Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in normotensive atherosclerotic patients: a collaborative meta-analysis of randomized trials

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Aims

It is unclear whether angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) are beneficial in individuals with, or at increased risk for, atherosclerotic vascular disease who are normotensive.

Methods and results

Two investigators independently searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from 1980 to 2011, bibliographies, and contacted primary study authors for randomized placebo-controlled outcome trials evaluating ACE-I or ARB which enrolled at least 1000 patients with, or at increased risk for, atherosclerotic vascular disease and followed them for at least 12 months. We approached all eligible trials to obtain data stratified by baseline systolic pressures. We pooled data from 13 trials of 80,594 patients; outcomes included 9,043 all-cause deaths, 5,674 cardiovascular deaths, 3,106 myocardial infarctions, and 4,452 strokes. Angiotensin-converting enzyme inhibitors or ARB reduced the composite primary outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke by 11% (95% confidence interval 7–15%), with no variation in efficacy across baseline systolic blood pressure strata. In patients with baseline systolic pressure <130 mmHg, ACE-I or ARB reduced the composite primary outcome by 16% (10–23%) and all-cause mortality by 11% (4–18%)—this benefit was consistent across all subgroups examined including those without systolic heart failure (OR: 0.81, 95% CI: 0.75–0.88) and those without diabetes (OR: 0.79, 95% CI: 0.70–0.89).

Conclusion

Angiotensin-converting enzyme inhibitors or ARB are beneficial in patients with, or at increased risk for, atherosclerotic disease even if their systolic pressure is <130 mmHg before treatment.

Keywords

Atherosclerosis • Renin angiotensin system modulation • Meta-analysis

Introduction

Although numerous guidelines contain statements about the cardioprotective effects of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) in patients with, or at increased risk for, atherosclerosis, there is inconsistency between guidelines on whether these agents should be prescribed to individuals with normal blood pressures (BP) (i.e. those with SBP <130 mmHg).1,2 While an early report from the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) reported that the benefits of ACE-I or ARB on cardiovascular outcomes were largely mediated through blood pressure reduction, >93% of the patients in that analysis were hypertensive at baseline.3 Although secondary analyses of various ACE-I or ARB trials reported that cardiovascular benefits were similar whether or not patients had ‘hypertension’ at baseline,4–7 the definition of hypertension varied between studies and these conclusions were based on non-significant interaction tests which were...
underpowered due to the small number of events among patients without hypertension.

A recent meta-analysis reported that antihypertensive therapy reduced clinical events in patients with cardiovascular disease regardless of baseline blood pressure, but the trials that were pooled evaluated numerous drug classes (including combinations of agents), did not apply uniform definitions for hypertension (several studies used clinical history rather than actual BP measurements), and where BP was available the authors lumped data for patients with normal (<130 mmHg) and borderline/high normal (130–139 mmHg) blood pressures together using aggregate published data. As the authors themselves acknowledged, the primary limitation of this meta-analysis was the dearth of studies reporting the outcomes of interest for normotensive(s). The BPLTTC also recently reported that the benefits of antihypertensive drugs were similar across baseline blood pressure strata, but the SBP strata examined were ≤140, 140–159, 160–179, and ≥180 mmHg.

Thus, the question of whether ACE-I or ARB is beneficial in individuals with, or at increased risk for, atherosclerotic vascular disease who have normal SBP (<130 mmHg) remains unanswered.

Methods

After finalizing a protocol, two investigators (F.M. and I.M.) independently searched MEDLINE (1980 to March 2011), CENTRAL—Cochrane Library (1980–March 2011), and EMBASE (1980–2011). We supplemented this search with a hand search of the reference lists of review articles and primary studies identified in the electronic search. We identified all placebo-controlled randomized trials with sample size ≥1000 patients with, or at increased risk for, atherosclerotic vascular disease, who received ACE-I or ARB for at least 12 months, and in whom cardiovascular endpoints (death, myocardial infarction (MI), or stroke) were prospectively measured. Trials in which patients were randomized to initial combination therapy or were taking more than one modulator of the renin-angiotensin system (e.g. spironolactone plus ACE-I or ARB) were not included in this analysis as it would be impossible to derive unbiased estimates for the treatment effect of the ACE-I or ARB alone. We also excluded any trials conducted exclusively in patients with hypertension (i.e. trials which excluded patients with blood pressures in the normal range).

