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P-wave polarity of atrial premature complex predicts cardiovascular events in a community-dwelling population

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Key words: atrial premature complexes, P-wave, stroke

Objectives: To examine the association between the polarity of atrial premature complexes (APC) and stroke.

Design: A prospective study.

Setting and participants: A total 11,092 participants in the JMS-cohort study after excluding patients with atrial fibrillation included in this study. We analyzed stroke events in patients with (N=136) and without APC (N=10,956). In regard to polarity of APC, patients were subcategorized as having (1) negative (N=39) or non-negative (N=97) P wave in aVR, and (2) positive (N=28) or non-positive (N=108) P wave in aVL.

Outcome measures: The primary endpoint was stroke.

Results: Patients with APC were older than patients without APC (64.1±9.2 vs. 55.1±11.6 yrs, 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) APC. This difference was significant (log rank 12.9, p<0.001), but APC was not an independent predictor of stroke after adjusting for age, gender, body mass index, hypertension, and diabetes (p=0.17). Stroke incidence in APC patients with non-negative P wave in aVR was significantly higher than that in patients without APC (log rank 20.1, p<0.001), and non-negative P wave in aVR was

found to be an independent predictor of stroke (hazard ratio 1.81, 95% CI 1.01-3.23). The incidence of stroke in APC patients with non-positive P in aVL was also significantly higher than that in patients without APC (log rank 15.3, p<0.001), but non-positive P in aVL was not an independent stroke predictor (hazard ratio 1.75, 95% CI 0.96-3.20).

Conclusions: The prognosis of patients with APC with non-negative P in aVR was poor.

Strengths and limitations of this study

1. The strength of this study is the first paper to study about the association between the polarity of APC and stroke using by large-scale and long follow-up cohort study.
2. Data were obtained from a large cohort study.
3. The origin of APC was not confirmed by an invasive procedure.
4. The number of patients with APC was small. Lack of enough statistical power (type II error) is an issue.

Introduction

Atrial fibrillation (AF) is a major risk factor of stroke and associated with the severity of stroke, and is a common disease with aging (1-3).

Atrial premature complexes (APC) are found in healthy subjects (4). However, frequent APC is associated with AF and stroke events (5,6). In the general population, the detection of even a single APC by electrocardiography (ECG) is associated with AF and cardiovascular death (7). Thus APC is an important predictor of cardiovascular events via AF.

The diagnosis in focus of focal atrial tachycardia is diagnosed based on the polarity of the P wave in 12-lead ECG (8). The origin of APC associated with AF has also been investigated by using Holter ECG (9). However, the association between the polarity of the P wave of APC obtained by 12-lead ECG and stroke remains unclear.

The aim of this study was to evaluate the association between the polarity of morphology of APC in 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 was a prospective study 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 (10). Baseline data were collected between April 1992 and July 1995. We enrolled 12,331 patients who participated in the JMS-cohort study after excluding patients with AF (Figure 1).

ECG Analysis and classification of APC

ECG was measured at a paper speed of 25 mm/sec 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, Japan). ECGs were manually analyzed by a single cardiologist who was blinded to the patient information.

Figure 1 shows the protocol of this study. We analyzed stroke events in patients with APC (N=136) and patients without APC (N=10,956). In regard to the polarity of the P wave of APC, subjects were subcategorized as having (1) negative P wave (N=39) or non-negative P wave (N=97) in aVR, and (2) positive P wave (N=28) or non-positive P wave (N=108) in aVL. Negative P wave in aVR and positive P wave in aVL were judged based on a unipolar negative wave (Figure 2).

The levels of intra-observer agreement were found to be acceptable in the determination of APC polarity (intra-observer agreement: κ statistic=0.58 in measurement of aVR and 0.63 in measurement of aVL).

Endpoint

The details of follow-up and the diagnostic criteria are shown elsewhere (10). Briefly, most subjects were followed-up with repeat examinations each year. Those examined were asked whether they had any history of stroke, myocardial infarction or sudden death. Subjects with such a history were asked for the time of these incidents and the names 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 hospitalized. Finally, public health nurses visited the absent subjects to obtain additional information. For all subjects, if an incident case was suspected, forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained (11).

The primary endpoint was stroke. The diagnostic criterion for stroke was sudden onset of a focal and nonconvulsive neurological deficit that lasted for

more than 24 h (12). Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurologic deficit was completely cleared within 24 h from the onset of symptoms.

Diagnosis of the stroke events was determined under the consensus of all the members of the diagnostic committee.

Ethical issues

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health checkup.

Statistical analysis

Data are shown as the mean±SD or as a 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 the Bonferroni test.

Cumulative incidences of stroke in the groups classified by the presence/absence of APC or by the polarity of the P wave of APC were plotted

as Kaplan-Meier curves, and the differences were assessed by the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) of the incidences of stroke in the subgroups were calculated using Cox regression analyses after adjustments for age, gender, body mass index, hypertension, and diabetes.

SPSS version 20.0 software (IBM, Armonk, NY) was used for the statistical analysis. 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. No patients were involved in the design or performance of the study. No plans were set in place to spread the results of the research to study participants.

Results

The mean follow-up period was 11.8±2.4 years. Stroke events were observed; there were 411 stroke events in patients without APC, and 13 stroke events in patients with APC.

The incidence of stroke in patients with APC and patients without APC is shown in Fig. 3A. The difference in incidence of stroke was significant (log rank

12.9, p<0.001). The difference in incidence of stroke in patients according to the P wave polarity is shown in Fig. 3B and C. The incidence of stroke in APC patients with non-negative P in aVR was significantly higher than that in patients without APC (log rank 20.1, p<0.001), and the incidence of stroke in APC patients with non-positive P in aVL was also significantly higher than that in patients without APC (log rank 15.3, p<0.001).

Table 1. Patient characteristics

	Patients without APC	Patients with APC		
	(N=10,956)	negative P wave in aVR (N=39)	non-negative P wave in aVR (N=97)	p
Age (y)	55.6±11.2	64.9±8.0	63.7±9.6	<0.001
Male (%)	62	56	60	0.71
Body mass index (kg/m^2)	23.1±3.1	21.9±2.6	22.6±2.9	0.013
Hypertension (%)	23	38	37	0.022
Diabetes (%)	8	3	10	0.67
Systolic BP (mmHg)	130±21	131±22	136±20	0.018
Diastolic BP (mmHg)	78±12	74±15	79±12	0.12
T-cholesterol (mg/dL)	193±35	195±38	188±36	0.41
HDL-cholesterol (mg/dL)	51±13	52±16	52±14	0.90

Table 1 shows the baseline characteristics of the patients with APC according to the polarity of the P wave in aVR. Patients with APC with non-

negative P in aVR were older (64.1±9.2 vs. 55.1±11.6 yrs, p<0.001), and had higher systolic blood pressure (136±20 vs. 130±21mmHg, p=0.015) than patients without APC.

Figure 4 shows the results of the Cox proportional hazard model. After adjusting for age, gender, body mass index, hypertension, and diabetes, APC was not an independent predictor (HR 1.48, 95% CI 0.85-2.59, p=0.17), but APC of non-negative P in aVR was an independent predictor of stroke (HR 1.81, 95% CI 1.01-3.23, p=0.045). APC of non-positive P in aVL was not an independent predictor of stroke (HR 1.75, 95% CI 0.96-3.20, p=0.069).

Discussion

The main findings of this study were that the prognosis of patients with APC with negative P in aVR was good, but that in patients with APC with non-negative P in AVR was poor. APC was not an independent predictor of stroke after adjusting for age and gender.

In this study, APC was associated with stroke before adjustment of covariates. The result is concordant with past reports. However, the prevalence of APC is affected by age. APC was not an independent predictor of stroke after adjusting

for age and gender in this study. Conen et al. conducted Holter ECG in 1,742 individuals in the general population who were older than 50 years of age (4). The median of APC was 1.27/h, the number of APC increased according to age, and APC was the second-strongest independent predictor of cardiovascular events after age. Huang et al. conducted a metaanalysis of the association between APC and cardiovascular events (13). Frequent APC conferred a 1.38-fold increase in the risk of cardiovascular events, and a 1.41-fold increase in the risk of stroke. Murakoshi et al. investigated the stroke risk conferred by APC in 63,197 individuals in a general population based on a single measurement of 12-ECG (14). They found that APC conferred a 1.63-fold increase in the risk of stroke death in females, and a significant increase in the risk of AF onset in both males (a 4.87-fold increase in onset risk) and females (a 3.87-fold increase). However, in the ARIC study, APC was not an independent predictor of stroke (HR 1.30, 95% CI 0.92-1.83) (15). The results on the association between stroke and APC were not concordant. Additional investigations into the association between stroke and APC will be needed, including studies accounting for the APC frequency and patient characteristics.

The stroke risk of APC patients with negative P in aVR was similar to that of

patients without APC, but the stroke risk of APC patients with non-negative P in aVR was high. There have been no reports on the association between stroke and the polarity of APC. Polarity of aVL in atrial tachycardia is useful to diagnose 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 (16). Most of the atrial electrical excitation of APC from left pulmonary vein firing is in the rightward direction anatomically, but that of APC from the right pulmonary vein firing is not. Atrial electrical excitation of APC in the right atrial septum does not proceed in the leftward direction. On the other hand, most of the atrial electrical excitation of APC in the near to 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. Such APC presenting with a negative P wave in aVR might be “benign,” because the origin of the APC was not associated with a trigger of AF, based on the fact that most AF triggers are pulmonary veins (17). Sinus arrhythmia might sometimes be misdiagnosed as APC. In such cases, the polarity of the P wave is usually negative in aVR, and considered as benign arrhythmia.

Conclusions

The prognosis of patients with APC with negative P in AVR was good, but that of patients with APC with non-negative P in AVR was poor. Polarity of APC was useful to predict stroke events in a community-dwelling population.

Contributors: TK analyzed the data and prepared the first draft of the manuscript. YI did 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.

Competing interests: TK has received scholarship fund from Mitsubishi Tanabe Pharma Corporation. KK has received research grant from A &D Co.; Omron Helthcare Co.; Roche Diagnostics K.K.; MSD K.K.; Astellas Pharma Inc.; Otsuka Holdings Co.; Otsuka Pharmaceutical Co.; Sanofi K.K.; Shionogi & Co.; Sanwa Kagaku Kenkyusho Co.; Daiichi Sankyo Co.; Sumitomo Dainippon Pharma Co.; Takeda Pharmaceutical Co.; Mitsubishi Tanabe Pharma Co.; Teijin Pharma; Boehringer Ingelheim Japan Inc.; Pfizer Japan Inc.; Fukuda Denshi Co.

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Figure legends

Figure 1. Study protocol.

APC; Atrial premature complexes, ECG: electrocardiography.

Figure 2. The 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 APC was observed in the aVR and aVL lead (black arrow). (B) A case of non-negative P wave in aVR and non-positive P wave in aVL. Neither the polarity of APC in aVR nor that in aVL could be determined (white arrows).

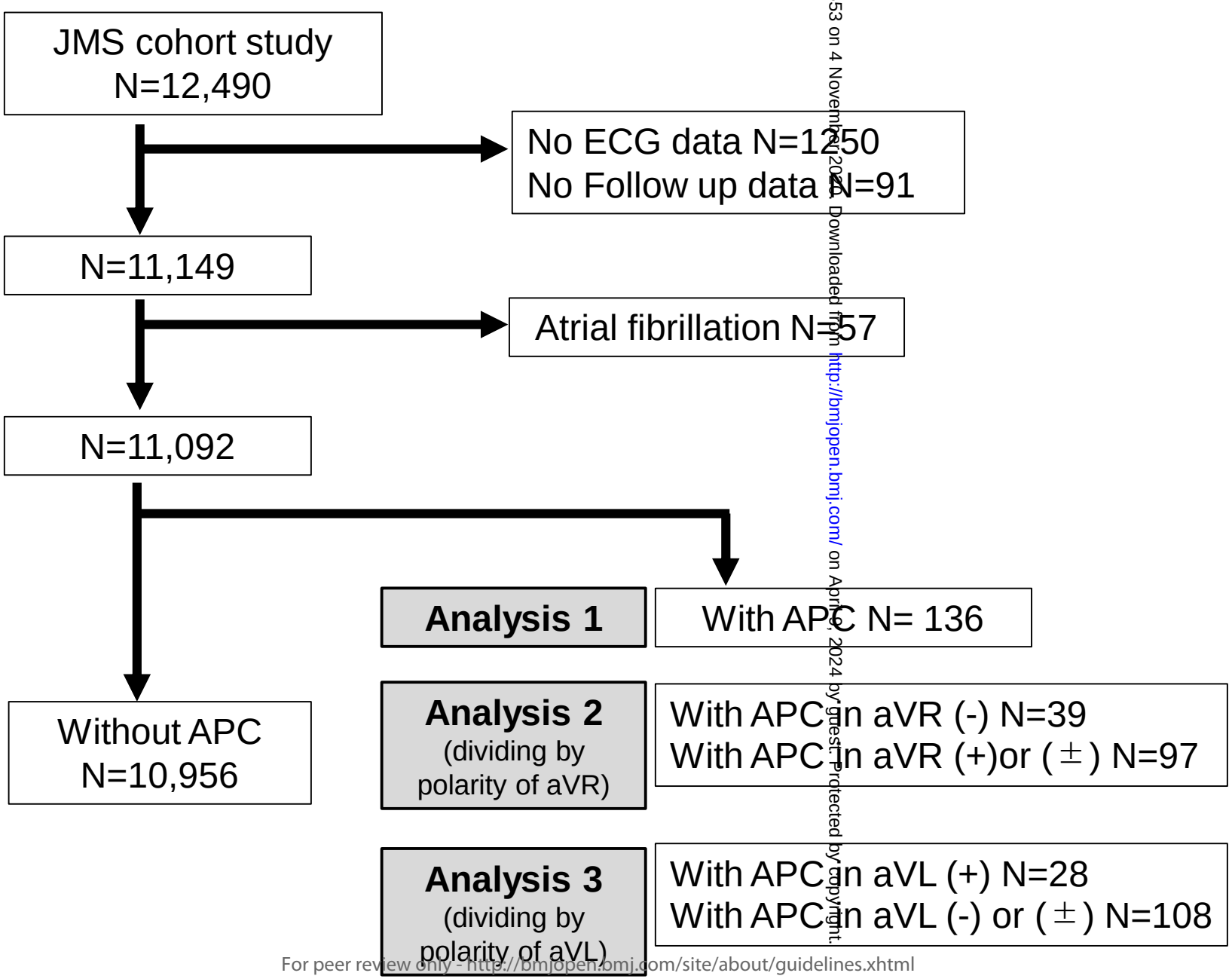
APC; Atrial premature complexes.

