Hypertension and Migraine in the Northern Manhattan Study

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Objective: To investigate the association between migraine and hypertension in the Northern Manhattan Study (NOMAS), a multiethnic community-based sample.

Design: Cross-sectional cohort study.

Participants:1338 NOMAS participants (mean age 68.1±9.6 years, 37% male, 15% non-Hispanic White, 19% non-Hispanic Black, 67% Hispanic).

Setting: Northern Manhattan community.

Intervention: Participants were assessed for migraine symptoms using a self-report questionnaire based on criteria from the International Classification of Headache Disorders. Hypertension was defined as blood pressure ≥140/90 mm Hg, the patient's self-reported hypertension, or use of anti-hypertensive medications. Duration (≤9 years vs >9 years) and control (BP<140/90) of hypertension were examined. We estimated the association between hypertension and migraine (overall and with/without aura) using logistic regression, adjusting for sociodemographic and vascular risk factors.

Results: The majority of participants (80%) had no migraine, 6% had migraine with aura, and 15% had migraine without aura. Hypertension was present in 76% of the study population (7% had controlled hypertension ≤9 years duration, 5% controlled hypertension >9 years duration, 41% uncontrolled hypertension ≤9 years duration, 23% uncontrolled hypertension >9 years duration). Hypertension was associated with migraine (OR: 1.76, 95% CI: 1.21-2.54), both with and without aura. This association was particularly apparent for those with uncontrolled and long duration hypertension.

Conclusion: Hypertension, particularly uncontrolled and of long duration, is associated with migraine, both with and without aura, in a predominantly Hispanic community-based cohort. *Ethn Dis*. 2016;26(3):323-330; doi:10.18865/ed.26.3.323

Keywords: Hypertension; Migraine; Aura; Epidemiology; Race; Ethnicity

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Introduction

Migraine is a common, disabling, primary headache disorder with systemic vascular involvement, autonomic dysfunction, and a wide range of ischemic vascular disorders.[1,2] Individuals with migraine, particularly migraine with aura, are at risk for both ischemic and hemorrhagic forms of stroke, ischemic heart disease, myocardial infarction, angina, coronary revascularization procedures, and vascular mortality.[3] Individuals with migraine have an adverse cardiovascular risk profile, including hypertension. Although the exact mechanisms to explain increased vascular events are not fully understood, hypertension, smoking and the use of oral contraceptives have been found to increase the risk of ischemic stroke for young women with migraine.[4]

Studies assessing the association between migraine and hypertension, both diastolic and systolic, have yielded conflicting results.[5] One study found a positive association between headache and hypertension for both sexes independent of age.[6] In a clinic-based study, hypertension was more common in the headache group than in the general population; after adjusting for age and sex, positive associations were found for tension-type headache and chronic tension-type headache, but less so for migraine.[6] In contrast, multiple population studies suggest no association between migraine and hypertension or an inverse relationship.[7] The comorbidity of migraine and hypertension is of particular interest, as one study showed an increase risk of stroke/TIA in subjects with migraine and hypertension as compared with the hypertension-only group in all age ranges.[8] Continued research on the relationship between hypertension and migraine is clearly needed and

underscored by the high prevalence of both conditions. Furthermore, research is needed in populations of diverse race/ethnicity, as both conditions have shown disparities across race/ethnic groups.[9] Therefore, the aim of this analysis was to assess the relationship between hypertension, particularly its duration and control, with migraine in the Northern Manhattan Study (NOMAS), a large multiethnic, community-based study.

Methods

Study Population

The Northern Manhattan Study is a longitudinal population-based study designed to study incidence and risk factors for stroke in a community of diverse race/ethnicity. Northern Manhattan is a well-defined area of New York City made up of 63% Hispanic, 20% Non-Hispanic Black, and 15% non-Hispanic White residents. Details about recruitment and enrollment have been published previously.[10] Briefly, from 1993-2001, participants were identified using random-digit dialing and recruited to have an in-person assessment with the following eligibility criteria: a) never been diagnosed with a stroke; b) aged >40 years; and c) resided in Northern Manhattan for ≥3 months, in a household with a telephone. The enrollment response rate was 75% and the overall participation rate was 69%, resulting in a final cohort of 3,298 participants. The study was approved by the IRBs of Columbia University and the University of Miami. All participants provided written informed consent.

