Description of Antihypertensive Use in Patients With Resistant Hypertension Prescribed Four or More Agents

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See Editorial Commentary, pp XX–XX

Abstract—Data describing the use of recommended antihypertensive agents in the resistant hypertension population are limited. Treatment recommendations for resistant hypertension include maximizing diuretic therapy by using chlorthalidone and/or adding an aldosterone antagonist. Additional recommendations include combining antihypertensive agents from different drug classes. This retrospective cohort study describes antihypertensive use in patients with resistant hypertension defined as the concurrent use of ≥4 antihypertensive agents. Claims data from the Medstat MarketScan Commercial Claims and Encounter database were used to identify patients with resistant hypertension based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes and National Drug Codes between May 1, 2008 and June 30, 2009. Of the 5 442 410 patients with hypertension in the database, 140 126 met study criteria. The most frequently prescribed antihypertensive classes were angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (96.2%), diuretics (93.2%), calcium channel blockers (83.6%), and β-blockers (80.0%). Only 3.0% and 5.9% of patients were on chlorthalidone or an aldosterone antagonist, respectively. A total of 15.6% of patients were treated with angiotensin-converting enzyme inhibitor plus angiotensin receptor blocker. Our findings demonstrate that frequently prescribed antihypertensive agents for the treatment of resistant hypertension included guideline-recommended first-line agents. However, evidence-based and recommended agents, such as chlorthalidone and aldosterone antagonists, were underused. Moreover, minimally efficacious combinations, such as an angiotensin-converting enzyme inhibitor with an angiotensin receptor blocker, were prescribed at higher rates than evidence-based and recommended agents. **(*Hypertension*. 2011;58:00-00.)**

Key Words: hypertension ■ hypertension/drug treatment ■ antihypertensive agents/classification/therapeutic use ■ aldosterone antagonists ■ chlorthalidone ■ drug therapy ■ combination

National Health and Nutrition Examination Survey data from 2005 to 2008 have estimated that 33.5% of United States adults have hypertension.[1] Among these patients, 71% reported using antihypertensive drug therapy, and 48% of those who are aware of their hypertension had controlled blood pressure (BP) <140/90 mm Hg.[1] Resistant hypertension is defined as persistent BP elevations above goal despite the use of ≥3 antihypertensive medications of different classes at optimal doses, one preferably being a diuretic.[2] Resistant hypertension also includes patients at goal BP on ≥4 antihypertensives from different classes.[2] Recent analyses of National Health and Nutrition Examination Survey data from 2003 to 2008 have shown an 8.9% prevalence of resistant hypertension, representing 12.8% of all hypertensive adults treated with drug therapy.[3]

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identifies angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), and diuretics as first-line therapy for hypertension based on data demonstrating reductions in cardiovascular events.[4] Treatment with first-line agents are globally recommended in the JNC 7 guidelines for all of the patients with hypertension, including resistant hypertension.[4] A 2008 scientific statement by the American Heart Association provided treatment recommendations for resistant hypertension.[2] A primary recommendation is to maximize diuretic therapy, because fluid retention is a major cause of resistant hypertension.[2,5] This can be accomplished by using the preferred thiazide (chlorthalidone), adding an aldosterone antagonist (spironolactone or eplerenone), and/or using a loop diuretic in patients with chronic kidney disease (CKD).[2] This scientific statement highlighted the role of primary hyperaldosteronism as a

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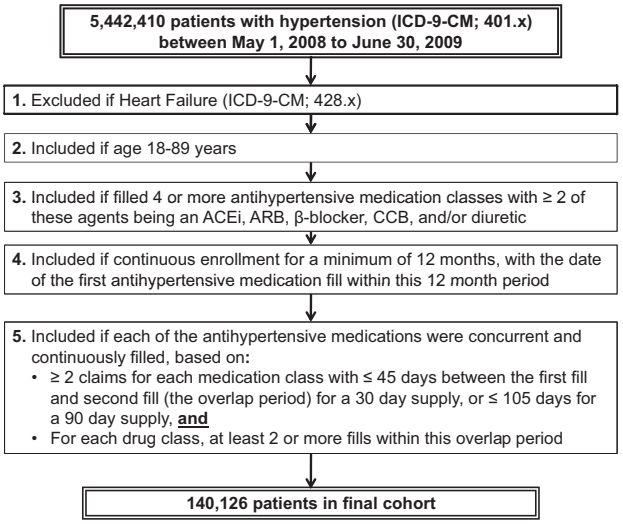

