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Significance of Screening the General Population for Potential Cardiovascular Diseases with a Combination Assay of B-type Natriuretic Peptide and High Sensitive Troponin I

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Abstract

Objectives: With increasing number of deaths by cardiovascular diseases, to develop an efficient method to screen the general population, such as a screening using biomarkers, for potential cardiovascular diseases is essential. We assessed the effectiveness of a combination assay of B-type natriuretic peptide (BNP) and cardiac troponin I (TnI) in detecting individuals with high cardiovascular risks.

Methods: BNP and TnI were determined using Abbott Architect immunoassays in 950 subjects who visited Takeda Hospital Medical Examination Center for the annual health check.

Results: The BNP level and TnI level were independently and positively associated with the Framingham Risk Score (FRS). The presence of hypertension and CKD were positively, but that of dyslipidemia was negatively associated with the BNP level, while the presence of hypertension and dyslipidemia were positively associated with the TnI level. In a BNP-TnI plot where BNP is in the X-axis and TnI was in the Y-axis, we categorized the subjects into quadrants with the BNP cut-off (40.0 pg/mL) and the TnI cut-off (26.2 pg/mL); quadrant A (upper left), quadrant B (lower left), quadrant C (lower right) and quadrant D (upper right). In quadrants A, B, C and D, the number of subjects were 9, 932, 9 and 0, respectively. By assessing the differences between pairs of quadrants among quadrant A, B and C in terms of age, body mass index (BMI), systolic blood pressure (SBP), heart rate (HR), cardio-thoracic ratio (CTR), vital capacity (VC), haemoglobin (Hb), platelet count (PLT), uric acid (UA), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) and the FRS, BMI, CTR and the FRS were higher in quadrants A than quadrant B while age, CTR, PLT and the FRS were higher in quadrants C than quadrant B. The factors that differentiated quadrants A and C were age, BMI and TG.

Conclusion: We conclude that not only BNP but also TnI could provide important information for cardiovascular risks in the general population due to its ability to detect the different high risk population as BNP could detect.

Keywords: Troponin I; BNP; Body mass index; Risk factors; Framingham risk score; General population; Screening; Cardiovascular disease; Primary prevention

Introduction

Cardiovascular diseases are the second leading cause of death in Japan [1]. In a rapidly aging country such as Japan, incidence of cardiovascular diseases is increasing, which has become one of the greatest concerns for the welfare of the population as well as a governmental financial burden for medical expenditures. Therefore, it is important to develop an efficient method to screen the general population for potential cardiovascular diseases, such as a screening using biomarkers.

B-type natriuretic peptide (BNP) was discovered by Sudoh et al. [2] is predominantly expressed in the ventricles and is secreted in response to several factors, including myocardial stretch, increased myocardial pressure, or cell hypoxia. BNP produces pharmacological effects such as vasorelaxation, diuresis, natriuresis, and inhibition of the renin-angiotensin-aldosterone system [3]. Because the plasma BNP level is correlated with the severity of cardiac dysfunction in patients with heart failure, BNP is often used for diagnosis, stratification and monitoring of heart failure [4]. BNP has also been shown to be useful for assessing the coronary heart disease risk in the general population and shows a correlation with hypertension and the Framingham Risk Score (FRS) [5].

Cardiac troponin I (TnI) is a protein expressed in myocardium constituting one of three subunits of troponins T, I and C. Because troponin I and T are expressed as cardio-specific isoforms in the myocardium, they are ideally suited for the detection of myocardial damage [6]. Due to the development of high sensitive troponin assays, the measurement of troponin for the diagnosis of acute coronary syndrome (ACS) is recommended as the most reliable biomarker [7,8]. High sensitive troponin I assays have been shown to be useful not only for diagnosis of ACS but also for predicting cardiovascular events such as congestive heart failure in patients with stable coronary artery

disease [9] or pulmonary hypertension [10]. In the general population in which the troponin I values measured by high sensitive assays, but not by contemporary troponin I assays, significantly improved the predictions of cardiovascular events and coronary deaths [11]

Due to the different release mechanisms of BNP and TnI, we predicted that a wider range of cardiovascular diseases could be detected by screening the general population using a combination of BNP and high sensitive troponin I assays. Therefore, the objectives for this study were as follows:

1) To determine whether elevation of BNP or TnI occurred in individuals with increased cardiovascular risks such as the ones having elevated risk factors or the ones with the diseases related to cardiovascular diseases.