Figure 3. Stroke events according to APC. (A) Stroke events according to APC, (B) Stroke events according to APC style in aVR, (C) Stroke events according to APC style in aVL.

APC; Atrial premature complexes.

Figure 4. Hazard ratios according to type of APC.

APC; Atrial premature complexes.



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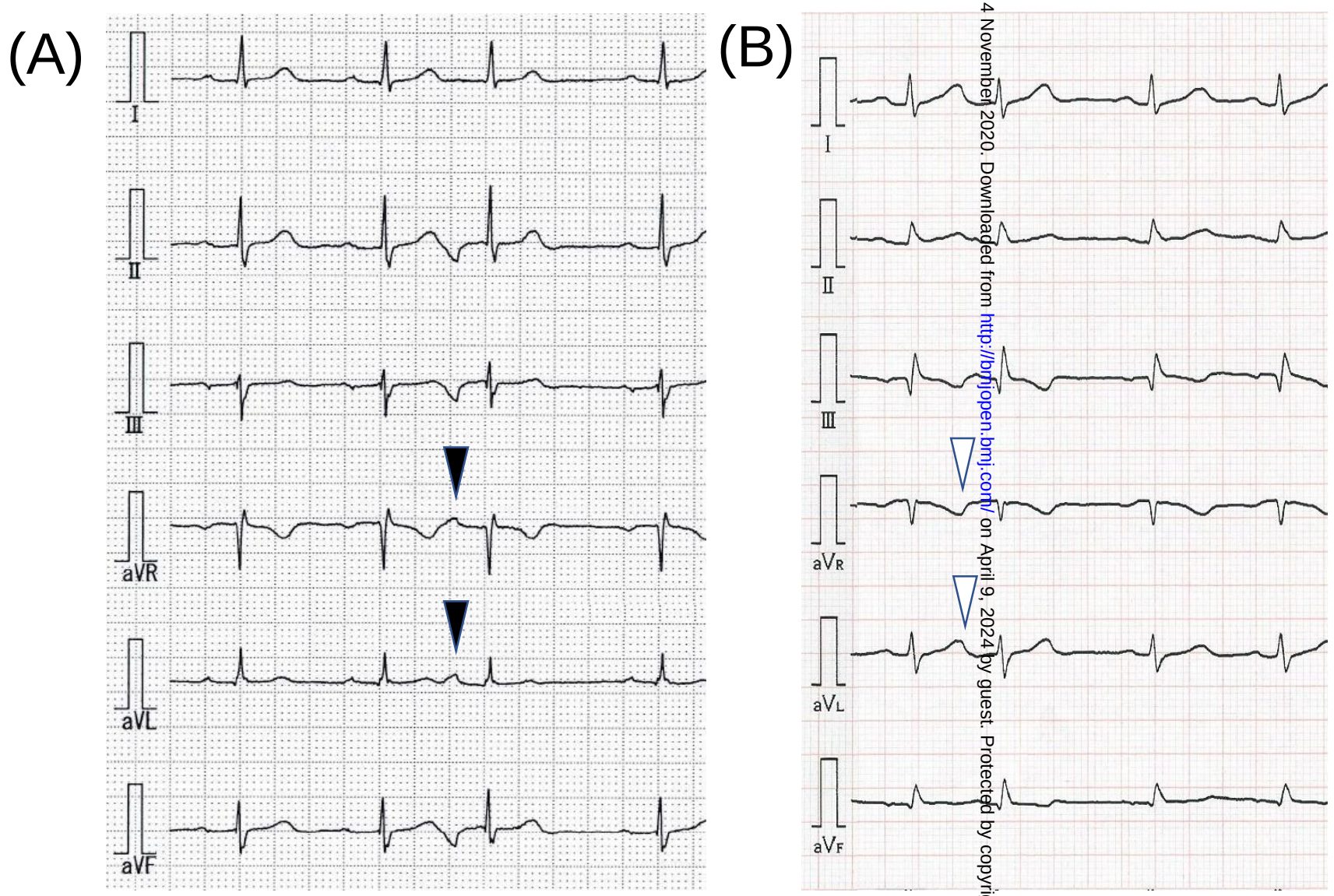

Figure 2.

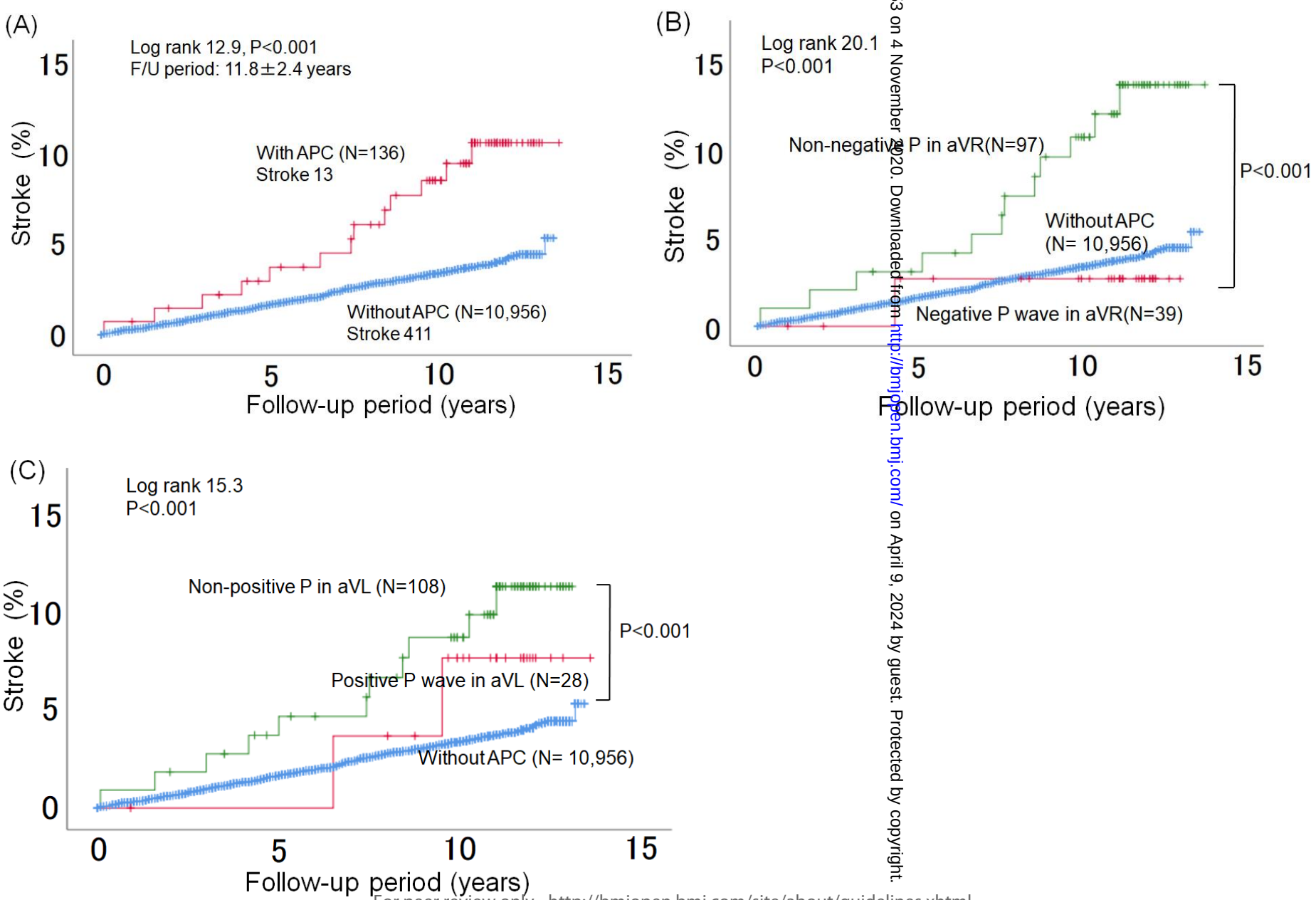

Figure 3.

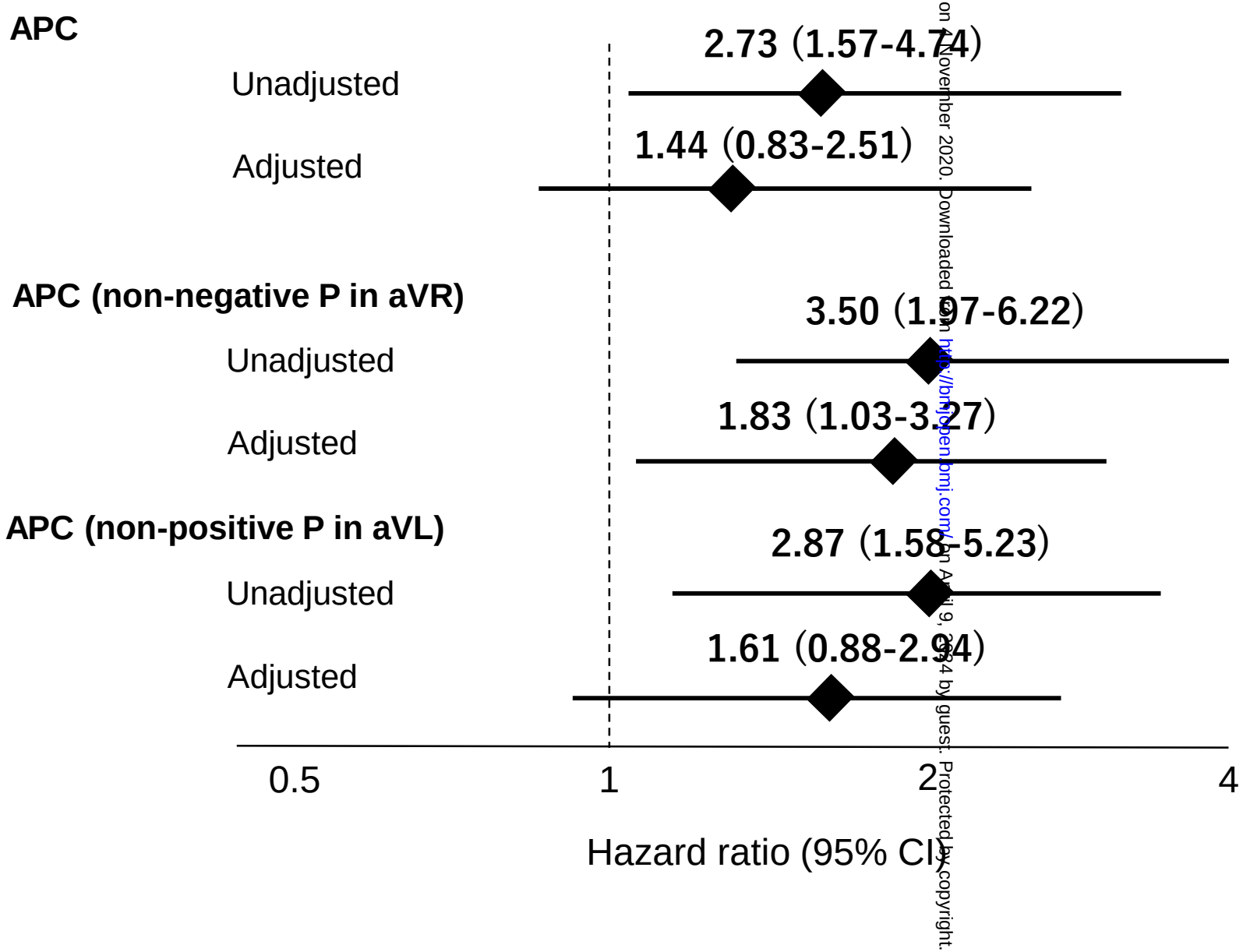

Figure 4.

