Electrocardiogram Screening for Left High R-Wave Predicts Cardiovascular Death in a Japanese Community-Based Population: NIPPON DATA90

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Authors:

Koshi NAKAMURA [a], Tomonori OKAMURA [a], Takehito HAYAKAWA [b], Takashi KADOWAKI [a], Yoshikuni KITA [a], Akira OKAYAMA [c] and Hirotsugu UESHIMA [a] for the NIPPON DATA90 Research Group[+]

[a] Department of Health Science, Shiga University of Medical Science, Ostu, Japan

[b] Department of Public Health Science, Shimane University School of Medicine, Izumo, Japan

[c] Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan

[+] Members of the Research Group are listed in the Appendix.

Corresponding Author:
Koshi NAKAMURA, MD
Department of Health Science, Shiga University of Medical Science
Seta Tsukinowa-cho, Otsu 520-2192, Japan
Tel: +81-77-548-2191 Fax: +81-77-543-9732
E-mail: ksnkmr@belle.shiga-med.ac.jp

〖 Abstract and Key Words 〗

Little is known about the efficacy of left ventricular hypertrophy diagnosed by electrocardiography for predicting cardiovascular disease in a general Japanese population. In a large cohort of participants selected randomly from the overall Japanese population, we attempted to evaluate the usefulness of a high amplitude R-wave (left high R-wave) on the electrocardiogram for predicting cardiovascular death. A total of 6,688 Japanese (mean age, 50.7 years old; 57% women) free of previous cardiovascular disease and use of anti-hypertensive agents at baseline were followed for 10 years, from 1990 to 2000. Left high R-wave on the electrocardiogram (the Minnesota Code, 3-1 or 3-3) was found in 9.4% of the 6,688 participants, in 14.6% of the 2,413 hypertensives and in 4.1% of the 4,275 normotensives. During the follow-up period, 128 participants died due to cardiovascular disease. After adjustment for systolic blood pressure and other risk factors, left high R-wave conferred an increased risk of cardiovascular death; the hazard ratio among all the participants was 1.88 (95% confidence interval, 1.22-2.89; $p<0.01$), that among hypertensives was 1.97 (1.20-3.24; $p=0.01$), and that among normotensives was 1.66 (0.69-3.98; $p=0.26$). The population attributable risk percent of left high R-wave for cardiovascular death was 7.6% among all participants, 12.4% among hypertensives and 4.1% among normotensives. Left high R-wave on electrocardiogram, irrespective of the level of systolic blood pressure, was a predictive marker for cardiovascular death among community-dwelling Japanese.

Key Words: left ventricular hypertrophy; electrocardiogram; high amplitude R-wave (left high R-wave); the Minnesota Code; cardiovascular disease

〖 Introduction 〗

Chronic exposure to elevated blood pressure causes organ damage such as left ventricular hypertrophy (*1*). Early detection of left ventricular hypertrophy may be necessary to identify individuals at higher cardiovascular risk who need a more clinical intervention to improve their health (*2*). Although elevated blood pressure is also a risk factor for higher cardiovascular mortality (*3*), casual measurement of blood pressure may lack accuracy because of the intrinsic variability of blood pressure and possible errors in its measurement (*4-6*). Therefore, organ damage such as left ventricular hypertrophy may provide a better estimate of high cardiovascular risk than casually measured blood pressure. Japanese have a higher incidence of hypertensive cardiovascular disease, as well as a higher mortality from such disease, as compared with Western populations (*7-9*), mainly due to the high prevalence of hypertension in Japan (*10, 11*). Thus, electrocardiogram screening to estimate the risk of left ventricular hypertrophy may be useful in the Japanese population. Although a few previous studies have indicated that left ventricular hypertrophy diagnosed by electrocardiography has value as a predictor of cardiovascular disease in the general population, these studies were conducted only in Western populations (*12-14*).

