Table 1
Risk characteristics among cases and control subjects by cardiovascular disease

	N	Age, years	Men, %	Systolic blood pressure, mmHg	Diastolic blood pressure, mmHg	Hypertension, %	Alcohol intake, g/day	Current smokers, %	Diabetes, %	HDL-cholesterol, mmol/l	Total serum cholesterol, mmol/l
Total stroke											
Case	345	66.8	53	143.4***	83.1***	50***	10.7	32**	8	1.16	5.10*
Control subjects	345	67.3	53	136.3	78.6	36	9.5	23	6	1.18	5.30
Intraparenchymal hemorrhage											
Case	76	66.4	51	143.3**	83.1	49	12.3	25	4	1.17	4.98*
Control subjects	76	66.0	51	134.0	79.1	38	7.1	10	1	1.17	5.34
Subarachnoid hemorrhage											
Case	66	61.9	38	146.5	88.3	58**	11.1	29	6	1.16	5.20
Control subjects	66	62.0	38	132.6	76.5	35	7.5	20	3	1.13	5.36
Ischemic stroke											
Case	115	68.7	68	144.1	80.5	47*	9.6	41	10	1.19	5.06
Control subjects	115	67.6	68	135.8	79.4	31	11.9	29	10	1.20	5.20
Coronary heart disease											
Case	150	66.8	54	141.3	80.1	48	8.4	36	15**	1.11	5.49
Control subjects	150	66.4	54	137.1	77.6	37	9.6	31	5	1.16	5.30

* $p < 0.05$ compared with control subjects.
** $p < 0.01$ compared with control subjects.
*** $p < 0.001$ compared with control subjects.

levels <4.14 (160), 4.14–4.64 (160–179), 4.65–5.16 (180–199), 5.17–5.68 (200–219), 5.69–6.20 (220–239), 6.21–6.71 (240–259), and ≥6.72 mmol/l (260 mg/dl) with conditional logistic regression models. Adjustments for systolic blood pressure (mmHg), HDL-cholesterol (mmol/l), ethanol intake category (never, former, and current drinking <23, 23–45, 46–68, and ≥69 g/day), smoking status (never, former, and current 1–19 and ≥20 cigarettes/day), and diabetes (yes) were conducted for multivariate analysis. Test for a linear trend across the total cholesterol categories was conducted by linear regression, using a median variable of total cholesterol in each total cholesterol category. All p-values for statistical tests were two-tailed and values <0.05 represented statistical significance. All confidence intervals were estimated at the 95% level. All analyses were conducted using the SAS statistical package Version 8.2 (Statistical Analysis System Inc., Cary, NC).

3. Results

We examined age-adjusted mean values or proportions of major cardiovascular risk factors between the subjects with and without blood samples in the JACC study. The respective mean values of age were 57 and 58 years for men, and 58 and 57 years for women. The respective age-adjusted mean values of body mass index were 22.6 and 22.8 kg/m^2 for men, and 22.8 and 23.2 kg/m^2 for women. The respective age-adjusted proportions of hypertensions (systolic blood pressure ≥140, diastolic blood pressure ≥90 mmHg and/or antihypertensive medication use) were 50 and 45% for men, and 24 and 18% for women; those of current smokers were 54 and 54% for men, and 6 and 4% for women.

During the 10-year follow-up, we identified 345 deaths due to stroke and 150 due to coronary heart disease. Total stroke comprised 76 intraparenchymal hemorrhages, 66 subarachnoid hemorrhages, and 115 ischemic strokes.

Table 1 shows risk characteristic of cardiovascular disease compared with control subjects. The average age was 67 years for total stroke and coronary heart disease, varying from 62 years for subarachnoid hemorrhage to 69 years for ischemic stroke. The proportion of men was 53% for total stroke and 54% for coronary heart disease, varying from 38% for subarachnoid hemorrhage to 68% for ischemic stroke. Systolic and diastolic blood pressure levels, and the prevalence of hypertension and current smokers were higher among persons with total stroke than in control subjects; this trend was most evident for intraparenchymal hemorrhage. The prevalence of diabetes was higher in subjects with coronary heart disease than controls. Mean values of alcohol intake were not different between cases and control subjects for total stroke, each stroke subtype and coronary heart disease. Mean values of serum total cholesterol were 0.20 and 0.36 mmol/l lower for total stroke and intraparenchymal hemorrhage than for control subjects, but were not different between cases and control subjects for other stroke subtypes or coronary heart disease.

Table 2 shows univariate and multivariable odds ratios (95% CIs) for total stroke, stroke subtypes, and coronary heart disease according to seven categories of total cholesterol levels. Persons with total cholesterol levels <4.14 mmol/l (160 mg/dl) had a significantly higher risk of mortality from

Please cite this article as: Renzhe Cui et al., Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study, Atherosclerosis (2006), doi:10.1016/j.atherosclerosis.2006.08.022

Table 2
Univariate and multivariable odds ratios of stroke, stroke subtypes, and coronary heart disease according to serum total cholesterol levels

	Serum cholesterol, mmol/l (mg/dl)						*p* for trend
	<4.14 (160)	4.14–4.64 (160–179)	4.65–5.16 (180–199)	5.17–5.68 (200–219)	5.69–6.20 (220–239)	6.21–6.71 (240–259)	≥7.22 (260)	
Total stroke								
Case/control subjects	69/46	48/50	81/63	50/69	49/54	23/34	25/29	
Age, sex, community-matched OR	1.00	0.65 (0.38–1.13)	0.84 (0.51–1.37)	0.48 (0.28–0.83)	0.55 (0.31–0.97)	0.41 (0.21–0.82)	0.56 (0.27–1.16)	0.006
Multivariable OR	1.00	0.71 (0.41–1.25)	0.90 (0.54–1.51)	0.46 (0.26–0.81)	0.55 (0.34–0.99)	0.43 (0.21–0.88)	0.57 (0.27–1.22)	0.007
Intraparenchymal hemorrhage								
Case/control subjects	19/7	8/15	17/14	11/13	11/12	6/7	4/8	
Age, sex, community-matched OR	1.00	0.16 (0.04–0.61)	0.48 (0.15–1.51)	0.34 (0.10–1.14)	0.39 (0.12–1.30)	0.33 (0.08–1.41)	0.13 (0.02–0.74)	0.06
Multivariable OR	1.00	0.09 (0.02–0.44)	0.35 (0.10–1.26)	0.21 (0.05–0.90)	0.20 (0.04–0.92)	0.12 (0.02–0.80)	0.12 (0.02–0.88)	0.02
Subarachnoid hemorrhage								
Case/control subjects	10/13	12/7	14/8	8/13	11/10	3/7	8/8	
Age, sex, community-matched OR	1.00	2.40 (0.63–9.15)	1.85 (0.44–7.85)	0.78 (0.19–3.20)	1.36 (0.32–5.80)	0.42 (0.05–3.24)	1.03 (0.17–6.17)	0.57
Multivariable OR	1.0	1.90 (0.43–8.41)	1.08 (0.21–5.48)	0.40 (0.07–2.16)	1.53 (0.27–8.61)	0.30 (0.02–3.96)	0.60 (0.08–4.73)	0.57
Ischemic stroke								
Case/control subjects	24/15	16/18	32/25	16/25	11/17	9/9	7/6	
Age, sex, community-matched OR	1.00	0.55 (0.20–1.38)	0.79 (0.36–1.72)	0.38 (0.15–0.98)	0.39 (0.14–1.13)	0.60 (0.20–1.83)	0.79 (0.18–3.42)	0.15
Multivariable OR	1.00	0.59 (0.22–1.58)	0.99 (0.41–2.38)	0.39 (0.14–1.13)	0.38 (0.12–1.20)	0.69 (0.19–2.49)	0.87 (0.18–4.24)	0.31
Coronary heart disease								
Case/control subjects	11/14	23/23	30/29	25/27	30/31	13/17	18/9	
Age, sex, community-matched OR	1.00	1.26 (0.47–3.36)	1.28 (0.49–3.31)	1.13 (0.49–2.86)	1.24 (0.49–3.15)	1.02 (0.34–3.07)	2.33 (0.77–7.02)	0.52
Multivariable OR	1.00	1.64 (0.58–4.65)	1.69 (0.62–4.64)	1.47 (0.55–3.93)	1.59 (0.59–4.29)	1.00 (0.32–3.93)	3.74 (1.11–12.6)	0.55

Multivariable adjustment: systolic blood pressure (mmHg), HDL-cholesterol (mmol/l), ethanol intake (never, former, and current drinking <23, 23–45, 46–68, and ≥69 g/day), smoking status (never, former, and current 1–19 and ≥20 cigarettes/day), and diabetes (yes).

Please cite this article as: Renzhe Cui et al., Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study, Atherosclerosis (2006), doi:10.1016/j.atherosclerosis.2006.08.022

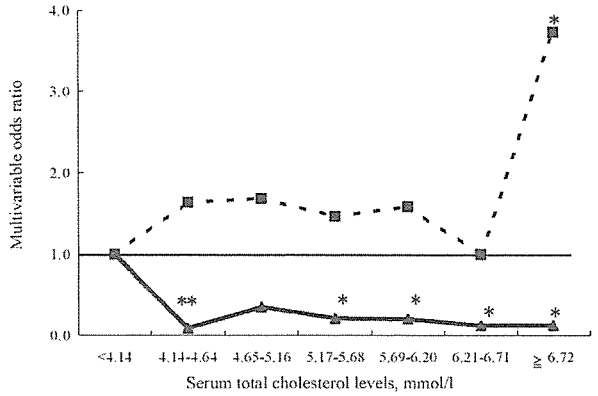


Fig. 1. Multivariable odds ratios of mortality from intraparenchymal hemorrhage and coronary heart disease according to serum total cholesterol levels. Solid line: intraparenchymal hemorrhage; dotted line: coronary heart disease. The reference group included persons with serum total cholesterol of <4.14 mmol/l (160 mg/dl): $^{*}p<0.05$; $^{**}p<0.01$.

intraparenchymal hemorrhage than those with higher levels (Table 2; Fig. 1). Compared to persons with serum total cholesterol levels <4.14 mmol/l (160 mg/dl), those with serum levels ≥7.22 mmol/l (260 mg/dl) had a significantly lower risk of mortality from intraparenchymal hemorrhage but not for ischemic stroke; the multivariable odds ratios were 0.12 (0.02–0.88), p for trend = 0.02 for intraparenchymal hemorrhage and 0.87 (0.18–4.24), p for trend = 0.31 for ischemic stroke.

