年が772人であった．未曾有の大災害があった2011年は，心筋梗塞発症数の大幅な増加を予想していたが，過去2年とほぼ同数であり，年間を通してみると福島県全体の発症総数には東日本大震災の影響が見えてこない．図5に示すように，県内でも津波被害の大きかった太平洋沿岸部について検討すると，2011年の年間心筋梗塞発症数は27%増加した．しかし，細かく見ていくと南部のいわき地区では40%増加したが，北部の相双地区では逆に10%減少していた．これらの結果の解釈には注意が必要である．福島県では震災に引き続いて発生した原子力発電所の事故により，原発周辺地区では緊急避難を余儀なくされ，人口および医療機関が大幅に減少した．図3のような結果になったのは，原発周辺の相双地区から比較的放射線量の低い南部のいわき地区に相当数の人口移動があったためと考えられる．したがって，倒壊被害の大きさと心筋梗塞の発症に相関関係のみられた阪神淡路大震災[8]のような視点からの検討は事実上不可能である．また，住民の避難先はいわき地区だけではなく広範囲にわたっており，さらに複数回の移動をくり返した人々がほとんどであった．住民票は元の市町村のままであり，第三者がそれらの動きをすべて把握するのは難しかった．県外に避難した人々も少なからず存在し，その間に心筋梗塞を発症した場合，われわれの調査からは漏れてしまう．2011年末の福島県の推計人口は住民票ベースで198万人と2009年の204万人から約6万人減少していた[19]．さらに住民票を移さずに県外に一時避難しているケースもあり，正確な人口把握は難しいのが実情であるが，県の人口が減っているとすれば，発症数は同数でも発症率はわずかに増加(人口10万人あたり38.5人→39.0人)したことになる．

東日本大震災の特殊性

東日本大震災においては，これまで国内外から報告されているほど急性冠症候群の発症やそれによる死亡率は増加していないようである．それはこの地震の形態が内陸あるいは大都市直下型ではなく，沿岸部の海底プレートを震源とした津波を伴う震災であったことと関係があると考えられる．実際に人的被害の大半は地震の揺れそのものではなく，引き続き東北沿岸を襲った大津波によるものであり，阪神淡路大震災や新潟県中越地震とは被害形態が大きく異なっている．通常の災害では多数の負傷者のうち一部が死亡する(負傷者＞死亡者)が，東日本大震災ではこれが当てはまらなかった(死亡者＞負傷者)．死者(行方不明者を含む)と負傷者の比率は阪神淡路大震災では1：6.8[5]，新潟県中越地震では1：71[9]であったが，東日本大震災では1：0.32[20]と負傷者に比べて死者の割合が圧倒的に多かった．震災により強いストレスを受けた人々に急性冠症候群発症のリスクが高まるとすると，東日本大震災においてはその高リスクの人々の多くが津波に襲われて命を奪われてしまったことになる．全体像の把握には岩手県や宮城県のデータも必要であるが，東日本大震災では被災形態が阪神淡路大震災や新潟県中越地震とは大きく異なることに留意しなければならないであろう．

災害時の循環器科診療

筆者は3.11地震の瞬間は心臓カテーテル室にいた．検査を終了して止血中であった患者が2名，不安定狭心症で冠動脈造影を行うため，大腿動脈穿刺を行う直前の患者が1名いた．凄まじい揺れでデジタル血管撮影装置は一時作動しなくなったが，じきに復旧した．カテーテル検査台上の患者の治療をどうするか迷っているうちに，院内の災害対策本部から外科手術中の患者の対処について基本方針が伝えられた．それによると①新たな手術は原則開始しない，②既に手術が始まっており，やり遂げなければ生命に危険が及ぶものは可及的速やかに遂行する，というものであった．心臓カテーテル室でもそれに準じて，患者の発作が落ち着いていたため，手技を延期することに決めた．その間にも津波の甚大な被害情報が断続的に入り，医療従事者，患者共々「これはただ事ではない」という心境になっていった．当院では地震後，電気は早期に復旧したが断水が続いた．さらに物流の遮断があり，治療器材や薬品供給の見通しが不透明となったため，予定されていたカテーテル検査や治療はすべて中止とした．ま

