


# BMJ Open Association between P wave polarity in atrial premature complexes and cardiovascular events in a community-dwelling population

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## ABSTRACT

**Objective** To examine the association between polarity of atrial premature complexes (APCs) and stroke.

**Design** A prospective study.

**Setting and participants** A total of 11 092 participants in the Jichi Medical School cohort study were included after excluding patients with atrial fibrillation. We analysed stroke events in patients with (n=136) and without (n=10 956) APCs. With regard to polarity of APCs, patients were subcategorised into having (1) negative (n=39) or non-negative (n=97) P waves in augmented vector right (aVR), and (2) positive (n=28) or non-positive (n=108) P waves in augmented vector left (aVL).

**Outcome measures** The primary endpoint was stroke.

**Results** Patients with APCs were significantly older than those without APCs (64.1±9.2 vs 55.1±11.6 years, p<0.001). The mean follow-up period was 11.8±2.4 years. Stroke events were observed in patients with (n=13 events) and without (n=411 events) APCs. This difference was significant (log-rank 12.9, p<0.001); however, APCs were not an independent predictor of stroke after adjusting for age, sex, height, body mass index, current drinking, diabetes, systolic blood pressure, prior myocardial infarction, prior stroke and high-density lipoprotein-cholesterol (p=0.15). The incidence of stroke in patients with APCs and non-negative P wave in aVR was significantly higher than in patients without APCs (log-rank 20.1, p<0.001), and non-negative P wave in aVR was revealed to be an independent predictor of stroke (HR 1.84, 95% CI 1.02 to 3.30). The incidence of stroke in patients with APC with non-positive P wave in aVL was also significantly higher than in patients without APC (log-rank 15.3, p<0.001), and non-positive P wave in aVL was an independent predictor of stroke (HR 1.92, 95% CI 1.05 to 3.54).

**Conclusions** The presence of APCs with non-negative P wave in aVR or non-positive P wave in aVL on 12-lead ECG was associated with a higher risk of incident stroke.

## INTRODUCTION

Atrial fibrillation (AF) is a major risk factor of stroke, is associated with severity of stroke and is a common disease with ageing.<sup>1–3</sup> Atrial premature complexes (APCs) are found in healthy subjects.<sup>4</sup> However, APCs are also associated with cardiovascular death<sup>5</sup> and ischaemic

## Strengths and limitations of this study

- Data were from a large cohort study over an 11-year period.
- Stroke events in patients with atrial premature complexes (APCs) categorised according to polarity of APCs were evaluated.
- The polarity of APCs was associated with the origin of APCs.
- The origin of APCs was not confirmed by an invasive procedure.
- There was a small number of patients with APCs.

stroke.<sup>6</sup> In the general population, the detection of even a single APC by ECG is associated with AF and cardiovascular death.<sup>7</sup> Kamel *et al*<sup>8</sup> reported that a mechanistic link between APC as a biomarker of cardiovascular/atrial myocardial disease was much more evident in patients who had experienced stroke. Thus, the presence of APCs is a notable predictor of stroke, but the precise role played by APCs in stroke events remains unclear.

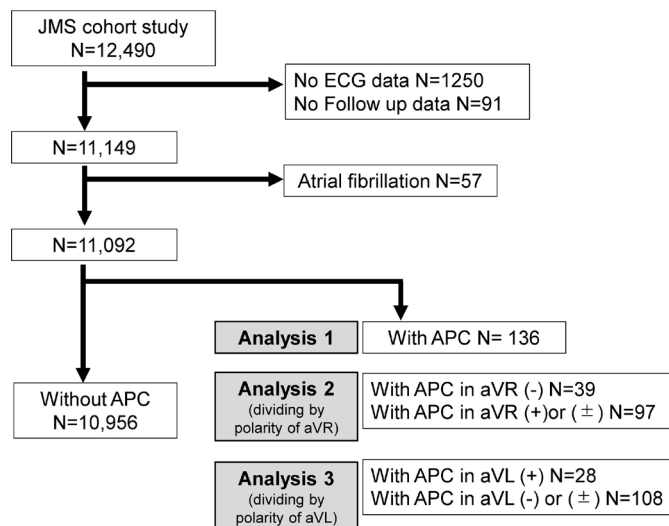
The diagnosis of focal atrial tachycardia is based on the polarity of the P wave on 12-lead ECG.<sup>9</sup> The origin of APCs associated with AF has also been investigated using Holter ECG.<sup>10</sup> Most of the triggers of AF originate from pulmonary veins<sup>11</sup>; however, a method for ECG assessment of the atrial electrical excitation of APCs from firing of left pulmonary vein has not been established. The association between the polarity of the P wave of APCs obtained by 12-lead ECG and stroke has also been unclear.