We contacted the primary authors of all potentially eligible studies identified in our literature search to obtain outcome data stratified by baseline SBP. We assigned events in an intention to treat fashion and only evaluated the first event in each patient for each outcome. Our primary outcome was the composite of cardiovascular death, non-fatal MI, or non-fatal stroke and we censored patients in our primary analysis at the time they had the first of these events. However, for event-specific analyses (e.g. all-cause mortality), we included all follow-up time until that event (e.g. if a patient suffered a stroke and then 1 year later died they were included in both the stroke analysis and the all-cause mortality analysis). All outcomes were defined as per the primary studies; all of the included trials reported independent adjudication of outcomes.

We extracted data from all trials in duplicate and independently, and pooled data across trials within each SBP strata using the Peto fixed effects model in Review Manager, version 5 (The Cochrane Collaboration, Copenhagen, Denmark). We examined whether the estimates of treatment effect differed across the three SBP strata using the two-sided Breslow–Day test (defining a P-value of 0.05 as statistically significant) and performed meta-regression analyses using the weighted least squares method.

We extracted data within each trial for eight a priori specified subgroups which were not mutually exclusive (older/younger than 65 years, known coronary disease, prior cerebrovascular disease, prior systolic heart failure yes/no, and diabetes mellitus yes/no), and pooled the data, again stratified by SBP at baseline.

Results

Of the 7636 citations identified in our search, we retrieved 140 for detailed evaluation and identified 20 potentially eligible trials (kappa: 0.95 for inter-rater agreement on study eligibility—Figure 1). After contact with all primary study authors, we obtained individual patient data from 10 trials and trial data stratified by baseline SBP from another three trials.

The 13 trials we included provided information on 80,594 patients (Table 1). All were high-quality trials with blinded adjudication of endpoints and key trial eligibility criteria were outlined in Table 1—of particular note, only three trials had BP-specific entry criteria and in all cases it was the exclusion of individuals with very high levels. Mean ages ranged between 55 and 67 years, mean SBP at baseline ranged between 126 and 152 mmHg, mean SBP reduction in the first 6 months ranged between 3.8 and 5.8 mmHg vs. placebo, and most patients (median 79%) were also taking non-ACE-I/ARB antihypertensive therapy during the trial.

The relative benefits of ACE-I or ARB on our primary composite outcome (OR: 0.89, 95% CI: 0.85–0.93, between trial heterogeneity I² 25%) did not vary across SBP strata (Figure 2, P = 0.13). Meta-regression using all 80,594 patients revealed that age, baseline SBP, degree of SBP reduction during the trial, and duration of trial were not significantly associated with the magnitude of benefit on our primary outcome with ACE-I/ARB (e-Appendix Supplementary material online, Table S1). Outcome-specific analyses confirmed the benefits of ACE-I/ARB for each component of our primary outcome as well as for all-cause mortality (Table 2). Although the magnitude of the benefits differed between baseline SBP strata for some of the outcomes (with the between strata comparison achieving statistical significance for cardiovascular death), in general the benefits were greatest in those patients with SBP <130 mmHg at baseline and the between-trial heterogeneity was smallest in these patients.

Specific to our research question, ACE-I or ARB demonstrated benefits on all cardiovascular outcomes in patients with baseline SBP <130 mmHg with minimal heterogeneity between trials (Figure 2, Table 2), and with consistency across our a priori defined subgroups including those patients without systolic heart failure or diabetes (Table 3). Of note, although ACE-I/ARB did not exhibit benefit in the relatively small number of normotensive patients with systolic heart failure, they were associated with substantial benefit in systolic heart failure patients with SBP ≥140 mmHg (OR: 0.70, 95% CI: 0.51–0.95). Although we analysed
outcomes using <130 mmHg as our lowest stratum, an exploratory post hoc analysis sub-stratifying this group by JNC seven categories revealed consistent results: pooled OR 0.81 (95% CI: 0.73–0.91, I²: 15%) for cardiovascular death, MI, or stroke in the 10,280 patients with SBP <120 mmHg at baseline and pooled OR 0.85 (95% CI: 0.77–0.95, I²: 0%) in the 13,642 patients with baseline SBP 120–129 mmHg. An analysis stratified by type of agent (ACE-I or ARB) revealed similar benefits with both classes in normotensive patients (e-Appendix Supplementary material online, Table S2).

