ABSTRACT

Impacts of body mass index on risks for all-cause mortality and cardiovascular disease in elderly Japanese people.

Kozo Tanno*[1], Toru Kuribayashi*[2], Masaki Ohsawa*[1], Kazuyoshi Itai*[1], Toshiyuki Onoda*[1] Yumi Yaegashi*[1], Kiyomi Sakata*[1], Motoyuki Nakamura*[3], Yuki Yoshida*[4], Akira Ogawa*[4], Yasuo Terayama*[5], Kazuko Kawamura*[6], Akira Okayama*[7], and The Iwate KENCO study group

*[1] Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University

*[2] Faculty of Education, Iwate University

*[3] Division of Cardiology, Department of Internal Medicine, School of Medicine, Iwate Medical University

*[4] Department of Neurosurgery, School of Medicine, Iwate Medical University

*[5] Division of Neurology, Department of Internal Medicine, School of Medicine, Iwate Medical University

*[6] Iwate Health Service Association

*[7] The First Institute of Health Service, Japan Anti-Tuberculosis Association

We examined the impacts of body mass index (BMI, kg/m^2) on risks for all-cause mortality and cardiovascular disease (CVD) in elderly Japanese people. A total of 4,745 men and 7,262 women aged 65 years or older without a history of CVD (stroke or myocardial infarction (MI)) were enrolled and were followed through 2007 (mean, 2.7 years). Multivariate hazard ratios (HRs) and their 95% confidence intervals (CIs) for all-cause mortality and CVD incidence were calculated by groups according to BMI categories (<18.5, 18.5 - 22.9, 23.0 - 24.9 (reference), 25.0 - 27.4, 27.5 - 29.9, ≥30.0) using Cox's regression models with adjustments for known cardiovascular risk factors. During the follow-up period, 275 deaths and 239 cases of incident CVD (210 strokes and 30 MIs) were recorded. Compared with persons with a BMI of 23.0 - 24.9, significantly higher risks for all-cause mortality were observed in men with a BMI less than 18.5 (HR (95% CI): 2.04 (1.04 - 3.98)) and in women with a BMI of 30 or more (3.12 (1.58 - 6.15)). However, the risk for all-cause mortality was not high in men with a BMI less than 18.5 after excluding smokers (0.78 (0.10 - 6.11)). Men with BMIs of 18.5 - 22.9, 27.5 - 29.9 and 30 or more had higher risks for incident CVD with marginal significance (HRs: 1.56 ($p = 0.064$), 1.86 ($p = 0.067$) and 2.34 ($p = 0.084$)). Among elderly people, lean male smokers and obese females have higher risks for all-cause mortality and obese males have a higher risk for CVD. Obesity is an important risk factor for death and for CVD incidence even in elderly Japanese people.

Key Words : *Body mass index, all-cause mortality, cardiovascular disease, elderly people, cohort study, smoking*

Received Sep. 2 • Accepted Dec. 25, 2009. (JJCDP 45:9-21, 2010)

臨床研究

慢性腎臓病と血清高感度CRP値との関連性
―地域住民における横断研究(IWATE-KENCO study)

Chronic kidney disease is associated with increased serum C-reactive protein level ; A cross-sectional study of the general population (IWATE-KENCO study)

肥田頼彦[1)] 高橋智弘[1)] 瀬川利恵[1)] 田中文隆[1)] 小野田敏行[2)]
板井一好[2)] 坂田清美[2)] 川村和子[3)] 岡山 明[4)] 中村元行[1)]

1) 岩手医科大学付属病院循環器・腎・内分泌内科，2) 岩手医科大学衛生学公衆衛生学講座，
3) 岩手予防医学協会，4) 結核予防会

《Abstract》

慢性腎臓病(chronic kidney disease；CKD)は，心血管疾患の危険因子であるとされている．また，炎症はアテローム性動脈硬化症および腎機能障害に関与すると考えられている．しかし，わが国の一般地域住民における血清CRP値と糸球体濾過値(GFR)との関連性についての研究はない．今回，われわれは岩手県北地域住民(n＝26,332，平均年齢＝62歳)を対象に血清CRP値とGFRあるいはCKDとの関連を検討した．血清CRP値の上昇とGFRの低下は従来からの動脈硬化の危険因子で調整しても関連性がみられ($p<0.02$)，CKDとの間にも明らかな関連性がみられた($p<0.0001$)．結論として，炎症はGFR低下とCKDへの進行に寄与する重要な因子である可能性が示唆された．

Yorihiko Koeda[1)], Tomohiro Takahashi[1)], Toshie Segawa[1)], Fumitaka Tanaka[1)], Toshiyuki Onoda[2)], Kazuyoshi Itai[2)], Kiyomi Sakata[2)], Kazuko Kawamura[3)], Akira Okayama[4)], Motoyuki Nakamura[1)]

1) Division of Cardiology, Department of Internal Medicine and Memorial Heart Center, Iwate Medical University, 2) Department of Preventive Medicine, Iwate Medical University, 3) Iwate Health Service Association, 4) Japan Anti-Tuberculosis Association

Key words
- 慢性腎臓病
- 糸球体濾過値
- 心腎連関
- 炎症
- 横断研究
- 心血管疾患

(2009.3.17 原稿受領；2009.8.27 採用)

背景

近年，慢性腎臓病(chronic kidney disease；CKD)は心血管疾患の独立した危険因子である[1)]．わが国では地域住民の約3～13%がCKD患者であり[2)～4)]，CKD患者において心血管疾患の発症率が有意に高いことが近年の縦断研究で報告されている[1)～3)5)]．また，CKDが心血管イベントを発症するリスクは，末期腎不全に陥るリスクよりも高率であり，CKDの指標である糸球体濾過値(glomerular filtration rate；GFR)低下例では，それらが認められない例と比較して心血管死亡率が明らかに高い[5)]．

CKD患者において心血管イベントが発生する機序としては，耐糖能異常やリポ蛋白代謝異常，Ca・P代謝異常による動脈硬化，尿毒素やホモシスティンによる血管内皮障害，レニン・アンジオテンシン(renin-angiotensin；RA)系亢進による酸化ストレスや体液量増加，交感神経系亢進，貧血，炎症などがあげられ

る[6]．特に，炎症は腎機能障害とアテローム性動脈硬化症の進行に関与しているとされている[7]~[10]．CKD患者における炎症は，マクロファージの活性化，インターロイキン(interleukin；IL)-6や腫瘍壊死因子(tumor necrosis factor；TNF)-αなどのサイトカイン分泌亢進が原因で冠動脈プラーク破綻による虚血性心疾患の発症と関連すると考えられている[11]．近年，欧米人を対象とした高感度CRP値とCKDとの関連についての報告が散見される[12]~[14]．しかし，わが国の一般地域住民では欧米人と比較し高感度CRPの値は低いとされ[15][16]，高感度CRP値とCKDとの関連は明らかではない．そこで，今回われわれは岩手県北地域住民を対象に，高感度CRP値とGFRあるいはCKDとの関連性についての横断的検討を行った．

方法

岩手県北地域コホート研究は，2002年から2004年にかけて，二戸医療圏，久慈医療圏および宮古医療圏の岩手県北部17市町村で健康診査を受けた者31,318名(男性11,003名，女性20,315名)のうち，本研究参加の同意が得られた26,469名(同意取得率84.5%)を対象とした(IWATE-KENCO study)[17][18]．今回，われわれはこのうち血清高感度CRP値を測定した40歳以上の25,928名(男性8,958名，女性16,970名，平均62歳)における血清高感度CRP値とGFRやCKDとの関連性について検討を行った．なお，当コホート研究では，すべての研究参加者からインフォームドコンセントを取得し，研究内容については岩手医科大学倫理委員会の倫理審査承認を得た．

喫煙や飲酒をはじめとする生活習慣や内服歴などの問診については，自記式の問診調査票を用いて行った．血圧は，排尿後最低5分間の座位安静の後2回測定し，その平均値を測定値とした．採血は随時，座位で末梢静脈から行った．血液検体は，採血後直ちに遠心分離し，各種測定を行った．血清クレアチニン値の測定原理は酵素法で，測定機器には日立7700(日立ハイテクノロジーズ，東京)を用いた．血清高感度CRP値の測定原理は免疫比濁法で，測定機器にはネフェロメータⅡ(Dade Behring社，Deerfield，IL，USA)を用いた．

推算GFRは，推算GFR(mL/分/1.73m^2)＝194×$Cr^{-1.094}$×$Age^{-0.287}$(女性はさらに×0.739)の推算式を用いて算出した[19]．また，推算GFRが60mL/分/1.73m^{2}未満のものをCKDと定義した．

推算GFRと高感度CRP値との関連については，年齢，糖尿病(HbA_{1c}≧6.5%または空腹時血糖≧200mg/dL)，高血圧(平均収縮期血圧≧140mmHgまたは平均拡張期血圧≧90mmHgまたは降圧薬内服)，高脂血症(総コレステロール≧240mmHgまたは脂質改善薬内服)および肥満(BMI≧25)を調整因子とした線形回帰を用いて多変量解析を行った．CKDと高感度CRP値との関連についても，線形回帰と同様の項目を調整因子としたロジスティック回帰で多変量解析を行った．血清高感度CRP値は正規分布していないため，統計解析にあたっては対数変換を行った．なお，統計解析ソフトにはSPSS 11.0 for Windowsを用いた．

結果

表1は，研究対象である地域住民の臨床的特性を男女別に示したものである．血清クレアチニン値の中央値は全体で0.70mg/dL，男性が0.83mg/dL，女性が0.64mg/dLであり，男性のほうが有意に高かった(p＜0.0001)．推算GFRの平均値は全体で75.6mL/分/1.73m^2，男性で76.1mL/分/1.73m^2，女性で75.4mL/分/1.73m^{2}と男性で有意に高かった(p＜0.0001)．血清高感度CRP値の中央値は全体で0.40mg/L，男性で0.50mg/L，女性で0.40mg/Lであり，男性で有意に高かった(p＜0.0001)．

また，**表1**には従来から知られている心血管疾患の危険因子(糖尿病，高血圧，高脂血症，肥満，喫煙歴)およびCKDの有病率も男女別に示した．糖尿病，高血圧，喫煙率，CKDの割合は男性で有意に高く，高脂血症と肥満については女性で有意に高かった．CKDの有病率は全体で12.7%，男性13.7%，女性12.1%であった．年齢別にすると，CKDの有病率は65歳未満

