ORIGINAL ARTICLE

Plasma Natriuretic Peptide Levels and the Risk of Cardiovascular Events and Death

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ABSTRACT

BACKGROUND

The natriuretic peptides are counterregulatory hormones involved in volume homeostasis and cardiovascular remodeling. The prognostic significance of plasma natriuretic peptide levels in apparently asymptomatic persons has not been established.

METHODS

We prospectively studied 3346 persons without heart failure. Using proportional-hazards regression, we examined the relations of plasma B-type natriuretic peptide and N-terminal pro–atrial natriuretic peptide to the risk of death from any cause, a first major cardiovascular event, heart failure, atrial fibrillation, stroke or transient ischemic attack, and coronary heart disease.

RESULTS

During a mean follow-up of 5.2 years, 119 participants died and 79 had a first cardiovascular event. After adjustment for cardiovascular risk factors, each increment of 1 SD in log B-type natriuretic peptide levels was associated with a 27 percent increase in the risk of death (P=0.009), a 28 percent increase in the risk of a first cardiovascular event (P=0.03), a 77 percent increase in the risk of heart failure (P<0.001), a 66 percent increase in the risk of atrial fibrillation (P<0.001), and a 53 percent increase in the risk of stroke or transient ischemic attack (P=0.002). Peptide levels were not significantly associated with the risk of coronary heart disease events. B-type natriuretic peptide values above the 80th percentile (20.0 pg per milliliter for men and 23.3 pg per milliliter for women) were associated with multivariable-adjusted hazard ratios of 1.62 for death (P=0.02), 1.76 for a first major cardiovascular event (P=0.03), 1.91 for atrial fibrillation (P=0.02), 1.99 for stroke or transient ischemic attack (P=0.02), and 3.07 for heart failure (P=0.002). Similar results were obtained for N-terminal pro–atrial natriuretic peptide.

CONCLUSIONS

In this community-based sample, plasma natriuretic peptide levels predicted the risk of death and cardiovascular events after adjustment for traditional risk factors. Excess risk was apparent at natriuretic peptide levels well below current thresholds used to diagnose heart failure.

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Atrial natriuretic peptide and B-type natriuretic peptide are secreted from cardiomyocytes in response to atrial or ventricular wall stretch.[1] The natriuretic peptides have a fundamental role in cardiovascular remodeling, volume homeostasis, and the response to ischemia.[1-4] Clinical investigations of these peptides have focused on their diagnostic usefulness for heart failure and left ventricular dysfunction and their prognostic usefulness after acute coronary syndromes and heart failure.[5-12]

A few reports have suggested that elevated plasma natriuretic peptide levels in nonhospitalized persons are associated with an increased risk of death, but these studies have largely been restricted to very elderly persons.[13-16] We were interested in examining the relations of natriuretic peptides to the incidence of cardiovascular events, heart failure, and atrial fibrillation in an ambulatory cohort. We prospectively studied a large, community-based sample of persons in whom plasma natriuretic peptide levels were routinely measured and who were followed for the occurrence of major cardiovascular events and death.

METHODS

STUDY SAMPLE

The design and selection criteria of the Framingham Offspring Study have been described previously.[17] The 3532 participants who attended the sixth examination cycle (1995 through 1998) were eligible for the present investigation. We excluded 186 attendees for the following reasons: heart failure in 40, a serum creatinine level of more than 2.0 mg per deciliter (177 μmol per liter) in 16, unavailability of natriuretic peptide levels in 78, missing covariate data in 49, and missing follow-up data in 3. After exclusions, 3346 participants (95 percent) remained eligible. Participants underwent a clinical and laboratory evaluation and echocardiography, as described previously.[5,18] Study protocols were approved by the institutional review board of Boston Medical Center. Written informed consent was obtained from all participants.