The risk of mortality from coronary heart disease was higher in persons with serum total cholesterol levels ≥6.72 mmol/l (260 mg/dl), compared to those with levels <4.14 mmol/l (160 mg/dl); the multivariate odds ratios was 3.74 (1.11–12.6), $p = 0.03$ (Table 2; Fig. 1).

The sex-specific association between serum total cholesterol levels and risk of mortality from coronary heart disease was examined among persons with serum total cholesterol of 240–259 and ≥260 mg/dl (not shown in table); the respective multivariable odds ratios were 0.98 (0.20–4.75) and 3.26 (0.54–19.7) for men, and 0.57 (0.06–5.47) and 2.30 (0.22–23.7) for women.

4. Discussion

The present large prospective study examined the relationships between serum total cholesterol with total stroke, subtype strokes and coronary heart disease using a nested-case control design. To our knowledge, this the first prospective study to show the contrasting association of serum total cholesterol levels with mortality from intraparenchymal hemorrhage and coronary heart disease among Asian population. We observed that low serum total cholesterol levels (<4.14 mmol/l) were strongly associated with increased risk of mortality from intraparenchymal hemorrhage. This result is consistent with the finding of previous prospective studies in Japanese men [7,15], Japanese-American men [8,16], American men [3,9], and Swedish women [10]. Furthermore, there was an inverse relationship of saturate fat intake, a major determinant of serum cholesterol levels, with the incidence or mortality from intraparenchymal hemorrhage [17,18]. A meta-analysis reported that each 1 mmol/l higher level of total cholesterol was associated with 20% decreased risk of fatal hemorrhagic stroke [2]. Previous pathological studies in Japanese and Japanese-American indicated that angionecrosis, i.e. loss of medial smooth-muscle cells in small intracerebral penetrating arteries [19] was associated with low serum total cholesterol levels [19,20], and this pathology led to rupture of small intraparenchymal cerebral arteries. Another 6-year follow-up study of 350,977 American men screened in the multiple risk factor intervention trial (MRFIT) showed that the association between low levels of serum cholesterol and risk of intraparenchymal hemorrhage is confined to hypertensive patients [3]. Another study reported that the inverse association was confined to ≥65 years elderly men [9]. The potential effects hypertension on serum total cholesterol–mortality relationship could not be examined in the present study because of the small number of cases in those subgroups.

The association between serum total cholesterol and risk of mortality from ischemic stroke has been inconsistent. In our study, persons with serum total cholesterol levels <4.14 mmol/l (160 mg/dl) tended to have the increased risk of mortality from ischemic stroke, as previously reported in NIPPON DATA [15]. On the other hand, a meta-analysis reported that a non-significant positive association between cholesterol and the risk of fatal ischemic stroke in both Asian and non-Asian populations in the Asian-Pacific region [2].

The increased risk of mortality from coronary heart disease in the presence of high serum total cholesterol levels was consistent with the findings of previous Japanese studies [15,21–23], Chinese study [24] and South Korean study [25], in addition to studies in western countries. A meta-analysis [2] showed that in persons with serum cholesterol ≥6.2 mmol/l (240 mg/dl), the relative risk of coronary heart disease was 1.5-fold higher compared to those with <4.5 mmol/l (174 mg/dl).

The present study has several potential limitations. First, approximately 35% of the total participants have provided blood samples. However, there were no apparent differences in age-adjusted means values or proportions of major cardiovascular risk factors between the subjects with and without blood samples. Thus, a selection bias may be small in the evaluation of associations between serum cholesterol levels and cardiovascular disease mortality. Second, we used frozen serum to estimate total cholesterol concentrations and we did not examine long-term changes in cholesterol in the stored serum samples. However, a previous study confirmed that total serum total cholesterol levels were stable in serum samples stored for up to 7 years at −70 °C [26]. Third, we had non-fasting blood samples in the present study. However, no significant impacts of non-fasting were reported for serum

Please cite this article as: Renzhe Cui et al., Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study, Atherosclerosis (2006), doi:10.1016/j.atherosclerosis.2006.08.022

total and HDL-cholesterol levels [27]. Fourth, we used the mortality data, not incidence data as endpoints, which may lead to misclassification in the diagnosis of stroke subtype in particular. However, the widespread use of computed tomography scans in Japanese local hospital since the 1980s has probably made the death certificate diagnosis of stroke subtype sufficiently accurate [28,29].

In conclusion, we showed that low serum total cholesterol levels were associated with increased risk of mortality from intraparenchymal hemorrhage, while high levels were associated with increased risk of mortality from coronary heart disease among Japanese.

Acknowledgments

The authors sincerely express their appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine, and the former chairman of the JACC study, and to Dr. Haruo Sugano, the former Director, Cancer Institute, Tokyo, who greatly contributed to the initiation of the JACC study.

The JACC study has been supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, and 11181101).

References

[1] Stamler J, Daviglus ML, Garside DB, et al. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 2000;284:311–8.

[2] Zhang X, Patel A, Horibe H, et al., Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. Int J Epidemiol 2003;32:563–72.

[3] Iso H, Jacobs Jr DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989;320:904–10.

[4] Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. Br Med J 1994;309:11–5.

[5] Benfante R, Yano K, Hwang LJ, et al. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men. Stroke 1994;25:814–20.

[6] Nakayama T, Date C, Yokoyama T, et al. A 15.5-year follow-up study of stroke in a Japanese Provincial City: the Shibata Study. Stroke 1997;28:45–52.

[7] Ueshima H, Iida M, Shimamoto T, et al. Multivariate analysis of risk factors for stroke. Eight-year follow-up study of farming villages in Akita, Japan. Prev Med 1980;9:722–40.

[8] Kagan A, Popper JS, Rhoads GG. Factors related to stroke incidence in Hawaii Japanese men. The Honolulu Heart Study. Stroke 1980;11:14–21.

[9] Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. Stroke 1996;27:1993–8.

[10] Gatchev O, Rastam L, Lindberg G, et al. Subarachnoid hemorrhage, cerebral hemorrhage, and serum cholesterol concentration in men and women. Ann Epidemiol 1993;3:403–9.

[11] Hart CL, Hole DJ, Smith GD. The relation between cholesterol and haemorrhagic or ischaemic stroke in the Renfrew/Paisley study. J Epdemiol Community Health 2000;54:874–5.

[12] Suh I, Jee SH, Kim HC, et al. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. Lancet 2001;357:922–5.

[13] Ohno Y, Tamakoshi A, the JACC Study Group. Japan collaborative cohort study for evaluation of cancer risk sponsored by Monbusho (JACC study). J Epidemiol 2001;11:144–50.

[14] Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. J Atheroscler Thromb 2003;10:145–53.

[15] Okamura T, Kadowaki T, Hayakawa T, et al., Nippon Data80 Research Group. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–80.

[16] Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. Stroke 1989;20:1460–5.

[17] Iso H, Stampfer MJ, Manson JE, et al. Prospective study of fat and protein intake and risk of intraparenchymal hemorrhage in women. Circulation 2001;103:856–63.

[18] Iso H, Sato S, Kitamura A, et al. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. Am J Epidemiol 2003;157:32–9.

[19] Konishi M, Iso H, Komachi Y, et al. Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries. The Akita Pathology Study. Stroke 1993;24:954–64.

[20] Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. Am J Epidemiol 1990;131:579–88.

[21] Konishi M, Iso H, Iida M, et al. Trends for coronary heart disease and its risk factors in Japan: epidemiologic and pathologic studies. Jpn Circ J 1990;54:428–35.

[22] Okamura T, Tanaka H, Miyamatsu N, et al., for the NIPPON DATA80 research group. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis 2006;March(8) [Epub ahead of print].

[23] Kitamura A, Iso H, Naito Y, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. Circulation 1994;89:2533–9.

[24] Zhang XF, Attia J, D'Este C, Yu XH, Wu XG. A risk score predicted coronary heart disease and stroke in a Chinese cohort. J Clin Epidemiol 2005;58:951–8.

[25] Song YM, Sung J, Kim JS. Which cholesterol level is related to the lowest mortality in a population with low mean cholesterol level: a 6.4-year follow-up study of 482,472 Korean men. Am J Epidemiol 2000;151:739–47.

[26] Shih WJ, Bachorik PS, Haga JA, Myers GL, Stein EA. Estimating the long-term effects of storage at −70 °C on cholesterol, triglyceride, and HDL-cholesterol measurements in stored sera. Clin Chem 2000;46:351–64.

[27] Weiss R, Harder M, Rowe J. The relationship between nonfasting and fasting lipid measurements in patients with or without type 2 diabetes mellitus receiving treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Clin Ther 2003;25:1490–7.

[28] Sankai T, Miyagaki T, Iso H, et al. A population-based study of the proportion by type of stroke determined by computed tomography scan. Nippon Koshu Eisei Zasshi 1991;38:901–9 [in Japanese].

[29] Kita Y, Okayama A, Ueshima H, et al. Stroke incidence and case fatality in Shiga, Japan 1989–1993. Int J Epidemiol 1999;28:1059–65.

