[MC, 8-3], Q-wave evidence of myocardial infarction [MC, 1-1], ventricular tachycardia [MC, 8-2], supraventricular tachycardia [MC, 8-4], and AV nodal delay [MC, 8-6] were also excluded. Consequently, the remaining 8,572 participants (3,808 men and 4,764 women) were included in the analysis (figure 1).

Information on a history of CVD, diabetes, the baseline use of antihypertensive medications, and smoking and drinking habits were obtained from interviews by public health nurses. Non-fasting blood samples were drawn and centrifuged within 60 minutes of collection. Casual glucose concentration was measured by the cupric-neocuproine method[13]. The glucose concentration obtained by the cupric-neocuproine method was corrected by an equation to the value that would have been measured by the glucose-oxidase method, which is the correct standard[14]. Serum total cholesterol was measured by an auto analyzer (SMA 12/60; Technicon, Tarrytown) in one specific laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Since 1975, the laboratory has been certified by the CDC-NHLBI Lipid Standardization Program by Center for Disease Control and Prevention (CDC, Atlanta, GA)[15], for precision and accuracy of cholesterol measurements. Baseline blood pressure was measured in each subject after 5 minutes of rest in a seated position. The measurement was performed by trained public health nurses at each public health center using a standard mercury sphygmomanometer placed on the right arm. Hypertension was defined as systolic blood pressure ≥140mm Hg, diastolic blood pressure ≥90mm Hg, use of antihypertensive agents or any combination of these[16]. Body height in stocking feet and body weight in light clothing were measured and body mass index (BMI) was calculated as body weight (kg) divided by square of body height (m). The frequency of drinking per week and average number of cigarettes per day were assessed using questionnaires.

During the baseline survey, a standard 12-lead ECG was recorded in the supine position. Each ECG was read twice by two different researchers according to the MC criteria, which was developed to document significant ECG pattern changes using objective criteria[17]. Codes in agreement were accepted, whereas inconsistent codes were decided by a panel of study epidemiologists and cardiologists[11]. The participants were categorized into four groups according to the ECG findings: (a) isolated left high R-waves [MC 3.1, 3.3], (b) isolated ST-T abnormalities [MC 4-1 to 4-3 and/ MC 5-1 to 5-3], (c) ST-T abnormalities with left high R-waves [MC 3.1, 3.3 with MC 4-1 to 4-3 and/ MC 5-1 to 5-3] and (d) normal ECG findings. The ECG was classified as normal in the absence of left high R-waves and ST-T abnormalities.

During the 24-years follow-up, we used the National Vital statistics database of Japan to identify the underlying causes of deaths of the participants who died during the

follow-up by date of birth, sex, date of death and area code of the place of death with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. The details of the classification used in the present study are described elsewhere[11,12]. CVD (ICD-9 code: 393 to 459 and ICD-10 code: I00 to I99), CHD (ICD-9 code: 410 to 414 and ICD-10 code: I20 to I25) and stroke (ICD-9 code: 430 to 438 and ICD-10 code: I60 to I69) were identified. Approval for the study was obtained from the Institutional review Board of Shiga University of Medical Science (No. 12-18, 2000).

We used analysis of variance (ANOVA) for continuous variables and a $\chi 2$-test for categorical variables to compare baseline characteristics among the four participant groups. The outcome events studied were CVD, CHD, and stroke mortality. We used Cox proportional hazards models to estimate the hazard ratios (HR) with 95% confidence intervals (CIs) of mortality for the presence of 'isolated left high R-waves', 'isolated ST-T abnormalities', and 'ST-T abnormalities with left high R-waves' in comparison to 'normal ECG' findings which served as the reference category. Separate analyses were carried out for CVD, CHD, and stroke. In multivariable models, we included traditional cardiovascular risk factors as potential confounding factors, namely age at study entry, body mass index (BMI), systolic blood pressure, serum total cholesterol, blood glucose, history of smoking (never, current , ex-smoker) and alcohol drinking (never, current , ex-drinker) and antihypertensive medication (yes, no) as confounding factors. These covariates were considered in the multivariable models based on clinical judgment and statistical significance based on univariate analysis. The models in which gender was combined were also adjusted for sex. The performance of the multivariable models was quantified by Harrell's concordance statistics (c-index), a generalization of the area under the receiver-operating characteristic curve that allows for censored data[18]. Calibration was assessed graphically by plotting the predicted probability (using the full model) against actual probability (observed in our cohort) across ten decile categories based on predicted risk[18].

Results

The baseline characteristics of the participants (men and women) that had ST-T abnormalities with left high R-waves, isolated ST-T abnormalities, isolated left high R-waves, and a normal ECG are shown in Table 1. Age, systolic and diastolic blood pressure, blood glucose, serum cholesterol, drinking habit and the use of antihypertensive medication were significantly different among the four groups for both sexes.

During a total follow-up period of 181,545 person years (average: 21.2 years), there were 2,244 deaths among the participants, including 750 deaths due to all CVD, 149 deaths due to CHD and 353 deaths due to stroke.

