Received: 16 November 2022 | Revised: 19 January 2023 | Accepted: 28 February 2023

DOI: 10.1002/pds.5607

ORIGINAL ARTICLE

WILEY

High-throughput screening for prescribing cascades among real world statin initiators

Scott M. Vouri[1] | Earl J. Morris[1] | Marta Walsh[1] | Jessica Agalliu[2] | Alyssa Dempsey[2] | Leonie Hochleitner[1] | Matthew R. Muschett[1] | Stephan Schmidt[3] | Carl J. Pepine[4,5] | Steven M. Smith[1,4,5]

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

[2]College of Pharmacy, University of Florida, Gainesville, Florida, USA

[3]Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, Florida, USA

[4]Division of Cardiovascular Medicine, Department of Medicine, College of Medicine, University of Florida, Gainesville, Florida, USA

[5]Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville, Florida, USA

Correspondence
Steven M. Smith, Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida, PO Box 100496, Gainesville, FL 32610-0496, USA.
Email: ssmith@cop.ufl.edu

Funding information
UF College of Pharmacy

Abstract

Purpose: Statins are among the most prevalent medications prescribed and associated with adverse events that may prompt additional treatment (i.e., a prescribing cascade). No comprehensive assessment of statin-related prescribing cascades has been performed to our knowledge.

Methods: We utilized sequence symmetry analysis to iteratively screen prescribing sequences of all therapeutic classes ("marker" classes) based on Level 4 Anatomical Therapeutic Chemical codes among adult statin initiators, using IBM Marketscan commercial and Medicare supplemental claims databases (2005–2019). Order of initiation and secular trend-adjusted sequence ratios were calculated for each statin-marker class dyad, among marker class initiators ±90 days of statin initiation. Among signals classified as prescribing cascades, we calculated naturalistic number needed to harm (NNTH) within 1 year as the inverse of the excess risk among exposed.

Results: We identified 2 265 519 statin initiators (mean ± *SD* age, 56.4 ± 12.0 years; 48.7% women; 7.5% with cardiovascular disease). Simvastatin (34.4% of statin initiators) and atorvastatin (33.9%) were the most commonly initiated statins. We identified 160 significant statin-marker class dyad signals, of which 35.6% ($n = 57$) were classified as potential prescribing cascades. Of the top 25 strongest signals (lowest NNTH), 12 were classified as potential prescribing cascades, including osmotically acting laxatives (NNTH, 44, 95% CI 43–46), opioids + non-opioid combination analgesics (81, 95% CI 74–91), and first-generation cephalosporins (204, 95% CI 175–246).

Conclusions: Using high-throughput sequence symmetry analysis screening, we identified previously known prescribing cascades as well as potentially new prescribing cascades based on known and unknown statin-related adverse events.

KEYWORDS
HMG-CoA reductase inhibitors, prescribing cascade, sequence symmetry analysis, statins

Dr. Scott M. Vouri worked for the University of Florida at the time this study was conducted; he is now an employee of Pfizer. Ms. Marta Walsh worked for the University of Florida at the time this study was conducted; she is now an employee of the Mayo Clinic (Rochester, MN).

Prior presentations: Preliminary results from this project were previously presented at the International Conference for Pharmacoepidemiology, Copenhagen, Denmark, August, 2022.

Key Points

- A prescribing cascade occurs when an initial therapy (e.g., a statin) causes some adverse event (e.g., myopathy) that prompts use of an additional therapy (e.g., analgesic).
- Using prescription sequence symmetry analysis on ~2.3 million statin initiators, we screened 524 medication classes to detect occurrence of statin-related prescribing cascades and identified 160 (31%) having a prescribing cascade signal
- Among these signals, 57 (36%) were classified as potentially true prescribing cascades based on expert review
- Of the top 25 strongest signals (lowest number needed to harm), 12 were classified as potential prescribing cascades, including osmotically acting laxatives, opioids/non-opioid combination analgesics, and first-generation cephalosporins.

Plain Language Summary

Statins are among the most commonly-prescribed medications and are associated with side effects that are sometimes treated with other medications (a "prescribing cascade"). Among adult new statin users, we assessed prescribing sequences of statin and 524 other therapeutic "marker" classes. Order of initiation (statin then marker or vice-versa) and sequence ratios were calculated for each combination. Among positive signals (i.e., those with a higher ratio of patients who started the marker after the statin than before the statin), we calculated the naturalistic number needed to harm (NNTH), a measure of how many people would need to initiate a statin for one person to experience the prescribing cascade within 1 year. We identified 2 265 519 statin initiators (mean age, 56.4 years; 49% women; 7.5% with cardiovascular disease). Simvastatin and atorvastatin (each 34% of statin initiators) were the most commonly initiated statins. We identified 160 significant statin-marker class signals, of which 35.6% ($n = 57$) were considered potential prescribing cascades by expert reviewers. Of the top 25 strongest signals (lowest NNTH), 12 were potential prescribing cascades, including osmotically acting laxatives, opioids + non-opioid combination pain medications, and cephalosporin antibiotics. Herein, we confirmed known prescribing cascades and identified potentially new prescribing cascades from statin-related adverse events.

1 | INTRODUCTION

HMG-CoA reductase inhibitors (statins) are a cornerstone for primary and secondary atherosclerotic cardiovascular disease (ASCVD) prevention.[1] In 2013, greater than 1 in 4 adults received ≥1 statin prescription, totaling >221 million prescriptions filled within that year in the United States alone.[2] Statins are generally well-tolerated; however, their ubiquitous use exposes millions of individuals to potentially treatment-limiting adverse events.[3] The most well-known adverse event is myalgia, occurring in ~5% of statin initiators, although estimates are higher in older adults.[4] Because of the notoriety of this adverse event, myalgias comprise nearly three-quarters of all statin-related adverse events reported by physicians.[5] Other lesser known or unknown statin-related adverse events may go undetected, prompting subsequent prescribing of a new medication to treat statin-related adverse events – a phenomenon known as a prescribing cascade.[6–8]

Cardiovascular-related prescribing cascades are considered high priority targets for deprescribing.[9] To date, seven statin-related prescribing cascades have been described (Table S1 in the supplement).[10–17] However, many of these cascades reflect known adverse events observed in large clinical trials or from spontaneous adverse event reporting and thus may have been expected. Although these hypothesis-driven approaches provide clinically important insight into the presence and magnitude of prescribing cascades, they are not designed to discover new cascades, particularly those unrelated to previously known statin adverse events. Given the expansive use of statins and the few known statin-related prescribing cascades, additional statin-related prescribing cascades likely exist and signals of such cascades may be detectable via high-throughput screening approaches. Discovery of new cascades could facilitate clinical support systems to prevent and mitigate statin-related prescribing cascades and increase rates of deprescribing for one of the most utilized medication classes in adults. Therefore, we aimed to implement a high-throughput signal detection program, using the sequence symmetry analysis (SSA), to identify potential statin-related prescribing cascades using real-world data among patients with commercial insurance and/or Medicare supplemental coverage.

