Prognostic Value of ST-T Abnormalities and Left High R Waves With Cardiovascular Mortality in Japanese (24-Year Follow-Up of NIPPON DATA80)

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Little is known about the prognostic value of ST-segment depression and/or T wave (ST-T abnormalities) with or without left high R waves on electrocardiogram recorded at rest for death from cardiovascular disease (CVD) in Asian populations. Japanese participants without a history of CVD and free of major electrocardiographic (ECG) abnormalities were followed for 24 years. Subjects were divided into 4 groups based on baseline ECG findings: isolated left high R waves, isolated ST-T abnormalities, ST-T abnormalities with left high R waves, and normal electrocardiogram. Cox proportional hazard model was used to estimate risk of CVD mortality in groups with ECG abnormalities compared to the normal group. Of 8,572 participants (44.4% men, mean age 49.5 years; 55.6% women, mean age 49.4 years), 1,142 had isolated left high R waves, 292 had isolated ST-T abnormalities, and 128 had ST-T abnormalities with left high R waves at baseline. Multivariable-adjusted hazard ratios of ST-T abnormalities with left high R waves for CVD mortality were 1.95 (95% confidence interval 1.25 to 3.04) in men and 2.68 (95% confidence interval 1.81 to 3.97) in women. Isolated ST-T abnormalities increased the risk for CVD death by 1.66 times (95% confidence interval 1.01 to 2.71) in men and 1.62 times (95% confidence interval 1.18 to 2.24) in women. Association of ECG abnormalities with CVD mortality was independent of age, body mass index, systolic blood pressure, serum cholesterol, blood glucose, smoking and drinking, and antihypertensive medication. In conclusion, ST-T abnormalities with or without left high R waves on electrocardiogram recorded at rest constitute an independent predictor of CVD mortality in Japanese men and women. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;107:1718–1724)

The standard electrocardiogram recorded at rest is the most widely used noninvasive tool for assessing cardiovascular risk in epidemiologic studies and clinical practice. ST-segment depression and/or an inverse or flat T wave (ST-T abnormalities) are the most sensitive changes on electrocardiogram.[1–3] In addition, left high R-wave electrocardiographic (ECG) manifestation of left ventricular hypertrophy (LVH) is often seen in association with ST-T abnormalities.[4,5] Several epidemiologic studies have reported that LVH with ST-T abnormalities increase cardiovascular disease (CVD) risk.[4,6–10] However, these studies investigating the prognostic value of ST-T abnormalities and left high R waves were performed predominantly in Western populations. Information about the prognostic value of ST-T abnormalities in the presence or absence of left high R waves is meager in Asian populations that have a higher stroke rate and lower incidence of coronary heart disease (CHD). In a population with a markedly lower coronary mortality, such as the Japanese, the benefit of ECG screening may be different from Western populations. The aim of the present study was to assess the independent prognostic value of ST-T abnormalities with or without left high R waves for mortality from CVD and its subtypes in a large cohort of participants selected randomly from the overall Japanese population.

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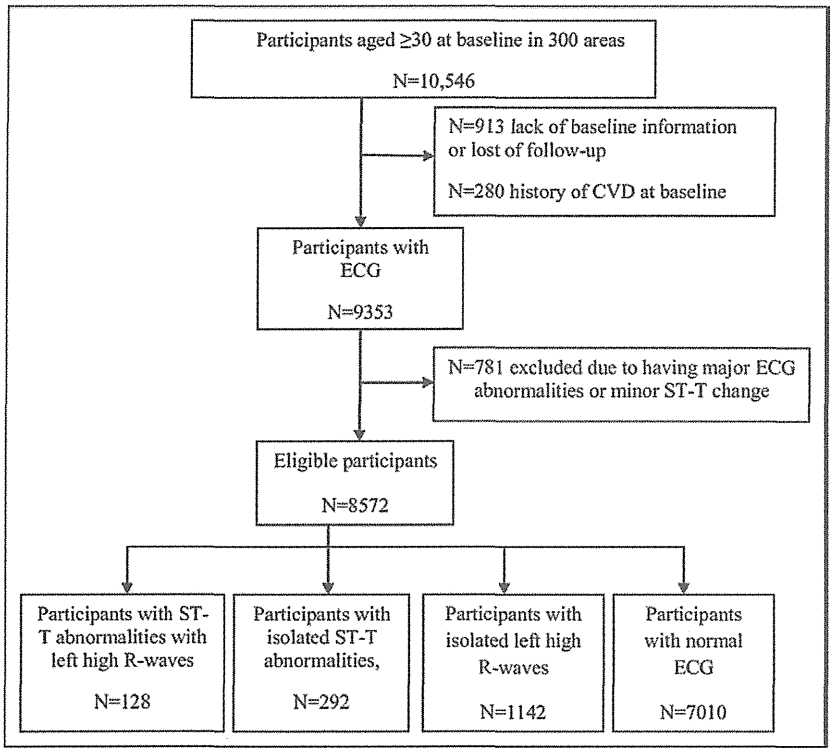

Figure 1. Flow chart of study participants shows exclusion of some participants and assignment of remaining participants to electrocardiographic groups.

Methods

The dataset of the cohort study of the National Survey on Circulatory Disorders comprising the National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged (NIPPON DATA) was used. The present study analyzed data from NIPPON DATA80, in which a baseline survey was performed in 1980. Details of this cohort have been reported elsewhere.[11,12] In brief, 300 areas were selected by stratified random sampling and all residents ≥30 years old in these areas were invited to participate. In total 10,546 residents (4,639 men and 5,907 women) participated in the survey (response rate 76.6%). Baseline surveys were carried out at local public health centers. Participants were followed for 24 years until November 2004.

In this present study, we excluded participants who had a history of CHD or stroke at baseline (n = 280), missing information at baseline, or were lost to follow-up (n = 913). In addition, participants with baseline ECG abnormalities (n = 781) including third-degree atrioventricular block (Minnesota Code [MC] 6.1), second-degree atrioventricular block (MC 6.2), Wolf-Parkinson-White syndrome (MC 6.4), complete left bundle branch block (MC 7.1), complete right bundle branch block (MC 7.2), minor ST segment (MC 4.4), nonspecific T-wave abnormalities (MCs 5.4 to 5.5), atrial fibrillation (MC 8.3), Q-wave evidence of myocardial infarction (MC 1.1), ventricular tachycardia (MC 8.2), supraventricular tachycardia (MC 8.4), and atrioventricular nodal delay (MC 8.6) were 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 and diabetes, baseline use of antihypertensive medications, and smoking and drinking habits were obtained from interviews by public health nurses. Nonfasting 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, New York) in 1 specific laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Since 1975, the laboratory has been certified by the Centers for Disease Control and Prevention/National Heart, Lung, and Blood Institute Lipid Standardization Program by Center for Disease Control and Prevention (Centers for Disease Control and Prevention, Atlanta, Georgia)[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 ≥140 mm Hg, diastolic blood pressure ≥90 mm 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 was calculated as body weight (kilograms) divided by square of body height (meters). Frequency of drinking per week and average number of cigarettes per day were assessed using questionnaires.

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

	Normal Electrocardiogram	ST-T Abnormalities With Left High R Waves	Isolated ST-T Abnormalities	Isolated Left High R Waves	p Value
Men					
Number	2,854	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 (mm Hg)	134.7 ± 18.6	167.9 ± 27.1	154.2 ± 25.7	142.7 ± 21.3	<0.001
Diastolic blood pressure (mm Hg)	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	4,156	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 (mm Hg)	131.04 ± 20.1	161.6 ± 29.1	144.2 ± 22.4	142.0 ± 21.4	<0.001
Diastolic blood pressure (mm Hg)	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 (Minnesota Codes 3.1 and 3.3), isolated ST-T abnormalities (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3), ST-T abnormalities with left high R waves (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3 with 3.1 and 3.3). Values presented as number or percentage of participants or mean ± SD.