Table 2 shows age-adjusted and multivariable-adjusted HRs for deaths from all CVD in the four groups that were stratified based on ECG abnormalities. Participants that had ST-T abnormalities with left high R-waves and those with isolated ST-T abnormalities had a higher risk for CVD mortality compared with the normal ECG group in both sexes. In participants that had ST-T abnormalities with left high R-waves, the multivariable-adjusted HR for CVD mortality was 1.95 in men and 2.68 in women. In participants that had isolated ST-T abnormalities, the multivariable-adjusted HRs for deaths due to CVD were 1.66 in men and 1.62 in women.

For all participants, the multivariable-adjusted HRs of CHD mortality for the presence of ST-T abnormalities with left high R-waves and of isolated ST-T abnormalities were significantly higher compared with the normal ECG group (Table 3). In men, the age-adjusted HR of CHD mortality was significantly higher in participants that had ST-T abnormalities with left high R-waves and in those that had isolated ST-T abnormalities; however multivariable- adjustment attenuated the significance. In women, the multivariable-adjusted HR of CHD mortality for ST-T abnormalities with left high R-waves was 2.62 and that for isolated ST-T abnormalities was 2.39.

For stroke mortality, the multivariable-adjusted HRs for ST-T abnormalities with left high R-waves was significantly higher compared with the normal ECG group in all participants (Table 4). Similar results were also observed for the risk of stroke mortality in men and in women. Isolated ST-T abnormalities did not show any higher risk of stroke death in either sex. Isolated left high R-waves were not associated with a significant risk of CVD, CHD or stroke mortality in either sex.

The discriminative performances of the final models for CVD, CHD and stroke were c=0.89, c=89, and c=0.90, respectively. The final models also showed good calibration. The final model for the effect of ST-T abnormalities on CVD showed significantly better fit than model that only included standard cardiovascular risk factors when assessed by the likelihood ratio test to evaluate whether the global model fit improved after the addition of the ECG measurements. Also the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were lower in the full models. On the other hand, the discriminative performance was similar among the two models (c = 0.89 and 0.88, respectively). Similar was observed across the models for CHD as well as stroke.

Discussion

There have been insufficient data of ST-T abnormalities with a long follow up period from the Asian populations which has low CHD events and high stroke incidence feature. The few studies done in the Japanese populations were predominantly for stroke events, but ST-T abnormalities along with or without left high R-waves did not show adequate results for CVD or CHD mortality [19] . In the present study, we observed that ST-T abnormalities with left high R-waves were associated with an increased risk for CVD, CHD and stroke mortality in men and women. There was also an increased risk for CVD and CHD mortality when isolated ST-T abnormalities were present.

The ECG changes of ST-T abnormality are often transient and not specific, together with a strong relation with high blood pressure, makes it difficult to determine their precise pathophysiologic mechanism[1]. Hypertension affects the heart by inducing LVH. LVH increases the risk for cardiovascular events through its effects on ventricular function[20], the coronary circulation[21-23] and arrthythmogenesis[23]. LVH is also associated with carotid structural changes[24] and asymptomatic cerebrovascular damage[25]. These changes all increase the risk of events from CVD. Our findings points towards the predictive suitability of the ST-T abnormalities with left high R-waves for mortality from CVD, CHD, and stroke in general Japanese population as well.

Based on data from the Chicago Heart Association Detection Project in Industry[9], Liao et al. found a gender difference in the relationship between ST-T abnormalities and the risk of death from CHD over 11.5 years of follow-up. In their multivariable analysis, which included 9,203 men and 7,818 women aged 40 to 64 years and free of CHD at baseline, the sex difference in risk ratios was of borderline significance (p=0.09). In contrast to this finding, other studies that analyzed ECG data in men and women reported that changes in the initial ECG had similar prognostic value in both sexes for events from CVD or CHD[1,4,10]. De Bacquer et al. followed participants (5208 men and 4746 women) for 13 years and found that ischemic changes with ST depression or T wave abnormalities in the baseline ECG or ECG changes indicative LVH were associated with CVD mortality[7]. In that study, the predictive value was similar in both men and women and was independent of major ECG abnormalities and traditional cardiovascular risk factors. Previous studies conducted in Asian populations, especially Japanese, did not examine whether gender influenced the relationship between these ECG abnormalities and CVD mortality[19]. As in Western populations, in the current study, we observed that ST-T abnormalities with left high R-waves as well as isolated ST-T abnormalities had similar prognostic value for all deaths from CVD as well as deaths from CHD in both men and women. Although the risk associated with these ECG abnormalities was independent of established cardiovascular

risk factors for women, but the multivariate adjusted higher risk for death due to CHD did not reach significance for men, which to some extent might be attributed to the limited statistical power.

