

# Automatically assessed P-wave predicts cardiac events independently of left atrial enlargement in patients with cardiovascular risks: The Japan Morning Surge-Home Blood Pressure Study

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## Abstract

A prolonged P-wave in electrocardiography (ECG) reflects atrial remodeling and predicts the development of atrial fibrillation (AF). The authors enrolled 810 subjects in the Japan Morning Surge Home Blood Pressure (J-HOP) study who had  $\geq 1$  cardiovascular (CV) risk factor. The duration of P-wave was automatically analyzed by standard 12-lead electrocardiogram. Left atrial (LA) enlargement and left ventricular hypertrophy (LVH) were measured on echocardiography. The primary end points were fatal/nonfatal cardiac events: myocardial infarction, sudden death, and hospitalization for heart failure. The maximum P-wave duration (Pmax) from the 12 leads was selected for analysis. The authors compared four prolonged P-wave cutoffs (Pmax = 120, 130, 140, 150 ms) and cardiac events. LA diameter and left ventricular mass index (LVMI) were significantly associated with Pmax ( $r = 0.08$ ,  $P = .02$  and  $r = 0.17$ ,  $P < .001$ , respectively). When the cutoff level was Pmax 120 or 130 ms, prolonged P-wave was not associated with cardiac events ( $P = .45$  and  $P = .10$ ), but when a prolonged P-wave was defined as Pmax  $\geq 140$  ms ( $n = 50$ ) or Pmax  $\geq 150$  ms ( $n = 19$ ), the patients in those groups had significantly higher incidence of cardiac events than others ( $P < .001$  and  $P = .03$ ). A Cox proportional hazards model including age, gender, body mass index, smoking, regular drinker, hypertension, dyslipidemia, diabetes, office systolic blood pressure, heart rate, LA enlargement, and LVH revealed that prolonged P-wave defined as Pmax  $\geq 140$  ms was independently associated with cardiac events (hazard ratio: 4.23; 95% confidence interval: 1.30–13.77;  $P = .02$ ). In conclusion, the automatically assessed prolonged P-wave was associated with cardiac events independently of LA enlargement and LVH in Japanese patients with CV risks.

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## 1 | INTRODUCTION

Hypertension, obesity, and diabetes increase atrial electrophysiological and morphological remodeling by ischemic, metabolic, and inflammatory factors.<sup>1,2</sup> Chronic atrial stress under those conditions promotes atrial myocyte hypertrophy, fibrosis, and gap junction modulation, providing a mechanism for pro-arrhythmic mechano-electric feedback.<sup>1</sup> Prolonged P-wave on 12-lead electrocardiogram (ECG) reflects atrial electrical remodeling.

In the previous studies, prolonged P-wave was associated with left atrial (LA) indices (ie, LA dilatation),<sup>3,4</sup> prolonged A-wave acceleration times, reduced LA stroke volume, and reduced LA ejection fraction on echocardiography.<sup>5</sup> P-wave duration is a significant predictor of developing atrial fibrillation.<sup>6-10</sup> In addition, prolonged P-wave was associated with cardiovascular (CV) death and all-cause mortality,<sup>11,12</sup> and increment in the P-wave duration was associated with increase in CV death.<sup>13</sup> Therefore, P-wave prolongation not only reflects atrial remodeling but also plays a role as a marker of cardiac events.

However, there has been no examination of the relationship among P-wave duration, blood pressure (BP) levels, LA/ left ventricle (LV) morphology on echocardiography and cardiac events. The aim of this study was to evaluate the association among automatically assessed P-wave duration, BP, LA diameter, LV hypertrophy (LVH), and cardiac events in patients with CV risk factors.

## 2 | METHODS

The Japan Morning Surge Home Blood Pressure (J-HOP) study was an observational 5-year prospective study that recruited 4310 patients who had at least one of the following CV risk factors: hypertension, dyslipidemia, diabetes, smoking, and history of angina pectoris/myocardial infarction/heart failure/stroke.<sup>14</sup> The study protocol was registered on the University Hospital Medicine Information Network Clinical Trials Registry: #UMIN00000894.

### 2.1 | Study populations

We obtained ECG data of 834 outpatients who underwent automatic analysis ECG at the Jichi Medical University School of Medicine. After excluding 24 patients with atrial fibrillation, we finally analyzed 810 patients with the max P-wave duration.

