Stroke is the leading neurological cause of death and disability, but, despite awareness of many modifiable vascular risk factors for stroke, the United States continues to record 800,000 events each year. Identifying circulating biomarkers associated with a disease outcome, such as stroke or coronary heart disease, has been a time-honored method to improve our understanding of disease pathophysiology and improve risk prediction, but it has proven challenging to identify such markers associated with stroke risk. In a recent attempt to identify circulating biomarkers associated with stroke, higher levels of B-type natriuretic peptide (BNP) were found, along with an elevated urinary albumin/creatinine ratio, to be associated with a 30% to 40% greater risk of stroke and transient ischemic attack.

Natriuretic peptides are biologically plausible biomarkers for stroke risk because of their role in regulation of intravascular volume and blood pressure, and their relationship with cardiac structure and function. The prohormone of BNP, proBNP, is stored within granules in cardiac myocytes and is released when the cardiac myocytes are stretched; this happens with ventricular volume expansion or pressure overload. ProBNP is cleaved by a previously unknown enzyme into 2 fragments: the inactive N-terminal proBNP and the bioactive peptide BNP. The transmembrane serine protease responsible for this cleavage has recently been characterized in vitro and in animal models and named corin because of its abundant presence in the heart.

In this issue of Stroke, Peng et al describe the results of a case-control study investigating the association of serum levels of corin with first-ever ischemic or hemorrhagic stroke. Consecutive stroke cases (481 ischemic and 116 hemorrhagic) were recruited from 3 Chinese hospitals during 5 months in 2014. Cases were compared with healthy community participants (2498 controls) randomly recruited in 2010 from the district of Suzhou, outside of Shanghai. Overall, women had lower median levels of serum soluble corin than men. In sex-stratified analyses, persons with an ischemic or hemorrhagic stroke had lower levels than stroke-free controls. Both women and men were significantly more likely to have either type of stroke if their circulating corin levels were in the lowest quartile. In men, risk of ischemic stroke was 5-fold higher and risk of hemorrhagic stroke was 17.5-fold higher among persons with corin levels in the lowest quartile compared with persons with corin levels in the top quartile. In women, the risks were 3- and 8.5-fold higher, respectively, and risks persisted in multivariable analyses adjusting for conventional stroke risk factors. This is the first study of serum corin levels in stroke patients, and the results should be considered hypothesis generating. Further caution is warranted because the study was restricted to relatively young, Chinese patients with less severe strokes (median NIHSS score was 4).

Corin is found in the heart and the kidneys. What are the potential pathophysiologic mechanisms underlying the relationship between corin and risk of stroke? The related, but more short-lived atrial natriuretic peptide is also converted from its prohormone by corin. BNP and atrial natriuretic peptide regulate salt-water balance and fluid volume by promoting sodium excretion (natriuresis) in the kidneys. They also have vasodilatory actions and thus decrease blood pressure both through vasodilation and reduced intravascular volume. Furthermore, they modulate ventricular remodeling and slow ventricular hypertrophy. BNP levels show a compensatory elevation in heart failure, and serve as a biomarker for diagnosis and to track effective treatment. Because corin is critical for the activation of these natriuretic peptides, reduced corin activity in humans and in animal models seems to be associated with heart failure and hypertension, both stroke risk factors.

Hypertension is the most important risk factor for stroke. In mice lacking or deficient in corin, salt-sensitive hypertension has been observed. Gene variants have also been identified among humans. Dries et al sequenced the corin gene to identify 2 nonsynonymous, nonconservative single nucleotide polymorphisms (Q568P and T555I) in near-complete linkage disequilibrium, thus describing a single minor I555 (P568) corin gene allele, that was significantly associated with risk for hypertension in 3 cohorts, the Dallas Heart Study, the Multiethnic Study of Atherosclerosis, and the Chicago Genetics of Hypertension Study. These minor alleles were present in ≈12% of the black participants and <0.5% of the white participants. Serum levels of corin were not measured in this genetic association study. Another corin gene mutation was identified in a family of hypertensive patients in China. These researchers demonstrated that cells transfected with the mutant allele expressed corin normally in vitro, however, with reduced activity in processing proatrial natriuretic peptide, probably because the mutation altered the structure or function of the enzyme. Small case-control studies have begun to demonstrate that serum soluble corin levels may be lower in patients with hypertension and heart failure and possibly higher in pregnancy-associated hypertension.
The biological significance of higher or lower than normal levels of serum soluble corin remain uncertain. Previous research investigated hypertension and corin levels among the same healthy community participants from Suzhou, China that generated the current article’s control cohort.13 Participants with coronary heart disease, stroke, causes for secondary hypertension, and persons already on antihypertensive medications were excluded and the investigators controlled for conventional risk factors for hypertension, such as obesity. Surprisingly, higher corin levels were associated with hypertension in this relatively healthy sample, in contrast to animal models where corin deficiency predicted hypertension. Although elevated BNP levels have been most strongly associated with risk of cardioembolic subtype of ischemic stroke, secondary analysis in this study did not reveal an association of lower corin levels with cardioembolic stroke. Rather, associations were noted with atherothrombotic and hemorrhagic strokes. Perhaps the subsample with cardioembolic stroke was too small, reducing power to detect an effect. Corin may be acting through alternative biological pathways besides those discussed (eg, lower BNP has been associated with greater insulin resistance and visceral adiposity),13 or measurements may need to focus on corin activity or changes in corin levels over time.

The results of the study by Peng et al1 should be interpreted in light of these caveats. The authors present a proof of concept that corin may be a candidate biomarker for stroke.14 Their findings persisted after excluding stroke patients with history of angina, myocardial infarction, coronary insufficiency, heart failure, or atrial fibrillation. The authors acknowledge that a causal relationship between corin levels and hypertension or stroke would be difficult to infer from a cross-sectional study and further, that biological activity of membrane bound corin may be a more important measure to study. It is unknown how or whether corin shedding from the cell surface is regulated, or whether certain disease states would alter that regulation.

In cardiovascular disease, corin and natriuretic peptides are critical mediators. It remains to be seen whether corin proves to be a useful biomarker for stroke, or a suitable drug target. The heart of the matter will be whether causality can be established between corin and stroke risk. This will certainly require further prospective research because the key Bradford–Hill criterion for probable causality in epidemiological studies, temporality, can only be established prospectively. Subsequent research will need to explore the incremental clinical use, if any, of measuring corin for stroke risk prediction and to improve outcomes for patients.

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**Disclosures**

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Heart of the Matter
Hugo J. Aparicio and Sudha Seshadri

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