Therapeutic Benefits of ACE Inhibitors and Other Antihypertensive Drugs in Patients With Type 2 Diabetes

**OBJECTIVE** — To assess whether ACE inhibitors are superior to alternative agents for the prevention of cardiovascular events in patients with hypertension and type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — This study is a review and meta-analysis of randomized controlled trials that included patients with type 2 diabetes and hypertension who were randomized to an ACE inhibitor or an alternative drug, were followed for ≥2 years, and had adjudicated cardiovascular events.

**RESULTS** — A total of 4 trials were eligible. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial (n = 470) compared enalapril with nisoldipine, the Captopril Prevention Project (CAPPP) (n = 572) compared captopril with diuretics or β-blockers, the Fosinopril Versus Amlodipine Cardiovascular Events Trial (FACET) (n = 380) compared fosinopril with amlodipine, and the U.K. Prospective Diabetes Study (UKPDS) (n = 758) compared captopril with atenolol. The cumulative results of the first 3 trials showed a significant benefit of ACE inhibitors compared with alternative treatments on the outcomes of acute myocardial infarction (63% reduction, P < 0.001), cardiovascular events (51% reduction, P < 0.001), and all-cause mortality (62% reduction, P = 0.010). These findings were not observed in the UKPDS. The ACE inhibitors did not appear to be superior to other agents for the outcome of stroke in any of the trials. None of the findings were explained by differences in blood pressure control.

**CONCLUSIONS** — Compared with the alternative agents tested, ACE inhibitors may provide a special advantage in addition to blood pressure control. The question of whether atenolol is equivalent to captopril remains open. Conclusive evidence on the comparative effects of antihypertensive treatments will come from large prospective randomized trials.

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**Abbreviations:** ABCD, Appropriate Blood Pressure Control in Diabetes; CAPPP, Captopril Prevention Project; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Trial; HOPE, Heart Outcomes Prevention Evaluation; RR, relative risk; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
The following elements were abstracted: design, sample size, randomized treatments, follow-up time, average age, sex distribution, average BMI, proportion of participants with macroalbuminuria, duration of diabetes, baseline systolic and diastolic arterial pressures, and the number of events (including acute myocardial infarction, stroke, combined cardiovascular events, and all-cause mortality) occurring in each treatment group.

The initial search identified 195 articles. Of those, 4 trials met all of the inclusion criteria. Those trials were the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (7), the diabetic group of the Captopril Prevention Project (CAPPP) (8), the Fosinopril Versus Amlodipine Cardiovascular Events Trial (FACET) (9), and the UKPDS (Table 1) (10). The recently published Swedish Trial in Old Patients with Hyper-tension-2 compared the use of β-blockers or diuretics with the use of ACE inhibitors or Ca2+ antagonists and was not included because outcome data in the subgroup of patients with diabetes in that study were not published and were not available from the authors (B. Dahlof, personal communication) (11).

For the combined outcome of cardiovascular events, we adopted the definition used in each trial. In the ABCD trial, the cardiovascular events included cardiovascular death, fatal and nonfatal acute myocardial infarction, congestive heart failure requiring hospitalization, fatal or nonfatal stroke, and pulmonary infarction. Because the number of events in patients with diabetes was not reported in the CAPPP, we estimated these numbers by using the sample size, the relative risk (RR) (95% CI), and the P value of the difference between the 2 treatment groups. In the CAPPP, the cardiovascular events included cardiovascular deaths, fatal and nonfatal acute myocardial infarction, and fatal or nonfatal stroke. In the FACET, the cardiovascular events included fatal and nonfatal acute myocardial infarction, fatal and nonfatal stroke, and angina requiring hospitalization. In the UKPDS, the combined endpoint of cardiovascular events was not reported. We calculated the total number of cardiovascular events by adding the number of fatal and nonfatal acute myocardial infarctions and strokes, the number of congestive heart failure events, and the number of sudden deaths. Because more than 1 event may have occurred in a single patient, this method is likely to have slightly overestimated the number of patients with cardiovascular events in the UKPDS.

The overall relative risk (85% CI) of each outcome was calculated with Petos method (12). Cochran's test for heterogeneity was used to assess the extent to which the differences among the trial results were because of random fluctuations (13).

