Geriat Med. 48(11) : 1559～1561, 2010

高齢者の安全な薬物療法　第23回

監修：秋下　雅弘，葛谷　雅文

降圧薬合剤使用には注意が必要

西永　正典
東京大学高齢社会総合研究機構特任准教授

2006年2種類の降圧薬，アンジオテンシンⅡ受容体拮抗薬(ARB)のロサルタンカリウムとサイアザイド系利尿薬のヒドロクロロチアジドが配合された降圧薬の合剤が販売された．世界的には1995年以降，フランス，米国をはじめとして82カ国で承認され，広く臨床で使用されている．その後，ここ2～3年の間に，少量の利尿薬とARBの降圧薬合剤が次々と販売され(表1)，その市場は確実に増大している．

それらの合剤の特徴は，ARB単独で用いられる効果に比し，比較的強い降圧効果を発揮するが，利尿薬配合量が少量のため，その副作用を十分認識されずに使用されることも少なくない．また，高齢者では，合併症や非典型的な症状のため，副作用と認識されにくく，その発見が遅れる場合もある．本稿では，われわれが経験した苦い症例を中心に概説する．

症例呈示

84歳/女性

主訴：食欲低下，ふらついて歩けない．

既往歴：うつ病で精神科通院中．

生活歴：長年小学校の教員を勤め，定年後はご主人と2人だけの生活．近くに住む娘が1人いるが，時々旅行に行ったりして楽しんでいる．

総合的機能評価：基本的ADLは保たれている(Barthel index：95/100点)，手段的ADLは，服薬能力，家事(炊事，掃除，洗濯)，買物，金銭管理，電話，交通機関の利用(車の運転はご主人)も可能であった．ミニメンタルテストは28/30点，Geriatric depression scale 15では6/15点．

現病歴：近医に十数年前から高血圧の診断で降圧薬(カルシウム拮抗薬)をもらって服用していたが，顔が火照るなどの症状があり，服薬を止めていた．体重が3カ月で7kg以上減少するため，近くの総合病院で採血，内視鏡やエコー，CTなどの検査を受けるも異常が認められず，食欲低下や昼夜逆転なども出現したため，当科を受診．総合的機能評価などから認知機能低下よりもうつ症状が目立ったため，精神科紹介入院となる．抗うつ薬が著効し，食欲も改善，その後，体重ももとのレベルに戻った．精神科入院中から，高血圧に対してロサルタン50mgが処方され，入院中は138/78前後でコントロールされていたが，退院後より体重がもとのレベルに戻るに伴って，抗うつ薬(トリプタノール)は漸減，しかし，次第に家庭血圧値が上昇，特に起床時の血圧値が180/95を超えることが多くなったため，当科外来を受診し，腎機能が正常範囲(eGFR：65)，カルシウム拮抗薬で副作用が出たことがあること，抗うつ薬が漸減中で服用薬剤数の増加を望まなかったため，これまで服用してきたロサルタンに加えて，少量のサイアザイド系利尿薬のヒドロクロロチアジド配合の合剤を服用することにした．

表1　アンジオテンシンⅡ受容体拮抗薬(ARB)と降圧利尿薬の配合薬

ARB		降圧利尿薬	
ロサルタンカリウム	50 mg/	ヒドロクロロチアジド	12.5 mg
バルサルタン	80 mg/	ヒドロクロロチアジド	6.25 mg
バルサルタン	80 mg/	ヒドロクロロチアジド	12.5 mg
カンデサルタンシレキセチル	4 mg/	ヒドロクロロチアジド	6.25 mg
カンデサルタンシレキセチル	8 mg/	ヒドロクロロチアジド	6.25 mg
テルミサルタン	40 mg/	ヒドロクロロチアジド	12.5 mg
テルミサルタン	80 mg/	ヒドロクロロチアジド	12.5 mg

	初診時	1回目入院(うつ)	外来時	14日後	2回目入院(低Na血症)	
	家庭血圧(朝) 164/88	入院中(朝) 138/78	家庭血圧(朝) 176/92	家庭血圧(朝) 142/78	退院前(朝) 136/74	
	カルシウム拮抗薬内服していなかった	ロサルタン 50 mg	ロサルタン 50 mg ⇩ ロサルタン 50 mg/HCTZ 12.5 mg		ロサルタン 50 mg	
体重(kg)	52	46	48	47	46	47
Na(mEq)	142	144	139	136	124	134
K(mEq)	3.9	4.2	3.8	3.7	3.6	3.9
Cl(mEq)	102	108	104	101	92	100
BUN(mg/dL)	14	18	16	12	22	16
CRE(mg/dL)	0.66	0.70	0.64	0.70	0.92	0.72

家庭血圧は受診前7日間の平均値　HCTZ：ヒドロクロロチアジド　BUN：尿素窒素　CRE：クレアチニン

図1　本症例の経過(84歳，女性)

経過

2週間後の外来再来では，朝の血圧値も140/75程度に落ち着き(就寝前は130/70くらい)，娘さんと1泊2日の旅行に行ってくるとのことで調子はよかった．合剤に変更後1カ月，娘さんからうつが再発し，食事がほとんど食べられない．歩行にも不安定さが増し，精神科で抗うつ薬が増量されたがあまり効果がないとの電話があったため，早めに受診してもらった．血清ナトリウム値が124 mEqと低下し，入院の上，降圧薬をロサルタンのみに戻し，電解質をゆっくり補正すると活気が少しずつ戻り，食欲も改善，歩行も安定し(MRIなどでほかの合併症もなく)，低ナトリウム血症も改善して入院7日目に退院した(図1)．

解説

高齢者では多剤併用や服薬管理能力の低下が原因で服薬アドヒアランスに問題を生ずることが知られている．具体的には，用法や薬効の理解度，認知機能，薬剤包装の開封能力，処方薬剤数，最近の処方変更が高齢者の服薬アドヒア

高齢者における降圧薬合剤使用のポイント

- 近年，降圧薬を中心に多くの合剤が市場に出回るようになった．
- 高齢者では服薬アドヒアランスを考えると，なるべく服薬数を少なくするため，合剤を用いることが臨床の現場では増えている．
- 合剤を用いても薬物相互作用のリスクは変わらず，薬剤数が少なくなるため，むしろ有害作用に対する警戒が薄まる可能性は否定できない．
- 高齢者では，合併症や非典型的な症状のため，副作用と認識されにくい．

ランスと深く関連する[1]．

2008 年の HYVET 試験の結果により，80 歳代の高齢者であっても，脳卒中や心不全の発症を減少するなど降圧薬による治療の効果が確認された．特に高齢者では服薬アドヒアランスを考えると，なるべく 1 剤，あるいは合剤にまとめることが合理的であると考えられ，『高血圧治療ガイドライン 2009』においても，「合剤の使用により服薬錠剤数を少なく，処方を単純化することは，アドヒアランス改善に有用である」としており[2]，降圧薬合剤の使用頻度は今後さらに高まるであろう．

しかし，秋下が指摘するように，合剤を用いても薬物相互作用のリスクは変わらず，薬剤数が少なくなるため，かえって有害作用に対する警戒が薄くなる可能性は否定できない[3]．

また，2 成分を含んでいることから，過度の降圧が起こる可能性もあり，本薬を安易に高血圧治療の第 1 選択薬としては用いるべきではない．このことは，添付文書の「用法・用量」にも明記されているが，さらに，「高齢者への投与について，高齢者では低ナトリウム血症，低カリウム血症があらわれやすい．75 歳以上の高齢者に対する安全性は確立していない(使用経験がない)」と記載されており，われわれの苦い経験を含めて十分に留意したい．

文　献

1) 葛谷雅文ほか：高齢者服薬コンプライアンスに影響を及ぼす諸因子に関する研究．日老医誌 **37**：363-370，2000.
2) 日本高血圧学会高血圧治療ガイドライン作成委員会：高血圧治療ガイドライン 2009，ライフサイエンス出版，東京，2009.
3) 秋下雅弘：服薬カレンダーと合剤を用いて管理できた独居の超高齢高血圧症例．Geriat Med **48**：541-543，2010.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

Four Blood Pressure Indexes and the Risk of Stroke and Myocardial Infarction in Japanese Men and Women: A Meta-Analysis of 16 Cohort Studies

Katsuyuki Miura, Hideaki Nakagawa, Yasuo Ohashi, Akiko Harada, Masataka Taguri, Toshio Kushiro, Atsuhiko Takahashi, Masanori Nishinaga, Hirofumi Soejima, Hirotsugu Ueshima and for the Japan Arteriosclerosis Longitudinal Study (JALS) Group

Circulation 2009;119;1892-1898; originally published online Mar 30, 2009;
DOI: 10.1161/CIRCULATIONAHA.108.823112
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2009 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/cgi/content/full/119/14/1892

Subscriptions: Information about subscribing to Circulation is online at
http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/reprints

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

Four Blood Pressure Indexes and the Risk of Stroke and Myocardial Infarction in Japanese Men and Women

A Meta-Analysis of 16 Cohort Studies

Katsuyuki Miura, MD, PhD; Hideaki Nakagawa, MD, PhD; Yasuo Ohashi, PhD; Akiko Harada, PhD; Masataka Taguri, MA; Toshio Kushiro, MD, PhD; Atsuhiko Takahashi, MD, PhD; Masanori Nishinaga, MD, PhD; Hirofumi Soejima, MD, PhD; Hirotsugu Ueshima, MD, PhD; for the Japan Arteriosclerosis Longitudinal Study (JALS) Group

Background—Information has been sparse on the comparison of 4 blood pressure (BP) indexes (systolic BP [SBP], diastolic BP, pulse pressure, and mean BP [MBP]) in relation to long-term incidence of stroke and myocardial infarction, particularly in middle-aged and older Asians.