Baseline Data Collection

At baseline, participants were interviewed by trained bilingual research assistants in English or Spanish, and the study physicians conducted physical and neurological examinations. Baseline interviews included standardized questions adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control regarding smoking and other cardiovascular risk factors. Race-ethnicity was based upon self-identification through a series of questions modeled after the US Census and conforming to standard definitions outlined by Directive 15.[11] Smoking was categorized as never, former, or current (within the past year) smoking of cigarettes, pipes or cigars. Diabetes mellitus was defined by fasting glucose ≥126 mg/dL, the patient's self-reported diabetes, or use of insulin or oral anti-diabetic medication. Body mass index (BMI) was calculated in kg/m^2. Mild-moderate alcohol use was defined as current drinking of >1 drink per month and ≤2 drinks per day. Physical activity was defined as the frequency and duration of 14 different recreational activities during the 2-week period before the interview, as described previously.[10] Blood samples were drawn after an overnight fast. Plasma levels of cholesterol and triglycerides were measured using standardized enzymatic procedures with a Hitachi 705 automated spectrophotometer (Boehringer Mannheim, Mannheim, Germany). HDL was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid.

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Hypertension

Blood pressure was measured twice, before and after the physical examination, with mercury sphygmomanometers and appropriately sized cuffs, and was averaged. Hypertension was defined as a blood pressure ≥140/90 mm Hg, the patient's self-reported hypertension, or use of anti-hypertensive medications. Hypertension (present vs absent) was the primary independent variable of interest. We also examined duration and control of hypertension. Duration was defined as the time from self-reported diagnosis of hypertension to the date of baseline interview, and was categorized as >9 years and ≤9 years because 9 years represented the median hypertension duration in the NOMAS cohort, as defined previously.[11] We categorized individuals into four groups: a) long duration (diagnosis >9 years prior to interview) and controlled hypertension (BP <140/90 mm Hg); b) short duration (diagno-

sis ≤9 years prior to interview) and controlled hypertension (BP<140/90 mm Hg): c) long duration (diagnosis >9 years prior to interview) and uncontrolled (BP ≥140/90 mm Hg; and d) short duration (diagnosis ≤9 years prior to interview) and uncontrolled hypertension (BP ≥140/90 mm Hg). In logistic regression models, these four groups were all compared to those without hypertension as the reference.

Migraine

Migraine history was included in the interviews for participants recruited after 1998. Migraine status was based on self-report using a questionnaire, with additional questions closely adhering to the International Classification of Headache Disorders-2 criteria for migraine, as previously described. Migraine without aura was defined as recurrent headache with attacks lasting 4-72 hours; unilateral, pulsating, aggravated by physical activity and associated with nausea and/or photophobia and phonophobia. Migraine with aura was defined as recurrent headache with attacks of completely reversible focal neurological symptoms lasting less than 60 minutes following aura symptoms. Aura was defined as visual changes such as spots, stars, lines, or flashing lights. The primary dependent variable of interest was migraine (yes vs no), and secondary outcomes were migraine with aura and migraine without aura, individually compared to no migraine.

Statistical Analysis

First, the covariates were examined in relation to migraine status using chi-square tests and t-tests. Second, logistic regression models were constructed to examine the association between hypertension (yes vs no) and categories of hypertension duration and control in relation to migraine presence. Covariates were chosen a priori. The first model was adjusted for age only. Model 2 also included sex, race/ethnicity, and education (high school completion, yes vs no). Model 3 additionally adjusted for smoking, diabetes, BMI, moderate alcohol use, HDL, LDL, and moderate-heavy physical activity. Stratified analyses by race/ethnicity were also conducted. Lastly, a similar sequence of multinomial logistic regression models was constructed to examine the relationship between hypertension (presence and duration/control categories) with categories of migraine (with aura, without aura vs. no migraine). Statistical significance was defined as P<.05.

