Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers for Coronary Heart Disease and Stroke Prevention

Paolo Verdecchia, Gianpao Reboldi, Fabio Angeli, Roberto Gattobigio, Maurizio Bentivoglio, Lutgarde Thijs, Jan A. Staessen, Carlo Porcellati

Abstract—We investigated whether protection from coronary heart disease (CHD) and stroke conferred by angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) in hypertensive or high-risk patients may be explained by the specific drug regimen. We extracted summary statistics regarding CHD and stroke from 28 outcome trials that compared either ACEIs or CCBs with diuretics, β-blockers, or placebo for a total of 179 122 patients, 9509 incident cases of CHD, and 5971 cases of stroke. CHD included myocardial infarction and coronary death. In placebo-controlled trials, ACEIs decreased the risk of CHD (P<0.001), and CCBs reduced stroke incidence (P<0.001). There were no significant differences in CHD risk between regimens based on diuretics/β-blockers and regimens based on ACEIs (P=0.46) or CCBs (P=0.52). The risk of stroke was reduced by CCBs (P=0.041) but not by ACEIs (P=0.15) compared with diuretics/β-blockers. Because heterogeneity between trials was significant, we investigated potential sources of heterogeneity by meta-regression. Examined covariates were the reduction in systolic blood pressure (BP), drug treatment (ACEIs versus CCBs), their interaction term, sex, age at randomization, year of publication, and duration of treatment. Prevention of CHD was explained by systolic BP reduction (P<0.001) and use of ACEIs (P=0.028), whereas prevention of stroke was explained by systolic BP reduction (P=0.001) and use of CCBs (P=0.042). These findings confirm that BP lowering is fundamental for prevention of CHD and stroke. However, over and beyond BP reduction, ACEIs appear superior to CCBs for prevention of CHD, whereas CCBs appear superior to ACEIs for prevention of stroke. (Hypertension. 2005;46:386-392.)

Key Words: antihypertensive therapy • myocardial infarction • stroke

Outcome trials showed that a persistent reduction in blood pressure (BP) reduces the risk of coronary heart disease (CHD) and stroke.1,2 The antihypertensive drugs tested in these trials have different pharmacological properties and mechanisms of action. Experimental studies and clinical trials with intermediate outcomes suggested that ancillary properties of antihypertensive drugs3–6 might play a role in the prevention of cardiovascular complications independent of BP. In the second cycle of meta-analyses of the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC),7 angiotensin-converting enzyme inhibitors (ACEIs) reduced the risk of major cardiovascular events not dissimilarly from diuretics and β-blockers together, as well as from calcium channel blockers (CCBs). Because the BP reduction was slightly lesser (1 to 2 mm Hg) in patients treated with ACEIs than in those treated with other drugs, ancillary properties of ACEIs might have influenced cardiovascular outcome with mechanisms partially independent of BP lowering. The BPLTTC analysis also showed a trend toward a lesser risk of stroke with regimens based on CCBs.7

In a previous meta-regression analysis, we demonstrated that the benefit of antihypertensive drug treatment was largely attributable to BP reduction.8,9 In the present analysis, we refined our meta-regression approach. Including the most recent evidence from clinical trials, we reinvestigated the BP-dependent and BP-independent effects of ACEIs and CCBs in the prevention of CHD and stroke in patients with hypertension or high cardiovascular risk.

Materials and Methods
We searched for randomized controlled outcome trials that met all of the following prespecified criteria: (1) comparison between old antihypertensive drugs (diuretics, β-blockers) or placebo with new drugs (ACEIs or CCBs); (2) publication before December 31, 2004, in peer-reviewed journals indexed in Medline; (3) inclusion of

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patients with hypertension or high cardiovascular risk but without overt heart failure at entry; (4) prespecified and well-defined end points, including CHD and stroke, the former being a composite of myocardial infarction and coronary death; (5) measurement of systolic BP at baseline and follow-up; (6) follow-up of ≥2 years; and (7) sample size of ≥100 subjects. We searched for eligible studies through Medline using research methodology filters. The final search identified 28 trials, which fulfilled all inclusion criteria. Two of us (P.V. and F.A.) extracted the data on the basis of an intention-to-treat approach. We accepted the definition of CHD and stroke as reported in the individual reports.