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Conclusions: Presence of APC with non-negative P in aVR on 12-lead ECG is associated with higher risk of incident stroke.

Strengths and limitations of this study

1. The strength of this study is the first paper to study about the association between the polarity of APC and stroke using by large-scale and long follow-up cohort study.

2. Data were obtained from a large cohort study.

3. The origin of APC was not confirmed by an invasive procedure.

4. The number of patients with APC was small, and the number of APC-positive samples from patients with incident stroke and ischemic stroke events was also small.

Introduction

Atrial fibrillation (AF) is a major risk factor of stroke and associated with the severity of stroke, and is a common disease with aging (1-3).

Atrial premature complexes (APC) are found in healthy subjects (4). However, APC is associated with cardiovascular death (5) and ischemic stroke (6). In the general population, the detection of even a single APC by electrocardiography (ECG) is associated with AF and cardiovascular death (7). Kamel et al. reported that a mechanistic link between APC as a biomarker for cardiovascular/atrial myocardial disease was much more evident in patients who had experienced stroke (8). Thus APC is a notable predictor of stroke, but the precise role played by APC in stroke events remains unclear.

The diagnosis in focus of focal atrial tachycardia is diagnosed based on the polarity of the P wave in 12-lead ECG (9). The origin of APC associated with AF has also been investigated by using Holter ECG (10). Most of AF triggers originate from pulmonary veins (11), but the ECG assessment of the atrial electrical excitation of APC from the left pulmonary vein firing is not established. The association between the polarity of the P wave of APC obtained by 12-lead ECG and stroke remains unclear.

The aim of this study was to evaluate the association between the polarity of morphology of APC in 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 was a prospective study 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 (12). 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 APC

ECG was measured at a paper speed of 25 mm/sec 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, Japan). ECGs were manually analyzed by a single cardiologist who was blinded to the patient information.

Figure 1 shows the protocol of this study. We analyzed stroke events in patients with APC (N=136) and patients without APC (N=10,956). P waves inscribed

above the isoelectric line were classified as positive, those below as negative, those above and below (or conversely, below and above) as biphasic and flat P waves as isoelectric according to a past report (9) (Figure 2). In regard to the polarity of the P wave of APC, subjects were subcategorized as having (1) negative P wave (N=39) or non-negative P wave (including positive, biphasic and flat P wave, N=97) in aVR, and (2) positive P wave (N=28) or non-positive P wave (including negative, biphasic and flat P wave, N=108) in aVL.

Classification was performed by a single cardiologist (TK), and the kappa was evaluated in 30 cases. The levels of intra-observer agreement were found to be acceptable in the determination of APC polarity (intra-observer agreement: κ statistic=0.58 in measurement of aVR and 0.63 in measurement of aVL).

Endpoint

The details of follow-up and the diagnostic criteria are shown elsewhere (12). Briefly, most subjects were followed-up with repeat examinations each year. Subjects with such a history were asked for the time of these incidents and the names 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 hospitalized. Finally, public health nurses visited the absent subjects to obtain additional information. For all subjects, if an incident case was suspected, forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained (13).

The primary endpoint was stroke. The diagnostic criterion for stroke was sudden onset of a focal and nonconvulsive neurological deficit that lasted for more than 24 h (14). Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurologic deficit was completely cleared within 24 h from the onset of symptoms.

Diagnosis of the stroke events was determined under the consensus of all the members of the diagnostic committee.

Ethical issues

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health

checkup.

Statistical analysis

Data are shown as the mean±SD or as a 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 the Bonferroni test.

Cumulative incidences of stroke and ischemic stroke in the groups classified by the presence/absence of APC or by the polarity of the P wave of APC were plotted as Kaplan-Meier curves, and the differences were assessed by the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) of the incidences of stroke in the subgroups were calculated using Cox regression analyses after adjustments for age, sex, height, and current smoking.

SPSS version 20.0 software (IBM, Armonk, NY) was used for the statistical analysis. 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. No patients were involved in the design or performance of the study. No plans were set in place to spread the results of the research to study participants.

Results

The mean age of subjects was 55.7± 11.2 years, the average BMI was 23.1±3.1 kg/m^2, and the percentages of male sex, hypertension and diabetes were 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 ischemic stroke events) in patients without APC, and 13 stroke events (9 ischemic stroke events) in patients with APC.

Table 1 shows the baseline characteristics of the patients with APC according to the polarity of the P wave in aVR and aVL. Patients with APC with non-negative P in aVR were older (63.7±9.6 vs. 55.6±11.2 yrs, p<0.001), and had higher systolic blood pressure (136±20 vs. 130±21mmHg, p=0.015) than patients without APC.

Table 1. Patient characteristics

	Patients without APC (N=10,956)	Patients with APC		Patients with APC	
		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 (y)	**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/m²)	**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**
Hypertension (%)	**17**	**24**	**27***	**48***	**20****
Diabetes (%)	**4**	**3**	**4**	**4**	**4**
Prior stroke (%)	**1**	**0**	**3**	**4**	**2**
Prior myocardial infarction (%)	**1**	**5*****	**1**	**4**	**2**
Systolic BP (mmHg)	**130±21**	**131±22**	**136±20***	**142±26****	**132±19**
Diastolic BP (mmHg)	**78±12**	**74±15**	**79±12**	**81±13**	**77±13**
T-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**

BP: blood pressure; HDL: high density lipoprotein. * p<0.05, ** p<0.01, *** p<0.001 vs. patients without APC.

The incidence of stroke in patients with APC and patients without APC is shown in Fig. 3A. The difference in incidence of stroke was significant (log rank 12.9, p<0.001). The difference in incidence of stroke in patients according to the P wave polarity is shown in Fig. 3B and C. The incidence of stroke in APC patients with non-negative P in aVR was significantly higher than that in patients without APC (log rank 20.1, p<0.001), and the incidence of stroke in APC patients with non-positive P in aVL was also significantly higher than that in patients without APC (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, ~~gender~~ sex, height and current smoking, APC was not an independent predictor (HR 1.48, 95% CI 0.85-2.59, p=0.17), but APC of non-negative P in aVR was an independent predictor of stroke (HR 1.81, 95% CI 1.01-3.23, p=0.045). APC of non-positive P in aVL was not an independent predictor of stroke (HR 1.75, 95% CI 0.96-3.20, p=0.069).

We also conducted an analysis of ischemic stroke events by Cox proportional hazard model (Figure 4B). Before adjusting for covariates, APC, APC of non-negative P in aVR, and APC of non-positive P in aVL were predictors of ischemic stroke [APC: HR 2.92 (95% CI 1.50-5.68); APC of non-negative P in aVR: HR 3.61 (95% CI 1.79-7.30); APC of non-positive P in aVL: HR 2.82 (95% CI 1.34-5.99)]. However, after adjustment for age, sex, height, and current smoking, those factors were not independent predictors of stroke (Figure 4B).

We divided patients into two groups by age: patients ≥65 years and those <65 years. Among patients less than <65 years, before adjusting for covariates, APC, APC of non-negative P in aVR, and APC of non-positive P in aVL were not significantly associated with stroke [APC: HR 2.11 (95% CI 0.67-6.58), p=0.20; non-negative P in aVR: HR 2.80 (955 CI 0.89-8.75), p=0.077; non-positive P in aVL: HR 2.44 (95% CI 0.78-7.64), p=0.12]. However, among patients aged 65

years or more, before adjusting for covariates, APC of non-negative P in aVR was associated with stroke [hazard ratio 2.23 (95% CI: 1.14-4.35), p=0.019]. APC and APC of non-positive P in aVL were not significantly associated with ischemic stroke [APC: HR 1.72 (0.91-3.24), p=0.094; non-positive P in aVL: HR 1.82 (95% CI 0.90-3.68), p=0.098].

Discussion

The main findings of this study were that the prognosis of patients with APC with negative P in aVR was good, but that in patients with APC with non-negative P in aVR was poor. APC was not an independent predictor of stroke after adjusting for age and sex.

In this study, APC was associated with stroke before adjustment of covariates. The result is concordant with past reports. However, the prevalence of APC is affected by age. APC was not an independent predictor of stroke after adjusting for age and sex in this study. Conen et al. conducted Holter ECG in 1,742 individuals in the general population who were older than 50 years of age (4). The median of APC was 1.27/h, the number of APC increased according to age, and APC was the second-strongest independent predictor of cardiovascular

events after age. Huang et al. conducted a metaanalysis of the association between APC and cardiovascular events (15). Frequent APC conferred a 1.41-fold increase in the risk of stroke. Murakoshi et al. investigated the stroke risk conferred by APC in 63,197 individuals in a general population based on a single measurement of 12-ECG (16). They found that APC conferred a 1.63-fold increase in the risk of stroke death in females. However, in the ARIC study, APC was not an independent predictor of stroke (HR 1.30, 95% CI 0.92-1.83) (17). The results on the association between stroke and APC were not concordant. Himmelreich et al. conducted a meta-analysis for the outcome of stroke based on dichotomized Holter data, and the hazard ratio was 2.54 (18). Additional investigations into the association between stroke and APC will be needed, including studies accounting for the APC frequency and patient characteristics.

The stroke risk of APC patients with negative P in aVR was similar to that of patients without APC, but the stroke risk of APC patients with non-negative P in aVR was high. There have been no reports on the association between stroke and the polarity of APC. Polarity of aVL in atrial tachycardia is useful to diagnose 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 (19). Most of AF

triggers originate from pulmonary veins (11). Most of the atrial electrical excitation of APC from left pulmonary vein firing is in the rightward direction anatomically, but that of APC from the right pulmonary vein firing is not. Atrial electrical excitation of APC in the right atrial septum does not proceed in the leftward direction. On the other hand, most of the atrial electrical excitation of APC in the near to 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. Such APC presenting with a negative P wave in aVR might be “benign,” because the origin of the APC was not associated with a trigger of AF. Sinus arrhythmia might sometimes be misdiagnosed as APC. In such cases, the polarity of the P wave is usually negative in aVR, and considered as benign arrhythmia.

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

covariates. The modest kappa statistic for APC polarity 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 inter-observer agreement. Finally, we did not obtain data on the proportion of patients who received anticoagulation and AF during follow-up, which could have affected stroke events.

Conclusions

Presence of APC with non-negative P in aVR on 12-lead ECG is associated with higher risk of incident stroke. Polarity of APC was useful to predict stroke events in a community-dwelling population.

Contributors: TK analyzed the data and prepared the first draft of the manuscript. YI did 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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Figure legends

Figure 1. Study protocol.

APC; Atrial premature complexes, ECG: electrocardiography.

Figure 2. The 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 APC was observed in the aVR and aVL lead (black arrow). (B) A case of non-negative P wave in aVR and non-positive P wave in aVL. Neither the polarity of APC in aVR nor that in aVL could be determined (white arrows).

APC; Atrial premature complexes.

Figure 3. Stroke events according to APC. (A) Stroke events according to APC, (B) Stroke events according to APC style in aVR, (C) Stroke events according to APC style in aVL. Ischemic stroke events according to APC. (D) Ischemic stroke events according to APC, (E) Ischemic stroke events according to APC style in aVR, (F) Ischemic stroke events according to APC style in aVL.

APC; Atrial premature complexes.

Figure 4. Hazard ratios according to type of APC.

APC; Atrial premature complexes.