It has been reported that ST-T abnormalities are associated with an increased risk of stroke incidence and mortality[19, 26]. Both men and women with major ST-T abnormalities had approximately a 3-fold higher age-adjusted relative risk and a 2-fold higher multivariable- adjusted relative risk for total stroke incidence[19]. In our study, though we found that isolated ST-T abnormalities did not show any association with future stroke death risk, an elevated risk of stroke mortality in participants with ST-T abnormalities with left high R-waves was observed. This might be attributed to the fact that left high R-wave, the ECG manifestation of LVH, is associated with prolonged severe hypertension which is strongly related to stroke death.[27]

Regarding the isolated left high R-wave, similar to our results, Larsen et al. reported that voltage-only LVH was not associated with excess future CVD mortality or events due to ischemic heart disease[2]. Though voltage-only LVH was initially described in the Framingham study as carrying half the prognostic information of ECG LVH with ST depression and negative T wave with respect to CVD, but later information from the Framingham study indicates that adjustment for coexistent hypertension eliminates the excess risk.[8]

The participants in this study were from a nation-wide cohort study and were selected by a stratified random sampling method. Accordingly, the results of the present study are applicable to general Japanese population. Furthermore, the participants in our study were followed for 24 years, and this long follow-up period increases the extrapolative value of the study. Additionally, the final models showed reasonably well discriminative ability and calibration. These models showed better fit than simple corresponding models those only consisted conventional cardiovascular risk factors.

The characteristics and clinical significance of ST-T abnormalities and/or left high R-wave was poorly characterized among the asymptomatic general population in Japan. In our study we observed significant relation of ST-T abnormalities and/or left high R-wave with increased future risk for CVD and CHD death. The association was independent of major conventional cardiovascular risk factors. ECGs obtained for any clinical reason or incorporated in any routine health service in adults should be examined carefully for the presence of ST-T abnormalities and/or left high R-wave. Thus physicians and patients could consider more intensive management of modifiable risk factors in those with ST-T abnormalities and/or left high R-wave to prevent adverse outcomes.

There are some limitations of the current study. We analyzed the relationship between ST-T abnormalities, left high R-waves and CVD mortality using a single 12-lead ECG at baseline. It is well recognized that single biologic measurements are subject to variability, and it is possible that the observed ECG abnormalities could have changed over time. This might have led to underestimation of the strength of the HR due to misclassification. Second, the ECGs were coded by visual reading in our study. Computerized ECG analysis is thought to be more reliable than visual reading[28]; however, the ECG reading in this study was performed under the best standardized quality control by well-trained physicians. The ECG itself has some limitations for detecting LVH, as compared with the echocardiogram[29], although the ECG is simpler and less expensive. We used nonfasting blood samples in our study. The pathophysiological meanings of the blood glucose levels ought to be different among the participants depending on the time from last meal. Although we adjusted for a number of conventional cardiovascular risk factors, we could not adjust for the effect of some potential confounding factors, such as type of antihypertensive treatment, their dosage, adherence and pharmacological changes over time. We also did not adjust for competing risk of non-cardiovascular death while estimating the risk across the ECG categories, rather we used conventional survival analysis. In the NIPPON DATA, the cause of death was examined using the National Vital Statistics databases. The cause of death, identified based on the death certificate, was determined by the attending doctors and the diagnosis was not validated by independent investigators. Finally, the end point in this study was CVD mortality. Our study findings need to be further extended using CVD incidence capturing cohort.

Acknowledgments

This study was supported by the grant-in-aid of the Ministry of Health, Labor and Welfare under the auspices of Japanese Association for Cerebro-cardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare, and the Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health [H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, H19-Chouju-Ippan-014] and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus [H22-Jyunkankitou-Seisyu-Sitei-017]). Nahid Rumana is supported by the Research Fellowship and Research Grants-In-Aid (P-21.09139) from the Japan Society of Promotion of Science (JSPS), Tokyo, Japan. We appreciate the members of the NIPPON DATA80 Research Group[11].

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Figure legend

Figure 1.

Flow chart of the study participants. The exclusion of the participants and assignment of participants to the electrocardiography groups are shown in this flow chart.
N, number of participants; ECG, electrocardiography; CVD, cardiovascular disease.

Table 1: Baseline characteristics of the participants according to the different electrocardiographic groups: NIPPON DATA80, 1980-2004, Japan

