Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients

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Aims
Renin–angiotensin–aldosterone system (RAAS) inhibitors are well established for the reduction in cardiovascular morbidity, but their impact on all-cause mortality in hypertensive patients is uncertain. Our objective was to analyse the effects of RAAS inhibitors as a class of drugs, as well as of angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs) separately, on all-cause mortality.

Methods and results
We performed a pooled analysis of 20 cardiovascular morbidity–mortality trials. In each trial at least two-thirds of the patients had to be diagnosed with hypertension, according to the trial-specific definition, and randomized to treatment with an RAAS inhibitor or control treatment. The cohort included 158 998 patients (71 401 RAAS inhibitor; 87 597 control). The incidence of all-cause death was 20.9 and 23.3 per 1000 patient-years in patients randomized to RAAS inhibition and controls, respectively. Overall, RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00, \(P = 0.032\)), and a 7% reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99, \(P = 0.018\)). The observed treatment effect resulted entirely from the class of ACE inhibitors, which were associated with a significant 10% reduction in all-cause mortality (HR: 0.90, 95% CI: 0.84–0.97, \(P = 0.004\)), whereas no mortality reduction could be demonstrated with ARB treatment (HR: 0.99, 95% CI: 0.94–1.04, \(P = 0.683\)). This difference in treatment effect between ACE inhibitors and ARBs on all-cause mortality was statistically significant (\(P\)-value for heterogeneity 0.036).

Conclusion
In patients with hypertension, treatment with an ACE inhibitor results in a significant further reduction in all-cause mortality. Because of the high prevalence of hypertension, the widespread use of ACE inhibitors may result in an important gain in lives saved.

Keywords
Hypertension • ACE inhibitor • ARB • Meta-analysis • Mortality

Introduction
The World Health Organization describes hypertension as the number one risk factor for mortality, as worldwide annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP)-related diseases, particularly cardiovascular diseases (CVD).\(^1\) For that reason, the guidelines of hypertension and cardiology societies emphasize that hypertension treatment should aim...
The benefits of antihypertensive treatment on cardiovascular morbidity are thought to be mainly due to the BP-lowering effect per se, independent of the class of drug employed, as has been demonstrated with β-blockers, diuretics, calcium channel blockers, and recently with the renin–angiotensin–aldosterone system (RAAS) inhibitors. Blockade of the RAAS is one of the key therapeutic targets in patients with hypertension, as an overactive RAAS is strongly associated with high BP. The RAAS controls circulating volume and electrolyte balance in the human body and is therefore an important regulator of haemodynamic stability. RAAS inhibitors are the most widely prescribed class of drugs for the management of hypertension. Currently, the most clinically relevant pharmacological agents that block the RAAS are angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers (ARBs). Both drugs block angiotensin II, but ACE inhibitors are characterized by a decrease in the degradation of bradykinin leading to a release of nitric oxide and prostaglandins resulting in additional vasodilatation. These differences in modes of action between ACE inhibitors and ARBs might have clinical implications for patients with hypertension.

Reductions in both cardiovascular morbidity and mortality have been well demonstrated with RAAS inhibitors across specific populations that were selected and included for a criterion other than hypertension per se. For example, SOLVD (enalapril in heart failure), HOPE (ramipril in patients with high CVD risk), and EUROPA (perindopril in stable coronary disease) demonstrated significant reductions in the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke with ACE inhibitors. In these trials, less than half of the patients enrolled had prevalent hypertension. The beneficial effects of RAAS inhibitors on all-cause mortality (a guideline-recommended goal of antihypertensive therapy) have not been convincingly demonstrated in the indication of hypertension. Further, most (antihypertensive) trials in which the clinical effects of RAAS inhibitors were evaluated were underpowered for this endpoint. To evaluate the impact of RAAS inhibitors on all-cause and cardiovascular mortality for their main indication, hypertension, we undertook a meta-analysis of all prospective randomized controlled trials that compared RAAS inhibitors with control therapy in different populations in which the absolute majority of the patients had hypertension, and where the expected benefits would mainly come from a decrease in BP.

