pressure lowering efficacy. In a study by Andersson et al.[57] in patients with mild to moderate hypertension the effect on diastolic blood pressure at trough was slightly but significantly more pronounced for candesartan 16 mg daily compared to losartan 50 mg daily. Candesartan 8 mg daily was equal to losartan 50 mg daily, and losartan 100 mg daily was not examined. In a study by Kassler-Taub et al.[58] 567 patients were randomized (1:1:1:1) to once-daily therapy with placebo, 100 mg losartan, 150 mg irbesartan, or 300 mg irbesartan for 8 weeks. Reductions from baseline in trough-seated diastolic blood pressure and trough-seated systolic blood pressure with 300 mg irbesartan were greater than with 100 mg losartan. Throughout the study, the antihypertensive effect of 150 mg irbesartan was the same as that of 100 mg losartan. Oparil et al.[59] found that irbesartan 150 to 300 mg . day $^{-1}$ ± hydrochlorothiazide had a slightly but significantly greater blood pressure lowering effect than losartan 50 to 100 mg . day $^{-1}$ ± hydrochlorothiazide, after 12 weeks.
Table 7  Blood pressure lowering efficacy comparing different AT₁-receptor blockers to enalapril

<table>
<thead>
<tr>
<th>AT₁-receptor blocker</th>
<th>n</th>
<th>Enalapril</th>
<th>n</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan 4–8 mg</td>
<td>80</td>
<td>10–20 mg</td>
<td>81</td>
<td>Equal</td>
<td>[46]</td>
</tr>
<tr>
<td>Candesartan 12 mg</td>
<td>65</td>
<td>10 mg</td>
<td>71</td>
<td>Equal</td>
<td>[51]</td>
</tr>
<tr>
<td>Irbesartan 75–300 mg</td>
<td>95</td>
<td>10–40 mg</td>
<td>96</td>
<td>Equal</td>
<td>[52]</td>
</tr>
<tr>
<td>Irbesartan 150–300 mg</td>
<td>103</td>
<td>20–40 mg</td>
<td>56</td>
<td>Equal</td>
<td>[53]</td>
</tr>
<tr>
<td>Losartan 50–100 mg</td>
<td>200</td>
<td>10–20 mg</td>
<td>199</td>
<td>Equal</td>
<td>[54]</td>
</tr>
<tr>
<td>Valsartan 80 mg</td>
<td>137</td>
<td>20 mg</td>
<td>69</td>
<td>Equal</td>
<td>[42]</td>
</tr>
</tbody>
</table>

treatment in a study of 370 patients with mild to moderate hypertension. In a study by Hedner et al. [60] in 1369 patients with mild to moderate essential hypertension, valsartan 80/160 mg was as well tolerated and as effective as losartan 50/100 mg in lowering mean sitting diastolic and systolic blood pressure, and valsartan 160 mg had a significantly higher responder rate than losartan 100 mg.

However, based on a meta-analysis adjusting for differences between studies with losartan, valsartan, candesartan, and irbesartan in hypertension, the American Food and Drug Administration concluded that there are no significant differences between AT₁-receptor blockers in terms of blood pressure lowering efficacy (U.S.A. FDA, product label).

The frequency of side effects is very low for AT₁-receptor blockers, and is equal to that of placebo. According to the Swedish Drug Administration, there are few reports of side effects, and serious reactions such as Quincke’s oedema, vasculitis, bronchospasm, severe neurological reactions, and severe psychiatric disorders, occur but are very uncommon. AT₁-receptor blockade has been reported to be safe and well tolerated even in hypertensive patients with chronic renal disease, including those on haemodialysis [61]. There is some indication that AT₁-receptor blockers might provide an advantage over other antihypertensive agents as regards quality of life. In a study by Dahlöf et al. [62] comparing losartan to amlodipine in 898 patients with mild-to-moderate hypertension, losartan was superior to amlodipine in terms of psychological general well-being after 12 weeks of treatment.

