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Research article

Characteristics, management, and blood pressure control in patients with apparent resistant hypertension in the US

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A B S T R A C T

Background: Per treatment guidelines, resistant hypertension is defined as uncontrolled blood pressure (BP) while taking 3 concomitant antihypertensives (AHTs) or controlled BP while taking ≥4 AHTs. Characteristics, AHT therapy use, and BP control were analyzed in US patients with hypertension who were prescribed ≥3 classes of AHT medications.

Methods: This retrospective analysis of the Optum® Electronic Health Record Database evaluated patients ≥18 years of age with a diagnosis of hypertension classified based on the number of prescribed AHT medication classes (3, 4, or ≥5). For the primary analysis, uncontrolled hypertension was defined as systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg. For secondary analyses, uncontrolled hypertension was defined as SBP ≥130 mmHg or DBP ≥80 mmHg.

Results: 207,705 patients with hypertension and concurrent use of ≥3 AHT medication classes were included. Diuretics, beta blockers, ACE inhibitors and/or ARBs, and CCBs were the most prescribed classes; thiazides and thiazide-like agents were the most prescribed diuretics. Among patients who were prescribed 3, 4, or ≥5 AHT medication classes, approximately 70% achieved a BP goal of <140/90 mmHg; approximately 40% achieved BP <130/80 mmHg. After ≥1 year of follow-up, the number of concurrent AHT medication classes was unchanged from baseline in the majority of patients and the prevalence of uncontrolled hypertension (≥140/90 mmHg) was similar.

Conclusions: This study illustrates suboptimal BP control in many patients with apparent resistant hypertension despite the use of multidrug regimens and suggests a need for new drug classes and regimens that effectively manage resistant hypertension.

1. Introduction

Hypertension is a major cause of morbidity and mortality worldwide [1]. It is a leading cause of cardiovascular (CV) disease (including ischemic heart disease, stroke, and heart failure), chronic kidney disease (CKD), and all-cause mortality [1–3]. The prevalence of hypertension is expected to continue to increase as the global population ages [1]. Approximately 10%–15% of treated hypertensive patients have resistant hypertension [4–6]. In the absence of confirmatory tests, resistant hypertension is defined as blood pressure (BP) measurements above goal despite concomitant use of ≥3 antihypertensive (AHT) medications, which usually includes a diuretic, or requiring ≥4 AHT medications to control BP [4,6,7].

Improving AHT therapies for resistant hypertension is critical, as numerous studies have shown that patients with resistant

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hypertension are at high risk for poor outcomes [2]. In retrospective studies of 200,000 to 400,000 patients, those with resistant hypertension were nearly 2 times more likely to experience CV events (eg, myocardial infarction, ischemic heart disease, heart failure), stroke, CKD or end-stage renal disease, and death than those without resistant hypertension [8,9]. Resistant hypertension also is associated with worse outcomes in patients with some comorbidities, including CKD, ischemic heart disease, obesity, diabetes, and obstructive sleep apnea [2]. Accordingly, resistant hypertension is associated with substantial medical and financial burdens resulting from treatment costs, disability, and premature death [5]. It is critical to identify more effective strategies for managing patients with resistant hypertension and improve their prognosis.

The American College of Cardiology (ACC)/American Heart Association (AHA) 2017 guidelines on the management of hypertension generally recommend a target BP <130/80 mmHg for hypertensive patients, independent of age or comorbid conditions [10]. Before the ACC/AHA guidelines were updated, the target BP in most guidelines was <140/90 mmHg [11,12]. Several guidelines have maintained <140/90 mmHg as the primary BP target in the general population, with a reduction to <130/80 mmHg for patients at higher risk of CV complications [13–15]. As expected, use of the newer guideline recommendations for BP targets resulted in an increase in the prevalence of apparent resistant hypertension (from 18% to 20%). Pseudo-resistance, resulting from inaccurate BP measurements, the "white-coat effect," undertreatment, and poor adherence could not be excluded from this estimate [7].

The updated ACC/AHA recommendations take a stepwise treatment approach for the treatment of hypertension. The initial 3 therapies include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), a diuretic, and a calcium channel blocker (CCB). The next steps include the addition of a mineralocorticoid receptor antagonist (MRA), followed by a beta blocker, and then agents from other classes [2]. Patients with apparent resistant hypertension are distinctly characterized by a variable clustering of demographic (ie, older age, male sex, Black race) and clinical characteristics (multiple comorbidities, physiologic abnormalities) [6]. As a result, AHT prescribing patterns also are distinct in this patient population.