Please cite this article as: Renzhe Cui et al., Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: The JACC study, Atherosclerosis (2006), doi:10.1016/j.atherosclerosis.2006.08.022

D. 今後の計画

死亡者の追跡は、概ね 2 年ごとに実施しており、既に平成 15 年度までの調査が完了している。来年度は総務省からの許可が得られ次第、平成 16 年～18 年の追跡を実施する予定である。

今年度は、前述の研究の他、ナトリウム・カリウム摂取と循環器死亡の関連、魚摂取と循環器死亡の関連、高血圧治療者における血圧値と循環器死亡（いわゆる J カーブ現象）の関連、運動と喫煙の相互作用と循環器死亡についての分析や心突然死の要因分析に着手しており、一部については論文を投稿中である。これらの研究については来年度中に完了する予定である。

2.　大迫コホート

分担研究者
今井　潤・東北大学大学院薬学研究科医療薬学講座臨床薬学分野・教授

研究協力者
大久保孝義・東北大学大学院薬学研究科医薬開発構想寄附講座・助教授
目時　弘仁・東北大学大学院医学系研究科内科病態学講座臨床薬学分野・大学院生

1)大迫コホートの現況

大迫（おおはさま）コホート研究は、24 時間自由行動下血圧および家庭における自己測定血圧（家庭血圧）を用いた世界初の住民ベースの疫学研究であるという特色を持ち、これまでの 10 年以上の追跡を通じ、「我が国発、世界初」のエビデンスを発信し続けてきた。

また、55 歳以上の住民に対し、頭部 MRI 撮影、頚動脈超音波検査、脈波伝播速度、Augmentation Index, 指尖容積脈波、24 時間ホルター心電図、認知機能検査（ミニメンタルテスト・反応時間)、および動脈硬化関連血液尿生化学パラメーター（クレアチニンクリアランス、尿中微量アルブミン、BNP、フィブリノーゲン、リポプロテイン(a)、血漿レニン活性、高感度 CRP)、脈波伝播速度、等の測定も実施している。

その他、近年の糖尿病増加を考慮に入れ、35歳以上の住民に対し、75g経口糖負荷試験（OGTT）による糖尿病検診を開始している。

また、1998年に35歳以上の全町民を対象に、生活習慣全般についての詳細なアンケート調査を実施し、4268名より有効回答を得ている。

以下に本年度の主要な研究結果について示す（○のついた論文については日本語要約と公表論文別刷を、　2)最新の研究成果　に別途掲載)。

■　24 時間自由行動下血圧を用いた追跡研究

○Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hara A, Hirose T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebro- and cardiovascular mortality: the Ohasama Study. *Journal of Hypertension,* 2006; 24:1841-1848.

Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama Study. *Hypertension* 2006; 47:149-154.

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 four ambulatory blood pressure monitoring－derived blood pressure indices: the Ohasama study. *Hypertension* 2006;48:877-82.

■ 家庭血圧を用いた追跡研究

○Asayama K, Ohkubo T, Kikuya M, Obara T, Metoki H, Inoue R, Hara A, Hirose T, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by home 'morning' versus 'evening' blood pressure values: the Ohasama study. *Hypertension* 2006;48:737-743.

■ 家庭血圧の医療経済効果に関する研究

Funahashi J, Ohkubo T, Fukunaga H, Kikuya M, Takada N, Asayama K, Metoki H, Obara T, Inoue R, Hashimoto J, Totsune K, Kobayashi M, Imai Y. The economic impact of the introduction of home blood pressure measurement for the diagnosis and treatment of hypertension. *Blood Pressure Monitoring.* 2006; 11:257-267.

■ 白衣効果とパーソナリティーに関する研究

Hozawa A, Ohkubo T, Obara T, Metoki H, Kikuya M, Asayama K, Totsune K, Hashimoto J, Hoshi H, Arai Y, Satoh H, Hosokawa T, Imai Y. Introversion associated with large differences between screening blood pressure and home blood pressure measurement: the Ohasama study. *Journal of Hypertension* 2006 24:2183-2189.

■ ウエスト周囲系の基準値についての研究

Ohkubo T, Kikuya M, Asayama K, Imai Y. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care.* 29: 1986-7, 2006.

■ 左室肥大と動脈スティッフネスとの関連についての研究

Watabe D, Hashimoto J, Hatanaka R, Hanazawa T, Ohba H, Ohkubo T, Kikuya M, Totsune K, Imai Y.. Electrocardiographic left ventricular hypertrophy and arterial stiffness: the Ohasama study. *American Journal of Hypertension.* 2006;19:1199-205.

2)最新の研究成果

1. 夜間血圧、早朝血圧と脳心血管病死亡との関連に関する検討

Metoki H, et al. Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebro- and cardiovascular mortality: the Ohasama Study. *Journal of Hypertension,* 2006; 24:1841-1848.

要約

24時間自由行動下血圧測定により1日の各時間帯の血圧値の評価が可能となり、注目されている。本研究では、24時間にわたる2時間の収縮期血圧の平均値(2h-SBP)と脳心血管疾患死亡リスクとの関連を検討した。

大迫コホートでは40歳以上の住民1542名が30分間隔での24時間自由行動下血圧測定を行っている。連続した2時間における30分毎、計4回の測定値の平均を'2h-SBP'と定義した。1時間毎に計24回の2h-SBPを算出し(移動平均)、1日の中での推移を観察した。死亡リスクとの分析は、年齢・性別・喫煙歴・ベースライン時での降圧治療の有無・脳心血管疾患・糖尿病・高脂血症の有無で補正した、Cox比例ハザードモデルを用いて行った。

2h-SBPの移動平均値が1つ以上欠損していた182名を除いた1360名を本解析の対象とした。平均追跡期間は10.6年間であり、この間に232名の死亡が観察された。

脳心血管死亡リスクは、ほとんどの時間帯における血圧上昇と関連していたが、昼間の2h-SBPとの関連は弱かった。出血性脳卒中による死亡リスクは早朝と昼間における2h-SBPと有意に関連していたが、夜間の2h-SBPとの関連は弱かった。脳梗塞、虚血性・非虚血性心疾患による死亡リスクは、いずれも夜間の2h-SBPと有意に関連していたが、昼間の2h-SBPとは関連していなかった。これらを合わせた死亡リスクは、夜間や早朝の2h-SBPと有意に関連したが昼間の2h-SBPとは弱い関連を示すのみであった。

測定回数が増加するに従い、血圧値の予後予測能は増加することが知られている。従って、測定回数の違いが各時間帯の血圧値の予後予測能の評価に影響を与える可能性がある。本研究は、1日の中の異なる時間帯の血圧値の測定回数を同一として比較を行った最初の研究である。今回の結果により、早朝及び昼間の高い血圧は出血性脳卒中による死亡と関連し、夜間の高い血圧は脳梗塞及び心疾患による死亡と関連することが明らかとなった。従って、24時間に亘る厳密な血圧コントロールにより、脳心血管疾患全体による死亡リスクの減少が期待されると考えられる。

Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebrovascular and cardiovascular mortality: the Ohasama Study

Hirohito Metoki[a,b], Takayoshi Ohkubo[b,c], Masahiro Kikuya[a], Kei Asayama[c], Taku Obara[a,b], Azusa Hara[a,b], Takuo Hirose[a,b], Junichiro Hashimoto[b,c], Kazuhito Totsune[a,b], Haruhisa Hoshi[d], Hiroshi Satoh[b,e] and Yutaka Imai[a,b]

Objective To clarify whether high blood pressure (BP) at a particular time of day is associated with cerebrovascular and cardiovascular mortality risk.

Methods Cerebrovascular and cardiovascular mortality in 1360 individuals aged 40 years and older in Ohasama, Japan, was followed for an average of 10.6 years. We used 2-h moving averages of the BP (a total of 24 average BP measurements for two consecutive hours based on four BP readings taken every 30 min) to compare the predictive power of BP taken during a 24-h period given the same number of measurements. The associations between cerebrovascular and cardiovascular mortality risk and the 2-h moving averages of systolic blood pressure (2 h-SBP) recorded over 24 h were analysed using a Cox proportional hazards model after adjusting for possible confounding factors.

Results The total cerebrovascular and cardiovascular mortality risk was significantly associated with elevated 2 h-SBP recorded during the night and early morning periods. Haemorrhagic stroke mortality was significantly associated with elevated daytime 2 h-SBP. Cerebral infarction mortality and heart disease mortality were significantly associated with elevated night-time 2 h-SBP.

Conclusion High BP at different times of day were associated with different subtypes of cerebrovascular and cardiovascular mortality risk. *J Hypertens* 24:1841–1848

Journal of Hypertension 2006, 24:1841–1848

Keywords: blood pressure, cardiovascular disease, cerebrovascular disorders, circadian rhythm, population

[a]Departments of Clinical Pharmacology and Therapeutics, [b]Planning for Drug Development and Clinical Evaluation, [c]Environmental Health Sciences, [d]Tohoku University 21st Century COE Program Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai and [e]Ohasama Hospital, Iwate, Japan

Correspondence to Takayoshi Ohkubo, MD, PhD, Department of Planning for Drug Development and Clinical Evaluation, Clinical Pharmacology and Therapeutics, Tohoku University Hospital, 1-1, Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8574, Japan
Tel: +81 22 717 8590; fax: +81 22 717 8591;
e-mail: tohkubo@mail.tains.tohoku.ac.j

Sponsorship: This work was supported by grants for scientific research (nos. 14657600, 14370217, 15790293, and 1654041) from the Ministry of Education, Culture, Sports, Science, and Technology; and health science research grants and medical technology evaluation research grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; Uehara Memorial Foundation; and Takeda Medical Research Foundation.

Received 24 February 2006 **Revised** 6 April 2006
Accepted 18 April 2006

Introduction

It has been reported that a single blood pressure (BP) value measured by an ambulatory BP monitoring device on rising in the morning has a higher predictive value for future cerebrovascular and cardiovascular events than does BP measured on fitting the ambulatory BP monitoring device or the average of three BP measurements taken under standardized conditions in the hospital or office [1]. Staessen *et al.* [2] reported in the Syst-Eur substudy that elevated night-time BP had a stronger predictive power than elevated daytime BP for cerebro and cardiovascular mortality, as well as for fatal and non-fatal cardiac diseases. However, they did not show that the predictive power of elevated daytime BP was different from that of elevated night-time BP for the risk of mortality from stroke. It is known that the predictive power of BP for cerebro and cardiovascular disease risk increases as the number of measurements increases [3,4]. In the present study, we calculated 2-h moving averages of systolic blood pressure (2 h-SBP, the average BP of four consecutive measurements measured every 30 min) over a 24-h period. We then analysed the relationship between the 2 h-SBP and cerebro and cardiovascular disease mortality risk, as well as the relationships between the 2 h-SBP and the risk of cerebro and cardiovascular disease subtypes, such as haemorrhagic stroke, cerebral infarction, ischaemic heart disease, and non-ischaemic heart disease.

