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Corresponding Author: Dr. Fumitaka Tanaka, M.D.

Corresponding Author's Institution: Iwate Medical University

First Author: Kentaro Tanaka, M.D.

Order of Authors: Kentaro Tanaka, M.D.; Fumitaka Tanaka, M.D.; Toshiyuki Onoda, M.D.; Kozo Tanno, M.D. PhD.; Masaki Ohsawa, M.D.; Kazuyoshi Itai, PhD.; Kiyomi Sakata, M.D.; Shinichi Omama, M.D.; Kuniaki Ogasawara, M.D.; Yasuhiro Ishibashi, M.D.; Toru Kuribayashi, PhD; Akira Okayama, M.D. PhD.; Motoyuki Nakamura, M.D.

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Prognostic Value of Electrocardiographic Left Ventricular Hypertrophy on Cardiovascular Risk in a Non-hypertensive Community-based Population

Kentaro Tanaka, MD[a], Fumitaka Tanaka, MD[a*], Toshiyuki Onoda, MD, PhD[b], Kozo Tanno, MD, PhD[b], Masaki Ohsawa, MD, PhD[b], Kiyomi Sakata, MD, PhD[b], Shinichi Omama, MD[c], Kuniaki Ogasawara, MD[c], Yasuhiro Ishibashi, MD[d], Kazuyoshi Itai, PhD[e], Toru Kuribayashif, PhD[f], Akira Okayama, MD, PhD[g], Motoyuki Nakamura, MD[a]

On behalf of Iwate-Kenco Study Group

Departments of [a]Internal Medicine, [b]Hygiene and Preventive Medicine, [c]Neurosurgery, and [d]Neurology, Iwate Medical University, Morioka, Japan; [e]Department of Nutritional Sciences, Morioka University, Takizawa, Japan; [f]Department of Health and Physical Education, Faculty of Education, Iwate University, Morioka, Japan; and [g]the Research Institute of Strategy for Prevention, Tokyo, Japan.

Running title: Prognostic value of ECG-LVH in Non-hypertensives

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*Corresponding author:

Name: Fumitaka Tanaka, MD

Address: 19-1 Uchimaru, Morioka, Iwate, Japan.

Phone: 81-19-651-5111.

E-mail: ftanaka@iwate-med.ac.jp

Abstract

The appearance of left ventricular hypertrophy on 12-lead electrocardiography (ECG-LVH) has been shown to be a predictor for the incidence of cardiovascular disease (CVD) in hypertensive individuals and the general population, but not in non-hypertensive individuals. A total of 7,603 individuals ≥ 40 years of age who were free of CVD in the general population were followed for the incidence of CVD. ECG-LVH was defined according to criteria of either the Sokolow-Lyon (SL) voltage, Cornell voltage (CV), or Cornell voltage product (CP). During the average 9.7 ± 2.2 years of follow-up, 604 individuals (7.9%) had their first CVD events. In non-hypertensive participants, the hazard ratio (HR) for the incidence of CVD after full adjustment by potential confounders significantly increased in ECG-LVH by any criteria (HR = 1.78 in the SL voltage, 1.68 in the CV, 1.72 in the CP, all $p < 0.020$) compared to no ECG-LVH. Furthermore, in these participants, the net reclassification improvement and integrated discrimination improvement were higher with the model including both any ECG-LVH parameters and the Framingham 10-year risk score (FRS) than the model with the FRS alone (all $P < 0.050$). In conclusion, in the absence of hypertension, ECG-LVH predicts the increased risk of developed CVD and provides additional prognostic value in the CVD risk assessment using established risk factors, suggesting that evaluation of ECG-LVH is useful for

identifying non-hypertensive individuals at an increased risk of CVD.

