Chapter 4

Cost-Effectiveness of Angiotensin Receptor Blockers in Patients with Hypertension: a Comparative Analysis Using Clinical Trial and Observational Data

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Submitted to an International Journal
Pharmaceutisch Weekblad 2008;2(1):2-7 [in Dutch]

ABSTRACT

Background: Hypertension is an independent risk factor for cardiovascular diseases, resulting in an enormous burden to society, both in terms of health and costs. Therefore, further health gains and related cost-savings achieved by optimizing antihypertensive treatment is of highly importance. The aim of this study was to conduct a pharmacoeconomic analysis to estimate the costs and effects of treatment with angiotensin II receptor blockers (ARBs) in Dutch hypertensive patients.

Methods: The pharmacoeconomic analysis was twofold, firstly, we estimated cost-effectiveness based on a published, randomized, double-blind clinical trial comparing blood pressure lowering of olmesartan, losartan, valsartan and irbesartan. For this purpose, blood pressure lowering after 8 of treatment was inserted in the Framingham risk functions to estimate cardiovascular complications using an international health-economic model. Secondly, a cost-minimization analysis was done using daily practice prescription data from IADB.nl, a database covering a population of 500,000 adherent to 50 pharmacies.

Results: After 8 weeks, the trial-based analysis showed that treatment with olmesartan versus losartan, valsartan, and irbesartan, resulted in a statistically larger decrease in blood pressure (11.5 versus 8.2, 7.9 and 9.9 mmHg (P<0.05), respectively). Furthermore, olmesartan resulted in more complications averted. Based on reductions found in within-trial blood pressures, cost-effectiveness for olmesartan, losartan, valsartan,
and irbesartan was estimated at €39,100, €77,100, €70,700, and €50,900 per cardiovascular complication averted, respectively. Pharmacy data showed that trial-dosing at 1 ‘Defined Daily Dose’ (DDD) was not found in daily practice. On average, losartan, valsartan and irbesartan were consequently dosed above 1 DDD varying from 1.19-1.38 DDD, whereas olmesartan was dosed lower at 0.88 DDD and therefore resulting in (relatively) lower costs. **Conclusion:** Based on the exact trial data, olmesartan was estimated to be the most cost-effective option of the four ARBs based on within-trial blood pressure levels after 8 weeks. However, due to differences found in within-trial versus daily practice dosing and absence of effectiveness data from daily practice, confirmation is needed from further prospective studies comparing ARBs based on comparable blood pressure control including hard endpoints.

**INTRODUCTION**

Cardiovascular diseases are a leading cause of death and a great burden to health-care budgets in Europe. In the Netherlands, 9.2% of total health-care expenditures are attributable to costs for cardiovascular diseases (€ 5.3 billion). Hypertension is generally known as an independent risk factor for cardiovascular diseases (e.g. myocardial infarction, angina pectoris, stroke, heart failure, and peripheral heart disease), and is one of the risk-factors associated with mortality. Therefore, health gains and cost-savings could be achieved by optimizing antihypertensive treatment. Recommended or suggested type of antihypertensive therapy is dependent on several factors which relate to the severity of the disease (e.g. essential hypertension or hypertension due to related to specific cardiovascular diseases and/or diabetes) and therefore newer generally more effective and expensive antihypertensives are preferably prescribed to those subjects with increased cardiovascular risk.

Among other things, cost considerations play an increasing role in treatment decisions. Dutch treatment guidelines recommend – also based on cost considerations – in general to start with diuretics in patients with uncomplicated hypertension to achieve adequate blood pressure control below 140/90 mmHg. In case of insufficient blood pressure control, β-blockers, calcium channel antagonists or angiotensin-converting enzyme (ACE-) inhibitors should be added. Angiotensin II receptor blockers (ARBs) – a rather new class of agents with proven efficacy and placebo-like tolerability are often only considered in case of ACE-intolerance, due to cost considerations, daily practice experience and “evidence”. Dutch prescription data among a population 500,000 indicate correspondingly low (initial) use of ARBs; around 4% of first antihypertensive prescriptions and 8% of total number of antihypertensives prescribed refer to ARBs.
A comparative economic analysis for ARBs adds to discussions on rational prescribing of different types of ARBs. Therefore, the aim of this study was to estimate and compare the costs and effects of different ARBs in treating patients with essential hypertension in The Netherlands.

**Methods**

The present analysis was two-fold: data on costs and effectiveness for olmesartan, losartan, valsartan, and irbesartan were analysed based on (i) a clinical study of Oparil et al.\textsuperscript{15}, and (ii) by using daily practice pharmacy dispensing data. Such an approach is in line with the guidelines of “good pharmacoeconomic practice”, which on the one hand require an analysis of cost-effectiveness based on data from a randomised clinical trial, and on the other hand information based on observational data\textsuperscript{16-19}.

