Electrocardiographic Left Atrial Abnormality and Stroke Subtype in ARIC

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Abstract

Objective—To assess the relationship between abnormally increased P-wave terminal force in lead V_1 ($PTFV_1$), an electrocardiographic (ECG) marker of left atrial abnormality, and incident ischemic stroke subtypes. We hypothesized that associations would be stronger with non-lacunar stroke, since we expected left atrial abnormality to reflect the risk of thromboembolism rather than in-situ cerebral small-vessel occlusion.

Methods—Our cohort comprised 14,542 participants 45-64 years of age prospectively enrolled in the Atherosclerosis Risk in Communities (ARIC) study and free of clinically apparent atrial fibrillation (AF) at baseline. Left atrial abnormality was defined as $PTFV_1$ >4,000 μV*ms. Outcomes were adjudicated ischemic stroke, non-lacunar (including cardioembolic) ischemic stroke, and lacunar stroke.

Results—During a median follow-up period of 22 years (interquartile range, 19-23 years), 904 participants (6.2%) experienced a definite or probable ischemic stroke. A higher incidence of stroke occurred in those with baseline left atrial abnormality (incidence rate per 1,000 person-

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years, 6.3; 95% CI, 5.4-7.4) than in those without (incidence rate per 1,000 person-years, 2.9; 95% CI, 2.7-3.1; $P < 0.001$). In Cox regression models adjusted for potential confounders and incident AF, left atrial abnormality was associated with incident ischemic stroke (HR, 1.33; 95% CI, 1.11-1.59). This association was limited to non-lacunar stroke (HR, 1.49; 95% CI, 1.07-2.07) as opposed to lacunar stroke (HR, 0.89; 95% CI, 0.57-1.40).

Interpretation—We found an association between ECG-defined left atrial abnormality and subsequent non-lacunar ischemic stroke. Our findings suggest that an underlying atrial cardiopathy may cause left atrial thromboembolism in the absence of recognized AF.

Atrial fibrillation (AF) is associated with a 3- to 5-fold heightened risk of ischemic stroke.[1] This risk has long been ascribed to stasis of blood and thrombus formation resulting from the loss of an organized atrial rhythm.[2] However, the heart-rhythm disturbance that characterizes AF is associated with other atrial derangements such as endothelial dysfunction,[3] fibrosis,[4] impaired myocyte function,[5] and chamber dilatation.[6] Recent evidence suggests that these other atrial derangements play an independent role in causing stroke, and that the dysrhythmia that defines AF is not always necessary for left atrial thrombus formation and embolization to occur.[7-13] In a prospective study of patients with pacemakers or defibrillators, 31% of those with both AF and stroke had no evidence of AF during 8 months of heart-rhythm monitoring prior to their stroke, and manifested the dysrhythmia for the first time after the stroke.[13] Therefore, the heart-rhythm disturbance may not fully account for the association between AF and stroke.

We recently found that abnormally increased P-wave terminal force in lead V_1 ($PTFV_1$)— the most commonly used electrocardiographic (ECG) marker of left atrial abnormality[14]—is associated with ischemic stroke[11] and radiographic evidence of vascular brain injury[12] in patients with apparent normal sinus rhythm. These findings were unchanged regardless of adjustment for incident diagnoses of AF during follow-up, suggesting that ECG-defined left atrial abnormality reflects atrial dysfunction that can cause stroke even in the absence of AF.

This hypothesis would be further strengthened by demonstrating associations between left atrial abnormality and specific ischemic stroke subtypes. We hypothesize that ECG-defined left atrial abnormality is a marker of an atrial cardiopathy that may result in thrombus formation and embolization to the brain, rather than a marker of generally increased vascular risk from systemic factors such as hypertension and atherosclerosis. Since cardiac embolism typically results in large or cortical strokes rather than small subcortical strokes (lacunar strokes),[15] we expect a stronger association between left atrial abnormality and non-lacunar stroke than with lacunar stroke. Such a specific association would be consistent with our hypothesis that left atrial abnormality can cause thromboembolism in the absence of AF. We previously found an association between left atrial abnormality and incident ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) cohort,[16] but this analysis did not adjust for AF and did not compare ischemic stroke subtypes. Therefore, we examined the hypothesis that ECG-defined left atrial abnormality is more strongly associated with non-lacunar rather than lacunar stroke in this cohort, and adjusted for diagnosis of AF during follow-up.

