Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials

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ABSTRACT

Objective To evaluate the cardiovascular outcomes and other outcomes associated with angiotensin receptor blockers.

Design Systematic review of randomised controlled trials with meta-analysis and trial sequential analysis (TSA).

Data sources and study selection Medline, Embase, and CENTRAL searches for randomised clinical trials, until August 2010, of angiotensin receptor blockers compared with controls (placebo/active treatment) that enrolled at least 100 participants and had a follow-up of at least one year.

Data extraction Myocardial infarction, death, cardiovascular death, angina pectoris, stroke, heart failure, and new onset diabetes.

Results 37 randomised clinical trials included 147 020 participants and had a total follow-up of 485 166 patient years. When compared with controls (placebo/active treatment), placebo, or active treatment, angiotensin receptor blockers were not associated with an increase in the risk of myocardial infarction (relative risk 0.99, 95% confidence interval 0.92 to 1.07), death, cardiovascular death, or angina pectoris. Compared with controls, angiotensin receptor blockers were associated with a reduction in the risk of stroke (0.90, 0.84 to 0.98), heart failure (0.87, 0.81 to 0.93), and new onset diabetes (0.85, 0.78 to 0.93), with similar results when compared with placebo or with active treatment. Based on trial sequential analysis, there is no evidence even for an average 5.0-7.5% (upper confidence interval 5-11%) relative increase in myocardial infarction (absolute increase of 0.3%), death, or cardiovascular death with firm evidence for relative risk reduction of stroke (at least 1%, average 10%) (compared with placebo only), heart failure (at least 5%, average 10%), and new onset diabetes (at least 4%, average 10%) with angiotensin receptor blockers compared with controls.

Conclusions This large and comprehensive analysis produced firm evidence to refute the hypothesis that angiotensin receptor blockers increase the risk of myocardial infarction (ruling out even a 0.3% absolute increase). Compared with controls, angiotensin receptor blockers reduce the risk of stroke, heart failure, and new onset diabetes.

INTRODUCTION

The provocative editorial by Verma and Strauss in the BMJ in 2004 stating that angiotensin receptor blockers “may increase myocardial infarction—and patients may need to be told” led to extensive scrutiny of outcome data with these drugs. This controversy was a direct fallout from the publication of the valsartan antihypertensive long term use evaluation (VALUE) trial, in which the primary hypothesis stated that “in hypertensive patients at high cardiovascular risk, for the same level of blood pressure control, valsartan will be more effective than amlodipine in reducing cardiac morbidity and mortality.” Unexpectedly, there was a significant 19% relative increase in the prespecified secondary outcome measure of myocardial infarction in the valsartan arm compared with the amlodipine arm.

In 2008 a Cochrane Collaboration review found angiotensin receptor blockers to be as effective as angiotensin converting enzyme inhibitors at reducing blood pressure, though the effect was modest. The blood pressure lowering treatment trials’ collaboration has shown similar blood pressure dependent effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers for the risk of stroke, coronary heart disease, and heart failure. The authors cautioned, however, that there was evidence of a blood pressure independent effect on the risk of major coronary disease events only for angiotensin converting enzyme inhibitors, not for angiotensin receptor blockers. In addition, more recent trials like the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), a thorough, double blind prospective randomised trial, documented equal outcome efficacy of an angiotensin receptor blocker (telmisartan) and an angiotensin converting enzyme inhibitor in a high risk population, though there was a trend towards better prevention of stroke in the angiotensin receptor blocker arm and towards...
better prevention of coronary artery disease in the angiotensin converting enzyme inhibitor (ramipril) arm.

We evaluated the risk of cardiovascular and other outcomes with angiotensin receptor blockers in general and tested the hypothesis of increased risk of myocardial infarction with angiotensin receptor blockers found in previous studies and analyses.

**METHODS**

**Eligibility criteria**

We searched PubMed, Embase, and CENTRAL using the terms: ‘angiotensin receptor blockers’, ‘angiotensin receptor antagonists’, ‘ARBs’, and the names of individual angiotensin receptor blockers in humans until August 2010. Appendix 1 on bmj.com gives details of the search and the MeSH terminologies used. We checked the reference lists of review articles, meta-analyses, and original studies identified by the electronic searches to find other eligible trials. There was no language restriction for the search. Authors of trials were contacted when results were unclear or when relevant data were not reported. In addition, we searched Food and Drug Administration (FDA) dockets by hand searching all documents submitted for drug approval/labelling change as well as the minutes from FDA meetings available on the FDA website. There was no formal protocol for this systematic review.

To be included in this analysis, eligible trials had to fulfil the following criteria: randomised clinical trials of participants comparing angiotensin receptor blockers with controls (placebo or active treatment); follow-up of at least one year; at least 100 participants enrolled; and reporting any of myocardial infarction, death, cardiovascular death, angina pectoris, stroke, heart failure, and new onset diabetes mellitus. We excluded studies in which angiotensin receptor blockers were not first line agents or studies/treatment arms in which angiotensin receptor blockers were used in combination with an angiotensin converting enzyme inhibitor.

