Table 1. Baseline Characteristics by Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Age, y	55 (11)	58 (12)	59 (11)	62 (12)	<0.0001
Women, %	64	63	55	51	<0.0001
Systolic blood pressure, mm Hg	128 (20)	132 (22)	136 (21)	138 (21)	<0.0001
Diastolic blood pressure, mm Hg	76 (11)	78 (11)	79 (11)	79 (12)	<0.0001
Hypertension,* %	29	39	45	52	<0.0001
ECG abnormalities,† %	15	15	16	18	0.1
Diabetes,‡ %	6	9	16	17	<0.0001
Waist, cm	77.4 (8.8)	80.6 (9.0)	83.8 (8.8)	83.8 (9.5)	<0.0001
Body mass index, kg/m^2	22 (3)	23 (3)	24 (3)	24 (3)	<0.0001
Total cholesterol, mmol/L	5.21 (1.02)	5.38 (1.09)	5.44 (1.11)	5.40 (1.13)	0.002
Triglycerides, mmol/L	1.15 (0.99)	1.37 (1.22)	1.56 (1.71)	1.48 (1.02)	<0.0001
HDL cholesterol, mmol/L	1.38 (0.30)	1.34 (0.31)	1.27 (0.29)	1.22 (0.30)	<0.0001
LDL cholesterol,§ mmol/L	3.30 (1.01)	3.41 (1.12)	3.46 (1.14)	3.50 (1.09)	0.0009
Metabolic syndrome, %	14	24	33	39	<0.0001
Current smoker, %	19	20	26	35	<0.0001
Current alcohol use, %	27	27	35	33	0.006
Regular exercise, %	10	9	9	12	0.2

Values are means (SD) or frequencies.

hs-CRP indicates high-sensitivity C-reactive protein; ECG, electrocardiographic; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.

†Minnesota codes 3-1 or 4-1,2,3.

‡Fasting glucose e ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.

§LDL cholesterol level was estimated using the Friedewald formula.

major clinical subgroups defined by the absence or presence of other cardiovascular risk factors are shown in Table 4. There were comparable effects of hs-CRP on the risk of CHD for participants who were and those who were not hypertensive (*P* homogeneity=0.7). Likewise, there were no clear differences in the effects of hs-CRP for participants with and without other cardiovascular risk factors such as diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits (all *P* homogeneity >0.4).

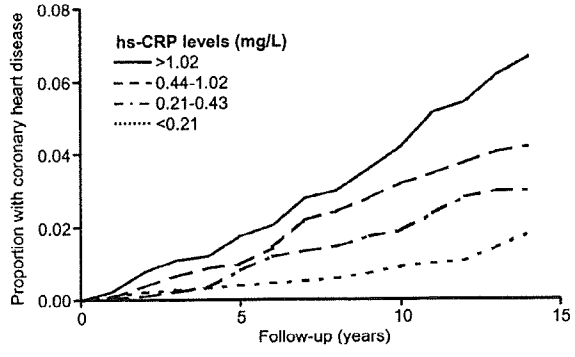

Figure. Age- and sex-adjusted cumulative incidence of coronary heart disease according to quartiles of high-sensitivity C-reactive protein. hs-CRP indicates high-sensitivity C-reactive protein.

Discussion

The present analysis demonstrated that serum hs-CRP levels were clearly associated with future coronary events in a general population of Japanese. The association between hs-CRP and CHD was strong and continuous down to very low hs-CRP levels of less than 0.21 mg/L. These associations remained strong even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, the effects of hs-CRP were comparable for subjects with and without other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, and smoking habits.

Large-scale nested case-control studies have reported that participants with incident CHD had higher levels of hs-CRP.[5,6,8–11] Likewise, large-scale cohort studies have clearly demonstrated that hs-CRP levels predicted future coronary events.[7,12] However, these studies were mainly conducted in Western populations, and it is unclear to what extent these associations apply to Japanese populations. The Honolulu Heart Program has reported a clear association between hs-CRP levels and the future development of CHD in a population of Japanese Americans.[20] The present analysis from the Hisayama Study confirmed the results from these previous observational studies in a general population of Japanese, finding that the relative risks of increasing hs-CRP levels for the development of CHD were similar to those

Table 2. Incidence Rates and Adjusted Hazard Ratios for Development of Coronary Heart Disease According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
No. of events/person-years	11/8589	22/8297	36/8073	60/7485	
Crude incidence rate (per 1000 person-years)	1.3	2.7	4.5	8.0	
Age- and sex-adjusted incidence rate (per 1000 person-years)	1.6	3.3	4.5	7.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.75 (0.85 to 3.61)	2.55 (1.30 to 5.02)	3.96 (2.07 to 7.57)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.60 (0.77 to 3.31)	1.97 (0.98 to 3.95)	2.98 (1.53 to 5.82)	0.0002

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

obtained from other observational studies conducted in Western populations[5–12] or in a population of Japanese Americans.[20] These findings suggest that hs-CRP is an important risk factor for CHD among Japanese as well as among Westerners.

In the present analysis, hs-CRP levels in Japanese (median 0.43 mg/L) were much lower than those in Western populations (median approximately 1.5 to 2.0 mg/L).[21,22] This is consistent with the findings of other cross-sectional studies in which Asian subjects had lower hs-CRP levels compared to Western subjects.[21–24] The reason for this ethnic difference is not clearly resolved, but genetic diversity has been reported to influence hs-CRP levels.[25] The relatively low BMI in Japanese and differences in diet and lifestyle may also have modulated hs-CRP levels.[26] The Honolulu Heart Program reported a median hs-CRP level of 0.54 mg/L among Japa-

Table 3. Mortality Rates and Adjusted Hazard Ratios for Total and Cause-Specific Deaths According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Total deaths					
No. of events/person-years	79/8624	106/8365	143/8181	217/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	12.7	15.2	18.9	23.5	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.08 (0.81 to 1.45)	1.30 (0.99 to 1.72)	1.80 (1.39 to 2.34)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.13 (0.84 to 1.51)	1.41 (1.06 to 1.87)	1.85 (1.41 to 2.43)	<0.0001
Cardiovascular deaths					
No. of events/person-years	16/8624	28/8365	47/8181	67/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	2.2	3.7	6.0	7.2	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.75 to 2.55)	2.15 (1.22 to 3.80)	2.77 (1.60 to 4.80)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.40 (0.75 to 2.60)	2.28 (1.27 to 4.09)	3.00 (1.70 to 5.28)	<0.0001
Noncardiovascular deaths					
No. of events/person-years	63/8624	78/8365	96/8181	150/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	10.5	11.5	12.9	16.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.00 (0.72 to 1.40)	1.09 (0.79 to 1.50)	1.55 (1.15 to 2.08)	0.0004
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.06 (0.76 to 1.48)	1.18 (0.85 to 1.64)	1.56 (1.14 to 2.13)	0.001

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 4. Age- and Sex-Adjusted Hazard Ratios of High-Sensitivity C-Reactive Protein (Highest vs Lowest Quartiles) for Development of Coronary Heart Disease Among Major Clinical Subgroups Defined by the Absence or Presence of Other Cardiovascular Risk Factors

	No. of Events/Person-Years			
	Highest Quartile (hs-CRP>1.02 mg/L)	Lowest Quartile (hs-CRP<0.21 mg/L)	Hazard Ratio* (95% CI)	*P* Homogeneity
Hypertension†				
Absent	18/3843	6/6224	3.18 (1.25 to 8.08)	0.7
Present	42/3643	5/2365	4.27 (1.68 to 10.82)	
Diabetes‡				
Absent	45/6276	9/8122	3.73 (1.81 to 7.68)	0.7
Present	15/1210	2/467	2.84 (0.65 to 12.43)	
Obesity§				
Absent	45/5113	10/7412	3.63 (1.81 to 7.28)	0.7
Present	15/2373	1/1177	5.42 (0.71 to 41.35)	
Hypercholesterolemia‖				
Absent	32/4448	5/5975	4.74 (1.83 to 12.26)	0.4
Present	28/3037	6/2614	2.83 (1.16 to 6.88)	
Metabolic syndrome¶				
Absent	27/4340	7/7068	3.34 (1.44 to 7.75)	1.0
Present	29/2631	3/1122	3.31 (1.00 to 10.92)	
Current smoking				
Absent	34/4910	9/7030	3.39 (1.61 to 7.15)	0.5
Present	26/2576	2/1559	5.94 (1.40 to 25.12)	

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.
*Hazard ratios for the highest vs the lowest quartile of high-sensitivity C-reactive protein.
†Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.
§Body mass index ≥25kg/m^2.
‖Total cholesterol ≥5.69 mmol/L.
¶Defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

nese Americans without CHD,[20] which was lower than that of Western populations but higher than that obtained from the present analysis. These findings suggest that lower hs-CRP levels among Asian populations are derived from differences in genetic factors as well as differences in BMI, diet, and lifestyle.

Another important finding obtained from the present analysis is that the association between hs-CRP levels and CHD was continuous from very low hs-CRP levels and that a slightly elevated hs-CRP level of more than 1 mg/L was clearly associated with increased risk of future coronary events in Japanese. Similar findings were obtained from the Honolulu Heart Program, whose subjects were Japanese American.[20] A low cut-off point of hs-CRP (<1 mg/L) has also been suggested as the target of lipid lowering therapy with statin for maximum reduction of recurrent coronary events or deaths among Western patients with acute coronary syndrome.[27–29] These findings imply that the association between hs-CRP and CHD are likely to be continuous down to very low hs-CRP levels among Asian as well as Western subjects. The American Heart Association and the Centers for Disease Control have recommended categorizing subjects using hs-CRP cut-off points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively, based mainly on the findings obtained from studies done in Western populations.[30] Among Asian subjects whose hs-CRP levels are much lower than those of Western subjects, however, an hs-CRP level of >1 mg/L is likely to be the cut-off point for the high-risk category.

