Received: 26 July 2023 | Revised: 2 October 2023 | Accepted: 9 October 2023

DOI: 10.1111/jgs.18683

CLINICAL INVESTIGATION

Journal of the American Geriatrics Society

Association of a calcium channel blocker and diuretic prescribing cascade with adverse events: A population-based cohort study

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Abstract

Background: Prescribing cascades occur when a drug adverse event is misinterpreted as a new medical condition and a second, potentially unnecessary drug, is prescribed to treat the adverse event. The population-level consequences of prescribing cascades remain unknown.

Methods: This population-based cohort study used linked health administrative databases in Ontario, Canada. The study included community-dwelling adults, 66 years of age or older with hypertension and no history of heart failure (HF) or diuretic use in the prior year, newly dispensed a calcium channel blocker (CCB). Individuals subsequently dispensed a diuretic within 90 days of incident CCB dispensing were classified as the prescribing cascade group, and compared to those not dispensed a diuretic, classified as the non-prescribing cascade group. Those with and without a prescribing cascade were matched one-to-one on the propensity score and sex. The primary outcome was a serious adverse event (SAE), which was the composite of emergency room visits and hospitalizations in the 90-day follow-up period. We estimated hazard ratios (HRs) with 95% confidence intervals (CI) for SAE using an Andersen–Gill recurrent events regression model.

Results: Among 39,347 older adults with hypertension and no history of HF who were newly dispensed a CCB, 1881 (4.8%) had a new diuretic dispensed within 90 days after CCB initiation. Compared to the non-prescribing cascade group, those in the prescribing cascade group had higher rates of SAEs (HR: 1.21, 95% CI: 1.02–1.43).

Funding information
Canadian Institutes of Health Research, Grant/Award Number: PJT-153060

Conclusions: The CCB-diuretic prescribing cascade was associated with an increased rate of SAEs, suggesting harm beyond prescribing a second drug therapy. Our study raises awareness of the downstream impact of the CCB-diuretic prescribing cascade at a population level and provides an opportunity for clinicians who identify this prescribing cascade to review their patients' medications to determine if they can be optimized.

KEYWORDS
older adults, prescribing cascade, serious adverse events

INTRODUCTION

Adverse drug events occur frequently in older adults and in some cases cause harm serious enough to result in emergency room visits and hospitalizations.[1–3] An estimated 16% of emergency room visits by older adults are for adverse drug events.[4] Recognizing the prescribing sequence leading to these events is important because it provides an opportunity to intervene and deprescribe by reducing doses and, in some cases, stopping the drug therapy to prevent these events. A prescribing cascade occurs when a drug adverse event is misinterpreted as a new medical condition and a second, potentially unnecessary drug, is prescribed to treat the adverse drug event. This concept described in the 1990s[5,6] is now recognized as a major contributor to polypharmacy, with more than 100 prescribing cascades identified.[7,8] It has been incorporated into deprescribing protocols internationally.[9] Addressing prescribing cascades is an important, yet underutilized, strategy to reduce medication harm caused by prescribing a potentially unnecessary second drug therapy and the cascade of subsequent harmful events that may follow.

Large population-based cohort studies demonstrate that prescribing cascades occur[10–12] and link new users of sodium glucose co-transporter 2 inhibitors to dispensing of an anti-mycotic drug among those with diabetes,[13] calcium channel blockers (CCB) to the initiation of diuretic therapy among those with hypertension[10,14–16] and gabapentinoid dispensing to the initiation of diuretic therapy among those with new lower back pain.[11] We know from individual case reports and qualitative interviews that prescribing cascades are associated with the development of adverse events including confusion,[17] incontinence,[12] and head injury,[18] and have important impacts on the quality of life.[19,20] Yet, we know little about the downstream impact that prescribing cascades can precipitate at a population-level, requiring emergency room visits and hospitalizations.[10]

In this study, we use a population-based cohort of older women and men who did, and did not, experience a CCB-diuretic prescribing cascade[10] to compare the rate of subsequent serious adverse events (SAE), as measured by emergency room visits or hospitalizations. We selected the CCB-diuretic prescribing cascade because these drug therapies are widely prescribed, the CCB-diuretic prescribing cascade has been rigorously studied,[10,14,15] and we had the novel opportunity to extend our rigorous population-based study demonstrating the existence of the CCB-diuretic cascade to explore subsequent SAEs.[10]

Key points

- Prescribing cascades occur when a drug adverse event is misinterpreted as a new medical condition and a second, potentially unnecessary drug, is prescribed to treat the adverse event.
- Findings from this population-based cohort study suggest that older adults in the prescribing cascade group experienced a significantly higher rate of serious adverse events within 90 days of follow-up compared to those in the non-prescribing cascade group.
- The secondary analysis suggests a similar trend when extending the follow-up period to 180 days.