NATRIURETIC PEPTIDE ASSAYS

B-type natriuretic peptide and N-terminal pro–atrial natriuretic peptide were measured with the use of high-sensitivity, noncompetitive immunoradiometric assays (Shionogi). The lower limits of detection were 4 pg per milliliter for the assay of B-type natriuretic peptide and 94 pmol per liter for the assay of N-terminal pro–atrial natriuretic peptide. The average interassay coefficients of variation were 12.2 percent for B-type natriuretic peptide and 12.7 percent for N-terminal pro–atrial natriuretic peptide.

OUTCOMES

Participants were monitored regularly for the occurrence of cardiovascular outcomes and death. A committee of three investigators reviewed all suspected cardiovascular events by examining hospital records, clinic notes, and pathology reports. Investigators had no knowledge of the results of plasma natriuretic peptide measurements. A Framingham Heart Study neurologist evaluated participants with suspected cerebrovascular events, and a separate review committee that included a neurologist adjudicated these events.

Major cardiovascular events included recognized myocardial infarction, coronary insufficiency, death from coronary heart disease, heart failure, and stroke. Coronary heart disease included recognized or unrecognized myocardial infarction, coronary insufficiency, and angina pectoris. Prevalent cardiovascular disease was defined by prior coronary heart disease, stroke or transient ischemic attack, or intermittent claudication. Criteria for the diagnoses of cardiovascular events have been described elsewhere.[18] Participants were also followed for the development of atrial fibrillation, defined as atrial fibrillation or atrial flutter on an electrocardiogram obtained from a hospital record, office visit, or Framingham Study clinic visit. Electrocardiographic findings were verified by a Framingham Heart Study cardiologist.

STATISTICAL ANALYSIS

We examined the association between base-line levels of plasma natriuretic peptides and six prespecified end points: death from any cause, a first major cardiovascular event, heart failure, atrial fibrillation, stroke or transient ischemic attack, and coronary heart disease. We analyzed plasma natriuretic peptide levels as categorical variables and as continuous variables after natural logarithmic transformation to normalize their distribution. In categorical analyses, we used prespecified thresholds corresponding to the 80th percentile values of each peptide. Owing to sex-based differences in the distributions of plasma natriuretic peptide levels,[19,20] we established separate cutoff points for men and women. To assess whether a gradient of risk was

present across natriuretic peptide values, we performed analyses using three categories: lowest third, middle third, and highest third. Because the threshold of detection of the assay censored 38 percent of plasma B-type natriuretic peptide values in men, values of 4 pg per milliliter in men were assigned to the lowest category, with the remaining values split evenly between the upper two categories.

Cumulative incidence curves were estimated according to Gray's method.[21] We used multivariable proportional-hazards regression to examine the association of natriuretic peptide levels with each outcome.[22] Analyses were restricted to participants who had never had the outcome being studied. For end points other than death, death was a censoring variable. We adjusted analyses for age, sex, the presence or absence of hypertension and diabetes, the ratio of total to high-density lipoprotein cholesterol, the body-mass index, the serum creatinine level, and smoking status. Additional covariates were included for specific end points on the basis of prior reports[23-25]: prevalent atrial fibrillation (for major cardiovascular events, heart failure, and stroke or transient ischemic attack), prior myocardial infarction (for heart failure and atrial fibrillation), systolic murmur of grade 3/6 or more or any diastolic murmur (for heart failure and atrial fibrillation), and prevalent cardiovascular disease (for death and stroke or transient ischemic attack).

In secondary analyses, we also analyzed heart-failure outcomes using interim myocardial infarction (occurring after the base-line examination) as a time-dependent covariate to assess whether associations between natriuretic peptide levels and heart failure were mediated by an increased risk of myocardial infarction. Similarly, in the atrial-fibrillation analyses, we included a time-dependent covariate for the interim development of either myocardial infarction or heart failure, and in the analyses of stroke or transient ischemic attack, we adjusted for interim atrial fibrillation. In addition, we repeated the heart-failure analyses in a subgroup of participants without myocardial infarction at base line.

