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Refractory Hypertension: Determination of Prevalence, Risk Factors and Comorbidities in a Large, Population-Based Cohort

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Abstract

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Refractory hypertension is an extreme phenotype of antihypertensive treatment failure. Participants in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, a large (n=30,239), population-based cohort were evaluated to determine the prevalence of refractory hypertension and associated cardiovascular risk factors and comorbidities. Refractory hypertension was defined as uncontrolled blood pressure (systolic/diastolic ≥ 140/90 mm Hg) on ≥ 5 antihypertensive drug classes. Participants with resistant hypertension (systolic/diastolic ≥140/90 mm Hg on ≥ 3 or<140/90 mm Hg on ≥ 4 antihypertensive classes) and all treated hypertensive participants served as comparator groups. Of 14,809 REGARDS participants receiving antihypertensive treatment, 78 (0.5%) had refractory hypertension. The prevalence of refractory hypertension was 3.6% among participants with resistant hypertension(n=2,144) and 41.7% among participants on 5 or more antihypertensive drug classes. Among all hypertensive participants, African American race, male gender, living in the stroke belt or buckle, higher body mass index, lower heart rate, reduced estimated glomerular filtration rate, albuminuria, diabetes and history of stroke and coronary heart disease were associated with refractory hypertension. Compared to resistant hypertension, prevalence ratios for refractory hypertension were increased for African Americans (3.00, 95% CI 1.68 – 5.37) and those with albuminuria (2.22, 95% CI 1.40 – 3.52) and diabetes (2.09, 95% CI 1.32 – 3.31). The median 10-year Framingham risk for coronary heart disease and stroke was higher among participants with refractory hypertension compared to either comparator group. These data indicate that while resistant hypertension is relatively common among treated hypertensive patients, true antihypertensive treatment failure is rare.

Keywords

hypertension; refractory; resistant; treatment; risk factors

Introduction

Resistant hypertension, defined as uncontrolled blood pressure (BP) in spite of use of 3 or more antihypertensive agents from different classes or controlled blood pressure with use 4 or more agents[1], has an estimated prevalence of 10-15% among all treated hypertensive patients.[2-5] Multiple observational studies have found obesity, chronic kidney disease (CKD), diabetes and older age to be associated with resistanthypertension.[2-4,6-8] Patients with resistant hypertension are more likely to have cardiovascular disease, manifest as stroke, heart disease or congestive heart failure, compared to patients with more easily controlled hypertension.[6-11]

Recently, an extreme phenotype of antihypertensive treatment failure or “refractory hypertension” has been proposed. The initial description of refractory hypertension was based on a retrospective analysis of patients with resistant hypertension referred to a hypertension specialty clinic.[12] Of 304 consecutive patients with confirmed resistant hypertension, 29, or approximately 10%, were identified as having refractory hypertension defined as failure to control systolic and diastolic BP to <140/90 mmHg after a minimum of 6 months of treatment by a hypertension expert. Overall, patients with refractory hypertension were followed in the specialty clinic for an average of 11 months and were

receiving an average of 6 antihypertensive agents from different classes. In that report, patients with refractory hypertension had a higher prevalence of stroke history and prior hospitalization for heart failure compared to patients with controlled resistant hypertension (i.e., controlled BP on 4 or more antihypertensive agents from different classes).

The current study was designed to use a large, population-based cohort to determine the prevalence of refractory hypertension. Additionally, we identified factors associated with refractory hypertension and calculated the 10-year predicted risk for coronary heart disease (CHD) and stroke for participants with refractory hypertension. To do so, we evaluated participants with treated hypertension in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.[13] In order to characterize refractory hypertension, participants with resistant hypertension and all participants treated with antihypertensive medication were used as comparator groups.

Methods

Study Recruitment

The REGARDS study has been described previously.[13] Briefly, adults ≥ 45 years of age from all 48 continental US states and the District of Columbia were enrolled between January 2003 and October 2007 (n=30,239). By design, the REGARDS study oversampled African Americans and residents of the “stroke buckle” (coastal North Carolina, South Carolina, and Georgia) and “stroke belt” (the remainder of North Carolina, South Carolina, and Georgia as well as Alabama, Mississippi, Tennessee, Arkansas and Louisiana) for enrollment. The current analysis was limited to REGARDS participants who reported a history of hypertension and were taking antihypertensive medication (treated hypertension; n=14,854). We subsequently excluded 45 participants who were missing systolic BP or diastolic BP resulting in a final analytic cohort of 14,809 participants. The REGARDS study protocol was approved at all participating centers by the Institutional Review Boards governing research in human participants. All participants provided informed consent.