We defined current smoking status as smoking status or not. Alcohol exposure was defined as regular consumption of alcoholic drinks. Hyperlipidemia was defined as a total cholesterol level  $\geq 240$  mg/dl or treated hyperlipidemia. Subjects were considered to have diabetes if they reported a diabetes, or if they were taking medications for diabetes or had fasting blood sugar  $\geq 126$  mg/dl. Blood pressure was obtained after a rest period of at least 5 min using an automatic manometer at the local medical center. Office BP was calculated as the average of three consecutive measurements.

Hypertension was defined as systolic BP  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg, use of hypertension medications, or diagnosis of hypertension by a physician. Patients with any of the following were excluded: chronic renal failure requiring hemodialysis; other serious illnesses (eg, end-stage cancer, active connective tissue disease); alcohol or drug addiction; or inability to attend hospital visits or provide informed consent.

### 2.2 | ECG and echocardiography measurement

Standard 12-lead surface electrocardiography (25 mm/s, 1 mV/cm, and 100 Hz) was conducted, and the duration of the P-wave was automatically analyzed in each lead using the 12-lead ECG analysis system (Fukuda Denshi, Tokyo). P-wave duration was measured from the P-wave onset (conclusion of the T-P segment) to its offset (return to baseline for the remaining PR interval). The maximum P-wave duration (Pmax) from the 12 leads was selected for analysis. We set the cutoff levels of Pmax as 120, 130, 140, and 150 ms. 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. The LVH of ECG (ECG-LVH) was defined as  $\geq 244$  mV  $\times$  ms according to the Losartan Intervention for Endpoint Reduction in Hypertension Study.<sup>15</sup>

Echocardiography was obtained with the echocardiographic window at the left sternal border with the patient in the left lateral position. Two-dimensional M-mode or B-mode imaging was obtained according to the guidelines of the American Society of Echocardiography.<sup>16</sup> Measurements of the left atrial (LA) dimension were made at end systole by the long-axis view. We defined LA enlargement (LAE) as an LA dimension  $\geq 40$  mm.<sup>17,18</sup> Left ventricular mass (LVM) was obtained using the formula validated by the American Society of Echocardiography:  $LVM = 0.8 \times 1.04 [(IVS + LV ID + PWT)^3 - LVID^3] + 0.6$  g, where IVS is interventricular septum, LVID is LV internal diameter, and PWT is inferolateral wall thickness. The LVM index (LVMI) was calculated as LVM/body surface area. LVH by echocardiography (echo-LVH) was defined as LVMI  $> 115$  g/m<sup>2</sup> in men and  $> 95$  g/m<sup>2</sup> in women as reported in the previous guideline.<sup>16</sup> We obtained 758 patients' LA diameter and 757 patients' LVMI on echocardiography.

### 2.3 | Primary end point

The primary end points of this study were (1) fatal and nonfatal acute myocardial infarction, (2) sudden death within 24 h of the abrupt onset of symptoms, and (3) fatal and nonfatal heart failure that required admission. 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 including home BP data.

## 2.4 | Statistical analysis

Statistical analysis was performed using SPSS (version 26; IBM Inc, Chicago, IL, USA). Data are expressed as percentages, mean, and standard deviations (SD). The differences between groups were analyzed using the chi-square test for categorical variables and using the independent *t* test for continuous variables. The event-free survival curve was derived using Kaplan-Meier analysis. The hazard ratio of prolonged P-wave and P-wave duration (per 10 ms) was evaluated by using the Cox proportional hazard model with adjustment for age, gender, body mass index, smoking, regular drinker, hypertension, dyslipidemia, diabetes, office systolic BP, heart rate, LAE, and echo-LVH. Receiver-operating characteristic (ROC) analysis was used to determine optimal cutoff values with corresponding sensitivity and specificity of P-wave duration for the primary end point. A difference was considered significant if the probability value was  $<0.05$ .

