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Apparent Treatment-resistant Hypertension Among Individuals with History of Stroke or Transient Ischemic Attack

Virginia J. Howard, PhD,[a] Rikki M. Tanner, PhD,[a] Aaron Anderson, MD,[b] Marguerite R. Irvin, PhD,[a] David A. Calhoun, MD,[c] Daniel T. Lackland, DrPH,[d] Suzanne Oparil, MD,[c] Paul Muntner, PhD[a]

[a]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham; [b]Department of Neurology, Emory University, Atlanta, Ga; [c]Division of Cardiovascular Disease, Department of Medicine, School of Medicine, University of Alabama at Birmingham; [d]Department of Neurosciences, Medical University of South Carolina, Charleston.

ABSTRACT

BACKGROUND: Blood pressure control is a paramount goal in secondary stroke prevention; however, high prevalence of uncontrolled blood pressure and use of multiple antihypertensive medication classes in stroke patients suggest this goal is not being met. We determined the prevalence and factors associated with apparent treatment-resistant hypertension in persons with/without stroke or transient ischemic attack.

METHODS: Data came from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national, population-based cohort of 30,239 black and white adults aged ≥45 years, enrolled 2003-2007, restricted to 11,719 participants with treated hypertension. Apparent treatment-resistant hypertension was defined as (1) uncontrolled blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) with ≥3 antihypertensive medication classes, or (2) use of ≥4 antihypertensive medication classes, regardless of blood pressure level. Poisson regression was used to calculate characteristics associated with apparent treatment-resistant hypertension.

RESULTS: Among hypertensive participants, prevalence of apparent treatment-resistant hypertension was 24.9% (422 of 1694) and 17.0% (1708 of 10,025) in individuals with and without history of stroke or transient ischemic attack, respectively. After adjustment for cardiovascular risk factors, the prevalence ratio for apparent treatment-resistant hypertension for those with versus without stroke or transient ischemic attack was 1.14 (95% confidence interval, 1.03-1.27). Among hypertensive participants with stroke or transient attack, male sex, black race, larger waist circumference, longer duration of hypertension, and reduced kidney function were associated with apparent treatment-resistant hypertension.

CONCLUSIONS: The high prevalence of apparent treatment-resistant hypertension among hypertensive persons with history of stroke or transient ischemic attack suggests the need for more individualized blood pressure monitoring and management.

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KEYWORDS: Predictors; Prevalence; Resistant hypertension; Secondary prevention; Stroke; Transient ischemic attack

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Requests for reprints should be addressed to Virginia J. Howard, PhD, University of Alabama at Birmingham, School of Public Health, Department of Epidemiology, Ryals 210F, 1720 2nd Avenue S, Birmingham, AL 35294-0022.

E-mail address: vjhoward@uab.edu

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Hypertension is considered to be the most important risk factor for primary and secondary stroke prevention.[1,2] In persons with history of stroke, the prevalence of hypertension is high, with estimates ranging from 70% to 82%.[3-7] Although there have been few clinical trials examining blood pressure (BP) treatment in secondary prevention, meta-analyses of such trials show that risk of recurrent stroke is reduced with antihypertensive medications.[8-10] American Heart Association/American Stroke Association guidelines recommend BP reduction for prevention of recurrent stroke as well as prevention of other vascular events in persons who have had an ischemic stroke or transient ischemic attack (TIA).[1,2]

Control of BP after stroke is a substantial challenge. Reports of risk factor management in stroke survivors have described low prevalence of BP control.[5,7,11-16] Among 2830 black and white participants in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study who reported a physician diagnosis of stroke or TIA, 2200 (78%) were being treated for hypertension, but 732 (33.3%) had uncontrolled BP (ie, systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg).[12] Uncontrolled hypertension among black stroke survivors is a particular challenge.[12,15,16] Reasons for this are multifactorial and include medication nonadherence/nonpersistence/nonfulfillment due to costs, side effects, complexity of treatment regimen, not receiving regular medical care, treatment-resistant hypertension, and lack of healthy behaviors such as physical activity.[17-19] Because stroke is considered a cardiac risk equivalent, such a comorbid condition increases the complexity of treating hypertension.[20,21]

Apparent treatment-resistant hypertension is defined as uncontrolled BP on 3 or more antihypertensive medication classes or, regardless of BP, being on 4 or more antihypertensive medication classes.[19] There are few studies on the burden of apparent treatment-resistant hypertension in secondary stroke prevention. The objective of this study was to determine the prevalence and factors associated with apparent treatment-resistant hypertension among those with a history of stroke or TIA in the REGARDS cohort.