Methods

Study population

The present study is part of a longitudinal observational study of individuals who have been participating in the BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. The characteristics of this cohort have been described in previous reports [5,6]. In the present

0263-6352

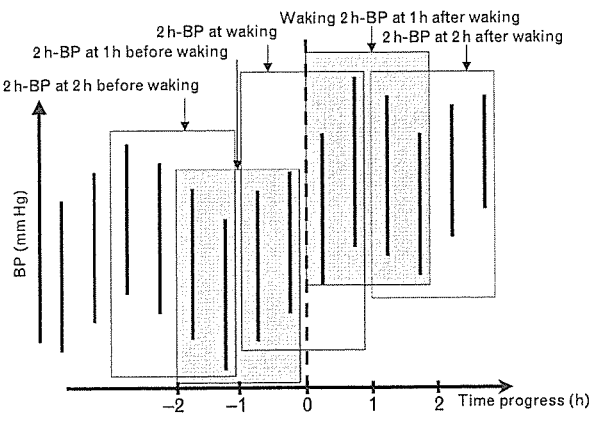
study of inhabitants of Ohasama who were 40 years old and over ($n = 2716$), hospitalized individuals ($n = 121$), demented or bedridden individuals ($n = 31$), and those who worked outside of Ohasama ($n = 575$) were excluded. A total of 1989 eligible individuals were thus identified; of these, 1542 individuals gave their informed consent and participated in this study. The representativeness of the study participants has been fully described in a previous paper [6]. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Ambulatory blood pressure monitoring and devices

Ambulatory BP monitoring was performed using the ABPM-630 (Nippon Colin, Komaki, Japan), a fully automatic device that utilizes the cuff-oscillometric method to measure BP, which was preset to measure BP every 30 min. The devices were validated [7] and met the criteria of the Association for the Advancement of Medical Instrumentation [8]. An ambulatory BP monitoring device was attached by well-trained public health nurses who visited the participants' homes on a weekday morning and detached the device the next morning. The participants were asked to report their daily activities, including the time they went to bed and the time they got up. Artifactual measurements during recordings were defined according to previously described criteria [9] and were omitted from the analysis.

We defined the averages of four SBP readings obtained every 30 min during each consecutive 2 h in a day (moving averages) as the '2 h-SBP' (see Fig. 1). When any readings were omitted because of artifactual measurements, the remaining readings (minimum of one) obtained during the 2 h were used for the calculations. An average of 3.92 measurements was available over a 2-h period. Use of the 2 h-SBP allows us to compare the predictive value of BP taken during different periods using the same number of BP measurements. The 2-h moving averages of diastolic blood pressure (2 h-DBP) were defined in the same manner as the 2 h-SBP.

Fig. 1



Definition of the moving average of the 2-h systolic blood pressure/2-h diastolic blood pressure (2 h-SBP/2 h-DBP). We defined the averages of four SBP/DBP readings obtained during two consecutive hours in a day (moving averages) as the 2 h-SBP/2 h-DBP. The horizontal line indicates time (hours) from waking. The vertical line shows the blood pressure (BP) (mmHg).

Follow-up

Residence in Ohasama as of 31 December 2001 was confirmed by the residents' registration cards. In Japan, these cards are accurate and reliable because they are used for pensions and social security benefits. Causes of death were investigated by accessing the national mortality registry, in which the underlying cause of death is listed on the certificate according to the recommendations of the 10th revision of the World Health Organization's International Classification of Diseases. Cerebro and cardiovascular mortality was defined as mortality related to disease of the circulation system (International Classification of Diseases, 10th revision, code 'I'). The details of the adjudication characteristics of the causes of death used in the Ohasama study have been described previously [6].

Statistical analysis

The associations between the 2 h-SBP analysed over a 24-h period and the cerebro and cardiovascular disease mortality risks were estimated using a Cox proportional hazards model, and adjusted for age, sex, smoking, the use of antihypertensive drugs at baseline, as well as a history of cerebro and cardiovascular complications, diabetes mellitus, and hypercholesterolemia. When the mortality risk was analysed, we excluded death within the first 2 years to exclude a reverse-causality bias possibly derived from subjects with a lower BP being in poor health. Such an analysis of the results from the Ohasama population has been described previously [10].

A two-tailed P value less than 0.05 was taken to indicate statistical significance. A two-tailed P value less than 0.002 (0.05 divided by 24) was also taken to indicate statistical significance when the Bonferroni correction was applied, because we calculated each relative hazard (RH) of the 2-h BP for cerebro and cardiovascular mortality 24 times. We analysed data using the SAS package (version 9.1, SAS Institute Inc., Cary, North Carolina, USA). The RHs are expressed with 95% confidence intervals (CI). Values are expressed as mean (SD).

Results

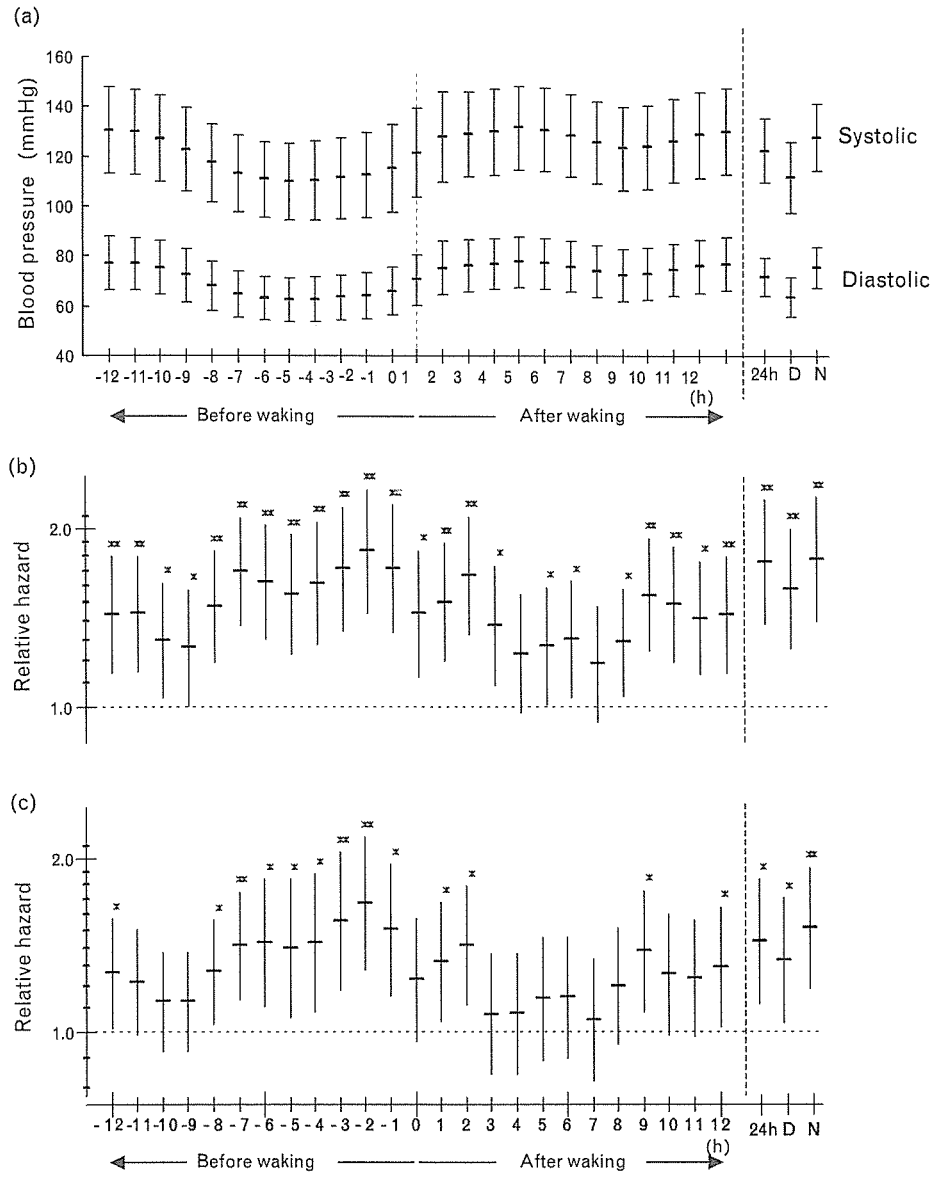
Baseline characteristics

Of the 1542 individuals in whom 24-h SBP was measured, 182 were not included in the present analysis because

of the lack of one or more 2 h-SBP moving averages. There were no significant differences in the baseline characteristics between the 182 excluded individuals and the 1360 individuals who remained in the study. The mean age of participants was 61.3 (10.6) years, and 64% were women. The individuals slept a mean of 8.4 (1.1) hours.

The mean ambulatory 24-h BP was 122.8 (12.9)/71.8 (7.6) mmHg, the mean ambulatory daytime BP was 128.3 (13.7)/75.9 (8.3) mmHg, and the mean ambulatory night-time BP was 111.9 (14.3)/63.8 (7.9) mmHg. The 2 h-SBP/2 h-DBP over the 24-h period and their standard deviations (SD) are shown in Fig. 2a; the mean 2 h-SBP/2 h-DBP 2 h before waking was 112.8 (17.0)/64.4

Fig. 2



Circadian blood pressure variation (a) and the relative hazard of the total cerebrovascular and cardiovascular disease mortality risk per 1-SD elevation of systolic blood pressure (b) and diastolic blood pressure (c). Relative hazards and 95% confidence intervals were adjusted for age, sex, smoking status, and the use of antihypertensive medication, as well as for a history of cerebrovascular and cardiovascular diseases, hypercholesterolemia, and diabetes mellitus. Numbers on the left-hand side panel of the figure indicate the 2-h moving averages of blood pressure over the 24-h period. 24 h, D, and N on the right-hand side panel indicate conventional 24-h, daytime, and night-time mean blood pressures, respectively. $^{*}P < 0.05$, $^{**}P < 0.002$ (Bonferroni adjustment).