During the baseline survey, a standard 12-lead electrocardiogram was recorded in the supine position. Each electrocardiogram was read 2 times by 2 different researchers according to 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] Participants were categorized into 4 groups according to ECG findings: (1) isolated left high R waves (MCs 3.1 and 3.3); (2) isolated ST-T abnormalities (MCs 4.1 to 4.3 and/or MCs 5.1 to 5.3); (3) ST-T abnormalities with left high R waves (MCs 3.1 and 3.3 with MCs 4.1 to 4.3 and/or MCs 5.1 to 5.3); and (4) normal ECG findings. Electrocardiogram was classified as normal in the absence of left high R waves and ST-T abnormalities.

During the 24-year follow-up, we used the National Vital Statistics database of Japan to identify underlying causes of deaths of participants who died during follow-up by date of birth, gender, date of death, and area code of place of death with permission from the Management and Coordination Agency, Government of Japan. Underlying causes of death were coded according to the *International Classification of Disease, Ninth Revision* through the end of 1994 and the *International Classification of Disease, 10th Revision* from the beginning of 1995. Details of classification used in the present study are described elsewhere.[11,12] CVD (ninth revision codes 393 to 459 and 10th revision codes I00 to I99), CHD (ninth revision codes 410 to 414 and 10th revision codes I20 to I25), and stroke (ninth revision codes 430 to 438 and 10th revision codes 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 for continuous variables and chi-square test for categorical variables to compare baseline characteristics among the 4 participant groups. Outcome events studied were CVD, CHD, and stroke mortality. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals of mortality for presence of isolated left high R waves, isolated ST-T abnormalities, and ST-T abnormalities with left high R waves compared 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, 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 multivariable models based on clinical judgment and statistical significance based on univariate analysis. Models in which gender was combined were also adjusted for gender. Performance of multivariable models was quantified by Harrell 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 10 decile categories based on predicted risk.[18]

Results

Baseline characteristics of participants (men and women) who had ST-T abnormalities with left high R waves, isolated ST-T abnormalities, isolated left high R waves, and normal electrocardiogram are listed in Table 1. Age, systolic and

Table 2
Hazard ratios for all cardiovascular disease mortalities in four groups by electrocardiographic findings: NIPPON DATA80, 1980 to 2004, Japan

	All CVD Mortalities			
	Normal Electrocardiogram	ST-T Abnormalities With Left High R Waves	Isolated ST-T Abnormalities	Isolated Left High R Waves
Men				
Number	2,854	68	58	828
Cardiovascular disease death	254	25	19	77
Mortality (per 1,000 person-years)	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	4,156	60	234	314
Cardiovascular disease death	268	30	46	31
Mortality (per 1,000 person-years)	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	7,010	128	292	1,142
Cardiovascular disease death	522	55	65	108
Mortality(per 1,000 person-years)	3.5	32.1	12.5	4.6
Age- and gender-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 (Minnesota Codes 3.1 and 3.3), isolated ST-T abnormalities (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3), ST-T abnormalities with left high R wave (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3 with 3.1 and 3.3). Values presented as hazard ratio (95% confidence interval). 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. Gender was included when overall hazard ratios were estimated.

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

	CHD Mortality			
	Normal Electrocardiogram	ST-T Abnormalities With Left High R Waves	Isolated ST-T Abnormalities	Isolated Left High R Waves
Men				
Number	2,854	68	58	828
Coronary heart disease death	50	5	4	16
Mortality (per 1,000 person-years)	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	4,156	60	234	314
Coronary heart disease death	51	5	12	6
Mortality (per 1,000 person-years)	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	7,010	128	292	1,142
Coronary heart disease death	101	10	16	22
Mortality (per 1,000 person-years)	0.7	5.8	3.1	0.9
Age- and gender-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 (Minnesota Codes 3.1 and 3.3), isolated ST-T abnormalities (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3), ST-T abnormalities with left high R waves (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3 with 3.1 and 3.3). Values presented as hazard ratio (95% confidence interval). 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. Gender was included when overall hazard ratios were estimated.

diastolic blood pressures, blood glucose, serum cholesterol, drinking habit, and use of antihypertensive medication were significantly different among the 4 groups for women and men.

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

Table 2 lists age-adjusted and multivariable-adjusted HRs for deaths from all CVDs in the 4 groups that were stratified based on ECG abnormalities. Participants who had

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

	Stroke Mortality			
	Normal Electrocardiogram	ST-T Abnormalities With Left High R Waves	Isolated ST-T Abnormalities	Isolated Left High R Waves
Men				
Number	2,854	68	58	828
Stroke death	131	12	4	40
Mortality (per 1,000 person-years)	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	4,156	60	234	314
Stroke death	120	16	17	13
Mortality (per 1,000 person-years)	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	7,010	128	292	1,142
Stroke death	251	28	21	53
Mortality (per 1,000 person-years)	1.7	16.4	4.0	2.2
Age- and gender-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 (Minnesota Codes 3.1 and 3.3), isolated ST-T abnormalities (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3), ST-T abnormalities with left high R waves (Minnesota Codes 4.1 to 4.3 and/or 5.1 to 5.3 with 3.1, 3.3). Values presented as hazard ratio (95% confidence interval). 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. Gender was included when overall hazard ratios were estimated.

ST-T abnormalities with left high R waves and those with isolated ST-T abnormalities had a higher risk for CVD mortality compared to the normal ECG group in men and women. In participants who had ST-T abnormalities with left high R waves, multivariable-adjusted HRs for CVD mortality were 1.95 in men and 2.68 in women. In participants who had isolated ST-T abnormalities, multivariable-adjusted HRs for deaths from CVD were 1.66 in men and 1.62 in women.

For all participants, multivariable-adjusted HRs of CHD mortality for presence of ST-T abnormalities with left high R waves and of isolated ST-T abnormalities were significantly higher compared to the normal ECG group (Table 3). In men, age-adjusted HR of CHD mortality was significantly higher in participants who had ST-T abnormalities with left high R waves and in those who had isolated ST-T abnormalities; however, multivariable adjustment attenuated the significance. In women, 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, multivariable-adjusted HRs for ST-T abnormalities with left high R waves was significantly higher compared to the normal ECG group in all participants (Table 4). Similar results were observed for risk of stroke mortality in men and in women. Isolated ST-T abnormalities did not show any higher risk of stroke death in women or men. Isolated left high R waves were not associated with significant risk of CVD, CHD, or stroke mortality in men or women.

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 effect of ST-T abnormalities on CVD showed significantly better fit than the model that included only standard cardiovascular risk factors when assessed by the likelihood-ratio test to evaluate whether the global model fit improved after the addition of ECG measurements. Also, the Akaike information criterion and Bayesian information criterion were lower in the full models. In contrast, discriminative performance was similar between the 2 models (c = 0.89 and 0.88, respectively). Similar observations were found across models for CHD and stroke.

Discussion

There have been insufficient data of ST-T abnormalities with a long follow-up period from Asian populations, which have low CHD events and a high stroke incidence. The few studies performed in Japanese populations were predominantly for stroke events, but ST-T abnormalities 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.

ECG changes of ST-T abnormality are often transient and not specific, and the strong relation of these changes to high blood pressure makes determining their precise pathophysiologic mechanism difficult.[1] Hypertension affects the heart by inducing LVH. LVH increases the risk for cardiovascular events through its effects on ventricular function,[20] coronary circulation,[21–23] and arrhythmogenesis.[23] LVH is

also associated with carotid structural changes[24] and asymptomatic cerebrovascular damage.[25] These changes increase the risk of events from CVD. Our findings point toward the predictive suitability of ST-T abnormalities with left high R waves for mortality from CVD, CHD, and stroke in the general Japanese population.