Methods

Study Design and Population

The Atherosclerosis Risk in Communities (ARIC) study prospectively enrolled 15,792 community-dwelling men and women 45-64 years of age. Four field centers across the country (Washington County, MD; Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN) recruited participants in 1987-1989. Participants returned for three follow-up examinations during the follow-up time period (1990-1992, 1993-1995, and 1996-1998), and continue to be followed via annual telephone calls to ascertain study end points. Endpoints are further ascertained from examination of lists of hospital discharges that include any cardiovascular diagnoses from hospitals in the study communities. For this analysis, we excluded participants with hemorrhagic stroke, AF at baseline, missing or unreliable baseline ECG data, or missing data on other baseline covariates.

Measurements

Digital 12-lead ECGs were obtained at baseline and at the three follow-up examinations using MAC PC ECG machines (Marquette Electronics, Milwaukee, WI). All ECGs were inspected for technical errors and adequate quality at the EPICORE Center at the University of Alberta (Edmonton, Alberta, Canada) during the initial phases of the study and at the EPICARE Center at Wake Forest University (Winston-Salem, North Carolina, USA) during later phases. Our primary predictor variable was left atrial abnormality, defined by the commonly used ECG criterion of $PTFV_1$ >4,000 μV*ms.[14, 17-20] $PTFV_1$ was defined as the duration (ms) times the absolute value of the depth (μV) of the downward deflection (terminal portion) of the median P-wave in lead V_1 (Figure 1). In our study, the waveforms required to calculate $PTFV_1$ (P'_{dur} and P'_{amp} in V_1) were automatically measured from the baseline ECG using the GE Marquette 12-SL program (GE Marquette, Milwaukee, WI). These digital waveform measurements have a time resolution of approximately 2 ms and an amplitude resolution of approximately 5 μV.[21] To validate the accuracy of the automated ECG measurements used to derive $PTFV_1$, the waveforms required to calculate $PTFV_1$ (P'_{dur} and P'_{amp} in V_1) were manually measured from ECGs in a subset of 150 participants by a single investigator (H.K.) blinded to the automated measurements, and the calculated $PTFV_1$ values were then compared. This analysis demonstrated an excellent inter-rater correlation coefficient (0.82; 95% CI, 0.76-0.87). Furthermore, the classification of $PTFV_1$ as normal (4,000 μV*ms) versus abnormal (>4,000 μV*ms) based on automated measurements had a 94% agreement rate when compared with the manual scoring of these 150 ECGs. These findings are consistent with prior work demonstrating that the ascertainment of left atrial abnormality based on automated measurements by the 12-SL program has a positive predictive value of 100% and a negative predictive value of 99.8% when compared to the review of the ECG by two cardiologists.[22]

Our outcomes were definite or probable ischemic stroke, lacunar ischemic stroke, and non-lacunar ischemic stroke. Details of methods used to ascertain and classify strokes in ARIC have been previously published.[23] Cases of possible stroke were first identified during annual telephone calls or review of hospital discharge diagnoses. Medical records pertaining to these possible stroke events were then reviewed and abstracted by a single trained nurse at

a central site (University of Minnesota). Based on these abstracted records, the occurrence and type of stroke was classified by a software algorithm that applied validated criteria from the National Survey of Stroke by the National Institute of Neurological Disorders and Stroke.[24] This software algorithm classified strokes as hemorrhagic, cardioembolic, or thrombotic. A physician investigator independently reviewed the medical record and separately determined the occurrence of stroke and whether it was hemorrhagic, cardioembolic, or thrombotic. Cases of disagreement between the software program and physician reviewer were adjudicated by a second physician. In cases of a definite thrombotic stroke, the physician reviewer further adjudicated these as lacunar or non-lacunar. Diagnoses of lacunar stroke were based predominantly on characteristic imaging findings while accounting for the available data on symptomatology. A definite lacunar infarction required anatomic locations typical of lacunar infarctions (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter), and an estimated infarct size of 2 cm or an infarct of unstated size. All other definite thrombotic strokes, as well as all definite cardioembolic strokes, were classified as non-lacunar. All stroke adjudications were performed while blinded to PTFV$_1$ classifications.

Since AF may explain the association between ECG-defined left atrial abnormality and stroke,[16] we examined this association after adjusting for incident AF. Cases of AF were identified from study visit ECGs and by review of hospital discharge diagnoses.[25] At each study exam, a standard supine 12-lead resting ECG was recorded with the MAC PC ECG software used for automatic coding. A cardiologist visually confirmed all AF cases automatically detected from the study ECG. Information on hospitalizations during follow-up was obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnosis codes collected by trained abstractors. AF during follow-up was defined by International Classification of Diseases, 9th Revision codes 427.31 or 427.32. AF cases detected in the same hospitalization as open cardiac surgery were not included since these are usually considered transient.[26] Hospital diagnosis codes for AF ascertainment have been shown to have good positive predictive value.[27]