CLINICAL SIGNIFICANCE

- Among hypertensive participants with stroke/transient ischemic attack, after multivariable adjustment, male sex, black race, larger waist circumference, longer duration of hypertension, and reduced kidney function were associated with higher prevalence of apparent treatment-resistant hypertension.
- Sensitivity analysis of only those participants with a stroke or transient attack whose medications included a diuretic resulted in attenuation of the increased risk of apparent treatment-resistant hypertension for blacks but not whites.

METHODS

REGARDS is a national, population-based cohort study of 30,239 community-dwelling individuals, aged ≥45 years at enrollment in 2003-2007. Details of methods have been previously described.[22,23] REGARDS was designed to investigate causes of regional and black-white disparities in stroke mortality with oversampling of blacks and residents of the "buckle" of the Stroke Belt[24] (coastal plain region of North Carolina, South Carolina, and Georgia), and the rest of the Stroke Belt[25] (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Individuals were randomly selected from a commercially available list and contacted by mail, followed by telephone for recruitment and verbal consent. Exclusion criteria included self-reported medical conditions (such as cancer) that would prevent long-term participation, or being on a waiting list for a nursing home. The final sample comprised 21% from the stroke buckle, 35% from the rest of stroke belt area, and 44% from the other 40 contiguous states, and was 42% black, 55% female. Using a computer-assisted telephone interview, trained interviewers obtained demographics, medical history, and risk factors. A brief physical examination including BP measurements, blood and urine samples, and an electrocardiogram was conducted during an in-home visit 3 to 4 weeks after the telephone interview. Participants were asked to provide all prescription and nonprescription medications they had taken in the past 2 weeks, and medication names (but not dosages) were recorded during the in-home visit. Written consent was obtained during the in-person evaluation. Biological samples were stored and analyzed at the central laboratory at the University of Vermont, and electrocardiograms were read centrally by electrocardiographers at Wake Forest University who were blinded to clinical data. The institutional review boards of participating institutions approved the study methods. The primary analysis for this report was limited to participants who reported history of hypertension with concurrent use of antihypertensive medication determined from medication inventory (n = 15,004.) We excluded participants missing data on SBP or DBP (n = 87), history of stroke or TIA (n = 221), or self-reported antihypertensive medication use (n = 23), reducing the number to 14,673. The primary analysis cohort consisted of 11,719, excluding participants with uncontrolled hypertension who were taking 1 or 2 antihypertensive medications (n = 2954) because they did not meet criteria for apparent treatment-resistant hypertension; however, these individuals were included in secondary analysis described below.

During the in-person examination, 2 BP measurements were taken by a trained technician using a standard protocol and regularly tested aneroid sphygmomanometer (American

Diagnostic Corporation, Hauppauge, NY) after the participant was seated for 5 minutes. When possible, measurements were taken in the left arm; a large-size cuff was used if the arm circumference was greater than 13 inches. The cuff was inflated to 20 mm Hg above the pulse obliteration level and slowly deflated. This process was repeated after a 30-second rest period to obtain the second BP on the same arm. Quality control was monitored by central examination of digit preference, and retraining of technicians took place as necessary.[26] Systolic BP and DBP were defined as the average of 2 measurements. Uncontrolled blood pressure was defined as SBP $\geq$140 mm Hg and/or DBP $\geq$90 mm Hg; apparent treatment-resistant hypertension was defined as uncontrolled BP on 3 or more antihypertensive medication classes or, regardless of BP level, being on 4 or more antihypertensive medication classes.[19] Antihypertensive medication classes were coded from the in-home medication inventory and defined using classes in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[27-29] The classes included angiotensin-converting enzyme inhibitors, aldosterone receptor blockers, α-blockers, angiotensin receptor blockers, β-blockers, calcium channel blockers, central-acting agents, diuretics, and direct vasodilators. One-pill combinations were coded into multiple medication classes.[28] Medication adherence was assessed using the 4-item Morisky Medication Adherence Scale, with a score of 0 indicating perfect adherence.[30]

Assessment of Stroke/TIA Status

History of stroke or TIA was characterized using the question, "Were you ever told by a physician that you had a mini-stroke or TIA, also known as a transient ischemic attack?" and the same question asking about stroke. Participants were categorized as no history of stroke or TIA, TIA only, stroke (with or without TIA), and the combined category of stroke or TIA.

