Table 2. Age- and Sex-Adjusted Incidences (per 1000 Person-Years) of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L				
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Stroke					
No. of events	56	62	74	79	
Age- and sex-adjusted incidence	7.4	8.1	10.1	10.2	0.13
Ischemic stroke					
No. of events	37	47	47	60	
Age- and sex-adjusted incidence	4.9	6.3	6.8	7.9	0.07
Atherothrombotic					
No. of events	9	12	9	21	
Age- and sex-adjusted incidence	1.2	1.6	1.2	3.3*	0.03
Lacunar					
No. of events	14	21	25	33	
Age- and sex-adjusted incidence	2.0	2.6	2.9	3.8*	0.02
Cardioembolic					
No. of events	14	14	12	6	
Age- and sex-adjusted incidence	1.7	2.1	2.4	0.8	0.07
Hemorrhagic stroke					
No. of events	19	15	27	19	
Age- and sex-adjusted incidence	2.6	1.8	3.3	2.3	0.95
CHD					
No. of events	25	28	43	48	
Age- and sex-adjusted incidence	3.4	3.4	5.5*	6.6†	<0.001

*$P<0.05$, †$P<0.01$ vs lowest quartile.

estimated the HRs for the occurrence of nonembolic infarction, including ATI and LI, as well as of CHD, by dividing the subjects into 4 groups according to the presence or absence of high LDL cholesterol levels (the fourth quartile, ≥3.89 mmol/L for nonembolic infarction; the third and fourth quartiles, ≥3.25 mmol/L for CHD) and the metabolic syndrome after adjustments for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Compared with a reference group with neither high LDL cholesterol levels nor the metabolic syndrome, the risk of developing nonembolic infarction was significantly high in the group with high LDL cholesterol levels alone and in the group with both high LDL cholesterol levels and the metabolic syndrome, whereas it was marginally significant for the group with the metabolic syndrome alone. Similarly, the risk for the development of CHD was elevated in both the group with high LDL cholesterol without the metabolic syndrome and the group with high LDL cholesterol and the metabolic syndrome. The risk of CHD was also significant for the group with the metabolic syndrome alone.

Discussion

In a long-term, prospective study of a general Japanese population, we demonstrated positive and significant associations between serum LDL cholesterol level and risk for the development of ATI and CHD. These associations remained unchanged even after adjustment for other lipid fractions as well as other confounding factors, namely, age, sex, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. In addition, the impact of high LDL cholesterol on CVD appeared to be similar to that of the metabolic syndrome. On the other hand, the association between LDL cholesterol level and the risk of CEI was negative and significant after adjusting for the aforementioned risk factors. To our knowledge, this is the first prospective cohort study to investigate the association between LDL cholesterol and the development of subtypes of ischemic stroke.

Several prospective studies have investigated the association between LDL cholesterol and ischemic stroke, but the results were not unanimous. The Cardiovascular Health Study[18] reported a positive association between LDL cholesterol and the risk of ischemic stroke, whereas the Atherosclerosis Risk in Communities Study[19] and the Framingham Study[20] found no clear associations. In the present analysis, LDL cholesterol level was not clearly associated with the risks of stroke and ischemic stroke, but these associations were heterogeneous across ischemic stroke subtypes. Because LI and CEI seem to have a less potent relation with elevated LDL cholesterol,[21,22] inclusion of those subtypes may mask the positive association between LDL cholesterol and ATI. This heterogeneity in the associations of LDL cholesterol level and ischemic stroke subtypes may be a reason for the controversial results obtained from previous studies that investigated the outcome of "total" ischemic stroke.

Table 3. Age-, Sex-, and Multivariate-Adjusted HRs and 95% CIs for the Development of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L					
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend	Continuous Scale
Stroke						
No. of events	56	62	74	79		
Age- and sex-adjusted HR (95% CI)	1.0	0.96 (0.66–1.37)	1.12 (0.84–1.69)	1.23 (0.86–1.75)	0.13	1.08 (0.95–1.23)
Multivariate-adjusted HR (95% CI)	1.0	0.94 (0.64–1.38)	1.15 (0.79–1.67)	1.23 (0.84–1.81)	0.16	1.07 (0.93–1.24)
Ischemic stroke						
No. of events	37	47	47	60		
Age- and sex-adjusted HR (95% CI)	1.0	1.08 (0.70–1.67)	1.17 (0.75–1.80)	1.45 (0.95–2.21)	0.07	1.15 (0.99–1.35)
Multivariate-adjusted HR (95% CI)	1.0	1.05 (0.66–1.66)	1.05 (0.66–1.68)	1.35 (0.85–2.14)	1.19	1.11 (0.94–1.31)
Atherothrombotic						
No. of events	9	12	9	21		
Age- and sex-adjusted HR (95% CI)	1.0	1.14 (0.48–2.71)	0.98 (0.39–2.50)	2.31 (1.03–5.16)*	0.03	1.51 (1.14–1.99)§
Multivariate-adjusted HR (95% CI)	1.0	1.35 (0.54–3.35)	1.19 (0.45–3.17)	2.84 (1.17–6.93)*	0.02	1.60 (1.19–2.16)§
Lacunar						
No. of events	14	21	25	33		
Age- and sex-adjusted HR (95% CI)	1.0	1.29 (0.65–2.54)	1.58 (0.81–3.05)	2.00 (1.05–3.80)*	0.02	1.23 (1.00–1.53)
Multivariate-adjusted HR (95% CI)	1.0	1.19 (0.57–2.50)	1.41 (0.69–2.89)	1.69 (0.83–3.43)	0.11	1.13 (0.90–1.43)
Cardioembolic						
No. of events	14	14	12	6		
Age- and sex-adjusted HR (95% CI)	1.0	0.83 (0.39–1.75)	0.80 (0.37–1.75)	0.39 (0.15–1.04)	0.07	0.71 (0.51–1.00)
Multivariate-adjusted HR (95% CI)	1.0	0.75 (0.34–1.63)	0.59 (0.25–1.38)	0.44 (0.12–0.96)*	0.03	0.64 (0.44–0.94)‡
Hemorrhagic stroke						
No. of events	19	15	27	19		
Age- and sex-adjusted HR (95% CI)	1.0	0.69 (0.35–1.36)	1.24 (0.68–2.24)	0.83 (0.43–1.59)	0.95	0.94 (0.74–1.20)
Multivariate-adjusted HR (95% CI)	1.0	0.71 (0.35–1.47)	1.41 (0.75–2.65)	1.01 (0.50–2.05)	0.53	1.02 (0.79–1.33)
CHD						
No. of events	25	28	43	48		
Age- and sex-adjusted HR (95% CI)	1.0	1.02 (0.60–1.76)	1.77 (1.07–2.91)*	2.00 (1.22–3.28)†	<0.001	1.29 (1.08–1.53)§
Multivariate-adjusted HR (95% CI)	1.0	1.01 (0.56–1.80)	1.68 (0.99–2.84)	1.57 (0.91–2.73)	0.03	1.15 (0.95–1.39)

Multivariate adjustment was made for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. For the continuous scale, HR is given for each 1-mmol/L increase in LDL cholesterol.

*$P<0.05$, †$P<0.01$ vs lowest quartile; ‡$P<0.05$, §$P<0.01$.

The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.[23,24] Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.

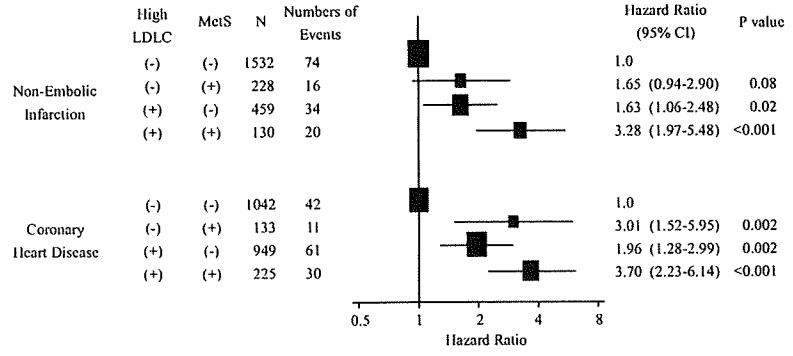

Figure. Multivariate-adjusted HRs for the development of nonembolic infarction and CHD according to the presence or absence of high LDL cholesterol and the metabolic syndrome. Multivariate adjustment was made for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Centers of the boxes are placed at the estimates of HRs. Horizontal lines indicate 95% CIs, and sizes of boxes are proportional to the numbers of events. LDLC indicates LDL cholesterol; MetS, metabolic syndrome.

In our cohort, the association between LDL cholesterol and the risk of LI was no longer significant after multivariate adjustment, suggesting that elevated LDL cholesterol was not an independent risk factor for the development of LI. Our previous report showed that multiple risk factors were related to the occurrence of LI,[14] and case-control studies on the relation between LDL cholesterol level and LI have reported varied associations.[21,22,25] One study reported a significant association between elevated LDL cholesterol and the risk of LI,[25] another study observed lower LDL cholesterol levels in LI cases,[22] and another study found no significant association.[21] Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion.[26] Lipohyalinosis is a vasculopathy caused by hypertension,[26] whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol,[23,24] but cardioembolism seems less related to elevated LDL cholesterol.[22,25] These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

An inverse relation between LDL cholesterol level and the risk of CEI was observed in our earlier population in the 1960s,[14] and the same association was found in the present investigation after adjustment for confounding factors. Although the reason for this association is unknown, a plausible explanation is that a lowered cholesterol level might increase the risk of CEI through the increased occurrence of atrial fibrillation,[27] a predominant risk factor for CEI. Additional clinical and experimental evidence is needed to elucidate the mechanism underlying this association.

The results of previous prospective studies of the association between LDL cholesterol and hemorrhagic stroke have been inconsistent; a significant inverse association was reported in women in the Framingham Study,[20] whereas a nonsignificant association was observed in the Cardiovascular Health Study.[18] Lipid-lowering trials recently conducted in Japan[28,29] and a meta-analysis of >90 000 subjects enrolled in statin trials[8] found no apparent increase in the risk of hemorrhagic stroke. A nonsignificant association between LDL cholesterol and the risk of hemorrhagic stroke observed in our data was in accord with the findings of a previous prospective study[18] and intervention trials.[8,28,29]

Several prospective studies conducted in Western countries have reported positive associations between LDL cholesterol and the risk of CHD.[30] Among Japanese, no study has investigated the association between LDL cholesterol level and the risk of CHD, but several prospective studies have shown that total cholesterol is a strong risk factor for CHD.[31,32] The findings obtained from the present analysis support the results from those prospective studies and, for the first time, have demonstrated a positive association between calculated LDL cholesterol and the risk of CHD in a general Japanese population.