2 | METHODS

2.1 | Data sources

We used MarketScan Commercial and Medicare Supplemental Claims databases (IBM Corp) from January 2005 to December 2019. These

US nationwide administrative claims databases contain deidentified person-level information on employees, their dependents, and retirees with employer-sponsored or Medicare Supplemental insurance and capture health care utilization and enrollment records across various settings, including outpatient visits, hospital stays, and pharmacy claims. The study was considered exempt by the University of Florida institutional review board. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline to ensure appropriate reporting.[18]

2.2 | Design

We used high-throughput SSA screening to identify potential statin-related prescribing cascades.[19,20] This hypothesis-free pharmacovigilance approach uses a case-only study design to assess temporality of an index drug initiation (i.e., statin) relative to initiation of all other "marker" drugs (i.e., all other medication classes) hereafter referred to as statin-marker class dyads.[21,22] Included patients were statin initiators (see Table S2 for complete list of statin products), who had their first statin fill between 2007–2018, inclusive, were aged ≥20 years at statin initiation, and had ≥720 days of continuous enrollment before and ≥360 days after statin initiation. These continuous enrollment requirements were chosen to ensure true new use of statins, to capture all marker drug use during the year prior to and after statin initiation, and to meet requirements for sensitivity analyses (described further below).

We used Anatomical Therapeutic Chemical (ATC) codes to group marker drugs hierarchically into medication classes for high-throughput screening. The ATC classification system is maintained by the World Health Organization and classifies medications into groups at 5 levels, where Level 1 indicates the broad anatomical group ($n = 14$ total), Level 4 indicates the chemical subgroup/drug class (see Table S3 for example), and Level 5 indicates the specific drug/chemical substance ($n \approx 5000$ total). Among statin initiators, we identified the first claim for any marker drug within a given ATC Level 4 subgroup. In other words, if an individual filled multiple different medications (unique ATC Level 5) within a given ATC Level 4 subgroup, we only included the date of first fill within the ATC Level 4 subgroup. Next, we required the marker drug initiation to occur within ±90 days of statin initiation for the primary analysis as to focus on acute onset adverse events.[23] In sensitivity analyses, we extended that window to ±180 and ±360 days to assess for adverse events with longer induction periods. Patients were excluded if they had a claim for any drug within the same marker drug class in the 720 to 361 days prior to statin initiation. For each ATC Level 4 subgroup, all included patients in the statin-marker drug dyad were evaluated using the SSA. These analyses were completed iteratively until all ATC Level 4 subgroups were evaluated. Baseline characteristics (age, sex, calendar year of statin initiation, Charlson Comorbidity Index, specific statin medication, statin intensity, or if a combination product) of statin initiators were measured at the time of statin initiation or in the 360 days prior to statin initiation (Tables S4 and S5).[24,25]

2.3 | Analyses

For each unique statin-marker class dyad, we determined the crude sequence ratio (cSR) as the number of patients who initiated the marker class after statin initiation divided by the number of patients who initiated the marker class before the statin. Excess initiation of a marker class after the statin, relative to before the statin, results in a cSR >1 and may indicate presence of a prescribing cascade.

Each statin-marker class dyad was represented graphically by plotting the distribution of timing of marker class initiation (in 10-day intervals), relative to statin initiation, for each exposure window (±90, 180, 360 days) surrounding statin initiation. To adjust for secular trends in medication use (i.e., increasing or decreasing use of statins or marker drugs during the study period), we calculated a null-effect ratio, which is essentially the odds ratio of the exposure occurring prior to the event in the source population and which accounts for the sequence ratio that would be expected absent any causal association (i.e., due to incident medication use trends).[26] We then estimated an adjusted sequence ratio (aSR) with 95% confidence interval (CI) by dividing the cSR by the null-effect ratio. All aSRs with a lower CI limit >1 were considered statistically significant under the assumption that no within-person time-varying bias exists.[27]

For each statin-marker class dyad considered statistically significant, we estimated excess risk among exposed and corresponding naturalistic number needed to harm (NNTH) within 1 year. The NNTH represents the number of patients needed to be exposed (to the index drug, i.e., a statin) for one additional patient to experience the prescribing cascade by initiating the marker drug.[20,28] Excess risk among exposed was calculated as the difference between the number of patients initiated on the marker class after statin initiation and the number of patients initiated on the same marker class before statin initiation, divided by the total number of statin initiators, standardized to a rate per 1000 person-years accounting for a 90-day exposure window in the primary analysis. The NNTH was calculated as the inverse of the excess risk among exposed, that is, the number of patients needed to be treated with a statin to experience one prescribing cascade within that marker class.[20]

