Impact of medical checkup parameters on major adverse cardiovascular events in the general Japanese population

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Abstract

Medical checkup plays a role in the identification of individuals with increased cardiovascular risk. We assessed predictors of major adverse cardiovascular events (MACEs) among parameters examined during medical checkup in the general Japanese population. A total of 13,522 individuals (52.8 ± 12.3 years) who participated in our medical checkup program were enrolled and followed up for 64,748 person-years, with the endpoint of MACE. MACE included cardiovascular death, non-fatal myocardial infarction, unstable angina, decompensated heart failure, stroke, and other cardiovascular events that required hospitalization. During the follow-up, MACE occurred in 196 participants. The risk of MACE was significantly increased across the quartiles of baseline B-type natriuretic peptide (BNP) levels (logrank, $P < 0.001$). Multivariate Cox-hazard analysis demonstrated that male sex, age, systolic blood pressure, and BNP at baseline independently correlated with future MACE after adjustment for confounders, while the impact of BNP was the most significant among the variables investigated. These results suggest that BNP levels, obtained during medical checkup examination, is an independent and the most significant predictor of MACE. The inclusion of BNP as part of medical checkup parameters may improve the quality of screening for individuals at increased cardiovascular risk and prevent cardiovascular disease.

Introduction

The number of patients with cardiovascular disease, such as coronary heart disease, heart failure, and stroke, in Japan is estimated to be 2.85 million (approximately 2% of the Japanese population), and the cardiovascular mortality is about 23.5% of the total death from cardiovascular diseases [1]. Cardiovascular disease is not only a leading cause of death [2] but also seriously affects healthy life expectancy. Therefore, several policies that target the general population have been developed to reduce the morbidity and mortality of cardiovascular disease. Although numerous factors are involved in the development of cardiovascular disease, most of them are modifiable and lifestyle related [3–7]. Medical checkup in the general population can help to identify individual modifiable risk factors, which can improve health or prevent cardiovascular disease.

Medical checkup is routinely performed annually for employees or community residents, and most of the Japanese population undergo periodical (usually annual) medical checkup. In 2019, about 74% of men and 66% of women in Japan had annual/periodical medical checkup [8]. These medical checkups are primarily aimed at preventing lifestyle-related diseases such as major adverse cardiovascular events (MACE). A medical checkup examination usually includes several tests, such as anthropometry, blood pressure, glucose tolerance and lipid profile tests, that evaluate the risk of cardiovascular disease. Although most of these factors are useful for the risk evaluation of MACE, the impact of each on the development of MACE has not been investigated. Therefore, the present study was designed to investigate significant predictors of MACE among clinical tests performed during medical checkup programs.

Results

Baseline characteristics of participants in the present study are listed in Table 1. The mean value of each parameter in Table 1 was within the normal reference range. Participants on medication for hypertension, diabetes mellitus, or dyslipidemia were 2,119 (60.4% of all participants with hypertension), 712 (62.8%), and 1,115 (19.7%), respectively. After the baseline examination during the medical checkups, the participants were followed up, with MACE as the endpoint. The actual follow-up period of the present study was 64,748 person-years, and the median follow-up period was 1,827 days (range, 105–3,181 days). During the follow-up period, MACE occurred in 196 participants (Table 2).

Table 1
Baseline characteristics of study participants

	Total (*n* = 13,522)
Sex; male, n (%)	8140 (60.2%)
Age (years)	52.8 ± 12.3
Body mass index (kg/m^2)	22.7 ± 3.3
Waist circumference (cm)	83.4 ± 9.1
Systolic blood pressure (mmHg)	123.6 ± 15.9
Diastolic blood pressure (mmHg)	75.9 ± 9.9
Pulse rate (bpm)	63.4 ± 9.4
Fasting plasma glucose (mg/dL)	96.7 ± 18.7
HbA1c (%)	5.68 ± 0.66
LDL-C (mg/dL)	120.4 ± 28.7
HDL-C (mg/dL)	60.0 ± 14.4
Triglyceride (mg/dL)	108.7 ± 77.2
Serum creatinine (mg/dL)	0.76 ± 0.19
eGFR (mL/min per 1.73 m^2)	78.8 ± 14.6
Uric acid (mg/dL)	5.37 ± 1.39
Hemoglobin (g/dL)	14.0 ± 1.4
Sokolow-Lyon voltage (mV)	2.41 ± 0.79
BNP (pg/mL)	10.7 [6.4–17.8]
Current smoking status (%)	3,062 (22.6%)
Frequent alcohol consumption (%)[A]	5,327 (39.4%)
Proteinuria (%)	273 (2.0%)

Data are presented as mean ± SD, as *n* (%) or median [interquartile range].

