Association of P-Wave Axis With Incident Atrial Fibrillation in Diabetes Mellitus (from the ACCORD Trial)

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Abnormal P-wave axis may reflect preclinical atrial dysfunction and has been associated with an increased risk of incident atrial fibrillation (AF) in the general population. Patients with diabetes mellitus (DM) have a higher prevalence of AF, but the association of abnormal P-wave axis and the risk of incident AF in those with diabetes has not been previously explored. For this analysis, we included 8,965 eligible participants from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. P-wave axis was automatically measured on study electrocardiogram and visually confirmed, with the normal range being between 0° and 75°. At baseline, 8% of the study population had an abnormal P-wave axis. During 43,856 person-years of follow-up, there were 145 cases of incident AF. Using multivariable-adjusted Cox proportional hazards models, participants with abnormal P-wave axis had an increased risk of incident AF (hazard ratio 2.65, 95% confidence interval 1.76 to 3.99, $p < 0.0001$). Findings were similar in prespecified subgroups, without evidence of effect modification. Both left- and right-axis deviation of the P-wave were associated with incident AF. Our results suggest that abnormal P-wave axis is associated with incident AF in those with DM and that this relation is conserved in prespecified subgroups. There may be utility in considering P-wave axis values from routine ECGs in these patients. **(Am J Cardiol 2020;128:191−195)**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an incidence that increases with age, which may reflect the burden of the progressive accumulation of predisposing comorbidities.[1−3] Studies have shown that diabetes mellitus (DM) is an independent risk factor for developing AF.[4−6] Although no screening method for risk of developing AF has been agreed upon, recent studies indicate that the P-wave axis (PWA), historically used in screening for lung disease, may be useful in predicting incidence of arrhythmias.[2,7−11] The PWA is readily available, yet scarcely utilized, on routine ECGs. Normal PWA is typically defined between 0 and +75°.[12] Several studies examining this in the general population discovered that abnormal PWA is associated with an increased risk of AF and of all-cause and cardiovascular mortality.[10,13,14] There appears to be a parallel effect between abnormal PWA and DM on the incidence of AF, yet this association with PWA has not been studied specifically in those with diabetes. Therefore, we examined the relationship between abnormal PWA and incident AF in participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

Methods

This is a retrospective analysis of prospectively-collected data from the ACCORD trial. The design and conduct of the ACCORD trial has been previously described.[15] Briefly, 10,251 individuals with type 2 DM from 77 sites across the United States and Canada were randomly assigned to intensive or standard glucose-lowering methods and monitored for health outcomes. The participants were also enrolled in either a lipid trial or a blood pressure trial to assess a total of 3 risk factors for cardiovascular disease, namely hyperglycemia, dyslipidemia, and hypertension. An electrocardiogram (ECG) was obtained in each participant at baseline, every 2 years, and at the end of the trial. Those with baseline ECGs of inadequate quality for assessment of PWA or AF at baseline were excluded. The reported PWA was used for analysis, with normal being defined as a value between 0 and 75°.

Study ECGs were obtained by trained electrocardiographers via standardized protocol on a GE Marquette (Milwaukee, Wisconsin) MAC 1200 electrocardiograph at a sampling rate of 500 Hz. All ECGs were digitally-transmitted to a central core laboratory for processing and coding—the Epidemiological Cardiology Research Center (EPICARE) at Wake Forest School of Medicine. Study ECGs were visually checked for quality and then automatically

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There was no specific funding from any funding bodies that supported the present analysis.

See page 194 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2020.05.009

processed using the GE Marquette 12-SL program. The PWA was derived from automated measurements and visually confirmed by trained ECG coders at EPICARE. ECGs were read for incident AF at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, North Carolina.

