Received: 28 July 2022 | Revised: 6 September 2022 | Accepted: 2 October 2022

DOI: 10.1111/jgs.18103

CLINICAL INVESTIGATION

Journal of the American Geriatrics Society

Continued potassium supplementation use following loop diuretic discontinuation in older adults: An evaluation of a prescribing cascade relic

Grace Hsin-Min Wang PharmD, MS[1] | Earl J. Morris PharmD, MPH[1] | Steven M. Smith PharmD, MPH[1,2] | Jesper Hallas MD, DrMedSc[3,4] | Scott M. Vouri PharmD, PhD[1,2]

[1]Department of Pharmaceutical Outcomes & Policy, University of Florida College of Pharmacy, Gainesville, Florida, USA

[2]Center for Drug Evaluation and Safety, University of Florida, Gainesville, Florida, USA

[3]Department of Pharmacology, Odense University Hospital, Odense, Denmark

[4]Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark

Correspondence
Scott M. Vouri, Department of Pharmaceutical Outcomes & Policy, University of Florida College of Pharmacy, PO Box 100496, Gainesville, FL 32610, USA.
Email: svouri@ufl.edu

Funding information
National Institute on Aging, Grant/Award Number: K08AG066854

Abstract

Background: The use of a new medication (e.g., potassium supplementation) for managing a drug-induced adverse event (e.g., loop diuretic-induced hypokalemia) constitutes a prescribing cascade. However, loop diuretics are often stopped while potassium may be unnecessarily continued (i.e., relic). We aimed to quantify the occurrence of relics using older adults previously experiencing a loop diuretic-potassium prescribing cascade as an example.

Methods: We conducted a prescription sequence symmetry analysis using the population-based Medicare Fee-For-Service data (2011–2018) and partitioned the 150 days following potassium initiation by day to assess the daily treatment scenarios (i.e., loop diuretics alone, potassium alone, combination of loop diuretics and potassium, or neither). We calculated the proportion of patients developing the relic, proportion of person-days under potassium alone, the daily probability of the relic, and the proportion of patients filling potassium after loop diuretic discontinuation. We also identified the risk factors of the relic.

Results: We identified 284,369 loop diuretic initiators who were 8 times more likely to receive potassium supplementation simultaneously or after (i.e., the prescribing cascade), rather than before, loop diuretic initiation (aSR 8.0, 95% CI 7.9–8.2). Among the 66,451 loop diuretic initiators who subsequently (≤30 days) initiated potassium, 20,445 (30.8%) patients remained on potassium after loop diuretic discontinuation, and 9365 (14.1%) patients subsequently filled another potassium supplementation. Following loop diuretic initiation, 4.0% of person-days were for potassium alone, and daily probability of the relic was the highest after day 90 of loop diuretic initiation (5.6%). Older age, female sex, higher diuretic daily dose, and greater baseline comorbidities were risk factors for the relic, while patients having the same prescriber or pharmacy involved in the use of both medications were less likely to experience the relic.

Conclusions: Our findings suggest the need for clinicians to be aware of the potential of relic to avoid unnecessary drug use.

This study was submitted and presented at the 38th International Conference for PharmacoEpidemiology (ICPE).

KEYWORDS
loop diuretics, older adults, potassium supplementation, prescribing cascade relic

INTRODUCTION

The use of a new medication for managing a drug-induced adverse event constitutes a prescribing cascade.[1] A recent review showed that at least 340 prescribing cascades have been described using the sequence symmetry analysis, including calcium channel blockers-loop diuretics,[2] gabapentinoids-loop diuretics,[3] cholinesterase inhibitors-anticholinergics.[4,5] Another commonly-observed prescribing cascade is the use of potassium supplementation following loop diuretic-induced hypokalemia,[6] which is intentional and appropriate in most cases,[7] and therefore is considered a standard clinical care.[8]

Providers or patients should discontinue loop diuretics if they are no longer needed[9,10] or are bothersome for the patient.[11] In general, discontinuation of loop diuretics should be accompanied by discontinuation of potassium supplementation. However, the occurrence of this phenomenon, to our knowledge, has not been described in previous literature. As such, we defined this phenomenon as a "prescribing cascade relic" ("relic" hereafter). In this study, we aimed to (1) evaluate the "loop diuretic-hypokalemia-potassium supplementation" prescribing cascade, and (2) quantify the presence and identify the risk factors of continued potassium supplementation use following loop diuretic discontinuation (i.e., relic) among older adults previously experiencing a loop diuretic-potassium supplementation prescribing cascade.

Key points

- We defined the phenomenon in which the medication used to treat a drug-induced adverse event (e.g., potassium supplementation) is continued while the medication causing the drug-induced adverse event (e.g., loop diuretic) is no longer taken as a "prescribing cascade relic" because it is the remaining portion of a prescribing cascade with no current clinical use.
- Continued potassium use following loop diuretic discontinuation among older adults previously experiencing a loop diuretic-potassium prescribing cascade is a common example of relic.
- Older age, female sex, higher diuretic daily dose, and greater baseline comorbidities were risk factors of this relic, while patients having the same prescriber or pharmacy involved in their loop diuretic and potassium use were less likely to experience this relic.

Why does this paper matter?

Clinicians should be aware of the potential of a prescribing cascade relic to avoid unnecessary drug use.

METHODS

Data source

We used Medicare Part A, B, and D fee-for-service data comprised of a 5% sample of beneficiaries (2011–2015) and a 15% sample of beneficiaries enriched with oversampling of Floridians (2016–2018).[12] The study was approved by the University of Florida institutional review board. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline to ensure appropriate reporting.[13] All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC) between Oct 2021 and May 2022.

