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Journal
Mayo Clinic Proceedings, 88(10)

ISSN
0025-6196

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Publication Date
2013-10-01

DOI
10.1016/j.mayocp.2013.06.017

Published in final edited form as:
Mayo Clin Proc. 2013 October ; 88(10): 1099–1107. doi:10.1016/j.mayocp.2013.06.017.

Characteristics of Resistant Hypertension in a Large Ethnically Diverse Hypertension Population of an Integrated Health System

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Abstract

Objective—To evaluate the prevalence and characterize resistant hypertension from a large representative population with successful hypertension management and reliable health information.

Patient and Methods—We performed a cross sectional study using clinical encounter, laboratory, and administrative information from the Kaiser Permanente Southern California health system during 1/1/2006–12/31/2007. From individuals age >17 years with hypertension, resistant hypertension was identified and prevalence determined. Multivariable logistic regression was used to calculate odds ratios (OR) with adjustments for demographics, clinical variables, and medication use.

Results—Among 470,386 hypertensive individuals, 12.8% were identified as resistant representing15.3% of those on medications. Overall, 37,061 (7.9%) had uncontrolled hypertension while on ≥ 3 medicines. OR (95% confidence interval) for resistant hypertension were greater for black race (1.68, 1.62–1.75), older age (1.11, 1.10–1.11 for every 5 year increase), males (1.06, 1.03–1.10), and obesity (1.46, 1.42–1.51). Medication adherence rates were higher in resistant hypertension (93 vs 90%, p<0.001). Chronic kidney disease (1.84, 1.78–1.90), diabetes (1.58, 1.53–1.63), and cardiovascular disease (1.34, 1.30–1.39) were also associated with higher risk for resistant hypertension.

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Financial Support and Disclosure: No other authors have any conflicts of interest relevant to this manuscript.

Conclusion—Within a more standardized hypertension treatment environment, we observed a rate of resistant hypertension comparable to past studies using more fragmented data sources. Past observations have been limited due to non-representative populations, reliability of the data, heterogeneity of the treatment environments, and less than ideal control rates. This cohort which was established with an electronic medical record based approach has the potential to provide a better understanding of resistant hypertension and outcomes.

Background

As the overall awareness and subsequent control of hypertension improves in the United States, an emerging subpopulation that is resistant to therapy is becoming more evident. It has been suggested that the resistant hypertension population is at disproportionately higher risk for target organ damage and cardiovascular events compared to the general hypertension population[1–6]. To this end, the recognition and identification of those with resistant hypertension is of particular importance as these individuals may necessitate further diagnostic evaluations and benefit from specific interventions. Moreover, they may help us better understand response to current hypertension treatment practices which can pave the way for earlier, more efficient and novel management strategies.

The described rates of resistant hypertension are becoming more consistent. Historically, reported estimates of resistant hypertension have ranged from as little as 5% in unselected hypertension populations to as high as 50% in subspecialty hypertension clinics[7,8]. Resistant hypertension has been operationally defined as failure to achieve blood pressure control on 3 or more medications or those who require 4 or more medications regardless of blood pressure[2,9]. Our current understanding and estimates of resistant hypertension are derived from cross sectional population samplings[1,10,11], retrospective cohort evaluations[12,13], and sub analyses of large clinical trials[14–18]. Populations such as National Health and Nutrition Examination Survey (NHANES) and other cohorts have estimated the prevalence of resistant hypertension in the 10–15% range among those with hypertension[1,10,11,19,20].

Despite these efforts, the estimation of the prevalence of resistant hypertension is challenging. Pseudo elevated blood pressures, heterogeneous practice patterns, and difficulty in assessing adherence to the medication regimen affect the accurate identification of resistant hypertension[21–23]. Previous observations have their own respective limitations due to the type of populations studied, reliability of the information, and less than ideal blood pressure control. Thus, the existent estimates have been derived from fragmented data on specialized populations with low hypertension control rates.

