JAMA Internal Medicine | Original Investigation | LESS IS MORE

Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension

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IMPORTANCE Calcium channel blockers (CCBs) are commonly prescribed agents for hypertension that can cause peripheral edema. A prescribing cascade occurs when the edema is misinterpreted as a new medical condition and a diuretic is subsequently prescribed to treat the edema. The extent to which this prescribing cascade occurs at a population level is not well understood.

OBJECTIVE To measure the association between being newly dispensed a CCB and subsequent dispensing of a loop diuretic in older adults with hypertension.

DESIGN, SETTING, AND PARTICIPANTS A population-based cohort study was performed using linked health administrative databases of community-dwelling adults 66 years or older with hypertension and new prescription drug claims from September 30, 2011, to September 30, 2016, in Ontario, Canada. The dates of analysis were September 1, 2018, to May 30, 2019.

EXPOSURES Individuals who were newly dispensed a CCB were compared with the following 2 groups: (1) individuals who were newly dispensed an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and (2) individuals who were newly dispensed an unrelated medication.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) with 95% CIs were estimated for individuals who were dispensed a loop diuretic within 90 days of follow-up using Cox proportional hazards regression models.

RESULTS The cohort included 41 086 older adults (≥66 years) with hypertension who were newly dispensed a CCB, 66 494 individuals who were newly dispensed another antihypertensive medication, and 231 439 individuals who were newly dispensed an unrelated medication. At index (ie, the dispensing date), the mean (SD) age was 74.5 (6.9) years, and 191 685 (56.5%) were women. Individuals who were newly dispensed a CCB had a higher cumulative incidence at 90 days of being dispensed a loop diuretic than individuals in both control groups (1.4% vs 0.7% and 0.5%, $P < .001$). After adjustment, individuals who were newly dispensed a CCB had increased relative rates of being dispensed a loop diuretic compared with individuals who were newly dispensed an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (HR, 1.68; 95% CI, 1.38-2.05 in the first 30 days after index [days 1-30]; 2.26; 95% CI, 1.76-2.92 in the subsequent 30 days [days 31-60]; and 2.40; 95% CI, 1.84-3.13 in the third month of follow-up [days 61-90]) and individuals who were newly dispensed unrelated medications (HR, 2.51; 95% CI, 2.13-2.96 for 1-30 days after index; 2.99; 95% CI, 2.43-3.69 for 31-60 days after index; and 3.89; 95% CI, 3.11-4.87 for 61-90 days after index). This association persisted, although slightly attenuated, from 90 days to up to 1 year of follow-up and when restricted to a subgroup of individuals who were newly dispensed amlodipine.

CONCLUSIONS AND RELEVANCE Many older adults with hypertension who are newly dispensed a CCB subsequently receive a loop diuretic. Given how widely CCBs are prescribed, interventions are needed to raise clinicians' awareness of this common prescribing cascade to reduce the prescribing of potentially unnecessary medications that may cause harm.

JAMA Intern Med. doi:10.1001/jamainternmed.2019.7087
Published online February 24, 2020.

Invited Commentary
Supplemental content

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Calcium channel blockers (CCBs) are first-line agents for hypertension management[1,2] and rank among the 10 most commonly used prescription medications in North America.[3,4] Clinicians may preferentially prescribe CCBs, particularly in older adults, because of their favorable adverse event profile and the limited need for routine laboratory monitoring.[5] However, CCBs commonly cause peripheral edema, with an incidence ranging from 2% to 25% depending on the CCB type, dosage, and duration of therapy.[5-7] Amlodipine poses the greatest concern because it is the most widely used CCB and is more likely to lead to peripheral edema than nondihydropyridine (DHP) CCBs and newer lipophilic DHP CCBs.[5] Peripheral edema can be distressing to patients and can alter their quality of life, prompting individuals to seek medical attention or discontinue therapy.[5]

The presentation of peripheral edema may lead a prescriber to manage the symptom with a diuretic,[8] with preferential prescription of loop diuretics because they promote greater fluid loss than other diuretic classes.[9] However, CCB-induced edema is not caused by fluid overload, and treating euvolemic individuals with a diuretic places them at increased risk of overdiuresis, leading to falls, urinary incontinence, acute kidney injury, electrolyte imbalances, and a cascade of other downstream consequences to which older adults are especially vulnerable.[6,10-12] This risk, particularly for falls and related injuries, is greatest immediately after receipt of a new diuretic prescription.[11] In addition to these harms, prescribing an additional and potentially unnecessary medication has costs for individuals and health systems.

