

ORIGINAL ARTICLE

Left ventricular hypertrophy by electrocardiogram as a predictor of success in home blood pressure control: HOMED-BP study

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Few studies have focused on the effect of organ damage on achievement of long-term home blood pressure (BP) control. Based on the nationwide home BP-based trial data, we aimed to investigate the factors associated with home BP control, in particular, left ventricular hypertrophy (LVH) using the electrocardiogram in patients who started antihypertensive drug treatment. According to the trial protocol, we defined BP as controlled when systolic home BP reached specified targets (125–134 mm Hg in usual control (UC), $n = 1261$; <125 mm Hg in tight control (TC), $n = 1288$). At baseline, before drug treatment started, the mean Sokolow–Lyon voltage was 2.57 ± 0.87 mV, and the mean Cornell product was 1573 ± 705 mm·ms. The numbers of patients who achieved the target BP level in the UC and TC groups were 892 (70.7%) and 576 (44.7%), respectively. In both the UC and TC groups, systolic home BP at baseline was significantly lower in patients who achieved target levels than in those who did not achieve target levels ($P < 0.0001$). Sokolow–Lyon voltage was significantly lower in patients who achieved target levels than in those who did not ($P \leq 0.0055$). The Cornell product levels in each group were similar ($P \geq 0.12$), although significantly different between patients who did or did not achieve the target level when the UC and TC groups were combined for analysis ($P = 0.031$). Sokolow–Lyon voltage was significantly associated with achievement of home BP control in the multivariable-adjusted model (odds ratio, 1.13; 95% confidence intervals, 1.02–1.26; $P = 0.015$), but Cornell product was not ($P = 0.13$). These results indicate the difficulty of sufficient antihypertensive treatment when untreated patients had target organ damage, that is, LVH diagnosed by Sokolow–Lyon voltage.

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INTRODUCTION

Left ventricular hypertrophy (LVH) is one of the major types of target organ damage caused by hypertension.¹ Electrocardiography is usually the first test performed to assess LVH in clinical practice because electrocardiography is easy to perform, widely available and inexpensive.² Sokolow–Lyon voltage, which represents abnormally high voltage of the QRS complex, has been most commonly used for diagnosing LVH by electrocardiography.³ Recently, the Cornell product, which is based on correlation with left ventricular mass index, has also been commonly used.^{4,5} However, the utility of electrocardiography for the diagnosis of LVH is unclear.^{6,7} Electrocardiography shows similar specificity but lower sensitivity for the diagnosis of LVH compared with echocardiography.⁸ To identify the current conditions and prognoses of patients accurately, we need

to further establish the potential of LVH diagnosis based on electrocardiograms.

The causes of uncontrolled hypertension in clinic blood pressure (BP) include: older age,⁹ higher baseline systolic BP,¹⁰ the presence of LVH and obesity (body mass index > 30 kg m⁻²).¹¹ Although self-measured home BP has higher predictive power than conventional clinic BP measurements,^{12,13} few studies have focused on factors for achievement of long-term home BP control.¹⁴ Izzo *et al.*¹⁵ reported that initial left ventricular mass is a significant predictor of uncontrolled clinic BP. However, the association between LVH and long-term home BP control is not clear. Based on the multicenter Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) trial,^{13,16,17} we aimed to investigate determinant factors for achievement of target home BP,

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and in particular the impact of LVH, determined by electrocardiography, as well as other organ damage in patients with mild-to-moderate hypertension who started antihypertensive treatment.

METHODS

Study population

The HOMED-BP study was a multicenter clinical trial with PROBE (prospective, randomized, open-label, blinded end point evaluation)¹⁸ design. The HOMED-BP protocol complies with the Helsinki declaration for the investigation of human subjects¹⁹ and is registered with the UMIN Clinical Trial Registry, number C00000137 (<http://www.umin.ac.jp/ctr>). The institutional review board of the Tohoku University Graduate School of Medicine approved the study protocol, and all study participants gave written informed consent.

