ORIGINAL ARTICLE

Use of Prescription Medications That Potentially Interfere With Blood Pressure Control in New-Onset Hypertension and Treatment-Resistant Hypertension

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BACKGROUND
Withdrawing medications that interfere with blood pressure (BP) is recommended in patients with uncontrolled BP, yet real-world use of such agents is not well characterized among individuals with hypertension. We aimed to evaluate the use of BP-interfering prescription medications among US patients with hypertension.

METHODS
This retrospective drug utilization study used medical and prescription claims (January 2008 to December 2014) in the MarketScan commercial claims database. We included adults, aged 18–65 years, with a hypertension diagnosis (*International Classification of Diseases, Ninth Revision*, code 401) and ≥1 antihypertensive medication fill. Two hypertension cohorts were examined—new antihypertensive drug users (incident hypertension) and patients requiring titration to a fourth antihypertensive (incident treatment-resistant hypertension [TRH]). Patient-level exposure to BP-interfering medications was assessed 6 months before and after the index date, defined as the first prescription fill of an antihypertensive drug or the first occurrence of overlapping use of ≥4 antihypertensive drugs.

RESULTS
We identified 521,028 patients with incident hypertension and 131,764 patients with incident TRH. The most prevalent BP-interfering prescription medications were nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophens, and hormones. Overall, 18.3% of the incident hypertension cohort and 17.6% of the incident TRH cohort initiated a BP-interfering medication following antihypertensive titration. Among patients previously taking a BP-interfering medication, 57.6% with incident hypertension and 64.9% with incident TRH refilled that medication after antihypertensive intensification.

CONCLUSIONS
The use of prescription BP-interfering medications, especially NSAIDs, is prevalent among patients requiring intensification of their antihypertensive regimen. Greater efforts to limit the use of these medications, where feasible, may be required among patients with uncontrolled hypertension.

Keywords: acetaminophen; blood pressure; hypertension; interference; prevalence; nonsteroidal anti-inflammatory drugs; resistant hypertension.

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Hypertension, the most common chronic disease, affects approximately 103.3 million adults in the United States and 1.4 billion adults worldwide.[1,2] Prior studies have demonstrated the importance of blood pressure (BP) reduction and linked uncontrolled hypertension to an increased cardiovascular risk.[3–6] Although attaining high BP control rates is feasible in the clinical trial setting, achieving similarly high BP control in the real world has been challenging. For example, awareness and treatment of hypertension have increased substantially over the past half century in the United States; yet, these changes have been followed by only modest improvements in BP control nationwide.[7] Moreover, difficult-to-control hypertension phenotypes, such as treatment-resistant hypertension (TRH), continue to rise.[7]

The exact etiologies contributing to uncontrolled BP are incompletely understood but may include suboptimal regimens, nonadherence, and clinical inertia. Drug interactions also may play a significant role and numerous medications have been shown to increase BP and interfere with BP control.[8] Identification and withdrawal of potentially interfering medications is generally recommended as part of the management of uncontrolled hypertension, particularly in patients with more severe and difficult-to-treat phenotypes such as TRH.[9] Yet, little is known regarding the scale of use of these medications in the general population with hypertension, and particularly, in patients with more difficult-to-control phenotypes requiring antihypertensive regimen titration. Therefore, we aimed to characterize the use of medications that can interfere with BP control among patients with hypertension. Because the use of interfering medications is most pertinent, clinically, in patients with uncontrolled BP, we focused our investigation on analyzing

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the use of these medications in conjunction with incident hypertension and incident TRH—i.e., in patients requiring initial antihypertensive therapy or substantial antihypertensive titration, respectively. The latter group was included to explore the extent to which these drugs may contribute to particularly difficult-to-control hypertension phenotypes and to allow for comparison between early and more advanced stages of hypertension.

