Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials

Summary

Background This programme of overviews of randomised trials was established to investigate the effects of angiotensin-converting-enzyme (ACE) inhibitors, calcium antagonists, and other blood-pressure-lowering drugs on mortality and major cardiovascular morbidity in several populations of patients. We did separate overviews of trials comparing active treatment regimens with placebo, trials comparing more intensive and less intensive blood-pressure-lowering strategies, and trials comparing treatment regimens based on different drug classes.

Methods The hypotheses to be investigated, the trials to be included, and the outcomes to be studied were all selected before the results of any participating trial were known. Individual participant data or group tabular data were provided by each trial and combined by standard statistical techniques.

Findings The overview of placebo-controlled trials of ACE inhibitors (four trials, 12 124 patients mostly with coronary heart disease) revealed reductions in stroke (30% [95% CI 15–43]), coronary heart disease (20% [11–28]), and major cardiovascular events (21% [14–27]). The overview of placebo-controlled trials of calcium antagonists (two trials, 5520 patients mostly with hypertension) showed reductions in stroke (39% [15–56]) and major cardiovascular events (28% [13–41]). In the overview of trials comparing blood-pressure-lowering strategies of different intensity (three trials, 20 408 patients with hypertension), there were reduced risks of stroke (20% [2–35]), coronary heart disease (19% [2–33]), and major cardiovascular events (15% [4–24]) with more intensive therapy. In the overviews comparing different antihypertensive regimens (eight trials, 37 872 patients with hypertension), several differences in cause-specific effects were seen between calcium-antagonist-based therapy and other regimens, but each was of borderline significance.

Interpretation Strong evidence of benefits of ACE inhibitors and calcium antagonists is provided by the overviews of placebo-controlled trials. There is weaker evidence of differences between treatment regimens of differing intensities and of differences between treatment regimens based on different drug classes. Data from continuing trials of blood-pressure-lowering drugs will substantially increase the evidence available about any real differences that might exist between regimens.


*Members listed at end of paper

Blood Pressure Lowering Treatment Trialists’ Collaboration, Institute for International Health, University of Sydney, PO Box 576, Newtown, Sydney, New South Wales 2042, Australia

Correspondence to: Dr Bruce Neal (e-mail: bneal@med.usyd.edu.au)

Introduction

By the mid 1990s, evidence about the effects of blood-pressure-lowering regimens based mainly on diuretics and β-blockers was available from a series of randomised controlled trials involving a total of more than 47 000 hypertensive patients.1–4 Systematic overviews (or meta-analyses) of these trials showed that reductions in blood pressure of about 10–12 mm Hg systolic and 5–6 mm Hg diastolic conferred relative reductions in stroke risk of 38% and in risk of coronary heart disease of 16% within just a few years of beginning treatment.4–6 The sizes of these effects were broadly consistent with those predicted from observational studies of the long-term associations of blood pressure with risk of stroke and coronary heart disease.4–6 Additionally, the sizes of these effects were similar in various major subgroups of trials and patients, and seemed to be largely independent of differences in disease event rates among patients assigned control. The few studies that directly compared the effects of diuretics and β-blockers detected no clear differences in risk of stroke or coronary heart disease.10–12 Similarly, the few studies that had directly compared newer agents such as angiotensin-converting-enzyme (ACE) inhibitors and calcium antagonists with diuretics or β-blockers also failed to detect any clear differences.13–16 However, these studies were individually and collectively too small to detect any plausibly modest differences (eg, 10–15% differences in relative risk) in the cause-specific effects of the regimens compared.

In addition to this evidence from patients with high blood pressure, other relevant evidence was available at that time from trials of several of the same agents in other groups of patients. Overviews of randomised controlled trials of β-blockers among patients with coronary disease had shown reductions of about a fifth in the risk of reinfarction or death.17 Overviews of trials of ACE inhibitors among patients with heart failure or left-ventricular dysfunction showed reductions of between a quarter and a fifth in the risks of death, myocardial infarction, or hospital admission for heart failure,18,19 but few data were available about the effects of these agents among patients with preserved left-ventricular function. An overview of trials of ACE inhibitors among patients with acute myocardial infarction also showed relative reductions of about 7% in the risk of death.20 Overviews of trials of calcium antagonists among patients with coronary heart disease10,12,21 had provided some evidence suggestive of increased mortality with dihydropyridine agents (mainly short-acting nifedipine) and reduced mortality with non-dihydropyridine agents (diltiazem and verapamil), but the available data were too few to provide reliable evidence about any such separate effects or, indeed, any overall effect of calcium antagonists.10

