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Calcium channel blockers and risk of AD: the Baltimore Longitudinal Study of Aging

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Abstract

Objective: To investigate the association between use of calcium channel blockers (CCB), dihydropyridine (DHP) or nondihydropyridine (nonDHP) type CCB and risk of developing Alzheimer's Disease (AD) or mortality. There is evidence suggesting that calcium plays a key role in changes in the brain leading to AD. Previous reports suggest a possible role for CCB in the treatment of AD. However, there are some indications that CCB increase mortality in patients with cardiac disease. **Methods:** Subjects were 1092 participants in the Baltimore Longitudinal Study of Aging (BLSA) older than 60 years of age. Data on CCB use was collected prospectively for up to 19 years. Cox proportional hazards regression was used to estimate relative risks (RR) and confidence intervals (CI) of AD and mortality associated with use of CCB or use of only DHP or nonDHP-CCB. Analyses were adjusted for gender, education, smoking, blood pressure and history of heart problems. **Results:** Use of DHP-CCB was not associated with a significantly reduced risk of AD compared to non-users, although the estimate of the RR was low with DHP-CCB (RR = 0.30, 95% CI = 0.07–1.25, $P = 0.10$). Use of nonDHP-CCB was not associated with reduced risk of AD and the estimate of the RR risk was close to one (RR = 0.82, 95% CI = 0.37–1.83, $P = 0.63$). In addition, there was no increase in mortality among users of DHP-CCB (RR = 0.64, 95% CI = 0.32–1.29, $P = 0.21$) or nonDHP-CCB (RR = 1.10, 95% CI = 0.65–1.87, $P = 0.72$). **Conclusion:** Users of DHP-CCB and nonDHP-CCB in this study did not have a significantly reduced risk of AD. © 2004 Elsevier Inc. All rights reserved.

Keywords: Alzheimer's disease; Calcium channel blocker; Dihydropyridine; Longitudinal study; Prevention

1. Introduction

Several lines of evidence suggest that calcium plays a key role in age-related changes in the brain that lead to Alzheimer's Disease (AD) and dementia. Free intracellular calcium is one of the most important messengers for many signal transduction pathways of neurons, and alterations in intracellular calcium homeostasis are critically involved in brain aging, memory and cell death. According to a "calcium hypothesis" of AD [15–17], arising from numerous preclinical in-vitro studies [1,4,8,29,36,37], disturbances in calcium homeostasis are the proximal cause of neurodegeneration in AD [17]. There is a large body of evidence from pre-clinical experimental models and from human subjects that

alterations in calcium signaling occur during initial phases of AD, even before the development of overt symptoms or any obvious extracellular amyloid-beta pathology. Calcium dysfunction then appears to augment amyloid-beta formation and TAU hyperphosphorylation [17]. Other preclinical studies also provide strong evidence that amyloid-beta peptides, which are produced in excess and deposited on hippocampal and cortical neurons in AD, could inappropriately stimulate calcium-permeable channels and lead to elevation of intracellular calcium [4,37].

Four types of voltage-operated Ca^{2+} channels are involved in the influx of Ca^{2+} , namely T-, L-, P/Q- and N-channels [31]. L-channels are located primarily on neuronal cell bodies [3] and are the binding sites for clinically used dihydropyridine (DHP), phenylalkylamine (PAA) and benzothiazepine (BTZ) calcium channel blockers (CCB) [31]. The most commonly used DHP-CCB, amlodipine,

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was a much more potent neuroprotective agent than some other DHP-CCB, due to its different chemical structure (charged) and its inhibition of cellular oxidative stress [21]. Based on these findings, it was hypothesized [28] that in AD use of L-type CCB, especially DHP-type, could prevent or delay onset of the disease by blocking the inappropriately increased transmembranous transport of Ca^{2+} through L-channels into neurons, which leads to cell death if CCB use is initiated early in the course of AD, prior to development of symptoms. The most extensive studies with CCB in the treatment of AD have been done with nimodipine [8,11], an L-type CCB of the dihydropyridine group [26], and some of these reported slowing of several aspects of AD-related decline. In one multicenter double-blind placebo controlled study of 227 patients, patients receiving nimodipine showed slowing of several aspects of AD-related decline, such as disruption of daily living activities, deteriorating scores on functional and cognitive function tests [34].

