Angiotensin II receptor blockers and myocardial infarction: deeds and misdeeds

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Background **A recent editorial published by Verma and Strauss, entitled 'Angiotensin receptor blockers and myocardial infarction', examined, through a partial analysis of individual trials, the use of angiotensin receptor blockers (ARBs) in a variety of clinical settings. This editorial was reported widely in the lay press and media, and generated disappointment and concern among physicians in many countries, probably because of its provocative subtitle in the *British Medical Journal*: 'These drugs may increase myocardial infarction and patients may need to be told'.**

Objective and methods **In order to explore the influence of ARBs on myocardial infarction, we performed a more comprehensive and updated meta-analysis, taking into account all major international, randomized trials using ARBs compared with another active drug or conventional therapy (placebo), and reporting information on rates of myocardial infarction.**

Results **We found no significant differences in fatal and non-fatal myocardial infarction between treatment with ARBs, placebo or active treatment, and the same result was obtained when considering only trials in which ARBs were compared with angiotensin-converting enzyme inhibitors (ACEIs), or when pooling all trials together. The pooled analysis of these trials shows that the relative risk of myocardial infarction lies substantially on the indifference line.**

Conclusion **Our analysis demonstrates that, at this time, there is no evidence of increased risk of myocardial infarction in patients treated with ARBs. *J Hypertens* 23:2113–2118 © 2005 Lippincott Williams & Wilkins.**

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Keywords: acute myocardial infarction, angiotensin II receptor blockers, clinical trials, meta-analysis, relative risk

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Introduction

The primary aim of the health services in most countries is to provide the best medical assistance and proper information to individual citizens [1–3]. Within this process, new, effective drugs with the best achievable profile of safety and tolerability are evaluated and eventually approved for clinical use [1–3]. In order to guarantee to patients health-care measures based on evidence, rather than on a physician's beliefs and clinical experience, the results of large, randomized trials and the recommendations of guidelines are taken into account [1–3]. However, the results of trials in specific areas may not provide sufficient evidence or may even be conflicting. For this reason, meta-analyses are often performed and proposed to the scientific community, to overcome the limits of individual trials. Together with randomized trials, meta-analysis, when thorough, well balanced and properly designed, may reach the statistical power to suggest or support clinical conclusions, and they represent a useful support to clinical research today. In this process, however, it is important to identify clearly, and possibly predefine, the features of the studies included in the meta-analysis, as well as to make the analysis as thorough as possible. In the recent past, an unbalanced approach to meta-analysis [4] produced long-term unjustified diffidence, in the medical community and among patients, towards a class of effective antihypertensive drugs, which was then dismantled by the accumulating evidence in favour of their cardiovascular protective effect and safety.

A recent editorial published in the *British Medical Journal* (*BMJ*) by Verma and Strauss, entitled 'Angiotensin receptor blockers and myocardial infarction' [5], examined, through a partial and incomplete analysis of some individual trials, the influence of angiotensin II receptor blockers (ARBs) on myocardial infarction in a variety of clinical settings. Because of the provocative nature of this article, and in particular of its subtitle in the *BMJ* 'These drugs may increase myocardial infarction and patients may need to be told' [5], this editorial was reported widely in the lay press and media. For instance, in Italy one of the major weekly magazine brought to patients' and physicians' attention, about 4 months later, the suspicion that all ARBs (providing all individual commercial names) may induce myocardial infarction

[6]. This obviously produced anxiety among patients taking an ARB, as well as uncertainty and disappointment among physicians routinely prescribing ARBs.

This phenomenon raises ethical questions about publishing superficial editorials with appealing titles and no solid scientific basis, which can generate journalistic scoops. Several letters and replies from scientists criticized the article by Verma and Strauss [5], because of incomplete and subjective analysis of some ARBs trials [7–11]. These authors took into account only some selected trials, excluding many others. In particular, only the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [12], the Candesartan Cilexitil in Heart failure: Assessment of Reduction in Morbidity and Mortality (CHARM) Alternative Trial [13], the Study on Cognition and Prognosis in the Elderly (SCOPE) [14] and the Reduction in End-points in Patients with Non-insulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study [15] were considered. In the interpretation of the authors, these studies support a detrimental role of ARBs in favouring development of myocardial infarction. This interpretation, however, is based on a misleading and heterogeneous analysis. The authors, in fact, arbitrarily transformed a different percentage of myocardial infarction risk reduction between ARBs and the other arm of treatment in each study, into a major risk induction of myocardial infarction by ARBs. In addition, the considered studies were mostly underpowered to sufficiently analyse differences in myocardial infarction. Finally, they did not use consistent parameters for their comparisons.

