ACE inhibitors and ARBs: cost-effectiveness and safety

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Keywords: angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), hypertension, safety, cost-effectiveness

Abstract
Medicines that affect the renin-angiotensin-aldosterone system are effective in several diseases. Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II, while angiotensin-receptor blockers (ARBs) selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT1). Studies found that the two drug classes are equally safe and effective at managing hypertension, and have similar effects on other risk factors and clinical outcomes in patients with essential hypertension. It has also been confirmed that ARBs are less likely to cause coughing, but it has been suggested that this side-effect might be less common with ACE inhibitors than randomised trials indicate. Therefore, two important questions arise: which drug class is more effective, and what would the effect be if the two classes were used together? A recent study reported that restricting the prescribing of ARBs, so that they are given only to patients who are intolerant to ACE inhibitors, could save millions of dollars in health care costs, without any adverse effects on cardiovascular health. Despite the fact that both ACE inhibitors and ARBs are important in the treatment of essential hypertension, there is a lack of comparative evidence of the long-term benefits and harms of these two classes of agents. Only a few studies have compared ACE inhibitors and ARBs for periods longer than one year, and there is a lack of research on the pharmacoeconomic aspects of these two drug classes. More studies are needed.

Introduction
Medicines that affect the renin-angiotensin-aldosterone system are effective in treating several diseases. Using them safely and cost-effectively is a basic clinical skill needed by prescribers to treat chronic disease in adults.

The main effector peptide of the renin-angiotensin system is angiotensin II, which has neural, renal, cardiovascular and adrenal effects. Two classes of medicines affect angiotensin II, namely angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs). ACE inhibitors block the conversion of angiotensin I to angiotensin II, while ARBs selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT1). Neither of these drug classes is 100% effective in achieving its biochemical goal. Therefore, it is important for prescribers to know which drug class is more effective, and what the effect would be if the two classes were used together. A recent study reported that restricting the prescribing of ARBs, so that they are given only to patients who are intolerant to ACE inhibitors, could save millions of dollars in health care costs, without any adverse effects on cardiovascular health.

Angiotensin-converting enzyme inhibitors
ACE inhibitors reduce blood pressure by interfering with the conversion of angiotensin I to angiotensin II, and by inhibiting the degradation of bradykinin, thereby decreasing peripheral vascular resistance, without causing reflex tachycardia. Angiotensin II is a powerful vasoconstrictor and stimulus for aldosterone release. ACE inhibitors reduce blood pressure in many hypertensive patients, regardless of plasma renin activity. Their antihypertensive effect is enhanced by a low-salt diet. Because they provide renal protection, they are the drugs of choice for patients with diabetes, and may be preferred when treating black patients.

Currently available ACE inhibitors in South Africa include captopril, benazepril, cilazapril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril and trandolapril. They are primarily used to treat hypertension and congestive heart failure, reduce mortality in patients with heart failure, prevent progressive post-infarction heart failure, reduce cardiovascular outcomes in patients at high risk, and are renoprotective in diabetics and patients with renal disease with proteinuria.

Potential side-effects of ACE inhibitors include:

- A dry, irritating cough (the most common side-effect).
- Angioedema (the most serious side-effect) affects the oropharynx, and can be fatal. It is the most common side-effect among black patients, smokers and those with a history of allergy.
- A skin rash.
- Hyperkalemia (especially in patients with chronic renal failure, and those taking potassium-sparing diuretics, potassium supplements or nonsteroidal anti-inflammatory...
drugs (NSAIDs)).
- Dysgeusia (an altered sense of taste).
- Reversible acute renal failure, if stenosis affects one or both kidneys.
- Proteinuria, which is rare at the recommended doses.
- Neutropenia.
- Hypotension with initiation of treatment. Therefore, it is often recommended that ACE inhibitors are taken at night before going to bed.

ACE inhibitors are the least likely of the antihypertensives to cause erectile dysfunction, and are contraindicated in pregnancy.5

**Angiotensin-receptor blockers**

ARBs block angiotensin II receptors, and therefore also interfere with the renin-angiotensin system. Angiotensin II receptor blockers and ACE inhibitors are equally effective as antihypertensives.4 However, angiotensin II receptor blockers may provide added benefits via tissue ACE blockade.4

Available ARBs in South Africa are candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan.3 They are used in the treatment of essential hypertension (especially if left ventricular hypertrophy is present), to reduce the progression of microalbuminuria, and retard that of established nephropathy in type 2 diabetics. They may also be used in combination with ACE inhibitors in the treatment of cardiac failure.3 Therefore, the two classes have the same beneficial effects in patients with left ventricular failure, or with nephropathy due to diabetes. An angiotensin II receptor blocker, used with an ACE inhibitor or a β-blocker, reduces the hospitalisation rate of heart failure patients.4