**Selection and quality assessment**

Two authors (SB and SK) independently assessed trial eligibility and risk of trial bias and extracted data ($k=0.96)$. Disagreements were resolved by consensus. The risk of bias was assessed by using the components recommended by the Cochrane Collaboration: sequence generation of allocation; allocation concealment; blinding of participants, staff, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The trials did not differ for the last three components. Trials with high or unclear risk for bias for any one of the first three components were considered as at high risk of bias. Otherwise, they were considered as low risk of bias.

**Data extraction and synthesis**

We evaluated myocardial infarction, death, cardiovascular death, angina pectoris, stroke, heart failure, and new onset diabetes mellitus. In all of the analyses reported, “control” refers to either placebo or active treatment comparator.

**Statistical analysis**

We carried out an intention to treat meta-analysis in line with recommendations from the Cochrane Collaboration and the PRISMA statement using standard software (Stata 9.0, StataCorp, TX). Heterogeneity was assessed with the $I^2$ statistic. $I^2$ is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) with $I^2 <25$% considered as low and $I^2 >75$% as high. The pooled effect for each group of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). The risk ratio was calculated with the random effects model of DerSimonian and Laird. Publication bias was estimated visually with funnel plots and with Begg’s test and the weighted regression test of Egger. Given that the results might be different based on the comparison group (placebo or active treatment), we performed the primary analyses after stratifying the studies based on the comparator (placebo or active treatment).

**Subgroup analyses**

We performed subgroup analyses of trials with low risk of bias compared with trials with high risk of bias and cohort enrolled (hypertension or non-hypertension) trials. We estimated the difference between the estimates of the subgroups according to tests for inter action. $P<0.05$ indicates that the effects of treatment differ between the tested subgroups.

**Trial sequential analysis**

In a single trial, interim analyses increase the risk of type I error. To avoid an increase of overall type I error, monitoring boundaries can be applied to decide
whether a single randomised trial could be terminated early because of the P value being sufficiently small. Because no reason exists why the standards for a meta-analysis should be less rigorous than those for a single trial, analogous trial sequential monitoring boundaries can be applied to meta-analysis as trial sequential analysis should be less rigorous than those for a single trial because of the P value being sufficiently small.14 15 Cumulative meta-analyses of trials are at risk of producing random errors because of few data and repetitive testing of accumulating data, and the requirement for the amount of information analogous to the sample size of a single optimally powered clinical trial might not be met.14 15

The underlying assumption for trial sequential analysis is that significance testing and calculation of the confidence intervals are performed each time a new trial is published. Trial sequential analysis depends on the quantification of the required amount of information. In this context, the smaller the required amount, the more lenient the trial sequential analysis, thus the more lenient the criteria for significance.14 15 A required diversity ($D^2$) adjusted information size was calculated, $D^2$ being the relative variance reduction when the meta-analysis model is changed from a random effects into a fixed effect model.14 $D^2$ is the percentage of the variability between trials and constitutes the sum of the variability between trials. It is an estimate of sampling error after consideration of the required information size. $D^2$ is different from the intuitively