Covariates

Age, race, sex, education, annual household income, smoking, alcohol use, physical activity, and duration of hypertension (calculated in years, based on response to the question, "How old were you when you were first told that you have high blood pressure?") were defined by self-report. Physical activity level was defined by response to the question, "How many times per week do you engage in intense physical activity, enough to work up a sweat?," categorized as 4 or more times per week, 1-3 times per week, or none. History of myocardial infarction was defined by self-report or evidence from study electrocardiogram. Diabetes was defined as fasting glucose level $\geq$126 mL/dL (or $\geq$200 mL/dL if participant was nonfasting), or self-reported medication use for glucose control. Statin use was obtained from medication inventory. High-sensitivity C-reactive protein (CRP), total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured centrally. C-reactive protein was analyzed in batches by particle-enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, Ill) with interassay coefficients of variation of 2.1%-5.7%. Total cholesterol, HDL, and glucose were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Rochester, NY).[23] The isotope-dilution mass spectrometry-traceable serum creatinine method was used to determine estimated glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration equation.[31] Urinary albumin was measured with the BN ProSpec Nephelometer from Dade Behring (Marburg, Germany), and urinary creatinine was measured with a rate-blanked Jaffé procedure, using the Modular-P analyzer (Roche/Hitachi, Indianapolis, Ind). Albumin-to-creatinine ratio (ACR) was categorized as $<$30 or $\geq$30 mg/g.

Statistical Analyses

Characteristics of participants and prevalence of apparent treatment-resistant hypertension were calculated for participants with no history of stroke or TIA, history of TIA alone, history of stroke (with or without TIA), and history of stroke or TIA. Poisson regression was used to calculate the crude and multivariable-adjusted prevalence ratios (PRs) of apparent treatment-resistant hypertension by stroke/TIA status. The initial model adjusted for age, race, and sex. A second model additionally adjusted for geographic region (stroke belt, buckle, or other), education, income, physical activity, smoking, alcohol use, waist circumference, diabetes, total cholesterol, HDL cholesterol, statin use, CRP, history of myocardial infarction, and duration of hypertension. The final model added eGFR and ACR (log transformed). Four sensitivity analyses were conducted: (1) restricted to participants with perfect medication adherence, (2) including participants with uncontrolled BP on 1 to 2 antihypertensive medication classes, (3) using an alternative definition of apparent treatment-resistant hypertension that excluded individuals who met the definition of apparent treatment-resistant hypertension who were not taking a diuretic, and (4) because blacks may have low-renin hypertension and be more responsive to treatment with a diuretic, analysis was repeated only for those taking a diuretic.

RESULTS

Among participants who were treated for hypertension, 18.2% (2130 of 11,719) had apparent treatment-resistant hypertension. There was a monotonic increase in prevalence of apparent treatment-resistant hypertension across the stroke/TIA spectrum: 17.0% among persons with negative history, 22.8% in those with TIA only, and 26.0% in those with stroke (**Table 1**.) As expected, participants with history

Table 1 Characteristics of REGARDS Hypertensive Participants by History of Stroke or TIA (n = 11,719)