Methods and Results—The Japan Arteriosclerosis Longitudinal Study Group conducted a meta-analysis of 16 cohort studies in Japan. A total of 48 224 men and women 40 to 89 years of age participated at baseline, and 1231 stroke events and 220 myocardial infarction events occurred during an average 8.4-year follow-up. Multivariate-adjusted hazard ratios with a 1-SD higher value for each BP index were determined by Poisson regression. Analyses were also done in 4 age-sex groups. All 4 BP indexes were significantly related to all stroke risk. Stroke risk was most strongly related to MBP and SBP in both sexes and most weakly related to pulse pressure. Both stroke subtypes, ischemic and hemorrhagic, were most strongly related to MBP and SBP in both sexes. In addition, in men and women 70 to 89 years of age, MBP or SBP showed the strongest relation to all stroke risk. Myocardial infarction risk was most strongly related to SBP or MBP in both sexes. For any end points in any age-sex groups, pulse pressure was not the strongest predictor.

Conclusions—The long-term incident risk of stroke and myocardial infarction associated with high BP in East Asian populations should be assessed mainly on the basis of SBP. MBP also may be an important predictor, but pulse pressure is a less important predictor for cardiovascular disease risk. (***Circulation*. 2009;119:1892-1898.**)

Key Words: blood pressure ■ cohort studies ■ myocardial infarction ■ meta-analysis ■ stroke

Blood pressure (BP) is an established major risk factor for cardiovascular diseases.[1–4] Risk relationships for both systolic BP (SBP) and diastolic BP (DBP) are generally regarded to be continuous, graded, strong, independent of other risk factors, and etiologically significant. Some data suggest that SBP is a stronger predictor of cardiovascular diseases than DBP,[5–8] and several epidemiological studies have reported that pulse pressure (PP), the difference between SBP and DBP, is a useful predictor for coronary heart disease, especially in older people.[9–11] However, cohort studies including older people have revealed that the relationship between PP and mortality from all cardiovascular diseases and coronary heart disease is not as strong as those for other BP indexes.[12–15] Regarding stroke, 2 large-scale cohort study collaborations, as well as other cohort studies, have shown that PP is less useful in predicting long-term stroke risk than SBP.[14–18] However, the majority of the study participants in these studies were white (even in 1 study from the Asia Pacific region), and there are few investigations including only Asian people, in whom stroke occurrence is relatively high compared with that in Western countries. Two relatively small-scale studies have been reported recently from Japan, although investigations by sex, age groups, and stroke subtype (ischemic and hemorrhagic) have not been fully performed.[19,20] Therefore, it is still uncertain which BP index is the best for predicting future incidence of cardiovascular diseases in various age-sex groups of pure East Asian populations or whether the importance of BP indexes differs for predicting ischemic stroke and hemorrhagic stroke risks.

Received June 2, 2008; accepted February 10, 2009.

From the Department of Health Science, Shiga University of Medical Science, Otsu (K.M., H.U.); Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa (H.N.); Department of Biostatistics, Graduate School of Health Sciences and Nursing, University of Tokyo, Tokyo (Y.O., A.H., M.T.); Department of Cardiology, Nihon University Surugadai Hospital, Tokyo (T.K.); Nihon University Health Planning Center, Tokyo (A.T.); Department of Medicine and Geriatrics, Kochi University School of Medicine, Kochi (M.N.); and Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto (H.S.), Japan.

The online Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.823112/DC1.

Reprint requests to Katsuyuki Miura, MD, PhD, Department of Health Science, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga, 520-2192, Japan. E-mail miura@belle.shiga-med.ac.jp

© 2009 American Heart Association, Inc.

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.823112**

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

Clinical Perspective p 1898

The Japan Arteriosclerosis Longitudinal Study–Existing Cohorts Combine (JALS-ECC) is a pooling project based on individual participant data from existing high-quality prospective cohort studies in Japan.[21] This meta-analysis of 16 cohort studies allowed detailed investigations with >1000 stroke events and 200 myocardial infarction (MI) events from >400 000 person-years of follow-up in middle-aged and older Japanese men and women. The specific goals of this research are to assess in these East Asian population samples which of these 4 BP indexes is the best predictor of incident stroke and MI risk among the 4 indexes, whether the best predictor differs by sex, whether the best predictor differs between middle-aged people and older people, and whether the best predictor differs by stroke subtype (ischemic and hemorrhagic).

Methods

Study Population

The rationale, study design, and methods of the JALS-ECC have been described elsewhere.[21] In brief, cohort studies were potentially eligible for inclusion in this project if they satisfied the following criteria: (1) Japanese population; (2) prospective cohort study; (3) at least 3000 persons-years of follow-up; (4) date of birth (or age), gender, height, weight, BP, and total cholesterol recorded at baseline; and (5) date of death or age at death (for death from stroke or coronary heart disease at least) recorded during follow-up. Quality control of collected cohort data was performed at the JALS Coordinating Center. Consequently, individual records for each of the 66 691 participants in 21 cohort studies were included in this project, with 82.7% of the participants from community-based cohorts and 17.3% from workplace-based cohorts. Permission to submit cohort data to the JALS central office was obtained from each institutional review board for ethical issues.

Baseline Data

The JALS Study Group requested data for individual participants from the collaborating investigators. The data requested for each participant included date of baseline survey, date of birth or age at baseline, gender, height, weight, history of cardiovascular diseases, BP (SBP and DBP), total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking habits, and alcohol consumption. Among the 16 cohorts analyzed, BP was measured by standard sphygmomanometer in 13 cohorts, by random-zero sphygmomanometer in 1 cohort, and by automatic cuff–oscillometric device in 2 cohorts. BP was measured once in 11 cohorts, twice in 4 cohorts, and 3 times in 1 cohort. Mean values were used in cohorts with ≥2 BP values.

End Points

In each cohort, vital status and the incidence of stroke and/or MI were ascertained during the follow-up period through the use of population-based stroke and/or MI registration systems, death certificates, medical records in hospitals, and/or questionnaires. The diagnosis of stroke was based on typical clinical features and characteristic changes on computed tomographic and/or magnetic resonance imaging brain scans and typically was based on criteria from the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study[22] or from the World Health Organization.[23] The diagnosis of MI was based on chest pain, cardiac enzyme levels, and ECGs and typically was based on criteria from the MONICA study.[22] Disease classifications were made with the *International Classification of Disease*, 9th revision (ICD-9), as follows: stroke (ICD-9: 430, 431, 433, 434, 436), cerebral infarction (ICD-9: 433 to 434), cerebral hemorrhage (ICD-9: 431), subarachnoid hemorrhage (ICD-9: 430), and MI (ICD-9: 410). Cerebral hemorrhage and subarachnoid hemorrhage were classified as hemorrhagic stroke.

Exclusions

From 21 cohorts of the JALC-ECC, 3 cohorts were excluded because of a lack of assessment of stroke and/or MI incidence as a study end point, and 2 cohorts were excluded because of a lack of baseline assessment of body mass index, serum total cholesterol, and/or cigarette smoking. From the remaining 60 616 participants in 16 cohorts, participants <40 or ≥90 years of age (n=7484) and those lacking baseline examination data (n=4223) were excluded. Among the remaining 48 909 participants, 685 participants (1.4%) withdrew during the follow-up period. Thus, the report was based on a total of 48 224 participants (21 061 men, 27 163 women) with the following age-sex breakdown: 18 596 men 40 to 69 years of age, 2465 men 70 to 89 years of age, 23 557 women 40 to 69 years of age, and 3606 women 70 to 89 years of age. Among the 16 cohorts, analyses for stroke were performed in 15 cohorts (40 982 participants) in which stroke events were surveyed, and analyses for MI were performed in 13 cohorts (36 015 participants) in which MI events were surveyed.

Statistical Analyses

MBP was calculated as SBP/3+2DBP/3,[24] and PP was calculated as SBP minus DBP. For each BP index considered separately as a continuous variable, a mixed-effect Poisson regression model with a random intercept for each cohort was used to determine multivariate-adjusted hazard ratios (HRs) for a level greater by 1 SD. Wald χ^2 analyses also were used to compare the strength of relationships. A model included both SBP and DBP simultaneously to assess their independent relationships with adjustment for each other. Another model included both MBP and PP simultaneously to assess their independent relationships. HRs were adjusted for other major risk factors and for potential confounders, which were age (years, continuous) and body mass index (kg/m^2, continuous), serum total cholesterol (mg/dL, continuous), and cigarette smoking (current smoker or not), as fixed effects. For each end point of all stroke, ischemic stroke, hemorrhagic stroke, and MI, these analyses were done for men and women separately. For all stroke, analyses also were done for each of 4 age-sex groups. HRs were estimated on the basis of a theory of quasi-likelihood by PROC GLIMMIX in the SAS program for Windows, release 9.1.3 (SAS Institute Inc, Cary, NC).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Characteristics of the 16 cohorts are shown in Table 1. There were 1 cohort from Hokkaido Island, 12 cohorts from Honshu (Main) Island, 1 cohort from Shikoku Island, and 2 cohorts from Kyushu Island. Three cohorts were from workplaces. A total of 48 224 participants were followed up for an average of 8.4 years; there was a total observation of 407 213 person-years. A total of 1231 stroke events and 220 MI events were recorded during the follow-up period. Baseline characteristics of participants are shown in Table 2. Mean age was 56.7 years, and mean body mass index was 23.2 kg/m^2. The smoking rate was much higher in men (53.8%) than in women (4.5%).

Table 3 shows the numbers and rates of stroke and MI events in the surveyed cohorts. The crude rate of all stroke incidence was higher in men than in women. Ischemic stroke accounted for 74% of all strokes in men and 58% in women. Crude MI incidence rate also was higher in men than in women. MI incidence was less than one third of stroke incidence in men and less than one sixth in women.

