Papers

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, however, not 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 who are otherwise at high risk for cardiovascular events.[1–8] Angiotensin receptor blockers theoretically produce more complete inhibition of angiotensin II and are better tolerated than ACE inhibitors.[9–11] Recent trials have, however, not shown their superiority and have been equivocal on their comparative effect.[12–14] Verma and Strauss

concluded that the use of angiotensin receptor blockers may even confer a risk of harm, specifically through their association with higher rates of myocardial infarction.[15] This has caused much concern over using these agents, with many healthcare professionals and patients asking whether angiotensin receptor blockers should be avoided.

Recent, high profile withdrawals of commonly prescribed medications such as rofecoxib have heightened public awareness and concern over adverse drug reactions. In the case of angiotensin receptor blockers, we thought that it would be important to review systematically all available evidence before drawing conclusions on harm. We conducted a systematic review of all published controlled trials to determine the association of angiotensin receptor blockers and myocardial infarction.

Methods

We used standard systematic review techniques, as outlined by the Cochrane Collaboration.[16] To evaluate the potential association between use of angiotensin receptor blockers and risk of myocardial infarction, we reviewed the medical literature to identify controlled trials comparing use of angiotensin receptor blockers with placebo therapy and with ACE inhibitors. We searched Medline, Embase, and the Cochrane central register of controlled trials, each from inception to December 2004. The search combined terms related to myocardial infarction ("myocardial infarction", "heart infarction", "death", "mortality") with terms related to angiotensin receptor blockers ("candesartan", "irbesartan", "losartan", "valsartan", "olmesartan", "telmisartan", "eprosartan"), using Boolean operators and database specific syntax. We also hand searched references from review articles and meta-analyses of angiotensin receptor blockers.

According to prespecified criteria, 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, reported myocardial infarction as either a prespecified outcome or as an adverse event, and were published in English. We excluded all secondary analyses if myocardial infarction events were provided in the parent study. Two reviewers (JAE, GG) independently screened abstracts for eligibility, rejecting those that were not controlled trials, and separate reviewers (MAM, SHS) independently assessed the full text of the remaining articles for final inclusion or exclusion. Disagreements were resolved by the vote of a third reviewer (JAE). We 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.[17]

Data collection and outcome measures

Two reviewers (MAM, SHS) used standardised data collection forms to extract data from studies for trial design, country of origin, patients' characteristics, interventions, and outcomes. We verified accuracy of data by comparing collection forms from each reviewer. We documented all reported myocardial infarctions, 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 myocardial infarction rather than total numbers of myocardial events. Where data on myocardial infarction were included as a composite end point, we recorded the components of adverse cardiac outcomes that were provided and subsequently 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, and we ultimately used the best obtainable data in our analysis.

Statistical analysis

We entered data into 2×2 tables and used Cochrane Review Manager software (RevMan 4.2.7, Cochrane, Copenhagen, Denmark) to analyse our results. For studies that found no events in one of the treatment groups, the program uses a correction factor of 0.5 for all cells, to avoid division by 0. 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;[18] 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.[19] 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.[20]

Results

Figure 1 summarises the process of identifying studies eligible for inclusion in our analysis. We reviewed the full text of 128 articles from 2742 studies identified from our initial literature search and hand search. A total of 24 studies met criteria for inclusion, and we could ascertain data on myocardial infarction for 19.[13 14 21–37] We excluded four controlled studies identified in the literature search because the control arms were usual care,[38] atenolol,[39] amlodipine,[40] and hydrochlorothiazide.[41] 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 (table 1). Allocation concealment was adequate in eight studies (42%), inadequate in two studies (11%), and unclear in the remaining nine studies (47%). With the exception of the study by Di Pasquale et al,[36] treatment was assigned in a randomised fashion. Participants were blinded in 19 studies (100%), investigators in 17 studies (89%), and outcome assessors in 18 (95%). Finally, patients were analysed by the intention to treat principle in 15 of the studies (79%).

