Levels of Cornell Voltage and Cornell Product for Predicting Cardiovascular and Stroke Mortality and Morbidity in the General Japanese Population

Joji Ishikawa, MD, PhD; Shizukiyo Ishikawa, MD, PhD; Kazuomi Kario, MD, PhD;
Jichi Medical School (JMS) Cohort Study Investigators Group

Background: ECG-diagnosed left ventricular hypertrophy (LVH), the Cornell voltage (CV: ≥ 2.8 mV in males and ≥ 2.0 mV in females) or Cornell product (CP: ≥ 244.0 mV $\times$ ms), were selected in Western countries for their ability to diagnose anatomical LVH.

Methods and Results: We aimed to elucidate the CV and CP values that were associated with a significantly increased risk of cardiovascular or stroke mortality and morbidity in a Japanese general population ($n=10,172$). In the receiver-operating curves analysis of CV and CP for predicting the risks, the area under the curve in females was greater than in males. In a quintile-based multivariate analysis that was performed separately for females and males, the mortality and morbidity risks of CV were significantly increased at the highest quintile of CV (>1.71 mV) in females. In males, the mortality risk was significantly increased at the highest quintile of CV (>2.04 mV). Additionally, in the parallel analysis of CP that included both males and females, the morbidity risk was significantly elevated in subjects with CP belonging to the 4th (158.7–193.4 mV $\times$ ms; hazard ratio=1.387) or 5th quintiles (≥ 193.5 mV $\times$ ms; hazard ratio=1.507), compared with those with CP values within the lowest quintile (<101.9 mV $\times$ ms).

Conclusions: Cardiovascular and stroke risks may be elevated at lower levels of CV and CP in Japanese subjects, especially females. (*Circ J* 2014; **78**: 465–475)

Key Words: Cornell product; Cornell voltage; ECG; Left ventricular hypertrophy; Sokolow-Lyon voltage

Left ventricular hypertrophy (LVH) can be evaluated using 12-lead ECG¹ and for the diagnosis of ECG-LVH, either the standard voltage criteria reported by Sokolow-Lyon² or the Cornell voltage (CV) and Cornell product (CP) (CV $\times$ QRS duration) criteria has been used in clinical studies.³ The cutoff levels for ECG-LVH (CV ≥ 2.8 mV in males, ≥ 2.0 mV in females; CP ≥ 244.0 mV $\times$ ms, Sokolow-Lyon voltage ≥ 3.8 mV)⁴ were chosen for their ability to diagnose echocardiographic LVH^{5–7} in Western populations. In addition, these 3 criteria for ECG-LVH were reported as associated with increased morbidity and mortality;^{8–11} however, they displayed low sensitivity for diagnosing echocardiographic LVH,¹² and the risks of mortality¹³ and stroke events¹⁴ associated with ECG-LVH were found to be independent of echocardiographic LVH. Recently, ECG-LVH has been considered to be a marker of electrical remodeling of the myocardium, rather than just a marker of anatomical LVH.¹⁵ Therefore, the threshold levels of the abovementioned parameters for diagnosing echocardiographic LVH might differ from the levels at which the

risk of cardiovascular or stroke morbidity is significantly increased.

The purpose of this study was to evaluate the CV, CP, and Sokolow-Lyon voltage at which individuals from a Japanese general population are at a significantly increased risk of cardiovascular and stroke mortality/morbidity.

Methods

Subjects

The Jichi Medical School (JMS) Cohort Study was initiated in 1992, with the primary aim of clarifying the risk factors for cardiovascular and cerebrovascular disease in the general Japanese population. The details of the protocol of the JMS Cohort Study have been reported previously.^{16,17} Baseline data were collected between April 1992 and July 1995 in 12 rural districts of Japan (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshiba, Akaike, Wara, Hokudan, Yamato, and Takasu) using a government-sponsored mass screening sys-

Received April 9, 2013; revised manuscript received September 6, 2013; accepted October 2, 2013; released online November 26, 2013
Time for primary review: 20 days

Division of Cardiovascular Medicine, Department of Internal Medicine, Jichi Medical University School of Medicine (J.I., K.K.); Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University (S.I.), Shimotsuke, Japan

Mailing address: Joji Ishikawa, MD, PhD, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University, School of Medicine, 3311-1 Yakushiji, Shimotsuke 329-0498, Japan. E-mail: george@jichi.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-13-0470

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Table 1. Characteristics of Study Subjects

Variable	Total (n=10,172)	Males (n=3,830)	Females (n=6,342)	P between males and females
Age, years	55.4±11.2	55.2±11.7	55.5±11.0	0.112
Body mass index, kg/m ²	23.1±3.1	23.0±2.9	23.2±3.2	<0.001
Smoking habit				<0.001
Past smoker, %	12.6	28.3	2.9	
Current smoker, %	22.6	50.1	5.7	
Alcohol drinking >20 g/day	27.6	27.0	28.0	0.257
Hyperlipidemia, %	35.4	34.9	35.8	0.363
Status of diabetes				<0.001
Impaired fasting glucose, %	2.6	3.6	1.9	
Diabetes, %	3.5	5.0	2.6	
Systolic blood pressure, mmHg	129.3±21.0	131.4±20.6	128.1±21.2	<0.001
Diastolic blood pressure, mmHg	77.4±12.3	79.3±12.3	76.3±12.2	<0.001
Hypertension, %	34.2	36.9	32.6	<0.001
Antihypertensive medication use, %	11.1	9.4	12.2	<0.001
S in lead V1, mV	0.93±0.41	0.98±0.44	0.91±0.39	<0.001
R in lead V5, mV	1.74±0.62	1.96±0.67	1.60±0.55	<0.001
SV1+RV5, mV	2.67±0.83	2.94±0.87	2.51±0.76	<0.001
S in lead V3, mV	1.03±0.53	1.22±0.57	0.93±0.48	<0.001
R in lead aVL, mV	0.35±0.24	0.33±0.25	0.36±0.24	<0.001
SV3+RaVL, mV	1.38±0.58	1.54±0.62	1.28±0.54	<0.001
QRS duration, ms	85.4±13.8	89.1±14.1	83.2±13.0	<0.001
Cornell product, mV×ms	150.1±57.7	138.3±62.2	157.2±53.6	<0.001