Over the past 5 years, a new series of trials has been completed, and several other trials started in efforts to further elucidate the effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs on mortality and major cardiovascular morbidity in several
populations of patients including those with hypertension, diabetes mellitus, coronary heart disease, or renal disease. Before the results of any of these new trials were known, some studies were recognised as being too small individually to detect moderate, though potentially important, cause-specific effects of treatments or differences between treatment effects. Therefore, in July, 1995, the principal investigators from all of the large-scale trials that were in progress or in advanced stages of planning met and agreed to collaborate in a programme of prospectively planned overviews in which treatment effects and treatment differences would be estimated from the combined results of individual studies. Separate overviews were planned for trials that compared active treatment regimens with placebo, those that compared more intensive with less intensive blood-pressure-lowering strategies, and trials that assessed treatment regimens based on different drug classes. Estimates of treatment effects and treatment differences from these overviews should be subject to less random error than those from any one constituent trial, since they would be based on larger numbers of cause-specific outcomes. Additionally, by prospectively defining the studies to be included, the hypotheses to be addressed, and the outcomes to be studied, the estimates from these overviews might be less subject to bias than those from other overviews in which the studies, hypotheses, and outcomes are selected retrospectively with full knowledge of the individual study results. This report provides results from the first prospectively planned cycle of overviews in which the studies, hypotheses, and the outcomes to be studied, the estimates from these overviews had been included in these analyses, with the best of our knowledge, all trials satisfying the criteria listed above have been included in these analyses, with the full cooperation and participation of each principal investigator.

### Methods

#### Trial eligibility

The criteria for selection of trials for inclusion in these overviews were prespecified in the protocol for this project. Trials were eligible for inclusion if they met one of the following criteria: (1) randomisation of patients between a blood-pressure-lowering drug and placebo or other inactive control (irrespective of whether the intent of study treatment was to lower blood pressure and irrespective of whether patients were selected on the basis of high blood pressure); (2) randomisation of patients between different blood-pressure goals; or (3) randomisation of patients between antihypertensive regimens based on different blood-pressure-lowering agents. In addition, eligible trials were required to have a planned minimum of 1000 patient-years of follow-up in each randomised group, and not to have published or presented their main results before July, 1995.

Studies that included patients selected mainly on the basis of high blood pressure, diabetes mellitus, coronary heart disease, peripheral vascular disease, cerebrovascular disease, or renal disease were eligible for inclusion in these overviews. Trials involving patients selected mainly on the basis of other disorders such as acute myocardial infarction or heart failure were not included, since most of these trials were already the subject of other collaborative meta-analyses. For trials to be included in this first cycle of analyses, follow-up had to be complete and outcome data available by July, 2000. To the best of our knowledge, all trials satisfying the criteria listed above have been included in these analyses, with the full cooperation and participation of each principal investigator.

#### Data collection and verification

Data from individual study participants or summary data tables were sought with respect to baseline characteristics, rates of discontinuation of randomised agents. In addition, eligible trials were required to have a planned minimum of 1000 patient-years of follow-up in each randomised group, and not to have published or presented their main results before July, 1995.

Studies that included patients selected mainly on the basis of high blood pressure, diabetes mellitus, coronary heart disease, peripheral vascular disease, cerebrovascular disease, or renal disease were eligible for inclusion in these overviews. Trials involving patients selected mainly on the basis of other disorders such as acute myocardial infarction or heart failure were not included, since most of these trials were already the subject of other collaborative meta-analyses. For trials to be included in this first cycle of analyses, follow-up had to be complete and outcome data available by July, 2000. To the best of our knowledge, all trials satisfying the criteria listed above have been included in these analyses, with the full cooperation and participation of each principal investigator.

#### Prespecified comparisons and hypotheses

The comparisons prespecified in the protocol can be broadly divided into three groups. The first group comprises two separate comparisons of blood-pressure-lowering drugs with placebo: ACE-inhibitor-based regimens versus placebo, and calcium-antagonist-based
regimens versus placebo. The second group comprises comparisons of more intensive and less intensive blood-pressure-lowering regimens. The third group comprises three separate comparisons of different drug regimens intended to produce similar blood-pressure reductions: ACE-inhibitor-based regimens versus diuretic-based or \( \beta \)-blocker-based regimens; calcium-antagonist-based regimens versus diuretic-based or \( \beta \)-blocker-based regimens (with separate analyses of the main prespecified subgroups of calcium antagonists: dihydropyridine and non-dihydropyridine agents); and ACE-inhibitor-based regimens versus calcium-antagonist-based regimens. For each of these prespecified comparisons, the null hypothesis of no difference between regimens in their effects on primary study outcomes was tested.

