Keywords: angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, clinical trials, renin-angiotensin system

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JRAAS 2001;2 (suppl 2):S12–S16

Angiotensin II receptor blockers and cardiovascular outcomes: the evidence now and in the future
Michael Weber

Abstract
The blood-pressure-lowering efficacy of both angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) has been clearly demonstrated in recent years, although there is evidence that within the ARB class the individual therapies are not necessarily identical in terms of sustained and consistent antihypertensive efficacy over the entire dosing period. However, the results of the recent HOPE study have demonstrated that ACE-I have a wider role to play in treating cardiovascular disease, and support the idea that ACE inhibition specifically has a vascular protective effect. The most dramatic benefits were seen in patients with systolic blood pressures in the hypertensive range. The ability of the ACE-I to provide protective effects beyond blood pressure control may be due to their ability to attenuate the breakdown of kinins as well as a role in reducing angiotensin II. These data pose the question as to whether the pharmacological properties of the ARBs, in addition to their antihypertensive efficacy, may also play a significant role in influencing cardiovascular outcomes. A number of prospective long-term studies, including VALUE, SCOPE, LIFE, VALIANT, OPTIMAAL, VAL-HEFT and CHARM I-III, are investigating the effects of the ARBs of mortality and morbidity in patients with cardiovascular disease. These studies should answer important questions with respect to the role that ARBs may have in influencing cardiovascular outcomes, although it remains to be seen whether ARBs can match the protective effects of ramipril in high-risk patients. Given the excellent tolerability of the ARBs, it will be of value to examine the influence of ARBs on cardiovascular outcomes in all relevant patient groups.

Introduction
There is clear evidence that the angiotensin II receptor blockers (ARBs) are effective in reducing elevated blood pressure (BP) and are well tolerated. However, the key question is whether these agents can also influence cardiovascular outcomes in the long term. In an attempt to answer this question, a range of clinical trials are currently planned or in progress aimed at investigating the long-term effects of the ARBs on morbidity and mortality.

Completed studies
Various clinical trials involving treatment with losartan,1,3 candesartan,1 valsartan1 and irbesartan6 have investigated long-term treatment effects on mortality, morbidity and parameters of renal function (Table 1).

Losartan, the first of the ARBs to be investigated, has been studied in three clinical trials (ELITE-I, ELITE-II and RENAAL).3 The ELITE-I study (Evaluation of Losartan In The Elderly)2 was originally planned as a safety rather than outcome trial. However, the results of this study indicated the possibility of a higher probability of survival with losartan than with an angiotensin converting enzyme inhibitor (ACE-I), and prompted the initiation of the larger follow-up study (ELITE-II),2 in patients with congestive heart failure. Although there was no significant difference in outcomes between patients treated with an ARB or an ACE-I, losartan appeared to be better tolerated. It is still uncertain how these two drug classes compare in terms of their effects on clinical endpoints. Many investigators consider that a definitive answer will not be forthcoming until the results of further trials are available.

The RENAAL study (Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan)4 was a pivotal placebo-controlled trial in diabetic nephropathy patients, chiefly aimed at investigating the effects of ARB treatment on renal function and the maintenance of renal function, although cardiovascular morbidity and mortality were also investigated. Although a placebo arm was legitimate on ethical grounds when the trial started, the study was subsequently terminated slightly earlier than planned as the number of clinical events achieved the pre-specified target. The results of RENAAL, presented at the Annual Meeting of the American Society of Hypertension in May 2001, indicated that losartan provided significant renal protection independent of BP-lowering effects.

The RESOLVD (Randomised Evaluation of Strategies for Left Ventricular Dysfunction) trial1 investigated the effect of treatment with candesartan, enalapril, or their combination on left ventricular dysfunction. The results of the pilot study indicated that the combination of candesartan and enalapril was more beneficial in preventing left ventricular remodelling than either agent alone.