The metabolic syndrome has been shown to be a clear risk factor for CVD,[33] but LDL cholesterol level is not involved in the definition of the metabolic syndrome. In the present analysis, comparable and independent effects were observed for elevated LDL cholesterol and the metabolic syndrome on the risks of nonembolic infarction and CHD. The highest risk was observed for the subgroup with both an elevated LDL cholesterol value and the metabolic syndrome. Similar results were found in a prospective study of a Danish cohort.[34] All of these results imply that management of LDL cholesterol as well as the metabolic syndrome is important for the prevention of ischemic stroke and CHD.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, almost perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD, including ischemic stroke subtypes. One limitation of our study is that our findings are based on a 1-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the relation observed in the present study, because a random misclassification of such nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Another limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation. This equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and CVD. It is unlikely that the bias of LDL cholesterol values that occurred through calculation, if any, would have strengthened the association between LDL cholesterol and ATI or CHD observed in the present analysis.

In conclusion, we have shown that elevated LDL cholesterol is a significant risk factor for developing ATI as well as CHD in a general Japanese population. Because LDL cholesterol level is independent of the metabolic syndrome for the development of CVD, lowering a patient's LDL cholesterol level should be considered together with treatment of other metabolic disorders for the prevention of CVD.

Acknowledgment

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

Source 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.

Disclosures

None.

References

1. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256: 2823–2828.
2. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med*. 1989;320:904–910.
3. Wannamethee SG, Shaper AG, Ebrahim S. HDL cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*. 2000; 31:1882–1888.

4. Ueda K, Hasuo Y, Kiyohara Y, Wada J, Kawano H, Kato I, Fujii I, Yanai T, Omae T, Fujishima M. Intracerebral hemorrhage in a Japanese community, Hisayama: incidence, changing pattern during long-term follow-up, and related factors. *Stroke*. 1988;19:48–52.
5. Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. *BMJ*. 1994;309: 11–15.
6. Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR Jr, Terao A, Baba S, Sankai T, Ito M. Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries: the Akita Pathology Study. *Stroke*. 1993;24:954–964.
7. Soyama Y, Miura K, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Kagamimori S, Nakagawa H. High-density lipoprotein cholesterol and risk of stroke in Japanese men and women: the Oyabe Study. *Stroke*. 2003;34:863–868.
8. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366: 1267–1278.
9. Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2004;117:596–606.
10. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
11. National Institute of Neurological Disorders and Stroke Ad Hoc Committee. Classification of cerebrovascular diseases III. *Stroke*. 1990;21: 637–676.
12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
13. Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol*. 1986;43:71–84.
14. 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.
15. 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.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
17. Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P, Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. *Asia Pac J Clin Nutr*. 2002;11(suppl 8):S732–S737.
18. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, Furberg CD. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52:1639–1647.
19. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2003;34:623–631.
20. Gordon T, Kannel WB, Castelli WP, Dawber TR. Lipoproteins, cardiovascular disease, and death: the Framingham Study. *Arch Intern Med*. 1981;141:1128–1131.
21. Adams RJ, Carroll RM, Nichols FT, McNair N, Feldman DS, Feldman EB, Thompson WO. Plasma lipoproteins in cortical versus lacunar infarction. *Stroke*. 1989;20:448–452.
22. Lindgren A, Nilsson-Ehle P, Norrving B, Johansson BB. Plasma lipids and lipoproteins in subtypes of stroke. *Acta Neurol Scand*. 1992;86: 572–578.
23. Yasaka M, Yamaguchi T, Shichiri M. Distribution of atherosclerosis and risk factors in atherothrombotic occlusion. *Stroke*. 1993;24:206–211.
24. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Risk factors and segment-specific carotid arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1996;27:69–75.
25. Amarenco P, Labreuche J, Elbaz A, Touboul PJ, Driss F, Jaillard A, Bruckert E. Blood lipids in brain infarction subtypes. *Cerebrovasc Dis*. 2006;22:101–108.
26. Fisher CM. Lacunar strokes and infarcts: a review. *Neurology*. 1982;32: 871–876.
27. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.
28. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet*. 2006; 368:1155–1163.
29. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369: 1090–1098.
30. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370: 1829–1839.
31. Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens*. 1990;8(suppl):S9–S15.
32. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis*. 2007;190:216–223.
33. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuryuya 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.
34. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C. Metabolic syndrome, low-density lipoprotein cholesterol, and risk of cardiovascular disease: a population-based study. *Atherosclerosis*. 2006;189: 369–374.

Impact of blood pressure levels on different types of stroke: the Hisayama study

Hisatomi Arima[a], Yumihiro Tanizaki[a], Koji Yonemoto[a], Yasufumi Doi[b], Toshiharu Ninomiya[a], Jun Hata[a], Masayo Fukuhara[a], Kiyoshi Matsumura[b], Mitsuo Iida[b] and Yutaka Kiyohara[a]

Objective Clinical uncertainty remains whether the blood pressure classification and risk stratifications recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) are useful in predicting the risks of stroke and its subtypes in the general Japanese population.

Methods A total of 1621 stroke-free residents of a Japanese community aged at least 40 years were followed up for 32 years. Outcomes were total and cause-specific stroke (lacunar infarction, atherothrombotic infarction, cardioembolic infarction, cerebral haemorrhage and subarachnoid haemorrhage). Incidence was calculated by the pooling of repeated observations method.

Results The age-adjusted incidence of total stroke rose progressively with higher blood pressure levels in both sexes (both P for trend <0.0001). A similar pattern was observed for lacunar infarction in both sexes and for cerebral haemorrhage in men: the differences were significant between optimal blood pressure and grades 1–3 hypertension (all $P<0.05$). The age-adjusted incidence of atherothrombotic infarction in either sex and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension (all $P<0.05$). These associations remained substantially unchanged even after adjustment for other risk factors. In regard to risk stratification, the age-adjusted incidence of stroke significantly increased with the level of risk in both sexes.

Conclusion Our findings suggest that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines are useful in predicting the risk of stroke in a general Japanese population, but the magnitude and patterns of the impact of blood pressure categories are different among stroke subtypes. *J Hypertens* 27:2437–2443 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2009, 27:2437–2443

Keywords: blood pressure, stroke, stroke subtype, prospective cohort study, risk factor

Abbreviations: JSH, Japanese Society of Hypertension; LVH, left ventricular hypertrophy; TOD, target organ damage

[a]Department of Environmental Medicine and [b]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Correspondence to Hisatomi Arima, MD, The Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
Tel: +81 92 652 3080; fax: +81 92 652 3075;
e-mail: harima@envmed.med.kyushu-u.ac.jp

Received 24 February 2009 Revised 5 June 2009
Accepted 13 July 2009

Introduction

Recent guidelines for the management of hypertension recommend assessment of total cardiovascular risk using risk factors, target organ damage (TOD) and pre-existing cardiovascular disease, as well as blood pressure levels [1–3]. These classifications have primarily been established based on clinical and epidemiological studies that investigated the risks of coronary heart disease, stroke and other forms of cardiovascular diseases in Western populations. However, there has been shown to be significant heterogeneity in the incidences of stroke and the frequencies of stroke subtypes between Asian and Western populations: the stroke incidence is higher, as is the proportion of stroke due to parenchymatous small arterial lesions, in Asian populations than in Western populations [4–7]. Because of the heterogeneity in the pathogenesis of stroke subtypes, the impact of blood pressure levels should be evaluated separately for each stroke subtype. Despite clear evidence of the associations between blood pressure levels and the incidence of total stroke [1–3,7–10], clinical uncertainty remains about the impact of blood pressure on the risks of different types of stroke, particularly on the risks of cerebral infarction subtypes.

The Hisayama study is a prospective cohort study of cardiovascular disease conducted in the town of Hisayama, Japan [6,11,12]. During the study period, 93% of the first-ever stroke patients underwent morphological examinations by autopsy and/or brain imaging, and more than 80% of the total number of surviving patients participated in five repeated follow-up examinations. This characteristic study design provided us an

A free communication on a portion of this study was presented at the 18th Scientific Meeting of the European Society of Hypertension/the 22nd Scientific Meeting of the International Society of Hypertension held in Berlin in June 2008.

0263-6352 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins

DOI:10.1097/HJH.0b013e328330e882

opportunity to classify stroke into different types with a high degree of accuracy and to assess the stroke incidence, taking into account the dynamic transition of blood pressure. In the present article, we examined whether the blood pressure classification and risk stratifications recently recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [3] are useful in predicting the occurrence of stroke and its subtypes in Japanese.

Methods

Study population and follow-up survey

In 1961, 1621 stroke-free residents of the town of Hisayama, aged 40 years or over (participation rate 88%), were enrolled in the present study [6,11,12]. Members of this cohort have received follow-up evaluations for 32 years from 1 November 1961 through 30 October 1993. Health examinations were repeated in 1967, 1974, 1978, 1983 and 1988, and the participation rates for these examinations were 96, 87, 85, 81 and 98%, respectively.

For patients who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office of the town, and used this system to gather information on new events of stroke, inclusive of suspected cases [6,11,12]. When stroke occurred or was suspected, physicians in the study team examined the patients and evaluated their detailed clinical information. The clinical diagnosis of stroke was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. During the follow-up period, 1063 patients died, and 861 of these (81%) underwent autopsy to pathologically verify the cause of death and type of stroke. Only two patients were lost to follow-up.

