Abstract—To investigate the impact of treatment on cardiovascular mortality and morbidity, we assessed outcomes in patients with hypertension and diabetes who received co-amilozide or nifedipine in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension. Participants had to be 55 to 80 years of age, with hypertension (≥150/95 or ≥160 mm Hg) and at least one additional cardiovascular risk factor. Patients received 30 mg nifedipine once daily or co-amilozide (25 mg hydrochlorothiazide and 2.5 mg amiloride) daily. Doses were doubled if target blood pressures (<140/90 mm Hg) were not achieved. Primary (composite of cardiovascular death, myocardial infarction, heart failure, and stroke) and secondary outcomes (composite of primary outcomes, including all-cause mortality and death from vascular and nonvascular causes) were assessed by means of intent-to-treat analyses. There was no significant difference in the incidence of primary outcomes between nifedipine-treated and co-amilozide–treated patients with diabetes at baseline (n=1302) (8.3% versus 8.4%; relative risk, 0.99, 95% CI, 0.69 to 1.42; P=1.00). A significant benefit for nifedipine-treated patients was seen for the composite secondary outcome (14.2% versus 18.7%; relative risk, 0.76, 95% CI, 0.59 to 0.97; P=0.03). Among patients without diabetes at baseline (n=5019), there was a significant difference in the incidence of new diabetes (nifedipine 4.3% versus co-amilozide 5.6%, P=0.023). Nifedipine GITS once daily is as effective as diuretic therapy in reducing cardiovascular complications in hypertensive diabetics. Nifedipine-treated patients were also less likely to have diabetes or have secondary events (a composite of all-cause mortality, death from a vascular cause, and death from a nonvascular cause) than co-amilozide recipients. Our results suggest that nifedipine could be considered as first-line therapy for hypertensive diabetics. (Hypertension. 2003;41:431-436.)

Key Words: calcium channel blockers | diabetes mellitus | diuretics | nifedipine | mortality | morbidity

Hypertensive patients with diabetes mellitus must receive antihypertensive drugs because this therapeutic intervention substantially lowers their high absolute risk of cardiovascular morbidity and mortality. 1,2 Whether the benefit depends on the reduction in blood pressure itself or is due (at least in part) to the different protective properties of the drugs used is a matter of debate. This is because trials have so far provided conflicting results: In some trials, diabetic patients receiving treatment with ACE inhibitors or angiotensin II antagonists had lower rates of cardiovascular morbidity and mortality than patients receiving diuretics, β-blockers, or calcium antagonists. 3–6 This has also been the case in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, in which a comparison of the calcium channel blocker nisoldipine and the ACE inhibitor enalapril in patients with diabetes and hypertension revealed a significantly higher incidence of fatal and nonfatal myocardial infarction in the nisoldipine recipients. 4 However, further analysis of patients enrolled in the ABCD trial identified additional myocardial infarctions in both treatment groups that reduced the above difference without altering the overall conclusions of the study. 7 Furthermore, in several other trials, comparisons between new and conventional treatments as well as between ACE inhibitors and calcium antagonists have shown no substantial differences in cardiovascular morbidity and mortality rates. 8–12 In a review of trials completed between 1990 and 2000, Kaplan 13 concluded that there are no concerns about the use of calcium channel blockers in patients with diabetes.

The intervention as a Goal in Hypertension (INSIGHT) study demonstrated that nifedipine and diuretic therapy with...
co-amilozide had comparable efficacy in preventing overall cardiovascular or cerebrovascular complications in patients with hypertension and at least one additional cardiovascular risk factor. In this report, we describe cardiovascular outcomes in patients enrolled in INSIGHT who had diabetes at baseline.

Methods

Design of the Trial
The design of INSIGHT has been described previously. In brief, patients were randomly assigned to receive either 30 mg nifedipine daily or co-amilozide (25 mg hydrochlorothiazide and 2.5 mg amiloride) daily (step 1). Patients whose blood pressure fell by <20/10 mm Hg or remained >140/90 mm Hg could receive 1 of 4 dose-titration steps (steps 2 to 5): dose doubling of the randomized drug; addition of 25 mg atenolol daily (or 5 mg enalapril daily if atenolol was contraindicated); dose doubling of the additional drug; and addition of any other antihypertensive drug except calcium channel blockers or diuretics. Use of add-on medications (steps 3 to 5) was recorded during the study. The inclusion criteria for INSIGHT have been described previously and included age 55 to 80 years, hypertension (blood pressure ≥150/95 or ≥160 mm Hg), and at least one additional cardiovascular risk factor, which could include diabetes mellitus.