**Sensitivity analysis**

The 13 trials we included in this analysis contained over five times the amount of data (11,005 patients with cardiovascular death, non-fatal MI, or non-fatal stroke) as the 7 trials which were not able to provide outcome data stratified by baseline SBP (1618 patients with the composite primary outcome), and the 15 trials excluded as they were too small (no patients with the composite primary outcome). Moreover, pooled results between the trials we included and those we did not include were similar—for example, the odds ratio for stroke (the outcome most closely linked to SBP epidemiologically) did not differ between the 13 included trials (4452 strokes, OR: 0.91, 95% CI: 0.86–0.97) and the 12 trials which reported this outcome but were not included as SBP data were unavailable or they were too small (308 strokes, OR: 0.93, 95% CI: 0.74–1.17). Finally, three of the trials we were not able to include due to lack of data availability (Val-HEFT, PEACE, and CHARMS) have independently reported that the impact of ACE-I/ARB in their studies was similar in normotensive and hypertensive patients.5,8,24

**Discussion**

Our findings confirm that ACE-I or ARB are beneficial in normotensive high-risk patients and support calls to base decisions about
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Sample Size</th>
<th>Average Duration of Follow-up</th>
<th>Comparators and Daily Target Doses</th>
<th>Key Eligibility Criteria</th>
<th>Primary Outcome</th>
<th>Mean Age (SD)</th>
<th>Male (%)</th>
<th>Mean SBP at Baseline (mmHg)</th>
</tr>
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<tbody>
<tr>
<td><strong>Systolic heart failure</strong></td>
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<tr>
<td>SOLVD prevention and treatment11,12</td>
<td>1992</td>
<td>4220</td>
<td>39 m</td>
<td>Enalapril 20 mg vs. placebo</td>
<td>LVEF ≤ 0.35</td>
<td>All-cause mortality, CV death, the development of HF, and hospitalization for HF</td>
<td>59 (10)</td>
<td>91</td>
<td>125 (17)</td>
</tr>
<tr>
<td>SAVE13</td>
<td>1992</td>
<td>2231</td>
<td>42 m</td>
<td>Captopril 150 mg vs. placebo</td>
<td>LVEF &lt; 0.40 after myocardial infarction</td>
<td>(i) Death, hospitalization for HF, or left ventricular remodelling</td>
<td>59 (6)</td>
<td>82</td>
<td>113 (15)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>(ii) CV death, hospitalization for reinfarction or angina, and revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRACE14</td>
<td>1993</td>
<td>1749</td>
<td>36 m</td>
<td>Trandolapril 4 mg vs. placebo</td>
<td>LVEF ≤ 0.35 after myocardial infarction</td>
<td>All-cause mortality</td>
<td>68 (10)</td>
<td>71</td>
<td>121 (18)</td>
</tr>
<tr>
<td><strong>Atherosclerosis (CAD, PAD, or cerebrovascular disease) or atherosclerosis risk trials</strong></td>
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<tr>
<td>HOPE10</td>
<td>2000</td>
<td>9297</td>
<td>54 m</td>
<td>Ramipril 10 mg vs. placebo</td>
<td>Older than 55 years, known CV disease or diabetes plus one other CV risk factor; not known to have HF, reduced LVEF, or overt nephropathy; no BP criteria beyond exclusion of patients with ‘uncontrolled HTN’</td>
<td>CV death, MI, or stroke</td>
<td>66 (7)</td>
<td>73</td>
<td>139 (20)</td>
</tr>
<tr>
<td>RENAAL15</td>
<td>2001</td>
<td>1513</td>
<td>40.8 m</td>
<td>Losartan 100 mg vs. placebo</td>
<td>Type 2 diabetes and nephropathy; no BP criteria beyond exclusion of patients with BP ≥ 200/110</td>
<td>Death or doubling in serum creatinine or end-stage renal disease</td>
<td>60 (7)</td>
<td>63</td>
<td>152 (19)</td>
</tr>
<tr>
<td>PROGRESS16</td>
<td>2001</td>
<td>2561</td>
<td>47 m</td>
<td>Perindopril 4 mg vs. placebo</td>
<td>History of stroke or TIA within the previous 5 years; no clear indication nor contraindication to ACE-I; no BP criteria</td>
<td>Fatal and non-fatal stroke</td>
<td>65 (10)</td>
<td>68</td>
<td>144 (19)</td>
</tr>
<tr>
<td>CAMELOT17</td>
<td>2002</td>
<td>1313</td>
<td>24 m</td>
<td>Enalapril 20 mg vs. placebo</td>
<td>Angiographically documented CAD and DBP &lt; 100 mmHg; patients with reduced LVEF or moderate to severe heart failure symptoms excluded</td>
<td>CV death, non-fatal MI, resuscitated cardiac arrest, coronary revascularization, HF or angina hospitalization, fatal or non-fatal stroke or TIA, and new diagnosis of peripheral vascular disease</td>
<td>58 (10)</td>
<td>73</td>
<td>129 (16)</td>
</tr>
<tr>
<td>EUROPA18</td>
<td>2003</td>
<td>13 665</td>
<td>50 m</td>
<td>Perindopril 8 mg vs. placebo</td>
<td>Stable CAD without clinical heart failure; SBP 110–180 mmHg; creatinine &lt; 150 μmol/L</td>
<td>CV death, non-fatal MI, resuscitated cardiac arrest</td>
<td>60 (9)</td>
<td>85</td>
<td>137 (15)</td>
</tr>
<tr>
<td>DIABHYCAR19</td>
<td>2004</td>
<td>4912</td>
<td>48 m</td>
<td>Ramipril 1.25 mg vs. placebo</td>
<td>Type 2 DM, older than 50 years, with albuminuria but serum creatinine &lt; 150 μmol/L, without chronic heart failure; no BP criteria</td>
<td>CV death, non-fatal MI, stroke, HF hospitalization, or end-stage renal failure</td>
<td>65 (8)</td>
<td>70</td>
<td>145 (15)</td>
</tr>
<tr>
<td>DREAM20</td>
<td>2006</td>
<td>5269</td>
<td>36 m</td>
<td>Ramipril 15 mg vs. placebo</td>
<td>Dysglycaemia but not frank diabetes, older than 30 years, no CV disease; no BP criteria</td>
<td>New diabetes or death</td>
<td>55 (11)</td>
<td>41</td>
<td>136 (18)</td>
</tr>
</tbody>
</table>
the prescription of these agents on each patient’s cardiovascular risk rather than just their BP level. Observational studies consistently demonstrate a strong log-linear relation between blood pressure levels and macrovascular outcomes (particularly stroke) at SBP > 115 mmHg. As most hypertensive individuals have at least one other cardiovascular risk factor, treatment approaches targeting those at highest cardiovascular risk will be associated with greater absolute benefits than prevention strategies based on individual risk factors.