We used data from the baseline examination to adjust for the following potential confounders: age, sex, race, body mass index, smoking status, diabetes, systolic blood pressure, antihypertensive medication use, low-density lipoprotein level, coronary heart disease, and heart failure. Age, sex, and race were self-reported. Tobacco use was defined as current or former cigarette smoking. Diabetes was defined as a fasting glucose level 126 mg/dL (or non-fasting glucose 200 mg/dL), a physician diagnosis of diabetes, or use of diabetes medications. Systolic blood pressure was obtained from each participant using sphygmomanometers to measure two readings in the sitting position after 5 minutes of rest, with the average of the 2 measurements used as the final reading. The use of antihypertensive medications was self-reported. Body mass index was defined as the weight in kilograms divided by the square of the height in meters. Low-density lipoprotein levels were assayed from serum samples obtained as part of the baseline study visit. Prevalent heart failure was defined as present if participants reported taking heart failure medications or if participants met all three of the Gothenburg criteria.[28] Prevalent coronary heart disease (CHD) was defined by a history of physician-diagnosed myocardial infarction, electrocardiographic Q waves, coronary artery bypass surgery, or coronary angioplasty.

Statistical Analysis

Categorical variables were reported as frequencies and percentages, and continuous variables as means and standard deviations. Differences between groups were tested using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Based on prior work,[11] $PTFV_1$ values >99.9th percentile were considered extreme outliers and excluded from the analysis; in sensitivity analyses, these potentially outlying values were retained after visual inspection of these ECGs confirmed that all had abnormally increased $PTFV_1$ (>4,000 µV*ms) that was not due to artifact. Kaplan-Meier estimates and the log-rank test were used to compare cumulative rates of stroke between participants with and without left atrial abnormality. Follow-up time was defined as the period from the initial ARIC study visit until any ischemic stroke, death, loss to follow-up, or December 31, 2010. Cox proportional hazards regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between left atrial abnormality and stroke.

Multivariable models were constructed with incremental adjustments. Model 1 adjusted for basic demographic characteristics (age, sex, and race). Model 2 included covariates from Model 1 plus body mass index, smoking status, diabetes, systolic blood pressure, antihypertensive medication use, low-density lipoprotein level, coronary heart disease, and heart failure. Model 3 included Model 2 covariates plus incident AF as a time-dependent covariate. Additionally, since clinically apparent AF often follows a long period of subclinical AF,[29] Model 4 adjusted for incident AF as a time-fixed covariate (i.e., we assumed that incident AF was present since baseline in a subclinical form). The proportional hazards assumption was not violated in our analyses. We also constructed a restricted cubic spline model to examine the graphical dose-response relationship between $PTFV_1$ values and the multivariable HR for stroke, incorporating knots at the 5th, 50th, and 95th percentiles. We used interaction terms to compare associations across subgroups defined by age (above or below the median), sex, and race (white or black).[16] We defined statistical significance for the main effect model and interaction terms as $P < 0.05$. SAS version 9.3 (Cary, NC) was used for all analyses.

Results

Of the 15,792 participants from the original ARIC cohort, 202 lacked baseline ECG data, 110 had hemorrhagic strokes, 31 had $PTFV_1$ values that appeared to be extreme outliers, 36 had AF at baseline, and 871 were missing data on baseline covariates. Among the 14,542 participants eligible for our analysis, the mean age at baseline was 54 (±5.8) years; 26% of the participants were black, and 55% were female. The incidence rate of AF was 7.0 (95% CI, 6.7-7.4) per 1,000 person-years, and during a median follow-up of 22 years (interquartile range, 19-23 years), 1,906 participants (13.1%) were diagnosed with AF. The 1,473 participants (10.1%) with ECG-defined left atrial abnormality ($PTFV_1$ >4,000 µV*ms; Figure 2) were generally older, more often male, more often black, and more likely to have vascular risk factors at baseline (Table 1).

Nine hundred and four participants (6.2%) experienced a definite or probable ischemic stroke (incidence rate per 1,000 person-years, 3.2; 95% CI, 3.0-3.4). A higher incidence of stroke occurred in those with left atrial abnormality (incidence rate per 1,000 person-years,

6.3; 95% CI, 5.4-7.4) than in those without (incidence rate per 1,000 person-years, 2.9; 95% CI, 2.7-3.1; $P < 0.001$; Figure 3). The risk of ischemic stroke was observed to increase curvilinearly with increases in $PTFV_1$ values, as shown graphically in a restricted cubic spline model adjusted for baseline covariates (Figures 4 and 5).