[A]Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

	Total (*n* = 13,522)
Hypertension (%)	3,511 (26.0%)
Diabetes mellitus (%)	1,134 (8.4%)
Dyslipidemia (%)	5,652 (41.8%)
Metabolic syndrome (%)	1,681 (12.4%)
Data are presented as mean ± SD, as *n* (%) or median [interquartile range].	
[A]Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.	
Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.	

Table 2
Major adverse cardiovascular events during the follow-up period

	Total (*n* = 196)
Cardiovascular death	12
Non-fatal myocardial infarction	37
Unstable angina	7
Decompensated heart failure	15
Stroke	66
Other cardiovascular events	59
Major adverse cardiovascular event is defined as cardiovascular death, non-fatal myocardial infarction, unstable angina, decompensated heart failure, stroke, and other cardiovascular events requiring hospitalization (aortic aneurysm, aortic dissection, and effort angina pectoris).	

Retrospective analysis of cardiovascular risk

Retrospective comparison of groups with and without MACE during the follow-up period revealed differences in baseline characteristics between the two groups (Table 3). Risk factors such as age and blood pressure were higher in participants with MACE compared to those without MACE, although the difference between the two groups was not marked.

Table 3
Comparison of participants with and without major adverse cardiovascular event during follow-up: Retrospective analysis

	with MACE (*n* = 13326)	without MACE (*n* = 196)
Gender; male, n (%)	7980 (59.9%)	160 (81.6%)*
Age (years)	52.7 ± 12.3	61.3 ± 8.9*
Body mass index (kg/m^2)	22.7 ± 3.3	23.3 ± 2.9*
Waist circumference (cm)	83.4 ± 9.1	86.4 ± 8.3*
Systolic blood pressure (mmHg)	123.4 ± 15.9	131.8 ± 15.7*
Diastolic blood pressure (mmHg)	75.8 ± 9.9	79.5 ± 10.3*
Pulse rate (bpm)	63.4 ± 9.4	62.4 ± 9.9
Fasting plasma glucose (mg/dL)	96.6 ± 18.5	101.1 ± 24.9*
HbA1c (%)	5.68 ± 0.66	5.87 ± 0.84*
LDL-C (mg/dL)	120.4 ± 28.7	120.5 ± 28.4
HDL-C (mg/dL)	60.1 ± 14.4	56.4 ± 14.1*
Triglyceride (mg/dL)	108.5 ± 77.3	118.7 ± 66.6
Serum creatinine (mg/dL)	0.76 ± 0.19	0.82 ± 0.21*
eGFR (mL/min per 1.73 m^2)	78.9 ± 14.5	73.6 ± 15.0*
Uric acid (mg/dL)	5.37 ± 1.39	5.84 ± 1.22*
Hemoglobin (g/dL)	14.0 ± 1.5	14.1 ± 1.4
Sokolow-Lyon voltage (mV)	2.41 ± 0.79	2.73 ± 0.87*
BNP (pg/mL)	10.6 [6.3–17.7]	15.2 [9.5–28.8]*

Data are presented as mean ± SD, as *n* (%) or median [interquartile range].

*$P < 0.05$ compared with "without MACE" (unpaired *t* test, Mann-Whitney U test [BNP and Follow-up period] or Chi-squared test [current smoking status, frequent alcohol consumption, proteinuria, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome]).

[A]Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

	with MACE (*n* = 13326)	without MACE (*n* = 196)
Current smoking status (%)	3015 (22.6%)	47 (24.0%)
Frequent alcohol consumption (%)[A]	5240 (39.3%)	87 (44.4%)
Proteinuria (%)	271 (2.0%)	2 (1.0%)
Hypertension (%)	3413 (25.6%)	98 (50.0%)*
Diabetes mellitus (%)	1103 (8.3%)	31 (15.8%)*
Dyslipidemia (%)	5555 (41.7%)	97 (49.5%)*
Metabolic syndrome (%)	1635 (12.3%)	46 (23.5%)*
Follow-up period (day)	1828 [1061–2553]	1230 [699–1888]*
Data are presented as mean ± SD, as *n* (%) or median [interquartile range].		
*$P < 0.05$ compared with "without MACE" (unpaired *t* test, Mann-Whitney U test [BNP and Follow-up period] or Chi-squared test [current smoking status, frequent alcohol consumption, proteinuria, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome]).		
[A]Frequent alcohol consumption was defined as the consumption of alcohol six or seven times per week.		
Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.		