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

Risk factor assessment

At each examination, blood pressure was measured three times using a standard sphygmomanometer after resting for at least 5 min in a supine position. Korotkoff phase 5 was taken as the diastolic blood pressure unless the sounds persisted at zero, in which case Korotkoff phase 4 was recorded. The mean of three measurements was used in the present analysis. We collected medical history and lifestyle information and conducted physical and neurological examinations. Information on antihypertensive treatment, smoking habits and alcohol intake was obtained using a standard questionnaire, and these factors were classified as being either habitually used or not used. Left ventricular hypertrophy (LVH; Minnesota code 3-1), ST depression (4-1, 2, 3 except for 3-1) and atrial fibrillation (8-3) on electrocardiography (ECG) were separately evaluated. Body weight and height were measured, and body mass index (BMI, kg/m^2) was calculated. Proteinuria was tested by the sulfosalicylic acid method in 1961 and 1967, and by the test paper method in 1974, 1978, 1983 and 1988. Serum cholesterol levels were determined by the Zak-Henly method, including a modification by Yoshikawa, in 1961 and 1967; by the Zurkowski method in 1974; and by the enzymatic method in 1978, 1983, and 1988 [13,14]. Glucose intolerance was determined by an oral glucose tolerance test in patients with glycosuria in 1961 and 1967, casual blood glucose levels in 1974, 1978 and 1983, and a 75-g oral glucose tolerance test in 1988, as well by reference to any medical history of diabetes at each examination [15,16].

Blood pressure classification and risk stratification

The JSH 2009 guidelines propose the following blood pressure categories: optimal blood pressure (systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg), normal blood pressure (120–129/80–84 mmHg), high normal blood pressure (130–139/85–89 mmHg), grade 1 hypertension (140–159/90–99 mmHg), grade 2 hypertension (160–179/100–109 mmHg) and grade 3 hypertension ($\geq$180/110 mmHg) [3]. The guidelines also recommend a risk stratification system that determines the whole cardiovascular risk using blood pressure categories and the presence or absence of other risk factors and TOD. In this study, risk factors were defined as age ($\geq$65 years), dyslipidemia (total cholesterol >5.7 mmol/l), glucose intolerance and obesity (BMI ≥ 25 kg/m^2), and TOD was defined as electrocardiographic LVH (Minnesota code 3-1) and 1+ or more positive proteinuria. On the basis of the risk stratification system of the JSH 2009 guidelines, we classified patients into four risk groups. Specifically, the no additive risk group included patients with optimal and normal blood pressure and those with high-normal blood pressure who did not have risk factors or TOD. The low-risk group included patients with grade 1 hypertension who did not have risk factors or TOD. The moderate-risk group included patients with high-normal blood pressure and grade 1 hypertension who had one to two risk factors and those with grade 2 hypertension who did not have risk factors or TOD. The high-risk group included patients with high-normal blood pressure and grade 1 hypertension who had three or more risk factors, glucose intolerance or TOD, patients with grade 2 hypertension who had 1 or more risk factors, glucose intolerance or TOD and patients with grade 3 hypertension.

Stroke definition

The diagnosis of stroke was based on clinical information and the autopsy findings [6]. In principle, stroke was defined as a sudden onset of nonconvulsive and focal

neurological deficits persisting for more than 24 h, and the stroke was then classified as cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage or undetermined type of stroke. Cerebral infarction was further divided into four clinical categories: lacunar infarction, atherothrombotic infarction, cardioembolic infarction or undetermined type of cerebral infarction, based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [17], the criteria for the type of stroke of the TOAST study [18] and the Cerebral Embolism Task Force [19].

During the follow-up period, a total of 410 patients (200 men and 210 women) developed a first-ever stroke, and 381 of these (93%) underwent morphological examinations, including an examination of the cerebrospinal fluid, cerebral angiography, recent brain imaging including computed tomography and magnetic resonance imaging, echocardiography, carotid duplex imaging, and autopsy. Autopsies were performed on 303 stroke cases (74%). Of the 410 stroke cases that developed, 374 (181 men and 193 women) who participated in a follow-up examination within the 7 years previous to the stroke occurrence were eligible for the present study. These stroke cases were divided into 270 cases of cerebral infarction (128 men and 142 women), 68 of cerebral haemorrhage (45 and 23), 32 of subarachnoid haemorrhage (6 and 26) and four of an undetermined type of stroke (2 and 2). The cerebral infarction cases were further subdivided into 153 cases of lacunar infarction (72 and 81), 58 of atherothrombotic infarction (26 and 32), 51 of cardioembolic infarction (28 and 23) and eight of an undetermined type of cerebral infarction (2 and 6).

Statistical analysis

The incidence of stroke and its subtypes was calculated by the pooling of repeated-observations method [12,20,21]. This technique is a generalized person-years approach that incorporates all repeated examinations. It treats each examination interval as a mini follow-up study, in which the nearest risk factor measurements are employed to predict an event in the interval. Observations over multiple intervals are pooled into a single sample to predict the short-term risk of an event. The incidence was compared and the hazard ratios were estimated by the time-dependent Cox's proportional hazards model, in which risk factors other than age and sex were allowed to change in accordance with data from the five follow-up examinations. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Table 1 shows the mean values or frequencies of risk factors for stroke at each examination by sex. The mean age was 56 years for men and 57 years for women at

Table 1 Means (±SD) or frequencies of risk factors at each examination among men and women

	Men						Women					
Risk factors	1961 ($n=707$)	1967 ($n=559$)	1974 ($n=396$)	1978 ($n=341$)	1983 ($n=278$)	1988 ($n=259$)	1961 ($n=914$)	1967 ($n=768$)	1974 ($n=599$)	1978 ($n=546$)	1983 ($n=436$)	1988 ($n=442$)
Age (years)	56±11	60±10	66±9	68±7.3	72±7	75±6	57±12	61±10	67±9	69±8	72±7	75±6
Systolic blood pressure (mmHg)	135±26	141±28	145±26	139±23	142±24	140±23	135±26	137±27	146±26	145±23	148±24	143±25
Diastolic blood pressure (mmHg)	79±14	82±14	80±12	79±11	80±12	77±12	77±13	79±13	79±12	79±11	79±11	75±11
Blood pressure category (%)												
Optimal (<120/80 mmHg)	30.0	24.5	17.7	20.2	15.5	18.9	32.4	29.0	15.0	13.9	11.2	15.6
Normal (120–129/80–84 mmHg)	18.3	13.8	13.9	14.7	16.2	16.2	16.1	13.9	13.4	13.2	10.8	15.4
High-normal (130–139/85–89 mmHg)	13.3	14.0	13.6	18.8	14.4	15.4	14.3	12.1	14.0	15.0	15.4	14.3
Grade 1 (140–159/90–99 mmHg)	19.4	22.2	27.5	27.0	31.3	30.9	19.4	25.4	30.2	32.1	31.2	30.8
Grade 2 (160–179/100–109 mmHg)	10.6	14.7	15.4	13.2	15.5	11.6	10.9	11.5	16.2	18.9	22.5	16.5
Grade 3 (≥180/110 mmHg)	8.5	10.9	11.9	6.2	7.2	7.0	6.9	8.1	11.2	7.0	8.9	7.5
Antihypertensive agent (%)	2.1	15.4	13.6	19.8	24.1	23.9	2.2	18.1	12.0	17.6	23.6	25.1
Left ventricular hypertrophy (%)[a]	22.0	17.5	19.4	19.1	23.3	18.2	10.3	10.2	10.2	15.0	21.9	14.8
ST depression (%)[b]	2.1	1.1	5.3	2.6	3.0	3.9	3.8	2.6	7.5	5.3	6.0	6.4
Atrial fibrillation (%)[c]	0.7	1.1	3.3	3.2	3.7	4.3	0.7	0.8	1.3	1.3	1.0	2.1
Glucose intolerance (%)	12.2	15.2	20.7	21.4	22.3	25.9	4.8	5.1	9.8	11.7	13.8	25.2
Body mass index (kg/m^2)	21.5±2.4	21.5±2.4	21.2±2.7	21.4±3.0	21.3±3.2	21.5±3.0	21.7±2.9	22.1±3.3	22.2±3.5	22.2±3.4	22.0±3.4	22.1±3.5
Total cholesterol (mmol/l)	3.9±0.9	4.1±0.8	4.6±0.9	4.6±1.0	4.8±1.0	4.6±1.0	4.2±1.0	4.6±1.0	5.1±0.9	5.3±1.0	5.4±1.0	5.4±1.1
Proteinuria (%)	7.1	3.8	16.4	6.3	13.6	8.5	9.4	3.6	13.4	4.8	9.4	7.8
Smoking habits (%)	76.2	70.2	67.0	60.7	52.5	45.2	17.1	14.9	12.2	11.3	8.3	10.9
Alcohol intake (%)	69.3	61.7	61.5	55.1	54.0	52.1	8.3	4.7	5.2	6.4	6.4	6.1

[a] Minnesota code 3-1. [b] Minnesota codes 4-1, 2, 3 except for 3-1. [c] Minnesota code 8-3.

baseline. The mean systolic blood pressure levels and frequency of hypertension (grades 1–3) slightly increased from 1961 to 1988 for both men and women. The frequency of patients taking antihypertensive agents increased from 2.1% in 1961 to 23.9% in 1988 among men and from 2.2 to 25.1% among women. The frequency of glucose intolerance and mean total cholesterol levels also increased from 1961 to 1988 in both sexes.

Incidence and adjusted hazard ratio for stroke and its subtypes

Tables 2 and 3 show the age-adjusted incidence of total stroke and its subtypes according to the blood pressure categories of the JSH 2009 guidelines [3] by sex. The incidence of total stroke and its subtypes, except for that of subarachnoid haemorrhage, was higher in men than in women. In both sexes, the stroke incidence increased steeply with elevation in blood pressure levels (both P for trend <0.0001); the differences between optimal blood pressure and grades 1–3 hypertension were statistically significant (all $P<0.01$). These associations remained significant even after controlling for age, LVH, ST depression and atrial fibrillation on ECG, glucose intolerance, BMI, total cholesterol, smoking habits and alcohol intake in either sex (both P for trend <0.0001). Similar patterns were observed for cerebral infarction in both sexes and for cerebral haemorrhage in men (all P for trend <0.0001). For women, the incidence of cerebral haemorrhage significantly increased in grade 2 hypertension ($P=0.02$), as did the incidence of subarachnoid haemorrhage in grade 3 hypertension ($P=0.01$). For men, subarachnoid haemorrhage did not show a clear relationship with the blood pressure categories, probably due to the small number of events. With regard to subtypes of cerebral infarction, the incidence of lacunar infarction increased with elevation of blood pressure levels in both sexes (both P for trend <0.0001). In contrast, the incidence of atherothrombotic infarction sharply increased in grade 3 hypertension for both sexes (both $P<0.05$), and the incidence of cardioembolic infarction significantly increased in grade 3 hypertension for women ($P=0.04$). Comparable associations were observed between blood pressure categories and stroke even after excluding patients taking antihypertensive agents at each examination.