Other randomized trials not included in our meta-analysis (as they were not single-agent placebo-controlled studies) have shown that combination antihypertensive therapies which include ACE-I or ARB provide greater cardiovascular protection than combination therapies without either agent, even when similar degrees of BP reduction are achieved. Moreover, although the ADVANCE trial was not eligible for our meta-analysis as it tested combination ACE-I and diuretic therapy against placebo, the ADVANCE results are broadly consistent with the findings of our meta-analysis (14% RRR in all-cause mortality in type 2 diabetes, with no evidence of an interaction between baseline SBP and treatment effect). Our results are also consistent with a recent meta-analysis of 13 randomized trials (only two of which were included in our analysis) of intensive vs. standard BP control in diabetes which reported greater reductions in stroke and all-cause mortality with more intensive BP control (≤ 130 mmHg), but no difference in microvascular outcomes.

In discussing the use of ACE-I or ARB in normotensive individuals, the issue of drug safety arises. Although adverse effects were not systematically assessed in a similar method across all of the trials we meta-analysed (thus preventing pooling of this data), two placebo controlled trials of ACE-I or ARB conducted exclusively in normotensive individuals have reported that ACE-I/ARB treated patients exhibited lower rates of adverse effects than those treated with placebo. In addition, a meta-analysis of those placebo-controlled ACE-I/ARB trials which systematically monitored serum creatinine confirmed that treatment with these agents is associated with less risk of deteriorating renal function compared with placebo treatment.

While the benefits of ACE-I/ARB were remarkably consistent for all of the outcomes we analysed in patients with baseline SBP < 130 mmHg (with between-trial heterogeneity I² ranging from 0 to 9%), the trial results in patients with higher baseline SBPs exhibited substantially more heterogeneity. This is perhaps not surprising since the vast majority of these overtly hypertensive patients were taking other antihypertensive drugs as well, resulting in substantially more ‘noise’ from confounding medications in patients who were hypertensive at baseline. In addition, it is worth noting that in patients with baseline SBP < 130 mmHg, the benefits of ACE-I/ARB were consistent across all of our a priori defined subgroups, including those patients without heart failure or diabetes.

