The renin–angiotensin system: a review of trials with angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents

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Introduction

Angiotension-converting enzyme (ACE) inhibitors have been very successful in patients with vascular disease, in particular for hypertension, left ventricular dysfunction and vascular protection. Angiotensin receptor blocking drugs (ARBs) were developed later and differ from ACE inhibitors in several ways. We are now beginning to see the results of large studies of ARBs in high-risk patients and some head-to-head comparisons between these two classes of drugs which reduce the actions of angiotensin II. This review considers these trials under the headings of heart failure, hypertension, renal function, and high-risk cardiovascular disease/coronary heart disease.

Key Words: Hypertension, left ventricular dysfunction, left ventricular hypertrophy, myocardial infarction, heart failure, cough, endothelium, plaque rupture.

Although controversial, it appeared that the modest reduction in blood pressure (3-3/1-4 mmHg) that occurred with the ACE inhibitor ramipril in HOPE could not account for more than a relatively small proportion of the benefit observed (substantial reductions in stroke [32%], MI [20%] and cardiovascular death [25%]). A more detailed analysis that examined this further confirmed that the benefits were greater than expected based on previous blood pressure lowering trials and on the blood pressure–risk relationship in the placebo group in HOPE[5]. This latter analysis of placebo epidemiology thus countered the suggestion that these higher risk patients received enhanced benefit from blood pressure reduction. There was clear benefit even in normotensive patients[5]. The benefits observed were additive to those of other well-proven treatments, and were as powerful[5,6].

The mechanisms involved in this blood pressure independent effect are probably multiple, involving reduction in left ventricular hypertrophy (LVH)[7], stabilization of atheromatous plaques by reduction in metallaproteinase action at the fibrous cap[8] and improvement in endothelial function. Of course, the reduction in blood pressure is also probably beneficial.

Because ACE inhibitors may not be tolerated by some patients (perhaps 10–20%), largely because of the
A complication of dry cough, there has been great interest in the development of agents that attack the renin–angiotensin system more selectively, in the form of angiotensin receptor blockers (ARBs). These differ from ACE inhibitors by several known effects and probably by several as yet unknown mechanisms. The known differences are that ARBs (which are angiotensin II type 1 receptor blockers) increase stimulation of angiotensin II type 2 receptors via the compensatory rise in angiotensin II, and because they do not increase levels of bradykinin they are much less likely to cause cough. ACE inhibitors when used long-term may also lose their initial benefit, because of the conversion of angiotensin I to angiotensin II by non-ACE, neutral peptidases.[9].

We are now beginning to see the results of large studies of ARBs in high-risk patients and some head-to-head comparisons between these two classes of drugs, both of which reduce the actions of angiotensin II (Table 1). I review these trials under the headings heart failure, hypertension, renal function and high-risk cardiovascular disease/coronary heart disease.