In this study, we evaluated the characteristics of US-based patients taking ≥3 AHT medications, the use of different AHT medication classes, and BP goal attainment in 2019 using real-world data from a national cohort registered in a large, established database. The primary objectives were to determine the prevalence of uncontrolled hypertension, evaluate the use of different AHT treatment regimens, and to perform longitudinal analyses of changes in the use of different AHT medication classes.

2. Materials and methods

2.1. Study design

This was a retrospective cohort study of US-based adults with a ≥6-month history of treated hypertension and concomitant use of ≥3 AHT medications.

The study design included a 365-day lookback period to establish hypertension cases and exposure to hypertension medications, an AHT medication assessment period, identification of 2 office-based BP measurements, and follow-up for longitudinal outcomes (Fig. 1). The index date was the date when entry criteria were met and when follow-up began.

Patient records were obtained from the large, nationwide Optum® Electronic Health Record Database. This dataset includes de-identified, longitudinal, patient-level medical record data for 80 million patients treated at 700 hospitals and 7000 clinics across the United States. The database includes records of prescriptions, medication administrations, vital signs, diagnoses, procedures, and laboratory findings.

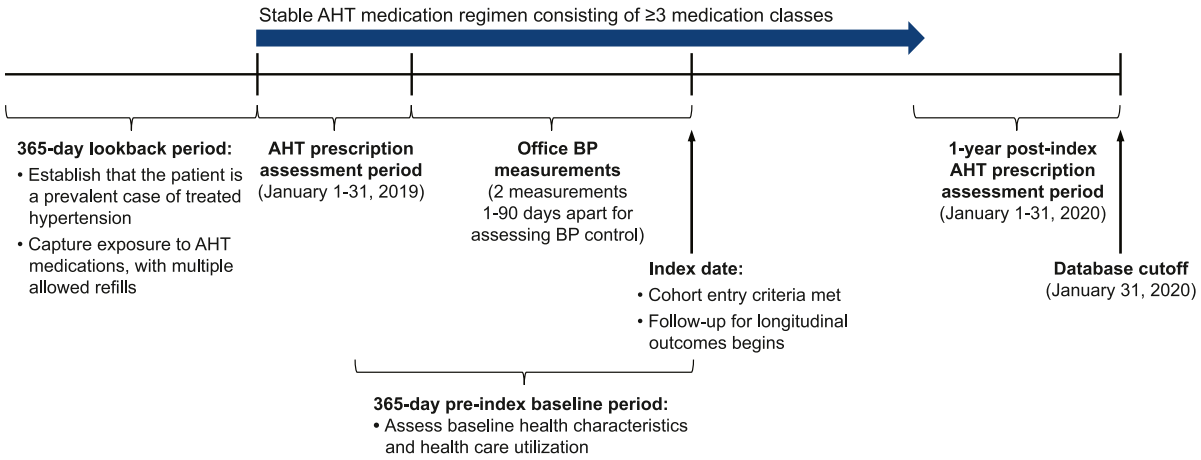

Fig. 1. Study design. AHT, antihypertensive; BP, blood pressure.

2.2. Patients

To be included, patients had to be ≥18 years of age on the index date and have ≥365 days of electronic health record (EHR) activity before January 1, 2019. Eligible patients had a diagnosis of hypertension and were prescribed an AHT medication ≥183 days before the index date. In addition, eligible patients were required to be taking a stable regimen (ie, no AHT medications were added or discontinued) of ≥3 AHT medications between January 1, 2019 and January 31, 2019. This regimen was designated as the index regimen and was ended when a new AHT medication class was added or a component of the regimen was discontinued. Finally, eligible patients were required to have 2 office-based BP measurements on distinct dates ≤90 days apart between January 31, 2019 and December 31, 2019, the end of the index AHT regimen, or the last clinic visit, whichever was earliest. Pregnant women and patients with documented secondary causes of hypertension were excluded.

