Electrocardiographic P terminal force in lead V1, its components, and the association with stroke and atrial fibrillation or flutter

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BACKGROUND The electrocardiographic (ECG) marker P terminal force V1 (PTFV1) is generally perceived as a marker of left atrial pathology and has been associated with atrial fibrillation or flutter (AF).

OBJECTIVE The purpose of this study was to determine the association between PTFV1 components (duration and amplitude) and incident AF and stroke/transient ischemic attack (TIA).

METHODS The study included patients with an ECG recorded at the Copenhagen General Practitioners Laboratory in 2001 to 2011. PTFV1 $\geq$4 mV·ms was considered abnormal. Patients with abnormal PTFV1 were stratified into tertiles based on duration (PTDV1) and amplitude (PTAV1) values. Cox regressions adjusted for age, sex, and relevant comorbidities were used to investigate associations between abnormal PTFV1 components and AF and stroke/TIA.

RESULTS Of 267,636 patients, 5803 had AF and 18,176 had stroke/TIA (follow-up 6.5 years). Abnormal PTFV1 was present in 44,549 subjects (16.7%) and was associated with an increased risk of AF and stroke/TIA. Among patients with abnormal PTFV1, the highest tertile of PTDV1 (78–97 ms) was associated with the highest risk of AF (hazard ratio [HR] 1.37; 95% confidence interval [CI] 1.23–1.52) and highest risk of stroke/TIA (HR 1.13; 95% CI 1.05 –1.20). For PTAV1, the highest tertile (78–126 μV) conferred the highest risk of AF and stroke/TIA (HR 1.20; 95% CI 1.09–1.32; and HR 1.21; 95% CI 1.14–1.25, respectively).

CONCLUSION Abnormal PTFV1 was associated with an increased risk of AF and stroke/TIA. Increasing PTDV1 showed a dose–response relationship with the development of AF and stroke/TIA, whereas the association between PTAV1 and AF was less apparent.

Funding Sources: The authors have no funding sources to disclose. Disclosures: Dr Atwater reports consulting fees from Biosense Webster, Medtronic, Abbott, and Biotronik; serving on the advisory board of Biosense Webster and Medtronic; research funding from Abbott Medical and Medtronic; speaking fees from Medtronic; employment at the Inova Heart and Vascular Institute; and spouse employment at Eli Lilly Pharmaceuticals. Dr Nielsen is employed by Regeneron Pharmaceuticals, Inc.; and holds equity in the company. Dr Hansen is employed by Johnson & Johnson. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. **Address reprint requests and correspondence:** Dr Lecia Dixen Wolder, Department of Cardiology, Aalborg University Hospital, Blegdalsparken 23, 1st Floor Right, 9000 Aalborg, Denmark. E-mail address: lecia.b.dixen@gmail.com.

 https://doi.org/10.1016/j.hrthm.2022.11.010

KEYWORDS Atrial fibrillation; Atrial flutter; Electrocardiography; P terminal force; Stroke

(Heart Rhythm 2023;20:354–362)

Introduction

Atrial fibrillation is the most common supraventricular arrhythmia and accounts for substantial morbidity and mortality,[1] with stroke being the most feared complication. Inter- and intra-atrial conduction abnormalities can be identified on the electrocardiogram (ECG), manifesting as a biphasic P wave, most often in lead V1. The terminal negative deflection of a biphasic P wave in lead V1 is referred to as the P terminal force V1 (PTFV1). PTFV1 is calculated as the product of its duration component (PTDV1) and its absolute amplitude component (PTAV1). An absolute PTFV1 value $\geq$4 mV·ms is considered abnormal.[2,3] PTFV1 is generally perceived as a marker of left atrial pathology, and abnormal PTFV1 has been associated with incident atrial fibrillation[4–6] and stroke.[7–10] However, the PTFV1 components (ie, duration and amplitude) and their individual associations with AF are not fully elucidated.

Increasing interest in early detection of patients at risk for developing atrial fibrillation or flutter (AF) is a priority issue, in terms of both patient safety and economic benefit. We investigated the prognostic value of an abnormal PTFV1 measurement for incident AF and stroke, including the individual associations between PTDV1 and PTAV1, and incident AF and stroke or transient ischemic attack (TIA).

Methods

Study population and setting

The study population consisted of patients with an ECG recorded in a primary care setting at the Copenhagen General Practitioners Laboratory (CGPL) in 2001 to 2011.[11] Patients were excluded if they had a diagnosis of AF before baseline ECG, by either International Classification of Diseases (ICD) codes or ECG as well as treatment with antiarrhythmic drugs commonly used to treat AF (for details, see Supplemental Material). Patients with ECG findings that made evaluation of P terminal force (PTF) unreliable (eg, second- and third degree atrioventricular block and atrial tachycardia (for details, see Supplemental Material) also were excluded. Cardiovascular diagnoses were previously validated in the Danish National Patient Registry with high predictive values for cardiovascular diagnoses, including AF.[12]

Baseline comorbidity and concomitant medical therapy

From the Danish National Patient Registry,[13] the following comorbidities present before the first ECG were identified from ICD-10 diagnosis codes: heart failure, cardiomyopathy, ischemic heart disease, other arrhythmias, other cardiac diseases, hypertension, chronic obstructive pulmonary disease, renal disease, diabetes, hyperthyroidism (including thyrotoxicosis), and hypothyroidism (for details, see Supplemental Material).

