

THE EFFECT OF NISOLDIPINE AS COMPARED WITH ENALAPRIL ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH NON-INSULIN-DEPENDENT DIABETES AND HYPERTENSION

RAYMOND O. ESTACIO, M.D., BARRETT W. JEFFERS, M.S., WILLIAM R. HIATT, M.D., STACY L. BIGGERSTAFF, M.S., NANCY GIFFORD, R.N., AND ROBERT W. SCHRIER, M.D.

ABSTRACT

Background It has recently been reported that the use of calcium-channel blockers for hypertension may be associated with an increased risk of cardiovascular complications. Because this issue remains controversial, we studied the incidence of such complications in patients with non-insulin-dependent diabetes mellitus and hypertension who were randomly assigned to treatment with either the calcium-channel blocker nisoldipine or the angiotensin-converting-enzyme inhibitor enalapril as part of a larger study.

Methods The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial is a prospective, randomized, blinded trial comparing the effects of moderate control of blood pressure (target diastolic pressure, 80 to 89 mm Hg) with those of intensive control of blood pressure (target diastolic pressure, 75 mm Hg) on the incidence and progression of complications of diabetes. The study also compared nisoldipine with enalapril as a first-line antihypertensive agent in terms of the prevention and progression of complications of diabetes. In the current study, we analyzed data on a secondary end point (the incidence of myocardial infarction) in the subgroup of patients in the ABCD Trial who had hypertension.

Results Analysis of the 470 patients in the trial who had hypertension (base-line diastolic blood pressure, ≥ 90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations, and smoking behavior in the nisoldipine group (235 patients) and the enalapril group (235 patients) throughout five years of follow-up. Using a multiple logistic-regression model with adjustment for cardiac risk factors, we found that nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions (a total of 25) than enalapril (total, 5) (risk ratio, 9.5; 95 percent confidence interval, 2.3 to 21.4).

Conclusions In this population of patients with diabetes and hypertension, we found a significantly higher incidence of fatal and nonfatal myocardial infarction among those assigned to therapy with the calcium-channel blocker nisoldipine than among those assigned to receive enalapril. Since our findings are based on a secondary end point, they will require confirmation. (N Engl J Med 1998;338:645-52.)

©1998, Massachusetts Medical Society.

CARDIOVASCULAR disease accounts for 40 percent of overall mortality in the United States¹ and is the leading cause of death among persons with non-insulin-dependent diabetes mellitus (NIDDM).^{2,3} Strategies to reduce this risk include the appropriate treatment of hypertension. However, the choice of antihypertensive agents may also affect the risk of cardiovascular events. In this regard, the angiotensin-converting-enzyme (ACE) inhibitors have been demonstrated to increase survival after an acute myocardial infarction⁴⁻⁶ and among patients with congestive heart failure.⁷⁻⁹ Calcium-channel-blocking drugs are also indicated for the treatment of a variety of cardiovascular diseases, including angina pectoris, systemic and pulmonary hypertension, certain cardiac arrhythmias, and Raynaud's phenomenon.¹⁰ ACE inhibitors have been shown to be effective antihypertensive drugs for both patients with diabetes and those without diabetes. Studies have demonstrated the efficacy of ACE inhibitors in slowing the progression of diabetic nephropathy in patients with insulin-dependent diabetes mellitus (IDDM) and possibly those with NIDDM.¹¹⁻¹⁵ At present, calcium-channel blockers are among the most frequently prescribed antihypertensive medications in the country.¹⁰ However, although calcium-channel blockers are an important part of the therapeutic armamentarium against cardiovascular diseases, concern has been aroused about these drugs, particularly the short-acting dihydropyridine derivatives. Recent studies have focused attention on the possibility that some of these agents may increase the risk of cardiovascular events in patients without diabetes.¹⁶⁻¹⁸

The Appropriate Blood Pressure Control in Dia-

From the Colorado Prevention Center (R.O.E., B.W.J., W.R.H., S.L.B., N.G., R.W.S.); the Division of General Internal Medicine (R.O.E.), the Division of Renal Diseases and Hypertension (B.W.J., N.G., R.W.S.), the Divisions of Geriatrics and Cardiology (W.R.H.), Department of Medicine, and the Section of Vascular Medicine (W.R.H.), University of Colorado Health Sciences Center; and the Department of Community Health Services, Denver Health (R.O.E.) — all in Denver. Address reprint requests to Dr. Schrier at the Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Health Sciences Center, 4200 E. Ninth Ave., Box B-178, Denver, CO 80262.