Hypertensive patients with left ventricular hypertrophy have a substantially increased risk of cardiovascular complications, including death, compared to hypertensive patients without left ventricular hypertrophy. The 5-year mortality in patients with hypertension and ECG signs of left ventricular hypertrophy may be as high as 30%, whereas it is around 1% in those with uncomplicated hypertension [63]. Activation of the renin–angiotensin system is believed to fundamentally contribute to the development of left ventricular hypertrophy [1]. In meta-analyses, ACE inhibitors have been shown to be superior to other antihypertensive drugs in terms of reduction of left ventricular hypertrophy, over and above the blood pressure lowering effects [64,65]. In a recent meta-analysis by Dahlöf et al. (unpublished data), almost 5000 patients and 245 studies performed up to the end of 1994 were included, many of which were performed using modern dihydropyridines. In this meta-analysis ACE inhibitors were still superior to other antihypertensive drugs in this context, although the inclusion of studies investigating modern dihydropyridines tended to improve the position of calcium channel blockers. Although this and other recent meta-analyses indicate that long-acting dihydropyridines might be as equally effective as ACE inhibitors in this regard [66,67], the effect on myocardial hypertrophy, beyond the blood pressure decrease, is believed to be attributed to the blockade of the cardiac renin–angiotensin system to a substantial degree [68]. Retrospective studies distinctly indicate a prognostic benefit from regression of left ventricular hypertrophy [69–72], but there are no prospective studies examining this relationship. Since AT₁-receptor blockers might be more efficacious than ACE inhibitors in blocking the deleterious effects of angiotensin II, for instance on the myocardium and vascular walls [1], they have the potential to be equal to or superior than ACE inhibitors in terms of regression of left ventricular hypertrophy and myocardial fibrosis. There are no available results from clinical studies comparing AT₁-receptor blockers and ACE inhibitors regarding regression of left ventricular hypertrophy.

However, there are some reports on comparisons between AT₁-receptor blockers and other antihypertensive agents in this context [73–77]. To date all such studies have lacked sufficient power to demonstrate any difference between AT₁-receptor blockers and other antihypertensive agents regarding the effect on left ventricular hypertrophy.

The role of substances which interfere with the renin–angiotensin system in the treatment of hypertension has yet to be definitely established since the effects of ACE inhibitors and AT₁-receptor blockers on morbidity and mortality in hypertension are largely undocumented. The only exception, so far, is the CAPPP (Captopril Prevention Project) study [78] in which the ACE inhibitor captopril was shown to prevent morbid and mortal cardiovascular events, equal to that of traditional treatment with diuretics and beta-blockers. The effects of AT₁-receptor blockers, in comparison to traditional antihypertensive therapy, on morbidity and mortality in hypertension are currently under investigation in large trials (Table 8).
Table 8  Ongoing trials assessing the effects of AT1-receptor blockers on mortality in hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Type of patients</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFE</td>
<td>Losartan</td>
<td>Left ventricular hypertrophy</td>
<td>9194 (recruited)</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan</td>
<td>At least one additional risk factor</td>
<td>14 400 (planned)</td>
</tr>
<tr>
<td>SCOPE</td>
<td>Candesartan</td>
<td>Age 70–89 years</td>
<td>4000 (planned)</td>
</tr>
</tbody>
</table>

LIFE=Losartan In hypertension For End-point reduction; VALUE=Valsartan Antihypertensive Long-term Use Evaluation; SCOPE=Study on COgnition and Prognosis in Elderly.

Ongoing trials with AT1-receptor blockers in hypertension

The LIFE trial

The LIFE trial \[79,80\] (Losartan In hypertension For End-point reduction) is the first study assessing the effect of an AT1-receptor blocker on mortality in patients with hypertension. The study is randomized and double-blind. Losartan is compared to atenolol in terms of effects on mortality, morbidity, and regression of left ventricular hypertrophy in patients with left ventricular hypertrophy at baseline, according to specific ECG criteria. The inclusion has been finalized with 9194 patients. The study is expected to be completed in 2001.

The VALUE trial

The VALUE trial\[81\] (Valsartan Antihypertensive Long-term Use Evaluation) is a randomized and double-blind study which will include 14 400 patients at least 50 years of age with hypertension plus at least one additional risk factor for cardiovascular mortality. The primary aim is to investigate the effect of valsartan in comparison to amlodipine on cardiac mortality, and secondary end-points include hospitalization for heart failure and myocardial infarction. The study is planned to be stopped when 1450 primary end-points have been reached, and is planned to run for around 4 years.

