EFFECTS OF CALCIUM-CHANNEL BLOCKADE IN OLDER PATIENTS WITH DIABETES AND SYSTOLIC HYPERTENSION

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ABSTRACT

Background Recent reports suggest that calcium-channel blockers may be harmful in patients with diabetes and hypertension. We previously reported that antihypertensive treatment with the calcium-channel blocker nitrendipine reduced the risk of cardiovascular events. In this post hoc analysis, we compared the outcome of treatment with nitrendipine in diabetic and nondiabetic patients.

Methods After stratification according to center, sex, and presence or absence of previous cardiovascular complications, 4695 patients (age, ≥60 years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg were randomly assigned to receive active treatment or placebo. Active treatment consisted of nitrendipine (10 to 40 mg per day) with the possible addition or substitution of enalapril (5 to 20 mg per day) or hydrochlorothiazide (12.5 to 25 mg per day) or both, titrated to reduce the systolic blood pressure by at least 20 mm Hg and to less than 150 mm Hg. In the control group, matching placebo tablets were administered similarly.

Results At randomization, 492 patients (10.5 percent) had diabetes. After a median follow-up of two years, the systolic and diastolic blood pressures in the placebo and active-treatment groups differed by 8.6 and 3.9 mm Hg, respectively, among the diabetic patients. Among the 4203 patients without diabetes, systolic and diastolic pressures differed by 10.3 and 4.5 mm Hg, respectively, in the two groups. After adjustment for possible confounders, active treatment was found to have reduced overall mortality by 55 percent (from 45.1 deaths per 1000 patients to 26.4 deaths per 1000 patients), mortality from cardiovascular disease by 76 percent, all cardiovascular events combined by 69 percent, fatal and nonfatal strokes by 73 percent, and all cardiac events combined by 63 percent in the group of patients with diabetes. Among the nondiabetic patients, active treatment decreased all cardiovascular events combined by 26 percent and fatal and nonfatal strokes by 38 percent. In the group of patients receiving active treatment, reductions in overall mortality, mortality from cardiovascular disease, and all cardiovascular events were significantly larger among the diabetic patients than among the nondiabetic patients (P=0.04, P=0.02, and P=0.01, respectively).

Conclusions Nitrendipine-based antihypertensive therapy is particularly beneficial in older patients with diabetes and isolated systolic hypertension. Thus, our findings do not support the hypothesis that the use of long-acting calcium-channel blockers may be harmful in diabetic patients. (N Engl J Med 1999;340:677-84.)

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CARDIOVASCULAR disease is the leading cause of morbidity and mortality among patients with diabetes mellitus.[1] Calcium-channel blockers have been found to be safe and effective for the treatment of various cardiovascular disorders, as well as for the prevention of renal complications in patients with diabetes mellitus.[2,3] However, in 1995, a meta-analysis suggested that short-acting dihydropyridine calcium-channel blockers may provoke rather than prevent myocardial infarction in patients with coronary heart disease.[4] This study sparked a controversy, which has recently been fueled by a series of articles[5-9] and commentaries[10] suggesting that calcium-channel blockers, including second-generation dihydropyridines, such as amlodipine[5] and nisoldipine,[6] may be harmful, particularly in patients with hypertension and diabetes mellitus.

The Systolic Hypertension in Europe (Syst-Eur) Trial recently reported that antihypertensive therapy initiated with the dihydropyridine nitrendipine reduced the risk of fatal and nonfatal stroke, as well as all cardiovascular events combined, in older patients with isolated systolic hypertension.[11,12] The present study is a post hoc analysis of the data in the Syst-Eur trial to determine whether nitrendipine had different effects on the long-term outcome in diabetic and nondiabetic patients with hypertension.