betes (ABCD) Trial was designed to test the primary hypothesis that intensive blood-pressure control, as compared with moderate control, would prevent or slow the progression of diabetic nephropathy, neuropathy, retinopathy, and cardiovascular events.¹⁹ The secondary hypothesis was that a long-acting dihydropyridine calcium-channel blocker (nisoldipine) would have an effect equivalent to that of an ACE inhibitor (enalapril) in preventing or delaying the progression of these complications. The present study grew out of the recommendation of the Data and Safety Monitoring Committee that nisoldipine treatment be terminated in the subgroup of patients with hypertension. The committee's recommendation and this report were based on data from a mean of five years of follow-up on the effects of nisoldipine and enalapril on the incidence of cardiovascular events among patients with hypertension and NIDDM in the ABCD Trial. In our report we focus only on the findings of the interim analysis of data on the cohort with hypertension; the entire study is expected to be completed on June 1, 1998.

METHODS

Study Design

After the cohorts with and without hypertension were prospectively defined, patients were randomly assigned to moderate or intensive antihypertensive treatment. Within the moderate-treatment and intensive-treatment groups, patients were further randomly assigned to receive either nisoldipine or enalapril as a first-line antihypertensive medication. The primary objective of the study was to determine the relative effects of moderate and intensive blood-pressure control on the change in the creatinine clearance rate among both the normotensive and the hypertensive patients, all of whom had NIDDM. The design of the ABCD Trial has been described previously.¹⁹ The study was approved by the institutional review board of the University of Colorado Health Sciences Center. All patients gave written informed consent.

Study Participants

The patients enrolled in the ABCD Trial were between the ages of 40 and 74 years at the time of recruitment and were identified according to diagnosis-related groups from the pharmacy and billing lists of participating health care systems in the Denver metropolitan area. All patients in the ABCD Trial had NIDDM, diagnosed according to criteria based on those of the World Health Organization report of 1985.²⁰ All enrolled subjects had diastolic blood pressure of 80 mm Hg or higher and were receiving no antihypertensive medications at the time of randomization. Patients were excluded if they had a known allergy to dihydropyridine calcium-channel blockers or ACE inhibitors, had had a myocardial infarction or cerebrovascular accident within the previous six months, had undergone coronary-artery bypass surgery within the previous three months, had had unstable angina pectoris within the previous six months, had New York Heart Association class III or IV congestive heart failure, had an absolute need for therapy with ACE inhibitors or calcium-channel blockers, were receiving hemodialysis or peritoneal dialysis, or had a serum creatinine concentration greater than 3 mg per deciliter (265 μ mol per liter).

Base-Line Evaluation

During a single-blind placebo run-in period lasting 7 to 11 weeks, all base-line studies were performed.¹⁹ Cardiovascular dis-

ease was identified at base line in patients who met one or more of the following criteria: (1) coronary artery disease, indicated by the patient's report of a previous myocardial infarction, coronary-artery bypass graft, or angioplasty, electrocardiographic findings consistent with a previous myocardial infarction, or a base-line treadmill exercise test that was positive for cardiac ischemia; (2) angina, identified by means of the Rose questionnaire²¹; (3) cerebrovascular accident, reported by the patient; (4) congestive heart failure; (5) abnormal ankle-brachial index, defined as a value less than 0.95²²; and (6) evidence of left ventricular hypertrophy on the base-line electrocardiogram. Details of the studies performed have been reported previously.²³

Randomization and Therapy

After the placebo run-in period, each patient's mean base-line diastolic blood pressure was determined at two separate visits. The study population was subsequently divided prospectively into two cohorts, a group without hypertension (mean base-line diastolic blood pressure, 80 to 89 mm Hg) and a group with hypertension (mean base-line diastolic blood pressure, \geq 90 mm Hg). In the normotensive cohort, patients were randomly assigned to one of two treatment strategies: intensive treatment with the goal of decreasing the diastolic blood pressure by 10 mm Hg from the mean base-line value (with further random assignment to receive either nisoldipine or enalapril), or moderate treatment with no intended change in the base-line diastolic blood pressure (these patients were thus randomly assigned to receive placebo). Thus, in the normotensive group, 50 percent of the patients received placebo, 25 percent nisoldipine, and 25 percent enalapril. A similar approach was used for the patients with hypertension. Patients were randomly assigned either to intensive treatment, with a target diastolic blood pressure of 75 mm Hg, or to moderate treatment, with a target diastolic blood pressure of 80 to 89 mm Hg. Unlike the normotensive group, however, all the patients with hypertension received active treatment (50 percent nisoldipine and 50 percent enalapril).