| Trial | No of people | Comparison | Hypertension | Follow-up (years) | Age (years) | Diabetes (%) | Hypertension (%) |
|-------|--------------|------------|--------------|------------------|-------------|--------------|-----------------|
| ALPINE, 2003 | 393 | Candesartan v HCTZ | Hypertension | 1 | 55 | 48 | 100 |
| CASEI, 2008 | 4703 | Candesartan v amlodipine | Hypertension | 3.2 | 64 | 55 | 100 |
| CHARM-added, 2003 | 2548 | Candesartan v placebo | Heart failure | 3.4 | 64 | 79 | 48.2 |
| CHARM-alternative, 2003 | 2028 | Candesartan v placebo | Heart failure | 2.8 | 66 | 68 | 50 |
| CHARM-preserved, 2003 | 3023 | Candesartan v placebo | Heart failure | 3 | 67 | 60 | 44.3 |
| DETAIL, 2004 | 250 | Telmisartan v enalapril | Hypertension, diabetes with nephropathy | 5 | 61 | 73 | 100 |
| DIRECT-Prevent 1, 2008 | 1421 | Candesartan v placebo | Normotensive, DM type 1 without retinopathy | 4.7 | 30 | 57 | 0 |
| DIRECT-Prevent 1, 2008 | 1905 | Candesartan v placebo | Normotensive, DM type 1 with retinopathy | 4.8 | 32 | 58 | 0 |
| DIRECT-Prevent 2, 2008 | 1905 | Candesartan v placebo | Normotensive, DM type 2 with retinopathy | 4.7 | 57 | 50 | 62 |
| E-COST, 2005 | 2048 | Candesartan v conventional | Hypertension | 3.1 | 66.9 | 48 | 100 |
| E-COST-R, 2005 | 141 | Candesartan v conventional | Hypertension with CRI | 3.1 | 67 | 59 | 100 |
| ELITE, 1997 | 722 | Losartan v captopril | Heart failure | 1 | 74 | 67 | 57 |
| ELITE II, 2000 | 3152 | Losartan v captopril | Heart failure | 1.5 | 71 | 30 | 49 |
| GISSI-AMI, 2007 | 1442 | Valsartan v placebo | Atrial fibrillation | 1 | 68 | 62 | 85.3 |
| HI-CREATE, 2009 | 2049 | Candesartan v conventional | Hypertension and CAD | 4.2 | 65 | 20 | 100 |
| IDNT (CCB), 2003 | 1146 | Irbesartan v amlodipine | DM 2 and nephropathy | 2.6 | 59 | 64 | 100 |
| IDNT (placebo), 2003 | 1148 | Irbesartan v placebo | DM 2 and nephropathy | 2.6 | 59 | 68 | 100 |
| I-Preserve, 2008 | 4128 | Irbesartan v placebo | Heart failure | 4.1 | 72 | 40 | 88.5 |
| IRMA 2, 2001 | 611 | Irbesartan v placebo | Hypertensive, diabetes with microalbuminuria | 2 | 58 | 68 | 100 |
| JIKEI, 2007 | 3081 | Valsartan v conventional | Hypertension | 3.1 | 65 | 66 | 87.5 |
| Kondo et al, 2003 | 406 | Candesartan v control | CAD | 2 | 65 | 76 | 43.5 |
| KYOTO, 2009 | 3031 | Valsartan v conventional | Hypertension | 3.3 | 66 | 57 | 100 |
| LIFE, 2002 | 9193 | Losartan v atenolol | Hypertension | 4.8 | 67 | 46 | 100 |
| MOSES, 2005 | 1352 | Eprosartan v nitrendipine | Hypertensive with stroke | 2.5 | 68 | 54 | 100 |
| NAVIGATOR, 2008 | 9306 | Valsartan v placebo | Impaired glucose tolerance | 6.5 | 64 | 49 | 77.5 |
| ONTARGET, 2008 | 17118 | Telmisartan v ramipril | Vascular disease | 4.7 | 66 | 73 | 69 |
| OPTIMAAL, 2002 | 5477 | Losartan v captopril | AMI | 2.7 | 67 | 71 | 36 |
| PROFESS, 2008 | 20322 | Telmisartan v placebo | Stroke | 2.5 | 66 | 64 | 74 |
| RASS (ACEI), 2009 | 190 | Losartan v enalapril | DM 1, normotensive | 5 | 30 | 47 | 0 |
| RASS (placebo), 2009 | 191 | Losartan v placebo | DM 1, normotensive | 5 | 29 | 46 | 0 |
| RENAAL, 2001 | 1513 | Losartan v placebo | DM 2 and nephropathy | 3.4 | 60 | 63 | 93.5 |
| ROAD, 2007 | 360 | Losartan v benazepril | CRI without DM | 3.7 | 50 | NR | 63 |
| SCOPE, 2003 | 4937 | Losartan v captopril | Hypertension | 3.7 | 76 | 36 | 100 |
| Suzuki, 2008 | 366 | ARB v control | Hypertension and haemodialysis | 3 | 60 | 59 | 93 |
| Takahashi et al, 2006 | 80 | Candesartan v control | Hypertensive and haemodialysis | 1.6 | 61 | 59 | 81 |
| TRANSCEND, 2008 | 5926 | Candesartan v placebo | Vascular disease | 4.7 | 67 | 57 | 76.5 |
| VAL-HeFT, 2001 | 5010 | Valsartan v placebo | Heart failure | 1.9 | 63 | 80 | NR |
| VALIANT, 2003 | 9818 | Valsartan v captopril | Heart failure | 2 | 65 | 69 | 55.5 |
| VALUE, 2004 | 15245 | Valsartan v amlodipine | Hypertension | 4.2 | 67 | 58 | 100 |

AMI=acute myocardial infarction; ARB=angiotensin receptor blockers; CAD=coronary artery disease; CRI=Chronic renal insufficiency; CCB=calcium channel blockers; DM=diabetes mellitus.
obvious adjusting factor based on the common quantification of heterogeneity, the inconsistency ($I^2$), which might underestimate the required information size.16

The trial sequential analysis was performed with a desire to maintain an overall 5% risk of type I error, being the standard in most meta-analyses and systematic reviews, and we calculated the required information size (that is, the meta-analysis information size needed to detect or reject an intervention effect of a 20% relative risk reduction for benefit but a stricter more rigorous sequential testing of a 10% and then a 2.5-7.5% relative risk increase for harms, with a risk of type II error of 10-20%, at a power of 80-90%).14 15