Data are shown as mean±standard deviation (SD) or percentage. P values were evaluated using Student's t-test between men and women. P<0.05 was considered statistically significant.

tem ([Data S1](#)). In each community, a local government office sent personal invitations by mail to all potential subjects in accordance with the Health and Medical Service Law for the aged. At baseline, the total number of subjects in the JMS Cohort Study was 12,490 (4,911 males and 7,579 females). The participation rate varied from community to community (26–90%), and the overall participation rate of those invited to the mass screening examination program was 65.4%.¹⁸

ECG Measurement and Interpretation

ECG were obtained at a paper speed of 25 mm/s and a gain of 10 mm/mV (or 5 mm/mV) using the ECG devices at the participating institutes. A trained person, who did not know the subjects' backgrounds, assessed the subjects' ECG parameters at a central laboratory using a ruler with 0.01-mm gradations. Both the Sokolow-Lyon voltage (SV1+RV5) and CV (RaVL+SV3)^{3,19} were measured. QRS duration was measured manually from lead II (or lead I or III if the measurement of QRS duration was difficult from lead II) based on a single heartbeat. CP without adjustment for sex was calculated as the product of CV and the subsequent QRS duration. CP with adjustment for sex was also calculated using the aforementioned equation after 0.6 mV was added to females' CV, following previous reports^{3,19} and the Japanese Society of Hypertension 2009 (JSH2009) guideline for the Management of Hypertension.⁴ The interobserver (between the trained person and a cardiologist) and intraobserver (of the trained person) variations in CV were 0.09±0.08 mV and 0.02±0.05 mV, respectively, and those of the CP were 1.5±35.7 mV×ms and 21.6±27.0 mV×ms, respectively. We compared the Sokolow-Lyon voltage, CV and CP data obtained in the present study with those described in a previous report about the Losartan Intervention for Endpoint (LIFE) reduction in hypertension

study²⁰ and those written in the JSH 2009 guideline⁴ [in which Sokolow-Lyon LVH is defined as ≥3.8 mV (38 mm); CV LVH is defined as 2.8 mV (28 mm) in males and 2.0 mV (20 mm) in females; and CP LVH is defined as 244.0 mV×ms (2,440 mm×ms)].

Informed Consent

The internal review board of Jichi Medical University School of Medicine approved the study and written informed consent for the study was given individually by all subjects during the mass screening health check-up examinations.

Follow-up and Diagnostic Criteria

The mass screening examination system was used to check the subjects every year for 10 years. After the initial follow-up period of 10 years, follow-up was extended until the end of 2005 for mortality only. We asked the subjects directly whether they had suffered a stroke or cardiovascular event since enrolling in the study. When a subject did not undergo the annual screening examination, we contacted them or their family members by mail or phone to confirm whether they had suffered any cardiovascular events or died. If a subject had been taken to a medical facility because of a cardiovascular event or death, a doctor or health nurse associated with the JMS Cohort Study visited the facility and checked the patient's medical records. When an incident case was suspected, we applied for permission and then photocopied any relevant brain computed tomography or magnetic resonance imaging (if a cerebrovascular event was suspected) scans and/or ECG (if myocardial infarction was suspected). When a subject that we were unable to contact during the follow-up period died, a death certificate was collected from the appropriate public health center with the permission of the Agency of General Affairs and the Ministry

Table 2. Hazard Ratios of Cornell and Sokolow-Lyon Voltages (as Continuous Variables) for Morbidity and Mortality in Males and Females

	All-cause mortality				CCS mortality				CCS morbidity (fatal and nonfatal)			
	HR	95% CI	P value		HR	95% CI	P value		HR	95% CI	P value	
Males												
Cornell voltage per 0.1 mV increase												
Unadjusted	1.028	1.014	1.041	<0.001	1.045	1.020	1.070	<0.001	1.038	1.020	1.056	<0.001
Age adjusted	1.025	1.011	1.040	0.001	1.048	1.019	1.077	<0.001	1.038	1.018	1.058	<0.001
Multivariate adjusted	1.025	1.010	1.041	0.001	1.040	1.008	1.072	0.013	1.022	1.001	1.044	0.043
Sokolow-Lyon voltage per 0.1 mV increase												
Unadjusted	1.002	0.991	1.012	0.778	1.022	1.000	1.046	0.052	1.032	1.017	1.047	<0.001
Age adjusted	1.000	0.990	1.011	0.950	1.020	0.998	1.042	0.069	1.029	1.015	1.044	<0.001
Multivariate adjusted	0.998	0.987	1.008	0.653	1.013	0.991	1.035	0.247	1.019	1.005	1.034	0.009
Females												
Cornell voltage per 0.1 mV increase												
Unadjusted	1.058	1.042	1.073	<0.001	1.078	1.055	1.101	<0.001	1.080	1.065	1.095	<0.001
Age adjusted	1.031	1.011	1.052	0.002	1.063	1.028	1.101	<0.001	1.072	1.051	1.093	<0.001
Multivariate adjusted	1.031	1.010	1.052	0.003	1.058	1.021	1.097	0.002	1.056	1.033	1.079	<0.001
Sokolow-Lyon voltage per 0.1 mV increase												
Unadjusted	1.045	1.031	1.058	<0.001	1.047	1.021	1.073	<0.001	1.052	1.035	1.069	<0.001
Age adjusted	1.029	1.016	1.043	<0.001	1.028	1.004	1.054	0.025	1.038	1.021	1.054	<0.001
Multivariate adjusted	1.029	1.015	1.043	<0.001	1.029	1.003	1.056	0.029	1.028	1.011	1.045	0.001