Patients with hypertension, diabetes, and thyroid disease often awe diagnosed and treated exclusively in the primary care setting. Because diagnoses from primary care settings are unavailable, relevant medication was used as a proxy for these comorbidities. For example, antidiabetic medicines prescribed within 180 days before the first ECG were used to define diabetes (for details, see Supplemental Materials).

Hypertension was defined as a combination therapy of at least 2 antihypertensive drugs with a maximum of 100 days between consecutive prescriptions both within a 5-year period before inclusion.

All ICD and Anatomical Therapeutic Chemical codes used in the definition of comorbidities and concomitant medical therapy are provided in the Supplemental Material. Information on all dispensed prescription drugs sold in Denmark since 1995 was provided in the Registry of Medicinal Products Statistics.[14,15]

PTF and its components

Digital 12-lead ECGs of 10-second duration were stored in the MUSE® Cardiology Information System (GE Healthcare, Wauwatosa, WI).[11] All ECGs were recorded at a resolution of 4.88 μV/least significant bit @ 500 samples per second and filtered using 0.05-Hz (high-pass) and 150-Hz (low-pass) settings. The 12SL algorithm Version 241 (GE Healthcare, Milwaukee, WI) was used to automatically measure ECG parameters.

PTFV1 (in the presence of a biphasic P wave with positive/negative configuration) was defined as the duration (in milliseconds) times the absolute value of the peak terminal negative component (in millivolts) of the P wave in lead V1. In agreement with previous studies, we categorized absolute PTFV1 values into the following categories: abnormal PTFV1 $\geq$4 mV·ms (PTFV1-abnormal); normal 0 $\leq$ PTFV1 $\leq$ 4 mV·ms (PTFV1-normal); or nonexistent if the product of duration and amplitude was zero (PTFV1-none).[4,6,16,17] A high agreement between the automated and manual measurements of PTAV1 and PTDV1 was found (Supplemental Figures 1 and 2). To reduce the impact of extreme outliers, patients with PTDV1 or PTAV1 values $\geq$99.75th percentile were excluded.

Among patients with abnormal PTFV1, the duration component PTDV1 and amplitude component PTAV1 were divided into tertiles. The cutoff values for PTDV1 were 38–69 ms (low); 70–77 ms (mid); and 78–97 ms (high). The cutoff values for absolute PTAV1 were 43–62 μV (low); 63–77 μV (mid); and 78–126 μV (high).

Outcome measures

The primary outcomes were incident AF (ICD-10: I-48, atrial fibrillation or flutter) and stroke or TIA (ICD-10: I-63, I-64, G-45), with death as competing event.

Statistical analysis

Categorical variables are given as frequency (percentage) and continuous variables as median with corresponding 25th–75th percentiles [p25–p75]. Accordingly, the χ^2 and Mann-Whitney or Kruskal-Wallis tests were performed to test for differences across study groups. Cumulative incidence curves were generated using the Aalen-Johansen estimator to illustrate the time trends in development of AF.

Among patients with PTFV1, a multivariate Cox regression adjusted for age, sex, congestive heart failure, hypertension, cardiomyopathy, ischemic heart disease, other cardiac arrhythmias, other cardiac diseases, chronic obstructive pulmonary disease, renal disease, diabetes, hypothyroidism, hyperthyroidism (including thyrotoxicosis) was used to investigate the association between PTDV1 and PTAV1 individually and incident AF and stroke/TIA, using the group of patients with normal terminal negative component in V1 (PTFV1-normal) and patients without a negative component (PTFV1-none) as a combined reference group. Comorbidities included congestive heart failure, hypertension, cardiomyopathy, ischemic heart disease, valvular heart disease, other cardiac arrhythmias, other cardiac diseases, chronic obstructive pulmonary disease, renal disease, diabetes, stroke/TIA, hyperthyroidism, and hypothyroidism. Patients with stroke/TIA as comorbidity in relation to statistical analyses with stroke/TIA as primary outcome were excluded.

The interaction between variables was examined using likelihood ratio tests with a significance level of $P < .01$. No interaction between the PTDV1 and PTAV1 was present.

The linearity of continuous variables was also examined through likelihood ratio tests against adding cubic splines to continuous variables. Age was found to violate linearity and was consequently added as a categorical variable based on 20th percentiles (cutoff values at 46, 56, 63 and 72 years of age). Schoenfeld residuals were evaluated to test the assumption of the hazards proportionality and were fulfilled.

Using multivariable Cox regression, restricted cubic splines with 3 knots were added to display the hazard ratio (HR) of AF and stroke/TIA development as a function of PTDV1 and PTAV1 as continuous variables. The knots were added by computer optimized fitting.

For the cubic splines, PTDV1 of 70 ms was used for the lowest PTAV1 tertile as reference for duration, and for amplitude an absolute value for PTAV1 of 70 μV was used for the lowest PTDV1 tertile.

The correlation between PTDV1 and PTAV1 was charted in a scatter plot, and the coefficient of determination (r^2) was calculated (Supplemental Figure 3).