All end points were assessed by an independent critical events committee. The progress of the study was monitored by an independent data and safety monitoring committee. The study was performed according to the principles of good clinical practice and the declaration of Helsinki and was approved by the relevant ethics committees. All patients gave informed written consent.

Blood pressure was measured 3 times after a 5-minute rest. After the initial dose-titration period, patients returned for assessment 3 times per year when blood pressure and heart rate were recorded. The primary outcome was the composite end point of incidence of cardiovascular death, myocardial infarction, heart failure, and stroke. The secondary outcome was the composite of all-cause death, death from a vascular cause, and death from a nonvascular cause. As part of our analysis, we also assessed the number of patients in whom diabetes mellitus developed during treatment. Diabetes at baseline was diagnosed using the 1985 World Health Organization (WHO) definition (ie, the most recent definition available at the time of the initiation of the INSIGHT study), that is, a random capillary blood glucose measurement >11.0 mmol/L or use of antidiabetic drugs.

Statistical Analysis
The subgroup analyses in the diabetic population in INSIGHT and of the development of diabetes within the nondiabetic population were prespecified in the study protocol. INSIGHT was designed to have 90% power to detect a 25% relative difference between treatment groups at the 5% (2-sided) level of significance. In the present study, relative risks and 95% CIs are quoted for the randomized comparisons. Odds ratios and 95% CIs are quoted for the nonrandomized comparisons of patients who had diabetes at baseline with those who were not diabetic. Logistic regression was used to compare multivariate and univariate results to adjust for possible effects of age and proteinuria (variables shown to be modestly imbalanced within the diabetic and nondiabetic subgroups). The Fisher exact test was used to compare all categoric data. All analyses were carried out using SPSS version 10.0 (SPSS Inc, 2001).

Results

Patient Characteristics
A total of 6321 patients were enrolled in INSIGHT, of whom 1302 had diabetes at baseline. Demographic characteristics and risk factors were well balanced between the nifedipine and co-amilozide treatment groups. Combining the treatment groups revealed some differences between diabetics and nondiabetics. Diabetics were less likely than nondiabetics to have a family history of cardiovascular disease, to have hypercholesterolemia, or to be smokers but were more likely to have proteinuria (Table 1). Mean age was slightly lower in the nifedipine-treated patients with diabetes than in the co-amilozide recipients (66.0 versus 65.1 years), whereas among nondiabetics, patients in the nifedipine group were more likely to have proteinuria than patients in the co-amilozide group (Table 1).

Blood Pressure Control and Heart Rate
Decreases in blood pressure were similar in nifedipine-treated and co-amilozide–treated patients in the subgroups with and without diabetes (Table 2). In patients with diabetes, systolic blood pressure decreased from 175 mm Hg in nifedipine-treated patients and 176 mm Hg in co-amilozide–treated patients at baseline to 144 and 145 mm Hg, respectively, at the final visit. In both the nifedipine-treated and co-amilozide–treated groups, diastolic blood pressure decreased from 98 mm Hg at baseline to 82 mm Hg at the final visit. Similar changes in systolic and diastolic blood pressure were noted in the patients who did not have diabetes at baseline. Heart rate decreased to a similar slight extent in nifedipine-treated and co-amilozide–treated patients both in the subgroups with and without diabetes (Table 2). Diabetic patients treated with co-amilozide required significantly more add-on medication than patients treated with nifedipine (P=0.027). Patients with diabetes required more add-on therapy (steps 3 to 5) than nondiabetic patients (Table 3). Among the patients with diabetes at baseline, 57% of nifedipine-treated patients and 51% of co-amilozide recipients received no additional drugs, compared with 64% and 62%, respectively, among nondiabetics. ACE inhibitors were administered to 1933 patients (61%) in the nifedipine group and 1880 patients (59%) in the co-amilozide group. Among patients with diabetes at baseline, 697 (54%) received an ACE inhibitor, compared with 1811 (36%) of the patients with no diabetes.

Outcomes in Diabetic and Nondiabetic Patients
In the group with diabetes at baseline, the percentages of patients with primary outcomes were similar in the nifedipine–treated and co-amilozide–treated groups (Figure). Among patients given ACE inhibitors, there were no significant differences in the percentage of patients with primary or secondary end points between the nifedipine and co-amilozide groups. Similarly, there was no significant difference in primary and secondary outcomes between the treatment groups within the subgroup of patients who were not given ACE inhibitors. In the nifedipine-treated group, 8.3% of patients had primary outcomes, compared with 8.4% in the co-amilozide–treated group (relative risk, 0.99; 95% CI, 0.69, 1.42; P=1.00). Significantly fewer nifedipine-treated patients had secondary outcomes (a composite of all-cause death, death from a vascular cause, and death from a nonvascular cause) than co-amilozide–treated patients (14.2% versus 18.7%; relative risk, 0.76; 95% CI, 0.59, 1.42; P=0.03) (Figure). There were no significant differences between the nifedipine-treated and co-amilozide–treated groups in the incidence of stroke, coronary heart disease, congestive heart...
failure, major cardiovascular events, cardiovascular deaths, or total deaths ($P>0.05$ in all cases) (Table 4).