Prospective analysis of cardiovascular risk

Most of the classic risk factors showed correlation with the risk of MACE, while low-density lipoprotein cholesterol, triglycerides or current smoking habit did not show such correlation in the univariate analysis (Table 4). Among the variables investigated, BNP at baseline correlated with MACE with the greatest hazard ratio. When the participants were divided into four groups according to the quartiles of baseline BNP levels, the risk of MACE was significantly increased across the quartiles (Fig. 1). Factors that showed significant correlation with MACE in univariate analysis and other important factors were adjusted for in a multivariate analysis (Table 4). Regression analysis showed that male sex, age, systolic blood pressure, and Sokolow-Lyon voltage were independently associated with MACE; however, in a model where BNP was added as an independent variable, there was no significant correlation of Sokolow-Lyon voltage with MACE, and BNP was the most significant predictor of MACE among the factors included in the model (Table 4).

Table 4
Cox-hazard regression analysis investigating factors that predict the incidence of major adverse cardiovascular events

	Univariate		Multivariate A		Multivariate B	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Sex; male, n (%)	< 0.001	2.827 (1.968–4.059)	0.019	1.676 (1.091–2.574)	0.005	1.849 (1.199–2.850)
Age (years)	< 0.001	1.067 (1.053–1.082)	< 0.001	1.061 (1.045–1.076)	< 0.001	1.047 (1.030–1.063)
Body mass index (kg/m^2)	0.007	1.057 (1.015–1.100)	—	—	—	—
Waist circumference (cm)	< 0.001	1.034 (1.019–1.049)	0.078	1.017 (0.998–1.036)	0.061	1.018 (0.999–1.037)
Systolic blood pressure (mmHg)	< 0.001	1.028 (1.019–1.036)	0.008	1.013 (1.003–1.022)	0.021	1.011 (1.002–1.020)
Diastolic blood pressure (mmHg)	< 0.001	1.032 (1.018–1.046)	—	—	—	—
Pulse rate (bpm)	0.414	0.994 (0.978–1.009)	0.677	0.997 (0.981–1.012)	0.917	1.001 (0.986–1.016)
Fasting plasma glucose (mg/dL)	< 0.001	1.009 (1.004–1.014)	—	—	—	—
HbA1c (%)	< 0.001	1.311 (1.150–1.495)	0.158	1.137 (0.951–1.359)	0.114	1.154 (0.966–1.379)
LDL-C (mg/dL)	0.980	1.000 (0.995–1.005)	0.578	0.998 (0.993–1.004)	0.892	1.000 (0.995–1.006)

Multivariate A: Adjustment for male sex, age, waist circumference, systolic blood pressure, pulse rate, HbA1c, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.

Multivariate B: Additional adjustment for logBNP.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

	Univariate		Multivariate A		Multivariate B	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
HDL-C (mg/dL)	0.002	0.983 (0.972–0.993)	0.482	0.996 (0.985–1.007)	0.334	0.994 (0.983–1.006)
Triglyceride (mg/dL)	0.085	1.001 (1.000–1.003)	—	—	—	—
Serum creatinine (mg/dL)	< 0.001	1.682 (1.378–2.054)	0.223	1.288 (0.857–1.936)	0.303	1.259 (0.812–1.953)
eGFR (mL/min per 1.73 m^2)	< 0.001	0.974 (0.964–0.984)	—	—	—	—
Uric acid (mg/dL)	< 0.001	1.273 (1.153–1.405)	0.087	1.111 (0.985–1.254)	0.083	1.112 (0.986–1.255)
Hemoglobin (g/dL)	0.230	1.063 (0.962–1.175)	—	—	—	—
Sokolow-Lyon voltage (mV)	< 0.001	1.535 (1.309–1.802)	0.018	1.231 (1.036–1.462)	0.057	1.178 (0.995–1.394)
logBNP	< 0.001	5.068 (3.356–7.656)	—	—	< 0.001	2.696 (1.700–4.277)
Current smoking status (%)	0.531	1.111 (0.800–1.543)	0.191	1.267 (0.888–1.806)	0.214	1.252 (0.879–1.785)
Frequent alcohol consumption (%)[A]	0.175	1.212 (0.917–1.613)	—	—	—	—
Proteinuria (%)	0.477	0.603 (0.150–2.429)	—	—	—	—

Multivariate A: Adjustment for male sex, age, waist circumference, systolic blood pressure, pulse rate, HbA1c, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.

