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Predictors of 10-year changes in levels of N-terminal pro B-type natriuretic peptide and cardiac troponin I in the elderly☆

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ABSTRACT

Background: Measurement of N-terminal pro B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) might be useful for monitoring of cardiovascular disease in the elderly. However, it is not clear whether changes in these biomarkers are associated with changes in the cardiovascular risk profile and if this pattern could be modified by changes in lifestyle habits or medications.
Methods: We measured levels of NT-proBNP and cTnI in community-dwelling subjects (PIVUS study) upon visits scheduled at age 70 ($n = 1007$), 75 ($n = 825$) and 80 ($n = 602$). The associations of these biomarkers with repeated measurements of clinical variables (risk factors, lifestyle habits, echocardiographic data and medications) were investigated using sex-adjusted linear mixed random effect models.
Results: NT-proBNP and cTnI were positively associated with increasing age. NT-proBNP, but not cTnI, was affected by changes of renal function and the degree of obesity. NT-proBNP was more closely related than cTnI to changes in echocardiographic estimates of cardiac geometry and function. Biomarker levels and/or their changes were inversely associated with a physically more active lifestyle (both NT-proBNP and cTnI) and statin treatment at age 70 (only cTnI). Changes in smoking status or antihypertensive treatment had no effect on biomarker levels.
Conclusions: Changes in NT-proBNP and cTnI levels are associated with different patterns of cardiovascular disease burden when using a longitudinal approach. However, levels of both biomarkers and their changes also reflect changes in the cardiovascular risk profile that might be modifiable. This is an important aspect for the use of any cardiovascular biomarker in an elderly population.

1. Introduction

Cardiovascular (CV) disease is the main cause of mortality worldwide and its prevalence is increasing with higher age. Assessment of elderly subjects regarding the presence and progress of CV disease is of considerable importance and a major challenge for health care providers. According to current routines, clinical assessment should include each subject's history, a physical examination including ECG recordings and measurement of metabolic parameters. These estimates however, cover only part of the individual CV risk panorama and their interpretation often depends on the experience of each physician.

Measurement of circulating CV biomarkers might overcome these problems. Biomarkers reflect distinct pathways and indicate the presence of subclinical CV disease that could go undetected otherwise. If measured serially, changes in biomarker levels might moreover, detect evolving CV disease, thereby allowing for the initiation of beneficial medical interventions. In particular the B-type natriuretic peptides and cardiac troponins have gained much interest in this regard [1]. Both biomarkers are closely related to cardiac structural and functional abnormalities, to CV risk and provide incremental information on each other [2–4]. However, it is at present not clear whether changes in these biomarkers might be associated with changes in the CV risk profile, and if this pattern could be modified by changes in lifestyle habits or medications.

The PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study is a longitudinal cohort study investigating the mechanisms of CV disease in elderly men and women [5]. Visits had been scheduled when the study participants were age 70, 75 and 80 years. At these instances, blood samples for measurement of N-terminal pro B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) were drawn. The aim of the present analysis was to investigate the associations of longitudinal changes in both biomarkers with changes in

Abbreviations: cTnI, cardiac troponin I; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LA, left-atrial; LV, left-ventricular; LVEF, left-ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; WOSCOPS, West of Scotland Coronary Prevention Study.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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clinical variables during the 10-year observation period. We hypothesized that the approach of using longitudinal data would improve the identification of associations between biomarkers, CV risk factor profile and disease states, since cross-sectional studies are often biased by reverse causation and confounding.

2. Material and methods

2.1. Study population

All subjects aged 70 years living in Uppsala, Sweden were eligible for participation in PIVUS [5]. Potential study participants were randomly chosen from the registry of community inhabitants. Of the 2025 subjects invited, 1016 participated in the study and answered a questionnaire about their medical history, lifestyle habits and regular medication and underwent extensive CV examinations including echocardiography, invasive and non-invasive vascular testing and blood tests. This was repeated upon each visit. Written informed consent had been obtained from all participants, the study protocol was approved by the local ethics committee and complies with the Declaration of Helsinki of 1975 as revised in 2008.

