Electrocardiographic ST-T Area Assessed by a Computerized Quantitative Method and Its Relation to Cardiovascular Events: The J-HOP Study

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BACKGROUND
Although many studies have reported that the presence of minor or major ST-T change of electrocardiography (ECG) was associated with a risk of cardiovascular events, it is not clear whether there is a difference in the prognostic power depending on the summation of ST-T area (ST-T area) assessed by a quantitative method.

METHODS
Electrocardiograms were performed in 834 clinical patients with one or more cardiovascular risks. ST-T area was assessed as the area enclosed by the baseline from the end of the QRS complex to the end of the ST-T segment using a computerized quantitative method. We used the lower magnitude of ST-T area in the V5 or V6 lead for the analysis.

RESULTS
After a mean follow-up 8.4 ± 2.9 years (7,001 person-years), there were 92 cardiovascular events. With adjustment for covariates, the results from Cox proportional hazards models (Model 1) suggested that the lowest quartile of ST-T area was associated with a higher risk for cardiovascular outcome compared with the remaining quartile groups (hazard ratio, 2.08; 95% confidence interval, 1.36–3.16, P < 0.01). Even when adding the ECG left ventricular hypertrophy by Cornell voltage (Model 2) and Cornell product (Model 3) to Model 1, the significance remained (both P < 0.01). When we used ST-T area as a continuous variable substitute for the lowest quartile of ST-T area, these associations were similar in all models (all P < 0.01).

CONCLUSION
The lower summations of ST-T area assessed by a computerized quantitative method were associated with increased risk of cardiovascular disease incidence in a clinical population.

Keywords: blood pressure; cardiovascular events; cardiovascular risk; clinical population; electrocardiography; hypertension.

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Electrocardiography (ECG) is a simple, noninvasive, and standardized procedure for the diagnosis of heart disease. The presence of major ST-T changes on ECG, usually consisting of ≥1 mm concave down-sloping of the strain T segment (ST-segment depression) and/or asymmetrical T-wave inversion in the lateral leads, has often been observed and has been associated with cardiovascular events both in a general and a hypertensive population.1–4 Although minor ST-T changes are also observed in subjects without clinical signs of heart disease, it is controversial whether the presence of minor ST-T changes is a cardiovascular risk. Several cohort studies have shown that the presence of minor ST-T changes was a cardiovascular risk,3–8 but others have found no association between minor ST-T changes and cardiovascular events,9 or that the association was limited to men in general population.10 These disparate results may be due to no assessment of quantitative method for minor ST-T changes on ECG. The determination of minor and major ST-T changes on ECG varies depending on not only the magnitude of depression of the ST segment but also the asymmetric figure of the inverted T wave. Therefore, we hypothesized that the lower summation of ST-T area assessed by a quantitative method may also be associated with increased risk of cardiovascular events. To test this hypothesis, we examined the association between the summations of ST-T area assessed by a computerized quantitative method and risk of cardiovascular events using data from the Japanese general practice population.

METHODS
Patients
This study was a subanalysis of a prospective observational study known as the Japan Morning Surge-Home Blood Pressure (J-HOP) study. The J-HOP study consecutively

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recruited patients who were seen from January 2005 to May 2012 by doctors from 71 institutions throughout Japan, and followed up through March 2018 for outcomes. Detailed information of this study has been reported previously. All patients provided written informed consent. The ethics committee of the internal review board of the Jichi Medical University School of Medicine, Tochigi, Japan, approved the protocol. A total of 4,310 ambulatory outpatients who had one or more cardiovascular risks were enrolled in the J-HOP study during the enrollment period. For this study, we analyzed 834 of these patients in whom ECG was performed using the FCP-7541 (Fukuda Denshi, Tokyo), an ECG device that permits quantitative assessment of the ST-T area.

Cardiovascular risk definition and other measurements

Diabetes was defined by self-report of the use of diabetes medication, fasting plasma glucose ≥126 mg/dl, or hemoglobin A1c (National Glycohemoglobin Standardization Program) ≥6.5%. Dyslipidemia was defined by self-report of the use of lipid-lowering medication, total cholesterol level ≥240 mg/dl, triglycerides ≥150, or high-density lipoprotein <40 mg/dl. Preexisting cardiovascular disease (CVD), including angina pectoris, myocardial infarction, and stroke, was ascertained at baseline. Three office blood pressure (BP) and pulse rate (PR) readings were taken at 15-second intervals on 2 different occasions, and their means (6 readings) were defined as the office BP and PR.

