aged 65 years and older in 2000. Each year from 2000 to 2003, every individual aged 65 years or older was invited to the annual health checkup organized by the municipal health center. Without considering duplicates, the number of persons who participated in the checkup was 348 in 2000, 337 in 2001, 384 in 2002 and 361 in 2003. The first visit to the checkup service was defined as entry into the present longitudinal study. Of the 577 individuals who entered the study, 18 who had lumbar pain and gibbosity were excluded because measurement of baPWV was not applicable. The remaining 559 individuals (220 men and 339 women; mean age ± s.d. at entry, 76.6 ± 5.6 years)—26.7% of the number of Kahoku residents aged 65 years or older in 2000—were invited to have their baPWV measured. Of these 559 subjects, 29 were excluded; 15 had atrial fibrillation, 5 had a medical history of arteriosclerosis obliterans and 9 had an abnormal ankle/brachial pressure index of less than 0.9 as determined by plethysmography. Therefore, the effective sample size of this study was 530 subjects (207 men and 323 women; mean age at entry, 76.4 ± 5.6 years).

Ethical consideration

Written informed consent was obtained from each person at entry into the study. The study protocol was approved by the research ethics committee of Kochi Medical School, Kochi University, Japan.

Study variables

Medical history and examinations. Medical history was self-reported and confirmed by a physician at the baseline health checkup. Participants were defined as having a medical history of CVD if they had a history of stroke or heart disease such as ischemic heart disease, heart failure or arrhythmia. Body height and weight were measured in the health checkup at entry into the study. Body mass index was defined as weight (kg) divided by the square of height (m^2). Blood pressure (BP) measurements were performed in the morning in the health checkup at study entry. BP and pulse rate were recorded twice in the upper arm with an appropriately sized cuff at the level of the heart with the subject in a sitting position after a rest of at least 5 min, using an autosphygmomanometer (BP-203I; Colin Co., Komaki, Japan) according to the cuff-oscillometric method. For the analysis, we used an average of two measurements for BP and pulse rate.

Brachial–ankle pulse wave velocity measurements

baPWV was automatically measured using a form PWV/ABI instrument (Colin Co.), as previously described.[11,21] This device has four cuffs matched with oscillometric sensors, and the cuffs were wrapped around the upper arms and the ankles. The volume pulse forms of the bilateral brachial and tibial arteries were monitored during continuous deflation of the cuffs. The baPWV value was calculated by time-phase analysis of the right brachium and ankle and the left brachium and ankle, respectively. baPWV was measured after the subject had lain supine for at least 5 min. Measurements were performed twice, consecutively. An average of two baPWV measurements was used. Because there was a significant positive correlation between left and right baPWV (r=0.954, $P<0.001$), the right baPWV value was used in this study.

The participants were dichotomized according to a median value of baPWV. Those with baPWV $<18.675\,m\,s^{-1}$ (n=265) formed the low-baPWV group, and the subjects with baPWV $\geqslant 18.675\,m\,s^{-1}$ (n=265) constituted the high-baPWV group.

Laboratory variables

All participants had blood drawn in the health checkup at entry into this study. The samples were placed in cold storage immediately after collection and were analyzed within 48 h. Blood sugar, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, triglyceride, hemoglobin and albumin levels were determined.

Follow-up survey for prognosis

Survivorship of the participants for 3 years from entry into the study was followed. No study participant moved out of the municipality during the period. For those who died, we recorded the cause of death from the death certificate submitted to the municipality. Causes of death were coded according to the International Classification of Diseases, ninth edition.

Statistical analysis

All continuous variables were expressed as the mean ± s.d. The mean values between the two groups were compared using the Student's t-test. The χ^2-test was used to compare the proportions of specific categories for categorical variables. The Kaplan–Meier method was used to estimate unadjusted survival curves of the two baPWV groups. The log-rank test was used to compare the unadjusted survival curves. A Cox proportional hazards model was used to describe the association between baPWV and mortality while adjusting for age, sex and BP measures. A receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff value of baPWV for predicting total mortality and cardiovascular mortality. The value with the highest sum of sensitivity and specificity was used as the optimal cutoff value. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS 15.0J for Windows (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Baseline characteristics

The mean value of baPWV was $18.90 \pm 3.95\,m\,s^{-1}$ in all subjects. There was no significant difference in the means of baPWV between men and women (men, $18.81 \pm 4.01\,m\,s^{-1}$; women, $18.97 \pm 3.92\,m\,s^{-1}$, P=0.647). Table 1 shows the baseline characteristics according to the baPWV groups. The high-baPWV group was older and had a higher proportion of subjects taking antihypertensive medication than the low-baPWV group. There were no significant differences in body mass index, the proportion of current smokers, the use of medications for diabetes mellitus and hyperlipidemia or history of CVDs between the two groups. Systolic BP (SBP), diastolic BP, pulse pressure and pulse rate were higher in the high-baPWV group as compared with the low-baPWV group. No significant difference was found in the blood test results between the two groups.

Three-year mortality according to baPWV

In the 3 years after the onset of the study, 30 persons died, 10 of whom died as a result of CVDs. Table 2 shows the number and percentage of all-cause and cause-specific deaths during the 3 years. The high-baPWV group had higher proportions of both total deaths and deaths due to CVDs. There were no significant differences in the proportions of deaths due to other causes.

Kaplan–Meier curves showed that the high-baPWV group had a significantly higher probability of overall mortality (Figure 1a) and also of cardiovascular mortality (Figure 1b). After adjustment for age, sex and SBP, a high-baPWV level was significantly associated with an increased risk of 3-year total mortality (adjusted HR=2.98, 95% CI=1.25–7.07) and cardiovascular mortality (adjusted HR=10.01, 95% CI=1.21–82.49) (Table 3). When baPWV was treated as a continuous variable, a $1\,m\,s^{-1}$ increase in baPWV was significantly associated with an increased risk of 3-year total mortality (adjusted HR=1.09, 95% CI=1.00–1.18) and cardiovascular mortality (adjusted HR=1.12, 95% CI=1.01–1.25) after adjustment for age, sex and SBP. After adjustment for antihypertensive medication use in place of SBP, a high-baPWV level was still associated with an increased risk of 3-year total mortality (adjusted HR=2.66, 95% CI=1.17–6.05) and cardiovascular mortality (adjusted HR=8.53, 95% CI=1.07–67.76). This association remained after adjustment for pulse pressure in place of SBP (total mortality: adjusted HR=2.68, 95% CI=1.16–6.15; cardiovascular mortality: adjusted HR=9.09, 95% CI=1.14–72.65). After adjustment for pulse rate in place of SBP, this association again remained (total mortality: adjusted HR=2.45, 95% CI=1.07–5.62; cardiovascular mortality: adjusted HR=8.48, 95% CI=1.07–67.45), as well as after adjustment for medical history of CVD in addition to age, sex, and SBP (total mortality: adjusted HR=2.97, 95% CI=1.25–7.09; cardiovascular mortality: adjusted HR=9.01, 95% CI=1.08–74.90).

Table 1 Baseline characteristics according to the level of baPWV

	Low baPWV (n=265)	*High baPWV (n=265)*	*P-value*
Age (years)	75.1±5.4	77.7±5.5	<0.001
Men/women	103/162	104/161	1.000
Body mass index ($kg\,m^{-2}$)	23.0±3.4	23.1±3.6	0.857
Current smoking, *n* (%)	32 (12.1)	25 (9.4)	0.400
Antihypertensive medication, *n* (%)	94 (35.5)	133 (50.2)	0.001
Antihyperglycemic medication, *n* (%)	16 (6.0)	23 (8.7)	0.318
Antihyperlipidemic medication, *n* (%)	32 (12.1)	29 (10.9)	0.786
History of CVD, *n* (%)	30 (11.3)	27 (10.2)	0.779
Systolic blood pressure (mm Hg)	138.9±26.4	154.4±21.8	<0.001
Diastolic blood pressure (mm Hg)	77.7±10.8	85.5±11.5	<0.001
Pulse pressure (mm Hg)	61.2±24.0	68.9±17.2	<0.001
Pulse rate (b.p.m.)	70.8±11.7	76.3±12.7	<0.001
Blood sugar (mg per 100 ml)	114.8±27.5	117.9±31.1	0.225
Hemoglobin A1c (%)	5.3±0.6	5.4±0.8	0.144
Total cholesterol (mg per 100 ml)	194.7±30.5	198.6±35.6	0.184
HDL cholesterol (mg per 100 ml)	52.7±13.5	50.7±13.5	0.089
Triglyceride (mg per 100 ml)	128.9±84.5	141.9±81.3	0.072
baPWV ($m\,s^{-1}$)	15.89±1.80	21.92±3.13	<0.001

Abbreviations: baPWV, brachial–ankle pulse wave velocity; CVD, cardiovascular disease; HDL, high-density lipoprotein.
Low baPWV, $<18.675\,m\,s^{-1}$; high baPWV, $\geqslant 18.675\,m\,s^{-1}$.

Table 2 Three-year cause-specific mortality according to the level of baPWV

	Low baPWV (n=265)	*High baPWV (n=265)*	*P-value*
All-causes, *n* (%)	8 (3.0)	22 (8.3)	0.013
Cardiovascular diseases, *n* (%)	1 (0.4)	10 (3.8)	0.011
Stroke, *n* (%)	0 (0.0)	3 (1.1)	0.249
Heart disease, *n* (%)	1 (0.4)	7 (2.6)	0.068
Malignancy, *n* (%)	2 (0.8)	6 (2.3)	0.285
Pneumonia, *n* (%)	0 (0.0)	3 (1.1)	0.249
Others, *n* (%)	5 (1.9)	3 (1.1)	0.505

Abbreviation: baPWV, brachial–ankle pulse wave velocity.

Figure 2 shows the ROC curves used to define the optimal cutoff value of baPWV in relation to 3-year total/cardiovascular mortality. The area under the ROC curve for total mortality was 0.673 (95% CI=0.586–0.760), and that for cardiovascular mortality was 0.795 (95% CI=0.701–0.890). The optimal cutoff value of baPWV for total mortality was $19.63\,m\,s^{-1}$ (73% sensitivity and 63% specificity) and that for cardiovascular mortality was $19.63\,m\,s^{-1}$ (91% sensitivity and 62% specificity). A Cox proportional hazards model showed that a baPWV level $\geqslant 19.63\,m\,s^{-1}$ was significantly associated with an increased risk of 3-year total mortality (adjusted HR=5.3, 95% CI=2.2–12.7) and cardiovascular mortality (adjusted HR=18.7, 95% CI=2.2–157.6) after adjustment for age, sex and SBP. The optimal cutoff value produced higher point estimates of HRs than the cutoff at the median value.

DISCUSSION

This study showed that high baPWV was predictive of increased mortality, especially increased cardiovascular mortality, in community-dwelling older adults. This finding indicates that baPWV might be a useful marker of arterial stiffness in older adults. Arterial stiffness increases with advancing age and is accompanied by structural changes to the arterial system, including fragmentation and degeneration of elastin and increases in collagen.[1] An increase in arterial stiffness results in premature return of reflected waves in late systole and increases central SBP and pulse pressure. Therefore, systolic hypertension and increased pulse pressure are known to be markers of arterial stiffness and have been reported to be related to higher total/cardiovascular mortality in older adults.[22,23] In this study, SBP and pulse pressure had positive correlations with baPWV (SBP: $r=0.346$, $P<0.01$; pulse pressure: $r=0.211$, $P<0.01$). Moreover, high baPWV was associated with higher total/cardiovascular mortality, adjusted for SBP or pulse pressure. These results suggest that baPWV is a predictor of total/cardiovascular mortality independently of SBP and pulse pressure.