METHODS

Design of the Trial

The protocol of the Syst-Eur trial, described in detail elsewhere,[11-13] was approved by the ethics committees of the University

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*Other investigators participating in the Systolic Hypertension in Europe trial are listed in the Appendix.

of Leuven, Leuven, Belgium, and the participating centers and was implemented according to the Declaration of Helsinki.[14] Patients were eligible for the study if they were 60 years of age or older and had a systolic blood pressure ranging from 160 to 219 mm Hg systolic and a diastolic blood pressure below 95 mm Hg while they were seated, with a systolic pressure of 140 mm Hg or higher while they were standing. Diabetic patients were eligible only if their blood glucose concentrations were adequately controlled. Diabetes was defined according to the criteria of the World Health Organization[15]: a history of diabetes mellitus, treatment with antidiabetic drugs, or a fasting or nonfasting blood glucose concentration greater than or equal to 140 or 200 mg per deciliter (7.8 or 11.1 mmol per liter), respectively.

After stratification according to center, sex, and previous cardiovascular complications,[11,13] the patients were randomly assigned to double-blind treatment with active medication or placebo by means of a computer-generated schedule. The doses of the study medications were titrated stepwise, either alone or in combination, to reduce the systolic blood pressure while sitting by at least 20 mm Hg, to a level below 150 mm Hg.[13] Active treatment was initiated with nitrendipine (first-line medication) at a dose of 10 to 40 mg per day. If necessary, the calcium-channel blocker was combined with or replaced by enalapril (second-line medication) at a dose of 5 to 20 mg per day, hydrochlorothiazide (third-line medication) at a dose of 12.5 to 25 mg per day, or both drugs. In the control group, matching placebo pills were administered similarly. Patients who withdrew from double-blind treatment remained in open follow-up.[11-13]

Validation of End Points

An end-point committee, whose members were unaware of the treatment assigned, validated all end points by reviewing the patients' medical records and other documents, requesting detailed written information from the investigators, or both. Stroke, the primary end point in the Syst-Eur trial, was defined as a neurologic deficit persisting for more than 24 hours or leading to death, with no apparent cause other than vascular impairment. The diagnosis of acute myocardial infarction was based on the presence of at least two of the following three findings: characteristic chest pain, electrocardiographic changes, and elevated cardiac-enzyme levels. Congestive heart failure was defined on the basis of symptoms (such as dyspnea), clinical signs (such as ankle edema or rales), and the need for treatment with diuretics, vasodilators, or antihypertensive drugs. Sudden deaths included deaths of unknown cause occurring instantaneously or within 24 hours after the onset of acute symptoms and unattended deaths for which no likely cause could be established on the basis of an autopsy or the recent medical history. Cardiac end points included fatal and nonfatal heart failure, fatal and nonfatal myocardial infarction, and sudden death.

Statistical Analysis

Statistical analysis was performed according to the intention-to-treat principle, with the use of two-sided tests and SAS software.[11] Net differences in blood pressure after randomization between the active-treatment and placebo groups were calculated by subtracting the mean change from base line in the placebo group from the corresponding change in the active-treatment group.[16] Comparisons of means, proportions, and rates were performed with the standard normal z-test, the chi-square statistic, and the log-rank test, respectively. The effects of active antihypertensive treatment on end points and the interaction between diabetes and active treatment were determined by Cox multiple regression analysis, with adjustment for sex, presence or absence of previous cardiovascular complications, age, systolic blood pressure at enrollment, smoking status, and residence in eastern or western Europe. Previous analyses had demonstrated that, in addition to active treatment, these variables were significant predictors of one or more end points.[12]

RESULTS

Characteristics of the Patients

Of 4695 patients randomly assigned to receive active treatment or placebo, 492 (10.5 percent) had diabetes mellitus. Of these patients, 446 had a history of diabetes reported by the investigators, 229 had a fasting blood glucose concentration of 140.5 mg per deciliter (7.8 mmol per liter) or higher, and 13 had a nonfasting blood glucose concentration of 200.0 mg per deciliter (11.1 mmol per liter) or higher; 226 patients were receiving treatment with oral antidiabetic drugs, 12 with insulin, and 51 with both.