## 3 | RESULTS

The average age was  $62.6 \pm 10.9$  years, and the percentage of male subjects was 51.5% in this study. The baseline characteristics by P-wave cutoff level  $\geq 140$  ms are shown in Table 1. The average age and body mass index, the percentages of smokers, regular drinkers, diabetic patients, and patients with dyslipidemia were similar in both groups. The percentage of male patients and office systolic BP in the prolonged P-wave group ( $P_{\max} \geq 140$  ms) were higher than

TABLE 1 Patient characteristics

	P < 140 ms (n = 760)	P $\geq$ 140 ms (n = 50)	P
Age (years)	62.5 $\pm$ 10.8	64.2 $\pm$ 12.1	.270
Male (%)	50	68	.014
BMI (kg/m <sup>2</sup> )	24.5 $\pm$ 3.6	25.4 $\pm$ 3.4	.083
Smoking (%)	10	10	.953
Regular drinker (%)	19	26	.315
Hypertension (%)	90	94	.398
Dyslipidemia (%)	33	26	.284
Diabetes (%)	29	40	.121
Office SBP (mmHg)	139.2 $\pm$ 16.0	144.8 $\pm$ 19.7	.018
Office DBP (mmHg)	81.3 $\pm$ 11.5	82.9 $\pm$ 12.5	.356
Heart rate (bpm)	66.6 $\pm$ 11.8	72.3 $\pm$ 17.3	.024
ECG-LVH (%)	13	22	.163
LAD (%) n = 758	30	46	.048
Echo-LVH (%) n = 757	31	39	.238

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; ECG-LVH, left ventricular hypertrophy diagnosed by electrocardiography; Echo-LVH, left ventricular hypertrophy diagnosed by echocardiography; LAD, left atrial dilatation; SBP, systolic blood pressure.

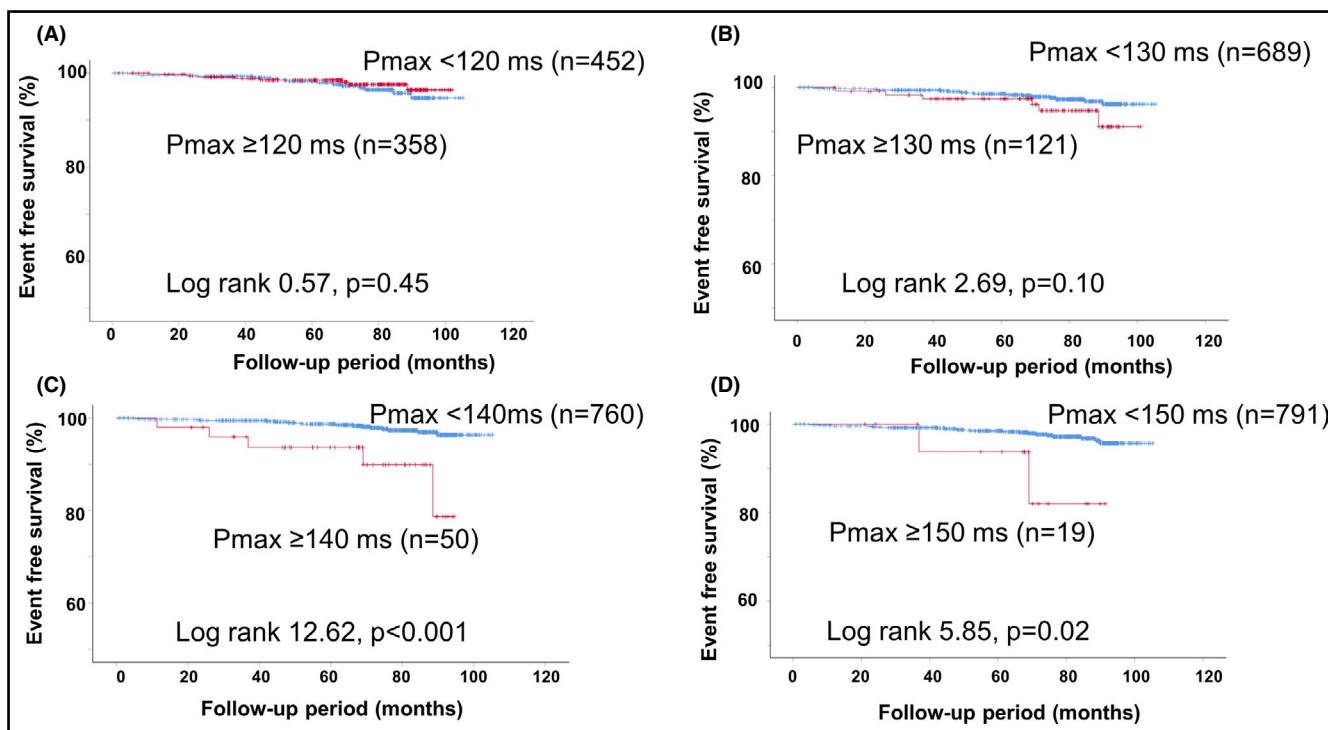
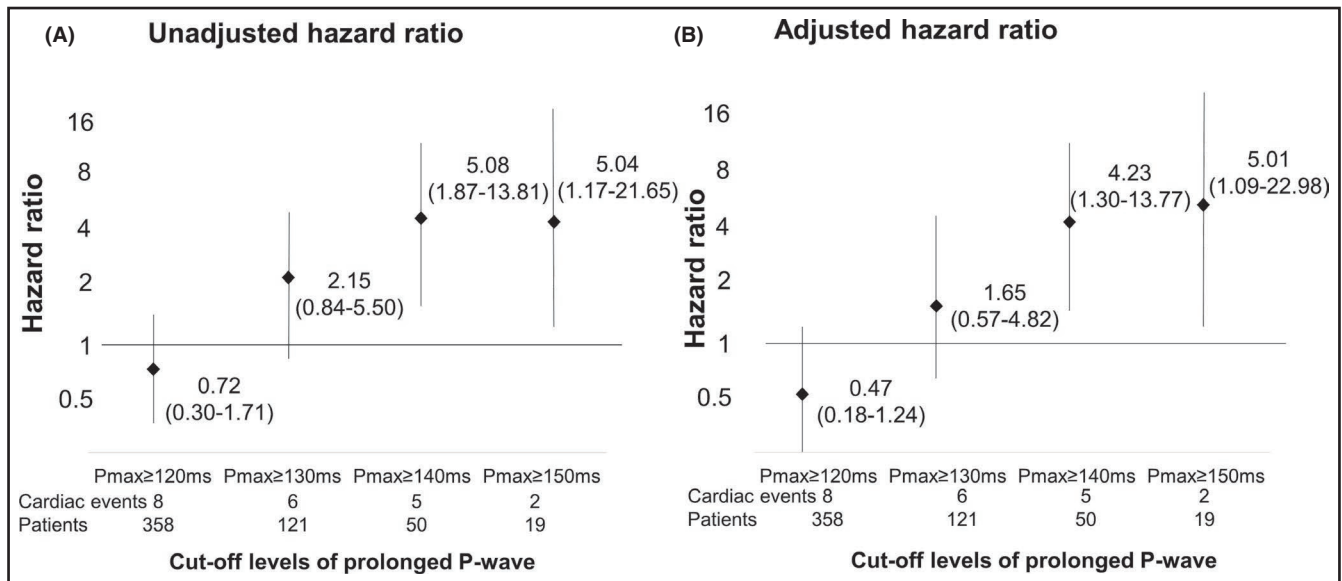


