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ORIGINAL REPORT

Nifedipine and Mortality Risk in the Elderly: Relevance of Drug Formulation, Dose and Duration

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SUMMARY

Purpose — This study examines the risk of all-cause and cardiac-related mortality associated with calcium channel blockers (CCBs) and other antihypertensives/diuretics compared with β-blockers among an elderly cohort. We explored variations in mortality risk according to CCB formulation, dose and duration of use.

Methods — Data are from the clinical sample of the Canadian Study of Health and Aging, a population-based prospective study of community and institutional residing persons aged 65+ years. The sample comprised 837 subjects without dementia and reporting use of 1+ antihypertensive/diuretic agents at baseline (1991) and with survival data during follow-up (1996).

Results — Risk of all-cause and cardiac-related mortality was significantly higher among nifedipine users (HR = 1.85, 95%CI 1.12, 3.05 and HR = 2.22, 95%CI 1.02, 4.84, respectively) compared with β-blocker users. After adjusting for covariates, the hazard ratios (95% confidence interval) for selected drug classes compared with β-blockers were: nifedipine HR = 1.82 (1.09–3.04), diltiazem/verapamil HR = 0.96 (0.58–1.60), loop diuretics HR = 1.84 (1.21–2.82), ACE inhibitors HR = 0.98 (0.54–1.78) and other diuretics/antihypertensives HR = 1.10 (0.70–1.72). Among nifedipine users, mortality risk increased with average daily dose and with recent (⩽6 months) initiation of therapy and remained significant for prolonged-acting formulations.

Conclusions — Older subjects exposed to the dihydropyridine calcium antagonist nifedipine had a significantly higher risk for all-cause and cardiac-related mortality during the 5-year follow-up than subjects using β-blockers. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — calcium-channel blockers; hypertension; mortality; elderly; prospective

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TAKE HOME POINTS

(1) The relationship of calcium-channel blockers and other antihypertensive agents with 5-year mortality was examined among 837 persons aged 65 years and older.
(2) Compared with β-blocker users, subjects using nifedipine had a significantly higher risk of all-cause and cardiac-related mortality during follow-up.
(3) Among nifedipine users, mortality risk increased with average daily dose and with recent initiation of therapy and remained significant for prolonged-acting formulations.
(4) The findings are consistent with previous research indicating an increased mortality risk associated with nifedipine use, especially among older and vulnerable patients.

INTRODUCTION

There is controversy regarding the use of calcium channel blockers (CCBs) in the management of hypertension among elderly persons. Relative to other antihypertensive agents, CCBs appear to be equally efficacious in terms of lowering blood pressure.[1,2] Findings regarding the beneficial effects of CCBs on surrogate endpoints like blood pressure suggest that these agents may also be comparable to diuretics and β-blockers in terms of lowering patients' risk for cardiovascular-related morbidity and mortality.[3] However, research conducted in recent years has contributed to an ongoing debate about the potential adverse cardiovascular effects associated with select CCBs among particular patient groups.[4–8]

Results from randomized clinical trials and observational studies suggest that relative to other antihypertensive agents, select CCBs, primarily the short-acting dihydropyridine agents (e.g. nifedipine), may increase patients' risk for acute myocardial infarction,[2,9] all-cause and cardiovascular mortality[10–16] and adverse cognitive and cerebrovascular effects.[17–20] These risks appear most evident for patients with a history of coronary heart disease (e.g. myocardial infarction) and with compromised cerebrovascular circulation. There is also evidence of a dose–response relation between nifedipine use and cardiovascular events[9] and mortality[10–12] among hypertensive patients with or without a history of heart disease. Conversely, other observational research conducted in the past 5 years has failed to demonstrate a significant association between CCB exposure and adverse cardiovascular events or mortality.[21–23]

Recent interpretations of the data have emphasized the relevance of CCB formulation. In this regard, several clinical trials have provided support for the relative safety of the long-acting, slow-release CCBs among hypertensive patients.[24,25] Beyond CCB dose and formulation, it is also possible that duration of use may be relevant to the adverse risks observed for select CCBs among older persons with or without concomitant diseases. This aspect of CCB use remains relatively unexplored in the literature.