	Normal ECG	ST-T abnormalities with left high R-waves	Isolated ST-T abnormalities	Isolated left high R-waves	p
Men					
Number	2854	68	58	828	
Age (years)	48.5±12.6	62.03±12.8	60.9±15.6	48.7±12.2	<0.001
Systolic blood pressure (mmHg)	134.7±18.6	167.9±27.1	154.2±25.7	142.7±21.3	<0.001
Diastolic blood pressure (mmHg)	82.1±11.6	90.7±15.6	87.9±14.3	86.1±12.7	<0.001
Body mass index (kg/m^2)	22.9±2.5	23.8±2.8	22.3±3.5	23.6±3.1	0.874
Serum total cholesterol (mg/dl)	185.9±32.6	180.3±30.9	192.1±27.5	185.7±32.7	0.024
Blood glucose (mg/dl)	129.5±37.6	157.1±61.5	150.02±49.4	128.2±33.6	<0.001
Current Smoker	62.6%	63.2%	69.0%	65.1%	0.239
Current Drinker	72.8%	64.7%	63.8%	83.3%	<0.001
Antihypertensive drug	7.0%	44.1%	32.8%	10.4%	<0.001
Women					
Number	4156	60	234	314	
Age (years)	48.4±12.6	64.6±12.2	57.8±14.1	53.6±12.5	<0.001
Systolic blood pressure (mmHg)	131.04±20.1	161.6±29.1	144.2±22.4	142.0±21.4	<0.001
Diastolic blood pressure (mmHg)	78.6±11.4	88.6±16.0	83.3±12.7	82.2±12.5	<0.001
Body mass index (kg/m^2)	22.8±3.3	22.9±4.2	23.9±3.7	22.1±3.01	0.005
Serum total cholesterol (mg/dl)	189.6±33.6	196.4±37.6	200.6±33.8	188.8±35.2	0.041
Blood glucose (mg/dl)	127.5±33.5	162.1±78.3	141.03±40.2	130.2±32.4	<0.001
Current Smoker	8.8%	16.7%	9.0%	8.9%	0.445
Current Drinker	20.6%	15%	14.1%	21.3%	0.042
Antihypertensive drug	8.3%	43.3%	23.1%	18.2%	<0.001

Isolated left high R-waves (MC 3.1, 3.3), Isolated ST-T abnormalities (MC4.1-4.3 and/or 5.1-5.3), ST-T abnormalities with left high R-waves (MC 4.1-4.3 and/or 5.1-5.3 with 3.1, 3.3). Values after ± indicate standard deviation.

Table 2. Hazard ratios for all cardiovascular disease mortality in the four groups by electrocardiographic findings: NIPPON DATA80, 1980-2004, Japan.

	All CVD mortality			
	Normal ECG	ST-T abnormalities with Left high R-waves	Isolated ST-T abnormalities	Isolated left high R-waves
Men				
Number	2854	68	58	828
CVD death	254	25	19	77
Mortality(/1000 person-year)	4.3	27.4	24.4	4.5
Age-adjusted hazard ratio	1.00	2.99 (1.97-4.53)	2.49 (1.55-3.98)	1.14 (0.88-1.46)
Multivariable-adjusted hazard ratio	1.00	1.95 (1.25-3.04)	1.66 (1.01-2.71)	1.02 (0.78-1.33)
Women				
Number	4156	60	234	314
CVD death	268	30	46	31
Mortality(/1000 person-year)	2.9	37.5	10.4	4.7
Age-adjusted hazard ratio	1.00	3.09(2.10-4.55)	1.66(1.21-2.28)	1.12(0.77-1.62)
Multivariable-adjusted hazard ratio	1.00	2.68(1.81-3.97)	1.62(1.18-2.24)	0.997(0.68-1.46)
Total participants				
Number	7010	128	292	1142
CVD death	522	55	65	108
Mortality(/1000 person-year)	3.5	32.1	12.5	4.6
Age & sex-adjusted hazard ratio	1.00	3.07(2.32-4.08)	1.89(1.45-2.45)	1.14(0.92-1.40)
Multivariable-adjusted hazard ratio	1.00	2.27(1.69-3.04)	1.59(1.23-2.08)	1.04(0.84-1.29)

Isolated left high R-waves (MC 3.1,3.3), Isolated ST-T abnormalities (MC4.1-4.3 and/or 5.1-5.3), ST-T abnormalities with left high R-wave (MC 4.1-4.3 and/or 5.1-5.3 with 3.1, 3.3). Values in parenthesis indicate 95% confidence interval. Multivariable-adjusted hazard ratio were adjusted for age, body mass index, serum cholesterol, blood glucose, history of smoking, drinking habit, systolic blood pressure, and antihypertensive medication. Sex was also included when the overall hazard ratios were estimated

Table 3. Hazard ratios for coronary heart disease mortality in the four groups by electrocardiographic findings: NIPPON DATA80, 1980-2004, Japan.

	CHD mortality			
	Normal ECG	ST-T abnormalities with Left high R-waves	Isolated ST-T abnormalities	Isolated left high R-waves
Men				
Number	2854	68	58	828
CHD death	50	5	4	16
Mortality(/1000 person-year)	0.8	5.5	5.1	0.9
Age-adjusted hazard ratio	1.00	3.64 (1.43-9.27)	3.14 (1.12-8.82)	1.17 (0.67-2.06)
Multivariable-adjusted hazard ratio	1.00	2.40 (0.89-6.44)	1.80 (0.61-5.29)	1.05 (0.59-1.88)
Women				
Number	4156	60	234	314
CHD death	51	5	12	6
Mortality (/1000 person-year)	0.6	6.3	2.7	0.9
Age-adjusted hazard ratio	1.00	2.93 (1.15-7.49)	2.42 (1.28-4.58)	1.15 (0.49-2.68)
Multivariable-adjusted hazard ratio	1.00	2.62 (1.02-6.76)	2.39 (1.25-4.59)	1.03 (0.44-2.43)
All participants				
Number	7010	128	292	1142
CHD death	101	10	16	22
Mortality(/1000 person-year)	0.7	5.8	3.1	0.9
Age & sex-adjusted hazard ratio	1.00	3.36 (1.74-6.52)	2.66 (1.55-4.58)	1.19 (0.74-1.89)
Multivariable-adjusted hazard ratio	1.00	2.48 (1.26-4.91)	2.10 (1.20-3.66)	1.10 (0.69-1.77)