We repeated the multivariable analyses with adjustment for echocardiographically determined left atrial diameter, left ventricular mass, and ventricular systolic dysfunction. Left ventricular mass was calculated according to the formula of the American Society of Echocardiography.[26] Left ventricular systolic dysfunction was defined as a qualitative reduction in the ejection fraction or fractional shortening of less than 0.29.[5]

We examined whether the relations of natriuretic peptide levels to the risk of events varied according to age, sex, body-mass index, or hypertension status by incorporating interaction terms in multivariable models with log-transformed natriuretic peptide values as predictor variables. We determined which peptide was more strongly associated with each outcome by examining which one could be entered first in stepwise multivariable regression models.

All analyses were performed with the use of SAS software (version 6.12).[27] A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

BASE-LINE CHARACTERISTICS

Base-line characteristics of the participants are shown in Table 1. Findings on physical examination, such as a third heart sound or elevated jugular venous pressure, were rare, occurring in 0.1 percent and 0.2 percent of the sample, respectively. Median and 80th percentile plasma natriuretic peptide values were higher in women than in men. Only 2.2 percent of men and 1.5 percent of women had B-type natriuretic peptide levels exceeding 80 pg per milliliter.

INCIDENCE OF DEATH OR CARDIOVASCULAR EVENTS

Table 2 shows the incidence of the various outcomes during a mean follow-up of 5.2 years. A total of 119 participants died, and 79 had a first cardiovascular event. The incidence rates of death, major cardiovascular events, heart failure, atrial fibrillation, and stroke or transient ischemic attack rose with increasing plasma natriuretic peptide levels. Figure 1 shows the cumulative incidence of death and of heart failure according to the level of B-type natriuretic peptide.

MULTIVARIATE ANALYSIS OF OUTCOMES

After adjustment for clinical risk factors, increasing plasma natriuretic peptide levels were associated with an elevated risk of death (an increase of 27 percent for B-type natriuretic peptide and 41 percent for N-terminal pro–atrial natriuretic peptide for each increment of 1 SD in log peptide values) (Tables 3 and 4). Values above the 80th percentile were associated with an increase in the risk of death of 62 percent and 76 percent, respectively. There was a

Table 1. Base-Line Characteristics.*

Characteristic	Men (N=1562)	Women (N=1784)
Age (yr)	59±10	58±10
Hypertension (%)	45	38
Diabetes (%)	12	8
Current cigarette smoking (%)	14	16
Serum cholesterol (mg/dl)		
Total	199±37	212±38
High-density lipoprotein	44±12	58±16
Body-mass index	28.6±4.4	27.3±5.7
Valvular heart disease (%)†	3	2
Prior myocardial infarction (%)	7	1
Electrocardiographic findings (%)		
Left atrial enlargement	3	1
Left ventricular hypertrophy‡	3	1
Use of beta-blockers (%)	14	11
Use of ACE inhibitors (%)	14	9
Plasma B-type natriuretic peptide		
Median (pg/ml)	6.2	10.0
80th Percentile (pg/ml)§	20.0	23.3
Lowest third		
Values (pg/ml)	≤4.0	≤5.9
No. of subjects	592¶	599
Middle third		
Values (pg/ml)	4.1–12.7	6.0–15.7
No. of subjects	485	588
Highest third		
Values (pg/ml)	≥12.8	≥15.8
No. of subjects	485	597
Plasma N-terminal pro–atrial natriuretic peptide		
Median (pmol/liter)	286	351
80th Percentile (pmol/liter)§	497	541
Lowest third		
Values (pmol/liter)	≤223	≤286
No. of subjects	518	594
Middle third		
Values (pmol/liter)	224–369	287–432
No. of subjects	525	596
Highest third		
Values (pmol/liter)	≥370	≥433
No. of subjects	519	594

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Valvular heart disease was defined by the presence of a systolic murmur of grade 3/6 or greater or any diastolic murmur.

‡ Left ventricular hypertrophy was defined by increased voltage and repolarization abnormalities on electrocardiography.

§ The 80th percentile values were the thresholds used to predict the risk of cardiovascular events.