We sought to identify and characterize resistant hypertension from an integrated health system with a relatively standardized model of hypertension care and high levels of control. We hypothesize that resistant hypertension prevalence rates will be lower in our large ethnically diverse population within a more ideal treatment environment and reliable capture of medication use.

Methods

Study Population

A cross-sectional study was performed on members of the Kaiser Permanente Southern California (KPSC) health system in the period January 1, 2006 to December 31, 2007. The KPSC healthcare system is a prepaid integrated health plan providing comprehensive care to 3.4 million individuals throughout Southern California from Bakersfield to San Diego at 14 medical centers and over 100 satellite clinics. During the study period, there were a total of 2.4 million adult members. The patient population is ethnically and socioeconomically

diverse, reflecting both the general population of the practicing area and the state of California[24]. Of the members in the KPSC electronic medical record, 42.7% are White, 35.2% Hispanic, 8.8% Black, and 10.2% Asian. All KPSC members have similar benefits and access to health care services, clinic visits, procedures, and co-pays for medications. Complete healthcare encounters are tracked using a common electronic medical record. All laboratory data, vitals assessments including blood pressure measurements and diagnostic and procedure codes are collected in our electronic health records as part of routine clinical care encounters. The study protocol was approved by the Kaiser Permanente Southern California Institutional Review Board and was exempt from informed consent.

The study population included individuals age 18 years and older with a minimum of four months continuous membership in the health plan. This time requirement was used to reliably capture hypertension diagnoses and co morbidities. Inclusion criteria were individuals who had documented hypertension and a blood pressure measurement. Hypertension was identified by inpatient and outpatient *International Classifications of Diseases, Ninth Revision* (ICD-9) codes specific to hypertension (401.xx, 402.xx, 403.xx, 404.xx, 405.xx). All individuals were required to have at least two visits with ICD-9 codes to determine prevalent hypertension during the study period to be included. The accuracy of ICD-9 coding for the diagnosis of hypertension has been previously validated[25]. The date of the outpatient blood pressure measurement closest to the second ICD-9 hypertension code was used as the index date. In those encounters with multiple blood pressure measurements, the lowest value was used for analysis to minimize white coat hypertension. Blood pressures were considered to be uncontrolled if either systolic blood pressure was greater than or equal to140 mmHg or diastolic blood pressure was greater than or equal to 90 mmHg. Individuals who did not have a blood pressure measurement or those who were diagnosed with secondary hypertension were excluded. Specifically, individuals with ICD-9 codes for renovascular disease, adrenal disorders, Cushing's syndrome, aortic coarctation, and secondary hypertension not specified were excluded from the study cohort. Sleep apnea was not excluded as it is often coexistent with hypertension and not necessarily a causative factor.

Co-morbidities

Co-morbidities, including diabetes mellitus, coronary artery disease, congestive heart failure, and cerebrovascular disease, were determined on the basis of inpatient and outpatient ICD-9 diagnoses codes. Chronic kidney disease (CKD) was identified and defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2 estimated from serum creatinine levels (when available) and the Chronic Kidney Disease Epidemiology Collaboration equation[26].

Assessment of Medication Use

Antihypertensive medication use was retrieved from the internal pharmacy dispensing records. Prescription orders, pharmacy fills, and refills are tracked for health plan members with pharmacy benefits. Individuals were determined to be on an antihypertensive medication if it was prescribed and filled within sixty days of the index date. They were considered to be on concomitant antihypertensive medications if there was a greater than 7 day overlap in medications. Medications that were prescribed and filled for less than 7 days were not considered.

Each antihypertensive medication was categorized into a specific drug class. Medication drug classes included thiazide-type diuretics, loop diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, dihydropyridine and nondihydropyridine calcium channel blockers, potassium-sparing diuretics, aldosterone

receptor blockers, alpha blockers, centrally acting alpha agonists, and direct renin inhibitors. Single pill combinations were assigned based on their individual components. The sum of individual blood pressure medications defined the number of antihypertensive medications taken by each person and may have included different medications from the same drug class.