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

Table 1. Characteristics of the 16 Cohorts in Japan

Cohort Name	Baseline Year	Sample Size, n	Follow-Up Period, y	Follow-Up, Person-y	Women, %	Mean Age at Baseline, y	Age Range at Baseline, y	Mean SBP, mm Hg	Mean DBP, mm Hg	BP Measurement Device	Stroke Events, n	MI Events, n
Tanno/Soubetsu	1991–1992	1512	6.3	9598	58.1	60.8	40–88	132.9	77.8	SP	54	14
Akita	1988	5194	11.8	61 438	65.8	57.1	40–89	131.7	79.2	SP	220	NA
Ikawa	1985–1990	2582	10.6	27 322	56.4	56.1	40–88	134.7	81.4	SP	118	15
Ohasama	1990–1995	2324	10.4	24 190	61.5	58.4	40–86	130.9	74.1	AD	157	NA
Kyowa	1985–1991	4467	9.9	44 181	57.1	54.8	40–83	136.7	81.5	SP	152	63
Tokamachi	1993	7242	8.0	57 931	67.0	60.0	40–89	128.1	73.7	SP	NA	29
Tokyo worker	1995	721	5.8	4146	25.9	51.9	40–68	125.0	82.3	AD	2	4
Toyama worker	1990	3034	10.7	32 369	34.3	46.8	40–65	119.6	74.2	SP	68	14
Oyabe	1988	4691	9.8	46 199	68.0	58.8	40–89	127.8	76.1	RZ	151	NA
Aichi worker	1997	2472	2.6	6508	0.0	52.3	40–70	130.0	79.6	SP	9	11
Yao	1985–1994	3799	9.6	36 449	65.2	54.0	40–87	132.2	79.7	SP	78	25
Shigaraki	1992–1997	2462	7.2	17 829	58.0	60.4	40–89	134.5	79.0	SP	69	13
Hiroshima	1992–1996	1848	4.0	7458	71.0	70.7	60–89	134.8	78.0	SP	67	11
Ohzu	1996–1998	2673	5.3	14 042	65.6	58.5	40–89	130.0	77.4	SP	37	3
Hisayama	1990	756	9.6	7242	60.4	60.8	42–87	133.0	77.8	SP	46	15
Kumamoto	1999–2000	2447	4.2	10 310	29.9	47.0	40–55	126.7	79.8	SP	3	3
Total/average		48 224	8.4	407213	56.3	56.7	40–89	130.4	77.8		1231	220

SP indicates sphygmomanometer; AD, automatic device (cuff-oscillometric); and RZ, random-zero sphygmomanometer.

Figure 1 shows multivariate-adjusted HRs of all stroke risk for each BP index greater by 1 SD in all men and in all women. All 4 BP indexes were positively and significantly related to all stroke risk in both sexes. Wald χ^2 indicated that MBP was the strongest predictor among 4 BP indexes and that SBP was a similarly strong predictor in both sexes. The relationships remained positive for both SBP and DBP after adjustment for each other in models including both SBP and DBP simultaneously, but these relationships were stronger for SBP. The relationships for PP were not as strong as those for the other 3 BP indexes, and these relationships were even weaker after adjustment for MBP. These results were similar between men and women.

Figure 2 shows results for ischemic stroke incidence in men and women. Wald χ^2 indicated that SBP and MBP were the strongest predictors of the 4 BP indexes in both sexes. DBP was no longer a significant predictor after adjustment for SBP in both sexes.

Table 2. Baseline Characteristics of Total Participants From the 16 Cohorts

Characteristic	Total	Men	Women
Participants, n	48 224	21 061	27 163
Age, y	56.7±10.6	56.0±10.5	57.3±10.6
SBP, mm Hg	130.4±19.2	131.6±19.0	129.5±19.3
DBP, mm Hg	77.8±11.5	79.6±11.7	76.3±11.1
PP, mm Hg	52.7±13.9	52.0±13.6	53.2±14.1
MBP, mm Hg	95.3±13.0	96.9±13.1	94.0±12.7
Body mass index, kg/m^2	23.2±3.1	22.9±2.9	23.3±3.2
Serum total cholesterol, mg/dL	200.0±36.6	194.0±36.1	204.1±36.3
Current cigarette smokers, %	26.1	53.8	4.5

Figure 3 shows results for hemorrhagic stroke incidence in men and women. Wald χ^2 indicated that MBP was the strongest predictor of the 4 BP indexes in both sexes but that both SBP and DBP were strong predictors. In men, a model including SBP and DBP simultaneously showed that DBP was strongly related to hemorrhagic stroke risk independently of SBP. PP was the weakest of the 4 BP indexes for predicting risk.

Figure 4 shows multivariate-adjusted HRs for all stroke incidence in each of the 4 age-sex groups. In men 40 to 69 years of age, Wald χ^2 indicated that MBP was the strongest of the 4 predictive indexes. In men 70 to 89 years of age, the strongest relationship also was observed for MBP. PP was the weakest predictor in both younger men and older men. A model including SBP and DBP simultaneously showed that both BP indexes were significantly and independently related to stroke risk in younger men but that only SBP was a significant predictor in older men. In both younger and older women, MBP showed stronger relationships to all stroke risk. The relationship of PP was not as strong as that of other BP indexes in both female age groups. There was no significant relationship between PP and stroke risk after adjustment for MBP in all four age-sex groups.

Figure 5 shows multivariate-adjusted HRs of MI incidence in all men and in all women. All 4 BP indexes were positively related to MI risk in both sexes, but some relationships were not statistically significant. Wald χ^2 indicated that SBP tended to be the strongest predictor among the 4 BP indexes and that MBP was a similarly strong predictor in both sexes. The relationships tended to be stronger for SBP after adjustment for DBP.

Information on antihypertensive medication at baseline was obtained in 7 cohorts (n=18 587). When all the above

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

Table 3. Total Numbers and Rates of Stroke and MI Incidence in 16 Cohorts*

	Men		Women	
End Point	Events, n	Rate per 10 000 Person-Years	Events, n	Rate per 10 000 Person-Years
All stroke (total participants)	632	43.8	599	29.2
Ischemic stroke	466	32.2	349	16.9
Hemorrhagic stroke	167	11.4	246	11.9
All stroke (baseline 40–69 y of age)	452	34.6	412	22.3
All stroke (baseline 70–89 y of age)	180	131.6	187	92.3
MI (total participants)	148	12.3	72	4.6

*Stroke events were from 15 cohorts; MI events were from 13 cohorts.

analyses were done in 15 878 participants without antihypertensive medication, the results were similar.

Discussion

The main findings from this meta-analysis of 16 cohort studies on stroke and MI incidence in middle-aged and older Japanese men and women are as follows. First, for predicting the incidence of all stroke, ischemic stroke, and MI, MBP or SBP was generally the strongest and PP was the weakest in any of the age-sex groups. Second, for hemorrhagic stroke incidence, MBP was the strongest predictor in both sexes, and DBP was more important than SBP in men. Third, PP was not the strongest of the 4 predictive indexes for any subtype of stroke in any of the age-sex groups, including older people.

Although several studies have shown PP to be a strong predictor of coronary heart disease and all cardiovascular diseases, especially in older people,[9–11] more recent larger cohort studies including older people have indicated that the relationship between PP and mortality from cardiovascular diseases and coronary heart disease was not as strong as other BP indexes.[12–15] Regarding stroke, 2 large-scale cohort studies collaborations and other recent cohort studies have reported PP to be less useful in predicting long-term stroke risk than SBP.[14–20] In one of those studies, the Asia Pacific Cohort Studies Collaboration, analyses similar to our study were performed for BP and fatal events of stroke and ischemic heart disease, comparing HRs for a 1-SD difference in each of 4 BP indexes.[15] The study showed that the strongest relationships to fatal stroke were observed for SBP in men 50 to 69 years of age (HRs ranged between 1.5 and 2.0) and in women

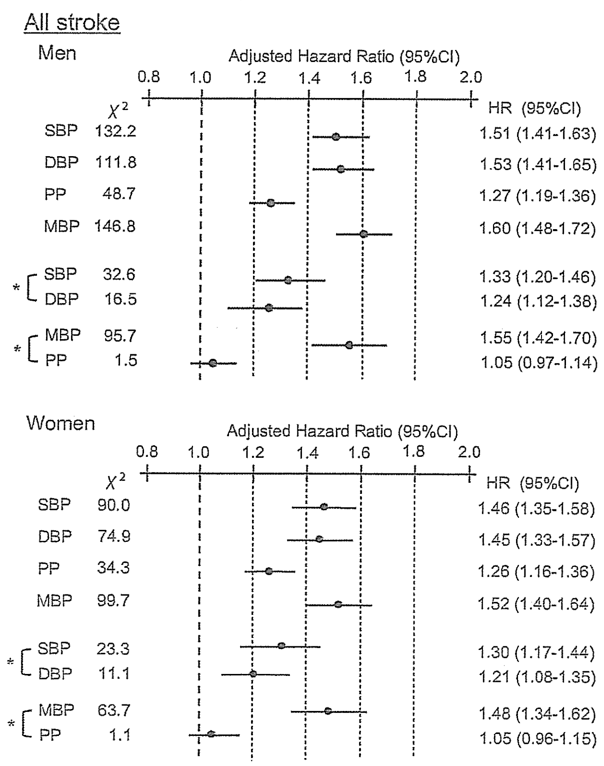

Figure 1. Adjusted HRs for 4 BP indexes for all stroke incidence by sex. HRs are calculated for each BP index higher by 1 SD and adjusted for age, body mass index, total cholesterol, and smoking through Poisson regression. *Two BP indexes are included in the same model.

