Do angiotensin II receptor blockers increase the risk of myocardial infarction?

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Received 22 March 2005; revised 8 July 2005; accepted 14 July 2005; online publish-ahead-of-print 4 August 2005

See page 2351 for the editorial comment on this article (doi:10.1093/eurheartj/ehi574)

Aims
The uncertainty surrounding safety of angiotensin receptor blockers (ARBs) increased after publication of experimental and clinical studies which suggested an excess risk of myocardial infarction (MI) in people treated with ARBs.

Methods and results
We performed a meta-analysis of randomised clinical trials, which compared ARBs with either a placebo or active drugs different from ARBs. Overall, ARBs were not associated with an excess risk of MI [odds ratio (OR): 1.03 in a random-effect model and 1.02 in a fixed-effect model]. In pre-specified subgroup analyses, incidence of MI did not differ between ARBs and either placebo (OR: 0.96; 95% CI: 0.84–1.10) or angiotensin-converting enzyme (ACE)-Inhibitors (OR: 0.99; 95% CI: 0.91–1.07). Incidence of MI was slightly higher with ARBs than with drug classes different from ACE-Inhibitors (OR: 1.16; P = 0.06 in a random-effect model and 0.017 in a fixed-effect model).

Cardiovascular mortality did not differ between ARBs and drugs different from ARBs (OR: 1.00 in a random-effect model and 0.99 in a fixed-effect model) and it was slightly lesser with ARBs than with placebo (OR: 0.91; 95% CI: 0.83–0.99; P = 0.042) in a pre-specified subgroup analysis.

Conclusion
Our findings do not support the hypothesis that ARBs increase the risk of MI.

KEYWORDS
Hypertension; Therapy; Myocardial infarction; Prognosis; Prevention; Meta-analysis

Introduction
Angiotensin II receptor blockers (ARBs) are increasingly used in patients with hypertension, heart failure, diabetic nephropathy, and other clinical conditions.1 Increasingly, their use is not limited to subjects with cough or other contraindications to angiotensin-converting enzyme (ACE)-Inhibitors. For example, in a large US sample of subjects aged ≥65 with left ventricular systolic dysfunction, a recent hospitalization for heart failure and no contraindications to use of ACE-Inhibitors, only 68% of subjects were actually taking an ACE-Inhibitor and an additional 8% of subjects were receiving an ARB.2

Long-term selective blockade of angiotensin II type 1 (AT1) receptors may lead to over-stimulation of angiotensin II type 2 (AT2) receptors. It is generally believed that AT2 receptor over-stimulation contributes to the beneficial effects of ARBs through vasodilatation and inhibition of hypertrophy and fibrosis.1 However, experimental studies suggested that AT2 receptor stimulation, in addition to beneficial effects, might trigger apoptosis and inhibition of angiogenesis,3–5 effects potentially leading to a depressed growth of collateral vessels even in a setting of ischaemia. It has also been suggested that inhibition of fibrosis might lead to a thinner cap of the atheroma, which would become more vulnerable to rupture because of the lesser collagen content.6 Notably, some of these potentially deleterious effects depend on the cell phenotype,7 leaving the question of the impact of these experimental findings in the general population unanswered.

In a recent review, Verma and Strauss7 examined results of some randomized trials, which compared an ARB with a different drug class in a variety of clinical conditions including hypertension, heart failure, and renal failure. The conclusion of the review was that ARBs may increase the risk of myocardial infarction (MI), and consequently, patients may need to be informed about the risk.7 As expected, the conclusion triggered not only a scientific debate but also an uncontrolled reporting by media and even anxious reactions in patients treated with ARBs. For example, a leading Italian tabloid headed its entire cover page ‘The drugs which cause harm’ and published an article inside which stated that ‘Clinical studies conclude that ARBs increase the risk of myocardial infarction’.8

Most of the criticisms moved to the review of Verma and Strauss regarded the lack of citation by these authors of some studies with ARBs,9 together with a greater emphasis on studies supporting the association between ARBs and increased risk of MI when compared with studies not supporting such association.10

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Consequently, we planned a formal meta-analysis of randomized clinical studies, which compared an ARB with either a placebo or an active drug different from ARBs.

**Methods**

We searched for randomized controlled outcome trials which met all of the following pre-specified criteria: (i) comparison between an ARB and either a placebo or drug classes different from ARBs regardless of the background therapy in either group; (ii) publication before 28 February 2005 in peer-reviewed journals indexed in Medline; (iii) MI as a pre-specified event, although not necessarily a primary endpoint; (iv) follow-up of at least 1 year; and (v) sample size of 500 subjects or more, as meta-analyses based on small trials may lead to biased results. We searched for eligible studies through Medline, using research methodology filters. The final search identified 11 trials which fulfilled all inclusion criteria. Two of us (P.V. and F.A.) extracted the data on the basis of an intention-to-treat approach. We accepted the definition of MI as reported in the individual reports. We also extracted the number of fatal cardiovascular events in each trial. The number of patients with MI in the Valsartan in Acute Myocardial Infarction (VALIANT) trial was not reported in the original article, but was drawn from the report submitted by the sponsor company to the Food and Drug Administration. The number of patients with MI in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was published later.