Keywords: cardiovascular disease, electrocardiography, left ventricular hypertrophy, epidemiology

Introduction

Left ventricular hypertrophy (LVH) has been acknowledged as a cardiac end-organ response to increased pressure or volume load and a key example of target organ damage due to hypertension.[1] For the diagnosis of LVH, 12-lead electrocardiography (ECG) has been widely used as a simple and inexpensive tool in the clinical setting. In addition, the appearance of LVH on ECG has been shown to be a predictor for the incidence of cardiovascular disease (CVD) in hypertensive individuals[2,3] or a general population including hypertensive individuals.[4,5,6]

Hypertension is a major risk factor of CVD; however, CVD can occur in individuals with no hypertension, as more than 50% of patients with coronary heart disease did not have a history of hypertension in international randomized clinical trials.[7] Therefore, the non-hypertensive population also is a target for the prevention of CVD events. Even in the absence of hypertension, ECG-LVH has been reported to be indicated by metabolic factors such as blood glucose and lipid, which are established CVD risk factors.[8] This evidence has prompted the hypothesis that ECG-LVH is a predictive marker for incident CVD in a non-hypertensive population; however, this has not yet been clarified.

This study thus was conducted to examine the utility of ECG-LVH in the prediction of incident CVD in non-hypertensive individuals in a Japanese

community-based sample.

Methods

Study participants

The Iwate-KENCO study cohort is a population-based prospective study conducted in Japanese residents of three districts (Ninohe, Kuji, and Miyako) in northern Iwate prefecture, in the northeast area of Honshu, Japan. Details of this cohort have been provided elsewhere.[9] Participants were recruited from a government-regulated health checkup program conducted between April 2002 and January 2005. Of the original cohort that agreed to participate in this study (n = 26,469), the ECG data recorded for the Ninohe district cohort were analyzed (n = 8,685). A total of 686 participants were excluded from the analysis for the following reasons: < 40 years of age (n = 360), prevalent CVD (myocardial infarction or stroke; n = 282), or missing data at baseline (n = 47). In addition, 396 participants with Wolff-Parkinson-White pattern, paced rhythm, complete left or right bundle branch block, or atrial fibrillation/flutter were excluded. Ultimately, 7,603 subjects (2,549 males and 5,054 females) were included in the analysis.

Outcomes

Patients with newly diagnosed stroke, acute myocardial infarction (AMI), sudden cardiac and unexpected death (SCUD), or heart failure were registered through

December 2012. Registration was initially performed by attending physicians at each hospital. To ensure the complete capture of all registrations, investigators consisting of physicians or trained research nurses visited and reviewed medical charts and/or discharge summaries at referral hospitals within the study area. Dates of death and relocation from the study area were annually or biannually confirmed by investigators who reviewed population-registration sheets at each local government office. People who were known to be alive at the end of the follow-up and those who had moved away from the study area were treated as censored cases.

The endpoint of the study was a composite cardiovascular outcome comprising stroke, AMI, SCUD, and heart failure. Stroke was defined on the basis of symptoms (sudden onset of a focal neurological deficit of 24-h duration) and brain imaging including brain computed tomography or magnetic resonance imaging, and was identified by local stroke registry data. [10] Heart failure was defined according to the Framingham criteria [11] and identified by investigators from medical records at all general hospitals located within the study area. AMI was defined according to the MONItoring of trends and determinants in CArdiovascular Disease (MONICA) criteria [12] and identified from hospital registration survey data. According to the WHO criteria for sudden death, SCUD was defined as sudden unexpected death either within 1 hour of symptom onset (event witnessed), or within 24 hour of having been observed

alive and symptom-free (unwitnessed). [13] SCUD was identified by reviewing death certificates filed at referral hospitals and/or public health centers in the study area and was determined by a committee consisting of cardiologists, neurologists, and epidemiologists. The study was approved by our institutional ethics committee.

Measurements

The body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). Participants completed a self-reported questionnaire to document their medical history, including current medications and lifestyle factors, such as smoking habit. Blood pressure (BP) was measured twice using an automatic digital sphygmomanometer after at least 5 minutes of rest in a sitting position, and the average of these two values was used for the analysis. Blood samples were drawn from an antecubital vein and collected into vacuum tubes containing a serum separator gel. Tubes were stored immediately after sampling in an icebox and transported to the laboratory within 8 hour after collection. The estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equations modified by a Japanese coefficient. [14]