2.2. Definitions of clinical variables

For the purpose of this investigation, we defined clinical variables as follows:

- Smoking is defined as current smoking;
- Antihypertensive medication is defined as continuous treatment with ACE-inhibitors, angiotensin II-receptor blockers, betablockers or calciumantagonists;
- Physical activity was classified by four groups: <2 times light exercise (no sweat) per week, ≥2 times light exercise per week, 1–2 times heavy exercise (sweat) per week, >2 times heavy exercise (sweat) per week;
- CV disease is defined as previous or incident (during the 10-year observation period) myocardial infarction, stroke, self-reported heart failure and atrial fibrillation.

2.3. Echocardiography

Echocardiography was performed to obtain information on left-atrial (LA) and left-ventricular (LV) dimensions, LV systolic and diastolic function, and LV mass index, as described previously [6,7].

2.4. Laboratory analysis

Biomarkers were analyzed in samples of EDTA-plasma obtained at baseline and the visits at 5 and 10 years. Samples were stored frozen in aliquots at −80° and had endured up to three freeze–thaw cycles before the analyses. NT-proBNP was measured using the Elecsys proBNP immunoassay (Roche Diagnostics, Mannheim, Germany). The intra-assay imprecision of this assay is <10% across the analytical range of 5 to 35,000 pg/mL [8]. For analysis of cTnI, the ARCHITECT *STAT* hsTnI assay (Abbott Laboratories, Abbott Park, IL) was used. According to the manufacturer, the level of detection of this assay is 1.9 ng/L. Results below this value were set to 1.4 ng/L, corresponding to square root of 1.9. The lowest concentration measurable with a 10% coefficient of variation has been reported as 5.6 ng/L [9].

2.5. Statistical analysis

Linear mixed random effects models were used to investigate the associations between biomarker levels, their changes and changes in the value of clinical variables. These models allowed for the incorporation of all subjects with available biomarker results from all of the three visits while assessing the interactions between groups and time, the latter coded as the respective visit. In the first set of models, we studied the longitudinal change in biomarker levels. In the second set of models, we investigated if baseline values of clinical variables (at age 70) could predict the change in biomarker levels by using interaction terms of the baseline value of each variable × time as independent variables with the biomarkers as dependent variables. In the third set of models, we studied the associations between the change in clinical variable values and the change in biomarker levels by including the change in the clinical variable as independent variable with the biomarkers as dependent variables. All models were adjusted for sex. The second and third sets of models were also adjusted for the baseline value of each respective clinical variable.

Continuous variables are reported as medians (with 25th and 75th percentiles) or means (with standard deviations). Categorical variables are expressed as frequencies and percentages. In all tests, a two-sided p-value <0.05 was considered significant. The software packages Stata 14 (Stata Corp., College Station, TX) and SPSS 21.0 (SPSS Inc., Chicago, IL) were used for the analyses.

3. Results

3.1. Changes in biomarker levels over time

In total, 1016, 826 and 602 subjects attended the visits at 70, 75 and 80 years. Of these, 1007, 825 and 600 subjects, respectively, had available results for NT-proBNP or cTnI and formed the sample population. Clinical characteristics including information on CV risk factors and disease states, lifestyle habits, medications and echocardiographic data are presented in Table 1. In subjects with available NT-proBNP results from any of the three visits ($n = 2430$), levels increased from 111 (65–183) ng/L at baseline to 125 (73–234) ng/L at 75 years and 167 (98–379) ng/L at 80 years. The corresponding levels for cTnI in subjects with available results from any of the three visits ($n = 2428$) were 3.4 (2.5–5.1) ng/L, 4.9 (3.6–7.1) ng/L and 3.2 (2.1–5.6) ng/L, respectively.