FIGURE 1 Primary end point and prolonged P-wave. P-wave cutoff levels of (A) 120 ms, (B) 130 ms, (C) 140 ms, and (D) 150 ms [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 2** Hazard ratio of cardiovascular events. (A) Unadjusted HR, (B) adjusted HR. Adjusted HR was adjusted for age, gender, body mass index, smoking, regular drinker, hypertension, dyslipidemia, diabetes, office systolic blood pressure, heart rate, left atrial dilatation, and left ventricular hypertrophy by echocardiography. HR, hazard ratio

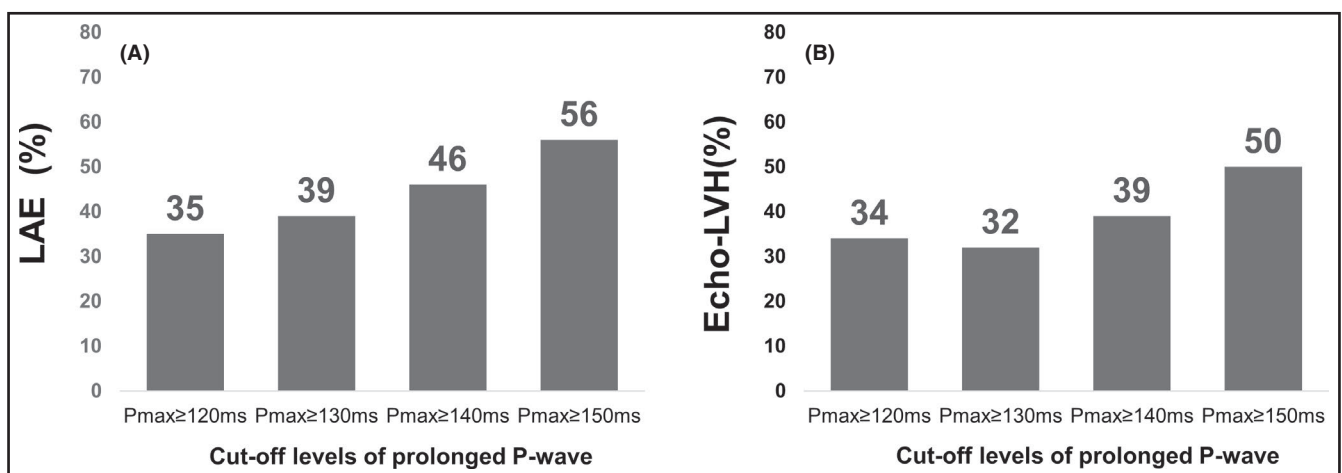
those in the control group ( $P_{max} < 140$  ms; percentage of males: 68% vs. 50%,  $P = .014$ ; office systolic BP:  $144.8 \pm 19.7$  mmHg vs.  $139.2 \pm 16.0$  mmHg,  $P = .018$ ). Heart rate in the prolonged P-wave group was also higher than that in the control group ( $72.3 \pm 17.3$  vs.  $66.6 \pm 11.8$  bpm,  $P = .024$ ).

### 3.1 | Primary end point and P-wave duration

There were 22 events during an average follow-up of  $6.9 \pm 2.0$  years. When the cutoff level was  $P_{max} 120$  ms and 130 ms, prolonged P-wave was not associated with cardiac events ( $P = .45$  and  $P = .10$ , respectively; Figure 1A,B), but when a prolonged P-wave was

defined as  $P_{max} \geq 140$  ms ( $n = 50$ ) and  $P_{max} \geq 150$  ms ( $n = 19$ ), the patients in that group had significantly higher cardiac events than others ( $P < .001$  and  $P = .02$ , respectively; Figure 1C,D).

Hazard ratios of cardiac events for each definition after Cox proportional hazard model are shown in Figure 2. Prolonged P-wave defined as  $P_{max} \geq 140$  ms was significantly associated with cardiac events after adjusting for age, gender, body mass index, smoking, regular drinker, hypertension, dyslipidemia, diabetes, office systolic BP, heart rate, and the percentages of LAE and echo-LVH (adjusted HR 4.23, 95% CI 1.30–13.77,  $P = .02$ ; Figure 2B). In addition, P-wave defined as  $P_{max} \geq 150$  ms was also independently associated with cardiac events (adjusted HR 5.01, 95% CI 1.09–22.98,  $P = .04$ ; Figure 2B). The hazard ratio for a 10-ms increase in max P-wave duration was



**FIGURE 3** The percentage of left atrial enlargement and left ventricular hypertrophy in patients with prolonged P-wave. LAE, left atrial enlargement; Echo-LVH, left ventricular hypertrophy diagnosed by echocardiography

TABLE 2 Overview of studies of the association between P-wave duration and events

Study	Population	Sample size	Age (y)	Men (%)	Systolic BP (mmHg)	Follow-up duration	Events	Cutoff level of P-wave duration (ms)	Hazard ratio (unadjusted)	Hazard ratio (adjusted)	Adjusting factors
Magnani <sup>12</sup> NHNESIII (2011)	White, Ethnic minorities Civilian population (n = 7486)		60 ± 13	48	134 ± 26	8.6 years (median)	679 CV deaths	140 154	- -	2.14 3.21	Age, gender, race, heart rate, body mass index, smoking, dyslipidemia, hypertension, diabetes
Kaykha <sup>13</sup> (2010)	Veterans Inpatients, outpatients In US (n = 40 020)		56 ± 14	100	-	6.1 years (mean)	3417 CV deaths	120	-	1.21 (P < .0001)	Age, heart rate, BMI
Ha <sup>14</sup> (2018)	Veterans In US (n = 20 827)		43 ± 8	91	-	17.8 years (mean)	888 CV deaths	120 140	1.79 (P < .001) 3.59 (P < .001)	1.53 (P < .001) 3.08 (P < .001)	Age, gender
Present study	Japanese Outpatients with CV risks (n = 810)		63 ± 11	51	139 ± 16	6.9 years (median)	22 cardiac events	140 150	5.08 (P = .001) 5.04 (P = .03)	4.23 (P = .02) 5.01 (P = .04)	Age, gender, heart rate, BMI, smoking, alcohol use, hypertension, dyslipidemia, diabetes, office systolic BP, left atrial enlargement, left ventricular hypertrophy

Abbreviations: BMI, body mass index; BP, blood pressure; CV, cardiovascular; NHANESIII, The Third National Health and Nutrition Examination Survey.

