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HYPERTENSION

Angiotension receptor blockers may be similarly effective to other antihypertensive drugs for primary prevention in the short term

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Background

Angiotensin receptor blockers have a recognised role for people with heart failure and nephropathy. Evidence is emerging about their effects in people with hypertension.

Objective

Cheung and colleagues assessed the effect of angiotensin receptor blockers in people with high blood pressure.

Method

The meta-analysis included three randomised controlled trials with 29,375 participants.

The authors did not report the search strategy. To be eligible for inclusion trials had to have average follow up of two years or more and at least 100 major cardiovascular events.

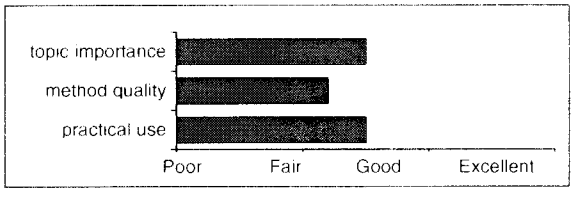
Main results

Two out of the three trials found that angiotensin receptor blockers reduced cardiovascular events and stroke compared to controls. Angiotensin receptor blockers had no significant effect on all-cause mortality compared to other antihypertensive drugs (relative risk ratio 0.96, 95% CI 0.88 to 1.06, $p = 0.45$). Angiotension receptor blockers were associated with increased myocardial infarction (relative risk ratio 1.12, 95% CI 1.01 to 1.26, $p = 0.041$) and decreased new-onset diabetes (relative risk ratio 0.80, 95% CI 0.74 to 0.86, $p < 00001$).

Authors' conclusions

The authors concluded that angiotensin receptor blockers appear similarly effective to other antihypertensive drugs. They suggested that a reduction in new-onset diabetes partly offsets a slightly increased risk of myocardial infarction.

Overall quality



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Commentary 1

Angiotensin-receptor-blockers (ARBs) are gaining popularity in the management of people with hypertension.[1] Besides lowering blood pressure, ARBs have excellent tolerability with minimal adverse effects. Furthermore, they have the potential advantage over ACE inhibitors of achieving a better blockade of the rennin-angiotensin-system (RAS). Angiotensin-II (A-II) can be generated through enzymatic pathways other than ACE, both directly from angiotensinogen and from A–I.

Another important advantage of ARBs is their possible effects beyond lowering blood pressure. A number of studies suggest that ARBs provide better organ protection at a similar degree of blood pressure lowering compared with other agents.[2–7] ARBs can induce a greater reduction in left ventricular mass, decrease proteinuria, delay the development of renal failure and improve vascular endothelial function. Whether these physiologic and clinical benefits translate into improved morbidity and mortality is not clear. The three major large clinical trials about ARBs had conflicting findings (LIFE, SCOPE and VALUE). A better estimate of the impact of ARBs on treatment outcome can be achieved through meta-analysis.

This study's contribution

Cheung and colleagues found that ARBs provided no additional benefit in all-cause mortality compared to other antihypertensive agents. In spite of their ability to prevent or delay the onset of diabetes, ARBs were associated with increased risk of myocardial infarction. This increased risk was based on the results of a single study (VALUE) in which people receiving valsartan had inferior blood pressure reductions compared to controls. The physiological advantage of ARBs and their capacity to provide better organ protection did not translate into significant improvements in other outcomes.

Clinical implications

ARBs have potential advantages over other antihypertensive agents. First, there are fewer adverse effects, which improves compliance. ARBs are possibly the most well-tolerated antihypertensive drugs. They have a placebo-like adverse effect profile.

Second, ARBs have a neutral or sometimes favorable metabolic effect.

Third, there is decreased risk of new-onset diabetes. However, the implications of this advantage for clinical endpoints may require a long period of observation.

Though ARBs provide no significant additional benefits over other antihypertensive agents regarding total mortality, they may be a reasonable alternative and may be the first choice for people with diabetes and in hypertensive patients with target organ damage, particularly left ventricular hypertrophy, proteinuria, and renal impairment.

Cheung and colleagues' meta-analysis stresses once again the importance of blood pressure control as a major factor in improving outcome in hypertensive people, particularly during the initial period of observation of two to four years.

Caveats

We need to consider a number of factors when comparing the effects of different antihypertensive medications on outcomes:

1. *Degree of reduction in blood pressure*: This seems to be the most significant determinant, at least in the short-term. It is not possible to draw conclusions about the superiority of one agent over another unless both achieve the same degree of blood pressure reduction. Any other advantages of an agent may be attributed to blood pressure reductions.

2. *Period of follow up*: Hypertension is a chronic disease and atherosclerotic complications take many years to develop. A long period of follow up may be needed to reverse the harmful effects of high blood pressure. Furthermore, the potential additional benefits or deleterious effects of different pharmacologic agents may take many years to develop. For instance, the harmful effects of impaired glucose tolerance produced by some agents may not be visible until after a long period of observation.

