

Is there a difference between an angiotensin-converting enzyme inhibitor and an angiotensin-specific receptor blocker for the treatment of hypertension?

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Introduction

The renin-angiotensin system (RAS) and angiotensin II, in particular, play a central role and have been implicated in the spectrum of cardiovascular disease (CVD), beginning with hypertension, diabetes mellitus, atherosclerosis, myocardial infarction (MI), strokes and heart failure.

Modulation of the RAS by the two most widely used inhibitors of the system, i.e. angiotensin-converting enzyme (ACE) inhibitors and angiotensin-specific receptor blockers (ARBs) plays a crucial role in the primary and secondary prevention of cardiovascular events. These drugs both target angiotensin II, but in different ways. The ACE inhibitor reduces the formation of angiotensin II, and the ARB blocks the angiotensin II receptor. This difference in action against angiotensin II has led to the longstanding issue of whether or not there is a clinically significant difference between the two when treating hypertension. Are they equally effective? The problem from a clinical viewpoint is that the majority of patients with hypertension also have other cardiovascular risk factors which increase the cardiovascular risk of hypertension, and which may change the choice of the drugs used, i.e. the concept of compelling indications.

Are renin-angiotensin system inhibitors better than other drugs when used as first-line antihypertensive drugs?

Forty-two studies with 65 733 participants were evaluated in a recent Cochrane meta-analysis.¹ The authors found that all-cause mortality was similar in evidence of moderately good quality when RAS inhibitors were used as initial monotherapy compared to other first-line antihypertensive agents, such as diuretics, calcium-channel blockers and beta blockers. First-line diuretics caused less strokes and heart failure than first-line RAS inhibitors. There was low-quality evidence on the effect on end-stage renal failure, and a conclusion could not be drawn in this regard. There were limited data on serious side-effects in these trials, and again therefore, conclusions about these drugs and serious side-effects could not be reached.

A comparison of angiotensin-converting enzyme inhibitors and angiotensin-specific receptor blockers

The Blood Pressure Lowering Treatment Trialists' Collaboration evaluated 27 randomised clinical trials with 158 709 patients with hypertension, with and without diabetes.² The authors came to the conclusion that total cardiovascular events were reduced to a comparable extent using ACE inhibitors and ARBs in patients with hypertension, in both diabetic and non-diabetic patients.

In 2009, Law, Morris and Wald evaluated 147 randomised clinical trials with 958 000 people with hypertension mainly, but other cardiac conditions were also included in this meta-analysis.³ They concluded that the five major classes of blood pressure (BP)-lowering drugs had a similar effect in reducing coronary heart disease events and strokes for a given reduction in BP, and that there was no evidence of a pleiotropic effect caused by any drug other than BP lowering. A reduction of BP was the most important factor in reducing cardiovascular events.

Twenty-five randomised clinical trials were evaluated in a meta-analysis in 2012, in a multiple-treatment meta-analysis of drugs used in the treatment of primary hypertension.⁴ It was concluded that a particular drug class did not stand out as superior across multiple CVD outcomes. There was little or no difference between commonly used BP-lowering drugs, including ACE inhibitors and ARBs.

ACE inhibitors and ARBs were compared in a 2014 Cochrane meta-analysis of nine randomised clinical trials involving 11 007 people.⁵ The authors concluded that there was no evidence of a difference in total mortality and cardiovascular outcomes between the two types of RAS inhibitors, although the ARBs were associated with a lower side-effect profile. However, according to the authors, there was a possibility of publication bias in these studies.

Concerns were raised in the literature that ARBs may be responsible for an increase in MI when used in the treatment of CVD. A meta-analysis in this regard, one of many on the subject, was published in 2012.⁶ This study evaluated the controversial issue using all available data at that stage. It was concluded that ARBs have a neutral effect on modifying MI and cardiovascular mortality risk. There was no definite evidence that ARBs increased

Table 1: Guideline recommendations on the use of angiotensin-converting enzyme inhibitors and angiotensin-specific receptor blockers in the treatment of hypertension

	Younger people (< 55 or < 60 years)	Older people or of black origin
Step 1	ACE inhibitor or an ARB	
Step 2	ACE inhibitor or an ARB + calcium-channel blocker (preferred?), or ACE inhibitor or an ARB + diuretic	Calcium-channel blocker or diuretic
Step 3	ACE inhibitor or an ARB + calcium-channel blocker + diuretic	

ACE: angiotensin-converting enzyme, ARB: angiotensin-specific receptor blocker

the risk of MI. The authors concluded that ARBs remain the most tolerable class of antihypertensive drugs.

The authors of a comprehensive meta-analysis of 55 randomised clinical trials on 195 267 people with hypertension sought to evaluate the effect of various classes of antihypertensive drugs.⁷ Twelve randomised clinical trials and 13 randomised comparisons involving 35 707 patients with hypertension were suitable for data analysis, in which an ACE inhibitor was used compared to placebo, and 13 randomised clinical trials on 65 256 patients in which an ARB was used as an antihypertensive agent compared to placebo. There was a difference of -2 to -4 mmHg between the ACE inhibitor and placebo, and a difference of -2 to -3.7 mmHg between the ARB and placebo. Many other drugs were used as well by the patients in both arms of the trials. Despite the small reduction in BP, strokes were reduced by 20% [95% confidence interval (CI): 7-31] with the ACE inhibitor, and 9% (95% CI: 3-14) by the ARB. Coronary heart disease was significantly reduced by the ACE inhibitor by 13% (95% CI: 3-21), but the ARB did not reduce coronary heart disease significantly. Heart failure was significantly reduced by both the ACE inhibitor and the ARB. When used as monotherapy, neither of these two agents reduced cardiovascular mortality or all-cause mortality, probably because of the underlying use of multiple other lifesaving drugs in the trials. It remains difficult for the true effect to be determined because of this aspect.

What do the guidelines say?

The guidelines, especially the British National Institute of Clinical Excellence⁸ make the following recommendations (Table 1).

In general, to reach the goal BP of < 140/90 mmHg in anyone up to age 80, the majority of patients need a combination of drugs in which an ACE inhibitor or ARB feature in the combination. In many meta-analyses, including the large recent one in 2014,⁷ the large combination trials in which an ACE inhibitor or an ARB were used, were not included in the meta-analyses as these meta-analyses were on monotherapy.

There is probably no indication for combining an ACE inhibitor and an ARB as there is no additional benefit and there may be harm.⁹ There is also no indication for combining a RAS inhibitor and beta blocker in the treatment of hypertension to reduce BP. The combination produces little additional reduction in the BP when compared to the BP reduction achieved through monotherapy with either of these agents. This combination is used in secondary prevention after a MI and in heart failure to reduce mortality. The beneficial effect does not relate to BP reduction in these circumstances.

Conclusion

Many meta-analyses are available which aim to evaluate whether or not there is a significant clinical difference between ACE inhibitors and ARBs when used as monotherapy in the treatment of hypertension.

There does not seem to be any major clinical significant difference between these two agents. However, no real large, direct head-to-head randomised comparison trials have been conducted on these two agents in hypertension.

ARBs seem to have a neutral effect in reducing MI. ACE inhibitors do reduce MI. At this stage of the evidence, this may be the only real difference between the two.

The issue of which is of these agents is superior can be resolved by using combination therapy in hypertension as the majority of patients with hypertension require two or more drugs to control their BP. Whether or not there is a superior drug combination in hypertension treatment is the new debate.

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