<table>
<thead>
<tr>
<th>Study and population [reference]</th>
<th>Treatments</th>
<th>End-points</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE-I (722 CHF patients)[10]</td>
<td>Losartan versus captopril</td>
<td>Primary: renal function Secondary: mortality</td>
<td>No significant difference, but unexpected 46% lower risk for death in losartan group</td>
</tr>
<tr>
<td>ELITE-II (3152 CHF patients)[11]</td>
<td>Losartan versus captopril</td>
<td>Primary: mortality</td>
<td>No significant difference</td>
</tr>
<tr>
<td>RESOLVD (768 CHF patients)[12]</td>
<td>Candesartan versus enalapril (n = 109) versus candesartan + enalapril (n = 332)</td>
<td>Primary: changes in left ventricular function, quality of life, exercise tolerance</td>
<td>No significant difference between candesartan and enalapril, but significantly better LV function with combination of ACE inhibitor + ARB</td>
</tr>
<tr>
<td>Val-HeFT (2510 CHF patients; unpublished)</td>
<td>Valsartan (n = 2511) versus placebo (n = 2499)</td>
<td>Primary: mortality, and mortality and morbidity</td>
<td>No significant difference; the valsartan group had fewer hospitalizations</td>
</tr>
<tr>
<td>RENAAL (1513 diabetic nephropathy patients)[16]</td>
<td>Losartan versus placebo (ACE inhibitors excluded)</td>
<td>Renal function (serum creatinine), terminal renal failure, mortality (trial stopped early following publication of HOPE findings)</td>
<td>Significant renal protection by losartan (but SBP significantly 2–4 mmHg higher on ‘placebo’); losartan better tolerated</td>
</tr>
<tr>
<td>IRMA-2 (590 diabetic patients with microalbuminuria)[14]</td>
<td>Irbesartan 150 versus 300 mg . day$^{-1}$ (blood pressure =) versus placebo</td>
<td>Diabetic nephropathy</td>
<td>Irbesartan conferred renoprotection independently of blood pressure change</td>
</tr>
<tr>
<td>IDNT (1640 diabetic nephropathy patients with hypertension)[15]</td>
<td>Irbesartan versus amlodipine</td>
<td>Time to progression of composite end-point (doubling of baseline serum creatinine, end-stage renal failure and all-cause mortality)</td>
<td>Irbesartan significantly better in renal protection than amlodipine or other antihypertensive agents (‘placebo’)</td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CHF=congestive heart failure; ELITE=Evaluation of Losartan in the Elderly; HOPE=Heart Outcomes Prevention Evaluation; IDNT=Irbesartan Diabetes Nephropathy Trial; IRMA=Irbesartan Regression of Microalbuminuria Trial; LV=left ventricular; RENAAL=Reduction in Endpoints in NIDDM with the Angiotensin-II Antagonist Losartan; RESOLVD=Randomized Evaluation of Strategies for Left Ventricular Dysfunction; SBP=systolic blood pressure; Val-HeFT=Valsartan Heart Failure Trial.

Comparisons of ACE inhibitors and ARBs

Heart failure

Perhaps because of the proven benefits of ACE inhibitors in patients with heart failure, data from comparisons of ACE inhibitors with ARBs are much more numerous than in any other area. Despite this, there is still insufficient evidence to determine whether the two classes are equivalent. The Evaluation of Losartan in the Elderly (ELITE)-I trial[10] compared losartan (ARB; 50 mg . day$^{-1}$) with captopril (ACE inhibitor; 50 mg three times daily) in 722 elderly (aged over 65 years) heart failure patients who had not previously been treated with an ACE inhibitor. That trial took place over 48 weeks, and renal function was the primary outcome. There was no difference between the drugs, but losartan was better tolerated. There was significant reduction in all-cause mortality, which was unexpected because the trial was not powered to identify
mortality differences. This result was not confirmed in the subsequent, much larger mortality trial ELITE-II[11]; if anything captopril was non-significantly better, except that it was not as well tolerated as losartan.

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study[12] compared candesartan (ARB; three doses) or enalapril (ACE inhibitor; 20 mg . day\(^{-1}\)), or the combination of candesartan (two doses) plus enalapril (20 mg . day\(^{-1}\)) in 768 heart failure patients. The end-point was a combination of left ventricular function, exercise tolerance, quality of life, tolerability and neurohumeral responses. There were no significant differences, except that the combination of ACE inhibitor and ARB reduced blood pressure to a greater extent than did the other regimens and had a greater benefit for left ventricular function. However, the trial monitoring committee were concerned about a trend toward a higher event rate in the combination arm. Although the trial steering committee disagreed, the trial was stopped 6 weeks early. A large mortality study with candesartan (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) is underway.

The Valsartan Heart Failure Trial (VAL-HeFT; presented, but so far unpublished) tested the effect of adding the ARB valsartan or placebo to the regimens of 5010 heart failure patients (mostly New York Heart Association class 2 or 3), most of whom were already on an ACE inhibitor. Perhaps surprisingly there was identical mortality in the two groups, but less hospitalization in the valsartan group. A controversial subgroup analysis identified an adverse effect in those patients receiving an ACE inhibitor, valsartan and a beta-blocker. Many felt that this was probably due to play of chance and that as a post-hoc analysis it should be interpreted with caution. However, the overall results of Val-HeFT were not particularly encouraging for valsartan, except in another subgroup analysis of patients who were not on an ACE inhibitor.