2.4 | Classification of signals

All statistically significant signals (aSRs with 95% CIs >1) in the primary analysis underwent manual review through a systematic process to differentiate potential prescribing cascades from false positive signals, which could have been due to detection bias (i.e., new condition identified with corresponding new medication initiated during routine monitoring of statin), disease progression (i.e., new medications initiated to treat progression of underlying cardiovascular disease), therapeutic escalation (i.e., escalation of therapy [2nd or 3rd line treatments] in conditions unrelated to statin indication), or reverse causation (i.e., decreased statin initiation following the initiation of marker class [e.g., reduced statin treatment following cancer treatment]).[21,22] Signals not thought to represent potential prescribing

cascades were classified as "Other" when assessing for signal classification as these false positive signals may be due to multiple biases. Manual review was conducted in two stages. First, pharmacy trainees ($n = 4$) were trained by one of the principal investigators (SMV) in the use of primary (e.g., PubMed/MEDLINE searches), secondary (e.g., drug monographs, package inserts), tertiary (e.g., drug information databases) drug information sources for assessing potential prescribing cascades and their underlying mechanisms to support signal classification. Two pharmacy trainees reviewed each significant signal and assigned it an initial classification, as described above, along with supporting literature. These two pharmacy trainees independently developed material to provide literature support (i.e., findings and citations) for each significant signal including possible underlying mechanism(s) (i.e., putative statin-induced adverse events that might prompt marker drug use). Trainees then assigned an initial classification, as described above, for each signal. Two principal investigators with clinical expertise in cardiometabolic disease and aging (SMS, SMV) then independently classified each signal using material developed by pharmacy trainees and ad hoc literature evaluations, when needed. Agreement and a kappa statistic were generated between the two principal investigator reviewers. Finally, consensus was made by the principal investigators via discussion when disagreements occurred.

All analyses were conducted using SAS statistical software version 9.4 (SAS Institute). The hypothesis was 2-sided with an $\alpha < 0.05$, and aSR with a confidence interval range >1 considered statistically significant. Tableau Desktop 2021.2 was used to visualize results in an interactive fashion. Data were analyzed from March 2021 through February 2022.

3 | RESULTS

We identified 2 290 011 distinct statin initiators. The mean ± *SD* age of the cohort was 56.4 ± 12.0 years, and the cohort was comprised of 19.3% ($n = 442\,288$) patients aged ≥65 years, 48.7% women ($n = 1\,114\,591$), and 7.5% ($n = 171\,189$) had evidence of cardiovascular disease (Table 1). Simvastatin was the most commonly initiated statin (34.4%; $n = 788\,467$), followed by atorvastatin (33.9%; $n = 775\,503$) and pravastatin (14.0%; $n = 319\,628$). Only 2.9% ($n = 66\,336$) of patients initiated a statin as part of a fixed-dose combination product. Results of the high-throughput SSA screening are displayed interactively at: https://public.tableau.com/app/profile/cvmedlab/viz/ResultsofthehighthroughputSSAscreening/TableofContentsFlowchart.

Among the 524 ATC Level 4 subgroup marker drug classes in the primary analysis, 160 had a statistically significant aSR >1 (Table S6). Among these significant signals, agreement on signal classification (e.g., "Potential Prescribing Cascade" or "Other") between the two investigator reviewers was 83.75% ($\kappa = 0.63$). In total, 35.6% ($n = 57$) of the 160 statin-marker class dyad prescribing cascade signals were classified as potential prescribing cascades. When categorized at ATC Level 1, the most prevalent potential prescribing cascades belonged to the Alimentary Tract and Metabolism Anatomical group ($n = 17$), followed by the Nervous System group ($n = 12$). As shown in Figure 1, of the top 25 strongest significant signals (as ranked by aSR), 10 were classified as potential prescribing cascades, including polymyxins (aSR, 5.16, 95% CI 1.18–22.55), zinc (aSR, 2.62, 95% CI 1.42–4.87), and magnesium (aSR, 2.62, 95% CI 1.74–3.93). Figure 2 summarizes the top 25 statistically significant signals ranked by lowest NNTH. Among these, 12 were classified as potential prescribing cascades, including osmotically acting laxatives (NNTH 44, 95% CI 43–46), opioids in combination with non-opioid analgesics (NNTH 81, 95% CI 74–91), and first generation cephalosporins (NNTH 204, 95% CI 175–246). Other relevant potential statin-marker class

TABLE 1 Baseline characteristics of statin initiators included in the cohort.

Characteristics	Statin initiators ($n = 2\,290\,011$)
Age, years	
<65	1 847 723 (80.7)
≥65	442 288 (19.3)
Sex	
Male	1 175 420 (51.3)
Female	1 114 591 (48.7)
Calendar year	
2005–2010	923 284 (40.3)
2011–2014	821 998 (35.9)
2015–2019	544 729 (23.8)
Charlson comorbidity index	
0	119 936 (5.2)
1–2	936 228 (40.9)
3–4	934 049 (40.8)
≥5	299 798 (13.1)
Other comorbid conditions	
Atherosclerotic cardiovascular disease	171 189 (7.5)
Liver disease	107 334 (4.7)
Kidney disease	178 431 (7.8)
Statin intensity	
Low	420 023 (18.3)
Moderate	1 627 678 (71.1)
High	242 310 (10.6)
Statin Type	
Simvastatin	788 467 (34.4)
Lovastatin	91 074 (4.0)
Pravastatin	319 628 (14.0)
Fluvastatin	2546 (0.1)
Atorvastatin	775 503 (33.9)
Rosuvastatin	238 794 (10.4)
Pitavastatin	7663 (0.3)
Statin combination drugs	66 336 (2.9)

ATC4 Marker Class	Total N Prescribed Statin & Marker Drug	Marker After	Marker Before	Adjusted SR (95% CI)	PC Classification
Polymyxins (J01XB)	17	15	2	5.16 (1.18-22.55)	Potential PC
Vasopressin antagonists (C03XA)	11	8	3	3.93 (1.04-14.81)	Other
Other alkylating agents (L01AX)	113	84	29	2.86 (1.88-4.37)	Other
Zinc (A12CB)	50	36	14	2.62 (1.42-4.87)	Potential PC
Magnesium compounds (A02AA)	117	85	32	2.62 (1.74-3.93)	Potential PC
EGFR tyrosine kinase inhibitors (L01EB)	59	42	17	2.60 (1.48-4.56)	Other
Magnesium (A12CC)	157	111	46	2.50 (1.77-3.52)	Potential PC
Enzymes (B06AA)	244	171	73	2.38 (1.81-3.14)	Other
Dantrolene and derivatives (M03CA)	49	34	15	2.23 (1.21-4.09)	Potential PC
Vitamin K (B02BA)	561	388	173	2.21 (1.84-2.64)	Other
Antihypertensives for pulmonary arterial hypertension (C02KX)	67	45	22	2.14 (1.29-3.57)	Other
Gonadotropins (G03GA)	60	41	19	2.11 (1.22-3.63)	Other
Androgens & female sex hormones in combinations (G03EK)	48	32	16	2.03 (1.11-3.70)	Other
Antiarrhythmics, class Ib (C01BB)	300	205	95	2.03 (1.59-2.59)	Other
Other antianemic preparations (B03XA)	475	319	156	1.99 (1.64-2.41)	Other
Sodium (A12CA)	124	83	41	1.92 (1.32-2.79)	Other
Estrogens, combinations with other drugs (G03CC)	60	39	21	1.84 (1.08-3.13)	Potential PC
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)	4794	3108	1686	1.83 (1.72-1.94)	Potential PC
Iron in other combinations (B03AE)	230	147	83	1.82 (1.39-2.38)	Other
Iron bivalent, oral preparations (B03AA)	263	169	94	1.81 (1.41-2.33)	Other
Calcitonin gene-related peptide (CGRP) antagonists (N02CD)	61	44	17	1.79 (1.02-3.14)	Other
3-oxoandrosten (4) derivatives (G03BA)	839	536	303	1.76 (1.53-2.02)	Potential PC
Proteolytic enzymes (D03BA)	1505	956	549	1.73 (1.56-1.93)	Potential PC
Pregnadien derivatives (G03DB)	1513	962	551	1.72 (1.55-1.91)	Other
Phenothiazines with aliphatic side-chain (N05AA)	331	209	122	1.71 (1.37-2.14)	Potential PC