Given the high prevalence of hypertension among older individuals[26,27] and the fact that CCBs are among the most widely used antihypertensive agents in Canada[28] and the United States,[29] further investigation of the potential adverse effects of these medications is warranted. Although large randomized clinical trials would offer the strongest evidence to resolve the controversy about the risk/benefit ratio of specific CCBs relative to other antihypertensive agents, long-term follow-up data from such trials are not yet available. Evidence from previous clinical trials demonstrating the safety and efficacy of the longer-acting CCBs[24,25,30] may not be generalizable to older, frail patients due to methodological limitations including selection biases, the exclusion of older subjects with co-morbid conditions, high attrition rates, and the reliance on surrogate endpoints.[31,32] In evaluating the present controversy regarding the adverse cardiac effects of CCBs, it is crucial to examine the consistency of evidence across different epidemiological data sources.[33] The Canadian Study of Health and Aging (CSHA) provides an opportunity to replicate the findings reported by recent epidemiologic investigations in the United States with data from a population-based sample of elderly Canadian men and women.

The primary objective of the present study was to examine the risk of all-cause and cardiac-related mortality associated with exposure to nifedipine, non-dihydropyridine CCBs, angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, and other diuretics or antihypertensives compared with β-blockers, among an elderly cohort. A second objective was to explore potential variations in mortality risk among nifedipine users according to drug formulation, dose and duration of use at baseline.

METHODS

Sample

The analyses are based on data from the 1991 and 1996 cycles of the CSHA. The CSHA is a population-based, prospective investigation of the epidemiology of dementia and other health issues among a representative sample of Canadians aged 65 years and older. The study was initiated in 1991 as a national collaborative investigation involving 18 centres grouped into five geographic regions. The total sample initially interviewed between February 1991 and May 1992 included 10,263 persons, 9008 from the community (response rate of 72.1%) and 1255 residing in institutions (response rate of 81.7%). The study excluded residents of the Northwest and Yukon Territories, Indian reservations and military units.

For the community sample, subjects were randomly selected from provincial health insurance plans with the exception of Ontario where sample selection was based on election and municipal records in the Enumeration Composite Record. To ensure adequate numbers in the older age ranges, there was oversampling of individuals aged 75–84 and 85+ years. In 15 of the 18 study centres, institutional subjects were randomly selected from residents in stratified random samples of institutions (nursing homes, chronic care facilities and collective dwellings) in each region. For the other three centres, institutional subjects were randomly selected from provincial health insurance databases.

All community subjects first underwent a standardized interview which included questions on sociodemographic characteristics, activities of daily living (ADL), current health problems, and a screening test for cognitive impairment, the Modified Mini-Mental State (3MS) Examination.[34] Subjects scoring below 78 on the 3MS, a random sample of those with a score of 78 or greater, and subjects unable to be screened because of hearing or other difficulties were invited to a clinical examination ($n = 1165$). All consenting institutional subjects underwent the clinical examination. This multidisciplinary clinical examination included a repeat 3MS, height and weight, review of medication use, vital signs, medical history and physical examination, and neuropsychologic testing (for those with 3MS scores of 50+). A consensus conference was held to review all available information and to categorize the individual as cognitively normal, cognitively impaired but not demented, or demented (using DSM-III-R criteria).[35] A more comprehensive description of the CSHA study design and methodology has been provided elsewhere.[36] In the second cycle of the study (CSHA-2), the original cohort was re-contacted an average of 5 years after the baseline examination. The follow-up assessment including drug use evaluation was equivalent to that used at the time of initial contact (CSHA-1).

The present analyses are restricted to subjects in the clinical sample identified at baseline as not having dementia and reporting use of one or more antihypertensive medications or diuretics ($n = 864$). This sample was further reduced to 837 since 23 subjects who died were found to have missing or inaccurate dates of death and four subjects reporting nifedipine use at baseline were excluded because they were using nifedipine on a PRN (as needed) basis only.

Measures

At the baseline clinical examination, subjects were asked to report their current prescription and over-the-counter drug use. A trained nurse reviewed and recorded all drug-related information, including drug name, dose and duration. For institutional subjects, drug data were obtained from review of their health record. The drug data were coded according to the American Hospital Formulary System Pharmacologic/Therapeutic Classification Scheme. We classified subjects into one of the following six drug classes: (1) nifedipine, (2) diltiazem or verapamil, (3) loop diuretics, (4) β-blockers, (5) angiotensin-converting enzyme (ACE) inhibitors and (6) other diuretics or antihypertensives. The two non-dihydropyridine CCBs, diltiazem and verapamil, were combined based on previous findings indicating comparable mortality risks for these two drugs relative to other antihypertensive medications[10] and because only 21 subjects in the present study reported verapamil use at time of assessment.