Patients assigned to active study medication received either nisoldipine (Sular, Zeneca, Wilmington, Del.; 10 mg per day, with increases to 20, 40, and 60 mg per day, plus placebo for enalapril) or enalapril (Vasotec, Merck, Whitehouse Station, N.J.; 5 mg per day, with increases to 10, 20, and 40 mg per day, plus placebo for nisoldipine). The drugs and placebos were administered in a double-blind manner. If the single study medication assigned did not achieve the target blood pressure, then open-label antihypertensive medications were added in a stepwise fashion until the target blood pressure was achieved. The open-label antihypertensive medications included metoprolol and hydrochlorothiazide. Additional antihypertensive medications were added at the discretion of the medical director of the study, but these did not include a calcium-channel blocker or ACE inhibitor.

End Points

In both the cohort with hypertension (470 patients) and the cohort without hypertension (480 patients), the primary end point was the effect of intensive or moderate blood-pressure control on the change in the 24-hour creatinine clearance, which was assessed every six months.¹⁹ Secondary end points included the effect of intensive as compared with moderate blood-pressure control on the incidence of cardiovascular events, retinopathy (determined by stereoscopic retinal photography²⁴), clinical neuropathy,²⁵ urinary albumin excretion,²⁶ and left ventricular hypertrophy (as measured by M-mode echocardiography²⁷).

All cardiovascular events were reviewed by an independent endpoints committee whose members were blinded to the patients' assigned treatment groups. Cardiovascular outcomes were defined as death due to cardiovascular events (sudden death, progressive heart failure, fatal myocardial infarction, fatal arrhythmias, cerebrovascular accidents, or ruptured aortic aneurysm); nonfatal myocardial infarction; nonfatal cerebrovascular accident; heart failure requiring hospital admission; or pulmonary infar-

tion. Data on all hospital admissions that appeared to be related to a cardiovascular event were reviewed by the end-points committee.

The diagnosis of myocardial infarction was based on medical records reviewed by the end-points committee. For myocardial infarction to be diagnosed, the patient had to have at least two of the following: a history of retrosternal pain, with or without radiation to the shoulder, arms, jaws, or abdomen, that lasted at least 30 minutes and did not respond to nitroglycerin during the attack; electrocardiographic abnormalities indicative of myocardial infarction; and changes in the concentrations of one or more of the enzymes creatine kinase, aspartate aminotransferase, and lactate dehydrogenase.

After 67 months of study, the Data and Safety Monitoring Committee observed a significant difference in the rate of cardiovascular events between the subgroups of patients treated with the two study drugs in the hypertensive cohort only. On the basis of this information, the committee recommended the discontinuation of nisoldipine therapy among the patients with hypertension and the continuation of blinded therapy among the normotensive patients. This report focuses only on the findings in the hypertensive cohort.

Statistical Analysis

SAS software (SAS Institute, Cary, N.C.) was used for all statistical analyses. When examining cardiovascular end points (nonfatal myocardial infarction, cerebrovascular accidents, congestive heart failure requiring hospital admission, death from cardiovascular causes, and the combined end point of nonfatal and fatal myocardial infarction), we used chi-square analysis to examine the univariate relation between each cardiovascular end point and the study-drug assignment. A multiple logistic-regression model was used to examine the effect of the assigned drug, with adjustment for other known or suspected cardiovascular risk factors. In addition, a multiple logistic-regression model was used to test for an interaction between the study-drug assignment and the blood-pressure-control intervention. All values are reported as means ±SD.

A survival-analysis approach was also used to compare the survival curves between the patients randomly assigned to enalapril with those randomly assigned to nisoldipine. The survival analyses were performed in three ways: with Kaplan-Meier survival curves for groups of patients randomly assigned to the two study drugs; with a proportional-hazards regression model incorporating the randomly assigned drug; and with a proportional-hazards regression model incorporating a time-dependent variable accounting for exposure to the study medication.

The first two approaches followed the intention-to-treat principle, whereas the third approach took into account the actual time intervals during which study medication was received by each patient. The Kaplan-Meier survival analysis was performed according to the LIFETEST procedure (SAS version 6.12), which calculates a nonparametric estimate of the survival distribution. For the proportional-hazards regression models, we used the PHREG procedure (SAS version 6.12), which generates a semi-parametric regression analysis of survival data based on the Cox proportional-hazards model and allows time-dependent covariates to be introduced into the model.

