

ORIGINAL REPORT

Use of calcium channel blockers as antihypertensives in relation to mortality and cancer incidence: a population-based observational study

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SUMMARY

Purpose Treatment with blood pressure lowering drugs may reduce morbidity and mortality. However, the efficacy and effectiveness may differ between antihypertensive agents. The current investigation aimed to compare mortality and cancer incidence in hypertensive patients treated with calcium channel blockers (CCB) or with other antihypertensive drugs (AHD).

Methods All patients in two outpatient clinics treated with AHD who underwent an annual check-up during 1989 or 1990 were selected. Fatal events were identified through 1997 and incident cancers through 1998.

Results Two hundred and fourteen patients on CCB and 1029 on other AHD were identified. Overall mortality and the combined mortality from myocardial infarction and stroke were higher in CCB users; hazard ratios adjusted for sex, age, comorbidity and other and risk factors were 1.84 (95% CI 1.25–2.72) and 2.37 (95% CI 1.27–4.44), respectively. The risk estimates for cancer mortality and for cancer incidence did not differ significantly.

Conclusions Results from clinical trials as well as observational studies, including the present one, indicate a higher mortality risk and a higher cardiovascular morbidity risk associated with use of CCB. Accordingly, CCB should not be regarded as first line drugs in hypertension. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS—calcium channel blockers; hypertension; mortality; cancer incidence; observational study

PURPOSE

Treatment of hypertension with blood pressure lowering drugs may reduce morbidity and mortality. However, this need not signify that (all) beneficial effects are consequent to blood pressure lowering *per se*. In addition, the efficacy and effectiveness may differ between different agents.

Treatment of hypertension with calcium channel blockers (CCB) has been the subject of controversy

since the mid-1990s.¹ A recent meta-analysis of nine randomized clinical trials compared treatment based on CCB with treatment based on other antihypertensive drugs (AHD). The study indicated that the risk of stroke did not differ but that the risk of myocardial infarction and heart failure was more than 25% higher among those on CCB.² Another overview of randomized trials reported a 12% (RR 1.12, 95% CI 1.0–1.26) higher coronary heart disease risk and also a 12% (RR 1.12, 95% CI 0.95–1.33) higher heart failure risk in patients allocated to CCB-based therapy than in patients allocated to diuretic-based or beta blocker-based therapy.³ This study also reported a higher risk of coronary heart disease and heart failure in patients on CCB-based therapy than in patients on ACE inhibitor based therapy.³

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While clinical trials are necessary to assess the *potential* benefits of a certain treatment, pharmacoepidemiologic studies are needed to obtain information on the outcome under routine conditions. This is especially important with respect to patients with comorbidity, as randomized clinical trials often exclude such patients. A 16-year observational study of 5000 patients with hypertension indicated that total, cardiovascular and coronary mortality was higher among those treated with CCB than among those treated with ACE inhibitors.⁴ An increased risk of cancer in CCB-treated patients has also been reported⁵ but has been refuted in other reports.^{6–8} To obtain further data on the CCB issue, the current investigation compared all-cause mortality, cardiovascular mortality, cancer mortality and cancer incidence during a 9-year period in 1243 patients with hypertension treated with CCB or with other AHD at start of follow-up.

SUBJECTS AND METHODS

Patients

In the County of Skaraborg, Sweden, an intervention programme to improve the control of hypertension in the population was launched in 1977. The project included recommendations for detection, diagnosis, treatment and follow-up of hypertensive patients. Special outpatient clinics were established in the primary care units in six communities, including the clinics in Skövde and Skara.

All patients at Skövde and Skara outpatient clinics having ongoing treatment with AHD and with a diagnosis of hypertension who underwent an annual check-up during 1989 or 1990 were selected for this study. However, when cancer incidence was calculated, only patients free from cancer at inclusion were considered.

Information on systolic blood pressure, smoking habits, and co-morbidity was derived from computerized patient records. Patients on CCB at inclusion were classified as users of CCB. Patients on other AHD at inclusion, but not on CCB, were classified as users of other AHD. Smoking habits were coded as current smokers or non-smokers.