2) To determine whether BNP and TnI complement with each other in detecting a larger population with higher cardiovascular risks.

Materials and Methods

Study population

952 subjects who visited Takeda Hospital Medical Examination Center for their annual health evaluation participated in this study. Upon excluding two subjects with the estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2, 950 subjects were enrolled.

Study design

The study was designed to comply with the Declaration of Helsinki in 1964 and obtained approval of the Institutional Review Board at Takeda Hospital. Informed consent was obtained from each subject before they participated in this study. Adequate care was taken to ensure that the privacy of each subject was preserved.

Clinical tests

The clinical tests included body mass index (BMI), heart rate (HR), systolic and diastolic blood pressures (SBP and DBP), cardiothoracic ratio (CTR) by echocardiography and vital capacity (VC). Information about gender, age, medical history and smoking habit was collected from all subjects in interviews.

Laboratory tests

All the blood samples were drawn in a sitting position in the morning after the subjects had been fasted since the previous night. All the subjects were evaluated with biochemistry and hematology tests as well as Architect STAT High Sensitive Troponin I (Abbott Laboratories, Illinois, USA) and Architect BNP-JP (Abbott Laboratories, Illinois, USA) tests. The biochemistry test was performed on JCA-8060 (JEOL Ltd., Tokyo, Japan) that included albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), uric acid (UA), creatinine (CRE), blood urea nitrogen (BUN), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), hemoglobin A1c (HbA1c) and fasting blood glucose (FBG). The hematology test was performed on E-2100 (Sysmex Corporation, Kobe, Japan) that included white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (Ht) and platelet count (PLT).

The eGFR was calculated according to the revised equations for the Japanese population as reported previously [12].

Calculation of the FRS

The FRS was calculated according to the methods of D'Agostino et al. [13].

Association with diseases

To assess the associations of BNP or TnI with diseases related with cardiovascular risks, including hypertension, dyslipidemia, diabetes, chronic kidney disease (CKD) and hyper-uricemia, we defined each disease as follows:

The presence of hypertension was defined when a subject was under the treatment of the disease, the SBP was more than 139 mmHg or the DBP was more than 89.

The presence of dyslipidemia was defined when a subject was under the treatment of the disease or had steatosis, a high-density lipoprotein cholesterol (HDL-C) level less than 40 mg/dL, an LDL-C level more than 139 mg/dL or a TG level more than 149 mg/dL.

The presence of diabetes was defined when a subject was under the treatment of the disease, had a fasting blood glucose (FBG) level more than 125 mg/dL or an HbA1c value more than 6.4%.

The presence of CKD was defined when a subject was under the treatment of the disease, had an eGFR less than 60 mL/min/1.73 m^2 or had positive urine protein results.

The presence of hyper-uricemia was defined when a subject was under the treatment of the disease, had gout, or their uric acid (UA) level was more than 6.9 mg/dL.

Comparisons of BNP-TnI quadrants

Using the clinical cut-off values of BNP [14] and TnI [15], we defined quadrants according to BNP and TnI levels as follows:

1) Quadrant A: BNP equal to or less than 40.0 pg/mL and TnI more than 26.2 pg/mL

2) Quadrant B: BNP equal to or less than 40.0 pg/mL and TnI equal to or less than 26.2 pg/mL

3) Quadrant C: BNP more than 40.0 pg/mL and TnI equal to or less than 26.2 pg/mL

4) Quadrant D: BNP more than 40.0 pg/mL and TnI more than 26.2 pg/mL

With these quadrants, we assessed factors that differentiated pairs of quadrants by performing the Wilcoxon's test. For the assessment, we chose age, BMI, SBP, HR, CTR, VC, Hb, PLT, UA, eGFR, BUN, LDL-C, HDL-C, TG, HbA1c, FBG as the parameters with possible cardiovascular risks. We also included the FRS to confirm whether quadrants A and C were associated with the FRS.

