Received: 23 February 2020 | Revised: 8 April 2020 | Accepted: 20 April 2020

DOI: 10.1002/rth2.12365

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

N-Terminal pro-B-type natriuretic peptide and stroke risk across a spectrum of cerebrovascular disease: The REasons for Geographic and Racial Differences in Stroke cohort

Kara K. Landry MD | Suzanne E. Judd PhD[2] | Dawn O. Kleindorfer MD[3] | George Howard DrPH[2] | Virginia J. Howard PhD[4] | Neil A. Zakai MD, MSc[1,5] | Mary Cushman MD, MSc[1,5]

[1]Department of Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont

[2]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, Alabama

[3]Department of Neurology, University of Cincinnati, Cincinnati, Ohio

[4]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama

[5]Department of Pathology and Laboratory Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont

Correspondence
Mary Cushman, Department of Medicine, University of Vermont, 360 South Park Drive, Colchester, VT 05446.
Email: mary.cushman@uvm.edu

Funding information
This research project is supported by cooperative agreement U01 NS041588 cofunded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis, or interpretation of the data.

Abstract

Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP), a commonly used clinical marker of cardiac function, is associated with the presence of stroke symptoms and is a strong risk factor for future atrial fibrillation, stroke, and all-cause mortality. Few data are available on the association between NT-proBNP levels and stroke recurrence.

Objective: We studied the relationship between NT-proBNP and risk of future ischemic stroke across the continuum of preexisting cerebrovascular conditions: asymptomatic, prior stroke symptoms, prior transient ischemic attack (TIA), and prior stroke.

Methods: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort enrolled 30,239 black and white Americans aged 45 years and older from 2003 to 2007. With 5.4 years follow-up, baseline NT-proBNP was measured in 892 participants who developed ischemic stroke and a 4328-person cohort random sample. Hazard ratios of stroke by baseline NT-proBNP were calculated in groups based on the presence of prebaseline cerebrovascular conditions.

Results: In the fully adjusted model, elevated NT-proBNP was associated with stroke risk in participants without a preexisting cerebrovascular condition (hazard ratio [HR], 2.32; 95% confidence interval [CI], 1.84-2.94) and in participants with a history of stroke symptoms (HR, 1.67; 95% CI, 1.01-2.78) or transient ischemic attack (HR, 2.66; 95% CI, 1.00-7.04) but not among those with prior stroke (HR, 1.26; 95% CI, 0.71-2.21).

Conclusions: These findings support the potential for NT-proBNP testing to identify people who are at highest risk for future stroke.

KEYWORDS

NT-proBNP, risk factors, stroke cerebrovascular disease

Essentials

- N-terminal pro-B-type natriuretic peptide (NT-proBNP) is measured in blood as a marker of heart function.
- We measured it in a large study on stroke risk.
- High NT-proBNP more than doubled stroke risk in people who were healthy or had prior transient ischemic attack.
- High NT-proBNP did not predict recurrence of stroke in people who already had stroke
- NT-proBNP may be useful to predict stroke

1 | INTRODUCTION

Each year in the United States 795 000 people experience a stroke, and 185 000 are recurrent strokes.[1] The prevalence of transient ischemic attack (TIA) is 5 million; however, the true prevalence is likely far greater, as many patients fail to report symptoms of a TIA to their health care provider.[2,3] Indeed, a history of stroke symptoms among people aged 45 and older without a clinical history of stroke or TIA was present in ~18% of adults ≥45 years of age in one study.[4] Individuals with prior stroke, TIA, or stroke symptoms are at high risk of future stroke.[1,5-10] Recently, we reported that stroke symptoms are associated with a biomarker profile consistent with presence of cardiovascular disease,[11] suggesting these symptoms represent covert cerebrovascular disease.

Given the considerable risk of stroke in patients with preexisting cerebrovascular disease, knowledge of factors that would further stratify the stroke risk profile of this population is needed. Among patients with prior stroke or TIA, modifiable risk factors for stroke are known, and clinical scoring is available to predict stroke risk.[1,12-14] Novel biomarkers may also help clinicians further identify patients at most risk, and aid our understanding of the underlying pathophysiology.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a clinical marker of cardiac function that predicts recurrent cardiovascular events in those with coronary heart disease. It also reflects atrial cardiopathy in relation to stroke risk.[15,16] Higher NT-proBNP is associated with presence of stroke symptoms,[11] which is a strong risk factor for incident stroke in the general population[17,18] and for future atrial fibrillation in initially healthy people.[19,20] In one study, NT-proBNP was a risk factor for stroke in participants with a history of atrial fibrillation,[21] adding prognostic information beyond clinical risk scores.[22,23] In a population-based study of patients with prior stroke and TIA, NT-proBNP was predictive of all-cause death.[24] Finally, higher NT-proBNP is also a powerful predictor of cognitive decline,[25] a condition also reflecting general cerebrovascular health. Few data are available on the association between NT-proBNP and stroke risk in those with a prior history of TIA or stroke,[26,27] as these patients are at highest risk for future stroke; study of NT-proBNP and stroke risk in this group is needed and may help guide secondary prevention initiatives.