The potential neuroprotective effects of CCBs have been evaluated in both preclinical [1,7,8,29,36] and clinical studies [9]. The only known studies examining the association between CCB use and prevention of the development of new cases of AD in older adults have been equivocal. One showed no association between CCB use and cognitive decline [25]. Conversely, data from the Syst-Euro Study clinical trial [10] showed that, nitrendipine (a DHP-CCB) significantly reduced the incidence of dementia by 55%. In the present prospective study, the association between the use of CCB and the risk of developing AD was evaluated by self-reported prospective data on medication use from the Baltimore Longitudinal Study of Aging (BLSA). We were particularly interested in whether the association between CCB use and risk of AD were specific to dihydropyridine (DHP) and nondihydropyridine (nonDHP) types of CCB. In addition, we explored the association between use of the different CCB types (DHP and nonDHP) on the risk of all-cause mortality.

2. Methods

2.1. Study population

The Baltimore Longitudinal Study of Aging (BLSA) is a study of normal aging conducted at the Gerontology Research Center (GRC) by the National Institute on Aging. Subjects are volunteers recruited mainly from the Baltimore-Washington area who are predominantly white (93%), from middle or upper socioeconomic brackets. Over 50% have at least a college degree. Participants return every 2 years to the GRC for 2.5 days of multidisciplinary evaluations, which include medical history (including heart problems), medication usage, physical and neurological examination and neuropsychological testing, as well as numerous other BLSA protocols [32].

2.2. Measurements

2.2.1. Use of calcium channel blockers

Information on medication use was collected during each biennial examination. Since 1980, participants have been asked to list all medications used since their last visit, or for the past 2 years for those completing their first visit. They were instructed to include all over the counter medications, e.g. vitamins, laxatives and others, as well as prescription medications for special conditions. Since 1990, participants have also been asked to bring in their medication bottles to validate the reporting. Medications were then coded by drug class as, for example, CCB. All commercially available forms of nifedipine, nicardipine, isradipine, felodipine and amlodipine were coded as DHP-CCB whereas all forms of verapamil and diltiazem were coded as nonDHP-CCB.

2.2.2. Clinical diagnosis

The diagnostic status of each participant was assigned during a multidisciplinary conference to determine cognitive status. All information available on each participant, including physical examination, neurological examination, neuropsychological testing, laboratory tests, personal medical records, and informant questionnaires were used to determine cognitive status. A clinical diagnosis was made according to DSM-III-R criteria [2] for dementia and NINCDS-ADRDA criteria [23] for possible and probable Alzheimer's disease (see [14] for more detailed description of procedures).

2.3. Data analyses

The main objective of this paper was to estimate the effect of CCB use on the risk of developing AD. Cox proportional hazards regression [6] with delayed entry was used to estimate the relative risk (RR) of developing AD. Chronological age was used as the time scale in the Cox model. Age at entry was considered as the age at the first visit on or after 1980. The model compares each case of AD with all subjects in the study who were alive and free of AD at the age when the AD case was diagnosed. Subjects who develop AD during follow-up contribute information up to their age of diagnosis, while other subjects contribute information up to their age at their last visit, their age at death, age when lost to follow-up or age when diagnosed with another dementia. This work includes visits and follow-up examinations done up to September 30th, 1999. Subjects without dementia were included in the analyses if they had at least one visit to the BLSA between 1980 and 1999, had at least one additional follow-up evaluation for determination of outcome, and their age at last follow-up was greater than sixty years.

First, risk of developing AD was compared between subjects who used CCB and subjects who did not use CCB. In a separate analysis, the risk of developing AD was compared between subjects who used either DHP-CCB or nonDHP-CCB and subjects who did not use CCB. Use of

CCB was included in the analyses as two time-dependent binary covariates. The first binary covariate was defined as 0 before the first reported use of DHP-CCB and 1 thereafter. The second binary covariate was defined as 0 before the first reported use of nonDHP-CCB and 1 thereafter. In addition, the length of CCB use and the risk of AD were further analyzed as a time-dependent categorical duration-of-use variable (<2 years, >2 years). In all analyses, covariates were included together in the Cox regression model. All subjects were eliminated from further analysis at the last time CCB use was assessed. Analyses were adjusted for the potential confounding effects of gender, education, smoking, systolic and diastolic blood pressure, and history of heart problems. The relative risks for the Cox models were estimated by SAS[®] PROC PHREG version 8.01. Results were considered as significant if $P = 0.05$ or less.