Prescribing cascade

Study design

We conducted a prescription sequence symmetry analysis (PSSA) to assess the proposed prescribing cascade (i.e., loop diuretic-hypokalemia-potassium supplementation), which compares the order of the initiation of the marker drug (i.e., potassium supplementation) versus the index drug (i.e., loop diuretics).[14] In the absence of a prescribing cascade, the initiation rate of the marker drug before the index drug generally matches the initiation rate of the marker drug after the index drug. That is, a symmetrical prescribing pattern before and after the index drug initiation is expected. Conversely, evidence of greater initiation of the marker drug after the index drug, compared with initiation of the marker drug before the index drug, results in an asymmetrical prescribing pattern, indicating a potential prescribing cascade.[15] PSSA has the

advantage of being a self-controlled, case-only study design. Thus, time-invariant confounders (e.g., sex, genetic factors) are inherently controlled.[16] PSSA has also reported moderate sensitivity and high specificity when evaluating known prescribing cascades and prescribing sequences not associated with prescribing cascades.[17] Moreover, the symmetry assumption of the PSSA assumption was recently confirmed via medical record chart review, which provides further support to the methodology.[18]

Study population

Briefly, we identified adults aged ≥66 years initiating loop diuretics between 2011 and 2018 with continuous enrollment in Medicare Part A, B, and D ≥360 days before and ≥180 days after diuretic initiation (i.e., $t0_a$).[19] If the patient initiated loop diuretics several times within this time frame (i.e., no prescription in the prior year), then only the first initiation of loop diuretics was evaluated. Individuals receiving potassium supplementation or diagnosed with hypokalemia within −360 to −181 days of $t0_a$ were excluded to ensure new use of potassium supplementation and to minimize the effect of underlying hypokalemia.[19] In other words, we restricted eligibility to patients initiating potassium supplementation within ±180 days of $t0_a$.[20] Patients initiating a loop diuretic and potassium supplementation on the same day were categorized into the same group as those initiating after $t0_a$ in the main analysis, under the assumption that providers often proactively initiate potassium supplementation to prevent diuretic-induced hypokalemia.[21]

Statistical analysis

Crude sequence ratios (cSR) and 95% confidence intervals (CI) were calculated to estimate the temporality of the initial prescriptions of the index and marker drugs. We divided the number of patients who initiated the marker drug together with or within 180 days after the index drug by the number of patients who initiated the marker drug within 180 days before the index drug to obtain the crude SR.[15,19] Considering that the prescribing trend may change over time, we calculated the adjusted SR (aSR) by dividing the cSR by the null-effect SR (SR_{null}) following the equation mentioned in Takeuchi et al.[22] which incorporates secular trends of both the index and marker drugs over the study period. To estimate the incidence of the prescribing cascade (i.e., loop diuretics-hypokalemia-potassium supplementation), we calculated the difference in the number of patients between those who initiated potassium supplementation together with or later than loop diuretic initiation and those initiating potassium supplementation prior to loop diuretic initiation, and divided the result by the number of loop diuretic initiators.[23] Then, we adjusted the results by the length of observation time and reported the incidence.

We stratified the study population by several covariates that may be associated with the prescribing cascade or the relic and calculated the aSRs in different subgroups, including age (categorized into 65–75 years, 76–85 years, and >85 years),[24] sex,[25] and daily dose of loop diuretics (converted to furosemide equivalents[26] and expressed in units of defined daily doses [DDD][27]) because loop diuretic-induced hypokalemia is dose-dependent.[26] Comorbidities and comedications reportedly associated with serum potassium level were also included,[28] such as congestive heart failure (CHF),[29] hypertension,[30] alcohol abuse,[31] diabetes,[32] liver disease,[33] renal failure,[34] and the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB),[35] oral corticosteroids,[36] nonsteroidal anti-inflammatory drugs (NSAID).[37] We also included Charlson Comorbidity Index (CCI)[38] because multiple chronic diseases can affect serum potassium.[39] Finally, we included concordance of prescribers and, separately, pharmacies (i.e., loop diuretics and potassium supplementation were prescribed by the same prescriber/dispensed in the same pharmacy) based on the hypothesis that the occurrence of prescribing cascade may be higher, while that of relic may be lower in patients encountering the same prescribers/pharmacies because they are more likely to be aware of the potential hypokalemia following loop diuretics, and thus tend to initiate potassium supplementation upon initiating loop diuretics and discontinue potassium supplementation once loop diuretics are stopped.[40,41] Comorbidities were identified during the baseline period (−360, t0a) using the ICD-9 and ICD-10 coding algorithms for Elixhauser comorbidities (Table S1),[42] and comedications were identified using Anatomical Therapeutic Chemical (ATC) codes (Table S2), which were linked to National Drug Codes.[43]

We also calculated the relative aSR within each stratum by dividing the aSR of one subgroup (e.g., female) by the aSR of the prespecified reference group (e.g., male).[44]

Sensitivity analysis

For evaluating the prescribing cascade, we conducted two sensitivity analyses. First, we adjusted the exposure window length to 90 days before and after index drug prescription to evaluate time-dependent fluctuation in patients' conditions.[20] Second, we excluded patients who initiated both loop diuretics and potassium supplementation on the same day, similar to previous PSSAs.[19]

Prescribing cascade relic

Study population

For evaluating this relic, we identified older adults initiating loop diuretics between 2011 and 2018 with continuous enrollment between −360 days to 180 days of loop diuretic initiation (i.e., $t0_a$).[19] We excluded those receiving potassium supplementation or diagnosed with hypokalemia within −360 days of $t0_a$ to ensure the new use of potassium supplementation was associated with loop diuretic use instead of underlying hypokalemia.[19] We then restricted the population to loop diuretic initiators who initiated potassium supplementation within 30 days of $t0_a$ because we anticipated this prescribing cascade to occur shortly after loop diuretic initiation.[21]

Statistical analysis

We utilized several ways to estimate the occurrence of the relic (i.e., ≥1 day of potassium supplementation supply following the end date of loop diuretic prescription). First, we calculated the proportion of patients who developed the relic of any length and those with the relic of >30 cumulative days (i.e., a total of 30 days of potassium supplementation supply following the end date of loop diuretic prescription) among patients experiencing the loop diuretics-potassium prescribing cascade. Second, we partitioned the observation time, by day, from the date of potassium supplementation initiation (i.e., $t0_b$) through 150 days after $t0_b$, and utilized the Medicare Part D claims data to understand the daily treatment scenarios of each patient (Figure S1).[45,46] Mutually exclusive treatment scenarios included (1) loop diuretics alone; (2) potassium supplementation alone; (3) a combination of loop diuretics and potassium supplementation; (4) neither. While scenarios 1, 3, and 4 are clinically appropriate, scenario 2 (i.e., relic) may be associated with unnecessary drug use. We then calculated the proportion of days at risk (PDR) by dividing the person-days under scenario 2 by person-days among all treatment scenarios (Figure S1).[47] Third, we calculated the proportion of patients using potassium supplementation alone compared with all treatment scenarios by day (i.e., daily probability of the relic)[45] and generated a line graph to show the daily probability of the relic during the 150-day follow-up.