Multivariate B: Additional adjustment for logBNP.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Risk of hypertension, diabetes, dyslipidemia, and metabolic syndrome

In another series of analyses, the predictive value of hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome for MACE was investigated (Fig. 2 and Table 5). Although participants having such diseases or syndrome showed increased risk of MACE in the Kaplan-Meier analysis (Fig. 2) and univariate analysis (Table 5), multivariate Cox-hazard analysis demonstrated that hypertension, diabetes mellitus, and metabolic syndrome, but not dyslipidemia, were the independent predictors of MACE (Table 5).

Table 5
Cox-hazard regression analysis investigating the predictive value of lifestyle-related diseases for MACE

	Univariate		Multivariate A		Multivariate B	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
[a]Hypertension (%)	< 0.001	2.809 (2.121–3.720)	0.006	1.548 (1.133–2.114)	0.012	1.497 (1.094–2.048)
[b]Diabetes mellitus (%)	< 0.001	2.989 (2.003–4.461)	0.002	1.918 (1.268–2.901)	0.002	1.928 (1.274–2.918)
[c]Dyslipidemia (%)	0.029	1.367 (1.032–1.812)	0.724	1.054 (0.787–1.413)	0.339	1.156 (0.859–1.555)
[d]Metabolic syndrome (%)	< 0.001	2.032 (1.456–2.836)	0.073	1.370 (0.972–1.931)	0.047	1.417 (1.005–1.998)
Multivariate A:						
[a]Hypertension was adjusted for male sex, age, waist circumference, pulse rate, HbA1c, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.						
[b]Diabetes mellitus for male sex, age, waist circumference, systolic blood pressure, pulse rate, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.						
[c]Dyslipidemia for male sex, age, waist circumference, systolic blood pressure, pulse rate, HbA1c, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.						
[d]Metabolic syndrome for male sex, age, pulse rate, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.						
Maltivariate B: Additional adjustment for logBNP.						
Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.						

Sub-analysis in participants without medication

In a univariate sub-analysis of participants who were no on medication that could affect the cardiovascular system (*n* = 10,475), male sex, age, blood pressure, serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, Sokolow-Lyon voltage, proteinuria, and BNP were significantly associated with MACE (Table 6). However, male sex, age, and BNP were the only independent predictors of developing MACE (Table 6, multivariate B).

Table 6
Cox-hazard regression analysis investigating factors that predict the incidence of major adverse cardiovascular events in participants without medication

	Univariate		Multivariate A		Multivariate B	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Sex; male, n (%)	< 0.001	2.680 (1.643–4.373)	0.083	1.792 (0.928–3.463)	0.036	2.038 (1.049–3.958)
Age (years)	< 0.001	1.070 (1.050–1.090)	< 0.001	1.066 (1.045–1.087)	< 0.001	1.051 (1.029–1.075)
Body mass index (kg/m^2)	0.339	1.030 (0.969–1.095)	—	—	—	—
Waist circumference (cm)	0.075	1.020 (0.998–1.043)	0.656	1.006 (0.979–1.035)	0.555	1.008 (0.981–1.036)
Systolic blood pressure (mmHg)	< 0.001	1.029 (1.017–1.041)	0.033	1.015 (1.001–1.029)	0.056	1.013 (1.000–1.027)
Diastolic blood pressure (mmHg)	< 0.001	1.044 (1.024–1.064)	—	—	—	—
Pulse rate (bpm)	0.367	0.990 (0.968–1.012)	0.841	0.998 (0.975–1.021)	0.858	1.002 (0.980–1.025)
Fasting plasma glucose (mg/dL)	0.641	1.003 (0.991–1.015)	—	—	—	—
HbA1c (%)	0.482	1.116 (0.822–1.515)	0.262	0.762 (0.473–1.226)	0.286	0.773 (0.481–1.241)
LDL-C (mg/dL)	0.207	1.004 (0.998–1.011)	0.469	1.003 (0.995–1.010)	0.223	1.005 (0.997–1.012)

Multivariate A: Adjustment for male sex, age, waist circumference, systolic blood pressure, pulse rate, HbA1c, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.