In a large, population-based cohort study of black and white Americans followed for 5.4 years, we evaluated the association of baseline NT-proBNP with risk of future ischemic stroke across a continuum of preexisting cerebrovascular conditions, ranging from asymptomatic to those with stroke symptoms, to those with a prior TIA and those with prior stroke.

2 | METHODS

2.1 | Subjects

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study enrolled 30 239 adults ≥45 years old, 42% black and 58% white, 45% men and 55% women, from the contiguous United States, to study reasons for geographic and black-white disparities in stroke mortality. The study was approved by institutional review boards of participating centers, and detailed study methods were published.[28] Participants were recruited from commercially available lists (Genesys, Inc) in 2003-2007, with potential participants contacted by telephone and invited to participate. A telephone interview was conducted to obtain verbal informed consent and collect demographics, risk factors, and medical history. Trained professionals then visited each participant's home to collect written consent and fasting morning blood and urine samples and take blood pressure and other physical measurements, medication inventory, and an electrocardiogram, which was centrally read. Blood samples were collected as previously described[29] and shipped overnight to a central laboratory at the University of Vermont for analysis and storage.

Participants or their proxies are telephoned every 6 months to update health status. Medical records were obtained in the case of death, suspected cerebrovascular event, or occurrence of stroke symptoms elucidated using the well-established Questionnaire for Verifying Stroke-Free Status.[30] Positive responses to these questions were previously associated with health outcomes including stroke in REGARDS.[6,31-33] Records were reviewed and centrally adjudicated by ≥2 stroke experts.[34] Stroke was defined as focal neurological symptoms lasting ≥24 hours or nonfocal symptoms with positive imaging for stroke. Strokes were classified as ischemic or hemorrhagic, and hemorrhagic strokes were excluded from this analysis.

For this study, we enlarged a prior case cohort study of risk factors for first-time stroke that included 572 ischemic stroke cases and a 1104-person cohort random sample selected in 2011.[17] Stratification of the cohort sample was on age, sex, and race groups. The enlarged case cohort sample for this study included 320 additional first-time or recurrent ischemic strokes ascertained through

2014 and 3224 more cohort random sample participants selected with the same stratification factors.

2.2 | Study definitions

Baseline "cerebrovascular conditions" were defined as asymptomatic, stroke symptoms, TIA or stroke.[6] Prebaseline stroke or TIA was defined upon enrollment by self-report as previously reported.[6] Baseline history of stroke symptoms was defined as positive response to any of the 6 questions from the Questionnaire for Verifying Stroke-Free Status.[30] The 6 stroke symptoms were sudden onset of any of unilateral painless weakness, unilateral numbness or dead feeling, painless loss of vision unilaterally or bilaterally, hemifield vision loss, loss of ability to understand what people were saying, or loss of ability to express oneself verbally or in writing.

Age, race, sex, alcohol consumption, and current smoking were determined by self-report. Heavy alcohol consumption was defined as >2 drinks daily for men and >1 drink daily for women. Hypertension was defined as self-reported use of medications to lower blood pressure or blood pressure ≥140/90 mm Hg. Diabetes was defined as fasting glucose ≥126 mg/dL (or nonfasting glucose ≥200 mg/dL if the participant was not fasting) or self-reported antidiabetes medication use. Dyslipidemia was defined as triglycerides ≥240 mg/dL, low-density lipoprotein ≥160 mg/dL, or high-density lipoprotein ≤40 mg/dL. Left ventricular hypertrophy was classified by electrocardiogram.[35] Atrial fibrillation was by self-report or electrocardiogram evidence. History of heart disease was defined as self-reported prebaseline myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty/stenting, or evidence of MI on electrocardiogram. Use of warfarin, statins, and/or aspirin was by self-report.

Baseline NT-proBNP was measured in serum using the Roche Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN, USA) with an interassay coefficient of variation of <5%. Laboratory methods in REGARDS have been previously described in detail.[29] B-type natriuretic peptide (BNP) measured in serum was validated against plasma both in our lab and by the manufacturer (R^2 > 0.99, regression equation. There were 219 (4%) missing BNP values due to missing blood samples or technical issues. For all analyses, NT-proBNP was dichotomized with elevated levels defined as >75th percentile (137 pg/mL) based on prior analysis of its association with stroke in REGARDS.[17] In secondary analysis, NT-proBNP was analyzed as a continuous variable.