METHODS

Study design and data sources

We performed a drug utilization study to examine the use of potential BP-interfering medications among 2 hypertension cohorts: (i) patients with incident hypertension, requiring initial pharmacological antihypertensive treatment and (ii) patients with incident TRH, requiring the addition of a fourth antihypertensive agent. We analyzed medical and prescription administrative claims data from January 2008 to December 2014 in the MarketScan commercial claims database, which is representative of Americans receiving employer-based insurance (approximately 55% of the US population).[10] MarketScan covers approximately 30 million patients annually and receives health-care utilization data from 130 employer-sponsored health plans across the United States. The study was designed by the authors and approved by the Institutional Review Board at the University of Florida.

Cohort development

Figure 1 summarizes cohort identification for those with incident hypertension and incident TRH. In both cohorts, we included adults aged 18–65 years, with evidence of primary hypertension (*International Classification of Diseases,*

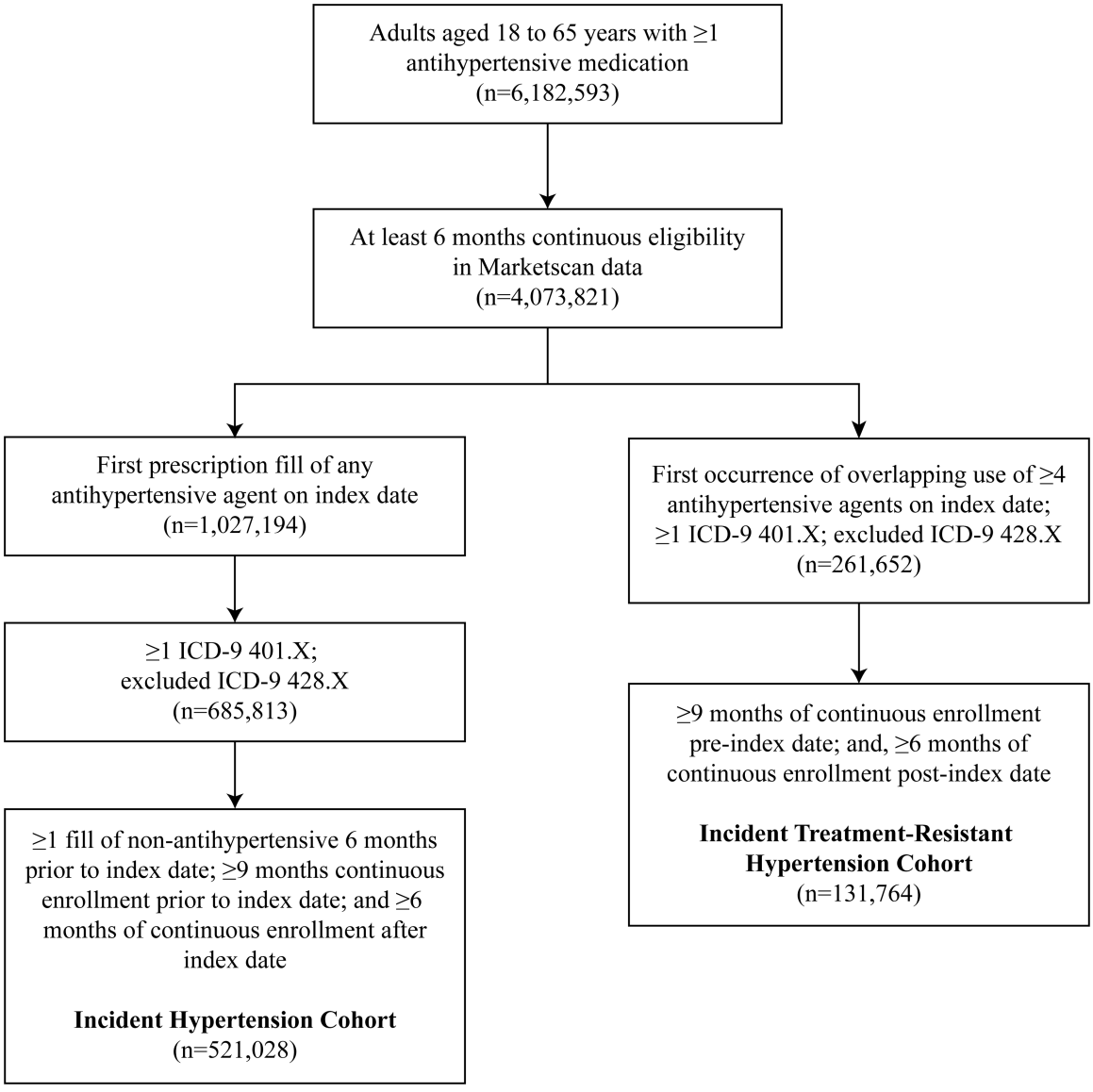

Figure 1. Flow diagram illustrating the development of the 2 hypertensive cohorts. Abbreviation: TRH, treatment-resistant hypertension.

Ninth Revision, code 401.X) and no evidence of heart failure (*International Classification of Diseases, Ninth Revision*, code 428.X). For the incident hypertension cohort, we identified patients newly initiated on an antihypertensive medication after a 6-month look-back period. To ensure pharmacy utilization, patients were required to have at least 1 non-antihypertensive prescription fill during this look-back period. The index date for the incident hypertension cohort was defined as the first fill date for an antihypertensive medication. A detailed description of the development of the incident TRH cohort has been previously published.[11] Briefly, the incident TRH cohort was derived from all patients with treated hypertension, including patients with incident hypertension during the study period and patients with prevalent treated hypertension at study entry. Patients with incident TRH were required to have at least 60 days of overlapping use of ≥4 antihypertensive drugs, and each antihypertensive drug was required to have been filled at least twice. The index date for the incident TRH cohort was defined as the first occurrence of concurrent use of 4 antihypertensive drugs. For both cohorts, patients were also required to have continuous health-care eligibility 9 months before, and 6 months after, their index date. Comorbid conditions were assessed in the 9-month period before and including the index date.