In the HOMED-BP study,^{13,16} patients with mild-to-moderate hypertension with a minimum age of 40 years were recruited from 457 general practices throughout Japan. Treatment-naïve patients as well as previously treated patients whose antihypertensive drug treatment could be discontinued for ≥ 2 weeks qualified for enrollment. Off treatment, eligible patients had a home BP of 135–179 mm Hg systolic or 85–119 mm Hg diastolic. Randomization was based on a computerized random number function with a minimization algorithm running on a central server at Tohoku University (Sendai, Japan), considering sex, age and systolic and diastolic home BP. In a 2 \times 3 design, eligible patients were randomized to usual control (UC; ranging from 125 to 134 mm Hg systolic and from 80 to 84 mm Hg diastolic) *vs.* tight control (TC; < 125 mm Hg systolic and 80 mm Hg diastolic) of home BP and to the initiation of antihypertensive drug treatment with calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockade. The first patient was randomized on 6 June 2001, and the last patient on 7 October 2009. Moreover, the HOMED-BP Management Committee decided to continue the operation of the HOMED-BP system until the end of 2012; therefore, we collected BP data and ascertained outcomes until 31 December 2012.^{13,17}

From the 3518 randomized patients, 969 were excluded from analysis because home BP at follow-up was not available ($n = 371$) or because information on Sokolow–Lyon voltage or Cornell product was missing ($n = 628$). Therefore, the number of patients statistically analyzed totaled 2549 (1261 in UC and 1288 in TC). The clinical characteristics of the 969 excluded patients are shown in Supplementary Table S1. In the present analysis, we defined achievement of BP control as systolic BP that reached the target range (125–134 mm Hg in UC, < 125 mm Hg in TC) because systolic pressure is an overriding risk factor in middle-aged and older people.^{20,21}

Data collection

At each visit, after the patients had rested in the sitting position for ≥ 2 min, practitioners obtained two consecutive measurements of BP and heart rate

using the validated²² oscillometric OMRON HEM-907IT device (Omron Healthcare, Kyoto, Japan). The clinic BP was the average of these two readings. Patients received spoken and written instructions on BP self-measurement and the utilization of the validated²³ oscillometric HEM-747IC-N monitors (Omron Healthcare). The monitor stores up to 350 BP and heart rate readings in its memory. The home BP used for determining eligibility and treatment adjustments at each visit was the average of the morning readings available over 5 days immediately preceding the visit. Patients were asked to measure BP once every morning after ≥ 2 min of rest in the sitting position during the whole study period. They had to obtain these measurements within 1 h of awakening, before breakfast and before taking antihypertensive medication.

At each visit, the central server received the home and clinic BP data from local practices and immediately displayed them on the screen of the local computer along with advice for treatment adjustment based on a computerized algorithm, as described elsewhere.^{13,16} Doctors were allowed to modify the treatment advice throughout the follow-up period according to the condition of the patients, drug adoption in each clinic or their judgement.

According to the study protocol,¹⁶ we obtained information, including physical measurements, medical records, electrocardiogram measurements and laboratory test data from each practice.

Definitions

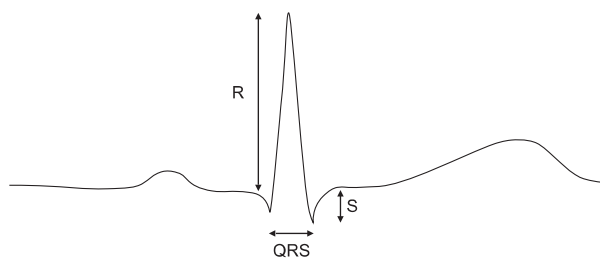
Body mass index was defined as body weight in kilograms divided by height in meters squared. We calculated the Sokolow–Lyon voltage ($RV_5 + SV_1$; mV)³ and Cornell product ($(RaV_L + SV_3) \times$ QRS duration in men; $(RaV_L + SV_3 + 6) \times$ QRS duration in women; mm·ms)^{4,5} as electrocardiographic diagnostic criteria (Figure 1).²⁴ Estimated glomerular filtration rate (eGFR) was calculated with the Japanese Equation²⁵: Estimated glomerular filtration rate ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) = $194 \times$ serum creatinine^{-1.094} \times age^{-0.287} ($\times 0.739$, for women). We used the defined daily dose index to standardize the hypertensive drug uses.²⁶ The defined daily dose is defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology and is the assumed average maintenance dose per day for a drug used for its main indication in adults.²⁶

Statistical analysis

For database management and statistical analysis, we used the SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as an alpha level < 0.05 in two-sided tests. All data are expressed as the mean \pm s.d. unless otherwise stated.