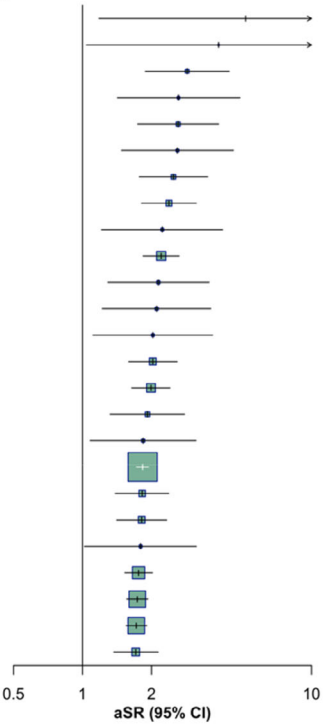

FIGURE 1 Top 25 strongest significant signals from sequence symmetry analyses of statin-marker class dyads by adjusted sequence ratio. PC, prescribing cascade; SR, sequence ratio. Forest plot square sizes are weighted by the Total *N* prescribed both a statin and marker drug.

ATC4 Marker Class	Total N Prescribed Statin & Marker Drug	Marker After	Marker Before	NNtH (95% CI)	PC Classification
Osmotically acting laxatives (A06AD)	61,118	37,002	24,116	44 (43-46)	Potential PC
Opioids in combination with non-opioid analgesics (N02AJ)	153,018	79,985	73,033	81 (74-91)	Potential PC
Platelet aggregation inhibitors excl. heparin (B01AC)	55,789	31,174	24,615	88 (83-94)	Other
Other lipid modifying agents (C10AX)	15,304	9,701	5,603	143 (137-150)	Other
Other ophthalmologicals (S01XA)	21,886	12,526	9,360	181 (168-197)	Other
First-generation cephalosporins (J01DB)	64,742	33,768	30,974	204 (175-246)	Potential PC
Propulsives (A04AA)	25,313	14,071	11,242	205 (186-228)	Potential PC
Electrolyte solutions (A12BA)	31,810	17,333	14,477	211 (189-240)	Other
Natural opium alkaloids (N02AA)	16,517	9,546	6,971	222 (205-243)	Other
Antiarrhythmics, class III (C01BD)	8,363	5,291	3,072	262 (247-280)	Other
Sulfonamides, plain (C03CA)	37,401	19,935	17,466	267 (229-322)	Other
Glucagon-like peptide-1 (GLP-1) analogues (A10BJ)	9,015	5,524	3,491	288 (268-312)	Potential PC
Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH)	12,818	7,405	5,413	292 (266-324)	Potential PC
Direct factor Xa inhibitors (B01AF)	8,224	5,024	3,200	318 (295-346)	Other
Nicotinic acid and derivatives (C04AC)	7,277	4,514	2,763	331 (308-359)	Other
Nicotinic acid and derivatives (C10AD)	7,276	4,513	2,763	331 (308-359)	Other
Salicylic acid and derivatives (N02BA)	10,813	6,284	4,529	333 (303-372)	Other
Phenothiazine derivatives (R06AD)	25,161	13,344	11,817	357 (303-438)	Potential PC
Enemas (A06AB)	9,691	5,591	4,100	391 (352-442)	Potential PC
Combinations of oral blood glucose lowering drugs (A10BD)	11,337	6,389	4,948	396 (352-455)	Potential PC
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)	4,794	3,108	1,686	406 (380-438)	Potential PC
Aldosterone antagonists (C03DA)	9,656	5,481	4,175	450 (398-521)	Other
Other opioids (N02AX)	48,783	24,992	23,791	478 (354-743)	Potential PC
Angiotensin II receptor blockers (ARBs), plain (C09CA)	46,341	23,768	22,573	483 (359-743)	Other
Phenothiazines with piperazine structure (N05AB)	5,299	3,225	2,074	499 (455-556)	Potential PC

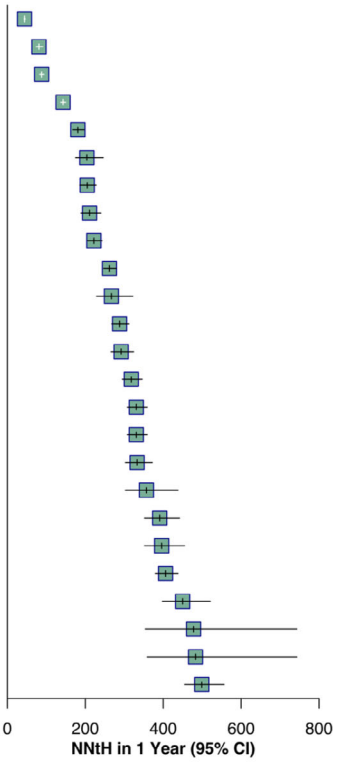

FIGURE 2 Top 25 strongest signals from sequence symmetry analyses of statin-marker class dyads by naturalistic number need to harm. NNtH, naturalistic number needed to harm (within 1 year); PC, prescribing cascade.