To also investigate the effects of BP lowering per se, our quantitative review included placebo-controlled as well as actively controlled trials. Reference treatment consisted of old antihypertensive drugs (diuretics or β-blockers) or placebo. Experimental treatment was based on new antihypertensive drugs (ACEIs or CCBs). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for CHD and stroke for each trial separately and for combinations of studies according to fixed- and random-effect models. We tested the null-hypothesis of homogeneity across individual studies by the Q test. In the presence of significant heterogeneity, we used a random-effect model. We assessed the influence of individual studies on pooled effect sizes by excluding 1 study at the time according to Tobias’ method. If the point estimate of the combined effect size with 1 study omitted lies outside the CI of the overall estimate with all available trials contributing, then the study in question had an excessive influence. We tested for publication bias using the methods described by Begg and Egger. We expressed our results as mean±SD unless otherwise indicated. All P values are for 2-sided tests. Analyses were done using the Stata version 8.2 (StataCorp LP) and SAS version 8.2 (SAS Institute Inc) packages.

Metaregression Analysis

To investigate potential sources of heterogeneity between different trials, we performed a weighted random-effect metaregression analysis using the SAS mixed-model procedure and the Stata macro “metareg.” Potential effect modifiers included: (1) the baseline-corrected differences in achieved systolic BP (follow-up minus baseline) between regimens based on either ACEIs or CCBs versus the reference group; (2) drug regimen (ACEIs versus CCBs); (3) the interaction term between the change in systolic BP and the drug regimen in relation to outcome; (4) duration of follow-up; (5) sex distribution; (6) age at randomization; and (7) year of publication. We used metaregression analysis to test the relationship between outcome and these explanatory variables. For the metaregression analysis, ORs were logarithmically transformed and weighted by the inverse of the sum of the within-trial and residual between-trial variance. Final models only included covariates that significantly contributed to the between-study heterogeneity.

Results

Table 1 shows the main characteristics of the 28 eligible trials, which included 179 122 patients. Overall, 4810 cases of CHD and 3044 strokes occurred among 92 446 patients randomized to ACEIs or CCBs. The 86 676 control patients randomized experienced 4699 and 2927 incident cases of CHD and stroke, respectively. In sensitivity analyses, none of the trials had a significant influential effect on the overall estimates for CHD or stroke. None of the tests for publication bias achieved significance (P>0.10).

Coronary Heart Disease

Overall (Figure 1), treatment with ACEIs or CCBs compared with control (diuretics/β-blockers or placebo) resulted in a 7% lower risk of CHD (OR, 0.93; 95% CI, 0.87 to 0.99; P=0.024), with significant heterogeneity across the trials (P=0.013). We also calculated pooled estimates for specific comparisons: ACEIs versus placebo, ACEIs versus old drugs, CCBs versus placebo, and CCBs versus old drugs. Treatment based on ACEIs was associated with a 21% lesser risk of CHD (OR, 0.79; CI, 0.71 to 0.88; P<0.001) compared with placebo, whereas the odds for CHD did not differ between the regimens based on ACEIs and the regimens based on diuretics/β-blockers (OR, 0.97; CI, 0.90 to 1.05; P=0.46). Regimens based on CCBs were associated with a nonsignificant 17% lower risk of CHD (OR, 0.83; CI, 0.67 to 1.03; P=0.10) compared with placebo. For CHD, there were no significant differences between the regimens based on CCBs and those based on diuretics/β-blockers (OR, 1.02; CI, 0.96 to 1.09; P=0.52). The test of heterogeneity between subgroups was statistically significant (P=0.002).