Results

Data on migraine status was available for 1338 NOMAS participants, of whom 1065 (80%, 792 with hypertension, 273 with no hypertension) had no migraine, 78 (6%, 64 with hypertension, 14 with no hypertension) had migraine with aura, and 195 (15%, 160 with hypertension, 35 with no hypertension) had migraine without aura. The mean age was 68.1 ± 9.6 years, and 37% were male, 15% non-Hispanic White, 19% non-Hispanic Black, and 67% Hispanic. Table 1 shows the breakdown of the study population by the covariates of interest, overall and stratified by migraine status. Hypertension was present in 76% of the study population, and 7% had controlled hypertension of short duration, 5% had controlled hypertension of long duration, 41% had uncontrolled hypertension of short duration, and 23% had uncontrolled hypertension of long duration. The mean ± standard deviation for systolic blood pressure was 145 ± 21 mm Hg for the study population (median=140, range=90-235), and 147 ± 20 mm Hg among those with migraine (median=145, range=110-235), and 144 ± 21 mm Hg among those without migraine (median=140, range=90-225). The systolic blood pressure was higher among those with migraine as compared with those without migraine, t-test P=.03. Migraine prevalence did not vary by race/ethnicity (chi-square P=.19). However, the prevalence of hypertension did vary by race/ethnicity (chi-square P=.0002), as Blacks were most likely to have hypertension (84%), followed by Hispanics (76%), and Whites (67%).

Table 2 shows the association between hypertension presence and migraine status. In all three models, hypertension was positively associated with migraine (with and without aura combined). Hypertension was also positively associated with migraine without aura in all 3 models. The odds ratios were stronger for the relationship with migraine with aura. We examined potential effect modification by age by including interaction terms between age and hypertension status in model 3, but no effect modification was suggested (not shown). Though there was also no evidence of effect modification by race/ethnicity, the association be-

Table 1. Study population characteristics

	Study population (N=1338)	Migraine (n=273)	No migraine (n=1065)	P[a]
Age, mean±SD	68±10	67±9	69±10	.001
Male	498 (37)	68 (25)	430 (40)	<.0001
Race/ethnicity				.19
White	195 (15)	35 (13)	160 (15)	
Black	249 (19)	43 (16)	206 (19)	
Hispanic	894 (67)	195 (71)	699 (66)	
High school completion	511 (38)	87 (32)	424 (40)	.02
Smoking				.48
Current	206 (15)	37 (14)	169 (16)	
Former	489 (37)	97 (36)	392 (37)	
Never	642 (48)	139 (51)	503 (47)	
Diabetes	297 (22)	55 (20)	242 (23)	.36
BMI, mean±SD	28.32±5.47	28.45±5.50	28.29±5.47	.66
Moderate alcohol consumption	470 (35)	83 (30)	387 (36)	.07
HDL, mean±SD	45.55±13.91	45.33±14.25	45.60±13.83	.78
LDL, mean±SD	129.55±35.47	130.77±34.63	129.23±35.70	.53
Moderate-heavy physical activity	85 (6)	12 (4)	73 (7)	.14
Hypertension				.01[b]
No	322 (24)	49 (18)	273 (26)	
Yes	1016 (76)	224 (82)	792 (74)	
Controlled, short duration	89 (7)	15 (5)	74 (7)	
Uncontrolled, short duration	545 (41)	110 (40)	435 (41)	
Controlled, long duration	64 (5)	18 (7)	46 (4)	
Uncontrolled, long duration	305 (23)	79 (29)	226 (21)	

Data are n (%) unless specified otherwise.
a. From t-test or chi-square test
b. Hypertension presence vs absence, P=.01; global test of categories of hypertension duration and control, P=.01

tween hypertension and migraine appeared stronger among the White and Hispanic participants. In the fully-adjusted model 3, the OR for the association between hypertension and migraine was 2.42 (95% CI: .86-6.82) among Whites, 1.14 (95% CI: .39-3.33) among Blacks, and 1.76 (95% CI: 1.15-2.71) among Hispanics. It is important to emphasize that although the odds ratio was largest among Whites (2.42), the confidence bounds for this group contained the null value of 1, reflecting the small sample size in this strata. The only race/ethnic strata with a significant association between hypertension and migraine was Hispanics, representing the majority of the study population.

