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# High-Throughput Screening for Prescribing Cascades Among Real-World Angiotensin-Converting Enzyme Inhibitor Initiators

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## ABSTRACT

**Purpose:** Angiotensin-converting enzyme inhibitors (ACEIs) are commonly prescribed, but their adverse effects may prompt new drug prescription(s), known as prescribing cascades (PCs). We aimed to identify potential ACEI-induced PCs using high-throughput sequence symmetry analysis.

**Methods:** Using claims data from a national sample of Medicare beneficiaries (2011–2020), we identified new ACEI users aged ≥ 66 years with continuous enrollment ≥ 360 days before and ≥ 180 days after ACEI initiation. We screened for initiation of 446 other (non-antihypertensive) "marker" drug classes within ±90 days of ACEI initiation, generating sequence ratios (SRs) reflecting proportions of ACEI users starting the marker class after versus before ACEI initiation. Adjusted SRs (aSRs) accounted for prescribing trends over time. For significant aSRs, we calculated the naturalistic number needed to harm (NNTH), and significant signals underwent clinical review for plausibility.

**Results:** We identified 308 579 ACEI initiators (mean age 76.1 ± 7.5 years; 59.6% female; 88.6% with hypertension). Of 446 marker classes evaluated, 81 signals were significant, and 42 (52%) classified as potential PCs after clinical review. The strongest signals ranked by lowest NNTH included corticosteroids (NNTH 313; 95% CI, 262–392) and serotonin type 3 (5-$HT_3$) antagonists (NNTH 496; 95% CI, 392–689); the strongest signals ranked by highest aSR included sympathomimetics (aSR, 1.97; 95% CI, 1.10–3.53) and other antianemic preparations (aSR, 1.87; 95% CI, 1.31–2.67).

**Conclusion:** Identified prescribing cascade signals were indicative of known and possibly underrecognized ACEI adverse events in this Medicare cohort. The findings are hypothesis-generating and require further investigation to determine the extent and impact of the identified PCs on health outcomes.

**Prior Presentation**: Preliminary results from this study were presented at the American Heart Association Hypertension Scientific Sessions, 2023.

**Summary**

- A prescribing cascade occurs when a side effect from an initial therapy (e.g., ACEI) leads to the initiation of an additional therapy (e.g., corticosteroids).
- Using sequence symmetry analysis on 308 579 ACEI initiators, we screened 446 medication classes to detect ACEI-related prescribing cascades and identified 81 (18%) having a significant prescribing cascade signal.
- Among these signals, 42 (52%) were classified as potential prescribing cascades based on expert review.
- Of the strongest signals (lowest naturalistic number needed to harm), corticosteroids (NNTH 313) and serotonin (5-$HT_3$) antagonists (NNTH 496) were classified as potential prescribing cascades.
- Further research is needed to confirm these findings and to determine the impact of these potential prescribing cascades on patient outcomes.

## 1 | Introduction

The renin-angiotensin-aldosterone system (RAAS) regulates vascular resistance, tissue perfusion, and electrolyte balance and is central to the pathophysiology of hypertension, heart failure, and renal disease [1–3]. Angiotensin-converting enzyme inhibitors (ACEIs) reduce angiotensin II formation and are recommended by major hypertension guidelines as first-line treatment for elevated blood pressure in adults, especially those with comorbidities such as diabetes or cardiovascular disease [4–12]. Consequently, ACEIs are among the most prescribed medications, with lisinopril ranked as the fourth most prescribed drug in the United States in 2022 [13–15].

While effective and generally well-tolerated, the extensive use of ACEIs exposes millions to potential treatment-limiting adverse events (AEs). Among the most well-known AEs are cough, angioedema, and fetal toxicity during pregnancy [16–31]. There may be other lesser-known or unknown AEs, and many case reports have not been further evaluated, primarily due to a lack of data [32]. When ACEI-induced AEs are not directly attributed to ACEIs, a new medication is used to treat the ACEI-related AE—a phenomenon known as a prescribing cascade (PC) [33, 34]. Such scenarios can predispose patients to polypharmacy and trigger a series of negative outcomes. Therefore, recognizing PCs and their negative consequences is critical in preventing polypharmacy and informing deprescribing initiatives [35].

Several previous examples of ACEI-related PCs have been reported (Table S1). For example, a recent case report highlighted a patient being prescribed cough medicine to manage ACEI-induced cough [36, 37]. Additional case reports have documented patients treated with glucocorticoids and antihistamines for swelling of the tongue suspected to be ACEI-induced angioedema [38, 39]. However, these prior reports have been relegated to targeted investigations of well-known ACEI-related AEs leading to PCs. A more comprehensive, untargeted approach may reveal additional PCs occurring with lesser-known AEs or those that are not as easily attributable to ACEIs. Therefore, we aimed to conduct high-throughput signal detection using a pharmacovigilance approach, known as sequence symmetry analysis (SSA), to screen for potential ACEI-related PCs among older individuals.

## 2 | Methods

### 2.1 | Data Sources

We used claims data from a 5% national sample of Medicare beneficiaries with fee-for-service (FFS) coverage from 2011 to 2015, plus 1 million FFS beneficiaries in Florida, and a 15% national sample of Medicare FFS beneficiaries, plus all FFS beneficiaries in Florida from 2016 to 2020. Medicare is a US federal insurance program for adults aged ≥65 years and others with qualifying conditions that captures inpatient and outpatient services, pharmacy claims, and beneficiary characteristics. 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 [40].