Stroke

Treatment with ACEIs or CCBs conferred an 11% reduction in the risk of stroke (OR, 0.89; 95% CI, 0.82 to 0.97; P=0.005) compared with diuretics/β-blockers or placebo (Figure 2). Use of ACEIs was associated with a significant decrease in stroke incidence (OR, 0.84; 95% CI, 0.72 to 0.97; P=0.020) compared with placebo. The risk of stroke was similar in treatment with ACEIs compared with diuretics/β-blockers (OR, 1.09; 95% CI, 0.96 to 1.24; P=0.15). Treatment with CCBs lowered the risk of stroke by 35% (OR, 0.65; CI, 0.55 to 0.78; P<0.001) compared with placebo and by 8% compared with old drugs (OR, 0.92; CI, 0.85 to 0.99; P=0.041). There was heterogeneity (P<0.001) among the pooled results of these subgroups of trials.

Metaregression Analysis

Because of the heterogeneity among the trials, we modeled the risk of CHD and stroke on the between-group differences in achieved systolic BP (baseline−follow-up/experimental−control), drug treatment (ACEIs versus CCBs), the interaction term between BP difference and drug treatment, and other potential effect modifiers. Larger differences in systolic BP predicted greater reductions in the risk of CHD (Table 2; Figure 3) and stroke (Table 2; Figure 4). As shown in Table 2, BP reduction had similar effects on the prevention of CHD and stroke (15% per 10 mm Hg). Moreover, independent of the BP difference, ACEIs were superior to CCBs for prevention of CHD (P=0.028), whereas CCBs were superior to ACEIs for prevention of stroke (P=0.042). None of the other potentially explanatory variables achieved statistical significance. In particular, neither for CHD (P=0.10) nor for stroke (P=0.27) did the interaction term between systolic BP reduction and drug treatment achieve statistical significance. The between-trial variance explained by our metaregression models was 87% for CHD and 55% for stroke. Notably, the differences in systolic BP gave the largest contribution to the amount of explained variance for CHD (62%) as well as stroke (66%).

Discussion

This quantitative overview confirms that ACEIs and CCBs protect against CHD and stroke mainly by reducing BP. In addition, over and beyond BP lowering, ACEIs appear
superior to CCBs for the prevention of CHD, whereas CCBs appear superior to ACEIs for protection against stroke. These data have relevant clinical implications in suggesting that the ancillary properties of these drug classes might provide specific contributions to the prevention of CHD and stroke, respectively. Other potential modifiers or confounders of the outcome results, including the patients’ age and sex distribution and year of publication of the trials, did not contribute to the variance explained by our metaregression models.

Role of BP Lowering
In a metaregression analysis of 27 major trials, we demonstrated previously that BP lowering was the major determinant of the benefits of antihypertensive treatment on all-cause and cause-specific cardiovascular outcomes. The 2003 update of this meta-analysis provided consistent results. Along similar lines, the BPLTTC reported that in studies comparing tight to usual BP control, the reduction in CHD and stroke produced by antihypertensive treatment increased with lower BP targets, and that in other trials, it was proportional to the differences in the achieved systolic BP between randomized groups. However, none of the previously published metaregression studies investigated whether, for the same degree of BP lowering, prevention of stroke was superior to the protection against CHD. We found that a 10 mm Hg decrease in systolic BP antihypertensive treatment prevented CHD and stroke to a similar relative extent. The absolute benefit (ie, the number of patients to be treated to prevent 1 event) depends

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Drug</th>
<th>No. of Patients (exp/ref)</th>
<th>No. of Male Subjects</th>
<th>Age (years)</th>
<th>Follow-Up (years)</th>
<th>No. of CHD (exp/ref)</th>
<th>No. of Stroke (exp/ref)</th>
<th>ΔSBP</th>
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<tr>
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<td>12951</td>
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<td>796/1362</td>
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<td>2981</td>
<td>72</td>
<td>4</td>
<td>173/195</td>
<td>112/167</td>
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<td>962</td>
<td>58</td>
<td>2</td>
<td>14/19</td>
<td>8/12</td>
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<tr>
<td>CAPP113</td>
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<td>48/52</td>
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<td>410</td>
<td>56</td>
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<td>21/17</td>
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<td>308/309</td>
<td>506</td>
<td>61</td>
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<td>7/4</td>
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<td>6797</td>
<td>64</td>
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<td>222/220</td>
<td>71/92</td>
<td>3</td>
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<td>4626</td>
<td>64</td>
<td>3</td>
<td>67/102</td>
<td>150/255</td>
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</table>

exp indicates experimental; ref, reference.
on the rate of CHD or stroke in the population to which the present findings might be extrapolated. The present analysis also includes actively controlled trials in which all randomized patients received BP drugs as well as trials involving normotensive patients with high cardiovascular risk. These characteristics may have blunted the divergence between the regression lines of CHD and stroke in relation to BP gradients. Moreover, the disclosure of fully divergent relations might require a range of systolic BP gradients larger than those explored in the present overview (−5 to 15 mm Hg).