表1　対象者の男女別臨床指標の比較

	全体	男性	女性
年齢(歳)	62.0±11.4	63.8±11.4	61.0±11.6
収縮期血圧(mmHg)	127.0±19.5	130.6±19.5	125.1±20.2
拡張期血圧(mmHg)	75.2±11.1	78.2±11.1	73.6±11.1
Body Mass Index(kg/m^2)	24.0±3.0	23.9±3.0	24.0±3.4
HbA_{1c}(%)	5.12±0.73	5.14±0.73	5.10±0.63
血清クレアチニン値(mg/dL)	0.70±0.20	0.83±0.20	0.64±0.13
eGFR(mL/分/1.73m^2)	75.6±15.8	76.1±15.8	75.4±15.3
総コレステロール値(mg/dL)	200.2±32.5	191.1±32.5	204.9±32.4
HDLコレステロール値(mg/dL)	59.4±15.2	55.9±15.2	61.3±14.4
中性脂肪(mg/dL)	116.7±83.9	125.3±83.9	112.2±66.9
血清高感度CRP値(mg/L)*	0.40(0.20～0.90)	0.50(0.30～1.00)	0.40(0.20～0.80)
糖尿病(%)	5.2	7.6	4.0
高血圧(%)	41.0	45.8	38.5
高脂血症(%)	15.7	9.3	19.0
肥満(%)	35.8	34.3	36.5
現喫煙(%)	12.6	30.9	2.9
CKD(%)	13.7	13.7	12.1

平均値±SD．*中央値(25～75%タイル値)

で6.9%，65歳以上75歳未満で15.8%，75歳以上で28.3%と高年齢層で高くなった．

図に，CKDの有無で分けた血清高感度CRP値の中央値の差を示す．男女ともに，CKDを有するほうが，CKDがない群と比較して血清高感度CRP値の中央値が有意に高かった(p＜0.0001)．血清高感度のCRP値の中央値は，CKDを有する男性で0.60mg/L(n＝1,226)，有さない男性で0.50mg/L(n＝7,732)，CKDを有する女性で0.50mg/L(n=2,054)，有さない女性で0.40mg/L(n＝14,783)であった．全体では，CKDを有する群の血清高感度CRP値の中央値は0.50mg/L(n＝22,515)，有さない群で0.40mg/L(n＝3,280)であった．対象集団を年齢階層別の血清高感度CRP値の中央値は，65歳未満で0.40mg/L，65歳以上75歳未満で0.50mg/L，75歳以上で0.60mg/Lと年齢があがるにつれ上昇した．

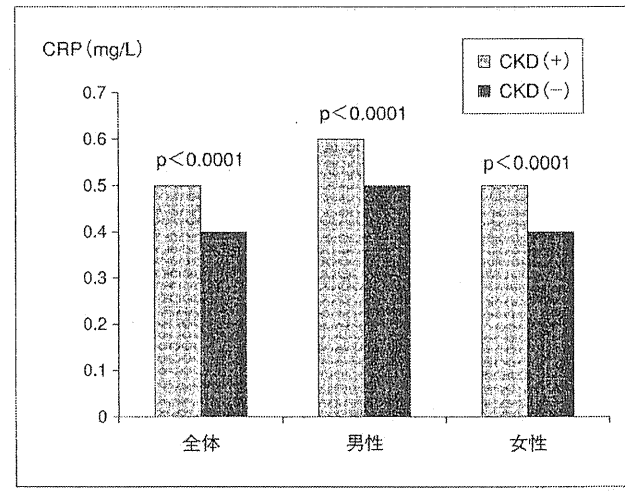

図　CKDの有無による血清高感度CRP値(mg/L)の中央値の差

対象集団をCKDの有無で2群に分け，2群間における高感度CRP値の比較にはMann-WhitneyのU検定を用いた．

推算GFRと年齢，糖尿病，高血圧，高脂血症，肥満および血清高感度CRP値との関連について，線形回帰を用いた多変量解析の結果を表2に示す．推算GFRと年齢，高血圧，肥満との間には，負の相関が認められた．また，ほかの危険因子(年齢，糖尿病，高血圧，高脂血症，肥満)で調整した後も，男女とも血清高感度CRP値上昇が推算GFR減少に関連した．逆に，糖尿病と高脂血症では，推算GFRに対してむ

表2　推算GFRと臨床指標の関係(多変量線形回帰分析)

	男性		女性	
	Standardized β	p値	Standardized β	p値
年齢(歳)	−0.388	＜0.0001	−0.393	＜0.0001
糖尿病	0.031	＜0.005	0.038	＜0.0001
高血圧	−0.028	＜0.05	−0.024	＜0.0001
高脂血症	0.057	＜0.0001	0.045	＜0.0001
肥満	−0.074	＜0.0001	−0.031	＜0.0001
log CRP値	−0.025	＜0.02	−0.021	＜0.0001

しろ正の相関が認められた.

CKDを目的変数(カテゴリー)とするロジスティック回帰を用いた多変量解析の結果を表3に示す. 全体でみるとCKDは年齢, 高血圧, 高脂血症, 肥満, 血清高感度CRP値と有意に関連することが判明した. 糖尿病については, 男女とも有意な関連性を認めなかった. 肥満については, 男性ではCKDの存在と関連を認めたが, 女性ではその関連性は明らかではなかった.

表3　CKDの有無と各臨床指標との関連(多変量ロジステック回帰分析)

	全体		
	オッズ比	95%信頼区間	p値
年齢(歳)	1.078	1.074～1.083	＜0.0001
糖尿病	0.823	0.699～0.970	＜0.05
高血圧	1.248	1.152～1.351	＜0.0001
高脂血症	1.290	1.170～1.423	＜0.0001
肥満	1.184	1.093～1.283	＜0.0001
log CRP値	1.251	1.157～1.354	＜0.0001
	男性		
	オッズ比	95%信頼区間	p値
年齢(歳)	1.088	1.080～1.097	＜0.0001
糖尿病	0.845	0.669～1.067	ns
高血圧	1.261	1.107～1.435	＜0.0001
高脂血症	1.710	1.402～2.085	＜0.0001
肥満	1.447	1.267～1.652	＜0.0001
log CRP値	1.238	1.093～1.097	＜0.002
	女性		
	オッズ比	95%信頼区間	p値
年齢(歳)	1.075	1.069～1.081	＜0.0001
糖尿病	0.805	0.639～1.015	ns
高血圧	1.255	1.134～1.389	＜0.0001
高脂血症	1.184	1.057～1.327	＜0.005
肥満	1.064	0.961～1.177	ns
log CRP値	1.275	1.151～1.412	＜0.0001

考察

近年の報告で, うっ血性心不全や急性心筋梗塞などの心疾患患者におけるCKDは, その心疾患の重症度にかかわらず独立した予後規定因子であることが明らかにされており, 2006年AHAの報告においても, GFRと微量アルブミン尿の2点をスクリーニングし, 早期からのリスク管理することが推奨されている[20]. わが国の一般地域住民においてもCKDが心血管疾患の独立した危険因子であることが示されている[2)3)]. また近年, CKDの発症機序に酸化ストレス, 高インスリン血症, エネルギー代謝の低下や低アルブミン血症, 炎症などとの関連が注目されている[6)]. 今回, われわれは一般地域住民におけるCKDと軽微な炎症状態すなわち血清高感度CRP値との関連を明らかにする目的で本横断研究を行った.

本研究における血清高感度CRP値の中央値は, 欧米人を対象とした報告[20)～22)]と比較して低値であった. 血清高感度CRP値の性差については, 欧米においては女性のほうが高いという報告[20)21)]と, 男性のほうが高いという報告[22)23)]があり, 一定の見解は得られていない. 日本人を対象としたコホート研究では,

血清高感度CRP値は男性のほうが高値と報告されている[15)16)]．本研究では，男性で血清高感度CRP値が有意に高かった．その理由として，①血清高感度CRP値は高年齢・糖尿病・高血圧とともに上昇することが知られているが，本コホートにおいてはそれらの頻度が男性で女性よりも高かったこと，②本コホートの喫煙率は男性で30.9%，女性で2.9%(**表1**)と大きな差があり，それが今回の結果と関連した可能性があることなどがあげられる．喫煙によって歯周炎が生じ，血清高感度CRP値を上昇させ心血管疾患のリスクとなることはよく知られている[24)]．また，喫煙は歯周炎のほか，気道や消化器などの炎症にも関与することが報告されている[25)26)]．

推算GFRを目的変数とした線形回帰において，糖尿病と高脂血症が推算GFRとの間にむしろ正の相関を認めたことについては，糖尿病や高脂血症の初期の段階で，GFRが亢進することと関与していると思われる．本研究における糖尿病患者の平均HbA_{1c}値は平均7%と比較的軽症(早期)であり，この可能性を支持するものと考える．また，CKDの有無に関与する因子として，ロジスティック回帰にて糖尿病は男女ともに選択されなかった．その理由としても，この軽度の糖尿病の存在が関与している可能性が考えられる．

本研究の結果と一致して，Leeらは韓国の都市住民において糖尿病と高血圧を除外した場合，血清CRP値が高い群ではメタボリックシンドロームの有無にかかわらずCKDの罹患率が有意に高いと報告している[27)]．本研究では，高齢者の割合が多い地方の一般地域住民を対象としており，糖尿病と高血圧を有する者が多いため，この両疾患患者を除外することなく，むしろ調整因子として多変量解析を行ったが，この韓国の都市部における研究と同様の結果が得られた．

本研究では，男性にのみ肥満とCKDの関連がみられた．この理由は本研究では明らかでない．しかし，脂肪組織から分泌されるアディポサイトカインや肥満でのレニン・アンジオテンシン系亢進，インスリン抵抗性により惹起された高インスリン血症などが腎障害を進展させることが知られており，肥満関連腎症と呼称される．沖縄の検診データでは，肥満は男性が女性よりもCKDに対する影響が大きいと報告されている[28)]．肥満とCKDの関連に性差がみられる理由について言及している報告は少なく，その関連性は明らかではないが，飲酒，喫煙歴，性ホルモンなど男性特有の要因が肥満と腎障害の進展になんらかの影響を及ぼしている可能性がある．

問題点と今後の展望

本研究の尿検査は1回限りの随時尿によるもので，CKDの定義にあたっては，尿中アルブミンや尿蛋白の有無は考慮に入れていない．しかし，一般地域住民の尿中微量アルブミンと血清高感度CRP値との間に有意な相関があったとの報告もあり[16)]，尿中アルブミンを測定し，その結果をCKDの定義に含めて統計解析を行ったとしても，おそらく今回の結果とは大きな差はないものと思われる．本研究ではすべての対象者に対して腹囲測定は行っておらず，CT検査も施行していないため，肥満の指標として内臓脂肪面積や腹囲ではなくBMIを用いた．