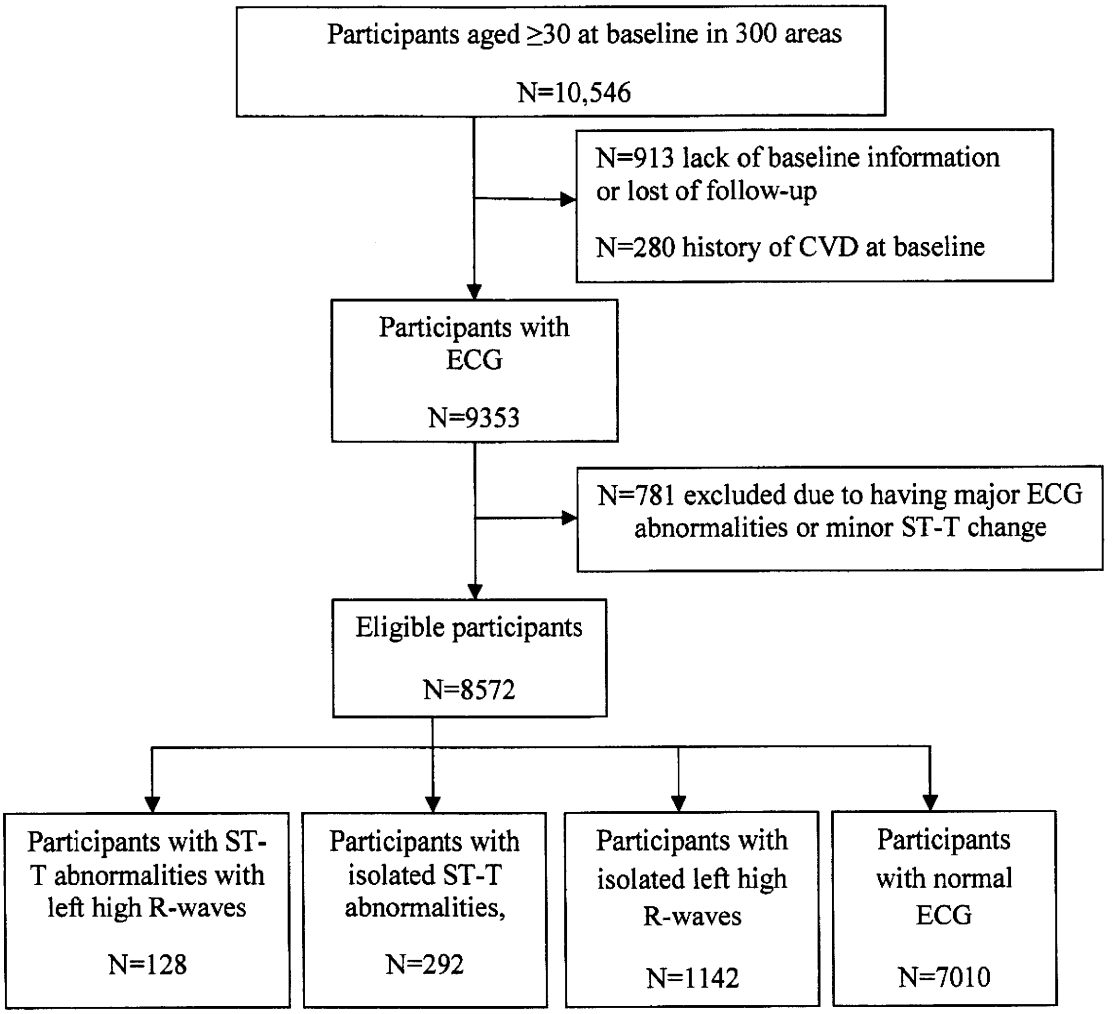
Isolated left high R-waves (MC 3.1, 3.3), Isolated ST-T abnormalities (MC4.1-3.4 and/or 5.1-5.3), ST-T abnormalities with left high R-waves (MC 4.1-4.3 and/or 5.1-5.3 with 3.1, 3.3). Values in parenthesis indicate 95% confidence interval. Multivariable-adjusted hazard ratio were adjusted for age, body mass index, serum cholesterol, blood glucose, history of smoking, drinking habit, systolic blood pressure, and antihypertensive medication. Sex was also included when the overall hazard ratios were estimated.

Table 4. Hazard ratios for stroke mortality in the four groups by electrocardiographic findings: NIPPON DATA80, 1980-2004, Japan.

