Title: Angiotensin II Receptor Blockers: A Comparative Effectiveness Review

Date: 10 April 2008

Context and policy issues:

Angiotensin II receptor blockers (ARB’s) are a class of drugs that affect the renin-angiotensin-aldosterone system. ARB’s bind to angiotensin II receptors, which then prevents angiotensin II from exerting its effects on those receptors. Blocking the action of angiotensin II reduces vasoconstriction, the retention of sodium and water, sympathetic nervous system activation, and constriction of blood vessels in the kidneys. The result is a decrease in blood pressure, a reduction in protein loss from the kidneys, and a reduction in left ventricular hypertrophy (a thickening of the left ventricular muscle wall).

Approximately 27% of the Canadian population between the ages of 35 and 64 and 50% of the population over the age of 65 have hypertension. Hypertension is an important and commonly encountered modifiable risk factor for heart disease and contributes to 66% of strokes and 35% and 20% of heart attacks in women and men, respectively. Canadian clinical practice guidelines for the treatment of hypertension consider ARB’s to be first-line therapy in individuals with hypertension not complicated by another condition, and first-line therapy in individuals with hypertension who have left ventricular hypertrophy or diabetes with or without protein in the urine. There are currently six ARB’s on the Canadian market (including losartan, eprosartan, irbesartan, valsartan, telmisartan and candesartan) approved for use in hypertension. According to the guidelines, ARB’s are second-line agents in individuals with a prior myocardial infarction, heart failure or nondiabetic kidney disease, or intolerance to angiotensin converting enzyme inhibitors. Losartan is approved for use in individuals with type 2 diabetes who have hypertension and protein in their urine and individuals with hypertension and left ventricular hypertrophy. Several of the ARB’s are also approved for use in other conditions not necessarily accompanied by hypertension. Candesartan and valsartan are approved for the treatment of heart failure and valsartan is also approved for treatment following myocardial infarction.
As there are several ARBs available in Canada, choosing one ARB over another to include on a national formulary may be dependent on a number of factors including the indications for which the ARB is approved, the strength of evidence to support its use in a variety of indications, its cost and, importantly, its comparative effectiveness. This report will review the comparative clinical effectiveness of the different ARB’s which could potentially help in decision-making at the level of the publicly funded healthcare system.

Research question:

What is the comparative effectiveness of angiotensin II receptor blocker for reducing blood pressure, kidney protection and other outcomes?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and March 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and comparative studies.

Summary of findings:

Health technology assessments

No health technology assessments were identified that included head-to-head comparisons of the effectiveness of ARB’s.

Systematic reviews and meta-analyses

One meta-analysis was identified that compared telmisartan to losartan in titration-to-response studies. The objective of the meta-analysis was to compare the ability of the two ARB’s to reduce blood pressure during the last six hours of a 24-hour dosing interval. The meta-analysis included two randomized, double-blind, double-dummy trials performed in people with mild to moderate hypertension, defined as a seated diastolic blood pressure (DBP) between 95 mmHg and 109 mmHg following a run-in phase. To be included, patients also had to have an average 24-hour DBP that was greater or equal to 85mmHg immediately before starting active treatment. In addition, patients had to be able to stop current therapy for four weeks and receive placebo during that time. One study was conducted exclusively in the United States and the other included centers in Canada, Europe, and South Africa. Following a four week single-blind placebo run-in period, patients were randomized to received telmisartan (n=360) 40mg titrated up to 80mg if needed or losartan (n=360) 50mg titrated up to 100mg if needed after four weeks. Both medications were administered as once daily doses and patients were monitored with 24 hour ambulatory blood pressure monitoring (ABPM) and during clinic visits for eight weeks. In the telmisartan and losartan groups, the average ages were 53.2 and 54.4 years old, respectively, and in both groups the majority of patients were male. In terms of efficacy, the average mean reduction in blood pressure during the last six hours of the dosing interval (measured with 24 hour ABPM) was significantly greater (p<0.01) in the telmisartan group (6.6 ± 0.4 mmHg) than the losartan group (5.1 mmHg ± 0.4 mmHg ). This was the primary outcome measure of the analysis. DBP and systolic blood pressure (SBP) were both significantly lower in
the telmisartan group each hour of the final six hours of the dosing interval, but the overall blood pressure response did not differ between telmisartan and losartan, nor did the adjusted mean blood pressure reduction. The authors concluded that telmisartan was more effective in lowering blood pressure during the last six hours of a 24 hour dosing period. It should be noted that the product monograph for losartan recommends twice daily dosing or increasing the dose in those individuals whose blood pressure control is not maintained at the end of the dosing interval. As well, the methodology of the meta-analysis was not described in sufficient detail to assess how rigorous it was. It appears that a pooling of participants from two methodologically similar studies was used for the meta-analysis instead of data collected from a systematic review of the available literature.