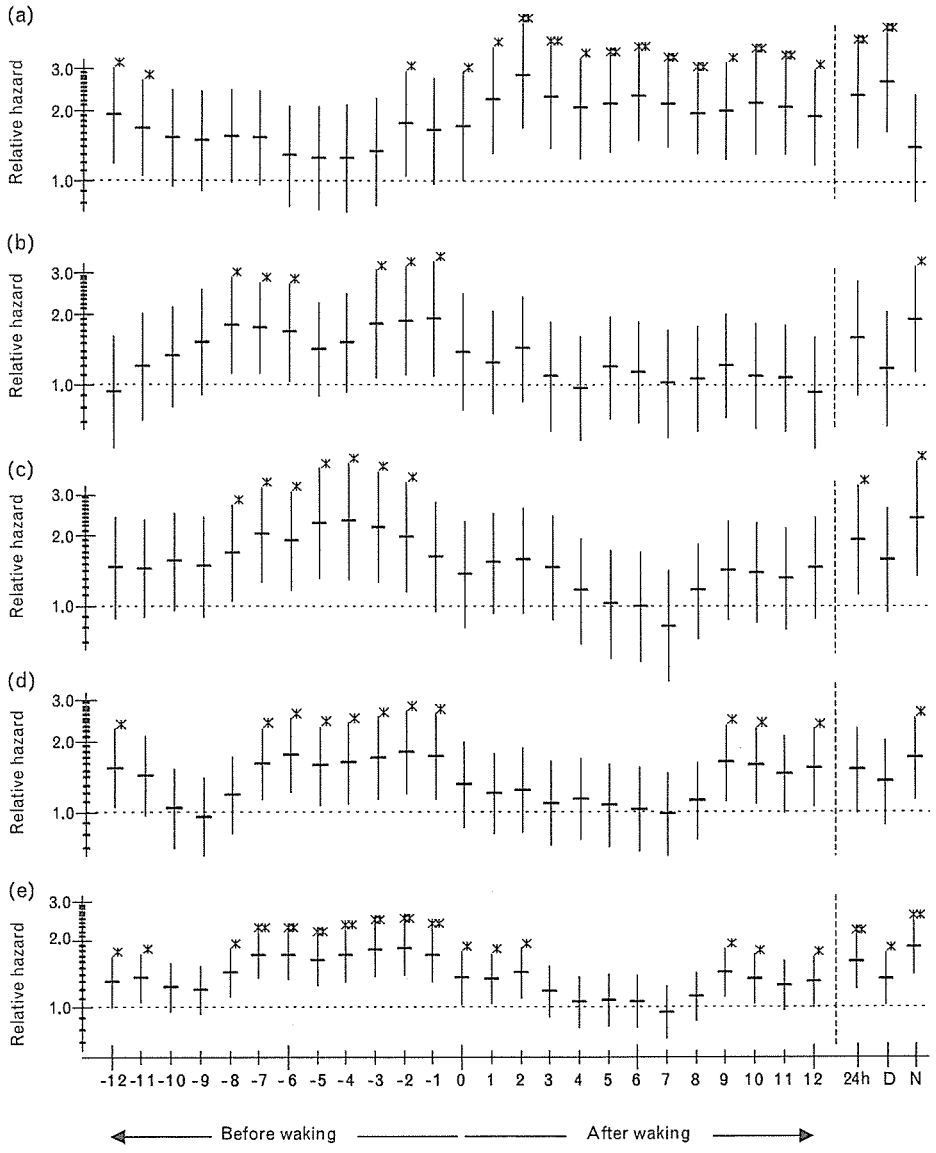
(9.4) mmHg, 2 h after waking it was 129.2 (17.2)/76.5 (10.4) mmHg, and 4 h after waking it was 131.7 (16.8)/77.8 (10.1) mmHg.

Overall, 256 patients (19%) were classified as current or ever smokers, and 407 (30%) were receiving antihypertensive medication. A history of cerebrovascular complications was identified in 65 individuals (5.1%), cardiovascular complications in 18 individuals (1.3%), diabetes in 222 individuals (16%), and hypercholesterolemia in 211 individuals (16%).

Follow-up and outcome

The mean duration of follow-up was 10.6 years (maximum 14.3 years). Twenty-seven participants (2%) moved away from the region and were lost to follow-up. There

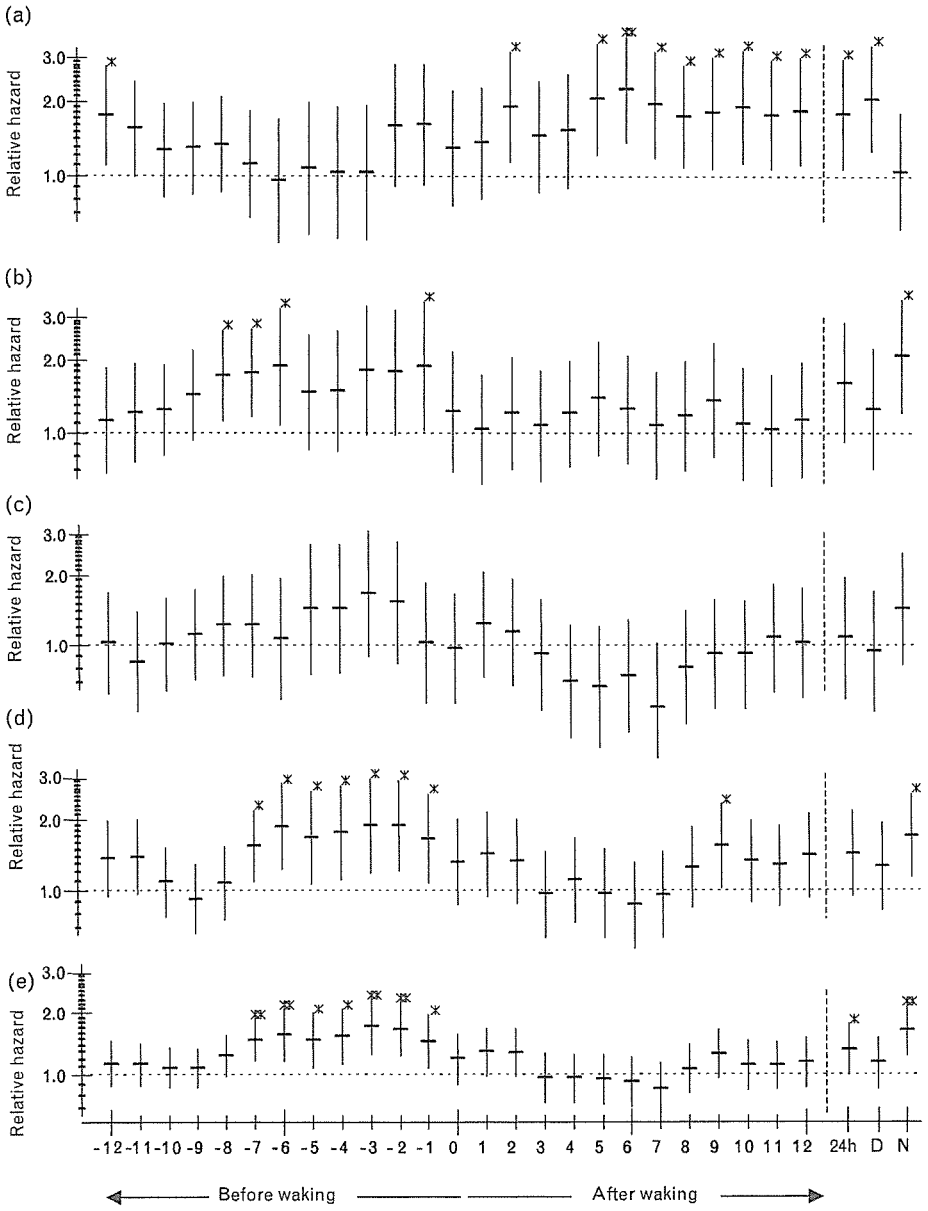
Fig. 3



Relative hazard of the mortality risk per 1-SD elevation of systolic blood pressures. Relative hazards and 95% confidence intervals for the mortality risk of (a) haemorrhagic stroke, (b) cerebral infarction, (c) ischaemic heart disease, (d) non-ischaemic heart disease, and (e) composite of cerebral infarction and heart diseases per 1-SD elevation of systolic blood pressures. Each analysis was adjusted for age, sex, smoking status, and the use of antihypertensive medication, as well as for a history of cerebrovascular and cardiovascular diseases, hypercholesterolemia, and diabetes mellitus. Numbers on the left-hand side panel of the figure indicate the 2-h moving averages of systolic blood pressure over a 24-h period. 24 h, D, and N on the right-hand side panel indicate conventional 24-h, daytime, and night-time mean systolic BPs, respectively. $^{*}P < 0.05$, $^{**}P < 0.002$ (Bonferroni adjustment).

were 232 deaths (17%) among the 1360 individuals, of which 81 were from cerebro or cardiovascular diseases, including 43 from heart disease (19%) and 38 from stroke (16%). Of the 43 heart disease cases, 17 died from ischaemic heart disease (40%). Of the remaining 26 cases, 10 died from heart failure, six from cardiac sudden death, three from arrhythmia, and seven from various other cardiac disorders. Of the 38 stroke cases, 18 (47%) died from composite haemorrhagic stroke, including 11 (29%) from cerebral haemorrhage and seven (18%) from

Fig. 4



Relative hazard of the mortality risk per 1-SD elevation of diastolic blood pressures. Relative hazards and 95% confidence intervals for the mortality risk of (a) haemorrhagic stroke, (b) cerebral infarction, (c) ischaemic heart disease, (d) non-ischaemic heart disease, and (e) composite of cerebral infarction and heart diseases per 1-SD elevation of diastolic blood pressures. Each analysis was adjusted for age, sex, smoking status, and the use of antihypertensive medication, as well as for a history of cerebrovascular and cardiovascular diseases, hypercholesterolemia, and diabetes mellitus. Numbers on the left-hand side panel of the figure indicate the 2-h moving averages of diastolic blood pressure over a 24-h period. 24 h, D, and N on the right-hand side panel indicate conventional 24-h, daytime, and night-time mean diastolic blood pressures, respectively. $*P < 0.05$, $**P < 0.002$ (Bonferroni adjustment).

subarachnoid haemorrhage. There were 17 (45%) deaths from cerebral infarction, and three (8%) from stroke of an undefined type.