3. *Multifactorial nature of atherosclerotic cardiovascular disease*: High blood pressure is only one risk factor among many contributing to atherosclerosis. Controlling hypertension will not solve the problem completely. High blood pressure is commonly associated with other cardiovascular risk factors such diabetes, dyslipidemia, obesity, and

impaired glucose tolerance. Drugs influence the cardiovascular risk profile differently depending on their metabolic effects, anti-inflammatory action, changes in prothrombotic and procoagulant state, and oxidative stress.

4. *Baseline characteristics of the study population*: Age, gender, ethnicity, and presence of target organ damage can influence the effects of drugs.

5. *Effects other than blood pressure lowering*: Some antihypertensive medications can provide additional advantages beyond simple reduction in blood pressure, including anti-ischaemic, anti-arrhythmic, anti-remodeling, anti-proteinuric and anti-atherosclerotic effects. These effects should be considered when interpreting the results of trials comparing antihypertensive agents.

Commentary 2

ARBs are a class of modern antihypertensive agents which are well-tolerated and have various beneficial effects in hypertension, heart failure, and renal disease.[8] In primary prevention, all major classes of drugs (beta-blockers, diuretics, ACE-inhibitors and ARBs) are recommended to help reach target blood pressure levels. More than two thirds of people with hypertension need combination therapy to reach goal blood pressure values. Higher doses, more drugs, or both may be needed in those at high risk, where lower target values are recommended.

It remains uncertain whether there are significant differences between drug classes in the reduction of cardiovascular events. A recent meta-analysis of 13 randomised trials suggested that beta-blockers may be inferior in preventing hypertension despite the undisputed beneficial effects of beta-blockers after acute coronary events.[9]

This study's contribution

Cheung and colleagues evaluated 252 studies about ARBs for primary prevention of hypertension, of which only three were judged suitable for further analysis. The meta-analysis adds to knowledge about the role of ARBs for treating people with hypertension and underlines the effect of ARBs in reducing new onset diabetes. The authors conclude that the most important aim is to reach target blood pressure values.

It is remarkable that elderly people (aged 70-89 years) benefit to a similar or even greater degree from antihypertensive therapy with an ARB compared to younger people.

Caveats

The authors concede several limitations of the meta-analysis due to the heterogeneity of the study populations and study designs. As an example, the three studies differed significantly in the average age of participants (67 years in VALUE and LIFE, 76 years in SCOPE) and control drug (atenolol in LIFE, amlodipine in VALUE, and placebo in SCOPE). There were also differences between groups in blood pressure lowering.

The duration of the trials was probably too short (4 to 5 years) to assess the effects of ARBs, including reduction of new onset diabetes. The sequelae of diabetes emerge several years after the onset of the disease and may not have been adequately registered. This is similar to other hypertension trials, including ALLHAT, where a decrease in new-onset diabetes was observed with an ACE-inhibitor.[10]

The authors did not analyse adverse effects. However, all three trials found a low rate of adverse effects in the ARB group compared to controls. This is important for improving adherence to treatment.

Implications

In daily clinical life, most people with hypertension need combination therapy to reach goal blood pressure levels. Often we do not succeed in reaching the target values. The reasons are manifold, including poor combination of drugs, inadequate dosage, low adherence, and adverse effects. The more we use potent, long-acting and well tolerated drugs in a meaningful combination, the higher will be the rate of adherent patients reaching target blood pressure values. ARBs, especially those with a high trough-to-peak ratio, are a class of drugs that add to our armamentarium in treating high blood pressure.

Commentary 3

Although ARBs have been found to have a role in treatment of people with heart failure[11–14] and nephropathy,[15–17] their role for people with hypertension remains uncertain. Clinical trials of ARB in

people with essential hypertension have varied in terms of the specific ARBs used, the type of participants, the outcomes assessed, and overall results.

Implications

The criteria for inclusion in this meta-analysis were appropriate and clear. The sensitivity analysis including two additional large trials provides further validation of the results.

It is interesting that in the studies where ARBs controlled blood pressure better, there were reductions in stroke incidence. In the study where ARBs did not control blood pressure as well as in the control group, there was a non-significant increase in strokes in those receiving ARBs. Consequently, the authors concluded that there was insufficient evidence to support warning against use of ARBs in hypertension but starting treatment with Valsartan alone (VALUE trial) may be hazardous.

ARB therapy prevents new-onset diabetes. This analysis found that the number needed to treat to prevent a new case of diabetes is 255.

Overall, it is not clear that ARBs are superior to other antihypertensive drugs for preventing myocardial infarction and stroke in people with moderate to high-risk hypertension. The emphasis must remain on detecting and treating blood pressure to goal in order to prevent poor outcomes. Achieving control will require a multi-drug strategy in most cases.[18,19]

Caveats

The studies in this analysis varied in their inclusion criteria, the control drugs used, and outcomes.

It is possible that in people with moderate-risk hypertension, ARBs have different effects compared to high-risk hypertensives with evidence of end-organ damage.

The study did not receive any sponsorship.

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