Plasma N-terminal fragments of natriuretic propeptides predict the risk of cardiovascular events and mortality in middle-aged men

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Received 15 August 2005; revised 20 February 2006; accepted 23 March 2006; online publish-ahead-of-print 18 April 2006

Aims The prognostic significance of N-terminal pro-A-type (NT-proANP) and pro-B-type natriuretic peptides (NT-proBNP) is not well documented in population-based prospective studies. We, therefore, studied if both NT-proANP and NT-proBNP are predictive for overall death, cardiovascular events, and atrial fibrillation (AF) among middle-aged men without heart failure or AF at baseline.

Methods and results Plasma NT-proANP and NT-proBNP were measured in a representative population-based sample of 905 men (age 46–65 years) from eastern Finland. There were 110 deaths [58 cardiovascular and 40 coronary heart disease (CHD)] and 59 cases of AF during a follow-up of 10 years. The multivariable adjusted risk for overall was 1.35-fold (95% CI 1.15–1.57) and 1.52-fold (95% CI 1.21–1.91) for CHD death for each SD (160.8 pmol/L) increment in NT-proANP. The respective risks were 1.26-fold (95% CI 1.12–1.42) and 1.44-fold (95% CI 1.22–1.60) for each SD (58.9 pmol/L) increment in NT-proBNP. The adjusted risks for future AF were 1.46 (P < 0.001) and 1.72-fold (P < 0.001) for each SD increment in NT-proANP and NT-proBNP, respectively.

Conclusion The main finding of the present study is that NT-proANP and NT-proBNP are strong predictors of death from cardiovascular and other causes including AF. These natriuretic peptides add to the prognostic value of conventional risk factors and provide a non-invasive measure for identifying men with high risk of death and its co-morbidities.

KEYWORDS Atrial fibrillation; Coronary heart disease; Mortality; Natriuretic peptides; Population study

Natriuretic peptides are typically recommended for use in diagnosis of heart failure, whereas the prognostic significance of A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) is not well known in general populations without symptoms of cardiac dysfunction. Previous studies indicate that natriuretic peptides are markers of pressure or volume overload in left atrium and ventricle in patients with symptomatic cardiac disease and they play a key part in circulatory homeostasis. In addition, natriuretic peptides may differ from other biomarkers such as troponin and C-reactive protein, as natriuretic peptides are counter-regulated hormones that play an active role in response to myocardial stretch and ischaemic injury.

A few studies have suggested that elevated natriuretic peptides may be related to the risk of death among elderly subjects from urban population or apparently asymptomatic subjects. The levels of BNP and N-terminal fragment of proBNP (NT-proBNP) may reflect the severity of myocardial ischaemia, even when myocardial necrosis has not yet occurred. This is in accordance with studies showing that natriuretic peptides are associated with poor prognosis without elevation in markers of myocardial necrosis in acute coronary syndromes. These findings suggest that ischaemia may induce the release of natriuretic peptides. B-type natriuretic peptide and NT-proBNP have been shown to provide prognostic information in patients with acute coronary syndromes.

However, the prognostic value of natriuretic peptides with respect to the risk of acute coronary syndromes, atrial fibrillation (AF), heart failure, coronary heart disease (CHD) death and overall mortality is recently reported in two prospective cohort studies. These results were based mainly on older individuals, but few data is available on the predictive value of both NT-proBNP and N-terminal fragments of proA-type (NT-proANP) in middle-aged men.

Prospective population studies may provide useful information regarding the prognostic value of natriuretic peptides.
peptides as compared with conventional risk factors and C-reactive protein. Thus, we investigated the prognostic value of the NT-proANP and NT-proBNP with regard to the risk of acute coronary syndromes, cardiovascular death, CHD death, overall death including its co-morbidities such as AF and heart failure in a population-based sample of men. We also compared if NT-proANP and NT-proBNP provides additional prognostic value over C-reactive protein.