Categorical variables were compared using the χ^2 test, and Student's *t*-tests or Wilcoxon tests were applied to continuous variables appropriately according to its distribution normality. As electrocardiographic diagnostic criteria, we compared Sokolow–Lyon voltage *vs.* Cornell product with systolic home BP in relation to the correlation coefficients. Logistic regression models were then used to estimate the multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between electrocardiographic indices and management of hypertension. The models were adjusted for baseline home BP, sex, age, smoking, drinking, previous cardiovascular disease, duration of the state of hypertension, defined daily dose and the following laboratory tests that can represent each organ relevant to its cardiovascular risks: hemoglobin concentration, white blood cell counts, platelet counts, serum γ -glutamyltransferase level, estimated glomerular filtration rate, total cholesterol level, plasma glucose level, and proteinuria. Target home BP, UC *vs.* TC, was further adjusted among all patients. Missing values were complemented by Multiple Imputation using a Markov single-chain Monte Carlo method.²⁷ The imputation model included all covariables entered in the logistic regression model. Sensitivity analyses were conducted to ascertain that imputations did not weaken or inflate the reported associations.

Based on Sokolow–Lyon voltage, we also divided patients according to the quartile points of the population (< 1.93 , 1.93–2.50, 2.50–3.09 and ≥ 3.09 mV) as well as the electrocardiographic diagnostic criteria of LVH (≥ 3.50 mV) and computed ORs and CIs of achievement of home BP level in a higher category. Furthermore, we analyzed logistic regression models dividing patients between UC and TC. ORs and CIs of patients' achieving hypertension management with the threshold of 135 mm Hg in systolic pressure, which has been widely



$$\text{Sokolow-Lyon voltage (mV)} = RV_{5(6)} + SV_1$$

$$\text{Cornell product (mm} \times \text{ms)} = (RaV_L + SV_3) \times \text{QRS duration (men)}$$

$$(RaV_L + SV_3 + 6) \times \text{QRS duration (women)}$$

Figure 1 Criteria of left ventricular hypertrophy (LVH) based on the electrocardiogram. LVH was defined as follows: Sokolow–Lyon voltage ≥ 3.50 mV, Cornell product ≥ 2440 mm·ms.²⁴

Table 1 Baseline characteristics

	Total (n = 2549)	No. of missing	Usual control (n = 1261)		Tight control (n = 1288)	
			Achieved (n = 892)	Not achieved (n = 369)	Achieved (n = 576)	Not achieved (n = 712)
Women, n (%)	1302 (51.2)	0	468 (52.5)	173 (46.9)	314 (54.5)	347 (48.7)*
Age, years	60.0 ± 9.9	0	59.9 ± 9.5	60.9 ± 10.2	58.7 ± 9.4	60.8 ± 10.6‡
Body mass index, kg m ⁻²	24.4 ± 3.4	21	24.4 ± 3.5	24.3 ± 3.4	24.5 ± 3.2	24.3 ± 3.5
Current smoker, n (%)	534 (20.9)	0	164 (18.4)	94 (25.5)†	126 (21.9)	150 (21.1)
Current habitual drinking, n (%)	1242 (48.7)	0	415 (46.5)	188 (50.0)	282 (49.0)	357 (50.1)
Previous cardiovascular disease, n (%)	80 (3.1)	0	21 (2.4)	10 (2.7)	21 (3.6)	28 (3.9)
Duration of state of hypertension (years)	4.3 ± 6.6	14	4.2 ± 6.3	4.7 ± 6.7	4.4 ± 7.1	4.0 ± 6.3
<i>Laboratory blood test</i>						
Hemoglobin, g dl ⁻¹	14.1 ± 1.4	13	14.2 ± 1.4	14.1 ± 1.4	14.1 ± 1.4	14.1 ± 1.5
White blood cells, 10 ³ μl ⁻¹	5.95 ± 1.57	21	5.86 ± 1.51	6.09 ± 1.64*	5.94 ± 1.50	6.03 ± 1.65
Platelets, 10 ⁴ μl ⁻¹	23.7 ± 5.7	42	23.5 ± 5.5	23.7 ± 6.5	23.9 ± 5.6	23.7 ± 5.8
γ-glutamyltransferase, IU l ⁻¹	29 (11–138)	41	29 (12–137)	32 (12–179)*	28 (11–133)	29 (11–128)
AST, IU l ⁻¹	23 (15–45)	14	23 (15–44)	23 (15–47)	22 (15–42)	22 (15–41)
ALT, IU l ⁻¹	21 (11–57)	8	20 (11–55)	21 (11–52)	21 (11–57)	20 (10–52)
Urea nitrogen, mg dl ⁻¹	14.4 (9.6–21.6)	447	14.7 (9.7–21.7)	15.0 (9.0–21.9)	14.0 (9.5–21.0)	14.6 (9.8–22.0)†
eGFR, ml min ⁻¹ 1.73 m ⁻²	72.8 ± 17.3	22	73.2 ± 17.0	72.9 ± 18.6	74.3 ± 16.9	71.2 ± 17.1†
Creatinine, mg dl ⁻¹	0.75 (0.50–1.10)	22	0.74 (0.50–1.10)	0.78 (0.50–1.12)	0.70 (0.50–1.10)	0.80 (0.50–1.11)‡
Uric acid, mg dl ⁻¹	5.40 ± 1.41	55	5.40 ± 1.40	5.42 ± 1.40	5.31 ± 1.41	5.46 ± 1.42
Sodium, mEq mol ⁻¹	141.4 ± 2.2	127	141.5 ± 2.2	141.3 ± 2.4	141.4 ± 2.1	141.4 ± 2.2
Potassium, mEq mol ⁻¹	4.1 (3.6–4.9)	125	4.1 (3.6–4.9)	4.2 (3.6–4.9)	4.1 (3.6–4.9)	4.1 (3.5–5.0)
Chloride, mEq mol ⁻¹	103.4 ± 2.6	136	103.3 ± 2.5	103.2 ± 2.7	103.6 ± 2.4	103.3 ± 2.8
Total cholesterol, mg dl ⁻¹	209 (157–269)	13	208 (157–269)	209 (151–268)	210 (159–273)	207 (157–268)
Plasma glucose, mg dl ⁻¹	104.9 ± 30.6	106	105.0 ± 29.9	106.3 ± 33.2	103.8 ± 29.0	105.0 ± 31.3
Proteinuria, n (%)	405 (16.7)	117	128 (15.1)	74 (21.2)†	88 (15.9)	115 (16.9)
<i>Indexes of electrocardiogram</i>						
Sokolow–Lyon voltage, mV	2.57 ± 0.87	0	2.53 ± 0.84	2.68 ± 0.88†	2.48 ± 0.84	2.63 ± 0.90†
Cornell product, mm·ms	1573 ± 705	0	1529 ± 700	1595 ± 658	1576 ± 676	1615 ± 752