Since it was possible that some subjects in the early stages of dementia may have differentially recalled information regarding medication use, we performed analyses using lagging. Lagging [5] was used in the analyses to minimize the possibility of differential recall. In lagging, the information on reported CCB use close to the time of diagnosis of cases was ignored. As an example, for a subject who was diagnosed with AD at age 80, any information regarding use of CCB between ages 78 and 80 was ignored. Similarly, for all non-cases who comprise the risk set (or the set of subjects to whom the particular case is compared), the information regarding CCB use between ages 78 and 80 was also ignored. Lagging, therefore, relates the risk of disease to exposure accumulated up to 2 or 4 years before diagnosis rather than up to the time of diagnosis. We examined the effect of 2 and 4 years of lagging by performing separate analyses for each of the lag-times.

We also looked at the association between DHP-CCB or nonDHP-CCB use on the risk of all-cause mortality. A similar analysis to the one described above was used in this part of the study. Subjects who died during follow-up may contribute to the analysis up to their age of death, while other subjects may contribute information up to the age when lost to follow-up. Follow-up was defined as the time between the first visit on or after 1980 and either death or September 30th, 1999. The risk of dying was compared between subjects who used either DHP-CCB or nonDHP-CCB, and subjects who did not use CCB. Use of CCB was included in the analyses as two time-dependent binary covariates as described above. The analyses also adjusted for the potential confounding effects of gender, education, smoking, systolic and diastolic blood pressure, and history of heart problems.

3. Results

3.1. Demographic characteristics

The 1092 (685 men and 407 women) participants included in the study were highly educated, with 72% hav-

Table 1
Demographic characteristics of all subjects and Alzheimer's disease cases included in the study

	Study sample	AD cases
<i>N</i>	1092	115
Number of men	685 (62.7%)	63 (54.8%)
Mean years of follow-up (range)	11.0 (0.3–19.6)	8.7 (0.6–17.9)
Mean number of visits (range)	9.0 (1–27)	8.0 (1–27)
Mean age at last follow-up (range)	78.1 (61.1–104.2)	84.5 (61.8–104.2)
Number with college education or higher	787 (72.2%)	84 (73.0%)
CCB use during follow-up	220 (20.2%)	18 (15.7%)
Dihydropyridine	116 (10.6%)	6 (5.2%)
Nondihydropyridine	142 (13.0%)	12 (10.4%)

Categorical variables are described by the number and percentage in each category. Continuous variables are described by mean and range. CCB: calcium channel blocker, AD: Alzheimer's disease.

ing attained a college education or higher, and had an average age of 78.1 years at last follow-up (Table 1). At some time during follow-up, 20% of subjects reported the use of CCB (11% DHP-CCB; 13% nonDHP-CCB; 3% both). Information about the indication for treatment with CCB was available in 90.0% of the DHP-CCB group and 82.3% of the nonDHP-CCB group (Table 2). In the DHP-CCB group, 45.4% of the subjects reported essential hypertension, 46.1% ischemic heart disease and 0.01% arrhythmia as the indication for the medication use. Similarly, in the nonDHP-CCB group, 41.2% of the subjects reported essential hypertension, 40.1% ischemic heart disease and 0.08% arrhythmia as the indication for the medication use.

3.2. Risk of AD

The RR of AD associated with use of any CCB compared to non-users was 0.63 (95% CI = 0.31–1.28) for a 2-year lag, and 0.71 (95% CI = 0.33–1.51) for a 4-year lag. In contrast, the RR of AD associated with >2 years of CCB use compared to non-users was 0.51 (95% CI = 0.202–1.292) for a 2-year lag and 0.424 (95% CI = 0.13–1.38) for a 4-year lag.

Table 3 and Fig. 1 show the results of DHP-CCB and nonDHP-CCB use and the risk of AD. The RR of AD, when comparing DHP-CCB users versus non-users, was 0.30 (95% CI = 0.07–1.25) for a 2-year lag and 0.45 (95% CI = 0.11–1.87) for a 4-year lag. Use of nonDHP-CCB was not associated with a reduced risk of AD (RR = 0.82, 95% CI = 0.37–1.83 for a 2-year lag; RR = 0.82, 95% CI = 0.35–1.95 for a 4-year lag). Thus, use of DHP-CCB did not significantly change the risk of AD, although the estimate of RR was substantially lower in DHP-CCB users than in nonDHP-CCB users or non users. The results are adjusted for gender, education, smoking, blood pressure, and history of heart problems.