The aim of this study was to evaluate the association between the polarity of APCs on 12-lead ECG and stroke events in a general population.

## METHODS

### Study population

This study was conducted as part of the Jichi Medical School (JMS) cohort study, which



**Figure 1** Study protocol. APC, atrial premature complex; aVL, augmented vector left; aVR, augmented vector right; JMS, Jichi Medical School.

was a prospective study designed to assess cardiovascular and cerebrovascular diseases in the Japanese general population. The details of the protocol of the JMS cohort study have been reported elsewhere.<sup>12</sup> Baseline data were collected between April 1992 and July 1995. We enrolled 11 092 patients who participated in the JMS cohort study after excluding patients with AF (figure 1).

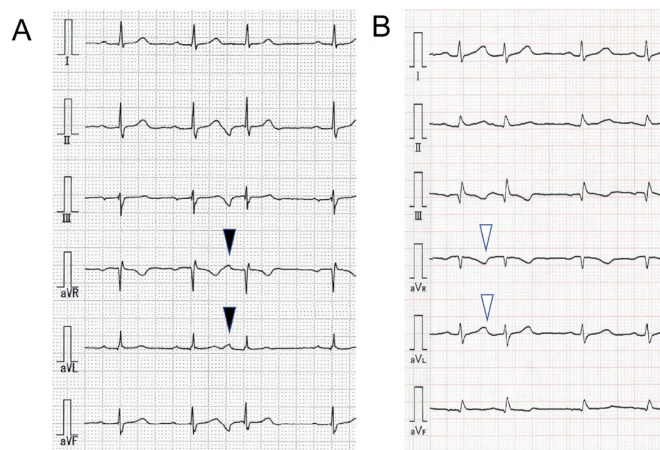
### ECG analysis and classification of APCs

ECG was measured at a paper speed of 25 mm/s and gain of 10 mm/mV (or 5 mm/mV) using ECG devices available at the participating institutes (FCP130-A9, FCP145-M4 and FCP270-M5; Fukuda Denshi, Tokyo). ECGs were manually analysed by a single cardiologist who was blinded to patients' information.

Figure 1 illustrates the study protocol. We analysed stroke events in patients with APCs (n=136) and patients without APCs (n=10956). Based on a previous report,<sup>9</sup> P waves inscribed above the isoelectric line were classified as positive, those below were classified as negative, those above and below (or conversely, below and above) were classified as biphasic, and isoelectric P waves were classified as flat (figure 2).

With regard to the polarity of the P wave of APCs, we subcategorised the patients into having (1) negative P wave (n=39) or non-negative P wave (including positive, biphasic and flat P wave, n=97) in augmented vector right (aVR), and (2) positive P wave (n=28) or non-positive P wave (including negative, biphasic and flat P wave, n=108) in augmented vector left (aVL).

Classification was performed by a single cardiologist (TK), and the kappa was evaluated in 30 cases. The level of intraobserver agreement in determining polarity in APCs was found to be acceptable (intraobserver agreement:  $\kappa$  statistics=0.58 in the measurement of aVR and 0.63 in the measurement of aVL).



**Figure 2** Definition of polarity in aVR and aVL. (A) A case of non-negative P wave in aVR and positive P wave in aVL. A clear unipolar positive P wave of an APC was observed in the aVR and aVL leads (black arrow). (B) A case of non-negative P wave in aVR and non-positive P wave in aVL. Neither the polarity of an APC in aVR nor that in aVL could be determined (white arrows). APCs, atrial premature complexes; aVL, augmented vector left; aVR, augmented vector right.