**RESULTS** — In the 4 eligible trials (the ABCD trial, the CAPPP, the FACET, and the UKPDS), the total number of participants was 2,180 (1,133 randomized to an ACE inhibitor and 1,047 randomized to an alternative active agent) with a total follow-up experience of 13,300 person-years. The participants' characteristics according to treatment are shown in Table 1. In the ABCD trial, the FACET, and the UKPDS, systolic (Fig. 1) and diastolic blood pressure decreased significantly with both treatments. In the ABCD trial and the UKPDS, no significant differences were evident in blood pressure control among the randomized treatment groups. In the FACET, the patients randomized to amldopine achieved a significantly lower systolic blood pressure level than patients randomized to fosinopril. Data on blood pressure control in the diabetic patients of the CAPPP have not been reported.

The number of events by treatment group in each trial is shown in Table 2, and the relative risks (95% CIs) of outcomes for ACE inhibitors versus other agents are depicted in Fig. 2. In the ACE inhibitor group, the risk of acute myocardial infarction was significantly decreased in the ABCD trial and the CAPPP, was nonsignificantly lower in the FACET, and was non-significantly higher in the UKPDS compared with the alternative treatment. For the outcome of stroke, no significant differences were evident among treatments in any of the trials. In the ACE inhibitor group, the risk of combined cardiovascular events was significantly decreased in the ABCD trial, the CAPPP, and the FACET, and was nonsignificantly increased in the UKPDS compared with the alternative treatment; the risk of all-cause mortality was significantly decreased in the ABCD trial and the CAPPP, was nonsignificantly lower in the FACET, and was non-significantly higher in the UKPDS compared with the alternative treatment.
Therapeutic benefits of ACE inhibitors

Figure 1—Systolic blood pressure changes during follow-up according to treatment in the ABCD trial, the FACET, and the UKPDS. The data of the CAPPP have not been reported.

were 0.73 (0.54–0.99), 0.86 (0.59–1.26), 0.77 (0.61–0.91), and 0.85 (0.64–1.12), respectively. To identify potential outliers, we tested the heterogeneity of the results of the trials for individual outcomes of interest through iterative analyses. The test for heterogeneity was significant for the outcomes of acute myocardial infarction and cardiovascular events when the data of the UKPDS were combined with the other 3 trials (P < 0.001 for both outcomes) but not when the UKPDS was excluded from the meta-analysis. Thus, only the data for the ABCD trial, the CAPPP, and the FACET were used in the formal meta-analytic calculations. When the data of the ABCD trial, the CAPPP, and the FACET were combined, the patients randomized to an ACE inhibitor had a significantly lower risk of acute myocardial infarction and cardiovascular events, and all-cause mortality than those randomized to an alternative treatment (P < 0.001, P < 0.001, and P = 0.010, respectively) (Fig. 2). Moreover, no heterogeneity was found with the reduced dataset. No such differences were evident for the outcome of stroke.

CONCLUSIONS—This review identified 4 trials in which patients with type 2 diabetes and hypertension were randomized to either an ACE inhibitor or to an alternative antihypertensive treatment and were followed for ≥2 years. The results of these trials have been previously reviewed (5), but to our knowledge, this is the first quantitative meta-analysis of their outcome data. The cumulative results of 3 trials (the ABCD trial, the CAPPP, and the FACET) showed a significant benefit of ACE inhibitors compared with alternative treatments on the outcomes of acute myocardial infarction (63% reduction, P < 0.001), cardiovascular events (51% reduction, P < 0.001), and all-cause mortality (62% reduction, P = 0.010). These findings were not observed in the UKPDS, which compared captopril with atenolol. The ACE inhibitors did not appear to be superior to other agents for the outcome of stroke in any of the trials.

Why do the results of the UKPDS differ from those of the other trials? One possible explanation may be because of differences in population characteristics. In the UKPDS, diabetes was newly diagnosed compared with the other studies (Table 1). The duration of follow-up in the UKPDS is another difference from the other trials. Another explanation is the selective dropout from the trial. Patients randomized to atenolol were more likely to drop out of the randomized treatment (10), and they possibly received an ACE inhibitor if they had a compelling indication such as albuminuria or left ventricular dysfunction. The net effect of such a selective dropout would be to diminish any differences between atenolol and captopril. The potential frequent crossover between groups renders many aspects of the UKPDS difficult to interpret (14). Another plausible hypothesis is that the selective β-blocker atenolol is equivalent to captopril. Recent reports indicate in both normotensive and hypertensive individuals that the suppression of angiotensin II levels achieved with β-blockade is similar to that obtained with an ACE inhibitor (15). To confirm the hypothesis of equivalence of captopril and atenolol, one must assess the relative risk of events in the CAPPP by using diuretics and individual β-blockers. The divergent effects found in the UKPDS compared with the other 3 trials indicate that the overall evidence of the comparative effects of ACE inhibitors is not yet conclusive.

