Evaluation of a Beta-Blocker–Edema–Loop Diuretic Prescribing Cascade: A Prescription Sequence Symmetry Analysis

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BACKGROUND

Drug-related adverse events associated with antihypertensive therapy may result in subsequent prescribing of other potentially harmful medications, known as prescribing cascades. The aim of this study was to assess the magnitude and characteristics of a beta-blocker–edema–loop diuretic prescribing cascade.

METHODS

A prescription sequence symmetry analysis was used to assess loop diuretic initiation before and after initiation of beta-blockers among patients 20 years or older without heart failure, atrial fibrillation, other arrythmias, or use of calcium channel blocker within a U.S. private insurance claims database (2005–2018). The temporality of loop diuretic initiation relative to a beta-blocker or negative control (renin-angiotensin system blocker) initiation was tabulated. Secular trend-adjusted sequence ratios (aSRs) with 95% confidence intervals (CIs) compared the initiation of loop diuretic 90 days before and after initiation of beta-blockers.

RESULTS

Among 988,675 beta-blocker initiators, 9,489 patients initiated a new loop diuretic prescription 90 days after and 5,245 patients before beta-blocker initiation, resulting in an aSR of 1.78 (95% CI, 1.72–1.84). An estimated 1.72 beta-blocker initiators per 100 patient-years experienced the prescribing cascade in the first 90 days. The aSR was disproportionately higher among older adults (aSR 1.97), men (aSR 2.25), and patients who initiated metoprolol tartrate (aSR 2.48), labetalol (aSR 2.18), or metoprolol succinate (aSR 2.11). Negative control results (aSR 1.09, 95% CI, 1.05–1.13) generally corroborated our findings, but suggested modest within-person time-varying confounding.

CONCLUSIONS

We observed excess use of loop diuretics following beta-blocker initiation that was only partially explained by secular trends or hypertension progression.

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Initially submitted August 11, 2021; date of first revision November 12, 2021; accepted for publication January 29, 2022; online publication February 1, 2022.

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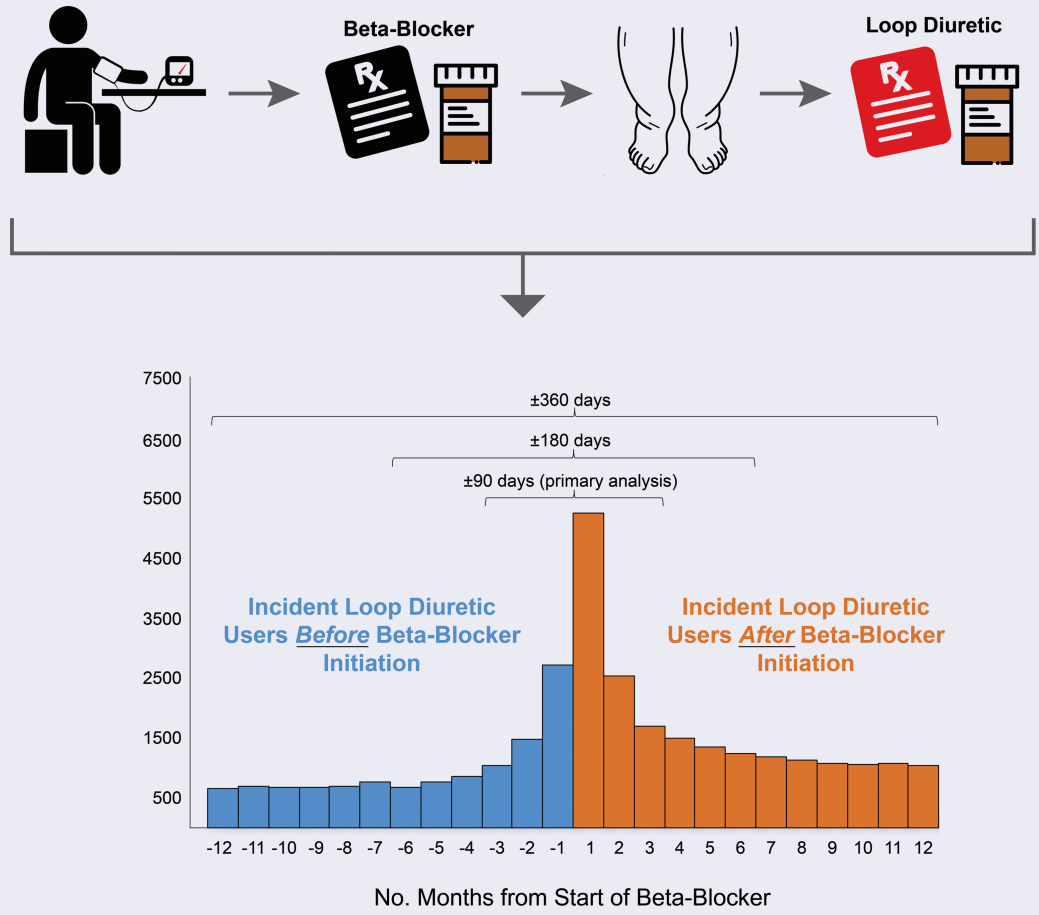
GRAPHICAL ABSTRACT



