Procalcitonin and Midregional Proatrial Natriuretic Peptide as Biomarkers of Subclinical Cerebrovascular Damage

The Northern Manhattan Study

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Background and Purpose—Chronic infections and cardiac dysfunction are risk factors for stroke. We hypothesized that blood biomarkers of infection (procalcitonin) and cardiac dysfunction (midregional proatrial natriuretic peptide [MR-proANP]), previously associated with small vessel stroke and cardioembolic stroke are also associated with subclinical cerebrovascular damage, including silent brain infarcts and white matter hyperintensity volume.

Methods—The NOMAS (Northern Manhattan Study) was designed to assess risk factors for incident vascular disease in a multiethnic cohort. A subsample underwent brain magnetic resonance imaging and had blood samples available for biomarker measurement (n=1178). We used logistic regression models to estimate the odds ratios and 95% confidence intervals (95% CIs) for the association of these biomarkers with silent brain infarcts after adjusting for demographic, behavioral, and medical risk factors. We used linear regression to assess associations with log-white matter hyperintensity volume.

Results—Mean age was 70±9 years; 60% were women, 66% Hispanic, 17% black, and 15% were white. After adjusting for risk factors, subjects with procalcitonin or MR-proANP in the top quartile, compared with the lowest quartile were more likely to have silent brain infarcts (adjusted odds ratio for procalcitonin, 2.2; 95% CI, 1.3–3.7 and for MR-proANP, 3.3; 95% CI, 1.7–6.3) and increased white matter hyperintensity volume (adjusted mean change in log-white matter hyperintensity volume for procalcitonin, 0.29; 95% CI, 0.13–0.44 and for MR-proANP, 0.18; 95% CI, 0.004–0.36).

Conclusions—Higher concentrations of procalcitonin, a marker of infection, and MR-proANP, a marker of cardiac dysfunction, are independently associated with subclinical cerebrovascular damage. If further studies demonstrate an incremental value for risk stratification, biomarker-guided primary prevention studies may lead to new approaches to prevent cerebrovascular disease. **(*Stroke*. 2017;48:604-610. DOI: 10.1161/STROKEAHA.116.014945.)**

Key Words: biomarkers ■ brain infarction ■ risk factor ■ stroke ■ white matter

Subclinical cerebrovascular disease (SCVD), as manifested by silent brain infarcts (SBI) or white matter hyperintensities (WMHs) visualized on magnetic resonance imaging (MRI), has been associated with incident ischemic stroke[1] and cognitive dysfunction and dementia.[2,3]

There is little data on blood biomarkers and their association with SCVD, but such knowledge could help identify novel preventive and therapeutic targets for stroke, cognitive dysfunction, and dementia simultaneously. For this purpose, the measurement of blood biomarkers, which may indicate underlying subclinical pathological processes, could be an important adjunct to traditional risk assessment.

Chronic infections have been associated with stroke risk and cognitive impairment even after adjusting for other potential confounders.[4,5] Serum procalcitonin concentrations correlate with the extent and severity of microbial invasion.[6] In a recent study nested within in the NOMAS (Northern Manhattan Study), procalcitonin concentrations were associated specifically with small vessel stroke.[7]

Higher natriuretic peptide levels reflect the severity of cardiac dysfunction.[8] There is increasing evidence supporting the potential role of elevated natriuretic peptides as risk factors for cognitive impairment.[9] Midregional proatrial natriuretic peptide (MR-proANP) has been shown to be associated specifically with cardioembolic stroke pathogenesis.[7,10]

Both chronic infections and underlying cardiac dysfunction may be risk factors not only for overt ischemic stroke but also for SCVD. Thus, we hypothesized that procalcitonin, as a surrogate for bacterial infections, and MR-proANP, as a marker of cardiac dysfunction, previously associated with

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small vessel stroke and cardioembolic stroke,[7] respectively, would also be associated with MRI measures of SCVD in the ethnically diverse Northern Manhattan population.