In the present analysis, the effects of hs-CRP on the risks of future coronary events were independent of other cardiovascular risk factors and did not differ between participants with and those without traditional risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits. These results suggest that measurement of hs-CRP is likely to provide additional information for the detection of high-risk individuals among subjects without traditional risk factors as well as for the detection of extremely high-risk individuals among those with traditional risk factors. This finding is consistent with other observational studies suggesting that inclusion of hs-CRP into risk prediction models improves the accuracy of cardiovascular risk classification.[31,32]

Several limitations of our study should be discussed. The primary limitation is that we estimated the cut-off point of hs-CRP for detection of high-risk subjects based on analysis using quartile groupings despite continuous relationships between hs-CRP and the risks of CHD. The cut-off point

could change depending on the way of grouping the subjects or on the way of selecting the reference group. Given that this limitation might have overestimated the cut-off point, the true cut-off point for detection of high-risk subjects may be lower than 1 mg/L. A second limitation is that our findings are based on a 1-time measurement of serum hs-CRP, which may not accurately reflect the status of a study participant. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A third limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.[10] The last limitation is that our study lacked information on drug use at baseline and during the follow-up period. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.[33] However, these medications were rarely used in Japan in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings. It is also known that some medications have been shown to be beneficial for prevention of CHD, and high-risk individuals with higher hs-CRP levels were likely to receive these medications. Given that this limitation might have underestimated the association between hs-CRP and CHD, the true association may be stronger than that obtained from the present analysis.

In conclusion, the present analysis has clearly demonstrated that hs-CRP levels were associated with future coronary events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. High-risk approaches for the prevention of CHD using hs-CRP measurement are likely to provide additional protection against the burden of CHD in Japan.

Sources of Funding

This study was supported in part by Grants-in-Aid for Scientific Research A (No.18209024) and C (No.19590633) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Disclosures

None.

References

1. World Health Organization. *The Atlas of Heart Disease and Stroke.* Geneva: World Health Organization; 2004.
2. World Health Organization. *Preventing Chronic Disease: A Vital Investment.* Geneva: World Health Organization; 2005.
3. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. *Stroke.* 2003;34:2349–2354.
4. Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation.* 1995;91:2488–2496.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973–979.
6. Folsom AR, Aleksic N, Catellier D, Juncja HS, Wu KK. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J.* 2002;144:233–238.
7. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* 2002;347:1557–1565.
8. Luc G, Bard JM, Juhan-Vague I, Ferrieres J, Evans A, Amouyel P, Arveiler D, Fruchart JC, Ducimetiere P. C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME Study. *Arterioscler Thromb Vasc Biol.* 2003;23:1255–1261.
9. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med.* 2004;351:2599–2610.
10. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.* 2004;350:1387–1397.
11. Boekholdt SM, Hack CE, Sandhu MS, Luben R, Bingham SA, Wareham NJ, Peters RJ, Jukema JW, Day NE, Kastelein JJ, Khaw KT. C-reactive protein levels and coronary artery disease incidence and mortality in apparently healthy men and women: the EPIC-Norfolk prospective population study 1993–2003. *Atherosclerosis.* 2006;187:415–422.
12. Sattar N, Murray HM, McConnachie A, Blauw GJ, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Murphy MB, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG, Shepherd J. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation.* 2007;115:981–989.
13. Wakugawa Y, Kiyohara Y, Tanizaki Y, Kubo M, Ninomiya T, Hata J, Doi Y, Okubo K, Oishi Y, Shikata K, Yonemoto K, Maebuchi D, Ibayashi S, Iida M. C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. *Stroke.* 2006;37:27–32.
14. Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, Tanaka K, Ohkubo K, Nakamura H, Abe I, Fujishima M, Iida M. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama Study. *Arch Intern Med.* 2003;163:361–366.
15. Arima H, Kiyohara Y, Kato I, Tanizaki Y, Kubo M, Iwamoto H, Tanaka K, Abe I, Fujishima M. Alcohol reduces insulin-hypertension relationship in a general population: the Hisayama study. *J Clin Epidemiol.* 2002;55:863–869.
16. World Health Organization. *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision - II Edition.* Geneva: World Health Organization; 2004.
17. Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499–502.
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP). *JAMA.* 2001;285:2486–2497.
19. World Health Organisation/International Association for the Study of Obesity/International Obesity Task Force. *The Asia-Pacific Perspective: Redefining Obesity and its Treatment.* Available at: http://www.diabetes.com.au/pdf/obesity_report.pdf.
20. Sakkinen P, Abbott RD, Curb JD, Rodriguez BL, Yano K, Tracy RP. C-reactive protein and myocardial infarction. *J Clin Epidemiol.* 2002;55:445–451.
21. Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *Am J Cardiol.* 2004;93:1238–1242.
22. Matthews KA, Sowers MF, Derby CA, Stein E, Miracle-McMahill H, Crawford SL, Pasternak RC. Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *Am Heart J.* 2005;149:1066–1073.
23. Ishikawa J, Tamura Y, Hoshide S, Eguchi K, Ishikawa S, Shimada K, Kario K. Low-grade inflammation is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives: the Jichi Medical School ABPM Study, wave 1. *Stroke.* 2007;38:911–917.

24. Matsushita K, Yatsuya H, Tamakoshi K, Yang PO, Otsuka R, Wada K, Mitsuhashi H, Hotta Y, Kondo T, Murohara T, Toyoshima H. High-sensitivity C-reactive protein is quite low in Japanese men at high coronary risk. *Circ J.* 2007;71:820–825.
25. MacGregor AJ, Gallimore JR, Spector TD, Pepys MB. Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clin Chem.* 2004;50:130–134.
26. Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clin Chem.* 2003;49:1258–1271.
27. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med.* 2005;352:20–28.
28. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. *J Am Coll Cardiol.* 2005;45:1644–1648.
29. Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation.* 2006;114:281–288.
30. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO III, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the Am Heart Association. *Circulation.* 2003;107:499–511.
31. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med.* 2006;145:21–29.
32. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* 2007;297:611–619.
33. Pearson TA, Bazzarre TL, Daniels SR, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Hong Y, Mensah GA, Sallis JF Jr, Smith S Jr, Stone NJ, Taubert KA. Am Heart Association guide for improving cardiovascular health at the community level: a statement for public health practitioners, healthcare providers, and health policy makers from the Am Heart Association Expert Panel on Population and Prevention Science. *Circulation.* 2003;107:645–651.

Original Article

Arterial Stiffness and QT Interval Prolongation in a General Population: The Hisayama Study

Daisuke MAEBUCHI[1)], Hisatomi ARIMA[1)], Toshiharu NINOMIYA[1)], Koji YONEMOTO[1)], Michiaki KUBO[1)], Yasufumi DOI[2)], Yumihiro TANIZAKI[2)], Kiyoshi MATSUMURA[2)], Mitsuo IIDA[2)], and Yutaka KIYOHARA[1)]

Few population studies have addressed the association of QT interval prolongation with clinical or subclinical arterial disease. The primary objective here was to examine the relationship between the pulse wave velocity (PWV) and the heart rate–corrected QT interval duration (QTc). This is a cross-sectional study, based on a survey of a general population of Japanese. We examined 2,666 community-dwelling individuals without history of cardiovascular disease, aged 40 or over. The PWV was measured between the brachial and ankle regions (baPWV). QTc was estimated using Bazett's equation. The age-adjusted mean values of QTc increased progressively with rising baPWV levels for either sex: for men, 397, 401, 403, and 406 ms for quartile groups defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s, respectively ($p<0.0001$ for trend); for women, 406, 410, 414, and 417 ms for quartile groups defined by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s, respectively ($p<0.0001$ for trend). When male and female subjects were combined, this positive relationship between baPWV and QTc remained significant, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium, alcohol intake, and smoking habits ($p<0.0001$ for trend). In conclusion, baPWV is independently associated with QT interval prolongation. (*Hypertens Res* 2008; 31: 1339–1345)

***Key Words*: pulse wave velocity, QT interval duration, epidemiology**

Introduction

The QT interval duration on an ECG represents the duration of ventricular depolarization and repolarization (*1*, *2*). It has been suggested that disturbance of cardiac ion channels (*1*, *2*), decreased autonomic tone (*3*), and myocardial ischemia/infarction (*4*) extend the QT interval duration, but the etiology of the acquired form of QT interval prolongation has not been clearly defined. Recently, several epidemiological studies have shown that QT interval prolongation predicts the risks of clinical arterial disease (*5–9*) as well as sudden cardiac death (*5*). Likewise, a few cross-sectional studies have suggested a positive association between QT interval prolongation and subclinical arterial disease, such as carotid intima media thickness (*10–12*). However, there is significant uncertainty about the association between QT interval prolongation and other forms of subclinical arterial disease.

From the [1)]Department of Environmental Medicine and [2)]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

This study was supported in part by a Grant-in-Aid for Scientific Research C (No. 18209024), a grant for the Special Coordination Fund for Promoting Science, and a grant for the Technology and Innovative Development Project in Life Sciences from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Address for Reprints: Hisatomi Arima, M.D., Ph.D., Yutaka Kiyohara, M.D., Ph.D., Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Maidashi 3–1–1, Higashi-ku, Fukuoka 812–8582, Japan. E-mail: harima@envmed.med.kyushu-u.ac.jp; kiyohara@envmed.med.kyushu-u.ac.jp

Received November 3, 2007; Accepted in revised form March 11, 2008.

