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Calcium Antagonists and Mortality in Patients With Coronary Artery Disease: A Cohort Study of 11,575 Patients

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Objectives. **This study sought to establish the risk ratio for mortality associated with calcium antagonists in a large population of patients with chronic coronary artery disease.**

Background. **Recent reports have suggested that the use of short-acting nifedipine may cause an increase in overall mortality in patients with coronary artery disease and that a similar effect may be produced by other calcium antagonists, in particular those of the dihydropyridine type.**

Methods. **Mortality data were obtained for 11,575 patients screened for the Bezafibrate Infarction Prevention study (5,843 with and 5,732 without calcium antagonists) after a mean follow-up period of 3.2 years.**

Results. **There were 495 deaths (8.5%) in the calcium antagonist group compared with 410 in the control group (7.2%). The age-adjusted risk ratio for mortality was 1.08 (95% confidence interval [CI] 0.95 to 1.24). After adjustment for the differences between the groups in age and gender and the prevalence of previous myocardial infarction, angina pectoris, hypertension, New York Heart Association functional class, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes and current smoking, the adjusted risk ratio declined to 0.97 (95% CI 0.84 to 1.11). After further adjustment for concomitant medication, the risk ratio was estimated at 0.94 (95% CI 0.82 to 1.08).**

Conclusions. **The current analysis does not support the claim that calcium antagonist therapy in patients with chronic coronary artery disease, whether myocardial infarction survivors or others, harbors an increased risk of mortality.**

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For the last two decades calcium antagonists have been among the most widely used drugs for the treatment of angina pectoris and hypertension. Numerous studies have shown that calcium antagonists (e.g., nifedipine, verapamil, diltiazem, amlodipine and others) were therapeutically effective in patients with chronic stable angina pectoris: they not only ameliorated symptoms but also objectively decreased ischemia on exercise test, reduced ST segment changes on ambulatory electrocardiographic monitoring, increased coronary artery blood flow and improved ventricular dysfunction associated with ischemia (1–4). Studies of hypertensive patients showed that calcium antagonists were as effective as antihypertensive agents and were free of many of the side effects of diuretics and beta-adrenergic blocking agents (5).

Several clinical trials and meta-analyses of the clinical trials of calcium antagonists in myocardial infarction and unstable angina pectoris suggested that the drugs had an unfavorable effect on mortality (6–14). In a recent report Furberg et al. (15) suggested that the use of short-acting nifedipine at moderate and high doses may cause an increase in overall mortality in patients with coronary artery disease, and that a similar effect may be produced by other calcium antagonists, in particular those of the dihydropyridine type. Because long-term safety data are lacking for most calcium antagonists, the aim of the present study was to estimate the risk ratio for mortality associated with calcium antagonists in a large population of patients with chronic coronary artery disease, 70% of whom had at least one previous myocardial infarction. Data were collected in patients screened for participation in the Bezafibrate Infarction Prevention (BIP) study (16).

Methods

Between February 1, 1990, and October 30, 1992, clinical data on more than 20,000 male and female patients aged 45 to 74 years and presumed to have coronary artery disease were recorded in the log books of 18 cardiology departments in Israel. A total of 15,502 patients with an established diagnosis of chronic coronary artery disease were screened for inclusion

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in the BIP study, and they comprised the population in the BIP registry. The BIP study (16), a placebo-controlled, secondary prevention study, is currently being conducted on 3,122 patients in 18 cardiology departments in Israel with the aim of assessing the efficacy of the long-term administration of bezafibrate on the reduction of fatal and nonfatal coronary events in patients with coronary artery disease.

All the patients screened for the BIP study underwent a medical examination and a blood test after fasting for 14 h. Medical, historical and drug intake data were recorded. The diagnosis of coronary artery disease was made in patients with documented myocardial infarction or typical angina pectoris in whom there was also a positive exercise test, evidence of myocardial ischemia revealed by radionuclear studies or at least 60% stenosis of one major coronary artery. Patients who had undergone percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were considered for study entry if the procedure had been performed at least 6 months before inclusion into the study.

The current analysis is restricted to the patients who had been screened but had not been included in the BIP study. Mortality data on 11,575 of the 15,502 screenees, after a mean follow-up period of 3.2 years (range 2.0 to 4.6), were obtained by matching the patients' identification number with their life status in the Israeli Population Registry. Death certificates and diagnosis at hospital discharge were coded using the system described in the ninth edition of the *International Classification of Disease* (ICD-9), in which coronary artery disease is denoted by codes 410 to 414.

