Angiotensin receptor blockers in preventing stroke: A systematic review and meta-analysis of randomized controlled trials

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Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used in patients who are at high risk of cardiovascular events. A consensus has emerged that ACEIs can reduce the risk of stroke. This programme of overviews of randomized trials was established to investigate the effects of ARBs on the risk of stroke in patients at risk for cardio-cerebrovascular events. Electronic databases were searched up to January 2009, for randomized clinical trials comparing ARBs with other active treatments and placebo in patients at risk for cardio-cerebrovascular events. Data were extracted for patients’ characteristics, interventions, quality of trials, and rates of stroke. The efficacy measures were the odds ratios of strokes. We did separate overviews of trials comparing ARBs with placebo, with ACEIs, and with calcium antagonists. The pooled effects were calculated using the random effects model. Twenty three with 1832 patients were included in the analysis. The overview of placebo-controlled trials (11 trials, 44961 patients) revealed ARBs was associated with a significant reduction in the risk of stroke, with a pooled odds ratio of 0.91 (0.84 to 0.98). In the overview of trials comparing ARBs with ACEIs (6 trials, 26537 patients), there were no significant reduced risks of stroke (odds ratio 0.93, 0.84 to 1.03). In the overviews comparing ARBs with calcium antagonists (4 trials, 22446 patients), no significant difference was found, with a pooled ratio of 1.16 (0.91 to 1.48). Evidence of the benefits of ARBs on the risk of stroke is provided by the overviews of placebo-controlled trials. There was no evidence of differences when comparing ARBs with ACEIs, and with calcium antagonists. Therefore, ARBs should be regarded as suitable treatments for preventing stroke in patients who are at high risk of cardiovascular events.

Key words: Stroke, angiotensin receptor blockers, meta-analysis.

INTRODUCTION

Stroke is the second most frequent cause of death in the world and is responsible for about 5 million deaths each year (Murray et al., 1997). Overwhelming evidence indicates that elevated blood pressure is the strongest risk factor for stroke, whose occurrence in approximately two thirds of cases is dependent on an unrecognized or uncontrolled elevation in blood pressure (Kearney et al., 2005). Among the different therapeutic classes of antihypertensive agents, inhibitors of the renin-angiotensin system are widely used in patients who are at high risk of cardiovascular events. Evidence is very strong for the use of angiotensin converting enzyme inhibitors (ACEIs) to reduce the risk of stroke (Teo et al., 2000; Yusuf et al., 2000; Staessen et al., 2001; Bosch et al., 2002; Neal et al., 2002). Angiotensin receptor blockers (ARBs) theoretically produce more complete inhibition of angiotensin II and are better tolerated than ACEIs (Elliott, 2000). However, recent trials concluded that ARBs did not
lower the rates of stroke (Yusuf et al., 2008; Massie et al., 2008). This hindered the drawing of conclusions for clinical practice, and caused much concern over using these agents.

To determine the effective of ARBs in the prevention of stroke, we undertook a systematic review and meta-analysis of all published randomized controlled trials of ARBs in patients who are at high risk of cardio-cerebrovascular events.

METHODOLOGY

This meta-analysis was performed according to a predetermined protocol described in the following paragraph, and the QUOROM guidelines were followed at all stages of the process (Moher et al., 1999). Because strong evidence benefits of ACEIs and calcium antagonist was provided by a previous meta-analysis (Neal et al., 2000). We did separate overviews of trials comparing ARBs with placebo, with ACEIs, and with calcium antagonists.

Search strategy

Published trials of ARBs in preventing stroke were identified through a systematic search of MEDLINE, EMBASE, and the Cochrane central register of controlled trials, each from inception to January 2009. The search combined terms related to drugs (including MeSH search using exp angiotensin II type 1 receptor blockers*, and keyword search using words candesartan, irbesartan, losartan, valsartan, olmesartan, telmisartan, eprosartan, and angiotensin receptor blocker*), and terms related to diseases (including MeSH search using exp stroke*, exp cerebrovascular disorders*, and exp cerebrovascular diseases*, and keyword search using words stroke*, cerebrovascular disorder*, cerebrovascular disease*, cerebrovascular accident*, cerebral accident*, cerebral vascular accident*, and cerebrovascular event*), with a filter to restrict results to controlled trials, meta-analysis and systematic reviews. We also searched the reference lists of original reports and meta-analyses of studies involving ARBs, retrieved through the electronic searches, to identify studies not yet included in the computerized databases.