Methods

Study Population

NOMAS is a population-based cohort study among 3298 initially stroke-free participants identified using random digit dialing with dual-frame sampling to identify telephone numbers. NOMAS was designed to evaluate the effects of medical, socioeconomic, and other risk factors on the incidence of vascular disease in a stroke-free multiethnic community cohort. Methods of participant recruitment, evaluation, and follow-up have been previously reported.[11] Briefly, subjects were eligible if they (1) had never had a stroke diagnosed, (2) were >40 years of age, and (3) resided in Northern Manhattan in a household with a telephone. Participants underwent a thorough baseline examination. Standardized questions about vascular risk factors were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System as defined previously.[12] Changes in health or vital status were determined through annual telephone follow-up and clinical examinations. The Institutional Review Boards at Columbia University Medical Center and the University of Miami approved the study. All participants gave informed consent to participate in the study.

MRI Sample

Participants included in this analysis were part of a sample recruited from the NOMAS cohort to undergo brain MRI scans, using the following criteria: (1) age ≥50 years, (2) no contraindications to MRI, and (3) willing to sign informed consent. To maximize recruitment, an additional 199 participants, who were household members of existing NOMAS participants (n=1091), were recruited into the MRI sample for a total of 1290 participants. Out of these 199 household members, 29 (15%) were blood relatives. Imaging was performed on a 1.5-T MRI system (Philips Medical Systems, Best, The Netherlands). Stored frozen serum samples, drawn at the time of the MRI, were available in 1178 subjects from this subcohort.

MRI Examination

The processing of MRI scans in NOMAS has been published.[13,14] Briefly, the presence or absence of SBI was determined from the size, location, and imaging characteristics of the lesion.[15] Lesions were ≥3 mm in size with CSF density on the subtraction image, in a vascular distribution, and distinct from circle of Willis vessels and perivascular spaces if in the basal ganglia. Interobserver agreement for SBI detection was 93.3%.[16]

Analyses for WMH volume (WMHV) were performed using semiautomated measurements of pixel distributions and mathematical modeling of pixel-intensity histograms for cerebrospinal fluid and brain (white and gray matter) to identify the optimal pixel-intensity threshold to distinguish cerebrospinal fluid from brain matter. Analyses were performed using a custom-designed image analysis package (QUANTA 6.2 using a Sun Microsystems Ultra 5 workstation). WMHV was calculated as percent total intracranial volume to correct for differences in head size[17] and log-transformed to achieve a normal distribution (logWMHV). All analyses were performed blind to participant identifying information and biomarker measurements.

Biomarker Measurements

At baseline, blood samples were obtained, centrifuged, and frozen at −80°C in 1 mL aliquots until the time of analysis. The samples of 1178 subjects with available serum were shipped on dry ice to the Department of Clinical Chemistry, University Hospital of Zurich, for biomarker measurements. Samples were thawed at 4°C before measurements and analyzed within 1 hour, thus reducing preanalytic errors. Procalcitonin concentrations were measured using a sensitive assay with a detection limit of 0.007 ng/mL (B·R·A·H·M·S-us PCT-sensitive KRYPTOR, Thermo-Scientific, BRAHMS, Hennigsdorf Berlin, Germany). MR-proANP concentrations were measured using an immunoassay with a detection limit of 2.1 pmol/L (B·R·A·H·M·S KRYPTOR, Thermo Scientific, BRAHMS). Quality control was maintained using standardized procedures. All testing was performed in a batched analysis, blinded to all clinical data. Stability at room temperature and after freezing and thawing cycles has been documented for both biomarkers.[18,19]

Statistical Analyses

We calculated descriptive statistics for the clinical, demographic, and biomarker variables. The primary outcomes for this analysis were (1) the presence of SBI (dichotomous variable) and (2) WMHV (continuous variable). The main variables, procalcitonin and MR-proANP, were log transformed to achieve linearity and analyzed continuously and by quartile to facilitate clinical interpretation. Odds ratios (ORs for SBI) and β-coefficients (β for WMHV) and 95% confidence intervals (95% CI) were calculated, unadjusted, and adjusted for demographic and vascular risk factors. Covariates included predictors of ischemic stroke and WMHV in previous analyses in NOMAS, including age at the time of MRI, sex, race-ethnicity, education, and insurance status, physical activity, smoking status, moderate alcohol consumption, diabetes mellitus, cardiac disease, including atrial fibrillation, systolic and diastolic blood pressures, low-density lipoprotein, and high-density lipoprotein. We also included estimated glomerular filtration rate because these biomarkers undergo renal clearance. We assessed potential effect modification of the association between the biomarker levels and the outcomes by each vascular risk factor.