今回の研究で，一般地域住民における炎症とCKDとの間に関連があることは明らかとなったものの，横断研究であるため因果関係についてまでは不明である．また，CKDにおいて血清高感度CRPの上昇が心血管イベントの引き金や予知マーカーとなり得るか否かの評価もできていない．また，CKDにおいてCRP値を下げることが心血管疾患発症率を抑制するかどうかについても明らかになっていない．しかし，最近の研究によると，スタチン，運動，禁煙などによって血清高感度CRP値とともに心血管系リスクも低下する可能性が報告されている[29)～31)]．今後はこのコホートを縦断的に追跡調査し，CKDと血清高感度CRP値が心血管疾患発症にどう影響するのか(例えば，血清高感度CRP高値のCKDは，CRP低値のCKDと比較して心血管予後はどうか，など)について検討を要するものと考える．

まとめ

高感度CRP値と推算GFRとの間には負の相関が認められた．また，CKDを有する群で高感度CRP値が有意に高かった．結論として，炎症はGFRの低下およびCKDに関連することが示唆された．

なお，本稿の要旨は，第72回日本循環器学会総会・学術集会で報告した．

文　献

1) Go AS, Chertow GM, Fan D, et al : Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004 ; **351** : 1296-1305
2) Nakamura K, Okamura T, Hayakawa T, et al : Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan : NIPPON DATA90. *Circ J* 2006 ; **70** : 954-959
3) Ninomiya T, Kiyohara Y, Kubo M, et al : Chronic kidney disease and cardiovascular disease in a general Japanese population : the Hisayama Study. *Kidney Int* 2005 ; **68** : 228-236
4) Imai E, Horio M, Watanabe T, et al : Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol* 2009 ; **13** : 621-630
5) Hallan SI, Dahl K, Oien CM, et al : Screening strategies for chronic kidney disease in the general population : follow-up of cross sectional health survey. *BMJ* 2006 ; **333** : 1047
6) Sarnak MJ, Levey AS, Schoolwerth AC, et al : Kidney disease as a risk factor for development of cardiovascular disease : a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003 ; **108** : 2154-2169
7) Oberg BP, McMenamin E, Lucas FL, et al : Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int* 2004 ; **65** : 1009-1016
8) Bash LD, Erlinger TP, Coresh J, et al : Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 2009 ; **53** : 596-605
9) Koenig W, Sund M, Fröhlich M, et al : C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men : results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999 ; **99** : 237-242
10) Ridker PM, Hennekens CH, Buring JE, Rifai N : C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000 ; **342** : 836-843
11) Hage FG, Venkataraman R, Zoghbi GJ, et al : The scope of coronary heart disease in patients with chronic kidney disease. *J Am Coll Cardiol* 2009 ; **53** : 2129-2140
12) Utaka S, Avesani CM, Draibe SA, et al : Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr* 2005 ; **82** : 801-805
13) Suliman ME, Qureshi AR, Stenvinkel P, et al : Inflammation contributes to low plasma amino acid concentrations in patients with chronic kidney disease. *Am J Clin Nutr* 2005 ; **82** : 342-349
14) Goicoechea M, de Vinuesa SG, Lahera V, et al : Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. *J Am Soc Nephrol* 2006 ; **17**(12 Suppl 3) : S231-S235
15) Yamada S, Gotoh T, Nakashima Y, et al : Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population : Jichi Medical School Cohort Study. *Am J Epidemiol* 2001 ; **153** : 1183-1190
16) Nakamura M, Onoda T, Itai K, et al : Association between serum C-reactive protein levels and microalbuminuria : a population-based cross-sectional study in northern Iwate, Japan. *Intern Med* 2004 ; **43** : 919-925
17) 小野田敏行，西　信雄，板井一好，ほか：岩手県北地域住民の性別年齢階級別BMI，血圧，血清脂質，HbA1C値，喫煙及び飲酒状況について　岩手県北地域コホート研究参加者11,499名のベースライン調査結果から．岩手公衛会誌 2004 ; **16** : 82-89
18) Ohsawa M, Itai K, Tanno K, et al : Cardiovascular risk factors in the Japanese northeastern rural population. *Int J Cardiol* 2009 ; **137** : 226-235
19) Matsuo S, Imai E, Horio M, et al : Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009 ; **53** : 982-992
20) Brosius FC 3rd, Hostetter TH, Kelepouris E, et al : Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease : a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council ; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention ; and the Quality of Care and Outcomes Research Interdisciplinary Working Group : developed in collaboration with the National Kidney Foundation. *Circulation* 2006 ; **114** : 1083-1087
21) Ridker PM, Cushman M, Stampfer MJ, et al : Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997 ; **336** : 973-979

22) Ridker PM, Buring JE, Shih J, et al : Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998 ; **98** : 731-733
23) Tracy RP, Lemaitre RN, Psaty BM, et al : Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997 ; **7** : 1121-1127
24) Harris TB, Ferrucci L, Tracy RP, et al : Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999 ; **106** : 506-512
25) Loos BG, Craandijk J, Hoek FJ, et al : Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000 ; **71** : 1528-1534
26) Gompertz S, Bayley DL, Hill SL, Stockley RA : Relationship between airway inflammation and the frequency of exacerbations in patients with smoking related COPD. *Thorax* 2001 ; **56** : 36-41
27) Shimoyama T, Everett SM, Fukuda S, et al : Influence of smoking and alcohol on gastric chemokine mRNA expression in patients with Helicobacter pylori infection. *J Clin Pathol* 2001 ; **54** : 332-334
28) Lee JE, Choi SY, Huh W, et al : Metabolic syndrome, C-reactive protein, and chronic kidney disease in nondiabetic, nonhypertensive adults. *Am J Hypertens* 2007 ; **20** : 1189-1194
29) Tokashiki K, Tozawa M, Iseki C, et al : Decreased body mass index as an independent risk factor for developing chronic kidney disease. Decreased body mass index as an independent risk factor for developing chronic kidney disease. *Clin Exp Nephrol* 2009 ; **13** : 55-60
30) Ridker PM, Danielson E, Fonseca FA, et al : Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008 ; **359** : 2195-2207
31) Reichert V, Xue X, Bartscherer D, et al : A pilot study to examine the effects of smoking cessation on serum markers of inflammation in women at risk for cardiovascular disease. *Chest* 2009 ; **136** : 212-219
32) Mora S, Cook N, Buring JE, et al : Physical activity and reduced risk of cardiovascular events : potential mediating mechanisms. *Circulation* 2007 ; **116** : 2110-2118

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Renal Disease

Plasma B-Type Natriuretic Peptide Level and Cardiovascular Events in Chronic Kidney Disease in a Community-Based Population

Masafumi Sakuma, MD; Motoyuki Nakamura, MD; Fumitaka Tanaka, MD; Toshiyuki Onoda, MD*; Kazuyoshi Itai, PhD*; Kozo Tanno, MD*; Masaki Ohsawa, MD*; Kiyomi Sakata, MD*; Yuki Yoshida, MD**; Kazuko Kawamura, MS†; Shinji Makita, MD; Akira Okayama, MD††

Background: Plasma B-type natriuretic peptide (BNP) levels are confounded by renal dysfunction, so this study examined whether plasma BNP might be a reliable biomarker of the onset of cardiovascular (CV) events in a population-based cohort with impaired renal function.

Methods and Results: Baseline data, including plasma BNP, serum creatinine, and urinary protein levels, were determined in participants from a community-based population. Estimated glomerular filtration rate (eGFR) was calculated, and chronic kidney disease (CKD) was defined as either: eGFR <60 ml·min^{-1}·1.73 m^{-2} and/or proteinuria (CKD definition-1) or GFR <60 ml·min^{-1}·1.73 m^{-2} (CKD definition-2). The CV endpoint was surveyed prospectively. The cohorts were followed for 5,275 person-years for CKD definition-1, and for 4,350 person-years for CKD definition-2. The CV event-free survival rate in the highest BNP quartile in either CKD definition was the lowest among the quartile groups (P<0.001). In multivariate Cox regression models adjusted by traditional CV risk factors and atrial fibrillation, relative risk (RR) for CV events was significantly higher in the highest BNP quartile compared with the lowest BNP quartile (CKD definition-1, RR 3.51, P<0.01: CKD definition-2, RR 4.67, both P<0.01).

Conclusions: Plasma BNP level provides strong predictive information about the future onset of CV events in CKD subjects selected from the general population. (*Circ J* 2010; **74:** 792–797)

Key Words: General population; Heart failure; Renal failure; Stroke

Chronic kidney disease (CKD), defined as reduced glomerular filtration rate (GFR) and/or proteinuria, increases the risk of cardiovascular (CV) disease and endstage renal disease.[1] In population-based studies, the prevalence of CKD has been shown to be 7% in persons aged more than 30 years and to be increased 23–36% in persons aged more than 65 years.[2] The trend in the prevalence of CKD has been speculated to increase over time in line with the recent increasing prevalence of diabetes, obesity, and hypertension.[3] Several reports have emphasized that early identification and treatment of CKD are necessary to prevent serious outcomes in this disorder.[1,4] However, considering the large number of persons with CKD in the general population, it may not be easy to provide pharmacological and non-pharmacological interventions for all stages of CKD. In view of these limitations, it may be practical to select CKD subjects at relatively high risk for CV diseases from the general population, and then provide treatment to prevent their onset. However, there are no established markers to stratify CV risk in CKD subjects with mild renal dysfunction, such as stage 3 CKD, in the mass screening setting.

Editorial p632

Natriuretic peptide family proteins, including B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-pro BNP), are released from the heart in response to increased intracardiac pressure, cardiac pump dysfunction, hypertensive ventricular hypertrophy, and myocardial ischemia. In community-based studies, increased circulating levels of BNP and NT-pro BNP have been reported to relate to a high risk of CV events and mortality.[5,6] The high prevalence of CV events in the group with elevated plasma levels of BNP and NT-proBNP is believed related to the high prevalence of subclinical heart disease. However, plasma concentrations of BNP and NT-proBNP increase as GFR declines in patients

Received November 6, 2009; accepted December 14, 2009; released online February 17, 2010 Time for primary review: 25 days
Department of Internal Medicine (Cardiology Division), *Department of Preventive Medicine, **Department of Neurosurgery, Iwate Medical University, †Iwate Health Service Association, Morioka and ††The First Anti-tuberculosis Association, Tokyo, Japan
Mailing address: Motoyuki Nakamura, MD, Division of Cardiology, Department of Internal Medicine and Memorial Heart Center, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan. E-mail: nkmrmoto@iwate-med.ac.jp
ISSN-1346-9843 doi:10.1253/circj.CJ-09-0834

with and without apparent cardiac disorders.[7,8] In view of these facts, it is unclear whether plasma BNP levels would be a reliable biomarker for predicting CV events in the cohort of CKD selected from a community-based population.

