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N-terminal-proB-type natriuretic peptide predicts cardiovascular disease events in HIV-infected patients

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Abstract

Background—Cardiovascular disease (CVD) is increasing in HIV-infected patients. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a significant predictor of CVD in the general population. We aimed to quantify the risk of CVD events associated with NT-proBNP at baseline in the Strategies for Management of Anti-Retroviral Therapy study.

Methods—In a nested case–control study, NT-proBNP was measured at baseline in 186 patients who experienced a CVD event over an average of 2.8 years of follow-up and in 329 matched controls. Odds ratios (ORs) associated with baseline levels of NT-proBNP for CVD were estimated using conditional logistic regression.

Results—At baseline median NT-proBNP [interquartile range (IQR)] was 48.1 (18.5, 112.9) pg/ml in patients who developed a CVD event and 25.7 (12.4, 50.2) pg/ml in controls. The unadjusted OR for the highest versus the lowest quartile was 3.7 [95% confidence interval (CI) 2.1–6.5, $P < 0.0001$]. After adjustment for baseline covariates and CVD risk factors, OR was 2.8 (95% CI 1.4–5.6, $P = 0.003$); with additional adjustment for IL-6, high-sensitivity C-reactive protein and D-dimer, OR was 2.3 (95% CI 1.1–4.9, $P = 0.02$).

Conclusions—Higher levels of NT-proBNP are associated with increased risk of CVD in HIV patients after considering established CVD risk factors and markers for inflammation and thrombosis.

Keywords

AIDS; antiretroviral therapy; cardiovascular disease events; HIV; NT-proBNP; SMART

Introduction

Advances in management of HIV disease and antiretroviral therapy (ART) during the last decade have led to prolonged disease-free survival in a majority of individuals with HIV infection [1,2]. Cardiovascular disease (CVD) is now a leading cause of death among HIV-infected patients [3]. There is evidence that the rate of acute myocardial infarction (MI) in HIV-infected patients may be higher than in the general population even after adjustment for anthropometric factors, race, hypertension, diabetes and dyslipidemia [4]. The independent effect of HIV may be of a similar magnitude to that of established cardiovascular risk factors [5]. The aging of the HIV-infected population coupled with the risk of CVD associated with HIV, makes screening for CVD an important part of HIV management. Insufficient data currently exist to recommend a screening strategy different from that for non-HIV-infected patients [6].

In the Strategies for Management of Anti-Retroviral Therapy (SMART) study, episodic ART was associated with an excess risk of AIDS, all-cause mortality, and serious non-AIDS diseases compared to continuous ART [7]. Serious non-AIDS diseases were dominated by CVD. An analysis of stored specimens from SMART showed that high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and D-dimer were strongly related to all-cause mortality and that interrupting ART may further increase the risk of death by raising IL-6 and D-dimer levels [8].

In recent years, there has been a progressive extension of indications for measurement of natriuretic peptides in the diagnosis and prediction of CVD [9]. B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by ventricular myocytes during periods of increased ventricular stretch and wall tension. BNP plays an important role in the regulation of blood pressure, blood volume, and sodium balance. On secretion, the BNP precursor is split into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP). Measurement of circulating levels of BNP or NT-proBNP has been recommended in the diagnosis and prognosis of patients with symptoms of left-ventricular dysfunction and for risk stratification of patients with acute coronary syndromes [10–12].

Recently a systematic review and meta-analysis of 40 prospective studies indicated strong associations between circulating concentration of natriuretic peptides and CVD risk in general populations and in patients with stable vascular disease [13]. Natriuretic peptides have been studied in a limited number of HIV patients with left-ventricular dysfunction, myocarditis or pulmonary hypertension [14–16]. In a sample of participants from the Women's Interagency HIV Study (WIHS), an ongoing, multicenter study of natural history of HIV disease in women, it was shown that HIV-infected women had higher mean NT-proBNP levels compared to HIV-uninfected women, but that the differences were attributable to factors such as anemia, kidney disease, and hepatitis co-infection [17]. There are no studies on the prognostic value of natriuretic peptide levels in HIV-infected individuals. Therefore we carried out a nested case–control study to quantify the risk of CVD associated with elevated NT-proBNP within the SMART study.