### Endpoint

The details of the follow-up and the diagnostic criteria are shown elsewhere.<sup>12</sup> Briefly, most of the subjects were followed up with repeat examinations each year. Subjects with stroke events were asked for the time of these incidents and the name of the hospitals where they were treated. Subjects who did not come to the screening examination were contacted by mail or phone. In addition, the medical records at all nearby hospitals were checked to determine whether these subjects had been hospitalised. Finally, public health nurses visited the subjects who were absent during screening to obtain additional information. For all subjects, if an incident case was suspected, the forms for stroke incidence were filled out and duplicate CT films or MRI films for strokes were obtained.<sup>13</sup>

The primary endpoint was stroke. The diagnostic criterion for stroke was sudden onset of a focal and non-convulsive neurological deficit that lasted for more than 24 hours.<sup>14</sup> Stroke events included ischaemic stroke (cerebral infarction and cerebral embolism), haemorrhagic stroke (cerebral haemorrhage and subarachnoid haemorrhage) and undefined type of stroke. We excluded transient ischaemic attacks in which the neurological deficit was completely cleared within 24 hours from the onset of symptoms.

The diagnosis of stroke events was determined on consensus of all members of the diagnostic committee.

Written informed consent for the study was obtained individually from all of the subjects during mass screening examination and health check-up.

### Statistical analysis

Data are shown as mean $\pm$ SD or as percentage. The  $\chi^2$  test was used for categorical data, and analysis of variance

was used for comparisons among the groups. Intergroup differences were tested by Bonferroni test.

The incidence of stroke and ischaemic stroke in the groups classified by the presence/absence of APCs or by the polarity of the P wave of APCs was plotted as Kaplan-Meier curves, and the differences were assessed by log-rank test. The HR and 95% CI of the incidence of stroke and ischaemic stroke in the subgroups were calculated using Cox regression analyses after adjustment for age, sex, height, body mass index (BMI), current drinking, diabetes, systolic blood pressure (SBP), prior myocardial infarction (MI), prior stroke and high-density lipoprotein (HDL)-cholesterol (traditional cardiovascular risk factors).

SPSS V.20.0 software was used for statistical analyses. A probability value <0.05 was considered statistically significant.

### Patient and public involvement

No patients were involved in setting the research questions or the outcome measures, and in the design or performance of the study. No plans were set in place to disseminate the results of the research to study participants.

### RESULTS

The mean age of the subjects was 55.7±11.2 years, with an average BMI of 23.1±3.1 kg/m<sup>2</sup>. The percentage of men, those with hypertension and those with diabetes was 38%, 17% and 4%, respectively. The mean follow-up period was 11.8±2.4 years. Stroke events were observed; there

were 411 stroke events (267 ischaemic stroke events) in patients without APCs and 13 stroke events (9 ischaemic stroke events) in patients with APCs.

Table 1 summarises the baseline characteristics of the patients with APCs according to the polarity of the P wave in aVR and aVL. Patients with APCs with non-negative P in aVR were significantly older (63.7±9.6 vs 55.6±11.2 years,  $p<0.001$ ) and had significantly higher SBP (136±20 vs 130±21 mm Hg,  $p=0.015$ ) than patients without APCs.

The incidence of stroke/ischaemic stroke in patients with and without APCs is shown in figure 3A–F. The difference in the incidence of stroke was significant (log-rank 12.9,  $p<0.001$ ). The difference in the incidence of stroke in patients according to P wave polarity is shown in figure 3B,C. The incidence of stroke in patients with APCs with non-negative P in aVR was significantly higher than in patients without APCs (log-rank 20.1,  $p<0.001$ ), and the incidence of stroke in patients with APCs with non-positive P in aVL was also significantly higher than in patients without APCs (log-rank 15.3,  $p<0.001$ ).

Figure 4A shows the results of the Cox proportional hazard model of stroke events. After adjusting for age, sex, height, BMI, current drinking, diabetes, SBP, prior MI, prior stroke and HDL-cholesterol, APC was no longer an independent predictor (HR 1.51, 95% CI 0.86 to 2.65,  $p=0.15$ ), but APCs of non-negative P in aVR and APCs of non-positive P in aVL were independent predictors of stroke (APCs of non-negative P in aVR: HR 1.84, 95% CI 1.02 to 3.30,  $p=0.042$ ; APCs of non-positive P in aVL: HR 1.92, 95% CI 1.05 to 3.54,  $p=0.035$ ).