As compared with the 4203 nondiabetic patients, the diabetic patients had a higher mean blood glucose concentration (147.7 vs. 92.0 mg per deciliter [8.2 vs. 5.1 mmol per liter]), body-mass index, defined as the weight in kilograms divided by the square of the height in meters (28.3 vs. 27.0), and serum triglyceride concentration (168.3 vs. 141.7 mg per deciliter [1.9 vs. 1.6 mmol per liter]) and a lower mean high-density lipoprotein cholesterol concentration (50.3 vs. 54.1 mg per deciliter [1.3 vs. 1.4 mmol per liter]) ($P<0.001$ for all comparisons). In the diabetic patients, the mean (±SD) systolic blood pressure at randomization was 175.3±10.5 mm Hg, and the mean diastolic pressure was 84.5±6.3 mm Hg; in the nondiabetic patients, the mean pressures were 173.7±9.9 and 85.6±5.8 mm Hg, respectively. Thus, the patients with diabetes had a mean systolic blood pressure that was 1.7 mm Hg higher than that in the nondiabetic patients but a diastolic blood pressure that was 1.1 mm Hg lower, so that the pulse pressure was 2.8 mm Hg wider in the diabetic patients (90.9±11.4, vs. 88.1±11.2 mm Hg in the nondiabetic patients; $P<0.001$).

A significantly larger proportion of diabetic patients had used antihypertensive drugs before enrollment (61.8 percent, vs. 44.8 percent of the nondiabetic patients), had had previous cardiovascular complications (35.0 percent vs. 29.3 percent), or had proteinuria at the time of enrollment (15.5 percent vs. 8.5 percent). On the other hand, the diabetic and nondiabetic groups had similar proportions of women (64.6 percent and 67.1 percent, respectively) and smokers (6.3 percent and 7.4 percent, respectively).

Blood-Pressure Control

The median duration of follow-up was two years. The proportion of patients who received multiple study drugs and the proportion who withdrew from the double-blind protocol and received open-label treatment increased faster in the placebo group than in the active-treatment group ($P<0.001$). However, antihypertensive treatment was similar in the diabetic and nondiabetic patients (Table 1). Furthermore, similar proportions of diabetic and nondiabetic patients were taking lipid-lowering drugs at random-

TABLE 1. STUDY MEDICATIONS RECEIVED BY DIABETIC AND NONDIABETIC PATIENTS.

MEDICATION*	DIABETIC		NONDIABETIC	
	PLACEBO (N=240)	ACTIVE TREATMENT (N=252)	PLACEBO (N=2057)	ACTIVE TREATMENT (N=2146)
	no. of patients (%)			
None or unknown	4 (1.7)	3 (1.2)	40 (1.9)	34 (1.6)
Only nitrendipine	88 (36.7)	140 (55.6)	771 (37.5)	1179 (54.9)
Only enalapril	0	0	4 (0.2)	2 (0.1)
Only hydrochlorothiazide	0	0	0	0
Nitrendipine plus enalapril	61 (25.4)	69 (27.4)	531 (25.8)	557 (26.0)
Nitrendipine plus hydrochlorothiazide	2 (0.8)	1 (0.4)	16 (0.8)	20 (0.9)
Enalapril plus hydrochlorothiazide	0	0	0	0
Nitrendipine plus enalapril plus hydrochlorothiazide	85 (35.4)	39 (15.5)	695 (33.8)	354 (16.5)

*Patients in the placebo group received placebo pills that matched the active medication.

TABLE 2. BENEFIT OF ANTIHYPERTENSIVE TREATMENT IN DIABETIC AND NONDIABETIC PATIENTS.*

OUTCOME	DIABETIC				NONDIABETIC			
	PLACEBO (N=240)	ACTIVE TREATMENT (N=252)	BENEFIT OF TREATMENT (95% CI)	P VALUE	PLACEBO (N=2057)	ACTIVE TREATMENT (N=2146)	BENEFIT OF TREATMENT (95% CI)	P VALUE
	end points/ 1000 patient-years (no. of events)		%		end points/ 1000 patient-years (no. of events)		%	
Mortality								
Overall	45.1 (26)	26.4 (16)	41 (−9 to 69)	0.09	21.6 (111)	19.8 (107)	8 (−20 to 30)	0.55
Cardiovascular causes	27.8 (16)	8.3 (5)	70 (19 to 89)	0.01	11.9 (61)	10.0 (54)	16 (−22 to 42)	0.37
Fatal and nonfatal end points								
All cardiovascular events	57.6 (31)	22.0 (13)	62 (19 to 80)	0.002	31.4 (155)	23.5 (124)	25 (5 to 41)	0.02
Stroke	26.6 (15)	8.3 (5)	69 (14 to 89)	0.02	12.3 (62)	7.8 (42)	36 (5 to 57)	0.02
Cardiac events	27.1 (15)	11.7 (7)	57 (−6 to 82)	0.06	19.7 (99)	15.4 (82)	22 (−5 to 42)	0.10