Electrocardiography

ECGs were recorded digitally at 10 mm/mV calibration and a speed of 25 mm/second using the FCP-7541 device described earlier. The summation of ST-T area (ST-T_area, msec·mV) was assessed as the area enclosed by the baseline from the end of the QRS complex (J-point) to the end of the ST wave. Examples of measurement of ST-T_area are shown in Figure 1. We used the lower magnitude of ST-T_area in the V5 or V6 lead for the analysis in this study, because a previous study reported that ST depression in the lateral lead was a strong marker of increased morbidity and mortality. To assess reproducibility, a subset of 95 patients (the number of type A, B, and C in Figure 1 were 74, 14, and 7, respectively) underwent repeated measurement of ST-T_area analysis approximately 1 minute after their first assessment. The regression coefficient was 0.97.

According to the method used in previous reports, the Cornell voltage (CV) was automatically measured by a computer, and then the Cornell product (CP) was determined as the product of the CV multiplied by the QRS duration. CV-left ventricular hypertrophy (LVH) was defined as ≥2.8 mV in males and ≥2.0 mV in females. CP-LVH was defined as ≥244 mV × ms according to the Losartan Intervention for Endpoint Reduction in Hypertension Study.

Outcomes ascertainment

Vital status was ascertained through March 2018, with an average follow-up period of 8.4 ± 2.9 years (7,001 person-years). In this study, composite cardiovascular outcomes were as follows: (i) fatal and nonfatal stroke (transient ischemic attack was not included); (ii) fatal and nonfatal coronary artery disease (CAD), defined as acute myocardial infarction, angina pectoris requiring percutaneous coronary intervention, and sudden death within 24 hours of the abrupt onset of symptoms; (iii) acute decompensated heart failure; and (iv) acute aortic dissection. If events occurred on ≥2 occasions, the first occurrence was included in the analysis. Evidence regarding the aforementioned cardiovascular outcomes was ascertained by ongoing reports from a general physician at each institute. When patients failed to come to the hospital, we interviewed them and/or their families by telephone. The end-point committee adjudicated all events by reviewing the patients’ files and source documents or by requesting more detailed written information from investigators. The committee was blinded to individual clinical characteristics. Additional details are given in the Supplementary Data section.

Figure 1. Sample ST-T area summations. The summation of ST-T area (ST-T_area, msec·mV) was assessed as the area enclosed by the baseline from the end of the QRS complex (J-point) to the end of the T wave and ST wave (TE) in V5 and V6 leads. (A) A normal ST segment and positive T-wave pattern: the ST-T_area is calculated as a positive value. (B) ST segment depression and a positive T-wave pattern: the area from the J-point to the cross point is calculated as a negative value (Area I). The area from the cross point to TE is calculated as a positive value (Area II). The ST-T_area is defined as the summation of Area I + Area II (if |Area I| > |Area II|, the ST area is calculated as a negative value). (C) ST segment depression and a negative T-wave pattern: the ST-T_area is calculated as a negative value.
Statistical analysis

All statistical analyses were performed with STATA version 14.1 (STATACorp; College Station, TX). Data are presented as the mean ± SD for continuous variables and proportions for categorical variables. Patients were classified into quartiles of ST-$T_{area}$. Differences in prevalence between two groups were compared with χ² analysis, and mean values of continuous variables were compared with an unpaired Student's t-test. Event rates were calculated and plotted according to the Kaplan–Meier product limit method, and statistical significance was tested for the linear trend across groups with the log-rank statistic. We used Cox proportional hazards models to examine the associations between ST-$T_{area}$ as categorical and continuous variables and risks for cardiovascular outcome. The proportionality assumption for the Cox analyses was confirmed graphically. Covariates included traditional risk factors (age, sex, current smoking, a history of diabetes, dyslipidemia, body mass index, antihypertensive medication use, and preexisting CVD [i.e., angina pectoris, acute myocardial infarction, and stroke]). The model including these covariates was defined as the base model (Model 1). Model 2 included the covariates used in Model 1 and CV-LVH, and Model 3 included the covariates used in Model 1 and CP-LVH. We calculated the hazard ratios and 95% confidence intervals for cardiovascular events associated with ST-$T_{area}$ as categorical and continuous variables. The likelihood ratio values were used to evaluate the goodness-of-fit of predictive models. We repeated Cox regression models for subgroup analyses in study subjects stratified by those with or without LVH. In addition, we performed a test for interaction to examine the effect of modification in those with or without LVH. To identify the ST-$T_{area}$ that best predicted the incidence of cardiovascular events, its cutoff value was defined by the receiver operator curve. Two-sided P-values <0.05 were defined as statistically significant.

RESULTS

The included participants (n = 834) had a lower age (62.7 vs. 65.4 years; P < 0.001); lower percentages of current smokers (10.2% vs. 12.8%; P = 0.041), daily drinkers (19.8% vs. 29.4%; P < 0.001), and dyslipidemia (32.7% vs. 42.6%; P < 0.001); and lower clinic systolic BP (139.4 vs. 141.7 mm Hg; P < 0.001) than those not included (n = 3476; Supplementary Table 1). In contrast, the included participants had higher proportions of men (51.7% vs. 45.9%; P = 0.003), diabetes (29.4% vs. 23.3%; P < 0.001), preexisting CVD (19.7% vs. 11.1%; P < 0.001), higher body mass index (24.6 vs. 24.2 kg/m²; P = 0.005), and clinic PR (72.5 vs. 70.9 bpm; P < 0.001) than those not included.