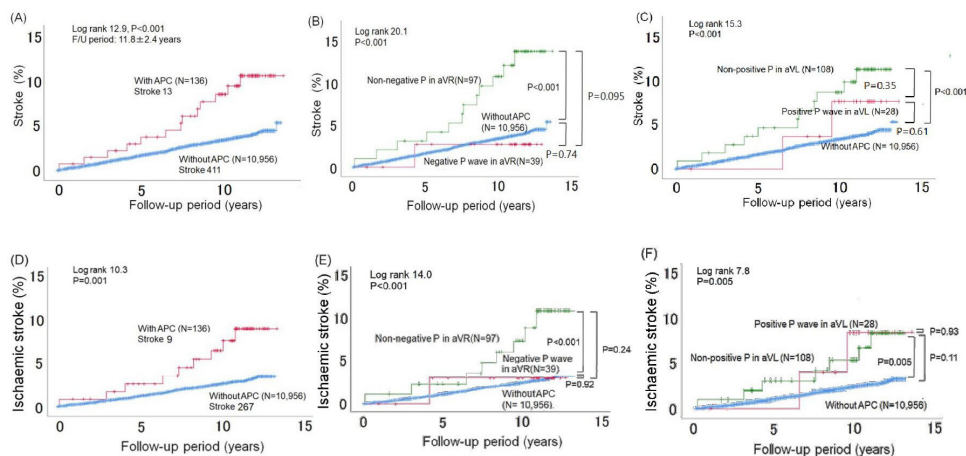
**Table 1** Patient characteristics

	Patients with APCs				
	Patients without APCs (n=10956)	Negative P wave in aVR (n=39)	Non-negative P wave in aVR (n=97)	Positive P wave in aVL (n=28)	Non-positive P wave in aVL (n=108)
Age (years)	55.6±11.2	64.9±8.0***	63.7±9.6***	65.9±8.7***	63.6±9.3***
Male (%)	38	44	40	43	41
Height (cm)	155±9	153±9	153±8	151±8	153±8
Body mass index (kg/m <sup>2</sup> )	23.1±3.1	21.9±2.6*	22.6±2.9	22.5±3.0	22.4±2.8*
Current smoker (%)	21	23	21	32	19
Current drinker (%)	44	39	33	36	34
Hypertension (%)	17	24	27*	48*	20**
Diabetes (%)	4	3	4	4	4
Prior stroke (%)	1	0	3	4	2
Prior MI (%)	1	5***	1	4	2
Systolic BP (mm Hg)	130±21	131±22	136±20*	142±26**	132±19
Diastolic BP (mm Hg)	78±12	74±15	79±12	81±13	77±13
Total cholesterol (mg/dL)	193±35	195±38	188±36	195±34	188±38
HDL-cholesterol (mg/dL)	51±13	52±16	52±14	54±16	51±14

\* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$  versus patients without APCs.

APC, atrial premature complex; aVL, augmented vector left; aVR, augmented vector right; BP, blood pressure; HDL, high-density lipoprotein; MI, myocardial infarction.





**Figure 3** Stroke events according to APCs. Stroke events according to (A) APCs, (B) APC style in aVR, (C) APC style in aVL. Ischaemic stroke events according to APC. Ischaemic stroke events according to (D) APCs, (E) APC style in aVR and (F) APC style in aVL. APCs, atrial premature complexes; aVL, augmented vector left; aVR, augmented vector right; F/U, follow-up.

We also conducted a Kaplan-Meier curve analysis of ischaemic stroke (figure 3D–F) and analysed the ischaemic stroke events by Cox proportional hazard model (figure 4B). Before adjusting for covariates, APCs, APCs of non-negative P in aVR and APCs of non-positive P in aVL were predictors of ischaemic stroke (APCs: HR 2.92 (95% CI 1.50 to 5.68); APCs of non-negative P in aVR: HR 3.61 (95% CI 1.79 to 7.30); and APCs of non-positive P in aVL: HR 2.82 (95% CI 1.34 to 5.99)). However, after adjustment for age, sex, height, BMI, current drinking, diabetes, SBP, prior MI, prior stroke and HDL-cholesterol, those factors were no longer independent predictors of ischaemic stroke (figure 4B).