In the multivariate-adjusted model, age, body mass index, alcohol drinking habit, smoking status, presence of hyperlipidemia, status of diabetes, systolic blood pressure, and antihypertensive medication use were also entered into the Cox regression analysis. CCS, combined cardiovascular and stroke; HR, hazard ratio; CI, confidence interval.

of Health, Labor, and Welfare. Data on changes of residence during the study were obtained annually from each municipal government. Cause of death and events were determined independently by an endpoints committee, which included radiologists, neurologists, and cardiologists, in accordance with the criteria outlined by the World Health Organization's Monitoring of Trends and Determinants in Cardiovascular Disease (WHO MONICA) project.²¹ The diagnostic criteria are shown in [Data S1](#).

Statistical Analysis

Among the 12,490 subjects who were initially enrolled in the JMS Cohort Study, we analyzed 10,172 subjects who had adequate follow-up data, after excluding 2,318 subjects with no ECG recordings (n=1,285), immeasurable ECG findings (n=28), complete left bundle branch block (n=20), complete right bundle branch block (n=189), QRS duration >200 ms (n=3), atrial fibrillation (n=53), no blood pressure data (n=160), no information about their antihypertensive medication use (n=430), or a history of myocardial infarction and/or stroke (n=150).

Data are shown as the mean±1 standard deviation for continuous variables, and as percentages for dichotomous variables. Differences in characteristics between the male and female subjects were evaluated using Student's t-test or the chi-square test. The area under the receiver-operating characteristic (AUC) curve was used to compare the abilities of the Cornell and Sokolow-Lyon voltages to predict combined cardiovascular and stroke (CCS) mortality and morbidity. Kaplan-Meier curves were constructed to visualize the risk levels associated with each CP quintile in the unadjusted models. The mortality and morbidity risk levels in both the unadjusted models and those that had been adjusted for conventional cardiovascular risk factors were evaluated using Cox regression analysis in all subjects (for CP and Sokolow-Lyon voltage), as

well as separately for males and females (for the Sokolow-Lyon and CVs). The computer software SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) was used for all analyses, and P<0.05 was considered statistically significant.

Results

Study Subjects

The subjects' characteristics are shown in [Table 1](#). The male and female subjects displayed similar mean ages, but systolic and diastolic blood pressures were significantly higher in the males than the females. Sokolow-Lyon (S in lead V1 and R in lead V5) and CVs (S in lead V3 and R in lead aVL) were significantly greater in males than in females. The distributions of CV in males and females, and that of unadjusted and sex-adjusted CP in females and males are shown [Figure S1](#). In females, CP without adjustment for sex was smaller than that in males. When 0.6 mV (6 mm) was added to the CV in the calculation of females' CP,⁴ the 75th and 95th percentiles of CP became similar between males and females.

Follow-up

We followed up the subjects for a mean period of 140.9±30.7 months (1,432,728 person-years) for mortality and 127.4±30.7 months (1,295,453 person-years) for morbidity. During the follow-up period, there were 794 deaths from any cause, comprising 183 deaths from cardiovascular or stroke events (12 deaths from vascular disease, 76 deaths from cardiac disease, 95 deaths from cerebrovascular disease), 320 deaths from malignant disease, and 291 deaths from other causes (suicide, trauma, lung disease, liver disease, and infection). In addition, 422 subjects suffered their first cardiovascular or stroke event (70 cases of cardiovascular events, 362 cases of stroke events, 10 cases of both cardiovascular and stroke events; including

Figure 1. Receiver-operating curves of Cornell voltage for predicting combined cardiovascular and stroke mortality in males (**A**) and females (**B**) and cardiovascular and stroke morbidity in males (**C**) and females (**D**). Data are shown as mean values (95% confidence intervals). AUC, area under the curve.

both fatal and nonfatal events).

Analysis of Sokolow-Lyon and CVs as Continuous Variables

The risks of all-cause mortality, CCS mortality, and CCS morbidity associated with increases in the Sokolow-Lyon and CVs are shown separately for males and females in **Table 2**. In males, multivariate analysis found that each 0.1 mV (1 mm) increase in the CV was associated with 4.0%, and 2.2% increases in CCS mortality, and CCS morbidity, respectively. In females, multivariate analysis found that these risks increased by 5.8%, and 5.6%, respectively, with each 0.1 mV (1 mm) increase in the CV. Each 0.1 mV (1 mm) increase in the Sokolow-Lyon voltage was associated with 1.3%, and 1.9% increase, respectively, in CCS mortality and morbidity in males, and 2.9% and

2.8% increase, respectively, in CCS mortality and morbidity in females.

The results of a parallel analysis of the risks associated with each component of the Sokolow-Lyon voltage (ie, S in lead V1 and R in lead V5) and CV (ie, S in lead V3 and R in lead aVL) are shown in **Table S1** (males and females).

