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ORIGINAL ARTICLE

Calcium channel blockers, ACE inhibitors, and the risk of cancer in hypertensive patients: a report from the Department of Health Hypertension Care Computing Project (DHCCP)

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Objective: **Recent studies have shown inconsistent results on the risk of cancer in hypertensive patients using calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors. We investigated a large number of patients from the Department of Health Hypertension Care Computing Project (DHCCP) observational database treated with these drugs for hypertension to see whether the use of CCBs for hypertension is associated with an increased risk of cancer mortality and the use of ACE inhibitors with a reduction.**
Design: **Matched case-control study and a longitudinal study of survival from 1 year after presentation.**
Patients: **A total of 11663 patients treated for hypertension from 1971 through 1987. They were recruited on presentation to one of the hospital hypertension clinics or general practices involved.**
Main outcome measures: **Death with any mention of cancer on the death certificate in patients treated with an Index drug group; CCBs, ACE inhibitors, beta adrenergic blocking drugs (BBs), or receiving a diuretic. The treatment groups were mutually exclusive.**
Results: **A total of 391 cases of cancer were matched with 1050 controls. In this case-control study the adjusted relative risk estimate in comparison to diuretic treatment for CCBs was 0.79 (95% CI 0.37 to 1.69), and for CCBs plus a diuretic, 1.05 (0.65 to 1.69). Non-significant results were also observed for ACE inhibitors (1.48 (0.43 to 5.1), and 1.40 (0.56 to 3.50) with a diuretic), and also for the BB and methyldopa groups. In the longitudinal survival study, the adjusted relative risk estimate for CCBs was 1.1 (0.60 to 1.94) and 1.0 (0.53 to 1.86) for CCBs plus a diuretic, and for ACE inhibitors 1.33 (0.37 to 4.76) and 1.47 (0.67 to 3.23), respectively.**
Conclusions: **In this population there was no increased cancer mortality with the use of CCBs and a relative risk greater than 1.7 to 2.0 was excluded with 95% confidence. The suggestion that ACE inhibitors reduce cancer mortality was not supported with best estimates of relative risk of 1.3 to 1.5 and exclusion of values less than 0.4 to 0.7.**
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Introduction

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension, and in the treatment of coronary heart disease, although CCBs have not yet been shown to reduce cardiac mortality in the latter condition.[1–11]

In the last few years, concerns have been raised about an association of an increased risk of cancer in users of CCBs. In 1996, Pahor *et al*[12] reported an increased risk of cancer among hypertensive patients treated with CCBs. The relative risk compared with those on beta-blockers was 2.02 (95% CI 1.16 to 3.54).[12] The cohort study was extended to the general older population showing a significantly increased risk of cancer in the patients treated with CCBs compared with those not taking these drugs (70% excess hazard ratio).[13] The limitations of both studies were mainly the small numbers (61 and 47 cases, respectively). More recently, associations between the use of CCBs and incident invasive breast carcinoma in postmenopausal women were found.[14] The hazard ratio was 2.57 (95% CI 1.47 to 4.49), and in combination with oestroderm it was even stronger (hazard ratio: 4.48, 95% CI 1.58 to 12.75). However, in several subsequent studies no increased risk of cancer was found in association with the use of CCBs.[15–19] And in the prospective

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randomised Syst-Eur Trial in patients over 60 and isolated systolic hypertension, first line treatment with a CCB, nitrendipine, tended to reduce cancer mortality, not to increase it.[20]

Following this controversy, an Ad Hoc Subcommittee of the Liaison Committee of the WHO and the International Society of Hypertension reviewed the effects and safety of CCBs. They concluded that 'the available evidence from observational studies does not provide good evidence of an adverse effect of calcium antagonists on cancer risk'.[21]

The latest controversy arises from a publication by Lever *et al*[22] proposing that angiotensin-converting enzyme (ACE) inhibitors protect against cancer with relative risks of between 0.65 and 0.72. This is supported to some extent by the findings of Jick *et al*[23] of a relative risk of ACE inhibitors compared to beta-blockers of 0.79 (95% CI 0.38 to 1.06), but not by other studies.[24]

In this report from the Department of Health Hypertension Care Computing Project (DHCCP) observational database we looked at patients treated with CCBs and ACE inhibitors who died and had any mention of cancer on their death certificate. In addition to a matched case-control study we performed a longitudinal study of survival from 1 year after presentation. Patients treated with CCBs or ACE inhibitors for hypertension were compared with those treated with diuretics, beta-adrenergic blocking drugs, or methyldopa in order to assess the possible increased risk of cancer mortality.