RESULTS
Study selection
We identified 37 trials (39 comparator arms) that satisfied our inclusion criteria (fig 1). The 39 comparator arms included 17 arms that compared angiotensin receptor blockers with placebo and 22 arms that compared angiotensin receptor blockers with active treatment (table 1). We excluded the combination arms Table 2 | Blood pressure, dose of drugs used, and quality of included trials in systematic review of angiotensin receptor blockers and risk of myocardial infarction

| Trial | Baseline blood pressure* | Final blood pressure* | Quality of study† | Mean dose (mg) | Source of data |
|-------|--------------------------|-----------------------|------------------|---------------|---------------|
| ALPINE19 | 155/97 155/97 | 134/83 132/84 | +++ NR | Published |
| CASE20 | 163/92 163/92 | 136/77 134/77 | +++ NR | Published |
| CHARM-added21 | 125/75 126/75 | NR NR | +++ 24 | Published and FDA dockets |
| CHARM-alternative22 | 130/77 130/77 | NR NR | +++ 23 | Published and FDA dockets |
| CHARM-preserved23 | 136/78 136/78 | NR NR | +++ 25 | Published and FDA dockets |
| DETAIL24 | 153/85 152/86 | 146/79 149/82 | +++ NR | Published |
| DIRECT-Prevent15-26 | 116/72 116/72 | NR NR | +++ NR | Published |
| DIRECT- Protect15-26 | 117/74 117/73 | NR NR | +++ NR | Published |
| DIRECT- Protect 25-27 | 131/77 131/78 | NR NR | +++ NR | Published |
| E-COST28 | 162/91 166/96 | 140/79 138/81 | ++ 7 | Published |
| E-COST-R29 | 145/79 145/79 | 134/73 133/74 | ++ 7 | Published |
| ELITE30 | 137/79 137/79 | NR NR | +++ 42.6 | Published |
| ELITE II31 | 134/78 134/78 | NR NR | +++ NR | Published |
| GISSI-AP32 | 138/82 139/82 | 134/NR 137/NR | +++ NR | Published |
| HIJ-CREATE33 | 137/76 136/76 | 132/73 128/72 | +++ NR | Published |
| IDNT (CCB)34 | 160/87 159/87 | 140/77 141/77 | +++ NR | Published and FDA dockets |
| IDNT (Placebo)34 | 160/87 158/87 | 140/77 144/80 | +++ NR | Published and FDA dockets |
| I-Preserve35 | 135/90 135/90 | 142/83 144/83 | +++ NR | Published and FDA dockets |
| JIKEI36 | 139/81 139/81 | 131/77 132/78 | ++ 82 | Published |
| Kondo et al37 | 129/76 128/76 | 127/75 126/76 | ++± NR | Published |
| KYOTO38 | 157/88 157/88 | 133/76 133/76 | ++ NR | Published |
| LIFE39 | 174/98 175/98 | 144/81 145/81 | +++ NR | Published |
| MOSES40 | 151/84 152/87 | 138/81 136/80 | ++ 63 | Published |
| NAVIGATOR41 | 139/83 140/83 | 133/78 136/80 | +++ NR | Published |
| ONTARGET42 | 142/82 142/82 | NR NR | +++ NR | Published |
| OPTIMAAL43 | 123/72 123/71 | NR NR | +++ 45 | Published |
| PROFESS44 | 144/84 146/84 | NR NR | +++ NR | Published |
| RASS (ACEI)45 | 120/70 120/71 | 115/66 113/66 | ++± NR | Published |
| RASS (Placebo)46 | 120/70 119/70 | 115/66 117/68 | ++± NR | Published |
| RENAAL47 | 132/82 132/82 | 140/74 142/74 | +++ NR | Published and FDA dockets |
| ROAD48 | 151/86 150/86 | NR NR | ++ NR | Published |
| SCOPE49 | 166/90 167/90 | 145/80 149/82 | +++ 11.6 | Published |
| Suzuki50 | 154/81 156/82 | 140/80 140/78 | ++ NR | Published |
| Takahashi et al51 | 153/82 152/85 | 153/83 149/80 | ++ NR | Published |
| TRANSCEND52 | 141/82 141/82 | NR NR | +++ NR | Published |
| VAL-Heft53 | 123/76 124/76 | 118/NR 123/NR | +++ 254 | Published and FDA dockets |
| VALENT54 | 123/72 123/72 | 127/75 127/76 | ++ 247 | Published and FDA dockets |
| VALUE5 | 155/87 155/88 | 139/79 138/78 | +++ 151.7 | Published |

NR = not reported; FDA = Food and Drug Administration.
*Diastolic/systolic mm Hg.
†Risk of bias according to sequence generation of allocation, allocation concealment, and blinding; + represents low bias risk, − high bias risk, and ± unclear bias risk.
Baseline characteristics

Tables 1 and 2 summarise the baseline characteristics of the included trials. The 37 trials randomised 147 020 participants, 73 298 (49.8%) to angiotensin receptor blockers and 73 722 (50.2%) to controls. The average follow-up was 3.3 years (range 1-6.5 years), with a total follow-up across all trials of 485 166 patient years.

Among the 37 randomised controlled trials, 12 were considered at high risk of bias (table 2) and the rest as low risk. Data on outcomes were abstracted both from the original publication and the Food and Drug Administration dockets (when available) (table 2).
Angiotensin receptor blockers and outcomes

Angiotensin receptor blockers were not associated with any increase in the risk of myocardial infarction when compared with controls (relative risk 0.99, 95% confidence interval 0.92 to 1.07; P = 0.85) (fig 2). The results were similar when angiotensin receptor blockers were compared with either placebo or with active treatment (P = 0.15 for interaction) (fig 2). There was low to moderate heterogeneity and no evidence for publication bias (see fig A1 in appendix 2 on bmj.com). Similarly, angiotensin receptor blockers were not associated with any increase in the risk of...
death (1.00, 0.97 to 1.02; P=0.75) (fig 3), cardiovascular death (0.99, 0.94 to 1.04; P=0.73) (fig 4), or angina (0.95, 0.85 to 1.06; P=0.37) (fig 5) when compared with controls. The results were similar when angiotensin receptor blockers were compared with either placebo or with active treatment for all of the above outcomes (P>0.05 for interaction for all comparisons) (figs 2-5). There was no to low heterogeneity and no evidence for publication bias for the outcomes of death and cardiovascular death (see figs A2-A3 in appendix 2 on bmj.com). For the outcome of angina, there was high heterogeneity but no evidence for publication bias (see fig A4 in appendix 2 on bmj.com).

