Dihydropyridine calcium channel blockers and cardiovascular outcomes in elderly patients: A population-based study

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BACKGROUND: Dihydropyridine calcium channel blockers are widely used for the treatment of hypertension and angina. Despite safety concerns associated with short-acting agents, increasing evidence supports the safety of long-acting dihydropyridines. Although amlodipine is the best studied of these, there are few studies comparing it with nifedipine.

OBJECTIVE: To examine the association between hospitalization for acute coronary syndromes and treatment with amlodipine or extended-release nifedipine in patients 65 years of age and older. The primary objective was a composite of hospital admission for angina or acute myocardial infarction.

METHODS: The present population-based, retrospective cohort study used linked health care databases from Ontario. Propensity scores were used to identify highly similar patients started on amlodipine or extended-release nifedipine between April 1997 and March 2002. Time-to-event analysis was conducted using Cox proportional hazards models.

RESULTS: The analysis included 24,190 patients (44% male; mean age 75 years) treated with amlodipine or extended-release nifedipine (n=12,095 each). The number of patients reaching the primary end point was 362 (3%) and 294 (2.4%) in the amlodipine and nifedipine groups, respectively. The groups were similar in a large number of demographic and clinical characteristics. No significant differences were observed among users of extended-release nifedipine (adjusted hazard ratio 0.91, 95% CI 0.74 to 1.13) relative to amlodipine.

CONCLUSIONS: These findings suggest that amlodipine and extended-release nifedipine are not associated with differential rates of acute coronary events in older patients.

Key Words: *Acute coronary syndrome; Acute myocardial infarction; Angina; Dihydropyridine calcium channel blockers*

Les inhibiteurs calciques dihydropyridines et les issues cardiovasculaires chez les patients âgés : Une étude en population générale

HISTORIQUE : Les inhibiteurs calciques dihydropyridines sont largement utilisés dans le traitement de l'hypertension et de l'angine. Malgré les inquiétudes relatives à leur innocuité en association avec des agents à action rapide, de plus en plus de données probantes étayent l'innocuité des dihydropyridines à action prolongée. Bien que l'amlodipine soit l'agent le plus étudié, quelques études la comparent à la nifédipine.

OBJECTIF : Examiner l'association entre l'hospitalisation par suite d'un syndrome coronarien aigu et un traitement à l'amlodipine ou à la nifédipine à action prolongée chez des patients de 65 ans et plus. L'objectif primaire était un composite d'hospitalisation en raison d'une angine ou d'un infarctus aigu du myocarde.

MÉTHODOLOGIE : La présente étude rétrospective de cohortes en population générale a fait appel à des bases de données en santé reliées provenant de l'Ontario. Les indices de propension ont permis de repérer les patients hautement similaires qui avaient commencé un traitement à l'amlodipine ou à la nifédipine à action prolongée entre avril 1997 et mars 2002. Des modèles de régression des hasards proportionnels de Cox ont servi à l'analyse du délai jusqu'à l'événement.

RÉSULTATS : L'analyse incluait 24 190 patients (44 % d'hommes, âge moyen de 75 ans) traités à l'amlodipine ou à la nifédipine à action prolongée (n=12 095 chacun). Trois cent soixante-deux patients (3 %) prenant de l'amlodipine et 294 (2,4 %) prenant de la nifédipine ont atteint le paramètre ultime primaire. Les deux groupes partageaient un grand nombre de caractéristiques démographiques et cliniques. Les auteurs n'ont observé aucune différence significative entre les utilisateurs de nifédipine à action prolongée (ratio de risque rajusté de 0,91, 95 % IC 0,74 à 1,13) par rapport aux utilisateurs d'amlodipine.

CONCLUSIONS : D'après ces observations, l'amlodipine et la nifédipine à action prolongée ne s'associent pas à des taux différentiels d'événements coronariens aigus chez les patients âgés.

Calcium channel blockers (CCBs) are widely used for the management of hypertension and angina. Prescription drug sales of CCBs in the United States accounted for US\$11.6 billion in 2004, ranking them as the eighth largest drug class in prescription sales (1). Amlodipine is the most frequently prescribed CCB among the most commonly used prescription drugs in adults in the United States (2).