Recently, in a large cohort of participants selected randomly from the overall Japanese population, we attempted to determine whether left ventricular hypertrophy diagnosed by an electrocardiogram, irrespective of the casual systolic blood pressure level, would be a predictive marker for cardiovascular death among a community-dwelling population, and then to evaluate the utility of electrocardiogram screening for detecting left ventricular hypertrophy. We focused on the high amplitude R-wave (left high R-wave), which is an essential component of the electrocardiogram

findings for left ventricular hypertrophy (*12, 14*).

〖 Methods 〗

Study Design and Participants

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged) is a series of cohort studies conducted by the National Survey on Circulatory Disorders, Japan. In the present study, we analyzed data from NIPPON DATA90; the details of the present cohort have been reported previously (*3, 15-18*).

A total of 8,384 community residents (3,504 men and 4,880 women; ≥ 30 years old) from 300 randomly selected districts participated in the baseline survey in 1990 and were followed until November 15, 2000. The overall population aged 30 and greater in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population. Of the 8,384 participants, 1,696 were excluded for the following reasons: previous coronary heart disease or stroke (n = 261), presence of atrial fibrillation on the electrocardiogram (n = 147), use of anti-hypertensive agents (n = 1,202), some information missing at the baseline survey (n = 122), and failure to obtain access due to incomplete residential information at the first survey (n = 182). We excluded participants with atrial fibrillation, because it is also a major risk factor for cerebral embolism, which makes it difficult to assess the risk of left high R-wave (*19*). The remaining 6,688 participants (2,853 men and 3,835 women) were included in the analysis.

Follow-up Survey

The underlying causes of death for the National Vital Statistics were coded according

to the 9th International Classification of Disease for deaths occurring through the end of 1994 and the 10th International Classification of Disease for deaths occurring from the beginning of 1995. The details of the classification in the present study are described elsewhere (*3, 15-18*).

We were permitted to use National Vital Statistics by the Management and Coordination Agency, Government of Japan. The present study was approved by the Institutional Review Board of Shiga University of Medical Science for ethical issues (No.12-18, 2000).

Baseline Examination

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after an acclimation period. Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg or both, whereas normotension was defined as SBP < 140 mmHg and DBP < 90 mmHg.

A standard 12-lead electrocardiogram was recorded in the supine position. Each electrocardiogram was coded independently by two researchers according to the Minnesota Code (*20*). Codes in agreement were accepted, whereas codes in disagreement were adjusted by a panel of epidemiologists and cardiologists. Left high R-wave was defined as R-wave in V5 or V6 > 2.6 mV, or R-wave in Ⅰ, Ⅱ, Ⅲ or aVF > 2.0 mV, or R-wave in aVL > 1.2 mV (the Minnesota Code, 3-1), and/or R-wave in Ⅰ > 1.5 mV but $\leq$ 2.0 mV, or S-wave in V1 plus R-wave in V5 or V6 > 3.5 mV (the Minnesota Code, 3-3). ST-T abnormalities were defined as ST-T depression (the Minnesota Code, 4-1 to 4-3), and/or an inverse or flat T wave (the Minnesota Code, 5-1 to 5-3).

Non-fasting blood samples were obtained and the serum was separated and centrifuged soon after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. These samples were shipped to one laboratory (SRL, Tokyo) for blood measurements. Serum total cholesterol was measured enzymatically. Lipid measurements were standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute Lipids Standardization program (*21*). Hypercholesterolemia was defined as serum total cholesterol $\geq$ 6.2 mmol/L, the use of medications for hypercholesterolemia or both. Plasma glucose was also measured enzymatically. Diabetes mellitus was defined as plasma glucose $\geq$ 11.1 mmol/L, the use of medications for diabetes mellitus or both. Body mass index was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on smoking, drinking, and medical histories.