Risk stratification

Figure 1 shows the age-adjusted incidence of stroke by risk groups defined by the risk stratification system proposed by the JSH 2009 guidelines [3] among men and women. The stroke incidence increased steeply with the elevation of risk levels for men and women (both P for trend <0.0001): compared to the no-additive risk group, the stroke incidence was significantly higher in the moderate and high-risk groups for both sexes (all $P<0.05$) and also in the low-risk group for women ($P=0.008$).

Table 2 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among men

				Hypertension			
Type of stroke	Optimal	Normal	High-normal	Grade 1	Grade 2	Grade 3	P trend
Total stroke							
Age-adjusted incidence (per 1000 person-years)	3.1	5.3	5.4	10.0**	20.9**	54.2**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.64 (0.76–3.56)	1.52 (0.70–3.31)	3.31 (1.73–6.32)**	4.22 (2.16–8.25)**	5.75 (2.93–11.30)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	2.4	2.8	3.8	6.9**	8.9**	19.5**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.54–3.48)	1.37 (0.55–3.41)	3.10 (1.47–6.55)**	3.29 (1.50–7.21)**	4.88 (2.24–10.65)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	1.4	1.1	1.8	4.8**	6.4**	11.2**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.11 (0.29–4.15)	1.49 (0.45–4.96)	3.09 (1.13–8.47)*	3.26 (1.14–9.30)*	4.66 (1.63–13.32)**	0.0003
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.0	1.0	0.4	1.0	1.1	6.1*	0.0001
Multivariate-adjusted hazard ratio (95% CI)	–	1 (reference)	0.45 (0.04–4.94)	2.27 (0.48–10.87)	2.48 (0.47–12.97)	5.08 (1.04–24.89)*	0.0004
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	1.0	0.7	1.6	1.1	1.2	1.5	0.18
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.89 (0.19–4.12)	0.81 (0.18–3.79)	1.52 (0.44–5.21)	0.99 (0.24–4.14)	1.39 (0.32–6.06)	0.57
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.9	1.2	3.0*	7.4**	34.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	2.22 (0.37–13.34)	2.95 (0.53–16.38)	5.59 (1.21–25.75)*	9.30 (1.98–43.61)**	12.04 (2.47–58.66)**	<0.0001
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.3	1.6	0.0	0.1	0.5	0.3	0.66
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.28 (0.28–38.13)	–	1.16 (0.07–19.67)	1.90 (0.09–41.01)	3.41 (0.15–76.27)	0.83

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P<0.05$. ** $P<0.01$ vs. normal blood pressure for atherothrombotic infarction and vs. optimal blood pressure for other types of stroke.

Table 3 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among women

Type of stroke	Optimal	Normal	High-normal	Hypertension			P trend
				Grade 1	Grade 2	Grade 3	
Total stroke							
Age-adjusted incidence (per 1000 person-years)	2.0	2.5	3.9	6.3**	11.8**	22.4**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.53 (0.60–3.89)	2.19 (0.93–5.16)	3.92 (1.84–8.35)**	4.89 (2.24–10.67)**	7.51 (3.39–16.64)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	1.4	2.1	2.0	4.6**	6.1**	14.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.78 (0.58–5.47)	1.91 (0.65–5.65)	3.91 (1.52–10.06)**	4.38 (1.66–11.57)**	7.14 (2.68–19.05)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	0.6	1.8	2.0	2.5*	3.3**	6.8**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.71 (0.76–18.00)	4.68 (1.01–21.62)	4.82 (1.11–20.90)*	6.25 (1.41–27.76)*	8.28 (1.82–37.70)**	0.002
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.6	0.3	0.0	0.9	1.4	5.3*	0.002
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.50 (0.05–5.59)	–	2.26 (0.48–10.64)	1.92 (0.37–9.87)	3.66 (0.71–19.07)	0.02
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	0.2	0.0	0.0	1.1	1.1	1.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	–	4.26 (0.50–36.59)	4.73 (0.49–45.67)	11.09 (1.18–104.43)*	0.0008
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.2	0.5	0.6	0.5	4.6*	2.4	0.01
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.27 (0.29–36.62)	4.76 (0.48–47.33)	4.33 (0.47–39.71)	13.11 (1.45–18.55)*	7.40 (0.59–92.52)	0.02
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.0	1.3	1.0	1.0	5.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	2.22 (0.36–13.67)	3.62 (0.73–17.93)	4.03 (0.71–22.97)	10.50 (1.86–59.20)**	0.0009

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$, ** $P < 0.01$ vs. optimal blood pressure.

Fig. 1

Age-adjusted incidence of total stroke by risk groups among men and women. *$P < 0.05$, †$P < 0.01$ vs no additive risk.

Discussion

The present analysis demonstrated strong associations between the blood pressure categories defined by the JSH 2009 guidelines [3] and the incidence of stroke among general Japanese patients. The incidence of total stroke increased with elevation of blood pressure categories and became significantly higher in patients with grades 1–3 hypertension than in those with optimal blood pressure levels. There were also strong associations between the JSH 2009 blood pressure categories and most of the stroke subtypes. These associations did not change even after adjustment for other cardiovascular risk factors. The incidence of stroke also increased with elevation of the risk levels defined by the risk stratification system recommended by the guidelines. A cohort study conducted in Japan has also demonstrated the validity of the risk stratification system of the JSH 2009 guidelines [22]. These findings support the hypothesis that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese.

The incidence of stroke in each blood pressure category in the present analysis was similar to that obtained from other observational studies conducted in Japan [23,24], but was higher than that observed in Western populations [25,26]. These findings are consistent with those of previous epidemiological and clinical studies that demonstrated heterogeneous risks of stroke between Asian and Western populations [5,7,27].

Large-scale cohort studies have clearly demonstrated that blood pressure levels predicted future stroke events in Japan [10,12,23,24,28–32] as well as other countries around the world [7,8]. A number of cohort studies have demonstrated separately significant effects of blood

pressure on the risks of cerebral infarction and cerebral haemorrhage [7,8]. However, few observational studies have examined the association between blood pressure and the risks of cerebral infarction subtypes [6,33]. Our study confirmed the results from previous observational studies and provided more detailed information about the strong association of blood pressure levels with the risks of stroke subtypes in a general population of Japanese. This finding is directly in line with beneficial effects of blood pressure-lowering treatment for most of the stroke subtypes observed in randomized controlled trials [34–37].

In our study, despite the significant associations between blood pressure categories and the incidence of most stroke subtypes, the magnitude and patterns of the impact of blood pressure categories were different among stroke subtypes. The incidence of lacunar infarction in men and women and that of cerebral haemorrhage in men continuously increased with rising blood pressure categories, and the differences were significant between optimal blood pressure and grades 1–3 hypertension, whereas the incidence of atherothrombotic infarction in both sexes and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension. Cerebral haemorrhage and lacunar infarction occur primarily in conjunction with arteriolosclerosis of the cerebral penetrating arteries. These arteries are tiny and mostly arise from larger arteries as unbranching end arteries, and are considered to be directly influenced by blood pressure [38]. In contrast, atherosclerotic diseases of cervical or intracranial large arteries, including atherothrombotic infarction and possibly subarachnoid haemorrhage, generally progress as part of a slow pathoanatomic process that may take a long time to reach a clinical end stage [39], and therefore only severe hypertension may have been able to accelerate the atherosclerotic process in our patients. The weak association between blood pressure and cardioembolic infarction may be due to the fact that hypertension indirectly influences the onset of cardioembolic infarction through the development of embolic sources such as atrial fibrillation and myocardial infarction.

There are several potential limitations to the findings in our study. First, it is possible that our results are biased, because some patients did not return for the follow-up examinations. However, more than 80% of the total number of surviving stroke-free patients participated in each examination, suggesting that such a bias did not invalidate the present findings. Second, we were unable to ascertain all risk factors, TOD and cardiovascular disease for the risk stratification of patients; for example, a family history of premature cardiovascular disease, subclinical atherosclerosis and low estimated glomerular filtration rate were difficult to identify. This limitation was likely to contribute to an underestimation of the stroke risk associated with risk groups, and our estimates for the impact of risk groups on the risk of stroke are probably quite conservative. Finally, cardiovascular risk factors and the risks of stroke and its subtypes have changed in Japan during the long-term follow-up period. However, we used the pooling of repeated-observations method, in which risk factors were allowed to change in accordance with data from the follow-up examinations, and therefore this bias is not likely to invalidate the present findings.

In conclusion, the findings of the present study clearly indicate that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese. Though the magnitude and pattern of the impact of blood pressure were different among stroke subtypes, blood pressure levels were associated with the incidence of most stroke subtypes, suggesting that blood pressure lowering is likely to provide protection against a variety of stroke subtypes.

Acknowledgements

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.

There are no conflicts of interest.

References

1 World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**:1983–1992.

2 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.

3 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, *et al.*, on behalf of the Japanese Society of Hypertension Committee. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**:3–107.

4 Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. *Stroke* 1986; **17**:648–655.

5 Menotti A, Jacobs D, Blackburn H, Kromhout D, Nissinen A, Nedeljkovic S, *et al.* Twenty-five-year prediction of stroke deaths in the Seven Countries Study: the role of blood pressure and its changes. *Stroke* 1996; **27**:381–387.

6 Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, *et al.* Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke* 2000; **31**:2616–2622.

7 Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular diseases in the Asia-Pacific region. *J Hypertens* 2003; **21**:707–716.

8 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**:1903–1913.

9 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.

10 Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, *et al.*, and the Japan Arteriosclerosis longitudinal Study (JALS) group. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. *J Hypertens* 2009; **27**:357–364.

11 Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 1966; **21**:64–89.

12 Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, *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.

13 Yoshikawa H, Yoneyama Y, Kitamura M, Oyama H, Arimatu Y, Takahashi Z, *et al.* Study on the quantitative determination of serum total cholesterol by the ferric chloride method [in Japanese]. *Igaku-no-Ayumi* 1960; **33**:375–381.

14 Fujii I, Ueda K, Yanai T, Hasuo Y, Kiyohara Y, Wada J, *et al.* Changes in various blood chemical constituents in relation to menopause. The Hisayama study [in Japanese]. *Jpn J Geriatr* 1986; **23**:50–58.

15 Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, *et al.* Prevalence of type 2 (noninsulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama study. *Diabetologia* 1993; **36**:1198–1203.