Data Collection

Baseline REGARDS study data were collected through a telephone interview, self-administered questionnaire, and in-home examination. Participants' age, gender, smoking status, education, annual household income, physical activity, alcohol consumption, symptoms of depression, and self-report of prior physician diagnosed co-morbid conditions (e.g., hypertension, diabetes, stroke, coronary heart disease [CHD]) were collected during computer-assisted telephone interviews that were administered by trained staff. Symptoms of depression were assessed by the 4-item Center for Epidemiologic Studies Depression Scale (CES-D).[14] During the in-home examination, trained professionals measured weight, height, heart rate, and BP, an electrocardiogram (ECG) was performed, and blood and spot urine samples were collected. Additionally, all prescription and over the counter pill bottles were reviewed for medications taken over the prior 2 week period. High medication adherence was defined as scoring ≤1 using the 4-item Morisky Medication Adherence Scale (MMAS).[15] Following the in-home examination, a self-administered questionnaire that

included the Block 98 Food Frequency Questionnaire[16] was given to the participant to complete and mail back to the REGARDS study coordinating center.

Coronary heart disease was defined as a self-reported history of myocardial infarction or revascularization procedure or ECG evidence of a myocardial infarction. Prevalent stroke at baseline was defined as a self-reported history during the telephone interview. Current smoking was defined as answering yes to the following two questions: “Have you smoked at least 100 cigarettes in your lifetime?” and “Do you smoke cigarettes now, even occasionally?” Physical activity was assessed with the question “How many times per week do you engage in intense physical activity, enough to work up a sweat?” Response options were “none”, “1 to 3 times per week”, or “≥ 4 times per week.” Participants who answered “none” were considered physically inactive. Heavy alcohol consumption among men and women was defined as > 14 and > 7 drinks per week, respectively. Diabetes was defined by serum glucose ≥ 126 mg/dL for participants who fasted ≥ 8 hours or a serum glucose ≥ 200 mg/dL for those who did not fast prior to their blood draw or by self-report of a prior diagnosis while not pregnant with concurrent use of insulin or oral hypoglycemic medications. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. High-sensitivity C-reactive protein (hs-CRP) was measured by particle enhanced immunonephelometry. High hs-CRP was defined as > 3 mg/L. Left ventricular hypertrophy (LVH) was defined by the presence on the study ECG. The isotope-dilution mass spectrometry (IDMS)-traceable serum creatinine method was used to estimate glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[17] Reduced eGFR was defined as levels < 60 ml/min/1.73 m^2. Albuminuria was defined by a urinary albumin to urinary creatinine ratio ≥ 30 mg/g. The food frequency questionnaire (FFQ) was used to estimate the average dietary intake for one year prior to participants' in-home visits. Nutrient analysis was conducted by Nutrition Quest. A DASH dietary score was created using methods similar to those described by Fung et al.[18] Depressive symptoms were defined by scoring ≥ 4 on the CES-D scale. High medication adherence was defined as a score ≤ 1 on the MMAS. The 10-year Framingham CHD and stroke risk scores were calculated for participants without a history of CHD or stroke, respectively.[19,20]

Measurement of Blood Pressure and Definition of Refractory Hypertension

During the in-home examination, BP was measured twice by trained examiners following a standardized protocol using aneroid sphygmomanometers. For at least five minutes, participants sat with both feet on the floor prior to the first BP measurement. The two BP measurements were taken thirty seconds apart. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medication. BP control was defined as systolic BP < 140 mmHg and diastolic BP < 90 mmHg. Based on the pill bottle review, medications were coded into drug classes. Antihypertensive medication classes included angiotensin converting enzyme-inhibitors (ACEi), alpha blockers, angiotensin-receptor-blockers (ARB), beta blockers, calcium-channel blockers (CCB), central acting agents, diuretics, mineralocorticoid receptor antagonists (MRA) and direct vasodilators. One-pill-combinations were classified into the different respective classes. Medication dosage information was not recorded. Resistant hypertension was defined as taking ≥ 3

classes of antihypertensive medication with systolic BP ≥140 or diastolic BP ≥90 mmHg or taking ≥ 4 classes of antihypertensive medication with systolic BP <140 and diastolic BP <90 mmHg. Refractory hypertension was defined as taking ≥ 5 classes of antihypertensive medication with systolic BP ≥140 mmHg or diastolic BP ≥ 90 mmHg.