All testing was 2-tailed, and $P<0.05$ was considered statistically significant. All calculations were performed using SAS v9.1.3 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Demographics and clinical characteristics of the study population (n=1178) are summarized in Table 1. The mean age of the sample at the time of brain MRI was 69.8±8.9 years, 60% were women, and the majority (66%) were Hispanic. Median procalcitonin levels were 0.0254 µg/L (IQR 0.015–0.039 µg/L) and median MR-proANP levels were 90.2 pmol/L (IQR 62.2–132.8 pmol/L).

In this MRI cohort with available blood, 168 participants (15%) had at least 1 SBI and the median WMHV (WMHV/TCV×100) was 0.35% intracranial volume (IQR 0.21%–0.75% intracranial volume). Biomarker distribution according to the presence of SBI is shown in Figures 1 and 2.

Association of Procalcitonin With MRI Measures of SCVD

In the unadjusted analysis, procalcitonin concentration was associated with the prevalence of SBI (OR, 1.32 per SD of log-procalcitonin; 95% CI, 1.12–1.56). This association remained after adjusting for demographic and vascular risk factors (OR, 1.25 per SD of log-procalcitonin; 95% CI, 1.03–1.50). When analyzed by quartiles, individuals in the top procalcitonin quartile were more likely to have SBI compared with those in the lowest quartile (unadjusted OR, 2.44; 95% CI, 1.51–3.96; Table 2). After adjusting for demographic and vascular risk factors, those with procalcitonin in the top quartile, compared with the lowest quartile, remained

Table 1. Baseline Demographics and Risk Factors of the Northern Manhattan Study MRI Subsample With Serum Samples Available for This Analysis (n=1178)

Sociodemographic Characteristics	Mean (±SD) or Median (IQR); n (%)
Age at the time of MRI in years	69.8 (±8.9)
Women	707 (60%)
Race–Ethnicity	
Hispanic	780 (66%)
Non-Hispanic black	200 (17%)
Non-Hispanic white	171 (15%)
Other	25 (2%)
Less than high school education	632 (54%)
Medicaid or no insurance	555 (47%)
Medical comorbidities	
Current tobacco use	184 (16%)
Moderate alcohol use*	484 (41%)
Mean systolic blood pressures in mm Hg	137 (±8)
Mean diastolic blood pressures in mm Hg	78 (±10)
Estimated glomerular filtration rate	78 (±20)
Cardiac disease†	
Diabetes mellitus‡	228 (19%)
Laboratory parameters	
High-density lipoprotein, mg/dL	53.4 (±17)
Low-density lipoprotein, mg/dL	115 (±35.3)
Procalcitonin, μg/L	0.025 (0.015–0.039)
MR-proANP, pmol/L	90.2 (62.2–132.8)

IQR indicates interquartile range; MRI, magnetic resonance imaging; and MR-proANP, midregional proatrial natriuretic peptide.

*Moderate alcohol use=≤2 servings of alcohol per day (reference all other groups).

†Cardiac disease=coronary artery disease, congestive heart failure, and atrial fibrillation.

‡Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, the subject's self-report of diabetes mellitus, or insulin or hypoglycemic agent use.

more likely to have SBI (adjusted OR, 2.16; 95% CI, 1.26–3.69; Table 2). We found no effect modification by vascular risk factors.

Greater procalcitonin concentration was also associated with greater WMHV (unadjusted mean change in logWMHV per SD of log-procalcitonin 0.18; 95% CI, 0.13–0.24), and this association remained after adjusting for demographic as well as for vascular risk factors (adjusted mean change in logWMHV per SD of log-procalcitonin 0.10; 95% CI, 0.04–0.15). Individuals in the top procalcitonin quartile, compared with the lowest quartile, also had greater WMHV (unadjusted mean change in logWMHV 0.52; 95% CI, 0.37–0.68). This association remained after adjusting for demographic and vascular risk factors (adjusted mean change in logWMHV 0.29; 95% CI, 0.13–0.44; Table 3). We found no effect modification by vascular risk factors.