Based on data from the Chicago Heart Association Detection Project in Industry, Liao et al[9] found a gender difference in the relation between ST-T abnormalities and 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 40 to 64 years of age and free of CHD at baseline, the gender 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 on initial electrocardiogram had similar prognostic value in women and men for events from CVD or CHD.[1,4,10] Bacquer et al[7] followed participants (5,208 men and 4,746 women) for 13 years and found that ischemic changes with ST-segment depression or T-wave abnormalities on baseline electrocardiogram or ECG changes indicative of LVH were associated with CVD mortality. In that study, the predictive value was similar in 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 relation between these ECG abnormalities and CVD mortality.[19] As in Western populations, in the present study, we observed that ST-T abnormalities with left high R waves and isolated ST-T abnormalities had similar prognostic value for all deaths from CVD and deaths from CHD in men and women. Although the risk associated with these ECG abnormalities was independent of established cardiovascular risk factors for women, multivariate-adjusted higher risk for death from 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] Men and women with major ST-T abnormalities had an approximately threefold higher age-adjusted relative risk and a twofold higher multivariable-adjusted relative risk for total stroke incidence.[19] In our study, although we found that isolated ST-T abnormalities did not show any association with future stroke death risk, an increased 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, an ECG manifestation of LVH, is associated with prolonged severe hypertension, which is strongly related to stroke death.[27]

Regarding isolated left high R wave, similar to our results, Larsen et al[4] reported that voltage-only LVH was not associated with excess future CVD mortality or events from ischemic heart disease. Although voltage-only LVH was initially described in the Framingham study as carrying 1/2 the prognostic information of ECG LVH with ST-segment depression and negative T wave with respect to CVD, subsequent information from the Framingham study indicated that adjustment for coexistent hypertension eliminates the excess risk.[8]

The participants in this study were from a nationwide cohort study and were selected by a stratified random sampling method. Accordingly, the results of the present study are applicable to the 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. In addition, the final models showed reasonable discriminative ability and calibration. These models showed better fit than simple corresponding models consisting of only conventional cardiovascular risk factors.

The characteristics and clinical significance of ST-T abnormalities and/or left high R wave have been poorly characterized in the asymptomatic general population in Japan. In our study we observed a significant relation of ST-T abnormalities and/or left high R wave to increased future risk for CVD and CHD death. Association was independent of major conventional cardiovascular risk factors. Electrocardiograms obtained for any clinical reason or incorporated in any routine health service in adults should be examined carefully for 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 present study. We analyzed the relation among ST-T abnormalities, left high R waves, and CVD mortality using a single 12-lead electrocardiogram at baseline. It is well recognized that single biological measurements are subject to variability, and the observed ECG abnormalities could have changed over time. This might have led to underestimation of the strength of the HR because of misclassification. Electrocardiograms 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 electrocardiogram itself has some limitations for detecting LVH compared to the echocardiogram,[29] although the electrocardiogram is simpler and less expensive. We used nonfasting blood samples in our study. The pathophysiologic meanings of blood glucose levels ought to be different in participants depending on time from last meal. Although we adjusted for many conventional cardiovascular risk factors, we could not adjust for the effect of some potential confounding factors such as type of antihypertensive treatment, dosage, adherence, and pharmacologic changes over time. We also did not adjust for competing risk of noncardiovascular death while estimating risk across ECG categories; rather, we used conventional survival analysis. In the NIPPON DATA, cause of death was examined using the National Vital Statistics databases. Cause of death, identified from the death certificate, was determined by the attending doctors and the diagnosis was not validated by independent investigators. The end point in this study was CVD mortality. Our study findings need to be extended using a CVD incidence-capturing cohort.

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International Diabetes Federation

Brief report

Diabetes and life expectancy among Japanese – NIPPON DATA80

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ABSTRACT

Life expectancy (LE) among the Japanese population with or without diabetes mellitus was estimated. LE in 40-year old men and women was 41.1 and 47.5 years in those without diabetes and 32.3 and 40.9 years in those with diabetes. The LE of 40-year old men and women with diabetes was 8.8 and 6.6 years shorter than in those without diabetes. Diabetes mellitus leads to a decrease in LE. The presence of impaired glucose tolerance also affected LE inversely.

1. Introduction

Life expectancy (LE) at birth in Japan is now the longest in the world [1,2]. Along with the demographic transition of the aging population, epidemiologic and nutritional transitions are underway causing non-communicable diseases like diabetes mellitus to be on the rise in Japan [3–5]. Studies measuring the impact of diabetes mellitus on LE have been predominantly performed in Western populations [6,7]. On the other hand the effect of diabetes mellitus on LE has not been reported in the Japanese population. This information will be of importance for this aging society as it is unclear how diabetes affects LE in this population with the highest longevity in the world. In the present study, we estimated the LE among Japanese with or without diabetes mellitus.

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2. Data source

We analyzed data from the NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged) cohort, whose participants were selected in 1980 using a stratified random sampling method of residents aged 30 years or older in 300 census tracts throughout Japan. The details of this cohort have been reported elsewhere [8–11]. In brief, a total of 10,546 residents participated in the survey. After excluding those who had missing information at baseline or were lost to follow-up ($n = 941$), the remaining 9605 (4228 men and 5377 women) were included in the current analysis.

3. Diabetes mellitus

After obtaining blood samples at the baseline survey, plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan). Plasma concentrations of glucose were measured by the cupric-neocuproline method and the values were converted to the value of glucose oxidase method [12]. Diabetes mellitus was defined as any casual serum glucose level ≥200 mg/dL, fasting serum glucose level ≥126 mg/dL, use of antihyperglycemic medications, or self-reported history of diabetes. Participants with casual blood glucose concentrations between 140 and <200 mg/dL or whose fasting blood glucose concentrations fell between 110 and <126 mg/dL were categorized as having impaired glucose tolerance (IGT).

4. Statistical analysis

Age-specific mortality rates, stratified by diabetes status, were calculated for the NIPPON DATA80 cohort with the person-year method [13]. Age bands used in this calculation were set at five years. The age categories began at 40–44 years and the highest age category was set at age 85 years and over. The abridged life table method was used to calculate LE. The fraction of the last age interval of life [9,14] was used to construct an abridged life table. We also calculated 95% confidence intervals of LE in each age group using Byer's method [15].

5. Results

The proportion with diabetes in the baseline survey was 5.4% in men and 2.9% in women. IGT was present among 5.0% men and 3.6% women. Table 1 shows the LEs and Table 2 shows the corresponding mortality rates among the participants with different diabetes status from age 40 until age 85 year and over. LE in 40-year old men and women was 41.1 years and 47.5 years in those without diabetes and was 32.3 years and 40.9 years in those with diabetes. The LE of 40-year old men and women with diabetes was 8.8 and 6.6 years shorter than in those without diabetes (Table 3). The LEs for men and women with IGT was also shorter than in those without diabetes. The longer LE for participants without diabetes in comparison to the participants with IGT or diabetes was observed across all the age groups for both genders.

Table 1 – Diabetes status and life expectancies in Japanese men and women. NIPPON DATA80.

Gender	Index age (year)	Diabetes status					
		No diabetes		Impaired glucose tolerance		Diabetes	
		LE	(95%CI)	LE	(95%CI)	LE	(95%CI)
Men	40	41.1	(40.6–41.7)	36.9	(34.7–39.2)	32.3	(27.3–37.4)
	45	36.3	(35.7–36.8)	31.9	(29.7–34.2)	31.9	(30.1–33.7)
	50	31.8	(31.3–32.3)	27.4	(25.3–29.5)	26.9	(25.1–28.7)
	55	27.2	(26.7–27.7)	23.8	(21.9–25.6)	22.3	(20.5–23.9)
	60	22.9	(22.4–23.4)	20.6	(19.0–22.1)	18.9	(17.5–20.4)
	65	18.8	(18.4–19.3)	16.5	(15.1–17.9)	15.4	(14.2–16.8)
	70	15.0	(14.6–15.5)	12.3	(11.0–13.6)	12.2	(11.0–13.4)
	75	11.7	(11.3–12.1)	9.4	(8.2–10.6)	9.5	(8.4–10.6)
	80	9.1	(8.7–9.4)	6.9	(5.9–8.1)	6.8	(5.8–7.9)
	85	6.9	(6.7–7.1)	5.8	(5.2–6.3)	6.0	(5.4–6.6)
Women	40	47.5	(47.0–48.0)	45.8	(43.47–48.04)	40.9	(38.1–43.7)
	45	42.7	(42.2–43.1)	40.8	(38.47–43.04)	35.9	(33.1–38.7)
	50	37.9	(37.5–38.4)	36.7	(35.18–38.15)	30.9	(28.1–33.7)
	55	33.2	(32.8–33.7)	31.7	(30.18–33.15)	26.7	(24.3–29.1)
	60	28.7	(28.3–29.1)	26.7	(25.18–28.15)	23.1	(21.3–25.01)
	65	24.3	(23.9–24.7)	21.9	(20.44–23.32)	18.4	(16.6–20.2)
	70	20.0	(19.6–20.4)	17.9	(16.62–19.15)	15.7	(14.2–17.2)
	75	16.1	(15.7–16.4)	13.7	(12.51–14.83)	11.5	(10.0–12.9)
	80	12.5	(12.2–12.8)	10.2	(9.16–11.16)	9.5	(8.3–10.8)
	85	9.8	(9.6–10.0)	7.1	(6.43–7.71)	7.9	(7.1–8.6)

LE, Life expectancy.