**Randomized controlled trials**

**Left Ventricular Hypertrophy (LVH)**

One double-blind RCT was identified that compared the efficacy of losartan and valsartan in LVH. The study included 17 men and 13 women, with an average age of 48±8 years, who had untreated hypertension and concentric LVH demonstrated on an echocardiogram. People with congestive heart failure, cardiomyopathy, disease of the conductive system or valves, atrial fibrillation, angina, or previous myocardial infarction were excluded. The participants were randomized to either losartan 50mg to 100mg once daily (n=16) or valsartan 80mg to 160mg once daily (n=16) for four weeks. Participants whose blood pressure was not adequately controlled after this time were withdrawn from the study (n=2). Doppler echocardiography was performed before treatment, when blood pressure was initially controlled, and after six months to assess for changes in left ventricular function. A statistically significant decrease from baseline in SBP was observed with both ARB’s at the time of initial blood pressure control and after six months. However, there were no significant differences in average SBP when the two treatment groups were compared at the time of initial blood pressure control and after six months. In both groups, the left ventricular ejection fraction and fractional shortening did not change after six months of treatment. In both groups the left ventricular mass index (a predictor of cardiovascular morbidity and mortality) was reduced but in the valsartan group the degree of reduction was statistically significantly greater than in the losartan group (p<0.05). Other measures of left ventricular performance were improved over baseline with both losartan and valsartan but were not significantly different between the two ARB’s. The authors concluded that further research and larger trials are needed to determine whether improvements in left ventricular performance with either ARB reduce the risk of cardiovascular events.

**Hypertension**

Four RCTs were identified that compared the effectiveness in hypertension of two or more ARB’s available in Canada. The details of these studies can be found in the text and table 1 below. The main outcome measures of the study are presented in detail in the table. Details of other endpoints are described in the text.

Baguet et al. compared candesartan to losartan or placebo (all administered once daily) for six weeks in patients with mild to moderate hypertension, without any titration of dose. There was no rationale provided for the selection of these dosages. Blood pressure was assessed during clinic visits with a sphygmomanometer and with ABPM. The study was described as double-blind, but it was not clear whether the outcome evaluators were blinded. Three-hundred and ten participants were randomized after the placebo run-in, but 54 did not provide at least one complete set of 24 hour ABPM and were excluded. The primary outcome measure was the
mean change in DBP from baseline to 24 hours after the last dose of study medication, based on ABPM. Approximately 60% of the study population was male and the average age was 54.2 years. The average decrease in DBP from baseline was significantly larger with candesartan when compared with losartan (p<0.05) or placebo (p<0.001). The average decrease in SBP from baseline for both ARB’s was also significantly larger than placebo (p<0.001), but did not differ between ARB’s. Other endpoints were also assessed, including decreases in SBP and DBP 36 hours after the last dose of medication, changes in SBP and DBP during the day, during the evening, 12 hours after dosing, or 24 hours after dosing and the change in heart rate from baseline. Blood pressure lowering was significantly greater with candesartan than losartan for DBP, but not for SBP, for all of these endpoints. For heart rate, changes from baseline were not significantly different between the two ARB’s, or compared to placebo. The authors concluded that blood pressure control with candesartan 8mg daily was superior to losartan 50mg once daily.