### 2.2 | Design

We used high-throughput SSA to identify potential ACEI-related PCs [41–43]. Sequence symmetry analysis is a self-controlled, hypothesis-free pharmacovigilance approach that employs a case-only study design to assess the temporality of an "index" drug (or class) initiation (i.e., ACEIs) relative to the initiation of a "marker" drug (or class), hereafter referred to as ACEI-marker class dyads [44, 45]. Included patients were ACEI initiators who had their first ACEI fill between 2011 and 2019, inclusive, were aged ≥66 years at ACEI initiation, and had ≥360 days of continuous insurance coverage before, and ≥180 days after, ACEI initiation (Figure S1). Continuous insurance coverage requirements were chosen to ensure genuine new use of ACEI, to capture all marker drug use during the 180 days prior to and after ACEI initiation, and to meet requirements for sensitivity analyses (described further below).

We used Anatomical Therapeutic Chemical (ATC) codes to hierarchically group marker drugs into medication classes for high-throughput screening. The ATC classification system is maintained by the World Health Organization and classifies medications into groups at five levels, where Level 1 indicates the broad anatomical group ($n = 14$ total), Level 4 indicates the chemical subgroup/drug class, and Level 5 indicates specific drugs/chemical substances ($n \approx 5000$) (Table S2) [46]. Among ACEI initiators, we identified the first claim for any marker drug within a given ATC Level 4 subgroup. If an individual filled multiple different medications (unique ATC Level 5) within a given ATC Level 4 subgroup during the study period, we only included the date of the first fill within the ATC Level 4 subgroup. We required the marker drug initiation to occur within ±90 days of ACEI initiation for the primary analysis to focus on acute onset AEs and excluded all patients initiated on other classes of antihypertensive on the same day as ACEI initiation (Table S3) [47]. We chose a 90-day window to provide

adequate time for clinical visits and subsequent prescribing decisions while minimizing the impact of within-patient time-varying confounders [48]. Recognizing that varying the time window could impact the observation of PCs, a sensitivity analysis was conducted using a ±180-days window to allow for the identification of AEs (and subsequent PCs) with longer induction periods.

For each ATC Level 4 subgroup, all included patients in the ACEI-marker drug dyad were evaluated using the SSA methodology. The analyses were completed iteratively until all ATC Level 4 subgroups were evaluated, excluding only ATC Level 4 subgroups representing other antihypertensive classes. Baseline characteristics (age, sex, calendar year of ACEI initiation, Charlson Comorbidity Index, specific ACEI medication, and other comorbidities) of ACEI initiators were measured at the time of ACEI initiation or in the 360 days prior to ACEI initiation [49, 50].

## 2.3 | Analyses

For each unique ACEI-marker class dyad, we determined the crude sequence ratio (cSR) as the number of patients who initiated the marker class after ACEI initiation, divided by the number of patients who initiated the marker class before the ACEI. Excess initiation of a marker class after the ACE inhibitor, relative to before the ACEI, results in a cSR > 1 and may indicate the presence of a prescribing cascade. To account for secular trends in medication use (e.g., increasing or decreasing use of ACEI or the marker class over time), we derived the null-effect sequence ratio for each ACEI-marker dyad. Briefly, the null-effect sequence ratio is the expected sequence ratio in the absence of any causal relationship between the marker and index drug, based on population-level prescribing trends [41]. We then estimated an adjusted sequence ratio (aSR) by dividing the cSR by the null-effect ratio for each ACEI-marker class dyad to adjust for background prescribing trends [41, 48, 51]. The Morris and Gardner method was used to estimate the 95% confidence intervals (CI) of the aSRs [52]. All aSRs with a lower CI limit > 1 were considered statistically significant under the assumption that no within-person time-varying bias exists.

Each ACEI-marker class dyad was represented graphically by plotting the distribution of the timing of marker class initiation (in 10-day intervals) relative to ACEI initiation for each exposure window (±90 and ±180 days) surrounding ACEI initiation. In addition, for each ACEI-marker class dyad considered statistically significant, we estimated excess risk among exposed and the corresponding naturalistic number needed to harm (NNTH) within 1 year. Excess risk among exposed was calculated as the difference between the number of patients initiated on the marker class after ACEI initiation and the number of patients initiated on the same marker class before ACEI initiation, divided by the total number of ACEI 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 an ACEI for one additional patient to experience one prescribing cascade with that marker class, consistent with the "naturalistic" NNTH approach [53, 54].

## 2.4 | Classification of Signals

All statistically significant signals in the primary analysis underwent manual review through a systematic process to differentiate potential PCs from false positive signals. False positive signals could be attributable to detection bias (i.e., new condition identified with a corresponding new medication initiated during routine monitoring of the ACEI), disease progression (i.e., new medication initiated to treat progression of underlying cardiovascular disease), therapeutic escalation (i.e., escalation of therapy [2nd or 3rd line treatments] in conditions unrelated to ACE inhibitor indication), or reverse causation (i.e., decreased ACEI initiation following the initiation of marker class [e.g., reduced ACEI treatment following late-stage cancer treatment]). Signals not considered to be potential PC 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 (Figure S2). First, pharmacy trainees ($n = 3$) were trained by study investigators (SMS and KMS) in the use of primary (e.g., PubMed/MEDLINE searches), secondary (e.g., drug monographs, package inserts), and tertiary (e.g., drug information databases) drug information sources for assessing potential PCs and their underlying mechanisms to support signal classification. Each significant signal was assigned to the three pharmacy trainees, who independently reviewed the signals and assigned an initial classification, as described above, along with supporting literature. Two pharmacists with clinical expertise in medication and patient safety then independently classified each signal using material developed by pharmacy trainees and ad-hoc literature evaluations when needed. In cases of disagreement between the clinically trained pharmacists, consensus was reached by the same clinical pharmacists together with senior study investigators (SMS, EJM).