Why does this paper matter?

Findings identify the need for clinicians to consider whether their patients are taking a medication to treat the adverse event of another medication, to reduce potentially preventable severe adverse events arising from prescribing cascades.

METHODS

Cohort creation

The cohort was constructed using linked health administrative databases containing information as part of the

publicly funded universal Ontario Health Insurance Plan (OHIP) in Ontario, Canada. Ontario is Canada's most populous province, with 2.7 million residents 65 years of age and older.[21] All medically necessary prescription drugs are publicly funded for these residents through the Ontario Drug Benefit (ODB) program. Data sources for information on physician services, ambulatory and hospital care, and prescription medications are listed in Supplementary Table 1. Individual-level race and ethnicity data are unavailable. These datasets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

The cohort consisted of community-dwelling adults, aged 66 years or older with hypertension, who were newly dispensed any CCB drug (no CCB drug dispensed in the prior 1 year) available from the ODB between September 30, 2011, and September 30, 2016.[10] We excluded individuals if they (1) were not an Ontario resident for 2 years preceding the index date (defined in the exposure group and comparison group as below), (2) were not dispensed at least one ODB drug within 2 years prior to the index date, (3) had a hospitalization in the month prior to the index date (hospital medication use is not captured), or (4) had a long-term care home admission in the 6 months preceding index to restrict to community-dwelling older adults. Further, we restricted our cohort to minimize the impact of any potential confounding attributed to chronic conditions. Specifically, we excluded those with conditions that may lead to edema, including heart failure (HF) or end-stage renal disease, in the prior year. We also restricted the cohort to those with no history of any antihypertensive or diuretic dispensing in the prior year to capture new users. The definitions of relevant health conditions are listed in Supplementary Table 2.

Exposure: Prescribing cascade group

Individuals were classified as having a prescribing cascade if they fulfilled criteria for a prescribing cascade, defined as being dispensed Drug A followed by Drug B. Specifically, starting from the date Drug A (CCB) was initially dispensed, individuals were followed for 90 days to identify whether Drug B (diuretic) was dispensed. Individuals dispensed a diuretic during this period were classified as being in the prescribing cascade group and the index date was defined as the date Drug B (diuretic) was first dispensed (Figure 1). Drugs included in the study definitions are listed in Supplementary Table 2.

Comparison group: Non-prescribing cascade group

Individuals who were newly dispensed a Drug A (CCB), but not dispensed a Drug B (diuretic) within 90 days were