Keywords: beta-blockers; blood pressure; drug-induced adverse events; hypertension; loop diuretics; prescribing cascades

doi:https://doi.org/10.1093/ajh/hpac013

Beta-blockers are a common treatment option for hypertension, arrhythmias, acute ischemic syndromes, or heart failure, with demonstrated benefits on morbidity and mortality in secondary prevention.[1] Their use is ubiquitous, with over a third of U.S. adults receiving a beta-blocker regimen in 2013–2016.[2] However, these medications can be associated with adverse events that reduce quality of life and/or have other serious consequences.[3] Several of these adverse events are well-known, such as bradycardia and fatigue, although lesser-known events, such as peripheral edema, can also contribute to patient dissatisfaction.

Prior randomized-controlled trials suggest a higher risk for peripheral edema in patients assigned to beta-blocker treatment when compared to patients assigned to placebo.[4–6] This relatively high incidence contrasts with common unawareness about this particular side effect potential, positioning beta-blockers as candidates for prescribing cascades, which occur when a drug-induced adverse event is treated with a new medication instead of deprescribing the offending medication and using an alternative.[7] Such prescribing cascades contribute to worsening polypharmacy with the potential for unnecessary downstream consequences such as additional adverse events and increased healthcare utilization.[8,9] In the case of beta-blocker-induced edema, in the absence of congestive heart failure, atrial fibrillation, or arrhythmias, continuation of the beta-blocker and addition of a loop diuretic may constitute a prescribing cascade.[8]

The extent to which beta-blocker-induced peripheral edema results in excess use of a loop diuretic has not been explored. Therefore, we evaluated the risk for this prescribing cascade with beta-blockers, overall and for individual agents, among a large sample of commercially insured patients in the United States.

METHODS

Study Design

A prescription sequence symmetry analysis (PSSA) was used to assess for temporal patterns of loop diuretic

initiation relative to the initial beta-blocker prescription. This pharmacovigilance approach, using a case-only design, has produced similar results when compared with a cohort study design for other antihypertensive prescribing cascades.[8,10] A PSSA works by first identifying patients who initiated the medication suspected of causing a drug-induced adverse event (*index* drug, i.e., a beta-blocker) and, among these patients, selects everyone who initiated a medication potentially used to treat the adverse event (*marker* drug, i.e., a loop diuretic) within a specified *exposure window* (±90 days of index drug initiation).[11] Using the PSSA, pre-index drug initiation of marker drugs serves as a control in relationship to post-index drug initiation of marker drugs.[12] Therefore, if a similar number of patients initiate the marker drug before and after the index drug, then no prescribing cascade signal is observed, and the resulting graphical representation of prescription sequence appears symmetrical. However, in the case of a positive prescribing cascade signal, the marker drug is initiated more often after the index drug compared to before resulting in an asymmetric pattern, which can be quantified (see Statistical Analysis). Additionally, a benefit of the PSSA, when compared to a traditional cohort study, is that time-invariant confounders (e.g., age, sex, comorbidities) are inherently adjusted, reducing the need for complex multivariable analyses.[13]

Data source

IBM MarketScan Commercial and Medicare Supplemental Claims data from January 2005 to December 2018 were used for the presented analyses. These U.S. nationwide administrative claims databases contain longitudinal, person-level information of healthcare utilization across all settings, including outpatient visits, hospital stays, and pharmacy dispensings. The study population includes employees and their dependents, and retirees with employer-sponsored or government Medicare supplemental insurance. The study was exempted from review by the University of Florida institutional review board because of its use of deidentified data. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline to ensure appropriate reporting.[14]