Methods

Subjects

The analyses were carried out with the participants of the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), a longitudinal population-based study designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes. The study population is a representative sample of men living in the city of Kuopio and its surrounding rural communities, who were 46–65 years of age at baseline. The baseline examinations were performed between 1991 and 1993. Of 1229 potentially eligible and randomly selected men, 1038 (83%) volunteered to participate at baseline examinations. Of the invited men, 107 declined, 52 could not participate because of death, severe illness, or relocation, and 32 could not be contacted. The 984 participants with no missing data were included for the present study. Men with a history of heart failure (n = 69) or AF (n = 10) were excluded leaving 905 men in the statistical analysis. The KIHD was approved by the Research Ethics Committee of the University of Kuopio, and each participant gave written informed consent.

Assessment of N-terminal fragments of natriuretic peptides

At the beginning of the study, samples for measuring plasma concentrations of natriuretic propeptides were collected into tubes at room temperature and then frozen. The plasma concentrations of NT-proANP and NT-proBNP were determined with radioimmunoassays utilizing antisera directed to NT-proANP16–79 and NT-proBNP10–29, as described in detail previously.18 The sensitivities of the assays were 60 and 40 pmol/L plasma, respectively.

Assessment of other risk factors

C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-reactive Protein Assay, DPC, Los Angeles, USA). This C-reactive protein assay has been standardized against the WHO International Reference Standard for C-reactive protein immunomassay. Blood pressure was measured by an experienced nurse using a random-zero sphygmomanometer (cuff size 14 x 54 cm, Hawksley, Lancing, UK) after 5 and 10 min of rest in a seated position in a quiet room between 8:00 a.m. and 10:00 a.m.19 The collection of blood specimens, measurement of fasting levels of serum lipids and creatinine, assessment of smoking, and presence of diabetes mellitus are described elsewhere.10,21 The life-long exposure to smoking (cigarette pack-years) was estimated as the product of the number of smoking years the number of tobacco products smoked daily at the time of examination. Body mass index was computed as the ratio of weight (in kilograms) to the square of height (in meters). CHD was defined as having either a history of myocardial infarction (on the basis of standard criteria including characteristic symptoms with either typical ECG criteria or elevations of cardiac enzymes), angina pectoris on effort or the use of nitroglycerin for chest pain once a week or more frequently. Medical history, the use of medications, and family history of diseases were assessed using self-administered questionnaires. Information about medical history and the use of medications were checked during a medical examination. Family history of CHD was defined as CHD in parents or in the first degree relatives before the age of 55 in men and before the age of 65 in women. All the above mentioned covariates were measured at the same time as the N-terminal fragments of natriuretic propeptides.

Ascertainment of follow-up events

Every resident of Finland has a unique personal identifier that is used in registers. Deaths were ascertained by linkage with the national causes of Death Register using the personal identifiers. There were no losses to follow-up. All deaths that occurred between January 1991 and December 2002 were included. Cardiovascular causes of deaths, AF, and heart failure were coded according to the Ninth International Classification of Disease (ICD) codes (numbers 390–459) and the Tenth ICD codes (numbers 100–99). The subjects were hospitalized due to AF or had AF when hospitalized due to other reasons.

Each suspected coronary event (ICD-9 codes 410–414 and ICD-10 codes I20–I25) was classified into: (i) a definite acute myocardial infarction; (ii) a probable acute myocardial infarction; (iii) a typical acute chest pain episode of more than 20 min indicating CHD, which were considered as the endpoint. The coronary register data were annually cross-checked with the data obtained from the computerized national hospital discharge and death registers. The collection of data and the diagnostic classification of non-fatal and fatal coronary events from the beginning of 1991 to the end of 2002 were prospectively obtained by computer linkage with the national hospital discharge and death certificate registers according to the multinational WHO MONICA (MONItoring of Trends and Determinants in Cardiovascular Diseases) project. The first fatal or non-fatal event was coded as an acute coronary event.

Statistical analysis

Descriptive data are presented as mean and standard deviations for continuous data and percentages for categorical data. The associations of plasma NT-proANP and NT-proBNP with the risk of death, AF, acute coronary events, and heart failure were analysed using risk factor-adjusted Cox proportional hazards models. These analyses were restricted to participants who had never had AF or heart failure. The correlations between plasma natriuretic peptides and risk factors were analysed using Pearson’s correlation test.