¶ This subgroup includes more than a third of the men because 38 percent of men had plasma B-type natriuretic peptide levels of no more than 4 pg per milliliter, the lower limit of detection of the assay. Twenty-five percent of women had plasma B-type natriuretic peptide levels of 4 pg per milliliter or less.

significant trend toward an increased risk of death across all three categories (lowest third, middle third, and highest third) of N-terminal pro–atrial natriuretic peptide levels (adjusted hazard ratio, 1.44 per category increment; P=0.01) but not of B-type natriuretic peptide levels. Plasma B-type natriuretic peptide levels and N-terminal pro–atrial natriuretic peptide levels were also associated with an elevated risk of a first major cardiovascular event (an increase of 28 percent and 30 percent, respectively, for each 1 SD increment in log peptide values) (Tables 3 and 4). B-type natriuretic peptide levels above the 80th percentile were associated with a 76 percent increase in risk. There was no significant trend toward increasing cardiovascular risk across the three categories of peptide values.

The levels of B-type natriuretic peptide and N-terminal pro–atrial natriuretic peptide strongly predicted the risk of heart failure, with an increase in the adjusted risk of 77 percent and 94 percent, respectively, per 1 SD increment in log peptide values (Tables 3 and 4). Peptide levels above the 80th percentile were associated with an increase in risk by a factor of three and five, respectively. There were significant trends toward an increasing risk of heart failure across the three categories of B-type natriuretic peptide values (adjusted hazard ratio, 1.99 per category increment; P=0.009) and N-terminal pro–atrial natriuretic peptide values (adjusted hazard ratio, 1.93 per category increment; P=0.02). Results were similar in analyses that adjusted for the occurrence of interim myocardial infarction (adjusted hazard ratios, 1.59 per 1 SD increment in log B-type natriuretic peptide values and 1.82 per 1 SD increment in log N-terminal pro–atrial natriuretic peptide values; P<0.003 for both comparisons) and in analyses restricted to participants without prior myocardial infarction (adjusted hazard ratios, 2.02 and 2.10, respectively; P<0.001 for both comparisons). The exclusion of participants with B-type natriuretic peptide levels of more than 80 pg per milliliter did not attenuate the findings (adjusted hazard ratio, 1.90 per 1 SD increment in log B-type natriuretic peptide values; P<0.001).

Plasma natriuretic peptide levels were also associated with the risk of atrial fibrillation (an increase in risk of 66 to 72 percent per SD increment in log peptide values) (Tables 3 and 4). Values of either peptide that were above the 80th percentile were associated with a doubling of the risk. Trends across the three categories of peptide values were significant for both B-type natriuretic peptide (adjusted hazard

Table 2. Crude Incidence Rates According to the Plasma Natriuretic Peptide Level.*

Outcome	No. of Events/Total No. at Risk	B-Type Natriuretic Peptide Level			N-Terminal Pro–Atrial Natriuretic Peptide Level		
		Lowest Third	Middle Third	Highest Third	Lowest Third	Middle Third	Highest Third
		rate/1000 person-years (95 percent confidence interval)					
Death	119/3346	4.4 (0.7–8.2)	4.4 (0.4–8.4)	11.9 (5.5–18.4)	2.7 (0.0–5.8)	5.1 (1.0–9.3)	12.8 (6.2–19.5)
First major cardiovascular event	79/3036	3.8 (0.2–7.3)	3.8 (0.0–7.6)	8.0 (2.2–13.8)	2.7 (0.0–5.8)	6.1 (1.4–10.8)	6.6 (1.4–11.9)
Heart failure	41/3346	0.7 (0.0–2.1)	1.4 (0.0–3.7)	5.2 (0.9–9.5)	0.9 (0.0–2.6)	1.0 (0.0–2.9)	5.3 (1.1–9.6)
Atrial fibrillation	68/3260	1.7 (0.0–4.0)	2.7 (0.0–5.8)	8.3 (3.7–13.8)	1.5 (0.0–3.9)	3.3 (0.0–6.7)	7.6 (2.3–12.8)
Stroke or transient ischemic attack	53/3276	1.3 (0.0–3.4)	2.0 (0.0–4.6)	6.4 (1.5–11.2)	1.2 (0.0–3.3)	3.1 (0.0–6.4)	5.2 (0.9–9.5)
Coronary heart disease events	85/3106	5.1 (1.0–9.2)	3.4 (0.0–7.0)	7.7 (2.1–13.4)	3.5 (0.0–7.0)	5.7 (1.2–10.2)	7.0 (1.7–12.3)

