# **Epidemiology/Population**

## **Refractory Hypertension**

## Determination of Prevalence, Risk Factors, and Comorbidities in a Large, Population-Based Cohort

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## See Editorial Commentary, pp 447–448

Abstract—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=30239), 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 mmHg on ≥3 or <140/90 mmHg on ≥4 antihypertensive classes) and all participants treated for hypertension served as comparator groups. Of 14809 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=2144) and 41.7% among participants on ≥5 antihypertensive drug classes. Among all participants with hypertension, black race, male sex, living in the stroke belt or buckle, higher body mass index, lower heart rate, reduced estimated glomerular filtration rate, albuminuria, diabetes mellitus, and history of stroke and coronary heart disease were associated with refractory hypertension. Compared with resistant hypertension, prevalence ratios for refractory hypertension were increased for blacks (3.00; 95% confidence interval, 1.68–5.37) and those with albuminuria (2.22; 95% confidence interval, 1.40–3.52) and diabetes mellitus (2.09; 95% confidence interval, 1.32–3.31). The median 10-year Framingham risk for coronary heart disease and stroke was higher among participants with refractory hypertension when compared with those with either comparator group. These data indicate that although resistant hypertension is relatively common among treated patients with hypertension, true antihypertensive treatment failure is rare. (Hypertension. 2014;63:451-458.)

**Key Words:** diabetes mellitus, type 2 ■ hypertension ■ risk factors ■ therapeutics

 $\mathbf{R}$  esistant hypertension, defined as uncontrolled blood pressure (BP) despite use of  $\geq 3$  antihypertensive agents from different classes or controlled BP with the use of  $\geq 4$  agents, has an estimated prevalence of 10% to 15% among all participants treated for hypertension. Multiple observational studies have found obesity, chronic kidney disease, diabetes mellitus, and older age to be associated with resistant hypertension. And older age to be associated with resistant hypertension. And older age to be associated with resistant hypertension. And older age to be associated with resistant hypertension are more likely to have cardiovascular disease, manifest as stroke, heart disease, or congestive heart failure when compared with patients with more easily controlled hypertension.

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. <sup>12</sup> Of 304 consecutive patients with confirmed resistant hypertension,

29, or ≈10%, were identified as having refractory hypertension defined as failure to control systolic and diastolic BP to <140/90 mm Hg 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 when compared with patients with controlled resistant hypertension (ie, controlled BP on ≥4 antihypertensive agents from different classes).

The current study was designed to use a large, population-based cohort to determine the prevalence of refractory hypertension. In addition, we identified factors associated with refractory hypertension and calculated the 10-year predicted risk for coronary heart disease (CHD) and

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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 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 aged ≥45 years from all 48 continental United States and the District of Columbia were enrolled between January 2003 and October 2007 (n=30239). By design, the REGARDS study oversampled blacks 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=14854). We subsequently excluded 45 participants who were missing systolic or diastolic BP resulting in a final analytic cohort of 14809 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, sex, smoking status, education, annual household income, physical activity, alcohol consumption, symptoms of depression, and self-report of prior physician diagnosed comorbid conditions (eg, hypertension, diabetes mellitus, stroke, 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 Epidemiological Studies Depression scale.14 During the in-home examination, trained professionals measured weight, height, heart rate, and BP; an ECG was performed; and blood and spot urine samples were collected. In addition, all prescription and over-the-counter pill bottles were reviewed for medications taken for the prior 2-week period. High medication adherence was defined as scoring ≤1 using the 4-item Morisky Medication Adherence Scale. 15 After 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.

CHD 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 2 questions: Have you smoked ≥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× 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 mellitus 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 before 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 was calculated by dividing weight in kilograms by height in meters squared. High-sensitivity C-reactive protein was measured by particle-enhanced immunonephelometry. High-sensitivity C-reactive protein was defined as >3 mg/L. Left ventricular hypertrophy (LVH) was defined by the presence on the study ECG. The isotope-dilution mass spectrometry-traceable serum creatinine method was used to estimate glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>17</sup> Reduced eGFR was defined as levels <60 mL/min per 1.73 m<sup>2</sup>. Albuminuria was defined by a urinary albumin:urinary creatinine ratio ≥30 mg/g. The Food Frequency Questionnaire was used to estimate the average dietary intake for 1 year before participants' in-home visits. Nutrient analysis was conducted by NutritionQuest. A Dietary Approaches to Stop Hypertension (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 Center for Epidemiological Studies Depression scale. High medication adherence was defined as a score ≤1 on the Morisky Medication Adherence Scale. 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 BP and Definition of **Refractory Hypertension**

During the in-home examination, BP was measured twice by trained examiners after a standardized protocol using aneroid sphygmomanometers. For ≥5 minutes, participants sat with both feet on the floor before the first BP measurement. The 2 BP measurements were taken 30 seconds apart. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the use of antihypertensive medication. BP control was defined as systolic BP <140 mm Hg and diastolic BP <90 mm Hg. On the basis of pill bottle review, medications were coded into drug classes. Antihypertensive medication classes included angiotensin-converting enzyme-inhibitors, α-blockers, angiotensin-receptor-blockers, β-blockers, calcium-channel blockers, 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 mm Hg or taking ≥4 classes of antihypertensive medication with systolic BP <140 mmHg and diastolic BP <90 mmHg. Refractory hypertension was defined as taking ≥5 classes of antihypertensive medication with systolic BP ≥140 mm Hg or diastolic BP  $\geq$  90 mm Hg.

