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

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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
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.22,23 In a population-based study of patients with prior stroke, TIA, or stroke symptoms were at high risk of future stroke.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 population17,18 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 described29 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.5,31-33 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 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. Prebaseline stroke or TIA was defined upon enrollment by self-report as previously reported. Baseline history of stroke symptoms was defined as positive response to any of the 6 questions from the Questionnaire for Verifying Stroke-Free Status. 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. 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. B-type natriuretic peptide (BNP) measured in serum was validated against plasma both in our lab and by the manufacturer (R² > 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. 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. 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." 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...
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,\textsuperscript{17,18,37} and our findings confirm this and extend knowledge, finding associations among those with prior TIA
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 fibrillation.

**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 trend of the HR across groups

aAdjusted for age, race, sex, age × race.
bAdditionally adjusted for hypertension, diabetes, systolic blood pressure, lipid levels, tobacco use, heavy alcohol consumption, history of heart disease, aspirin, warfarin, statins, and atrial fibrillation.
fibrillation status, an important determinant of NT-proBNP. 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,\textsuperscript{10} future stroke risk,\textsuperscript{6,8} and elevated levels of stroke risk biomarkers, including NT-proBNP.\textsuperscript{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 CHA2DS2-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, but this instrument uses only clinical variables. NT-proBNP is a very strong independent risk factor for incident atrial fibrillation and stroke risk.\(^\text{21,26}\) Further, prior studies have shown that NT-proBNP improves stroke risk prediction in atrial fibrillation over the CHA2DS2-VASc score, which might allow for a more dynamic risk prediction that can be monitored over time and guide anticoagulation treatment.\(^\text{22,23}\)

The HR of stroke with elevated NT-pro-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, atrioptathy—in this setting.\(^\text{17,19,20,37-41}\)

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.\(^\text{40}\) 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.\(^\text{17,18}\) 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.

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RELATIONSHIP DISCLOSURE
The authors declare nothing to report.

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**SUPPORTING INFORMATION**

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

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