Multivariate B: Additional adjustment for logBNP.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

	Univariate		Multivariate A		Multivariate B	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
HDL-C (mg/dL)	0.375	0.994 (0.980–1.008)	0.629	1.004 (0.989–1.019)	0.728	1.003 (0.988–1.018)
Triglyceride (mg/dL)	0.607	1.001 (0.998–1.003)	—	—	—	—
Serum creatinine (mg/dL)	< 0.001	4.541 (1.961–10.51)	0.640	1.457 (0.301–7.058)	0.743	1.301 (0.270–6.268)
eGFR (mL/min per 1.73 m^2)	0.002	0.977 (0.962–0.992)	—	—	—	—
Uric acid (mg/dL)	0.003	1.229 (1.072–1.408)	0.455	1.070 (0.896–1.278)	0.410	1.077 (0.902–1.286)
Hemoglobin (g/dL)	0.709	1.026 (0.897–1.173)	—	—	—	—
Sokolow-Lyon voltage (mV)	< 0.001	1.649 (1.319–2.061)	0.031	1.310 (1.025–1.674)	0.068	1.251 (0.984–1.591)
logBNP	< 0.001	5.336 (2.925–9.732)	—	—	0.004	2.772 (1.393–5.519)
Current smoking status (%)	0.849	0.956 (0.605–1.512)	0.827	1.057 (0.645–1.731)	0.820	1.059 (0.647–1.734)
Frequent alcohol consumption (%)[A]	0.068	1.439 (0.974–2.126)	—	—	—	—
Proteinuria (%)	0.021	0.462 (0.240–0.889)	—	—	—	—

Multivariate A: Adjustment for male sex, age, waist circumference, systolic blood pressure, pulse rate, HbA1c, LDL-C, HDL-C, serum creatinine, uric acid, Sokolow-Lyon voltage, and current smoking status.

Multivariate B: Additional adjustment for logBNP.

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Discussion

The present study demonstrated that plasma BNP level examined during medical checkups of the general Japanese population is a strong independent predictor of MACE. The addition of BNP to the medical checkup parameters may improve the quality cardiovascular disease prediction and, thereby, may play a role in cardiovascular disease prevention.

BNP is synthesized and secreted from ventricular cells mainly in response to an increase in ventricular volume or pressure [9–13]. There is increasing evidence that circulating levels of plasma BNP is a reliable marker of left ventricular function and the severity and prognosis of heart failure [11–13]. However, careful interpretation is necessary because numerous factors, such as sex, age, blood pressure, kidney function, and obesity, seriously affect BNP levels [11–15]. Furthermore, the clinical significance of relatively low levels of peptide seems to be obscure. Although the normal reference value for BNP level is 18.4 pg/ml or less, values above the normal reference value do not necessarily indicate heart failure. The Japanese Heart Failure Society set a cut-off point of 40 pg/ml for plasma BNP concentration to identify patients with mild heart failure and of 100 pg/mg to identify patients with heart failure requiring medication [16]. Thus, a BNP predictive value that is less than 40 pg/ml been considered low for identifying heart failure. The median value and interquartile range of BNP in the present study was 10.7 and 6.4–17.8 pg/ml, respectively, which clearly demonstrates the clinical significance of relatively low levels of BNP in the general population. The present results are consistent with that of a previous study demonstrating that relatively low levels of BNP were associated with death and various cardiovascular diseases [17]. It is noteworthy that BNP measured during medical checkup predicts MACE independent of classic risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking. This present finding implies that BNP and classic risk factors play a complementary role in the prediction and, thereafter, prevention of cardiovascular events. The results of the sub-analysis conducted on participants without medication that may affect the cardiovascular system further support the concept that BNP is a strong independent predictor of MACE. However, careful interpretation is necessary because more than a half of participants with hypertension, diabetes mellitus, or dyslipidemia were excluded from the sub-analysis and blood pressure, glucose tolerance, and lipid profile were nearly normal in most of the participants included in the sub-analysis.

The mechanism underlying the association between BNP and future occurrence of MACE was not elucidated in the present study. The prediction of heart failure using BNP levels is easy to understand when considering the mechanism of BNP secretion [9–13]. Latent left ventricular dysfunction induced by subclinical or concealed myocardial ischemia may have increased BNP levels, resulting in its prediction of clinical myocardial ischemia, such as myocardial infarction, unstable angina, or angina requiring hospitalization for percutaneous coronary intervention. In line with the speculation, BNP is predictive of silent myocardial ischemia in patients with non-obstructive hypertrophic cardiomyopathy [18], and BNP predicts recurrence of angina pectoris [19]. Stroke was the most frequent MACE in the present study. Recent studies have suggested that salt intake causes mild BNP elevation (below 30 pg/ml) in the general population [15, 20] and that excessive salt intake is an independent risk factor for cardiovascular

events [21]. Thus, the mild increase of BNP observed in the present study may at least partially reflect excessive salt intake. BNP is also elevated in patients with hypertension, and increasing blood pressure stimulates BNP secretion [22], suggesting that an increase in BNP may have partially occurred following mild blood pressure elevation although adjustment for blood pressure in Cox regression analysis did not eliminate the significant correlation between BNP and MACE.