Identification and selection of interfering medications

We performed a literature review of English-language publications between January 1966 and September 2016 from searches of PubMed using key terms "blood pressure," "interfering," "drugs," "drug-induced," and "hypertension." Review articles describing medications or substances that can potentially interfere with BP control and contribute to secondary hypertension were individually searched for additional references.[8,12,13] Interfering medications were then selected based on the availability of published data supporting their effects on increasing BP. Where possible, we combined interfering medications according to therapeutic class (i.e., nonsteroidal anti-inflammatory drugs [NSAIDs]) or putative mechanism of BP elevation. Specifically, drugs were assigned to one of the following categories: acetaminophen, angiogenesis inhibitors, antidepressants, aspirin, buspirone, corticosteroids, erythropoiesis-stimulating agents, hormones, immunosuppressants, NSAIDs, stimulants, and sympathomimetics. NSAIDs were also studied individually. Only systemic formulations (e.g., oral, parenteral) of the drugs were included in our analysis. Specific drugs included within each category are listed in Supplementary Table 1.

Analysis

We analyzed utilization patterns of prescription BP-interfering medications among patients with incident hypertension and incident TRH, and used these prescription fill data as a surrogate for drug exposure (as commonly used in pharmacoepidemiology studies[14–16]) to determine the proportion of patients in each cohort who were exposed to the specific BP-interfering drug or class of drugs. For hormones only, the denominator was women in each cohort. We calculated the patient-level daily exposure by using the date of fill and reported days' supply of the BP-interfering drug. The daily exposure of the drug was plotted to assess use of the specific BP-interfering drug or drug class during the 6 months before and 6 months after the index date for each cohort. Because our focus was on any exposure to these drugs, we collapsed all drug strengths/doses and products into a single exposure variable for each drug. Overall use of a given drug or class was operationalized as proportion of patients exposed to the drug or class on the index date.