Methods

SMART study design

Between January 2002 and January 2006, 5472 HIV-infected patients with a CD4⁺ cell count above 350 cells/ μ l were randomized to episodic ART (drug conservation) or continuous ART (viral suppression) [7]. Viral suppression patients taking ART at entry continued taking it, and those not taking it initiated ART after randomization. For the viral suppression group, available ART was to be used in an uninterrupted manner with the goal

of maximal and continuous suppression of HIV replication. The experimental drug conservation strategy entailed intermittent use of ART for periods defined by CD4⁺ cell count until January 2006, at which time the study participants were advised to re-introduce ART due to an increased risk of opportunistic disease and death [18]. All participants were followed until 11 July 2007 (study closure). Patients were asked to consent to storing blood for future research, and only samples for consenting patients were used. The SMART study was approved by the ethics committee of each clinical site and of the University of Minnesota.

Nested case–control study of cardiovascular outcomes

Criteria for CVD events, defined as coronary heart disease (CHD), atherosclerotic non-CHD (stroke and peripheral arterial disease), congestive heart failure (CHF) and CVD or unwitnessed death, have been previously described [19]. For CVD cases with a blood specimen available for analysis (186 patients) and for two controls ($n = 329$) (for some controls the sample was not sufficient to measure NT-proBNP) matched on country, age (within 5 years), sex, and approximate date of randomization (within 3 months), NT-proBNP was measured at baseline (study entry) on stored plasma. Blood specimens were collected in lavender top tubes containing EDTA anticoagulant. Specimens were maintained at room temperature until it was centrifuged. Centrifugation of the blood specimen took place within 4 h of collection at forces of 1200g at room temperature for 15 min. Plasma was transferred to 2.0-ml Sarstedt transport tubes and stored at -70°C .

NT-proBNP assays were performed by electrochemiluminescence (Elecsys proBNP; Roche Diagnostics GmbH, Mannheim, Germany). All samples were analyzed blinded to case and control status and to treatment group. As part of a separate investigation, two inflammatory markers hsCRP and IL-6, and D-dimer were measured on the same samples by the Laboratory for Clinical Biochemistry Research at the University of Vermont [8]. Plasma creatinine and estimated glomerular filtration rate (eGFR) were available in, respectively, 160 cases and 287 controls.

Statistical methods

Conditional logistic regression was used to study associations of baseline NT-proBNP levels with CVD. Selected analyses were also performed for nonfatal CHD events (defined as clinical and silent MI, coronary revascularization and coronary artery disease requiring drug treatment), nonfatal atherosclerotic non-CHD (defined as stroke and peripheral arterial disease), CHF and fatal CVD (defined as cardiovascular death and unwitnessed death) [19]. Analyses by quartile of NT-proBNP concentration were performed and odds ratios (ORs) for each of the upper three quartiles versus the lowest quartile (reference group) are cited along with 95% confidence intervals (CIs). Quartiles were estimated from the levels of the cases and controls combined. In addition to models that categorized NT-proBNP according to quartiles, models with continuous levels of NT-proBNP after natural log ($\log_e$) transformation are also considered and the ORs associated with a 1 $\log_e$ higher level are reported. In addition to the matching variables (age, sex, country and randomization date) that were considered in univariate analyses, the following additional baseline covariates were considered in multivariate models: BMI, race, HIV-RNA and ART status, smoking, prior CVD (MI, stroke or coronary artery disease requiring revascularization), prior CHF, diabetes, total/high-density lipoprotein (HDL)-cholesterol ratio, use of blood pressure (BP)-lowering drugs, hepatitis co-infection, CD4⁺ and major baseline ECG abnormalities. Separate models with additional adjustment for $\log_e$ -transformed levels of D-dimer, IL-6 and hsCRP were also considered. To assess whether the association between NT-proBNP and CVD varied by treatment group and baseline factors, interaction terms were included in the logistic models. The association between NT-proBNP and other covariates at study entry

were studied using linear regression analysis. Pearson correlation coefficients were used to assess the associations between $\log_e$ -transformed levels of NT-proBNP and hsCRP, IL-6 and D-dimer. Statistical analyses were performed using SAS (Version 9.1; SAS Institute, Cary, North Carolina, USA). All reported *P*-values are two-sided.