Study population

Beta-blocker *initiators* were identified among patients aged ≥20 years who had at least 720 days of continuous enrollment before and 360 days after their initial beta-blocker claim. Patients with an inpatient or outpatient diagnosis of heart failure within 720 days before and 360 days after the initial beta-blocker claim were excluded since use of a loop diuretic for heart failure–related fluid overload would not be considered a prescribing cascade (Supplementary Appendix 1). Additionally, patients initiated on a calcium channel blocker within 720 days before and 360 days after beta-blocker initiation were excluded as these agents are associated with edema and can cause a similar prescribing cascade.[8,10] Finally, patients with arrythmias (Supplementary Appendix 1) were excluded since there are few alternatives for rate control among patients who are unable to utilize a calcium channel blocker resulting in the risk versus benefit assessment of a beta-blocker prescribing cascade and arrythmias may be independently associated with edema.[15] We identified the *initial loop diuretic claim* (e.g., furosemide, bumetanide, torsemide, ethacrynic acid) within 90 days before or after the initial beta-blocker claim, and excluded patients initiating both index and marker drugs on the same date.[16,17] We utilized a 90-day exposure window as the primary analysis to minimize within-patient time-varying bias (i.e., loop diuretics are generally used later in an antihypertensive regimen, suggesting hypertension progression, which could create a similar asymmetric pattern not attributable to a prescribing cascade).[18] We performed sensitivity analyses using 180-day and 360-day exposure windows to assess for the potential of delayed diagnosis (and subsequent treatment) for drug-induced edema.

We performed stratified analyses among subpopulations based on age (<65 and ≥65 years), sex, calendar year, initial beta-blocker medication (acebutolol, atenolol, bisoprolol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, propranolol, carvedilol, labetalol), and diagnosis of chronic kidney disease (Supplementary Appendix 1).

To account for potential false positive signals related to loop diuretic use as subsequent line therapy for additional blood pressure-lowering (e.g., within-person time-varying bias), we performed additional analyses using negative control index drugs (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]) not known to cause edema, in place of beta-blockers.[8,18] This negative control analysis was in addition to utilizing the pre-index drug utilization of the marker drug (i.e., pre-beta-blocker initiation of loop diuretics) as the control since this control only accounts for time-invariant confounding. More specifically in these negative control analyses, we restricted the cohort to patients without a diagnosis of heart failure or arrythmia who were initiated on either an ACE inhibitor or ARB as the index drug, again with loop diuretics as the marker drug. This analysis excluded patients initiating a beta-blocker or calcium channel blocker within ±90 days of the index ACE inhibitor or ARB. We performed similar stratified and sensitivity analyses for the negative control as in the primary analyses.

Statistical analysis

Crude sequence ratios (cSRs) were calculated as the number of patients initiating the loop diuretic after the initial beta-blocker claim divided by the number of patients initiating a loop diuretic before the initial beta-blocker claim. We graphically represented the cSR by plotting initial loop diuretic claims within 90 days before and after the initial beta-blocker claim, in 30-day increments.[19] To adjust for secular trends in medication use (i.e., increasing or decreasing use of loop diuretics or beta-blockers during the study period), we calculated the null-effect sequence ratio. The null-effect sequence ratio estimates the expected sequence ratio in the absence of a causal relationship, given population-based background prescribing trends. An adjusted sequence ratio (aSR) with 99% confidence intervals (CIs) was then calculated by dividing the cSR by the null-effect ratio.[20]

The cumulative incidence proportion of loop diuretic initiation attributable to beta-blocker initiation was estimated as the difference in subjects who initiated beta-blocker followed by loop diuretic minus subjects who initiated loop diuretic before the by beta-blocker divided by the number of beta-blocker initiators in the cohort.[8] Incidence and accompanying 99% confidence intervals were estimated for each exposure window (90, 180, and 360 days) and standardized per 100 patient-years. We also calculated the estimated incidence of this prescribing cascade among beta-blocker initiators in 3 periods (i.e., 2007–2010, 2011–2014, and 2015–2018) and among the previously described subpopulations using stratum-specific incidence estimates.

