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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(2) 心電図時計方向回転および反時計方向回転と心血管疾患死亡リスク (NIPPON DATA80, 24 年追跡)

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目的：

Einthoven が心電図を発明した 1895 年以来不明であった時計方向回転および反時計方向回転の意義を心血管疾患死亡リスクとの関連について検討した。

方法：

1980 年に無作為抽出した全国 300 ヵ所において 30 才以上の男女を対象として検診と生活習慣調査を行い、心筋梗塞または脳卒中の既往のない 9,067 人(男性 44%、 女性 51%)を 24 年間追跡した。

結果：

追跡期間中に総死亡が 2,581 人、心血管死が 887 人、心筋梗塞死が 179 人、心不全死が 173 人、脳卒中死が 411 人あった。生化学検査値、他の心電図所見および交絡因子を調整して行った Cox 解析の結果、時計方向回転は以下の死亡と有意な正の関連があった：男女合わせた心不全死 (ハザード比[HR]=1.79, 95%信頼区間[CI]: 1.13-2.83, P=0.013);男および男女の心血管死 (男 HR=1.49 [1.12-1.98], P=0.007; 男女 HR=1.28 [1.02-1.59], P=0.030)；男および男女の総死亡(男 HR=1.19 [1.00-1.49], P=0.0496; 男女 HR=1.15 [1.00-1.32], P=0.045)。反時計方向回転は以下の死亡と有意な負の関連があった：男女の脳卒中死 (HR=0.77 [0.62-0.96], P=0.017);男および男女の心血管死(男：HR=0.74 [0.59-0.94], P=0.011;男女 HR=0.81 [0.70-0.94], P=0.006); 女性の総死亡(HR=0.87 [0.77-0.98], P=0.023)。

結論：

他の心電図所見および交絡因子とは独立して時計方向回転は男および男女の心血管死と正の関連が、反時計方向回転は男および男女の血管死と負の関連があった。

Prognostic Values of Clockwise and Counter-Clockwise Rotation for Cardiovascular Mortality in Japanese (24 Year Follow-up of NIPPON DATA80).
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Prognostic Values of Clockwise and Counter-Clockwise Rotation for Cardiovascular Mortality in Japanese (24 Year Follow-up of NIPPON DATA80)

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Abstract

Background- - Although clockwise (CWR) and counter-clockwise rotation (CCWR) are distinct findings of ECG, their prognostic significance is almost never studied.

Methods and Results- - We studied prognostic values of CWR and CCWR on total, cardiovascular disease (CVD) and subtype mortality using the NIPPON DATA80 database with a 24-year follow-up. At the baseline in 1980, data were collected on study participants, ages 30 years and over, from randomly selected areas in Japan. We followed 9,067 participants (44% men, mean age 51). During the 24 year follow-up, there were 2,581 total, 887 CVD, 179 CHD, 173 HF, and 411 stroke mortality. The multivariate-adjusted hazard ratio (HR) using the Cox model including biochemical and other ECG variables revealed that CWR was significantly positively associated with heart failure (HF) in men and women combined (HR=1.79, 95% confidence intervals [CI]: 1.13-2.83, P=0.013), CVD in men and combined (HR=1.49 [1.12-1.98], P=0.007 in men; HR=1.28 [1.02-1.59], P=0.030 in combined), and total mortality in men and combined (HR=1.19 [1.00-1.49], P=0.0496 in men; HR=1.15 [1.00-1.32], P=0.045 in combined). CCWR was significantly inversely associated stroke in combined (HR=0.77 [0.62-0.96], P=0.017), CVD in men and combined (HR=0.74 [0.59-0.94], P=0.011 in men; HR=0.81 [0.70-0.94], P=0.006 in combined), and total mortality in women (HR=0.87 [0.77-0.98], P=0.023).

Conclusions- -We found a significant positive association of CWR, and a significant inverse association of CCWR with CVD mortality in men, and in men and women combined, independent of confounding factors including other ECG changes.

Key words: electrocardiography, clockwise and counter-clockwise rotation, cardiovascular mortality

Since the first report by Einthoven of accurate recording of the electrocardiogram (ECG) and its development as a clinical tool in 1895 [1], the early phase of studies of ECG was devoted to descriptions of ECG changes in disease conditions, such as arrhythmia [2-5], angina pectoris [6], myocardial infarction [7], or to formation of diagnostic criteria from comparative evaluations between ECG findings and anatomical 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 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 [11-23].

