Angiotensin II receptor blockers and myocardial infarction: an updated analysis of randomized clinical trials

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Objective **To evaluate the effects of treatments based on angiotensin II receptor blockers (ARBs) on the risk of myocardial infarction (MI), cardiovascular and all-cause death, as compared with conventional treatment or placebo.**

Methods **We performed a meta-analysis of all available major international, randomized clinical trials (20 trials, $n = 108\,909$ patients, mean age 66.5 ± 4.1 years), published by 31 August 2008, comparing ARBs with other drugs or conventional therapies (placebo) and reporting MI incidence.**

Results **During a mean follow-up of 3.3 ± 1.1 years, a total of 2374/53 208 and 2354/53 153 cases of MI were recorded in ARB-based groups and in comparator arms, respectively [odds ratio (OR) 95% confidence interval (CI) 1.008 (0.950–1.069)]. Risks of MI were not different when tested in different clinical conditions, including hypertension, high cardiovascular risk, stroke, coronary disease, renal disease and heart failure. No significant differences in the risk of MI between treatment with ARBs versus placebo [OR 95% CI 0.944 (0.841–1.060)], beta-blockers and diuretics [OR 95% CI 0.970 (0.804–1.170)], calcium channel blockers [OR 95% CI 1.112 (0.971–1.272)], or angiotensin-converting enzyme (ACE) inhibitors [OR 95% CI 1.008 (0.926–1.099)] were observed. Analysis of trials comparing combination therapy based on ARBs plus ACE inhibitors versus active treatments or placebo showed equivalent MI risk [OR 95% CI 0.996 (0.896–1.107)].**

Conclusion **The present meta-analysis indicates that the risk of MI is comparable with use of ARBs and other antihypertensive drugs in a wide range of clinical conditions.**

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Keywords: angiotensin-converting enzyme inhibitors, acute myocardial infarction, angiotensin II receptor blockers, cardiovascular disease, clinical trials, hypertension

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BP, blood pressure; CCBs, calcium-channel blockers; CHARM, Candesartan cilexitil in Heart failure assessment of Reduction in morbidity and Mortality; CI, confidence interval; DETAIL, Diabetics Exposed to Telmisartan and Enalapril; ELITE, evaluation of losartan in the elderly; IDNT, Irbesartan Diabetic Nephropathy Trial; Jikei Heart Study, Valsartan in a Japanese population with hypertension and other cardiovascular disease; LIFE, Losartan Intervention for Endpoint reduction in hypertension; MI, myocardial infarction; MOSES, MOrbidity and Mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint; OPTIMAAL, Optimal Treatment in Myocardial Infarction with the Angiotensin II Antagonist Losartan; OR, odds ratio; PRoFESS, Prevention Regimen For Effectively avoiding Second Strokes; RENAAL, Reduction in Endpoints in patients with Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; SCOPE, Study on Cognition and Prognosis in the Elderly; TRANSCEND, Telmisartan Randomized Assessment Study in ACE intolerant patients with cardiovascular Disease; Val-HeFT, Angiotensin II Receptor Blocker Valsartan in Congestive Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction Trial

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Introduction

In the last decade, numerous clinical trials have investigated pharmacological therapies based on angiotensin II receptor blockers (ARBs) in cardiovascular and renal diseases [1]. The results have led to the conclusion that these drugs are well tolerated and effective, favouring their recommendation and use for the clinical management of hypertension, and the prevention and treatment of cardiac, cerebrovascular and renal diseases [2,3]. In recent years, however, the efficacy of ARBs in preventing myocardial infarction (MI) has been questioned, generating an active debate in the medical community. Some reports [4,5] have suggested that ARBs may be less effective than angiotensin-converting enzyme (ACE) inhibitors in preventing MI; the most recent analysis by Strauss and Hall [6] concludes that 'ARBs may, indeed, increase the risk of MI', and commentaries from the same authors [7,8] remark that 'ACE inhibitors and ARBs differ for the most important cardiovascular endpoints (e.g. MI and cardiovascular death)'. Other meta-analyses [9–15] and commentaries [16] have challenged this view, but they do not close the controversy [17,18].

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During the last 2 years, several large clinical trials comparing ARBs with other active treatments or placebo in high cardiovascular risk patients have been concluded [19–24]. The results of these studies offer an excellent opportunity to scrutinize the influence of ARBs on MI risk in much larger population samples than those previously used [25–38]. In addition, since ARB-based therapy has been investigated in a wide range of clinical conditions, this new analysis may provide much broader insights than hitherto available on the use of ARBs.