Results

Table 1 gives baseline characteristics for CVD cases and matched controls. In univariate analyses, prior AIDS, current smoking status, diabetes, prior CVD, major resting ECG abnormalities, use of BP-lowering drugs and use of lipid-lowering drugs were associated with an increased risk of CVD. In addition, HDL-cholesterol was lower and total/HDL was higher in CVD cases compared to controls. Baseline hsCRP, IL-6 and D-dimer were significantly higher in CVD cases than controls. At baseline median NT-proBNP [interquartile range (IQR)] was 48.1 (18.5, 112.9) pg/ml in patients who developed a CVD event and 25.7 (12.4, 50.2) pg/ml in the matched control patients ($P < 0.0001$). In the male cases ($n = 151$) baseline median NT-proBNP was 46.2 (19.8, 101.4) pg/ml and 24.1 (11.9, 42.8) pg/ml in the male controls ($n = 262$), whereas in the female cases ($n = 35$), NT-proBNP was 62.6 (17.9, 132.2) compared with 41.2 (15.6, 69.4) pg/ml in the female controls ($n = 67$). There was no difference in plasma creatinine in the cases 0.81 (0.71, 0.90) mg/dl and the controls 0.81 (0.70, 0.94) mg/dl. Median eGFR in the cases was 101.6 (88.8, 121.2) ml/min per 1.73m^2 and 103.5 (89.2, 120.5) ml/min per 1.73m^2 in controls. There was 6.3% of the study patients with an eGFR below 60 ml/min per 1.73m^2 in the cases and 2.8% in the controls.

Baseline factors associated with higher levels of NT-proBNP in controls were older age ($P < 0.0001$), female sex ($P = 0.03$), hepatitis co-infection ($P = 0.003$), prior CVD ($P = 0.02$), major ECG abnormalities ($P = 0.0002$) and use of BP-lowering drugs ($P < 0.0001$). NT-proBNP levels did not vary according to ART at entry. There was a positive association between NT-proBNP and IL-6 ($r = 0.24$, $P < 0.0001$) and D-dimer ($r = 0.19$, $P = 0.0006$); however, there was no association with hsCRP ($r = 0.06$, $P = 0.29$). There were some differences regarding the correlation between hsCRP and NT-proBNP in presence or absence of co-infection with hepatitis B/C. In the mono-HIV-infected patients ($n = 260$) there was a significant correlation between hsCRP and NT-BNP ($r = 0.19$, $P = 0.003$), whereas the correlation in the co-infected HIV-patients was negative and not significant ($r = -0.19$, $P = 0.12$) ($P = 0.004$ for difference in correlation coefficients).

There was a positive correlation between serum creatinine and NT-proBNP ($r = 0.18$, $P = 0.002$) and an inverse relationship between eGFR and NT-proBNP ($r = -0.24$, $P < 0.0001$).

Table 2 summarizes the ORs of the upper quartiles versus the lower quartile of NT-proBNP and per 1 log higher NT-proBNP for CVD events. The unadjusted OR for CVD for the highest quartile (37.1% of cases and 18.2% of controls) versus the lowest quartile (17.2% of cases and 29.2% of controls) was 3.7 (95% CI 2.1–6.5, $P < 0.0001$). The OR per 1 $\log_e$ higher NT-proBNP for CVD events was 1.6 (95% CI 1.3–1.8, $P < 0.0001$). After adjustment for baseline covariates these ORs were 2.8 (95% CI 1.4–5.6, $P = 0.003$) and 1.4 (95% CI 1.2–1.7, $P = 0.001$), respectively. After adjustment for covariates that also included baseline levels of $\log_e$ IL-6, hsCRP and D-dimer, these ORs were 2.3 (95% CI 1.1–4.9, $P = 0.02$) and 1.3 (95% CI 1.0–1.6, $P = 0.04$). Adjusting for eGFR did not impact the ORs for CVD beyond the adjustment for other baseline risk factors.

Excluding cases and controls with prior CVD or prior CHF at entry resulted in unadjusted ORs for CVD for the highest versus lowest quartile and for 1 $\log_e$ increase of 2.6 (95% CI 1.4–4.7, $P = 0.002$) and 1.5 (95% CI 1.2–1.8, $P = 0.0001$), respectively. After adjusting for

baseline covariates these ORs were 2.2 (95% CI 1.1–4.5, $P = 0.03$) and 1.4 (95% CI 1.1–1.7, $P = 0.006$). Additional adjustment for $\log_e$ IL-6, hsCRP and D-dimer resulted in ORs of 1.9 (95% CI 0.9–4.2, $P = 0.10$) and 1.3 (95% CI 1.0–1.6, $P = 0.07$).