Aortic stiffness is closely related to total and cardiovascular mortality.[3–10] cfPWV is regarded to be the gold standard of aortic PWV measurement, and the association between cfPWV and cardiovascular mortality has been reported in older adults.[7,24] In contrast to cfPWV measurements, which require a specialized technique, baPWV is a new method for measuring PWV that does not require a specialized technique. Four cuffs matched with oscillometric sensors are wrapped

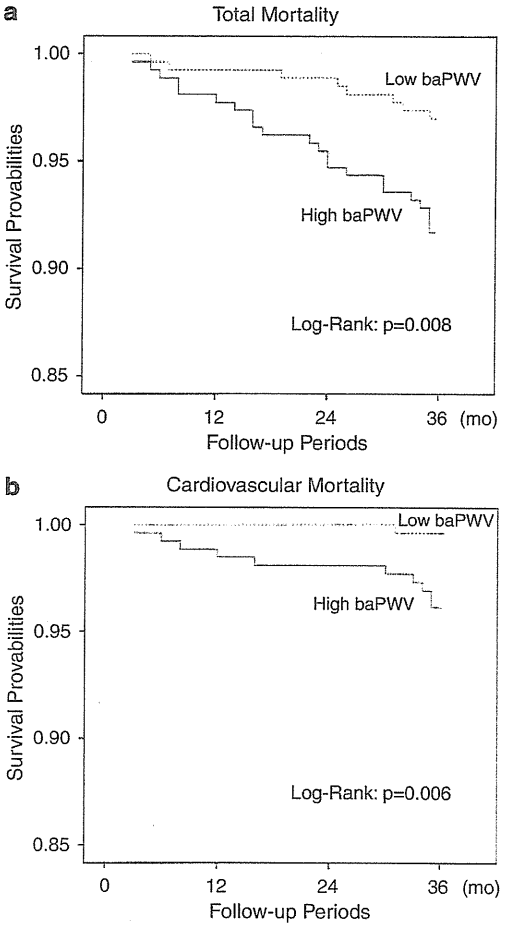

Figure 1 (**a**) Kaplan–Meier curves of total mortality. Survival probabilities according to brachial–ankle pulse wave velocity. (**b**) Kaplan–Meier curves of cardiovascular mortality. Survival probabilities according to brachial–ankle pulse wave velocity.

Table 3 The relation between baPWV and 3-year all-cause/cardiovascular mortality

	All-cause mortality (n=30)		*Cardiovascular mortality (n=11)*	
	Hazard ratio (95% CI)	P-*value*	*Hazard ratio (95% CI)*	P-*value*
baPWV (high/low)	2.98 (1.25–7.07)	0.013	10.01 (1.21–82.49)	0.032
Age (1 year increased)	1.06 (1.00–1.13)	0.057	1.14 (1.04–1.25)	0.006
Sex (men/women)	2.23 (1.06–4.68)	0.034	2.60 (0.75–9.09)	0.134
SBP (1 mm Hg increased)	0.99 (0.97–1.01)	0.270	0.99 (0.96–1.02)	0.401

Abbreviations: baPWV, brachial–ankle pulse wave velocity; SBP, systolic blood pressure.

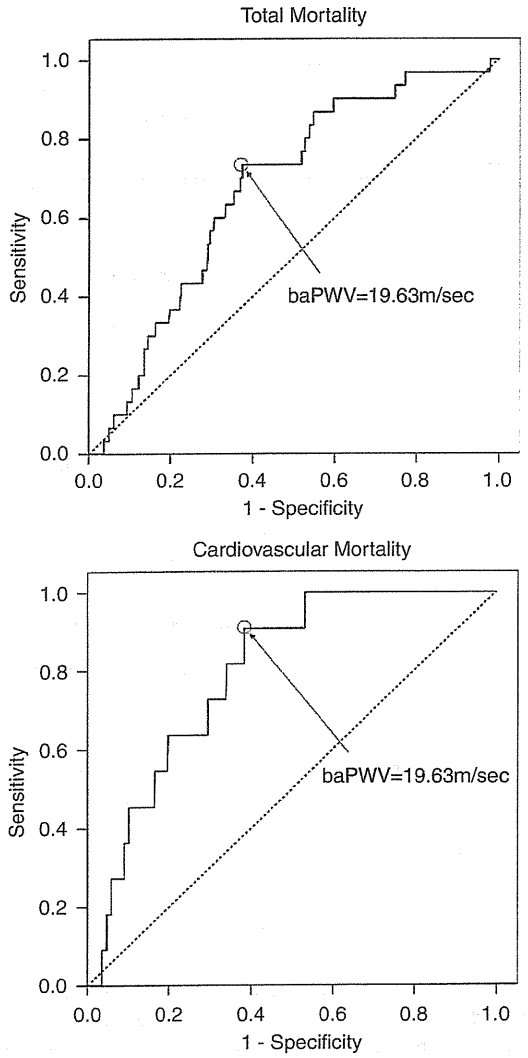

Figure 2 Receiver-operating characteristic curves to define the optimal cutoff value of baPWV in relation to 3-year total/cardiovascular mortality. Total mortality: area under the curve=0.673 (95% CI=0.586–0.760); optimal cutoff of baPWV=19.63 m s^{-1} (73% sensitivity and 63% specificity). Cardiovascular mortality: area under the curve=0.795 (95% CI=0.701–0.890); optimal cutoff of baPWV=19.63 m s^{-1} (91% sensitivity and 62% specificity).

around the upper arms and the ankles. A high reproducibility of baPWV measurements obtained with this method has been reported (correlation coefficient: interobserver reproducibility=0.98, intraobserver reproducibility=0.87).[21] Another feature of baPWV measurements is that they yield data for both the central and peripheral arteries. baPWV has been reported to be closely correlated with aortic PWV obtained by an invasive measurement using a catheter tip manometer (correlation coefficient=0.87)[21] and with cfPWV (correlation coefficient=0.73).[25] baPWV was comparable to cfPWV in predicting the presence of both stroke and coronary artery disease.[25]

Although 12.00 m s^{-1} of cfPWV was recommended as a cutoff value in hypertensive patients,[26] the optimal cutoff value of cfPWV in older adults has not been reported. With regard to the cutoff value of baPWV, 17.00 m s^{-1} was the optimal cutoff value for predicting recurrence of cardiovascular events, including coronary reintervention, reinfarction and readmission for congestive heart failure, stroke and cardiac death, in patients with history of hospitalization as a result of acute coronary syndrome.[16] In addition, 18.00 m s^{-1} was the optimal cutoff value for predicting recurrence of cardiovascular events, including reinfarction and readmission for congestive heart failure, stroke and cardiac death in patients with acute coronary syndrome.[16] This study showed the optimal cutoff value of baPWV in relation to 3-year total/cardiovascular mortality, and it suggested that the cutoff value of baPWV in community-dwelling older adults was higher than that in clinical populations.

A potential intervention for the improvement of arterial compliance might be targeted to community-dwelling older adults with high baPWV. It was reported that 3 months of aerobic exercise and brisk walking increased central arterial compliance in middle-aged and older healthy men.[27] In addition, it was reported that aortic PWV was reduced by dietary sodium restriction in healthy postmenopausal women.[28] Therefore, education for changing a sedentary lifestyle and reducing sodium intake might be considered for community-dwelling older adults with high baPWV. Among the limitations of this study were the small number of participants and the short follow-up period. Consequently, the number of total deaths, including cardiovascular deaths, was small. Therefore, the analysis of the association between baPWV and prognosis, especially between baPWV and cause-specific mortality, may not be reliable. This study should thus be considered preliminary; a longitudinal study with a large cohort is necessary to confirm the relationship with long-term mortality. Second, it has been reported that antihypertensive drugs decrease baPWV, and the degree of the decrease varies according to the class of antihypertensive drug.[29] Although in our study the presence or absence of on medication use was self-reported and confirmed by a physician, on the classes of antihypertensive drugs was not confirmed. A study of a population including a larger number of subjects taking distinct classes of antihypertensive drugs is necessary.

In conclusion, high baPWV was associated with higher mortality in community-dwelling older adults, indicating that noninvasive assessment of arterial stiffness by baPWV may be useful for predicting prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by a grant-in-aid from the Japan Arteriosclerosis Prevention Fund.

1 Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises part I: aging arteries: a 'set up' for vascular disease. *Circulation* 2003; **107**: 139–146.
2 Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease, functional markers. *Circulation* 2004; **109**(25 Suppl 1): IV-31–IV-46.
3 Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434–2439.
4 Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**: 1111–1117.
5 Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
6 Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**: 2085–2090.
7 Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 2005; **111**: 3384–3390.
8 Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, Yamane K, Kohno N. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J* 2005; **69**: 259–264.
9 Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006; **113**: 657–663.
10 Hansen TW, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; **113**: 664–670.
11 Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, Hinohara S. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis* 2003; **166**: 303–309.
12 Yamashina A, Tomiyama H, Arai T, Hirose K, Koji Y, Hirayama Y, Yamamoto Y, Hori S. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003; **26**: 615–622.
13 Imanishi R, Seto S, Toda G, Yoshida M, Ohtsuru A, Koide Y, Baba T, Yano K. High brachial-ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. *Hypertens Res* 2004; **27**: 71–78.
14 Ohmine T, Miwa Y, Yao H, Yuzuriha T, Takashima Y, Uchino A, Takahashi-Yanaga F, Morimoto S, Maehara Y, Sasaguri T. Association between arterial stiffness and cerebral white matter lesions in community-dwelling elderly subjects. *Hypertens Res* 2008; **31**: 75–81.
15 Kim DH, Kim J, Kim JM, Lee AY. Increased brachial-ankle pulse wave velocity is independently associated with risk of cerebral ischemic small vessel disease in elderly hypertensive patients. *Clin Neurol Neurosurg* 2008; **110**: 599–604.
16 Tomiyama H, Koji Y, Yambe M, Shiina K, Motobe K, Yamada J, Shido N, Tanaka N, Chikamori T, Yamashina A. Brachial-ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. *Circ J* 2005; **69**: 815–822.
17 Matsuoka O, Otsuka K, Murakami S, Hotta N, Yamanaka G, Kubo Y, Yamanaka T, Shinagawa M, Nunoda S, Nishimura Y, Shibata K, Saitoh H, Nishinaga M, Ishine M, Wada T, Okumiya K, Matsubayashi K, Yano S, Ichihara K, Cornélissen G, Halberg F, Ozawa T. Arterial stiffness independently predicts cardiovascular events in an elderly community—longitudinal investigation for the longevity and aging in Hokkaido County (LILAC) study. *Biomed Pharmacother* 2005; **59** (Suppl 1): S40–S44.
18 Kitahara T, Ono K, Tsuchida A, Kawai H, Shinohara M, Ishii Y, Koyanagi H, Noguchi T, Matsumoto T, Sekihara T, Watanabe Y, Kanai H, Ishida H, Nojima Y. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. *Am J Kidney Dis* 2005; **46**: 688–696.
19 Matsubayashi K, Okumiya K, Wada T, Osaki Y, Fujisawa M, Doi Y, Ozawa Y. Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. *Stroke* 1997; **28**: 2169–2173.
20 Nishinaga M, Takata J, Okumiya K, Matsubayashi K, Ozawa T, Doi Y. High morning home blood pressure is associated with a loss of functional independence in the community-dwelling elderly aged 75 years or older. *Hypertens Res* 2005; **28**: 657–663.
21 Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
22 Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; **355**: 865–872.
23 Glynn RJ, Chae CU, Guralnik JM, Taylor JO, Hennekens CH. Pulse pressure and mortality in older people. *Arch Intern Med* 2000; **160**: 2765–2772.
24 Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 2001; **21**: 2046–2050.
25 Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens* 2009; **27**: 2022–2027.
26 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B, Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.
27 Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 2000; **102**: 1270–1275.
28 Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR, Davy KP, DeSouza CA. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol* 2001; **38**: 506–513.
29 Takami T, Shigemasa M. Efficacy of various antihypertensive agents as evaluated by indices of vascular stiffness in elderly hypertensive patients. *Hypertens Res* 2003; **26**: 609–614.