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate. Values are shown as number of patients (percentage) or mean ± s.d. for continuous variables while γ-glutamyltransferase, AST, ALT, blood urea nitrogen, creatinine, potassium and total cholesterol are shown as median (5–95% confidence intervals). Proteinuria that was diagnosed in the protein reading on dip-stick testing was ≥ 1+. Formulae of the indexes of electrocardiogram are shown in Figure 1. Usual control: 125–134 mm Hg in systolic home blood pressure; Tight control: < 125 mm Hg in systolic home blood pressure. Significance of the difference between the achieved and not achieved groups: **P* < 0.05; †*P* < 0.01, and ‡*P* < 0.001.

accepted as definition of hypertension for home BP,^{28,29} were also analyzed. In the sensitivity analysis, diabetes mellitus was defined by fasting plasma glucose ≥ 7.0 mmol l⁻¹ (≥ 126 mg dl⁻¹), hemoglobin A1c ≥ 6.5% or treatment with antidiabetic agents.^{13,17} Finally, we calculated the ORs of clinic BP instead of home BP and analyzed the association between Sokolow–Lyon voltage and the management of hypertension based on clinic BP.

RESULTS

The baseline characteristics of the study population are shown in Table 1. The mean age was 60.0 ± 9.9 years, and 1302 (51.2%) patients were women. The numbers of patients who achieved the target BP in UC and TC were 892 (70.7%) and 576 (44.7%), respectively. In both the UC and TC groups, systolic home BP at baseline was significantly lower in patients who achieved target BP than in those who did not (Table 2; 150.3 ± 12.5 mm Hg vs. 155.1 ± 12.5 mm Hg in UC, *P* > 0.0001; 149.4 ± 12.0 vs. 153.5 ± 12.4 mm Hg in TC, *P* > 0.0001), whereas diastolic home BPs did not differ (*P* ≥ 0.074). Clinic BP values at baseline were similar regardless of the achievement of home BP control (*P* > 0.13), except for diastolic clinic BP among TC (*P* = 0.0012).