*The benefit was expressed as the percent reduction in the event rate for the active-treatment group. Negative numbers indicate increases in the event rate. CI denotes confidence interval.

ization (3 to 4 percent) or started to take such drugs during follow-up (2 to 3 percent).

The blood pressure decreased to the same extent in the diabetic and nondiabetic patients. After a median of two years of follow-up, mean systolic and diastolic pressures in the patients with diabetes had fallen by 13.5±16.5 and 2.9±7.8 mm Hg, respectively, in the placebo group and by 22.1±14.5 and 6.8±8.2 mm Hg, respectively, in the active-treatment group. Among the nondiabetic patients, mean systolic and diastolic pressures were reduced by 13.0±16.9 and 2.2±7.8 mm Hg, respectively, in the placebo group and by 23.3±16.2 and 6.7±8.3 mm Hg, respectively, in the active-treatment group. Thus, the net differences in systolic and diastolic pressures between the placebo and active-treatment groups were 8.6 and 3.9 mm Hg, respectively, among the diabetic patients and 10.3 and 4.5 mm Hg, respectively, among the nondiabetic patients ($P=0.40$ for the comparison of systolic pressure between the diabetic and nondiabetic patients and $P=0.44$ for the comparison of diastolic pressure between the diabetic and nondiabetic patients).

Outcome in Diabetic and Nondiabetic Patients

Among the diabetic patients, active treatment significantly reduced the incidence of all end points except overall mortality; among the nondiabetic patients, active treatment significantly reduced only the incidence of all cardiovascular complications and the incidence of stroke (Table 2).

Cox regression with adjustments for sex, presence or absence of previous cardiovascular complications, age, systolic blood pressure at enrollment, smoking status, and residence in eastern or western Europe showed that in the group of diabetic patients, active treatment reduced overall mortality by 55 percent, mortality from cardiovascular causes by 76 percent, all cardiovascular events by 69 percent, fatal and nonfatal stroke by 73 percent, and all cardiac events by 63 percent (Fig. 1). In the group of nondiabetic patients, active treatment reduced all cardiovascular events by 26 percent and fatal and nonfatal stroke by 38 percent. The effect of active treatment on overall mortality, mortality from cardiovascular causes, and all cardiovascular events combined was greater in the group of patients with diabetes than in the group without diabetes ($P=0.04$, $P=0.02$, and $P=0.01$, respectively).

Overall mortality was higher in the diabetic patients than in the nondiabetic patients (Table 2). However, active antihypertensive treatment eliminated the excess cardiovascular risk in the diabetic patients (Table 3). In the placebo group, the adjusted relative hazard for the diabetic patients as compared with the nondiabetic patients was higher than 2.0 ($P<0.001$) for each end point except all cardiac events combined, whereas in the active-treatment group, the relative hazard for the diabetic patients was approximately 1.0 or less for all the end points (with P values ranging from 0.36 to 0.96).

The incidence of all cardiovascular events combined was also calculated separately for patients who continued to receive nitrendipine alone and for those who received any combination of nitrendipine, enalapril, and hydrochlorothiazide (or matching placebo pills) or enalapril alone. In the placebo group, the event rates among the diabetic patients were approximately twice as high as those among the patients without diabetes, regardless of the treatment regimen (Tables 2 and 4). In the active-treatment group, the excess cardiovascular risk among the diabetic patients was reduced to that among the nondiabetic patients; this was true whether treatment consisted only of nitrendipine or whether other medications were used in addition to or instead of nitrendipine (Table 4).