The incidence of adverse events is low. Angioedema occurs, but much less frequently than with ACE inhibitors.4 Precautions for use of angiotensin II receptor blockers in patients with renovascular hypertension, hypovolemia, and severe heart failure, are the same as those for ACE inhibitors.4 Other potential side-effects of ARBs include headache, dizziness, nausea and hypotension. Angiotensin II receptor blockers are similar to ACE inhibitors, but contraindicated in pregnancy.5

**Safety of ACE inhibitors vs. ARBs**

Studies found that the two drug classes are equally safe and effective at managing hypertension, and have similar effects on other risk factors and clinical outcomes in patients with essential hypertension.6 They also confirmed that ARBs are less likely to cause coughing, but suggested that this side-effect might be less common with ACE inhibitors than randomised trials indicate.4 Therefore, the benefits of ARBs are similar to those of ACE inhibitors, but if the patient develops a chronic cough as a side-effect of an ACE inhibitor, an ARB should be prescribed. Table I gives a summary of the rate of cough as a side-effect of ACE inhibitors vs. ARBs. Both ACE inhibitors and ARBs should not be taken by women who are pregnant, or who plan on becoming pregnant.

**Cost-effectiveness of ACE inhibitors vs ARBs**

The use of ARBs increased by more than 4 000% in Canada from 1996-2006, yet the benefit of ARBs over ACE inhibitors has not been conclusively proven, except for a reduction in dry cough.3 This led a group of researchers to conduct a study on the cost-effectiveness of these two drug classes.3 A cost-minimisation analysis with a decision-tree model, using a societal perspective over a period of one year, was conducted.3 They found that if access to ARBs had been restricted in 2006, the potential cost savings to the Canadian health care system might have been more than 77.1 million Canadian dollars, without any adverse effect on cardiovascular health.1 From a pharmacoeconomic perspective, this is a significant finding. However, similar studies in other countries are scarce.

**Table I: Cough as a side-effect of ACE inhibitor and ARB therapy**

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<tr>
<th>Research setting</th>
<th>ACE inhibitor (%)</th>
<th>ARB (%)</th>
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<tbody>
<tr>
<td>Randomised controlled trials</td>
<td>9.9</td>
<td>3.2</td>
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<tr>
<td>Cohort-based studies</td>
<td>1.7</td>
<td>0.6</td>
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</table>

a = angiotensin-converting enzyme inhibitors, b = angiotensin-receptor blockers

While ACE inhibitors and ARBs both target the renin system and are clinically regarded as effectively equivalent, it is not clear whether this is appropriate. For example, ACE inhibitors do not entirely block the production of angiotensin II because of the presence of unaffected converting enzymes. Also, ACE inhibitors are associated with well-known adverse events not shared by ARBs, of which cough and angioedema are examples. A recent study also suggested that ARBs may be associated with a slightly increased cancer risk, but more research is needed.7 The Food and Drug Administration (FDA) is reviewing information related to ARBs, but has not reached a conclusion that ARBs cause an increased risk of cancer. It appears that the benefits of taking ARBs outweigh the possible risks.7 Therefore, it would be clinically useful to have a better understanding of the relative safety and cost-effectiveness of these two drug classes. Matchar et al2,8 conducted extensive research on the comparative effectiveness of ACE inhibitors vs. ARBs. They analysed 69 reports, based on 61 different studies that directly compared an ACE inhibitor and an ARB, in adults with essential hypertension. A summary of their results is given in Table II. The full report is available on the Internet and provides a comprehensive comparison of these drugs classes.2

In chronic kidney disease, a meta-analysis by Kunz et al9 concluded that ACE inhibitor and ARB monotherapy are similarly effective at reducing proteinuria, but a combination of the two angiotensin-2-suppressing drugs works better than either agent individually. However, a blanket recommendation to combine them is regarded as premature because there is little evidence that the combination would improve clinical outcomes over monotherapy, and the safety of such combination therapy is largely undefined.
Table II: Evidence of comparative long-term benefits and harms of ACE inhibitors vs. ARBs for essential hypertension\(^{1,2}\)