Subjects and methods

Source of data

The study population was drawn from the Department of Health Hypertension Care Computing Project (DHCCP), a multi-centre computer-based observational study of patients being treated for hypertension in the United Kingdom.[25–27]

Patients

Eligible persons included patients who entered the system on presentation to one of the hospital hypertension clinics or general practices involved. All patients were included irrespective of level of blood pressure. The study started in 1971 and currently contains records of 11663 patients recruited up to 31 December, 1987. Details at presentation and subsequent attendance were recorded. The Office of Population Censuses and Surveys holds a flagged record of all the patients and gives notification of any emigration or deaths. All deaths and their causes were recorded up to 31 October, 1995. The causes of deaths and risk factors for survival have been previously published.[10,25–27] Death certificates were coded according to the eight revision of the International Classification of Diseases for any mention of a cause of death. The codes for cancer were 1400–2099.

Statistics

Two main analyses were performed:

(1) A case-control study of those dying who had any mention of cancer on their death certificate compared with controls alive at the time of their matched case's death.

Cases were hypertensive patients on an Index treatment at last recorded encounter prior to death and had any mention of cancer on their death certificate. Up to three controls for each case were identified and were matched for age (within ±10 years), gender, year of presentation (within ±5 years), and clinic attended. Additional adjustments were made for cigarette smoking habit at presentation (ever smoked *vs* never smoked), treated blood pressure and also for age and year of presentation, as the matching limits were broad. The Index antihypertensive drugs we studied were calcium channel blockers (CCBs), beta adrenergic blocking drugs (BBs), methyldopa, angiotensin-converting enzyme (ACE) inhibitors and diuretics. Nine treatment groups were defined (Table 1). These were mutually exclusive but included other antihypertensive medications such as vasodilators. The CCBs prescribed were nifedipine (short acting and slow release, but not the gastrointestinal transmission system), diltiazem, and verapamil. Detailed information about dosage, formulations and duration of use of individual drugs were not available for this study. Controls were hypertensive patients who were alive and receiving an Index treatment before their matched case's death. Survival has been determined for a maximum of 22 years (average: 11 years), from presentation to the clinics.

There were 399 cases. Eight cases could not be matched with a control but the rest were matched with up to three controls, giving 391 cases and 1050 controls. Smoking status was not known in 44 cases and 97 controls. The reference treatment group consisted of those on a diuretic but not a second Index drug.

The most important reasons for exclusion were, had not received one of the Index drugs (3767) but a different treatment, and controls that were not required as a maximum of three were selected (4005).

(2) A longitudinal study of survival of patients in the Index treatment groups defined in (1) above. Between 3 and 12 months of follow-up, there were 614 subjects treated with a CCB and 212 treated with an ACE inhibitor, respectively. A total of 3041 subjects were prescribed a different Index drug. Survival was determined from 1 year of follow-up. A total of 805 patients who additionally received an adrenergic neurone blocker or older vasodilators such as hydralazine were excluded. The Cox proportional hazards model was used to adjust survival for age, gender, smoking at presentation, year of presentation, treated systolic blood pressure and clinic attended.[28]

Table 1 Characteristics at presentation of the reference group and the eight treatment groups. The treatment groups were mutually exclusive, but included other treatments not listed in the table

Treatment given	*No.*	*Average age (range)*	*% Male*	*Average year of presentation (range)*	*% Smoker*
Diuretic	2525	53.6 (16–90)	45.4	1979 (71–86)	31.8
CCB	349	54.4 (21–85)	55.3	1984 (74–86)	27.9
ACE Inhibitor	93	50.2 (19–86)	54.8	1984 (74–86)	25.4
BB	99	48.2 (24–72)	65.7	1978 (71–86)	39.1
Methyldopa	367	54.7 (15–85)	48.2	1977 (71–86)	33.4
CCB + Diuretic	643	55.1 (26–85)	48.8	1983 (71–86)	30.2
ACE + Diuretic	151	54.1 (25–78)	49.7	1982 (72–86)	33.1
BB + Diuretic	269	52.4 (23–76)	47.2	1978 (71–86)	31.7
Methyldopa + Diuretic	1007	56.7 (20–83)	44.3	1976 (71–86)	32.5
Number with information	5503	5498	5503	5503	4808