All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC). To account for multiple testing, we chose to report 99% confidence intervals.

RESULTS

In total, 12,218,359 patients were identified as beta-blocker initiators. After applying health plan enrollment and exclusion criteria (Figure 1), the final study cohort for the primary analysis comprised 14,734 patients who initiated a loop diuretic, including 4,875 (33.1%) aged ≥65 years, 8,272 (56.1%) women, and 3,615 (24.5%) with chronic kidney disease (Table 1). Metoprolol tartrate was the most frequently initiated beta-blocker (n = 4,178 [28.4%]) followed by metoprolol succinate (n = 3,567 [24.2%]), carvedilol (n = 2,014 [13.7%]), and atenolol (n = 1,811 [12.3%]).

Results of the primary and stratified analyses are presented in Table 1. Loop diuretics were initiated 81% more often after beta-blocker initiation than before (cSR, 1.81). Adjustment for secular prescribing trends attenuated the sequence ratio slightly (aSR, 1.78; 99% CI, 1.72–1.84). Excess initial loop diuretic use tended to occur soon after initial beta-blocker initiation as shown in Figure 2.

In the stratified analyses, the aSR was disproportionately higher among older adults (aSR 1.97, 99% CI, 1.85–2.09) than younger adults (aSR 1.68, 95% 1.62–1.75) and men (aSR 2.25, 99% CI, 2.13–2.37) than women (aSR 1.49, 99% CI, 1.43–1.56). Additionally, we observed different aSRs among individual beta-blockers in which 6 of 10 beta-blockers studied had a positive signal, indicated by the lower bound of the 99% confidence interval > 1. The strongest signals were seen with metoprolol tartrate (aSR 2.48, 99% CI, 2.32–2.65) and labetalol (aSR, 2.18, 99% CI, 1.87–2.56), followed by metoprolol succinate (aSR, 2.11, 99% CI, 1.97–2.27). No significant signal was observed for acebutolol, nadolol, nebivolol, or propranolol; although, confidence intervals became wider due to smaller sample size, especially for acebutolol (aSR 1.58, 99% CI, 0.57–4.34).

Among beta-blocker initiators, we estimated 1.72 excessive initiations of loop diuretics per 100 patient-years. Among subpopulations, the estimated incidence of the prescribing cascade per 100 patient-years was highest among older vs. younger adults (4.09 vs. 1.25), men vs. women (2.36 vs. 1.23), and patients with vs. without chronic kidney disease (4.82 vs. 1.40; Table 1). There was a slight decrease in the prescribing cascade incidence over the duration of the study period (2007–2010, 1.87; 2011–2014, 1.56; 2015–2018, 1.72).

We conducted several sensitivity analyses. First, when applying restrictions to the exposure window, we observed findings similar to the primary analysis, for both the 180-day exposure window (aSR, 1.76; 99% CI, 1.71–1.81; Supplementary Appendix 3) and 360-day exposure window (aSR, 1.71; 99% 1.67–1.74; Supplementary Appendix 4). The negative control analysis replacing beta-blocker initiation