Statistical methods. Results of continuous variables are reported as mean value ± SD. The chi-square and Student *t* tests were used to determine the significance of differences between proportions and means, respectively. The adjusted relative risk of mortality associated with calcium antagonist use was estimated using the Cox proportional hazards model (17). The statistical power of detecting clinically meaningful differences with a mortality rate of 7.2% in nonusers of calcium antagonists was 0.90, under a type 1 error of 0.05 and an odds ratio as large as 1.25 (corresponding to a mortality rate of ~9.2% in calcium antagonist users). The power declined progressively to 0.74, 0.50 and 0.030, with declining odds ratios of 1.2, 1.15 and 1.1.

Results

Demographics and clinical characteristics. Table 1 summarizes the characteristics of patients being treated with calcium antagonists compared with those not receiving the drugs (control subjects). At the screening visit, 5,843 patients were treated with either nifedipine, verapamil or diltiazem, the only calcium antagonists approved in Israel at that time. The control group consisted of 5,732 patients who did not receive calcium antagonist. The clinical characteristics of both groups were similar, except that there were more patients with grades II to IV angina pectoris and hypertension in the calcium antagonist group and more patients in the control group were receiving beta-blockers and digoxin. The clinical characteristics of the 3,122 patients included in the BIP study were similar to the 11,575 patients not recruited for the BIP study, except that there were more men (92%), more patients who had had a myocardial infarction (77%) and fewer patients suffering from diabetes mellitus (10%).

Table 1. Baseline Clinical Characteristics of 11,575 Study Patients

	Calcium Antagonist Group (n = 5,843)	Control Group (n = 5,732)
Age (yr)	60.4	59.2
Weight (kg)	75 ± 12	75 ± 12
Systolic BP (mm Hg)	137 ± 19	133 ± 19
Diastolic BP (mm Hg)	82 ± 10	81 ± 10
Heart rate (beats/min)	71 ± 10	71 ± 10
Men	75	82
NYHA functional class		
I	66	76
II	27	19
III/IV	7	5
History of MI	70	72
Current angina (CCS)		
None	30	49
I	32	30
II	34	19
III/IV	4	2
Hypertension	38	29
Diabetes mellitus	23	20
CVA	2.2	1.5
PVD	5	3
COPD	3.6	2.5
Current smoker	10	11
Drug therapy		
Beta-blockers	29	39
Digoxin	3	7
Diuretic drugs	16	16
Antiarrhythmic agents	5	7
Aspirin	56	58

Data presented are mean value, mean value ± SD or number (%) of patients. BP = blood pressure; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; CVA = cerebral vascular accident; MI = myocardial infarction; NYHA = New York Heart Association; PVD = peripheral vascular disease.

Mortality rates in users and nonusers of calcium antagonists. Table 2 summarizes the mortality figures in both groups. There were 495 (8.5%) deaths in the calcium antagonist group compared with 410 (7.2%) deaths in the control group. The age-adjusted risk ratio (RR) for mortality was 1.08 (95% confidence interval [CI] 0.95 to 1.24). After adjustment for the differences between the groups in age and gender and the prevalence of previous myocardial infarction, angina pectoris, hypertension, New York Heart Association functional class, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes and current smoking, the RR declined to 0.97 (95% CI 0.84 to 1.11) (Table 3). On further adjustment for the above-mentioned characteristics, the calculation of the RR for the different subgroups was consistent with a significantly increased mortality risk for patients <55 years of age in the