Statistical Analysis

An unpaired Student's *t*-test or Chi-square test was used to compare risk characteristics at baseline between participants with and without left high R-wave. A Cox proportional hazards model was used to calculate the hazard ratio of hypertension compared to normotension for death due to all-causes, cardiovascular disease, stroke and heart disease. This model incorporated the following variables as covariates: age, sex, body mass index, smoking habit (non-, ex- or current smoker, using two dummy variables with the non-smoker as a reference), drinking habit (non-, ex- or daily drinker, using two dummy variables with the non-drinker as a reference), diabetes mellitus and hypercholesterolemia. The significance of an interaction between SBP and left high R-wave as a predictor of cardiovascular death was tested using an interaction term for the continuous and categorical variables in a multivariate-adjusted model. Similarly, a

Cox proportional hazards model was used to calculate the hazard ratio of left high R-wave for death, as compared with the absence of left high R-wave, incorporating the same covariates listed above and SBP. We estimated the proportion of cardiovascular death attributable to left high R-wave taking into account its prevalence and hazard ratio—i.e. the population attributable risk percent—among all the participants after both sexes were combined using the following formula: [the prevalence of left high R-wave * (adjusted hazard ratio - 1)] / [1 + the prevalence of left high R-wave * (adjusted hazard ratio – 1)].

The hazard ratio analyses for the left high R-wave and the population attributable risk percent of the left high R-wave were repeated among hypertensive and normotensive participants.

The statistical analysis package SPSS 11.0J for Windows was used for statistical processing. All probability values were two-tailed, and the significance level was set at $p<0.05$.

〖 Results 〗

The follow-up time for the 6,688 participants (mean age, 50.7 years old) in the present study was 64,340 person-years. There were 521 deaths among the total group of participants, 55 deaths due to strokes and 73 deaths due to heart diseases. Among the total participants, 9.4% had left high R-wave on their baseline electrocardiogram. Of 2,413 hypertensives, 12.4% had left high R-wave, whereas this condition was present in only 4.1% of 4,275 normotensives.

The mean values or proportions of risk characteristics at baseline for male and female participants with and without left high R-wave are summarized in Table 1. Of 2,853

male participants (mean age, 51.4 years old), 15.3% had left high R-wave on the electrocardiogram, whereas 5.0% of 3,835 female participants (mean age, 50.2 years old) had this electrocardiogram abnormality. For men and women, mean values of blood pressure and body mass index, and the prevalence of hypertension were significantly higher among participants with than without left high R-wave. The prevalence of ST-T abnormalities on the electrocardiogram in participants with left high R-wave was 6.9% for men and 11.5% for women.

Among all participants, the hypertensives had a multivariate-adjusted hazard ratio of 1.65 (95% confidence interval, 1.13-2.41; p=0.01) for cardiovascular death, 2.35 (1.24-4.48; p<0.01) for stroke and 1.45 (0.88-2.39; p=0.14) for heart disease death, as compared with the normotensives. The interaction for cardiovascular death between SBP and left high R-wave was not significant in the multivariate-adjusted model (p=0.33).

Among all participants, those with left high R-wave had a multivariate-adjusted hazard ratio of 1.88 (1.22-2.89; p<0.01) for cardiovascular death, as compared to those without left high R-wave, as shown in Table 2. The population attributable risk percent of left high R-wave for cardiovascular death was 7.6%, when using a prevalence of 9.4% and a hazard ratio of 1.88.

Among the hypertensive participants, those with left high R-wave had a multivariate-adjusted hazard ratio of 1.97 (1.20-3.24; p<0.01) for cardiovascular death, as compared with those without left high R-wave, as shown in Table 3. The population attributable risk percent of left high R-wave for cardiovascular death was 12.4%, when a prevalence of 14.6% and a hazard ratio of 1.97 were used. On the other hand, the normotensive participants with left high R-wave had a multivariate-adjusted hazard

ratio of 1.66 (0.69-3.98; p=0.26) for cardiovascular death, as compared with those without left high R-wave, as shown in Table 4. The population attributable risk percent of left high R-wave for cardiovascular death was 4.1%, when using a prevalence of 6.4% and a hazard ratio of 1.66.