Statistical Analysis

Characteristics were calculated separately for 3 groups of participants: (1) those with refractory hypertension, (2) those with resistant hypertension, excluding those with refractory hypertension, and (3) all individuals with hypertension taking antihypertensive medications, excluding those with refractory hypertension (i.e., all treated individuals receiving <5 classes of antihypertensive medication or individuals with controlled BP on ≥ 5 classes of antihypertensive medication). The prevalence of refractory hypertension was calculated as the proportion of all participants taking ≥ 5 antihypertensive medication classes among all participants with resistant hypertension and among all participants with hypertension taking antihypertensive medication. Since we did not know if participants with uncontrolled BP while receiving 3 or 4 classes of antihypertensive agents would have been properly classified as having refractory hypertension or controlled resistant hypertension with additional titration of treatment, we also calculated the prevalence of refractory hypertension among all patients with resistant hypertension after excluding this group of participants.

Next, we investigated factors associated with refractory hypertension. To do so, we calculated prevalence ratios for refractory hypertension versus resistant hypertension and separately versus all treated individuals with hypertension using Poisson regression with robust standard errors. Factors investigated include age, race, sex, geographic region of residence, income, education, reduced eGFR, albuminuria, diabetes, elevated hs-CRP, LVH, history of stroke, history of CHD, physical activity, alcohol consumption, DASH diet score, cigarette smoking, depressive symptoms, medication adherence, heart rate, and body mass index. Initially, unadjusted prevalence ratios were calculated. Subsequently, prevalence ratios were calculated after adjustment for age, race, sex, and geographic region of residence. Due to the limited number of cases of refractory hypertension, adjustment for additional covariates was not performed. Finally, we calculated the median 10-year CHD and stroke risks for participants with refractory hypertension, resistant hypertension and all treated hypertensive participants.[21,22] Using quantile regression, we calculated the age, race, sex, and geographic region of residence-adjusted difference in the median 10-year CHD and stroke risks for individuals with refractory hypertension versus resistant hypertension and versus all treated hypertensive participants, separately. Chained equations were used to impute 10 data sets for missing data.[23] Analyses were conducted in Stata/I.C. 12.1 (Stata Corporation, College Station, TX).

Results

Prevalence of Refractory Hypertension

Of the 14,809 REGARDS participants receiving antihypertensive treatment, 78 had refractory hypertension. This translates into an overall prevalence of refractory hypertension

among all treated hypertensive participants of 0.5%. Among participants with resistant hypertension (n=2,144), the prevalence of refractory hypertension was 3.6%. Among participants with resistant hypertension (n=827), excluding the participants uncontrolled on 3 or 4 classes of antihypertensive agents, the prevalence of refractory hypertension was 9.6%. Among participants taking 5 or more classes of antihypertensive medication (n=187), the prevalence of refractory hypertension was 41.7%.

Participant Characteristics

Antihypertensive medication use for the 78 participants with refractory hypertension is shown in Figure 1. All participants with refractory hypertension were receiving a diuretic and an ACEi or an ARB. The diuretics being used were predominately hydrochlorothiazide (52.6%) or a loop diuretic (44.9%). Chlorthalidone was being used infrequently (3.9%) and amiloride not at all. Only 18% were receiving a MRA. Participants with refractory hypertension were more likely to be receiving a beta blocker (93.6%) compared to participants with resistant hypertension (72.9%) or all treated hypertensive participants (36.7%). Almost all participants with refractory hypertension (89.4%) had a high level of medication adherence.

REGARDS participants with refractory hypertension were similar in age to their counterparts with resistant hypertension and all treated hypertensives, but had a higher mean BMI (Table 1). Participants with refractory hypertension were more likely to be African American, male, a resident of the stroke belt or buckle states and have a lower socioeconomic status based on household income and/or achieved education level. Small differences in average heart rate were observed between the 3 groups. Additionally, those with refractory hypertension more commonly had reduced eGFR, albuminuria, diabetes, LVH and a history of stroke or CHD. Heavy alcohol consumption was lower in participants with refractory hypertension while the DASH diet scores were similar in the 3 groups.

Factors Associated with Refractory Hypertension

In an unadjusted comparison to resistant hypertension, African American race, albuminuria, and diabetes were associated with higher prevalence ratios for refractory hypertension (Table 2). These associations persisted after adjusting for age, race, sex, and geographic region.

In an unadjusted comparison to all hypertensive participants, African American race, male gender, higher body mass index, reduced eGFR, albuminuria, diabetes, LVH, prior stroke and prior CHD were associated with increased prevalence ratios of refractory hypertension (Table 3). After multivariable adjustment, each of these factors except LVH remained associated with refractory hypertension. A higher heart rate was associated with a lower prevalence ratio for refractory hypertension both before and after multivariable adjustment. In the adjusted model, living in the stroke buckle was associated with an increased likelihood of having refractory hypertension with a prevalence ratio of 2.02 (95% CI 1.14 - 3.58).