Table 1. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,089 Men

Variables	Brachial-ankle pulse wave velocity (cm/s)				*p* for trend
	963–1,369 (*n*=270)	1,370–1,560 (*n*=273)	1,561–1,840 (*n*=276)	1,841–3,690 (*n*=270)	
Age (years)	51.4±8.4	55.6±9.6	60.2±9.7	68.9±8.9	<0.0001
Heart rate (bpm)	60.1±9.9	63.4±9.9	65.2±10.0	70.4±9.9	<0.0001
Systolic blood pressure (mmHg)	116.4±16.4	126.9±14.9	138.9±15.0	151.2±16.4	<0.0001
Diastolic blood pressure (mmHg)	71.1±9.9	78.6±9.9	84.6±10.0	91.2±9.9	<0.0001
Hypertension (%)	11.8	29.4	60.8	89.5	<0.0001
Antihypertensive drugs (%)	5.1	13.6	22.2	21.2	<0.0001
β-Blocker (%)	2.3	2.8	5.7	3.5	0.15
Calcium channel blocker (%)	4.3	9.3	20.7	16.5	<0.0001
ACE inhibitor (%)	0.9	2.8	5.0	5.1	0.0014
ARB (%)	1.8	5.6	3.0	4.1	0.65
ECG abnormalities (%)	11.5	14.5	17.4	18.9	0.001
Total cholesterol (mmol/L)	5.0±0.9	5.0±0.9	5.1±0.9	5.1±0.9	0.23
HDL cholesterol (mmol/L)	1.5±0.4	1.5±0.4	1.4±0.4	1.5±0.4	0.46
LDL cholesterol (mmol/L)	3.1±0.9	3.1±0.8	3.0±0.8	3.0±0.9	0.25
Triglyceride (mmol/L)	1.3±1.4	1.5±1.3	1.9±1.3	1.9±1.5	<0.0001
Dyslipidemia (%)	46.6	50.5	55.4	59.8	0.002
Fasting plasma glucose (mmol/L)	5.8±1.5	6.1±1.4	6.3±1.3	6.7±1.5	<0.0001
HbA1c (%)	4.9±0.8	5.0±0.8	5.1±0.8	5.3±1.0	<0.0001
Diabetes (%)	12.6	15.0	20.5	43.7	<0.0001
BMI	23.0±3.3	23.4±3.3	23.8±3.3	23.8±3.3	0.01
Obesity (%)	30.2	29.5	32.0	53.2	0.09
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.10
Serum potassium (mmol/L)	4.4±0.3	4.4±0.3	4.3±0.3	4.3±0.3	0.08
Alcohol intake (%)	65.7	65.1	74.2	75.5	0.0006
Habitual smoking (%)	55.7	45.1	45.1	37.3	0.04

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Aortic pulse wave velocity (PWV) is an established marker for subclinical arterial disease (*13*, *14*) as well as for arterial stiffness (*15*). Brachial-ankle PWV (baPWV) has also been shown to be closely associated with aortic PWV and to be an excellent functional marker for subclinical arterial disease (*16*).

The present cross-sectional study evaluates the association of baPWV with heart rate–corrected QT interval duration (QTc) in a general population of Japanese.

Methods

Study Population

The Hisayama Study is an ongoing population-based epidemiological study designed to investigate the morbidity and mortality of cardiovascular disease and its risk factors in the town of Hisayama, Japan. The design of the Hisayama Study has been described in detail elsewhere (*17*). The present cross-sectional study was based on a screening survey conducted in 2002 and 2003. A total of 3,328 residents aged 40 years or over (77.6 % of the total population of this age group) participated in the examination and underwent a comprehensive assessment including baPWV and ECG. Of these, 242 subjects for whom there was no information on baPWV or ECG, 54 subjects who were likely to have peripheral arterial disease (ankle-brachial index <0.9), 189 subjects with atrial fibrillation or intraventricular conduction disturbance (QRS interval >120 ms), 30 subjects with elevated heart rate (>100 beats/min), 22 subjects who did not take a fasting blood test, 16 subjects taking medication affecting the QT interval duration (*i.e.*, antiarrhythmic drugs, antibiotics, antipsychotic agents or antihistamines) (*2*), 111 subjects with a history of cardiovascular disease (myocardial infarction, coronary revascularization or stroke), and 30 subjects who refused to participate in the present study were excluded from the analyses. The final study group comprised 2,666 subjects (1,089 men and 1,577 women).

Table 2. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,577 Women

Variables	Brachial-ankle pulse wave velocity (cm/s)				p for trend
	900–1,269 (n=395)	1,270–1,493 (n=392)	1,494–1,821 (n=396)	1,822–4,128 (n=394)	
Age (years)	49.7±6.8	56.0±8.4	62.7±9.2	71.5±8.4	<0.0001
Heart rate (bpm)	62.9±11.9	64.9±9.9	68.6±10.0	72.8±11.9	<0.0001
Systolic blood pressure (mmHg)	107.5±17.9	121.7±15.8	135.2±15.9	150.5±19.9	<0.0001
Diastolic blood pressure (mmHg)	63.9±11.9	73.5±9.9	80.2±10.0	87.4±11.9	<0.0001
Hypertension (%)	3.2	16.9	50.2	85.5	<0.0001
Antihypertensive drugs (%)	2.5	7.4	25.7	47.5	<0.0001
β-Blocker (%)	0.2	1.4	2.6	6.0	0.0001
Calcium channel blocker (%)	1.9	6.1	20.5	38.1	<0.0001
ACE inhibitor (%)	0.0	0.5	7.3	6.9	<0.0001
ARB (%)	0.2	0.9	5.1	9.8	<0.0001
ECG abnormalities (%)	3.0	8.4	10.3	30.9	<0.0001
Total cholesterol (mmol/L)	5.2±1.0	5.5±0.9	5.6±0.9	5.4±1.0	0.01
HDL cholesterol (mmol/L)	1.8±0.5	1.8±0.4	1.7±0.4	1.6±0.5	0.0002
LDL cholesterol (mmol/L)	3.2±0.9	3.4±0.8	3.4±0.8	3.3±1.0	0.15
Triglyceride (mmol/L)	0.9±0.8	1.1±0.7	1.3±0.7	1.4±0.9	<0.0001
Dyslipidemia (%)	49.2	53.5	58.8	68.4	0.0001
Fasting plasma glucose (mmol/L)	5.4±1.2	5.8±1.1	6.0±1.1	6.4±1.3	<0.0001
HbA1c (%)	4.8±0.8	5.0±0.6	5.1±0.6	5.3±0.8	<0.0001
Diabetes (%)	3.1	8.6	12.4	34.3	<0.0001
BMI	21.7±4.0	22.8±4.0	23.6±4.0	24.0±4.0	<0.0001
Obesity (%)	28.4	24.6	30.5	39.6	0.0004
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.01
Serum potassium (mmol/L)	4.3±0.4	4.3±0.4	4.3±0.4	4.2±0.4	0.003
Alcohol intake (%)	22.5	29.3	31.1	29.3	0.69
Habitual smoking (%)	21.0	6.3	9.4	4.7	0.49

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Measurements of QTc and baPWV

Standard, resting 12-lead ECG was performed using an ECG device (FCP-4266; Fukuda Denshi, Tokyo, Japan) in the supine position in the morning. Heart rate (bpm) and QT interval duration (ms) were determined automatically using the PI-10 ECG Analysis Program (Fukuda Denshi). The program calculated the QT interval duration from the beginning of QRS to the end of the T wave. The QT interval duration was corrected for heart rate by calculating QTc according to Bazett's equation (*18*).

$$\text{QTc} = \text{QT interval duration [ms]}/(60/\text{heart rate})^{1/2}$$

The baPWV was measured in the supine position after at least 5 min of rest using a volume-plethysmographic apparatus (Form PWV/ABI; Colin, Komaki, Japan), as described previously (*19*). Briefly, cuffs to measure baPWV were wrapped on both brachia and ankles. PWV at the brachia and ankles were recorded using a semiconductor pressure sensor. Volume waveforms were stored with automatic gain analysis and quality adjustment. BaPWV was automatically calculated according to the following equation: $\text{baPWV} = (L_a - L_b)/T$, with L_a being the distance from the heart to each ankle, L_b the distance from the heart to the right upper arm, and T the time delay from the right brachial waveform to each ankle waveform.

All clinical examinations including 12-lead ECG, measurement of baPWV and blood test were conducted on the same day.

Relevant Factors

At baseline examination, a self-administrated questionnaire concerning current drug use including antihypertensive agents (*e.g.*, β-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker), smoking, and alcohol intake was completed in advance by each participant and was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. Blood pressure was measured three times

after the subject had rested for at least 5 min using a semiautomatic device (BP203RVIII; Colin) based on the cuff-oscillometric principle with the subject in the sitting position. The mean of the three measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or current use of antihypertensive agents. ECG abnormalities were defined as Q wave (Minnesota codes, 1–1, 2, 3), left ventricular hypertrophy (3–1) or ST depression (4–1, 2, 3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kg divided by height in m squared. Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids, plasma glucose levels, serum calcium, and potassium. Serum total cholesterol, triglycerides, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Hemoglobin A1c levels were measured by high-performance liquid chromatography. Dyslipidemia was defined as total cholesterol ≥5.68 mmol/L, LDL-cholesterol ≥4.13 mmol/L, HDL-cholesterol <1.03 mmol/L, triglycerides ≥1.69 mmol/L, or current use of lipid-lowering agents. Diabetes was defined according to the criteria recommended by the American Diabetes Association (*20*), in addition to a medical history of diabetes. Obesity was defined as BMI ≥25.0 kg/m^2.

Statistical Analysis

The age-adjusted frequencies of relevant factors in quartile groups defined by baPWV were calculated by means of the direct method using the total study population as a standard and were compared using age-adjusted logistic regression models. The age-adjusted mean values of QTc and relevant factors in quartile groups defined by baPWV were calculated using covariance analysis and compared using multiple regression models. Multivariate-adjusted mean values of QTc in the four baPWV groups were estimated using multiple regression models including age, gender, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium levels, alcohol intake, and habitual smoking. Comparisons of the relationships of baPWV with QTc among subgroups were carried out by adding an interaction term to the statistical models. p values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS program package (SAS Institute, Cary, USA).