* Differences in the numbers of subjects at risk are due to the exclusion of subjects who previously had the specified event (i.e., those with prevalent disease). The proportions of events that occurred among women were as follows: death, 34 percent; first major cardiovascular event, 44 percent; heart failure, 37 percent; atrial fibrillation, 41 percent; stroke or transient ischemic attack, 45 percent; and coronary heart disease, 47 percent.

ratio, 1.71 per category increment; P=0.004) and N-terminal pro–atrial natriuretic peptide (adjusted hazard ratio, 1.46 per increment; P=0.047). In analyses adjusting for the occurrence of interim myocardial infarction and heart failure, the hazard ratio remained significant: 1.49 per 1 SD increment in log B-type natriuretic peptide values (P=0.001) and 1.59 per 1 SD increment in log N-terminal pro–atrial natriuretic peptide values (P=0.002).

Plasma levels of B-type natriuretic peptide and N-terminal pro–atrial natriuretic peptide also predicted the risk of stroke or transient ischemic attack (adjusted hazard ratios of 1.53 and 1.37, respectively, per 1 SD increment in log peptide values) (Tables 3 and 4). Values above the 80th percentile were associated with a doubling of the risk. There was a significant trend across the three categories of B-type natriuretic peptide levels (adjusted hazard ratio, 1.71 per category increment; P=0.01) but not of N-terminal pro–atrial natriuretic peptide levels (P=0.27). These results were unchanged after adjustment for the occurrence of interim atrial fibrillation (data not shown). In contrast to other cardiovascular events, the risk of coronary heart disease was not associated with plasma natriuretic peptide levels (Tables 3 and 4).

SECONDARY ANALYSES

Additional analyses were performed to investigate whether natriuretic peptide levels predicted the risk of events because of their association with increased left ventricular mass, left atrial diameter, or left ventricular systolic dysfunction. Adjustment for these three echocardiographic variables (in addition to the clinical covariates) attenuated the association between log B-type natriuretic peptide values and death (P=0.29), log B-type natriuretic peptide values and first major cardiovascular events (P=0.25), and log N-terminal pro–atrial natriuretic peptide values and first major cardiovascular events (P=0.32). However, both peptides continued to be significant predictors of the risk of heart failure (adjusted hazard ratios, 1.56 per 1 SD increment in log B-type natriuretic peptide values and 1.95 per 1 SD increment in log N-terminal pro–atrial natriuretic peptide values; P<0.02 for both comparisons) and atrial fibrillation (adjusted hazard ratios, 1.43 per 1 SD increment in log B-type natriuretic peptide values and 1.41 per 1 SD increment in log N-terminal pro–atrial natriuretic peptide values; both P<0.03). The association between log B-type natriuretic peptide values and the risk of stroke or a transient ischemic attack also remained significant