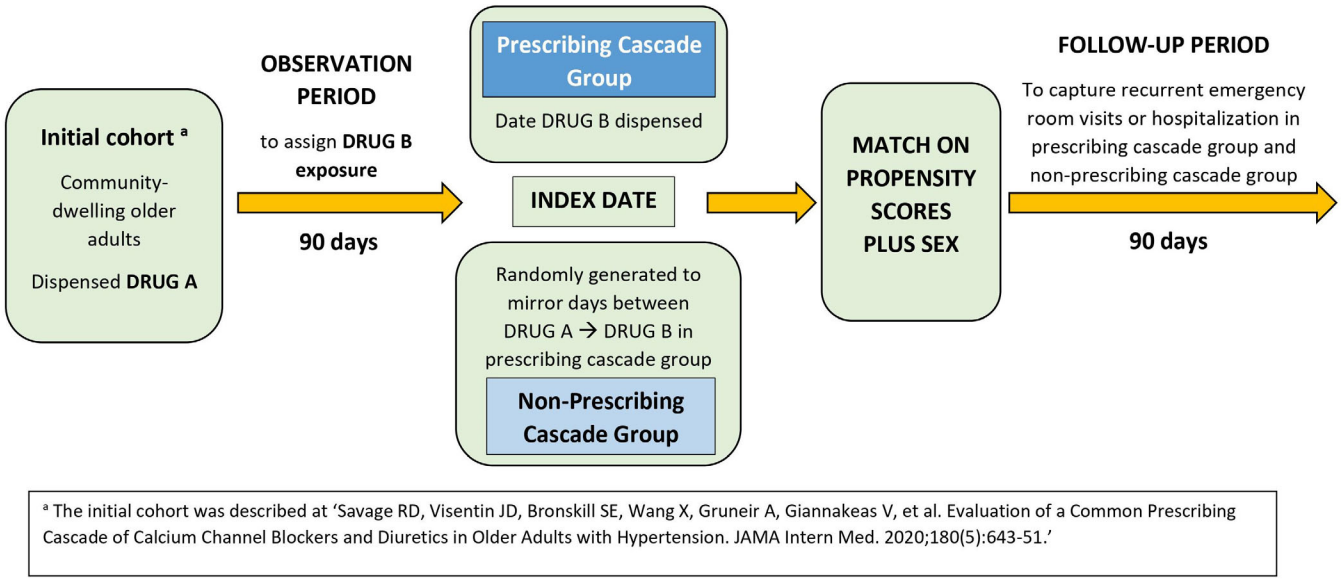

FIGURE 1 Flowchart of study design. Community-dwelling older adults newly dispensed Drug A (calcium channel blocker) were followed for 90 days to identify the cascade exposure status. Those who were dispensed Drug B (diuretic) within the 90-day period were assigned to the prescribing cascade group and those who were not were assigned to the non-prescribing cascade group. The index date for the prescribing cascade group was the date Drug B was dispensed, whereas the index date for the non-prescribing cascade group was a synthetic index date assigned at random based on the empirical distribution of the prescribing cascade group index dates (see Section 2). The groups were then matched based on propensity score and sex and followed for a subsequent 90-day period for recurrent emergency room visits or hospitalizations.

classified as being in the non-prescribing cascade group. For those in the non-prescribing cascade group, we randomly generated a corresponding index date. This index date was based on the empirical distribution of lag intervals obtained from the prescribing cascade group (defined as time from dispensing Drug A to dispensing Drug B). Next, this lag interval was added to the date of dispensing of Drug A in the non-prescribing cascade group to create a "synthetic" index date. This ensured that the time from dispensing Drug A to the index date would be similar in both the prescribing cascade and in the non-prescribing cascade group, avoiding survivor bias in the prescribing cascade group.[22] Those in the non-prescribing cascade group who died prior to their synthetic index date were excluded.

Observation period and outcome measurement

The primary outcome was a SAE, defined as a composite of emergency room visits or hospitalizations, within 90 days of the index date. Because there could be multiple emergency room visits or hospitalizations after the index date, our analytic approach captured multiple SAEs in the follow-up period.

Death was treated as a competing risk. Individuals were censored at admission to a long-term care home, or the end of the 90-day follow-up period. Additionally, individuals in the non-prescribing cascade group, who were prescribed a diuretic 90 days following CCB initiation and during the follow-up period, were censored on the date the drug was dispensed.

To investigate SAEs taking more time to come to medical attention, we performed a secondary analysis, whereby the groups were followed for 180 days from the index date.

As an initial exploratory analysis, we examined the primary reason for the emergency room visit and hospitalization, and aggregated it using groupings of the first 3 digits of the International Classification of Diseases, 10th Revision, Canadian Enhanced Edition diagnostic codes.[23]

Descriptive variables

We captured demographic characteristics (age, sex, neighborhood-level income, and rurality), prior health service utilization (outpatient physician visits, emergency room visits, and hospitalizations), comorbidities, and drug therapies (see Supplementary Table 2) to describe the population. Other variables relevant to the specific CCB-diuretic prescribing cascades were previously reported.[10,11] All variables were ascertained on the individual's index date.

Statistical analyses

Baseline demographic and clinical characteristics were reported (See Supplementary Table 3 and Supplementary Table 4). Propensity score matching was used to reduce the effects of differences in observed baseline variables between the prescribing cascade and the non-prescribing cascade groups. The propensity score, the probability of receiving Drug B (diuretic), indicating a prescribing cascade, conditional on measured baseline variables was estimated using a logistic regression model.[24] The baseline variables used in the propensity model included 31 variables (Supplementary Table 3) that incorporated demographic information (including age), health system utilization (prior year), and comorbidities that included chronic conditions linked to edema. These variables also included drug therapies, specifically, CCB type and dose, concurrent antihypertensives, and concurrent medications linked to edema. Individuals in the prescribing cascade group were matched 1:1 on the logit of the propensity score with those in the non-prescribing cascade group, using a caliper width of 0.2 times the standard deviation of the logit of the propensity score. This reduced differences between the groups predispose them to emergency room visits or hospitalizations. In addition, we hard-matched on sex. We assessed balance between the prescribing cascade and non-prescribing cascade group in the matched samples using standardized differences. A value of <0.1 was used to indicate adequate balance between groups.[24,25] The distribution of the propensity scores among the prescribing cascade and the non-prescribing cascade groups before and after matching are provided, demonstrating that the propensity scores were sufficiently overlapping between the groups after matching (Supplementary Figure 1).