In addition, angiotensin receptor blockers were associated with a 10% reduction in the risk of stroke (P=0.01) (fig 6), a 13% reduction in the risk of heart...
failure (P<0.001) (fig 7), and a 15% reduction in the risk of diabetes (P<0.001) (fig 8) compared with controls. The results were similar when angiotensin receptor blockers were compared with either placebo or with active treatment for all of the above outcomes (P>0.05 for interaction for all comparisons) (fig 6-8). There was no to moderate heterogeneity and no evidence for publication bias for the outcomes of stroke and heart failure (see figs A4-A5 in appendix 2 on bmj.com). For the outcome of new onset diabetes, there was moderate to high heterogeneity and no evidence for publication bias (see fig A6 in appendix 2 on bmj.com).

Trial sequential analysis
The required diversity (D=52%) adjusted information size for the outcome of myocardial infarction was calculated based on a proportion of 4.14% events in the control group and evaluating initially for a 10% relative risk increase (absolute risk increase of 0.4% corresponding to a number needed to harm of 250) and then followed by a 7.5% relative risk increase (absolute risk increase of 0.3% corresponding to a number needed to harm of 333) with angiotensin receptor blockers, at \( \alpha = 5\% \) and \( \beta = 20\% \) (80% power) (see fig B1 in appendix 3 on bmj.com). The cumulative z curve crosses neither the traditional boundary nor the trial sequential monitoring boundary but does cross the futility boundary, suggesting firm evidence for a lack of even an average 7.5% relative risk increase (upper confidence limit 11%) of myocardial infarction with angiotensin receptor blockers (see fig B1 in appendix 3 on bmj.com). Similarly, the cumulative z curve crossed the futility boundary, suggesting firm evidence for lack of on average a 4% relative risk increase (upper confidence limit 7%) in death (see fig B2 in appendix 3 on bmj.com).
on bmj.com), a lack of on average a 5% relative risk increase (upper confidence limit 5%) in cardiovascular death (see fig B3 in appendix 3 on bmj.com), and a lack of on average a 15% relative risk increase (upper confidence limit 12%) in angina (see fig B4 in appendix 3 on bmj.com) with angiotensin receptor blockers compared with controls.

For the outcome of stroke, however, the cumulative z curve crossed the traditional boundary but not the trial sequential monitoring boundary, suggesting lack of evidence for a 7.5% relative risk reduction in stroke with angiotensin receptor blockers compared with controls (see fig B4 in appendix 3 on bmj.com). The boundary was crossed, however, for firm evidence for at least a 1% relative risk reduction (average 10%) in stroke compared with placebo. When compared with active treatment, neither the traditional boundary nor the trial sequential monitoring boundary was crossed for a 15%
relative risk reduction with angiotensin receptor blockers. In addition, the futility boundary was not crossed, suggesting the need for more evidence to establish additional benefits of angiotensin receptor blockers over active treatment. Similarly, the cumulative z curve crossed the trial sequential monitoring boundary, suggesting firm evidence for at least a 5% relative risk reduction (average 10%) in heart failure with angiotensin receptor blockers (see fig B5 in appendix 32 on bmj.com) and at least a 4% relative risk reduction (average 10%) in diabetes (see fig B6 in appendix 3 on bmj.com) when compared with controls.

Sensitivity analysis
Subgroup analysis based on trial quality (low risk of bias versus high risk of bias) and cohort enrolled (hypertension versus non-hypertension trials) did not make any noticeable difference for the above analyses.
The risk reduction of stroke, angina, and heart failure was higher in trials at high risk of bias compared with those at low risk of bias (though directionally similar) (table 3). Similarly, the risk reduction for heart failure and new onset diabetes was higher in hypertension trials compared with non-hypertension trials (though directionally similar) (table 3).

**DISCUSSION**

In this meta-analysis we found no evidence to support the theory that angiotensin receptor blockers increase the risk of myocardial infarction. We included 485 166 patient years of follow-up, and, with 80% power, found, on average, a lack of 7.5% relative risk increase (upper confidence limit 11%) (absolute increase of 0.3% corresponding to a number needed to harm of ≥333) of myocardial infarction with angiotensin receptor blockers compared with controls. Similar results were seen for the outcome of death, cardiovascular death, and angina. In addition, the data provide firm evidence for relative risk reduction of stroke (at least 1%, average 10%) (versus placebo only), heart failure (at least 5%, average 10%), and new onset diabetes (at least 4%, average 10%) with angiotensin receptor blockers compared with controls.