The first set of models (longitudinal analysis of biomarker changes) demonstrated that time was independently associated with levels of NT-proBNP (β-coefficient 21.349 [95% confidence interval 12.075 to 30.623]; $p < 0.001$) and cTnI (β-coefficient 0.233 [95% confidence interval 0.073 to 0.392]; $p = 0.004$). This indicates that after adjustment for sex, levels of both biomarkers increased over time.

Table 1
Clinical characteristics.

	70 years ($n = 1007$)	75 years ($n = 825$)	80 years ($n = 600$)
Males	503 (50.0%)	407 (49.3%)	303 (50.5%)
Biomarkers			
NT-proBNP (ng/L)	111 (65–183)	125 (73–234)	167 (98–379)
cTnI (ng/L)	3.4 (2.5–5.1)	4.9 (3.6–7.1)	3.2 (2.1–5.6)
CRP (mg/L)	1.9 (1.0–3.5)	2.1 (1.1–4.0)	1.7 (0.9–2.9)
History			
Previous MI	72 (7.2%)	75 (9.1%)	66 (11.1%)
Previous PCI/CABG	54 (5.4%)	73 (8.9%)	65 (10.9%)
Previous stroke	36 (3.6%)	56 (6.8%)	63 (10.6%)
History of heart failure	35 (3.5%)	47 (5.7%)	52 (8.8%)
Atrial fibrillation	38 (3.7%)	72 (8.7%)	101 (17.3%)
Risk factors			
Smoking	107 (10.6%)	51 (6.2%)	18 (3.0%)
Diabetes	87 (8.7%)	93 (11.3%)	69 (11.5%)
Hypertension	726 (72.1%)	671 (81.6%)	482 (80.6%)
Waist circumference (cm)	91.2 ± 11.6	94.2 ± 11.8	96.3 ± 11.8
Body mass index (kg/m^2)	27.0 ± 4.3	26.9 ± 4.4	26.9 ± 4.5
Systolic BP (mm Hg)	150 ± 23	149 ± 19	147 ± 19
Physical activity			
1	1 (0.1%)	0	3 (0.5%)
2	14 (1.4%)	8 (1.0%)	69 (12.2%)
3	904 (91.6%)	758 (93.7%)	468 (82.8%)
4	68 (6.9%)	43 (5.3%)	25 (4.4%)
eGFR (mL/min/1.73 m^2)	86.3 ± 16.4	70.8 ± 13.7	62.2 ± 14.7
Metabolic parameters			
Glucose (mmol/L)	5.0 (4.6–5.4)	4.9 (4.5–5.4)	4.9 (4.6–5.6)
Cholesterol (mmol/L)	5.4 ± 1.0	5.4 ± 1.1	5.1 ± 1.1
LDL-cholesterol (mmol/L)	3.4 ± 0.9	3.4 ± 0.9	3.2 ± 0.9
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.5	1.4 ± 0.4
Triglycerides (mmol/L)	1.3 ± 0.6	1.4 ± 0.7	1.2 ± 0.6
Echocardiographic data			
LA diameter (mm)	39 ± 7	41 ± 7	43 ± 7
LVEDD (mm)	47 ± 5	50 ± 6	52 ± 6
LVMI (g/m^2)	43.2 ± 13.2	43.4 ± 12.7	45.6 ± 12.5
LVEF (%)	76.3 ± 9.4	73.3 ± 8.1	70.5 ± 8.5
E/A ratio	0.96 ± 0.28	0.93 ± 0.29	0.93 ± 0.38
Medication			
Antihypertensive drugs	312 (31.3%)	399 (48.5%)	361 (60.3%)
Statins	149 (14.8%)	210 (25.5%)	197 (33.2%)

Data given as numbers (with percentages) or medians (with 25th, 75th percentiles). Patients with missing data were excluded from the analyses.
CRP: C-reactive protein; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; BP: Blood pressure; eGFR: estimated glomerular filtration rate; LA: left atrium; LVEDD: left-ventricular end-diastolic diameter; LVMI: left-ventricular mass index; LVEF: left-ventricular ejection fraction.