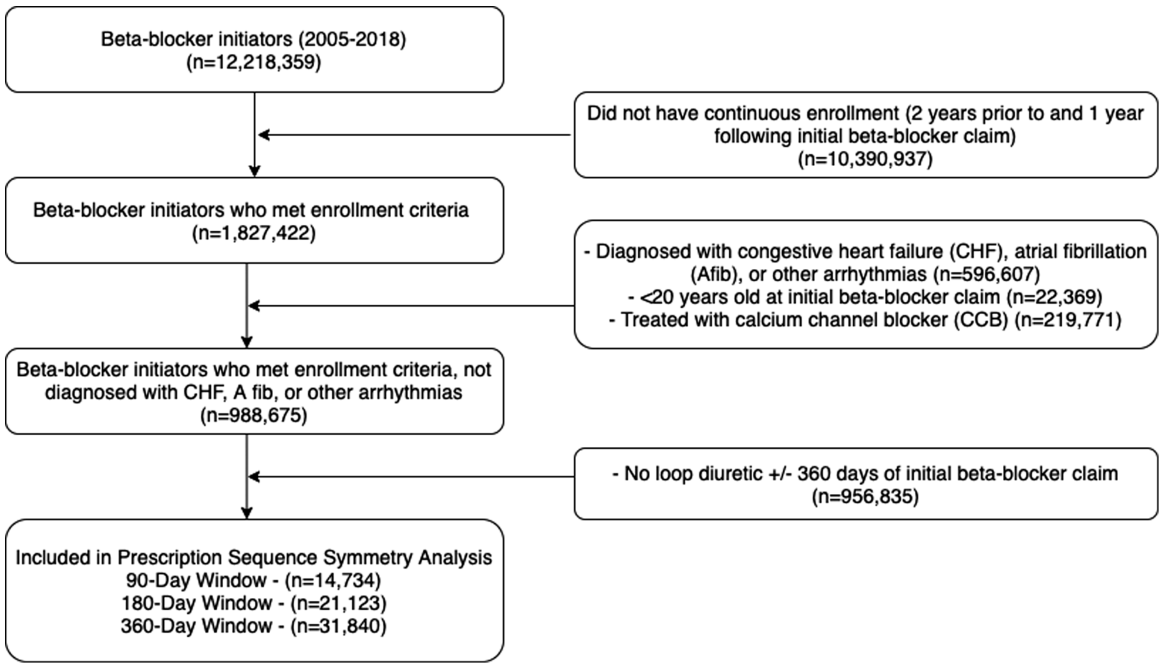


Figure 1. Flow diagram for development of study cohort.

Table 1. Prescribing order of initial loop diuretic and initial beta-blocker

BB	BB initiators (*n*)[a]	Total number (*n*)	Number of patients on loop diuretic (*n*)		Null-effect ratio	Crude sequence ratio	Adjusted sequence ratio (99% CI)	Incidence per 100 person-years
			After BB	Before BB				
Primary analysis	988,675	14,734	9,489	5,245	1.02	1.81	1.78 (1.72–1.84)	1.72
Age								
20–64 years	825,164	9,859	6,216	3,643	1.01	1.71	1.68 (1.62–1.75)	1.25
≥65 years	163,511	4,875	3,273	1,602	1.04	2.04	1.97 (1.85–2.09)	4.09
Sex								
Men	426,953	6,462	4,492	1,970	1.01	2.28	2.25 (2.13–2.37)	2.36
Women	561,722	8,272	4,997	3,275	1.02	1.53	1.49 (1.43–1.56)	1.23
Chronic kidney disease								
Yes	91,618	3,615	2,359	1,256	1.02	1.88	1.85 (1.72–1.98)	4.82
No	897,057	11,119	7,130	3,989	1.02	1.79	1.75 (1.69–1.82)	1.40
Year								
2007–2010	365,575	5,991	3,851	2,140	1.02	1.80	1.76 (1.67–1.86)	1.87
2011–2014	370,511	5,342	3,393	1,949	1.03	1.74	1.70 (1.61–1.79)	1.56
2015–2018	252,589	3,401	2,245	1,156	1.03	1.94	1.88 (1.75–2.02)	1.72
Individual BB medications								
Acebutolol	737	16	10	6	1.06	1.67	1.58 (0.57–4.34)	2.17
Atenolol	165,303	1,811	1,118	693	1.03	1.61	1.56 (1.42–1.71)	1.03
Bisoprolol	28,468	262	163	99	1.06	1.65	1.56(1.21–2.00)	0.90
Carvedilol	67,806	2,014	1,241	773	1.02	1.61	1.58 (1.44–1.73)	2.76
Labetalol	37,576	721	496	225	1.01	2.20	2.18 (1.87–2.56)	2.88
Metoprolol succinate	249,016	3,567	2,439	1,128	1.02	2.16	2.11 (1.97–2.27)	2.11
Metoprolol tartrate	179,789	4,178	2,988	1,190	1.02	2.51	2.48 (2.32–2.65)	4.00
Nadolol	12,301	432	176	256	0.99	0.69	0.70 (0.58–0.84)	*
Nebivolol	58,245	667	332	335	1.03	0.99	0.96 (0.83–1.12)	*
Propranolol	189,434	1,066	526	540	1.01	0.97	0.97 (0.86–1.09)	*

Abbreviations: BB, beta-blockers; CI, confidence interval.