Follow-up

The Swedish mortality register,⁹ including data on the cause of death in all subjects living in Sweden at the time of death, was used to identify fatal events from 1989 through 1997. Incidence of malignant cancer was obtained from the Swedish cancer register for the time period 1989 through 1998. It is estimated

that 96% of all diagnosed cancers are reported to the cancer register.¹⁰

Statistical methods

Proportional hazard models (Cox regression analysis) were used to compare hazard ratios for mortality rates and cancer incidence in CCB users with those in users of other AHD. Hazard ratios for mortality (Model A), and cancer incidence were adjusted for age and sex. Hazard ratios for mortality (Model B) were additionally adjusted for study area, smoking habits, number of antihypertensive drugs used, systolic blood pressure, history of myocardial infarction, angina pectoris, cerebrovascular disease, intermittent claudication, cancer, and diabetes mellitus.

RESULTS

From 1 January 1989, to 31 December 1990, 214 patients on CCB and 1029 on other AHD but not on CCB were identified. About 70% of the CCB users were on felodipine (Plendil[®]). Basic characteristics are given in Table 1. Patients on CCB were more often men, were more often smokers, and more often had a history of angina pectoris, myocardial infarction, stroke and diabetes mellitus. Patients on CCB were also on a greater number of antihypertensive drugs and had marginally higher diastolic and lower systolic blood pressure.

Mortality

In total, 222 out of 1243 patients died in the period up to 31 December 1997. Overall mortality and the combined mortality from myocardial infarction and stroke were significantly higher in CCB users, adjusted hazard ratios 1.84 (95% CI 1.25–2.72) and 2.37 (95% CI 1.27–4.44), respectively. The risk estimates for cancer mortality and for other causes beside myocardial infarction, stroke and cancer did not differ significantly (Table 2, Model B). When only 772 non-smoking patients free from co-morbidity were considered, the adjusted overall mortality hazard ratio was 1.94 (95% CI 1.03–3.65). Furthermore, when only 271 non-smoking patients free from co-morbidity who were on exactly two different AHD were considered, the adjusted overall mortality hazard ratio was 2.04 (95% CI 0.75–5.55).

Cancer incidence

During follow-up the CCB and other AHD users, free from cancer at baseline, contributed 1675 and 8329

Table 1. Patient characteristics at inclusion

	Users of calcium channel blockers <i>N</i> = 214		Users of other antihypertensive drugs <i>N</i> = 1029	
	<i>N</i>	%	<i>N</i>	%
History of				
Myocardial infarction	10	4.8	15	1.5
Angina pectoris	18	8.7	39	3.9
Intermittent claudication	5	2.4	21	2.1
Stroke	5	2.4	19	1.9
Cancer	12	5.6	70	6.8
Diabetes	19	9.2	55	5.5
Smoker	58	28	176	17
Male sex	143	67	432	42
Systolic blood pressure (mmHg)	150		154	
Diastolic blood pressure (mmHg)	85		87	
Age (years)	61.3		63.7	
No of AHD (average)	2.2		1.6	
Treated with CCB	214	100	0	0
Treated with diuretics	56	26	548	45
Treated with beta blocker	136	64	651	63
Treated with ACE inhibitors	36	17	173	17
Treated with AHD not listed above	10	5	171	17

Table 2. Overall and cause-specific mortality in 214 users of calcium channel blockers (CCB) with 1029 users of other antihypertensive drugs (AHD) as reference

Cause of death (1989–1997)	CCB		Other AHD		Model A*		Model B [†]	
	No. of deaths	N/1000 patient-years	No. of deaths	N/1000 patient-years	OR	95% CI	OR	95% CI
IHD and stroke	23	15.4	68	8.9	2.53	1.53–4.17	2.37	1.27–4.44
Cancer	14	9.4	50	6.5	1.42	0.77–2.60	1.34	0.68–2.63
Other causes	13	8.7	57	7.5	1.63	0.87–3.05	1.68	0.78–3.62
All causes	50	33.4	172	22.5	1.84	1.32–2.55	1.84	1.25–2.72

OR, Odds ratios; IHD, ischaemic heart disease.

*Model A adjusted for sex and age.

[†]Model B adjusted for sex, age, study area, smoking habits, number of antihypertensive drugs used, systolic blood pressure, history of myocardial infarction, angina pectoris, cerebrovascular disease, intermittent claudication, cancer, and diabetes. In Model B 16 users of CCB and 164 users of other AHD were excluded due to missing information on co-variables.