CV Cutoff Levels and the Risk of CCS Morbidity Separately in Males and Females

The area under curve (AUC) values of the receiver-operating characteristic (ROC) curves of the Cornell and Sokolow-Lyon voltages for predicting CCS mortality and CCS morbidity are shown separately for males and females (**Figure 1**). In females, the AUC of the CV was greater than that of Sokolow-

Table 3. Multivariate Adjusted Hazard Ratios (HR) of the Quintile of Cornell Voltage (CV) for Mortality and Morbidity in Males and Females

Quintile of CV	Univariate analysis				Multivariate analysis			
	HR	95% CI		P value	HR	95% CI		P value
Males								
All-cause mortality								
Q1, ≤1.03 mV	Ref.				Ref.			
Q2, 1.04–1.35 mV	1.284	0.948	1.741	0.107	1.163	0.856	1.580	0.334
Q3, 1.36–1.64 mV	1.052	0.767	1.443	0.754	1.014	0.737	1.394	0.932
Q4, 1.65–2.03 mV	1.262	0.929	1.715	0.136	1.138	0.835	1.551	0.412
Q5, ≥2.04 mV	1.767	1.325	2.356	<0.001	1.622	1.205	2.183	0.001
CCS mortality								
Q1, ≤1.03 mV	Ref.				Ref.			
Q2, 1.04–1.35 mV	1.636	0.794	3.371	0.182	1.376	0.664	2.853	0.390
Q3, 1.36–1.64 mV	0.997	0.448	2.220	0.995	0.850	0.380	1.905	0.694
Q4, 1.65–2.03 mV	1.839	0.905	3.738	0.092	1.473	0.718	3.022	0.290
Q5, ≥2.04 mV	2.713	1.389	5.302	0.003	2.094	1.047	4.189	0.037
CCS morbidity								
Q1, ≤1.03 mV	Ref.				Ref.			
Q2, 1.04–1.35 mV	1.589	1.003	2.516	0.049	1.335	0.840	2.122	0.222
Q3, 1.36–1.64 mV	0.988	0.596	1.639	0.962	0.860	0.517	1.431	0.561
Q4, 1.65–2.03 mV	1.859	1.188	2.910	0.007	1.472	0.936	2.315	0.095
Q5, ≥2.04 mV	2.076	1.336	3.226	0.001	1.402	0.888	2.212	0.147
Stroke event								
Q1, ≤1.03 mV	Ref.				Ref.			
Q2, 1.04–1.35 mV	1.599	0.935	2.734	0.086	1.360	0.793	2.334	0.264
Q3, 1.36–1.64 mV	1.171	0.664	2.067	0.585	1.021	0.576	1.808	0.944
Q4, 1.65–2.03 mV	2.150	1.291	3.580	0.003	1.730	1.033	2.899	0.037
Q5, ≥2.04 mV	2.334	1.409	3.867	0.001	1.597	0.948	2.689	0.079
MI event								
Q1, ≤1.03 mV	Ref.				Ref.			
Q2, 1.04–1.35 mV	1.339	0.587	3.053	0.488	1.107	0.481	2.550	0.811
Q3, 1.36–1.64 mV	0.396	0.124	1.262	0.117	0.352	0.110	1.131	0.080
Q4, 1.65–2.03 mV	1.151	0.489	2.711	0.748	0.864	0.362	2.065	0.743
Q5, ≥2.04 mV	1.181	0.502	2.783	0.703	0.784	0.321	1.913	0.592
Females								
All-cause mortality								
Q1, ≤0.83 mV	Ref.				Ref.			
Q2, 0.84–1.11 mV	1.201	0.806	1.788	0.368	1.081	0.725	1.614	0.702
Q3, 1.12–1.37 mV	1.155	0.772	1.729	0.483	0.790	0.525	1.189	0.258
Q4, 1.38–1.70 mV	1.479	1.009	2.168	0.045	0.951	0.644	1.404	0.800
Q5, ≥1.71 mV	2.297	1.610	3.277	<0.001	1.207	0.832	1.751	0.321
CCS mortality								
Q1, ≤0.83 mV	Ref.				Ref.			
Q2, 0.84–1.11 mV	2.350	0.828	6.672	0.108	2.161	0.757	6.164	0.150
Q3, 1.12–1.37 mV	2.993	1.088	8.235	0.034	1.682	0.604	4.685	0.320
Q4, 1.38–1.70 mV	3.191	1.169	8.711	0.024	1.769	0.641	4.887	0.271
Q5, ≥1.71 mV	7.296	2.863	18.594	<0.001	3.015	1.155	7.870	0.024
CCS morbidity								
Q1, ≤0.83 mV	Ref.				Ref.			
Q2, 0.84–1.11 mV	1.176	0.650	2.129	0.592	0.989	0.545	1.795	0.970
Q3, 1.12–1.37 mV	1.348	0.756	2.403	0.312	0.862	0.481	1.547	0.619
Q4, 1.38–1.70 mV	2.104	1.235	3.583	0.006	1.206	0.702	2.072	0.497
Q5, ≥1.71 mV	4.441	2.729	7.229	<0.001	1.901	1.146	3.155	0.013
Stroke event								
Q1, ≤0.83 mV	Ref.				Ref.			
Q2, 0.84–1.11 mV	1.031	0.551	1.933	0.923	0.872	0.464	1.638	0.670
Q3, 1.12–1.37 mV	1.262	0.691	2.304	0.449	0.809	0.440	1.486	0.494
Q4, 1.38–1.70 mV	2.112	1.223	3.646	0.007	1.218	0.699	2.123	0.486
Q5, ≥1.71 mV	4.226	2.558	6.982	<0.001	1.817	1.078	3.064	0.025

(Table 3 continued the next page.)