In multivariable Cox regression models adjusted for baseline confounders as well as incident AF, ECG-defined left atrial abnormality was associated with incident ischemic stroke of any type (HR, 1.33; 95% CI, 1.11-1.59; Table 2). After excluding 474 participants with unknown ischemic stroke subtype or probable but not definite stroke, 430 participants had a definite ischemic stroke with a known subtype, of which 256 (59.6%) were non-lacunar and 174 (40.4%) lacunar. The association between left atrial abnormality and stroke was limited to non-lacunar stroke (HR, 1.49; 95% CI, 1.07-2.07) as opposed to lacunar stroke (HR, 0.89; 95% CI, 0.57-1.40; Table 2). Associations with any ischemic stroke or non-lacunar stroke remained similar whether or not incident AF was included in our models (Table 2). Our results were essentially the same in sensitivity analyses retaining all $PTFV_1$ values instead of excluding values >99.9th percentile. We found no significant evidence of variation in the association between left atrial abnormality and stroke across subgroups defined by age, sex, or race (Table 3).

Discussion

We found an association between abnormally increased baseline $PTFV_1$—an ECG marker of left atrial abnormality[17, 30-33]—and incident ischemic stroke in a large, prospective, population-based study. This association was limited to cases of non-lacunar (as opposed to lacunar) stroke, which is consistent with the hypothesis that ECG-defined left atrial abnormality signals a specific risk of cardiac embolism as opposed to global vascular risk. The relationship between left atrial abnormality and stroke did not change with adjustment for incident AF, suggesting that ECG-detected left atrial abnormality is associated with stroke independently of AF.

These results build on other recent studies that call into question whether AF—the dysrhythmia itself—is always a necessary step in the pathogenesis of left atrial thromboembolism. In a recent study of patients with pacemakers or defibrillators, 31% of those with both subclinical AF and stroke did not manifest atrial dysrhythmia until after their stroke, despite undergoing continuous heart-rhythm monitoring for a median 8 months before the stroke.[13] Some of these strokes may have been due to causes other than cardiac embolism (e.g., lacunar stroke or atherosclerotic artery-to-artery embolism), but recent studies suggest that some resulted from atrial derangements besides the dysrhythmia that defines AF. Serum NT-proBNP as well as left atrial size and function on echocardiography have been associated with ischemic stroke independently of AF.[7-10] We recently found that ECG-defined left atrial abnormality was associated with ischemic stroke in the Multi-Ethnic Study of Atherosclerosis[11] and with radiographic evidence of vascular brain injury in the Cardiovascular Health Study;[12] in both studies, these associations were essentially the same whether or not we adjusted for incident AF in our models, and were essentially the same in participants without any documented AF throughout follow-up. The present findings from the ARIC cohort build on these findings by indicating a specific link between atrial

abnormality and stroke subtypes that are not due to in-situ cerebral arterial occlusion. Cases of occult left atrial thromboembolism that were unrecognized because of the absence of AF would be expected to be classified as one of the non-lacunar stroke subtypes, not as lacunar stroke, which has a distinct clinical and radiographic profile. Thus, although there may be unmeasured confounding from atherosclerosis, our findings reduce the likelihood that the link between left atrial abnormality and stroke is due simply to global vascular risk factors such as hypertension. These results further support the hypothesis that atrial cardiopathy can cause stroke in the absence of AF, and that the presence of AF is not always necessary for embolization to occur from the left atrium.

This study has several limitations. First, participants did not undergo continuous heart-rhythm monitoring to rule out subclinical AF, and we therefore cannot entirely exclude subclinical AF as a mediator in the relationship between left atrial abnormality and stroke. However, if AF were a significant mediator, the addition of incident AF diagnoses to our models should change the strength of association between left atrial abnormality and stroke, whereas we found essentially the same associations regardless of whether or not we included incident AF as a covariate. Even if undetected subclinical AF does explain some of the association between markers of atrial cardiopathy and stroke, as a practical matter measurements such as $PTFV_1$ are easier and less costly to obtain than prolonged heart-rhythm monitoring, suggesting that atrial markers other than AF could be found to more reliably diagnose the presence of atrial cardiopathy and its associated thromboembolic risk. Nevertheless, studies of the association between left atrial abnormality and stroke in patients undergoing continuous heart-rhythm monitoring would be valuable. Second, the long duration between baseline ECG measurements and stroke outcomes may have attenuated associations between left atrial abnormality and our outcomes. Third, it is possible that some cases classified as left atrial abnormality in our study actually involved right atrial abnormality. However, due to the positions of the left and right atria in relation to the location of the ECG electrode recording V_1, left atrial abnormality typically manifests as increased amplitude of the terminal portion of the P-wave while right atrial abnormality usually manifests as increased amplitude of the early portion of the P-wave.[14] This makes it unlikely that cases classified as left atrial abnormality in our study actually represented right atrial abnormality. Furthermore, misclassification of right atrial abnormality as left atrial abnormality should serve to attenuate any relationships between apparent left atrial abnormality and stroke, given that right atrial abnormality would not be expected to cause stroke in the majority of patients without a patent foramen ovale. Therefore, any misclassification would likely have biased our findings towards the null hypothesis. Fourth, we lacked morphological data about the left atrium, and future analyses incorporating additional markers of atrial dysfunction may more thoroughly delineate the relationship between atrial cardiopathy and stroke. Fifth, we relied on automated ECG measurements that are not routinely reported by current ECG systems. However, $PTFV_1$ can be reliably measured manually,[34, 35] and accumulating evidence regarding the association between ECG-defined left atrial abnormality and stroke could feasibly spur the routine reporting of $PTFV_1$ on ECGs, since it is a capability that available ECG systems already possess.[36]