Adverse drug events (ADEs) (eg, CCB-induced edema) that are misinterpreted as new medical conditions and can be associated with subsequent prescription of a potentially unnecessary drug therapy have been described as prescribing cascades.[13-15] The prescribing cascade concept has gained international recognition as an important contributor to the global challenge of problematic polypharmacy.[16] Characterizing prescribing cascades and their prevalence is important to reduce potentially inappropriate drug prescribing, adverse events, avoidable downstream medical conditions, and unnecessary costs.[13-15] Recognizing prescribing cascades is also a key component of the deprescribing process.[17] Although a 2016 case report[18] and a recent cross-sectional observational study[19] provide evidence of the CCB-diuretic prescribing cascade, these studies lack comparator groups, prospective follow-up, and data on the time to event. Therefore, the clinical importance and consequences of this prescribing cascade at a population level are unknown. In this study, we compared the rate at which a population-based cohort of older adults with hypertension and newly dispensed a CCB were subsequently dispensed a loop diuretic with 2 comparison groups who were newly dispensed other medications.

Key Points

Question Are older adults who begin taking a calcium channel blocker more likely to be subsequently prescribed a diuretic, leading to a prescribing cascade, than those who began taking other medications?

Findings In a population-based cohort study of 41 086 older adults with hypertension, being newly dispensed a calcium channel blocker was associated with a statistically significantly higher rate of being subsequently dispensed a loop diuretic within 90 days compared with 2 groups (n = 66 494 and n = 231 439) who began taking other medications.

Meaning Many older adults who begin taking a calcium channel blocker may subsequently experience a prescribing cascade; steps can be taken to avoid prescribing unnecessary medications that can cause harm and are costly.

Methods

Study Design and Setting

We conducted a population-based, retrospective cohort study using health administrative data collected as part of the publicly funded universal health insurance program in Ontario, Canada. Ontario is Canada's most populous province, with an estimated 2.3 million older adults (≥65 years).[20] Data sources on physician services, ambulatory and hospital care, and prescription medications for adults 66 years or older in Ontario, Canada, are listed in eTable 1 in the Supplement. These data sets were linked using unique encoded identifiers and analyzed at ICES, Toronto, Ontario, Canada. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Cohort Creation

First, we identified residents of Ontario, Canada, with prevalent hypertension[21] as of September 30, 2016, using a validated algorithm (eTable 2 in the Supplement). The study flowchart is shown in the eFigure in the Supplement. This algorithm was applied to health records dating back as early as 1988. Next, we identified the exposed and comparison groups by searching for new prescription drug claims within the Ontario Drug Benefit (ODB) claims database between September 30, 2011, and September 30, 2016 (the accrual period). The dates of analysis were September 1, 2018, to May 30, 2019. Individuals whose relevant drug claim date preceded their hypertension diagnosis date were excluded. Once the groups based on prescription drug use were defined, a set of exclusion criteria were applied. Individuals were excluded if they (1) had died as of their index date (ie, the dispensing date), (2) were 65 years or younger or 110 years or older, (3) were not a resident of Ontario in the 2 years prior, (4) were ineligible for publicly funded health insurance at any point in the preceding year, and (5) did not have at least 1 ODB claim within the 2 preceding years to ensure they were using the ODB. Individuals were also excluded if they (6) had a diagnosis of heart failure or end-stage renal disease in the prior year (defined in eTable 2 in the Supplement) because these conditions are associated with peripheral edema; (7) had been hospitalized within 1 month preceding their index date because we are unable to track medication

use during hospitalization stays; (8) were long-term care residents in the prior 6 months to restrict the cohort to community-dwelling older adults; and (9) were dispensed an antihypertensive medication or a diuretic in the prior 12 months to improve the likelihood that diuretic dispensing during the follow-up period was related to the exposure.

CCB Exposure

Individuals were classified as exposed if they had a new prescription claim for any of the CCBs available in the provincial drug formulary (ie, amlodipine, felodipine, nifedipine, diltiazem hydrochloride, and verapamil hydrochloride) within the ODB claims database during the 5-year accrual period (September 30, 2011-September 30, 2016) (eTable 2 in the Supplement). The first date of the first prescription claim (the dispensing date) was used as the index date. New use was defined by the absence of a CCB claim in the prior year.