DISCUSSION

The results of this double-blind, placebo-controlled trial indicate that antihypertensive treatment beginning with a dihydropyridine calcium-channel blocker was particularly beneficial in diabetic patients as compared with nondiabetic patients. The cardiovascular benefit was the same whether the patients continued to receive nitrendipine alone or subsequently received enalapril, hydrochlorothiazide,

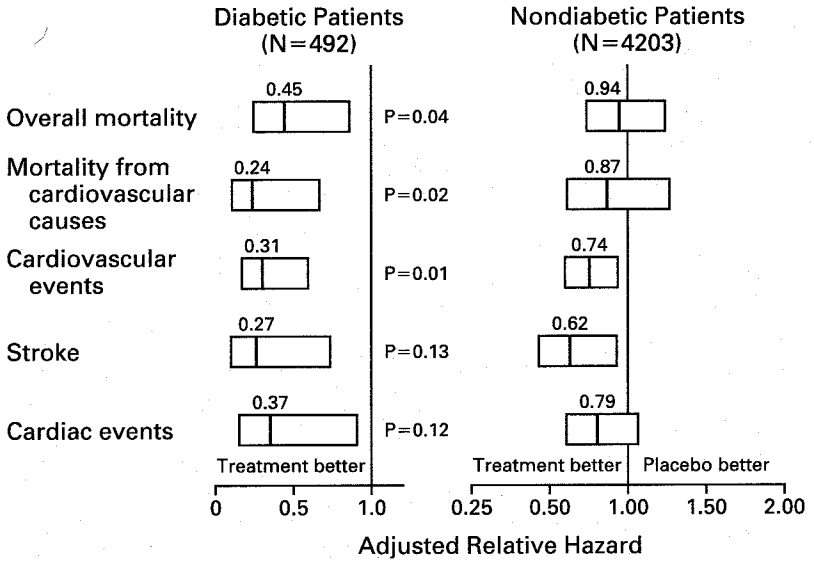

Figure 1. Adjusted Relative Hazards Associated with Active Treatment as Compared with Placebo in Diabetic and Nondiabetic Patients.

The relative hazards were adjusted for sex, age, previous cardiovascular complications, systolic blood pressure at enrollment, smoking status, and residence in eastern or western Europe. The P values are for the interaction between treatment and diabetes and indicate whether the treatment effect was significantly associated with the presence or absence of diabetes at enrollment. Cardiovascular events, stroke, and cardiac events included fatal and nonfatal events. The bars indicate the 95 percent confidence intervals. The numbers above the bars indicate the benefit of the active treatment as compared with placebo.

TABLE 3. ADJUSTED RELATIVE HAZARD FOR DIABETIC PATIENTS.*

END POINT	PLACEBO	ACTIVE TREATMENT
	relative hazard (95% CI)	
Mortality		
Overall	2.21 (1.43–3.41)	1.10 (0.65–1.88)
Cardiovascular causes	2.50 (1.43–4.37)	0.69 (0.28–1.74)
Fatal and nonfatal end points		
All cardiovascular events	2.07 (1.40–3.05)	0.86 (0.48–1.52)
Stroke	2.16 (1.22–3.82)	0.98 (0.39–2.49)
Cardiac events†	1.57 (0.91–2.72)	0.69 (0.32–1.51)

*The reference group was patients without diabetes. Relative hazards were adjusted for sex, age, previous cardiovascular complications, systolic blood pressure at enrollment, smoking status, and residence in eastern or western Europe. CI denotes confidence interval.

TABLE 4. RATE OF ALL CARDIOVASCULAR EVENTS COMBINED, ACCORDING TO DIABETIC STATUS AND STUDY MEDICATION.