Apparent resistant hypertension was defined per treatment guidelines as having uncontrolled BP while taking 3 concomitant AHT medication classes or having controlled BP while taking ≥4 concomitant AHT medication classes [2]. This definition is consistent with previous epidemiologic studies of resistant hypertension [5,6,16] and clinical guidelines for the diagnosis and management of resistant hypertension [2]. The 2018 AHA treatment guidelines for resistant hypertension distinguish apparent, true, and pseudo-resistant hypertension. In this study, it was not possible to distinguish true and pseudo-resistant hypertension primarily because the availability of out-of-office BP measurements in the database is limited and because treatment adherence could not be assessed. Importantly, it was not possible to observe the key distinguishing characteristic of patients with true versus pseudo-resistant hypertension (ie, whether the patients would have been at their BP goal had they been taking optimal AHT therapy).

2.3. AHT therapy

Patients were classified into mutually exclusive groups based on the number of distinct AHT medication classes (3, 4, or ≥5) for which there were active prescriptions as of the index date. Twelve classes of AHT medications were evaluated: alpha blockers; ARBs; ACE inhibitors; beta blockers; CCBs; central alpha agonists; direct renin inhibitors; MRAs (spironolactone, eplerenone, and fixed-dose combinations containing spironolactone or eplerenone); vasodilators; and loop, thiazide, and potassium-sparing diuretics (amiloride, triamterene, and fixed-dose combinations containing amiloride or triamterene). Patients taking combination medications were considered to be exposed to each constituent drug class.

2.4. Data extraction

Baseline systolic BP (SBP) and diastolic BP (DBP) were defined based on the mean of the 2 office-based measurements. To account for the different definitions in guidelines, we defined controlled versus uncontrolled hypertension 2 ways. For the primary analyses, we defined controlled hypertension as BP <140/90 mmHg and uncontrolled hypertension as SBP ≥140 mmHg or DBP ≥90 mmHg. This definition is consistent with those used in previous epidemiologic studies of the prevalence of resistant hypertension based on data from the National Health and Nutrition Examination Survey (NHANES) [5], Kaiser Permanente Southern California [6], and the UK Clinical Practice Research Datalink [16]. For the secondary analyses, we defined uncontrolled hypertension as SBP ≥130 mmHg or DBP ≥80 mmHg. This definition is consistent with the 2017 ACC/AHA guidelines [10].

A number of patient demographic characteristics were evaluated on the index date, including age, sex, race and ethnicity, type of health insurance coverage, and geographic region. Clinical characteristics evaluated included comorbid conditions, identified based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases, Tenth Revision* (ICD-10) codes and as components of the Charlson Comorbidity Index (CCI) [17], possible causes of secondary hypertension [2], cardiometabolic risk factors and complications, and other health conditions of interest (ie, depression, anxiety, osteoarthritis, and anemia).

The CCI accounts for the number and severity of comorbid diseases in patients being evaluated for their risk of death in longitudinal studies [18]. CCI score was calculated for each patient as a measure of overall health status and comorbidity burden during the pre-index and index periods. Body mass index (BMI) and current smoking status were evaluated as categorical variables.

2.5. Statistical analysis

The prevalence of controlled hypertension was quantified using simple proportions and exact Clopper-Pearson 95% confidence intervals (CIs); comparisons of BP control rates across groups defined by number of AHT medication classes prescribed were made using chi-squared tests. Likewise, the prevalence of different AHT treatment combinations at the medication class level was quantified using proportions and compared across groups defined by number of AHT medication classes using chi-squared tests. The analysis of longitudinal changes in AHT management was restricted to ≥1 year of follow-up data and assessed the number of AHT medication classes patients were taking in January 2020. Evaluation of changes in BP control was performed at 1 year post-index, restricting patient data to 1 year of follow-up and 2 office-based BP measurements at 1 year post-index, using McNemar's test.

All patient data were stratified by the number of AHTs prescribed concurrently (ie, 3, 4, or ≥5). All statistical analyses were performed using Instant Health Data (IHD) Platform (Panalgo, Inc., Boston, MA) and SAS version 9.4 (SAS Institute, Cary, NC). All authors had full access to all of the data reported, and the corresponding author takes responsibility for the integrity of the data and data analysis.

3. Results

3.1. Patient demographic and clinical characteristics

A total of 207,705 patients with hypertension and concurrent use of ≥3 AHT medication classes were included in the analyses. With the exception of median age (range, 69–70 years), baseline patient demographics were significantly different among the groups taking 3, 4, or ≥5 AHT medication classes (all $P < 0.0001$; Table 1). The largest percentages of patients had commercial health insurance or were on Medicare; notably smaller percentages of patients were on Medicaid, other types of insurance, or were uninsured. All 3 groups had a median BMI >30.0 kg/m^2, the traditional cut point for obesity.