Characteristic	No History of Stroke or TIA (n = 10,025)	History of TIA Only (n = 596)	History of Stroke, With or Without TIA (n = 1098)	*P* value
Age, y	65.7 (8.9)	69.4 (9.0)	68.1 (8.8)	<.001
Men	4195 (41.8)	233 (39.1)	534 (48.6)	<.001
Black race	4957 (49.5)	256 (43.0)	607 (55.3)	<.001
Region				.225
Non-belt	4276 (42.7)	275 (46.1)	498 (45.4)	
Belt	3532 (35.2)	197 (33.1)	376 (34.2)	
Buckle	2217 (22.1)	124 (20.8)	224 (20.4)	
Income <$20,000	1961 (19.6)	137 (23.0)	330 (30.1)	<.001
Less than high school education	1399 (14.0)	107 (18.0)	253 (23.1)	<.001
Waist circumference, cm	99.2 (15.6)	98.8 (15.4)	99.8 (16.0)	.340
Current smoking	1261 (12.6)	78 (13.1)	185 (16.9)	<.001
Current alcohol use	3358 (34.2)	167 (28.5)	279 (25.8)	<.001
Physical activity				<.001
None	3666 (37.0)	264 (45.0)	529 (49.2)	
1-3 times per wk	3551 (35.9)	198 (33.7)	301 (28.0)	
4+ times per wk	2678 (27.1)	125 (21.3)	245 (22.8)	
Duration of hypertension, y	11.0 (5.0-22.0)	15.0 (7.0-25.0)	15.0 (7.0-26.0)	<.001
Diabetes	2875 (29.7)	217 (37.8)	425 (40.4)	<.001
History of myocardial infarction	1484 (15.1)	149 (25.7)	315 (29.4)	<.001
Statin use	4222 (42.1)	289 (48.5)	625 (56.9)	<.001
Total cholesterol, mg/dL	186.1 (39.0)	182.2 (40.3)	180.4 (41.9)	<.001
HDL cholesterol, mg/dL	50.6 (15.7)	49.3 (14.4)	48.4 (14.9)	<.001
C-reactive protein, mg/L	2.6 (1.2-6.0)	2.5 (1.1-6.2)	2.8 (1.2-6.3)	.241
eGFR, mL/min/1.73 m^2	81.7 (21.8)	75.7 (23.2)	74.7 (23.6)	<.001
Albumin-to-creatinine ratio, mg/g	8.0 (4.9-17.9)	10.2 (5.5-26.6)	12.8 (6.0-39.4)	<.001
Systolic blood pressure, mm Hg	126.4 (13.7)	127.9 (14.8)	128.5 (15.6)	<.001
Diastolic blood pressure, mm Hg	75.8 (8.7)	74.6 (9.0)	75.4 (9.6)	.032
2 or more prior strokes*	—	—	275 (25.6)	—
Apparent treatment-resistant hypertension	1708 (17.0)	136 (22.8)	286 (26.0)	<.001
Diuretic use	5785 (57.7)	370 (62.1)	643 (58.6)	.102
β-Blocker use	3786 (37.8)	282 (47.3)	529 (48.2)	<.001
Calcium channel blocker use	3907 (39.0)	265 (44.5)	520 (47.4)	<.001
ACE inhibitor use	4291 (42.8)	255 (42.8)	539 (49.1)	<.001
ARB use	2758 (27.5)	163 (27.4)	290 (26.4)	.740
α-Blocker use	627 (6.3)	33 (5.5)	102 (9.3)	<.001
Aldosterone antagonist use	231 (2.3)	16 (2.7)	37 (3.4)	.085
Vasodilator use	69 (0.7)	5 (0.8)	22 (2.0)	<.001
Central acting agent use	38 (0.4)	4 (0.7)	5 (0.5)	.524
No. of antihypertensive medication classes being taken				
0	0	0	0	—
1	3044 (30.4)	144 (24.2)	246 (22.4)	<.001
2	3563 (35.5)	192 (32.2)	323 (29.4)	<.001
3	2502 (25.0)	183 (30.7)	362 (33.0)	<.001
4	775 (7.7)	69 (11.6)	130 (11.8)	<.001
5+	141 (1.4)	8 (1.3)	37 (3.4)	<.001

Numbers are mean (standard deviation) or number (percentage), except for duration of hypertension, C-reactive protein, and albumin-to-creatinine ratio, which are presented as median (25th percentile, 75th percentile).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Limited to individuals with a history of stroke.

of stroke or TIA had a poorer cardiovascular risk profile (ie, lower household income, more likely to be smokers, less physically active, have diabetes, and history of myocardial infarction) than those without such a history (Table 1).

After adjustment for age, race, and sex, compared with those with no history of stroke or TIA, participants with history of TIA were 31% (PR 1.31; 95% confidence interval [CI], 1.12-1.52) more likely to have apparent

treatment-resistant hypertension, and those with a history of stroke were 36% (PR 1.36; 95% CI, 1.22-1.52) more likely to have apparent treatment-resistant hypertension (Table 2). Adjustment for risk factors attenuated this increased risk to 15% (PR 1.15; 95% CI, 0.97-1.36) for those with TIA alone, and to 18% (PR 1.18; 95% CI, 1.05-1.33) for those with history of stroke. Further adjustment for measures of kidney function (eGFR and ACR) attenuated the excess to 13% (PR 1.13; 95% CI, 0.96-1.34 for history of TIA only and PR 1.13; 95% CI, 1.00-1.27 for history of stroke). In the fully adjusted model, participants in the combined group of stroke or TIA were 14% (PR 1.14; 95% CI, 1.03-1.27) more likely to have apparent treatment-resistant hypertension than those with no history of stroke or TIA.

Among the 1694 participants with history of stroke or TIA treated for hypertension, after age and race adjustment, being a man was associated with higher PR for apparent treatment-resistant hypertension (PR 1.29; 95% CI, 1.09-1.52; Table 3.) Additionally, after age and sex adjustment, black race was associated with a higher PR for apparent treatment-resistant hypertension (PR 1.62; 95% CI, 1.36-1.93). After adjustment for age, race, and sex, larger waist circumference, longer duration of hypertension, diabetes, history of myocardial infarction, statin use, eGFR <60 mL/min/1.73m^2, and ACR ≥ 30 mg/g were each associated with a higher PR for apparent treatment-resistant hypertension. The prevalence of apparent treatment-resistant hypertension decreased monotonically with increasing levels of physical activity. After multivariable adjustment, being a man remained associated with a higher PR for apparent treatment-resistant hypertension, as well as black race, larger waist circumference, longer duration of hypertension, and eGFR <60 mL/min/1.73m^2, and ACR ≥ 30 mg/g.