Table 2 – Diabetes and mortality rates in Japanese men and women. NIPPON DATA80.

Gender	Age group (year)	Diabetes categories											
		No diabetes				IGT				DM			
		PY	*n*	MR	95%CI	PY	*n*	MR	95%CI	PY	*n*	MR	95%CI
Men	40–44	6322	4	0.6	(0.2–1.5)	239	0	0.0	–	105	3	28.6	(7.7–75.4)
	45–49	8785	28	3.2	(2.2–4.5)	341	1	2.9	(0.2–12.8)	197	0	0.0	–
	50–54	11,100	31	2.8	(1.9–3.9)	448	5	11.2	(4.2–24.4)	375	1	2.7	(0.2–11.6)
	55–59	11,374	63	5.5	(4.3–7.0)	495	8	16.2	(7.6–30.4)	541	9	16.6	(8.2–30.3)
	60–64	10,188	91	8.9	(7.2–10.9)	497	5	10.1	(3.8–22.0)	618	11	17.8	(9.4–30.8)
	65–69	8755	126	14.4	(12.0–17.1)	526	6	11.4	(4.7–23.4)	664	17	25.6	(15.5–40.0)
	70–74	7100	177	24.9	(21.5–28.8)	486	19	39.1	(24.3–59.8)	596	25	41.9	(27.8–60.9)
	75–79	4954	227	45.8	(40.1–52.1)	366	23	62.8	(40.9–92.6)	434	25	57.6	(38.2–83.6)
	80–84	3017	214	70.9	(61.9–80.9)	220	26	118.2	(79.0–170.4)	254	33	129.9	(91.0–180.1)
	85+	1837	267	145.3	(128.7–163.6)	115	20	173.9	(109.5–263.2)	138	23	166.7	(108.5–245.7)
Women	40–44	8218	7	0.9	(0.4–1.7)	149	0	0.0	–	72	0	0.0	–
	45–49	11,320	15	1.3	(0.8–2.1)	212	1	4.7	(0.3–20.6)	129	0	0.0	–
	50–54	14,439	23	1.6	(1.0–2.3)	306	0	0.0	–	190	1	5.3	(0.4–23.0)
	55–59	14,792	47	3.2	(2.4–4.2)	442	0	0.0	–	251	3	12.0	(3.2–31.5)
	60–64	13,938	60	4.3	(3.3–5.5)	561	1	1.8	(0.1–7.8)	336	1	3.0	(0.2–13.0)
	65–69	12,470	81	6.5	(5.2–8.0)	587	6	10.2	(4.2–21.0)	410	11	26.8	(14.2–46.4)
	70–74	10,493	126	12.0	(10.0–14.2)	598	6	10.0	(4.1–20.6)	451	5	11.1	(4.2–24.2)
	75–79	7854	163	20.8	(17.7–24.1)	513	13	25.3	(14.2–42.1)	405	24	59.3	(38.9–86.7)
	80–84	5184	209	40.3	(35.1–46.1)	335	15	44.8	(26.1–72.0)	274	21	76.6	(48.8–114.9)
	85+	3895	399	102.4	(92.8–112.9)	198	28	141.4	(96.0–201.4)	165	21	127.3	(81.1–190.8)

PY, person-years, *n*, number of events, MR, mortality rate (per 1000), CI, confidence intervals. Mortality rates were estimated by person-year methods.

6. Discussion

In this study we observed a significant reduction of LE in those with diabetes mellitus. We observed that the LE of participants with diabetes was seven to nine years shorter than the LE of people without diabetes for both genders in middle age group categories. The presence of IGT also was associated with shorter LE than for the non-diabetic population.

The differences in LE observed between diabetes and non-diabetic people was similar to that found in other studies. Franco et al. [6], studying the participants from the

Table 3 – Difference in life expectancy by diabetes status in Japanese men and women. NIPPON DATA80.

Gender	Index age (year)	Difference in life expectancy (95%CI)	
		No diabetes vs. impaired glucose tolerance	No diabetes vs. diabetes
Men	40	4.2 (1.9, 6.5)	8.8 (3.7, 13.9)
	45	4.3 (2.0, 6.6)	4.4 (2.4, 6.2)
	50	4.4 (2.2, 6.6)	4.9 (3.0, 6.8)
	55	3.4 (1.5, 5.3)	4.9 (3.2, 6.8)
	60	2.3 (0.7, 3.9)	4.0 (2.4, 5.5)
	65	2.3 (0.9, 3.8)	3.4 (2.0, 4.7)
	70	2.7 (1.3, 4.1)	2.8 (1.5, 4.1)
	75	2.3 (1.0, 3.5)	2.2 (1.0, 3.4)
	80	2.2 (0.9, 3.2)	2.3 (1.1, 3.3)
	85	1.1 (0.5, 1.7)	0.9 (0.3, 1.5)
Women	40	1.7 (-0.6, 4.1)	6.6 (3.8, 9.4)
	45	1.9 (-0.4, 4.2)	6.8 (4.0, 9.6)
	50	1.2 (-0.3, 2.8)	7.0 (4.2, 9.8)
	55	1.5 (0.0, 3.1)	6.5 (4.1, 9.0)
	60	2.0 (0.5, 3.6)	5.6 (3.7, 7.5)
	65	2.4 (0.9, 3.9)	5.9 (4.0, 7.7)
	70	2.1 (0.8, 3.4)	4.3 (2.7, 5.8)
	75	2.4 (1.2, 3.6)	4.6 (3.1, 6.1)
	80	2.3 (1.3, 3.4)	3.0 (1.7, 4.3)
	85	2.7 (2.0, 3.4)	1.9 (1.1, 2.7)

Framingham Heart Study, reported that men and women aged 50 years with diabetes lived on average 7.5 and 8.2 years less than their nondiabetic equivalents. Gu et al. [16] observed that the median LE was 8 years lower for diabetic subjects aged 55–64 years. Similarly, Narayan et al. [17] estimated that the presence of diabetes among non-Hispanic, 50-year-old men would result in a loss of 8 years in LE. Though all these studies have shown a reduction in LE in association with diabetes mellitus, it is important to note that direct comparability across studies needs caution due to differences in methodology, data used, reporting year, and characteristics of the populations studied.

There are several limitations in this study. As classification of diabetes status was only made with the information available in the baseline survey and with the assumption that the diabetes status of individuals did not change during the follow-up period, possible misclassification of diabetes mellitus related categories might influence our results. It is not possible to be certain how much change of diabetes status would occur during this 24-year period. The influence of this misclassification might affect the difference of LE among groups. It also needs to be recognized that the differences in mortality risks may not be instigated by diabetes alone. Clustering of other metabolic risk factors as hypertension and obesity will also influence risk [10].

In conclusion, LEs of participants with and without diabetes mellitus were examined using data from a representative Japanese cohort and a substantial decrease in LE was observed in both men and women with diabetes mellitus.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A

The NIPPON DATA80/90 Research Group

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Prognostic Values of Clockwise and Counterclockwise Rotation for Cardiovascular Mortality in Japanese Subjects

A 24-Year Follow-Up of the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980–2004 (NIPPON DATA80)

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Background—Although clockwise rotation and counterclockwise rotation are distinct findings of the ECG, their prognostic significance is rarely studied.