To categorize subjects with exposure to various antihypertensive/diuretic drug class combinations, we first examined the mortality risk for subjects exposed to particular combinations relative to those exposed to a single drug class only. Subjects exposed to loop diuretics only and those exposed to any loop diuretic–other drug combinations were found to have a similar mortality risk which was significantly higher than the risk associated with any other drug class or drug combination. As a

result, subjects reporting use of any loop diuretic–other drug combination were classified with those reporting use of a loop diuretic only. Similarly, based on findings of their comparable mortality risks, subjects exposed to any nifedipine–other drug combination (excluding loop diuretics) were grouped with those exposed to nifedipine only and those exposed to any diltiazem/verapamil–other drug combination (excluding loop diuretics) were grouped with those exposed to diltiazem/verapamil only. Next, those using any β-blocker–other drug combination (excluding loop diuretics and CCBs) were grouped with those using β-blockers only. This process was repeated for users of ACE inhibitors. Based on this classification, 23 nifedipine users and 38 diltiazem/verapamil users were grouped with loop diuretic users. All analyses reported here were repeated with the CCB–loop combination users grouped with their respective CCB class (nifedipine or diltiazem/verapamil) and the findings regarding the mortality risk estimates obtained for the CCB groups relative to β-blocker users were unchanged.

The following covariates were examined as potential confounding or effect modifying factors: age, sex, other drug use (digoxin, nitrate, aspirin and non-aspirin nonsteroidal anti-inflammatory drugs (NSAID), history of chronic health conditions (stroke and diabetes) and hypertension, clinical symptoms (cardiac, intermittent claudication) as recorded by the examining physician, setting systolic/diastolic blood pressure, smoking status and 3MS score. Cardiac symptoms include chest pain, dyspnea, palpitations, and/or edema. A specific question on current and past smoking behaviours was not asked of subjects included in the clinical sample of the CSHA. However, a question on subjects' current or past heavy smoking ('has he/she ever been a heavy smoker, say 20 or more cigarettes a day for a year or more?') was asked as part of the informant interview. The informant was a relative or friend identified by the subject. CSHA baseline measures of self-rated health, activities of daily living and body mass index, were excluded from the analyses because of relatively large proportions of the sample with missing values for these variables (32.6, 32.0 and 10.4%, respectively).

At follow-up in 1996, data on the subjects' mortality status and date of death (if relevant) were obtained from the informant identified by the subject at baseline, and Provincial vital statistics. Information on cause of death was obtained from death certificate data. Specifically, cardiac-related mortality was defined as a recorded underlying cause of death of one of the following: acute myocardial infarction, other forms of ischemic heart disease, angina, other diseases of endocardium, dysrhythmias, congestive heart failure, and other unspecified heart disease or heart failure.

Analysis

Bivariate associations were examined using cross-tabulations and chi-square tests of significance for categorical variables and *t*-tests for continuous variables. Bivariate associations between the selected antihypertensive/diuretic medications, demographic and health-related variables and mortality were examined using univariate Cox proportional hazards regression models.[37] The outcome of interest represented time to death (in days) calculated as the interval between the date of the nurse's clinical assessment and the recorded date of death during follow-up to 31 October 1996. Factors significant at the bivariate level were entered into multivariate Cox proportional hazards regression models to examine the independent effects and relative importance of specific subject characteristics and antihypertensive/diuretic exposure on subject survival. Multivariate analysis of cardiac-related mortality was not performed because of problems with relatively small numbers and missing values. Specifically, 19 subjects who died did not have data on cause of death and several of the covariates examined (e.g. diastolic blood pressure and intermittent claudication) exhibited a higher proportion of missing values among CCB compared with β-blocker users.

Antihypertensive/diuretic drug use was coded using dummy variables comparing specific drug classes to the reference group of β-blockers. We selected β-blocker users as the reference group since they were found to have the lowest crude mortality rate and because CCBs and β-blockers are both indicated for the treatment of hypertension or angina. Nifedipine users were categorized into high and low daily dose groups using the median value. To evaluate recent compared with longer-term nifedipine users, and to ensure adequate cell sizes, we categorized duration of use as $\leqslant 6$ months, 7–12 months and >12 months. Duration of nifedipine use was assessed at the baseline (1991) interview. All analyses were performed using the SAS (version 6.12) software packages.[38]

Table 1 — Distribution of drug use, demographic and health characteristics and crude mortality rates (per 1000 person-years) according to antihypertensive/diuretic drug use among CSHA subjects ($n = 837$)