Cumulative incidence curves were used to visually assess patterns of SAEs over time, for the first event only, in the prescribing cascade and non-prescribing cascade groups.

We estimated an Andersen–Gill recurrent events regression model[26] to compare rates of SAEs between the prescribing cascade and non-prescribing cascade groups, allowing for multiple events for each subject, while treating death as a competing risk. In a prespecified sensitivity analysis, an intention-to-treat analysis was conducted and older adults in the non-prescribing cascade group were not censored if they were prescribed a diuretic during the follow-up period. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies (see Supplementary Table 5).

Subgroup analysis

A subgroup analysis was defined a priori to explore sex differences. This analysis was important because women are more likely than men to experience adverse drug events which may lead to SAEs.[27]

Ethics statement

The use of data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

Study cohort

Among 39,347 older adults with hypertension and no history of HF who were newly dispensed a CCB, 1881 (4.8%) had a new diuretic dispensed within 90 days after CCB initiation and 1866 (99.2%) were successfully matched.

Before matching, there were differences between the prescribing cascade and non-prescribing cascade groups with respect to age, use of drug therapies, and health system utilization in the year prior (Supplementary Table 3). After propensity score matching, there were no meaningful differences between the prescribing cascade and non-prescribing cascade groups on potential measured confounders (see Supplementary Table 4 for details), as none exceeded our a priori threshold of a standardized difference of 0.1.

Baseline characteristics

Key baseline characteristics of the prescribing cascade group and their matched non-prescribing cascade group are listed in Table 1. At the index date, the cohort included 1151 (61.7%) females in the prescribing cascade group, with a mean age of 76.4 years. Overall, 24.0% of the prescribing cascade group had five or more chronic conditions and 49.5% had emergency room visits and 18.9% had a hospitalization in the prior year. Baseline variables stratified by sex are shown in Supplementary Table 4.

Primary outcome

Overall, 382 (20.5%) of the prescribing cascade and 315 (16.9%) of the non-prescribing cascade group had one or more SAE in the 90 days follow-up period (Table 2). A total of 267 (14.3%) of those in the prescribing cascade and 229 (12.3%) in the non-prescribing cascade group had at least one emergency room visit and 170 (9.1%) of those in the prescribing cascade and 126 (6.8%) in the non-prescribing cascade group had at least one hospitalization. In addition, 25 individuals in the prescribing cascade (1.3%) and 22 (1.2%) in the non-prescribing cascade group died (Table 2). Cumulative incidence curves demonstrated that the incidence of SAEs was higher in the prescribing cascade than the non-prescribing cascade group over time. This difference was observed starting shortly after the 90 days follow-up began (Figure 2). Overall, the rate of SAE per 1000 person-days of follow-up was 3.61 in the prescribing cascade group and 2.99 in the non-prescribing cascade group. Compared to those in the non-prescribing cascade group, those in the prescribing cascade group had a higher rate of SAEs during the 90 days follow-up (cause-specific hazard ratio (HR): 1.21, 95% CI: 1.02–1.43 (see Table 3)).

Reason for visit

The most common reason for an emergency room visit or a hospitalization was for a disease of the circulatory system (Table 4). Further, diseases of the circulatory system accounted for proportionately more emergency room visits and hospitalizations among the prescribing cascade group (19.2% emergency room visits and 30.5% hospitalizations) than in the non-prescribing cascade group (5.4% and 17.5%). These visits were mostly for hypertension, atrial fibrillation, and HF.

Secondary analysis

In a secondary analysis, we found a similar trend when extending the follow-up period to 180 days. Compared to individuals in the non-prescribing cascade group, those in the prescribing cascade group had a higher rate of

TABLE 1 Baseline characteristics of prescribing cascade group (calcium channel blocker-diuretic) and non-prescribing cascade group (calcium channel blocker only) after propensity score matching.[a]