Quintile of CV	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
MI event						
Q1, ≤ 0.83 mV	Ref.			Ref.		
Q2, 0.84–1.11 mV	1.964	0.360–10.722	0.436	1.612	0.292–8.892	0.584
Q3, 1.12–1.37 mV	1.493	0.249–8.934	0.661	0.959	0.157–5.838	0.963
Q4, 1.38–1.70 mV	1.984	0.363–10.831	0.429	1.054	0.188–5.900	0.952
Q5, ≥ 1.71 mV	4.065	0.863–19.143	0.076	1.591	0.319–7.944	0.571

In the multivariate adjusted model, age, sex, body mass index, alcohol drinking habit, smoking status, presence of hyperlipidemia, status of diabetes, systolic blood pressure, and antihypertensive medication use were also entered into the Cox regression analysis. MI, myocardial infarction; Ref., reference. Other abbreviations as in Table 2.

Figure 2. Receiver-operating curve of Cornell product for predicting combined cardiovascular and stroke mortality in males (**A**) and females (**B**) and cardiovascular and stroke morbidity in males (**C**) and females (**D**). Data are shown as mean values (95% confidence intervals). AUC, area under the curve.

Lyon voltage, but in males, the AUC of the CV was similar to that of the Sokolow-Lyon voltage. The AUC of the CV in males was only marginally significant 0.584 (P=0.005). In the quintile-based multivariate-adjusted model for males, the highest quintile of the CV (>2.04 mV) was associated with an increased risk of CCS mortality and the 4th (1.65–2.03 mV) and highest (≥2.04 mV) quintile of CV was associated with an increased risk of stroke events (Table 3). In the parallel analysis for females, the highest quintile of the CV (>1.71 mV) was associated with an increased risk of CCS mortality and morbidity (Table 3). In both males and females, the highest quin-

tiles of the CV associated with CCS risks were lower than the risk levels shown in the JSH2009 guideline.⁴

Unadjusted and Gender-Adjusted CP and the Risk of CCS Morbidity Separately in Males and Females

Because there were no data that showed whether the adjustment of 0.6 mV (6 mm) in the calculation of females' CP was appropriate in a Japanese population, we evaluated CP cutoff levels without adjustment for sex separately in males and females. In males, the AUCs of the CP for predicting CCS mortality (0.562, P=0.037) and morbidity (0.543, P=0.03) were only

Table 4. Hazard Ratios (HR) of Cornell Product (CP) and Sokolow-Lyon Voltage (as Continuous Variables) for Morbidity and Mortality in Total Subjects

	CP per 10.0 mV×ms				Sokolow-Lyon voltage per 0.1 mV			
	HR	95% CI	P value		HR	95% CI	P value	
All-cause mortality								
Unadjusted	1.023	1.011	1.034	<0.001	1.030	1.021	1.038	<0.001
Age and gender adjusted	1.025	1.013	1.036	<0.001	1.011	1.003	1.019	0.006
Multivariate adjusted	1.025	1.013	1.037	<0.001	1.009	1.000	1.017	0.041
CCS mortality								
Unadjusted	1.049	1.027	1.071	<0.001	1.040	1.024	1.057	<0.001
Age and gender adjusted	1.047	1.024	1.070	<0.001	1.025	1.008	1.041	0.003
Multivariate adjusted	1.040	1.016	1.064	0.001	1.020	1.004	1.038	0.017
CCS morbidity								
Unadjusted	1.047	1.033	1.062	<0.001	1.047	1.036	1.058	<0.001
Age and gender adjusted	1.045	1.030	1.060	<0.001	1.033	1.022	1.044	<0.001
Multivariate adjusted	1.030	1.015	1.046	<0.001	1.023	1.012	1.035	<0.001
Stroke event								
Unadjusted	1.052	1.037	1.068	<0.001	1.045	1.033	1.057	<0.001
Age and gender adjusted	1.048	1.033	1.064	<0.001	1.033	1.021	1.044	<0.001
Multivariate adjusted	1.034	1.018	1.051	<0.001	1.023	1.011	1.035	<0.001
MI event								
Unadjusted	1.008	0.968	1.049	0.707	1.052	1.027	1.078	<0.001
Age and gender adjusted	1.018	0.980	1.057	0.362	1.029	1.004	1.055	0.025
Multivariate adjusted	1.001	0.963	1.041	0.948	1.019	0.993	1.045	0.157

CP was calculated after adding 6 mm to the CP for women. In the multivariate adjusted model, age, sex, body mass index, alcohol drinking habit, smoking status, presence of hyperlipidemia, status of diabetes, systolic blood pressure, and antihypertensive medication use were also entered into the Cox regression analysis.

Abbreviations as in Tables 2,3.

marginally significant (Figure 2). The Kaplan-Meier curve of males' CP quintiles for predicting CCS morbidity is shown in Figure 3A. In the quintile-based analysis of CP (Table S2), the highest quintile of CP (>185.2 mV×ms) was associated with CCS mortality risk.

In females, the AUCs of the CP for predicting CCS mortality and morbidity were greater than those in males. The Kaplan-Meier curve of females' CP quintiles for predicting CCS morbidity is shown in Figure 3B. The 4th (unadjusted CP, 114.1–144.0 mV×ms; gender-adjusted CP, 164.1–197.2 mV×ms) and highest (unadjusted CP, ≥144.1 mV×ms; gender-adjusted CP ≥197.3 mV×ms) quintile of the CP were associated with increased CCS morbidity (Table S2).