た，病院全体としても通常外来はストップし，災害医療態勢にシフトした．当院は三次救命救急センターならびに二次被曝医療機関であったため，救急患者はすべて受け入れる方針で対処した．震災後すぐに深刻なガソリン不足となり，郊外に立地する当院では通勤に支障が出てきたことや，携帯電話が不通で通常のオンコールでは緊急カテーテルの呼び出しを行うことが難しくなったことなどにより，当科では交替で病院に泊まり込むローテーション態勢をとった．病院の売店からは物資がなくなり，配給されるおにぎりを食べながら診療にあたった．ローテーションが明けて自宅に戻ると，散乱した部屋の片付けや給水所に子供と一緒に列をつくる(1人5 *l* までなど制限がついたため)日々を過ごした．水道が復旧したのは約1週間後，ガソリン不足が収束したのは1カ月近く経過してからだった．その間，県内の避難所を巡回し，心エコー検査や下肢静脈エコー検査を行い，弾性ストッキングの配布と生活指導などを通して肺血栓塞栓症の予防キャンペーンなども行った[21]．こうした体験を通してあらためて感じたことは，医療活動は様々な人や物，さらに情報に支えられているということである．急性冠症候群の緊急治療にしても，放射線技師や看護師など医療スタッフが確保でき，電気が使えてアンギオ装置が稼働し，カテーテルやステントなどの治療材料，点滴や抗血小板薬などの薬剤がそろっていなければ，スタンダードな治療はできない．病院自体が被災したり，地震や津波に耐えてもライフラインが寸断され，物資の供給が受けられなかったりする状況では，現場の医師だけが頑張っても治療には限界がある．こうした場合には広域での相互支援が不可欠となる．今回の震災でも近隣各県はもとより全国からのご支援をいただいた．患者を東京の医療施設に搬送したこともあった．それらの応援支援を最大限に生かすためには，やはり正確な情報の収集と分析(どこでどんな困難に直面して，何が不足して，何が必要か)，そしてそれをもとにした的確な判断と行動が不可欠である．そのためにも通信手段の確保は非常に重要である．震災後は電話の繋がりが非常に悪くなり，防災無線など，緊急時の通信網整備の重要性がクローズアップされたのは記憶に新しい[22,23]．

おわりに

今回の大震災を通してわれわれは様々なことを経験したが，そのうちの大きな一つは「災害に決まった形はない」ということである．もちろんこれまでの教訓が活かされた事例も多数あり，被災直後からの深部静脈血栓症やたこつぼ型心筋症に対する啓発活動はその好例である．一方で従来のパターンには当てはまらない状況も多く生じた．本稿の主題である急性冠症候群の発症動向もその一つと考えられるが，津波による被害形態や福島県においては原発事故による避難が影響した可能性が高い．被災エリアの広い東日本大震災では地域によって様々なパターンがあったと思われる．いずれにしても，地震や津波そのものから生き延びたからには，その後の病気に対する治療の不備で命を失うような事態は極力避けなければならない．そのためには現場で臨機応変に対応する医療従事者の努力と，その努力を無駄にさせないための情報伝達手段の確保および後方支援が重要であることを改めて強調して本稿を終わりたい．

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Sex-Specific Threshold Levels of Plasma B-Type Natriuretic Peptide for Prediction of Cardiovascular Event Risk in a Japanese Population Initially Free of Cardiovascular Disease