To assess initiation of interfering drugs after intensifying antihypertensive therapy, we identified the proportion of new users ("initiators") for each interfering drug or class after the index date in each cohort. This measure was operationalized as the proportion of patients with an initial prescription fill occurring within 6 months after the index date. Additionally, to investigate continued use of interfering drugs following a need for antihypertensive therapy titration, we evaluated users in both cohorts who continued to fill a specific BP-interfering medication after the index date ("continuers"). This measure was operationalized as the proportion of patients with at least 1 prescription refill during the 6 months after the index date, among patients who had filled the same drug or class before the index date.

RESULTS

Among 4.07 million adult patients receiving any antihypertensive medication and having ≥6 months of continuous eligibility, we identified 521,028 patients (12.8%) meeting our study criteria for having incident hypertension and sufficient follow-up before and after the initial antihypertensive fill (Figure 1). Similarly, we identified 261,652 patients (6.4%) meeting our criteria for incident TRH, of whom 131,764 patients had sufficient follow-up before and after the addition of their fourth antihypertensive agent. Characteristics of these study populations are summarized in Table 1. Patients in the incident hypertension cohort were younger, with a mean age of 51.1 years, compared to patients in the incident TRH cohort (mean age of 56.6 years). A higher proportion of patients with incident hypertension were women (50.9%) compared to patients in the incident TRH cohort (37.9%). Diabetes mellitus was the most common comorbid condition in both cohorts (21.8% of incident hypertension and 41.6% of incident TRH). Chronic kidney disease was more prevalent in the TRH cohort.

Overall use of BP-interfering medications

Figure 2 displays the proportion of patients exposed to selected classes in both cohorts. Additional drugs or classes are displayed in Supplementary Figures 1 and 2. In the incident hypertension cohort, the most prevalent BP-interfering prescription medications on the index date were hormones (11.1% [of women only]), acetaminophen (8.4%), and NSAIDs (9.2%), whereas the least prevalent were erythropoiesis-stimulating agents (0.01%), angiogenesis inhibitors (0.04%), and aspirin (0.35%). In the incident TRH cohort, the most prevalent BP-interfering prescription medications

Table 1. Baseline characteristics of the two study cohorts

Characteristic	Incident hypertension (*n* = 521,028)	Incident TRH (*n* = 131,764)
Age (years)	51.1 ± 9.9	56.6 ± 6.6
Women	265,437 (50.9)	49,995 (37.9)
Comorbidity		
DM	113,515 (21.8)	54,760 (41.6)
Diabetic neuropathy	2,386 (0.46)	1,236 (0.94)
CKD	8,873 (1.70)	10,226 (7.76)
MI or other IHD	44,396 (8.52)	22,962 (17.4)
Hemorrhagic stroke	1,437 (0.28)	566 (0.43)
Ischemic stroke/TIA	19,200 (3.69)	8,007 (6.08)
PAD or PVD	11,898 (2.28)	5,367 (4.07)
Depression	23,282 (4.47)	3,456 (2.62)
Anxiety	53,489 (10.3)	6,513 (4.94)
Osteoarthritis	64,903 (12.5)	19,455 (14.8)
Chronic pain	9,738 (1.87)	1,350 (1.02)
ADHD	6,921 (1.33)	414 (0.31)

Data are presented as *n* (%) or mean ± SD. Abbreviations: ADHD, attention deficit hyperactivity disorder; CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischemic heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; TRH, treatment-resistant hypertension.

on the index date were NSAIDs (9.2%), hormones (8.8% [of women only]), and acetaminophen (5.1%), whereas the least prevalent were angiogenesis inhibitors (0.03%), erythropoiesis-stimulating agents (0.08%), and sympathomimetics (0.20%). Interestingly, the prevalence of BP-interfering medications on the index date (i.e., the date of antihypertensive initiation or titration) was not demonstrably higher among those with TRH, compared to those with incident hypertension.