Variable	% (number)	Mean (SD)	Mortality rate/1000 person-years (number)	
			All-cause	Heart disease*
Antihypertensive/diuretic				
β-blocker	11.8 (99)		63 (28)	27 (11)
ACE inhibitor	8.6 (72)		73 (22)	30 (8)
Other diuretic/antihyp.	24.6 (206)		87 (75)	31 (22)
Loop diuretic	32.1 (269)		187 (169)	105 (70)
Nifedipine	9.1 (76)		115 (34)	61 (15)
Diltiazem/verapamil	13.7 (115)		75 (36)	51 (23)
Digoxin	22.9 (192)			
Nitrate	19.8 (166)			
Aspirin	27.1 (227)			
Non-aspirin NSAID	16.8 (141)			
Age (years)		80.4 (6.9)		
Sex				
Female	67.3 (563)			
Male	32.7 (274)			
Heavy smoker (ever)†	30.6 (246)			
History of stroke†	14.4 (119)			
History of diabetes†	14.2 (117)			
History of arterial hypertension†	59.5 (493)			
Intermittent claudication†	6.1 (50)			
Cardiac symptoms†	41.2 (340)			
3MS score†		75.4 (14.5)		
Systolic blood pressure†		145.2 (23.6)		
Diastolic blood pressure†		76.7 (12.4)		

*Recorded on death certificate as underlying cause of death, includes acute myocardial infarction, other forms of ischemic heart disease, angina, other diseases of endocardium, dysrhythmias, congestive heart failure, and other unspecified heart disease or heart failure (total $n = 622$; 19 subjects excluded because of missing values for cause of death).
†Variables do not sum to 837 due to missing values.

RESULTS

Table 1 presents the distribution of the demographic, health and drug variables examined for the 837 study participants. The mean age of the sample was 80.4 (SD = 6.9) years and 67.3% were women. Approximately 57% of the sample exhibited some degree of cognitive impairment (i.e. 3MS score < 78) and the mean 3MS score was 75.4 (SD = 14.5). Among study subjects, there were 364 deaths during 3293 person-years of follow-up (111 deaths per 1000 person-years) and 149 cardiac-related deaths during 2755 person-years (54 deaths per 1000 person-years). Subjects reporting use of loop diuretics had the highest crude rate of all-cause (187 per 1000 person-years) and cardiac-related (105 per 1000 person-years) mortality, followed by subjects reporting use of nifedipine (115 and 61 deaths per 1000 person-years for all-cause and cardiac-related mortality, respectively). The lowest crude rates were observed among β-blocker users (63 and 27 deaths per 1000 person-years for all-cause and cardiac-related mortality, respectively).

The distribution of baseline demographic and health characteristics according to antihypertensive/diuretic drug group is presented in Table 2. Subjects using nifedipine were significantly more likely than β-blocker users to report a history of hypertension at baseline (77.6 and 61.6%, respectively). Nifedipine users also exhibited relatively higher baseline rates for stroke history and cardiac symptoms and a lower mean diastolic blood pressure compared with β-blocker users (not statistically significant). Relative to β-blocker users, subjects using the nondihydropyridine CCBs diltiazem or verapamil were significantly more likely to report cardiac symptoms and nitrate use

Table 2 — Percentage distribution (number) of baseline demographic and health characteristics according to antihypertensive/diuretic drug use among CSHA subjects ($n = 837$)

Characteristic	Antihypertensive/diuretic drug use					
	β-blocker	ACE Inhibitor	Other diuretic/ antihyp.	Loop diuretic	Nifedipine	Diltiazem/ verapamil
Digoxin use	14.1 (14)	16.7 (12)	13.1 (27)	41.6 (112)	9.2 (7)	17.4 (20)
Nitrate use	14.1 (14)	8.3 (6)	8.7 (18)	27.5 (74)	21.1 (16)	33.0 (38)‡
Age mean (SD)	77.8 (6.5)	80.0 (6.6)	80.1 (7.3)	82.6 (6.8)	78.6 (6.4)	79.3 (6.1)
Sex (female)	62.6 (62)	61.1 (44)	74.3 (153)	67.7 (182)	67.1 (51)	61.7 (71)
Heavy smoker (ever)	28.1 (27)	31.4 (22)	25.9 (50)	31.7 (82)	32.0 (24)	37.3 (41)
History of stroke	13.1 (13)	11.4 (8)	12.3 (25)	15.7 (42)	20.0 (15)	14.2 (16)
History of diabetes	8.1 (8)	11.4 (8)	10.8 (22)	22.0 (58)	10.5 (8)	11.5 (13)
History of hypertension	61.6 (61)	91.4 (64)	65.7 (134)	41.7 (111)	77.6 (59)*	56.6 (64)
Intermittent claudication	6.1 (6)	5.6 (4)	3.5 (7)	7.6 (20)	8.1 (6)	6.3 (7)
Cardiac symptoms	35.7 (35)	25.4 (18)	18.9 (38)	53.0 (141)	47.4 (36)	63.2 (72)‡
SBP mean (SD)	150.9 (25.9)	156.1 (26.9)	143.1 (21.3)	141.9 (24.2)	146.4 (22.7)	143.7 (20.2)*
DBP mean (SD)	80.3 (12.9)	82.2 (14.4)	75.9 (11.6)	74.6 (11.9)	77.4 (13.4)	75.7 (11.0)†