Baseline patient characteristics were significantly different when comparing across groups that were taking 3, 4, or ≥5 AHT medication classes (all $P < 0.0001$). Incidence rates of comorbidities at baseline (most commonly diabetes) trended higher as the number of AHT medication classes increased from 3 to ≥5, and many patients experienced multiple comorbidities. The rate of diabetes, renal disease, heart failure, cerebrovascular disease, and myocardial infarction was highest in patients prescribed ≥5 AHT medication classes. Median CCI scores, evaluating risk of 10-year mortality in patients with multiple comorbidities, were relatively low across the treatment groups. The CCI score was highest, indicating an increased risk of mortality, in patients prescribed ≥5 AHT medication classes.

3.2. Prescribed AHT medication classes

Diuretics were the most prescribed AHT medication class overall; thiazides and thiazide-like agents were the most prescribed diuretics in this population. ACE inhibitors and/or ARBs, beta blockers, and CCBs also were highly prescribed AHT medication classes. Significant differences in the proportion of patients on AHT medication classes were observed by number of medication classes used (all $P < 0.0001$ across all groups; Table 2). In the group of patients taking 3 AHT medication classes, 26.0% of patients were not taking any diuretics and 74.0% of patients were taking at least 1 diuretic. Diuretics were nearly always part of the treatment regimens for patients taking 4 or ≥5 AHT medication classes (89.1% and 95.6%, respectively). Beta blocker use increased in frequency in patients prescribed a greater number of AHT medication classes (62.9%, 83.8%, and 92.9% of patients prescribed 3, 4, or ≥5 AHT medication classes, respectively; Table 2). MRAs were used by 5.1%, 14.1%, and 25.8% of patients prescribed 3, 4, or ≥5 AHT medication classes, respectively (Table 2).

3.3. BP goals

Among patients who were prescribed 3, 4, or ≥5 AHT medication classes, the proportion of patients achieving BP goal by either threshold was significantly different across groups, with 74.2%, 72.3%, and 67.4% achieving a BP goal of <140/90 mmHg, respectively, and 40.8%, 41.7%, and 38.8% achieving a BP goal of <130/80 mmHg, respectively ($P < 0.0001$ across BP treatment goal groups by number of AHT medication classes; Fig. 2A). In the analysis stratified by diuretic use, the percentage of patients who achieved either BP goal were significantly higher among those who were prescribed a diuretic versus those who were not ($P < 0.0001$ across number of

Table 1
Characteristics of eligible patients with prevalent hypertension stratified by the number of concurrent AHT medication classes.

Characteristic	3 AHT medication classes (n = 137,471)	4 AHT medication classes (n = 52,803)	≥5 AHT medication classes (n = 17,431)	*P*-value across treatment groups
Median age, years (IQR)	69 (60–77)	70 (62–78)	70 (62–78)	<0.0001
Female sex, n (%)	73,548 (53.5)	25,391 (48.1)	6979 (40.0)	<0.0001
Race, n (%)				<0.0001
Caucasian/White	114,752 (86.7)	42,921 (84.2)	13,661 (81.0)	
African American/Black	16,101 (12.2)	7568 (14.9)	3093 (18.3)	
Asian	1514 (1.1)	473 (0.9)	106 (0.6)	
Health insurance coverage, n (%)				<0.0001
Commercial	62,634 (49.4)	22,446 (45.1)	7014 (42.2)	
Medicare	52,296 (41.3)	22,476 (45.2)	7999 (48.1)	
Medicaid	5750 (4.5)	2479 (5.0)	931 (5.6)	
Other	2892 (2.3)	1154 (2.3)	335 (2.0)	
Uninsured	3124 (2.5)	1171 (2.4)	360 (2.2)	
Median BMI, kg/m^2 (IQR)	31.4 (27.3–36.7)	32.1 (27.7–37.6)	33.0 (28.4–38.6)	<0.0001
Median CCI score, (IQR)	1 (0–2)	2 (0–3)	2 (1–4)	<0.0001
Selected baseline comorbidities, n (%)				
Diabetes	54,259 (39.5)	25,546 (48.4)	9890 (56.7)	<0.0001
Renal disease	27,099 (19.7)	14,583 (27.6)	6755 (38.8)	<0.0001
Heart failure	23,050 (16.8)	14,519 (27.5)	6654 (38.2)	<0.0001
Cerebrovascular disease	15,608 (11.4)	7416 (14.0)	3193 (18.3)	<0.0001
Myocardial infarction	10,340 (7.5)	5756 (10.9)	2623 (15.0)	<0.0001

AHT, antihypertensive; BMI, body mass index; CCI, Charlson Comorbidity Index; IQR, interquartile range.