To demonstrate the predictive value of plasma NT-proANP and NT-proBNP were separately entered into a forced Cox model including previously established cardiovascular risk factors (age, smoking, diabetes, systolic blood pressure, family history of coronary disease, presence or absence of CHD, body mass index, serum low-density lipoprotein (LDL) and high-density lipoprotein (HDL)-cholesterol, C-reactive protein, serum creatinine), and the use of anti-hypertensive medications. We analysed plasma NT-proANP and NT-proBNP as continuous (per SD change) and categorical variable. In categorical analyses, we used threshold corresponding 90th percentile values of plasma natriuretic peptides.

The risk of AF was also analysed as categorical variable when natriuretic peptides were classified in quartiles. In the analysis of AF, the subjects were divided according to the distribution of NT-proANP and NT-proBNP observed in the sample. Relative hazards, adjusted for risk factors, were estimated as anti-logarithms of coefficients for independent variables. Their confidence intervals were estimated under the assumption of asymptotic normality of the estimates. The cumulative risk of AF was calculated using the Kaplan-Meier method. The assumption of proportional hazards was examined by plotting the hazard rates against the follow-up time in the four exposure categories (Figure 1A). A value of P < 0.05 was considered significant. All statistical analyses were performed using SPSS 11.5 for Windows.
Results

Baseline characteristics

The mean age of the subjects was 55.8 years (range 46.4–65.4 years). Median values for NT-proANP and NT-proBNP were 231 and 56 pmol/L, and 1.39 mmol/L for C-reactive protein. Other characteristics of the subjects are shown in Table 1. The prevalence of cerebrovascular stroke, hypertension, and CHD were 2.4, 30.4, and 18.6%, respectively.

NT-proANP had a weak positive correlation with age ($r = 0.389$, $P < 0.001$) and C-reactive protein ($r = 0.126$, $P < 0.001$), and NT-proBNP correlated weakly with age ($r = 0.181$, $P < 0.001$) and C-reactive protein ($r = 0.139$, $P < 0.001$).

Follow-up events

A total of 110 deaths occurred during the median follow-up of 9.8 years (range 0.1–11.8 years), of which half of these deaths ($n = 58$) were due to cardiovascular causes, 41 were due to CHD, and 52 deaths were due to non-cardiovascular reasons. There were 105 acute coronary events, 59 cases for AF, and 19 cases for heart failure.

The associated risk factors

The strongest risk predictors for death from any cause were age (relative hazard 1.05 per year, 95% CI 1.02–1.09, $P < 0.001$), smoking (relative hazard 2.60, 95% CI 1.75–3.86, $P < 0.001$), systolic blood pressure (relative hazard 1.15 per 10 mmHg, 95% CI 1.04–1.29, $P = 0.007$), the use of anti-hypertensive medications (relative hazard 1.75, 95% CI 1.14–2.72, $P = 0.018$), and C-reactive protein (relative hazard 1.02 per 1 mmol/L, 95% CI 1.01–1.04, $P = 0.031$) when also diabetes, family history of CHD, presence or absence of CHD, body mass index, serum LDL- and HDL-cholesterol, and serum creatinine level were taken into account.

NT-proANP, NT-proBNP, and mortality

The age-adjusted risk was 1.35-fold (95% CI 1.17–1.56, $P < 0.001$) for overall death and 1.53-fold (95% CI 1.26–1.86, $P < 0.001$) for CHD death for each SD (160.8 pmol/L) increment in NT-proANP. The respective age-adjusted risks were 1.29 (95% CI 1.16–1.43, $P < 0.001$) for overall death and 1.43 (95% CI 1.26–1.63, $P < 0.001$) for CHD death for each SD (58.9 pmol/L) increment in NT-proBNP. When these propeptides were further adjusted with smoking, diabetes, systolic blood pressure, family history of CHD, presence or absence of CHD, body mass index, serum LDL- and HDL-cholesterol, C-reactive protein, serum creatinine, and the use of anti-hypertensive medications, the risk of overall death and CHD death were 1.35 and 1.52 for NT-proANP, and 1.26 and 1.44 for NT-proBNP, respectively (Table 2). There was no association between NT-proANP and NT-proBNP and non-cardiovascular death.