CKD is usually defined by 2 biomarkers of renal function: urinary protein and reduced GFR. Several community-based studies have applied only the latter definition.[9-11] However, it is uncertain whether these biomarkers (GFR and urinary protein) provide complementary or overlapping information for CV risk. Cirillo et al reported that the use of only 1 of the biomarkers underscores the potential to misclassify patients as having or lacking CKD, thus misinterpreting the CV risk.[12] Therefore, the present study used 2 definitions of CKD to examine whether plasma BNP might be a reliable biomarker for predicting onset of CV diseases in a CKD cohort selected from a community-based general population.

Methods

Study Population

The original cohort of the Iwate-KENCO study was recruited from a community-based population living in Ninohe, Kuji, and Miyako districts of northern Iwate prefecture, Japan. The details of the recruitment and measurements of the cohort were shown in previous reports.[13,14] The total number of participants who agreed to join the Iwate-KENCO study in the 3 districts was 26,469 (original cohort). Of the original cohort living in Ninohe and Kuji districts (n=15,927), 15,394 subjects (97%) had BNP measurements (BNP cohort: men 5,288; women 10,106).

Subjects were excluded from the present analysis for the following reasons: age under 40 (n=575); history of CV events, such as myocardial infarction, stroke or heart failure (n=507); missing data of serum creatinine level (n=28), body mass index (n=47), ECG tracing (n=717), or blood pressure (n=4); estimated GFR $<30\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$ (n=28). The final statistical analysis included 13,526 subjects (men 4,542; women 8,984). The study protocol was approved by the university ethics committee and local institutional review committees. All participants gave written informed consent.

Definition of CKD

The eGFR was calculated using an equation from the Modification Diet in Renal Disease Study (MDRD) for the Japanese population.[15] A urine sample was obtained during a multiphase health examination and urinary protein was semi-quantitatively determined using a dipstick test (Uropaper alpha II, Eiken): proteinuria was defined as trace or more. CKD was defined in the present study in 2 ways: (1) eGFR $<60\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$ and/or proteinuria (CKD definition-1); (2) eGFR $<60\,ml\cdot min^{-1}\cdot 1.73\,m^{-2}$ (CKD definition-2).

Measurements

Blood samples were drawn from a peripheral vein while the subject was seated. When blood samples for routine blood testing were being taken, an additional 2 ml was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately in an icebox after sampling and transported to the laboratory each afternoon where they were centrifuged at 1,500 g for 10 min. After separation, plasma samples were stored frozen at −20°C until transportation to the Shionogi central laboratory for assaying (Osaka, Japan). Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi). Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and interassay coefficients of variation were 5% and 6%, respectively. Serum creatinine level was determined by an enzymatic method using an auto-analyzer (Hitachi 7700).

All subjects used a self-reported questionnaire to confirm their medical history, including status (yes/no) of prescribed drugs for hypertension, diabetes, hypercholesterolemia, stroke, angina, heart failure and myocardial infarction. Smoking status (current, past smoker or non-smoker) was also assessed by questionnaire.

Risk Factor Definitions

Systemic blood pressure was measured by experienced technicians. All subjects were seated for at least 5 min before measurement using an automatic device (BP-103i II, model 513000, Nippon Colin). Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Diabetes was ascertained by non-fasting glucose concentration ≥200 mg/dl and/or hemoglobin A_{1c} value ≥6.5% and/or use of antidiabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration ≥240 mg/dl and/or the use of antilipidemic medications.

Outcome

A follow-up survey assessing mortality, migration, and the incidence of heart failure, acute myocardial infarction and sudden death, and stroke was carried out after the baseline study. All deaths and migrations were confirmed by the official resident registration data issued by the local government offices.

Admission cases of heart failure in the cohort were checked by the regional registration survey data, which records primary hospital discharge diagnoses in the study area. The cases of heart failure were objectively defined by the Framingham criteria.[16] Details of this register have been described previously.[17] The event of non-sudden fatal myocardial infarction was also based on hospital registration survey data. The diagnosis of acute myocardial infarction was based on the Monica study criteria.[18] Sudden cardiac death within 1 h of the onset of acute illness was examined using death records and then checked against medical records of the hospitals within the survey areas. Stroke registry was used for the outcome study.[19] Stroke was defined as a sudden onset of focal neurological deficit ≥24 h duration and confirmed by brain computed tomography or magnetic resonance imaging.

Statistical Analysis

Continuous variables are shown as mean±SD. CKD subjects were divided into quartiles according to their baseline plasma BNP levels. To compare results among quartiles, ANOVA or chi-square test was used as appropriate. Survival from entry into the study was estimated using the Kaplan-Meier method, followed by a trend test (log rank). The association between baseline plasma BNP levels and endpoint CV diseases (new onset of heart failure, acute myocardial infarction/sudden cardiac death, and stroke) was evaluated. Using a Cox proportional hazards regression model, hazard ratios (HR) for plasma BNP with CV events were assessed. In this multivariable proportional-hazards regression model,

Table 1. Clinical Characteristics by BNP Quartile in Each CKD Definition

	CKD (definition-1), BNP quartile and range						CKD (definition-2), BNP quartile and range					
	Total	Q1 ≤11.2	Q2 11.3–22.7	Q3 22.8–42.9	Q4 ≥43.1	P value	Total	Q1 ≤11.9	Q2 12.0–23.5	Q3 23.6–43.4	Q4 ≥43.6	P value
n	1,901	478	473	475	475		1,578	395	394	395	394	
Age (years)	67.9±9.0	62.7±9.4	67.0±8.1	69.0±7.8	72.8±7.3	<0.001	68.7±8.4	64.4±8.9	67.7±7.8	69.7±7.4	72.9±7.1	<0.001
M/F	727/1,174	220/258	161/312	155/320	191/284	<0.001	552/1,026	159/236	131/263	118/277	144/250	<0.02
BMI	24.5±3.4	25.0±3.3	24.6±3.4	24.0±3.3	24.2±3.4	<0.001	24.4±3.3	24.8±3.2	24.5±3.2	23.9±3.3	24.2±3.4	<0.002
eGFR (ml·min^{-1}·1.73 m^{-2})	57.4±12.7	61.8±16.5	57.2±11.4	55.1±10.6	55.4±10.6	<0.001	52.9±5.4	54.0±4.9	53.2±5.0	52.4±5.7	51.8±5.6	<0.001
Proteinuria (%)	22.7	28.2	20.9	17.1	24.6	<0.001	6.9	4.8	6.6	5.6	10.7	<0.01
Blood hemoglobin (g/dl)	13.6±1.5	14.2±1.4	13.6±1.3	13.3±1.3	13.4±1.6	<0.001	13.5±1.4	13.9±1.4	13.6±1.3	13.3±1.3	13.3±1.5	<0.001
Hypertension (%)	53.8	47.1	50.7	50.7	66.5	<0.001	52.8	45.8	51.5	48.6	65.2	<0.001
Antihypertensive drugs (%)	37	27	36	35	49	<0.001	38	29	37	34	50	<0.001
Hyperlipidemia (%)	19	28.5	18.4	15.8	13.3	<0.001	19.1	28.1	19.3	14.4	14.5	<0.001
Diabetes (%)	7.5	9.2	8	4.6	8.2	<0.05	5.3	3.5	6.6	3.5	7.6	<0.02
Smoking (%)	11.8	16.7	9.3	8.8	12.2	<0.001	9.1	10.6	8.1	7.6	9.9	0.396
Atrial fibrillation (%)	3.1	0.4	0.2	1.1	10.5	<0.001	2.9	0.5	0.3	1.0	9.9	<0.001

BNP, B-type natriuretic peptide; CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

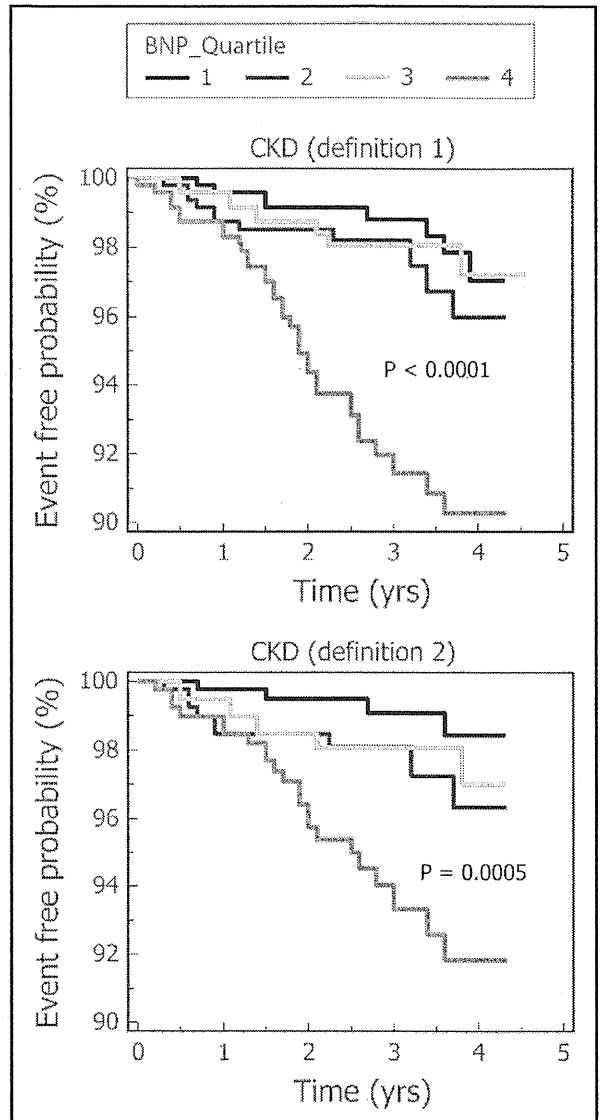

Figure. Kaplan-Meier curves of cardiovascular event-free probability according to quartile of plasma B-type natriuretic peptide (BNP) in chronic kidney disease (CKD) definition-1 (**Upper**) and CKD definition-2 (**Lower**)

adjustments were made in the analyses for age, body mass index, and the presence or absence of hypertension, diabetes, hypercholesterolemia, current smoking, and atrial fibrillation. 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. All statistical analyses were performed using SPSS software (Chicago, IL, USA). A significant difference was defined as $P<0.05$.