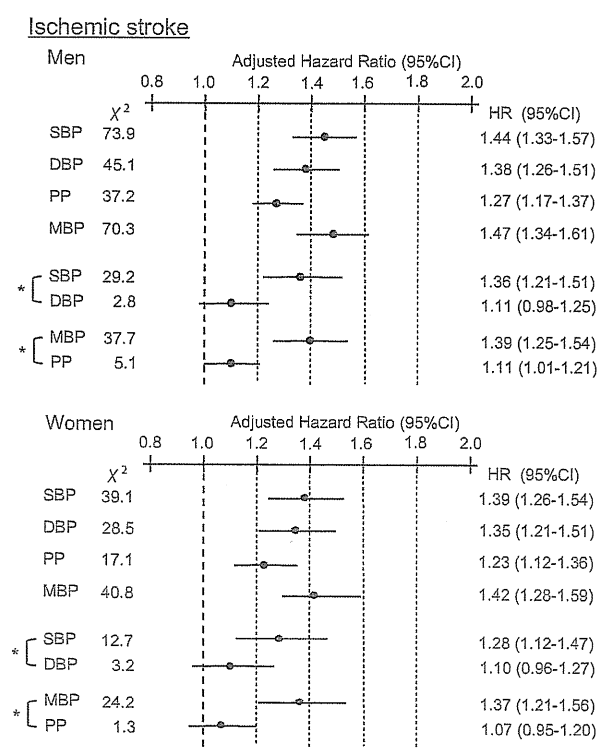

Figure 2. Adjusted HRs for 4 BP indexes for ischemic stroke incidence by sex. *Two BP indexes are included in the same model.

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

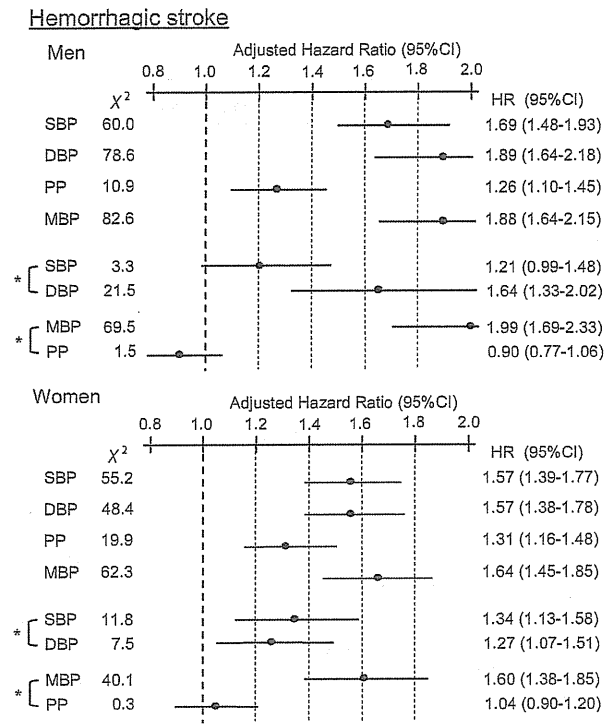

Figure 3. Adjusted HRs for 4 BP indexes for hemorrhagic stroke incidence by sex. *Two BP indexes are included in the same model.

of all age groups (HRs ranged between 1.3 and 1.9). MBP and DBP in men <50 years of age (HR, 2.5) and PP and SBP in men ≥70 years of age (HR, 1.4) showed similarly strong relationships. These results are similar to our results. Major differences between this study and ours were that the study end point was mainly fatal events, not incidence, and that, although the study was conducted in the Asia Pacific region, a large number of the study participants were white Australians. Two recent cohort studies on stroke from Japan were small in scale[19,20]; therefore, the present study is the first large-scale meta-analysis of pure Asian subjects to provide detailed analyses on 4 BP indexes and incident stroke and MI risk by various age-sex groups and by stroke subtypes.

A few studies have investigated the relationship between BP indexes and stroke incidence in older people.[16,19] In the Cardiovascular Health Study, 5888 men and women ≥65 years of age (mean age, 73 years) participated from 4 US centers, and the adjusted stroke risk for a 1-SD difference in each BP was higher for SBP (HR, 1.34) than for DBP (HR, 1.29) and PP (HR, 1.21) when analyses were done in men and women combined.[16] Another finding from a relatively small Japanese cohort in men and women 65 to 79 years of age (mean age, 70 years) was that PP was less important than SBP in men and than SBP and DBP in women.[19] In older participants 70 to 89 years of age in the present study, SBP was more strongly related to stroke incidence than PP in both sexes. SBP appears to be a more effective predictive measure of the future risk of stroke incidence than PP, even in older men and women in both Western and Asian populations.

For MI risk, our findings that SBP and MBP were the best predictors and that PP was less important were similar to

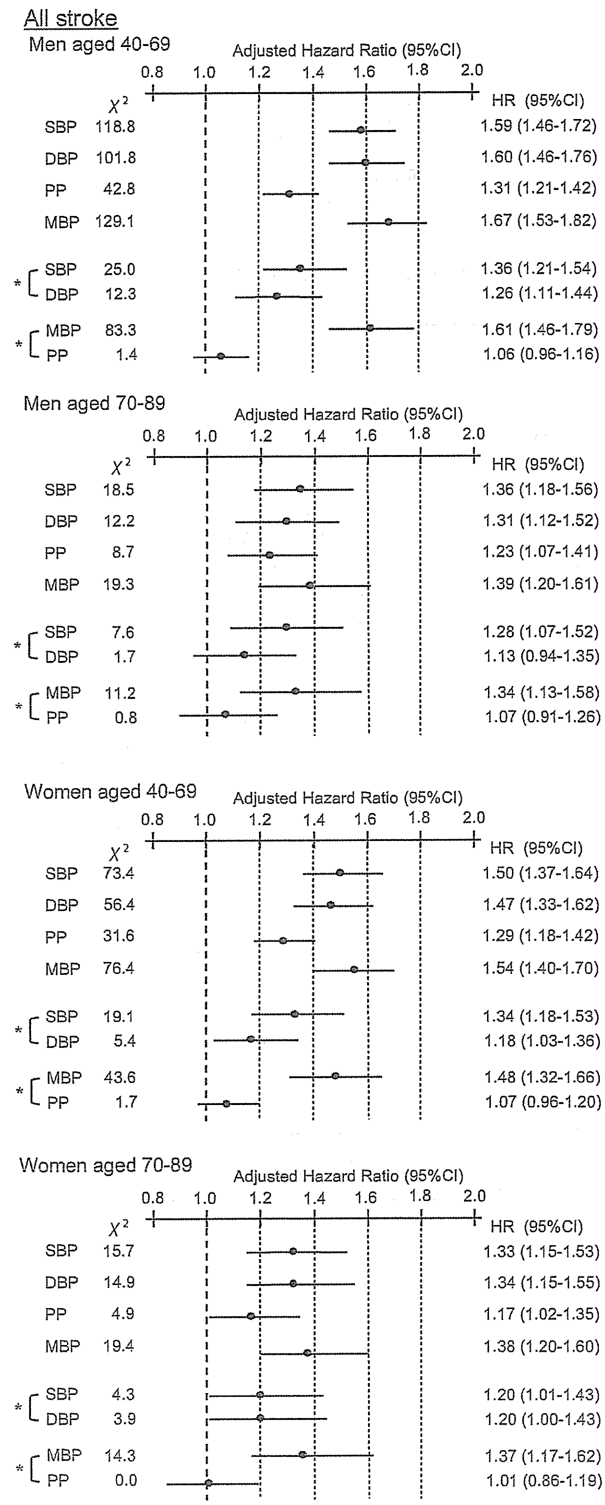

Figure 4. Adjusted HRs for 4 BP indexes for all stroke incidence by 4 age-sex groups. *Two BP indexes are included in the same model.

previous findings from other large-scale meta-analyses.[14,15] However, because of the low MI incidence rate in Japanese and therefore the small number of MI events, analyses by 4 age-sex groups were statistically difficult in this study.

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

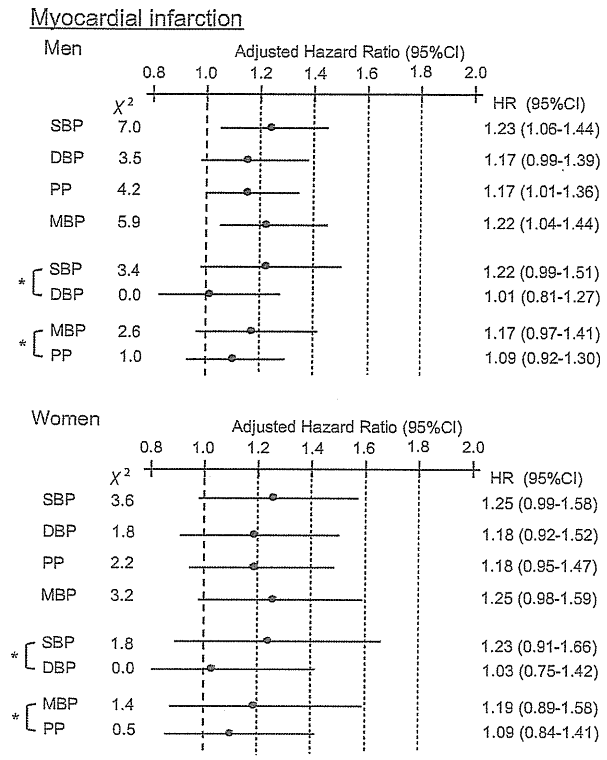

Figure 5. Adjusted HRs for 4 BP indexes for myocardial infarction incidence by sex. *Two BP indexes are included in the same model.

Recent discussions on the diagnosis and treatment of high BP have focused on SBP more than DBP, especially in older people.[6–8,25] However, in the present study, the relationship between DBP and hemorrhagic stroke incidence was stronger than or as strong as that of SBP in men and women, respectively. Moreover, the relationship between DBP and all stroke incidence was as strong as that for SBP, whereas DBP was positively related to the risk after adjustment of SBP; similar findings were reported in previous reports.[15,19] These results indicate a role for DBP in the long-term evaluation of all stroke, especially hemorrhagic stroke, in both sexes. In fact, in middle-aged people, previous epidemiological studies have shown that cardiovascular disease risk generally increased with DBP level in each stratum of SBP level.[2,13,26]

MBP tended to be the strongest predictor of stroke and MI risk, together with SBP, in both sexes. MBP could be a slightly better predictor of long-term cardiovascular disease risk than SBP and DBP in East Asian populations. However, use of this index may not currently be practical in daily clinical and public health practice because there are no guidelines for hypertension diagnosis and management using MBP.