Association of MR-proANP With Measures of SCVD

In the unadjusted analysis, MR-proANP concentration was associated with SBI (OR, 1.67 per SD of log MR-proANP; 95% CI, 1.42–1.97); this association remained after adjusting for demographic and vascular risk factors (OR, 1.54 per SD of log MR-proANP; 95% CI, 1.22–1.94). When analyzed by quartiles, individuals in the top MR-proANP quartile were more likely to have SBI compared with those in the lowest quartile (unadjusted OR, 3.99; 95% CI, 2.39–6.65). This association remained after adjusting for demographic and vascular risk factors (adjusted OR, 3.31; 95% CI, 1.74–6.32; Table 2). We found no effect modification by vascular risk factors.

MR-proANP concentration was further associated with WMHV (unadjusted mean change in logWMHV per SD of logMR-proANP 0.28; 95% CI, 0.22–0.33), although this linear association was no longer statistically significant after adjusting for demographic and vascular risk factors (adjusted mean change in logWMHV per SD of logMR-proANP 0.05; 95% CI, −0.01 to 0.12). When analyzed by quartiles, participants with MR-proANP levels in the top quartile had greater WMHV than those in the lowest quartile (unadjusted mean change in logWMHV 0.74; 95% CI, 0.59–0.90) and this persisted after adjusting for sociodemographic and vascular risk factors, although the effect was attenuated (adjusted mean change in logWMHV 0.18; 95% CI, 0.004–0.36; Table 3). We found no effect modification by baseline vascular risk factors.

Discussion

In this urban, multiethnic, population-based sample, procalcitonin, a marker of bacterial infection, and MR-proANP, a marker for cardiac dysfunction, were each independently associated with 2 measures of subclinical cerebrovascular damage, SBI and WMHV. However, the association of MR-proANP concentrations with WMHV was less pronounced compared with the association with SBI.

Silent brain infarction serves as an imaging biomarker of vascular brain health. SBI has been associated with traditional vascular risk factors, as well as with future clinical stroke,[20] cognitive decline, and dementia.[3,21] The independent association of SBI with future stroke, however, after adjusting for vascular risk factors suggest that SBIs reflect either an overall effect of uncontrolled vascular risk factors better than the presence or absence of each individual factor or that other, yet unknown, factors play a role in the association with stroke and dementia. These unknown factors may include underlying chronic infection, measured by procalcitonin, or subclinical cardiac disease, measured by MR-proANP.

Recent findings in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) suggest that mechanisms of SBI and white matter hyperintensities are intimately connected.[22] In these patients, the majority of incident lacunes developed proximal to a white matter hyperintensity along the course of perforating vessels supplying the respective brain region.[22] With the caveat that not all SBI or WMH defined by MRI are definitely of vascular origin, this finding provides indirect evidence that both imaging markers are good surrogates of small

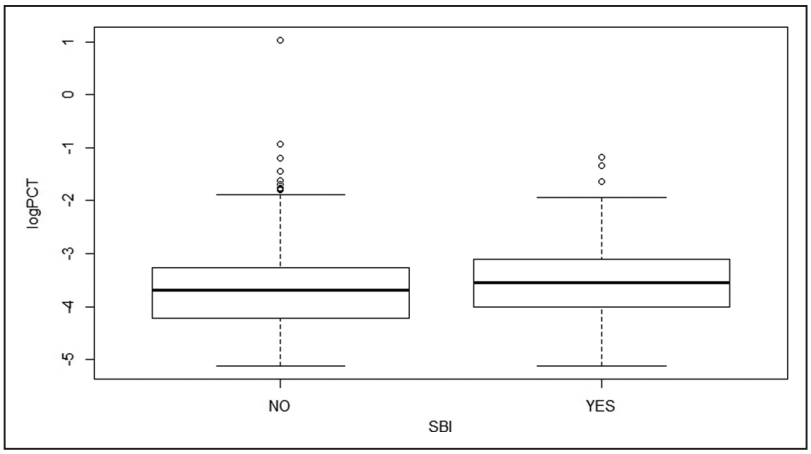

Figure 1. Distribution of log-procalcitonin (PCT) concentrations according to the presence of silent brain infarcts (SBI).

vessel disease, including consecutive overt strokes and eventually vascular dementia.