Angiotensin receptor blockers—cardioprotection vs. cerebroprotection

The 2004 results of the VALUE trial, in which the angiotensin receptor blocker valsartan produced a significant relative increase in myocardial infarction compared with amlodipine, has fuelled a debate on the safety of this class of drugs. In VALUE, those in the amlodipine arm had a modest but significantly lower blood pressure than those in the angiotensin receptor blockers arm (1.8 mm Hg systolic and 1.5 mm Hg diastolic) and a significantly lower blood pressure in the first three months, but whether this difference can explain the results has been contested.

Angiotensin II exerts most of its deleterious effects (vasoconstriction, increased cardiac contractility, renal tubular sodium reabsorption, cell proliferation, vascular and cardiac hypertrophy, inflammatory responses, and oxidative stress) via angiotensin I receptors, while the angiotensin II receptors counterbalance some of these effects. Angiotensin receptor blockers exert their action on angiotensin I receptors, which not only block the deleterious effect of angiotensin II but also results in overstimulation of angiotensin II receptors, probably resulting in antihypertrophic and antifibrotic effects. The angiotensin receptor blockers were thus thought

| Trial                  | Events | Relative risk (95% CI) | Weight (%) | Relative risk (95% CI) |
|------------------------|--------|------------------------|------------|------------------------|
| Placebo                | ARBs   | Control                |            |                        |
| CHARM-alternative      | 44/1013| 53/1015                | 4          | 0.83 (0.56 to 1.23)    |
| CHARM-added            | 72/1276| 72/1272                | 5          | 1.00 (0.73 to 1.37)    |
| NAVIGATOR              | 1532/4631| 1722/4675            | 17         | 0.90 (0.85 to 0.95)    |
| PROFESS                | 125/10 146| 151/10 186         | 8          | 0.83 (0.66 to 1.05)    |
| SCOPE                  | 106/2477| 130/2460               | 7          | 0.81 (0.63 to 1.04)    |
| TRANSCEND              | 359/2954| 393/2972               | 12         | 0.92 (0.80 to 1.05)    |
| **Random effects subtotal:** | 2238/22 497| 2521/22 580       | 53         | 0.90 (0.85 to 0.94)    |
| **Fixed effects subtotal:** |          |                        | 0.89 (0.85 to 0.94) |
| Active                 | ARBs   | Control                |            |                        |
| ALPINE                 | 1/197  | 8/196                  | 11         | 0.12 (0.02 to 0.99)    |
| CASE                   | 37/2354| 58/2349                | 3          | 0.64 (0.42 to 0.96)    |
| HIJ-CREATE             | 7/1024 | 18/1025                | 1          | 0.39 (0.16 to 0.93)    |
| KYOTO                  | 58/1517| 86/1514                | 5          | 0.67 (0.49 to 0.93)    |
| LIFE                   | 241/4605| 319/4588               | 11         | 0.75 (0.64 to 0.89)    |
| ONTARGET               | 399/8542| 366/8576              | 12         | 1.10 (0.95 to 1.26)    |
| VALUE                  | 690/7649| 845/7596              | 15         | 0.81 (0.74 to 0.89)    |
| **Random effects subtotal:** | 1433/25 888| 1700/25 844     | 47         | 0.77 (0.64 to 0.93)    |
| **Fixed effects subtotal:** |          |                        | 0.84 (0.79 to 0.90) |
| **Random effects overall:** | 3671/48 385| 4221/48 424            | 100        | 0.85 (0.78 to 0.93)    |
| **Fixed effects overall:** |          |                        | 0.87 (0.84 to 0.91) |

**Fig 8** Angiotensin receptor blockers (ARBs) and new onset diabetes mellitus, stratified by comparison group (placebo v active treatment)
to not only provide blockade of the renin-angiotensin system but also to allow for favourable stimulation of angiotensin II receptors. More recent studies, however, seem to suggest that chronic overstimulation of angiotensin II receptors might also exert a hypertrophic and antiangiogenic influence on cardiovascular tissues and that therefore the “long term consequences of ARB therapy might be less beneficial and could even be harmful in some circumstances.” In addition, the pluripotential effects of angiotensin converting enzyme inhibitors have been attributed to upstream blockade of the renin-angiotensin axis, which also inhibits the degradation of kinins to inactive metabolites resulting in raised concentration of bioactive kinins such as bradykinin, which has been found to have several possible benefits such as anti-arrhythmic effects and reducing infarct size (mediated through ischaemic preconditioning and nitric oxide/prostacyclin related vascular protection). These pathophysiological mechanisms provide some mechanistic insight into the alleged inferiority of angiotensin receptor blockers compared with angiotensin converting enzyme inhibitors and potentially explain the adverse outcomes.