Kaiser Permanente Hypertension Treatment

Since 2005, KPSC has internally advocated and made available a simplified hypertension treatment algorithm with recommendations to guide therapy for all physicians treating and managing hypertension (please see appendix 1). This algorithm has since been revised (in 2009) with the most significant difference being the addition of a mineralocorticoid receptor antagonist as a second line agent along with beta blockers. During the study period of January 1, 2006 to December 31, 2007, hypertension control rates in the KPSC population were estimated to be 65–70% (appendix 2).

Resistant Hypertension and Study Objectives

The primary objective was to determine the prevalence of resistant hypertension among the population of individuals identified with hypertension. Individuals were classified as having resistant hypertension if their systolic blood pressure was greater than or equal to 140mmHg and/ or their diastolic blood pressure was greater than or equal to 90mmHg while prescribed three different antihypertensive medications concurrently; or prescribed 4 or more medications concomitantly regardless of blood pressure control.

Classes of antihypertensive medications used and frequency of use were also evaluated. Characteristics in terms of demographics and co morbidities of individuals who met criteria for resistant hypertension were compared to those with non-resistant hypertension.

Medication adherence was based on dispensed medications and the frequency of refills. The proportion of days covered for each antihypertensive medication was calculated as a surrogate for medication adherence. This was based on the 180 days ***prior*** to the second ICD-9 coded date for hypertension. For any antihypertensive medications prescribed for greater than 30 days within that period, the proportion of days covered was calculated using the first and last prescription date, supply amount, and gaps in pill supply. Those with an average proportion of days covered of at least 80% for their medications prescribed were considered adherent. Medication adherence was determined for each antihypertensive medication.

Statistical Analysis

Differences in age and laboratory values between those with and without resistant hypertension were tested with the non-parametric Kruskal-Wallis test. For comparisons of sex and race, chi-square tests were used. Multivariable logistic regression analyses were used to estimate the odds ratio (OR) with 95% confidence intervals for resistant hypertension with adjustment for age, sex, race, body mass index (BMI) ≥ 30, presence of co morbidities which included diabetes mellitus, CKD, ischemic heart disease, congestive heart failure, and cerebrovascular disease. All statistical analyses were generated using SAS Version 9.2 (SAS Institute Inc., Cary, North Carolina) statistical software. Results with p-values < 0.05 were considered statistically significant.

Results

Hypertension Cohort

A total of 498,891 individuals within KPSC were identified with hypertension during the study period. This represented 21% of all adults in the health plan. Secondary hypertension

was identified in 642 resulting in 498,249 individuals with non secondary hypertension. Another 27,863 had blood pressures missing leaving 470,386 members in the study analysis (Figure 1). The average age of the hypertension population was 65 years with females accounting for 55% (Table 1). The hypertension cohort consisted of 43% whites, 21% Hispanics, 13% blacks, and 8% Asians.

The mean blood pressure was 133/75 mm Hg amongst the entire hypertension population (Table 1). Within this hypertension population, 67.2% were considered blood pressure controlled (<140/90) among all hypertensive individuals. Among hypertensive individuals who were treated with medications, 68.2% were considered controlled. The average number of anti-hypertensive medications used was 2.1 per person. The majority of the hypertension population was either on one (31%) or two (31%) medications. 74,904 (16%) were not taking any medications.

Resistant Hypertension

Overall, 60,327 hypertensive individuals met the criteria for resistant hypertension. This accounted for 12.8% of all hypertensive individuals and 15.3% of those taking medications (Table 1). Within the resistant hypertension population, 31,637 individuals were identified as uncontrolled on 3 medicines and 28,600 were on 4 or more medicines regardless of control. Among those on 4 or more medicines, 5,424 individuals were uncontrolled. Thus, 37,061 (7.9%) of the hypertension population had blood pressure uncontrolled on 3 or more medicines.