The number of fatal cardiovascular events was available for all trials except one study omitted lies outside the CI of the overall estimate with all available trials contributing, then the study in question has an excessive influence. We tested for publication bias using the methods described by Begg and Mazumdar and Egger et al. All P-values are for two-sided tests. Analyses were done using the Stata, version 8.0 (StataCorp LP, College Station, TX, USA).

**Results**

The 11 eligible trials (Table 1) included 31,958 patients randomized to ARBs and 32,423 patients randomized to either placebo or different drug classes. The number of patients with MI was 2228 in one group and 2218 in the other. The number of deaths was 3072 with ARBs and 3153 with drugs different from ARBs.

**Overall (Figure 1)**, treatment with ARBs was not associated with a higher risk of MI when compared with treatments with drugs different from ARBs (OR: 1.02 with a random-effect model and 1.03 with a fixed-effect model; P = 0.45 and 0.46, respectively). There was no significant heterogeneity across the trials (P = 0.29). We also calculated pooled estimates for pre-defined subgroups: ARBs vs. placebo, ARBs vs. ACE-Inhibitors, and ARBs vs. non-ACE-Inhibitors. Treatment based on ARBs was associated with a non-significant 4% lesser risk of MI compared with placebo and a non-significant 1% lesser risk of MI compared with ACE-Inhibitors. Treatment based on ARBs was associated with a slightly higher risk of MI when compared with drug classes different from ACE-Inhibitors (OR: 1.16; P = 0.06 in a random-effect model and 0.017 in a fixed-effect model).

In the pooled estimate (Figure 2), mortality did not differ between ARBs and drugs different from ARBs (OR: 1.00 in a random-effect model and 0.99 in a fixed-effect model) with a significant heterogeneity across the trials (P = 0.019). In

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**Table 1** Comparative trials between ARBs and either placebo or ACE-Inhibitors or different antihypertensive drug classes

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental/reference</th>
<th>Design</th>
<th>Number of patients (experimental/reference)</th>
<th>Number of AMI (experimental/reference)</th>
<th>Number of CV death (experimental/reference)</th>
<th>Age (years)</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>Candesartan/placebo</td>
<td>RCT/DB</td>
<td>3803/3796</td>
<td>176/190</td>
<td>691/769</td>
<td>65.9/66.0</td>
<td>3.1</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan/placebo</td>
<td>RCT/DB</td>
<td>579/569</td>
<td>44/46</td>
<td>52/46</td>
<td>59.3/58.3</td>
<td>2.6</td>
</tr>
<tr>
<td>RENAAL</td>
<td>Losartan/placebo</td>
<td>RCT/DB</td>
<td>751/762</td>
<td>50/68</td>
<td>158/155</td>
<td>60/60</td>
<td>3.4</td>
</tr>
<tr>
<td>SCOPE</td>
<td>Candesartan/placebo</td>
<td>RCT/DB</td>
<td>2477/2460</td>
<td>70/63</td>
<td>145/152</td>
<td>76.4/76.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Val-Heft</td>
<td>Valsartan/placebo</td>
<td>RCT/DB</td>
<td>2511/2499</td>
<td>83/72</td>
<td>29/40</td>
<td>66.6/67.7</td>
<td>1.9</td>
</tr>
<tr>
<td>ELITE</td>
<td>Losartan/captopril</td>
<td>RCT/DB</td>
<td>352/370</td>
<td>3/4</td>
<td>12/24</td>
<td>74/73</td>
<td>1</td>
</tr>
<tr>
<td>ELITE II</td>
<td>Losartan/captopril</td>
<td>RCT/DB</td>
<td>1578/1574</td>
<td>31/28</td>
<td>230/199</td>
<td>71.4/71.5</td>
<td>1.5</td>
</tr>
<tr>
<td>OPTIMAAL</td>
<td>Losartan/captopril</td>
<td>RCT/DB</td>
<td>2744/2733</td>
<td>384/379</td>
<td>420/363</td>
<td>67.6/67.2</td>
<td>2.7</td>
</tr>
<tr>
<td>VALIANT</td>
<td>Valsartan/placebo</td>
<td>RCT/DB</td>
<td>4909/4909</td>
<td>820/840</td>
<td>827/830</td>
<td>65.0/64.9</td>
<td>2.1</td>
</tr>
<tr>
<td>IDNT</td>
<td>Irbesartan/amlodipine</td>
<td>RCT/DB</td>
<td>579/567</td>
<td>44/27</td>
<td>52/37</td>
<td>59.3/59.1</td>
<td>2.6</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan/atenolol</td>
<td>RCT/DB</td>
<td>4605/4588</td>
<td>198/188</td>
<td>204/234</td>
<td>66.9/66.9</td>
<td>4.8</td>
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<tr>
<td>VALUE</td>
<td>Valsartan/amlodipine</td>
<td>RCT/DB</td>
<td>7649/7596</td>
<td>369/313</td>
<td>304/304</td>
<td>67.2/67.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial; DB, double blind.