Among the various subclasses of CCBs, the long-acting dihydropyridines, including amlodipine, felodipine and extended-release formulations of nifedipine, are recommended for the treatment of hypertension in patients with stable angina pectoris (3,4). CCBs are also indicated as adjuncts in the management of refractory hypertension or refractory ischemia in heart failure patients for whom beta-blockers and nitrates are ineffective. In this scenario with left ventricular dysfunction, amlodipine is the preferred agent (5,6).

While dihydropyridine CCBs share a similar mechanism of action, the clinical activity of short- versus long-acting formulations varies. Indeed, some studies suggest that short-acting preparations, such as short-acting nifedipine, have more adverse effects (7,8). However, increasing evidence supports the safety of long-acting CCB formulations (9-15).

Although a class effect is often assumed, there are few comparative trials of the efficacy of different long-acting dihydropyridine CCBs, and it remains unclear whether the drugs are associated with differential rates of coronary events (16-20). The available agents differ in cost, with amlodipine being the most expensive agent (Ontario Drug Benefit program price per month, not including dispensing fee, is \$46.34 for amlodipine [5 mg] and \$33.76 for nifedipine extended-release [30 mg]) (21,22). We explored the association between the use of either amlodipine or extended-release nifedipine, and hospital

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TABLE 1
Baseline patient characteristics

	Study cohort	
	Amlodipine	Nifedipine
Number of patients (number of women, % women)	12,095 (6804, 56)	12,095 (6804, 56)
Age, years (mean $\pm$ SD)	75 $\pm$ 6	75 $\pm$ 6
Low income status, n (%)	2598 (22)	2702 (22)
Admission in past year, n (%)	6049 (50)	5997 (50)
Number of prescription drugs in previous year (mean $\pm$ SD)	12 $\pm$ 6	13 $\pm$ 6
Hospital admission and procedures in previous 5 years, n (%)		
Acute myocardial infarction	7573 (63)	7570 (63)
Ischemic heart disease	7538 (62)	7577 (63)
Cerebrovascular accident	1712 (14)	1827 (15)
Peripheral vascular disease	6792 (56)	6792 (56)
Congestive heart failure	2162 (18)	2255 (19)
Angiography	1458 (12)	1482 (12)
Angioplasty	233 (2)	192 (2)
Coronary artery bypass graft	694 (6)	714 (6)
Renal disease	112 (<1)	104 (<1)
Malignant disease	929 (8)	1031 (9)
Drug use 1 year before index date, n (%)		
ACEIs and ARBs	3353 (28)	3360 (28)
Acetylsalicylic acid	4568 (38)	4643 (38)
Anticoagulants	1164 (10)	1258 (10)
Antihyperglycemics	2138 (18)	2204 (18)
Beta-blockers	6023 (50)	6031 (50)
CCBs (non-DHP)	2109 (17)	2190 (18)
Digoxin	1454 (12)	1538 (13)
Diuretics		
Loop diuretics	2258 (19)	2362 (20)
Thiazide diuretics	3157 (26)	3239 (27)
Potassium-sparing diuretics	1347 (11)	1368 (11)
Nitrates	6074 (50)	6013 (50)
Statins	4007 (33)	3929 (33)
Other lipid-lowering drugs	416 (3)	437 (4)
Other antihypertensive drugs	771 (6)	809 (7)

ACEIs Angiotensin-converting enzyme inhibitors; ARBs Angiotensin receptor blockers; CCBs Calcium channel blockers; DHP Dihydropyridine

admission for acute coronary syndrome events (angina pectoris, unstable angina and acute myocardial infarction [AMI]) in older patients.

METHODS

Design

A population-based retrospective cohort study was conducted by linking the administrative health care databases of more than 1.4 million Ontario residents 65 years of age and older from April 1, 1997, to March 31, 2002. These patients have universal access to prescription drug coverage, hospital care and physician services. The present study was approved by the ethics review board of Sunnybrook Health Sciences Centre, Toronto.