**Study outcomes**

The primary outcomes for the foregoing comparisons were also prespecified: (1) stroke defined as a non-fatal stroke or death from cerebrovascular disease; (2) coronary heart disease defined as non-fatal myocardial infarction, death from coronary heart disease, or sudden death; (3) heart failure defined as heart failure causing death or requiring hospital admission; (4) death from any cardiovascular cause; (5) major cardiovascular events including stroke, myocardial infarction, heart failure, or death from any cardiovascular cause (as defined above); and (6) total mortality. Various secondary outcomes were also prespecified and these will be the subjects of other reports. In some instances, the definition of outcome events reported in publications from individual studies varied from those used in these analyses.

**Statistical analyses**

All analyses were done with tabular data that were either provided directly by study investigators or generated from data on individual patients sent to the collaboration coordinating centre. Analyses for each primary outcome were based on the first relevant outcome event experienced by a participant (irrespective of whether any other primary outcomes preceded this). Analyses were done with the “metan” routine in STATA (Stata statistical software version 6.0, Stata Corporation, College Station, TX, USA). Relative risks and 95% CI for each outcome were calculated separately for each of the studies according to the principle of intention to treat (relative risk=[patients with events in intervention group (ei)/total patients randomised to intervention group (ni)]/ [patients with events in control group (ec)/total patients randomised to control group (nc)]). Overall estimates of effect were calculated with a fixed-effect model, where the log relative risk for each trial was weighted by the reciprocal of the variance of the log relative risk (variance of the log relative risk=[1/(c-1/n)+1/(c-1/n)]). The assumption of homogeneity of treatment effect between different individual studies and subgroups of studies was tested with \( \chi^2 \) tests of homogeneity. Analyses of continuous variables such as age, blood pressure, and duration of follow-up were based on data from individual studies weighted by study or group size.

**Results**

**Characteristics of trials and patients included**

Outcome data were available from 15 studies that collectively included 74,969 patients (Table 1). The mean age of all participants was 62 years and 53% were male. Six studies provided outcome data from comparisons of an active agent with a placebo (five of which were among patients with cardiovascular disease or diabetes mellitus); three provided outcome data from comparisons of blood-pressure-lowering regimens of different intensities among hypertensive patients (two studies also involved comparisons of different active agents); and eight studies provided outcome data from comparisons of regimens based on different drug classes among patients with hypertension.

**Rate of discontinuation of study treatment and achievement of blood-pressure goals**

Data on the rate of discontinuation of randomised treatments were provided by five of the six trials comparing

---

### Table 2: Blood-pressure differences, proportion remaining on randomised treatments, and proportion achieving blood-pressure goals