Ethical Considerations

The ethics committee of Kyushu University approved this study, all participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

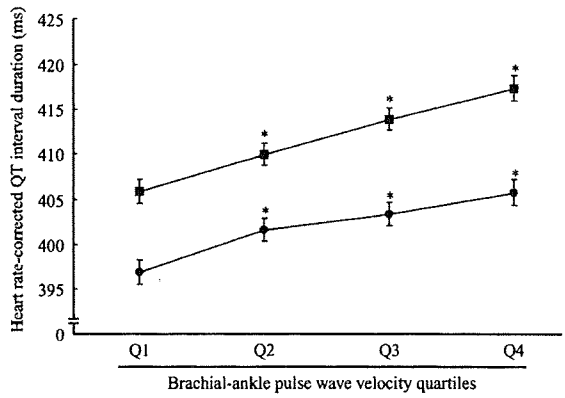

Fig. 1. *Age-adjusted mean values of heart rate–corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels for men (solid circles) and women (solid boxes). For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater. The centers of the circles or boxes are placed at the estimates of mean values. Vertical lines represent SEM for mean values. *$p<0.01$ vs. the lowest quartile group. $p<0.0001$ for trend in both men and women.*

Results

The mean value of QTc was 401.7 ms (SD, 21.5; range, 328.0–494.0) for men and 411.7 ms for women (SD, 23.3; range, 295.0–554.0). Baseline characteristics of male and female participants according to quartile groups defined by baPWV are shown in Tables 1 and 2, respectively. For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s. The subjects with higher baPWV levels were significantly older. The frequencies of hypertension, dyslipidemia, diabetes, obesity, and alcohol intake increased with rising baPWV levels, while an inverse association was observed for the frequency of habitual smoking.

Figure 1 shows the age-adjusted mean values of QTc according to quartiles of the baPWV levels by sex. The age-adjusted mean values of QTc linearly increased with rising baPWV levels for men and women: for men, 396.7, 401.4, 403.2, and 405.6 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend); for women, 405.7, 409.9, 413.8, and 417.4 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend). When the Friedrich formula was used for estimation of QTc, similar associations were observed between baPWV and QTc in both men and women

Table 3. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and Relevant Factors

	Quartiles of brachial-ankle pulse wave velocity				*p* for trend	*p* for homogeneity
	Q1	Q2	Q3	Q4		
Hypertension						
No (n=1,618)	402.4±0.9	405.8±0.9	408.8±1.3	410.8±1.9	<0.0001	0.43
Yes (n=1,048)	402.8±3.9	408.8±2.0	409.7±1.3	412.8±1.2	0.01	
Dyslipidemia						
No (n=1,202)	403.1±1.4	405.9±1.3	410.0±1.4	408.6±1.8	0.03	0.14
Yes (n=1,464)	401.3±1.4	407.0±1.2	408.8±1.1	414.5±1.2	<0.0001	
Diabetes						
No (n=2,243)	402.4±1.0	406.4±0.9	408.7±0.9	411.9±1.2	<0.0001	0.39
Yes (n=423)	404.1±3.8	407.6±2.7	411.7±2.2	412.9±1.9	0.06	
Obesity						
No (n=1,938)	402.7±1.1	406.4±1.0	408.7±1.0	411.2±1.2	<0.0001	0.19
Yes (n=728)	401.7±2.0	406.9±1.7	410.5±1.6	414.8±1.8	<0.0001	
ECG abnormalities						
No (n=2,196)	402.2±1.0	405.8±0.9	409.1±0.9	411.8±1.2	<0.0001	0.43
Yes (n=470)	402.3±3.7	411.1±2.9	410.6±2.3	413.7±2.1	0.04	
Alcohol intake						
No (n=1,504)	404.3±1.4	408.1±1.2	410.6±1.2	413.6±1.3	<0.0001	0.34
Yes (n=1,162)	399.8±1.4	404.4±1.3	407.6±1.3	410.9±1.6	<0.0001	
Habitual smoking						
No (n=2,068)	403.9±1.2	407.2±1.0	409.7±1.0	413.7±1.1	<0.0001	0.21
Yes (n=598)	397.2±1.6	404.1±1.7	408.1±1.8	407.5±2.3	0.0003	

Values are age- and sex-adjusted means±SEM.

Table 4. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and the Number of Relevant Factors

Number of relevant factors	Quartiles of brachial-ankle pulse wave velocity				*p* for trend
	Q1	Q2	Q3	Q4	
0–1 (n=903)	406.0±1.6	404.0±1.4	408.1±1.4	411.6±1.7	0.001
2–3 (n=1,313)	402.5±1.4	404.8±1.3	409.4±1.3	410.4±1.5	0.003
4–7 (n=450)	407.4±2.3	407.7±2.2	413.9±2.2	413.5±2.4	0.02

Values are age- and sex-adjusted means±SEM. Relevant factors: hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, and habitual smoking.

(p<0.0001 for trend in both sexes). In the following analyses, male and female subjects were combined because the relationships of baPWV to QTc were comparable between men and women.

Table 3 shows the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels for subgroups of participants defined on the basis of the presence or absence of hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, or smoking habits. There were comparable relationships between baPWV and QTc for participants who were and were not hypertensive. Likewise, there were no interactions in the relationships of baPWV with QTc between subgroups defined by every other relevant factor (all p values for interaction >0.05). There were also comparable relationships of baPWV with QTc between participants who were and were not taking antihypertensive agents or lipid-lowering agents (p for interaction >0.5). We also estimated the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels by the number of relevant factors (Table 4). There was a significantly positive relationship between baPWV and QTc in each of the groups defined by a number of cardiovascular risk factors of 0–1, 2–3, and 4–7.

Figure 2 shows the multivariate-adjusted mean values of QTc according to quartiles of the baPWV levels. The multivariate-adjusted mean values of QTc significantly increased with rising baPWV levels, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes,

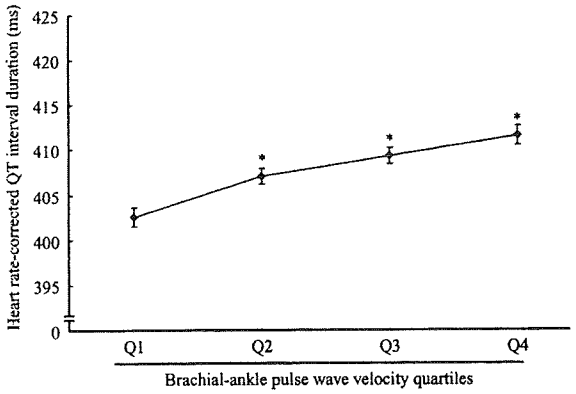

Fig. 2. *Multivariate-adjusted mean values of heart rate–corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels. The centers of the boxes are placed at the estimates of mean values. Other conventions are the same as in Fig. 1. Mean values and p values are adjusted for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes mellitus, obesity, serum calcium and potassium, alcohol intake, and smoking habits.* $*p < 0.01$ *vs. the lowest quartile group.* $p < 0.0001$ *for trend.*

obesity, serum calcium, serum potassium, alcohol intake, and smoking habits ($p<0.0001$ for trend).

Discussion

To our knowledge, this is the first study to address the associations between baPWV and QTc in a general population without preexisting cardiovascular disease. In the present analysis, the mean values of QTc increased with rising baPWV levels for both men and women. These associations remained strong and continuous, even after controlling for traditional cardiovascular risk factors, suggesting an independent relationship between subclinical arterial disease (atherosclerosis) and QT interval prolongation.

In the present study, there were strong and continuous relationships between QTc and baPWV, which has been shown to be a functional marker for subclinical atherosclerotic disease in central and peripheral arteries (*16*, *21*). Ours is the largest study to have investigated the association between subclinical arterial disease and QT interval prolongation, but there have been a few other cross-sectional studies addressing this question using other structural markers of subclinical arterial disease (*10–12*). The Insulin Resistance Atherosclerosis Study (IRAS) investigated the association between carotid intima media thickness and QTc in 912 nondiabetic subjects without coronary artery disease and found a close association between carotid atherosclerosis and QT interval prolongation (*10*). The Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk also showed a positive correlation between carotid intima media thickness and QT interval duration in 1,199 clinically healthy subjects (*11*). These observational data support our hypothesis that subclinical arterial disease is associated with QT interval prolongation.

It is well known that the QT interval is affected by heart rate (*18*, *22*). In order to control for the confounding effects of heart rate, we used QTc, which was estimated by Bazett's formula, and found significant associations between baPWV and QTc. When the Friedrich formula was used for estimation of QTc instead of Bazett's formula, similar associations were observed. We also investigated the association between baPWV and crude QT interval duration and found significantly positive relationships even after adjustment for heart rate, ECG abnormalities, and other cardiovascular risk factors (data not shown). These results suggest that baPWV is significantly associated with QT interval duration and this association is independent of the effects of heart rate.

The mechanism underlying the association between subclinical arterial disease and the acquired form of QT interval prolongation has not been clearly defined. Subclinical arterial disease and subsequent arterial stiffness may increase ventricular load and, as a consequence, may promote myocardial and electrophysiological remodeling, resulting in QT interval prolongation (*23*, *24*). Another possible mechanism is that microvascular atherosclerosis in the coronary artery, which is strongly related to systemic arterial disease, may lead to subendocardial ischemia and thus extend QT interval duration (*25*).

One limitation of our study is that we have no information on subjects with congenital long QT syndrome. However, the prevalence of the congenital long QT syndrome has been reported to be less than 0.1% (*26*). Furthermore, in our subjects the relationship between baPWV and QTc was strong and continuous, even after excluding participants with QT intervals of 440 ms or more ($p<0.0001$ for trend). Thus, the influence of congenital long QT syndrome would seem to have been negligible. Another limitation is that information on repeated measurements of baPWV and QTc is limited. This fact made it difficult for us to conduct longitudinal analysis.

In conclusion, we found close associations between baPWV and QTc for men and women without histories of cardiovascular disease. These associations were independent of hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, alcohol intake, and smoking habits. Thus, subclinical arterial disease appears to contribute to the pathogenesis of QT interval prolongation. Future longitudinal studies are necessary to clarify the causal relationship between subclinical arterial disease and QT interval prolongation.