The SCOPE trial

The SCOPE trial (Study on COgnition and Prognosis in Elderly) will include 4000 patients between 70 and 89 years of age with a blood pressure of 160–179/90–99 and a Mini Mental score of more than 24. Patients will be randomized to treatment with candesartan cilexitil or placebo. The primary end-point is any major cardiovascular event, and secondary end-points include Mini Mental score and quality of life.

AT1-receptor blockers in the treatment of heart failure

Left ventricular systolic dysfunction, with or without symptoms of heart failure, is a very common condition. According to a population study from Scotland, almost 8% of individuals between the ages of 25 and 74 years have a left ventricular ejection fraction of less than 35%\[82\]. Since the prevalence increases with age this problem is certainly of even greater importance if the whole adult population is considered. Renin–angiotensin system inhibition by ACE inhibitors is recommended by the European Society of Cardiology\[83\] as the first line treatment in left ventricular systolic dysfunction (ejection fraction 35 to 40% or less) irrespective of symptoms of heart failure, and ACE inhibitors are also recommended to be considered in all patients with heart failure requiring treatment with diuretics. Consequently, as many as 10% of the adult population may be candidates for ACE inhibitor treatment. Despite the fact that the effects of ACE inhibitors on physical capacity, morbidity, and mortality in patients with left ventricular systolic dysfunction irrespective of symptoms of heart failure are well documented\[84–90\], these agents are used in less than 30% of patients with symptomatic heart failure in western society. In patients with asymptomatic left ventricular systolic dysfunction, they are most likely even more under-used. A factor strongly contributing to the low prescription of ACE inhibitors to heart failure patients is, according to a British investigation, a fear among physicians of possible side-effects, especially hypotension and renal failure\[91\]. Most likely, an agent relatively free of side-effects but similarly efficacious to ACE inhibitors would be used more widely. There is much to indicate that AT1-receptor blockers constitute an example of such a drug.

Short-term studies so far conducted in heart failure patients indicate that AT1-receptor blockers are well tolerated and have beneficial haemodynamic effects\[92–97\]. The clinical documentation of AT1-receptor blockers in heart failure patients, based on studies with losartan and irbesartan, suggests that AT1-receptor blockers are at least as efficacious as ACE inhibitors, whereas the side-effect profile is more favourable\[95–98\]. In the ELITE (Evaluation of Losartan In The Elderly) study\[99\], a long-term study on AT1-receptor antagonism in heart failure patients, 722 patients aged 65 years or more, with chronic symptomatic heart failure mainly caused by ischaemic heart disease, were examined. In patients treated with losartan (target dose 50 mg daily), all-cause mortality during 48 weeks of follow-up was 46% lower (P<0·05) than in those receiving captopril 50 mg three times daily. There was no difference between

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the two groups with respect to hospitalization for heart failure, whereas the rate of all-cause hospitalization was significantly lower in the losartan group. This study was not primarily designed to study the effects of losartan on mortality or hospitalization, but was designed to examine the effects of losartan on renal function, which was affected equally by losartan and captopril. Furthermore, since the number of deaths was small caution should be exercised as regards the effect of losartan on mortality in patients with heart failure. Based on these results, there is general agreement that patients who have an indication for ACE inhibitor treatment but who cannot tolerate this regimen are likely to benefit from treatment with losartan. Losartan is also registered in around 10 countries for treatment of heart failure.

In November 1997 the results from the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) study were presented at the American Heart Association meeting. The design of the study has been published[99]. The study included 769 patients with symptomatic heart failure. Patients were randomized into one of six arms: candesartan cilexetil in three different doses (4, 8, and 16 mg daily), a combination of candesartan in two different doses (4 and 8 mg daily) plus enalapril 10 mg twice daily, or enalapril 10 mg twice daily. Subsequently some of the patients were also randomized to additional metoprolol or placebo. The aim of the study was to assess the effects of the different treatment regimens on exercise capacity, safety and tolerability, neurohormones, ventricular function, quality of life and symptoms. It was not designed to study mortality. The study was interrupted prematurely after 43 weeks of follow-up on the grounds of a presumed negative effect of candesartan in comparison with enalapril. There were a greater number of cardiovascular events, including deaths, among patients treated with candesartan or the combination compared with those treated solely with enalapril (Table 9). These differences were, however, not statistically significant. The results of this study do not allow for conclusions regarding the effects of candesartan on mortality in patients with heart failure. However, these results appear to contradict the results of the ELITE study. This has caused a debate regarding potential differences between AT1-receptor blockers, and it has been suggested that a drug that blocks the AT1-receptor too effectively may even cause harm. The seemingly contradictory results of ELITE and RESOLVD might, however, be due to chance, and the only safe conclusion that can be drawn from these results is that large mortality studies with AT1-receptor blockers in patients with heart failure are very much needed before the role of AT1-receptor blockers in the treatment of heart failure can be finally established.