Characteristics	Prescribing cascade group $N = 1866$	Non-prescribing cascade group $N = 1866$	Standardized difference
Demographics			
Female sex, *n* (%)	1151 (61.7)	1151 (61.7)	0
Age, years (mean, SD)	75. 8 (7.3)	76.4 (7.8)	0.077
Low-income, *n* (%)	308 (16.5)	349 (18.7)	0.058
Rural residence, *n* (%)	200 (10.7)	186 (10.0)	0.025
Health system utilization (1-year look-back)			
Primary care visit, *n* (%)	1821 (97.6)	1825 (97.8)	0.014
Cardiologist or nephrologist visit	992 (53.2)	947 (50.8)	0.048
Home care service, *n* (%)	260 (13.9)	286 (15.3)	0.039
Emergency department visit, *n* (%)	921 (49.4)	924 (49.5)	0.003
Hospitalization, *n* (%)	365 (19.6)	353 (18.9)	0.016
Comorbidities			
Time since the first documentation of hypertension prior to cohort entry, years (mean, SD)	11.0 (7.1)	11.3 (7.2)	0.032
Chronic disease burden, *n* (%)			
1	162 (8.7)	138 (7.4)	0.047
2	414 (22.2)	418 (22.4)	0.005
3	493 (26.4)	503 (27.0)	0.012
4	356 (19.1)	360 (19.3)	0.005
5 or more	441 (23.6)	447 (24.0)	0.008
Chronic conditions that can cause peripheral edema, *n* (%)			
Cancer	331 (17.7)	354 (19.0)	0.032
Diabetes	422 (22.6)	430 (23.0)	0.010
Chronic liver disease	34 (1.8)	40 (2.1)	0.023
Chronic kidney disease	213 (11.4)	204 (10.9)	0.015
Stroke	79 (4.2)	97 (5.2)	0.046
Drug therapies			
Type of calcium channel blocker, *n* (%)			
Amlodipine	1410 (75.6)	1407 (75.4)	0.004
Felodipine	16 (0.9)	20 (1.1)	0.022
Nifedipine	167 (8.9)	154 (8.3)	0.025
Verapamil	11 (0.6)	19 (1.0)	0.048
Diltiazem	264 (14.1)	268 (14.4)	0.006
Dose of calcium channel blocker[b], *n* (%)			
Lower than recommended starting dose	337 (18.1)	338 (18.1)	0.001
Low-dose range	1015 (54.4)	984 (52.7)	0.033
High-dose range	497 (26.6)	525 (28.1)	0.034
Higher than maximum recommended dose	17 (0.9)	19 (1.0)	0.011

TABLE 1 (Continued)

Characteristics	Prescribing cascade group $N = 1866$	Non-prescribing cascade group $N = 1866$	Standardized difference
Number of concurrent medications (excluding calcium channel blocker) (mean, SD)	4.51 (2.76)	4.49 (2.76)	0.005
Concurrent antihypertensive medications (mean, SD)	0.41 (0.65)	0.42 (0.65)	0.011
Concurrent medications by class known to cause peripheral edema, *n* (%)			
Non-steroidal anti-inflammatory drugs	166 (8.9)	183 (9.8)	0.031
Steroids (corticosteroids, estrogens, progestins, testosterone)	82 (4.4)	79 (4.2)	0.008
Gabapentinoids (pregabalin, gabapentin)	60 (3.2)	62 (3.3)	0.006
Dopamine agonists (pramipexole, ropinirole)	9 (0.5)	12 (0.6)	0.021

[a]Detailed data and standardized difference between prescribing cascade and non-prescribing cascades in women and men before and after matching are listed in Supplementary Table 3 and Supplementary Table 4.
[b]The definitions of dose of calcium channel blocker are listed in Supplementary Table 2.

SAEs during the 180 days follow-up (HR: 1.19, 95% CI: 1.03–1.37) (Table 3).

Sensitivity analysis

We conducted a prespecified sensitivity analysis, in which older adults in the comparison group were not censored if they were prescribed a diuretic during the 90- and 180-day follow-up period, with similar findings (Table 3).

Subgroup analysis

Among women, those in the prescribing cascade group had more SAEs (20.0%) compared to women in the non-prescribing cascade group (15.8%) (Table 2). The rate of SAEs was significantly higher in the prescribing cascade group (HR: 1.38, 95% CI: 1.11–1.71) (Table 3). Among men, those in the prescribing cascade group had more SAEs (21.3%) compared to men in the non-prescribing cascade group (18.6%) (Table 2). The rate of SAEs was not significantly different for men between the prescribing cascade and non-prescribing cascade groups (HR: 1.02, 95% CI: 0.78–1.33) (Table 3).