Trials selection

Published and unpublished trials fulfilling the following inclusion criteria were included in the present meta-analysis: (i) study design, randomized clinical trials, which all should have adequate Institutional Review Board (IRB) and consent processes; (ii) population, patients who are at high risk of cardio-cerebrovascular events, including patients with hypertension, patients with diabetes, patients with heart failure, and patients with recent stroke; (iii) intervention, ARBs versus placebo or another anti-hypertensive agent; (iv) outcome measurement, the rate of stroke.

After completion of the searches, two review authors (YBD and XHL) working independently assessed the titles and abstracts of all obtained reports for a rough judgment of an article’s eligibility. The full text copies of possibly and definitely relevant trials were obtained and assessed by the two authors independently according to the definitions in the criteria. Only trials meeting these criteria were assessed for methodological quality. For the publications reporting on the same study population, the article reporting the results of the last endpoint was included, and data that could not be obtained from this publication were obtained from others.

The observers were blinded to the names of the authors and their institutions, the names of the journals, sources of funding, and

acknowledgments, as well as the funder of the study.

Data extraction and end points

Data extraction was performed by two reviewers (YBD and XHL) independently. Any disagreement was resolved by discussion. For each study and each type of treatment, the following data were extracted: the authors of the study, the year of publication, information on study design (whether randomization, allocation concealment, intention to treat analysis, double blind or single blind, parallel or crossover), location of trial, length of study, number of subjects, patient age, sex, race, type of diagnosis, and number of patients with stroke. Numeric discrepancies between the two independent data extractions were resolved after discussion.

We documented all reported strokes, fatal or non-fatal, according to the definition used by the authors of individual studies and confirmed that cases represented actual numbers of patients with strokes rather than total numbers of cerebrovascular events. Where data on stroke were included as a composite end point, we recorded the components of cerebrovascular events that were provided and subsequently contacted study authors for the rates of strokes. We also contacted authors for complete details on cerebrovascular events for those studies in which only fatal or non-fatal strokes were reported, and we ultimately used the best obtainable data in our analysis.

Qualitative assessment

Two authors (in duplicate by YBD and XHL) used standard criteria (allocation concealment, blinding, intention to treat analysis, loss to follow-up) to appraise study quality, in addition to quantitative quality assessment by using the scoring system developed by Jadad et al. (1996). The quality scoring system was followed as: (i) allocation concealment, coded as adequate (1 score), inadequate or unclear (0 score); (ii) blinding, coded as double-blind (2 scores), single-blind (1 score), and open label (0 score); (iii) intention to treat analysis, coded as used (1 score), not used or unable to assess (0 score); and (iv) lost to follow-up, coded as given (1 score), and not given (0 score). “Poor quality” refers to a Jadad score less than 3.

Statistical analysis

The statistical analysis was performed by RevMan software version 4.2.6 (Cochrane Collaboration, Oxford, United Kingdom). For each study, we calculated odds ratios and combined them for the pooled odds ratio with 95% confidence intervals. We used the standard DerSimonian and Laird random effects model for primary analysis (DerSimonian and Laird, 1986). We chose this method a priori to account for potential variation between studies owing to differences in study populations. We also performed Mantel-Haenszel fixed effects analyses for estimating pooled odds ratios, to account best for the limited data available from some of the component studies (Mantel and Haenszel, 1959). Heterogeneity was tested using the Cochran Q test and inconsistency (the percentage of total variance across studies that is due to heterogeneity rather than chance) of treatment effects was measured across all comparisons of the end point (Higgins et al., 2003; Higgins and Thompson, 2002). We constructed standard funnel plots to investigate the potential for publication bias influencing the analysis (Sterne et al., 2001).

RESULTS

The flow of the randomized controlled trials included in
Figure 1. Flow diagram showing citations retrieved from literature searches and number of trials included in the meta-analysis. ARBs: Angiotensin receptor blockers.

Our analysis is as shown in Figure 1. We reviewed the full text of 208 articles from 1105 studies identified from our initial literature search and hand search. A total of 23 studies met the criteria for inclusion. We excluded three randomized controlled trials, because the classes of the control arms were multitherapy (Suzuki and Kanno, 2005; Mochizuki et al., 2007) and atenolol (Dahlöf et al., 2002). Therefore, 20 randomized controlled trials were included in the final meta-analysis (Pitt et al., 1997, 2000; Granger et al., 2000, 2003; Dickstein and Kjekshus, 2002; Berl et al., 2003; Matsumori, 2003; Lithell et al., 2003; Schrader et al., 2003, 2005; McMurray et al., 2003; Yusuf et al., 2003, 2008a,b,c; Barnett et al., 2004; Julius et al., 2004; McMurray et al., 2006; Ogihara et al., 2008; Massie et al., 2008).