All data management were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC) and statistical analyses using R Core Team (2020). $P < .05$ was considered significant for all statistical analysis except for interactions, for which $P < .01$ was used.

Ethics approval

The study was approved by the Danish Data Protection Agency (j.nr. 2008-58-0028, internal reference RN-2016-3). Ethical approval is not required for register-based studies in Denmark. Due to Statistics Denmark legislation, data used to conduct this study cannot be shared.

Results

Patient characteristics

A total of 267,636 patients had an ECG recorded by their general practitioner and were included in the study (Figure 1). Among these patients, 44,549 (16.7%) were identified as having abnormal PTFV1. During median follow-up of 6.5 years [3.8–9.4 years], 5902 patients developed AF, 18,176 developed stroke/TIA, 25,924 (9.6%) died, 5914 were lost to follow-up (due to emigration). and the remaining 231,141 (86.0%) were followed to the end of the study period on December 31, 2012.

Baseline clinical characteristics of the study population are given in Tables 1, 2, and 3 for the PTFV1 subgroups,

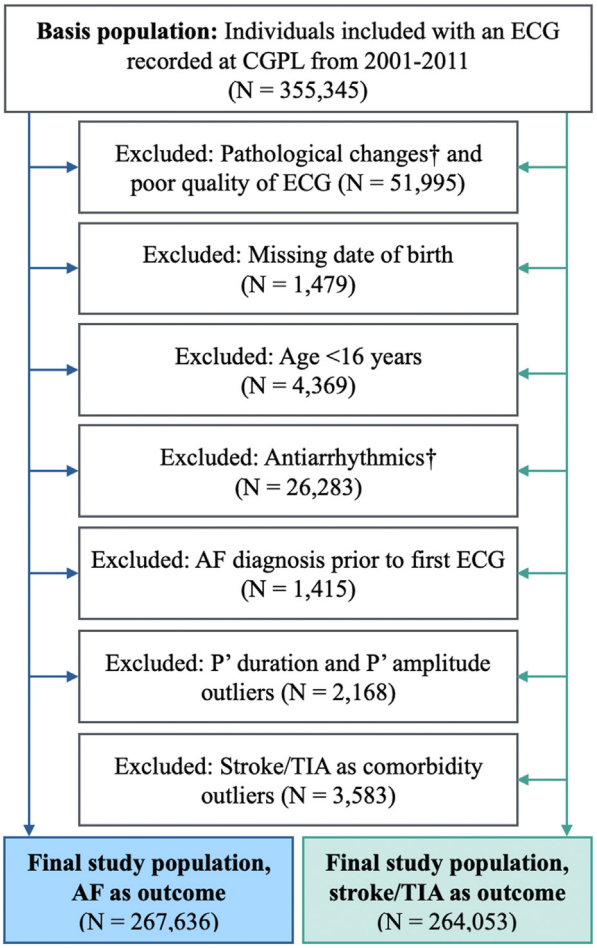

Figure 1 Patient selection flow chart showing exclusion criteria with respective number of patients. †See Supplemental Material. AF = atrial fibrillation or flutter; CGPL = Copenhagen General Practitioners Laboratory; ECG = electrocardiogram; TIA = transient ischemic attack.

Table 1 Clinical characteristics of the study population: P terminal force divisions

Variable	PTFV1-none and PTFV1-normal (n = 223,087)	PTFV1-abnormal (n = 44,549)	*P* value
Age at ECG recording (y)	50.2 [38.4–62.2]	58.6 [39.8–63.5]	<.001
Female sex	126,122 (56.5)	23,505 (52.8)	<.001
Follow-up time (y)	6.6 [3.9–9.4]	6.3 [3.7–9.3]	<.001
Congestive heart failure	578 (0.3)	211 (0.5)	<.001
Hypertension	24,247 (10.9)	8151 (18.3)	<.001
Cardiomyopathy	82 (0.0)	40 (0.1)	<.001
Ischemic heart disease*	3382 (1.7)	1180 (2.6)	<.001
Valvular heart disease	125 (0.1)	103 (0.2)	<.001
Other cardiac arrhythmias	585 (0.3)	103 (0.2)	.26
Other cardiac diseases	243 (0.1)	55 (0.1)	.45
Chronic obstructive pulmonary disease	4508 (2.0)	1054 (2.4)	<.001
Renal disease	413 (0.2)	115 (0.3)	.0019
Diabetes	4117 (1.8)	1181 (2.7)	<.001
Stroke or TIA	2803 (1.3)	780 (1.8)	<.001
Hyperthyroidism†	977 (0.4)	241 (0.5)	.0036
Hypothyroidism	2256 (1.0)	469 (1.1)	.44

Data for clinical characteristics of the study population according to P terminal force V1 (PTFV1) divisions (PTFV1-none vs PTFV1-abnormal).
Values are given as median [Q1–Q3] or n (%) unless otherwise indicated.
ECG = electrocardiogram; TIA = transient ischemic attack.
*Including previous myocardial infarction.
†Including thyrotoxicosis.

PTDV1 tertile groups, and PTAV1 tertile groups, respectively. Generally, the prevalence of comorbidities and the median age increased in concordance with higher PTDV1 and PTAV1 tertiles compared to the combined reference group (PTFV1-normal and PTFV1-none).