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Elevated plasma B-type natriuretic peptide (BNP) levels have been reported to be related to a high risk for cardiovascular (CV) disease in the general population. However, there has been no accurate determination of the threshold levels of plasma BNP that indicate an increased potential for the development of general CV events (i.e., heart failure, stroke, and myocardial infarction) and the validity of these levels for predicting CV events compared to classic risk markers. To establish gender-specific thresholds of plasma BNP levels associated with increased risk for CV disease in the general population, baseline BNP levels were determined in community-dwelling adults (n = 13,209, mean age 62 ± 10 years,) and CV events in the cohort were captured prospectively. The cohort was divided by deciles of plasma BNP level in each gender. A Cox proportional-hazards model was used to determine the relative hazard ratios among the deciles. In addition, to compare the utility of plasma BNP to the Framingham 10-year risk score for predicting general CV events, receiver-operating characteristic analysis was performed. During follow-up, CV events were identified in 429 patients in the cohort. Compared to the reference decile level (first to fourth), the hazard ratio was significantly increased from the ninth decile in men (greater than approximately 37 pg/ml) and the highest decile in women (greater than approximately 55 pg/ml). The area under the curve generated on receiver-operating characteristic analysis of plasma BNP testing was comparable to that for the Framingham risk scoring system (0.67 vs 0.68 in men, 0.63 vs 0.68 in women; p = NS for both). In conclusion, within a community-based general population with no CV history, plasma BNP levels higher than defined thresholds show increased risk for general CV events, and the predictive ability for CV events occurring within several years may be comparable to that of an established long-standing risk score. **(Am J Cardiol 2011;108:1564–1569)**

In the present study, we measured plasma B-type natriuretic peptide (BNP) in a large-scale population-based sample of >13,000 men and women. This cohort was followed prospectively for >5 years to ascertain the incidence of cardiovascular (CV) events, including heart failure, stroke, and myocardial infarction. To determine gender-specific threshold levels of plasma BNP, the relation between plasma BNP deciles and risk for CV events was determined. In addition, to validate plasma BNP testing for the prediction of general CV events, its predictive ability was compared to an established CV risk scoring system.

Methods

This study is part of the Iwate-KENCO study, a population-based prospective cohort study to investigate heath status and CV risks in Japanese residents living in the Iwate prefecture, northeast Honsyu, Japan. Details about this cohort are provided elsewhere.[1] In brief, the original cohort (n = 26,469) was recruited from April 2002 and January 2005 in 3 districts (Ninohe, Kuji, and Miyako in the Iwate prefecture). The baseline survey included routine anthropometric measurements, blood pressure measurement, electrocardiography, routine laboratory assessment, and a self-administered lifestyle questionnaire. This study protocol was approved by our institutional ethics committee. All participants gave written informed consent.

Of the original cohort living in the Ninohe and Kuji districts (n = 15,927), 15,394 subjects (96.6%) agreed to provide additional blood samples for the measurement of

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plasma BNP levels, and these are designated as the BNP cohort in the present study. Subjects were excluded from this cohort on the basis of the following characteristics: age <40 years (n = 575) or >80 years (n = 330), serum creatinine level ≥2.0 mg/dl (n = 10), and missing data for blood pressure (n = 3), anthropometrics (n = 47), and/or routine blood tests (n = 4). The final statistical analysis was therefore performed on 13,209 subjects (4,365 men, 8,844 women; mean age 62.1 years).

A follow-up survey assessing mortality, migration, and the incidence of CV events was carried out after the baseline study. We defined CV events as stroke, congestive heart failure, and myocardial infarction requiring hospitalization. Hospital admissions for congestive heart failure and myocardial infarction in the cohort were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. Heart failure was defined by Framingham criteria,[2] and registration of myocardial infarction was based on criteria used in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study.[3] Stroke events were identified by accessing the prefecture stroke registration program conducted by the Iwate Medical Association. Stroke diagnostic criteria in this registry are based on those published by the World Health Organization and defined as the sudden onset of neurologic symptoms.[4] To ensure that nearly all appropriate cases had been identified, researchers in each registration study periodically retrieved and reviewed medical charts and/or discharge summaries for patients admitted to the cardiology, neurology, neurosurgery, and internal medicine wards of all hospitals located within the study district.