Although our study followed a pre-specified analytic plan, included thousands of cardiovascular outcomes in a variety of patients, and generated precise estimates of the treatment effects of ACE-I or ARB among nearly 24 000 patients with SBPs in the normal range, there are some limitations. First, our analyses focused on baseline SBP and are not suitable for defining optimal
Figure 2 Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on cardiovascular death, non-fatal MI, or non-fatal stroke, stratified by baseline SBP.
<table>
<thead>
<tr>
<th>Trials</th>
<th>Events/participants</th>
<th>d-SBP/d-DBP^a (mmHg)</th>
<th>Events</th>
<th>Heterogeneity between trials</th>
<th>P-value for differences across SBP strata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>861/12 046</td>
<td>1004/11 876</td>
<td>−4.5/−2.3</td>
<td>0.83</td>
<td>0.75–0.91</td>
</tr>
<tr>
<td>130–139</td>
<td>521/8415</td>
<td>539/8296</td>
<td>−5.3/−2.9</td>
<td>0.93</td>
<td>0.82–1.06</td>
</tr>
<tr>
<td>140+</td>
<td>1368/19 925</td>
<td>1381/20 036</td>
<td>−4.6/−2.4</td>
<td>1.00</td>
<td>0.92–1.08</td>
</tr>
<tr>
<td>All patients</td>
<td>2750/40 386</td>
<td>2924/40 208</td>
<td>0.93</td>
<td>0.88–0.98</td>
<td>0.001</td>
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<tr>
<td>All-cause death</td>
<td></td>
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</tr>
<tr>
<td>&lt;130</td>
<td>1358/12 046</td>
<td>1477/11 876</td>
<td>−4.5/−2.3</td>
<td>0.89</td>
<td>0.82–0.96</td>
</tr>
<tr>
<td>130–139</td>
<td>864/8415</td>
<td>876/8296</td>
<td>−5.3/−2.9</td>
<td>0.96</td>
<td>0.86–1.06</td>
</tr>
<tr>
<td>140+</td>
<td>2224/19 925</td>
<td>2244/20 036</td>
<td>−4.6/−2.4</td>
<td>1.00</td>
<td>0.94–1.06</td>
</tr>
<tr>
<td>All patients</td>
<td>4446/40 386</td>
<td>4597/40 208</td>
<td>0.95</td>
<td>0.91–1.00</td>
<td>0.006</td>
</tr>
<tr>
<td>Fatal/non-fatal MI</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>358/9368</td>
<td>402/9221</td>
<td>−4.5/−2.3</td>
<td>0.84</td>
<td>0.73–0.97</td>
</tr>
<tr>
<td>130–139</td>
<td>295/7750</td>
<td>333/7652</td>
<td>−5.3/−2.9</td>
<td>0.86</td>
<td>0.73–1.01</td>
</tr>
<tr>
<td>140+</td>
<td>775/19 254</td>
<td>943/19 331</td>
<td>−4.6/−2.4</td>
<td>0.81</td>
<td>0.74–0.89</td>
</tr>
<tr>
<td>All patients</td>
<td>1428/36 372</td>
<td>1678/36 204</td>
<td>0.83</td>
<td>0.77–0.89</td>
<td>0.15</td>
</tr>
<tr>
<td>Fatal/non-fatal stroke</td>
<td></td>
<td></td>
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<tr>
<td>&lt;130</td>
<td>463/12 046</td>
<td>518/11 876</td>
<td>−4.5/−2.3</td>
<td>0.88</td>
<td>0.78–1.01</td>
</tr>
<tr>
<td>130–139</td>
<td>437/8415</td>
<td>410/8296</td>
<td>−5.3/−2.9</td>
<td>1.05</td>
<td>0.91–1.20</td>
</tr>
<tr>
<td>140+</td>
<td>1233/19 925</td>
<td>1391/20 036</td>
<td>−4.6/−2.4</td>
<td>0.88</td>
<td>0.82–0.96</td>
</tr>
<tr>
<td>All patients</td>
<td>2133/40 386</td>
<td>2319/40 208</td>
<td>0.91</td>
<td>0.86–0.97</td>
<td>0.33</td>
</tr>
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</table>