Procalcitonin was first shown in the early 1990s to be a sepsis-induced protein detectable in patient plasma.[23] Currently, procalcitonin is used to guide antibiotic use in patients with lower respiratory tract infections.[24] If procalcitonin concentrations are >0.5 µg/L, acute bacterial pneumonia is very likely, and antibiotic treatment is strongly recommended. procalcitonin synthesis and secretion are upregulated by lipopolysaccharides and certain bacteria-specific proinflammatory mediators (eg, interleukin-1β, tumor necrosis factor-α, and interleukin-6) and are downregulated as concentrations of these substances decrease during recovery from infection.[25,26] Interestingly, a polymorphism in the gene encoding the monocyte receptor for bacterial lipopolysaccharide (CD14) was specifically associated with large atherosclerotic and small vessel stroke, but not other types of stroke.[27] In a pilot case-cohort analysis in NOMAS, we found an association of procalcitonin with stroke risk, and in particular with small vessel stroke. The biological role of procalcitonin in vivo at low concentrations in stroke-free people has to date been largely unexplored. On the basis of our data from this and our previous analysis,[7] we propose that even low concentrations of procalcitonin may reflect ongoing subclinical inflammatory processes triggered by bacterial endotoxins, which, in turn, contribute to the small vessel damage that causes some SCVD,[28,29] as well as overt small vessel stroke.

Brain natriuretic peptide (BNP) and N-terminal pro-B-natriuretic peptide (NT-proBNP), as members of the family of the natriuretic peptides, have also been associated with incident stroke in some studies,[30,31] as well as with WMH and SBI in the ARIC (Atherosclerosis Risk in Communities) study. In addition, higher NT-proBNP concentrations were prospectively associated with increased incident SBIs and WMH progression >8 years of follow-up.[32] Our search did not reveal previous studies of MR-proANP, another member of the family of the natriuretic peptides, in relation to SBI or WMHV. Concerning mortality in patients with chronic heart failure, MR-proANP outperformed BNP and NT-proBNP. The proportion of explained variance showed that MR-proANP (4.36%) was a significantly stronger predictor of death than either NT-proBNP (2.47%, $P<0.0001$) or BNP (2.42%, $P<0.0001$). Both a new assay technology and the high biological stability of MR-proANP are potential explanations for these findings.[33] The pathophysiological mechanism explaining the independent associations of MR-proANP with SBI and to a lesser extent with WMHV in our study needs confirmation. We hypothesize that high MR-proANP concentrations indicate the presence of underlying early atrial pathology, thus leading to silent strokes, but only to a slight increase in WMHV, which is less likely to have exclusively a cardioembolic pathogenesis and could also reflect effects, such as relative hypoperfusion primarily based on other pathomechanisms. White matter lesions can occur with acute[34] and also chronic cerebral

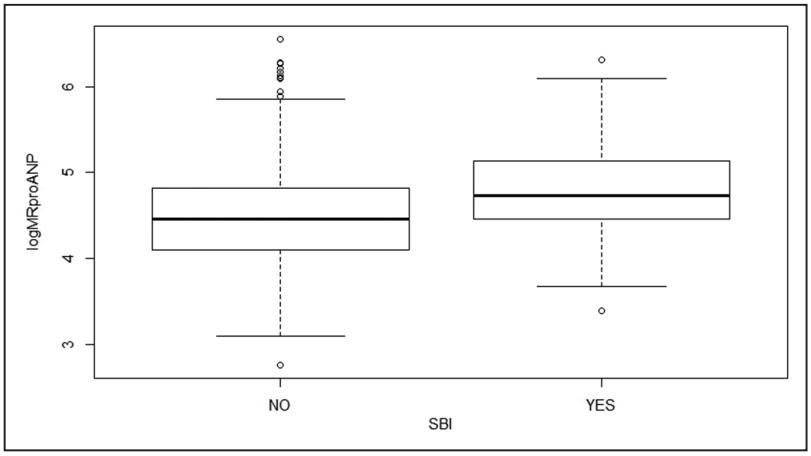

Figure 2. Distribution of log-midregional proatrial natriuretic peptide (MR-proANP) concentrations according to the presence of silent brain infarcts (SBI).