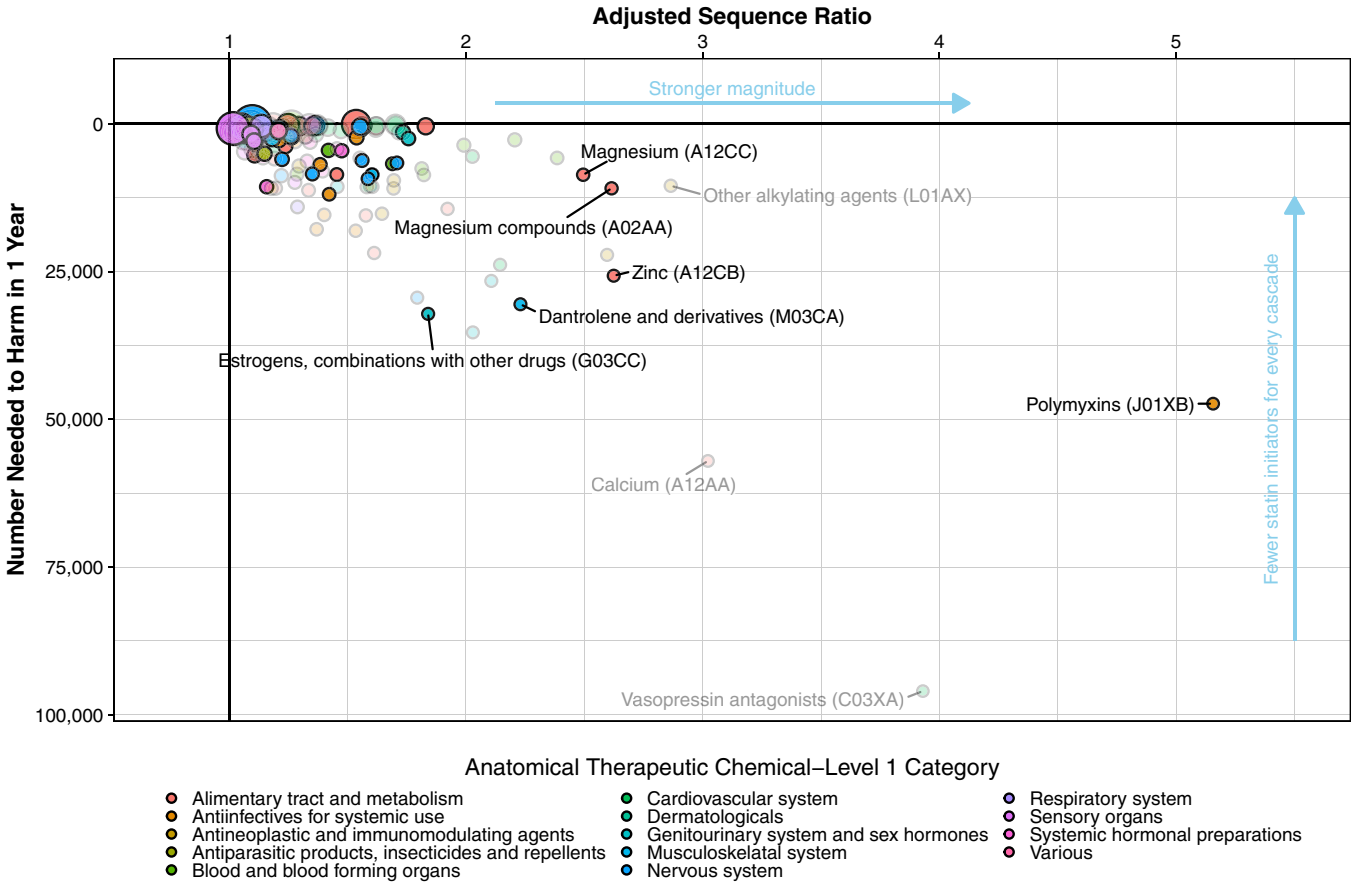

FIGURE 3 Significant statin-marker class dyad signals by adjusted sequence ratio and naturalistic number needed to harm. Dyads are grouped (color-coded) at the Anatomical Therapeutic Chemical Level 1 category. Dyads classified as potential prescribing cascades are highlighted whereas those classified as non-prescribing cascades are faded. Labeled dyads are examples of potential prescribing cascades and non-prescribing cascades.

dyad prescribing cascades, as ranked by NNTH, included propulsives (NNTH 205; 95% CI, 186–228), anticholinesterases for cognitive impairment (NNTH 1250; 95% CI, 989–1734), 3-oxoandrosten-4-derivatives (NNTH 2479; 95% CI, 2113-3099), anticholinesterases for myasthenia gravis (NNTH, 9282; 95% CI, 6767–17 693), and dantrolene and its derivatives (NNTH 30523; 95% CI, 22279–95 187). The completed findings of signals by NNTH and excess risk among exposed are available in the online visualization noted above.

Figure 3 (and the interactive plot linked above) summarizes statistically significant statin-marker class dyads by NNTH and aSR and highlights those that were classified as potential prescribing cascades. A majority of potential prescribing cascades had an ASR <2 and NNtH <25 000 with few signals with a strong magnitude but otherwise rare occurrences including Magnesium (A12CC), Magnesium compounds (A02AA), Estrogens, combination with other drugs (G03CC), Zinc (A12CB), Dantrolene and derivatives (M03CA), and Polymyxins (J01XB).

Additional sensitivity analyses using 180-day and 360-day exposure windows revealed, in general, qualitatively similar results to the main analysis. These findings can be further explored using our interactive visualization, as above.