We observed a relatively consistent use of antidepressants, acetaminophen, buspirone, and NSAIDs among patients with incident hypertension in the 6 months before and after the index date. The use of hormones, stimulants, and sympathomimetics remained consistent during the 6 months before the index date, and steadily decreased thereafter. Among the incident TRH cohort, we observed relatively consistent use of antidepressants, acetaminophen, buspirone, hormones, NSAIDs, and stimulants in the 6 months before and after the index date. Sympathomimetic use gradually decreased during the 6 months before the index date and continued to decrease thereafter.

Prescription fill patterns following antihypertensive therapy intensification

Table 2 summarizes the proportion of "initiators" (patients with an *initial* fill of an interfering medication after the index date) and "continuers" (patients with a *refill* of an interfering medication after the index date) of each BP-interfering medication, by cohort. Additional details regarding initiators and continuers of individual NSAIDs are displayed in Supplementary Table 2. Overall, 18.3% of the incident hypertension cohort and 17.6% of the incident TRH cohort initiated a BP-interfering medication following antihypertensive titration (i.e., after the index date). Relatively few hormonal prescriptions were initiated after the index date in either cohort (incident hypertension, 14.2%; incident TRH, 10.3%). The initiation of acetaminophen, corticosteroids, NSAIDs, and stimulants after the index date did not differ significantly between hypertension cohorts.

Overall, 57.6% of patients with incident hypertension and 64.9% of patients with incident TRH were continued on a BP-interfering medication after the index date (Table 2). The most common medications continued in both cohorts were stimulants, hormones, angiogenesis inhibitors, and antidepressants. Sympathomimetics were the most likely class to not be continued within both cohorts, with 81.4% in the hypertension cohort and 77.6% in the TRH cohort not continuing these medications after the index date (i.e., after antihypertensive regimen intensification). Comparing the 2 hypertension cohorts, those with TRH were more likely to continue all studied classes or drugs during the 6 months after the index date.

DISCUSSION

Our study used MarketScan administrative claims data to assess utilization patterns of prescription medications known to interfere with BP control. We studied utilization of these drugs among 2 hypertensive cohorts: (i) patients with hypertension initiating their first antihypertensive agent and (ii) patients with TRH initiating a fourth antihypertensive agent. Importantly, we showed routine use of medications that can potentially interfere with BP control in both hypertensive cohorts. Additionally, we found that the use of these BP-interfering medications remained fairly consistent throughout the intensification period of antihypertensive therapy among patients with hypertension or TRH. To our knowledge, this is the first study to look at BP-interfering medication patterns among patients with incident hypertension and incident TRH.

Overall, the most commonly filled BP-interfering prescription medications in both hypertension cohorts were NSAIDs, acetaminophen, and hormones. NSAIDs are thought to exert their BP-related effects by decreasing synthesis of prostaglandins with vasodilatory and natriuretic activities, thereby promoting fluid retention in the kidneys.[17] Previous observational studies have associated use of NSAIDs with increased risk for developing hypertension[18–20] as well as chronic kidney disease among patients with hypertension.[21] Furthermore, the magnitude of drug-induced BP elevations may differ between NSAIDs, with nonselective NSAIDs potentially causing larger changes in BP compared to cyclooxygenase-2 selective NSAIDs.[22] Our study also found a relatively high prevalence of prescription acetaminophen fills in both hypertension cohorts. Acetaminophen can prompt a clinically significant increase in BP,[23] possibly through the