10-year CHD and stroke risk

Among participants without a history of CHD or stroke, the median Framingham 10-year CHD risk score for participants with refractory hypertension was 50% higher than the risk score for participants with resistant hypertension and more than double the risk score for all treated hypertensive participants (Table 4). The median Framingham 10-year stroke risk score for all participants with refractory hypertension was 28% higher than the risk score for participants with resistant hypertension and more than double the risk score compared to all treated hypertensive participants. After adjustment for age, race, sex, and geographic region of residence, the median 10-year predicted risk of a CHD event and stroke event was 4.0 (95% CI: 0.8 – 7.2) and 5.1 (95% CI: 1.8 – 8.5) percentage points higher, respectively, among those with refractory hypertension versus resistant hypertension. After adjustment, the 10-year predicted CHD and stroke risk was 7.0 (95% CI: 4.6 – 9.5) and 8.1 (95% CI: 5.9 – 10.3) percentage points higher, respectively, among those with refractory hypertension versus all participants treated for hypertension.

Discussion

In the current analysis of a large observational study including adults from across the US, 0.5% of participants receiving antihypertensive treatment and 3.6% of participants with resistant hypertension had refractory hypertension. These findings represent the first determination of antihypertensive treatment failure in a large, population-based cohort. The observed prevalence of <1% of treated hypertensive individuals indicates that true antihypertensive treatment failure may be extremely rare. However, the current findings also indicate that as the number of medications needed to treat hypertension increases, the likelihood of remaining uncontrolled increased dramatically, from 3.6% of those needing 4 or more classes of antihypertensive medications to over 40% of participants taking 5 or more classes.

A prior description of patients with refractory hypertension was based on a retrospective analysis of patients referred to the University of Alabama at Birmingham (UAB) Hypertension Clinic.[12] The term refractory hypertension was used to identify patients failing maximum antihypertensive therapy, defined as patients whose BP remained uncontrolled after a minimum of 6 months of treatment by a hypertension expert and in spite of use of a multidrug regimen that included a long-acting diuretic (chlorthalidone) and a MRA (either spironolactone or eplerenone). In that analysis, 10% of 304 patients originally referred to UAB with resistant hypertension (i.e., uncontrolled on 4 medications) never achieved BP control in spite of being adherent to regimens that included an average of 6 antihypertensive medications from different classes. A lower prevalence of refractory hypertension (3.6%) was observed among those with resistant hypertension in the current analysis of over 14,000 people with hypertension enrolled in this population-based study. The lower prevalence of refractory hypertension in a generalized hypertensive cohort compared to patients referred to a hypertension specialty clinic, undoubtedly, reflects the referral bias of more severe patients being seen by hypertension specialists.

In the current analysis, participants with refractory hypertension were compared both to participants with resistant hypertension and to all treated hypertensive participants in order

to identify characteristics of individuals with refractory hypertension versus lesser degrees of treatment resistance and to hypertension in general. After multivariable adjustment, African American race, albuminuria and diabetes were strongly associated with having refractory hypertension regardless of comparator group. Likewise, participants with refractory hypertension had higher 10-year Framingham CHD and stroke risk scores than those with resistant hypertension and all treated hypertensive participants. Additionally, prior CHD and stroke were 2-3 times more common compared to all treated hypertensive participants. Undoubtedly related to higher BP levels, participants with refractory hypertension appear to have a markedly increased CV risk.

In the prior retrospective assessment of patients with refractory hypertension, a distinguishing characteristic of this group was a significantly higher heart rate compared to the participants with controlled resistant hypertension.[12] This was interpreted to suggest heightened sympathetic output as a potentially important underlying etiology of refractory hypertension. In the current analysis, however, the mean heart rate was not different in the participants with refractory hypertension compared to participants with resistant hypertension and was even lower when compared to all treated hypertensive participants. A lack of difference in heart rate may have been related, in part, to the greater use of beta blockers in participants with refractory hypertension, which may have masked higher resting heart rates. The absence of a higher heart rate would argue against differences in sympathetic output between the 3 groups. However, an important difference between the prior and current analyses is that individuals in the earlier study had more extreme cases of refractory hypertension than those included in the current analysis. In the prior study, all of the patients had been referred to a hypertension specialty clinic, their BP remained uncontrolled on an average of 6 medications, including, in all patients, chlorthalidone and spironolactone, and their hypertension was more severe compared to that documented in the current study (mean systolic/diastolic BP: 168/94 vs. 155/83 mm Hg, respectively).[12] Whether refractory hypertension is characterized by a higher resting heart rate needs additional testing, including with 24-hr ambulatory monitoring of heart rate.