### Ongoing trials with AT1-receptor blockers in heart failure

There are three ongoing large trials investigating the effects of AT1-receptor blockers in patients with heart failure, using losartan, valsartan, and candesartan (Table 10). In addition, there are two trials investigating the effects of losartan and valsartan, respectively, in high-risk patients after myocardial infarction (Table 10).

### The ELITE II trial

To test the hypothesis that losartan is superior to captopril in terms of a reduction of mortality and morbidity in patients with heart failure, the losartan heart failure survival study, ELITE II, is currently being conducted. Elderly patients who have not previously been treated with an ACE inhibitor or an AT1-receptor blocker are randomized to either losartan 50 mg twice daily, or to captopril 50 mg three times daily. The study will go on until 510 deaths have occurred, and it is hypothesized that losartan will reduce mortality compared to captopril by at least 25%. The enrolment of patients was stopped by May 1998, when 3152 patients had been included. Results from this study are expected to be available by the end of 1999 or early 2000.

### The Val-HeFT trial

Sometime in 1999 the Val-HeFT (Valsartan Heart Failure Trial) study is expected to have included 5250 patients with heart failure, and it has been hypothesized that it could provide important information on the role of valsartan in the treatment of heart failure.

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**Table 9  Results of the RESOLVD study**

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>Candesartan (n=328)</th>
<th>Combination (n=332)</th>
<th>Enalapril (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6.1</td>
<td>8.7</td>
<td>3.7</td>
<td>0.148</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>13.1</td>
<td>9.3</td>
<td>7.5</td>
<td>0.136</td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>26.3</td>
<td>24.7</td>
<td>22.9</td>
<td>0.76</td>
</tr>
<tr>
<td>Death + hospitalization for heart failure</td>
<td>16.8</td>
<td>17.2</td>
<td>10.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Death + all hospitalizations</td>
<td>29</td>
<td>30</td>
<td>24</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Presented by Salim Yusuf at the American Heart Association meeting 11 November 1997. All patients treated with candesartan cilexetil in monotherapy constituted one group; all patients treated with the combination of candesartan cilexetil and enalapril constituted another group; those treated with enalapril alone constituted the third group.
patients with symptomatic heart failure as well as left ventricular systolic dysfunction and dilation. At baseline, patients will be on optimal treatment for heart failure, meaning that almost all patients will be treated with an ACE inhibitor. Since patients are randomized to valsartan or placebo, the study will primarily compare the effects on mortality and morbidity of a combination of an ACE inhibitor (open) and valsartan with that of an ACE inhibitor (open) alone. The hypothesis is that the valsartan group will show a 20% lower mortality rate compared to the placebo group. The study will go on until 906 deaths have occurred, and is expected to be concluded 2002.

**The CHARM trial**

The CHARM (Candesartan cilexitil in Heart failure Reduction in Mortality and morbidity) trial will investigate the effects of losartan compared to placebo in patients with symptomatic heart failure. It is powered for an approximate 20% reduction in the primary end-point cardiovascular mortality or heart failure hospitalization. It is divided in three parts. Part 1 will include 1700 patients with left ventricular ejection fraction 40% or less and intolerance to ACE inhibitors. Part 2 will include 2300 patients with left ventricular ejection fraction 40% or less, who are on treatment with an ACE inhibitor which will be continued during the study period. Part 3 will include 2000 patients with left ventricular ejection fraction above 40%. The study is expected to be completed in 2002.

**The OPTIMAAL trial**

The OPTIMAAL (Optimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan) trial will include 5004 patients after a myocardial infarction. Patients who have signs or symptoms of heart failure, and/or a left ventricular ejection fraction of 35% or less, and/or a left ventricular diameter of 65 mm or more, and/or Q-waves in anterior leads on the ECG may be included. Patients will be randomized to losartan or captopril. The study will go on until 937 deaths have occurred, which is expected to be some time at the end of 2002 or the beginning of 2003.