RESULTS

Table 1 shows the base-line characteristics of the subjects with hypertension according to their random assignment to nisoldipine or enalapril. Patients assigned to receive enalapril had a significantly lower high-density lipoprotein (HDL) cholesterol concentration (P=0.03). As Table 2 shows, a higher percentage of patients randomly assigned to receive enalapril had an abnormal ankle-brachial index (P=

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS, ACCORDING TO ASSIGNED STUDY MEDICATION.*

CHARACTERISTIC	NISOLDIPINE (N=235)	ENALAPRIL (N=235)
Sex (M/F)	160/75	157/78
Age (yr)	57.2±8.2	57.7±8.4
Race or ethnic group (no.)		
Non-Hispanic white	156	158
African American	33	32
Hispanic white	38	41
Other	8	4
Family history of coronary artery disease (%)	49	45
Duration of diabetes mellitus (yr)	8.7±6.6	8.5±6.8
Fasting glucose (mg/dl)†	189±69	191±67
Glycosylated hemoglobin (%)	11.7±3.1	11.5±3.2
Duration of hypertension (yr)	11.2±9.5	12.2±10.5
Systolic blood pressure (mm Hg)	155±19	156±17
Diastolic blood pressure (mm Hg)	98±7	98±7
Current or former smoker (%)	64	60
Pack-yr of smoking	21±29	17±27
Receiving antilipid agents (%)	6.0	2.6
Cholesterol (mg/dl)‡		
Total	218±60	218±49
HDL	43±14	40±13
LDL	128±38	130±37
Triglycerides (mg/dl)§	294±536	288±287
Body-mass index¶	31.3±5.6	31.9±5.9

*Plus-minus values are means ±SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. LDL concentrations were not calculated if the triglyceride concentration was 400 mg per deciliter or greater.

†To convert values for glucose to millimoles per liter, multiply by 0.05551.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

§To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

¶The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

0.008) and evidence of angina on the Rose questionnaire (P=0.02), as compared with those assigned to receive nisoldipine.

Figure 1 shows the level of blood-pressure control in the groups given the two study medications throughout the study; no significant differences were seen. Ninety-nine patients in the enalapril group took a beta-blocker, as compared with 89 patients in the nisoldipine group (P=0.035). One hundred nineteen patients assigned to enalapril took a diuretic agent, as did 93 assigned to nisoldipine (P=0.02). Figure 2 shows that the concentrations of glycosylated hemoglobin and total cholesterol were similar in the patients assigned to the two study medications. Other metabolic variables, such as the low-density lipoprotein cholesterol and triglyceride concentrations, the number of patients who smoked,

TABLE 2. DISTRIBUTION OF COMPLICATIONS AT BASE LINE, ACCORDING TO STUDY MEDICATION.

COMPLICATION	NISOLDIPINE (N = 235)	ENALAPRIL (N = 235)
Diabetic nephropathy		
Creatinine clearance*	88.4±45.5	82.7±26.9
Overt albuminuria (%)†	18	19
Diabetic retinopathy (%)	61	60
Diabetic neuropathy (%)	45	44
Previous myocardial infarction (%)	6	8
Cardiovascular disease (%)‡	51	58
History of coronary artery disease	25	24
Angina on Rose questionnaire	2	6
Previous cerebrovascular accident	3	2
Previous congestive heart failure	1	2
Abnormal ankle-brachial index	7	14
Left ventricular hypertrophy on electrocardiogram	30	36

*Values for creatinine clearance are mean (±SD) rates in milliliters per minute per 1.73 m² of body-surface area. To convert these values to millimoles per liter, multiply by 0.01667.

†Overt albuminuria was defined as a urinary albumin excretion rate above 200 µg per minute.

‡For details of the criteria for cardiovascular disease at base line, see the text. Several patients met more than one of the criteria for cardiovascular disease.

and the number of pack-years of smoking, also did not differ significantly between the patients assigned to enalapril and those assigned to nisoldipine.