In the age-adjusted models, C-reactive protein was not related to an increased risk of cardiovascular death, whereas NT-proANP (hazard ratio 1.43 per SD, 95% CI 1.19–1.72, $P < 0.001$) and NT-proBNP (hazard ratio 1.38 per SD, 95% CI 1.19–1.60, $P < 0.001$) were related to the risk of cardiovascular death. Both C-reactive protein (hazard ratio 1.07 per SD (3.75 mmol/L), 95% CI 1.01–1.13, $P = 0.022$) and NT-proANP (hazard ratio 1.29 per SD, 95% CI 1.12–1.49, $P = 0.001$) were related to the risk of all-cause death, respectively. On the other hand, when both C-reactive protein and NT-proBNP with age were included in the model, C-reactive protein was not a significant predictor of death ($P = 0.069$), whereas NT-proBNP was predictive (hazard ratio 1.23 per SD, 95% CI 1.10–1.38, $P < 0.001$). Furthermore, C-reactive protein was not predictive for cardiovascular death in these multi-variable models when NT-proANP or NT-proBNP was included in the model. However, C-reactive protein was related to increased risk of overall death per 3.75 mmol/L (SD) increment when additionally adjusted for NT-proANP (hazard ratio 1.18 per SD, 95% CI 1.02–1.37, $P = 0.021$) or NT-proBNP

Figure 1  Multivariable adjusted cumulative curves for the risk of AF according to quartiles of N-terminal fragments of ANP and BNP: (A) quartiles for N-terminal proA-type natriuretic peptide were <167, 167–231, 232–329, and >329 pmol/L; (B) quartiles for N-terminal proB-type natriuretic peptide were: <40, 41–56, 57–89, and >89 pmol/L.
Table 1  Baseline demographic characteristics of the 905 men in the Kuopio Ischemic Heart Disease Risk Factor Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55.8±6.6</td>
<td>46.4–65.4</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4±3.5</td>
<td>19.5–41.8</td>
</tr>
<tr>
<td>Smoker (%) (n)</td>
<td>28.0 (253)</td>
<td></td>
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<tr>
<td>Cigarette pack-years of smokingb</td>
<td>7.6±15.7</td>
<td>0–135.0</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>76.4±111.7</td>
<td>0–972.0</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.1±16.6</td>
<td>97.0–204.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>88.9±9.9</td>
<td>60.0–127.0</td>
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<tr>
<td>Serum total cholesterol (mmol/L)</td>
<td>5.2±0.94</td>
<td>2.68–9.25</td>
</tr>
<tr>
<td>Serum LDL-cholesterol (mmol/L)</td>
<td>3.92±0.84</td>
<td>1.21–7.01</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mmol/L)</td>
<td>1.11±0.29</td>
<td>0.46–2.51</td>
</tr>
<tr>
<td>Plasma fibrinogen (g/L)</td>
<td>3.15±0.58</td>
<td>1.4–5.4</td>
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<tr>
<td>Serum creatinine (µmol/L)</td>
<td>90.4±13.4</td>
<td>28.0–214.0</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>3.30±3.75</td>
<td>0.11–95.70</td>
</tr>
<tr>
<td>Plasma NT-proANP (pmol/L)</td>
<td>269.32±160.78</td>
<td>26.0–1482.0</td>
</tr>
<tr>
<td>Median (pmol/L)</td>
<td>231.0</td>
<td></td>
</tr>
<tr>
<td>90th percentilec</td>
<td>455.0</td>
<td></td>
</tr>
<tr>
<td>Plasma NT-proBNP (pmol/L)</td>
<td>75.78±58.90</td>
<td>24.0–658.0</td>
</tr>
<tr>
<td>Median (pmol/L)</td>
<td>56.0</td>
<td></td>
</tr>
<tr>
<td>90th percentilec</td>
<td>133.0</td>
<td></td>
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</table>