Table 2
AHT medication classes prescribed to all eligible patients with prevalent hypertension, stratified by the number of concurrent medication classes.

AHT medication use, n (%)*	3 AHT medication classes (n = 137,471)	4 AHT medication classes (n = 52,803)	≥5 AHT medication classes (n = 17,431)	*P*-value across treatment groups
Any diuretic	101,663 (74.0)	47,023 (89.1)	16,659 (95.6)	<0.0001
Thiazide/thiazide-like diuretic	76,616 (55.7)	31,676 (60.0)	11,332 (65.0)	<0.0001
Loop diuretic	27,994 (20.4)	19,645 (37.2)	9841 (56.5)	<0.0001
Potassium-sparing diuretic[a]	9195 (6.7)	4898 (9.3)	2285 (13.1)	<0.0001
ACEi/ARB	113,598 (82.6)	47,156 (89.3)	16,133 (92.6)	<0.0001
Beta blocker	86,414 (62.9)	44,250 (83.8)	16,193 (92.9)	<0.0001
Calcium channel blocker	67,072 (48.8)	35,750 (67.7)	14,138 (81.1)	<0.0001
Alpha blocker	16,539 (12.0)	11,067 (21.0)	6713 (38.5)	<0.0001
Mineralocorticoid receptor antagonist[b]	7043 (5.1)	7441 (14.1)	4489 (25.8)	<0.0001
Vasodilator	3191 (2.3)	4470 (8.5)	5261 (30.2)	<0.0001
Central alpha agonist	2875 (2.1)	3261 (6.2)	3949 (22.7)	<0.0001
Renin inhibitor	73 (0.1)	47 (0.1)	57 (0.3)	<0.0001

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AHT, antihypertensive. *Fixed-dose combination medications were counted in each constituent drug class. Columns total >100% as patients were prescribed 3, 4, or ≥5 medication classes.

[a] Includes amiloride, triamterene, and fixed-dose combinations containing amiloride or triamterene.

[b] Includes spironolactone, eplerenone, and fixed-dose combinations containing spironolactone or eplerenone.

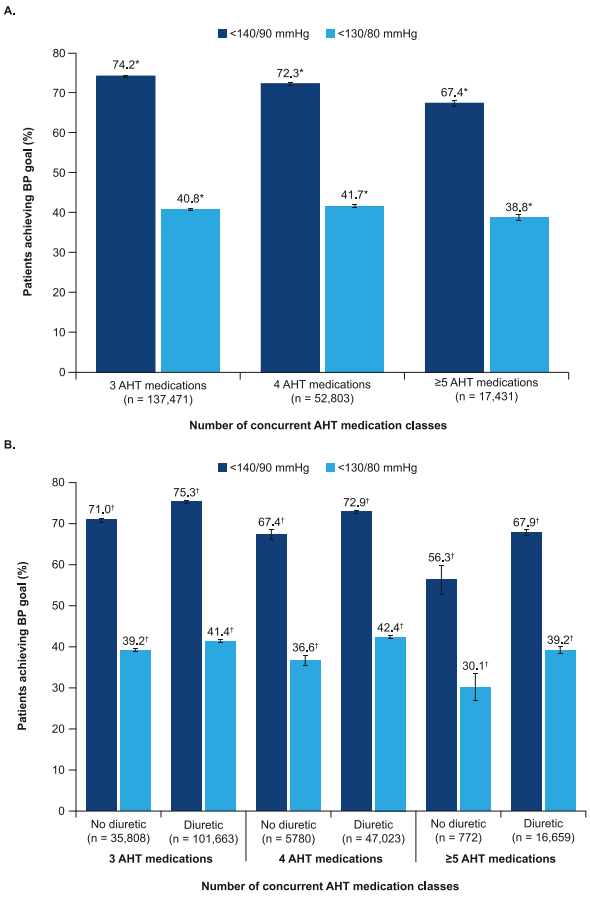

Fig. 2. Percentage of (A) all patients and (B) patients stratified by diuretic use achieving BP goals (<140/90 mmHg or <130/80 mmHg) by number of prescribed AHT medication classes. AHT, antihypertensive; BP, blood pressure. *$P < 0.0001$ across BP treatment goal groups by number of AHT medication classes. †$P < 0.0001$ across number of AHT medication classes groups by diuretic use.