2.3 | Outcome

The primary outcome was ischemic stroke. Medical records were reviewed and centrally adjudicated by ≥2 stroke experts.[34] Stroke events were defined following the World Health Organization's definition as "rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."[36] Events not meeting this definition but characterized by symptoms lasting < 24 hours, with neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes." Strokes were further classified as ischemic or hemorrhagic, and hemorrhagic strokes were excluded.

2.4 | Statistical methods

Means and percentages were calculated for participant characteristics by baseline cerebrovascular condition. We calculated hazard ratios (HRs) of stroke by baseline cerebrovascular disease status using Cox proportional hazard models with 2 levels of adjustment and weighted for the stratified sampling of the cohort sample. We tested an interaction term with time to assure that the proportional hazards assumption was not violated. The first model included age, sex, race, and the known age-race interaction term. The second model added risk factors for recurrent stroke: hypertension status; diabetes; systolic blood pressure; lipid levels; tobacco use; heavy alcohol consumption; history of heart disease; atrial fibrillation; and use of warfarin, statins, and/or aspirin.

Kaplan-Meier plots were used in the cohort random sample to visually display the incidence of stroke among 8 cross-classified groups based on baseline cerebrovascular condition and presence or absence of elevated NT-proBNP. HRs of stroke with elevated NT-proBNP in participants with each baseline cerebrovascular condition were calculated using the same methods as above. Differences in the HRs of stroke for elevated NT-proBNP in groups classified by type of baseline cerebrovascular condition were compared by calculating an interaction term P value for NT-proBNP cerebrovascular condition status, with $P < .10$ indicating significance. To enhance power for detecting interactions, sensitivity analysis employed NT-proBNP as a continuous variable, calculating the HR of stroke per standard deviation higher concentration. A second sensitivity analysis tested a higher NT-proBNP cutoff of 250 pg/mL, which is planned for use to detect atrial cardiopathy after stroke in a clinical trial of secondary prevention of stroke, the Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA) trial (http://www.clinicaltrials.gov NCT03192215. NLM identifier: NCT03192215). Finally, we performed an exploratory analysis stratified on atrial fibrillation status.

3 | RESULTS

The analysis included 5013 participants; 4328 in the cohort random sample and 892 stroke cases (with 207 participants in both groups, as expected in a case-cohort study). Table 1 shows baseline characteristics in the cohort sample by prebaseline cerebrovascular condition; there were 3056 participants without any condition, 738 with prior stroke symptoms, 196 with history of TIA, and 338 with prior stroke. A greater percentage of stroke risk factors and use of stroke prevention medications was seen in participants

TABLE 1 Demographic, health characteristics, and biomarker concentrations by baseline cerebrovascular condition status in the cohort random sample

Risk factor, mean (SD) or percent	Asymptomatic	Stroke Symptoms	TIA	Previous stroke
N	3056	738	196	338
Age, y	64 (25)	65 (24)	70 (22)	69 (22)
Sex, female	50.3	53.3	53.8	42.2
Race, black	45.9	57.8	41.8	57.4
Current smoking	13.1	17.4	8.8	14.9
Diabetes	19.3	27.8	26.4	29
Systolic blood pressure, mm Hg	127 (43)	129 (46)	130 (42)	130 (45)
Antihypertensive medication use	48.1	56.1	74.2	71.3
Dyslipidemia	54.0	59.5	64.3	60.7
Cardiovascular disease	15.6	20.4	34.1	36.0
Atrial fibrillation	7.9	12.2	14.3	14.2
Left ventricular hypertrophy	9.6	13	9.9	14.9
Statin use	28.3	31	46.2	42.6
β-Blocker use	21.5	25.5	35.7	39.3
Warfarin use	3.7	3.4	6.6	13.2
Aspirin use	31.4	32.7	52.7	56.1
NT-proBNP (pg/mL)	75 (21)	89 (21)	140 (29)	148 (28)

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; TIA, transient ischemic attack.

with a history of stroke symptoms, TIA, or stroke. NT-proBNP was gradually higher across increasing severity of prebaseline cerebrovascular condition.

Kaplan-Meier plots showing the incidence of stroke by prebaseline cerebrovascular condition and elevated NT-proBNP in the 4238 participants in the cohort random sample are shown in the Figure 1.

A history of stroke symptoms, TIA, and prior stroke were significantly associated with risk of future stroke in a minimally adjusted model (Table 2). Effects were larger with increasing severity of prebaseline cerebrovascular condition; for example, those with prior stroke were at much higher risk of recurrent stroke than those with only a history of stroke symptoms (HR, 2.77 vs. 1.25). In a fully adjusted model, these associations were modestly attenuated, but the pattern was not changed.