During follow-up (Model A), the CCB users and other AHD users contributed 1497 and 7641 patient years, respectively. The mean follow-up time was 7.4 years.

patient-years respectively. The mean follow-up time was 8.6 years. One-hundred and thirty new cases of cancer, 23 in users of CCB and 107 in users of other AHD, were reported after baseline through to 31 December 1998. The number of incident cancers per 1000 patient years were 13.7 and 12.8 respectively. The cancer incidence hazard ratio in users of CCB with users of other AHD as reference, adjusted for age and sex, was 1.05, 95% confidence interval 0.67–1.67.

CONCLUSION

Like several previous studies, the present study indicated a less favourable outcome in patients on CCB than in those on other AHD. Overall mortality and combined mortality from myocardial infarction and stroke were significantly higher in patients on CCB than among patients treated with other AHD.

Although CCB users had a higher level of risk factors at baseline, the overall mortality hazard ratio

only changed marginally when adjusted for possible confounders, including co-morbidity, smoking habits and number of different AHD used. To further eliminate indication bias and severity bias, overall mortality hazard ratios were calculated for the non-smoking subjects with no co-morbidity, as well as for patients of this subgroup who were on exactly two AHD. These results indicated no substantial changes of the risk estimates.

Absolute mortality in the present study was substantial higher than reported in *randomized* trials. The NORDIL study¹¹ reported 9.2 and 9.0 deaths per 1000 patient-years in hypertensive patients on diltiazem and diuretics/beta blockers respectively. The mean age of the NORDIL patients was 60.4 years at inclusion and could be estimated to 62.7 years during follow-up. About 50% were men. Thus, overall mortality was less than one-third of the overall mortality in only marginally older patients on CCB and less than half of overall mortality in patients on other AHD in the present study. Furthermore, hypertensive patients in the INSIGHT study,¹² although of the same age as patients in the present study, had considerably lower overall mortality, 16.1 deaths per 1000 patient-years in nifedipine-treated patients and 15.7 deaths per 1000 patient-years in those on enalapril.

On the other hand, other *observational* studies have reported overall mortality similar to or higher than in the present study. Thus, among patients of the Glasgow Blood Pressure Clinic with non-malignant hypertension (mean age 52.3 years during follow-up), overall mortality was 41.4 deaths per 1000 patient-years for men and 22.1 deaths per 1000 patient-years for women.¹³

Obviously, hypertensive patients in most randomized trials are at lower absolute mortality risk than hypertensive patients from population samples with similar sex distribution and age. Therefore, many results from randomized trials are not generally representative. This is most apparent for absolute mortality risk, but, it cannot be excluded that differences in patient characteristics between participants of randomized trials and routine clinical patients influence even relative risks. Apparently, routine clinical patients may be more vulnerable.

Cancer mortality and cancer incidence did not differ significantly between the treatment groups. Although the results indicated a 34% (but non-significant) higher cancer mortality risk in CCB users, cancer incidence was not elevated. Cardiovascular co-morbidity in CCB users whose cause of death was coded as cancer may have contributed to a higher mortality from cancer in CCB users.

Limitations of the study

Although adjustments were made for possible confounders including medical history, it cannot be excluded that residual confounding somehow affected the results, i. e. confounding by indication or severity not revealed the way patient records were scanned. Nor was information available on blood pressure control when the actual treatment was initiated. A CCB may have been added to or replaced ongoing treatment due to inappropriate blood pressure control. However, blood pressure control during follow-up is affected by the treatment and should not be regarded a confounding factor.

A second limitation is that patients were classified as users of CCB and users of other AHD based only on status at inclusion. In some patients, the initial treatment may have been discontinued, and additional AHD may have been added. Most probably, CCB had been prescribed to patients classified as users of other AHD. Thereby, the differences in mortality rates due to the different treatments are probably underestimated. Third, since the majority of the CCB users were on felodipine it may be inappropriate to generalize the results to other CCBs.

Results from clinical trials as well as observational studies, including the present one, indicate a higher mortality risk and a higher cardiovascular morbidity risk associated with use of CCB. Accordingly, CCB should not be regarded as first line drugs in hypertension.

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