We also conducted two post hoc analyses to minimize the probability of overestimating the risk of the relic. First, we described the mean and median days of supply of loop diuretics and potassium supplementation to evaluate if the relic was a result of the differences in treatment durations. Second, we identified patients who filled a subsequent potassium supplementation and those who initiated a potassium supplement beyond the presumed loop diuretic discontinuation (i.e., date of prescription plus days of supply and a 7-day grace period[48]) to quantify the intentional use of potassium supplementation. For continuous variables, we presented with mean and standard deviation (SD); for categorical variables, we reported number and proportion. In addition, we identified the risk factors of having the relic/having a relic of >30 cumulative days compared with no relic among patients undergoing the prescribing cascade by using logistic regression to calculate the odds ratios (OR) and the 95% CI of the aforementioned covariates used in the subgroup analysis of prescribing cascade (e.g., age, sex, daily dose of loop diuretics, etc).[49]

Sensitivity analyses

When assessing the relic, we repeated the analysis in patients initiating both loop diuretics and potassium supplementation on the same day based on the hypothesis that prescribers who initiated both drugs on the same day may be more aware that these medications need to be taken together, thereby leading to a lower risk of the relic.[40]

RESULTS

Prescribing cascade

We identified 284,369 loop diuretic initiators who met the eligibility criteria (Figure 1). Most patients had a diagnosis of hypertension (90.3%, Table S3), and furosemide was the most commonly initiated loop diuretic (94.0%). Loop diuretic initiators who initiated potassium supplementation within ±180 days (n = 98,266; 34.6%) were over 8 times more likely to receive potassium supplementation simultaneously or after, rather than before, loop diuretic initiation, after adjusting for the prescribing trends (aSR 8.0, 95% CI 7.9–8.2, Table 1), with an estimated incidence of 546 (95% CI 542–550) per 1000 patient-years. This result yielded an asymmetrical prescribing pattern (Figure 2).

Sensitivity analysis restricting the exposure window to 90 days yielded a higher aSR (11.9, 95% CI 11.6–12.2, Table 1) as well as estimated incidence (1059 per 1000 patient-years, 95% CI 1051–1067), compared with the main analysis. When excluding patients who initiated both loop diuretics and potassium supplementation on the same day, the aSR reduced to 2.2 (95% CI 2.1–2.2), with a lower estimated incidence of 95 (95% CI 93–97) per 1000 patient-years.

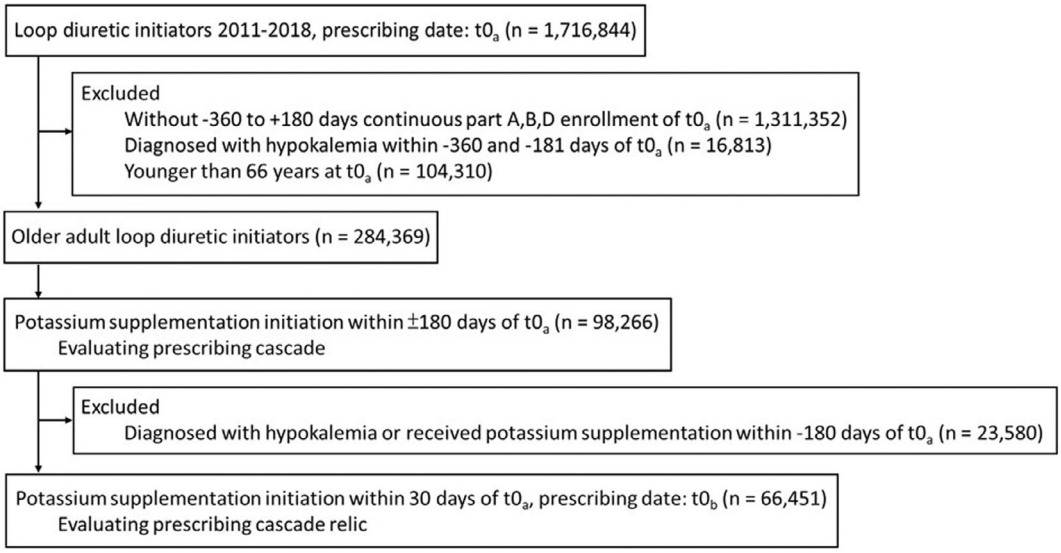

FIGURE 1 Study population selection flowchart.

TABLE 1 Adjusted sequence ratio (aSR) and the estimated incidence of the "loop diuretic–potassium supplementation" prescribing cascade

	aSR (95% CI)	Estimated incidence, per 1000 Loop diuretic initiators–year
180-day exposure window	8.0 (7.9–8.2)	546 (542–550)
180-day exposure window excluding those who initiated both medications on the same day	2.2 (2.1–2.2)	95 (93–97)
90-day exposure window	11.9 (11.6–12.2)	1059 (1051–1067)

Prescribing cascade relic

Of the 284,369 loop diuretic initiators, 66,451 (23.4%) were subsequently prescribed potassium supplementation within 30 days (Figure 1), with potassium chloride (99.6%) being the most common potassium supplement. Among these patients, 20,445 (30.8%) remained on potassium after loop diuretic discontinuation (i.e., relic), including 4814 (7.2%) who received greater than 30 cumulative days of potassium supplementation during follow-up (Table 2). In total, 4.0% of all person-days were exposed to potassium supplementation alone (i.e., PDR) during the 150-day follow-up. In our post hoc analysis, we found that among patients undergoing the relic, the mean and median duration of loop diuretics were 31.8 and 30 days, respectively, similar to those for potassium supplementation (i.e., 32.3 and 30 days, respectively).