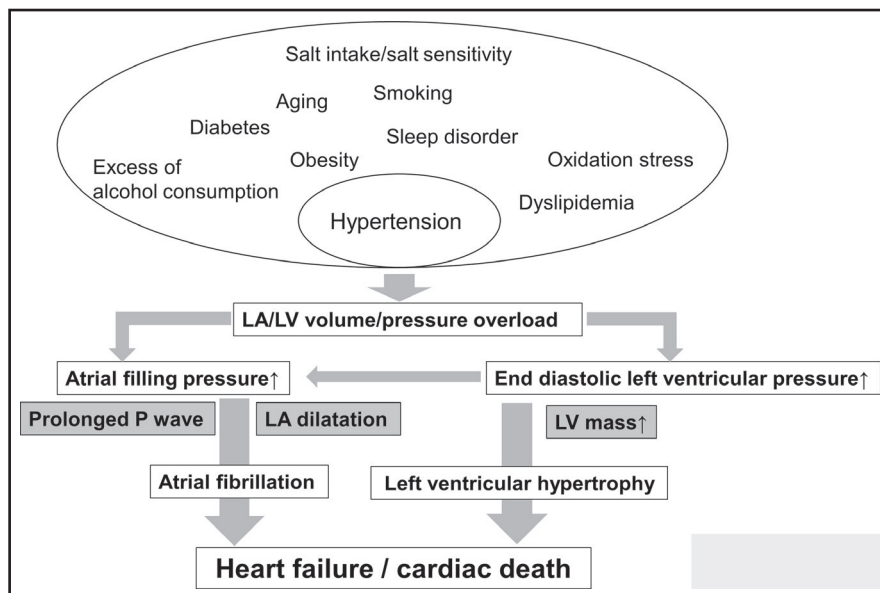


FIGURE 4 The percentage of left atrial enlargement and left ventricular hypertrophy. LA, left atrial; LV, left ventricular

1.12 (95% CI 0.85–1.47,  $P = .41$ ). The cutoff point of P-wave duration was 137 ms, and the area under the ROC curve was 0.513.

### 3.2 | Echocardiography parameter and P-wave duration

Both LA diameter ( $r = 0.08$ ,  $P = .02$ ) and left ventricular mass index ( $r = 0.17$ ,  $P < .001$ ) were significantly associated with Pmax. The P-wave duration was linearly associated with the percentage of LAE and LVH on echocardiography (Figure 3).

## 4 | DISCUSSION

The main result of this study was that prolonged P-wave duration  $\geq 140$  ms was associated with cardiac events in Japanese outpatients with CV risks. Office systolic BP was significantly higher in patients in the Pmax  $\geq 140$  ms group compared to those in the Pmax  $< 140$  ms group. Finally, increased P-wave duration was linearly associated with the percentage of LAE and LVH.

In this study, P-wave duration  $\geq 140$  ms was associated with cardiac events. The cutoff level of prolonged P-wave varies among previous reports, and no specific definition of prolonged P-wave has been established. The previously reported data on the relation between P-wave duration and cardiac events are shown in Table 2. When the cutoff level was Pmax 120 ms and 130 ms, prolonged P-wave was not associated with cardiac events in our study. On the other hand, when a prolonged P-wave was defined as Pmax  $\geq 140$  ms and Pmax  $\geq 150$  ms, the patients with prolonged P-wave had significantly higher cardiac events than the others. In our study, subjects with Pmax  $\geq 140$  ms had a 4.23-fold greater risk of cardiac events

after adjusting for age, gender, body mass index, smoking, regular drinker, hypertension, dyslipidemia, diabetes, office systolic BP, heart rate, and the percentages of LAE and echo-LVH.

