International Journal of Cardiology 201 (2015) 104–109

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Plasma pro-brain natriuretic peptide and electrocardiographic changes in combination improve risk prediction in persons without known heart disease☆

Peter G. Jørgensen [a,b,c,*,1], Jan S. Jensen [a,b,c,1], Merete Appleyard [a,1], Gorm B. Jensen [a,1], Rasmus Mogelvang [a,d,1]

[a] The Copenhagen City Heart Study, Frederiksberg Hospital, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark
[b] Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Kildegårdsvej 28, DK-2900 Hellerup, Denmark
[c] Institute of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen N., Denmark
[d] Department of Cardiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen O, Denmark

ARTICLE INFO

Article history:
Received 10 May 2015
Received in revised form 25 June 2015
Accepted 29 July 2015
Available online 1 August 2015

Keywords:
Primary prevention
Electrocardiography
Plasma pro-BNP

ABSTRACT

Background: Though the electrocardiogram(ECG) and plasma pro-brain-natriuretic-peptide (pro-BNP) are widely used markers of subclinical cardiac injury and can be used to predict future cardiovascular disease(CVD), they could merely be markers of the same underlying pathology. We aimed to determine if ECG changes and pro-BNP are independent predictors of CVD and if the combination improves risk prediction in persons without known heart disease.

Methods: Pro-BNP and ECG were obtained on 5454 persons without known heart disease from the 4th round of the Copenhagen City Heart Study, a prospective cohort study. Median follow-up was 10.4 years. High pro-BNP was defined as above 90th percentile of age and sex adjusted levels. The end-points were all-cause mortality and the combination of admission with ischemic heart disease, heart failure or CVD death.

Results: ECG changes were present in 907 persons and were associated with high levels of pro-BNP. In a fully adjusted model both high pro-BNP and ECG changes remained significant predictors: all-cause mortality(high pro-BNP, no ECG changes: HR: 1.43(1.12–1.82);$P = 0.005$, low pro-BNP, ECG changes: HR: 1.22(1.05–1.42); $P = 0.009$, and both high pro-BNP and ECG changes: HR: 1.99(1.54–2.59);$P < 0.001$), CVD event(high pro-BNP, no ECG changes: HR: 1.94(1.45–2.58);$P < 0.001$, low pro-BNP, ECG changes: HR: 1.55(1.29–1.87);$P < 0.001$, and both high pro-BNP and ECG changes: HR: 3.86(2.94–5.08);$P < 0.001$). Adding the combination of pro-BNP and ECG changes to a fully adjusted model correctly reclassified 33.9%(26.5–41.3);$P < 0.001$ on the continuous net reclassification scale for all-cause mortality and 49.7%(41.1–58.4);$P < 0.001$ for CVD event.

Conclusion: Combining ECG changes and pro-BNP improves risk prediction in persons without known heart disease.

1. Introduction

In primary risk prediction, identification of persons with subclinical heart disease may help prevent transition to overt disease. Both plasma pro-brain-natriuretic-peptide (plasma pro-BNP) and the ECG are widely accessible, established as part of the diagnostic workup of persons suspected for heart disease and useful in primary risk prediction in persons without known heart disease. Elevated levels of plasma pro-BNP and presence of electrocardiographic (ECG) changes, including pathological Q-waves, ST segment and T-wave changes (ST–T changes), left ventricular hypertrophy (LVH) and bundle branch block (BBB), are markers of subclinical cardiac impairment in persons without known heart disease, but while plasma pro-BNP is secreted in response to atrial or ventricular wall stress, the origin of ECG changes is more diverse. However, both occur in a wide range of pathological cardiac conditions including left ventricular dysfunction, left ventricular hypertrophy and ischemic heart disease and both are associated with increased risk of death and cardiovascular disease in persons without known heart disease [1–5].