All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC), visualized with R (2023.09.1) and Tableau (2023.06.2 + 561).

# 3 | Results

We identified 308 579 initiators of ACEI. The baseline characteristics of the cohort are summarized in Table 1. Briefly, 59.6% were female, and the mean ± SD age was 76 ± 7.5 years, with 50.6% aged between 66 and 74 years. The vast majority (85.5%) of patients were Non-Hispanic White, whereas 6.9% were Black. Most patients (72%) had a Charlson Comorbidity Index score ≥ 5. Lisinopril was the most commonly initiated ACEI (88.4%), followed by benazepril and enalapril, each 3.7% of the cohort.

Among 446 marker drug classes analyzed, 81 statistically significant signals were identified in the 90-day primary analyses (Table S4). We did not observe new signals in the 180-day

**TABLE 1** | Baseline characteristics of ACE inhibitor initiators included in the cohort.

| Patient characteristics | ACE inhibitor initiators ($n = 308\,579$) |
|---|---|
| Age, years | 76 ± 7.5 |
| 65–74 | 156 090 (50.6%) |
| 75–84 | 106 808 (34.6%) |
| 85–94 | 41 961 (13.6%) |
| ≥ 95 | 3720 (1.2%) |
| Female | 183 972 (59.6%) |
| Race | |
| American Indian/Alaska Native | 1154 (0.4%) |
| Asian/Pacific Islander | 4959 (1.6%) |
| Black | 21 179 (6.9%) |
| Hispanic | 9294 (3.0%) |
| Non-Hispanic White | 263 748 (85.5%) |
| Other | 4109 (1.3%) |
| Unknown | 4136 (1.3%) |
| Charlson's comorbidity index | |
| 3–4 | 86 263 (28.0%) |
| ≥ 5 | 222 316 (72.0%) |
| Comorbidities | |
| Atrial fibrillation | 50 268 (16.3%) |
| Cerebrovascular disease | 64 170 (20.8%) |
| Chronic obstructive pulmonary disease | 76 830 (24.9%) |
| Chronic renal failure | 52 854 (17.1%) |
| Congestive heart failure | 50 115 (16.2%) |
| Dementia | 21 124 (6.9%) |
| Diabetes mellitus | 110 503 (35.8%) |
| Diabetes with sequelae | 43 967 (14.3%) |
| Hypertension | 257 228 (83.6%) |
| Ischemic heart disease | 95 193 (30.9%) |
| Malignancy lymphoma leukemia | 45 402 (14.7%) |
| Myocardial infarction | 25 351 (8.2%) |
| Peripheral vascular disease | 57 872 (18.8%) |
| Rheumatic disease | 16 063 (5.2%) |
| Transient ischemic attack | 32 822 (10.6%) |
| Year of ACE inhibitor initiation | |
| 2012 | 30 797 (8.5%) |
| 2013 | 27 202 (7.5%) |
| 2014 | 30 900 (8.6%) |
| 2015 | 24 922 (6.9%) |
| 2016 | 25 279 (7.01%) |
| 2017 | 68 758 (19.1%) |
| 2018 | 63 147 (17.5%) |
| 2019 | 37 574 (12.2%) |
| ACE inhibitor initiated | |
| Benazepril | 11 271 (3.7%) |
| Captopril | 778 (0.3%) |
| Enalapril | 11 046 (3.7%) |
| Fosinopril | 584 (0.2%) |
| Lisinopril | 272 644 (88.4%) |
| Moexipril | 110 (0.0%) |
| Perindopril | 134 (0.0%) |
| Quinapril | 1843 (0.6%) |
| Ramipril | 9986 (3.2%) |
| Trandolapril | 183 (0.1%) |

*Note:* Data represents mean ± standard deviation or *n* (%).

analyses. Of the 81 significant signals identified in the 90-day analysis, 50 (62%) were also significant in the 180-day analysis. All high-throughput screening results are interactively displayed at: https://public.tableau.com/app/profile/cvmedlab/viz/ACE_newdata/TableofContentsFlowchart2, with significant aSRs presented in Table S4, non-significant signals in Table S5, and the results of all sensitivity analyses in Table S6. The top 30 aSRs are summarized in Figure 1. After clinical review, 42 (52%) signals were classified as potential PCs, and the remaining 39 (48%) were classified as unlikely to be a prescribing cascade. When categorized at ATC Level 1, the most prevalent potential prescribing cascades belonged to the Alimentary Tract and Metabolism ($n = 17$), followed by the Nervous System ($n = 14$). As shown in Figure 1, among the top 30 strongest significant signals (as ranked by aSR) classified as potential PCs were sympathomimetics (R01BA; e.g. pseudoephedrine, phenylephrine combinations) (aSR, 1.97; 95% CI, 1.10–3.53); other antianemic preparations (B03XA; e.g., erythropoietin, darbepoetin alfa) (aSR, 1.87; 95% CI, 1.31–2.67); and other nasal preparations (R01AX; e.g., ipratropium bromide) (aSR, 1.80; 95% CI, 1.36–2.38). Figure 2 summarizes the top 30 statistically significant signals ranked by lowest NNTH. Those classified as potential PCs included