16 Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, *et al.* The association of the insulin resistance syndrome with impaired glucose tolerance and NIDDM in the Japanese general population: the Hisayama study. *Diabetologia* 1994; **37**:897–904.

17 Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990; **21**:637–676.

18 Adams H, Bendixen B, Kappelle L, Biller J, Love B, Gordon D, Marsh EI. Classification of subtype of acute ischemic stroke: definition for use in a multicenter clinical trial. *Stroke* 1993; **24**:35–41.

19 Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol* 1986; **43**:71–84.

20 Cupples LA, D'Agostino RB, Anderson K, Kannel WB. Comparison of baseline and repeated measure covariate techniques in the Framingham Heart Study. *Stat Med* 1988; **7**:205–222.

21 Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, *et al.*, for the PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. *J Hypertens* 2006; **24**:1201–1208.

22 Asayama K, Ohkubo T, Sato A, Hara A, Obara T, Yasui D, *et al.* Proposal of a risk-stratification system for the Japanese population based on blood pressure levels: the Ohasama study. *Hypertens Res* 2008; **31**:1315–1322.

23 Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, *et al.* Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension* 2008; **52**:652–659.

24 Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: the JPHC study. *Am J Hypertens* 2009; **22**:273–280.

25 Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med* 2006; **119**:133–141.

26 Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, *et al.*, for the Women's Health Initiative Investigators. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation* 2007; **115**:855–860.

27 Steg PG, Bhatt DL, Wilson PW, D'Agostino R, Ohman EM, Rother J, *et al.* One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; **297**:1197–1206.

28 NIPPON DATA80 Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese - NIPPON DATA80. *J Hum Hypertens* 2003; **17**:851–857.

29 Asayama K, Ohkubo T, Kikuya M, Metoki H, Hoshi H, Hashimoto J, *et al.* Prediction of stroke by self-measurement of blood pressure at home versus casual screening blood pressure measurement in relation to the Joint National Committee 7 classification: the Ohasama study. *Stroke* 2004; **35**:2356–2361.

30 Obara F, Saitoh S, Takagi S, Shimamoto K. Influence of hypertension on the incidence of cardiovascular disease in two rural communities in Japan: the Tanno-Sobetsu study. *Hypertens Res* 2007; **30**:677–682.

31 Ishikawa S, Kazuomi K, Kayaba K, Gotoh T, Nago N, Nakamura Y, *et al.* Linear relationship between blood pressure and stroke: the Jichi Medical School Cohort Study. *J Clin Hypertens (Greenwich)* 2007; **9**:677–683.

32 Murakami Y, Hozawa A, Okamura T, Ueshima H, and the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group (EPOCH-JAPAN). Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension* 2008; **51**:1483–1491.

33 Davis BR, Vogt T, Frost PH, Burlando A, Cohen J, Wilson A, *et al.*, for the Systolic Hypertension in the Elderly Program Cooperative Research Group. Risk factors for stroke and type of stroke in persons with isolated systolic hypertension. *Stroke* 1998; **29**:1333–1340.

34 Perry H, Davis B, Price T, Applegate W, Fields W, Guralnik J, *et al.*, for the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 2000; **284**:465–471.

35 Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, *et al.*, on behalf of the HOPE Investigators. Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; **324**:699–702.

36 Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, *et al.*, for the PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS trial. *Stroke* 2004; **35**:116–121.

37 Kizer JR, Dahlof B, Kjeldsen SE, Julius S, Beevers G, de Faire U, *et al.* Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention For Endpoint Reduction in Hypertension Study. *Hypertension* 2005; **45**:46–52.

38 Mohr JP. Lacunes. *Stroke* 1982; **13**:3–11.

39 Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, *et al.* Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997; **337**:516–522.

Hypertension Research (2009) 32, 1119–1122

www.nature.com/hr

ORIGINAL ARTICLE

Development and validation of a cardiovascular risk prediction model for Japanese: the Hisayama study

Hisatomi Arima[1], Koji Yonemoto[1], Yasufumi Doi[2], Toshiharu Ninomiya[1], Jun Hata[1], Yumihiro Tanizaki[1], Masayo Fukuhara[1], Kiyoshi Matsumura[2], Mitsuo Iida[2] and Yutaka Kiyohara[1]

The objective of this paper is to develop a new risk prediction model of cardiovascular disease and to validate its performance in a general population of Japanese. The Hisayama study is a population-based prospective cohort study. A total of 2634 participants aged 40 years or older were followed up for 14 years for incident cardiovascular disease (stroke and coronary heart disease (myocardial infarction, coronary revascularization and sudden cardiac death)). We used data among a random two-thirds (the derivation cohort, n=1756) to develop a new risk prediction model that was then tested to compare observed and predicted outcomes in the remaining one-third (the validation cohort, n=878). A multivariable cardiovascular risk prediction model was developed that incorporated age, sex, systolic blood pressure, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and smoking. We assessed the performance of the model for predicting individual cardiovascular event among the validation cohort. The risk prediction model demonstrated good discrimination (c-statistic=0.81; 95% confidence interval, 0.77 to 0.86) and calibration (Hosmer–Lemeshow χ^2-statistic=6.46; P=0.60). A simple risk score sheet based on the cardiovascular risk prediction model was also presented. We developed and validated a new cardiovascular risk prediction model in a general population of Japanese. The risk prediction model would provide a useful guide to estimate absolute risk of cardiovascular disease and to treat individual risk factors.
Hypertension Research (2009) **32**, 1119–1122; doi:10.1038/hr.2009.161; published online 18 September 2009

Keywords: cardiovascular disease; epidemiology; risk factors; risk prediction model

INTRODUCTION

Cardiovascular disease is estimated to be one of the leading causes of death in Japan, as well as other countries around the world, placing a burden on the community.[1] Although the incidence and mortality of cardiovascular disease in Japan have declined over several decades, the risk of cardiovascular events remains high.[2] Additional protection will require an effective strategy for prevention of cardiovascular disease. Among a number of cardiovascular prevention strategies, high-risk approaches are likely to be one of the most effective strategies for prevention of cardiovascular disease.[3] To identify individuals at high risk of cardiovascular disease, a number of risk prediction tools have been developed.[4–15] However, currently available risk prediction tools of cardiovascular disease are derived mainly from studies carried out in Western populations and few risk prediction tools are developed for general Japanese populations. The objective of this paper is to develop a new cardiovascular risk prediction model and to validate its performance in a general population of Japanese.

METHODS

Study design and participants

Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[2,16,17] In 1988, a screening survey for this study was performed in the town. A total of 2742 residents aged 40 years or older (80.9% of the total population of this age group) consented to participate in the examination.[2,18–21] After the exclusion of 106 subjects with a history of cardiovascular disease and two subjects who died during the examination, the remaining 2634 individuals were enrolled in this study.

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

Follow-up survey

The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. A detailed description of the study methods has been published previously.[2,18–21] In brief, the health status of any subject who had not undergone a regular examination or who had moved out

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Correspondence: Dr H Arima, Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: harima@envmed.med.kyushu-u.ac.jp
Received 29 June 2009; revised 13 August 2009; accepted 20 August 2009; published online 18 September 2009

of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, 577 subjects died, of whom 438 (75.9%) underwent autopsy. Only one participant was lost to follow-up.

Outcomes

The primary outcome of the present analysis was cardiovascular disease. Cardiovascular disease was defined as first-ever development of coronary heart disease or stroke. The criteria for a diagnosis of coronary heart disease included first-ever acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[2] Acute myocardial infarction was diagnosed when a subject met at least two of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic changes; and (4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes, and was detected by electrocardiography, echocardiography, cardiac scintigraphy or autopsy. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 h. The diagnosis of stroke and the determination of its pathological type were based on the clinical history, neurological examination and all available clinical data, including brain CT/MRI and autopsy findings.[2]

Risk factors

Sitting blood pressure was measured three times at the right upper arm using a sphygmomanometer after 5 min of rest; an average of three measurements was used for the analysis. Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was defined by a 75 g oral glucose tolerance test and by fasting ($\geqslant$7.0 mmol l^{-1}) or postprandial ($\geqslant$11.1 mmol l^{-1}) blood glucose levels or by the use of hypoglycemic agents. Total cholesterol, high-density lipoprotein cholesterol and triglyceride levels were determined enzymatically. Low-density lipoprotein (LDL) cholesterol level was estimated using the Friedewald formula.[22] Information on smoking habits was obtained using a standard questionnaire and was classified as either current or not.

Statistical analysis

Two-thirds of the study participants (n=1756) were randomly assigned to a risk prediction model derivation cohort and the remaining one-third (n=878) were reserved as an independent validation cohort using random digits generated by the Mersenne Twister method.[23] Among subjects allocated to the derivation cohort, a new risk prediction model was developed using Cox's proportional hazards model. Covariates included in Cox's proportional hazards model were age, sex, systolic blood pressure, diabetes, LDL cholesterol, high-density lipoprotein cholesterol and smoking habits that were traditional risk factors for cardiovascular disease established in the Hisayama study.[16,17,20,21] The performance of the risk prediction model was then tested among subjects allocated to the validation cohort. Ability of the risk prediction model to discriminate persons who experience a cardiovascular disease from those who do not were evaluated using c-statistic,[24] and calibration of the risk prediction model was evaluated using a Hosmer–Lemeshow χ^2-statistic with 8 d.f. The cardiovascular risk prediction model was translated into a risk score sheet using methods developed in the Framingham Heart Study.[25] To facilitate easier understanding of the concept of risk, 'vascular age' was also included in the risk score sheet. An individual's vascular age was calculated as the age of a person with the same predicted risk but with all other risk factor levels in optimal ranges.[10] All analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA).

Table 1 Baseline characteristics in the derivation and the validation cohorts

	Derivation cohort (n=1756)	*Validation cohort (n=878)*
Age, years	59 (12)	59 (12)
Men	43%	40%
Systolic blood pressure, mm Hg	134 (21)	133 (22)
Diastolic blood pressure, mm Hg	78 (12)	77 (11)
Diabetes	11%	13%
LDL cholesterol, mg per 100 ml	131 (43)	133 (41)
HDL cholesterol, mg per 100 ml	50 (12)	50 (12)
Current smoker	24%	27%

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Values are means (s.d.) or frequencies.
SI conversion factors: to convert LDL and HDL cholesterol to millimoles per liter, multiply by 0.0259.