The resistant hypertension population had an average blood pressure of 143/74 mm Hg. Those with resistant hypertension were older (69 years vs 65 years, $p<0.001$), more likely to be obese (49 vs 42%, $p<0.001$), and had greater proportion of blacks (19 vs 12%) compared to non-resistant hypertension individuals. Resistant hypertension individuals also had a greater prevalence of co morbid conditions such as diabetes (49 vs 31%, $p<0.001$), ischemic heart disease (42 vs 23%, $p<0.001$), cerebrovascular disease (17 vs 9%, $p<0.001$), and CKD (52vs 30%, $p<0.001$).

In terms of the class of medications used in the resistant hypertension population, diuretics or calcium channel blockers were the most frequently prescribed class of medication at 97% followed by renin angiotensin system blockers (82%) and beta blockers (77%) (Table 2).

Medication Adherence

In the 395,482 individuals with hypertension who were prescribed medications, the proportion with at least 80% of days covered was 90% for the entire cohort. Ninety three percent of the resistant hypertension population had at least 80% of days covered compared to 89.8% for the non-resistant hypertension individuals ($p<0.001$).

Regression Analyses

Multivariable logistic regressions analyses demonstrated that the resistant hypertension population had significantly different characteristics compared to the non-resistant population (Table 3). These were demonstrated in both the crude and the adjusted analyses. In the adjusted regressions, every 5 year age increase demonstrated an OR (95% CI) of 1.11 (1.10 – 1.11). Black race [1.68 (1.62– 1.75)], BMI ≥30 [1.46 (1.42 – 1.51)], and male gender [1.06 (1.03–1.10)] were also associated with greater likelihood for resistant hypertension. Chronic kidney disease had an increased risk for resistant hypertension [OR of 1.84 (1.78–1.90)]. Additional co morbid conditions that were also associated with greater risk for resistant hypertension were diabetes mellitus [1.58 (1.53 – 1.63)], ischemic heart disease [1.34 (1.30– 1.39)], and cerebrovascular disease [1.17 (1.13 – 1.22)]. In the subset of

resistant hypertension individuals with proportion of days covered below 80%, the associations were similar to those identified as resistant hypertension with greater than or equal to 80% of days covered.

Discussion

We found a significant proportion of resistant hypertension with a prevalence of 12.8% among all hypertensive individuals and 15.3% among those on medications. Using a stricter criteria, 7.9% of the hypertension population had uncontrolled blood pressure on 3 or more medicines. Hypertensive individuals who were male, black race, obese, and older were more likely to be have resistant hypertension. Diabetes mellitus, ischemic heart disease, congestive heart failure, and CKD were co morbidities that were also associated with resistant hypertension. The resistant hypertension population surprisingly had slightly better adherence to their prescribed anti-hypertensive medications.

The resistant hypertension population is emerging as a focus of concern and there are many unanswered questions in regard to this subgroup of hypertensive individuals. The described rates of resistant hypertension are continually rising and have paralleled the increasing identification and treatment of hypertension[11,19]. The resistant subgroup itself may be a specialized population prone to worsened outcomes and thus may warrant different treatment strategies. In addition, the fact that they are resistant to our current treatment methods may highlight the need to reevaluate our present hypertension guidelines at least for certain subpopulations. Ultimately, the development of a better understanding the resistant hypertension population may provide insights into improving control and outcomes across all hypertensive individuals.

Our findings were drawn from a study environment that we felt had a better ability to identify resistant hypertension due to higher blood pressure control rates and also had more reliable patient information. This is in comparison to past observations that entailed more fragmented information and less consistent treatment environments[2,7,10–13,27–30]. In addition, our study population was racially and ethnically diverse and thus reflective of a representative treatment population[24]. The clinical information in our study was derived from a real-world clinical practice setting compared to previous observations from different information sources. Hypertensive individuals were observed under real life situations and clinical care environments. Conversely, clinical trials study specific target populations using age and co morbidity based inclusion criteria. Very often specific protocols for drug selection, dose titration, and adherence are closely monitored. These artificial situations make their respective prevalence estimates difficult to generalize to the overall population[14,16,17,31,32]. Our clinical practice environment included a large, representative, and ethnically diverse population. The diversity within our population was comparable to the NHANES population[24]. However, our study had more reliable capture of medication use and co morbidities due to our comprehensive electronic medical records.