Diagnosed diseases or family history of disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (%) (n)</td>
<td>18.6 (169)</td>
</tr>
<tr>
<td>Cerebrovascular stroke (%) (n)</td>
<td>2.4 (22)</td>
</tr>
<tr>
<td>Diabetes (%) (n)d</td>
<td>5.0 (45)</td>
</tr>
<tr>
<td>Claudication (%) (n)</td>
<td>30.4 (276)</td>
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<tr>
<td>Hypertension (%) (n)</td>
<td>2.4 (34)</td>
</tr>
<tr>
<td>Chronic bronchitis (%) (n)</td>
<td>4.9 (44)</td>
</tr>
<tr>
<td>Family history of CHD (%) (n)</td>
<td>53.0 (481)</td>
</tr>
<tr>
<td>Family history of hypertension (%) (n)</td>
<td>54.1 (491)</td>
</tr>
</tbody>
</table>

Regular use of medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prevalence (n)</th>
</tr>
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<tbody>
<tr>
<td>Anti-hypertensive medications (%) (n)</td>
<td>24.4 (222)</td>
</tr>
<tr>
<td>Medications for hypercholesterolaemia (%) (n)</td>
<td>6.2 (56)</td>
</tr>
<tr>
<td>β-blockers (%) (n)</td>
<td>10.1 (91)</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>9.5 (86)</td>
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</table>

*Plus–minus values are means ± SD.
bPack–years denote the life-long exposure to smoking which was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.
cThe 90th percentile values were the threshold used to predict the risk of outcomes.
dDiabetes was defined as fasting blood glucose ≥6.1 mmol/L or a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment.

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Table 2  Relative risks of main outcomes per 1 unit (SD) change in N-terminal fragments of NT-proANP and NT-proBNP in 905 men from eastern Finnish population study

<table>
<thead>
<tr>
<th>Outcome (no. of events)</th>
<th>Relative risk per 160.8 pmol/L increment in proANP</th>
<th>Relative risk per 59.9 pmol/L increment in proBNP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Risk ratio*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Death (110)</td>
<td>1.35</td>
<td>1.15–1.57</td>
</tr>
<tr>
<td>CVD death (58)</td>
<td>1.48</td>
<td>1.21–1.81</td>
</tr>
<tr>
<td>CHD death (40)</td>
<td>1.52</td>
<td>1.21–1.91</td>
</tr>
<tr>
<td>AF (59)</td>
<td>1.72</td>
<td>1.41–2.09</td>
</tr>
<tr>
<td>Heart failure (19)</td>
<td>1.76</td>
<td>1.24–2.48</td>
</tr>
</tbody>
</table>

*Adjusted for age, cigarette smoking, diabetes, systolic blood pressure, family history of CHD, presence or absence of CHD, body mass index, serum LDL- and HDL-cholesterol, C-reactive protein, serum creatinine level, and the use of anti-hypertensive medications.
(hazard ratio 1.17 per SD, 95% CI 1.01–1.34, \( P = 0.031 \)), respectively.

Among men with the highest 90th percentile of NT-proANP (>455.0 pmol/L) had a 1.98-fold (95% CI 1.18–3.32, \( P = 0.009 \)) risk of overall death and 2.11-fold (95% CI 1.07–4.19, \( P = 0.032 \)) risk of cardiovascular death after adjustment for risk factors. The respective risk among men above the highest 90th percentile of NT-proBNP (>133 pmol/L) were 2.01 (95% CI 1.23–3.29, \( P = 0.005 \)) and 2.30 (95% CI 1.23–4.23, \( P = 0.009 \)).

NT-proANP and NT-proBNP were associated with the risk of death in different risk groups, after adjustment for risk factors (Table 3). However, NT-proANP was not statistically significantly related to the risk of death among men with good lipid profile and low level of C-reactive protein, whereas NT-proBNP was not clearly predictive in men with low serum LDL-cholesterol levels. We found that the interaction between NT-proANP and serum LDL-cholesterol level with respect to death was statistically significant (\( P = 0.013 \)), whereas the interaction between NT-proBNP and lipid levels was not significant (\( P = 0.103 \)). Furthermore, the interaction between natriuretic peptides and CRP was not statistically significant.

**NT-proANP, NT-proBNP, and the risk of acute coronary events**

There was an association between one SD increment in NT-proBNP and the risk of acute coronary events (hazard ratio 1.19, 95% CI 1.05–1.36, \( P = 0.007 \)) when adjusted for age. After adjustment for other risk factors, the respective risk was 1.16 (95% CI 1.00–1.34, \( P = 0.056 \)). The age-adjusted risk per one SD increment in NT-proANP was 1.18 (95% CI 1.00–1.39, \( P = 0.055 \)), and after adjustment for other risk factors, the relationship was not statistically significant.