The transitional zone is related to the direction of the QRS axis in the horizontal plane. Although clockwise (CWR) and counter-clockwise rotation (CCWR) are distinct findings of ECG, their clinical values have not been studied enough and their prognostic significance has almost never been studied. The aim of the present study was to assess the independent prognostic values of CWR and CCWR 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 Non-communicable 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 and over, in the participating health districts was 13,771. All of them were invited to participated 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 DATA 80, 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 the baseline (N=164), or loss to follow-up (N=1,105). 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 atrio-ventricular block (MC 7-1),

Wolf-Parkinson-White syndrome (MC 6-4-), and complete left bundle branch block (LBBB)(MC 7-1)[26, 27]. The final sample comprised 9,067 participants (3,958 men and 5,109 women). There were no significant differences between participants who were lost to follow-up and those who were included in the current 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 min of rest. Hypertension was defined as systolic blood pressure ≥140mm Hg, diastolic blood pressure ≥90mm Hg, use of antihypertensive agents or any combination of these. Height and weight were measured in stocking feet and light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also carried out using 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 habit, and present and past medical histories.

Casual blood samples were drawn and centrifuged within 60 min 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 previously described [30]. Codes in agreement were accepted, whereas inconsistent codes were decided by a panel of study epidemiologists and cardiologists [28]. Major ECG findings for the present study were CCWR (MC9-4-1: a transition zone at V3 or rightward of V3), and CWR (MC9-4-2: a transition zone at V4 or leftward of V4). 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 V3 and dominant R in V4 are defined as normal rotation. Normal rotation ECGs have isoelectric transitional zone in between V3 and V4, that were found in the majority of cases. Additional ECG findings (www.sph.umn.edu/epi/ecg/mncode.pdf [27]) that we examined were mild Q wave abnormality (MC1-3-), frontal plane QRS axis deviations (MC2-1, 2-2, 2-3), high R wave (MC3-1 to 3-4), ST depression (MC4-1 to 4-4), T abnormality (MC5-1 to 5-5), combination of high R plus either ST depression, or T abnormality (LVH_ST), first- or second-degree atrio-ventricular block (1° or 2° AV block) (MC6-2- or 6-3), intraventricular conduction disturbances (BBB) other than LBBB (MC7-2-1- to 7-8), ventricular premature beats (VPC)(MC8-1-2), atrial fibrillation (AF)(MC8-3), sinus tachycardia (MC8-7), sinus bradycardia (MC8-8), low QRS voltage (MC9-1), ST elevation (MC9-2), tall P wave (MC9-3-1), and long P wave (MC9-3-2) [26, 27]

Although reproducibility of ECG findings was not checked in this study. A previous study by de Bruyne, et al. showed that reproducibility of QRS axis deviation was excellent[31].

We presume reproducibility of CRW and CCWR should be similarly good. The prevalence of normal rotation, CWR, and CCWR 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.

Endpoint Determination

To determine cause of death- after 24 years 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 9th International Classification of Disease (ICD-9) through the end of 1994 and 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 to 459 and ICD-10: I00 to I99), CHD (ICD-9: 410 to 414 and ICD-10: I20 to I25), heart failure (HF) (ICD-9: 428 and ICD-10: I50), stroke (ICD-9: 430 to 438 and ICD-10: I60 to I69), chronic obstructive pulmonary disease (COPD) (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 three groups according to ECG horizontal plane rotation (normal, CWR, and CCWR). The chi-square test was used to compare dichotomous variables, followed by *a post hoc* application of Bonferroni's method. A one-way analysis of variance was used to compare means among the groups, followed by a *post hoc* application of Dunnett's test when the F value showed a significant difference at $p < 0.05$. Prevalence of CWR and CCWR among age- and BMI groups was also examined. To obtain trend P, Mantel-Haenszel was used.

To examine the factors associated with CHD, HF, stroke, CVD, and total mortality, multivariate-adjusted hazard ratios (HR) were calculated using a Cox proportional hazards model. Men and women were analyzed separately in model 1 to model 3, and combined in model 4. Covariates in model 1 were age, and ECG horizontal plane rotation (normal, CWR, and CCWR; normal was taken as a reference). Model 2: model 1 + BMI (5 categories divided at 18.5, 23, 25, and 30 kg/m^2; 8.5-23: a reference), hypertension, cigarette smoking (never and past smokers, 3 current smokers categories divided at 20, and 40 cigarettes/day; never smokers: a reference), alcohol drinking (ex-drinker or current drinker, never-drinker; never drinkers: a reference), serum total cholesterol, and blood glucose concentrations (standardized to have the mean=0 and standard deviation=1), serum creatinine (divided at 75 percentile,1.0 mg/dl), and interaction terms. Model 3: model 2 + 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 (LVH_ST), 1° or 2° AV block, BBB other than LBBB, VPC, AF,

sinus tachycardia , sinus bradycardia, low QRS voltage, ST elevation, tall P wave, and long P wave), and interaction terms. Model 4: model 3 + sex indicator, and interaction terms. In addition, the following sensitivity analyses for model 4 CVD mortality were done: dichotomizing at age 60, subgroup analyses by frontal axis groups, and by smoking groups, removing participants with AF; and removing participants with LVH_ST. We tested proportionality via generating the time dependent covariates by creating interactions of the predictors and a function of survival time and included in the models. None of these were significant. Also, by using "test" statement, we tested all the time dependent covariates all 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 were significant, the interaction terms were included in the models.