We categorised the patients into two groups by age: patients  $\geq 65$  years and those  $< 65$  years. Among patients  $< 65$  years, before adjusting for covariates, APCs, APCs

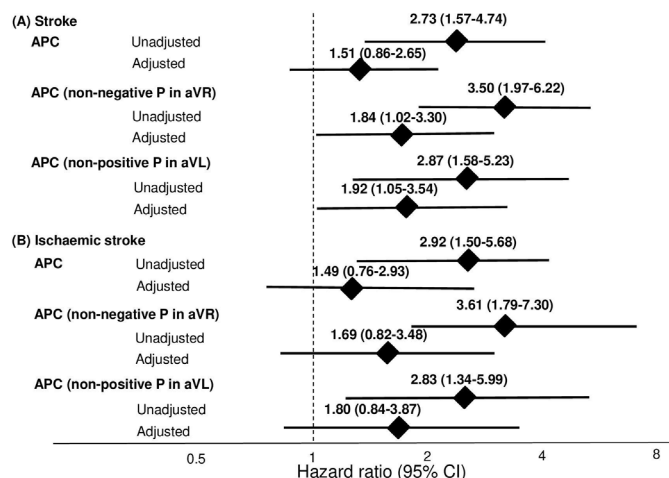
of non-negative P in aVR and APCs of non-positive P in aVL were not significantly associated with stroke (APCs: HR 2.11 (95% CI 0.67 to 6.58),  $p=0.20$ ; non-negative P in aVR: HR 2.80 (95% CI 0.89 to 8.75),  $p=0.077$ ; non-positive P in aVL: HR 2.44 (95% CI 0.78 to 7.64),  $p=0.12$ ). However, among patients aged 65 years or more, before adjusting for covariates, APCs of non-negative P in aVR were associated with stroke (HR 2.23 (95% CI 1.14 to 4.35),  $p=0.019$ ). APCs and APCs of non-positive P in aVL were not significantly associated with stroke (APCs: HR 1.72 (95% CI 0.91 to 3.24),  $p=0.094$ ; non-positive P in aVL: HR 1.82 (95% CI 0.90 to 3.68),  $p=0.098$ ).

## DISCUSSION

The main findings of this study were that the prognoses of patients with APCs with negative P in aVR or positive P wave in aVL were good, but poor for patients with APCs with non-negative P in aVR or non-positive P wave in aVL. The presence of APCs was not an independent predictor of stroke after adjusting for age, sex, height, BMI, current drinking, diabetes, SBP, prior MI, prior stroke and HDL-cholesterol.

In this study, APC was associated with stroke before adjusting for covariates. This result is concordant with previous reports. However, the prevalence of APCs is affected by age. The presence of APCs was not an independent predictor of stroke after adjusting for covariates in this study. Conen *et al*<sup>4</sup> conducted Holter ECG in 1742 individuals in the general population who were older than 50 years of age. The median number of APCs was 1.27 per hour; the number of APCs increased according to age, and the presence of APCs was the second strongest independent predictor of cardiovascular events, after age. Huang *et al*<sup>15</sup> conducted a meta-analysis of the association between APCs and cardiovascular events. Frequent APCs were associated with a 1.41-fold increased risk of stroke.

Murakoshi *et al*<sup>7</sup> investigated the risk of stroke caused by APCs in 63 197 individuals in a general population based



**Figure 4** HR according to type of APCs. Adjusted for age, sex, height, body mass index, current drinking, diabetes, systolic blood pressure, prior myocardial infarction, prior stroke and high-density lipoprotein-cholesterol. (A) HR of stroke according to type of APCs. (B) HR of ischaemic stroke according to type of APCs. APCs, atrial premature complexes; aVL, augmented vector left; aVR, augmented vector right.

on a single measurement of 12-lead ECG and observed that APCs were associated with a 1.63-fold increased risk of stroke death in women. However, in the Atherosclerosis Risk in Communities (ARIC) study, the presence of APCs was not an independent predictor of ischaemic stroke (HR 1.30, 95% CI 0.92 to 1.83).<sup>16</sup> The strength of the results on the association between ischaemic stroke and APCs might be less than that of the results on the association between any type of stroke and APCs. Himmelreich *et al*<sup>17</sup> conducted a meta-analysis of the outcome of ischaemic stroke based on dichotomised Holter data and found that the HR was 2.54. Additional investigations into the association between stroke and APC will be needed, including studies accounting for the frequency of APCs and patient characteristics.