We hypothesized that, taken all evidence together, RAAS inhibitors would produce a significant mortality reduction compared with (contemporary) control therapy. Although the primary aim of this meta-analysis decided a priori was to evaluate RAAS inhibitors as a class of drugs, we realized that ACE inhibitors and ARBs have partly different modes of action. Therefore, we decided to also study these two classes of drugs separately.
the mean diastolic blood pressure and systolic blood pressure (SBP) at
baseline, the percentage of male participants, the percentage of
patients with diabetes mellitus, renal insufficiency, and hypertension,
as well as the total follow-up time (until death) in years.

**Endpoint definition**
The endpoints of this pooled analysis were all-cause and cardiovascular
mortality during long-term follow-up. Data on all-cause death were
available for all trials. Data on cardiovascular death were not available
for RENAAL, IDNT, MOSES, and CASE-J.

We aimed to provide estimates of the incidence of these endpoints
in patients randomized to RAAS inhibitors and control therapy, as well
as estimates of the absolute and relative reduction in the incidence of
the endpoints by RAAS inhibitors. Since the duration of follow-up
varied between the trials, we decided to base our analyses on the mor-
tality incidence rate (IR), which was assumed to be constant over time
in each of the comparison groups. The IR is defined as the number of
patients who reached the endpoint in the comparison group divided by
the patient-years of follow-up in the corresponding group (i.e. the sum
of the follow-up times for each individual). The latter figure is equal to
the number of patients multiplied by their mean follow-up duration.

To obtain the trial- and treatment-arm specific mean follow-up dur-
ation, the following five-step approach was applied. Firstly, we
observed whether the mean follow-up time per treatment arm was

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ADIS clinical trials insight
Drug class: antihypertensive
AND age is adult OR elderly
AND study design is randomised
AND phase is III OR III/IV OR IV
AND text contains ‘mortality’ OR ‘morbidity’ OR ‘death’
AND Co-morbidity is Hypertension
= 148

Potentially relevant publications identified and screened for retrieval (n=512)
Publications excluded on basis of title, abstract review (n=181):
  - without a clinical outcome (n=64)
  - not related to the topic of our meta-analysis (n=38)
  - treatment did not include RAAS inhibitors (n=79)

Publications retrieved for more detailed evaluation (n=331)
Publications excluded after obtaining the full text (n=282):
  - not a prospective morbidity-mortality RCT (n=212)
  - duplicated publication (n=22)
  - excluded on basis of study population: heart failure, acute coronary
    syndrome, acute stroke, atrial fibrillation and post-cardiac surgery (n=53)

Potentially appropriate randomised controlled trials for meta-analysis (n=44)
Randomised Controlled Trials excluded (n=24):
  - less than 2/3 of patients diagnosed with hypertension (n=8)
  - less than 10 events in all trial participants (n=6)
  - less than 100 patients in one trial arm (n=6)
  - All-cause mortality not reported (n=1)
  - RAAS inhibitors used in both treatment arms (n=5)

Randomised controlled trials included in meta-analysis (n=20)
RAAS, renin-angiotensin–aldosterone system; RCT, randomized clinical trials.

**Figure 1** Flow diagram of trial search and selection process. RAAS, renin-angiotensin-aldosterone system; RCT, randomized clinical trials.
stated in the paper. If this was not available, we then derived it from the reported death rate by dividing the total number of deaths by the annual death rate. If these data were not available, then the mean follow-up time was estimated from incidences that were derived from Kaplan–Meier curves, in combination with the number of patients that were reported to be at risk at several follow-up points. Finally, if we were not able to compute the mean follow-up duration for each treatment arm separately, we used the mean follow-up time that was reported for all trial participants together.

Statistical analysis
For each individual trial, the treatment-arm specific all-cause and cardiovascular mortality IR was determined. We evaluated the assumption that the mortality rate is constant over time by visually inspecting the Kaplan–Meier curves of the studies in this meta-analysis, comparing different time windows within each Kaplan–Meier curve. We did not find any major deviation from this assumption. Furthermore, we realized that the follow-up time within each of the trials is relatively short (the overall mean follow-up duration is 4.3 years). Thus, on average, during the course of the trial, patients became only 4 years older. In view of this fact, it seems reasonable to assume that the IRs were constant over time.

Information on follow-up times is needed to obtain estimates of absolute risks (and absolute treatment effects). However, because of the assumptions that we used, our IR estimates might be somewhat inaccurate. Therefore, we based our estimates of relative treatment effects on the hazard ratios (HRs) and confidence intervals (CIs) or standard errors that were reported for each trial. Actually, HRs were available for all trials, except for RENAAAL, SCOPE, and pilot HYVET. For these trials, we calculated HRs based on the IRs in the separate treatment arms.