Table 2. Association of Biomarkers With Silent Brain Infarcts

Parameter	Unadjusted, OR (95% CI)	Model 1, OR (95% CI)*	Model 2, OR (95% CI)†
Procalcitonin			
First quartile	Reference		
Second quartile	1.5 (0.9–2.6)	1.4 (0.8–2.4)	1.4 (0.8–2.4)
Third quartile	1.4 (0.9–2.4)	1.3 (0.7–2.2)	1.2 (0.7–2.2)
Fourth quartile	2.4 (1.5–4.0)	1.9 (1.1–3.2)	2.2 (1.3–3.7)
MR-proANP			
First quartile	Reference		
Second quartile	1.3 (0.8–2.4)	1.4 (0.8–2.6)	1.5 (0.8–2.8)
Third quartile	2.3 (1.4–4.0)	2.0 (1.1–3.6)	1.9 (1.1–3.6)
Fourth quartile	4.0 (2.4–6.7)	2.8 (1.5–5.2)	3.3 (1.7–6.3)

CI indicates confidence interval; OR, odds ratio; and MR-proANP, midregional proatrial natriuretic peptide.

*Model 1: adjusted for age, sex, race-ethnicity, education, and insurance status.

†Model 2: adjusted for covariates in Model 1 plus physical activity, smoking status, moderate alcohol consumption, cardiac disease, diabetes mellitus, systolic and diastolic blood pressures, low-density lipoprotein, high-density lipoprotein, and estimated glomerular filtration rate.

ischemia,[35] but nonarteriolar and nonischemic mechanisms for WMH have also been proposed,[36] including venous sclerosis with subsequent venous hypertension,[37] all of which are less prone to be associated with an underlying cardiac disease. The association of MR-proANP with WMHV, compared with the association with SBI, was thus more attenuated after adjustment, pointing to the fact that other comorbidities such as smoking are probably more important risk factors for an increase in WMHV.

Our study has limitations. Our cross-sectional analysis does not allow for determining causal relationships, and we cannot exclude the possibility of residual confounding. Our findings require replication in an external sample to ensure validity. Also, repeated measurements of the selected biomarkers and their change over time may be a better indicator of SCVD than levels measured at a single baseline point. Furthermore, we did not perform direct comparison of procalcitonin with other markers of infection or inflammation, such as C-reactive protein, nor did we compare MR-proANP with NT-proBNP. However, in a previous study of high-sensitivity CRP (C-reactive protein) in NOMAS, we did not find a significant independent association of CRP with incident stroke.[38] Similarly, in a previous analysis of a subgroup of the NOMAS MRI cohort including different inflammatory markers, CRP was not independently associated with silent infarcts or white matter disease after adjusting for other risk factors and biomarkers.[39] Finally, the blood samples were stored at −80°C for several years, which could lead to some protein degradation. Degradation would, however, have affected subjects with and without SBI similarly, and probably would have biased our results toward the null.

The strengths of this study include the population-based multiethnic cohort, including a large proportion of Hispanics who are frequently under-represented in other cohort studies, and detailed clinical information on participants, permitting us to adjust for numerous potential covariates. Finally, this study provides prospectively planned imaging sequences to specifically assess subclinical cerebrovascular damage as an important risk factor for overt stroke and dementia.

In conclusion, we report associations of procalcitonin and MR-proANP with SCVD. This study was aimed at identifying novel markers reflecting different potential mechanisms that may contribute to subclinical vascular disease. Whether these markers will be of clinical use in the future remains to be determined. If, however, other studies confirm these associations, and if further studies show an incremental value for risk stratification, we may in the future base the selection for specific primary

Table 3. Association of Top Quartile of Procalcitonin and MR-proANP With Log-Total White Matter Hyperintensity Volume

Parameter	Univariate Analysis Parameter Estimate (95% CI)	Model 1 Parameter Estimate (95% CI)*	Model 2 Parameter Estimate (95% CI)†
Procalcitonin			
First quartile	Reference		
Second quartile	0.20 (0.04 to 0.35)	0.08 (–0.06 to 0.22)	0.09 (–0.06 to 0.23)
Third quartile	0.31 (0.15 to 0.46)	0.21 (0.06 to 0.35)	0.19 (0.05 to 0.34)
Fourth quartile	0.52 (0.37 to 0.68)	0.29 (0.15 to 0. 44)	0.29 (0.13 to 0.44)
MR-proANP			
First quartile	Reference		
Second quartile	0.08 (–0.07 to 0.23)	–0.02 (–0.16 to 0.13)	–0.03 (–0.17 to 0.12)
Third quartile	0.29 (0.14 to 0.44)	0.00 (–0.15 to 0.15)	–0.01 (–0.16 to 0.15)
Fourth quartile	0.74 (0.59 to 0.90)	0.22 (0.06 to 0.39)	0.18 (0.004 to 0.36)

CI indicates confidence interval; and MR-proANP, midregional proatrial natriuretic peptide.