In the baseline survey, all participants underwent routine anthropometric measurements, electrocardiography, blood pressure measurements, and laboratory assessments. In addition, a self-administered questionnaire was used to ascertain lifestyle factors such as smoking habits and medical history, including stroke, congestive heart failure, and myocardial infarction. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure were determined with an automatic device with the subject in a sitting position for ≥5 minutes before measurement. Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current antihypertensive therapy. Diabetes was defined as a nonfasting glucose concentration ≥200 mg/dl, and/or a glycosylated hemoglobin value ≥6.5%, and/or current antidiabetic therapy. Hypercholesterolemia was defined as total cholesterol level ≥240 mg/dl and/or current lipid-lowering therapy. Enzymatic methods were used to measure serum total cholesterol levels, serum creatinine, and blood glucose. Glycosylated hemoglobin was measured quantitatively using high-performance liquid chromatography. Smoking was defined as current smoking. Estimated glomerular filtration rate was calculated using an equation (estimated glomerular filtration rate [ml/min/1.73 m^2] = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$) from the Modification of Diet in Renal Disease (MDRD) study for the Japanese population.[5] The 10-year risk for general CV disease was calculated using the Framingham 10-year risk

Table 1
Baseline characteristics according to plasma B-type natriuretic peptide deciles in men

Variable	Total	D1–D4	D5	D6	D7	D8	D9	D10
Number	4,365	1,741	441	441	434	436	436	436
BNP (pg/ml)	14.2 (6.3–28.3)	5 (2.1–7.6)	12.3 (11.4–13.2)	16.3 (15.3–17.5)	21.3 (19.8–22.8)	28.3 (26.5–30.5)	41.4 (37.5–46.5)	76.5 (63.4–116.7)
Age (years)	63.3 ± 9.8	58.3 ± 10.0	62.9 ± 9.0	65.5 ± 8.4	65.8 ± 8.1	67.6 ± 7.2	68.1 ± 7.4	69.7 ± 6.2
BMI (kg/m^2)	23.9 ± 2.9	24.1 ± 2.9	24.0 ± 3.0	23.9 ± 2.8	23.7 ± 2.9	23.6 ± 2.8	23.5 ± 2.9	23.7 ± 3.0
Hypertension	43.8%	35.1%	41.0%	46.5%	45.6%	49.8%	56.6%	57.6%
Diabetes mellitus	9.6%	9.8%	8.2%	11.6%	9.0%	10.1%	8.9%	9.2%
Smoker	33.9%	39.1%	33.1%	30.2%	32.7%	31.7%	28.0%	27.1%
Hypercholesterolemia	10.5%	14.5%	9.1%	9.3%	7.1%	8.5%	7.6%	5.7%
eGFR (ml/min/1.73 m^2)	77.2 ± 15.3	80.0 ± 15.3	77.3 ± 15.1	76.4 ± 15.6	76.5 ± 15.0	74.8 ± 14.7	75.8 ± 15.2	71.3 ± 13.3
Antihypertensive drugs	23.3%	15.8%	21.8%	25.9%	26.0%	27.5%	32.8%	35.3%
Framingham risk score	13.8 ± 4.4	12.8 ± 4.5	13.7 ± 4.3	14.5 ± 4.3	14.5 ± 4.1	14.8 ± 4.1	14.9 ± 4.2	15.1 ± 4.1

Data are expressed as median (interquartile range), as mean ± SD, or as percentages.
D = decile; eGFR = estimated glomerular filtration rate.

Table 2
Baseline characteristics according to plasma B-type natriuretic peptide deciles in women

Variable	Total	D1–D4	D5	D6	D7	D8	D9	D10
Number	8,844	3,539	880	880	893	882	885	885
BNP (pg/ml)	16.9 (8.8–29.8)	7.3 (3.8–10.4)	15.0 (14.1–15.9)	18.7 (17.8–19.7)	23.5 (22.2–25.0)	29.8 (28.0–31.9)	40.4 (37.1–43.8)	66.1 (55.1–88.0)
Age (years)	61.6 ± 9.7	58.1 ± 9.5	60.7 ± 9.4	60.9 ± 9.6	63.2 ± 9.0	64.3 ± 8.7	65.3 ± 8.3	68.7 ± 7.2
BMI (kg/m^2)	24.2 ± 3.4	24.2 ± 3.4	24.0 ± 3.3	24.0 ± 3.4	24.1 ± 3.4	24.0 ± 3.3	24.0 ± 3.5	24.4 ± 3.7
Hypertension	38.2%	29.5%	35.1%	36.0%	43.8%	43.2%	47.2%	59.0%
Diabetes mellitus	5.4%	5.3%	4.7%	4.8%	5.0%	6.2%	5.2%	7.2%
Smoker	2.5%	3.5%	1.7%	2.5%	1.9%	2.0%	2.3%	0.8%
Hypercholesterolemia	20.3%	23.3%	18.0%	18.9%	21.2%	19.7%	14.5%	17.2%
eGFR (ml/min/1.73 m^2)	75.8 ± 15.0	78.6 ± 14.9	76.5 ± 14.8	76 ± 13.9	74.7 ± 14.1	73.9 ± 15.2	73.2 ± 14.7	69.5 ± 14.8
Antihypertensive drugs	23.8%	16.8%	22.8%	21.5%	28.4%	27.4%	29.9%	41.2%
Framingham risk score	11.9 ± 4.6	10.8 ± 4.6	11.2 ± 4.5	11.7 ± 4.5	12.4 ± 4.5	12.6 ± 4.4	13.1 ± 4.4	14.3 ± 4.0