The VAL-HEFT trial (VALsartan HEart Failure Trial)5 had an interesting study design focusing mainly on addition of treatment with valsartan at a very high dose (160 mg twice daily), to ongoing heart failure therapy, typically including an ACE-I. The results of VAL-HEFT, presented at the 50th Scientific session of the American College of Cardiology, Orlando, Florida, in March 2001, indicated that addition of valsartan to pre-existing ACE-I therapy had no addition-
al benefit on mortality, although the combined endpoint of mortality + morbidity (including hospitalisation) did favour the combination treatment. Patients who were not treated with beta-blockers appeared to derive additional benefit from this combination, and in a relatively small sub-group of patients who were not being treated with an ACE-I, there appeared to be a dramatic benefit associated with the use of the ARB compared with placebo.

In the IDNT study (Irbesartan type II Diabetic Nephropathy Trial), hypertensive patients with Type 2 diabetes mellitus were treated with either irbesartan, amiodipine or placebo to a fairly aggressive BP endpoint. The design of the IDNT study was conceptually similar to the RENAAL study. The results of the IDNT study, presented at the Annual Meeting of the American Society of Hypertension in May 2001, showed that irbesartan provided significant renal protection independent of BP-lowering effects.

Considering these completed studies together, it can be concluded that the ARBs are at least very useful alternatives to the ACE-I in these patient groups. Whether they are superior, or useful in combination, will become clearer as further clinical trials progress.

### Ongoing studies

There are up to eight ongoing studies investigating the effects of treatment with losartan, candesartan, valsartan and telmisartan on mortality, morbidity and renal function in patients with cardiovascular disease (Table 2).

The OPTIMAAL study (OPtical Therapy In Myocardial Infarction with the Angiotensin II Antagonist Losartan) is a mortality study comparing losartan with captopril in patients at risk of heart failure or with left ventricular dilatation. It is an important study because if, as many predict, it demonstrates long-term benefits for losartan, it will increase clinical confidence that this group of drugs are of particular value for patients either with or at risk of heart failure.

LIFE (Losartan Intervention For Endpoint reduction) is probably the definitive hypertension trial. The study population comprises hypertensive patients aged between 55–80 years with ECG evidence of left ventricular hypertrophy (LVH). These entry criteria were chosen as LVH is considered an ‘enricher’, i.e., the presence of LVH makes it more likely that these hypertensive patients will experience adverse cardiovascular events and thus enhances the study’s ability to discriminate between the treatment groups. LIFE is a comparison between losartan and the beta-blocker atenolol with mortality and morbidity endpoints. The investigators have the option to increase the daily dose of losartan from 50 mg to 100 mg, and if needed, to add hydrochlorothiazide. There are identical options for patients in the atenolol arm.

### Table 1 Complete clinical trials investigating the effects of the angiotensin II receptor blockers (ARBs) in patients with cardiovascular disease.

| Study & population | Treatments | Endpoints | Outcome |
|--------------------|------------|-----------|---------|
| ELITE I (CHF patients) | Losartan (n=352) vs. captopril (n=370) | 1° = renal fx, 2° = mortality | 1° = no significant difference, 2° = 46% lower risk of death in losartan group |
| ELITE II (CHF patients) | Losartan (n=1578) vs. captopril (n=1574) | 1° = mortality | 1° = no significant difference |
| RESOLVD (CHF patients) | Candesartan (n=327) vs. enalapril (n=109) vs. candesartan + enalapril (n=332) | 1° = changes in 6 MWD, EF, NYHA, VV | 1° = no significant difference |
| Val-HEFT (CHF patients) | Valsartan (n=2511) vs. placebo (n=2499) | 1° = mortality, and mortality and morbidity | 1° = mortality alone similar but significant reductions in all-cause mortality and morbidity in the valsartan group driven largely by reduction in number of hospitalisations |
| RENAAL (Diabetic nephropathy) | Losartan vs. placebo | Renal function (serum creatinine) terminal renal failure, mortality | 1° = significant renal protection by losartan when compared with conventional antihypertensive agents |
| IDNT (Diabetic nephropathy with hypertension) | Irbesartan vs. enalapril | Time to progression of composite endpoint (doubling of baseline serum creatinine, end-stage renal failure and all-cause mortality) | 1° = irbesartan significantly better in protecting renal function than amiodipine or conventional antihypertensive agents |
has completed enrolment, and follow-up will be completed by the end of 2001, with results expected during 2002.