Table 2
Characteristics of subjects who used calcium channel blockers at some time during follow-up

	DHP	NonDHP	Both
N	78	104	38
AD cases	6 (7.7%)	12 (11.5%)	0 (0%)
Number of deaths	16 (21%)	42 (40%)	9 (24%)
Men	46 (59.0%)	75 (72.1%)	25 (65.8%)
Mean years of follow-up (range)	12.4 (0.6–19.5)	12.5 (2.0–19.4)	13.2 (4.3–19.0)
Mean age at last follow-up (range)	80.1 (62–94)	80.4 (62–94)	80.9 (60–93)
College education or higher	46 (59.0%)	83 (79.8%)	28 (73.7%)
History of heart problems	54 (69.2%)	93 (89.4%)	34 (89.5%)
Hypertension	54 (69.2%)	67 (64.4%)	23 (60.5%)
History of smoking	51 (65.4%)	69 (66.4%)	23 (60.5%)

Categorical variables are described by the number and percentage in each category. Continuous variables are described by mean and range. DHP: dihydropyridine, nonDHP: nondihydropyridine, AD: Alzheimer’s disease Hypertension defined as systolic >160 and diastolic >95.

Table 3
Relative risk of AD associated with use of calcium channel blockers

Type of CCB	Years of lagging	Relative risk	95% CI	P-value	Number of AD cases
Non-users	2	1.00	Reference	–	76
Dihydropyridine		0.30	0.07–1.25	0.10	
Nondihydropyridine		0.82	0.37–1.83	0.63	
Non-users	4	1.00	Reference	–	80
Dihydropyridine		0.45	0.11–1.87	0.27	
Nondihydropyridine		0.82	0.35–1.95	0.65	

Model adjusted for gender, education, smoking, blood pressure, and history of heart problems; CCB: calcium channel blocker; AD: Alzheimer’s disease; CI: confidence interval.

3.3. Risk of mortality

The same 1092 subjects were included in the analyses for the second objective of the study. Subjects were followed for

an average of 13 years and were on average 80.1 years of age at last follow-up. There were 382 subjects who died during the follow-up period. Neither DHP-CCB nor nonDHP-CCB had an effect on the risk of all-cause mortality (Table 4). All

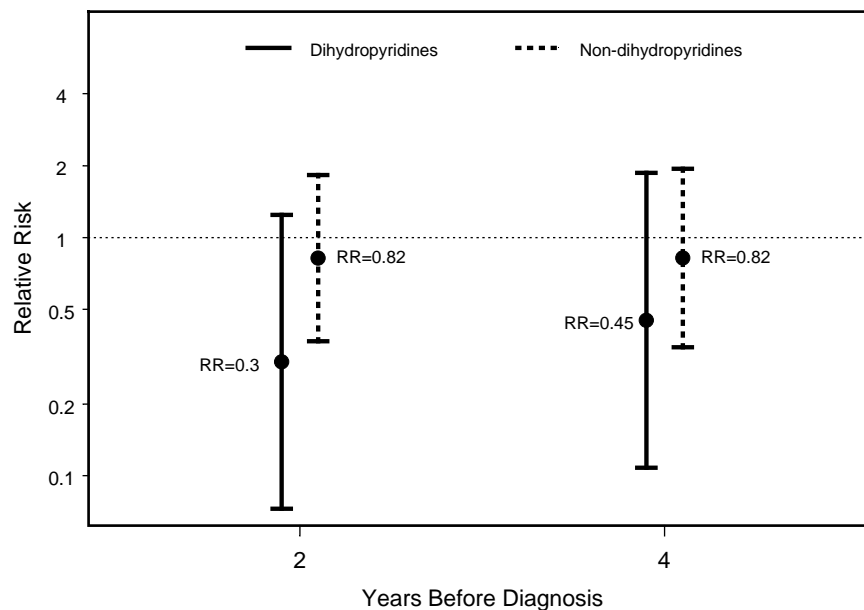


Fig. 1. Adjusted relative risks and 95% confidence intervals for calcium channel blocker types Non-users of calcium channel blockers were used as the reference group; relative risks are adjusted for gender, education, smoking, blood pressure, and history of heart problems. RR: relative risk, log scale.

Table 4
Relative risk of mortality associated with use of calcium channel blockers

Type of CCB	Years of lagging	Relative risk	95% CI	P-value	Number of deaths
Non-users	2	1.00	Reference	–	129
Dihydropyridine		0.64	0.32–1.29	0.21	
Nondihydropyridine	4	1.10	0.65–1.87	0.72	204
Non-users		1.00	Reference	–	
Dihydropyridine		1.03	0.62–1.72	0.91	
Nondihydropyridine		1.36	0.89–2.08	0.16	

Model adjusted for gender, education, smoking, blood pressure, and history of heart problems. CCB: calcium channel blocker; CI: confidence interval.

results are adjusted for gender, education, smoking, blood pressure and history of heart problems.