MEDICATION	DIABETIC		NONDIABETIC	
	PLACEBO (N=240)	ACTIVE TREATMENT (N=252)	PLACEBO (N=2057)	ACTIVE TREATMENT (N=2146)
	end points/1000 patient-years (no. of events)			
Only nitrendipine	91.6 (13)	23.7 (7)	42.5 (64)	25.6 (68)
Other study medications with or without nitrendipine*	45.5 (18)	20.3 (6)	26.5 (91)	21.3 (56)

*This category included enalapril alone, hydrochlorothiazide alone, and any combination of nitrendipine, enalapril, and hydrochlorothiazide.

or both drugs in addition to or instead of nitrendipine.[17] The relative benefit of antihypertensive treatment has been similar in many outcome trials, but the absolute benefit has varied widely according to the number of end points observed in the control group.[18] The results of our study are different in that both the relative benefit and the absolute benefit were significantly greater in diabetic patients than in nondiabetic patients. Active treatment reduced the rate of all cardiovascular events combined by 69 percent in the diabetic patients but by only 26 percent in the patients without diabetes. In terms of the absolute benefit, the event rates in the placebo group suggest that antihypertensive treatment for five years would prevent 178 major cardiovascular events in every 1000 diabetic patients treated, as compared with only 39 such events in every 1000 nondiabetic patients.

The Systolic Hypertension in the Elderly Program (SHEP) trial was the first study of antihypertensive treatment in older patients with isolated systolic hypertension (systolic blood pressure, 160 to 219 mm Hg; diastolic blood pressure, less than 90 mm Hg).[19] The SHEP trial demonstrated that the incidences of nonfatal stroke and nonfatal myocardial infarction were lower in patients receiving treatment with a low-dose diuretic (12.5 to 25 mg of chlorthalidone per day) than in those not receiving diuretic treatment. Type 2 diabetes mellitus was present at randomization in 583 of the 4736 patients in the SHEP trial (12.3 percent).[20] Among the patients randomly assigned to placebo, the risks of cardiovascular events in the diabetic and nondiabetic groups were similar to those in our study (Fig. 2). There were also similar reductions in net systolic and diastolic blood pressure in the diabetic patients (SHEP trial, 9.8 and 2.2 mm Hg, respectively; our study, 8.6 and 3.9 mm Hg, respectively) and the nondiabetic patients (SHEP trial, 12.5 and 4.1 mm Hg, respectively; our study, 10.3 and 4.5 mm Hg, respectively). In the SHEP trial, antihypertensive treatment reduced the incidence of cardiovascular complications by 34 percent in both the diabetic patients (95 percent confidence interval, 54 to 6 percent) and the nondiabetic patients (95 percent confidence interval, 45 to 21 percent),[20] whereas in our study, the diabetic patients fared better than the nondiabetic patients. The results of these two studies suggest that in diabetic patients with hypertension, long-acting dihydropyridines may provide better cardiovascular protection than low-dose thiazides. The superior protective effect of dihydropyridines may be due to the absence of metabolic side effects,[21,22] such as glucose intolerance and perturbation of the serum lipid profile, to which diabetic patients treated with thiazides may be particularly vulnerable.[23] In addition, calcium-channel blockers may provide renal protection[2,3] and may have beneficial effects on the rheologic properties of the blood[24] and on endothelial function.[25,26]

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[6] which enrolled 470 diabetic patients, reported a significantly higher incidence of fatal and nonfatal cases of myocardial infarction in the group of patients randomly assigned to treatment with nisoldipine (25 cases) than in the group treated with enalapril (5 cases). However, the ABCD trial was designed to study changes in creatinine clearance, and myocardial infarction was only a secondary end point.[6] Treatment status and doses with regard to the double-blind study medication being used at the time of infarction were not reported. Because more patients in the enalapril group received diuretics (119, vs. 93 in the nisoldipine group; $P=0.02$) and beta-blockers (95 vs. 89, $P=0.04$) and because more patients in the nisoldipine group stopped taking the study medication (142, vs. 129 in the enalapril group; $P=0.22$), overall cardiovascular protection may have been greater in the enalapril group. Any cardiovascular event may be the forerunner of myocardial infarction. For this reason, information about initial cardiovascular events might also have been helpful in