Comparison Groups

Individuals with hypertension and no claims for a CCB during the accrual period or in the year before their index date were eligible as comparators. Two comparison groups were identified: one that comprised new users of other antihypertensive medications and a second that acted as a more general comparator. Individuals in the other antihypertensive medication comparison group were newly dispensed an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) during the accrual period, with no ACEI or ARB claims in the year before their index date (ie, first dispensing date of ACEI or ARB during the accrual period) (eTable 2 in the Supplement). The general comparison group had at least 1 unrelated (ie, non-CCB) new drug claim during the accrual period. If there were multiple claims, 1 drug subclass was randomly selected, and a 1-year look-back period was used to ensure there were no claims for the same drug subclass. An index date was assigned based on the selected claim's dispensing date.

Observation Period and Outcome Measurement

Individuals were observed for 90 days after their index date for evidence of the development of a prescribing cascade. The primary outcome was being dispensed a loop diuretic (ie, furosemide) (eTable 2 in the Supplement). Loop diuretics were selected as the primary outcome because they are more likely than other diuretics to be used to treat edema and are not generally recommended for management of hypertension, unlike thiazide or thiazide-like diuretics.[1,2] Individuals were followed up until they were dispensed a loop diuretic, discontinued CCB treatment (the time to next prescription exceeding 1.5 times the total days supplied of the current medication prescription[22]), were hospitalized, died, or until the end of the observation period. Because other diuretics may also be used to treat edema, we considered any diuretic use as a secondary outcome (ie, amiloride, chlorthalidone, eplerenone, hydrochlorothiazide, indapamide, spironolactone, or triamterene, in addition to furosemide) (eTable 2 in the Supplement). As an a priori sensitivity analysis, the observation period was extended to 12 months to account for delays in health care–seeking behavior and/or delayed onset of edema.[5] Post hoc, a sensitivity analysis was conducted in which other antihypertensive medication comparators were censored if individuals discontinued ACEI or ARB treatment to address the potential for differential follow-up in exposed and comparator groups because of discontinuation of treatment.

Covariates

Baseline characteristics included sociodemographic variables (eg, age, sex, and income), medical history (eg, duration of hypertension and comorbidities), health system use (eg, hospitalizations and emergency department visits), and concurrent drug therapies (**Table 1** and eTable 2 in the Supplement). The covariates were selected because they have been shown to be associated with the development of edema or diuretic use.[5,23-25]

Statistical Analysis

Descriptive statistics were used to evaluate the sociodemographic and clinical characteristics of cohort members at their index date. Standardized differences exceeding 0.10 (or 10%) were used to identify differences in baseline covariates between the exposed and comparison groups.[26]

Unadjusted cumulative incidence functions between the exposed and comparison groups were compared using the Gray test (2-sided). Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs for receipt of a loop diuretic, adjusting for a set of covariates assessed a priori, including age, sex, number of comorbidities (to account for variations in risk), and 6-month categories of the index date (to account for changes in drug trends or patient care over the study period). This analysis was repeated for the secondary outcome of any diuretic use. To be consistent with the definition of a prescribing cascade, we excluded individuals from our analysis who were dispensed a loop diuretic on their index date (for the primary outcome) (ie, 316 individuals [0.8%] who were newly dispensed a CCB, 760 individuals [1.1%] in the other antihypertensive medication comparator group, and 1872 individuals in the general comparator group [0.8%]) or who were dispensed any diuretic on their index date (for the secondary outcome) (ie, 1638 [4.0%] in the loop diuretic group, 4673 [7.0%] in the other antihypertensive group, and 5761 [2.5%] in the general comparator group).

We found that the association of new exposure to a CCB with the hazard of receiving a loop diuretic was time dependent using Shoenfeld residual plots. Therefore, we estimated HRs within 3 strata of follow-up time for the main analysis (1-30, 31-60, and 61-90 days) and in 2 strata of 91 to 180 days and 181 to 365 days for the extended observation period. Statistical tests were 2 sided, with $P < .05$ interpreted as statistically significant.