Figure 1. Description of the study criteria and design.

potential secondary cause in ≈20% of resistant hypertension patients, which may explain the effectiveness of adding an aldosterone antagonist.[2] Additional recommendations include the use of antihypertensive combinations consisting of agents with different mechanisms of action, encouraging the use of combinations that include a diuretic and preferential use of a mixed α/β-blocker when β-blocker therapy is used.[2] Strategies proven to enhance adherence with drug therapy (eg, use of fixed-dose combination [FDC] products) are also encouraged.[6]

Recent National Health and Nutrition Examination Survey data demonstrate that the most common types of antihypertensives used in patients with resistant hypertension are diuretics (85.6% of patients).[3] Other first-line agents (ie, ACEi, ARB, β-blocker, and CCB) are also commonly used.[3] There are no data (observational in clinic settings or within secondary databases) available describing the use of recommended antihypertensives for the treatment of resistant hypertension (eg, chlorthalidone and aldosterone antagonist). The aim of this study was to describe overall antihypertensive use and examine the use of recommended antihypertensives for the treatment of resistant hypertension at a population level using data from a national claims database.

Methods

Study Design

A retrospective analysis was performed using enrollment, medical, and pharmacy claims data from the Medstat MarketScan Commercial and Claims Encounter database (Thomson Medstat, Ann Arbor, MI). The MarketScan database provides anonymous claims data for individual patients covered by commercial health plans and represents several different employers in the United States. Claims data were used to identify prescribing of antihypertensives in resistant hypertension patients from May 1, 2008 to June 30, 2009. The data collected included medical (ICD-9-CM) and pharmacy claims files (National Drug Codes [NDCs]), which were used to identify diagnoses and antihypertensive prescribing, respectively. This study was approved by the research team's institutional review board. Figure 1 describes the overall study criteria and design.

Inclusion Criteria

The study cohort was composed of patients 18 to 89 years of age with a diagnosis of hypertension (ICD-9-CM, 401.X). Patients were then included if they filled ≥4 antihypertensive agents concurrently based on NDC claims during the study period, of which 2 had to be a JNC 7–recommended first-line agent (ACEi, ARB, β-blocker, CCB, and diuretic).[4] Patients were only included if they were continuously enrolled in their health plan for a minimum of 12 months, with the date of the first antihypertensive medication fill from each specified drug class being within this 12-month period.

Exclusion Criteria

Patients with a diagnosis of heart failure (ICD-9-CM, 428.X) were excluded, because several antihypertensives are indicated for the treatment of this population but are not exclusively prescribed for hypertension.

Antihypertensive Prescription Fill Behavior

Antihypertensive Use

A master list of all of the medications and dosage forms in the United States between May 1, 2008 and June 30, 2009, was used to identify all available antihypertensive agents and their corresponding NDCs. For each NDC, a general drug class (eg, diuretic) and specific subclass (eg, thiazide) was assigned. Doses of individual medications were identified using dose-specific NDCs. This NDC coding scheme was used to apply the inclusion criteria, identify prescription claims (fills), and describe prescribing. Prescription claims reported the quantity of each antihypertensive agent that was filled and was used to determine the days' supply.

Each antihypertensive agent had to be filled at least twice following ICD-9-CM coding for hypertension with no more than a 45-day lapse between the first fill and second fill for a 30-day supply and no more than a 105-day lapse between the first fill and second fill for a 90-day supply. If individuals filled 2 prescriptions of different agents within the same drug class (eg, 2 different β-blockers), they were considered to have met the definition described above.

Concurrent Antihypertensive Use

The first and second prescription fills of ≥4 antihypertensive agents (following the diagnosis of hypertension) had to overlap with all of the other antihypertensive agents to be considered concurrent antihypertensive use. If individual antihypertensive agents were prescribed using different NDCs from different manufacturers, they were considered to be 1 distinct medication from the same antihypertensive medication class. For example, if different NDC claims for hydrochlorothiazide were processed because different doses were prescribed (eg, 25.0 plus 12.5 mg), the prescription fill was only counted as 1 distinct medication.

Objectives

The first objective of this study was to describe the overall use of antihypertensives in this resistant hypertension population. The use of JNC 7–recommended first-line antihypertensive drug classes was described (ACEi, ARB, β-blocker, CCB, and diuretic). In addition, the use of second-line agents (α1-adrenergic receptor antagonists, α2-adrenergic receptor agonists, direct renin inhibitor [aliskiren], direct vasodilators [hydralazine and minoxidil], central-acting adrenergic agent [methyldopa], and rauwolfia alkaloid [reserpine]) was also described.