Significance of CP and Sokolow-Lyon Voltage in All Subjects

In the whole study population, when the CP was subjected to multivariate analysis as a continuous variable, each 10 mV×ms (100 mm×ms) increase was found to be associated with 4.0% and 3.0% increases in the risks of CCS mortality and CCS morbidity, respectively (Table 4). In the whole study population, each 0.1 mV (1 mm) increase in the Sokolow-Lyon voltage was associated with a 2.0% and 2.3% increases in the risks of CCS mortality and CCS morbidity, respectively (Table 4).

Kaplan-Meier curves of the relationships between each CP quintile and CCS morbidity in the whole study population are shown in Figure 3C. The risks of CCS morbidity were increased in the subjects with CPs that were in the 4th or 5th quintiles. Even after adjusting for conventional confounding cardiovascular risk factors in the Cox proportional hazards model, the subjects with CPs in the 4th (158.7–193.4 mV×ms) or 5th quintile (≥193.5 mV×ms) were significantly more likely to suffer CCS morbidity than those with CPs that fell within

the lowest quintile (CP <101.9 mV×ms) (Table S3). Therefore, a CP threshold of approximately 160.0 mV×ms was found to be associated with significant increases in CCS morbidity in this study. When the subjects were stratified into 3 groups using cutoff levels of 160.0 and 244.0 mV×ms, the subjects with CPs between 160.0 and 244.0 mV×ms had a 1.32-fold higher risk of CCS mortality than those with CP <160.0 mV×ms (Table 5).

Kaplan-Meier curves of the relationships between each Sokolow-Lyon voltage quintile and CCS morbidity in the whole study population are shown in Figure 3D. The risks of CCS morbidity were marginally increased even in subjects with a Sokolow-Lyon voltage in the 4th quintile (Table S4). A Sokolow-Lyon voltage threshold of approximately 3.0 mV (30 mm) seemed to be associated with significant increases in CCS morbidity in this study. When the subjects were stratified into 3 groups using cutoff levels of 3.0 and 3.8 mV, the subjects with Sokolow-Lyon voltage between 3.0 and 3.8 mV had a 1.46-fold higher risk of CCS morbidity than those with Sokolow-Lyon voltage <3.0 mV (Table 5).

Discussion

In the present study, the Sokolow-Lyon voltage, CV, and CP as continuous variables were associated with significantly increased risks of CCS morbidity. Subjects with the highest quintile of CV had an increased risk of CCS mortality or morbidity, and the levels were 2.04 mV for males and 1.71 mV for females. The CP predicted CCS morbidity even at levels between 160.0 and 244.0 mV×ms in the total population that included both males and females, but it was largely attributable to the CCS morbidity in females. The Sokolow-Lyon voltage predicted

Table 5. (1) Multivariate Adjusted Hazard Ratios (HR) of Cornell Product (CP) Stratified by 160.0 and 244.0 mV×ms for Mortality and Morbidity in Total Subjects (2) Multivariate Adjusted Hazard Ratios (HR) of Sokolow-Lyon Voltage Stratified by 3.0 and 3.8 mV for Mortality and Morbidity in Total Subjects

CP	N. of event	Crude incidence (%)	N. per 1,000 person-years	Univariate analysis				Multivariate analysis			
				HR	95% CI		P value	HR	95% CI		P value
All-cause mortality											
<160.0mV×ms	442	6.2	6.02	Ref.				Ref.			
160.0–244.0mV×ms	266	7.1	6.83	1.156	0.991	1.348	0.065	1.205	1.028	1.413	0.022
≥244.0mV×ms	86	13.0	12.27	2.036	1.607	2.579	<0.001	1.829	1.434	2.334	<0.001
CCS mortality											
<160.0mV×ms	93	1.0	1.27	Ref.				Ref.			
160.0–244.0mV×ms	66	1.6	1.69	1.345	0.976	1.853	0.070	1.207	0.866	1.684	0.267
≥244.0mV×ms	24	2.7	3.42	2.812	1.792	4.413	<0.001	2.105	1.317	3.363	0.002
CCS morbidity											
<160.0mV×ms	205	3.3	3.08	Ref.				Ref.			
160.0–244.0mV×ms	164	5.1	4.66	1.527	1.241	1.878	<0.001	1.324	1.069	1.640	0.010
≥244.0mV×ms	53	8.7	8.44	2.732	2.014	3.706	<0.001	1.809	1.321	2.479	<0.001
Stroke event											
<160.0mV×ms	171	2.8	2.57	Ref.				Ref.			
160.0–244.0mV×ms	141	4.2	3.99	1.575	1.257	1.972	<0.001	1.339	1.061	1.690	0.014
≥244.0mV×ms	50	7.9	7.94	3.097	2.252	4.259	<0.001	2.030	1.461	2.822	<0.001
MI event											
<160.0mV×ms	40	0.6	0.60	Ref.				Ref.			
160.0–244.0mV×ms	27	0.8	0.76	1.276	0.783	2.080	0.327	1.257	0.758	2.084	0.375
≥244.0mV×ms	3	0.5	0.46	0.779	0.241	2.519	0.677	0.564	0.171	1.854	0.345
Sokolow-Lyon voltage											
All-cause mortality											
<3.0mV	476	6.8	5.80	Ref.				Ref.			
3.0–3.8mV	199	8.8	7.53	1.310	1.108	1.549	0.002	1.034	0.872	1.226	0.698
≥3.8mV	119	12.6	10.94	1.940	1.584	2.377	<0.001	1.216	0.985	1.502	0.069
CCS mortality											
<3.0mV	105	1.5	1.28	Ref.				Ref.			
3.0–3.8mV	47	2.1	1.78	1.407	0.993	1.994	0.055	1.124	0.788	1.604	0.519
≥3.8mV	31	3.3	2.85	2.329	1.557	3.484	<0.001	1.523	0.999	2.322	0.051
CCS morbidity											
<3.0mV	216	3.1	2.90	Ref.				Ref.			
3.0–3.8mV	130	5.8	5.44	1.883	1.511	2.345	<0.001	1.457	1.165	1.824	0.001
≥3.8mV	76	8.0	7.77	2.767	2.129	3.597	<0.001	1.674	1.272	2.202	<0.001
Stroke event											
<3.0mV	185	2.7	2.48	Ref.				Ref.			
3.0–3.8mV	114	5.1	4.77	1.929	1.524	2.443	<0.001	1.510	1.186	1.921	0.001
≥3.8mV	63	6.6	6.44	2.668	2.002	3.554	<0.001	1.665	1.234	2.247	0.001
MI event											
<3.0mV	37	0.5	0.49	Ref.				Ref.			
3.0–3.8mV	20	0.9	0.82	1.670	0.969	2.877	0.065	1.145	0.658	1.992	0.632
≥3.8mV	13	1.4	1.30	2.655	1.411	4.994	0.002	1.293	0.666	2.510	0.448