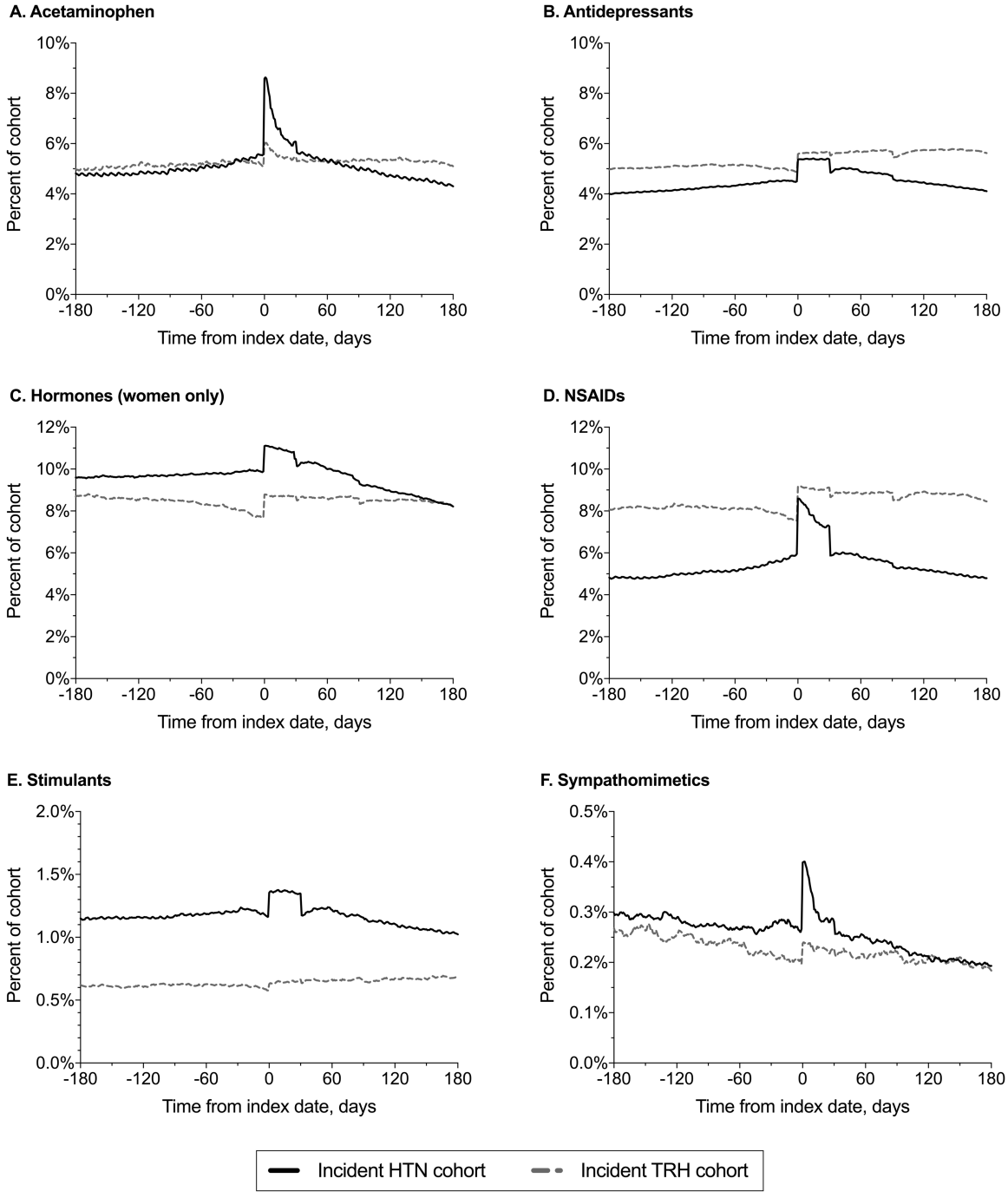

Figure 2. Trends in exposure to selected blood pressure (BP)-interfering medications 6 months before and after the index date in the 2 study cohorts. The peak in BP-interfering medications on the index date (day 0) occurs because both the cohort-defining event (new antihypertensive exposure) and the outcome (BP-interfering medication exposure) represent prescription drug fills and patients tend to synchronize medication fills on the same date. That is, for patients taking multiple chronic medications, fills tend to coalesce around a single date in a refill period. Data on remaining BP-interfering medications are contained in Supplementary Figure 1. Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; TRH, treatment-resistant hypertension.