Recommendations for treating resistant hypertension are consistent in suggesting use of multiple-drug regimens that include a long-acting diuretic and a MRA.[1,24] Consistent with these recommendations, in the current study, all participants classified as having refractory hypertension were receiving a diuretic. However, in contrast with the recommendations, only 18% of the participants with refractory hypertension were receiving a MRA. These findings confirm the results of other analyses of large, population-based, observational cohorts indicating underuse of MRAs for treatment of resistant hypertension. For example, in an analysis of the National Health and Nutrition Examination Surveys (NHANES) between 1988 and 2008, Egan et al found that as of 2005-2008, only 4.4% of participants whose BP remained uncontrolled on 3 or more classes of antihypertensive medication were receiving a MRA.[3] Combined with the current findings, these observations highlight the ongoing need to better inform practicing clinicians on how to construct effective multi-drug antihypertensive regimens.

The design of the current study did not allow us to distinguish “apparent” from “true” refractory hypertension. Ambulatory monitoring was not done and cases of white coat

hypertension could not be identified. However, all BP measurements were done at the participants' homes, which should have minimized white coat effects. Adherence was assessed by the 4-item Morisky questionnaire, a validated measure of medication adherence.[16] A more objective measure, such as assessment of prescription refill rates, however, may have found a lower adherence rate than indicated by self-report. This may be particularly relevant to the current analysis as it is well established that adherence tends to decrease as the number of prescribed pills increases. For example, a recent analysis of patients referred to a German hypertension specialty clinic for resistant hypertension found that only 40 of 76 patients (53%) were adherent with prescribed medications based on liquid-chromatography-mass spectrometry analysis for antihypertensive drugs or their corresponding metabolites in the patients' urine.[25] Lastly, we were not able to quantify the dosages for each of the prescribed agents, and so could not assess the degree to which under-treatment contributed to apparent treatment failure. Having been able to account for these causes of pseudo-treatment failure would have resulted in a prevalence of true refractory hypertension even lower than the observed 0.5%. Such an anticipated reduction in the prevalence further emphasizes our primary conclusion that even though apparent resistant hypertension is common, true refractory hypertension is, in contrast, very rare.

The current study is strengthened by analysis of a large, rigorously characterized cohort, including a relatively large number of participants with refractory hypertension. All participants classified as having refractory hypertension were receiving a diuretic as part of their antihypertensive regimen. Adherence was documented by use of a validated questionnaire.[16] Study limitations include not being able to exclude pseudo-refractory hypertension secondary. While drug classes are included in the REGARDS dataset, dosages of the individual agents are not. Accordingly, the current analysis may have overestimated the cases of resistant and refractory hypertension because of use of less than optimal dosing. Also not available were biological assessments known to be relevant to mechanisms of resistant hypertension, including serum aldosterone and plasma renin levels and the presence and severity of obstructive sleep apnea. Finally, with only 78 cases of refractory hypertension we lacked statistical power to study its association with mortality and cardiovascular disease outcomes during follow-up.

Perspectives

The current study characterizes a novel phenotype of antihypertensive treatment failure referred to as refractory hypertension in a large nationwide cohort of African American and white US adults. The study found that refractory hypertension is uncommon overall, but its prevalence is high among patients prescribed a large number of antihypertensive medications. The present study demonstrates underuse of MRAs in individuals failing to achieve blood pressure control on other classes of antihypertensive medications. These findings highlight the opportunity to further reduce the occurrence of refractory hypertension through use of effective antihypertensive regimens, including preferential use of spironolactone and long-acting thiazide diuretics such as chlorthalidone.

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Novelty and Significance

1. What is new?

- Refractory hypertension, a novel phenotype of antihypertensive treatment failure, is defined as uncontrolled hypertension on 5 or more antihypertensive medications.
- Evaluation of a large, population-based population indicates the prevalence of refractory hypertension to be 0.5% of all participants being treated for hypertension

2. What is relevant?

- Antihypertensive treatment failure is uncommon in a population-based cohort indicating that hypertension can generally be controlled with continued titration of antihypertensive treatments

3. Summary

Refractory hypertension identifies a phenotype of antihypertensive treatment failure. It is uncommon in a population-based population but is characterized by an increased prevalence of risk factors and comorbidities.