Mortality risk of total cerebro and cardiovascular diseases

The total cerebro and cardiovascular mortality risk was significantly associated with elevated night-time and morning 2 h-SBP, whereas it was less markedly associated with daytime 2 h-SBP (Fig. 2b); the RH of a 1-SD elevation of 2 h-SBP 2 h before waking was 1.83 (95% CI 1.44–2.33), 2 h after waking it was 1.67 (95% CI 1.32–2.10), and 4 h after waking it was 1.23 (95% CI 0.98–1.56). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 1.76 (95% CI 1.39–2.25), 1.59 (95% CI 1.25–2.01) and 1.78 (95% CI 1.40–2.27), respectively (Fig. 2b). Even after the Bonferroni adjustment for multiple assessments, elevated night-time and morning 2 h-SBP remained significantly associated with composite cerebro and cardiovascular mortality (Fig. 2b). The associations between 2 h-DBP and the total cerebro and cardiovascular mortality risk showed similar tendencies (Fig. 2c).

Mortality risk of haemorrhagic stroke

The mortality risk of haemorrhagic stroke was significantly associated with elevated morning and daytime 2 h-SBP, whereas the association was less marked for night-time 2 h-SBP (Fig. 3a); the RH of a 1-SD mmHg elevation of 2 h-SBP 2 h before waking was 1.77 (95% CI 1.06–2.99), 2 h after waking it was 2.87 (95% CI 1.72–4.79), and 4 h after waking it was 2.08 (95% CI 1.27–3.41). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 2.37 (95% CI 1.42–3.93), 2.73 (95% CI 1.67–4.45) and 1.42 (95% CI 0.84–2.40), respectively. The associations between 2 h-DBP and the mortality risk of haemorrhagic stroke showed similar tendencies (Fig. 4a).

Mortality risk of cerebral infarction

The mortality risk of cerebral infarction was significantly associated with night-time 2 h-SBP, although it was not associated with elevated daytime 2 h-SBP (Fig. 3b); the RH of a 1-SD mmHg elevation of 2 h-SBP 2 h before waking was 1.89 (95% CI 1.11–3.20), 2 h after waking it was 1.44 (95% CI 0.86–2.42), and 4 h after waking it was 0.97 (95% CI 0.59–1.62). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 1.60 (95% CI 0.92–2.80), 1.19 (95% CI 0.68–2.10), and 1.94 (95% CI 1.16–3.25), respectively. The associations between 2 h-DBP and the mortality risk of cerebral infarction showed similar tendencies (Fig. 4b).

Mortality risk of heart disease

The mortality risk of ischaemic heart disease and the mortality risk of non-ischaemic heart disease were significantly associated with elevated night-time 2 h-SBP, whereas they were less markedly associated with elevated daytime 2 h-SBP (Fig. 3c and d, respectively); the RH for ischaemic heart disease of a 1-SD mmHg elevation of the 2 h-SBP 2 h before waking was 1.98 (95% CI 1.15–3.42), 2 h after waking it was 1.58 (95% CI 0.94–2.65), and 4 h after waking it was 1.16 (95% CI 0.69–1.96). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 1.94 (95% CI 1.13–3.35), 1.58 (95% CI 0.95–2.65) and 2.38 (95% CI 1.34–4.22), respectively. The RH for non-ischaemic heart disease of a 1-SD mmHg elevation of the 2 h-SBP 2 h before waking was 1.80 (95% CI 1.20–2.70), 2 h after waking it was 1.25 (95% CI 0.83–1.87), and 4 h after waking it was 1.14 (95% CI 0.76–1.70). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 1.51 (95% CI 1.00–2.28), 1.34 (95% CI 0.89–2.03) and 1.70 (95% CI 1.13–2.54), respectively. The 2 h-DBP associations with the mortality risk of ischaemic heart disease and the mortality risk of non-ischaemic heart disease were less remarkable but showed similar tendencies (Fig. 4c and d, respectively).

The composite mortality risk of non-haemorrhagic cerebrovascular disease and heart disease was significantly associated with elevated night-time and morning 2 h-SBP, whereas it was only weakly associated with elevated daytime 2 h-SBP (Fig. 3e); the RH of a 1-SD mmHg elevation of 2 h-SBP 2 h before waking was 1.84 (95% CI 1.40–2.42), 2 h after waking it was 1.44 (95% CI, 1.11–1.87), and 4 h after waking it was 1.06 (95% CI 0.82–1.39). The RH of a 1-SD elevation of the conventional 24-h, daytime, and night-time SBP were 1.61 (95% CI 1.22–2.12), 1.35 (95% CI 1.03–1.77) and 1.88 (95% CI 1.43–2.47), respectively. The 2 h-DBP associations with the composite mortality risk of non-haemorrhagic cerebrovascular disease and heart disease showed similar tendencies (Fig. 4e).

The use of antihypertensive medication did not affect the results of any of the analyses (all P for interactions > 0.1).

Discussion

In the present study we examined the relationship between 2 h-SBP moving averages calculated over a 24-h period and the risk of mortality from different types of cerebro and cardiovascular diseases in a general population, using a Cox regression model adjusted for possible confounding factors. BP elevations during particular times of the day were associated with different risks for the various cerebro and cardiovascular disease subtypes.

The predictive value of BP has been reported to increase with an increase in the number of measurements [3,4]. However, no study has compared BP values obtained during different periods of the day (night-time, morning,

and daytime) with the same number of BP measurements. When a simple average of the BP values recorded every 30 min during the night-time (8 h) is calculated, 16 measurements are obtained; similarly, a simple average of the daytime (16 h) BP values recorded every 30 min yields 28 measurements. Therefore, if the predictive power of daytime BP were found to be stronger than that of night-time BP, this could be a reflection of the larger number of measurements taken during the day. The present study is the first to compare the predictive value of average BP obtained during different time periods of a day based on the same number of BP measurements.

Previous studies have reported that there was a higher morbidity and mortality of cerebro and cardiovascular diseases in the morning [11–13]. On the basis of these studies, elevated morning BP has been assumed to have a high predictive value for all cerebro and cardiovascular diseases. The results of the present study also demonstrated that an elevated morning BP has a strong predictive power for total cerebro and cardiovascular disease mortality risk (Fig. 2b). On the other hand, Staessen *et al.* [2] reported in the Syst-Eur substudy that an elevated night-time ambulatory BP had a stronger predictive power for cerebro and cardiovascular morbidity and mortality than elevated daytime and 24-h ambulatory BP. The result of the present study also show that elevated night-time BP has a strong predictive power for the total cerebro and cardiovascular mortality risk (Fig. 2b).

With respect to stroke morbidity and mortality, the Syst-Eur substudy showed no consistent results; elevated daytime BP had a stronger predictive power for stroke than elevated night-time BP in the placebo group, whereas elevated night-time BP tended to have a stronger predictive power in the active treatment group [2]. In the present study, BP elevations during certain periods of the day had their own unique associations with different subtypes of stroke (Fig. 3). Elevated night-time BP had a strong predictive power for cerebral infarction mortality risk and heart disease mortality risk, whereas elevated daytime BP had a strong predictive power for haemorrhagic stroke mortality risk. A high BP in the morning and a high daytime BP may cause intracerebral haemorrhage through mechanical and haemodynamic effects of BP on the vasculature. On the other hand, a continuously high BP load throughout the night may be associated with cerebral infarction and heart diseases because of its atherogenic effect.

It is possible that the control of daytime BP, including morning BP, reduces the risk of intracerebral haemorrhage, whereas antihypertensive treatment targeting night-time BP reduces the risks of cerebral infarction and heart disease. Over the past three decades, the incidence of cerebral haemorrhage has decreased dramatically in Japan, whereas the incidence of cerebral infarction has increased [14]. In Japan during the 1980s and early 1990s, the antihypertensive drugs that were taken once a day in the morning could not maintain their antihypertensive effect throughout the entire 24-h period [15]. Such drug regimens decreased the daytime BP, as shown in the Ohasama cohort [16], and may have decreased cerebral haemorrhage morbidity and mortality [14]. It is possible that 24-h BP control, including night-time and early morning, could reduce cerebral infarction mortality and heart disease mortality. In this study, however, changes over time in antihypertensive drug treatments were not assessed. This may have introduced a bias in the relationship between baseline BP and cardiovascular disease risks. Further research is necessary to determine whether antihypertensive treatments that alter circadian BP variation change the risk of cardiovascular diseases.

The present study found that BP elevations during certain periods of the day are predictive of mortality from specific subtypes of cerebro and cardiovascular disease. This study was not designed to determine whether BP elevation during a certain period of a day is predictive of the occurrence of a cerebro or cardiovascular disease event during a particular period of a day. More research using another approach would be necessary to determine whether such an association exists.

In conclusion, BP elevations occurring during different periods of the day are associated with specific subtypes of cerebro and cardiovascular disease risk. An elevated night-time BP was associated with increased cerebral infarction mortality and heart disease mortality, whereas elevated daytime BP were associated with increased intracerebral haemorrhage mortality.

Acknowledgements

The authors would like to thank the staff members of the Iwate Prefectural Stroke Registry for their valuable support in this follow-up survey.

References

1 Gosse P, Cipriano C, Bemurat L, Mas D, Lemétayer P, N'Tela G, Clementy J. Prognostic significance of blood pressure measured on rising. *J Hum Hypertens* 2001; **15**:413–417.
2 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, *et al.* Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999; **282**:539–546.
3 Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997; **29**:22–29.
4 Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, *et al.* How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; **22**:1099–1104.
5 Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, *et al.* Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000; **18**:847–854.

6 Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; **20**:2183–2189.

7 Imai Y, Abe K, Sasaki S, Minami N, Munakata M, Sekino H, *et al.* Determination of clinical accuracy and nocturnal blood pressure pattern by new portable device for monitoring indirect ambulatory blood pressure. *Am J Hypertens* 1990; **3**:293–301.

8 Association for the Advancement of Medical Instrumentation. *American national standards for electronic or automated sphygmomanometers.* Washington, DC: AAMI; 1987.

9 Imai Y, Nihei M, Abe K, Sasaki S, Minami N, Munakata M, *et al.* A finger volume-oscillometric device for monitoring ambulatory blood pressure: laboratory and clinical evaluations. *Clin Exp Hypertens A* 1987; **9**:2001–2025.

10 Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, *et al.* Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama Study. *Hypertension* 2005; **45**:240–245.

11 Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, *et al.* Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985; **313**:1315–1322.

12 Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, Stone PH. Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987; **75**:131–138.

13 Tsementzis SA, Gill JS, Hitchcock ER, Gill SK, Beevers DG. Diurnal variation of and activity during the onset of stroke. *Neurosurgery* 1985; **17**:901–904.