Cumulative incidence of AF and stroke/TIA

The cumulative incidences of AF and stroke/TIA over a 10-year period are shown in Figure 2. The cumulative incidence of both AF and stroke/TIA was greatest among patients with abnormal PTFV1.

Risk of AF

Figure 3 shows the HR for AF and stroke/TIA for each tertile of PTDV1 and PTAV1 in patients with abnormal PTFV1 using normal/nonexistent PTDV1 as the reference group. Mid and high PTDV1 were associated with a higher risk of developing AF (HR 1.14; 95% confidence interval [CI] 1.01–1.28; and HR 1.37; 95% CI 1.23–1.52, respectively), whereas the lowest tertile of the PTDV1 was not associated with an increased risk of AF (HR 1.02; 95% CI 0.90–1.15).

Table 2 Baseline clinical characteristics of the study population: PTDV1 tertiles

Variable	Lowest duration tertile (n = 15,438)	Mid duration tertile (n = 13,632)	Highest duration tertile (n = 15,479)	*P* value
Age at ECG recording (y)	56.3 [47.9–68.2]	58.2 [47.9–68.2]	61.0 [39.8–63.5]	<.001
Female sex	8328 (53.9)	7235 (53.1)	7942 (51.3)	<.001
Follow-up time (y)	6.4 [3.7–9.3]	6.4 [3.8–9.4]	6.3 [3.7–9.2]	<.001
Congestive heart failure	57 (0.4)	60 (0.4)	94 (0.6)	<.001
Hypertension	2276 (14.7)	2417 (17.7)	3458 (22.3)	<.001
Cardiomyopathy	13 (0.1)	14 (0.1)	13 (0.1)	.0012
Ischemic heart disease*	347 (2.2)	341 (2.5)	492 (3.2)	<.001
Valvular heart disease	27 (0.2)	37 (0.3)	39 (0.3)	<.001
Other cardiac arrhythmias	37 (0.2)	32 (0.2)	34 (0.2)	.67
Other cardiac diseases	21 (0.1)	14 (0.1)	20 (0.1)	.68
Chronic obstructive pulmonary disease	377 (2.4)	302 (2.2)	375 (2.4)	<.001
Renal disease	44 (0.3)	29 (0.2)	42 (0.3)	.0068
Diabetes	420 (2.7)	353 (2.6)	408 (2.6)	<.001
Hyperthyroidism†	76 (0.5)	84 (0.6)	81 (0.5)	.010
Hypothyroidism	164 (1.1)	140 (1.0)	165 (1.1)	.86
Stroke or TIA	231 (1.5)	220 (1.6)	329 (2.1)	<.001

Data for clinical characteristics of the study population according to P terminal force V1 duration component (PTDV1) tertiles.
Values are given as median [Q1–Q3] or n (%) unless otherwise indicated.
Abbreviations as in Table 1.
*Including previous myocardial infarction.
†Including thyrotoxicosis.

Table 3 Baseline clinical characteristics of the study population: PTAV1 tertiles

Variable	Lowest amplitude tertile (n = 16,357)	Mid amplitude tertile (n = 12,374)	Highest amplitude tertile (n = 15,835)	*P* value
Age at ECG recording (y)	59.0 [49.0–68.9]	57.6 [46.7–67.9]	59.0 [47.9–62.2]	<.001
Female sex	7660 (46.8)	5887 (47.6)	7497 (47.4)	<.001
Median follow-up time (Q1-Q3)	6.5 (3.8-9.4)	6.4 (3.8-9.3)	6.2 (3.6-9.2)	<.001
Congestive heart failure	65 (0.4)	52 (0.4)	94 (0.6)	<.001
Hypertension	3085 (18.9)	2113 (17.1)	2953 (18.7)	<.001
Cardiomyopathy	18 (0.1)	12 (0.1)	10 (0.1)	<.001
Ischemic heart disease*	395 (2.4)	323 (2.6)	462 (2.9)	<.001
Valvular heart disease	29 (0.2)	23 (0.2)	51 (0.3)	<.001
Other cardiac arrhythmias	24 (0.1)	44 (0.4)	35 (0.2)	.0037
Other cardiac diseases	19 (0.1)	11 (0.1)	25 (0.2)	.28
Chronic obstructive pulmonary disease	384 (2.3)	247 (2.0)	423 (2.7)	<.001
Renal disease	39 (0.2)	34 (0.3)	42 (0.3)	.014
Diabetes	420 (2.6)	344 (2.8)	417 (2.6)	<.001
Hyperthyroidism†	91 (0.6)	65 (0.5)	85 (0.5)	.031
Hypothyroidism	168 (1.0)	138 (1.1)	163 (1.0)	.73
Stroke or TIA	295 (1.8)	214 (1.7)	271 (1.7)	<.001

Data for clinical characteristics of the study population according to absolute amplitude values of P terminal force V1 component (PTAV1).
Values are given as median [Q1–Q3] or n (%) unless otherwise indicated.
Abbreviations as in Table 1.
*Including previous myocardial infarction.
†Including thyrotoxicosis.

Figure 3 also shows that PTAV1 was less consistently associated with AF across tertiles than PTDV1. The HRs for AF in the low and high tertiles of PTAV1 were 1.20 (95% CI 1.09–1.32) and 1.15 (95% CI 1.04–1.27), respectively. In the mid tertile, the HR for AF was 1.03 (95% CI 0.92–1.16).