Acknowledgements

The authors thank the residents of Hisayama for their participation in the survey and the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

References

1. Lepeschkin E, Surawicz B: The measurement of the Q-T interval of the electrocardiogram. *Circulation* 1952; **6**: 378–388.
2. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM: What clinicians should know about the QT interval. *JAMA* 2003; **289**: 2120–2127.
3. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF: Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 1991; **34**: 182–185.
4. Tomassoni G, Pisano E, Gardner L, Krucoff MW, Natale A: QT prolongation and dispersion in myocardial ischemia and infarction. *J Electrocardiol* 1998; **30** (Suppl): 187–190.
5. Dekker JM, Schouten EG, Klootwijk P, Pool J, Kromhout D: Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. *Circulation* 1994; **90**: 779–785.
6. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR: Heart rate–corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol* 2004; **43**: 565–571.
7. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE: Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J* 1999; **20**: 278–284.
8. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS: The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med* 2003; **115**: 689–694.
9. Okin PM, Devereux RB, Howard BV, Fabsitz RR, Lee ET, Welty TK: Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: the Strong Heart Study. *Circulation* 2000; **101**: 61–66.
10. Strohmer B, Pichler M, Iglseder B, Paulweber B: Relationship of QT interval duration with carotid intima media thickness in a clinically healthy population undergoing cardiovascular risk screening. *J Intern Med* 2005; **257**: 238–246.
11. Festa A, D'Agostino R Jr, Rautaharju P, *et al*: QT interval a marker of subclinical atherosclerosis in nondiabetic subjects? The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 1999; **30**: 1566–1571.
12. Takebayashi K, Aso Y, Matsutomo R, Wakabayashi S, Inukai T: Association between the corrected QT intervals and combined intimal-medial thickness of the carotid artery in patients with type 2 diabetes. *Metabolism* 2004; **53**: 1152–1157.
13. Nichols WW: Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; **18**: 3S–10S.
14. Sawabe M, Takahashi R, Matsushita S, *et al*: Aortic pulse wave velocity and the degree of atherosclerosis in the elderly: a pathological study based on 304 autopsy cases. *Atherosclerosis* 2005; **179**: 345–351.
15. Sugawara J, Hayashi K, Yokoi T, *et al*: Brachial-ankle pulse wave velocity: an index of central arterial stiffness? *J Hum Hypertens* 2005; **19**: 401–406.
16. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
17. Arima H, Tanizaki Y, Kiyohara Y, *et al*: Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med* 2003; **163**: 361–366.
18. Bazett HC: An analysis of time relations of the electrocardiogram. *Heart* 1920; **7**: 353–370.
19. Kobayashi K, Akishita M, Yu W, Hashimoto M, Ohni M, Toba K: Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity. *Atherosclerosis* 2004; **173**: 13–18.
20. The Expert Committee on the Diagnosis and Classification: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183–1197.
21. Tomiyama H, Yamashina A, Arai T, *et al*: 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.
22. Oikarinen L, Nieminen MS, Viitasalo M, *et al*: QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 2004; **43**: 1029–1034.
23. Westerhof N, O'Rourke MF: Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens* 1995; **13**: 943–952.
24. Watabe D, Hashimoto J, Hatanaka R, *et al*: Electrocardiographic left ventricular hypertrophy and arterial stiffness: the Ohasama study. *Am J Hypertens* 2006; **19**: 1199–1205.
25. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y: Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol* 1993; **21**: 1497–1506.
26. Skinner J: Guidelines for the Diagnosis and Management of Familial Long QT Syndrome. *Heart Lung Circ* 2007; **16**: 22–24.

Secular Trends in the Incidence of and Risk Factors for Ischemic Stroke and Its Subtypes in Japanese Population

Michiaki Kubo, MD, PhD*; Jun Hata, MD, PhD*; Yasufumi Doi, MD, PhD; Yumihiro Tanizaki, MD, PhD; Mitsuo Iida, MD, PhD; Yutaka Kiyohara, MD, PhD

Background—The study of long-term trends in the incidence of and risk factors for ischemic stroke subtypes could offer insights into primary and secondary prevention.

Methods and Results—We established 3 cohorts of residents ≥40 years of age in 1961, 1974, and 1988 in the Japanese community of Hisayama. Morphological examinations by autopsy or brain imaging were performed on most of the ischemic stroke cases developed in these cohorts. When 13-year follow-up data were compared, the age-adjusted incidence of ischemic stroke and lacunar infarction declined significantly from the first to the third cohort for both sexes, whereas the incidences of atherothrombotic and cardioembolic infarction did not change during this period. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. A rapid increase in the prevalence of metabolic disorders may have offset the impact of improvements in hypertension control and resulted in a slowdown of the decline in the incidence of ischemic stroke in the cohorts in the present study; however, hypertension still makes a large contribution to the development of ischemic stroke.

Conclusions—These findings suggest that in the Japanese population, the incidence of ischemic stroke has declined significantly over the past 40 years, probably owing to better management of hypertension. There is a need for greater primary prevention efforts in the treatment of hypertension and metabolic disorders. (***Circulation.* 2008;118:2672-2678.**)

Key Words: cerebral infarction ■ morbidity ■ risk factors ■ hypertension ■ trend

Stroke continues to be a major public health concern worldwide. In Japan, it is the third leading cause of death and a major neurological cause of long-term disability.[1] The increase in the elderly population that accompanies the improvement in life expectancy is expected to further increase stroke prevalence. On the other hand, there have been major advances in the identification and management of stroke risk factors and the treatment of acute stroke. The study of temporal trends in stroke incidence provides insights into the effect of these factors. Several epidemiological studies have reported that the declining or stable incidence of stroke is likely attributable to better treatment of risk factors over time.[2–8] On the basis of their 50 years of follow-up data, the authors of the Framingham Study recently showed that the age-adjusted incidence of stroke decreased significantly in men and women owing to the improved control of hypertension and smoking.[2] In Japan, the incidence of stroke declined by 60% from 1964 to 1983 in a rural population.[7] We also found in a Japanese urban area that the incidence of ischemic stroke declined markedly between the 1960s and 1970s as a result of hypertension control, but this declining trend was slowed in the late 1980s and 1990s, probably because of an increase in metabolic disorders.[8]

Clinical Perspective p 2678

Because the pathogenesis, prognosis, and treatment differ among ischemic stroke subtypes,[9,10] the evaluation of temporal trends in the incidence of and risk factors for ischemic stroke subtypes may contribute to more effective primary and secondary prevention of ischemic stroke. However, morphological features of the brain were not readily available before the widespread use of computed tomography and magnetic resonance imaging, and the definition of ischemic stroke subtypes was not determined until the early 1990s.[11–13] Therefore, there is little information on the effect of the changes in cardiovascular risk factors on secular trends in the incidence of ischemic stroke and its subtypes.

The Hisayama Study is a population-based study that has established several cohorts at times that correspond to periods of remarkable lifestyle changes in Japan.[8,14–16] One of the

From the Department of Environmental Medicine (M.K., J.H., Y.T., Y.K.) and Department of Medicine and Clinical Science (Y.D., M.I.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, and Laboratory for Genotyping Development (M.K.), Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Yokohama, Kanagawa, Japan.

*The first 2 authors contributed equally to this work.

Correspondence to Michiaki Kubo, MD, Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, Suehiro-cho 1-7-22, Tsurumi, Yokohama, Kanagawa, 230-0045, Japan. E-mail mkubo@src.riken.jp

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.107.743211

characteristics of this study is that most of the deceased study subjects underwent autopsy examination from the beginning of the study, and thus, the morphological features of the brains examined by autopsy or brain imaging are available for most of the stroke cases in each cohort.[8,14] Furthermore, study-team physicians performed physical and neurological examinations on the subjects who developed stroke and collected detailed clinical information throughout the study period. These characteristics of the study design enabled us to examine secular trends in the incidence of and risk factors for ischemic stroke subtypes. We previously reported the steadily declining incidence of lacunar infarction (LAI) using 12-year follow-up data of the first 3 cohorts.[17] In this article, we extend the follow-up period of these cohorts to 13 years and compare the impact of cardiovascular risk factors on the incidence of ischemic stroke subtypes.

Methods

Study Population

The Hisayama Study, an epidemiological study of cerebrovascular-cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town was ≈8000 in 2007, and full community surveys of the residents have been repeated since 1961. The study design and characteristics of the subject population have been described in detail elsewhere.[14–16] Briefly, we established 4 study cohorts from Hisayama residents ≥40 years of age in 1961, 1974, 1988, and 2002 after screening examinations. In 1961, a total of 1658 subjects in that age group consented to participate in the screening examination (participation rate 90.1%). After the exclusion of subjects with a history of stroke or myocardial infarction and subjects who died or moved out of town during the examination, 1618 subjects were enrolled as the first cohort. Similarly, after excluding subjects with a history of stroke or myocardial infarction, we established a second cohort consisting of 2038 subjects from 2135 participants (participation rate 81.2%) in 1974, a third cohort of 2637 subjects from 2742 participants (participation rate 80.9%) in 1988, and a fourth cohort of 3123 subjects from 3328 participants (participation rate 77.6%) in 2002. The health status of these cohort populations was followed up every year by repeated health examinations or by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Only 2 subjects in the first cohort, 2 in the second cohort, and 1 in the third cohort were lost to follow-up. The development of cardiovascular diseases in the study populations was also checked by a daily monitoring system organized by the study team, local physicians, and members of the local health and welfare office. When the subjects died, autopsy examinations were performed at the Department of Pathology, Kyushu University.

Measurement of Cardiovascular Risk Factors

Details of the measurement of cardiovascular risk factors in each cohort were published previously.[8,14–16] In brief, blood pressures were measured 3 times with subjects in a recumbent position in 1961 and in a sitting position in 1974, 1988, and 2002, and hypertension was defined as a mean systolic blood pressure ≥140 mm Hg, a mean diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988 and 2002, in addition to medical history of diabetes. Serum cholesterol levels were measured by the Zak-Henly method with the modification by Yoshikawa in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988 and 2002. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dL). Body height and weight were measured with subjects in light clothing without shoes, and obesity was defined as body mass index ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standardized questionnaire and was categorized as current habitual use or not. Current drinking was also categorized as light (1 to 33 g/d) or heavy (≥34 g/d) drinking according to daily ethanol intake.

