Trends in Antihypertensive Medication Use Among US Patients With Resistant Hypertension, 2008 to 2014

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See Editorial Commentary, pp 1346–1348

Abstract—Little is known of US trends in antihypertensive drug use for patients with treatment-resistant hypertension (TRH). We analyzed antihypertensive use among patients with TRH (treated with ≥4 antihypertensive drugs concurrently) from July 2008 through December 2014 using Marketscan administrative data. We included adults aged 18 to 65 years, with ≥6 months of continuous enrollment, a hypertension diagnosis, and ≥1 episode of overlapping use of ≥4 antihypertensive drugs; patients with heart failure were excluded. We identified 411 652 unique TRH episodes from 261 652 patients with a mean age of 55.9 years. From 2008 to 2014, we observed an increased prevalence, among TRH episodes, of β-blockers (+6.8% [79% to 85.8%]) and dihydropyridine calcium antagonists (+8.1% [69.1% to 77.2%]), and a decreased prevalence of angiotensin-converting enzyme inhibitors (−12.5% [60.4% to 47.9%]) and nondihydropyridine calcium antagonists (−5.0% [15% to 10%]). The prevalence of most other classes changed by <5% from 2008 to 2014. Thiazide diuretic use was largely unchanged from 2008 to 2014, with hydrochlorothiazide being by far the most prevalent thiazide diuretic; chlorthalidone use increased only modestly (+2.6% [3.8% to 6.4%]). Aldosterone antagonist use increased only modestly (+2.9% [7.3% to 10.2%]). Use of optimal regimens increased steadily (+13.8% [50.8% to 64.6%]) during the study period, whereas combined angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use declined (−11.4% [17.7% to 6.3%]). Our results highlight the persistent infrequent use of recommended therapies in TRH, including spironolactone and chlorthalidone, and suggest a need for better efforts to increase the use of such approaches in light of recent evidence demonstrating their efficacy. **(*Hypertension*. 2016;68:1349-1354. DOI: 10.1161/HYPERTENSIONAHA.116.08128.)** ● **Online Data Supplement**

Key Words: antihypertensive agents ■ chlorthalidone ■ hypertension ■ resistant hypertension ■ spironolactone ■ trends

Hypertension is the most common chronic disease worldwide and is a well-known risk factor for cardiovascular morbidity and mortality.[1] Treatment-resistant hypertension (TRH), defined as requiring ≥4 antihypertensive agents to achieve blood pressure (BP) control, affects ≈8% to 12% of the general hypertensive population and perhaps ≤40% of patients with hypertension and more advanced cardiovascular disease.[2–5] Moreover, the prevalence of TRH seems to be increasing in the United States, highlighting the importance in addressing this rising health care problem.[6,7] Previous studies have shown that TRH is associated with worse health-related quality of life[8] and increased risk of cardiovascular outcomes and mortality relative to nonresistant hypertension.[3,5,9,10]

In 2008, the American Heart Association (AHA) published a scientific statement identifying specific management strategies for patients with TRH, including promoting use of long-acting thiazide diuretics (eg, chlorthalidone and indapamide), addition of aldosterone receptor antagonists to the existing regimens, and withdrawal of potentially interfering medications (eg, nonsteroidal anti-inflammatory drugs)[11]; these recommendations have been largely echoed elsewhere.[12,13] Some of these pharmacological strategies have been subsequently shown to substantially lower BP and facilitate greater BP control.[14,15] However, little is known about the extent to which these strategies have been implemented in the United States since the 2008 scientific statement. Moreover, scarce data exist on antihypertensive use patterns among patients with TRH in the United States. A better understanding of these patterns could facilitate development of focused strategies to improve medical management in this high-risk hypertension phenotype. Therefore, we aimed to characterize antihypertensive drug use, generally, among patients with apparent TRH from July 2008 through December 2014 using nationally representative (for adults in employer-based insurance programs) claims data. We also aimed to explore the extent to which pharmacological

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strategies recommended in the 2008 AHA scientific statement have been implemented among patients with TRH.

Methods

Study Design and Data Sources

We performed a retrospective cohort study to examine antihypertensive medication trends after the introduction of the 2008 AHA scientific statement on TRH. We analyzed medical and prescription claims data from January 2008 to December 2014 in the Marketscan commercial claims database, which contains nationally representative data for patients covered under employer-based insurance programs (≈55% of the US population[16]). Marketscan covers ≈30 million patients annually and receives health care utilization data from 130 employer-sponsored health plans. The study was designed by the authors and was approved by the Institutional Review Board at the University of Florida.