【 Discussion 】

In the present prospective, community-based study, left high R-wave on the electrocardiogram predicted an increased risk of cardiovascular mortality, which was independent of casual SBP level and other risk factors.

The electrocardiogram is a simple, inexpensive and widely-available test. Because Japanese have a higher incidence or mortality from hypertensive cardiovascular disease than Western populations (*7-9*), electrocardiogram screening may be useful to evaluate organ damage or presence of left ventricular hypertrophy resulting from prolonged, severe hypertension (*1*). Left ventricular hypertrophy increases the risk for cardiovascular events through its effects on ventricular function (*22*), the coronary circulation (*23-25*) and arrhythmogenesis (*25*). Left ventricular hypertrophy is also associated with carotid structural changes (*26*) and asymptomatic cerebrovascular damage (*27*). For these reasons, a left high R-wave on the electrocardiogram may increase the risk for death from both heart disease and stroke. Thus, it is not surprising that in the present study, left high R-wave predicted an increase in mortality from heart disease, and tended to predict an increase in mortality from stroke as well. The increased risk of death from strokes may support the idea that the left high R-wave is a marker for the presence of a severe carotid structural change.

Only a few studies in Western countries have evaluated the association between left

ventricular hypertrophy as diagnosed by the electrocardiogram and cardiovascular disease among a general population (*12-14*). A similar study was conducted among a general population in Denmark, whose members were 25 to 74 years old, free of previous coronary heart disease, and not using any anti-hypertensive agents (*14*). In this Danish population, 14.6%, 1.6% and 1.5% of subjects had voltage-only left ventricular hypertrophy, left ventricular hypertrophy with a negative T wave, and left ventricular hypertrophy with ST depression and a negative T wave on the electrocardiogram, respectively (*14*). The multivariate-adjusted hazard ratios for cardiovascular mortality of these three electrocardiogram findings after 7 years of follow-up were 1.28 (0.92-1.77), 2.16 (1.25- 3.74) and 2.96 (1.87-4.68), respectively (*14*). Accordingly, among the Danish population, the population attributable risk percent of left ventricular hypertrophy for cardiovascular disease was 8.0%, when these three electrocardiogram findings were combined. This population attributable risk percent was similar to the population attributable risk percent in the present study.

The utility of electrocardiogram screening for risk of cardiovascular death is evident. It is quite likely that we may be able to use the electrocardiogram to select high-risk individuals from those who are regarded as normotensives by the casual measurement of blood pressure alone (e.g., masked hypertension) (*4*). However, an issue as to the cost-effectiveness of electrocardiogram screening exists: for what population should we perform electrocardiographic screening when taking into account the cost-effectiveness? This issue needs further evaluation in future studies.

The present study has several limitations. First, it is generally better to stratify left ventricular hypertrophy on the electrocardiogram into two subgroups, a definite left ventricular hypertrophy group (left high R-wave with ST-T abnormalities), and a

possible left ventricular hypertrophy group (left high R-wave without ST-T abnormalities) (*12, 14*). However, we focused on left high R-wave irrespective of ST-T abnormalities. One reason for this was the limited number of ST-T abnormalities (3.1%) in the present population, which made stratification based on these electrocardiogram abnormalities difficult. Second, the electrocardiogram has some limitations for detecting left ventricular hypertrophy, as compared with the echocardiogram (*28*), although the electrocardiogram is simpler and less expensive. Finally, the analyses in the present study were performed among community-dwelling Japanese after excluding those with a history of cardiovascular disease and those taking anti-hypertensive agents. Therefore, the results of the present study may not be directly relevant to or adaptable to other populations.