Results

As shown in Table 1, the number of cases of CKD definition-1 was 1,901 (727 in men, 1,174 in women). In this type of CKD, the prevalence within the community-based population was 14% (16% in men, 13% in women). The mean age was 67.9 years, and the mean eGFR was 57.4 ml·min^{-1}·

Table 2. Event Rates and HR for CVD by BNP Quartile in CKD

BNP quartile (pg/ml)	All CVD events/ 1,000 person-years	Age-sex adjusted HR (95%CI)	P value	Multivariate adjusted HR* (95%CI)	P value
CKD (definition 1)					
Q1 (≤11.2)	5.7	1.0		1.0	
Q2 (11.3–22.7)	8.6	1.77 (0.70–4.49)	0.226	1.83 (0.72–4.66)	0.203
Q3 (22.8–42.9)	7.1	1.47 (0.55–3.93)	0.439	1.62 (0.60–4.37)	0.341
Q4 (≥43.1)	25.9	4.71 (2.04–10.90)	<0.001	4.59 (1.97–10.73)	<0.001
CKD (definition 2)					
Q1 (≤11.9)	3.5	1.0		1.0	
Q2 (12.0–23.5)	8.4	2.58 (0.79–8.48)	0.118	2.48 (0.75–8.19)	0.135
Q3 (23.6–43.4)	7.7	2.39 (0.70–8.12)	0.164	2.56 (0.75–8.73)	0.134
Q4 (≥43.6)	20.3	5.56 (1.83–16.90)	<0.003	5.54 (1.81–16.97)	<0.003

*Adjusted for age, sex, BMI, current smoking, hypertension, diabetes, hypercholesterolemia, eGFR, and atrial fibrillation. HR, hazard ratios; CVD, cardiovascular disease; CI, confidence interval. Other abbreviations see in Table 1.

1.73 m^{-2}. Proteinuria was found in 23% of the subjects. The percentages of cases of hypertension, diabetes, and atrial fibrillation were 54%, 7.5%, and 3.1%, respectively. The median plasma BNP level was 22.7 pg/ml.

The number of cases of CKD definition-2 was 1,578 (552 in men, 1,026 in women), and the prevalence was 12% (12% in men, 11% in women) within the community-based population. The percentages of hypertension, diabetes, and proteinuria were 53%, 5.3%, and 6.9%, respectively. The prevalence of atrial fibrillation was 2.9%. The median plasma BNP level was 23.5 pg/ml (Table 1).

The cohorts were followed for 5,275 person-years in CKD definition-1, and for 4,350 person-years in CKD definition-2, respectively. Composite CV events (heart failure, acute myocardial infarction, sudden cardiac death, stroke) during the follow-up period (mean, 2.8 years) occurred in 62 cases in the CKD definition-1 group and in 43 cases in the CKD definition-2 group. The number of CV events/1,000 person-years was 11.7 and 9.9 in the CKD definition-1 and definition-2 groups, respectively.

Kaplan-Meier curves for the CV event-free rate according to the BNP quartiles in both CKD cohorts are shown in Figure. The CV event-free rate was significantly lower in the highest quartile of BNP (>43 pg/ml) in both CKD cohorts (CKD definition-1, P<0.0001; CKD definition-2, P<0.0005 by log-rank test).

As shown in Table 2, in the CKD definition-1 group, the number of CV events/1,000 person-years among BNP quartiles (Q) was 5.7 in Q1, 8.6 in Q2, 7.1 in Q3, and 25.9 in Q4. Similarly, in the CKD definition-2 group, the number was 3.5, 8.4, 7.7, and 20.3, respectively. CV events occurred in the highest quartile group of each CKD cohort (P<0.001 for both definitions).

After adjustment for age and sex, Cox regression analysis was performed to analyze the relationship between plasma BNP level and the risk of CV events (Table 2). The HR obtained from the Cox proportional model for the highest quartile of plasma BNP was significantly higher than that for the lowest quartile for CKD definition-1 (HR 4.71; 95% confidence interval (CI) 2.04–10.9; P<0.001) and for CKD definition-2 (HR 5.56; 95%CI 1.83–16.9; P<0.003). In addition, after multivariate adjustment of the models (age, sex, BMI, smoking, hypertension, diabetes, hypercholesterolemia, atrial fibrillation, and eGFR), similar results were obtained (Table 2). The HR in the highest quartile was significantly higher compared with the lower quartile groups (HR 4.59 in CKD definition-1 group, P<0.001; HR 5.54 in CKD definition-2 group, P<0.003).

Discussion

The present study demonstrates that for the first time in CKD cohorts defined by different criteria and selected from a community-based population, the subgroup with the highest plasma BNP quartile had a 4- to 5-fold higher CV risk, including heart failure, stroke, myocardial infarction, and sudden cardiac death compared with the subgroup with the lowest plasma BNP quartile. This relationship was robust even after adjustment for classical CV risk factors. Our observations suggest that the plasma BNP level is a useful tool for stratifying CV risk within a CKD cohort selected from a general population.

In cohort studies without renal dysfunction, Wang et al reported that the subgroup with plasma levels of BNP over the 80th percentile had a 3-fold higher risk of new onset of heart failure and a 2-fold higher risk of brain transient ischemic attack than subjects showing plasma levels below the 80th percentile.[5] Similarly, in a general population without subjects with elevated serum creatinine levels, Kistorp et al demonstrated that subjects who had higher plasma NT-proBNP levels above the 80th percentile had a 3-fold higher risk of CV diseases than the subjects who had plasma NT-proBNP levels below the 80th percentile.[6] However, no studies have yet examined whether plasma levels of natriuretic peptides might be effective for stratifying the CV risk within a large number of CKD subjects selected from the general population. This may have been because of concerns that plasma natriuretic peptide levels might increase in the absence of organic cardiac disorders, and thus confound the relationship between the plasma level and CV events in this setting, as the important clearance site of the natriuretic peptide family protein is the kidney.[20]

There are several possible explanations for the fact that an elevated plasma BNP level was associated with a high risk for CV events, as demonstrated in the present study. First, the increased level of plasma BNP might be a marker for more advanced renal dysfunction, and deterioration of renal function is usually associated with an accumulation of traditional CV risk factors[21] and there may be related increases in homocysteine, inflammation, oxidative stress, and thrombogenic factors.[1,4] These factors may impair endothelial function, lead to progression of atherosclerosis, and thus increase

the risk of CV events in CKD subjects. Second, the plasma BNP level has been reported as increased with progression of anemia, which is independent of the degree of cardiac dysfunction.[22,23] In this regard, an elevated plasma BNP level may indicate advanced anemia, and thus be a marker at a high risk of CV events in CKD subjects. In fact, several reports have demonstrated that the prevalence of future onset of coronary artery disease and heart failure were significantly elevated in subjects with anemia.[24–26] Third, elevated levels of plasma BNP denote impaired cardiac function, including latent structural heart diseases, cardiac volume overlord, and myocardial ischemia, and thus such patients are prone to CV disorders.

In the present study, although there were no significant differences in the levels of eGFR and blood hemoglobin between the 3rd rd and the 4th BNP quartiles, CV events were clearly prevalent in the highest quartile group. These findings indicate that the first and the second explanations are unlikely, and thus the third hypothesis may be the more possible. However, left ventricular function and morphological data were unavailable in the present cohort study, and it was unclear whether patients with structural heart disease or impaired cardiac function were more common in the 4th quartile than in the lower quartiles. In previous studies using echocardiography, a plasma level of plasma BNP >40–50 pg/ml was a useful marker with high sensitivity and specificity for identifying subjects with latent structural heart disease, including left ventricular dysfunction, valvular heart diseases, cardiomyopathy, and atrial fibrillation.[27–29] In view of these findings, a CKD subgroup with elevated plasma BNP levels tends to show subclinical structural cardiac disorders and is associated with a high risk for heart failure, ischemic stroke, and coronary artery diseases. In accordance with this hypothesis, several reports have suggested that an increased plasma BNP level in patients with renal dysfunction is mainly caused by cardiac overload and intrinsic organic heart disease rather than renal dysfunction.[30–32]

Incidentally, the present study found that CKD definition-1 using reduced GFR and/or proteinuria captured a greater number of subjects with CV events than CKD definition-2 using reduced GFR only (62 cases for definition-1 vs 43 cases for definition-2). This observation suggests that definition-1 is more useful for the definition of CKD in terms of CV risk stratification. Measurement of 2 biomarkers (GFR and urinary protein) is therefore be recommended for the selection of CKD subjects within apparent healthy populations.

Study Limitations

Although the present study with its large sample size is a prospective community-based study that included routine biochemical data, several limitations must be considered when interpreting the results. More than 35% of the CKD subjects were receiving antihypertensive agents at baseline. Several types of antihypertensive drugs, such as angiotensin-converting enzyme-inhibitors and angiotensin II receptor blockers, reduce the onset of CV events. The present study did not evaluate the effects of these drugs on the incidence of CV events. However, the percentage of subjects receiving antihypertensive drugs increased with the quartiles of plasma BNP level (Table 1), which suggests that the CKD subjects with higher plasma BNP levels were likely to receive these medications. This limitation might have underestimated the association between plasma BNP level and CV events. The urine dipstick test used in the present CKD definition is usually regarded as not being accurate for the diagnosis of persistence proteinuria. However, in a previous population-based study, trace proteinuria on dipstick test had good reproducibility and high sensitivity and specificity for detection of micro-albuminuria in an elderly population.[33] In this regard, the inclusion criterion for CKD definition-1 in the present study was a trace result for dipstick test.

In conclusion, the plasma BNP level provides strong predictive information about the future onset of CV events in subjects with mildly reduced renal function. This result implies that plasma BNP measurement is a powerful tool for stratifying CV risk in CKD subjects selected from the general population.

Acknowledgments

This study was supported in part by the Japan Arteriosclerosis Prevention Fund, and grants-in-aid for the scientific research fund of the Ministry of Education, Science, and Culture of Japan (20590836). The authors thank the Northern Iwate Heart Disease Registry Consortium for permission to use regional registry data for heart failure.