Risk factor definition

Hypertension was defined as either systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, and/or the current use of antihypertensive agents. Diabetes was defined as a random blood glucose level ≥ 200 mg/dl, a fasting blood glucose level ≥ 126 mg/dl, a glycosylated hemoglobin (NGSP equivalent value) ≥ 6.5%, and/or current anti-diabetic therapy. Dyslipidemia was defined as total cholesterol levels ≥ 240 mg/dl, high-density lipoprotein cholesterol (HDL-C) levels < 40 mg/dl, and/or current lipid lowering therapy. A smoking habit was defined as currently smoking. As the classical risk index, the Framingham 10-year risk score (FRS) was calculated on the basis of the categorical values for age, total cholesterol, HDL-C, systolic BP, treatment for hypertension, smoking status, and diabetes status. [15]

ECG

At the baseline examination, the study participants underwent standard supine 12-lead ECG after a minimum 5-minute rest period. Blinded to the participants' clinical data, two trained research nurses assessed the participants' ECG parameters. The Sokolow-Lyon (SL) voltage (SV1 + RV5/V6) and Cornell voltage (CV; SV3 + RaVL) were measured on three consecutive heartbeats. The QRS duration on three consecutive heartbeats was measured from lead II (or lead I, III, or aVF when the measurement of QRS duration was difficult from lead II). The Cornell voltage product

(CP) was calculated as the product of the CV times the QRS duration. From the average of these measured values, ECG-LVH was defined according to the following criteria: the SL voltage ≥ 3.8 mV; the CV > 2.8 mV for men and > 2.0 mV for women; the CP ≥ 244 mV × ms. [16,17]

The intraclass and interclass correlation coefficients for the measured ECG parameters were analyzed with the MedCalc statistics software program (Version 17.7.2, 2017; MedCalc Software, available from https://www.medcalc.org). The intraobserver variation for the measured SL voltage and CP was 0.9947 (0.9920-0.9964) and 0.9693 (0.9544-0.9793) for observer A and 0.9772 (0.9658-0.9848) and 0.9581 (0.9377-0.9718) for observer B, respectively. The interobserver (between observers A and B) variations for the measured SL voltage and CP were 0.9930 (0.9896-0.9953) and 0.9717 (0.9579-0.9809), respectively.

Statistical analyses

The baseline data are presented as the mean ± standard deviation (SD) or percentage. The comparison of continuous variables at baseline was performed by a one-way analysis of variance with the Scheffe's post hoc test among the categories classified according to the presence or absence of hypertension and ECG-LVH by any criteria. The χ^2 test was used for the comparison of categorical variables.

The onset time of the first event was considered the primary endpoint. Age and sex-adjusted survival curves were built using the Kaplan–Meier method and compared using the log-rank test. The multivariate regression analysis was adjusted as follows: model 1: age, sex; model 2: systolic BP, BMI, eGFR, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no) in addition to model 1. A Cox regression analysis was used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals for composite CVD events in order to estimate the effect on the study outcome of the categories classified according to the presence or absence of ECG-LVH and hypertension. Furthermore, to estimate the CVD risk attributed to the presence of ECG-LVH, the population-attributable fraction (PAF) was calculated as Pe × (HR – 1) / HR, in which Pe is the proportion of incident cases in each risk category and HR is the full multiple-adjusted HR.

To determine the improvement in the model discrimination with the inclusion of ECG-LVH parameters into the FRS, we calculated the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). The NRI is centered on reclassification tables constructed separately for individuals with or without an outcome endpoint and quantifies the correct movement: upward for events and downward for nonevents. [18] The IDI represents the mean difference in predicted probabilities between models with and without the new marker. [18] All of the data were

analyzed with the SPSS statistical software program (version 11.0) or R software program (version 3.1.3; available from https://www.r-project.org). $P < 0.05$ was considered to be statistically significant.

Results

Table 1 shows the characteristics of the study participants categorized according to the presence or absence of hypertension and ECG-LVH by any criteria. In non-hypertensive participants with ECG-LVH, compared to those without ECG-LVH, the age, BP, glycosylated hemoglobin and FRS were likely to be higher, whereas the BMI, eGFR, and the prevalence of current smokers were likely to be lower. The prevalence of LVH by the criteria of the SL voltage, CV, and CP in non-hypertensive participants was 1,180 (15.5%), 1,041 (13.7%), and 703 (9.2%), respectively, values that were lower than the prevalence in hypertensive participants (all $p < 0.001$, figure 1).