central cyclooxygenase-3 pathway.[8] However, acetaminophen is often suggested as an alternative to NSAIDs in patients with cardiovascular disease, including hypertension, which may potentially explain, in part, the high use of acetaminophen observed in our study. Additionally, we included fixed-dose combination drugs containing acetaminophen (e.g., hydrocodone–acetaminophen) in our analysis, which may have also contributed. Of note, our study evaluated the use of prescription NSAIDs and acetaminophen in patients with incident hypertension and incident TRH; therefore, the overall prevalence of use of these drugs—i.e., including both prescription and over-the-counter use—is assuredly higher. In the general US adult population, approximately 20% of patients report frequent prescription or nonprescription

Table 2. Proportion of continuers and initiators of blood pressure-interfering medications by hypertension cohort

	Continuers[a]		Initiators[b]	
BP-interfering medication/class	Incident hypertension	Incident TRH	Incident hypertension	Incident TRH
Any medication	57.6	64.9	18.3	17.6
Angiogenesis inhibitors	72.9	82.1	26.4	23.0
Antidepressants	69.2	82.5	21.0	12.1
Aspirin	43.7	64.3	35.7	19.1
Acetaminophen	43.6	45.4	23.4	24.0
Buspirone	47.8	73.4	31.5	15.4
Corticosteroids	26.0	30.8	29.0	30.1
ESAs	31.1	71.7	39.6	19.1
Hormones	68.3	76.4	14.2	10.3
Immunosuppressants	49.7	67.2	25.7	16.8
NSAIDs	40.0	53.7	24.7	22.4
Stimulants	73.0	77.0	15.2	15.0
Sympathomimetics	18.6	22.4	27.0	28.9

Data are presented as % of users for the specific BP-interfering medication. Abbreviations: BP, blood pressure; ESAs, erythropoietin stimulating agents; NSAIDs, nonsteroidal anti-inflammatory drugs; TRH, treatment-resistant hypertension.

[a]Patients with at least one prescription *refill* after initiation of the cohort-defining antihypertensive drug (i.e., after the index date), among all patients with an *initial* fill of the respective BP-interfering medication during the pre-index period. The proportion of patients not continuing the interfering medication concurrently with antihypertensive intensification can be derived as 1—continuers. For example, 40% of the patients with incident hypertension who had a prescription fill of an NSAID before antihypertensive intensification continued that NSAID after antihypertensive intensification, whereas 60% did not continue the NSAID.

[b]Patients with an *initial* prescription fill of the respective BP-interfering medication after initiation of the cohort-defining antihypertensive drug, among all patients with at least one prescription fill of the respective BP-interfering medication. For example, 24.7% of the patients with incident hypertension with ≥1 prescription fill of an NSAID started that NSAID only after antihypertensive intensification.

nonnarcotic analgesic (i.e., NSAIDs, acetaminophen, aspirin) use, defined as nearly every day for at least 1 month.[24] Frequent monthly use (≥15 days/month) of over-the-counter ibuprofen, acetaminophen, and aspirin in the general US adult population has previously been reported to be approximately 3.1%, 5.3%, and 9.8%, respectively.[25] Another study found the prevalence of overall NSAID use among patients with hypertension to be about 16%.[26] Therefore, our study likely underestimated the true prevalence of NSAIDs, acetaminophen, aspirin, and sympathomimetics in these populations with hypertension because we were not able to assess over-the-counter use.

Relatively consistent use of BP-interfering medications was observed in both incident hypertension and incident TRH cohorts, particularly during the 6-month period after the index date. Whether continued use of such medication indicates appropriate or inappropriate care cannot be determined from these data. For classes that are clearly indicated regardless of the presence of hypertension (e.g., erythropoietin-stimulating agents or angiogenesis inhibitors), our findings may indicate appropriate care. On the other hand, it is possible that our results suggest a lack of recognition for some of these BP-interfering drugs during the time of antihypertensive intensification, particularly for patients with incident TRH.