Subgroup Analyses

All subgroup analyses were defined a priori. We stratified analyses by sex given that women have been reported to be more likely than men to experience CCB-related edema.[27] Because amlodipine is more likely to result in edema than other CCB

Table 1. Characteristics of Study Population of Older Adults With Hypertension

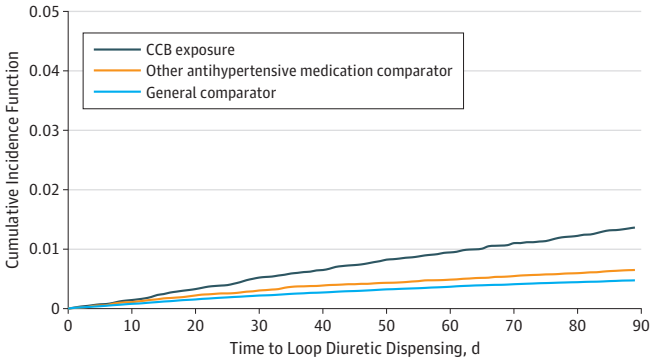
Characteristic	Exposure to Newly Dispensed CCB, No. (%) (n = 41 086)	Other Antihypertensive Medication Comparator, No. (%) (n = 66 494)	Standardized Difference[a]	General Comparator, No. (%) (n = 231 439)	Standardized Difference[a]
Sociodemographics					
Age, mean (SD), y	74.8 (7.0)	74.0 (6.6)	0.1192	74.6 (7.0)	0.0281
Female sex	24 384 (59.3)	35 773 (53.8)	0.1121	131 528 (56.8)	0.0511
Low-income older adult	6632 (16.1)	8874 (13.3)	0.0789	27 350 (11.8)	0.1249
Neighborhood income quintile					
1, Lowest	7790 (19.0)	11 766 (17.7)	0.0327	38 490 (16.6)	0.0609
2	8605 (20.9)	13 525 (20.3)	0.0149	45 726 (19.8)	0.0295
3	8288 (20.2)	13 181 (19.8)	0.0087	45 648 (19.7)	0.0112
4	8309 (20.2)	13 943 (21.0)	0.0184	49 964 (21.6)	0.0336
5, Highest	7974 (19.4)	13 867 (20.9)	0.0361	50 940 (22.0)	0.0642
Missing data	120 (0.3)	212 (0.3)	0.0048	671 (0.3)	0.0004
Rural residence	4139 (10.1)	7810 (11.7)	0.0536	28 629 (12.4)	0.0728
Medical History 1 y Before Index Date					
Duration of hypertension at index, mean (SD), y	10.9 (7.1)	9.5 (7.0)	0.1926	10.2 (6.7)	0.1043
Chronic disease burden, mean (SD), No.	3.2 (1.5)	3.1 (1.4)	0.0218	3.2 (1.4)	0.0132
1	4494 (10.9)	6576 (9.9)	0.0343	22 303 (9.6)	0.0428
2	10 536 (25.6)	17 438 (26.2)	0.0133	61 382 (26.5)	0.0200
3	11 210 (27.3)	19 457 (29.3)	0.0439	66 755 (28.8)	0.0347
4	7749 (18.9)	12 615 (19.0)	0.0028	43 958 (19.0)	0.0034
≥5	7097 (17.3)	10 408 (15.7)	0.0437	37 041 (16.0)	0.0341
Comorbid chronic conditions that can cause peripheral edema					
Cancer	6432 (15.7)	10 444 (15.7)	0.0014	41 941 (18.1)	0.0659
Diabetes	10 812 (26.3)	20 179 (30.3)	0.0896	51 431 (22.2)	0.0956
Chronic liver disease	504 (1.2)	827 (1.2)	0.0015	3009 (1.3)	0.0066
Chronic kidney disease	3070 (7.5)	3494 (5.3)	0.0909	10 141 (4.4)	0.1312
Stroke	1494 (3.6)	2298 (3.5)	0.0098	6215 (2.7)	0.0544
Health System Use 1 y Before Index Date					
≥1 Primary care visit	38 902 (94.7)	62 972 (94.7)	0.0008	209 206 (90.4)	0.1638
≥1 Specialist visit[b]	16 005 (39.0)	23 322 (35.1)	0.0804	65 834 (28.4)	0.2237
≥1 Home care service	3618 (8.8)	5147 (7.7)	0.0387	22 782 (9.8)	0.0357
≥1 Hospitalization	4101 (10.0)	5650 (8.5)	0.0513	18 603 (8.0)	0.0679
≥1 Emergency department visit	13 290 (32.3)	19 104 (28.7)	0.0786	61 608 (26.6)	0.1259
Drug Therapies					
Distinct drugs claimed in previous year, mean (SD)	5.5 (4.4)	5.3 (4.1)	0.0440	5.0 (3.9)	0.1326
Concurrent medications, excluding CCB, mean (SD)	3.1 (2.5)	3.8 (2.3)	0.2941	3.7 (2.2)	0.2515
Concurrent antihypertensive medications, mean (SD)	0.1 (0.4)	1.0 (0.2)	2.9846	0.1 (0.3)	0.1614
ACEI	1890 (4.6)	42 192 (63.5)	1.5849	8340 (3.6)	0.0503
ARB	1585 (3.9)	24 320 (36.6)	0.8920	4432 (1.9)	0.1162
β-Blocker	1490 (3.6)	1973 (3.0)	0.0369	3786 (1.6)	0.1246
α1-Adrenergic antagonist	111 (0.3)	82 (0.1)	0.0331	411 (0.2)	0.0196
α2-Adrenergic agonist	17 (0)	7 (0)	0.0192	57 (0)	0.0092
Vasodilator	181 (0.4)	101 (0.2)	0.0531	154 (0.1)	0.0744
Concurrent medication classes known to cause edema					
NSAIDs	3558 (8.7)	5231 (7.9)	0.0288	29 257 (12.6)	0.1293
Corticosteroids	1225 (3.0)	1626 (2.4)	0.0330	11 933 (5.2)	0.1102
Gabapentinoids	859 (2.1)	1484 (2.2)	0.0097	6965 (3.0)	0.0583
Dopamine agonists	177 (0.4)	233 (0.4)	0.0129	1157 (0.5)	0.0102