*Unable to calculate incidence if aSR is not statistically signficant.

with the initiation of an ACE inhibitor or ARB produced a modest positive signal in the primary analysis (aSR 1.09, 99% CI, 1.05–1.13; Figure 3), suggesting slight within person time-varying bias and a possible overestimation of the effect size in the primary analysis (Supplementary Appendix 2). Similar findings were seen across all stratified analyses with the negative control except in age in which there was a slightly higher aSR among adults ≥65 years (aSR 1.20) compared with adults aged 20–64 (aSR 1.03; Supplementary Appendix 2). When expanding exposure windows to 180 and 360 days, a further increase in the aSR for the negative control was noted for both the 180-day exposure window (aSR, 1.18; 99% CI, 1.14–1.21) and 360-day exposure window (aSR, 1.29; 99% CI, 1.27–1.32), while there were slight decreases in aSR for the beta-blocker aSR, as noted above, thus further reinforcing the use of a 90-day exposure window to mitigate within-person time-varying bias.

DISCUSSION

Peripheral edema is a well-known adverse effect of some antihypertensive drugs, most notably dihydropyridine calcium channel blockers.[8,10] Although less often, edema can also occur in response to beta-blocker therapy. In the present analysis, we sought to determine whether a beta-blocker–peripheral edema–loop diuretic cascade may also exist in clinical practice, whereby initiation of beta-blockers would be associated with a subsequent increase in loop diuretic use. After excluding patients with heart failure or arrhythmias (up to 720 days before through 360 days after beta-blocker initiation) and those treated with any type of calcium channel blocker during that same period of time, we observed signals supporting such a prescribing cascade, as evidenced by the overall aSR of 1.78 (99% CI, 1.72–1.84). In this commercially insured U.S. population, we further observed this prescribing cascade to have an estimated incidence of 1.72 per 100 beta-blocker initiators. Qualitatively similar findings were observed in stratified analyses, although the magnitude of the effect was larger in older adults and in men. We also observed some variation across beta-blockers, with the strongest effect sizes noted for metoprolol and labetalol, whereas no significant effect was noted for nadolol, nebivolol, and acebutolol, though confidence intervals for some agents were wide due to small sample size. To our knowledge, this is the first study to support the presence of this prescribing cascade.

The presence of a beta-blocker–peripheral edema–loop diuretic prescribing cascade has some mechanistic support. Vasodilator-related peripheral edema is a prevalent adverse effect of many antihypertensive drugs. Although peripheral edema is most pronounced with direct vasodilators (e.g., hydralazine, minoxidil) and dihydropyridine calcium channel blockers, it can also occur with some anti-adrenergic, mostly alpha-adrenergic blocker agents.[21] Several mechanisms may be responsible for this effect, but most pertinent to anti-adrenergic agents may be that arteriolar vasodilation increases intracapillary pressure with resultant fluid transudation into the interstitium.

Accordingly, we hypothesized that beta-blockers with additional vasodilatory activity (e.g., carvedilol, labetalol, nebivolol) would be most likely cause prescribing cascades; however, these medications had mixed signals including no signal (nebivolol, aSR 0.96), comparatively weaker yet significant signal (carvedilol, aSR 1.58), and strong signal (labetalol, aSR 2.18). It is possible our findings reflect providers' knowledge of differential risks for edema based on individual beta-blockers' vasodilatory activity resulting in the avoidance of subsequent loop diuretic use in patients who develop edema thus reducing the aSR. However, our strongest signals were observed with metoprolol tartrate, labetalol, and metoprolol succinate, suggesting that other mechanisms may drive edema occurrence with beta-1 selective agents. For example, beta-blocker initiation may be accompanied by a compensatory rise in sympathetic nervous system activity,