A large proportion of patients in both cohorts were continued with a BP-interfering medication throughout the study period, indicating that prescription refill patterns of an interfering drug remained consistent following escalation of their antihypertensive regimen. Additionally, the incident TRH cohort had slightly higher proportions of continuers compared with the incident hypertension cohort. This finding is not surprising given that TRH is generally associated with higher comorbidity burden compared to the general population with hypertension[27–29] and thus would be expected to have greater use of chronic medications overall. Conversely, a similar or slightly higher rate of patients in the incident hypertension cohort were newly initiated on some BP-interfering medications compared to those in the incident TRH cohort in our study. A possible explanation for our observation is that clinicians are recognizing the difficulty with attaining BP control in patients with TRH, and therefore, are more vigilant with new prescriptions for these medications in this more severe hypertension phenotype. Overall, our results on prescription fill patterns following antihypertensive intensification suggest that BP-interfering drugs are more likely to be continued in the TRH population; however, these medications are less likely to be initiated after intensification of antihypertensive regimen with a fourth agent.

The major strengths of this study include the use of longitudinal (2008–2014) large-scale commercial prescription and medical claims data generally representative of Americans receiving employer-based health insurance. Another important strength of this study is the inclusion of an incident TRH cohort as a comparison to the incident hypertension cohort. Our study is the first to characterize the use of BP-interfering medications in this more severe hypertensive phenotype, in which withdrawal of interfering drugs may have a significant improvement on BP control.[9] Moreover, because of the stringent criteria used to identify patients with TRH (i.e., requiring overlapping prescription fills of ≥4 antihypertensive drugs with high adherence, per fill data), our study cohort likely represents a largely treatment-adherent patient population. Accordingly, we believe any misclassification of pseudoresistance (due to nonadherence) as true TRH is minimal. This study also has notable limitations. First, administrative claims data only include prescription drugs filled through insurance; therefore, our focus was on characterization of prescribed medications that may interfere with BP. Over-the-counter use of drugs that may interfere with BP, such as NSAIDs, acetaminophen, aspirin, and sympathomimetics, are not available in claims data and could not be assessed in this study. Therefore, our results are only representative of prescription drug use and caution should be made when interpreting the overall

prevalence of these medications. Second, claims data do not contain clinical information such as BP. Therefore, the extent to which uncontrolled BP prompted antihypertensive initiation or titration in both cohorts is not known. Nevertheless, it seems likely that the vast majority of patients in both cohorts had at least borderline uncontrolled BP that necessitated the medication titration. Relatedly, we were not able to assess BP response to antihypertensive titration and whether such response differed according to the continuation, discontinuation, or concurrent initiation of interfering medications. Third, prescription fill data were used as a surrogate measure of actual exposure to these drugs. Fill data have been previously validated for such purposes and this approach is common in pharmacoepidemiology studies.[14–16] However, it is likely that at least some patients filling these interfering medications administered them sparingly or not at all. Finally, the data source used herein does not include patients aged ≥65 years, thus our results may not generalize to older patients.

Our results provide data regarding the use of medications that can potentially interfere with BP control and underscore the routine use of many of these medications among patients requiring antihypertensive intensification. More than half of the patients in both the incident hypertension and the incident TRH cohorts continued to fill BP-interfering medications even after antihypertensive regimen initiation or titration. We were not able to determine whether such continuation was appropriate vs. inappropriate; however, it seems likely that there exist at least some opportunities to reevaluate continued need for such therapy. Incorporating systematic processes to identify BP-interfering medications during routine follow-up may be beneficial in this regard, particularly for patients with more difficult-to-control BP. For example, one approach within electronic health records might be clinical decision support systems with automated detection of BP-interfering meds that, at the time of prescribing a new antihypertensive or a dose titration, query the provider on the need for continued use of the BP-interfering medication. Such an approach might reduce the prescribing cascade—i.e., prescribing of medications to treat the effects of other medications—as well as minimize costs, treatment burden, and risk for treatment-emergent adverse effects.

SUPPLEMENTARY MATERIAL

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

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DISCLOSURE

The authors declared no conflict of interest.

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