Statistical analyses

JMP 11.0.0 (SAS) was used for the statistical analyses. The 95th percentiles of the BNP distribution and the 99th percentiles of the TnI distribution in the population in this study were determined using the robust statistical method described in the Clinical & Laboratory Standards Institute (CLSI) document C28-A3c [16]. The differences of

the basic characteristics by gender were assessed by the Wilcoxon's test. The associations of BNP or TnI with the FRS were assessed by univariable followed by multivariable linear regression analyses in each gender. The associations of BNP or TnI with the diseases related with cardiovascular risks were assessed by multivariable linear regression analyses. For these analyses, the presence or absence of a disease was encoded as "0 (absent)" or "1 (present)."

Results

Characteristics of the subjects

We summarized the background characteristics of the 950 subjects in Table 1. All the parameters were significantly different by gender except for the age, CTR, eGFR, LDL-C, HbA1c, and the presence of CKD.

Parameters	Unit	Female (N=439)	Male (N=511)	P-value
		Median (25%ile, 75%ile)	Median (25%ile, 75%ile)	
Age	years	53.0 (46.5, 60.0)	54.0 (46.5, 60.0)	0.079
BMI	kg/m^2	21.4 (19.5, 23.5)	23.3 (21.6, 25.5)	<0.001
SBP	mmHg	114.0 (103.0, 125.5)	120.0 (111.0, 132.0)	<0.001
DBP	mmHg	72.0 (64.0, 81.0)	79.0 (71.0, 88.0)	<0.001
HR	bpm	73 (67, 80)	70 (63, 78)	<0.001
CTR	%	44.4 (41.3, 47.6)	44.7 (41.7, 47.5)	0.335
VC	L	2.9 (2.5, 3.2)	4.1 (3.7, 4.5)	<0.001
WBC	/uL	4800 (4000, 5600)	5300 (4450, 6350)	<0.001
RBC	10^4/uL	437 (417, 459)	483 (459, 510)	<0.001
Hb	g/dL	13.1 (12.4, 13.6)	14.9 (14.2, 15.5)	<0.001
Ht	%	40.1 (38.1, 41.6)	45.0 (43.0, 46.8)	<0.001
PLT	10^4/uL	23.6 (20.7, 26.6)	22.5 (18.5, 26.0)	<0.001
ALB	g/dL	4.4 (4.3, 4.6)	4.5 (4.3, 4.7)	<0.001
AST	U/L	20.0 (18.0, 24.0)	22.0 (18.5, 26.0)	<0.001
ALT	U/L	17.0 (14.0, 24.0)	22.0 (17.0, 30.0)	<0.001
GGT	U/L	18.0 (14.0, 24.5)	32.0 (22.5, 55.5)	<0.001
UA	mg/dL	4.5 (3.9, 5.0)	6.1 (5.2, 6.8)	<0.001
eGFR	mL/ min/1.73 m^2	70.8 (63.5, 79.6)	71.5 (65.1, 78.0)	0.792
BUN	mg/dL	13.0 (11.0, 16.0)	14.0 (12.0, 16.0)	<0.001
LDL-C	mg/dL	122.0 (102.5, 142.0)	125.0 (106.0, 146.0)	0.220
HDL-C	mg/dL	76.0 (64.0, 87.0)	59.0 (50.0, 70.0)	<0.001
TG	mg/dL	71.0 (55.0, 99.0)	102.0 (73.0, 146.5)	<0.001
HbA1c	% (NGSP)	5.6 (5.5, 5.8)	5.7 (5.5, 5.9)	0.119
FBG	mg/dL	95.0 (90.0, 100.0)	101.0 (95.0, 108.0)	<0.001
FRS	years	6.0 (3.0, 10.0)	10.0 (7.0, 13.0)	<0.001
CKD	%	16.4	14.9	0.518
Dyslipidemia	%	39.9	64	<0.001
Hypertension	%	22.8	38.6	<0.001
Diabetes	%	3.9	8	0.008