	Stroke mortality			
	Normal ECG	ST-T abnormalities with Left high R-waves	Isolated ST-T abnormalities	Isolated left high R-waves
Men				
Number	2854	68	58	828
Stroke death	131	12	4	40
Mortality(/1000 person-year)	2.2	13.2	5.1	2.3
Age-adjusted hazard ratio	1.00	2.69 (1.47-4.90)	0.98 (0.36-2.65)	1.15 (0.81-1.64)
Multivariable-adjusted hazard ratio	1.00	1.58 (0.83-3.01)	0.62 (0.22-1.73)	1.00 (0.69-1.45)
Women				
Number	4156	60	234	314
Stroke death	120	16	17	13
Mortality(/1000 person-year)	1.3	20.0	3.9	2.0
Age-adjusted hazard ratio	1.00	3.82 (2.23-6.54)	1.39 (0.83-2.33)	1.04 (0.59-1.85)
Multivariable-adjusted hazard ratio	1.00	3.07 (1.77-5.32)	1.30 (0.77-2.18)	0.92 (0.52-1.65)
All participants				
Number	7010	128	292	1142
Stroke death	251	28	21	53
Mortality(/1000 person-year)	1.7	16.4	4.0	2.2
Age & sex-adjusted hazard ratio	1.00	3.20 (2.15-4.77)	1.29 (0.82-2.02)	1.13 (0.84-1.53)
Multivariable-adjusted hazard ratio	1.00	2.20 (1.45-3.34)	1.05 (0.67-1.66)	1.02 (0.75-1.38)

Isolated left high R-waves (MC 3.1, 3.3), Isolated ST-T abnormalities (MC4.1-4.3 and/or 5.1-5.3), ST-T abnormalities with left high R-waves (MC 4.1-4.3 and/or 5.1-5.3 with 3.1, 3.3). Values in parenthesis indicate 95% confidence intervals. Multivariable-adjusted hazard ratios were adjusted for age, body mass index, serum cholesterol, blood glucose, history of smoking, drinking habit, systolic blood pressure and antihypertensive medication. Sex was also included when the overall hazard ratios were estimate.

Figure 1.


Participants aged ≥30 at baseline in 300 areas
N=10,546
N=913 lack of baseline information or lost of follow-up
N=280 history of CVD at baseline
Participants with ECG
N=9353
N=781 excluded due to having major ECG abnormalities or minor ST-T change
Eligible participants
N=8572
Participants with ST-T abnormalities with left high R-waves
N=128
Participants with isolated ST-T abnormalities,
N=292
Participants with isolated left high R-waves
N=1142
Participants with normal ECG
N=7010

(7) 耐糖能異常と血圧レベル別の循環器疾患死亡リスク:NIPPONDATA90

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A. 研究目的

近年，わが国では糖尿病患者や耐糖能異常者が急激に増加している。耐糖能異常は糖尿病に進展していない耐糖能障害(IGT)から循環器疾患の危険因子となることが知られている。また，高血圧は循環器疾患の最大の険因子であり，高血圧者には耐糖能異常の合併が多く，予後をさらに悪くすることは内外から報告されている。しかしながら，わが国で、血圧一般住民を対象に耐糖能異常（IGT）の予後を血圧階層別に検討した成績は少ない。

そこで本研究では，1990 年度に実施された循環器疾患基礎調査対象の追跡研究の成績からヘモグロビン A1c(HbA1c)により判定した耐糖能異常の循環器疾患死亡(脳血管疾患死亡，心臓疾患死亡)と、耐糖能異常の血圧階層別の循環器疾患死亡の耐糖能異常合併による影響を検討した。

B. 対象方法

NIPPON DATA 90 データセットは無作為抽出された全国 300 カ所の約 10,000 人を調査客体として、地域保健婦による問診、血圧測定、採血が実施され制度管理された方法で血液生化学検査値が測定されたものである。採血は駆血帯を使用し、座位にて肘静脈から行い、HbA1c は抗凝固剤（EDTA－２K）入り真空採血管（末梢血液一般検査およびヘモグロビン A１c 用)、血糖は NaF 入り真空採血管により採取した。測定は、株式会社エスアールエルで行われ、HbA1c の測定はラッテクス凝集比濁法を、血糖は酵素法を用いた。

本解析では 1990 年循環器疾患基礎調査成績から随時血糖値、糖尿病病歴に加えて HbA1c 値を加味して耐糖能異常を判定した。すなわち解析対象は、①糖尿病(糖尿病の既往がある、あるいは随時血糖≧200mg/dl、あるいは HbA1c≧5.6%)の有無が判定され、③2000 年までの 10 年間における生死の判定と死因が同定されたものとなる。HbA1c 基準値は 1997 年および 2007 年の厚生労働省実施の糖尿病実態調査で採用された「糖尿病の可能性を否定できない人」を判定するカットオフポイント HbA1c≧5.6%とした。生死の判定は死亡診断書の記載により確定した。上記①②を満たす解析対象は 7,721 人(女性 4,498 人、男性 3,223 人)である。また対象を収縮期血圧階層別（収縮期血圧 130mmHg 未満、130～139mmHg 、140～149mmHg、150～159mmHg、160mmHg 以上の五群に分類した。性、年齢、BMI、血圧値、総コレステロール値、クレアチン値、喫煙（現在喫煙中）の有無を共変量として用いた。以上より耐糖能異常の有無での循環器疾患死亡を endpoint にした解析を行った。