In our data set, the study by Bakris et al[22] compared losartan with both a placebo arm and an enalapril arm; we therefore included the study in both analyses. We did not use information from the amlodipine arm of the irbesartan diabetic nephropathy trial.[25] Two studies investigated the use of angiotensin receptor blockers in hypertensive patients,[21 22] four studies in patients with
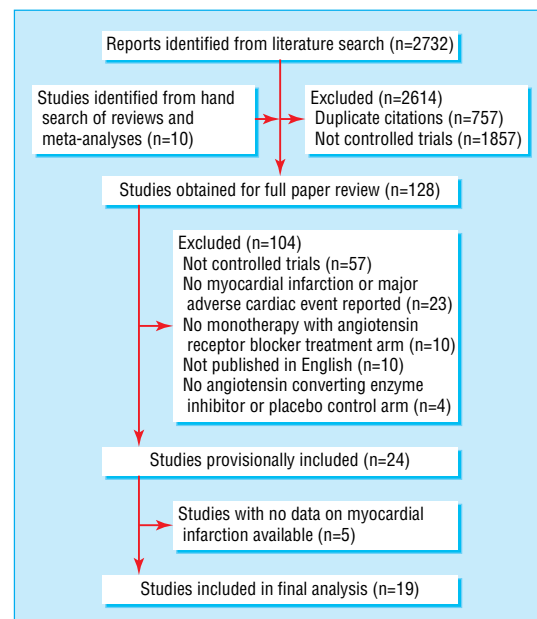

Fig 1 Flow diagram showing citations retrieved from literature searches and number of trials included in analysis

diabetes mellitus and nephropathy,[23–26] 10 studies in patients with heart failure,[14 27–35] and three studies in patients with a recent myocardial infarction or ischaemic syndrome.[13 36 37] Myocardial infarction, major adverse cardiac events, or cardiac mortality was an adjudicated study end point in nine studies,[13 14 21 24 25 28–30 33] whereas myocardial infarction was reported as an adverse event or was reported by the investigators in 10 studies that had primarily physiological or drug tolerability outcomes.[22 23 26 27 31 32 34–37] Finally, nine studies allowed for comparison between angiotensin receptor blockers and ACE inhibitors,[13 14 22 26 33–37] and 11 studies allowed for comparison between angiotensin receptor blockers and placebo.[21–25 27–32] Funnel plots for the angiotensin receptor blockers compared with placebo studies and angiotensin receptor blockers compared with ACE inhibitor studies are qualitatively symmetrical, indicating the absence of publication bias (fig 2). Other important study characteristics, including number of subjects, mean age, sex, and duration of follow-up, are summarised in the table.

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

In this analysis we included two hypertension trials, three trials of patients with diabetes and nephropathy, and six heart failure trials, with a total of 10 656 subjects allocated to treatment with angiotensin receptor blockers and 10 406 subjects allocated to placebo. In the group that was treated with angiotensin receptor blockers, 436 myocardial infarctions occurred (4.09%), compared with 450 myocardial infarctions in the placebo group (4.32%). 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 3). 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).

Characteristics of controlled trials of angiotensin receptor blocker use that report myocardial infarction

