The role of angiotensin receptor blockers in the prevention of cardiovascular and renal disease: time for reassessment?

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Abstract

Angiotensin receptor blockers (ARB) have been recommended as a first option for the management of hypertension by guidelines, particularly in patients at high cardiovascular risk. The preference for ARB in these conditions is based on their neutral metabolic effects, and on direct cardiac and renal protective effects independent of the blood pressure-lowering effect (pleiotropic effects). Nonetheless, six large clinical trials designed to demonstrate such effects in patients at high cardiovascular risk, comparing ARB with placebo, failed to demonstrate any cardiovascular protection by ARB. In two trials there was higher cardiovascular mortality in patients treated with ARB. Their putative beneficial effect in the prevention of atrial fibrillation was not confirmed in four major clinical trials specifically designed to investigate this effect. Moreover, in various recent trials, treatment with ARB led to worse renal outcomes, such as an increased incidence of microalbuminuria, renal impairment and decreased glomerular filtration rate. The role of ARB for the prevention of cardiovascular and renal disease should be re-examined.

Angiotensin receptor blockers (ARB) are among the best-selling blood pressure-lowering agents worldwide. The British National Institute of Clinical Excellence (NICE) guidelines indicate ARB as a first line option in patients younger than 55 years of age.[1] The Joint National Committee-VII and European guidelines recommend ARB as preferred alternatives to ACEi for patients with various co-morbidities or cardiovascular risk factors.[2 3] This preference is based on their neutral or beneficial metabolic effects, and on putative cardiac and renal protective effects independent of their blood pressure-lowering effect—pleiotropic effects. Corporate bias, allied with massive commercial promotion, may explain part of this preference as well.[4] Large clinical trials designed to demonstrate protective effects, mostly comparing ARB with placebo on top of usual treatment, have failed to demonstrate additional cardiovascular protection by ARB and suggested that they may be associated with worse renal outcomes.

Clinical trials comparing ARB with other blood pressure agents

The LIFE trial was the only major trial that showed the superiority of an ARB over another blood pressure drug in the prevention of cardiovascular outcomes in patients with hypertension or at high cardiovascular risk.[5] Nonetheless, conclusions were limited because atenolol was an inadequate comparator,[6] and more patients on losartan used diuretics.[7]

In the VALUE study,[8] there was no difference in the incidence of a combination of cardiovascular events in patients treated with valsartan or amlodipine. The incidence of fatal and non-fatal myocardial infarction, a prespecified secondary endpoint, was higher in patients treated with valsartan (p=0.02).

Placebo-controlled trials with ARB

Blood pressure-lowering agents should no longer be compared to placebo in clinical trials with cardiovascular outcomes, since the totality or the major part of their efficacy is derived from their effect on blood pressure.[9] Despite this, many placebo-controlled trials of ARB have been published recently. Unexpectedly, ARB were not superior to placebo and adverse outcomes emerged.

In the SCOPE trial[10] the incidence of a composite cardiovascular outcome—cardiovascular death, non-fatal stroke and non-fatal infarct—was 26.7 per 1000 patient-years in elderly patients treated with candesartan and 30.0 per 1000 patient-years in participants that received placebo (p=0.19).

The TRANSCEND trial enrolled patients with cardiovascular disease or diabetes with end-organ damage who were intolerant to ACE inhibitors, to telmisartan or placebo.[11] The incidence of cardiovascular death, myocardial infarction, stroke or hospitalisation for heart failure was 15.7% in the telmisartan arm compared with 17% in the placebo arm (p=0.22).

Telmisartan was also compared with placebo in the secondary prevention of stroke in the PROFESS trial,[12] which enrolled more than 20 000 patients. A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group experienced a recurrent stroke (p=0.23).

The NAVIGATOR trial investigated the efficacy of valsartan to prevent various cardiovascular outcomes and diabetes in patients with impaired glucose tolerance and cardiovascular disease or risk factors.[13] The incidence of core cardiovascular events was identical in patients treated with valsartan or placebo (8.1%).