4 | DISCUSSION

With the use of high-throughput SSA screening, we systematically evaluated statin-marker class dyad prescribing cascade signals across all ATC Level 4 subgroups ($n = 524$). Overall, we detected 160 signals that warranted further exploration. After classification, we determined 32.5% ($n = 57$) of these signals were potential statin-marker class dyad prescribing cascades. We subsequently ranked potential statin-marker class dyad prescribing cascades by (1) aSR as a measure of magnitude of the signal and (2) NNTH or excess risk to the exposed as a measure of impact within the population. In terms of considering the clinically meaningful impact (e.g., identifying prescribing cascades that impact the most patients), NNTH or excess risk among exposed is likely the preferred ranking order, and has been used in prior high-throughput SSA screening evaluation.[22]

Using NNTH, our strongest signal thought to be a potential prescribing cascade was osmotically acting laxatives (A06AD [e.g., magnesium citrate, lactulose] with a NNTH of 44 [22.55 excess cases per 1000 patient-years]). These findings may reflect risk of constipation observed in randomized controlled trials of statins, which showed up to 6.6% of statin-treated patients reporting

constipation.[29,30] However, although constipation is listed as a common side effect in the approved labeling for most statins, it is worth noting that a causal relationship between statins and gastrointestinal effects has not been clearly established.[31–33] Several analgesic-related signals were detected, likely indicative of the well-known association between statins and myalgias.[34–36] For example, opioids in combination with non-opioid analgesics (N02AJ [e.g., oxycodone with acetaminophen, tramadol with acetaminophen] had an NNTH of 81 [12.33 excess cases per 1000 patient-years]). Topical NSAIDs (M02AA [e.g., topical diclofenac] were also detected as a potential prescribing cascade but with a larger NNTH of 1569 [0.64 excess cases per 1000 patient-years]).

Other statin-related adverse events that may have resulted in potential prescribing cascades include skin infections (cephalosporins [e.g., cephalexin]; J01DB),[17,37] cognitive impairment (anticholinesterases [e.g., donepezil], N06DA),[38,39] nausea (propulsives [e.g., ondansetron; A04AA], phenothiazine derivatives [e.g., promethazine; R06AD]), low testosterone (G03BA; 3-oxoandrosten-4-derivatives [e.g., testosterone]),[40] myasthenia gravis (N07AA; acetylcholinesterases [e.g., pyridostigmine]),[41,42] and rhabdomyolysis (dantrolene and derivatives; M03CA).[43,44] We also found potential prescribing cascades that may be results of previously unknown adverse events including tremor (N03AA; barbiturates and derivatives [e.g., primidone]) and ear infections (antibiotics [e.g., neomycin otic]; A07AA) although there is a known association between statins and hearing loss.[45,46]

We were also able to replicate several previously evaluated statin-related prescribing cascades. We identified similar findings with phenothiazines with piperazine structure (e.g., prochlorperazine; N05AB) compared to findings using the Australian Department of Veteran's Affairs (aSRs of 1.55 vs. 1.50).[10] As previously noted, we also had similar findings with acetylcholinesterases (e.g., donepezil, N06DA) compared to an analysis using Korean National Health Insurance Service data (aSRs of 1.30 vs. 1.44).[15] We identified a strong signal for skin infections (cephalosporins [e.g., cephalexin]; J01DB) however, found no signal for beta-lactamase resistant penicillins (e.g., dicloxacillin; J01CF) somewhat contrasting findings from the Australian Department of Veterans' Affairs data.[17] Additionally, we classified signals involving medications used to treat diabetes mellitus as a potential prescribing cascade (Combinations of oral blood glucose lowering drugs [e.g. metformin and sulfonylureas], A10BD; Alpha glucosidase inhibitors [e.g. acarbose], A10BF; Dipeptidyl peptidase 4 (DPP-4) inhibitors [e.g. sitagliptin], A10BH; Glucagon-like peptide-1 (GLP-1) analogs [liraglutide], A10BJ; Sodium-glucose co-transporter 2 (SGLT2) inhibitors [e.g. empagliflozin], A10BK; Other blood glucose lowering drugs, excluding insulins [e.g. pramlintide], A10BX). Similar finding was noted using aggregated glucose-lowering medications as the marker drug also using Australian Department of Veterans' Affairs data.[17] However, it is difficult to disentangle the known association between statins and diabetes with therapeutic progression for cardiometabolic syndrome, and the latter may play a significant role in the observed associations.

We were unable to replicate some other potential statin-related prescribing cascade identified in prior research. For example, we could not replicate previous signals associated with quinine (P01BC)[11] and medications for overactive bladder (e.g., oxybutynin, mirabegron [G04BD]).[12] Differences in timing of these studies—and by extension, prevailing statin initiation patterns at the time of study conduct—may help explain these apparent discrepancies. For example, the identification of a statin–overactive bladder medication prescribing cascade stems from database mining in Japan in 2006–2013, and was identified only with pravastatin, which was initiated relatively infrequently (14% of new statin users) in our study. We likewise could not replicate previous findings involving benzodiazepine-related drugs (e.g., zolpidem [N05CF]); however, we did identify a potential prescribing cascade with other benzodiazepines commonly used to treat sleep disorders (e.g., temazepam [N05CD]).[13] Moreover, we were unable to replicate a prior signal associated with hepato-protective drugs, identified by Zhang et al, as these marker drugs are not commercially available in the United States.[16]

Overall, 64.4% ($n = 103$) of signals were classified as "Other" and there were unlikely to be prescribing cascades due to a variety of factors. For example, the subsequent prescribing of other lipid modifying agents (e.g., ezetimibe; C10AX) was viewed as likely being indicative of disease progression. Additionally, the subsequent prescribing of antineoplastic and immunomodulating agents (ATC Level 1 – L), which comprised 9.7% of the presumed false positive statin-marker class dyad prescribing cascade signals, were likely indicative of reverse causation. In other words, it may be more likely there is a decrease in statin initiation following antineoplastic and immunomodulating agent initiation rather than an increase in antineoplastic and immunomodulating agent initiation following statin initiation. We also identified signals that were deemed likely due to detection bias (e.g., Vitamin B12 treatment due to deficiencies likely identified during statin monitoring). In a previous evaluation using high-throughput SSA screening to assess non-vitamin K antagonist oral anticoagulants-related prescribing cascades, 9 of the top 20 signals, as ranked by NNTH, were classified as false positive prescribing cascade signals.[22] Our findings were similar when restricting to the top 25 signals, as ranked by NNTH, in which 13 signals were classified as false positives signals.