Sensitivity Analyses

The results were markedly similar when restricted to 9912 participants reporting perfect medication adherence (Supplementary Table 1, available online). After multivariable adjustment, participants with history of stroke or TIA were 14% (PR 1.14; 95% CI, 0.99-1.30) more likely to have apparent treatment-resistant hypertension than those with no history of stroke/TIA. Including participants with uncontrolled BP on 1 or 2 classes of antihypertensive medications (n = 14,673) did not change the results substantially (Supplementary Table 2, available online). Using the alternative definition of apparent treatment-resistant hypertension (excluding individuals who met the definition of apparent treatment-resistant hypertension who were not taking a diuretic), the results remained statistically significant; participants with history of stroke/TIA were 18% (PR 1.18; 95% CI, 1.05-1.32) more likely to have apparent treatment-resistant hypertension than those with no history of stroke/TIA (Supplementary Table 3, available online). Finally, restriction of analysis to those with treatment including a diuretic reduced the likelihood of black participants having apparent treatment-resistant hypertension, with the age−race−sex-adjusted PR decreasing from 1.62 (CI, 1.09-1.52) to 1.30 (CI, 1.10-1.54) and the multivariable adjusted PR decreasing from 1.34 (CI, 1.10-1.63) to 1.15 (CI, 0.94-1.39) (Supplementary Table 4, available online).

DISCUSSION

Treatment and control of hypertension has long been recognized as among the most important goals in secondary stroke prevention.[8,32-34] Our results suggest that the prevalence of apparent treatment-resistant hypertension is higher among those with TIA than their counterparts without a history of TIA/stroke and higher still among those with a history of stroke. Although the goal of BP control among those with cerebrovascular symptoms is important, achieving that goal in individuals after stroke has been shown to be particularly challenging.[5,11-15,35] In addition, among those with stroke or TIA, there are groups of

Table 2 Prevalence Ratios (and 95% CIs) for Apparent Treatment-resistant Hypertension Associated with History of TIA, History of Stroke, and History of Combined Stroke or TIA Among REGARDS Study Participants

Parameter	n	Crude Prevalence Ratio (95% CI)	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	+ Adjustment for Stroke Risk Factors* Prevalence Ratio (95% CI)	+ Adjustment for Measures of Kidney Function† Prevalence Ratio (95% CI)
Mutually exclusive symptomatic strata					
No history of stroke or TIA	10,025	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
History of TIA only	596	1.34 (1.15-1.56)	1.31 (1.12-1.52)	1.15 (0.97-1.36)	1.13 (0.96-1.34)
History of stroke (with or without TIA)	1098	1.50 (1.35-1.67)	1.36 (1.22-1.52)	1.18 (1.05-1.33)	1.13 (1.00-1.27)
History of stroke or TIA combined (relative to no history of stroke/TIA)	1694	1.46 (1.33-1.61)	1.37 (1.24-1.50)	1.18 (1.07-1.31)	1.14 (1.03-1.27)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, and duration of hypertension.

†Adjusted for model above, plus estimated glomerular filtration rate and albumin-to-creatinine ratio (log transformed).

Table 3 Prevalence Ratios for Apparent Treatment-resistant Hypertension Associated with Study Covariates Among REGARDS Study Participants with History of Stroke or TIA