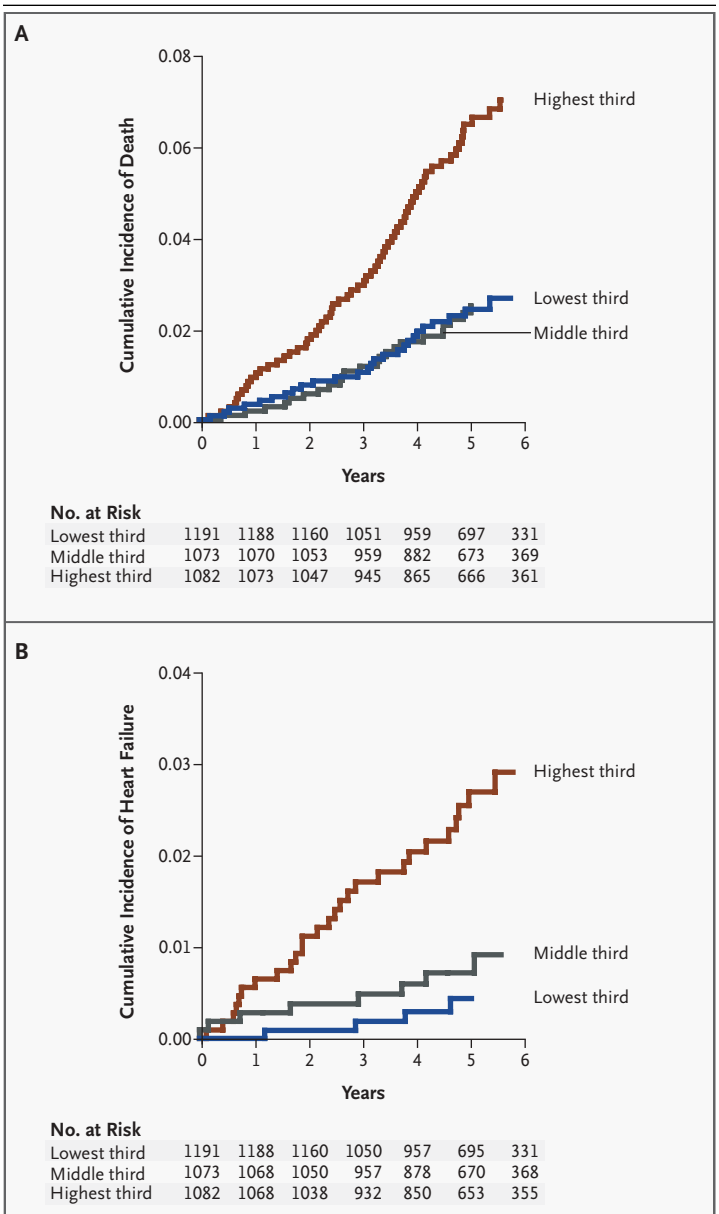

Figure 1. Cumulative Incidence of Death (Panel A) and Heart Failure (Panel B), According to the Plasma B-Type Natriuretic Peptide Level at Base Line.

The lowest third, middle third, and highest third of plasma B-type natriuretic peptide levels were 4.0 pg per milliliter or less, 4.1 to 12.7 pg per milliliter, and 12.8 pg per milliliter or more, respectively, for men and 5.9 pg per milliliter or less, 6.0 to 15.7 pg per milliliter, and 15.8 pg per milliliter or more, respectively, for women. Follow-up results are truncated after six years.

(adjusted hazard ratio, 1.64 per 1 SD increment; P=0.004), as did the association between log N-terminal pro–atrial natriuretic peptide values and the risk of death (adjusted hazard ratio, 1.32 per 1 SD increment; P=0.02).

The association between natriuretic peptide levels and outcomes did not vary according to age, sex, body-mass index, or the presence or absence of hypertension. Additional analyses adjusting for systolic blood pressure, diastolic blood pressure, and the use of antihypertensive therapy (instead of the presence of hypertension) yielded results similar to those of the main analyses.

Plasma levels of B-type natriuretic peptide and N-terminal pro–atrial natriuretic peptide were highly correlated (Spearman coefficient, 0.67; P<0.001). In stepwise models adjusting for known risk factors, the log B-type natriuretic peptide value was selected before the log N-terminal pro–atrial natriuretic peptide value for all outcomes except death. For every model, the presence of either peptide prevented the other peptide from being included, when a P value of less than 0.05 was the criterion for inclusion.

DISCUSSION

We found that plasma natriuretic peptide levels predicted a wide range of cardiovascular outcomes and provided information that was incremental to that obtained from established risk factors. The relation was strongest for heart failure and atrial fibrillation, but we also observed important associations between plasma natriuretic peptide levels and the risk of death from any cause, stroke or transient ischemic attack, and first major cardiovascular events. Although our results were consistent for both natriuretic peptides, B-type natriuretic peptide levels outperformed N-terminal pro–atrial natriuretic peptide levels with respect to most outcomes.