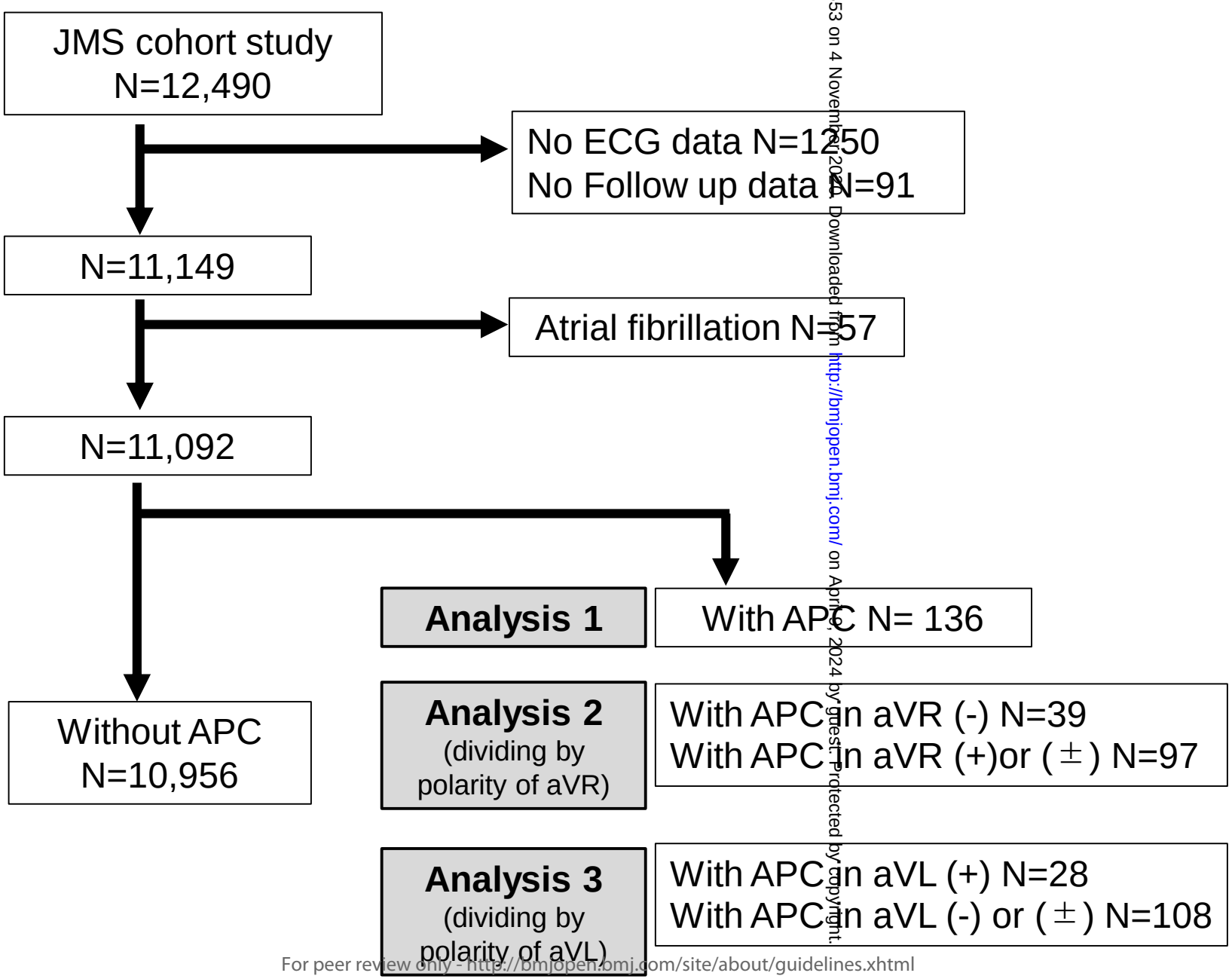


Figure 1.

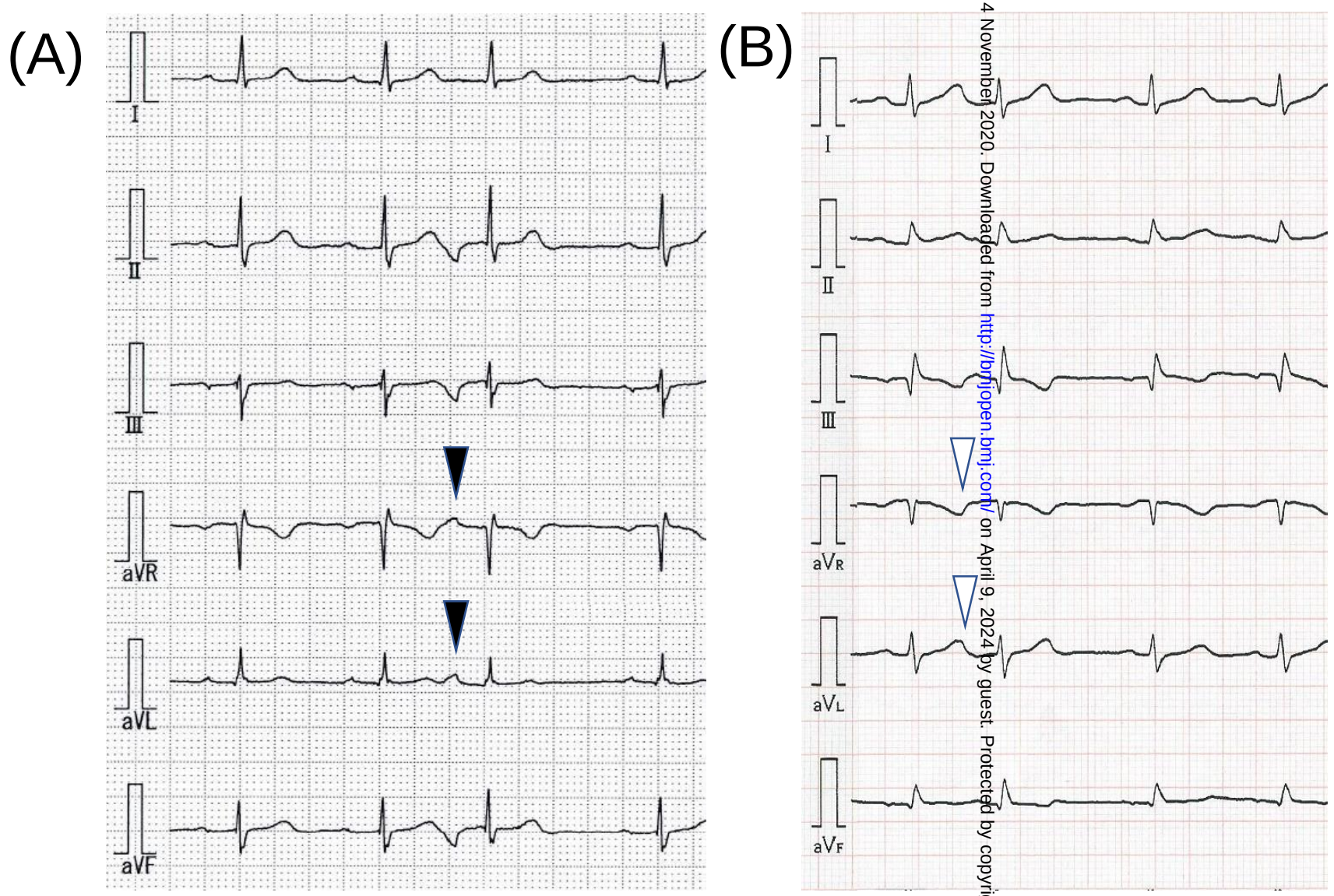


Figure 2.

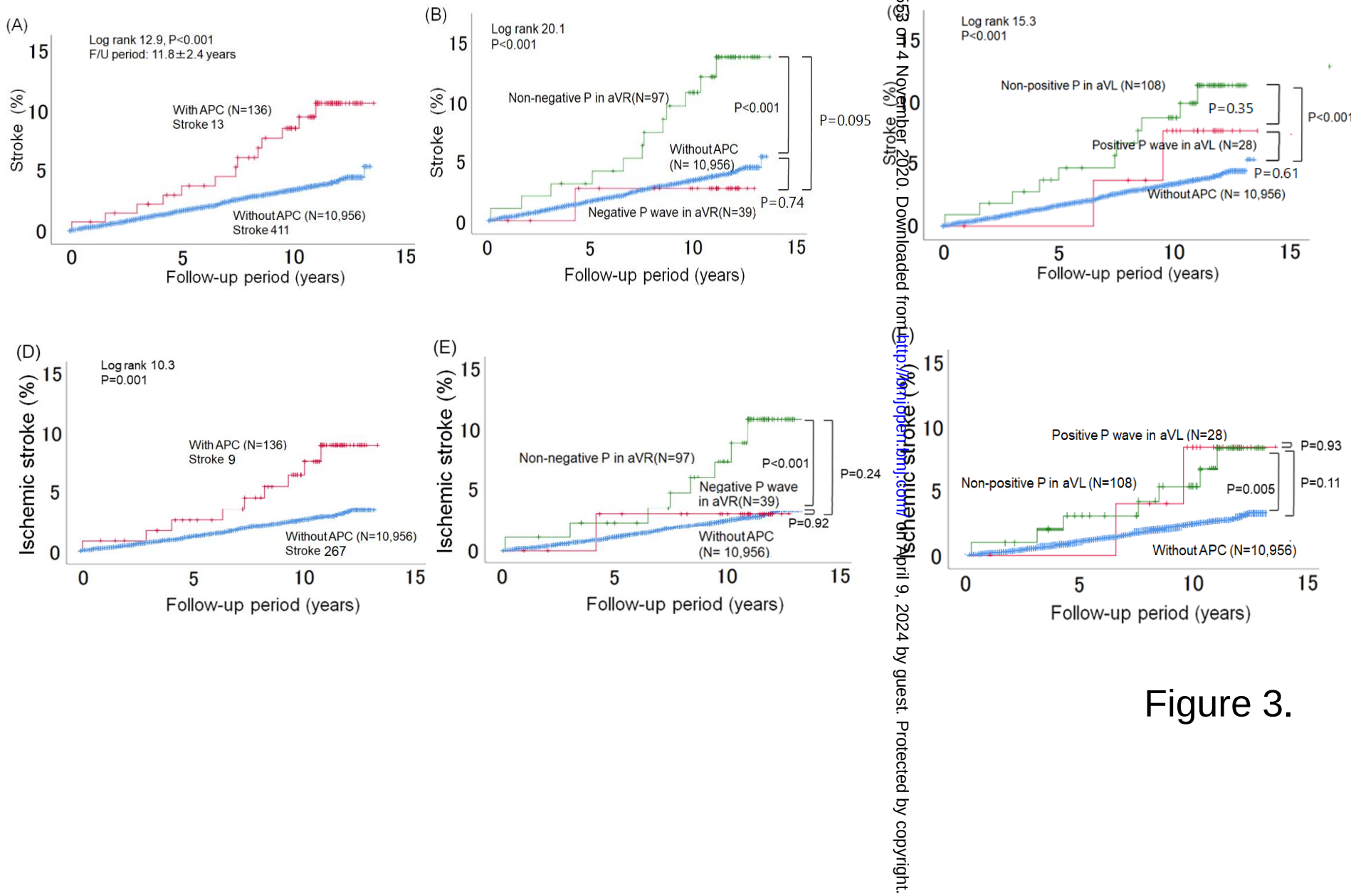
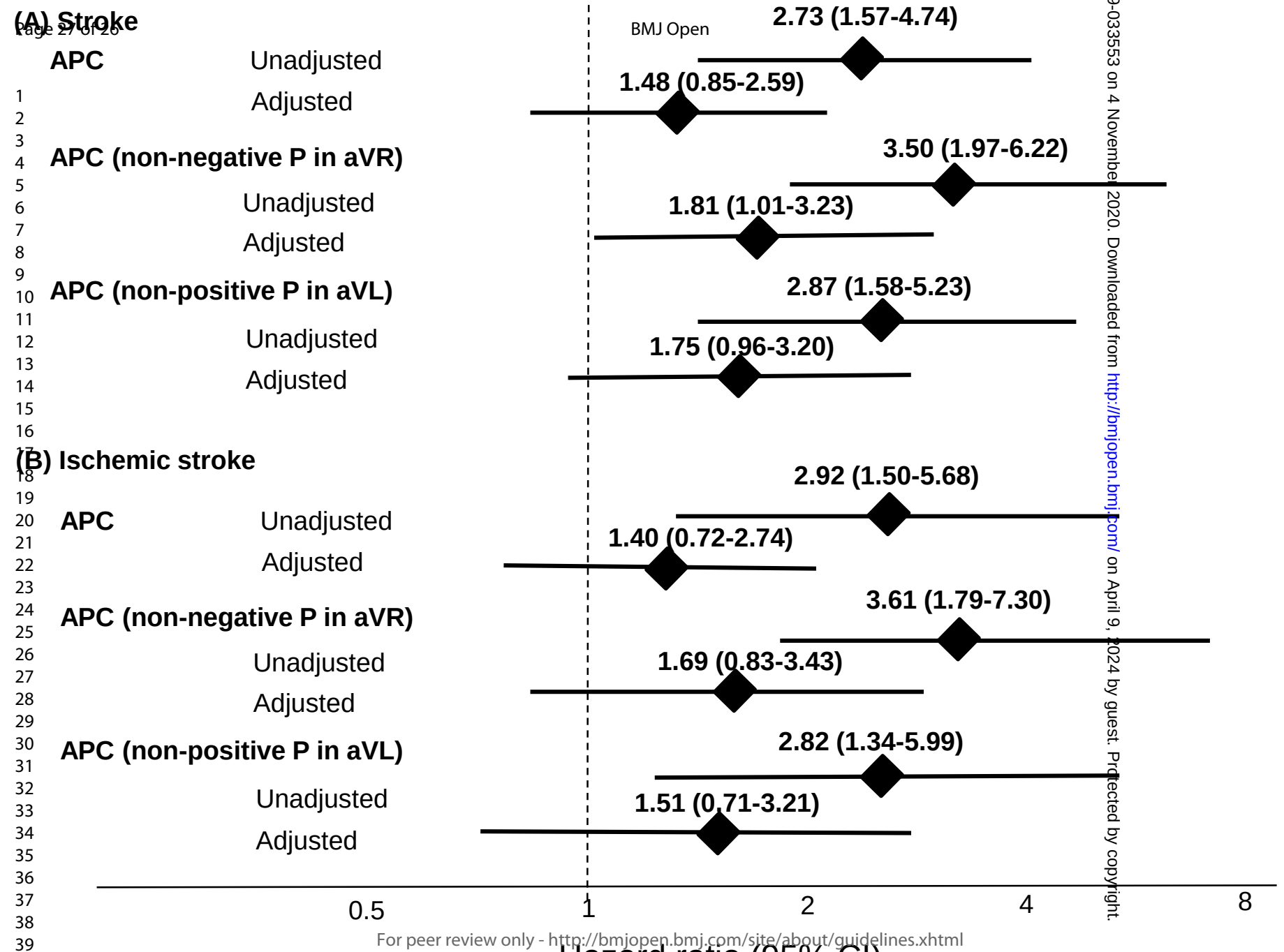


Figure 3.