In conclusion, left high R-wave on the electrocardiogram, irrespective of casual SBP, serves as an independent predictor of cardiovascular death among a community-dwelling population. In order to identify individuals at high cardiovascular risk and to improve their health outcomes, electrocardiogram screening for left high R-wave is recommended.

〖 Acknowledgements 〗

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【 References 】

1 Panidis IP, Kotler MN, Ren JF, Mintz GS, Ross J, Kalman P: Development and regression of left ventricular hypertrophy. *J Am Coll Cardiol* 1984; **3:** 1309-1320.

2 Okin PM, Devereux RB, Jern S, *et al*: LIFE Study Investigators: Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292:** 2343-2349.

3 Nippon Data 80 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 data 80. *J Hum Hypertens* 2003; **17:** 851-857.

4 Ohkubo T, Kikuya M, Metoki H, *et al*: Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; **46:** 508-515.

5 Hozawa A, Ohkubo T, Kikuya M, *et al*: Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. *Hypertens Res* 2002; **25:** 57-63.

6 Kawabe H, Saito I, Saruta T: Status of home blood pressure measured in morning and evening: evaluation in normotensives and hypertensives in Japanese urban population. *Hypertens Res* 2005; **28:** 491-498.

7 Tanaka H, Iso H, Yokoyama T, Yoshiike N, Kokubo Y: Major Health Problems (Cerebrovascular Disease). In: Detels R, McEwen J, Beaglehole R, Tanaka H, eds: Oxford Textbook of Public Health 4th ed, Vol 3. Oxford: Oxford University Press, 2001, pp1193-1226.

8 Omae T, Oita J, Ueda K: The Japanese experience in hemorrhagic stroke. *J Hypertens* 1994; **12(Suppl 10):** S19-23.

9 Kita Y, Okayama A, Ueshima H, *et al*: Stroke incidence and case fatality in Shiga, Japan 1989-1993. *Int J Epidemiol* 1999; **28:** 1059-1065.

10 Shimamoto T, Iso H, Iida M, Komachi Y: Epidemiology of cerebrovascular disease: stroke epidemic in Japan. *J Epidemiol* 1996; **6(Suppl):** S43-47.

11 Ueshima H, Okayama A, Kita Y, Choudhury SR: Current epidemiology of hypertension in Japan. *Nippon Rinsho* 1997; **55:** 2028-2033 (in Japanese).

12 Kannel WB, Gordon T, Offutt D: Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969; **71:** 89-105.

13 Kannel WB: Left ventricular hypertrophy as a risk factor: the Framingham experience. *J Hypertens* 1991; **9(Suppl 2)**: S3-9.

14 Larsen CT, Dahlin J, Blackburn H, *et al*: Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave; the Copenhagen City Heart Study. *Eur Heart J* 2002; **23:** 315-324.

15 Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H: What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253:** 169-180.

16 Okamura T, Hayakawa T, Kadowaki T, *et al*: Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. *Am Heart J* 2004; **147:** 1024-1032.

17 Ueshima H, Choudhury SR, Okayama A, *et al*: Cigarette smoking as a risk

factor for stroke death in Japan. NIPPON DATA80. *Stroke* 2004; **35:** 1836-1841.

18 Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H: The NIPPON DATA90 Research Group: The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. *Atherosclerosis* 2006; **184:**143-150.

19 Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978; **28:** 973-977.

20 Prineas RJ, Crow RS, Blackburn H: The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Littleton: John Wright-PSG Inc, 1982.

21 Nakamura M, Sato S, Shimamoto T: Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003; **10:** 145-153.

22 Wachtell K, Rokkedal J, Bella JN, *et al*: Effect of electrocardiographic left ventricular hypertrophy on left ventricular systolic function in systemic hypertension (The LIFE Study). Losartan Intervention For Endpoint. *Am J Cardiol* 2001; **87:** 54-60.