Cardiovascular Events

In the enalapril group, there were 5 deaths due to cardiovascular disease, as compared with 10 in the nisoldipine group (Table 3). There were fewer myocardial infarctions in the enalapril group than in the nisoldipine group (nonfatal myocardial infarctions, 5 vs. 22; P=0.001 by the chi-square test; fatal and nonfatal myocardial infarctions combined, 5 vs. 25; P=0.001 by the chi-square test) (Table 3). The rate of myocardial infarction during the five-year study period was nearly one per year in the enalapril group as compared with roughly five per year in the nisoldipine group. This relation was maintained among both the patients assigned to intensive treatment (12 fatal or nonfatal myocardial infarctions among patients given nisoldipine, as compared with 4 in the enalapril group; P=0.03 by the chi-square test) and those assigned to moderate treatment (13 and 1, respectively; P=0.002 by the chi-square test). As Table 3 shows, the adjusted risk ratio for the nisoldipine-treated patients as compared with those given enal-

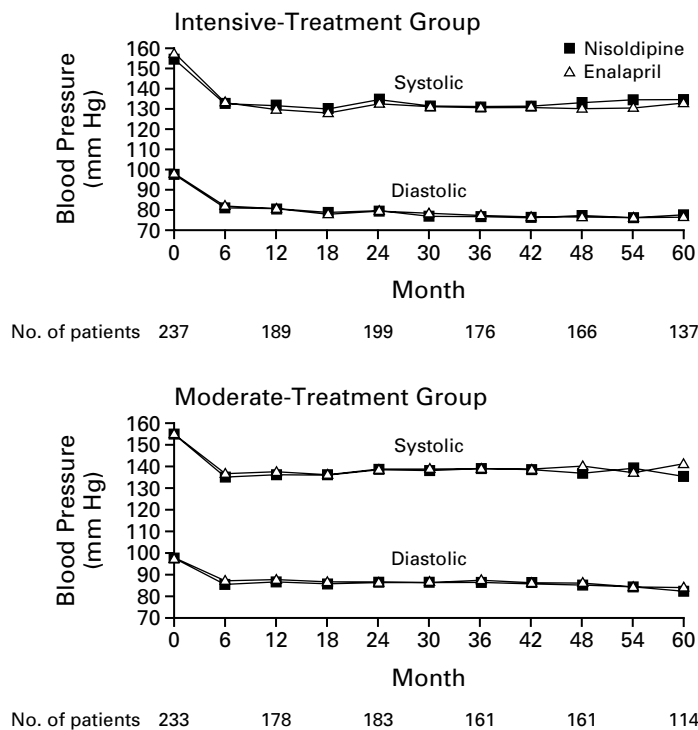


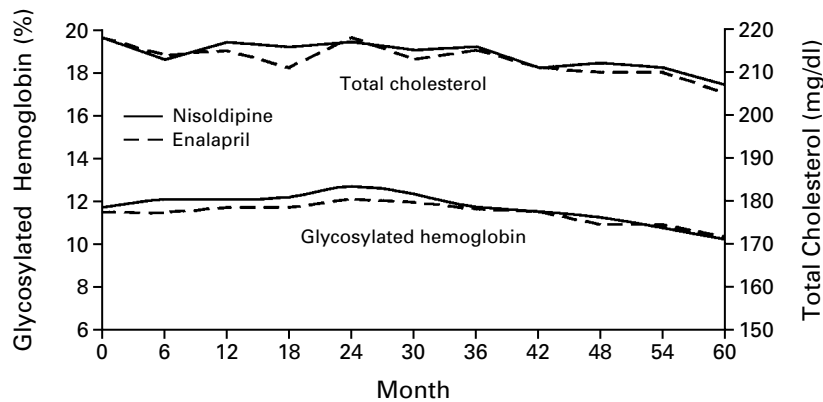
Figure 1. Systolic and Diastolic Blood Pressure during the Study among Patients in the Intensive-Treatment and Moderate-Treatment Groups Who Were Assigned to Receive Nisoldipine or Enalapril as First-Line Antihypertensive Medication.

The numbers below each panel show the number of patients in the analysis.

april was 7.0 (95 percent confidence interval, 2.3 to 21.4) for the combined end point of fatal or nonfatal myocardial infarction. In addition, a test for interaction between study-drug assignment and blood-pressure-control strategy showed that no interaction was present. Two of the 5 patients with myocardial infarction in the enalapril group had had a previous myocardial infarction, noted at base line, as compared with 2 of the 25 patients in the nisoldipine group (P=0.12).

In the Kaplan–Meier survival analyses, the survival

curves appeared to separate early and remained distinct. Both the log-rank test and the Wilcoxon test (P<0.001) and the proportional-hazards regression model (P<0.001) showed a significant difference between the two drugs. When a time-dependent covariate reflecting exposure to the drug was introduced into the model, the results did not change (P<0.001). This finding indicates that patients taking nisoldipine were more likely to have a myocardial infarction and to have one earlier than patients taking enalapril.