Table 2 and Figure 1 show the association between categories of hypertension duration and control with migraine status. Controlled hypertension of short duration was not associated with migraine. Uncontrolled hypertension of short duration was associated with an increased risk of migraine in all 3 models, and particularly with an increased risk of migraine without aura. The positive associations for uncontrolled and controlled hypertension of long duration with migraine presence were even stronger. These associations were particularly apparent for migraine with aura (vs no migraine). Individuals with hypertension of long duration, whether uncontrolled or controlled, had a greater than two-fold increased odds of having migraine with aura as compared with participants with no hypertension.

Discussion

In this multi-ethnic urban population, we found that hypertension was associated with migraine, both with and without aura. This association was particularly apparent for those with hypertension of long duration (>9 years), both controlled and uncontrolled. However, the data suggest that having uncontrolled hypertension even of shorter duration (≤9 years) was also associated with increased migraine prevalence. In other words, those with uncontrolled or controlled hypertension of long duration were more likely to report migraines. Migraine with aura, in particular, was observed more frequently among those with long-term hypertension in our study.

The prevalence of hypertension varied significantly across race/ethnic groups, with the highest prevalence observed among Blacks and the lowest among Whites. Though significant effect modification by race/ethnicity was not observed for the relationship between hypertension and migraine, the power to detect effect modification was limited, and the results suggest that the association may be strongest among Whites

and weakest among Blacks. However, the confidence bounds overlapped and the associations were not significant in either of these smaller subpopulations. Therefore, larger studies are needed to confirm our findings.

Historically, the association between migraine and hypertension has yielded inconsistent results; meanwhile, little attention has been paid to ethnic differences. Our results differ from epidemiological studies from the Nord-Trondelag Health Survey, which showed a strong inverse relationship between hypertension and migraine.[7] In contrast, migraine was a predictor for hypertension in Finland.[12] When comparing the comorbidities of migraine and hypertension with migraine or hypertension alone in a large, multicenter, cross-sectional study in Italy, the patients with both migraine and hypertension had a more frequent family history of migraine and hypertension than both the migraine and hypertension groups alone.[8] To the best of our knowledge, this is the first study to show a relationship between migraine and long duration controlled or uncontrolled hypertension in a large community sample of predominantly Hispanics.

The association between migraine and hypertension may be driven by environmental factors, shared biological factors, or a genetic vulnerability. Environmental and lifestyle factors that may be associated with both migraine and hypertension include dietary factors (ie, salty foods), physical inactivity, chronic stress; both are linked to the metabolic syndrome.[13] Occupational stressors have been linked to migraine, higher ambulatory blood pressures, and more

Table 2. Hypertension and migraine in the Northern Manhattan Study

	Migraine (yes vs no), OR (95% CI)	Migraine with aura vs no migraine, OR (95% CI)	Migraine without aura vs no migraine, OR (95% CI)
Hypertension (present vs absent)			
Model 1	1.70 (1.21-2.39)	1.98 (1.08-3.62)	1.62 (1.09-2.40)
Model 2	1.65 (1.16-2.34)	1.88 (1.01-3.49)	1.59 (1.07-2.37)
Model 3	1.76 (1.21-2.54)	1.86 (.98-3.55)	1.72 (1.13-2.63)
Hypertension duration and control			
Short duration (≤9 years) controlled vs no hypertension			
Model 1	1.19 (.63-2.24)	1.84 (.68-5.02)	.97 (.45-2.11)
Model 2	1.11 (.58-2.12)	1.67 (.60-4.65)	.93 (.42-2.03)
Model 3	1.06 (.53-2.10)	1.43 (.47-4.34)	.91 (.40-2.07)
Short duration (≤9 years) uncontrolled vs no hypertension			
Model 1	1.49 (1.03-2.16)	1.43 (.73-2.80)	1.52 (.99-2.32)
Model 2	1.48 (1.01-2.16)	1.39 (.70-2.76)	1.53 (.99-2.34)
Model 3	1.63 (1.09-2.42)	1.46 (.72-2.97)	1.69 (1.08-2.65)
Long duration (>9 years) controlled vs no hypertension			
Model 1	2.49 (1.33-4.69)	3.82 (1.36-10.76)	2.15 (1.03-4.46)
Model 2	2.27 (1.19-4.31)	3.40 (1.16-9.90)	1.98 (.95-4.14)
Model 3	2.39 (1.21-4.70)	2.26 (1.05-4.87)	2.82 (.89-8.96)
Long duration (>9 years) uncontrolled vs no hypertension			
Model 1	2.22 (1.48-3.34)	3.04 (1.51-6.15)	2.00 (1.26-3.19)
Model 2	2.12 (1.40-3.22)	2.92 (1.42-6.01)	1.92 (1.19-3.08)
Model 3	2.27 (1.45-3.54)	2.94 (1.38-6.27)	2.07 (1.24-3.45)

