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EDITORIAL COMMENT

# Upstream Enzyme of Natriuretic Peptide Pathway

## Is Soluble Corin a Predictor of Future Stroke Events?*

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The natriuretic peptide (NP) pathway protects the cardiovascular system via natriuresis, diuresis, and vasodilatation. Under physiological conditions that maintain homeostasis, a myocardial stretch induces the release of NPs from cardiomyocytes. In the clinical setting of heart failure, atrial natriuretic peptide (ANP) and brain-type natriuretic peptide (BNP) have been used for bedside testing for diagnosis and treatment. The emergence of angiotensin receptor-neprilysin inhibitors has further generated interest in the metabolism of the NP pathway. Whereas neprilysin degrades NPs, corin—a transmembrane type II serine protease—cleaves the precursors of NPs (pro-NPs) to produce bioactive NPs and N-terminal pro-NPs. Corin is highly expressed in myocardial cells, and it primarily targets the ANP pathway on the cell surface. The initial form of ANP is an inactive pre-pro-ANP comprising 151 amino acids, translated from the *NPPA* gene. After post-translational modification, pro-ANP is stored in the intracellular granules of the atrial cardiomyocytes. Upon stimulation from atrial cardiomyocytes via volume receptors, pro-ANPs are activated by corin on the cell membrane and released into circulation as ANP, comprising 28 amino acids. Soluble corin is shed from the myocardial cell membrane by ADAM10 as ~180 kDa fragments that are further degraded to inactive ~160 and ~100 kDa corin fragments through an autocleavage process.[1] Similarly, corin cleaves pro-BNP to yield active-type BNP; furin is the primary processing enzyme in the process of BNP activation.[2]

Although it is unclear whether the levels of circulating and soluble corin and membrane-anchored corin are correlated, the role of soluble corin as a biomarker has been studied in patients with cardiovascular and cerebrovascular diseases (CVDs), especially hypertension, heart failure, acute coronary artery diseases, and stroke. Recent studies have shown that demographic and metabolic factors are associated with circulating corin levels. Hence, age, obesity, systolic blood pressure, and dyslipidemia positively correlate with corin levels, whereas smoking and alcohol consumption negatively correlate with corin levels.[3] In addition to such long-term factors, a decrease in circulating corin levels is associated with unstable cardiovascular conditions such as acute coronary syndrome,[4,5] heart failure,[6,7] and stroke.[8] As soluble corin is associated with many risk factors and clinical conditions in CVD, multicollinearity should be considered when interpreting the roles of soluble corin. Furthermore, the association between corin levels and future cardiovascular events has not been investigated; thus, prospective longitudinal studies are warranted to elucidate the clinical implications of circulating corin levels.

In this issue of *JACC: Asia*, Chen et al[9] report the clinical impact of soluble corin on future events of CVD through a 10-year observation of a large community-based population in China (2,498 healthy participants above the age of 30). In this longitudinal study, the concentration of soluble corin was measured at the time of enrollment, and the study population was followed up every 2 years, from 2010 to 2020, to identify cardiovascular events, including unstable coronary artery conditions (acute coronary syndrome and acute myocardial infarction), stroke, and cardiovascular death. A cross-sectional cohort study from the same study cohort was published in

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2015, which reported that hypertensive patients showed a higher corin level with an independent predictive effect in diagnosing hypertension.[3] During the 10-year follow-up after enrollment, a total of 210 CVD events (nonfatal stroke, nonfatal coronary artery disease, death from stroke, and death from coronary artery disease in 81, 139, 7, and 8 participants, respectively) and 50 non-CVD deaths were identified, and 214 participants were lost to follow-up (completion rate of 10-year follow-up, 91.4%). Notably, the participants who experienced CVD events during the observation period showed higher concentrations of serum corin at the time of enrollment. In the multivariate analysis, baseline corin concentration, which was derived from the effect of stroke events, remained an independent predictor of CVD.

Chen et al [9] should be congratulated on their work demonstrating the association between serum corin level and future cardiovascular events via a long-term observation of a large study population. In the comparison between the lowest and highest quartile cohorts, the HR was 1.62 for all cardiovascular events (95% CI: 1.07-2.46; $P = 0.024$) and 2.79 for stroke events (95% CI: 1.40-5.56; $P = 0.004$) after adjusting the demographic and metabolic factors influencing circulating corin levels (age, sex, education level, current smoking, current drinking, systolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting glucose, and antihypertension medications). This finding suggests the utility of soluble corin in cardiovascular risk stratification of the general population.

The mechanisms underlying the association between corin levels and future stroke remain to be investigated. First, as mentioned by the author, the activity of circulating soluble corin is unclear; therefore, to determine the role of corin levels in the NP pathway, simultaneous measurements of NP concentrations as the end products of the system are warranted. Neprilysin also acts as a modulator of the NP system; however, its mechanism of action requires comprehensive understanding. Second, the association between atrial fibrillation and corin levels cannot be ignored when investigating the impact of the latter on future stroke events. A previous study reported an association between atrial fibrillation and corin levels.[10] In 1 possible scenario, the cohort with a higher corin level might have been associated with asymptomatic subclinical atrial fibrillation related to stroke caused by cardiac embolism. Unfortunately, the prevalence of atrial fibrillation was not investigated during the study period. Finally, in my opinion, it remains inconclusive as to whether corin levels can be used as an independent predictor of CVD events or if it can only act as a surrogate marker of known risk factors. Indeed, including serum corin levels in the multivariable risk prediction model using traditional risk factors did not increase performance. Despite these limitations, Chen et al,[9] from the longitudinal cohort study, have provided an important finding that soluble corin is a useful biomarker for risk stratification of the general population, raising further interesting hypotheses in this research field.

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**KEY WORDS** cardiovascular disease, corin, prospective longitudinal study