The CHARM study (Candesartan in Heart failure - Assessment of Reduction in Mortality and morbidity) is a key trial comparing the effects of treatment with candesartan or placebo in patients with heart failure. These patients have either reduced or normal left ventricular ejection fraction, depending on whether or not they are receiving ACE-I. Results are expected in 2002–2003. The SCOPE study (Study on COgnition and Prognosis in the Elderly) is investigating the effect of treatment with candesartan in older patients with mild hypertension on the combined endpoint of cardiovascular mortality and non-fatal MI and non-fatal stroke. Results are expected in 2003–2004.

The VALIANT study (VALsartan In Acute myocardial infarction Trial) is one of a number of studies being performed with valsartan. Patients included in this study have previously experienced a myocardial infarction (MI) and have some

| Study | Group | Primary endpoints | No. | Drug (mg) | F/U |
|-------|-------|------------------|-----|-----------|-----|
| OPTIMAAL | ≥50 years; anterior Q wave MI or new LBBB or signs of heart failure or LVSD/dilatation | All-cause mortality | 5476 | Captopril 50 t.i.d. vs. losartan 50 o.d. | Until a total of 937 deaths |
| LIFE | Age 55–80; trough sitting DBP 98–115 mmHg; LVH; high risk for CV morbidity/mortality | Combined morbidity and mortality | 9218 | Losartan (50, 100) + atenolol (50, 100) + HCT 12.5 titrated to 140/90 | ≥4 years; until 1040 pts experience primary CV event |
| CHARM I - III | LVEF ≤40%; ACE-I-treated (n=2300) LVEF ≤40% ACE-I-treated (n=1700) LVEF ≥40% not ACE-I-treated (n=2500) | All-cause mortality (all studies). Combined mortality/morbidity in each study | 6500 | Candesartan 32 o.d. vs. placebo o.d. titrated as tolerated | 2 years |
| SCOPE | Age 70–89; mild hypertension (DBP 90–99 mmHg; SBP 160–179 mmHg); MMSE score ≥24 | Combined CV mortality + non-fatal MI + non-fatal stroke. Also cognitive function and QoL | 4964 | Candesartan (8, 16) vs. placebo. In addition to HCTZ 12.5 standardised prior to study. Other antihypertensives excluded | 2–3 years |
| VALIANT | Post-MI + signs of LVSD and/or HF | All-cause mortality | 14,500 | Valsartan 160 b.d. vs. captopril 50 t.i.d. vs. C50 t.i.d. + V80 t.i.d. Titrated as tolerated | 2700 deaths |
| VALUE | High cardiovascular risk; essential systolic or diastolic hypertension; age ≥50 years | Cardiac morbidity/mortality | 14,400 | Valsartan (80–160) o.d. vs. amlodipine (5–10) o.d. Titrated as tolerated | 6 years or until primary endpoint reached in 1450 pts |
| ABCD-2V | Type 2 diabetes; normotensive/hypertensive | Nephropathy | 772 | Valsartan (80, 160) vs. placebo. HCT 12.5 or 25 and metoprolol 50, 100, 200 added as needed | 5 years |
| DETAIL | Type 2 diabetic patients with essential hypertension (SBP ≤180) and diabetic nephropathy (albumin excretion rate <1000 µg/min & CC <140 µmol/L) | Change in GFR | 272 | Telmisartan 80 mg vs. enalapril 20 mg | 5 years |
evidence of left ventricular systolic dysfunction. VALIANT is similar to the SAVE (Survival And Ventricular Enlargement) trial with captopril.14 In VALIANT, the effects of treatment with valsartan 160 mg twice daily, captopril three times daily, or the combination of these two agents is being investigated. The results are due in 2003–2004.