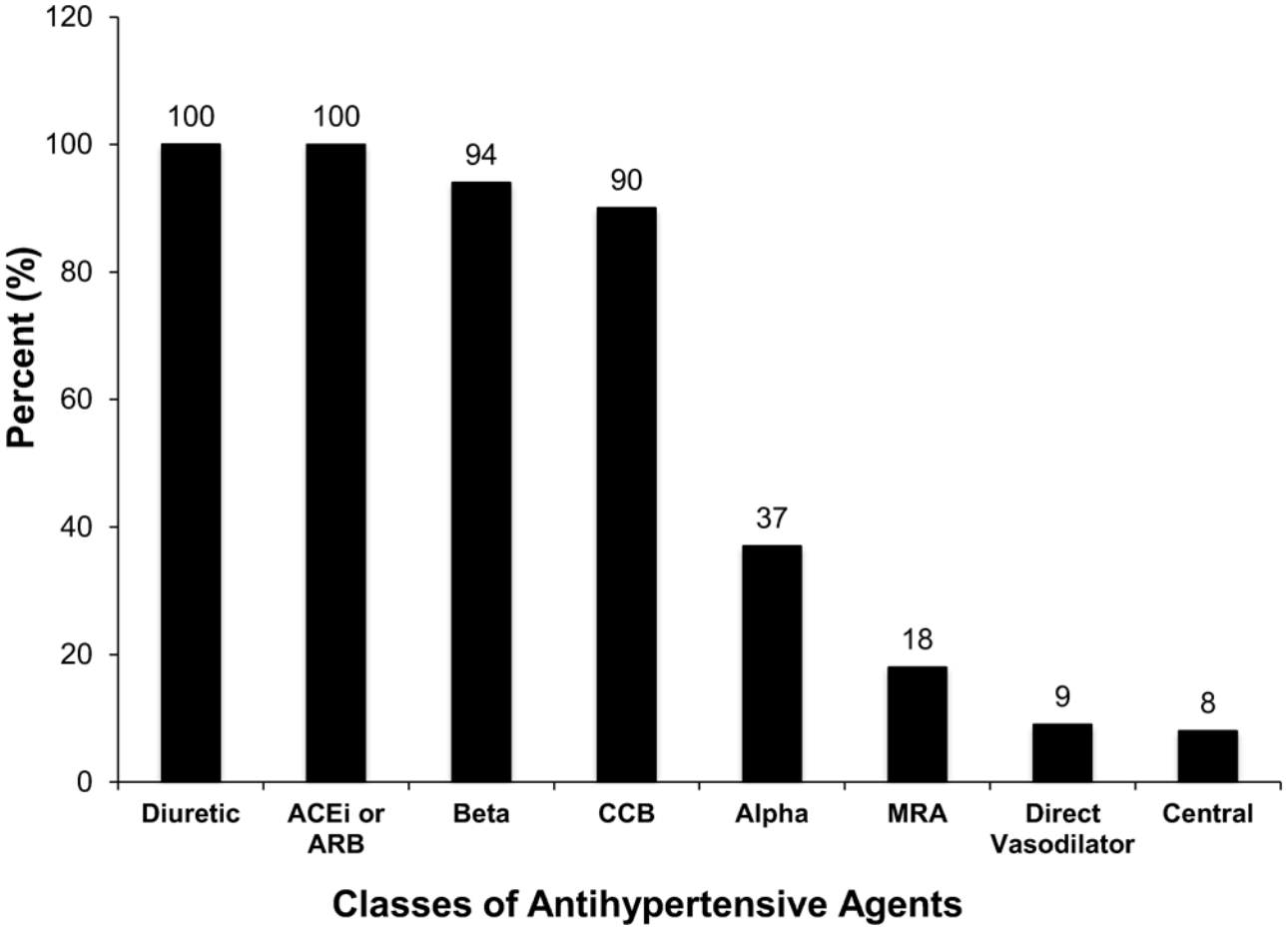

Figure 1.

Use of antihypertensive medication classes among study participants with refractory hypertension (n=78). ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; Beta: beta antagonist; Alpha: alpha antagonist; MRA: mineralocorticoid receptor antagonist; Central: central acting agent.

Table 1

Characteristics of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study population with refractory hypertension, resistant hypertension and treated hypertension.