Since the publication of the VALUE trial, several large randomised trials (ONTARGET, TRANSCEEND) have been published that showed no increase in adverse outcomes with angiotensin receptor blockers. None of these trials by themselves had adequate power for the individual outcomes. Our meta-analysis showed firm evidence of a lack of significant effect of angiotensin receptor blockers on myocardial infarction, ruling out even a 0.3% (number need to harm ≥ 333) absolute increase in the risk of myocardial infarction with angiotensin receptor blockers. The analyses, however, do not rule out a <0.3% absolute increase of myocardial infarction with angiotensin receptor blockers, though this is likely to be clinically less important. The results were similar, with the cumulative z curve crossing the futility boundary for the outcomes of death, cardiovascular death, and angina. In addition, there was a significant benefit for the outcomes of stroke, heart failure, and new onset diabetes mellitus. Whether this is due to angiotensin II receptor stimulation (for example, in the brain) or to better tolerability (and hence a better effect on blood pressure and compliance) of this class of drugs is not known.

Of note, although there was no harm with treatment with angiotensin receptor blockers, despite lower blood pressure compared with placebo, there was no detectable beneficial effect for the outcome of myocardial infarction or cardiovascular mortality. Angiotensin receptor blockers, however, were as effective as the active treatment group for these outcomes. Thus angiotensin receptor blockers, unlike angiotensin converting enzyme inhibitors seem not to have any special “cardioprotective” effects, even when compared with placebo. In contrast, for the outcome of stroke, angiotensin receptor blockers were effective at reducing the risk compared with placebo. When compared with active treatment, there was benefit only in the fixed effects model but not in the random effects model, but the point estimate favoured angiotensin receptor blockers. Trial sequential analysis, however, suggests that we need more data before we can make robust decisions on this outcome.

While the results from our sensitivity analysis were largely similar, the risk reduction in trials at low risk of bias was smaller in magnitude, although significant. Thus the risk reduction for the outcomes of stroke, heart failure, and new onset diabetes with angiotensin receptor blockers is modest.

Trial sequential analysis

Conventional meta-analysis does not take into consideration the information size, the number of accrued events, and the effect size and the inference depends on the test for significance and the confidence interval, which can often be spuriously narrow. Not infrequently, non-significant results are simply inferred as “more evidence is needed.” Trial sequential analysis incorporates both the information size and the effect size and is therefore helpful in making more robust inferences. In the setting of a non-significant result, trial sequential analysis helps decide whether “more evidence is needed” (when the futility boundary is not crossed) or rule out a given effect size (if the futility boundary is crossed), thus reducing this uncertainty. As can been seen in all of the analyses, while conventional meta-analysis promises a greater effect size (for significant results) or lack of small effect size (for non-significant results), the trial sequential analysis, taking into consideration the effect size and information size,

Table 3 | Sensitivity analysis (angiotensin receptor blockers versus controls) with numbers from random effects model

| Outcomes                | Relative risk (95% CI) | Relative risk (95% CI) |
|-------------------------|------------------------|------------------------|
|                         | High bias risk trials  | Low bias risk trials   | P value* |
| Death                   | 0.95 (0.82 to 1.11)    | 1.00 (0.97 to 1.03)    | 0.51     |
| Cardiovascular death    | 0.94 (0.76 to 1.16)    | 0.99 (0.94 to 1.05)    | 0.64     |
| Myocardial infarction   | 0.91 (0.74 to 1.11)    | 1.00 (0.93 to 1.09)    | 0.40     |
| Stroke                  | 0.73 (0.62 to 0.86)    | 0.95 (0.88 to 1.03)    | 0.004    |
| Angina                  | 0.65 (0.45 to 0.96)    | 1.03 (0.93 to 1.14)    | 0.02     |
| Heart failure           | 0.70 (0.58 to 0.86)    | 0.90 (0.84 to 0.97)    | 0.02     |
| New onset diabetes      | 0.60 (0.38 to 0.97)    | 0.87 (0.80 to 0.94)    | 0.11     |
| Hypertension trials     | 0.97 (0.92 to 1.03)    | 1.00 (0.97 to 1.04)    | 0.37     |
| Non-hypertension trials | 0.98 (0.90 to 1.07)    | 0.99 (0.93 to 1.05)    | 0.85     |

*For interaction.
Angiotensin receptor blockers are important in the treatment of cardiovascular conditions. Previous studies have shown an increased risk of myocardial infarction with these drugs and have raised concern among physicians and patients.

**WHAT THIS STUDY ADDS**

There is firm evidence to refute the hypothesis of angiotensin receptor blockers increasing the risk of myocardial infarction (ruling out even a 0.3% absolute increase).

Compared with controls (active treatment or placebo), angiotensin receptor blockers reduce the risk of stroke, heart failure, and new onset diabetes. Despite lower blood pressure with angiotensin receptor blockers when compared with placebo, there was also no detectable beneficial effect for the outcome of myocardial infarction or cardiovascular mortality.

Study limitations

As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for dose of drugs used or compliance with assigned treatment. Though detailed sensitivity analyses were undertaken, given heterogeneity in the study protocols, clinically relevant differences could have been missed and might be better assessed in a meta-analysis of individual patient data. In addition, there could be additional confounders not accounted for in the analysis. Also, not all of the trials reported each of the outcomes analysed. The subgroup analyses might suffer from multiple testing. The results of the sensitivity analyses are best described as secondary and hypothesis generating only.