DeRosa et al.\textsuperscript{13} compared telmisartan to eprosartan or placebo given once daily for 12 months in people with type 2 diabetes and mild hypertension. No rationale was given for the selection of dosages, which were not titrated during the 12 month study period. Blood pressure was assessed at clinic visits using a sphygmomanometer. The study was described as double-blind, but it was not clear whether the outcome evaluators were blinded. The primary blood pressure endpoints were DBP and SBP taken at six-month and 12-month clinic visits. The authors did not state whether they assessed adherence to the study medications or placebo. It was not clear how many patients who were randomized actually completed the study. The average age of participants in each group was 53 to 55 years and the percentage of males ranged from 50-55%. Both ARB’s were superior to placebo in lowering SBP and DBP at 6 and 12 month follow-up. For change in SBP from baseline, the difference between telmisartan and eprosartan was not significant at 12months. However, the reduction in DBP from baseline was significantly greater with telmisartan versus eprosartan (p<0.05) after 12 months. The authors concluded that telmisartan was superior to eprosartan despite the finding that only a significant difference was observed for a reduction in DBP and not SBP.

Calvo et al.\textsuperscript{14} compared telmisartan to valsartan given once daily in a three month open-label study in people with previously untreated mild to moderate essential hypertension. There was no placebo run-in period. The authors stated that they selected the highest recommended and most widely used dosages for each ARB in Spain. There was no titration up to or past the initial dosages over the three-month study period. Blood pressure was measured at clinic visits using a sphygmomanometer and with 48 hours of ABPM at baseline and after three months. This was an open-label trial in terms of drug administration but ABPM was assessed in a blinded fashion. The study population was 46% male and the average age was 47.6 years old. It was not clear how many patients had follow-up data available. Adherence to the study medications was not reported. For clinic visits, statistically significant decreases from baseline in SBP and DBP were observed with both ARB’s, but differences between ARB’s were not significant. Reductions from baseline in average SBP and DBP based on 48 hours of ABPM were also significant for both ARB’s, and was significantly greater with valsartan than telmisartan. They also analyzed SBP and DBP readings every two hours for 24 hours after awakening with ABPM and demonstrated that blood pressure was significantly reduced with both ARB’s for the entire dosing period. For SBP, reductions were greater with valsartan at all points during the 24 hour dosing period, including the final six hours. For DBP, reductions were larger with valsartan than with telmisartan for the last six hours, but similar for the first six hours of the 24 hour dosing interval. The authors concluded that both ARB’s were effective in lowering blood pressure for the entire 24 hour dosing period, but valsartan was more effective towards the end of the dosing interval.
Lacouriere et al.\textsuperscript{15} report on a pooled analysis of two identical studies that compared telmisartan 40mg to 80mg once daily to valsartan 80mg to 160mg once daily for mild to moderate hypertension for eight weeks following a two to four week placebo run-in period. Dosages were initiated at the lower dose of the range for two weeks then and titrated up for the remaining six weeks for all patients. There was no rationale provided for the selection of dosages. Blood pressure was measured during study visits with a sphygmomanometer and with 24 hours of ABPM at baseline and during active treatment. Efficacy was assessed with the average blood pressure during the last 6 hours of the dosing interval compared to baseline. Midway through the study, the effect of a missed dose was assessed by administering one day of placebo and monitoring with 24 hours of ABPM. The study defined change in DBP for these outcomes as the primary outcomes measures of the study. The average age of study participants was 54 years and 69\% were male. Study follow-up was incomplete (93\% to 95.5\% in each group) and there was no explanation for drop-outs. During the last six hours of the dosing interval and after a missed dose, DBP and SBP reductions were greater with telmisartan than with valsartan. Other study endpoints included clinic cuff SBP and DBP, which was not significantly different between the two ARB’s for either SBP or DBP. The authors concluded that telmisartan 80mg once daily produced significant reductions in blood pressure for the entire dosing interval and reduced blood pressure to a greater magnitude than valsartan 160 mg once daily.