14 Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, *et al.* Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. *Stroke* 2003; **34**:2349–2354.

15 Muratani H, Fukiyama K, Kamiyama T, Kimura Y, Abe K, Ishii M, *et al.* Current status of antihypertensive therapy for elderly patients in Japan. *Hypertens Res* 1996; **19**:281–290.

16 Chonan K, Hashimoto J, Ohkubo T, Tsuji I, Nagai K, Kikuya M, *et al.* Insufficient duration of action of antihypertensive drugs mediates high blood pressure in the morning in hypertensive population: the Ohasama Study. *Clin Exp Hypertens* 2002; **24**:261–275.

2. 朝晩の家庭血圧測定値の臨床的有用性に関する研究

別添論文

Asayama K, et al. Prediction of stroke by home 'morning' versus 'evening' blood pressure values: the Ohasama study. *Hypertension* 2006;48:737-743.

要約

朝・起床時の家庭血圧は、脳心血管疾患の発症予測能が高いことが明らかとなっている。しかし、晩・就床直前の家庭血圧測定値の予後予測能については、本邦の高血圧治療ガイドラインで測定法が明記されているにもかかわらず、これまで検証されていなかった。

40 才以上で朝晩の家庭血圧を 3 日以上測定した大迫コホート参加者 1766 例（脳卒中の既往者を除く）を研究対象とした。大迫研究における家庭血圧測定条件は高血圧治療ガイドラインに準拠しており、朝は起床後 1 時間以内（排尿後・朝食前・服薬前）に、晩は就床直前（飲酒や入浴の有無は問わず）に、それぞれ 2 分以上の安静の後に、1 機会に 1 回の測定とした。まず、対象者の朝の家庭血圧値ならびに晩の家庭血圧値を連続変量として表した場合の脳血管疾患発症リスクを求めた。次に、それぞれの高血圧の有無で図 1 のように正常血圧 (NT)群、朝の高血圧 (M-HT)群、晩の高血圧 (E-HT)群、朝晩の持続性高血圧 (S-HT)群の計 4 群に分類し、NT 群を基準とした各群の脳血管疾患発症リスクを算出した。解析にはいずれも、交絡因子で補正した Cox 比例ハザードモデルを用いた。

全対象者の朝の家庭血圧平均は 125.0/75.0 mmHg、晩の家庭血圧平均は 123.0/73.2 mmHg であった。平均 10.6 年 (最大 13.9 年)の観察期間中に 156 例の初発脳卒中が発症した。朝・晩とその平均の各家庭血圧が、収縮期血圧で 10mmHg、拡張期血圧で 5mmHg 上昇するごとの脳血管疾患発症のハザード比を求めたところ，朝の家庭血圧に限らず，晩の家庭血圧、平均家庭血圧のいずれの指標も高い脳血管疾患発症予測能を有していた。随時血圧の測定値が得られた 1661 例について、家庭血圧と随時血圧を同一モデルに投入した場合、随時血圧の予後予測能が消失するほど家庭血圧の有用性は高かった。

M-HT 群の脳血管疾患リスクは、S-HT 群と同様、 NT 群より有意に高値であったが、E-HT 群と NT 群の脳血管疾患リスクに有意差は認められなかった。降圧薬服用者 504 名を対象としたサブ解析では、M-HT 群の脳血管疾患リスクは一層高くなったが、E-HT 群の脳血管疾患リスクは NT 群と有意な差を認めなかった。

朝の高血圧群は、朝晩の持続性高血圧群と同程度に高い脳血管疾患予測能を有しており、その傾向は降圧薬服用者で一段と強いものであった。このことから、朝・晩の家庭血圧測定が高血圧診療に有用であること、また家庭血圧に基づいた場合の朝の高血圧、更には朝の不十分な降圧が脳心血管疾患の危険因子であることが示唆された。

Prediction of Stroke by Home "Morning" Versus "Evening" Blood Pressure Values

The Ohasama Study

Kei Asayama, Takayoshi Ohkubo, Masahiro Kikuya, Taku Obara, Hirohito Metoki, Ryusuke Inoue, Azusa Hara, Takuo Hirose, Haruhisa Hoshi, Junichiro Hashimoto, Kazuhito Totsune, Hiroshi Satoh, Yutaka Imai

Abstract—Predictive power of self-measured blood pressure at home (home BP) for cardiovascular disease risk has been reported to be higher than casual-screening BP. However, the differential prognostic significance of home BP in the morning (morning BP) and in the evening (evening BP), respectively, has not been elucidated. In the Ohasama study, 1766 subjects (≥40 years) were followed up for an average of 11 years. The predictive power for stroke incidence of evening BP was compared with that of morning BP as continuous variables. The Cox regression model demonstrated that evening BP and morning BP predicted future stroke risk equally. Subjects were also assigned to 1 of 4 categories based on home BP. In this analysis, stroke risk in morning hypertension ([HT] morning BP ≥135/85 mm Hg and evening BP <135/85 mm Hg; relative hazard (RH): 2.66; 95% CI:1.64 to 4.33) and that in sustained HT(morning BP and evening BP ≥135/85 mm Hg; RH: 2.38; 95% CI: 1.65 to 3.45) was significantly higher than that in normotension (morning BP and evening BP <135/85 mm Hg). The risk in morning HT was more remarkable in subjects taking antihypertensive medication (RH: 3.55; 95% CI: 1.70 to 7.38). Although the risk in evening HT (morning BP <135/85 mm Hg and evening BP ≥135/85 mm Hg) was higher than that in normotension, the differences were not significant. In conclusion, morning BP and evening BP provide equally useful information for stroke risk, whereas morning HT, which indicates HT specifically observed in the morning, might be a good predictor of stroke, particularly among individuals using anti-HT medication. (***Hypertension.* 2006;48:737-743.**)

Key Words: self-measurement ■ home blood pressure ■ stroke ■ general population ■ morning-home blood pressure ■ evening-home blood pressure ■ Ohasama study

Self-measurement of blood pressure (BP) at home (home BP) by individual patients is highly reproducible and reliable and is acknowledged worldwide as a useful clinical tool.[1–4] We have reported previously the strong predictive power of home BP measurements in the morning for cardiovascular disease mortality and stroke incidence.[5–7] It is generally agreed that the prognostic power of home BP is higher than casual-screening BP in accordance with these recent studies.[5–8]

Several guidelines recommended that home BP should be measured both in the morning and in the evening (eg, European Society of Hypertension guidelines based on the German Hypertension League recommendation[9,10]), and it has been recommended in the 7th Report of the Joint National Committee that the home BP level should be evaluated as the average of all of the BP values measured.[1] Because of circadian BP variation and other latent confounding factors, the characteristics of home BP in the morning (morning BP) and that in the evening (evening BP) must be different.[11,12] Our previous study showed that there was a substantial difference between morning BP and evening BP.[11] Moreover, antihypertensive medications were reported to affect circadian BP variation.[13] Although morning BP values have a high predictive power, little is known about the predictive value of evening BP. Bobrie et al[8] demonstrated that the home BP, which was averaged from the morning BP and evening BP readings, had good prognostic value among elderly (≥60 years) hypertensive patients. However, the clinical significance of the home BP in the evening versus that in the morning was unclear. The purpose of the present study is to evaluate the clinical significance of evening BP as well as morning BP for prediction of stroke incidence using data derived from the Ohasama study, a long-term cohort study in the northern part of Japan.

Received April 3, 2006; first decision April 7, 2006; revision accepted August 2, 2006.

From the Departments of Planning for Drug Development and Clinical Evaluation (K.A., T.O., J.H., Y.I.), Clinical Pharmacology and Therapeutics (M.K., T.O., H.M., A.H., T.H., K.T., Y.I.), and Environmental Health Sciences (H.S.), Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation (K.A., T.O., H.M., R.I., J.H., K.T., H.S., Y.I.), Tohoku University 21st Century Center of Excellence Program, Sendai, Japan; and Ohasama Hospital (H.H.), Hanamaki, Japan.

Correspondence to Kei Asayama, Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai, 980-8574, Japan. E-mail keitish@fc5.so-net.ne.jp

Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000240332.01877.11

Methods

Study Population

The present study is a part of the longitudinal observational study of subjects who have been participating in our home BP measurement project in Ohasama, a rural community in the northern part of Japan, since 1987. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. Informed consent was obtained from each subject.

The socioeconomic and demographic characteristics of this region and the details of the selection procedure of study populations have been described previously.[5–7,14–16] There were 1913 eligible individuals aged ≥40 years who measured their morning BP ≥3 times (3 days). This criterion was based on our previous observation that home BP level obtained for the first 3 days was not significantly different from that obtained for the entire study period.[14] For the current analysis, we excluded 56 individuals who did not measure their evening BP ≥3 times. Because 91 individuals had a previous history of stroke, they were excluded from the present analysis to examine the risk of the first onset of stroke. Therefore, the study population consisted of 1766 individuals.

BP Measurements

Physicians and well-trained public health nurses conducted health education classes to inform the subjects on how to measure and record home BP. After their ability to measure home BP was verified, subjects were asked to measure their own BPs once in the morning, in the sitting position within 1 hour after awaking, and after ≥2 minutes of rest and to record the measurements for 4 weeks. When individuals were taking antihypertensive medications, morning BP was measured before taking medications. Subjects were also asked to measure their BPs once in the evening just before going to bed for 4 weeks. We allowed subjects to measure their own BP ≥2 times on each occasion; however, the first measurement value from each occasion was the value that was used for analysis to exclude subjects' selection biases. All of the subjects were instructed to hold their cuff-covered arms at heart level during home BP measurements. These procedures were described in detail in our previous report[14] and followed the Japanese guidelines for self-monitoring of BP at home.[3] Home BP was measured using the HEM 401C (Omron Healthcare Co Ltd), a semiautomatic device based on the cuff-oscillometric principle, which generates a digital display of both systolic and diastolic BP.[17]

Casual BP was measured among 1661 of the 1766 study subjects. Subjects were seated and at rest for ≥2 minutes, then casual BP was consecutively measured 2 times by nurses or technicians. A semiautomatic BP measuring device (USM700F; Ueda Electronic Work Co, Ltd) based on the microphone method was used.[14] Casual BP of each subject was the average of 2 consecutive casual BP readings taken at the beginning of the study.