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<thead>
<tr>
<th>Indicator</th>
<th>Strength of evidence</th>
<th>Conclusion</th>
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<tr>
<td>Blood pressure control</td>
<td>High</td>
<td>ACE inhibitors and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. This conclusion is based on evidence from 50 studies (47 RCTs, one non-randomised controlled clinical trial, one retrospective cohort study and one case-control study) in which 13 532 patients, receiving an ACE inhibitor or an ARB, were surveyed for a period of 12 weeks to five years (median 16.5 weeks). Blood pressure outcomes were confounded by additional treatments and varying dose escalation protocols.</td>
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<td>Mortality and major cardiovascular events</td>
<td>Moderate</td>
<td>Due to insufficient numbers of deaths or major cardiovascular events in the included studies, it was not possible to discern any differential effect of ACE inhibitors vs. ARBs for these critical outcomes. In nine studies that reported mortality, myocardial infarction, or clinical stroke as outcomes among 3 356 subjects, 16 deaths and 13 strokes were reported. This may reflect low event rates among otherwise healthy patients, and relatively few studies with extended follow-up.</td>
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<tr>
<td>Quality of life</td>
<td>Low</td>
<td>No differences were found in measures of general quality of life. This is based on four studies, two of which did not provide quantitative data.</td>
</tr>
<tr>
<td>Rate of use of a single anti-hypertensive</td>
<td>High</td>
<td>There was no statistically evident difference in the rate of treatment success based on the use of a single antihypertensive for ARBs, as compared to ACE inhibitors. The trend toward the less frequent addition of a second agent to an ARB was heavily influenced by retrospective cohort studies where medication discontinuation rates were higher in ACE inhibitor-treated patients, and by RCTs with very loosely defined protocols for medication titration and switching.</td>
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<tr>
<td>Risk factor reduction and other intermediate outcomes</td>
<td>Moderate</td>
<td>There were no consistent differential effects of ACE inhibitors vs. ARBs on several potentially important clinical outcomes, including lipid levels, progression to type 2 diabetes mellitus, markers of carbohydrate metabolism/diabetes control, measures of left ventricular mass or function, and progression of renal disease, either based on creatinine, glomerular filtration rate or proteinuria. Relatively few studies assessed these outcomes over the long term.</td>
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For adult patients with essential hypertension, how do ACE inhibitors and ARBs differ in safety, adverse events, tolerability, persistence and adherence?

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<td>High (cough, withdrawals due to adverse events) to moderate (persistence/adherence) to low (angioedema)</td>
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<td>ACE inhibitors have been consistently shown to be associated with a greater risk of cough than ARBs. The pooled odds ratio (Peto) = 0.32. For RCTs, this translates to a difference in rates of cough of 6.7% (&quot;NNT = 15&quot;). However, for cohort studies with lower rates of cough, this translates to a difference of 1.1% (NNT = 87). This is generally consistent with evidence reviewed regarding withdrawals due to adverse events, in which the NNT is on the order of 27; that is, one more withdrawal per 27 patients treated with an ACE inhibitor vs. an ARB. There was no evidence of differences in rates of other commonly reported specific adverse events. Angioedema was reported only in patients treated with ACE inhibitors. However, because angioedema was rarely explicitly reported in the included studies, it was not possible to estimate its frequency in this population. ACE inhibitors and ARBs have similar rates of adherence based on pill counts. This result may not be applicable outside the clinical trial setting. Rates of continuation with therapy appear to be somewhat better with ARBs than with ACE inhibitors. However, due to the variability in definitions, limitations inherent in longitudinal cohort studies, and relatively small sample sizes for ARBs, the precise magnitude of this effect is difficult to quantify.</td>
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Are there subgroups of patients based on demographic characteristics (age, racial and ethnic groups and gender), use of other medications concurrently, or co-morbidities for which ACE inhibitors or ARBs are more effective, associated with fewer adverse events, or better tolerated?

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<td>Very low</td>
<td>Evidence does not support conclusions regarding the comparative effectiveness, adverse events, or tolerability of ACE inhibitors and ARBs for any particular patient subgroup.</td>
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\(a =\) angiotensin-converting enzyme inhibitors, \(b =\) angiotensin-receptor blockers, \(c =\) randomised controlled trial, \(d =\) number needed to treat

**Conclusion**

Despite the fact that both ACE inhibitors and ARBs are important in the treatment of essential hypertension, there is a lack of comparative evidence of the long-term benefits and harms of these two classes of agents. In particular, there is a lack of information about death or major cardiovascular events, and data on adverse events are inconsistently reported. Only nine studies compared ACE inhibitors and ARBs for periods longer than one year, and there is also a lack of research on the pharmacoeconomic aspects of these two drug classes. More studies are needed.

**References**