Table 2. Calcium Antagonists and Age-Adjusted Mortality: Subgroup Analysis

	Mortality		
	Calcium Antagonist Group	Control Group	RR (95% CI)
Total	495 (8.5)	410 (7.2)	1.08 (0.95–1.24)
Men	390 (8.9)	331 (7.0)	1.18 (1.02–1.36)
Women	105 (7.1)	79 (7.6)	0.83 (0.62–1.12)
Past MI	401 (9.8)	337 (8.2)	1.11 (0.96–1.28)
No MI	92 (5.3)	72 (4.5)	1.06 (0.78–1.44)
Hypertension	212 (9.5)	139 (8.4)	1.09 (0.88–1.35)
No hypertension	281 (7.8)	271 (6.7)	1.04 (0.88–1.24)
Diabetes	178 (13.3)	146 (12.7)	0.98 (0.79–1.22)
No diabetes	316 (7.0)	264 (5.8)	1.10 (0.94–1.30)
PVD	46 (15.9)	43 (22.2)	0.66 (0.43–1.00)
NO PVD	442 (8.0)	365 (6.6)	1.10 (0.96–1.27)
COPD	35 (16.7)	25 (17.6)	0.87 (0.52–1.46)
No COPD	457 (8.2)	383 (6.9)	1.08 (0.94–1.24)
NYHA functional class			
I	289 (7.7)	232 (5.5)	1.30 (1.09–1.54)
II	135 (8.9)	120 (11.7)	0.68 (0.53–0.86)
III/IV	60 (14.2)	44 (15.8)	0.76 (0.52–1.13)
Angina (CCS)			
None	138 (7.8)	154 (5.5)	1.29 (1.02–1.63)
I	136 (7.2)	120 (7.0)	0.94 (0.74–1.20)
II	191 (9.7)	109 (10.2)	0.88 (0.69–1.11)
III/IV	29 (13.7)	22 (21.2)	0.54 (0.31–0.94)
Smoker			
Current	59 (9.7)	58 (9.5)	0.93 (0.64–1.33)
Past	256 (8.5)	189 (6.5)	1.22 (1.01–1.47)
Never	175 (8.0)	155 (7.3)	1.00 (0.80–1.24)

Data presented are number (%) of patients. CI = confidence interval; RR = risk ratio; other abbreviations as in Table 1.

Table 3. Calcium Antagonists and Mortality, Adjusted for Age, Gender, Previous Myocardial Infarction, Angina, New York Heart Association Functional Class, Hypertension, Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease, Diabetes and Current Smoking

	Mortality		
	Calcium Antagonist Group	Control Group	RR (95% CI)
Total	495 (8.5)	410 (7.2)	0.97 (0.84–1.11)
Men	390 (8.9)	331 (7.0)	1.01 (0.86–1.18)
Women	105 (7.1)	79 (7.6)	0.87 (0.64–1.18)
Age (yr)			
<55	69 (5.8)	55 (3.5)	1.39 (0.96–2.01)
55–64	191 (7.1)	178 (7.2)	0.82 (0.67–1.02)
65–75	235 (12.0)	177 (10.6)	1.05 (0.86–1.29)
Past MI	401 (9.8)	337 (8.2)	0.98 (0.84–1.14)
No MI	92 (5.3)	72 (4.5)	0.94 (0.68–1.30)
Hypertension	212 (9.5)	139 (8.4)	1.03 (0.82–1.28)
No hypertension	281 (7.8)	271 (6.7)	0.94 (0.79–1.12)
Diabetes	178 (13.3)	146 (12.7)	0.89 (0.71–1.12)
No diabetes	316 (7.0)	264 (5.8)	1.04 (0.87–1.24)
NYHA functional class			
I	289 (7.7)	232 (5.5)	1.19 (0.99–1.42)
II	135 (8.9)	120 (11.7)	0.68 (0.53–0.86)
III/IV	60 (14.2)	44 (15.8)	0.81 (0.54–1.21)
Angina (CCS)			
None	138 (7.8)	154 (5.5)	1.21 (0.95–1.55)
I	136 (7.2)	120 (7.0)	0.92 (0.72–1.18)
II	191 (9.7)	109 (10.2)	0.84 (0.66–1.07)
III/IV	29 (13.7)	22 (21.2)	0.58 (0.32–1.06)

Data presented are number (%) of patients. Abbreviations as in Tables 1 and 2.

calcium antagonist group, for patients without angina pectoris and for patients in the functional class I, although the 95% CI included "1" for all these subgroups. Conversely, it was consistent with reduced mortality for the patients with a functional class higher than I and for those with angina pectoris. On further adjustment for concomitant use of other medications (beta-blockers, aspirin, nitrates and diuretic drugs) the RR was not markedly altered—0.94 with a 95% CI 0.82 to 1.08.

Of the 5,843 patients treated with calcium antagonists, 3,320 received diltiazem (57%), 1,999 nifedipine (34%) and 350 verapamil (6%). In addition, 174 patients (3%) were treated with a combination of two calcium antagonists. The mortality rates for the three single calcium antagonist groups were 8.0%, 8.8% and 8.6%, respectively (the differences were not significant) (Table 4).