AHT medication classes groups by diuretic use; Fig. 2B).

3.4. Effects after 1 year

Among the 14,366 patients with ≥1 year of follow-up, 49.6%, 40.8%, and 39.0% of patients taking 3, 4, or ≥5 AHT medication classes, respectively, at baseline remained on the same number of concurrent AHT medication classes ($P < 0.0001$ overall; Fig. 3). For patients with a change in the number of concurrent AHT medication classes, a decrease was more commonly observed than an increase. Less than 15% of patients receiving 3 or 4 AHT medication classes at baseline increased to more AHT medication classes after 1 year. A small proportion of patients were prescribed no AHT medications after 1 year (2%–5% across all subgroups). BP control, measured as the prevalence of uncontrolled hypertension (≥140/90 mmHg), was not significantly different between baseline and 1-year post-index for patients with ≥1 year of follow-up and 2 outpatient BP records at the 1-year follow-up date (Fig. 4).

4. Discussion

In this retrospective analysis of real-world data from a large, nationwide database, a large percentage of US-based patients with apparent treatment-resistant hypertension did not meet BP goals despite receiving prescriptions for ≥3 AHT medication classes.

Patient characteristics were consistent with known risk factors for hypertension, including older age, male sex, Black race, and comorbidities [2,19]. Although most patients were treated with diuretics in accordance with the most recent hypertension guidelines [10], 26% of those taking 3 AHT medication classes did not receive this drug class; however, 89% and 96% of those taking 4 and ≥5 AHT medication classes, respectively, were taking ≥1 diuretic. It should be noted that patients in any of these treatment groups may have received diuretics for comorbid conditions other than hypertension. Current US guidelines recommend MRAs as the 4th drug class for patients with resistant hypertension [10]. However, our data showed low use of MRAs among those taking 4 AHT medication classes (14%), and higher uptake of MRA among those taking ≥5 AHT medication classes (26%). MRAs are not used in patients with advanced renal disease; however, we do not have information regarding the stage of renal disease among the patients in this study. By contrast, our data showed high use of beta blockers as part of a 4-AHT-medication regimen.

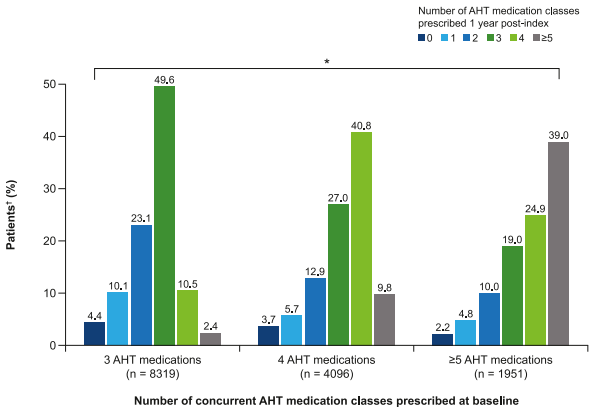

Fig. 3. Number of AHT medication classes prescribed after 1 year of follow-up by number of AHT medication classes prescribed at baseline. AHT, antihypertensive. *$P < 0.0001$ across all groups by number of medication classes. †Patients with ≥1 year of follow-up.

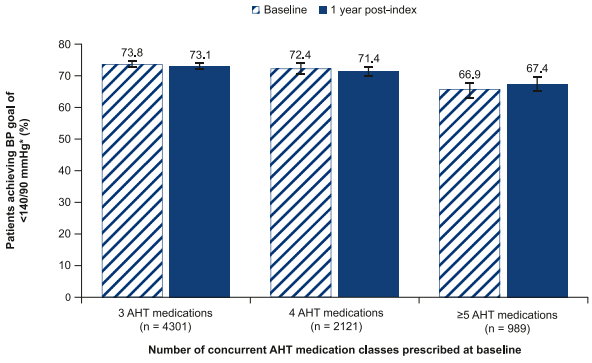

Fig. 4. Percentage of patients achieving BP goal (<140/90 mmHg) at baseline and after 1 year of follow-up by number of AHT medication classes at baseline. AHT, antihypertensive; BP, blood pressure. *Includes patients with 1 year of follow-up and 2 outpatient BP assessments at 1 year.