The VALUE study (VALsartan Antihypertensive Long-term Use Evaluation)22 is another very large hypertension trial, somewhat similar in design to the LIFE study,4 but instead of using LVH to enrich the subjects, the presence of multiple risk factors has been used to select the middle-aged group for study. VALUE compares the effect of treatment with valsartan 80 or 160 mg once daily with amlodipine 5 or 10 mg, as needed to control BP on morbidity and mortality. VALUE is a relatively long study and results will not be available until 2004–2005.

The ABCD-2V study (Appropriate Blood pressure Control in Diabetes 2 – Valsartan) is a follow-up study to the ABCD study.11 The primary endpoint will be nephropathy in Type II diabetics treated with valsartan or with metoprolol three times daily, and an aggressive BP target. The results may be available in 2002–2003.

The DETAIL study (Diabetics Exposed to Telmisartan And Enalapril)12 is a smaller study investigating the effects of treatment with telmisartan and enalapril on renal function and BP in 272 patients. Although DETAIL is not a definitive endpoint study, it will provide useful information on the effects of treatment with telmisartan on proteinuria.

ONTARGET trial

Background

The HOPE study (Heart Outcomes Prevention Evaluation)13 study using the ACE-I, ramipril, forms the background to the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study with telmisartan. HOPE was not conducted specifically in hypertensive patients but in a range of patients with many kinds of vascular disease or with uncomplicated diabetes. In the HOPE study, there was a greater than 20% reduction in the combined cardiovascular endpoint, and mortality, MI and stroke were all reduced to a remarkable extent.

Since BP fell relatively modestly in this study, its results have been interpreted as showing that interfering with the renin-angiotensin system (RAS) per se will produce sharp cardiovascular benefits. Systolic BP fell by only 3 mmHg in the ramipril group and was unchanged in the placebo group, and diastolic BP fell by 3 mmHg in the ramipril group compared with 2 mmHg in the placebo group. The total reduction in BP was only 3/1. The BP results of this study may be explained by postulating a clear benefit of interrupting the RAS independent of BP effects. Even so, analysis of systolic BPs in the HOPE data reveals that, compared with placebo, the greatest benefits of the ACE-I are seen in those patients who entered the study with relatively hypertensive BPs.

A proportion of patients in this study had BPs in the region of 140–150 mmHg and, examining the placebo group, these patients seemed at greatest risk. However, these patients also had the greatest benefit when treated with the ACE-I. Thus the results of this study suggest that a history of hypertension appears to be associated with vulnerability to cardiovascular disease, more so than elevated BP alone can perhaps explain, and indicate the possibility that thoughtful drug selection throughout the range of BPs might help in optimising outcomes.

Aims and design

ONTARGET will compare the efficacy of telmisartan with ramipril, either alone or in combination, in preventing cardiovascular endpoints. As there will be a small group of patients intolerant of ACE-I, it is possible to compare telmisartan with placebo.

The combination of telmisartan and ramipril is being assessed in ONTARGET because it may offer a more complete blockade of the RAS, and may result in improved haemodynamic control particularly at the end of the dosing interval. There may also be additive cardiovascular protective effects as suggested by the results of the ValHeFT trial,3 particularly in the absence of beta-blockers. Recent studies suggest there are added renal protective effects when an ACE-I and ARB are used in combination, as observed in a recent study combining lisinopril and losartan.10

Three-armed studies like ONTARGET need to recruit large numbers of patients. Close to 32,000 or 33,000 patients will be followed for up to five or six years, and it will be the largest ARB trial to date with over 100,000 patient treatment years.

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