During the average 9.7 ± 2.2 years of follow-up, 604 individuals (7.9%) had their first CVD events, comprising 439 events of stroke, 94 events of AMI/SCUD, and 71 events of heart failure. The Kaplan–Meier curves showed that the cumulative event-free rate of composite CVD with adjustment for the age and sex was significantly higher in non-hypertensive individuals with ECG-LVH than in those with no ECG-LVH ($p < 0.002$ for all ECG-LVH criteria, Figure 2).

Table 2 shows the relationship between the category classified according to the presence or absence of hypertension and ECG-LVH, and the risk of CVD events after the adjustment for potential confounding factors in the Cox model. In

non-hypertensive participants, the HR for the incidence of CVD after full adjustment significantly increased in ECG-LVH by all criteria (HR = 1.78 in the SL voltage, 1.68 in the CV, 1.72 in the CP, all $p < 0.020$) compared to no ECG-LVH. The PAF to developed stroke was 5.6% and 14.4% from the presence of ECG-LVH under any criteria of the SL voltage, CV, or CP in non-hypertensive and in hypertensive participants, respectively (Table 2).

Table 3 shows the reclassification improvement for the CVD risk prediction model by the inclusion of ECG-LVH parameters into the FRS model. The NRI and IDI were 0.215 and 0.006 for the inclusion of SL voltage, 0.150 and 0.004 for the inclusion of CV, and 0.094 and 0.002 for the inclusion of CP, respectively, all of which were statistically significant (Table 3).

Discussion

The key finding in this study is that even in the absence of hypertension, ECG-LVH predicts the increased risk of incident CVD and improves the accuracy of reclassification in the traditional risk prediction model. This result suggests that applying ECG-LVH criteria in routine clinical practice can help appropriately identify non-hypertensive individuals at an increased risk of CVD.

LVH is acknowledged as a measure of hypertensive organ damage and a predictor for incident CVD in hypertensive individuals.[2,3] Furthermore, in the general population, a relationship between ECG-LVH and the risk of incident CVD has been reported.[4,5,6] This might be mediated in part through hypertensive vascular atherosclerosis. In the health 2000 survey among the Finnish adult population, ECG-LVH in non-hypertensive individuals was not related to the risk of incident CVD, in contrast to that in hypertensive individuals.[2] In a Japanese normotensive cohort, CP-LVH was a predictor for incident stroke, but ECG-LVH by the SL voltage criteria was not.[19] However, in the present non-hypertensive participants, ECG-LVH by any criteria of the SL voltage, CV, and CP were related to the increased risk of CVD. The reasons for this discrepancy are unclear but may involve differences in participants' characteristics and the measured outcomes as the endpoint, as the incidence of stroke was much higher than that of coronary heart disease in the present Japanese

population, in contrast to western populations.

The heart is a key target organ of high BP, and the myocardium responds to increased afterload by developing LVH. However, left ventricular mass is also determined by nonhemodynamic factors, such as genetic factors [20], insulin resistance [21], obesity [22], and alcohol intake [23], independent of BP. It was recently reported that the adipokine resistin was an indicator of left ventricular mass independent of BP. [24] Furthermore, a study targeting non-hypertensive patients by Al-Daydamony et al. showed that the independent indicators of LVH were fasting blood glucose, hemoglobin A_1c, triglyceride, HDL-C, and BMI, but not systolic BP. [8] This study suggested that the relationship between metabolic factors and LVH is mediated through the effect of insulin on the stimulation of myocardial cell growth, the activation of the sympathetic nervous system, or the effect of several inflammatory substances released from adipocytes. However, these mechanisms may not be able to explain our findings sufficiently, as the relationship between ECG-LVH and the incidence of CVD was independent of BMI and the status of dyslipidemia and diabetes in our non-hypertensive subjects. In contrast, a Japanese prospective cohort study has reported that, in a general population without hypertension, LVH as defined by the SL voltage or CP was closely associated with future incidence of hypertension and correlated with increased BP. [25] This study suggests that transient (but frequent)

increases in the BP and cardiac output that precede the development of hypertension cause LVH. This may be a potential mechanism underlying the relationship between ECG-LVH and CVD incidence in the non-hypertensive subjects in our study.