<table>
<thead>
<tr>
<th>Acronym</th>
<th>SBP/DBP at entry (mm Hg)</th>
<th>Blood-pressure differences (treatment-control) during follow-up (mm Hg)</th>
<th>Proportion remaining on randomised treatment or achieving blood-pressure goal (%)</th>
<th>Duration of follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
<td>Study treatment</td>
<td>Control*</td>
</tr>
<tr>
<td>Trials comparing active treatment and placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOPE</td>
<td>139/79</td>
<td>-3</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>PART2</td>
<td>132/79</td>
<td>-6</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>QUIET</td>
<td>123/74</td>
<td>NA</td>
<td>NA</td>
<td>72</td>
</tr>
<tr>
<td>SCAT</td>
<td>130/78</td>
<td>-4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PREVENT</td>
<td>129/79</td>
<td>-5</td>
<td>69</td>
<td>78</td>
</tr>
<tr>
<td>SYST-EUR</td>
<td>174/86</td>
<td>-10</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>Trials comparing more intensive and less intensive blood-pressure-lowering strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABOC-hypertensive†</td>
<td>155/98</td>
<td>-6</td>
<td>49</td>
<td>89</td>
</tr>
<tr>
<td>HOT2</td>
<td>169/105</td>
<td>-3</td>
<td>55</td>
<td>80</td>
</tr>
<tr>
<td>UKPDS-HDS§</td>
<td>160/94</td>
<td>-10</td>
<td>56</td>
<td>91</td>
</tr>
<tr>
<td>Trials comparing regimens based on different drug classes*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPP†</td>
<td>161/99</td>
<td>-3</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>STOP-M†</td>
<td>194/98</td>
<td>&lt;1</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>UKPDS-HDS§</td>
<td>160/94</td>
<td>+1</td>
<td>78</td>
<td>65</td>
</tr>
<tr>
<td>INSIGHT§</td>
<td>173/99</td>
<td>-1</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>NICS EH†</td>
<td>172/94</td>
<td>+2</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>NORDIL</td>
<td>173/106</td>
<td>-1</td>
<td>77</td>
<td>92</td>
</tr>
<tr>
<td>VHAS</td>
<td>169/102</td>
<td>-1</td>
<td>78</td>
<td>77</td>
</tr>
<tr>
<td>ABOC-hypertensive†</td>
<td>155/98</td>
<td>-1</td>
<td>45</td>
<td>40</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure, DBP=diastolic blood pressure, NA=not available. *In all studies except ABOC, group randomised to \( \beta \)-blocker and/or diuretic therapy designated control. †Group randomised to calcium antagonist designated control, group randomised to ACE inhibitor designated control. Mean BP levels achieved: 132/78 mm Hg in more intensive vs 138/86 mm Hg in less intensive group. (Mean BP levels achieved: 144/82 mm Hg in more intensive vs 154/87 mm Hg in less intensive group. (Blood pressure difference (2/2 mm Hg) present between randomised groups at study entry. Group randomised to \( \beta \)-blockers/diuretics designated control, group randomised to ACE inhibitors or calcium antagonists designated treatment (in this table only). Elsewhere, groups randomised to ACE inhibitors or calcium antagonists are considered as separate treatment studies.

---

For personal use only. Not to be reproduced without permission of The Lancet.
hypertension (table 2).

whereas it was 174/86 mm Hg in the SYST-EUR trial,41

three trials comparing more intensive versus less intensive

treatment at the end of follow-up (mean 4·9 years). Data on

Discontinuation data were also provided by all eight trials

treated group

(treatment at the end of follow-up (mean 3·8 years).

(2 test for homogeneity.

2 test for homogeneity.

Figure 2: Comparisons of calcium-antagonist-based therapy

with placebo

p homog=p-value from χ² test for homogeneity.

Among the placebo-controlled trials of ACE inhibitors, differences in blood pressure between randomised groups during follow-up ranged from 3/1 mm Hg in HOPE44 to 6/4 mm Hg in PART 241 (weighted average in all trials: 3/1 mm Hg). In SYST-EUR, the difference in blood pressure between randomised groups during follow-up was 10/5 mm Hg (weighted average in the two placebo-controlled trials of calcium antagonists: 9/5 mm Hg).

In the trials comparing more intensive and less intensive blood-pressure-lowering strategies, differences in blood pressure between randomised groups during follow-up ranged from 3/3 mm Hg in HOT47 (most intensively treated group vs others) to 10/5 mm Hg in UKPDS-HDS42-45 (weighted average in all trials, 3/3 mm Hg).

In the trials comparing different active agents, the average blood pressure at entry was 171/101 mm Hg (table 2) and differences between randomised groups during follow-up were mostly small (0–3 mm Hg systolic). One of the larger differences was seen in the CAPPP study,29 however, a similar difference was present at entry, suggesting some non-random allocation of treatment rather than a difference in the effects of the treatments assigned. For this reason, in the overview comparing ACE-inhibitor-based regimens and diuretic-based or β-blocker-based regimens, separate analyses of outcome have been done: one including CAPP and one excluding it. In the other trials that compared ACE-inhibitor-based regimens and diuretic-based or β-blocker-based regimens, there was no difference in blood pressure during follow-up. There was also no difference
in blood pressure during follow-up in the trials comparing regimens based on dihydropyridine calcium antagonists with diuretic-based or β-blocker-based regimens, but there was a 3 mm Hg higher systolic pressure during follow-up among patients assigned treatment based on non-dihydropyridine calcium antagonists than among those assigned diuretic-based or β-blocker-based regimens.