Statistical analyses were used to calculate mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Unadjusted analyses used analysis of variance for continuous variables and Chi-square tests for categorical variables. Two-sided p-values below 0.05 were considered to be statistically significant. Outcomes were assessed according to the intention-to-treat principle. Cox proportional hazards modeling was used to compare the risk of incident AF as a function of the baseline PWA. Initial analysis was unadjusted, with subsequent analyses iteratively adjusting for covariates believed to be of clinical importance, starting with demographics (model 1; adjusted for age, sex, and race), then history of cardiovascular disease, smoking, body mass index, treatment assignment, and mean systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and HbA1c. Time-independent proportionality assumptions wereassessed by examining the Martingale residual plot. Sensitivity analyses were performed by stratifying by age above or below study median (61.9 years), sex, and race, separately. All statistical analyses were conducted at Wake Forest University School of Medicine using SAS version 9.4 (Cary, North Carolina).

Results

A total of 8,965 participants were divided into two groups based on their PWA, one with normal and the other with abnormal baseline values. The 2 groups had several similar baseline characteristics including sex, race, systolic blood pressure, and heart rate. Participants with abnormal PWA were more likely to be older, have a lower body mass index, and a higher prevalence of cardiovascular disease. A full description of baseline characteristics is available in Table 1.

Of the 8,281 participants with a baseline normal PWA, 114 (1.4%) developed incident AF whereas 31 (4.5%) of the 684 participants with abnormal PWA developed AF. After adjustment for included covariates, abnormal PWA remained associated with an increased risk of AF (hazard ratio [HR] 2.69, 95% confidence interval [CI] 1.77 to 3.97; Table 2). Table 3 demonstrates a consistent heightened risk of AF in abnormal PWA participants in all prespecified subgroups of interest, except in non-whites.

As a sensitivity analysis, we explored the risk of incident AF by comparing right-axis deviation versus left-axis deviation of the P-wave. Among the 684 participants with abnormal PWA, 202 had left-axis deviation of the P-wave (median −19°, range −1° to −34°) and 482 had right-axis deviation of the P-wave (median 106°, range 76 to 142). In the fully-adjusted Cox proportional hazards model, compared to those with normal PWA, both left-axis deviation (HR 2.13, 95% CI 1.03 to 4.39, p = 0.04) and right-axis deviation (HR 2.85, 95% CI 1.81 to 4.48, p < 0.0001) were associated with a comparable risk of incident AF.

Figure 1 shows the cumulative incidence of AF throughout the study. The cumulative incidence of AF was almost twice that in participants with abnormal PWA compared with those with normal PWA.

Discussion

This study analyzing data from the ACCORD trial demonstrates an increased incidence of AF in those with abnormal PWA. Those with abnormal PWA are at least twice as

Table 1
Baseline characteristics of study participants (n = 8,965)

Variable	P-wave axis		p-Value*
	Normal(n = 8,281)	Abnormal(n = 684)	
Age (years)	62.5 ± 6.5	64.9 ± 7.1	< 0.0001
Men	61.2%	63.9%	0.16
White	62.2%	65.2%	0.12
Baseline cardiovascular disease	34.7%	40.2%	0.004
Smoker, Current	13.9%	17.1%	0.02
Body Mass Index (kg/m^2)	32.2 ± 5.3	31.1 ± 5.7	< 0.0001
Systolic Blood Pressure (mm Hg)	136.0 ± 16.5	137.1 ± 16.9	0.12
Diastolic blood pressure (mm Hg)	74.8 ± 10.2	73.1 ± 10.5	< 0.0001
Total cholesterol (mg/dl)	183.4 ± 40.3	180.2 ± 38.4	0.04
High-density lipoprotein (mg/dl)	41.6 ± 11.0	42.7 ± 12.2	0.01
Low-Density Lipoprotein (mg/dl)	105.0 ± 33.1	103.2 ± 32.5	0.16
Triglycerides (mg/dl)	187.6 ± 117.8	172.0 ± 104.7	0.0008
Hemoglobin A1c	8.28 ± 1.00	8.25 ± 0.99	0.50
Antihypertensive use	83.0%	83.2%	0.93
Aspirin use	55.5%	54.6%	0.65
Statin use	63.7%	65.6%	0.35
P-wave axis (degrees)	47.4 ± 15.7	58.1 ± 55.4	< 0.0001
Heart rate ($minute^{-1}$)	69.3 ± 11.2	69.4 ± 11.5	0.79

Continuous variables described as mean ± standard deviation.
Categorical variables described as frequency (percentage).
* p-Value as calculated by ANOVA for continuous and Chi-square for categorical variables.