### **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 (ie, 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. Because we did not know whether 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 individuals treated for hypertension using Poisson regression with robust SEs. Factors investigated include age, race, sex, geographic region of residence, income, education, reduced eGFR, albuminuria, diabetes mellitus, elevated high-sensitivity C-reactive protein, 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. Because of 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 participants treated for hypertension. <sup>21,22</sup> 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 participants treated for hypertension, separately. Chained equations were used to impute 10 data sets for missing data. <sup>23</sup> Analyses were conducted in Stata/I.C. 12.1 (Stata Corporation, College Station, TX).

#### **Results**

### Prevalence of Refractory Hypertension

Of the 14809 REGARDS participants receiving antihypertensive treatment, 78 had refractory hypertension. This translates into an overall prevalence of refractory hypertension among all participants treated for hypertension of 0.5%. Among participants with resistant hypertension (n=2144), 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 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 the Figure. All participants with refractory hypertension were receiving a diuretic and an angiotensin-converting enzyme-inhibitors or an angiotensin-receptor-blockers. 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

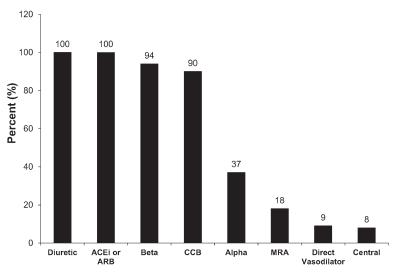
be receiving a  $\beta$ -blocker (93.6%) when compared with participants with resistant hypertension (72.9%) or all participants treated for hypertension (36.7%). Almost all participants with refractory hypertension (89.4%) had a high level of medication adherence.

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

#### **Factors Associated With Refractory Hypertension**

In an unadjusted comparison with resistant hypertension, black race, albuminuria, and diabetes mellitus 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 with all participants with hypertension, black race, male sex, higher body mass index, reduced eGFR, albuminuria, diabetes mellitus, 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% confidence interval [CI], 1.14–3.58).



**Classes of Antihypertensive Agents** 

**Figure.** The use of antihypertensive medication classes among study participants with refractory hypertension (n=78). ACEi indicates angiotensin-converting enzyme-inhibitor; alpha,  $\alpha$  antagonist; ARB, angiotensin receptor blocker; beta,  $\beta$  antagonist; central, central acting agent; CCB, calcium-channel blockers; and MRA, mineralocorticoid receptor antagonist.

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=2066	n=14731
Age, y	66.0±1.0	67.6±0.2	66.3±0.1
Black, %	80.8	60.0	50.5
Men, %	53.8	48.8	42.8
Geographic region, %			
Stoke belt	38.5	34.3	35.2
Stroke buckle	27	20.7	21.1
Other region	34.5	45	43.7
Systolic blood pressure, mm Hg	154.8±1.7	141.5±0.4	131.2±0.1
Diastolic blood pressure, mm Hg	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 <sup>2</sup>	33.6±0.8	32.2±0.1	30.7±0.1
Household income, <\$20000, %	34.2	28.9	25.4
<high %<="" education,="" school="" td=""><td>21.8</td><td>19.7</td><td>15.5</td></high>	21.8	19.7	15.5
eGFR <60 mL/min per 1.73 m², %	35.1	27.3	17.1
Albuminuria (ACR ≥30 mg/g), %	54.5	32.8	20.2
Diabetes mellitus, %	67.4	45.1	30.8
hs-CRP>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	44.2	42
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 represent mean ±SE or percentage. ACR indicates albumin creatinine ratio; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; and hs-CRP, high-sensitivity C-reactive protein.

#### 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 participants treated for hypertension (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 when compared with all participants treated for hypertension. 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) 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

<sup>\*</sup>All resistant hypertension participants except those with refractory hypertension.

<sup>†</sup>All treated hypertensive participants except those with refractory hypertension.

Table 2. Prevalence Ratios for Refractory Hypertension When Compared With Individuals With Resistant Hypertension

	Prevalence Ratio (95% Confidence Interval)		
Characteristic	Model 1	Model 2	
Age, 10 y	0.81 (0.62–1.05)	0.90 (0.69–1.17)	
Black vs white	2.72 (1.56-4.74)	3.00 (1.68-5.37	
Men vs women	1.22 (0.79-1.88)	1.51 (0.97–2.35	
Geographic region			
Stroke belt vs nonbelt	1.19 (0.76–1.86)	1.62 (0.98–2.67)	
Stroke buckle vs nonbelt	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 <sup>2</sup>	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 education<="" school="" td=""><td>1.13 (0.67-1.91)</td><td>0.93 (0.53-1.64</td></high>	1.13 (0.67-1.91)	0.93 (0.53-1.64	
eGFR <60 mL/min per 1.73 m <sup>2</sup>	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 mellitus	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	

Model 1: unadjusted; model 2: adjusted for age, race, sex, and geographic region or residence. ACR indicates albumin creatinine ratio; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; and hs-CRP, high-sensitivity C-reactive protein.