The Sokolow–Lyon voltage at baseline averaged 2.57 ± 0.87 mV, and the Cornell product was 1573 ± 705 mm·ms. Both LVH indexes were significantly correlated with each other (*r* = 0.16, *P* > 0.0001),

and 532 patients (20.8%) had LVH based on Sokolow–Lyon criteria and/or Cornell product. However, the number of patients with LVH diagnosed by electrocardiogram was 353 (13.9%) when based on Sokolow–Lyon voltage and 251 (9.9%) when based on Cornell product, and only 72 patients fulfilled both diagnostic criteria (2.8%; κ = 0.14).

The Sokolow–Lyon voltage was significantly higher in patients without achievement of the target BP than those whose BP did not (Table 1; *P* ≤ 0.0055). This difference was also observed when the UC and TC groups were combined (2.65 ± 0.89 vs. 2.51 ± 0.84 mV, *P* = 0.0001). Although the Cornell product level was significantly different when both groups were combined (1608 ± 721 vs. 1547 ± 691 mm·ms, *P* = 0.031), statistical significance was not observed in either the UC or the TC group (*P* ≥ 0.12). The correlation between systolic home BP and Sokolow–Lyon voltage was also significant (*r* = 0.16, *P* > 0.0001) and tended to be stronger than that between systolic home BP and Cornell product (*r* = 0.11, *P* > 0.0001).

Based on the aforementioned results, we used Sokolow–Lyon voltage as the representative index of LVH. The multivariable-adjusted ORs of failure to achieve target BP when Sokolow–Lyon voltage was treated as the continuous variable are shown in Table 3. After the adjustment of baseline systolic home BP, which was significantly associated with the achievement of target BP (OR, 1.26;

Table 2 Blood pressure level and defined daily dose

	Usual control (n = 1261)			Tight control (n = 1288)	
	Total (n = 2579)	Achieved (n = 892)	Non-achieved (n = 369)	Achieved (n = 576)	Non-achieved (n = 712)
<i>Home measurements, mm Hg</i>					
Baseline					
Systolic blood pressure	151.7 ± 12.5	150.3 ± 12.5	155.1 ± 12.5 [†]	149.4 ± 12.0	153.5 ± 12.4 [†]
Diastolic blood pressure	89.8 ± 10.1	89.6 ± 1.0	89.8 ± 11.4	90.5 ± 9.1	89.5 ± 10.4
On treatment					
Systolic blood pressure	129.1 ± 13.0	123.4 ± 7.2	144.9 ± 9.3 [†]	117.5 ± 5.5	137.3 ± 11.2 [†]
Diastolic blood pressure	76.0 ± 9.5	73.9 ± 7.8	81.9 ± 11.0 [†]	71.8 ± 6.9	79.1 ± 10.0 [†]
<i>Clinic measurements, mm Hg</i>					
Baseline					
Systolic blood pressure	154.5 ± 17.6	154.1 ± 17.9	155.8 ± 17.0	154.0 ± 17.5	154.7 ± 17.5
Diastolic blood pressure	90.2 ± 12.3	90.3 ± 12.1	89.6 ± 12.9	91.6 ± 12.0	89.3 ± 12.5*
On treatment					
Systolic blood pressure	129.5 ± 17.0	127.2 ± 15.0	136.9 ± 19.0 [†]	123.8 ± 15.4	133.3 ± 17.4 [†]
Diastolic blood pressure	74.1 ± 11.7	73.1 ± 10.5	77.1 ± 14.0 [†]	72.1 ± 10.7	75.5 ± 12.3 [†]
Defined daily dose, U	1.80 ± 1.18	1.67 ± 1.09	1.87 ± 1.19*	1.74 ± 1.17	1.92 ± 1.27*

Values are shown as mean ± s.d. Usual control: 125–134 mm Hg in systolic home blood pressure; Tight control: <125 mm Hg in systolic home blood pressure. On-treatment clinic blood pressure and defined daily dose were unavailable from 48 and 9 patients, respectively. Significance of the difference between achieved and not achieved groups: **P*<0.01, †*P*<0.0001.