次に血圧レベル別に耐糖能異常の有無で生存率を求め，各因子を Cox の比例ハザードモデルにより調整した。

C. 研究結果

10 年間の総死亡は 810 名、循環器疾患死亡者は 247 名でありそれぞれ対象に占める割合は 9.9%と 3.0%であり循環器疾患死亡が総死亡の 30%弱を占め、現在の日本人の死亡構造と一致する。初年度対象 7、721 名の耐糖能異常の有無別の検査成績を表 1 に示す。耐糖能異常群では男性の比率が大きく、年齢、収縮期・拡張期血圧値、BMI、総コレステロール値、クレアチニン値は耐糖能異常群で有意に高値であった。

図 1 に耐糖能異常有無別の累積循環器死亡をカプランマイヤー法にて示した。粗循環器疾患死亡は耐糖能異常で 6.3%、正常耐糖能で 2.5%（ログランク検定 χ 二乗値：44.0：$p<0.0001$）であり、耐糖能異常で 2.52 倍死亡率が上昇した。次ぎに Cox 比例モデルにより循環器疾患死亡の各因子の相対リスクを検討した（表 2）。耐糖能異常は循環器疾患死亡の相対リスクを 1.710 とし、同時に、男性、年齢、喫煙、既往歴が危険因子となった。

血圧階層別、耐糖能異常の有無別に 10 年間の循環器疾患の粗死亡率を検討すると血圧階層が上昇するに従い死亡率が上昇し、これに耐糖能異常が加わると死亡率がさらに上昇した。さらに Cox 比例モデルにより性、年齢、BMI、クレアチン値、喫煙有無で調整した、収縮期血圧値 130mmHg 未満の正常耐糖能を reference とした場合の相対危険度を図 3 に示した。収縮期血圧では 130 mmHg 未満に比較して正常耐糖能では 140～149 mmHg 階級以上の血圧で循環器患死亡リスク上昇が観察されたが，耐糖能異常では 130～139 mmHg レベル以上で有意なリスク上昇がみられた。

D. 考察

高血圧に他の危険因子が合併すると予後が劣悪化することは，アメリカの Framingham 研究，ヨーロッパの PROCAM 研究などで示されている。わが国でも上田らの報告では，高血圧からの心筋梗塞発症例について検討すると喫煙群，高コレステロール群からの発症が多かったとし，高血圧と他の動脈硬化危険因子の相乗効果が心筋梗塞発症に多く関与する可能性を示唆している。しかし，日本人集団で長期の観察から血圧値と耐糖能異常合併を検討して実際の相対危険を算出した報告は少ない。

我々の成績でも、HbA1 c 5.6%以上の耐糖能異常で循環器疾患死亡血圧が増加することが示された。そして reference に比較して耐糖能異常群では収縮期血圧 130 mmHg 以上で有意に循環器疾患死亡リスクが上昇し耐糖能異常の合併ではより低い血圧階級からリスクが上昇することが示された。

今回の解析結果では，収縮期血圧 130～139 mmHg の血圧レベルで正常耐糖能の相対危険度 0.84 に対して耐糖能異常では 2.43 であり、二倍以上のリスクの上昇がある。

収縮期血圧 130～139 mmHg は正常高値血圧に分類される範囲であるが，正常高値血圧は一般住民では対象数が多く，疾患発症に対する寄与危険は大きくなる。実際の心血管事故の防止をはかるためには，正常高値血圧でも耐糖能異常を診断し管理する必要があると考えられる。また 130mmHg の血圧階層では正常耐糖能と耐糖能異常では循環器疾患死亡リスクに有意の差違は認められず（p=0.164）、血圧管理の際には 130mmHg 未満の収縮期血圧を目標値とする現行の高血圧治療ガイドラインを支持する。

本検討は，初年度の測定値をもとに血圧レベル，耐糖能異常の有無を分類し，その後の予後を観察した前向き研究である。通常の前向き研究と同様に，初年度以降の治療開始や，あらたな血圧値の上昇，あらたな耐糖能異常の出現については考慮されていない。この点，観察された相対危険は実際の血圧や耐糖能異常の影響を過小評価している可能性がある。また，本研究ではエンドポイントを死亡としている。エンドポイントを循環器疾患発症としてリスクの評価を行うと耐糖能異常の意義はさらに大きくなると考えられる。

E. 結論

以上，一般住民を対象に 10 年間の前向き疫学調査から血圧階層別に耐糖能異常の心血管疾患死亡へ与える影響を報告した。正常血圧者においても耐糖能異常では，より低い血圧レベルから心血管疾患予防を考慮する必要があると考えられ、耐糖能異常の血圧管理の際には 130 未満を目指すことの妥当性が示された。