Results

A total of 6406 patients had a record of treatment with one or more of the designated Index drugs, ie, CCBs, ACE inhibitors, BBs, methyldopa or diuretics; of these, 1637 (26%) received a CCB, 696 (11%) an ACE inhibitor, 5373 (84%) a diuretic, 1887 (29%) methyldopa, and 743 (12%) a BB. These drugs may have been taken concurrently or consecutively for a variable length of time prior to death: 2525 (39%) received only a diuretic. Of the CCB group, 73% also received at some time a diuretic, 23% an ACE inhibitor, 16% methyldopa and 10% a BB. A total of 903 patients received more than one Index drug apart from a diuretic and had to be excluded. The population baseline characteristics in the eight treatment groups are shown in Table 1.

Patients treated with methyldopa with or without a diuretic had been enrolled earlier and were older than those in the other groups. The percentage of smokers was similar in all groups ($P = 0.55$). The patients given a diuretic alone or with any other drug except for one of the Index drugs constituted the reference group with a relative risk of one.

Analysis I

The results of the matched case-control study are shown in Table 2. There was no excess of cancer deaths in any of the eight treatment groups compared with the diuretic reference group. The unadjusted relative risk in patients treated with a CCB was 1.01 and after adjustment for age, smoking, blood pressure and year presented it was 0.79 (95% CI 0.37 to 1.69). The corresponding results for CCBs with a diuretic were 0.92 and 1.05 (95% CI 0.65 to 1.69), respectively. The adjusted results for ACE inhibitors were 1.48 (95% CI 0.43 to 5.05) and 1.40 (95% CI 0.56 to 3.50) for those not taking and taking a diuretic, respectively. This analysis was repeated for all cases and controls without matching but with all adjustments. There were 399 cases and 5104 controls and again, no differences were found.

Table 2 Distribution of cases and controls according to treatment group. Relative risk in different drug combinations of dying and having any mention of cancer on the death certificate (analysis I). Up to three controls per case alive at the time the case died

Treatment	*No. of cases*	*No. of controls*	*RR*	*Adjusted RR (95% CI)*
Diuretic	172	478	1.000	1.000
CCB	17	47	1.005	0.785 (0.37–1.69)
ACE Inhibitor	6	12	1.390	1.478 (0.43–5.05)
BB	5	21	0.662	0.719 (0.26–1.98)
Methyldopa	30	78	1.069	0.986 (0.63–1.67)
CCB + Diuretic	35	106	0.918	1.046 (0.65–1.69)
ACE + Diuretic	8	20	1.112	1.395 (0.56–3.50)
BB + Diuretic	18	64	0.782	0.833 (0.47–1.49)
Methyldopa + Diuretic	100	224	1.241	1.155 (0.83–1.61)
Total	391	1050		

Adjusted RR, Relative risk adjusted for age, gender, year of presentation, smoking at presentation and clinic attended.

Analysis II

Table 3 compares the survival of patients in the different groups from 1 year of follow up, with an Index treatment between three and 12 months after presentation. The age and sex adjusted death rates of cancer were significantly higher in patients treated with methyldopa plus a diuretic (adjusted RR 1.47, 95% CI 1.05 to 2.06), but not in those treated with a CCB. The total number of cancer deaths was 291, out of which 35 were treated with a CCB and 14 with an ACE inhibitor. The adjusted RR with a CCB was 1.08 (95% CI 0.60 to 1.94) and with a CCB plus a diuretic 0.99 (95% CI 0.53 to 1.86). The corresponding results for an ACE inhibitor were 1.33 (95% CI 0.37 to 4.76) and 1.47 (95% CI 0.57 to 3.23), respectively. The adjusted RR for other Index drugs varied between 0.84 and 1.47.