Table 2 Regression coefficients and hazard ratios for the cardiovascular risk prediction model in the derivation cohort

	β	*Hazard ratio*	*95% CI*
Age, years	0.05775	1.059	1.046–1.073
Men	0.55569	1.743	1.264–2.404
Systolic blood pressure, mm Hg	0.01701	1.017	1.011–1.023
Diabetes	0.51977	1.682	1.193–2.370
LDL cholesterol, mg per 100 ml	0.00257	1.003	0.999–1.006
HDL cholesterol, mg per 100 ml	−0.01182	0.988	0.977–1.000
Current smoker	0.35287	1.423	1.024–1.978

Abbreviations: 95% CI, 95% confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: to convert LDL and HDL cholesterol to millimoles per liter, multiply by 0.0259.

RESULTS

The baseline characteristics of the subjects allocated to the derivation cohort and those to the validation cohort are shown in Table 1. There were no clear differences in these baseline characteristics between two cohorts.

During 14 years of follow-up, 216 cardiovascular events were observed in the derivation cohort and 125 in the validation cohort. The cardiovascular risk prediction model including covariates of age, sex, systolic blood pressure, diabetes, LDL cholesterol, high-density lipoprotein cholesterol and smoking habits were developed in the derivation cohort. The multivariate-adjusted regression coefficients and hazard ratios for the risk prediction model are shown in Table 2.

The performance of the risk prediction model was then evaluated among the validation cohort. In terms of discrimination, the c-statistic was as high as 0.81 (95% confidence interval, 0.77 to 0.86). Figure 1 demonstrates the calibration plots comparing actual and predicted cardiovascular events by deciles of risk. The calibration χ^2-statistic for the risk prediction model was 6.46 (d.f.=8), indicating excellent goodness of fit (P=0.60). The top 30% of predicted risk identified 70% of subjects who experienced cardiovascular disease during follow-up (sensitivity). Proportion of subjects without cardiovascular events who were not in the top 30% of predicted risk was 79% (specificity).

Tables 3 and 4 provide risk score sheets that can be used for estimation of the multivariable risk of cardiovascular disease at 10

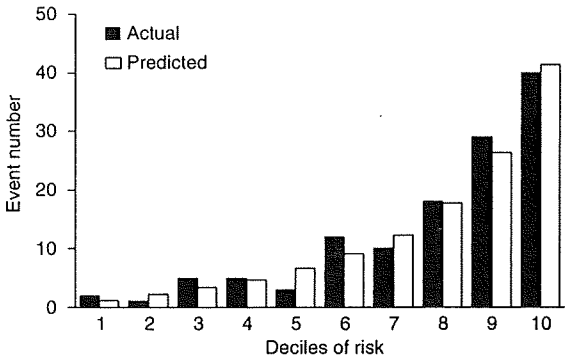

Figure 1 Actual and predicted cardiovascular events by deciles of risk in the validation cohort. Hosmer–Lemeshow χ^2-statistic=6.46, d.f.=8, P=0.60.

Table 3 Cardiovascular risk points

Points	*Age (years)*	*Sex*	*SBP (mm Hg)*	*Diabetic*	*LDL cholesterol (mg per 100 ml)*	*HDL cholesterol (mg per 100 ml)*	*Smoker*
0	40–44	Women	<119	No	<140	⩾40	No
1	45–49		120–139		⩾140	<40	Yes
2	50–54	Men	140–159	Yes			
3	55–59		160–179				
4	60–64		⩾180				
5	65–69						
6	70–74						
7	75–79						
8	⩾80						

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
SI conversion factors: to convert LDL and HDL cholesterol to millimoles per liter, multiply by 0.0259.

years. Table 4 also provide a different quantification of the same risk in the form of vascular age.

DISCUSSION

In this paper, a new risk prediction model of cardiovascular disease has been developed using data obtained from a prospective cohort study of a general Japanese population. The risk prediction model demonstrated good performance in regard to both discrimination and calibration. A simple risk score sheet based on the cardiovascular risk prediction model was also presented. This simple risk prediction tool of cardiovascular disease for Japanese would provide a useful guide to estimate absolute risk of cardiovascular disease and to treat individual risk factors.

Large-scale cohort studies have developed a number of risk prediction tools of cardiovascular disease.[4–15] However, these risk prediction tools were mainly derived from studies carried out in Western populations and few risk prediction tools are developed among general Japanese populations. The NIPPON DATA 80 derived a cardiovascular risk prediction tool, in which age, sex, systolic blood pressure, glucose levels, total cholesterol and smoking habits were included as risk factors, using data obtained from a 19-year prospective cohort study of general Japanese populations, although the outcome of NIPPON DATA 80 risk charts was death from cardiovascular causes.[5] The Jichi Medical School (JMS) cohort study developed 10-year risk prediction tools for incidence of myocardial infarction[14] and stroke,[15] in which age, sex, systolic blood pressure, diabetes, total cholesterol and smoking habits were included as risk factors, using data obtained from a population-based prospective study of general Japanese populations. The present analysis from the Hisayama study developed a new risk prediction tool for incidence of cardiovascular disease in a general population of Japanese using similar risk factors used in the previous observational studies of Japanese. Cumulative incidence rates of cardiovascular events at 10 years estimated from the present risk prediction tool were almost similar to combined risks of myocardial infarction and stroke obtained from the JMS risk charts[14,15] and this finding supports the validity and the generalizability of the Hisayama risk prediction model.

Table 4 Estimated cardiovascular risk at 10 years and vascular age according to risk points

Points	*Risk[a] (%)*	*Vascular age for men[b] (years)*	*Vascular age for women[b] (years)*
0	1.4	—	40–44
1	1.8	—	45–49
2	2.4	40–44	50–54
3	3.2	45–49	55–59
4	4.2	50–54	60–64
5	5.6	55–59	65–69
6	7.4	60–64	70–74
7	9.8	65–69	75–79
8	12.8	70–74	80–84
9	16.7	75–79	85–89
10	21.7	80–84	90–94
11	27.8	85–89	95–99
⩾12	>30	⩾90	⩾100

[a]Estimated cardiovascular risk at 10 years.
[b]Age of a person with the same predicted risk but with all other risk factor levels in optimal ranges.

Several limitations of our study should be discussed. One limitation is a lack of external validation of the risk prediction model. However, split sample validation is an established method for internal validation of a risk prediction model and is widely used in other studies.[9,12] Similarity to the JMS risk chart[14,15] also supports the validity of the Hisayama risk prediction model. Another limitation is that LDL cholesterol, as a continuous variable, did not reach statistical significance in the derivation cohort. However, LDL cholesterol is an established risk factor for cardiovascular disease in the Hisayama study[21] and thus we included LDL cholesterol into the risk prediction model. A third limitation is that our findings are based on a one-time measurement of risk factors (for example, systolic blood pressure, plasma glucose levels, LDL cholesterol levels and high-density lipoprotein cholesterol levels), which may not accurately reflect the status of a study participant. A fourth limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation,[22] although the equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and cardiovascular disease. These limitations may have resulted in underestimation of the predicted risk among subjects at high risk of cardiovascular disease.

In conclusion, we developed and validated a new cardiovascular risk prediction model in a general population of Japanese. The risk prediction model would provide a useful guide to identify the individuals at high risk of cardiovascular disease in Japan. High-risk

approaches for the prevention of cardiovascular disease using the present risk prediction tool are likely to provide additional protection against the burden of cardiovascular disease in Japan.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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.

1 World Health Organization. *The atlas of heart disease and stroke*. World Health Organization: Geneva, 2004.
2 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.
3 World Health Organization. *Preventing chronic disease: a vital investment*. World Health Organization: Geneva, 2005.
4 Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, for the SCORE Project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24**: 987–1003.
5 NIPPON DATA 80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J* 2006; **70**: 1249–1255.
6 Wu Y, Liu X, Li X, Li Y, Zhao L, Chen Z, Rao X, Zhou B, Detrano R, Liu K, for the USA-PRC Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology Research Group and the Chine Multicenter Collaborative Study of Cardiovascular Epidemiology (China MUCA) Research Group. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. *Circulation* 2006; **114**: 2217–2225.
7 Asia pacific Cohort Studies Collaboration. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health* 2007; **61**: 115–121.
8 Mendis S, Lindholm LH, Mancia G, Whitworth J, Alderman M, Lim S, Heagerty T. World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. *J Hypertens* 2007; **25**: 1578–1582.
9 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.
10 D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743–753.
11 Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008; **371**: 923–931.
12 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *Br Med J* 2008; **336**: 1475–1482.
13 Teramoto T, Ohashi Y, Nakaya N, Yokoyama S, Mizuno K, Nakamura H, for the MEGA Study Group. Practical risk prediction tools for coronary heart disease in mild to moderate hypercholesterolemia in Japan: originated from the MEGA study data. *Circ J* 2008; **72**: 1569–1575.
14 Matsumoto M, Ishikawa S, Kayaba K, Gotoh T, Nago N, Tsutsumi A, Kajii E, the Jichi Medical School (JMS) Cohort Study Group. Risk charts illustrating the 10-year risk of myocardial infarction among residents of Japanese rural communities: the JMS Cohort Study. *J Epidemiol* 2009; **19**: 94–100.
15 Ishikawa S, Matsumoto M, Kayaba K, Gotoh T, Nago N, Tsutsumi A, Kajii E, the Jichi Medical School (JMS) Cohort Study Group. Risk charts illustrating the 10-year risk of stroke among residents of Japanese rural communities: the JMS Cohort Study. *J Epidemiol* 2009; **19**: 101–106.
16 Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens* 1990; **8**: S9–S15.
17 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.
18 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.
19 Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, Hata J, Matsumura K, Iida M, Kiyohara Y. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1385–1391.
20 Doi Y, Kubo M, Yonemoto K, Ninomiya T, Iwase M, Arima H, Hata J, Tanizaki Y, Iida M, Kiyohara Y. Fasting plasma glucose cutoff for diagnosis of diabetes in a Japanese population. *J Clin Endocrinol Metab* 2008; **93**: 3425–3429.
21 Imamura T, Doi Y, Arima H, Yonemoto K, Hata J, Kubo M, Tanizaki Y, Ibayashi S, Iida M, Kiyohara Y. LDL cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke* 2009; **40**: 382–388.
22 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.
23 Matsumoto M, Nishimura T. Mersenne Twister: a 623-dimensionally equidistributed uniform pseudorandom number generator. *ACM Trans on Modeling and Computers Simulations* 1998; **8**: 3–30.
24 Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004; **23**: 2109–2123.
25 Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham study risk score functions. *Stat Med* 2004; **23**: 1631–1660.

ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease

Association of Kidney Function With Coronary Atherosclerosis and Calcification in Autopsy Samples From Japanese Elders: The Hisayama Study

Toshiaki Nakano, MD, PhD,[1,2] Toshiharu Ninomiya, MD, PhD,[3] Shinji Sumiyoshi, MD, PhD,[1] Hiroshi Fujii, MT,[1] Yasufumi Doi, MD, PhD,[3] Hideki Hirakata, MD, PhD,[4] Kazuhiko Tsuruya, MD, PhD,[2] Mitsuo Iida, MD, PhD,[2] Yutaka Kiyohara, MD, PhD,[3] and Katsuo Sueishi, MD, PhD[1]

Background: Chronic kidney disease (CKD) is associated with increased risk of coronary heart disease. However, information regarding the histopathologic characteristics of coronary atherosclerosis in individuals with CKD is scarce. This study investigated the relationship between CKD and severity of coronary atherosclerosis in population-based autopsy samples.

Study Design: Cross-sectional study.

Setting & Participants: 126 individuals randomly selected from 844 consecutive population-based autopsy samples.

Predictor: Estimated glomerular filtration rate (eGFR) calculated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation.

Outcomes: Severity of atherosclerosis in 3 main coronary arteries, including atherosclerotic lesion types defined using the American Heart Association classification; stenosis rates; and coronary calcified lesions.

Measurements: The relationship between CKD and severity of coronary atherosclerosis was evaluated using generalized estimating equation methods.

Results: Frequencies of advanced atherosclerotic lesions increased gradually as eGFR decreased (33.6%, 41.7%, 52.3%, and 52.8% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; *P* for trend = 0.006). This relationship was substantially unchanged even after adjustment for potential confounding factors (ORs, 1.40 [95% CI, 0.76-2.55], 2.02 [95% CI, 0.99-4.15], and 3.02 [95% CI, 1.22-7.49] for eGFRs of 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively). Frequencies of calcified lesions of coronary arteries also increased gradually with lower eGFRs (*P* for trend = 0.02). Hypertension and diabetes were associated with increased risk of advanced coronary atherosclerosis and calcification of coronary arteries in individuals with decreased eGFR.

Limitations: Cross-sectional study, absence of data for proteinuria, and extremely high proportion of aged people.

Conclusions: The autopsy findings presented here suggest that CKD is associated significantly with severity of coronary atherosclerosis. Patients with CKD should be considered a high-risk population for advanced coronary atherosclerosis.

Am J Kidney Dis 55:21-30.

INDEX WORDS: Chronic kidney disease; coronary atherosclerosis; population risk; coronary artery stenosis; glomerular filtration rate; coronary disease.

Editorial, p. 1

Chronic kidney disease (CKD) is a significant public health problem, affecting 10%-15% of the adult general population in developed countries.[1-3] CKD is associated with increased risks of cardiovascular disease and death.[4-7] A higher incidence rate of myocardial infarction and excessive cardiac mortality have been documented repeat-

From the [1]Pathophysiological and Experimental Pathology, Department of Pathology, [2]Department of Medicine and Clinical Science, and [3]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University; and [4]First Department of Internal Medicine, Fukuoka Red Cross Hospital, Fukuoka, Japan.

Received March 31, 2009. Accepted in revised form June 22, 2009. Originally published online as doi:10.1053/j.ajkd.2009.06.034 on September 22, 2009.

Address correspondence to Toshiaki Nakano, MD, PhD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: toshink@med.kyushu-u.ac.jp

0272-6386/09/5501-0007$36.00/0
doi:10.1053/j.ajkd.2009.06.034

edly in patients with CKD.[6-10] Cardiac failure is more common in patients with advanced CKD, showing a prevalence of ~40%.[11]

Several autopsy-based studies have shown a higher prevalence of arteriosclerotic lesions in individuals with CKD than in those without CKD.[12-14] Furthermore, patients with end-stage renal disease show more advanced atherosclerotic lesions with calcification in coronary arteries than the general population.[14] However, these studies were conducted in hospital-based populations, which are prone to underlying disease. Additionally, there are few studies investigating the histopathologic findings of coronary arteries in individuals with moderate stage of CKD.

The Hisayama Study is a prospective population-based study of cardiovascular disease risk factors in Japanese people[15] and is characterized by autopsy verification of the cause of death in ~80% of those who died.[16,17] The present study assessed the relationship between decreased kidney function and severity of coronary atherosclerosis in population-based autopsy samples.

METHODS

Study Population

The Hisayama Study was established in 1961 in the town of Hisayama, a suburban community adjacent to Fukuoka City in a metropolitan area of Kyushu Island in southern Japan. The population of Hisayama is ~7,000 and has been stable for 40 years. Full community surveys of residents have been repeated since 1961.[18] From January 1988 to November 2005, a total of 1,162 residents of Hisayama died; of these, 844 underwent autopsy examination. Individuals without health examination data within 3 years before death were excluded. The remaining 482 individuals were classified into 4 categories based on estimated glomerular filtration rate (eGFR): ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2 (data from the most recent health examination). Eighteen individuals had an eGFR < 30 mL/min/1.73 m^2. The individuals included in this study were randomly selected using a computer-generated random number from each category of eGFR level after matching for age at death and sex in a 1:2 ratio against individuals in the <30-mL/min/1.73 m^2 category. A final total of 126 individuals (49 men, 77 women) were enrolled in this study (Fig 1). The median period from the last health examination to death was 1.0 years (quartile [Q] 1 to 3, 0.0-2.0).

Risk Factors

At each health examination, study participants undertook a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The completed questionnaire was checked by trained interviewers. Blood pressures were measured 3 times using a standard mercury sphygmomanometer at each examination, with mean values used for the analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive agents. Blood samples were collected after overnight fasting. Serum creatinine was measured using the Jaffé method. Hemoglobin A_{1c} was measured using high-performance liquid chromatography. Diabetes mellitus was diagnosed as hemoglobin A_{1c} level ≥ 6.0%. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined enzymatically. Dyslipidemia was defined as total cholesterol concentration ≥ 220 mg/dL, high-density lipoprotein cholesterol concentration ≤ 40 mg/dL, or triglyceride concentration ≥ 150 mg/dL.

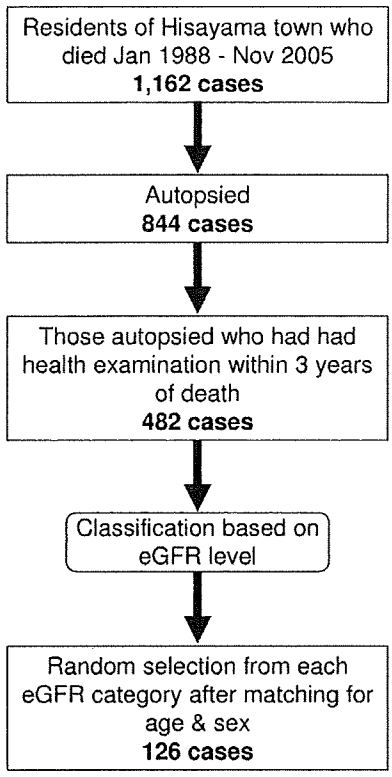

Figure 1. Flow diagram for study enrollment. Abbreviation: eGFR, estimated glomerular filtration rate.

Definition of CKD

eGFR was estimated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation,[19] and is given by the following equation (only 5 variables are shown because the multiplier for black race was not applicable to this population):

$$\text{eGFR (mL/min/1.73 m}^2) = 170 \times [\text{serum creatinine (mg/dL)}]^{-0.999}$$

$$\times [\text{age (years)}]^{-0.176}$$
$$\times [\text{serum urea nitrogen (mg/dL)}]^{-0.170}$$
$$\times [\text{serum albumin (g/dL)}]^{0.318}$$
$$\times [0.762 \text{ if female}]$$

eGFR levels were classified into 4 categories: ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[20]

For sensitivity analyses, eGFR also was estimated using the 4-variable MDRD Study equation modified with the Japanese Society of Nephrology–Chronic Kidney Disease Initiative coefficient (ie, the JSN-CKDI equation)[21]:

$$\text{JSN-eGFR (mL/min/1.73 m}^2) = 0.808 \times 175$$
$$\times [\text{serum creatinine (enzymatic method [mg/dL])}]^{-1.154}$$
$$\times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}]$$

where the value of serum creatinine measured using the Jaffé method was converted to values for the enzymatic method by subtracting 0.207 mg/dL.[22]

Coronary Artery Morphological Examination

Heart tissue obtained at autopsy was immersed in 10% buffered formaldehyde for at least 24 hours, making sure to include the 3 main coronary arteries. The right coronary artery (segment 1), left anterior descending coronary artery (segment 6), and left circumflex coronary artery (segment 11) were dissected free from the surface of the heart, cut perpendicular to the long axis at 3-mm intervals, and embedded in paraffin. The segment of the vessel showing the most severe stenosis was selected for histological examination, excluding areas near the branching site. Three blocks were excluded because the segments of the coronary arteries were not adequately defined. In total, 375 blocks were obtained and all blocks for each individual were cut into 3-μm-thick serial sections in 1 sequence (1 block provided insufficient sample to estimate the extent of arterial stenosis). Sections from each block were serially subjected to hematoxylin and eosin, elastica–van Gieson, and Masson trichrome staining. Histological examinations were made without reference to the associated clinical information by 2 independent pathologists (T. Nakano and S.S. in blinded assessments).

Estimation of Atherosclerotic Lesions

Atherosclerotic lesions found in each section were classified into 6 types in accordance with the definitions proposed by the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA)[23]: type I (initial lesion), intimal thickening with isolated foam cells; type II (fatty-streak lesion), intimal thickening with intracellular lipid accumulation; type III (intermediate lesion), type II changes and small extracellular lipid pools; type IV (atheroma), type II changes and core of extracellular lipid; type V (fibroatheroma), lipid core and fibrotic layer to lesions, or mainly calcified, or mainly fibrotic; and type VI (complicated lesion), disrupted lesion with hematoma or hemorrhage or thrombotic deposits. The AHA classification defines advanced atherosclerotic lesions as types IV-VI.[23] Lesion calcification was assessed on hematoxylin and eosin-stained paraffin sections from all specimens.