There are several noteworthy strengths of our study, including the first high-throughput SSA screening for prescribing cascades conducted in the United States and on one of the most prescribed drugs classes which included over 2 million new users.[2] We classified all significant signals instead of restricting assessment to a certain aSR or NNtH threshold as in past research.[22] This approach allowed us to assess signals impacting few patients which is potentially helpful in identifying adverse events with low incidence. Additionally, we used the SSA which inherently controls for time-invariant covariates (e.g., sex) and uses the pre-statin initiation window as a control group. Finally, we reported our aggregate findings publicly allowing for greater transparency.

Nevertheless, our study also had important limitations. Classification of signals was based on an evaluation of data and clinical knowledge and may be subject to misclassification; however, classification was determined by multiple evaluators via consensus. Second, findings may be overestimated due to within-person time varying bias (e.g., disease progression); however, we attempted to mitigate such overestimation by

restricting marker initiation to a 90-day exposure window rather than a 180- or 360-day window, as is most common in other SSA research.[20] This approach was informed by exploration of negative controls as described in our prior work.[27] Third, we studied a commercially-insured population, with limited numbers of older individuals (<20% aged ≥65 years), thus our findings may not be generalizable to older individuals. Finally, we did not account for multiple testing and it is likely that our high-throughput approach prompted spurious associations. Prior work has suggested corrections for multiple testing may not be advantageous in this setting.[21,47,48] Nevertheless, we acknowledge that our findings are hypothesis-generating, and need additional confirmation in a traditional cohort study is necessary for confirmation.[49]

5 | CONCLUSION

Using the high-throughput SSA screening, we identified previously known prescribing cascades, new potential prescribing cascades based on known statin-related adverse events, and new potential prescribing cascades based on previously unknown adverse events. This approach to identify prescribing cascades should be considered hypothesis-generating; however, our findings could be used to generate discussions in clinical practice on the risk versus benefits of continued statin therapy in light of the initiation of potentially unnecessary medications.

AUTHOR CONTRIBUTIONS

Steven M. Smith and Scott M. Vouri conceived and designed the study, secured funding for the study, and contributed to the first draft of the manuscript. Earl J. Morris, Marta Walsh, Scott M. Vouri, and Steven M. Smith were responsible for statistical analysis and visualization of the data. All authors made substantial contributions to interpretation of the data and results, and reviewed, provided critical revisions, and approved the final manuscript.

ACKNOWLEDGMENTS

This work was funded by the UF College of Pharmacy through an internal PROSPER award.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

This study was conducted using IBM® Marketscan commercial and Medicare supplemental claims databases, pursuant to a data use agreement between the University of Florida and IBM that prevents sharing of data entrusted to the University of Florida. However, qualified researchers can obtain such data directly from IBM®. SAS code used in this study is available from the Corresponding Author on reasonable request.

ETHICS STATEMENT

This work was approved as Exempt by the University of Florida Institutional Review Board.

ORCID

Scott M. Vouri https://orcid.org/0000-0002-0411-2160
Earl J. Morris https://orcid.org/0000-0002-6092-8906
Marta Walsh https://orcid.org/0000-0002-0266-3612
Carl J. Pepine https://orcid.org/0000-0002-6011-681X
Steven M. Smith https://orcid.org/0000-0002-0201-839X

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563-e595. https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000677
2. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013. *JAMA Cardiol*. 2017;2:56-65. http://cardiology.jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2016.4700
3. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39:E38-E81.
4. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;40:567-572.
5. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. *Atherosclerosis*. 2016;245:111-117.
6. McCarthy LM, Visentin JD, Rochon PA. Assessing the scope and appropriateness of prescribing cascades. *J Am Geriatr Soc*. 2019;67:1023-1026. https://onlinelibrary.wiley.com/doi/10.1111/jgs.15800
7. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315:1096-1099.
8. Rochon PA, Gurwitz JH. The prescribing cascade revisited. *Lancet*. 2017;389:1778-1780. https://linkinghub.elsevier.com/retrieve/pii/S0140673617311881
9. Anderson TS, Steinman MA. Antihypertensive prescribing cascades as high-priority targets for deprescribing. *JAMA Intern Med*. 2020;180:651-652.
10. Caughey GE, Roughead EE, Pratt N, Shakib S, Vitry AI, Gilbert AL. Increased risk of hip fracture in the elderly associated with prochlorperazine: is a prescribing cascade contributing? *Pharmacoepidemiol Drug Saf*. 2010;19:977-982. https://onlinelibrary.wiley.com/doi/10.1002/pds.2009
11. Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM. Nocturnal leg cramps and prescription use that precedes them: a sequence symmetry analysis. *Arch Intern Med*. 2012;172:120-126.
12. Fujimoto M, Higuchi T, Hosomi K, Takada M. Association of statin use with storage lower urinary tract symptoms (LUTS): data mining of prescription database. *Int J Clin Pharmacol Ther*. 2014;52:762-769.
13. Takada M, Fujimoto M, Yamazaki K, Takamoto M, Hosomi K. Association of statin use with sleep disturbances: data mining of a spontaneous reporting database and a prescription database. *Drug Saf*. 2014;37:421-431.
14. Nishtala PS, Chyou T-Y. Exploring New Zealand prescription data using sequence symmetry analyses for predicting adverse drug reactions. *J Clin Pharm Ther*. 2017;42:189-194. https://onlinelibrary.wiley.com/doi/10.1111/jcpt.12491
15. Park S-K, Baek Y-H, Pratt N, Kalisch Ellett L, Shin J-Y. The uncertainty of the association between proton pump inhibitor use and the risk of dementia: prescription sequence symmetry analysis using a Korean healthcare database between 2002 and 2013. *Drug Saf*. 2018;41:615-624. http://link.springer.com/10.1007/s40264-018-0638-2