In the present article, we report a meta-analysis of all major morbidity/mortality trials with ARBs, published through March 2005, which provided specific information about myocardial infarction as an end point or a pre-specified event [12–22].

Methods

Data searching and selection

We reviewed the medical literature to identify all major, randomized, controlled, multicentre, morbidity and mortality clinical trials, evaluating the efficacy of ARBs in patients at risk for fatal and non-fatal myocardial infarction, both as part of the primary end point or as a secondary end point. Only the studies including selected data on myocardial infarction as an end point or a pre-specified event were considered for further analysis.

A computerized literature search was carried out using the Pub-Med database up to March 2005. According to these criteria, a total of 11 trials were included in the meta-analysis [12–22]. The Angiotensin II Receptor Blocker Valsartan in Congestive Heart Failure Trial (Val-HeFT) [23] was not included because selected

Table 1 Clinical trials considered in the meta-analysis. Type of angiotensin receptor blockers (ARBs), dosages and duration of treatment, comparator, and main characteristics of the study population of each trial are shown

Trial	ARB	Dosage	Duration of treatment (months)	Comparator	Sample size	Age (years)	Basal BP levels (mmHg)		Final BP levels (mmHg)		Primary outcome
							ARB	Other	ARB	Other	
ELITE [19]	Losartan	50 mg daily	10.8	Captopril	722	73 ± 4	137/79	137/79	nr	nr	Increase in serum creatinine by 26.5 μmol/l or more (0.3 mg/dl or more) frome baseline
ELITE II [20]	Losartan	50 mg daily	18	Captopril	3152	71 ± 5	134/78	134/78	nr	nr	All-cause mortality or sudden death
IDNT [21]	Irbesartan	300 mg daily	30	Amlodipine	1715	59 ± 7	160/87	159/87	nr	nr	Doubling or serum creatinine from baseline, development of end-stage renal disease, or death from any cause
RENAAL [15]	Losartan	50 mg daily	40	Placebo	1513	60 ± 7	152/82	153/82	140/74	142/74	Doubling or serum creatinine from baseline, development of end-stage renal disease, or death from any cause
SCOPE [14]	Candesartan	16 mg daily	43	Placebo	4937	76 ± 8	166/90	166/90	145/80	148/81	Cardiovascular death, myocardial infarction and stroke
OPTIMAAL [18]	Losartan	50 mg daily	31	Captopril	5477	67 ± 4	123/72	122/71			All-cause mortality
LIFE [17]	Losartan	50 mg daily	56	Atenolol	9193	67 ± 3	174/97	174/97	144/81	145/81	Cardiovascular death, myocardial infarction and stroke
VALUE [12]	Valsartan	160 mg daily	72	Amlodipine	15 245	67 ± 7	154/87	154/87	139/79	137/77	Cardiovascular death, myocardial infarction and stroke
CHARM – Alternative [13]	Candesartan	32 mg daily	33.7	Placebo	2028	67 ± 2	129/79	130/77	nr	nr	Cardiovascular death or hospital admission for heart failure
CHARM – Preserved [16]	Candesartan	32 mg daily	33.6	Placebo	3020	67 ± 1	136/77	136/77	nr	nr	Cardiovascular death or hospital admission for heart failure
VALIANT [22]	Valsartan	80 mg twice daily	24.7	Captopril	14 703	65 ± 6	123/73	123/72	nr	nr	All-cause mortality

nr, Not reported.