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Difference between calcium channel blocker and β-blocker group is statistically significant: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Table 3 — Unadjusted and adjusted§ hazards ratios (95% confidence intervals) for mortality‖ associated with antihypertensive/diuretic drug use, demographic and selected health characteristics among CSHA subjects ($n = 837$)

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Antihypertensive/diuretic		
β-blocker (ref group)	1.00	1.00
ACE inhibitor	1.15 (0.66, 2.00)	0.98 (0.54, 1.78)
Other diuretic/antihyp.	1.39 (0.90, 2.14)	1.10 (0.70, 1.72)
Loop diuretic	3.05 (2.04, 4.55)¶	1.84 (1.21, 2.82)†
Nifedipine	1.85 (1.12, 3.05)*	1.82 (1.09, 3.04)*
diltiazem/verapamil	1.19 (0.72, 1.94)	0.96 (0.58, 1.60)
Digoxin	1.98 (1.59, 2.47)¶	1.33 (1.02, 1.72)*
Nitrate	1.45 (1.14, 1.84)†	1.31 (0.98, 1.74)
Age (10-year increase)	1.98 (1.69, 2.32)¶	1.75 (1.45, 2.10)¶
Sex (female)‖	0.78 (0.63, 0.97)*	0.78 (0.62, 0.99)*
History of stroke	1.61 (1.24, 2.09)‡	1.76 (1.31, 2.35)‡
History of diabetes	1.37 (1.04, 1.80)*	1.23 (0.91, 1.66)
Intermittent claudication	1.75 (1.21, 2.54)†	1.63 (1.10, 2.41)*
Cardiac symptoms	1.25 (1.02, 1.55)*	0.93 (0.73, 1.20)
3MS score (10-point increase)	0.83 (0.78, 0.88)¶	0.87 (0.81, 0.93)‡
Diastolic BP (10 mm Hg increase)	0.81 (0.74, 0.88)¶	0.86 (0.78, 0.94)†
History of arterial hypertension	0.66 (0.54, 0.82)¶	0.94 (0.74, 1.21)

§Obtained from multivariate Cox proportional hazards regression model adjusted for all factors listed above.
‖Follow-up during 1991–1996, 364 subjects lost because of death compared with 473 censored subjects.
‖May be substituted with smoking since these two variables are highly correlated.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$; ¶$p \leqslant 0.0001$.

at baseline and to have significantly lower mean systolic and diastolic blood pressures.

Table 3 presents the unadjusted and adjusted hazard ratios (95% confidence intervals) for all-cause mortality associated with the antihypertensive/diuretic drug groups and demographic and health characteristics examined among CSHA subjects. When compared with β-blocker users, only those using loop diuretics (HR = 3.05) or nifedipine (HR = 1.85) were found to have a significantly increased risk of mortality. Comparable findings were found for cardiac-related

mortality (HRs of 3.83 and 2.22 for loop diuretics and nifedipine, respectively — data not shown). Other factors with a positive significant association with all-cause mortality included digoxin (HR = 1.98) and nitrate (HR = 1.45) use, age (HR = 1.98 for a 10-year increase), history of stroke (HR = 1.61) or diabetes (HR = 1.37), intermittent claudication (HR = 1.75), and cardiac symptoms (HR = 1.25). Conversely, there was a significantly lower mortality risk observed for female subjects (HR = 0.78), those with higher 3MS scores (better cognitive functioning, HR = 0.83 for a 10-point increase), a higher diastolic blood pressure (HR = 0.81 for 10 mmHg increase) and for subjects with a history of arterial hypertension (HR = 0.66). Systolic blood pressure showed a similar, but less significant, association to that observed for diastolic blood pressure and thus was excluded from the final model. Aspirin and non-aspirin NSAID use were not significantly associated with mortality in the present sample.

After adjusting for age, sex, other drug use, history of chronic health conditions, clinical symptoms, blood pressure, and cognitive status, the hazard ratios (95% confidence interval) for mortality among subjects exposed to select antihypertensive/diuretic drug groups relative to those exposed to β-blockers were: nifedipine HR = 1.82 (1.09–3.04), diltiazem/verapamil HR = 0.96 (0.58–1.60), loop diuretics HR = 1.84 (1.21–2.82), ACE inhibitors HR = 0.98 (0.54–1.78), and other diuretics or antihypertensives HR = 1.10 (0.70–1.72). The magnitude of risk for loop diuretics relative to β-blockers was considerably lower compared with the unadjusted estimate likely reflecting the relatively high prevalence of adverse comorbid health and underlying cardiac conditions among loop diuretic users (Table 2). Other factors which remained significant in the multivariate model included digoxin use, age, sex, history of stroke, intermittent claudication, 3MS score and diastolic blood pressure.