Statistical analysis was performed using a Cox hazard model. In the multivariate-adjusted model, conventional risk factors of age, sex, body mass index, alcohol drinking habit, smoking status, presence of hyperlipidemia, status of diabetes, systolic blood pressure, and antihypertensive medication use were also entered into the model.

Abbreviations as in Tables 2,3.

CCS morbidity even at levels between 3.0 and 3.8 mV. These results suggested that the CV and CP and Sokolow-Lyon voltage predicted future CCS morbidity at even lower levels than those described in the JSH2009 guideline⁴.

The mean CV in the present study was lower than that found in the Framingham study,¹⁰ in which the mean CV was 1.95 mV for males and 1.99 mV for females, but was comparable to

the values reported in a previous study of Japanese patients (1.34±0.59 mV in normotensive subjects and 1.96±0.79 mV in untreated hypertensive subjects).²² It was also reported that Korean patients displayed lower CV cutoff levels for detecting echocardiogram LVH (2.0 mV in males and 1.6 mV in females) compared with Western populations²³ and the levels were close to the cutoff levels of CV for predicting CCS risks in this

study. Moreover, the CV levels that were associated with significantly increased risks of CCS morbidity in this study were lower than those observed in the Framingham study, in which the highest CV quartile (≥ 2.4 mV) was significantly associated with cardiovascular mortality compared with the lowest CV quartile. Although no data regarding echocardiogram or cardiac MRI-diagnosed LVH were obtained in this study, Asian subjects might tend to have lower CVs, and hence require lower thresholds for detecting anatomical LVH than Western subjects, and this might lead to lower cutoff levels of CV for predicting cardiovascular and stroke events.

The predictive values of CV and CP for CCS morbidity were greater in females than in males. In males, the AUC of the CP for predicting CCS mortality and morbidity was smaller than for females, and it was difficult to determine a threshold of the CP. Even though there were no data to justify the adjustment (0.6 mV to females' CV) of CP in this Japanese population, the gender-adjusted CP shifted the distribution of females' CP similar to that of males'. Therefore, this adjustment seemed reasonable to evaluate the CCS risk of the CP. On the other hand, the risk of the CP for predicting CCS morbidity in the total population depended largely on the CCS risk in females.

The CP was also found to be associated with CCS morbidity, even in subjects with a CP between 160.0 and 244.0 mV $\times$ ms. The CV and CP, which are used as markers of electrical remodeling, could also be early risk markers of CCS morbidity, because they represent myocardial electrical properties that include myocyte hypertrophy and cardiac fibrosis. It has been previously reported that the presence of CP LVH (≥ 244.0 mV $\times$ ms) is predictive of future cardiovascular mortality regardless of the presence or absence of echocardiographic LVH.^{13,14} On the other hand, in the LIFE Study,²⁰ in which those who fulfilled the CP or Sokolow-Lyon voltage criteria for ECG-LVH at baseline were enrolled, the CP, as a time-varying parameter, was found to be associated with cardiovascular mortality in patients with CP ≥ 300.0 mV $\times$ ms, but not in those with a CP between 250.1 and 300.0 mV $\times$ ms or those with a CP between 200.0 and 250.0 mV $\times$ ms. In a previous study, the CP was found to be associated with increased blood pressure and impaired glucose metabolism,¹⁷ and the results of the present study suggest that there should be further research into the effectiveness of early intervention against cardiovascular risk factors such as hypertension and/or impaired glucose metabolism in patients with a marginally increased CP.

The Sokolow-Lyon voltage was found to be associated with CCS morbidity, even in subjects with a voltage between 3.0 and 3.8 mV. In the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS),²⁴ patients with a Sokolow-Lyon voltage between 3.5 and 4.0 mV were associated with an increased risk of cardiovascular events, and the ROC curve for predicting cardiovascular events was greater at the cutoff level of 2.7 mV. The results of our study in a general population support those of the JATOS study,²⁴ which was performed in elderly hypertensive patients.

Study Limitations

The following limitations existed in the present study. (1) We did not obtain any data about echocardiographic LVH. Okin et al.²⁵ reported that the utility of ECG-LVH for detecting echocardiographic LVH varies by race, although it was previously reported that the CP is associated with echocardiographic LVH in Japanese patients.²² (2) We did not obtain any data that would allow us to determine whether the CV adjustment used for females (6 mm) is appropriate for Japanese women. We performed parallel analyses using a CV adjustment of 4 mm,

and the results were broadly similar. (3) Measurement of ECG parameters was performed manually by a trained person, and the reproducibility of the measurements was confirmed.