Data sources

The administrative health care databases in Ontario allow for cohort identification, comorbidity assessment and end point ascertainment. The Ontario Drug Benefit program database records prescription drugs dispensed to all Ontario residents 65 years of age and older. An overall error rate of less than 1% in this drug database has been reported (23). Patients were not studied during their first year of eligibility for prescription drug benefits (age 65 years) to avoid incomplete medication records.

Hospitalization data were obtained from the Canadian Institute for Health Information discharge abstract database, which contains a detailed record of all admissions. The Ontario Health Insurance Plan provides physician claims data for inpatient and outpatient services, and the Ontario Registered Persons Database contains basic demographic and vital statistics information for every Ontario resident. The databases were linked anonymously using encrypted individual health card numbers.

Cohort identification

A cohort of patients 66 years of age and older who had at least one prescription for amlodipine during the study period and a second cohort of closely matched patients prescribed extended-release nifedipine were identified. To identify an inception cohort, individuals who received any dihydropyridine CCB in the year preceding the initial prescription were excluded. To identify patients with a history of coronary artery disease, the analysis was restricted to subjects with a previous hospital admission for AMI (*International Classification of Diseases*, ninth revision [ICD-9] code 410), ischemic heart disease (IHD) (ICD-9 code 411 or 413), a physician's diagnosis of angina or a prescription for nitrates (isosorbide dinitrate, mononitrate, nitroglycerine) in the year before the index date, defined as the date of first prescription of either amlodipine or extended-release nifedipine. Follow-up was limited to a maximum of two years for all patients.

For both drug cohorts, the duration of exposure was defined as the period of continuous, exclusive enrolment in the study medication group after the index date. The mandatory 'day supply' variable of the pharmacy database allowed for estimation of the intended duration of every prescription. If patients were dispensed a drug before the end of this period, the excess drug supply was carried over to the next prescription's day supply estimation. Individuals were allowed a 50% grace period on the previous day's supply to refill the next prescription. If they did not refill their prescription for the study drug during these successive time windows, they were considered to have discontinued the drug. Patients exposed to a medication from another study drug cohort were censored at that time.

Propensity score

Propensity-based matching was used to maximize the comparability of the two study groups. Propensity score methods were used to select amlodipine users who most closely resembled the smaller number of extended-release nifedipine users (24). A structured, iterative process similar to that described by Rosenbaum and Rubin (25) was used to construct a propensity score using multivariable logistic regression for each individual that predicted the receipt of extended-release nifedipine, as opposed to amlodipine, by balancing all characteristics shown in Table 1. The iterative algorithm included main effects only, without interaction terms. Propensity scores were calculated for all possible amlodipine matches for each extended-release nifedipine user at every index date. Once the final propensity score model was developed and scores were calculated for all potential amlodipine patients using matches, all eligible amlodipine users were identified using matches for each extended-release nifedipine user (using calipers of 0.2 SD of the propensity score). The number of possible amlodipine users who could serve as matches to each of the respective extended-release nifedipine users was further restricted by age (within one year), sex, number of distinct drugs as a marker of comorbidity, and the year and quarter of the index date. From these, one amlodipine user was randomly selected for each extended-release nifedipine user. Extended-release nifedipine users whose propensity scores were too high to permit matching to a comparable control subject were excluded from all matched analyses. Because propensity score matching was used as a design strategy and the patients were well matched, individual propensity scores were not included in the final model. The analysis was rerun, with the individual propensity score included, and the results did not change.

Primary outcome

The primary outcome was a composite of hospital admission with a primary diagnosis of an acute coronary syndrome, defined as a most responsible diagnosis of IHD (ICD-9 code 411), unstable angina (ICD-9 code 413) or myocardial infarction (ICD-9 code 410). A recent study (26) evaluating coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario found that coding for such admissions in our databases showed a sensitivity and specificity of 88.8% and 92.8%, respectively, for myocardial infarction. The sensitivity and specificity for unstable angina and chest pain not yet diagnosed were much lower. Similar findings have been reported in other studies, which found high predictive values for a most responsible diagnosis of myocardial infarction in Ontario and Montreal (Quebec) hospitals (27,28). Another study (29) examining coding for stroke risk factors found that coding for coronary artery disease or IHD had a high sensitivity and specificity of 98% and 95%, respectively.