Because of the large variety in active (and control) treatments, we used a random-effects model to compute an overall pooled HR, even in case statistical tests for heterogeneity across trials were nonsignificant. Statistical heterogeneity was tested by Cochran’s Q statistic, and a P-value <0.10 (two sided) was considered to indicate heterogeneity among trials. The degree of heterogeneity was presented as an I² value. Publication bias was assessed by visually examining funnel plot asymmetry and quantified by using an Egger regression test to calculate two-tailed P-values.

We hypothesized that the mortality reduction by antihypertensive drugs might be influenced by age, gender, baseline SBP, BP reduction during follow-up, and follow-up time. To evaluate this hypothesis, we conducted linear regression analyses, based on trial-level data (so-called ‘meta-regression’). The trial-specific mean age, percentage of men, mean SBP, mean difference in BP reduction after 1 year of follow-up between RAAS inhibitors and control therapy, and mean follow-up time were considered as explanatory variables of the natural logarithm of the trial-specific hazard ratio (lnHR) for all-cause mortality. In this analysis, trial-level observations were weighed according to the inverse of the squared standard error of lnHR, thus taking into account the amount of ‘statistical information’ that is produced by each trial. Secondly, by including follow-up time in this analysis we were able to assess whether the mortality incidence ratio is constant over time.

Although we hypothesized that, taken all evidence together, RAAS inhibitors as a class of drugs would produce a homogenous treatment effect in terms of a mortality reduction compared with (contemporary) control therapy, we also performed stratified analyses according to the class of drug (ACE inhibitor vs. ARBs), as we realized that ACE inhibitors and ARBs have partly different modes of action. We also performed stratified analyses according to type of control (placebo vs. active treatment), and percentage of patients with diabetes mellitus or renal insufficiency at baseline (>50% vs. <50%)

Pooled HRs for all-cause mortality were determined using a random effects model for each stratum, and differences between strata were studied.

All statistical tests were two-sided, and a P-value < 0.05 was considered significant. We used SAS 9.2 for Windows for data analysis.

Results

Patient characteristics
On average, 91% of the trial participants were hypertensive according to the definition used in each trial. The mean baseline SBP was 153 mmHg (range of the means across trials 135–182), the mean age was 67 years (range of the means across trials 59–84) and 58% of participants were men (range of this percentage across trials 36–80; Table 1).

All-cause mortality
During a mean follow-up of 4.3 years, 6284 of the patients assigned to an RAAS inhibitor reached the endpoint of all-cause death. This corresponds with an IR of 20.9 deaths per 1000 patient-years. During the same period, a total of 8777 patients assigned to control therapy had all-cause death, implying an IR of 23.3 deaths per 1000 patient-years. RAAS inhibition was associated with a statistically significant reduction in all-cause mortality in three individual trials, ASCOT-BPLA, ADVANCE, and HYVET (Figure 2).

In all 20 trials grouped together, treatment with an RAAS inhibition was associated with a statistically significant 5% reduction in all-cause mortality (HR: 0.95, 95% CI: 0.91–1.00, P = 0.032; Figure 2). The degree of heterogeneity in the treatment effect across all trials was low (I²: 15%) and non-significant (P = 0.266). No funnel-plot asymmetry was visualized, and the P-value using an Egger regression test for all-cause mortality was >0.10 (intercept −0.3, 95% CI: −1.3–0.68; P = 0.53), indicating no evidence for publication bias.

Cardiovascular mortality
Excluding the four trials that did not report on cardiovascular mortality, 2570 patients assigned to RAAS inhibition had cardiovascular death. Based on a total of 295 617 patient-years of follow-up, the IR was 8.7 per 1000 patient-years. The IR in patients assigned to control therapy was 10.1 per 1000 patient-years (3773 events;
### Table 1  Baseline characteristics of study population in 20 trials (n = 158,998)