Morphometry of Luminal Stenosis in the Coronary Artery

All arteries were analyzed quantitatively for stenosis rate using computerized planimetry according to Taylor et al.[24] Morphometry was performed using National Institutes of Health (NIH) Image software (version 1.63; NIH, Bethesda, MD). Elastica-van Gieson–stained sections were magnified and digitized to measure the luminal internal and external elastic lamina perimeters. Arterial areas were calculated from diameter values derived from the measured arterial perimeter (area = πr^2) to avoid artifacts from vessel shape distortion during processing. Plaque areas were calculated as the differences between internal elastic lamina and luminal area measurements. Percentage luminal stenosis was calculated as plaque area/internal elastic lamina area × 100.[24]

Statistical Analysis

The SAS software package for Windows, version 9.1 (SAS Institute Inc, Cary, NC) was used to perform statistical analyses. Trends in mean values or frequencies of variables across subgroups of eGFR level were tested using linear regression analysis or logistic regression analysis, respectively. Mean stenosis rates according to eGFR levels were calculated using a linear mixed model to account for correlation between vessels within a patient. Stenosis rates between vessels correlated fairly, with a correlation coefficient range of 0.21-0.32. This analysis was carried out using the procedure "MIXED" in SAS. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using the generalized estimating equation methods to deal with modeling the correlation among repeated outcomes within a patient.[25] Correlation coefficients for the probabilities of advanced atherosclerosis and calcified lesion between vessels ranged from 0.08-0.34 and 0.25-0.37, respectively. These analyses were performed using procedure "GENMOD" in SAS. Trends in relationships between eGFR levels and risk of outcomes were tested by adding the median value of eGFR for each category to the relevant model. Two-tailed $P < 0.05$ was defined as statistically significant.

RESULTS

Baseline Characteristics

Table 1 lists baseline clinical and demographic characteristics of individuals included in the study according to eGFR levels. Individuals with lower eGFRs had higher systolic blood pressure and calcium-phosphorus product and lower hematocrit values. Frequency of hyper-

Table 1. Laboratory Variables and Risk Factors According to Kidney Function

	eGFR (mL/min/1.73 m²)				*P* for Trend
	≥60	45-59	30-44	<30	
eGFR (mL/min/1.73 m²)	72 (68-85)	55 (51-58)	40 (37-43)	21 (19-25)	
No. of patients	36	36	36	18	
Age (y)	84 ± 6	85 ± 6	85 ± 8	85 ± 7	0.8
Men (%)	39	39	39	39	0.9
Serum creatinine (mg/dL)	0.9 (0.8-1.0)	1.1 (1.0-1.3)	1.5 (1.3-1.7)	2.5 (2.0-3.2)	<0.001
Serum urea nitrogen (mg/dL)	16 (12-18)	19 (16-24)	24 (19-27)	39 (29-46)	<0.001
Serum albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.5	3.9 ± 0.5	3.7 ± 0.4	0.1
Systolic blood pressure (mm Hg)	141 ± 23	142 ± 29	143 ± 29	165 ± 29	0.01
Diastolic blood pressure (mm Hg)	73 ± 12	74 ± 14	75 ± 10	77 ± 13	0.2
Use of antihypertensive agent (%)	28	36	56	50	0.03
Hypertension (%)	61	58	78	94	0.006
Hemoglobin A_{1c} (%)	5.2 ± 0.8	5.7 ± 1.5	5.4 ± 0.8	5.4 ± 0.9	0.6
Diabetes (%)	11	22	19	22	0.3
Total cholesterol (mg/dL)	184 ± 37	190 ± 43	195 ± 53	186 ± 45	0.6
High-density lipoprotein cholesterol (mg/dL)	60 ± 17	52 ± 13	56 ± 17	53 ± 15	0.3
Triglycerides (mg/dL)	76 (65-102)	91 (81-124)	88 (68-123)	113 (70-167)	0.1
Calcium-phosphorus product (mg²/dL²)	29 ± 6	31 ± 5	31 ± 4	33 ± 5	0.005
Hematocrit (%)	37 ± 5	37 ± 6	35 ± 5	30 ± 6	<0.001
Smoking habit (%)	19	28	6	17	0.3
Alcoholic intake (%)	17	11	11	6	0.3
Median time from last health examination (y)	1.0 (0.5-2.0)	2.0 (0.5-2.0)	1.5 (0.5-3.0)	1.0 (0-2.0)	0.7
Causes of death					
Malignant neoplasms (%)	28	31	28	0	0.2
Heart diseases (%)	17	17	11	11	0.1
Cerebrovascular diseases (%)	17	11	3	11	0.4
Other diseases of circulatory system (%)	0	6	6	6	0.2
Infectious diseases (%)	17	19	33	22	0.5
Other causes (%)	19	6	8	33	0.08

Note: Values expressed as mean ± SD, frequency, or median (Q1-Q3). Hypertension was defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive agent. Diabetes was defined as hemoglobin A_{1c} level ≥ 6.0%. Trends were tested using linear regression analysis for continuous variables or logistic regression analysis for categorical variables. Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.0167; serum creatinine in mg/dL to μmol/dL, ×76.26; serum albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; total and high-density lipoprotein cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviation: eGFR, estimated glomerular filtration rate.

tension and use of antihypertensive agents increased significantly with decreased eGFR. Mean values or frequencies of other potential risk factors were not statistically different among eGFR levels.

Relationship Between Kidney Function and Severity of Atherosclerotic Lesions

Figure 2 shows a typical coronary artery for subgroups of eGFR levels. Age- and sex-ad-

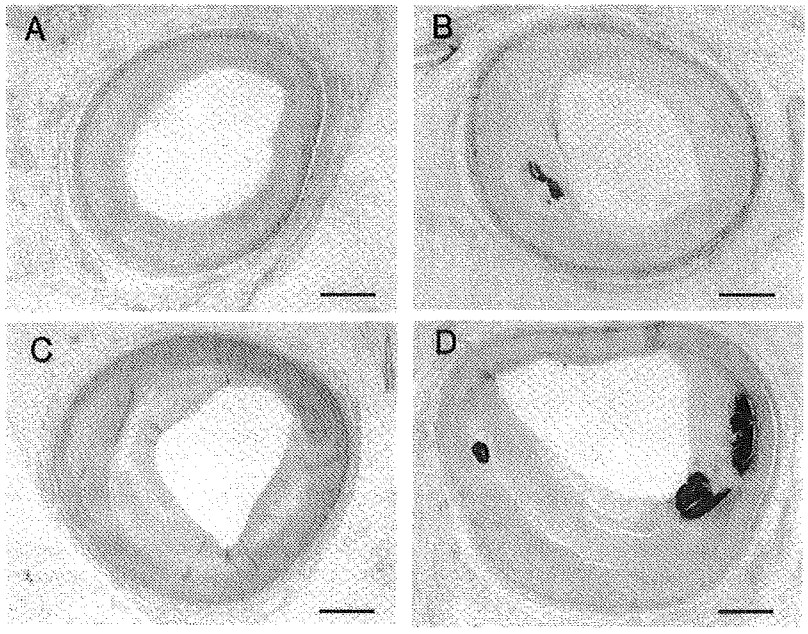

Figure 2. Typical arteries for each classification by glomerular filtration rate (GFR). (A-D) Typical light microscopic views of coronary arteries from respective cases with estimated GFRs (A) ≥60, (B) 45-59, (C) 30-44, and (D) <30 mL/min/1.73 m^2. Stenosis rates of respective arteries were (A) 36.8%, (B) 42.3%, (C) 54.2%, and (D) 58.9%. All sections were stained with hematoxylin and eosin. Scale bars = 1.0 mm.

justed mean values for coronary artery stenosis rate increased significantly with lower eGFRs (mean, 46.7% ± 1.9% [SE], 49.2% ± 1.9%, 51.9% ± 1.9%, and 53.7% ± 2.7% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; P for trend = 0.02).

Figure 3 shows proportions of atherosclerotic lesions using the AHA classification according to eGFR level. Prevalences of advanced atherosclerotic lesions defined as types IV-VI were 34.3% for eGFR ≥ 60 mL/min/1.73 m^2, 41.7% for eGFR of 45-59 mL/min/1.73 m^2, 52.3% for eGFR of 30-44 mL/min/1.73 m^2, and 52.8% for eGFR < 30mL/min/1.73 m^2. Individuals in the latter 2 categories had a significantly higher proportion of advanced atherosclerotic lesions on autopsy than those with eGFR ≥ 60 mL/min/1.73 m^2. The risk of advanced atherosclerosis was doubled in individuals with eGFR < 45 mL/min/1.73 m^2 compared with those with eGFR ≥ 60 mL/min/1.73 m^2 after adjustment for potential confounding factors, including age, sex, hypertension, diabetes, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, calcium-phosphorus product, hematocrit, smoking habit, and alcohol intake (Table 2).

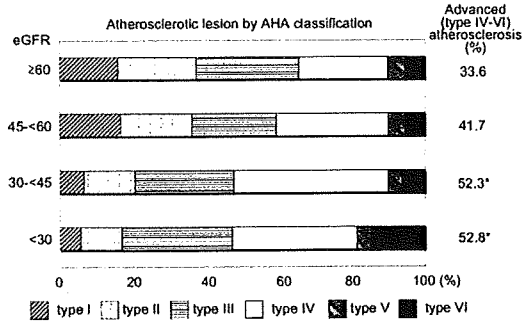

Figure 3. Proportions of atherosclerotic lesion types using American Heart Association (AHA) classification by level of kidney function. Percentages of advanced atherosclerosis (AHA types IV-VI) for each estimated glomerular filtration rate (eGFR) level is shown at the right side of the graphs. *P < 0.05 vs eGFR ≥ 60 mL/min/1.73 m^2.

Prevalence of Calcified Lesion in Coronary Artery According to Kidney Function

In a case of AHA type VI in the subgroup of eGFR < 30 mL/min/1.73 m^2, the arterial intima was thickened and associated with calcified plaque and hematoma (Fig 4).

Many coronary artery samples showed intimal calcified lesions, but there was no medial calcification in any specimen examined. Prevalences of calcified lesions were 36.5% for eGFR ≥ 60 mL/min/1.73 m^2, 37.0% for eGFR of 45-59 mL/min/1.73 m^2, 44.9% for eGFR of 30-44 mL/min/1.73