^d-SBP (d-DBP), mean SBP (DBP) reduction for placebo group — mean SBP (DBP) reduction for intervention group, where SBP (DBP) reduction = mean SBP (DBP) at baseline−mean SBP (DBP) at 6 month (or at last visit before clinical event if event occurred within first 6 months). The Forest plots illustrating trial-specific outcome events are provided in e-Appendix Supplementary material online, figures S1–S4.
SBP targets—elucidation of these targets awaits the results of ongoing trials. Second, our data set included few patients with SBP <110 mmHg given trial eligibility criteria. Third, our results are limited to the short- and medium-term effects of ACE-I or ARB given the duration of the trials we studied; although prior studies have established longer-term legacy effects from exposure to ACE-I.35 Fourth, as the target doses of ACE-II/ARB did not differ greatly between trials, there was insufficient spread in this data to perform a meta-regression for the impact of target dose on benefits. While some may argue that we should not have included patients with heart failure in these analyses, our subgroup analysis excluding patients with systolic heart failure (see Table 3) confirmed that the benefits of ACE-I or ARB in normotensive patients are present in patients without known heart failure. Sixth, our analyses are based on single clinic-based BP measurements and we acknowledge this does not capture other prognostic factors such as BP variability and instability and may underestimate the degree of BP reduction achieved with ACE-I or ARB.36 Finally, despite exhaustive efforts, we were unable to obtain outcome data stratified by baseline SBP from 7 of the 20 potentially eligible ACE-II/ARB trials. However, as discussed in our ‘Sensitivity analysis’ section, our SBP-stratified analyses included 11 005 of the 12 623 events in these 20 trials and overall pooled results (i.e. not stratified by baseline SBP) were very similar between the trials we included and those who were unable to obtain data from.

In conclusion, as ACE-I or ARB are efficacious in preventing cardiovascular events and death in individuals with, or at high risk for, atherosclerosis even when their SBP is in the normal range, the choice to prescribe these agents should be based on the assessment of each patient’s cardiovascular risk rather than just their measured blood pressure.

Authors’ contributions
F.M., I.M., K.T., G.D., and S.Y. contributed to study conception and design. Data were provided with the kind permission of the various study principal investigators listed below as RAS modulator meta-analysis investigators. H.J. performed statistical analyses. F.M. wrote all drafts of this manuscript; all RAS modulator meta-analysis investigators reviewed and commented on manuscript drafts and gave final approval to submit for publication. F.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary material
Supplementary material is available at European Heart Journal online.

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Conflict of interest: None declared for F.M., and conflicts of interest/funding for other RAS Modulator meta-analysis investigators listed in the primary publication for each trial.

Appendix
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MacMahon (BP Lowering Treatment Trialists Collaboration, PROGRESS); Hertzl Gerstein (DREAM); Michel Marre (DIABYCAR); Kim Fox and Maarten Simoons (EUROPA); Steven Nissen (CAMELOT); Hiddo Lambers Heerspink, Barry Brenner, and Dick De Zeeuw (RENAAL); Marc Pfeffer (SAVE); Lars Kober (TRACE); Hans-Christoph Diener and Ralph Sacco (PROFESS).

References


Detection of myocardial bridging induced ischaemia during cardiac catheterization by dobutamine-stress electrocardiographic body surface mapping

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A 30-year-old female presented with chronic atypical chest pain. Exercise sestamibi showed mild anterior ischaemia. Coronary angiography did not reveal coronary artery disease, but there was a long segment of myocardial bridging (MB) (Panel A) in the distal left anterior descending artery. There was dynamic (30% diameter) stenosis during systole at rest (Panel B). To further evaluate the significance of the MB, intravenous dobutamine was infused (5–20 μg/kg/min) which resulted in increased systolic compression (>50% stenosis) (Panel C; see Supplementary material online, Movie S1). The drug study was performed in conjunction with an 80-lead electrocardiographic (ECG) body surface map (PRIME ECG®, Verathon, Inc., Bothell, WA, USA), which did not show ST-segment deviation at rest (Panel D). During the peak dose of dobutamine, the patient’s chest pain was reproduced and there was up to 1–2 mm of ST-segment depression (blue territory) across the anterior chest leads with reciprocal ST-segment elevation (red territory, Panel E). Due to the failure of medical therapy, the patient underwent surgical ‘unroofing’ of the bridge which resulted in complete resolution of her symptoms.

Our case illustrates a useful approach for diagnosing clinically significant MB during cardiac catheterization by detecting ischaemia during dobutamine provocation using a sensitive body surface ECG map. While this device is not widely available, most laboratories have the capability to perform 12-lead ECG monitoring, which may be a reasonable alternative. The case also highlights the fact that a diagnosis of MB should be considered in young patients with chronic chest pain and normal coronary arteries.

Supplementary material is available at European Heart Journal online.