Study	Angiotensin receptor blocker	Control arm	No of subjects	Mean age in years	% women	Follow-up in years	Quality score[17]
Subjects with hypertension							
SCOPE (2003)[21]	Candesartan	Placebo	4937	76.4	64.5	3.7	5
Bakris et al (2002)[22]	Losartan	Placebo and enalapril	405	52.4	43.5	0.2	3
Subjects with type 2 diabetes and nephropathy							
Haneda et al (2004)[23]	Candesartan	Placebo	127	63.1	31.5	0.2	3
RENAAL (2001)[24]	Losartan	Placebo	1513	60.0	36.8	3.4	5
IDNT (2003)[25]	Irbesartan	Placebo and amlodipine	1715	58.9	33.8	2.6	5
DETAIL (2004)[26]	Telmisartan	Enalapril	250	60.6	27.2	5.0	5
Subjects with heart failure							
ARCH-J (2003)[27]	Candesartan	Placebo	292	63.7	15.4	0.4	3
CHARM-Added (2003)[28]	Candesartan	Placebo	2548	64.0	21.3	3.4	5
CHARM-Alternative (2003)[29]	Candesartan	Placebo	2028	66.6	31.9	2.8	5
CHARM-Preserved (2003)[30]	Candesartan	Placebo	3023	67.2	40.1	3.1	5
SPICE (2000)[31]	Candesartan	Placebo	270	65.0	31.1	0.2	4
Val-HeFT (2001)[32]	Valsartan	Placebo	5010	62.7	20.0	1.9	5
ELITE (1997)[33]	Losartan	Captopril	722	73.5	30.6	0.9	4
ELITE II (2000)[14]	Losartan	Captopril	3152	71.5	30.6	1.5	4
HEAVEN (2002)[34]	Valsartan	Enalapril	141	67.5	26.2	0.2	4
REPLACE (2001)[35]	Telmisartan	Enalapril	378	64.0	11.0	0.2	3
Subjects with recent myocardial infarction or ischaemic syndrome							
Di Pasquale et al (1999)[36]	Losartan	Captopril	73	63.5	27.4	0.2	3
OPTIMAAL (2002)[13]	Losartan	Captopril	5477	67.4	28.8	2.7	5
Spinar et al (2000)[37]	Losartan	Captopril	201	65.9	29.9	0.1	2

SCOPE=study on cognition and prognosis in the elderly; RENAAL=reduction of end points in NIDDM with the angiotensin II antagonist losartan; IDNT=irbesartan diabetic nephropathy trial; DETAIL=diabetics exposed to telmisartan and enalapril; ARCH-J=assessment of response to candesartan in heart failure in Japan; CHARM=candesartan in heart failure: assessment of reduction in mortality and morbidity; SPICE=study of patients intolerant of converting enzyme inhibitors; Val-HeFT=valsartan in heart failure trial; ELITE=evaluation of losartan in the elderly; HEAVEN=heart failure valsartan exercise capacity evaluation; REPLACE=replacement of angiotensin converting enzyme inhibition; OPTIMAAL=optimal trial in myocardial infarction with the angiotensin II antagonist losartan.

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

Figure 4 shows the results of the comparison of treatment with angiotensin receptor blockers and ACE inhibitors with respect to risk of myocardial infarction in one hypertension study, one diabetes and nephropathy study, four heart failure studies, and three recent studies of myocardial infarction or ischaemic

syndrome. 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). This summary effect size was driven mainly by the OPTIMAAL study,[13] which accounted for 86.8% of the weighted odds ratio in the random effects model, with an individual study odds ratio of 1.01 (0.87 to 1.16).

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

In our analysis of treatment with angiotensin receptor blockers compared with placebo including 21 062 patients, we found no significant difference between groups in the incidence of myocardial infarction, although the 95% confidence intervals 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,[29] which contributed more than 13% to the weighted pooled odds ratio and was the only study to
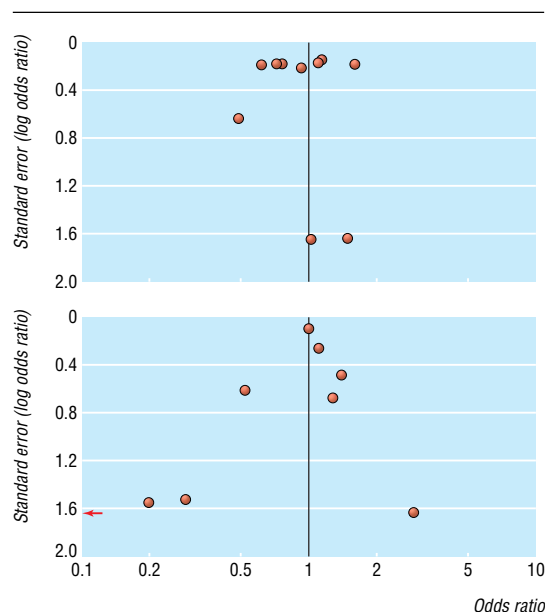

Fig 2 Top: Funnel plot of studies comparing angiotensin receptor blockers and placebo. Bottom: Funnel plot of studies comparing angiotensin receptor blockers and angiotensin converting enzyme (ACE) inhibitors

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 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[28] and ValHeFT[32] 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. Although we have not shown a clear relative benefit on myocardial infarction of treatment with angiotensin receptor blockers compared with placebo, our results indicate that this class of medications is unlikely to be harmful.