Methods and Results—We studied prognostic values of clockwise and counterclockwise rotation on total, cardiovascular disease (CVD), and subtype mortality using the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980–2004 (NIPPON DATA80) database with a 24-year follow-up. At baseline in 1980, data were collected on study participants aged ≥30 years from randomly selected areas in Japan. We followed 9067 participants (44% men; mean age, 51 years). During the 24-year follow-up, mortality was as follows: 2581 total, 887 CVD, 179 coronary heart disease, 173 heart failure, and 411 stroke. The multivariate-adjusted hazard ratio (HR) with the use of the Cox model including biochemical and other ECG variables revealed that clockwise rotation was significantly positively associated with heart failure in men and women combined (HR=1.79; 95% confidence interval [CI], 1.13–2.83; P=0.013), CVD in men and in men and women combined (HR=1.49; 95% CI, 1.12–1.98; P=0.007 in men; HR=1.28; 95% CI, 1.02–1.59; P=0.030 in combined), and total mortality in men and in men and women combined (HR=1.19; 95% CI, 1.00–1.49; P=0.0496 in men; HR=1.15; 95% CI, 1.00–1.32; P=0.045 in combined). Counterclockwise rotation was significantly inversely associated stroke in men and women combined (HR=0.77; 95% CI, 0.62–0.96; P=0.017), CVD in men and in men and women combined (HR=0.74; 95% CI, 0.59–0.94; P=0.011 in men; HR=0.81; 95% CI, 0.70–0.94; P=0.006 in combined), and total mortality in women (HR=0.87; 95% CI, 0.77–0.98; P=0.023).

Conclusions—We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise rotation with CVD mortality in men and in men and women combined, independent of confounding factors including other ECG changes. (***Circulation*. 2012;125:1226-1233.**)

Key Words: cardiovascular mortality ■ clockwise and counterclockwise rotation ■ electrocardiography

Since the first report by Einthoven[1] of accurate recording of the ECG and its development as a clinical tool in 1895, the early phase of ECG studies was devoted to descriptions of ECG changes in disease conditions, such as arrhythmia,[2–5] angina pectoris,[6] and myocardial infarction,[7] or to formation of diagnostic criteria from comparative evaluations between ECG findings and anatomic changes, such as left ventricular hypertrophy (LVH).[8] Publication of studies on prognostic values of ECG changes arrived in the1960s, when LVH by ECG was found to show an increase in cardiovascular disease (CVD) mortality in hospital-based patients,[9] as well as in general populations.[10] The other ECG changes that have been

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shown to have prognostic significance are Q-wave abnormalities, ST-T abnormalities with or without high left R waves, prolonged QRS duration, and atrial fibrillation (AF).[11–23]

Clinical Perspective on p 1233

The transitional zone is related to the direction of the QRS axis in the horizontal plane. Although clockwise rotation and counterclockwise rotation are distinct findings of ECG, their clinical values have not been well studied, and their prognostic significance has been studied only rarely. The aim of the present study was to assess the independent prognostic values of clockwise rotation and counterclockwise rotation for mortality due to CVD and its subtypes in a large cohort of participants obtained from randomly selected health districts in Japan.[24,25]

Methods

Participants

Cohort studies of the National Survey on Circulatory Disorders, Japan, are known as NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere.[24,25]

Three hundred health districts throughout Japan were randomly selected. The overall population aged ≥30 years in the participating health districts was 13 771. All of them were invited to participate in the study. Among them, a total of 10 546 community-based participants agreed to participate in the study. The participation rate was 76.6% (10 546 of 13 771) before exclusion for reasons mentioned below. The survey consisted of history taking, physical examinations, blood tests, a standard 12-lead ECG recording in the supine position, and a self-administered questionnaire on lifestyle. For the present study, participants were followed up to 2004 (NIPPON DATA80, 1980–2004).

Participants were excluded from follow-up because of missing baseline data (n=124), a past history of coronary heart disease (CHD) or stroke at baseline (n=164), or loss to follow-up (n=1105). The latter group was excluded because of the absence of a permanent address that was needed to link to vital statistical records. We also excluded 86 participants with baseline ECG abnormalities including moderate or severe Q-wave abnormalities (Minnesota Code [MC] 1-1 or 1-2), third-degree atrioventricular block (MC 7-1), Wolff-Parkinson-White syndrome (MC 6-4), and complete left bundle-branch block (MC 7-1).[26,27] The final sample comprised 9067 participants (3958 men and 5109 women). There were no significant differences between participants who were lost to follow-up and those who were included in the present study in terms of several risk factors.

Biochemical and Baseline Examinations

The baseline surveys were conducted at public health centers according to a standardized manual. Blood pressure was measured by trained research nurses using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 minutes of rest. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, use of antihypertensive agents, or any combination of these. Height and weight were measured in subjects without shoes and with light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also performed with the use of a self-administered questionnaire. Participants were asked about their alcohol drinking habit (never, past, occasional, and daily drinkers). Reported information was confirmed by public health nurses through interviews with the study participants regarding smoking, drinking habits, and present and past medical histories.

Casual blood samples were drawn and centrifuged within 60 minutes of collection and stored at −70°C until analyses, as described previously.[24,25,28,29]

The ECG findings were independently evaluated by 2 trained researchers in each of 12 institutions according to the MC, as described previously.[30] Codes in agreement were accepted, whereas inconsistent codes were decided on by a panel of study epidemiologists and cardiologists.[28] Major ECG findings for the present study were counterclockwise rotation (MC 9-4-1: a transition zone at V_3 or rightward of V_3) and clockwise rotation (MC 9-4-2: a transition zone at V_4 or leftward of V_4). Thus, MC defines normal rotation as ECG coded neither as 9-4-1 nor as 9-4-2. In other words, ECGs showing dominant S in V_3 and dominant R in V_4 are defined as normal rotation. Normal-rotation ECGs have an isoelectric transitional zone in between V_3 and V_4, which was found in the majority of cases. Additional ECG findings (http://www.sph.umn.edu/epi/ecg/mncode.pdf)[27] that we examined were mild Q-wave abnormality (MC 1-3), frontal plane QRS axis deviations (MC 2-1, 2-2, 2-3), high R wave (MC 3-1 to 3-4), ST depression (MC 4-1 to 4-4), T-wave abnormality (MC 5-1 to 5-5), combination of high R plus either ST depression or T abnormality, first- or second-degree atrioventricular block (MC 6-2 or 6-3), intraventricular conduction disturbances (bundle-branch block) other than left bundle-branch block (MC 7-2-1 to 7-8), ventricular premature beats (MC 8-1-2), AF (MC 8-3), sinus tachycardia (MC 8-7), sinus bradycardia (MC 8-8), low QRS voltage (MC 9-1), ST elevation (MC 9-2), tall P wave (MC 9-3-1), and long P wave (MC 9-3-2).[26,27]

Although reproducibility of ECG findings was not checked in this study, a previous study by de Bruyne et al[31] showed that reproducibility of QRS axis deviation was excellent. We presume that reproducibility of clockwise rotation and counterclockwise rotation should be similarly good. The prevalence values of normal rotation, clockwise rotation, and counterclockwise rotation in the present study, the baseline study of which was done in 1980, were 51.7%, 6.9%, and 41.4%, respectively, and those in the study done in 1990 in different participants were 50.7%, 7.0%, and 42.3%, respectively. These results may support good reproducibility of the ECG findings.

End Point Determination

To determine cause of death after 24-year follow-up, we used the National Vital Statistics database of Japan with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) through the end of 1994 and according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) from the beginning of 1995. The details of classification in the present study are described elsewhere.[16,22,23] CVD (*ICD-9*: 393–459 and *ICD-10*: I00 to I99), CHD (*ICD-9*: 410–414 and *ICD-10*: I20 to I25), heart failure (HF) (*ICD-9*: 428 and *ICD-10*: I50), stroke (*ICD-9*: 430–438 and *ICD-10*: I60 to I69), and chronic obstructive pulmonary disease (*ICD-9*: 491, 492 and *ICD-10*: J41 to J44) were identified. Approval for the study was obtained from the institutional review board of Shiga University of Medical Science (No. 12-18, 2000).

Statistical Analysis

SAS version 9.2 for Windows (SAS Institute, Cary, NC) was used throughout the analyses. Variables were compared among the 3 groups according to ECG horizontal plane rotation (normal, clockwise rotation, and counterclockwise rotation). The χ^2 test was used to compare dichotomous variables, followed by a post hoc application of the Bonferroni method. A 1-way ANOVA was used to compare means among the groups, followed by a post hoc application of the Dunnett test when the F value showed a significant difference at $P<0.05$. Prevalence of clockwise rotation and counterclockwise rotation among age and BMI groups was also examined. To obtain P for trend, the Mantel-Haenszel test was used.