Smoking was significantly correlated with sex among CSHA subjects (58% of men and 17.3% of women were reported as current or past heavy smokers). Consequently smoking was excluded from the multivariate analysis because of problems with collinearity. However, variations in the multivariate model with smoking included or substituted for sex had no effect on the risk estimates reported for the antihypertensive/diuretic drug groups.

Table 4 — Adjusted* hazards ratios (95% confidence intervals) for mortality† associated with nifedipine formulation, dose and duration of use at baseline among CSHA subjects

Variable	Number	Adjusted HR (95% CI)
Nifedipine		
Short-acting	41	1.64 (0.88, 3.03)
Prolonged action	35	2.07 (1.11, 3.85)‖
Nifedipine‡		
⩽30 mg/day	33	1.50 (0.74, 3.02)
⩾40 mg/day	35	2.19 (1.19, 4.03)‖
Nifedipine§		
⩽6 months	11	3.75 (1.54, 9.13)¶
7–12 months	11	0.82 (0.25, 2.74)
>12 months	43	1.70 (0.92, 3.12)

*Obtained from multivariate Cox proportional hazards regression model adjusted for digoxin and nitrate use, age, sex history of stroke, diabetes and arterial hypertension, intermittent claudication, cardiac symptoms, MMMS score and diastolic blood pressure. Reference group = β-blocker users.
†Follow-up during 1991–1996, 364 subjects lost because of death compared with 473 censored subjects.
*$p < 0.05$; †$p < 0.01$.
‡Eight subjects with missing dose.
§Eleven subjects with missing duration.

Table 4 presents the adjusted hazard ratios for all-cause mortality for nifedipine compared with β-blocker users according to nifedipine drug formulation, dose and duration of use recorded at baseline. Mortality risk was significantly increased among users of the prolonged- but not the short-acting formulation of nifedipine. At baseline (1991), no subjects reported using extended-release nifedipine. A significantly increased risk of mortality was also observed for subjects reporting nifedipine use of 40 mg/day or greater, but not among those reporting 30 mg/day or less. Additional analyses illustrated a significant association between nifedipine drug formulation (short versus prolonged action) and dose. That is, most short-acting users reported a dose of 30 mg/day or less whereas most prolonged-action users reported a dose of 40 mg/day or greater. Due to the association between nifedipine formulation and dose, we also examined the mortality risk associated with selected formulation–dose categories (data not shown). The findings illustrated a two-fold increased risk of mortality for users of both short and prolonged-acting nifedipine at doses of ⩾40 mg/day. This risk was significant among prolonged-acting nifedipine users only. When

stratified by duration of nifedipine use at baseline, only subjects reporting nifedipine use for 6 months or less exhibited a significantly increased mortality risk, although subjects with nifedipine use of greater than 12 months also showed an elevated mortality risk. After excluding short-term users ($\leqslant$6 months), the mortality risk associated with nifedipine use was in the same direction, although of borderline statistical significance (adjusted HR = 1.63, 95% CI 0.95–2.80).

DISCUSSION

This prospective, population-based investigation showed that older subjects exposed to the dihydropyridine calcium antagonist nifedipine had a significantly higher risk for all-cause and cardiac-related mortality during the 5-year follow-up than subjects using β-blockers. Subjects reporting use of a nondihydropyridine CCB (diltiazem or verapamil), ACE inhibitor or other antihypertensive/diuretic (excluding loop diuretics), at baseline did not significantly differ from β-blocker users in terms of their mortality risk. The findings further indicated an increase in all-cause mortality risk with increasing nifedipine dose ($\geqslant$40 mg/day compared with $\leqslant$30 mg/day) and, in particular, with a short duration of nifedipine exposure at baseline. There was a higher risk of all-cause mortality among users of both short- and prolonged-acting nifedipine, but only the association with the prolonged-acting formulation reached statistical significance. The risk estimates for all-cause mortality observed for nifedipine users were unchanged by adjustment for several potential confounding factors including age, sex, history of chronic conditions, current cardiovascular symptoms, other drug use, diastolic blood pressure and cognitive function.