Table 2 Incidence of myocardial infarction (MI) in each trial with angiotensin receptor antagonists (ARB) versus placebo

	Arm of treatment									
	ARB		Placebo							
Trial	MI	Total	MI	Total	RR	CI 95%		Standard error, lg(RR)	*z*	*P*
CHARM – Alternative [13]	75	1013	48	1015	1.566	1.101	2.225	0.17943	2.498	0.012
CHARM – Preserved [16]	57	1514	73	1509	0.779	0.554	1.092	0.17297	−1.449	0.147
SCOPE[a] [14]	70	2477	63	2460	1.104	0.789	1.544	0.17131	0.575	0.565
RENAAL [15]	50	751	68	762	0.747	0.525	1.060	0.17906	−1.636	0.102
Total	252	5755	252	5746	0.998	0.842	1.184	0.08711	−0.018	0.986

Relative risk (RR) and confidence interval (CI 95%), standard error, *z* and *P* values are reported. [a]Patients of the placebo arm in this study were permitted to receive antihypertensive therapy.

information on myocardial infarction was not available, whereas the Added-arm of CHARM [24] was not included, because ARBs were added to angiotensin-converting enzyme inhibitors (ACEIs) and their specific effect could not be extrapolated. The parameters derived from each trial were the number of patients, type of cardiovascular disease, type of ARB, dosage and duration of the treatment and type of comparator (active or placebo), mean age and standard deviation of age, baseline and final blood pressure levels, rates of events (end points), including all-cause mortality, cardiovascular mortality, rates of myocardial infarction, stroke and heart failure, or other pre-specified events.

Statistical analysis

We conducted a systematic review of each trial identified. As authors used different epidemiological indexes to elaborate confidence interval and probability, we had to recalculate these parameters with uniform criteria. Secondly, we had to calculate confidence interval and probability for myocardial infarction as a separate end point for those trials in which it was considered as part of cardiovascular morbidity and mortality. We then pooled all data, weighting them with the inverse variance criteria and the DerSimonian random effects model [25,26], assigning a greater weight to more detailed and representative studies. For detecting heterogeneity we computed the Poisson heterogeneity or dispersion test statistic approximately distributed as a chi-square. We then calculated the weighted pooled odds ratio with 95% confidence intervals (CIs), the relative risk, the standardized normal z and the probability (P value). A chi-squared test was used to assess heterogeneity.

Results

In our meta-analysis we have taken into account the following trials: VALUE [12], Losartan Intervention for End-point Reduction in Hypertension (LIFE) [17], Optimal Treatment in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) [18], Evaluation of Losartan In The Elderly (ELITE) I [19], ELITE II [20], Irbesartan Diabetic Nephropathy Trial (IDNT) [21] and Valsartan in Acute Myocardial Infarction Trial (VALIANT) [22] for ARBs compared with another active drug (including ACEIs); CHARM-Alternative [13], SCOPE [14] and RENAAL [15] and CHARM-Preserved [16] for comparison between ARBs and conventional therapy (placebo). Table 1 summarizes the major characteristics of the considered trials, assembled in relation to the comparing group (either placebo, active treatment or ACEIs).

As shown in Tables 2 and 3, differences in fatal and non-fatal myocardial infarction between ARB treatment and placebo (Table 2) or active treatment (Table 3) never achieved statistical significance. The same result was

Table 3 Incidence of myocardial infarction in each trial performed with angiotensin receptor antagonists (ARB) versus another active drug

	Arm of treatment									
	ARB		Active drug							
Trial	MI	Total	MI	Total	RR	CI 95%		Standard error, lg(RR)	*z*	*P*
LIFE [17]	198	4605	188	4588	1.049	0.863	1.276	0.09967	0.483	0.629
OPTIMAAL [18]	384	2744	379	2733	1.009	0.885	1.151	0.06717	0.135	0.892
ELITE I [19]	1	352	4	370	0.263	0.030	2.340	1.11555	−1.198	0.231
ELITE II [20]	31	1578	28	1574	1.104	0.666	1.832	0.25827	0.384	0.701
IDNT [21]	39	579	25	567	1.528	0.937	2.490	0.2493	1.700	0.089
VALUE [12]	369	7649	313	7596	1.171	1.010	1.356	0.07512	2.099	0.036
VALIANT [22]	275	4909	302	4909	0.911	0.777	1.067	0.08087	−1.158	0.247
Total	1297	22416	1239	22337	1.043	0.967	1.125	0.03858	1.094	0.274

Relative risk (RR), confidence interval (CI 95%), standard error, *z* and *P* values are reported.

