Are ARBs now first-line therapy for hypertension?

Gordon McInnes BSc, MD, FRCP, FFPM, FBPharmacolS

Now that generic ARBs are available and ACE inhibitors have consequently lost their cost advantage, Professor McInnes makes the case for starting antihypertensive treatment with an ARB.

In the British Hypertension Society (BHS)/NICE guidelines for the management of uncomplicated essential hypertension, ie where there is no compelling indication or contraindication for a particular therapy, an ACE inhibitor or angiotensin-II receptor blocker (ARB) is recommended as first-line treatment in individuals aged less than 55 years, and a calcium-channel blocker (CCB) in those 55 years or older and in people of Afro-Caribbean heredity.

Thus, age and race are used as surrogates for renin-angiotensin system (RAS) activity. The blood pressure-lowering effect of RAS-blockers in younger, white people, who tend to have renin-dependent hypertension, is greater than that of a CCB; in contrast, older and black people, who tend towards low-renin hypertension, respond preferentially to CCBs.1

Underpinning this approach to initiation of drug treatment for hypertension is evidence that the benefit of antihypertensive therapy is proportional to blood pressure lowering.2,3 Reduction of blood pressure therefore takes priority while mechanism of action of antihypertensive drugs is relatively unimportant.

As generic ACE inhibitors were much less expensive than patented ARBs, the BHS/NICE guidelines express a preference for ACE inhibition with an ARB reserved for those unable to tolerate an ACE inhibitor.

Since the publication of these guidelines, several ARBs have come off patent (candesartan, irbesartan, losartan and valsartan) and now have costs on a par with generic ACE inhibitors. As unit cost is no longer an issue, is there now a case for starting treatment with a generic ARB in preference to an ACE inhibitor?

Extra benefits with ACE inhibitors?

At first sight, the answer to this question appears straightforward. ARBs have blood pressure-lowering efficacy equivalent to that of ACE inhibitors but are better tolerated.4 Both drug classes are associated with few adverse events but, while about 15 per cent of people treated with ACE inhibitors develop a dry, irritating cough,5 ARBs have a side-effect profile indistinguishable from that of placebo.4

However, there are those who argue that the rationale for the BHS/NICE guidelines is unsound since ACE inhibitors,
The BH S/N IC E guidelines recommend an A C E inhibitor or ARB in younger white patients; is there now not a case for initiating treatment with an ARB?

Figure 2. The BH S/N IC E guidelines recommend an A C E inhibitor or ARB in younger white patients; is there now not a case for initiating treatment with an ARB?

despite similar blood pressure reduction, have benefits not shared by ARBs. 

There has been much speculation that ACE inhibitors have specific outcome advantages. Based on the results of trials such as HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), it is suggested that these drugs reduce cardiovascular risk independent of blood pressure changes. Furthermore, it is proposed that ARBs lack this benefit and may even increase the risk of MI.

Although meta-regression analysis does not support an effect different from that expected from blood pressure reduction with either class of RAS-blocker, reports continue to appear proposing a disparate effect on outcomes of ACE inhibitors and ARBs.

The most recent suggests that ACE inhibition is associated with a 10 per cent reduction in all-cause mortality while no such effect is seen with an ARB.

The findings from this study have been hugely influential and therefore the conclusions require careful scrutiny. The method used was a pooled, or network, meta-analysis that depends on indirect comparisons of trials with different drugs, different designs and in different patient populations. An unintended consequence of such analyses is the potential for introduction of bias. There was, for example, marked imbalance between the ACE inhibitor and ARB trials with regard to absence of active comparators (ACE inhibitor trials 43 per cent vs ARB trials 15 per cent). Thus, ACE inhibitor trials might be expected to be associated with better outcomes.

Furthermore, while an ARB was first-line therapy in all ARB trials included, in almost 50 per cent of ACE inhibitor trials other drugs were first line making the influence of ACE inhibition uncertain.

Despite these biases, reduction in cardiovascular mortality, where there is a plausible role for RAS-blockade, did not differ between ACE inhibitor and ARB trials.

Head-to-head trials

Such cross-trial comparisons are common but hazardous because of the potential biases. The best method to compare drugs is direct (head-to-head) randomised trials in large populations.

Although not included in the above analysis, there have been no less than six such large-scale comparisons of ACE inhibitors and ARBs. A meta-analysis of these trials shows no difference between the drug classes for all-cause mortality, cardiovascular mortality, MI or stroke.

Thus, ARBs are not inferior to ACE inhibitors in the prevention of cardiovascular events or death and, in all the trials, ARBs are better tolerated.

Conclusion

Based on the best evidence, it appears that ARBs and ACE inhibitors are interchangeable in terms of blood pressure lowering and reduction in cardiovascular outcomes but ARBs have an advantage in tolerability. Now that there is no cost differential, ARBs should replace ACE inhibitors for initiation of antihypertensive therapy in appropriate individuals.

References


Declaration of interests

Professor McInnes has received honoria from Bayer, Boehringer Ingelheim, Novartis, Servier and Takeda, and has received research grants from Bayer, Boehringer Ingelheim and Pfizer.

Gordon McInnes is professor emeritus, Institute of Cardiovascular and Medical Sciences, Gardner Institute, Western Infirmary, Glasgow

Letters

If you have any issues you would like to air with your colleagues or comments on articles published in Prescriber, the Editor would be pleased to receive them and, if appropriate, publish them on our Letters page. Please send your comments to:

The Editor, Prescriber, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.com