Table 1 shows the baseline characteristics for the total population included in this study. Table 2 shows the baseline characteristics according to quartiles of ST-$T_{area}$. Age; prevalences of antihypertensive medication; preexisting CVD, CV-LVH, and CP-LVH; and clinic PR were incrementally higher in each quartile in order from highest to lowest. In contrast, the prevalence of men and clinic diastolic BP were incrementally higher in each quartile in order from lowest to highest.

During follow-up, 92 cardiovascular events occurred (32 stroke, 36 CAD, 19 acute decompensated heart failure, and 5 acute aortic dissection events). The incidence of cardiovascular events was incrementally higher in each quartile in order from lowest to highest (Table 2). The percentages of cardiovascular event-free patients during the follow-up period are shown in Figure 2. The patients with the lowest quartile of ST-$T_{area}$ exhibited a worse prognosis than any other group.

Table 3 shows the hazard ratio of the lowest quartile of ST-$T_{area}$ and its continuous variable for cardiovascular outcome. With adjustment for covariates, the results from Cox proportional hazards models suggested that the lowest quartile of ST-$T_{area}$ was associated with a higher risk of cardiovascular outcome. The model fit assessed by log-likelihood ratio changes was also more improved when we added the lowest quartile of ST-$T_{area}$ into the base models. When we added CV-LVH (Model 2) or CP-LVH (Model 3) into Model 1, the model fit assessed by log-likelihood ratio changes for cardiovascular outcome did not improve.
However, when we added the lowest quartile of ST-T area into Model 2 or Model 3, the model fit assessed by log-likelihood ratio changes was also more improved. Lower ST-T area was associated with a risk of cardiovascular events when we used ST-T area as a continuous variable substitute for the lowest quartile of ST-T area. In the stratified analysis, both the lowest quartile of ST-T area and ST-T area as a continuous variable were associated with a risk of cardiovascular events in the population with or without LVH. There was no interaction between ST-T area and cardiovascular events according to LVH (Supplementary Table 2). The optimal cutoff value of ST-T area from the receiver operator curve for predicting the incidence of cardiovascular events was 0.017 msec•mV.

**DISCUSSION**

This study showed that lower ST-T area assessed by a computerized quantitative method was associated with an increased risk of cardiovascular events in a model that included conventional cardiovascular risk in a clinical population of patients with more than one cardiovascular risk factor. Moreover, this association remained in the model even when the CV (a conventional prognostic marker of ECG) and CP LVH were added to the base model including conventional cardiovascular risk. To the best of our knowledge, this is the first study to show a linear association between lower ST-T area and cardiovascular risk using a computerized quantitative method. Although the majority of previous prospective studies showed that depression of the ST-T segment was associated with a risk of cardiovascular events, some of these studies indicated that the extent of the depression of ST-T segment was related to the degree of impact of cardiovascular risk. Ohira et al. reported that in a general population, both males and females with major ST-T change had a greater incidence of stroke compared with those without major ST-T change. The same study found that minor ST-T change was associated with stroke incidence in men, but not in women.
similarly reported that major ST-T change was associated with an increased risk of stroke but minor ST-T change was not in a general Japanese population. Thus, in the case of the association between cardiovascular risk and ST-T change as a dichromatic variable—i.e., with minor/major ST-T change or without—the clinical significance may remain inconclusive. The Strong Heart Study revealed that absolute ST-T segment deviation of over 50 μV in any ECG lead predicted cardiovascular and all-cause mortality in a general American Indian population. 17

It is important to note that the assessment in this previous study was performed using only the magnitude (depth) of depression of the ST-T segment. However, the form of ST-T depression consists not only of the depth of the ST-T segment but also the asymmetric figure of the inverted T wave. Therefore, ST-T area may be important as a novel and simple prognostic marker.