Lourdes Rexach, MD, PhD
Coordinator of Palliative Care Unit
University Hospital Ramón y Cajal
Madrid, Spain

Miel Ribbe, MD, PhD
VU University Medical Center
Amsterdam, the Netherlands

Nele Van Den Noortgate, MD, PhD
Department of Geriatric Medicine
University Hospital Ghent, Ghent, Belgium

ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Sophie Pautex, Vito Curiale, Lourdes Rexach, and Nele Van Den Noortgate: study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript. Mathias Pfisterer and Miel Ribbe: study concept and design, acquisition of subjects and data, analysis and interpretation of data.

Sponsor's Role: None.

REFERENCES

1. Davies E, Higginson IJ, editors. Better Palliative Care for Older People. Geneva: World Health Organization, 2004.
2. An ageing problem. Lancet Oncol 2004;5:459.
3. Fried LP, Ferrucci L, Darer J et al. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59A:255–263.
4. Kapo J, Morrison LJ, Liao S. Palliative care for the older adult. J Palliat Med 2007;10:185–209.
5. Goldstein NE, Morrison RS. The intersection between geriatrics and palliative care: A call for a new research agenda. J Am Geriatr Soc 2005;53:1593–1598.
6. Burt J, Raine R. The effect of age on referral to and use of specialist palliative care services in adult cancer patients: A systematic review. Age Ageing 2006;35:469–476.
7. Coleman EA, Boult C. Improving the quality of transitional care for persons with complex care needs. J Am Geriatr Soc 2003;51:556–557.
8. Evers MM, Meier DE, Morrison RS. Assessing differences in care needs and service utilization in geriatric palliative care patients. J Pain Symptom Manage 2002;23:424–432.
9. Phillips RS, Hamel MB, Covinsky KE et al. Findings from SUPPORT and HELP: An introduction. Study to understand prognoses and preferences for outcomes and risks of treatment. Hospitalized elderly longitudinal project. J Am Geriatr Soc 2000;48:S1–S5.
10. Duursma S, Castleden M, Cherubini A et al. European Union Geriatric Medicine Society. Position statement on geriatric medicine and the provision of health care services to older people. J Nutr Health Aging 2004;8:190–195.
11. Sepulveda C, Marlin A, Yoshida T et al. Palliative care: The World Health Organization's global perspective. J Pain Symptom Manage 2002;24:91–96.

COMMUNITY-BASED GERIATRIC ASSESSMENT AND PREVENTIVE INTERVENTION LOWERED MEDICAL EXPENSES FOR THE ELDERLY

To the Editor: Before the introduction of the national long-term care insurance system, it was reported that community-based geriatric assessment might lower the increasing rate of medical expenses in a rural town in Kochi Prefecture, Japan.[1] Even after the introduction of the national long-term care insurance system in 2000, total medical expenses for older adults has increased with the growth of the older population in Japan. Since 2004, community-based comprehensive geriatric assessments and interventions have been performed for older adults living in Tosa Town, Kochi Prefecture, Japan. Geriatric assessments included a comprehensive annual health-related questionnaire of all eligible people aged 65 and older (75–95% response rate) and annual geriatric examinations for people aged 75 and older (30–40% participant rate).[2] This longitudinal community-based project in cooperation with local government and resident organizing committees has attained several medical achievements: early detection of latent diabetes mellitus or impaired glucose tolerance in older adults because of community-based oral glucose tolerance tests,[3] improvement of impaired glucose tolerance by lifestyle change interventions,[4] increasing public awareness of hypertension in older adults,[5] public education of dietary diversity,[6] and early detection of fallers[7] by introducing a fall risk index that can be completed in a brief amount of time.[8]

In parallel with medical and geriatric achievements of the community-based project, an additional achievement regarding changes in medical expenses for the elderly in this town was found. Changes in medical expenses from 2004 to 2007 in Tosa Town, where we have intervened, compared with medical expenses for older adults in two other communities (Motoyama Town and Kochi City) in Kochi prefecture and the average medical expenses of 35 communities in Kochi Prefecture[9] are reported here. Kochi prefecture is located in Shikoku province in southwestern Japan and has 11 cities and 24 towns with a total population of 796,292 people, of whom 25.9% were aged 65 and older in 2006. Tosa Town is one of the 24 small towns in Kochi Prefecture and had a population of 4,632 people, of whom 40.6% were aged 65 and older in 2006. This comparative study on changes in medical expenses for older adults included two control communities: Motoyama Town, which neighbors Tosa Town and has a sociodemographic profile similar to that of Tosa Town, and Kochi City, which is the seat of Kochi prefecture. Total populations (and % of the population aged $\geq$ 65) in Motoyama Town and Kochi City in 2006 were 4,374 (37.9%) and 333,484 (20.5%), respectively.

Figure 1 compares annual changes in medical expenses in the national medical insurance system for one person aged 65 and older in Tosa Town from 2004 to 2007 with expenses in Motoyama Town, in Kochi City, and the average from 35 communities in Kochi Prefecture. Although medical expenses for older adults increased over the 4 years in Motoyama Town and Kochi City and in Kochi prefecture in general, expenses in Tosa Town decreased yearly from 2004 to 2007. The decrease in medical expenses for older adults in Tosa Town is probably due to community-based geriatric assessments and preventive interventions introduced since 2004. In 2007, differences in medical expenses between Tosa Town and neighboring Motoyama Town reached 140,000 Japanese yen (approximately $1,075) for each elderly person each year, which totals approxi-

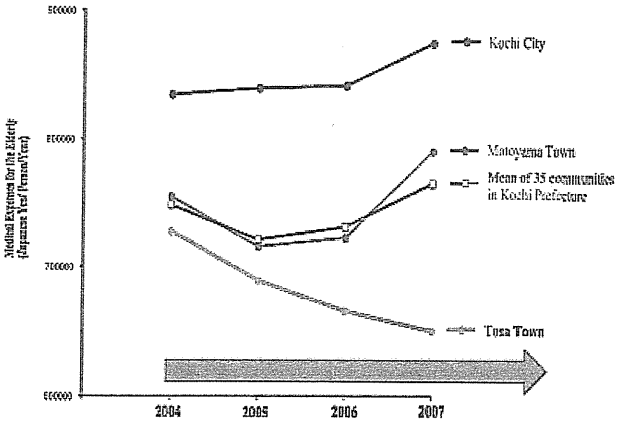

Figure 1. Annual changes in medical expenses for one person aged 65 and older in Tosa Town from 2004 to 2007, compared with expenses in Motoyama Town, in Kochi City, and the average expenses of 35 communities in Kochi Prefecture.

mately 200,000,000 Japanese yen (~ $2 million) for 1,500 elderly persons in each town. The total annual budget of community-based geriatric assessments and preventive interventions in our project is 10 million Japanese yen (~ $100,000). The decrease in medical expenses in Tosa Town suggests that it might be worthwhile to consider the community-based project not only from the perspective of geriatric achievements, but also from the financial dimension.

The elderly population is rapidly growing in Japan, especially in Kochi Prefecture. The percentage of the population aged 65 and older was greater than 30% in three of 11 cities and in 21 of 24 towns in Kochi prefecture.[9] Considering public health results and financial conditions, community-based strategies to prevent disease and promote health of older adults are urgently needed in each community. In conclusion, community-based and field-setting geriatric assessment and preventive intervention may be extremely beneficial for health promotion of older adults and financial efficiency.

Kozo Matsubayashi, MD, PhD
Taizo Wada, MD, PhD
Center for Southeast Asian Studies
Kyoto University
Kyoto, Japan

Masayuki Ishine, MD
Ryota Sakamoto, MD, PhD
Kiyohito Okumiya, MD, PhD
Research Institute for Humanity and Nature
Kyoto, Japan

Motonao Ishikawa, MD, PhD
Gaku Yamanaka, MD, PhD
Naomune Yamamoto, MD, PhD
Kuniaki Otsuka, MD, PhD
Medical Center East
Tokyo Women's Medical University
Tokyo, Japan

Masanori Nishinaga, MD, PhD
Yoshinori Doi, MD, PhD
Department of Geriatrics and Medicine
Kochi University
Kochi, Japan

Shogo Murakami, MD, PhD
First Department of Internal Medicine
Osaka Medical College
Osaka, Japan

Michiko Fujisawa, MD, PhD
Wildlife Research Center
Kyoto University
Kumamoto, Japan

Shoki Yano, MD, PhD
Hokkaido Institute of Public Health
Sapporo, Japan

ACKNOWLEDGMENTS

We cordially thank all of the elderly participants and governmental and nongovernmental staff in Tosa Town. Field medical works were partly supported by the Grant-in-Aid of JSPS Global COE Program (E-04): In Search of Sustainable Humanosphere in Asia and Africa, and by a research project of Human Life, Aging, Disease in High Altitude Environments: Physiological-medical, ecological and cultural adaptation in great "highland civilizations" in Research Institute for the Humanity and Nature.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Kozo Matsubayashi and Masayuki Ishine: study design and preparation of letter. Taizo Wada, Ryota Sakamoto, Kiyohito Okumiya, Motonao Ishikawa, Gaku Yamanaka, Naomune Yamamoto, Kuniaki Otsuka, Masanori Nishinaga, Yoshinori Doi, Shogo Murakammi, and Mihiko Fujisawa: field studies and analysis, interpretation, and discussion of data. Shoki Yano: arrangement of field settings in Tosa Town.

Sponsor's Role: None.

REFERENCES

1. Matsubayashi K, Okumiya K, Wada T et al. Improvement in self-care independence may lower the increasing rate of medical expenses for the community-dwelling older people in Japan. J Am Geriatr Soc 1998;46:1484–1485.
2. Ishimoto Y, Wada T, Hirosaki M et al. Health-related differences between participants and nonparticipants in community-based geriatric examinations. J Am Geriatr Soc 2009;57:360–362.
3. Fujisawa M, Ishine M, Okumiya K et al. Trends in diabetes. Lancet 2007; 369:1257–1257.
4. Okumiya K, Ishine M, Wada T et al. Lifestyle changes after oral glucose tolerance test improve glucose intolerance in community-dwelling elderly people after 1 year. J Am Geriatr Soc 2008;56:767–769.
5. Ishine M, Okumiya K, Hirosaki M et al. Prevalence of hypertension and its awareness, treatment, and satisfactory control through treatment in elderly Japanese. J Am Geriatr Soc 2008;56:374–375.
6. Kimura Y, Wada T, Ishine M et al. Food diversity is closely associated with activities of daily living, depression, and quality of life in community-dwelling elderly people. J Am Geriatr Soc 2009;57:922–924.

7. Ishimoto Y, Wada T, Hirosaki M et al. Age and sex significantly influence fall risk in community-dwelling elderly people in Japan. J Am Geriatr Soc 2009; 57:930–932.
8. Wada T, Ishimoto Y, Hirosaki M et al. Twenty-one-item fall risk index predicts falls in community-dwelling Japanese elderly. J Am Geriatr Soc 2009;57: 2369–2371.
9. Central Office of Kochi Prefecture. [on-line]. Available at http://www.pref.kochi.lg.jp/ (in Japanese) Accessed August 2009.