Statistical analysis

Time-to-event analysis for the primary outcome of admission for IHD or myocardial infarction was performed with Cox proportional hazards modelling to adjust for covariates outlined in Table 1. The study also controlled for the number of prescription drugs dispensed in the year before the index date, a validated index of comorbidity (30). Patients were censored at the time of switching or stopping the initial dihydropyridine CCB prescription.

All analyses were completed with SAS for UNIX, version 8.2 (SAS Institute, USA). All statistical tests were two-sided and used $P=0.05$ as the threshold for statistical significance.

RESULTS

Of approximately 1.4 million potential patients 66 years of age and older, 68,312 individuals who commenced amlodipine and 14,545 individuals who commenced extended-release nifedipine met the inclusion criteria during the study period. Using propensity score-based matching, 12,095 nifedipine patients (83%) were closely matched to patients initiated on amlodipine. A total of 24,190 patients were dispensed amlodipine or extended-release nifedipine during the study period. The two groups were highly similar in terms of a large number of demographic and clinical characteristics (Table 1). All variables in Table 1 were included in the propensity score model, as well as age, sex, a number of distinct drugs, and the year and quarter of the index date.

Patients were followed up for a total of 319 and 291 days (10,549 and 9639 patient-years) for the amlodipine and nifedipine groups, respectively. No significant differences in the composite end point of admission for angina or AMI were found among users of amlodipine or nifedipine (adjusted hazard ratio 0.91, 95% CI 0.74 to 1.13). The number of patients reaching the primary end point was 362 (3.0%) and 294 (2.4%) in the amlodipine and nifedipine groups, respectively (Table 2). The admission rate per 100 person-years was 3.4 in the amlodipine group and 3.1 in the nifedipine group. All covariates outlined in Table 1 were controlled for in the final Cox model, as well as the year and quarter of the index date to account for temporal effects. It was confirmed that the proportional hazards assumption was valid for the variables included in the model.

DISCUSSION

We found no significant difference in the incidence of acute coronary syndromes among users of nifedipine relative to amlodipine. Regardless of the varying pharmacological properties of these agents, our results suggest that extended-release nifedipine has a similar efficacy profile to amlodipine in patients with a history of IHD. Despite the lack of comparative data to support one agent over another, preferential prescribing occurs in practice, as demonstrated by the large number of patients on amlodipine who met our inclusion criteria

TABLE 2
Study outcomes

	Amlodipine	Nifedipine
Sample size, n	12,095	12,095
Number of patients with an admission, n (%)	362 (3)	294 (2)
Follow-up time, days (mean $\pm$ SD)	319 $\pm$ 262	291 $\pm$ 257
Total follow-up, person-years	10,549	9639
Admission rate per 100 person-years, n	3.4	3.1
Unadjusted hazard ratio (95% CI)	1.0	0.9 (0.9–1.1)
Adjusted hazard ratio (95% CI)	1.0	0.9 (0.7–1.1)

**The unadjusted and adjusted hazard ratios in the amlodipine group were used as a reference*

compared with a much lower number for nifedipine. This may be reflective of the clinical trials that have studied amlodipine (6,14).

There is increasing evidence of the safety and efficacy of long-acting CCBs. Definitive evidence that the long-acting dihydropyridine CCBs are not associated with an increase in cardiovascular events was most recently provided by the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) (14). Prescribing of CCBs will continue to be high because this class is recommended among other first-line agents for the treatment of hypertension and ischemia. Careful consideration must be given to cost, because substantial cost savings can be made by prescribing the cheaper agent in this class of frequently prescribed agents.

Our study has several limitations that merit emphasis. We did not examine felodipine because of the rarity of its use during our study period. We had no direct measures of blood pressure, dose or adherence to medications. The lack of clinical data on patients' blood pressure is also a limitation of our study. However, the blood pressure-lowering effects of the agents in the present study are similar. Dose information was not collected; therefore, it is possible that the effects may be confounded by dose.

The present study was the first to examine the association between the use of either amlodipine or extended-release nifedipine and hospital admission for acute coronary syndromes. These comparative data are needed to aid in making clinically sound and cost-effective prescribing decisions.

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