

Angiotensin receptor blockers and risk of myocardial infarction: systematic review

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Abstract

Objective To evaluate the effect of angiotensin receptor blockers on the risk of myocardial infarction in patients at risk for cardiovascular events.

Design Systematic review of controlled trials of angiotensin receptor blockers.

Data sources Medline, Embase, Cochrane central register of controlled trials, hand search, and contact with investigators.

Selection of studies Predefined criteria were used to select controlled clinical trials comparing use of angiotensin receptor blockers with angiotensin converting enzyme (ACE) inhibitors or placebo in patients at risk for cardiovascular events. Data were extracted for patients' characteristics, interventions, quality of trials, and rates of myocardial infarction.

Results 19 studies with 31 569 patients were included in the analysis. Two studies investigated the use of angiotensin receptor blockers in hypertensive patients, four studies in patients with diabetes and nephropathy, 10 studies in patients with heart failure, and three in patients with recent myocardial infarction or ischaemic syndrome. 11 studies of 21 062 patients allowed for comparison between angiotensin receptor blockers and placebo; nine studies of 10 625 patients allowed for comparison between angiotensin receptor blockers and ACE inhibitors. Use of angiotensin receptor blockers was not associated with increased risk of myocardial infarction compared with placebo (odds ratio 0.94, 95% confidence interval 0.75 to 1.16) nor with increased risk of myocardial infarction compared with ACE inhibitors (1.01, 0.87 to 1.16).

Conclusions Treatment with angiotensin receptor blockers was not associated with a significantly increased risk of myocardial infarction. The 95% confidence intervals do not, however, exclude an increase of up to 16% in the risk of myocardial infarction or a reduction in risk of up to 25%. Until further information specifically dealing with this issue is available from large prospective trials, our findings may alleviate recent concerns over the safety of this class of medications.

Introduction

Evidence is very strong for the use of angiotensin converting enzyme (ACE) inhibitors to reduce morbidity and mortality in patients with left ventricular dysfunction, in patients with recent myocardial infarction, and in patients otherwise at high risk for cardiovascular events. Angiotensin receptor blockers theoretically produce more complete inhibition of angiotensin II and are better tolerated than ACE inhibitors.¹⁻³ Recent trials have not, however, shown their superiority and have been equivocal on their comparative effect.⁴⁻⁶ Verma and Strauss concluded that angiotensin receptor blockers may even confer a risk of harm,

specifically through their association with higher rates of myocardial infarction.⁷ We thought it important to review the evidence and conduct a systematic review to determine the association between angiotensin receptor blockers and myocardial infarction before drawing conclusions on harm.

Methods

We identified controlled trials comparing use of angiotensin receptor blockers with placebo therapy and with ACE inhibitors by searching Medline, Embase, and the Cochrane central register of controlled trials, each from inception to December 2004. We also hand searched references from review articles and meta-analyses of angiotensin receptor blockers.

We included all original studies if they were controlled clinical trials, incorporated monotherapy with angiotensin receptor blockers in at least one of the treatment arms, had a control group of either placebo or ACE inhibitor, reported myocardial infarction either as a prespecified outcome or as an adverse event, and were published in English. Two reviewers independently screened abstracts, and separate reviewers independently assessed the full text of the remaining articles. Disagreements were resolved by a third reviewer. We used standard criteria to appraise study quality, in addition to quantitative quality assessment using the scoring system developed by Jadad.

Data collection and outcome measures

Two reviewers used standardised data collection forms for data extraction. We verified the accuracy of data by comparing collection forms. We documented all reported myocardial infarctions, fatal or non-fatal, according to the definition used by the authors of individual studies. Where data on myocardial infarction were included as a composite end point, we recorded the components of adverse cardiac outcomes and contacted study authors for rates of myocardial events. We also contacted authors for complete details on myocardial events for those studies in which only fatal or non-fatal myocardial infarctions were reported.

Statistical analysis

For each study, we calculated odds ratios and combined them for the pooled odds ratio. We used the standard random effects model for primary analysis. We also performed fixed effects analyses for estimating pooled odds ratios, to account best for the limited data available from some of the studies. We used the *Q* statistic for all comparisons to evaluate heterogeneity of treatment effects between studies. We constructed standard funnel plots to investigate the potential for publication bias influencing the analysis.