Adjusted for age, gender, height and smoking

Figure 4.

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The association between the polarity of P-wave in atrial premature complexes and cardiovascular events in a community-dwelling population

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Running title: APCs and stroke

Key words: atrial premature complex, P-wave, stroke

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

Design: A prospective study.

Setting and participants: A total 11,092 participants in the JMS-cohort study after excluding patients with atrial fibrillation were included in this study. We analyzed stroke events in patients with (n=136) and without APCs (n=10,956). In regard to the polarity of APCs, the patients were subcategorized as having (1) negative (n=39) or non-negative (n=97) P waves in aVR, and (2) positive (n=28) or non-positive (n=108) P waves in aVL.

Outcome measures: The primary endpoint was stroke.

Results: The patients with APCs were significantly older than those without APCs (64.1±9.2 vs. 55.1±11.6 yrs, 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), but 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 stroke incidence in the patients with APCs and non-

negative P wave in aVR was significantly higher than that in the 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 (hazard ratio [HR] 1.84, 95%CI 1.02–3.30). The incidence of stroke in the APC patients with non-positive P in aVL was also significantly higher than that in the patients without APCs (log rank 15.3, p<0.001), and non-positive P in aVL was an independent stroke predictor (HR 1.92, 95%CI 1.05–3.54).

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.

Strengths and limitations of this study

1. Data were from a large cohort study over an 11-year period.
2. Stroke events in patients with APCs divided by the polarity of APCs were evaluated.
3. The polarity of APCs was associated with the origination of APCs.
4. The origin of APCs was not confirmed by an invasive procedure.
5. The number of patients with APCs was small.

Introduction

Atrial fibrillation (AF) is a major risk factor of stroke, is associated with the severity of stroke, and is a common disease with aging (1–3). Atrial premature complexes (APCs) are found in healthy subjects (4). However, APCs are also associated with cardiovascular death (5) and ischemic stroke (6). In the general population, the detection of even a single APC by electrocardiography (ECG) is associated with AF and cardiovascular death (7). Kamel et al. reported that a mechanistic link between APCs as a biomarker for cardiovascular/atrial myocardial disease was much more evident in patients who had experienced stroke (8). 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 in 12-lead ECG (9). The origin of APCs associated with AF has also been investigated by using Holter ECG (10). Most of the triggers of AF originate from pulmonary veins (11), but the method for ECG assessment of the atrial electrical excitation of APCs from the firing of the left pulmonary vein is not 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 in 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 was a prospective study 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 (12). 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 (Fig. 1).

ECG analysis and classification of APCs

ECG was measured at a paper speed of 25 mm/sec 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 analyzed by a single cardiologist who was blinded to the patient information.

Figure 1 illustrates the study protocol. We analyzed stroke events in

patients with APCs (n=136) and patients without APCs (n=10,956). Based on a past report (9), 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 (Fig. 2).

In regard to the polarity of the P wave of APCs, we subcategorized the patients as having (1) negative P wave (n=39) or non-negative P wave (including positive, biphasic, and flat P wave, n=97) in aVR, and (2) positive P wave (n=28) or non-positive P wave (including negative, biphasic and flat P wave, n=108) in aVL.

Classification was performed by a single cardiologist (T.K.), and the kappa was evaluated in 30 cases. The levels of intra-observer agreement were found to be acceptable in the determination of polarity in APCs (intra-observer agreement: κ statistic=0.58 in the measurement of aVR and 0.63 in the measurement of aVL).

Endpoint

The details of the follow-up and the diagnostic criteria are shown elsewhere (12). 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 names 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 hospitalized. Finally, public health nurses visited the absent subjects to obtain additional information. For all subjects, if an incident case was suspected, the forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained (13).

The primary endpoint was stroke. The diagnostic criterion for stroke was sudden onset of a focal and nonconvulsive neurological deficit that lasted for more than 24 h (14). Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurologic deficit was completely cleared within 24 h from the onset of symptoms.

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

Ethical issues

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health checkup.

Statistical analysis

Data are shown as the mean±SD or as a percentage. The $\chi 2$ test was used for categorical data, and an analysis of variance was used for comparisons among the groups. Intergroup differences were tested by the Bonferroni test.

The incidences of stroke and ischemic stroke in the groups classified by the presence/absence of APCs or by the polarity of the P wave of APCs were plotted as Kaplan-Meier curves, and the differences were assessed by the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) of the incidences of stroke and ischemic stroke in the subgroups were calculated using Cox regression analyses after adjustments 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 ver. 20.0 software (IBM, Armonk, NY) was used for the 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. No patients were involved in the design or performance of the study. No plans were set in place to spread the results of the research to study participants.

Results

The mean age of the subjects was 55.7±11.2 years, the average BMI was 23.1±3.1 kg/m^2, and the percentages of male, hypertension, and diabetes were 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 ischemic stroke events) in the patients without APCs, and 13 stroke events (9 ischemic stroke events) in the patients with APCs.

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

Table 1. Patient characteristics

	Patients without APCs (n=10,956)	Patients with APCs			
		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 (y)	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^2)	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 (mmHg)	130±21	131±22	136±20*	142±26**	132±19
Diastolic BP (mmHg)	78±12	74±15	79±12	81±13	77±13
T-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 vs. patients without APCs. BP: blood pressure; HDL: high-density lipoprotein; MI: myocardial infarction.

The incidence of stroke/ ischemic stroke in the patients with APCs and that in the patients without APCs are shown in Figure 3A-F. The difference in incidence of stroke was significant (log rank 12.9, p<0.001). The difference in the incidence of stroke in the patients according to the P-wave polarity is shown in Figure 3B and C. The incidence of stroke in the APC patients with non-negative P in aVR was significantly higher than that in the patients without APCs (log rank 20.1, p<0.001), and the incidence of stroke in the APC patients with non-positive P in aVL was also significantly higher than that in the 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 not an independent predictor (HR 1.51, 95%CI 0.86–2.65, 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 1.02–3.30, p=0.042; APCs of non-positive P in aVL: HR 1.92, 95%CI 1.05–3.54, p=0.035).

We also conducted the Kaplan-Meier curve of ischemic stroke (Fig. 3D–F) and analyzed the ischemic stroke events by Cox proportional hazard model (Fig.

4B). Before adjusting for covariates, APCs, APCs of non-negative P in aVR, and APCs of non-positive P in aVL were predictors of ischemic stroke [APCs: HR 2.92 (95%CI 1.50-5.68); APCs of non-negative P in aVR: HR 3.61 (95%CI 1.79–7.30); and APCs of non-positive P in aVL: HR 2.82 (95%CI 1.34–5.99)]. However, after adjustment for age, sex, height, BMI, current drinking, diabetes, SBP, prior MI, prior stroke, and HDL-cholesterol, those factors were not independent predictors of ischemic stroke (Fig. 4B).

We divided the patients into two groups by age: patients ≥65 years and those <65 years. Among the 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 0.67–6.58), p=0.20; non-negative P in aVR: HR 2.80 (95%CI 0.89–8.75), p=0.077; non-positive P in aVL: HR 2.44 (95%CI 0.78–7.64), p=0.12]. However, among the patients aged 65 years or more, before adjusting for covariates, APCs of non-negative P in aVR was associated with stroke [HR 2.23 (95%CI 1.14–4.35), p=0.019]. APCs and APCs of non-positive P in aVL were not significantly associated with stroke [APCs: HR 1.72 (95%CI 0.91–3.24), p=0.094; non-positive P in aVL: HR 1.82 (95%CI 0.90–3.68), p=0.098].

Discussion

The main findings of this study were that the prognoses of the patients with APCs with negative P in aVR or positive P wave in aVL were good, but the that in the patients with APCs with non-negative P in aVR or non-positive P wave in aVL were poor. 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 the adjustment of covariates. The result is concordant with past 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. conducted Holter ECG in 1,742 individuals in the general population who were older than 50 years of age (4). The median number of APCs was 1.27/h; 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. conducted a meta-analysis of the association between APCs and cardiovascular events (15). Frequent APCs conferred a 1.41-fold increase in the

risk of stroke.

Murakoshi et al. investigated the stroke risk conferred by APCs in 63,197 individuals in a general population based on a single measurement of 12-ECG (7), and they observed that APCs conferred a 1.63-fold increase in the risk of stroke death in females. However, in the ARIC study, the presence of APCs was not an independent predictor of ischemic stroke (HR 1.30, 95%CI 0.92–1.83) (16). The strength of the results on the association between ischemic stroke and APCs might be less than that between any type of stroke and APCs. Himmelreich et al. conducted a meta-analysis for the outcome of ischemic stroke based on dichotomized Holter data, and the HR was 2.54 (17). Additional investigations into the association between stroke and APC will be needed, including studies accounting for the frequency of APCs and patient characteristics.

The stroke risk of APC patients with negative P in aVR was similar to that of the patients without APCs, but the stroke risk of the 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 to diagnose 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 (18). Most triggers of AF originate from pulmonary veins (11). 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 in the near to 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 a trigger of AF. Sinus arrhythmia might sometimes be misdiagnosed as APC. In such cases, the polarity of the P wave is usually negative in aVR or positive P wave in aVL and considered benign arrhythmia. The prevalence of APCs was relatively low in the present study, but in past reports APCs were associated with AF and cardiovascular events, including ischemic stroke (6,7). Thus, risk stratification by the polarity of APCs might be helpful to detect AF earlier and prevent cardiovascular events.

The strength of this study is that it is the first paper to study the association

between the polarity of APCs and stroke by 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 ischemic stroke events was also small. Potentially insufficient statistical power (type II error) was an issue, and we could not check interactions between covariates. Further studies enrolling large numbers of patients with APCs are needed. The modest kappa statistic 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 inter-observer agreement. Finally, we did not obtain data on LDL-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 to predict stroke events in a community-dwelling population.

Contributors: TK analyzed 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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Data sharing statement

No data are available.

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Figure legends

Figure 1. Study protocol. APC: atrial premature complexes; ECG: electrocardiography.

Figure 2. The 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*).

APC; Atrial premature complexes.

Figure 3. Stroke events according to APCs. (A) Stroke events according to APCs, (B) Stroke events according to APC style in aVR, (C) Stroke events according to APC style in aVL. Ischemic stroke events according to APC. (D) Ischemic stroke events according to APCs, (E) Ischemic stroke events according to APC style in aVR, (F) Ischemic stroke events according to APC style in aVL.

APC; Atrial premature complexes.