Characteristic	Refractory hypertension	Resistant hypertension*	All treated hypertensives†
	n = 78	n = 2,066	n = 14,731
Age (years)	66.0 ± 1.0	67.6 ±0.2	66.3 ± 0.1
African American (%)	80.8	60.0	50.5
Male (%)	53.8	48.8	42.8
Geographic Region (%)			
Stoke belt	38.5	34.3	35.2
Stroke buckle	27.0	20.7	21.1
Other region	34.5	45.0	43.7
Systolic blood pressure (mmHg)	154.8 ±1.7	141.5 ±0.4	131.2 ±0.1
Diastolic blood pressure (mmHg)	83.4 ±1.7	79.7 ±0.3	77.6 ±0.1
Heart rate (bpm)	64.0 ± 1.2	65.6 ±0.6	67.4 ± 0.2
Body mass index (kg/m^2)	33.6 ± 0.8	32.2 ±0.1	30.7 ± 0.1
Household income, <$20,000 (%)	34.2	28.9	25.4
<High school education (%)	21.8	19.7	15.5
eGFR <60 ml/min/1.73m^2 (%)	35.1	27.3	17.1
Albuminuria (ACR ≥30 mg/g) (%)	54.5	32.8	20.2
Diabetes (%)	67.4	45.1	30.8
hsCRP > 3 mg/L (%)	53.7	49.1	46.5
Left ventricular hypertrophy (%)	23.1	18.3	13.1
Prior stroke (%)	20.5	13.1	9.2
Prior coronary heart disease (%)	43.6	34.9	22.9
Physical activity (%)	52.9	56.1	61.1
Heavy alcohol consumption (%)	24.4	30.4	33.0
DASH diet score	23.5 ± 0.6	23.6 ±0.1	23.8 ± 0.0
Smoking status (%)			
Never	47.5	43.6	44.3
Past	41.0	44.2	42.0
Current	11.5	12.2	13.7
Depressive symptoms (%)	16.8	13.7	12.4
High medication adherence (%)	89.4	91.5	92.4

Numbers in table are mean ± standard error or percentage.

BPM, beats per minute; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; hs-CRP, high sensitivity c-reactive protein

*All resistant hypertension participants except those with refractory hypertension.

†All treated hypertensive participants except those with refractory hypertension.

Table 2

Prevalence ratios for refractory hypertension compared to individuals with resistant hypertension.

Characteristic	Prevalence ratio (95% confidence interval)	
	Model 1	Model 2
Age, 10 years	0.81 (0.62 – 1.05)	0.90 (0.69 – 1.17)
African American versus white	2.72 (1.56 – 4.74)	3.00 (1.68 – 5.37)
Male versus female	1.22 (0.79 – 1.88)	1.51 (0.97 – 2.35)
Geographic Region		
Stroke belt versus non-belt	1.19 (0.76 – 1.86)	1.62 (0.98 – 2.67)
Stroke buckle versus non-belt	1.39 (0.85 – 2.28)	1.89 (1.08 – 3.29)
Heart rate (bpm)	0.84 (0.56 – 1.25)	0.76 (0.51 – 1.13)
Body mass index (kg/m^2)	1.15 (0.99 – 1.32)	1.10 (0.94 – 1.29)
Household income, <$20,000	1.27 (0.78 – 2.05)	1.17 (0.69 – 2.00)
<High school education	1.13 (0.67 – 1.91)	0.93 (0.53 – 1.64)
eGFR <60 ml/min/$1.73m^2$	1.42 (0.89 – 2.28)	1.52 (0.94 – 2.45)
Albuminuria (ACR ≥30 mg/g)	2.36 (1.51 – 3.70)	2.22 (1.40 – 3.52)
Diabetes	2.44 (1.52 – 3.92)	2.09 (1.32 – 3.31)
hs-CRP	1.00 (0.97 – 1.02)	0.99 (0.97 – 1.02)
Left ventricular hypertrophy	1.33 (0.79 – 2.22)	1.18 (0.70 – 2.01)
Prior stroke	1.68 (0.98 – 2.86)	1.56 (0.91 – 2.67)
Prior coronary heart disease	1.42 (0.91 – 2.20)	1.59 (1.00 – 2.52)
Physical activity	0.88 (0.57 – 1.37)	0.84 (0.54 – 1.30)
Alcohol consumption	0.74 (0.45 – 1.24)	0.80 (0.47 – 1.36)
DASH diet score	0.698 (0.76 – 1.24)	1.04 (0.82 – 1.33)
Smoking status		
Never	1 (reference)	1 (reference)
Past	0.88 (0.57 – 1.37)	0.91 (0.59 – 1.40)
Current	0.94 (0.47 – 1.86)	0.83 (0.43 – 1.60)
Depressive symptoms	1.25 (0.70 – 2.25)	1.17 (0.65 – 2.12)
High medication adherence	0.78 (0.38 – 1.61)	0.77 (0.38 – 1.56)

BPM, beats per minute; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; hs-CRP, high sensitivity c-reactive protein.