Nearly half of the CVD cases (43.5%) in the present study occurred in participants who were non-hypertensive at baseline (Table 2). In these participants, applying the SL voltage resulted in a 21.5% reclassification improvement for the risk prediction model by the FRS alone (Table 3). Furthermore, 5.6% of the overall CVD incidence was attributable to non-hypertensive subjects under any ECG-LVH criteria (Table 2). The 12-lead ECG, which is a simple and inexpensive test, may therefore be a useful tool for identifying individuals at CVD risk among large populations of non-hypertensive subjects.

The present study had several limitations. First, this study recorded ECG and identified the clinical data and prescribed drugs such as antihypertensive agents only at baseline. The changes in clinical data and the induction of medical treatment during follow-up may have affected the outcomes. However, these information were not identified in the present study. Second, ECG-LVH may not necessarily reflect the presence or absence of true LVH, as the various ECG-LVH criteria have shown low sensitivity but high specificity for the diagnosis of echography-defined LVH. [26] However, this limitation would lead to underestimation in our findings regarding the

ECG-LVH-related risk, since a low sensitivity implies that those diagnosed with no LVH by ECG likely had true LVH. Third, outpatients with no hospital admission were not registered, even if they developed CVD events. This raises the possibility that CVD events without hospital admission, such as mild cases of heart failure, were not captured. Finally, in the present study conducted in a Japanese population, the cumulative incidence of stroke was much higher than that of AMI/SCUD (5.8% vs. 1.2%), consistent with reports from previous Japanese epidemiological studies. [27 28] Therefore, our results may not be simply extrapolated to populations of other races/ethnicities.

In conclusion, in the absence of hypertension, ECG-LVH predicts an increased risk of incident CVD and provides an additional prognostic value to the assessment of CVD risk by established risk factors, suggesting that evaluation of ECG-LVH is useful for identifying non-hypertensive individuals at an increased risk of CVD.

Conflicts of interest:

The authors have no conflicts of interest to declare.

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300 Japan.

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References

1. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011;123:327-334.
2. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, Huikuri HV, Anttila I, Nikus K, Kähönen M, Jula A, Niiranen TJ. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *J Hypertens*. 2016;34:959-966.
3. Edison ES, Yano Y, Hoshide S, Kario K. Association of electrocardiographic left ventricular hypertrophy with incident cardiovascular disease in Japanese older hypertensive patients. *Am J Hypertens*. 2015;28:527-534.
4. Leigh JA, O'Neal WT, Soliman EZ. Electrocardiographic Left Ventricular Hypertrophy as a Predictor of Cardiovascular Disease Independent of Left Ventricular Anatomy in Subjects Aged ≥65 Years. *Am J Cardiol*. 2016;117:1831-1835.
5. Porthan K, Niiranen TJ, Varis J, Kantola I, Karanko H, Kähönen M, Nieminen MS, Salomaa V, Huikuri HV, Jula AM. ECG left ventricular hypertrophy is a stronger risk factor for incident cardiovascular events in women than in men in the general population. *J Hypertens*. 2015;33:1284-1290.
6. Okwuosa TM, Soliman EZ, Lopez F, Williams KA, Alonso A, Ferdinand KC. Left

ventricular hypertrophy and cardiovascular disease risk prediction and reclassification in blacks and whites: the Atherosclerosis Risk in Communities Study. *Am Heart J*. 2015; 169:155-161.

7. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Ellis SG, Lincoff AM, Topol EJ. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290:898-904.
8. Al-Daydamony MM, El-Tahlawi M. What Is the Effect of Metabolic Syndrome without Hypertension on Left Ventricular Hypertrophy? *Echocardiography*. 2016;33:1284-1289.
9. Nakamura M, Onoda T, Itai K, Ohsawa M, Satou K, Sakai T, Segawa T, Sasaki J, Tonari Y, Hiramori K, Okayama A. Association between serum C-reactive protein levels and microalbuminuria: a population-based cross-sectional study in northern Iwate, Japan. *Intern Med* 2004;43:919-925.
10. Omama S, Yoshida Y, Ogawa A, Onoda T, Okayama A. Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset. *J Neurol Neurosurg Psychiatry* 2006;77:1345-1349.
11. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *N Engl J Med*

1971;285:1441-1446.

12. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90:583-612.
13. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, Kron J, Zheng ZJ, Mensah G, McAnulty J. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol* 2004;44:1268-1275.
14. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 2010;56:32-38.
15. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*.2008;117:743-753.
16. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlöf B; LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy

during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA*.2004;292:2343-2349.

17. 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.

18. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*.2008;27:157-172.

19. Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE, Pickering TG, Shimada K, Kario K; 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.

20. Post WS, Larson MG, Myers RH, Galderisi M, Levy D. Heritability of left ventricular mass: The Framingham Heart Study. *Hypertension* 1997;30:1025–1028.

21. Phillips RA, Krakoff LR, Dunaif A, Finegood DT, Gorlin R, Shimabukuro S. Relation among left ventricular mass, insulin resistance, and blood pressure in non-obese subjects. *J Clin Endocrinol Metab* 1998;83:4284–4288.

22. Brady TM. The Role of Obesity in the Development of Left Ventricular Hypertrophy Among Children and Adolescents. *Curr Hypertens Rep*. 2016;18:3.

23. Manolio TA, Levy D, Garrison RJ, Castelli WP, Kannel WB. Relation of alcohol intake to left ventricular mass: the Framingham Study. *J Am Coll Cardiol*. 1991;17:717–721.

24. Norman G, Norton GR, Libhaber CD, Michel F, Majane OH, Millen AM, Sareli P, Woodiwiss AJ. Independent associations between resistin and left ventricular mass and myocardial dysfunction in a community sample with prevalent obesity. *Int J Cardiol* 2015;196:81–87.

25. Takase H, Sugiura T, Murai S, Yamashita S, Ohte N, Dohi Y. Use of Electrocardiography to Predict Future Development of Hypertension in the General Population. *Medicine (Baltimore)*. 2016;95:e3483.

26. Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. *BMJ*. 2007;335:711.

27. Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: the JPHC Study. *Am J Hypertens* 2009;22:273-280.

28. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H,

Tsuryuya K, Iida M, Kiyohara Y. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. *Stroke* 2007;38:2063-2069.

401 **Figure legends**

402 **Figure 1.** Prevalence of electrocardiographic left ventricular hypertrophy at baseline.
403 LVH = left ventricular hypertrophy.

404 **Figure 2.** Kaplan-Meier curves of cumulative cardiovascular events-free rate with
405 adjustment for the age and sex according to the presence or absence of hypertension
406 and ECG-LVH. *Asterisk* denotes $p < 0.001$ for comparison versus the group with no
407 LVH and no hypertension. LVH = left ventricular hypertrophy; CVD = cardiovascular
408 disease.

Table

Table 1. Baseline characteristics according to the presence or absence of ECG-LVH in non-hypertensive and hypertensive participants