**Clinical Trial Data and Cost-Effectiveness**

Oparil et al.\textsuperscript{15} studied antihypertensive effectiveness of olmesartan, losartan, valsartan, and irbesartan in subjects with essential hypertension (defined as a diastolic blood pressure (DBP): 100-115 mmHg). Patients with a recent cardiovascular event history were excluded for the trial. A total of 588 patients were randomised and were treated with one “Defined Daily Dose” (DDD) per day of olmesartan (20 mg), losartan (50 mg), valsartan (80 mg), and irbesartan (150 mg), respectively. The DDD represents an International unit of measurement based on average maintenance dose, which should enable presentation and comparison of level of drug-use\textsuperscript{19}.

Changes in blood pressures 2, 4 and 8 weeks after start of antihypertensives were collected. The primary endpoint of the Oparil study\textsuperscript{15} was the change from baseline DBP at week 8. After 8 weeks, statistically significant larger decrease in blood pressure was achieved with olmesartan (-11.5 mmHg) compared with losartan (-8.2 mmHg; $P < 0.0002$), valsartan (-7.9 mmHg; $P < 0.0001$), and irbesartan (-9.9 mmHg; $P = 0.04$), respectively\textsuperscript{20}. Next to this, sufficient combined systolic and diastolic blood pressure control (<140/90 mmHg) was achieved in 32.4% of the patients on olmesartan versus 16.1% on losartan, 14.5% on valsartan, and 25.9% on irbesartan, respectively\textsuperscript{20}. Figure 1 shows that the percentage of patients having sufficient blood pressure control below 140/90 mmHg with olmesartan was not statistically different from blood pressure control found with irbesartan, but significant differences were found regarding the other 2 ARBs.

For the economic analysis, we assumed a hypothetical patient population of 100,000 which was distributed over within-trial observed blood pressure values after 8 weeks of study follow-up. Costs and effects
of olmesartan, losartan, valsartan, and irbesartan were calculated based on a simulation model as applied for the US situation and described in detail by Simons et al\textsuperscript{21}. For our analysis, the model was adapted to the Dutch situation by using Dutch cost estimates for cardiovascular and cerebrovascular complications. Blood pressures at 8 weeks and patient characteristics such as age and gender, were inserted in the Framingham risk functions to estimate cardiovascular complications\textsuperscript{22,23}. The model was used to estimate the reduction in cardiovascular risk for each treatment group after 1 and 5 years compared with the baseline cardiovascular risk. Table 1 presents costs (2006 values) for cardiovascular complications as inserted in the model\textsuperscript{24,25}. Official 2006 Dutch drug prices were used and calculated as price per DDD: €0.62 for 20 mg olmesartan, €0.74 for 50 mg losartan, €0.63 for 80 mg valsartan, and €0.70 for 150 mg irbesartan\textsuperscript{26}. Costs and complications were discounted at 4% and 1.5%, respectively according to the Dutch pharmacoeconomic guidelines\textsuperscript{16}. Cost-effectiveness was expressed in net costs per cardiovascular complication averted.

Table 1  Dutch cost estimates for cardiovascular complications in 2006 values\textsuperscript{18,19}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>6434</td>
</tr>
<tr>
<td>Other cardiovascular disease\textsuperscript{1}</td>
<td>3697</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5650</td>
</tr>
<tr>
<td>Other chronic heart disease\textsuperscript{2}</td>
<td>3052</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Average costs of estimates for heart failure (€ 5709) and peripheral heart disease (€ 1684);  
\textsuperscript{2}Average costs of estimates for angina pectoris (€ 4662) and coronary insufficiency (€ 1441).

**Cost-Minimization on Observational Data**

Daily practice dosing (“Prescribed Daily Dose”; PDD) of olmesartan, losartan, valsartan, and irbesartan was analyzed to compare with within-trial dosing of 1 DDD. Daily practice dosing of antihypertensives is generally expected to be titrated to achieve adequate blood pressure control\textsuperscript{5-8}. Following this, daily practice effectiveness of ARBs could be assumed to be comparable with potentially different PDDs and costs. Therefore, a cost-minimization analysis with assuming comparable effectiveness was conducted using daily practice prescription data from IADB.nl, a pharmacy dispensing database of 50 general pharmacies, covering a population of 500,000\textsuperscript{13,14}. Daily practice doses of ARBs at first prescription and after 180 days were evaluated. All patients that had started treatment with either olmesartan, losartan, valsartan, or irbesartan, and possible concomitant use of antihypertensives other than ARBs were included from IADB.nl.
Percentage patients with sufficient blood pressure control (<140/90 mmHg) after 8 weeks based on once daily 20 mg olmesartan, 50 mg losartan, 80 mg valsartan, or 150 mg irbesartan. $^*P = 0.002$ for losartan versus olmesartan; $^†P < 0.001$ for valsartan versus olmesartan; and $^‡P = NS$ for irbesartan versus olmesartan [Source: Oparil et al20].