Figure 4 shows spline curves for PTAV1 and PTDV1 and the risk of AF. Figure 4A shows 1 spline curve for each tertile of PTAV1. The spline curves show an elevated risk of AF for PTDV1 >75 ms, and this risk was consistent across all PTAV1 tertiles but was more pronounced for the lowest and highest PTAV1 tertiles. Figure 4B shows 1 spline curve for each tertile of PTDV1. The risk of AF increases additively according to higher PTDV1 tertiles with increasing PTAV1.

Figure 5 shows spline curves for PTAV1 and PTDV1 and the risk of stoke/TIA. Figure 5A shows spline curves for PTDV1 and the risk of stoke/TIA, 1 spline curve for each tertile of PTAV1. The highest PTAV1 tertile showed the strongest risk of stroke/TIA compared to the lowest and mid PTAV1 tertiles. Patients with stroke or TIA as comorbidity were excluded in relation to statistical analysis with stroke/TIA as outcome. Figure 5B shows 1 spline curve for each tertile of PTDV1, with a dose–response like increased risk of stroke/TIA for PTDV1 consistent across all PTAV1 tertiles.

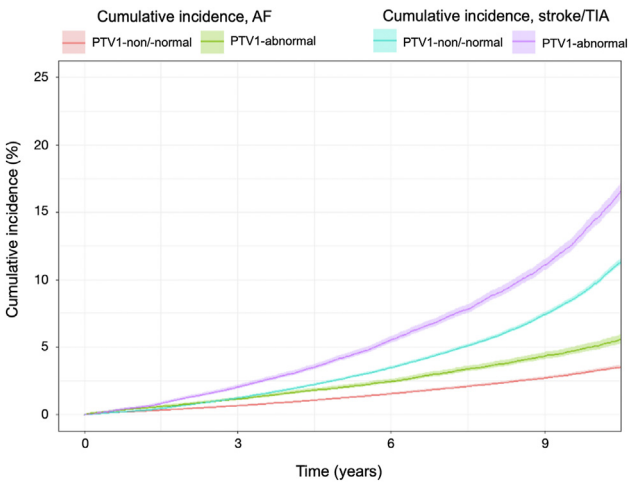

Figure 2 The 10-year cumulative incidence of AF in patients with P terminal force V1 (PTV1)-non and PTV1-normal *(red)* and PTV1-abnormal *(green)* and cumulative incidence of stroke/TIA in patients with PTV1-non and PTV1-normal *(blue)* and PTFV1-abnormal *(purple)*. Abbreviations as in Figure 1.

Risk of stroke/TIA

Figure 3 shows the HR for stroke/TIA for the tertiles of PTDV1 and PTAV1 in patients with abnormal PTFV1 using normal/nonexistent PTDV1 as the reference group. Both mid and high PTDV1 tertiles had an increased risk of developing stroke/TIA (HR 1.11; 95% CI 1.03–1.19; and HR 1.13; 95% CI 1.05–1.20, respectively). The lowest tertile of the PTDV1 was not associated with an increased risk of stroke/TIA (HR 1.02; 95% CI 0.92–1.10).

Figure 3 shows that the highest PTAV1 was associated with an increased risk of stroke/TIA (HR 1.21; 95% CI 1.14–1.29), whereas associations were weaker for the mid and lowest PTAV1 tertiles (HR 1.06; 95% CI 0.99–1.13; and HR 1.07; 95% CI 0.99–1.14, respectively).

Figure 3 shows that the highest risk of stoke/TIA is found among the highest tertiles for PTAV1 and PTDV1.

Discussion

In this large study of 267,636 primary care patients, we assessed the association between the individual components