Angiotensin receptor blockers versus ACE inhibitors

As ACE inhibitors have been shown unequivocally to reduce cardiac morbidity and mortality among patients at risk for cardiovascular events, a prespecified comparative analysis with ACE inhibitors was necessary to assess better the safety and rela-
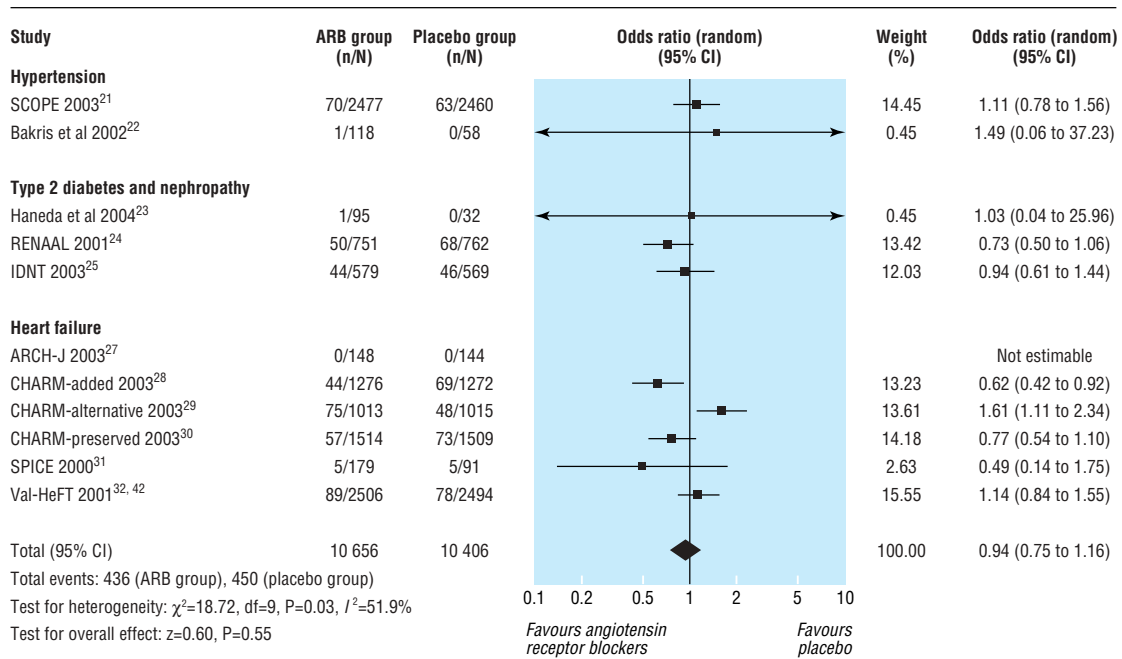
Study	ARB group (n/N)	Placebo group (n/N)	Odds ratio (random) (95% CI)	Weight (%)	Odds ratio (random) (95% CI)
Hypertension					
SCOPE 2003[21]	70/2477	63/2460		14.45	1.11 (0.78 to 1.56)
Bakris et al 2002[22]	1/118	0/58		0.45	1.49 (0.06 to 37.23)
Type 2 diabetes and nephropathy					
Haneda et al 2004[23]	1/95	0/32		0.45	1.03 (0.04 to 25.96)
RENAAL 2001[24]	50/751	68/762		13.42	0.73 (0.50 to 1.06)
IDNT 2003[25]	44/579	46/569		12.03	0.94 (0.61 to 1.44)
Heart failure					
ARCH-J 2003[27]	0/148	0/144			Not estimable
CHARM-added 2003[28]	44/1276	69/1272		13.23	0.62 (0.42 to 0.92)
CHARM-alternative 2003[29]	75/1013	48/1015		13.61	1.61 (1.11 to 2.34)
CHARM-preserved 2003[30]	57/1514	73/1509		14.18	0.77 (0.54 to 1.10)
SPICE 2000[31]	5/179	5/91		2.63	0.49 (0.14 to 1.75)
Val-HeFT 2001[32, 42]	89/2506	78/2494		15.55	1.14 (0.84 to 1.55)
Total (95% CI)	10 656	10 406		100.00	0.94 (0.75 to 1.16)
Total events: 436 (ARB group), 450 (placebo group)					
Test for heterogeneity: $\chi^2=18.72$, df=9, P=0.03, $I^2=51.9\%$					
Test for overall effect: z=0.60, P=0.55					