4. Discussion

In this prospective study, we evaluated the association between reported use of CCB and the risk of developing AD. Reported use of any CCB or use of DHP-CCB or nonDHP-CCB alone did not significantly change the risk of developing AD. With reported use of DHP-CCB, there was a trend for decreasing the risk of developing AD, indicated by low absolute value of RR (0.30), which approached significance ($P = 0.10$), that was not seen with reported use of nonDHP-CCB ($R = 0.80$, $P = 0.63$). The failure to demonstrate a clearly significant reduction in RR with DHP-type CCB, which only became available in the late 1980's, may be due to the high variability (95% CI = 0.07–1.25) in the limited population using these relatively recently introduced drugs during the time course of our study (1980–1999).

CCB, particularly DHP-CCB, are mainly used for anti-hypertensive treatment. Some longitudinal studies have reported a correlation between elevated midlife systolic blood pressure and cognitive decline [18,30] and between elevated diastolic blood pressure and increased risk for AD [13,33]. Adjusting for blood pressure in the present study did not change our results. In addition, indications for treatment with CCB (e.g. hypertension or cerebrovascular disease) could be associated with different vascular conditions. This could affect the outcome of the study by increasing the probability of a diagnosis of vascular dementia and decreasing the probability of a diagnosis of AD. In the present study, however indications for treatment were very similar for both the DHP-CCB group and the nonDHP-CCB group. It is also well known that smoking has cardiovascular effects, but there is controversy in the literature about the effect of smoking on the development of AD [19,20,24,27,35]. Adjusting for smoking, in the current study, did not change the results.

One limitation of our study was the small number of incident AD cases and DHP-CCB and nonDHP-CCB users, which may have limited our ability to detect a significant association and introduced the likelihood of a type II error. We were also limited in our ability to analyze the use of the

two types of CCB as distinct groups. We attempted to analyze CCB use with four distinct categories: non users, users of only DHP-CCB, users of only nonDHP-CCB, and users of both. However, because of the low numbers of subjects taking CCB, we were unable to estimate relative risks for all the groups using this classification. Additional studies are necessary to look at the use of CCB as potentially protective agents and apparent differential effects of the two types of CCB.

Another limitation was our limited information regarding duration of use and dosage. For example, we were not able to accurately determine for how long medication was used relative to the time its use was reported during a visit. In the present study, CCB use was defined as a binary variable. Thus, use of CCB for only limited periods would still result in a positive report of use, although it is likely that treatment with CCB for at least 3–6 months is required for effects on cognition [11]. However, when the length of CCB use and the risk of AD were further analyzed as a time-dependent categorical duration-of-use variable, there was a decrease in the absolute value of RR with increasing length of use (RR = 0.87 for <2 years, RR = 0.51 for >2 years). We also attempted a time-dependent analysis of DHP-CCB use and the risk of AD, but this was not possible due to the low number of subjects. In addition, medication use was only validated starting in 1990, by comparing self-report and medication bottles. This could result in a recall bias between 1980 and 1990. However, using lagging in the analyses minimized the possibility of differential recall.

In this study we also evaluated the effects of CCB on mortality, since others have provided evidence that short-acting DHP-CCB can increase the risk of mortality [12,22]. No relationship between mortality and use of DHP-CCB was found. A limitation of our study, however, is that we analyzed mortality from all causes, since we did not have the ability to identify deaths from cardiovascular or cerebrovascular disease. Therefore, an effect that might exist only in participants with cardiovascular disease may not have been detected. We did, however, adjust for a history of cardiac problems and this did not change the findings.

Strengths of our study are the prospective nature of our data and the long follow-up period. In addition, the cohort is well characterized in terms of dementia and AD diagnoses with direct examinations. We were also able to control for

potential confounders and to analyze both AD and mortality outcomes in the same cohort.

Our findings do not support the hypothesis that use of any CCB, or use of DHP-CCB in particular, significantly reduces the risk of developing AD. However, the estimate of the RR was substantially lower in users of DHP-CCB than in users of nonDHP-CCB and approached significance ($P = 0.10$). This suggests a need for further observational studies with larger numbers of incident AD cases and CCB users, particularly users of DHP type CCB, in other populations or in our population in future years to further document the influence of DHP-CCB use on AD incidence.

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