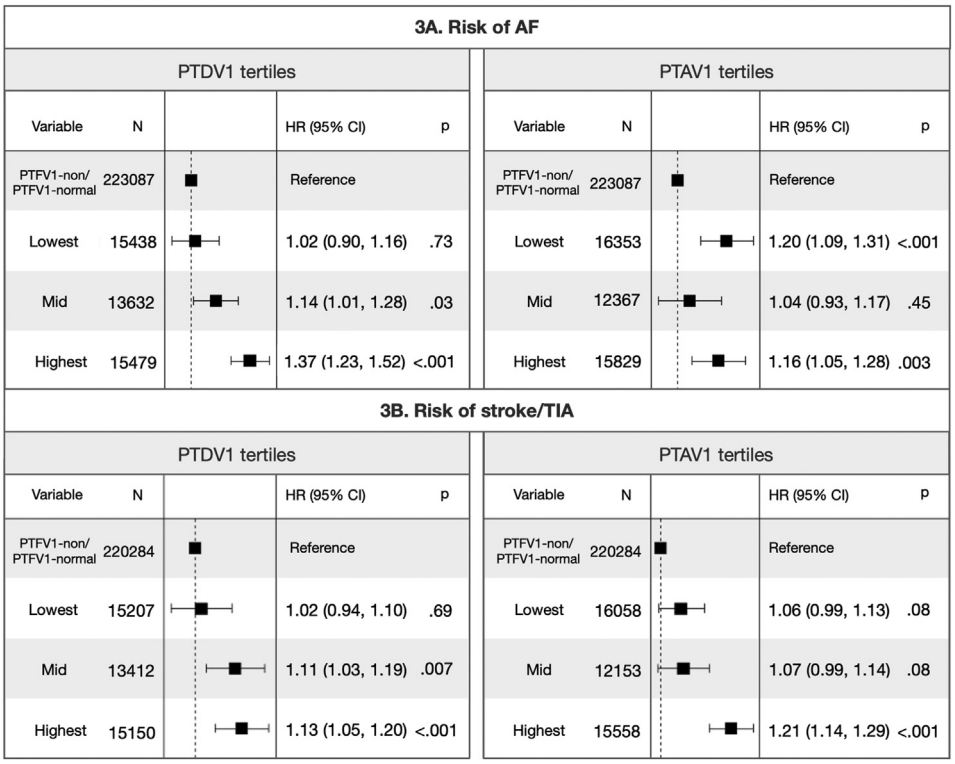

Figure 3 Multivariable-adjusted Cox model showing the hazard ratio (HR) for atrial fibrillation or flutter (AF) **(A)** and stroke/TIA **(B)** of P terminal force V1 duration component (PTDV1) and PTAV1 (P terminal force V1 amplitude component) grouped by tertiles. Analyses were adjusted for sex, age, congestive heart failure, hypertension, cardiomyopathy, ischemic heart disease, other cardiac arrhythmias, other cardiac diseases, chronic obstructive pulmonary disease, renal disease, diabetes, hypothyroidism, hyperthyroidism (including thyrotoxicosis). Reference group: combined PTFV1-normal and PTFV1-none. Patients with stroke or TIA as comorbidity were excluded in relation to statistical analysis with stroke/TIA as outcome. *Vertical dashed line* represents HR = 1. CI = confidence interval.

of an abnormal P-wave terminal force in V1 (ie, amplitude and duration) and development of AF and stroke/TIA. Our key finding was a significant positive dose–response association between PTDV1 and the development of AF. The PTAV1 component showed a U-shaped association with AF where the low and high tertiles groups but not the

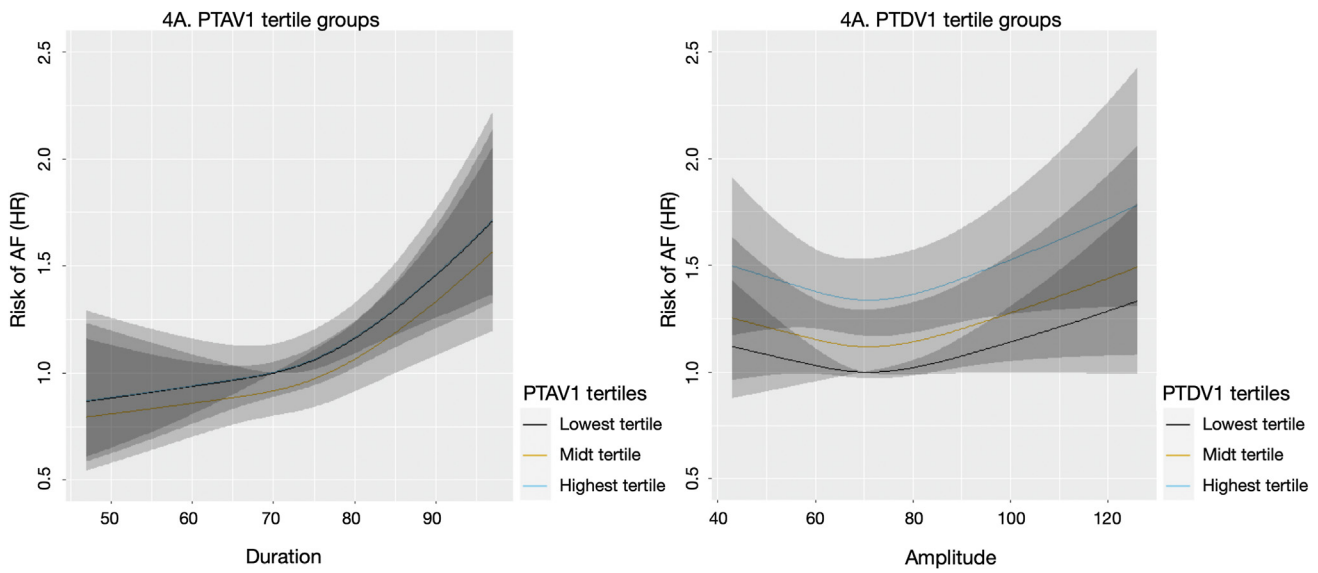

Figure 4 Risk of AF, and cubic spline curves of HR for PTAV1 and PTDV1 tertile groups. **A:** Duration as a continuous value on the x-axis, HR of AF on the y-axis, and PTAV1 tertiles plotted. Reference PTDV1 of 70 ms for the lowest PTAV1 tertile. **B:** Amplitude as a continuous value on the x-axis, HR of AF on the y-axis, and PTDV1 tertiles plotted. Reference PTAV1 of 70 μV for the lowest PTDV1 tertile. Abbreviations as in Figures 1 and 3.