23 Stojanovic MM, O'Brien E, Lyons S, Stanton AV: Silent myocardial ischaemia in treated hypertensives with and without left ventricular hypertrophy. *Blood Press Monit* 2003; **8:** 45-51.

24 Mansour P, Bostrom PA, Mattiasson I, Lilja B, Berglund G: Low blood pressure

levels and signs of myocardial ischaemia: importance of left ventricular hypertrophy. *J Hum Hypertens* 1993; **7:** 13-18.

25 Novo S, Barbagallo M, Abrignani MG, *et al*: Increased prevalence of cardiac arrhythmias and transient episodes of myocardial ischemia in hypertensives with left ventricular hypertrophy but without clinical history of coronary heart disease. *Am J Hypertens* 1997; **10:** 843-851.

26 Cuspidi C, Mancia G, Ambrosioni E, Pessina A, Trimarco B, Zanchetti A: APROS Investigators: Left ventricular and carotid structure in untreated, uncomplicated essential hypertension: results from the Assessment Prognostic Risk Observational Survey (APROS). *J Hum Hypertens* 2004; **18:** 891-896.

27 Selvetella G, Notte A, Maffei A, *et al*: Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. *Stroke* 2003; **34:** 1766-1770.

28 Reichek N, Devereux RB: Left ventricular hypertrophy: relationship of anatomic, echocardiographic and electrocardiographic findings. *Circulation* 1981; **63:** 1391-1398.

【 Appendix 】

+ List of the NIPPON DATA90 Research group:

NIPPON DATA90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged"

Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido),

Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).

Participating Researchers: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Heath Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo, Shimane), Shigeyuki Saito (Second Department of Internal Medicine School of Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yoshikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Hikone Public Health Center, Hikone, Shiga).

Participating Research Associates: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa),Shigemichi Tanaka (Department of Cardiology, Cardiovascular Center, Teine Keijinkai, Sapporo, Hokkaido), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Katsuhiko Kawaminami (Department of Public Health Policy, National

Institute of Public Health, Wako, Saitama), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

Table 1. Baseline risk characteristics in 1990 of 6,688 participants based on sex and left high R-wave on the electrocardiogram: NIPPON DATA90.

	Men			Women		
	Left high R-wave			Left high R-wave		
	Absent (n=2,417)	Present (n=436)		Absent (n=3,644)	Present (n=191)	
Age (years) †	51.2 ± 13.2	52.5 ± 13.3	*	49.9 ± 13.2	57.6 ± 13.9	*
Body mass index (kg/m^2) †	22.9 ± 3.0	22.8 ± 2.7		22.6 ± 3.2	21.8 ± 2.9	*
Smoking habit ‡						
Never smoker (%)	21.8	21.1		88.0	89.5	
Ex-smoker (%)	21.2	22.0		2.5	0.5	
Current smoker (%)	57.0	56.9		9.5	9.9	
Drinking habit ‡						
Never drinker (%)	37.3	29.4		92.3	93.7	
Ex-drinker (%)	5.5	6.4	*	1.0	0.5	
Daily drinker (%)	57.2	64.2		6.7	5.8	
Systolic blood pressure (mmHg) †	133.6 ± 17.8	142.4 ± 21.1	*	129.0 ± 18.4	143.1 ± 23.5	*
Diastolic blood pressure (mmHg) †	81.9 ± 10.9	86.3 ± 12.2	*	77.7 ± 10.8	83.1 ± 14.3	*
Hypertension (%) ‡	39.3	55.3	*	30.5	58.6	*
ST-T abnormalities on the electrocardiogram (%) ‡	1.4	6.9	*	3.4	11.5	*
Diabetes mellitus (%) ‡	6.5	7.3		2.9	5.8	*
Hypercholesteloremia (%) ‡	14.7	17.0		18.8	18.3	

Values located after the mark, ±, indicate standard deviation. The mark, *, indicates statisitically significant difference between two groups ($p<0.05$). † Unpaired Student's t-test. ‡ Chi-square test.