References

1. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108:** 2154–2169.
2. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: Systematic review. *BMC Public Health* 2008; **8:** 117.
3. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298:** 2038–2047.
4. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. *Circulation* 2007; **116:** 85–97.
5. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350:** 655–663.
6. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005; **293:** 1609–1616.
7. Tsutamoto T, Wada A, Sakai H, Ishikawa C, Tanaka T, Hayashi M, et al. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2006; **47:** 582–586.
8. Austin WJ, Bhalla V, Hernandez-Arce I, Isakson SR, Beede J, Clopton P, et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Pathol* 2006; **126:** 506–512.
9. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study. *Kidney Int* 2005; **68:** 228–236.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–1305.
11. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, et al. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circ J* 2006; **70:** 954–959.
12. Cirillo M, Lanti MP, Menotti A, Laurenzi M, Mancini M, Zanchetti A, et al. Definition of kidney dysfunction as a cardiovascular risk factor: Use of urinary albumin excretion and estimated glomerular filtration rate. *Arch Intern Med* 2008; **168:** 617–624.
13. Ohsawa M, Itai K, Tanno K, Onoda T, Ogawa A, Nakamura M, et al. Cardiovascular risk factors in the Japanese northeastern rural population. *Int J Cardiol* 2009; **137:** 226–235.
14. Makita S, Nakamura M, Satoh K, Tanaka F, Onoda T, Kawamura K, et al. Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. *Atherosclerosis* 2009; **204:** 234–238.
15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in

Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
16. McKee PA, Castelli WP, McNamara PM, McKee PA, Feinleib M. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446.
17. Ogawa M, Tanaka F, Onoda T, Ohsawa M, Itai K, Sakai T, et al. A Community based epidemiological and clinical study of hospitalization of patients with congestive heart failure in northern Iwate, Japan. *Circ J* 2007; **71:** 455–459.
18. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90:** 583–612.
19. Omama S, Yoshida Y, Ogawa A, Onoda T, Okayama A. Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset. *J Neurol Neurosurg Psychiatry* 2006; **77:** 1345–1349.
20. van Kimmenade RR, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, et al. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. *J Am Coll Cardiol* 2009; **53:** 884–890.
21. Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: Overall burden and rates of treatment and control. *Arch Intern Med* 2006; **166:** 1884–1891.
22. Fukuta H, Ohte N, Mukai S, Saeki T, Kobayashi K, Kimura G. Anemia is an independent predictor for elevated plasma levels of natriuretic peptides in patients undergoing cardiac catheterization for coronary artery disease. *Circ J* 2008; **72:** 212–217.
23. Wold Knudsen C, Vik-Mo H, Omland T. Blood haemoglobin is an independent predictor of B-type natriuretic peptide (BNP). *Clin Sci* 2005; **109:** 69–74.
24. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Takeshita A, Yokoshiki H, et al; JCARE-CARD Investigators. Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan: A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73:** 1901–1908.
25. Walker AM, Schneider G, Yeaw J, Nordstrom B, Robbins S, Pettitt D. Anemia as a predictor of cardiovascular events in patients with elevated serum creatinine. *J Am Soc Nephrol* 2006; **17:** 2293–2298.
26. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, et al. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol* 2002; **40:** 27–33.
27. Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. *Heart* 2002; **87:** 131–135.
28. Niinuma H, Nakamura M, Hiramori K. Plasma B-type natriuretic peptide measurement in a multiphasic health screening program. *Cardiology* 1998; **90:** 89–94.
29. Seki S, Tsurusaki T, Kasai T, Taniguchi I, Mochizuki S, Yoshimura M. Clinical significance of B-type natriuretic Peptide in the assessment of untreated hypertension. *Circ J* 2008; **72:** 770–777.
30. Palmer SC, Richards AM. Does renal clearance differ between the B-type natriuretic peptides (BNP versus NT-proBNP)? *J Am Coll Cardiol* 2009; **53:** 891–892.
31. Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, et al. Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. *Am J Kidney Dis* 2004; **44:** 420–428.
32. Sagnella GA. Measurement and significance of circulating natriuretic peptides in cardiovascular disease. *Clin Sci* 1998; **95:** 519–529.
33. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. *Clin Exp Nephrol* 2007; **11:** 51–55.

ELSEVIER

International Journal of Cardiology 143 (2010) 124–129

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Gender-specific risk stratification with plasma B-type natriuretic peptide for future onset of congestive heart failure and mortality in the Japanese general population

Motoyuki Nakamura [a,*], Fumitaka Tanaka [a], Toshiyuki Onoda [b], Tomohiro Takahashi [a], Masafumi Sakuma [a], Kazuko Kawamura [c], Kozo Tanno [b], Makaski Ohsawa [b], Kazuyoshi Itai [b], Kiyomi Sakata [b], Shinji Makita [a], Akira Okayama [d]
On behalf of the Iwate KENCO study groups

[a] *Departments of Internal Medicine, Iwate Medical University, Morioka, Japan*
[b] *Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Japan*
[c] *Iwate Health Service Association, Morioka, Japan*
[d] *Japan Anti-Tuberculosis Association, Tokyo, Japan*

Received 26 April 2008; received in revised form 22 November 2008; accepted 29 January 2009
Available online 9 March 2009

Abstract

Background: Elevated plasma B-type natriuretic peptide (BNP) levels suggest a high risk for future onset of cardiovascular events including congestive heart failure (CHF) and mortality. In the general population, although median plasma BNP levels have been reported to be higher in women than in men, the incidence of CHF and mortality are lower in women. However, no studies have examined gender-specific risk stratification of plasma BNP levels for future onset of CHF and mortality.
Methods: Subjects of this study were recruited from our general population. Baseline data including plasma BNP were determined in 13,466 subjects (men 4527, women 8939; median age = 64 yrs). A multivariate Cox regression analysis was performed to examine the predictive ability of plasma BNP for new onset of CHF and mortality.
Results: The mean follow-up duration was 2.9 years. After adjustment for traditional cardiovascular risk factors including atrial fibrillation, hazard ratios for CHF development for values above the 75th percentile of BNP were 13.4 ($p<0.001$) in men and 8.5 ($p<0.001$) in women. Similarly, each increment of 1SD in log BNP levels increased the hazard ratio by 8.8 ($p<0.001$) in men, and 6.7 ($p<0.001$) in women. The area under the receiver operating characteristic curve was significant for prediction of the onset of CHF (men; 0.853, women; 0.838). In addition, increased plasma BNP levels implied high risk of any-cause mortality in men (above the 75th percentile; hazard ratio = 1.8, $p=0.005$: increment of 1SD; hazard ratio = 1.4, $p=0.024$), but this relationship was suboptimal in women.
Conclusion: Measurements of plasma BNP provides strong predictive information about future onset of CHF in both sexes, with predictive ability for death being effective especially in men.

Keywords: Mortality; Community; Non-white; Japanese

B-type natriuretic peptide (BNP) has been recognized as a hormone released with its biologically inactive N-terminal peptide (NT-proBNP) from the heart [1,2]. It has been suggested that cardiac secretion of BNP is increased by elevated left ventricular end-diastolic pressure, decreased

* Corresponding author. Department of Internal Medicine, Division of Cardiology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan. Tel.: +81 19 651 5111e2321; fax: +81 19 626 4406.
E-mail address: nkmrmoto@iwate-med.ac.jp (M. Nakamura).

0167-5273/$ - see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2009.01.076

cardiac systolic/diastolic function, hypertensive heart disease, atrial fibrillation, and myocardial ischemia [3–7]. It is therefore expected that measurement of plasma BNP levels would provide useful information for identification of subjects at high risk of CHF due to various phenotypes of structural heart disease [8,9].

In fact, Wang et al. have shown for the first time that a 1standard deviation increment in plasma BNP as well as elevated plasma BNP above the 80th percentile was associated with a significant increase in the risk of new onset of CHF and any-cause mortality in the Framingham general population [10]. Similar positive associations between plasma NT-proBNP levels and risk of cardiovascular events including onset of CHF and mortality have been reported in the Danish general population [11]. These previous studies have suggested that plasma levels of BNP or NT-proBNP may serve as a possible screening tool for subjects at high risk of CHF and death within the general population. However, few studies have examined the utility of plasma BNP measurement as a predictor of future onset of CHF by a sex-stratified analysis, because women have a relatively lower incidence of CHF and higher median plasma BNP levels than men [12–14].

Moreover, subjects of previous studies were mainly drawn from white populations [10,11]. No studies have confirmed the relationship between plasma BNP levels and cardiovascular events and mortality in community-based cohorts taken from non-white populations. The incidence and prevalence of cardiovascular events including CHF has been reported to differ among ethnic groups [15]. In the general population, several reports have shown that plasma BNP levels are affected by anthropometric factors such as body mass index [16] and genetic features [17], and this may alter the utility of plasma BNP measurement as a predictor of cardiovascular events.

These suggest that the relationship between plasma BNP levels and cardiovascular outcomes should be evaluated separately in men and women, and it may also be important to examine whether the relationship is applicable in other ethnic populations. The present study has therefore sought to determine whether 1) plasma BNP levels are associated with an increased risk of CHF and any-cause death in both sexes in the general population; and 2) the relationship between plasma BNP and cardiovascular outcome observed in the white population is valid in other ethnic groups, specifically the Japanese population.

1. Methods

1.1. Study population

The original cohort of the Iwate-KENCO study was recruited from the community-dwelling population living in the three districts (Ninohe, Kuji, and Miyako) of the northern Iwate prefecture, Japan. This region has a resident population of over 144,000 adults over the age of 40 years based on census data from October 2005. The cohort was recruited from subjects of a government-regulated multiphasic health checkup for the general population. Invitations to participate in the multiphasic health screening program were issued by government offices in each municipality.

The total number of participants who agreed to join the Iwate-KENCO study in the three districts was 26,469 (original cohort). The acceptance rate for participation from government-regulated health screening was 84.5%. Of the original cohort living in Ninohe and Kuji districts (n=15,927), 15,394 subjects (97%) had BNP measurements (BNP cohort: men 5288; women 10,106). Subjects were excluded from this cohort for the following reasons: age under 40 (575), history of cardiovascular events such as myocardial infarction, stroke or heart failure (507), and missing covariates (846). The final statistical analysis was therefore performed on 13,466 subjects (men 4527; women 8939: Table 1). This study protocol was approved by our university ethics committee and local institutional review committees. All participants gave written informed consent.

1.2. BNP assay

Non-fasting blood samples were drawn from the antecubital vein while participants were seated. Blood samples were collected into vacuum tubes. While blood samples for routine blood testing were being taken, an additional 2 ml sample of venous blood was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately after sampling in an icebox and transported to the Iwate Health Service Association

Table 1
Baseline characteristics of study population, the Iwate KENCO study.