NO. OF PATIENTS						
Total cholesterol	469	359	373	325	322	286
Glycosylated hemoglobin	454	353	373	325	322	286

Figure 2. Glycosylated Hemoglobin and Total Cholesterol Values in Patients Assigned to Receive Nisoldipine or Enalapril. To convert values for total cholesterol to millimoles per liter, multiply by 0.02586. The numbers shown below the graph are the numbers of patients in the analysis.

TABLE 3. LOGISTIC-REGRESSION ANALYSES OF CARDIOVASCULAR OUTCOMES AND TOTAL DEATHS, ACCORDING TO TREATMENT GROUP.*

OUTCOME	NISOLDIPINE (N = 235)	ENALAPRIL (N = 235)	RISK RATIO (95% CI)	ADJUSTED RISK RATIO (95% CI)†
Fatal or nonfatal myocardial infarction	25	5	5.5 (2.1–14.6)	7.0 (2.3–21.4)
Nonfatal myocardial infarction	22	5	4.8 (1.8–12.8)	5.9 (1.9–18.2)
Cerebrovascular accident	11	7	1.6 (0.6–4.2)	2.2 (0.7–7.1)
Congestive heart failure	6	5	1.2 (0.4–4.0)	1.3 (0.3–5.9)‡
Death from cardiovascular causes	10	5	2.0 (0.7–6.1)	1.4 (0.4–5.1)
Death from any cause	17	13	1.3 (0.6–2.8)	1.0 (0.4–2.3)

*CI denotes confidence interval.

†The risk ratios have been adjusted for base-line variables, which include age, sex, duration of diabetes, duration of hypertension, history of coronary artery disease, systolic and diastolic blood pressure, pack-years of smoking, body-mass index, the concentrations of glucose, glycosylated hemoglobin, use of lipid-lowering medications, total cholesterol, HDL cholesterol, and triglycerides, ankle-brachial index, and use of beta-blockers and diuretic agents. Seventeen subjects were not included because of missing data on glycosylated hemoglobin values (7 subjects), pack-years of smoking (2), HDL cholesterol concentration (3), and ankle-brachial index (5).

‡The risk ratio was not adjusted for the use of lipid-lowering medications and beta-blockers because of collinearity.

TABLE 4. REASONS FOR DISCONTINUING THE STUDY MEDICATION.

REASON	NISOLDIPINE (N=235)	ENALAPRIL (N=235)
	no. of patients	
Adverse effects and concurrent illnesses		
Edema	20	11
Kidney failure	2	1
Cough	8	13
Confusion	2	0
Headache	10	1*
Cancer	2	0
Hyperkalemia	2	0
Gastrointestinal disease	4	1
Impotence	2	2
Platelet abnormality	0	2
Malaise or fatigue	0	7*
Rash	1	1
Tinnitus	0	2
Hyperglycemia	1	0
Total	54	41
Voluntary reasons		
Nephropathy†	6	8
Moved	12	12
Other	20	21
Total	38	41
Death or cardiovascular event		
Death	14	10
Coronary artery disease‡	14	14
Myocardial infarction	9	4
Congestive heart failure	8	7
Uncontrolled hypertension	2	8*
Cerebrovascular accident	2	2
Vascular disease	0	1
Hypotension	1	1
Total	50	47
Grand total	142	129

* $P < 0.05$ for the comparison with the nisoldipine group, by the chi-square test.

†The patients' physicians recommended that they switch to open-label therapy with an angiotensin-converting-enzyme inhibitor.

‡Coronary artery disease was diagnosed when the patient had one or more of these findings: angina, a positive thallium test, or a positive angiogram that resulted in a decision by the primary care physician to switch to open-label medication.

Reasons for Discontinuation of the Study Medication

Table 4 shows the reasons for the discontinuation of the study medication by 142 patients in the nisoldipine group and 129 in the enalapril group ($P = 0.225$). Significantly more patients discontinued nisoldipine than enalapril because of headaches ($P = 0.009$). Significantly more discontinued enalapril because of malaise or fatigue ($P = 0.005$) or uncontrolled hypertension ($P = 0.04$). Patients continued to receive the study medication after a myocardial infarction unless their primary care physician requested that it be discontinued.

DISCUSSION

The ABCD Trial was designed to compare the effects of blood-pressure control at different intensities and of different types of antihypertensive medications on complications of diabetes. The intention-to-treat analyses of the data from a mean of five years of follow-up of the cohort with hypertension demonstrated a significantly lower rate of fatal and non-fatal myocardial infarctions among the patients randomly assigned to the ACE inhibitor enalapril than among those assigned to the calcium-channel blocker nisoldipine.