To examine the factors associated with CHD, HF, stroke, CVD, and total mortality, multivariate-adjusted hazard ratios (HRs) were calculated with the use of a Cox proportional hazards model. Men and women were analyzed separately in model 1 to model 3 and were

Table 1. Baseline Characteristics and Mortality According to ECG Rotation Groups: NIPPON DATA80, 1980 to 2004

	Men (Subtotal=3958)				Women (Subtotal=5109)			
Rotation	Normal	Clockwise	Counterclockwise	*P*	Normal	Clockwise	Counterclockwise	*P*
n (%)	2216 (56.0)	326 (8.2)	1416 (35.8)		2470 (48.4)	298 (5.8)	2341 (45.8)	
Age, y	50.3±13.2	53.6±13.4†	49.9±12.7	<0.001	51.2±13.3	54.7±13.5†	49.9±13.1†	<0.001
BMI, kg/m^2	22.5±2.9	21.9±3.0†	22.8±2.8†	<0.001	22.7±3.3	23.1±4.5	23.0±3.3*	0.013
Hypertension, %	50.6	53.1	48.9	0.332	43.1	52.0†	38.1†	<0.001
Smoker, %	64.1	67.5	60.0†	0.008	8.9	10.4	8.6	0.596
Alcohol drinker, %	49.5	46.3	46.0	0.101	3.0	3.7	2.7	0.530
Cholesterol, mg/dL	185.2±32.4	184.1±32.9	187.2±32.7	0.130	190.5±34.2	196.0±35.6*	190.5±33.6	0.025
Blood glucose concentration, mg/dL	101.9±30.9	105.7±32.0	101.6±34.2	0.105	100.6±28.7	107.6±41.2†	100.0±26.4	<0.001
Creatinine, mg/dL	1.05±0.16	1.08±0.56	1.06±0.24	0.096	0.85±0.18	0.86±0.18	0.84±0.13	0.051
CHD death, %	2.4	3.4*	1.5	0.047	1.8	3.0	1.7	0.275
HF death, %	1.7	3.7*	1.5	0.022	2.0	4.7†	1.7	0.002
Stroke death, %	5.6	8.3	4.0	0.004	4.6	4.7	3.2*	0.028
CVD death, %	11.3	18.7†	7.8†	<0.001	9.9	14.1*	7.6*	<0.001
COPD death, %	0.45	1.23	0.35	0.115	0.20	0	0.13	0.631
Total death, %	34.7	47.9†	31.1*	<0.001	25.3	33.9†	20.9†	<0.001

Values are shown as mean±SD or percentages. Baseline characteristics and mortality due to cardiovascular disease (CVD) and its subtypes were compared among the 3 groups according to ECG horizontal plane rotation (normal, clockwise, and counterclockwise). The χ^2 test was used to compare dichotomous variables, followed by a post hoc application of the Bonferroni method. A 1-way ANOVA was used to compare means among groups, followed by a post hoc application of the Dunnett test when the *F* value showed a significant difference at $P<0.05$. NIPPON DATA80 indicates National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004; BMI, body mass index; alcohol drinker, those participants who admitted to drinking alcohol daily; smoker, those participants who admitted to smoking currently; cholesterol, serum total cholesterol concentration; CHD, coronary heart disease; HF, heart failure; and COPD, chronic obstructive pulmonary disease.

*$P<0.05$; †$P<0.01$, compared to Normal.

combined in model 4. Covariates in model 1 were age and ECG horizontal plane rotation (normal, clockwise rotation, and counterclockwise rotation; normal was taken as a reference). Model 2 consisted of model 1 plus BMI (5 categories divided at 18.5, 23, 25, and 30 kg/m^2; 18.5–23=reference), hypertension, cigarette smoking (never and past smokers and 3 current smoker categories divided at 20 and 40 cigarettes per day; never smokers=reference), alcohol drinking (ex-drinker or current drinker and never drinker; never drinkers=reference), serum total cholesterol and blood glucose concentrations (standardized to have the mean=0 and SD=1), serum creatinine (divided at 75th percentile, 1.0 mg/dL), and interaction terms. Model 3 consisted of model 2 plus ECG findings (mild Q-wave abnormality, frontal plane QRS axis deviations, combination of high R [MC 3-1 to 3-4] plus either ST depression or T abnormality, first or second degree atrioventricular block, bundle-branch block other than left bundle-branch block, ventricular premature beats, AF, sinus tachycardia, sinus bradycardia, low QRS voltage, ST elevation, tall P wave, and long P wave), and interaction terms. Model 4 consisted of model 3 plus sex indicator and interaction terms. In addition, the following sensitivity analyses for model 4 CVD mortality were performed: dichotomizing at age 60 years, subgroup analyses by frontal axis groups and by smoking groups, removing participants with AF, and removing participants with a combination of high R plus either ST depression or T abnormality. We tested proportionality by generating the time-dependent covariates by creating interactions of the predictors and a function of survival time and including them in the models. None of these were significant. In addition, by using a "test" statement, we tested all of the time-dependent covariates at once. This also was not significant. We confirmed the linearity assumption by plotting each continuous predictor variable against the martingale residuals from a Cox model. The additivity was tested by checking interaction terms between age, sex indicators, and other predictors. If any of these was significant, the interaction terms were included in the models.

Results

Descriptive Statistics

During follow-up for 24 years (191 484 person-years), 27 chronic obstructive pulmonary disease deaths (19 in men, 8 in women), 179 CHD deaths (86 in men, 93 in women), 173 HF deaths (70 in men, 103 in women), 411 stroke deaths (209 in men, 202 in women), 887 CVD deaths (423 in men, 464 in women), and 2581 total deaths (1365 in men, 1216 in women) were ascertained.

Baseline characteristics, total mortality, and mortality due to chronic obstructive pulmonary disease, CVD, and its subtypes according to ECG rotation groups are shown in Table 1. Among men, 56.0% were in the normal rotation group, 8.2% in the clockwise rotation group, and 35.8% in the counterclockwise rotation group. In men, in the clockwise rotation group, mean age and prevalence of CHD, HF, CVD, and total death were higher than in men in the normal group, whereas mean BMI was lower than in men in the normal group. In contrast to these differences, in men in the counterclockwise rotation group, mean BMI was higher, and the prevalence values of current smokers, CVD, and total death were lower than in men in the normal group.

Among women, 48.4% were in the normal rotation group, 5.8% in the clockwise rotation group, and 45.8% in the counterclockwise rotation group. In women in the clockwise rotation group, mean age, total cholesterol, blood glucose, and prevalence of hypertension, HF, CVD, and total death were higher than in women in the normal group. In contrast

Table 2. Baseline ECG Characteristics According to ECG Rotation Groups: NIPPON DATA80, 1980 to 2004

	Men (Subtotal=3958)				Women (Subtotal=5109)			
Rotation	Normal	Clockwise	Counterclockwise	*P*	Normal	Clockwise	Counterclockwise	*P*
Mild Q wave (MC 1-3), %	1.94	4.29*	0.85*	<0.001	1.38	1.68	0.94	0.277
Axis (−30° to −90°), %	2.12	4.60*	1.13	<0.001	1.26	7.38†	0.68	<0.001
Axis (+120° to −150°), %	0.09	0.61	0	0.007	0.12	0.34	0	0.084
Axis (+90° to +119°), %	1.76	8.90†	0.42†	<0.001	1.42	6.04†	0.26†	<0.001
High R, %	25.2	16.3†	25.4	0.001	10.0	8.39	8.20	0.078
ST depression, %	4.42	6.75	2.75*	0.001	6.52	9.37*	5.77	0.028
T-wave inversion, %	6.00	11.0†	4.94	<0.001	10.8	15.4*	9.74	0.010
LVH_ST, %	4.29	5.52	3.04	0.052	3.40	4.36	2.39	0.044
First- or second-degree atrioventricular block, %	3.16	3.37	2.82	0.800	1.82	2.35	1.45	0.399
BBB other than LBBB, %	8.88	7.36	5.37†	<0.001	4.70	5.37	3.59*	0.097
VPC, %	0.90	1.84	1.13	0.289	1.13	1.01	1.32	0.788
AF, %	0.63	3.07†	0.07*	<0.001	0.57	4.03†	0.30	<0.001
Sinus tachycardia, %	0.90	0.92	0.35	0.139	1.90	4.03*	1.45	0.007
Sinus bradycardia, %	2.89	4.29	3.18	0.386	0.61	0.67	0.43	0.649
Low voltage, %	0.32	0.92	0.42	0.273	1.90	4.03*	0.64†	<0.001
ST elevation, %	7.40	8.28	7.70	0.836	0.40	0.67	0.34	0.685
Tall P, %	0.18	0.31	0.07	0.534	0.08	0	0	0.343
Long P, %	0.59	0.61	0.56	0.993	0.20	0.34	0.13	0.659

Values are shown as percentages. Baseline ECG characteristics were compared among the 3 groups according to ECG horizontal plane rotation (normal, clockwise, and counterclockwise). The χ^2 test was used to compare dichotomous variables, followed by a post hoc application of the Bonferroni method. NIPPON DATA80 indicates National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004; axis, QRS axis in frontal plane; LVH_ST, combination of high R plus either ST depression or T abnormality; BBB, bundle-branch block; LBBB, left bundle-branch block; VPC, ventricular premature contractions; and AF, atrial fibrillation.