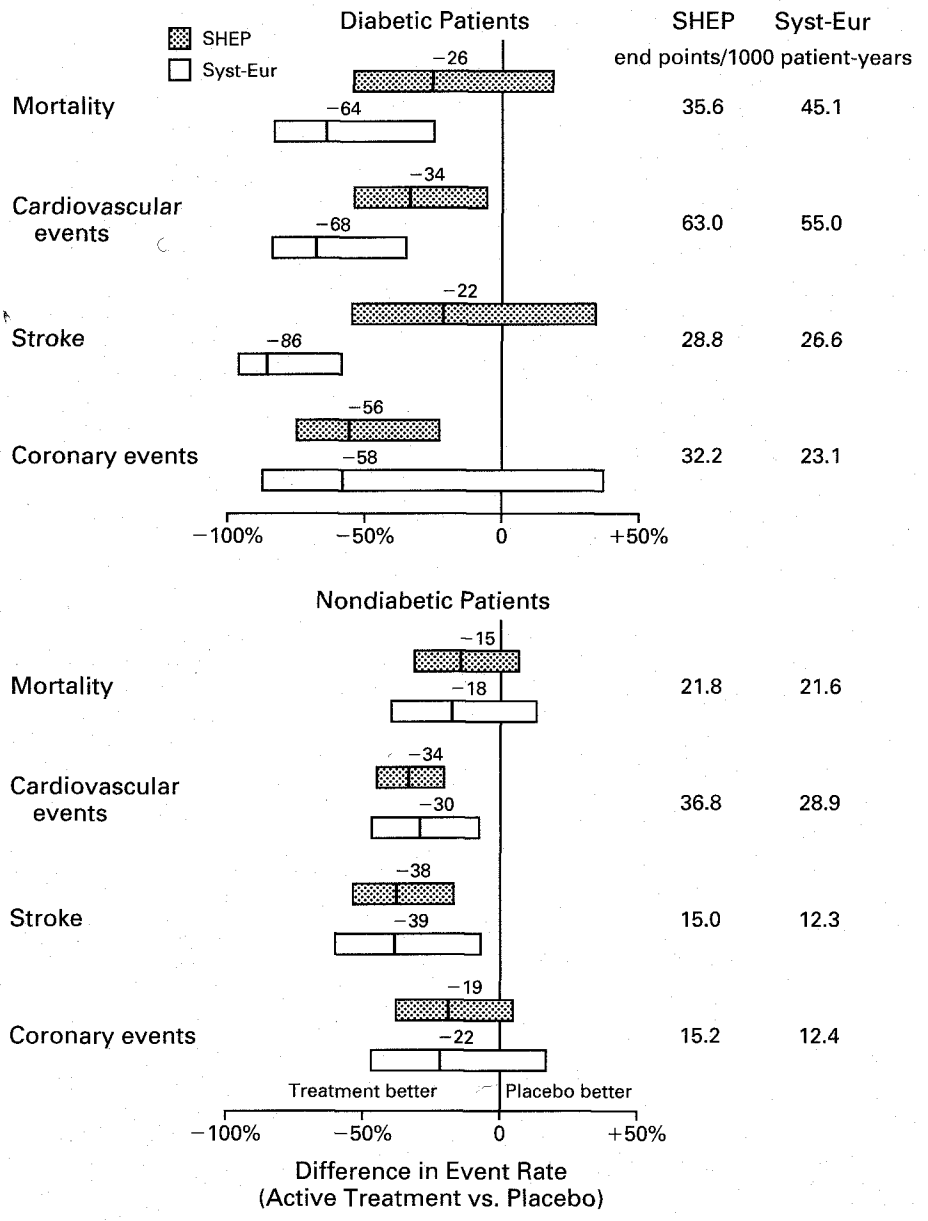

Figure 2. Outcomes in the Systolic Hypertension in the Elderly Program (SHEP) Trial and in the Syst-Eur Trial.