The high blood pressure control rates in our treatment environment allowed us to better identify resistant hypertension but limited some of the generalizability of our findings. Hypertension control rates were around 67% compared to 50% in NHANES during the same period[19]. Our clinical practice environment had high rates of blood pressure awareness, treatment, and control. The higher control rates are partially attributable to a standardized approach to hypertension management. Kaiser Permanente health system uses an internal hypertension treatment guideline that is JNC based[9,33] which is followed by a large proportion of the practitioners. In addition, health providers receive similar training in blood pressure measurement techniques which contribute to more reliable and reproducible blood pressure information. Standardizing hypertension care also minimizes hypertension control

variations from heterogeneity in practice patterns. Thus we feel that we were able to more accurately identify resistant hypertension in our clinical care environment. Using similar criteria, 7.9% of our hypertension population had uncontrolled blood pressure on 3 or more medicines compared to 13.4% in the most recent evaluation of the NHANES population[34]. We feel that our lower rates are attributed to less therapeutic inertia as evidenced by the fact that 84% of KPSC hypertensive individuals were treated with medicines compared to only 48% in NHANES. The comparison to NHANES underscores the fact that our hypertension control rates are not what are observed in the rest of the country. Thus the applicability of our findings may not be as encompassing to the rest of the hypertension world. However, the Kaiser Permanente treatment environment can potentially highlight or exemplify what can be done in the real-world setting that takes advantage of decision support and more standardization of practice.

Historically, the study of resistant hypertension has been a challenge due to multiple factors that confound the proper identification of this population. Medication adherence has been a major confounder due to the fact that the very definition of resistant hypertension is based on the assumption that individuals are fully adherent to their medication regimen of 3 or more medications. Though imperfect, we used an operational definition of resistant hypertension that is similar to the one used by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) and the American Heart Association[2,9]. While our study did not have information on medication use behaviors per se on each hypertensive individual, we did use the data within the pharmacy medication records detailing medications prescribed to and filled by individuals. With this information, we assessed adherence using proportion of days covered. Thus some measure of adherence was available on the more than 60,000 individuals in our resistant hypertension cohort. Although it does not completely answer the question of adherence, we did find that more than 90% of the resistant hypertension population had greater than 80% proportion of days covered in regards to their anti-hypertensive medications. Proportion of days covered has been well accepted surrogate for adherence and its values have correlated with clinical outcomes[3536,37].

The cross sectional design was a potential limitation of our study in that it could not evaluate persistence to medication use per se as a longer detailed follow up examination would provide. A longitudinal analysis is underway to evaluate persistence to medications by evaluating refill rates over longer durations. To this end, medication adherence and physician practice patterns need to be better studied and utilized to more accurately identify resistant hypertension. Additional potential limitations of our study and findings include the use of single blood pressure measurements, the lack of information on medication dosages, and the overall heterogeneity in treatment by individual practitioners despite having an internal hypertension treatment guideline.

Conclusion

Within a large representative hypertension population, we identified and characterized a resistant hypertension cohort that accounted for a substantial proportion (12.8%) of the hypertension population. The resistant hypertension population was older, more likely to be black, had better adherence, and had more co morbidities. This cohort established by an electronic medical record based approach has the potential to improve our understanding of resistant hypertension by addressing many of the current knowledge gaps including longitudinal outcomes. Studying this cohort may provide greater insights that lead to more efficient and effective strategies to manage hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Eric P. Brass, MD PhD at Harbor-UCLA Medical Center for his invaluable contributions to methodology and scientific insight into drafting of this manuscript.

This study was partially funded by an investigator initiated research grant from Novartis Pharmaceuticals (J.J.S. PI) and supported by Kaiser Permanente Southern California Regional Research. Support was also provided by a research grant from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health (R01 DK078106) to K.K.Z.