Figure 4. Hazard ratios according to type of APCs. APC; Atrial premature complexes; HDL: high-density lipoprotein

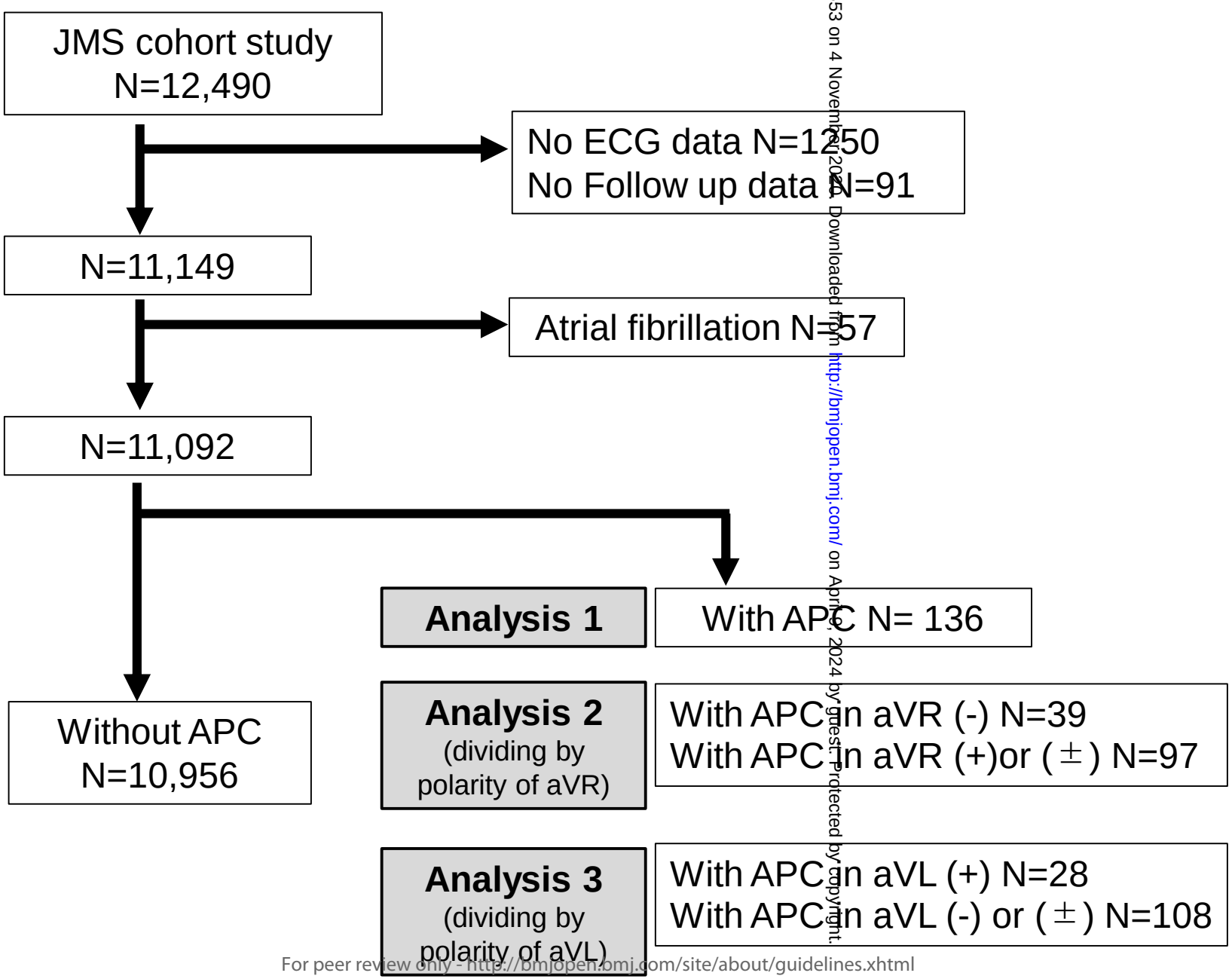


Figure 1.

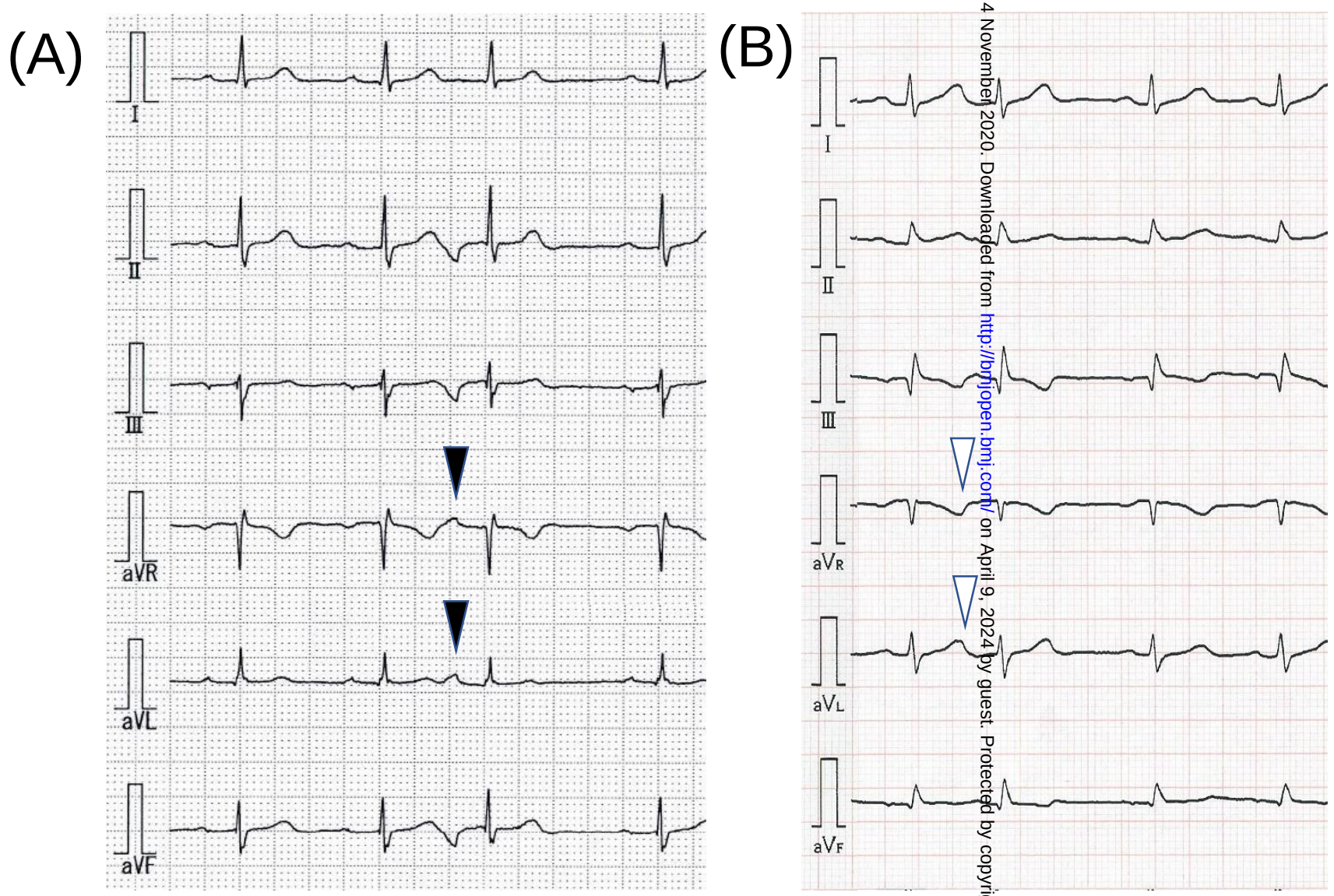


Figure 2.

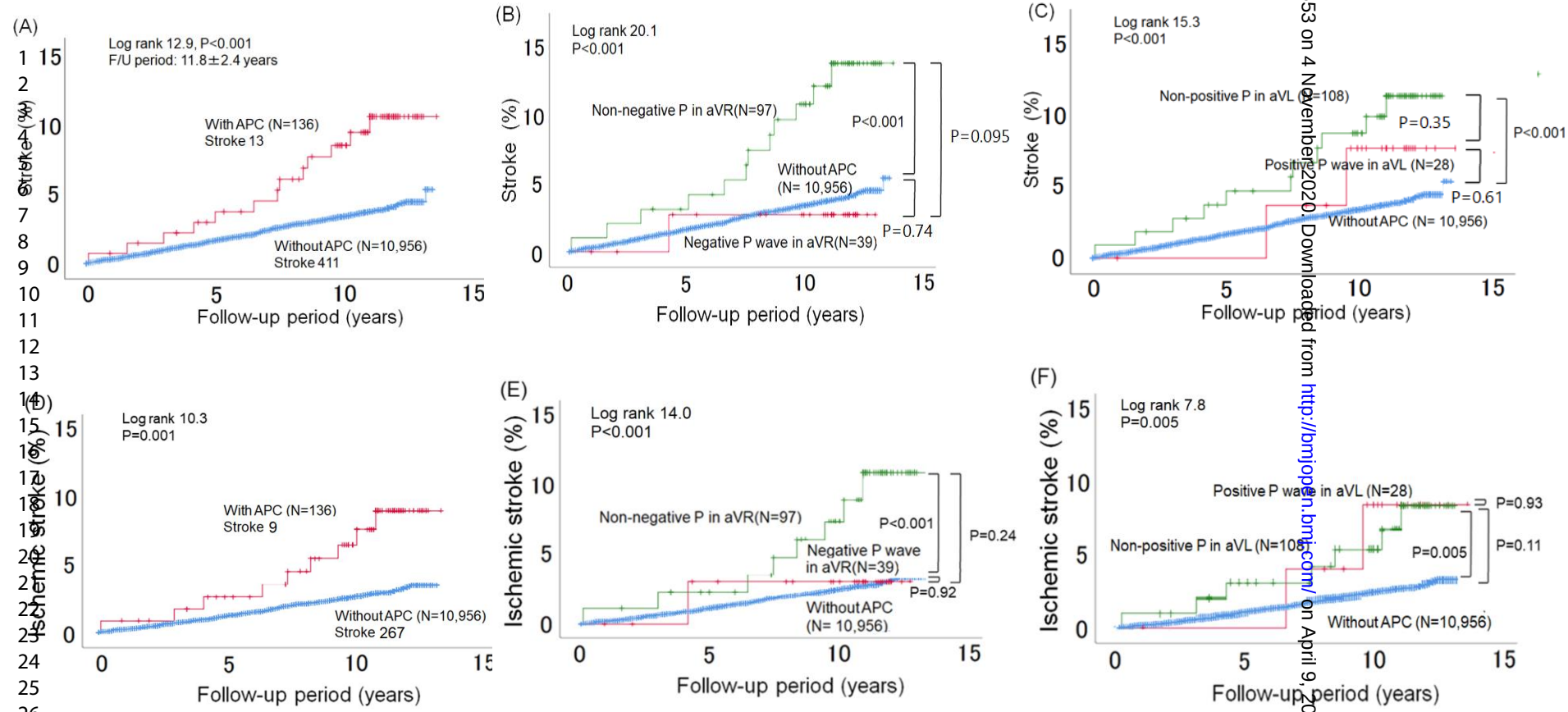
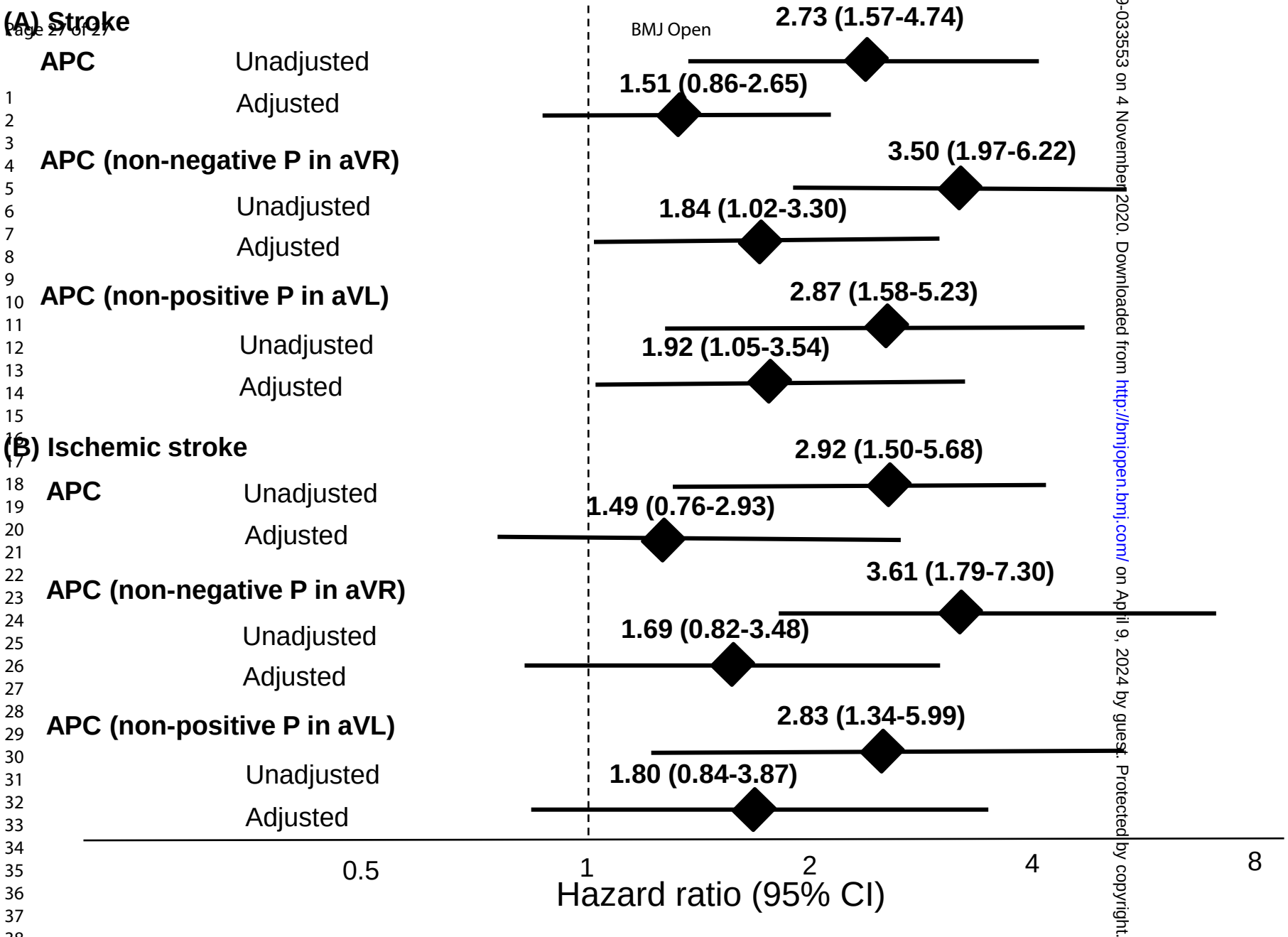


Figure 3.