For this purpose, in the present study, we analysed all available major, international, randomized, clinical trials comparing the effects of ARB-based treatment on the risk of MI, cardiovascular and total death as compared with treatments based on active comparators or placebo. We also explored these relationships according to the prevalent underlying clinical condition.

Methods

Data searching and selection

The methodological approach has been described previously [10]. Briefly, a computerized literature search was carried out using the PubMed database up to 31 August 2008 with the aim of identifying all clinical trials evaluating the effect of an ARB-based treatment and reporting the incidence of MI either as the primary endpoint or as a predefined secondary endpoint [10].

The selected clinical trials had to fulfil the following criteria [10]: international, randomized, controlled design published in peer-reviewed journals indexed in medical databases; information on baseline blood pressure (BP) levels as well as on the type of antihypertensive treatment; duration of follow-up of at least 2 years; sample size of at least 200 participants; and information on absolute incidence of MI, cardiovascular and all-cause mortality.

Statistical analysis

The statistical analysis was performed using SPSS version 12.0 (Chicago, Illinois, USA), NCSS 2007 and STATA version 10.0 packages. Continuous variables were expressed as weighted mean ± SD. Odds ratios (OR) and 95% confidence intervals (CI) for each outcome were calculated separately for each of the studies according to the principle of the intention-to-treat analysis. Overall estimates of the effect were calculated with a fixed-effects model, according to the meta-analytical technique [39–41]. The assumption of homogeneity of treatment effect between different individual studies and subgroups of studies was tested using the chi-square test for homogeneity; in the presence of heterogeneity ($P < 0.05$), the random-effects model was applied. When appropriate, publication bias was tested as previously described [42,43]. The statistical power of the subgroup analysis was tested using G*Power 3.0.3. Statistical significance was accepted for P values less than 0.05.

Results

Population characteristics

Twenty trials, for a total of 108 909 patients, fulfilled the selection criteria and were included in the present analysis [19–37]. Among the clinical trials initially selected, one [38] could not be included because specific information on MI was not available. The general characteristics of the selected trials, including year of publication, mean duration of follow-up, type and dosage of ARB and comparators and mean SBP and DBP differences between treatment arms, are shown in Table 1.

The trials explored the efficacy of ARB-based therapy in different clinical settings: arterial hypertension [19,21,30], high cardiovascular risk profile with and without hypertension [22,24,31], coronary artery disease (post-MI) [29,36], history of stroke [19,22,32], renal disease with and without hypertension and/or diabetes mellitus [27,28,37], and heart failure [25,26,33–35]. Among these populations, 53 208 patients were randomized to receive an ARB, 18 292 to receive ACE inhibitors and 14 663 to receive a combination of ACE inhibitors and ARBs. The remaining patients were exposed to no renin–angiotensin system based strategy, including diuretics and beta-blockers ($n = 5583$) or calcium-channel blockers (CCBs) ($n = 8834$). In addition, 19 473 patients were randomized to receive placebo plus optimal standard treatment for their clinical condition.

Incidence of myocardial infarction, cardiovascular and all-cause mortality

Over an average follow-up of 3.3 ± 1.1 years, there were 2374/53 208 and 2354/53 153 cases of MI in ARB-treated and non-ARB-treated patients, respectively ($P = $ NS). Although data from individual trials showed noticeable differences, the overall risk of MI between ARB-treated and non-ARB-treated patients was not significantly different both when all patients were considered and when the comparisons were made separately for the different clinical conditions (Fig. 1).

No increased MI risk was observed when ARBs were compared with placebo on top of optimal pharmacological treatment without ARBs [OR 95% CI 0.944 (0.841–1.060)] [23,24,28,32,33,35]. No significant differences were found when ARB-based therapy was compared with conventional antihypertensive therapies, including diuretics and beta-blockers [OR 95% CI 0.970 (0.804–1.170)] [19,21,30], CCBs [OR 95% CI 1.112 (0.971–1.272)] [20,28,31] or ACE inhibitors [OR 95% CI 1.008 (0.926–1.099)] [22,25,26,29,36,37]. Finally, analysis of trials comparing combination therapy based on ARBs plus ACE inhibitors versus other active treatments or placebo showed that MI risk substantially lies on the indifference line [OR 95% CI 0.996 (0.896–1.107)] [22,29,34,36].