Several inferences can be drawn from our data. First, a single determination of plasma natriuretic peptide levels provides prognostic information in unselected members of the community. Second, plasma natriuretic peptide levels may be elevated before the onset of clinically apparent cardiovascular disease, a critical attribute if these assays are to be used in broader populations.[28] Third, plasma natriuretic peptide values within a range currently regarded as normal may be associated with an increased risk of adverse outcomes. The prespecified B-type natriuretic peptide thresholds used to predict cardiovascular events in this cohort (80th percentile values of 20.0 pg per milliliter for men and 23.3 pg per milliliter for women) are well below contemporary thresholds used for the diagnosis of heart failure (80 to 100 pg per milliliter).[8,29] It is un-

Table 3. Multivariate Analysis of the Association of Plasma B-Type Natriuretic Peptide (BNP) Levels and Outcomes.*

Outcome	Adjusted Hazard Ratio per 1 SD Increment in Log BNP Values (95% CI)	P Value	Adjusted Hazard Ratio for BNP Values above 80th Percentile (95% CI)	P Value
Death†	1.27 (1.06–1.52)	0.009	1.62 (1.08–2.42)	0.02
First major cardiovascular event‡	1.28 (1.03–1.59)	0.03	1.76 (1.06–2.92)	0.03
Heart failure‡§	1.77 (1.31–2.41)	<0.001	3.07 (1.51–6.26)	0.002
Atrial fibrillation§	1.66 (1.30–2.11)	<0.001	1.91 (1.13–3.25)	0.02
Stroke or transient ischemic attack†‡	1.53 (1.16–2.02)	0.002	1.99 (1.09–3.62)	0.02
Coronary heart disease events	1.10 (0.89–1.37)	0.37	1.30 (0.79–2.15)	0.30

* For all outcomes, the hazard ratios were adjusted for age, sex, presence or absence of hypertension, ratio of total to high-density lipoprotein cholesterol, smoking status, presence or absence of diabetes mellitus, body-mass index, and serum creatinine level. CI denotes confidence interval.
† The analysis was also adjusted for the presence or absence of prevalent cardiovascular disease.
‡ The analysis was also adjusted for the presence or absence of prevalent atrial fibrillation.
§ The analysis was also adjusted for the presence or absence of valvular disease and prevalent myocardial infarction.

Table 4. Multivariate Analysis of the Association of Plasma N-Terminal Pro–Atrial Natriuretic Peptide (N-ANP) Levels and Outcomes.*

Outcome	Adjusted Hazard Ratio per 1 SD Increment in Log N-ANP Values (95% CI)	P Value	Adjusted Hazard Ratio for N-ANP Values above 80th Percentile (95% CI)	P Value
Death†	1.41 (1.14–1.74)	0.001	1.76 (1.15–2.68)	0.009
First major cardiovascular event‡	1.30 (1.02–1.67)	0.04	1.52 (0.89–2.59)	0.12
Heart failure‡§	1.94 (1.37–2.75)	<0.001	5.02 (2.32–10.85)	<0.001
Atrial fibrillation§	1.72 (1.30–2.28)	<0.001	2.09 (1.21–3.62)	0.008
Stroke or transient ischemic attack†‡	1.37 (0.99–1.89)	0.06	2.08 (1.11–3.89)	0.02
Coronary heart disease events	1.12 (0.88–1.42)	0.35	0.87 (0.50–1.51)	0.62

* For all outcomes, the hazard ratios were adjusted for age, sex, presence or absence of hypertension, ratio of total to high-density lipoprotein cholesterol, smoking status, presence or absence of diabetes mellitus, body-mass index, and serum creatinine level. CI denotes confidence interval.
† The analysis was also adjusted for the presence or absence of prevalent cardiovascular disease.
‡ The analysis was also adjusted for the presence or absence of prevalent atrial fibrillation.
§ The analysis was also adjusted for the presence or absence of valvular disease and prevalent myocardial infarction.

likely that our results were driven by extreme B-type natriuretic peptide values, because less than 2 percent of the participants had levels above 80 pg per milliliter.