The second objective was to describe the use of evidence-based and recommended therapy and minimally efficacious therapy for the treatment of this resistant hypertension population. Evidence-based and recommended antihypertensive therapy described in this population included evaluating the overall use of chlorthalidone and aldosterone antagonists. The use of loop diuretics in patients with CKD, mixed α/β-blockers when β-blocker therapy was prescribed, and FDC products was also assessed. Additional information gathered included the prescribed doses of chlorthalidone, hydrochlorothiazide, and spironolactone to assess optimal dosing of diuretic therapy. Minimally efficacious antihypertensive therapy described in this population included the use of ACEi with ARB and the use of a same drug class combination (eg, ACEi with ACEi). The combi-

Table 1. Baseline Characteristics

Characteristic	No. of Patients (N = 140 126)
Age in years, mean	63.8
Men	76 423 (54.5)
Women	63 703 (45.5)
Comorbidities	
Diabetes mellitus	42 749 (30.5)
Primary aldosteronism	333 (<1.0)
Obstructive sleep apnea	9709 (6.9)
Acute myocardial infarction	2265 (1.6)
Ischemic heart disease	4655 (3.3)
Old myocardial infarction	2036 (1.5)
Angina	6225 (4.4)
Other ischemic heart disease chronic	20 528 (14.6)
Atherosclerotic vascular disease*	1949 (1.4)
Heart disease	1175 (<1.0)
Transient ischemic attack	2935 (2.1)
Cerebrovascular disease	2529 (1.8)
Late effects of cerebrovascular disease	1478 (1.1)
Aortic aneurism and dissection	1702 (1.2)
Peripheral vascular disease	4731 (3.4)
Nephrotic syndrome	558 (<1.0)
Chronic kidney disease	8039 (5.7)

Comorbidities were identified by International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes. Data are n (%) unless otherwise specified.

*Atherosclerotic vascular disease includes coronary artery disease, cerebrovascular disease, aortic aneurism, and peripheral vascular disease.

nation of 2 diuretics from different subclasses (eg, loop with a thiazide) and the combination of dihydropyridine with nondihydropyridine CCB were not considered same drug class combinations.

Statistical Analysis

All of the analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC). Descriptive statistics were presented.

Results

There were 5 442 410 patients with hypertension identified based on ICD-9-CM, and 140 126 met study criteria for this definition of resistant hypertension. Baseline characteristics are presented in Table 1. The mean age was 63.8 years, and 54.5% were men. The majority of patients were prescribed 4 antihypertensive agents, and a small number of patients were prescribed 5, 6, or ≥7 antihypertensive agents (84.2%, 13.3%, 2.1%, and <1%, respectively). Based on ICD-9-CM diagnosis codes, 30.5% of patients had a diagnosis of diabetes mellitus, 22.5% had a history of atherosclerotic vascular disease, 5.7% had reported CKD, and <1.0% had reported nephrotic syndrome or primary aldosteronism.

During the 14-month study period, 134 754 patients (96.2%) were prescribed an ACEi and/or an ARB. The percentage use of all of the antihypertensive classes is presented in Table 2. Diuretics were the second most common agents and were prescribed in 130 629 patients (93.2%), and the most common subclass of diuretic was a thiazide

Table 2. Antihypertensive Agents Used for the Treatment of Resistant Hypertension

Antihypertensive Medication Class	No. of Patients (N = 140 126)
ACEi	84 133 (60.0)
ARB	72 519 (51.8)
β-blocker	112 121 (80.0)
CCB	117 106 (83.6)
Dihydropyridine	97 655 (69.7)
Nondihydropyridine	21 069 (15.0)
Diuretic	130 629 (93.2)
Aldosterone antagonist	8212 (5.9)
Loop	26 375 (18.8)
Potassium sparing	1232 (<1.0)
Thiazide	111 758 (79.8)
α1-Adrenergic receptor antagonist	17 086 (12.2)
α2-Adrenergic receptor agonist	19 745 (14.1)
Direct renin inhibitor (aliskiren)	4706 (3.4)
Other	6529 (4.7)
Hydralazine	4443 (3.2)
Minoxidil	1712 (1.2)
Methyldopa	451 (<1.0)
Reserpine	30 (<1.0)