The present study confirmed the importance of the identification of individuals with metabolic syndrome as well as other classic risk factors. Although waist circumference, high-density lipoprotein cholesterol, or triglyceride alone was not an independent risk factor for MACE in the present observational study, a cluster of mild metabolic disorders independently predict future cardiovascular events. Low-density lipoprotein cholesterol or current smoking habit did not show significant correlation with MACE. Relatively low levels of low-density lipoprotein cholesterol in the present study participants and the presence of ex-smokers may have affected the results, although detailed mechanisms are uncertain.

The interpretation of the present results is limited by the following points. The participants were participants in our annual medical checkup program, and selection bias is possible. The outcome was confirmed by telephone or letter in some participants who did not visit our hospital after baseline examination, leading to a likelihood of an inaccurate diagnosis of the outcome in those participants. Although the large number of participants included in the present study may overcome some of these limitations, a study with more participants and longer observation period is necessary to arrive at a definite conclusion.

In conclusion, plasma BNP levels measured during medical checkup could serve as an excellent predictor of a cardiovascular event. BNP combined with the evaluation of other risk factors may improve the predictive quality of medical checkups in the general Japanese population.

Methods

Study design

The present cohort study recruited participants in our annual medical checkup program. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Enshu Hospital. All participants provided written informed consent prior to the start of the study and on each follow-up visit.

Study participants and procedures

The study subjects were recruited from a group of participants examined between 2008 and 2015 (n = 13,878). Our medical checkup program included an interview regarding health status, anthropometry, chest radiography, electrocardiography, and laboratory assessment of cardiovascular risk factors. Participants with a history of MACE (n = 154) or with missing data (n = 172) were excluded and the remaining participants (n = 13,522) were included in the present study. The participants were followed up

for 64,748 person-years, with the endpoint being the onset of MACE. The outcome was confirmed using a questionnaire at medical checkup, medical records, phone call, or letter. Possible association between MACE and clinical test parameters at baseline including sex, age, waist circumference, blood pressure, kidney function, fasting plasma glucose, lipid profile, hemoglobin, electrocardiogram (ECG), smoking habit, and alcohol consumption were investigated. In a sub-analysis, participants with medications that may affect the cardiovascular system were excluded, and the remaining participants were included in the analysis (n = 10,475). MACE was defined as cardiovascular death, non-fatal myocardial infarction, unstable angina, decompensated heart failure, stroke, and other cardiovascular events requiring hospitalization. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5% [23], or the use of antidiabetic medications, and dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL [24], or the use of antidyslipidemic medications. Metabolic syndrome was defined based on the Japanese diagnostic criteria (waist circumference ≥ 85 cm for males and ≥ 90 cm for females and 2 or more of the following three criteria: (1) triglycerides ≥ 150 mg/dL and/or high-density lipoprotein cholesterol < 40 mg/dL, (2) systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, and (3) fasting plasma glucose ≥ 110 mg/dL) [25]. The GFR was estimated using the modified Modification of Diet in Renal Disease study formula for the Japanese population [26]. Urinary protein was determined using a dipstick method (Arkray, Kyoto, Japan), which was interpreted by trained technicians and recorded as −, ±, 1+, 2+, 3+; proteinuria was defined as obtaining a result of 1+, 2+, or 3+. For the measurement of BNP, 3 ml of blood was transferred to plastic tubes containing 4.5 mg of 2Na-ethylenediamine-tetraacetic acid. Plasma samples were prepared within 30 min by pre-cooled centrifuge, immediately frozen, and stored at − 70°C until they were analyzed. The plasma BNP concentration was determined using a commercially available chemiluminescence enzyme immunoassay (MI02 Shionogi BNP kit; Shionogi, Osaka, Japan) [27]. Participants reported the frequency of alcohol consumption as ranging from 0 to 7 times/week, with frequent alcohol consumption defined as 6 or 7 times/week.

Statistical analysis

All analyses were performed using IBM SPSS statistics 24 (IBM SPSS, Chicago, Illinois, USA). Data are presented as mean ± SD or as number and percentage of participants, except for data on BNP and follow-up period, which are expressed as median values and interquartile ranges. In addition, because the distribution of BNP was skewed to the right, log-transformed BNP was used for statistical analysis. Any significant difference between the means of two normally distributed data was determined using unpaired t tests. Chi-squared test was used to compare categorical data. The impact of medical examination parameters on the incidence of MACE was investigated using Cox-hazard regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In all cases, two-tailed tests were used, and P < 0.05 was considered statistically significant.