Definition of Ischemic Stroke Subtypes

Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit that persisted for >24 hours and was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, or undetermined type.[8] The diagnoses of ischemic stroke subtypes were made on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study[12] and Cerebral Embolism Task Force.[13] We classified ischemic stroke subtypes into 4 categories: LAI, atherothrombotic infarction (ATI), cardioembolic infarction (CEI), and undetermined subtype. Details of the diagnostic criteria of ischemic stroke subtypes have been published previously.[10] Briefly, LAI was diagnosed as the presence of a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subject had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[13] The category of undetermined stroke included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphological information. We considered morphological findings significant and used clinical features as reference information.

During the 13-year follow-up period, first-ever ischemic stroke developed in 134 subjects (83 cases of LAI, 28 of ATI, 17 of CEI, and 6 of undetermined subtype) in the first cohort, in 142 subjects in the second cohort (76 cases of LAI, 29 of ATI, 34 of CEI, and 3 of undetermined subtype), and in 154 subjects in the third cohort (74 cases of LAI, 42 of ATI, 38 of CEI, and 0 of undetermined subtype). Among these, morphological examinations by autopsy or brain imaging were performed on 90.3% (autopsy rate 90.3%) in the first cohort, 97.2% (autopsy rate 87.5%) in the second cohort, and 100.0% (autopsy rate 72.4%) in the third cohort.

Statistical Analysis

The prevalences of possible risk factors were adjusted for age by the direct method and were examined for trends across cohorts by the Cochran-Mantel-Haenszel χ^2 test with 10-year age groupings. Age-adjusted mean values of risk factors were calculated by the covariance method, and their trends were tested by the linear regression model. The incidences of first-ever ischemic stroke and its subtypes were calculated by the person-year method with adjustment for age by the direct method. The world standard population was used as a standard population. The age-adjusted incidences among the first 3 cohorts were compared with the use of the Cox proportional hazards model. Age and sex-adjusted hazard ratios (HRs) and 95% CIs of cardiovascular risk factors for the development of ischemic stroke and its subtypes were estimated by the Cox proportional hazards model in each cohort, and the population attributable risk fraction of each risk factor was calculated.

Ethical Considerations

The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

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

Table 1. Trends in Age-Adjusted Prevalence of Cardiovascular Risk Factors Among 4 Examinations of the Hisayama Study by Sex

	Men					Women				
Variables	1961 (n=705)	1974 (n=855)	1988 (n=1110)	2002 (n=1315)	*P* for Trend	1961 (n=913)	1974 (n=1183)	1988 (n=1527)	2002 (n=1808)	*P* for Trend
Age, y	55±11	56±11	57±12	60±12	<0.001	57±12	58±12	59±12	62±13	<0.001
Hypertension, %	38.4	43.1	44.1	42.0	0.25	35.9	40.1	35.1	31.3	<0.001
Antihypertensive agents, %	2.0	8.4	13.2	18.2	<0.001	2.1	7.4	13.4	16.6	<0.001
Systolic BP, mm Hg*	162±18	157±18	151±18	148±18	<0.001	163±19	161±19	154±19	149±19	<0.001
Diastolic BP, mm Hg*	91±11	90±11	87±11	89±11	0.011	88±11	87±11	83±11	86±11	<0.001
Glucose intolerance, %	11.6	14.1	39.3	54.5	<0.001	4.8	7.9	30.0	35.5	<0.001
Obesity, %	7.0	11.6	24.1	29.3	<0.001	12.9	21.5	23.8	24.0	<0.001
Body mass index, kg/m^2	21.3±2.8	21.7±2.8	22.8±2.8	23.5±2.8	<0.001	21.7±3.4	22.5±3.3	22.9±3.3	22.9±3.4	<0.001
Hypercholesterolemia, %	2.8	12.2	26.9	25.8	<0.001	6.6	19.9	41.6	41.6	<0.001
Total cholesterol, mmol/L	3.9±0.9	4.7±0.9	5.1±0.9	5.1±0.9	<0.001	4.2±1.0	5.0±1.0	5.5±1.0	5.4±1.0	<0.001
Atrial fibrillation, %	0.7	1.6	1.6	1.1	0.84	0.5	0.4	0.9	0.6	0.55
Current smoking, %	75.0	73.3	50.4	46.9	<0.001	16.6	10.2	6.9	8.5	<0.001
Current drinking, %	69.6	63.8	61.5	71.7	0.043	8.3	5.7	9.5	29.1	<0.001
Light drinking, %	43.4	31.9	29.5	37.7	...	8.2	5.5	8.0	27.1	...
Heavy drinking, %	26.3	31.9	32.0	34.0	...	0.1	0.2	1.5	2.0	...

BP indicates blood pressure. Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or current use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol level ≥5.7 mmol/L (220 mg/dL). Obesity was defined as body mass index ≥25.0 kg/m^2. Current drinking was divided into light (1 to 33 g) and heavy (≥34 g) drinking according to daily ethanol intake.

*Mean systolic and diastolic BPs among hypertensive subjects in each examination.

Results

Trends in Cardiovascular Risk Factors

We compared the age-adjusted prevalence of cardiovascular risk factors at baseline examination among the 4 cohorts by sex (Table 1). During the 40-year period from 1961 to 2002, the populations grew 5 years older in both sexes. The age-adjusted prevalence of hypertension was stable at ≈40% in men (*P* for trend=0.25) and decreased significantly in women (*P* for trend <0.001), whereas the proportion of individuals using antihypertensive agents increased consistently with time in both men and women. As a result, age-adjusted mean blood pressures among hypertensive men and women decreased significantly throughout the study period. In contrast, the age-adjusted prevalence of glucose intolerance and obesity increased greatly over the study period for both sexes. More than half of men and one third of women had glucose intolerance in 2002. The age-adjusted prevalence of hypercholesterolemia increased 10-fold in men and 6-fold in women from 1961 to 1988 but was unchanged in 2002. The age-adjusted prevalence of current smoking for men was 4-fold higher than that for women in 1961, and it decreased significantly with time for both sexes. The prevalence of current drinking increased significantly for both sexes in 2002.

Trends in Incidence of Ischemic Stroke Subtypes

We then compared the age-adjusted incidence of ischemic stroke using the results of a 13-year follow-up in the first 3 cohorts (1st, 2nd, and 3rd cohort). The age-adjusted incidence of ischemic stroke declined significantly for both sexes throughout the cohorts: It significantly declined by 56% for men and by 40% for women from the first to the third cohort (*P* for trend <0.001 for either sex; Table 2). In regard to ischemic stroke subtypes, the age-adjusted incidence of LAI for men declined significantly by 54% from the first to the second cohort, and it continued to decline by 39% from the second to the third cohort (*P* for trend <0.001). The age-adjusted incidence of LAI for women also declined by 25% from the first to the second cohort, and it continued to decline by 17% from the second to the third cohort (*P* for trend=0.003). The age-adjusted incidence of ATI and CEI did not change significantly among the cohorts for either sex.

Trends in Proportion of Ischemic Stroke Subtype

The proportions of ischemic stroke subtypes among the cohorts are shown by sex in the Figure. For men, the proportion of subjects with LAI decreased steadily from the first to the third cohort, whereas the proportions with ATI and CEI increased. For women, the proportion of the subjects with CEI increased slightly from the first to the third cohort, but the proportions of those with the other subtypes were constant among the cohorts.

Trends in the Effect of Cardiovascular Risk Factors on Ischemic Stroke

Because both cardiovascular risk factors and the incidence of ischemic stroke changed dramatically, we compared the impact of cardiovascular risk factors on the development of ischemic stroke among the first 3 cohorts (Table 3). In the first cohort, hypertension was a powerful risk factor for ischemic stroke (age- and sex-adjusted HR 3.25, 95% CI 2.17 to 4.86) and largely contributed to its occurrence (population attributable risk fraction 51%). The impact of hypertension gradually declined during the study period; however, hyper-

Table 2. Age-Adjusted Incidence Rate (per 1000 Person-Years) of Ischemic Stroke and Its Subtypes Among 3 Cohorts of the Hisayama Study by Sex, With a 13-Year Follow-Up in Each Cohort

	Men				Women			
	1st Cohort (7456 PY)	2nd Cohort (9655 PY)	3rd Cohort (12 333 PY)	*P* for Trend	1st Cohort (10 294 PY)	2nd Cohort (13 762 PY)	3rd Cohort (17 953 PY)	*P* for Trend
Ischemic stroke								
No. of events	72	70	70		62	72	84	
Incidence rate	8.73	5.44	3.85	<0.001	4.28	3.06	2.57	<0.001
LAI								
No. of events	48	34	30		35	42	44	
Incidence rate	5.68	2.59	1.59	<0.001	2.41	1.81	1.50	0.003
ATI								
No. of events	14	14	22		14	15	20	
Incidence rate	1.88	1.03	1.23	0.27	0.96	0.61	0.54	0.084
CEI								
No. of events	9	21	18		8	13	20	
Incidence rate	1.08	1.74	1.03	0.43	0.58	0.56	0.53	0.86
Undetermined subtype								
No. of events	1	1	0		5	2	0	
Incidence rate	0.09	0.09	0.00	0.20	0.33	0.08	0.00	0.004

PY indicates person-years.

tension was still a significant risk factor and made the largest contribution to the development of ischemic stroke even in the third cohort (HR 1.83, 95% CI 1.29 to 2.58, population attributable risk fraction 30%). Glucose intolerance was also a significant risk factor for ischemic stroke in the first cohort. The effect of glucose intolerance on the occurrence of ischemic stroke was reduced and was not significant in the second cohort, but it appeared to be a significant risk factor in the third cohort. The population attributable risk fraction for glucose intolerance decreased from 13% in the first cohort to 4% in the second cohort and then increased to 13% in the third cohort. Obesity appeared to be a significant risk factor for ischemic stroke in every cohort, and its population attributable risk fraction was increased gradually from 6% in the first cohort to 9% in the third cohort. Hypercholesterolemia, smoking habits, and alcohol intake were not significant risk factors for ischemic stroke in any of the cohorts. In the multivariate analysis that included all risk factors, hypertension was a significant risk factor for ischemic stroke, and its HR decreased from 2.92 (95% CI 1.93 to 4.41) in the first cohort to 1.71 (95% CI 1.20 to 2.45) in the third cohort. Glucose intolerance was an independent risk factor for ischemic stroke in the first cohort (HR 1.91, 95% CI 1.23 to 2.95) but was not significant in the third cohort (HR 1.28, 95% CI 0.93 to 1.78). Obesity was not a significant risk factor in any of the cohorts after adjustment for other risk factors. We tried to investigate the effect of cardiovascular risk factors on ischemic stroke subtypes, but we could not find reliable evidence of an effect of these risk factors on the development of each subtype, probably because of the small number of events.