From a physiological viewpoint, mean arterial pressure is regulated by changes in cardiac output and systemic vascular resistance, and MBP is an approximate measure of mean arterial pressure. PP has been reported to be a good indicator of arterial stiffness, especially in older people.[27,28] To look at the independent relationships of these 2 indexes to cardiovascular disease risk, a model including MBP and PP simultaneously was used in this study. Generally, PP was not significantly related to stroke and MI risk after adjustment of MBP. However, because PP is an incomplete metric of arterial stiffness and is affected by other factors, our study results would not definitely deny the physiological importance of arterial stiffness for cardiovascular disease risk.

A limitation of the present study is that, because this is a meta-analysis of 16 cohort studies, the methods of BP measurement were not well standardized. Another limitation is a lack of information at baseline on antihypertensive medication. The inclusion of some participants whose BP was controlled by medication would underestimate the relationship between BP and stroke risk. Similar results were observed in subgroup analyses for participants not receiving antihypertensive medications. Moreover, each BP index was included as a continuous variable in our statistical models under an assumption that there is a linear relationship between BP and stroke risk.

There are a number of possible implications of our results for the primary prevention of cardiovascular diseases in East Asian populations. First, the long-term incident stroke and MI risk of high BP should be assessed mainly by SBP. DBP should be given careful consideration for its independent relationship to stroke risk. Second, emphasis on PP should be avoided, even in older people, for the prediction of future cardiovascular disease risk. Third, the relationships between MBP and the risk of stroke and MI were generally as strong as those for SBP. However, the use of this index may not currently be practical in daily clinical and public health practice.

Source of Funding

This study was supported by the Japan Arteriosclerosis Prevention Fund.

Disclosures

None.

References

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease, part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765–774.
2. Stamler J, Stamler R, Neaton D. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med.* 1993;153:598–615.
3. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens.* 2003;21:707–716.
4. Whelton PK. Epidemiology of hypertension. *Lancet.* 1994;344:101–106.
5. Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease: the Framingham study. *Am J Cardiol.* 1971;27:335–346.
6. Black HR. The paradigm has shifted, to systolic blood pressure. *Hypertension.* 1999;34:386–387.
7. Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Levy D. Differential impact of systolic and diastolic blood pressure level on JNC-VI staging. *Hypertension.* 1999;34:381–385.
8. Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol.* 2000;85:251–255.
9. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation.* 1999;100:354–360.

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

10. Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension.* 1998;32:560–564.
11. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension.* 1997;30:1410–1415.
12. Miura K, Dyer AR, Greenland P, Daviglus ML, Hill M, Liu K, Garside DB, Stamler J. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: the Chicago Heart Association Detection Project in Industry Study. *Hypertension.* 2001;38:232–237.
13. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, Grimm R, Cohen J, Stamler J, for the MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA.* 2002;287: 2677–2683.
14. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.
15. Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension.* 2003;42:69–75.
16. Psaty BM, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, O'Leary DH, Bryan RN, Anderson M, Lumley T. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *Arch Intern Med.* 2001; 161:1183–1192.
17. Weitzman D, Goldbourt U. The significance of various blood pressure indices for long-term stroke, coronary heart disease, and all-cause mortality in men: the Israeli Ischemic Heart Disease Study. *Stroke.* 2006;37: 358–363.
18. Bowman TS, Gaziano JM, Kase CS, Sesso HD, Kurth T. Blood pressure measures and risk of total, ischemic, and hemorrhagic stroke in men. *Neurology.* 2006;67:820–823.
19. Miura K, Soyama Y, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Yoshita K, Kagamimori S, Nakagawa H. Comparison of four blood pressure indexes for the prediction of 10-year stroke risk in middle-aged and older Asians. *Hypertension.* 2004;44:715–720.
20. Inoue R, Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hoshi H, Hashimoto J, Totsune K, Satoh H, Kondo Y, Imai Y. Predicting stroke using 4 ambulatory blood pressure monitoring-derived blood pressure indices: the Ohasama Study. *Hypertension.* 2006;48:877–882.
21. Japan Arteriosclerosis Longitudinal Study (JALS) Group. Japan Arteriosclerosis Longitudinal Study–Existing Cohorts Combine (JALS-ECC): rationale, design, and population characteristics. *Circ J.* 2008;72: 1563–1568.
22. WHO MONICA project. *MONICA Manual, Revised Edition.* Geneva, Switzerland: Cardiovascular Diseases Unit, World Health Organization; 1990.
23. World Health Organization. *Cerebrovascular Diseases: Prevention, Treatment, and Rehabilitation.* Geneva, Switzerland: World Health Organization; 1971. Technical Report Series No. 469.
24. Ferguson JJ, Randall OS. Systolic, diastolic, and combined hypertension: differences between groups. *Arch Intern Med.* 1986;146:1090–1093.
25. Izzo JL, Levy D, Black HR. Importance of systolic blood pressure in older Americans. *Hypertension.* 2000;35:1021–1024.
26. Neaton JD, Wenthworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316 099 white men. *Arch Intern Med.* 1992;152: 56–64.
27. Franklin SS, Gustin IVW, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation.* 1997;96:308–315.
28. Mitchell GF. Pulse pressure, arterial compliance and cardiovascular morbidity and mortality. *Curr Opin Nephrol Hypertens.* 1999;8:335–342.

CLINICAL PERSPECTIVE

Information has been sparse on the comparison of 4 blood pressure (BP) indexes (systolic BP, diastolic BP, pulse pressure, and mean BP) in relation to long-term incidence of stroke and myocardial infarction, particularly in middle-aged and older Asians. The present meta-analysis of 16 cohort studies investigated >1000 stroke events and 200 myocardial infarction events from >400 000 person-years of follow-up in middle-aged and older Japanese men and women. For predicting all stroke, ischemic stroke, and myocardial infarction, mean BP or systolic BP was generally the strongest and pulse pressure was the weakest in any of the age-sex groups. For hemorrhagic stroke, mean BP was the strongest predictor in both sexes, and in men, diastolic BP was more important than systolic BP. Pulse pressure was not the strongest of the 4 BP indexes for any subtype of stroke in any of the age-sex groups, including older people. For the primary prevention of cardiovascular diseases in East Asian populations, the long-term risk of stroke and myocardial infarction should be assessed mainly by systolic BP. Diastolic BP should also be given careful consideration for its independent relationship to stroke risk. Emphasis on pulse pressure should be avoided even in older people for the prediction of future cardiovascular disease risk. Although mean BP was important in addition to systolic BP, use of this index may not be practical in daily clinical and public health practice at present.

Downloaded from circ.ahajournals.org at KOCHI UNIVERSITY on February 16, 2010

Geriatrics Gerontology 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2009; **9**: 148–154

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

B-type natriuretic peptide is predictive of hospitalization in community-dwelling elderly without heart diseases

Yuji Shimizu,[1] Masanori Nishinaga,[1] Jun Takata,[1] Ichiro Miyano,[1,2] Kiyohito Okumiya,[3] Kozo Matsubayashi,[4] Toshio Ozawa,[5] Nobufumi Yasuda[2] and Yoshinori Doi[1]

Departments of [1]Medicine and Geriatrics, and [2]Public Health, Kochi Medical School, Kochi, [3]Research Institute for Humanity and Nature, [4]Center for Southeast Asian Studies, Kyoto University, Kyoto, and [5]Tokyo Metropolitan Geriatric Center, Tokyo, Japan

Aim: To examine prospectively the relationship between plasma B-type natriuretic peptide (BNP) levels in community-dwelling elderly and their hospitalization.

Methods: A total number of 644 subjects aged 65 years or older were recruited from the annual community health examinations. Those with a history of stroke or neurological findings were not included. After excluding those with old myocardial infarction, left ventricular dysfunction, moderate or severe valvular disorders, atrial fibrillation, renal insufficiency, and history of hospitalization within 1 year, 602 participants (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study. Antihypertensive medications, activities of daily living (ADL) score and history of hospitalization were assessed by annual interview. Measurement of casual blood pressure, Mini-Mental State Examination, electrocardiography and echocardiography were performed. Plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c levels were also examined. A follow-up survey was performed for the occurrence and reasons for hospitalization.

Results: During a median follow up of 37 months, 112 subjects were hospitalized. After adjustment for conventional risk factors of hospitalization using the Cox proportional hazard model, each increment of 1 standard deviation in log BNP levels was associated with a 36% increase in the risk of hospitalization ($P = 0.02$). Plasma BNP levels were significantly higher in the hospitalized subjects due to stroke, heart diseases, dementia, pneumonia and also difficulty to live alone than those of the subjects without hospitalization.

Conclusion: Plasma BNP level is a very useful biochemical marker predictive of future hospitalization in community-dwelling independent elderly people without apparent heart diseases.

Keywords: B-type natriuretic peptide, community-dwelling elderly, hospitalization.

Accepted for publication 9 December 2008.