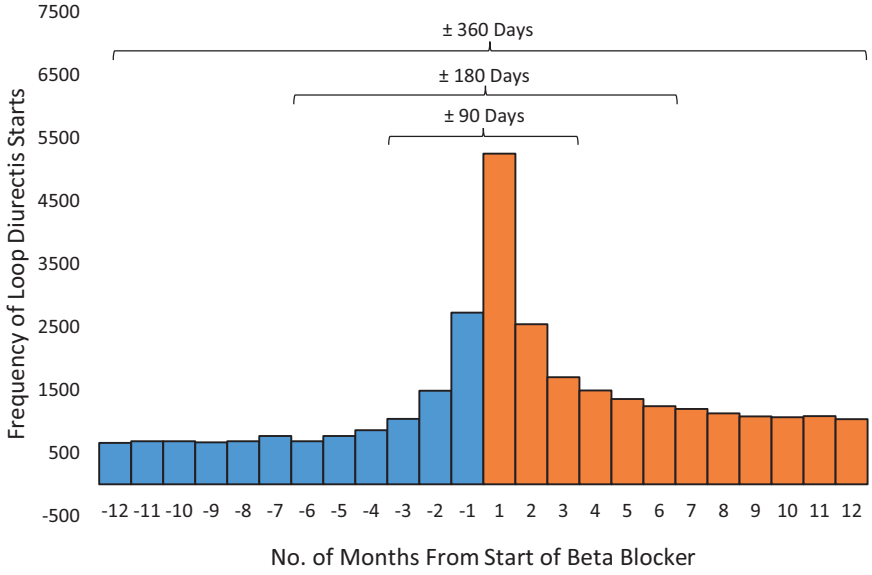


Figure 2. Assessment of prescription sequence symmetry of initial loop diuretic prescription within 360 days of initial beta-blocker prescription.

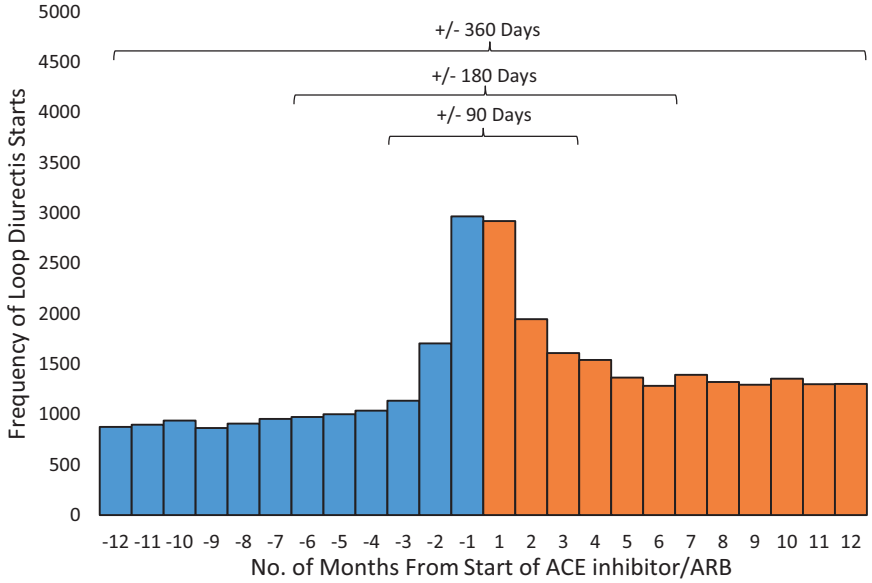


Figure 3. Assessment of prescription sequence symmetry of initial loop diuretic prescription within 360 days of initial ACE inhibitor or ARB (negative control) prescription.

including renal sympathetic nerve activity, that promotes sodium and fluid retention, particularly early in therapy. Such an effect may be prominent in agents with β-adrenergic selectivity because of unopposed norepinephrine stimulation at α-adrenergic receptors.[22] Alternatively, it is possible that these signals at least partially reflect exacerbations of underlying and undiagnosed left ventricular dysfunction.

Although our overall findings support the existence of a beta-blocker–loop diuretic prescribing cascade, we identified a modest, statistically significant signal in the negative control analysis (ACE inhibitor or ARB; aSR 1.09, 99% CI, 1.05–1.13), suggesting some within-patient time-varying bias. We suspect the likely cause for this finding is hypertension progression, namely that loop diuretics are typically used as add-on therapy in more advanced antihypertensive regimens. Such effects have been identified in other prescribing cascade research.[19] Moreover, within-patient time-varying bias is the likely explanation of this finding as the signal of the negative control strengthened with larger exposures (aSR 1.09 for 90 days, aSR 1.18 for 180 days, and 1.29 for 360 days) while the beta-blocker remained relatively unchanged (aSR 1.78 for 90 days, 1.76 for 180 days, and 1.71 for 360 days).