Table 1: RCTs Comparing the Efficacy of ARB’s for Hypertension

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>INTERVENTION</th>
<th>INCLUSION AND EXCLUSION CRITERIA</th>
<th>MAIN RESULTS</th>
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<tbody>
<tr>
<td>Baguet et al., 2006\textsuperscript{12}</td>
<td>Candesartan 8mg once daily (n=87)</td>
<td>Inclusion: Age 18 to 75 Mild to moderate HTN (DBP 95-115mmHg after a 2 to 4 week placebo run-in)</td>
<td>Mean change in DBP (mmHg) from baseline to 24 hours after the last dose of study medication:</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled 6 week multicentre study</td>
<td>Losartan 50mg once daily (n=89)</td>
<td>Exclusion: Severe HTN, secondary HTN, heart failure, MI in previous six months, heart valve abnormalities, angina, arrhythmia, stroke, severe renal or hepatic impairment, high serum potassium, contraindication or known hypersensitivity to ARB’s</td>
<td>Candesartan: -7.3 ± 6.9 \hspace{1cm} Losartan: -5.1 ± 4.9 \hspace{1cm} Placebo: -0.3 ± 6.5 (p&lt;0.05 candesartan versus losartan) \hspace{1cm} (p&lt;0.001 candesartan versus placebo) \hspace{1cm} (p&lt;=0.05 losartan versus placebo)</td>
</tr>
<tr>
<td>14-day placebo run-in if not previously on antihypertensives</td>
<td>Placebo (n=80)</td>
<td></td>
<td>Mean change in SBP (mmHg) from baseline to 24 hours after the last dose of study medication:</td>
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<tr>
<td>28-day placebo run-in if previously on antihypertensives</td>
<td></td>
<td></td>
<td>Candesartan: -10.8 ± 11.3 \hspace{1cm} Losartan: -8.8 ± 8.9 \hspace{1cm} Placebo: +1.2 ± 9.9 (p=NS candesartan versus losartan) \hspace{1cm} (p&lt;0.001 candesartan versus placebo) \hspace{1cm} (p&lt;0.001 losartan versus placebo)</td>
</tr>
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<tr>
<td>DeRosa et al., 2004&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Telmisartan 40mg once daily (n=40)</td>
<td>Inclusion: Type 2 diabetes according to the American Diabetes Association Criteria for at least two years</td>
<td>Mean change in SBP (mmHg) from baseline: Telmisartan: +8±2 Eprosartan: +7±2 (p=NS telmisartan versus eprosartan) (p&lt;0.01 placebo versus both ARBs)</td>
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<tr>
<td></td>
<td>Eprosartan 600mg once daily (n=39)</td>
<td>Mild essential hypertension according to WHO-ISH criteria on repeated measurements</td>
<td>Mean change in DBP (mmHg) from baseline at 12 months: Telmisartan:+ 8±2 Eprosartan: +4±2 (p&lt;0.05 telmisartan versus eprosartan) (p&lt;0.05 placebo versus both ARBs)</td>
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<td></td>
<td>Placebo (n=40)</td>
<td>Exclusion: Secondary or malignant HTN, unstable angina, MI in previous six months, liver dysfunction, renal impairment or contraindications to ARB or ACEI's.</td>
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<td></td>
<td>Calvo et al., 2004&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Telmisartan 80mg once daily (n=34)</td>
<td>Conventional SBP (mmHg) Measurements at Follow-up: Telmisartan Baseline: 151.5±16.4 3-month: 140.8±21.2 (p&lt;0.001 versus baseline) Valsartan: Baseline: 156.5±14.9 3-month: 140.7±19.7 (p&lt;0.001 versus baseline) Difference between ARB’s in change from baseline not significant.</td>
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<td>Valsartan 160mg once daily (n=36)</td>
<td>Inclusion: Previously untreated mild to moderate essential HTN defined as SBP between 140-179mmHg or DBP between 90-109mmHg Ambulatory BP measurements that confirmed: 24 hour mean SBP/DBP above 130/80mmHg, the diurnal mean above 135/85mmHg and the nocturnal mean above 12/70mmHg</td>
<td>Conventional DBP (mmHg) Measurements at Follow-up: Telmisartan Baseline: 89.3±12.1 3-month: 80.7±14.6 (p&lt;0.001 versus baseline) Valsartan: Baseline: 91.9±10.5 3-month: 81.4±13.3 (p&lt;0.001 versus baseline) Difference between ARB’s in change from baseline not significant.</td>
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<td>Exclusion: Shift workers, heavy drinkers, heavy exercisers, severe arterial HTN, secondary HTN, cardiac disease (including angina, heart failure), stroke, nephropathy, retinopathy, prior myocardial infarction or revascularization</td>
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</table>
Reduction from Baseline in Average SBP (mmHg) based on 48 Hour ABPM:
Telmisartan: 10.8
Valsartan: 18.6
(p<0.001 telmisartan versus valsartan)