On the other hand, CHD prevention and BP reduction might be more closely related than conceived previously, particularly in high-risk patients. For example, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, hypertensive patients, of whom 46% and 20% had a history of CHD or stroke, respectively, were randomized to an angiotensin II receptor antagonist or a CCB. Over the whole follow-up (median 4.9 years), systolic BP was on average 2.2 mm Hg higher on valsartan than amlodipine, and the rates of myocardial infarction and stroke were similarly elevated.
on valsartan by 19% and 15%, respectively. In the HOPE study, in which systolic BP was lower on ramipril than it was on placebo by 4 mm Hg at 1 month, 3 mm Hg at 2 years, and 3 mm Hg at the end of the study, incidence of myocardial infarction and stroke was lower by 20% and 32%, respectively, in the ACEI group. The central role of BP reduction also emerged in the PROGRESS study (Perindopril Protection Against Recurrent Stroke Study), in which systolic BP fell versus control by 5 and 12 mm Hg in the perindopril and perindopril plus indapamide strata, respectively, with a significant risk reduction for stroke only in the ACEI plus diuretic group.

Ancillary Properties of ACEIs and CCBs

In some but not all clinical studies, the renin-angiotensin system showed an association with the risk of CHD. ACEIs possess pharmacological properties, which could delay the development of atherosclerosis and increase plaque stability. In addition, ACEIs may shift the fibrinolytic balance from coagulation to lysis by reducing the angiotensin II-dependent production and secretion of plasminogen activator inhibitor-1. Results of our overview support the hypothesis that for the same degree of BP lowering, ACEIs might be superior to CCBs in the protection against incident or recurrent CHD. Conversely, compared with diuretics/β-blockers or placebo, CCBs might provide better protection against stroke than ACEIs. The mechanisms underlying the specific protection against stroke conferred by CCBs remain to be clarified. Lacidipine, a dihydropyridine CCB, reduced progression of carotid atherosclerosis independent of the reduction in clinic and ambulatory BP. The double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial already showed a 50% reduction in the incidence of dementia after a median follow-up of 2.0 years, a benefit overwhelmingly attributable to the prevention of Alzheimer’s disease.

Study Limitations

The benefits of ACEIs for prevention of stroke might have been underestimated because placebo was given on top of active medications in comparative trials with ACEIs, whereas placebo coincided with a no-treatment strategy in 3 trials. In addition, the latter studies have been performed in cohorts at high risk of stroke, thus providing a potential framework to maximize the benefits of CCBs. The same argument also applies for CHD in 10 trials, in which ACEIs were tested against placebo or older drugs. Other limitations inherent to all meta-analyses performed without access to individual patient data originate from potential differences between trials in the definition and validation of end points and in the clinical characteristics of the randomized patients. Finally, we did not execute a metaregression analysis for heart failure. Our overview was focused on CHD and stroke. Some heterogeneity exists across trials in the criteria used for diagnosis of heart failure.

Perspectives

In the present overview of 28 outcome trials, which compared new antihypertensive drugs (ACEIs or CCBs) with old antihypertensive drugs (diuretics or β-blockers) or placebo,
the risk of CHD was decreased by the BP reduction and the use of ACEIs. Furthermore, BP reduction and the use of CCBs independently reduced the incidence of stroke. The important clinical implication from our overview is that ACEIs might confer specific protection against CHD, and CCBs might confer specific protection against stroke, independent of their antihypertensive effect. Thus, the combination between these 2 classes of drugs could offer the rationale for a broad-spectrum cardiovascular prevention. However, BP lowering holds center stage in the prevention of major cardiovascular complications in patients with hypertension or high cardiovascular risk.

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