| ATC4 Marker Class | Total | After Marker | Before Marker | PC Classification | aSR (95% CI) |
|---|---|---|---|---|---|
| Amino acids (B05XB) | 19 | * | * | Other | 5.71 (1.67 - 19.60) |
| Other cicatrizants (D03AX) | 27 | * | * | Other | 3.33 (1.26 - 8.79) |
| Monoamine oxidase B inhibitors (N04BD) | 73 | 50 | 23 | Other | 2.19 (1.34 - 3.59) |
| Sympathomimetics (R01BA) | 49 | 31 | 18 | Potential PC | 1.97 (1.10 - 3.53) |
| Other antianemic preparations (B03XA) | 130 | 83 | 47 | Potential PC | 1.87 (1.31 - 2.67) |
| Other nasal preparations (R01AX) | 212 | 137 | 75 | Potential PC | 1.80 (1.36 - 2.38) |
| Carbohydrates (V06DC) | 99 | 66 | 33 | Potential PC | 1.78 (1.17 - 2.71) |
| Proteolytic enzymes (D03BA) | 859 | 536 | 323 | Other | 1.67 (1.45 - 1.91) |
| Sodium-glucose co-transporter 2 inhibitors (A10BK) | 688 | 424 | 264 | Other | 1.59 (1.37 - 1.86) |
| Electrolyte solutions (B05XA) | 396 | 243 | 153 | Potential PC | 1.56 (1.28 - 1.91) |
| Antiarrhythmics, class Ib (C01BB) | 485 | 296 | 189 | Other | 1.55 (1.29 - 1.86) |
| Other systemic drugs for obstructive airway diseases (R03DX) | 140 | 85 | 55 | Potential PC | 1.51 (1.08 - 2.12) |
| Selective beta-2-adrenoreceptor agonists (R03AC) | 744 | 441 | 303 | Potential PC | 1.48 (1.28 - 1.72) |
| Butyrophenone derivatives (N05AD) | 304 | 182 | 122 | Potential PC | 1.47 (1.17 - 1.84) |
| Nicotinic acid and derivatives (C10AD) | 171 | 99 | 72 | Other | 1.47 (1.09 - 2.00) |
| Antiallergic agents, excl. corticosteroids (R01AC) | 1908 | 1124 | 784 | Potential PC | 1.41 (1.29 - 1.55) |
| Pregnadien derivatives (G03DB) | 1043 | 615 | 428 | Potential PC | 1.41 (1.25 - 1.59) |
| Biguanides (P01BB) | 155 | 90 | 65 | Other | 1.41 (1.03 - 1.94) |
| Drugs for hyperkalemia and hyperphosphatemia (V03AE) | 642 | 373 | 269 | Potential PC | 1.38 (1.18 - 1.61) |
| Opioid anesthetics (N01AH) | 637 | 370 | 267 | Other | 1.38 (1.18 - 1.62) |
| Specific immunoglobulins (J06BB) | 2714 | 1636 | 1078 | Other | 1.37 (1.27 - 1.48) |
| Antidotes (V03AB) | 270 | 158 | 112 | Other | 1.36 (1.07 - 1.73) |
| Glycogenolytic hormones (H04AA) | 345 | 199 | 146 | Other | 1.34 (1.08 - 1.66) |
| Phenylpiperidine derivatives (N02AB) | 665 | 381 | 284 | Potential PC | 1.34 (1.15 - 1.56) |
| Leukotriene receptor antagonists (R03DC) | 3678 | 2130 | 1548 | Potential PC | 1.34 (1.25 - 1.43) |
| Bile acid sequestrants (C01AC) | 1232 | 707 | 525 | Potential PC | 1.32 (1.18 - 1.48) |
| Glycopeptide antibacterials (J02XA) | 450 | 258 | 192 | Other | 1.31 (1.08 - 1.57) |
| Fatty acid derivatives (N03AG) | 797 | 457 | 340 | Other | 1.31 (1.14 - 1.51) |
| Antipropulsives (A07DA) | 1989 | 1132 | 857 | Potential PC | 1.31 (1.20 - 1.43) |
| Anti-androgens (L02BB) | 253 | 144 | 109 | Other | 1.31 (1.01 - 1.68) |

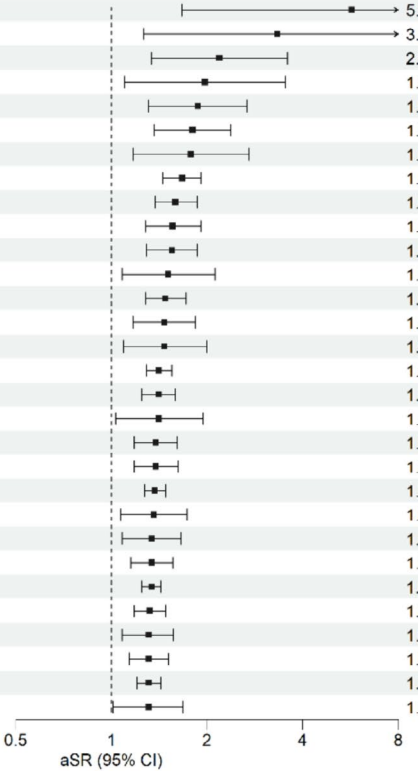


**FIGURE 1** | Top 30 strongest significant signals from sequence symmetry analyses of ACE inhibitors-marker class dyads by adjusted sequence ratio. aSR, adjusted sequence ratio; ATC4, Anatomical Therapeutic Chemical—Level 4; CI, confidence interval; PC, prescribing cascade.