*P<0.05; †P<0.01, compared to Normal.

to these differences, for women in the counterclockwise rotation group, mean age was lower, mean BMI was higher, and the prevalence values of hypertension, stroke, CVD, and total death were lower than in women in the normal group.

Baseline ECG characteristics according to ECG rotation groups are shown in Table 2. In men in the clockwise rotation group, prevalence values of a mild Q wave, left axis and mild right axis deviations, T-wave inversion, and AF were higher than in men in the normal group, whereas prevalence of a high R wave was lower than in men in the normal group. In men in the counterclockwise rotation group, the prevalence values of a mild Q wave, mild right axis deviation, ST depression, bundle-branch block other than left bundle-branch block, and AF were lower than in men in the normal groups. In women in the clockwise rotation group, prevalence values of left axis and mild right axis deviations, ST depression, T-wave inversion, AF, sinus tachycardia, and low voltage were higher than in women in the normal group. In women in the counterclockwise rotation group, prevalence values of mild right axis deviation and low voltage were lower than in women in the normal groups.

Associations of Age and BMI Categories With Clockwise Rotation and Counterclockwise Rotation

Associations of age and BMI categories with clockwise rotation and counterclockwise rotation are shown in Tables 3 and 4. In both men and women, prevalence of clockwise rotation became higher as age increased. In contrast, prevalence of counterclockwise rotation in women became lower as age increased. In both men and women, prevalence of clockwise rotation became lower in the middle BMI groups; in contrast, prevalence of counterclockwise rotation was higher in the middle BMI groups.

Associations of Clockwise Rotation and Counterclockwise Rotation With Total Mortality and Mortality Due to CVD and Its Subtypes

Results of Cox analyses on the associations of clockwise rotation and counterclockwise rotation with total mortality and mortality due to CVD and its subtypes are shown in Table 5. In general, clockwise rotation tended to be positively associated and counterclockwise rotation tended to be inversely associated with total mortality and mortality due to CVD and its subtypes. Clockwise rotation was significantly positively associated with HF in men and women combined (model 4) (HR=1.79; 95% confidence interval [CI], 1.13–2.83; P=0.013), CVD in men and in men and women combined (model 3 HR=1.49; 95% CI, 1.12–1.98; P=0.007 in men; model 4 HR=1.28; 95% CI, 1.02–1.59; P=0.030 in combined), and total mortality in men and in men and women combined (model 3 HR=1.19; 95% CI, 1.00–1.49]; P=0.0496 in men; model 4 HR=1.15; 95% CI, 1.00–1.32; P=0.045 in combined). Counterclockwise rotation was sig-

Table 3. Prevalence of Clockwise and Counterclockwise Rotation According to Age Groups: NIPPON DATA80, 1980 to 2004

	Age Group, y							
	30–39	40–49	50–59	60–69	70–79	≥80	*P* for Difference	*P* for Trend
Men, n	1013	1061	924	585	323	52		
Clockwise, %	6.1	6.8	8.6	12.5	10.5	11.5	<0.001	<0.001
Counterclockwise, %	36.5	37.5	35.7	32.8	35.3	23.1	0.347	0.387
Women, n	1297	1301	1223	806	395	87		
Clockwise, %	3.7	4.8	7.1	7.0	8.9	10.3	<0.001	<0.001
Counterclockwise, %	49.7	47.4	43.8	43.4	40.8	37.9	0.060	0.001

Prevalence of clockwise and counterclockwise rotation among age groups was examined. The χ^2 test was used to obtain *P* for difference. To obtain *P* for trend, the Mantel-Haenszel test was used. NIPPON DATA80 indicates National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004.

nificantly inversely associated with stroke in men and women combined (model 4 HR=0.77; 95% CI, 0.62–0.96; *P*=0.017), CVD in men and in men and women combined (model 3 HR=0.74; 95% CI, 0.59–0.94; *P*=0.011 in men; model 4 HR=0.81; 95% CI, 0.70–0.94; *P*=0.006 in combined), and total mortality in women (model 3 HR=0.87; 95% CI, 0.77–0.98; *P*=0.023). A subgroup analysis by dichotomizing the participants at age 60 years yielded similar results with some loss of statistical significance (age ≤60 years: HR for clockwise rotation=1.53; 95% CI, 1.02–2.29; *P*=0.039; HR for counterclockwise rotation=0.80; 95% CI, 0.60–1.07; *P*=0.127; age >60 years: HR for clockwise rotation=1.19; 95% CI, 0.91–1.55; *P*=0.148; HR for counterclockwise rotation=0.83; 95% CI, 0.70–0.99; *P*=0.0341). Subgroup analyses by frontal axis groups and by smoking groups yielded similar results but lost statistical significance. The 2 sensitivity analyses (removing the participants with AF or removing the participants with a combination of high R plus either ST depression or T abnormality) yielded similar results.

Discussion

We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise rotation with CVD mortality in men. We also found a significant positive association of clockwise rotation with HF in men and women combined and with total mortality in men and in men and women combined. The findings were independent of other confounding factors including blood chemical measurements and other ECG findings.

The prognostic values of major and minor ECG abnormalities at baseline for subsequent risk of incidence and/or death from CVD have been studied extensively throughout the long history of ECG studies. Other ECG changes that have been shown to have prognostic significance are Q-wave abnormalities, ST-T abnormalities with or without left high R waves, prolonged QRS duration, and AF.[11–23] Although clockwise rotation and counterclockwise rotation are distinct findings on ECG, their clinical values have not been well studied, and their prognostic significance has seldom been studied. One exceptional study was done by Rajala et al,[32] who found that stroke mortality showed the highest association with clockwise rotation and left high R waves among most of the participants aged ≥85 years. Horibe et al[30] studied the relationship between ECG findings coded by the MC system and all-cause mortality using the NIPPON DATA80 database with follow-up for 19 years and noted that the HR of participants with clockwise rotation was significantly high. No further investigation was made.

Some studies have investigated the mechanisms of clockwise rotation and counterclockwise rotation. Tahara et al[33] examined computed tomographic scans of 102 participants to compare the anatomic position of the cardiac septum and ECG position of the transitional zone. They concluded that approximately two thirds of clockwise rotation and counterclockwise rotation could be explained by anatomic rotation of the heart in the horizontal plane around the long axis, and in

Table 4. Prevalence of Clockwise and Counterclockwise Rotation According to Body Mass Index Groups: NIPPON DATA80, 1980 to 2004

	Body Mass Index Group, kg/m^2						
	<18.5	18.5–23	23–25	25–30	≥30	*P* for Difference	*P* for Trend
Men, n	253	2,084	855	733	33		
Clockwise, %	14.2	8.5	6.4	7.4	9.1	0.029	0.053
Counterclockwise, %	28.1	33.8	39.9	39.7	26.3	0.002	<0.001
Women, n	369	2495	1077	1015	153		
Clockwise, %	11.1	4.7	4.3	7.3	13.1	<0.001	0.033
Counterclockwise, %	36.9	45.9	48.1	46.6	45.8	0.042	0.010

Prevalence of clockwise and counterclockwise rotation among body mass index groups was examined. The χ^2 test was used to obtain *P* for difference. To obtain *P* for trend, the Mantel-Haenszel test was used. NIPPON DATA80 indicates National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004.