DISCUSSION

We demonstrate among a population-based cohort of hypertensive older adults newly dispensed a CCB, with no history of HF or diuretic dispensing in the prior year, that those in the CCB-diuretic prescribing cascade group had a 1.2 times higher rate of experiencing a SAE as measured by an emergency room visit or hospitalization over 90 days compared with those in the non-prescribing cascade group. Women with a prescribing cascade were more likely than women in the non-prescribing cascade group to develop a SAE leading to an emergency room visit or hospitalization. This is consistent with information that older women are particularly vulnerable to adverse events.[27] Our results remained consistent when follow-up was extended to 180 days.

Using emergency room visits and hospitalizations as our measure of SAE allowed us to capture the range of anticipated and unanticipated ways that this prescribing cascade may impact the health of older adults. As might be anticipated, edema may trigger an emergency room visit or hospitalization to investigate for possible circulatory disease including HF.[28] While those with a history of HF or prior use of a diuretic were excluded from our cohort, SAEs experienced by those in the prescribing cascade group were more frequently for circulatory diseases than in the non-prescribing cascade group. We recognize that SAEs may also be for unanticipated reasons. Rosenberg et al.[18] reported a prescribing cascade in an older adult where the use of a cholinesterase inhibitor led to gastrointestinal upset, and the patient's decision to self-medicate with bismuth led to bismuth toxicity, a fall and head injury, and an intensive care unit admission.[18] This demonstrates the importance of using a

TABLE 2 Proportion of those in the prescribing cascade and non-prescribing cascade group with a serious adverse events (emergency room visit or hospitalization) associated with the calcium channel blocker-diuretic prescribing cascades during 90- and 180-day follow-up periods.

	Overall		Women		Men	
	Prescribing cascade group ***N* = 1866** ***n* (%)**	**Non-prescribing cascade group** ***N* = 1866** ***n* (%)**	**Prescribing cascade group** ***N* = 1151** ***n* (%)**	**Non-prescribing cascade group** ***N* = 1151** ***n* (%)**	**Prescribing cascade group** ***N* = 715** ***n* (%)**	**Non-prescribing cascade group** ***N* = 715** ***n* (%)**
90 days follow-up						
Any serious adverse events						
n, (%)	382 (20.5)	315 (16.9)	230 (20.0)	182 (15.8)	152 (21.3)	133 (18.6)
Mean (SD)	0.32 (0.77)	0.26 (0.74)	0.31 (0.76)	0.23 (0.63)	0.33 (0.79)	0.32 (0.89)
Emergency room visit						
n (%)[a]	267 (14.3)	229 (12.3)	167 (14.5)	138 (12.0)	100 (14.0)	91 (12.7)
Mean (SD)	0.21 (0.62)	0.19 (0.63)	0.22 (0.65)	0.16 (0.54)	0.19 (0.57)	0.23 (0.76)
Hospitalization						
n (%)[b]	170 (9.1)	126 (6.8)	92 (8.0)	67 (5.8)	78 (10.9)	59 (8.3)
Mean (SD)	0.11 (0.37)	0.08 (0.30)	0.09 (0.33)	0.07 (0.27)	0.14 (0.42)	0.10 (0.34)
Death[c]	25 (1.3)	22 (1.2)	13 (1.1)	14 (1.2)	12 (1.7)	8 (1.1)
180 days follow-up						
Any serious adverse events						
n, (%)	556 (29.8)	481 (25.8)	338 (29.4)	297 (25.8)	218 (30.5)	184 (25.7)
Mean (SD)	0.55 (1.12)	0.46 (1.11)	0.54 (1.12)	0.41 (0.89)	0.56 (1.11)	0.53 (1.39)
Emergency room visit						
n (%)[a]	416 (22.3)	353 (18.9)	262 (22.8)	226 (19.6)	154 (21.5)	127 (17.8)
Mean (SD)	0.37 (0.90)	0.32 (0.94)	0.39 (0.95)	0.29 (0.73)	0.34 (0.80)	0.36 (1.19)
Hospitalization						
n (%)[b]	249 (13.3)	201 (10.8)	138 (12.0)	112 (9.7)	111 (15.5)	89 (12.4)
Mean (SD)	0.17 (0.50)	0.14 (0.44)	0.15 (0.44)	0.12 (0.41)	0.22 (0.58)	0.17 (0.50)
Death[c]	43 (2.3)	37 (2.0)	22 (1.9)	24 (2.1)	21 (2.9)	13 (1.8)

Abbreviation: SD, Standard deviation.
[a]At least one emergency room visit.
[b]At least one hospitalization.
[c]Death was treated as a competing risk and was not included in any serious adverse events.

broad measure of SAEs when exploring the potential harm associated with prescribing cascades in older adults.