Table 2. Risk of death over 10 years of follow-up (1990-2000) from all-causes and specific causes predicted by left high R-wave on the electrocardiogram among 6,688 participants: NIPPON DATA90.

	Overall		Men		Women	
	Left high R-wave		Left high R-wave		Left high R-wave	
	Absent (n=6,061)	Present (n=627)	Absent (n=2,417)	Present (n=436)	Absent (n=3,644)	Present (n=191)
Person-years of follow-up period	58,476	5,863	23,030	4,057	35,446	1,806
Death due to all-causes						
Cases	429	92	235	68	194	24
Mortality (per 1,000 person-years)	7.3	15.7	10.2	16.8	5.5	13.3
Age and sex-adjusted hazard ratio †	1.00	1.53 (1.22-1.91)*	1.00	1.67 (1.27-2.18)*	1.00	1.25 (0.82-1.92)
Multivariate-adjusted hazard ratio ‡	1.00	1.47 (1.17-1.85)*	1.00	1.64 (1.25-2.15)*	1.00	1.25 (0.81-1.92)
Multivariate-adjusted hazard ratio §	1.00	1.47 (1.16-1.85)*	1.00	1.64 (1.24-2.16)*	1.00	1.21 (0.78-1.87)
Death due to cardiovascular disease						
Cases	105	28	54	16	51	12
Mortality (per 1,000 person-years)	1.8	4.8	2.3	3.9	1.4	6.6
Age and sex-adjusted hazard ratio †	1.00	1.96 (1.29-2.97)*	1.00	1.70 (0.97-2.98)	1.00	2.21 (1.17-4.15)*
Multivariate-adjusted hazard ratio ‡	1.00	1.92 (1.26-2.92)*	1.00	1.68 (0.96-2.95)	1.00	2.25 (1.18-4.29)*
Multivariate-adjusted hazard ratio §	1.00	1.88 (1.22-2.89)*	1.00	1.68 (0.95-2.98)	1.00	2.12 (1.10-4.09)*
Death due to stroke						
Cases	43	12	16	6	27	6
Mortality (per 1,000 person-years)	0.7	2.0	0.7	1.5	0.8	3.3
Age and sex-adjusted hazard ratio †	1.00	2.17 (1.14-4.13)*	1.00	2.18 (0.85-5.59)	1.00	2.11 (0.87-5.12)
Multivariate-adjusted hazard ratio ‡	1.00	2.18 (1.14-4.17)*	1.00	2.17 (0.84-5.61)	1.00	2.25 (0.90-5.63)
Multivariate-adjusted hazard ratio §	1.00	1.93 (0.99-3.74)	1.00	1.97 (0.74-5.21)	1.00	2.04 (0.80-5.16)
Death due to heart disease						
Cases	57	16	35	10	22	6
Mortality (per 1,000 person-years)	1.0	2.7	1.5	2.5	0.6	3.3
Age and sex-adjusted hazard ratio †	1.00	1.98 (1.13-3.45)*	1.00	1.63 (0.81-3.30)	1.00	2.55 (1.03-6.30)*
Multivariate-adjusted hazard ratio ‡	1.00	1.94 (1.11-3.39)*	1.00	1.64 (0.81-3.33)	1.00	2.48 (0.98-6.26)
Multivariate-adjusted hazard ratio §	1.00	2.06 (1.16-3.64)*	1.00	1.69 (0.82-3.46)	1.00	2.57 (1.00-6.58)*

Values in parentheses indicate 95% confidence interval of hazard ratios. The mark, *, indicates statisitically significant difference between two groups ($p<0.05$).

† Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age. ‡ Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, body mass index, smoking habit, drinking habit, diabetes mellitus and hypercholesterolemia. § Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, body mass index, smoking habit, drinking habit, diabetes mellitus, hypercholesterolemia and systolic blood pressure. Sex was also adjusted, when men and women were combined.