**Combined AT₁-receptor blockade and ACE inhibition**

Theoretically, it may be beneficial to combine AT₁-receptor blockade and ACE inhibition, especially if there is concern that AT₁-receptor blockade alone will not secure the positive effects of ACE inhibition deriving from a decreased breakdown of bradykinin. It is, however, also possible that combined therapy is less effective than AT₁-receptor blockade alone, because combined therapy may lead to formation of less angiotensin II, in turn causing less AT₂-receptor stimulation than would AT₁-receptor blockade alone. Furthermore, combined therapy will most likely cause the same side effects as ACE inhibition alone.

There are few reports from clinical studies with combined ACE inhibition and an AT₁-receptor blockade. Azizi et al. reported that combined therapy induced an additional mean blood pressure reduction in comparison to both monotherapy with an ACE inhibitor and an AT₁-receptor blocker alone, in 12 mildly sodium depleted normal subjects. In a 10 day study,

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Drug</th>
<th>Comparison</th>
<th>n</th>
<th>Powered for mortality reduction (%)</th>
<th>Expected concluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE II</td>
<td>Losartan</td>
<td>Captopril</td>
<td>3121</td>
<td>25</td>
<td>1999/2000</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>Valsartan (open ACE inhibitor)</td>
<td>Placebo (open ACE inhibitor)</td>
<td>5250 (planned)</td>
<td>15</td>
<td>2002</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan</td>
<td>Placebo (± open ACE inhibitor)</td>
<td>6000 (planned)</td>
<td>—</td>
<td>2002</td>
</tr>
<tr>
<td>OPTIMAAL</td>
<td>Losartan</td>
<td>Captopril</td>
<td>5004 (planned)</td>
<td>20</td>
<td>2000</td>
</tr>
<tr>
<td>VALIANT</td>
<td>Valsartan + captopril</td>
<td>Captopril</td>
<td>14 500 (planned)</td>
<td>comb: 15–17%</td>
<td>2002/2003</td>
</tr>
</tbody>
</table>

Table 10: Ongoing mortality trials with AT₁-receptor blockers in cardiac failure

Di Pasquale

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reported that combined ACE inhibition and AT1-receptor blockade was safe in 44 patients following a myocardial infarction. In a 6-week study of 119 patients with chronic symptomatic heart failure, combined therapy with losartan and enalapril showed numerically greater effects in terms of suppression of aldosterone and norepinephrine compared to monotherapy with enalapril 20 and 40 mg daily\[103\]. There were, however, no statistically significant differences between groups. The combined therapy also was safe and well tolerated. In a 2-week study of 43 patients with chronic symptomatic heart failure, combining losartan with maximally recommended or tolerated ACE inhibition was shown to be safe and to cause further vasodilatation\[104\]. In a 12 week study\[105\] the addition of irbesartan to conventional therapy for heart failure, including ACE inhibitors, was well tolerated and was at least equal, in terms of exercise capacity and left ventricular ejection fraction, to placebo in 109 patients with mild to moderate heart failure.

Conclusions

There is a convincing rationale for inhibition of the renin–angiotensin system by blocking the AT1-receptors in patients with cardiovascular disease, and in some countries AT1-receptor blockers are already established therapy in hypertension with approximately 4 years of clinical experience. They have been found to be adequately efficacious in terms of blood pressure reduction, extremely well tolerated, and safe. Promising results have also been shown in terms of regression of left ventricular hypertrophy. By more effectively blocking the deleterious effects of angiotensin II, AT1-receptor blockers may improve on the modest mortality reduction shown for ACE inhibitors in patients with heart failure and asymptomatic left ventricular systolic dysfunction. Furthermore, due to their excellent tolerability, AT1-receptor blockers may diminish the problem with the substantial underuse of ACE inhibitors in these patients. Indeed, losartan is registered in some countries for use in heart failure and preliminary data available from clinical trials indicate that AT1-receptor blockers may be at least as effective as ACE inhibitors, but with a considerably more favourable side effect profile. A large number of mortality studies using different AT1-receptor blockers in various forms of cardiovascular disease will establish the role of AT1-receptor blockers in the treatment of cardiovascular disease in the near future.

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