Discussion

One main purpose of these analyses was to investigate the possible increased cancer risk in users of CCBs. In our study, we included hypertensive patients of all age groups who died and had any mention of cancer on their death certificate. In the matched case-control study (analysis I, Table 2), no excess cancer mortality for CCBs was found (RR 0.79 to 1.05), and the 95% CI excluded a relative risk over 1.69. These results are in accordance with earlier studies. In a population-based cohort study accruing 32540 person-years, Olsen *et al*[15] did not find an increased risk for cancer in users of CCBs. During a follow-up period of up to 3 years the incidence for total cancer was 1.02 (95% CI 0.89 to 1.16) for men and 0.97 (0.83 to 1.12) for women, with no indication of an excess rate in the subgroup of likely long-term users. In the STEPHY II prospective cohort study with a follow-up after 3 years, no increased cancer risk was found in an elderly mid-European population treated with CCBs, although the cases of concern were very few.[18] The odds ratio for fatal and non-fatal cancer was 1.12 (95% CI 0.69 to 1.84). In a recent case-control drug surveillance study, the use of CCBs was unrelated to the risk of cancer overall.[16] A total of 9513 patients aged 40 to 69 years with a primary cancer of various sites were included and 352 cases in users of CCBs having taken the drug at least 1 year before admission were found, yielding a RR of 1.1 (95% CI 0.9 to 1.3). However, there was a statistically significant association with bladder cancer among males (RR: 1.5, 95% CI 1.1 to 2.1), and cancer of the kidney was more frequent, both in users of CCBs (RR 1.8, 95% CI 1.1 to 2.7) and in users of beta-blockers (RR 1.8, 95% CI 1.3 to 2.5). These results agree with an earlier study,[15] whereas in the Nurses' Health Study with female nurses self-reporting the use of CCBs, a somewhat increased risk was found only for lung carcinoma (RR 2.01, 95% CI 1.16 to 3.49).[19] Nevertheless, the overall cancer incidence (RR 1.02, 95% CI 0.83 to 1.26), and cancer mortality (RR 1.25, 95% CI 0.91 to 1.72) was not increased. In a nested case-control analysis (446 cases, 1750 controls), Jick *et al*[23] could not confirm a high degree of risk but could not exclude a small excess. The adjusted RR estimates were 1.27 (95% CI 0.98 to 1.63) for users of CCBs compared with beta-blockers, the reference group. This increased risk was probably not causal, since it was independent of duration of use and was not restricted to specific cancers. Our relative risk estimates in the longitudinal study ranged between 0.99 and 1.08 (Table 3). This longitudinal analysis was extended to assess the survival of patients from 1 year after presentation and treated with a CCB for at least 1 year, compared to the 8438 subjects never given a CCB. This revealed a RR of 0.98 and had a 95% CI that excluded a RR greater than 1.35.

Table 3 Cancer mortality. Survival experience from 12 months according to treatment at 3–12 months (analysis II). Treatment groups were mutually exclusive and patients on adrenergic neurone blockers or vasodilators were excluded

Treatment given	*No.*	*No. of cancer deaths*	*Age and sex adjusted death rate/ 1000 py*	*Adjusted RR for cancer deaths (95% CI)*
Diuretic	1880	136	5.99	1.000
CCB	359	20	6.61	1.081 (0.60–1.94)
ACE Inhibitor	109	6	7.71	1.333 (0.37–4.76)
BB	99	5	4.39	0.857 (0.41–1.71)
Methyldopa	425	34	5.43	0.986 (0.65–1.49)
CCB + Diuretic	255	15	6.79	0.989 (0.53–1.86)
ACE + Diuretic	103	8	9.19	1.468 (0.67–3.23)
BB + Diuretic	152	9	4.95	0.838 (0.41–1.71)
Methyldopa + Diuretic	485	58	8.18	1.471 (1.05–2.06)

Adjusted RR, Relative risk adjusted for age, gender, year of presentation, smoking at presentation and clinic attended.

In a recent meta-analysis of the incidence of cancer in controlled trials of verapamil, no increased risk of cancer or deaths with verapamil was found.[17] Thirty-nine trials with 11201 patients were eligible, and the odds ratio was 1.20 (95% CI 0.60 to 2.42) for verapamil users *vs* active controls, and 0.73 (95% CI 0.39 to 1.39) *vs* placebo, respectively. In our study, the CCBs used were nifedipine, verapamil, and diltiazem, respectively; but more detailed information are not available.