Table 5. Clockwise and Counterclockwise Rotation and Mortality: NIPPON DATA80, 1980 to 2004

	Men						Women					
	Clockwise			Counterclockwise			Clockwise			Counterclockwise		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
CHD												
Model 1	1.33	0.70–2.55	0.386	0.64	0.39–1.07	0.086	1.37	0.67–2.82	0.356	0.97	0.63–1.48	0.872
Model 2	1.34	0.70–2.58	0.383	0.60	0.35–0.999	0.0496	1.53	0.74–3.19	0.256	1.09	0.70–1.69	0.715
Model 3	1.37	0.71–2.67	0.351	0.57	0.34–0.96	0.034	1.67	0.78–3.56	0.183	1.13	0.72–1.77	0.583
Model 4	1.38	0.84–2.27	0.198	0.83	0.60–1.15	0.269	≤Men and women combined					
HF												
Model 1	2.09	1.09–4.02	0.026	1.01	0.59–1.72	0.986	1.83	1.00–3.35	0.048	0.88	0.58–1.29	0.448
Model 2	1.90	0.98–3.68	0.058	1.02	0.60–1.75	0.941	1.96	1.07–3.59	0.030	0.89	0.58–1.37	0.606
Model 3	1.50	0.72–3.13	0.275	1.07	0.62–1.86	0.810	1.62	0.80–3.30	0.181	1.06	0.61–1.84	0.828
Model 4	1.79	1.13–2.83	0.013	0.98	0.70–1.37	0.911	≤Men and women combined					
Stroke												
Model 1	1.42	0.94–2.15	0.100	0.78	0.57–1.07	0.120	0.82	0.47–1.42	0.475	0.70	0.53–0.94	0.019
Model 2	1.32	0.87–2.02	0.191	0.79	0.58–1.09	0.146	0.82	0.46–1.46	0.494	0.72	0.53–0.97	0.029
Model 3	1.37	0.89–2.11	0.148	0.78	0.57–1.08	0.132	0.77	0.43–1.40	0.395	0.74	0.55–1.00	0.050
Model 4	1.06	0.75–1.49	0.749	0.77	0.62–0.96	0.017	≤Men and women combined					
CVD												
Model 1	1.58	1.19–2.00	0.001	0.74	0.59–0.93	0.010	1.14	0.82–1.58	0.433	0.79	0.65–0.95	0.015
Model 2	1.48	1.12–1.96	0.007	0.74	0.59–0.93	0.011	1.16	0.83–1.63	0.384	0.83	0.68–1.01	0.059
Model 3	1.49	1.12–1.98	0.007	0.74	0.59–0.94	0.011	1.12	0.79–1.59	0.524	0.87	0.71–1.06	0.176
Model 4	1.28	1.02–1.59	0.030	0.81	0.70–0.94	0.006	≤Men and women combined					
Total												
Model 1	1.33	1.12–1.57	0.001	0.94	0.84–1.06	0.336	1.11	0.90–1.37	0.317	0.84	0.75–0.95	0.004
Model 2	1.24	1.04–1.47	0.016	0.97	0.86–1.09	0.595	1.11	0.90–1.38	0.319	0.86	0.76–0.97	0.011
Model 3	1.19	1.00–1.42	0.0496	0.99	0.88–1.11	0.824	1.09	0.88–1.35	0.441	0.87	0.77–0.98	0.023
Model 4	1.15	1.00–1.32	0.045	0.93	0.85–1.01	0.090	≤Men and women combined					

Multivariate-adjusted hazard ratios (HR) of mortality associated with clockwise and counterclockwise rotation in comparison with normal rotation are shown. We calculated HR using a Cox proportional hazards model. Men and women were analyzed separately and combined. For the following models, the following covariates were included: model 1, age+ECG (normal, clockwise rotation, and counterclockwise rotation; normal was taken as a reference); model 2, model 1+body mass index (5 categories), hypertension, cigarette smoking (5 categories), alcohol drinking (3 categories), serum total cholesterol and blood glucose concentrations, serum creatinine (cutoff at 1.0 mg/dL), and significant interaction terms; model 3, model 2+other ECG findings and significant interaction terms; and model 4, model 3+sex indicator and significant interaction terms. NIPPON DATA80 indicates National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004; CI, confidence interval; CHD, coronary heart disease; HF, heart failure; and CVD, cardiovascular disease.

the remaining one third of cases, other factors such as vertical heart were responsible. It is also known that counterclockwise rotation is more common in healthy young individuals.[34,35] A higher prevalence of clockwise rotation was reported in the setting of acute massive pulmonary thromboembolism.[36–38] Counterclockwise rotation was reported to occur after right pneumonectomy.[39] Except for age-specific differences in the prevalence of clockwise rotation and counterclockwise rotation, many of these reports appear to be unrelated to situations in the present study.

We speculate regarding the reasons for the harmful effect of clockwise rotation and the beneficial effect of counterclockwise rotation on CVD mortality. First, the age-specific prevalence of clockwise rotation and counterclockwise rotation may be related. Clockwise rotation was more prevalent and, in contrast, counterclockwise rotation was less prevalent in the older age groups in the present study. These findings are consistent with the aforementioned studies.[34,35] Second, less prevalent clockwise rotation and more prevalent counterclockwise rotation among those in the middle BMI groups may also be related because it has been shown that a U-shaped relationship is at work between BMI and several outcomes.[40] Third, mild Q wave, axis deviation, ST depression, T-wave inversion, and AF were more prevalent among participants with clockwise rotation than in normal participants in men and women. Many of these features were less prevalent among participants with counterclockwise rotation than in normal male and female participants. Some of these ECG features have been shown to be associated with untoward outcomes.[10–24] Although all of the factors mentioned thus far were included as confounding factors in multivariate Cox analyses, we cannot exclude the possibility that the adjustment might not have been complete. Further studies are needed to elucidate the mechanisms involved in the harmful

effect of clockwise rotation and beneficial effect of counterclockwise rotation on CVD mortality. The clinical significance of clockwise rotation and counterclockwise rotation, which has been ignored for >100 years, is worth noting.

We had a large cohort of participants who were obtained from randomly selected health districts in Japan. The participants in our study were observed for 24 years, which is a long follow-up period and increases the value of our study substantially.

Study Limitations

There are some limitations to the present study. First, 1105 participants (≈10%) were lost to follow-up. There were no significant differences between participants who were lost to follow-up and those who were included in the present study in terms of several risk factors. Therefore, the potential bias regarding the participants lost to follow-up may be negligible. However, unobserved information related to outcomes might have led participants to drop out of our study early. We cannot exclude that this might lead to a bias. Second, our study participants were limited to only Japanese men and women. Although previous studies showed that other ECG findings with proven prognostic values in the United States and Europe were also applicable in Japanese men and women,[17,20,22,30] confirmation studies in a non-Japanese population may be needed. Third, we used a single ECG at baseline. It is well recognized that single biological measurements are subject to variability, and ECG abnormalities may have changed over time. In addition, it is possible that lead placement variability affected the transition point of the V leads. This might lead to dilution and underestimation of the strength of the relative risk relations as a result of misclassification. Fourth, MC was coded by visual reading in our study. Computerized ECG analysis is reportedly superior to visual reading for better reliability[41]; however, ECG reading in the study was performed under the best standardized quality control by well-trained physicians.

Conclusions

We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise rotation with CVD mortality in men and in men and women combined, independent of confounding factors including other ECG changes.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The transitional zone is related to the direction of the QRS axis in the horizontal plane. Although clockwise rotation and counterclockwise rotation are distinct findings on ECG, their clinical values have not been well studied, and their prognostic significance has been studied rarely. In this study, we assessed the independent prognostic values of clockwise rotation and counterclockwise rotation for mortality due to cardiovascular disease and its subtypes in a large cohort of participants obtained from randomly selected health districts in Japan. We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise rotation with cardiovascular disease mortality in men and in men and women combined, independent of confounding factors including other ECG changes. Although the mechanisms for these associations are not clear at present, in clinical practice, we may need to pay attention to these ECG changes that have been ignored for more than a century.