Abbreviations List

NHANES	National Health and Nutrition Examination Survey
KPSC	Kaiser Permanente Southern California
ICD-9	*International Classifications of Diseases, Ninth Revision*
CKD	chronic kidney disease
OR	odds ratio
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
eGFR	estimated glomerular filtration rate

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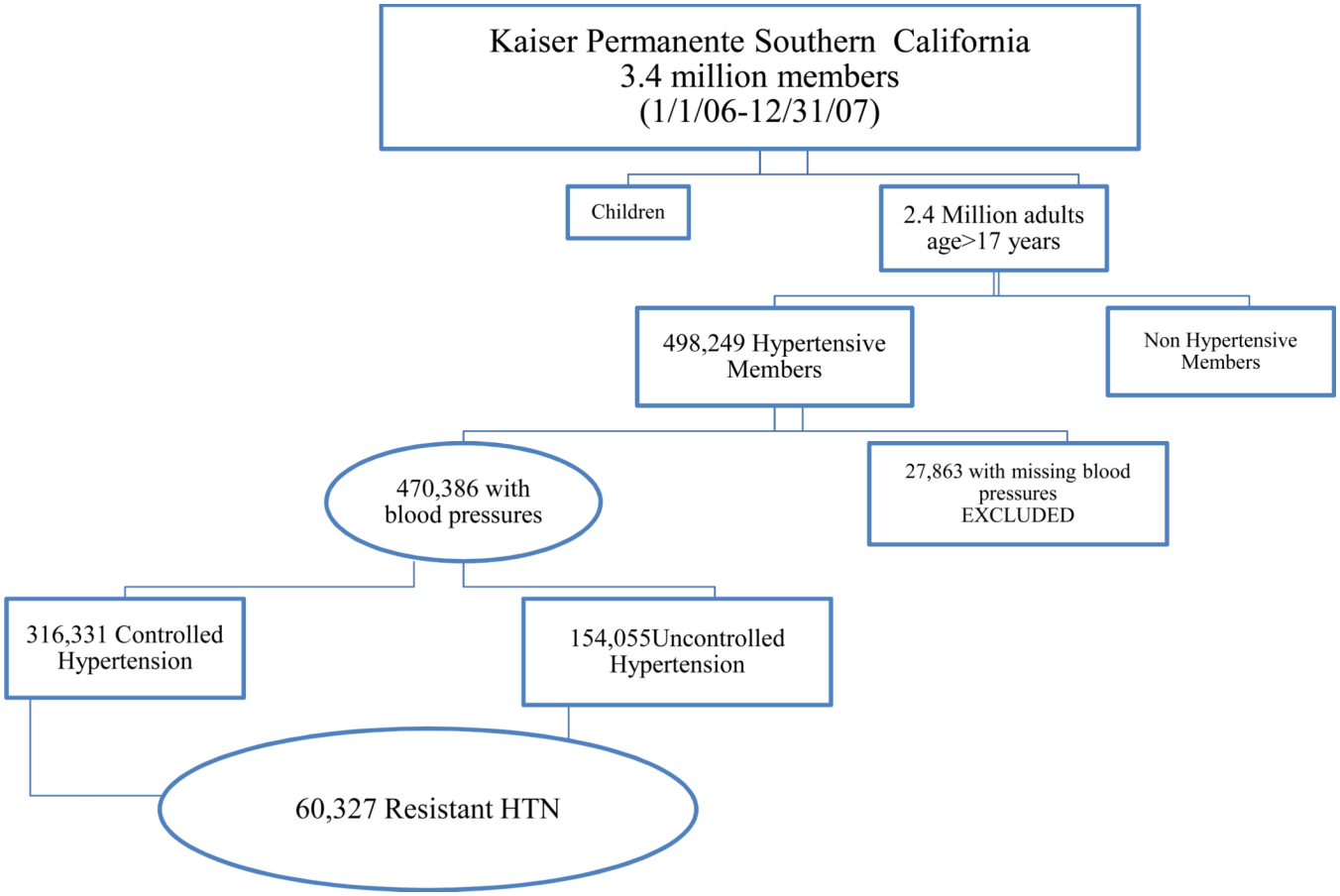

Figure 1.