**Effects on mortality and major cardiovascular morbidity**

Data on vital status at the end of follow-up were available for more than 95% of randomised patients in all trials. Complete data on total mortality, cardiovascular death, and coronary-heart-disease events were provided by all studies. One trial was unable to provide any data on non-fatal strokes, and two trials were unable to provide any data on heart-failure events. Several others were unable to provide data on non-fatal heart failure requiring hospital admission but were able to provide data on non-fatal heart failure defined on the basis of other objective criteria such as new signs and symptoms or the requirement for increased treatment, and these data have been included in the present analyses.

**Trials comparing active treatment and placebo**—Each study comparing ACE inhibitors with placebo (figure 1) was done among patients selected on the basis of a history of cardiovascular disease or diabetes mellitus rather than blood pressure. One study provided most of the data: of the 1860 cardiovascular events and the 1165 deaths from all causes, 88% and 90%, respectively, were seen in the HOPE study. Among patients assigned ACE-inhibitor therapy, there were significant reductions of 20–30% in stroke, coronary heart disease, major cardiovascular events, and cardiovascular death, as well as a reduction in total mortality. There was no significant reduction in the risk of heart failure (p=0·11), although the 95% CIs did not exclude a possible moderate advantage for patients assigned ACE-inhibitor therapy. For none of the outcomes was there any evidence of significant heterogeneity between the results of individual studies (all p>0·2).
Later trials compared more intensive and less intensive blood-pressure-lowering strategies. In the studies comparing blood-pressure-lowering regimens of different intensity, 1035 major cardiovascular events and 838 deaths from all causes were reported (figure 3). Among patients assigned the more intensive blood-pressure-lowering strategy, there were significant reductions of 15–20% in the risks of stroke, coronary heart disease, and major cardiovascular disease events. There were no significant reductions in coronary heart disease, heart failure, or total mortality (all p>0.1), but the 95% CIs did not exclude the moderate advantages for patients assigned calcium-antagonist-based therapy. For none of the outcomes was there any clear evidence of heterogeneity between the results of the two individual studies (all p>0.2).

Trials comparing more intensive and less intensive blood-pressure-lowering strategies—In the studies comparing blood-pressure-lowering regimens of different intensity, 1035 major cardiovascular events and 838 deaths from all causes were reported (figure 3). Among patients assigned the more intensive blood-pressure-lowering strategy, there were significant reductions of 15–20% in the risks of stroke, coronary heart disease, and major cardiovascular disease events. There were no significant reductions in coronary heart disease, heart failure, or total mortality (all p>0.1), but the 95% CIs did not exclude the moderate advantages for patients assigned more intensive therapy. For total mortality, there was some evidence of heterogeneity between the results of the two individual studies (all p>0.2).
Trials comparing different active treatments—Overall, in the trials comparing ACE-inhibitor-based regimens with diuretic-based or β-blocker-based regimens, 2022 major cardiovascular events and 1257 deaths from all causes were seen (figure 4). There were no detectable differences between randomised groups in the risks of any of the outcomes studied (all \( p > 0.1 \)), but for most of the comparisons, moderate differences in cause-specific outcomes (eg, a 10% difference in the relative risk of coronary heart disease) were not excluded by the 95% CIs. There was borderline significant evidence of heterogeneity between the results of individual studies for stroke (\( p = 0.05 \)), because of an apparent excess of strokes among patients assigned ACE-inhibitor-based treatment in CAPPP—a difference that could be largely explained by the higher initial blood pressure of patients assigned ACE-inhibitor-based therapy in this study. Exclusion of CAPPP from the overview analyses decreased the evidence of heterogeneity for this outcome, and did not materially alter the overall results for any outcome.

In the trials that compared calcium-antagonist-based regimens with diuretic-based or β-blocker-based regimens, 2485 major cardiovascular events and 1552 deaths from all causes were seen (figure 5). Among patients assigned calcium-antagonist-based therapy, there was a significant 13% lower risk of stroke (95% CI 2–23) than among those assigned diuretic-based or β-blocker-based therapy. Additionally, there was a 12% greater risk of coronary-heart-disease events of borderline significance (0–26) among those assigned calcium-antagonist-based therapy. There were no significant differences between randomised groups in the relative risks of heart failure, major cardiovascular events, cardiovascular deaths, or total mortality (all \( p > 0.1 \)). Although moderate differences in heart-failure risk were not excluded by the 95% CIs, all but minor differences in major cardiovascular events and total mortality were excluded. For all outcomes, there was no evidence of significant heterogeneity between individual studies (\( p > 0.25 \)) between subgroups defined by class of calcium antagonist (dihydropyridine vs non-dihydropyridine, all \( p > 0.4 \)), or between subgroups defined by primary control treatment (diuretic alone vs diuretic or β-blocker, all \( p > 0.08 \)).