| Trial acronym | Year | n     | Active drug                      | Control                      | Mean follow-up, years | Hypertension, % | Mean SBP, mmHg | Mean age (years) | Men, % | IR in control group |
|---------------|------|-------|----------------------------------|------------------------------|----------------------|-----------------|----------------|------------------|--------|---------------------|
| RENAAL        | 2001 | 1513  | Losartan                         | Placebo                      | 3.09                 | 96.3            | 153            | 60.0             | 63.2   | 66.0                |
| IDNT          | 2001 | 1715  | Irbesartan                       | Amlodipine or placebo        | 2.86                 | 100             | 159            | 58.9             | 66.5   | 54.0                |
| LIFE          | 2002 | 9193  | Losartan with and without HCTZ    | Atenolol with and without HCTZ| 4.82                 | 100             | 174            | 66.9             | 46.0   | 19.5                |
| ALLHAT        | 2002 | 3357  | Lisinopril                       | Chlorothalidone or amlodipine| 5.01                 | 100             | 146            | 66.9             | 53.3   | 28.5                |
| ANBP-2        | 2003 | 6083  | ACE inhibitor (enalapril)         | Diuretic (HCTZ)              | 4.06                 | 100             | 168            | 71.9             | 49.0   | 17.1                |
| SCOPE         | 2003 | 4937  | Candesartan                      | Placebo                      | 3.74                 | 100             | 166            | 76.4             | 35.5   | 29.0                |
| pilot HYVET   | 2003 | 1283  | Lisinopril                       | Diuretic or no treatment     | 1.12                 | 100             | 182            | 83.8             | 36.6   | 55.4                |
| JMIC-B        | 2004 | 1650  | ACE inhibitor                     | Nifedipine                   | 2.25                 | 100             | 146            | 64.5             | 68.8   | 6.2                 |
| VALUE         | 2004 | 15245 | Valsartan                        | Amlodipine                   | 4.32                 | 100             | 155            | 67.3             | 57.6   | 24.8                |
| MOSES         | 2005 | 1352  | Eprosartan                       | Nifedipine                   | 2.50                 | 100             | 152            | 68.1             | 54.2   | 31.0                |
| ASCOT-BPLA    | 2005 | 19257 | Amlodipine with and without perindopril | Atenolol with and without bendroflumethiazide | 5.50 | 100 | 164 | 63.0 | 76.6 | 15.5 |
| JIKEI HEART   | 2007 | 3081  | Valsartan                        | Non-ARB                      | 2.81                 | 87.6            | 139            | 65.0             | 63.3   | 6.2                 |
| ADVANCE       | 2007 | 11140 | Perindopril with indapamide       | Placebo                      | 4.30                 | 68.7            | 145            | 66.0             | 57.5   | 19.8                |
| HYVET         | 2008 | 3845  | Indapamide with and without perindopril | Placebo                      | 2.11                 | 89.9            | 173            | 83.6             | 39.5   | 59.3                |
| PRoFESS       | 2008 | 20332 | Telmisartan                      | Placebo                      | 2.50                 | 74.0            | 144            | 66.2             | 64.0   | 29.1                |
| TRANSCEDE     | 2008 | 5926  | Telmisartan                      | Placebo                      | 4.67                 | 76.4            | 141            | 66.9             | 57.0   | 25.2                |
| CASE          | 2008 | 4703  | Candesartan                      | Amlodipine                   | 3.30                 | 100             | 163            | 63.8             | 55.2   | 11.1                |
| HIJ-CREATE    | 2009 | 2049  | Candesartan                      | Non-ARB                      | 4.03                 | 100             | 135            | 64.8             | 80.2   | 14.3                |
| KYOTO HEART   | 2009 | 3031  | Valsartan                        | Non-ARB                      | 2.92                 | 100             | 157            | 66.0             | 57.0   | 7.2                 |
| NAVIGATOR     | 2010 | 9306  | Valsartan                        | Placebo                      | 6.10                 | 77.5            | 140            | 63.8             | 49.4   | 11.5                |

HCTZ, hydrochlorothiazide; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; SBP, systolic blood pressure; IR, incidence rate per 1000 patient-years.
372,105 patient-years of follow-up), resulting in a significant 7% overall reduction in cardiovascular mortality (HR: 0.93, 95% CI: 0.88–0.99, \( P = 0.018 \); Figure 2). The degree of heterogeneity in treatment effect across all trials was low (I\(^2\): 23%) and non-significant (\( P = 0.194 \)). There was no evidence of publication bias.