Studies of patients with symptomatic cardiac disease indicate that natriuretic peptide levels are markers of increased atrial or ventricular strain, typically from pressure or volume overload.[30,31] In ambulatory persons, elevated natriuretic peptides probably reflect similar processes, but manifestations of this strain may be subtle, and the underlying causes less apparent. Although it is difficult to measure strain or filling pressures directly in an epidemiologic setting, echocardiographic features related to abnormal loading conditions (such as left ventricular mass and systolic dysfunction) correlate with natriuretic peptide levels,[5,6] even after adjustment for other cardiovascular risk factors.[6,32] Accordingly, adjustment for echocardiographic variables appears to attenuate the association between peptide levels and most outcomes.

We found that higher natriuretic peptide levels

predicted the risk of heart failure and atrial fibrillation, even after accounting for left ventricular mass and systolic dysfunction. This observation may reflect a dissociation between echocardiographic findings and filling pressures in some persons, particularly in the presence of diastolic dysfunction.[7] Additional mechanisms may also be important, such as up-regulation of the natriuretic peptide axis in the setting of subclinical vascular disease. The natriuretic peptides have a fundamental role in vascular function and remodeling, by potentiating the effects of nitric oxide,[33] inhibiting lipid insudation in the vascular wall,[34] and increasing parasympathetic tone.[35]

Prior studies relating natriuretic peptide levels to the risk of heart failure and atrial fibrillation have been cross-sectional[36,37] or restricted to select samples.[10,38] Stroke was one of our prespecified outcomes, because an association between polymorphisms of the gene for atrial natriuretic peptide and the risk of stroke has been noted.[39,40] We found that plasma natriuretic peptide levels predict the risk of stroke.

We did not find an association between baseline plasma natriuretic peptide levels and the risk of coronary heart disease. Some studies have shown a correlation between plasma natriuretic peptide levels and myocardial infarction in patients with acute coronary syndromes, but these associations have been relatively weak.[9,10,41,42] Data from patients with acute coronary syndromes may not apply to ambulatory persons.

The strengths of our investigation include the large, community-based sample, the use of high-sensitivity assays, and the use of continual surveillance for multiple outcomes according to standardized criteria. Nevertheless, our findings should be confirmed in other cohorts. Also, since the Framingham Study cohort is predominantly white, our results may not be generalizable to non-whites. We had limited statistical power to perform separate analyses of high-risk subgroups, such as persons with diabetes, or to examine the risk of death from cardiovascular causes separately from the risk of death from any cause.

Although our natriuretic peptide cutoff points were derived from a community-based sample, it is important to recognize that cutoff points vary among assays.[20] Also, the risks associated with increasing natriuretic peptide levels may be continuous rather than restricted to values above a threshold. We had limited statistical power to evaluate a threshold effect. Studies with longer-term follow-up may provide further insight.

We report the prospective association between plasma natriuretic peptide levels and a range of cardiovascular outcomes in a community-based cohort. The prognostic information provided by plasma natriuretic peptide levels is incremental to that provided by traditional cardiovascular risk factors. Although echocardiography may provide more specific information regarding cardiac structure, its high cost makes it an impractical screening tool in asymptomatic persons.[43] Furthermore, measurement of plasma natriuretic peptide levels and echocardiography may be complementary tests in some circumstances, because peptide levels may be a marker of elevated filling pressures, which may otherwise be detectable only with invasive tests.

Although these data raise the possibility that measurement of natriuretic peptides may aid in the early detection of cardiovascular disease, additional investigations are needed to validate our results and to evaluate the screening characteristics of these peptides, including comparisons with markers that were not investigated in our study (e.g., C-reactive protein). Further studies are also warranted to determine whether a finding of elevated plasma natriuretic peptide levels in asymptomatic persons should trigger further diagnostic tests, such as echocardiography.

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