Table 3. Risk of death in hypertensives from all-causes and specific causes over 10 years of follow-up (1990-2000) associated with left high R-wave on the electrocardiogram: NIPPON DATA90.

	Overall		Men		Women	
	Left high R-wave		Left high R-wave		Left high R-wave	
	Absent (n=2,060)	Present (n=353)	Absent (n=950)	Present (n=241)	Absent (n=1,110)	Present (n=112)
Person-years of follow-up period	19,509	3,235	8,927	2,197	10,582	1,038
Death due to all-causes						
Cases	235	68	119	47	116	21
Mortality (per 1,000 person-years)	12.0	21.0	13.3	21.4	11.0	20.2
Age and sex-adjusted hazard ratio †	1.00	1.67 (1.27-2.18)*	1.00	1.94 (1.38-2.72)*	1.00	1.30 (0.81-2.07)
Multivariate-adjusted hazard ratio ‡	1.00	1.62 (1.23-2.13)*	1.00	1.89 (1.33-2.67)*	1.00	1.28 (0.79-2.07)
Multivariate-adjusted hazard ratio §	1.00	1.63 (1.23-2.15)*	1.00	1.87 (1.31-2.65)*	1.00	1.31 (0.81-2.13)
Death due to cardiovascular disease						
Cases	68	22	31	12	37	10
Mortality (per 1,000 person-years)	3.5	6.8	3.5	5.5	3.5	9.6
Age and sex-adjusted hazard ratio †	1.00	1.91 (1.18-3.09)*	1.00	1.77 (0.91-3.46)	1.00	1.85 (0.92-3.72)
Multivariate-adjusted hazard ratio ‡	1.00	1.85 (1.13-3.01)*	1.00	1.74 (0.88-3.41)	1.00	1.75 (0.85-3.62)
Multivariate-adjusted hazard ratio §	1.00	1.97 (1.20-3.24)*	1.00	1.89 (0.95-3.75)	1.00	1.79 (0.87-3.72)
Death due to stroke						
Cases	33	9	14	4	19	5
Mortality (per 1,000 person-years)	1.7	2.8	1.6	1.8	1.8	4.8
Age and sex-adjusted hazard ratio †	1.00	1.66 (0.79-3.47)	1.00	1.38 (0.45-4.23)	1.00	1.80 (0.67-4.84)
Multivariate-adjusted hazard ratio ‡	1.00	1.60 (0.76-3.39)	1.00	1.32 (0.42-4.08)	1.00	1.84 (0.65-5.17)
Multivariate-adjusted hazard ratio §	1.00	1.64 (0.77-3.50)	1.00	1.46 (0.46-4.61)	1.00	1.82 (0.64-5.13)
Death due to heart disease						
Cases	33	13	17	8	16	5
Mortality (per 1,000 person-years)	1.7	4.0	1.9	3.6	1.5	4.8
Age and sex-adjusted hazard ratio †	1.00	2.24 (1.18-4.28)*	1.00	2.08 (0.90-4.84)	1.00	2.16 (0.79-5.91)
Multivariate-adjusted hazard ratio ‡	1.00	2.12 (1.10-4.10)*	1.00	2.09 (0.89-4.90)	1.00	1.85 (0.65-5.25)
Multivariate-adjusted hazard ratio §	1.00	2.40 (1.23-4.68)*	1.00	2.26 (0.95-5.40)	1.00	2.08 (0.73-5.94)

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or both. Values in parentheses indicate 95% confidence interval of hazard ratios. The mark, *, indicates statisitically significant difference between two groups ($p<0.05$). † Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age. ‡ Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, body mass index, smoking habit, drinking habit, diabetes mellitus and hypercholesterolemia. § Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, body mass index, smoking habit, drinking habit, diabetes mellitus, hypercholesterolemia and systolic blood pressure. Sex was also adjusted, when men and women were combined.