**Angiotensin-converting enzyme inhibitors vs. AT1 receptor blockers**

All seven trials together, ACE inhibitors were associated with a statistically significant 10% reduction in all-cause mortality (IR: 20.4 vs. 24.2 deaths per 1000 patient-years; HR: 0.90, 95% CI: 0.84–0.97, \( P = 0.004 \)). No significant mortality reduction could be demonstrated with ARB treatment (13 trials; IR: 21.4 vs. 22.0 deaths per 1000 patient-years; HR: 0.99, 95% CI: 0.94–1.04, \( P = 0.683 \)). This difference in the treatment effect between ACE inhibitors and ARBs was statistically significant (P-value for interaction 0.036). Apparently, the observed mortality reduction in the overall group of RAAS inhibitors was completely driven by the beneficial effect of the ACE inhibitors.

As far as the ACE inhibitor trials are concerned, the largest mortality reductions were observed in ASCOT-BPLA, ADVANCE, and HYVET, all of which studied the ACE inhibitor perindopril (pooled HR: 0.87, 95% CI: 0.81–0.93, P-value < 0.001). However, there was no evidence of heterogeneity among the ACE inhibitor trials in the effect of the studied ACE inhibitor regimen on all-cause mortality (P-value for heterogeneity 0.310, I\(^2\): 16%; Figure 3). There was also no evidence of heterogeneity in the effect of ARBs (P-value for heterogeneity 0.631, I\(^2\): 0%).

Patients randomized to an ACE inhibitor had 9.1 cardiovascular deaths per 1000 patient-years, compared with 11.2 in their controls (HR: 0.88; 95% CI: 0.77–1.00; \( P = 0.051 \)). In the ARB trials, the IRs were 8.8 and 9.2 cardiovascular deaths per 1000 patient-years for patients assigned to ARB and control therapy, respectively (HR: 0.96; 95% CI: 0.90–1.01; \( P = 0.143 \)). The test for heterogeneity in effects on cardiovascular mortality between ACE inhibitors and ARBs was statistically non-significant (\( P = 0.227 \)).

**Meta-regression**

Multiple linear regression analysis showed a significant (\( P = 0.035 \)) association between the trial-specific mean SBP (measured at baseline), and the relative mortality reduction by RAAS blockade. The mortality reduction was largest in trials with the highest mean

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**Figure 2** All-cause and cardiovascular mortality treatment effect of renin–angiotensin–aldosterone system blockade in all included trials. HR, hazard ratio; CI, confidence interval; RAAS, renin–angiotensin–aldosterone system. Overall \( P = 0.032 \) for all-cause mortality. Overall \( P = 0.018 \) for cardiovascular mortality.
baseline BP values. Secondly, there was a significant ($P = 0.008$) relation between the trial specific mean difference in BP between the studied RAAS inhibitor and control therapy at 1-year follow-up, and the mortality reduction produced by the RAAS inhibitor. The mortality reduction was largest in trials with the largest difference in mean SBP reduction. No significant association was found between the trial-specific mean age, man/woman ratio, mean follow-up time and the mortality reduction by RAAS blockade. Mean follow-up time was also not related to the observed mortality reduction, supporting our hypothesis that the mortality incidence ratio is constant over time (at least for the mean duration of 4.3 years).

**Stratified analyses**

Similar HRs for all-cause mortality were found in clinical trials that compared RAAS inhibition with placebo (HR: 0.95, 95% CI: 0.88–1.02, $P = 0.177$) and with active control (HR: 0.95, 95% CI: 0.91–1.01, $P = 0.066$; $P$-value for interaction 0.889). Likewise, no heterogeneity in treatment effect was observed with respect to the percentage of participants with diabetes mellitus or renal insufficiency.

**Discussion**

This meta-analysis, which included almost 160,000 patients, sought to evaluate the effect of RAAS inhibitors as a class of drugs on total and cardiovascular mortality in their main indication hypertension. Overall, the results show a 5% reduction in all-cause mortality during a 4-year follow-up period associated with the class of RAAS inhibitors. This mortality reduction was found when compared with placebo, as well as in comparison with other BP-lowering drugs. However, in a stratified analysis according to the class of drug, it was shown that the observed overall all-cause mortality reduction was almost completely a result of the beneficial effect of the class of ACE inhibitors (10% relative reduction in all-cause mortality), whereas the ARBs showed a neutral treatment effect. The findings are firm, as the analysis included a large number of patient-years (677,005) and endpoints (15,061 deaths). The findings are relevant to clinical practice, as they are based on data from well-designed randomized trials encompassing a broad population of patients with high BP, who were well-treated for concomitant risk factors and who represent usual hypertensive patients seen today.