Figure 1 summarizes the cohort development strategy. We included adults between the ages of 18 and 65 years, with ≥1 International Classification of Diseases, 9th Revision (ICD-9), diagnostic code for hypertension (401.X) and at least 6 months of continuous enrollment in their health plan, before the determination of TRH status. We excluded individuals with any heart failure ICD-9 diagnostic code (428.X) during this 6-month continuous enrollment period because many of the classes of medications indicated for treatment in this specific patient population may not be exclusively prescribed for hypertension. From this curated data set, we further restricted the patient population to those with any period of at least 60 days of overlapping use of ≥4 antihypertensive drugs. We used the dispensing dates and the reported days supply to string together consecutive fills for a given antihypertensive drug. To account for a modest level of nonadherence, we inflated the days supply by 30%. Each antihypertensive drug was required to have been filled at least twice, and at least 2 of the antihypertensive drugs had to fall into any of the following major antihypertensive classes: angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), diuretic, β-blocker, or calcium channel blocker (CCB). A patient could contribute >1 TRH episode during the follow-up period as long as the inclusion and exclusion criteria were met for each subsequent episode (Figure S1 in the online-only Data Supplement). Because we used antihypertensive agents as the unit of analysis to define TRH episodes, our definition implicitly allowed for dosage titrations within the same TRH episode.

Statistical Analysis

We analyzed antihypertensive use among each TRH episode as the proportion of all TRH episodes in which a drug or class of drugs was present. We calculated aggregate proportions by quarter calendar years to assess temporal trends. Because we required ≥6 months of continuous enrollment before the index date of a TRH episode, the earliest quarter included was quarter 3 (ie, July through September) of 2008. Where applicable, we aggregated drug use according to the class (ie, ACE-I), rather than the individual agents (ie, lisinopril). In specific, drugs were categorized into one of the following categories: ACE-I, ARB, thiazide (and thiazide like) diuretic, β-blocker, nondihydropyridine CCB, dihydropyridine CCB, loop diuretic, aldosterone receptor antagonist (eplerenone and spironolactone), amiloride, α_1-receptor antagonist, α_2-receptor agonist, aliskiren, and miscellaneous agents (reserpine, hydralazine, and minoxidil). We also assessed use of specific agents, including the various thiazide diuretics, aldosterone antagonists and amiloride. We performed a sensitivity analysis excluding patients with a coronary artery disease ICD-9 diagnostic code (410.X and 414.X) and assessed trends in commonly recommended antihypertensive drugs in this patient population (ie, β-blockers, ACE-Is, ARBs, and nondihydropyridine CCBs). In final, we assessed general measures of the use of optimal and suboptimal regimens. Optimal regimen use was assessed via 2 definitions: (1) any thiazide or loop diuretic contained in the ≥4 drug regimen or (2) a ≥4 drug regimen containing a thiazide or loop diuretic, along with a dihydropyridine CCB, and either an ACE-I or ARB (but not both).[11,15] Suboptimal regimen use was assessed in the context of dual renin–angiotensin system blockade with an ACE-I and ARB.[11] Time trend analyses testing for the presence of a linear trend in antihypertensive use were performed.

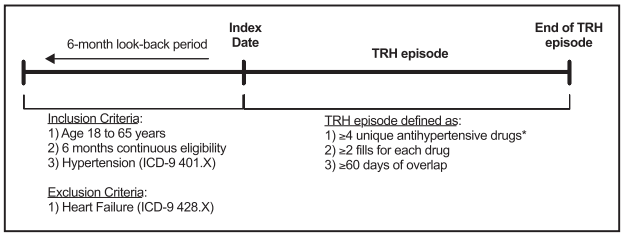

Figure 1. Schematic depiction of the study criteria and design. *At least 2 antihypertensive drugs had to be from major antihypertensive classes, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, or calcium channel blockers. TRH indicates treatment-resistant hypertension.

Results

We identified 261 854 patients with a total of 411 652 TRH episodes. Characteristics of the study population are summarized in Table. The mean±SD number of episodes per patient was 1.57±1.02. Mean patient age was 55.9 years, and 60% of patients were men. Diabetes mellitus was the most common comorbid condition (41.4% of episodes) followed by myocardial infarction (16.2% of episodes). Chronic kidney disease (CKD) was identified in 8.7% of TRH episodes. The mean number of antihypertensive drugs per TRH episode was 4.21±0.02.