Declarations

Declarations

Competing interests

The authors declare no competing interests.

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Author contributions

YD and HT designed the study; HT collected, TS and HT analyzed, and TS and YD interpreted the data. YD drafted the manuscript and YS revised the manuscript. All authors reviewed the manuscript.

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Figures

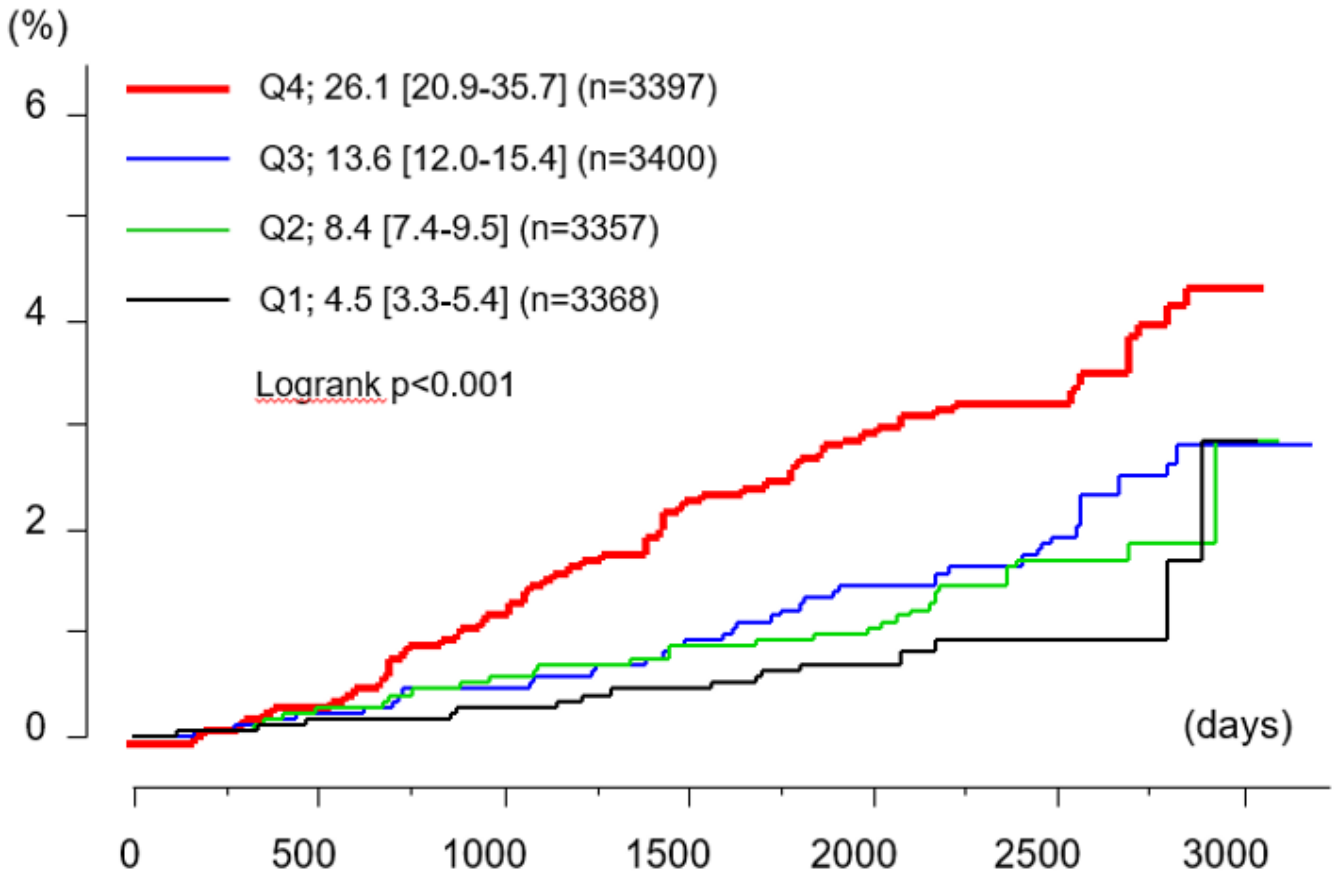

Figure 1

Kaplan-Meier analysis showing the influence of baseline BNP levels on the risk of major adverse cardiovascular events.