Hyper-uricemia	%	0.9	22.1	<0.001
Current smoker	%	5.9	24.3	<0.001
BNP	pg/mL	95%ile (95% CI) 23.1 (21.0, 28.9)	95%ile (95% CI) 17.8 (15.6, 23.7)	<0.001
TnI	pg/mL	99%ile (95% CI) 23.5 (11.5, 136.0)	99%ile (95% CI) 26.8 (17.5, 65.2)	<0.001

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; CTR: Cardiothoracic Ratio; VC: Vital Capacity; WBC: White Blood Cell Count; RBC: Red Blood Cell Count; Hb: Haemoglobin; Ht: Haematocrit; PLT: Platelet Count; ALB: Albumin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma Glutamyl Transferase; UA: Uric Acid; eGFR: Estimated Glomerular Filtration Rate; BUN: Blood Urea Nitrogen; LDL-C: Low-density Lipoprotein Cholesterol; HDL-C: High-density Lipoprotein Cholesterol; TG: Triglyceride; HbA1c: Hemoglobin A1c; FBG: Fasting Blood Glucose; FRS: Framingham Risk Score; CKD: Chronic Kidney Disease; BNP: B-type Natriuretic Peptide; TnI: Cardiac Troponin I.

Table 1: Background Characteristics of the Subjects.

Association with the FRS

Gender	Parameters	Univariable			Multivariable		
		Beta	SE	P-value	Beta	SE	P-value
Females	Intercept				5.969	0.284	<0.001
	BNP	0.095	0.024	<0.001	0.088	0.023	<0.001
	TnI	0.092	0.025	<0.001	0.083	0.025	<0.001
Males	Intercept				9.197	0.267	<0.001
	BNP	0.148	0.026	<0.001	0.140	0.025	<0.001
	TnI	0.157	0.038	<0.001	0.142	0.037	<0.001

Table 2: Univariable and multivariable linear regression analyses for the association of BNP and TnI with the FRS; FRS: Framingham Risk Score; SE: Standard Error; BNP: B-type Natriuretic Peptide; TnI: Cardiac Troponin I.

Parameters	BNP			TnI		
	Beta	SE	P-value	Beta	SE	P-value
Intercept	8.054	0.406	<0.001	0.908	0.336	0.007
Hypertension	1.938	0.571	0.001	1.971	0.472	<0.001
Dyslipidemia	-2.347	0.533	<0.001	1.081	0.441	0.014
Diabetes	0.845	0.880	0.338	-0.761	0.729	0.296
CKD	1.869	0.711	0.009	0.359	0.588	0.541
Hyper-uricemia	-1.259	0.796	0.114	0.798	0.659	0.226

Table 3: Multivariable Linear regression analyses for the association of BNP and TnI with diseases related with cardiovascular risks; SE: Standard Error; BNP: B-type Natriuretic Peptide; TnI: Cardiac Troponin I; CKD: Chronic Kidney Disease.

The associations of the BNP or TnI level with the FRS in each gender by the linear regression analyses were shown in Table 2. The BNP and TnI levels were significantly and independently associated with the FRS in both genders (Table 3).

Association with diseases

By the multivariable linear regression analyses, the presence of hypertension and CKD were positively, but that of dyslipidemia was negatively associated with the BNP level, while the presence of hypertension and dyslipidemia were positively associated with the TnI level.