General Trends in Antihypertensive Use

Trends in antihypertensive use by quarter from 2008 through 2014 are displayed in Figure 2 and Table S1. Thiazide diuretic use increased modestly from third quarter (Q3), in 2008 (80.1%), to fourth quarter (Q4), in 2014 (82.1%; P_{trend}<0.001). We observed a steady decrease in ACE-I use from 60.9% of episodes in Q3 2008 to 47.9% of episodes in Q4 2014 (P_{trend}<0.001). Dihydropyridine CCB use increased by 6.8% of TRH episodes (P_{trend}<0.001), whereas nondihydropyridine CCB use decreased modestly (−5%; P_{trend}<0.001) during the same time period. β-blocker use increased from 79% in Q3 2008 to 86% in Q4 2014 (P_{trend}<0.001). Renin inhibitor use peaked in 2011 at 7.8%, and thereafter steadily decreased to 1.3% by Q4 2014 (P_{trend}<0.001). The use of ARBs remained relatively consistent from Q3 2008 through Q4 2014. Use of the miscellaneous antihypertensive classes increased steadily throughout the study period (+2.5%; P_{trend}<0.001). A sensitivity analysis excluding patients with coronary artery disease (16.2% of the overall study population) showed no substantial difference in the use of antihypertensive drugs typically recommended in such patients (ie, β-blockers, ACE-Is, ARBs, and nondihydropyridine CCBs) when compared with the overall population (Figure S2).

Individual Antihypertensives Within Select Classes

Changes in use among individual thiazides are displayed in Figure 3. Hydrochlorothiazide was by far the most prevalent thiazide diuretic, making up ≈92.9% of all thiazides used in TRH episodes during Q4 2014. Chlorthalidone use increased only from 3.8% (Q3 2008) to 6.4% (Q4 2014; P_{trend}<0.001), and indapamide use remained virtually unchanged at 0.94% in Q4 2014 (P_{trend}<0.001). Use of aldosterone receptor

Table. Baseline Study Population Characteristics

Characteristic	N (%) or Mean±SD
Number of patients	261 854
Number of treatment episodes	411 652
Number of episodes per patient	1.57±1.02
TRH episode length, d	221±196
Patient age, y	55.9±7.1
Patient sex, male	156 937 (59.98%)
Comorbidities (% of episodes)	
DM	170 398 (41.39%)
CKD	35 856 (8.71%)
MI or other ischemic HD	66 665 (16.19%)
Hemorrhagic stroke	1860 (0.45%)
Ischemic stroke/TIA	23 948 (5.82%)
PAD/PVD	16 035 (3.90%)

CKD indicates chronic kidney disease; DM, diabetes mellitus; HD, heart disease; MI, myocardial infarction; PAD, peripheral arterial disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; and TRH, treatment-resistant hypertension.

antagonists increased modestly (+2.9%; P_{trend}<0.001) from Q3 2008 to Q4 2014 (Figure 4), almost exclusively because of an increasing spironolactone use (+2.5%; P_{trend}<0.001). Use of amiloride, recommended as an alternative to aldosterone antagonists in the 2008 AHA scientific statement, remained essentially unchanged during the study period.

Optimal and Suboptimal Combinations

Trends in specific antihypertensive regimens are illustrated in Figure 5. Antihypertensive combinations containing any diuretic (thiazide or loop) remained largely unchanged throughout the study period (92% of all TRH episodes; P_{trend}=0.03). Use of a 3-drug optimal regimen containing any thiazide or loop diuretic, any dihydropyridine CCB, and either an ACE-I or ARB (but not both), increased steadily from 50.8% (Q3 2008) to 64.6% (Q4 2014; P_{trend}<0.001). With regard to suboptimal combinations, concomitant ACE-I and ARB use decreased substantially from 17.7% (Q3 2008) to 6.3% (Q4 2014; P_{trend}<0.001).

Discussion

TRH represents an increasingly common and clinically challenging hypertension phenotype that has gained substantial recognition in recent years. Despite this increased recognition, little is known of treatment patterns for this high-risk phenotype in the United States, or whether recommendations made in the 2008 AHA scientific statement on TRH have been implemented broadly. In accordance, we used nationally representative (for American adults with employer-based insurance) claims data to assess trends in antihypertensive drug use from 2008 to 2014 among patients with TRH who were taking ≥4 antihypertensive drugs. Importantly, we showed that recommended antihypertensive agents (ie, chlorthalidone and aldosterone receptor antagonists) remained underused in the TRH population. To our knowledge, this is the first study to look at 7 years of longitudinal treatment patterns in the United States since the publication of the AHA scientific statement on TRH.