Because of the slight imbalances in baseline characteristics (Table 1), logistic regression analyses were performed to compare primary and secondary outcomes, with adjustment for age and proteinuria. Conclusions remained unchanged in both cases, so only the univariate analyses are reported.

In the group without diabetes at baseline, the percentages of patients with primary outcomes were similar in nifedipine-treated and co-amilozide–treated patients (Figure). In the nifedipine-treated group, 5.8% of patients had primary outcomes, compared with 5.1% in the co-amilozide–treated group (relative risk, 1.15; 95% CI, 0.91, 1.24; $P=0.05$) (Figure).

There was also no significant difference in the percentages of patients who had each event. Nondiabetic patients were more likely to have no primary or secondary events, and there was no significant difference between the nifedipine-treated and co-amilozide–treated patients (11.6% versus 11.0%, respectively; $P=0.48$).

### Incidence of New Diabetes Mellitus

The number of patients with no diabetes at baseline who had newly diagnosed diabetes mellitus during the study was significantly lower in the nifedipine-treated group ($n=136, 4.3\%$) than in the co-amilozide–treated group ($n=176, 5.6\%$; $P=0.023$). Among patients with newly diagnosed diabetes, 5 nifedipine-treated patients (0.2%) and 6 co-amilozide–treated patients (0.2%) had primary events during the INSIGHT follow-up.

### Discussion

The present analysis of data collected from a relatively large subgroup of diabetic hypertensive patients enrolled in INSIGHT showed that the incidence of the composite end point of myocardial infarction, stroke, congestive heart failure, and cardiovascular death in patients receiving antihypertensive treatment with nifedipine GITS was similar to that seen with co-amilozide (a combination of a thiazide and a potassium-retaining diuretic). However, compared with diuretics, treatment with nifedipine-GITS was associated with a lower incidence of (1) vascular and nonvascular deaths combined and (2) new cases of diabetes mellitus. This suggests that a long-acting dihydropyridine calcium channel blocker is as
between the 2 treatment groups was 1.3% over a treatment duration of ≈4 years. This was not due to differences in the number of patients who received an ACE inhibitor as added treatment because this was similar in the nifedipine and diuretic group. The difference in the development of new diabetes was not sufficient to cause a difference in cardiovascular morbidity and mortality rates over the same period. However, if the trend continues, it is likely to lead to risk reductions over 10 to 20 years because (1) the increased risk of cardiovascular disease brought about by diabetes is considerable,16 and (2) this is the case both for native diabetes and for diabetes induced by antihypertensive drugs.17 A number of studies have reported increased risks for the development of diabetes in patients treated with diuretics and β-blockers,15,18–20 but it appears that ACE inhibitors and calcium channel blockers have either no effect or reduce the likelihood of new diabetes.21,22 Assessing the incidence of new diabetes should therefore be part of all trials that aim to determine the protective effect of antihypertensive drugs and predict the benefits beyond the actual trial duration. To date, this has been done only in some trials, most of which have shown that the incidence of new diabetes is less with calcium antagonists,14 ACE inhibitors, and angiotensin II antagonists5,23 than with diuretics and β-blockers, which appear to increase the incidence of new diabetes beyond that seen in untreated hypertensive individuals.24 This may be accounted for by the different effects on insulin sensitivity, which are favorable with calcium antagonists, ACE inhibitors, and angiotensin II antagonists and unfavorable with diuretics and β-blockers.25,26

The reduction in systolic and diastolic blood pressure was similar in the diabetic and nondiabetic subgroups of INSIGHT, regardless of whether treatment was based on nifedipine or diuretics. In the nondiabetic subgroup, however, on-treatment systolic blood pressure was slightly (1.8 mm Hg) but significantly less in the diuretic than in the nifedipine-treated patients, with no difference in the incidence of primary or secondary outcomes. This could be due to the fact that nifedipine has direct organ-protective properties in addition to the protection provided by the blood pressure lowering per se. It could also mean, however, that even in the high-risk patients enrolled in the INSIGHT study, a blood pressure difference of 1.8 mm Hg was too small to have a pathophysiological effect, that the duration of the study was too short for differences in outcome to become

 effective as conventional antihypertensive drugs for preventing major nonfatal and fatal cardiovascular events in patients with diabetes and hypertension. It also suggests that calcium channel blockers may have some advantages when all events are taken into account and that they are better than conventional treatments at countering the greater tendency in hypertensive patients for the development of diabetes mellitus.15