Results

Descriptive Statistics

During follow-up for 24 years (191,484 person-years), 27 COPD death (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 death (1,365 in men, 1,216 in women) were ascertained.

Baseline characteristics, total, COPD, CVD and its subtype mortality according to ECG rotation groups are shown in Table 1. Among men, 56.0% of them were in the normal rotation group, 8.2% in CWR, and 35.8% in CCWR group. In men, in CWR group, mean age, the prevalence of CHD, HF, CVD, and total death were higher than in men in the normal group, while mean BMI was lower than in men in the normal group. In contrast to these differences, in men in CCWR group, mean BMI was higher, and the prevalence of current smokers, CVD and total death were lower than in men in the normal group.

Among women, 48.4% of them were in the normal rotation group, 5.8% in CWR group, and 45.8% in CCWR group. In women in the CWR group, mean age, TOTAL CHOLESTEROL, blood sugar, the prevalence of hypertension, HF, CVD and total death were higher than in women in the normal group. In contrast to these differences, for women in CCWR group, mean age was lower; mean BMI was higher, and the prevalence of hypertension, stroke, CVD, 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 CWR groups, prevalence of a mild Q wave, left axis and mild right axis deviations, T inversion, and AF were higher than in men in the normal group, while prevalence of a high R wave was lower than men in the normal group. In men in CCWR group, the prevalence of a mild Q wave, mild right axis deviation, ST depression, BBB other than LBBB, and AF were lower than in men in the normal groups. In women in CWR groups, prevalence of left axis

and mild right axis deviations, ST depression, T inversion, AF, sinus tachycardia, and low voltage were higher than in women in the normal group. In women in CCWR group, the prevalences of mild right axis deviation, and low voltage were lower than in women in the normal groups.

Associations of Age and BMI Categories with CCW, and CCWR

Associations of age and BMI categories with CWR, and CCWR are shown in Table 3. Both in men and women, prevalence of CWR became higher as age increased. In contrast, prevalence of CCWR in women became lower as age increased. Both in men and women, prevalence of CWR became lower in the middle BMI groups; in contrast, prevalence of CCWR was higher in the middle BMI groups.

Associations of CWR and CCWR with Total, CVD and its Subtype Mortality

Results of Cox analyses on the associations of CWR and CCWR with total, CVD and its subtype mortality are shown in Table 4. In general, CWR tended to be positively, and CCWR inversely, associated with total, CVD and its subtype mortalities. CWR was significantly positively associated with heart failure (HF) in men and women combined (model 4) (HR=1.79, 95% confidence intervals [CI]: 1.13-2.83, P=0.013), CVD in men and combined (model 3 HR=1.49 [1.12-1.98], P=0.007 in men; model 4 HR=1.28 [1.02-1.59], P=0.030 in combined), and total mortality in men and combined (model 3 HR=1.19 [1.00-1.49], P=0.0496 in men; model 4 HR=1.15 [1.00-1.32], P=0.045 in combined). CCWR was significantly inversely associated stroke in combined (model 4 HR=0.77 [0.62-0.96], P=0.017), CVD in men and combined (model3 HR=0.74 [0.59-0.94], P=0.011 in men; model 4 HR=0.81 [0.70-0.94], P=0.006 in combined), and total mortality in women (model 3 HR=0.87 [0.77-0.98], P=0.023). A subgroup analysis by dichotomizing the participants at age 60 yielded similar results with some loss of statistical significance (age≤60 year: HR for CWR=1.53 [1.02-2.29], P=0.039; HR for CCWR=0.80[0.60-1.07], P=0.127; age> 60 year: HR for CWR=1.19 [0.91-1.55], P=0.148; HR for CCWR=0.83 [0.70-0.99], P=0.0341). Subgroup analyses by frontal axis groups, and by smoking groups yielded the similar results but losing statistical significance. The two sensitivity analyses, namely removing the participants with AF or removing the participants with LVH_ST, yielded the similar results.