Thus, despite the initial enthusiasm following ELITE-I, the current general consensus is to favour ACE inhibition where tolerated[13]. Other trials in congestive heart failure are ongoing.

**Hypertension**

Although studies using blood pressure as an outcome have shown similar efficacy of ACE inhibitors and ARBs, large mortality trials are lacking, perhaps because such a study would need to be very large to show a significant benefit of one agent over another. Nevertheless, execution of such studies is important because recent trials that tested the renal protection benefits of ARBs in diabetic persons[14–16] and the recent HOPE blood pressure–risk analysis[5] all suggest that the benefits of ACE inhibitors may be largely or wholly independent of blood pressure modification. Certainly, the ARBs are very well tolerated blood pressure lowering drugs; they also lack the side effect of cough, and studies have found little evidence of treatment effect ‘escape’ (thus far).

**Renal function**

Three important trials that have addressed the preservation of renal function in diabetic patients have recently been reported in the same issue of the New England Journal of Medicine.

The Irbesartan Regression of Microalbuminuria Trial (IRMA)-2[14] was a blinded randomized international study, co-ordinated from Denmark, that tested the effect on the progression to nephropathy of two doses of irbesartan (150 or 300 mg . day\(^{-1}\)) or placebo. A total of 590 hypertensive patients with diabetes and microalbuminuria were assigned to three parallel arms and were followed for 2 years. As expected, blood pressure control in the placebo group necessitated more diuretics, beta-blockers and calcium channel blockers (non-dihydropyridine) than were required in the irbesartan groups. The on-treatment blood pressure was no different between 150 mg . day\(^{-1}\) irbesartan and placebo (approximately 144/83 mmHg), but was significantly lower on 300 mg . day\(^{-1}\) irbesartan. The numbers of patients who developed nephropathy (overnight urinary albumen >200 µg . min\(^{-1}\)) were 30, 19 and 10 in the placebo, 150 mg and 300 mg groups, respectively (\(P=0.001\)). Serious adverse events were more frequent on placebo (18.9% versus 14.9% in the combined irbesartan groups). Thus, there was a clear difference in the primary outcome that was independent of the modest differences in systolic blood pressure (diastolic blood pressure was identical in the three groups).

The Irbesartan Diabetes Nephropathy Trial (IDNT)[15] tested 300 mg . day\(^{-1}\) irbesartan, 10 mg . day\(^{-1}\) amlodipine and placebo in three parallel groups. A total of 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomized to achieve a target blood pressure of 135/85 mmHg. The outcome was time to the primary composite outcome (a doubling of baseline serum creatinine, end-stage renal disease, or all-cause mortality). The mean blood pressure during the trial was significantly higher (3.3 mmHg; \(P=0.02\)) and 23% less than in the placebo group, but this difference was believed insufficient to account for the clear superiority of irbesartan over both placebo and amlodipine. (Both active treatment groups achieved similar blood pressures.) The unadjusted relative risk for the primary outcome in the irbesartan group was 20% less than in the placebo group (\(P=0.02\)) and 23% less than in the amlodipine group (\(P=0.006\)).

The third study (Reduction in Endpoints in NIDDM with the Angiotensin-II Antagonist Losartan [RENAAL]) tested 1513 patients (aged 31–70 years, with nephropathy and type 2 diabetes) to either losartan 50–100 mg . day\(^{-1}\) or to conventional antihypertensive treatment (but excluding ACE inhibitors). When the results of the HOPE study[4] were reported, the safety committee of RENAAL recommended stopping the study at 3–4 years as opposed to the planned 4- to 5-year mean follow-up. There was a 2–4 mmHg lower systolic blood pressure in the losartan group over the course of the trial. There was a 16% lower risk for reaching the primary outcome in the losartan group (43.5% versus 47.1% on placebo; \(P=0.02\)), which was unchanged (15%) after allowing for differences in blood pressure.
These trials are of considerable interest in that they provide evidence (at least for hypertension and diabetic nephropathy) that the benefits of angiotensin blockade are largely independent of reduction in blood pressure. These findings corroborate the conclusions of the HOPE study\cite{4,5}. However, they do not resolve the important issue of whether ACE inhibitors are equivalent or superior to ARBs in such patients, for whom there is much evidence of the benefits of ACE inhibition, for example in the MICRO-HOPE study\cite{17}. That study, a substudy of the main HOPE trial, examined the effect of ramipril versus placebo on cardiovascular and renal function in the 3577 patients with diabetes included in the HOPE study. These outcomes were significantly improved. Ramipril reduced the risk of overt nephropathy both in those with and in those without microalbuminuria at baseline ($P = 0.02$).