In summary, we found an association between a marker of left atrial abnormality on ECG and the risk of non-lacunar ischemic stroke. This association appeared independent of AF

diagnoses, suggesting that an underlying atrial cardiopathy can cause left atrial thromboembolism without necessarily manifesting with AF. Such a condition may explain some proportion of the 30% of ischemic strokes that currently lack a known cause.[37, 38] Given the proven benefit of anticoagulant therapy in preventing left atrial thromboembolism in patients with AF, future studies may be worthwhile to determine optimal markers of atrial cardiopathy and the effect of anticoagulant therapy in patients with conclusive evidence of atrial cardiopathy but no clear evidence of AF.

Acknowledgments

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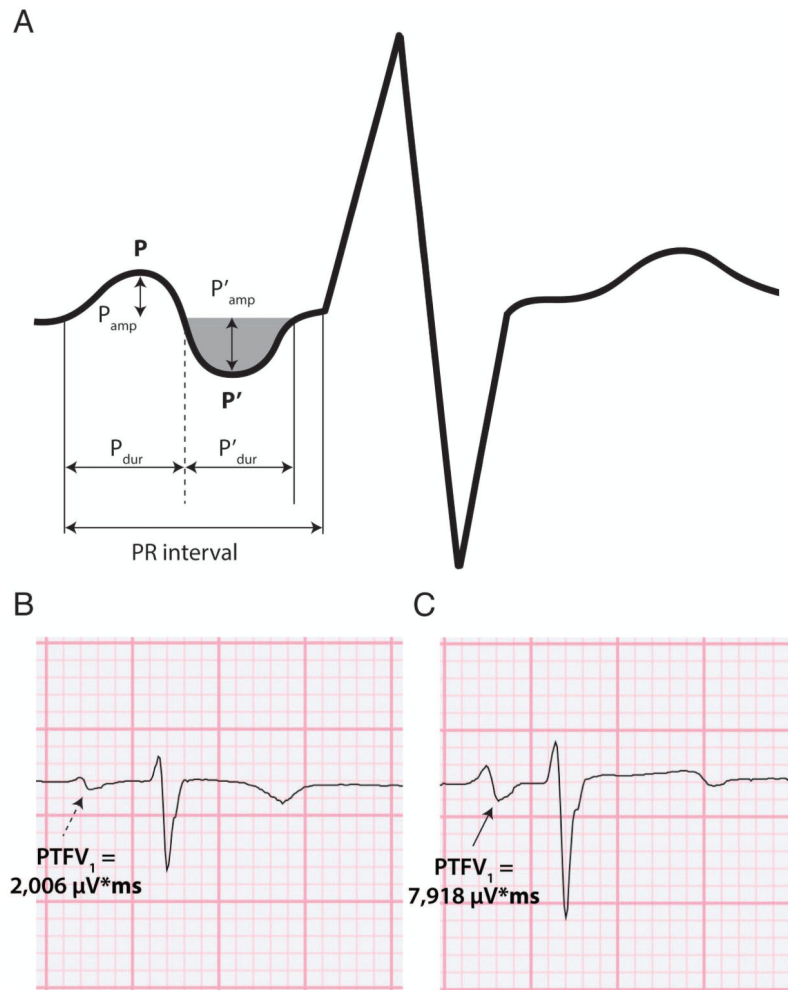
Figure 1.
Schematic Illustration and Examples of Normal and Abnormal P-Wave Terminal Force in Electrocardiogram Lead V_1 (PTFV$_1$).