Discussion

In Israel calcium antagonists are among the most commonly used drugs for patients with cardiovascular disease. Fifty percent of the patients screened for the BIP study were receiving one of the three calcium antagonists approved in Israel for the treatment of angina pectoris or hypertension. The mortality analysis over a period of 3.2 years showed a slightly greater mortality in the calcium antagonist group; however, because of the different prevalences of some clinical characteristics between the groups, an additional analysis was performed to adjust statistically for these differences. The second analysis eliminated the mortality difference between the two groups. An attempt was made to identify subgroups in which treatment may have been harmful and others in which it may have been beneficial. The analysis of the mortality in the various subgroups revealed a trend toward more deaths among patients <55 years of age, patients with coronary artery disease but without clinical angina pectoris and patients in functional class I. Conversely, mortality of patients in functional class >I and of patients with angina pectoris was lower when they were treated with a calcium antagonist. These analyses should be

Table 4. Distribution of Various Calcium Antagonists

Calcium Antagonist	No. (%) of Pts	Mortality [no. (%) of pts]
Nifedipine	1,999 (34)	176 (8.8)
Verapamil	350 (6)	30 (8.6)
Diltiazem	3,320 (57)	266 (8.0)
Combination	174 (3)	23 (13.2)

Pts = patients.

interpreted with caution because they have not yet been verified in a randomized, prospective trial. Moreover, examination of the effects of treatment in multiple subgroups increases the possibility of observing extreme results by chance. No difference in mortality was noted between the nifedipine, verapamil and diltiazem groups in this study.

Comparison with previous studies. In their recent study, Furberg et al. (15) concluded that short-acting nifedipine in moderate to high doses may cause an increase in overall mortality. However, the data they cite show no significantly increased risk at doses of 30 to 60 mg/day, thus their conclusion was drawn on a dose of 80 mg/day, which is unusually high for nifedipine. In the early 90s, most patients in Israel were treated with 30 to 60 mg of short-acting nifedipine. Thus, our observational results are in full agreement with the experimental ones from other studies (18,19) of patients in the chronic stage of their coronary artery disease. In these studies the 6-month mortality rate was similar for the nifedipine and control patients.

It had been previously pointed out that implicating a wide range of calcium antagonists on the basis of several studies with short-acting nifedipine is unjustified (20–22). Indeed, two studies suggested that verapamil (7) and diltiazem (11) have been efficacious in reducing mortality in certain patient groups. It is also questionable to make judgments on the safety and efficacy of antihypertensive treatment with a new generation of calcium antagonists using data from studies on previous generations of calcium antagonists. These are currently being examined in clinical trials (23).

Study limitations. We have tried to address the recent and ongoing heated controversy over the use of calcium antagonists in patients with cardiovascular disease (20,22–25). We are aware of the obvious limitations of conducting an observational analysis on groups with different characteristics and statistically adjusting for the differences, rather than judging an effect of medication on mortality (24) in a randomized clinical trial. In addition to the observational nature of our results, we have relied on a single report of therapy for each patient made available to us during a screening examination. Certainly, therapy may undergo several changes, even within a relatively short follow-up period. We assumed that crossover between the three calcium antagonists was limited and that, rather than discontinuing the medication, any major changes that might have been made would probably entail the addition of new drugs such as angiotensin-converting enzyme inhibitors.

Despite these limitations, the results we derived from a large number of patients with chronic coronary artery disease may be a meaningful contribution to the recent discussion on the safety of calcium antagonists in patients with coronary artery disease.

Conclusions. After an average follow-up period of 3.2 years, patients treated with calcium antagonists exhibited a slight, statistically nonsignificant increase in mortality compared with control subjects. Multivariate analysis adjusting for variables that reflect the clinical severity of coronary artery disease eliminated any indication of increased risk. These results consistently failed to show an association between calcium antagonist therapy and mortality. Routine prophylactic treatment with calcium antagonists of patients during the acute phase of myocardial infarction has never been indicated. Thus, calcium antagonists should be reserved for clear-cut clinical indications. The current analysis does not support the claim that calcium antagonist therapy in patients with coronary artery disease, whether myocardial infarction survivors or others, harbors an increased risk of mortality.

Appendix

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