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Standardized difference relative to the exposed group.

[b] Cardiologist or nephrologist.

Figure. Cumulative Incidence of Being Dispensed a Loop Diuretic Among Older Adults With Hypertension Who Were Newly Dispensed a Calcium Channel Blocker (CCB) Compared With Other Antihypertensive Medication Comparators and General Comparators



No. at risk										
CCB exposure	40 768	40 009	39 015	38 292	28 709	28 176	27 221	26 221	25 671	24 889
Other antihypertensive medication comparator	65 734	65 202	64 700	64 268	63 922	63 588	63 299	63 001	62 711	62 450
General comparator	229 565	226 539	224 451	222 763	221 329	220 034	218 840	217 730	216 719	215 750

By 90 days, individuals newly dispensed a CCB had a higher cumulative incidence of receiving a loop diuretic (1.4%) compared with the other antihypertensive medication comparator group (0.7%) and the general comparator group (0.5%) ($P < .001$).

types, we also stratified analyses by type of CCB (amlodipine or nonamlodipine CCBs). In addition, we examined whether there was a dose-dependent response.[5] We categorized CCB dosage as low or high based on the last dosage prescribed during the follow-up period. Low dosages were considered to be one-half of the maximum daily dose or less (ie, ≤5 mg of amlodipine and felodipine, ≤30 mg of nifedipine, or ≤240 mg of diltiazem hydrochloride extended release or verapamil hydrochloride sustained release) as described in prior studies.[5,28,29] Subgroup analyses were conducted over the 90-day and extended 12-month observation periods.

Results

Study Cohort

The final study cohort included 41 086 older adults with hypertension who were newly dispensed a CCB, 66 494 individuals in the other antihypertensive medication group, and 231 439 individuals in the general comparator group (eFigure in the Supplement). At the index date (ie, the dispensing date), the mean (SD) age was 74.5 (6.9) years, and 191 685 (56.5%) were women. Compared with individuals in the 2 comparison groups, those who were newly dispensed a CCB were more likely to be low-income older adults and to have a longer duration of hypertension at index but were similar with regard to other measured covariates (Table 1 and eTable 3 in the Supplement [stratified by sex]). Users of CCBs were primarily prescribed amlodipine (79.6%), followed by diltiazem (9.6%), nifedipine (9.1%), verapamil (0.9%), and felodipine (0.9%).