Table 2
P-wave axis and risk of incident atrial fibrillation

P-wave axis	Cases	Follow-up*(person-years)*	Model 1Unadjusted		Model 2Adjusted for demographics		Model 3Fully adjusted	
			HR ± 95% CI	p-Value	HR ± 95% CI	p-Value	HR ± 95% CI	p-Value
Normal *(n = 8,281)*	114	40,566	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–
Abnormal *(n = 684)*	31	3,290	3.34 (2.21−4.90)	<0.0001	2.69 (1.77−3.97)	<0.0001	2.65 (1.76−3.99)	<0.0001

Model 1 is unadjusted.
Model 2 adjusts for age, sex, and race.
Model 3 adjusts for the covariates in Model 2, with the addition of history of cardiovascular disease, smoking, BMI, treatment assignment, and mean SBP, total cholesterol, HDL cholesterol, and HbA1c.

Table 3
P-wave axis and risk of incident atrial fibrillation by subgroup

Subgroup		HR (95% CI)	p-Value	Interaction p-Value
Age *(years)*	<61.9	4.05 (1.75 − 9.37)	0.001	0.24
	≥61.9	2.47 (1.55 − 3.94)	0.0001	
Sex	Male	2.48 (1.54 − 3.99)	0.0002	0.65
	Female	3.35 (1.50 − 7.46)	0.003	
Race	White	2.62 (1.68 − 4.09)	< 0.0001	0.95
	Non-White	2.83 (0.94 − 8.53)	0.06	

Model adjusted for age, sex, race, history of cardiovascular disease, smoking, BMI, treatment assignment, and mean SBP, total cholesterol, HDL cholesterol, and HbA1c.

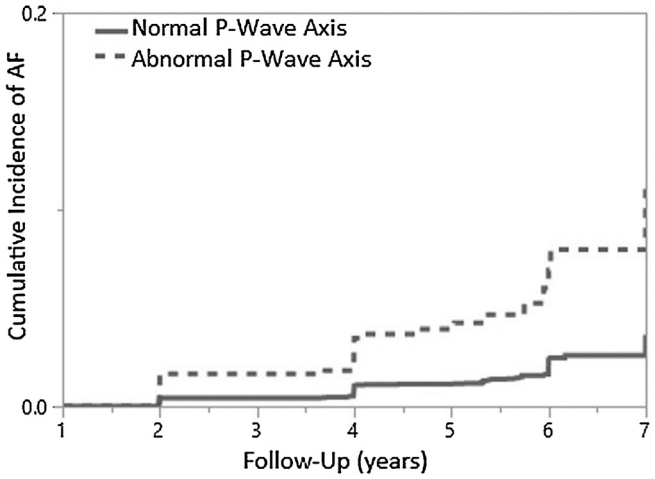

Figure 1. Cumulative incidence of atrial fibrillation stratified by P-wave axis.

likely to develop AF. This result persists after adjusting for demographics and factors reflecting increased risk of cardiovascular disease, such as mean systolic blood pressure, total cholesterol, and HbA1c, and is conserved in subgroups.

The PWA reflects the net vector of atrial depolarization specifically in the frontal plane, and this is influenced by anatomic and pathologic features of the atria.[2,9] These findings build upon existing studies that have examined the relation between PWA and AF. One group looking at the Cardiovascular Health Study found a 17% increase in the risk of AF in abnormal PWA patients when compared with normal PWA patients.[10] Another group using data from the Atherosclerosis Risk in Communities study found that 19% of patients with abnormal PWA developed AF, and that those with abnormal PWA were 2.34 times as likely to develop incident AF (HR 2.34, 95% CI 2.12 to 2.58) in adjusted models.[9] They also noted an increased risk of AF as the PWA decreased below 14° or went above 55°.[9] When looking at ECG parameters after cryptogenic stroke, one group found that abnormal PWA is one of the best predictor variables for AF with an odds ratio of 3.31 (95% CI 1.49 to 7.35) in the first week after the neurovascular event.[16] We found similar evidence with higher HR in our multivariate analysis when looking at PWA and AF in patients with diabetes mellitus, which itself predisposes patients to AF and cardiovascular disease.