Favours angiotensin receptor blockers — Favours placebo

Fig 3 Effect of angiotensin receptor blockers compared with placebo on risk of myocardial infarction

Study	ARB group (n/N)	ACE Inhibitor (n/N)	Odds ratio (random) (95% CI)	Weight (%)	Odds ratio (random) (95% CI)
Hypertension					
Bakris et al 2002[22]	1/118	0/113		0.20	2.90 (0.12 to 71.88)
Type 2 diabetes and nephropathy					
DETAIL 2004[26]	10/120	8/130		2.18	1.39 (0.53 to 3.64)
Heart failure					
ELITE 1997[33]	4/352	8/370		1.39	0.52 (0.16 to 1.74)
ELITE II 2000[14]	31/1578	28/1574		7.64	1.11 (0.66 to 1.85)
HEAVEN 2002[34]	0/70	2/71		0.22	0.20 (0.01 to 4.18)
REPLACE 2001[35]	0/301	1/77		0.20	0.08 (0.00 to 2.10)
Recent myocardial infarction or ischaemic syndrome					
Di Pasquale et al 1999[36]	0/23	3/50		0.23	0.29 (0.01 to 5.82)
OPTIMAAL 2002[13]	384/2744	379/2733		86.83	1.01 (0.87 to 1.18)
Spinar et al 2000[37]	5/100	4/101		1.12	1.28 (0.33 to 4.90)
Total (95% CI)	5406	5219		100.00	1.01 (0.87 to 1.16)
Total events: 435 (ARB group), 433 (ACE group)					
Test for heterogeneity: $\chi^2=6.28$, df=8, P=0.62, $I^2=0\%$					
Test for overall effect: z=0.12, P=0.91					

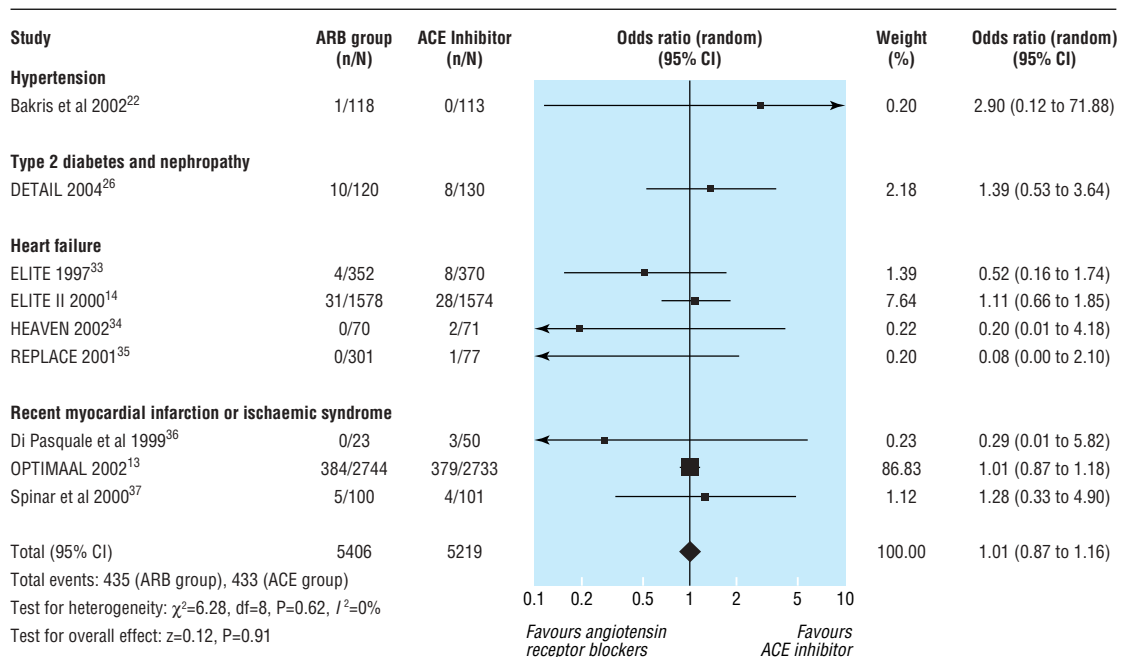Favours angiotensin receptor blockers — Favours ACE inhibitor