GERO-ECONOMICS

To the Editor: Dear Congressional Representative and Program Administrator:

Not being an economist I hesitated to venture into the fray, but a geriatrician who could provide a different perspective might clarify, at least a bit, the debate about how to fund our healthcare system and the retirement years. The purpose of a national healthcare plan and a national retirement package is to maximize each individual's function and quality of life throughout the full span of life. We must recognize that healthcare and retirement needs are intertwined.

As most readers of this *Journal* know, the age of 65 as a starting point for the beginning of "old age" has no basis in physiology. Politicians, rather than scientists or physicians, were responsible for making that decision in the 19th and early 20th centuries. In those times, life expectancy was far shorter than it is today, assuring planners that relatively few would achieve the distinction of being elderly. Therefore, the costs of a national healthcare system and a national retirement system would have been modest. It was only after life expectancy at birth in the developed nations increased from approximately 47 years to almost 80 years that funding these programs became a significant issue.

To be successful and cost efficient, it is necessary for the designers of healthcare and retirement programs to have an appreciation of the aging process and the advent of chronic illness. Aging may be viewed as a process characterized by a diminution in reserve capacity in most organ systems, albeit to a different degree in each and with considerable variation from person to person. In addition, over the course of a lifetime, most of us accumulate a number of chronic diseases. Diabetes mellitus, arthritis, hypertension, coronary heart disease, cerebrovascular disease, and even many cancers are appropriately viewed as chronic conditions, rather than acute illnesses, under most circumstances. Such illnesses diminish the reserve capacity further.

The changes associated with aging and chronic illness cause the elderly population to be far from homogeneous. Therefore, perhaps the retirement system could be designed to mesh more closely with the health status of those it is supporting. For example, perhaps there might be an option for a perfectly well 65-year-old to receive a considerably smaller retirement benefit between the ages of 65 and 75 and a considerably larger benefit during the years that follow. This would allow that person to have some money early on but far more money when that individual might need the funds to remain independent or to reside at home. This might also decrease the costs to Medicaid, the funding source for the majority of nursing home beds.

Furthermore, as a long-time practicing geriatrician, I can assure you that there are innumerable opportunities to save money in the healthcare system and improve the outcomes for older adults at the same time. Many incentives in the healthcare system foster unnecessary costs, not to mention poor clinical outcomes. Payment for many procedures is outrageously excessive compared with payment for the comprehensive evaluation of an older adult with multiple chronic illnesses.[1] Payment for preventive health measures is often inadequate. Unnecessary testing and hospitalization are associated with huge costs. How often does a physician order multiple studies and admit an older adult to a hospital for fear of charges of malpractice? Are not huge numbers of admissions for congestive heart failure, pneumonia, and many of the other most common conditions unnecessary?[2,3] If we were able to eliminate some of the waste in the healthcare system, we could add those savings to more-effective healthcare programs and the associated retirement programs.

Geriatric medicine is coming to have an influence on other medical specialties from general surgery to emergency medicine. Perhaps it should influence some of our associates in economics as well as those concerned with healthcare and retirement planning.

R. Knight Steel, MD
Hackensack University Medical Center
Division of Geriatrics
Hackensack, NJ

ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the author and has determined that the author has no financial or any other kind of personal conflicts with this paper.

Author Contributions: The author wrote the entire letter.

Sponsor's Role: None.

REFERENCES

1. Steel RK. Please lend a hand. J Roy Soc Med 2007;100:528.
2. Leff B, Burton L, Mader SL et al. Hospital at home feasibility and outcomes of a program to provide hospital-level care at home for acutely ill older patients. Ann Intern Med 2005;143:798–808.
3. Leff B, Burton L, Mader SL et al. Comparison of stress experienced by family members of patients treated in hospital at home with that of receiving traditional acute hospital care. J Am Geriatr Soc 2008;56:117–123.

SOUND-ALIKE SYNDROMES REVISITED

To the Editor: A year ago I wrote of a newly described concern, "Sound-Alike Syndromes" when one of our facility's new admissions suffered from Morvan's syndrome when Marfans was expected.[1] Much to my surprise, another example appeared, this time to my amusement.

A 95-year-old resident of our facility was admitted to a local medical center after a syncopal episode of unclear

Plasma Adiponectin Levels and Left Ventricular Remodeling in Hypertrophic Cardiomyopathy

Hiroaki KITAOKA,[1] MD, Toru KUBO,[1] MD, Makoto OKAWA,[1] MD, Naohito YAMASAKI,[1] MD, Yoshihisa MATSUMURA,[1] MD, Masanori NISHINAGA,[1] MD, *and* Yoshinori L. DOI,[1] MD

SUMMARY

Adiponectin, which is an adipose-derived protein with antiatherosclerogenic activities, has been reported to be elevated in patients with heart failure. However, there are no reports on the significance of adiponectin in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to elucidate the clinical significance of plasma adiponectin levels in HCM patients.

Clinical characteristics, echocardiographic parameters, and levels of plasma B-type natriuretic peptide (BNP) and adiponectin were evaluated in 106 HCM patients. The plasma adiponectin levels were 10.8 ± 6.3 (range, 2.7-37.3) μg/mL. Plasma adiponectin levels were positively related to age and inversely related to body mass index (BMI). Among echocardiographic parameters, % fractional shortening (r = -0.20, P = 0.03) and maximum LV wall thickness (r = -0.23, P = 0.02) were inversely related to plasma adiponectin levels. A significant correlation between plasma adiponectin levels and BNP levels was also observed (r = 0.27, P = 0.005). In multivariate analysis, BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels.

Plasma adiponectin levels are associated with impaired LV systolic function in HCM patients, but not with the LV outflow gradient. Together with BNP, adiponectin can be a useful biomarker for assessing disease severity in HCM patients. (Int Heart J 2010; 51: 51-55)

Key words: Hypertrophic cardiomyopathy, Adiponectin, B-type natriuretic peptide, LV remodeling, Heart failure

Hypertrophic cardiomyopathy (HCM), a relatively prevalent genetic cardiac disease caused by mutations in genes encoding sarcomere proteins, is clinically defined as left ventricular (LV) hypertrophy with heterogeneous clinical and morphological features in the absence of other cardiovascular diseases.[1,2] The clinical and morphological features are diverse and the natural history varies from an asymptomatic and benign clinical course to sudden premature death.[3-5]

Biomarkers are molecules that are objectively measured by laboratory techniques, which can give us useful information in patients with cardiovascular disease, including HCM.[6] Adipocytokine adiponectin is an adipose-derived protein and shows antiatherosclerogenic and insulin-sensitizing effects. The low plasma levels of adiponectin are associated with type 2 diabetes and ischemic heart disease.[7-11] Moreover, the novel cardiovascular effects of adiponectin have attracted considerable attention in patients with LV hypertrophy and chronic heart failure.[12-16] However, the significance of adiponectin has not yet been evaluated in patients with HCM. The purpose of this study was to elucidate the significance of plasma adiponectin levels in HCM.

METHODS

Patients and study protocol: The study group included 106 patients with HCM diagnosed based on echocardiographic demonstration of a hypertrophied left ventricle (maximum wall thickness ≥ 15 mm) in the absence of systemic hypertension or other cardiac disease that could produce the magnitude of evident hypertrophy. Clinical characteristics, and electrocardiographic, echocardiographic and laboratory findings were determined for all patients during a clinically stable period. Patients with renal failure (serum creatinine ≥ 2.0 mg/dL), myocardial infarction or malignancy were excluded from the study. The study protocol was approved by the Ethics Committee on Medical Research at our institute and written informed consent was provided by all patients.

Echocardiography: Echocardiographic studies were performed using a Sequoia 512 (Mountain View, CA, USA). The dimensions of the left ventricle and the left atrium were measured and the magnitude and distribution of LV hypertrophy were assessed from two-dimensional images. The greatest wall thickness measured at any site in the left ventricle was regarded as the maximum thickness. The LV outflow pressure gradient was also measured using a continuous-wave Doppler under basal conditions.

Based on echocardiographic findings, the morphologic

From the [1] Department of Medicine and Geriatrics, Kochi Medical School, Kochi, Japan.

Address for correspondence: Hiroaki Kitaoka, MD, Department of Medicine and Geriatrics, Kochi Medical School, Oko-cho, Nankoku-shi, Kochi 783-8505, Japan.

Received for publication July 13, 2009.

Revised and accepted August 31, 2009.

subtype of HCM was defined as 1) *obstructive* (LV outflow gradient of ≥ 30 mmHg), 2) *nonobstructive*, 3) *apical* (LV wall thickening confined to the most distal region at the apex below the papillary muscle level), and 4) *dilated phase* (LV systolic impairment defined as % fractional shortening of < 25%).

Moreover, 79 patients with preserved LV systolic function were studied by tissue Doppler imaging (TDI) to evaluate the relationship between plasma adiponectin levels and diastolic function. The peak velocity of early (E) and late (A) waves and the E/A ratio were determined from transmitral flow velocity using an apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets during diastole. Tissue Doppler velocity was measured during early diastole (Ea) at the septal and lateral corners of the mitral annulus from the apical 4-chamber view by positioning the sample volume at the lateral margin of the mitral annulus. Finally, the septal and lateral E/Ea ratio was also calculated.[17]

Laboratory measurements: Peripheral venous blood samples were collected from the antecubital vein after the patients had remained supine for at least 15 minutes without discontinuing drugs. The plasma adiponectin level was measured using a sandwich enzyme-linked immunosorbent assay system (adiponectin ELISA kit, Otsuka Pharmaceutical Co., Japan). In addition, the plasma BNP level was also measured using an enzyme immunoassay (TOSOH II(BNP), TOSOH Co., Japan).

Statistical analysis: Data are presented as the mean ± SD. The nonparametric Wilcoxon rank-sum test was used to compare plasma adiponectin levels between two groups. Variables with non-normal distribution were transformed logarithmically. Correlations between plasma adiponectin levels and other variables were evaluated using univariate linear regression analysis. By forward stepwise multiple regression analysis, parameters that were associated with plasma adiponectin at the level of $P < 0.10$ on univariate analysis were analyzed. Analysis of variance (ANOVA) was used for comparison between groups and the significances of individual differences were evaluated by Tukey's HSD procedure if ANOVA was significant. A level of $P < 0.05$ was considered to indicate statistical significance.

Table I. Relationship Between Plasma Adiponectin Level and Echocardiographic Variables in All Patients

Variable	Mean ± SD	r	P
LV end-diastolic dimension (mm)	46 ± 6	0.07	0.47
LV end-systolic dimension (mm)	27 ± 7	0.20	0.04
%fractional shortening (%)	41 ± 8	-0.20	0.03
Left atrial dimension (mm)	45 ± 7	0.10	0.28
Maximum LV wall thickness (mm)	20 ± 4	-0.23	0.02

SD indicates standard deviation; and LV, left ventricular.

Results

Patient characteristics: The patients were aged 63 ± 13 years and 69 (65%) were male. Body mass index (BMI) was 24.2 ± 2.8 kg/m^2 and 43 patients (41%) had a BMI of > 25 kg/m^2. Most of the patients had no or mild symptoms and 7 (7%) had symptoms of severe heart failure (New York Heart Association functional class III). Thirty-six patients (34%) had a family history of HCM. Patients had the following HCM subtypes: obstructive (n = 10), nonobstructive (non-apical) (n = 67), apical (n = 24), and dilated phase (n = 5). Of these 106 patients, 47 were administered beta-blockers and 35 were taking calcium antagonists. In addition, 30 patients were taking either angiotensin converting enzyme inhibitors or angiotensin receptor blockers for mild systemic hypertension or heart failure due to LV systolic impairment. None had been prescribed PPAR-γ agonists.