Discussion

We found a significant positive association of CWR, and a significant inverse association of CCWR with CVD mortality in men. We also found a significant positive association of CWR with HF in men and women combined, and 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 the baseline for subsequent risk of incidence and/or death from CVD have been extensively studied

throughout the long history of ECG studies. The 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 CWR and CCWR are distinct findings of ECG, their clinical values have not been studied enough and their prognostic significance has seldom been studied. One exceptional study was done by Rajala et al., who found that stroke mortality showed the highest association with CWR and left high R waves among most of the participants aged 85 or over [32]. Horibe et al. studied the relationship between ECG findings coded by the MC system to all-cause mortality using the NIPPON DATA80 database with follow-up for 19 years, and noted that the HR of participants with CWR was significantly high [30]. No further investigation was made.

There have been some studies to investigate the mechanisms of CWR and CCWR. Tahara et al. examined CT-scans of 102 participants to compare the anatomic position of the cardiac septum and ECG position of the transitional zone [33]. They concluded that about two-thirds of CWR and CCWR could be explained by anatomical rotation of the heart in the horizontal plane around the long axis, and in the remaining one-third of cases, other factors such as vertical heart were responsible. It is also known that CCWR is more common in healthy young individuals [34, 35]. A higher prevalence of CWR was reported in the setting of acute massive pulmonary thromboembolism [36-38]. CCWR was reported to occur after right pneumonectomy [39]. Except for age-specific differences in the prevalence of CWR and CCWR, many of these reports appear to be unrelated to the situations in the present study.

We speculate regarding the reasons for the harmful effect of CWR and beneficial effect of CCWR on CVD mortality. First, the age-specific prevalence of CWR and CCWR may be related. Namely, CWR was more prevalent and, in contrast, CCWR was less prevalent, in the older age groups in the present study. These findings are consistent with the previous studies mentioned above [34, 35]. Secondly, less prevalent CWR and more prevalent CCWR among those in the middle BMI groups may also be related, because it has been shown that a U-shape relationship is at work between BMI and several outcomes [40]. Thirdly, mild Q wave, axis deviation, ST depression, T inversion and AF were more prevalent among participants with CWR than in normal participants in men and women. Many of these features were less prevalent among participants with CCWR 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 so far mentioned factors 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 for the harmful effect of CWR and beneficial effect of CCWR on CVD mortality. It is worth noting the clinical significances of CWR and CCWR that have been ignored for more than 100 years.

We had a large cohort of participants 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 current study. Firstly, we had 1,105 participants (about 10%) lost to follow-up. There were no significant differences between participants who were lost to follow-up and those who were included in the current 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 lead participants to drop out of our study early. We cannot excluded that this might lead to a bias. Secondly, our study participants were limited to only Japanese men and women. Although previous studies showed other ECG findings with proven prognostic values in the U.S. and Europe were also applicable in Japanese men and women [17, 20, 22, 30], confirmation studies in non-Japanese population may be needed. Thirdly, we used a single ECG at the baseline. It is well recognized that single biologic measurements are subject to variability and ECG abnormalities could have changed over time. Also, there is the possibility of lead placement variability affecting the transition point of the V leads. These might lead to dilution and underestimation of the strength of the relative risk relations due to 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 significant positive association of CWR, and significant inverse association of CCWR 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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Table 1 Baseline Characteristics and Mortality According to ECG Rotation Groups ---- NIPPON DATA80, 1980-2004

	Men (subtotal=3,958)				Women (subtotal=5,109)			
Rotation	**Normal**	**Clockwise**	**CounterCW**	**P**	**Normal**	**Clockwise**	**CounterCW**	**P**
N (%)	2,216 (56.0)	326 (8.2)	1,416 (35.8)		2,470 (48.4)	298 (5.8)	2,341 (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/m2)	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
BS (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 the mean±SD, or in %. * P<0.05, † P<0.01. Baseline characteristics and CVD and its subtype mortality were compared among the three groups according to ECG horizontal plane rotation (normal, clockwise, and counter-clockwise). The chi-square test was used to compare dichotomous variables, followed by *a post hoc* application of Bonferroni's method. A one-way analysis of variance was used to compare means among the groups, followed by a *post hoc* application of Dunnett's test when the F value showed a significant difference at $p < 0.05$. CounterCW=counter-clockwise, BMI=body mass index, Alcohol drinker=those participants who admitted to drinking alcohol daily, Smoker= those participants who admitted to smoke currently, Cholesterol=serum total cholesterol concentration, BS=blood glucose concentration, CHD=coronary heart disease, HF=heart failure, CVD=cardiovascular diseases, COPD=chronic obstructive pulmonary disease.