Variable	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	Multivariable-adjusted* Prevalence Ratio (95% CI)
Age, per 10 y	1.07 (0.97-1.18)	0.97 (0.86-1.09)
Men	1.29 (1.09-1.52)	1.23 (1.01-1.49)
Black race	1.62 (1.36-1.93)	1.34 (1.10-1.63)
Region		
Nonbelt	1 (ref)	1 (ref)
Belt	1.05 (0.87-1.26)	1.07 (0.88-1.32)
Buckle	1.10 (0.88-1.37)	1.05 (0.84-1.32)
Income <$20,000	1.03 (0.86-1.24)	0.98 (0.81-1.19)
Less than high school education	1.09 (0.90-1.32)	1.13 (0.92-1.38)
Waist circumference, per 15 cm	1.28 (1.18-1.38)	1.21 (1.11-1.33)
Duration of hypertension, per 10 y	1.19 (1.13-1.26)	1.18 (1.11-1.26)
Diabetes	1.59 (1.34-1.88)	1.18 (0.97-1.43)
Current smoking	0.80 (0.62-1.02)	0.86 (0.65-1.13)
Alcohol use	0.94 (0.77-1.14)	1.00 (0.80-1.24)
Physical activity		
None	1 (ref)	1 (ref)
1-3 times per wk	0.82 (0.67-0.99)	0.88 (0.72-1.09)
4+ times per wk	0.74 (0.59-0.94)	0.86 (0.67-1.09)
History of myocardial infarction	1.27 (1.06-1.51)	1.10 (0.91-1.33)
Statin use	1.31 (1.11-1.55)	1.19 (0.97-1.45)
Total cholesterol, per 40 mg/dL	0.98 (0.91-1.07)	1.06 (0.96-1.15)
HDL-cholesterol, per 15 mg/dL	0.93 (0.84-1.02)	1.01 (0.91-1.13)
C-reactive protein >3 mg/L	1.09 (0.91-1.29)	0.93 (0.78-1.12)
eGFR <60 mL/min/1.73 m^2	1.47 (1.24-1.75)	1.39 (1.15-1.68)
Albumin-to-creatinine ratio ≥30 mg/g	1.78 (1.51-2.09)	1.48 (1.23-1.79)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, duration of hypertension, estimated glomerular filtration rate, and albumin-to-creatinine ratio (log transformed).

individuals with particularly high prevalence of apparent treatment-resistant hypertension, including blacks (with 34% increased PR), men (with a 23% increase), and those with evidence of kidney disease (a 48% increase among those with ACR ≥30 mg/g, and a 39% increase among those with an eGFR <60 mL/min/1.73 m^2). Smaller (but still statistically significant) increases in the prevalence of apparent treatment-resistant hypertension were observed among those with less regular physical activity, those with larger waist size, and those with longer duration of hypertension. These findings suggest that a diagnosis of apparent treatment-resistant hypertension may be particularly appropriate for further diagnostic evaluations and more intensive monitoring to meet BP targets.

Because of the cross-sectional nature of these data, the direction of causation between the apparent treatment-resistant hypertension and the stroke event cannot be determined (ie, whether the higher prevalence of apparent treatment-resistant hypertension is a product of the stroke, or the stroke was a product of previously existing apparent treatment-resistant hypertension). However, because hypertension is such a powerful risk factor for stroke, one could presume that the difficult-to-control hypertension existed before the stroke event. If this is the case, then the difficult-to-control hypertension contributed to the stroke event, and the higher prevalence of resistant hypertension likely places the stroke survivor at continued higher risk for subsequent stroke and other vascular events. Whether apparent treatment-resistant hypertension plays a differential role in recurrent stroke risk separate from hypertension that is easier to control is currently being investigated using data from the REGARDS cohort.

Our results are similar to those from the large Kaiser Permanente Southern California health system. They show a 21.0% prevalence of apparent treatment-resistant hypertension in 49,081 individuals with confirmed cerebrovascular disease (by ICD-9 codes), and after multivariable adjustment for risk factors, a 17% (95% CI, 1.13-1.22) increased risk of having resistant hypertension.[36] Within all persons with resistant hypertension, after multivariable adjustment, they found increased risk for age (per 5 years), men, blacks, and persons with body mass index ≥30 kg/m^2, eGFR <60 mL/min/1.73 m^2, diabetes, ischemic heart disease, and congestive heart failure,[36] very similar to the factors we found within our cohort of individuals with stroke/TIA history. They reported that, in general, all individuals with

resistant hypertension had better adherence to antihypertensive medications than those without resistant hypertension. Our study extends this report by the use of a national, population-based study and identifying factors associated with apparent treatment-resistant hypertension specific to persons with a history of stroke and TIA.

Hypertension control rates in secondary stroke prevention studies have ranged from 30% to 67% over time periods ranging from 6 months to 5 years after stroke.[4,5,11-15,35] Reasons for uncontrolled hypertension are multifaceted and involve the individual patient, the healthcare providers, and the healthcare system. Individual reasons for lack of control in persons being treated for hypertension include patient noncompliance, inadequate therapy, and inappropriate therapy, with the latter 2 linked to potential for apparent treatment-resistant hypertension. Failure to diagnose and manage apparent treatment-resistant hypertension may be contributing to stroke recurrence rates as well as rates of incident stroke. That persons of African ancestry are more likely to have apparent treatment-resistant hypertension and specific associated pathophysiology of hypertension (ie, low-renin hypertension, etc) has been suggested as a major contributor to the black−white stroke disparity.[37] Therefore, especially in blacks, it is recommended that physicians take an individualized approach to assess and manage BP levels, including additional diagnostic evaluations including measurement of plasma renin, aldosterone-changing medications, and incorporating advice related to lifestyle changes.[19,38] The supplemental analysis restricted to those taking diuretic medication showed a substantial mediation of the risk in blacks, suggesting that treatment with diuretics may be a key to this individualized approach.