In Table 3, the primary analysis results showed that the association of elevated NT-proBNP with future stroke differed significantly by baseline cerebrovascular condition (*P* interaction = 0.02 in fully adjusted model). In minimally and fully adjusted models, elevated NT-proBNP was associated with risk of stroke in asymptomatic participants and in participants with a history of stroke symptoms or with prior TIA but not in those with prior stroke. The risk was largest for those with prior TIA, who had a nearly 3-fold increased risk. In the 2 sensitivity analyses in Table 3, evaluating log NT-proBNP as a continuous variable or with a cutoff of 250 pg/mL; the difference in the association of NT-proBNP with future stroke by baseline cerebrovascular condition had a similar pattern.

Because of the strong association of NT-proBNP with atrial fibrillation, we stratified the above analysis by atrial fibrillation status (Table 4). Among those with a history of stroke symptoms, those with prior TIA, and those who were asymptomatic, the association of elevated NT-proBNP with future stroke was higher in those with than without a history of atrial fibrillation (though confidence intervals were wide), but there remained no association among those with prior stroke, regardless of atrial fibrillation status. The HR of stroke for elevated NTproBNP among participants on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was nearly identical to the HR in the overall population (data not shown).

4 | DISCUSSION

In this large cohort study of black and white Americans aged 45 and older, higher NT-proBNP concentration was associated with future stroke risk in asymptomatic participants and in those with a history of stroke symptoms or TIA, but the association was less apparent in people with a history of prior stroke. Among the 3 former groups, these associations seemed larger in those with a history of atrial fibrillation, but remained present as well for those without atrial fibrillation.

NT-proBNP is a risk marker for future first-time stroke in the general population,[17,18,37] and our findings confirm this and extend knowledge, finding associations among those with prior TIA