**Trials characteristics and trials quality**

The IDNT compared irbesartan with both a placebo arm and an amlodipine arm; we therefore included the study in both analyses. Eleven studies provided outcome data from comparisons of an ARB with a placebo; six provided outcome data from comparisons of an ARB with an ACEI; and four provided outcome data from comparisons of an ARB with a calcium antagonist. The characteristics of 20 randomized controlled trials included in the present analysis are shown in Table 1.
Table 1. Methodological characteristics of 23 randomized controlled trials in the present meta-analysis.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Design</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>Number of patients</th>
<th>Disease history at entry</th>
<th>Mean age (years)</th>
<th>Women (%)</th>
<th>Follow-up (years)</th>
<th>Lost to follow-up (%)</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPICE (Granger et al., 2000, 2003)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>270</td>
<td>Heart failure</td>
<td>65.7</td>
<td>31.1</td>
<td>0.2</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>IDNT (Berl et al. 2003)</td>
<td>DB-P</td>
<td>Irbesartan</td>
<td>Placebo</td>
<td>1148</td>
<td>Type 2 diabetes and nephropathy</td>
<td>58.8</td>
<td>32.0</td>
<td>2.6</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>ARCH-LJ (Matsumori et al., 2003)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>292</td>
<td>Heart failure</td>
<td>63.7</td>
<td>15.4</td>
<td>0.4</td>
<td>4.5</td>
<td>3</td>
</tr>
<tr>
<td>SCOPE (Berl T et al., 2003)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>4937</td>
<td>Hypertension</td>
<td>76.4</td>
<td>64.5</td>
<td>3.7</td>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>ACCESS (Schrader et al., 2003, 2005)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>339</td>
<td>Stroke</td>
<td>68.1</td>
<td>69.9</td>
<td>1.0</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>CHARM-Added (McMurray et al., 2003, 2006)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>2548</td>
<td>Heart failure</td>
<td>64.0</td>
<td>21.3</td>
<td>3.4</td>
<td>0.2</td>
<td>5</td>
</tr>
<tr>
<td>CHARM-Alternative (Granger et al., 2000, 2003)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>2028</td>
<td>Heart failure</td>
<td>66.6</td>
<td>31.9</td>
<td>2.8</td>
<td>0.1</td>
<td>5</td>
</tr>
<tr>
<td>CHARM-Preserved (Yusuf et al., 2003)</td>
<td>DB-P</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>3023</td>
<td>Heart failure</td>
<td>67.2</td>
<td>40.1</td>
<td>3.1</td>
<td>0.1</td>
<td>5</td>
</tr>
<tr>
<td>PROFESSION (Yusuf et al., 2008)</td>
<td>DB-P</td>
<td>Telmisartan</td>
<td>Placebo</td>
<td>20332</td>
<td>Stroke</td>
<td>66.2</td>
<td>36.0</td>
<td>2.5</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>ACCESS (Schrader et al., 2003, 2005)</td>
<td>DB-P</td>
<td>Irbesartan</td>
<td>Placebo</td>
<td>4128</td>
<td>Heart failure</td>
<td>72.0</td>
<td>60.3</td>
<td>4.1</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>TRANSCEDE (Yusuf et al., 2008; Teo et al., 2008)</td>
<td>DB-P</td>
<td>Telmisartan</td>
<td>Placebo</td>
<td>5926</td>
<td>CHD, PVD, CVD, diabetes</td>
<td>66.9</td>
<td>43.0</td>
<td>4.7</td>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>ELITE II (Pitt et al., 1997)</td>
<td>DB-P</td>
<td>Losartan</td>
<td>Captopril</td>
<td>722</td>
<td>Heart failure</td>
<td>73.5</td>
<td>33.3</td>
<td>0.9</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>OPTIMAAL (Dickstein and Kjekshus, 2002)</td>
<td>DB-P</td>
<td>Losartan</td>
<td>Captopril</td>
<td>3152</td>
<td>Heart failure</td>
<td>71.4</td>
<td>30.6</td>
<td>1.5</td>
<td>0.1</td>
<td>4</td>
</tr>
<tr>
<td>DETAIL (Barnett et al., 2004)</td>
<td>DB-P</td>
<td>Telmisartan</td>
<td>Enalapril</td>
<td>250</td>
<td>Type 2 diabetes and nephropathy</td>
<td>60.6</td>
<td>27.2</td>
<td>5.0</td>
<td>0.8</td>
<td>5</td>
</tr>
<tr>
<td>VALIANT (Mcmurray et al., 2006)</td>
<td>DB-P</td>
<td>Valsartan</td>
<td>Captopril</td>
<td>14703</td>
<td>Myocardial infarction</td>
<td>65.0</td>
<td>31.4</td>
<td>2.1</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>ONTARGET (Yusuf et al., 2008; Teo et al., 2008)</td>
<td>DB-P</td>
<td>Telmisartan</td>
<td>Ramipril</td>
<td>17118</td>
<td>CHD, PVD, CVD, diabetes</td>
<td>66.4</td>
<td>26.8</td>
<td>4.7</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>IDNT (Berl et al., 2003)</td>
<td>DB-P</td>
<td>Irbesartan</td>
<td>Amlodipine</td>
<td>1146</td>
<td>Type 2 diabetes and nephropathy</td>
<td>59.2</td>
<td>35.7</td>
<td>2.6</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>VALUE (Julius et al., 2004)</td>
<td>DB-P</td>
<td>Valsartan</td>
<td>Amlodipine</td>
<td>15246</td>
<td>Hypertension</td>
<td>67.2</td>
<td>42.4</td>
<td>4.2</td>
<td>0.6</td>
<td>5</td>
</tr>
<tr>
<td>MOSES (Schrader et al., 2003, 2005)</td>
<td>SB-P</td>
<td>Eprosartan</td>
<td>Nitrendipine</td>
<td>1352</td>
<td>Stroke</td>
<td>67.9</td>
<td>45.8</td>
<td>2.5</td>
<td>1.9</td>
<td>4</td>
</tr>
<tr>
<td>CASE-J (Ogihara et al., 2008)</td>
<td>OL-P</td>
<td>Candesartan</td>
<td>Amlodipine</td>
<td>4728</td>
<td>Hypertension</td>
<td>63.8</td>
<td>44.8</td>
<td>3.2</td>
<td>2.9</td>
<td>2</td>
</tr>
</tbody>
</table>