Fig 4 Effect of angiotensin receptor blockers compared with angiotensin converting enzyme inhibitors on risk of myocardial infarction

tive effect of angiotensin receptor blockers on the risk of myocardial infarction. In this analysis, we found no difference in this risk between the arms receiving angiotensin receptor blockers and ACE inhibitors. Similar to our analysis comparing angiotensin receptor blockers with placebo, the 95% confidence interval included an up to 16% increased risk of myocardial infarction down to a 13% reduction with angiotensin receptor blockers. Although our evaluation included nine component studies, all of which had 95% confidence intervals crossing 1.0, the overall effect was most heavily influenced by the OPTIMAAL study.[13] In this trial, the angiotensin receptor blocker losartan was not found to be superior or non-inferior to the ACE inhibitor captopril with respect to overall mortality in very high risk patients after myocardial infarction, and the rate of reinfarction was virtually identical between groups. Although angiotensin receptor blockers were found to be non-superior in large randomised controlled trials,[12-14 43] 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.[44]

Angiotension 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,[15] which drew attention to results from several recent studies, including the VALUE trial,[40] the CHARM-alternative[29] and CHARM-preserved[30] trials, and the SCOPE,[21] LIFE,[39] and RENAAL[24] trials. Our analysis, which included all but the LIFE[39] and VALUE[40] trials (excluded from our analysis because they did not have placebo or ACE inhibitor control groups), highlights the importance of assessing all available evidence by using systematic methods, before drawing conclusions.

Limitations

Although we tried to conduct a thorough review of the existing literature, our study has limitations inherent to any systematic review. Firstly, we were unable to obtain data on myocardial infarction events from all studies identified in our literature search. Perhaps most notably, data on myocardial infarction from the valsartan in acute myocardial infarction trial (VALIANT),[12] which included 14 703 patients, were not available for our analysis. We informally tested the potential impact of the unavailable data from this trial 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 of VALIANT had a myocardial infarction, and 0 patients in the captopril arm were admitted to hospital for myocardial infarction. In this scenario, the pooled odds ratio in our ACE-inhibitor controlled analysis changed from 1.01 (0.87 to 1.16) to 1.40 (0.25 to 7.80). Despite the addition of almost 10 000 patients to our study total, we would still observe no significant association between use of angiotensin receptor blockers and myocardial infarction risk compared with ACE inhibitors. We would further speculate that data from other potential sources not included in our study (from smaller trials, unpublished reports) would not significantly influence our results. Similarly, excluding the non-randomised trial[36] would have little impact on our findings. Other limitations of our study 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.

> ### What is already known on this topic
>
> Evidence from randomised controlled trials of angiotensin receptor blockers have shown variable effects on cardiovascular events
>
> ———
>
> A recent editorial by Verma and Strauss 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

Conclusions

We conducted a systematic quantitative review of angiotensin receptor blockers and the risk of myocardial infarction. Until information specifically dealing with this issue is available from large, prospectively designed trials, such as the ONTARGET/TRANSCEND trials,[45] we must rely on the weight of available evidence to guide decisions on the management of individual patients' decisions. Our results show that treatment with angiotensin receptor blockers is not associated with increased incidence of myocardial infarction.

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