Participants were divided into four groups according the to the quartiles of baseline BNP levels (Q1–4). The median values and interquartile ranges are shown in the figure. MACE is defined as cardiovascular

death, non-fatal myocardial infarction, unstable angina, decompensated heart failure, stroke, and other cardiovascular events requiring hospitalization.

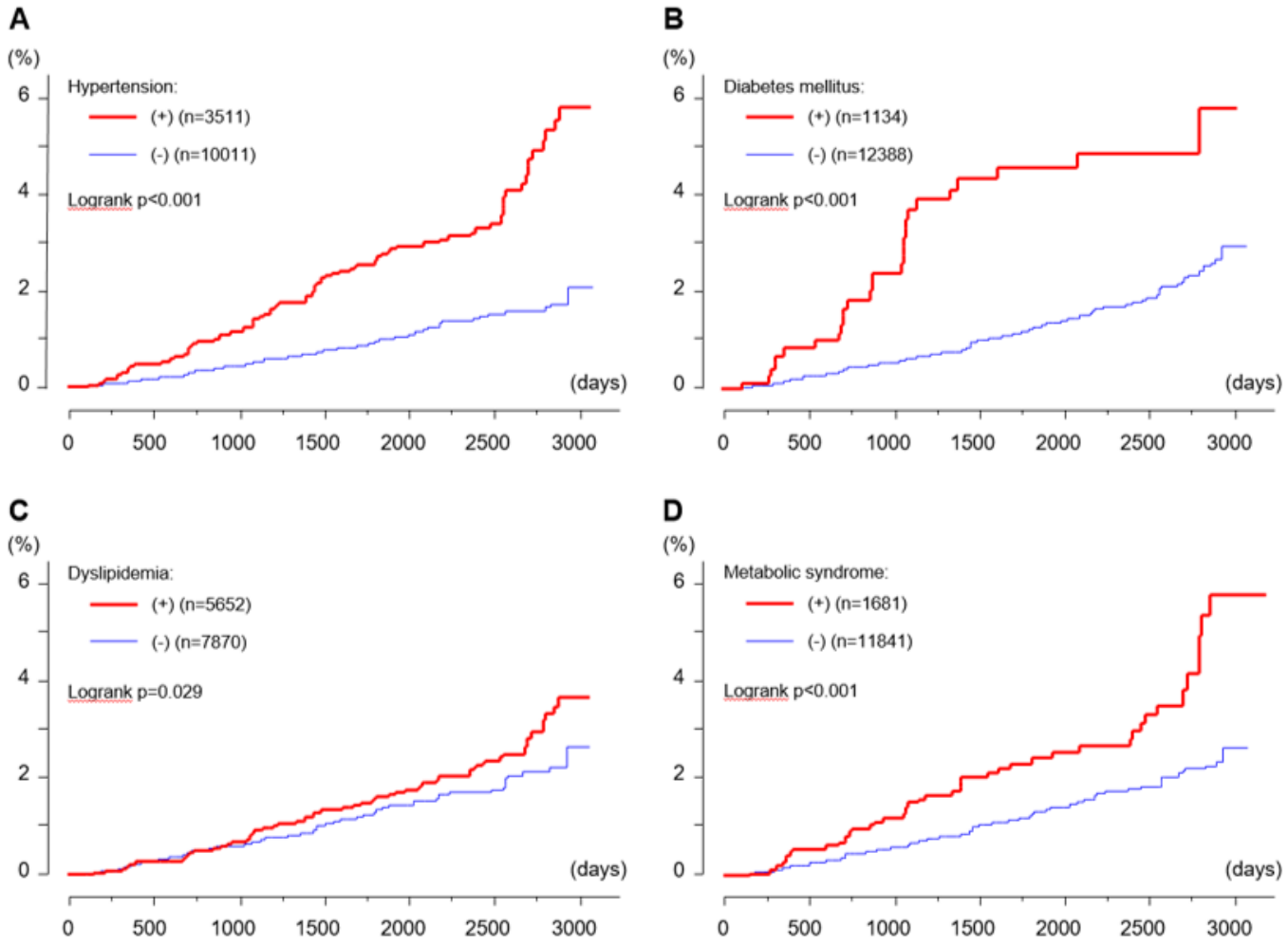

Figure 2

Kaplan-Meier analysis showing the influence of hypertension (A), diabetes mellitus (B), dyslipidemia (C), and metabolic syndrome (D) at baseline on the risk of major adverse cardiovascular events.

MACE is defined as cardiovascular death, non-fatal myocardial infarction, unstable angina, decompensated heart failure, stroke, and other cardiovascular events requiring hospitalization.