Our findings are consistent with several,[10–16] but not all,[21–23] previous studies in this area. Some of this inconsistency may reflect important differences in the samples investigated. CSHA participants included in the present analyses represent only those who underwent the clinical examination. They are relatively less healthy and more cognitively impaired than the general older Canadian population (see Table 1). The average age of CSHA participants included in our analyses (80.4 years) was also relatively higher than that observed for samples included in previous research which failed to demonstrate a significant association with CCB use.[21–23] It is known that the hypotensive effects of the dihydropyridine CCBs may be increased in elderly patients due to both a decreased clearance and altered pharmacodynamics.[39–41] Our results concerning nifedipine, diltiazem and verapamil are consistent with proposed underlying mechanisms, particularly those regarding the proischemic and proarrhythmic effects of the short-acting dihydropyridine CCBs.[11,42,43]

The phenomenon of reflex sympathetic activation and tachycardia has been noted to be less pronounced with the long-acting CCB formulations accounting for their lower risk profile.[7,23,44] Although the absence of subjects using extended-release nifedipine at baseline precluded our investigation of the mortality risk for users of long-acting CCBs, we did find a significantly higher mortality risk among users of prolonged-acting nifedipine. The MIDAS investigation,[2] a randomized clinical trial among 883 hypertensive patients, also illustrated an increased risk of adverse events (MI, stroke, heart failure, angina and death) among users of the intermediate-acting dihydropyridine CCB isradipine compared with diuretic users. In the recent case–control study by Alderman *et al.*,[16] the intermediate-acting CCBs were combined with the short-acting CCBs, but the authors also reported a non-significant increased risk for cardiovascular events (deaths and hospitalizations) among users of the intermediate-acting agents when analyzed separately.

Further analyses of data from both of the above investigations have illustrated that the increased adverse events observed for CCB users appear to be restricted to hypertensive patients with impaired glucose metabolism[45] or non-insulin dependent diabetes.[46] Similar findings have also been reported for such patients exposed to long-acting dihydropyridine CCBs.[47–49] However, the relevance of such findings are unclear and subject to debate, particularly since a recent analysis of data from the Syst-Eur trial failed to illustrate any increased adverse health risks among older hypertensive patients with diabetes receiving active treatment with a long-acting dihydropyridine CCB.[50] An interaction term between CCB use and history of diabetes was examined in the present analyses, but was not found to be significant. This may reflect the relatively non-specific nature of our indicator (history of diabetes) or the fact that few subjects using nifedipine reported a history of this condition at baseline (see Table 2).

To date, the relevance of duration of CCB use to risk of adverse outcomes among older persons has been relatively unexplored in the literature. In the present analyses, subjects reporting a relatively short duration of nifedipine use at baseline ($\leqslant 6$ months) exhibited almost a fourfold increase in mortality risk during follow-up after adjusting for several potential confounding factors. This significantly greater risk among recent nifedipine users may reflect a number of factors. One explanation is that recent users may represent those exposed to inappropriately high initial nifedipine doses. However, our analyses indicated that nifedipine dose increased with duration of use. This may explain the non-significant increased risk of mortality observed among subjects reporting a relatively longer duration of use (>12 months) at baseline. Although duration of use may also reflect exposure to a particular type of CCB, nifedipine formulation and duration of use were not related in the present sample.

It has also been noted that there may be a greater risk for bias due to confounding by indication for subjects recently starting drug therapies.[9] In their preliminary analyses, Psaty *et al*.[9] found that recent starting of CCBs and β-blockers (<30 days) was strongly associated with risk of MI. Consequently, they argued that recent use is likely to represent a marker for suspected coronary disease (i.e. angina). However, as illustrated in Table 2, a relatively large percentage (78%) of nifedipine users, including short-duration users (73%) (data not shown), reported a history of hypertension at baseline. Also, nifedipine users did not significantly differ from β-blocker users with respect to baseline rates of chronic conditions or cardiovascular symptoms. Further, short-term nifedipine users appeared to be relatively *less* ill than other nifedipine users (e.g. no short-term users had a history of diabetes, one had intermittent claudication, two had a history of stroke, one reported digoxin use and two reported nitrate use). However, relative to other nifedipine users, short-term users were more likely to be women (10/11) and were relatively older (mean age = 80.6 years). An alternative explanation is that the increased risk among recent users may reflect a particularly vulnerable subgroup with a greater likelihood for experiencing adverse effects related to nifedipine use.