PTFV$_1$ was defined as the absolute value of the amplitude (P'$_{amp}$) multiplied by the duration (P'$_{dur}$) of the terminal portion of the P-wave (P'; shaded area) in lead V_1 of a standard 12-lead electrocardiogram (Panel A). Panel B shows an example of a P-wave with normal PTFV$_1$ (dashed arrow), while Panel C shows an example of a P-wave with abnormally increased PTFV$_1$ (solid arrow). Note the wider and deeper downward deflection of the P-wave in Panel C compared with Panel B.
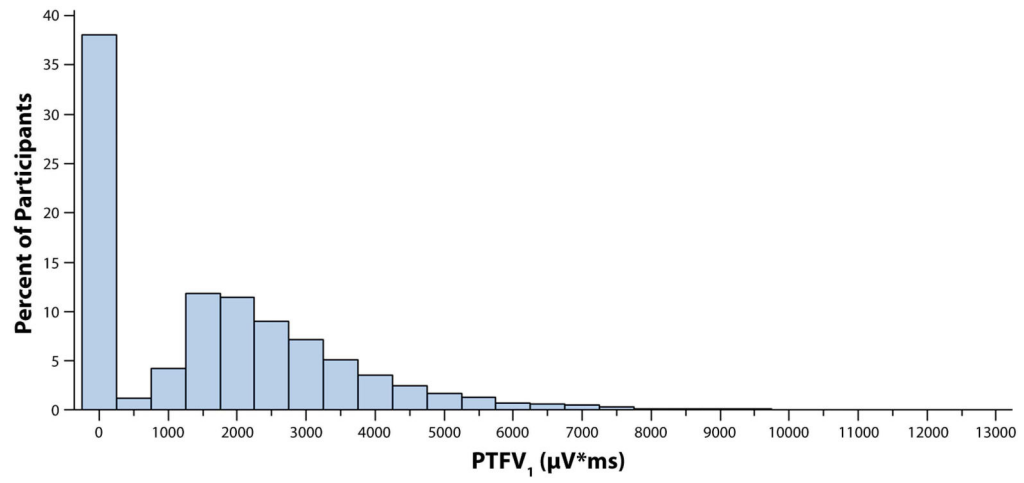
Figure 2.
Distribution of Baseline Values of P-Wave Terminal Force in Electrocardiogram Lead V_1 ($PTFV_1$).
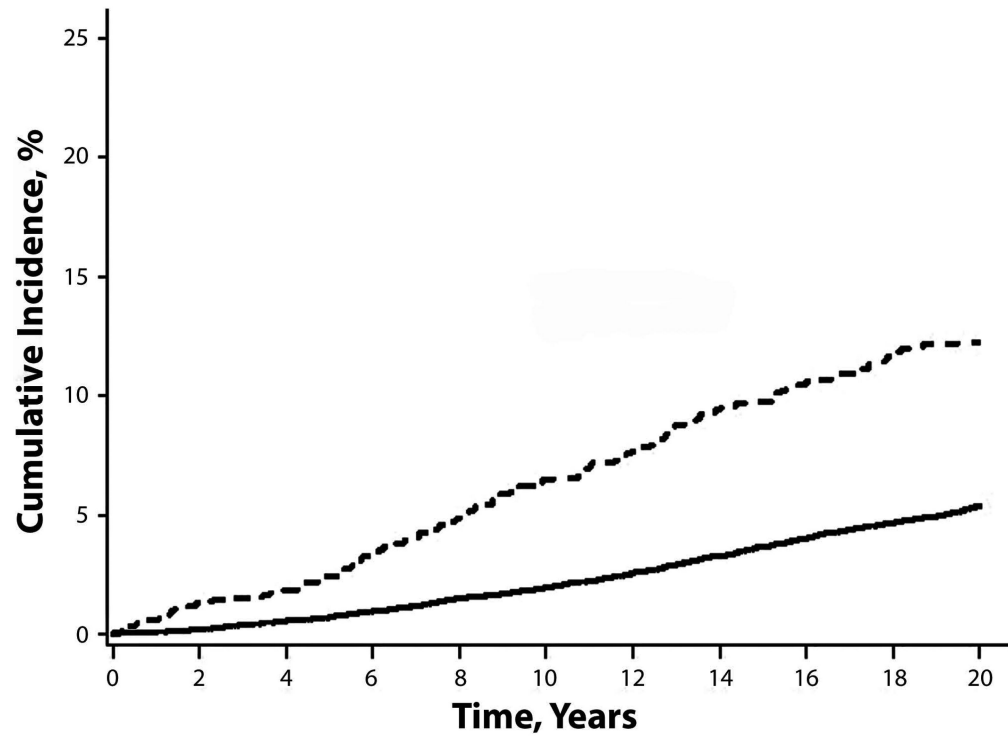
Figure 3.
Cumulative Incidence of Ischemic Stroke, Stratified by Baseline Left Atrial Abnormality. Left atrial abnormality was defined as P-wave terminal force in electrocardiogram lead V_1 >4,000 μV*ms. The dashed line represents study participants with left atrial abnormality, and the solid line those without left atrial abnormality. The difference in cumulative rates between groups was significant by the log-rank test ($P < 0.001$).
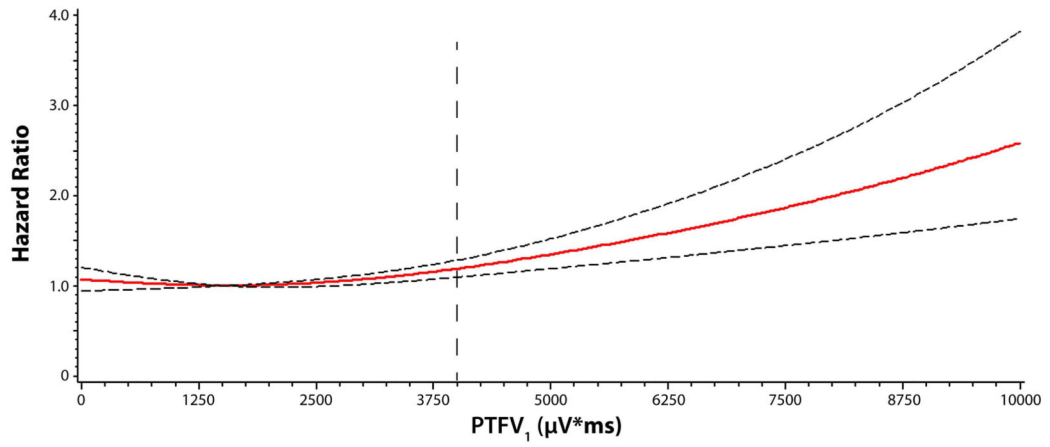
Figure 4.
Relationship Between P-Wave Terminal Force in Electrocardiogram Lead V_1 (PTFV$_1$) and the Risk of Incident Ischemic Stroke.