DB-P: Double blind parallel; SB-P: single blind parallel; OL-P: open-label parallel; Non-RASI: conventional drugs other than inhibitors of renin-angiotensin system; Non-ARB: conventional drugs other than angiotensin receptor blockers; CHD: coronary heart disease; PVD: peripheral vascular disease; CVD: cerebrovascular disease.

All trials had a prospective parallel design. Eleven trials had the maximum Jadad score of 5; four trials scored 4, four scored 3, and one scored 2 (Table 1). Allocation concealment was adequate in fourteen studies (70%), and unclear in the remaining six studies (30%). Treatment was assigned in a randomized fashion. Participants were blindered in 18 studies (90%), investigators in 18 studies (90%), and outcome assessors in 19 (95%). Finally, patients were analyzed by the intention to treat principle in 19 of the studies (95%). Funnel plots for the studies comparing ARBs with placebo, and with ACEIs are qualitatively symmetrical, indicating the absence of publication bias (Figure 2).

Effect of ARBs compared with placebo in preventing stroke

Eleven trials were included in this analysis,
involving a total of 44961 patients with hypertension, heart failure, diabetes, coronary heart disease, peripheral vascular disease, or cerebrovascular disease. 1332 (5.92%) of 22516 patients receiving ARBs experienced stroke, compared with 1456 (6.49%) of 22445 patients receiving placebo. Overall, ARBs was associated with a significant decrease of the rate of stroke, with a pooled odds ratio of 0.91 (95% confidence interval 0.84 to 0.98) from the random effects model (Figure 3). There was no significant heterogeneity in this analysis ($\chi^2=6.83$, $P=0.74$, $I^2=0\%$). Analysis using the fixed effects model similarly showed a significant decrease of the stroke rate by using ARBs (pooled odds ratio 0.91, 0.84 to 0.98).

**Effect of ARBs compared with angiotensin converting enzyme inhibitors in preventing stroke**

Six trials comparing ARBs with ACEIs reported the rate of stroke, with a total of 26537 patients, who are at high risk of cardio-cerebrovascular events, included in this analysis. There was no significant heterogeneity in this analysis ($\chi^2=4.51$, $P=0.48$, $I^2=0\%$). Strokes occurred in 717 (3.93%) of 18245 patients receiving ARBs and 768 (4.20%) of 18292 patients receiving ACEIs. There was no significant reduction in the risk of stroke, although a possible moderate advantage for patients assigned ARB therapy was not excluded, resulting in a pooled odds ratio being 0.93 (0.84 to 1.03) by random effects analysis (Figure 4) and 0.93 (0.84 to 1.04) by fixed effects analysis.