Also, while each marker is well recognized as predictor on its own, their mutual association is less elucidated and the value of combining the markers to further improve risk stratification is unknown. And, though Neeland et al. found that combining NT-pro-BNP and electrocardiographic evidence of left ventricular hypertrophy identified particularly malignant phenotypes [6], the correlation and prognostic value of

☆ **Funding**: The study was funded by the Danish Heart Foundation (00-1-4-75-22877).
* Corresponding author at: Herlev and Gentofte Hospital, University of Copenhagen, Post 835, Kildegårdsvej 28, 2900 Hellerup, Denmark.
E-mail address: petergodsk@gmail.com (P.G. Jørgensen).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2015.07.100
0167-5273/

plasma pro-BNP and Q-waves, ST–T changes and BBB remains to be examined.

Hence, we sought to evaluate the mutual association between plasma pro-BNP and overall ECG changes and to investigate whether plasma pro-BNP and ECG changes can be used interchangeably or if combining plasma pro-BNP and the ECG will improve the detection of persons with subclinical heart disease and provide incremental prognostic information.

2. Methods

2.1. Cohort

The Copenhagen City Heart Study is a prospective cohort study of cardiovascular risk factors and was initiated in 1976. 19,329 predominantly white Caucasians – stratified by gender and 5-year age intervals – living within a well-defined area of Copenhagen City Centre were randomly invited and 14,223 participated (participation rate: 73.6%). In all, 4 rounds of examinations have been conducted (1972–74, 1981–83, 1991–94 and 2001–03) and for each round, the surviving persons were invited again and the cohort was supplemented with persons from the younger strata. For this purpose, participants in the 4th round were included. In this, 12,900 persons were invited and 6237 participated.

All subjects gave informed consent to participate, and the study was performed in accordance with the Second Helsinki Declaration and approved by the regional ethics committee.

2.2. Health examination

Blood pressure was measured after 5 min of rest with a cuff adjusted to arm circumferential. Smoking status and family history of coronary heart disease was self-reported. Body mass index was weight in kilograms divided by the square of the height. Low-density lipoprotein cholesterol and serum-creatinine were measured at baseline. Diabetes mellitus was either self-reported, measured fasting plasma-glucose ≥ 11.1 mmol/l or Hb1Ac > 7.0% [7,8]. Known heart disease was defined as either ischemic heart disease or known congestive heart failure. Ischemic heart disease was self-reported and defined as either a history of hospital admission due to myocardial infarction, previous percutaneous coronary intervention or coronary artery bypass grafting and known congestive heart failure was defined as prior hospitalization for this condition.

2.3. ECG

At inclusion, a 12 lead ECG was obtained and classified according to the Minnesota Code Classification System. The ECG was reviewed by two independent reviewers and in case of disagreement, a 3rd reviewer adjudicated. The Minnesota Codes 1.1.x–1.3.x represent Q and QS patterns with decreasing severity, the Minnesota Codes 4.1–4.3 represent ST segment depression of downward or horizontal sloping of decreasing amplitude and the Minnesota Codes 5.1–5.3 represent T-wave inversions or diphasic T-waves in leads with mostly upright QRS or R amplitude ≥ 5.0 mm. ECG changes were defined as either one of the abovementioned ECG changes including ventricular conduction defects (7.1.x and 7.2.x) and left ventricular hypertrophy (3.1 and 3.2).

2.4. Plasma pro-B-type natriuretic peptide

The plasma pro-BNP concentration was measured at inclusion with a processing independent assay. The results obtained using this assay are fully comparable to the commercially available Modular N-terminal-pro-BNP assay by Roche (Karlsruhe, Germany) as previously described [9]. Individuals with age and sex adjusted levels of plasma pro-BNP above the 90th percentile were arbitrarily considered having high levels of plasma pro-BNP.

2.5. End-points

The end-points were all-cause mortality and the composite of CVD mortality and admission with non-fatal ischemic heart disease and/or heart failure (CVD event). The Danish National Board of Health's National Patient Registry and Register of Cause of Death were used to obtain information on vital status and CVD mortality (ICD-10 codes I00–99) and admission with CVD events was defined as ICD-10 codes I20–I25 and

Table 1
Baseline characteristics.