The plot displays the results of a restricted cubic spline model (see text for details). The dotted horizontal lines represent the 95% confidence interval, and the dotted vertical line represents the threshold of 4,000 µV*ms that was used to define left atrial abnormality.

Figure 5.
Relationship Between P-Wave Terminal Force in Electrocardiogram Lead V_1 (PTFV$_1$) and the Risk of Incident Non-Lacunar Stroke.

The plot displays the results of a restricted cubic spline model (see text for details). The dotted horizontal lines represent the 95% confidence interval, and the dotted vertical line represents the threshold of 4,000 μV*ms that was used to define left atrial abnormality.
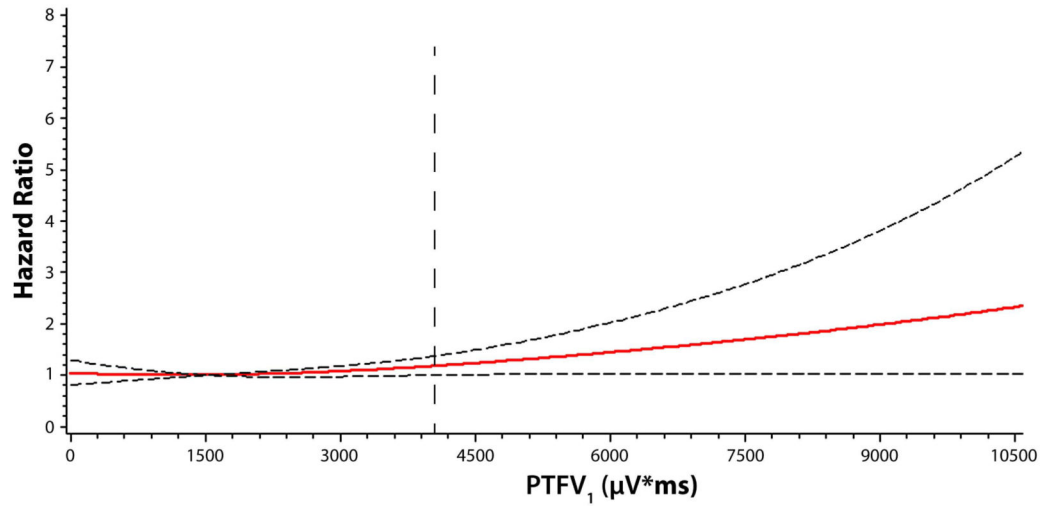
Table 1

Baseline Characteristics of ARIC Study Participants, Stratified by Abnormally Increased P-Wave Terminal Force in ECG Lead V_1 (PTFV$_1$)