The most commonly used antihypertensive classes in this study were thiazide diuretics, β-blockers, dihydropyridine CCBs, ACE-Is, and ARBs. These results are consistent with previous cross-sectional studies in the TRH population.[17,18] Using data from the National Ambulatory Medical Care Surveys, Fontil et al[19] observed nonsignificant increases between 2006 and 2010 in the use of β-blockers, CCBs, and aldosterone receptor antagonists, similar to the trends found in our study. In contrast, the authors saw thiazide diuretic use decrease slightly during the study period, whereas we observed no substantial change in the prevalence of thiazide diuretics among TRH regimens. These results seem to be at odds with the steady increase in use of thiazide diuretics occurring in the general hypertensive population.[20] In addition, thiazide diuretic use was substantially higher in our study (≈82% versus ≈55%). These conflicting results are possibly because of the differences in data sets and TRH case definition. Interestingly, we observed an unexpected decrease in the proportion of regimens containing an ACE-I during the study period. Although of a lower magnitude, Fontil et al[19] observed a similar trend in the use of ACE-I. These observations are possibly discordant with National Health and Nutrition Examination Survey (NHANES) data showing generally stable ACE-I use in multidrug regimens from 2001 to 2010 in the general hypertension population.[20]

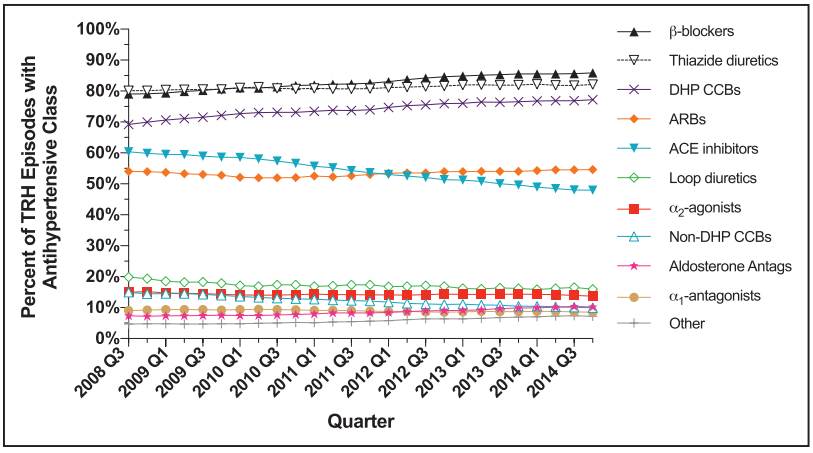

Figure 2. Trends in antihypertensive class use by quarter, 2008 through 2014. ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; and DHP, dihydropyridine.

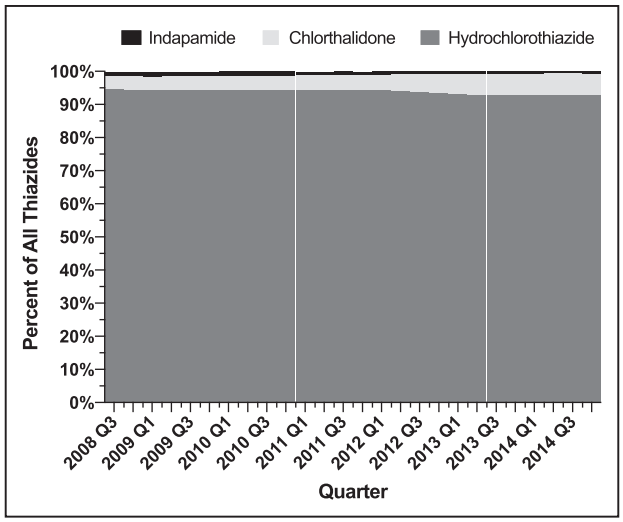

Figure 3. Thiazide diuretic use by individual drugs from 2008 to 2014.