Limitations

This study has limitations. First, it is possible that there was residual confounding in studying the relationship between the prescribing cascade and SAEs. For example, adults in the prescribing cascade group may have higher rates of SAEs as a result of preexisting health conditions. While we could not account for all confounders, a series of steps were taken to measure factors that may contribute to confounding. Specifically, we restricted our cohort to those with no history of a condition associated with edema. Further, we included only those with newly treated hypertension and no recent prior use of a diuretic. In addition, we used propensity-based matching to ensure that our prescribing cascade group was as similar as

possible to the non-prescribing cascade group at baseline; we expect differences in health care utilization to be negligible between both groups, and rates for standard follow-up to be similar. There were 31 baseline variables used in the propensity model, including, but not limited to: demographic information, health system utilization (prior year), comorbidities that included chronic conditions linked to edema, and drug therapies such as CCB type and dose, concurrent antihypertensives, and concurrent medications linked to edema. Though we recognize the possibility of residual confounding, we believe we have minimized confounding among measured variables in our analysis. A second limitation is that we examined SAEs that occurred within 90 days of the onset of the prescribing cascade; however, hypertension is a chronic condition, and many older people are prescribed a CCB long-term and are thus susceptible to prescribing cascades over time. Third, we were unable to pursue subgroup analyses by race as race-based data were not available.

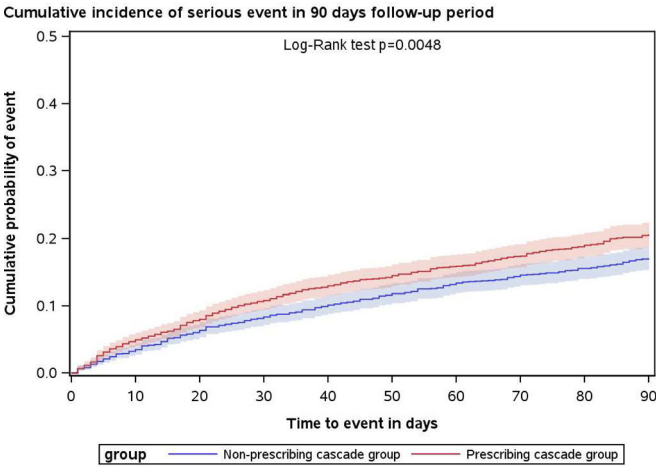

FIGURE 2 Cumulative incidence of serious adverse events in the 90-day follow-up period. Cumulative incidence of serious adverse events among older adults with prescribing cascade (calcium channel blocker + diuretic) compared with those in non-prescribing cascade group (calcium channel blocker only). These curves are based on the time to the first serious adverse event for each individual.

Implications

Our results have important implications for clinical practice. In Canada, an estimated 24% of older adults use CCBs for a range of cardiac conditions including but not limited to hypertension.[29] Raising awareness that a prescribing cascade can be associated with a SAE is an important step to reducing these potentially preventable SAEs and provides further impetus for clinicians to ask if their patients are taking a medication to treat the adverse event of another medication.[30] Yet, it is often difficult to obtain this information, particularly for older adults, because they have often been on these therapies for years and this information may not be readily available in their medical charts.[17] Piggott[30] has described the benefit of using a clinical process map to help clinicians make visible the sequence of events that can lead to a prescribing cascade and harm. This pencil-and-paper process involves sketching out the sequence of events that occur following the initiation of a drug therapy, identifying possible links between a drug therapy and a new medical condition, and the subsequent investigations and adverse events.[30] By helping clinicians to visualize the process, the clinical process map can raise awareness about prescribing cascades. In doing so, the visualization can prevent unnecessary diagnostic tests and referrals.

Finding an association between the initial drug therapy, a new medical condition, and the prescribing of a new drug therapy can be facilitated by knowing three pieces of information: when a drug was started, why it was started, and who started it.[19] This information allows the sequence of prescribing indicating a prescribing cascade to become clear and potentially avoids additional investigations that may be initiated to rule out potentially more serious diagnoses.[28] Further, it is important to

TABLE 3 Association between a calcium channel blocker-diuretic prescribing cascade and serious adverse events.