We identified 9395 (14.1%) patients who subsequently refilled a potassium supplement after the estimated loop diuretic discontinuation date. Moreover, we found that daily probability of the relic was the highest after day 90 (5.6%) as demonstrated in the line graph (Figure 3).

In multivariable analyses comparing patients with the relic versus those without, age above 85 years (OR, 95% CI 1.3, 1.2–1.4), female sex (1.2, 1.1–1.2), a higher daily dose of loop diuretics (1.2, 1.1–1.2), diagnosis with CHF (1.2, 1.2–1.3), and higher CCI (1.2, 1.1–1.3) were risk factors for the relic (Table 2). By contrast, concordant pharmacies (OR, 0.7; 95% CI, 0.6–0.8) and concordant prescribers (OR, 0.3; 95% CI, 0.3–0.3) were associated with reduced risk of the relic. The proportion of patients experiencing the relic ranged from 27.6% to 35.6% among all subgroups except for those encountering discordant prescribers (60.5%) and discordant pharmacies (56.4%). Similarly, the proportion of patients undergoing the relic for >30 cumulative days ranged from 6.5% to 8.8% among all subgroups except for those encountering discordant prescribers (12.4%) and discordant pharmacies (11.9%).

In sensitivity analyses, we further restricted the study population to 56,661 patients initiating potassium supplementation on the same day as loop diuretics, of which 14,028 (24.8%, Table S4) experienced the relic, 3595 (6.3%) had the relic for >30 cumulative days, and the PDR during the 150-day follow–up was 3.4%, all of which showed a lower risk compared with the main analysis

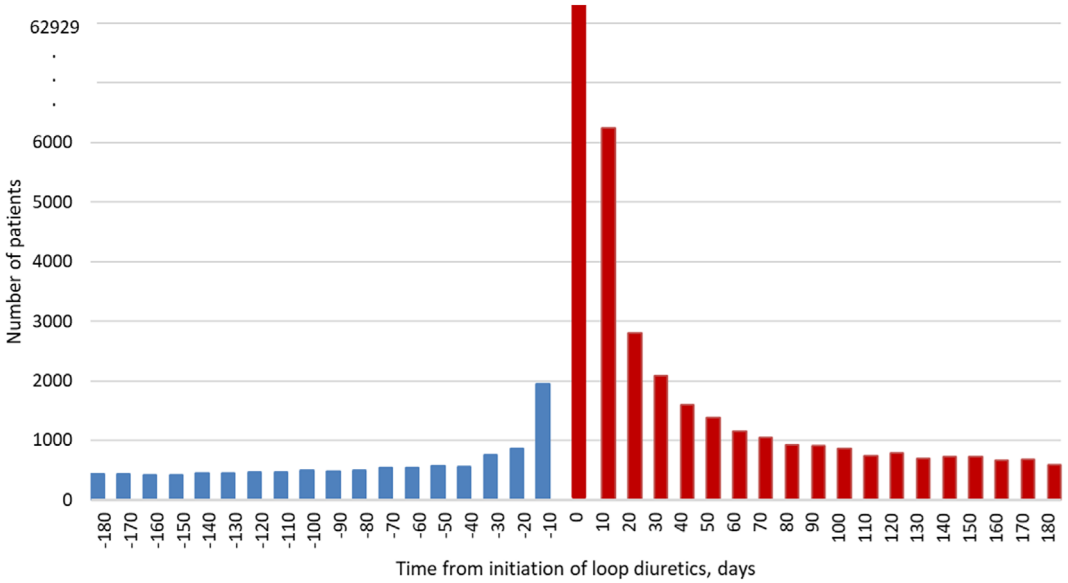

FIGURE 2 Prescribing pattern of potassium supplementation using the initiation of loop diuretics as day 0. Prescription sequence symmetry analysis (PSSA) is a pharmacovigilance approach, which can be used to evaluate prescribing cascades by estimating the excess initiation of the marker drug (e.g., potassium supplementation) to treat the suspected adverse drug event following new use of the index drug (e.g., loop diuretics) when compared to initiation of the marker drug before the index drug. If there is no such relationship between the two drugs, then the probability of initiating a marker drug before or after an index drug are supposed to be equal. Therefore, we would expect a symmetrical prescribing pattern before and after the initiation of index drug. Conversely, if such a relationship exists, then patients are more likely to initiate a marker drug after an index drug than before it, resulting in an asymmetrical prescribing pattern. We found that the prescribing pattern of potassium supplementations using the initiation of loop diuretics as day 0 is asymmetric, suggesting the presence of the "loop diuretic-potassium supplementations" prescribing cascade.

(Figure S2). Risk factors, daily probability of the relic, and the proportion of patients initiating potassium supplementation after loop diuretic discontinuation were similar to the main analysis.

DISCUSSION

As expected, we found that older adult loop diuretic initiators were over 8 times more likely to receive potassium supplementation simultaneously or after, rather than before, loop diuretic initiation, consistent with a high incidence of the "loop diuretic-hypokalemia-potassium supplementation" prescribing cascade. In sensitivity analyses excluding those who initiated loop diuretics and potassium supplementation on the same day, we obtained qualitatively similar results, as well as findings consistent with a previous PSSA conducted in New Zealand, which showed the new use of furosemide was associated with subsequent potassium supplementation initiation (aSR 2.9, 95% CI 2.8–3.1).[50]

More surprisingly, our findings suggested that as many as 1 in 3 loop diuretic initiators undergoing this prescribing cascade continued potassium supplementation during the 150-day follow-up, and the daily probability of the relic was the highest approximately 90 days after potassium supplementation initiation. Even considering a more conservative definition of the relic (>30 cumulative days of potassium supplementation after loop diuretic discontinuation), the relic occurred in up to 7.2% of patients, and 14.1% of patients refilled their potassium supplementation again after the estimated date of loop diuretic discontinuation. Our findings suggest that a potentially significant proportion of patients may not be consistently taking – and importantly, discontinuing – loop diuretics and potassium supplementation concomitantly.