Model 1: age-adjusted
Model 2: controlling for age, sex, race/ethnicity, education
Model 3: model 2+smoking, diabetes, BMI, alcohol, HDL, LDL, physical activity

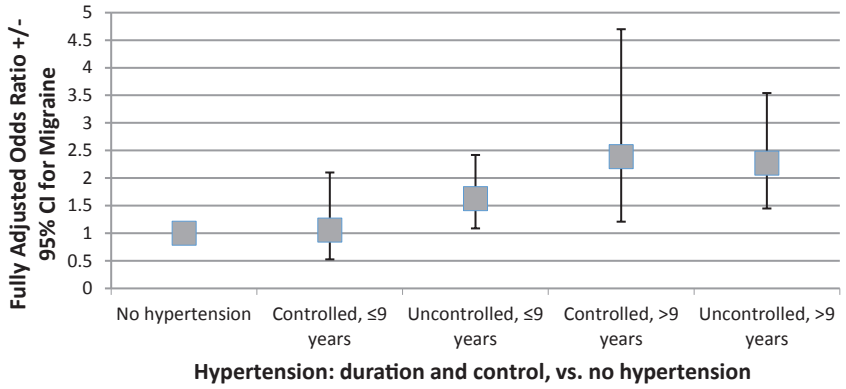

Figure 1. Association of hypertension duration and control with migraine presence.
Association (OR and 95% CI) for categories of hypertension duration and control in relation to migraine presence, adjusted for age, sex, race/ethnicity, education, smoking, diabetes, BMI, alcohol, HDL, LDL, and physical activity, in the Northern Manhattan Study. The reference for the hypertension categories is no hypertension.

recently ischemic stroke.[14,15] Lastly, although within the class of anti-hypertensive drugs, several are known to be migraine preventive that could reduce the association between migraine and uncontrolled hypertension, non-steroidal anti-inflammatory agents are first-line medications for migraine but are well-known to induce secondary hypertension.

In terms of shared biological factors, brainstem regions that control the cardiovascular system also modulate pain; moreover, the hypothalamus and insula have an increasingly recognized role in migraine pathophysiology and control autonomic pathways important for blood pressure control.[16] The renin-angiotensin system may be an underlying mechanism linking migraine with hypertension. Angiotensin I-converting enzyme is thought to be involved in blood pressure control and vascular tension; both angiotensin converting enzyme inhibitors and angiotensin II receptor blockers have shown efficacy for migraine prevention.[17,18] The possible association between migraine with aura and elevated angiotensin-converting enzyme levels due to genetic deletion, may be one explanation for the association between migraine and hypertension although there is conflicting evidence.[19,20] Underlying mechanisms may also include sympathetic nervous overactivity for hypertension, which has also been postulated as underlying mechanism for migraine.[2] In our older cohort, long-duration hypertension may be associated with migraine due to the increased sympathetic nerve activity observed as a consequence of aging.[21] In a transcranial Doppler study, static autoregulatory properties were impaired in the anterior and cerebellar circulation of patients with migraine with aura. Although further work is needed, these findings may explain why long-term hypertension was more frequent in the migraine with aura group in our study.[22]

In this multi-ethnic urban population, we found that hypertension was associated with migraine, both with and without aura.

We suspected that there might be ethnic and racial factors in the association of migraines and hypertension, which could conceivably contribute to greater stroke risks in Blacks and Hispanics. Both hypertension and migraine are risk factors for silent brain lesions, both white matter hyperintensities and silent brain infarctions, as well as adverse cardiac and cerebrovascular events.[23,24] In a prior NOMAS study assessing migraine as a risk factor for stroke, no interaction between migraine and hypertension was found; this may have been due to a low power to detect a difference.[25] In another study, the presence of hypertension and migraine was found to increase the risk of stroke/TIA in the low Framingham risk score group.[8] Ethnic differences in carotid artery diameter and stiffness were observed in Hispanics but not Blacks or among Whites; and, there is some evidence that migraine may be associated with enhanced arterial stiffness.[26] Endothelial dysfunction is associated with hypertension and has been postulated in migraine; however, a recent meta-analysis showed a lack of association between endothelial dysfunction and migraine.[27]