	Non-hypertensives			Hypertensives		
	No LVH	LVH	P value	No LVH	LVH	P value
Number (%)	3,988 (81%)	939 (19%)		1,586 (59%)	1,090 (41%)	
Age (years)	60.0 ± 10.6	64.4 ± 9.5	< 0.001	65.8 ± 9.4	67.0 ± 8.9	< 0.001
Sex (men)	35.5%	38.2%	0.113	30.4%	27.0%	0.057
Systolic blood pressure (mmHg)	115.9 ± 12.6	121.5 ± 12.0	< 0.001	144.3 ± 16.1	148.9 ± 17.8	< 0.001
Diastolic blood pressure（mmHg)	70.1 ± 8.3	72.1 ± 8.1	< 0.001	82.6 ± 10.0	84.3 ± 10.6	< 0.001
Body mass index (kg/m^2)	23.4 ± 3.0	23.0 ± 3.1	< 0.001	25.1 ± 3.6	24.6 ± 3.4	0.001
Estimated GFR (ml/min/1.73m^2)	79.0 ± 9.8	77.6 ± 10.0	0.020	74.5 ± 10.5	74.3 ± 11.0	0.608
Hemoglobin A_1c (%)	5.38 ± 0.70	5.44 ± 0.80	0.009	5.51 ± 0.80	5.51 ± 0.80	0.968
Diabetes mellitus	5.1%	6.6%	0.064	9.3%	8.8%	0.732
Total cholesterol (mg/dl)	203.5 ± 33.0	202.8 ± 32.0	0.523	208.1 ± 32.7	209.1 ± 33.5	0.445
High density lipoprotein cholesterol (mg/dl)	60.5 ± 15.1	61.5 ± 14.7	0.075	59.2 ± 14.9	60.5 ± 15.1	0.029
Dyslipidemia	16.6%	15.9%	0.591	21.5%	22.2%	0.668
Antihypertensive medication				40.0%	43.3%	0.129
Current smoker	16.0%	12.8%	0.014	11.5%	9.9%	0.206
Framingham risk score	9.4 ± 4.6	10.8 ± 4.0	< 0.001	15.0 ± 3.7	15.6 ± 3.5	< 0.001

Data are presented as mean ± SD or percentage. LVH are defined as presence of any ECG-LVH criteria. ECG = electrocardiogrphy; LVH = left ventricular hypertrophy; GFR = glomerular filtration rate.

Table

Table 2. Hazard ratios for cardiovascular events in the category classified according to the presence or absence of ECG-LVH and hypertension

	No. of subjects	No. of events	No./1,000 person years	Sex and age adjusted HR and 95% CI		P value	P for trend	Multivariable adjusted HR* and 95% CI		P value	P for trend	PAR**
Sokolow-Lyon voltage												
No hypertension												
without LVH	4,349	203	4.7	1.00				1.00				
with LVH	578	60	11.0	1.73	1.30 - 2.31	0.001		1.78	1.33 - 2.39	< 0.001		4.4%
Hypertension												
without LVH	2,074	248	12.7	2.15	1.77 - 2.60	< 0.001		1.78	1.39 - 2.28	< 0.001		18.0%
with LVH	602	93	16.9	2.52	1.97 - 3.23	< 0.001		2.06	1.50 - 2.81	< 0.001		7.9%
							0.001				< 0.001	
Cornell voltage												
No hypertension												
without LVH	4,511	226	5.1	1.00				1.00				
with LVH	416	37	9.2	1.76	1.24 - 2.51	0.020		1.68	1.18 - 2.39	0.00		2.5%
Hypertension												
without LVH	2,051	258	13.4	2.10	1.75 - 2.52	< 0.001		1.74	1.36 - 2.21	< 0.001		18.1%
with LVH	625	83	14.3	2.47	1.89 - 3.22	< 0.001		1.97	1.42 - 2.72	< 0.001		6.8%
							< 0.001				< 0.001	
Cornell product												
No hypertension												
without LVH	4,679	240	5.2	1.00				1.00				
with LVH	248	23	9.6	1.78	1.16 - 2.74	0.002		1.72	1.12 - 2.65	0.01		1.6%
Hypertension												
without LVH	2,221	268	12.8	1.98	1.65 - 2.36	< 0.001		1.64	1.29 - 2.08	< 0.001		17.3%
with LVH	455	73	17.6	2.94	2.24 - 3.86	0.006		2.37	1.71 - 3.29	0.10		7.0%
							< 0.001				< 0.001	
Any LVH criteria												
No hypertension												
without LVH	3,988	179	4.5	1.00				1.00				
with LVH	939	84	9.3	1.67	1.29 - 2.17	< 0.001		1.68	1.29 - 2.19	< 0.001		5.6%
Hypertension												
without LVH	1,586	183	12.2	2.11	1.71 - 2.60	< 0.001		1.80	1.39 - 2.34	< 0.001		13.5%
with LVH	1,090	158	15.8	2.68	2.15 - 3.34	< 0.001		2.22	1.67 - 2.97	< 0.001		14.4%
							< 0.001				< 0.001	

* Hazard ratio in a multivariate Cox proportional hazards model including age, sex, body mass index, systolic blood pressure, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking status (yes or no). LVH = left ventricular hypertrophy. CI = confidence interval.