Adiponectin levels and clinical characteristics: The mean plasma adiponectin level of the patients was 10.8 ± 6.3 (range, 2.7-37.7) μg/mL. The mean adiponectin level in females was higher than that in males (13.1 ± 6.9 μg/mL versus 9.6 ± 5.6 μg/mL, P = 0.002). Plasma adiponectin levels were positively related to age (r = 0.22, P = 0.02) and inversely related to BMI (r = -0.27, P = 0.004). Nineteen patients with atrial fibrillation showed higher plasma adiponectin levels compared to those with sinus rhythm (14.6 ± 9.2 μg/mL versus 10.0 ± 5.2 μg/mL, P = 0.03). The

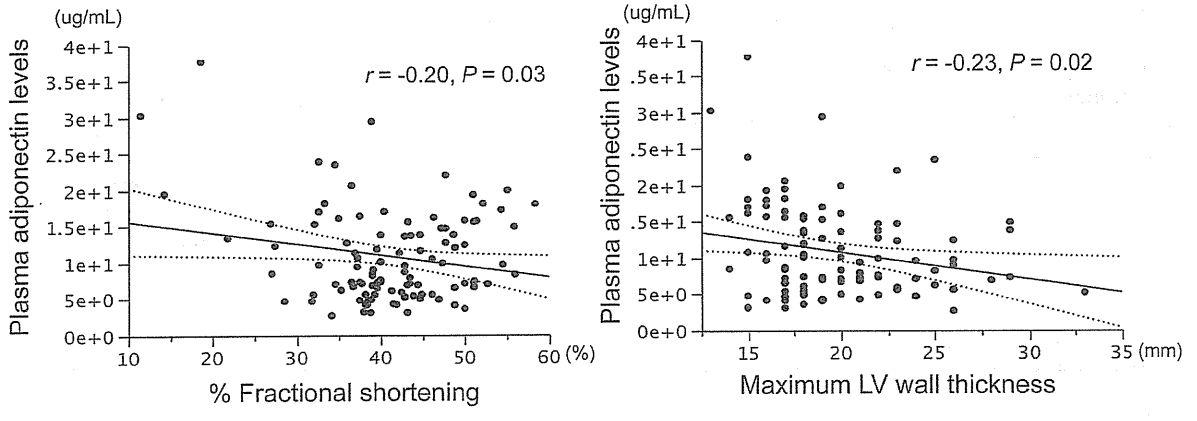

Figure 1. Relationship between plasma adiponectin levels and echocardiographic parameters such as % fractional shortening and maximum left ventricular (LV) wall thickness. The dotted lines represent the 95% confidence limit for the fitted line.

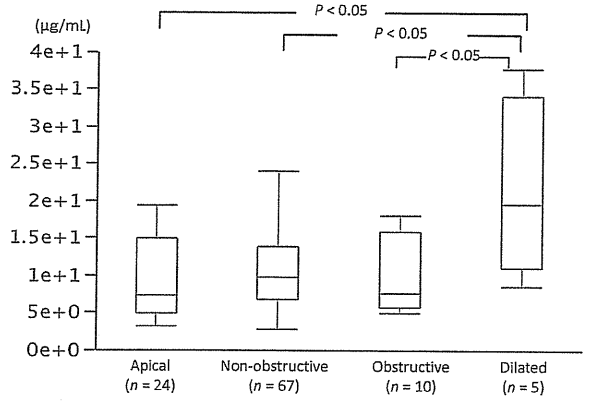

Figure 2. Comparison of plasma adiponectin levels in subtypes of hypertrophic cardiomyopathy. Adiponectin levels were higher in dilated HCM than in other subtypes of HCM.

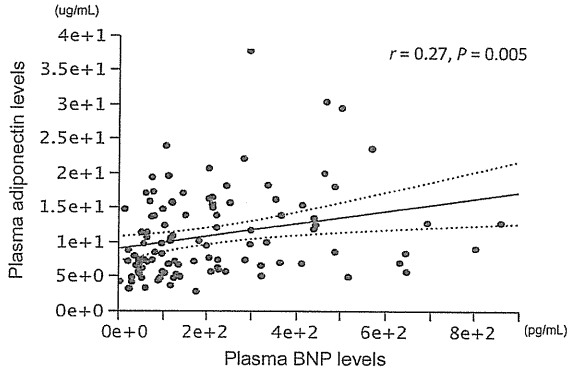

Figure 3. Relationship between plasma adiponectin levels and BNP levels. The dotted lines represent the 95% confidence limit for the fitted line.

plasma adiponectin levels in 7 patients with severe heart failure symptoms were slightly higher than those in patients with no or mild symptoms (13.8 ± 8.6 μg/mL versus 10.6 ± 6.1 μg/mL, P = NS). The plasma adiponectin levels did not differ according to the drug administered, including beta-blockers, calcium antagonists, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Adiponectin levels and echocardiographic findings: Table I shows the relationship between the plasma adiponectin levels and echocardiographic parameters in all patients. The plasma adiponectin levels were positively related to LV end-systolic dimension, and inversely related to % fractional shortening and maximum LV wall thickness (Figure 1). The plasma adiponectin levels in obstructive HCM did not differ from that in other subtypes of HCM (10.9 ± 6.3 μg/mL versus 10.0 ± 5.2 μg/mL, P = NS). As a consequence, plasma adiponectin levels in patients with dilated HCM were significantly higher than those in patients with other HCM subtypes (Figure 2).

Relation between plasma levels of adiponectin l and BNP: The mean plasma BNP level was 211 ± 187 (range, 4-861) pg/mL. Plasma BNP levels were positively related to plasma adiponectin levels (Figure 3).

Table II. Stepwise Multiple Regression Analysis in All Patients

Variable	F	P
Age	1.39	0.24
Gender (male 1)	3.05	0.08
BMI	8.95	0.003
% Fractional shortening	6.04	0.01
Maximum LV wall thickness	3.27	0.07
Plasma BNP levels	8.14	0.005

BMI indicates body mass index; and BNP, B-type natriuretic peptide.

Table III. Stepwise Multiple Regression Analysis in Patients With Preserved LV Systolic Function

Variable	F	P
Age	6.04	0.16
Gender (male 1)	2.98	0.08
BMI	3.23	0.07
Septal E/Ea	1.14	0.29
Plasma BNP levels	3.26	0.08

LV indicates left ventricular; BMI, body mass index; E, peak velocity of early (E) waves determined from transmitral flow velocity; Ea, early diastole velocity at the corners of the mitral annulus by tissue Doppler imaging; and BNP, B-type natriuretic peptide.

Multivariate analysis: Forward stepwise multiple regression analysis showed that BMI, % fractional shortening, and plasma BNP levels were independent predictors of plasma adiponectin levels (Table II).

Diastolic dysfunction and plasma adiponectin levels in patients with preserved LV systolic function: There were no significant correlations between plasma adiponectin levels and conventional echocardiographic parameters in patients with preserved LV systolic function. Plasma adiponectin levels were significantly related to septal E/Ea ratio (r = 0.24, P = 0.03) and plasma BNP levels (r = 0.25, P = 0.01). However, by multivariate analysis, septal E/Ea was not an independent predictor of plasma adiponectin levels (Table III).

Discussion

To the best of our knowledge, this is the first report to describe the significance of plasma adiponectin in patients with HCM. The main finding of this study is that the levels of plasma adiponectin were related to LV systolic impairment due to LV remodeling in patients with HCM.

Adiponectin and LV systolic impairment: Measurement of biomarkers such as neurohormones, inflammatory biomarkers, and metabolic biomarkers can help in understanding the pathophysiology of cardiovascular disease.[18] For example, circulating levels of BNP constitute an established predictor of outcome in patients with chronic heart failure

associated with acquired cardiac disease. Recently, metabolic biomarkers have gained attention in various cardiovascular diseases. Adiponectin is an antiatherosclerogenic and insulin-sensitizing protein comprising 247 amino acids produced by white adipose tissue. It is abundant in circulating plasma, with concentrations between 5-10 μg/mL in humans. Adiponectin is related to type 2 diabetes, essential hypertension, and ischemic heart disease.[7-11,16] Interestingly, several investigators have recently found elevated plasma adiponectin levels in patients with heart failure, and have suggested that it might be a prognostic predictor.[12-14] Tsutamoto and colleagues identified elevated plasma adiponectin levels in patients with chronic heart failure and found that it was an independent prognostic predictor.[14] Although the precise mechanism of elevation of adiponectin is unclear in patients with heart failure, the following explanations can be considered.[19,20] Firstly, progression to severe heart failure is often associated with weight loss, which results in an increase in the plasma adiponectin level. Secondly, mRNA and protein expression of the adiponectin receptor adipoR1 is increased in the left ventricle of the infarcted, compared with the normal mouse heart. Moreover, adiponectin-knockout mice develop exacerbated LV dilatation, myocyte hypertrophy, and contractile dysfunction after myocardial infarction compared with wild-type mice.[21] Therefore, adiponectin might protect the heart from LV remodeling, although it is unclear whether or not high adiponectin levels are a compensatory mechanism.

The clinical and pathological characteristics of HCM involve a number of diverse mechanisms. Therefore, measurement of biomarkers may be useful to assess the pathophysiology, disease severity, and prognosis in HCM. For example, it has been reported that plasma BNP and N-terminal proBNP levels are related to heart failure symptoms and might be related to prognosis in patients with HCM.[22,23] Plasma BNP levels are affected by several factors such as LV outflow tract gradient, LV wall thickness, LV diastolic function, and LV systolic impairment.[24,25]

However, there are no reports on the significance of adiponectin in HCM. We found here that the plasma adiponectin levels were not affected by the LV outflow gradient and were independently related to LV systolic impairment due to LV remodeling. A significant proportion (5-10%) of patients with HCM progress to LV systolic impairment due to LV remodeling (so called dilated HCM or end-stage HCM).[26-28] To recognize this clinical entity is important because this subgroup of patients develops refractory heart failure and has a poor prognosis. A precise explanation for the relationship between LV systolic impairment and high plasma adiponectin levels in HCM is difficult in our study. However, a recent report showed the natriuretic peptides (atrial natriuretic peptide and BNP) enhance adiponectin production by human adipocytes both *in vivo* and in patients with heart failure.[29] As we have shown, plasma adiponectin levels were related to plasma BNP levels in this study. Therefore, plasma adiponectin levels might be partially regulated by plasma BNP levels also in patients with HCM.

In conclusion, plasma adiponectin levels can be a useful marker, particularly with other biomarkers such as BNP, for assessing disease severity such as a decline in LV systolic function in patients with HCM.

Study limitations: Several limitations are associated with this study. Firstly, the adiponectin level was measured only at one point. Secondly, angiotensin converting enzyme inhibitors or angiotensin receptor blockers were prescribed for some patients due to mild systemic hypertension or LV systolic dysfunction. Previous studies have shown that angiotensin converting enzyme inhibitors or angiotensin receptor blockers increased the plasma adiponectin levels and the effect of beta-blockers is controversial.[30-31] Therefore, it could not be ruled out that plasma adiponectin levels were influenced by the medication, although we did not identify any statistically significant relationship between them.