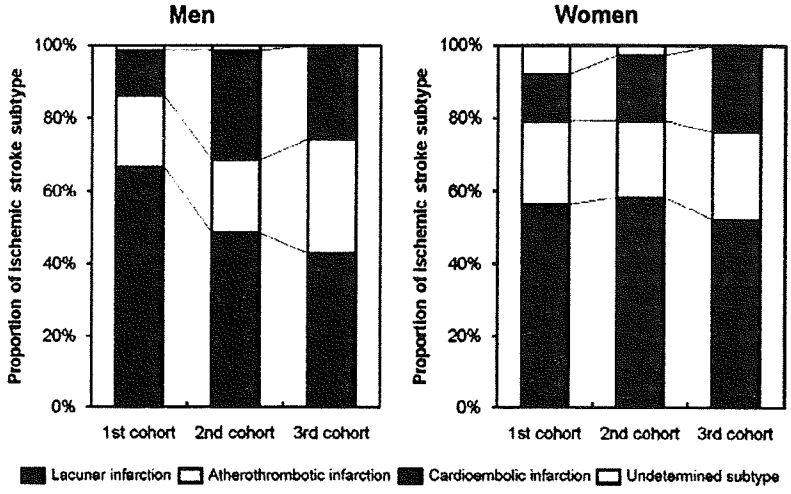

Figure. Proportion of ischemic stroke subtypes among the 3 cohorts of the Hisayama Study by sex.

Table 3. Age- and Sex-Adjusted HRs of Cardiovascular Risk Factors for Ischemic Stroke Among 3 Cohorts of the Hisayama Study

	1st Cohort			2nd Cohort			3rd Cohort		
	HR (95% CI)	P	PAF	HR (95% CI)	P	PAF	HR (95% CI)	P	PAF
Hypertension	3.25 (2.17–4.86)	<0.001	0.51	3.09 (2.05–4.65)	<0.001	0.53	1.83 (1.29–2.58)	<0.001	0.30
Glucose intolerance	2.45 (1.60–3.74)	<0.001	0.13	1.38 (0.87–2.17)	0.17	0.04	1.41 (1.02–1.94)	0.036	0.13
Obesity	1.83 (1.12–3.00)	0.017	0.06	1.63 (1.04–2.57)	0.034	0.07	1.54 (1.07–2.21)	0.021	0.09
Hypercholesterolemia	1.07 (0.50–2.29)	0.87	0.00	1.42 (0.95–2.12)	0.085	0.07	0.96 (0.68–1.35)	0.80	−0.02
Current smoker	1.27 (0.85–1.90)	0.24	0.10	0.83 (0.55–1.24)	0.36	-0.08	1.33 (0.89–1.98)	0.16	0.07
Current drinker	0.99 (0.65–1.51)	0.94	-0.01	1.45 (0.96–2.19)	0.081	0.12	1.09 (0.72–1.64)	0.70	0.02

PAF indicates the population attributable risk fraction.

Discussion

By comparing the incidence of ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the first to the third cohort for both sexes, whereas the incidence of ATI and CEI remained stable. During the study period, blood pressure levels among hypertensive subjects decreased significantly with time as a result of the popularization of antihypertensive medication. The prevalence of smoking habits declined steadily for both sexes. Contrary to these declining trends, the prevalence of metabolic disorders, namely, obesity, glucose intolerance, and hypercholesterolemia, increased steeply with time. These changes in cardiovascular risk factors might affect the incidence of ischemic stroke and its subtypes.

Hypertension is the most powerful risk factor for ischemic stroke.[9] In the first cohort, hypertension contributed to approximately half of the occurrence of ischemic stroke. During the study period, the age-adjusted prevalence of hypertension declined in women, and the proportion of all participants receiving hypertensive treatment increased steeply in both sexes. This improvement of hypertension control resulted in a decrease in age-adjusted mean systolic blood pressure level of 14 mm Hg among hypertensive subjects in both sexes. Because of this improved control of hypertension, the impact of the disease on the development of ischemic stroke was seen to weaken in the third cohort. The Framingham Study also showed a decline in the annual incidence of nonembolic stroke during a follow-up period of 50 years or more.[2] During this period, the mean systolic blood pressure level, prevalence of hypertension, and proportion of all participants receiving treatment for hypertension improved significantly. These reductions in the incidence of ischemic stroke and improvements in treatment for hypertension were similar to the findings of the present study. Our previous study showed that the impact of hypertension was similar for all ischemic stroke subtypes.[10] These results suggest that better management of hypertension might have made the biggest contribution to the declining trend in the incidence of ischemic stroke, especially of LAI; however, hypertension was still a significant risk factor in the third cohort and had a large attributable risk fraction for ischemic stroke. Because half of the hypertensive subjects did not undergo treatment for hypertension in the third cohort, there is a need for greater primary prevention efforts to improve the treatment of hypertension.

In subjects in the present study, the age-adjusted prevalence of metabolic disorders, such as obesity, hypercholesterolemia, and glucose intolerance, increased greatly during the past 40 years, probably owing to the westernization of the Japanese lifestyle. When we examined the impact of these metabolic disorders on the development of ischemic stroke, glucose intolerance was a significant risk factor in the first and the third cohort, and the impact of obesity was constant throughout the study period. Both glucose intolerance and body mass index have been shown to be significant risk factors for ischemic stroke and LAI.[10,18] Moreover, obesity is closely related to other cardiovascular risk factors and jointly increases the risk of ischemic stroke.[19] Our previous study also showed that the accumulation of metabolic disorders (that is, metabolic syndrome) was a significant risk factor for the development of ischemic stroke in our third cohort.[20] We speculate that the improved management of hypertension and the worsening of metabolic disorders cancelled each other out and resulted in the slowdown of the declining trend of the incidence of LAI and the sustained incidence of ATI.

Smoking is a widely accepted risk factor for ischemic stroke in Western populations, but this relationship is controversial for Japanese.[10,21,22] In the present study cohorts, the declining prevalence of smoking habits closely mirrored the declining trend in the incidence of ischemic stroke; however, smoking habits had little impact on the incidence of ischemic stroke in the present study cohorts. One possible explanation is that the association between smoking and the risk of ischemic stroke is only evident in populations with moderate to high levels of serum cholesterol.[23] A recent review of cardiovascular mortality trends in Japan[23] showed that the increase in serum cholesterol appeared mainly in young to middle-aged people. In contrast, elderly people, a high-risk group for ischemic stroke, continued to maintain a lower cholesterol level. However, the prevalence of smoking habits is still high in Japanese men, and therefore, the adverse influence of smoking might appear in the current generation of younger men, with a higher cholesterol level to be seen in the future.

LAI is the most common subtype of ischemic stroke in the Japanese population, unlike in Western populations.[1] Among subjects in the present study, because of the decreased incidence of LAI and the sustained incidences of ATI and CEI, the proportion of ischemic stroke subtypes has become closer to that of Western populations in men (Figure).

However, the pattern of ischemic stroke subtypes differed from that of Western populations, with subjects in the present study showing a high proportion of LAI even in recent years (43% for men and 52% for women in the third cohort). A recent hospital-based registration study in an urban area[24] and a study of 16 992 patients with acute ischemic stroke from rural areas in Japan[25] also showed a higher prevalence of LAI than of other subtypes. One possible explanation for this is the racial difference in the genetic susceptibility of LAI. We recently found 2 susceptibility genes for ischemic stroke, *PRKCH* and *AGTRL1*, in a genome-wide association study.[26,27] A single-nucleotide polymorphism in the *PRKCH* gene increased the risk of LAI, but this single-nucleotide polymorphism is specific to Asian populations.[27]

The present study has several limitations. First, the number of events of subtypes other than LAI was relatively small, and therefore, the power to assess trends in the incidence of and risk factors for ischemic stroke subtypes was weak. Second, there were a large number of subjects overlapping among the cohorts. Indeed, 916 of the subjects in the first cohort also accounted for 45% of the population of the second cohort. In addition, a total of 1229 subjects in the second cohort also participated in the third cohort (47% of the third cohort). However, we treated the overlapping subjects as in any life table analysis, establishing every cohort after excluding subjects with prior stroke or myocardial infarction at baseline. Therefore, these overlapping populations were not considered to distort the incidence trends in the present study. Third, the measurement of blood glucose and the criteria for glucose intolerance were different among the cohorts, which suggests an underestimation of the prevalence of glucose intolerance in the former cohorts. Nevertheless, the rapid changes in other risk factors in the present study are in accordance with the results of the National Nutritional Survey and other surveys of Japan.[23] Finally, the methods of case ascertainment and the diagnostic sensitivity of imaging techniques changed dramatically during the study period. The proportion of case subjects with of incident ischemic stroke who received diagnostic imaging tests increased over time. Echocardiography and carotid scanning were rarely performed in the former cohorts (3.0% and 0% in the first cohort, 29.6% and 4.2% in the second cohort, and 61.7% and 27.3% in the third cohort, respectively). Therefore, it is possible that the trends in the incidence of ATI and CEI were less accurate than the trends for LAI. Nonetheless, we believe that the findings of the present study reflect the actual secular trends in the incidence of ischemic stroke subtypes and their risk factors in the Japanese population, because we performed comprehensive surveillance, including autopsy examinations, in most of the cases.