Since the findings were based on a secondary end point of the study, the results should be interpreted cautiously. Nonetheless, there was a significantly lower incidence of myocardial infarction in the enalapril group, despite the potentially higher base-line risk of cardiovascular events in that group. Specifically, patients randomly assigned to receive enalapril had lower HDL cholesterol concentrations and a higher prevalence of an abnormal ankle-brachial index, which has been shown to be an independent predictor of death from cardiovascular causes,^{28,29} on entry into the study. Moreover, the difference between the two study medications was still striking after adjustment for other variables that may influence the incidence of cardiovascular end points.

Another confounding variable that may have affected our results was the percentage of patients who discontinued the assigned study medication. The rate of discontinuation was not significantly different for the two drugs. In an attempt to address this concern, we performed time-to-event analyses that also included a time-dependent covariate reflecting exposure to the drug. The results indicated that the survival curves for the two drugs differed significantly. Not only were patients assigned to enalapril less likely to have a myocardial infarction, but the time to a first event was longer than among the patients assigned to nisoldipine, thus further corroborating the results. The current report does not include findings in the normotensive cohort of the study, since the Data and Safety Monitoring Committee did not find a significant difference between the patients assigned to the two medications with respect to cardiovascular events. By the design of the study, 50 percent of the normotensive patients were receiving the study medication and 50 percent placebo. Thus, only 25 percent of the patients without hypertension were receiving nisoldipine, and 25 percent were receiving enalapril; the power of this portion of the study to detect significant differences was therefore limited. This portion of the study is still ongoing.

Despite their potential benefits, much controversy has arisen recently regarding calcium-channel blockers.³⁰⁻³⁴ A number of recent retrospective studies have demonstrated an association between the use

of calcium-channel blockers (specifically nifedipine) and cardiovascular morbidity.^{16,17} Thus, it is important to consider whether enalapril reduces the risk of myocardial infarction, whether nisoldipine increases the risk of myocardial infarction, or whether a combination of these effects occurs. Although comparisons with historical controls are not ideal, the rate of myocardial infarction among patients with NIDDM who were randomly assigned to therapy with nisoldipine in our study (10 percent over a period of five years) is not significantly different from that in other recent studies of patients with NIDDM (6 to 14 percent over a five-year period).³⁵⁻³⁷ Therefore, it is plausible that our findings resulted from a protective effect of enalapril. It should be stressed, however, that in the present study, we cannot distinguish among a deleterious effect of nisoldipine, a protective effect of enalapril, and a combination of both as the reason for the difference we observed.

In summary, a prospective, randomized, blinded clinical study in a population of patients with NIDDM and hypertension demonstrated that treatment with enalapril for a mean of five years was associated with a lower incidence of myocardial infarction than was treatment with nisoldipine for the same period. Since our findings are based on data on a secondary end point, the conclusions regarding the use of calcium-channel blockers and ACE inhibitors in patients with NIDDM must be evaluated on the basis of the results of other clinical trials. In any case, our data indicate that an ACE inhibitor is the preferred antihypertensive agent, rather than a dihydropyridine calcium-channel blocker, for the prevention of cardiovascular complications, specifically myocardial infarction, in patients with NIDDM.

Supported by the Bayer Pharmaceutical Company and by a grant (DK50298-02) from the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Hiatt is the recipient of an Academic Award in Vascular Disease from the National Institutes of Health.

We are indebted to the members of the Data and Safety Monitoring Committee for their guidance: Paul W. Whelton, M.D., Tulane University, New Orleans; Roger Sherwin, M.D., University of Maryland, Baltimore; Ralph D'Agostino, Sr., Ph.D., Boston University, Boston; and Kevin Higgins, M.D., Bayer Pharmaceuticals, West Haven, Conn.