Older age, female sex, a higher daily dose of loop diuretics, and higher CCI were factors associated with the continued use of potassium supplementation after loop diuretic discontinuation (i.e., relic). The potentially unnecessary drug use may result in unnecessary pill burden, hyperkalemia, increasing the risk for diarrhea, abdominal pain, muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias,[51] especially in older adults.[52] Additionally, patients having the same prescriber or pharmacy prescribe or dispense their loop diuretic and potassium prescribing were substantially less likely to experience the relic. We hypothesize that these prescribers and pharmacies may be more cognizant of the co–utilization of these medications and

TABLE 2 Proportion of individuals who remained on potassium after loop diuretic discontinuation among those who had the loop diuretic–potassium prescribing cascade within 30 days of loop diuretic initiation among different strata

			Prescribing cascade Relic		Relic for >30 days	
	Loop diuretic initiators, *n* (%)	Potassium initiation ≤30 days, *n* (%)	*n* (%)	Odds ratio (95% CI)	*n* (%)	Odds ratio (95% CI)
Total	284,369 (100.0)	66,451 (100.0)	20,445 (30.8)	N/A	4814 (7.2)	N/A
Loop diuretic						
Furosemide	267,211 (94.0)	63,529 (95.6)	19,416 (30.6)	Reference	4559 (7.2)	Reference
Bumetanide	8785 (3.1)	1696 (2.6)	603 (35.6)	1.2 (1.1–1.3)	150 (8.8)	1.2 (1.0–1.5)
Torsemide	8373 (2.9)	1226 (1.8)	426 (34.8)	1.2 (1.0–1.3)	105 (8.6)	1.2 (1.0–1.5)
Age (years)						
66–75	110,499 (38.9)	26,547 (40.0)	7422 (28.0)	Reference	1731 (6.5)	Reference
76–85	107,554 (37.8)	24,922 (37.5)	7810 (31.3)	1.1 (1.1–1.2)	1927 (7.7)	1.2 (1.2–1.3)
>85	66,316 (23.3)	14,982 (22.6)	5213 (34.8)	1.3 (1.2–1.4)	1156 (7.7)	1.3 (1.2–1.4)
Sex						
Male	113,200 (39.8)	28,132 (42.3)	8171 (29.1)	Reference	1965 (7.0)	Reference
Female	171,169 (60.2)	38,319 (57.7)	12,274 (32.0)	1.1 (1.1–1.2)	2849 (7.4)	1.1 (1.1–1.2)
Race						
White	247,913 (87.2)	59,423 (89.4)	18,317 (89.6)	Reference	4296 (89.2)	Reference
Black	19,682 (6.9)	3365 (5.1)	1114 (5.5)	1.1 (1.0–1.1)	278 (5.8)	1.2 (1.0–1.4)
Other	3118 (1.1)	713 (1.1)	195 (1.0)	0.8 (0.7–1.0)	48 (1.0)	0.9 (0.7–1.3)
Asian	4456 (1.6)	975 (1.5)	239 (1.2)	0.7 (0.6–0.8)	50 (1.0)	0.7 (0.5–0.9)
Hispanic	6058 (2.1)	1207 (1.8)	360 (1.8)	0.8 (0.7–1.0)	86 (1.8)	1.0 (0.8–1.2)
Native American	936 (0.3)	231 (0.4)	79 (0.4)	1.1 (0.8–1.5)	18 (0.4)	1.2 (0.7–1.9)
Unknown	2206 (0.8)	537 (0.8)	141 (0.7)	0.9 (0.7–1.1)	38 (0.8)	1.1 (0.8–1.5)
Medicaid eligibility	98,191 (34.5)	22,179 (33.4)	7349 (36.0)	1.2 (1.2–1.3)	1546 (32.1)	0.9 (0.9–1.0)
Year						
2011–2013	43,798 (15.4)	10,550 (15.9)	3338 (31.6)	Reference	818 (7.8)	Reference
2014–2016	79,027 (27.8)	18,901 (28.4)	5829 (30.8)	1.0 (0.9–1.0)	1407 (7.4)	0.9 (0.8–1.0)
2017–2018	161,544 (56.8)	37,000 (55.7)	11,278 (30.5)	1.0 (0.9–1.0)	2589 (7.0)	0.8 (0.8–0.9)
Daily dose						
<DDD	180,330 (63.4)	35,821 (53.9)	10,596 (29.6)	Reference	2385 (6.7)	Reference
≥DDD	104,039 (36.6)	30,630 (46.1)	9849 (32.2)	1.2 (1.1–1.2)	2429 (7.9)	1.3 (1.2–1.3)
Comorbidities						
CHF	95,953 (33.7)	22,826 (34.4)	8054 (35.3)	1.2 (1.2–1.3)	1958 (8.6)	1.3 (1.2–1.4)
Hypertension	256,727 (90.3)	59,201 (89.1)	18,395 (31.1)	1.0 (1.0–1.1)	4343 (7.34)	1.1 (0.9–1.2)
Alcohol abuse	7179 (2.5)	1528 (2.3)	495 (32.4)	1.1 (1.0–1.2)	112 (7.3)	1.0 (0.8–1.3)
Diabetes	116,663 (41.0)	25,333 (38.1)	7831 (30.9)	1.0 (0.9–1.0)	1865 (7.4)	1.0 (0.9–1.1)
Liver disease	5868 (2.1)	1012 (1.5)	349 (34.5)	1.1 (0.9–1.2)	78 (7.7)	1.1 (0.9–1.4)
Renal failure	73,930 (26.0)	13,176 (19.8)	4377 (33.2)	1.0 (0.9–1.0)	975 (7.4)	1.0 (0.9–1.0)
Comedications						
RAAS inhibitors	184,021 (64.7)	42,020 (63.2)	13,144 (31.3)	1.0 (1.0–1.1)	3170 (7.5)	1.1 (1.0–1.2)
Oral steroids	153,838 (54.1)	36,008 (54.2)	11,291 (31.4)	1.1 (1.0–1.1)	2653 (7.4)	1.1 (1.0–1.1)