ACEi indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. Data are n (%) unless otherwise specified.

prescribed in 79.8% of patients. Of the patients prescribed a thiazide, 94.2% were prescribed hydrochlorothiazide, and 89.4% prescribed a loop diuretic were prescribed furosemide. Dihydropyridine CCBs were prescribed more commonly than nondihydropyridine CCBs (69.7% versus 15.0%, respectively). The most common β-blockers prescribed are shown in Figure 2. More than 74% of patients (103 779 of 140 126) were prescribed the combination of an ACEi or ARB plus CCB plus diuretic. Alternative agents (eg, α1-adrenergic receptor antagonists, α2-adrenergic receptor agonists, and direct renin inhibitor) were rarely prescribed.

Only 4267 patients (3.0%) in this study were prescribed chlorthalidone. A slightly higher number of patients, 8212

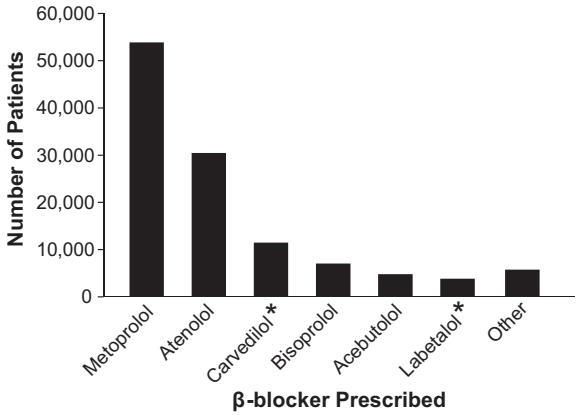

Figure 2. Number of patients on different β-blockers. *Mixed α/β-blocker.

Table 3. No. of FDC Products Prescribed

FDC Product Prescribing	No. of Patients (N = 88 514)
No. of FDC products per patient	
1	74 286
2	14 157
≥3	71

FDC indicates fixed-dose combination.

patients (5.9%), were prescribed an aldosterone antagonist, of which spironolactone was used in 7771 patients (94.6%). Logistic regression identified the presence of primary aldosteronism, younger age, being female, and the total number of unique antihypertensive classes prescribed as characteristics associated with a higher likelihood of being prescribed chlorthalidone and/or an aldosterone antagonist.

A loop diuretic was prescribed in 26 375 patients (18.8%). Of the 8039 patients with a diagnosis of CKD, only 2121 (26.4%) were prescribed a loop diuretic. In patients prescribed chlorthalidone, hydrochlorothiazide, and/or spironolactone, the mean doses based on NDC claims were 25.4, 21.1, and 31.9 mg, respectively.

In this study, the 2 most common β-blockers were metoprolol and atenolol (38.5% and 21.8%, respectively). A small number, ≈11.0%, of patients in the study were on a mixed α/β-blocker (ie, carvedilol and labetalol).

Table 3 describes the number of FDC products prescribed. A total of 88 514 patients (63.2%) were prescribed 1 or more 2-drug FDC product(s), and an overall total of 102 813 FDC products was prescribed. The most common FDC products prescribed are presented in Figure 3. Thiazide diuretics were used in 69.8% of all FDC products, and hydrochlorothiazide accounted for 95.0% of thiazide-containing FDC products.

During the 14-month study duration, 21 898 patients (15.6%) were prescribed concurrent therapy with an ACEi and ARB (see Figure 4). Logistic regression identified the presence of nephrotic syndrome, diabetes mellitus, CKD

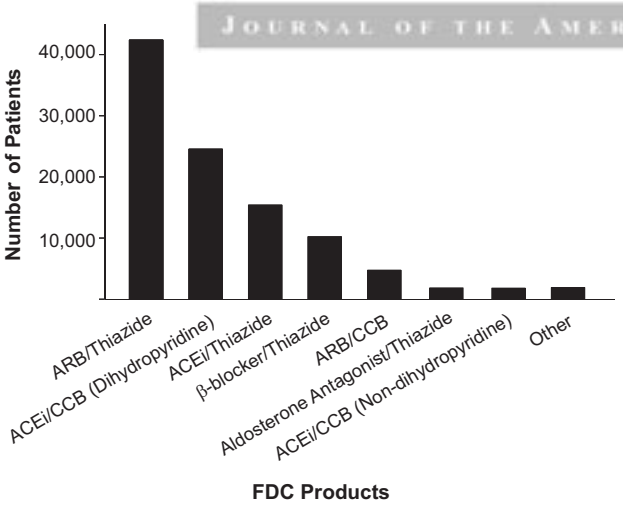

Figure 3. Number of patients on different fixed-dose combination products. FDC indicates fixed-dose combination; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