Data are expressed as median (interquartile range), as mean ± SD, or as percentages.
D = decile; eGFR = estimated glomerular filtration rate.

Figure 1. Crude incidence of CV events per 1,000 person-years among baseline plasma BNP deciles in men *(closed bars)* and women *(open bars)*.

score, including age, gender-specific cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diabetes, and cigarette smoking.[6]

Blood samples for routine laboratory testing were drawn from the antecubital vein with the subject in a sitting position. While blood samples were being collected into vacuum tubes, an additional 2-ml sample of venous blood was collected into a test tube containing ethylenediaminetetraacetic acid sodium. Tubes were stored immediately after sampling in an icebox and were transported to the laboratory <8 hours after collection. They were then centrifuged at 1,500g for 10 minutes. After separation, the plasma samples were stored frozen at −20°C until the time of assay. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shionogi, Osaka, Japan) <4 months after blood sampling. Cross-reactivity of the antibodies was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and interassay coefficients of variation were 5% and 6%, respectively. The lower detection limit of the assay was 0.05 pg/ml.

Continuous variables are expressed as mean ± SD. The cohort was divided into deciles according to baseline plasma BNP levels. To compare baseline data among the BNP deciles, 1-way analysis of variance and chi-square tests were used as appropriate. Differences in clinical characteristics between men and women were tested using unpaired Student's *t* test or Mann-Whitney U tests. We defined the end point as general CV events (i.e., a composite of stroke, heart failure, and myocardial infarction). The association between baseline plasma BNP levels and the end point was evaluated using a Cox proportional-hazards regression model. The gender-specific hazard ratios (HR) for each BNP decile's end point were assessed. In this multivariate regression model, adjustments were made in the analysis for age, BMI, diabetes, hypertension, hypercholesterolemia, atrial fibrillation, estimated glomerular filtration rate, and current smoking. For analyses of CV incidence, person-years were censored at the date of CV events, the date of emigration from the study area, the date of death, or the end of the follow-up period, whichever came first. To compare the predictive abilities of plasma BNP testing to the Framingham 10-year risk scoring system, receiver-operating-characteristic curves were constructed. The area under the curve (AUC) and 95% confidence interval (CI) for each ROC curve were calculated to provide a measure of the overall diagnostic accu-