Characteristic[a]	PTFV$_1$ >4,000 µV*ms[b] (N = 1,473)	PTFV$_1$ ≤ 4,000 µV*ms (N = 13,069)	P value[c]
Age, mean (SD), years	56 (5.5)	54 (5.7)	<0.001
Male	763 (51.8)	5,747 (44.0)	<0.001
White	889 (60.4)	9,846 (75.3)	<0.001
Tobacco use	955 (64.8)	7,542 (57.7)	<0.001
Diabetes	286 (19.4)	1,348 (10.3)	<0.001
Low-density lipoprotein, mean (SD), mg/dl	141 (42.0)	137 (39.0)	<0.001
Body mass index, mean (SD) mg/kg^2	29 (5.7)	28 (5.3)	<0.001
Systolic blood pressure, mean (SD), mm Hg	129 (23.0)	120 (18.0)	<0.001
Antihypertensive medication use	701 (47.6)	3,646 (27.9)	<0.001
Coronary heart disease	158 (10.7)	528 (4.0)	<0.001
Heart failure	135 (9.2)	519 (4.0)	<0.001

Abbreviations: ARIC, Atherosclerosis Risk in Communities; ECG, electrocardiogram; PTFV$_1$, P-wave terminal force in lead V$_1$; SD, standard deviation.

[a]Data are presented as number (%) unless otherwise specified.

[b]PTFV$_1$ was defined as the absolute value of the amplitude of the terminal portion of the P-wave in ECG lead V$_1$ multiplied by its duration. Abnormal PTFV$_1$ was defined as >4,000 µV*ms.

[c]Differences between groups were compared using the chi-square test for categorical variables and the Wilcoxon-rank sum test for continuous variables.

Table 2

Associations between Abnormally Increased P-Wave Terminal Force in ECG Lead V_1 (PTFV$_1$) and Incident Ischemic Stroke Subtypes

Outcome[a]	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Any ischemic stroke[f]	1.69 (1.42-2.01)	1.31 (1.10-1.57)	1.33 (1.11-1.59)	1.29 (1.08-1.54)
Ischemic stroke subtypes[g]				
Non-lacunar stroke	1.83 (1.33-2.52)	1.44 (1.04-1.99)	1.49 (1.07-2.07)	1.44 (1.04-1.99)
Lacunar stroke	1.22 (0.79-1.89)	0.88 (0.57-1.38)	0.89 (0.57-1.40)	0.91 (0.58-1.42)

[a]**Results are reported as the hazard ratio (95% confidence interval) for values of PTFV1 >4,000 µV*ms compared to 4,000 µV*ms. PTFV$_1$ was defined as the absolute value of the amplitude of the terminal portion of the P-wave in ECG lead V$_1$ multiplied by its duration.**

[b]**Adjusted for baseline age, sex, and race.**

[c]**Adjusted for Model 1 covariates plus baseline body mass index, smoking status, diabetes, systolic blood pressure, antihypertensive medication use, low-density lipoprotein level, coronary heart disease, and heart failure.**

[d]**Adjusted for Model 2 covariates plus atrial fibrillation as a time-dependent covariate.**

[e]**Adjusted for Model 2 covariates plus atrial fibrillation as a time-fixed covariate.**

Table 3

Associations between Abnormally Increased P-Wave Terminal Force in ECG Lead V_1 (PTFV$_1$) and Incident Ischemic Stroke Across Subgroups Defined by Age, Sex, and Race

Subgroup[a]	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]	P Value for Interaction[f]
Age[g]					0.29
<54 y	2.03 (1.46-2.84)	1.29 (0.91-1.81)	1.29 (0.91-1.82)	1.23 (0.87-1.74)	
54 y	1.68 (1.37-2.05)	1.35 (1.10-1.66)	1.38 (1.12-1.70)	1.32 (1.08-1.63)	
Sex					0.36
Male	1.87 (1.48-2.35)	1.46 (1.15-1.85)	1.50 (1.19-1.91)	1.44 (1.13-1.82)	
Female	1.50 (1.14-1.96)	1.19 (0.91-1.56)	1.19 (0.91-1.57)	1.18 (0.90-1.55)	
Race					0.84
White	1.56 (1.22-1.99)	1.25 (0.97-1.61)	1.29 (1.00-1.66)	1.17 (0.91-1.51)	
Black	1.85 (1.45-2.37)	1.38 (1.07-1.78)	1.38 (1.07-1.77)	1.42 (1.10-1.83)	

[a] Results are reported as the hazard ratio (95% confidence interval) for values of PTFV1 >4,000 µV*ms compared to 4,000 µV*ms.

[b] Adjusted for age, sex, and race.

[c] Adjusted for Model 1 covariates plus baseline body mass index, smoking status, diabetes, systolic blood pressure, antihypertensive medication use, low-density lipoprotein level, coronary heart disease, and heart failure.

[d] Adjusted for Model 2 covariates plus atrial fibrillation as a time-dependent covariate.

[e] Adjusted for Model 2 covariates plus atrial fibrillation as a time-fixed covariate.

[f] Interactions tested using Model 2.

[g] Dichotomized at the median age for study participants.