Only two trials directly compared ACE-inhibitor-based regimens and calcium-antagonist-based regimens (figure 6), and most of the data were provided by one of these studies: of the 1178 major cardiovascular events and 774 deaths from all causes in these two trials, 93% and 96%, respectively, were observed in the STOP-2 study. In another study (the ABCD trial, hypertensive subgroup), randomised treatment was discontinued before the scheduled end of follow-up because of an apparently extreme difference in coronary heart disease in favour of patients assigned the ACE inhibitor (data are not yet available from the non-hypertensive subgroup of this trial). The combined analysis suggested a reduced risk of coronary-heart-disease events among the patients assigned ACE-inhibitor-based therapy, but for this outcome and for major cardiovascular events, there was significant heterogeneity (\( p = 0.01 \) and 0.04, respectively) between the results of the two studies. Although the 95% CIs for coronary heart disease in STOP-2 did not exclude possible moderate advantages for ACE-inhibitor-based therapy, the results of the three trials of calcium antagonists exclusively, there was no clear evidence of differences in coronary heart disease or heart failure. However, the estimates of treatment effect from this predominantly hypertensive population of patients largely preclude adverse effects of the magnitude suggested by earlier overviews of other trials of dihydropyridine calcium antagonists exclusively, there was no clear evidence of differences in coronary heart disease or heart failure. For this reason, the combined analysis suggested a reduced risk of coronary heart disease or heart failure among patients with left-ventricular dysfunction or acute myocardial infarction. Although there was no clear evidence of a reduction in the risk of heart failure as defined, the 95% CIs did not exclude possible benefits of moderate magnitude among those assigned ACE-inhibitor therapy. The number of endpoints and the widespread prehospital use of ACE inhibitors in patients with any manifestation of heart failure would have limited the ability of this overview to detect any true benefits of treatment. Several other randomised trials have provided clear evidence that ACE inhibitors prevent heart failure in other high-risk situations, and in the largest of the studies included in this overview there was evidence of a benefit of ACE inhibitors for heart failure when a wider definition of this outcome was used.

The overview of placebo-controlled trials of calcium antagonists shows that these agents reduced the risks of stroke and major cardiovascular events by about 30–40%, mainly among elderly patients with isolated systolic hypertension among whom study treatment reduced blood pressure by much the same amount as that observed in earlier trials of diuretic-based or β-blocker-based therapy. In this overview, which involved studies of dihydropyridine calcium antagonists exclusively, there was no clear evidence of reductions in coronary heart disease or heart failure. However, the estimates of treatment effect from this predominantly hypertensive population of patients largely preclude adverse effects of the magnitude suggested by earlier overviews of other trials of dihydropyridine agents (mainly short-acting nifedipine) among patients with acute myocardial infarction or unstable angina. For these major cardiac outcomes, there were still too few events included in the present overview to detect plausibly moderate cause-specific effects, and the 95% CIs for estimates of treatment effects do not exclude the possible existence of similar benefits for coronary heart disease or heart failure.

Discussion The results of the first cycle of analyses from this programme of prospectively designed overviews show that benefits of blood-pressure-lowering drugs are not limited to regimens based on diuretics or β-blockers. The overview of placebo-controlled trials of ACE inhibitors shows that, with only a modest reduction in blood pressure, these agents decreased the risks of stroke, coronary heart disease, and major cardiovascular events by 20–30% among high-risk patients selected on the basis of a history of cardiovascular disease or diabetes mellitus. Although patients in these trials were not selected on the basis of high blood pressure, a large number of individuals with treated hypertension were included, and in the largest of the studies, there were similar proportional benefits of ACE inhibitors among those with or without hypertension. The demonstration of benefits of ACE inhibitors for stroke and risk of coronary heart disease in the heterogeneous high-risk populations included in this overview extend the evidence of benefits beyond those reported by other overviews of randomised controlled trials of ACE inhibitors among patients with left-ventricular dysfunction or acute myocardial infarction.