corticosteroids (R01AD; e.g., fluticasone, mometasone) (NNTH 313, 95% CI 262–392), serotonin (5-HT3) antagonists (A04AA; e.g., ondansetron) (NNTH 496, 95% CI 392–689), and osmotically acting laxatives (A06AD; e.g., lactulose, macrogol, and sodium sulfate) (NNTH 553; 95% CI, 437–768).

Figure 3 summarizes statistically significant ACEI-marker class dyads by NNTH and aSR and highlights those that were classified as potential prescribing. A majority of potential PCs had an aSR < 2 and NNTH < 12 500 with few signals with a strong magnitude but otherwise rare occurrences, including sympathomimetics (R01BA; e.g., phenylephrine, pseudoephedrine) and other cicatrizants (D03AX; e.g., becaplermin).

## 4 | Discussion

Using population-based, high-throughput SSA, we identified classes of medication prescribed in excess after ACEI initiation compared to before ACEI initiation. We assessed 446 unique drug classes and identified 81 statistically significant signals, of which 42 were identified as potential ACEI-related PCs by clinically trained evaluators. Signals were ranked based on (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. Although not all PCs are harmful prescribing per se, NNTH was used for consistency with established epidemiological terminology and as a practical measure for identifying PCs with significant clinical impact, as demonstrated in prior high-throughput SSA screening research [44, 55].

Ranking signals using NNTH, most of the 10 strongest signals are linked to potential prescribing cascades related to allergic reactions, bronchospasms, and other bronchial hyperreactivity. The mechanism of ACEIs likely explains these findings, as substance P and bradykinin accumulation in the airways trigger histamine release from mast cells [56–58]. In total, nearly one-in-four potential PCs reflected medication classes indicated for conditions affecting the respiratory system. For example, the strongest signal was observed for corticosteroids (R01AD) with an NNTH of 313, comprised of preparations for local treatment in nasal congestion or for prophylaxis and treatment of allergic rhinitis (e.g., beclometasone, flunisolide, budesonide, triamcinolone, and fluticasone). Evidence from clinical trials, observational studies, and case reports have also shown that ACEIs can cause rhinitis, nasal congestion, and bronchospasm [16, 59].

Another known AE of ACEIs is angioedema. ACEIs are responsible for 30% of all angioedema cases, and more than half of these cases occur within the first week of initiating ACEI therapy, although it may occur any time, from hours to years into treatment [18, 19, 60–63]. ACEI-induced angioedema typically affects the lips, tongue, face, and upper airway [60, 64, 65]. The intestines may also be affected, leading to symptoms like acute abdominal pain, diarrhea, and other gastrointestinal symptoms, but this presentation may be less well-recognized. The unspecific manifestation of angioedema may explain the excess prescription of corticosteroids (R01AD) like fluticasone; leukotriene receptor antagonists, non-steroidal antiallergic agents (R01AC), such as azelastine; and adrenergics in combination with anticholinergics (R30AL) (e.g., formoterol and glycopyrronium bromide)