Our finding that hydrochlorothiazide remains the most commonly used thiazide diuretic is not surprising given its overwhelming use in the general hypertensive population. However, chlorthalidone use remains remarkably low in patients with TRH, despite evidence suggesting its superior BP-lowering ability and possible greater reductions in major adverse cardiovascular outcomes in most,[21–24] but not all, hypertensive populations.[25] In specific, chlorthalidone was present in only 6.4% of TRH episodes with any thiazide diuretic and only 5.3% of all TRH episodes, by the end of 2014. Previous studies from 2010 and earlier have suggested similarly low use of chlorthalidone (1.4% of all office visits for patients with TRH, or 3% of all patients with TRH).[17,19] Use of indapamide was even lower in our study (<1%), which may be related, in part, to our younger (<65 years) study population. Whether indapamide use would have been greater in an older population (eg, as enrolled in the Hypertension in the Very Elderly Trial[26]) is not known.

Spironolactone use increased by ≈38% from 2008 to 2014 but remained low overall, present in only ≈1 in 10 TRH episodes. Previous studies have also shown suboptimal use of aldosterone receptor antagonists within the TRH population[17,19] and only modestly increased use shortly following the publication of the 2008 AHA scientific statement.[19] Our results extend these findings with much more recent data and provide greater granularity with regard to specific agents in a much larger cohort. However, these findings are concerning in light of recent studies demonstrating that spironolactone consistently provides significantly greater BP reductions compared with other fourth-line agents, including β-blockers or α_1-receptor antagonists.[15] Whether the 2015 publication of the rigorous PATHWAY-2 trial will have any substantial impact on aldosterone antagonist utilization remains to be seen.

In final, we observed optimistic trends in the use of optimal regimens and the avoidance of suboptimal regimens in this cohort. First, we found that >90% of TRH regimens, throughout the study period, contained a thiazide (primarily) or loop diuretic. This level of diuretic use seems to be substantially higher than that seen in the general hypertensive population, where diuretics are present in only one third of multidrug regimens.[20] Second, we observed a substantial increase in the prevalence of regimens containing a diuretic, dihydropyridine CCB, and an ACE-I or ARB (but not both); as of 2014, this combination was prevalent in nearly two third of TRH episodes. Although data are lacking on the best 3-drug antihypertensive regimen to reduce major adverse outcomes, this 3-drug backbone is generally considered an optimal approach for most patients.[11,15] We also found that the prevalence of suboptimal regimens containing both an ACE-I and ARB drastically decreased throughout the study period, likely as a result of the increasing evidence that ACE-I/ARB combination seems to be associated with increased risk of adverse renal outcomes and few benefits in most hypertensive or otherwise high-risk populations.[27] Of note, we excluded patients with heart failure, in which there is some evidence of benefit with combined ACE-I/ARB therapy.[28,29]

The major strengths of this study include the use of large-scale commercial prescription and medical claims data representative of Americans receiving employer-based health insurance, which allowed for ascertainment of medication fills over a 7-year period, through 2014. Another notable strength of this study is the TRH case definition: because

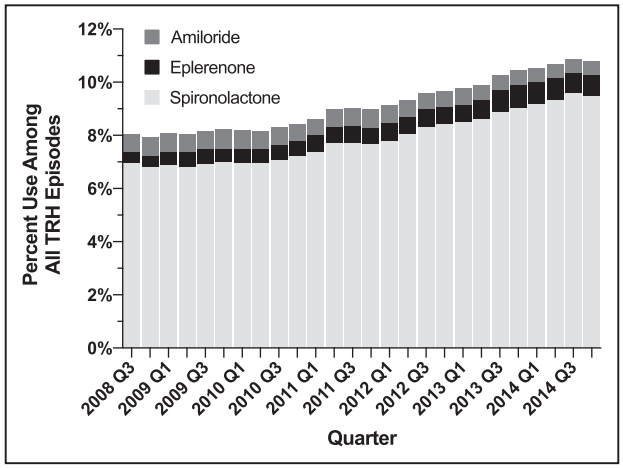

Figure 4. Aldosterone antagonist and amiloride use, by drug, from 2008 through 2014.