Table 3 Logistic regression analysis for the non-achievement of blood pressure control when systolic home blood pressure is included in the model

Variables (vs. or per increment)	Odds ratio	95% Confidence intervals	P-value
Sokolow–Lyon voltage (1 mV)	1.13	(1.02–1.26)	0.015
Systolic home blood pressure (10 mm Hg)	1.26	(1.17–1.36)	<0.0001
Women (vs. men)	0.75	(0.59–0.95)	0.019
Age (5 years)	1.07	(1.02–1.12)	0.0083
Body mass index (1 kg m ⁻²)	0.99	(0.96–1.02)	0.43
Current smoker	1.01	(0.81–1.27)	0.90
Current habitual drinking	1.01	(0.82–1.23)	0.94
Previous cardiovascular disease	1.01	(0.62–1.63)	0.97
Duration of state of hypertension (years)	1.00	(0.98–1.01)	0.48
<i>Laboratory blood test</i>			
Hemoglobin (1 mg dl ⁻¹)	0.90	(0.84–0.97)	0.0084
White blood cells (1 × 10 ³ μl ⁻¹)	1.07	(1.01–1.14)	0.028
Platelets (1 × 10 ⁴ μl ⁻¹)	1.00	(0.98–1.02)	0.96
γ-Glutamyltransferase (1 s.d.)	1.06	(0.96–1.17)	0.27
eGFR (10 ml min ⁻¹ 1.73 m ⁻²)	0.95	(0.90–1.00)	0.071
Total cholesterol (10 mg dl ⁻¹)	0.99	(0.96–1.01)	0.30
Plasma glucose (10 mg dl ⁻¹)	1.01	(0.98–1.04)	0.69
Proteinuria	1.31	(0.96–1.79)	0.086
Defined daily dose (U)	1.04	(0.97–1.13)	0.29
Tight control (vs. usual control)	3.17	(2.67–3.76)	<0.0001

Abbreviation: eGFR, estimated glomerular filtration rate. We calculated the multivariate adjusted odds ratios and 95% confidence intervals for the association between electrocardiographic index and non-achievement of target blood pressure level in the usual and tight control group by logistic regression models. All variables shown in the table were entered into the model. γ-Glutamyltransferase is shown by logarithmic transformation.

95% CI, 1.17–1.36; *P*<0.0001), a 1-mV increment of Sokolow–Lyon voltage resulted in a 13% increase in patients who did not achieve target BP (*P*=0.015). The ORs of failure to achieve target BP were similar, 1.14 (95% CI, 0.98–1.33; *P*=0.089) and 1.13 (95% CI, 0.98–1.30; *P*=0.084), when patients were divided into UC and TC,

respectively. When we set the same criteria of hypertension in home systolic BP, 135 mm Hg to TC as well as UC, the risk of being hypertensive during the follow-up period was marginal among all patients (OR per 1-mV increment, 1.10; 95% CI, 0.99–1.22; *P*=0.083).

Figure 2 shows the multivariate ORs when we set four different Sokolow–Lyon voltage criteria, such as 3.50 mV (as the LVH definition), 3.09 mV (upper quartile of patients), 2.50 mV (median) and 1.93 mV (lower quartile). None of the thresholds had a significant impact on achievement of target BP regardless of total, UC and TC (*P*≥0.063), except in patients with Sokolow–Lyon voltage ≥2.50 mV (Figure 2; *P*=0.043).

When we calculated ORs of the diabetes mellitus variable (based on plasma glucose level), diabetes mellitus was not found to be significantly associated with home BP control as shown in Supplementary Table S2 (OR, 1.06; 95% CI, 0.83–1.36).

Clinic BP was not significantly associated with the achievement of home BP control (*P*=0.56), whereas Sokolow–Lyon voltage was still a significant predictor of successful home BP control (OR, 1.19; 95% CI, 1.08–1.32; *P*=0.0005) (Supplementary Table S3). The multivariate-adjusted ORs when UC and TC patient groups were separately analyzed were 1.19 among UC (95% CI 1.03–1.38; *P*=0.022) and 1.19 among TC (95% CI 1.04–1.37; *P*=0.013). In the dichotomous analysis, when systolic clinic BP was included in the models, patients with Sokolow–Lyon voltage ≥3.09, ≥2.50 and ≥1.93 mV did not achieve home BP control level significantly more often than the other corresponding patients (Supplementary Figure S1; *P*<0.006). When we focused on the achievement of clinic systolic BP control level (<140 mm Hg systolic), Sokolow–Lyon voltage was not significantly associated with clinic BP control (*P*=0.94), whereas high plasma glucose was a significant predictor for worse control of clinic BP (*P*=0.0078; Supplementary Table S4). Cornell product was significantly but marginally associated with achievement of home BP control when systolic clinic BP was adjusted in the multiple regression model (OR, 1.14; 95% CI, 1.01–1.29; *P*=0.035), although it was not significant when systolic home BP was used for the adjustment (*P*=0.13). Further sensitivity analysis based on 2343 selected