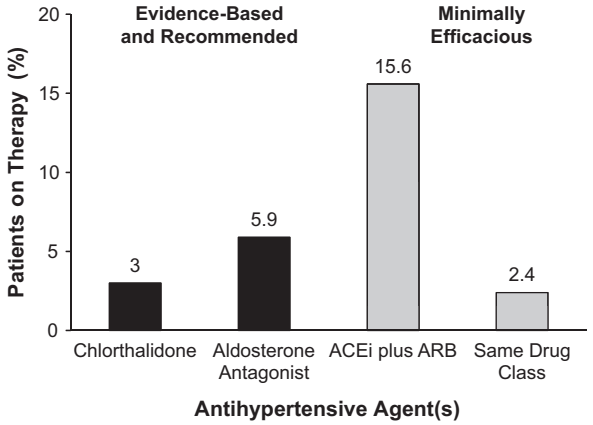

Figure 4. Percentage of patients on evidence-based and recommended versus minimally efficacious antihypertensive therapy. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

(stages 1, 2, or 3), younger age, being male, and the total number of unique antihypertensive classes prescribed as characteristics that were associated with a higher likelihood of being prescribed an ACEi with ARB. Only 3305 patients (2.4%) were prescribed 2 agents from the same drug class. More than half of these patients (1867) were prescribed 2 CCBs; however, 1498 were prescribed a dihydropyridine with a nondihydropyridine CCB.

Discussion

This study used a claims database to describe the overall use of antihypertensives among a patient population with resistant hypertension. Based on the predetermined definition used to identify patients with resistant hypertension in this study, the prevalence of resistant hypertension was 2.6%, which is less than what has been described previously. Characteristics of patients with resistant hypertension in this study are similar to previous reports and confirm a high prevalence of diabetes mellitus and atherosclerotic vascular disease.[3,7,8] The prevalence of CKD was higher in this population compared with previous data, and the prevalence of primary aldosteronism was low.[3,9–12]

The most commonly prescribed antihypertensive classes in this study were ACEi, ARB, β-blocker, CCB, and/or diuretic, which are consistent with evidence-based guideline recommendations for first-line treatment.[4,13] Compared with recent National Health and Nutrition Examination Survey data, more patients in this resistant hypertension population were on an ACEi, ARB, β-blocker, CCB, and/or diuretic (60.0% versus 57.0%, 51.8% versus 40.9%, 80.0% versus 75.5%, 83.6% versus 66.5%, and 93.2% versus 85.6%, respectively).[3] Importantly, most patients were prescribed an ACEi or ARB plus CCB plus diuretic, which is considered an effective and generally well-tolerated 3-drug combination.[2] Alternative therapies were rarely used. Evidence-based and recommended antihypertensives in this population, including the use of chlorthalidone and/or an aldosterone antagonist and the use of a mixed α/β-blocker when a β-blocker was prescribed, were underused.[2]

Volume overload is a common contributor to resistant hypertension.[2] The American Heart Association recommendations emphasize the optimization of diuretic therapy in resistant hypertension patients.[2] Evidence supports thiazide diuretics as first-line agents for the treatment of hypertension based on demonstrated reductions in stroke and other major cardiovascular events.[14,15] Evidence suggests that chlorthalidone is a more effective thiazide diuretic than hydrochlorothiazide for BP lowering and may possibly be better at cardiovascular event lowering.[16–18] Because of its more potent antihypertensive effects, chlorthalidone is the preferred thiazide diuretic in resistant hypertension patients.[2] Despite this evidence, the use of hydrochlorothiazide was higher than the use of chlorthalidone (75.1% versus 3.0%, respectively), which may be partially explained by a lower drug cost for hydrochlorothiazide and availability of hydrochlorothiazide in several FDC products. The use of chlorthalidone was very limited despite evidence-based recommendations to use this thiazide.[16–18]

A major cause of hypertension in patients with CKD is fluid retention.[5] Loop diuretics effectively decrease extracellular fluid volume in patients with CKD and are preferred over a thiazide diuretic in patients with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2.[5] Despite this recommendation, the use of loop diuretics in patients with CKD appeared low.[2] However, this estimation may be inaccurate, because CKD was not always coded by stage; therefore, glomerular filtration rate <30 mL/min per 1.73 m^2 was not always evident.