	Men	Women
Number	4527	8939
Age (years)		
Mean (±SD)	64.1±10.3	62.0±10.0
Median	66.0	63.0
Plasma BNP (pg/ml)		
1st quartile	<6.5	<8.9
2nd quartile	6.5–14.8	8.9–17.1
3rd quartile	14.8–30.0	17.1–30.4
4th quartile	≥30.0	≥30.4
Systolic blood pressure (mmHg)		
Mean (±SD)	130.1±19.4	125.5±19.7
Median	128.5	123.5
Diastolic blood pressure (mmHg)		
Mean (±SD)	77.8±10.8	73.7±10.8
Median	77.5	73.0
Hypertension (%)	44.4	38.8
Antihypertensive drugs (%)	23.6	24.3
Body mass index (kg/m2)		
Mean (±SD)	23.9±2.9	24.1±3.4
Median	23.8	23.9
Atrial fibrillation (%)	3.0	0.6
HbA1c (%)		
Mean (±SD)	5.2±0.8	5.1±0.6
Median	5.0	5.0
Diabetes (%)	8.0	4.3
Antidiabetic medication (%)	4.6	2.4
Total cholesterol (mg/dl)		
Mean (±SD)	193.2±32.6	206.7±31.8
Median	191.0	206.0
Hypercholestrolemia (%)	10.3	20.3
Antihypercholestrolemic drugs (%)	2.8	7.3
HDL-cholesterol (mg/dL)		
Mean (±SD)	56.4±15.4	61.8±14.5
Median	54.0	60.0
Current smoking (%)	33.4	2.5
Regular alcohol intake (%)	61.7	11.1
Regular exercise (%)	17.0	10.5

laboratory each afternoon. They were then centrifuged at 1500 g for 10 min. After separation, plasma samples were stored frozen at −20 °C until transportation to the Shionogi central laboratory for the assay. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi, Japan). Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and inter-assay coefficients of variation were 5% and 6%, respectively.

1.3. Risk factor definitions

Subjects used a self-reported questionnaire to document medical history including status (yes or no) of prescribed drugs for hypertension, diabetes, hypercholesterolemia, stroke, angina, CHF and myocardial infarction. Smoking habits (current or non-smoker), regular alcohol intake (yes or no), and regular exercise (≥60 min of exercise and ≥8 times per month) were also assessed by a questionnaire developed by the study committee. Systolic and diastolic blood pressures were determined with an automated sphygmomanometer with subjects seated for at least 5 min 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 the use of antihypertensive medication. Body height was measured with participants in stocking feet and weight was measured wearing light clothing. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Diabetes was ascertained by detection of a non-fasting glucose concentration ≥200 mg/dl and/or HbA1c value ≥6.5% [18] and/or a use of anti-diabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration ≥240 mg/dl and/or the use of anti-lipidemic medications.

1.4. Outcome

A follow-up survey assessing mortality, migration, and the incidence of CHF was carried out after the baseline study. Admission cases of CHF in the cohort were checked by the regional registration survey data for heart diseases, which records primary hospital discharge diagnoses in the study area. Details of this register have been described previously [15]. The cases of CHF were objectively defined by Framingham criteria [19]. All deaths and migration were confirmed by the official resident registration data issued by the local government offices.

1.5. Statistical analysis

Continuous variables are shown as median or mean. Owing to the purpose of the present study, the following analyses were performed separately in men and women. Participants were divided into quartiles according to their baseline plasma BNP levels. Survival from entry into the study was estimated using the Kaplan–Meier method, followed by a trend test (Log rank). We evaluated the association between baseline plasma BNP levels and two clinical endpoints (new onset of CHF and death from any cause). Using a Cox proportional hazards regression model, hazard ratios (HRs) for plasma BNP with each outcome were assessed. In these analyses, plasma BNP levels were used as a categorical variable and as continuous variables after natural logarithmic transformation. For the categorical analyses, we used prespecified thresholds corresponding to the 75th percentile values. In this multivariable proportional-hazards regression model, we adjusted analyses for age, body mass index, and the presence or absence of hypertension, diabetes, hypercholesterolemia, current smoking, regular exercise and atrial fibrillation. Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of plasma BNP throughout the range of concentrations as an indicator of CHF or all cause of mortality. The area under the curve and 95% confident interval (CI) of each ROC curve were calculated to provide a measure of the overall diagnostic accuracy of the test. All statistical analysis was performed using SPSS software. A significant difference was defined as $p<0.05$.

2. Results

2.1. Baseline characteristics of the cohort

The median age of male and female cohorts was 66 in men, and 63 in women, respectively (Table 1). The number of women participants was approximately twice the number of men. The median plasma BNP level was higher in women than men (17.1 pg/ml versus 14.8 pg/ml; $p<0.001$). The prevalence of hypertension, atrial fibrillation, diabetes, current smoking, regular alcohol intake tended to be higher in men than in women.

2.2. Congestive heart failure and all-cause death

During the 2.9 year follow-up period, there were 44 cases of new onset CHF (men=23; women=21). The crude incidence rate of CHF was 1.75/1000 person-years in men and 0.82/1000 person-years in women. In addition, a total of 182 participants died from any cause (men=106; women=76). The crude death rate was 8.07/1000 person-years in men and 2.98/1000 person-years in women. The event free probabilities for CHF according to BNP quartiles are shown in Fig. 1. In both sexes, the highest quartile showed the lowest event free rate for onset of CHF (p for trends: men, $p<0.0001$; women, $p<0.0001$). Similarly, mortality rate increased with increasing quartile levels of plasma BNP (p for trends: men, $p<0.0001$; women, $p=0.0014$) (Fig. 2).

2.3. Multivariate analysis of outcomes

Increased plasma BNP levels predicted new onset of CHF even after adjusting for cardiovascular risk factors such as age, atrial fibrillation, BMI, current smoking, diabetes, hypercholesterolemia, hypertension, regular alcohol intake, and exercise habit in both sexes. As shown in Table 2, male participants with plasma BNP values above the 75th percentile had 13.4-fold increased risk of onset of CHF (95% CI, 4.1 to 43.6; $p<0.001$) relative to those with values equal to or below. In women, the association between the risk of CHF and plasma BNP above the 75th percentile was also significant (hazard ratio=8.5; 95% CI, 2.9 to 25.3: $p<0.001$). When plasma BNP was analyzed as a continuous variable, increasing plasma BNP for each 1SD increment in log BNP was associated with an increased risk of onset of CHF, with adjusting hazard ratios of 8.8 (95% CI, 3.9 to 20.1; $p<0.001$) in men and 6.7 (95% CI, 2.9 to 15.3: $p<0.001$) in women.

Median plasma BNP levels were higher in subjects complicated with atrial fibrillation than in subjects in sinus rhythm (men, 106.0 pg/ml versus 14.3 pg/ml; $p<0.001$: women, 118.0 pg/ml versus 17.0 pg/ml; $p<0.001$). To eliminate possible confounding effects of atrial fibrillation on the onset of CHF and plasma BNP, participants with atrial fibrillation at baseline were excluded from the analysis. The relationship between plasma BNP levels above the 75th percentile (categorical variable) and risk of CHF onset remained robust in both men (hazard ratio=15.5; 95% CI, 4.5 to 53.9: $p<0.0001$) and women (hazard ratio=7.9; 95% CI, 2.6 to 23.9: $p<0.001$) (Table 2). The risk of CHF for each 1SD increment in log BNP increased 12.8-fold in men (95% CI, 5.4 to 30.5; $p<0.0001$), and 7.5-fold in women (95% CI, 3.2 to 17.5; $p<0.001$) after exclusion of subjects with atrial fibrillation at baseline.

In men, the hazard ratio for mortality according to plasma BNP as a categorical variable (above the 75th percentile) was 1.8 (95% CI, 1.2 to 2.7; $p=0.005$). Also, a 1SD increment in plasma BNP as a log transformed value was associated with a significant (1.4-fold) increase in the hazard ratio for death (95% CI, 1.0 to 1.8; $p=0.024$) in men (Table 2). However, in women, the association between plasma BNP and mortality was not significant (above the 75th percentile, $p=0.41$: each 1SD increment, $p=0.23$).

2.4. ROC analysis

As shown in Fig. 3, the overall power of plasma BNP for prediction of CHF was significant. The optimal threshold of BNP for prediction of CHF was 32 pg/ml (sensitivity; 83%, specificity; 77%) in men, and 62 pg/ml

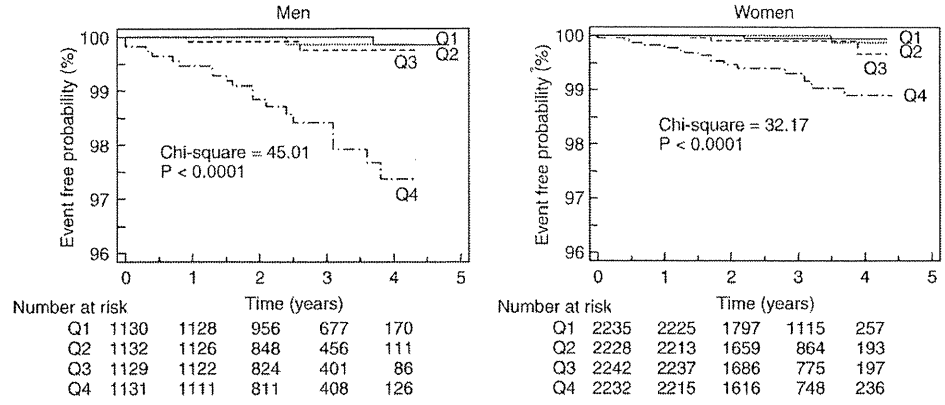

Fig. 1. Kaplan–Meier curves of unadjusted cumulative CHF free probabilities according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

(sensitivity; 67%, specificity; 94%) in women, respectively. The area under the ROC curve was 0.853 (95% CI, 0.842 to 0.863) in men, and 0.838 (95% CI, 0.830 to 0.845) in women, respectively. The predictive ability of plasma BNP for all-cause of death as represented by the area under the curve was lower than that for CHF (men; 0.665, women; 0.615).

3. Discussion

The present study has found that elevated plasma BNP in the middle aged and elderly general population serves as a significant indicator of high risk for future onset of CHF in both men and women. This relationship remains statistically robust even after adjustment for clinical risk factors for CHF and after exclusion of subjects having atrial fibrillation at baseline. In addition, increased plasma BNP is a useful biomarker for prediction of high risk for any cause mortality in men, whereas this relationship was obscure in women.