For these comparisons, the end points were standardized according to the definitions used in the SHEP trial.[19,20] The two right-hand columns show the number of events per 1000 patient-years in the placebo groups in the two trials. The bars indicate the 95 percent confidence intervals. The numbers above the bars indicate the benefit of the active treatment as compared with placebo.

interpreting the results of the ABCD trial, but such data were not presented.[6]

In the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial,[5] significantly fewer patients receiving fosinopril had acute myocardial infarction or stroke or were hospitalized for angina pectoris (14 of 189 patients, vs. 27 of 191 treated with amlodipine). However, the trial had an open design, and events were documented by asking the patients whether they had been hospitalized or had had any other event. Unlike the findings in the ABCD trial,[6] the differences in outcomes between the amlodipine and fosinopril groups were accounted for not primarily by myocardial infarction (which occurred in 13 patients in the fosinopril group and 10 in the amlodipine group) but by hospitalization for angina (4 vs. 0) or

stroke (10 vs. 4).[5] The results of the trial are difficult to interpret, because 58 patients randomly assigned to receive fosinopril (31 percent) and 50 assigned to receive amlodipine (26 percent) crossed over and received a combination of the two drugs.

In the Established Populations for Epidemiologic Studies of the Elderly study, the higher mortality associated with the use of calcium-channel blockers was attributable not to coronary heart disease but to cancer and gastrointestinal bleeding.[27] Other findings suggesting that calcium-channel blockers may be contraindicated in diabetic patients were obtained from a reanalysis[7] of a case–control study[28] with a relatively small number of diabetic patients (34 of 344) and from a randomized clinical trial that excluded patients with overt diabetes mellitus.[8,29] On the other hand, in keeping with our findings, the Hypertension Optimal Treatment trial[30] demonstrated that the tighter control of blood pressure (target diastolic blood pressure, 80 mm Hg rather than 90 mm Hg) achieved with felodipine used as the first-line agent resulted in lower rates of all cardiovascular events in the group of 1501 patients with diabetes (relative risk, 0.49; 95 percent confidence interval, 0.29 to 0.81; P=0.005) but not in the overall study population of 18,790 patients (relative risk, 0.93; 95 percent confidence interval, 0.78 to 1.12; P=0.50).

In conclusion, our trial demonstrated that dihydropyridine-based antihypertensive treatment is particularly beneficial in older diabetic patients with isolated systolic hypertension. Thus, our findings do not support the hypothesis that the use of long-acting calcium-channel blockers may be harmful in diabetic patients.

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APPENDIX

The Syst-Eur Trial was part of the BIOMED Research Program, sponsored by the European Union, and was conducted in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League. The following investigators were responsible for the coordination of 198 participating clinical centers in 11 eastern European countries and 12 western European countries: *trial coordinators* — R. Fagard and J.A. Staessen; *regional coordinators* — G.G. Arabidze (Belarus and the Russian Federation), W.H. Birkenhäger (the Netherlands), C.J. Bulpitt (United Kingdom), M. Carrageta (Portugal), H. Celis (Belgium), F. Forette (France), J. Kocemba (Poland), G. Leonetti (Italy), C. Nachev (Bulgaria), E.T. O'Brien (Ireland), E. Ritz (Germany), J.L. Rodicio (Spain), J. Rosenfeld (Israel), and J. Tuomilehto (Finland, Estonia, and Lithuania); *coordinators of general practices* — H. Celis, with the help of J. Heyrman, G. Stibbe, M. Van den Haute, and Y. Yodfat; *Steering Committee* — G.G. Arabidze, P. De Cort, R. Fagard, F. Forette, K. Kawecka-Jaszcz, G. Leonetti, C. Nachev, E.T. O'Brien, J.L. Rodicio, J. Rosenfeld, J. Tuomilehto, J. Webster, and Y. Yodfat; *Ethics Committee* — W.H. Birkenhäger, C.T. Dollery, and R. Fagard; *Data Monitoring Committee* — C.J. Bulpitt, A.E. Fletcher, J.A. Staessen, and L. Thijs; *Endpoint Committee* — P.W. de Leeuw, R. Fagard, G. Leonetti, and J.C. Petrie, with the help of H. Vanhanen (associate member); *Publication Committee* — W.H. Birkenhäger, C.J. Bulpitt, J.A. Staessen, and A. Zanchetti; and *Drug Committee* — H. Celis, G. Demol, P. Demol, R. Fagard, G.E. Hübner, and J.A. Staessen. The complete list of Syst-Eur investigators appears in Staessen et al.[11,12]

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