In nondiabetic patients enrolled in INSIGHT, the absolute difference in the percentages of patients with new diabetes

### TABLE 3. Use of Add-On Medications to Achieve Blood Pressure Targets

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving add-on medication</td>
<td>Nifedipine n (%)</td>
<td>Co-Amilozide n (%)</td>
</tr>
<tr>
<td>Steps 3–5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One additional drug, steps 3–4*</td>
<td>214 (33.0)</td>
<td>239 (36.5)</td>
</tr>
<tr>
<td>Two or more additional drugs, step 5†</td>
<td>65 (10.0)</td>
<td>81 (12.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Enalapril (or atenolol if enalapril was contraindicated); †enalapril (or atenolol) and any other antihypertensive drug except calcium-channel blockers or diuretics.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡χ² test for trend.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diabetic patients had slightly higher average blood pressures at baseline, which resulted in slightly higher on-treatment values. Furthermore, add-on medications were more frequently needed in diabetic than in nondiabetic patients. Finally, in diabetic patients diastolic blood pressure was reduced well below 90 mm Hg (82 mm Hg) but systolic blood pressure remained around 140 mm Hg. These results are consistent with the conclusions of other studies that effective antihypertensive treatment in diabetic patients requires more drugs, with a limited chance of reaching the perhaps too ambitious target systolic blood pressure values (130 mm Hg) which, according to current guidelines, provide the greatest degree of protection.27–29

Three further points should be mentioned. First, our data on the differential incidence of new diabetes and on combined primary and secondary end points add to the evidence provided by recent studies that similar reductions in blood pressure may be accompanied by different degrees of morbidity and mortality, thereby supporting the independent roles of the blood pressure-specific and organ-protective properties of the drugs used. Second, they provide further evidence that calcium antagonists are suitable for diabetic hypertensive patients, contrary to the contention that treatment should make selective use of drugs that interfere with the renin-angiotensin system. To date, this contention does not appear to be supported by the available data, because treating diabetic patients with systolic hypertension using a calcium antagonist markedly reduced cardiovascular morbidity and mortality rates compared with placebo.30 Furthermore, in patients with diabetic nephropathy, administration of an angiotensin II antagonist did not affect cardiovascular morbidity to a different degree than administration of a calcium antagonist.31

Finally, patients included in studies showing the marked renal and cardiovascular protective effects of angiotensin II antagonists or ACE inhibitors in diabetes have usually required chronic administration of a calcium antagonist to achieve effective blood pressure control.32,33

The final point concerns the fact that although diabetes is associated with greater cardiovascular morbidity, there were insufficient events in the diabetic subgroup of INSIGHT to make an adequately powered comparison of the primary end point between nifedipine and diuretic-based treatments. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, losartan was more effective than atenolol at reducing cardiovascular and all-cause morbidity and mortality in patients with hypertension, diabetes, and left ventricular hypertrophy.34 However, the majority of studies and substudies have been inadequately powered to compare cardiovascular protection with different antihypertensive drug regimens in diabetes.3–6,11,12 Meta-analysis of the available data will therefore be needed to give comparisons adequate statistical power.

### Acknowledgments

This study was sponsored by Bayer AG.

#### TABLE 4. Patients With Primary or Secondary Outcomes in the Diabetic Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine (n=649) n (%)</th>
<th>Co-Amilozide (n=653) n (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>17 (2.6)</td>
<td>19 (2.9)</td>
<td>0.90 (0.47, 1.72)</td>
</tr>
<tr>
<td>CHD: MI and sudden death</td>
<td>28 (4.3)</td>
<td>25 (3.8)</td>
<td>1.13 (0.66, 1.91)</td>
</tr>
<tr>
<td>CHF</td>
<td>9 (1.4)</td>
<td>6 (0.9)</td>
<td>1.51 (0.54, 4.22)</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td>46 (7.1)</td>
<td>49 (7.5)</td>
<td>0.95 (0.64, 1.39)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>19 (2.9)</td>
<td>19 (2.9)</td>
<td>1.01 (0.54, 1.88)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>44 (6.8)</td>
<td>59 (9.0)</td>
<td>0.75 (0.52, 1.09)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; MI, myocardial infarction; CHF, congestive heart failure; MI, myocardial infarction; and SD, standard deviation.
References


Outcomes With Nifedipine GITS or Co-Amilozide in Hypertensive Diabetics and Nondiabetics in Intervention as a Goal in Hypertension (INSIGHT)
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