The risk of stroke in patients with APC with negative P in aVR was similar to that of patients without APCs, but the risk of stroke in patients with APCs with non-negative P in aVR was high. There have been no reports on the association between stroke and the polarity of APCs. The polarity of aVL in atrial tachycardia is useful in diagnosing the origin of atrial tachycardia, and the diagnosis of atrial tachycardia using the polarity of aVL has also been adapted for the diagnosis of APC.<sup>18</sup> Most triggers of AF originate from pulmonary veins.<sup>11</sup> Most of the atrial electrical excitation of APCs from left pulmonary vein firing is in the rightward direction anatomically, but that of APCs from right pulmonary vein firing is not. Atrial electrical excitation of APCs in the right atrial septum does not proceed in the leftward direction.

On the other hand, most of the atrial electrical excitation of APCs near the sinus node or free wall of the right atrium is considered to be in the leftward direction and could result in a negative P wave in aVR or a positive P wave in aVL. Such APCs presenting with a negative P wave in aVR or a positive P wave in aVL might be 'benign' because the origin of the APCs was not associated with an AF trigger. Sinus arrhythmia might sometimes be misdiagnosed as APC. In such cases, the polarity of the P wave is usually negative in aVR or positive in aVL and considered benign arrhythmia. The prevalence of APCs was relatively low in the present study, but in previous reports APCs were associated with AF and cardiovascular events, including ischaemic stroke.<sup>6,7</sup> Thus, risk stratification by polarity of APCs might be helpful in detecting AF earlier and preventing cardiovascular events.

The strength of this study is that it is the first paper to investigate the association between polarity of APCs and stroke using a large-scale and long-term follow-up cohort. Several limitations should also be noted. The origin of APCs was not confirmed by an invasive procedure. The number of patients with APCs was small, and the number of APC-positive samples from patients with incident stroke and ischaemic stroke events was also small. Potentially insufficient statistical power (type II error) was an issue, and we could not check the interactions between covariates. Further studies enrolling large numbers of patients with APCs are needed. The modest kappa statistics for

the polarity of APCs was also a limitation. Compared with the QRS wave, the P wave had a tiny potential, and the P wave data were obtained from a previous report. It is now possible to obtain digital ECG data; had such data been available at the time of our analyses, it might have improved the interobserver agreement. Finally, we did not obtain data on low-density lipoprotein-cholesterol, educational level, alcohol use or physical activity, or the proportion of patients who received anticoagulation and AF during follow-up, which could have affected stroke events.

## CONCLUSIONS

The presence of APCs with non-negative P wave in aVR or non-positive P wave in aVL on 12-lead ECG was associated with a higher risk of incident stroke. The polarity of APCs was useful in predicting stroke events in a community-dwelling population.

**Contributors** TK analysed the data and prepared the first draft of the manuscript. YI performed the data analyses. SI conceived the study design and reviewed the manuscript. KK supervised the data collection and reviewed the final manuscript. All authors approved the final version.

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**Competing interests** TK has received scholarship funding from Mitsubishi Tanabe Pharma. KK has received research grants from A&D, Omron Healthcare, Roche Diagnostics KK, MSD KK, Astellas Pharma, Otsuka Holdings, Otsuka Pharmaceutical, Sanofi KK, Shionogi & Co, Sanwa Kagaku Kenkyusho, Daiichi Sankyo, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Teijin Pharma, Boehringer Ingelheim Japan, Pfizer Japan and Fukuda Denshi.

**Patient consent for publication** Not required.

**Ethics approval** The internal review board of the Jichi Medical University School of Medicine approved this study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available.

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