Although there was no clear evidence of a reduction in the risk of heart failure as defined, the 95% CIs did not exclude possible benefits of moderate magnitude among those assigned ACE-inhibitor therapy. The small number of endpoints and the widespread prehospital use of ACE inhibitors in patients with any manifestation of heart failure would have limited the ability of this overview to detect any true benefits of treatment. Several other randomised trials have provided clear evidence that ACE inhibitors prevent heart failure in other high-risk situations, and in the largest of the studies included in this overview there was evidence of a benefit of ACE inhibitors for heart failure when a wider definition of this outcome was used.

The overview of placebo-controlled trials of calcium antagonists shows that these agents reduced the risks of stroke and major cardiovascular events by about 30–40%, mainly among elderly patients with isolated systolic hypertension among whom study treatment reduced blood pressure by much the same amount as that observed in earlier trials of diuretic-based or β-blocker-based therapy. In this overview, which involved studies of dihydropyridine calcium antagonists exclusively, there was no clear evidence of reductions in coronary heart disease or heart failure. However, the estimates of treatment effect from this predominantly hypertensive population of patients largely preclude adverse effects of the magnitude suggested by earlier overviews of other trials of dihydropyridine agents (mainly short-acting nifedipine) among patients with acute myocardial infarction or unstable angina. For these major cardiac outcomes, there were still too few events included in the present overview to detect plausibly moderate cause-specific effects, and the 95% CIs for estimates of treatment effects do not exclude the possible existence of similar benefits for coronary heart disease or heart failure.
to those shown in the trials of blood-pressure lowering with diuretic-based and β-blocker-based regimens among patients with hypertension.1-5,6

The overviews comparing the effects of more intensive and less intensive blood-pressure-lowering strategies provided some evidence of potentially important differences between treatment regimens of differing intensity. These trials based on randomised controlled trials of ACE inhibitors, calcium antagonists, and β-blockers, patients assigned the lowest blood-pressure targets (diastolic blood pressure ≤75 to <85 mm Hg) experienced lower risks of stroke, coronary heart disease, and major cardiovascular events, although the exact sizes of all such differences remain uncertain because of the wide 95% CIs. Nevertheless, the results of these studies are broadly consistent with the effects predicted from observational epidemiological studies of the associations of blood pressure with cardiovascular disease risks and from the previous randomised controlled trials of blood-pressure-lowering drugs among patients with hypertension.1,7 Although we cannot determine from these overviews the level of blood pressure at which disease risks are most reduced, the benefits seen were achieved with blood-pressure levels substantially lower than those routinely achieved in clinical practice.

The overviews of trials comparing blood-pressure-lowering regimens based on different drugs provide some evidence that there may be moderate, though potentially important, differences between drug classes in their effects on cause-specific outcomes. In particular, the results of the overview comparing calcium-antagonist-based regimens with diuretic-based or β-blocker-based regimens suggest a lower risk of stroke and a greater risk of coronary heart disease among patients assigned calcium antagonists. Since these trends were similar in trials of dihydropyridine and non-dihydropyridine calcium antagonists, the results provide no clear support for the hypothesis that there may be qualitatively different effects of these agents on coronary risks.1,7,8 Additionally, the results provide no clear evidence of a deficit in stroke avoidance with non-dihydropyridine agents, despite their lesser effect on systolic blood pressure in the trials included in this overview. However, for stroke and coronary heart disease, the 95% CIs were wide and the size of any true differences between calcium-antagonist-based regimens and diuretic-based or β-blocker-based regimens could not be determined reliably.

In the overview comparing ACE-inhibitor-based regimens with calcium-antagonist-based regimens, extreme reductions in the risk of coronary heart disease among patients assigned ACE-inhibitor-based therapy were seen in one small trial with very few events,9,10 but no such difference was detected in the other much larger study with many more events.11 The small trial was stopped early on the basis of an apparent difference in fatal or non-fatal myocardial infarction, and so its results could provide an inflated estimate of any real treatment difference,12 which might explain the heterogeneity. For these reasons, the combined analysis of coronary-heart-disease events from these two trials does not provide reliable evidence of a difference between ACE-inhibitor-based and calcium-antagonist-based regimens in their effects on this outcome. There was also some evidence of a reduced risk of heart failure among patients assigned ACE-inhibitor-based therapy (with all of the evidence provided by the larger of the two trials), but once again, the 95% CI were wide and the true size of any difference between regimens could not be determined reliably. In the overview comparing ACE-inhibitor-based regimens with diuretic-based or β-blocker-based regimens, there was no clear difference between groups in any of the outcomes studied. However, while all but small differences in major cardiovascular events were excluded by the 95% CIs, plausibly moderate differences in cause-specific outcomes such as heart failure could not be excluded.