Median NT-proBNP for cases and controls by type of event are given with the unadjusted ORs (4th/1st quartile) and per 1 log higher NT-proBNP in Table 3. Of the 186 CVD events, 95 were attributed to nonfatal CHD. There were 47 nonfatal atherosclerotic non-CHD cases, 17 cases of nonfatal congestive heart failure and 27 cases of fatal CVD. A weaker association of NT-proBNP with nonfatal atherosclerotic non-CHD was evident than for other CVD. The strongest associations seen were for nonfatal congestive heart failure and for fatal CVD.

There were 82 CVD events in the continuous viral suppression group, whereas there were 104 CVD events in the intermittent ART (drug conservation) group. Associations between NT-ProBNP and CVD were similar for drug conservation (OR 1.8, $P = 0.0003$) and viral suppression (OR 1.4, $P = 0.03$) treatment groups ($P = 0.38$ for interaction for model with $\log_e$ transformed levels).

Discussion

This is the first study on the relationship of NT-proBNP levels and risk of CVD in HIV patients. We found that higher NT-proBNP is associated with greater risk of CVD and this increased risk persisted after adjustment for other cardiovascular risk factors, including baseline IL-6, hsCRP and D-dimer.

Data on BNP and NT-pro-BNP in HIV patients are very limited. Elevated levels of BNP have been described in case reports in HIV patients with HIV-related cardiomyopathy [14,20]. In another small study the incidence of myocardial dysfunction in an HIV-infected population receiving state-of-the-art treatment was examined in 91 HIV-infected patients with a radionuclide left and right ventriculography as well as measurement of BNP [16]. Only 63 patients (69%) agreed to participate in a follow-up study with a mean follow-up of 4.5 years. No patients had increased BNP and no change in mean plasma BNP was found. In the Women's Interagency HIV Study (WIHS) 454 HIV-infected and 200 HIV un-infected participants had NT-proBNP determination [17]. Mean NT-proBNP was 142.4 ± 524.8 ng/l (= pg/ml) in the HIV-infected women and 73.6 ± 115.1 ng/l (= pg/ml) in the non-HIV-infected women. These mean levels were higher than in our female study population (mean = 87.1 pg/ml), but the standard deviation was also higher (SD = 196.7 pg/ml for women in SMART). Among HIV-infected women in WIHS, NT-pro-BNP levels were not associated with measures of severity of HIV infection or with ART use. Differences were due to non-HIV factors such as anemia, kidney disease, and HCV co-infection. The mechanism underlying increased natriuretic peptide levels with female sex even in the general population is unclear. Some suggest that the role of estrogen status could play a role in sex differences for NT-proBNP [21]. Recently Hsue *et al.* [22] described the prevalence of echocardiographic abnormalities in 196 HIV-infected individuals and 56 controls. They found that HIV-infected patients had a higher prevalence of diastolic dysfunction and higher left-ventricular mass index as compared with controls. Plasma BNP levels were available in 227 participants and the BNP levels were significantly higher among the HIV-infected patients and higher BNP was associated with a higher left ventricular mass index but not with diastolic dysfunction.

Our study population like many HIV study cohorts have a high prevalence of cardiovascular risk factors. We compared our study results with the recently published meta-analysis of 40 prospective studies regarding B-type natriuretic peptides and cardiovascular risk in non-

HIV-infected individuals [13]. Data were collected from 40 long-term prospective studies involving a total of 87 474 participants and 10 625 incident CVD outcomes. In comparison of individuals in the top third with those in the bottom third of baseline values of natriuretic peptides, the combined risk ratio, adjusted for several conventional risk factors was 2.82 (95% CI 2.40, 3.33). The risk ratio for the top versus bottom third of the distribution of BNP was similar across cohorts with different background CVD risk: 2.68 (95% CI 2.07, 3.47) for 11 studies of the general population, 3.35 (95% CI 2.38, 4.72) for 11 studies of people with elevated risk factors, and 2.60 (95% CI 1.99, 3.38) for 18 studies including patients with stable CVD. We calculated the risk ratio for the upper tertile (≥ 50 pg/ml) versus the bottom tertile (< 19 pg/ml) from our study population, and the unadjusted OR was 3.21 (95% CI 1.98, 5.21). With adjustment for traditional risk factors, the OR was 2.65 (1.50, 4.69), and with adjustment for risk factors and IL-6, hsCRP and D-dimer, the OR was 2.33 (1.27, 4.28). These estimates are comparable to those for the general population as repeated in the meta-analysis.