Adjusted for age, sex, height, body mass index, current drinking, diabetes, systolic blood pressure, prior myocardial infarction, prior stroke, and HDL-choresterol.

Figure 4.

STROBE Statement

Checklist of items that should be included in reports of *cohort studies*

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The association between P-wave polarity in atrial premature complexes and cardiovascular events in a community-dwelling population

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The association between P-wave polarity in atrial premature complexes and cardiovascular events in a community-dwelling population

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Running title: APCs and stroke

Key words: atrial premature complex, P-wave, stroke

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

Design: A prospective study.

Setting and participants: A total 11,092 participants in the JMS-cohort study were included in this study after excluding patients with atrial fibrillation. We analyzed stroke events in patients with (n=136) and without APCs (n=10,956). In regard to the polarity of APCs, the patients were subcategorized as having (1) negative (n=39) or non-negative (n=97) P waves in aVR, and (2) positive (n=28) or non-positive (n=108) P waves in aVL.

Outcome measures: The primary endpoint was stroke.

Results: The patients with APCs were significantly older than those without APCs (64.1±9.2 vs. 55.1±11.6 yrs, 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), but 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 stroke incidence in the patients with APCs and non-

negative P wave in aVR was significantly higher than that in the 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 (hazard ratio [HR] 1.84, 95%CI 1.02–3.30). The incidence of stroke in the APC patients with non-positive P wave in aVL was also significantly higher than that in the patients without APCs (log rank 15.3, p<0.001), and non-positive P wave in aVL was an independent stroke predictor (HR 1.92, 95%CI 1.05–3.54).

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.

Strengths and limitations of this study

1. Data were from a large cohort study over an 11-year period.
2. Stroke events in patients with APCs divided by the polarity of APCs were evaluated.
3. The polarity of APCs was associated with the origination of APCs.
4. The origin of APCs was not confirmed by an invasive procedure.
5. The number of patients with APCs was small.

Introduction

Atrial fibrillation (AF) is a major risk factor of stroke, is associated with the severity of stroke, and is a common disease with aging (1–3). Atrial premature complexes (APCs) are found in healthy subjects (4). However, APCs are also associated with cardiovascular death (5) and ischemic stroke (6). In the general population, the detection of even a single APC by electrocardiography (ECG) is associated with AF and cardiovascular death (7). Kamel et al. reported that a mechanistic link between APCs as a biomarker for cardiovascular/atrial myocardial disease was much more evident in patients who had experienced stroke (8). 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 in 12-lead ECG (9). The origin of APCs associated with AF has also been investigated by using Holter ECG (10). Most of the triggers of AF originate from pulmonary veins (11), but a method for ECG assessment of the atrial electrical excitation of APCs from the firing of the 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 in 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 was a prospective study 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 (12). 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 (Fig. 1).

ECG analysis and classification of APCs

ECG was measured at a paper speed of 25 mm/sec 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 analyzed by a single cardiologist who was blinded to the patient information.

Figure 1 illustrates the study protocol. We analyzed stroke events in

patients with APCs (n=136) and patients without APCs (n=10,956). Based on a past report (9), 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 (Fig. 2).

In regard to the polarity of the P wave of APCs, we subcategorized the patients as having (1) negative P wave (n=39) or non-negative P wave (including positive, biphasic, and flat P wave, n=97) in aVR, and (2) positive P wave (n=28) or non-positive P wave (including negative, biphasic and flat P wave, n=108) in aVL.

Classification was performed by a single cardiologist (T.K.), and the kappa was evaluated in 30 cases. The levels of intra-observer agreement were found to be acceptable in the determination of polarity in APCs (intra-observer agreement: κ statistic=0.58 in the measurement of aVR and 0.63 in the measurement of aVL).

Endpoint

The details of the follow-up and the diagnostic criteria are shown elsewhere (12). 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 names 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 hospitalized. Finally, public health nurses visited the absent subjects to obtain additional information. For all subjects, if an incident case was suspected, the forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained (13).

The primary endpoint was stroke. The diagnostic criterion for stroke was sudden onset of a focal and nonconvulsive neurological deficit that lasted for more than 24 h (14). Stroke events included ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage), and undefined type of stroke. We excluded transient ischemic attacks in which the neurologic deficit was completely cleared within 24 h from the onset of symptoms.

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

Ethical issues

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health checkup.

Statistical analysis

Data are shown as the mean±SD or as a percentage. The $\chi 2$ test was used for categorical data, and an analysis of variance was used for comparisons among the groups. Intergroup differences were tested by the Bonferroni test.

The incidences of stroke and ischemic stroke in the groups classified by the presence/absence of APCs or by the polarity of the P wave of APCs were plotted as Kaplan-Meier curves, and the differences were assessed by the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) of the incidences of stroke and ischemic stroke in the subgroups were calculated using Cox regression analyses after adjustments 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 ver. 20.0 software (IBM, Armonk, NY) was used for the 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. No patients were involved in the design or performance of the study. No plans were set in place to spread the results of the research to study participants.

Results

The mean age of the subjects was 55.7±11.2 years, the average BMI was 23.1±3.1 kg/m^2, and the percentages of males, hypertension, and diabetes were 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 ischemic stroke events) in the patients without APCs, and 13 stroke events (9 ischemic stroke events) in the patients with APCs.

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

Table 1. Patient characteristics

	Patients without APCs (n=10,956)	Patients with APCs			
		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 (y)	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^2)	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 (mmHg)	130±21	131±22	136±20*	142±26**	132±19
Diastolic BP (mmHg)	78±12	74±15	79±12	81±13	77±13
T-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 vs. patients without APCs. BP: blood pressure; HDL: high-density lipoprotein; MI: myocardial infarction.

The incidence of stroke/ischemic stroke in the patients with APCs and that in the patients without APCs are shown in Figure 3A–F. The difference in incidence of stroke was significant (log rank 12.9, p<0.001). The difference in the incidence of stroke in the patients according to the P-wave polarity is shown in Figure 3B and C. The incidence of stroke in the APC patients with non-negative P in aVR was significantly higher than that in the patients without APCs (log rank 20.1, p<0.001), and the incidence of stroke in the APC patients with non-positive P in aVL was also significantly higher than that in the 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 not an independent predictor (HR 1.51, 95%CI 0.86–2.65, 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 1.02–3.30, p=0.042; APCs of non-positive P in aVL: HR 1.92, 95%CI 1.05–3.54, p=0.035).

We also conducted a Kaplan-Meier curve analysis of ischemic stroke (Fig. 3D–F) and analyzed the ischemic stroke events by Cox proportional hazard

model (Fig. 4B). Before adjusting for covariates, APCs, APCs of non-negative P in aVR, and APCs of non-positive P in aVL were predictors of ischemic stroke [APCs: HR 2.92 (95%CI 1.50–5.68); APCs of non-negative P in aVR: HR 3.61 (95%CI 1.79–7.30); and APCs of non-positive P in aVL: HR 2.82 (95%CI 1.34–5.99)]. However, after adjustment for age, sex, height, BMI, current drinking, diabetes, SBP, prior MI, prior stroke, and HDL-cholesterol, those factors were not independent predictors of ischemic stroke (Fig. 4B).

We divided the patients into two groups by age: patients ≥65 years and those <65 years. Among the 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 0.67–6.58), p=0.20; non-negative P in aVR: HR 2.80 (95%CI 0.89–8.75), p=0.077; non-positive P in aVL: HR 2.44 (95%CI 0.78–7.64), p=0.12]. However, among the 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 1.14–4.35), p=0.019]. APCs and APCs of non-positive P in aVL were not significantly associated with stroke [APCs: HR 1.72 (95%CI 0.91–3.24), p=0.094; non-positive P in aVL: HR 1.82 (95%CI 0.90–3.68), p=0.098].

Discussion

The main findings of this study were that the prognoses of the patients with APCs with negative P in aVR or positive P wave in aVL were good, but those in the patients with APCs with non-negative P in aVR or non-positive P wave in aVL were poor. 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 the adjustment of covariates. This result is concordant with past 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. conducted Holter ECG in 1,742 individuals in the general population who were older than 50 years of age (4). The median number of APCs was 1.27/h; 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. conducted a meta-analysis of the association between APCs and cardiovascular events (15). Frequent APCs conferred a 1.41-fold increase in the

risk of stroke.

Murakoshi et al. investigated the stroke risk conferred by APCs in 63,197 individuals in a general population based on a single measurement of 12-ECG (7), and they observed that APCs conferred a 1.63-fold increase in the risk of stroke death in females. However, in the ARIC study, the presence of APCs was not an independent predictor of ischemic stroke (HR 1.30, 95%CI 0.92–1.83) (16). The strength of the results on the association between ischemic stroke and APCs might be less than that of the results on the association between any type of stroke and APCs. Himmelreich et al. conducted a meta-analysis for the outcome of ischemic stroke based on dichotomized Holter data, and found that the HR was 2.54 (17). Additional investigations into the association between stroke and APC will be needed, including studies accounting for the frequency of APCs and patient characteristics.

The stroke risk of APC patients with negative P in aVR was similar to that of the patients without APCs, but the stroke risk of the 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 to diagnose 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 (18). Most triggers of AF originate from pulmonary veins (11). 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 in the near to 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 a trigger of AF. 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 past reports APCs were associated with AF and cardiovascular events, including ischemic stroke (6,7). Thus, risk stratification by the polarity of APCs might be helpful to detect AF earlier and prevent cardiovascular events.

The strength of this study is that it is the first paper to investigate the association between the polarity of APCs and stroke by 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 ischemic stroke events was also small. Potentially insufficient statistical power (type II error) was an issue, and we could not check interactions between covariates. Further studies enrolling large numbers of patients with APCs are needed. The modest kappa statistic 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 inter-observer agreement. Finally, we did not obtain data on LDL-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 to predict stroke events in a community-dwelling population.

Contributors: TK analyzed 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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Data sharing statement

No data are available.

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Figure legends

Figure 1. Study protocol. APCs: atrial premature complexes; ECG: electrocardiography.

Figure 2. The 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.

Figure 3. Stroke events according to APCs. (A) Stroke events according to APCs, (B) Stroke events according to APC style in aVR, (C) Stroke events according to APC style in aVL. Ischemic stroke events according to APC. (D) Ischemic stroke events according to APCs, (E) Ischemic stroke events according to APC style in aVR, (F) Ischemic stroke events according to APC style in aVL.

APCs: Atrial premature complexes.

Figure 4. Hazard ratios according to type of APCs. APCs: Atrial premature complexes; HDL: high-density lipoprotein.

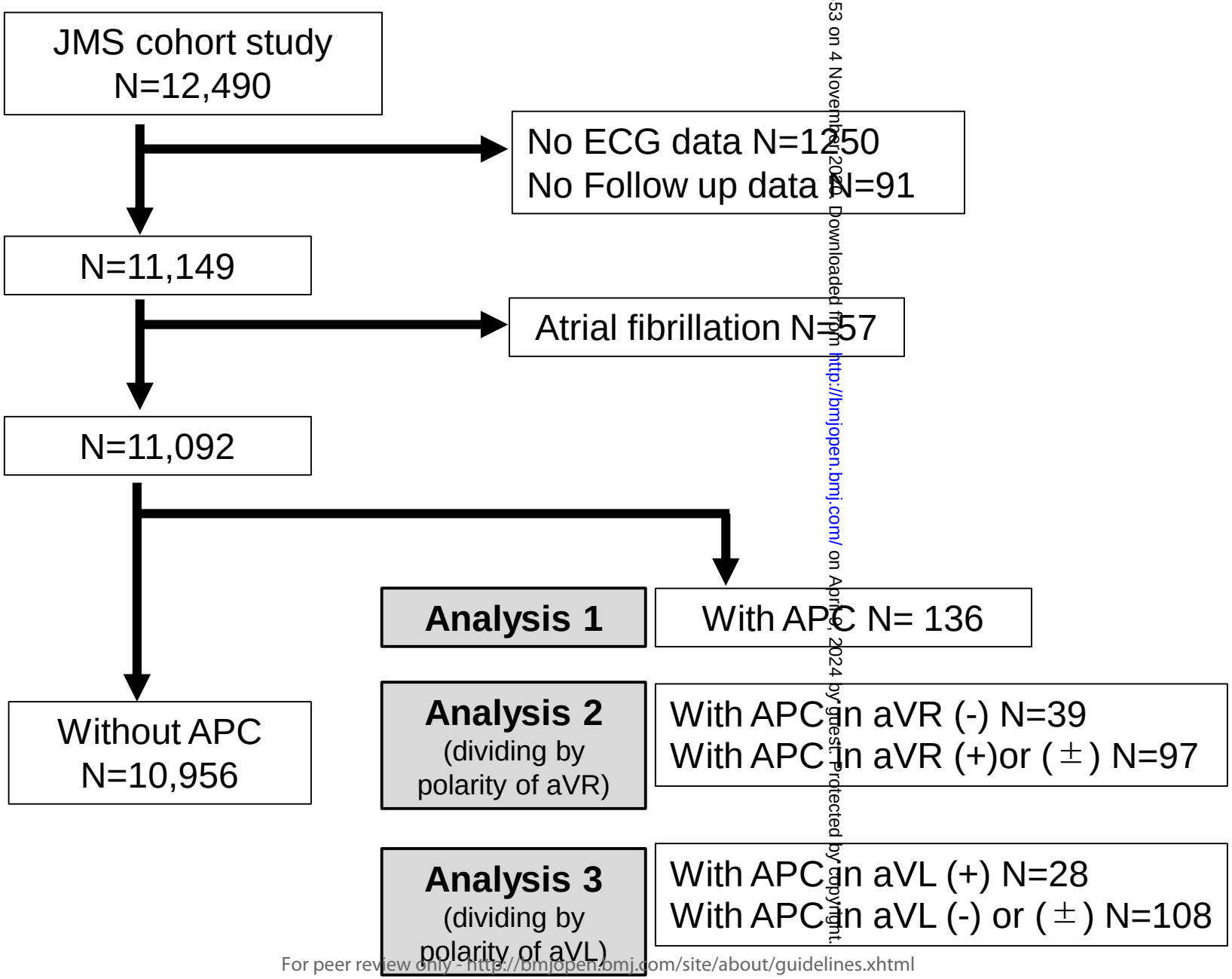


Figure 1.