Comparisons of BNP-TnI quadrants

By the definition described in the Methods, we obtained 9, 932, 9 and 0 subjects in quadrant A, B, C and D, respectively (Figure 1 and Table 4). We then assessed the differences between pairs of quadrants among quadrants A, B and C using the Wilcoxon's test. The BMI, CTR and the FRS were significantly higher in quadrant A than quadrant B. The age, CTR, PLT and the FRS were significantly higher and the PLT were significantly lower in quadrant C than quadrant B. The Age was significantly lower, but the BMI and TG were significantly higher in quadrant A than quadrant C.

Parameters	Quadrant A (N=9)	Quadrant B (N=932)	Quadrant C (N=9)	P-value		
	Median (25%ile, 75%ile)	Median (25%ile, 75%ile)	Median (25%ile, 75%ile)	A *vs.* B	B *vs.* C	C *vs.* A
Gender				0.915	0.915	1.000
Age	59.0 (56.0, 68.0)	54.0 (47.0, 60.0)	71.0 (68.0, 77.0)	0.120	<0.001	0.047
BMI	25.6 (23.8, 25.8)	22.5 (20.6, 24.6)	20.1 (19.8, 24.5)	0.010	0.218	0.020
SBP	122.0 (115.0, 128.0)	117.0 (107.0, 128.0)	119.0 (113.0, 130.0)	0.466	0.407	0.965
HR	78.0 (63.0, 87.0)	71.0 (65.0, 79.0)	77.0 (72.0, 84.0)	0.560	0.242	0.860
CTR	46.3 (45.9, 49.1)	44.6 (41.5, 47.6)	47.2 (44.2, 53.6)	0.020	0.020	0.894
VC	3.5 (2.9, 4.0)	3.4 (2.9, 4.1)	3.7 (2.1, 3.9)	0.787	0.463	0.659
Hb	13.9 (13.9, 15.1)	14.0 (13.1, 15.0)	13.9 (12.8, 14.3)	0.759	0.636	0.689
PLT	22.2 (19.4, 23.6)	23.0 (20.2, 26.1)	18.9 (15.7, 20.0)	0.241	0.002	0.145
UA	6.1 (4.8, 6.7)	5.2 (4.4, 6.3)	5.7 (4.5, 6.3)	0.324	0.898	0.452
eGFR	73.9 (65.9, 81.3)	71.2 (64.6, 78.6)	65.7 (55.8, 77.2)	0.593	0.217	0.216
BUN	14.0 (13.0, 15.0)	14.0 (11.0, 128.0)	14.0 (13.0, 17.0)	0.585	0.368	0.789
LDL-C	124.0 (114.0, 135.0)	124.0 (104.0, 145.0)	114.0 (96.0, 126.0)	0.939	0.196	0.249
HDL-C	57.0 (54.0, 65.0)	67.0 (55.0, 80.0)	63.0 (56.0, 81.0)	0.081	0.876	0.250
TG	127.0 (75.0, 237.0)	86.0 (61.8, 124.3)	84.0 (61.0, 97.0)	0.057	0.390	0.038
HbA1c	5.8 (5.7, 6.0)	5.6 (5.5, 5.9)	5.7 (5.4, 5.7)	0.158	0.971	0.418
FBG	98.0 (96.0, 106.0)	97.0 (92.0, 105.0)	104.0 (95.0, 108.0)	0.446	0.222	0.724
FRS	12.0 (11.0, 14.0)	8.0 (6.0, 12.0)	13.0 (12.0, 17.0)	0.006	0.002	0.561

BMI: Body Mass Index; SBP: Systolic Blood Pressure; HR: Heart Rate; CTR: Cardio-thoracic Ratio; VC: Vital Capacity; Hb: Haemoglobin; PLT: Platelet Count; UA: Uric Acid; eGFR: Estimated Glomerular Filtration Rate; BUN: Blood Urea Nitrogen; LDL-C: Low-density Lipoprotein Cholesterol; HDL-C: High-density Lipoprotein Cholesterol; TG: Triglyceride; HbA1c: Hemoglobin A1c; FBG: Fasting Blood Glucose; FRS: Framingham Risk Score.