There are still several questions unanswered why NT-proBNP is a highly predictive factor in HIV-infected patients for CVD events for levels considered to be in normal range. Increased plasma BNP is found in patients with infections in the absence of severe sepsis or septic shock [23]. The existence of a direct association between infections and BNP is supported by evidence from in-vitro studies, which showed that *Escherichia coli* endotoxin (LPS) and pro-inflammatory cytokines have a direct effect on BNP transcription and translation in cardiomyocytes [24,25]. Vila *et al.* [26] studied plasma NT-proBNP response to LPS administration in a randomized, placebo-controlled, cross-over design in 10 healthy individuals for 6 h. LPS administration induced a continuous increase in plasma NT-proBNP that reached peak values after 6 h [40.7 ± 7.9 pg/ml (LPS) versus 16.1 ± 3.2 pg/ml (placebo), $P = 0.023$]. Microbial translocation is a potential cause of system immune activation in chronic HIV infection. Circulating lipopolysaccharide, an indicator of microbial translocation, is significantly increased in chronically HIV-infected individuals [27]. It is possible that this mechanism may be involved in the release of NT-proBNP in HIV-infected individuals.

The SMART study demonstrated that IL-6 and D-dimer are associated with all-cause mortality as well as with CVD in HIV patients. There is an association between IL-6 and D-dimer with NT-proBNP in this study and an association between hsCRP and NT-proBNP in participants not co-infected with hepatitis. The association between NT-proBNP, IL-6 and D-dimer has been studied in patients with congestive heart failure by Marcucci *et al.* [28]. They also found that there was a significant correlation between NT-proBNP and IL-6, hsCRP and D-dimer. HIV is associated with inflammation and subclinical vascular disease [29], which will activate the coagulation system. This inflammatory cascade and subclinical vascular disease will have an impact on the myocardium leading to the release of NT-proBNP as expression of CVD.

There are some limitations in this study. Only baseline levels of NT-proBNP were assessed. Future work should consider values more proximal to CVD events and also consider the effect of ART on NT-proBNP levels. Some subcategories of CVD events were small. NT-proBNP is also related to eGFR and renal function [30]. It is known that HIV-infected patients are at risk for progression of renal disease [31]. The relationship between NT-BNP and progression of renal disease in HIV should be further explored.

In conclusion, higher levels of NT-proBNP are associated with increased risk of CVD in HIV-infected patients. Further studies are warranted to determine if NT-proBNP can be used for early detection of CVD in HIV-infected patients and if ART influences levels of NT-proBNP.

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Table 1
Baseline characteristics, cardiovascular disease risk factors and lipid profile of cardiovascular disease cases and matched controls with NT-proBNP results

	CVD cases (N = 186)	Controls (N = 329)	P-value *
Treatment group (% DC)	55.9	46.2	0.04
Demographics			
Age (median, IQR)	50 (44, 56)	49 (43, 55)	NA
Sex (% female)	18.8	20.4	NA
Black (%)	39.2	37.7	0.53
CD4 ⁺ (cells/ μ l) (median, IQR)	579 (460, 837)	606 (464, 784)	0.35
CD4 ⁺ nadir (cells/ μ l) (median, IQR)	236 (130, 339)	244 (133, 340)	0.70
HIV-RNA $\leq$ 400 copies/ml (%)	68.3	70.9	0.49
Prior AIDS-related illnesses (%)	36.6	24.9	0.007
Hepatitis B (%)	2.7	0.6	0.07
Hepatitis C (%)	16.1	20.4	0.16
CVD risk factors			
Current smoker (%)	48.4	36.8	0.008
Diabetes (%)	18.3	7.3	0.0004
Prior MI, stroke or CAD (%)	12.4	4.9	0.002
Prior CHF (%)	3.8	1.5	0.08
Major ECG abnormality (%)	19.8	9.3	0.002
Blood pressure-lowering drugs (%)	43.5	28.9	0.0009
Lipid-lowering drugs (%)	29.6	21.6	0.05
Lipids			
Total cholesterol (mg/dl) (median, IQR)	199 (171, 235)	191 (170, 227)	0.14
HDL cholesterol (mg/dl) (median, IQR)	38 (31, 48)	41 (34, 52)	0.04
LDL cholesterol (mg/dl) (median, IQR)	112 (91, 142)	110 (88, 134)	0.27
Triglycerides (mg/dl) (median, IQR)	198 (140, 319)	179 (125, 289)	0.69
Total/HDL cholesterol (median, IQR)	5.6 (4.0, 6.8)	4.7 (3.7, 5.9)	0.03
Biomarkers			
hsCRP (μ g/ml) (median, IQR)	3.89 (1.57, 7.68)	2.06 (0.95, 4.46)	<0.0001
IL-6 (pg/ml) (median, IQR)	3.11 (1.95, 4.91)	2.12 (1.35, 3.53)	<0.0001
D-dimer (μ g/ml) (median, IQR)	0.31 (0.18, 0.57)	0.24 (0.15, 0.45)	0.002
eGFR ^a (ml/min per 1.73m ²) (median, IQR)	101.6 (88.8, 121.2)	103.5 (89.2, 120.5)	0.23
eGFR ^a <60 ml/min per 1.73m ² (%)	6.3	2.8	0.13
NT-proBNP (pg/ml) (median, IQR)	48.1 (18.5, 112.9)	25.7 (12.4, 50.2)	<0.0001