Reduction in mortality is the primary goal of antihypertensive therapy.² Paradoxically, the effect of RAAS inhibitors on mortality...
in hypertensive patients remained uncertain and had never been systematically evaluated. To our knowledge, no prior published meta-analysis investigated the efficacy of RAAS inhibitors on all-cause and cardiovascular mortality in their main indication of hypertension. Previous analyses in for example heart failure or coronary artery disease populations (with or without hypertension) demonstrated a reduction in cardiovascular events, stroke, and mortality.\textsuperscript{36,37} In addition, a pooled analysis of trials in patients with cardiovascular disease (including hypertension) concluded that the reduction in cardiovascular mortality and stroke with RAAS inhibitors is BP dependent.\textsuperscript{38} In our analyses, the significant reduction in cardiovascular mortality associated with RAAS inhibition supports previous literature.

As stated, the primary aim of this meta-analysis decided a priori was to test the hypothesis that RAAS inhibitors as a class of drugs would have a beneficial effect on total mortality in hypertension, when compared with contemporary control antihypertensive therapy. However, as we realized that, among the RAAS inhibitors, the ACE inhibitors and ARBs have different mechanisms of action, we also decided to study whether there was a differential effect on mortality between these two classes of drugs. Indeed, our analysis clearly showed that nearly all of the mortality reduction was observed with ACE inhibitors. Contrary, there was no clear benefit from the ARBs. This was supported by the sensitivity analysis which showed a significant stronger treatment effect in the ACE inhibitor trials compared with the ARB trials. With respect to this finding several points deserve consideration.

The reduced effect of ARBs on mortality when compared with ACE inhibitors has also previously been discussed.\textsuperscript{39,40} A recent meta-analysis of 37 ARB trials also failed to detect a reduction in all-cause or cardiovascular mortality in a broad population of patients.\textsuperscript{41} The differences in the modes of action between ACE inhibitors and ARBs, and the small-but-definite BP-independent reduction in CAD mortality with ACE inhibitors, which has not been observed with ARBs or other antihypertensive agents, might contribute to this finding.\textsuperscript{42} On the other hand, others have demonstrated that BP-dependent beneficial effects in the prevention of stroke and heart failure are similar for ACE inhibitors and ARBs. ACE inhibitors and ARBs have also been shown to be equally effective in preventing atrial fibrillation and new-onset diabetes.\textsuperscript{33,43} Furthermore, it should be emphasized that we did not design this meta-analysis to make a head-to-head comparison between ACE inhibitors and ARBs. The finding that the beneficial effect is seen in the ACE inhibitor population as opposed to the ARB population should be considered a post hoc observation. Given the nature of meta-analyses, which are per definition data-driven, the differential effect between ACE inhibitors and ARBs should be interpreted with caution to avoid overstating this subgroup finding vis-à-vis the a priori hypothesis. In this respect it should also be noted that the difference in effect on cardiovascular mortality between ACE inhibitors and ARBs was not statistically significant. Furthermore, two previous studies were designed to compare ACE inhibitors and ARBs in an hypertensive population, but both the ONTARGET (telmisartan vs. ramipril) and DETAIL (telmisartan vs. enalapril) trial did not show a differential treatment effect between ARBs and ACE inhibitors.\textsuperscript{15,45} Thus, at present, the results of this analysis do not warrant changing clinical practice treatment guidelines that recommend that an ARB may be used in ACE inhibitor-intolerant hypertensive patients.\textsuperscript{2} Hopefully, our findings will form the basis of further analysis and studies into the effects of BP treatment and total mortality which is the first line priority in the guidelines for the management of hypertension.