(Continues)

TABLE 2 (Continued)

	Loop diuretic initiators, *n* (%)	Potassium initiation ≤30 days, *n* (%)	Prescribing cascade Relic		Relic for >30 days	
			n (%)	Odds ratio (95% CI)	*n* (%)	Odds ratio (95% CI)
NSAIDs	84,634 (29.8)	19,703 (29.7)	5887 (29.9)	1.0 (0.9–1.0)	1433 (7.3)	1.0 (1.0–1.1)
CCI						
3–6	104,642 (36.8)	26,299 (39.6)	7259 (27.6)	Reference	1781 (6.8)	Reference
7–10	129,176 (45.4)	30,154 (45.4)	9674 (32.1)	1.1 (1.0–1.1)	2237 (7.4)	1.0 (0.9–1.1)
>11	50,551 (17.8)	9998 (15.1)	3512 (35.1)	1.2 (1.1–1.3)	796 (8.0)	1.1 (0.9–1.2)
Concordant pharmacies	–	65,044 (97.9)	19,652 (30.2)	0.7 (0.6–0.8)	4646 (7.1)	0.8 (0.7–1.0)
Concordant prescribers	–	60,991 (91.8)	17,144 (28.1)	0.3 (0.2–0.3)	4136 (6.8)	0.3 (0.3–0.3)

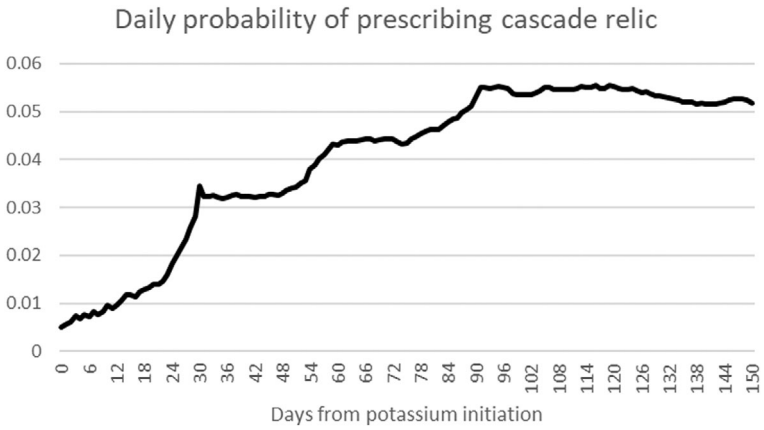

FIGURE 3 Line graph showing the daily probability of the prescribing cascade relic. The daily probability of the prescribing cascade relic (i.e., the proportion of potassium supplementation alone compared with all treatment scenarios) ranged from 0.005 to 0.055 (IQR: 0.021), which was the highest after day 90 of potassium supplementation initiation

may respond accordingly. Therefore, it is important for prescribers and pharmacies, especially those involved in both medications, to ask further questions to patients who take potassium supplementation despite no use of loop diuretics (e.g., history of diuretic use, recent potassium levels, etc).[53]

Strengths and limitations

In this study, we defined a new terminology to describe the continuation of the medication used to treat the adverse drug event (e.g., potassium supplementation) while the medication causing the adverse event (e.g., loop diuretics) is stopped, and we also described its occurrence and predictors using a nationally representative sample of the patients who were more likely to experience the prescribing cascade and relic. In addition, the results remained robust in subgroup analyses and sensitivity analyses. Therefore, this approach can be used as a framework to evaluate a prescribing cascade relic.

Our study also has several limitations. First, we used Medicare Part D data to determine patients' exposure to medications. Similar to other studies conducted using claims databases, prescription fills may not reflect perfect adherence, which may result in misclassification bias (i.e., we do not know whether patients were advised by their clinicians to stop potassium after loop diuretic discontinuation).[54] Second, we cannot determine if the continuation of potassium supplementation after discontinuing loop diuretics resulted from the relic or patients' underlying illnesses because we cannot identify serum levels of potassium from the claims database.[55] However, we excluded patients with prior hypokalemia to minimize the effect of their baseline conditions. In the future, we also plan to investigate whether a serum potassium lab was completed after prescribing cascade occurred. Third, loop diuretics may have been used intermittently and potassium supplementation used routinely, which may result in the occurrence of the relic but not a high potassium supplementation initiation rate after the presumed loop diuretic discontinuation. Fourth, the difference in the days supply between

loop diuretics and potassium supplementation could lead to overestimation of the relic when the treatment duration of potassium supplementation is longer than that of loop diuretics; however, we found that the mean and median duration of the two medications were similar. Fifth, even with the same days of supply, asynchronous medication refills may also result in overestimation of the relic when potassium supplementation is prescribed later than loop diuretics. However, our rates were only slightly reduced when restricting to patients who initiated loop diuretics and potassium supplementation on the same day.

CONCLUSIONS

Our findings confirm the high incidence of a loop diuretic-potassium supplementation prescribing cascade, with up to one–third of patients in this setting continuing to receive potassium supplementation despite loop diuretic discontinuation (i.e., relic). Older age, being female, higher daily dose of loop diuretics, and more comorbidities were risk factors of the relic, while patients having the same prescriber or pharmacy involved in their loop diuretic and potassium use were less likely to experience the relic. Clinicians should be aware of relic to avoid unnecessary drug use.