16. Zhang H, Wu J, Zhang Z, et al. Association of atorvastatin with the risk of hepatotoxicity: a pilot prescription sequence symmetry analysis. *Ther Clin Risk Manag*. 2019;15:803-810. https://www.dovepress.com/association-of-atorvastatin-with-the-risk-of-hepatotoxicity-a-pilot-pr-peer-reviewed-article-TCRM
17. Ko HHT, Lareu RR, Dix BR, Hughes JD, Parsons RW. A sequence symmetry analysis of the interrelationships between statins, diabetes and skin infections. *Br J Clin Pharmacol*. 2019;85:2559-2567. https://onlinelibrary.wiley.com/doi/10.1111/bcp.14077
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453-1457.
19. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology*. 1996;7:478-484.
20. Morris EJ, Hollmann J, Hofer AK, et al. Evaluating the use of prescription sequence symmetry analysis as a pharmacovigilance tool: a scoping review. *Res Soc Adm Pharm*. 2022;18:3079-3093.
21. Hallas J, Wang SV, Gagne JJ, Schneeweiss S, Pratt N, Pottegård A. Hypothesis-free screening of large administrative databases for unsuspected drug-outcome associations. *Eur J Epidemiol*. 2018;33:545-555.
22. Hellfritzsch M, Rasmussen L, Hallas J, Pottegård A. Using the symmetry analysis design to screen for adverse effects of non-vitamin K antagonist oral anticoagulants. *Drug Saf*. 2018;41:685-695. http://link.springer.com/10.1007/s40264-018-0650-6
23. Vouri SM, Morris EJ, Jiang X, et al. Evaluation of a beta-blocker–edema–loop diuretic prescribing cascade: a prescription sequence symmetry analysis. *Am J Hypertens*. 2022;35:601-609. https://academic.oup.com/ajh/article/35/7/601/6519626
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/-ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCN-A guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:E1082-E1143. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
25. 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;43:1130-1139. http://journals.lww.com/00005650-200511000-00010
26. 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;18:4. https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0457-7
27. Vouri SM, Jiang X, Morris EJ, Brumback BA, Winterstein AG. Use of negative controls in a prescription sequence symmetry analysis to reduce time-varying bias. *Pharmacoepidemiol Drug Saf*. 2021;30:1192-1199. https://onlinelibrary.wiley.com/doi/10.1002/pds.5293
28. Hallas J, Christensen RD, Stürmer T, Pottegård A. Measures of 'exposure needed for one additional patient to be harmed' in population-based case-control studies. *Pharmacoepidemiol Drug Saf*. 2014;23:868-874. https://onlinelibrary.wiley.com/doi/10.1002/pds.3635
29. Black DM, Bakker-Arkema RG, Nawrocki JW. An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med*. 1998;158:577-584. http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.158.6.577
30. Ballantyne CM, Blazing MA, Hunninghake DB, et al. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: results of the Comparative HDL Efficacy and Safety Study (CHESS). *Am Heart J*. 2003;146:862-869. https://linkinghub.elsevier.com/retrieve/pii/S000287030300440X
31. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207. http://www.nejm.org/doi/abs/10.1056/NEJMoa0807646
32. Shepherd J, Vidt DG, Miller E, Harris S, Blasetto J. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology*. 2007;107:433-443. https://www.karger.com/Article/FullText/100908
33. Pearlman M, Covin Y, Schmidt R, Mortensen EM, Mansi IA. Statins and lower gastrointestinal conditions: a retrospective cohort study. *J Clin Pharmacol*. 2017;57:1053-1063. https://onlinelibrary.wiley.com/doi/10.1002/jcph.895
34. Boccuzzi SJ, Bocanegra TS, Walker JF, Shapiro DR, Keegan ME. Long-term safety and efficacy profile of simvastatin. *Am J Cardiol*. 1991;68:1127-1131. https://linkinghub.elsevier.com/retrieve/pii/000291499190182K
35. Tomaszewski M, Stępień KM, Tomaszewska J, Czuczwar SJ. Statin-induced myopathies. *Pharmacol Rep*. 2011;63:859-866. https://linkinghub.elsevier.com/retrieve/pii/S1734114011706016
36. Keen HI, Krishnarajah J, Bates TR, Watts GF. Statin myopathy: the fly in the ointment for the prevention of cardiovascular disease in the 21st century? *Expert Opin Drug Saf*. 2014;13:1227-1239. http://www.tandfonline.com/doi/full/10.1517/14740338.2014.937422
37. Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. *Clin Infect Dis*. 2001;33:1352-1357. https://academic.oup.com/cid/article-lookup/doi/10.1086/323334
38. Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin therapy and risk of acute memory impairment. *JAMA Intern Med*. 2015;175:1399-1405. http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2015.2092
39. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy*. 2003;23:871-880. http://doi.wiley.com/10.1592/phco.23.7.871.32720
40. Schooling CM, Au Yeung SL, Freeman G, Cowling BJ. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med*. 2013;11:57. http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-11-57
41. Crisan E, Patil VK. Neuromuscular complications of statin therapy. *Curr Neurol Neurosci Rep*. 2020;20:47. https://link.springer.com/10.1007/s11910-020-01064-0
42. Sheikh S, Alvi U, Soliven B, Rezania K. Drugs that induce or cause deterioration of myasthenia gravis: an update. *J Clin Med*. 2021;10:1537 https://www.mdpi.com/2077-0383/10/7/1537
43. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*. 2001;35:1096-1107. http://journals.sagepub.com/doi/10.1345/aph.10228
44. Hohenegger M. Drug induced rhabdomyolysis. *Curr Opin Pharmacol*. 2012;12:335-339. https://linkinghub.elsevier.com/retrieve/pii/S1471489212000525
45. Liu M, Alafris A, Longo AJ, Cohen H. Irreversible atorvastatin-associated hearing loss. *Pharmacotherapy: J Hum Pharmacol Drug Ther*. 2012;32:e27-e34. https://onlinelibrary.wiley.com/doi/10.1002/PHAR.1040
46. Chung S-D, Chen C-H, Hung S-H, Lin H-C, Wang L-H. A population-based study on the association between statin use and sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg*. 2015;152:319-325. http://journals.sagepub.com/doi/10.1177/0194599814559382
47. Lai ECC, Pratt N, Hsieh CY, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. *Eur J Epidemiol*. 2017;32:567-582.
48. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med*. 2014;29:1060-1064.

49. Sinnott S, Lin K, Wang S, et al. Evaluating signals generated in a large-scale sequence symmetry analyses: macrolides and heart failure; and NSAIDs and pneumonia. *medRxiv*. 2020. doi:10.1101/2020.03.19.20038596

SUPPORTING INFORMATION

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

How to cite this article: Vouri SM, Morris EJ, Walsh M, et al. High-throughput screening for prescribing cascades among real world statin initiators. *Pharmacoepidemiol Drug Saf*. 2023; 1-10. doi:10.1002/pds.5607