It might be argued that the observed 5% relative mortality reduction in the overall group of RAAS inhibitors, and the 10% relative mortality reduction in the ACE inhibitor group is small, and only found to be statistically significant in our analysis because of statistical ‘overpowering’. Indeed, in meta-analyses clinically irrelevant treatment effects might become statistically significant (i.e. the estimated effect divided by the standard error is >1.96) simply because of the large size of the aggregate (or pooled) trials. In our view, however, the observed mortality reduction in this meta-analysis is clinically relevant indeed, for several reasons. Firstly, it should be realized that the treatment effect was reached in patients who did receive a broad range of other contemporary risk-reduction therapies, including statins, antiplatelet therapy, beta-blockers, diuretics, and other BP-lowering medication (note that, as per design, we included trials that were conducted during 2000–2011). Secondly, the estimated absolute mortality reduction was 2.4 per 1000 patient-years for the RAAS inhibitors as a group and 3.8 per 1000 patient-years for the class of ACE inhibitors. This is an interesting figure, particularly since the prevalence of hypertension in Western (CAD) populations is high,\textsuperscript{16} despite the widespread use of BP-lowering medication. Thus a wider application of these agents, in particular of ACE inhibitors, may have substantial effects on the population level. Interestingly, the observed mortality reduction was largest in trials with the highest baseline SBP. The observed mortality reduction may be used as an additional argument to stimulate patients to adhere to the prescribed treatment.

Limitations
Several limitations of our analysis have to be mentioned. Firstly, there was a great deal of variation between the studied populations. For example, trials used different definitions of hypertension, different dosages of the active and control drug, different target BP levels, different follow-up times, and in several studies patients had other concomitant conditions and background therapy. Although this does not hamper the generalizability of our results, it makes it challenging to accurately estimate the effect of RAAS inhibition in a broad range of routine clinical practice situations.

Secondly, this meta-analysis is based on trial level data, rather than on individual patient data. Information on background therapy and co-morbidities were not available in several trial reports. Thus, we could not reliably analyse the relation between these factors and the observed mortality reduction. Moreover, the treatment arm-specific follow-up time was not available in all trials, we therefore derived follow-up time from either the reported death rate, Kaplan–Meier curves, or mean follow-up duration. This is an approximation of the true follow-up time, and we appreciate that our estimates of mortality incidence might be somewhat over or underestimated. However, importantly, this methodology had not influenced the estimation of the observed relative mortality reduction, which was mainly based on the HRs that were reported for the separate trials.
Finally, this meta-analysis assumed a class effect among the different ACE inhibitors and ARBs. The validity of this concept was not challenged by formal statistical tests on heterogeneity of treatment effects among the different (ACE inhibitor and ARB) trials. Still, it should be realized that differences may exist between drugs within the same class that are simply missed due to lack of statistical power. It should therefore be emphasized that our findings should be interpreted in relation to the pharmacological properties of the applied agents.

**Conclusion**

This meta-analysis, which involved almost 160,000 patients, demonstrated that RAAs inhibitors as a class of antihypertensive drugs were associated with a significant 5% relative reduction in all-cause mortality in populations with a high prevalence of hypertension when compared with contemporary control antihypertensive therapy. Stratified subgroup analysis according to class of drug showed a differential treatment effect between ACE inhibitors and ARBs. The overall reduction in all-cause mortality resulted almost completely from the class of ACE inhibitors, which were associated with a statistically significant 10% relative reduction in all-cause mortality, whereas no mortality reduction was observed in the ARBs. In view of the high prevalence of hypertension in the general population, widespread use of ACE inhibitors may therefore result in a considerable gain in lives saved. The results of this study provide a convincing argument to improve treatment adherence in the millions of people around the world suffering from hypertension and its sequelae.