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表１　耐糖能異常有無での対象者の諸量の比較

	正常耐糖能群	耐糖能異常群	有意確率
男/女	2789/4149	434/349	0.0001
年齢（歳）	51.9±13.8	60.4±12.1	0.0001
SBP（mmHg）	134.4±20.5	144.4±20.3	0.0001
DBP（mmHg）	81.1±11.9	83.7±12.1	0.0001
BMI	22.8±3.1	23.8±3.6	0.0001
総コレステロール（mg/dl）	202.2±37.3	214.9±43.7	0.0001
随時血糖値（mg/dl）	98.1±17.5	146.8±73.7	0.0001
HbA1c（%）	4.8±0.33	6.36±0.78	0.0001
クレアチニン（mg/dl）	0.80±0.20	0.93±1.48	0.0001
既往歴	2.5%	6.3%	0.001

SBP:収縮期血圧値：DBP：拡張期血圧

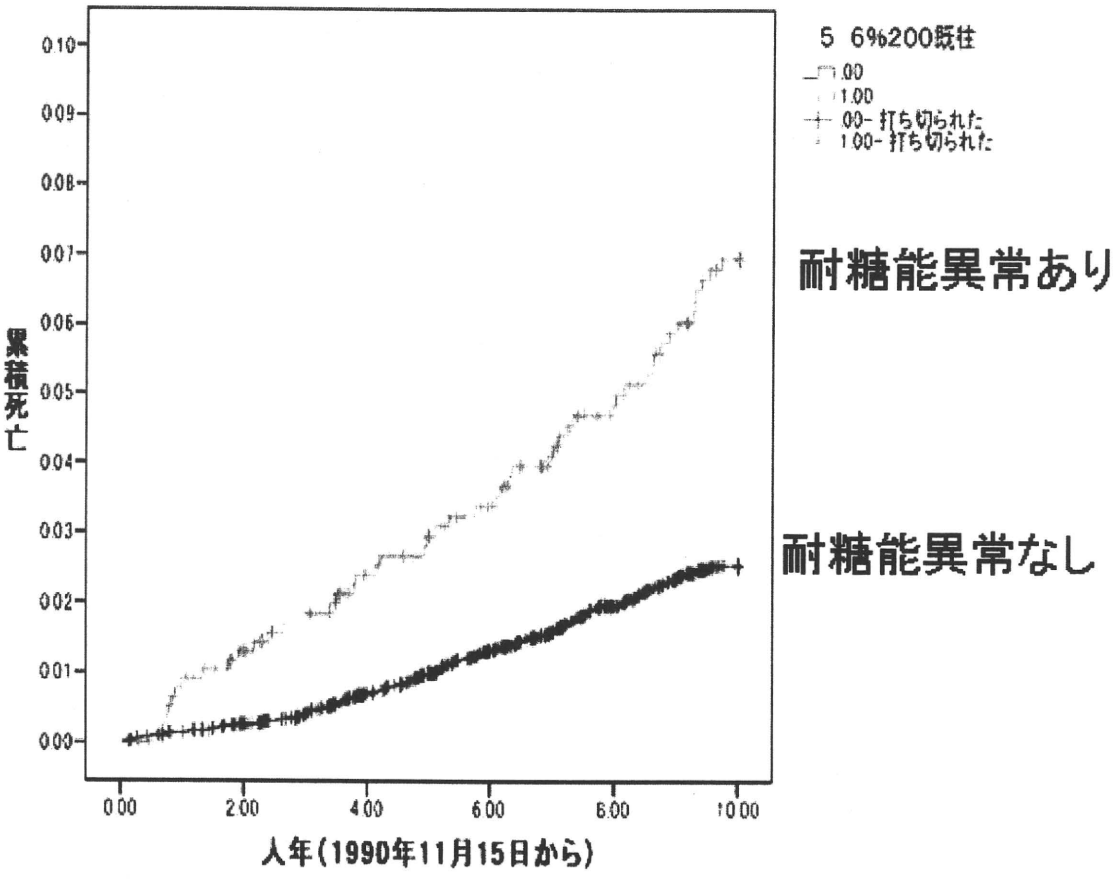

図1　耐糖能異常の有無による循環器疾患の累積死亡率

表2 Cox 比例ハザードモデル(循環器疾患死亡リスク)

	β	標準誤差	Wald	自由度	有意確率	Exp (B)
耐糖能群	0.536	0.169	10.029	1	0.002	1.710
男性	0.433	0.146	8.839	1	0.003	1.542
年齢	0.114	0.007	274.227	1	0.000	1.121
BMI	-0.046	0.022	4.282	1	0.039	0.955
SBP	0.006	0.003	3.090	1	0.079	1.006
クレアチニン	0.178	0.095	3.515	1	0.061	1.194
総コレ	-0.003	0.002	1.930	1	0.165	0.997
喫煙	0.262	0.098	7.154	1	0.007	1.300
既往歴	0.808	0.193	17.497	1	0.000	2.242