Table 4: Assessment of factors that differentiate quadrants defined by a BNP-TnI plot.

Discussion

In this study, we assessed the validity of the combination assay of BNP and hsTnI for the screening of cardiovascular risks in the general population. In the background characteristics by gender, there were significant differences between the gender. As for the most of the parameters related with cardiovascular risks including BMI, blood pressures, lipids, and HbA1c, higher cardiovascular risks were indicated in the male group compared with the female group. The percentages of the diseases related with cardiovascular diseases were higher and the FRS was also higher in the male group. As were reported previously [15,17,18], the TnI level was higher in the male group. As shown in the background characteristics mentioned above, the higher cardiovascular risks in the male group could account for the higher TnI level.

The BNP level, on the contrary, was lower in the male group, which is in agreement with the report by Kawai et al. [14]. Considering the report by Kawai et al. that the BNP level was negatively correlated with BMI [14], and the result that the BNP level was negatively correlated with dyslipidemia as shown in Table 3, we assumed that the suppression of the BNP level in the male group by the higher BMI and the higher percentage of dyslipidemia surpassed the elevation of the BNP level by the other risk factors.

From the result that the TnI and BNP levels were positively and independently associated with the FRS as shown in Table 2, both BNP and TnI levels would be elevated in individuals with higher cardiovascular risks, regardless of the difference of the baseline.

By the comparison of quadrants A, B and C, quadrants A and C showed significantly higher CTR and FRS than quadrant B as shown in Table 4. Quadrants A and C, therefore, could be thought as two high-

risk populations. The independent association of TnI and BNP with the FRS could be understood as that TnI and BNP are associated with these two independent populations, quadrants A and C, respectively.

The factors that differentiated quadrants A and C were age, BMI and TG. Together with the results that the BNP level was negatively associated with dyslipidemia while the TnI level was positively associated with it as shown in Table 3, it could be assumed that obesity is a key factor that differentiates these two populations. Because of the suppressed BNP level in quadrant A, the heart may be less protected and more susceptible to myocardial injury, giving ground to the TnI elevation.

The result that the median of the age in quadrant A (59.0) was significantly lower than that in quadrant C (71.0) may indicate cardiac diseases related with dyslipidemia develop faster than those without one.

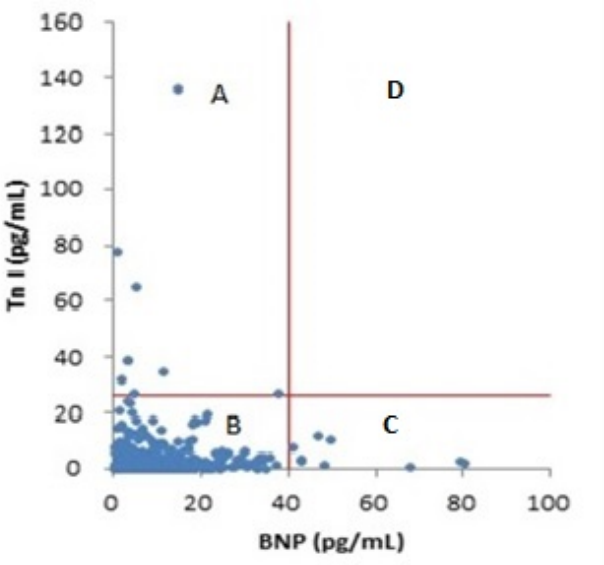

Figure 1: Graphical representation between BNP and Tnl. A, B, C and D are the designated quadrants.

Conclusion

In this study, we identified two populations with the high FRS, quadrants A and C, defined as low-BNP/high-TnI and high-BNP/low-TnI, respectively. Quadrants A and C were differentiated by age, BMI and TG.

Based on the above results, we concluded that not only BNP but also TnI could provide important information for cardiovascular risks in the general population due to its ability to detect the different high risk population as BNP could detect.

Conflicts of interest

The author certifies no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in a speaker's bureau; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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