Primary Outcome of Being Prescribed a Loop Diuretic Within 90 Days

By 90 days, individuals newly dispensed a CCB had a higher cumulative incidence of receiving a loop diuretic than individuals in the comparison groups (1.4% vs 0.7% [other antihypertensive medication comparators] and 0.5% [general comparators], $P < .001$) (**Figure**). The mean (SD) time to receipt of a loop diuretic was 69 (29) days for individuals who were newly dispensed a CCB, 87 (15) days for those in the other antihypertensive medication comparator group, and 87 (13) days for those in the general comparator group. After adjustment, individuals who were newly dispensed a CCB were dispensed a loop diuretic at higher rates than those in the other antihypertensive medication comparator group over the 3 periods (HR, 1.68; 95% CI, 1.38-2.05 for 1-30 days; 2.26; 95% CI, 1.76-2.92 for 31-60 days; and 2.40; 95% CI, 1.84-3.13 for 61-90 days) (**Table 2**). Being newly dispensed a CCB more than doubled the hazards of receiving a loop diuretic compared with the general comparators at all intervals (HR, 2.51; 95% CI, 2.13-2.96 in the first 30 days after index [days 1-30]; 2.99; 95% CI, 2.43-3.69 in the subsequent 30 days [days 31-60]; and 3.89; 95% CI, 3.11-4.87 in the third month of follow-up [days 61-90]) (Table 2).

Secondary Outcome of Any Diuretic Use Within 90 Days

By 90 days, individuals who were newly dispensed a CCB had a higher cumulative incidence of receiving any diuretic vs those in the comparison groups (4.5% vs 3.4% and 1.0%, $P < .001$); these proportions increased to 9.5% vs 7.3% and 3.0% by 1 year. The mean time to being dispensed any diuretic was similar to the time to loop diuretic dispensing. Individuals who were newly dispensed a CCB subsequently were prescribed any diuretic at higher rates than individuals in both of the comparison groups (eTable 4 in the Supplement).

Sensitivity Analyses

By 1 year of follow-up, 3.5% of individuals newly exposed to a CCB were dispensed a loop diuretic compared with 1.8% of those in the other antihypertensive medication comparator group and 1.4% of those in the general comparator group. Individuals who were newly dispensed a CCB had a higher rate of being dispensed a loop diuretic and any diuretic vs those in both comparison groups across all intervals when follow-up was extended to 12 months (Table 2 and eTable 4 in the Supple-

Table 2. Associations Between Being Dispensed a Calcium Channel Blocker (CCB) and Being Dispensed a Loop Diuretic in a Cohort of Older Adults With Hypertension

Comparison Group	HR (95% CI)				
	1-30 d	31-60 d	61-90 d	91-180 d	181-365 d
CCB exposure vs other antihypertensive medication comparator					
Crude	1.71 (1.41-2.08)	2.32 (1.80-2.99)	2.45 (1.88-3.19)	2.29 (1.90-2.76)	1.67 (1.41-1.98)
Adjusted[a]	1.68 (1.38-2.05)	2.26 (1.76-2.92)	2.40 (1.84-3.13)	2.24 (1.86-2.71)	1.64 (1.38-1.94)
CCB exposure vs general comparator					
Crude	2.37 (2.01-2.79)	2.86 (2.32-3.53)	3.72 (2.97-4.65)	3.08 (2.62-3.62)	2.15 (1.85-2.51)
Adjusted[a]	2.51 (2.13-2.96)	2.99 (2.43-3.69)	3.89 (3.11-4.87)	3.20 (2.72-3.76)	2.22 (1.90-2.60)

Abbreviation: HR, hazard ratio for time (in days) from index date.

[a] Adjusted for age, sex, low-income status, rural residence, duration of hypertension, chronic disease burden, concurrent antihypertensive medications, concomitant use of medication classes that may also produce peripheral edema, and index date.

Table 3. Associations Between Being Dispensed a Calcium Channel Blocker (CCB) and Being Dispensed a Loop Diuretic, by Type and Dosage of CCB Dispensed[a]

Comparison Group	Adjusted HR (95% CI)				
	1-30 d	31-60 d	61-90 d	91-180 d	181-365 d
CCB exposure vs other antihypertensive medication comparator					
Amlodipine	1.42 (1.14-1.77)	1.82 (1.36-2.42)	2.18 (1.63-2.91)	2.03 (1.65-2.50)	1.56 (1.29-1.89)
Nonamlodipine CCB	2.70 (2.05-3.56)	4.03 (2.85-5.71)	3.30 (2.21-4.92)	3.14 (2.33-4.21)	1.98 (1.46-2.70)
Low-dose CCB	1.71 (1.39-2.10)	2.11 (1.60-2.79)	2.42 (1.82-3.21)	1.90 (1.54-2.36)	1.43 (1.17-1.74)
High-dose CCB	1.70 (1.21-2.39)	2.96 (2.01-4.36)	2.59 (1.68-4.00)	3.55 (2.69-4.69)	2.66 (2.01-3.52)
CCB exposure vs general comparator					
Amlodipine	2.11 (1.74-2.55)	2.40 (1.87-3.08)	3.53 (2.74-4.55)	2.89 (2.41-3.48)	2.12 (1.78-2.52)
Nonamlodipine CCB	4.02 (3.13-5.18)	5.31 (3.87-7.29)	5.32 (3.66-7.74)	4.46 (3.37-5.89)	2.67 (1.98-3.61)
Low-dose CCB	2.55 (2.14-3.04)	2.78 (2.20-3.53)	3.91 (3.06-5.00)	2.71 (2.24-3.28)	1.93 (1.61-2.32)
High-dose CCB	2.57 (1.86-3.55)	3.97 (2.77-5.68)	4.26 (2.82-6.43)	5.14 (3.96-6.67)	3.67 (2.81-4.80)