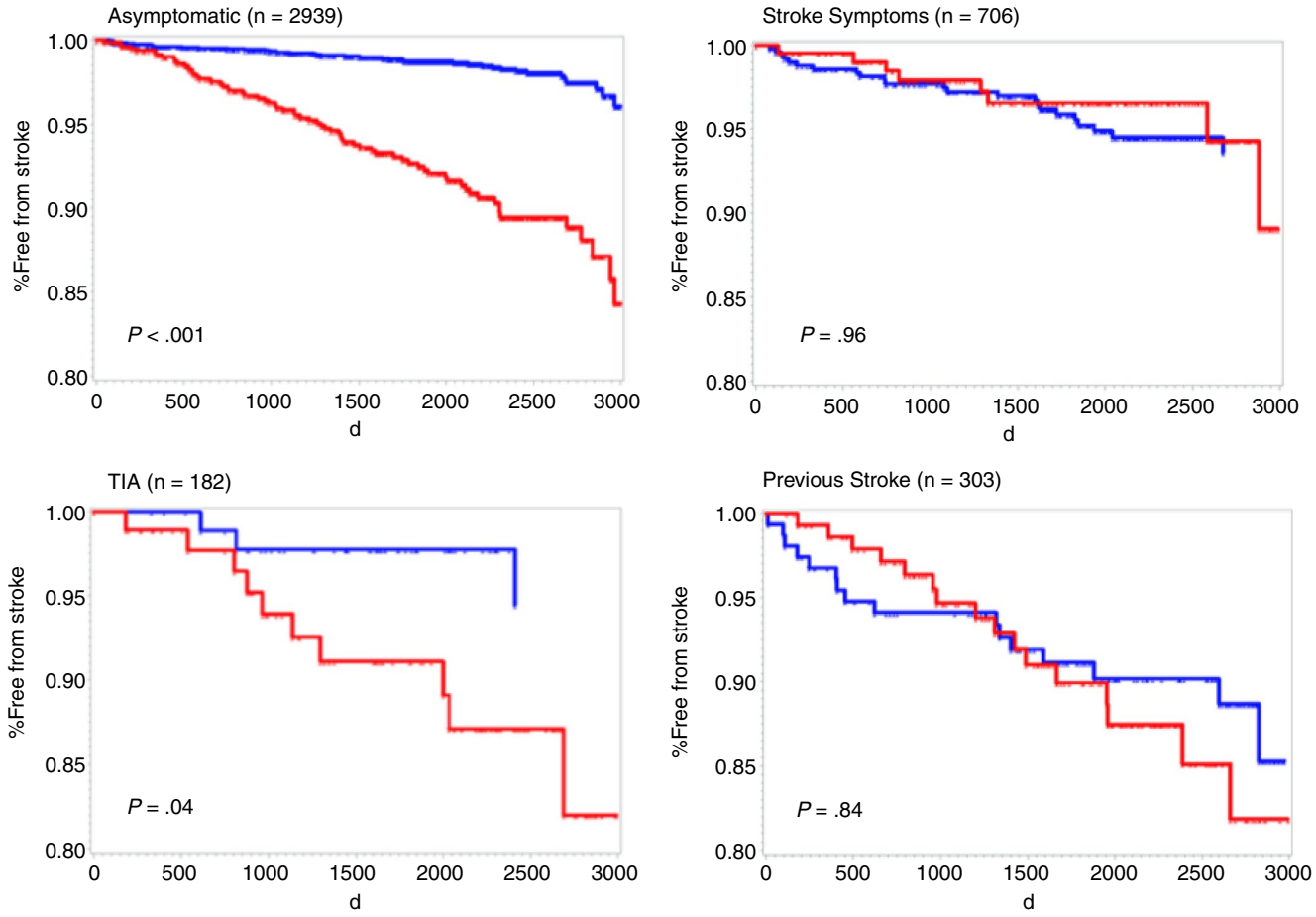

FIGURE 1 Kaplan-Meier plots of time to stroke by prebaseline cerebrovascular condition and elevated NT-proBNP in 4328 participants in the cohort random sample. Red line, elevated NT-proBNP (≥137 pg/mL). Blue line, normal NT-proBNP (<137 pg/mL). *P* values are from log-rank tests. NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA, transient ischemic attack

TABLE 2 Hazard ratio of stroke by prebaseline cerebrovascular condition status

	Asymptomatic	Stroke symptoms	TIA	Previous stroke	*P* trend*
At risk, N	3056	738	196	338	
Stroke, N	523	139	74	156	–
Minimally adjusted HR (95% CI)[a]	Ref	1.25 (1.02-1.54)	2.25 (1.69-3.01)	2.77 (2.20-3.50)	<.001
Fully adjusted HR (95% CI)[b]	Ref	1.15 (0.91-1.45)	1.87 (1.34-2.59)	2.37 (1.82-3.08)	<.001

Abbreviation: TIA, transient ischemic attack.

* P value for treand of the HR across groups

[a]Adjusted for age, race, sex, age × race.

[b]Additionally adjusted for hypertension, diabetes, systolic blood pressure, lipid levels, tobacco use, heavy alcohol consumption, history of heart disease, aspirin, warfarin, statins, and atrial fibrillation.

or stroke symptoms but not prior stroke. To our knowledge, the current study is the first large, population-based study to demonstrate an association between elevated NT-proBNP and future stroke risk in adults with a prior history of TIA, a group with a high risk of future stroke. Furthermore, other large studies of the relationship between NT-proBNP and recurrent stroke are not available. A small Japanese study reported that NT-proBNP > 300 pg/mL was associated with 1-year risk of recurrent stroke in stroke survivors with atrial fibrillation; the study had only 10 strokes in this group.[26] In our present study, using a lower cutoff (137 pg/mL) and a higher cutoff (250 pg/mL) yielded similar results, and neither cutoff was associated with increased stroke risk in those with prior stroke. A nested case-control study of clinical trial participants showed that very high NT-proBNP (>715 pg/mL) was modestly associated with recurrent ischemic stroke in patients with stroke or TIA; however, there was no adjustment for atrial

TABLE 3 Hazard ratio of stroke in each cerebrovascular disease group using different expressions of NT-proBNP

	Asymptomatic	Stroke symptoms	TIA	Prior stroke	*P* Interaction*
At risk, N	3056	738	196	338	
Stroke, n	523	139	74	156	
Primary analysis: HR for NT-proBNP ≥ 137 pg/mL versus < 137 pg/mL					
Cohort sample with elevated NT-proBNP, %	26.3	28.7	45.9	43.8	
Cases with elevated NT-proBNP, %	50.5	47.5	73.0	54.5	
Minimally adjusted HR (95% CI)[a]	2.49 (2.00-3.10)	2.29 (1.48-3.55)	3.07 (1.45-6.49)	1.52 (0.96-2.41)	.004
Fully adjusted HR (95% CI)[b]	2.32 (1.84-2.94)	1.67 (1.01-2.78)	2.66 (1.00-7.04)	1.26 (0.71-2.21)	.02
Sensitivity analysis for interaction testing: HR per SD higher log NT-proBNP (4.64 units)					
Minimally adjusted HR (95% CI)[a]	1.52 (1.39-1.66)	1.48 (1.28-1.73)	1.59 (1.23-2.05)	1.29 (1.10-1.53)	<.001
Fully adjusted HR (95% CI)[b]	1.44 (1.31-1.59)	1.35 (1.13-1.62)	1.20 (0.86-1.69)	1.21 (0.98-1.49)	<.001
Cohort sample with elevated NT-proBNP, %	17.3	20.3	35.2	33.1	
Cases with elevated NT-proBNP, %	37.1	34.5	58.1	41.7	
Minimally adjusted HR (95% CI)[a]	2.65 (2.09-3.35)	2.53 (1.59-4.03)	3.15 (1.42-7.00)	1.44 (0.89-2.33)	<.001
Fully adjusted HR (95% CI)[b]	2.36 (1.84-3.03)	1.98 (1.11-3.55)	2.10 (0.69-6.43)	1.34 (0.73-2.46)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA, transient ischemic attack.