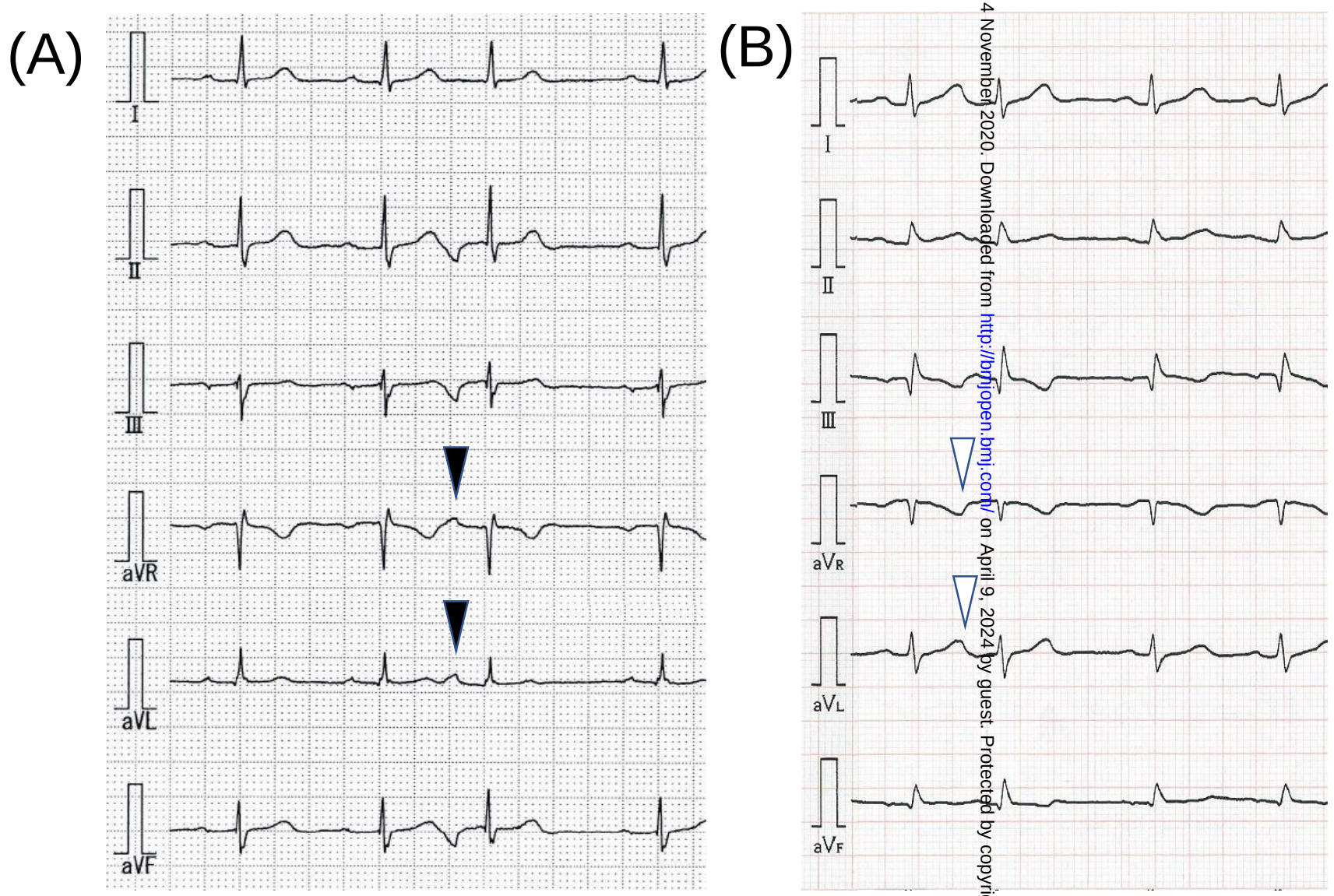


Figure 2.

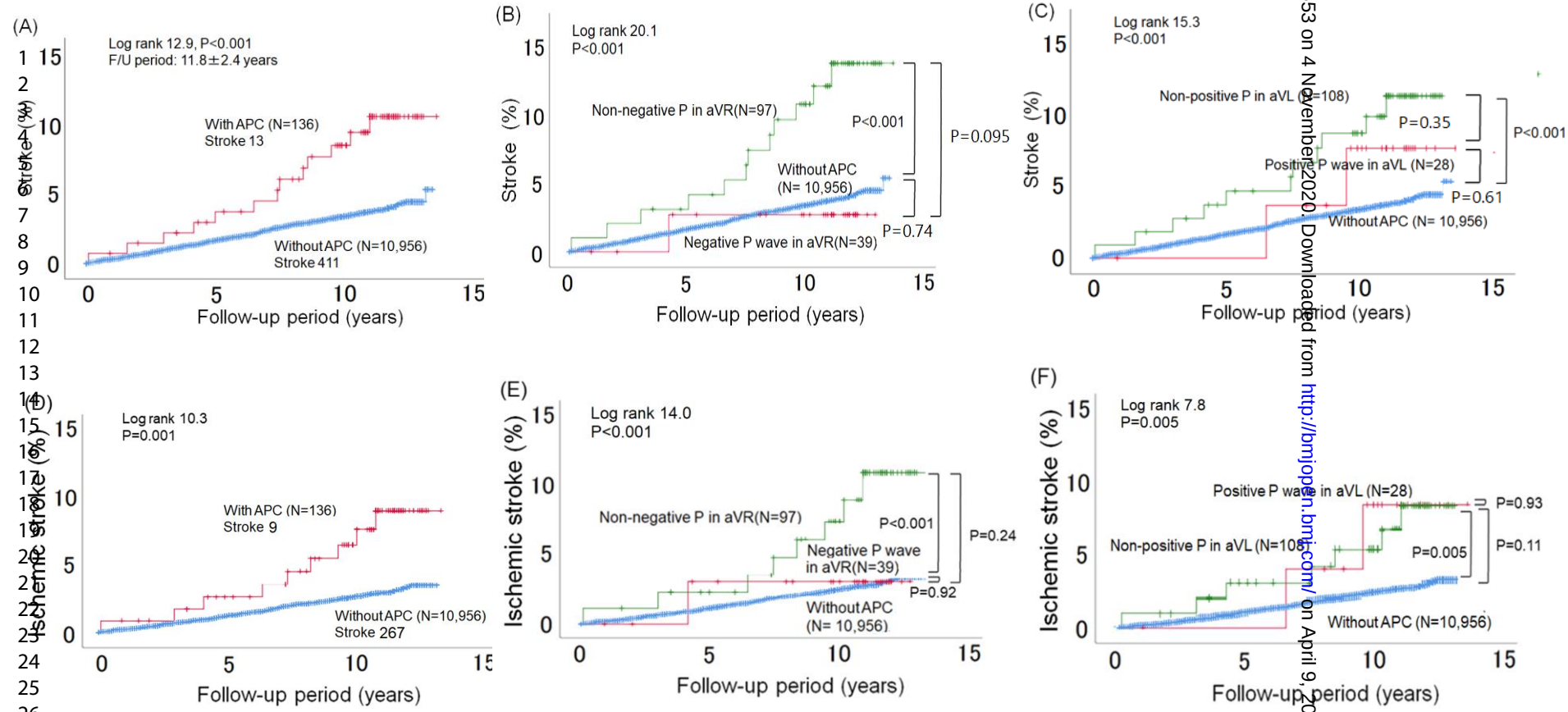
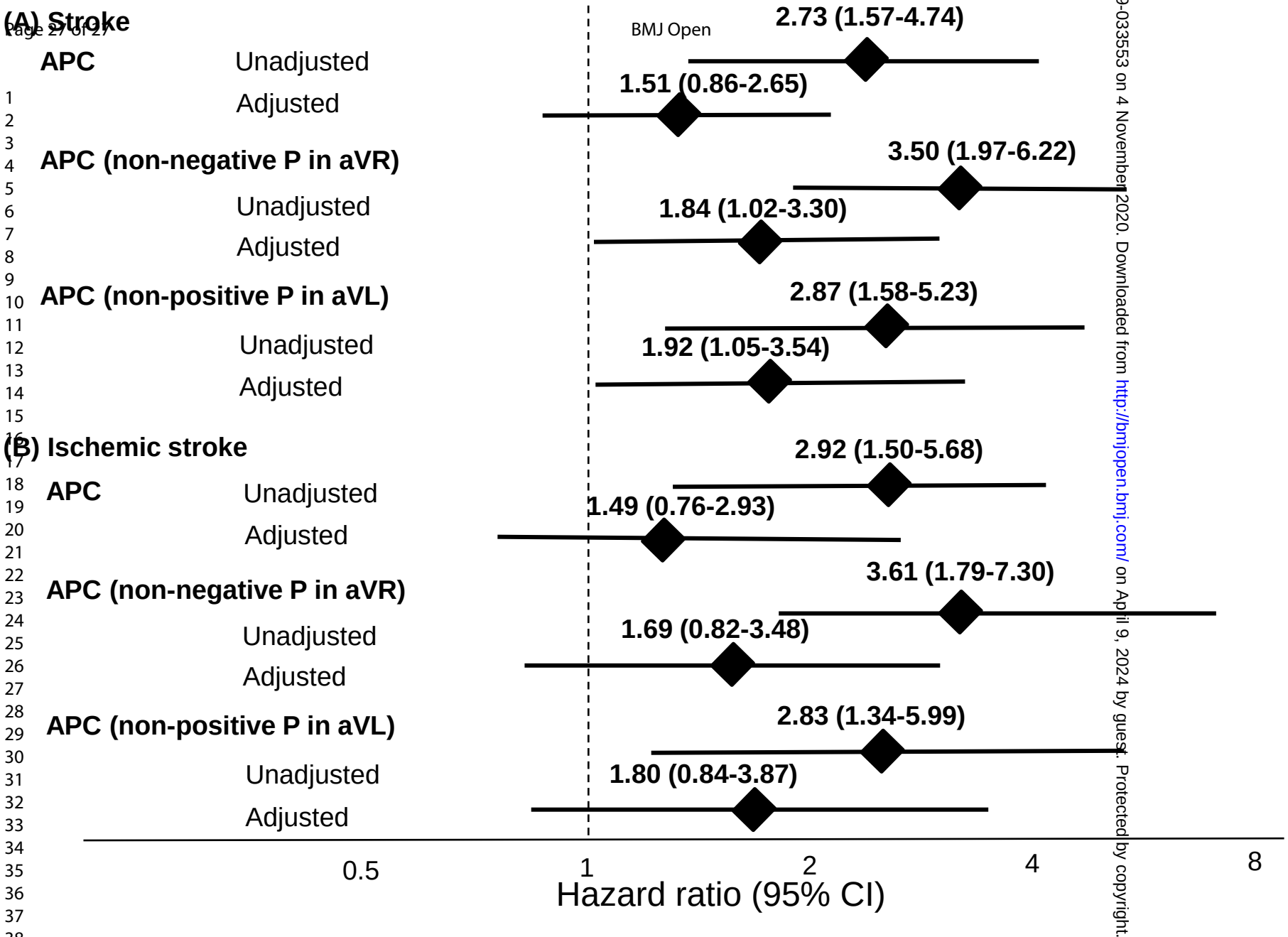


Figure 3.



Adjusted for age, sex, height, body mass index, current drinking, diabetes, systolic blood pressure, prior myocardial infarction, prior stroke, and HDL-choresterol.

Figure 4.

STROBE Statement

Checklist of items that should be included in reports of *cohort studies*

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