Wang et al. have reported that elevated levels of plasma BNP were a useful predictor of the risk of death and cardiovascular events including CHF in a mainly white US population living in Framingham [10]. The incidence of CHF is well known to be lower in women than in men. Conversely, median plasma BNP levels are reported to be higher in women than in men in the general population [12–14]. This appears to contradict the epidemiological fact of a lower prevalence of cardiovascular disorders in women. However, little information is available to show whether the relationship between plasma BNP and the risk of onset of CHF remains significant in both sexes. Subject numbers in these previous studies may have been insufficient for separate analysis of predictive values for CHF in each gender group. The present study has suggested for the first time that plasma BNP may be a feasible screening tool for identification of individuals at high risk of future development of CHF within an apparently healthy population without gender bias.

Moreover, there have been no reports about the predictive abilities of plasma BNP for any cardiovascular events in non-white populations having a different incidence of cardiovascular disease. The incidence of cardiovascular events including CHF differs among races, with the Japanese having a relatively lower rate [15,20–22]. Plasma BNP levels have been demonstrated to be affected by anthropometric factors such as body mass index [16], and to be modified by heritability and genetic factors in a community based sample [17]. These findings suggest that the distribution of plasma BNP in apparently healthy populations may differ among

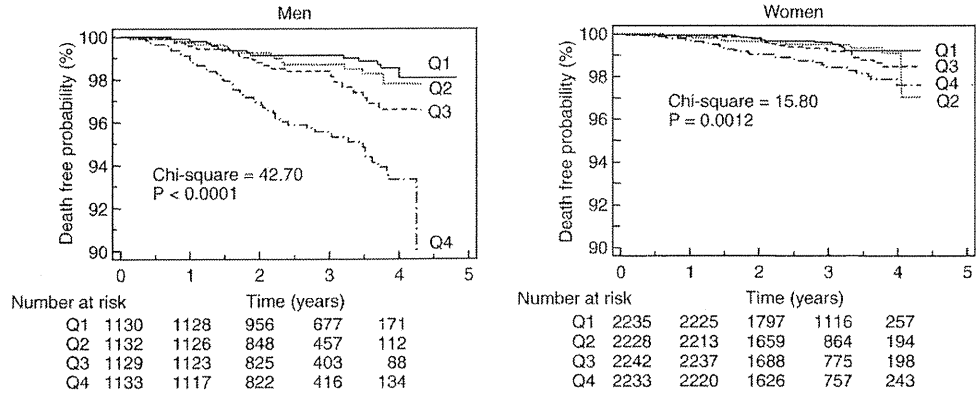

Fig. 2. Kaplan–Meier curves of unadjusted cumulative survival according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

Table 2
Multivariate analysis of the association of plasma BNP levels, congestive heart failure and death.

	Adjusted hazard ratio for BNP values above 75th percentile			Adjusted hazard ratio per 1SD increment in Log BNP		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Men						
Heart failure	13.45	4.15 to 43.56	0.001	8.84	3.88 to 20.13	0.001
Heart failure (ex. Afib)	15.50	4.46 to 53.88	0.001	12.85	5.41 to 30.51	0.001
All cause death	1.81	1.20 to 2.75	0.005	1.38	1.04 to 1.82	0.024
Women						
Heart failure	8.54	2.88 to 25.31	0.001	6.68	2.93 to 15.26	0.001
Heart failure (ex. Afib)	7.88	2.60 to 23.91	0.001	7.53	3.24 to 17.53	0.001
All cause death	1.22	0.76 to 1.98	0.408	1.17	0.90 to 1.53	0.231

The hazard ratios were adjusted for age, atrial fibrillation, BMI, current smoking, diabetes, hypercholesterolemia, hypertension, regular alcohol intake, and regular exercise: ex. Afib = analysis after exclusion of atrial fibrillation.

ethnicities and communities. It would therefore be important to confirm that the predictive ability of BNP for CHF reported in US and European populations could be extrapolated to other ethnic populations. The present study has established the relationship between plasma BNP levels and risk of CHF in a non-white, specifically Japanese, population. Thus the present study suggests that BNP testing may be useful even in a low-risk population.

In contrast to the value of plasma BNP for predicting future onset of CHF in either sex, the association between plasma BNP and all cause mortality was less robust after adjustment for cardiovascular risk factors especially in the female cohort. In several previous studies without gender-specific analysis, elevated plasma BNP or plasma NT-proBNP levels were associated with an increased risk of death in the general population [10,11,23,24]. The present study has confirmed this association in men only, with the reasons for the lack of predictive ability of BNP testing for all causes of death in women remained unknown. Although person-years among female subjects in the present study may not have been insufficient (>=25,000 person-years), the follow-up may have been shorter than those of earlier studies (>5 years). In addition, it seems that cardiovascular death rate among the present female cohort may have been lower due to the lower incidence of cardiovascular risk factors compared to the male cohort. These biases may account for the possible dissociation between mortality and plasma BNP in women.

3.1. Limitations

This study has several limitations. The capture of CHF during the follow-up period was restricted to hospitalized cases so that CHF patients treated at an outpatient clinic only may be missing from the follow-up data. As the Framingham criteria for CHF employed in this study tend to capture relatively advanced CHF, the observed predictive value of plasma BNP is assured in cases with clinically overt CHF. As echocardiographic parameters were not included in the baseline data, the reasons for the elevation of plasma BNP are not known. However, according to our previous cross-sectional cohort study of the general population, elevated plasma BNP concentrations has a significant sensitivity and specificity for screening several phenotypes of structural heart disease [8]. The predictive abilities of high plasma BNP levels may be due to the capability for selection of subjects who have underlying cardiac disorders which are prone to progress to overt CHF. More than 20% of our cohort was receiving antihypertensive agents at baseline. Several types of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers have been reported to reduce cardiovascular events and mortality in high risk subjects [25,26]. This type of drug also has been reported to reduce plasma levels of BNP [27]. In view of these findings, the present study did not assess the effects of these drugs on the incidence of outcomes or on plasma BNP levels. However, when the use of antihypertensive medication (yes or no) was entered into the multivariate regression model, the significance of the predictive ability of plasma BNP did not weaken for CHF (hazard ratios >5.0, $p<0.0001$; both above the 75th percentile level and each 1SD increment).

In conclusion, measurement of plasma BNP provides strong predictive information about future onset of CHF in both sexes, with the predictive ability for death effective especially in men.

Acknowledgements

This study was supported in part by the Japan Arteriosclerosis Prevention Fund, and grants-in-aid for the scientific research fund of the Ministry of Education, Science, and Culture of Japan (18590786 and 40172449), and of the Ministry of Health and Welfare of Japan (17120501). The

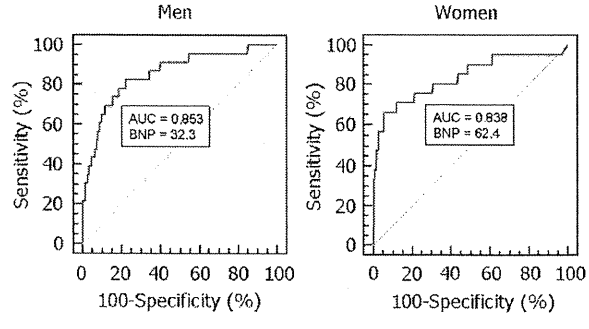

Fig. 3. Receiver-operating-characteristic curves of plasma BNP concentration to predict future onset of CHF.

authors thank the Northern Iwate Heart Disease Registry Consortium for permission to use regional registry data for heart failure.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [28].

References

[1] Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006;92: 843–9.
[2] Rao A, Hodgson L, Pearce D, Walsh J. BNP in the community – still work to be done. Int J Cardiol Feb 29 2008;124(2): 228–30.
[3] Nakamura M, Kawata Y, Yoshida H, et al. Relationship between plasma atrial and brain natriuretic peptide concentration and hemodynamic parameters during percutaneous transvenous mitral valvulotomy in patients with mitral stenosis. Am Heart J 1992;124: 1283–8.
[4] Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296: 2209–16.
[5] Kohno M, Horio T, Yokokawa K, et al. Brain natriuretic peptide as a cardiac hormone in essential hypertension. Am J Med 1992;92: 29–34.
[6] Inoue S, Murakami Y, Sano K, et al. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. J Card Fail 2000;6: 92–6.
[7] Arakawa N, Nakamura M, Aoki H, et al. Relationship between plasma level of brain natriuretic peptide and myocardial infarct size. Cardiology 1994;85: 334–40.
[8] Nakamura M, Endo H, Nasu M, et al. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002;87: 131–5.
[9] McKie PM, Burnett Jr JC. B-type natriuretic peptide as a biomarker beyond heart failure: speculations and opportunities. Mayo Clin Proc 2005;80: 1029–36.
[10] Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350: 655–63.
[11] Kistorp C, Raymond I, Pedersen F, et al. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA 2005;293: 1609–16.
[12] Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40: 976–82.
[13] Nakamura M, Tanaka F, Sato K, et al. B-type natriuretic peptide testing for structural heart disease screening: a general population-based study. J Card Fail 2005;11: 705–12.
[14] Kanda H, Kita Y, Okamura T, et al. What factors are associated with high plasma B-type natriuretic peptide levels in a general Japanese population? J Hum Hypertens 2005;19: 165–72.
[15] Ogawa M, Tanaka F, Onoda T, et al. A Community based epidemiological and clinical study of hospitalization of patients with congestive heart failure in northern Iwate, Japan. Circ J 2007;71: 455–9.
[16] Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109: 594–600.
[17] Wang TJ, Larson MG, Levy D, et al. Heritability and genetic linkage of plasma natriuretic peptide levels. Circulation 2003;108: 13–6.
[18] Kuzuya T, Nakagawa S, Satoh J, et al. Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Prac 2002;55: 65–85.
[19] McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285: 1441–6.
[20] Ho KK, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22: 6A–13A.
[21] Cowie MR, Wood DA, Coats AJ, et al. Incidence and aetiology of heart failure; a population-based study. Eur Heart J 1999;20: 421–8.
[22] Remes J, Reunanen A, Aromaa A, et al. Incidence of heart failure in eastern Finland: a population-based surveillance study. Eur Heart J 1992;13: 588–93.
[23] Wallen T, Landahl S, Hedner T, et al. Brain natriuretic peptide predicts mortality in the elderly. Heart 1997;77: 264–7.
[24] McKie PM, Rodeheffer RJ, Cataliotti A, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of heart failure. Hypertension 2006;47: 874–80.
[25] Arnold JM, Yusuf S, Young J, et al. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. Circulation 2003;107: 1284–90.
[26] Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363: 2022–31.
[27] Kohno M, Minami M, Kano H, et al. Effect of angiotensin-converting enzyme inhibitor on left ventricular parameters and circulating brain natriuretic peptide in elderly hypertensives with left ventricular hypertrophy. Metabolism 2000;49: 1356–60.
[28] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131: 149–50.