Table 1 General characteristics of clinical trials considered for the present analysis

Clinical trial	Publication (year)	Follow-up (years)	Age (years)	ARB	Group (*n*)	Dosage (mg)	Mean dose (mg)	Comparator	Group (*n*)	Dosage (mg)	Mean dose (mg)	SBP/DBP difference (mmHg)	Reference
ELITE I	1997	1.0	73.0	Losartan	352	50.0	42.6	Captopril	370	150.0	122.7	NA	[26]
ELITE II	2000	1.5	71.0	Losartan	1.578	50.0	NA	Captopril	1.574	150.0	NA	NA	[25]
IDNT	2001	2.6	59.0	Irbesartan	579	300.0	NA	Amlodipine	567	10.0	NA	−2.0/0.0	[27]
RENAAL	2001	3.4	59.0	Losartan	751	50.0	NA	Placebo	762	NA	NA	−1.0/0.0	[28]
OPTIMAAL	2002	2.7	60.0	Losartan	2.744	50.0	45	Captopril	2.733	150.0	132.0	NA	[29]
LIFE	2002	4.8	67.0	Losartan	4.605	50.0	82.0	Atenolol	4.588	50.0	79.0	−1.0/0.0	[30]
VALUE	2002	4.2	67.0	Valsartan	7.649	160.0	151.7	Amlodipine	7.596	10.0	8.7	2.0/2.0	[31]
SCOPE	2003	3.7	67.0	Candesartan	2.477	16.0	11.6	Placebo[a]	2.460	NA	NA	−3.0/−1.0	[32]
CHARM-Alternative	2003	2.9	76.0	Candesartan	1.013	32.0	23.0	Placebo	1.015	NA	27.0	−4.4/−3.9	[35]
CHARM-Preserved	2003	3.2	67.0	Candesartan	1.514	32.0	25.0	Placebo	1.509	NA	27.8	−6.9/−2.9	[33]
CHARM-Added	2003	3.5	64.1	Candesartan	1.276	32.0	NA	Placebo	1.272	NA	NA	−4.6/−3.0	[34]
VALIANT	2003	2.7	65.0	Valsartan	4.909	160.0	147	Captopril	4.909	150.0	117.0	0.1/−0.9	[36]
DETAIL	2004	5.0	61.0	Telmisartan	120	80.0	NA	Enalapril	130	20.0	NA	NA	[37]
MOSES	2005	2.5	67.9	Eprosartan	681	600.0	623.0	Nitrendipine	671	10.0	16.0	2.8/3.8	[20]
E-COST	2005	3.1	67.2	Candesartan	1.053	8.0	6.9	CT	995	NA	NA	5.2/2.6	[21]
JIKEI	2007	3.1	65.0	Valsartan	1.541	80.0	76.0	CT	1.540	NA	NA	−0.4/−18.4	[19]
ONTARGET	2008	4.8	66.4	Telmisartan	8.163	80.0	NA	Ramipril	8.102	10.0	NA	−0.9/−0.6	[22]
PROFESS	2008	3.7	66.1	Telmisartan	10.146	80.0	NA	Placebo	10.186	NA	NA	−3.8/−1.9	[23]
TRANSCEND	2008	4.8	66.9	Telmisartan	2.954	80.0	NA	Placebo	2.972	NA	NA	−4.0/−2.2	[24]

CHARM, Candesartan cilexitil in Heart failure: assessment of Reduction in morbidity and Mortality; DETAIL, Diabetics Exposed to Telmisartan and Enalapril; ; ELITE, Evaluation of Losartan In The Elderly; IDNT, Irbesartan Diabetic Nephropathy Trial; Jikei Heart Study, Valsartan in a Japanese population with hypertension and other cardiovascular disease; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; MOSES, MOrbidity and Mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint; OPTIMAAL, Optimal Treatment in Myocardial Infarction with the Angiotensin II Antagonist Losartan; PRoFESS, Prevention Regimen For Effectively avoiding Second Strokes; RENAAL, Reduction in Endpoints in patients with Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; SCOPE, Study on Cognition and Prognosis in the Elderly; VALIANT, Valsartan in Acute Myocardial Infarction Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE intolerant patients with cardiovascular Disease.
[a] Patients of the placebo arm in this study were permitted to receive antihypertensive therapy, including ARBs.