Correspondence: Dr Masanori Nishinaga MD, Department of Medicine and Geriatrics, Kochi Medical School, Oko-cho, Nankoku-shi, Kochi 783-8505, Japan. Email: nishinam@kochi-u.ac.jp

Author contribution: Y. S. conceived this study and protocol, echo study, analysis and interpretation of data, drafting and preparation of the manuscript; M. N. performed echo study, analysis and interpretation of data, and preparation of the manuscript; J. T. and I. M. provided technical assistance in echo study and analysis; K. O. and K. M. performed study design and analysis; N. Y. performed study design and preparation of the analysis; and Y. D. performed study design and protocol, and preparation of the manuscript.

doi: 10.1111/j.1447-0594.2009.00514.x
© 2009 Japan Geriatrics Society

Introduction

In our rapidly aging societies, it is very important to take preventive intervention for elderly people requiring care and medical treatment to reduce the numbers of frail elderly.[1] There have been many approaches to predict the risk of care-requiring, frail conditions based on the actual status of activities of daily living (ADL) of the elderly. However, there are few biochemical markers that represent frailty of the elderly, except for markers of poor nutrition, such as serum total cholesterol and albumin,[2,3] or electrolyte.[4]

B-type natriuretic peptide (BNP) is a member of the natriuretic peptide family;[5] biosynthesis of BNP is known to increase in the presence of cardiac failure.[6] Recent reports have suggested that elevated plasma BNP level is related to the development of stroke and transient cerebral ischemic attack.[7,8] A relationship between plasma BNP level and mortality was also reported in the elderly.[9] However, many of these reports are either limited to the very elderly accommodated in nursing homes[10,11] or the functionally-impaired elderly,[12] or have focused on the elderly with heart diseases.[13,14]

Thus, in the elderly living independently in the community, the clinico-epidemiological relevance of elevated plasma BNP level is unclear. We have therefore examined plasma BNP level in community-dwelling elderly people without apparent heart diseases, and discuss its usefulness as a marker of future hospitalization which can be thought as one of the events representing frailty of the elderly.

Methods

Subjects

A total of 644 independent subjects aged 65 years or older had been recruited from the annual community health examination between 2000 and 2003. The end of follow-up survey was 2004. By definition, those with a history of stroke and those with neurological findings were not included in this study. The patients had consented that the results of their health examinations be used. The study was performed in "K town", in a rural area of Japan, in which subjects older than 65 years account for 37% of the total population. We excluded 32 subjects who had been diagnosed with old myocardial infarction, moderate to severe mitral or aortic valvular disorders, or moderate to severe left ventricular dysfunction with fractional shortening of less than 20%, on first health examinations. Three subjects whose serum creatinine levels exceeded 2.0 mg/dL, and seven subjects who were diagnosed with atrial fibrillation were also excluded. Thus, 602 subjects (226 men, 376 women; mean age, 80.3 ± 6.2 years) remained eligible for this study.

Parameters

All subjects completed questionnaires regarding current ADL and antihypertensive medications. When the subjects had a history of brain magnetic resonance imaging (MRI) examination, a questionnaire regarding asymptomatic findings of MRI including lacunae and white matter lesions was also obtained. Seven items of ADL were assessed; namely, walking, ascending and descending stairs, feeding, dressing, toileting, and bathing, noting the help required on a 4-point scale as our previous study:[15] 3, completely independent; 2, need some help; 1, need much help; 0, completely dependent. The Barthel index[16] adjusted for Japanese lifestyle was also assessed. Cognitive function was evaluated by Mini-Mental State Examination (MMSE). Casual blood pressure with the average value of two readings at rest in sitting position was measured. All subjects had blood drawn when they participated in their first health examination. These blood samples were placed in cold storage immediately after collection and were measured within 48 h. As blood biochemical examination, plasma BNP, serum creatinine, total cholesterol, albumin and hemoglobin A1c (HbA1c) levels were determined. Plasma BNP was measured using a radioimmunoassay method with Sionoria (Shionogi, Tokyo, Japan). Electrocardiography was also performed. To examine the left ventricular systolic function and valvular disorder, echocardiography was performed by cardiologists.

Follow-up survey

We had followed up all of the subjects concerning hospitalization and evaluated the reasons for hospitalization following the first health examination till 2004. The district nurses confirmed the reasons for hospitalization. The median follow-up period was 37 months (range, 2–48 months). Concerning 112 subjects who were hospitalized, duration to hospitalization was also analyzed; the median duration to hospitalization was 22 months (range, 2–48 months). Six of the 602 subjects moved out of the community over the course of the investigation and were treated as censored data.

Statistical analysis

Hospitalized subjects were compared with those without hospitalization, according to demographic characteristics, age, sex, serum creatinine, total cholesterol, albumin, plasma BNP and HbA1c levels, systolic blood pressure, MMSE score, ADL score and antihypertensive medications.

Then, to confirm the usefulness of plasma BNP level as a predictive marker for hospitalization, we used age, sex, serum creatinine, total cholesterol, albumin and

© 2009 Japan Geriatrics Society

plasma BNP levels and asymptomatic brain MRI findings as covariates with the Cox proportional hazard model. In this analysis, log-transformed plasma BNP level was used for analysis because log plasma BNP exhibited a normal distribution.

Results

Characteristics of the study population

A total of 112 subjects were hospitalized during the follow up: 47 subjects died during hospitalization and 65 subjects survived. There were 490 healthy subjects who survived without hospitalization (Fig. 1). As shown in Table 1, compared with subjects without hospitalization, hospitalized subjects were older ($P < 0.001$) and included more men ($P = 0.02$). They had significantly higher plasma log BNP levels ($P < 0.001$). They also had higher serum creatinine levels ($P < 0.001$), lower serum total cholesterol levels ($P = 0.008$), lower serum albumin levels ($P = 0.003$), lower MMSE scores ($P < 0.001$) and lower ADL scores ($P < 0.001$). They had higher prevalence of asymptomatic brain MRI findings ($P < 0.001$) (Table 1).

Factors related to hospitalization

Plasma BNP level, ADL score, and asymptomatic brain MRI findings remained as factors significantly related to hospitalization, after analysis with the Cox proportional hazard model using age, sex, serum creatinine, serum total cholesterol, serum albumin and plasma BNP levels, MMSE score, ADL score and asymptomatic brain MRI findings as covariates. The adjusted hazard ratio of 1 standard deviation (SD) increment of log plasma BNP level was 1.36 (95% confidence interval [CI], 1.05–1.75; $P = 0.02$). That of one point decrement in ADL score was 1.23 (95% CI, 1.08–1.40; $P = 0.001$), and that for asymptomatic brain MRI findings was 3.24 (95% CI, 1.96–5.36; $P < 0.001$). Age, sex, serum creatinine, total cholesterol and albumin levels were not independently related to hospitalization (Table 2). The area under the receiver–operator curve (ROC) for plasma BNP and hospitalization was 0.620 (95% CI, 0.557–0.682).

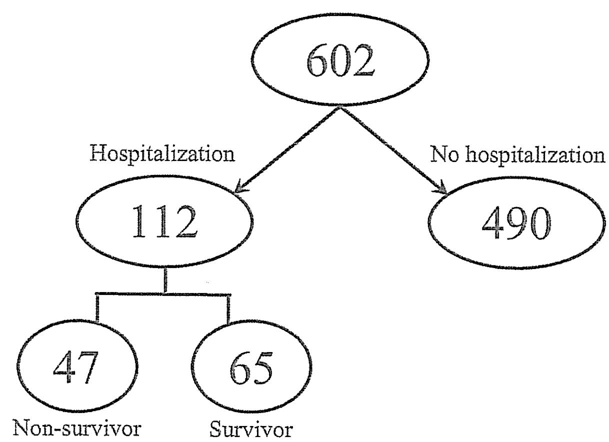

Figure 1 Study subjects and clinical course. Six hundred and two subjects were eligible for this study. A total of 112 subjects were hospitalized. A total of 47 subjects died during follow up. There were 65 subjects who were hospitalized but survived. There were 490 healthy subjects who survived without hospitalization.

Table 1 Baseline characteristics

Characteristics	Hospitalized subjects ($n = 112$)	Subjects without hospitalization ($n = 490$)	*P*-value*
Age (years)	83.2 ± 6.3	79.6 ± 5.9	<0.001
Men (%)	52/112 (46.4%)	174/490 (35.6%)	0.02
Creatinine (mg/dL)	0.86 ± 0.25	0.78 ± 0.18	0.001
Total cholesterol (mg/dL)	189 ± 39	199 ± 32	0.008
Albumin (mg/dL)	4.18 ± 0.36	4.26 ± 0.25	0.003
Log BNP (pg/mL)	1.75 ± 0.42	1.58 ± 0.34	<0.001
Hemoglobin A1c (%)	5.38 ± 0.64	5.46 ± 0.86	0.33
Casual systolic blood pressure (mmHg)	143 ± 21	143 ± 24	0.85
MMSE	25.9 ± 3.8	27.0 ± 2.8	0.005
ADL score (range 0–21)	20.2 ± 1.9	20.7 ± 1.1	<0.001
Asymptomatic brain MRI findings (%)	25/109 (22.9%)	39/486 (8.0%)	<0.001
Antihypertensive medications (%)	44/105 (41.9%)	176/445 (39.6%)	0.69

**P*-value was computed using two-sample Student's *t*-test (when continuous) or Fisher's exact test (when dichotomous). ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

© 2009 Japan Geriatrics Society

Table 2 Hazard ratios for hospitalization

Characteristics	Hazard ratios (95% CI)	P-value[§]
Age	1.03 (0.99–1.07)*	0.20
Men	1.48 (0.87–2.49)	0.14
Creatinine	1.11 (0.88–1.41)[†]	0.38
Total cholesterol	0.82 (0.64–1.04)[†]	0.10
Albumin	0.97 (0.77–1.23)[†]	0.81
Log BNP	1.36 (1.05–1.75)[†]	0.02
MMSE	1.05 (0.98–1.12)[‡]	0.15
ADL score	1.23 (1.08–1.40)[‡]	0.001
Asymptomatic brain MRI findings	3.24 (1.96–5.36)	<0.001

*1 year older. [†]1 standard deviation increment. [‡]1 point decrement. [§]P-value was computed using the Cox proportional hazard model. ADL, activities of daily living; BNP, B-type natriuretic peptide; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

Table 3 Reasons for hospitalization

Reasons	n
Malignancy	18 (16.1%)
Difficulty to live alone	13 (11.6%)
Stroke	12 (10.7%)
Heart diseases	11 (9.8%)
Orthopedic problems	10 (8.9%)
Dementia	9 (8.0%)
Pneumonia	6 (5.4%)
Chronic kidney disease	4 (3.6%)
Sepsis	2 (1.8%)
Liver failure	2 (1.8%)
Gallstone	2 (1.8%)
Asthma	2 (1.8%)
Others*	8 (7.1%)
Unknown causes	13 (11.6%)
Total	112 (100%)

*Bowel obstruction, diabetes mellitus, old tuberculosis, cataract, anorexia, pacemaker generator exchange, senile decay and accident.