Classically, depression of the ST segment and strain T of ECG have been accepted to be associated with LVH and coronary ischemia, 18, 19 and a relationship between depression of the ST segment or strain T of ECG and cardiovascular events has been shown in the general and hypertensive population. 20

Table 3. Hazard ratio of categorical (lowest quartile) and continuous variables of summation of ST-T area for cardiovascular events in the total population (n = 834)

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI)</th>
<th>Likelihood ratio, χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summation of ST-T area as a categorical variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 (base)</td>
<td>n/a</td>
<td>−551.9</td>
</tr>
<tr>
<td>Model 1 + ST-T area</td>
<td>2.08 (1.36–3.16)**</td>
<td>−546.4**</td>
</tr>
<tr>
<td>Model 2</td>
<td>n/a</td>
<td>−550.6</td>
</tr>
<tr>
<td>Model 2 + ST-T area</td>
<td>1.98 (1.28–3.07)**</td>
<td>−546.1**</td>
</tr>
<tr>
<td>Model 3</td>
<td>n/a</td>
<td>−550.1</td>
</tr>
<tr>
<td>Model 3 + ST-T area</td>
<td>1.95 (1.25–3.03)**</td>
<td>−545.9**</td>
</tr>
<tr>
<td>Summation of ST-T area as a continuous variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 (base)</td>
<td>n/a</td>
<td>−551.9</td>
</tr>
<tr>
<td>Model 1 + ST-T area, per 1 SD higher</td>
<td>0.78 (0.68–0.90)**</td>
<td>−547.7**</td>
</tr>
<tr>
<td>Model 2</td>
<td>n/a</td>
<td>−550.6</td>
</tr>
<tr>
<td>Model 2 + ST-T area, per 1 SD higher</td>
<td>0.80 (0.68–0.93)**</td>
<td>−547.3*</td>
</tr>
<tr>
<td>Model 3</td>
<td>n/a</td>
<td>−550.1</td>
</tr>
<tr>
<td>Model 3 + ST-T area, per 1 SD higher</td>
<td>0.80 (0.69–0.94)**</td>
<td>−547.1*</td>
</tr>
</tbody>
</table>

Adjustment factors for Model 1 included demographic variables (age and sex) + clinical characteristics (BMI, prevalent diabetes mellitus, dyslipidemia, and CVD, and use of antihypertensive medications). Adjustment factors for Model 2 included demographic variables + clinical characteristics + CV-LVH. Adjustment factors for Model 3 included demographic variables + clinical characteristics + CP-LVH. Abbreviations: HR, hazard ratio; CI, confidence interval.

*P < 0.05. **P < 0.01.
populations. In fact, in this study we found that patients with the lowest quartile of ST-T area had a significantly higher proportion of preexisting CVD and LVH criteria as assessed by CV and CP on ECG. However, the evaluation of these ECG abnormalities was performed visually and manually by trained staff and physicians, which may have caused under- or over-detection of the ECG strain. Although previous studies have reported an association between the depression of ST = T segment of ECG assessed by a computerized quantitative method with LVH and cardiovascular events, no report has performed quantitative assessment of ECG strain in recent decades. This is probably due to development and emphasis of other assessments of cardiac structure and function, such as echocardiography and magnetic resonance imaging. However, the high cost of these modalities has prevented them from being universally applied for cardiovascular risk prediction. In contrast, the ST-T area assessed by a computerized quantitative method is easy and relatively inexpensive, and thus may be useful for risk assessment in clinical practice.

Our study design did not allow for elucidation of the detailed mechanisms underlying the linear association between lower ST-T area and risk of cardiovascular events. Abnormalities of the ST-T segment occur in not only the established contexts mentioned earlier, such as LVH and CAD, but also in a range of other conditions, such as respiratory conditions, imbalances of sympathetic and parasympathetic neurohormonal effects, and acid–base respiratory conditions, imbalances of sympathetic and parasympathetic neurohormonal effects, and acid–base imbalances. Therefore, it seems unlikely that the difference in ST-T area could be explained simply by the degree of severity of LVH or CAD.

There are several limitations of this study. First, we did not evaluate the follow-up data of our patients with change in ST-T area. A previous report showed that patients who developed a new ECG strain-T pattern were at greater risk of cardiovascular events than those without. In the future, a study on the association between the change in ST-T area assessed by a computerized quantitative method and cardiovascular events will also be needed. Second, because ours was a relatively high risk population, a future study will be needed to confirm that our results are generalizable to other populations. Finally, the major limitation of this kind of outcome study is the lack of information during follow-up about ECG data and changes in related risk factors, especially clinic BP level. Without repeated assessment during the years of follow-up, we cannot assess the ST-T area or clinic BP change, which probably influenced the outcome. In the future, an outcome study including the date of the change in the ST-T area during follow-up is needed.

In conclusion, lower summation of ST-T area assessed by a computerized quantitative method was associated with an increased risk of CVD incidence in a clinical population of patients with more than one cardiovascular risk factor.

**DISCLOSURES**

Kario has received research grants from Teijin Pharma, Ltd., Novartis Pharma K.K., Takeda Pharmaceutical Co., Ltd., Omron Healthcare Co., Ltd., and Fukuda Denshi Co., Ltd, and honoraria from Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd. Mr Yoneyama and Mr Fukutani are employees of Fukuda Denshi Co., Ltd. The other authors report no conflicts.

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**SUPPLEMENTARY DATA**

Supplementary data are available at American Journal of Hypertension online.