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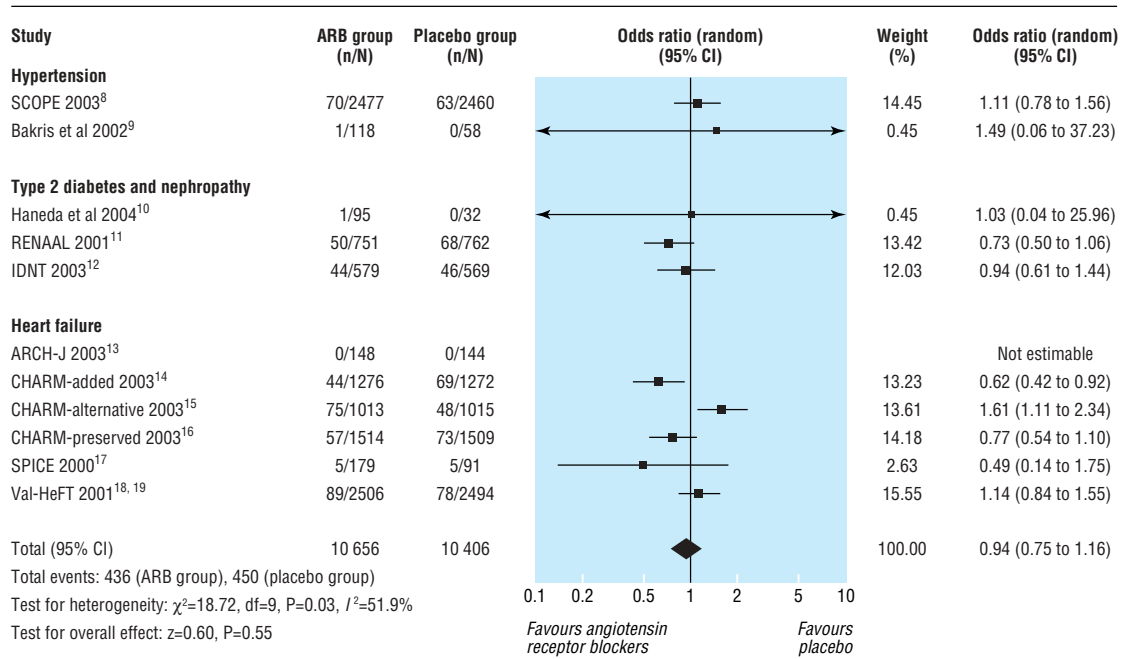


Fig 1 Effect of angiotensin receptor blockers compared with placebo on risk of myocardial infarction

Results

We reviewed the full text of 128 articles from 2742 studies. A total of 24 studies met criteria for inclusion, and we could ascertain data on myocardial infarction for 19. Agreement between two investigators for final study inclusion, measured by the κ statistic, was 0.75. All trials had a prospective, parallel design. Nine trials had the maximum Jadad score of 5; four trials scored 4, five scored 3, and one scored 2. Eleven studies allowed for comparison between angiotensin receptor blockers and placebo, and nine studies allowed for comparison between angiotensin receptor blockers and ACE inhibitors. Funnel plots for the angiotensin receptor blockers compared with placebo studies and angiotensin receptor blockers compared with ACE inhibitor studies are qualitatively symmetrical, implying the absence of publication bias. See bmj.com for full details of included studies.

Effect of angiotensin receptor blockers compared with placebo on risk of myocardial infarction

Among 10 656 subjects allocated to treatment with angiotensin receptor blockers, 436 myocardial infarctions occurred (4.09%) compared with 450 myocardial infarctions (4.32%) in the 10 406 subjects allocated to placebo. Overall, using angiotensin receptor blockers was not associated with a significant increase in the risk of myocardial infarction, with a pooled odds ratio of 0.94 (95% confidence interval 0.75 to 1.16) from the random effects model (fig 1). Analysis using the fixed effects model similarly showed no significant association of using angiotensin receptor blockers with risk of myocardial infarction (pooled odds ratio 0.95, 0.83 to 1.09).

Effect of angiotensin receptor blockers compared with angiotensin converting enzyme inhibitors on risk of myocardial infarction

Among 5406 patients receiving angiotensin receptor blockers, 435 myocardial events occurred (8.05%), compared with 433 events (8.30%) in 5219 patients

receiving ACE inhibitors, resulting in a pooled odds ratio close to unity (1.01, 0.87 to 1.16 by random effects analysis; 1.00, 0.87 to 1.16 by fixed effects analysis) (fig 2). This summary effect size was driven mainly by the OPTIMAAL study, which accounted for 86.8% of the weighted odds ratio in the random effects model.