**NT-proANP, NT-proBNP, risk of AF, and heart failure**

One SD increment in NT-proBNP was related to 48% (hazard ratio 1.48, 95% CI 1.31–1.68, \( P < 0.001 \)) increased risk of AF and one SD increment in NT-proANP amounts to 67% (hazard ratio 1.67, 95% CI 1.40–1.99, \( P < 0.001 \)) increased risk. The multivariable adjusted risks for AF were 1.46-fold and 1.72-fold for each SD increment in NT-proBNP and NT-proANP, respectively (Table 2). Men above the highest 90th percentile of NT-proBNP and NT-proANP had a 3.22-fold (95% CI 1.79–5.80, \( P < 0.0001 \)) and 2.59-fold (95% CI 1.38–5.00, \( P < 0.0001 \)) risk of AF after adjustment for risk factors, respectively. The risk of AF according to quartiles of natriuretic propeptides are shown in Table 4. The cumulative curves for the quartiles of natriuretic propeptides diverge during the follow-up (Figure 1).

The association between NT-proANP, NT-proBNP, and the risk of heart failure was significant although only a few new heart failure cases were observed. The risk for heart failure was from 1.6 to 1.7 according to one SD change in natriuretic peptides (Table 2).

**Discussion**

The main conclusion from our population-based study of the NT-proANP and NT-proBNP is that associated mortality for middle-aged men has increased significantly with higher
levels of natriuretic peptides. On the basis of this study, NT-proANP and NT-proBNP add to the prognostic value of conventional risk factors and provide a clinical measure for identifying men with high risk of death and its co-morbidities. The predictive power of both NT-fragments of natriuretic propeptides was stronger than C-reactive protein which has emerged to be a novel risk marker for cardiovascular outcomes.

Our study indicates that NT-proANP can be considered at least as a strong risk predictor as NT-proBNP, although BNP and NT-proBNP are widely used in the diagnosis of heart failure in clinical practice. In those patients with intermediate pre-test probability of heart failure, BNP would have clarified the diagnosis of majority of cases. Many of these studies showing natriuretic peptides as risk markers are based on clinical populations including subjects who were referred due to various symptoms such as dyspnoea and chest discomfort. In this study, NT-proBNP provides prognostic information in middle-aged subjects with and without other risk factors. However, the significant prognostic value of NT-proANP with respect to overall death was not observed among subjects with low serum LDL-cholesterol level.

It is possible that elevated natriuretic peptides may be due to a sustained elevation in left ventricle filling pressure. The activation of neurohumoral system may be a unifying feature among patients at high risk for death after acute coronary syndrome. It has been shown that BNP levels increased among patients at high risk for death after acute coronary events is not independent from other known risk factors. The lack of an independent association between the natriuretic peptides may be explained by the fact that BNP and NT-proBNP level are not related to the formation of unstable plaque in the coronary arteries. However, the recent population-based study and clinical study among older subjects showed that NT-proBNP was even stronger risk marker for major cardiovascular events or death than C-reactive protein. We observed that both NT-proANP and NT-proBNP were stronger predictors for cardiovascular death when compared with C-reactive protein.

The strengths of this study include its prospective population-based design with reliable data on various causes of diseases as specific major outcomes that were prospectively ascertained by Finnish National Discharge and Death Registry using personal identification codes, supplemented with data on natriuretic peptides, health status, and risk factors. This study represents a sample of middle-aged male population from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases. Our study emphasizes the importance of N-terminal fragments of natriuretic peptides in relatively homogenous middle-aged male population from eastern Finland, but whether the same association between natriuretic peptides and mortality from cardiovascular causes exists in females and other races require further studies. However, in a recent study, the association between natriuretic peptides and outcomes did not vary according to sex.