We found no evidence to support the findings by Pahor *et al*[12,13] of an excess of cancer deaths in patients treated with CCBs. In the elderly, they reported a hazard ratio of 1.72 (1.27 to 2.34) for cancer associated with CCBs. They speculated that inhibition of apoptosis by CCBs which interfere with calcium-triggered signals is a possible mechanism, resulting in a tumour-promoting activity of CCBs. Also Fitzpatrick *et al*[14] hypothesised that the higher incidence of invasive breast carcinoma can be explained through apoptosis or another hormonal mechanism. In 3198 postmenopausal women fol-

lowed for 5 years, 75 cases of cancer occurred; 55 in women not treated with a CCB and 20 in users of CCBs (hazard ratio: 2.57, 95% CI 1.47 to 4.49). The rate per 1000 person-years at risk was higher for immediate release than for sustained release formulations (14.8 and 8.1, respectively). On the other hand, some evidence suggests that CCBs might inhibit carcinogenesis, and in several studies CCBs, as inhibitors of P-glycoprotein, were successfully used as chemosensitizers in the treatment of various cancer types (advanced/metastatic breast cancer, non-small lung cancer, skin cancers, lymphomas).[29–39]

In the group receiving methyldopa plus a diuretic the adjusted RR was increased (1.47; 95% CI 1.05 to 2.06). This is consistent with our previous finding of a normal cancer mortality with atenolol treatment where the RR of methyldopa compared with atenolol was 1.5 in men (95% CI 1.0 to 2.2).[40] This excess cancer mortality occurred in earlier years of the study and may reflect confounding variables not fully accounted for by adjusting for the year of presentation and age.

For the ACE inhibitor groups the two analyses suggested adjusted RRs of between 1.33 and 1.48. There were smaller numbers of patient-years for those on an ACE inhibitor as the project started in 1971 when those drugs were not available. Therefore, the estimates for ACE inhibitors had wide confidence limits. Nevertheless, analysis II excluded a RR below 0.67 for ACE inhibitors plus a diuretic. The results suggested by Lever *et al*[22] with a reduced RR for cancer in users of ACE inhibitors (0.65 to 0.72) could not be confirmed. The present study did not support a large benefit from the use of ACE inhibitors, and thus differs from the Glasgow study. However the Glasgow results for CCBs and cancer agree with the present study.[41]

There are limitations to our analyses which are common to observational studies. First, we lack detailed information on why patients were originally prescribed a particular drug. We have not adjusted for concurrent therapies nor predisposing and concomitant conditions, eg, diabetes mellitus. This could make the determination of links between a drug and adverse outcome difficult. For example it has been suggested that diabetic patients using CCBs are at particularly high risk of cancer, possibly due to changes in the cholesterol and phospholipid content of cellular membranes in diabetes which leads to stronger binding of lipophilic agents such as CCBs.[42] Another problem is the small number of cancer deaths in some of the Index groups. We have not examined individual cancers and cannot rule out that some specific cancers might have been more frequent in one or the other treatment group. Third, the case-control study was based on the recorded prescription of the particular drugs at any time in the past. We have not investigated how regularly and for how long the patients took the drugs. Therefore, although adjusted for a number of confounding elements such as cigarette smoking, the observed cancer mortality in this analysis might not have been related to the particular drug, eg, methyldopa, but to different factors not considered in the study.

We have also assumed that different CCBs produce the same risks and this may not be so. In addition our analysis is based on exposure to a drug but not the amount consumed. If available, this would provide valuable additional information. We have previously reported that in this study of hypertensives mortality from cancer is lower than expected, presumably due to competing cardiovascular risks.[25] However, a general shift in cancer incidence, an increase or decrease, is likely to affect all drug groups equally.

Additional randomised trials are needed to solve the current controversy about the safety of calcium channel blockers. However, even large scale randomised trials may suffer from patient selection and relatively short-term follow-up. Nevertheless, the Syst-Eur Trial suggests that over a median follow-up period of 2 years, there is no excess cancer mortality on CCBs.[20] Today, there is little *prima facie* evidence that CCBs have a higher cancer mortality, although cardiovascular safety is still widely discussed.[7–11,15–20]

The importance of our study is that in the longitudinal analysis no excess mortality in patients treated with CCBs was found. Therefore, we suggest that no important cancer mortality is present with the use of CCBs in hypertensive patients. Moreover we cannot find any support for the suggestion that ACE inhibitors protect against cancer.

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