If ACE inhibitors are truly more beneficial than other agents for the treatment of hypertension in patients with diabetes, then what are the potential mechanisms? Blood pressure control did not differ significantly between treatments in the ABCD trial. In the FACET, the amlodipine group achieved a significantly lower systolic blood pressure level than the ACE inhibitor group. Total cholesterol levels were similar in both treatment groups in the ABCD trial and the FACET. Microal-

Table 2—Number of clinical events according to treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean follow-up (years)</th>
<th>ACE inhibitors</th>
<th>Other therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agent</td>
<td>n</td>
</tr>
<tr>
<td>ABCD (7)</td>
<td>5</td>
<td>Enalapril</td>
<td>235</td>
</tr>
<tr>
<td>CAPPP (8)</td>
<td>6.1</td>
<td>Captopril</td>
<td>309</td>
</tr>
<tr>
<td>FACET (9)</td>
<td>2.8</td>
<td>Fosinopril</td>
<td>189</td>
</tr>
<tr>
<td>UKPDS (10)</td>
<td>8.4</td>
<td>Captopril</td>
<td>400</td>
</tr>
</tbody>
</table>

Data are n: AMI, acute myocardial infarction; CV, cardiovascular events.
buminuria and serum creatinine levels during follow-up were similar in both treatment groups in the FACET. Metabolic control is another important factor that may affect cardiovascular outcomes. In the ABCD trial, the participants had poor metabolic control at baseline and during the 5 years of follow-up, but metabolic control was not significantly different between the ACE inhibitor and the Ca++ antagonist-treated group. In the FACET, the patients randomized to the ACE inhibitor or the Ca++ antagonist achieved similar HbA1c and fasting glucose levels during follow-up. Changes in blood pressure, metabolic control, or other risk factors during follow-up were not reported for diabetic patients enrolled in the CAPPP. Thus, from the published data, differences during follow-up. Changes in blood pressure control, metabolic control, or other measured risk factors likely explain the substantial difference in major cardiovascular events.

Several other mechanisms not measured in the reviewed trials may account for a greater therapeutic benefit of ACE inhibitors. ACE inhibitors may reduce cardiovascular risk by improving endothelial dysfunction (16), by reducing inflammation (17), and by promoting fibrinolysis through inhibition of plasminogen activator inhibitor 1 (18,19). The recently published Heart Outcomes Prevention Evaluation (HOPE) trial showed that the reduction in cardiovascular events with an ACE inhibitor was much greater than that expected from blood pressure reduction alone compared with placebo, which supports the view that additional mechanisms contribute to the prevention of cardiovascular events with ACE inhibition (20). The main findings of the HOPE trial were confirmed in patients with and without diabetes. The HOPE trial was not included in the present meta-analysis because the comparison group was treated with a placebo and not with an active agent as required by the inclusion criteria.

In summary, blood pressure reduction per se is necessary to prevent clinical complications in hypertensive patients (21), but additional clinical benefits can be achieved by non–blood pressure mechanisms. The evidence from the present review and meta-analysis of comparative trials in patients with hypertension and diabetes should not be considered conclusive. The available data support the view that, compared with the alternative agents tested, ACE inhibitors appear to provide a special advantage in addition to blood pressure control. The question of whether atenolol is equivalent to captopril remains open. Based on available data from comparative trials, using ACE inhibitors may be prudent as a first-line agent for the treatment of hypertension in patients with type 2 diabetes. Conclusive evidence on the comparative effects of antihypertensive treatments will come from large prospective randomized trials such as the Antihypertensive and Lipid Lowering Trial To Prevent Heart Attack Trial (22).

Figure 2—RR (95% CI) of outcomes for ACE inhibitors compared with other agents in the ABCD trial, the CAPPP, the FACET, the UKPDS, and in combined analyses.

Acknowledgments—The results of this study were presented at the 59th Annual Meeting of the American Diabetes Association, San Diego, CA, 19 June 1999.

References
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