In most of the trials included in these overviews, only about three-quarters of all randomised patients remained on assigned treatment at the end of follow-up. Such non-adherence makes it likely that analyses done by intention to treat, although keeping important biases to a minimum, will underestimate the effects of individual treatments and the differences between treatments that would be seen had there been full adherence to the randomised regimens.13 In the overview of active treatments versus placebo, withdrawal of treatment from patients assigned active therapy might have resulted in estimates of treatment effect that were at least an eighth smaller than might have been achieved with full adherence (assuming roughly constant rates of withdrawal throughout follow-up). The active treatment of some of those withdrawn from placebo would have further reduced the estimate of treatment effects, but to a lesser extent since the proportion beginning such treatment was small. Similarly, in the overviews comparing more intensive and less intensive blood-pressure-lowering strategies and different active regimens, non-adherence to randomised therapy and failure to reach blood-pressure goals could have obscured some moderate differences that might have otherwise been seen, and is likely to have resulted in underestimation of the differences that were detected.

By decreasing random error through the combination of results from several trials addressing the same question, and, by keeping bias to a minimum through prespecification of the studies to be included, hypotheses to be addressed and outcomes to be studied, the probability of the evidence provided by these overviews should be increased. In particular, these overviews will provide more reliable evidence than that provided by analyses based on published data from the same trials (since this was incomplete) and analyses in which decisions about the studies to include and outcomes to be investigated were all made after publication of individual trial results (when knowledge of the results could influence the decisions about the design and objectives of the analysis). However, although the results of these prospectively planned overviews provide answers to some of the questions they were designed to address, uncertainty remains about others. There are some unresolved issues about the cause-specific effects of treatments compared with none, such as the persisting uncertainty about effects of calcium antagonists on coronary heart disease and heart failure in hypertensive patients and others. There are other unresolved issues about differences between active regimens in their cause-specific effects. For example, although there is clear evidence from the placebo-controlled trials that, with only modest reductions in blood pressure, ACE inhibitors confer marked beneficial effects on the risks of major cardiovascular events in high-risk patients, there is no clear evidence from other trials in hypertensive patients and others. The effects of ACE-inhibitor-based therapy are any greater than those of diuretic-based or β-blocker-based regimens. Additionally, although there is clear evidence of benefits of calcium-antagonist-based regimens for stroke and major cardiovascular events in...
older hypertensive patients, the evidence suggestive of greater benefits for stroke and lesser benefits for coronary heart disease with calcium-antagonist-based regimens than with diuretic-based or β-blocker-based regimens is not sufficiently reliable to allow precise assessments of the differing balance of benefits and risks that might be experienced by patients at varying risks of stroke or coronary disease.

Resolution of many of these unresolved issues should be provided by results of ongoing or planned trials, and future rounds of analyses from this programme of prospectively-designed observations. Such analyses will eventually include data from at least 200 000 further patients from at least 25 randomised trials. The results should therefore increase the precision of estimates of cause-specific attributable benefits and harms, the effects of more intensive and less intensive blood-pressure-lowering strategies and between the effects of regimens based on ACE inhibitors, calcium antagonists, and diuretics or β-blockers. The results should also provide new estimates of the effects of angiotensin II antagonists compared with other agents, as well as substantially increasing the evidence available about the effects of various blood-pressure-lowering drugs in important subgroups of patients, such as those with diabetes mellitus, renal disease, or cerebrovascular disease. In this way, the collaborative programme should continue to provide important evidence about the treatment regimens likely to provide the greatest benefits to patients in various different circumstances.


Statistical analysis—C Algert, M Woodward.

Acknowledgments
We thank T Agnew, A Brennan, T Craven, L Dunn, L Hemphill, S Julius, J Lamke, M Magri, C Palmer, J Pogue, C Reid, R Scott, M Sou, J Sreatham, L This, N Vancini, and I Warnold for their comments and contributions to this report.

This project is done under the aegis of the WHO-International Society of Hypertension Liaison Committee. The project was supported by grants and awards provided by the National Health and Medical Research Council of Australia, the Medical Foundation of the University of Sydney, the National Heart Foundation of Australia, the Health Research Council of New Zealand, the British Heart Foundation, the International Society of Hypertension, AstraZeneca, Bayer AG, Bristol Myers-Squibb, GlaxoWellcome SpA, Hoechst AG, Merck, Pfizer, Searle and Servier.

References