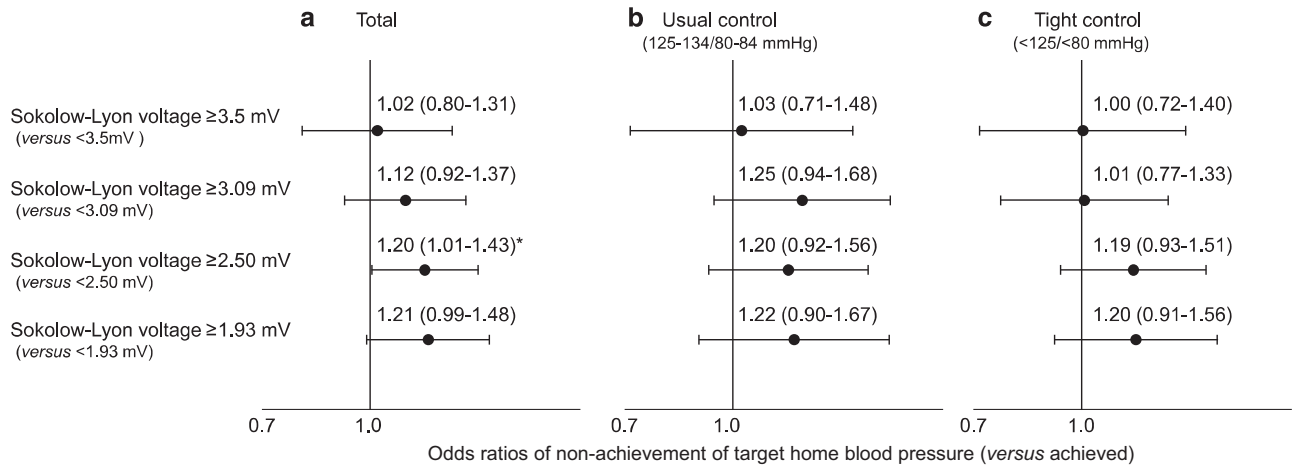


Figure 2 Odds ratios (ORs) of Sokolow–Lyon voltages for patients who fail to achieve target blood pressure (vs. patients who do achieve target) among (a) total, (b) usual control and (c) tight control groups when systolic home blood pressure was included in the models. Values are shown as ORs (95% confidence intervals). The models were adjusted for sex, age, smoking, alcohol consumption, previous cardiovascular disease, duration of state of hypertension, defined daily dose and the following laboratory test information: hemoglobin concentration, white blood cell counts, platelet counts, serum γ -glutamyltransferase level, eGFR, total cholesterol level, plasma glucose level, and proteinuria. Target home blood pressure, UC vs. TC, was further adjusted among all patients. None of the thresholds had a significant impact on the achievement of target blood pressure regardless of total, UC and TC ($P \geq 0.063$) except in patients with Sokolow–Lyon voltage ≥ 2.50 mV ($P = 0.043$). Mark indicates significance of ORs: * $P < 0.05$.

patients who had full baseline information, without applying multiple imputation, provided confirmatory results.

DISCUSSION

In the multivariable-adjusted model including baseline home BP, we found that (1) Sokolow–Lyon voltage was significantly higher in patients with a failure to achieve control group regardless of UC or TC grouping ($P \leq 0.0055$), whereas the Cornell product was not ($P \geq 0.12$), and (2) the achievement rate of BP control level among patients with antihypertensive treatment was 13% lower for each 1-mV increment of Sokolow–Lyon voltage at baseline. To our knowledge, this is the first study to indicate the difficulty of determining sufficient antihypertensive treatment based on self-measured home BP when untreated patients had target organ damage, that is, LVH diagnosed by Sokolow–Lyon voltage in electrocardiography.

The discrepancy between Sokolow–Lyon voltage and Cornell product on the achievement of BP control can be explained by the different measuring targets of each method (Figure 1). Sokolow–Lyon voltage represents the electric potential in the horizontal plane, which mainly reflects left ventricle wall thickness.^{3,30} Additionally, a previous study demonstrated that concentric hypertrophy was the most common type of left ventricular disorder in patients with resistant hypertension.³¹ Pressure overloaded left ventricle resulting in concentric hypertrophy is indicated by the increased ratio of left ventricle wall thickness to internal radius.³² The Cornell product is associated with volume overload,^{4,5} as the product of wave voltages and QRS duration can identify the left ventricular mass index more accurately than each component alone.⁵ In contrast to pressure overload, such volume-overloaded ventricles showed eccentric hypertrophy with an increased diameter but a normal ratio of left ventricle wall thickness to internal radius.³² The ratio of left ventricle wall thickness to internal radius was normal in patients with left ventricle volume overload but was increased in patients with pressure overload.³³ These findings suggest that pressure overload leads to thickening of the left ventricular wall in patients with hypertension. Sokolow–Lyon voltage at baseline may therefore reflect the difficulty of BP control by

antihypertensive drug treatment. Sokolow–Lyon voltage and Cornell product are strongly associated with pressure overload and volume overload, respectively; therefore, Sokolow–Lyon voltage is a better method for identifying LVH caused by hypertension.