Discussion

Treatment with angiotensin receptor blockers was not associated with an increased risk of myocardial infarction, according to our systematic review of 19 trials with 31 569 subjects. With a pooled odds ratio very close to unity in our analyses for angiotensin receptor blockers compared with placebo and compared with ACE inhibitor, our results indicate that an aggregate of patients with hypertension, diabetes and nephropathy, heart failure and left ventricular dysfunction, and patients with recent myocardial infarction or ischaemic syndrome were not at greater risk of myocardial infarction when treated with different angiotensin receptor blockers.

Angiotensin receptor blockers versus placebo

We found no significant difference between groups in the incidence of myocardial infarction, although the 95% confidence cannot rule out an increased risk of myocardial infarction of up to 16% or a reduced risk of up to 25%. Our evaluation of angiotensin receptor blockers compared with placebo included the CHARM-alternative trial, which contributed more than 13% to the weighted pooled odds ratio and was the only study to show an increase in myocardial infarction rates with use of angiotensin receptor blockers that reached significance. In this study, patients with left ventricular dysfunction and heart failure who were intolerant to ACE inhibitors were randomised to the angiotensin receptor blocker candesartan or placebo. Despite the observed increased incidence of myocardial infarction in the

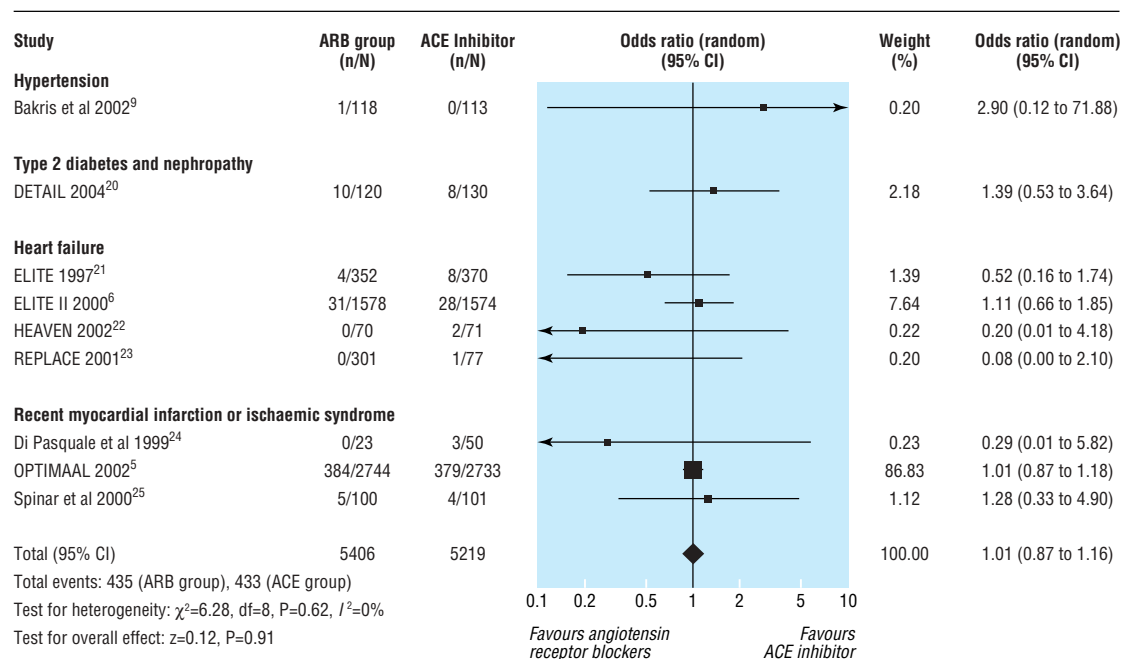


Fig 2 Effect of angiotensin receptor blockers compared with angiotensin converting enzyme inhibitors on risk of myocardial infarction

candesartan group, cardiovascular mortality fell overall with treatment with angiotensin receptor blockers. In contrast, among other patients with heart failure and similar background cardiovascular risk, including patients being treated with concomitant ACE inhibitors in the CHARM-added and ValHeFT trials, the point estimates were distributed across the 1.0 odds ratio, implying that using angiotensin receptor blockers is itself not significantly associated with risk of myocardial infarction.

