Elevated plasma natriuretic peptide levels were associated with cardiovascular events

Wang TJ, Larson MG, Levy D, et al. **Plasma natriuretic peptide levels and the risk of cardiovascular events and death.** N Engl J Med. 2004;350:655-63.

QUESTION

In asymptomatic persons without preexisting heart failure (HF), are elevated brain and proatrial natriuretic peptide levels associated with cardiovascular events, atrial fibrillation, and death?

METHODS

Design: Cohort study with mean 5.2-year follow-up (Framingham Offspring Study).

Setting: Community-based study in the United States.

Patients: 3346 participants (mean age 58 y, 53% women) of the Framingham Off-spring Study. Exclusion criteria were HF, serum creatinine > 177 µmol/L (> 2.0 mg/dL), unavailable natriuretic peptide levels, or missing covariate or follow-up data.

Risk factors: B-type natriuretic peptide (BNP) and N-terminal proatrial natriuretic peptide (N-ANP) measured using high-sensitivity, noncompetitive immunoradiometric assays. Other risk factors were age, sex, presence or absence of hypertension and diabetes, ratio of total–to–high-density lipoprotein cholesterol, body mass index, serum creatinine level, and smoking status.

Outcomes: All-cause mortality, a first major cardiovascular event (recognized myocardial infarction, coronary insufficiency, death from coronary heart disease, HF, and stroke), HF, atrial fibrillation, stroke or transient ischemic attack, and coronary heart disease events (recognized or unrecognized myocardial infarction, coronary insufficiency, and angina pectoris).

MAIN RESULTS

Natriuretic peptide levels were analyzed as continuous (logarithmic transformation) and categorical (> 80th percentile of each peptide as the cutpoint) variables. After adjustment for other cardiac risk factors, increased BNP levels were associated with increased all-cause mortality, first major cardiovascular event, heart failure, atrial fibrillation, and stroke or transient ischemic attack (Table). Values > 80th percentile were also associated with an increase in death, first major cardiovascular event, HF, atrial fibrillation, and stroke or transient ischemic attack (Table). Results were similar for N-ANP peptide (Table). The strongest association was for HF and atrial fibrillation. Neither peptide was associated with increased coronary heart disease events (Table).

CONCLUSION

In asymptomatic persons without preexisting heart failure, both elevated brain and proatrial natriuretic peptide levels were associated with increased incidence of cardiovascular events, particularly heart failure, atrial fibrillation, and death.

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Association of B-type natriuretic peptide (BNP) and N-terminal proatrial natriuretic peptide (N-ANP) levels with cardiovascular outcomes*

Outcomes	BNP		N-ANP	
	Adjusted HR per 1 SD increment in log BNP values (95% CI)	Adjusted HR for BNP values > 80th percentile (CI)	Adjusted HR per 1 SD increment in log N-ANP (CI)	Adjusted HR for N-ANP values > 80th percentile (CI)
All-cause mortality	1.27 (1.06 to 1.52)	1.62 (1.08 to 2.42)	1.41 (1.14 to 1.74)	1.76 (1.15 to 2.68)
First major CV event	1.28 (1.03 to 1.59)	1.76 (1.06 to 2.92)	1.30 (1.02 to 1.67)	1.52 (0.89 to 2.59)†
Heart failure	1.77 (1.31 to 2.41)	3.07 (1.51 to 6.26)	1.94 (1.37 to 2.75)	5.02 (2.32 to 10.85)
Atrial fibrillation	1.66 (1.30 to 2.11)	1.91 (1.13 to 3.25)	1.72 (1.30 to 2.28)	2.09 (1.21 to 3.62)
Stroke or TIA	1.53 (1.16 to 2.02)	1.99 (1.09 to 3.62)	1.37 (0.99 to 1.89)†	2.08 (1.11 to 3.89)
CHD events	1.10 (0.89 to 1.37)†	1.30 (0.79 to 2.15)†	1.12 (0.88 to 1.42)†	0.87 (0.50 to 1.51)†

*HR = hazard ratio; SD = standard deviation; TIA = transient ischemic attack; CHD = coronary heart disease. HRs adjusted for age, sex, presence or absence of hypertension or diabetes, ratio of total-to-high-density lipoprotein cholesterol, smoking status, body-mass index, and serum creatinine level. CI defined in Glossary.
†Not significant.

COMMENTARY

The identification of putative serum markers of cardiovascular risk is proceeding at an ever-increasing pace. The natriuretic peptides are one such class of markers, which when elevated above threshold values provide both diagnostic and prognostic information.

In this interesting study, Wang and colleagues extend this paradigm by showing that in addition to a risk associated with elevated levels, a graded relation exists between levels of BNP and N-ANP "within the normal range" and the risk for cardiovascular events over an average of 5.2 years in unselected, asymptomatic patients. However, like many recently identified markers of risk, much work remains to raise the measurement of natriuretic peptides for risk stratification in asymptomatic persons to the level of routine clinical practice. First, a better understanding of the pathophysiology underpinning the risk associated with low-level elevation in asymptomatic patients, particularly those without previous cardiovascular disease, is warranted so that screening can guide additional diagnostic testing and intervention to mitigate subsequent clinical risk. Second, it must be clearly shown that population screening adds incrementally to routine clinical evaluation. For example, although adjusting for clinical diagnoses did not alter observed associations, readily available clinical information, such as systolic blood pressure or pulse pressure, which has a known relation with the clinical outcomes of interest, was not considered. Third, a better understanding of normal biological variability in natriuretic peptide levels in healthy persons is mandatory so that results are meaningful at the level of an individual person and useful risk stratification boundaries can be established. Finally, once these issues are clearly resolved, to be most useful to clinicians in practice, a scale of risk based on actual measured values (rather than log transformations of data) will be necessary.

Thus, despite the intriguing observations presented by Wang and colleagues, at present it is premature to consider routine screening of natriuretic peptide levels for risk stratification in asymptomatic persons.

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