Prescribing cascade group versus non-prescribing cascade group	Hazard ratio (95% confidence interval) on any serious adverse events					
	Overall		Women		Men	
	90-day follow-up	180-day follow-up	90-day follow-up	180-day follow-up	90-day follow-up	180-day follow-up
Primary analyses[a]	1.21 (1.02–1.43)	1.19 (1.03–1.37)	1.38 (1.11–1.71)	1.29 (1.09–1.54)	1.02 (0.78–1.33)	1.05 (0.82–1.35)
Sensitivity analyses[b]	1.20 (1.01–1.42)	1.13 (0.97–1.31)	1.36 (1.10–1.69)	1.23 (1.03–1.47)	1.02 (0.77–1.33)	1.00 (0.78–1.27)

[a]Individuals in the non-prescribing cascade group prescribed any diuretic during the follow-up period were censored on the date the drug was dispensed.
[b]Individuals in the non-prescribing cascade group prescribed any diuretic during the follow-up period were not censored.

TABLE 4 Most common reasons for an emergency room visit or a hospitalization in the prescribing cascade and non-prescribing cascade groups.

ICD-10 Diagnosis group (Number, %)	Number of emergency room visits		Number of hospitalizations	
	Prescribing Cascade Group ($N = 402$)	Non-Prescribing Cascade Group ($N = 350$)	Prescribing Cascade Group ($N = 203$)	Non-Prescribing Cascade Group ($N = 143$)
Diseases of the circulatory system	77 (19.2)	19 (5.4)	62 (30.5)	25 (17.5)
Essential hypertension[a]	30 (7.5)	9 (2.6)	<=5	<=5
Atrial fibrillation and flutter[a]	10 (2.5)	<=5	12 (5.9)	<=5
Heart failure[a]	14 (3.5)	0	16 (7.9)	0
Injury, poisoning, and certain other consequences of external causes	64 (15.9)	56 (16.0)	8 (3.9)	16 (11.2)
Diseases of the musculoskeletal system and connective tissue	25 (6.2)	33 (9.4)	19 (9.4)	10 (7.0)
Diseases of the respiratory system	25 (6.2)	21 (6.0)	17 (8.4)	10 (7.0)
Diseases of the digestive system	18 (4.5)	26 (7.4)	21 (10.3)	12 (8.4)

[a]Three most common diseases of the circulatory system associated with emergency room visits and hospitalizations.

recognize that not all prescribing cascades are inappropriate. Careful thought may have been given to the decision to prescribe the diuretic therapy and the diuretic therapy may be the best of imperfect options available for addressing the needs of that patient.[31] For older adults prescribed multiple medications, a regular medication review is recommended to ensure that these medications remain the right combination for the individual patient and consistent with their goals of care.[10,31]

CONCLUSION

The CCB-diuretic prescribing cascade was associated with an increased rate of SAEs, defined as a composite of emergency room visits and hospitalizations, suggesting harm beyond prescribing a second drug. Our study raises awareness of the downstream impact of the CCB-diuretic prescribing cascade at a population level and provides an opportunity for clinicians who identify this prescribing cascade to review their patients' medications to determine if they can be optimized.

AUTHOR CONTRIBUTIONS

Xuesong Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rochon and All. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Rochon. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Wang. Obtained funding: Rochon. Administrative, technical, or material support: Giannakeas, Wu, Strauss. Study supervision: Rochon.

ACKNOWLEDGMENTS

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). Parts of this material are based on data and/or information compiled and provided by CIHI. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Parts of this report are based on Ontario Registrar General (ORG) information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or the Ministry of Government Services.

We wish to acknowledge the support provided by Andrea Lawson PhD, Joyce Li, and Amanda Giancola for this study. Dr. Rochon is supported by the RTO/ERO Chair in geriatric medicine from the University of Toronto.

FUNDING INFORMATION

This study was funded by the Canadian Institutes of Health Research grant PJT-153060.

CONFLICT OF INTEREST STATEMENT

Dr. Rochon is one of the Deputy Editors of the *Journal of the American Geriatrics Society*.

SPONSOR'S ROLE

Study funders/sponsors 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; nor the decision to submit the manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplementary Table 1. Description of ICES administrative health care databases used in the study.

Supplementary Table 2. Definitions of key variables.

Supplementary Table 3. Baseline characteristics of prescribing cascade group and non-prescribing cascade groups by sex before matching.

Supplementary Table 4. Baseline characteristics of prescribing cascade group and non-prescribing cascade groups by sex after matching.

Supplementary Table 5. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement—checklist of items that should be included in reports of cohort studies.

Supplementary Figure 1. Distribution of propensity score before and after matching.

How to cite this article: Rochon PA, Austin PC, Normand S-L, et al. Association of a calcium channel blocker and diuretic prescribing cascade with adverse events: A population-based cohort study. *J Am Geriatr Soc*. 2024;72(2):467-478. doi:10.1111/jgs.18683