REFERENCES

- National Center for Health Statistics. Advance report of final mortality statistics, 1986. *Mon Vital Stat Rep* 1988;37(6):Suppl:1-56.
- Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1987;30:123-31. [Erratum, *Diabetologia* 1987;30:364.]
- Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991;81:1158-62.
- Pfeiffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial: the SAVE Investigators. *N Engl J Med* 1992;327:669-77.
- ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and dermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343:1115-22.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
- The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
- Cohn JN. The management of chronic heart failure. *N Engl J Med* 1996;335:490-8.
- Manolio TA, Cutler JA, Furberg CD, Psaty BM, Whelton PK, Applegate WB. Trends in pharmacologic management of hypertension in the United States. *Arch Intern Med* 1995;155:829-37.
- Parving HH. Effects of ACE inhibitors on renal function in incipient and overt diabetic nephropathy. *J Diabetes Complications* 1996;10:133-5.
- Lewis EJ. Angiotensin-converting enzyme inhibition in type I diabetic nephropathy. *Contrib Nephrol* 1996;118:206-13.
- Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996;334:939-45.
- Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 1996;156:286-9.
- Parving HH, Rossing P, Hommel E, Smidt UM. Angiotensin-converting enzyme inhibition in diabetic nephropathy: ten years' experience. *Am J Kidney Dis* 1995;26:99-107.
- Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;274:620-5.
- Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326-31.
- Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. *JAMA* 1996;276:785-91.
- Savage S, Johnson Nagel N, Estacio RO, et al. The ABCD (Appropriate Blood Pressure Control in Diabetes) trial: rationale and design of a trial of hypertension control (moderate or intensive) in type II diabetes. *Online J Curr Clin Trials* 1993 Nov 24;Doc. No. 104:[6250 words; 128 paragraphs].
- Diabetes mellitus: report of a WHO study group. *WHO Tech Rep Ser* 1985;727:7-113.
- Heyden S, Bartel AG, Tabesh E, et al. Angina pectoris and the Rose questionnaire. *Arch Intern Med* 1971;128:961-4.
- Hiatt WR, Marshall JA, Baxter J, et al. Diagnostic methods for peripheral arterial disease in the San Luis Valley Diabetes Study. *J Clin Epidemiol* 1990;43:597-606.
- Estacio RO, Savage S, Nagel NJ, Schrier RW. Baseline characteristics of participants in the Appropriate Blood Pressure Control in Diabetes trial. *Control Clin Trials* 1996;17:242-57.
- Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs — an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 1991;98:Suppl:786-806.
- Report and recommendations of the San Antonio conference on diabetic neuropathy. *Ann Neurol* 1988;24:99-104.
- Mogensen CE. Microalbuminuria in diabetic renal disease. In: Mogensen CE, Standl E, eds. *Prevention and treatment of diabetic late complications*. New York: Walter de Gruyter, 1989:41-73.
- Devereux RB, Reichel N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 1977;55:613-8.
- Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology* 1995;46:211-9.
- McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991;87:119-28.
- Glasser SP, Ripa S, Garland WT, et al. Antianginal and antiischemic efficacy of monotherapy extended-release nisoldipine (Coat Core) in chronic stable angina. *J Clin Pharmacol* 1995;35:780-4.

- 31.** Heublein B, Amende I, Blanke PM, Baunack-Frost AR, Breuer HW. Nisoldipine versus isosorbide dinitrate in coronary heart disease: result of a double-masked study. *Clin Ther* 1996;18:448-59.
- 32.** Weinstein DB, Heider JG. Protective action of calcium channel antagonists in atherogenesis and experimental vascular injury. *Am J Hypertens* 1989;2:205-12.
- 33.** Lichtlen PR, Hugenholtz PG, Rafflenbeul W, Hecker H, Jost S, Deckers JW. Retardation of angiographic progression of coronary artery disease by nifedipine: results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). *Lancet* 1990;335:1109-13.
- 34.** Waters D, Lesperance J. Interventions that beneficially influence the evolution of coronary atherosclerosis: the case for calcium channel blockers. *Circulation* 1992;86:Suppl III:III-111-III-116.
- 35.** Janka HU, Dirschedl P. Systolic blood pressure as a predictor for cardiovascular disease in diabetes: a 5-year longitudinal study. *Hypertension* 1985;7:II-90-II-94.
- 36.** Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820-5.
- 37.** Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 1994;43:960-7.

CORRECTION

The Effect of Nisoldipine as Compared with Enalapril on Cardiovascular Outcomes in Patients with Non-Insulin-Dependent Diabetes and Hypertension

The Effect of Nisoldipine as Compared with Enalapril on Cardiovascular Outcomes in Patients with Non-Insulin-Dependent Diabetes and Hypertension . On page 645, the last two lines of the Results paragraph of the Abstract should have read, "(risk ratio, 7.0; 95 percent confidence interval, 2.3 to 21.4)," not "risk ratio, 9.5," as printed. Also, on page 647, the sentence that begins 11 lines from the bottom of the right-hand column should have read, "Ninety-nine patients in the enalapril group took a beta-blocker, as compared with 89 patients in the nisoldipine group ($P = 0.35$)," not " $(P = 0.035)$," as printed.