Non-invasive electrocardiography is commonly used to screen for cardiac dysfunction because the test can be conducted more safely, at lower cost and with shorter duration than echocardiography.^{34,35} However, the sensitivity of the electrocardiogram for predicting cardiovascular events was too low to be practical as a screening tool.⁶ Sensitivity and specificity for diagnosing LVH by echocardiography vs. electrocardiography are 93% and 95% vs. 21% and 95%, respectively.⁸ False-positive tests are likely to lead to harm through unnecessary invasive procedures, overtreatment and misdiagnosis.⁷ Our findings explore the novel usefulness of electrocardiography to predict achievement of antihypertensive drug management, which may be one step toward avoiding target organ damage in patients with hypertension.

Hemoglobin concentration and white blood cell counts were also significant predictors of uncontrolled home BP. Shankar *et al.*³⁶ reported that white blood cell count was related to incident hypertension, and this can explain the effect of elevated white blood cell count on hypertension, which involves chronic low-grade inflammation.³⁷ However, few studies demonstrated the positive association between BP control and white blood cell counts as well as hemoglobin concentration. Although C-reactive protein information was unavailable, our study would be the first to indicate that high white blood cell counts or hemoglobin are related to uncontrolled BP.

Plasma glucose level and diabetes mellitus were not associated with home BP control, which was different from the results of a previous study by Izzo *et al.*¹⁵ In the present study, glucose level was associated with worse clinic BP control during treatment (Supplementary Table S4); however, we emphasize that the HOMED-BP study was designed with the aim to home BP control. Clinic BP was treated as additional information, and the central server did not use the clinic BP for decision-making on antihypertensive medication. The difference in the prevalence of diabetes (15% in the present study vs. 5% in the

study by Izzo et al.¹⁵) might also contribute to this discrepancy between studies.

The present findings must be interpreted with potential limitations. First, the current population consisted of patients with mild-to-moderate essential hypertension with comparably low risk, and generalizability of the current findings is not guaranteed. Second, although the prevalence of LVH in this study population was reported to be 16–34%,^{24,38} the kappa coefficient of diagnosing LVH by Sokolow–Lyon voltage and Cornell product was only 0.14. However, similar to the case in the present study, in the Japanese nationwide surveillance study, 15.5% of 747 patients had LVH diagnosed by electrocardiogram, while 10.8% were diagnosed using Sokolow–Lyon voltage and 5.4% by Cornell product with little overlap.²⁴ Third, we failed to determine the threshold of LVH indices by the logistic regression model with home BP as covariate. Although the continuous trend for Sokolow–Lyon voltage was significant, we cannot apply our findings directly to establish a threshold for suggesting resistant hypertension in the screening process. Finally, we could not assess the drug differences among groups receiving calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockades because the number of patients was too small to compare the drug contribution to LVH for home BP control during follow-up. We adjusted the drug potency, represented by the defined daily dose, and the final on-treatment home BP level was similar among three drug classes in the HOMED-BP patients¹³; however, regressive effects of renin–angiotensin system inhibitors on LVH might affect home BP control.

In conclusion, the present study demonstrated that elevated Sokolow–Lyon voltage was an independent predictor for BP control failure even when systolic home BP was included in the multivariable-adjusted model. Although we failed to determine the threshold of LVH indices for adequate BP control, the importance of electrocardiographic measurement for patients with mild-to-moderate hypertension was demonstrated. Accurate electrocardiographic measurement in conjunction with home BP measurement is useful for long-term home BP control by antihypertensive drug treatment.

CONFLICT OF INTEREST

T Hanazawa is a full-time employee of GlaxoSmithKline. T Hanazawa is also a graduate student at Tohoku University and has contributed to this study independently of GlaxoSmithKline. Omron Healthcare gave research support to Y Imai. The other authors declare no conflict of interest.

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