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**References**

1. Ezzati M, Lopez AD, Rodgers A, Vos T, Lozano R. Comparative Risk Assessment Collaborating G. Selected major risk factors and global and global burden of disease. Lancet 2002;360:1347–1360.
2. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Haegerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ricochet E, Ambrosioni E, Lindholm LH, Manolis A, Nilsson PM, Redon J, Rutan B, Sitzer M, Svendsen O, Tardif J, Taskinen M, Waldmeir F, Vermisal T, Vlaminck A, Waeber B, Waeber G, Zanchetti A, Zenevits P. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1084–1157.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Joint National Committee on Prevention, Detection, Treatment of High Blood Pressure. National Heart, Blood I, National High Blood Pressure Education Program Coordinating C. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1084–1157.
4. Sllhut LT, Dorot FE, Kahn J, Lentz KE, Levine M. The biochemistry of the renin-angiotensin system and its role in hypertension. Am J Med 1976;63:737–748.
5. Marketou M, Kintsurashvili E, Pappanoiu KN, Lucero HA, Gavras I, Gavras H. Cardioprotective effects of a selective B(2) receptor agonist of bradykinin post-acute myocardial infarct. Am J Hypertension 2010;23:562–568.
6. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293–302.
7. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000;355:1031–1035.
8. Fox KM, Investigators EUROCUREPSSADY. Effect of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–788.
9. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shihlini S, Investigators RS. Effects of isorartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869.
10. Group NS, McMurray JJ, Holman RR, Bethel MA, Holzhauer B, Hua TA, Bekenov Y, Boolell M, Buse J, Buckle MY, Baxa AR, Chang JT, Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaiacz G, Gazzambide S, Giles T, Horton E, Ilkova H, Jensen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Marzetti E, Massey E, Nesta F, Pan C, Praper R, Rapits SA, Rutten GE, Sandstroem H, Schaper F, Sheen A, Schmitz O, Snay I, Sosa V, Stender S, Tamas G, Tognoni G, Tuomilehto J, Villamil AS, Vosar J, Calif RP. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–1490.
11. Mochizuki S, Dahlof B, Shimizu M, Iwaki K, Yoshikawa M, Taniguchi I, Ohta M, Yamada T, Ogawa K, Kanoe K, Kawai M, Seki S, Okazaki F, Taniguchi M, Yoshida S, Tajima N, Jikei Heart Study g. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. Lancet 2007;369:1431–1439.
12. Massie BM, Carson PE, McMurray JJ, Komadaj M, Mckelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;349:2455–2467.
13. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson S, Ostergren J, Yusuf S, Pocock S, Investigators C. Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall program. Lancet 2003;362:759–766.
14. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatin M, Velazquez E, Investigators AT. Benazepril plus amiodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417–2428.
15. Investigators O, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schwamcher H, Dagenais G, Sleight P, Anderson C, Telmesarnt, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559.
16. Pepine CJ, Handberg EM, Cooper DEhoff RM, Marks R, Kowey P, Messeri FH, Manica G, Cangiano JL, Garcia-Barrillo D, Keltai M, Erdine S, Bristal HA, Kolb HR, Bakris GL, Cohen JD, Parmiay WW, Investigators I. A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-TRandolam Study (INVEST): a randomised controlled trial. JAMA 2003;290:2805–2816.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
19. Kaski S, Hagiwara N, Hasoda S, Sumiyoshi T, Honda T, Haze K, Nagashima M, Origasa H, Urashima M, Ogawa H, Investigators H-C. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and
ACE inhibitors reduce mortality in hypertension

2097

29. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Patel A, Group AC, MacMahon S, Chalmers J, MacMahon B, Woodward M, Billot L, Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Ogihara T, Fujimoto A, Nakao K, Saruta T, Group C-JT. ARB candesartan and receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes: the VALUE randomised trial. Lancet 2005;366:1174–1183.

30. Dagenais GR, Pogue J, Fox K, Simonis ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–588.

31. Thompson AJ, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA 2011;305:913–922.

32. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b665.

33. Messeri FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006;144:884–893.

34. Strauss MH, Hall AS. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation 2006;114:838–854.

35. Bangalore S, Kumar S, Wettersey J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011;342:d2234.

36. Blood Pressure Lowering Treatment, Trialists C, Turnbull F, Neal B, Pfeffer M, Kostis J, Albert C, Woodward M, Chalmers J, Zanchetti A, MacMahon S. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens 2007;25:951–958.

37. Huang G, Xu BJ, Liu JX, He Y, Nie XL, Li Q, Hu YM, Zhao SQ, Wang M, Zhang WY, Liu XR, Wu T, Arkin A, Zhang TJ. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers decrease the incidence of arterial fibrillation: a meta-analysis. Eur J Clin Invest 2011;41:719–733.

38. Tocci G, Paneri F, Palano F, Sciarretta S, Ferrucci A, Kurta T, Mancia G, Volpe M. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and diabetes: a meta-analysis of placebo-controlled clinical trials. Am J Hypertens 2011;24:582–590.

39. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J. Diabetics Exposed to T, Enalapril Study G. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2003;351:1952–1961.

40. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U, Group ES. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil 2009;16:121–137.