**Effect of ARBs compared with calcium antagonists in preventing stroke**

Figure 5 shows the results of the comparison of treatment with ARBs and calcium antagonists. There were 441 (3.92%) of 11263 patients allocated to treatment with ARBs and 382 (3.42%) of 11183 patients allocated to conventional treatments, who experienced strokes. ARBs was associated with no significant reduction in the risk of stroke, with a pooled odds ratio of 1.16 (0.91 to 1.48) from
the random effects model. No significant heterogeneity was found in this analysis ($\chi^2=5.12$, $P=0.16$, $I^2=41.4\%$). Analysis using the fixed effects model showed that an almost significant decrease of the stroke rate by using ARBs, with a pooled odds ratio being 1.15 (1.00 to 1.32).

**DISCUSSION**

The results of this programme of prospectively designed overviews of data from 20 randomized clinical trials reveal that ARBs provide benefits on preventing stroke. With a significant reduction in the risk of stroke when comparing ARBs with placebo, and no significant difference when comparing ARBs with ACEIs, and with calcium antagonists, the results indicate that an aggregate of patients with hypertension, diabetes, heart failure, and patients with a history of cardio-cerebrovascular event were at lower risk of stroke when treated with different ARBs.

The overview of placebo-controlled trials of ARBs showed that these agents decreased the risks of stroke by 9% among high-risk patients, with the 95% confidence intervals of 2 to 16%. The point estimates of all eleven trials were distributed across the 1.0 odds ratio; however, eight of these estimates have shown a relative benefit on stroke of treatment with ARBs when compared with placebo. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial (Yusuf et al., 2008), which contributed more than 64% to the weighted pooled odds ratio, included 20332 patients who recently had an ischemic stroke, and revealed that telmisartan did not significantly lower the rate of recurrent stroke, or major cardiovascular events. Despite the observed negative result, this trial had the potential to cause confusion and inappropriate changes in practice due to misunderstandings.
about the noninferiority design (Anderson, 2008). The CHARM-added trial (McMurray et al., 2003), in which patients were randomized to candesartan or placebo as the additional treatment of ACEIs, showed an increased risk of stroke rates of 15%. However, the addition of candesartan to ACEIs led to a further clinically important reduction in overall cardiovascular events.

In the overview comparing ARB-based regimens with ACEI-based regimens, no difference in this risk between the arms receiving ARBs and ACEIs, with the 95% confidence interval included an up to 16% increased risk of stroke down to a 3% reduction with ARBs. All the six trials had 95% confidence intervals crossing 1.0. Although ARBs were found to be non-superior in all the trials, the finding of this overview supports the notion that they may be a safe and effective alternative for high-risk patients not taking ACEIs, as shown by a recent meta-analysis (Lee et al., 2004). In the overview comparing ARBs with calcium antagonists, there was no clear difference between groups, although the 95% confidence interval cannot rule out an increased risk of stroke up to 48% or a reduced risk of up to 9%. Although all the four trials had 95% confidence intervals crossing 1.0, plausibly moderate differences in stroke were found in three trials comparing ARBs with amlodipine (Berl et al., 2003; Julius et al., 2004; Ogihara et al., 2008). When we additionally included in a sensitivity analysis data from the three trials, a significant difference between ARBs and amlodipine was found, with a pooled odds ratio being 1.22 (1.01 to 1.46). Therefore, the benefit of amlodipine on the risk of stroke should be further evaluated in the future.

**Strengths and weaknesses**

An extensive literature search was conducted to retrieve all relevant eligible trials and investigators of the primary trials were contacted to provide additional information and collaboration. This collaboration with experts in the field should have minimized the potential for publication bias. In addition, funnel plots testing found little evidence for such a bias.

Although, we tried to conduct a thorough review of the existing literature, this present analysis has limitations inherent to any systematic review. One limitation of our systematic review is that our analyses of stroke rates were based on data pooled from trials of different durations. Some caution is therefore needed in their interpretation. Other potential sources of heterogeneity in the results are the patient population, and the diagnosis of the disease. A third limitation of this meta-analysis is that only published studies were included. To avoid the publication bias, we searched multiple databases. In addition, we explored asymmetry in funnel plots to detect potential publication biases, and no publication bias was found, because of no heterogeneity in funnel plots. Unfortunately, it is possible that we may have failed to include some papers, especially those published in other languages. A specific limitation of this analysis is that several trials lacked adequate allocation concealment, blinding, and intention to treat analysis, which may leave them vulnerable to bias. However, the studies that contributed the most weight to this meta-analysis were also the most methodologically stringent, and given the homogeneity of results across studies, it is unlikely that smaller, poorer-quality trials significantly biased the pooled estimates.

**REFERENCES**