Adiponectin has been reported to modulate hypertrophic signals and be related to diastolic function in patients with hypertension.[15,16] Therefore, it would be interesting to determine whether plasma adiponectin levels affect the degree of LV hypertrophy, LV mass, and LV diastolic function in patients with HCM. In this study using echocardiography, plasma adiponectin levels were inversely related to maximum LV thickness in all patients, but were not related to LV wall thickness in patients with preserved LV systolic function. Moreover, plasma adiponectin levels were not related to diastolic dysfunction assessed by TDI by multivariate analysis, although it was weakly related to septal E/Ea by univariate analysis. However, echocardiography including TDI is limited to assess LV mass and LV diastolic function in HCM.[32] Cardiac magnetic resonance is a useful tool with which to assess LV mass and myocardial fibrosis in HCM.[33,34] Therefore, further investigations are warranted to elucidate the significance and mechanisms of adiponectin for LV hypertrophy and diastolic dysfunction in patients with HCM.

References

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002; 287: 1308-20. (Review)
2. Elliot P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet 2004; 363: 1881-91.
3. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995; 26: 1699-708.
4. Maron BJ, Olivotto I, Spirito P, *et al.* Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000; 102: 858-64.
5. Cecchi F, Olivotto I, Betocchi S, *et al.* The Italian Registry for hypertrophic cardiomyopathy: a nationwide survey. Am Heart J 2005; 150: 947-54.
6. Cambronero F, Marín F, Roldán V, Hernández-Romerp D, Valdés M, Lip GY. Biomarkers of pathophysiology in hypertrophic cardiomyopathy: implications for clinical management and prognosis. Eur Heart J 2009; 30: 139-51. (Review)
7. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions, J Am Coll Cardiol 2007; 49: 531-8. (Review)
8. Kumada M, Kihara S, Sumitsuji S, *et al.* Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003; 23: 85-9.
9. Hotta K, Funahashi T, Arita Y, *et al.* Plasma concentration of a

novel adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20: 1595-9.
10. Hotta K, Funahashi T, Bodkin NL, *et al.* Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001; 50: 1126-33.
11. Lindsay RS, Funahashi T, Hanson RL, *et al.* Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360: 57-8.
12. Kistorp C, Faber J, Galatius S, *et al.* Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005; 112: 1756-62.
13. George J, Patal S, Wexler D, *et al.* Circulating adiponectin concentrations in patients with congestive heart failure. Heart 2006; 92: 1420-4.
14. Tsutamoto T, Tanaka T, Sakai H, *et al.* Total and high molecular weight adiponectin, hemodynamics, and mortality in patients with chronic heart failure. Eur Heart J 2007; 28: 1723-30.
15. Shibata R, Ouchi N, Ito M, *et al.* Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med 2004; 10: 1384-9.
16. Hong SJ, Park CG, Seo HS, Oh DJ, Ro YM. Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index. Blood Press 2004; 13: 236-42.
17. Sohn D, Chai I, Lee DJ, *et al.* Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474-80.
18. Tang WH, Francis GS, Morrow D, *et al.* National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007; 116: e99-109.
19. Kintscher U. Does adiponectin resistance exist in chronic heart failure? Eur Heart J 2007; 28: 1676-7.
20. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007; 73: 298-309. (Review)
21. Shibata R, Izumiya Y, Sato K, *et al.* Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol 2007; 42: 1065-74.
22. 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: 984-9.
23. Mutlu B, Bayrak F, Kahveci G, Degertekin M, Eroglu E, Basaran Y. Usefulness of N-terminal pro-B-type natriuretic peptide to predict clinical course in patients with hypertrophic cardiomyopathy. Am J Cardiol 2006; 98: 1504-6.
24. Nishigaki K, Tomita M, Kagawa K, *et al.* Marked expression of plasma brain natriuretic peptide is a special feature of hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 1996; 28: 1234-42.
25. Briguori C, Betocchi S, Manganelli F, *et al.* Determinants and clinical significance of natriuretic peptides in hypertrophic cardiomyopathy. Eur Heart J 2001; 22: 1328-36.
26. Thaman R, Gimeno JR, Murphy RT, *et al.* Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart 2005; 91: 920-5.
27. Harris KM, Spirito P, Maron MS, *et al.* Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006; 114: 216-25.
28. Kitaoka H, Kubo T, Okawa M, Hitomi N, Furuno T, Doi YL. Left ventricular remodeling of hypertrophic cardiomyopathy: longitudinal observation in rural community. Circ J 2006; 70: 1543-9.
29. Tsukamoto O, Fujita M, Kato M, *et al.* Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. J Am Coll Cardiol 2009; 53: 2070-7.
30. Furuhashi M, Ura N, Higashiura K, *et al.* Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 2003; 42: 76-81.
31. Yamaji M, Tsutamoto T, Tanaka T, *et al.* Effect of carvedilol on plasma adiponectin concentration in patients with chronic heart failure. Cir J 2009; 73: 1067-73.
32. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation 2007; 116: 2702-8.
33. Olivotto I, Maron MS, Autore C, *et al.* Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2008; 52: 559-66.
34. Nagueh SF, Mahmarian JJ. Noninvasive cardiac imaging in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2006; 48: 2410-22. (Review)

Geriatr Gerontol Int 2010; **10:** *219–224*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors prevent the progression of renal dysfunction in Japanese hypertensive patients

Masanori Kuwabara,[1] Toru Kubo,[2] Kanji Bando,[1] Yoko Hirakawa,[1] Hiroaki Kitaoka,[2] Masanori Nishinaga[2] and Yoshinori L Doi[2]

[1]*Department of Cardiovascular Medicine, Tosa Municipal Hospital, and* [2]*Department of Medicine and Geriatrics, Kochi Medical School, Kochi, Japan*

Aim: The aim was to determine whether the use of statins prevents the progression of chronic kidney disease (CKD) in hypertensive patients.

Methods: We retrospectively reviewed data obtained from hypertensive patients, and subjects with diabetes mellitus and those undergoing hemodialysis were excluded. At total of 227 patients were enrolled (83 men, mean age 73 years) and 90% of the patients were of CKD stage 2 or 3. The patients were divided into two groups: those treated with statins ($n = 93$) and those not treated with statins ($n = 134$). Renal function was evaluated by estimated glomerular filtration rate (eGFR).

Results: The statin group and the non-statin group were similar in age, sex, blood pressure, follow-up period and prescriptions of antihypertensive medicines. The eGFR in the statin group increased from 62 ± 14 to 66 ± 15 (mL/min per 1.73 m^2), whereas it decreased in the non-statin group from 69 ± 16 to 64 ± 18 (mL/min per 1.73 m^2). The annual eGFR improved in the statin group (2.5 ± 6.6 mL/min per 1.73 m^2/year), but decreased in the non-statin group (–3.3 ± 6.6 mL/min per 1.73 m^2/year) ($P < 0.001$). When the patients were divided into two groups by low-density lipoprotein (LDL) cholesterol levels at the second evaluation, annual eGFR improved in the group of LDL to below 100 mg/dL ($n = 99$) (0.4 ± 7.2 mL/min per 1.73 m^2/year), but decreased in the other group ($n = 128$) (–1.9 ± 7.0 mL/min per 1.73 m^2/year) ($P = 0.018$).

Conclusion: Lipid-lowering intervention with statins inhibits the progression of CKD in hypertensive patients. **Geriatr Gerontol Int 2010; 10: 219–224.**

Keywords: chronic kidney disease, hypertension, statins.

Introduction

The prevalence of chronic kidney disease (CKD) in developed countries, particularly in elderly people, is increasing.[1–4] According to the previous study, the prevalence is increasing in both men and women, which raises concern about future increases in renal failure and associated complications of CKD.[4–7] Although risk factors such as hypertension, diabetes and dyslipidemia seem to be linked to both renal and cardiovascular diseases, CKD has been shown to be an independent risk factor for the development and progression of cardiovascular disease.[5–10]

Administration of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, has become a

Accepted for publication 10 December 2009.

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

fundamental therapy in the management of patients with dyslipidemia. Previous large randomized trials have shown the benefits of statins for prevention of primary and secondary cardiovascular events.[11–13] Furthermore, although it had remained unclear whether the high mortality and morbidity rates in patients with CKD could be improved, several recent studies have shown that statins reduced major fatal and non-fatal cardiovascular event rates even in patients with CKD.[14,15] However, there are few reports concerning the inhibitory effect of statins on CKD progression, particularly in hypertensive patients.[16–19]

The purpose of this study was to determine whether the use of statins prevents the progression of renal dysfunction in hypertensive patients.

Methods

Subjects

We retrospectively reviewed data obtained from hypertensive patients who underwent serial blood examinations at least 12 months apart in Tosa Municipal Hospital, Kochi Prefecture, Japan. The study period was from April 2004 to March 2008. Subjects with diabetes mellitus and those undergoing hemodialysis were excluded. A total of 227 patients were enrolled as the subjects of this study. The study was approved by the Ethics Committee on Medical Research of Tosa Municipal Hospital.

Clinical evaluation

Renal function was evaluated by estimated glomerular filtration rate (eGFR). We estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula: $0.741 \times 175 \times \text{age}^{-0.203} \times \text{Cr}^{-1.154} \times 0.742$ (if female), where age is in years, creatinine (Cr) is in mg/dL, and GFR is in mL/min per 1.73 m^2 body surface area. Annual rate of change in eGFR was calculated by: (eGFR at follow up – eGFR at initial evaluation) × 12/eGFR at initial evaluation × interval (months).

The patients were divided into two groups: those treated with statins (statin group, $n = 93$) and those not treated with statins (non-statin group, $n = 134$). Use of statins was determined from patients' charts. Initiation of treatment with a lipid-lowering agent was performed at the discretion of the patient's primary physician. Furthermore, the statin group were divided into two groups: one group of patients who had already been treated with a statin before initial evaluation of this study (statin group A, $n = 60$) and one group of patients who commenced treatment after initial evaluation (statin group B, $n = 33$). The agents used, numbers of patients and daily doses were as follows: atorvastatin (10 mg/day), $n = 30$; rosuvastatin (2.5 mg/day), $n = 43$; and simvastatin (5 mg/day), $n = 20$.

Data analysis

All data are expressed as means ± standard deviation or frequencies (percentage). Differences in continuous variables were assessed using the Student's *t*-test. Pearson's χ^2-test was used for comparisons between non-continuous variables, and Fisher's exact test was used when expected frequency was lower than 5. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS ver. 14.0J.

Results

Study population

Clinical characteristics of the patients are shown in Table 1. A total of 227 patients (83 men and 144 women) were enrolled. The mean age of the patients was 73 ± 10 years. The majority of the patients (90%) were of CKD stage 2 (estimated GFR of 60–89.9 mL/min per 1.73 m^2) or stage 3 (estimated GFR of 30–59.9 mL/min per 1.73 m^2). The statin group and the non-statin group were similar in age, sex, blood pressure, follow-up period and prescriptions of antihypertensive medicines, including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB), calcium channel blockers, beta-blockers, alpha-blockers and diuretics. In the statin group, eGFR was lower than in the non-statin group at the initial evaluation. The two groups were similar in low-density lipoprotein (LDL) cholesterol levels at the initial evaluation, but LDL cholesterol level in the statin group was significantly lower than that in the non-statin group at the second evaluation. Coronary heart disease was observed in more patients in the statin group.