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*All-cause mortality.

*Cardiac mortality.
Figure 1  ARBs and risk of MI in randomized trials.

Figure 2  ARBs and risk of fatal events in randomized trials.
the pre-specified subgroup analyses, mortality was slightly lesser with ARBs than with placebo (OR: 0.91; 95% CI: 0.83–0.99; \( P = 0.042 \)), in the absence of heterogeneity across trials within this strata (\( P = 0.46 \)). Mortality was also not dissimilar between ARBs and ACE-Inhibitors (OR: 1.06 in a random-effect model and fixed-effect model), as well as drugs different from ACE-Inhibitors (OR: 0.99 in a random-effect model and 0.97 in a fixed-effect model).

The significant heterogeneity across trials in the subgroup analysis of ARBs and ACE-Inhibitors (\( P = 0.038 \)) was driven by results of the ELITE study and was significantly reduced after exclusion of this trial from analysis without significant changes in the overall effect size estimate.

In sensitivity analyses, none of the trials had a significant influential effect on the overall estimates (Figure 3) for both MI and fatal events. Formal tests for publication bias did not achieve statistical significance for both MI (Begg’s test: adjusted Kendall’s score = 4, \( P = 0.784 \); Egger’s test: slope = 0.0018, \( P = 0.980 \); bias = 0.2325, \( P = 0.720 \)) and mortality (Begg’s test: adjusted Kendall’s score = −4, \( P = 0.784 \); Egger’s test: slope = −0.0098, \( P = 0.914 \); bias = −0.0356993, \( P = 0.971 \)).

**Discussion**

The findings of our overview do not support the hypothesis that ARBs increase the risk of MI. The 95% CIs broadly crossed the identity line in the overall estimate as well as in the subgroup estimates of ARBs vs. placebo and ARBs vs. ACE-Inhibitors.

The subgroup estimate of ARBs vs. drug classes different from ACE-Inhibitors (LIFE,20 VALUE,21 and IDNT14 trials) showed a 16% higher risk of MI in the ARBs group when compared with the control group (Figure 1). In these trials, ARBs were losartan,20 valsartan,21 and irbesartan14 and the comparators were atenolol20 and amlopidine.14,21 As atenolol was not associated with a lesser risk of MI in a previous meta-analysis of nine trials,27 and amlopidine did not reduce the risk of MI in two placebo-controlled trials,28,29 these results would appear consistent with a net excess risk of MI with ARBs when compared with drug classes different from ACE-Inhibitors. However, most of the benefits disclosed by drugs different from ACE-Inhibitors over ARBs were dominated by results of the VALUE trial.21 In this trial, the 18% lesser incidence of MI with amlopidine compared with valsartan was associated with a greater antihypertensive effect of amlopidine over valsartan (by 4.0/2.1 mmHg in the first month and 2.0/1.6 mmHg over the entire study period). The VALUE investigators entirely attributed the higher incidence of MI in the valsartan group to the lesser antihypertensive effect in that group.21

However, in an analysis by Staessen et al.,30 the excess risk of MI in the valsartan group in the VALUE trial appeared superior to that predicted by a meta-regression model.31

Similar to MI, cardiovascular mortality did not differ between ARBs and drug different from ARBs (Figure 2). The significant heterogeneity across the trials was unlikely to exert a major effect on the overall estimate because the 95% CIs broadly crossed the identity line and the overall OR was 1.00 (95% CI: 0.91–1.99), using the random-effect model. In contrast, there was no heterogeneity across trials in the subgroup analysis, which showed a 9% lesser risk of mortality (\( P = 0.042 \)) with ARBs when compared with placebo. The result was largely driven by Val-Heft22 and CHARM trials.

In conclusion, evidence from randomized trials does not support the hypothesis that AT\(_2\) receptor over-stimulation produces harmful clinical effects. Current indications and contraindications to the use of ARBs in patients with hypertension, heart failure, and diabetic nephropathy should be maintained. In some randomized clinical trials currently ongoing with ARBs, MI is a pre-specified endpoint.32-34 In particular, the ONTARGET trial is a randomized comparison between an ACE-inhibitor and ARB and their combination and TRANSCEND a comparison between an ARB and placebo, in high-risk patients.32 These trials will provide a solid assessment of the effects of ARBs vs. placebo and ACE-Inhibitors in high-risk patients without overt heart failure. Results of these trials are expected between years 2007 and 2008.
Appendix

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Acknowledgement

We gratefully thank Miss Francesca Saveri for secretarial assistance.

Conflict of interest: none declared.

References