The devices met the criteria set by the Association for the Advancement of Medical Instrumentation.[18] We used a standard arm cuff for both casual and home BP measurements, because the arm circumference of subjects was ≤34 cm.

Classification of Groups Based on Home BP

The morning BP values and the evening BP values were averaged separately in individuals, eg, the morning BP value in an individual who measured his/her BP for 20 days was the average of these 20 measurements. The combined BP values were the average of morning BP and evening BP.

In the present analysis, we set the criteria of hypertension (HT) based on home BP as ≥135/85 mm Hg according to recent guidelines.[1,2,19] When a systolic or diastolic BP was in a different category, the higher category was applied. As shown in Figure 1, all of the subjects were assigned to 1 of 4 categories based on their own home BP: normotension ([NT] both morning BP and evening BP <135/85 mm Hg); morning HT (morning BP ≥135/85 mm Hg and evening BP <135/85 mm Hg); evening HT (morning BP <135/85 mm Hg and evening BP ≥135/85 mm Hg); and sustained HT (both morning BP and evening BP ≥135/85 mm Hg).

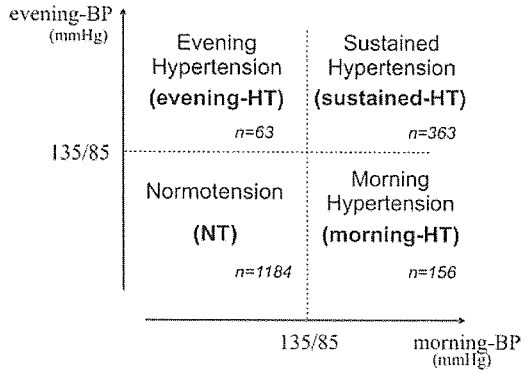


Figure 1. Classification of groups. morning-BP indicates home morning BP; evening-BP, home evening BP.

Follow-Up and Risk Assessment

We accumulated follow-up data from 1987 until December 31, 2001. The subjects' residence status in Ohasama was confirmed by registration cards. These cards are accurate and reliable, because they are used for pensions and social security benefits in Japan.

The incidence and past history of stroke and transient ischemic attack (TIA) were investigated through the Stroke Registration System of Iwate Prefecture, death certificates, receipt of National Health Insurance, and questionnaires sent to each household at the time of home BP measurement. The information was then confirmed by checking the medical records of Ohasama hospital where >90% of the subjects had their regular health checkups. We used computed tomography scans and MRI reports to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis included only the first event in those who had multiple nonfatal events. The diagnostic criteria of stroke, TIA, and their subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.[20]

Other information for individuals such as height, weight, smoking status, use of antihypertensive medication at baseline, or history of heart disease, hypercholesterolemia, or diabetes mellitus was obtained from questionnaires sent to each household at the time of home BP measurements, from records of annual health checkups, and from medical records at Ohasama Hospital. Subjects using lipid-lowering drugs or those with serum cholesterol levels of ≥5.68 mmol/L (220 mg/dL) were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥7 mmol/L (126 mg/dL), nonfasting glucose level of ≥11.11 mmol/L (200 mg/dL), or those using insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus. A past history of cardiovascular disease included a history of myocardial infarction, angina pectoris, atrial fibrillation, and cardiac failure.

Data Analysis

The risk of the first stroke or TIA onset was examined using the Cox proportional hazards model adjusted for possible confounding factors: age, sex, body mass index ≥25 kg/m^2, current or ex-smoking, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. The dependent variable was the number of days from the initial home BP measurement to the date of stroke, TIA, or censoring. Participants who died from causes other than fatal stroke or who were lost to follow-up were treated as censored.

The estimated relative hazard (RH) and the 95% CI of variables were derived from the coefficient and SEM determined by the Cox proportional hazards model. The RH is expressed as the RH for each 10-mm Hg (systolic) or 5-mm Hg (diastolic) increase in BP. Comparison of corresponding regression coefficients and log likelihoods

in the Cox model were used to compare the strength of each morning BP, evening BP, and combined BP. In the categorical analysis, the RH is expressed relative to the reference group (RH=1). Separate models were used for BP classification after verification of the assumption of proportionality for the Cox proportional hazards model.[21] We also assessed the interaction between antihypertensive medication and BP values or BP groups by adding an interaction variable to the Cox model.[21] All of the data were shown as mean (SD) unless otherwise stated. Student *t* test, Fisher's exact test, and ANOVA were used for appropriate analysis. A $P<0.05$ (2-sided test) was accepted as indicative of statistical significance. All of the statistical calculations were conducted using the SAS system (version 9.1, SAS Institute Inc).

Results

The characteristics of subjects classified by 4 BP categories and by use of antihypertensive medications are presented in Table 1. The mean (SD) age was 60.1 (11.0) years, whereas the average age in the sustained HT group was significantly higher than that in the other groups. The ratio of men to women was 40:60. The mean numbers of measurements for morning BP and evening BP of all of the subjects were 23.0 (7.0) and 23.6 (7.1), and the mean systolic/diastolic morning BP and evening BP values of all of the subjects were 125.0 (15.0)/75.0 (10.0) mm Hg and 123.0 (14.5)/73.2 (9.5) mm Hg, respectively. Of the 1766 study subjects, 504 (29%) were treated with antihypertensive medication at baseline, 394 (22%) were current or ex-smokers, 15 (1%) had a history of heart disease, 212 (12%) had a history of diabetes mellitus, and 204 (12%) had a history of hypercholesterolemia. Among 387 treated subjects, 72.9% were prescribed calcium channel blockers, 30.0% diuretics, 27.4% β-blockers, 10.9% angiotensin-converting enzyme inhibitors, 1.6% α-blockers, and 6.7% others.

The subjects were followed up for a median of 10.6 (interquartile range: 8.9 to 13.9) years to a maximum of 13.9 years. Thirty-four subjects (1.9%) had moved away and could not be followed up, and 262 deaths (14.8%) were identified from the residents' registration cards. We observed 156 incident cases of first stroke or TIA among the 1766 individuals: 106 (68%) cerebral infarctions, 31 (20%) intracerebral hemorrhages, 12 (8%) subarachnoid hemorrhages, 4 (3%) TIAs, and 3 (2%) unknown causes. Among untreated subjects, there were 78 (6.2%) stroke or TIA cases, whereas there were 78 (15.5%) cases among subjects taking antihypertensive medication.

Table 2 displays adjusted RH of occurrence of stroke or TIA incidences with a BP per increase of 10 mm Hg (systolic) and 5 mm Hg (diastolic). Among 1766 study subjects, the RHs for total stroke risk based on systolic morning BP, systolic evening BP, diastolic morning BP, and diastolic evening BP increased linearly with the elevation of BP values (all $P<0.0001$). Log likelihood tests indicated that the predictive power of diastolic combined BP was marginally superior to diastolic morning BP ($P=0.047$), whereas there were no significant differences between diastolic combined BP and evening BP and among systolic combined BP and each morning BP or evening BP (all $P>0.05$). In a subgroup of subjects treated with antihypertensive medication, morning BP and evening BP, respectively, predicted the risk of all of the subtypes of stroke except ischemic stroke based on systolic evening BP. No significant increase of hemorrhagic stroke risk was observed in the morning BP and in the evening BP among untreated subjects. There was no significant interaction between the use of antihypertensive medication and each BP value for stroke risk (all $P>0.05$). Among 1661 subjects who measured casual BP in addition to home BPs, adjustment of casual BP had little impact on the results; casual BP did not predict any subtype of stroke events independent of home BPs (Table 3; all $P>0.1$ for casual BP).

The risks of first stroke or TIA of the 4 categories based on morning BP and evening BP are shown in Figure 2. Among all of the subjects (Figure 2a), the risk of stroke in morning HT (RH: 2.66; 95% CI: 1.64 to 4.33) and that in sustained HT (RH: 2.38; 95% CI: 1.65 to 3.45) were significantly higher than the risk in NT. As shown in Figure 2b, the risk of stroke in morning HT was more remarkable when subjects were taking antihypertensive medications at baseline (RH: 3.55; 95% CI: 1.70 to 7.38). However, the interaction between use

TABLE 1. Clinical Characteristics Among Groups Classified by BP Categories and by Use of Antihypertensive Medication

	Classified by BP Categories					Antihypertensive Medication		
Variable	NT	Morning HT	Evening HT	Sustained HT	*P*	Untreated	Treated	*P*
No. of subjects	1184	156	63	363		1262	504	
Age, y	57.9±10.3	61.2±11.4	62.9±10.0	66.3±10.6	<0.0001	57.9±10.6	65.8±10.0	<0.0001
Male, %	35.1	63.5	30.2	48.2	<0.0001	41.1	37.5	0.2
Body mass index, kg/m^2	23.1±3.0	23.4±3.2	24.3±2.9	24.2±3.3	<0.0001	23.2±2.9	23.9±3.4	<0.0001
Past history of CVD, %	0.8	2.6	0.0	0.6	0.2	0.6	1.4	0.1
Diabetes, %	11.0	14.7	11.1	14.3	0.2	10.4	16.1	0.0009
Smoking, %	20.2	38.5	22.2	22.3	<0.0001	23.4	19.6	0.09
Hypercholesterolemia, %	10.3	11.5	9.5	16.0	0.03	7.5	21.8	<0.0001
Use of antihypertensive medication, %	17.5	46.8	42.9	54.3	<0.0001		N/A	
Systolic morning BP, mm Hg	117.0±9.2	136.8±8.3	129.2±3.9	145.2±10.3	<0.0001	121.3±13.5	134.4±14.4	<0.0001
Diastolic morning BP, mm Hg	70.6±7.1	84.0±7.0	76.0±6.0	85.3±9.5	<0.0001	73.3±9.4	79.0±10.2	<0.0001
Systolic evening BP, mm Hg	115.7±9.2	125.8±6.8	137.3±4.9	143.4±9.5	<0.0001	119.7±13.5	131.3±13.7	<0.0001
Diastolic evening BP, mm Hg	69.2±7.0	76.1±6.4	80.4±6.7	84.0±8.5	<0.0001	71.8±9.1	76.9±9.5	<0.0001

CVD indicates cardiovascular disease.