There are several strengths and limitations to our study. REGARDS is a geographically and socioeconomically diverse study of blacks and whites including a large number of participants with a history of physician-diagnosed stroke or TIA, and a standardized protocol with stringent quality control for BP and other measurements. Strengths also include that the person conducting the in-home visit did not know the participant's cerebrovascular history, and medications were obtained from inspection of the medication bottles in the participant's home. The high prevalence of apparent treatment-resistant hypertension may be attributable to nonadherence with treatment, but we did not have adherence specific to antihypertensive medications. In REGARDS, however, the majority of all apparent treatment-resistant hypertension individuals indicated being adherent with medication use in general.[28] The cross-sectional design of this analysis provides only a one-time assessment of BP, but misclassification was minimized because the definition of apparent treatment-resistant hypertension included a combination of measurements, medication inventory, and self-report. We did not rule out pseudoresistant hypertension defined by poor adherence or inadequate BP measurements. Covariates such as eGFR, ACR, and diabetes also were measured only once, and others were based on self-report. Important covariates such as heart failure may have been missed. Residual confounding remains a possibility similar to other epidemiologic studies. Although history of stroke and TIA was self-reported and subject to recall bias, previous work in REGARDS has shown strong associations with these history questions and subsequent stroke risk.[39] Additionally, another report showed self-report of stroke to have a positive predictive value of 79%, sensitivity of 80%, and specificity of 99%.[40] We do not have information on stroke type, but we would expect that the majority were ischemic, and BP recommendations do not vary by stroke subtype.[2]

In summary, we report that 1 in 4 persons with a history of stroke or TIA has apparent treatment-resistant hypertension, and we identified subgroups with an even higher prevalence of apparent treatment-resistant hypertension. This suggests the need for more individual BP monitoring and management.

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SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.02.008.

Supplementary Table 1 Prevalence Ratios for Apparent Treatment-resistant Hypertension Associated with Prevalent Stroke or TIA Combined, Prevalent Stroke, and Prevalent TIA Alone Among REGARDS Study Participants, Limited to Individuals Treated for Hypertension with Perfect Medication Adherence (n = 9912)

Parameter	n	Crude Prevalence Ratio (95% CI)	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	+ Adjustment for Stroke Risk Factors* Prevalence Ratio (95% CI)	+ Adjustment for Measures of Kidney Function† Prevalence Ratio (95% CI)
Mutually exclusive symptomatic strata					
No history of stroke or TIA	8473	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
History of TIA only	492	1.40 (1.15-1.70)	1.38 (1.13-1.67)	1.15 (0.93-1.42)	1.11 (0.90-1.38)
History of stroke (with or without TIA)	947	1.53 (1.34-1.76)	1.41 (1.23-1.62)	1.18 (1.01-1.37)	1.14 (0.97-1.33)
History of stroke or TIA combined (relative to no history of stroke/TIA)	1439	1.51 (1.34-1.70)	1.42 (1.26-1.60)	1.18 (1.04-1.35)	1.14 (0.99-1.30)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, and duration of hypertension.

†Adjusted for model above, plus estimated glomerular filtration rate, and albumin-to-creatinine ratio (log transformed).

Supplementary Table 2 Prevalence Ratios for Apparent Treatment-resistant Hypertension Associated with Prevalent Stroke or TIA Combined, Prevalent Stroke, and Prevalent TIA Alone Among REGARDS Study Participants, Limited to Individuals Treated for Hypertension (Including Those with Uncontrolled Blood Pressure on 1 to 2 Classes as Not Having Apparent Treatment-Resistant Hypertension) (n = 14,673)

Parameter	n	Crude Prevalence Ratio (95% CI)	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	+ Adjustment for Stroke Risk Factors* Prevalence Ratio (95% CI)	+ Adjustment for Measures of Kidney Function† Prevalence Ratio (95% CI)
Mutually exclusive symptomatic strata					
No history of stroke or TIA	12,572	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
History of TIA only	734	1.36 (1.16-1.60)	1.33 (1.14-1.56)	1.17 (0.98-1.39)	1.13 (0.95-1.34)
History of stroke (with or without TIA)	1367	1.51 (1.35-1.69)	1.38 (1.24-1.55)	1.19 (1.05-1.34)	1.14 (1.01-1.29)
History of stroke or TIA combined (relative to no history of stroke/TIA)	2101	1.48 (1.34-1.63)	1.39 (1.26-1.53)	1.20 (1.08-1.33)	1.15 (1.03-1.28)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, and duration of hypertension.