The pathophysiological mechanisms and causality responsible for the independent association between natriuretic peptides and mortality and its comorbidities cannot be deduced from the present study. We cannot rule out the possibility that pre-existent ventricular dysfunction or hypertrophy and renal impairment is the cause of NT-proANP and NT-proBNP elevation and the relation to outcome. By adjusting for history of CHD and blood pressure, as well as serum creatinine with other established risk factors, we attempted to minimize this effect. Second, in the current study, existing cardiovascular diseases were uncommon and, thus they cannot explain alone the observed results regarding the increased risk of cardiovascular death related to the natriuretic peptides. Third, it may be that previous studies have identified natriuretic peptides to predict heart failure, cardiovascular diseases, and prognosis, although these are not focused on the role of natriuretic peptides in asymptomatic populations. One exception is the Framingham study, which has shown the predictive value of BNP and NT-proANP with respect to cardiovascular events and death. However, they did not observe the value of natriuretic peptides as a risk predictor for CHD, although natriuretic peptides were predictive for AF and heart failure. This is consistent with our population study showing that the relationship between natriuretic peptides and acute coronary events is not independent from other known risk factors. The lack of an independent association between the natriuretic peptides may be explained by the fact that BNP and NT-proBNP level are not related to the formation of unstable plaque in the coronary arteries. On the other hand, recent studies have shown that natriuretic peptides are powerful determinants of cardiovascular events in patients with acute coronary syndromes, stable CHD, and cerebrovascular disease. It is recently reported that NT-proBNP and C-reactive protein provided better risk stratification when compared with NT-proBNP alone in subjects with stable coronary artery disease indicating that the risk for cardiovascular diseases is partly involved by an inflammatory process. However, the recent population-based study and clinical study among older subjects showed that NT-proBNP was even stronger risk marker for major cardiovascular events or death than C-reactive protein. We observed that both NT-proANP and NT-proBNP were stronger predictors for cardiovascular death when compared with C-reactive protein.

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natriuretic peptides reflect functional status among population-based sample. On the practical point of view, main focus of this study was to identify men at high risk for death, AF, and heart failure, regardless of the cause. The usefulness of different treatment strategies for those with high and low concentrations of NT-proANP and NT-proBNP needs further studies, and this study does not show if subjects with elevated natriuretic peptides should be treated more aggressively as patients with hypertension, heart failure, and AF are normally treated. Furthermore, the availability of latest echocardiographic technology was limited at the time of baseline examinations. In this study, we have no data on echocardiographic variables from the same timepoint as natriuretic peptides although echocardiography was performed at baseline examination.

The current study provides evidence that the test for natriuretic peptides may augment the prognostic value of currently available tools, and may help in risk stratification for fatal cardiovascular outcomes. NT-proANP and NT-proBNP are non-traditional parameters that improve currently available tools, and may help in risk stratification for fatal cardiovascular events, AF, and heart failure in a population-based cohort.

Fundings/support
This study was supported by the grants from National Heart, Lung, and Blood Institute of the USA (grant HL44199), Washington, DC; the Academy of Finland and the Finnish Ministry of Education, Helsinki, Finland; City of Kuopio, Kuopio, Finland; Juho Vainio Foundation, Helsinki, Finland; Finnish Cultural Foundation of Northern Savo, Kuopio, Finland; Finnish Medical Foundation, Helsinki, Finland; Maud Kuistila Foundation, Helsinki, Finland; the Finnish Foundation for Cardiovascular Research, Helsinki, Finland, and the Sigrid Juselius Foundation, Helsinki, Finland.

Acknowledgements
We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health, University of Kuopio, Kuopio, Finland, for data collection in the study, and Helka Koisti and Ulla Weckström for laboratory analyses.

Conflict of interest: none declared.

References
18. Conte MS, de Lemos JA, Sorensen JP, Dibbattite PM, Hambrecht S, Omland T, Sabatine MS, Lauer MS, Maisel AS. NT-proBNP needs further studies, and this study does not show if subjects with elevated natriuretic peptides should be treated more aggressively as patients with hypertension, heart failure, and AF are normally treated. Furthermore, the availability of latest echocardiographic technology was limited at the time of baseline examinations. In this study, we have no data on echocardiographic variables from the same timepoint as natriuretic peptides although echocardiography was performed at baseline examination.

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