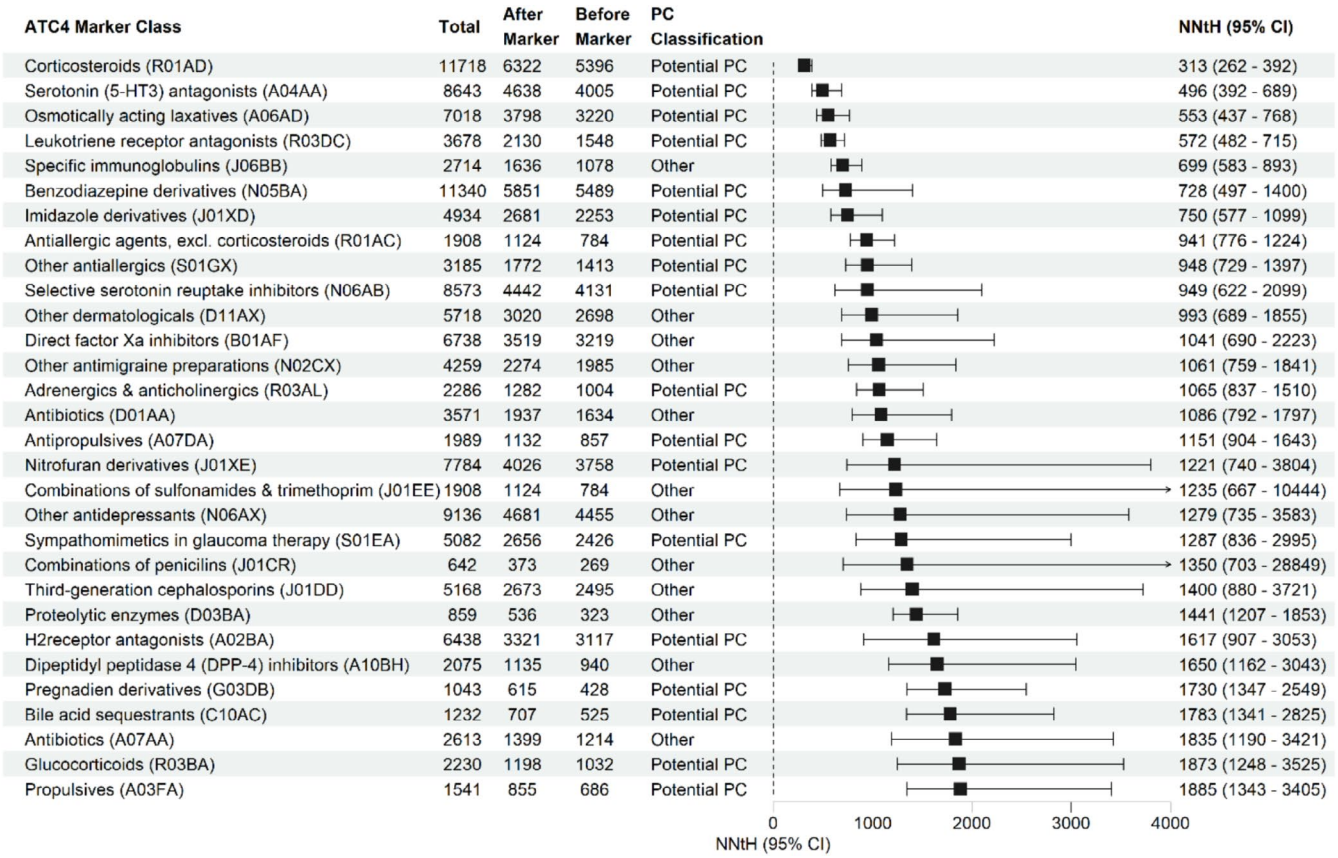


**FIGURE 2** | Top 30 strongest signals from sequence symmetry analyses of ACE inhibitor-marker class dyads by naturalistic number need to harm. ATC4, Anatomical Therapeutic Chemical—Level 4; CI, confidence interval; NNtH, naturalistic number needed to harm (within 1 year); PC, prescribing cascade.

for treating bronchospasm and other upper airway manifestation [66–68]. Similarly, several reports of visceral angioedema involving the jejunum, ileum, duodenum, and even the pylorus of the stomach following ACEI therapy could further explain the increased prescription of $H_2$-receptor antagonists (A02BA) such as ranitidine and famotidine, and other drugs for peptic ulcer and gastroesophageal reflux disease (A02BX), like sucralfate [45, 69–72].

Several anti-infective signals were detected, which could indicate an association between ACEI and infections: Imidazole derivatives (J01XD), nitrofuran derivatives (J01XE) (nitrofurantoin), and other aminoglycosides (J01GB) (gentamicin). The ACEI—unitary tract infections—medications used for UTI (e.g., nitrofurantoin) prescribing cascade has been reported in the literature previously [73–75]. Another study from the Netherlands, using SSA, supported similar findings with an adjusted sequence ratio (ASR) of 1.68 (95% CI 1.21–2.36) [75]. While there is evidence of a temporal relationship between the initiation of ACEI therapy and the onset of UTIs, the underlying mechanisms remain unclear. One proposed hypothesis is that ACEIs may reduce glomerular filtration rate (GFR), leading to lower urine output and, consequently, an increased risk of UTIs [76–78].

Angiotensin-converting enzyme inhibitors (ACEIs) are known to suppress erythropoietin production, resulting in a reduction in hematocrit levels. Such effects make ACEIs suitable for conditions like post-transplantation erythrocytosis, where lowering hematocrit is beneficial [79–87]. The decrease in hematocrit levels is exacerbated in individuals with chronic kidney disease (CKD), due to the accumulation of N-acetyl-seryl-aspartyl-lysyl-proline, which further inhibits erythropoiesis [88, 89]. The suppression of erythropoiesis may explain the excess prescription of other antianemic agents, such as erythropoietin and darbepoetin alfa (B03XA), as well as amino acids (B05XB) and electrolyte solutions (B05XA), in patients newly initiated on ACEIs. Other known ACEI-related AEs such as hyperkalemia and hyperphosphatemia may contribute to PCs leading to initiation of treatments for these conditions, including drugs for the treatment of hyperkalemia and hyperphosphatemia (V03AE) [27, 90–93].

After reviewing all the 81 potential prescribing cascade signals, we classified 39 (47%) as "other," that is, unlikely to be a prescribing cascade. Several factors were considered during the classification including the pharmacological profile of the medication, the time it takes for a plausible AE to occur after the index drug initiation, the possibility of reverse causation, and the probability that the signal is more likely due to disease progression rather than managing an AE. For example, the increased prescription of various diabetes medications following the initiation of ACEI—such as the sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK); thiazolidinediones (A10BG); biguanides; glucagon-like peptide-1 (GLP-1) analogues (A10BJ); other blood glucose lowering drugs, excluding insulins (A10BX); and combinations of oral blood glucose lowering drugs (A10BD)—were