Annual changes in eGFR

As shown in Table 1, eGFR in the statin group increased from 62 ± 14 to 66 ± 15 mL/min per 1.73 m^2 ($P < 0.001$), whereas it decreased in the non-statin group from 69 ± 16 to 64 ± 18 mL/min per 1.73 m^2 ($P < 0.001$). The annual eGFR improved in the statin group (2.5 ± 6.6 mL/min per 1.73 m^2/year) but decreased in the non-statin group (–3.3 ± 6.6 mL/min per 1.73 m^2/year) ($P < 0.001$) (Fig. 1). Among three statins, annual changes in eGFR of atorvastatin, rosuvastatin and simvastatin were 4.7 ± 7.3, 1.6 ± 6.3 and 1.2 ± 5.7 mL/min per 1.73 m^2/year, respectively (statistically no significant difference).

In 139 patients of CKD stage 2, annual eGFR improved in the statin group (2.6 ± 6.9 mL/min per

Table 1 Clinical characteristics of 227 hypertensive patients

	Patients with statin (n = 93)	Patients without statin (n = 134)	P
Age, years	72.6 ± 8.4	72.9 ± 10.9	0.959
Sex: male, n (%)	31 (33%)	52 (39%)	0.400
Initial systolic blood pressure, mmHg	133 ± 18	136 ± 16	0.337
Follow-up interval, months	16 ± 5	18 ± 6	0.113
eGFR at initial evaluation, mL/min per 1.73 m^2	62 ± 14	69 ± 16	0.003
eGFR at second evaluation, mL/min per 1.73 m^2	66 ± 15	64 ± 18	0.382
Creatinine at initial evaluation, mg/dL	0.79 ± 0.21	0.75 ± 0.23	0.160
Creatinine at second evaluation, mg/dL	0.75 ± 0.19	0.82 ± 0.29	0.05
CKD stage 2, n (%)	52 (56%)	87 (65%)	0.212
CKD stage 3, n (%)	33 (35%)	32 (24%)	0.073
LDL at initial evaluation, mg/dL	113 ± 29	114 ± 28	0.673
LDL at second evaluation, mg/dL	93 ± 23	116 ± 29	<0.001
Triglyceride at initial evaluation, mg/dL	143 ± 70	131 ± 67	0.210
Triglyceride at second evaluation, mg/dL	118 ± 54	134 ± 83	0.110
Medication, n (%)			
ACEI/ARB	56 (60%)	80 (60%)	0.938
Calcium antagonist	68 (73%)	94 (70%)	0.657
Beta-blocker	42 (45%)	50 (37%)	0.236
Alpha-blocker	8 (9%)	18 (13%)	0.296
Diuretics	19 (20%)	22 (16%)	0.440
Coronary heart disease, n (%)	35 (38%)	8 (6%)	<0.001
Previous myocardial infarction, n (%)	12 (13%)	1 (1%)	<0.001

Data shown as mean ± standard deviation or number (%). CKD stage 2 = eGFR of 60 to 89.9 mL/min per 1.73 m^2, CKD stage 3 = eGFR of 30 to 59.9 mL/min per 1.73 m^2. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

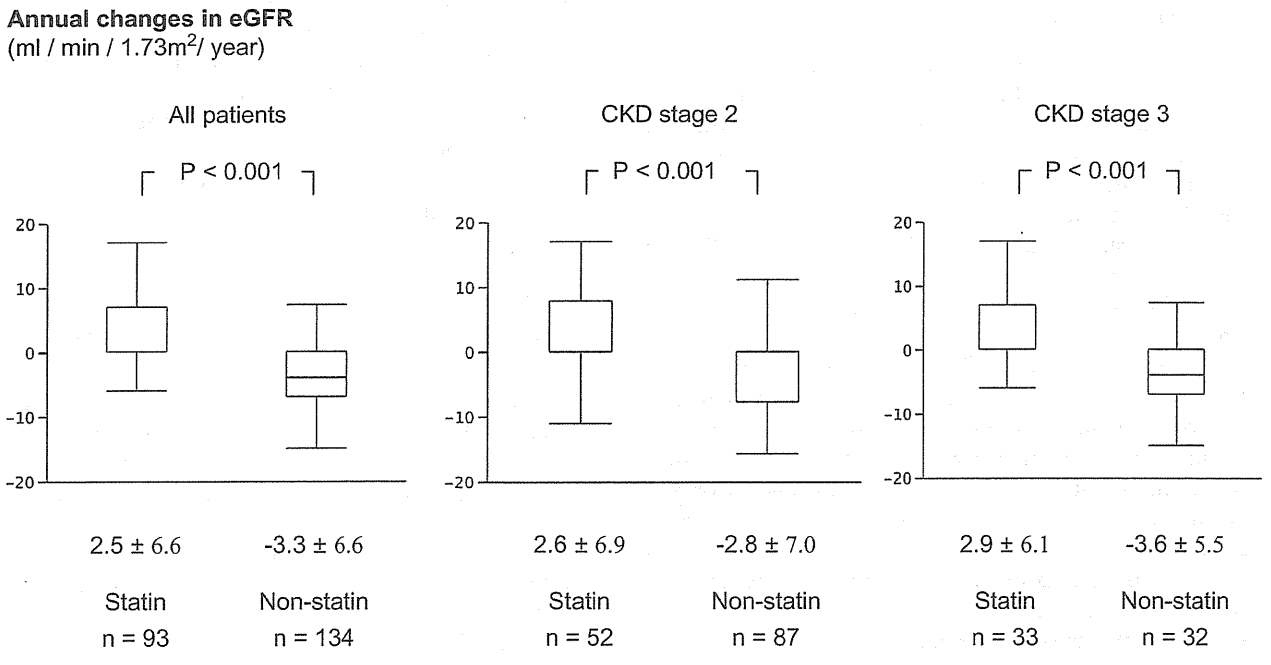

Figure 1 Difference of the annual changes in estimated glomerular filtration rate (eGFR) between the statin and non-statin groups. Data are shown as the means ± standard deviation.

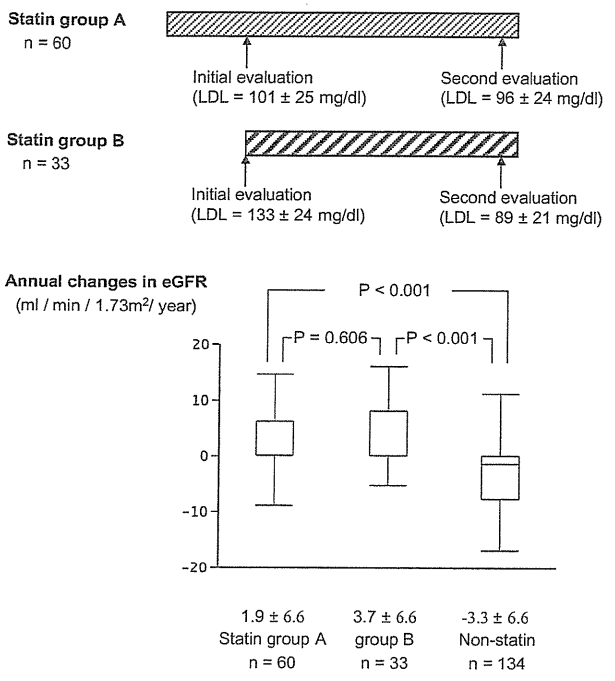

Figure 2 Low-density lipoprotein (LDL) cholesterol levels and the annual estimated glomerular filtration rate (eGFR) in statin groups A and B. Statin group A: patients who had already been treated with a statin before initial evaluation of this study. Statin group B: patients who commenced treatment after initial evaluation. Data of annual changes in eGFR are shown as the means ± standard deviation.

1.73 m^2/year) but decreased in the non-statin group (–2.8 ± 7.0 mL/min per 1.73 m^2/year) ($P < 0.001$) (Fig. 1). Such an effect of statins was observed in 65 patients of CKD stage 3.

As shown in Figure 2, in the statin group B, LDL cholesterol level at the second evaluation (89 ± 21 mg/dL) was significantly lower than that at the initial evaluation (133 ± 24 mg/dL). Both groups had increased annual eGFR and there was no significant difference between the two groups with statins ($P = 0.606$) (Fig. 2).

Annual changes in eGFR by LDL cholesterol levels

To determine whether the effect of improving renal function was lipid lowering, the patients were divided into two groups by LDL cholesterol levels at the second evaluation. Annual eGFR improved in the group of LDL to below 100 mg/dL ($n = 99$) (0.4 ± 7.2) but decreased in the other group ($n = 128$) (–1.9 ± 7.0) ($P = 0.018$) (Fig. 3).

When the patients were divided into two groups by LDL cholesterol levels of below or over 120 mg/dL, both groups reduced annual eGFR and there was no significant difference between the two groups.

Discussion

Chronic kidney disease is a common condition that is associated with variable rates of decline in kidney function.[1–4] CKD is expected to increase in Japan, and the prevalence of CKD in Japan is higher than that in the USA.[1,2,20] This increase is partly due to the increasing prevalence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus and metabolic syndrome.[2,5–10] It has been suggested that dyslipidemia is an important aggravating factor in the progression of renal insufficiency, either by promoting intrarenal atherosclerosis or through direct toxic effects of lipids on renal cells.[21,22] Drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) reduce serum cholesterol levels and are effective in reducing the excess of cardiovascular events.[11–15] Although several recent studies have shown that treatment with statins might reduce proteinuria in glomerular disease and reduce rates of kidney function loss, there have been few studies in which the effect of statins on renal function was investigated in a group of hypertensive patients without diabetes mellitus or coronary heart disease.[16–18] This is the first study showing that the use of statins inhibits the progression of renal dysfunction in Japanese patients with hypertension.

The cohort of the present study consisted of patients with relatively well-controlled hypertension and their clinical conditions were generally stable, though 43 (19%) of the 227 patients had coronary heart disease. Previous myocardial infarction was seen only in 13 (6%) of the patients in our cohort. Antihypertensive medicines used in this study were not different from those used in general clinical practice in Japan. ACEI/ARB and Ca antagonists were predominantly prescribed. In the group with statins and the group without statins, there was no clinical difference except that eGFR at the initial evaluation was lower and more patients had coronary heart disease in the statin group. Our study showed that eGFR increased in patients who received statins, whereas eGFR decreased in the non-statin group. Tonelli *et al.* reported that pravastatin reduced the rate of kidney function loss in patients with moderate CKD of stage 3 as defined by an eGFR of 30–59.9 mL/min per 1.73 m^2.[18] In the present study, this effect of statins was also observed in patients of CKD stage 2 (change in eGFR: 69 ± 8 to 72 ± 12 mL/min per 1.73 m^2) as well as in patients of CKD stage 3. A subgroup analysis of the GREACE study showed that Cr clearance declined over a period of 3 years in untreated dyslipidemic patients with coronary heart disease and normal renal function at baseline.[17] On the other hand, statin treatment prevented this decline and significantly improved renal function. Compared to the above-mentioned two studies, the patients in the present study were older, LDL cholesterol levels in our patients were lower, and