Abbreviation: HR, hazard ratio for time (in days) from index date.

[a] Fully adjusted for age, sex, low-income status, rural residence, duration of hypertension, chronic disease burden, concurrent antihypertensive medications, concomitant use of medication classes that may also produce peripheral edema, and index date.

ment). Censoring individuals in the other antihypertensive medication comparator group if they discontinued ACEI or ARB treatment reduced the mean length of follow-up by 14 days but did not appreciably change effect estimates (eTable 5 in the Supplement).

Subgroup Analyses

No sex differences in the association between new CCB exposure and subsequent diuretic dispensing were observed (eTable 6 in the Supplement). Individuals newly dispensed a CCB had a greater hazard of receiving a loop diuretic vs those in the comparison groups regardless of CCB type (ie, amlodipine vs nonamlodipine CCBs) (**Table 3**). The cumulative incidence of being dispensed a loop diuretic within 90 days was 1.2% for individuals newly dispensed amlodipine and 2.3% for those dispensed nonamlodipine CCBs. Although individuals newly prescribed amlodipine had a higher rate of being dispensed a loop diuretic up to 90 days after the index date than did those in the other antihypertensive medication comparator group (HR, 1.42; 95% CI, 1.14-1.77 for 1-30 days; 1.82; 95% CI, 1.36-2.42 for 31-60 days; and 2.18; 95% CI 1.63-2.91 for 61-90 days), the magnitude of association was greater in the smaller subgroup of individuals newly prescribed other CCBs (Table 3). The same pattern was observed for any diuretic use (eTable 7 in the Supplement). The magnitude of association was generally greater with high-dose CCBs (Table 3); however, a dose-dependent response was only observed for the secondary outcome of any diuretic use (eTable 7 in the Supplement).

Discussion

In a large, population-based cohort of older adults with hypertension, individuals who were newly dispensed a CCB experienced more than a 60% higher rate of being subsequently dispensed a loop diuretic compared with those who began taking other antihypertensive medications. Rates of loop diuretic dispensing increased within the first 30 days and

remained elevated throughout 1 year of follow-up. Findings were robust across CCB type and dosage.

Given how widely CCBs are prescribed, the results of the present study highlight a prescribing cascade that occurs in a large number of adults. In this study, 3.5% of older adults who were newly dispensed a CCB subsequently were prescribed a loop diuretic within 1 year; this proportion rose to 9.5% for any diuretic use. With more than 14 million people receiving an amlodipine prescription in the United States in 2016, this finding reflects 500 000 to 1.3 million new, potentially unnecessary diuretic prescriptions each year.[30] We believe that our findings corroborate those from a 2016 case report[18] and a 2018 cross-sectional study[19] of US patient visits, which found that a loop diuretic was continued or newly prescribed in 4.6% of visits at which a DHP CCB was continued, but the present study improves on this evidence by establishing temporality and examining the extent of this practice at a population level.

Because peripheral edema occurs more frequently in patients taking DHP CCBs compared with non-DHP CCBs (eg, verapamil and diltiazem),[5] we expected a stronger association between individuals who were newly dispensed a CCB and subsequent dispensing of a loop diuretic in the subgroup of individuals who were prescribed amlodipine vs those who were prescribed nonamlodipine CCBs. That we did not see this association may be attributed to differences in how edema was managed and/or the indication for CCB drug therapy. For example, individuals taking verapamil may have been prescribed a CCB to provide rate control for atrial fibrillation or tachyarrhythmia rather than solely to treat hypertension.[31] Therefore, higher rates of edema and resulting diuretic treatment may have been attributable to underlying cardiovascular illness. In this subgroup, diuretic therapy may have been appropriate. We excluded individuals with diagnosed heart failure and those with a history of antihypertensive or diuretic use in the preceding year to minimize these potential confounders, although undiagnosed individuals with heart failure or those who developed heart failure after their index date would have been included.