Pharmacy data generally lack information on diagnosis for a prescription of a specific drug. Therefore, and to possibly better approximate the specific population of patients with essential hypertension more precise, additional analyses were conducted with exclusion of patients with other cardiovascular co-medication (antihypertensives, diuretics, β-blockers, calcium-channel antagonists, and ACE-inhibitors) and/or antidiabetics at baseline. PDDs were calculated by dividing the total number of DDDs of a specific prescription by the number of days the drug was prescribed for. Average PDDs for the first prescription ($t = 0$) and for the last prescription within half a year follow-up ($t = 180$) were calculated for olmesartan, losartan, valsartan, and irbesartan, respectively.

Results

Results on complications and costs within a hypothetical cohort of 100,000 patients with essential hypertension and different blood pressure decreases with olmesartan, losartan, valsartan, and irbesartan – as found in the Oparil study15 – are presented in table 2. Olmesartan resulted in most cardiovascular complications and mortality averted after 1 and 5 year(s) and was also considered to be the cheapest as compared with the other ARBs. Cost-effectiveness per cardiovascular event averted –
compared to do-nothing and without any background blood pressure lowering therapy\textsuperscript{15} – was estimated at €39,100 for olmesartan, €77,100 for losartan, €70,700 for valsartan, and €50,900 for irbesartan.

Pharmacy data showed that within-trial-dosing at 1 DDD was not found in practice. On average losartan, valsartan and irbesartan were consequently dosed above 1DDD varying from 1.19-1.38 PDD, whereas olmesartan was dosed at 0.88 PDD (table 3). Results are similar in all groups stratified on co-medication as a proxy for disease severity. In contrast to losartan, valsartan, and irbesartan, there was no measurable increase of PDD in the olmesartan group over a treatment period of 180 days. According to dosing found in subjects without cardiovascular comedication at $t = 180$, annual cost per patient per year with olmesartan, losartan, valsartan, and irbesartan, would amount around €201, €321, €306, and €353, respectively.

**DISCUSSION**

Based on data from clinical study of Oparil et al\textsuperscript{15} applied to an International model and applying Dutch prices for medication and Dutch cost estimates for cardiovascular complications, olmesartan resulted in lowest drug costs and most complications and deaths averted compared with other ARBs. Notwithstanding considerable decreases in blood pressure for all four ARBs, olmesartan appeared to be the most favourable option from a pharmacoeconomic point of view, based on the trial.

It should be noted that hard cardiovascular endpoints were not registered during the study follow-up. These cardiovascular complications were estimated based on blood pressure decrease. We note that the present economic study was conducted based on one clinical study with large internal validity and possibly limited external validity. Higher external validity could be achieved by using data from formal meta-analyses including comparison on hard cardiovascular endpoints of other existing members of the ARB class (e.g. eprosartan, candesartan cilexetil, tasosartan, telmisartan).

The current study also investigated the relevance of within-trial dosing at 1 DDD compares to daily practice dosing of ARBs to achieve adequate blood pressure lowering. Daily practice data from IADB.nl\textsuperscript{13,14}, consequently showed relatively lower doses for olmesartan as compared to losartan, valsartan, and irbesartan. In daily practice, these latter three ARBs were titrated from initial average daily doses of 1.04 DDD losartan, 1.18 DDD valsartan, and 1.16 DDD irbesartan to respectively 1.18 DDD, 1.34 DDD, and 1.33 DDD after approximately half a year. Such a titration to a higher dose was not found for olmesartan, with a constant average
dose at 0.88 DDD. Given the already lowest per DDD price for olmesartan, olmesartan was the cheapest option of all four ARBs. So, the result of our observational analysis is in line with the trial-based cost-effectiveness analysis. However, data on effectiveness and baseline blood pressure level are unknown from daily practice IADB.nl data. Therefore, our cost-minimalization study is limited in a sense that it is not known to what extent our assumption of equal effectiveness and similar types of patients on different ARBs holds true. This is also related to possible differences in persistence on and adherence to ARB treatment in daily practice.

Although ARBs have shown placebo-like tolerability\textsuperscript{9-12} in a clinical trial setting, compliance in a real-world setting may be lower and might therefore reduce the actually achieved blood pressure lowering and corresponding cardiovascular risk reduction\textsuperscript{27}. The very low number of patients that received olmesartan in daily practice is another major limitation of our study, which makes it difficult to compare doses and to draw definite conclusions on our findings.