Large numbers of patients were prescribed a beta blocker regardless of the total number of AHT medication classes they had been prescribed. However, beta blockers may have been prescribed for indications other than hypertension, including comorbid heart failure and myocardial infarction.

This study was conducted after the ACC/AHA guidelines were updated in 2017 [10]. However, some of our results were not consistent with these updated recommendations. Important inconsistencies included the early and high use of beta blockers and the low use of MRAs. Additional research is needed to explore the potential reasons for the deviations from treatment guidelines in clinical practice.

As this was an observational study, it was not possible to identify the rationale for use of each drug. Use of thiazides, thiazide-like diuretics, and potassium-sparing diuretics to lower BP was to be expected, but loop diuretics may be used for reasons other than, or in addition to, BP reduction.

In addition, during a 1-year follow-up period, there was little change from baseline in the percentage of patients achieving BP goals. Up to 30% of patients taking 3 or 4 AHT medication classes had uncontrolled BP and, despite the availability of different classes of AHT medications, less than 15% of patients were prescribed an additional medication class, highlighting the lack of effective therapeutic options and/or a need for a change in prescribing patterns. Additional investigation is required to understand the temporal changes in real-world AHT prescribing practices, including drivers of drug class choices and the role of comorbidities, following publication of the latest hypertension management guidelines [2].

Our results should be interpreted in light of some limitations. This was a retrospective analysis of observational data and therefore limited by the information that was recorded in the original EHR and successfully translated into structured data elements in the database. It was not possible to distinguish between true resistant hypertension and pseudo-resistant hypertension as defined in clinical guidelines [2], including such measures as intended daily dose and adherence to medication. In this study, 2 office-based BP measurements were examined, which may not be enough information to accurately assess BP control. The term apparent treatment-resistant hypertension is used when at least 1 of either medication dose, adherence, or out-of-office BP monitoring is missing [20]. Other studies analyzing patients with resistant hypertension, including other database studies and an NHANES analysis, have faced and acknowledged these limitations [6,7,21]. In addition, this analysis assessed the number of AHT medication classes and not individual molecules or dosing, and the indication for which medications were prescribed could not be determined. If health care encounters were not recorded in the database (ie, from another provider or hospital), data were incomplete for patients' health conditions, medication use, health care encounters, and hospitalizations for adverse clinical outcomes. This study used data from one EHR system, which may have confounded results and contributed to the observation that 2%–5% of patients were no longer prescribed AHT medications after 1 year of follow-up. Finally, the percentage of Black patients was relatively low.

Despite these limitations, the results were derived from a large, population-based sample of patients with treated hypertension that reflected real-world practice patterns. EHR measures allowed for the assessment of SBP and DBP, and patients were followed longitudinally for changes in medication use.

5. Conclusions

Results from this real-world study of US-based patients with resistant hypertension showed that up to 61% of patients did not meet the BP goal of <130/80 mmHg endorsed by the 2017 ACC/AHA hypertension management guidelines [10]. Furthermore, up to 33% of these patients failed to meet the previous BP goal of <140/90 mmHg established by earlier treatment guidelines [11,12]. These findings indicate there is suboptimal BP control in many patients with apparent resistant hypertension and multiple comorbid conditions, despite the use of multidrug regimens, and suggest that new classes of drugs may be needed for certain patients to effectively manage their resistant hypertension. Further investigations are warranted to explore and compare the clinical and economic outcomes of patients with BP above goal versus those at or below goal.

Author contribution statement

Eric M. Ammann: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ellen S. O'Brien, Dejan Milentijevic, Akshay A. Kharat, Darren A. Talbot, William Canovatchel, Lloyd Haskell and Nabil S. Andrawis; Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. These data were made available by Optum and used under license for the current study and are not publicly available. Other researchers should contact https://www.optum.com.

Declaration of interest's statement

The authors declare the following conflict of interests: EMA, ESO, DM, AAK, WC, and LH are employees of Janssen and may be Johnson & Johnson stockholders. DAT is an employee of Idorsia Pharmaceuticals and is an Idorsia stockholder. NSA has provided consultancy advice to Janssen.

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