Subjects with relatively low (but not high) diastolic blood pressures at baseline were found to have a significantly increased risk for mortality. Concern regarding the potential adverse cardiovascular effects associated with an extreme reduction in blood pressure among hypertensive patients (J-curve relation) has been raised by several authors[42,51,52] and this question was recently investigated by the Hypertension Optimal Treatment (HOT) trial.[53] The findings of the HOT trial suggest that substantial reductions in diastolic blood pressure (and cardiovascular events) may be achieved with a treatment regimen based on a long-acting dihydropyridine CCB (felodipine). However, the data from this trial did not definitively exclude the possibility of a J-curve association since there was evidence of an increased (non-significant) risk for cardiovascular deaths and total mortality at the lowest diastolic blood pressures. Many have argued that this increased risk is likely the result of poor health or underlying coronary disease that also results in relatively lower diastolic blood pressure.[53] In a recent study by Boshuizen *et al*.,[54] a significant inverse association was also observed between blood pressure and all-cause mortality. However, contrary to our findings, this association did not remain significant after adjustment for selected indicators of poor health.

Others have shown that increased pulse pressure (due to an increase in systolic blood pressure or a decrease in diastolic blood pressure, or both) related to arterial stiffening may act as an independent risk factor for cardiovascular and all-cause mortality.[55–57] In the present analyses, we did not find a significant association between pulse pressure and mortality (data not shown). However, among the subgroup of patients with a history of arterial hypertension, a relatively high pulse pressure (top 20% of distribution, >88 mm Hg) did show a borderline significant association with all-cause mortality (HR = 1.37, 95% CI 0.98–1.91). Our failure to observe a significant positive association between pulse pressure and mortality may be due to the length of our follow-up since a previous study demonstrated a significant association for pulse pressure only after 10 years of follow-up.[56]

Non-steroidal anti-inflammatory drug (NSAIDS) and aspirin use were examined as potential confounding and/or effect modifying factors since these medications are commonly prescribed for elderly patients and may antagonize the blood pressure lowering effects of antihypertensive drugs.[58–60] We did observe relatively higher diastolic and systolic blood pressures among nifedipine users also exposed to NSAIDS, but not aspirin (data not shown). However, the

inclusion of NSAIDS in the full model did not alter the findings observed for nifedipine. Further, when stratified by NSAID use, a significantly increased mortality risk was only observed for nifedipine users not concurrently exposed to a NSAID, although the number of subjects using nifedipine and a NSAID was relatively small ($n = 16$).

A particular strength of this investigation is that it is based on data from a 5-year prospective study involving a large sample of older Canadians in community and institutional settings. This allows for the establishment of a temporal relationship between drug use and mortality and provides some support for the generalizability of the findings. However, the sampling strategy, age, and baseline 3MS scores of subjects in this investigation (Table 1) indicate that our sample represented a more vulnerable and less healthy group compared with samples examined in previous research. The timing of the CSHA assessments (1991 and 1996) prevented us from examining potential changes in antihypertensive/diuretic drug use over the follow-up. However, our preliminary analyses of subjects alive and assessed in both cycles indicate that most subjects (78%) taking a particular CCB at baseline also reported such use at follow-up.

Although our findings may illustrate a true increased mortality risk for older, frail persons exposed to short- or prolonged-acting nifedipine, an important limitation is the potential for confounding by indication. We attempted to control for possible comorbid differences between users of nifedipine and other agents with multivariate adjustment and by selecting β-blocker users as the reference group. As noted above, nifedipine users did not significantly differ from β-blocker users with respect to baseline rates of demographic and health characteristics or cardiovascular symptoms. However, the possibility remains that nifedipine may have been preferentially prescribed for more severely ill patients or that its use may represent a proxy for some unmeasured variable predisposing to an increased mortality risk. The potential for channelling bias,[61] where drugs with similar therapeutic indications may be selectively prescribed to patient groups that differ in terms of their pre-existing morbidity and/or prognosis, must be considered in the interpretation of our findings. The availability of only a general measure of cardiac symptoms at baseline also represents an important limitation of the study. The significant reduction in the risk estimate observed for loop diuretic users (a potentially 'sicker' subgroup with poorer prognosis) in the multivariate model suggests, however, that we did include a number of relevant confounding factors.

There has been considerable debate about whether the evidence supporting the potential adverse effects of the dihydropyridine CCBs among hypertensive patients warrants changes to prescribing patterns in relation to the use of the various antihypertensive agents.[6,62–64] Our findings indicate that the dihydropyridine CCBs such as nifedipine may pose a particular risk for certain vulnerable subgroups of elderly hypertensives (i.e. older, frail patients and recent users). However, the definitive risk/benefit analysis awaits findings from ongoing large long-term trials (e.g. ALLHAT)[65] that are comparing the various antihypertensive agents (including long-acting CCBs) in terms of clinically important outcomes such as myocardial infarction, heart failure and stroke.

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