[a]Adjusted for age, race, sex, age × race.

[b]Additionally adjusted for hypertension, diabetes, systolic blood pressure, lipid levels, tobacco use, heavy alcohol consumption, history of heart disease, aspirin, warfarin, statins, and atrial fibrillation.

**P* value for interaction of elevated NT-proBNP and baseline cerebrovascular disease.

TABLE 4 Elevated NT-proBNP[a] and stroke risk by prebaseline cerebrovascular condition status and history of atrial fibrillation

	Asymptomatic	Stroke symptoms	TIA	Previous stroke
Cohort sample, N	309	112	43	74
Stroke, N	72	23	17	29
HR (95% CI) Adjusted for age, race, age × race, sex	3.99 (2.12-7.51)	2.79 (0.77-10.2)	7.12 (0.68-74.7)	1.14 (0.32-4.04)
Without atrial fibrillation				
Cohort sample, N	3131	720	216	383
Strokes, N	451	116	57	127
HR (95% CI) Adjusted for age, race, age × race and sex	2.07 (1.62-2.65)	2.10 (1.29-3.40)	3.12 (1.23-7.90)	1.44 (0.86-2.41)
P interaction*	0.12	0.24	0.96	0.68

Abbreviations: HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIA, transient ischemic attack.

[a]HR for NT-proBNP ≥ 137 pg/mL versus <137 pg/mL.

**P* interaction if for the multiplicative interaction term of NT-proBNP and atrial fibrillation in each subgroup of prior cerebrovascular disease.

fibrillation status, an important determinant of NT-proBNP.[27] NT-proBNP was not associated with recurrent stroke in the present study; however, we used a lower cutoff level for NT-proBNP, adjusted for atrial fibrillation status, and studied a significantly larger population that represents the general population, not those eligible for a clinical trial.

A history of stroke symptoms is associated with silent brain infarction,[10] future stroke risk,[6,8] and elevated levels of stroke risk biomarkers, including NT-proBNP.[11] Taken together with the current findings that elevated NT-proBNP was associated with future stroke risk in these participants, it appears that a history of stroke symptoms likely reflects undiagnosed cerebrovascular disease.

Our findings support that NT-proBNP may add prognostication for future stroke risk in participants with atrial fibrillation. Specifically, among participants without prior cerebrovascular disease who had atrial fibrillation, we observed a 3.99-fold (95% confidence interval [CI], 2.12-7.51) increased risk of stroke with elevated BNP, while the HR was 2.07 (95% CI, 1.62-2.65) in those without cerebrovascular disease who did not have atrial fibrillation. While these 2 HRs were not statistically different, the high HR in participants with atrial fibrillation is consistent with previous research. Current American Heart Association guidelines recommend using the CHA_2DS_2-VASc (Cardiac failure or dysfunction, Hypertension, Age [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65 to 74, and Sex category [Female]) score to stratify stroke risk in atrial fibrillation, but this instrument uses only clinical variables. NT-proBNP is a very strong independent risk factor for incident atrial fibrillation[19,20,38] and stroke risk.[21,26] Further, prior studies have shown that NT-proBNP improves stroke risk prediction in atrial fibrillation over the CHA_2DS_2-VASc score, which might allow for a more dynamic risk prediction that can be monitored over time and guide anticoagulation treatment.[22,23]

The HR of stroke with elevated NTpro-BNP among participants without atrial fibrillation was lower than among those with atrial fibrillation, although we lacked statistical power to conclude a significant difference. The relatively strong associations in the absence of atrial fibrillation, with HRs 2- to 3-fold increased in those without prior stroke, support that NT-proBNP is a marker of atherosclerosis, cardiac dysfunction, or occult or future atrial fibrillation—for example, atriopathy—in this setting.[17,19,20,37-41]

Our results for the association of NT-proBNP with recurrent stroke were surprising and suggest that this biomarker would not have clinical utility in patients with prior stroke. However, a post hoc analysis from the Warfarin-Aspirin Recurrent Stroke Study found that elevated NT-proBNP may identify a subgroup of patients with noncardioembolic ischemic stroke without known atrial fibrillation who may benefit from anticoagulation therapy.[40] In that study, 49 of 1028 participants who had a very high level of NT-proBNP (above the 95th percentile value of 750 pg/mL) had a reduced risk of recurrent ischemic stroke or death when treated with warfarin compared with aspirin (HR, 0.30; 95% CI, 0.12-0.84). In the current study, we could not address this question directly, but our findings suggest that the population that may benefit the most from the use of NT-proBNP to gauge stroke risk is those with prior TIA because they have increased stroke risk and NT-proBNP predicted a high risk of future stroke in this group. Confirmation of our findings in patients with prior stroke or TIA is required.