Although literature regarding abnormal PWA exists and is growing, analysis of the directionality of axis deviation is still scarce. One group observed 56% of patients with abnormal PWA had right-axis deviation, whereas 41% had left-axis deviation when examining the prognostic role of abnormal PWA in patients undergoing revascularization or valve surgeries.[13] However, they did note that trending survival curves suggested worse overall and cardiovascular mortality for left-axis deviation than for right.[13] Our results suggesting a similar magnitude of association between incident AF and both left-axis deviation of the P-wave and right-axis deviation of the P-wave are additive to the existing literature. Because PWA can be an important indication of a predisposition to developing arrhythmias, it is important to understand what pathophysiology this measurement represents. Reviews discussing the substrate for AF have focused on the development of oxidative stress, atrial fibrosis and electrical autonomic remodeling.[17] Echocardiography demonstrates anatomical changes in hearts with AF including increased left atrial diameter, left ventricular wall thickness, and left ventricular fractional shortening.[18] One group showed that a PWA <30°on ECG is 90% specific, though insensitive, for detecting left atrial enlargement, which was confirmed on cardiovascular magnetic resonance imaging.[19] Thus, PWA is a valuable marker of underlying progressive atrial disease and co-morbidities that are associated with subsequent incident AF.

Although no mechanism has been definitively proven to demonstrate causality between DM and developing AF, several studies have been conducted examining this relation. There are 2 main groups of observations, anatomic and electrical. Impaired glucose metabolism is associated with increased left atrial diameter.[20] As discussed previously, these changes can be reflected by variations in PWA and are all indicative of risk factors for developing AF in the future.

Other studies examine electrical observations. Hyperglycemia is known to cause fibrotic changes and oxidative stress, which disrupts cellular functions and can cause neuronal dysfunction.[21,22]Impaired glucose metabolism leads to electrophysiologic changes including increased atrial activation time and lower atrial voltages.[20] Other electrical changes present in diabetic atria include increased susceptibility to atrial tachyarrhythmias − specifically, decreased conduction velocity, increased conduction heterogeneity, and increased action potential duration.[22] Further, it has been widely accepted that DM can cause autonomic dysregulation. Briefly, a heterogeneous density of sympathetic innervation in cardiac tissue and decreased effective refractory periods are present in animal models with DM, and these can both contribute to the formation of sustained arrhythmias.[23–25]

The strengths of this study include a large sample size and an adjusted analysis accounting for 2 other risk factors for cardiovascular disease, namely hypertension and dyslipidemia. This analysis should be considered in the context of its limitations. Our data did not include information regarding P-wave duration, P terminal sources in V1, or echocardiographic and magnetic resonance imaging data commenting on left atrial enlargement. These may be topics of future research. Abnormal PWA is a broad term that includes both right- and left-axis deviations, which can reflect different pathologies that may influence incident AF. Although Model 3 considered risk factors for cardiovascular disease other than hyperglycemia, it is possible that some patients had other subclinical disease processes or risk factors for AF that were not accounted for. When analyzing the data by race, a small sample size of non-whites may have limited our ability to find a significant difference. Further, although our model adjusted for several confounding factors, there is the possibility that other unidentified variables played a role as well.

In conclusion, our results suggest that abnormal PWA is associated with incident AF in those with DM and that this relationship is conserved in prespecified subgroups. There may be utility in considering PWA values from routine ECGs in these patients.

Author Contributions

Karanpreet K. Dhaliwal − writing (original draft); BharathiUpadhya − writing (review and editing); Elsayed Z. Soliman − conceptualization, writing (review and editing); Elijah H. Beaty − writing (review and editing); Joseph Yeboah − supervision, writing (review and editing); Prashant D. Bhave − writing (review and editing); Matthew J. Singleton − conceptualization, methodology, formal analysis, writing (review and editing), visualization, supervision. Dr. Matthew Singleton is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This manuscript was prepared using research materials obtained from the NHLBI Biological Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the NHLBI.

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