In the ACTIVE trial the incidence of a combination of stroke, myocardial infarction or death from vascular causes was identical (5.4 per 100 person-years) in patients with atrial fibrillation treated with irbesartan or placebo.[14]

In the ROADMAP trial, with patients with type 2 diabetes,[15] the incidence of cardiovascular complications or cardiovascular death was 4.3% in the olmesartan arm and 4.2% in the placebo arm (p=0.99). The number of deaths from a cardiovascular cause was unexpectedly higher in patients treated with olmesartan (15 vs 3, p=0.01).

In the ORIENT trial, which compared olmesartan with placebo in patients with type 2 diabetes with diabetic nephropathy,[16] the incidence of cardiovascular mortality was 3.5% in the olmesartan arm and 1.1% in the control group (p=0.09).

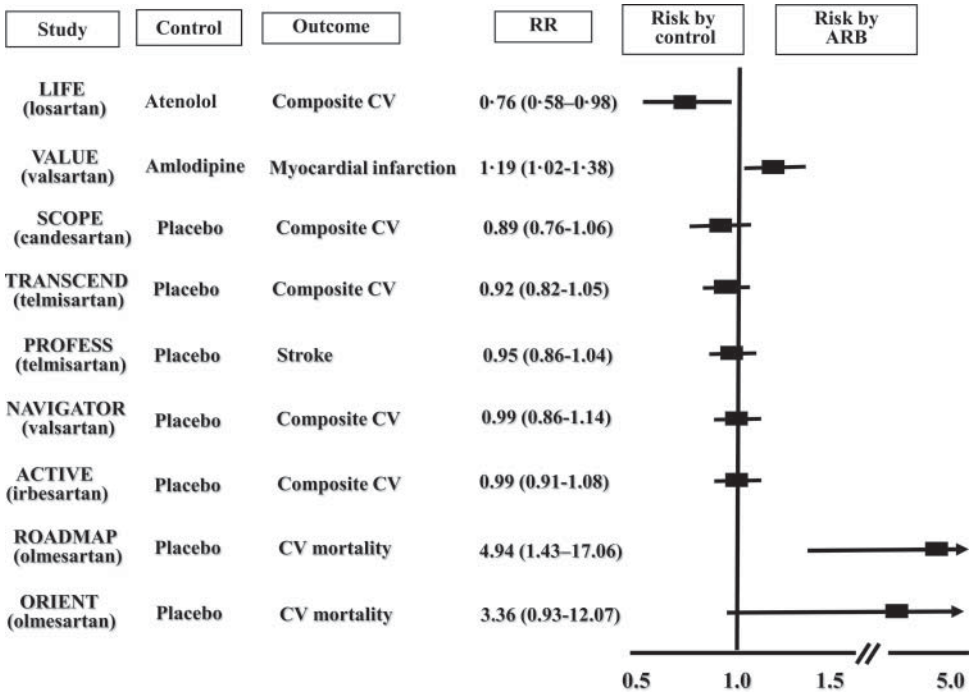

Figure 1 Relative risks and 95% CIs for the occurrence of cardiovascular outcomes in clinical trials comparing angiotensin receptor blocker with other drugs or placebo in patients with hypertension or high cardiovascular risk; the outcomes were the primary outcome of the studies or a co-primary or secondary outcome with significant difference between the trial arms (references in the text).

Figure 1 summarises the risks for major cardiovascular outcomes in studies that compared ARB with other agents and with placebo. With the exception of the LIFE trial, none of the remaining trials favoured ARB, including all studies controlled by placebo.

A meta-analysis by Law *et al*[17] identified only three trials comparing ARB with placebo in the prevention of coronary heart disease. There was no trial comparing ARB with placebo for stroke prevention at the time of that meta-analysis. In the comparison of ARB with other agents, the summary relative effect estimates were close to 1.0 but the CIs were wide both for heart disease and for stroke because of the small number of trials. A more recent meta-analysis identified more studies comparing ARB with placebo or active comparators[18] ARB were not inferior to placebo in the prevention of myocardial infarction (relative risk and 95% CI: 0.93, 0.81 to 1.07), supporting a bizarre conclusion for drugs that are used to prevent cardiovascular outcomes, that is, that ARB do not increase the risk of myocardial infarction. There was small protection against stroke, heart failure (less than the observed in trials with other blood pressure agents) and diabetes.