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; DC, drug conservation; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NA, not available; NT-proBNP, N-terminal-proB-type natriuretic peptide.

* P-value obtained from univariate conditional logistic model. Biomarkers are natural log transformed.

^a eGFR levels available for 160 cases and 287 controls.

Table 2
Odds ratio for cardiovascular disease for upper versus the lower quartile and per 1 log higher N-terminal-proB-type natriuretic peptide

Quartile	Unadjusted		Adjusted ^a		Adjusted ^b	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Q1	1.00	–	1.00	–	1.00	–
Q2	1.26 (0.73–2.18)	0.40	1.16 (0.60–2.21)	0.66	1.16 (0.59–2.28)	0.67
Q3	1.46 (0.86–2.47)	0.16	1.30 (0.70–2.42)	0.40	1.25 (0.65–2.43)	0.50
Q4	3.69 (2.10–6.47)	<0.0001	2.85 (1.44–5.65)	0.003	2.35 (1.14–4.85)	0.02
OR (per 1 log higher)	1.55 (1.30–1.83)	<0.0001	1.42 (1.15–1.74)	0.001	1.26 (1.01–1.58)	0.04

CI, confidence interval; OR, odds ratio.

^a Adjusted for baseline covariates: age, BMI, race, HIV-RNA and antiretroviral therapy status, smoking, prior cardiovascular disease (myocardial infarction, stroke or coronary artery disease), prior congestive heart failure, diabetes, total/high density lipoprotein cholesterol ratio, use of blood pressure lowering drugs, hepatitis co-infection, CD4⁺ and major baseline ECG abnormalities.

^b Adjusted for baseline covariates and loge transformed levels of D-dimer, interleukin-6 and high-sensitivity C-reactive protein.

Table 3
Median (interquartile range) N-terminal-proB-type natriuretic peptide (pg/ml) by event category and unadjusted odds ratios for cardiovascular disease by event category

Event	Cases		Controls	
	<i>N</i>	Median (IQR)	<i>N</i>	Median (IQR)
CHD	95	42.3 (17.2, 88.3)	163	24.6 (12.8, 45.4)
Atherosclerotic non-CHD	47	34.2 (15.7, 62.2)	88	25.4 (12.4, 49.2)
Congestive heart failure	17	166.1 (46.2, 470.3)	27	24.1 (10.0, 59.1)
CVD or unwitnessed death	27	68.8 (35.6, 149.4)	51	31.3 (12.1, 59.4)
Unadjusted ORs for CVD by event category				
Event	4th versus 1st quartile of NT-proBNP		Per 1 log higher NT-proBNP	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
CHD	3.0 (1.4–6.5)	0.005	1.5 (1.2–2.0)	0.001
Atherosclerotic non-CHD	1.8 (0.6–5.7)	0.29	1.3 (0.9–1.8)	0.13
Congestive heart failure	5.1 (0.9–29.9)	0.07	1.9 (1.1–3.1)	0.01
CVD or unwitnessed death	39.0 (3.2–467.8)	0.004	1.8 (1.1–2.7)	0.01

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; IQR, interquartile range; NT-proBNP, N-terminal-proB-type natriuretic peptide; OR, odds ratio.