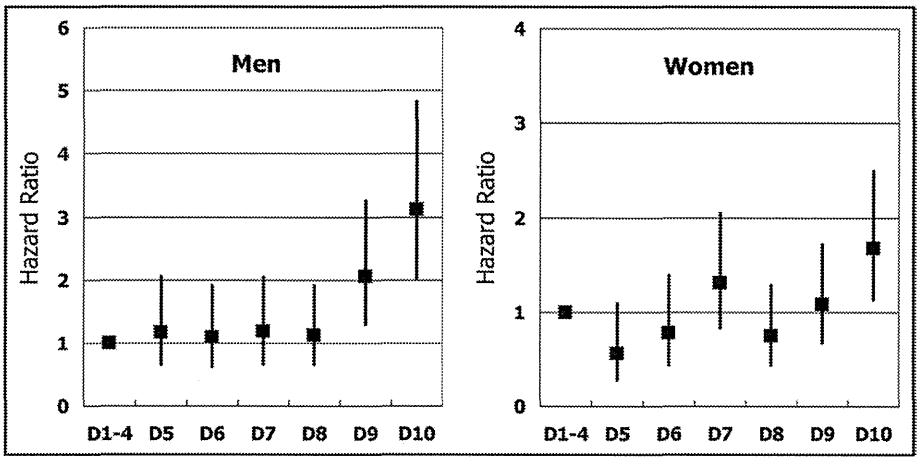

Figure 2. Multivariate-adjusted HRs and 95% CIs for risk for CV events according to plasma BNP decile in men *(left)* and women *(right)*.

racy of the test. The follow-up survey for congestive heart failure, stroke, and myocardial infarction was carried out after the baseline study through to March 2009. Migrations were confirmed by official resident registration data issued by the local government offices (October 2009). All statistical analyses were performed using SPSS version 11.0.1J (SPSS, Inc., Chicago, Illinois). A significant difference was defined as $p < 0.05$.

Results

Mean ages were 63.3 ± 9.8 years in men and 61.6 ± 9.7 years in women (Tables 1 and 2). The number of women was approximately twice the number of men. Plasma BNP levels and BMI were higher in women than in men (median BNP 16.9 vs 14.2 pg/ml, $p < 0.001$; mean BMI 24.2 ± 3.4 vs 23.9 ± 2.9 kg/m^2, $p < 0.001$). The prevalence of hypertension (44% vs 38%), atrial fibrillation (2.9% vs 0.6%), diabetes (9.6% vs 5.4%), and current smoking (33.9% vs 2.5%) was higher in men. The incidence of hypercholesterolemia was higher in women (10.5% vs 20.3%). The administration rates for hypertensive drugs was 23.3% in men and 23.8% in women ($p = 0.232$). The mean Framingham risk score in men was higher than that in women (13.8 ± 4.4 vs 11.9 ± 4.6).

During the mean follow-up period of 5.8 years, 430 CV events (215 in men, 215 in women) were recorded. When the lowest 4 (first to fourth) plasma BNP deciles were set to the reference, the crude incidence of CV events per 1,000 person-years increased with deciles in both genders (Figure 1). As shown in Figure 2, after adjustment for potential confounding factors in the Cox regression model, the relative HR for CV events increased according to deciles (p for trend <0.01 in men, p for trend <0.001 in women). Compared to the reference, the HR was significantly elevated in the ninth (HR 2.06, 95% CI 1.30 to 3.27) and tenth (HR 3.15, 95% CI 2.03 to 4.88) deciles in men and in the tenth decile only in women (HR 1.68, 95% CI 1.13 to 2.50). The thresholds for increased CV risk were greater than approximately 37 pg/ml in men and greater than approximately 55 pg/ml in women.

The overall power for predicting general CV events was comparable between plasma BNP level and Framingham risk score. The areas under the curve for plasma BNP were 0.669 (95% CI 0.629 to 0.710) in men and 0.634 (95% CI 0.593 to 0.676) in women. The areas under the curve did not differ significantly from those for the Framingham risk score (men 0.676, 95% CI 0.640 to 0.712; women 0.681, 95% CI 0.649 to 0.713).

Discussion

The present study has demonstrated that in the general population with no CV history or renal dysfunction, plasma BNP levels signaling increased CV risk are greater than the 80th percentile in men and the 90th percentile in women. The predictive ability of plasma BNP testing for general CV events is similar to that of the established total CV risk scoring system. The present study has therefore shown for the first time that increased plasma BNP levels higher than these gender-specific thresholds are a simple and useful marker for elevated risk for CV events in a community-based middle-aged and elderly population.

Several previously published studies have shown a significant association between plasma BNP and N-terminal pro-BNP (NT-proBNP) levels and CV events in the general population.[7–11] The Framingham study conventionally applied a single cutoff point (the 80th percentile) to examine the association between "high" BNP levels and CV events.[7] Linssen et al[10] recently reported that in a selected population mainly with urinary albumin excretion >10 mg/L, multivariate HRs for the risk for all-cause mortality increased gradually with increasing levels of plasma NT-proBNP, with no clear cut-off level in both genders. However, no studies have explored the threshold levels of BNP that indicate an increased risk for the future development of CV events.