Another recent meta-analysis[19] demonstrated that ACEi or ARB reduced the composite cardiovascular outcome by 11% in normotensive patients with evidence of atherosclerotic disease, but the relative contribution of each group was not presented. This limitation was overcome by a further meta-analysis of renin–angiotensin–aldosterone system (RAAS) inhibitors,[20] which showed that only ACEi were effective to prevent total mortality.

Most patients included in the ARB trials, irrespective of the criteria for inclusion, had hypertension. Despite this, the difference in office blood pressure between the active and placebo arms at the end of the placebo-controlled trials varied from only 2.9 to 4.0 mm Hg for systolic blood pressure and from 1.4 to 2.2 for diastolic blood pressure (table 1). Part of this small difference in blood pressure-lowering efficacy can be due to the use of other blood pressure agents by the participants in the trials. The absence of any beneficial trend in some trials, and the harmful trend in two of them, is unexplained. Nevertheless, these trials show that it is quite unlikely that ARB have blood pressure-independent pleiotropic cardiovascular effects.

Cardiac and renal effects of ARB

Putative cardiac and renal pleiotropic effects of ARB are the basis for their preferential indication to prevent the

Table 1 Blood pressure-lowering effect of angiotensin receptor blockerin placebo-controlled trials

Study (reference)	Drug	Systolic*	Diastolic*
SCOPE[10]	Candesartan	3.2	1.6
TRANSCEND[11]	Telmisartan	4.0	2.2
PROFESS[12]	Telmisartan	3.8	2.0
NAVIGATOR[13]	Valsartan	3.2	1.4
ACTIVE[14]	Irbesartan	2.9	1.9
ROADMAP[15]	Olmesartan	3.1	1.9

*Blood pressure, mm Hg.

recurrence of atrial fibrillation and microalbuminuria.[2 3] The evidence comes mostly from experimental studies, placebo-controlled trials and from a post-hoc analysis of the LIFE trial. New findings cast doubt upon these preferences.

The efficacy of ARB in the prevention of atrial fibrillation was not confirmed by four large studies specifically designed to investigate this outcome. In the GISSI-atrial fibrillation trial, valsartan was absolutely inert in the prevention of recurrence of atrial fibrillation.[21] In the ACTIVE trial,[14] irbesartan did not prevent atrial fibrillation diagnosed by electrocardiography or transtelephonic monitoring. In the ANTIPAF trial, 1 year therapy with olmesartan did not reduce the number of episodes of atrial fibrillation in patients without structural heart disease.[22] And finally, in the Japanese J-RHYTHM II Study, candesartan and amlodipine did not influence the rate of incidence of episodes of paroxysmal atrial fibrillation.[23]

Recent trials with ARB suggest that these agents may have adverse effects on the kidneys, particularly when used together with ACE inhibitors. In the RAAS study, a complex but well-designed trial, 285 normotensive patients with type 1 diabetes and normoalbuminuria were randomly assigned to receive losartan, enalapril or placebo.[24] After 5 years of follow-up, there was no differential change in mesangial fractional volume per glomerulus, the primary outcome. The 5-year cumulative incidence of microalbuminuria, a secondary outcome, was 6% in the placebo group, 4% in the enalapril group and 17% with losartan (p=0.01).

The addition of telmisartan to ramipril in order to get dual blockade of the renin–angiotensin axis in the ONTARGET trial[25] was associated with an increase of 33% in the incidence of renal impairment (p<0.001) and a (non-significant) higher rate of renal dialysis (p=0.10). The ROADMAP trial[15] reported a slightly lower incidence of microalbuminuria in patients randomised to olmesartan than in patients randomised to placebo, but the reduction in glomerular filtration rate was higher in patients treated with olmesartan instead of placebo. In the ACTIVE trial[14] the incidence of renal dysfunction leading to discontinuation of the drug almost doubled in patients treated with irbesartan (0.95%) versus placebo (0.53%). In the TRANSCEND trial,[26] the decrease in glomerular filtration rate was greater with telmisartan than with placebo (p<0.001).

Conclusion

The results of major clinical trials with ARB, mostly controlled by placebo, demonstrate that they do not add cardiovascular protection for a wide range of clinical conditions and are associated with harmful renal outcomes. As such, these results are hardly consistent with the recommendations of guidelines. The role of ARB in the prevention of cardiovascular and renal disease requires reassessment.

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