Maximizing the dose of diuretic therapy is an important treatment strategy in resistant hypertension. Doses of specific diuretics were analyzed in this study; however, the assumption was made when collecting these data that all of the doses reported represented the daily dose. Consistent with the dose used in clinical trials, the mean dose of chlorthalidone was 25 mg daily.[14,17,18] Although chlorthalidone is the recommended thiazide for patients with resistant hypertension, hydrochlorothiazide is the most often prescribed thiazide in clinical practice, and this was seen within this study cohort.[2] When hydrochlorothiazide is used, doses should be optimized, especially in resistant hypertension patients. The mean dose filled of hydrochlorothiazide in this population was 21 mg daily, indicating that this therapy may not have been optimized. Newer data demonstrate superior BP reduction with 50 mg of hydrochlorothiazide compared with 25 mg based on 24-hour ambulatory BP measurements.[19] Using higher doses of hydrochlorothiazide is a possible strategy to improve BP control in resistant hypertension.

Aldosterone antagonist use was low (5.9%) in this resistant hypertension population, despite proven effects and recommended use. Aldosterone antagonists target a potential underlying mechanism of resistant hypertension (hyperaldosteronism), and these agents are recommended in resistant hypertension patients as add-on therapy.[2] Newer data demonstrate that aldosterone antagonists provide significant BP reduction regardless of the diagnosis of primary aldosteronism.[20–25]

Compared with the low use of evidence-based and recommended antihypertensive therapies, the use of minimally efficacious antihypertensives in this population was high. Combination therapy has been classified by the American Society of Hypertension as preferred, acceptable, or less effective.[26] The combination of ACEi plus ARB is considered a less effective combination based on data showing increased adverse events with no cardiovascular event lowering when compared with ARB-based therapy.[26,27] As add-on therapy, spironolactone plus ACEi or ARB has been shown to have superior BP-lowering effects compared with ACEi/ARB combination therapy in patients with resistant hypertension.[28] In spite of lack of evidence to support this practice, 15.6% of patients in this study were prescribed the combination of an ACEi with ARB. Less than 1% of patients had a documented reason for an ACEi with ARB (eg, nephrotic syndrome).[29] Nephrotic syndrome, along with CKD, may not have been accurately or completely coded in this database. Regardless, the frequency of ACEi/ARB combination therapy indicates a need for improvement regarding the selection of preferred antihypertensive combinations.

There are many potential limitations of this study because of the claims-based methodology. First, resistant hypertension was defined by the number of antihypertensives prescribed and did not include patients based on BP measurements. The inclusion criteria of ≥2 JNC 7 first-line agents may be restrictive, but the sample size would have increased by only 61 if this requirement was removed. Second, several assumptions were made to identify the cohort including the following: (1) processing of NDCs through pharmacy claims was exclusively used to define prescribing of antihypertensive agents; (2) all of the antihypertensive agents were processed through one of the commercially available insurance plans; (3) ICD-9-CM diagnosis codes and NDCs were complete and accurate; and (4) antihypertensive agents were prescribed at optimal doses. Third, a short time frame between publication of guideline recommendations for resistant hypertension and the start of the study period may not have allowed adequate time for exposure and implementation of American Heart Association guideline recommendations. Despite limited time to change practice, data demonstrating excellent efficacy with chlorthalidone have been known for several years; however, spironolactone data in this patient population has only been described recently.[14,15,20–25] Fourth, the databases included only ICD-9-CM diagnosis codes and NDCs that were reported with successfully reimbursed medical and pharmacy claims. Race/ethnicity, smoking status, and all of the other noncoded information (eg, laboratory results) were not captured in this database, and we can only assume why the rates of antihypertensive prescribing were either lower or higher than expected.

Perspectives

First-line evidence-based antihypertensives were the most frequently prescribed agents in this resistant hypertension population; however, the minimally efficacious combination of an ACEi with ARB was prescribed more often than evidence-based and recommended treatments for resistant hypertension. Our data show that chlorthalidone and aldosterone antagonists are underprescribed in patients with resistant hypertension. Further clinical research is needed to identify

optimal treatment strategies for resistant hypertension patients, and focused clinician education regarding the optimal treatment of resistant hypertension is needed.

Disclosures

J.J.S. has been a consultant/speaker for Daiichi-Sankyo in the past.

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