Several studies have shown that median plasma BNP and NT-proBNP levels are higher in women,[12,13] although the incidence of CV events in the general population is usually lower in women than in men. This suggests that a gender-stratified analysis should be incorporated when determining cut-off levels of plasma BNP and NT-proBNP for predicting the future onset of CV events in the general population. However, no reports to date have shown which levels of plasma BNP increase the risk for CV events in either gender.

The present study has shown for the first time in an unselected general population that the adjusted HR was significantly increased from the ninth plasma BNP decile in men and the tenth decile in women. The association between plasma BNP and the future development of CV events may be because elevated plasma BNP is a significant biomarker for asymptomatic structural heart disease such as impaired left ventricular function, left ventricular hypertrophy, atrial dilatation and fibrillation, and myocardial ischemia. In accord with this concept, Struthers and Lang[14] suggested that BNP and NT-proBNP testing could be used to identify "pancardiac" target organ damage and may become to the heart what albuminuria is to the kidneys, that is, a useful biomarker for targeting organ damage in the CV system. In our previous cross-sectional study applying transthoracic echocardiography in the general population, plasma BNP concentrations >50 pg/ml showed sensitivity and specificity for several select phenotypes of structural heart disease that are prone to progress into several types of CV events.[15] The threshold plasma BNP levels that increased the HR (greater than approximately 37 pg/ml in men and greater than approximately 55 pg/ml in women) in the present study are lower compared to the previously reported cut-off level for detection of structural heart disease. This apparent discord may be due to the present study being longitudinal and the cut-off level being gender specific.

The present study suggests that the usefulness in terms of sensitivity and specificity of plasma BNP testing for predicting CV events differs little from the Framingham 10-year risk score for general CV events. This finding may indicate that the predictive ability of BNP testing is equivalent to that of the established risk calculation. However, such a conclusion may be premature, because the mean follow-up period of this study was shorter (<6 years) than the Framingham study (10 years). In fact, the established risk scoring includes lipids, blood pressure, smoking, and diabetes, which are long-standing risk factors for CV events. In contrast, plasma BNP may be unique in that it is instead identifying the end process of several types of cardiac damage itself. In view of this, plasma BNP testing could be useful for identifying subjects at high risk for several types of CV events within a few years. BNP may thus be a direct or novel biomarker for various types of intrinsic cardiac abnormalities rather than an additional biomarker for assessing long-term risk.

The present study had several strengths. This study included the largest general population sample in whom plasma BNP levels have been reported. The plasma BNP measurement was performed in fresh plasma samples without long-term freezing and repeated thawing. CV events were captured prospectively according to previously determined standard epidemiologic criteria and confirmed by the research staff at medical chart review. Baseline data including clinical characteristics and biochemical data were determined well before the start of the follow-up study.

Despite these merits, several limitations must be considered when interpreting the results. First, because echocardiographic evaluation was not included in the baseline data, the utility of the BNP testing could not be compared to that of echocardiography. However, several previous studies have reported that BNP testing remained independently predictive of future CV events after adjusting for echocardiographic variables.[7,11] Second, mean BMI was lower in our study than in previous general population reports.[7,9,10] Plasma BNP levels have been reported to be lower in obese subjects than in the lean population,[16,17] with 1 previous study demonstrating that each standard deviation increase in BMI was associated with a 16% to 18% decrement in plasma BNP.[16] It follows that threshold BNP levels may be slightly lower in predominantly obese populations. Third, according to population-based studies, the Japanese population has a lower incidence of CV events than Western countries. Thus, care must be taken before these data can be generalized to other ethnic groups. Fourth, McKie et al[18] recently demonstrated that the use of NT-proBNP as a CV risk predictor is worthless in healthy subjects, as verified by close clinical examination including echocardiography. This observation may not validate our results, because the present population comprises entirely healthy subjects and may include a substantial part of subjects with CV risk factors, as listed in Tables 1 and 2. Finally, the age range of our population may have been relatively narrow, with no subjects aged <40 years or >80 years.

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