Conclusions

By comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrated that the incidence of LAI declined significantly from the 1960s to the late 1990s, but LAI remained the most frequent subtype of ischemic stroke in the Japanese. The improvement in hypertension control might have had a major influence on this declining trend. However, hypertension still has a large impact on ischemic stroke, and the increasing prevalence of metabolic disorders might emerge as an additional risk in future cohorts. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

Sources of Funding

This study was supported in part by a grant-in-aid for scientific research A (No. 18209024) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosure

None.

References

1. Hachinski V. Stroke in Japanese. *Stroke*. 2006;37:1143.
2. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA*. 2006;296:2939–2946.
3. Mayo NE, Nadeau L, Daskalopoulou SS, Cote R. The evolution of stroke in Quebec: a 5-year perspective. *Neurology*. 2007;68:1122–1127.
4. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, Kissela B. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke*. 2006;37:2473–2478.
5. Kagan A, Popper J, Reed DM, MacLean CJ, Grove JS. Trends in stroke incidence and mortality in Hawaiian Japanese men. *Stroke*. 1994;25:1170–1175.
6. Sytkowski PA, D'Agostino RB, Belanger A, Kannel WB. Sex and time trends in cardiovascular disease incidence and mortality: the Framingham Heart Study, 1950–1989. *Am J Epidemiol*. 1996;143:338–350.
7. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, Kojima S. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation*. 1989;79:503–515.
8. Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, Iida M. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. *Stroke*. 2003;34:2349–2354.
9. Sacco RL. Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology*. 1997;49(suppl 4):S39–S44.
10. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama Study. *Stroke*. 2000;31:2616–2622.
11. Special report from the National Institute of Neurological Disorders and Stroke: classification of cerebrovascular disease III. *Stroke*. 1990;21:637–676.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III; TOAST Investigators. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke*. 1993;24:35–41.
13. Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol*. 1986;43:71–84.
14. Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res*. 1966;21:64–89.
15. Omae T, Ueda K, Kikumura T, Shikata T, Fujii I, Yanai T, Hasuo Y. Cardiovascular deaths among hypertensive subjects of middle to old age: a long-term follow-up study in a Japanese community. In: Onesti G, Kim KE, eds. *Hypertension in the Young and Old*. New York, NY: Grune & Stratton; 1981:285–297.
16. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Yoshitake T. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes*. 1996;45(suppl 3):S14–S16.
17. Kubo M, Kiyohara Y, Ninomiya T, Tanizaki Y, Yonemoto K, Doi Y, Hata J, Oishi Y, Shikata K, Iida M. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. *Neurology*. 2006;66:1539–1544.
18. Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, Ueshima H; NIPPON DATA80 Research Group. Body mass index and risk

of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. *Cerebrovasc Dis.* 2006;22:409–415.
19. Miyamatsu N, Kadowaki T, Okamura T, Hayakawa T, Kita Y, Okayama A, Nakamura Y, Oki I, Ueshima H. Different effects of blood pressure on mortality from stroke subtypes depending on BMI levels: a 19-year cohort study in the Japanese general population - NIPPON DATA80. *J Hum Hypertens.* 2005;19:285–291.
20. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuruya K, Iida M, Kiyohara Y. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama Study. *Stroke.* 2007;38:2063–2069.
21. Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in general population in Japan. *J Hypertens.* 1990;8:S9–S15.
22. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O; NIPPON DATA80 Research Group. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke.* 2004;35:1836–1841.
23. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J Atheroscler Thromb.* 2007;14:278–286.
24. Kitamura A, Nakagawa Y, Sato M, Iso H, Sato S, Imano H, Kiyama M, Okada T, Okada H, Iida M, Shimamoto T. Proportions of stroke subtypes among men and women ≥40 years of age in an urban Japanese city in 1992, 1997, and 2002. *Stroke.* 2006;37:1374–1378.
25. Kimura K, Kazui S, Minematsu K, Yamaguchi T; for the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Analysis of 16992 patients with acute ischemic stroke and transient ischemic attack in a hospital-based prospective registration study. *Cerebrovasc Dis.* 2004;18:47–56.
26. Hata J, Matsuda K, Ninomiya T, Yonemoto K, Matsushita T, Ohnishi Y, Saito S, Kitazono T, Ibayashi S, Iida M, Kiyohara Y, Nakamura Y, Kubo M. Functional SNP in an Sp1-binding site of *AGTRL1* gene is associated with susceptibility to brain infarction. *Hum Mol Genet.* 2007;16:630–639.
27. Kubo M, Hata J, Ninomiya T, Matsuda K, Yonemoto K, Nakano T, Matsushita T, Yamazaki K, Ohnishi Y, Saito S, Kitazono T, Ibayashi S, Sueishi K, Iida M, Nakamura Y, Kiyohara Y. A nonsynonymous SNP in *PRKCH* (protein kinase Cη) increases the risk of cerebral infarction. *Nat Genet.* 2007;39:212–217.

CLINICAL PERSPECTIVE

Stroke continues to be a major public health concern worldwide. Several epidemiological studies have reported that the declining or stable incidence of stroke is most often attributed to better treatment of risk factors over time. Here, by comparing the incidence of and risk factors for ischemic stroke subtypes among 3 cohorts established at different times in a Japanese community, we demonstrate that the age-adjusted incidence of ischemic stroke and of lacunar infarction declined significantly from the 1960s to the late 1990s, but lacunar infarction remains the most frequent subtype of ischemic stroke in the Japanese. Hypertension was a powerful risk factor for the development of ischemic stroke, and improvement of hypertension control would have largely influenced this declining trend: The age- and sex-adjusted hazard ratio of hypertension decreased from 3.25 (95% CI 2.17 to 4.86) in the first cohort to 1.83 (1.29 to 2.58) in the third cohort. However, hypertension still has a large impact on ischemic stroke, and the increase in metabolic disorders might emerge as an additional risk in the third cohort. The present study indicates the need for continued primary prevention efforts, particularly with respect to hypertension and metabolic disorders.

Impact of Kidney Disease and Blood Pressure on the Development of Cardiovascular Disease

An Overview From the Japan Arteriosclerosis Longitudinal Study

Toshiharu Ninomiya, MD, PhD; Yutaka Kiyohara, MD, PhD; Yosuke Tokuda, MS; Yasufumi Doi, MD, PhD; Hisatomi Arima, MD, PhD; Akiko Harada, PhD; Yasuo Ohashi, PhD; Hirotsugu Ueshima, MD, PhD; for the Japan Arteriosclerosis Longitudinal Study Group

Background—Kidney disease is associated with an increased risk of cardiovascular disease (CVD); however, there have been few well-designed prospective studies of this issue in Asian populations. Recent epidemiological studies have suggested that a lower blood pressure level may be associated with an increased risk of CVD in individuals with kidney dysfunction.

Methods and Results—Using data from 10 community-based cohort studies in Japan, we conducted follow-up on a total of 30 657 individuals 40 to 89 years of age without preexisting CVD or kidney failure and examined the relationship between reduced glomerular filtration rate (GFR) and the risk of CVD. During an average 7.4-year follow-up, 727 individuals experienced CVD. The age- and sex-adjusted incidence of CVD increased significantly in subjects with GFR of 60 to 89 mL · min^{-1} · 1.73 m^{-2} (4.3 per 1000 person-years, P=0.002) and in those with a GFR <60 mL · min^{-1} · 1.73 m^{-2} (6.5, P<0.001) compared with those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} (2.9). Even after adjustment for potential confounding factors, subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} had a 57% (95% CI 14% to 115%) greater risk of CVD than those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2}. The multivariate-adjusted hazard ratios of CVD increased in a log-linear manner with elevations in blood pressure levels, regardless of GFR levels (all P for trend <0.01).

Conclusions—Our findings suggest that a reduced GFR is a significant risk factor for CVD in the general Japanese population. Additionally, a log-linear association of blood pressure level with CVD risk was observed, without evidence of a J-curve association, regardless of GFR levels. (***Circulation.* 2008;118:2694-2701.**)

Key Words: cardiovascular diseases ■ blood pressure ■ kidney ■ meta-analysis

Kidney disease is increasingly being recognized as a leading public health issue. Chronic kidney disease, most commonly defined by a reduction in glomerular filtration rate (GFR) or the presence of proteinuria, affects 10% to 15% of the adult population in Western countries[1,2] and is associated with an increased risk of cardiovascular disease (CVD)[3–5]; however, there have been few well-designed large prospective studies in general Asian communities to date.[6–8]

Clinical Perspective p 2701

Blood pressure is an important determinant of the risk of CVD in the general population,[9,10] in which it has been well established that treatment for high blood pressure prevents CVD.[11] Blood pressure is commonly elevated in individuals with a reduced GFR,[4,5] which suggests that lowering blood pressure may offer significant benefits in this population. Recent prospective cohort studies, however, have reported that the risk of stroke or death for individuals with a reduced GFR is greater among those with systolic blood pressure levels below 120 mm Hg than among those with higher levels.[12,13] These data have raised concerns that lowering blood pressure may provide less benefit than previously believed, or may even be hazardous, in individuals with kidney dysfunction.

In the present report, we discuss the results of a pooling analysis from the Japan Arteriosclerosis Longitudinal Study–Existing Cohorts Combine (JALS-ECC), which is an overview of individual participant data from 21 community-based

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

From the Department of Environmental Medicine (T.N., Y.K., H.A.) and Department of Medicine and Clinical Science (Y.D.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department of Biostatistics/Epidemiology and Preventive Health Sciences (Y.T., A.H., Y.O.), School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan; and Department of Health Science (H.U.), Shiga University of Medical Science, Otsu, Japan.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/118/25/2694/DC1.

Correspondence to Yutaka Kiyohara, MD, PhD, Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka, 812-8582 Japan. E-mail kiyohara@envmed.med.kyushu-u.ac.jp

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.792903**