Hypertension and migraine are public health problems; the impact of the potential relationship between hypertension and migraine is underscored by the high prevalence of both of these conditions.[28] We did not find an association between race/ethnicity and migraine; however, race/ethnic differences exist in the incidence and control of hypertension in Blacks and Hispanics.[29,30] Although we did not report the prevalence of chronic migraine (>15 headache days/month during 3 months), in the American Migraine Prevalence and Prevention Study, Hispanics were most likely to have chronic migraine, mostly due to lower socioeconomic status.[31] In another study, individuals with moderate to severe levels of migraine disability were less likely to utilize the health care setting for migraine treatment, receive migraine medication, and obtain a headache diagnosis if they were African American as compared with Whites.[32] The combination of more disabling forms of migraine and lower access or less adequate health care utilization may drive the association.[9] While the role of traditional vascular risk factors in cardiovascular disease in individuals with migraine remains a subject of debate, the results of our study reinforce the importance of regular screening and treating elevated blood pressure, and

continued control of hypertension.

Our study is strengthened by the use of a large population-based and race/ethnicity diverse cohort, including a large proportion of Hispanic participants who are typically underrepresented in studies of migraine. However, limitations must be noted. The cross-sectional design prohibits inferences about causality or temporality for the association between hypertension and migraine. Therefore, the severity of migraine over time was not assessed. Both hypertension and migraine were identified using self-reported questionnaires, and therefore sensitive to recall bias. A history of headache was identified as migraine by the International Classification Headache Disorders II (ICHD-2), though. The prevalence of migraine observed in our cohort was consistent with well-established epidemiological studies using the ICHD-2, and the percentage with aura was also consistent with other study samples, suggesting that any bias was likely minimal. Though our definition of visual auras was confined to visual changes such as spots, stars, lines, flashing lights and is restrictive, inclusion of negative phenomena such as loss of vision, numbness and motor deficits may have been difficult to distinguish from transient ischemic attacks based on self-report. Migraine was assessed only in a subset of the NOMAS population. However, selection bias is unlikely as hypertension was unrelated to availability of data on migraine (not shown). Lastly, the power to detect effect modification by race/ethnicity was limited in this study population that was majority Hispanic; therefore, we suggest that future studies examine whether the relationship between hypertension and migraine is consistent across race/ethnic groups.

Conclusion

The results of our study suggest a strong association between hypertension and migraine, both with and without aura, in a predominantly Hispanic population of older adults. The association was particularly apparent for uncontrolled hypertension and hypertension of long duration. Future studies are needed, particularly longitudinal studies that may address the temporality of the relationship and whether better control of hypertension may reduce migraine burden. Lastly, given that our findings support the association between migraine and hypertension, additional studies by race/ethnicity should focus on mediators that may increase the prevalence and control of hypertension in individuals with migraine such as arterial stiffness, inactivity and dietary factors. The association between migraine and uncontrolled hypertension based on the JNC-8 hypertension guidelines is also of interest.[33,34] Lastly, the findings should be confirmed in other diverse cohorts of diverse race/ethnicity with younger age ranges as our findings may not be generalizable to non-Hispanic and younger populations.

Acknowledgments

Dr Monteith was supported by National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) supplements to promote diversity in health-related research; Dr Sacco, Dr Elkind, Dr Gardener were supported by NIH/NINDS R01 NS 29993, PIs; Dr Wright was supported by grants K02 NS 059729 and R01 HL 108623 and American Heart Association SDG 0735387 N; and Dr Rundek was supported by NINDS K24 NS 062737 grant.

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Gardener, Monteith, Rundek, Wright, Sacco; Acquisition of data: Wright, Elkind; Data analysis and interpretation: Gardener, Monteith, Rundek, Wright, Elkind, Sacco; Manuscript draft: Gardener, Monteith; Statistical expertise: Gardener; Acquisition of funding: Monteith, Wright, Elkind, Sacco; Administrative: Elkind, Sacco; Supervision: Rundek, Wright

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