**The population-attributable fraction from exposure for each category.

Table

Table 3: Reclassification for the CVD risk prediction model by the inclusion of ECG-LVH parameters into the Framingham 10-year risk score model

	Net reclassification improvement (95% CI)	P value	Integrated discrimination improvement (95% CI)	P value
Framingham 10-year risk score				
+ Sokolow-Lyon voltage	0.215 (0.132 - 0.298)	< 0.001	0.006 (0.003 - 0.008)	< 0.001
+ Cornell voltage	0.150 (0.067 - 0.233)	< 0.001	0.004 (0.002 - 0.006)	0.001
+ Cornell voltage product	0.094 (0.011 - 0.177)	0.026	0.002 (0.000 - 0.003)	0.047

CVD = cardiovascular disease; ECG-LVH = left ventricular hypertrophy on 12-lead electrocardiography; CI = confidence interval.

Figure

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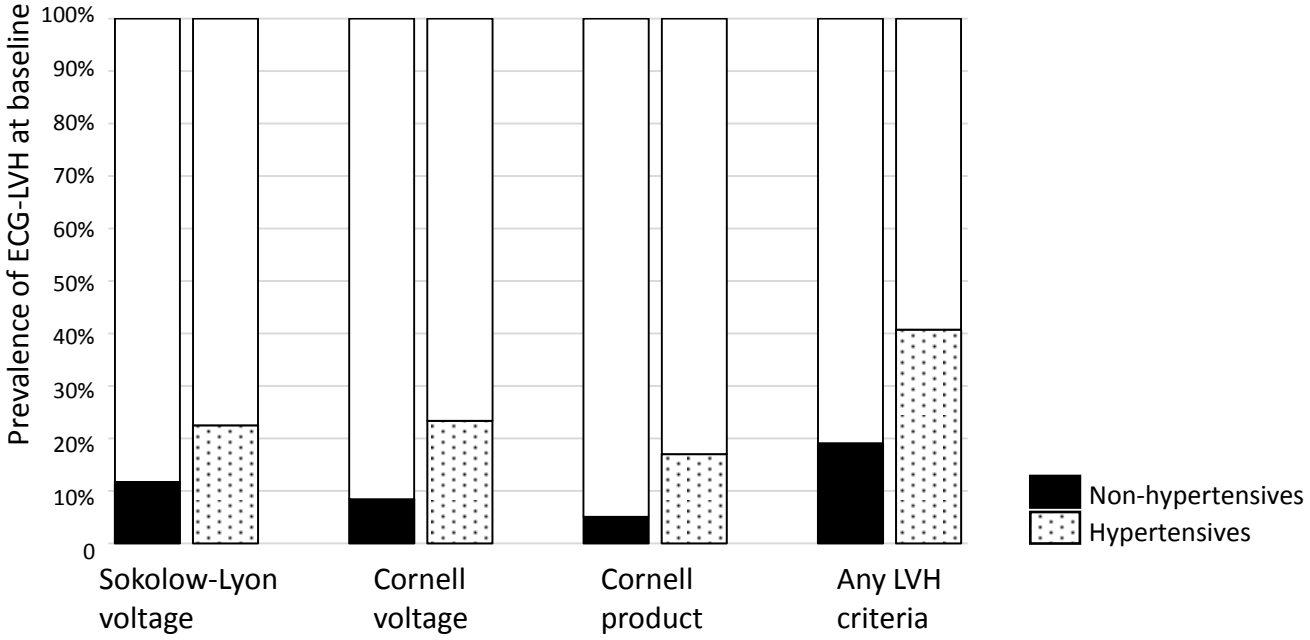
Figure 1



Figure

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Figure 2