	No ECG changes, low plasma pro-BNP n = 4150	No ECG changes, high plasma pro-BNP n = 409	ECG changes, low plasma pro-BNP n = 759	ECG changes, high plasma pro-BNP n = 136	P-value
Age (years)	56.9 (±16.1)	53.8 (±17.0)	66.2 (±15.9)	67.2 (±15.2)	<0.001
Age category, no (%)					
<40	667 (16.1)	94 (23.0)	65 (8.6)	9 (6.6)	<0.001
40–49	732 (17.6)	56 (13.7)	47 (6.2)	9 (6.6)	
50–59	780 (18.8)	90 (22.0)	94 (12.4)	16 (11.8)	
60–69	1032 (24.9)	96 (23.5)	190 (25.0)	31 (22.8)	
70–79	659 (15.9)	54 (13.2)	206 (27.1)	49 (36.0)	
80–89	271 (6.5)	19 (4.6)	147 (19.4)	20 (14.7)	
≥90	9 (0.2)	0 (0.0)	10 (1.3)	2 (1.5)	
Male sex, no (%)	1685 (40.6)	174 (42.5)	375 (49.4)	55 (40.4)	<0.001
Smokers, no (%)	2737 (66.3)	254 (62.3)	486 (64.1)	92 (67.6)	0.28
Systolic blood pressure (mm Hg)	134 (±22)	135 (±23)	150 (±23)	154 (±24)	<0.001
Systolic blood pressure category, no (%)					
<140	2607 (63.0)	260 (63.7)	253 (33.5)	38 (28.1)	<0.001
140–159	958 (23.1)	81 (19.9)	235 (31.1)	47 (34.8)	
160–179	450 (10.9)	47 (11.5)	186 (24.6)	28 (20.7)	
≥180	126 (3.0)	20 (4.9)	82 (10.8)	22 (16.3)	
Diastolic blood pressure (mm Hg)	78 (±11)	79 (±13)	82 (±13)	81 (±15)	<0.001
Diastolic blood pressure category, no (%)					
<90	3506 (84.7)	339 (83.1)	563 (74.5)	103 (76.9)	<0.001
90–99	474 (11.4)	51 (12.5)	126 (16.7)	19 (14.2)	
100–109	128 (3.1)	13 (3.2)	48 (6.4)	6 (4.5)	
≥110	32 (0.8)	5 (1.2)	19 (2.5)	6 (4.5)	
LDL-cholesterol (mmol/l)	3.5 (±1.0)	3.3 (±3.6)	3.6 (±1.0)	3.5 (±1.0)	<0.001
LDL-cholesterol category, no (%)					
<2.0	223 (5.4)	33 (8.1)	30 (5.3)	8 (5.9)	0.07
2.0–2.9	1203 (29.2)	123 (30.3)	212 (28.3)	46 (34.1)	
3.0–3.9	1506 (36.6)	140 (34.5)	254 (33.9)	45 (33.3)	
4.0–4.9	835 (20.3)	78 (19.2)	174 (23.2)	24 (17.8)	
≥5	302 (7.3)	25 (6.2)	69 (9.2)	12 (8.9)	
Body mass index (kg/m^2)	25.6 (±4.2)	25.6 (±4.4)	26.4 (±4.8)	26.2 (±5.0)	<0.001
Body mass index category, no (%)					
<18.5	53 (1.3)	6 (1.5)	11 (1.5)	5 (3.7)	<0.001
18.5–24.9	1975 (47.6)	199 (48.7)	314 (41.4)	56 (41.2)	
25.0–29.9	1555 (37.5)	146 (35.7)	284 (37.4)	49 (36.0)	
30.0–34.9	439 (10.6)	42 (10.3)	108 (14.2)	18 (13.2)	
≥35	125 (3.0)	16 (3.9)	42 (5.5)	8 (5.9)	
Diabetes, no (%)	311 (7.5)	28 (6.9)	108 (14.2)	22 (16.2)	<0.001

LDL = low-density lipoprotein.