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  $\geq 4$  classes of antihypertensive medications to >40% of participants taking  $\geq 5$  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 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 the 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 University of Alabama at Birmingham with resistant hypertension (ie, uncontrolled on 4 medications) never achieved BP control despite being adherent to regimens that included

Table 3. Prevalence Ratios for Refractory Hypertension When Compared With All Treated Individuals With Hypertension

	Prevalence Ratio (95% Confidence Interval)		
Characteristic	Model 1	Model 2	
Age, 10 y	0.97 (0.75–1.24)	1.08 (0.85–1.39)	
Black vs white	4.09 (2.33-7.18)	4.88 (2.79-8.72)	
Men vs women	1.55 (1.00-2.42)	2.00 (1.24-3. 07)	
Geographic region			
Stroke belt vs nonbelt	1.15 (0.73-1.81)	1.57 (0.94-2.63)	
Stroke buckle vs nonbelt	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 <sup>2</sup>	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 education<="" school="" td=""><td>1.51 (0.89-2.58)</td><td>1.09 (0.62-1.94)</td></high>	1.51 (0.89-2.58)	1.09 (0.62-1.94)	
eGFR<60 mL/min per 1.73 m <sup>2</sup>	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 mellitus	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)	

Model 1: unadjusted; model 2: adjusted for age, race, sex, and geographic region or residence. ACR indicates albumin creatinine ratio; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; and hs-CRP, high-sensitivity C-reactive protein.

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 >14000 people with hypertension enrolled in this population-based study. The lower prevalence of refractory hypertension in a generalized hypertensive cohort when compared with 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 participants treated for hypertension to identify characteristics of individuals with refractory hypertension versus lesser degrees of treatment resistance and to hypertension in general. After multivariable adjustment, black race, albuminuria, and diabetes mellitus were strongly associated with having refractory hypertension regardless of comparator group. Likewise, participants with refractory hypertension had higher 10-year Framingham CHD and stroke

Table 4. Framingham 10-Year CHD and Stroke Risk Scores for Individuals With Refractory Hypertension, Resistant Hypertension, and Treated Hypertension

Characteristic	Refractory	Resistant	Treated
10-y 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-y 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 coronary heart disease (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.

risk scores than those with resistant hypertension and all participants treated for hypertension. In addition, prior CHD and stroke were 2 to 3× more common when compared with all participants treated for hypertension. Undoubtedly related to higher BP levels, participants with refractory hypertension seem to have a markedly increased cardiovascular risk.

In the prior retrospective assessment of patients with refractory hypertension, a distinguishing characteristic of this group was a significantly higher heart rate when compared with the participants with controlled resistant hypertension.<sup>12</sup> This was interpreted to suggest heightened sympathetic output as a potentially important underlying the cause of refractory hypertension. However, in the current analysis, the mean heart rate was not different in the participants with refractory hypertension when compared with participants with resistant hypertension and was even lower when compared with all participants treated for hypertension. A lack of difference in heart rate may have been related, in part, to the greater use of β-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 among 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 when compared with that documented in the current study (mean systolic/diastolic BP, 168/94 versus 155/83 mm Hg, respectively). 12 Whether refractory hypertension is characterized by a higher resting heart rate needs additional testing, including with 24-hour 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.<sup>1,24</sup> 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 an 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 between 1988 and 2008, Egan et al<sup>3</sup> found that as of 2005 to 2008, only 4.4% of participants whose BP remained uncontrolled on ≥3 classes of antihypertensive medication were receiving a MRA. Combined with the current findings, these observations highlight the ongoing need to better inform practicing clinicians on how to construct effective multidrug 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 However, a more objective measure, such as assessment of prescription refill rates, may have found a lower adherence rate than indicated by self-report. This may be particularly relevant to the current analysis because 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 Finally, we were not able to quantify the dosages for each of the prescribed agents and so could not assess the degree to which undertreatment contributed to apparent treatment failure. Having been able to account for these causes of pseudotreatment failure would have resulted in a prevalence of true refractory hypertension even lower than the observed

<sup>\*</sup>Median (25%-75%).

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

 $<sup>\</sup>pm P$  value < 0.014.

<sup>§</sup>P value < 0.001.

<sup>||</sup>P value < 0.003.

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, 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 the use of a validated questionnaire. 16 Study limitations include not being able to exclude pseudorefractory hypertension secondary. Although drug classes are included in the REGARDS data set, 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 black 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 BP control on other classes of antihypertensive medications. These findings highlight the opportunity to reduce the occurrence of refractory hypertension through the use of effective antihypertensive regimens further, including preferential use of spironolactone and long-acting thiazide diuretics, such as chlorthalidone.

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### **Disclosures**

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## **Novelty and Significance**

#### What Is New?

- Refractory hypertension, a novel phenotype of antihypertensive treatment failure, is defined as uncontrolled hypertension on ≥5 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.

#### 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.

#### 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.