*Model 1: adjusted for age, sex, race/ethnicity, education, and insurance status.

†Model 2: adjusted for age, sex, race/ethnicity, education, insurances status, physical activity, smoking status, moderate alcohol consumption, cardiac disease, diabetes mellitus, systolic and diastolic blood pressures, low-density lipoprotein, high-density lipoprotein, and estimated glomerular filtration rate.

preventive interventions concerning underlying subclinical infections and heart disease on these biomarker levels. Given the multiple adverse health outcomes associated with SCVD in older individuals, these biomarker-guided interventions may have a clinically relevant impact and may be beneficial even for the prevention of both stroke and cognitive impairment.

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References

1. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
2. Wright CB, Festa JR, Paik MC, Schmiedigen A, Brown TR, Yoshita M, et al. White matter hyperintensities and subclinical infarction: associations with psychomotor speed and cognitive flexibility. *Stroke*. 2008;39:800–805. doi: 10.1161/STROKEAHA.107.484147.
3. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke*. 2010;41:600–606. doi: 10.1161/STROKEAHA.109.570044.
4. Elkind MS, Ramakrishnan P, Moon YP, Boden-Albala B, Liu KM, Spitalnik SL, et al. Infectious burden and risk of stroke: the Northern Manhattan Study. *Arch Neurol*. 2010;67:33–38. doi: 10.1001/archneurol.2009.271.
5. Katan M, Moon YP, Paik MC, Sacco RL, Wright CB, Elkind MS. Infectious burden and cognitive function: the Northern Manhattan Study. *Neurology*. 2013;80:1209–1215. doi: 10.1212/WNL.0b013e3182896e79.
6. Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med*. 2000;28:977–983.
7. Katan M, Moon YP, Paik MC, Mueller B, Huber A, Sacco RL, et al. Procalcitonin and midregional proatrial natriuretic peptide as markers of ischemic stroke: The Northern Manhattan Study. *Stroke*. 2016;47:1714–1719. doi: 10.1161/STROKEAHA.115.011392.
8. Moe GW, Howlett J, Januzzi JL, Zowall H; Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation*. 2007;115:3103–3110. doi: 10.1161/CIRCULATIONAHA.106.666255.
9. Kerola T, Nieminen T, Hartikainen S, Sulkava R, Vuolteenaho O, Kettunen R. B-type natriuretic peptide as a predictor of declining cognitive function and dementia–a cohort study of an elderly general population with a 5-year follow-up. *Ann Med*. 2010;42:207–215. doi: 10.3109/07853891003652542.
10. Katan M, Fluri F, Schuetz P, Morgenthaler NG, Zweifel C, Bingisser R, et al. Midregional pro-atrial natriuretic peptide and outcome in patients with acute ischemic stroke. *J Am Coll Cardiol*. 2010;56:1045–1053. doi: 10.1016/j.jacc.2010.02.071.
11. Elkind MS, Sciacca RR, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Relative elevation in baseline leukocyte count predicts first cerebral infarction. *Neurology*. 2005;64:2121–2125. doi: 10.1212/01.WNL.0000165989.12122.49.
12. Sacco RL, Benson RT, Kargman DE, Boden-Albala B, Tuck C, Lin IF, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly: the Northern Manhattan Stroke Study. *JAMA*. 2001;285:2729–2735.
13. Wright CB, Paik MC, Brown TR, Stabler SP, Allen RH, Sacco RL, et al. Total homocysteine is associated with white matter hyperintensity volume: the Northern Manhattan Study. *Stroke*. 2005;36:1207–1211. doi: 10.1161/01.STR.0000165923.02318.22.
14. Prabhakaran S, Wright CB, Yoshita M, Delapaz R, Brown T, DeCarli C, et al. Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. *Neurology*. 2008;70:425–430. doi: 10.1212/01.wnl.0000277521.66947.e5.
15. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, et al. Predictors of brain morphology for the men of the NHLBI twin study. *Stroke*. 1999;30:529–536.
16. Willey JZ, Moon YP, Paik MC, Yoshita M, Decarli C, Sacco RL, et al. Lower prevalence of silent brain infarcts in the physically active: the Northern Manhattan Study. *Neurology*. 2011;76:2112–2118. doi: 10.1212/WNL.0b013e31821f4472.
17. DeCarli C, Murphy DG, Tranh M, Grady CL, Haxby JV, Gillette JA, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995;45:2077–2084.
18. Struck J, Strebelow M, Tietz S, Alonso C, Morgenthaler NG, van der Hoeven JG, et al. Method for the selective measurement of amino-terminal variants of procalcitonin. *Clin Chem*. 2009;55:1672–1679. doi: 10.1373/clinchem.2008.123018.
19. Morgenthaler NG, Struck J, Thomas B, Bergmann A. Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. *Clin Chem*. 2004;50:234–236. doi: 10.1373/clinchem.2003.021204.
20. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. 2016;47:719–725. doi: 10.1161/STROKEAHA.115.011889.
21. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222. doi: 10.1056/NEJMoa022066.
22. Duering M, Csanadi E, Gesierich B, Jouvent E, Hervé D, Seiler S, et al. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. *Brain*. 2013;136(Pt 9):2717–2726. doi: 10.1093/brain/awt184.
23. Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med*. 2000;28:977–983.
24. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 2009;302:1059–1066. doi: 10.1001/jama.2009.1297.
25. Schuetz P, Raad I, Amin DN. Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis. *Curr Opin Crit Care*. 2013;19:453–460. doi: 10.1097/MCC.0b013e328363bd38.
26. Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab*. 2001;86:396–404. doi: 10.1210/jcem.86.1.7089.
27. Lichy C, Meiser H, Grond-Ginsbach C, Buggle F, Dörfer C, Grau A. Lipopolysaccharide receptor CD14 polymorphism and risk of stroke in a South-German population. *J Neurol*. 2002;249:821–823. doi: 10.1007/s00415-002-0726-0.
28. Fisher CM. The arterial lesions underlying lacunes. *Acta Neuropathol*. 1968;12:1–15.

29. Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. *Stroke*. 2016;47:554–560. doi: 10.1161/STROKEAHA.115.009627.
30. 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;45:1646–1650. doi: 10.1161/STROKEAHA.114.004712.
31. 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;44:961–967. doi: 10.1161/STROKEAHA.111.000173.
32. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, et al. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke*. 2013;44:1803–1808. doi: 10.1161/STROKEAHA.113.001128.
33. Moertl D, Berger R, Struck J, Gleiss A, Hammer A, Morgenthaler NG, et al. Comparison of midregional pro-atrial and B-type natriuretic peptides in chronic heart failure: influencing factors, detection of left ventricular systolic dysfunction, and prediction of death. *J Am Coll Cardiol*. 2009;53:1783–1790. doi: 10.1016/j.jacc.2009.01.057.
34. Conklin J, Silver FL, Mikulis DJ, Mandell DM. Are acute infarcts the cause of leukoaraiosis? Brain mapping for 16 consecutive weeks. *Ann Neurol*. 2014;76:899–904. doi: 10.1002/ana.24285.
35. de Groot M, Verhaaren BF, de Boer R, Klein S, Hofman A, van der Lugt A, et al. Changes in normal-appearing white matter precede development of white matter lesions. *Stroke*. 2013;44:1037–1042. doi: 10.1161/STROKEAHA.112.680223.
36. Fern RF, Matute C, Stys PK. White matter injury: Ischemic and nonischemic. *Glia*. 2014;62:1780–1789. doi: 10.1002/glia.22722.
37. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke*. 2009;40(Suppl 3):S48–S52. doi: 10.1161/STROKEAHA.108.537704.
38. Elkind MS, Luna JM, Moon YP, Liu KM, Spitalnik SL, Paik MC, et al. High-sensitivity C-reactive protein predicts mortality but not stroke: the Northern Manhattan Study. *Neurology*. 2009;73:1300–1307. doi: 10.1212/WNL.0b013e3181bd10bc.
39. Wright CB, Moon Y, Paik MC, Brown TR, Rabbani L, Yoshita M, et al. Inflammatory biomarkers of vascular risk as correlates of leukoariosis. *Stroke*. 2009;40:3466–3471. doi: 10.1161/STROKEAHA.109.559567.

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