The cohort analysis in National Health and Nutrition Examination Survey III reported that prolonged P-wave was significantly associated with CV death and all-cause mortality. The increase in the risk of CV death conferred by a prolonged P-wave duration of  $\geq 140$  ms was 2.14-fold and that by a prolonged P-wave duration  $\geq 154$  ms was 3.21-fold compared to a P-wave duration of 112 ms<sup>12</sup> In a study of ECGs and CV outcomes at a veterans medical center in the United States, in which the study cohort had a mean age of 56 years and mean follow-up of 6 years, the P-wave duration was a significant predictor of CV death after adjusting for age, heart rate, and body mass index.<sup>13</sup> Subjects with a P-wave duration  $>120$  ms had a 21% greater risk of CV death compared to subjects with a P-wave duration  $\leq 120$  ms<sup>13</sup> Moreover, in a long-term study at the same center, in which subjects with a mean age of 43 years were followed for a median duration of 17 years, prolonged P-wave duration was associated with 1.53–3.08 fold in CV death.<sup>11</sup> The reason for the difference in hazard ratios between these previous studies and our present study might be that our present study population consisted of Japanese with CV risks, who were older than the subjects in the previous studies. Generally, P-wave duration is associated with age<sup>19</sup> and prolonged with aging.<sup>12,20</sup> Asians, including Japanese, are more likely to have high salt sensitivity and salt intake than their Western counterparts.<sup>21</sup> The higher salt sensitivity causes cardiac volume overload and pressure overload and might result in heart failure and cardiac events.

Office systolic BP in the Pmax  $\geq 140$  ms group was significantly higher than that in the Pmax  $< 140$  ms group. In a large study with a general population in Finland, high BP was associated with prolonged P-wave independently of other CV risks.<sup>10</sup> Hypertension is a pathological condition associated with increased cardiac afterload,

and increased cardiac afterload leads to an increase in the LV end-diastolic pressure and further to increases in LA pressure and LA diameter.<sup>22</sup> Kishima et al reported that prolonged P-wave was independently associated with increased mean LA pressure and that LA size was not associated with P-wave duration.<sup>23</sup> Faggiano et al reported that the LA pressure measured by cardiac catheterization was more closely related to the signal-averaged P-wave duration than to the LA diameter.<sup>24</sup> Prolonged P-wave on ECG might represent LA remodeling, and LA remodeling was not only lead to developing AF but also played a role in progression of congestive heart failure (Figure 4). Recently, the associations between P-wave peak time and left ventricular diastolic function were reported.<sup>25,26</sup>

There has been no report on the relationship among P-wave duration on ECG, LAE, and LVH on echocardiography and cardiac events. In our study, the degree of prolonged P-wave was linearly associated with LAE and LVH. The percentages of LAE and LVH were <50% in the Pmax  $\geq$  140 ms group, while in the Pmax  $\geq$  150 ms group, they were 50% or above. Even after adjusting for the percentage of LAE, prolonged P-wave defined as a Pmax  $\geq$  140 ms was independently associated with cardiac events. Therefore, prolonged P-wave could be a cardiac event marker even in patients without atrial morphological abnormalities. A standard 12-lead ECG is a non-invasive and repeatable test that is available at most institutions. Therefore, P-wave-based risk stratification might be useful.

This study has several limitations. First, the sample size was relatively small, and small sample size might lead to statistical bias. Second, the subjects consisted exclusively of Japanese outpatients with high CV risks. Third, the left atrial volume is more representative of actual LA size than the anteroposterior diameter on echocardiographic analysis.<sup>16</sup> We were not able to obtain the data on left atrial volume by echocardiography. Thus, the accuracy of the left atrial diameter measurement may have been inadequate, which could have led to underestimation of the impact of atrial morphological remodeling. Further studies in a large population will be needed to examine how a prolonged P-wave relates to cardiac events and LA/LV load, including left atrial volume.

## 5 | CONCLUSIONS

The automatically assessed prolonged P-wave was associated with cardiac events independently of LA enlargement in Japanese patients with CV risks. Further large studies are needed to confirm our findings.

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### CONFLICT OF INTEREST

K. Kario has received research grants from Omron Healthcare and A&D Co. The other authors have no conflict of interest to declare.

### AUTHOR CONTRIBUTIONS

Kario K takes primary responsibility for this paper. Yokota A wrote the manuscript and did the statistical analysis. Kario K, Kabutoya T, and Hoshide S collected the patients' data. Kario K acquired research grants for the J-HOP study. Yokota A, Kabutoya T, Hoshide S, and Kario K reviewed/edited the manuscript.

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