With an alternative analysis using tertiles of the BNP level, the accumulated rate of hospitalization was significantly higher in subjects with highest plasma BNP levels (27.5%) than those with middle (14.4%) and lowest plasma BNP levels (13.4%) ($P < 0.001$). The difference of those with middle and lowest plasma BNP level was not significant. The odds ratio of highest tertile compared with lowest tertile as a risk for hospitalization was 2.07 (95% CI, 1.32–3.25; $P = 0.002$). Thus, there was no linear relationship between plasma BNP and hospitalization. The risk of hospitalization seemed to be drastically elevated in those with highest plasma BNP levels.

Reasons for hospitalization

Among the 112 subjects with hospitalization, malignancy was the most common reason for hospitalization ($n = 18$, 16.1%), followed by difficulty to live alone due to decline in ADL or cognitive function ($n = 13$, 11.6%), stroke ($n = 12$, 10.7%), heart diseases ($n = 11$, 9.8%), orthopedic problems ($n = 10$, 8.9%), dementia ($n = 9$, 8.0%), pneumonia ($n = 6$, 5.4%), renal failure ($n = 4$, 3.6%) and other causes ($n = 16$, 14.3%). The reason for hospitalization of 13 subjects (11.6%) could not be specified (Table 3).

The common reasons for hospitalization among 47 non-survivors were malignancy, heart diseases, stroke and pneumonia. On the other side, the common reasons for hospitalization among 65 survivors were difficulty to live alone, stroke, orthopedic problems and dementia. These conditions accorded well with the diseases ranked highly among the reasons for hospitalization in Japan according to past statistics.[1]

Plasma BNP levels of subjects according to reasons for hospitalization

We compared plasma BNP levels of hospitalized subjects to those of subjects without hospitalization according to the reasons for hospitalizations (Table 4). Plasma BNP levels of hospitalized subjects due to difficulty to live alone, heart diseases, stroke, dementia and pneumonia were significantly higher than those of the subjects without hospitalization. When heart disease and stroke were considered as cardiovascular disease, the adjusted hazard ratio of 1 SD increment of log plasma BNP level was 2.59 (95% CI, 1.53–4.40; $P < 0.001$). Plasma BNP levels of hospitalized subjects probably due to non-cardiovascular diseases including malignancy and orthopedic problems were not significantly different when compared with subjects without hospitalization (Table 4).

Discussion

Heart diseases and plasma BNP level

High plasma BNP level was an independent risk factor for future hospitalization in community-dwelling elderly without apparent heart diseases, even after adjustment for several confounding factors, including age, sex, serum creatinine, total cholesterol and albumin levels, MMSE score, ADL score and asymptomatic brain MRI findings. Thus, plasma BNP level can be considered as an independent predictive biomarker for hospitalization. As far as we know, no previous studies have shown a relationship between plasma BNP level and hospitalization of the community-dwelling

© 2009 Japan Geriatrics Society

Table 4 Plasma BNP levels according to reasons for hospitalization

Reasons (*n*)	Log BNP (pg/mL)	*P*-value†
Malignancy (18)	1.66 ± 0.35	0.3
Difficulty to live alone (13)	1.82 ± 0.43	0.01
Stroke (12)	1.85 ± 0.45	0.006
Heart diseases (11)	1.84 ± 0.40	0.01
Orthopedic problems (10)	1.59 ± 0.37	0.86
Dementia (9)	1.94 ± 0.41	0.001
Pneumonia (6)	1.96 ± 0.40	0.006
Chronic kidney disease (4)	1.80 ± 0.39	0.17
Others (29)*	1.65 ± 0.40	0.26

*Including unknown cause. †*P*-value was computed using two-sample Student's *t*-test vs subjects without hospitalization. BNP, B-type natriuretic peptide.

independent elderly. Measurement of plasma BNP level at health examination could be a simple and useful means of prediction for future hospitalization in the community-dwelling healthy elderly.

Plasma BNP level is elevated due to biosynthesis under conditions of heart failure. Many cardiac conditions, including systolic dysfunction,[17] diastolic dysfunction,[18,19] mitral regurgitation,[20] aortic stenosis,[21,22] pulmonary hypertension,[23] cardiomyopathy[24] and senile cardiac enlargement,[25] are associated with increase in BNP. In the present study, despite the fact that subjects with moderate to severe valvular disorders, old myocardial infarction and moderate to severe left ventricular systolic dysfunction were excluded, there were 11 subjects who were hospitalized because of newly developed conditions such as heart failure. Because plasma BNP is known to be useful to detect preclinical ventricular systolic and diastolic dysfunction,[26] it may also be useful for community-dwelling elderly who are at high risk of future hospitalization due to preclinical cardiac dysfunction.

Stroke and plasma BNP level

Among hospitalized subjects, there were 12 subjects who developed stroke and nine subjects with dementia. There have been several reports indicating a correlation between the occurrence of stroke and high plasma BNP level.[7,27–29] Relation of plasma BNP level and cognitive function was also reported.[30] Although the mechanism of these relationships remains unresolved, the elderly at high risk of stroke and dementia may show the elevation of plasma BNP level as seen in our study subjects.

There were 13 subjects who were hospitalized because of difficulty to live alone that was suggestive of decline in ADL by dementia and stroke. In fact, seven of these 13 subjects had asymptomatic brain MRI findings. The plasma BNP levels of these hospitalized subjects because of difficulty to live alone were significantly higher than that of subjects without hospitalization.

There were 10 hospitalized subjects with orthopedic problems with fracture and lower back pain. Although this can potentially be explained by the fact that decline in ADL due to stroke results in falls and fractures, plasma BNP levels in these subjects were not significantly increased. There are no clinical reports concerning the relationships among BNP level, bone fracture and osteoporosis. Further investigation of these relationships is required.

Chronic kidney disease and plasma BNP level

There were four subjects who were hospitalized due to chronic kidney disease. Plasma BNP level was elevated in these four subjects although it was not statistically significant. A correlation between chronic kidney disease and BNP elevation has been reported previously.[31,32] Many elderly subjects with normal creatinine may have impaired kidney function.[33] In addition, mild chronic kidney disease has been recently reported to be associated with the likelihood of decline in ADL and walking speed.[34] Further investigation regarding chronic kidney disease, BNP elevation and hospitalization may be warranted.

Study limitations

In this study, although district nurses conducted a follow-up survey of the diseases that caused hospitalization, the precision of the data can be challenged. For example, although subjects who were diagnosed with atrial fibrillation at the health examinations were excluded, those with paroxysmal atrial fibrillation might have been included. Also, it is possible that asymptomatic mild systolic and diastolic dysfunction might have been included.

Conclusion

High plasma BNP level was found in the community-dwelling elderly subjects who were later hospitalized

 © 2009 Japan Geriatrics Society

because of heart diseases, stroke and chronic kidney disease, which were known to be closely related to the frail elderly. Thus, plasma BNP level is a very useful serological biomarker for future hospitalization in apparently healthy elderly people living in the community.

Acknowledgment

This research was supported in part by a grant from the Japan Arterionsclerosis Prevention Fund.

References

1 Health, Labor and Welfare Ministry. *The Heisei 13 (2001) Fiscal Year Version*. Tokyo, Japan, 2001.
2 Reuben DB, Ix JH, Greendale GA, Seeman TE. The predictive value of combined hypoalbuminemia and hypocholesterolemia in high functioning community-dwelling older persons: MacArthur studies of successful aging. *J Am Geriatr Soc* 1999; **47**: 402–406.
3 Okamura T, Hayakawa T, Hozawa A *et al.* Lower levels of serum albumin and total cholesterol associated with decline in activities of daily living and excess mortality in a 12-year cohort study of elderly Japanese. *J Am Geriatr Soc* 2008; **56**: 529–535.
4 Auyeung TW, Lee JS. Prognostic significance of admission electrolyte disturbances in older people: a retrospective cohort study. *Geriatr Gerontol Int* 2007; **7**: 110–113.
5 Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. *Nature* 1988; **332**: 78–81.
6 Mukoyama M, Nakao K, Hosoda K *et al.* Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991; **87**: 1402–1412.
7 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**: 655–663.
8 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.
9 Wallén T, Landahl S, Hedner T, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. *Heart* 1997; **77**: 264–267.
10 Ueda R, Yokouchi M, Suzuki T, Otomo E, Katagiri T. Prognostic value of high plasma brain natriuretic peptide concentrations in very elderly persons. *Am J Med* 2003; **114**: 266–270.
11 Knight EL, Kiely DK, Fish LC, Marcantonio ER, Minaker KL. Atrial natriuretic peptide level contributes to a model of future mortality in the oldest old. *J Am Geriatr Soc* 1998; **46**: 453–457.
12 Witham MD, Gillespie ND, Hutcheon SD, Struthers AD, McMurdo ME. B-type natriuretic peptide is associated with mortality in older functionally impaired patients. *J Am Geriatr Soc* 2005; **53**: 1991–1995.
13 Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. *J Am Coll Cardiol* 2004; **43**: 1019–1026.
14 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.
15 Matsubayashi K, Okumiya K, Osaki Y, Fujisawa M, Doi Y. Frailty in elderly Japanese. *Lancet* 1999; **353**: 1445.
16 Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965; **14**: 61–65.
17 McDonagh TA, Robb SD, Murdoch DR *et al.* Biochemical detection of left ventricular systolic dysfunction. *Lancet* 1998; **351**: 9–13.
18 Lubien E, DeMaria A, Krishnaswamy P *et al.* Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation* 2002; **105**: 595–601.
19 Dahlström U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? *Eur J Heart Fail* 2004; **6**: 281–287.
20 Detaint D, Messika-Zeitoun D, Avierinos JF *et al.* B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. *Circulation* 2005; **111**: 2391–2397.
21 Bergler-Klein J, Klaar U, Heger M *et al.* Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004; **109**: 2302–2308.
22 Kupari M, Turto H, Lommi J. Diagnosing heart failure in aortic valve stenosis. *J Intern Med* 2004; **256**: 381–387.
23 Nagaya N, Nishikimi T, Uematsu M *et al.* Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; **102**: 865–870.
24 Maron BJ, Tholakanahalli VN, Zenovich AG *et al.* Usefulness of B-type natriuretic peptide assay in the assessment of symptomatic state in hypertrophic cardiomyopathy. *Circulation* 2004; **109**: 984–989.
25 Sayama H, Nakamura Y, Saito N, Kinoshita M, Suda M. Relationship between left ventricular geometry and brain natriuretic peptide levels in elderly subjects. *Gerontology* 2000; **46**: 71–77.
26 Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004; **109**: 3176–3181.
27 Ariyarajah V, Apiyasawat S, Najjar H, Mercado K, Puri P, Spodick DH. Frequency of interatrial block in patients with sinus rhythm hospitalized for stroke and comparison to those without interatrial block. *Am J Cardiol* 2007; **99**: 49–52.
28 Igarashi Y, Kashimura K, Makiyama Y, Sato T, Ojima K, Aizawa Y. Left atrial appendage dysfunction in chronic nonvalvular atrial fibrillation is significantly associated with an elevated level of brain natriuretic peptide and a prothrombotic state. *Jpn Circ J* 2001; **65**: 788–792.
29 Mabuchi N, Tsutamoto T, Maeda K, Kinoshita M. Plasma cardiac natriuretic peptides as biochemical markers of recurrence of atrial fibrillation in patients with mild congestive heart failure. *Jpn Circ J* 2000; **64**: 765–771.
30 Gunstad J, Poppas A, Smeal S *et al.* Relation of brain natriuretic peptide levels to cognitive dysfunction in adults >55 years of age with cardiovascular disease. *Am J Cardiol* 2006; 98: 538–540.
31 Buckley MG, Sethi D, Markandu ND, Sagnella GA, Singer DR, MacGregor GA. Plasma concentrations and comparisons of brain natriuretic peptide and atrial natriuretic