A total of 498,249 subjects were identified with non secondary hypertension which represented 21% of all adults in the KPSC population. Of these, 470,386 subjects with hypertension had at least one documented blood pressure measurement and were included in the study analysis.

Mayo Clin Proc. Author manuscript; available in PMC 2014 October 01.

Table 1

Characteristics of Subjects with and without Resistant Hypertension

Characteristics	All	Subjects without Resistant Hypertension	Subjects with Resistant Hypertension	p-value
	(N=470,386)	(N=410,059)	(N=60,327)	
Age, mean (SD)	65 (11)	65 (11)	69 (11)	<0.001
Gender				
Female, %	55	55	52	<0.001
Race				<0.001
White, %	43	42	45	
Black, %	13	12	19	
Hispanic, %	21	21	18	
Asian/Pacific, %	8	8	6	
Other, %	16	17	11	
BMI				<0.001
BMI < 30, %	56	57	50	
BMI ≥ 30, %	43	42	49	
Missing, %	1	1	1	
Blood Pressure				
[a]SBP, mean (SD)	133 (18)	132 (17)	143 (20)	<0.001
[b]DBP, mean (SD)	75 (11)	75 (11)	74 (13)	<0.001
Diabetes, %	33	31	49	<0.001
Ischemic Heart Disease (%)	25	23	42	<0.001
Congestive Heart Failure (%)	10	8	23	<0.001
Cerebrovascular Disease (%)	10	9	17	<0.001
Chronic Kidney Disease (%)	34	30	52	<0.001

[a]SBP = systolic blood pressure

[b]DBP= diastolic blood pressure

Table 2

Antihypertensive Medication Class Use amongst the General Hypertension and Resistant Hypertension population

Antihypertensive Medication Class	All Subjects	Non Resistant Hypertension	Resistant Hypertension
Diuretics/Natriuretics, %	56	50	97
Distal Diuretic, %	43	39	70
Loop Diuretic, %	6	4	24
Calcium Channel Blocker, %	18	12	56
Suppressors	39	32	82
Beta Blocker, %	37	32	78
Other Renin Suppressors, %	3	1	14
Blockers	52	47	90
[a]ACEI, %	45	40	72
[b]ARB, %	9	7	22
Other Meds	9	6	31

[a]ACEI = angiotensin converting enzyme inhibitor

[b]ARB = angiotensin receptor blocker

Table 3

Unadjusted and Adjusted Logistic Regression Analyses for Resistant Hypertension (Simultaneously Adjusting for Variables within Column)

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Age			
5 year increase	1.17 (1.16 – 1.18)	1.11 (1.10 – 1.11)	<0.001
Gender			
Female vs Male	0.92 (0.89 – 0.95)	0.94 (0.91 – 0.97)	<0.001
Male vs Female	1.09 (1.05 – 1.12)	1.06 (1.03–1.10)	<0.001
Race			
Black vs non Black	1.68 (1.62 – 1.74)	1.68 (1.62 – 1.75)	<0.001
[a]**BMI**			
BMI ≥ 30 vs BMI 0–29	1.31 (1.27 – 1.35)	1.46 (1.42 – 1.51)	<0.001
[b]**CKD**			
[c]eGFR<60 vs eGFR≥ 60	2.51 (2.44 – 2.58)	1.84 (1.78 – 1.90)	<0.001
Diabetes	1.89 (1.84 – 1.94)	1.58 (1.53 – 1.63)	<0.001
Ischemic Heart Disease	2.15 (2.09 – 2.22)	1.34 (1.30 – 1.39)	<0.001
Congestive Heart Failure	3.04 (2.94 – 3.14)	1.78 (1.72 – 1.86)	<0.001
Cerebrovascular Disease	1.84 (1.77 – 1.90)	1.17 (1.13 – 1.22)	<0.001

[a]BMI=body mass index

[b]CKD=chronic kidney disease

[c]eGFR= estimated glomerular filtration rate