Reduction from baseline in Average DBP (mmHg) based on 48 Hour ABPM:
Telmisartan: 8.4
Valsartan: 12.1
(p=0.014 telmisartan versus valsartan)

Inclusion post-placebo run-in phase:
Mild to moderate essential HTN defined as an average seated DBP of 95-109mmHg.
24 hour mean ambulatory DBP ≥ 85mmHg

Reduction from baseline in Average SBP (mmHg) based on 48 Hour ABPM:
Telmisartan: 11.1
Valsartan: 9.1
(p=0.007 telmisartan versus valsartan)

Reduction from baseline in Average DBP (mmHg) based on 48 Hour ABPM:
Telmisartan: 7.6
Valsartan: 5.6
(p=0.0004 telmisartan versus valsartan)

Reduction from baseline in 24 hour mean SBP after a missed dose:
Telmisartan: -10.7±6.2
Valsartan: -8.7±6.2
(p=0.0024 telmisartan versus valsartan)

Limitations

Overall, several issues in the available studies make it difficult to draw conclusions about the comparative efficacy of ARB’s in hypertension. All the studies involved individuals with mild to moderate hypertension and had extensive exclusion criteria. People with cardiovascular disease were generally excluded from all studies. Because of this, it is not clear whether these studies can be generalized to people with more severe hypertension or hypertension accompanied by other chronic medical conditions. Furthermore, definitions for the degree of
hypertension varied across studies. Three of the four studies were three month’s duration or less,\textsuperscript{12,14,15} which limits the ability to draw conclusions about the efficacy of the ARB’s for long-term control of blood pressure and their comparative efficacy for clinically significant outcomes, such as cardiovascular events or death. With the exception of one study,\textsuperscript{14} there was no rationale provided for the dosage chosen for the ARB’s compared. It is not clear if the selected dosages would be considered equivalent and according to some guidelines, it would seem that they were not.\textsuperscript{16} As well, none of the hypertension studies titrated the dose to attain a response, so it is not clear if similar conclusions would be drawn if dosages were titrated higher where possible. Some, but not all ARB’s, were given at maximum dosages. Importantly, the product monograph for valsartan states that it should be administered twice daily, so it is not surprising that telmisartan would be more effective when the two ARB’s are compared as once daily dosages. The two studies that compared telmisartan to valsartan\textsuperscript{14,15} produced somewhat contradictory results, which make it difficult to draw conclusions about their comparative efficacy.

For left ventricular hypertrophy, the one trial that was identified also had a number of limitations including small sample size and withdrawing participants who were randomized but did not achieve adequate blood pressure control after 4 weeks.\textsuperscript{11} These methodological issues may limit the accuracy of the observed treatment effect and the generalizability of this study to the larger population with hypertension.

Conclusions and implications for decision or policy making:

In summary, no single study or meta-analysis was identified that compared all of the ARB’s to each other, which complicates the ability to draw strong conclusions about the comparative effectiveness of ARB’s in hypertension. This is further hampered by conflicting results from more than one study comparing the same ARB’s (i.e, valsartan versus telmisartan). For left ventricular hypertrophy, there is only poor quality evidence from a single study. In order to help make a decision as to which ARB should be included on a national formulary, further well-designed studies are needed that are longer-term and involve clinically important outcomes such as cardiovascular events, mortality, and quality of life. Until more conclusive evidence is available, formulary decisions should also take clinical experience and acquisition costs into consideration.

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