Table 4 Incidence of myocardial infarction (MI) in each trial using angiotensin receptor antagonists (ARB) versus angiotensin-converting enzyme inhibitors (ACEI)

	Arm of treatment									
	ARB		ACEI							
Trial	MI	Total	MI	Total	RR	CI 95%		Standard error, lg(RR)	*z*	*P*
OPTIMAAL [18]	384	2744	379	2733	1.009	0.885	1.151	0.06717	0.135	0.892
ELITE I [19]	1	352	4	370	0.263	0.030	2.340	1.11555	−1.198	0.231
ELITE II [20]	31	1578	28	1574	1.104	0.666	1.832	0.25827	0.384	0.701
VALIANT [22]	275	4909	302	4909	0.911	0.777	1.067	0.08087	−1.158	0.247
Total	691	9583	713	9586	0.969	0.877	1.072	0.05139	−0.604	0.546

Relative risk (RR) and confidence interval (CI 95%), standard error, *z* and *P* values are reported.

obtained when considering only trials in which ARBs were compared with ACEIs (Table 4) or when pooling all trials together (Table 5). In particular, the data of myocardial infarction in the overall considered population was 5.49% for ARBs and 5.31% for other drugs (NS).

Figure 1 summarizes the overall analysis and shows that relative risk lies substantially on the indifference line and that confidence intervals (CIs) are small; in particular, CIs are smaller in the comparison of ARBs versus active treatment and ACEIs than in the comparison of ARBs versus placebo.

Discussion

The data of the meta-analysis presented in this article clearly demonstrate that in patients with different pathological conditions at high risk to develop myocardial infarction (including hypertension, type 2 diabetes, nephropathy, left ventricular hypertrophy, myocardial infarction, stroke and heart failure) [12–22], ARBs are no different from the best conventional treatment (placebo), ACEI or other active comparators (including beta-blockers and calcium-antagonists), when the rate of new incidence of myocardial infarction is considered. Therefore, at this time, the available information does not support, and actually rejects, the provocative conclusions of the editorial by Verma and Strauss [5] and their analysis based on the arbitrary choice of some of the available trials with ARBs.

In contrast, the data provided in our meta-analysis were obtained by using a comprehensive approach that included all available, major, randomized, controlled, international studies with ARBs, providing the rates of fatal and non-fatal myocardial infarction. Our approach may, indeed, recognize some limitations, because it includes very heterogeneous conditions and patients with different susceptibility to myocardial infarction. The meta-analytical approach, however, minimizes the impact of heterogeneity. It should be also pointed out that some of the studies that we considered, were largely underpowered for myocardial infarction as an end point. At the same time, however, our current approach has a major advantage: it is based on an unbiased analysis of all morbidity and mortality trials with ARBs, and then provides, in our opinion, a more comprehensive and balanced conclusion on the influence of ARBs on the development of myocardial infarction. Certainly, the present analysis goes far beyond the partial report by Verma and Strauss [5], which suffers from the lack of any formal statistical analysis.

In this regard, it should be noted that our analysis could not take into account the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) Trial [27], which was published in June 2005 and does not provide data on myocardial infarction. Moreover, in the MOSES population, which included high-risk hypertensive patients with history of stroke, events classified as acute coronary syndromes were more frequent in the nitrendipine arm than in the eprosartan arm (48 versus 39, respectively) [27].