†Adjusted for model above, plus estimated glomerular filtration rate, and albumin-to-creatinine ratio (log transformed).

Supplementary Table 3 Prevalence Ratios for Apparent Treatment-resistant Hypertension Associated with Prevalent Stroke or TIA Combined, Prevalent Stroke, and Prevalent TIA Alone Among REGARDS Study Participants, Limited to Individuals Treated for Hypertension and Excluding Those with Uncontrolled Blood Pressure on 1 to 2 Classes of Antihypertensive Medication (n = 11,435)

Parameter	n	Crude Prevalence Ratio (95% CI)	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	+ Adjustment for Stroke Risk Factors* Prevalence Ratio (95% CI)	+ Adjustment for Measures of Kidney Function† Prevalence Ratio (95% CI)
Mutually exclusive symptomatic strata					
No history of stroke or TIA	9786	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
History of TIA only	589	1.46 (1.24-1.71)	1.42 (1.21-1.66)	1.22 (1.03-1.45)	1.20 (1.01-1.43)
History of stroke (with or without TIA)	1060	1.52 (1.35-1.71)	1.39 (1.23-1.56)	1.19 (1.04-1.35)	1.14 (1.00-1.30)
History of stroke or TIA combined (relative to no history of stroke/TIA)	1649	1.52 (1.38-1.68)	1.42 (1.29-1.58)	1.22 (1.09-1.36)	1.18 (1.05-1.32)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, and duration of hypertension.

†Adjusted for model above, plus estimated glomerular filtration rate, and albumin-to-creatinine ratio (log transformed).

Supplementary Table 4 Prevalence Ratios for Apparent Treatment-resistant Hypertension Associated with Study Covariates Among REGARDS Participants with History of Stroke or TIA, Restricted to Those Taking a Diuretic (n = 1013)

Variable	Age, Race, Sex-adjusted Prevalence Ratio (95% CI)	Multivariable-adjusted* Prevalence Ratio (95% CI)
Age, per 10 y	1.08 (0.99-1.18)	0.96 (0.86-1.08)
Men	1.33 (1.14-1.56)	1.32 (1.08-1.59)
Black race	1.30 (1.10-1.54)	1.15 (0.94-1.39)
Region		
Nonbelt	1 (ref)	1 (ref)
Belt	1.09 (0.91-1.32)	1.12 (0.92-1.36)
Buckle	1.13 (0.91-1.39)	1.10 (0.88-1.37)
Income <$20,000	1.02 (0.86-1.22)	0.95 (0.79-1.15)
Less than high school education	1.10 (0.92-1.32)	1.16 (0.95-1.40)
Waist circumference, per 15 cm	1.17 (1.08-1.26)	1.13 (1.04-1.24)
Duration of hypertension, per 10 y	1.13 (1.07-1.19)	1.13 (1.06-1.20)
Diabetes	1.32 (1.12-1.56)	1.03 (0.85-1.25)
Current smoking	0.81 (0.63-1.05)	0.78 (0.59-1.04)
Alcohol use	0.97 (0.80-1.17)	0.94 (0.76-1.17)
Physical activity		
None	1 (ref)	1 (ref)
1-3 times per wk	0.83 (0.69-1.00)	0.83 (0.68-1.02)
4+ times per wk	0.83 (0.67-1.03)	0.87 (0.69-1.10)
History of myocardial infarction	1.24 (1.05-1.46)	1.11 (0.92-1.33)
Statin use	1.24 (1.06-1.47)	1.18 (0.97-1.44)
Total cholesterol, per 40 mg/dL	0.99 (0.91-1.08)	1.05 (0.96-1.15)
HDL-cholesterol, per 15 mg/dL	0.96 (0.87-1.05)	1.00 (0.90-1.12)
C-reactive protein >3 mg/L	1.07 (0.90-1.26)	0.97 (0.82-1.16)
eGFR <60 mL/min/1.73 m^2	1.21 (1.02-1.42)	1.17 (0.97-1.41)
Albumin-to-creatinine ratio ≥30 mg/g	1.57 (1.35-1.84)	1.45 (1.20-1.74)

CI = confidence interval; REGARDS = REasons for Geographic And Racial Differences in Stroke study; TIA = transient ischemic attack.

*Adjusted for age, race, sex, geographic region of residence, income, education, physical activity, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, high-density lipoprotein cholesterol, statin use, C-reactive protein, history of myocardial infarction, duration of hypertension, estimated glomerular filtration rate, and albumin-to-creatinine ratio (log transformed).