Strengths of this study include the use of a national population sample of black and white adults with objectively measured risk factors, longitudinal follow-up with high retention, and carefully adjudicated outcomes. The threshold level of NT-proBNP was selected a priori based on previous studies demonstrating levels that are associated with stroke risk.[17,18] Results, including the interaction testing, were similar considering NT-proBNP as a continuous variable and using a higher cutoff value. There are also limitations to consider. The association of NT-proBNP and recurrent stroke might have been underestimated due to bias. Specifically, it is possible that people with prior stroke at higher risk of recurrence based on factors related to elevated NT-proBNP were less likely to enter the study due to illness, so including people with stroke are not necessarily generalizable to all people with prior stroke. While we were able to control for many factors that influence NT-proBNP and stroke risk, we were unable to control for congestive heart failure status at baseline due to lack of data, including an echocardiogram. In the current study, prebaseline stroke and TIA were self-reported, so misclassification of these conditions is possible. We also did not know stroke subtype for those with prebaseline stroke; however, given that 80% of strokes are ischemic and these have lower case fatality than hemorrhagic stroke, it is likely most prebaseline strokes were ischemic. It is possible that NT-proBNP measured at the time of a stroke, or shortly after, might be a better predictor of recurrent stroke. We did not have the date of prior stroke to examine this as a confounder or effect modifier. Finally, in analysis stratified by atrial fibrillation, there were relatively few strokes, so we were not able to pursue multivariable adjustment.

In conclusion, these findings further elucidate the association of BNP with stroke risk. To consider clinical use of NT-proBNP measurement for stroke risk prediction in the groups most likely to benefit from this testing (those with atrial fibrillation or TIA), inception cohorts or clinical trials of NT-proBNP guided interventions are needed.

ACKNOWLEDGMENTS

The authors thank the other investigators, staff, and participants of the REGARDS study for their valuable contributions. A full list of investigators and institutions can be found at http://www.regardsstudy.org.

RELATIONSHIP DISCLOSURE

The authors declare nothing to report.

TWITTER

Suzanne E. Judd @suzjudd
Mary Cushman @MaryCushmanMD

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135:e146–e603.
2. Johnston SC, Sidney S, Bernstein AL, Gress DR. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. Neurology. 2003;60:280–5.
3. Howard VJ, Lackland DT, Lichtman JH, McClure LA, Howard G, Wagner L, et al. Care seeking after stroke symptoms. Ann Neurol. 2008;63:466–72.
4. Howard VJ, McClure LA, Meschia JF, Pulley L, Orr SC, Friday GH. High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Arch Intern Med. 2006;166:1952–8.

5. Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke. 2005;36:720–3.
6. Judd SE, Kleindorfer DO, McClure LA, Rhodes JD, Howard G, Cushman M, et al. Self-report of stroke, transient ischemic attack, or stroke symptoms and risk of future stroke in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Stroke. 2013;44:55–60.
7. Clark TG, Murphy MF, Rothwell PM. Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. J Neurol Neurosurg Psychiatry. 2003;74:577–80.
8. Kleindorfer D, Judd S, Howard VJ, McClure L, Safford MM, Cushman M, et al. Self-reported stroke symptoms without a prior diagnosis of stroke or transient ischemic attack: a powerful new risk factor for stroke. Stroke. 2011;42:3122–6.
9. Chambless LE, Toole JF, Nieto FJ, Rosamond W, Paton C. Association between symptoms reported in a population questionnaire and future ischemic stroke: the ARIC study. Neuroepidemiology. 2004;23:33–7.
10. Windham BG, Griswold ME, Shibata D, Penman A, Catellier DJ, Mosley Jr TH. Covert neurological symptoms associated with silent infarcts from midlife to older age: the Atherosclerosis Risk in Communities study. Stroke. 2012;43:1218–23.
11. Landry KK, Alexander KS, Zakai NA, Judd SE, Kleindorfer DO, Howard VJ, et al. Association of stroke risk biomarkers with stroke symptoms: the Reasons for Geographic and Racial Differences in Stroke cohort. J Thromb Haemost. 2017;15:21–7.
12. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:227–76.
13. Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S, et al. ABCD3 and ABCD3-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. Stroke. 2014;45:418–25.
14. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–236.
15. Beatty AL, Ku IA, Bibbins-Domingo K, Christenson RH, DeFilippi CR, Ganz P, et al. Traditional risk factors versus biomarkers for prediction of secondary events in patients with stable coronary heart disease: from the Heart and Soul Study. J Am Heart Assoc. 2015;4(7):e001646.
16. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: a mechanism of cryptogenic stroke. Expert Rev Cardiovasc Ther. 2017;15:591–9.
17. Cushman M, Judd SE, Howard VJ, Kissela B, Gutiérrez OM, Jenny NS, et al. N-terminal pro-B-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. Stroke. 2014;45:1646–50.
18. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. Stroke. 2013;44:961–7.
19. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, et al. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. Circulation. 2009;120:1768–74.
20. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation. 2010;121:200–7.
21. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation. 2012;125:1605–16.
22. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37:1582–90.
23. Roldán V, Vílchez JA, Manzano-Fernández S, Jover E, Gálvez J, Puche CM, et al. Usefulness of N-terminal pro-B-type natriuretic peptide levels for stroke risk prediction in anticoagulated patients with atrial fibrillation. Stroke. 2014;45:696–701.
24. Greisenegger S, Segal HC, Burgess AI, Poole DL, Mehta Z, Rothwell PM. Biomarkers and mortality after transient ischemic attack and minor ischemic stroke: population-based study. Stroke. 2015;46:659–66.
25. Cushman M, Callas PW, McClure LA, Unverzagt FW, Howard VJ, Gillett SR, et al. N-terminal pro-B-type natriuretic peptide and risk of future cognitive impairment in the REGARDS cohort. J Alzheimers Dis. 2016;54(2):497–503.
26. Shibazaki K, Kimura K, Aoki J, Sakai K, Saji N, Uemura J. Brain natriuretic peptide level on admission predicts recurrent stroke after discharge in stroke survivors with atrial fibrillation. Clin Neurol Neurosurg. 2014;127:25–9.
27. Campbell DJ, Woodward M, Chalmers JP, Colman SA, Jenkins AJ, Kemp BE, et al. Soluble vascular cell adhesion molecule 1 and N-terminal pro-B-type natriuretic peptide in predicting ischemic stroke in patients with cerebrovascular disease. Arch Neurol. 2006;63:60–5.
28. Howard VJ, Cushman M, Pulley LeaVonne, Gomez CR, Go RC, Prineas RJ, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135–43.
29. Gillett SR, Boyle RH, Zakai NA, McClure LA, Jenny NS, Cushman M. Validating laboratory results in a national observational cohort study without field centers: the Reasons for Geographic and Racial Differences in Stroke cohort. Clin Biochem. 2014;47:243–6.
30. Jones WJ, Williams LS, Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. Stroke. 2001;32:2232–6.
31. Kelley BJ, McClure LA, Letter AJ, Wadley VG, Unverzagt FW, Kissela BM, et al. Report of stroke-like symptoms predicts incident cognitive impairment in a stroke-free cohort. Neurology. 2013;81:113–8.
32. Colantonio LD, Gamboa CM, Kleindorfer DO, Carson AP, Howard VJ, Muntner P, et al. Stroke symptoms and risk for incident coronary heart disease in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Int J Cardiol. 2016;220:122–8.
33. Gao L, Meschia JF, Judd SE, Muntner P, McClure LA, Howard VJ, et al. What stroke symptoms tell us: association of risk factors and individual stroke symptoms in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. J Stroke Cerebrovasc Dis. 2012;21:411–6.
34. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. Ann Neurol. 2011;69:619–27.
35. Soliman EZ, Howard G, Prineas RJ, McClure LA, Howard VJ. Calculating Cornell voltage from nonstandard chest electrode recording site in the Reasons for Geographic and Racial Differences in Stroke study. J Electrocardiol. 2010;43:209–14.
36. Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders. Stroke. 1989;20:1407–31.

37. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 2004;350:655–63.
38. Silvet H, Young-Xu Y, Walleigh D, Ravid S. Brain natriuretic peptide is elevated in outpatients with atrial fibrillation. Am J Cardiol. 2003;92:1124–7.
39. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med. 2006;355:2631–9.
40. Longstreth Jr WT, Kronmal RA, Thompson JLP, Christenson RH, Levine SR, Gross R, et al. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. Stroke. 2013;44:714–9.
41. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engström G, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA. 2009;302:49–57.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Landry KK, Judd SE, Kleindorfer DO, et al. N-Terminal pro-B-type natriuretic peptide and stroke risk across a spectrum of cerebrovascular disease: The REasons for Geographic and Racial Differences in Stroke cohort. *Res Pract Thromb Haemost*. 2020;4:893–901. https://doi.org/10.1002/rth2.12365