Model 1 – Unadjusted.

Model 2 – Adjusted for age, race, sex, and geographic region or residence.

Table 3

Prevalence ratios for refractory hypertension compared to all treated individuals with hypertension

Characteristic	Prevalence ratio (95% confidence interval)	
	Model 1	Model 2
Age, 10 years	0.97 (0.75 – 1.24)	1.08 (0.85 – 1.39)
African American versus white	4.09 (2.33 – 7.18)	4.88 (2.79 – 8.72)
Male versus female	1.55 (1.00 – 2.42)	2.00 (1.24 – 3. 07)
Geographic Region		
Stroke belt versus non-belt	1.15 (0.73 – 1.81)	1.57 (0.94 – 2.63)
Stroke buckle versus non-belt	1.37 (0.83 – 2.25)	2.02 (1.14 – 3.58)
Heart rate (bpm)	0.58 (0.37 – 0.92)	0.54 (0.35 – 0.84)
Body mass index (kg/m^2)	1.34 (1.18 – 1.50)	1.36 (1.19 – 1.56)
Household income, <$20,000	1.52 (0.92 – 2.52)	1.28 (0.73 – 2.24)
<High school education	1.51 (0.89 – 2.58)	1.09 (0.62 – 1.94)
eGFR <60 $ml/min/1.73m^2$	2.60 (1.60 – 4.22)	2.84 (1.69 – 4.79)
Albuminuria (ACR ≥30 mg/g)	4.67 (2.99 – 7.30)	4.02 (2.53 – 6.41)
Diabetes	4.52 (2.80 – 7.32)	3.62 (2.26 – 5.81)
hs-CRP	1.39 (0.87 – 2.24)	1.36 (0.83 – 2.21)
Left ventricular hypertrophy	1.98 (1.17 – 3.35)	1.63 (0.95 – 2.81)
Prior stroke	2.54 (1.47 – 4.38)	2.23 (1.29 – 3.85)
Prior coronary heart disease	2.58 (1.65 – 4.03)	2.85 (1.77 – 4.59)
Physical activity	0.73 (0.46 – 1.13)	0.70 (0.44 – 1.09)
Alcohol consumption	0.66 (0.39 – 1.10)	0.74 (0.43 – 1.25)
DASH diet score	0.90 (0.72 – 1.44)	0.98 (0.77 – 1.24)
Smoking status		
Never	1 (reference)	1 (reference)
Past	0.96 (0.61 – 1.50)	0.93 (0.60 – 1.45)
Current	0.82 (0.41 – 1.64)	0.72 (0.37 – 1.43)
Depressive symptoms	1.42 (0.78 – 2.57)	1.34 (0.73 – 2.49)
High medication adherence	0.69 (0.33 – 1.43)	0.74 (0.36 – 1.55)

BPM, beats per minute; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; hs-CRP, high sensitivity c-reactive protein.

Model 1 – Unadjusted.

Model 2 – Adjusted for age, race, sex, and geographic region or residence.

Table 4

Framingham 10-year coronary heart disease (CHD) and stroke risk scores for individuals with refractory hypertension, resistant hypertension and treated hypertension.

Characteristic	Refractory	Resistant	Treated
10-year CHD risk*	17.5 (10.0 – 26.0)	11.7 (6.4 – 19.7)	7.9 (4.2 – 14.3)
	Difference in 10-year CHD risk†		
Refractory vs. resistant hypertension	Reference	4.0(0.8–7.2)‡	
Refractory vs. all treated hypertension	Reference		7.0 (4.6 – 9.5)§
10-year stroke risk†	20.8 (12.9 – 31.3)	16.2 (9.2 – 26.8)	9.5 (5.3 – 17.0)
	Difference in 10-year stroke risk†		
Refractory vs. resistant hypertension	Reference	5.1 (1.8 – 8.5)//	
Refractory vs. all treated hypertension	Reference		8.1 (5.9 – 10.3)§

Individuals with prevalent CHD at baseline were excluded from the 10-year CHD risk calculation. Individuals with prevalent stroke at baseline were excluded from the 10-year CHD risk calculation.

*Median (25% - 75%).

†Numbers reported are difference in median (95% confidence interval) 10-year risk after adjustment for age, race, sex, and geographic region of residence.

‡p-value < 0.014

§p-value < 0.001

//p-value < 0.003