Angiotensin receptor blockers versus ACE inhibitors

In this analysis, we found no difference in the risk of myocardial infarction between the arms receiving angiotensin receptor blockers and ACE inhibitors. The 95% confidence interval included an up to 16% increased risk of myocardial infarction down to a 13% reduction with angiotensin receptor blockers. The overall effect was most heavily influenced by the OPTIMAAL study. Although angiotensin receptor blockers were found to be non-superior in large randomised controlled trials,^{4-6 26} our finding supports the notion that they may be a safe and effective alternative for a select group of heart failure patients not taking ACE inhibitors, as shown by a recent meta-analysis.²⁷

Angiotensin receptor blockers do not increase risk of myocardial infarction

Our finding that angiotensin receptor blockers are not associated with an increased risk of myocardial infarction stands in contrast to the editorial by Verma and Strauss,⁷ which drew attention to results from several recent studies (see bmj.com). Our analysis, which included all but two of these studies (excluded because they did not have placebo or ACE inhibitor control groups), highlights the importance of assessing all available evidence by using systematic methods.

Limitations

Firstly, we were unable to obtain data on myocardial infarction events from all studies identified in our

literature search, most notably, data on myocardial infarction from the valsartan in acute myocardial infarction trial (VALIANT),⁴ which included 14 703 patients. We tested the potential impact of the unavailable data by assuming a “worst case scenario” in which all 919 patients admitted to hospital for myocardial infarction or heart failure, or both, in the valsartan arm had a myocardial infarction and no patients in the captopril arm were admitted to hospital. In this scenario we would still observe no significant association between use of angiotensin receptor blockers and myocardial infarction risk compared with ACE inhibitors. Similarly, excluding the one non-randomised trial would have little impact on our findings. Other limitations include potential variation in the definition of myocardial infarction between studies, the possibility of effects that are specific to angiotensin receptor blockers and dose dependent, and the potential confounding influence of other treatments.

Conclusions

We conducted a systematic quantitative review of angiotensin receptor blockers and the risk of myocardial infarction. Information specifically dealing with this issue is awaited from large, prospectively designed trials.²⁸ Until then, our results show that treatment with angiotensin receptor blockers is not associated with increased incidence of myocardial infarction.

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What is already known on this topic

Evidence from randomised controlled trials of angiotensin receptor blockers has shown variable effects on cardiovascular events

A recent editorial implied that angiotensin receptor blockers increase the risk of myocardial infarction

What this study adds

Our systematic review of all available data on angiotensin receptor blockers shows a neutral (not increased) impact of these agents on myocardial infarction

Although ACE inhibitors remain the agents of choice to reduce myocardial infarction, patients and healthcare providers need not worry about angiotensin receptor blockers increasing patients' risk for myocardial infarction

and has received honorariums and research grants from Merck Frosst, Merck-Schering, Pfizer, Sanofi-Aventis, and Novartis.
Ethical approval: Not required.

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Corrections and clarifications

Screening for abdominal aortic aneurysms: single centre randomised controlled trial

A couple of errors crept into this paper by Jes S Lindholt and colleagues (*BMJ* 2005;330:750-2). Firstly, the number of participants in the intervention group who were screened was 4852 (not 4860, as stated in the abstract and the results section). Secondly, the Y axis in figure 2 (figure 3 in the full version of the article on bmj.com) should be 0, 50, 100, 150, and 200 (not 0, 1, 2, 3, and 4).

Midlife obesity increases risk of future dementia

The final letter of the first author's name somehow "dropped off" during the editing of this letter by George Razay and Anthea Vreugdenhil (*BMJ* 2005;331:455, 20-27 Aug). The error has been corrected on bmj.com.

Comparison of amount of biomedical research originating from the European Union and the United States

The authors of this paper, Elpidoforos S Soteriades and Matthew E Falagas, have alerted us to errors in two columns of their table (*BMJ* 2005;331:192-4, 23 Jul). For the columns headed "Papers per \$bn" and "Citations per \$bn" the authors should have supplied values a 10th lower; therefore the given values should all have a decimal point before the final digit (although for Malta the given value 0.2 is correct). In addition, during editing we mangled the average population of France: it should be 58.6 (not 5.6) million.