Diuretic therapy may have also been appropriate among individuals requiring multiple agents for blood pressure control.[2] As mentioned previously, we excluded individuals with a recent history of antihypertensive or diuretic use in the preceding year. As such, the cohort included individuals with new-onset or mild hypertension for whom diuretics would unlikely be prescribed as part of guideline-based hypertension management.

No sex differences were observed in the association between new CCB exposure and subsequent diuretic dispensing, similar to findings reported in a recent US study,[19] despite the fact that women have higher rates of CCB-induced edema than men.[27] The lack of sex differences observed in this study may be attributable to differences in edema management or variations in CCB prescribing practices (ie, women may receive lower dosages or for shorter duration). Previous studies[32-35] failed to report results by sex; however, we believe that patient sex should be an ongoing consideration in future research on hypertension treatment, ADEs, and subsequent management.

Implications

Given the harms and costs associated with prescribing diuretics to treat CCB-induced edema, especially for vulnerable older adults, clinicians need to be aware of the prescribing cascade of CCBs and diuretics in adults with hypertension and how it can be avoided. At the outset, clinicians should consider whether an antihypertensive drug therapy is needed for blood pressure control in an older patient given the potential for many of these medications to increase the risk of falls and associated hip fractures.[36] If CCB therapy for management of hypertension is warranted and peripheral edema occurs, clinicians should consider whether peripheral edema is an ADE, even if the edema occurs later (ie, weeks to months) in the patient's course of treatment. Before prescribing a diuretic to manage the edema, clinicians should consider whether the CCB is still necessary, whether it could be discontinued or the dosage could be reduced, or whether the patient can be switched to another therapy.[13,15] Nonpharmacologic strategies to address peripheral edema should also be considered.

As described earlier, a CCB-diuretic prescribing cascade may be appropriate based on an individual's unique circumstances. Even when deemed appropriate, frequent reevaluation of the goals for care and ongoing assessments are recommended because the appropriateness of the treatment may change over time.[13]

Limitations

This study has limitations. The indication for prescribed medications is not included in the ODB nor is a standardized diagnostic code available for peripheral edema; as a result, we could not confirm that a dispensed diuretic was used to treat CCB-induced edema. By excluding patients with heart failure and end-stage renal disease, selecting loop diuretics as a primary outcome, and controlling for conditions and drug therapies known to lead to edema, we minimized other indications for diuretic prescribing. Prescribing cascades may precipitate other potentially harmful and costly actions beyond prescribing a second drug therapy.[15] Unnecessary diagnostic tests may be ordered if the edema is incorrectly thought to have another source (eg, heart failure) requiring further investigation. Because we were unable to measure these practices, the true burden of the CCB-diuretic prescribing cascade at a population level was likely underestimated. Future studies could examine the use of novel data sources to examine the broader-reaching consequences of prescribing cascades.

Conclusions

We observed that older adults with hypertension who were newly dispensed a CCB subsequently were dispensed a loop diuretic at higher rates than those who began taking other antihypertensive medications or unrelated medications. We believe that the results of the present study stress the need to raise awareness of this prescribing cascade and call for vigilance in preventing the cascade and its related harms.

ARTICLE INFORMATION

Accepted for Publication: December 4, 2019.

Published Online: February 24, 2020. doi:10.1001/jamainternmed.2019.7087

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Obtained funding: Bronskill, Rochon.
Administrative, technical, or material support: Savage, Visentin, Luke, Wu, McCarthy.
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Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by project grant PJT-153060 from the Canadian Institutes of Health Research (Dr Rochon [nominated principal applicant], Dr Bronskill [co-principal applicant], and Drs Gruneir and McCarthy [co-applicants]). This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Dr Savage is supported by a Canadian Institutes of Health Research Postdoctoral Fellowship [MFE 158218]. Dr Stall receives funding from the Canadian Institutes of Health Research Vanier Scholarship Program, the Eliot Phillipson Clinician-Scientist Training Program and the Clinician Investigator Program at the University of Toronto. Dr Rochon is the RTO/ERO Chair in Geriatric Medicine at the University of Toronto.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily those of the CIHI.

Additional Contributions: We thank IMS Brogan Inc for the use of their Drug Information Database.

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