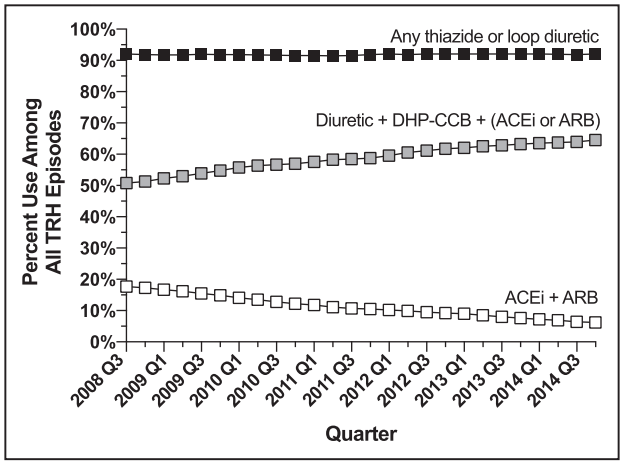

Figure 5. Trends in specific antihypertensive combinations from 2008 through 2014. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; and DHP, dihydropyridine.

of the stringent overlap required with prescription fills, the medication trend data presented here likely reflect a largely treatment-adherent patient population, whereas we excluded patients with pseudoresistance because of a substantial medication nonadherence. We cannot say with certainty that all patients with pseudoresistance, particularly from causes other than nonadherence, were excluded. However, the definition used herein (ie, use of ≥4 antihypertensive drugs concurrently regardless of BP control) defines a subset of high-risk individuals[5,30] and, thus, represents a clinically important hypertensive phenotype. This study also has other noteworthy limitations. First, claims data, such as those used here, do not contain vital signs, including BP. Therefore, individuals with uncontrolled BP on 3 antihypertensive agents, which would be considered as having TRH by the AHA definition,[11] were misclassified as having nonresistant hypertension in this study and not included in our analyses. Nevertheless, our stringent criteria should provide confidence in a TRH cohort with high sensitivity. Second, the TRH definition used herein did not allow for obtaining specific antihypertensive doses. Thus, we did not ascertain to what extent suboptimal dosing of antihypertensives influenced prescribing patterns. Third, the prevalence of CKD seems to be considerably lower in this study cohort (≈9%), compared with other studies where TRH is defined on the basis of clinical data (≈36%–40%).[7] However, diagnosis of CKD on the basis of ICD-9 diagnostic codes is known to vastly underestimate true CKD prevalence by as much as 80%.[31] In accordance, the ≈9% prevalence of CKD in our study (based on an ICD-9 code definition) likely corresponds to a true prevalence of CKD of ≤45%, in line with previous studies. Final, the data source used here does not contain data on patients aged ≥65 years, thus our results should not be extrapolated to older individuals with TRH.

Perspectives

Our results provide antihypertensive use data among working-aged US patients with TRH from 2008 through 2014. Importantly, our study reinforces and extends the previous cross-sectional data documenting the underutilization of recommended and effective medications for patients with TRH. Most notably, we found that the infrequent use of chlorthalidone and aldosterone antagonists (namely spironolactone) persisted from 2008 through 2014, despite recommendations for their use in patients with TRH for nearly a decade. However, the use of complementary and generally recommended first-line antihypertensives combinations—namely combining a diuretic, dihydropyridine CCB, and ACE-I or ARB (but not both)—increased substantially during the study period such that nearly two thirds of TRH episodes in 2014 contained this combination. These results suggest that some strides have been made in improving TRH regimen selection, but much greater efforts are needed to increase the use of recommended antihypertensive treatments among appropriate patients with TRH, especially in light of recently published evidence demonstrating their efficacy.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This article included the longest longitudinal study of antihypertensive treatment patterns among patients with resistant hypertension.
- We used nationally representative estimates for the US population in employer-based insurance programs through 2014.
- This study performed the first assessment of trends in generally recommended 3-drug antihypertensive regimen backbone (diuretic+dihydropyridine calcium channel blocker+angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).

What Is Relevant?

- Recommended antihypertensive drugs, namely chlorthalidone and aldosterone antagonists, remain substantially underused in patients with resistant hypertension.
- Use of optimal 3-drug antihypertensive backbones has increased from 2008 to 2014, whereas suboptimal regimens (ie, dual renin–angiotensin system inhibition) have decreased.
- Our results underscore the need to increase the efforts in using more effective therapies for the treatment of resistant hypertension.

Summary

Few data exist on antihypertensive use trends in treatment-resistant hypertension. In this nationally representative study (for US adults with employer-based insurance), we assessed trends in antihypertensive drug use among patients with treatment-resistant hypertension (defined by concurrent use of ≥4 antihypertensive drugs) from 2008 through 2014. We found persistently low use of recommended therapies for treatment-resistant hypertension, especially aldosterone receptor antagonists and chlorthalidone over this time frame. These data suggest that renewed efforts are needed to increase the use of evidence-based antihypertensive drug selection among patients with treatment-resistant hypertension.