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1. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. BMJ 2004;329:1264-8.
2. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekmans S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlopidine: the VALUE randomised trial. Lancet 2004;363:2222-31.
3. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev 2008;4:CD003822.
4. Messerli FH, Bangalore S. Antihypertensive efficacy of aliskiren: is hydrochlorothiazide an appropriate benchmark? Circulation 2009;119:371-3.
5. Tumbull FM, Neal B, Pfeffer M, Kostis JB, Woodward M, et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens 2007;25:951-8.
6. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-55.
7. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.0. Cochrane Collaboration, 2008.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
9. Brubrad MJ, Deeks J, Altman DG. Sibza: an alternative meta-analysis command. Stata Tech Bull Reprints 1998;8:86-100.
10. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988;7:889-94.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
13. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.
14. Brok J, Thorlund K, Gluud C, Wetterlev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008;61:763-9.
15. Wetterlev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;61:64-75.
16. Wetterlev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009;9:86.
17. Levy BI. Can angiotensin II type 2 receptors have deleterious effects in cardiovascular disease? Implications for therapeutic blockade of the renin-angiotensin system. Circulation 2004;109:8-13.
18. Liriz W, Wiemer G, Gohlke P, Unger T, Scholakens BA. Contribution of kinins to the cardiovascular actions of angiotensin-converting enzyme inhibitors. Pharmacol Rev 1995;47:25-49.
19. Lindholm LH, Persson M, Alauapiiv C, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly treated hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). J Hypertens 2003;21:1563-74.
20. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, et al. Effects of candesartan compared with amiodidine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. Hypertension 2008;51:393-8.
21. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-71.
22. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-
converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.

23 Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.

24 Banett AH, Bain SC, Bouter P, Karlborg B, Madsbad S, Jervell J, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952-61.

25 Bilous R, Chaturvedi N, Sjölie AK, Fuller J, Klein R, Orchard T, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med 2009;151:11-20, W3-4.

26 Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on prevention (DIRECT-Pretect 1) and progression (DIRECT-Pretect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet 2006;372:1394-402.

27 Sjölie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, et al. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Pretect 2): a randomised placebo-controlled trial. Lancet 2008;372:1385-93.

28 Suzuki H, Kanno Y. Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. Hypertens Res 2005;28:107-14.

29 Nakamura T, Kanno Y, Takenaka T, Suzuki H. An angiotensin receptor blocker reduces the risk of congestive heart failure in elderly hypertensive patients with renal insufficiency. Hypertens Res 2005;28:415-23.

30 Pitt B, Segal R, Martinez FA, Meurers G, Cowley AI, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly, ELITE). Lancet 1997;349:247-52.

31 Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, et al. Effect of losartan compared with captopril on mortality in cardiovascular outcomes in Japanese hypertensive patients. Lancet 2005;365:1852-7.

32 Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, et al. Effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes and nephropathy. N Engl J Med 2003;349:1203-12.

33 Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, et al. Angiotensin II receptor blocker-based vs non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HJ-CREATE). Eur Heart J 2009;30:1203-12.

34 Beil T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003;138:542-9.

35 Zile MR, Gaasch WH, Anand SS, Haass M, Little WC, Miller AB, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) trial. Circulation 2010;121:1393-405.

36 Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.

37 Parving HH, Lehnert H, Brochner-Mortensen J, Gorini S, Andersson S, Amer P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870-8.

38 Mochizuki S, Dahlof B, Shimizu M, Ikekawa K, Yoshikawa M, Taniguchi I, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Ikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. Lancet 2007;369:1631-9.

39 Kondo J, Sone T, Tsuboi H, Mukawa H, Morishima I, Uesugi M, et al. Effects of low-dose angiotensin II receptor blocker candesartan on cardiovascular events in patients with coronary artery disease. Am Heart J 2003;146:E20.

40 Sawada T, Yamada H, Dahlof B, Matsubara H, Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. Eur Heart J 2009;30:2461-9.

41 Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Bevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003.

42 Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomised controlled study (MOSES). Stroke 2005;36:1218-26.

43 McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauber B, Hua TA, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477-90.

44 Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360:752-60.

45 Yusuf S, Diener HC, Sacco RL, Cotton D, Oumpuu S, Lawton WA, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2006;359:1225-37.

46 Mauer M, Zinman B, Gardiner R, Suisa S, Sinaiko A, Strand T, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40-51.

47 Bierren BA, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.

48 Hou FF, Xie D, Zhang K, Chen PY, Zhang WR, Liang M, et al. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol 2007;18:1889-98.

49 Lihell H, Hansson L, Skoog I, Ehnfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. Hypertens 2003;21:875-86.

50 Suzuki H, Kanno Y, Sugahara S, Ikeda N, Shoda J, Takenaka T, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 2008;52:501-6.

51 Takahashi A, Takase H, Toriyama T, Sugita T, Kurita Y, Ueda R, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients with chronic heart failure: results from the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 2002;360:752-60.

52 Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet 2008;372:1174-83.

53 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

54 McMurray JJ, Solomon S, Pieper K, Reed S, Rouleau J, Velazquez E, et al. The effect of valsartan, captopril, or both on athrosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). J Am Coll Cardiol 2006;47:726-33.

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