In a more detailed analysis of reno-protection in HOPE, Mann et al.\cite{18} compared the effect of ramipril in 980 patients with mild renal insufficiency (serum creatinine $>1.4$ mg. dl$^{-1}$) versus that in 8307 patients with normal renal function. Patients with serum creatinine greater than 2.3 mg. dl$^{-1}$ were excluded. The primary outcome was the HOPE composite end-point of cardiovascular death, MI, or stroke. Renal insufficiency independently predicted a higher risk for reaching the primary outcome over 4-5 years (22-2% versus 15-1%; $P = 0.001$). Ramipril reduced risk equally in those with or without renal insufficiency, without any increase in adverse effects. Renal insufficiency was associated with a higher incidence of several other risk factors, such as hypertension, advanced age and male sex, but microalbuminuria and raised serum creatinine were independent predictors of achieving the primary outcome when those other risk factors were accounted for. This analysis therefore attested to the safety of ramipril in renal insufficiency, provided that the ACE inhibitor is titrated carefully and changes in creatinine and electrolytes are monitored.

**High risk patients**

In the place of the common trial design of enrolling patients with specific risk factors (e.g. hypertension, coronary heart disease, or stroke), the HOPE study\cite{4} developed the concept of recruiting patients at high cardiovascular risk, mainly because of older age, known vascular disease (80% had known coronary heart disease), or diabetes, with at least one additional risk factor. The HOPE study and its substudies that focused on diabetes\cite{17}, renal protection\cite{18}, LVH\cite{17}, carotid atheroma\cite{19} and hypertension\cite{5} all suggest that the observed benefit was partly or even largely independent of the modest reduction in blood pressure. Some of these other mechanisms involve reduction in LVH, independent of blood pressure modification. Angiotensin II is a potent stimulant for smooth muscle growth, and so the favourable effect of ramipril in reducing the development of LVH and in resolving existing LVH has a clear and rational basis. The Kaplan–Meier curves for the individual parts of the composite primary outcome in HOPE began to separate quite early in the trial. This might also infer a beneficial effect on plaque stabilization and/or endothelial function\cite{20}.

All of the above mechanisms have now been observed for ACE inhibition. As yet we have no comparable data for ARBs, although it appears likely to accrue over the next few years. Until we see the results of several ongoing trials with ARBs, it seems prudent to continue to use ACE inhibitors first and only use an ARB when patients are intolerant of ACE inhibition. There has been much speculation that the combination of ACE inhibitors and ARBs might have particular advantages\cite{21}. Certainly, the reduction in blood pressure is greater. At present, however, we lack adequate safety and mortality data. Trials are now addressing this, such as the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity study\cite{22}.

The HOPE team (and others) are about to start a logical successor to the HOPE study. The ONTARGET study (funded by Boehringer-Ingelheim) is a very large (24,000 patients), 5-year blinded study, which will compare ramipril with telmisartan and with their combination in three parallel groups of high-risk patients very similar to those recruited into HOPE.

In a parallel study (TRANSCEND), we will randomize over 4000 patients who are ACE intolerant to telmisartan or placebo. Telmisartan is an effective ARB with the longest half-life of any ARB developed thus far. The pharmacological properties and rationale for the use of ARBs have recently been reviewed, with particular consideration of experimental work on the combination of ARBs and ACE inhibitors\cite{22}.

**Conclusion**

Although ARBs are clearly effective, and more specific and better tolerated drugs for reducing the harmful effects of angiotensin II, we do not yet have insufficient data to recommend their use in patients who can tolerate ACE inhibition. Fortunately, more comparative data will become available over the next few years. Perhaps equally important, we will have data on the combination of these two highly effective classes of drugs.

**References**