In the overall population sample, cardiovascular mortality did not differ between ARB-treated and non-ARB-treated patients, either for the random-effects model [OR 95% CI 0.976 (0.935–1.018)] or the fixed-effects model [OR 95% CI 0.979 (0.919–1.044)]. Similar results were obtained for all-cause mortality for both models ([OR 95% CI 1.009 (0.971–1.048)] and [OR 95% CI 1.009 (0.970–1.050)], respectively).

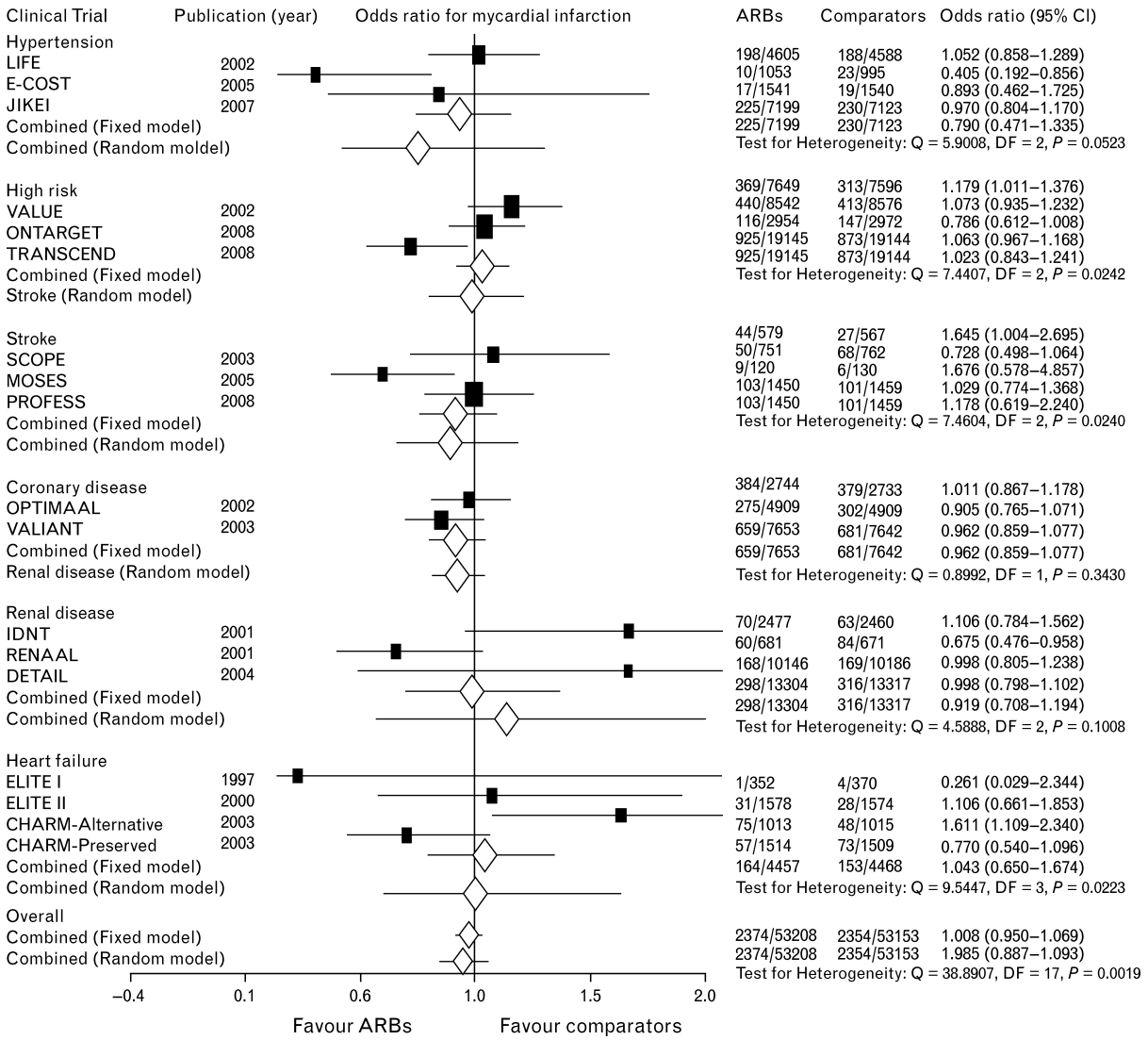
Discussion

In this meta-analysis of all available clinical trials [19–37], pharmacological treatment based on ARBs was associated with a risk of MI comparable with that observed in non-ARB-treated patients. Our study also demonstrates comparable risk of MI with ARBs or other treatments in different clinical conditions. Thus, our present findings do not support the claim that ARBs may offer less myocardial protection than other pharmacological treatments [4–6]. Our data substantially and temporally extend the results of previous smaller meta-analyses that also concluded a protective effect of ARBs against coronary events, which was comparable with that observed for other drug regimens [9–15,18,44,45]. Finally, we found that treatment based on ACE inhibitors and ARBs in combination is associated with similar risk of MI to that with any other antihypertensive treatment.

The reasons underlying the difference between our current findings and those reported in the most recent analysis by Strauss and Hall [6] rely not only on the larger size of our sample but also on major differences in the methodological approach. Although, in our analysis, all major interventional studies were considered to avoid a selection bias, the analysis of Strauss and Hall [6] was restricted to only 11 studies among those already available in 2007. The reasons underlying the selection operated by these authors can be synthetically related to their 'biological' hypothesis [6] that attenuation of both AT1-mediated and AT2-mediated effects are preferable to AT1 receptor antagonism associated with AT2 receptor stimulation, as in the case of ARB therapy. As a consequence, they decided to consider only the data in the absence of ACE inhibition. It is not completely clear whether this was the rationale to exclude three important clinical studies from the analysis. Whatever the case, the hypothesis that led to their selection strategy is not supported by the results of the three arms of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study [22], as related to MI, cardiovascular and all-cause death. Also, our findings on the effects of the combination therapy do not support their working hypothesis.