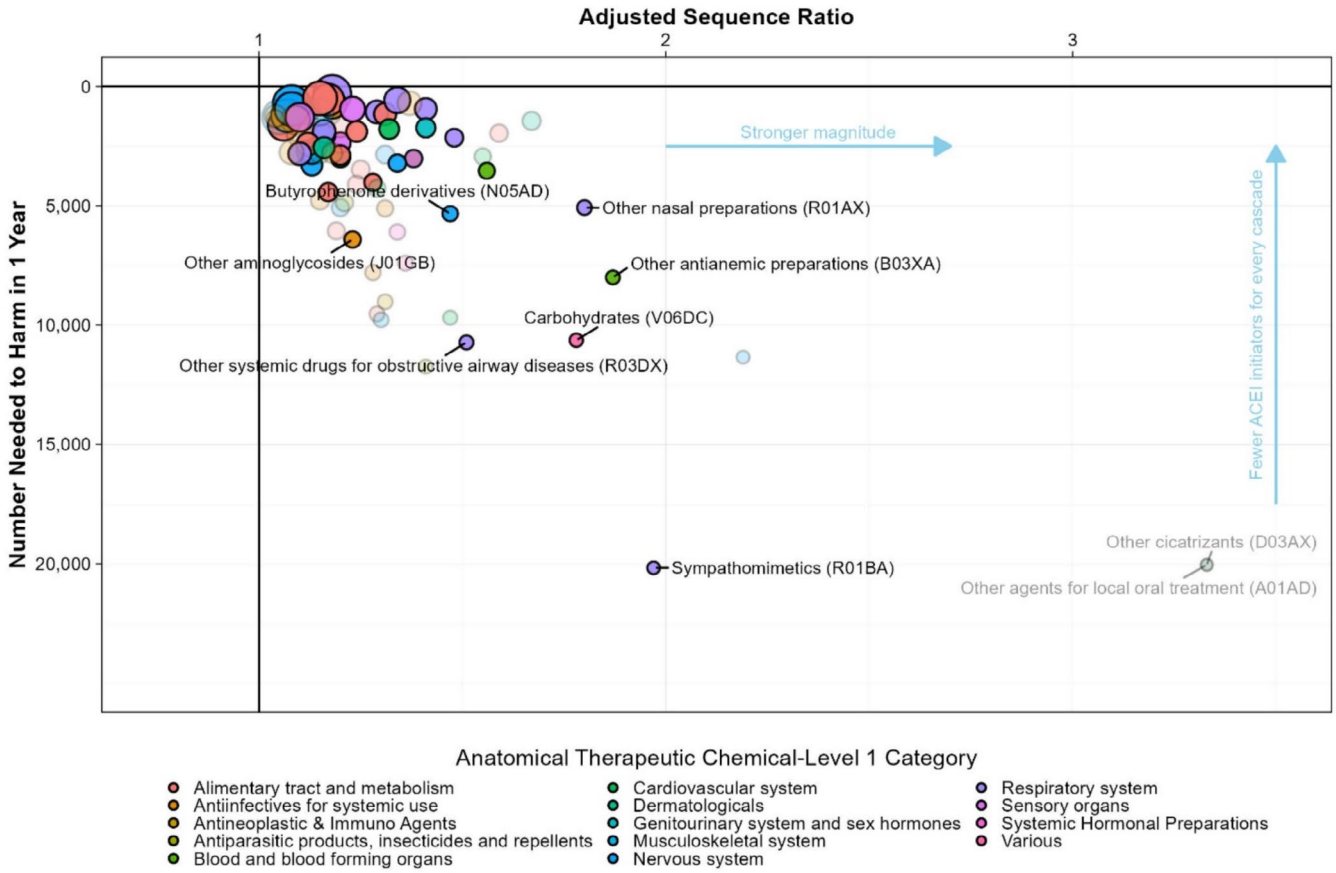


**FIGURE 3** | Significant ACE inhibitor-marker class dyad signals by adjusted sequence ratio and naturalistic number needed to harm. Dyads are grouped (color-coded) at the Anatomical Therapeutic Chemical Level 1 category. The faded dots are dyads classified as "other" while the colored dots are dyads classified as potential prescribing cascades weighted by the total number of prescriptions. Labeled dyads are examples of potential prescribing cascades and "other." All results from the high-throughput screening are displayed interactively at https://public.tableau.com/app/profile/cvmedlab/viz/ACE_newdata/TableofContentsFlowchart2.

thought to be attributed more to disease progression or confounding by indication. Hypertension is an independent risk factor for diabetes, and prior research, including from clinical trials, associates ACEIs with hypoglycemia [94–98]. Additionally, we identified signals with specific immunoglobulins (e.g., varicella/zoster immunoglobulin varicella/zoster immunoglobulin), tetanus vaccines (J07AM), and varicella-zoster vaccines (J07BK), which were determined to be likely detection bias. A plausible explanation for these observed signals could be the enhanced health surveillance that typically occurs when patients start new medications, leading to more frequent monitoring and detection of unrelated health events.

Lisinopril was the most prescribed ACEI in this study (88.4%), followed by benazepril and enalapril (3.7% each). Although ACEIs share a common mechanism of action, differences in chemical structure, pharmacokinetics, and elimination pathways may affect AEs profiles [99–104]. For instance, Captopril, a sulfhydryl-containing ACEI, has a lower incidence of angioedema, possibly due to its shorter half-life [105]. However, the sulfhydryl side group in captopril is also linked to a higher rate of maculopapular skin rashes and dysgeusia than is observed with other ACEIs [106]. Similarly, hypertensive patients with previous ACEI-associated cough reported less frequent cough with fosinopril compared to enalapril [107]. In contrast, evidence from seven head-to-head trials comparing AEs from ACEIs available in the U.S. among patients with hypertension found no significant differences in cough, angioedema, hyperkalemia, or acute renal impairment, with angioedema rates consistently reported at 4 per 1000 users across enalapril, lisinopril, and ramipril [104, 108–114]. While half-life and elimination pathways may explain some of the AE variations, the clinical impact of these pharmacologic differences remains unclear [103, 115–117]. Further research is needed to determine whether these differences result in distinct risks for AEs and PCs.