AUTHOR CONTRIBUTIONS

Scott M. Vouri initiated the collaborative project and developed the research question. Grace Hsin-Min Wang and Scott M. Vouri designed the study protocol, and drafted the manuscript. Scott M. Vouri is the guarantor. Grace Hsin-Min Wang, Earl J. Morris, Steven M. Smith, Jesper Hallas, and Scott M. Vouri edited the study protocol, interpreted the results, and reviewed the manuscript. Grace Hsin-Min Wang and Earl J. Morris wrote the statistical analysis plan and Grace Hsin-Min Wang conducted the statistical analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

FUNDING INFORMATION

Funding was provided by a K08 Career Development award from the National Institute on Aging (K08AG066854).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SPONSOR'S ROLE

The funding sources had no role in the study design, data collection, and analysis, manuscript preparation, or the decision to submit the manuscript for publication.

ORCID

Earl J. Morris https://orcid.org/0000-0002-6092-8906
Scott M. Vouri https://orcid.org/0000-0002-0411-2160

TWITTER

Scott M. Vouri *@VouriPharmD*

REFERENCES

1. Rochon PA, Gurwitz JH. The prescribing cascade revisited. *Lancet*. 2017;389(10081):1778-1780.
2. Vouri SM, Van Tuyl JS, Olsen MA, Xian H, Schootman M. An evaluation of a potential calcium channel blocker–lower-extremity edema–loop diuretic prescribing cascade. *J Am Pharm Assoc*. 2018;58(5):534-539. e4.
3. Vouri SM, Morris EJ, Wang GHM, Hashim Jaber Bilal A, Hallas J, Henriksen DP. Association between gabapentinoids and oedema treated with loop diuretics: a pooled sequence symmetry analysis from the USA and Denmark. *Br J Clin Pharmacol*. 2022;31(1):72-81.
4. Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med*. 2005;165(7):808-813.
5. Morris EJ, Hollmann J, Hofer A-K, et al. Evaluating the use of prescription sequence symmetry analysis as a pharmacovigilance tool: a scoping review. *Res Soc Adm Pharm*. 2021;18(7):3079-3092.
6. Huxel C, Raja A, Ollivierre-Lawrence MD. Loop diuretics. *StatPearls [Internet]*. StatPearls Publishing; 2021.
7. McCarthy LM, Visentin JD, Rochon PA. Assessing the scope and appropriateness of prescribing cascades. *J Am Geriatr Soc*. 2019;67(5):1023-1026. doi:10.1111/jgs.15800
8. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on potassium in clinical practice. *Arch Intern Med*. 2000;160(16):2429-2436.
9. Bain KT, Holmes HM, Beers MH, Maio V, Handler SM, Pauker SG. Discontinuing medications: a novel approach for revising the prescribing stage of the medication-use process. *J Am Geriatr Soc*. 2008;56(10):1946-1952. doi:10.1111/j.1532-5415.2008.01916.x
10. Rohde LE, Rover MM, Figueiredo Neto JA, et al. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. *Eur Heart J*. 2019;40(44):3605-3612. doi:10.1093/eurheartj/ehz554
11. Viana M, Laszczynska O, Mendes S, et al. Medication adherence to specific drug classes in chronic heart failure. *J Manag Care Pharm*. 2014;20(10):1018-1026.
12. Mues KE, Liede A, Liu J, et al. Use of the Medicare database in epidemiologic and health services research: a valuable source of real-world evidence on the older and disabled populations in the US. *Clin Epidemiol*. 2017;9:267-277. doi:10.2147/CLEP.S105613
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet (London, England)*. 2007;370(9596):1453-1457. doi:10.1016/s0140-6736(07)61602-x

14. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology*. 1996;7(5):478-484.
15. Lai ECC, Yang YHK, Lin SJ, Hsieh CY. Use of antiepileptic drugs and risk of hypothyroidism. *Pharmacoepidemiol Drug Saf*. 2013;22(10):1071-1079.
16. Cadarette SM, Maclure M, Delaney JAC, et al. Control yourself: ISPE-sponsored guidance in the application of self-controlled study designs in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2020;30(6):671-684.
17. Wahab IA, Pratt NL, Wiese MD, Kalisch LM, Roughead EE. The validity of sequence symmetry analysis (SSA) for adverse drug reaction signal detection. *Pharmacoepidemiol Drug Saf*. 2013;22(5):496-502.
18. Vouri SM, Morris EJ, Usmani SA, et al. Evaluation of the key prescription sequence symmetry analysis assumption using the Calcium Channel blocker - loop diuretic prescribing Cascade. *Pharmacoepidemiol Drug Saf*. 2021;31:72-81. doi:10.1002/pds.5362
19. Vouri SM, Jiang X, Manini TM, et al. Magnitude of and characteristics associated with the treatment of calcium channel blocker–induced lower-extremity edema with loop diuretics. *JAMA Netw Open*. 2019;2(12):e1918425.
20. Lai EC-C, Pratt N, Hsieh C-Y, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. *Eur J Epidemiol*. 2017;32(7):567-582.
21. Leonard CE, Razzaghi H, Freeman CP, Roy JA, Newcomb CW, Hennessy S. Empiric potassium supplementation and increased survival in users of loop diuretics. *PLoS One*. 2014;9(7):e102279.
22. Takeuchi Y, Shinozaki T, Matsuyama Y. A comparison of estimators from self-controlled case series, case-crossover design, and sequence symmetry analysis for pharmacoepidemiological studies. *BMC Med Res Methodol*. 2018;18(1):4. doi:10.1186/s12874-017-0457-7
23. Trenaman SC, Bowles SK, Kirkland S, Andrew MK. An examination of three prescribing cascades in a cohort of older adults with dementia. *BMC Geriatr*. 2021;21(1):297. doi:10.1186/s12877-021-02246-2
24. Cox JR, Shalaby WA. Potassium changes with age. *Gerontology*. 1981;27(6):340-344. doi:10.1159/000212495
25. Liu J, Li Q, Ren J, Liang X, Zhang Q, Han Y. Association of sex with serum potassium, sodium, and calcium disorders after hypertensive intracerebral hemorrhage. *World Neurosurg*. 2020;141:e367-e373. doi:10.1016/j.wneu.2020.05.137
26. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. 2014;7(2):261-270.
27. WHO Collaborating Centre for Drug Statistics Methodology [Internet]. DDD Definition and general considerations. [cited May 3, 2022]. Available from: https://www.whocc.no/ddd/definition_and_general_considera/
28. Viera AJ, Wouk N. Potassium disorders: hypokalemia and hyperkalemia. *Am Fam Physician*. 2015;92(6):487-495.
29. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes: a Danish population-based cohort study. *J Am Heart Assoc*. 2018;7(11):e008912.
30. Burrello J, Monticone S, Losano I, et al. Prevalence of hypokalemia and primary aldosteronism in 5100 patients referred to a tertiary hypertension unit. *Hypertension*. 2020;75(4):1025-1033.
31. Elisaf M, Liberopoulos E, Bairaktari E, Siamopoulos K. Hypokalaemia in alcoholic patients. *Drug Alcohol Rev*. 2002;21(1):73-76.
32. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. *World J Clin Cases*. 2014;2(10):488-496. doi:10.12998/wjcc.v2.i10.488
33. Jiménez JV, Carrillo-Pérez DL, Rosado-Canto R, et al. Electrolyte and Acid-Base disturbances in end-stage liver disease: a Physiopathological approach. *Dig Dis Sci*. 2017;62(8):1855-1871. doi:10.1007/s10620-017-4597-8
34. Gilligan S, Raphael KL. Hyperkalemia and hypokalemia in CKD: prevalence, risk factors, and clinical outcomes. *Adv Chronic Kidney Dis*. 2017;24(5):315-318. doi:10.1053/j.ackd.2017.06.004
35. Raebel MA. Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Cardiovasc Ther*. 2012;30(3):e156-e166. doi:10.1111/j.1755-5922.2010.00258.x
36. McKay L, Cidlowski J. Physiologic and pharmacologic effects of corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., eds. *Holland-Frei Cancer Medicine*. BC Decker; 2003:6.
37. Sahil F, Kumar J, Raiz G, et al. Association between long-term use of non-steroidal anti-inflammatory drugs and hyperkalemia in diabetic patients. *Cureus*. 2021;13(6):e15648.
38. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *J Clin Epidemiol*. 1996;49(12):1429-1433.
39. Tafesse E, Hurst M, Sugrue D, et al. Serum potassium as a predictor of adverse clinical outcomes in patients with increasing comorbidity burden. *Eur Heart J Qual Care Clin Outcomes*. 2022;8(1):61-69. doi:10.1093/ehjqcco/qcaa078
40. Farrell BJ, Jeffs L, Irving H, McCarthy LM. Patient and provider perspectives on the development and resolution of prescribing cascades: a qualitative study. *BMC Geriatr*. 2020;20(1):368. doi:10.1186/s12877-020-01774-7
41. Anderson TS, Steinman MA. Antihypertensive prescribing cascades as high-priority targets for deprescribing. *JAMA Intern Med*. 2020;180(5):651-652.
42. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
43. Kury FS, Bodenreider O. Mapping US FDA National Drug Codes to Anatomical-Therapeutic-Chemical Classes using RxNorm. 2017.
44. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326(7382):219.
45. Bykov K, Franklin JM, Li H, Gagne JJ. Comparison of self-controlled designs for evaluating outcomes of drug-drug interactions: simulation study. *Epidemiology*. 2019;30(6):861-866. doi:10.1097/ede.0000000000001087
46. Wang GH-M, Man KK, Chang W-H, Liao T-C, Lai EC-C. Use of antipsychotic drugs and cholinesterase inhibitors and risk of falls and fractures: self-controlled case series. *BMJ*. 2021;374:n1925.

47. Nau DP. *Proportion of days covered (PDC) as a preferred method of measuring medication adherence*. Vol 6. Pharmacy Quality Alliance; 2012:25.
48. Parker MM, Moffet HH, Adams A, Karter AJ. An algorithm to identify medication nonpersistence using electronic pharmacy databases. *J Am Med Inform Assoc*. 2015;22(5):957-961. doi:10.1093/jamia/ocv054
49. Szumilas M. Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry*. 2010;19(3):227-229.
50. Nishtala P, Ty C. Exploring New Zealand prescription data using sequence symmetry analyses for predicting adverse drug reactions. *J Clin Pharm Ther*. 2017;42(2):189-194.
51. Montford JR, Linas S. How dangerous is hyperkalemia? *J Am Soc Nephrol*. 2017;28(11):3155-3165.
52. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol*. 2017;245:277-284. doi:10.1016/j.ijcard.2017.07.035
53. Safety FP. *Pharmacists' Role in Medication without Harm*. International Pharmaceutical Federation; 2020.
54. Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. *BMC Med Res Methodol*. 2019;19(1):53. doi:10.1186/s12874-019-0695-y
55. Schneeweiss S, Rassen JA, Glynn RJ, et al. Supplementing claims data with outpatient laboratory test results to improve confounding adjustment in effectiveness studies of lipid-lowering treatments. *BMC Med Res Methodol*. 2012;12:180. doi:10.1186/1471-2288-12-180

SUPPORTING INFORMATION

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

Figure S1. Illustration of the daily treatment scenarios.

Figure S2. Line graph showing the daily probability of the prescribing cascade relic, restricting to patients who initiated both medications on the same day.

Table S1. ICD codes included.

Table S2. ATC codes of the study drugs.

Table S3. Prescribing Sequence of Initial Potassium Supplementation and Initial Loop Diuretics.

Table S4. Proportion of individuals developing the prescribing cascade relic after experiencing the "loop diuretic–potassium supplementation" prescribing cascade on the same day of loop diuretic initiation among different strata (sensitivity analysis).

How to cite this article: Wang GH-M, Morris EJ, Smith SM, Hallas J, Vouri SM. Continued potassium supplementation use following loop diuretic discontinuation in older adults: An evaluation of a prescribing cascade relic. *J Am Geriatr Soc*. 2022;1-11. doi:10.1111/jgs.18103