© 2009 Japan Geriatrics Society

peptide in normal subjects, cardiac transplant recipients and patients with dialysis-independent or dialysis-dependent chronic renal failure. *Clinical Science* 1992; **83**: 437–444.

32 Akiba T, Tachibana K, Togashi K, Hiroe M, Marumo F. Plasma human brain natriuretic peptide in chronic renal failure. *Clin Nephrol* 1995; **44** (Suppl 1): S61–64.

33 Giannelli SV, Patel KV, Windham BG, Pizzarelli F, Ferrucci L, Guralnik JM. Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. *J Am Geriatr Soc* 2007; **55**: 816–823.

34 Shlipak MG, Stehman-Breen C, Fried LF *et al.* The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis* 2004; **43**: 861–867.

 © 2009 Japan Geriatrics Society

Original Article

Current Trends in Lifestyle-Related Disease Management by General Practitioners: A Report from the "Heart Care Network" Groups

The Heart Care Network Groups

Aims: In Japan, it is believed that guidelines for lifestyle-related disease are used in routine clinical practice, however, there are few reports on the actual rate of healthcare conducted in accordance with these guidelines by general practitioners and on their usefulness in preventing cardiovascular events. Therefore, the Heart Care Network (HCN) groups were organized mainly by general practitioners treating lifestyle diseases in 62 areas of Japan.

Methods: The HCN has collected data on lifestyle diseases in high-risk patients in routine practices and investigated management conditions, guideline target achievement rates and medication. Additionally, the incidence of cardiovascular events was assessed.

Results: We analyzed 14,064 cases. The lipid profile, blood pressure, glycemic control were significantly improved over the 3 years. The incidence of cardiovascular events were significantly reduced by the achievement of target LDL cholesterol, systolic blood pressure and hemoglobin A1c and even after adjustment for age, gender, history of myocardial infarction, the reduction of these lifestyle-related parameters remains significant.

Conclusion: These results revealed the current trends in the healthcare activities of general practitioners, the management conditions for lifestyle diseases in CHD high-risk patients and their effects on reducing cardiovascular events.

J Atheroscler Thromb, 2009; 16:799-806.

Key words; Coronary heart disease, Hypertension, Hyperlipidemia, Diabetes mellitus

Introduction

In the past several years, the number of deaths due to coronary heart disease (CHD) has leveled off in Japan but is still the second-ranking cause of death[1]. Attention is focused on the strict management of "lifestyle diseases", such as hyperlipidemia, hypertension and diabetes mellitus as risk factors of CHD. To elucidate CHD risk factors, many epidemiological surveys have been performed to date. In the USA, epidemiological data have been published from studies on local residents and people undergoing health checks in the Framingham Heart Study[2,3], whereas in Japan similar data were collected in the Hisayama Study[4] and NIPPON DATA[5]. These studies and many others conclusively demonstrated that hyperlipidemia, hypertension and diabetes mellitus are independent risk factors for cardiovascular disease[6]. It has been reported that the risk for onset of cardiovascular events in patients with 4 risk factors, high BMI, hypertension, hyperglycemia, and hypercholesterolemia, was 31.3 times higher than in those with no risk factors[7], suggesting that combined multiple risk factors synergistically increase the overall cardiovascular risk[8].

In Japan, management targets for hypertension, hyperlipidemia and diabetes mellitus have been set in the Japanese Society of Hypertension Guidelines for the Management of Hypertension[9], Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases[10], and the Treatment Guide for Diabetes[11], respectively, based on data from Japan and overseas.

Although it is believed that these guidelines are used in routine clinical practice in Japan, there are few reports on the actual rate of healthcare conducted in accordance with these guidelines by general practitioners and on their usefulness in preventing cardiovascular events.

Under these circumstances, the Heart Care Network (HCN) research groups were organized mainly

Address for correspondence: Hiroyuki Daida, Department of Cardiology, Juntendo University, School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
E-mail: daida@juntendo.ac.jp
Received: April 2, 2009
Accepted for publication: May 28, 2009

by the local core hospital and 10 to 20 collaborating general practitioners who were treating lifestyle diseases in 62 local areas of Japan between 2000 and 2005 (see appendix). The HCN has collected data on lifestyle diseases in CHD high-risk patients in routine practices and investigated management conditions, guideline target achievement rates and medication conditions via research groups in each region.

In the present study, we compiled and reanalyzed HCN data from each region about 14,000 cases nationwide. From the results, it was possible to examine the healthcare activities of general practitioners, the management conditions for lifestyle diseases in CHD high-risk patients and their effects on reducing cardiovascular events.

Methods

Subjects

The subjects were adult (≥20 years old) patients with a history of myocardial infarction or with ≥2 lifestyle related diseases, such as hyperlipidemia, hypertension, and diabetes mellitus, who visited any of the 799 medical clinics or institutions participating in HCN research groups in 62 regions nationwide. Each clinic or institution tried to recruit at least 20 patients. The criteria for each disease on registration were as follows: for hyperlipidemia, LDL-cholesterol (LDL-C) ≥140 mg/dL or total cholesterol (TC) ≥220 mg/dL; hypertension, systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg; and diabetes mellitus, random blood glucose ≥200 mg/dL or fasting blood glucose (FBG) ≥126 mg/dL according to the Japanese guidelines for hypertension, hyperlipidemia and diabetes mellitus[9-11]. In addition, patients who were already receiving treatment for these diseases could be registered regardless of satisfying these criteria. The exclusion criteria were as follows: (1) the presence of known untreated neoplasms; (2) type I diabetes mellitus; (3) the presence of secondary hypertension; and (4) severe chronic pulmonary disease. Data of patients whose survey data could be obtained at least twice, i.e., those followed for ≥1 year were used for the analysis. Informed consent was obtained from all patients to participate in this study, which complied with the Declaration of Helsinki and proceeded according to the ethics policies of the involved clinic of institutions.

Data Collection

The survey items were height, body weight, chest x-ray findings (cardiothoracic ratio ≥50% or not), findings of fasting blood test such as TC, HDL-C, triglycerides (TG), LDL-C (calculated using the Friedewald formula or measured value in cases with triglycerides (TG) >400mg/dL), blood glucose, HbA1c, blood pressure measured in a seated position after 15 minutes rest on three separate occasions within 3 months prior to survey (average values of three measurements), medications, and incidence of cardiovascular events, including death associated with CHD, stroke, cardiogenic shock, sudden death, in addition to non-fatal myocardial infarction and stroke. Changes in healthcare activities (medications and status of application of lifestyle improvement program) and management conditions for CHD risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, smoking (smokers were defined as smoking at the time of the survey), and alcohol consumption (drinkers were defined as drinking ≥three times per week and drinking ≥1 unit of alcohol each time), were surveyed once a year, 4 times in total: at registration for the 3-year survey, and during the first, second, and third years of the survey, respectively. Guideline target achievement was determined by whether the mean of each value (LDL-C, SBP, HbA1c) obtained in each survey satisfied the guideline target level.

Statistical Analysis

Statistical analysis was performed using 1-way repeated measure analysis of variance (ANOVA) for changes in each of the measured values, and the chi-square test for the guideline target achievement rate. Kaplan-Meier estimation and the log-rank test were used for the onset of cardiovascular events. Cox proportional hazard models adjusting for age, gender and history of myocardial infarction were also used for multivariate analysis. In these survival analyses, cases without any events were censored at the date of the last survey.

The level of statistical significance was <5%. Values of blood pressure and age are expressed as the mean ± SD.

Results

Patient Characteristics

Of 15,055 registered patients, 14,064 patients (6,198 men and 7,866 women) whose survey data could be obtained at least twice were analyzed (mean number of recruited patients in each clinic or institution was 17.6 patients/institution). There were no significant differences in all characteristics between 14,064 patients and the residual 911 patients. The mean follow-up period was 960.7 days (range, 1-1095 days).