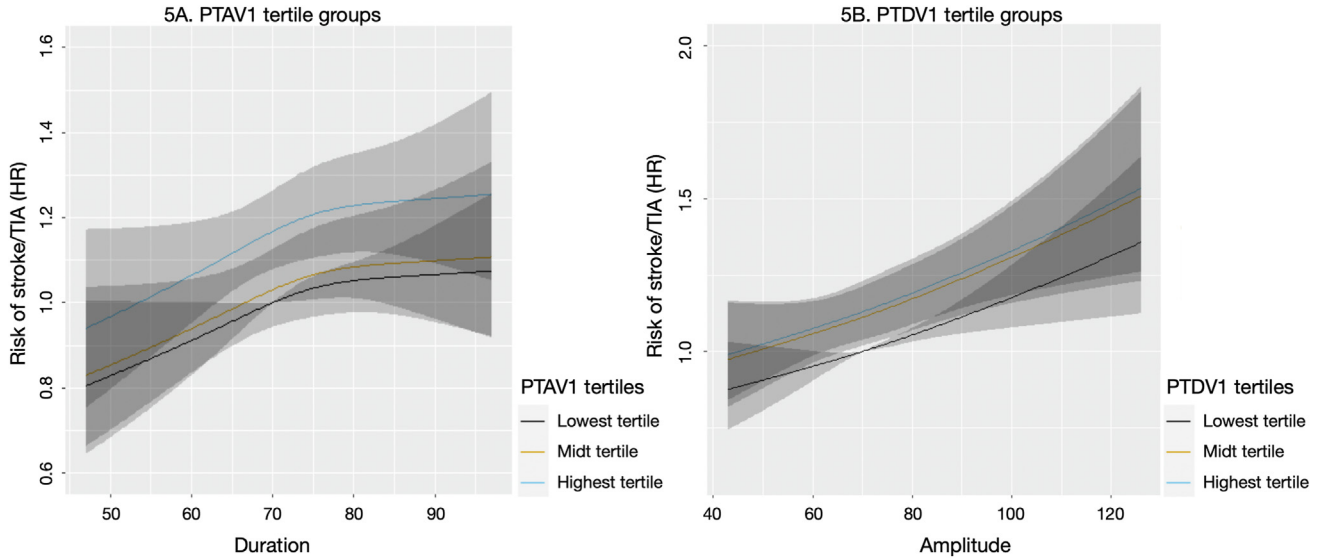

Figure 5 Risk of stroke/TIA, and cubic spline curves of HR for PTAV1 and PTDV1 tertile groups. **A:** Duration as a continuous value on the x-axis, HR of stroke/TIA on the y-axis, and PTAV1 tertiles plotted. Reference PTDV1 of 70 ms for the lowest PTAV1 tertile. **B:** Amplitude as a continuous value on the x-axis, HR of stroke/TIA on the y-axis, and PTDV1 tertiles plotted. Reference PTAV1 of 70 μV for the lowest PTDV1 tertile. Abbreviations as in Figures 1 and 3.

mid tertile group were significantly associated with AF. PTAV1 trended toward a weak incremental association to stroke/TIA. The interaction and correlation between PTDV1 and PTAV1 components were poor (Supplemental Figure 3).

Despite the highly selected nature of the population, when patients with different ECG pathologies possibly disposing for AF (eg, voltage criteria for left ventricular hypertrophy) were excluded, associations between PTDV1 and AF and stroke/TIA were seen.

The presence of abnormal PTFV1 ($\geq$4 mV·ms) is an indicator of left atrial abnormality in the form of enlargement, fibrosis, and strain, and a leftward and posteriorly directed left atrial depolarization vector is responsible for the appearance of a negative PTF in lead V1.[18,19] In addition, PTFV1 is more frequently reported with advancing age and increasing body mass index.[4,20] Although often considered as evidence of left atrial enlargement, it has been suggested that prolonged interatrial conduction more consistently plays a role in the genesis of the ECG appearance of PTFV1.[2] Another electrophysiological change seen among patients with AF is abnormal atrial repolarization, primarily seen as changes in the PTa and Ta segment on the ECG, although the amplitude generated by the altered repolarization may be too modest to manifest on the ECG.[2,21]

Furthermore, this study showed that AF and stroke-associated comorbidities, such as hypertension, diabetes, and ischemic heart disease, are overrepresented in patients with abnormal PTFV1 compared to patients with PTFV1-none/PTFV1-normal. This finding is in line with Eranti et al,[4] who found PTFV1 to be an indicator of elevated morbidity and mortality.

Our study demonstrated that patients with abnormal PTFV1 developed AF and stroke/TIA more frequently during the follow-up period than patients with normal or nonexisting PTFV1. These findings expand on data regarding the association between abnormal PTFV1 and the higher risk of AF as previously described by Eranti et al,[4] Soliman et al,[17] and Tereshchenko et al.[19] Eranti et al[4] assessed the association between PTFV1 and AF and found that a value $\geq$6 mV·ms was associated with an increased risk of developing AF, whereas there was no significant relationship between PTFV1 $\geq$4 mV·ms and AF. Tereshchenko et al[19] defined PTFV1 as the presence of biphasic P wave with the amplitude of the terminal negative phase $>$100 μV, or 1 small box on ECG scale. They reported that PTFV1 was a common finding (67.4%) among an adult study population (45–64 years) and was associated with a 5-fold increased risk of AF. The latter finding was supported by Soliman et al,[17] who found a clear association between PTFV1 and AF in the Atherosclerosis Risk in Communities (ARIC) study. Based on the large ARIC study population, Kamel et al[10] found PTFV1 to be associated with incident ischemic stroke. The association between PTFV1 and stroke persisted despite adjustment for atrial fibrillation.