Table 2  Cardiovascular complications averted within a hypothetical patient population of 100,000 subjects receiving 1 DDD of olmesartan, losartan, valsartan, and irbesartan, respectively

<table>
<thead>
<tr>
<th>Complications averted\textsuperscript{1}</th>
<th>Olmesartan</th>
<th>Losartan</th>
<th>Valsartan</th>
<th>Irbesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment period (in years)</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>- Stroke</td>
<td>27</td>
<td>313</td>
<td>18</td>
<td>209</td>
</tr>
<tr>
<td>- Other cardiovascular disease</td>
<td>288</td>
<td>1080</td>
<td>182</td>
<td>647</td>
</tr>
<tr>
<td>- Myocardial infarction</td>
<td>123</td>
<td>636</td>
<td>79</td>
<td>392</td>
</tr>
<tr>
<td>- Other chronic heart disease</td>
<td>63</td>
<td>181</td>
<td>37</td>
<td>111</td>
</tr>
<tr>
<td>- Cardiovascular mortality</td>
<td>24</td>
<td>361</td>
<td>17</td>
<td>230</td>
</tr>
<tr>
<td>Total</td>
<td>525</td>
<td>2571</td>
<td>333</td>
<td>1589</td>
</tr>
<tr>
<td>Drug costs (*1,000,000)</td>
<td>22.6</td>
<td>104.8</td>
<td>27.0</td>
<td>125.1</td>
</tr>
<tr>
<td>Savings (*1,000,000)</td>
<td>2.1</td>
<td>9.0</td>
<td>1.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Net costs (*1,000,000)</td>
<td>20.5</td>
<td>95.8</td>
<td>25.7</td>
<td>119.5</td>
</tr>
<tr>
<td>Net costs per complication Averted (*1000)\textsuperscript{2}</td>
<td>39.1</td>
<td>38.9</td>
<td>77.1</td>
<td>78.6</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Undiscounted; \textsuperscript{2}According to the Dutch guideline for pharmacoeconomic research, complications and costs (in 2006 values) were discounted at 1.5% and 4%, respectively\textsuperscript{46}. 

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Table 3  Number of patients (N), average number of PDD and standard deviation (SD) of the first prescription (t = 0) and after 180 days (t = 180) for all starters and stratified for comedication

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan</th>
<th>Losartan</th>
<th>Valsartan</th>
<th>Irbesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>PDD (SD)</td>
<td>N</td>
<td>PDD (SD)</td>
</tr>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>49</td>
<td>0.89 (0.28)</td>
<td>7636</td>
<td>1.05 (0.29)</td>
</tr>
<tr>
<td>t = 18</td>
<td>30</td>
<td>0.88 (0.32)</td>
<td>4754</td>
<td>1.19 (0.44)</td>
</tr>
<tr>
<td>Without cardiovascular comedication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>21</td>
<td>0.88 (0.22)</td>
<td>2733</td>
<td>1.04 (0.26)</td>
</tr>
<tr>
<td>t = 180</td>
<td>12</td>
<td>0.88 (0.24)</td>
<td>1668</td>
<td>1.18 (0.41)</td>
</tr>
<tr>
<td>Without anti-diabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 0</td>
<td>38</td>
<td>0.87 (0.23)</td>
<td>6574</td>
<td>1.04 (0.28)</td>
</tr>
<tr>
<td>t = 180</td>
<td>24</td>
<td>0.92 (0.33)</td>
<td>4051</td>
<td>1.19 (0.45)</td>
</tr>
</tbody>
</table>

*PDD is statistically different (based on T-test; P < 0.05) from 1 DDD as specified for the four different angiotensin II receptor blockers.

The US-study of Simons *et al*[^21] showed results comparable to the present study for the Netherlands. Other studies, of Conlin *et al*[^28], Püchler *et al*[^29], and studies of Stumpe *et al*[^30,31] found a comparable blood pressure lowering as found during the study of Oparil *et al*[^15]. In addition, these studies also indicated comparable incidence of adverse drug events for all four ARBs. Within our pharmacoeconomic analysis, we did not account for potential differences in type and severity of adverse events.

Notwithstanding the limitations mentioned, our economic evaluation based on a comparative analysis with ARBs in patients with essential hypertension, suggests that the cheapest ARB is most cost-efficient. To draw a definite conclusion, further analyses should be conducted and directed at head-to-head comparison of ARBs including comparable blood pressure control with hard cardiovascular endpoints.

**Conclusion**

Olmesartan was – based on differences in blood pressure control in one specific trial – estimated to be the most cost-effective option of the four ARBs investigated. Due to differences found in within-trial versus daily practice dosing and absence of effectiveness data from daily practice, confirmation is needed from further prospective studies comparing ARBs based on equal blood pressure control including hard cardiovascular endpoints.
ACKNOWLEDGEMENT

This study was financially supported by Daiichi-Sankyo Nederland BV, Zwanenburg, The Netherlands. A.A. Voors is a Clinical Established Investigator of the Netherlands Heart Foundation (2006T37). Previously, some of the authors received grants from other producers of ARBs.

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