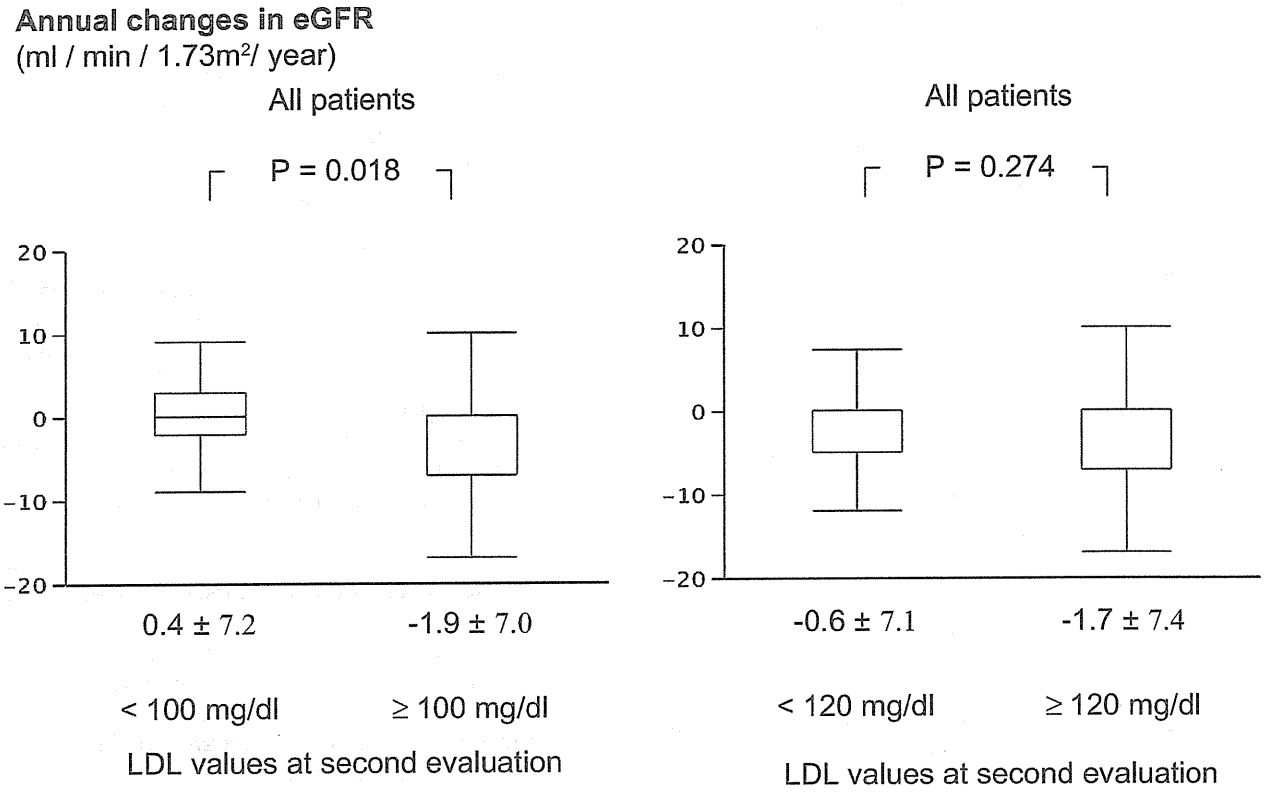

Figure 3 Annual changes in estimated glomerular filtration rate (eGFR) by low-density lipoprotein (LDL) cholesterol levels. The patients were divided into two groups by LDL cholesterol levels at the second evaluation. Data are shown as the means ± standard deviation.

there were more patients with hypertension and less patients with coronary heart disease. Our results suggest that statins have an inhibitory effect on CKD progression also in patients with a relatively stable clinical condition who have not suffered from cardiovascular events including myocardial infarction. Because treatment of risk factors for early CKD may be the best approach for preventing or delaying advanced outcomes, the results of our study indicate that early treatment with statins for hypertensive patients might reduce the risk of cardiovascular events as well as CKD progression.

It is not clear whether the mechanism by which statins inhibit the progression of renal dysfunction is lipid lowering itself or other pleiotropic effects such as antioxidative and anti-inflammatory effects. However, when the patients were divided into two groups by LDL cholesterol levels at the second evaluation, annual eGFR improved in the group of LDL cholesterol levels below 100 mg/dL, but decreased in the other group. On the other hand, when the patients were divided into two groups by LDL cholesterol levels of below or over 120 mg/dL, both groups reduced annual eGFR and there was no significant difference between the two groups. Although the appropriate dose of statins for obtaining a beneficial effect on renal function is unclear, subanalysis of the TNT study, in which the effects of intensive lipid lowering with atorvastatin were investigated in patients with coronary heart disease, showed that mean change in eGFR was significantly greater in patients treated with 80 mg atorvastatin than in those treated with 10 mg of the statin.[19] In this study, the difference between the 10- and 80-mg groups at the end of the study was statistically significant for LDL cholesterol in favor of 80 mg atorvastatin (LDL cholesterol 101.0 vs 79.7 mg/dL). These results indicate that it may be better to provide strong treatment, lowering LDL cholesterol to a level below 100 mg/dL, even in patients without coronary heart disease in order to prevent CKD progression.

There are several limitations in the present study. First, this study was not prospective and randomized. Second, the number of subjects was small and some of the statistical analyses might have been affected. In order to certify that the additional uptake of statins would be meaningful to clinical practice, further prospective studies on the inhibitory effects of statins on CKD development using larger numbers of patients with or without CKD are needed. Third, it is not known that there is any difference of effects of statins on preventing renal dysfunction among different statins.

In conclusion, the present study showed that statins inhibit the progression of renal dysfunction in hypertensive patients without diabetes mellitus. Early and strong lipid-lowering intervention with statins for hypertensive patients may reduce the risk of CKD progression.

References

1 Jones CA, McQuillan GM, Kusek JW *et al.* Serum creatinine levels in the US population: third National Health and Neutrition Examination Survey. *Am J Kidney Dis* 1998; **32**: 992–999.
2 Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–2047.
3 Imai E, Horio M, Yamagata K *et al.* Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. *Hypertens Res* 2008; **31**: 433–441.
4 Ninomiya T, Kiyohara Y. Chronic kidney disease and other disease. 1. Cardiovascular disease. *Nippon Naika Gakkai Zasshi* 2007; **96**: 887–893. (In Japanese.)
5 Brosius FC 3rd, Hostetter TH, Kelepouris E *et al.* Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease. *Circulation* 2006; **114**: 1083–1087.
6 Tonelli M, Wiebe N, Culleton B *et al.* Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; **17**: 2034–2047.
7 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.
8 Mcclellan WM, Flanders WD. Risk factors for progressive chronic kidney disease. *J Am Soc Nephrol* 2003; **14**: S65–S70.
9 Ninomiya T, Kiyohara Y, Kubo M *et al.* Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. *Am J Kidney Dis* 2006; **48**: 383–391.
10 Matsuo K, Inoue T, Node K. Estimated glomerular filtration rate as a predictor of secondary outcomes in Japanese patients with coronary artery disease. *J Cardiol* 2009; **53**: 232–239.
11 Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–1389.
12 Nakamura H, Arakawa K, Itakura H *et al.* Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006; **368**: 1155–1163.
13 Sever PS, Dahlof B, Poulter NR *et al.* ASCOT investigators. Prevention of coronary and stroke events with atrovastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outocomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised co trolled trial. *Lancet* 2003; **361**: 1149–1158.
14 Shepherd J, Kastelein JJ, Bittner V *et al.* TNT Investigators. Intensive lipid lowering with atrovastatin in patients with coronary heart disease and chronic kidney disease: the TNT Study. *J Am Coll Cardiol* 2008; **51**: 1448–1454.
15 Tonelli M, Isles C, Curhan GC *et al.* Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004; **110**: 1557–1563.
16 Lee TM, Su SF, Tsai CH. Effect of pravastatin on proteinuria in patients with well-controlled hypertension. *Hypertension* 2002; **40**: 67–73.
17 Athyros VG, Mikhailidis DP, Papageorgiou AA *et al.* The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. a subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004; **57**: 728–734.
18 Tonelli M, Isles C, Craven T *et al.* Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 2005; **112**: 171–178.
19 Shepherd J, Kastelein JJ, Bittner V *et al.* Treating to New Targets Investigators. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) Study. *Clin J Am Soc Nephrol* 2007; **2**: 1131–1139.
20 Imai E, Horio M, Iseki K *et al.* Prevalence of chronic kidney disease in Japanese general population predicted by MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007; **11**: 156–163.
21 Keane WF. The role of lipids in renal disease: future challenges. *Kidney Int* 2000; **57**: S27–S31.
22 Kasiske BL, O'Donnell MP, Kim Y, Keane WF. Treatment of hyperlipidemia in chronic progressive renal disease. *Curr Opin Nephrol Hypertens* 1993; **2**: 602–608.

Geriat. Med. 48(11)：1461～1462, 2010

序文：きょうから学ぶ高齢者在宅医療

西永　正典

わが国は，人類史上経験したことがない高齢化の「津波」に襲われる．それもここ30年以内に確実に，である．地震に対する備えはなされているのに，一方，著しい高齢化の「津波」に対する備えは十分といってよいのであろうか．

私ごとで恐縮だが，筆者がまだ駆け出しのころ，年に数回心不全で入退院を繰り返していた80歳代半ばの女性に出会った．公営住宅に独居で，心機能は低下し，ADLも低下して歩くこともままならなかった．当時は，転院やむなしとする状況であったが，御本人は在宅療養を強く望み転院を拒まれた．退院支援室を介して，あるいは個人的なつながりで在宅療養を引き受けてくれる先生を探し回ったが，高齢の慢性心不全患者を引き受けてくれる地元の先生は，当時はいなかった．総合機能評価とともに多職種協同で病院内外のスタッフや本人，家族と話し合いが重ねられ，リハビリテーションも施行された．訪問看護やヘルパーなど様々な手段を導入し，ようやく自宅退院にこぎ着けた．当時としては例外中の例外であった．退院してもすぐに緊急入院するのではないかと筆者だけでなく，スタッフの多くが心配していたと思う．しかし，多職種の方々から様々な生活情報が入ることで，利尿薬の量を調節し，半年に1回ほど数日間の検査入院で薬や社会的資源の再調整がなされ，結局，独居のまま90歳半ばに達するまで，生き生きと在宅療養を続けられた．入院回数，日数は定期的な検査・調整入院のみに減少し，心不全悪化による入院はなかった．また，医療費や介護費用をすべて含めても，入退院を繰り返していた1年前のそれらに比べて2/3程度に抑えられた(図)．が，何よりも最期まで「自宅に居られて幸せ」といっておられたことが，

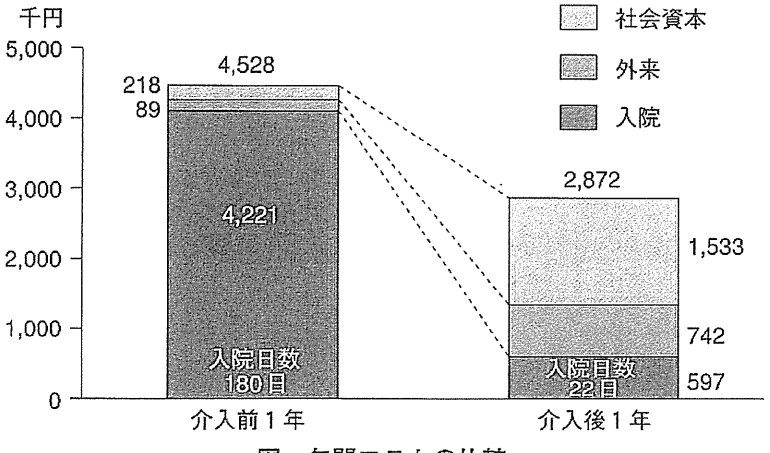

図　年間コストの比較

■にしなが　まさのり(東京大学高齢社会総合研究機構特任准教授)

病院における医療とともに，在宅における医療がいかに重要であるかを筆者に再認識させてくれた．

今や在宅医療は多くの方々の努力で，発展を続けている．老年医学においても，その意義は大きくなっているように思う．

本特集では，わが国の在宅医療の第一人者の方々に執筆をお願いし，快く引き受けていただいた．老年医学を学んでいるわれわれが，在宅医療をきょうからでも，さらに学べるようにと願って序文としたい．