In the present study, a dose–response relationship between PTDV1 and AF was observed, with a duration of the terminal negative component of the P wave in V1 exceeding 78 ms as the strongest indicator of AF (HR 1.37; 95% CI 1.23 –1.52). Soliman et al[17] reported PTDV1 to be the clearest indicator of AF, consistent with the results of the present study. To the best of our knowledge, this is the first study to examine the relationship between PTDV1 and stroke/TIA.

PTDV1 has been linked to the presence of atrial fibrosis, a well-known and important pathophysiological driver for atrial fibrillation. Win et al[22] found that diffuse left ventricular interstitial fibrosis (and likely related left atrial fibrosis) predominantly affected PTDV1 than PTAV1.

Ischemic stroke is a feared consequence of AF, especially because AF has been associated with more severe stroke

manifestations.[23] Stroke often precedes the diagnosis of AF and has been linked to the presence of occult AF. PTFV1-abnormal, particularly when generated by a long PTDV1, may be used as a predictor of ischemic stroke and AF in the clinical setting. Further studies will need to be undertaken in this regard.

Our study showed a U-shaped association between PTAV1 and AF. Several mechanisms could explain the less clear association between PTAV1 and the risk of AF and stroke/TIA found in our study. The amplitude of the terminal negative component of PTFV1 reflects a vector projection that can be altered through different factors, including the positioning of the heart and ECG electrode placement.[24,25] PTAV1 has been linked to altered mechanical function, including increased left atrial volume and strain.[22] Loew et al[26] suggested through computational modeling that only PTAV1 was increased by left atrial hypertrophy. Furthermore, AF only accounts for about one-third of ischemic strokes[27]; thus, the presence of left atrial alterations generating PTFV1 may only be present in a certain proportion of stroke patients. This underscores the possibility for a less apparent association between the components of PTFV1 and stroke/TIA. Despite this, left atrial enlargement has also been associated with stroke in the absence of AF,[28] thus underlining the importance of identifying left atrial enlargement.

Conceptually, increased PTAV1 may represent a more complex interplay among different stages of pathophysiological alterations, anatomic variability, and incorrect ECG electrode placement. This potentially lowers the reliability of PTAV1 as a predictor of AF and stroke/TIA compared to ,PTDV1 which is much less dependent on vector projections.[24] This might explain some of the results in our study, in which we did not identify a clear dose–response relationship between PTAV1 and risk of AF, whereas the relationship trended more toward a dose–response relationship between PTAV1 and stroke/TIA (Figure 5 and Supplemental Figure 4).

Study strengths and limitations

The main strength of this study is the ability to combine information from uniquely detailed registries on recorded ECGs, comorbidity, and concomitant pharmacotherapy. The primary limitation is largely related to the observational nature of the study, in that our findings are associations and may not necessarily be causal. Moreover, the lack of clinical information about possible lifestyle confounders (eg, body mass index, blood pressure, or substance abuse) may affect risk estimates. Other important limitations of this study are the lack of indications for ECG recording and medication, as well as the exact causes of death.

Of note, we used primary care patients, thus ensuring a lower degree of selection bias regarding patients with poor health status compared to studies of hospitalized patients, among whom morbidity and mortality are pronounced. Furthermore, Nielsen et al[11] previously reported no healthy responder bias for patients at CGPL.

Clinical implications

The identification of abnormal PTFV1, especially a significant PTDV1, may be associated with an increased risk of developing AF and stroke/TIA. Registration of a significant PTDV1 (eg, through machine learning algorithms) may allow for identification of patients who may benefit from strategies aimed at identifying and preventing AF, such as rhythm monitoring. Rhythm monitoring is a typical part of the diagnostic workup of patients with embolic stroke of unknown source. In this connection, artificial intelligence is increasingly being investigated as a tool for identifying ECG abnormalities such as AF.[29–33] Evidence is equivocal, and some studies show a possibility of improved and cost-effective detection of AF,[30,31,33] whereas other studies d not in a clinical setting.[32] In this matter, identification PTFV1, especially driven by a long PTDV1, could serve as a valuable predictive tool in identifying patients who would benefit from prolonged monitoring and who are at high risk for AF.

A prospective study evaluating the usefulness of PTFV1 and PTDV1 for identifying patients who may benefit from AF risk factor modification may be warranted. A registration of significant PTDV1 and/or PTFV1 through machine learning algorithms may be warranted and may serve as a spur to future research.

Conclusion

In this study, we found a dose–response relationship between the duration of the terminal negative component of the P wave in lead V1 and the risk of incident AF and stroke/TIA among patients from a primary care setting. The amplitude of the terminal negative component of the P wave in V1 was less consistently associated with risk of AF and stroke/TIA. Measures of PTFV1, particularly duration measures, may be useful for identifying high-risk patients who could be targeted with cardiovascular prevention strategies.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.11.010.

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