In stratified analyses, we identified several subgroups with comparatively stronger effect sizes and large differences in incidence. Comparing men versus women, there was a greater effect size (aSR 2.25 vs. 1.49) and higher incidence per 100 patient-years (2.36 vs. 1.23), with similar aSR and incidence among negative controls. We initially hypothesized women would be more likely to report edema,[23] and therefore practitioners more likely to initiate a loop diuretic; however, our contrary findings align with prior findings of the dihydropyridine calcium channel blocker–loop diuretic prescribing cascade.[8] It is also possible women may be more attuned to the relationship between beta-blocker initiation and adverse drug effects, and therefore alter or discontinue the beta-blocker regimen thus avoiding the prescribing cascade. Differential treatment approaches may also exist between men and women, such as the use of compression stockings, which was not explored in our study. We also noted a slightly stronger effect size in older versus younger adults (aSR 1.97 vs. 1.68). We suspect this difference is at least partially a result of within-person time-varying bias (e.g., hypertension progression) given that a similar difference in effect size was observed in the negative control analysis (older vs. younger adults: aSR 1.20 vs. 1.03).

Finally, the magnitude of the association was only slightly higher in patients with chronic kidney disease (aSR 1.85) vs. those without (aSR 1.75); however, the incidence of excessive loop diuretic prescribing was more pronounced among patients with chronic kidney disease (4.82 vs. 1.40 per 100 patient-years).

Our findings were strengthened by the use of stratified analyses to evaluate differences among subpopulations. Additionally, we incorporated a negative control analysis which suggests minimal within-person time-varying bias (potentially due to hypertension progression). We also excluded patients with atrial fibrillation or other arrythmias since arrythmias may be independently associated with edema. As noted by others,[24] prescribing cascades may not always be possible to avoid (e.g., potassium supplementation to treat loop diuretic-induced hypokalemia). In many patients it may be more appropriate to continue the beta-blocker (and loop diuretic) use instead of transitioning to a medication for rhythm control, given its proarrhythmic risk.[15,25,26] Finally, we used a narrow exposure window of 90 days as our primary analysis to ensure a more proximate relationships between beta-blocker initiation and the potential treatment of short-term adverse effects.

In addition to the strengths of our study summarized above, several limitations are noteworthy. First, we excluded patients filling calcium channel blocker prescriptions to

minimize the effects of these medications on edema, potentially reducing generalizability to patients with more complex antihypertensive regimen. Second, we excluded patients with a diagnosis of heart failure using validated measures with excellent specificity (>95%) and negative predictive value (75%). This definition, combined with signals that were more modest or absent altogether beta-blockers that are commonly used for patients with heart failure (e.g., carvedilol, nebivolol), suggest that misclassification of diagnosed heart failure was not a primary cause of the observed signals; however, we cannot exclude the possibility of misclassification where undiagnosed heart failure may provide alternative explanations for loop diuretic use.[27] Third, we relied on prescription fill data and could not confirm the consumption of the index or marker drugs. Significant nonadherence or nonpersistence would bias our analysis toward a null effect. Fourth, we did not restrict our sample to any one particular indication such as hypertension or other cardiovascular disease and it is possible patients may have been treated with beta-blockers for noncardiovascular indications (e.g., propranolol for migraine). Therefore, alternative treatments to replace beta-blockers after the development of edema may not necessarily be other antihypertensive agents. Fifth, we restricted our analyses to treatment with a loop diuretic and not all diuretics (including thiazides). Although we acknowledge thiazide diuretic may be used to treat drug-induced edema, within the construct of the PSSA, thiazide diuretics would likely appear to have a protective effect as they are more commonly prescribed before the initiation of beta-blockers in guideline-driven antihypertensive prescribing rather than following the initiation of beta-blockers to treat drug-induced edema.

In summary, we found increased utilization of loop diuretics following beta-blocker initiation among patients without heart failure, arrythmias, or use of calcium channel blockers. Our negative control analysis suggested modest bias in the overall findings. Nevertheless, the comparatively larger effect size in the main analysis supports the presence of a beta-blocker–loop diuretic prescribing cascade, with an incidence between 1 and 2 prescribing cascades per 100 person-years. These findings support the need for careful consideration of drug-induced edema, in patients presenting with such signs or symptoms who have recently started a systemic beta-blocker.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

FUNDING

None declared.

DISCLOSURE

The authors declared no conflict of interest.

ACKNOWLEDGMENT

Ann-Kathrin Hofer completed a portion of this project as Pharmacy Intern from Germany.

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