Several other points deserve to be mentioned. First, our data are in line with the conclusions of previous meta-analyses on ARBs and MI, which were based, however, on a smaller population sample [9–12,14], were limited to comparisons between the effect of ARBs and ACE inhibitors [13,15,18] and included smaller numbers of patients at high or very high cardiovascular risk. Second, our present findings provide solid evidence for the fact

Fig. 1



Comparison between angiotensin II receptor blocker based strategy and other active treatments or placebo in different clinical settings and in the overall study population in terms of the risk of myocardial infarction.

that ARBs are similar to comparators also for the incidence of cardiovascular and all-cause mortality.

Finally, this overall similarity between ARBs and non-ARB therapies supports the view of the recent European guidelines on the clinical management of arterial hypertension [3] that there is no specific advantage of one class of antihypertensive drugs versus another as far as myocardial protection is concerned, presumably because of the predominant protective effect of BP reduction *per se*. In our meta-analysis, the BP-lowering effect of different antihypertensive treatments was not included, but this has been addressed in other analyses that have used the meta-regression approach and demonstrated that the cardiovascular benefits largely depend on the BP-lowering efficacy of pharmacological treatment [12,15]. A difference in BP is also likely to explain the slight advantage of ACE inhibitors over ARBs reported for MI prevention by the Blood Pressure Lowering Treatment Trialists' Collaboration [18], insofar that, in that meta-analysis ACE inhibitor-treated patients showed a greater BP reduction compared with the ARB-treated ones.

Whatever the case, the results of present meta-analysis are against the possibility raised years ago that 'ARBs may increase the risk of MI' [4–6]. At the same time, our findings do not support the suggestion of a negative role of stimulation of AT2 subtype receptors by a residual unbound fraction of angiotensin II in patients chronically treated with ARBs [46,47].

Other recent analyses have revealed a superiority of ARBs over other antihypertensive classes in terms of regression of left ventricular hypertrophy [48], new-onset diabetes [49], stroke [15,44] and progression of renal disease [50]. In this view, our current observation that they are comparable to, and not worse than, other classes, including ACE inhibitors, in terms of MI protection, rules out a potential concern of physicians related to these compounds, and rather confirms their well tolerated use in a number of clinical indications.

Conclusion

The present large meta-analysis on clinical trials using ARBs provides evidence that these drugs are comparable to any other drug classes, including ACE inhibitors, against the risk of MI, cardiovascular mortality and all-cause mortality across the whole spectrum of cardiovascular diseases.

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