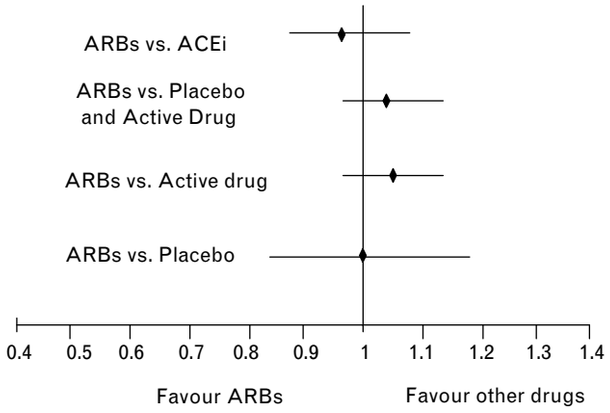
The article by Verma and Strauss [5] also provided unwarranted speculation on the potential mechanism

Table 5 Incidence of myocardial infarction (MI) in all considered trials pooled together

	Arm of treatment									
	ARB		Other drugs							
Trial	MI	Total	MI	Total	RR	CI 95%		Standard error, lg(RR)	*z*	*P*
Placebo and active drugs	1549	28171	1491	28083	1.036	0.966	1.110	0.03529	0.993	0.321

Relative risk (RR), confidence interval (CI 95%), standard error, *z* and *P* values are reported.

Fig. 1



Relative risk of myocardial infarction and its confidence interval (CI 95%) for angiotensin receptor blockers (ARBs) versus angiotensin converting enzyme inhibitors (ACEi), for all trials pooled together, for ARBs versus active drug and ARBs versus placebo.

underlying the 'toxic' effect of ARBs (e.g. AT_2 and inhibition of angiogenesis), and differentiating protective effects from ACEIs. It should be noted that the OPTIMAAL [18] and VALIANT [22] trials were arbitrarily excluded by Verma and Strauss [5]. Furthermore, most of the literature on AT_2 subtype receptors suggests a favourable role of these receptors on the cardiovascular system [28], and a vasoactive response [29]. However, in our opinion, it is premature any attempt to transfer the experimental observations on AT_2 (beneficial or detrimental) to humans, and especially, to explain the results of clinical trials.

The absence of significant difference in myocardial infarction between ARBs and ACEIs, observed in our meta-analysis, is particularly important, as the core of the current scientific debate is the interchangeable ability of these two classes of drugs to prevent such a hard end point. Our results basically support the recent European Guidelines on hypertension [1] recommending ARBs among those antihypertensive drugs capable of reducing cardiovascular morbidity and mortality, and ACC/AHA Practice Guidelines for the management of ST-elevation myocardial infarction [30], which propose ARBs as the second-line therapy, if an ACEI is not tolerated.

At this stage, there is wide agreement that ACE inhibition provides cardiac protection, while it is not fully established that ARBs are equivalent to ACEIs in terms of cardiac protection. However, the suggestion that ARBs could enhance the risk of myocardial infarction is totally unwarranted and is not supported by the available data. Future studies, in particular the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/ TRANSCEND) [31], will provide key information on the comparative capacity of ARBs and ACEIs to prevent myocardial infarction in patients at high risk.

Indeed, the narrative review by Verma and Strauss also speculated about the different protection of ACEIs and ARBs in diabetic patients [5]. In this regard, in a letter to the *BMJ*, Lewis [32] recently challenged this speculation, clarifying that in the analysis quoted by Verma and Strauss [5] data were mostly obtained in patients with type 1 diabetes aged 35 years on average, while data for ARBs were derived from patients with type 2 diabetes aged 59 years on average. Obviously, these two sets of patients are hardly comparable.

Finally, it should be mentioned that another independent meta-analysis, published in 2004, analysed the effects of ARBs on cardiovascular outcomes, including acute myocardial infarction, in patients with chronic heart failure and in patients at high risk for acute myocardial infarction [33]. The authors concluded that ARBs and ACEIs do not differ in efficacy for reducing all-cause mortality and heart failure hospitalizations. This conclusion is consistent with our current report.

In conclusion, medical editorials should not be based on superficial and subjective analysis of the literature and, most of all, should refrain from using titles (or subtitles) that may generate unjustified concern in the medical community and, primarily, among patients. Prestigious medical journals should exert a strict control on editorials, as they do with the peer review system on original articles. A more thorough analysis of the available studies on ARBs in the past few years does not suggest the existence of any differences between these compounds and other active treatment, including ACEIs. Because there is no solid demonstration of a major risk of myocardial infarction when treating patient with ARBs, physicians should be confident in prescribing ARBs when necessary, and, most of all, patients should be reassured when they receive a prescription with ARBs.

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