Conclusions

Both the CV and CP were predictors of CCS morbidity in a general Japanese population. The predictive value of CV and CP in females was greater than in males. The CV and CP predicted CCS morbidity at lower quintile levels than are written in the current guideline of the JSH2009.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and grants from the Foundation for the Development of the Community, Tochigi, Japan.

Disclosures

None.

References

- Jain A, Tandri H, Dalal D, Chahal H, Soliman EZ, Prineas RJ, et al. Diagnostic and prognostic utility of electrocardiography for left ventricular hypertrophy defined by magnetic resonance imaging in relationship to ethnicity: The Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2010; **159**: 652–658.
- Sokolow M, Lyon T. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949; **37**: 161–186.
- Molloy T, Okin P, Devereux R, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. *J Am Coll Cardiol* 1992; **20**: 1180–1186.
- Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
- Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part V. *Circulation* 2009; **119**: e251–e261, doi:10.1161/CIRCULATIONAHA.108.191097.
- Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic detection of left ventricular hypertrophy: Development and prospective validation of improved criteria. *J Am Coll Cardiol* 1985; **6**: 572–580.
- Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: Validation with autopsy findings. *Circulation* 1987; **75**: 565–572.
- Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969; **71**: 89–105.
- Kannel W, Gordon T, Castelli W, Margolis J. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: The Framingham Study. *Ann Intern Med* 1970; **72**: 813–822.
- Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; **90**: 1786–1793.
- Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, et al. Prognostic value of a new electrocardiographic method for diagnosis of left ventricular hypertrophy in essential hypertension. *J Am Coll Cardiol* 1998; **31**: 383–390.
- Schillaci G, Battista F, Pucci G. A review of the role of electrocardiography in the diagnosis of left ventricular hypertrophy in hypertension. *J Electrocardiol* 2012; **45**: 617–623.
- Sundstrom J, Lind L, Arnlov J, Zethelius B, Andren B, Lithell HO. Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men. *Circulation* 2001; **103**: 2346–2351.
- Kohsaka S, Sciacca RR, Sugioka K, Sacco RL, Homma S, Di Tullio MR. Additional impact of electrocardiographic over echocardiographic diagnosis of left ventricular hypertrophy for predicting the risk of ischemic stroke. *Am Heart J* 2005; **149**: 181–186.

15. Rodriguez-Padial L, Bacharova L. Electrical remodeling in left ventricular hypertrophy: Is there a unifying hypothesis for the variety of electrocardiographic criteria for the diagnosis of left ventricular hypertrophy? *J Electrocardiology* 2012; **45**: 494–497.
16. Ishikawa S, Gotoh T, Nago N, Kayaba K. The Jichi Medical School (JMS) Cohort Study: Design, baseline data and standardized mortality ratios. *J Epidemiol* 2002; **12**: 408–417.
17. Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE, et al; for the Jichi Medical School Cohort Study Investigators Group. Cornell product left ventricular hypertrophy in electrocardiogram and the risk of stroke in a general population. *Hypertension* 2009; **53**: 28–34.
18. Ishikawa S, Kayaba K, Gotoh T, Nago N, Nakamura Y, Tsutsumi A, et al. Incidence of total stroke, stroke subtypes, and myocardial infarction in the Japanese population: The JMS Cohort Study. *J Epidemiol* 2008; **18**: 144–150.
19. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. *J Am Coll Cardiol* 1995; **25**: 417–423.
20. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, et al; for the LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343–2349.
21. WHO MONICA Project Principal Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. *J Clin Epidemiol* 1988; **41**: 105–114.
22. Shirai T, Kasao M, Nozaki M, Nitta S. Evaluation of hypertensive cardiac abnormalities using the Cornell product. *Circ J* 2007; **71**: 731–735.
23. Park JK, Shin JH, Kim SH, Lim YH, Kim KS, Kim SG, et al. A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in Korean patients. *Korean Circ J* 2012; **42**: 606–613.
24. Jissho S, Shimada K, Taguchi H, Yoshida K, Fukuda S, Tanaka H, et al. Impact of electrocardiographic left ventricular hypertrophy on the occurrence of cardiovascular events in elderly hypertensive patients: The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Circ J* 2010; **74**: 938–945.
25. Okin P, Wright J, Nieminen MS, Jern S, Taylor A, Phillips R, et al. Ethnic differences in electrocardiographic criteria for left ventricular hypertrophy: The LIFE study. *Am J Hypertens* 2002; **15**: 663–671.

Supplementary Files

Supplementary File 1

Data S1. Methods

Figure S1. Distribution of Cornell voltage in (A) males and (B) females.

Table S1. Hazard ratios (HR) of each component of the Cornell voltage (R in lead aVL and S in lead V3) and Sokolow-Lyon voltage (S in lead V1 and R in lead V5) for all-cause mortality and combined cardiovascular and stroke (CCS) morbidity and mortality in males

Table S2. Multivariate adjusted hazard ratios (HR) of the quintile of unadjusted Cornell product (CP) for mortality and morbidity in Males and Females

Table S3. Multivariate adjusted hazard ratios (HR) of the quintile of Cornell product (CP) for mortality and morbidity in total subjects

Table S4. Multivariate adjusted hazard ratios (HR) of the quintile of Sokolow-Lyon voltage for mortality and morbidity in total subjects.

Please find supplementary file(s):
<http://dx.doi.org/10.1253/circj.CJ-13-0470>