Our study has several strengths. It is the first high-throughput SSA screening for PCs associated with ACEIs conducted in the US, focusing on one of the most prescribed drug classes using a nationally representative sample of the older population. We classified all significant signals and used an approach that allowed us to assess signals impacting relatively few patients. Additionally, we reported our aggregate findings publicly for transparency.

There are some limitations to note. Signal classification, based on data and clinical knowledge, may be subject to misclassification, though expert review and consensus-based decisions were used to minimize misclassification. The cohort consisted of Medicare beneficiaries, potentially limiting generalizability

to younger populations or those with different health insurance coverage. Additionally, 88% of the cohort were initiated on lisinopril, hence the results may be disproportionately impacted by AE profiles specific to lisinopril. Within-person time-varying biases, such as disease progression or new diagnoses, may also influence the findings, though we attempted to minimize this by restricting marker initiation to a 90-day exposure window around ACEI initiation. While the 90-day window allows for the capture of PCs associated with acute AEs, it may fail to detect PCs associated with AEs with longer latency periods. We did not adjust for multiple testing, which could increase the risk of spurious associations; however, previous studies suggest such corrections may not always be optimal [43, 44, 118, 119].

All potential prescribing cascades identified in this study require validation in well-designed cohort studies, with priority given to medication classes classified as potentially inappropriate for older adults by the Beers Criteria, those with low NNTH values, and those frequently prescribed to large patient populations [120]. For example, corticosteroids, benzodiazepines, and anticholinergics are high-priority, as they meet these criteria and are associated with adverse health outcomes, increased healthcare utilization, and costs [120–131]. Future cohort studies validating these PCs should address methodological limitations of the SSA approach, including using negative controls, adjustment for time-varying confounders, and varying exposure windows [132–135]. After validation, studies should evaluate the risks and benefits of the PCs to assess their clinical appropriateness and identify problematic PCs [136–138]. Such evaluations should also assess for clinical relevance, identify predictors, and characterize high-risk subpopulations. Research could also investigate drug classes prescribed less frequently following ACEI initiation to identify opportunities for drug repurposing.

## 5 | Conclusion

Using the high-throughput SSA screening in a population of Medicare beneficiaries, we identified previously known PCs, as well as new potential PCs based on known ACEI AEs and new potential PCs based on previously unknown AEs. While this approach to identifying PCs should be considered hypothesis-generating, nevertheless, our findings could initiate discussions in clinical settings to ensure that the benefits of ACEI are optimized while minimizing the risks of potentially harmful prescribing practices.

### 5.1 | Plain Language Summary

ACE inhibitors (ACEIs) are widely used to treat high blood pressure, but their side effects can sometimes lead to a prescribing cascade (PC), where additional medications are prescribed to manage these side effects. We conducted a study using Medicare data to identify potential prescribing cascades related to ACEIs. We looked at new ACEI users aged 66 and older, assessing whether they started any of 446 other medication classes within 90 days of initiating an ACEI. We compared how often these additional medications were started after the ACEI versus before it and calculated the risk of a prescribing cascade.

We studied 308 579 people who began using ACEIs, most of whom were female (59.6%) and had been diagnosed with high blood pressure (88.6%). Out of the 446 medication classes we analyzed, 81 were statistically significant prescribing cascade signals, with 42 classified as plausible prescribing cascades. Some of the strongest signals for potential cascades were found with corticosteroids and serotonin ($5\text{-}HT_3$) antagonists.

Our findings suggest that these PCs could be linked to known and possibly underrecognized side effects of ACEIs. However, since these results are hypothesis-generating, more research is needed to understand their impact on health outcomes and to reduce harmful prescribing practices.


### Author Contributions

Asinamai M. Ndai contributed to the study design and drafted the manuscript. Steven M. Smith, Earl J. Morris, and Scott M. Vouri conceived and designed the study and secured funding. Earl J. Morris, Asinamai M. Ndai, Shailina Keshwani, Scott M. Vouri, Kayla Smith, and Steven M. Smith were responsible for the statistical analysis and visualization of the data. All authors made substantial contributions to the interpretation of the data and results, reviewed, provided critical revisions, and approved the final manuscript.

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### Ethics Statement

The study was approved as Exempt by the University of Florida Institutional Review Board.

### Conflicts of Interest

Scott M. Vouri is a current employee at Pfizer Inc., but he was employed by the UF College of Pharmacy at the initiation of the project.

### Data Availability Statement

The study was conducted using CMS Medicare Fee-for-Service claims databases, pursuant to a data use agreement between the University of Florida and CMS that prevents the sharing of data entrusted to the University of Florida. However, qualified researchers can obtain such data directly from CMS. The SAS code used in this study is available from the Corresponding Author upon reasonable request.


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**Supporting Information**

Additional supporting information can be found online in the Supporting Information section.